Nucleophilic Eliminative Ring Fission

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I. Introduction

Elimination reactions have been widely reviewed and much attention has been paid to the relationship between structure and reactivity in this type of reaction. An intriguing aspect of the relationship between structure and reactivity is the contribution of ring strain to the formation and the cleavage of cyclic systems. It is the purpose of this review to bring together and discuss reactions of all types in which a multiple bond is formed with expulsion of a leaving group in such a way that fission of a ring system is involved. The different responses of various types of elimination to ring strain in the leaving group can thus be compared.

A. Scope of the Review

The range of eliminative ring fission reactions is very wide and this review will deal only with *nucleophilic* eliminative ring fission (Scheme I, reaction a). Homolytic (b) and electrophilic

SCHEME I

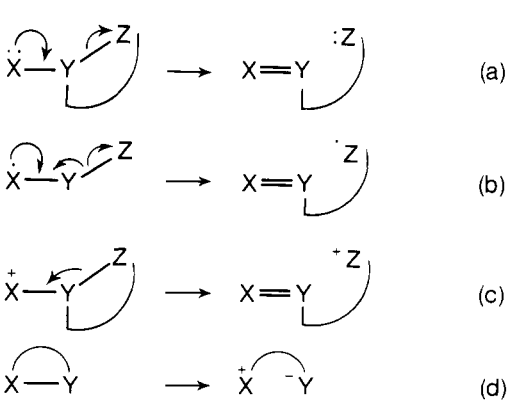

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TABLE I. Ring-Strain Energies (kcal mol^{-1}) of Systems

n		No. of atoms in ring	X = C	X = O	X = S	X = NH
0		3	27.43	27.28	19.78	26.87
1		4	26.04	25.51	19.64	
2		5	6.05	5.63	5.80	1.97
3		6	0.02	1.16	−0.15	−0.27

(c) ring fissions will not be discussed and neither will dissociative ring fission of type d.

All types of elimination reaction are included; the major sections deal with carbon–carbon and oxygen–carbon double bond forming reactions and the contrast in reactivity between these systems is particularly striking. Formation of triple bonds is also included as is formation of other carbon–heteroatom multiple bonds and bonds between heteroatoms. The majority of ring fission eliminations involve formation of multiple bonds, but higher order eliminations are also included to allow for overall comparisons.

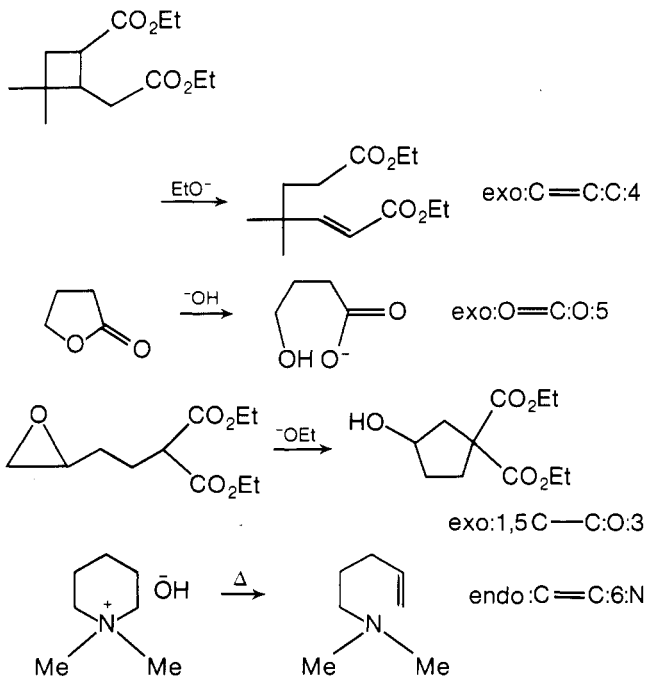
The result of many eliminative ring fission reactions is to produce an acyclic, unsaturated *isomer* so that the reactions may be regarded as molecular rearrangements. A number of general reviews of rearrangements contain appropriate references.[1-3]

B. Nomenclature and Classification

Two distinct types of eliminative ring fission exist. The more common is exocyclic ring fission (Scheme I, reaction a) in which *only one* of the atoms which forms part of the ring is involved in formation of a new bond as a result of the elimination reaction. The rarer type is endocyclic eliminative ring fission in which *both* of the atoms involved in the formation of a new bond as a result of the elimination reaction are also part of the ring system which undergoes cleavage.

The reactions discussed in the review are classified according to four criteria illustrated in Scheme II: (a) exo or endo, (b) type of bonding produced in the elimination, (c) the leaving group atom, and (d) the number of atoms in the cleaved ring.

SCHEME II



C. Ring Strain

The ring strains of carbocyclic and heterocyclic ring systems are in Table I. For the three- and four-membered rings, large strain energies are present, and it will be seen that the release of this ring strain energy in the transition state enables observation of reactions, particularly with carbon leaving groups, which are not seen in unstrained acyclic systems. It will also be seen that most observations are anecdotal; very little attempt has yet been made to quantify the effect of ring strain on reactivity in elimination reactions. Further, only in very few cases have mechanisms been assigned to the reactions described.

D. Arrangement of the Review

Exo reactions are considered first and within both exo and endo types, alkene-forming reactions are dealt with before carbonyl-forming reactions and those producing bonds between other atoms. Leaving group atoms are considered in the order C, O, S, N, and others, and finally ring sizes in ascending order.

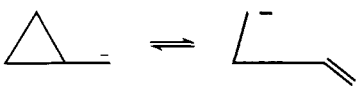
II. Exo:C=C:C Reactions. Eliminative Cleavage of Carbocycles

A. Exo:C=C:C:3. Cyclopropanes

In this type of process, expulsion of a carbon leaving group is involved. Carbon leaving groups are unknown in simple base-promoted alkene-forming eliminations and are very rare when elimination is activated by a carbanion-stabilizing group.[5] In recent work on quantification of leaving-group ability,[6] attempts to place carbon leaving groups on a scale with leaving groups with connections through atoms of groups 7, 6, and 5 of the periodic table have failed. It is certain that cleavage of a carbon–carbon bond in an alkene-forming elimination is very difficult.[6] It is all the more striking, therefore, that a large number of examples of eliminative ring fission of small rings has been described; the strain energy of the ring clearly compensates for the high activation energy required for expulsion of a carbon leaving group.

1. Poorly Activated Systems

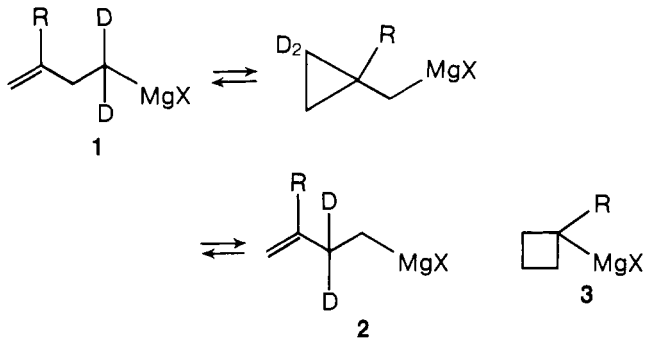
The simplest example of this reaction is the rearrangement of cyclopropylmethyl carbanions:



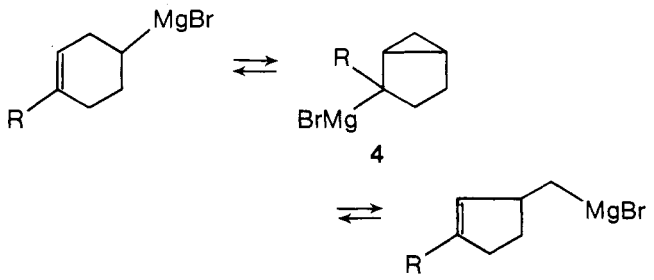
In the original examples described by Roberts and his coworkers,[7] the nature of the species involved in the reaction is indistinct. In later work[8,9] it was shown that the energy of activation for scrambling of a carbon label between positions 2 and 4 of but-3-enylmagnesium bromide was 19 kcal mol^{-1}, giving a mean lifetime of the cyclopropylcarbinyl species of $\geq 10^{-2}$ s. This work has been continued in a series of detailed studies by Maercker.[10-13]

No CIDNP signals are observed[14] in the rearrangement of but-3-enylmagnesium bromide which is decelerated by methyl

groups and accelerated by phenyl groups at C-4. All these observations are consistent with the intermediacy of a carbanion, and a substantial secondary deuterium isotope effect operates[10,11] in the equilibrium favoring **2** over **1**; **3** is definitely excluded as an intermediate. Related examples involving equilibration between five- and six-membered rings have also been reported.[12,13,15]

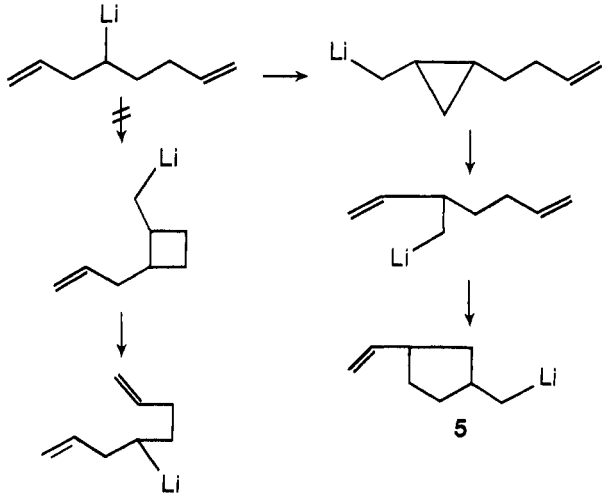


The intermediate **4** is not detectable by ^{1}H NMR.[12] When R = Ar, the rate of rearrangement decreases and $\rho_{Ar} = 1.4$.[15]

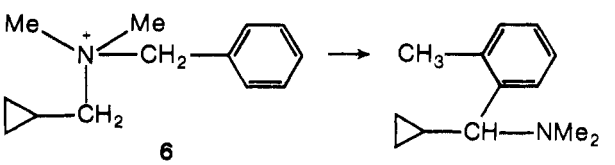


It has been shown that cyclopropylcarbinyllithium can be formed at −70 °C and be trapped with benzaldehyde before isotopic scrambling occurs.[16,17] Ring cleavage is obviously very rapid, and with cyclopropylmethyl phenyl ether lithiation causes eliminative ring fission faster than protonation of the carbanion by the starting material.[18] Lithiooctа-1,7-diene rearranges[19] to the five-membered ring lithio derivative (**5**) exclusively via formation and eliminative ring fission of a three-membered ring rather than the alternative four-membered ring; see Scheme III.

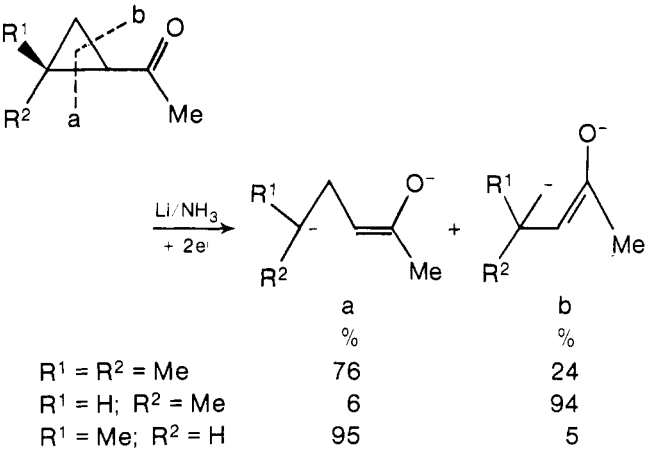
SCHEME III



By contrast, in the ammonium salt **6**, cyclopropylmethyl migration occurs *without* rearrangement.[20]

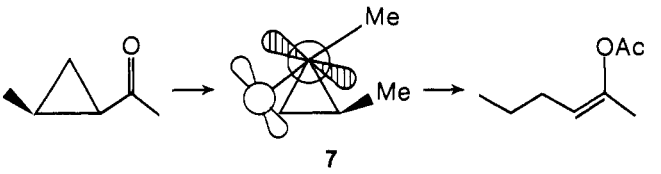


SCHEME IV



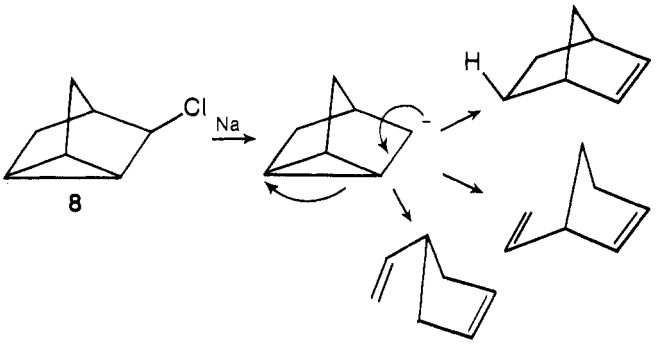
	a %	b %
$R^1 = R^2 = Me$	76	24
$R^1 = H$; $R^2 = Me$	6	94
$R^1 = Me$; $R^2 = H$	95	5

Cleavage of unsubstituted cyclopropane rings occurs when the exocyclic nucleophilic center is generated by electron transfer to alkyl cyclopropyl ketones.[21] With alkyl groups on the ring, the alternative modes of ring fission[22] are governed by overlap between the C_1–C_2 orbital and the π system of the carbonyl group (see Scheme IV). The more stable primary carbanion is formed predominantly only when the methyl and acetyl groups are trans. Trapping[23] of the enolate ion products as acetates shows that the cisoid conformation **7** is adopted in the ring fission process:

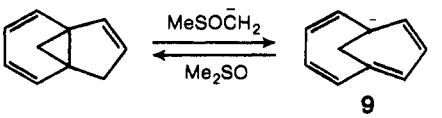


In the bridged system **8**, on generation of the carbanion, three products ensue[24] (Scheme V).

SCHEME V



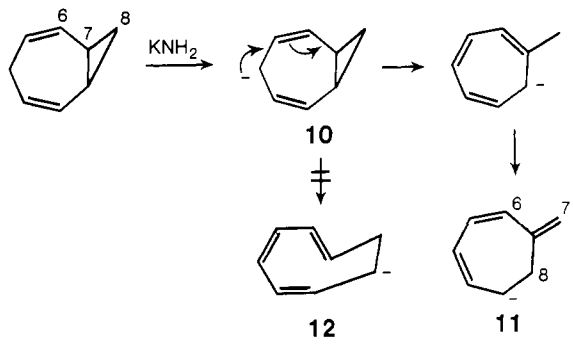
In fused bicyclic systems mildly activated by conjugated polyene systems, fission of the three-membered ring occurs[25-27] to give the aromatic 10-electron anion **9** which reprotonates



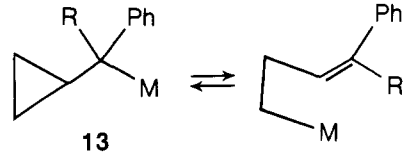
antiperiplanar to the re-formed bond in the three-membered ring. In **10**,[28] ring fission gives the product (**11**) of conrotatory ring fission and none of **12** (Scheme VI).

Activation of eliminative ring fission by carbanion-stabilizing

SCHEME VI



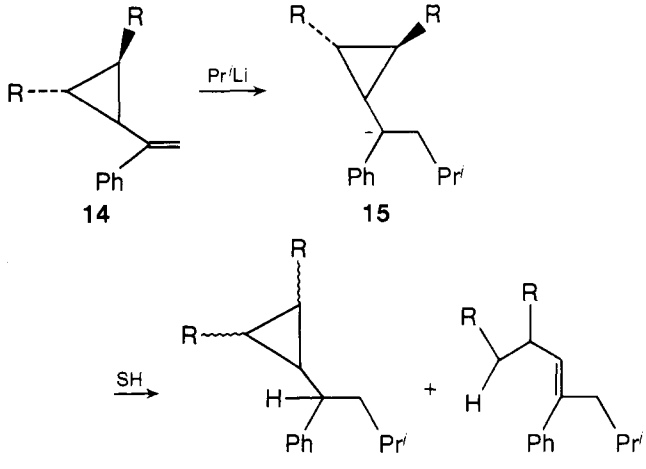
groups is to be expected; with phenyl activation, ring opening of the organometallics (**13**) is dependent on M:[29]



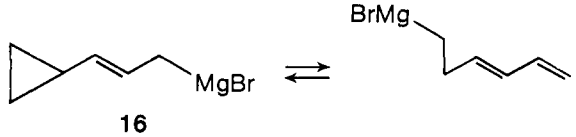
13

When R = H and M = K or Na, the ionic character of the C–M bond is high, stabilization by the phenyl group is high, and no ring fission occurs. With R = Ph, the lithium derivative (M = Li) is stable in THF but opens in Et_2O and recloses on addition of THF to the ethereal solution.[29]

Generation of a stabilized ion by nucleophilic addition as in **14** causes rapid ring fission[30,31] in that the intermediate anion **15** cannot be intercepted.[30,32] With methyl groups on the ring, the ring-cleaved ion is destabilized and all three configurations of the recyclized ion can be intercepted:



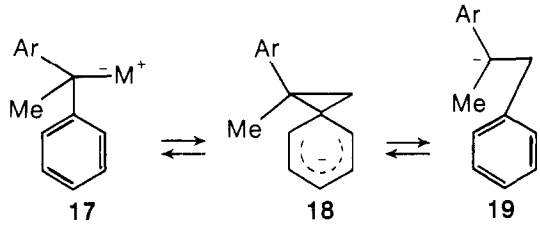
In ring fission of the more activated system[33] (**13**, R = Ph) generated from either open-chain Grignard reagent (M = MgBr), the cyclopropymethyl anion cannot be trapped, but in the vinylogue **16**, cyclopropyl derivatives form 32% of the product on quenching.



16

2. 1,2-Aryl Migrations

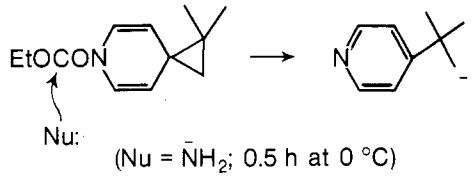
Rearrangement[34] of the ion **17** involves formation of the spirodienyl anion **18** which opens in principle in either direction, but overwhelmingly to give the more stable ion **19.** The possibility of intermolecular rearrangement is excluded by the failure of phenyllithium to add to α-methylstyrene. Later work with the ion



17 **18** **19**

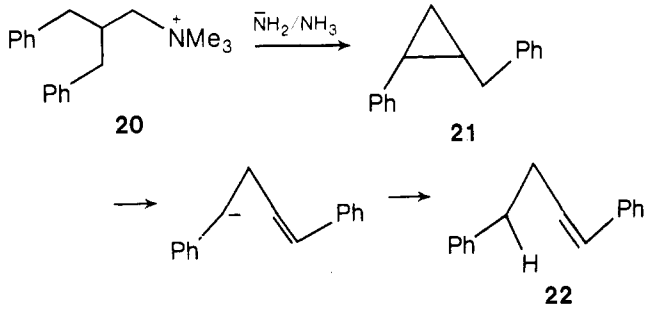
17 (Me = Ph) showed[35] no incorporation of radioactivity from radiolabeled phenyl- or benzyllithiums and the fact that in **17** the migratory aptitude of *p*-biphenylyl is 24.5 times as great as that of *m*-biphenylyl supports[36] the mechanism involving exo:C=C:C fission of **18.** This process, like others,[29] occurs in **17** with Ar = Me = H provided that M = Cs or K and the carbanion is highly reactive.[37]

The dihydropyridine derivatives behave similarly:[38]

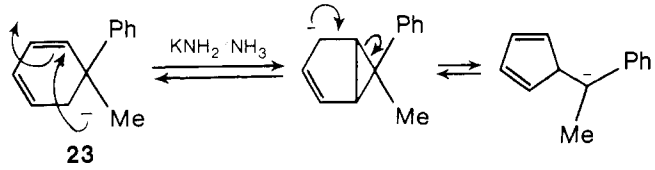


The more stable primary ion is formed and fission of the spirocarbocyclic ring does not occur when it is five membered and only mildly strained.[39]

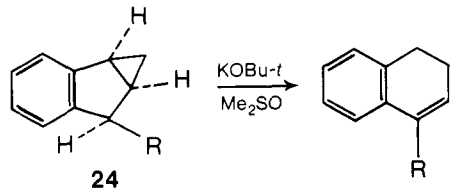
Stabilization of the leaving group is important in poorly activated systems, and the effect is also seen below in numerous instances. Treatment of the salt **20** with sodamide in ammonia gives[40] the rearranged alkene **22,** probably via the intermediate cyclopropane **21** which cleaves to give a benzylic carbanion:



Benzylic carbanions as leaving groups are also seen in rearrangement of the cyclohexadienyl anion **23**[41] and in **24.**[42] The reaction is about 10 times faster for R = H than R = Me, and there is a slight preference for elimination (antiperiplanar) in the configuration shown over the epimer.

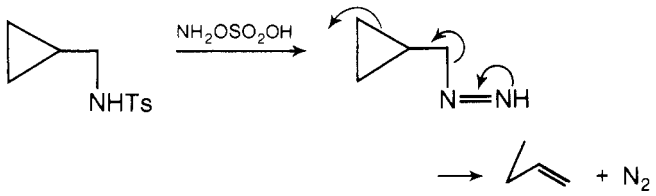


23

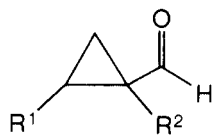


24

Provision of the electron pair from a diimide intermediate causes[43] ring fission without a stabilizing group at the origin or terminus:

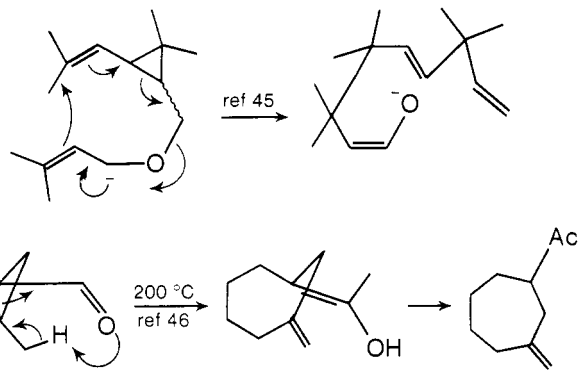


but treatment of the aldehyde **25** under Wolff–Kishner conditions causes ring fission[44] only when R^1 = Ph and R^2 = H and not vice versa.

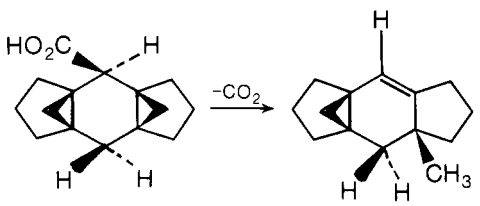


25

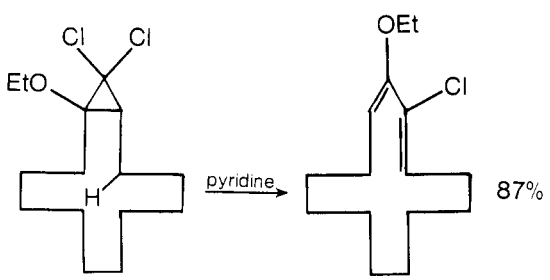
In recent examples, the electron pair can arise by way of rearrangements:



or by decarboxylation,[47,48] e.g.[48]

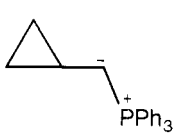


Ring fission may be followed by elimination in poorly activated systems. Typical examples are the cleavages of adducts of dichlorocarbene with vinyl ethers[49–52] and alkylidenefluorenes,[53] e.g.[50]

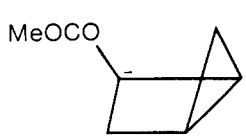


3. *Systems Activated by Carbanion-Stabilizing Groups*

The presence of a carbanion-stabilizing group greatly activates alkene-forming elimination and extends the range of leaving groups.[6] Formation of a stabilized carbanion, however,



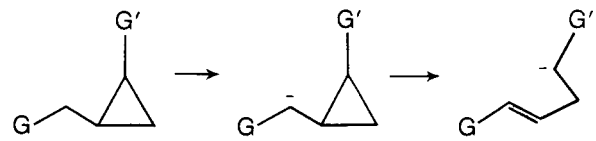
26



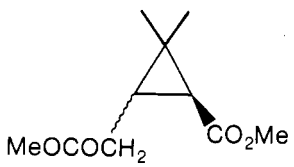
27

reduces the reactivity of the carbanion, and the ions **26**[54] and **27**[55] without a stabilized leaving group do not ring open.

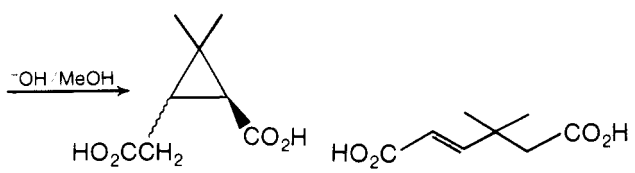
When, however, the leaving group is also stabilized, ring fission occurs easily. Examples in which carbalkoxy groups stabilize both carbanion and leaving group (G = CO_2R) are common:[56–62]



There is some evidence of stereochemical preference; in the diesters **28**[63] hydrolysis of the trans ester competes more favorably with ring fission than in the cis isomer:



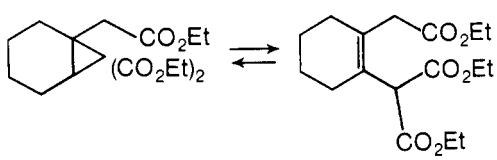
28



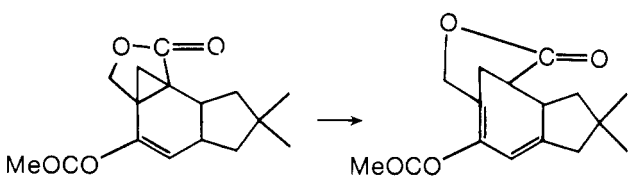
trans	89.6	10.4
cis	61.3	38.7

This may, however, be due to more rapid hydrolysis rather than slower ring fission. Calculations[64] suggest a low energy for the conformation most appropriate for antiperiplanar elimination when the ion is planar. When the ion is pyramidal, this ion is of slightly higher energy than the minimum.

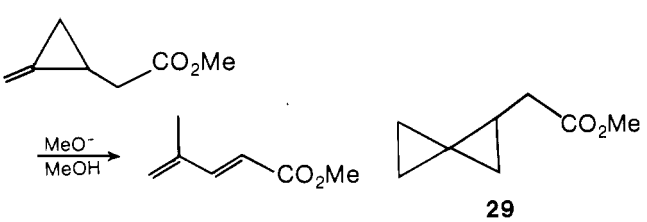
Considerable structural variation in terms of substituents on the cyclopropane ring is possible in this type: e.g., fused ring[65]



vinylogous and lactone stabilization (degradation of marasamic acid):[66]



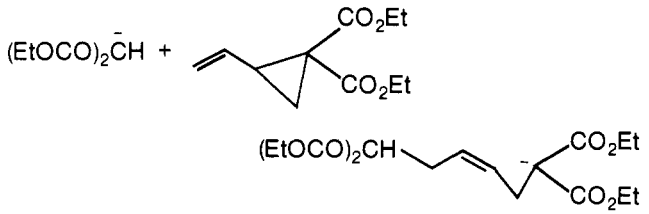
α-diketone activation[67] and a particularly intriguing example[68] in which the extra strain of a methylenecyclopropane suffices for ring opening with only mild allylic stabilization of the leaving group:



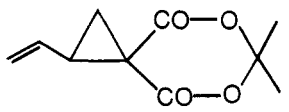
29

The spiro ester **29** is stable.

The carbanion which precedes ring fission may be generated by nucleophilic addition to a vinylcyclopropane, e.g.[69]

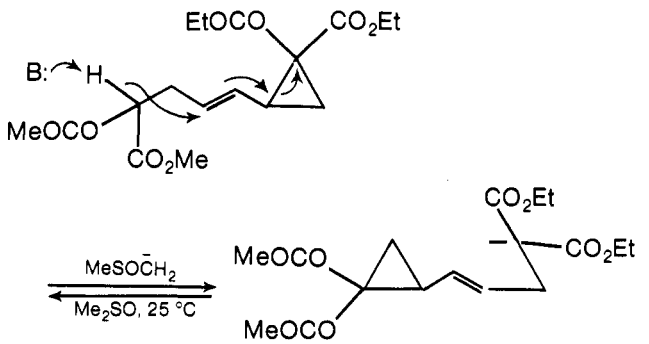


This reaction with malonate as nucleophile is a minor one as demonstrated by Danishefsky[70] but has been exploited in the synthesis of prostaglandin precursors.[71] The same type of reaction has been observed when the nucleophile is an enamine,[72] thiophenolate,[73] or dialkyl copperlithium.[74] Interestingly, in the bislactone **30** no attack on the carbon–carbon double bond is observable with piperidine, thiophenolate, or malonate ions.[75]

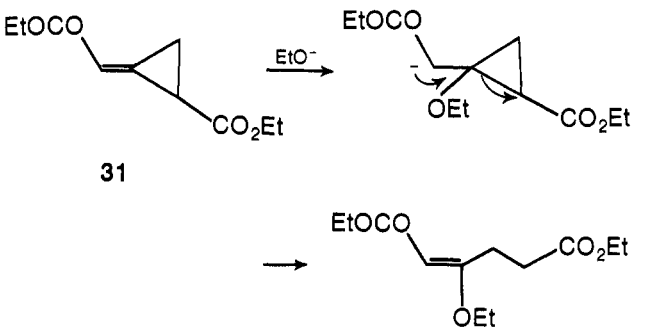


30

An intramolecular version of the reaction is seen[76] in the equilibration:



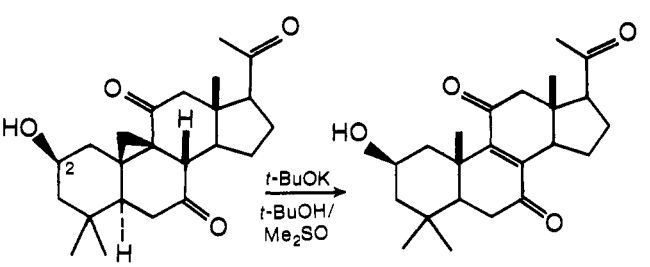
Addition–eliminative ring cleavage also probably occurs in reaction of the ester **31** with ethoxide ion:[77]



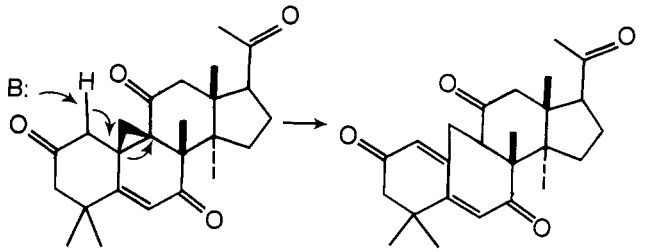
31

4. Oxo Activation

Several examples of this type are known, particularly in the steroids. Especially revealing instances have been reported by Barton and his co-workers[78] in the chemistry of curcurbitacin A:

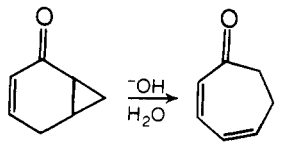


This reaction occurs without stabilization of the leaving group, but protonation of the carbanion by the β-hydroxyl group at C_2 is essential in this case; the reaction does not occur when this is α or absent. In another example, the importance of oxo-group activation on the occurrence of the reaction and upon its product is seen:[78]

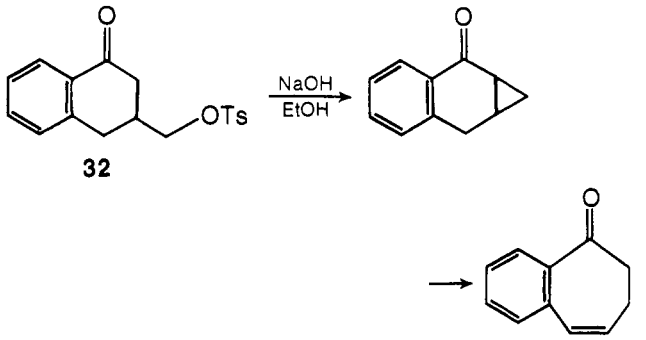


In the absence of the 2-oxo group, no reaction occurs. Related reactions are those of 2-oxocyclopropanes on alumina[79] and of β-hydroxycyclopropanes after oxidation in situ.[80]

The vinylogues of β-oxocyclopropanes cleave smoothly:[81]

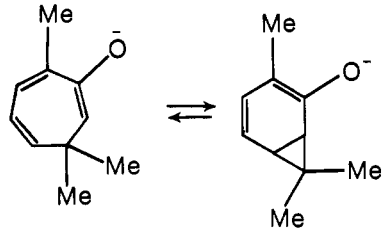


In this case the leaving group is also oxo-stabilized, and treatment of the tosyloxylmethyltetralone (**32**) with base undoubtedly involves intramolecular 1,3-nucleophilic displacement followed by eliminative fission of the cyclopropane thus formed:[82]



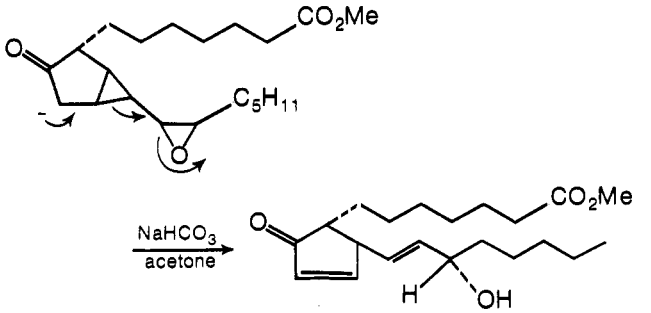
32

Similarly the equilibrium:

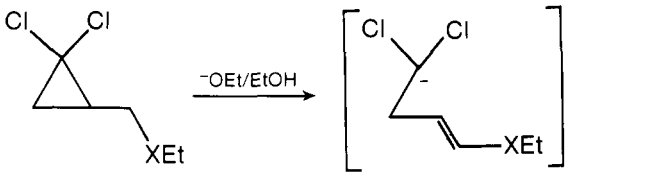


involves disrotatory electrocyclization of what is effectively a vinylogous exo-stabilized carbanion.[83]

The carbanion produced in an exo:C=C:C:3 reaction may itself initiate further reaction;[84,85] the reaction has been applied in prostaglandin synthesis and the second stage is an exo:C=C:O:3 reaction (section III.A). See, e.g.[85]



The paucity of quantitative work on eliminative ring fission is striking. In preliminary work on sulfonyl-activated systems, it has been found that the rate of reaction of the sulfone (**33**, X = SO_2) is 50 000 times greater than that of the sulfide (**33**, X = S) consistent with a dichloro-stabilized carbanion as leaving group. Unfortunately, the products undergo further complex reactions:[86]



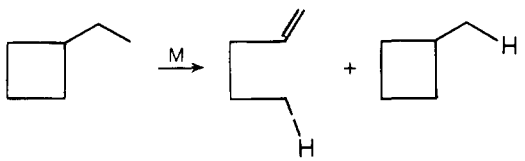
33

→ products

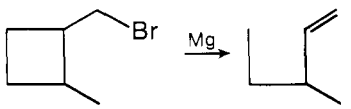
B. Exo:C=C:C:4

1. Unactivated Systems

The cleavage of cyclobutylmethyl organometallics, studied chiefly by Hill and his collaborators,[87,88] occurs as in the exo:C=C:C:3 reaction:



	%	%
Z = Cl; M = Na[87]	59	-
Z = Cl; M = Li[89]	93	7
Z = Br; M = Mg[88]	99.8	0.2

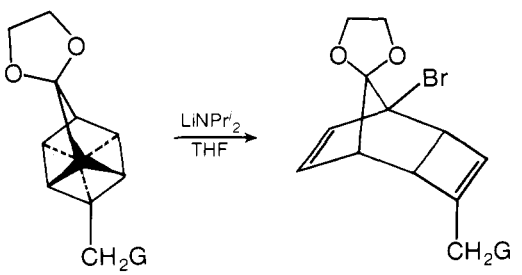


99%

i.e., primary $\bar{C} \gg$ secondary $\bar{C}$.[89] Rates of ring opening in the Grignard reaction are insensitive to solvent and structure, and a synchronous four-center process is suggested.[88] In later work,[90] equilibration between cis and trans disubstituted cyclobutanes is believed to involve reversible eliminative ring fission.

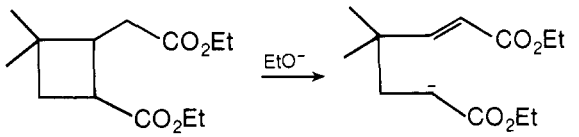
2. Activated Systems

The reaction requires either additional strain or a stabilized leaving group. Examples of the former type have been described by Klunder and Zwanenburg:[91,92]

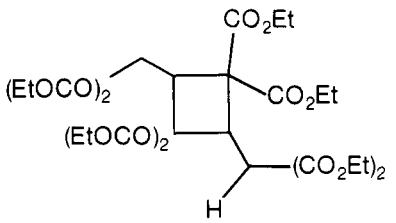


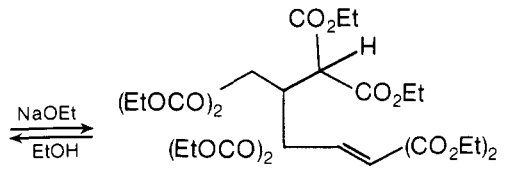
G = $PhSO_2$ or CN

The latter type is exemplified[93] by the four-membered analogue of the three-membered ring systems described earlier:[60]

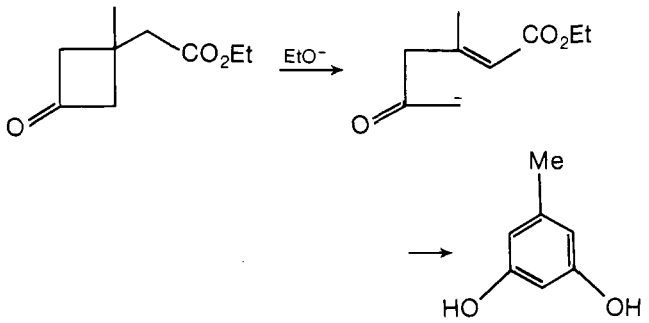


In systems highly activated by carbalkoxy groups toward both carbanion formation and leaving group stabilization, formation of equilibrium mixtures occurs:[94]



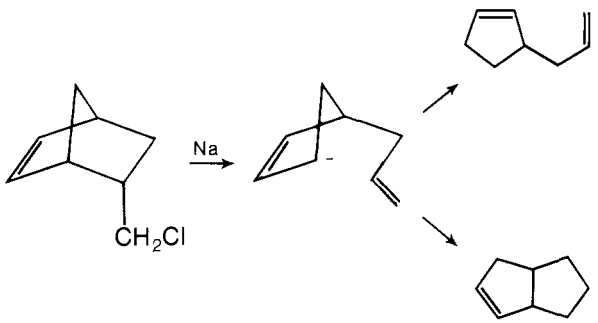


With carbalkoxy activation and oxo stabilization in a cyclobutanone, exo:C=C:C:4 cleavage[58] leads to a resorcinol derivative[95] as follows:

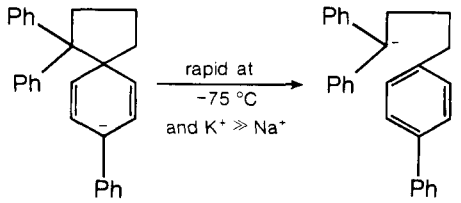


C. Exo:C=C:C:5

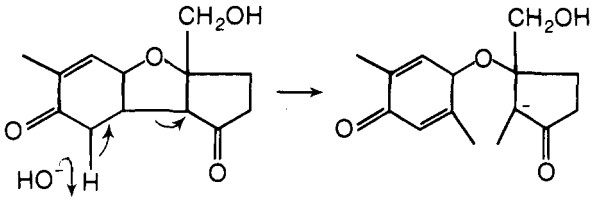
Eliminative cleavage of larger ring systems is rarely observed; ring strain no longer contributes to reactivity except in special cases. The following examples require: (i) formation of a stable 10π electron species[27] (section II.A); (ii) strain of a bridged six-membered ring giving an allylic anion:[96]



(significantly, in this case, no cleavage of the saturated analogue occurs; the extra strain engendered by the endo double bond is required); (iii) stabilization of the leaving group coincident with formation of an aromatic system:[97]

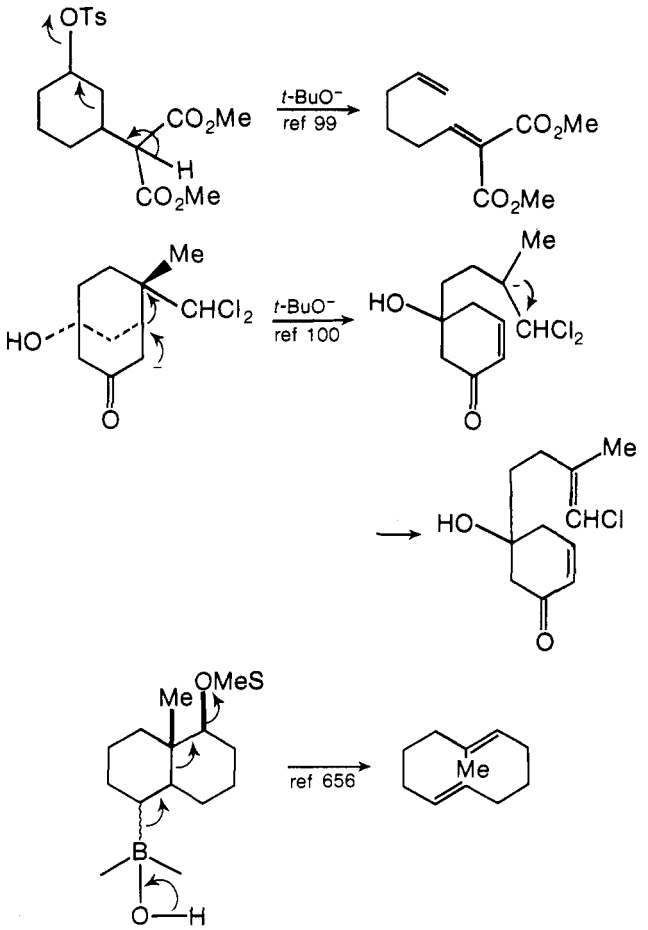


(iv) oxo-stabilization of the leaving group. An example is found in the chemistry of tricothecin[98] which provides three other examples of eliminative ring fission (sections VIII.A and VIII.B).



D. Exo:C=C:C:6

Examples are again rare. In each case, eliminative fission is followed by elimination of an excellent leaving group:

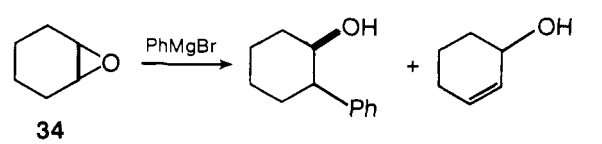


III. Exo:C=C:O Reactions. Eliminative Cleavage of Oxygen Heterocycles

A. Exo:C=C:O:3. Epoxides

There are many instances of this reaction type known[101,102] in many types of structure and with varying degrees of activation. Surprisingly, little quantitative work has been reported on the reaction; a few examples are noted below.

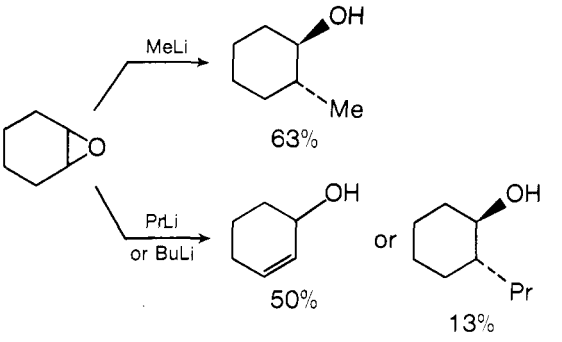
The earliest examples appear to have been recognized by Bedos[103,104] who showed that in reaction of epoxycyclohexane with phenylmagnesium bromide, not only was the expected substitutive product (**34**) formed but also the exo:C=C:O:3



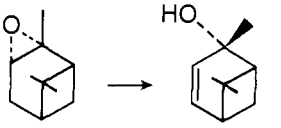
34

product, cyclohexenol. This reaction is formally a 1,2-elimination of an alkoxy group, a type not known in acyclic systems with this degree of activation nor in larger ring systems with less ring strain. The strain of the three-membered ring clearly promotes cleavage of the bond to the leaving group and the extent of this activation is discussed below.

The original observations have been succeeded by many related investigations with simple epoxides. Letsinger and his co-workers[105] showed that the competition between substitution (usual) and elimination (exceptional) depended on the steric bulk of the organometallic:

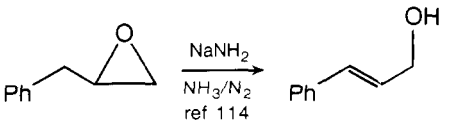


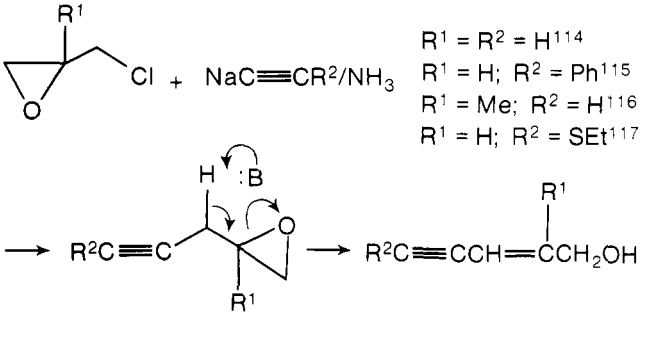
Other strongly hindered bases produce eliminative fission. Thus treatment of α-pinene epoxide with lithium diethylamide, a reagent much used in mechanistic studies (below), causes[106] the exo:C=C:O:3 process to occur:

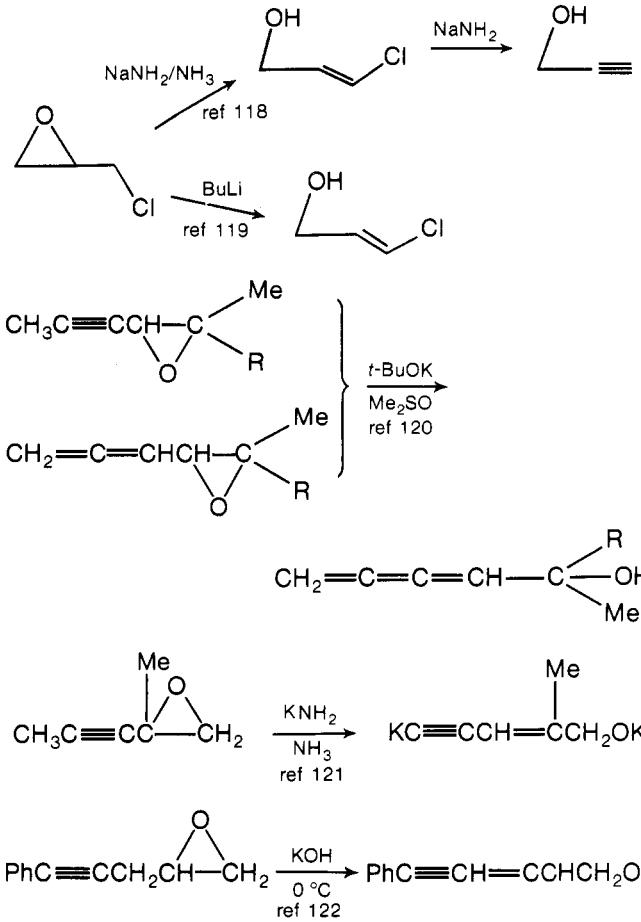


Similarly, passage of 1,2-epoxypropane over a lithium phosphate catalyst yields[107] allyl alcohol in useful yields, and epoxycycloalkanes readily give 3-hydroxycycloalkenes on activated alumina.[108] In polymerization of this epoxide with potassium hydroxide, the formation of unsaturated end groups can be accounted for by exo:C=C:O:3 eliminative ring fission.[109] This mode appears more likely than 1,1-elimination suggested earlier[110] and, interestingly, when the 1,1,1-trideuterio derivative is used,[109] the degree of unsaturation decreases in accord with the proposed mechanism. The results suggest a primary deuterium isotope effect of about 3.0. Later work has confirmed[111] that in polymerization of epoxides with potassium *tert*-butoxide in dimethyl sulfoxide, eliminative ring fission is the main transfer reaction. The incidence of nucleophilic eliminative ring fission in epoxide polymerization has been reviewed briefly.[112]

The reaction is further activated, just as are simple base-promoted eliminations,[113] by activating groups on carbon attached to the ring. Examples with differing types of modest activation are:

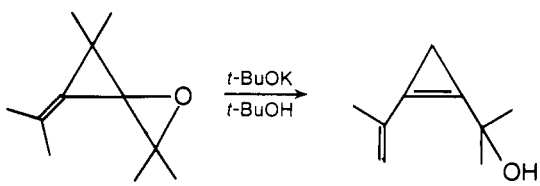




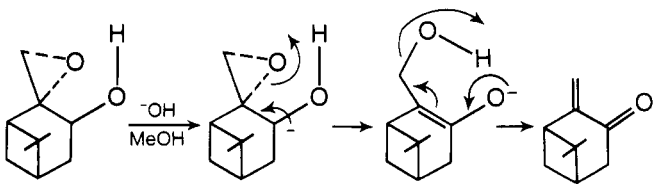


In poorly activated epoxycycloalkanes, eliminative ring opening is induced by reagents such as lithium diethylamide.[106,123,124] In cyclooctane, the exo:C=C:O:3 process is only 30% of the reaction pathway, the remainder being the transannular carbene insertion reaction[125] (section IX).

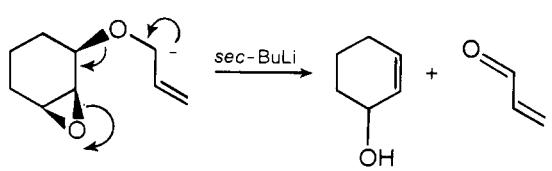
With allylic activation, strongly basic media are still required to effect eliminative ring fission,[126] a particularly interesting example being formation of a cyclopropene,[127] doubtlessly encouraged by the substantially lower strain in the cyclopropene than in the methylene cyclopropane:



Cleavage of epoxy-β-pinene occurs[128] with formation of the ketone:

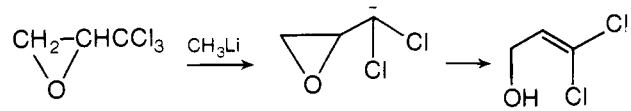


Ring cleavage under strongly basic conditions may also be preceded by carbonyl-forming elimination:[129]



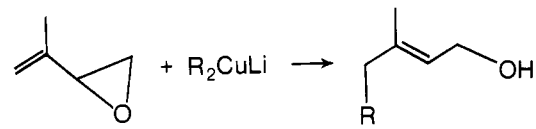
The reaction takes an alternative course in the trans isomer (sections III.B and VIII).

Related to the organometallic induced processes is the halogen–metal exchange in 1,1,1-trichloro-2,3-epoxypropane (**35**) by methyllithium[130] which precedes eliminative ring fission

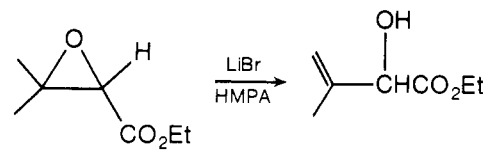


35

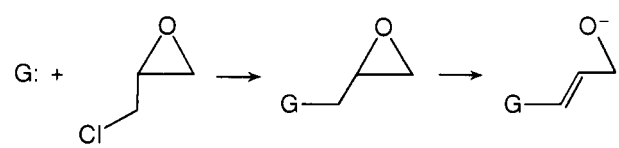
and reaction of dialkylcopperlithiums with epoxyisoprene by addition–eliminative ring fission:



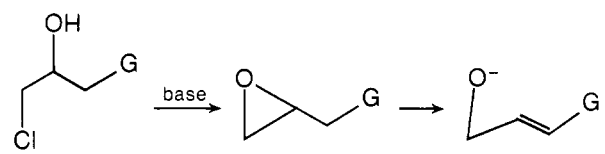
Very much milder conditions suffice in a reaction whose mechanism is not clear:[132]



When removal of the proton on carbon adjacent to the ring is more strongly activated by a carbanion-stabilizing group,[113] elimination becomes very much faster just as in acylic systems.[6] Even very mild bases then suffice to promote the reaction. Activated eliminative ring fission accounts for the failures to obtain substituted epoxides by displacement of chloride ion from epichlorohydrin by reagents such as toluene-*p*-sulfinate ion[133,134] and cyanide ion:[135]



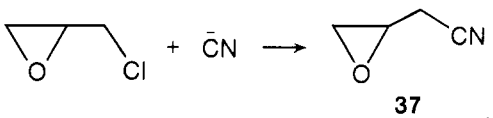
and the failure to obtain epoxides from halohydrins of the type



36

when G = CO_2R[136,137] CN[138,139], and RSO_2[133] unless special procedures are used.[136]

The reaction of epichlorohydrin with cyanide ion is particularly interesting; the product (**38**) is formed as a result of a complex series of reactions which follow nucleophilic eliminative fission of the epoxide **37**:[140]



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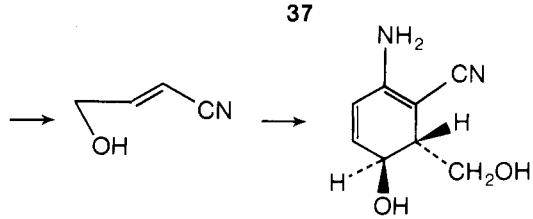
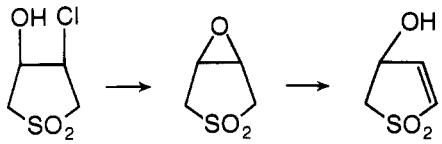


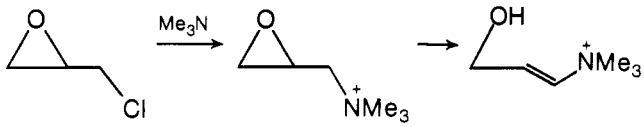
38

For the same reason a low yield of epoxide is found in reaction of the sulfone **39** with base,[141] and treatment of epichlorohydrin



39

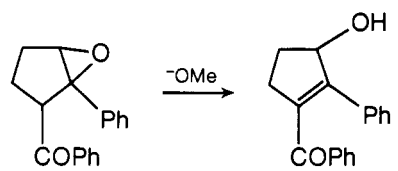
with trimethylamine gives the quaternary salt **40** which readily undergoes eliminative ring fission:[142]



40

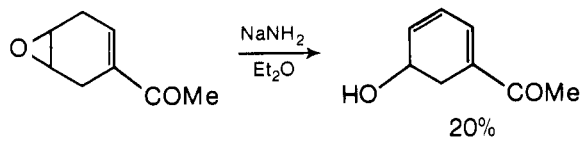
Many variations of substrate structure in nucleophilic ring fission of epoxides have been encountered. As activation by a carbanion-stabilizing group is increased, so milder conditions suffice for observation of the reaction in competition with others.[126]

Activation by a carbonyl group leads under mild conditions to γ-hydroxy-α,β-unsaturated ketones:[143]

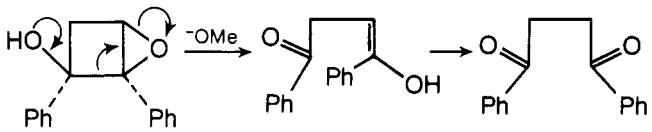


and the reaction in the steroid series places a carbon–carbon double bond in ring A,[144,145] B,[145] D,[146,147] and at the B/C ring junction.[148,149] Conditions are very mild; potassium carbonate suspended in methanol is typical. In these cases, the carbonyl group is part of the ring.

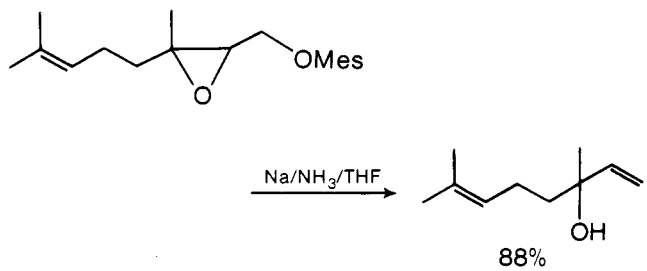
With an exocyclic carbonyl group, a vinylogue of the reaction is known;[150] conditions are probably unnecessarily vigorous.



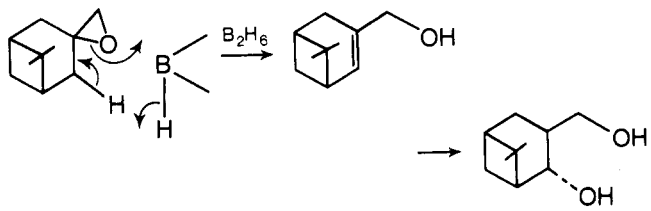
The exo C=C cleavage of epoxides may, interestingly, be activated by a prior eliminative ring fission. The example reported by Padwa's group[151] involves prior and easier (which see) exo:O=C:C:4 fission:



The reaction may also be initiated by electron transfer as in the production of linalool:[152]

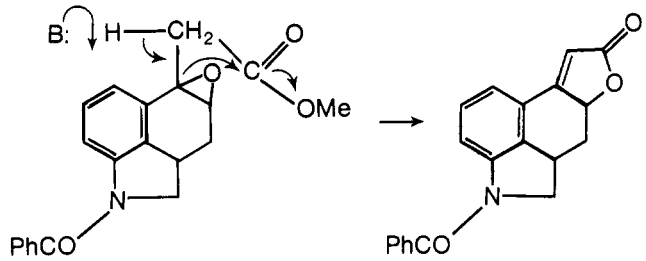


or occur in a multicenter reaction with diborane,[153] e.g.



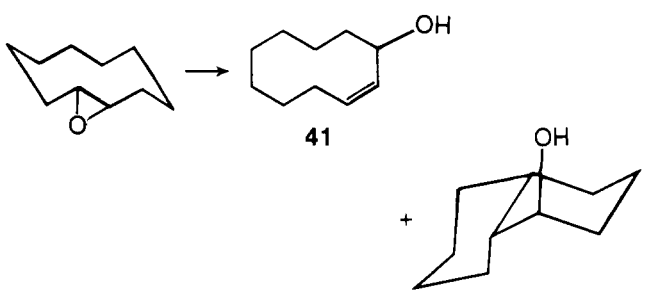
This pathway had been proposed[154] earlier for the hydroboration of epoxides, and, in confirmation, the intermediate allylic alcohol had been isolated. An alternative scheme not involving a nucleophilic eliminative ring fission has been advanced.[155] A related reaction is the conversion of medium ring epoxides to allylic alcohols with dibutylaluminum hydride.[156]

Activation of the exo:C=CO:3 reaction by an alkoxycarbonyl group leads to the synthesis of the biologically active butenolides.[157,158] The departing alkoxide ion is trapped by the electrophilic activating group:[157]



As expected, mild conditions suffice for ring cleavage of β,γ-epoxynitro compounds[159] and are applied in conversion of α,β-epoxyketones into γ-hydroxy-α-nitroalkenes.[657] Severe (probably unnecessarily) conditions have been used for eliminative ring fission in β,γ-epoxypropylphosphonium salts.[658]

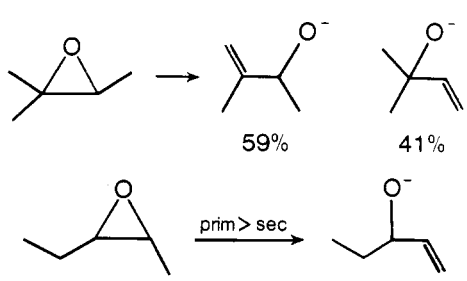
More detailed studies of the reaction have been reported by a number of groups. Cope et al.[160] showed that *trans*-cyclododecene oxide on treatment with lithium diethylamide gave both exo:C=C:O:3 product (**41**) and transannular carbene insertion as found in the cyclooctene series:[161]

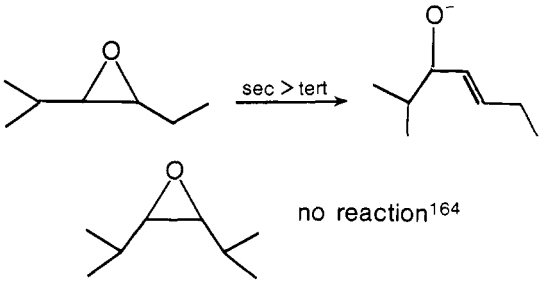


41

Nozaki's group has shown that treatment of the epoxides derived from either *cis*- or *trans*-cyclododecene gives the *trans*-en-ol only.[162]

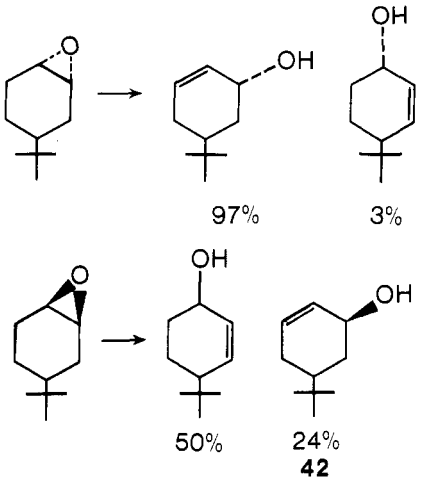
Rickborn's group[163–166] has made a number of detailed investigations in alkyl and cycloalkyl systems with the objective of defining regiospecificity and steric course: Regiospecificity[163] (base = $LiNEt_2$)





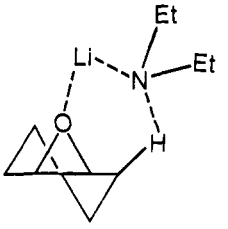
The preference for removal of a proton from a primary vs. secondary carbon is also seen[167] in eliminative fission of 1-methylepoxycyclohexanes on basic alumina.

In cyclic systems, the usual conformational preference for antiperiplanar elimination[168] is upset when attack on the appropriate proton by $LiNEt_2$ is interferred with by a bulky group:[163]



42

Formation of the allylic alcohol **42** is shown[165] by deuterium labeling to be the result of cis elimination expected on the basis of Sicher's[169] work on medium-ring systems with ion-paired bases:



In cyclic systems with an exocyclic epoxy group, strong preferences for endo- or exocyclic double bond formation are shown[164] (Table II). Particularly striking is the preferred formation of the cyclobutene isomer. The stereochemical restraint on the antiperiplanar mode must be sufficient to prevent exocyclic double bond formation, notwithstanding the formation of a highly strained product.

Always competing with nucleophilic eliminative fission is direct substitutive fission. For lithium alkylamides, the *N*-alkyl groups exert considerable influence on the product distribution, and for the bulky $^-NHPr^i$ ion, substitution is depressed relative to elimination in epoxycyclohexane[166] (see eq 1).

Products **43** and **46** are the products of competing elimination and substitution pathways. **44** arises by carbene formation from 1,1-elimination:

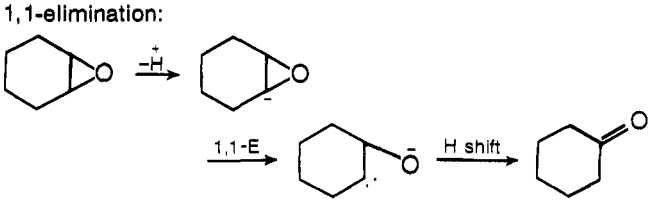
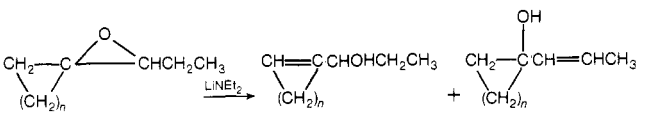
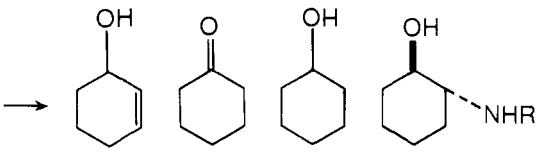


TABLE II. Products from Reactions of Exocyclic Epoxides with Lithium Diethylamide[164]



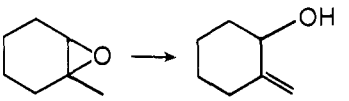
ring size (n + 2)	endo, %	exo, %
4	77	15
5	100	0
6 (slow reaction)	5	95
7	98	2
8	100	0
12	84 (min)	



	43	**44**	**45**	**46**	(1)
R = $PhCH_2$	26%	0%	0%	70%	
R = Pr^i	75	0.5	5	10	

Such change in the substitution:elimination ratio with bulk of the reagent had been seen earlier.[105]

The stereoelectronic requirements of the reaction ensure the synthetically useful conversion of α-methylepoxycycloalkanes to methylenecycloalkanols:[170]



and, provided reactions are carried out at very low temperatures, the butyllithium induced cleavage of chloromethyl epoxides is stereospecific.[171]

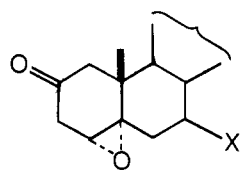
The requirement for antiperiplanar ring fission produces regiospecificity in bridged cyclic systems,[172-174] and it is suggested[172] that in medium rings studied by Cope[125] conformational restriction on β-eliminative ring fission promotes α-elimination via carbenes. When the ring size is increased to 10, conformational restrictions become less severe and at 12 members normal eliminative ring fission is the exclusive process. The balance between α-elimination (giving ketone) and β-elimination (the exo:C=C process) is determined by the availability of a trans antiperiplanar conformation of β proton and epoxy ring (Table III).

It is clear from the qualitative results described that eliminative cleavage of the O-C bond in an ether occurs very much more readily when this is constrained in a three-membered ring. Barton and Houminer[145] carried out the first kinetic measurements which throw light on the mechanism of the activated exo:C=C:O:3 process. The rate constants for reactions of the steroids **47** and **48** in triethylamine–ethanol are little affected by whether X = H or OH. For compound **47**, the primary deuterium isotope effect, k_H/k_D = 3.0. This shows that deprotonation of the ketone is rate determining, and it is not, therefore, surprising that anchimeric assistance by the neighboring hydroxyl group to leaving group departure is not found. Such assistance is very important when a cyclopropyl ring is cleaved[78] (section II.A).

TABLE III. Products from Reactions of Epoxycycloalkanes with Strong Bases

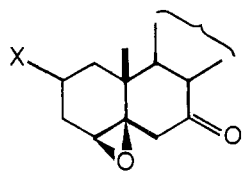
epoxide C_n	base	ene-ol, %	ketone, %	substitution, %	bicyclic alcohol	ref
5 (cis)	$LiNEt_2$	9	3	36	0	172
6 (cis)	$LiNEt_2$	70		small	0	172
7 (cis)	$LiNEt_2$	10	16	*a*	18	172
8 (cis)	$LiNEt_2$	16			70 (endo-cis)	125
8 (trans)	$LiNEt_2$	10	32[b]		55 (exo-cis)	125
10 (cis)	$LiNEt_2$	8			92[c]	160
10 (trans)	$LiNEt_2$	64			36[d]	160
12 (cis)	BuLi	*e,f*				162
12 (cis)	Bu_2AlH	80[f]				156
12 (trans)	BuLi	*e,f*				162

[a] Not identified. [b] Cycloheptanal. [c] *cis,cis*-1-Decalol (83%), *endo-cis*-bicyclo[5.3.0]decan-2-ol (9%). [d] *cis,trans*-1-Decalol. [e] Sole product. [f] Trans.



47

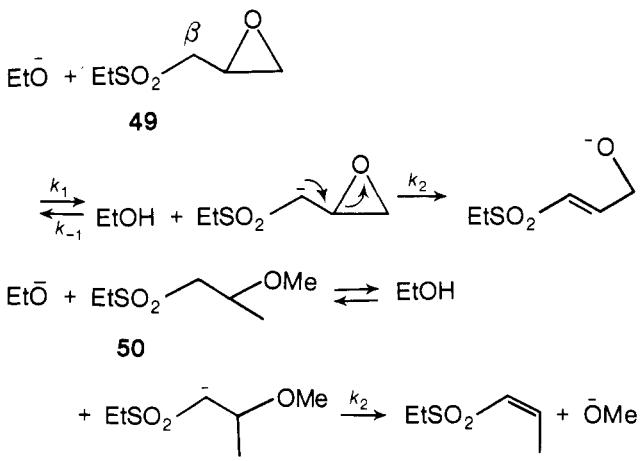
10^4k, α-3190
L mol^{-1} s^{-1}



48

α 1.83
β 9.5

Evaluation of the contribution to reactivity of the strain of the ring is highly significant; the first accurate comparison of strained and unstrained leaving groups in eliminations has recently been accomplished.[175] The rate of elimination in epoxide **49** has been compared with that in the corresponding open-chain ether **50.**



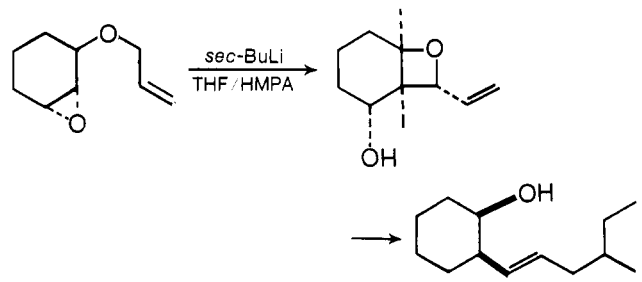
49

50

Deuterium labeling in the epoxide reveals a primary deuterium isotope effect (k_H/k_D at C_β = 2.6) again suggesting that the rate-determining step is deprotonation of the sulfone.[176] For the open-chain ether, the $(E1cB)_R$ mechanism[177] has been demonstrated[6] in which cleavage of the bond to the leaving group (k_2) is rate determining. The results show, therefore, an acceleration due to ring strain in the epoxide of not less than 2×10^6. Ring strain in epoxides is approximately 27 kcal mol^{-1},[4] suggesting that a substantial fraction of the ring strain contributes to lowering of the energy of activation for cleavage of the bond to the leaving group.

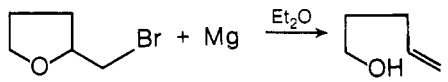
B. Exo:C=C:O:4

Examples of eliminative ring cleavage of oxetanes or related compounds are very rare. Addition of *sec*-butyllithium to the vinyloxetane is followed by exo:C=C:O:4 cleavage:[178]



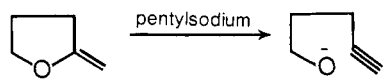
C. Exo:C=C:O:5

Treatment of tetrahydrofurfuryl halides with magnesium gives no Grignard reagent but instead ring fission to the alcohol **51.**[179]

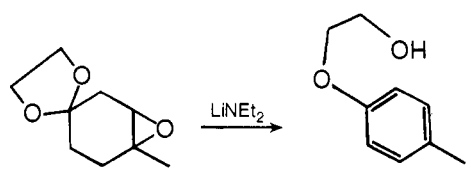


51

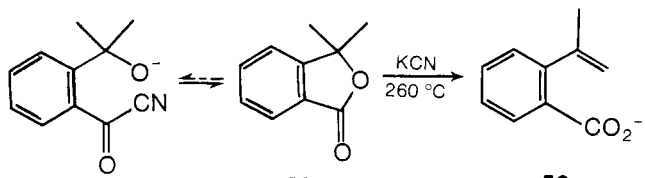
Methylenetetrahydrofuran similarly cleaves with very strong base:[180]



An example also without activation or leaving group stabilization involves exo:C=C:O:3 reaction as well:[123]

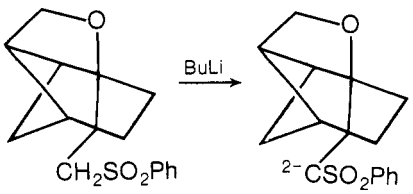


and in the lactone **52** a relatively weak base under severe conditions produces an early example[181] in which a much better leaving group[6] is expelled. Attack by cyanide ion at the carbonyl group is presumably the kinetic direction, but regeneration of the lactone from the alkoxyacyl cyanide allows leakage of the equilibrium to the observed product **53.**

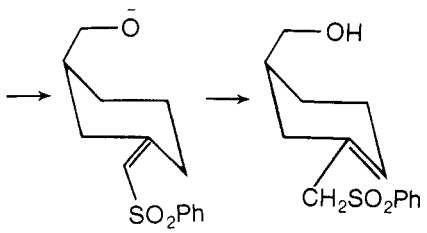


52 **53**

With a stabilized carbanion, cleavage of the tetrahydrofuran ring does not occur in a simple system, and in the sulfone **54** Bosworth and Magnus[182] have shown in an interesting study that cleavage occurs via the dianion **55:**

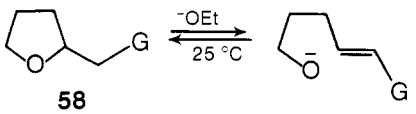


54 55



56 57

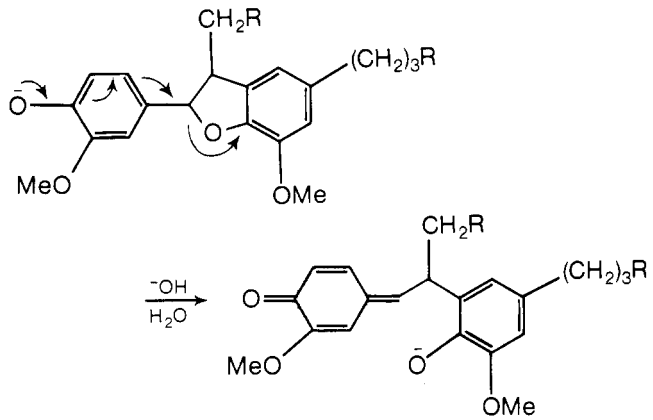
These conditions are exceptionally severe; it has been shown that the ethers **58,** G = $EtSO_2$,[175a] G = Ph_3P^+ [175b] open readily



58

under mild conditions but recyclize very rapidly. In Magnus' example, recyclization is obviated by isomerization of the alkene **56** to alkene **57.**

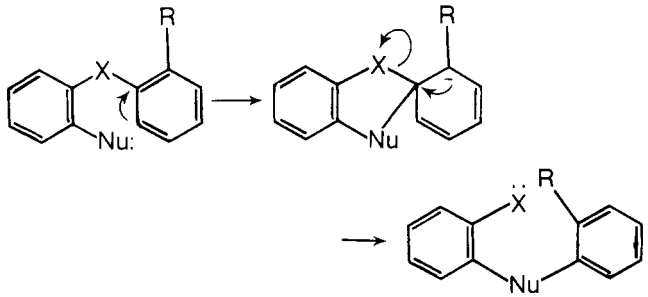
Ring opening in 2-arylbenzodihydrofurans has been reported to occur by way of quinonemethide intermediates,[183,184] e.g.[183]



and kinetics have been determined;[183] conditions are severe.[184]

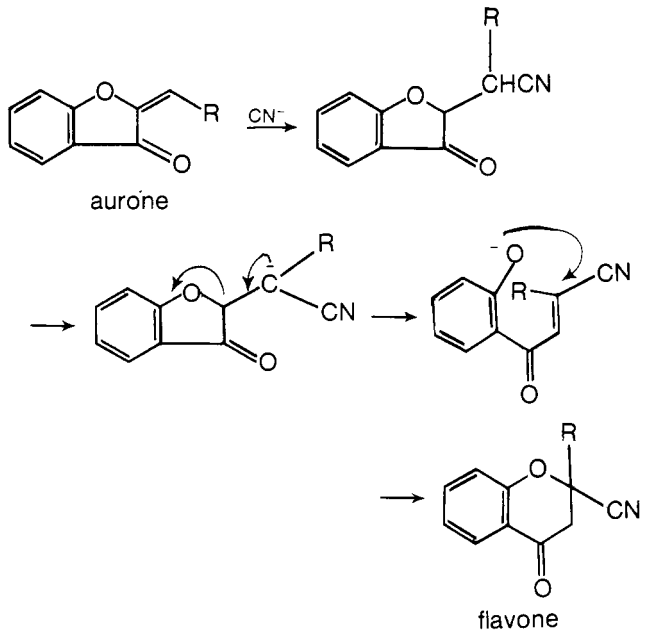
Rather similar reactions are seen in the rearrangements of aurones to flavones[185] (Scheme VII).

A common type of reaction, embracing not only exo:C=C:O:5 and 6 processes but others as well, is the Smiles rearrangement[186,187] and its variations. The general pattern of the reaction is:



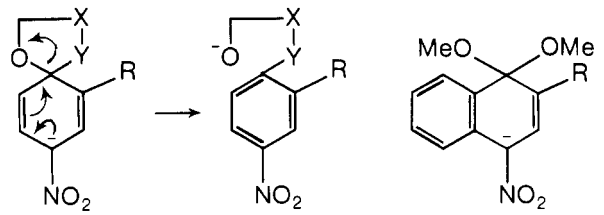
Generally, R = NO_2 and this nucleus often bears further carbanion-stabilizing groups to encourage nucleophilic addition.

SCHEME VII



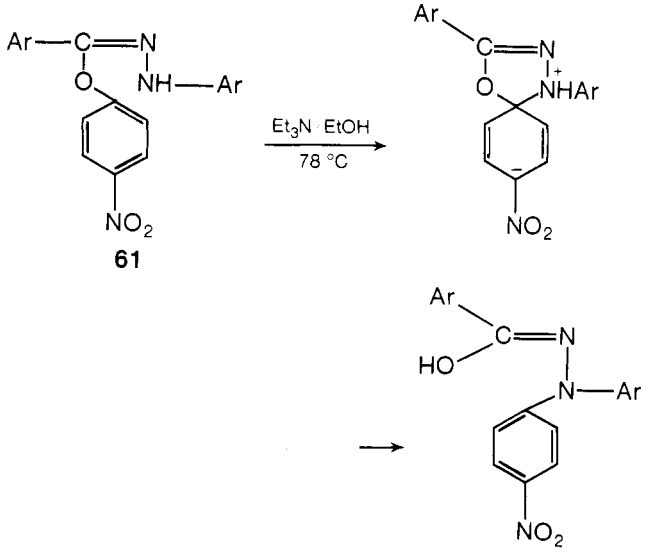
Breakdown of the spiro intermediate by an exo:C=C:X:5 reaction follows and the reactivity order is X = SO_2 > SO > S > O > N > C. This is the same series found for simple activated eliminations,[6] but reactivity is composite as it includes the addition stage.

Other examples of the exo:C=C:O:5 type consist of the cleavage of Meisenheimer-type complexes of nitro aromatics according to the general scheme:[188-191]



59 60

The energy of activation for opening of the benzo derivative of **59** (R = NO_2; Y = O; X = CH_2) is, surprisingly, *higher*[188] than that for the ion **60.**[192] For the ion **59** (R = NO_2, Y = NMe, and X = CH_2) ring opening in 80% Me_2SO is rapid ($k \sim 10^3$ s^{-1} at 21 °C) and is exclusively via O–C cleavage.[183] Similarly, in ion **59** (R = H, Y = NH, X = CH_2), ring cleavage is again very rapid[193,194] and exclusively via C–O fission. This is in accord with



61

leaving group preferences in activated alkene-forming eliminations.[6]

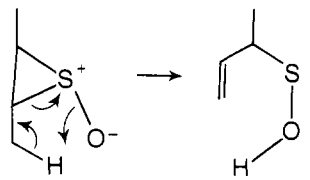
In the rearrangement of hydrazonyl ethers **61** the same leaving-group preference is seen in a reaction which again occurs[191] under very mild conditions.

IV. Exo:C=C:. Other Leaving Groups and Ring Sizes

By comparison with the systems considered earlier, sulfur and other leaving groups in eliminative ring fission have been little investigated. In the case of uncharged nitrogen systems this is not too surprising. The leaving group is considerably poorer;[6] in the sulfur system, however, the leaving group is substantially higher ranked, and the lack of examples is probably due to the lesser accessibility of this system.

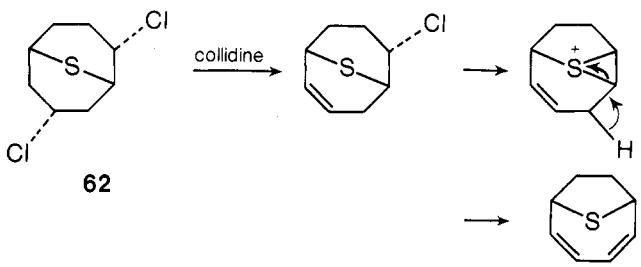
A. Exo:C=C:S:3

Appropriately substituted episulfoxides give allylic sulfenic acids[195,196] at room temperature:



The syn relationship of O and β-H is mandatory; decomposition to alkene and SO_2 otherwise occurs. The temperature of decomposition is notable; for acyclic sulfoxides undergoing eliminative thermolysis,[197] 100 °C is typical. The appropriate conformation is guaranteed for the cyclic system but ring strain must also play a part.

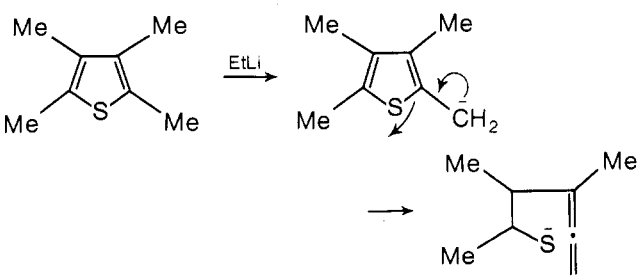
Eliminative cleavage of an episulfonium salt is suggested for reaction of the bridged sulfide (**62**) with mild bases:[198]



62

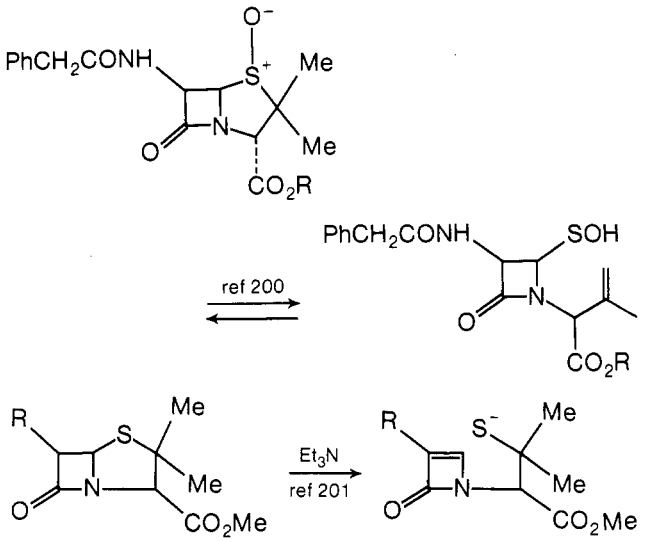
B. Exo:C=C:S:5

These reactions occur on treatment of tetraalkylthiophenes with very strong bases:[199]



In the absence of an alkyl group at C_3, endo fission (section IX) occurs initiated by deprotonation at this position.

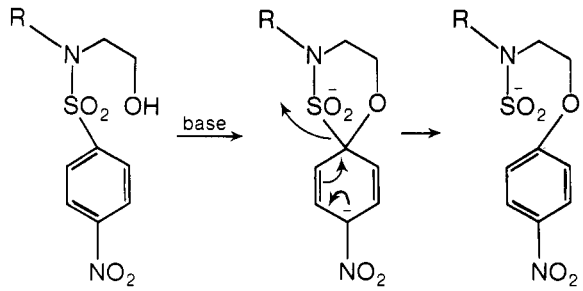
The exo:C=C:S:5 and -6 reaction is also common in cleavage of penicillin sulfoxides, typically:



This process in this particular type of system has been recently reviewed in detail.[202]

C. Exo:C=C:S:6

These reactions constitute the first ring-fission stage of interesting double Smiles-type rearrangements of the sulfonamides of β-hydroxyamines:[190,193]



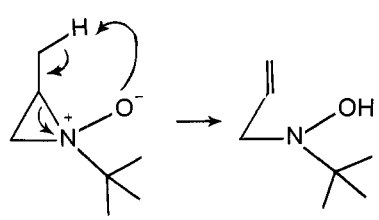
The initial product desulfinates and the free amino group initiates a subsequent exo:C=C:O:5 process discussed earlier.

D. Exo:C=C:N

The reaction is not common with neutral nitrogen leaving groups, but when the nitrogen atom is charged, the Hofmann exhaustive methylation of amines provides a rich catalogue of examples. This familiar reaction has been reviewed,[203] and a few examples only are chosen to illustrate the reaction as it falls within the scope of this review. The endo version of the reaction is discussed in section IX.

E. Exo:C=C:N:3

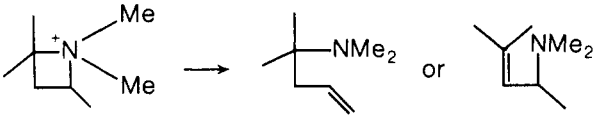
The aziridine *N*-oxide **62a** rearranges[659] rapidly even at −30 °C (E_A = 15 kcal mol^{-1}) by exo:C=C:N:3 fission in a manner entirely analogous to that of episulfoxides (section IV.A). Both strain and good leaving group ability favor the reaction.



62a

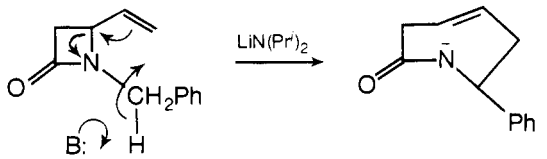
F. Exo:C=C:N:4

The product of elimination in the salt **63** is either **64** or **65**.[204] The former seems more probable as the result of better alignment of the rupturing bonds and involvement of a primary proton:



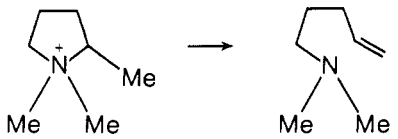
63 **64** (exo) **65** (endo)

Exo cleavage of a β-lactam is reported by Durst.[205] The nitrogen leaving group is stabilized and leaving ability thereby greatly increased.[6]

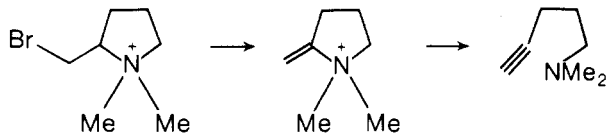


G. Exo:C=C:N:5

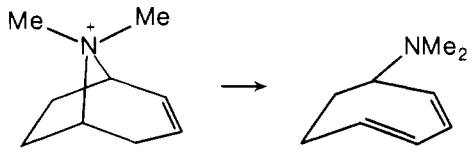
In pyrollidinium salts with an appropriate side chain, exo is preferred to endo elimination:[206]



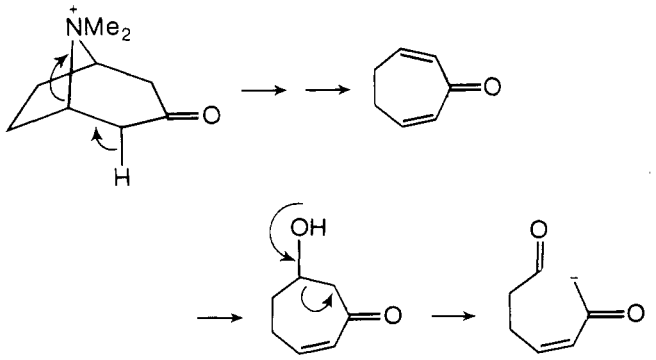
and the same preference is seen in an acetylene-forming elimination:[207]



Allylic activation promotes cleavage of the bridge in a tropidinium salt:[208]



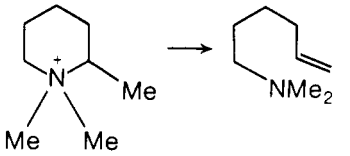
In a tropinonium salt, the exo:C=C:N:5 fission is oxo-activated and is succeeded by exo:O=C:C:7 fission of the resulting cycloheptadienone:[209]



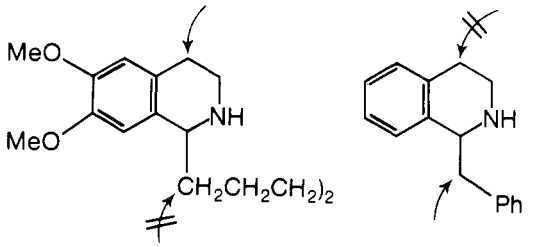
H. Exo:C=C:N:6

These reactions, together with their endo analogues, comprise much the largest series of examples of eliminative ring fission of ammonium salts because of the wide occurrence of alkaloids containing the piperidine ring, and the classical use of the reaction in their structure determinations.

Exo elimination is again preferred to endo, e.g.,[210]



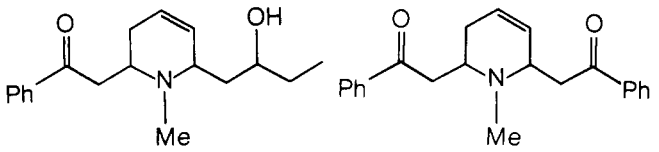
but not when the latter is benzylically activated as in **66**[211] (arrows denote positions of deprotonation). If both exo and endo are similarly activated, then exo elimination is preferred (**67**),[212]



66 **67**

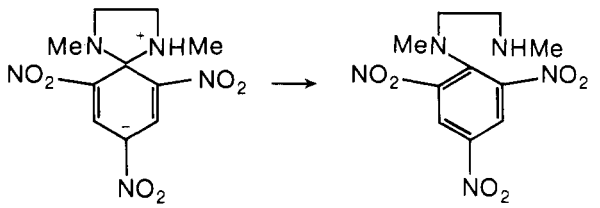
a preference probably underlined by conjugation in the product, but the balance between the two modes may be quite delicate as in the tubocurarines.[213]

Activation of the exo fission by, for example, oxo groups makes the reaction occur easily in the alkaloid **68**,[214] but in the alkaloid **69**,[215] the yield in the first step is very poor. This has not been explained.

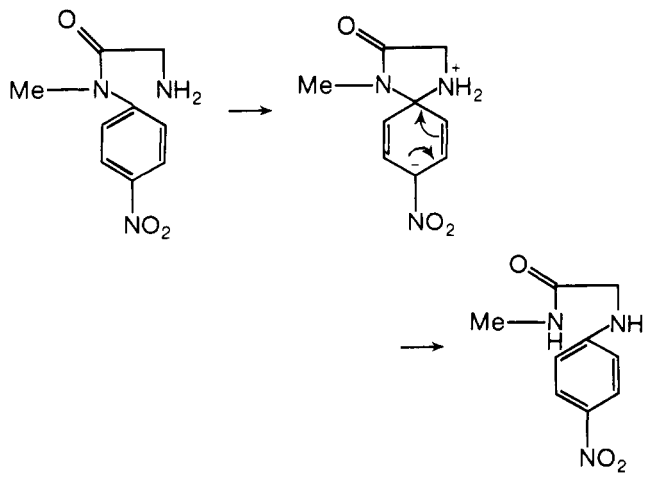


68 **69**

In a quite different context, the exo:C=C:N:5 mode occurs in Meisenheimer complexes formed from *N*-aryldiamines[216]



and glycinamides[217]



The oxo-stabilized nitrogen leaving group is, as expected, preferred.

V. Exo:O=C:C Reactions

In this reaction type, a carbonyl group is formed by elimination, and it is pertinent to compare this process with that in which carbon–carbon double bonds are formed. In acylic systems, the range of leaving groups is very restricted for alkene-forming reactions unless very severe conditions are employed[218] or activating groups are present.[6] In carbonyl-forming eliminations, however, a wide range of leaving groups may be expelled under mild conditions. Decomposition of the tetrahedral intermediate of carbonyl substitution is the exemplar; hydrolyses of acyl halides, carboxylic esters, and carboxamides all proceed readily as does reversion of cyanohydrin formation and the retro-aldol reaction. The last two examples provide a particularly notable contrast with alkene-forming reactions. Expulsion of these carbon leaving groups from a carbanion is very slow[6,219] and comparison of the range and reactivity in exo:O=C reactions (this section) with exo:C=C reactions (section II) should be made with this comparison in mind.

As usual, many nucleophilic ring fissions are rearrangements. Rearrangements involving the carbonyl group, many of which involve nucleophilic ring fission, have been reviewed.[220]

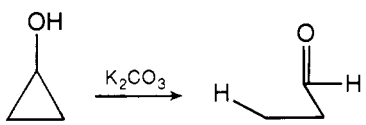
A. Exo:O=C:C:3

This section embraces carbonyl-forming eliminative fission of cyclopropanes. In exo:C=C:C:3 types (section II.A), cleavage of the cyclopropane does not occur unless the carbanion is very highly reactive, the leaving group bears a stabilizing group, or the ring is additionally strained. By contrast, a wide variety of exo:O=C:C:3 reactions occur under mild conditions.

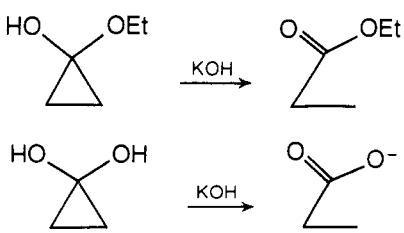
1. Base-Promoted Cleavage of Cyclopropanols

The chemistry of cyclopropanols has been reviewed[221-223] and brief references are made to exo:O=C fission.

Cleavage of cyclopropanol itself was discovered by Stahl and Cottle:[224]



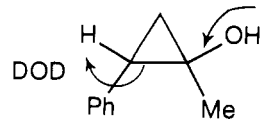
but the base-catalyzed rearrangement of cyclopropanone hydrate and of the ethyl hemiketal had been observed earlier.[225]



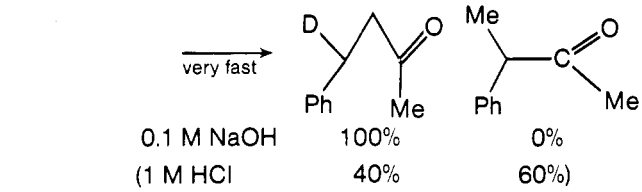
The combination of the energetically favorable carbonyl-forming mode of elimination with the ring strain of the three-membered ring causes ring fission under very mild conditions, notwithstanding the fact that the carbon leaving group is unstabilized.

A number of subsequent reports deal with the stereospecificity and regiospecificity of the reaction. De Puy[226] has shown that ring opening is regiospecific in the cyclopropanol **70.**

Deuterium incorporation from the solvent confirms the expected formation of the more stable benzyl carbanion and shows[227] that there is inversion of configuration at the carbon terminus. Acid (electrophilic) eliminative ring fission[226] provides



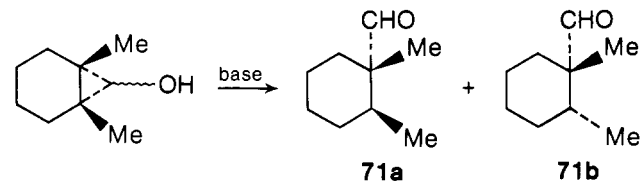
70



0.1 M NaOH	100%	0%
(1 M HCl	40%	60%)

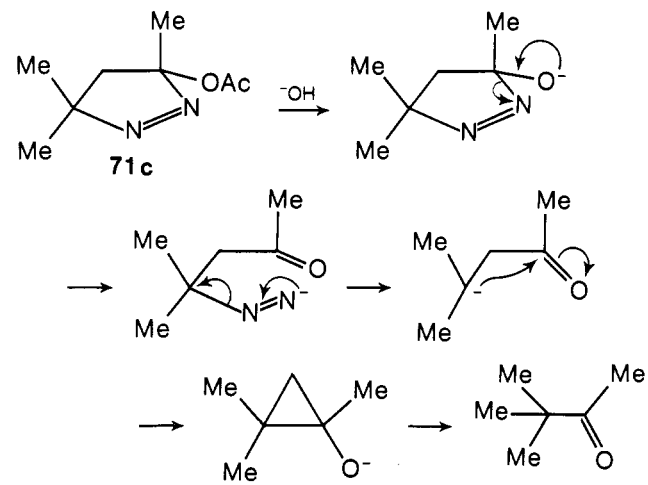
an interesting contrast; both alternative products are then formed in comparable amounts.

It has been demonstrated[228] that the steric course of cyclopropanol cleavage differs, just as does the steric course of protonation of other types of carbanion[229] with the base–solvent system. In *t*-BuOK/*t*-BuOH, retention (**71a**) is favored while inversion (**71b**) predominates with ethylene glycol. The reaction is the S_E1 type and the endo and exo isomers differ somewhat in stereochemical outcome owing to nonbonded interactions which develop in the product:

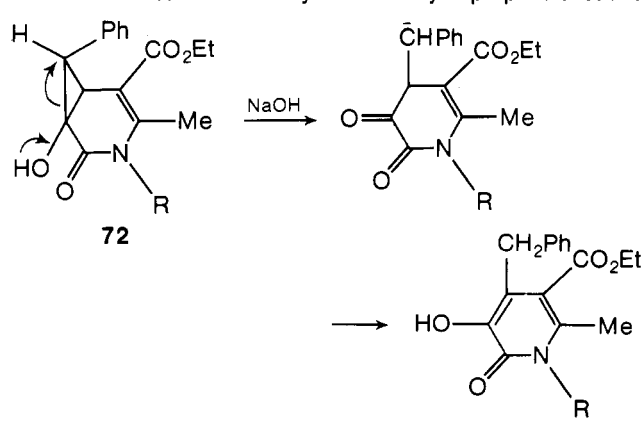


71a 71b

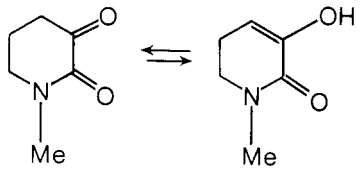
Formation of *tert*-butyl methyl ketone from the pyrazoline (**71c**) is accounted for[230] by an exo:O=C:N:5 (section VII) followed by exo:O=C:C:3 reaction. Note the formation of the primary carbanion in this example.



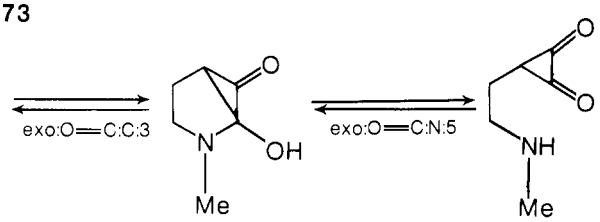
Exo:O=C reactions of bicyclic fused cyclopropanols lead to



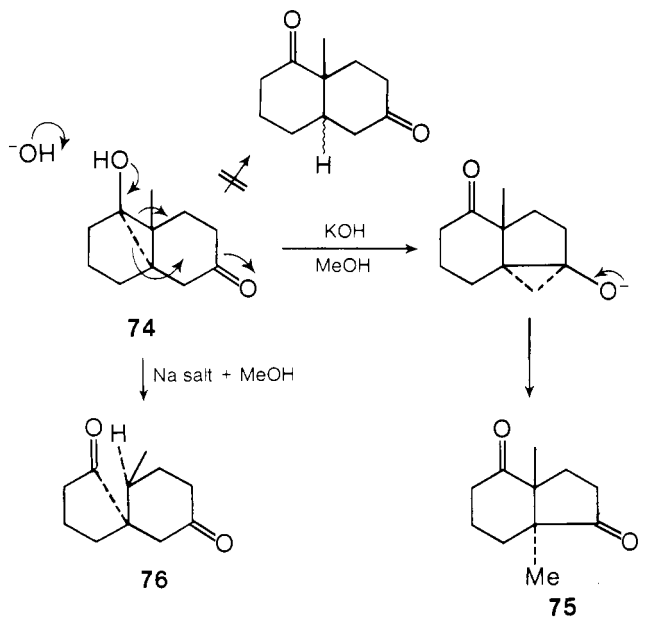
monocyclic rearrangement products from the pyridone derivative (**72**) and the pyridinedione (**73**).



73

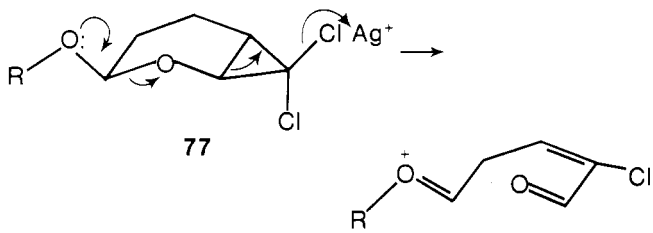


Sequential exo:O=C:C:3 reactions account [233] for one of the products (**75**) obtained from the tricyclic keto alcohol (**74**). The other (**76**), obtained under controlled conditions, results from the alternative cleavage of the cyclopropane ring:[660]



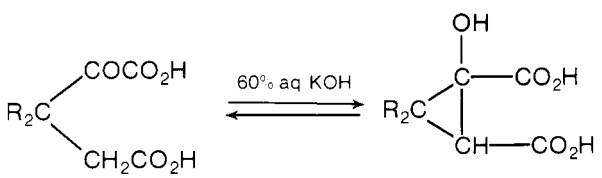
74 **76** **75**

Solvolysis of the bicyclic chloride **77** catalyzed by silver involves successive exo:O=C:O:6 (section VI) and exo:O=C:C:3 reactions.[234]



77

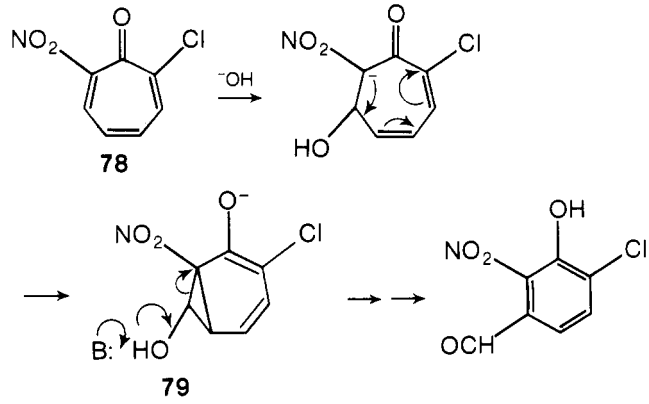
Equilibration between cyclopropanols and their open-chain isomers was reported in early work from Thorpe's group.[235,236]



R = Me	100%	0%
R = Et	38	62
R = Pr	29	71

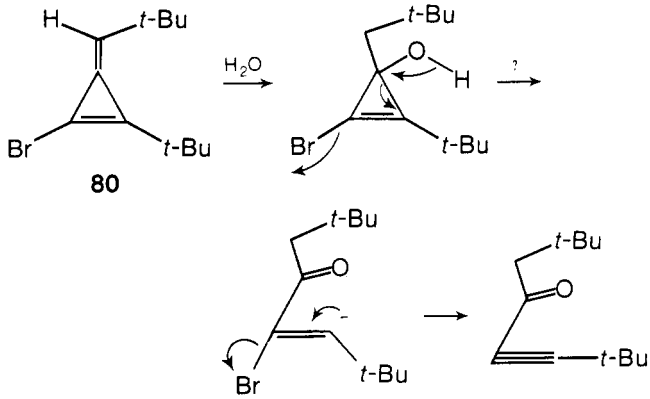
Bulky alkyl groups were suggested to close down the opposite tetrahedral angle and thus improve the concentration of cyclic product at equilibrium.

Finally, the interesting conversion of the tropone (**78**) to the aldehyde probably involves exo:O=C:C:3 fission of the norcaradiene intermediate **79**:[237]



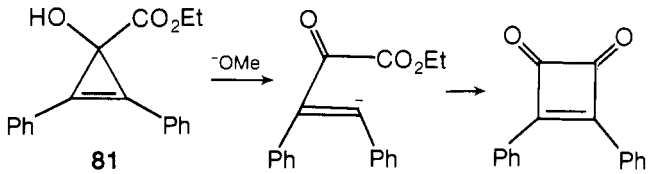
78 **79**

A dramatic example of the contribution of ring strain to reactivity in eliminative ring fission is[238] in the hydration and subsequent exo:O=C reaction of the methylenecyclopropene **80**. The high reactivity of methylenecyclopropanes in eliminative



80

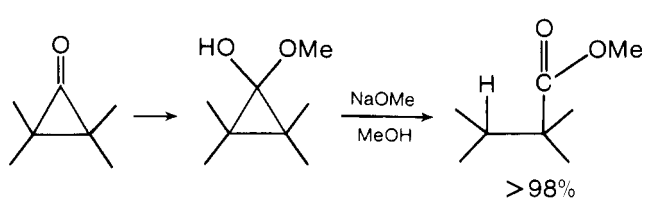
ring fission has been noted earlier (section II.A) and the cyclopropenol **81** cleaves readily under mild conditions;[239] comparison of reactivity with a saturated system would be of great interest as in this example the ring is more strained and the leaving group, being an sp^2 carbanion, presumably departs more easily:



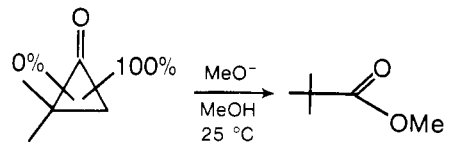
81

2. Cyclopropanones

It had long been suspected that the Favorskii reaction of α-halo ketones with bases involved cyclopropanone formation[240,241] among other possible pathways. The first direct demonstration that a cyclopropanone could be an intermediate leading to Favorskii products involved treatment of tetramethylcyclopropanone with methoxide ion in methanol:[242]

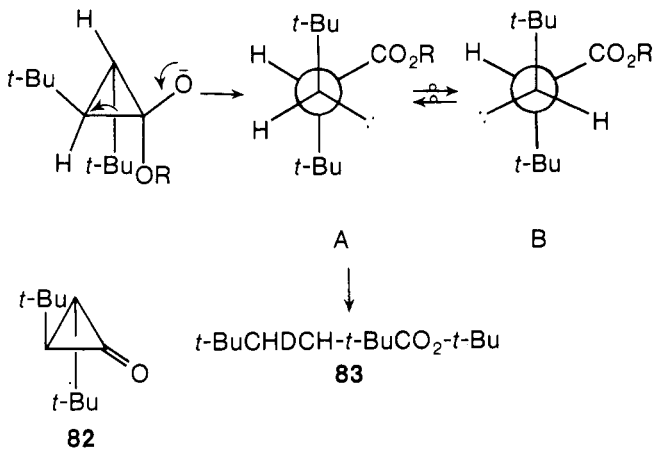


Later work by Turro and his co-workers established that, as expected, a primary carbanion was preferred to a tertiary one[243]

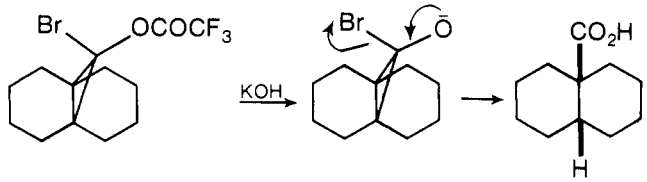


as leaving group. As substituents on the ring increase in number and size, the amount of elimination of the less stable carbanion increases,[244,245] but when the base is bulky, e.g., *t*-BuO⁻, the more stable carbanion is almost exclusively preferred.[244] As before,[226] the presence of a phenyl substituent causes the reaction to go exclusively in the direction of the more stable departing anion. Formation of the less stable anion from hindered substrates and small bases is attributed[245] to relief of strain in the transition state for ring fission.

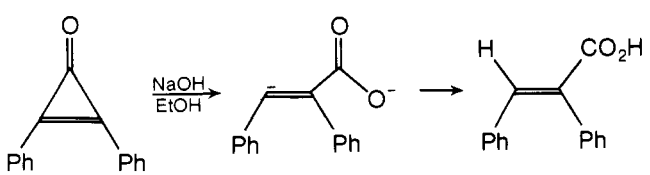
The same stereochemical result would be expected for the ketone–nucleophile reaction as for the alcohol–base reaction.[227] Interestingly, the ketone **82** yields[246] **83** with *retention* of configuration at the carbon terminus. It is suggested that the intermediate carbanion is better solvated in conformation A with participation by the neighboring alkoxycarbonyl group than in B which leads to inversion:



The cyclopropanone precursor may itself be generated by a carbonyl-forming elimination:[247]



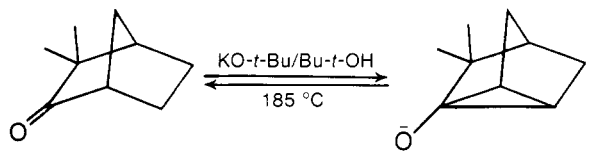
Cyclopropenones behave in an analogous manner; reactions have been extensively investigated by Breslow and his coworkers[248] who showed that, for example, diphenylcyclopropenone rapidly reacts with ethanolic sodium hydroxide to give *cis*-diphenylacrylic acid:



Leaving group stabilization is important; the bispropyl analogue is very much less reactive.[249] Other nucleophiles and systems[250] react similarly; their reactions are summarized in a recent review of cyclopropenone chemistry[251] and need not be further elaborated here. Ring strain again determines the very high reactivity in the nucleophilic eliminative process.

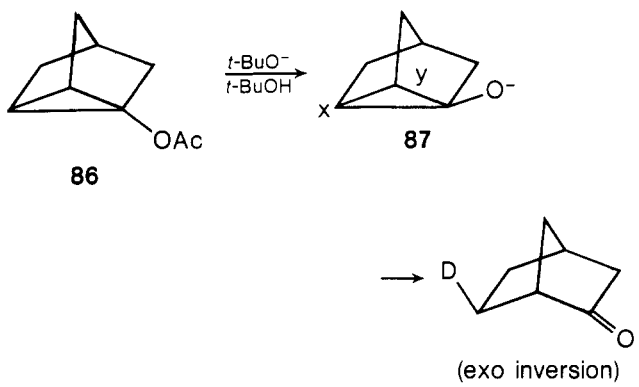
3. *Base-Catalyzed Rearrangements of Ketones. Homoenolization*[252]

Treatment[253,254] of (+)-camphenilone (**84**) with potassium *tert*-butoxide in *tert*-butyl alcohol-*O-d* racemizes the ketone and the rate of racemization is equal to the rate of incorporation of the first deuterium atom. The results are accounted for by formation of the symmetrical ion (**85**) opening of which to regenerate (**84**) is an exo:O=C:C:3 process. The interaction of a remote carbanion with a carbonyl group is referred to as homoenolization and may have higher orders than in the instance above (n = 2). Since Nickon's original publication,[253] many reports[252] of reactions of this type have appeared; for this review their interest is with the reverse process, homoketonization, and its dependence on structure.



84 **85**

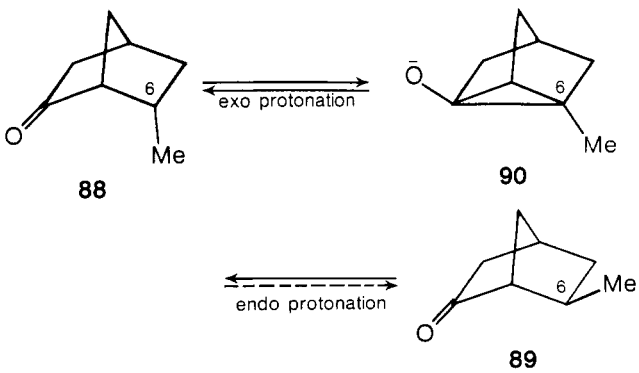
The steric course of homoketonization was determined[256] by basic hydrolysis under mild conditions of acetoxynortricyclene (**86**). This generates the ion **87** which undergoes exo:O=C:C:3 fission. The product, 2-norbornanone, is formed with capture of deuterium at either of the equivalent sites x and y giving exo isomer by inversion of configuration.[257,258] by contrast, acid conditions result in retention of configuration.



86 **87**

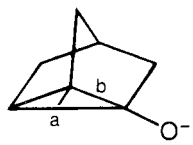
(exo inversion)

The interconversion of ketones **88** and **89** demonstrates[259] the much more rapid exo than endo protonation of the homoenolate anion **90.** Calculations[260] based on the principle of least motion suggest a semi-W transition state and abstraction of the exo proton in the reverse process of homoenolization.



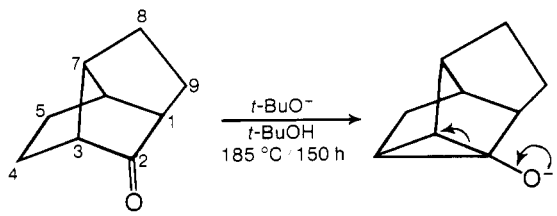
88 **90** **89**

Structural effects are quite marked and accountable on the basis of the stability of the carbanion formed in homoketonization. Thus in the ion **91** cleavage of bond a is preferred 20-fold over cleavage of bond b which leads to a tertiary carbanion, and inversion is favored over retention by a factor of 3.5.[261]

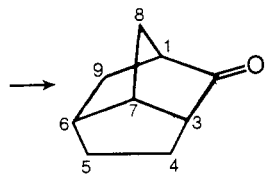


91

Homoketonization occurs in the intermediate in anionic rearrangement of bridged ring systems: e.g.[262,263]

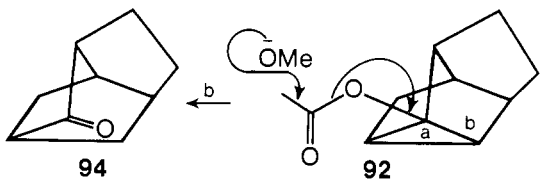


brexan-2-one

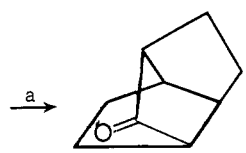


brendan-2-one

and yields are reasonable in spite of very severe conditions. The homoenolate ion from **92** can undergo either of the exo:O=C:C:3 fissions a or b yielding either brendan-2-one (**93**) or brexan-2-one (**94**):[263]



94 92

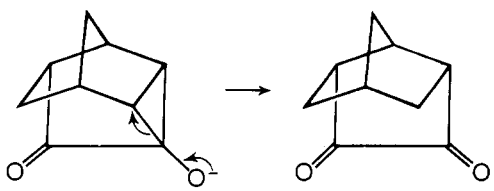


93

Fission b is preferred giving the ketone more stable by ca. 2.7 kcal mol^{-1} and in agreement with previous observations.[262]

Nickon et al.[252] have recently found that homoenolization and enolization can occur side by side. In camphor, deuterium-labeling experiments give relative rates of interconversion of camphor with the isocamphanones (Scheme VIII), establish homoketonization from C_8 and C_{10}, demonstrate epimerization of chiral centers β to carbonyl groups, and show that loss of β-exo hydrogen is more rapid than that of β-endo hydrogen.

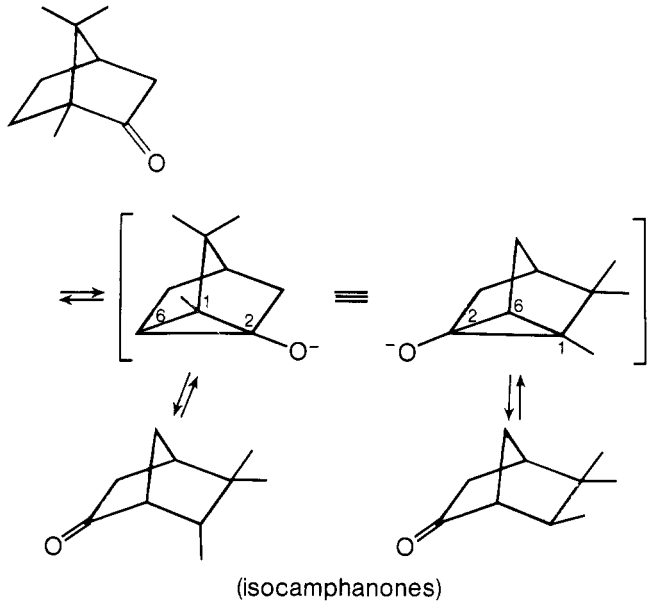
The exo:O=C:C:3 reaction:[264]



is part of a sequence of exo:O=C:C reactions initiated by an exo:O=C:C:4 process (section V.B).

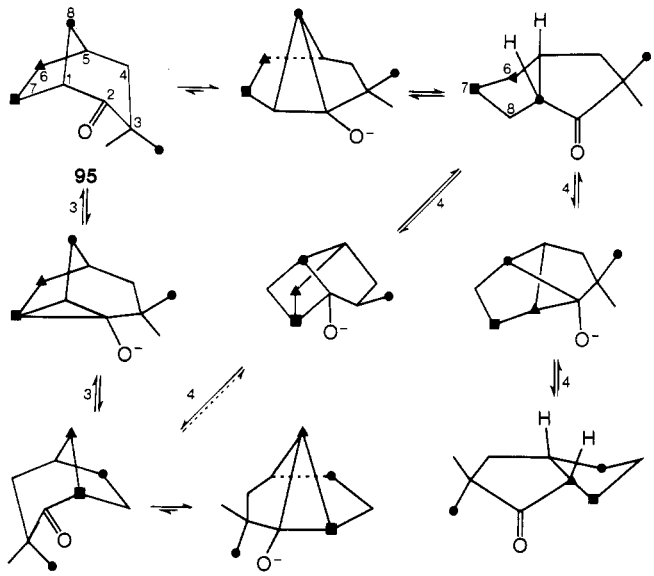
A complex series of exo:O=C:C:3 and -4 processes are implicated in the β- and γ-homoenolizations of the ketone **95** and its derived isomers[265] (Scheme IX).

SCHEME VIII

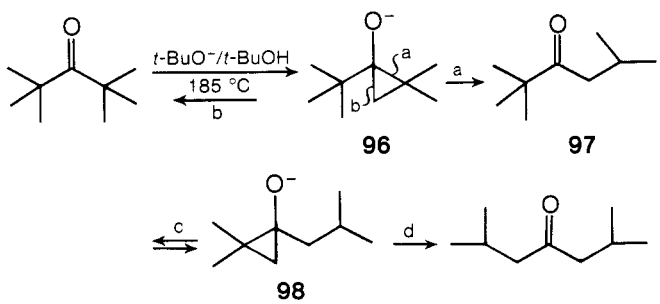


(isocamphanones)

SCHEME IX



Homoketonization has recently been observed[266] in open-chain systems. In the intermediate **96** from di-*tert*-butyl ketone, path a, giving a tertiary carbanion is only a factor of 3 slower than regeneration of the starting ketone by cleavage to a primary carbanion. This is attributed to strain in di-*tert*-butyl ketone which makes opening to ketone **97** more exothermic. The expected regioselectivity is restored in the anion **98** for which path c (primary carbanion) is much preferred over path d (tertiary carbanion):



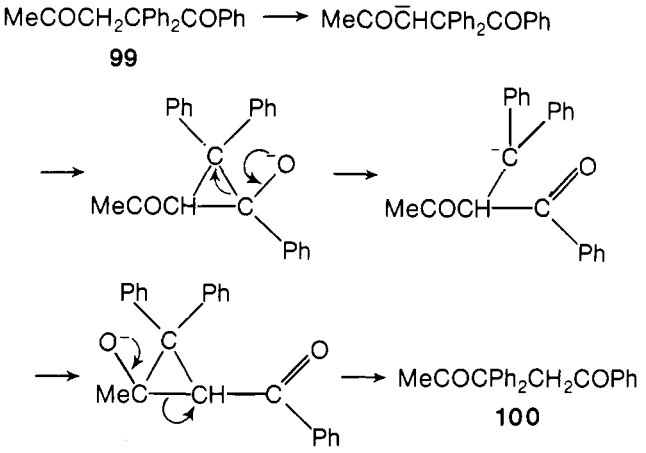
96 97

98

4. Rearrangements of γ-Diketones

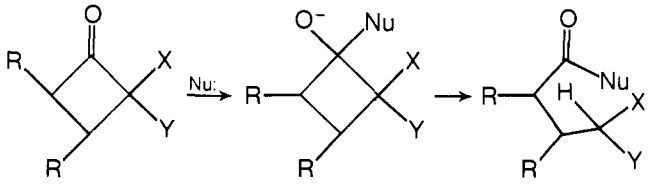
These reactions have been investigated by Yates and his co-workers.[267-269] Treatment of the ketone **99** with methanolic sodium methoxide gives[267,270] the isomer **100,** and two successive exo:O=C ring fissions are suggested (Scheme X). The correctness of this scheme is shown[268] by ^{13}C-labeling studies which exclude the unlikely alternative of two phenyl migrations. When the terminal alkyl group is bulky, e.g., Me = *t*-Bu, the rearrangement gives only the isomer of type **99** for steric reasons, but with two similar aryl groups, e.g., Ph and *p*-tolyl, equilibration between substantial proportions of each isomer is, as expected, found.[269]

SCHEME X



B. Exo:O=C:C:4

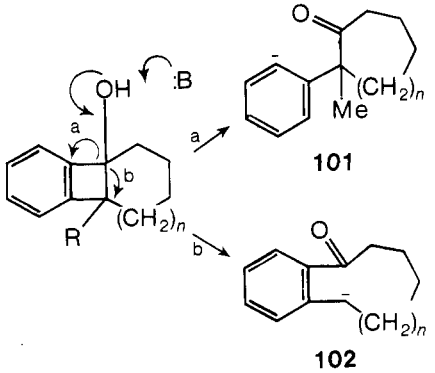
The assistance of ring strain is clearly evident in the family of ring cleavages conforming to the general pattern:



Examples embrace dibromides (R = R = H; X = Y = Br),[271] dichlorides (R, R = 2-cyclopentenyl; X = Y = Cl),[272,273] those in which the departing carbanion is stabilized by two phenyl groups (X = Y = Ph),[274-276] by a carbalkoxy group,[277] and by two sulfur atoms in cleavage of a dithioketal.[278] Conditions are generally mild, typically involving alcoholic alkoxide at ambient temperature.

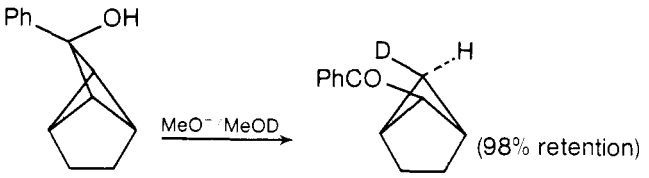
Closely related examples are seen in ring expansions of cyclobutanols[279] or their esters.[280] An interesting competition between the two directions of ring fission is seen in benzocyclobutanols[279] (Scheme XI).

SCHEME XI



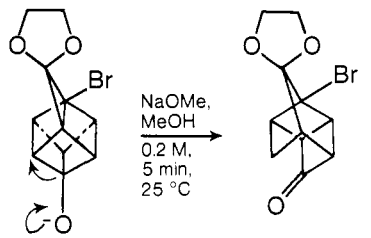
When R = H, formation of the more polarizable anion (**102**) is favored in HMPA rather than dimethoxyethane. When R = Me, however, inductive destabilization of the leaving group is sufficient to swing the delicate balance between the pathways to ion **101.**

In the tricycloheptanol derivative **103,** strain clearly assists departure of an unstabilized carbanion under mild conditions,[281] and retention of configuration goes against the Cram[229] generalization that inversion should occur in solvents of high dielectric constant. It is suggested that in this case the polar carbonyl group aggregates solvent on the "retention" side of the carbanion and thus promotes this steric outcome.

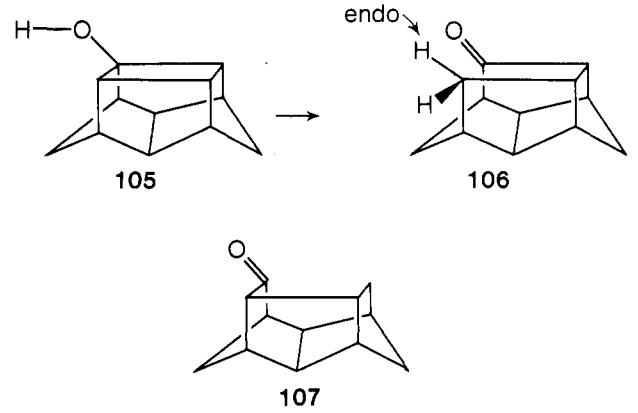


Exo:O=C:C:4 reaction is involved in the homoenolization-ketonization of the ketone **95** mentioned earlier[265] (section V.A).

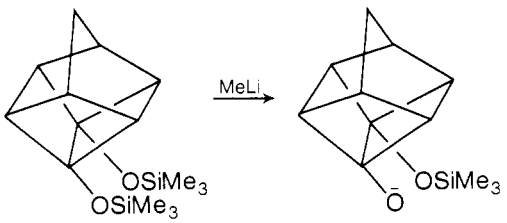
The cage alcohol **104** cleaves under mild conditions and specifically to give the less strained of the possible ketones.[282] The exo:C=C version of this reaction is known (section II.B) and, strikingly, requires much more vigorous conditions. The birdcage alcohol **105** gives the ketone **106** with potassium *t*-butoxide at 200 °C.[283] Three rings are cleaved simultaneously so the reaction is also an exo:O=C:C:5 and to process. Again, strain makes the reaction regiospecific: **107** is, not surprisingly, not formed; models show that **106** is less strained than **107.** Contemporary work[284] showed that the **107:106** equilibrium (via **105**) is 4:96, and recent work[285] has demonstrated that the solvent delivers the endo proton in the product contrary to earlier speculation.



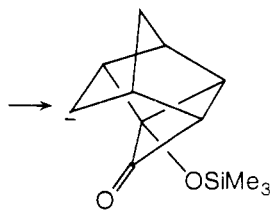
104



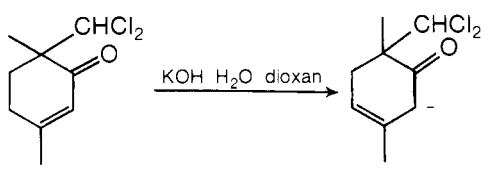
Miller and Dolce[264,286] have more recently described exo:O=C:C cleavages of homocubyl alcohols under mild conditions; the anion **108** cleaves rapidly but can be trapped by alkylation with $Et_3O^+BF_4^-$:[286]

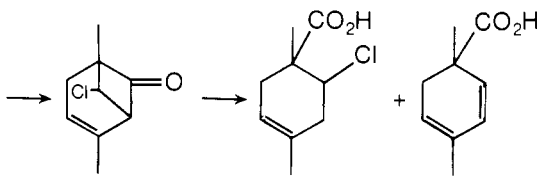


108



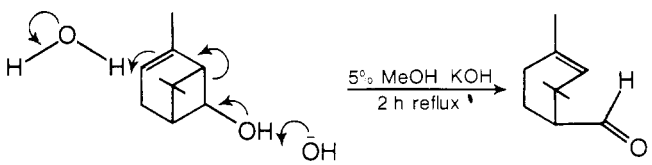
Cleavage of β-chlorocyclobutanones is involved in homo-Favorskii reactions of α-dichloromethylcyclohexanones,[287,288] e.g.,[288] as follows. This work corrects and amplifies a much





earlier investigation.[289]

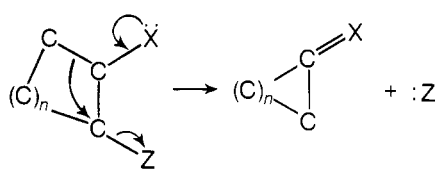
In the following examples, the exo:O=C:C:4 process is probably concerted with others which assist the initial ring fission. Cleavage of an epoxycyclobutane[151] has been referred to earlier (section III.A) and cleavage[290] of the alcohol **109** under mild conditions produces an aldehyde:



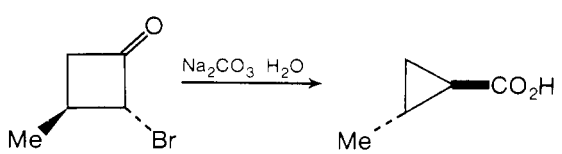
109

Ring contraction of α-halocyclobutanones involving exo:O=C:C:4 fission concerted with displacement of the leaving group has been widely investigated.[291-296]

The reaction conforms to the general type:[292]

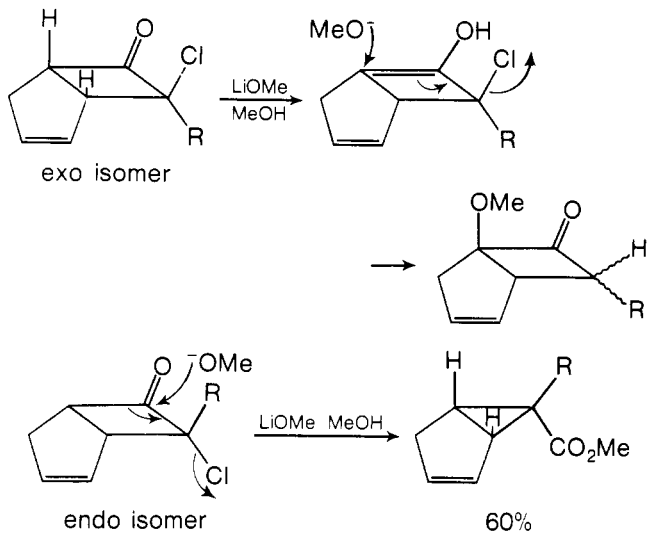


e.g.[291]



The reaction is stereospecific[293] and no deuterium is incorporated on carbon in reaction with 2-bromocyclobutanone, ruling out the involvement of a symmetrical intermediate.

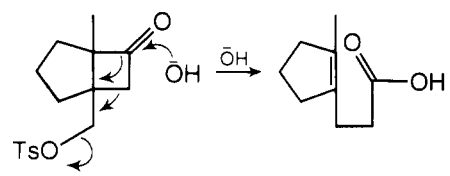
SCHEME XII



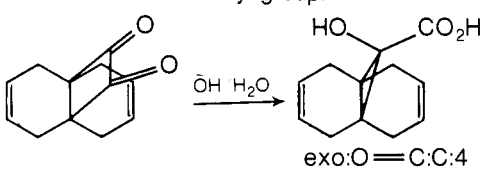
In fused cyclobutanones, the stereospecificity of the reaction imposes different reaction paths for epimers[293] (Scheme XII). For the exo isomer, S_N2' reaction with the favored approach of the nucleophile syn to the leaving group is preferred, but in the endo isomer, for which this course is not possible, the slower, semibenzilic rearrangement with exo:O=C:C:4 fission occurs. In aqueous sodium hydroxide, however, each isomer undergoes stereospecific ring contraction,[295] but formation of the exo acid from the exo halide becomes more reluctant, as the size of the group R increases, owing to nonbonded interactions between it and the adjacent five-membered ring.

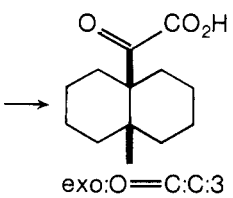
In the corresponding 6:4 systems, the ring contraction pathway maintains its stereospecificity, the exo halide giving the exo acid and the endo, the endo.[294]

Instead of substitution following exo:O:C:4 fission as in the preceding examples, fragmentation may ensue:[297]

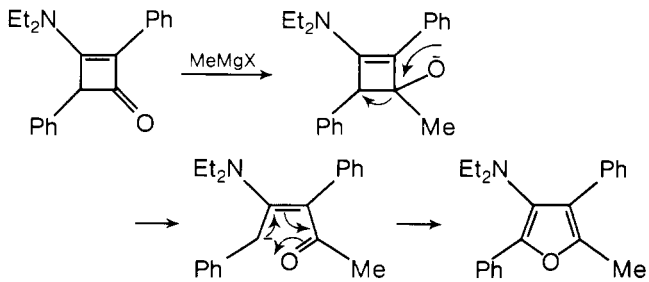


or addition to a carbonyl group:[298]





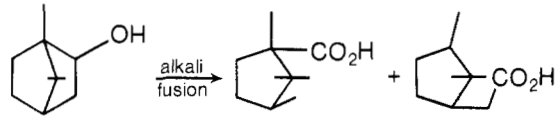
and[299]



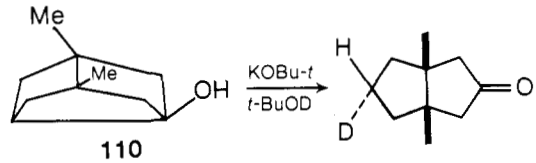
C. Exo:O=C:C:5

A large number of reactions of this type is known; as mentioned earlier, the range is not limited by the leaving group to anything like the same extent as the exo:C=C reaction. Generally, however, as the ring becomes less strained, stabilization of the leaving group or synchronization of the ring fission with other reactions, e.g., substitution or elimination, becomes important. Ring fissions of cycloalkanols and cycloalkanones have been reviewed.[300]

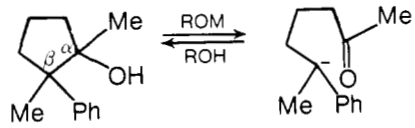
Ring fission of cycloalkanols[301] requires severe conditions even when ring-bridging raises the strain energy:



Fission of the alcohol **110** proceeds with >98% endo (retention) protonation[302] in contrast to examples encountered in homoketonization studies (section V.A). Cleavage of alcohols

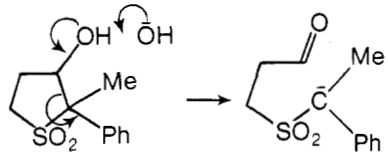


110



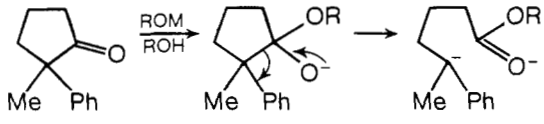
111 **112**

of type **111** figured importantly in studies of the steric course of electrophilic substitution.[303] The steric course is dependent on the relative configurations of the asymmetric centers and is interpreted in terms of open-chain intermediates (**112**) which can protonate, rotate, or recombine. In *tert*-butyl alcohol for example, the rate of epimerization at C_α is 20 times that at C_β. When the leaving group is stabilized as in **113,** ring cleavage occurs under quite mild conditions and protonation of the leaving group is specifically with inversion of configuration:[304]



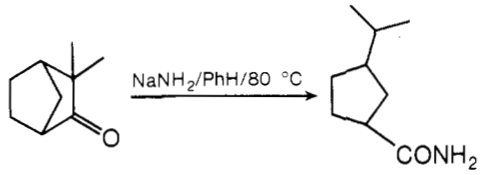
113

In cyclopentanones, nucleophilic addition generates an anion from which eliminative ring fission may proceed:[303]

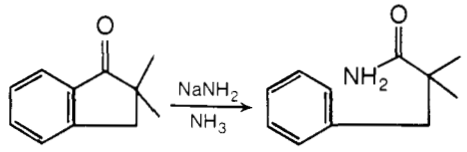


Again, the steric course of protonation varies with solvent; in *tert*-butyl alcohol, for example, it is 61% retention.

Alkali fusion of bridged cyclohexanones[305] just as for cyclohexanols[301] occurs under severe conditions, and the Haller–Bauer cleavage of cyclic, nonenolizable ketones[306] with metal amides, e.g.[307]



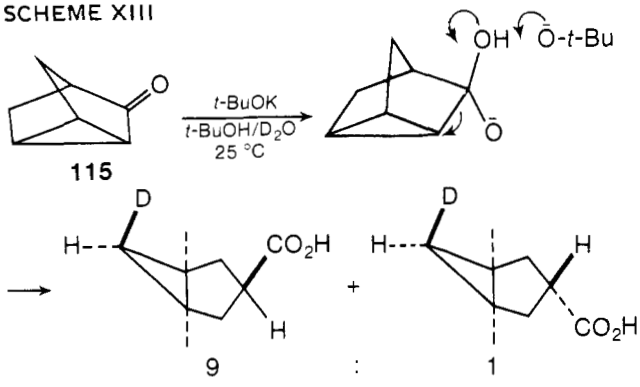
proceeds in a variety of cases. In the above example, surprisingly, the tertiary carbanion is preferred to the cyclic secondary one, but in the ketone **114**[308] formation of an sp^2-hybridized carbanion occurs:



114

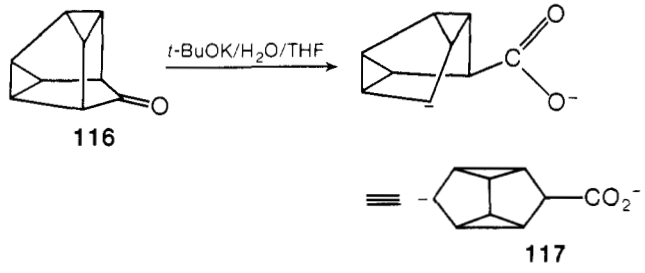
In cleavage of the strained ketone **115,** it has been shown[309] that *tert*-butoxide ion deprotonates the tetrahedral *anion* produced by addition of hydroxyl ion to the carbonyl group (Scheme XIII), and reaction proceeds predominantly with retention of configuration.

SCHEME XIII



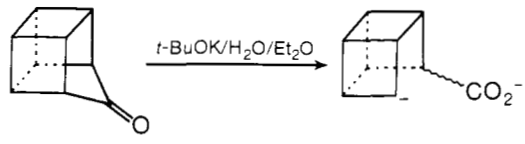
115

Strained cage ketones undergo eliminative cleavage without leaving group stabilization, e.g.,[310] **116** → **117.** In this case, the



116 **117**

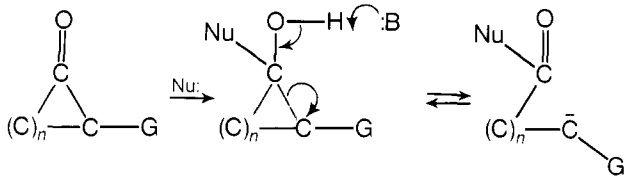
carbon–carbon bond is broken to give the mesomeric bishomoaromatic ion **117** and cleavage of **116** occurs 10^3 times faster than that in the more strained homocubanone **118** which lacks



118

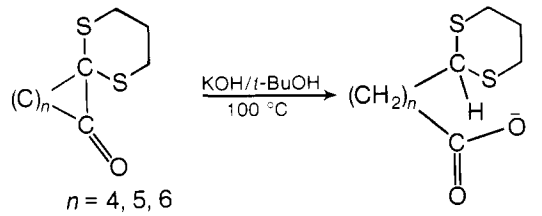
"product" stabilization. Other strained cage ketones cleave similarly without leaving group stabilization.[311]

When the leaving group is stabilized, a large number of exo:O=C:C:5 and -6 reactions are encountered in the reversal of carbanionic ring closure reactions, notably the Dieckman cyclization:[312]

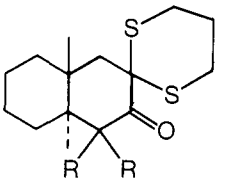


G = CO_2R, CN, RCO, etc.

Examples of this type may involve nucleophilic addition to a carbonyl group thus producing the exo nucleophilic center, e.g.,[313]



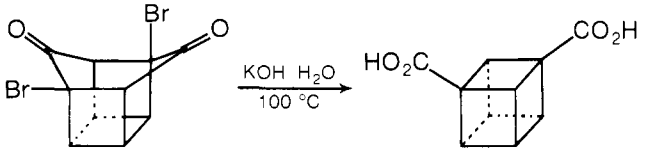
n = 4, 5, 6



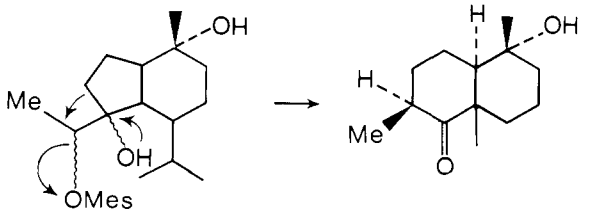
119

This reaction involves deprotonation of the tetrahedral *anion* intermediate as in an earlier instance[309] and can also be applied to *fused ring systems* such as **119** (R = R = H) but not **119** (R = R = Me because carbonyl addition is sterically blocked. O-Deprotonation of a β-hydroxylactone[314] also gives the reaction.

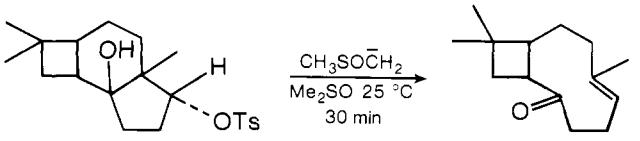
In many examples of exo:O=C:C:5 reactions, the ring fission is probably concerted with other processes notably intramolecular substitution of halide[311,315-318] or sulfonate ion[319] and *formation of a new carbon–carbon bond*, e.g.[317]



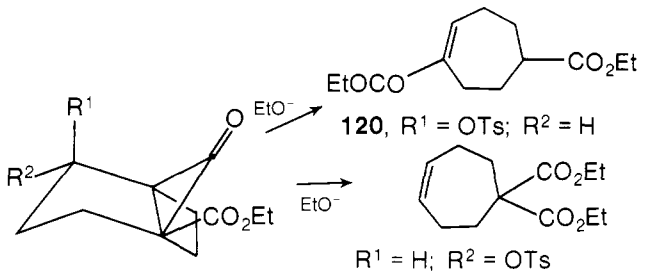
In this example, as in many others, formation of a new carbon–carbon bond is favored by juxtaposition in a strained system. The conformational requirements of the reaction are strict with a demand[320] for antiperiplanar relationship of leaving group and migrating bond. These cases lead from five- to four-membered rings; migration with substitution to give expansion is also known:[319]



Ring cleavage concerted with elimination is frequently encountered[321-323] and employed in synthesis, e.g., of caryophyllene:[324]



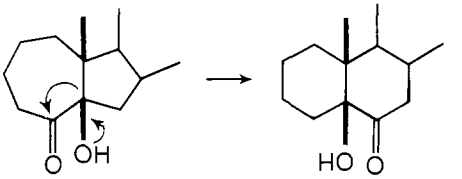
Again, stereoelectronic control is strict,[323] formation of ester **120** occurring stepwise.



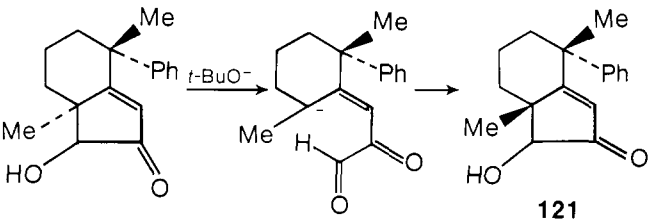
120, R^1 = OTs; R^2 = H

R^1 = H; R^2 = OTs

Addition to a carbonyl group subsequent to ring fission describes ring expansion–contraction reactions:[325]



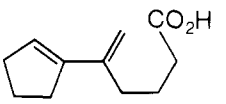
and epimerization at ring junctions,[326,327] e.g.,[326]



121

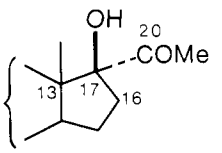
In this case the departing anion is vinylogously oxo-stabilized, and the high equilibrium constant in favor of isomer **121** is due to the preferment of diaxial interaction between two methyl groups rather than a methyl and phenyl group.

The interesting and complex conversion[328] of cyclopentanone to the acid **122** by dimsyl anion involves an exo:O=C:C:5 process:

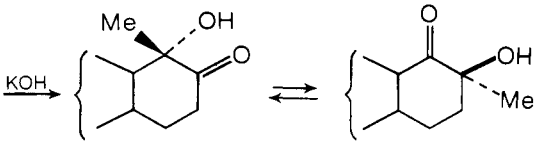


122

A series of bond migrations involving O=C fission followed by intramolecular[329] addition are found in ring D of steroidal hydroxy ketones.[330-338] They have largely been investigated and reviewed[330,338] by Taub, Wendler, and their collaborators, e.g.[330]



13,20 migration



123 **124**

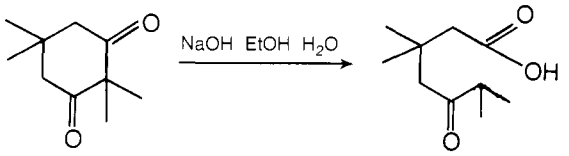
This gives the kinetic configuration **123**, but inversion occurs on long treatment with base.[337] Again, antiperiplanar migration is preferred[337] and it is concluded[337] that epimerization is re-

versible in the six-membered system as well as interconversion to the isomeric six-membered ring hydroxy ketones of type **124** which occurs via regeneration of the five-membered ring hydroxy ketone.[338] No completely satisfactory mechanistic picture of these rearrangements has been developed.[338]

D. Exo:O=C:C:6

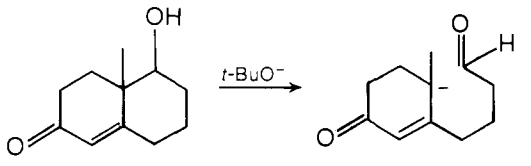
The pattern of this class of reactions is similar to the exo:O=C:C:5 series. No assistance is given by ring strain, and the carbon leaving group must either be stabilized or its departure concerted with another process.

Cleavage of the (nonenolic) diketone **125** occurs readily in base:[339]

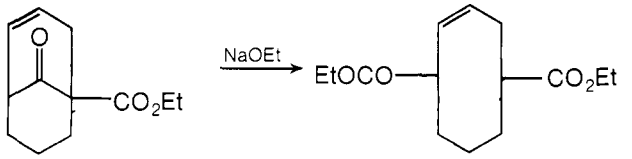


125

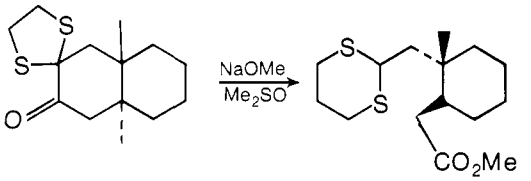
and similar fissions with vinylogously stabilized tertiary carbon leaving groups have been reported,[340-342] e.g.[341]



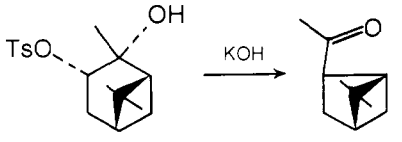
stabilization of the leaving group by an ester function[343]



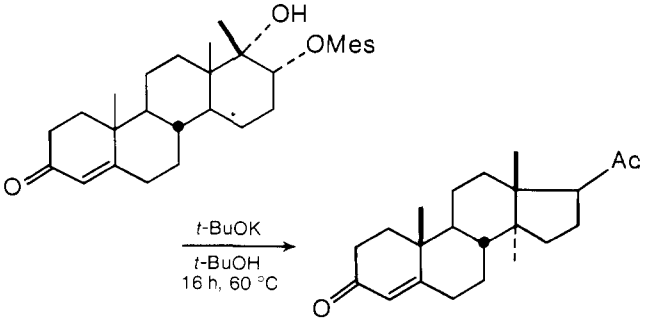
or in a dithioketal function:[344]



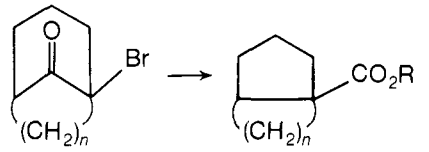
Cleavage of the ring is concerted with a displacement of a leaving group in many examples leading to ring contraction:[345]



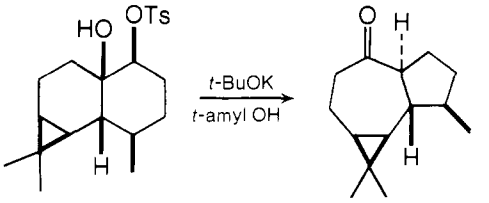
Conditions are quite severe:[346]



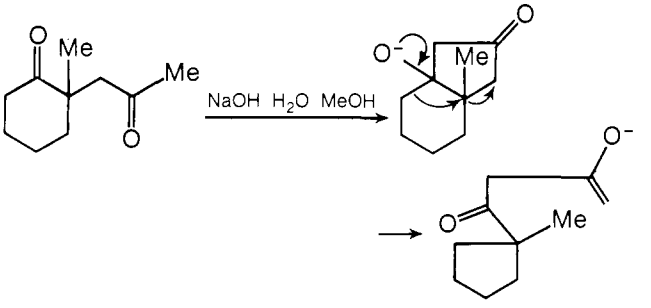
In bicyclic ketones,[347,348] fission is initiated by addition to the carbonyl group; when n = 3 both ethoxide and *tert*-butoxide give the new carbon–carbon bond without deuterium incorporation or racemization. This is consistent with ring fission being concerted with displacement (semibenzilic rearrangement). When n = 4, the same is true for ethoxide but not *tert*-butoxide. The latter base, less reactive in carbonyl addition but stronger, causes formation of the cyclopropanone which undergoes exo:C=C:C:3 fission as seen earlier (section II.A). When n = 4, transannular cyclopropanone formation is the sole reaction with either base.



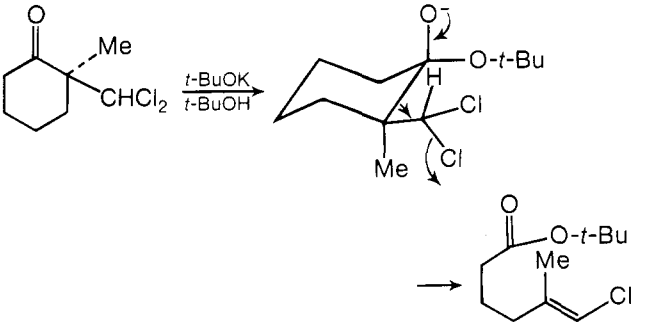
In fused bicyclic systems, ring expansion–contractions are seen[349,350] as in synthesis of aromadendrenes:[350]



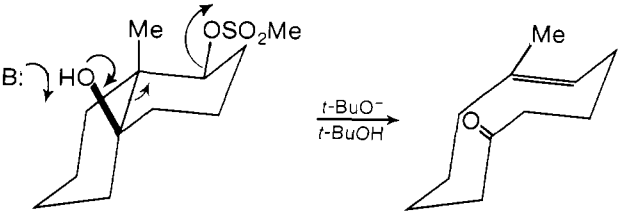
and an interesting ring expansion apparently involves displacement of an enolate ion with C–C fission:[351]



Cleavage of the ring may be concerted with elimination requiring a leaving group antiperiplanar to the rupturing bond. This is seen in a monocyclic system:[352]

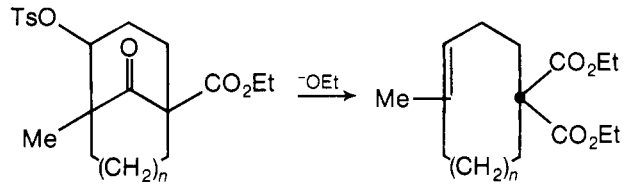


and in a series of decalins,[353-356] which are similarly stereospecific, e.g.[355]

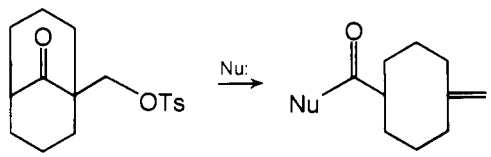


When the rupturing bond and the leaving group bond are not antiperiplanar, elimination but not ring fission results.[356] This type of reaction has been reviewed.[357]

Closely related reactions[358] occur in bridged medium-ring systems with hydroxyl[359] or, more commonly, carbonyl groups on the bridge[360-363] when elimination is initiated from the tetrahedral intermediate. The reaction is stereospecific,[359] and concerted loss of the equatorial leaving group in a conformationally favorable situation is shown by the nonreaction of the axial epimer:[363]

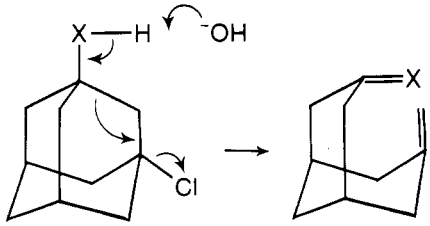


The reaction has been demonstrated for both n = 1 (exo:6) and 2 (exo:7).[358] Elimination to give an exo double bond is also known:[364]

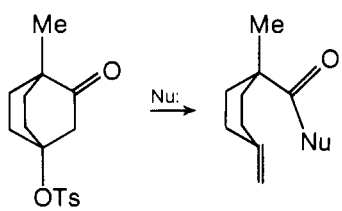


Nu = OH^-, NH_2^-, MeLi

Ring fission involving fragmentation has been reviewed[365] and the stereospecificity of these reactions is stressed. An interesting comparison is seen in the adamantyl system:[366,367]



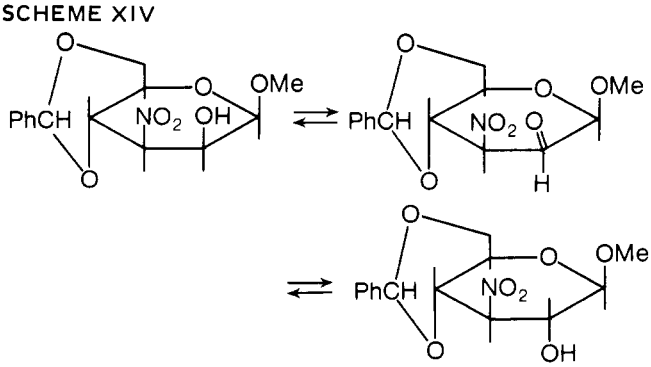
The reaction is 15 times faster for X = O[366] than for X = S,[367] (an exo:S=C:C:6 process), the difference being ascribed to the more favorable formation of a carbonyl than a thiocarbonyl group. Alignment of the ruptured bonds is perfect in these instances as in the fission of the ketone **126** following addition to the carbonyl group:[368]



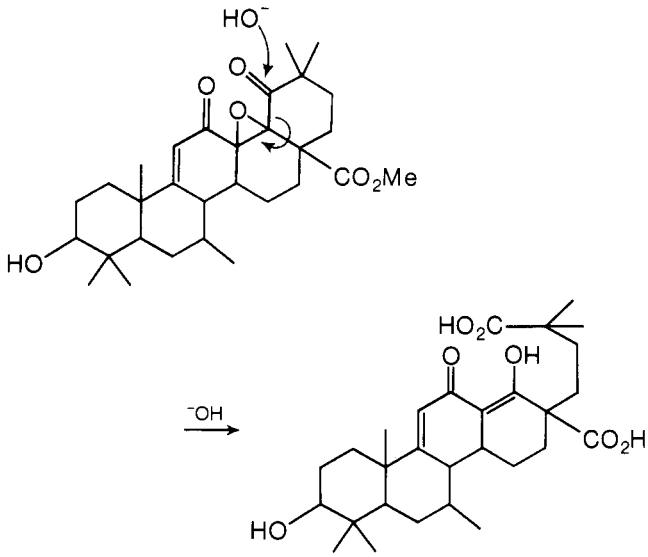
126

Nu = H^- ($LiAlH_4$), Me^- (MeLi)

SCHEME XIV

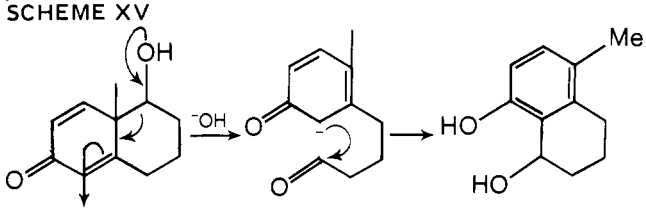


An unusual example of elimination subsequent to ring fission involves endo:C=C:O:3 elimination (section IX):[369]

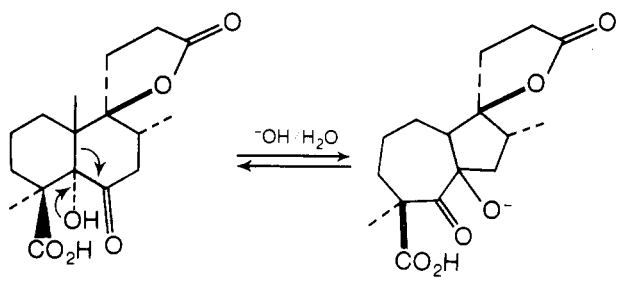


Finally, addition may follow the exo:O=C:C:6 fission. Ring cleavage and readdition to the carbonyl group formed accounts for the epimerization of nitro glycosides[370,371] (Scheme XIV) and for rearrangements of bicyclic ketones,[372-374] e.g.,[372] Scheme XV.

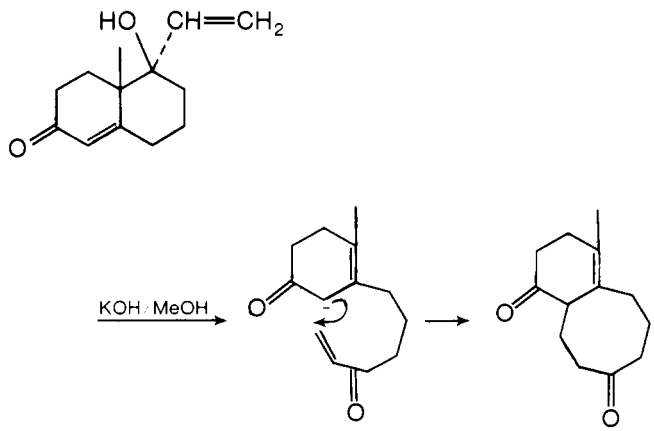
SCHEME XV



Ring contraction[375] and ring expansion-contraction[376] can be the outcome of this reaction type, described as a ring-ring tautomerism, e.g.[376]

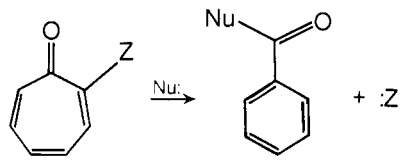


The carbon leaving group may also add to an appropriately placed electrophilic carbon-carbon double bond:[377]



E. Exo:O=C:C:7

Conversion of tropones and tropolones to benzene derivatives involves this type of ring fission but mechanisms are not always clear.[378]

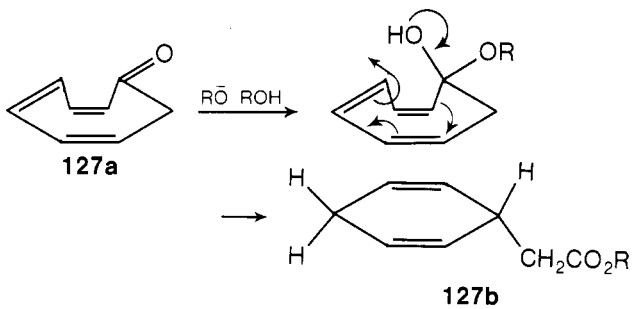


Addition–elimination–displacement probably accounts satisfactorily for the overall reaction. When free hydroxyl groups are present, ionization of the hydroxyl group depresses cleavage in tropolones but on alkylation of the hydroxyl group conditions become mild.

Similar cleavage of a cycloheptadienone follows exo:C=C:N:5 cleavage of a tropinonium salt[209] (section IV).

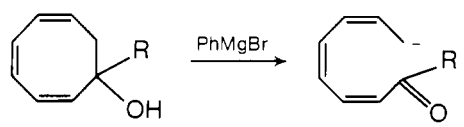
F. Exo:O=C:C:8

With the ketone **127a**, alkoxides cause exo:O=C ring fission and formation of 1,4-dihydrobenzene derivatives (**127b**):[379]



127a **127b**

The cyclooctatrienols **128** cleave on treatment with Grignard reagents. Again the pattern of leaving group stabilization is seen and, qualitatively, reaction is much more rapid when R = Ph than H, a rare example of a substituent effect at the forming carbonyl group in this type of reaction:[380]



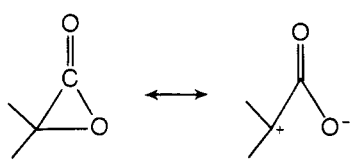
128

VI. Exo:O=C:O Reactions

This very common reaction type is seen in the reactions of lactones[381,382] and cyclic carbonates[383,384] with nucleophiles and in ring–chain tautomerism involving ring opening of cyclic hemiacetals and related systems.[385-388] Because these reactions have been widely reviewed in other contexts, examples are selected only to place them in the context of this review.

A. Exo:O=C:O:3

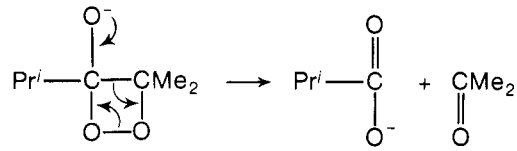
The rapid reactions[389] of α-lactones[390] with nucleophiles at carbon adjacent to the carbonyl group are entirely consistent with the dipolar formulation[390] of this species:



and there is no evidence for ring opening from a tetrahedral intermediate.

B. Exo:O=C:O:4

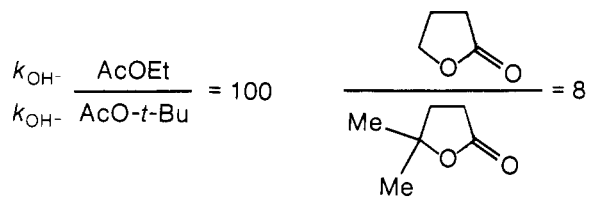
Quantitative study of the hydrolysis of β-lactones has been reported by Blackburn and Dodds,[382] who briefly review earlier work. The order of reactivity toward alkaline hydrolysis is $\delta > \beta > \gamma \geq \epsilon$. The greater reactivity of β than γ or ϵ lactones is ascribed to the relief of angle strain in the rate-determining attack of hydroxyl ion on the carbonyl group. The subsequent exo:O=C fission in the tetrahedral intermediate is rapid. Other reactions of β-lactones involving ring fission have been reviewed.[391] An unusual example is seen in the chemiluminescent fission of the dioxetan **128**:[392]



128

C. Exo:O=C:O:5 and -6

Hydrolysis of γ-lactones is very familiar[381,382,393-395] and the closely related exo:O=C:S:5 process is involved in hydrolysis of thiol γ-lactones.[395] Lactone hydrolysis is generally faster than that of open-chain analogues, and differences are more accentuated in ethanol than in Me_2SO. The greater reactivity of lactones over acyclic esters is ascribed[394] to the cisoid conformation, enforced in small and medium ring lactones. This increases polarization of the carbonyl group and hence susceptibility to nucleophilic addition which is the rate-determining process.[382] Lactones are also less sensitive to the adverse steric effects of substituents on the alkoxy-carbon atom[395] because approach of the hydroxyl ion to the carbonyl group is less obstructed. viz.



Hydrolysis of cyclic carbonates shows only small effects due to ring strain, and, as for lactones, addition is probably the rate-determining step. The ratio of C_6[384]:C_5[383]:acyclic (dimethyl carbonate)[396] is about 300:50:1.

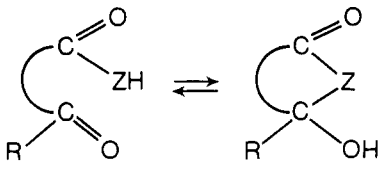
Hydrolysis of cyclic anhydrides has been widely studied; with a good leaving group such as acyloxy and the energetically advantageous formation of a carbonyl group, ring fission is not rate determining and structural effects operate upon the addition of the nucleophile.[397-399] Reactivity differences between ring sizes are not large; Eberson has shown that strain induced in succinic anhydride, for example, by annelation with a four-membered ring increases the rate of hydrolysis at pH 5.2 by a factor of 7.[398]

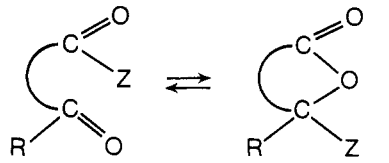
Polymerization of *N*-carboxy anhydrides involving successive carbonyl addition and ring-fission reactions has been reviewed.[400]

1. Ring-Chain Tautomerism

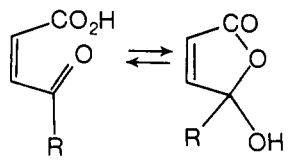
Intramolecular addition of nucleophiles to carbonyl groups is extremely common, and its reversal comes within the scope of this review. The equilibration involves ring–chain tautomerism and the topic has been reviewed.[386-388,401]

Valter[401] has reviewed ring–chain tautomerism of types A and B. In type A, reversal to the acyclic isomer is an exo:O=C:O

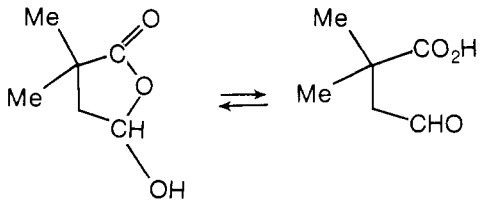




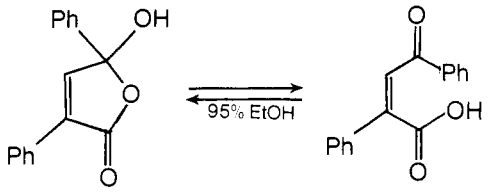
reaction. Several factors influence the position of equilibrium and the effects are analyzed in terms of the cyclization rather than ring fission.[401] The most pertinent factor here is the spatial one in which formation of the cyclic form is encouraged by juxtaposition of the interacting groups as in β-acyl-(*Z*)-acrylic acids.[402] Equilibrium constants in favor of the cyclic form may be in the region of 100.[402]



A few examples suffice to illustrate this reaction type:
Acid:aldehyde[403]

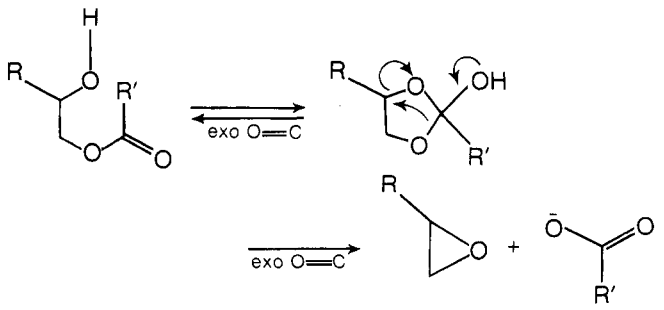


Ketone: acid[404]



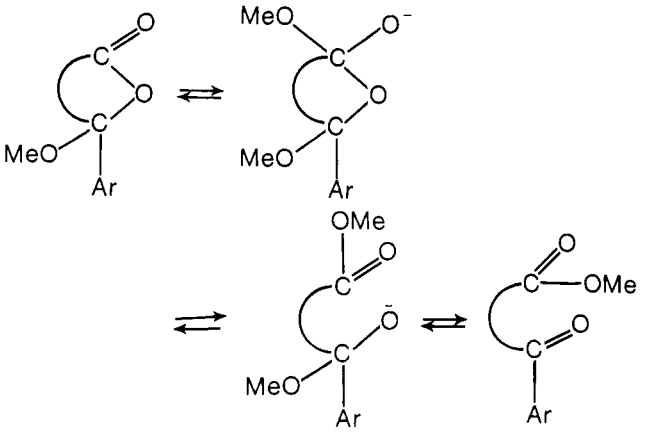
(see also ref 405 and 406)

Alcohol:ester[407]



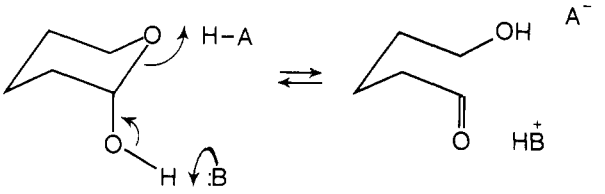
In this case, reversal of cyclization may occur in two different directions, the latter leading to epoxide and carboxylate ion.

Reactions of type B are exemplified by the base-initiated interconversion of acyl esters and pseudo esters:[408]

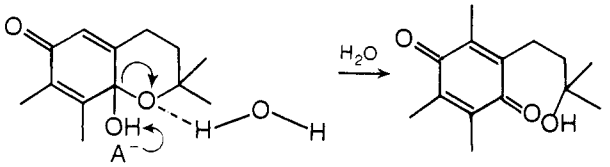


The five-membered-ring cyclic systems react more rapidly than the six-membered ring systems. Ring fission is assisted by strain in the five-membered ring as reflected in the substantially lower (3.2 kcal mol^{-1}) enthalpy of activation.

Reversal of hydroxyl to carbonyl group addition involves the exo:O=C process. The most common and significant example is found in the mutarotation of sugars which has been the subject of detailed mechanistic studies by Capon[388,409,410] and Neuberger.[411] For glucose in water, ring fission is concerted[410,411] with OH-deprotonation and O-protonation. Base catalysis involves rapid O-deprotonation and slow subsequent ring fission. Electron withdrawing groups at C_6 promote ring fission.[410]



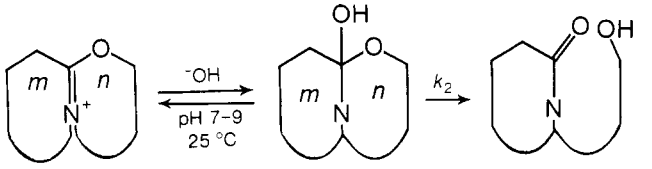
Ring fission in **129** has been studied as a model for the hemiketal intermediate in the oxidation of α-tocopherol to α-tocopherylquinone:[412]



129

The reaction is general acid/general base catalyzed.

Variation in rates of ring fission with ring size over more than one order of magnitude has been observed for the system **130**.[413] The maximum rate of ring cleavage is found when the

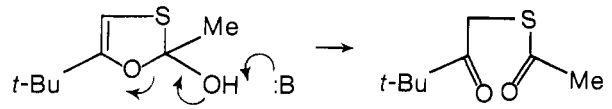


130

m	*n*	k_2 (L mol^{-1} s^{-1})
6	5	5270
7	5	3190
5	6	301
6	6	932

cleaved ring is most strained and the ring in which the carbonyl group is formed is least strained. As expected, oxygen as leaving group is preferred to nitrogen.

Cleavage of five-membered heterocyclic rings with two heteroatoms occurs similarly,[414,415] e.g.[414]



VII. Exo:X=C and X=Y Reactions

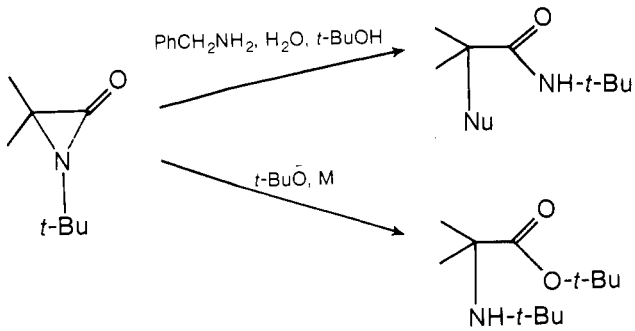
A. Exo:O=C:N

The pattern is very similar to that of exo:O=C:O reactions in the preceding section. Again, there is rather little evidence as to the significance of ring strain on reactivity; in the hydrolysis of lactams, the most typical reaction, formation and not decomposition of the tetrahedral intermediate is rate determining.

1. Exo:O=C:N:3

The chemistry of α-lactams (aziridinones) has been investigated in detail, notably by Baumgarten[416,417] and Sheehan[418-420]

In most reactions with nucleophiles, bond formation occurs at carbon adjacent to the carbonyl group[417,418,420] as in α-lactones. Alkoxides, however, attack the carbonyl group:[417-420] e.g.[418]



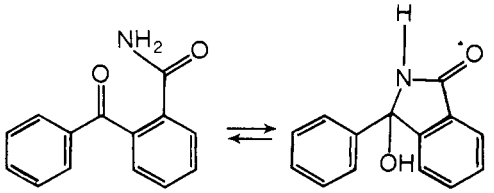
2. Exo:O=C:N:4

In the hydrolysis of β-lactams, it is concluded[421] that perhaps only angle deformation helps both addition and ring fission steps. β-Lactams are about 10 times as reactive as γ-lactams and 100 times as reactive as δ-lactams in alkaline hydrolysis. Comparison of β-lactams with acyclic analogues shows that ring strain accelerates expulsion of the nitrogen leaving group from the tetrahedral intermediate by at least 10^4.

3. Exo:O=C:N:5 and -6

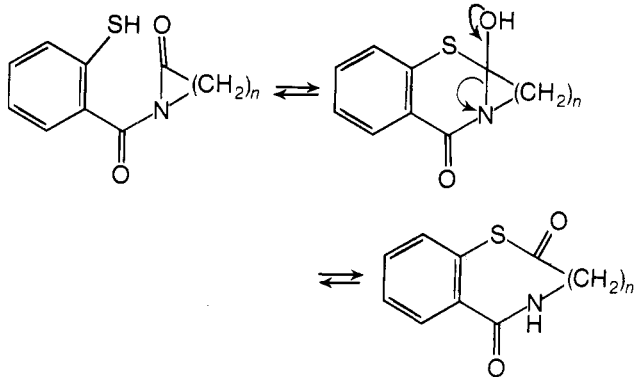
Hall[422] concludes from comparisons of lactams with open-chain amides as well as of cyclic with acyclic esters that differences in the hydrolysis rates are small. These are not due to ring strain affecting the rate-determining step. Ring strain, however, determines the tendency of lactams to polymerize.[423] Angle distortion, eclipsing, and steric inhibition of resonance in the amido function by enforced noncoplanarity all contribute to this strain.

In alkaline hydrolysis of piperidones, substantial equilibration between lactam and amino carboxylic acid salt formed by an exo:O=C:N:6 process is observed[661] and ring-chain tautomerism with amido nitrogen as the leaving group has been described,[424,425] e.g.[425]

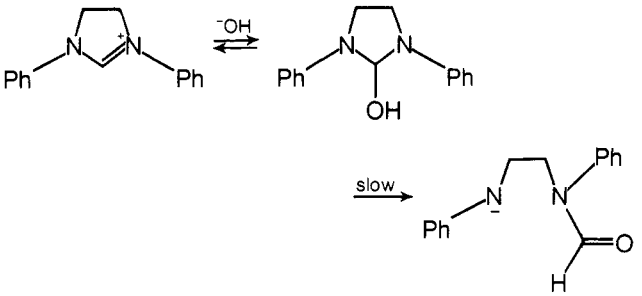


The ring form is favored by substituents on nitrogen that increase its basicity, and those which reduce the electrophilic character of the keto-carbonyl group favor the chain form. Equilibration between ring and chain forms is also seen in rearrangement of dihydropyridinediones[232] (section V.A).

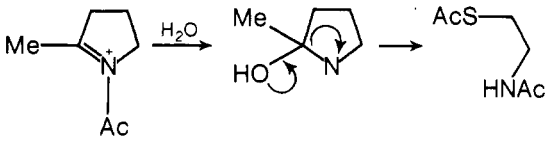
Other scattered observations of the exo:O=C:N process involve the cleavage of *N*-acyllactams by a neighboring thiol function:[426]



Nucleophilic addition to an imidazolinium ion gives a directly observable tetrahedral intermediate and ring fission occurs slowly thereafter:[427]



Cleavage of the *N*-acetylthiazolinium ion **131**[428] gives the *N,S*-diacylaminothiol.



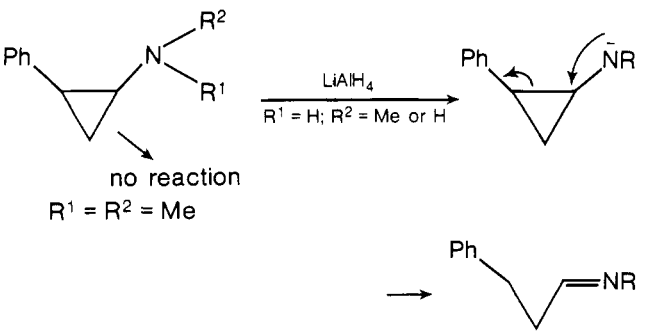
131

B. Exo:N=C

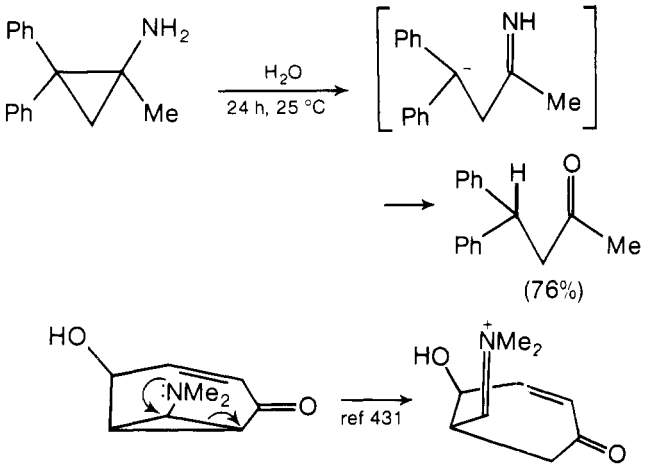
Much the commonest type is the N=C:C:3 reaction, undoubtedly assisted by the strain of the ring, but a limited series with large rings and differing leaving groups has been described.

1. Exo:N=C:C:3

With modest leaving group stabilization, the external nucleophile must be highly reactive:[429]

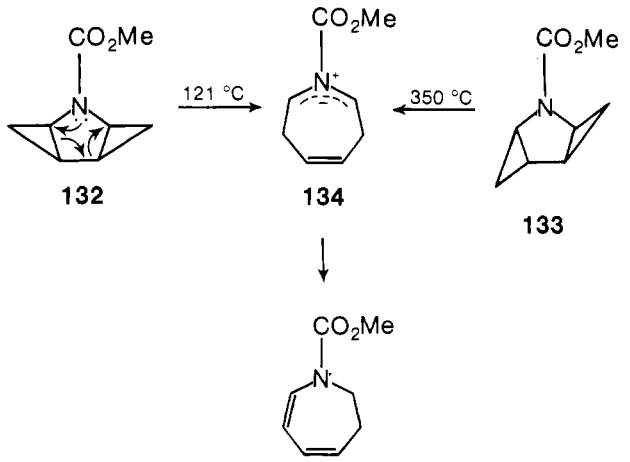


but a simple amino group suffices for cleavage under more vigorous conditions[429] or with greater leaving group stabilization:[430]

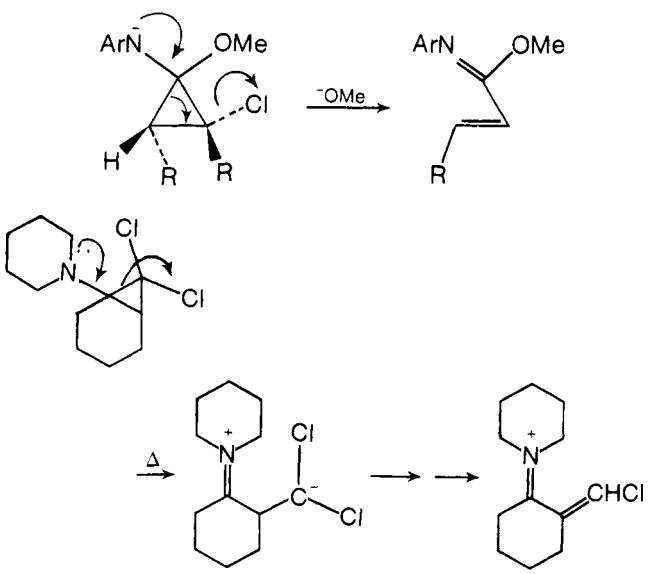


Substantial reactivity differences are seen in the conditions for cycloreversions of compounds **132** and **133**[432] (Scheme XVI). For the syn isomer **132** the process is reversion of $_{\pi}2_s$ + $_{\pi}4_s$, but for the anti isomer **133** $_{\pi}2_a$ + $_{\pi}4_a$. The stability of the dipole **134** is considerably increased by replacement of the *N*-carbomethoxy group by methyl, and cycloreversion of the anti isomer then occurs at 280 °C.

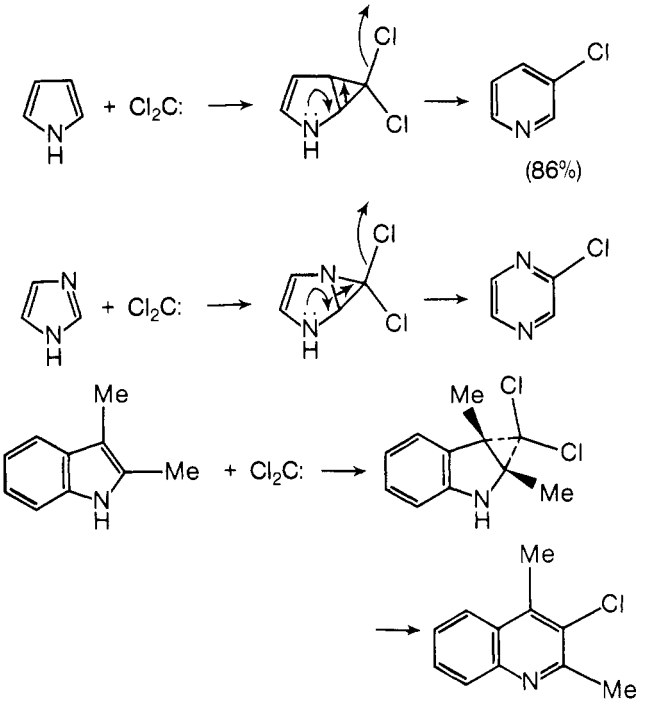
SCHEME XVI



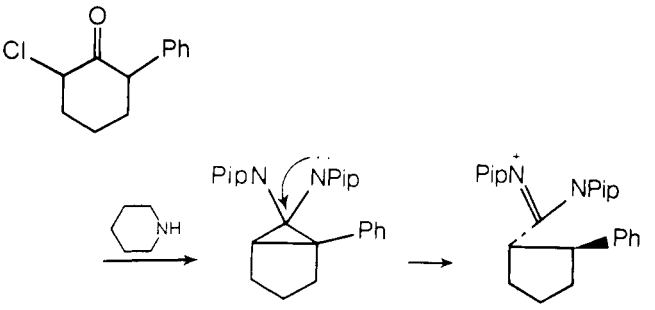
Exo:N=C fission may be followed by elimination:[433,434]



Many examples of the exo:N=C process follow additions of dichlorocarbene to nitrogen heterocycles:[435-437]

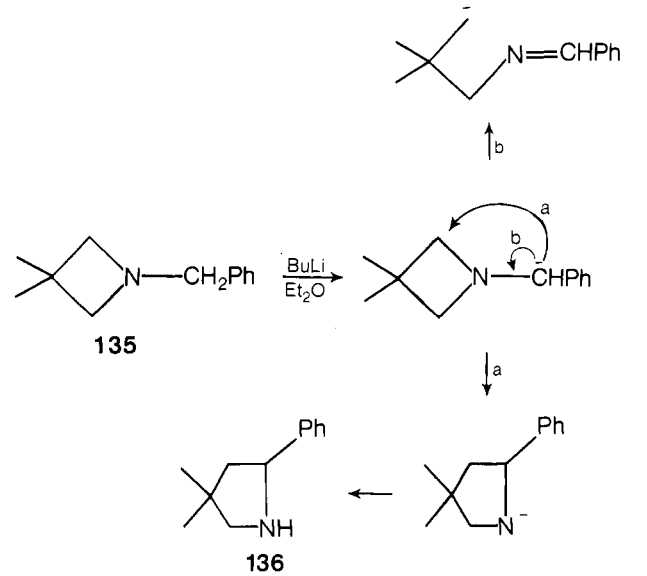


Exo:N=C:C:3 cleavage is probably involved in reaction of a Favorskii type:[438]

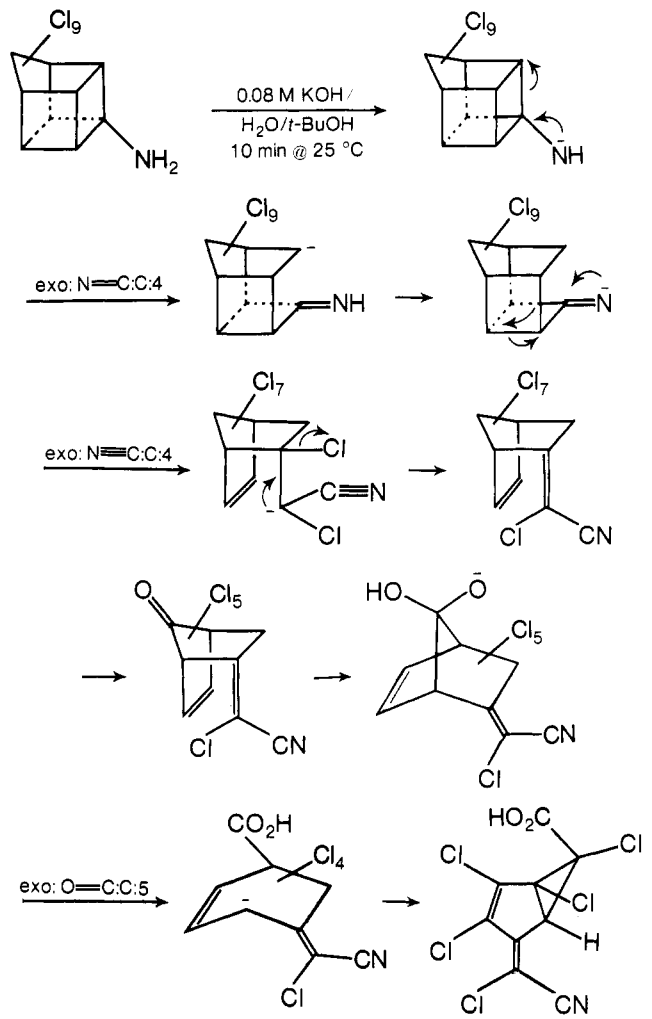


2. *Exo:N=C:C:4*

The role of ring strain is again clear in the examples reported. Treatment of the *N*-benzylazetidine (**135**) with butyllithium gives the pyrrolidine **136**.[439] Pathway a is a higher order elimination

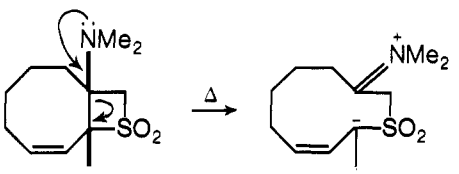


SCHEME XVII



(section VIII) and path b the exo:C=N:C:4 process. Strain is similarly important in assisting the cleavage of birdcage amines in rapid reactions.[318,440] Degradation of the ring strructure is profound and probably involves three types of eliminative ring fission[440] (Scheme XVII).

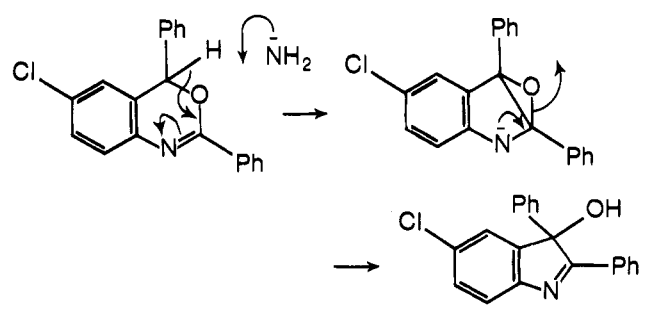
An exo:N=C:C:4 reaction with a stabilized leaving group has been reported by Paquette[441] and occurs under mild conditions.



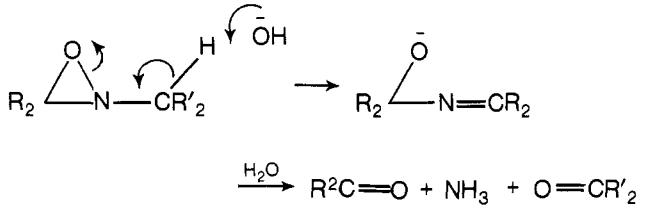
A very similar ring expansion involving a vinylogously oxo-stabilized leaving group has been reported by Kimura.[442]

3. Exo:N=C:O:

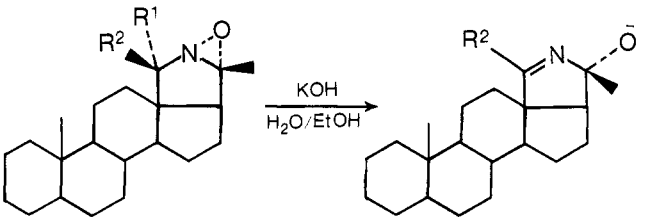
This reaction is seen in a benzoxazine ring contraction:[443]



Oxaziranes with hydrogen on carbon next to the ring rapidly give ammonia on treatment with aqueous alcoholic alkali via exo:C=N:O:3 fission and subsequent hydrolysis:[178]

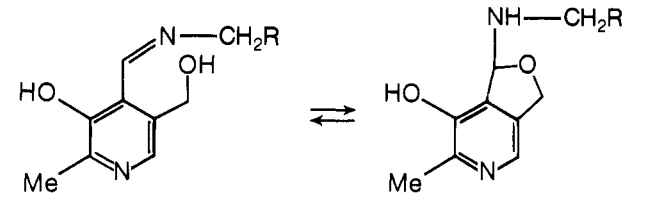


In the steroidal oxazirane:



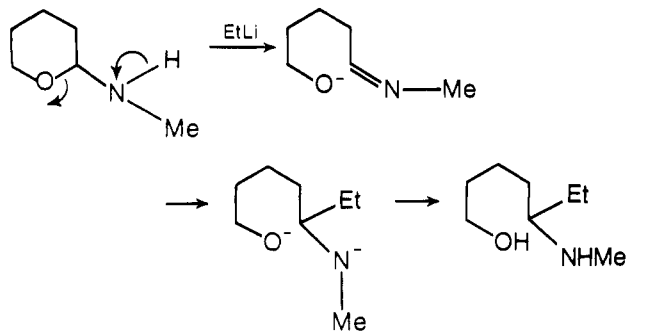
With R^1 = D and R^2 = H, deuterium is not removed showing that elimination is antiperiplanar and hence probably concerted E2.[487] This conclusion is supported by a recent observation of a substantial kinetic primary deuterium isotope effect for eliminative fission in oxaziranes.[630]

Fission of larger rings is known in several types; equilibration of the imine **137** with the aminodihydrofuran **138** involves exo: N=C:O:5 reaction,[444] and cleavage of a 2-aminooxazole is involved in an oxazole–imidazole conversion.[445] The exo:



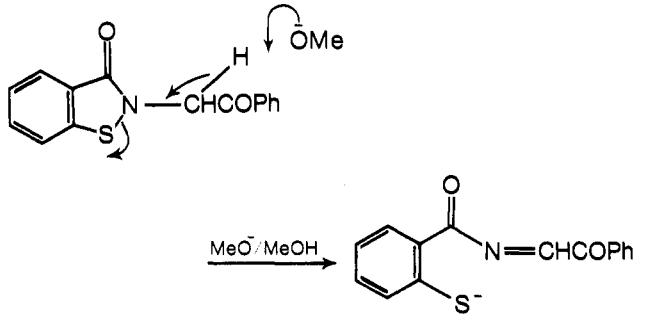
137 **138**

N=C:O:6 process occurs under severe conditions:[446]

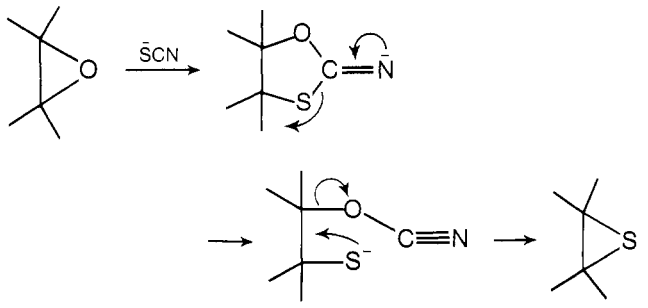


4. Exo:N=C:S:5

Grivas[447] has reported cleavage of 1,2-benzisothiazolin-3-ones:

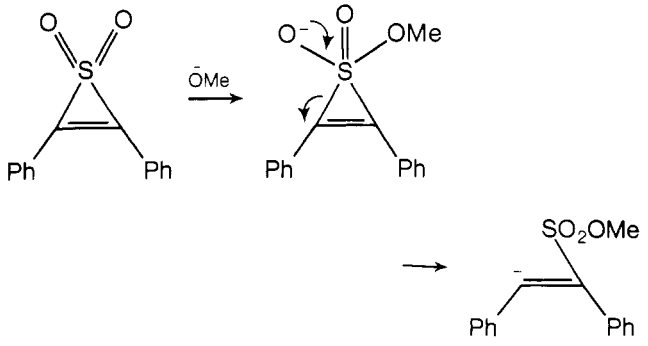


and exo:N≡C fission occurs in the reaction of thiocyanate ion with epoxides:[448]



C. Exo:O=S

Exo:O=S: fission appears to be involved in reaction of thiirene dioxides with alkoxides:[449]



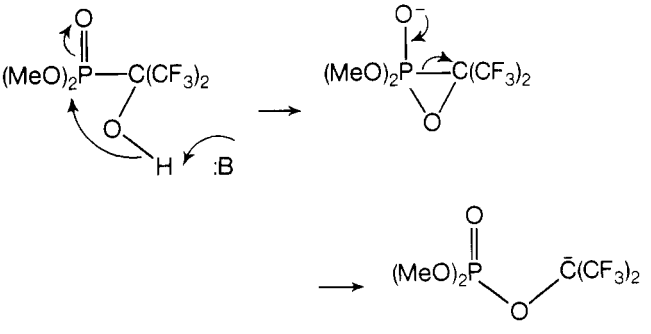
The reaction occurs 5 × 10^3 faster than with diphenylcyclopropenone in which aromaticity is destroyed in the carbonyl addition step and there is a notable reversal of reactivities of carbonyl and sulfonyl compounds.

Alkaline hydrolysis of cyclic five-membered ring sulfites is roughly 10^3 times faster than the open-chain analogues. The reaction probably involves exo:O=S ring fission but the acceleration is shown to be an entropy effect and not due to ring strain.[450,451]

D. Exo:O=P

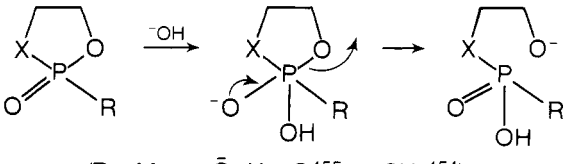
1. *Exo:O=P:C:3*

Rearrangement in the phosphonate apparently can be formulated as a P–C cleavage process:[452]



2. *Exo:O=P:O:5*

This type of reaction is common in cyclic phosphate[453] or phostonate[454] esters:



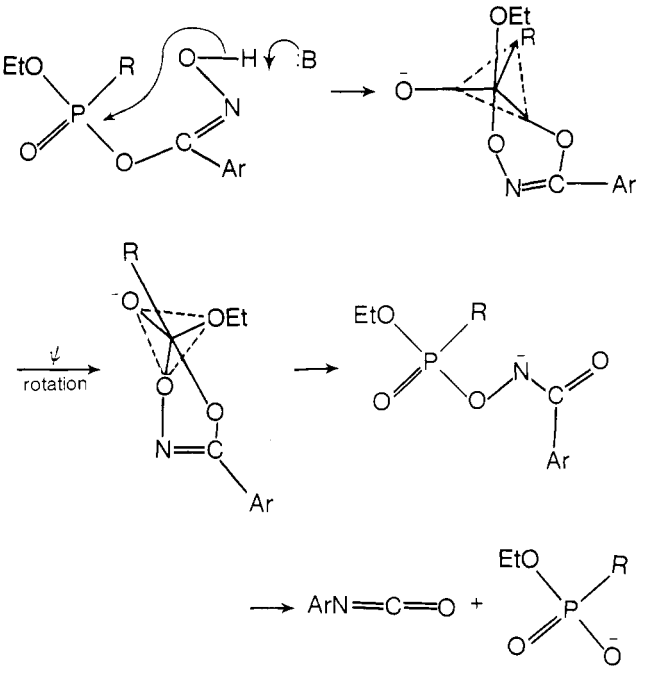
(R = Me or Ō; X = O[455] or CH_2[454])

The cyclic esters undergo alkaline hydrolysis ca. 10^7 times as fast as the acyclic analogues.[453,454] Thermochemical measurements[456] confirm that this very large acceleration is due to strain in the five-membered ring, which is relieved in formation of the transition state with an O–P–O angle of about 90° as against 110° in the substrate.

The six- and seven-membered ring analogues do not show any acceleration due to ring strain. Approximate relative reactivities in alkaline hydrolysis of five, six-, and seven-membered cyclic phosphates are 10^7 (minimum): 10:1.[455]

Cadogan and his collaborators[457] have described an example of the reaction in which cleavage of the ring involves departure of animidolyoxy group (Scheme XVIII).

SCHEME XVIII



VIII. Exo: Higher Order Eliminations

This section encompasses reactions which effectively involve intramolecular displacements by nucleophiles on ring systems. The reaction type is common for the exo:1,*n* Nu-C:O:3 type, i.e., intramolecular nucleophilic attack upon epoxides. It is otherwise relatively rare as only under special conditions are other ring systems susceptible to either inter- or intramolecular attack by nucleophiles.

Within each reaction type, reactions are classified in categories of increasingly higher order; in the 1,3 and 1,4 categories the products are, of course, considerably strained.

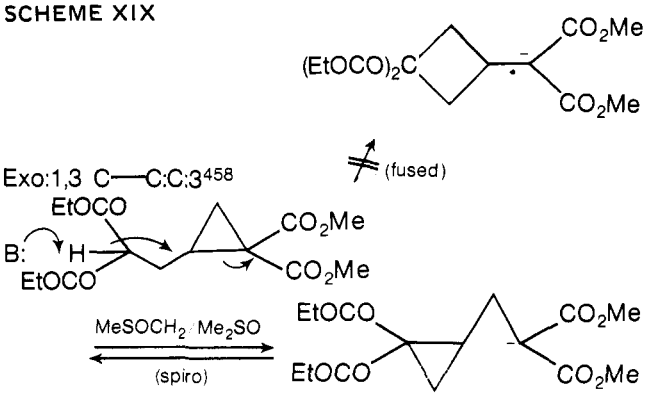
A. Exo:1,*n* C—C:C:*n*

Cyclopropanes are susceptible to ring opening by nucleophilic substitution only under special conditions, and the rarity of the intramolecular version of the reaction is unsurprising. Danishefsky and his collaborators have provided most of the examples.

1. *Exo:1,3 C—C:C:3*[458]

In the example in Scheme XIX, the exclusive preference for formation of the more strained three-membered ring via the *spiro* mode of reaction, over formation of the four-membered ring via the fused mode of reaction, is observed. This is in accordance with a general hypothesis[459] that when electron-acceptive conjugative groups are attached to the ring being formed, three-membered-ring formation is preferred over other sizes.

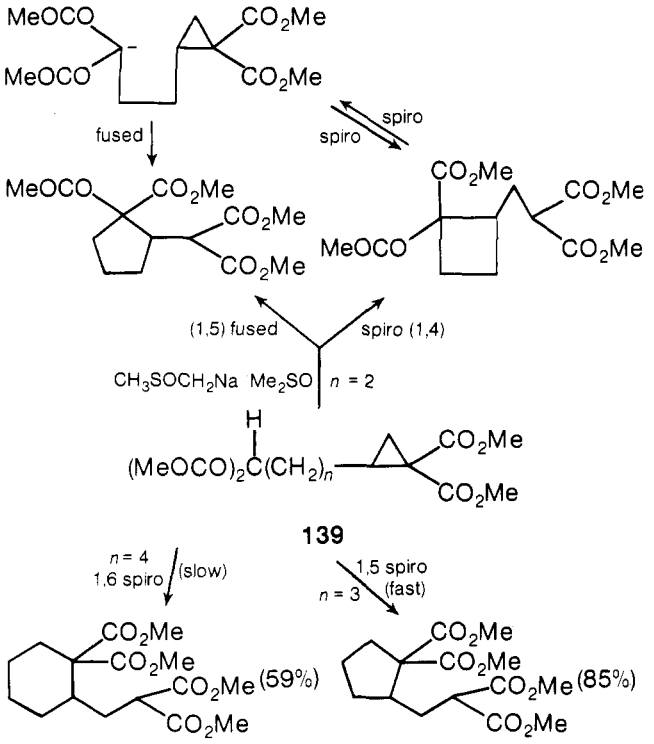
SCHEME XIX



2. *Exo:1,-3,-4, and -5 C—C:C:3,-4, and -5*

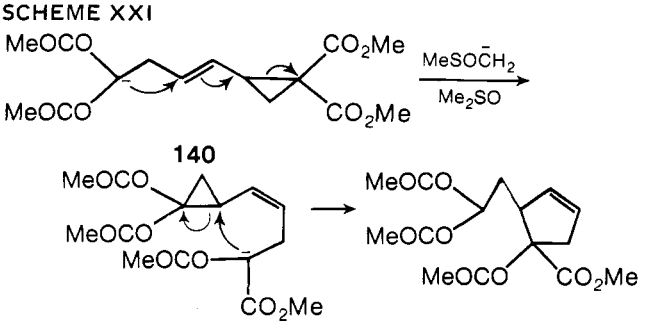
An interesting study has been made[460] of cyclization reactions in the system **139** (Scheme XX). The reaction can take place in *fused* or *spiro* modes, and in all cases the carbon leaving group is stabilized. Spiro-1,4-closure competes (2.5 times as fast) with

SCHEME XX

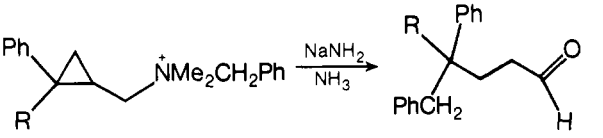


fused 1,5-closure, but spiro-1,5- and spiro-1,6-closures occur without competition from the fused alternatives. The preference for exo:C—C: elimination in the spiro mode is probably due to the requirements for the orientation of rearside attack on the electrophilic center. In the tetraester **140,** an exo:1,5 C—C:C3 reaction follows an initial exo:C=C:C:3 reaction (section II.A)[76]

SCHEME XXI

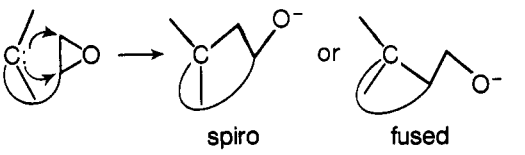


(Scheme XXI). An unusual example of this reaction type occurs in the salt:[461]



B. Exo:1,*n* C—C:O

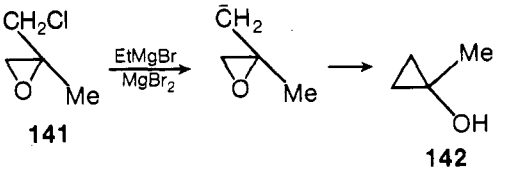
Intramolecular nucleophilic attack on epoxides. The reaction is of the general type:



The carbon nucleophile is often stabilized by a conjugative group and the reaction has recently assumed synthetic importance notably in the hands of Stork and his collaborators[462,463] who have described the conditions under which rings of differing sizes may be formed. Examples of many types are included in the review by Yandovskii and Ershov.[101]

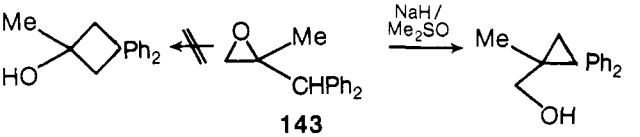
1. *Exo:1,3 C—C:O:3*

Examples in which the carbon nucleophile is poorly stabilized are rare. Treatment of the epoxide **141** with ethylmagnesium bromide gives the cyclopropanol **142,**[464] and treatment of certain polycylic epoxides, containing a judiciously placed proton, with aluminum alkoxides, gives hydroxycyclopropanes.[465]



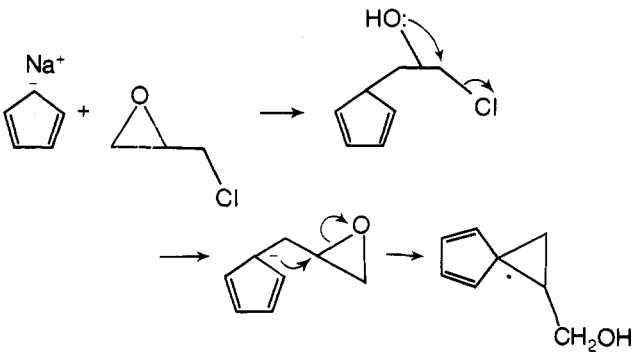
141 **142**

For epoxide **143,** the choice between three and four members in the cyclic product is offered.[466] Only the more highly strained three-membered ring is again obtained.[459]

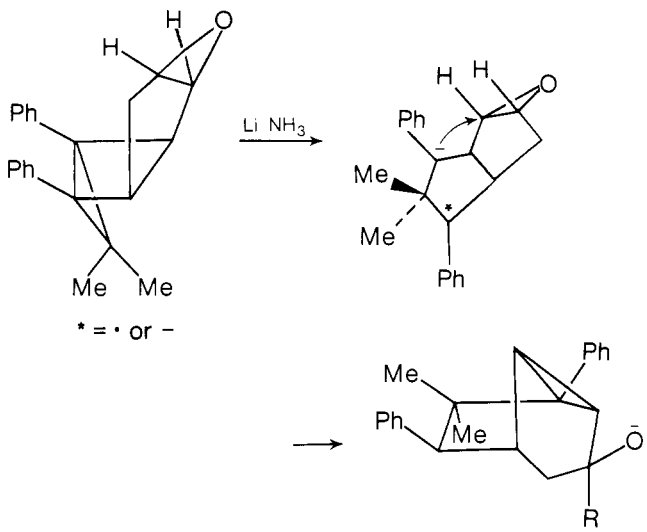


143

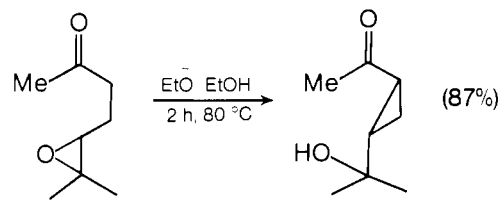
This type of reaction has been applied[466] to the synthesis of *trans*-chrysanthemic acid and in reaction of cyclopentadienide ion with epichlorohydrin.[467] The preference of three- vs. four-membered-ring formation is again seen:



Reductive fission of a cyclopropyl group generates a poorly stabilized carbon nucleophile which re-forms a new strained system by attack on an epoxy group:[468]

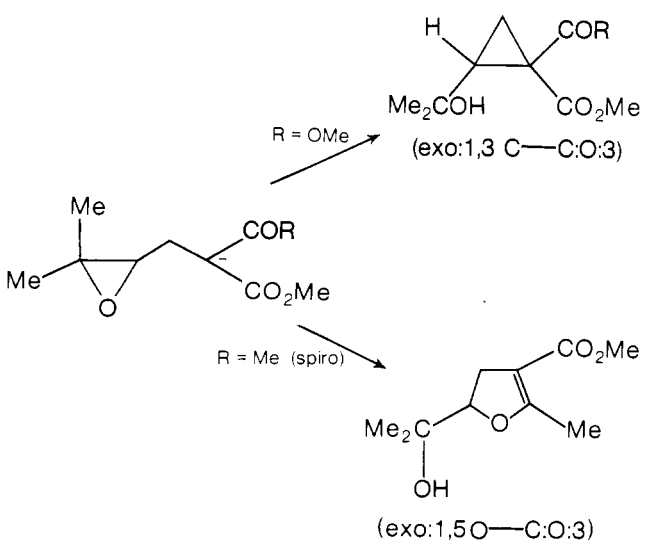


Stabilization of the carbon nucleophile by carbonyl groups is common and isomerization of γ,δ-epoxy ketones to α-oxocyclopropanes occurs under basic conditions. Simple cases have been reported for ketones[469-471] and malonic esters.[472,473] The reaction does not go for monocarboxyl activation, even under severe conditions,[474] e.g.[470]

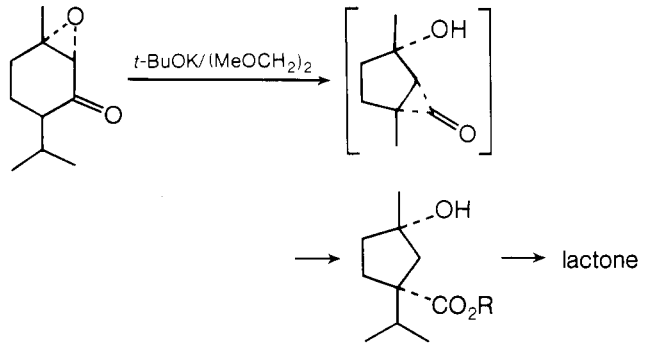


In glycidylmalonates, a cyclpropanol is formed,[473] but the reaction is not observed for the formation of larger rings.

When an oxo group is one of the carbanion-stabilizing groups, the exo:1,3 C—C:O:3 process giving[475] a cyclopropylmethanol derivative is in competition with the rival exo:1,5 O—C:O:3 process (section VIII.D) arising from ambident nucleophilicity of the oxo-stabilized ion. This yields[476] a dihydrofuran derivative:



SCHEME XXII

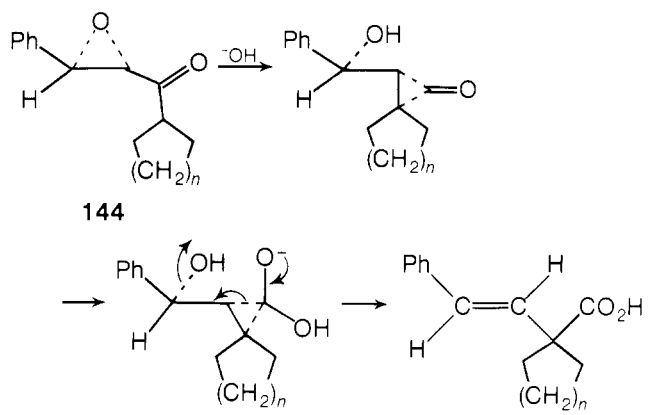


When the carbanion stabilizing carbonyl function is *between* the acidic proton and the epoxy function, a Favorskii-like reaction occurs[477,478] whose products depend upon the base–solvent system employed. The work of House[477] is typical (Scheme XXII).

Reactions of related epoxides[479-482] by Favorskii-type mechanisms are stereospecific with retention in the opening of the cyclopropanone ring. The products depend on the precise conditions employed.

In cycloalkyl epoxy ketones of type **144** (Scheme XXIII), the reactions[483] again proceed by way of the cyclopropanones. Only

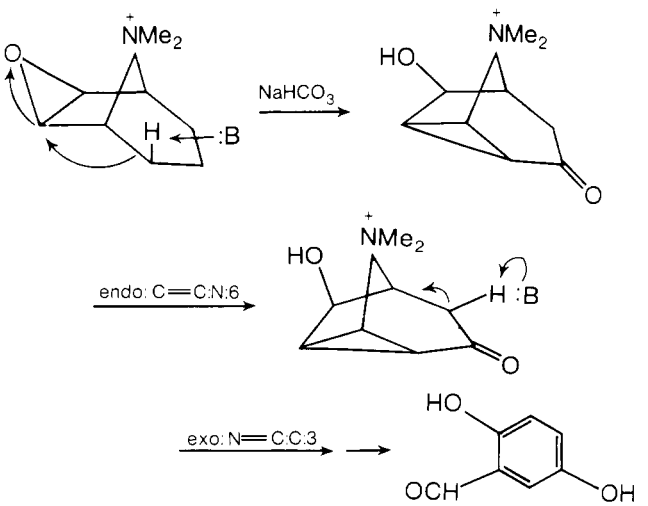
SCHEME XXIII



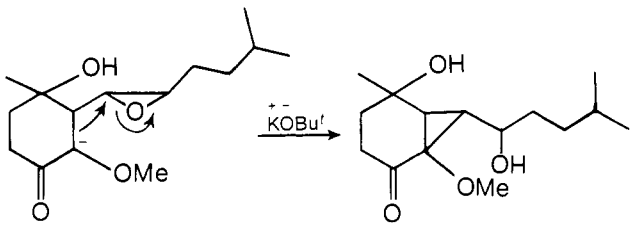
in the case where $n = 3$ does the reaction not occur; the carbanion, which must be planar, is not stable and endo elimination results (section IX).

A closely analogous example is seen in the first stage of a complex rearrangement of the bicyclic ketone **145.** The initial product **146** undergoes an endocyclic C=C ring fission followed by an exocyclic imine-forming elimination (section VII)[431] (Scheme XXIV).

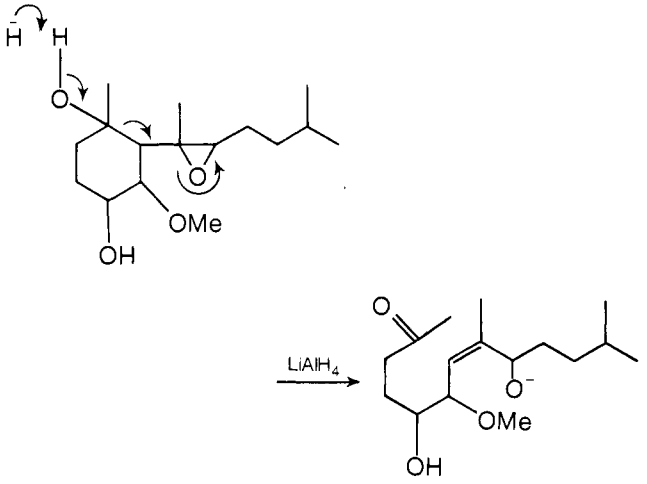
SCHEME XXIV



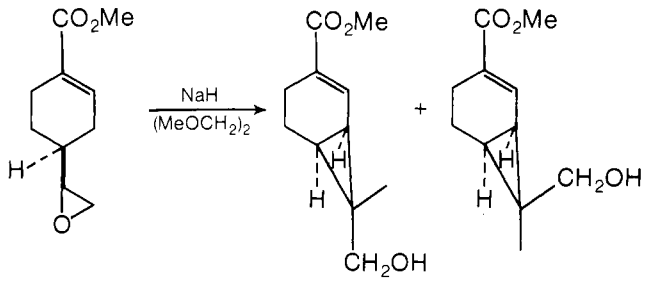
Similarly, in the chemistry of fumigallin[484] a carbonyl-stabilized carbanion initiates this reaction type:



On lithium aluminum hydride reduction, however, the carbonyl group is lost and instead two eliminative fissions occur exo: O=C:C:6 (section V) and exo:C=C:O:3:

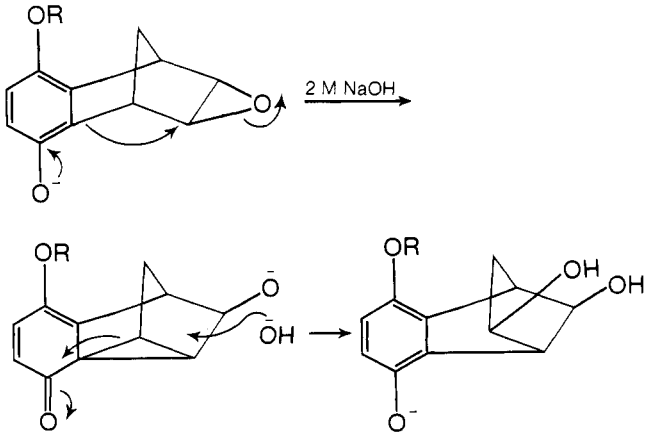


A vinylogous ester-stabilized carbanion leads to a bicyclo[4.1.0]heptane.[485] This system is interesting in two respects;

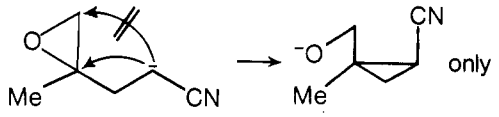


closure to either a cyclopropane or a cyclobutane may occur but only the former is obtained. Also, the hydroxymethyl group can be cis or trans the fused ring. The latter is preferred. Only in rather few instances of nucleophilic eliminative ring fission has the stereochemistry been clearly defined.

Phenolate ion in its ambident carbon form can initiate ring fission:[486]



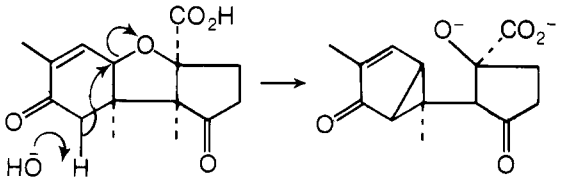
Stork and his collaborators[462,463] have demonstrated the synthetic value of eliminative ring fission of epoxides by cyano-stabilized carbanions. When the choice is between three- and four-membered ring formation, only the three-membered



ring is formed as discussed above. This is a further example of conjugative control.[459] When the choice is between four- and five-membered ring formation, the four-membered ring is much preferred.

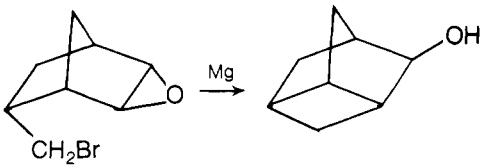
2. *Exo:1,3 C—C:O:5*

Reaction of a carbonyl-stabilized carbanion in a very unusual fission of a tetrahydrofuran ring is suggested for base-promoted reaction of a tricothecin derivative:[487]

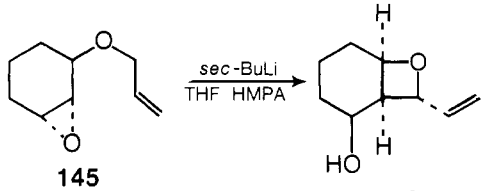


3. *Exo:1,4 C—C:O:3*

Cleavage of a bridged ring system[488,489] occurs in high yield from a nonstabilized carbanion. The alternative 1,5 mode is disfavored by ring strain.



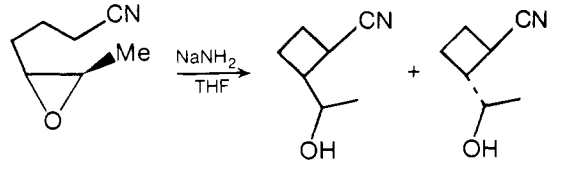
The allylic ion derived from **145** cyclizes[129] with cleavage of the oxirane ring and formation of the oxetane **146.** Excess of

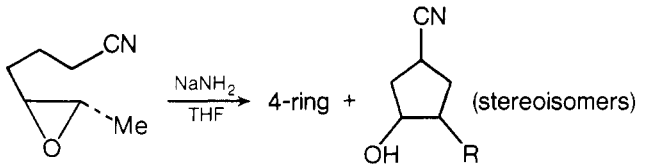


145 **146**

base causes a subsequent exo:C=C:O:4 process (section III.B). An early transition state is suggested for oxetane formation because of the ring strain involved. The exo:1,4 C—C:O:3 process requires rearside attack on the epoxy-carbon atom, a pathway not available in the cis isomer, which, instead, undergoes an exo:C=C:O:3 reaction (section III.A).

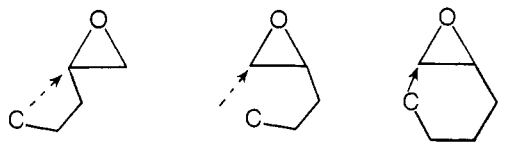
With cyano-stabilized carbanions, as reported by Stork,[462] four-membered ring formation is preferred to five, and this is confirmed for cis epoxides.[490] When the epoxide is trans-substituted, the five-membered ring is also obtained from the exo:1,5 C—C:O:3 mode which is not obstructed:[490]





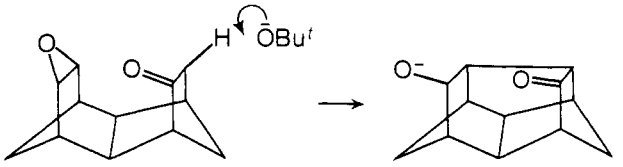
$$R = Me \quad \frac{4\text{-ring}}{5\text{-ring}} = \frac{1}{2.6}$$

The colinear arrangement of nucleophile, electrophile and leaving group is critical. This requirement imposes the preference for four- and six- vs. five-membered rings:[462,463]

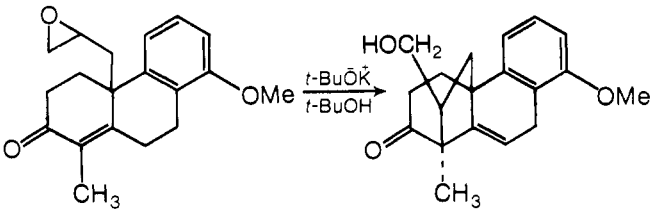


4. Exo:1,5 C—C:O:3

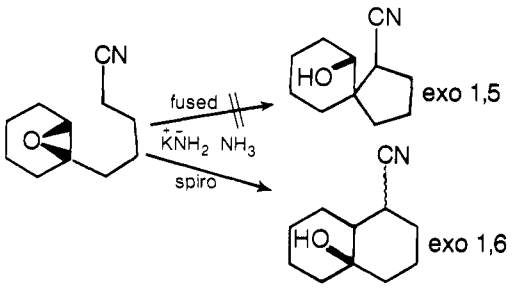
With an oxo-stabilized carbanion, the reaction has been applied to the synthesis of triquinacene:[491]



and of diterpene alkaloids,[492] a reaction which is striking in terms of preferential formation of the five-membered ring by attack at the secondary position of the epoxide:[492]



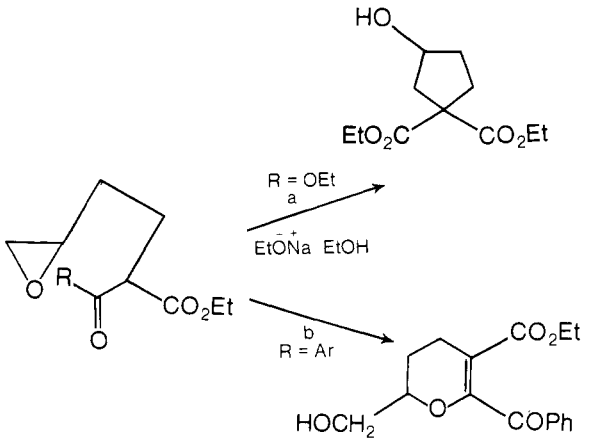
The disfavorment of the exo:1,5 C—C vs. 1,6 C—C mode is seen in cyano-stabilized carbanions reacting intramolecularly with epoxy groups.[463] This is again accounted for on the basis of restriction of the colinear trajectory of the nucleophile:



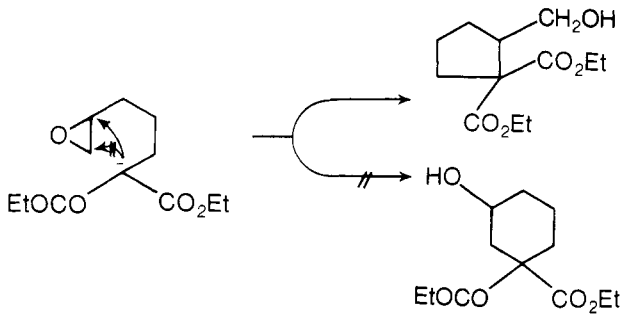
Ring closure reactions of 3,4-epoxybutylmalonates and β-keto esters show competition between (a) exo:1,5 C—C:O:3 and (b) exo:1,6:O—C:O:3 modes[493,494] (Scheme XXV). The more nucleophilic carbonyl group of a ketone gives the six-membered ring.

In related work, Cruickshank and Fishman[495] have shown that formation of a five-membered-ring is preferred to that of a six-membered ring even when this involves attack of the internal nucleophile at a secondary rather than primary position (Scheme XXVI).

SCHEME XXV

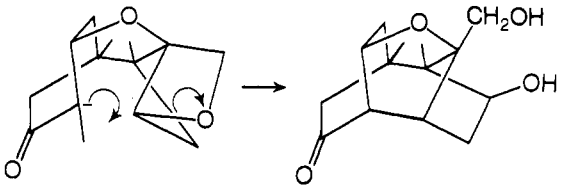


SCHEME XXVI



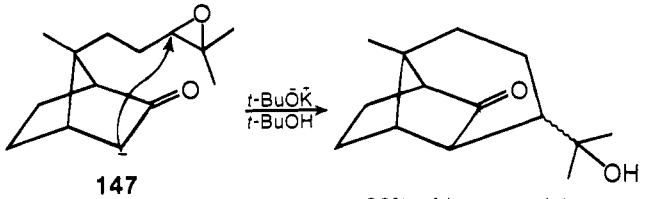
5. Exo:1,5 C—C:O:4

This rare type is also suggested to occur in a further tricothecin rearrangement:[487]



6. Exo:1,6 C—C:O:3

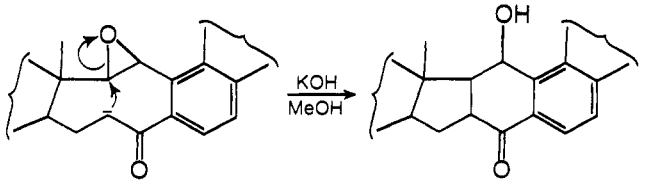
A carbonyl-stabilized carbanion is involved in such a reaction in the oxido ketone derived from caryophyllene. This was important in the structure proof of this compound,[496] and a further example is seen in formation of a diastereoisomeric mixture of alcohols from the bridged-ring ketone **147**:[497]



147

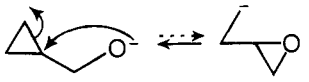
80% of isomer mixture

An interesting transannular example occurs in a ten-membered ring:[498]



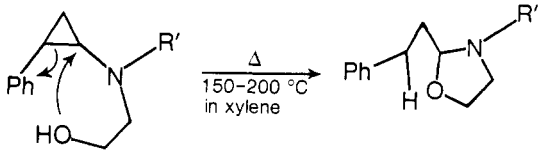
C. Exo:1,*n* O—C:C:*n*

The common type in this category is the exo:1,5 O—C:C:3. The 1,3 version would probably involve reversion to the cyclopropane, and few examples are known. As mentioned above,

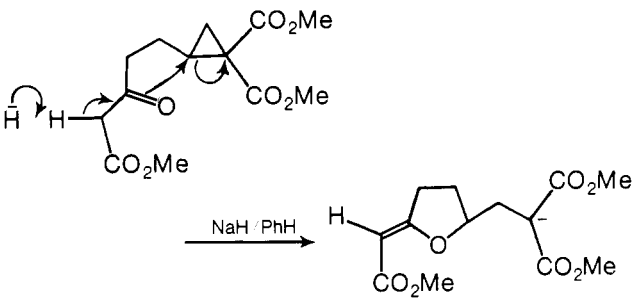


cyclopropanes are not very susceptible to nucleophilic substitution.

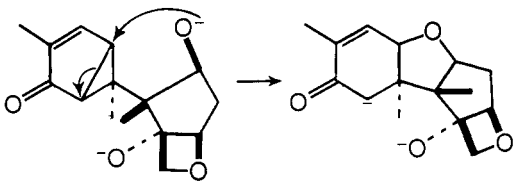
In a simple example with an alkoxide nucleophile:[499]



only mild conditions are required and the leaving group is only modestly stabilized. Danishefsky has described an example in which the oxygen nucleophile is an enolate ion and the leaving group is well stabilized:[500]

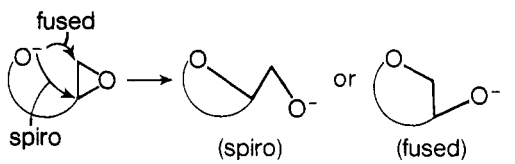


The tricothecin rearrangements[487] provide yet another example of eliminative fission in this category; the leaving group is oxo-stabilized:



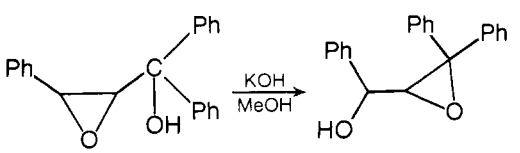
D. Exo:1,*n* O—C:O

In this type an O–C bond is formed in the cleavage of an epoxide by an oxygen nucleophile. The reaction type is particularly

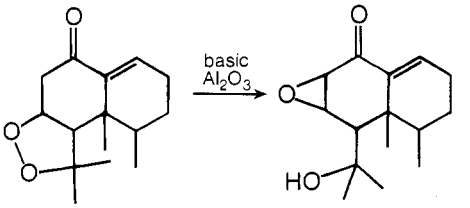


common in carbohydrate chemistry, and this area has been reviewed by Lemieux.[501] Examples of 1,*n* reactions with *n* = 3, 5, and 6 are all known. The following examples illustrate the variety of this type.

1. Exo:1,3 O—C:O:3[502]



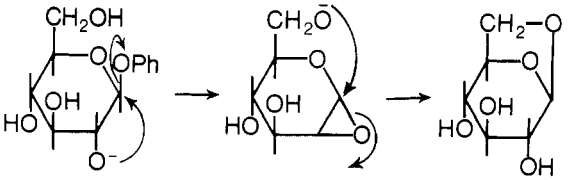
The 1,3 mode is also known with cleavage of a five-membered ring in unusual peroxidic structures studied by Rucker:[503]



Further reaction of the product involves an exo:1,5 C—O:O:5 process (below).

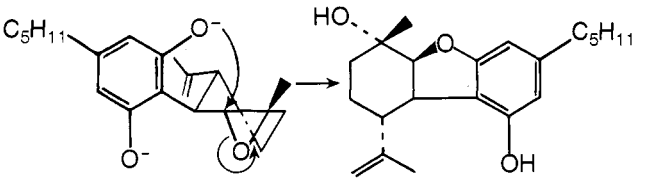
2. Exo:1,5 O—C:O:3

An intriguing example is reported by Hudson;[504] the initial formation of the epoxide is followed by rearside intramolecular nucleophilic attack by oxygen at C_6. The C_1 epimer is stable



presumably because rearside displacement of the phenoxy group, an unusual reaction in itself,[505] is impossible.

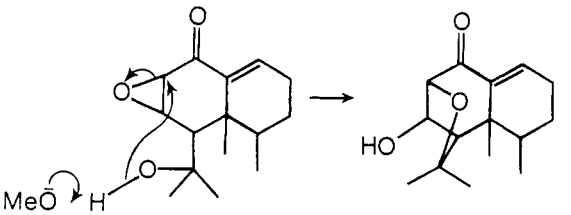
In the resorcinol drivative **148**,[506] formation of the five-membered ring, giving **149** by the spiro mode as a result of axial attack at the less hindered side on the three-membered ring, is



148 **149**

preferred. Some exo:1,6 O—C:O:3 reaction (fused) does, however, also occur.

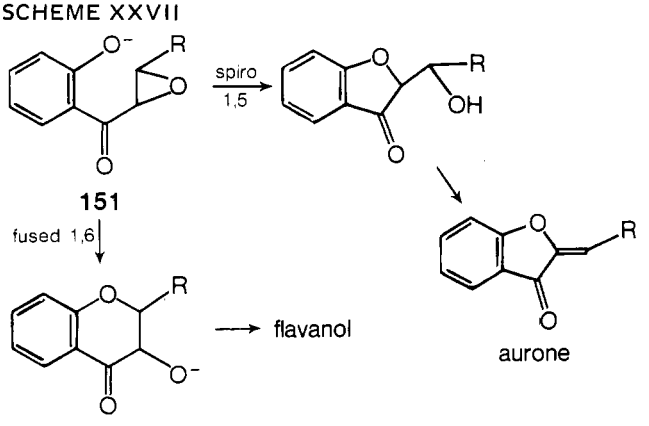
The fused mode of reaction is also seen in reaction of base with the product (**150**) of an exo:1,3 O—C:O:5 reaction (above):



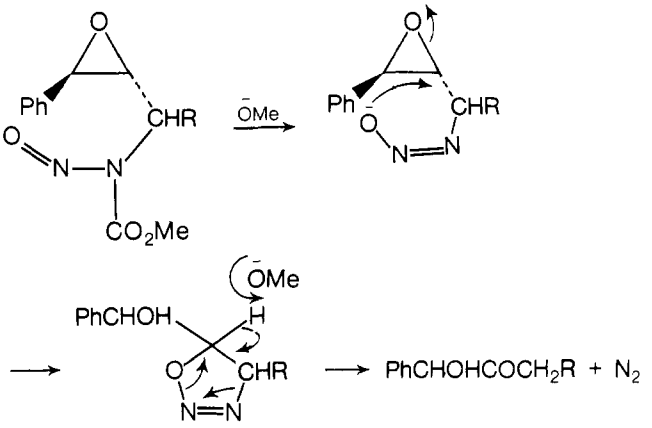
150

Both exo:1,5 and 1,6 O—C:O:3 modes occur in the base-catalyzed rearrangements of epoxychalcones **151**[508] (Scheme XXVII).

SCHEME XXVII



An unusual example of the 1,5-type is reported by Padwa[509] in which the nucleophile is diazotate ion. The initial product **152**

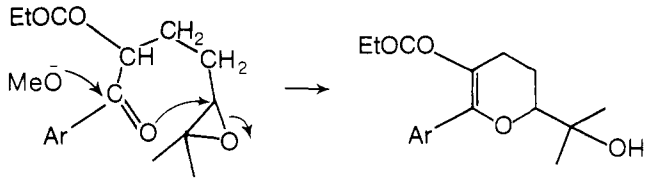


152

suffers further eliminative fission by the endo:C=C mode (section IX). In a related example, the nitro group acts as internal nucleophile.[510]

3. *Exo:1,6 O—C:O:3*

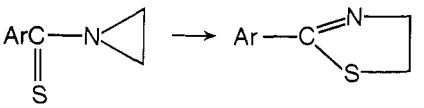
A recent example[494] involves nucleophilic complexation catalysis.[511] Methoxide is truly catalytic; it is regenerated in a



step subsequent to ring closure by elimination under activation by the alkoxycarbonyl group.

4. *Exo:1,4 S—C:N:3*

A few examples of aziridine ring expansions on the borderline of the scope of this review are known, e.g.[512]

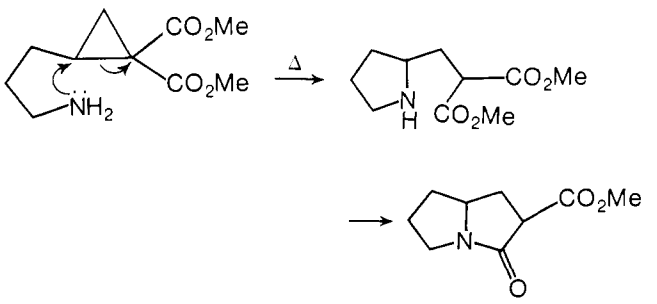


Aziridine ring expansions have been reviewed.[513]

E. Exo:1,*n* N—C:

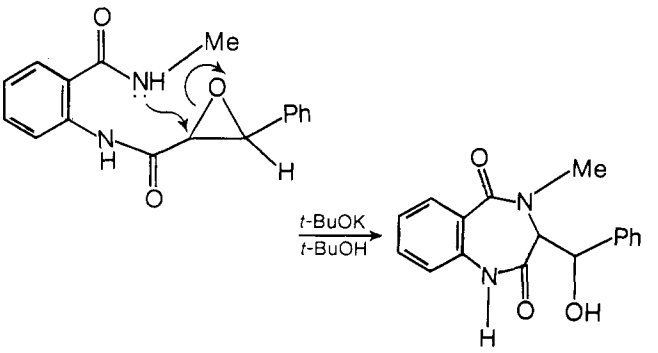
1. *Exo:1,5 N—C:C:3*

As mentioned earlier, cyclopropanes are not very susceptible to nucleophilic attack, and with a nitrogen nucleophile the carbon leaving group requires stabilization[514]



2. *Exo:N—C:O:3*

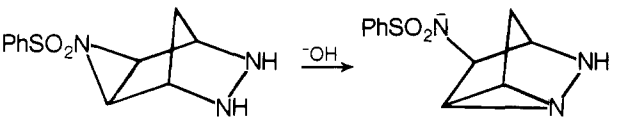
The 1,7-reaction with amido nitrogen as nucleophile was employed in the synthesis of cyclopenin:[515]



The 1,*n* reaction embraces intramolecular attack of nitrogen nucleophiles on epoxides. Surprisingly, the reaction is seldom encountered; reactions of amines with epichlorohydrin[516,517] yield β-amino epoxides, but these are stable to distillation and prefer to react with further epichlorohydrin than undergo exo:1,3 N—C:O:3 reactions.

3. *Exo:1,3 N—C:N:3*

Treatment of the *N*-sulfonylaziridine **153** with base produces a new aziridine with departure of the stabilized nitrogen leaving group:[518]



153

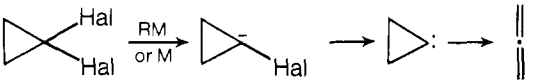
4. *Exo:1,3 C—N:N:4*

This type may be involved in the rearrangement of **135,** but an alternative is an exo:C=N process (section VII.B).[439]

IX. Endo Reactions

A. Endo:1,1:C:3. Cleavage of Cyclopropylcarbenes

The simplest reaction under this heading is the conversion of 1,1-dihalocyclopropanes to alkenes:[519]



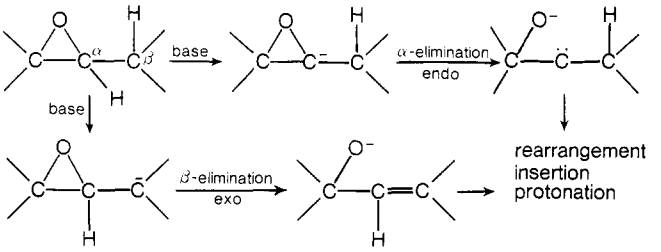
M = Li, Mg, Na

The mechanism of this reaction is not certain,[520] but carbenes have been proposed as intermediates[521] and products of inter- and intramolecular insertion[522] are consistent with this view. As elimination occurs to form a *cyclic* carbene which subsequently rearranges, the reaction is strictly outside the scope of this review and the reader is directed to other reviews.[523-525]

B. Endo:1,1:O:3. Cleavage of Epoxycarbenes

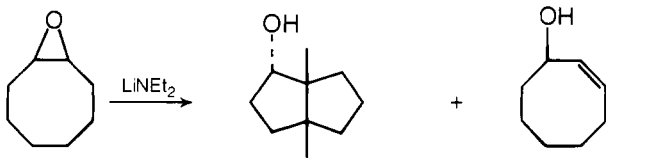
The general form of this reaction is given in Scheme XXVIII.

SCHEME XXVIII[a]



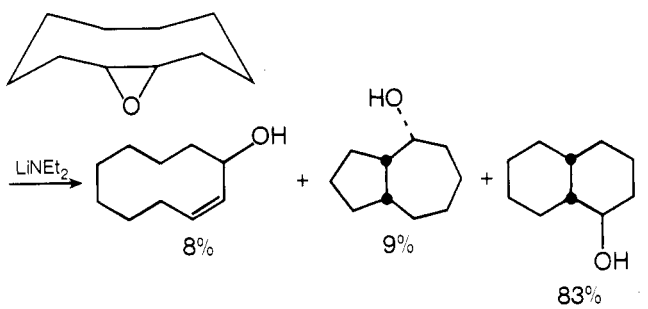
[a] Reactions may be stepwise, as shown, or concerted.

β-Deprotonation by the base gives the exo:C=C:O:3 pathway (section III.A), and in simple acyclic epoxides with β hydrogens, this is the sole eliminative route.[526] In medium-ring epoxides, products of both types of elimination are observed[125,160,161,527] (Table III), e.g.[125]



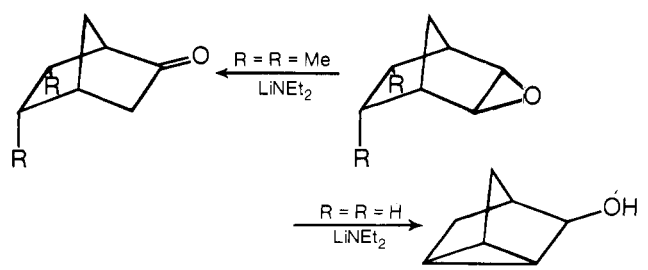
In this example, the major product results from α-deprotonation and endo ring fission with formation of the carbene and subsequent insertion into the C_5–H bond. 3,4-Epoxycyclooctene[527] behaves similarly. No exo process is observed in this instance presumably because β-elimination is sterically disfavored. The carbene produced gives both transannular insertion product and 3-cyclooctenone derived from hydrogen migration. By contrast, in the isomeric 5,6-epoxycyclooctene, β-elimination does compete[527] and no transannular insertion is observed.

In epoxycyclodecenes,[161] the geometric restraint on the exo:C=C:O:3 mode is reduced by the greater flexibility of the ring, and both it and the endo process occur together, the latter being detectable by deuterium labeling at the oxygen-bearing carbon atom. Both C_5[161,527] and C_6[161] insertions occur, e.g.[160]

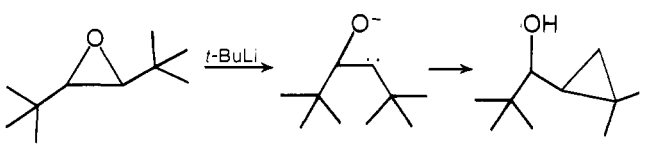


These and other transannular processes in medium rings have been reviewed.[528]

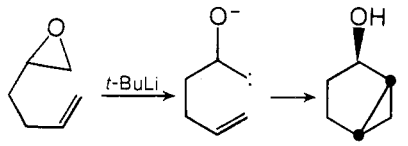
1,3-Insertion is characteristic of reactions of carbenes generated from epoxynorbornenes with strong bases.[529,530] When



the transannular insertion pathway is blocked by endo substituents, the alternative hydrogen migration to give a ketone occurs.[530] In these compounds as in epoxy-*tert*-butylethylene,[531] the exo:C=C:O pathway is blocked and in epoxydi-*tert*-butylethylene, 1,3-insertion to give a cyclopropane is found:[532]



Cyclopropanes are also formed in small yield by endo cleavage of epoxides followed by stereospecific intramolecular addition to a carbon–carbon double bond, further evidence of the involvement of carbenes:[532]



The endo:1,1 process, as strictly defined, is limited to epoxides, underlining again the poor leaving ability of carbon and neutral nitrogen leaving groups.[6]

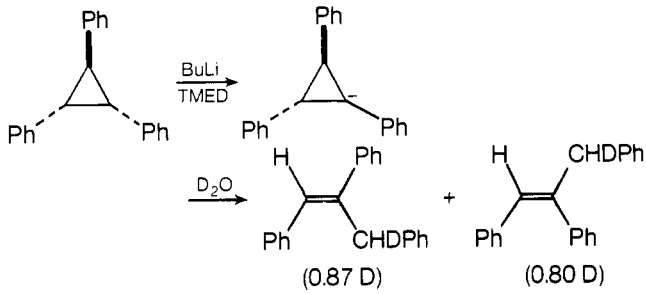
C. Endo:C=C:C:3

From the qualitative reports available, the endo:C=C reaction is not mainly restricted to the C:3 and O:3 modes, found in exo:C=C reactions. Ring strain and leaving group stabilization were seen to be important factors in the exo:C=C processes. In endo processes, alignment of the cleaving bonds suffers considerable restrictions which are worst for the smaller ring sizes although compensated for by the higher ground-state energies. Most examples have, however, required very strongly basic conditions.

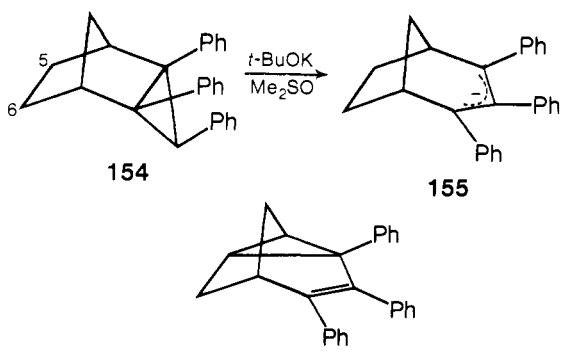
1. Poorly Stabilized Systems

trans-Triphenylcyclopropane with butyllithium cleaves to a mixture of alkenes[533] (Scheme XXIX). It is suggested that the

SCHEME XXIX



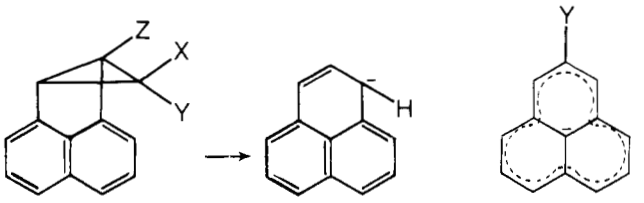
reaction is not concerted because a trans-coplanar arrangement of C–H and C–leaving group bonds cannot be achieved. Addition of butyllithium to triphenylcyclopropene similarly causes endo cleavage again, presumably, by way of an intermediate adduct anion.[533] In later work from the same group, the norbornane derivative **154** was reported to cleave under conditions which suffice for H/D exchange in *trans*-triphenylcyclopropane.[534]



Under severe conditions, ring opening to the ion **155** occurs in violation of the Woodward–Hoffmann rules if reaction is concerted. With a 5,6 double bond in **154** the product is **156.**

In a related system,[535] the lithium derivative (**157,** X = Li; Y

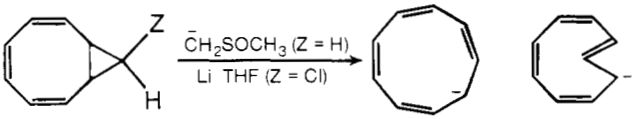
= Z = H) is protonated without ring fission even when the proton donor is a weakly acidic one such as tetrahydrofuran.



157 158 159

The bromide (**157,** X = Br; Y = H; Z = H) with butyllithium in THF undergoes halogen–metal exchange and subsequent protonation without ring opening and with retention of configuration. In hexane at 100 °C for short periods and subsequent treatment with D_2O, the product is the endo-deuterio compound (**157,** X = Z = H; Y = D). With an extended period of heating, ion **158** is obtained, as from the uncomplexed endo isomer (**157,** X = Z = H, Y = Li) to which the exo isomer is first converted. Ring opening must be disrotatory contrary to the Woodward–Hoffmann rules, and conditions are severe. The nitrile (**157,** X = CN, Y = Z = H) with lithium diethylamide in THF gives 2% of the blue anion (**159,** Y = CN). The isomeric lithium derivative (**157,** X = Y = H; Z = Li) also rearranges to **159** but with a hydrogen shift established by deuterium labeling to involve at least 57% of endo-proton (Y) migration.

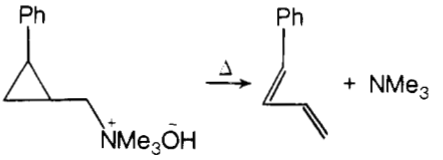
Formation of the 10π anion **161** has been accomplished by simple deprotonation (dimsyl anion) and endo:C=C:C:3 fission of the hydrocarbon **160** (Z = H):[536]



160 161 162

Treatment of the chloride **160** (Z = Cl) with lithium in THF gives the same result.[537-539] Later work showed that the expected product of conrotatory ring opening, the cis–cis–cis–trans structure **162,** is first formed and slowly isomerizes to the all cis structure.[540]

When elimination of a leaving group accompanies endo ring fission, the process occurs remarkably readily considering the moderate strength of the base and the poor activation of deprotonation:[541]



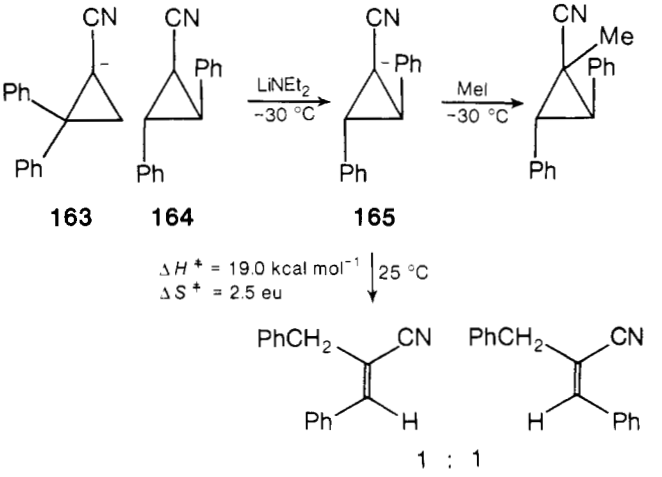
2. *Activated Systems*

In these remaining examples of endo:C=C:C:3 fission, proton removal is assisted by a carbanion stabilizing group such as CN, RCO, and notably, in the important early work of L. I. Smith, nitro. As noted earlier, conditions appear to be severer than those needed for deprotonation.

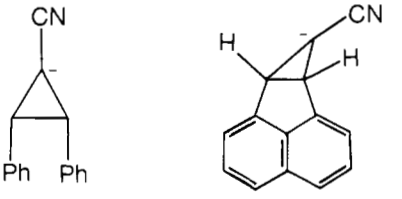
The ion **163** is stable to ring fission[542] (Scheme XXX), but with symmetrically disposed phenyl groups, the ion **165** can be characterized by alkylation at low temperatures and undergoes ring fission at higher temperatures to equal proportions of the *E* and *Z* alkenes.[543] Consistently, the rate of ring opening is independent of [base].

The reactivities of the cis (**166**) and trans (**165**) isomers have been compared.[544,545] The trans:cis ring-cleavage rate ratio is 43 at −25 °C, the difference being attributed to phenyl/proton interaction in the transition state for conrotatory ring fission. The

SCHEME XXX



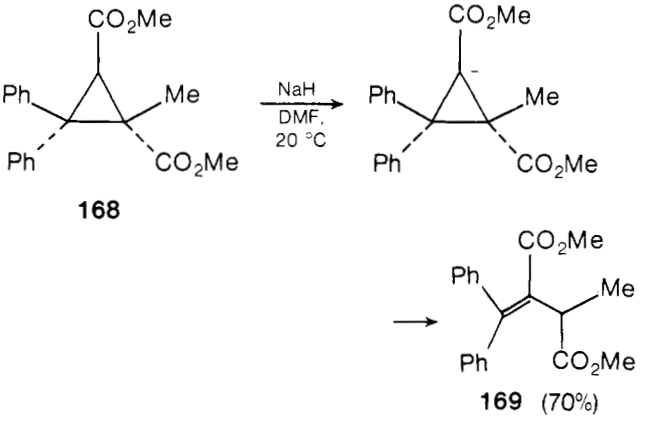
cis isomer opens 1.1 × 10^4 faster than the related ion (**167**), demonstrating the disfavorment of the disrotatory ring opening required in this structure. Rather similar behavior is seen in the



166 167

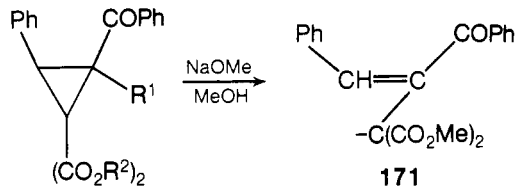
carboxylic acids corresponding to **164** and **165**;[546] deprotonation is probably rate determining for the trans isomer and ring fission for the cis isomer. These are again much more reactive than the analogue of **167.**

In all the following systems, ring cleavage follows after generation of a stabilized carbanion at a ring atom, provided that the carbon leaving group is also stabilized. Treatment of the diester **168** with sodium hydride causes[547] ring fission in good yield. The anion precursor of the product (**169**) is stabilized by the terminal groups, and, as mentioned above, cyclopropyl anions without stabilizing groups at *both* termini are relatively stable.[542] Ring



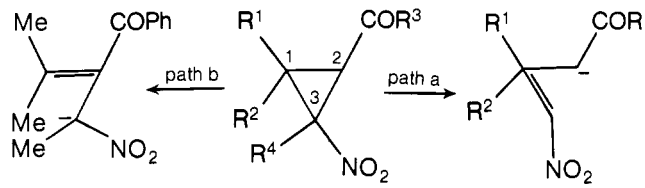
fission is very much slower than deprotonation; cis–trans equilibration in **168** occurs without ring scission in more mildly basic conditions.

Extensive studies of eliminative cleavage of activated, particularly nitro-, cyclopropanes have been made in the "pre-physical methods" period of 1910–1950. In the earlier work, Kohler and his collaborators showed that the cyclopropane **170** (R^1 = Me, R^2 = Et) gave no reaction with methanolic sodium methoxide.[548] With R^1 = H, however, ring opening gives the anion **171.**[549]



170 171

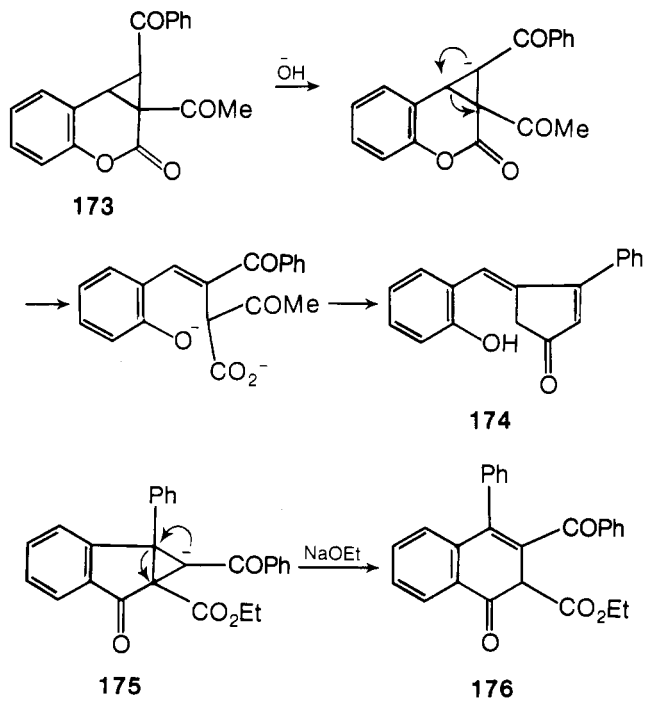
In cyclopropanes of type **172** in which $R^1 = R^4 = H$, $R^2 = Ph$, and R^3 = aryl[550] or alkyl[551] or, alternatively, $R^1 = R^2 = Me$, $R^4 = H$, and R^3 = aryl[552] or alkyl,[553] ring fission occurs by removal of the most (thermodynamically) acidic proton at C_3. Eliminative



172

cleavage of the C_1–C_2 bond follows, the leaving group being stabilized by the acyl group (path a). The end products usually result from elimination of nitrite from the primary products. When the nitro group is tertiary,[554,555] e.g., in **172** ($R^1 = R^2 = R^4 = Me$; $R^3 = Ph$),[554] cleavage occurs by removal of the proton at C_2 with C_3 as leaving group (path b). Elimination of a nitro-stabilized carbanion in an endo process activated by a nitro group (**172,** $R^1 = R^2 = Me$, $COR^3 = NO_2$; and $R^4 = H$) has more recently been demonstrated.[556] With mild base, H/D exchange occurs without ring fission, suggesting an $(E_1cB)_R$[6] mechanism for the reaction. Endo cleavage of nitrocyclopropanes has been reviewed briefly.[557]

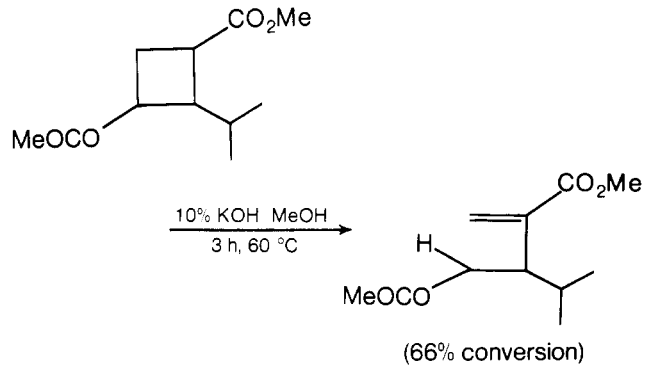
Endo:C=C:C:3 processes following the same pattern have been suggested in the conversion of the coumarin derivative **(173)** to the cyclopentenone (**174**).[558]



173 174 175 176

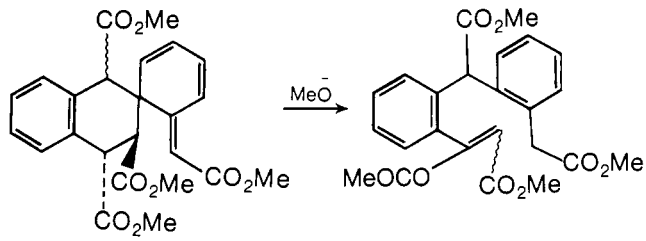
D. Other Endo:C=C:C

There are few instances. Maercker[10] has shown (above) that cyclobutylmagnesium halides are not involved in the equilibration of cyclopropylmethyl with butenylmagnesium halides. When deprotonation is activated *and* the leaving group is stabilized, a very slow endo:C=C:C:4 reaction can be achieved:[560]



(66% conversion)

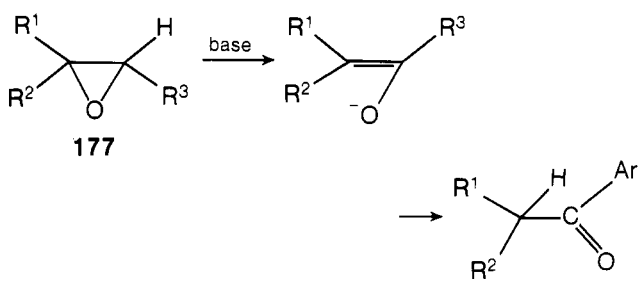
A particularly interesting example of an endo:C=C:C:6 reaction[561] involves a methylenecyclohexadienyl anion as leaving group further stabilized by attachment of a carbalkoxy group to the resonant system:



Carbon leaving groups are notoriously poor even when stabilized,[6] and there is little if any assistance from ring strain. The fact that the endo elimination is observable must be attributed to the exceptionally favorable situation of the leaving group.

E. Endo:C=C:O:3

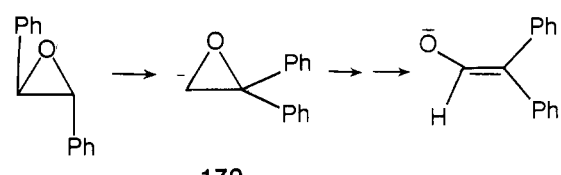
Epoxides which do not possess C–H bonds β to the ring undergo endo elimination with bases, giving aldehydes or ketones:



177

In poorly activated systems, e.g., **177** ($R^1 = R^2 = R^3$ = aryl), lithium diethylamide is required for the reaction;[562] the tetraphenyl compound (**177,** H = Ph) lacking an appropriate proton does not react. The bisaryl compound (**177,** $R^1 = R^2 = Ph$; $R^3 = H$) lacks a proton sufficiently acidic for its removal to initiate this reaction under these conditions, and only substitutive ring fission occurs. Phenyllithium, however, is a strong enough base to divert about 8% of the reaction to endo elimination in this epoxide,[563] and the resulting aldehyde reacts to give a secondary alcohol.

In a *trans*-1,2-bis(aryl) epoxide **178,** 1,2-phenyl migration before ring fission is suggested to occur in the anion **179.**[562] The

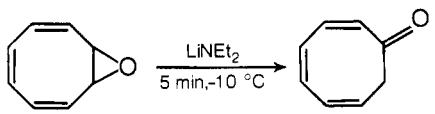


178 179

cis isomer undergoes simple endo:C=C:O:3 cleavage giving deoxybenzoin.[562]

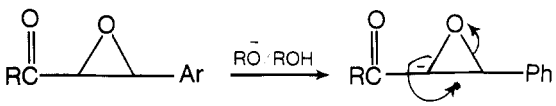
It does not seem likely[110] that unsaturation in polypropylene oxide is due to endo :C=C: elimination under the rather mild conditions used.

Epoxycyclooctatetraene **180** gives the ketone **181** rapidly in high yield in an analogous way:[564]

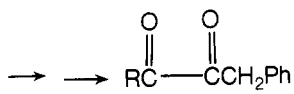


180 **181** (95%)

Endo elimination in epoxides is promoted by carbanion-stabilizing substituents attached to the ring, and many examples[483,565-571] are known to conform to the general pattern seen in epoxychalcones:

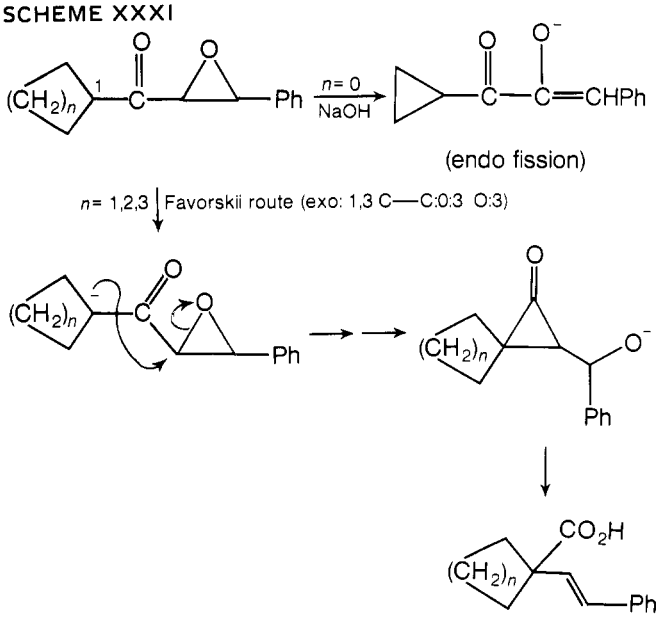


182

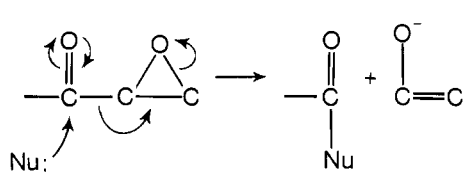


Cromwell and Setterquist have noticed[570] that for **182** (R = Ph and Ar = *o*-nitrophenyl), cis–trans equilibration under basic conditions occurs faster than endo ring fission, pointing to a preequilibrium carbanion mechanism with ring fission rate determining. Further indication that endo ring fission of epoxides is quite a difficult reaction is given[483] by the products from a series of epoxides (Scheme XXXI). Only when $n = 0$ and ring strain inhibits stabilization of a carbanion at C_1, does the endo fission occur. In larger rings, the carbanion developed at C_1 causes exo:C—C:O:3 fission of the epoxide in a Favorskii type of reaction (section VIII).

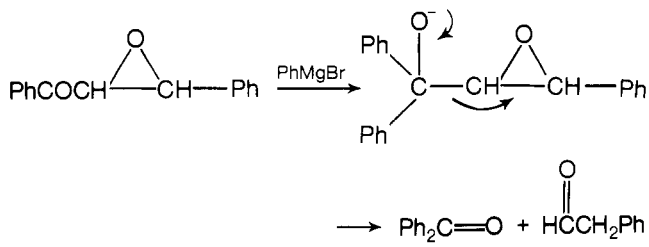
SCHEME XXXI



Fragmentation in α-oxo epoxides is sometimes observed[369,571] following the pattern:



as in reaction of phenylmagnesium bromide with epoxychalcone:[571]



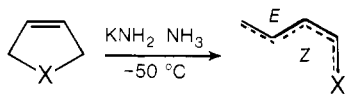
and of hydroxyl ion with a tricyclic epoxy ketone[369] (section V).

F. Endo:C=C:O:4

This type of reaction does not appear to have been described.

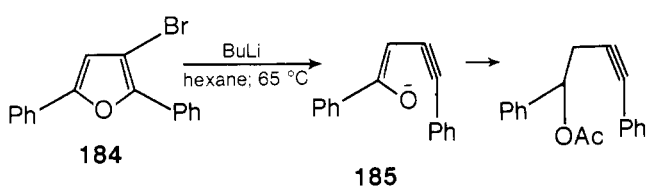
G. Endo:C=C: and -C≡C:O:5

Strong bases cause ring opening of dihydrofuran and thiophene derivatives stereospecifically[572] to the *E*/*Z* anion (**183**, X = O, S, SO_2) which does not convert to the *E*/*E* anion.

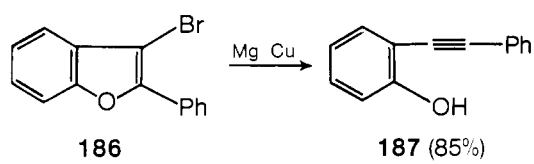


183

Several examples[573-576] of endo fission of furans to give acetylenes are known. Typically, in the furan **184**, halogen–metal exchange is followed by ring cleavage to the ion **185** trappable with acetic anhydride. Treatment of the benzofuran **186** with Mg/Cu alloy likewise causes ring opening to the acetylene **187**.[577]

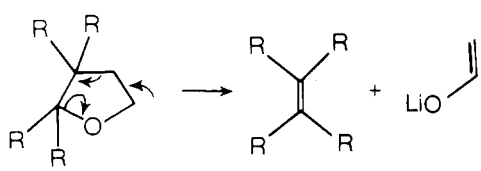


184 **185**



186 **187** (85%)

Tetrahydrofuryl anions (**188**) produced from THF and butyllithium[578] or propylsodium[579] undergo endo elimination with fragmentation. Activation of the process is seen in an unusual elimination–addition reaction of the ketosteroid **189**.[580]



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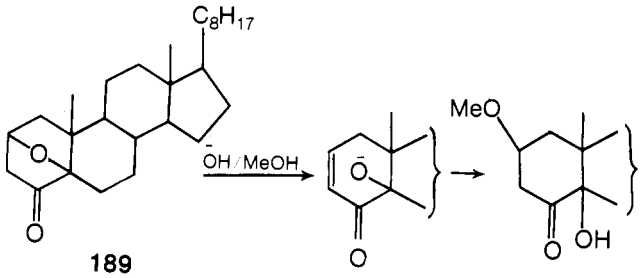
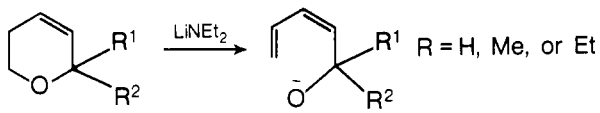


189

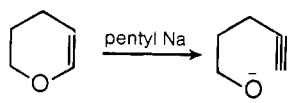
H. Endo:C=C:O:6

In a manner very similar to that described in the previous section, the poorly activated system **190** undergoes eliminative ring fission with strong bases:[581]



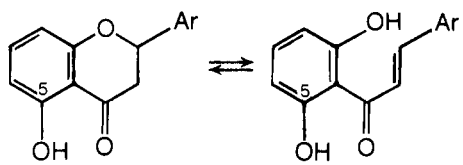
190 (50–70%)

The isomer **191** with pentylsodium gives the γ-acetylenic alcohol by endo:C≡C fission:[582]



191

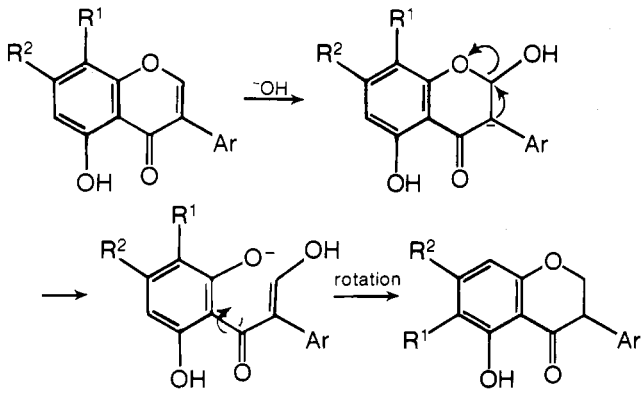
Flavanones and chalcones equilibrate in alkali, the flavanone → chalcone conversion being an endo:C=C:O:6 reaction:



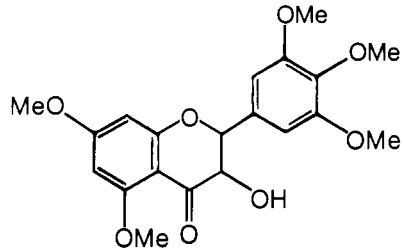
Equilibration is highly dependent on the hydroxyl substitution. With three free hydroxyl groups on aromatic nuclei including C_5, the flavanone is stable. An ionized hydroxyl group close to the site of deprotonation presumably inhibits this process in the elimination reaction although intramolecular hydrogen bonding is alleged to "stabilize the ring".[583] With two free hydroxyl groups and the hydroxyl group at C_5 absent, equilibrium constants around unity are found.

In a similar way, flavones and isoflavones undergo isomerization initiated by an endo:C=C:O:6 reaction[584] (Scheme XXXII), and analogous behavior is seen in flavonones.[584,585] Flavanones racemize readily in basic conditions, consistent with an eliminative ring fission and reclosure.[584]

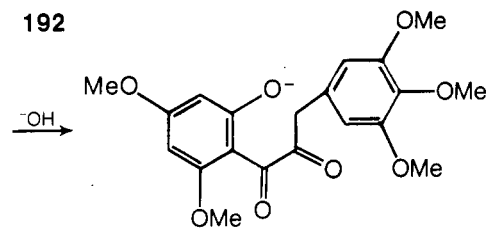
SCHEME XXXII



Dihydroflavonols (e.g.,**192**) are also unstable to bases, endo:C=C:O:6 elimination occurring under activation by the oxo group.[586] Dihydroxyflavanones, however, are stable to base



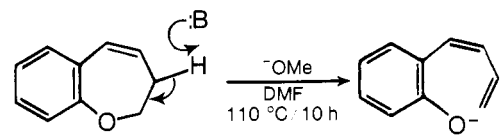
192



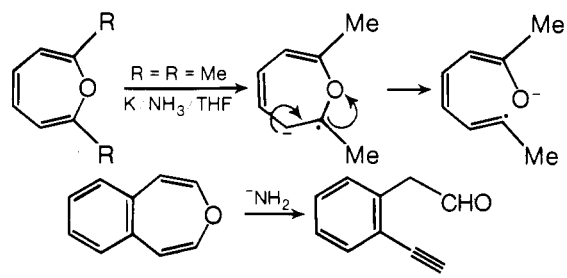
because, presumably, further deprotonation is disfavored. The monohydroxy derivatives, however, react.[587]

I. Endo:C=C:O:7

The known examples involve cleavage of poorly activated cyclic ethers under strongly basic conditions:[588]

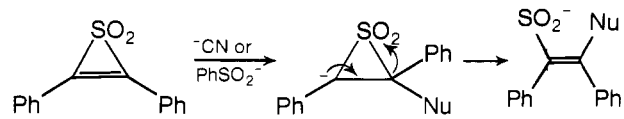


Endo fission in the same system but without the benzo group has been described[589] and in oxacycloheptatrienes, endo fission both by electron transfer and deprotonation occurs:[590]



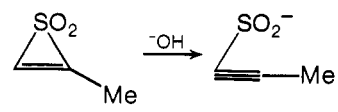
J. Endo:C=C:S:3

Three-membered rings containing sulfur are not very common and examples of this process are rare. Addition of nucleophiles to thiirene dioxides gives an ion which undergoes endo elimination:[591]



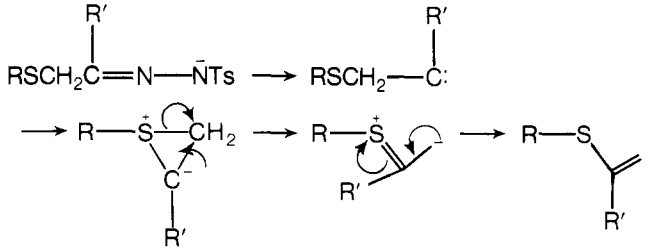
Ring opening has to compete with desulfination and is favored in aprotic solvents.

In the cleavage of the thiirene dioxide **193**,[592] the sulfinate ion produced is titratable, and it is notable that this process is



193

SCHEME XXXIII



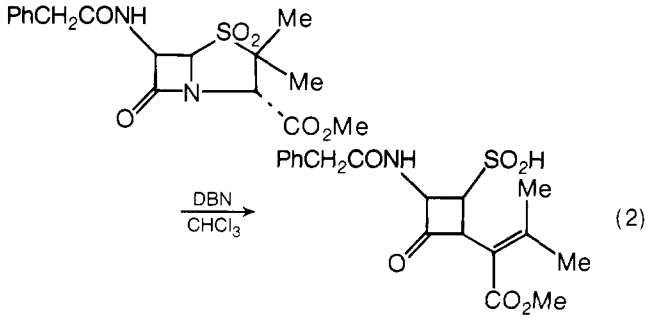
preferred to attack at sulfur. With two methyl groups attached to the ring, an exo:O=S:C:3 reaction may occur[449] (section VII). Decomposition of tosylhydrazones of β-keto sulfides yields vinyl sulfides putatively as shown in Scheme XXXIII.[593]

K. Endo:C=C:S:4

This type of reaction is apparently unknown.

L. Endo:C=C:S(Se):5

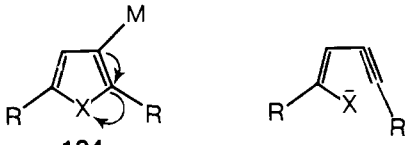
A substantial number of reactions in the penicillin series are known to involve cleavage of the thiazolidine ring. They follow the pattern:[594]



(2)

and the sulfur atom may be in various oxidation states. Ring fission reactions in the penicillin field have been reviewed recently.[595]

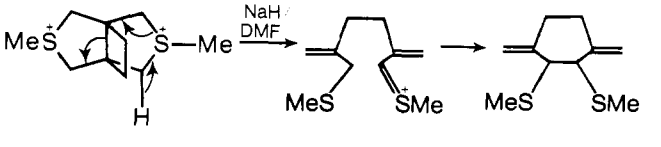
The second common type of endo:C=C:S:5 reaction is the cleavage of 3-thienyl organometallics.[596] Formation of the lithium derivative **194** (M = Li, R = Me) by halogen–metal exchange is followed by rapid ring scission when X = Se,[597,598] and the ion **195** is trappable by alkylation with the halide formed by exchange. When X = S, the lithium derivative **194** is much



194 **195**

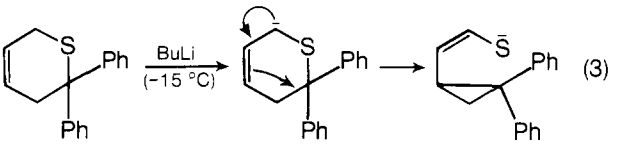
more stable and at −70 °C carbonation, for example, yields the thiophene-3-carboxylic acid.[599] At 25 °C, the lithium derivative ring opens and the isomeric ion **195** may be characterized by alkylation.[600] Recently, it has been shown[601] that 2-thienyllithium derivatives with an alkyl group or hydrogen atom at C_5 deprotonate at C_3 with further butyllithium in HMPA giving ring opening to ene–yne thiolates. These further eliminate sulfur to give dialkyldiacetylenes. Directly analogous reactions are seen in benzo[*b*]thiophene derivatives[602-606] and in thienothiophenes.[607]

Unusual examples of endo:C=C:S:5 fission have been reported by Lantos and Ginsburg[608] in propellane-type structures:



M. Endo:C=C:S:6

In the few known instances, the leaving group varies in stability from thiolate[609] (eq 3) and an oxo-activated example[610] (eq 4), through sulfinate[611] (eq 5) to sulfonium[612] (eq 6). In this



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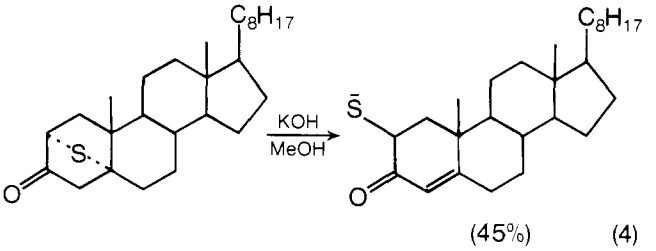
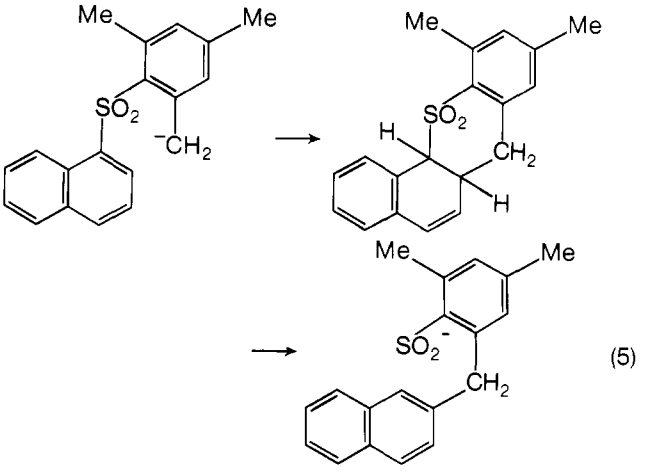


(45%) (4)



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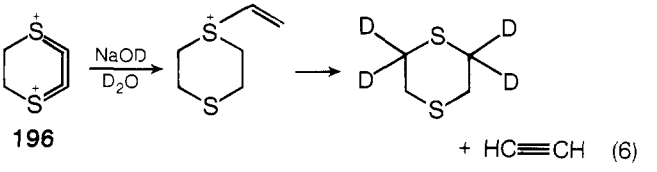


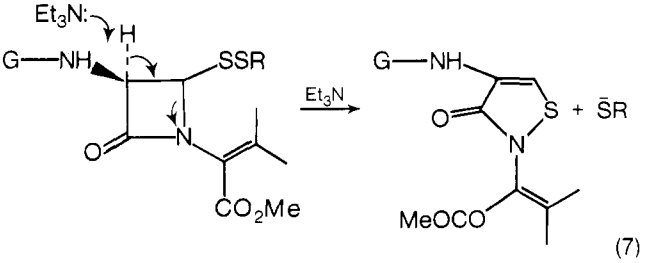
196 (6)

case, labeling in the product shows that endo fission is faster than H/D exchange in **196.**

N. Endo:C=C:N

Nitrogen as a neutral atom is a reluctant leaving group in both alkene[605] and carbonyl-forming[511] eliminations.

The endo:C=C:N:3 mode does not appear to have been reported, but the endo:C=C:N:4 process occurs in azetidinones related to penicillin[613] (eq 7). In this example, amido is the



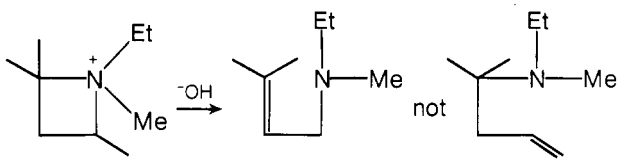
(7)

leaving group; strain is clearly assisting considerably. In acyclic systems, severe conditions are required with greater activation.[605]

Nitrogen departs in an endocyclic fragmentation which follows an exo:1,5 O—C:O:3 process[509] (section VIII).

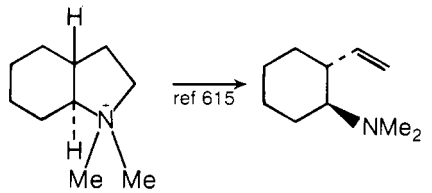
The most common instance of this reaction involves departure of the good[6] leaving group $-NR_3^+$. Quaternary salts of cyclic amines readily undergo Hofmann degradation via β-deprotonation, a reaction that has been important in classical studies of alkaloid structure[203] (see also section IV).

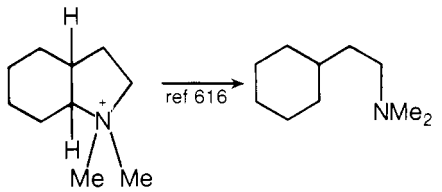
Competition between exo- and endo:C=C:N:4 eliminations has been discussed above (section IV). In the salt **197**, endo elimination is preferred, and the benefit of ring strain obviates elimination in the *N*-ethyl group:[614]



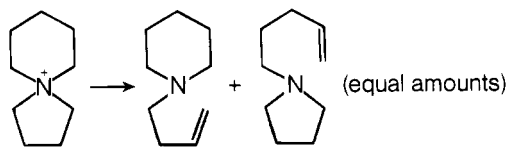
197

Endo:C=C:N:5 elimination occurs normally under strong stereodirection requiring a trans-coplanar proton



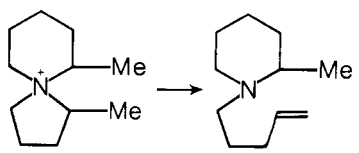


In the spiro salt **198** there is no distinct preference for either endo:5 or endo:6 modes,[617] but an α-methyl group switches

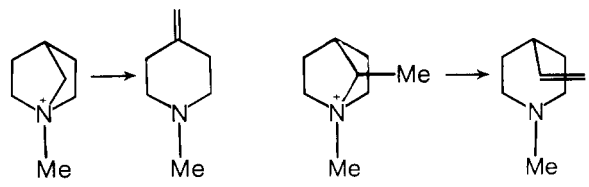


198

elimination exclusively to the exo:C=C:N:5 mode,[617] although the exo mode in a six-membered ring salt is known[210] (section IV).

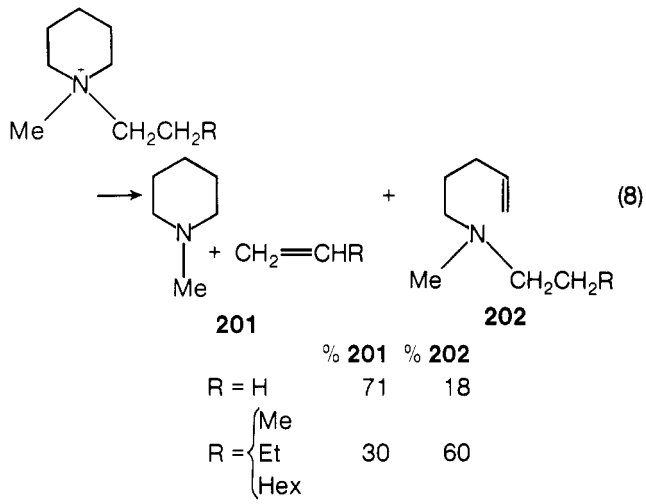


By contrast, in the bridged system **199**,[618] fission of the five-membered ring is exclusive, but the exo process dominates when structurally possible as in **200**.[619]



199 **200**

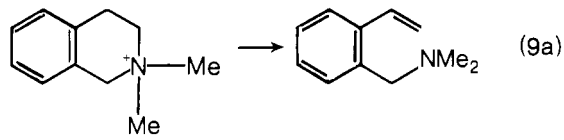
The balance between endo:C=C:N:6 fission and elimination through an *N*-alkyl group is delicately held[620] (eq 8). Benzylic

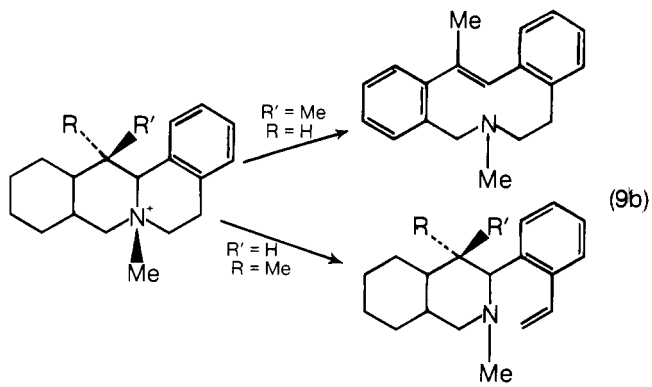


201 **202**

	% **201**	% **202**
R = H	71	18
R = Me		
R = Et	30	60
R = Hex		

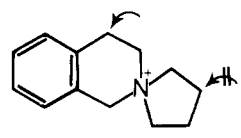
activation of the endo:6 reaction is common[621] (eq 9a). Stereospecificity is again strict[622] (eq 9b). In the first case, the





availability of an antiperiplanar proton allows preferential removal of a tertiary proton in preference to an unhindered secondary proton.

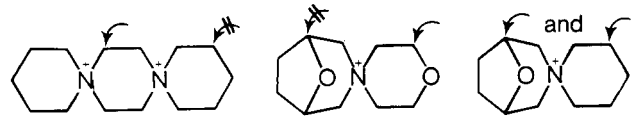
Benzylic activation leads to endo in preference to exo elimination[211] (section IV) and also swings the balance between endo:5 and endo:6 fission in **203**.[623] When both endo and exo



203

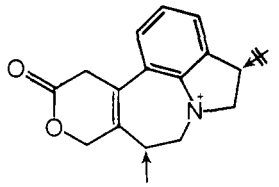
eliminations are benzylically activated, the latter is preferred[212] (section IV).

Endo:6 elimination appears to be inductively activated (**204**),[624] though effects are not strong: **205**[625] and **206**.[625]



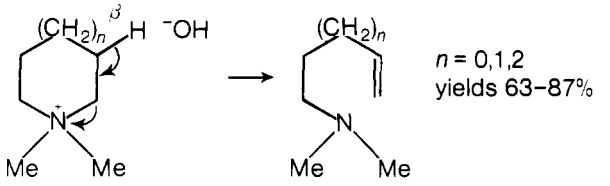
204 **205** **206**

Endo:7 elimination is preferred to the endo:5 reaction when both are comparably activated (**207**).[626]

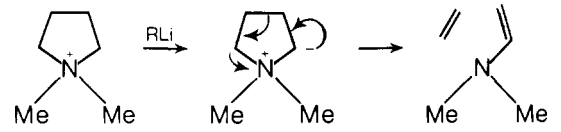


207

A range of cyclic quaternary salts has been investigated by Wittig's group.[627] When very strong bases are used, the ther-



modynamic acidity of the proton removed determines the reaction course. With butyl-[628] or phenyllithium,[629] the α-proton is removed and this initiates an endo fragmentation which does not involve an $\alpha'\beta$ reaction:

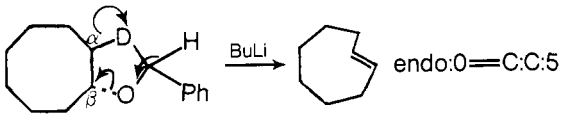


In complex alkaloids such as tubocurarine,[630] both exo: C=C:N:6 and endo:C=C:N:6 reactions occur side by side, but the exo mode is favored when β-H is benzylic and a stilbene system is generated.

O. Endo:O=C:C and O

1. Carbon Leaving Group

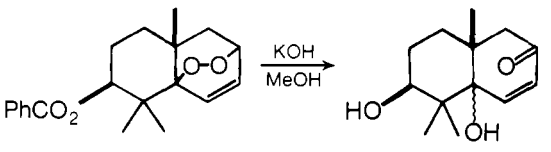
Recent examples of this uncommon reaction have been reported by Whitham in fragmentation reactions,[631,632] yielding alkenes. The reactions are applicable to stereospecific syntheses,



and are analogous to reversal of symmetry-allowed addition of an allylic anion to an alkene.

2. Oxygen Leaving Group

By definition, the reaction type refers to cleavage of endocyclic peroxides in five-[633] and six-membered rings.[634-636] All examples with six-membered rings are from the terpene series and the proton is abstracted from allylic carbon, e.g.[636]

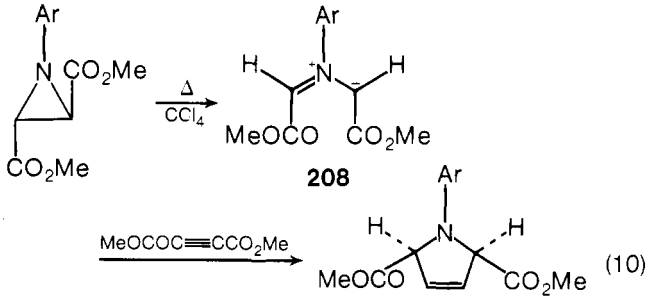


Only mild conditions are required; carbonyl-forming eliminations are unselective as to leaving group (see above) and the bond broken is weak.

P. Endo:N=C, O, and S

1. Carbon Leaving Groups

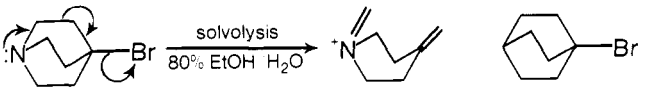
Suitably substituted aziridines undergo[637] conrotatory ring opening (eq 10) and the zwitterion **208** is stereospecifically



208

trappable provided that a sufficiently reactive dipolarophile is present. Disrotatory fission occurs under irradiation.[637] Cleavage of aziridinyllithiums occurs similarly.[638]

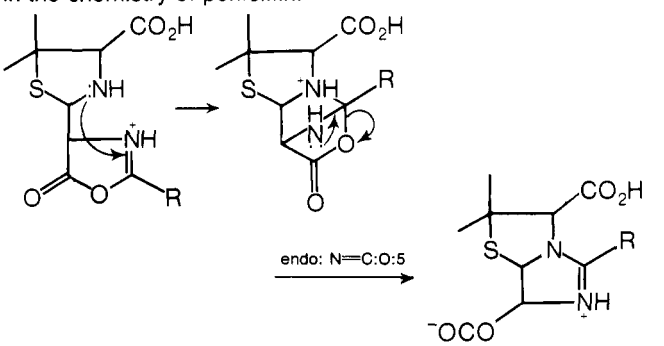
The endo:N=C reaction is also represented in numerous fragmentation reactions described by Grob and his collaborators.[365] A striking example is the fragmentation of quinuclidine derivatives,[639] which occurs 5.5 × 10^4 faster than for **209.**



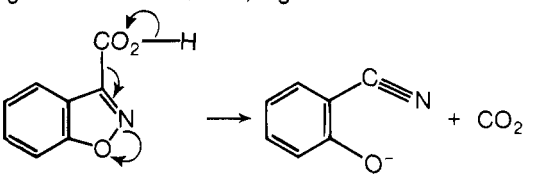
209

2. Oxygen and Sulfur Leaving Groups

The leaving group has considerable stability (on a pK_a LG-H criterion) in the reported examples. An interesting one appears in the chemistry of penicillin:[640]



and much more recently detailed studies due to Kemp[641,642] and others[643] have been made of nitrile forming eliminations in the cleavage of benzisoxazolines, e.g.[642,644]

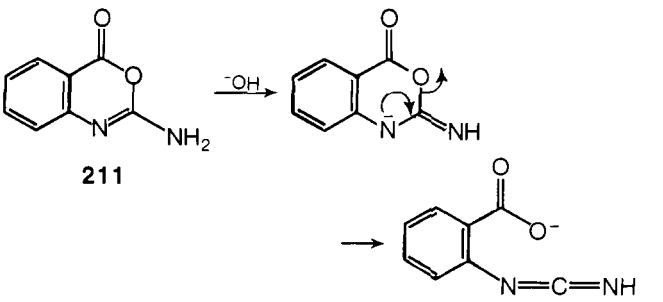


210

(endo:C≡N:O:5)

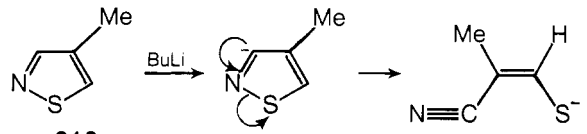
In this case, rates of fission are increased 10^8 fold by transfer from water to HMPA because of desolvation of the carboxylate ion.[645] Crown ethers have similar, smaller effects,[643] and in the simplest system (**210,** CO_2H = H)[641] cleavage is promoted by bases in an E2 reaction[646] for which the proton transfer process is highly defined.

An endo:N=C:O:6 process is suggested for the hydrolysis of the oxazine **211:**[647]



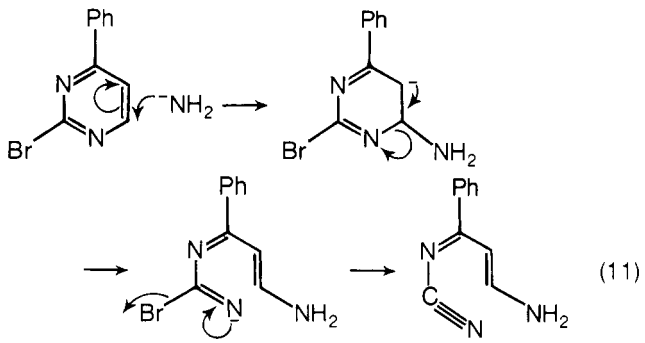
211

Endo:N≡C:S:5 fission of the isothiazole **212** produces the anion **213** alkylated by excess of butyl bromide in the medium.[648]



212 **213**

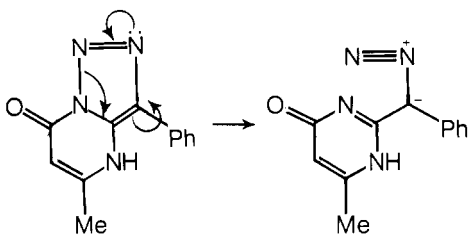
A series of ring fissions of triazines and pyrimidines has been described by Van der Plas and his collaborators,[649,650] e.g.,[649] eq 11.



(11)

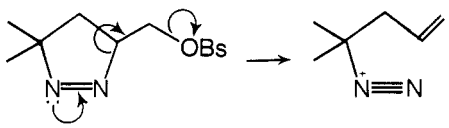
Q. Endo:N=N and N≡N

Examples involving carbon leaving groups are seen in rearrangement of **214**:[651]



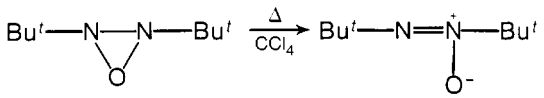
214

and fragmentation of **215**,[652] a diazonium ion being the initial product in each case. Again, departure of a carbon leaving group is encouraged by stabilization or fragmentation.



215

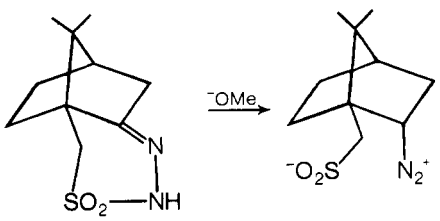
Oxygen is the leaving group in thermal rearrangement of the oxazine **216**:[653]



216

($t_{1/2}$ at 28 °C = 290 min)

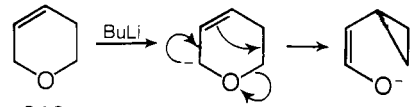
and sulfur in the ring fission of the sulfonylhydrazide derivative **217**:[654]



217

R. Endo:1,3 C—C:O:6

This process may be involved in cleavage of the dihydropyran **218**,[655] but the mechanism is not clear.



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X. Conclusions

A. Eliminative ring fission is a common reaction but subject to structural limitations which arise from limitations on the nature of the leaving group. Halogens, the most common type of leaving group in simple eliminations, are, of course, excluded. 'Onium leaving groups, which figure in a large number of exo and endo C=C:N processes, are also familiar in reactions in which ring fission is not involved. Carbanion and alkoxide leaving groups, the most common in eliminative ring fission, are rare in acyclic eliminations except when these are carbonyl or phosphonyl forming.

B. Summing up is appropriate for the three most common reaction types.

(a) Alkene-Forming Eliminations. These are very sensitive to leaving group variation. With the exception of 'onium leaving groups, reactions require substantial leaving group stabilization or ring strain or both. Consequently, the most common examples are exo:C=C:C- and -O:3 and endo:C=C:C:3 processes. Carbon–carbon bond cleavage, while almost unknown in acyclic alkene-forming eliminations, is particularly assisted by ring strain.

(b) Exo Higher Order Eliminations. These have even greater selectivity with respect to the leaving group. A large degree of ring strain is a *sine qua non*, and reactions are almost entirely confined to cyclopropanes and epoxides.

(c) Carbonyl-Forming Eliminations. These are the least selective with respect to the leaving group. Ring strain is thus a less important requirement for the reaction and exo:O=C:C:5 and -6 processes are common.

C. In spite of the widespread qualitative recognition of the importance of ring strain in almost all types of eliminative ring fission, very little mechanistic information is available. Recent work in the reviewer's group excepted, there has been *no* assessment of the contribution of ring strain to reactivity in reactions for which ring fission is rate determining.

D. There is a very wide range of reactions susceptible to the evaluation of ring strain and some of the largest observable effects of structure on reactivity are to be expected in this field. A particularly interesting aspect of eliminative ring fission is the evaluation of the contribution of ring strain to reactivity as the type of reaction and hence the degree of ring cleavage in the transition state varies.

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