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The Hard Soft Acids Bases (HSAB) Principle and Organic Chemistry

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I. Introduction

Interpretation and prediction of organic reactions are often complicated by the entanglement of electronic, steric, and a variety of other effects. In 1963, Pearson[1] brought forth a unifying concept by which chemical reactivities, selectivities, and stabilities of compounds may be readily rationalized. Chemical entities including atoms, molecules, ions, and free radicals are categorized as "hard" and "soft" Lewis acids or bases. The "hard" species in general have small atomic radius, high effective nuclear charge, and low polarizability, whereas "soft" ones possess the opposite characteristics.

We know from classical theory that a strong acid and a strong base form a stable complex, and a weaker acid and base will form a less stable one. The strength of Lewis acids and bases is heightened by increased charge and decreased radius of cations and anions. The complex stability, however, cannot be adequately estimated by considering the intrinsic strengths (S) alone; softness parameters (σ) have to be introduced. Thus the reaction

$$\mathrm{A} + :\mathrm{B} \rightleftharpoons \mathrm{A{:}B} \qquad (1)$$

is characterized by the equilibrium constant k, where

$$\log k = S_A S_B + \sigma_A \sigma_B$$

From this consideration and collation of experimental data, the "hard and soft acids and bases (HSAB) principle" was formulated. This principle states that acids show greater affinity for bases of the same class and *vice versa*. Thus hard acids (acceptors) tend to form strong bonds with hard bases (donors), but bind reluctantly or weakly to soft bases. The latter class of compounds interacts preferably with soft acids. In other words, a hard-soft combination is destabilized.

Classification of acids and bases according to their softness is summarized in Tables I and II. Reviews of the HSAB principle in general terms[2-5] as well as its application to multicenter reactions[6] and organic chemistry[7,8] have appeared. In this article, a more extensive survey of organic reactions in the light of the HSAB theory is presented. This encompasses the intriguing classical problem of C- *vs.* O-alkylations, the dichotomy of S$_N$2 and E2 reactions, the striking new findings in the domains of organosulfur and phosphorus chemistry, and many other aspects. Explanation of solvation phenomena has been omitted, and the discussion of free radical reactions is avoided simply because the latter are less well defined in acid-base terms. A consistent picture may be drawn from these, however.

The reader is referred to Pearson's excellent papers for background materials and to Klopman[9] for theoretical considerations. A brief outline of Klopman's perturbation treatment of two reactants R and S is described here. The perturbation energy of the approaching R, S may be approximated as

$$\Delta E = -q_r q_s \frac{\Gamma}{\epsilon} + \Delta_{\mathrm{solv}} + \sum_{\substack{m \\ \mathrm{occ}}} \sum_{\substack{n \\ \mathrm{unocc}}} \left[\frac{2(c_r^m)^2 (c_s^n)^2 \beta^2}{E_m^* - E_n^*} \right]$$

where q_r, q_s = total initial charges, Γ = Coulomb repulsion term, ϵ = local dielectric constant of solvent, Δ_{solv} = solvation energy, c_r^m, c_s^n = frontier orbital electron densities, β = extent of bonding in transition state, and $E_m^* - E_n^*$ = energy difference of frontier orbitals. When $|E_m^* - E_n^*|$ is large, very little charge transfer occurs; the reaction is primarily determined by the total charges on the reactants (charge-controlled reaction). On the other hand, when the two frontier orbitals are nearly degenerate, *i.e.*, $|E_m^* - E_n^*| \sim 0$, their interaction (electron transfer) becomes significant, and $E = 2c_r^m c_s^n \beta$. This frontier-controlled reaction is enhanced

TABLE I. Classification of Lewis Acids[1]

Hard	Soft
H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+, Tl^+, Hg^+
Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Mn^{2+}	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, CH_3Hg^+, $Co(CN)_5^{2-}$, Pt^{4+}, Te^{4+}
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+}, N^{3+}, Cl^{3+}, Gd^{3+}, Lu^{3+}	Tl^{3+}, $Tl(CH_3)_3$, BH_3, $Ga(CH_3)_3$, $GaCl_3$, GaI_3, $InCl_3$
Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+}, CH_3Sn^{3+}	RS^+, RSe^+, RTe^+
Si^{4+}, Ti^{4-}, Zr^{4+}, Th^{4+}, U^{4+}, Pu^{4+}, Ce^{3+}, Hf^{4+}, WO^{4+}	I^+, Br^+, HO^+, RO^+ I_2, Br_2, ICN, etc.
UO_2^{2+}, $(CH_3)_2Sn^{2+}$, VO^{2+}, MoO^{3+}	Trinitrobenzene, etc. Choranil, quinones etc.,
$Be(CH_3)_2$, BF_3, $B(OR)_3$	Tetracyanoethylene, etc.
$Al(CH_3)_3$, $AlCl_3$, AlH_3	O, Cl, Br, I, N, $RO\cdot$, $RO_2\cdot$
RPO_2^+, $ROPO_2^+$	M^0 (metal atoms)
RSO_2^+, $ROSO_2^+$, SO_3	Bulk metals
I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+}	CH_2, carbenes
RCO^+, CO_2, NC^+	
HX (H-bonding molecules)	

Borderline: Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, Sb^{3+}, Bi^{3+}, Rh^{3+}, Ir^{3+}, $B(CH_3)_3$, SO_2, NO^+, Ru^{2+}, Os^{2+}, R_3C^+, $C_6H_5^+$, GaH_3

by high polarizability and low solvation energies, and it leads to a covalent bonding and can be associated with soft-soft interaction.

By setting $\Gamma = 0$ for all acids and bases, Klopman has defined an intrinsic character (softness) $E\ddagger$. A hard base is characterized by a low value for the occupied frontier orbital; a hard acid is characterized by a high value for the energy of the empty frontier orbital.

Before going into discussion of the various organic aspects, it should be emphasized that HSAB does not explain chemical facts, but correlates most of them very nicely. It does not concern itself with detailed mechanism of reactions and is applicable to many transformations which can be regarded, in a broad sense, as involving acid-base pairings. Current theories remain valid for explanation of these facts.

A further reminder pertains to the importance of intrinsic strength of acids and bases which partake the reactions, in comparison with their hardness. A case in point is the combination of an extremely hard Lewis acid H^+ with an extremely soft Lewis base H^- which results in a highly stable hydrogen molecule. This reaction proceeds in fast rates and is highly exothermic.

II. Softness (Hardness) Scales

The important factors governing the softness of a species are its size, charge or oxidation state, electronic structure, and the other attached groups. As anticipated, a group having a heavier or more electropositive central atom is the softer base within a congeneric series, *e.g.*

$$R_3Sb > R_3As > R_3P > R_3N$$

$$CH_3^- > NH_2^- > OH^- > F^-$$

$$I^- > Br^- > Cl^- > F^-$$

$$S^{2-} > SO_3^{2-}$$

It may be compared with the electronegativity scale for these donor atoms.

Organic bases in which the donor atom is a carbon are soft. Carbon acids are comparatively soft also. Owing to the fact that hydrogen is more electropositive than carbon,[10] the hardness sequence of several carbonium ions follows the order of $C_6H_5^+ > (CH_3)_3C^+ > (CH_3)_2CH^+ > C_2H_5^+ > CH_3^+$. This scale was supported by thermodynamic data deduced from the reaction of alcohols with hydrogen sulfide. The validity need not be restricted to free cations, but it is understood that the more carbonium character a center attains during a reaction, the harder it will be. The increasing stabilities of isomeric butyl alcohols: *n* < iso < *sec* < *tert*, parallel the trend of hardness exhibited by the carbonium ion R^+, which is to combine with the hard hydroxide ion.

TABLE II. Classification of Bases[7]

Hard	Soft
H_2O, OH^-, F^-	R_2S, RSH, RS^-
$CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-}	I^-, SCN^-, $S_2O_3^{2-}$
CO_3^{2-}, ClO_4^-, NO_3^-	R_3P, R_3As, $(RO)_3P$
ROH, RO^-, R_2O	CN^-, RNC, CO
NH_3, RNH_2, N_2H_4	C_2H_4, C_6H_6
	H^-, R^-

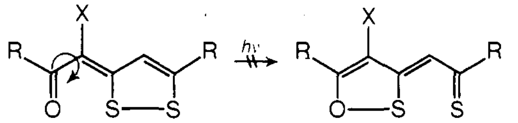
Borderline: $C_6H_5NH_2$, C_5H_5N, N_3^-, N_2, Cl^-, Br^-, NO_2^-, SO_3^{2-}

Replacement of hydrogen atoms in CH_3^+ by electronegative groups certainly would harden the cation. Since H^- is the softest base, CH_3^+ represents the extreme case in the softness scale of carbon acids bearing a positive charge. The only way to improve upon its softness is to remove a proton; thereby a carbene $:CH_2$ is created. A carbon radical is soft both as an acceptor or donor. Olefins act as soft bases.

Ni(0) [as in $Ni(CO)_4$] is soft, Ni(II) is borderline, but Ni(IV) is hard. The sulfur atom of RS^+ is a soft Lewis acid, but it becomes hard in RSO_2^+. Exceptions to this general trend have been found in Tl and Hg ions, those in the higher valence states being softer acids.[11]

III. Stability of Compounds and Complexes

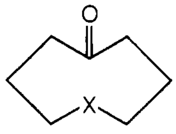
Substitution of an atom by another may confer great stability to a molecule or ion, or render it unstable or even nonexistent. The effect of substitution can often be predicted using the HSAB principle as a guide. Thus disulfides RSSR′ are stable, while sulfenyl esters RSOR′ are quite labile. The former class of compounds is composed of a soft-soft makeup and the latter, a soft-hard one. An interesting structural problem concerning the nature of photoisomers of thiathiophthene analogs has been resolved recently.[12] Cis-trans isomerization is involved instead of bond switching as previously postulated.[13] The bond switching process would involve breaking of a S-S bond and formation of a S-O bond and is unfavorable.



(2)

The acyl group RCO^+ is a hard Lewis acid; hence its combination with hard bases forms very stable molecules. These include carboxylic acids RCOOH, esters RCOOR′, and amides $RCONR'_2$. In contrast, its union with soft bases results in highly reactive or labile specimens such as thioesters RCOSR′ and acyl iodides RCOI.

Leonard and coworkers have thoroughly investigated the transannular interactions between a carbonyl group and a heteroatom diametrically situated in a mesocycle (**1**). Infrared, uv,[14] ORD,[15] dipole moment,[16] and other physical data indicate the existence of strong interaction N···C=O as in **2**; the corresponding sulfur analogs[17] show weaker interactions. Where the hetero group is a sulfoxide, participation through its oxygen atom (**3**) is observed.[18] The sulfoxide ammonium salt **4** has been shown[19] to assume a conformation in which hydrogen bonding between NH and the sulfoxide oxygen prevails.



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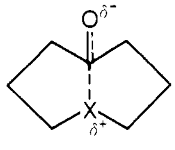

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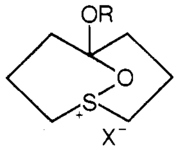

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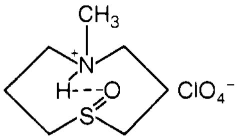

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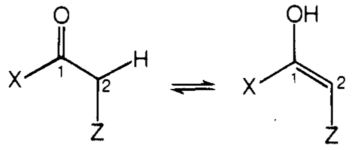
Thus the preference for hard-hard interaction is apparent from this study.

Lewis acid coordination with carbonyl compounds lowers the ν_{CO} absorption in the infrared. Since the donor atom is the hard oxygen, tighter and more stable complexes are formed between carbonyl compounds and hard Lewis acids which may be detected by infrared spectroscopy.[20] The following shifts exhibited by acetophenone are typical.

	Fe-Cl_3	Al-Cl_3	Ti-Cl_4	BF_3	Zn-Cl_2	Cd-Cl_2	Hg-Cl_2
$\nu_{O=O}$, cm^{-1}	130	120	118	107	47	38	31

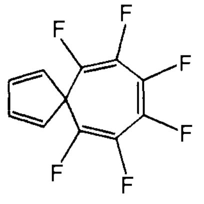
The substituent effect on the enolization phenomenon of carbonyl compounds may be analyzed in the HSAB context. When X of **5** is a hydrogen, C-1 is softened and enolization is favored. The C-1 of the enol form **6** is likely to be softer since it is doubly bonded to another carbon instead of oxygen as in the keto form. Aldol condensation[21] proceeds much more readily with aldehydes than with ketones. When X = Cl, OH, OR, and other electronegative functions, C-1 becomes harder, and enolization is discouraged.



5 **6** (3)

α-Substituents (Z) affect the ease of enolization accordingly. Electronegative groups such as halogens, carbonyl, etc., prefer direct bonding to a harder center which is available in the enol form (sp^2 *vs.* sp^3). Facilitation of enolization by these substituents is observed.

The fascinating cycloheptatriene-norcaradiene tautomerism[22] has now been largely clarified. There is a definite tendency for fluorine atoms to attach to the harder sp^2 carbon[23] of **7** rather than to the cyclopropane ring of a tautomer similar to the hydrogen analog **8**.[24,25] The tricyclic tautomer of **7** cannot be isolated.



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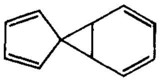

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Thermal reorganization of isonitriles to nitriles[26] is expected on the basis of HSAB concept.

$$R\overset{+}{N}\equiv\overset{-}{C} \xrightarrow{\Delta} RC\equiv N \qquad (4)$$

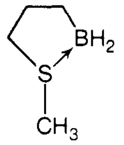
Ethers form very good complexes with boron trifluoride through a hard-hard O-F interaction. It has been pointed out that a maximal number of the same or similar groups flocked to a central atom tends to stabilize the final species, and the phenomenon is called "symbiosis."[27] Since both F and O are hard, it is not surprising that BF_3-OR_2 are stable. On the other hand, ethers are readily cleaved by boron tribromide.[28,29] The weaker B-Br bond as well as the O-C bond of the ethers are further enfeebled through complexation, which itself is a favorable event because two hard atoms form a dative bond. Collapse of the complexes by dissociating a bromide ion ensues which is followed by bromide attack (soft-soft) on carbon next to the oxonium center. These are very propitious processes.

Because boron (B^{3+}) is a hard Lewis acid, trimethyl borate $B(OCH_3)_3$ is more stable than $B(SCH_3)_3$. A recent thioacetalization procedure[30] employing trialkyl thioborate without catalyst has been achieved.

$$R_2C{=}O + B(SR')_3 \longrightarrow R_2C(SR')_2 \qquad (5)$$

This reaction parallels that of the BBr_3 cleavage of ethers in reasoning.

Borane, BH_3, also has a formal B^{3+} oxidation state. However, the hydride ions render the molecule sufficiently soft as manifested by the properties of 3-(methylthio)propylborane (**9**) which is more stable than the tetrahydrofuran complex **10**, and is distillable.[31]



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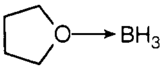


10

The extent of interaction between phenol and dialkyl chalcogenides R_2X falls off as X = O ≫ S > Se,[32] and is in line with relative compatibility in hardness between proton and the hydrogen bond acceptor. 2-Pyridones and the corresponding thiones and selenones are highly polarized. Although dipole moments increase in the direction of O < S < Se compounds, S and Se analogs exhibit weak ability to participate in hydrogen bonding.[33]

Evidence has been adduced for the following rapid equilibria[34] which involve soft-soft acid base interactions.

$$Me_2\overset{+}{S}{-}SMe\,BF_4^- + Me_2S_2 \rightleftharpoons Me_2S + (MeS)_2\overset{+}{S}Me\,BF_4^- \qquad (6)$$

$$(CH_3)_2\overset{+}{S}SCH_3\,BF_4^- + Me_2S \rightleftharpoons (CH_3)_2S + Me_2\overset{+}{S}SCH_3\,BF_4^- \qquad (7)$$

Mixed soft-hard interactions are so unfavorable that either the equilibria are biased completely on one side or are immeasurably slow by nmr standards.

$$Me_2\overset{+}{S}SMe + Me_2O \rightleftharpoons Me_2S + Me_2\overset{+}{O}SMe \qquad (8)$$

$$(CH_3)_2\overset{+}{S}OCH_3 + Me_2S \xrightleftharpoons{\text{slow}} (CH_3)_2S + CH_3\overset{+}{O}SMe_2 \qquad (9)$$

Studies such as shown below yield data of hard-soft characteristics of donors and acceptors.[35]

$$(CH_3)_3NBH_3 + (CH_3)_3P \xrightleftharpoons{20:80} (CH_3)_3PBH_3 + (CH_3)_3N \qquad (10)$$

Another case in point concerns with equilibrium between aminophosphines and diphosphines[36] at room temperature.

$$(CH_3)_2PN(CH_3)_2 + (CH_3)_2PH \overset{1\,t{:}89}{\rightleftharpoons} (CH_3)_2PP(CH_3)_2 + (CH_3)_2NH \quad (11)$$

Pearson has shown that the following reactions would be favored thermodynamically.

$$(CH_3)_3N + ZH_3 \longrightarrow (CH_3)_3Z + NH_3 \quad (12)$$

$$Z = P,\ As$$

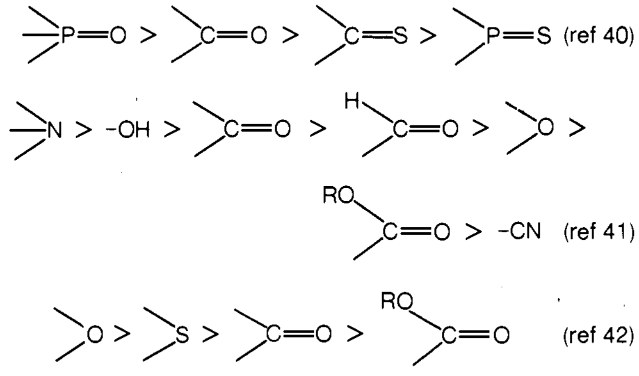
$$(CH_3)_2O + H_2S \longrightarrow (CH_3)_2S + H_2O \quad (13)$$

The relative inertness of divalent sulfur and trivalent phosphorus compounds toward proton but their aggressiveness in reactions with soft alkyl halides are well documented. Competition for alkyl halides among nitrogen and phosphorus atoms in aminophosphines[37] serves to illustrate HSAB theory.

$$R_2NPR'_2 + R''X \longrightarrow R_2N\overset{+}{P}R''R'_2\,X^- \quad (14)$$

$R_3M{=}X$ (M = P, As; X = S, Se) complexes easily with soft metal ions but not with hard acceptors.[38] This behavior is in direct contrast to $R_3M{=}O$.

Lanthanide shift reagents[39] have found wide applications in nuclear magnetic resonance studies of organic molecules. Specific coordination of the transition metal ions with functional groups is the prerequisite and basis for the observed spectral shifts. It is now established that thiols, thioethers, and phosphines (soft donors) form much weaker complexes with the metal ions in reagents which happen to be hard Lewis acids than do ethers and amines (hard donors), by correlation with the magnitude of proton resonance shifts in the proximal methylene or methyl groups. Quantitative measurements indicate the relative abilities of various groups as listed:

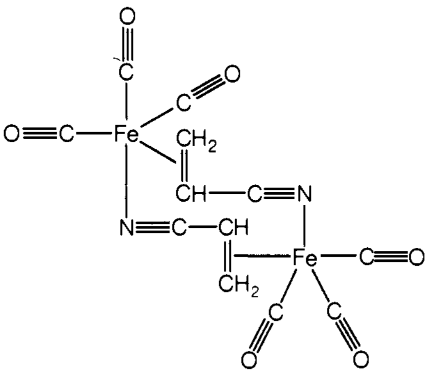


More recent data suggest the preference complexation by Eu(dpm)$_3$ at carbonyl rather than sulfur.[43]

Ions such as I_3^-, Br_3^-, charge-transfer complexes, and numerous organometallic compounds owe their stability to soft-soft interactions. Olefinic ligands, isonitriles, carbon monoxide, phosphines, sulfides, etc., are soft donors while zerovalent heavy metals are soft acceptors.

In the complex di-μ-acrylonitrile-bis(tricarbonyliron) (**11**) the acrylonitrile molecule uses both its π-bond and nitrogen as donors.[44] As expected, the nitrogen occupies an axial position which is preferred by harder ligands. It should also be noted that the CN→Fe bond is nonlinear; perhaps the nitrogen is softer in such a particular hybridization.

In recent years, several stable metal-carbene complexes (*e.g.*, **12**, **13**) have been synthesized.[45,46] Many carbenoids (*e.g.*, **14**, **15**)[47,48] have been postulated as reaction intermediates.[49] These are soft acid-soft base pairs.



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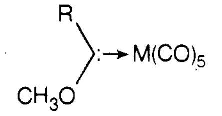
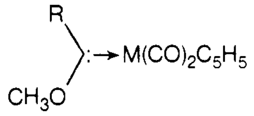


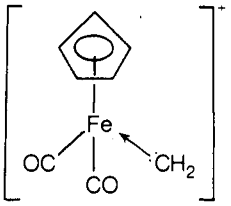
M = Cr, Mo, W

12



M = Mn, Re

13



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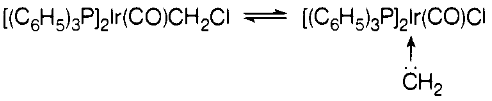


$$[(C_6H_5)_3P]_2Ir(CO)CH_2Cl \rightleftharpoons \underset{\overset{\uparrow}{\ddot{C}H_2}}{[(C_6H_5)_3P]_2Ir(CO)Cl}$$

15

Decomposition of diazo compounds to carbenes is strongly catalyzed by heavy metals (*e.g.*, Ag, Cu, Pd) and their cations, by a soft-soft coordination which weakens the C-N bond.[50-52]

The phosphorus and sulfur ylides are more stable than the nitrogen and oxygen analogs,[53] the former being composed formally of carbenes complexed to soft donors. The high stability of CH_2I^- compared with that of CH_2F^- is in conflict with classic theory of inductive stabilization, but it is predicted on the basis of HSAB principle.[7]

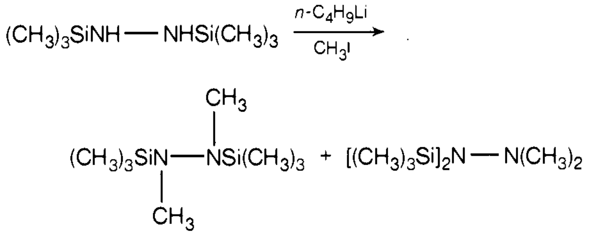
As mentioned before, the symbiotic effect has profound influence on stability of chemical entities. A few more examples are discussed here. Ordinary hemiacetals are less stable than acetals; even less so are hemithioacetals in comparison with hemiacetals and with thioacetals. Disproportionation of difluoromethane, and of formaldehyde, and the halogen exchange between iodotrifluoromethane and fluoromethane are assisted by symbiosis.[7]

$$2CH_2F_2 \longrightarrow CH_4 + CF_4 \quad (15)$$

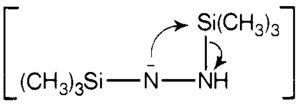
$$2CH_2O \longrightarrow CH_4 + CO_2 \quad (16)$$

$$CF_3I + CH_3F \longrightarrow CF_4 + CH_3I \quad (17)$$

The partial rearrangement observed during methylation of *N,N'*-bis(trimethylsilyl)hydrazine[54] may be explained by invoking the symbiotic effect (*cf.* **16**).



$$\mathrm{(CH_3)_3SiNH{-}NHSi(CH_3)_3 \xrightarrow[CH_3I]{\mathit{n}\text{-}C_4H_9Li} (CH_3)_3Si\underset{CH_3}{N}{-}\overset{CH_3}{N}Si(CH_3)_3 + [(CH_3)_3Si]_2N{-}N(CH_3)_2} \quad (18)$$



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IV. Reaction Selectivity

A. Alkylation *vs.* Acylation

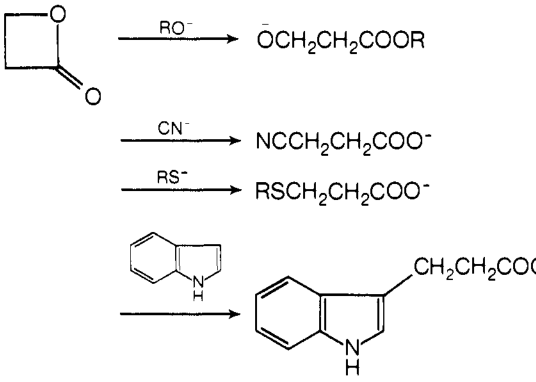
Saponification of carboxylic esters and amides is initiated by the addition of hydroxide ion to the acyl carbon to form a tetrahedral intermediate. The reaction is therefore subject to steric control. Hindered esters which are difficult to hydrolyze by standard techniques may be cleaved employing soft nucleophiles which attack specifically the alkyl carbon atom. Alkanethiolates are very efficient agents for the hydrolysis of phenacyl esters[55] and methyl esters[56] including mesitoate, podocarpate, and trisisopropylacetate. The method of potassium *tert*-butoxide in dimethyl sulfoxide[57] might involve the soft dimsyl anion as the reactive species.[58,59] The Taschner-Eschenmoser procedure (LiI-alkylpyridine)[60,61] and its various modifications[62,63] consist of nucleophilic attack on the methyl group by iodide ion.

$$\mathrm{RCOOCH_3 + LiI \longrightarrow RCOO^-Li^+ + CH_3I} \quad (19)$$

As expected, the harder the acyl carbon, the more susceptible it is to hydrolysis with hard bases. Trifluoro- and trichloroacetates[64] are readily hydrolyzed by aqueous or alcoholic ammonia at room temperature. It should be noted, however, that thiolates undergo S-alkylation on reaction with trichloroacetates.

$$\mathrm{Cl_3CCOOCH_2R + R'S^- \longrightarrow Cl_3CCOO^- + R'SCH_2R} \quad (20)$$

Even the extremely reactive β-propiolactone shows discrimination in its reactions with nucleophiles.



(21)[65]

(22)[66]

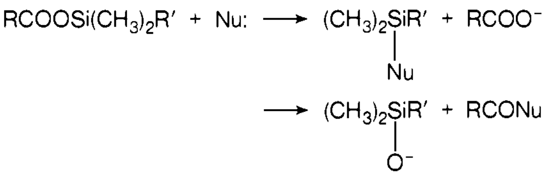
(23)[67,68]

(24)[69]

Reaction of β-propiolactone with trimethyltin methoxide and diethylamide gives respectively the methyl ester and diethylamide in which the stannyl group becomes bonded to the ethereal oxygen. Contrariwise, the corresponding tin halides and sulfides afford adducts *via* alkyl oxygen cleavage. Diethylaminotrimethylsilane and -germane also yield 3-diethylaminopropanoyloxy derivatives owing to softening of the nitrogen by virtue of $p\pi$–$d\pi$ interaction.[70]

The diethylphosphino analogs $(CH_3)_3MP(C_2H_5)_2$ [M = Sn, Si, Ge], in which the phosphorus atom is soft, promote cleavage of the C_β–O bond of β-propiolactone exclusively.[71]

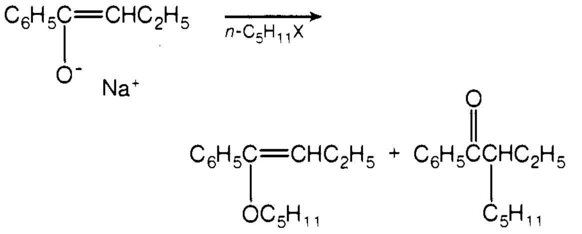
Some enlightening results have emerged from studies of nucleophilic attack on acyloxysilanes.[72] It has been demonstrated that organometallic reagents prefer reaction at the carbonyl function, whereas alcohols, alkoxides, and amines are mainly silicophilic. These observations are fully in accord with the hard nature of silicon; furthermore, they indicate the degree of hardness is higher than that of the ester carbonyl.



$$\mathrm{RCOOSi(CH_3)_2R' + Nu: \longrightarrow (CH_3)_2\underset{Nu}{Si}R' + RCOO^-} \quad (25)$$
$$\mathrm{\longrightarrow (CH_3)_2\underset{O^-}{Si}R' + RCONu}$$

B. C- *vs.* O-Alkylation

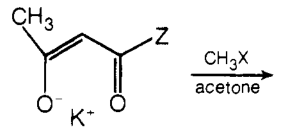
The dichotomy of C- *vs.* O-alkylation and acylation of enolates has intrigued organic chemists for a long time. The nature of cation, alkylating agent, solvent, reaction temperature, and medium homogeneity or heterogeneity play important roles.[73] The enolate ion is ambident; it possesses a hard oxygen and a soft carbon end. The O/C ratio often reflects the softness of the alkylating agent: the harder the reagent, the higher proportion of O-alkylated product results. Acetophenone gives O/C ratios of 0.1, 3.5, and 4.9 on reaction with ethyl iodide, dimethyl sulfate, and triethyloxonium fluoroborate, respectively.[74] A change in alkylation pattern of ketone enolates in dimethyl sulfoxide on varying the halogen atom in *n*-pentyl halides[75] has been observed, *e.g.*, eq 26.



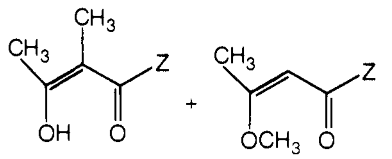
$$\mathrm{C_6H_5\underset{O^-\ Na^+}{C}{=}CHC_2H_5 \xrightarrow{\mathit{n}\text{-}C_5H_{11}X} C_6H_5\underset{OC_5H_{11}}{C}{=}CHC_2H_5 + C_6H_5\overset{O}{\overset{\|}{C}}\underset{C_5H_{11}}{C}HC_2H_5} \quad (26)$$

X		
X = Cl	1.2	1
Br	0.64	1
I	0.23	1

1,3-Dicarbonyl compounds also exhibit the same selectivities, as represented by eq 27.[76] Progressive in-



$Z = CH_3$; $X = I$
$Z = CH_3$; $X = {}^1/_2SO_4^{2-}$
$Z = OC_2H_5$; $X = {}^1/_2SO_4^{2-}$



(27)

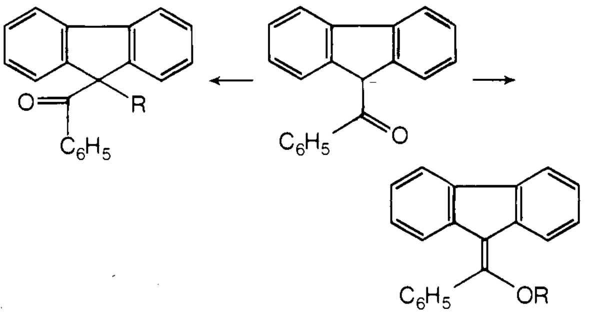
70%	-
26%	31%
30%	36%

crease in O-alkylation[77] in the series of RI, RBr, RCl was also revealed.

Systematic investigations have demonstrated that, in alkylation by *n*-alkyl halides or tosylates, the controlling factor is the hardness of the leaving group. With secondary halides or tosylates, the symbiotic effect of the leaving group is also important. In extreme cases where the alkylator is composed of a supersoft Lewis acid and a hard base (*e.g.*, allyl tosylate), or hard acid and soft base (*e.g.*, halomethyl methyl ether), the determining factor rests in the nature of the alkyl group.[78]

Of special interest is the reaction between benzophenone dianion $(C_6H_5)_2\bar{C}{-}O^-$ and CH_3X.[79] Even though the two negative charges are in adjacent atoms, no exception to the general rule is noted. The C/O ratios are 7.7 (CH_3I), 4.2 (CH_3Br), 2.7 (Me_2SO_4), and 0 (CH_3OTs).

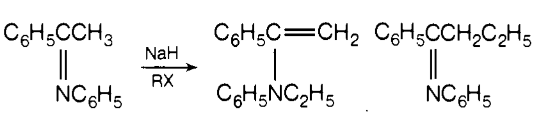
C-Allylation of sodium phenoxide[80] becomes prevalent as hydrogen bonding ability of the solvent augments. Solvation deactivates the hard oxygen atom and thereby favors C-substitution. Solvent effects are important in alkylation of 9-benzoylfluorene,[81] for in protic solvents C-alkylation predominates, but O-alkylation is observed in hexamethylphosphoric triamide, presumably due to poor solvation of the oxygen by the aprotic solvent molecules.



(28)

Alkylation of enolates with hard chloromethyl alkyl ethers[82] takes place exclusively at oxygen. Acylation also favors this hard site.[83] The hypothetical siliconium ions are harder than the corresponding carbonium ions; therefore only O-trimethylsilyl derivatives can be prepared by reaction of enolates with trimethylchlorosilane.[84,85]

Imine anions, being isoelectronic with enolates, respond in the same fashion to variation of leaving groups in alkylating agents (eq 29).[86] Dianions of the phenylhydrazones and oximes undergo selective C-alkylation with the first equivalent of alkyl halides.[87]



$$C_6H_5C(=NC_6H_5)CH_3 \xrightarrow[RX]{NaH} C_6H_5C(=CH_2)N(C_6H_5)C_2H_5 + C_6H_5C(=NC_6H_5)CH_2C_2H_5 \quad (29)$$

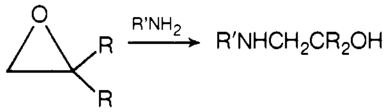
C_2H_5I	0.1	1
$(C_2H_5)_2SO_4$	1.2	1
$(C_2H_5)_3OBF$	22	1

Carboxylate anions can be converted into methyl esters[88] efficiently by reacting with dimethyl sulfate. Methyl halides are not effective, as anticipated from the HSAB viewpoint.

C. Reactions of Organosulfur Compounds

As a result of their soft nature, divalent sulfur compounds undergo many reactions radically different from those of the oxygen analogs. In the least, enormous disparity in reactivities are often noted.

Aminolysis of oxiranes[89] is rapid; however, ring opening of thiiranes by amines is much more sluggish. A remedy for the latter process has been found,[90] and this consists of weakening the C-S bond by coordinating the sulfur atom with the soft silver ion (eq 30 and 31). In the



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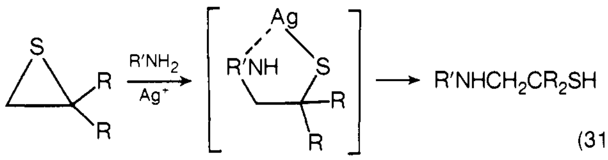


(31)

former reaction, the transition state is undoubtedly stabilized by both the incoming nitrogen and the departing oxygen atom. Operation of transition state symbiosis was first authenticated by Pearson and Songstad[91] who measured and analyzed the rates of the following displacement reactions in methanol.

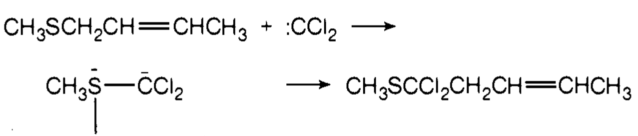
$$B^- + CH_3OTs \longrightarrow BCH_3 + TsO^- \quad (32)$$

$$B^- + CH_3I \longrightarrow BCH_3 + I^- \quad (33)$$

More recently, it has been demonstrated that[92] symbiotic effect is even larger in aprotic solvents such as acetonitrile.

Deoxygenation of oxiranes by the agency of trivalent phosphorus proceeds in low yields of olefin mixture and requires high temperatures. On the other hand, extrusion of sulfur from thiiranes is stereospecific and occurs at relatively low temperatures.[93] The results indicate that the thiophilic process is favorable as expected. Soft Lewis acids (*e.g.*, I_2) also effect the stereospecific desulfurization.[94]

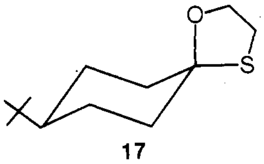
The divalent sulfur atom is softer than olefin as a donor; hence peracids (soft) oxidize the sulfur much more rapidly.[95] Carbenes and nitrenes are soft electrophiles; they are trapped mainly by the sulfur of vinyl sulfides.[96] Methyl crotyl sulfide affords an insertion product of dichlorocarbene,[97] probably *via* the Stevens rearrangement of an ylide.



$$CH_3SCH_2CH{=}CHCH_3 + :CCl_2 \longrightarrow CH_3\bar{S}(CH_2CH{=}CHCH_3){-}\bar{C}Cl_2 \longrightarrow CH_3SCCl_2CH_2CH{=}CHCH_3 \quad (34)$$

Internal competition between sulfur and an olefin linkage for a carbene leads to reaction at sulfur only, even though addition to the double bond is sterically favored, whereas attack on sulfur gives strained intermediates or products (eq 35).[98]

Acetals are very labile to aqueous acids, but thioacetals are remarkably stable. All the direct hydrolytic methods available for thioacetals to date involve coordination to the sulfur a soft or borderline acceptor such as Hg^{2+},[99-101] Ce^{4+},[102] Tl^{3+},[103] Ag^+,[104,105] Cu^{2-},[106] R^+,[107-110] Hal^+,[111] NH_2^+.[112] Chloramine T[113] may be considered as a nitrene complex, hence a soft Lewis acid.



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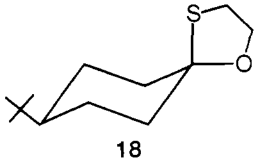

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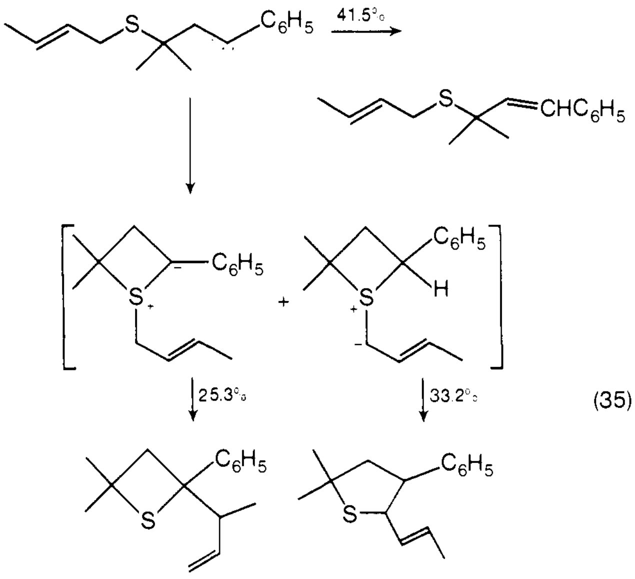

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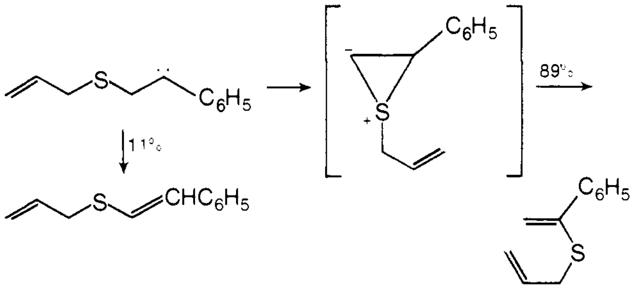
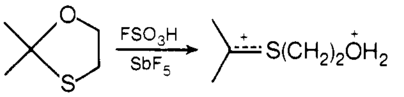
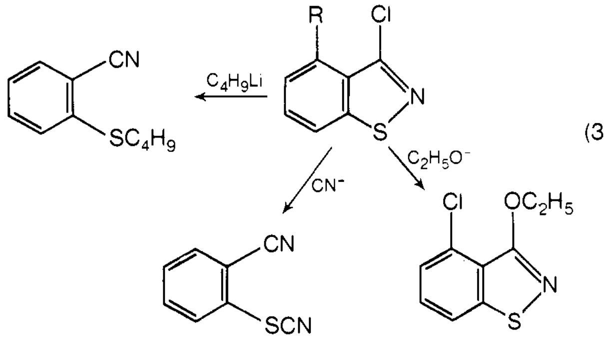


Secondary isotope effects clearly manifest that C-O bond scission occurs subsequent to protonation (necessarily at O) during acid hydrolysis of oxathiolanes **17** and **18**.[114] Direct observation of C-O bond cleavage has also been recorded (eq 36).[115]



(36)

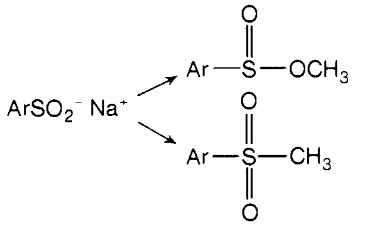
3-Chloro-1,2-benzisothiazoles undergo normal substitution at C-3 by ethoxide and amines,[116] but suffer ring cleavage when exposed to soft nucleophiles (eq 37).[117]



(37)

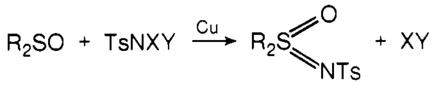
Sulfoxides are ambident nucleophiles which can be alkylated at either S or O. Dimethyl sulfoxide gives *O*-methylsulfonium brosylate[118] and *S*-methylsulfonium iodide[119] on treatment with the respective alkylators. The salt formation process is an S$_N$2 whose transition state can be regarded as an acid-base complex. O-Methylation of dimethyl sulfoxide is kinetically controlled; its transition state is symbiotically stabilized by S-O and BsO groups.

Alkylation of sodium *p*-toluenesulfinate[120] affords predominantly a sulfinate ester with CH_3X when X is a hard leaving group such as tosylate; methyl tolyl sulfone results in cases where X is soft (*e.g.*, I, OSOAr).



(38)

Copper-catalyzed decomposition of *p*-toluenesulfonyl azide or chloramine T in the presence of dimethyl sulfoxide constitutes a method for preparation of *N*-tosylsulfoximines[121,122] which are useful synthetic reagents.



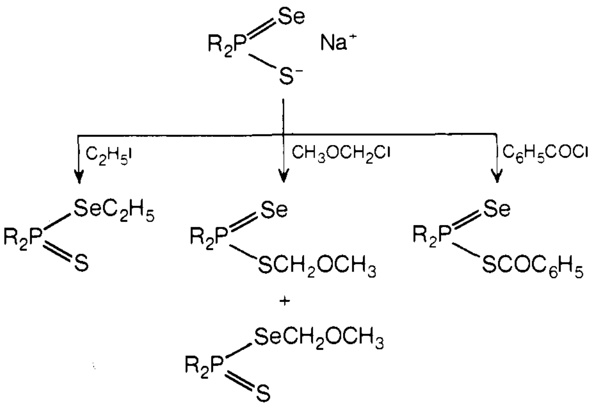
$$R_2SO + TsNXY \xrightarrow{Cu} R_2S(=O)=NTs + XY \quad (39)$$

The nitrenoid intermediates are trapped by the softer sulfur of sulfoxides. Similar interception of nitrenes has also been reported.[123]

(40)

X = O, S

Kinetically controlled reactions of thiophosphates give two different types of products[124] depending on the reaction partners. The following example[124a] illustrates the relative softness of sulfur and selenium.



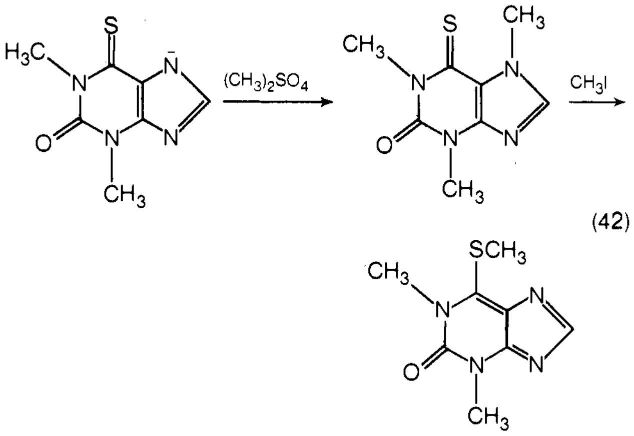
(41)

Optically active phosphine sulfides may be desulfurized to the corresponding phosphines with retention of configuration by lithium aluminum hydride.[125] The soft hydride ion chooses to attack the soft divalent sulfur instead of the relatively hard pentavalent phosphorus.

The harder and softer methylating agent, dimethyl sulfate and methyl iodide, respectively, react on N and S ends of thiopurines,[126] in accordance with prediction based on Pearson's principle (eq 42).

Thiocyanate anion is S,N-ambident. Since the terminal atoms belong to different categories according to the softness scale, each would display opposite affinity for a particular electrophile, *e.g.*, eq 43.

A rigorous investigation of aromatic and nucleophilic substitution of polynitrophenyl derivatives (ArX) by thiocyanate ion has demonstrated that the nature of X has profound influence on reaction rates. The rate ratio k_S/k_N spreads over a 10^5 range from X = py$^+$ to X =



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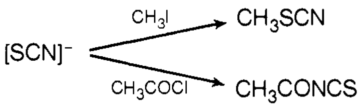
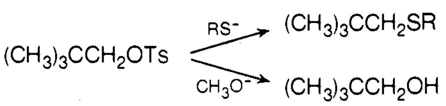


(43)

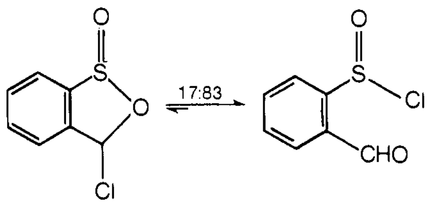
I.[127] The iodo derivative favors attack by the soft S end of thiocyanate so tremendously that these authors concluded that transition state symbiosis is much more reasonable (pronounced ?) in SNAr reactions because the entering and leaving groups are bonded to tetrahedral carbon and much closer to each other than they are in a SN2 transition state.

Direction of cleavage of 2,4-dinitrophenyl tosylate is dictated by the bases used.[128] Methoxide binds selectively (88%) to the sulfonyl sulfur whereas thiophenoxide releases the tosylate anion by first attaching itself to the soft aromatic carbon atom. Similar results are found in the aliphatic series.



(44)

The studies of Kice and coworkers have established that hardness of the sulfur atom falls off gradually in the order: sulfonyl > sulfinyl > sulfenyl.[129,130] Toward $ArSO_2^+$ reactivities of nucleophiles are $F^- > AcO^- \gg Cl^-$, suggesting that the sulfur is comparable to a sp^3 carbon. That $ArSO^+$ is medium soft has been deduced from the $Cl^- > AcO^- > F^-$ scale. Thus the following equilibrium[131] is understandable on the ground that borderline Cl^- is preferable to hard RO^- in combination with S.

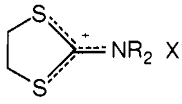


(45)

It should be remembered that for the carbon counterpart only the phthalide structure exists.

A report describing the behavior of tris(methylthio)methyl cation $(CH_3S)_3C^+$ toward various nucleophiles[132] supports the HSAB concept. Water neutralizes the carbonium center, whereas soft ions (Br^-, I^-, CN^-) attack the methyl group. Methanethiol adds to the central carbon, presumably because of the symbiotic effect. Triphenylphosphine attacks the sulfur atom.

Similarly, 2-dialkylamino-1,3-dithiolinium salts **19** react with hard bases (*e.g.*, OH^-, $ArNH_2$) at the carbonium center, at methylene carbons with soft donors (*e.g.*, RS^-) resulting in ring opening.[133]



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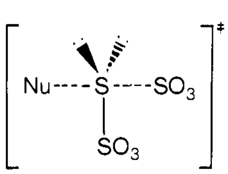

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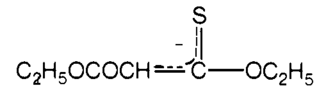
Displacement of sulfite from trithionate ion $S(SO_3)_2^{2-}$ occurs at the divalent sulfur with decreasing effectiveness as: $C_2H_5S^- > C_6H_5S^- > (C_6H_5)_3P > CN^-$. The transition state resembles that of the SN2 process on carbon.[134]

The anion of monothiomalonate



$$C_2H_5OCOCH{=}\overset{\overset{S}{\|}}{\overset{-}{C}}{-}OC_2H_5$$

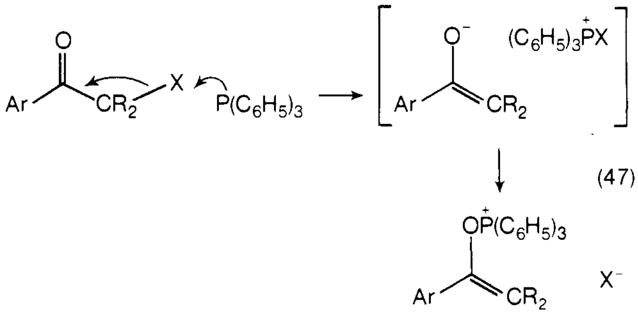
alkylates 1.7 times more readily at S than at C with ethyl iodide in ethanol.[134a]

D. Reactions of Organophosphorus Compounds

Phosphines are exceptionally powerful nucleophiles for soft acceptors. In a peptide synthesis based on redox condensation, triphenylphosphine forms salts with disulfides which serve to activate the carboxylic acid for the coupling reaction.[135] The overall transformation involves sequential soft-soft, hard-hard, and hard-hard interactions (eq 46).

$$(C_6H_5)_3P + R_2S \longrightarrow (C_6H_5)_3\overset{+}{P}SR\ RS^- \xrightarrow{R'COO^-,\ Cu^{2+}} R'COO\overset{+}{P}(C_6H_5)_3\ RS^- \xrightarrow{R''NH_2} R'CONHR'' \quad (46)$$

α-Bromocyclohexanone reacts with triphenylphosphine at 0°, while α-chlorocyclohexanone is inert even at 100°.[136] Direct attack of the α-halogen by phosphine is implied. Further studies on the enol phosphonium salt formation[137] sustantiate this contention (eq 47). However, enol phosphates are not generated in exactly the same manner.[138] The harder phosphites prefer adding to the carbonyl, and the ensuing betaines rearrange to phosphoranes which fragment subsequently to the products (eq 48).

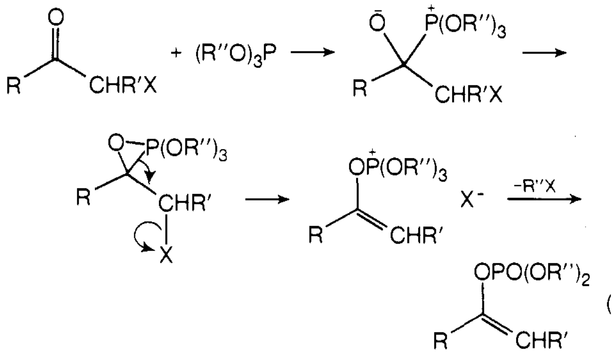


(47)

4-Bromocyclohexadienones undergo debromoaromatization[139] readily (eq 49).

By virtue of their softness, phosphines are excellent carbene traps.[140] Wittig reagents can thus be prepared, *e.g.*, eq 50.

The 1,2,4,6-tetraphenylphosphabenzene anion[141] alkylates kinetically on phosphorus with alkyl halides, but acylation takes place at the harder C-4 (eq 51).



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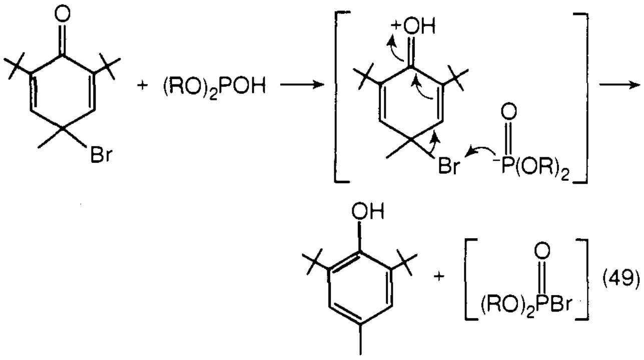

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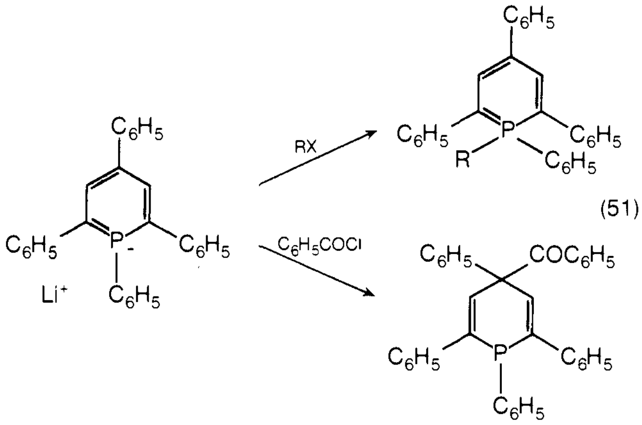
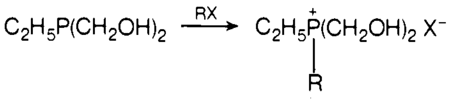
$(C_6H_5)_3P + CH_2Cl_2 + n\text{-}C_4H_9Li \longrightarrow (C_6H_5)_3P{=}CHCl$ (50)



(51)

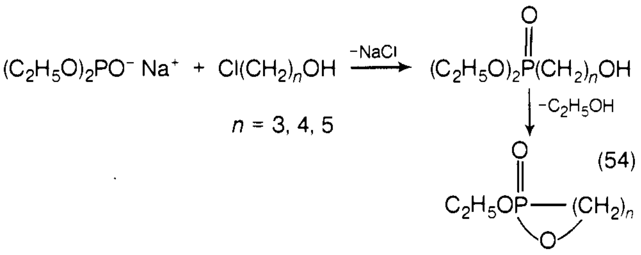
Selectivity is illustrated in alkylation and acylation of phosphino alcohols.[142]

$$(CH_3)_2PCH_2O^- Na^+ \xrightarrow{RCOCl} (CH_3)_2PCH_2OCOR \quad (52)$$



$$C_2H_5P(CH_2OH)_2 \xrightarrow{RX} C_2H_5\underset{R}{\overset{+}{P}}(CH_2OH)_2\,X^- \quad (53)$$

Sodium diethyl phosphite reacts with ω-chloroalkanols in such a manner that the process can be rationalized within the HSAB framework.[143] The first step is a soft-soft and ring closure is hard-hard combination. This last step is, of course, subject to steric control (see eq 54).



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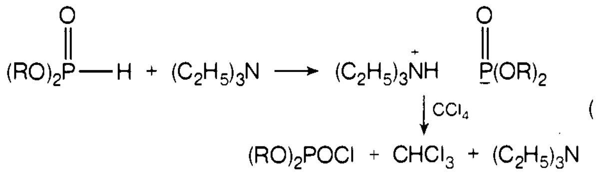
A mixture of dialkyl hydrogen phosphonate, triethylamine, and carbon tetrachloride is very effective for dehydration of aldoximes.[144] A proposed mechanism for the generation of the true reagent involves deprotonation of the phosphonate by the hard amine, and then the removal of a soft Cl^+ from carbon tetrachloride by the phosphorus of the ambident phosphite-phosphonate anion (eq 55).



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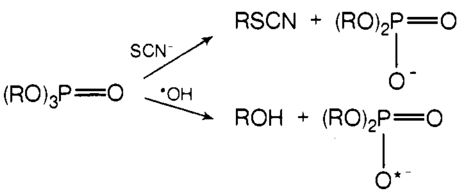
Teichmann and Hilgetag[145] have summarized and discussed nucleophilicities of phosphoryl oxygen and thiophosphoryl sulfur in terms of the HSAB principle.

Dealkylation of trialkyl phosphates[146,147] using soft and hard ions appears to follow divergent mechanisms (eq 56). For instance, thiocyanate ion attacks the soft

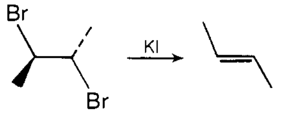


(56)

carbon atom of the alkoxy groups with its soft sulfur end, and hydroxide initiates the hydrolysis by adding to the hard pentavalent phosphorus atom, analogous to the common saponification of carboxylic esters.

E. Elimination and Substitution

Dehalogenation by iodide,[148] similar to that induced by zinc dust, proceeds stereospecifically. Undoubtedly it is a concerted elimination initiated by interaction between iodide and the electrophilic bromine.



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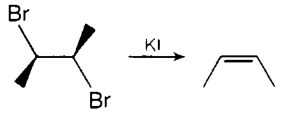
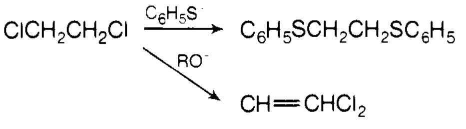


(58)

Halophilicity of trivalent phosphorus compounds, n-$(C_4H_9)_3P > (C_6H_5)_3P > (C_2H_5O)_3P$, has been revealed by studying the debromination of *vic*-dibromides.[149] Their reactivities parallel the relative softness of the phosphorus atom.

Debromination and dehydrobromination of *meso*- and *dl*-stilbene dibromides[150] in dimethylformamide have been scrutinized. Protophilicity and bromophilicity are $F^- > Cl^- >$ DMF and $I^- > Br^- > Cl^- > Sn^{2-} >$ DMF, respectively.

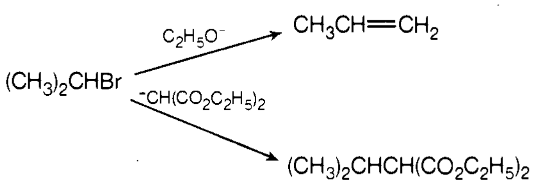
In other cases, variation of the base can often change the pathway from β-elimination to S$_N$2 substitution and *vice versa*. Soft bases favor displacement whereas hard bases generally promote elimination.



(59)

Halide ions, especially F^-, are very weak bases. However, tetraethylammonium fluoride effectively induces elimination of hydrogen bromide from 2-phenethyl bromide while the quaternary ammonium chloride and bromide give halogen exchange products only.[151] The fluoride ion chooses to abstract the hard proton.

Ethoxide and malonate anion have virtually identical proton basicities,[152] but are different significantly in hardness, and react in a different manner with 2-bromopropane.



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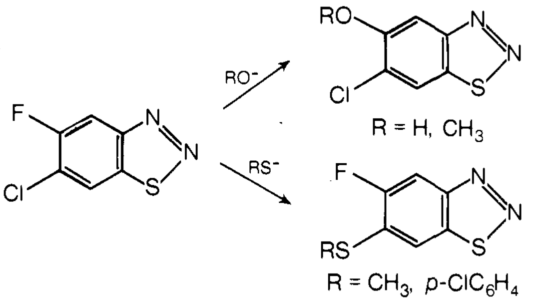
Change of leaving group in the substrate also affects the reaction course owing to symbiosis in the transition state.

$$RCH_2CH_2OTs \xrightarrow{(CH_3)_3CO^-} RCH_2CH_2OC(CH_3)_3 \quad (61)$$

$$RCH_2CH_2Br \xrightarrow{(CH_3)_3CO^-} RCH{=}CH_2 \quad (62)$$

The dependence of S$_N$Ar reaction site upon choice of bases is known.[153]



(63)

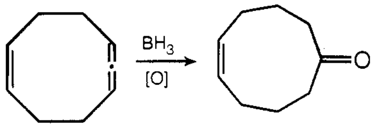
In the 1,3-elimination of bis(α-bromobenzyl) sulfones,[154] soft bases ($C_6H_5S^-$, I^-, H^-, $(C_6H_5)_3P$, Mg, Zn) attack the bromine atom to give stilbenes as final products, whereas hard bases (CH_3O^-, R_3N, DMF, DMA) abstract an α-hydrogen and lead to bromostilbenes. The reactions are stereospecific; thus the *meso* isomer affords *cis*-stilbene, *dl* isomer gives *trans*-stilbene predominantly, *meso* sulfone leads to *trans*-bromostilbene, and *dl*-sulfone leads to *cis*-bromostilbene (eq 64).

F. Addition to Double Bonds

Olefins are essentially soft donors. Similar to acetylenes, π-complexation with heavy (soft) metal ions such as Ag^+, Pt^{4+}, Pd^{2+}, are well known. Addition of halogens, pseudohalogens, etc., is commonly considered as to proceed *via* π-complex formation.

Solvatomercuration[155] is a polar addition which obeys the Markovnikov rule. Owing to the fact that the acetoxymercuric ion is soft, the reaction is much faster than ordinary polar additions.

In hydroboration,[156] the situation is somewhat different. Borane is a soft Lewis acid; complexation with olefins is also very favorable. However, this complex rapidly collapses to a four-center transition state en route to the product without participation of external nucleophiles. As regards the B-H bond, boron is evidently a hard acceptor and hydrogen as H^- a soft donor. Boron attacks mainly the central carbon of the allenic linkage which is harder than the terminal sp^2 atoms.[157]



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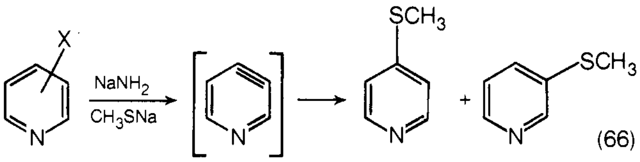
Cyclopropanation[158] of alkenes with carbenes has been developed into a useful synthetic method. The softer an olefin is, the more efficient carbene trap it will be.

Benzynes and arynes are very electrophilic and soft species. 3,4-Dehydropyridine (pyridyne) generated by elimination of hydrogen halides from 3- or 4-halopyridine gives equimolar amounts of 3- and 4-methiopyridines in the presence of methanethiol.[159] The strong hard base (*e.g.*, NH_2^-) cannot compete with the thiolate ion for pyridyne (eq 66). Similarly, benzyne affords thioethers as major products under these conditions.[160]



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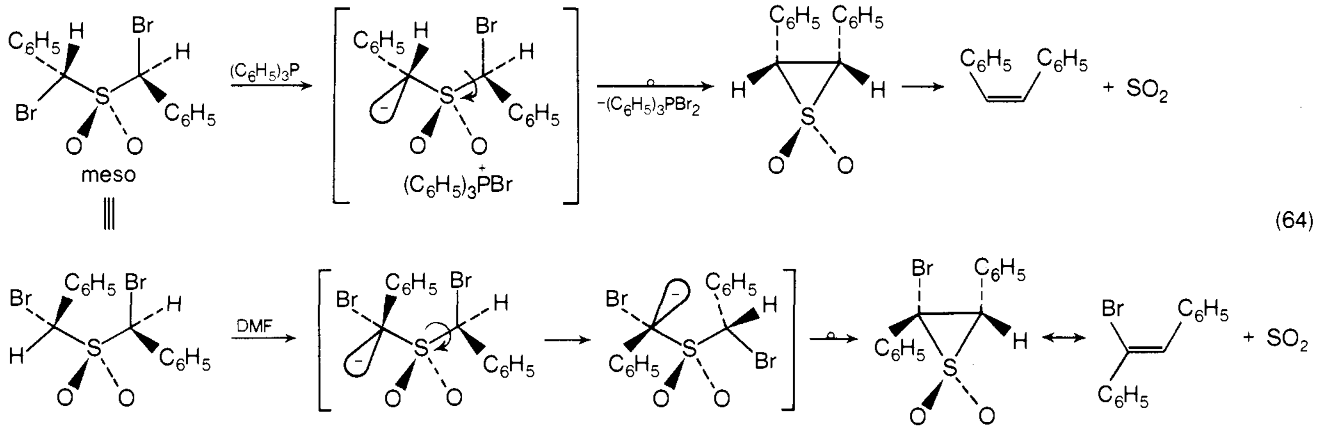
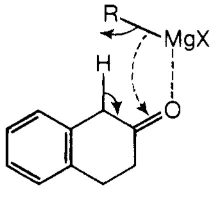
G. Addition to Carbonyl Compounds

Hydrazones, oximes, and semicarbazones are condensation products of ketones and aldehydes with hard bases. Soft bases such as alkylphosphines do not attack the carbonyl group.

β-Tetralone gives mainly an acetylene alcohol on treatment with ethynylmagnesium bromide. A significant



amount of starting material has been recovered after its exposure to vinylmagnesium chloride, and even more from the reaction with ethylmagnesium bromide.[161] The hardness of RMgX decreases in the order of R as acetylene > vinyl > ethyl; therefore it may be concluded that the hardest reagent prefers reaction at carbonyl and softest reagent tends to abstract the highly acidic proton.



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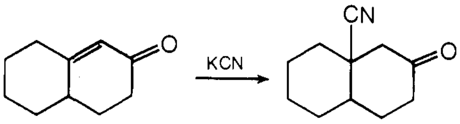
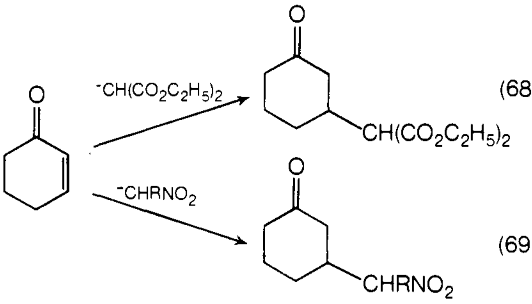
The β-carbon of an enone system is softer than the carbonyl carbon;[162] it is therefore not surprising that soft anions pursue a major or exclusive conjugate addition course.



(67)[163]



(68)[164]

(69)[165]

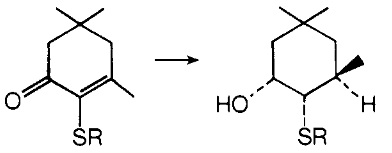
Hydride reduction of enones[166] has been discussed from the HSAB viewpoint. Replacement of some of the hydride ions by electron-withdrawing alkoxy groups hardens the reagents and thereby suppresses conjugate reduction. The ratio of 1,2 *vs.* 1,4 reduction of cyclopentenone varies from 14:86 by lithium aluminum hydride to a dramatic 90:9.5 by $LiAlH(OCH_3)_3$. α,β-Unsaturated esters can be converted to allylic alcohols[167] with $LiAlH_4$ in the presence of ethanol. Cholestenone gives 1,2 and 1,4 products in the proportion of 74:26 ($NaBH_4$) and 98:2 ($NaBH(OCH_3)_3$).

Since boron is more electronegative than aluminum, the B-H bond is more covalent than Al-H and therefore borohydrides are softer than aluminum hydrides. This explains why borohydrides are relatively inert to protic solvents (hard H^+ sources), and they tend to produce more conjugate reduction products. The harder Li^+ counterion favors 1,2-reduction[168] ($LiBH_4$ *vs.* $NaBH_4$).

Addition of an amine to the reducing system limits the transfer of only one hydride ion to the substrate; formation of alkoxyborohydrides is also inhibited. Thus one equivalent of pyridine changes the 1,2/1,4 ratio in carvenone reduction[169] from 36:64 to 0:100.

The enone structure is of tremendous importance in determining its reduction mode: α- and β-alkyl substituents generally discourage conjugate reduction.[170] Thus it is of particular interest to note that reduction of α-alkylthiocyclohexenones[171] with sodium borohydride leads to saturated alcohols. It is proposed that intramolecular hydride delivery is facilitated by sulfur participation (eq 70).

Aluminum hydrides in which the metal atom does not carry a formal negative charge are harder. Aluminum hydride[172] and diisobutylaluminum hydride[173] attack almost exclusively at the enone carbonyl.



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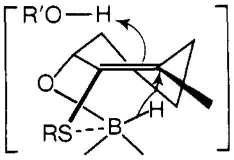


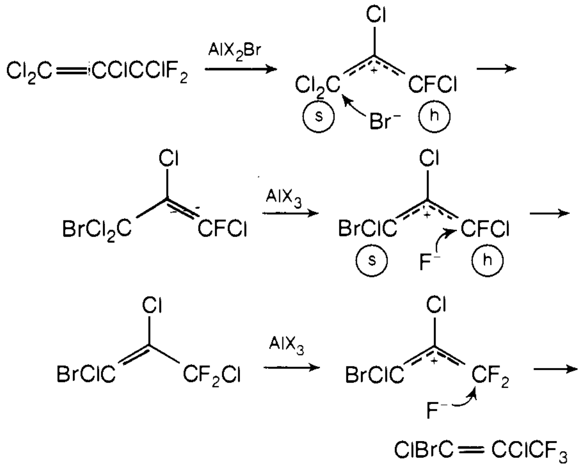
22

Organotin hydrides are soft reducers; 1,4-addition across enone systems[174] represents the major reaction pathway.

H. Miscellaneous

Cyclopropane rings protonate much faster than the softer olefinic linkages;[175] the reverse is true when interactions involve the soft Lewis acid IBr.

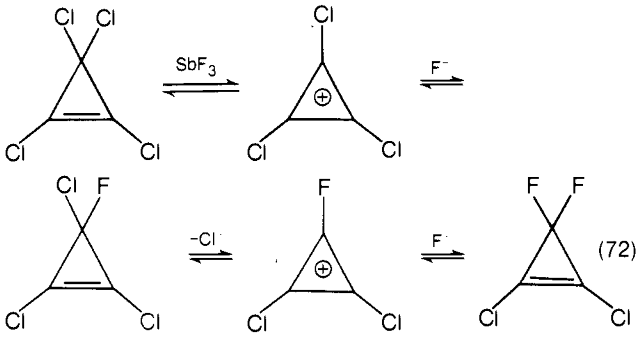
Halogen exchange of 3,3-difluorotetrachloropropene by Lewis acids has been studied.[176] With aluminum bromide, an unexpected disproportionation product, 1-bromo-1,2-dichloro-3,3,3-trifluoropropane, is obtained. The proposed mechanism invokes specific attack of soft (Br^-) and hard (F^-) ions at softer and harder carbonium centers, respectively (eq 71). The source of fluoride ion is from other concurrent processes, for aluminum fluoride is formed. Titanium tetrachloride is effective to catalyze these other reactions but not the one which generates the trifluoro compound. Both Al^{3+} and Ti^{4+} are hard and they combine preferentially with F^-. The difference in intrinsic strengths of AlF_3 and TiF_4 is the cause for divergence.



(71)

Halogen metathesis in other systems has been discussed in the light of HSAB principle. The exclusive production of 3,3-difluoro-1,2-dichlorocyclopropene[177] is a consequence of symbiotic effect. The original authors considered this in terms of double-bond-no-bond resonance. The two different terminologies may represent the same phenomenon here (eq 72).

Allylic rearrangement of 3-chloropentafluoropropene goes through an unsymmetrical cation, in contrast to the expectation that the softer Cl^- be abstracted. Symbiosis indicates, however, that formation of $SbF_4Cl_2^-$ is better than $SbF_3Cl_3^-$. The intrinsic strength of the cation may also determine the reaction pathway (eq 73).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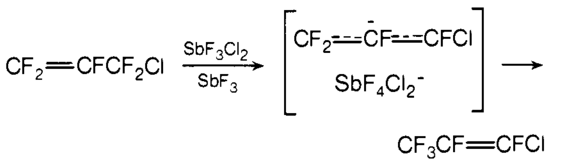
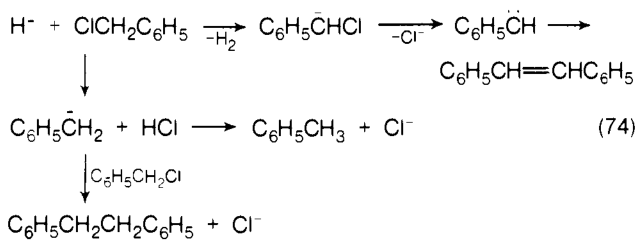


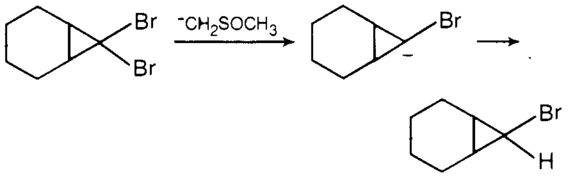
$$CF_2{=}CFCF_2Cl \xrightarrow[SbF_3]{SbF_3Cl_2} \left[\begin{matrix} CF_2{\cdots}\bar{C}F{\cdots}CFCl \\ SbF_4Cl_2^- \end{matrix}\right] \longrightarrow CF_3CF{=}CFCl \qquad (73)$$

Sodium hydride generated by the radical-anion method reacts with benzyl chloride at room temperature.[178] Stilbene derived by the carbene route is stable and hence not the precursor of bibenzyl. This latter product must be generated along with toluene *via* a dechlorination process as shown in eq 74.



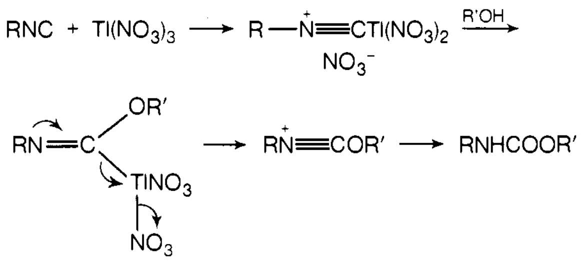
$$\begin{aligned} &H^- + ClCH_2C_6H_5 \xrightarrow[-H_2]{} C_6H_5\bar{C}HCl \xrightarrow[-Cl^-]{} C_6H_5\ddot{C}H \longrightarrow C_6H_5CH{=}CHC_6H_5 \\ &\downarrow \\ &C_6H_5\bar{C}H_2 + HCl \longrightarrow C_6H_5CH_3 + Cl^- \qquad (74) \\ &\downarrow C_6H_5CH_2Cl \\ &C_6H_5CH_2CH_2C_6H_5 + Cl^- \end{aligned}$$

Debromination of *gem*-dibromocyclopropanes by dimsyl anion again involves the removal of a soft halogen by a soft carbon base.[179]


(75)

Halogenation of sulfides proceeds *via* the Pummerer rearrangement. The mechanism has been further examined with the aid of kinetic isotope effects extracted from chlorination and bromination of thiophane.[180] Solvent and reagent effects are interpreted in terms of HSAB theory.

Conversion of isonitriles to carbamates by thallium(III) nitrate in the presence of an alcohol[181] is initiated by the soft-soft interaction between C and Tl (eq 76).



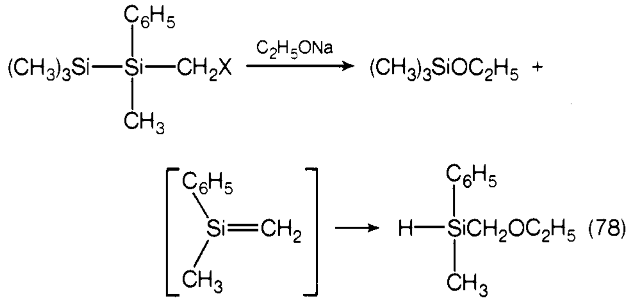
$$RNC + Tl(NO_3)_3 \longrightarrow R{-}\overset{+}{N}{\equiv}CTl(NO_3)_2\ NO_3^- \xrightarrow{R'OH} RN{=}C(OR')(TlNO_3) \longrightarrow R\overset{+}{N}{\equiv}COR' \longrightarrow RNHCOOR' \qquad (76)$$

Both triphenylmethyl chloride and perchlorate furnish the same product ratio on reaction with tetraphenylarsonium cyanide.[182] The electrophilic species must be the triphenylmethyl cation, and this carbonium ion is fairly soft since the predominant mode of charge neutralization involves the soft carbon end of the cyanide ion.

$$(C_6H_5)_3CX + (C_6H_5)_4As^+CN^- \longrightarrow \underset{90\%}{(C_6H_5)_3CCN} + \underset{10\%}{(C_6H_5)_3CNC} \qquad (77)$$

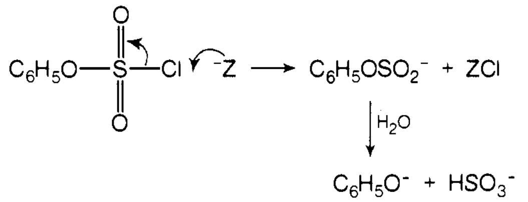
$X = Cl, ClO_4$

The hardness of silicon must be responsible for the unusual transformation depicted in eq 78.[183]



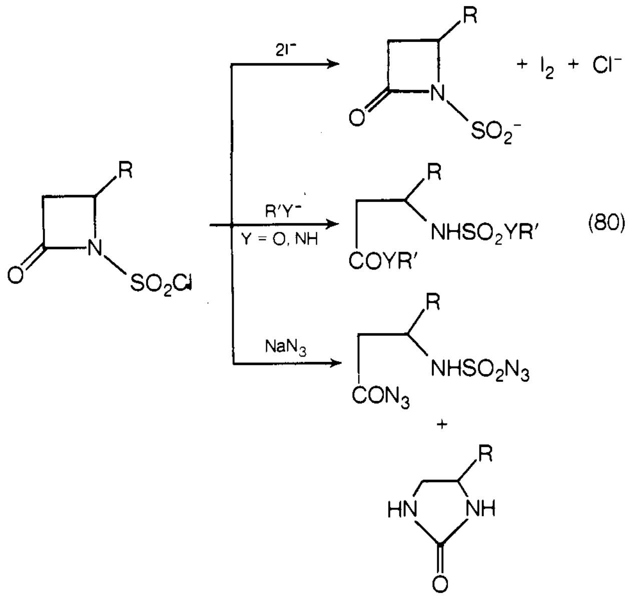
$$(CH_3)_3Si{-}Si(C_6H_5)(CH_3){-}CH_2X \xrightarrow{C_2H_5ONa} (CH_3)_3SiOC_2H_5 + \left[(C_6H_5)(CH_3)Si{=}CH_2\right] \longrightarrow H{-}Si(C_6H_5)(CH_3)CH_2OC_2H_5 \qquad (78)$$

Reaction rates of phenyl chlorosulfate with various anions follow the order of $S_2O_3^{2-} > CN^- > I^- > SO_3^{2-} > SCN^- > Br^- > Cl^-, F^-, CH_3COO^-$; thus it likely involves displacement at the soft chlorine rather than the hard sulfur of the sulfonyl group.[184]

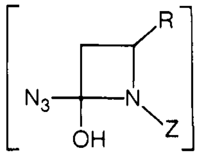


$$C_6H_5O{-}SO_2{-}Cl + {}^-Z \longrightarrow C_6H_5OSO_2^- + ZCl;\quad C_6H_5OSO_2^- \xrightarrow{H_2O} C_6H_5O^- + HSO_3^- \qquad (79)$$

N-Chlorosulfonylazetidones[185] possess three different electrophilic sites. Soft bases (*e.g.*, I^-) pick out the chlorine; hard bases (alkoxides, amines) attack the lactam carbonyl and the sulfonyl sulfur, both being hard centers. The reaction with borderline azide ion gives rise to a mixture of a diazide from hard-type attack, and a cyclic urea which must involve hydrolysis of the chlorosulfonamide through chlorine abstraction by the azide ion, simultaneous to the addition of a second azide to the carbonyl prior to the Schmidt rearrangement. It is apparent that the fate (ring opening *vs.* rearrangement) of the



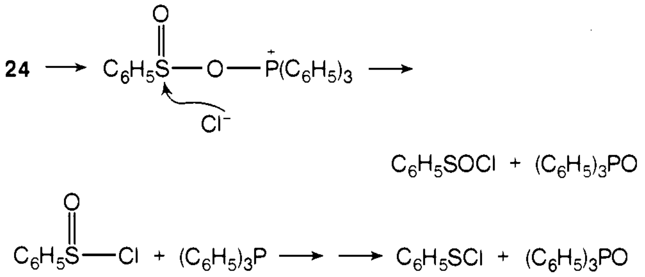
tetrahedral intermediate **23** depends on the nature of Z. When Z is a sulfinate anion or a negative charge, the ring-opening process becomes electronically unfavorable.



23

Based on HSAB concept, the failure in preparation of sulfonylnitriles, RSO_2CN, through reaction of sulfonyl chlorides with alkali cyanides is not surprising and actually expected.[186] The reduction of benzenesulfonyl chloride by triphenylphosphine[187] must be initiated by chlorine abstraction.

$$C_6H_5SO_2Cl + (C_6H_5)_3P \longrightarrow \underset{\textbf{24}}{C_6H_5SO_2^- + (C_6H_5)_3\overset{+}{P}Cl} \quad (81)$$



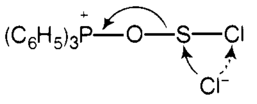
$$\textbf{24} \longrightarrow C_6H_5\overset{\overset{O}{\|}}{S}{-}O{-}\overset{+}{P}(C_6H_5)_3 \;\; Cl^- \longrightarrow C_6H_5SOCl + (C_6H_5)_3PO$$

$$C_6H_5\overset{\overset{O}{\|}}{S}{-}Cl + (C_6H_5)_3P \longrightarrow\, \longrightarrow C_6H_5SCl + (C_6H_5)_3PO$$

$$C_6H_5SCl + (C_6H_5)_3P \longrightarrow C_6H_5S^-\ (C_6H_5)_3\overset{+}{P}Cl \xrightarrow{C_6H_5SCl} (C_6H_5)_2S_2 + (C_6H_5)_3PCl_2$$

$$(C_6H_5)_3PCl_2 \xrightarrow{H_2O} (C_6H_5)_3PO$$
$$C_6H_5S^- \longrightarrow C_6H_5SH$$
$$C_6H_5SO_2^- \longrightarrow C_6H_5SO_2H$$

On treatment with thionyl chloride, triphenylamine undergoes ring substitution. On the other hand, triphenyl derivatives of other group VA elements (P, As, Sb, Bi) effect reduction of thionyl chloride.[188] Analysis of the triphenylphosphine reaction suggests formation of intermediate **25** by P → O; the oxygen atom is soft as an electrophile. The antimony and bismuth compounds attack the chlorine which is even softer.



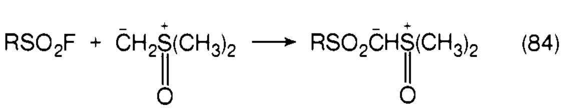
25

Wittig reagents have strongly nucleophilic soft carbon ends. It has been demonstrated that the chlorine atom of sulfonyl chlorides is removable by alkylidenephosphoranes.[189] For example, see eq 82. However, sulfonyl fluorides react quite differently (eq 83), although the order of softness is $Cl^+ > F^+ \gg ROS_2^+$. This is a case in which intrinsic strength is the dominating factor of the reaction. The fact that F^+ binds tightly to RSO_2^- forces the nucleophilic attack on S.

$$\begin{array}{c} RSO_2Cl + CH_2{=}P(C_6H_5)_3 \longrightarrow RSO_2^-\ (C_6H_5)_3\overset{+}{P}CH_2Cl \\ \Big\downarrow {\scriptstyle CH_2=P(C_6H_5)_3} \quad (82) \\ RSO_2^-\ (C_6H_5)_3\overset{+}{P}CH_3 + (C_6H_5)_3P{=}CHCl \end{array}$$

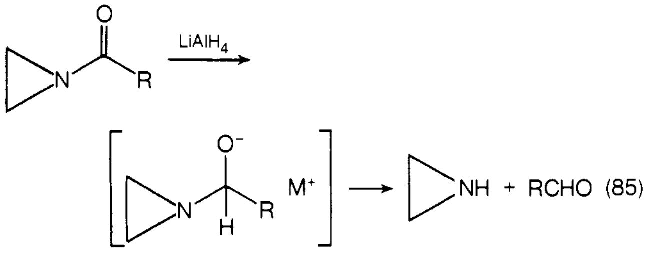
$$\begin{array}{c} RSO_2F + CH_2{=}P(C_6H_5)_3 \longrightarrow RSO_2CH_2\overset{+}{P}(C_6H_5)_3\,F^- \\ \Big\downarrow {\scriptstyle CH_2=P(C_6H_5)_3} \quad (83) \\ RSO_2CH{=}P(C_6H_5)_3 + (C_6H_5)_3\overset{+}{P}CH_3\,F^- \end{array}$$

A similar reaction between sulfonyl fluorides with dimethyloxosulfonium methylides has been reported.[190]



$$RSO_2F + \bar{C}H_2\underset{\underset{O}{\|}}{\overset{+}{S}}(CH_3)_2 \longrightarrow RSO_2\bar{C}H\underset{\underset{O}{\|}}{\overset{+}{S}}(CH_3)_2 \quad (84)$$

Lithium aluminum hydride is known to reduce the carbonyl of *N*-acylaziridines;[191] the softer sodium borohydride delivers a hydride ion to a ring carbon of *N*-carbethoxyaziridine.[192]



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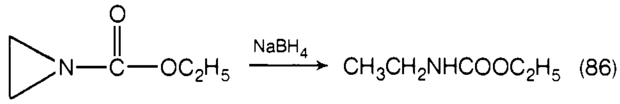
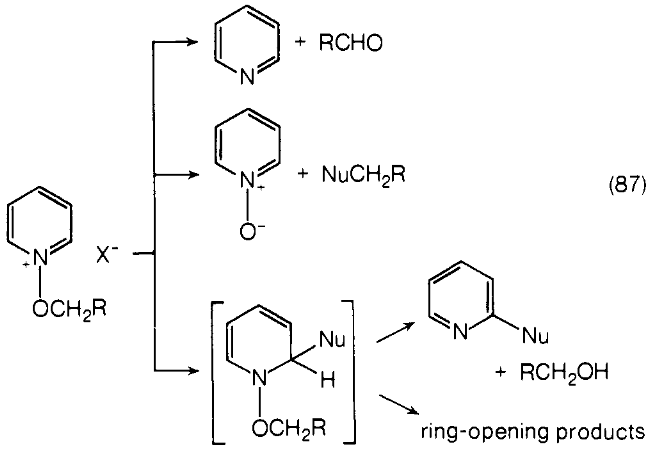


(86)

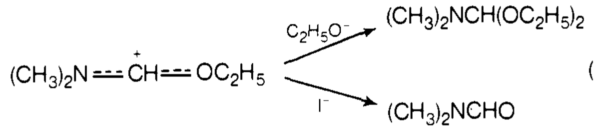
N-Alkoxypyridinium salts possess several centers open to attack by nucleophiles. Results of a study[193] generally bear out the validity of HSAB to these systems. Hard alkoxides remove an α-hydrogen from the side chain, soft anions (I^-, SCN^-, $S_2O_3^{2-}$) displace pyridine oxide from the carbon chain, whereas cyanide adds to C-2 of the pyridinium ring with ensuing elimination of the molecule of alcohol and rearomatization. Ring cleavage may follow the addition of a soft species to C-2, but these secondary reactions depend highly on the entering group (see eq 87).



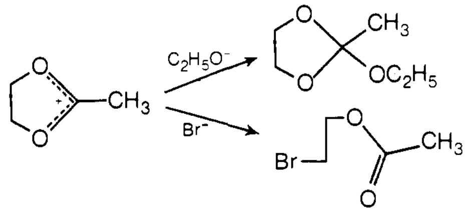
(87)

Reactions of nonaromatic ambident cations have been extensively investigated.[194] Representative cases are shown in eq 88 and 89.

Carbamates undergo complete O-protonation with acids. With the softer CH_3^+ electrophile in methyl fluoro-



$$(CH_3)_2N{\cdots}\overset{+}{C}H{\cdots}OC_2H_5 \xrightarrow{C_2H_5O^-} (CH_3)_2NCH(OC_2H_5)_2;\quad \xrightarrow{I^-} (CH_3)_2NCHO \qquad (88)$$



(89)

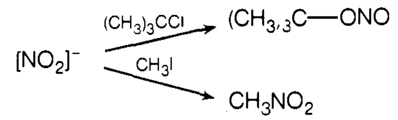
sulfonate, N-alkylation is favored under equilibrium conditions.[195]

$$(CH_3)_2NCOOCH_3 \xrightarrow{CH_3OSO_2F} (CH_3)_3\overset{+}{N}COOCH_3\,FSO_3^- \qquad (90)$$

Alkylation of sodium 9-fluorenone oximate[196] has been studied under special conditions in which dissociated ions or aggregates prevail. In the presence of a crown ether which occludes completely the cation, oximate undergoes almost exclusive (95-99%) O-methylation with methyl tosylate and 65% O-, 35% N-methylation with methyl iodide. Addition of sodium tetraphenylborate which suppresses dissociation of the sodium oximate reduces the alkylation of both methyl tosylate and methyl iodide to nearly the same rate and gives essentially the same ratio of O/N (*ca.* 43/57) alkylation.

Alkylation of 2-pyridone salts[197] is subject to cation control. Thus, the sodium salt gives essentially *N*-alkyl products with *n*-alkyl halides, whereas silver salts furnish exclusively O-alkylation in nonpolar solvents. The silver ion promotes carbonium character of, hence hardens, the alkylating agents thereby favoring attack by the harder oxygen of the ambident anion.

The ambident behavior of nitrite ion is well documented (eq 91).[198] 2,4-Dinitrohalobenzenes react very



$$[NO_2]^- \xrightarrow{(CH_3)_3CCl} (CH_3{,}_3C{-}ONO;\quad \xrightarrow{CH_3I} CH_3NO_2 \qquad (91)$$

discriminately with nitrite anion[199] according to the softness of their halogen. The harder they are, the higher proportion of O-attack appears, as exemplified by exclusive formation of dinitrophenol (after hydrolysis of the nitrite ester) in the case where fluorine is the leaving group, In the other extreme, dinitroiodobenzene gives trinitrobenzene. Clearly this is another manifestation of transition state symbiosis.

Reaction of nitramine anions $RNNO_2^-$ with benzyl halides occurs predominantly at nitrogen. With harder alkylator, *e.g.*, $ClCH_2OC_2H_5$, the O/N ratio is enhanced to approximately 1.[200]

Typical soft bases such as dimethyl sulfide[201] and iodide ion[202] attack the soft carbon of the O-alkyl group in alkoxydiazenium ions.

$$R_2NN{=}\overset{+}{O}R' \longleftrightarrow R_2\overset{+}{N}{=}NOR' \longleftrightarrow R_2N\overset{+}{N}OR'$$

26

Cyanogen halides are intriguing molecules which can react in many different ways. It has been known that thiocyanates are formed by combining thiols with cyanogen chloride.[203]

$$RSH + ClCN \longrightarrow RSCN + HCl \qquad (92)$$

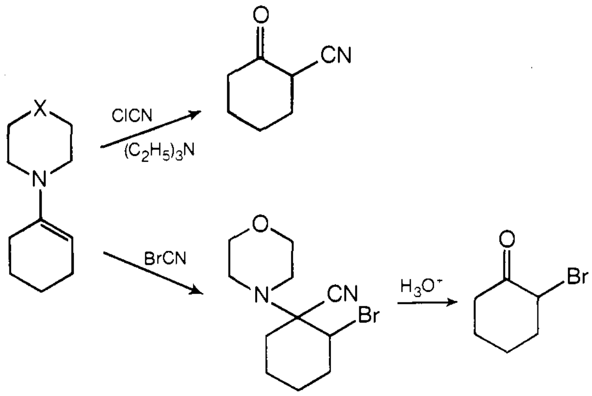
Recently it has been demonstrated that thiolates are oxidized by cyanogen bromide to disulfides[204] in good

$$RS^- + BrCN \xrightarrow[-CN^-]{} [RSBr] \xrightarrow[-Br^-]{RS^-} RSSR \qquad (93)$$

yields. Carboxylic acids are dehydrated to anhydrides[205] with cyanogen bromide.

To clarify these results, one must recognize the softness trend of $Br^+ > CN^- > Cl^+$. The polarizabilities of the pseudohalogens have been established which can be represented as $Cl^{\delta-}CN^{+}$ and $Br^{+}CN^{-}$.[206,207] In cyanogen iodide, the iodine atom is softer and more electrophilic.

Thus the anomalous patterns of α-cyanation[208] with ClCN and α-bromination[209] with BrCN emerged from enamine reactions are understandable from the preceding analysis. The β-carbon of an enamine system acts as a soft donor (eq 94). Similarly, the results of Grignard reactions[210] can be rationalized (eq 95).



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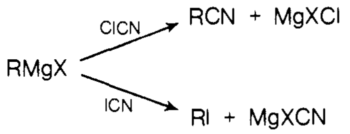
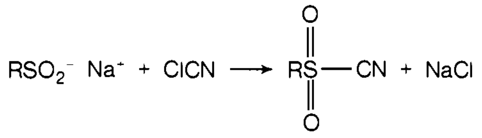


$$RMgX \xrightarrow{ClCN} RCN + MgXCl;\quad \xrightarrow{ICN} RI + MgXCN \qquad (95)$$

In a synthesis of sulfonylnitriles[211] from sodium sulfinates, the soft sulfur acts as a nucleophile to bond to the cyano group of cyanogen chloride.



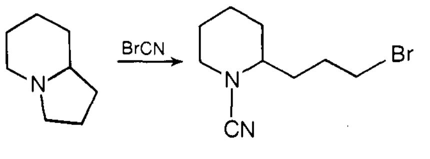
$$RSO_2^-\ Na^+ + ClCN \longrightarrow R\overset{O}{\underset{O}{S}}{-}CN + NaCl \qquad (96)$$

The anhydride formation mentioned further above presumably involves reactive intermediates of type **27**, which are generated from a union of hard oxygen base with the harder electrophile CN^+ from cyanogen bromide.

RCOOCN

27

The classical von Braun degradation[212] of tertiary amines to give bromocyanamides further provides unambiguous information in connection with the present discussion. In these cases, the hard amino nitrogen atom



(97)

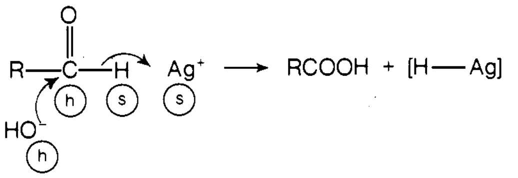
adheres itself to the harder CN^+ prior to C-N bond fission. Formally it is a four-centered exchange reaction, completely in accordance with HSAB principle in the regrouping of partners.

At this point the Saville rules[6] pertaining to multicenter reactions should be explicitly introduced. These rules specify ideal catalytic conditions for bond cleavage processes, provided that the substrate has a hard-soft combination.

Rule 1	N:	A-B	E
	h	h s	s
Rule 2	N:	A-B	E
	s	s h	h

Compatibility of the nucleophile and electrophile with the soft-hard nature of the groupings A and B is instrumental in facilitating the scission of A-B bond. Many of the reactions discussed involve such combinations.

Oxidation of aldehydes by silver oxide conforms to rule 1.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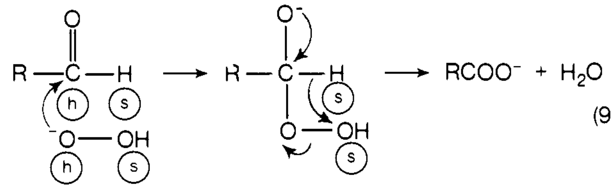
The Baeyer-Villiger reaction of aldehydes with alkaline hydrogen peroxide and the decomposition of tetrahedral intermediates from peracid oxidation may be illustrated as shown in eq 99 and 100.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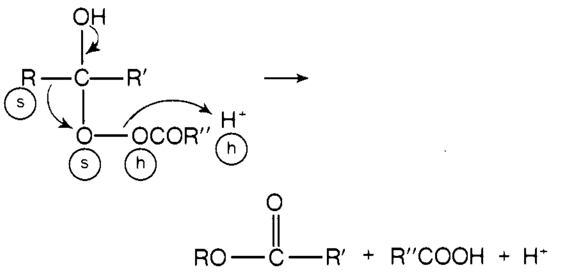
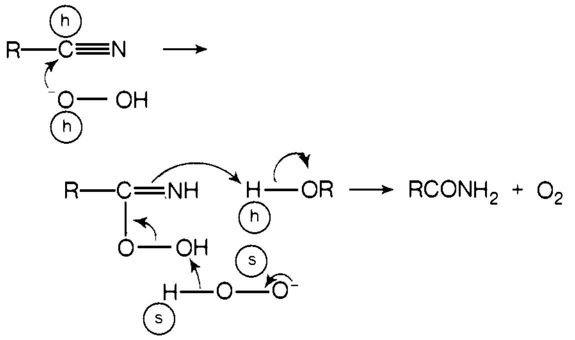
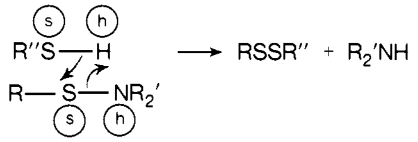

(100)

Hydrolysis of nitriles to amides[213] by alkaline hydrogen peroxide proceeds very readily. A reasonable mechanism has been formulated.


(101)

Sulfenamides react with thiols to furnish disulfides,[214] perhaps *via* a four-centered transition state (eq 102). Similar cleavage of the N-S bond can be performed by mixing with carbon disulfide (eq 103).[215]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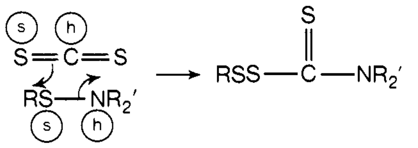
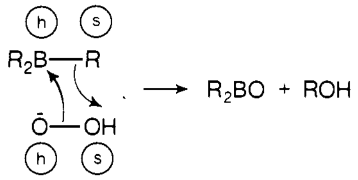
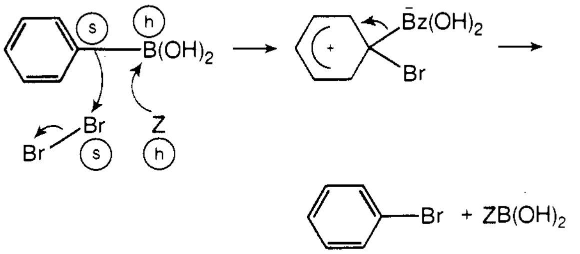

(103)

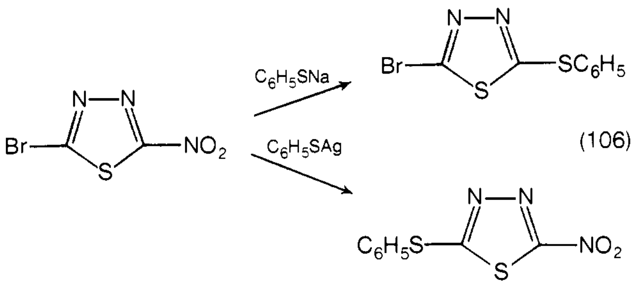
Cleavage of organoboranes is frequently accomplished by alkaline hydrogen peroxide.[216] The effectiveness of this reagent is believed to stem from ideal complementarity with the substrate.


(104)

Degradation of benzeneboronic acid by bromine is greatly facilitated by added hard bases such as water.[217] This fact suggests the intervention of a four-centered transition state. The hard base activates the aromatic ring indirectly by bonding with boron and is indispensable to eventual expulsion of the boron containing moiety.

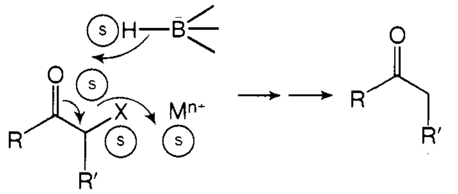

(105)

2-Bromo-5-nitro-1,3,4-thiadiazole undergoes interesting S$_N$Ar processes. Two different "monosubstituted" products are isolated from reactions with sodium and silver thiophenoxides, respectively (eq 106).[218] The sulfide anion interacts with either of the two ring carbons in the transition state; however, the counterion dictates actual site by selective complexing with the grouping of its like. Thus (s:s) silver-bromine or (h:h) sodium-oxygen (of the nitro group) pairing is responsible for the outcome of these displacements.


(106)

It is satisfying to note that a debromination procedure utilizes sodium borohydride and heavy metal salts;[219] another requires the cooperativity of lithium iodide and boron trifluoride.[220] The rules derived from HSAB concept indicate such are the correct combinations to be effective.

Debromination of α-bromoalkanophenones occurs with



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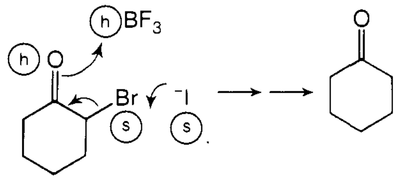
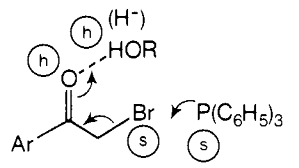


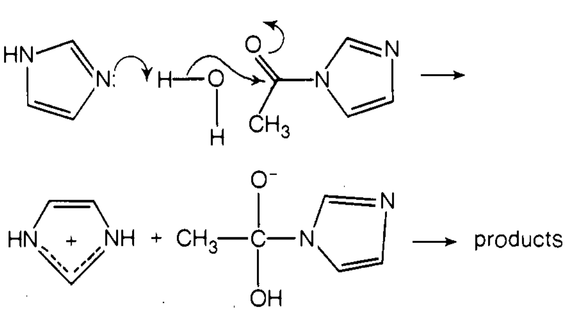
(108)

triphenylphosphine in ethanol and is both acid and alcohol catalyzed.[221] α-Chloro ketones fail to undergo analogous reaction. Trialkyl phosphites cannot be used as debrominating agent.



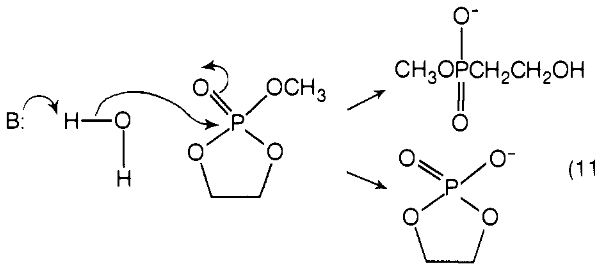
28

Saville's rules serve to indicate optimal catalytic conditions. However, it should be borne in mind that there exist many facile multicenter reactions which do not fall into the two categories. The hydrolysis rates of acetylimidazole[222] elevate with increasing imidazole buffer concentration (at constant pH). One of the most plausible mechanisms (eq 109) involves a h h-h h transition state.



(109)

Hydrolysis of methyl ethylene phosphate[223] has been similarly interpreted (eq 110).



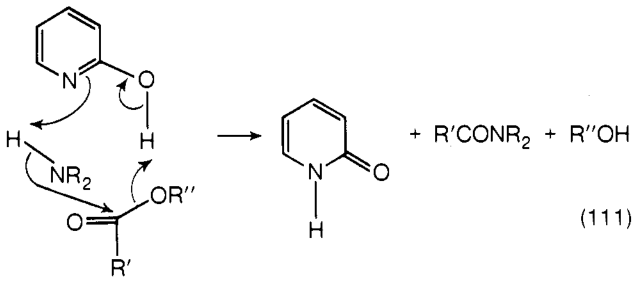
(110)

2-Hydroxypyridine is a very useful catalyst to promote aminolysis of esters (eq 111).[224]

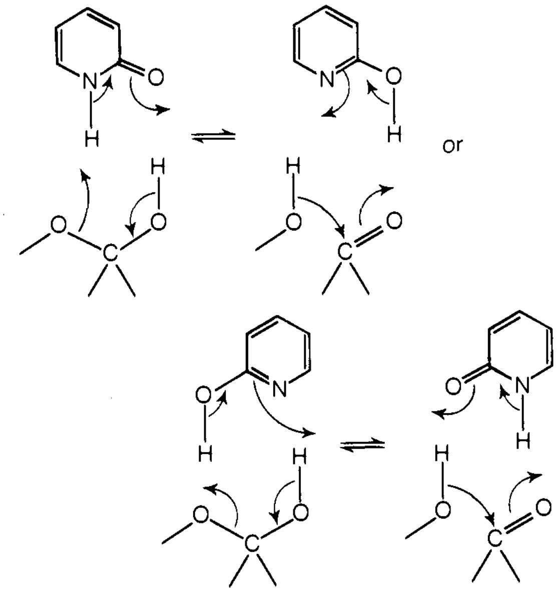
A less clear-cut case is the mutarotation[225] of α-D-tetramethylglucose in benzene, catalyzed by the same bifunctional reagent (eq 112).

A host of general acid-base catalyzed reactions belong to the same class. The transition states of some of these are depicted in structures 29-33.

The rate law for anisole bromination[231] contains a term which is second order with respect to bromine. The



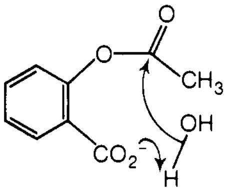
(111)



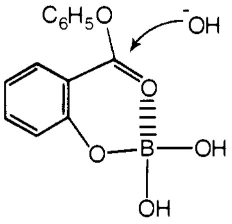
(112)

mechanism can be expressed as s s-(s) s four-centered substitution.

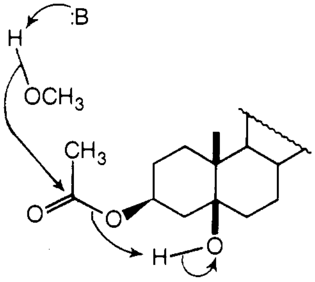
This soft pattern appears again in couplings between organocopper reagents and alkyl or aryl halides,[232] the Ullmann reaction,[233] and the decomposition of mercuriodiazo ester by iodine (see eq 114 and 115).[234]



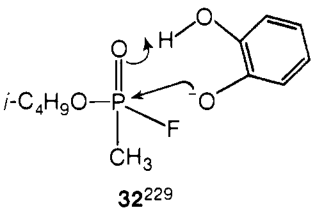
29[226]



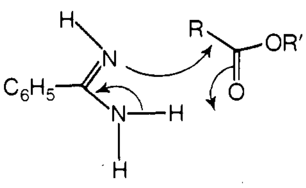
30[227]



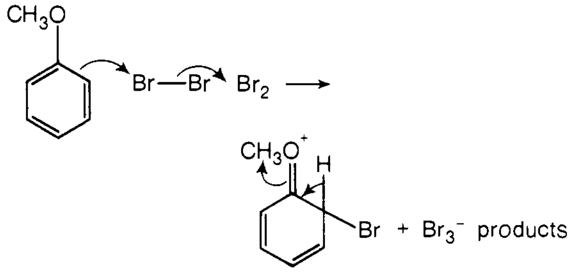
31[228]



32[229]



33[230]



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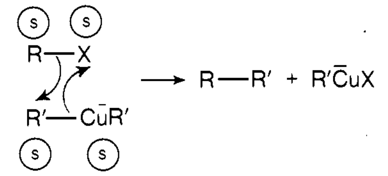

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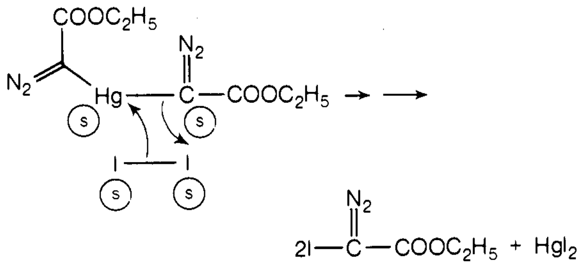
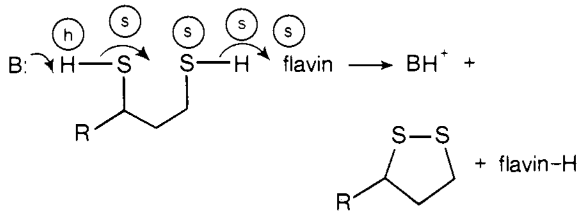


(115)

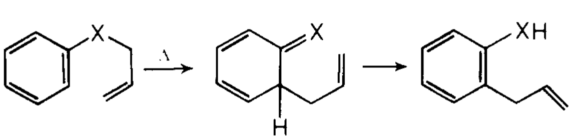
A very interesting and biochemically significant reaction is the dihydrolipoic acid reduction of riboflavin[235] which is subject to general base catalysis (eq 116).



(116)

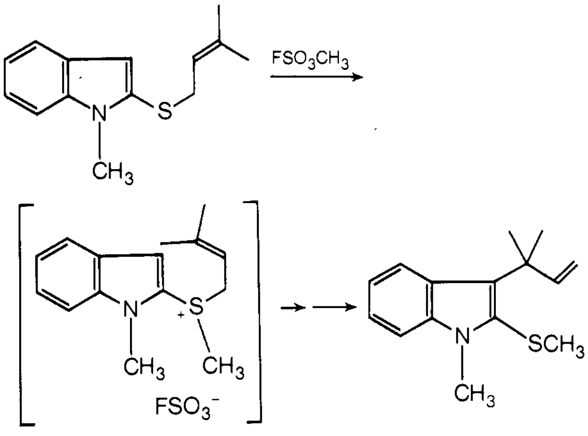
The regiospecificity of Diels–Alder reactions between dissymmetrical addends[236] arises from preferential formation of the first bond between the softest centers of the partners.

In aromatic Claisen rearrangements,[237] the oxygen version occurs at about 200°; S→C allyl shifts are more difficult to achieve (eq 117).[238] Formation of the intermediate dienone is the rate-determining step. Analysis of perturbance around the heteroatom X should furnish clues to relative reaction rates, as changes are the same elsewhere. Thus the problem is narrowed down to considering the net change of C(sp^3)-X to a C(sp^2)-X bond. Such a change is more favorable with X = O than that with X = S, because C(sp^2) is harder.



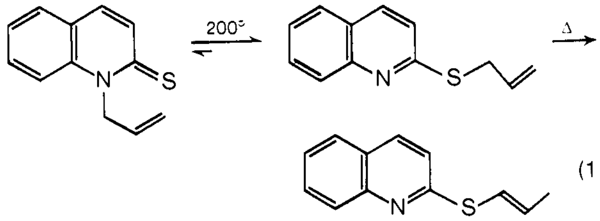
(117)

Amino-Claisen rearrangements are facilitated by Lewis acids.[239] It is therefore conceivable that sulfonium salts derived from allyl aryl sulfides would undergo rearrangement at lower temperatures. Such an effect due to sulfur atom hardening has been observed (eq 118).[240]



(118)

An interesting retro-thio-Claisen rearrangement[241] has been reported (eq 119).



(119)

The discussions of organic reactions in the light of the HSAB theory are by no means exhaustive. Rather, this is an article intended to illustrate and emphasize the applicability of Pearson's principle to a whole range of diverse subjects. To be realistic, the principle is an empirical one, and there are observations[242,243] not yet reconcilable with the theory. These minor inconsistencies are due to the present imperfect understanding of certain subtle aspects of bonding or other unaccounted factors.

The principle is extremely simple to apply, and enormously useful for rationalization of reaction site selectivity, for correlation of rates, and prediction of product structures and stabilities in a comparative sense.

Finally, it should be stressed that application of HSAB requires correct assignment of the acid and base components of a molecule which engages in a particular reaction. Furthermore, it is not possible, at the present stage of development to translate the principle into a quantitative tool, as the terms "softness" or "hardness" represent the collective property of a chemical entity which embodies such fundamental and diverse aspects as electronegativity, electron affinity, ionization potential, bond strength, nonbonding repulsion, London dispersion forces, solvation, etc.

V. Addendum

A monograph[244] dealing with HSAB has been published.

It has been shown that the soft dichlorocarbene does not coordinate with the hard oxygen atoms of the dioxolane group,[245] just as anticipated.

The symbiotic effect has been observed in gas-phase S_N2 reactions.[246] The same effect appears to dictate a rapid disproportionation of the initial 1:1 adduct of methyl o-phenylene phosphite with $C_2H_5OSC_6H_5$.[247]

The carbonyl group of choline selenol esters $RCOSeCH_2CH_2N^+(CH_3)_3X^-$ is susceptible to attack by thiols, yet stable to amines.[248] It is to be contrasted with the facile aminolysis of the corresponding thiol esters.

Anthrone also shows great selectivity in its alkylation.[249,250] Thus 9-alkoxy-anthracenes are obtained with alkyl sulfonates, and 10-alkyl- and 10,10-dialkylanthrones are produced when alkyl halides are used. C-Alkylation of benzoin by alkyl halides[251] is again in concordance with HSAB. α-Cyano carbanions undergo C-alkylation with alkyl halides but give ketenimine derivatives exclusively on reaction with trialkylsilyl chlorides.[252]

Thiol dimerization can best be achieved by exposure to soft oxidants. 2,4,4,6-Tetrabromocyclohexa-2,5-dienone is very effective owing to the availability of soft Br^+ at C-4 which serves to activate the thiols specifically.[253] The postulate of internal displacement on S by carboxylate in the disproportionation of 2-(phenyldithio)benzoic acid[254] finds no support in a more thorough study.[255] Such a pathway would be disfavored on HSAB ground. The methanesulfinate ion attacks disulfides with its soft S terminus to afford thiosulfonate esters.[256] Perfluorothioacetone forms a Bunté salt $(CF_3)_2CHS\text{-}SO_3^-$ with bisulfite, whereas a (2 + 1) adduct, $(CF_3)_2CHS\text{-}SC(CF_3)_2Cl$, is obtained on its treatment with HCl.[257] In both reactions a soft-soft S-S bond is formed.

Diazo compounds having a *β*-hetero substituent, $ArC(=N_2)CH_2Z$ ($Z = OR, NMe_2, SR$), decompose *via* carbenic rearrangement to afford olefinic products. Only hydrogen shift occurs in cases where $Z = OR, NMe_2$; on the other hand, thioether rearrangement predominates when $Z = SR$.[258] Specific soft-soft $>S \rightarrow :C<$ interaction accounts for the marked difference. Benzohydroxamic acid is less reactive than its *N*-methyl derivative toward aryl tosylates[259] because $C_6H_5CON(CH_3)O^-$ is harder than $C_6H_5C(O^-)=NOH$.

The dramatic increase in E2/SN2 ratio in the reactions of tosylates with oxalate *vs.* formate ions has been ascribed to a possible bidenate attack on hydrogen by the former.[260] It should be noted that oxalate is a harder base than formate. Hard nucleophiles (F^-, RO^-) displace the methylsulfonyl groups of 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine, whereas the softer CN^- and R_2NH species displace the chlorine(s).[261]

1,1-Dichloroallyllithium adds to ordinary ketones with its softer CCl_2 terminus, to aryl ketones and hexafluoroacetone with the harder CH_2 end.[262]

Marked increase in 1,4-reduction of enones by $LiAlH(SR)_3$ has been observed (*vs.* $LiAlH_4$).[263] The trend is in direct contrast to the behavior of the hardened alkoxyaluminum hydrides.

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