Chapter 7

Reactivity of Carbonyl Compounds

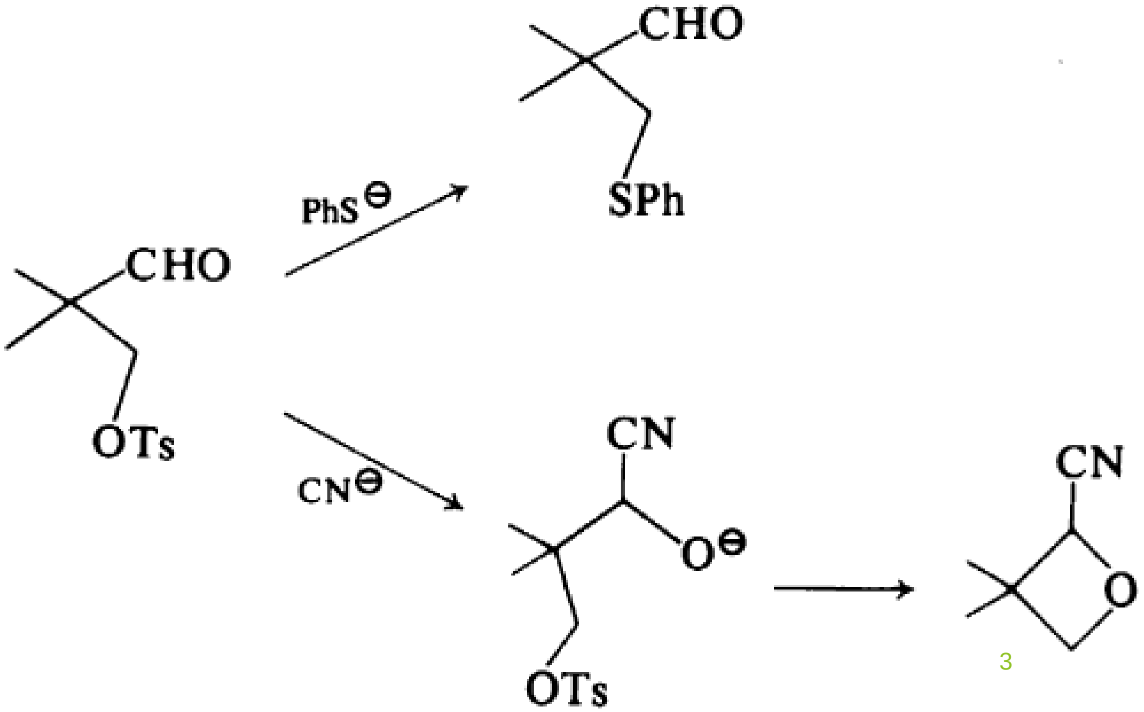
THE CARBONYL GROUP AS A HARD ACCEPTOR AND A HARD DONOR

The carbonyl group has a hard donor oxygen and a fairly hard acceptor carbon. For electrophilic attack, hard bases are preferred.

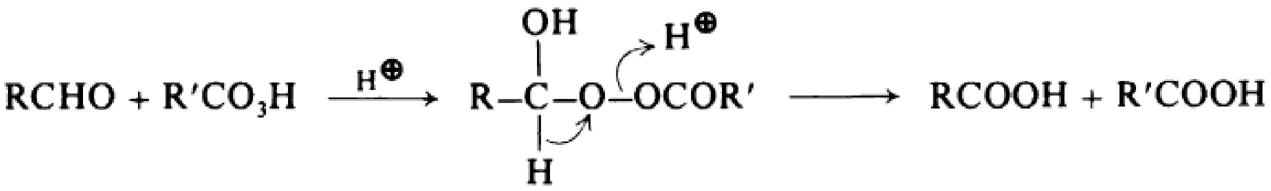
The ordinary carbonyl derivatives such as hydrazones, oximes, and semicarbazones are the condensation products derived from hard-hard interactions.

Soft bases such as alkylphosphines do not attack the carbonyl carbon under normal conditions.

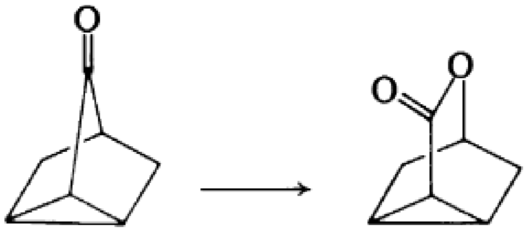
It is noteworthy that the soft benzenethiolate displaces the tosyloxy group, whereas the harder cyanide ion adds to the carbonyl group of 3-Tosyloxypivaldehyde. The tosyloxy group is then extruded from the cyanohydrin in a symbiotically favored process.



Baeyer-Villiger Oxidation



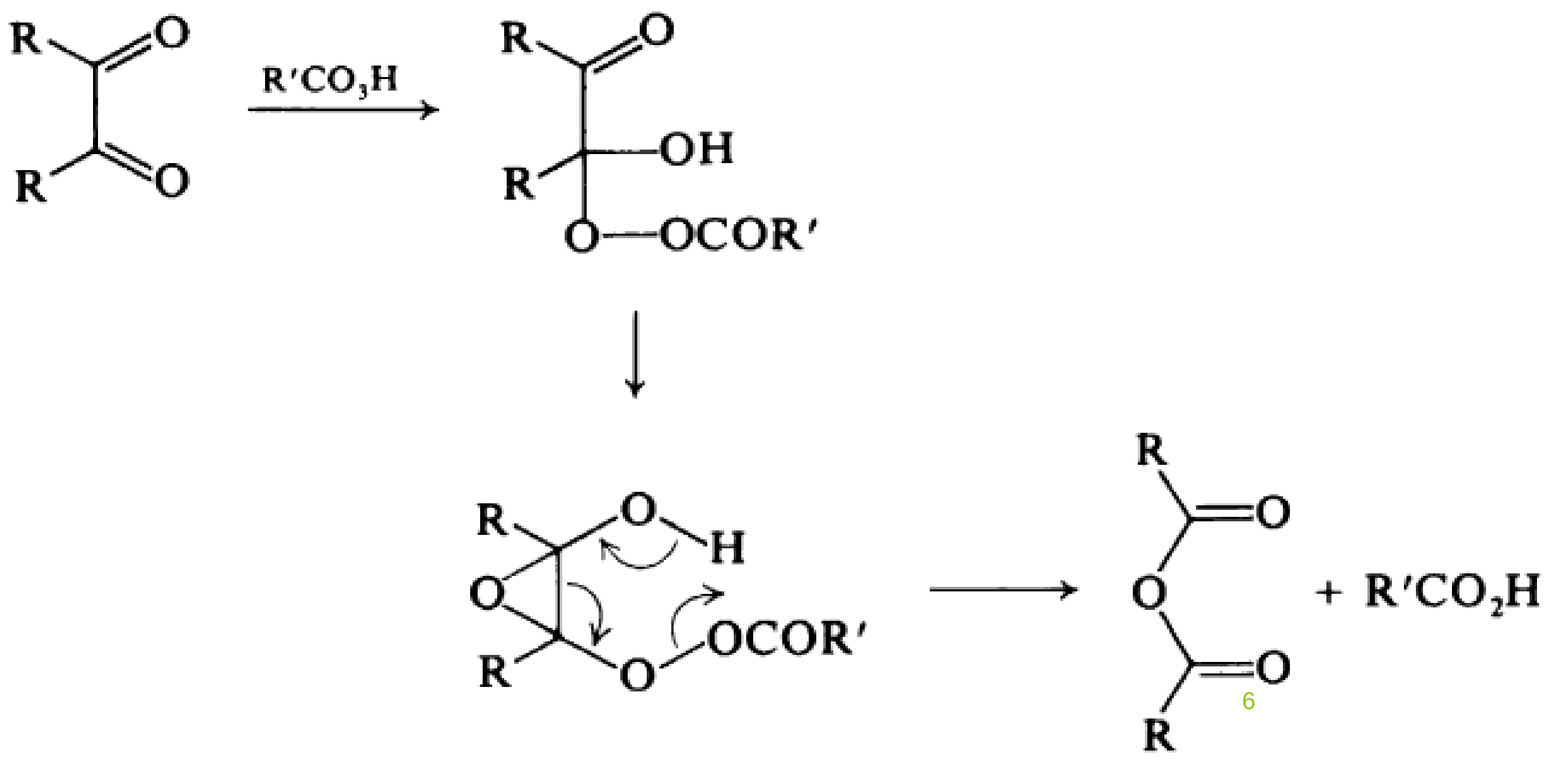
$$\mathrm{RCHO + R'CO_3H \xrightarrow{H^{\oplus}} R-\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-O-\overset{H^{\oplus}}{OCOR'} \longrightarrow RCOOH + R'COOH}$$



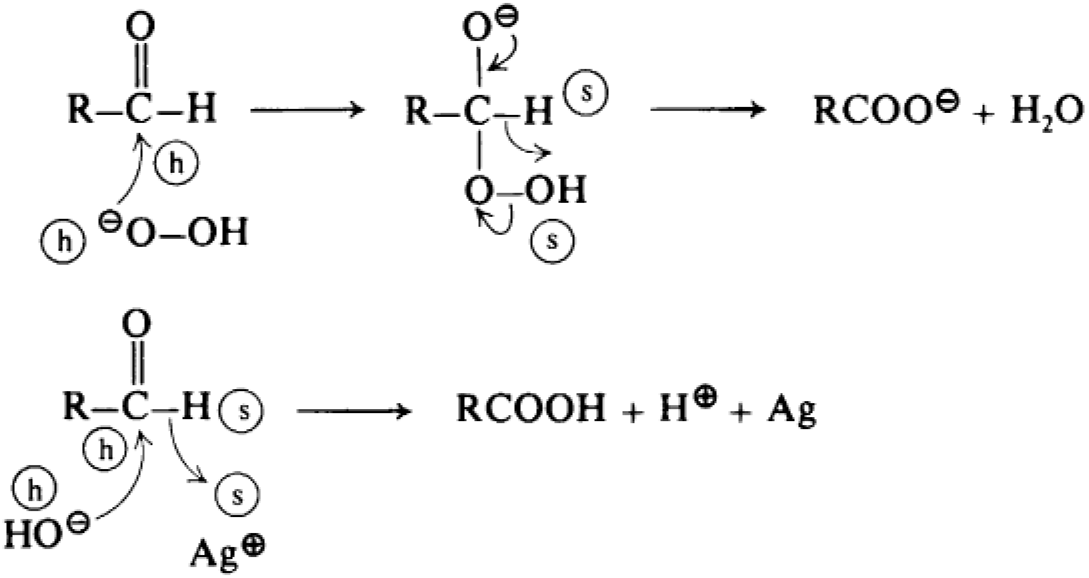
For unsymmetrical ketones, the approximate migratory aptitude for the alkyl groups follows the softness order tertiary >secondary > primary.

The greater migratory aptitude of aryl groups over the alkyls during the Baeyer-Villiger oxidation and related processes is due to the participation of the soft π system.

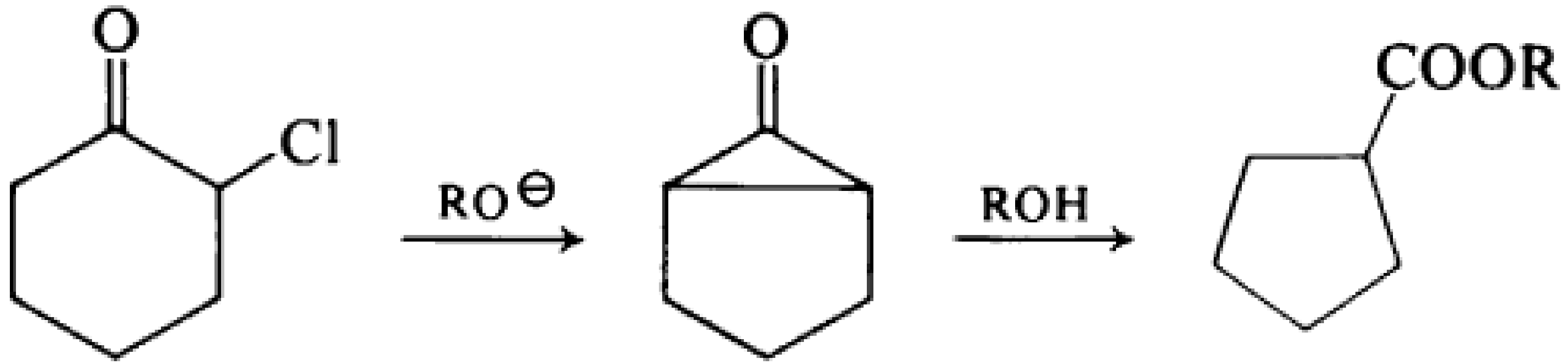
The oxidation of α-diketones to anhydrides by peracids appears to involve the hard carbonyl as migrant. mechanism may be formulated as follows.



Aldehydes are also oxidized to the corresponding carboxylic acids by either alkaline hydrogen peroxide or silver oxide. Saville's rule 1 is obeyed in both cases.

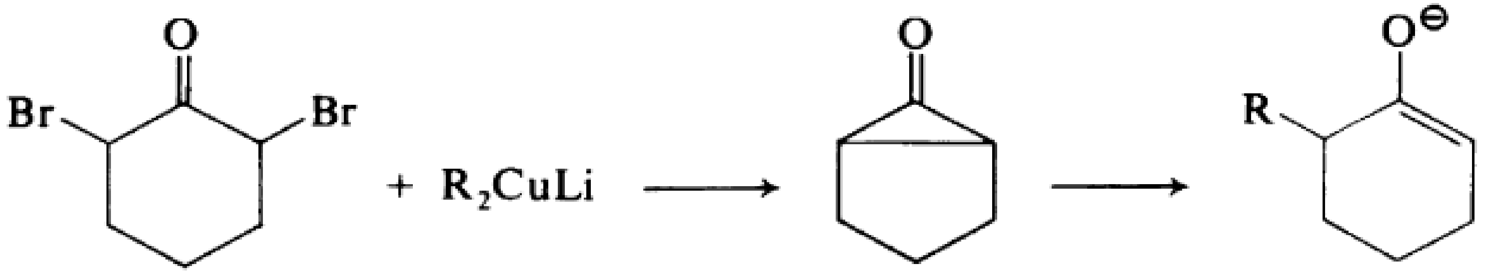


Favorskii Rearrangement



The conversion of α-haloketones to esters [Favorskii rearrangement] by alkoxide ions usually occurs via the Loftfield mechanism

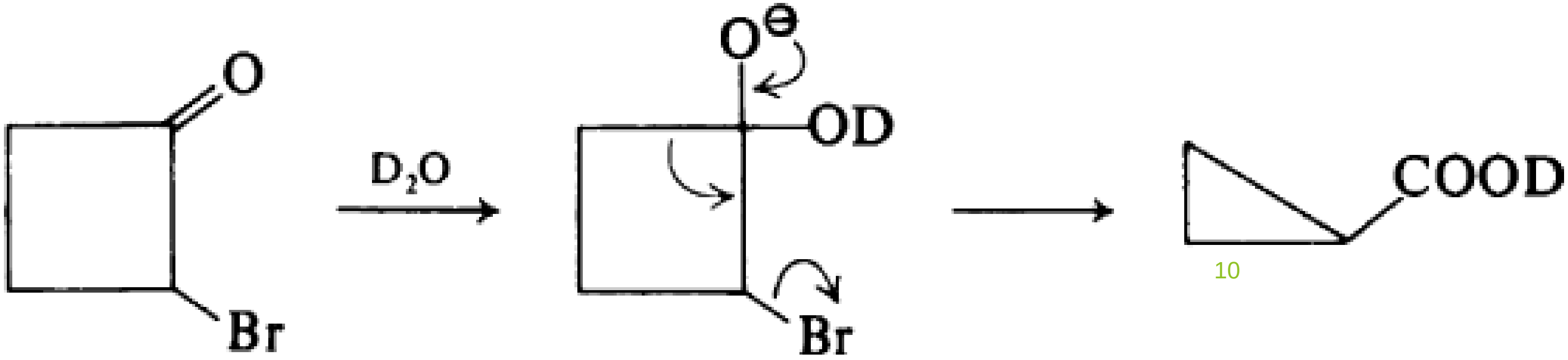
Treatment of α,α'-dibromoketones with lithium diorganocuprates gives rise to the Loftfield intermediates which undergo ring opening to generate enolate ions. Every step of the sequence represents a soft—soft interaction.



In Favorskii rearrangement of 2-bromocyclobutanone, the unusual hardness of the cyclobutanone carbonyl carbon certainly contributes to its electrophilicity toward hard donors such as water.

The increased hardness of the small ring ketonic carbon is due to the lower p character of its bonds (exocyclic) to the oxygen atom.

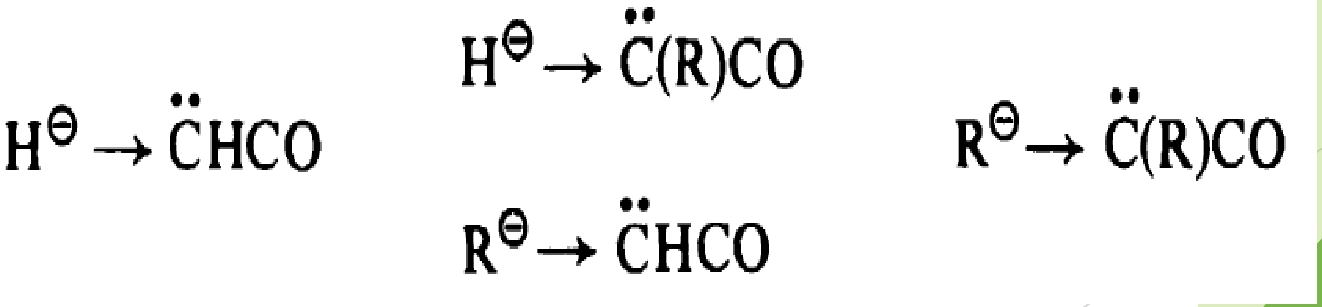
A similar ring contraction has been observed for 1,2-cyclobutanedione. Cyclobutanones undergo facile Baeyer-Villiger type oxidation by treatment with hydrogen peroxide alone.



Miscellaneous Reactions

A large part of carbonyl chemistry is concerned with enolization. Kinetic deprotonation of ketones suggests the following preference: CH_3CO >CH_2CO>CHCO. On considering the carbanions as acid-base complexes it becomes clear that the primary complex is better stabilized than the secondary one,

which is, in turn, more stable than the tertiary complex.

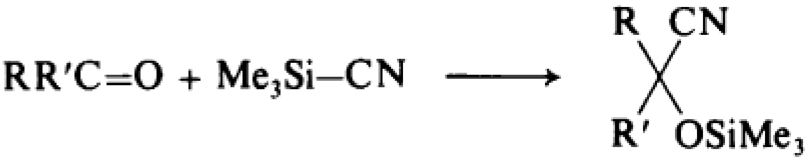


$$H^{\ominus} \rightarrow \ddot{C}(R)CO$$

$$H^{\ominus} \rightarrow \ddot{C}HCO \qquad R^{\ominus} \rightarrow \ddot{C}(R)CO$$

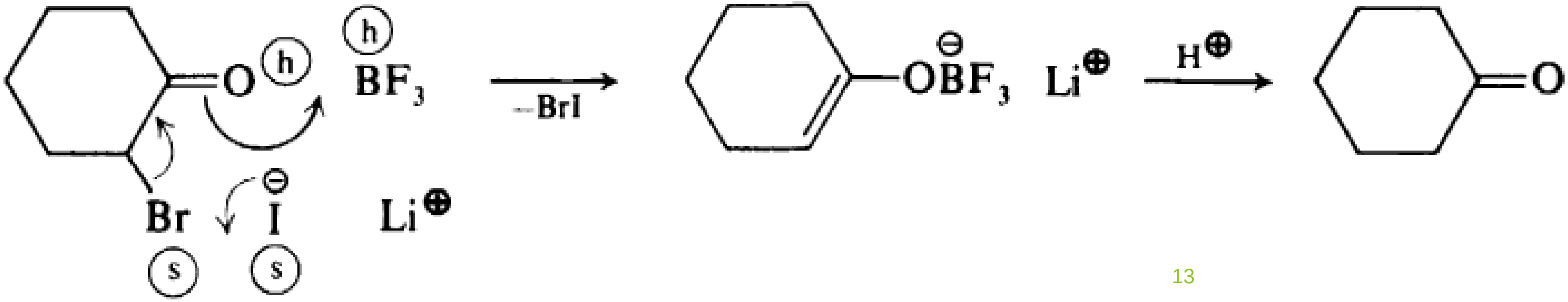
$$R^{\ominus} \rightarrow \ddot{C}HCO$$

The hard silicon atom forms strong bonds with oxygenated compounds. This property has been exploited in the direct preparation of cyanohydrin trimethylsilyl ethers. Strikingly the carbonyl group of p-benzoquinones can be protected by this method



A method for removal of halogen from α-bromoketones utilizes a combination of LiI and BF_3 as the reagents.

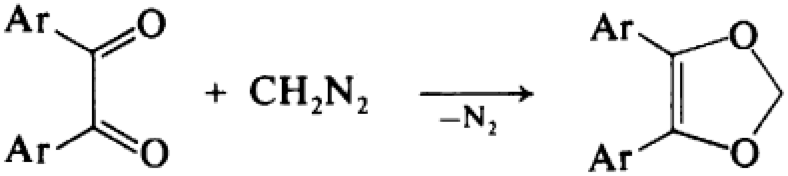
The hard-hard interaction between the carbonyl oxygen and the boron atom serves to activate the α-bromine toward attack by the soft iodide ion. The reaction is in accord with Saville's rule.



THE CARBONYL OXYGEN AS A SOFT ACCEPTOR

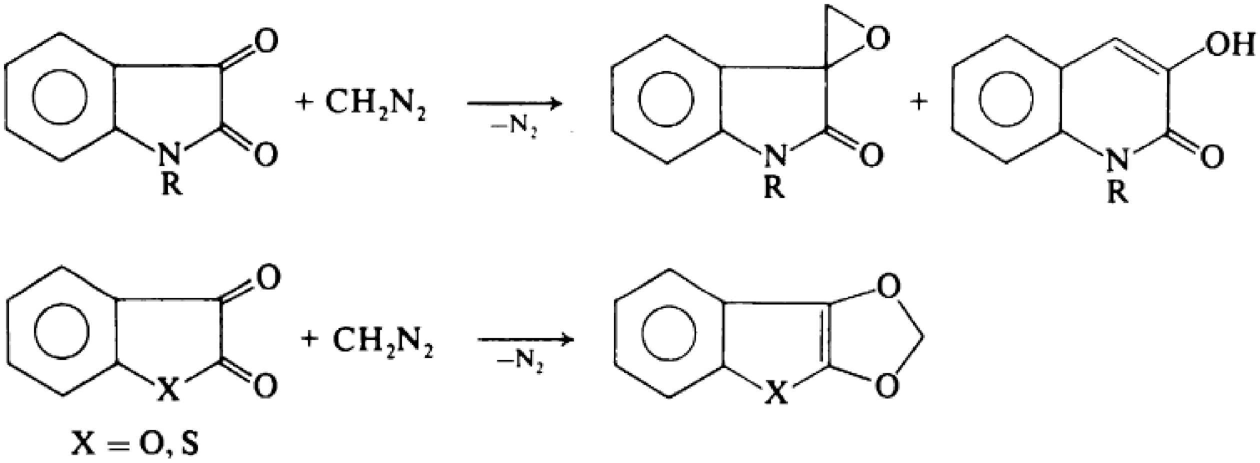
The reductive coupling of carbonyl compounds with active metals (Na, Mg, Al) yields pinacols. An electron transfer from the metal surface to the carbonyl oxygen (ketyl formation), a soft-soft interaction, is undoubtedly involved.

The reaction of diazomethane with α-diketones often leads to 1,3-dioxolines. It is plausible that attack on the carbonyl oxygen by the CH_2 of diazomethane is the initial step, for the zwitterion intermediates are somewhat stabilized.



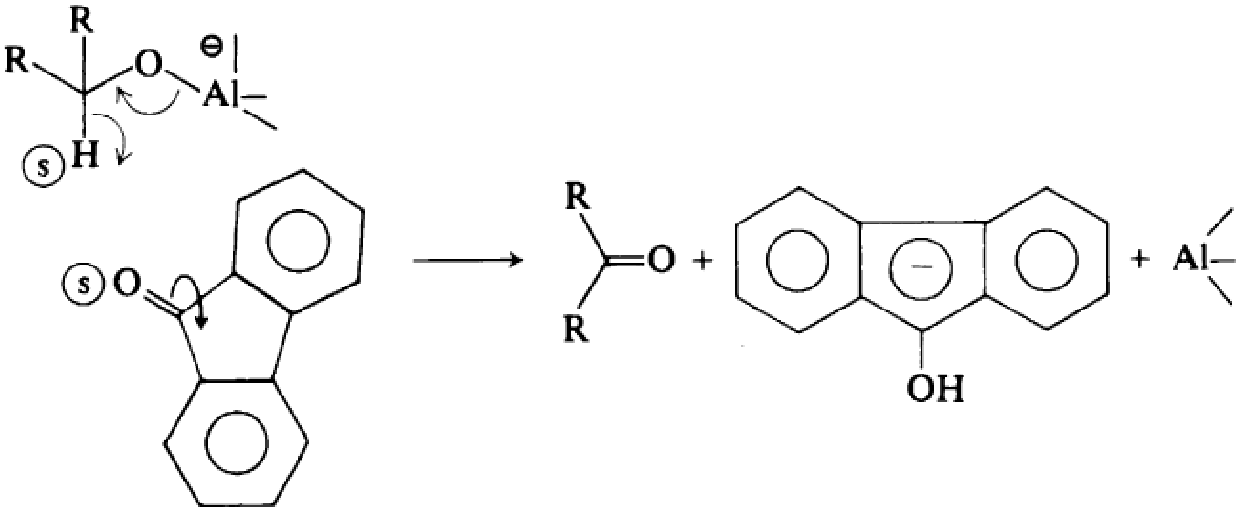
In the light of this, it is interesting to note that the isatin derivatives afford mixtures of epoxides and 3-hydroxycarbostyrils, whereas the oxygen and sulfur heterocycles provide the dioxolines.

The stabilization of the incipient carbanions generated during the addition of CH_2N_2 to the carbonyl oxygen by the neighboring lactone or thiolactone carbonyl is not shared by the isatin derivatives, as the lactam function is already polarized and can no longer serve as an electron sink. In other words, the keto carbonyl in isatin is not as polarizable as that in the O and S analogs.

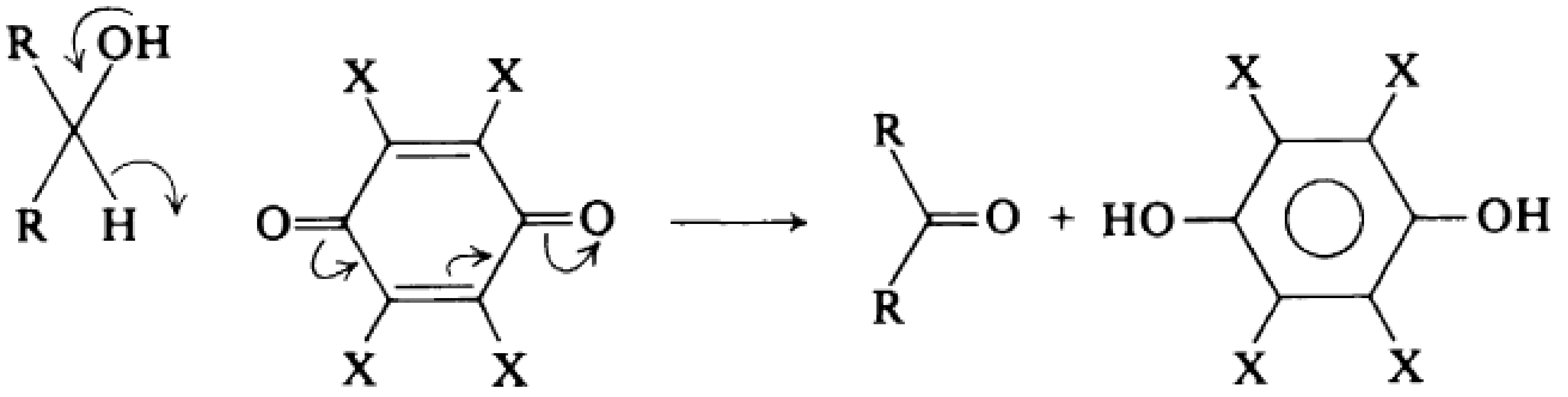


Isatin derivatives

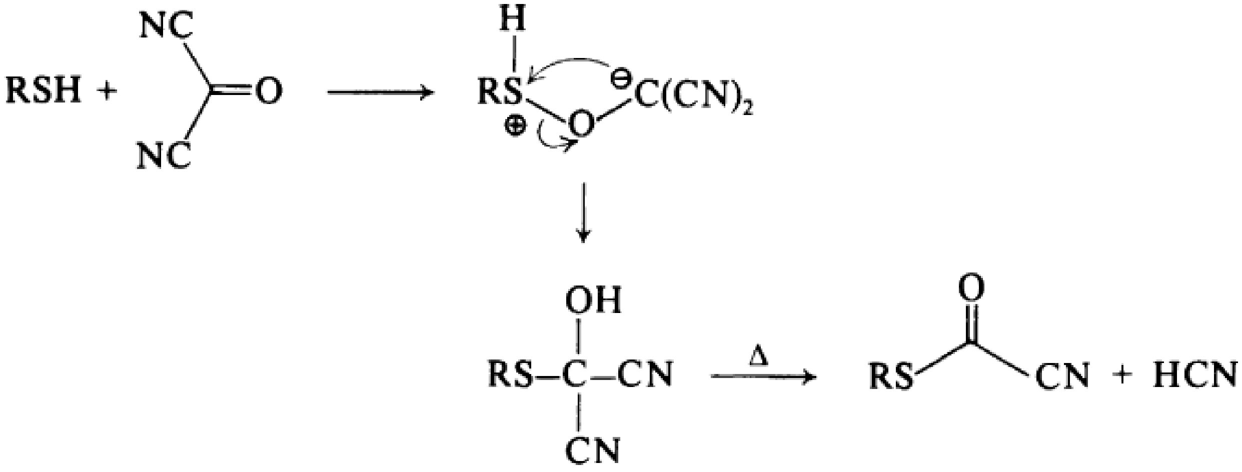
The Oppenauer oxidation of alcohols using fluorenone as a hydride acceptor may not proceed by the mechanism in which H^- is delivered to the carbon of the carbonyl group. The following description remains a distinct possibility.



The dehydrogenation of certain alcohols by quinones is thought to involve a hydride transfer.



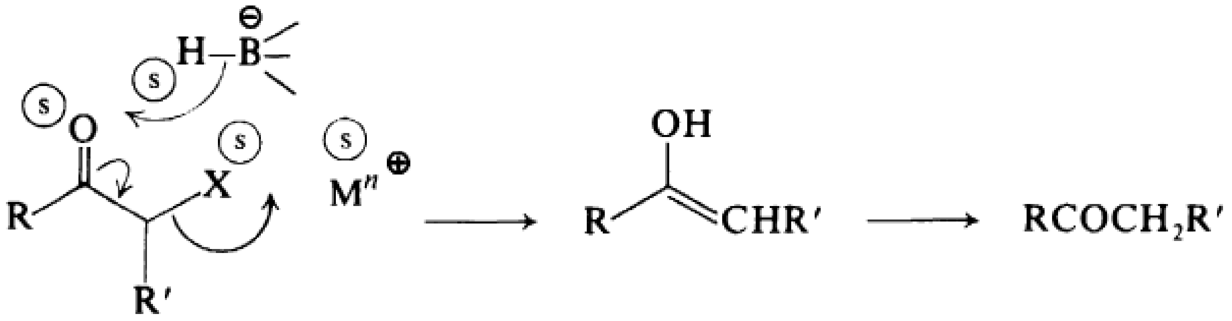
Cyanothioformates become accessible by the addition of thiols to carbonyl cyanide. Although the dicyanohydrin intermediates have been characterized, they may actually arise from a rearrangement of zwitterionic species containing an S—O bond.



Cyanothioformate

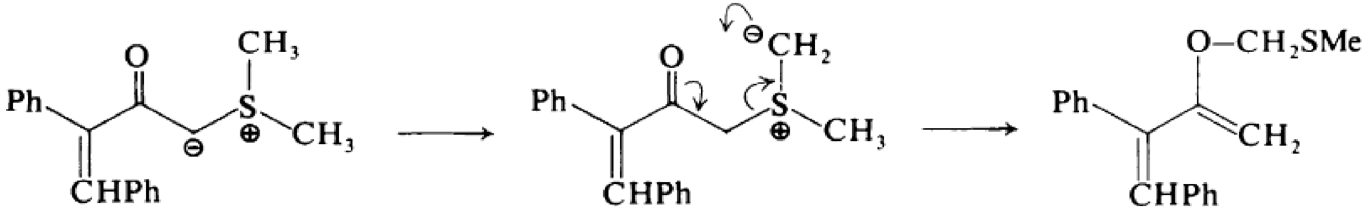
Another method for the debromination of α-bromoketones calls for the use of $NaBH_4$ in conjunction with heavy metal salts.

The S · · · S ~~~ S · · · S interactions in the transition state are the crucial requisite.

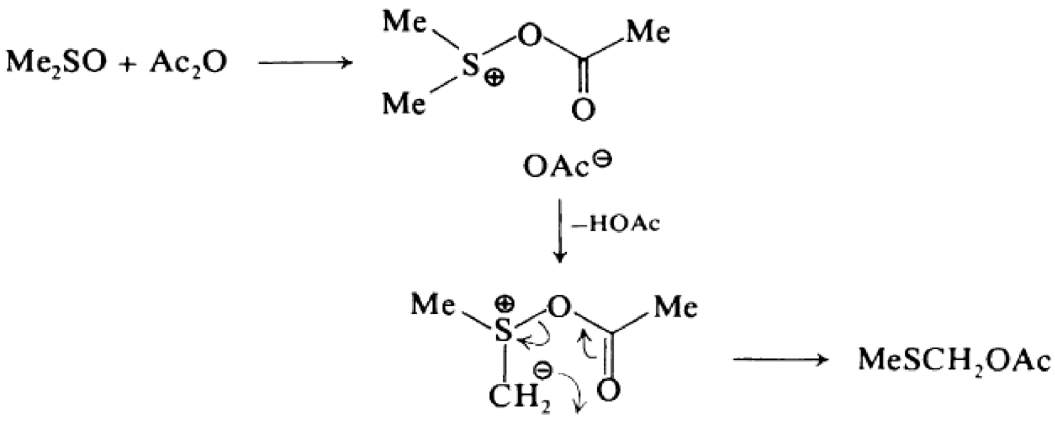


α-Bromoketones

The thermal rearrangement of a ketosulfonium ylide as depicted in the following equation proceeds via nucleophilic attack on the soft oxygen end of the carbonyl. A comparison of the mechanism with the Pummerer rearrangement is instructive.



Ketosulfonium ylide



Pummerer rearrangment

REACTIONS OF UNSATURATED CARBONYL COMPOUNDS

Complex Metal Hydride Reductions

The reduction of α,β-unsaturated ketones with complex metal hydrides has been examined from the HSAB viewpoint. From an analysis based on the reasonable assumptions that in the conjugate enone system C-4 is softer than C-2 (carbonyl carbon) and that the more covalent M-H bond corresponds to the softer hydride, a unified picture emerges.

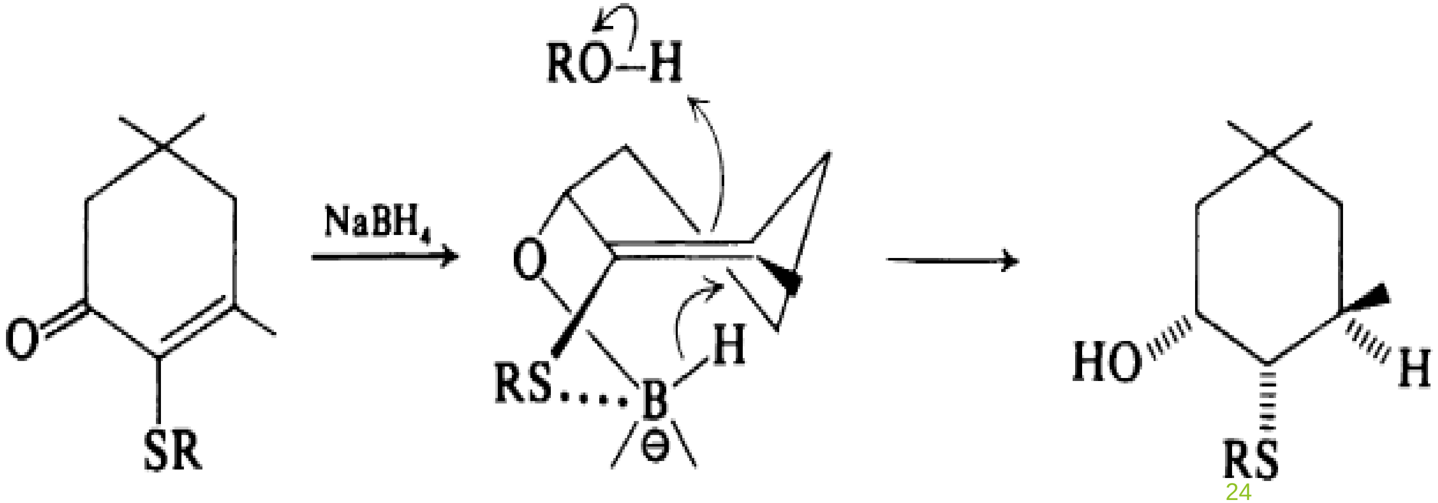
The replacement of some of the hydride ions by hard alkoxy groups suppresses the softer conjugate addition to the enones. The proportion of 1,2- vs. 1,4-reduction of cyclopentenone varies from 14:86 using $LiAlH_4$ to a dramatic 90:9.5 using lithium trimethoxyaluminum hydride.

The α,β -unsaturated esters are reduced to allylic alcohols by $LiAlH_4$ in the presence of ethanol. The ethoxyaluminum hydride is the active reducer.

The conjugate reduction of enones is easier than that for enal, because aldehyde carbonyl is softer than the ketone counterpart. Alkyl substituents in the α and *β* positions of the enones interfere with conjugate reduction. However, treatment of α-alkylthiocyclohexenones with $NaBH_4$ successfully gives saturated alcohols.

It has been proposed that intramolecular H^- delivery from a S-coordinated borohydride is involved. A marked increase in the 1,4-reduction of enones by $LiAlH(SR)_3$ is observed (see Table 7.1).

Symbiotic softening of the reagents by the thio substituents is responsible for the reversal of the alkoxy effects.



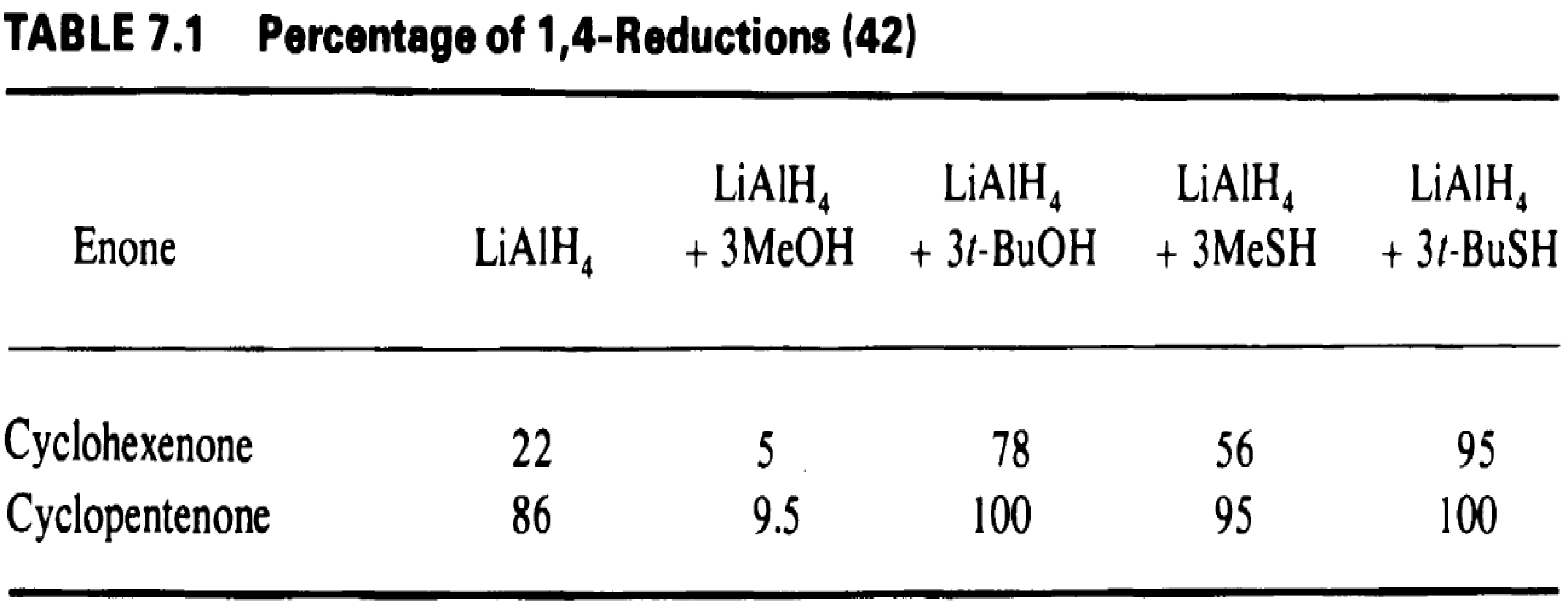


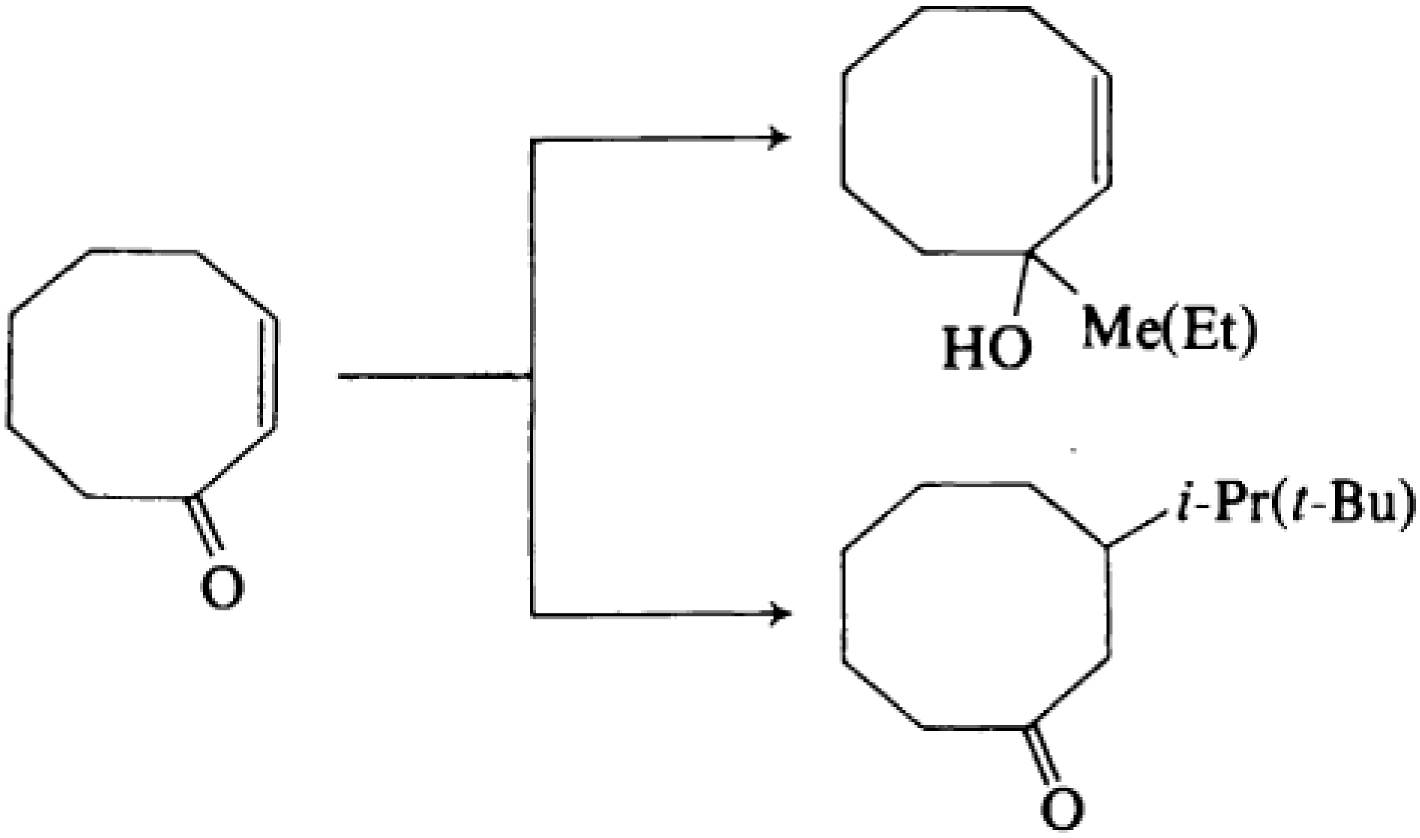
TABLE 7.1 **Percentage of 1,4-Reductions (42)**

Enone	$LiAlH_4$	$LiAlH_4$ + 3MeOH	$LiAlH_4$ + 3*t*-BuOH	$LiAlH_4$ + 3MeSH	$LiAlH_4$ + 3*t*-BuSH
Cyclohexenone	22	5	78	56	95
Cyclopentenone	86	9.5	100	95	100

Reactions with Organometallic Reagents

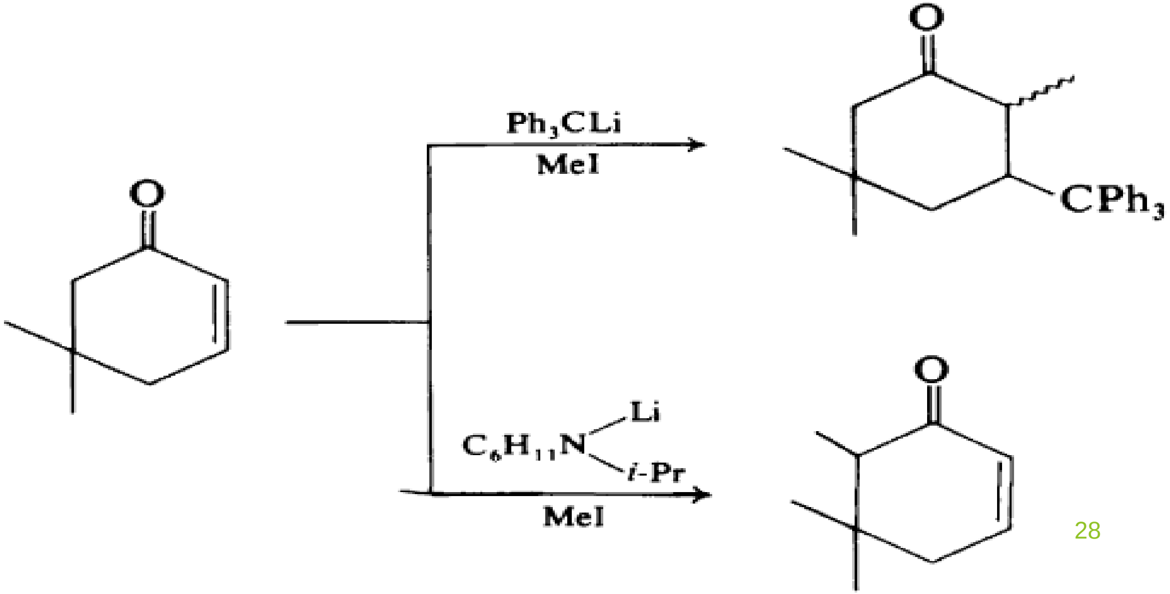
The hardness of the organometallic reagents (RLi > RMgX > RCu or R_2CuLi) is directly related to the metal atoms. In light of this, their reaction with enones is more readily understood.

Grignard reactions of 2-cyclooctenone are readily rationalized when one considers the hardness order: Me> Et> i-Pr>t-Bu.


HO
Me(Et)
i-Pr(t-Bu)
O
O

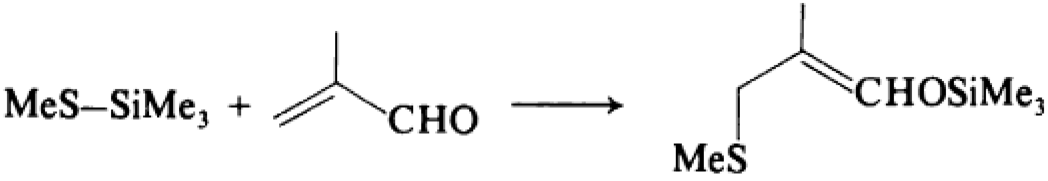
For a long time the trityl anion has been used as a proton abstractor of weakly acidic substances. Its inertness toward the ketonic function has been regarded as steric in origin.

It should be emphasized that the trityl anion is quite soft as demonstrated by the following reactions



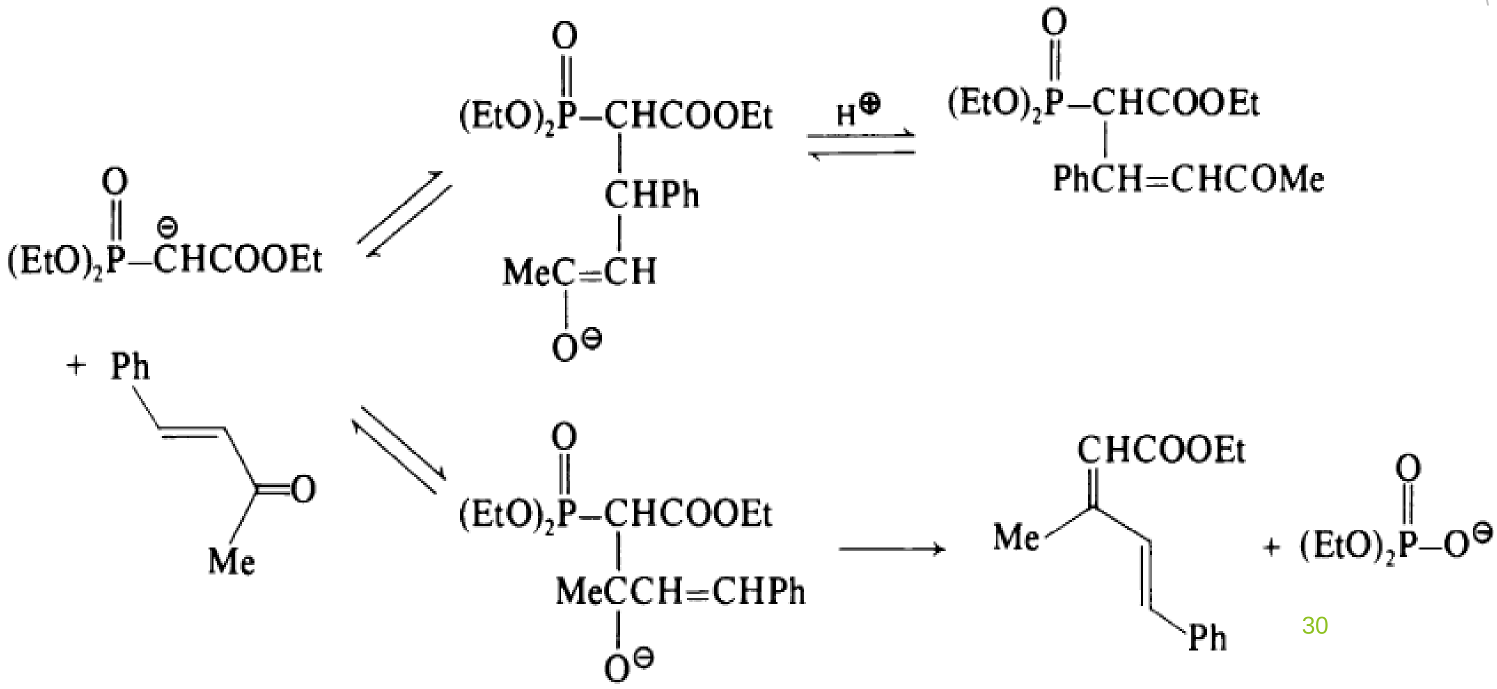
Reaction with Other Soft Bases

The 1,4-adducts are readily obtained when α,β-unsaturated carbonyl compounds are treated with methylthio(trimethyl)silane. The reaction conforms to Saville's rule as the product formation involves [s :s] S *:Cβ* and [h :h] O: Si interactions.



Dual pathways are available for the reaction of phosphonate anions with α,β-enones. The Michael addition is frontier orbital-controlled and is favored by the presence of proton sources, which quickly neutralize the charge on the enolate anions.

These products decrease with time because they are gradually channeled into the charge-controlled *Horner-Emmons olefination*.

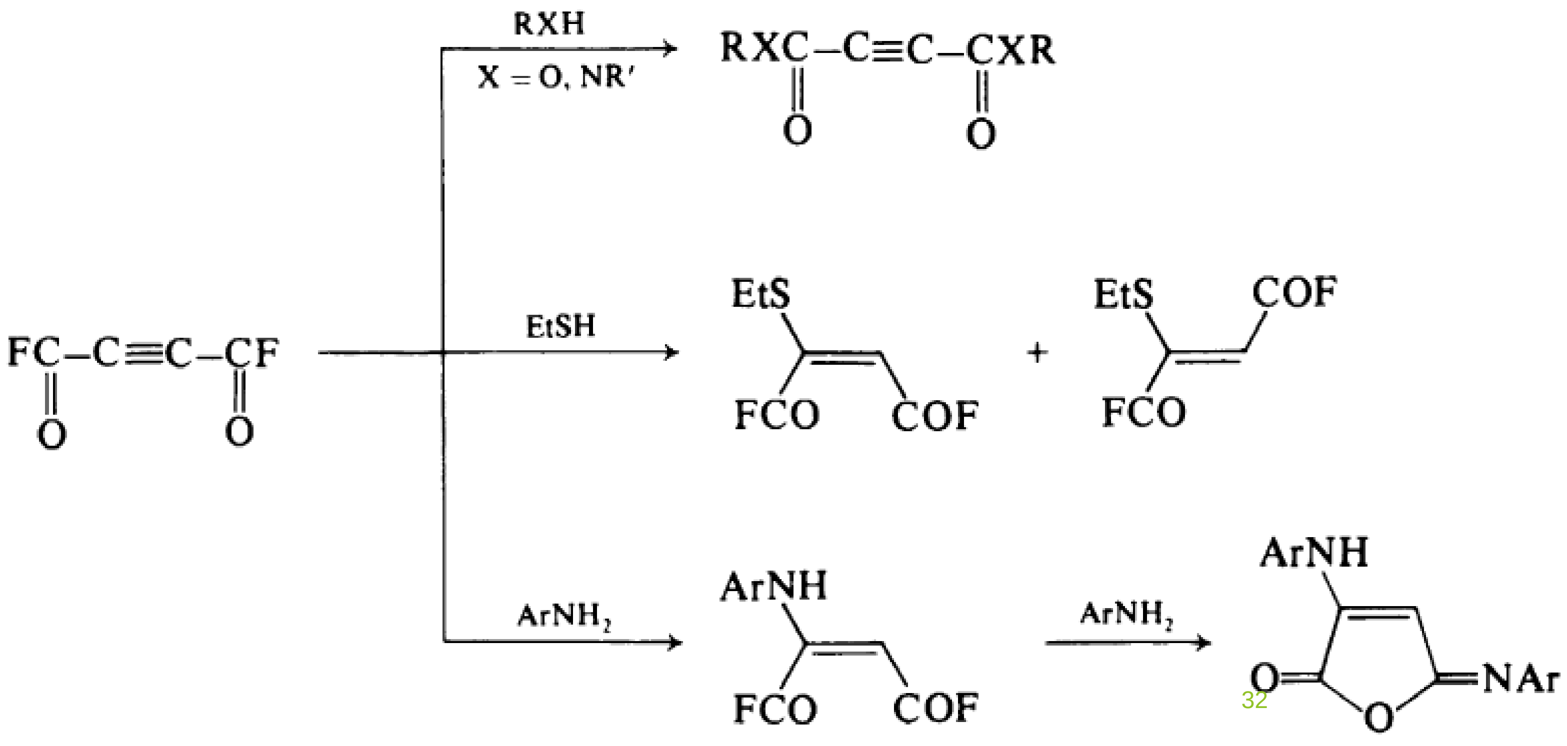


Michael Additions

The 1,4-addition to α,β-unsaturated systems may be catalyzed by hard bases. Tertiary phosphines are also effective catalysts. Instead of directly removing a proton from the donor, they add to the unsaturated systems to generate the harder zwitterionic bases, which are more favorable for proton abstraction.

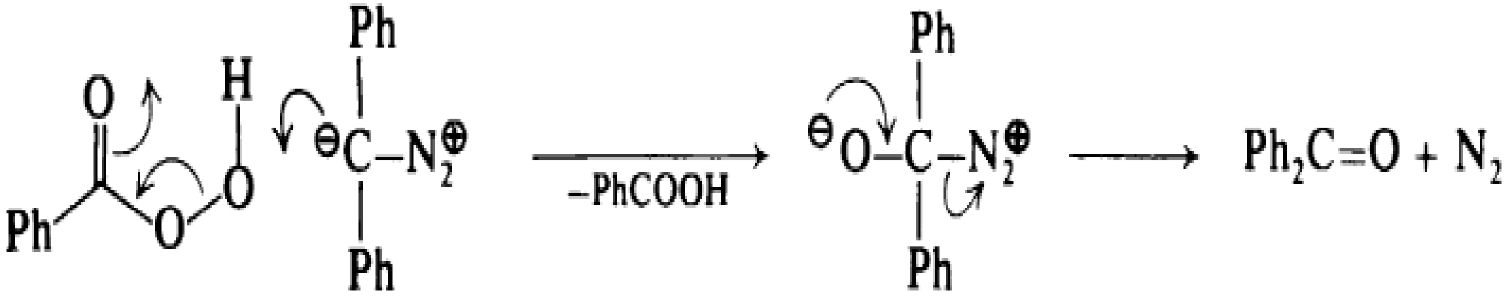
The attempt to add fluoride ion to α,β-unsaturated nitro compounds was doomed to fail because of the extreme hardness of the halide. It has been demonstrated that F^- is an effective Michael catalyst by virtue of its deprotonating ability.

Acetylenedicarbonyl fluoride reacts with alcohols and amines to furnish esters and amides, respectively. On the other hand, ethanethiol adds to the triple bond of the substrate despite the extremely high reactivity of the acyl fluoride carbonyl. Aromatic amines undergo both Michael addition and amidation.



ASPECTS OF SOME CARBOXYLIC ACID DERIVATIVES

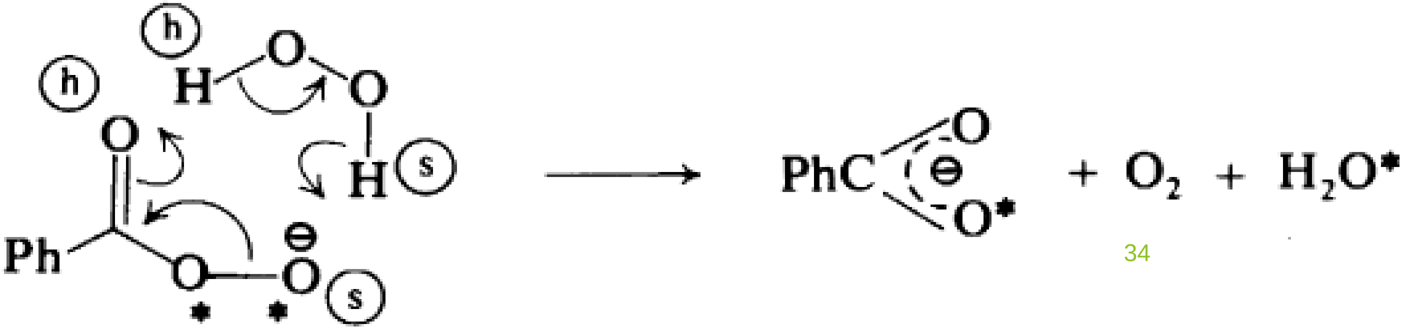
Peracids readily give up oxygen to soft bases. Thus, perbenzoic acid oxidizes diphenyldiazomethane to yield benzophenone, via an initial soft-soft interaction.



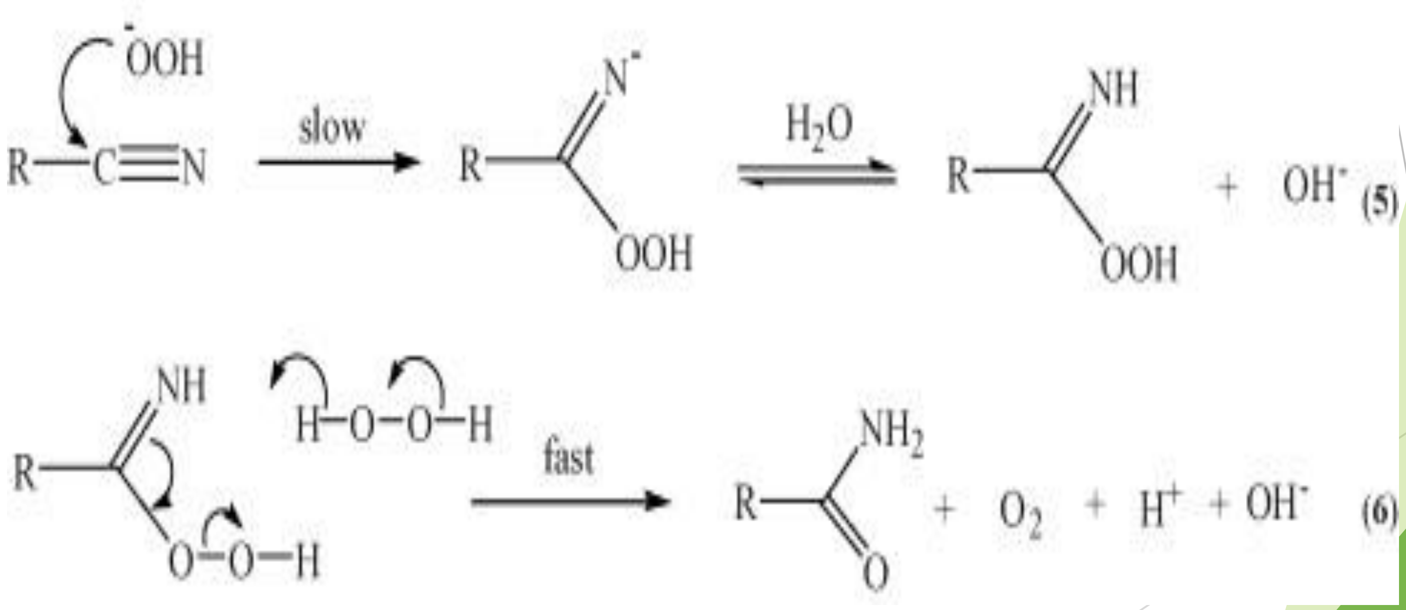
The reduction of valeryl peroxide with thiocyanate ion presumably proceeds by a sequential soft interaction between S and O, and S and S.

$$(n\text{-BuCOO})_2 + \text{KSCN} \longrightarrow n\text{-BuCOOSCN} + n\text{-BuCOOK} \xrightarrow{\text{KSCN}} 2n\text{-BuCOOK} + (\text{SCN})_2$$

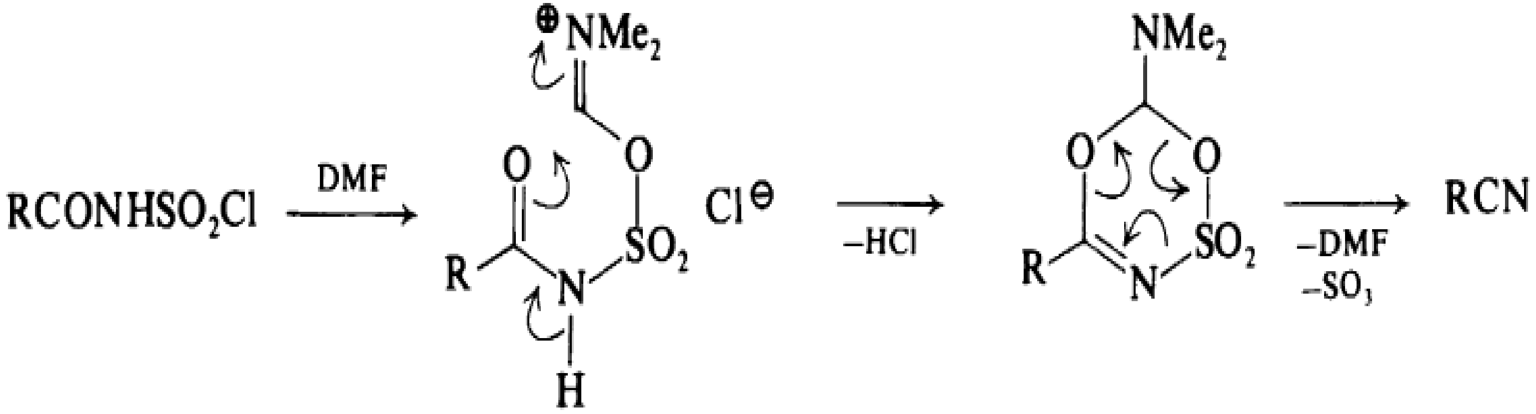
Sodium perbenzoate is reduced by hydrogen peroxide. Radioactive tracer studies suggest the following transition state with compatible reaction termini.



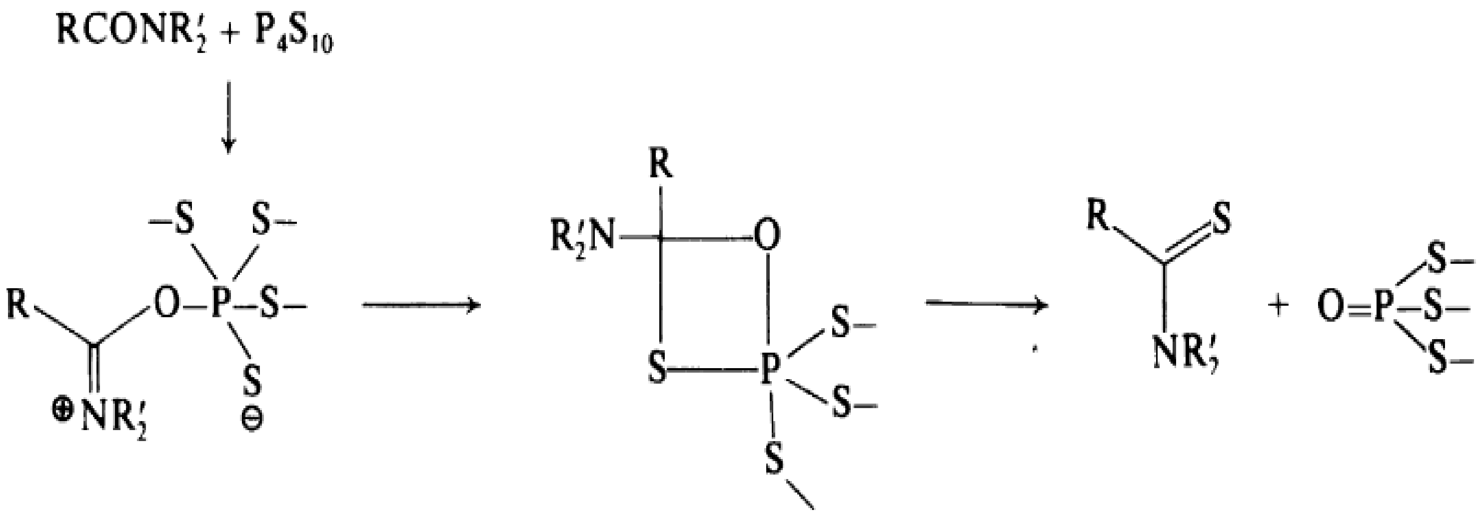
Nitrites are rapidly hydrated by treatment with hydrogen peroxide. The Wiberg mechanism is consistent with HSAB formulation.



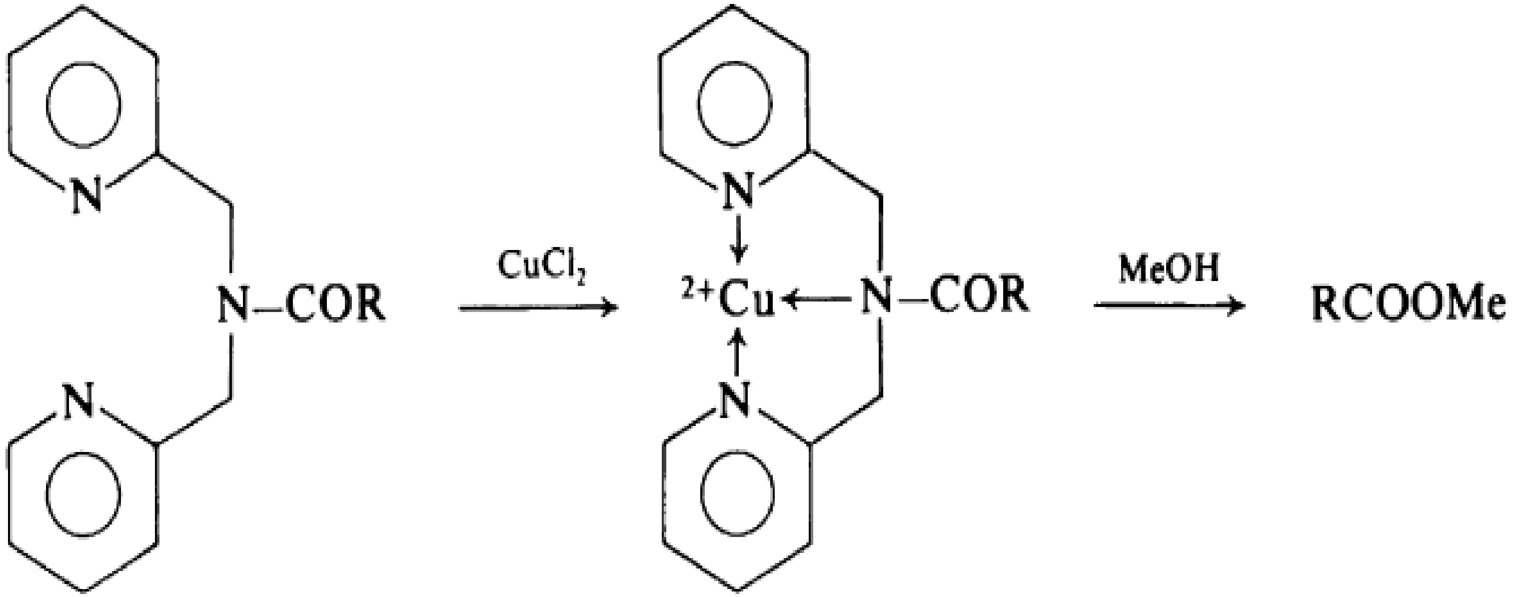
Nitriles are formed by dissolution of ***N*-chlorosulfonylamides in dimethylformamide** (DMF). The effectiveness of DMF is prescribed by the presence of proper hard centers.



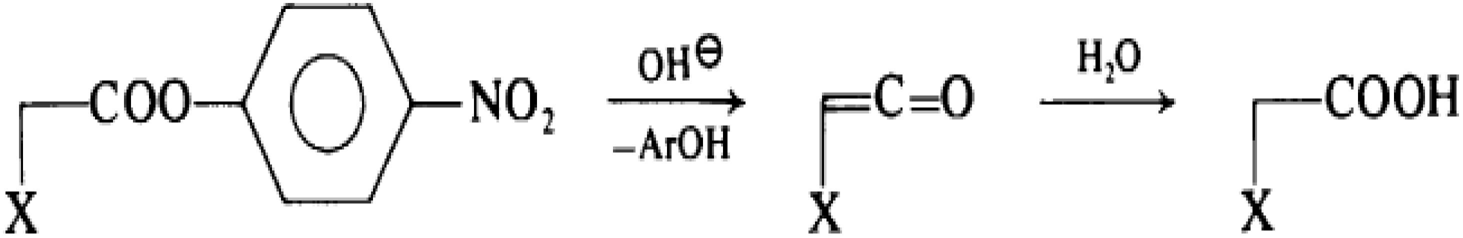
The conversion of amides into thioamides can be achieved by treatment with P_4S_{10}. This reaction exploits the intrinsically hard and oxaphilic nature of pentacovalent phosphorus which is bound to the sulfur atoms.



N**, *****N*****-Di(2-picolyl)carboxamides** **are methanolyzed in the presence of cupric chloride. The complexation of the nitrogen atoms renders the amidic carbonyl much harder and better responsive to the hard base methanol.**



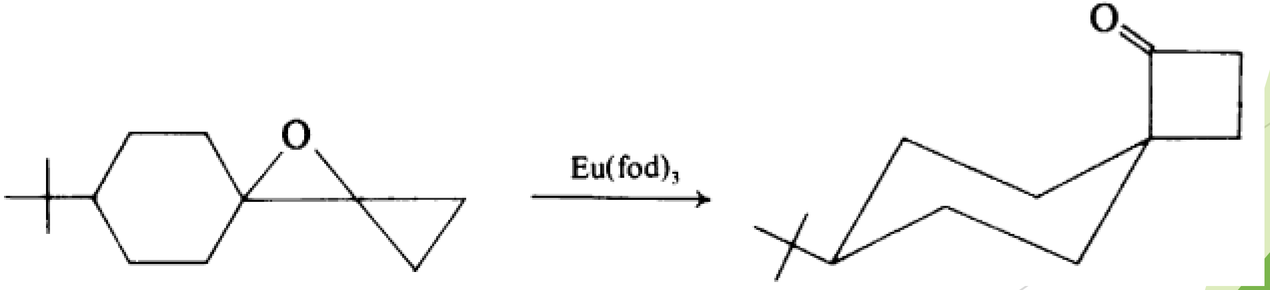
Saponification of certain esters such as *p*-nitrophenyl malonate and cyanoacetate proceeds via the ElcB mechanism. The *α* protons of these esters are very acidic (hard). *N*-Arylcarbamates also undergo alkaline hydrolysis by the same route.



$CNCH_2COOR$; $PhNHCOOR$

SOME CARBONYL-FORMING PROCESSES

In the absence of nucleophiles, Lewis acids (e.g., BF_3) promote isomerization of epoxides to carbonyl compounds. The highly strained oxaspiropentanes are transformed into cyclobutanones even by lithium salts or europium complexes. The essential feature is that a hard-hard interaction precedes bond migration.

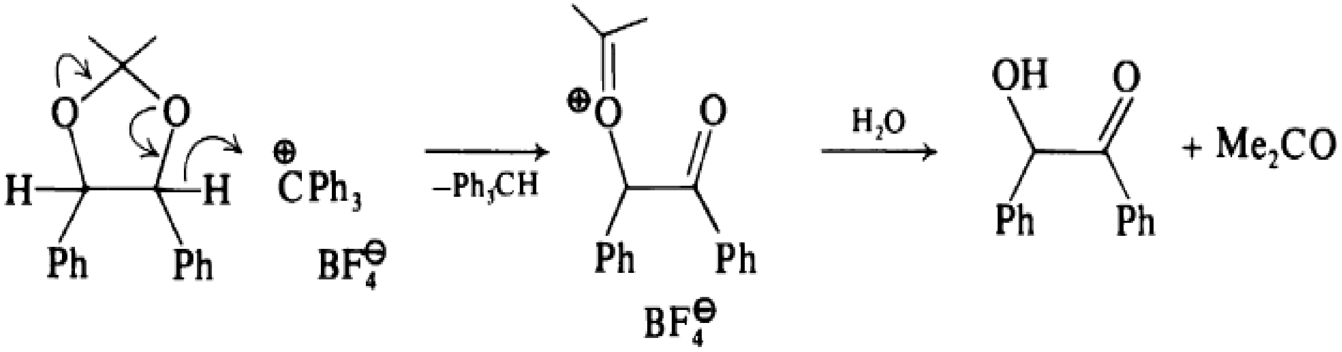


Oxaspiropentane

Hard-hard interaction

1,2-Diols can be dehydrogenated to α-ketols via their acetonides. The hydride acceptor is the relatively soft trityl cation.

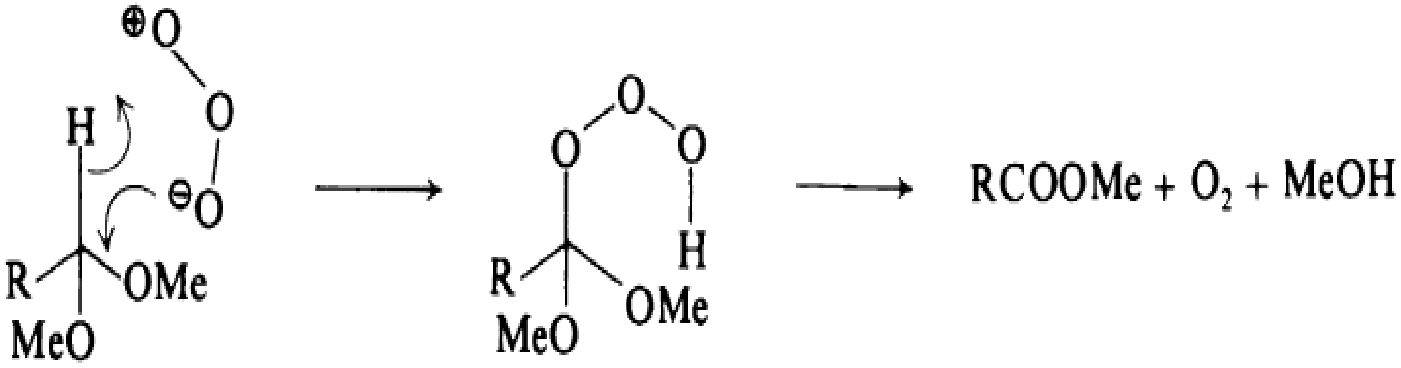
Dehydrogenation



Acetonide

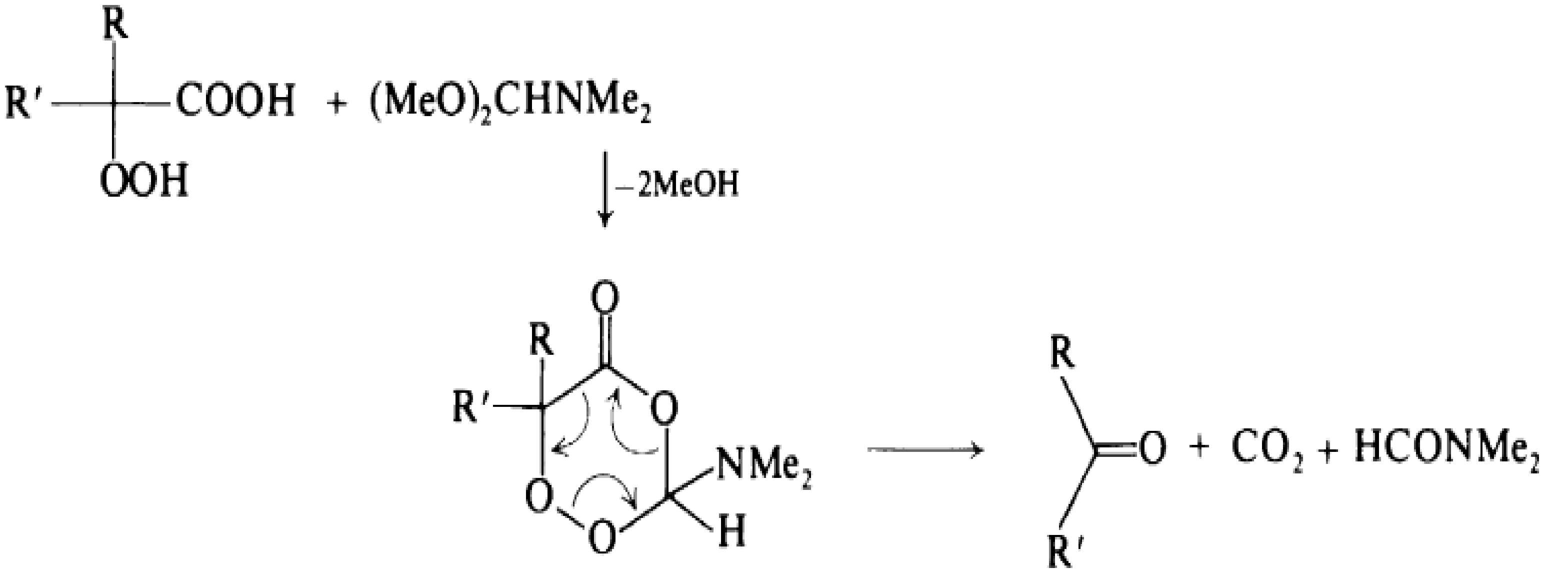
α-Ketol

The oxidation of acetals to esters may also involve hydride abstraction by the soft positive pole of the ozone molecule; the hard negative oxygen end occupies the site vacated by the hydride.



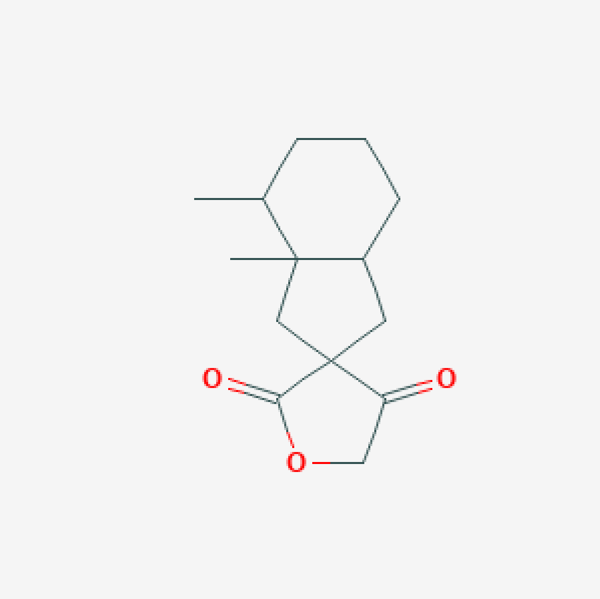
Soft-soft; Hard-hard

α-Hydroperoxycarboxylic acids undergo decarboxylative reduction to give the norketones on exposure to dimethylformamide dimethylacetal. The reaction consists of the formation and fragmentation of a cyclic intermediate.



Hard-hard (-CO2)

Soft-soft (Ketone formation)



Norketone