

# **Chapter 4**

## ***Displacement reactions***



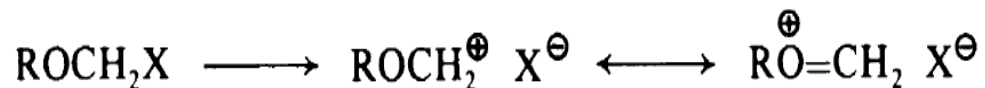
# GENERAL MECHANISMS

**Of the various kinds of organic reactions substitution, especially aliphatic nucleophilic substitution, is most amenable to HSAB correlation. The transition state of an SN process may be envisaged as an acid-base pairing, the nucleophile being equated to a donor base and the electrophilic center to an acceptor acid.**



Mechanistically there are two extremes, namely, the  $S_N1$  and the  $S_N2$  types of reaction according to the Ingold-Hughes designation. Winstein *et al* classified the reactions as *N* and *Lim*; they do not recognize  $S_N1$  and  $S_N2$  reactions as distinct processes.

The average relative rates for  $S_N2$  reactions are Me, 30; Et, 1; n-Pr, 0.4; n-Bu, 0.4; i-Pr, 0.025; i-Bu, 0.03; neopentyl,  $10^{-5}$ ; allyl, 40; and benzyl, 120. Heterosubstituents in  $\alpha$  position tend to enhance reaction rates through the assistance of ionization.



**Substrates having groups such as cyano and carbonyl in the  $\alpha$  position resist ionization. However, these compounds are very reactive in  $S_N2$  processes.**

**In terms of the HSAB concept, the heightened reactivity is simply due to the hardening of the reaction centers.**

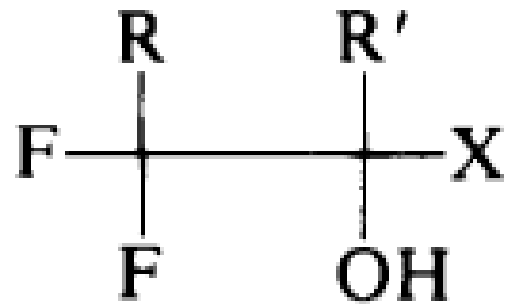
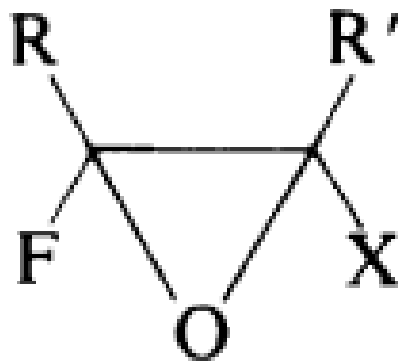
**It will be seen that the rate increase in the  $S_N2$  reactions for the  $\alpha$ -carbonyl substrates pertains only to those involving hard nucleophiles.**



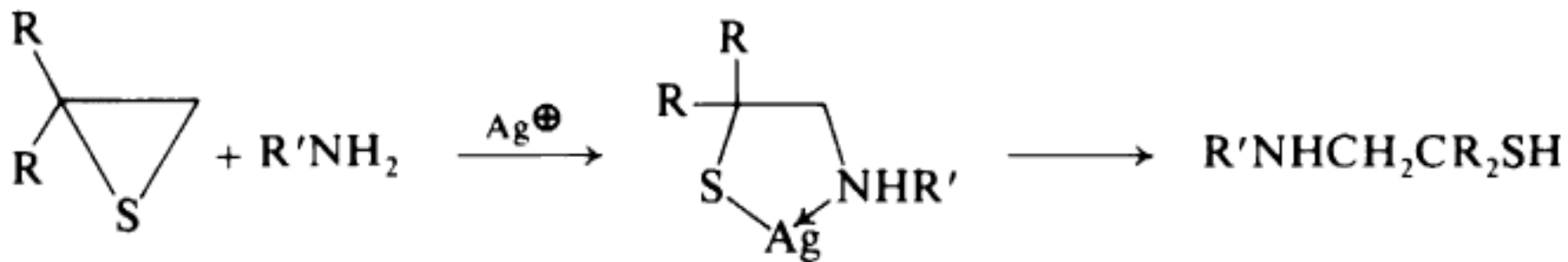
**In a theoretical investigation of the  $S_N2$  reactions three rules were formulated by Harris and Kurz.**

**One of these rules states that if an  $S_N2$  transition state involves nucleophilic atoms from different rows of the Periodic Table, an electron-withdrawing substituent at the central atom will tend to increase the order of the reacting bond to the lighter atom, and decrease the order of the other reacting bond. In other words, if the central atom is harder, it will bind more tightly to the harder nucleophile.**





Whereas epoxides are readily cleaved by ammonia and amines, ring opening of thiiranes is rather sluggish. The situation is ameliorated by adding silver ion to coordinate with the sulfur atom which then renders the ring C-S bond more permanently polarized (and hence *less polarizable*), i.e., the ring carbon becomes harder and more responsive to hard bases. Precedence for this activation is found in a one-step synthesis of sulfenamides from disulfides.



# NUCLEOPHILIC REACTIVITY

**A nucleophile is a reagent which supplies an electron pair to form a new bond between itself and another atom. Swain and Scott proposed that in describing properties of these species "basicity" be used solely in equilibria (thermodynamic) phenomena and "nucleophilicity" in rate (kinetic) phenomena.**

**Parker further suggested that the thermodynamic affinity for elements other than hydrogen be termed M-basicity, e.g., carbon basicity or sulfur basicity.**





**Swain and Scott:**

$$\log(k/k_0) = sn$$

**$s$  is a measure of substrate susceptibility to the nucleophile. It is defined as 1.0 for methyl bromide at 25°. The value of  $n$  for water is set at zero.**

$$\log(k/k_0) = \alpha E_n + \beta H$$

**Edwards has formulated a four-parameter equation comprising a nucleophilicity term and a basicity term for correlating electron donors with rates and equilibria.**



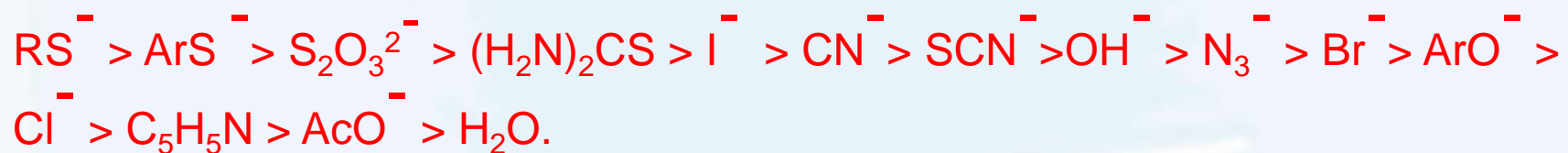
**Nucleophilicity has also been correlated with basicity and polarizability by**

$$\log(k/k_0) = AP + BH$$

**The relationship of  $E_n$  to the nucleophilic constant  $n$  of the Swain-Scott equation appears to be linear.**



In  $S_N2$  Reaction, a nucleophilic order is:



**Polarizability is the dominant factor. Since polarizability is intrinsically associated with chemical softness of a species, parallelism exists between nucleophilic order and softness order.**



The reactivity of  $\text{I}^-$  and  $\text{C}_6\text{H}_5\text{S}^-$  towards the displacement of *o*-substituted benzyl chlorides, on the one hand, and  $\text{MeO}^-$ , on the other, depends on the polarizability of the *ortho* substituent.

The rate ratio  $k_{\text{PhS}^-}/k_{\text{MeO}^-}$  for substitution varies from 512 for *p*-methoxy to 5300 for *p*-nitrobenzyl bromides. The former compound exhibits considerable carbenium ion character in the transition state, hence it reacts faster with  $\text{MeO}^-$  (hard-hard interaction).



The true nucleophilic order for halide ions was at one time nebulous. For example, in the displacement of n-butyl brosylate, two series of halides display opposite reactivity:



Winstein *et al.* ascribed the noncorrespondence of lithium salt reactivity to the intrinsic strength and increasing dissociation of salts with larger anions.



The apparent intrinsic nucleophilicities of halide ions have been determined by the thermal decomposition. Complications due to solvation are eliminated. It should be noted that the leaving group is a hard base.



$$k_{\text{X}}^{\text{rel}} \text{ for Cl:Br:I} = 620:7.7:1$$



**A completely different picture emerges when nucleophilic attack on the carbonyl carbon is examined. The nucleophilic order follows the basicity order more closely as demonstrated by reactions of *p*-nitrophenyl acetate with anilines, pyridines, imidazoles, oxyanions, etc.**

**The attack on the carbonyl proceeds via an addition-elimination mechanism in which the nucleophile acquires a partial positive charge prior to the transition state. The less encumbered electrophilic site and the need to involve only the substrate *p* orbitals permit closer approach of the attacking species.**



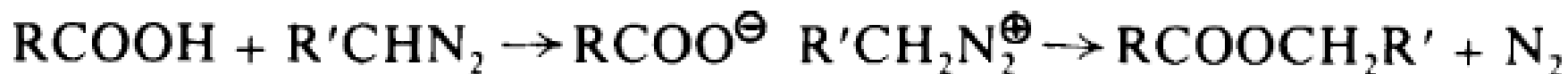
**Because the transition state structure is tight, the steric effect may become an important factor influencing nucleophilicity. The reduced steric demands around the nitrogen atoms of aziridines and azetidines are responsible, at least in part, for the greatly enhanced nucleophilicity toward ester carbonyl as compared with other amines having similar basicity.**





# FORMATION AND CLEAVAGE OF O-ALKYL BOND OF CARBOXYLIC ESTERS

The esterification of carboxylic acids with diazoalkanes has become a classical method. The success of the reaction stems from the interaction of two rather hard species which are simultaneously generated by proton transfer from the carboxylic acid to the *carbon of the diazoalkanes*.



**The combination of alkali metal salts of carboxylic acids and alkyl halides seldom finds use in ester synthesis owing to low yields. *The crucial O-C bond formation is a hard-soft interaction. In contrast, the efficient reaction of acyl halides with alcohols consists of a hard-hard interaction.***

**Improved techniques for ester formation invariably involves replacement of alkyl halides with the harder dialkyl sulfates or softening the carboxylate ion to accommodate the alkyl halides. The carboxylates of Cu(I), Tl(I), Ag(I), and Hg(II) have been successfully converted into esters.**



**Solvents also play an important role in regulating the reactivity of anions.**

**Hexamethylphosphoric triamide (HMPT) solvates alkali metal ions so strongly that the counter anions are practically free. Under such conditions the inherent bond strengths determine the ease of reaction.**

**Since the O-C bond is stronger than the C-X bonds (X = Cl, Br, I), facile displacement of halide ions by carboxylates in HMPT is a logical consequence.**



**Thiolate ions undergo S-alkylation on reaction with trichloroacetic esters in contrast to normal solvolysis of trifluoro- and trichloroacetates by hard bases. In refluxing dimethylformamide (DMF) the thiocyanate ion cleaves methyl and benzyl esters.**

**Alternatively, a eutectic melt of NaSCN-KSCN may be employed. The neutral mixture from the latter reaction consists of 96% MeSCN and 4% MeNCS, indicating a predominant displacement by the softer S terminus of the base.**

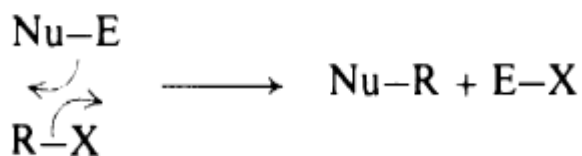


**It is well known that  $I^-$  is one of the softest common nucleophiles. The use of  $I^-$  in deblocking methyl esters has become a conventional procedure in organic synthesis. Nucleophilic attack by  $I^-$  on the methyl group [ $S_N2(C)$ ] is undisputedly operative.**



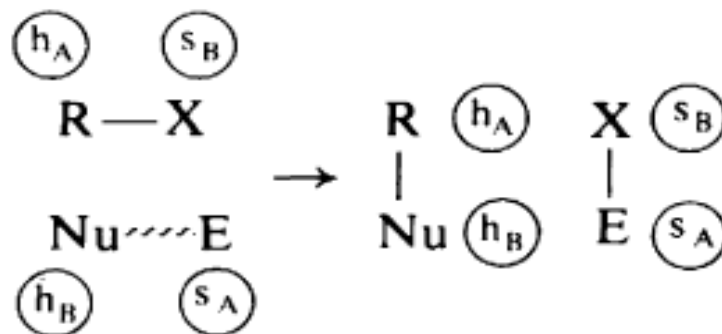
# MULTICENTERED REACTIONS: SAVILLE'S RULES

As substitution is assisted by precoordination of the leaving group with an electrophile, it becomes evident that a general form of the four-centered reaction involving cooperative action of a nucleophile (Nu) and an electrophile (E) on a substrate (push-pull mechanism) should proceed with greater facility. In addition,  $\pi$ -electron systems works in the same way.

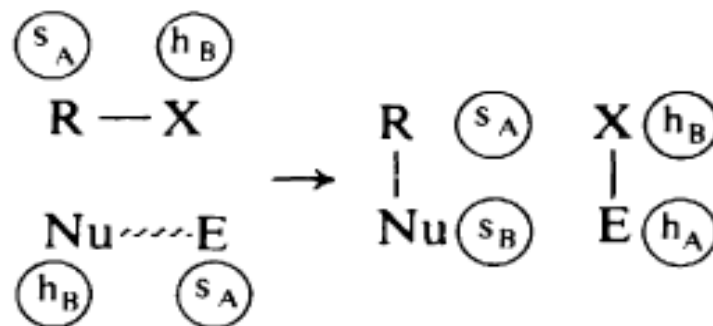


Saville deduced that the most effective way to achieve the desirable bond cleavage would be to provide a nucleophilic and an electrophilic species of the same (hard or soft) category as the acid A and the base B.

*Rule 1:*



*Rule 2:*



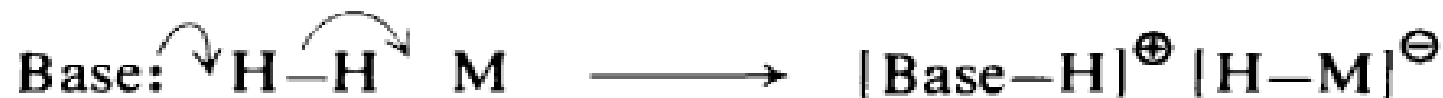
**His discussion of rule 1 extends to C-B bond cleavage, reactions of aldehydes, thioacids and esters, phosphoryl and sulfonyl compounds.**

**For rule 2 he gives examples of C-O bond fission, substitution at oxygen and sulfur, etc. Some of these are reiterated here.**





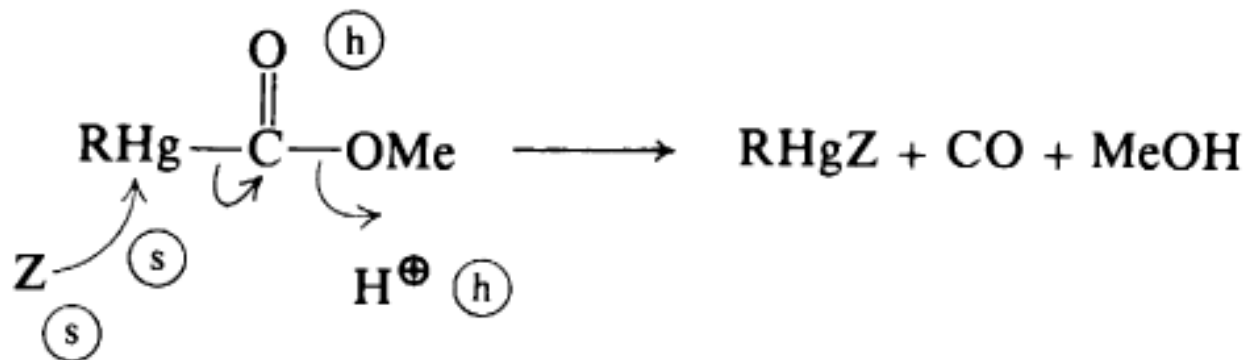
**A most striking phenomenon is the heterolysis of molecular hydrogen according to the following equation.**



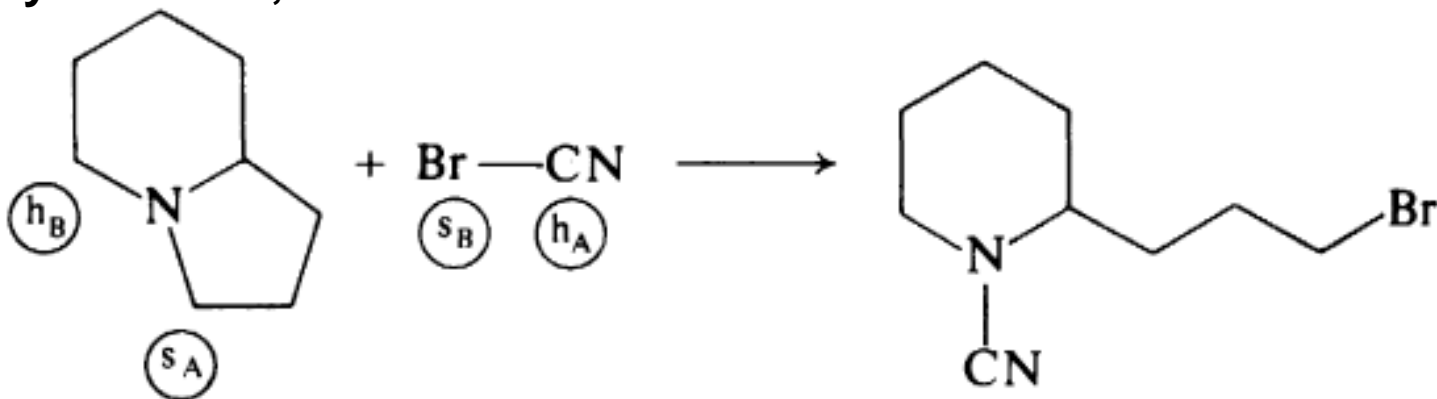
**Only the combination of a hard base (e.g., carboxylate ion, pyridines) and a soft metal cation (e.g., Ag(I), Hg(I), Hg(II), Cu(I), Pt(II)) is suitable. Saville's rule 1 is faithfully obeyed.**



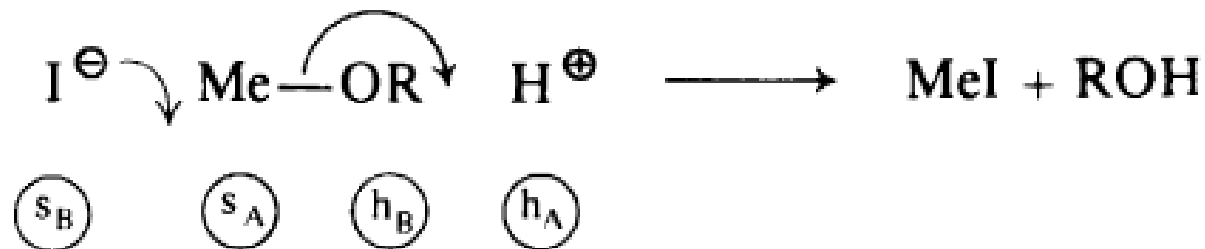
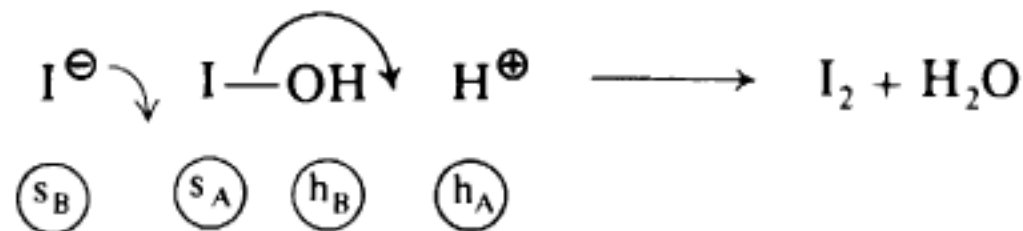
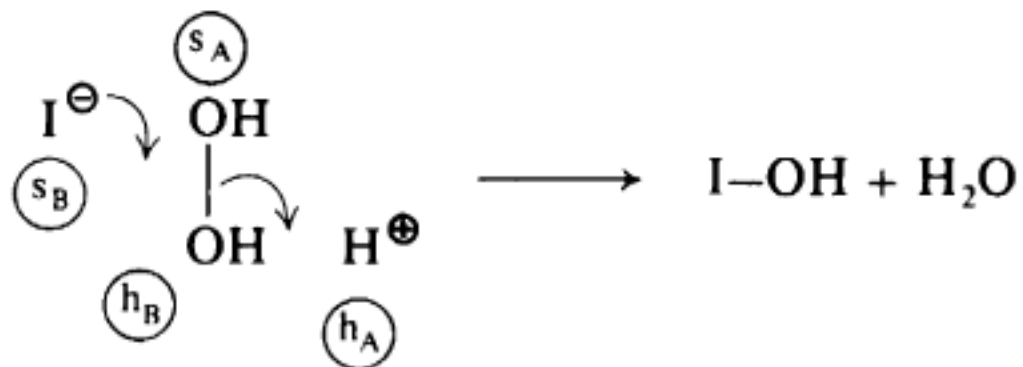
Methoxycarbonylmercury compounds undergo acid-catalyzed decomposition in the presence of "assistors" of a soft nature, e.g., RSH, I<sup>-</sup>, and Br<sup>-</sup>.



Tertiary amines are ruptured on exposure to cyanogen bromide to yield bromocyanamides, in accordance with Saville's rule.



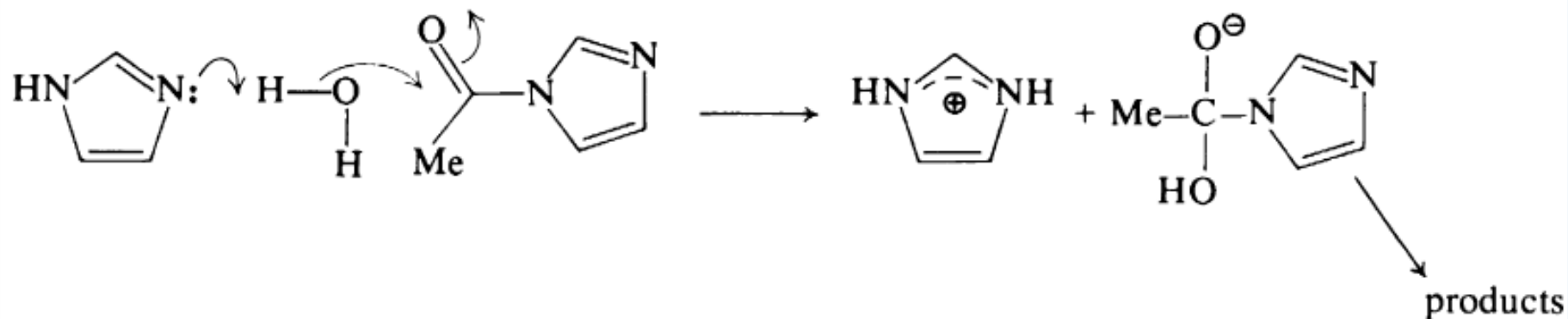
## Oxidation of the iodide ion with acidic H<sub>2</sub>O<sub>2</sub>



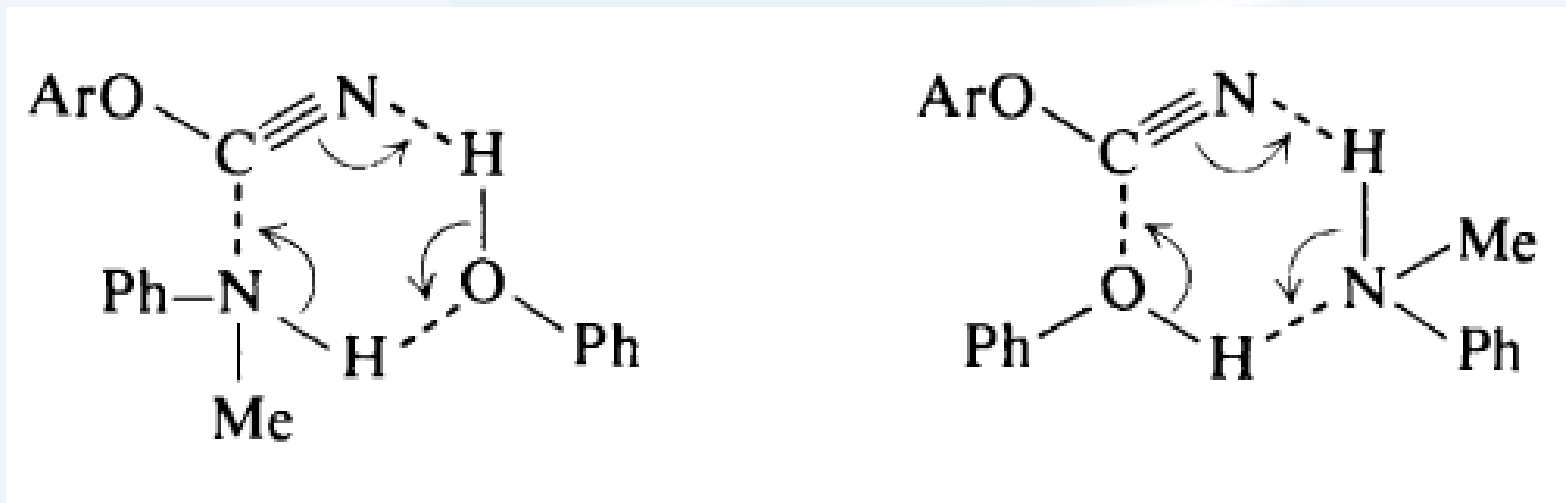
The classical Zeisel method for the determination of ether



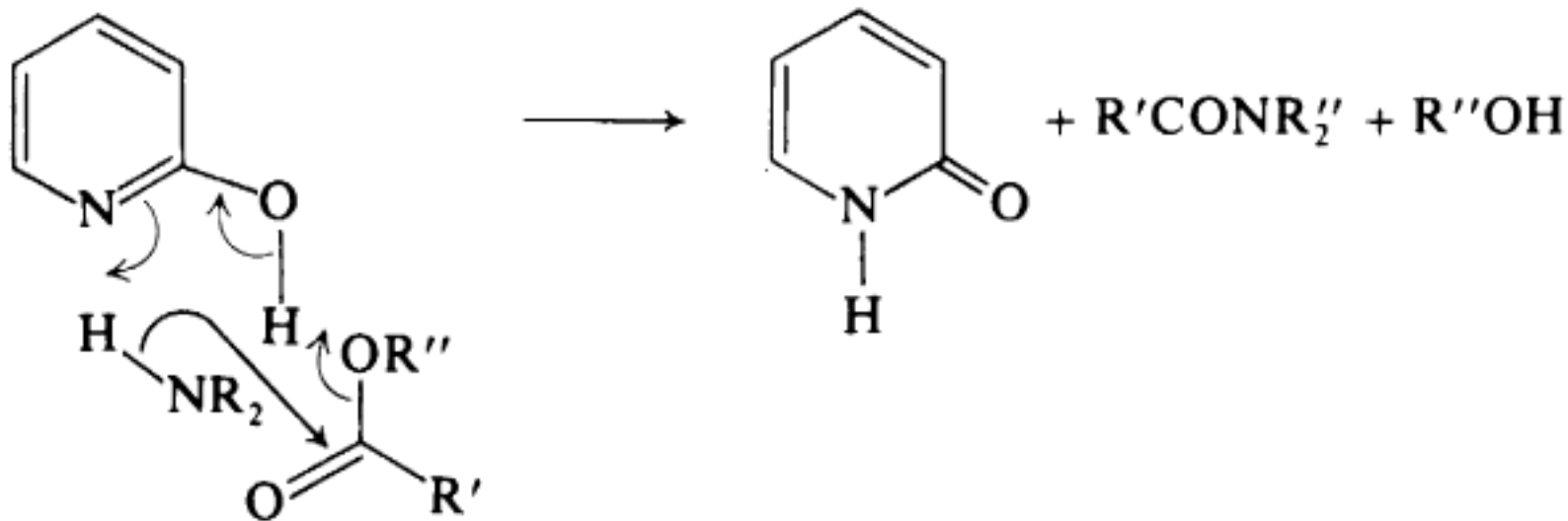
Alkyl fluorides cannot be prepared with this method. However, there exist many facile multicenter reactions which do not fall into either of the two categories. The hydrolysis rates for acetylimidazole rise with increasing imidazole buffer concentration, and this observation suggests a (h) .. (h)-(h) .. (h) transition state.



The addition of *N*-methylaniline to aryl isocyanate is catalyzed by phenol and the addition of phenol to the isocyanates is likewise catalyzed by *N*-methylaniline. Cyclic transition states have been proposed for these reactions. All these interactions are hard.



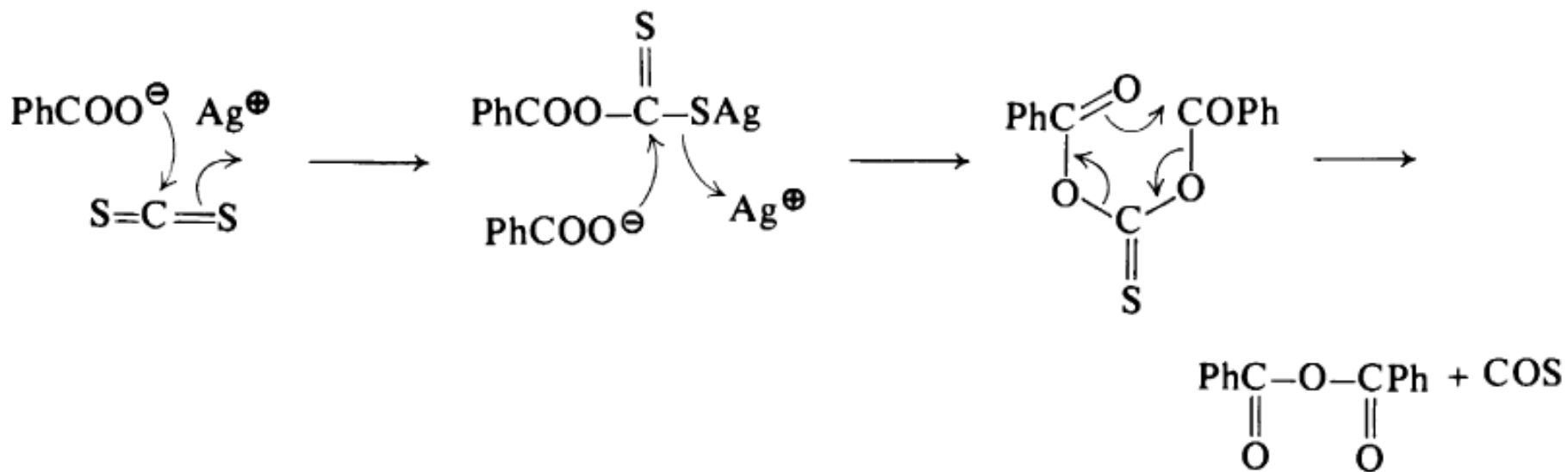
**2-Hydroxypyridine is a very useful catalyst for promoting aminolysis of esters.**



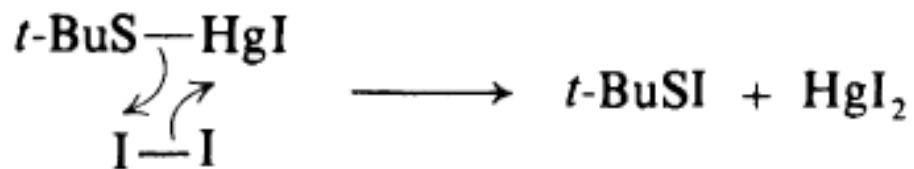
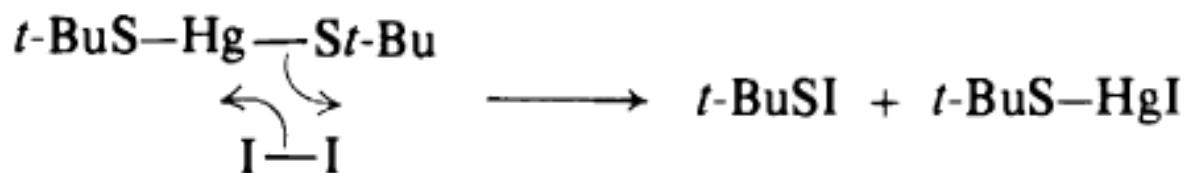
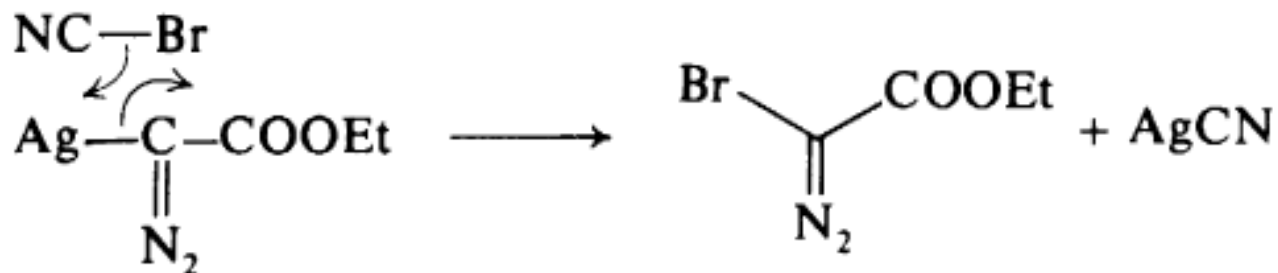
**eight centers; hard forces**



Although Saville rule 1 is shown in the first and second steps of the reaction of silver benzoate with carbon disulfide, the decomposition of the intermediary O,O-dibenzoylthiocarbonate proceeds with (h) · · (h) – (h) · ·(h) reorganization.



Four-centered reactions in which all the acid-base pairings are made up of soft species are also known.



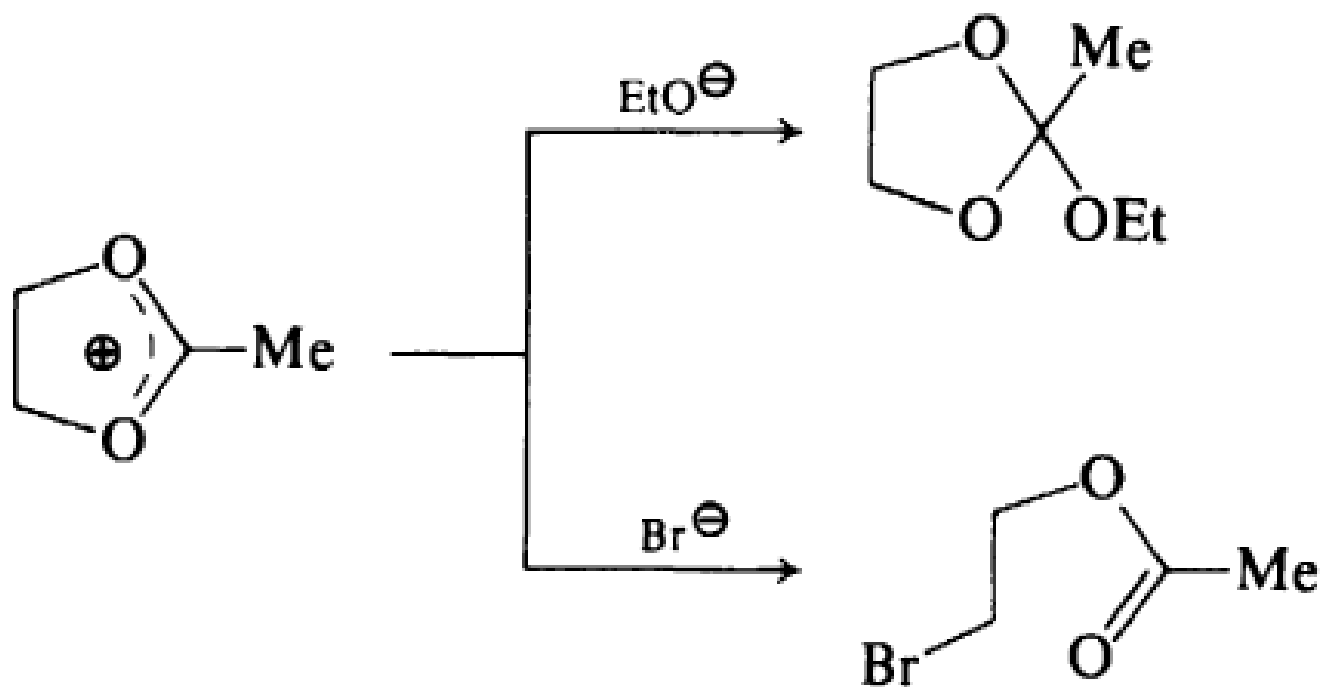


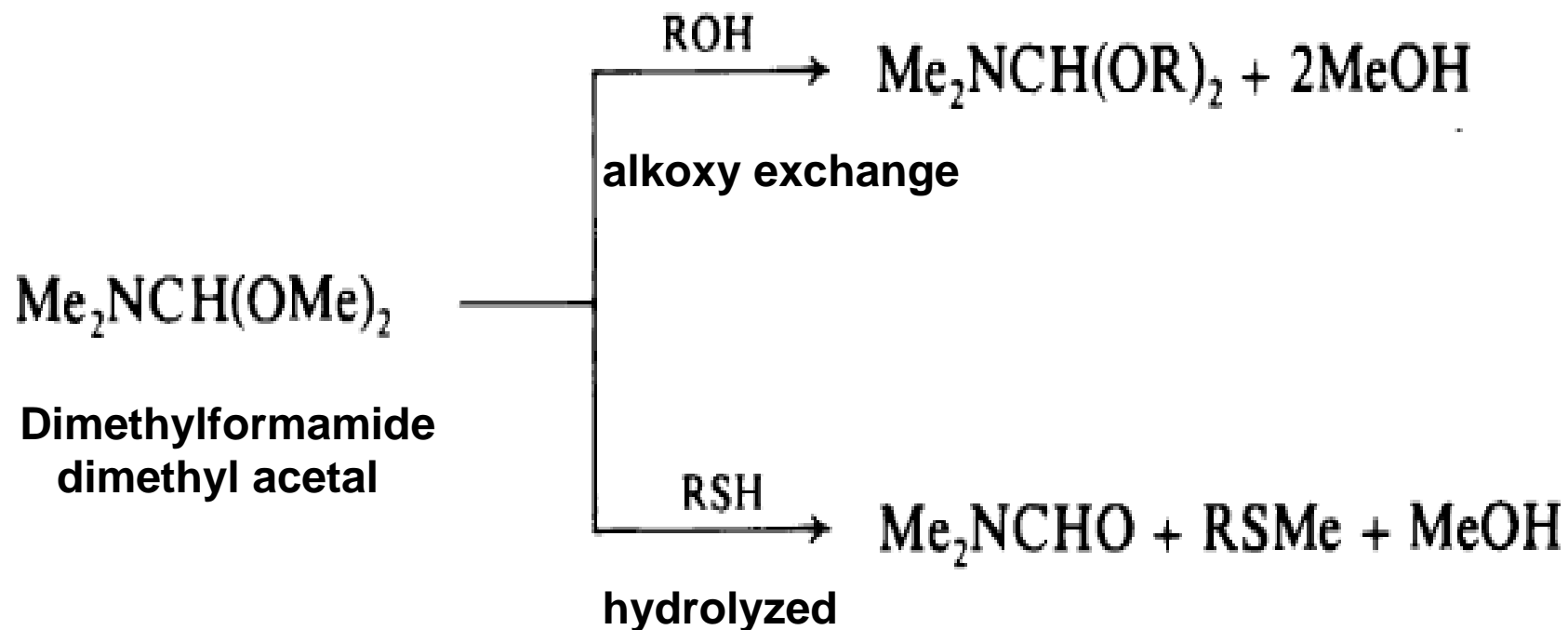
# AMBIDENT REACTIVITY

**Chemical species may possess two or more reactive sites which are often interrelated by tautomerism or mesomerism. Such entities are called *ambident*. They differ fundamentally from simple bifunctional compounds.**



# Ambident Electrophiles



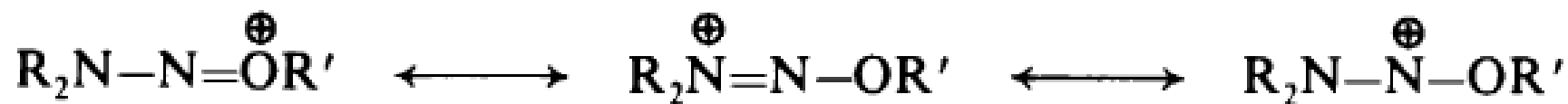


**Water neutralizes the carbenium center of tris(methylthio)methyl cation  $(\text{MeS})_3\text{C}^+$ , soft ions ( $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{CN}^-$ ) attack the methyl group, and methanethiol also adds to the central carbon atom as dictated by the symbiotic effect. Triphenylphosphine reacts at the S site.**

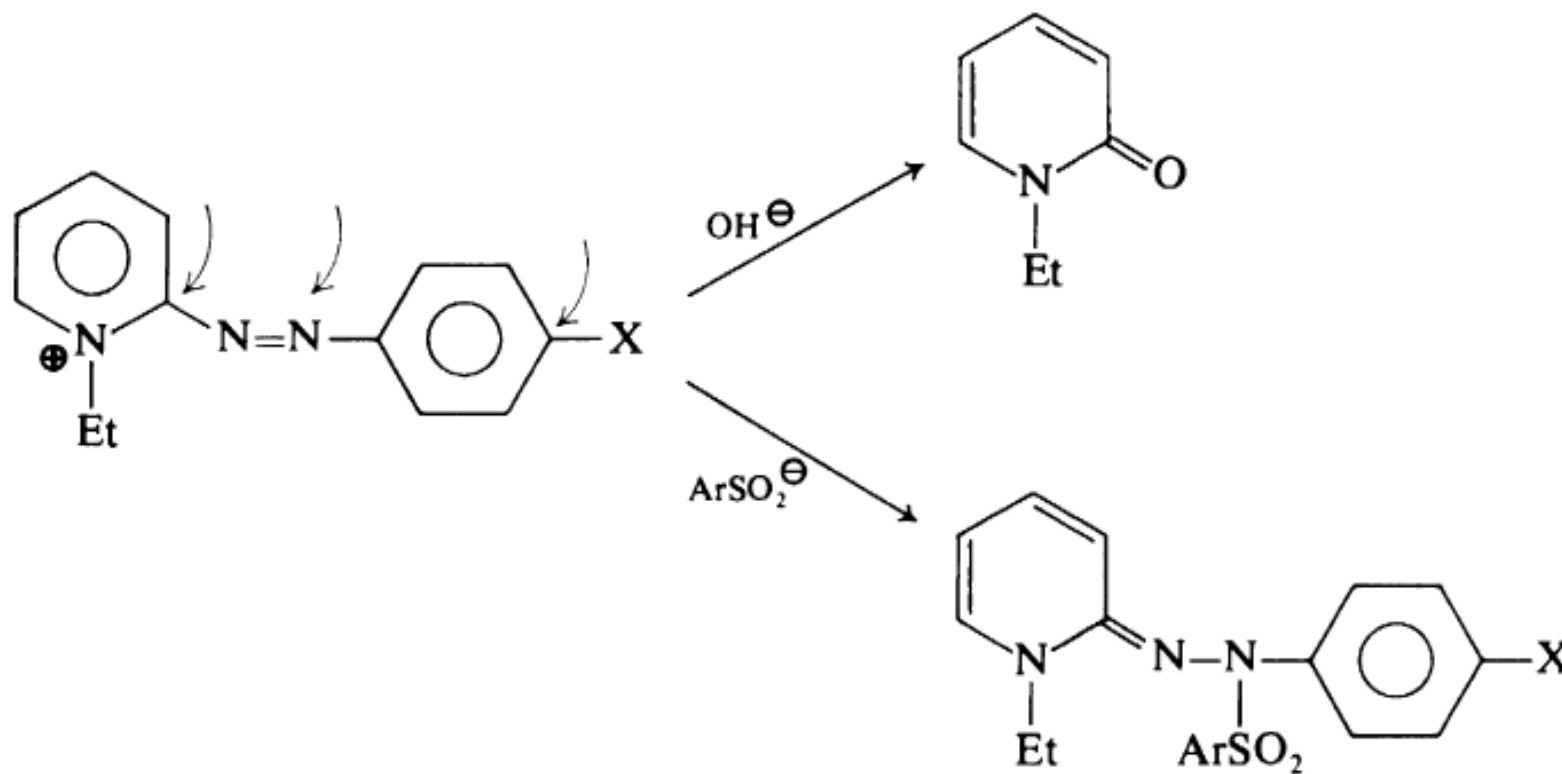
**The somewhat similar 2-dialkylamino-1,3-dithiolinium salts react with hard bases ( $\text{OH}^-$ ,  $\text{ArNH}_2$ ) at the carbenium site, with soft donors (e.g.,  $\text{RS}^-$ ) at methylene carbon atoms resulting in ring opening.**



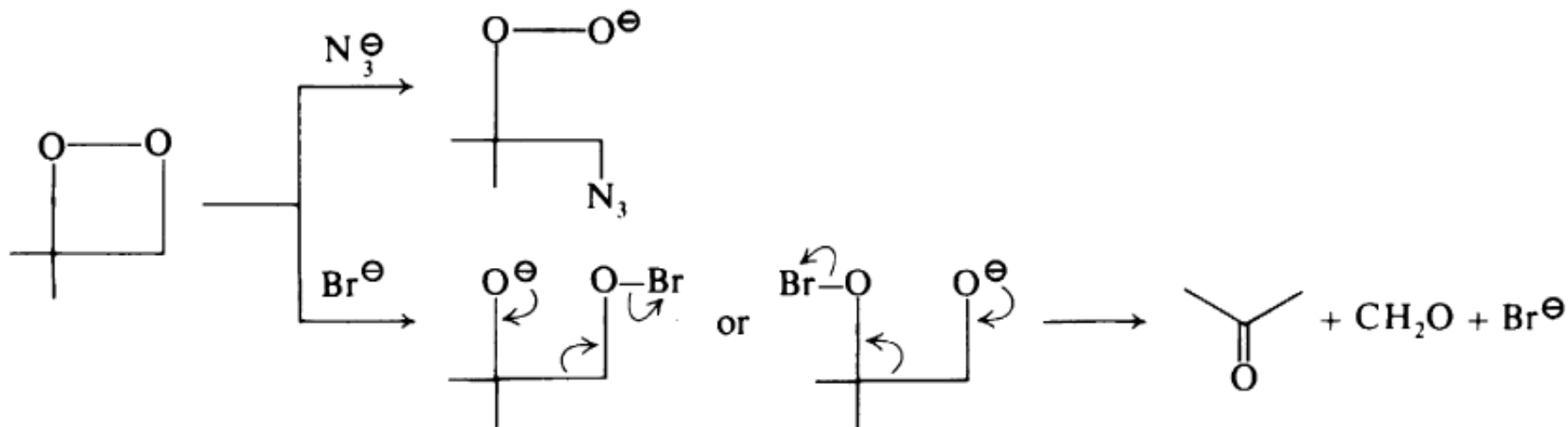
Typical soft bases such as  $\text{Me}_2\text{S}$  and  $\text{I}^-$  attack the softer carbon atom of the O-alkyl group of alkoxydiazonium ions.



Heterocyclic quaternary azo salts such as the pyridinium derivatives offer many sites for nucleophilic reaction. Again the mode of reaction is determined by the softness of the attacking species.



Kinetic and product analyses of 3,3-dimethyl-1,2-dioxetane indicate that azide ion displaces the peroxy group from carbon, whereas the bromide ion directly attacks the soft oxygen.



**The highly reactive  $\beta$ -propiolactone displays discriminatory reaction modes toward bases of different softness.**

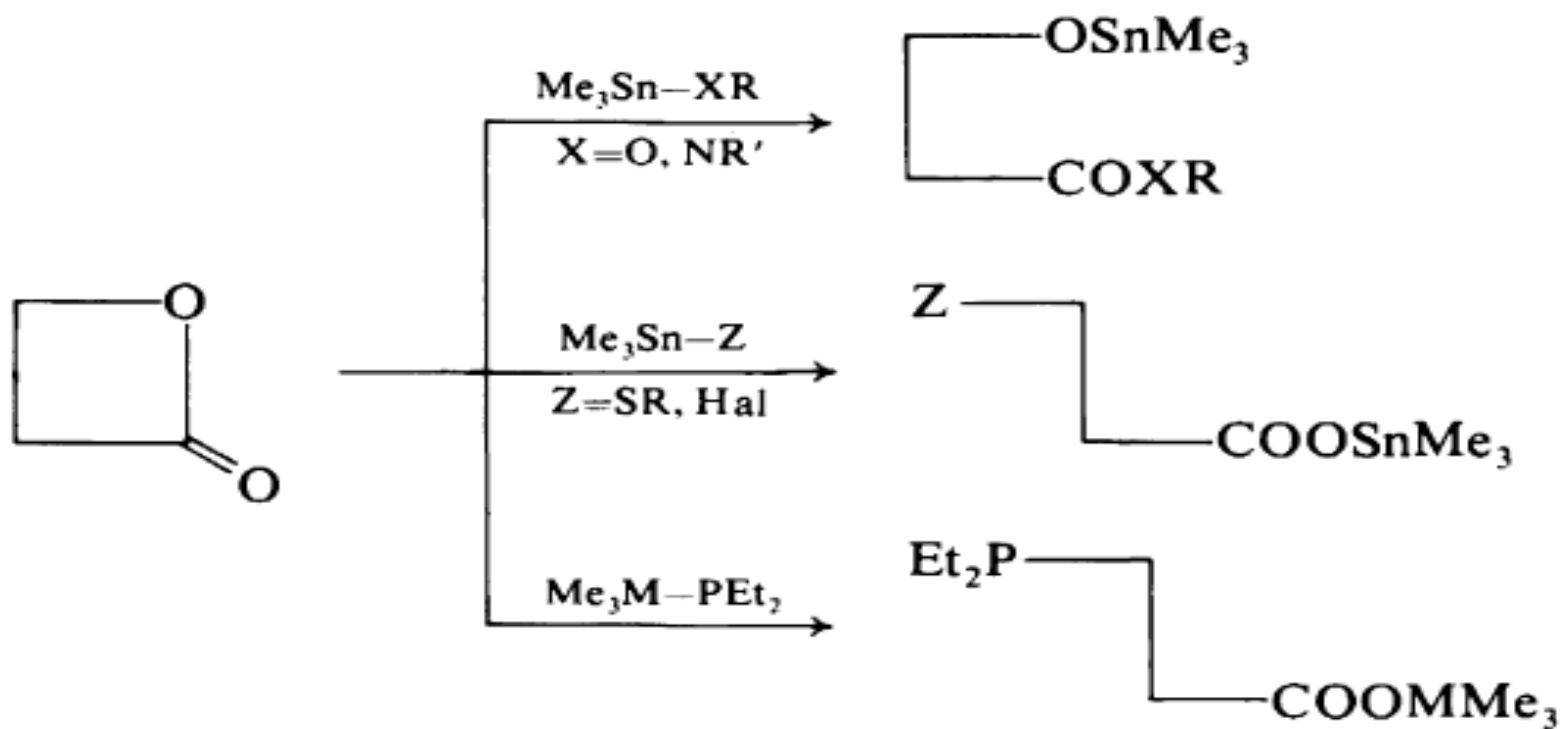
**For example, the hard alkoxide ion opens the lactone ring via addition to the acyl carbon whereas the soft cyanide and thiolate ions effect displacement at the  $\beta$  carbon.**

***Indole is alkylated at its  $\beta$  position to give 3-( $\beta$ -indolyl) propionic acid.***





# Ambident Reactivity



The cleavage of  $\beta$ -propiolactone with heterostannanes apparently proceeds via complexes in which the ethereal oxygen of the lactone is (loosely) linked to the tin atom.

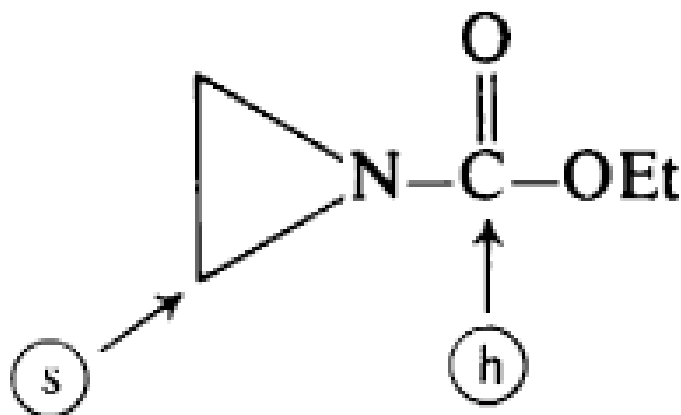
A hard hetero group (e.g., OR, NR<sub>2</sub>) is directed to bond with the acyl carbon. On the other hand, soft groups (SR, Hal) effect the formation of tin carboxylates.

The softer silicon and germanium atoms of diethylaminotrimethylsilane and -germane, respectively, impart a softer character to the nitrogen; thus, the interactions of these substances with  $\beta$ -propiolactone lead to  $\beta$ -dimethylaminopropionic acid derivatives.

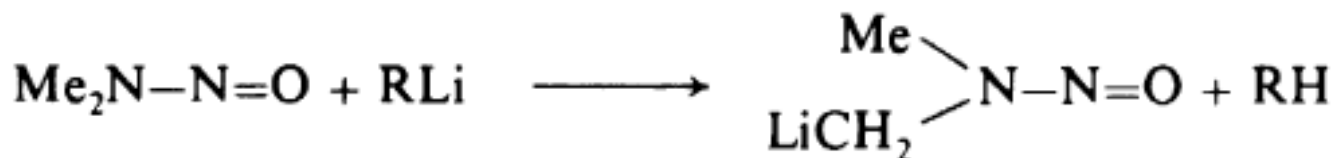
The diethylphosphino analogs Me<sub>3</sub>M-PEt<sub>2</sub> (M = Sn, Si, Ge), in which the phosphorus atom is soft, promote C $\beta$ -O bond rupture of  $\beta$ -propiolactone exclusively.



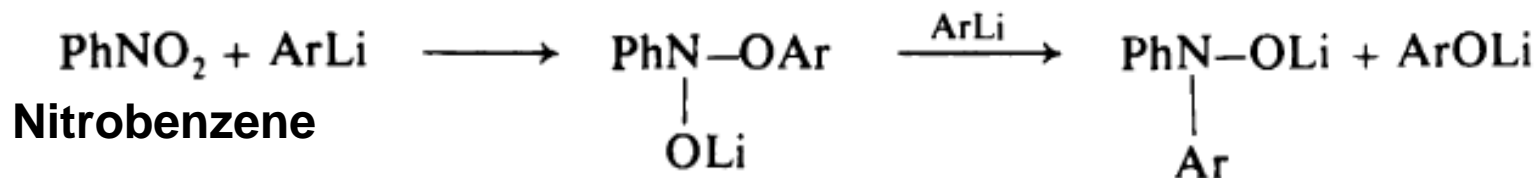
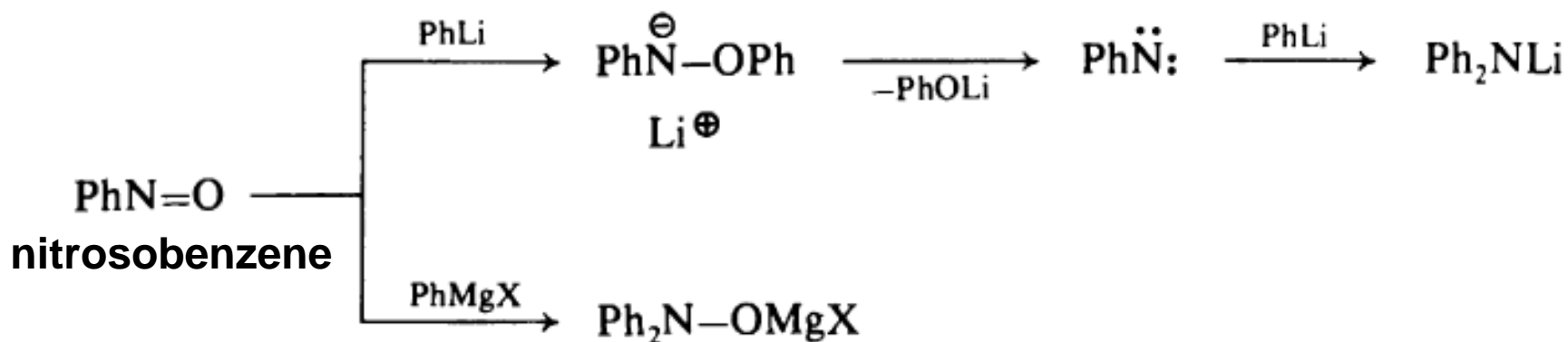
**N-Carbethoxyaziridine is an ambident electrophile with soft ring carbon sites and a hard carbonyl group.**



- Ⓢ attack:  $\text{H}^\ominus(\text{NaBH}_4)$ ,  $\text{PhNH}_2$ ,  $\text{Ph}_3\text{CLi}$
- Ⓜ attack:  $\text{H}^\ominus(\text{LiAlH}_4)$ ,  $\text{PNHLi}$ ,  $\text{RLi}$
- Ⓢ + Ⓜ attacks:  $\text{Ph}_2\text{CHLi}$  (soft 2 + hard 1)



Nitrosamines

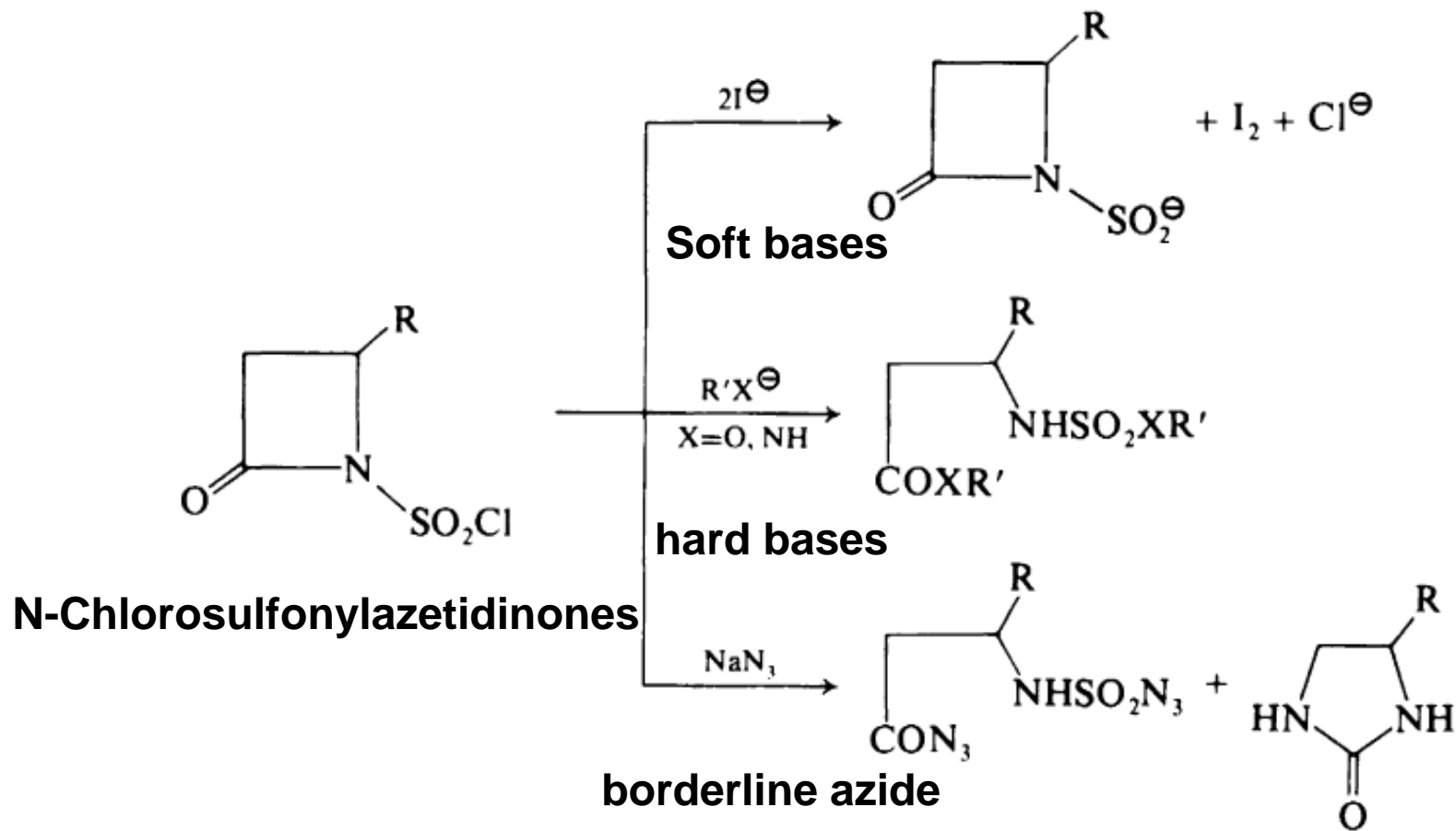


As acceptors both N and O of the nitroso group are quite soft.



**In perchloryl fluoride ( $\text{FClO}_3$ ) the fluorine is a soft acid. Formation of the C-F bond is observed when it is treated with carbanions. Thiolates are oxidized to disulfides by this reagent. This latter reaction presumably involves sulfenyl fluoride intermediates. In contrast, alkoxide ions effect displacement at chlorine to afford perchlorate esters or further transformation products.**



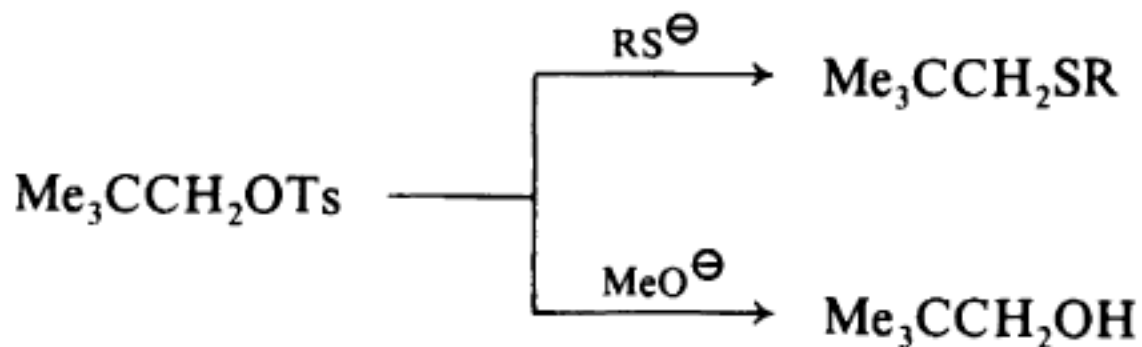


It seems that the fate (ring opening vs. rearrangement) of the tetrahedral azidohydrin intermediates depends on the nature of the N-substituent. If the substituent is a sulfinate anion or a negative charge, the ring-opening process becomes electronically unfavorable.





The failure to prepare sulfonylnitriles by reaction of sulfonyl halides with alkali cyanides is not at all surprising.



Tosylates are susceptible to nucleophilic attack at the hard S and the soft C centers. The site is determined by the hardness of the base employed.



# Ambident Nucleophiles

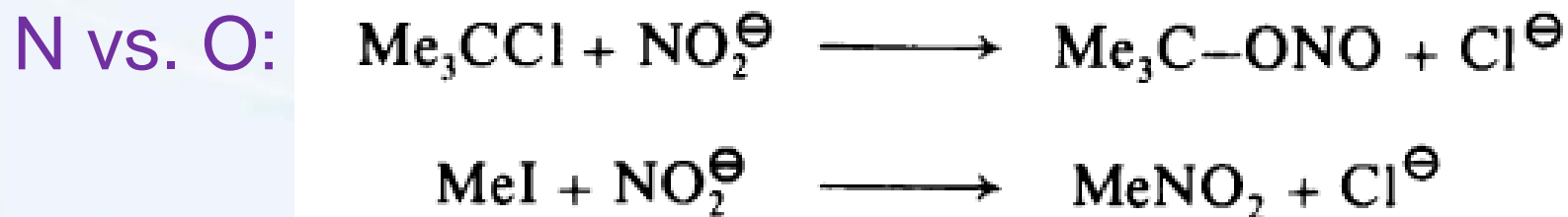
**Ambident nucleophilic reactivity is more intriguing and complex, as the reaction is influenced by numerous factors: counter cation, electrophile, solvent, temperature, and the inherent structural characteristics of the nucleophile.**

**Recently, Gompper and Wagner developed the concept of allopolarization in an attempt to describe substituent effects on reactions of ambident anions.**

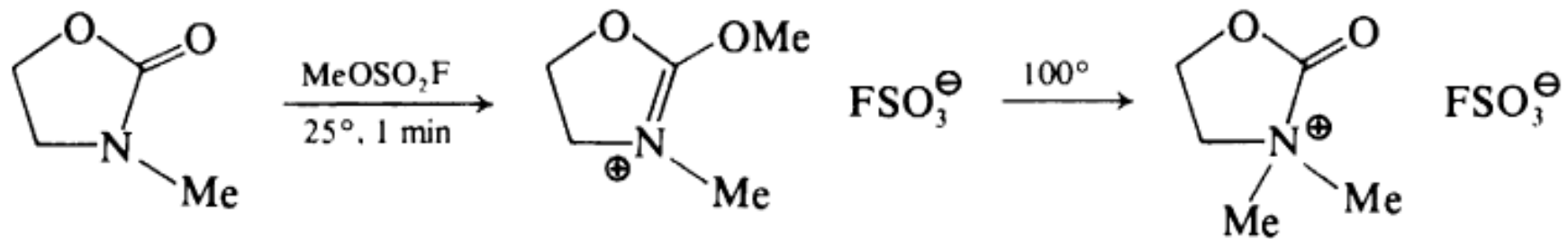
**allopolarization principle: Regioselectivities in reactions of ambident ions depend on the electronic effects of substituents**



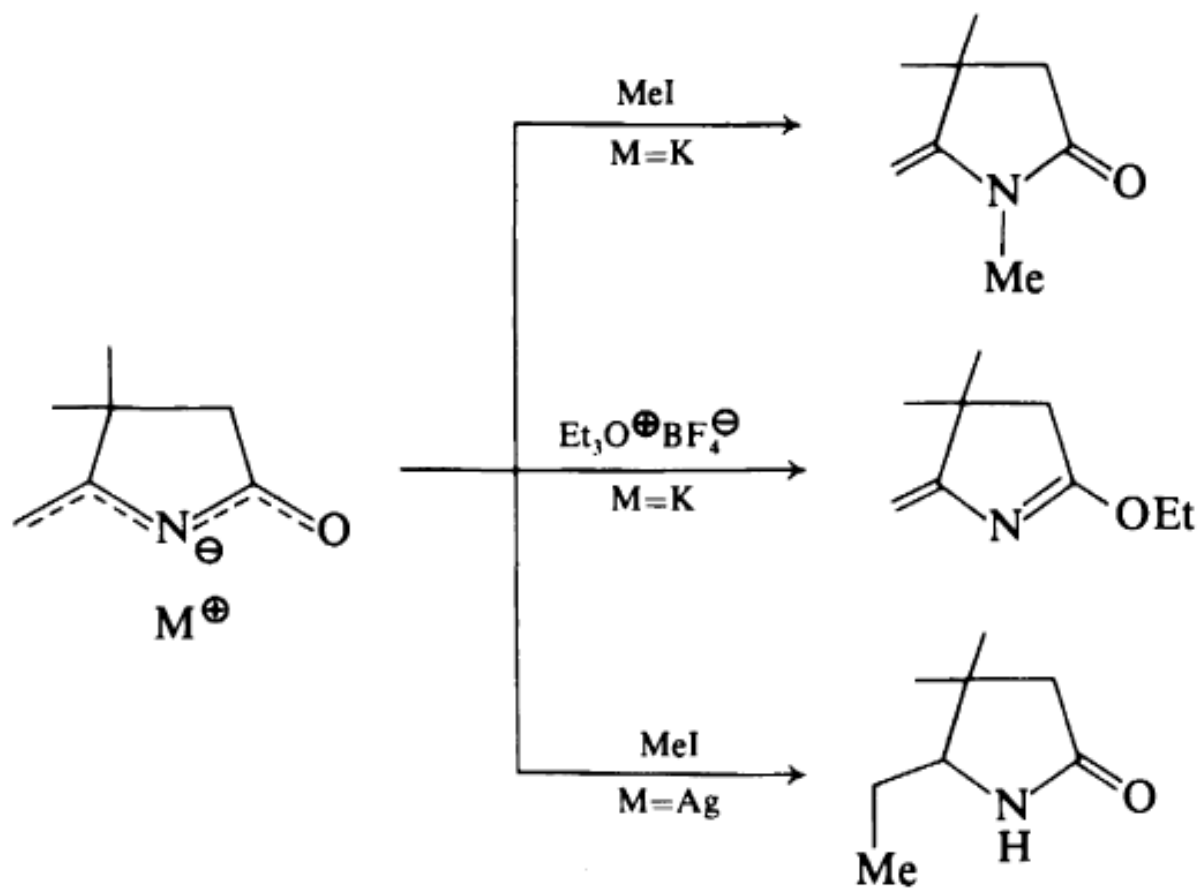




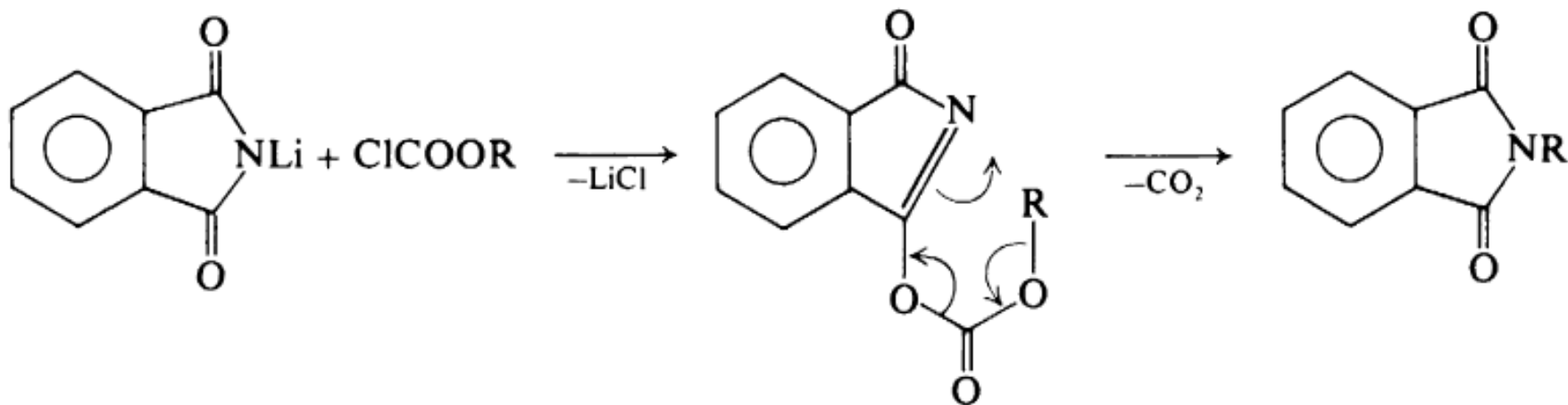
**Carbamates afford N-methylated products under equilibrium conditions. However, it has been demonstrated that O-methylation by MeOSO<sub>2</sub>F is rapid and the initial products tend to isomerize to the quaternary salts**



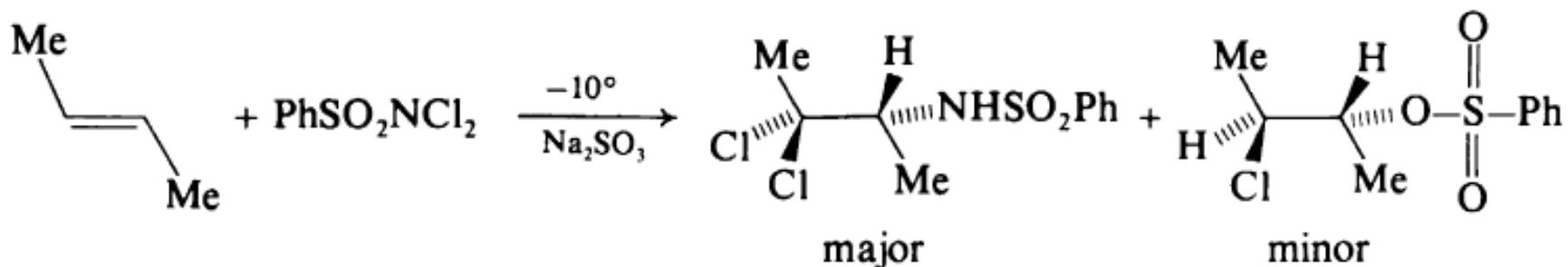
Enamides are ambident at C, N, and O, and accordingly they exhibit characteristic alkylation patterns. Selective C-methylation of the silver salt with MeI occurs because the vinylidene carbon is soft and the nitrogen site is blocked by its close association with the counter ion  $\text{Ag}^+$ .



Imides are alkylated with alkyl halides at N only. The formation of *N*-alkylimides by treatment of the lithium salts with alkyl chloroformates actually involves O-acylation, which is followed by decarboxylative alkyl transfer from O to N.

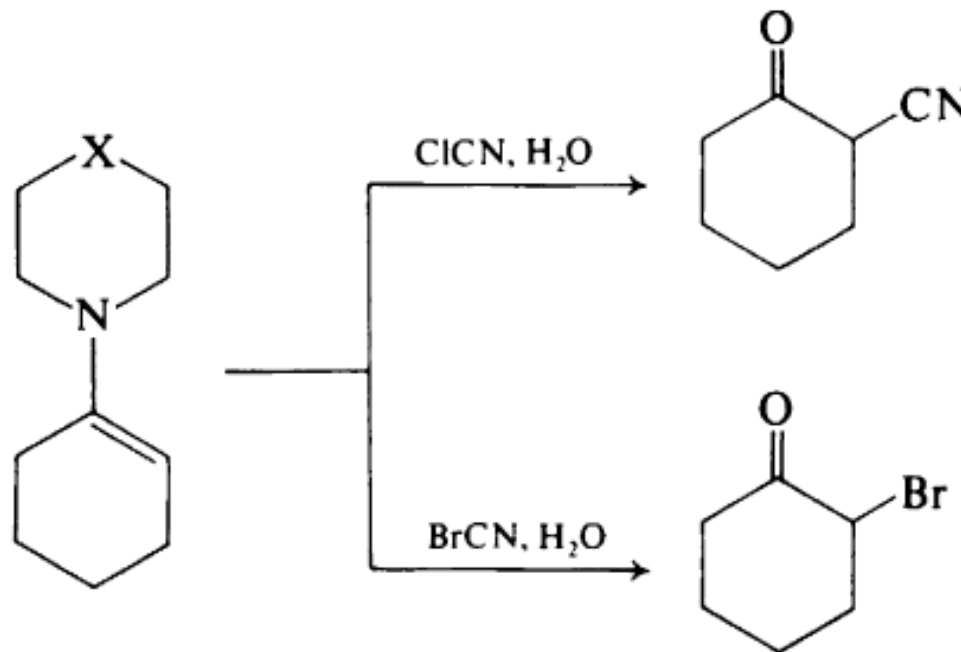


Addition of N,N-dichlorobenzenesulfonamide to 2-butene gives two products. The softer nitrogen end of the chlorosulfonamide anion seems to be more apt to approach the incipient carbenium center which is moderately hard.

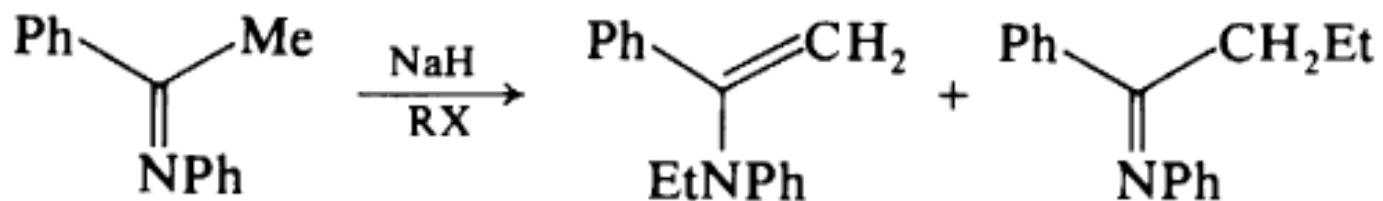


## N vs. C:

$\alpha$ -Cyanation of ketones can be achieved in a one-pot reaction via enamines. The electrophile is cyanogen chloride. The analogous reaction with cyanogen bromide takes a different course giving  $\alpha$ -bromoketones.



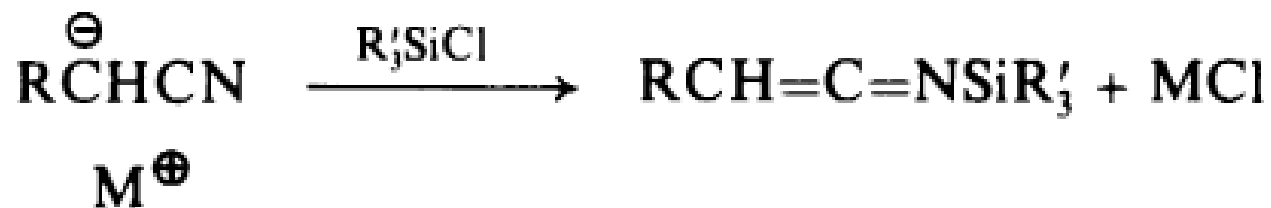
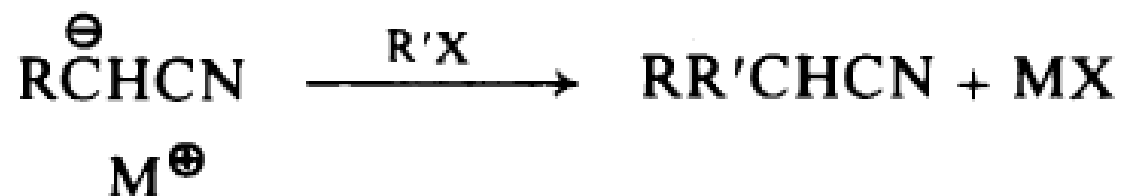
Imine anions attack alkylating agents in accordance with HSAB principle. The selectivity is very similar to that exhibited by the isoelectronic enolate ions.



$\text{RX} = \text{EtI}$	0.1	1
$\text{RX} = \text{Et}_2\text{SO}_4$	1.2	1
$\text{RX} = \text{Et}_3\text{O}^{\oplus}\text{BF}_4^{\ominus}$	22	1



**$\alpha$ -Cyano carbanions undergo C-alkylation with alkyl halides, but they give solely ketenimine derivatives on reaction with the hard trialkyl silyl chlorides**

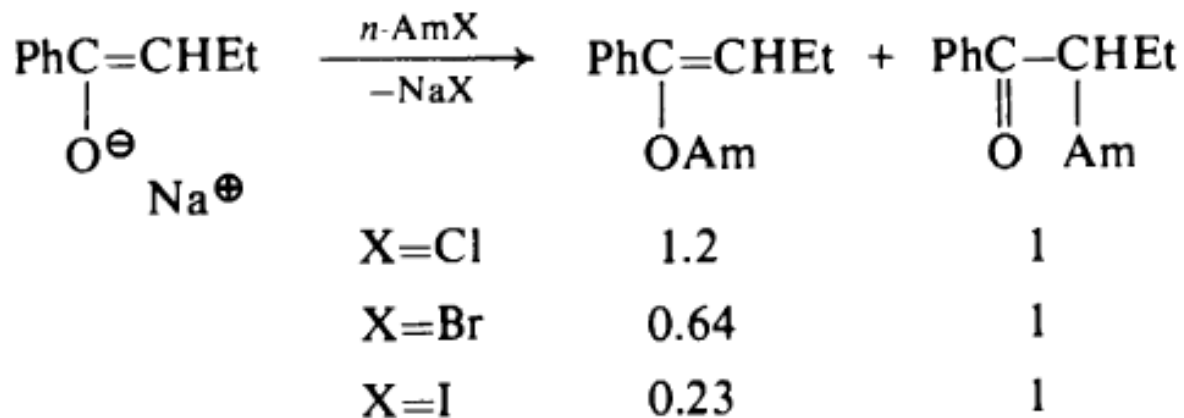


The cyanide ion is C, N-ambident. Alkali cyanides are extensively used in effecting transformation of alkyl halides into nitriles. Isonitrile formation is promoted by using  $\text{Ag}^+$  which polarizes the C-halogen bond rendering it more ionic (harder).



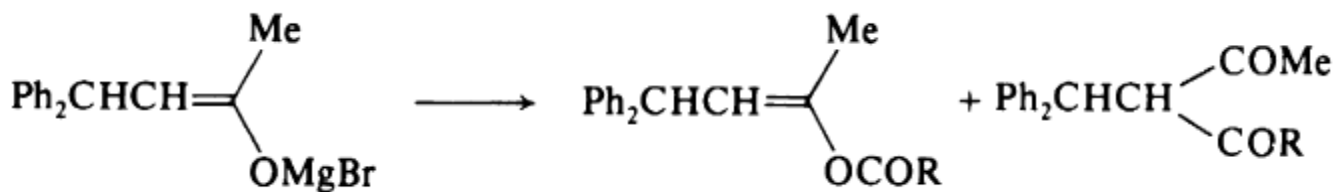


Amylation of butyrophenone enolate in dimethyl sulfoxide (DMSO) with reference to halide variation has also been studied. The lesser amount of enol ether formed corresponds to the softer halide.

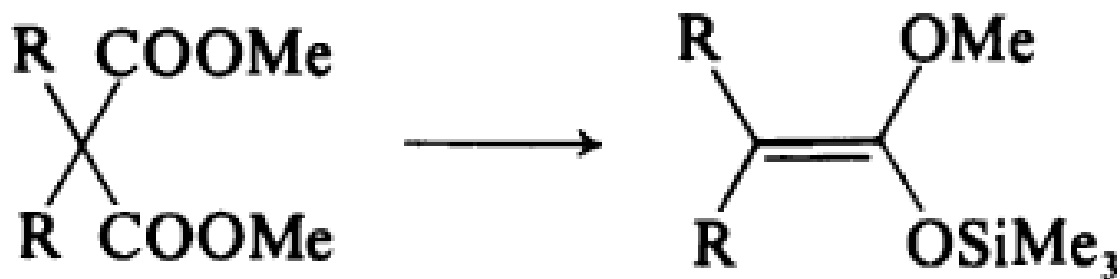


Solvent effects play an important role in the alkylation of 9-benzoylfluorene. In protic solvents C-alkylation predominates; O-alkylation becomes significant in HMPT, presumably owing to the strong solvation of the cations.

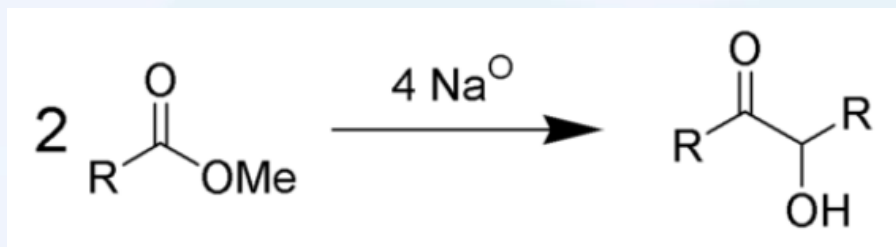
This phenomenon is discernible also during acylation of ketone enolates. The results of acylation of the bromomagnesium salt, generated by conjugate addition of Grignard reagent to benzalacetone, indicate a great enhancement of the O-acylation product fraction. This is accompanied by depletion of the C-alkylated compound when HMPT is added.



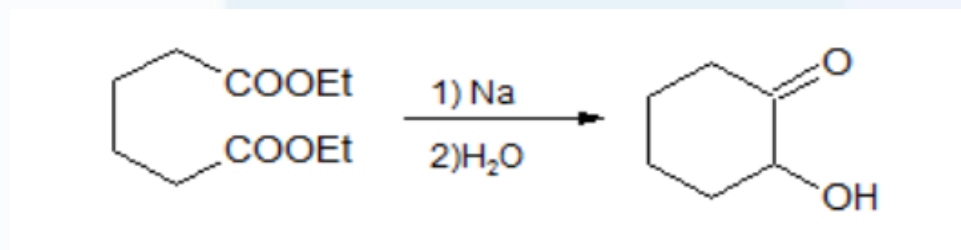
Disubstituted malonic esters are dealkoxycarbonylated under the modified acyloin condensation condition (Na-Me<sub>3</sub>SiCl). Thus, the intermediary ester enolates are also alkylated at the oxygen with the hard acid.



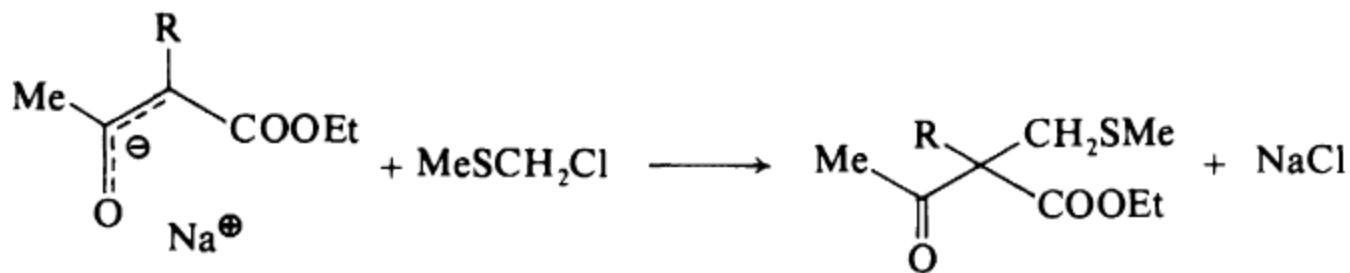
**Acyloin condensation** is a reductive coupling of two carboxylic esters using metallic sodium to yield an  $\alpha$ -hydroxyketone, also known as an acyloin

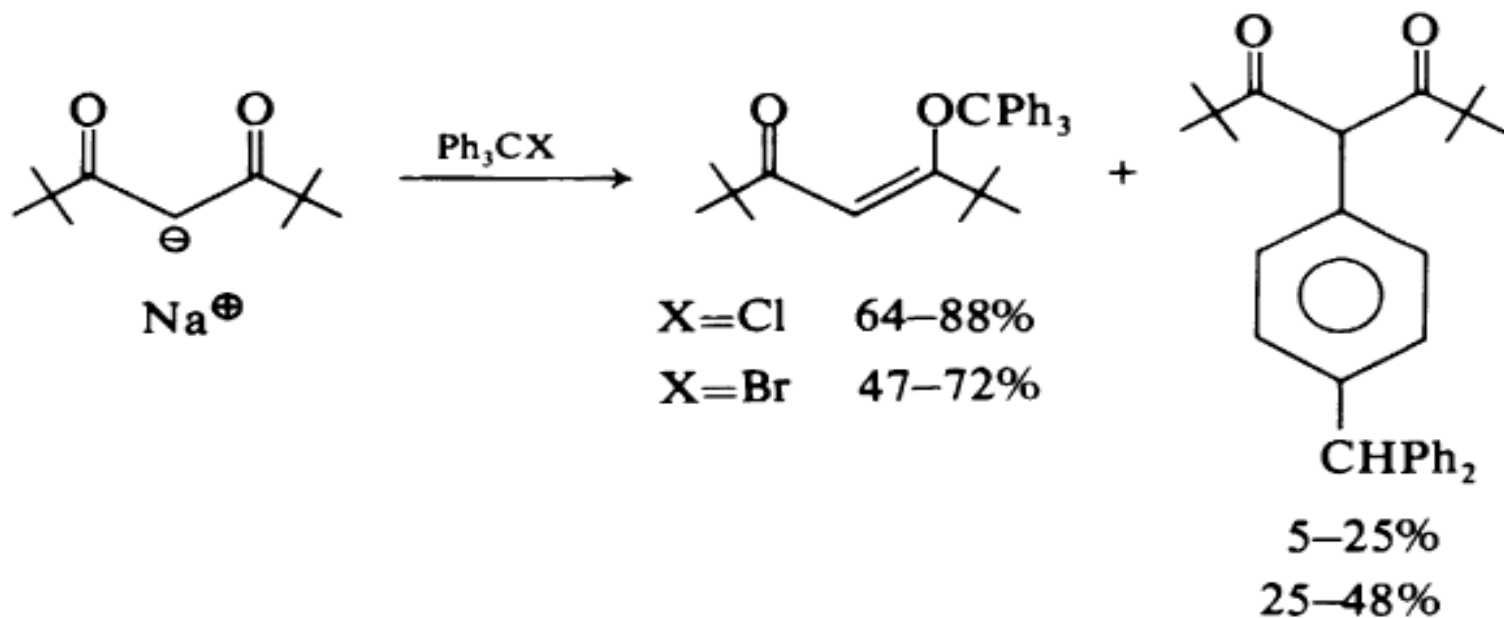


The reaction is most successful when  $R$  is aliphatic and inert. The reaction is performed in aprotic solvents with a high boiling point, such as benzene and toluene. The acyloin condensation of diesters favours intramolecular cyclisation over intermolecular



Exclusive O-alkylation of  $\beta$ -dicarbonyl compounds takes place with  $\text{ClCH}_2\text{OR}$  which resembles acyl halides. Transition state symbiosis contributes to the hard-type reaction. On the other hand, enolates attack the much softer  $\text{ClCH}_2\text{SMe}$  with their carbon termini.

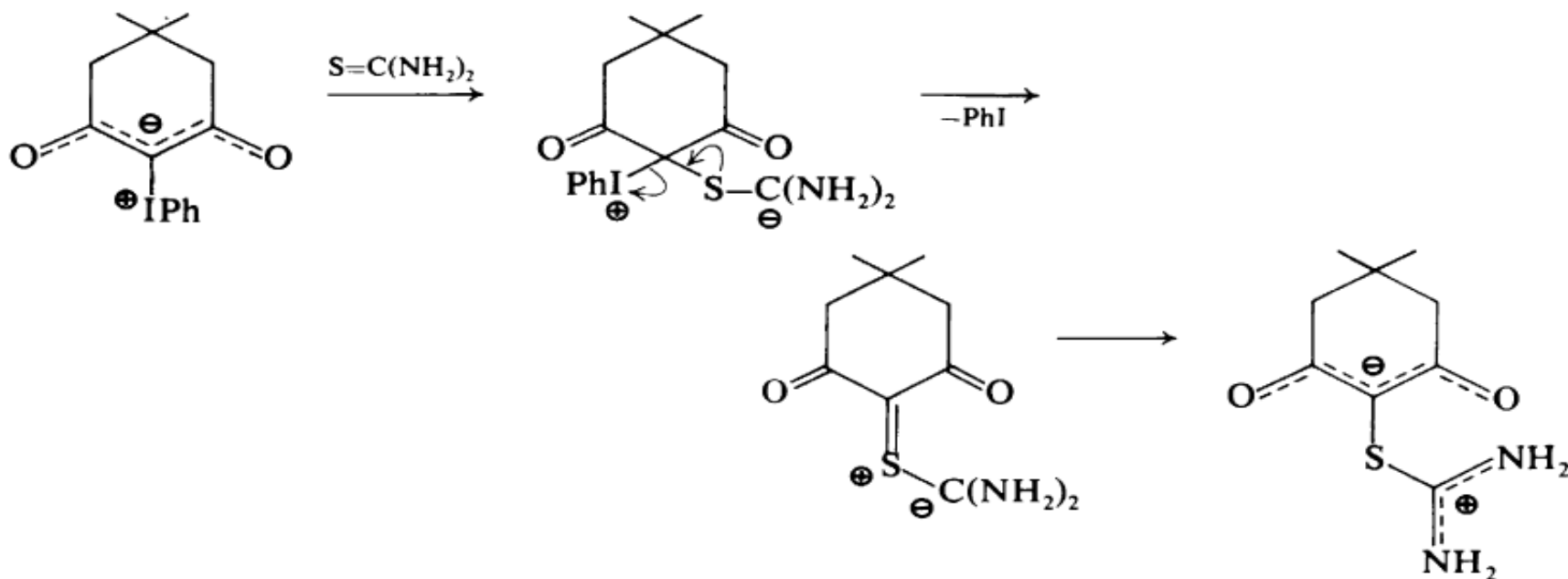




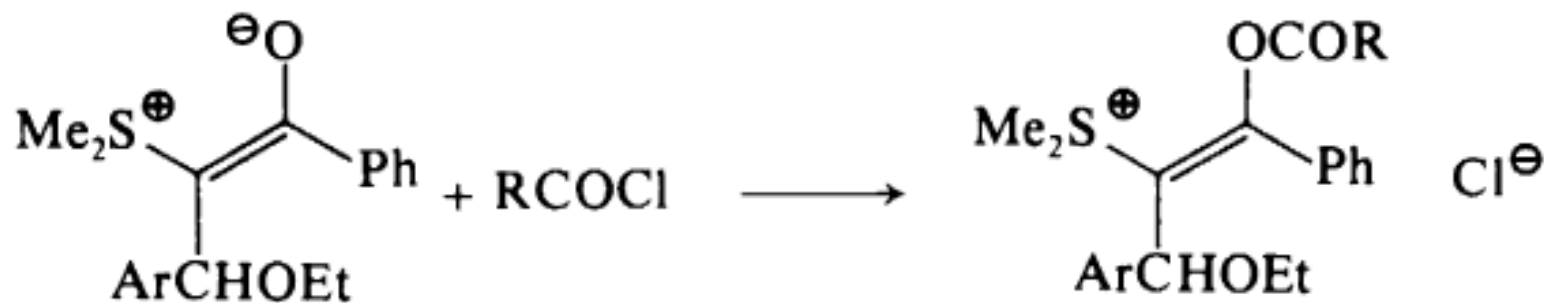
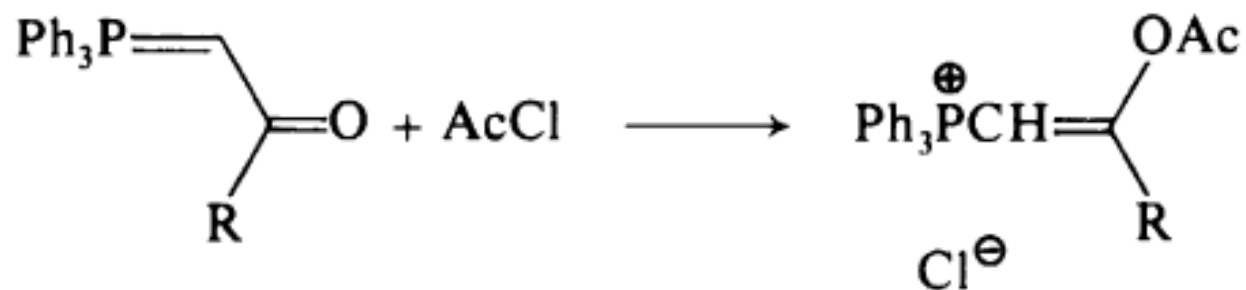
Zaugg *et al* reported the interaction of a hindered  $\beta$ -diketone enolate, sodiodipivaloylmethane, with trityl halides. O-Alkylation is more important with the chloride than with the bromide as usual. The striking feature of the reaction is that the carbanion attacks the aryl carbon of the electrophile as a consequence of steric repulsion.



The phenyliodonium dimedone ylide attacks diphenylketene with the oxygen atom. Interestingly, the reaction of the ylide with thiourea occurs at C-2, presumably via the following mechanism.



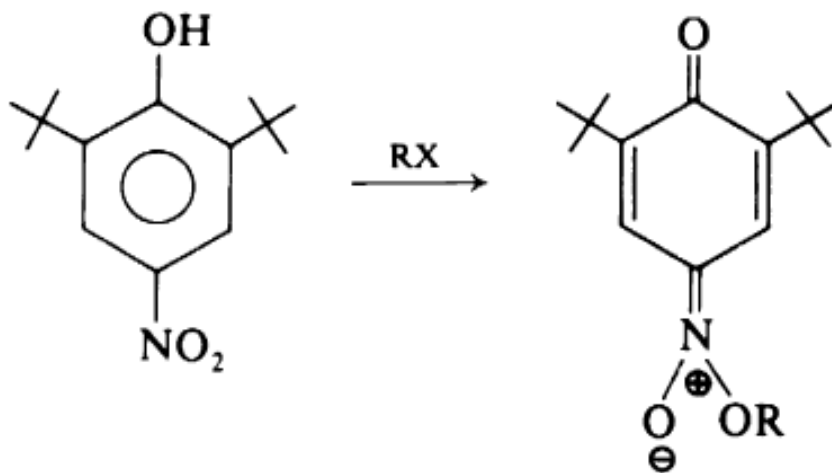
Stabilized ylides are acylated at oxygen.





2,6-Di-tert-butyl-4-nitrophenol is methylated by  $\text{CH}_2\text{N}_2$  and silylated by  $\text{ClSiMe}_3$  to give nitronate esters. Apparently steric crowding around the phenolic group forces the electrophiles to react with the alternative hard basic center.

The less hindered 2,6-diisopropyl-4-nitrophenol affords a mixture of methyl ether and nitronate ester.



Unsymmetrically substituted allyl carbanions are ambident. The reaction of phenylated allyl carbanions with various methylating agents has been investigated. The reactivity pattern corresponds with leaving group hardness.

1,1-Dichloroallyllithium adds to ordinary ketones with its softer  $\text{CCl}_2$  terminus, but to aryl ketones and hexafluoroacetone with its harder  $\text{CH}_2$  end.

