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CHEMOSELECTIVITY OF ORGANOMETALLIC REACTIONS
A HSAB APPRAISAL

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INTRODUCTION

Organic synthesis has now attained an unprecedented sophistication which is due in large measure to the influx of rapidly evolving organometallic methodologies. New reactions based on organometallic species have not only expanded the capability of fundamental transforms, but also imparted significant latitude to the strategic levels of synthesis. Furthermore, developments in certain areas of organometallic chemistry, especially homogeneous catalysis, hold great promise in revolutionizing the chemical industry.

In the broadest sense, organometallics encompass all organic compounds which contain metals and metalloids. In addition to substances which by puristic definition possess concrete carbon–metal bonds, π-complexes, coordination compounds, and compounds in which heteroatoms interpose carbon and metal elements may be included. These organometallics, as either reactants/reagents, or reaction intermediates, can exhibit fascinating reactivity profiles. The assessment of the diverse reactivity patterns is of great theoretical and pragmatic interest.

In a generalization of Lewis acid–base concept and by dividing the acids and bases into two categories (hard and soft) Pearson formulated the Hard and Soft Acids and Bases Principle.[1] This HSAB principle has provided the chemist a concise guidepost to correlate numerous chemical observations. While in organometallic chemistry a phenomenal body of esoteric results exists, a comprehensive treatment of those data from the HSAB standpoint has yet to be compiled and analyzed.

This article surveys a number of organometallic reactions with demonstrated usefulness in organic synthesis in terms of the HSAB principle. In keeping with a loose definition of organometallics some reactions involving inorganic (metallic) reagents but not the formation of organometallic intermediates or products are mentioned. Many interesting reactions participated by metalloids are also touched on, as well as some ylide chemistry which are not classified under the organometallic domain.

THE HSAB PRINCIPLE

Pearson's principle states that *hard acids prefer to coordinate to hard bases and soft acids to soft bases*. This implies both kinetic and equilibrium aspects.

The operational definitions for the hard and soft species are:

Soft base—donor atom of high polarizability, low electronegativity, is easily oxidizable and associated with empty, low-lying orbitals.

Hard base—donor atom of low polarizability, high electronegativity, is difficultly oxidizable, and associated with empty orbitals of high energy.

Soft acid—acceptor atom of low positive charge, large size, and having several easily excited outer electrons.

Hard acid—acceptor atom of high positive charge, small charge, and lacking easily excited outer electrons.

There are also *borderline* species which cannot be classified with certainty.

Typical hard/soft acids and bases are listed in Tables 1 and 2.

HARDNESS SCALES

A major defect of the HSAB principle pertains to the difficulty in its quantification. Over the years many scales of hardness and softness have been proposed, none of them seems to command wide applicability. Most recently, Parr and Pearson[2] have considered the ***absolute hardness*** η of a chemical species as half the derivative of its chemical potential with respect to the number of electrons:

$$\eta = \tfrac{1}{2}(\partial\mu/\partial N)_Z = -\tfrac{1}{2}(\partial X/\partial N)_Z = \tfrac{1}{2}(\partial^2 E/\partial N^2)_Z$$

where μ is the chemical potential, X is the absolute electronegativity, Z is the nuclear charge, N, the number of electrons, and E, the ground-state electronic energy.

Table 1

Hard acids
H^+, Li^+, Na^+, K^+ (Rb^+, Cs^+)
Be^{2+}, $Be(CH_3)_2$, Mg^{2+}, Ca^{2+}, Sr^{2+} (Ba^{2+})
Sc^{3+}, La^{3+}, Ce^{4+}, Gd^{3+}, Lu^{3+}, Th^{4+}, U^{4+}, UO_2^{2+}, Pu^{4+}
Ti^{4+}, Zr^{4+}, Hf^{4+}, VO^{2+}, Cr^{3+}, Cr^{6+}, MoO^{3+}, WO^{4+}, Mn^{2+}, Mn^{7+}, Fe^{3+}, Co^{3+}
BF_3, BCl_3, $B(OR)_3$, Al^{3+}, $Al(CH_3)_3$, $AlCl_3$, AlH_3, Ga^{3+}, In^{3+}
CO_2, RCO^+, NC^+, Si^{4+}, Sn^{4+}, CH_3Sn^{3+}, $(CH_3)_2Sn^{2+}$
N^{3+}, RPO_2^+, $ROPO_2^+$, As^{5+}
SO_3, RSO_2^+, $ROSO_2^+$
Cl^{3+}, Cl^{7+}, I^{5+}, I^{7+}
HX (hydrogen-bonding molecules)

Borderline acids
Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}
Rh^{3+}, Ir^{3+}, Ru^{3+}, Os^{2+}
$B(CH_3)_3$, GaH_3
R_3C^+, $C_6H_5^+$, Bi^{3+}
SO_2

Soft acids
$Co(CN)_5^{3-}$, Pd^{2+}, Pt^{4+}
Cu^+, Ag^+, Au^+, Cd^{2+}, Hg^+, Hg^{2+}, CH_3Hg^+
BH_3, $Ca(CH_3)_3$, $GaCl_3$, $GaBr_3$, GaI_3, Tl^+, $Tl(CH_3)_3$
CH_2, carbenes
π acceptors: trinitrobenzene, chloroanil, quinones, tetracyanoethylene, etc.
HO^+, RO^+, RS^+, RSe^+, Te^{4+}, RTe^+
Br_2, Br^+, I_2, I^+, ICN, etc.
O, Cl, Br, I, N, $RO\cdot$, $RO_2\cdot$, O_2
M^0 (metal atoms) and bulk metals

This can be correlated with the ionization potential I and electron affinity A of the species under consideration:

$$X = \tfrac{1}{2}(I + A)$$

$$\eta = \tfrac{1}{2}(I - A).$$

Thus, numerical parameters for several dozens of state-independent, environment-independent atoms, molecules, and ions are now available.

For our discussion there is little need for quantitative data. However, hardness trends have to be established, and the following are some useful reminders:

(1) *Hardness increases with increasing positive oxidation state*. For example, Ni(0) is soft, Ni(II) is borderline, Ni(IV) is hard; RS^+ is soft, $RS(O)^+$ is medium soft, $RS(O_2)^+$ is hard. Exceptions: Ti(III), Sn(IV), and Pb(IV) are softer than their respective lower valent ions because the *d* electrons in the latter species are shielded.

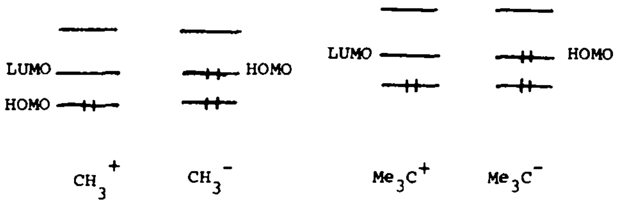
Table 2

Hard bases
NH_3, RNH_2, N_2H_4
H_2O, OH^-, O^{2-}, ROH, RO^-, R_2O
CH_3COO^-, CO_3^{2-}, NO_3^-, PO_4^{3-}, SO_4^{2-}, ClO_4^-
F^- (Cl^-)

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

Soft bases
H^-
R^-, C_2H_4, C_6H_6, CN^-, RNC, CO
SCN^-, R_3P, $(RO)_3P$, R_3As
R_2S, RSH, RS^-, $S_2O_3^{2-}$
I^-

(2) *Hardness is modified by surrounding ligands.* BH_3 is soft, while BF_3 is hard (H^- vs F^-). Hardness decreases in the series $Ph^+ > t\text{-}Bu^+ > i\text{-}Pr^+ > Et^+ > Me^+$. As H^- is softer than R^-, it follows that $Me^+ = 3H^-/C^{4+} < Et^+ = 2H^-, Me^-/C^{4+}$, etc. On the other hand, $Me^- > Et^- > i\text{-}Pr^- > t\text{-}Bu^-$ because $Me^- = 3H^+/C^{4-}$ is harder than $Et^- = 2H^+, Me^+/C^{4-}$, remember that H^+ is harder than Me^+, etc. This substituent effect may be explained in molecular orbital terms as idealized by the following diagram.



Alkyl groups raise the frontier orbital energies so that $E^*_{[R_nCH_{3-n}]}$ are higher than $E^*_{[R_{(n-1)}CH_{(4-n)}]}$. In a homologous series, the LUMO–HOMO splittings are expected to be very similar, therefore the more highly alkylated carbenium ion would be harder in view of its higher lying LUMO, the corresponding carbonion is softer because this high-lying MO becomes the HOMO.

(3) *Hardness is greater for the lighter member of a periodic family.*

$$R_3N > R_3P;\ R_2O > R_2S > R_2Se;\ F^- > Cl^- > Br^- > I^-$$

(4) *Hardness enhances as the core atom of an isoelectronic anion is heavier.*

$$CH_3^- < NH_2^- < OH^- < F^-$$

A reverse trend exists for the series of isoelectronic cations.

$$CH_3^+ > NH_2^+ > OH^+ > F^+$$

THEORETICAL BASIS OF THE HSAB PRINCIPLE

By far the most satisfying theoretical description of HSAB is the perturbation treatment by Klopman.[3] He has identified charge-controlled and frontier-controlled reactions which are equated with the hard–hard and soft–soft interactions, respectively.

Soft bases are donors with high lying orbitals and soft acids are acceptors having low lying empty orbitals. Interaction between the two types of reactants involves much electron transfer, because energy differences of the frontier orbitals are small. On the other hand, hard bases are donors with low lying, small orbitals and hard acids are acceptors with high lying empty orbitals; interaction between them is ionic.

A corollary to the intrinsic positioning of orbitals is that a hard (soft) acid becomes a soft (hard) base when supplied with an electron pair. Thus, the oxenium ion RO^+ is a soft acid, the oxide ion RO^- is a hard base.

SAVILLE'S RULES

The push–pull effect of reagents on organic reactions has been well recognized. It was Saville[4] who considered explicitly the effectiveness of such reagents in HSAB context. Two rules for optimally achieving bond cleavage (making) involve supply of a base and an acid of the same category (hard or soft) to polarize the electrofugal and the nucleofugal groups, respectively.

Rule 1:

$$Nu^h\!:\quad R^h - X^s \quad E^s \rightarrow Nu^h - R^h + X^s - E^s$$

Rule 2:

$$\mathrm{Nu^s}: \quad \mathrm{R^s - X^h} \quad \mathrm{E^h} \rightarrow \mathrm{Nu^s - R^s + X^h - E^h}$$

Best conditions will be that the substrate RX possesses maximal hard–soft disparity.

Numerous examples supporting Saville's rules are available. The remarkable splitting of molecular hydrogen[5] by a combination of a hard base (carboxylates, pyridines) and a soft metal ion (Ag(I), Cu(I), Hg(I), Pt(II), . . .) demonstrates that a strong H–H bond (hard–soft pair) can be severed under suitable conditions.

The very successful application of Saville's rule 2 is embodied in a method for ester cleavage by iodotrimethylsilane.[6] The soft iodide base attacks the ethereal carbon atom of the substrate while the O–C bond is being weakened by coordination of the oxygen atom with the silyl group. Chemicals which contain very different hard and soft moieties are conveniently called hard–soft reagents.

The Saville's rules should be extended to include reactions in which the reactive centers belong to the same class. For example, disulfides are cleaved readily at room temperature on exposure to a combination of methylmercury acetate and triethyl phosphite,[7] but not either one of the reagents. The observation evidently points to catalysis related to the two rules. Here a delicate operation of symbiosis (q.v.) and its perturbation along the reaction path are suggested.

SYMBIOSIS

Jørgensen[8] noted that metal ions prefer bonding to ligands of the same kind whether they are hard or soft. Mixed ligature often results in unstable species. The term "symbiosis" is then applied to describe this phenomenon of maximum flocking of either hard or soft ligands in the same complexes.

Symbiosis carries great significance in the chemistry of organotransition metals, it also is reflected in the relative reactivities of symmetrical and unsymmetrical organometallic compounds (e.g. Ph_2PbEt_2, Ph_4Pb, Et_4Pb).

The idea of symbiosis has also been extended to explain S_N2 reactions by Pearson and Songstad.[9] Symbiotic stabilization of the transition state results if the entering nucleophile and the leaving group are similar in hardness.

INTRINSIC STRENGTH

The crux of bond-making and bond-breaking reactions between an acid–base pair (A, B) lies in the strength of the chemical bond involved. In fact Pearson's statement of the HSAB principle takes the form:

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

where S's represent the strength factors, and the σ's are the hard–soft parameters.

Intervention of the strength factors could upset the HSAB principle. Most of the exceptions can thus be traced to this influence. In the real world of chemical reactions, the strength factors can never be neglected.

Another important point concerns with the notion that most of the properties characterizing hard species are in fact those characterizing strength. It need not be so, as there are hard but weak, soft yet strong species.

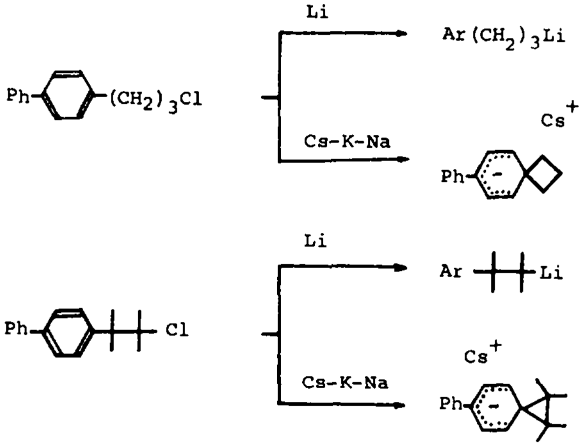
ORGANOALKALI METAL AND GRIGNARD REAGENTS

Some structural aspects

The most readily available and well-known organometallic compounds are those of light alkali and alkali earth elements. Because of the different hardness, these metal ions can have varying influence on the structure of the organic moiety.

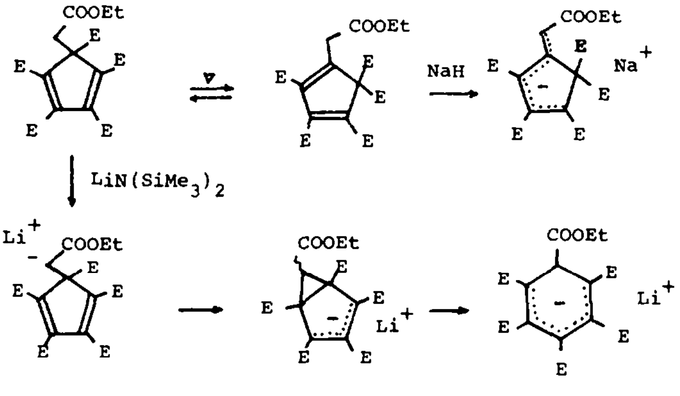
It has been shown by cmr study[10] that 7-phenylnorbornyllithium is pyramidal, whereas the corresponding potassium and cesium derivatives are planar. The sp^3 anion is harder than that having a pure *p*-character.

Different structures of organoalkali metal species may arise when aralkyl halides are treated with the metals.[11] Localized anions are formed from lithium/halide exchange, delocalized anions are preferred by K^+ and Cs^+.



The structure of deprotonated 9-acetyl-*Z,Z,Z,Z*-cyclonona-1,3,5,7-tetraene is a function of its counterion. Either [9]-annulene anion (K^+ salt) or a nonafulvene derivative (Li^+ salt) may be formed.[12]

The rearrangement of ethyl pentacarbomethoxycyclopentadienyl-acetate anion leads to either a 5- or 6-membered ring skeleton. The tendency for generation of a delocalized anion for Na^+ salt and a localized anion (harder) for the Li^+ salt accounts for the divergent reaction pathways.[13]



E = COOMe

The relative stabilities of metallated N,N-dimethylbenzylamines (Li: $o > \alpha$; Na: $\alpha > o$)[14] are associated with the hardness of the metal ions.

It is logical to expect that reaction conditions that affect the structure (hardness) of carbanions should have profound effects on the reaction courses. For example, sodiophenylacetonitriles attack on the sulfur atom of alkyl thiocyanates under phase-transfer conditions,[15] the lithio salts in nonpolar solvents prefer cyanation.[16]

$$\mathrm{PhCH(R)CN + EtSCN \xrightarrow[TEBA]{50\%\ NaOH} PhCR(CN)SEt}$$

$$\mathrm{PhCH_2CN + 2i\text{-}Pr_2NLi + 2\mathit{o}\text{-}ClC_6H_4CH_2SCN \xrightarrow{PhH} PhC(CN)_2Li}$$

$$\mathrm{+\ 2i\text{-}Pr_2NH + LiCN + (ArS)_2}$$

Different types of anionic species are involved. Both the dielectric constants of the reaction media and the nature of the counterions are the determining factors for the anion being soft (sp^2) or hard (sp^3).

Solvents alone play an important role in determining the anion structures. For example, the deprotonation of 2*H*-thiopyran in tetrahydrofuran occurs at C-6. However, in the presence of HMPA, a delocalized pentadienyl anion results.[17] Similarly, pyramidal allyllithium is converted to the delocalized *p*-type anion by solvating Li^+ with HMPA.

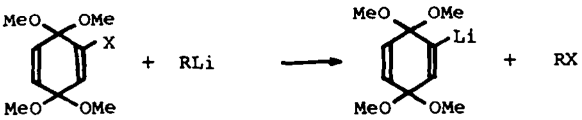
Deprotonation and metal–halogen exchange

The ease of formation of organometallics by treatment of organic halides with metals depends on the softness of the halides: $RI > RBr > RCl \gg RF$, because the heavier halogen is a better electron acceptor (with lower LUMO energy).

Organolithiums are quite basic, but they can be considered as soft species. This dichotomous property has been exploited in deprotonation as well as effecting metal–halogen exchange of organic compounds.

The gradational hardness of organolithiums causes varied efficiency of α-lithiation of N-nitrosodimethylamine:[18] t-BuLi 10%, n-BuLi 45%: MeLi 60%, PhLi 80%; i-PrNLi 95%.

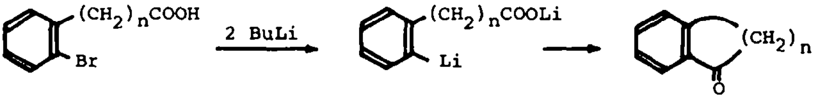
Lithium–halogen exchange[19] usually leads to a harder organolithium (alkynyl > alkenyl, aryl > alkyl). Since the reaction involves a soft–soft interaction, the softer lithium reagent should be more effective. The increasing competence of the reagent for promoting lithiation of 1-bromo-3,3,6,6-tetramethoxy-1,4-cyclohexadiene,[20] in the order of t-BuLi > sec-BuLi > n-BuLi ≫ MeLi > PhLi, indeed attests the correctness of such prediction. This trend is diametrically opposite to that observed in the hard proton abstraction process mentioned above.



Aryl halides, except fluorides, also undergo metal–halogen exchange with rates proportional to the polarizability of the C–X bond. The fact that *p*-cyanophenyllithium is obtained from treatment of the corresponding bromoarene with butyllithium indicates the preference for the soft interaction, while leaving the nitrile function unscathed.[21]

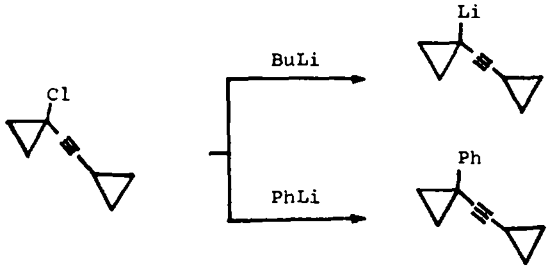
The conversion of bromobenzene to benzene-*d*, by successive treatment with n-BuLi and D_2O is impractical. However, the reaction is improved by adding the organometallic reagent to the substrate in D_2O-saturated ether.[22] Apparently the metal–halogen exchange proceeds much faster than the destruction of the reagent by D_2O. The presence of Me_3SiCl instead of heavy water in the medium allows for the preparation of trimethylsilylbenzene in good yield. The key to success for these procedures lies in the fact that both D_2O and Me_3SiCl are hard acids, whereas organometallic compounds are soft bases. n-BuLi attacks bromobenzene selectively to generate a harder base which reacts with the electrophile at a more leisurely pace.

The rapid Li–Br exchange is most critical to the success of a cyclic ketone synthesis from ω-(*o*-bromophenyl) alkanoic acids.[23] The greater difference in hardness between n-BuLi (vs ArLi) and the carboxylate group contributes to the suppression of bimolecular reaction.



n-2 65%
n-3 73%
n-4 48%

1-Chloro-1-(cyclopropylethynyl)cyclopropane undergoes halide–metal exchange with n-BuLi. Interestingly, an S_N2 displacement of the chlorine by a phenyl group of the harder PhLi reagent is noted.[24]



The debromination of *gem*-dibromocyclopropanes by dimsyl anion[25] involves removal of a soft halogen by the carbon base. The formation of allenes from the reaction of *gem*-dibromocyclopropanes with alkyllithiums[26] must proceed at its early stages by a similar mechanism. Halogen–metal exchange of a *gem*-dibromocyclopropane-carboxylic acid[27] is 2.5 times faster than proton abstraction from the acid! This is a remarkable demonstration of the HSAB axiom.

Lithium–chlorine exchange is apparently involved in the fragmentation of β-chloroethyl amines.[28]

Transmetallation

Common alkyllithiums are often used as reagents for Li–metal exchanges, especially in the synthesis of difficultly accessible organolithiums. The specific soft–soft interaction can be achieved in the presence of C–halogen bonds, as exemplified by the formation of *p*-bromophenyllithium[29] from bis(*p*-bromophenyl)mercury and n-butyllithium.

Allyllithium is now conveniently prepared by a Li–Sn exchange reaction.[30]

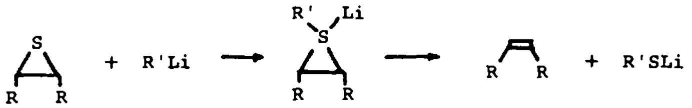
$$\mathrm{CH_2{=}CHCH_2SnPh_3 + PhLi \rightleftharpoons CH_2{=}CHCH_2\bar{S}nPh_4\ Li^+ \rightarrow CH_2{=}CHCH_2Li + Ph_4Sn}$$

In a comprehensive study of Li–main group element exchange reactions[31] it was found that a $\mathrm{Ph_2As}$ group attached to sp^3 or sp^2 carbon atom can be replaced only with difficulty. The Li–As exchange occurs rapidly in the case of the arsinoethynes.

$$\mathrm{Ph_2AsC{\equiv}CSiMe_3 + n\text{-}BuLi \xrightarrow{0^\circ} LiC{\equiv}CSiMe_3 + Ph_2AsBu}$$

The driving force for this metathesis is the more balanced HSAB relationship.

The chalcogenides are not metallic elements. However, their softness makes them very susceptible to attack by organolithiums. An extreme case is the desulfurization of thiiranes by such reagents (including lithium aluminum hydride).[32]

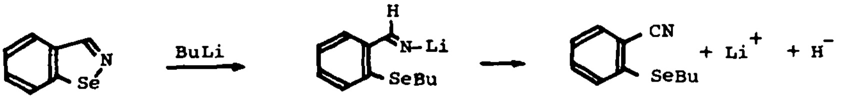


Tris(alkylthio)methide ions are generated by treatment of orthothiocarbonates with n-BuLi.[33]

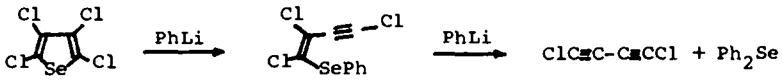
$$\mathrm{(RS)_4C + n\text{-}BuLi \rightarrow (RS)_3CLi + n\text{-}BuSR}$$

While 3-chloro-1,2-benzisothiazoles undergo substitution at C-3 with hard bases (alkoxides; amines), they suffer ring opening on exposure to soft bases such as n-BuLi, through attack of the reagents on sulfur.[34]

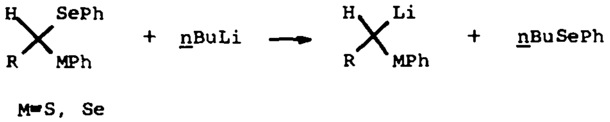
Interestingly, ring fission occurs when benzisoselenazole is treated with n-BuLi,[35] the absence of a leaving group at C-3 nevertheless. Apparently the high dissymmetry of the hard–soft N–Se bond prompts a ready cleavage by soft bases.



The selenophene ring is easily destroyed by reaction with alkyllithiums.[36,37]



The soft acid nature of the Se atom in selenothioacetals and diselenoacetals renders it susceptible to attack by organolithiums.[38] The behavior of these substances is notably different from that of dithioacetals in which deprotonation takes place.

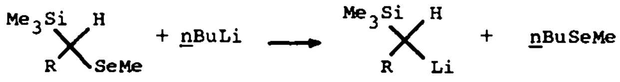


Two methods are available for synthesis of cyclopropanone diselenoketals[39]: (1) dehydrochlorination of 3-chloro-1,1-bis(alkylseleno)propanes with LDA, (2) treatment of 3-tosyloxy-1,1,1-tris(alkylseleno)propanes with BuLi. The hard and the soft bases used in each process serve to extract a proton and a seleno group, respectively.

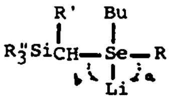
Gem-diselenocyclopropanes are lithiated by n-BuLi.[40] These lithio derivatives are softer than the S analogs, but they are harder than open-chain α-selenoalkyllithiums.

Cyclopropyl carbanions are harder bases because the exocyclic orbital has a higher *s*-character than sp^3.

α-Silylalkyl methyl selenides surrender the methylseleno group to n-BuLi. In contrast, the phenyl selenides undergo phenyl butyl exchange.[41]



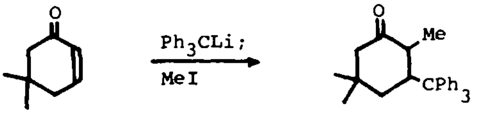
It is believed that tetravalent Se adducts are formed and then decomposed according to modes *a* or *b*, depending on the hardness of R. If R is harder than R''_3SiCHR', it takes precedence to capture Li which is a hard acid. Moreover, the cleavage of Se–C bond which has a higher hardness gap also stabilizes the system.[42]



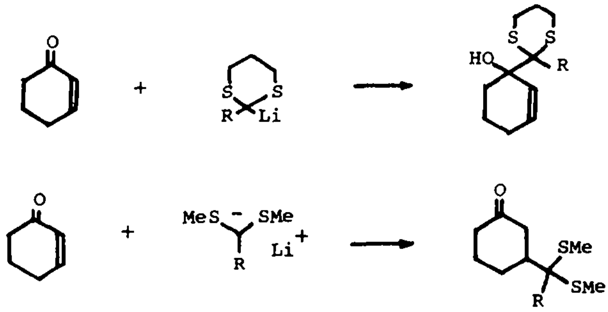
It is seen that thio and seleno groups stabilize an α-carbanion. *Ab initio* calculations[43] indicate a stereoelectronic cause and polarizability of the hetero atoms.

Reactions with organic compounds

The most thoroughly studied reactions of organolithiums and Grignard reagents are those involving carbonyl compounds. Owing to the relatively high order of hardness among organometallics, most alkyl/aryl–Li reagents add very readily to carbonyl substrates. If the lithiated carbon is sufficiently softened by ligands, e.g. in trityllithium, the reagent would effect 1,4-addition to alpha, beta-enones.[44]



2-Lithio-1,3-dithianes attack the carbonyl of enones,[39] whereas open-chain lithiodithioacetals can behave as Michael donors.[45]



The anionic carbon of a lithiodithioacetal might be expected to assume an sp^2-hybridization because of minimizing steric repulsion and stabilization by electron overlap. On the other hand, angle strain and increased 1,3-diaxial interaction which are introduced through C-2 rehybridization of the 1,3-dithiane ring could become excessive. Recent X-ray study[46] of 2-methyl-2-lithio-1,3-dithiane–TMEDA complex indicates a dimer structure in which equatorial Li atoms are coordinated to C-2 of one molecule as well as a S atom of another.

It should be remarked that in solution, TMEDA tends to solvate Li^+ strongly, and the softened dithiane anions become Michael donors.

If the lithio-1,3-dithiane carries a π-type substituent (COOMe, CN, etc.), it adds to enones also in 1,4-manner. Softening of the carbanion is evident.

The essentially soft base characteristic of organolithiums has been exploited in the one-pot synthesis of silyl ketones[47] and α-hydroxy ketones[48] as shown in the following equations.

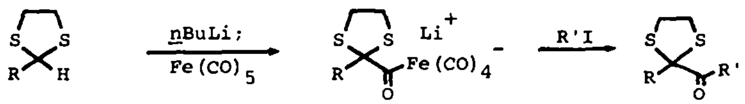
$$\mathrm{RLi + CO + Me_3SiCl \xrightarrow[-78^\circ]{} RCOSiMe_3}$$

$$\mathrm{RLi + CO + R'R''C{=}O \xrightarrow[-110^\circ]{} [RCOLi] \longrightarrow RCOC(OH)R'R''}$$

Diphenylcarbinols can be similarly obtained from phenyllithium, carbon monoxide and alkyl bromides.[49]

The soft–soft interaction between RLi and CO prevails in the presence of the hard acids. Among carbonyl compounds the chemoselectivity is most pronounced with esters, which is followed by ketones, and least so with aldehydes. The trend is that of increasing softness of the electrophiles which compete increasingly better with CO.

A synthesis of monoprotected α-diketones involves deprotonation of 2-substituted 1,3-dithiolanes (?) and reaction with pentacarbonyliron, and then an alkyl iodide.[50]



6-Phenyl-3,6-dihydropyrid-3-yllithium, obtained from addition of phenyllithium to pyridine, traps $Fe(CO)_5$. A number of carbonyl compounds can be prepared from the acylferrate intermediate.[51]

Various carbonyl substances such as aldehydes,[52] ketones,[53] esters,[53b,54] and amides,[55] based on acylferrates are now available. A facile method for the generation of the intermediates involves treatment of $Fe(CO)_5$ with organolithiums[56] or Grignard reagents.[55]

Alkylrhodium(I) complexes have been prepared by reaction of organolithiums/Grignard reagents with bis(triphenylphosphine)carbonylchlororhodium(I). On quenching with acyl chlorides, ketones are produced.[57]

$$\mathrm{MeLi} + (\mathrm{Ph_3P})_2\mathrm{RhCl(CO)} \longrightarrow (\mathrm{Ph_3P})_2\mathrm{RhMe(CO)} \xrightarrow{\mathrm{RCOCl}} \mathrm{RCOMe}$$

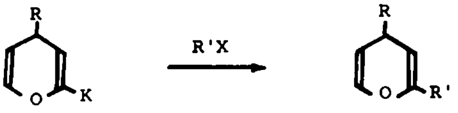
The increased polarizability of arene nucleus due to π-bonding with a tricarbonylchromium group renders such complexes reactive toward organolithium reagents.[58] A soft–soft interaction is involved in the C–C bond formation.

Because of its great softness, 1-phenylethyllithium adds to ethylene much more rapidly than other alkyllithiums, and more so than the harder aryllithiums. The rapid addition proceeds despite its thermodynamic stability.[59]

The trapping efficiency for 9,10-dehydrophenanthrene has been shown to be a function of donor softness:[60]

$$\mathrm{PhSLi} > \mathrm{PhLi} > \mathrm{C_5H_{10}NLi} > \mathrm{Ph(Me)NLi} > \mathrm{PhOLi}$$

The vinylic anion generated from 4*H*-pyran undergoes alkylation[61] with an efficiency depending on the hardness of the alkylating agent.



R=H,	R'X=MeI	4%
	Me_3SiCl	22%
R=Me,	R'X=EtBr	14%
	Me_3SiCH_2Cl	23%
	Me_3SiCl	48%

The greater softness of R_3SnLi in comparison with R_3CLi is reflected in their specific reactions with peresters at the oxygen.[62]

Although Grignard reagents and organolithiums can be used interchangeably in many synthetic occasions, diverse reactivity patterns can emerge because of intrinsic differences in their hardness. Many Grignard reactions proceed via free radical mechanisms,[63] and are characteristically soft.

Grignard discovered that alkylmagnesium halides attack cyanogen chloride and iodide in different ways.[64] The results are as expected from the soft nature of the organometallics.

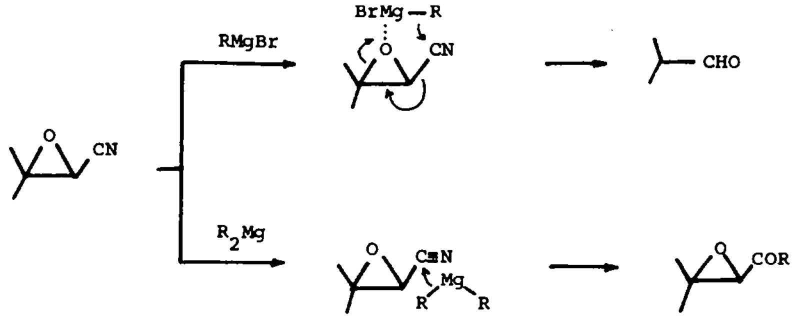
$$\mathrm{RMgX} + \mathrm{ClCN} \rightarrow \mathrm{RCN} + \mathrm{XMgCl}$$

$$\mathrm{RMgX} + \mathrm{ICN} \rightarrow \mathrm{RI} + \mathrm{XMgCN}$$

More recently, organotin compounds have been found to behave similarly.[65]

A synthesis of organic azides is by the reaction of Grignard reagents with benzenesulfonyl azide. The hard sulfonyl group is apparently immune to attack by the soft bases.

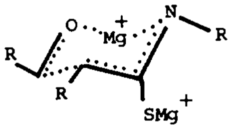
α-Cyanoepoxides exhibit interesting reactivity profiles toward organomagnesium compounds.[66] The determining factor is the selective coordination of the magnesium atom with the substrates. Thus complexation of the Grignard reagents with the harder epoxy oxygen preludes addition of the organic base at the cyano group. The cyano group acts as specific base for the magnesium atom of dialkylmagnesium reagents and directs the attack on site.



In the direct synthesis of triarylselenonium salts the yield data[67] indicate better reaction with a harder Grignard reagent. The tetravalent Se in $SeOCl_2$ is rather hard.

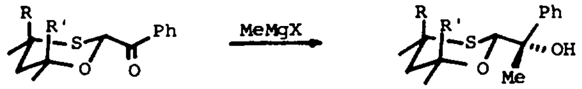
$$3ArMgX + SeOCl_2 \rightarrow Ar_3SeOMgX + 2MgXCl$$

The aldol condensation of the dianions of secondary thioamides with aldehydes is *threo* biased. Further enhancement of this stereoselectivity[68] is observed when the counterion Li^+ is replaced by Mg^{2+}.

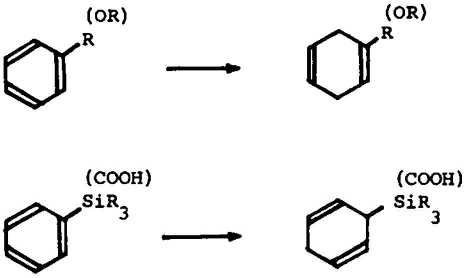


The *Z* transition state in which Mg is bound to both O and N atoms is favored symbiotically.

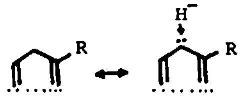
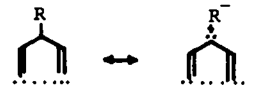
A remarkably stereoselective transfer of Me group from Grignard reagent to 2-benzoyl-4,4,6-trimethyl-2*R*,6*R*-oxathiane and -2*R*,4*S*-oxathiane[69] is most readily explained by a preferred complexation of Mg to the O but not the S atom of the heterocycle. The attack then proceeds according to the chelate model of Cram's rule.



Reduction of organic compound with alkali metals invariably involves one-electron transfer. Therefore such reactions are frontier-controlled. The regioselectivity pertaining to electrochemical and Birch reduction of aromatics is fascinating. Alkoxy and alkyl substituents favor the formation of 1-substituted 1,4-cyclohexadienes, whereas silyl[70] and carboxyl functions usually direct the reduction at the *ipso* and *para* positions. [Note: The *JCS* Perkin I 470 (1975) paper may at first sight give a wrong impression on the directing effect of silyl group, owing to overreduction involving cleavage of allylic silyl residues. A careful analysis indicates the prescribed pattern.]



Considering the relative stabilities of the carbanion intermediates which may be formulated as carbene complexes with anionic substituents:

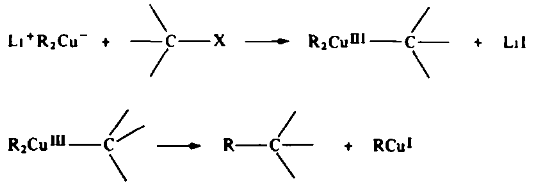
As a softer substituent anion has a larger stabilizing effect, the set on the left side is favored when R is an alkyl or alkoxy group which are harder than H^-. On the other hand, when R is a carboxyl or silyl substituent, the right-side set is more stable, since they are soft. [Note: silyl anions are soft, the carboxylate dianion has certain carbene character $^-C(O)O^- \leftrightarrow :C(O^-)_2$.]

Acyloin condensation is greatly improved by the addition of a chlorosilane.[71] This reaction involves ketyl formation prior to the coupling step. These intermediates and metallic sodium do not attack the chlorosilane rapidly (hard–soft incompatibility), therefore the latter reagent survives till hard bases appear. The hard bases, the enediolate and alkoxide ions, are detrimental to the reaction proper, because they can induce Claisen and/or Dieckmann reactions. Efficient removal of such anionic species by the chlorosilane suppresses the side reactions.

CHEMISTRY OF ORGANOCOPPERS

The softness of RLi, RMgX, and $RCu(R_2CuLi)$ in the increasing order is generally recognized. The very soft nature of organocopper species has enabled many chemoselective applications in synthesis.

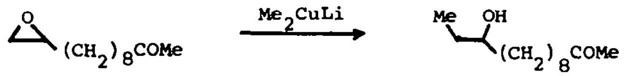
Corey and Posner[72] have explored the use of Gilman reagents (R_2CuLi) for coupling with organic halides. Lithium dimethylcuprate has a dimeric structure approximating D_{2h} symmetry[73] which may be important for the oxiative addition–reductive elimination process



Higher order, mixed organocuprates have been prepared and their reactivities studied.[74]

The reductive debromination of methyl 10,11-dibromoundecanoate can be achieved using Gilman reagent, but not with alkyllithiums.[75]

Nucleophilic attack on epoxides in the presence of a ketone group[76] presents no problem because the carbonyl function is relatively hard.



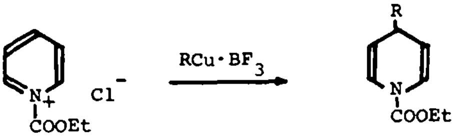
In connection with this general observation, it is intriguing to learn that 1,2-addition of dimethylcuprate to benzophenone[77] occurs. A common intermediate leads to the 1,2-adduct and benzophenone ketyl.[78]

2-Acetoxy-3-methyl-3-butenal bis(phenylthio)acetal undergoes 1,2-defunctionalization on treatment with cuprate reagent.[79] Selective attack on the thio group is preferred, although the terminal methylene is also an available soft acid center.

$$CH_2{=}C(Me)CH(OAc)CH(SPh)_2 \rightarrow CH_2{=}C(Me){-}CH{=}CHSPh$$

Allyl and propargyl acetates are usually displaced by organocuprates via an S_N2' mechanism. It has been reported that blocking the acetylenic carbon with a trimethylsilyl group enables direct substitution of a propargyl acetate,[80] for steric reasons. However, hardening of the acetylenic carbon may have also contributed to the change of chemoselectivity. The result is surprisingly different from those of displacement of propargylic sulfonates with Normant reagent.[81] Silyl allenes are obtained in many cases.

Addition of Cu reagents to N-carbethoxypyridinium chloride[82] takes place at C-4, the softest acid center. The reaction of N-phenacylpyridinium bromide results in the isolation of acetophenone.[83] It is reasonable to assume that 4-alkylpyridines are also produced.



There is a bias for harder nucleophiles to attack axially on cyclohexanones.[84] Thus the high percentage (>94%) of axial alcohol obtained from reaction of 4-t-butylcyclohexanone with lithium dimethylcuprate[85] is in keeping with the soft nature of the organometallic.

α,β-Unsaturated ketones undergo 1,4-addition with organocopper reagents. Regardless of mechanism,[86] delivery of the organic group to the β-C is expected for soft bases. The Kharasch reaction (Cu-catalyzed Grignard reaction with enones) most likely involves organocopper reactive species.

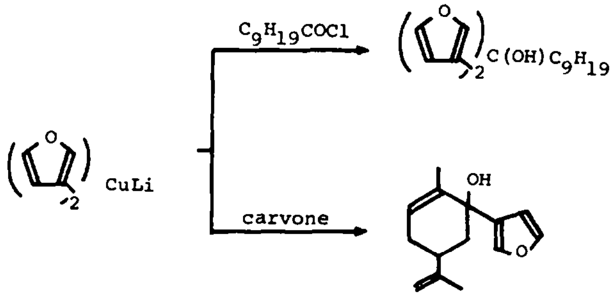
Early employment of Gilman reagents suffers from underutilization of the organic ligands. Cuprates containing a nonmigrating group have since been developed.[87] Among the stationary functions are the alkynyl, alkoxy, phenylthio and cyano units. The first two are harder than alkyl substituents, hence they are less prone to migrate to a soft acid center. The thio and cyano groups do not interfere with the alkyl transfer because they form strong bonds to Cu.

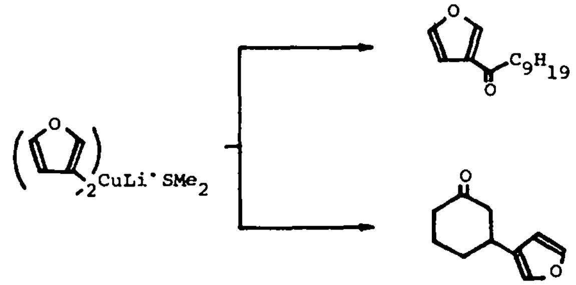
An example in which a Cu-bound alkynyl group becomes the dominant transferant is known.[88]

$$\mathrm{MeCH{=}CHCOCl + C_5H_{11}C{\equiv}C{-}\overset{-}{Cu}Me\ Li^+ \rightarrow \underset{78\%}{MeCH{=}CHCOC{\equiv}CC_5H_{11}}}$$

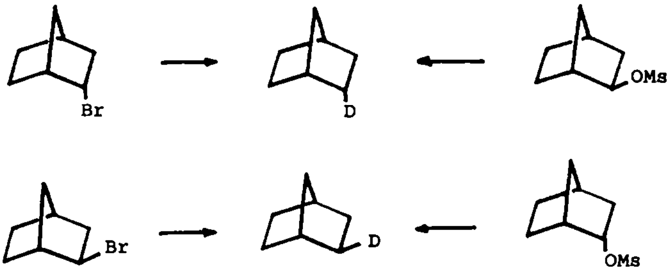
This striking observation is readily rationalized by invoking the HSAB principle. It is the nature of the reaction partner that dictates the group to be transferred; i.e. soft ligands to alkylating agents, hard ligands to acylating agents.

The sp^2 ligands in lithium di-(3-furyl)cuprate is apparently harder than most sp^3 dialkylcuprates. This change in hardness is revealed through reactions with carbonyl compounds.[89] Resoftening of this reagent is possible by the addition of dimethyl sulfide.





The reductive removal of halogen and mesyloxy group from the norbornyl system with a Cu(I) hydride has been studied[90] with regard to stereoconsequences.



Displacement of the mesyloxy group is formally an S_N2 process. The hydride reaction with the bromo compounds probably involves electron transfer, capture of bromine, and back-donation of hydrogen (deuterium) to the substrates within the ligand sphere of the copper complexes. The reason for the dichotomy must be hinged on the acceptor characteristics of bromine vis-à-vis the harder carbon.

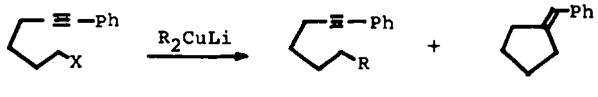
Similar duality exists during the coupling studies of benzyl derivatives with diorganocuprates.[83] It is now well known that diorganocuprates are soft nucleophiles which displace organohalides (bromides, iodides) with ease.[72,91]

$$PhCH_2\overset{+}{N}Me_3\overset{-}{I} \xrightarrow{n\text{-}Bu_2CuLi} PhCH_2Bu$$

$$2PhCH_2X \xrightarrow{R_2CuLi} PhCH_2CH_2Ph$$

X = halide

Interaction of 1-phenyl-6-halohexyne with lithium dialkylcuprates[92] leads to alkylated derivatives and benzylidenecyclopentane. The proportion of the cyclized product arising from metal–halogen exchange increases if either the halogen of the acetylene or R_2CuLi becomes softer.

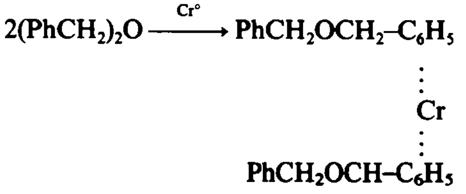


ORGANIC CHEMISTRY OF TRANSITION ELEMENTS

The presence of *d* electrons in late transition metals underlies the dominance of soft–soft interactions in the chemistry of these elements.

The degree of softness of a particular metal and auxiliary ligands determine the stability of σ and π complexes with carbon ligands. As the σ orbitals of carbon are harder than π orbitals, hardening of the metal by surrounding it with hard ligands favors the σ complex, and vice versa.

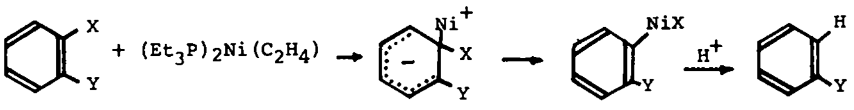
Selection of soft reactive locus by transition metals is evident in parallel experiments involving contact of atomized chromium with dibenzyl ether and dibenzyl sulfide.[93] Formation of a bisarene π-complex and desulfurization are the two separate events.



$$2(PhCH_2)_2O \xrightarrow{Cr^\circ} \begin{array}{c} PhCH_2OCH_2\text{–}C_6H_5 \\ \vdots \\ Cr \\ \vdots \\ PhCH_2OCH\text{–}C_6H_5 \end{array}$$

$$2(PhCH_2)_2S \xrightarrow[-S,\,-2H]{Cr^\circ} PhCH_2CHPh + PhCH{=}CHPh$$

The preferential debromination of *o*-bromochlorobenzene ($k_{Br}/k_{Cl} = 333$) by a Ni(0) complex indicates a strong bias for insertion of the metal into a softer C–X bond.[94]



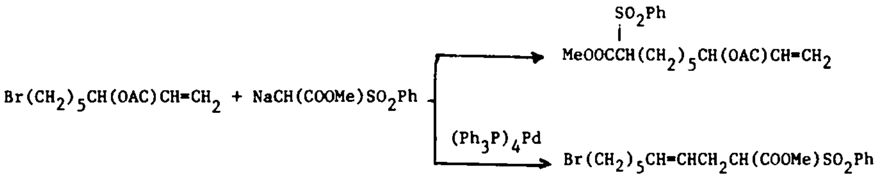
Nickel–phosphine complexes are very reactive toward catalyzing Grignard coupling with aryl and alkenyl halides.[95] Palladium(0) catalysts can also be used.[96]

$$\mathrm{PhCH{=}CHBr + CH_2{=}CHMgBr \rightarrow PhCH{=}CH{-}CH{=}CH_2}$$

Active transition metal species which are coordinatively unsaturated provide a template where organic substrates are brought together to react (via reductive elimination). Representative of such processes is hydroformylation whereby molecules of olefin, hydrogen and carbon monoxide are combined by a Co species.

A most fruitful area of research has been concerned with organopalladium compounds.[97] Olefins are converted to η^3-allylpalladium complexes which are susceptible to substitution at an allylic position. By virtue of this allylic activation new possibilities for making C–C and carbon–heteroatom bonds become available.

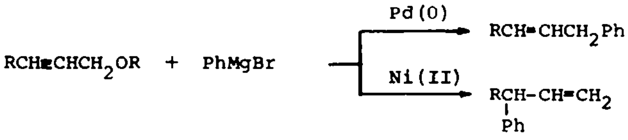
Unusual chemoselection has also been discovered which is germane to palladium-based chemistry. For example, the bifunctional alkylating agent 8-bromo-1-octen-2-yl acetate undergoes substitution by methyl benzenesulfonylacetate anion at either of the two sites in the presence or absence of a Pd catalyst.[98]



$$\mathrm{Br(CH_2)_5CH(OAC)CH{=}CH_2 + NaCH(COOMe)SO_2Ph} \rightarrow \mathrm{MeOOC\overset{SO_2Ph}{\overset{|}{C}}H(CH_2)_5CH(OAC)CH{=}CH_2}$$

$$\mathrm{Br(CH_2)_5CH(OAC)CH{=}CH_2 + NaCH(COOMe)SO_2Ph} \xrightarrow{\mathrm{(Ph_3P)_4Pd}} \mathrm{Br(CH_2)_5CH{=}CHCH_2CH(COOMe)SO_2Ph}$$

Regioselective cross-coupling of allylic ethers with phenylmagnesium bromide is catalyzed by Ni(II) and Pd(0) or Pd(II) complexes,[99] which involves the formation of η^3-allylmetal intermediates.

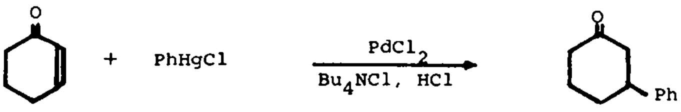


$$\mathrm{RCH{=}CHCH_2OR + PhMgBr} \xrightarrow{\mathrm{Pd(0)}} \mathrm{RCH{=}CHCH_2Ph}$$

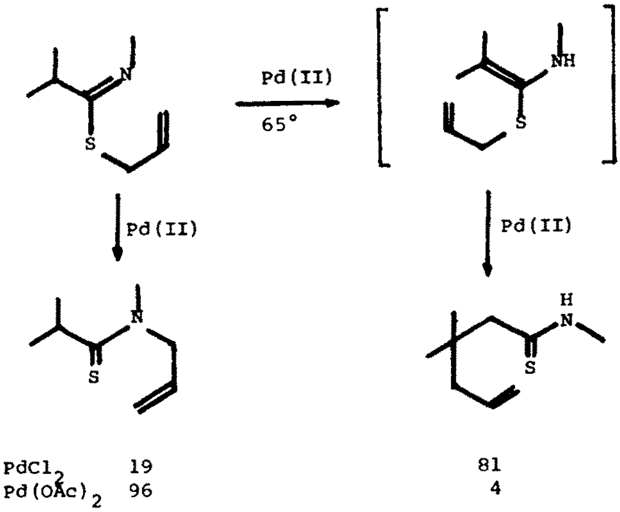
$$\mathrm{RCH{=}CHCH_2OR + PhMgBr} \xrightarrow{\mathrm{Ni(II)}} \mathrm{R\underset{\underset{Ph}{|}}{C}H{-}CH{=}CH_2}$$

Because Ni is harder, the complexes are more ionic and less symmetrical (with respect to the positions of the metal and the organic ligand), the positive charge residing in the allyl system must be localized more or less at the more highly substituted C atom. On the other hand, the essentially symmetrical η^3-allylpalladium complexes suffer attack by nucleophiles chiefly subject to steric effects, thus resulting in the release of internal olefins.

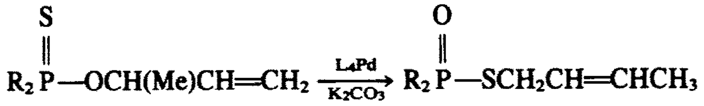
Many Pd-catalyzed organometallic reactions involve transmetallation to generate organopalladium species as the true reagents. Thus in the alkylation of olefins by organomercurials,[100] $\mathrm{RPdCl_3^{2-}}$ are actually involved.



Control of Pd(II)-catalyzed allyl shift in S-allylthioimidates can be exercised.[101] The use of the harder $\mathrm{Pd(OAc)_2}$ instead of $\mathrm{PdCl_2}$ results in a spectacular change in the ratio of S → C/S → N from 81 : 19 to 4 : 96.

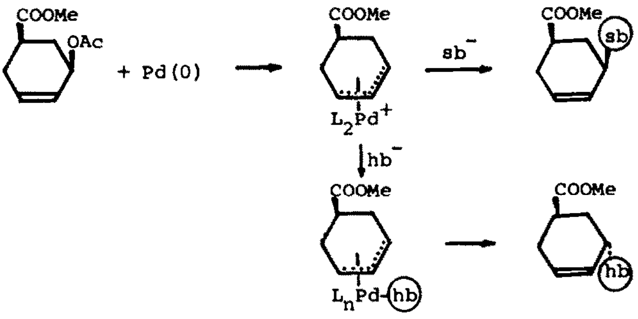


In O-allylthiophosphates, the allyl group undergoes O→ S rearrangement in the presence of L_4Pd catalysts.[102].



$$R_2\overset{\overset{S}{\|}}{P}\text{—OCH(Me)CH=CH}_2 \xrightarrow[K_2CO_3]{L_4Pd} R_2\overset{\overset{O}{\|}}{P}\text{—SCH}_2\text{CH=CHCH}_3$$

Attack on η^3-allylpalladium complexes is favored antarafacially by soft bases, suprafacially by hard bases.[103] Perhaps the metal ion has become harder because of the positive charge, and interacts with hard bases directly. The ensuing adducts then undergo reductive elimination which restricts delivery of the nucleophile to the allyl ligand from the *syn* face. On the other hand, softer bases tend to approach the allyl ligand from the side opposite to the hardened metal atom.



A regiochemical probe for hard/soft bases using 3-acetoxy-3-cyano-1-phenylpropene is less successful in my opinion. Perhaps the process is too complex for its regiochemistry to be controlled by HSAB-related factors alone.

The reactivities of isostructural transition metal alkyls toward carbonyl insertion usually decreases with descent of a triad.[104]

$$CpM(CO)_2Me + R_3P \rightarrow CpM(CO)(PR_3)COMe$$

$$M = Fe > Ru \gg Os$$

$$CpM(CO)_3R + Ph_3P \rightarrow CpM(CO)_2(PPh_3)COR$$

$$M = Cr, Mo > W$$

$$M(CO)_5R + L \rightarrow ML(CO)_4COR$$

$$M = Mn > Re$$

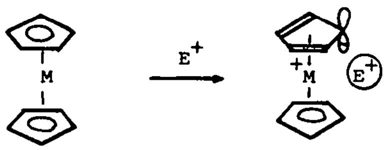
Both weaker C–M and softer acid nature of 3*d* metals vs 4*d* and 5*d* congeners are responsible for the reactivity trends.

For the migratory insertion of CO to rhodium alkyls,[105] the migratory aptitude is related to the softness of the alkyl substituent.

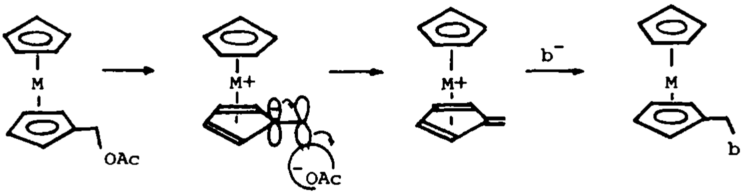
$$RhCl_2(PPh_3)_2R \xrightarrow{CO} RhCl_2(PPh_3)_2(CO)R \rightarrow RhCl_2(PPh_3)_2COR$$

$$R = Et > CH_2{=}CH \gg C_2H_4F$$

Previously the stereochemical aspects of electrophilic substitution of metallocenes were discussed.[106] In acylation, the attack comes from the outside (*anti* to the metal), and the order of reactivities is ferrocene > ruthenocene > osmocene. On the other hand, during mercuration, the electrophile approaches from the inside (*syn* to the metal). It is clear that (i) hard electrophiles align themselves farthest from the essentially soft metal in the transition states, and the charge-controlled reactions (acylation) occur more readily with the harder metallocenes, and (ii) soft electrophiles (e.g. Hg^{2+}) approach the aromatic ring from the same side as the metal which permits soft–soft interaction.



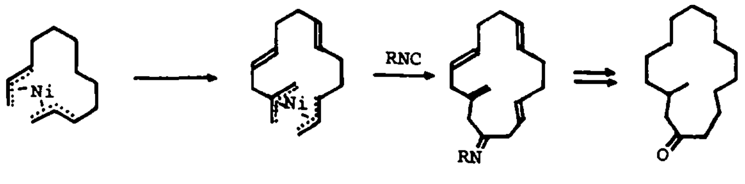
In the solvolysis of α-metallocenylmethyl acetates, the reactivity gradient osmocene > ruthenocene > ferrocene prevails. The ionization step may be envisioned as involving assistance from an electron pair of the ring. The geometry and electronic state of the metallocene moiety in the transition state must therefore resemble that in a substitution reaction by a soft acid.



It should be noted that the *syn*/*anti* preference is reversed in nucleophilic and electrophilic reactions.

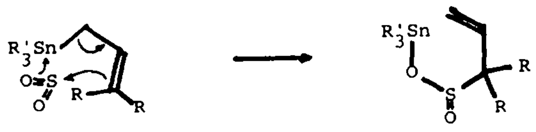
Diene oligomerization by Ni(0) species has been extensively studied. Formation of a bis(η^3-allyl) complex is followed by chain propagation via ligand displacement, and the reaction may be terminated by cyclization by soft ligand-induced reductive coupling.

Muscone synthesis involving insertion of dodecatrienyl nickel complex with allene then with t-butyl isocyanide[107] or carbon monoxide[108] typifies such a process.

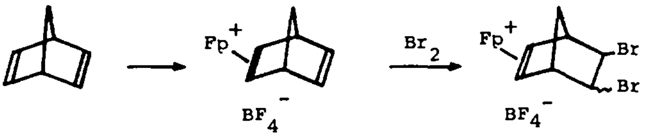


η-Allylmetals insert sulfur dioxide transpositionally. The production of either metal sulfone[109] or sulfinate[110] derivatives depends on the greater or lesser softness of the metal.

M = Re, Mn

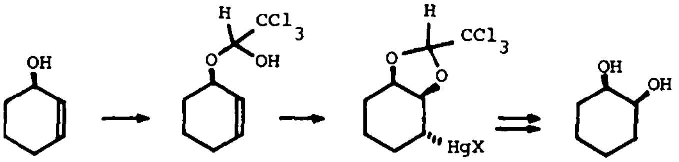


π-Complexation of olefins (and acetylenes) with heavy metal ions is well known and has a sound HSAB basis. The coordinated double bond is inert to electrophiles and it can be thereby protected. Bromination of norbornadiene without skeletal rearrangement is achieved via an Fe-complex.[111]



Many of the π-complexes are active electrophiles. Formation of a π-complex is the initial step of the industrially important Wacker process.[112] Recently, success has been reported for using olefins as alkylating agents by complexation with (η^5-cyclopentadienyl)dicarbonyliron.[113]

Solvomercuration of olefins is relatively facile. With a subsequent reduction of the C–Hg bond by soft hydrides, many functional groups can be introduced into a carbon skeleton. An application of this method is a stereoselective synthesis of *cis*-1,2-diols from allylic alcohols.[114]



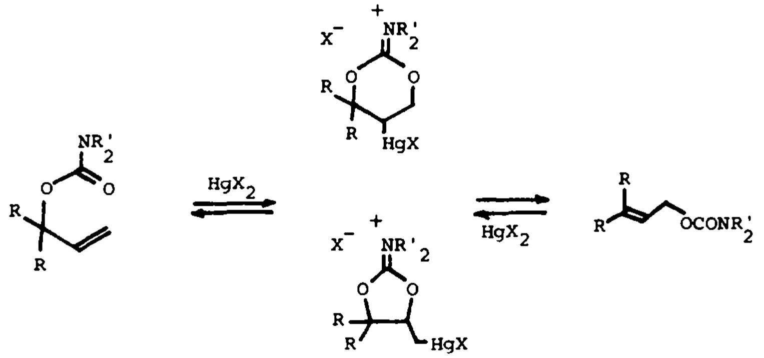
It is interesting to note that in the mercurinium intermediates positive charge is imparted on the carbon atoms and these acid centers are moderately hard. They react readily with water, alcohols, and amines. However, in the reaction of an olefin with mercury(II) nitrite or $HgCl_2$–$NaNO_2$ combination,[115] the nitrite ion uses its softer end to attack the mercurinium ion.

$$RCH{=}CH_2 + Hg(NO_2)_2 \rightarrow RCH(NO_2)CH_2HgNO_2$$

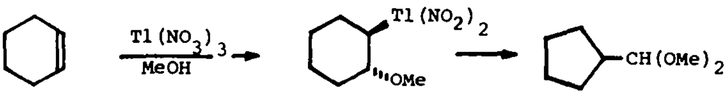
Cleavage of cinnamyl carboxylates can be effected via mercuriomethoxylation and treatment with thiocyanate ion.[116] Attack of the soft anion on the Hg atom triggers the release of the carboxylate.

$$RCOOCH_2CH{=}CHPh \xrightarrow[MeOH]{Hg(OAc)_2} RCOOCH_2CH(HgOAc)CH(OMe)Ph$$
$$\downarrow KSCN$$
$$RCOOK + AcOHgSCN + CH_2{=}CHCH(OMe)Ph$$

N,N-Dimethylcarbamic esters of allylic alcohols are effectively equilibrated in the presence of mercury(II) trifluoracetate.[117] This process is far superior to the acid-catalyzed isomerization due to the involving base (alkene) being soft.



Although Tl is not a transition metal, many aspects of its chemistry resemble those of mercury. Tl(III) salts react even faster than Hg(II) counterparts with olefins. Because of the weak (?) C–Tl bond, expulsion of Tl from the initial products often occurs.[118]



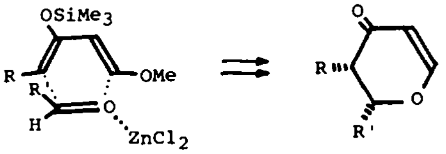
Complexation of Tl(III) to the soft end of isonitriles precedes alcoholation of the latter.[119] The initial soft–soft interaction transforms the isonitriles into hard acids.

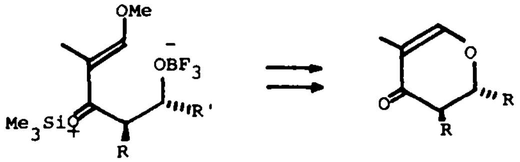
Belonging to the same subgroup of Hg is Zn. But because of it being lighter, Zn ion is harder (a borderline acid), and is generally regarded as a "mild" Lewis acid.

This classification fits perfectly the bonding situations found in Zn compounds. An X-ray study indicates Reformatsky reagents contain a Zn atom linked to both C and O atoms (dimeric structure).[120]

Cyclocondensation of siloxydienes with aldehydes[121] yields *cis*(-*erythro*)-dialkyldihydro-γ-pyrones in the presence of ZnCl$_2$. This pericyclic reaction occurs when ZnCl$_2$ forms an *E* chelate with the aldehydic oxygen which lines up with the diene in an *endo* transition state.

The reaction promoted by the harder BF$_3$·Et$_2$O proceeds via siloxonium intermediates, leading to *trans*(*threo*) products.

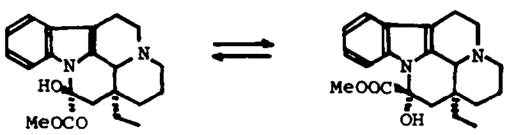




Heavy metal ions have been used to improve C–O bond formation reactions. The classical ester synthesis and Williamson ether synthesis, involving alkali metal salts of carboxylic acids and alcohols with alkyl halides, are at best of marginal synthetic value. By increasing the hardness gap of (destabilizing) one of the reactants, i.e. using salts of heavy such as Cu,[122] Ag,[123] Hg,[124] Tl,[125] Ni(acac)$_2$,[126] instead of alkali metal, which simultaneously pairs better with the eventual partner (halide ion), greatly increases the efficiency of the reaction.

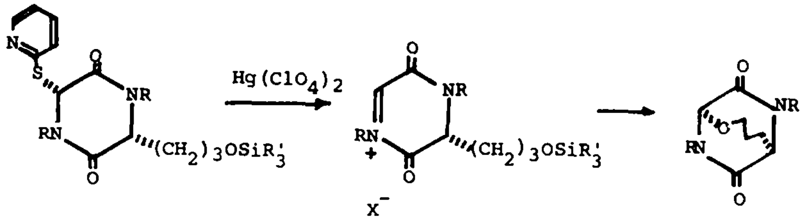
Conversion of nonactivated alkyl halides to carbonyl compounds by the Kornblum reaction (dimethyl sulfoxide) is difficult. The addition of an Ag salt[127] to polarize the C–X bond and thereby hardening the carbon acid is crucial. It must be remembered that the attacking nucleophile is a hard acid.

Equilibration of vincamine and epivincamine proceeds via the tetracyclic alpha-keto ester. It is catalyzed by soft metal ions (Hg^{2+}, Ag^+), but inhibited by harder ions (Fe^{2+}, Zn^{2+}).[128]

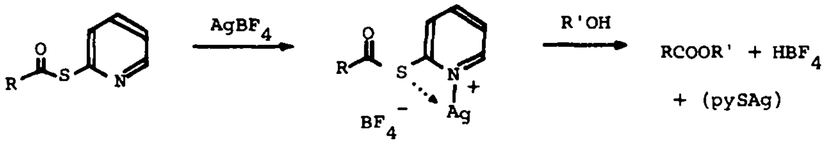


This phenomenon is due to selective coordination. Soft ions bind to the sufficiently soft indolic system (nitrogen and/or double bond), thereby weakening the C–N bond; harder ions interact with the OH group, rendering the ring opening difficult.

Removal of the thio substituent from 3-(siloxypropyl)-6-pyridylthiopiperazinedione derivatives with concomitant desilylative cyclization is effectively promoted by mercury(II) perchlorate.[129] The reagent furnishes both a soft acid and a hard base to fulfill Saville's optimal conditions.

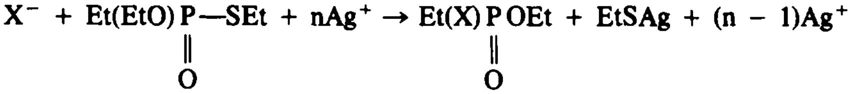


Alcoholysis of 2-pyridylthio esters is greatly assisted by silver tetrafluoroborate. This procedure has been applied to the synthesis of macrocyclic lactones.[130]



A study of the reaction with other thioesters[131] has shown the effectiveness of other metal ions such as Ag^+, Cu^+, Cu^{2+}. Mercuric ion is also useful if the substrate does not contain other soft base centers such as alkene linkages. It has also been observed that subtle variation in softness of the catalyst can cause dramatic changes in rates and yields of the reaction.

Aminolysis of thioesters with metal catalysis is also known.[132] The analogous hydrolysis of O, S-diethyl ethylphosphonothioate is promoted by a combination of Ag and fluoride ions.[133]



$$X^- + Et(EtO)\underset{\underset{O}{\|}}{P}\text{—}SEt + nAg^+ \rightarrow Et(X)\underset{\underset{O}{\|}}{P}OEt + EtSAg + (n-1)Ag^+$$

$$X = F, OH$$

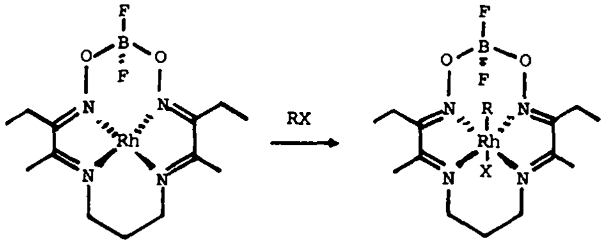
Many dethioacetalization procedures involve heavy metal[134] catalysis. The binding of metal ions with sulfur atom renders the neighboring carbon harder and susceptible to attack by water. Effective metal salts are those of Hg^{2+}, Tl^{3+}, Ag^+, Cu^{2+}.

Thionocarbonates of 1,2-diols are decomposed to olefins by treatment with iron pentacarbonyl[135] or bis(1,5-cyclooctadiene)nickel(0).[136] The latter reaction is stereoselective and it may involve extraction of the sulfur atom by the metal species to generate a carbene. This last step should be facilitated by the presence of the soft metal.

Stabilization of carbenes by heavy metals is now fully appreciated.[137] The softness of these metals and ions is responsible for their effectiveness in catalyzing decomposing of diazoalkanes[138] and azides.[139]

The reaction of transition metal nucleophiles with iodomethane and methyl tosylate has been thoroughly investigated.[140] These powerful bases are very soft.

Alkylation of a neutral rhodium(I) macrocycle[141] shows a preference for soft species.



$$R=\overbrace{\underbrace{\text{Me} > \text{Et}}_{20}\underbrace{\;> \underline{\text{n}}\text{Bu}}_{4}\underbrace{\;> \underline{\text{i}}\text{Pr}}_{300}}^{7200} \gg \underline{\text{c}}\text{C}_6\text{H}_{13};\ \underline{\text{t}}\text{BuCH}_2 \gg \underline{\text{t}}\text{Bu},$$

$$X=\underbrace{\overbrace{\text{I} > \text{Br} \sim \text{OTs}}^{3000} > \text{Cl}}_{10^6}$$

Bis(dimethylglyoximato)(pyridine)styrylcobalt(III) derivatives form styryl sulfides on reaction with arenesulfenyl chlorides.[142] No reaction with hard acids (ClCOOEt, i-AmONO, etc.) was discernible. The styryl group is a soft base by virtue of influence from the metal ion through back donation.

Competitive extraction of $Co(CO)_4^-$ and I^- by tetrabutylammonium ion indicates the cobaltate ion is 60 times more extractable into organic phase of the CH_2Cl_2–H_2O system.[143] This ion is apparently much softer.

Displacement of vinylic halides with cyanide ion is mediated by tetracyanocobaltate(I), and involves interaction of the soft metal anions with the π-bond, followed by C–Co σ bond formation.[144]

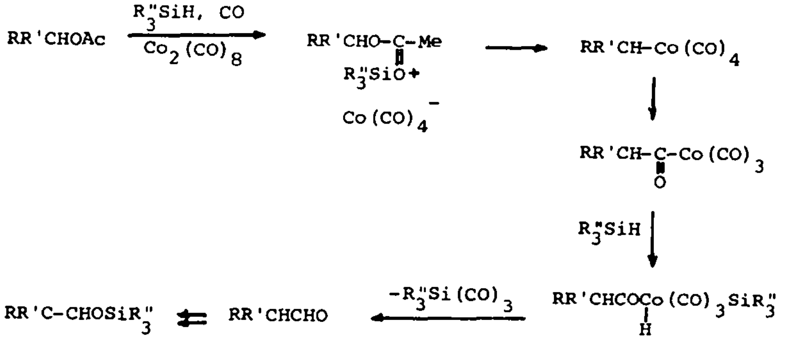
The nucleophilicity of various carbonylmetallates appear to fall in the order:[145] $Fe(CO)_4^{2-} > RFe(CO)_4^- > RCOFe(CO)_4^-$, as the expected softness.

Acylcarbonylmetallates such as $RCONi(CO)_3^-$ and $RCOFe(CO)_4^-$ are capable of transferring the acyl group to C-4 of alpha, beta-unsaturated carbonyl compounds.[146]

$$M^+\ RCOM(CO)_n^- + R'CH{=}CHCOR'' \rightarrow RCOCH(R')CH_2COR''$$

Similarly, hydridocarbonylmetallates are useful reducing agents which act on soft acids such as alkyl halides,[147] thiones,[148] and conjugate double bonds.[149]

An oxidative homologation of alkyl acetates,[150] by the reaction with silane and carbon monoxide and catalyzed by dicobalt octacarbonyl, proceeds via the formation of very reactive silyltetracarbonylcobalt. These reactive intermediates contain a hard acid (Si) binding to a soft base (Co). Accordingly, such species activate readily acetate function with formation of an ion pair. Collapse of the ion pair by S_N2 displacement, followed by rearrangement, reduction, and elimination to give an aldehyde. Enol silylation is the final step.



The crucial events involve formation of a powerful hard–soft reagent and its interaction with the substrate.

A closely related process is the synthesis of α-siloxy aldehydes.[151]

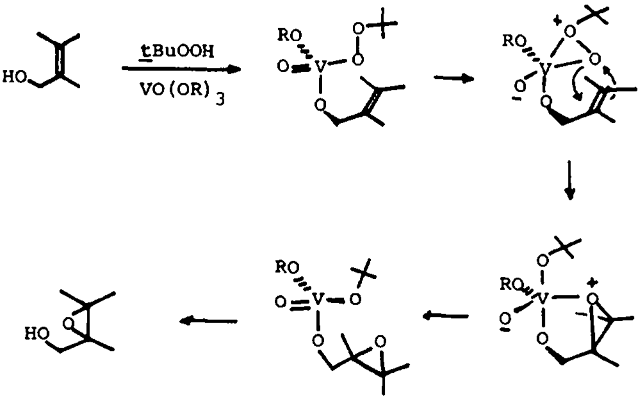
$$RCHO + R'_3SiH + CO \xrightarrow[Ph_3P]{Co_2(CO)_8} RCH(OSiR'_3)CHO$$

The reductive dimerization of benzaldehyde[152] with action of trimethylsilylpentacarbonylmanganese or bis(trimethylsilyl)-tetracarbonyliron also exploits the hardness gap of the organometallic reagents.

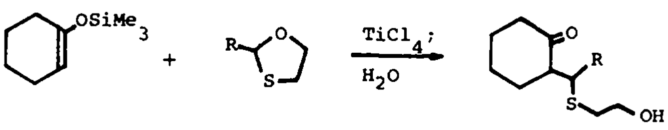
$$PhCHO + Me_3SiMn(CO)_5 \rightarrow Me_3SiOCPh \rightarrow \tfrac{1}{2}PhCH(OSiMe_3)CHPh(OSiMe_3)$$

We have witnessed certain facets of organotransition metal chemistry of the elements on the right side of the series. The early transition metals behave radically different in some respects. The high valent species of the early transition metal are hard.

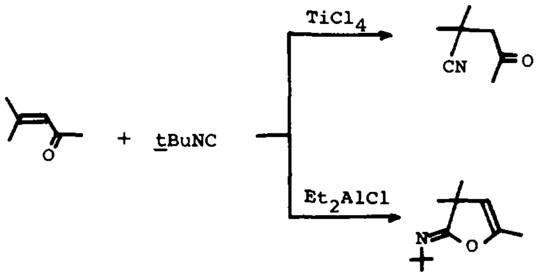
Ti(IV), V(V), and Mo(VI) are typical hard acids. The use of their salts as Friedel–Crafts catalysts is an established fact. More recently, these ions, especially V(V), have served as mediators for stereoselective epoxidation of allylic and homoallylic alcohols by t-alkylhydroperoxides.[153]



The hard acid nature (oxaphilicity) of Ti(IV) underlies the catalytic activity in many C–C bond formation processes.[154] The selectivity is shown by an alkylation with 1,3-oxathiolanes.



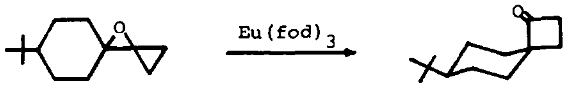
Conjugate hydrocyanation of enones may be achieved with t-butyl isocyanide and titanium tetrachloride.[155] Interestingly, the reaction promoted by organoaluminum compounds leads to N-t-butyl iminolactones.[156]



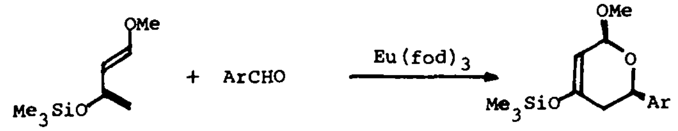
Both combinations of reagents behave as expected on HSAB basis, however, strength factors may have played an important role in determining the products. The stronger O–Ti bond vs O–Al bond perhaps disfavors "backbiting" with the O atom.

Titanium tetrachloride is a good shift reagent for NMR spectroscopy.[157] It binds most readily with the harder base centers, feebly or not at all with soft bases.

More commonly used NMR shift reagents are rare earth complexes.[158] These metal ions being very hard acids, they have also been employed as rearrangement inducer of spirooxiranes,[159] and



as selective activators of carbonyl group in enones for hydride reduction (*q.v.*), and of aldehydes in the participation in Diels–Alder reactions.[160]



CHEMISTRY OF ORGANOBORON AND ORGANOALUMINUM SPECIES

Hydroboration

The development of hydroboration reaction[161] has revolutionized the chemistry of organoboranes. The basis for this facile reaction is the soft nature of BH_3. The B–H bond can be regarded as a B^+H^- pair which adds across an alkene linkage so that the boron atom becomes attached to the less substituted carbon.

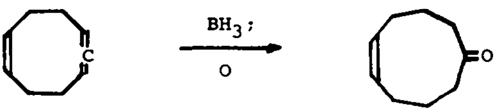
Numerous modified boranes are now available for effecting hydroboration. For example, chloroborane ($ClBH_2$) is a more regioselective agent,[162] owing to the heightened hardness of the B atom. Interestingly, the triphenylphosphine–borane complex is a solid stable to 3 N HCl and alkaline H_2O_2, but is capable of hydroborating alkenes. The hydroborating activity is further enhanced by activation with soft species such as iodomethane and sulfur.[163]

The stability of the complex derives from soft–soft interaction. The mutual softening effect renders the borane moiety resistant to hard bases. In the presence of another soft base such as an alkene, equilibrium of the complex with its components can be shifted and the borane intercepted. Addition of soft acids also helps displacement of the equilibrium as the triphenylphosphine is removed. Thus hydroboration under such conditions involves a push–pull mechanism.

$$\mathrm{Ph_3P{\cdot}BH_3} \rightleftharpoons \begin{array}{l} \mathrm{Ph_3P} \xrightarrow{\text{MeI or S}} \mathrm{Ph_3\overset{+}{P}Me\ I^-} \ \text{ or } \ \mathrm{Ph_3P{=}S} \\ \mathrm{BH_3} \xrightarrow{\mathrm{3RCH{=}CH_2}} \mathrm{(RCH_2CH_2)_3B} \end{array}$$

In hydroboration of styrene derivatives,[164] an electron-withdrawing substituent in the aromatic nucleus renders the benzylic carbon hard and hence induces a larger amount of boration at that center. Conversely, an electron-donating group tends to direct the C–B bond formation at the terminal carbon. Vinylferrocene, by having a soft aromatic unit, is borated to the extent of 98% at the end position,[165] as compared with 80% in styrene.

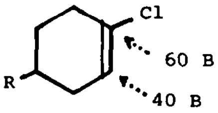
The central C atom of an allene molecule is the hardest acid center of the unsaturated system. Attachment of B to this site is observed.[166]

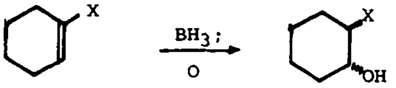


Hydroboration of 1-haloalkenes[167] and enol acetates places the boron atom predominantly at the α-C. However, enol ethers[167b] and enamines,[168] regardless of the degree of substitution on the double bond, give 1,2-difunctional products.

$$\mathrm{RCH{=}CHX + R'_2BH \longrightarrow RCH_2CH(X)BR'_2}$$

R = Et, Ph
X = Cl, Br





X = EtO, C_4H_8N

The halogen and the acetoxy group infuse hardness in the ipso carbon, making it a better partner for the B. Although alkoxy and amino substituents should exert a similar inductive effect, but it is swamped by resonance which fixes the nucleophilic center at the β carbon.

Degradation of organoboranes

Organoboranes and borates are biphilic toward both hard and soft bases. Thus they are readily attacked by oxy bases, ylides, carbenes, and azides. The adducts undergo 1,2-alkyl shift from B to a soft acid center, and the rearrangement products may then be deborated by appropriate work-up procedures.

$$\mathrm{R_3B + HOO^- \rightarrow R_3\overset{-}{B}\text{–}OOH \rightarrow R_2BO^- + ROH} \tag{169}$$

$$\mathrm{R_3B + R'COOH \rightarrow R_2B\text{–}OCOR' + ROH} \tag{170}$$

$$\mathrm{R_3B + ClO^- \rightarrow R_3\overset{-}{B}\text{–}OCl \rightarrow R_2B\text{–}OR + Cl^-} \tag{171}$$

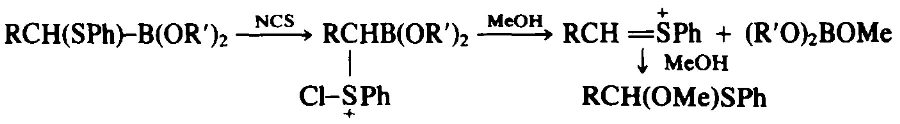
$$\mathrm{R_3B + R'_3NO \rightarrow R_3\overset{-}{B}\text{–}O\overset{+}{N}R'_3 \rightarrow R_2B\text{–}OR + R'_3N} \tag{172}$$

$$\mathrm{R_3B + CH{=}SMe_2 \rightarrow R_3\overset{-}{B}\text{–}CH_2\overset{+}{S}Me_2 \rightarrow R_2B\text{–}CH_2R + Me_2S} \tag{173}$$

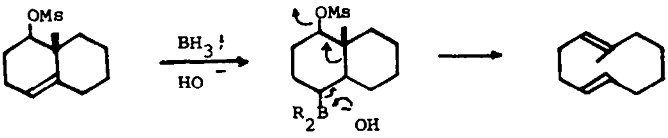
$$\mathrm{R_3B + :CH_2X \rightarrow R_3\overset{-}{B}\text{–}\overset{+}{C}HX \rightarrow R_2B\text{–}CH(X)R \rightarrow RB(X)\text{–}CHR_2} \tag{174}$$

$$\mathrm{R_3B + R'N_3 \rightarrow R_3\overset{-}{B}\text{–}\overset{+}{N}R' \rightarrow R_2B\text{–}NRR'} \tag{175}$$

Deboration of organoboranes/borates containing a hetero atom at a geminal, vicinal, or remote carbon may be pursued with the aid of HSAB consideration. The best conditions would consist availing the molecule a soft nucleofugal group to enable the use of a hard base to attack the boron center without interference.



$$\mathrm{RCH(SPh)\text{–}B(OR')_2} \xrightarrow{\text{NCS}} \underset{\substack{|\\ \mathrm{Cl\text{–}\underset{+}{S}Ph}}}{\mathrm{RCHB(OR')_2}} \xrightarrow{\text{MeOH}} \underset{\substack{\downarrow\ \text{MeOH}\\ \mathrm{RCH(OMe)SPh}}}{\mathrm{RCH{=}\overset{+}{S}Ph}} + \mathrm{(R'O)_2BOMe} \tag{176}$$



(177)

Boron reagent-mediated functional group exchange

Although B is classified as borderline acid, it really leans toward the hard side. Evidence for this contention comes from the facile thioacetalization,[178] selenoacetalization,[179] and mixed disulfide synthesis[180] shown in the following equations.

$$3R_2C{=}O + 2(R'X)_3B \rightarrow 3R_2C(XR')_2 + B_2O_3$$

$$X = S, Se$$

$$3ArS{-}OMe + (RS)_3B \rightarrow 3ArS{-}SR + (MeO)_3B$$

Mono(alkylthio)boranes are useful for cleavage of ethers.[181] A soft base (RS^-) is displaced, which in turn launches an attack on the carbon acid.

$$R_2O + R'SBH_2 \rightarrow R_2\overset{+}{O}{-}BH_2\ R'S^- \rightarrow RO{-}BH_2 + RSR'$$

The more commonly used reagent is boron tribromide[182] which operates on ethers by the same principle. The products are of course different.

While boron trichloride is employed occasionally for the same purpose, boron trifluoride generally forms stable ethereal complexes. The stability of the latter species probably originates from symbiosis among F and O ligands. And even if dissociation of F^- occurs, this extremely hard base would not initiate an S_N2 process on the essentially soft C atom.

Organoaluminum reactions

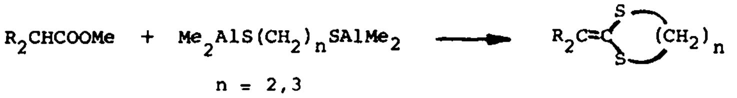
Al is a congener of B, and the two elements display similar chemical characteristics. One important difference is that B is a metalloid, where Al is a true metal. Consequently, the B center shows soft or hard properties depending heavily on its ligands; the Al center is hard in most occasions.

Analogous to the thioesterification reaction of carboxylic acids with B reagents, thioesters,[183] selenoesters,[184] and amides[185] are synthesized from methyl esters by treatment with alkylthio-, alkylseleno-, and amino-alanes, respectively. These alanes are more reactive than the boranes because they are typical hard–soft reagents (acid/base moieties with high hard/soft contrast).

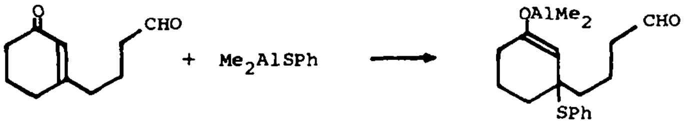
Bifunctional reagents are useful for transforming acetals into thioacetals,[186] and esters and lactones into ketene thioacetals and dithio orthoesters, respectively.[183] For all these reactions the alkoxy group of the ester becomes attached to the hard Al atom. That the carbonyl is left to combine with a softer base represents a compromise as the hard–hard interaction between Al and O (strong bond) far outweighs the loss of stability from the change of COOR to COXR.

$$RCOOMe + Me_2Al{-}XR'_n \rightarrow RCOXR'_n + Me_2AlOMe$$

$$X = S, Se, N$$

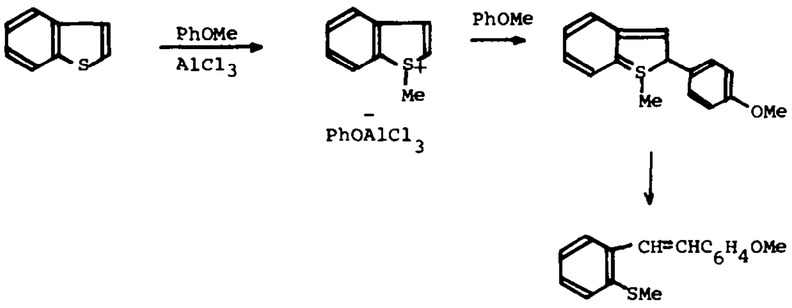


The reactions of these heteroalanes with 1,3-diene monoepoxides[187] and with enones[188] are also favorable processes whereupon the hard–soft reagent realign its components according to their properties.

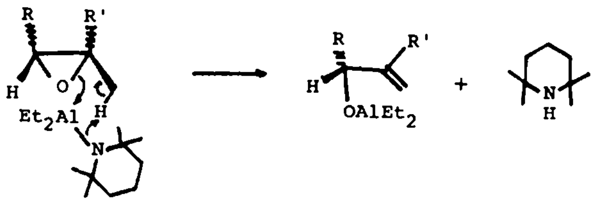


A combination of aluminum halide and a thiol is effective for cleaving esters, lactones,[189] and ethers.[190] This is one of the few methods specifically devised on the basis of HSAB considerations. The reagents provide a hard acid and a soft base to polarize the O–C bond of the substrates.

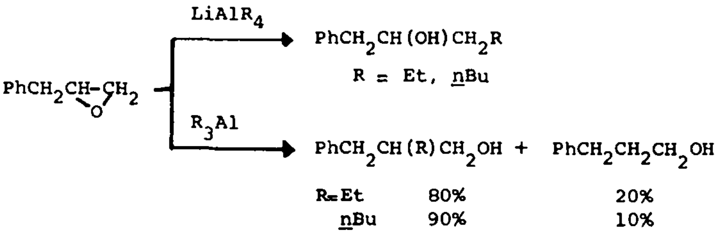
The formation of a stilbene from the reaction of benzo[*b*]thiophene with anisole and aluminum chloride follows the same principle.[191] S-Methylation transforms the heterocycle into an active electrophile that alkylates anisole.



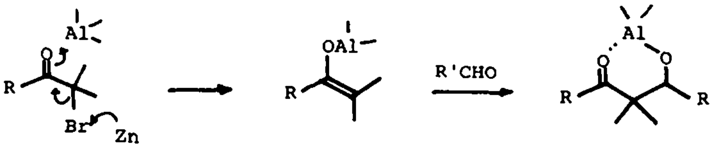
The conversion of epoxides to allyl alcohols can be accomplished by lithium dialkylamides. A more efficient reagent is N-diethylalanyl-2,2,6,6-tetramethylpiperidine.[192] A six-center transition state is adopted leading to new pairings of Al,O and H,N which are considered as better matches.



Unsymmetrical epoxides are cleaved by lithium tetraalkylaluminate and trialkylaluminum[193] in different manners. Alkyl transfer from the softer ate complexes takes place at the softer (less substituted) C atom, whereas the harder R^3Al reacts at the alternative position. It has been shown that ate complexes effect opening of epoxides with inversion of configuration, but trialkylaluminums give alcohols in which the configurations are retained.



A good method for effecting aldol condensation involves the treatment of an α-bromocarbonyl compound with Zn dust, diethylaluminum chloride and then an aldehyde.[194] Saville's condition is fulfilled and an aluminum enolate is generated with ease.



ORGANOSILICON REACTIONS

Reactivity of organosilanes is governed by the hardness of the Si acid center, and the strong bonds formed from union of Si with electronegative elements such as F and O.

The displacement sequence on Me_3SiX:[195]

$$F > RO > OCN > SCN > Cl > NC > H > Br > RS > RSe > I,$$

parallels the hardness scale of the nucleophile.

The greater affinity of Si for hard bases allows for the preparation of iodoethynyl(trimethyl)silane by methathesis.[196]

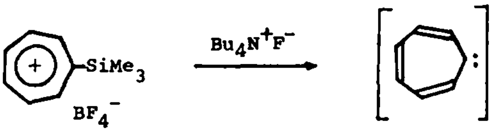
$$Me_3SiC{\equiv}CSiMe_3 + ICl \rightarrow Me_3SiC{\equiv}CI + Me_3SiCl$$

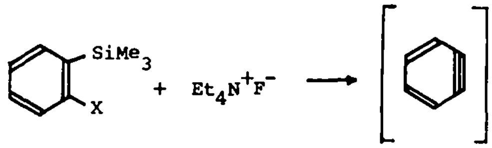
Even tertiary iodides can be prepared.[197]

From a halogen redistribution study between alkyl halides and iodotrimethylsilane, it has been found that RF > RCl > RBr (except allyl halides).[198]

$$RX + Me_3SiI \rightleftharpoons \overset{+}{RXSiMe_3}\,I^- \rightarrow RI + Me_3SiX$$

Other examples which demonstrate the powerful fluoride-seeking tendency of Si involve the generation of tropylidene[199] and benzyne[200] from silyltropenium salts and *o*-halotrimethylsilylbenzene, respectively.

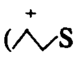




Ion cyclotron resonance studies of the interaction of ambident nucleophiles with Me_3Si^+ indicate a preference for the hard–hard mode.[201] Thus in unsaturated ethers a reaction takes place at oxygen and none at the double bonds. With alkoxy ketones, both oxygen sites participate.

Protection of alcohols by silylation is common practice. A rather selective method for silylating hydroxylic substances involves treatment with allyltrimethylsilane in the presence of a protic acid.[202]

$$ROH/RCOOH + CH_2{=}CH{-}CH_2SiMe_3 \xrightarrow{TsOH} ROSiMe_3/RCOOSiMe_3 + CH_2{=}CHCH_3$$

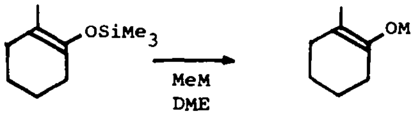
As the silylating agent is a much harder acid ($SiMe_3 \leftrightarrow$ $^+SiMe_3$) than many others, it is not surprising that thiophenol is not silylated under the same conditions.

During synthesis of gibberellins, difficulties were encountered regarding Wittig methylenation of the cyclopentanone. The hard bases present interfere with ring A functionalities and existing siloxy groups. The problem was resolved by addition of chloroethoxy(trimethyl)silane[203] which intercepts the deleterious species.

Ketones and aldehydes are converted to enoxysilanes under kinetic[204a] or thermodynamic [204b] conditions. However, C-silylation is totally absent.

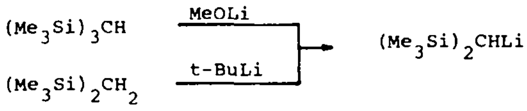
Enoxysilanes are also formed by treating α-hetero ketones with Zn/Me_3SiCl.[205] This reaction demonstrates Saville's rule in which hard–hard and soft–soft interactions are involved at two reaction termini.

The reverse process, i.e. enolate anion generation from enoxysilanes, is of synthetic significance in controlling the regiochemistry of ketone alkylation. It is generally promoted by methyllithium. The much depressed effectiveness of Grignard reagents for this cleavage[203] presumably reflects the less compatible hard–soft relationship.



M=Li 20°, 6 min
M=MgBr 85°, 24 h

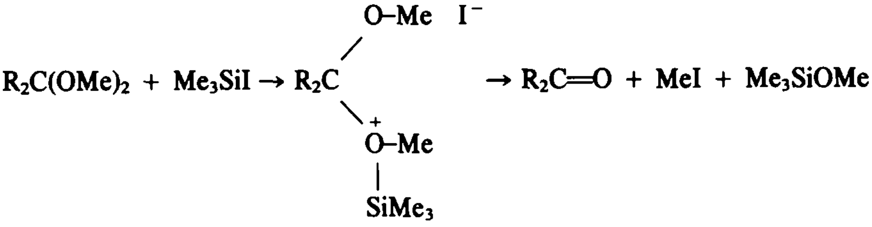
The two ways for the generation of bis(trimethylsilyl)methyllithium: using hard oxy bases to remove a silyl group from tris(trimethylsilyl)methane,[206] and abstracting a proton from bis(trimethylsilyl)methane with a hindered carbon base,[207] show the HSAB relevance.



The application of iodotrimethylsilane in organic synthesis exploits the weakness of Si–I bond and its hard–soft dissimilarity. Thus, its reaction with oxygenated organic molecules is blessed by Saville's rule.

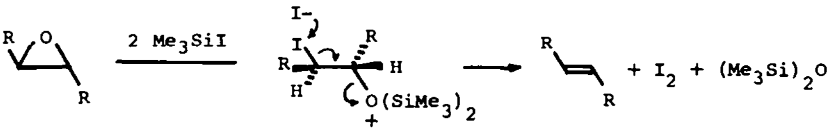
The method of ester and ether cleavage[6] by Me_3SiI has become very popular owing to mildness of conditions and selectivity. The similar cleavage of dialkylacetals to regenerate carbonyl compounds[208] cannot be extended to cleaving the thioacetal function, because the soft sulfur base is reluctant to interact with the hard Si of the reagent.

$$RCOOR' + Me_3SiI \rightarrow RCOOSiMe_3 + R'I$$

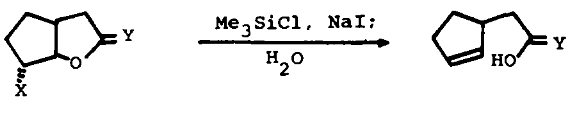


$$R_2C(OMe)_2 + Me_3SiI \rightarrow R_2C\begin{cases} O\text{–}Me \quad I^- \\ \overset{+}{O}\text{–}Me \\ \quad | \\ \quad SiMe_3 \end{cases} \rightarrow R_2C{=}O + MeI + Me_3SiOMe$$

Stereoselective deoxygenation of epoxides can be achieved by treatment with iodotrimethylsilane.[209] Interaction according to the HSAB principle gives rise to β-iodoethyl silyl ether intermediates which are prone to further attack by the reagent.

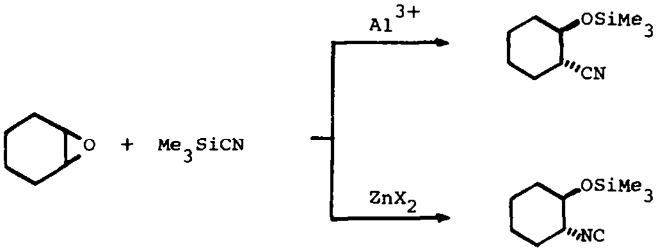


Closely related to this process in mechanistic aspects is the cleavage of β-oxy iodides, selenides, and sulfides by a combination of Me_3SiCl and sodium iodide.[210] The reagents contain a complement of hard acid and soft base which acts as electron puller and pusher (Saville's rule).



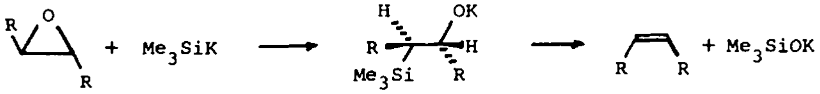
X = I, PhS, PhSe
Y = H_2, O

Epoxide opening with cyanotrimethylsilane is subjected to remarkable Lewis acid catalysis. When Al compounds are used, trimethylsilyl ethers of β-hydroxy nitriles are obtained.[211] On the other hand, the addition of zinc halides leads to the corresponding isonitriles.[212]



Coordination of the silyl group in the reagent by the epoxide leaves the CN ion free to complex with the Lewis acid. The harder Al^{3+} would bind to the N end, allowing the softer carbon to attack. A softer Zn^{2+} binds preferentially the softer carbon of CN, making available the nitrogen base to open the epoxide ring.

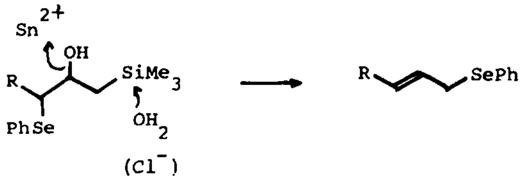
E,Z-Isomerization of olefins via epoxides can be achieved by treatment of the latter species with a triorganosilyl metal.[213] The first step involves a soft (Me_3Si^-)–soft (C^+) interaction which is followed by a hard (O^-)–hard (Me_3Si^+) counterpart during elimination of the heteroatom fragments.



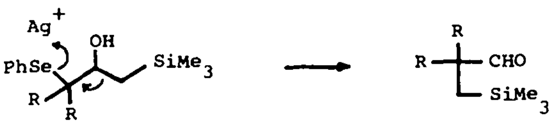
$R_2C{=}O$ + Me_3SiCH_2MgCl ⟶ $R_2C(OMgCl)CH_2SiMe_3$ ⟶ $R_2C\text{-}CH_2$

Such hard–hard interaction also underlies the success of the Peterson olefination.[214]

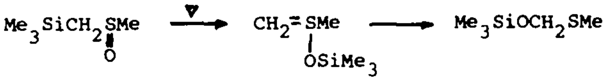
The elimination of trimethylsilanol from 2-hydroxy-3-trimethylsilylpropyl selenides is accompanied by allylic shift of the seleno group when the trifunctional substances are treated with stannous chloride.[215]



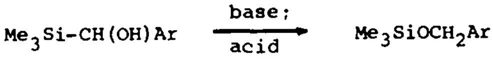
The (tertiary) selenides behave quite differently when exposed to silver ion.[215] A deselenylative rearrangement is triggered by a soft–soft interaction.



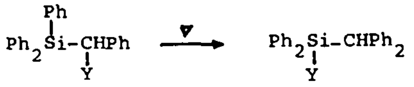
The thermal Sila-Pummerer rearrangement[216] of α-silyl sulfoxides leads to a more favorable hard-soft relationship (symbiosis) among various bonding atoms. Similar situations exist that cause Brook rearrangement[217] and related 1,2-shifts are represented by the following equations.



$$Me_3SiCH_2\underset{O}{\overset{}{S}}Me \xrightarrow{\Delta} CH_2{=}\underset{OSiMe_3}{S}Me \longrightarrow Me_3SiOCH_2SMe$$



$$Me_3Si{-}CH(OH)Ar \xrightarrow[acid]{base;} Me_3SiOCH_2Ar$$



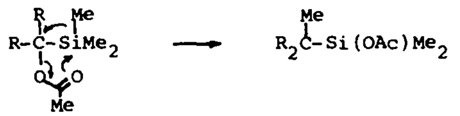
(218)

$$Ph_2\overset{Ph}{Si}{-}\underset{Y}{C}HPh \xrightarrow{\Delta} Ph_2\underset{Y}{Si}{-}CHPh_2$$

Y=F, Cl, OAc, OTs

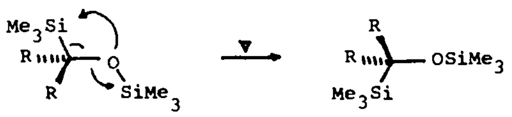
(219)

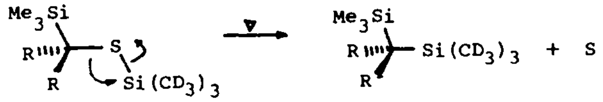
$$R_3Si{-}\underset{R''}{\overset{R'}{C}}{-}COOH \longrightarrow H{-}\underset{R''}{\overset{R'}{C}}{-}COOSiR_3$$



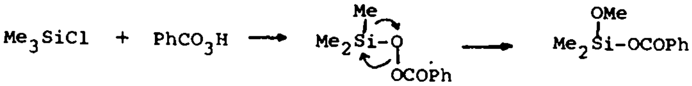
(220)

Although the dyotropic rearrangement of α-siloxyalkylsilanes proceeds readily at moderate temperatures, extrusion of S is the major reaction course for the congener.[221] The weak Si–S bond and the low compatibility in hardness between the two elements account for the decomposition.

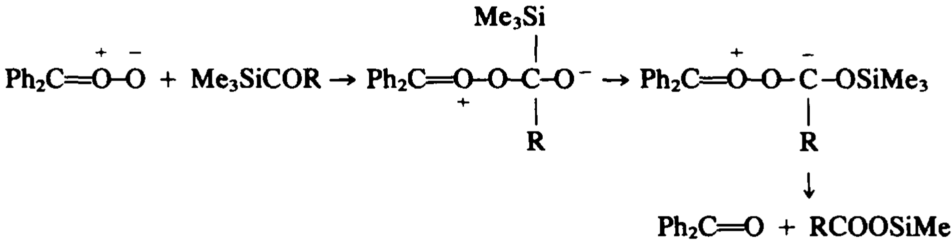




A 1,2-shift is also involved in the spontaneous rearrangement of organosilyl perbenzoates.[222] The migration of a soft alkyl group is followed (more or less synchronously) by that of a hard oxy base to the Si.



Benzophenone oxide formed by photooxygenation of diphenyldiazomethane is trapped by trimethylsilyl phenyl ketone through a hard–hard interaction. Rearrangement of the adduct via C → O *trans*-silylation furnishes trimethylsilyl benzoate.[223] The trapping efficiency increases as the hardness of the alkyl moiety of the ketone does.



$$Ph_2C{=}\overset{+}{O}{-}\overset{-}{O} + Me_3SiCOR \rightarrow Ph_2C{=}\underset{+}{O}{-}O{-}\underset{R}{\overset{Me_3Si}{C}}{-}O^- \rightarrow Ph_2C{=}\overset{+}{O}{-}O{-}\underset{R}{\overset{-}{C}}{-}OSiMe_3$$

$$\downarrow$$

$$Ph_2C{=}O + RCOOSiMe_3$$

The oxygen insertion by peracids into disilanes[224] involves formal attack by the soft Si, followed by recombination of the fragments, which is a hard–hard process.

$$\mathrm{R_3Si{-}SiR_3 + PhCOOOH \rightarrow R_3SiOSiR_3 + PhCOOH}$$

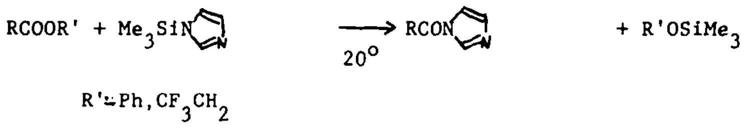
Although carbene and nitrene generation is normally very endothermic, the thermal decomposition of 1-trimethylsilyl-1-trimethylsiloxy-2-methylpropene[225] and N,O-bis(trimethylsilyl)arylhydroxylamines[226] gains some energy in an Si–O bond formation.

$$\mathrm{Me_2C{=}C(OSiMe_3)(SiMe_3)} \longrightarrow \mathrm{Me_2C{=}C\colon} + \mathrm{(Me_3Si)_2O}$$

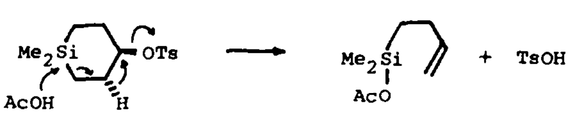
S,C-Bis(trimethylsilyl)thioacetylene is isomerized to bis(trimethylsilyl)thioketene on heating.[227] In the product both silyl substituents are bonded to a harder center.

$$\mathrm{Me_3SiC{\equiv}CSSiMe_3 \rightarrow (Me_3Si)_2C{=}C{=}S}$$

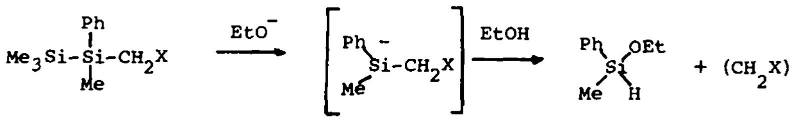
Synthesis of acylimidazoles by reaction of trimethylsilylimidazole with esters is possible only when a relatively hard alkoxy group is displaced.[228] Thioesters do not undergo similar reaction. An interesting HSAB consequence is witnessed.



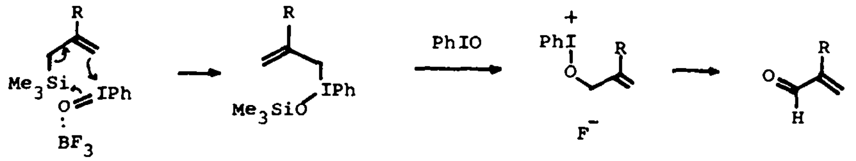
Acetolysis of dimethylsilacyclohexan-4-yl tosylate leads to a ring fragmentation.[229] This is triggered by attachment of the acetoxy group to Si.



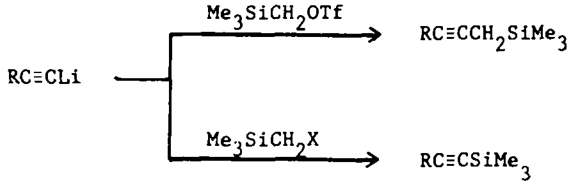
The high oxaphilicity of Si must be responsible for, at least in part, the breaking of the Si–Si bond in the following transformation.[230]



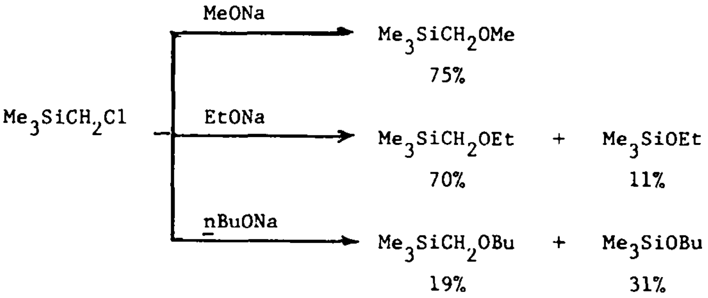
The oxidation of allylsilanes with iodosobenzene in the presence of boron trifluoride etherate[231] shows cooperative interactions at two reaction sites with a hard–soft reagent.



Halomethylsilanes lose the CH_2X group on reaction with lithium acetylides.[232] However, trimethylsilyl triflate undergoes a normal substitution by the same reagent, probably due to the hardening influence of the leaving group (symbiosis).

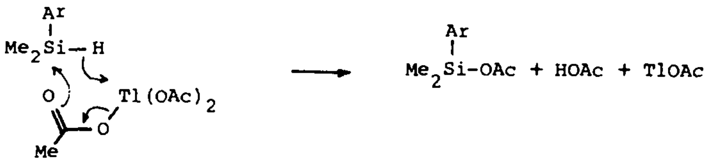


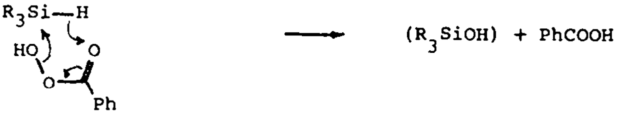
In $S_N2(C)$ reactions with primary alkoxide nucleophiles, the differences among homologous ions are inconsequential with respect to chemoselectivity. It is surprising that the reaction of alkoxides with chloromethyltrimethylsilane shows strong dependence on the length of the alkyl chain.[233] The results indicate that harder bases give more alkoxysilane products.



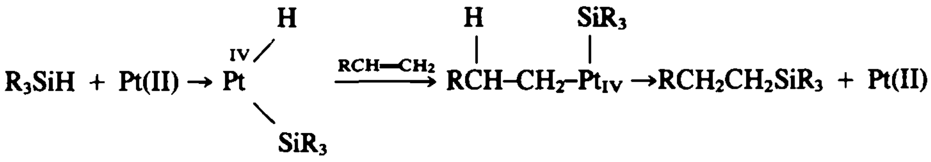
Hydride abstraction from the β-C of triorganosilyl (and -stannyl) derivatives[234] is made possible by a combination of hard base (F^-) and soft acid.

Oxidation of aryldimethylsilanes with thallium(III) acetate,[235] and the peracid oxidation of silanes[236] may involve HSAB-matched transition states as indicated.



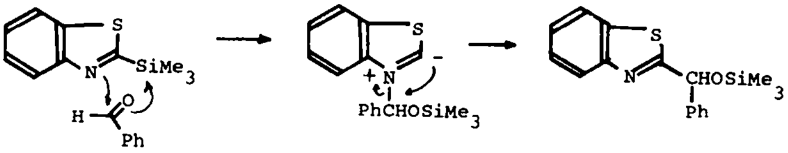


Hydrosilylation of olefins is catalysed by transition metal salts.[237] Splitting of the Si–H bond by the soft metal is crucial. An interesting aspect of this process is the conversion of a hard acid (Si^+) to a soft base (Si^-) which migrates to a soft acid center (C^+) on the metal template. The implication of such acid–base/hardness–softness inversion has been discussed.



$$R_3SiH + Pt(II) \rightarrow \overset{H}{\underset{SiR_3}{{}^{IV}Pt}} \xrightarrow{RCH=CH_2} \overset{H}{RCH}-CH_2-\overset{SiR_3}{Pt_{IV}} \rightarrow RCH_2CH_2SiR_3 + Pt(II)$$

2-Trimethylsilylbenzothiazole reacts very readily with carbonyl compounds,[238] resulting in an insertion of C–Si bond. The origin of this reactivity is the considerable hard–soft disparity between C-2 and Si atoms, the former being a rather soft base. Both the influence by the adjacent sulfur atom and a contribution from the canonical carbene structure render the carbon base soft.



1,4-Adducts are readily obtained when α,β-unsaturated carbonyl compounds are treated with silyl sulfides,[239] selenides,[240] cyanides,[241] iodides,[242] and phosphites.[243] Redistribution of bonding partners is favored on the HSAB ground.

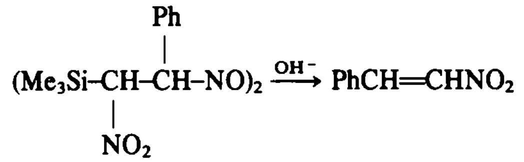
Another pertinent aspect to these condensations is the effectiveness of triphenylphosphine as initiator.[239] It acts by adding to the soft β-carbon of the enone system to generate a hard oxy base.

Conjugate addition of silanes to 1,1-bis(trihalomethyl)-2,2-dicyanoethylenes gives N-silyl products.[244]

$$(CF_3)_2C{=}C(CN)_2 + Me_3SiX \rightarrow (CF_3)_2CX{-}C(CN){=}C{=}NSiMe_3$$

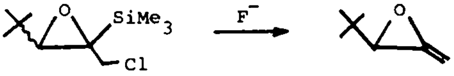
$$X = H,\ PhNH,\ MeS$$

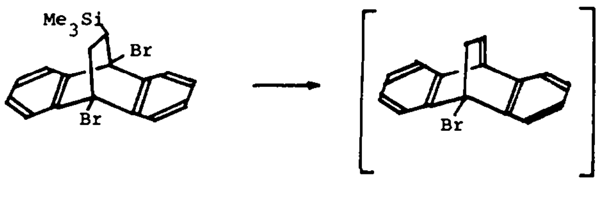
The pseudonitrite of ω-styrenyltrimethylsilane is decomposed by hydroxide ion to furnish β-nitrostyrene.[245]



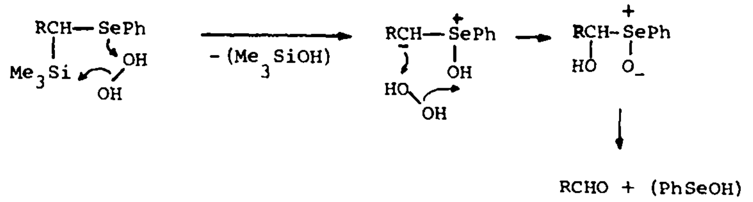
$$(Me_3Si{-}CH{-}\underset{\displaystyle NO_2}{\overset{\displaystyle Ph}{C}}H{-}NO)_2 \xrightarrow{OH^-} PhCH{=}CHNO_2$$

Beta-elimination of this type initiated by a hard base attack on silicon has been the key process for synthesis of many unusual molecules.[246,247]





The attachment of both a hard acid and a soft base to the same C atom presents a situation in which hard–soft reagents can engage in efficient bond-making and breaking processes. The rapid degradation of α-silyl selenides by hydrogen peroxide[248] is a case in point.



The silyl group hardens the base center to which it is linked. The relative inertness of thiosilanes toward alkyl halides[249] is understood. The reaction can be improved by the addition of sodium methoxide, both in terms of yields and conditions (25° vs 160–180°).[250]

$$R_3SiSR' + R''X \xrightarrow{NaOMe} R_3SiX + R'SR''$$

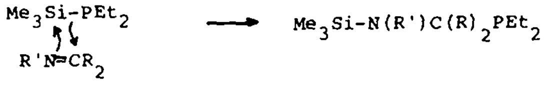
This hard base fulfills the role required by Saville's rule.

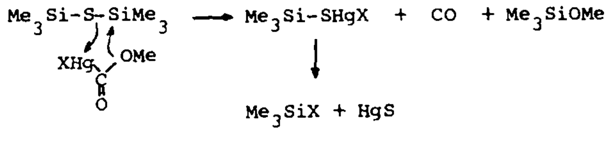
Replacement of the silyl residue of 1,2,2,3-tetramethylsilaimidazolidine by a carbonyl group has been effected by an unusual reaction with CO_2.[251]

Enamination of carbonyl compounds is easily accomplished by treatment with N,N-dialkyl-N-trimethylsilylamines.[252] This reaction, among others, bespeaks a preference of the silicon for the hardest bonding partner available.

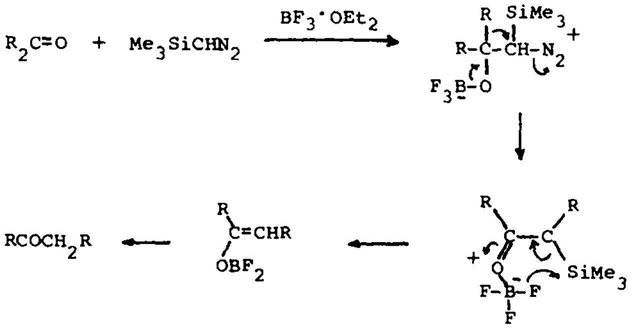
$$RCH_2COR' + 2Me_2NSiMe_3 \rightarrow RCH{=}C(R')NMe_2 + (Me_3Si)_2O + Me_2NH$$

In accordance with the HSAB principle, the following transformations proceed well.





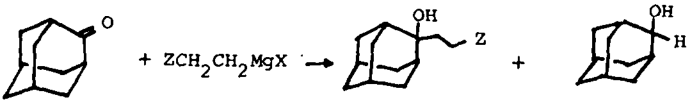
Diazoalkanes appear to be labilized by soft acids (decomposition by soft metal ions) and stabilized by an adjacent hard acid such as the carbonyl and the silyl group. Homologation of ketones by trimethylsilyldiazomethane is promoted by $BF_3{\cdot}Et_2O$.[256] This catalyzed reaction demonstrates better HSAB pairings in every step: the hardening by Si^+ in the diazomethane makes it a better nucleophile for the ketone, the softening effect of Si^- on the diazonium intermediate facilitates the migration of a soft R^-, and the presence of hard F^- is responsible to desilylation.



The role changing of the silyl group is amusing. When acting as an acid (bonded to a base), it has a hardening effect; as a base (bonded to an acid) it tends to soften the reactive center.

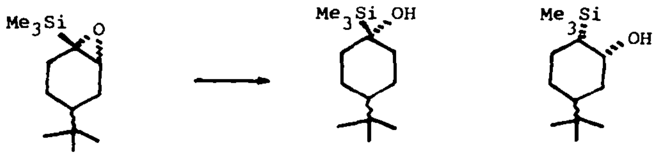
The similarity of Si to C═O in affecting the reactivity of an adjacent center has also been noted in the capability of triorganosilyl hydroperoxides to function as epoxidizing agents.[257] By hardening the neighboring O atom, both Si and C═O render the O–O bond dissymmetric in hardness term.

This effect may have contributed to the increased reduction of ketones by 2-trimethylsilylethylmagnesium halide.[258]



Z = Me$_3$Si	35%	65%
Me$_3$C	100%	0%

The epoxide mixture derived from 4-t-butyl-1-trimethylsilylcyclohexene is reduced to 1,1- and 1,2-hydroxy silanes in different ratios by LiAlH$_4$ and monochloroaluminum hydride.[259]

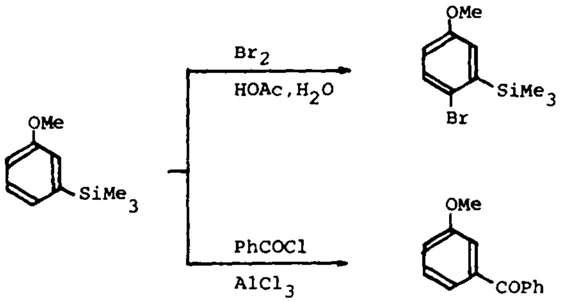


LiAlH$_4$	76%	24%
ClAlH$_2$	5%	95%

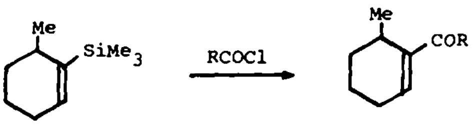
In simple HSAB terms the harder reagent effects a higher α-bond scission by attacking the harder acid center. The hardness of which is further increased by complexation with the Lewis acid. Conversely, the softer LiAlH$_4$ engages in an S$_N$2 displacement at the softer site.

The chemistry of allyl-, alkenyl-, and alkynylsilanes is dominated by the beta effect of Si. Ipso attack in the electrophilic substitution of arylsilanes with hard acids is similarly dictated by the Si.

Interestingly, bromination of *m*-trimethylsilylanisole occurs at the para position to the OMe group.[260] Formation of the σ-complex in which the softer bromine is geminal to the silyl group might be symbiotically destabilizing.



Acylation of alkenylsilanes is regioselective.[261] The Si atom renders the α-C hard, therefore this becomes the favorable reaction site for hard acids.



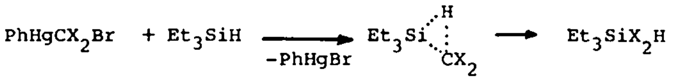
Common heteroalkenes (enol ethers, enamines, etc.) have *soft acid* substituents, and they react preferentially at the β-C atom.

The stereochemical course for substitution at Si follows the pattern that equatorial attack is favored by hard bases, axial attack by soft bases.[262] This steric dependence of $S_N2(Si)$ reaction on reagent hardness parallels that of the addition to conjugated ketones.

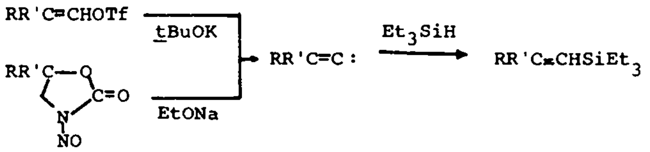
It is interesting to note that displacement of F from chiral Si[263] with soft allyllithium leads to a predominant inversion of configuration. When Li is complexed, the degree of inversion increases. It is because the allylic center undergoes hybridization change from "sp^3" to sp^2, and the anion has a pure p character.

In contrast, displacement using alkyllithium reagents occurs with much retention which is further magnified if the anion becomes more naked. The carbanion with smaller valence orbitals is harder, as a result of Li^+ removal.

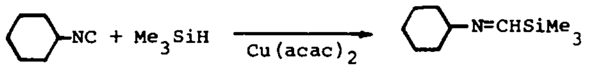
Silanes containing an Si–H bond are good hydride donors to soft acids. Their efficient insertion to carbenes and isocyanides is also due to hardness of Si which can support positive charge in the transition state.



$$PhHgCX_2Br + Et_3SiH \xrightarrow[-PhHgBr]{} Et_3Si\overset{H}{\underset{CX_2}{\vdots}} \longrightarrow Et_3SiX_2H \quad (264)$$

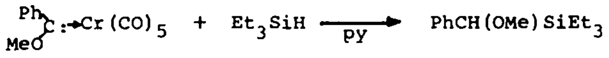


(265)



(266)

$$EtZnCH_2I + Et_3SiH \longrightarrow MeSiEt_3 \quad (267)$$



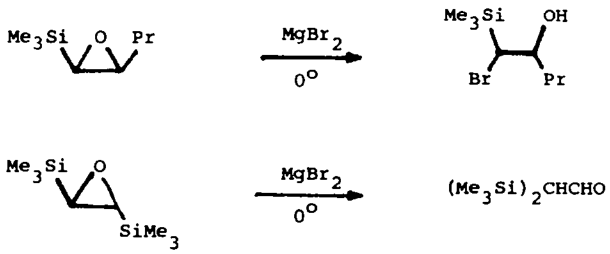
$$\overset{Ph}{\underset{MeO}{C}}{:}\!\rightarrow Cr(CO)_5 + Et_3SiH \xrightarrow[py]{} PhCH(OMe)SiEt_3 \quad (268)$$

Silylenes, like carbenes and nitrenes, are soft acids. Dimethylsilylene inserts more readily into thiosilanes than into oxysilanes,[269] because the sulfur donor is softer than the oxygen.

$$Me_3SiSR + Me_2Si{:} \rightarrow Me_3Si\text{–}Si(Me)_2\text{–}SR$$

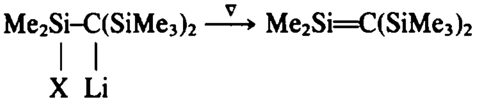
As mentioned in a previous paragraph, Si^- is a soft base. Thus the exclusive C-acylation of enolates with α-chloroalkyltrimethylsilyl ketones[270] is the result of softening effect on the carbonyl group.

The ring opening reactions of an α-silyl epoxide and an α,β-disilyl epoxide under the same conditions yield different types of products.[271] The cause of facile silyl migration is undoubtedly its softness.



Tetrakis(trimethylsilyl)plumbane has been prepared by a metathetic reaction between Pb(II) chloride and bis(trimethylsilyl)magnesium.[272] It should be noted that the bis-silyl derivative is not detectable. The softer Pb(IV) compound is formed because Si^- is a soft base.

The low rates of LiX elimination from α-lithio X-substituted silanes[273] when X^- is a fluoride or phosphate ion must be due to the great strengths of the Si–X bonds.



$$\underset{X}{Me_2Si}-\underset{Li}{C}(SiMe_3)_2 \xrightarrow{\nabla} Me_2Si{=}C(SiMe_3)_2$$

k: X = TsO > Cl > Br > I > $(PhO)_2P(O)O$ > PhS ~ F > $Ph_2P(O)O$

CHEMOSELECTIVITY OF MULTIFUNCTIONAL MOLECULES

In previous sections selective organic reactions of various groups of organometallic and -metalloid compounds have been presented in general outlines, in terms of the HSAB concept. The effectiveness of the HSAB principle in providing rationale for the observed chemoselectivity would be put to a true test when reactions of molecules containing functional groups of different hardness are compared. Ambident species are particularly intriguing substrates among these multifunctional compounds.

An ambident species is one that possesses two or more sites for participating in reactions. These species can often be represented by multiple resonance hybrids in which the reactive sites are exposed in one form or the other. By definition these ambident sites differ in hardness, therefore chemoselectivity of an ambident compound is most amenable to HSAB correlation.

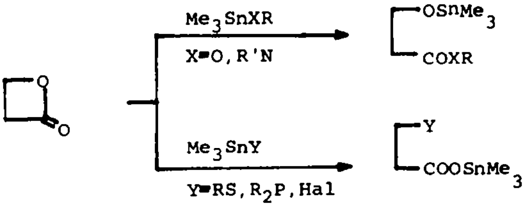
While pointing out the weakness of the HSAB tenet in not distinguishing kinetic and thermodynamic controls, and the nonuniform effect of the hardness factor inherent of neutral and ionic species, Gompper[274] developed an allopolarization concept to gauge the reactivities of ambident anions. By using the relative charge density as a polarity index correlations have been made of reaction selectivity changes as functions of polarity variations.

Electrophiles (acids, acceptors)

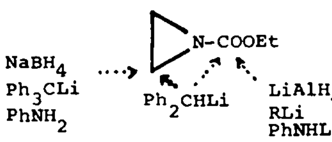
C *vs* C. β-Propiolactones exhibit ambident reactivities toward various bases. Depending on the nature of the reaction partner, the electrophilic attack may occur at the carbonyl center or the β-C atom. Thus, β-propiolactone reacts at the acyl carbon with most organolithiums and many Grignard reagents. However, softer organometallic compounds such as R_2Cd, Ph_2Zn, and $PhCH_2M$ (M = Li, MgCl)[275] and organocopper reagents[276] effect O–alkyl bond scission to give homologous propionic acids.

β-Vinyl-β-propiolactone shows exquisite regioselectivity in its reaction with nucleophiles. Very hard bases (e.g. NaOMe) are acylated, very soft nucleophiles prefer attack on the terminal vinyl carbon, and variable amounts of products arising from S_N2 displacement at C-3 result from reaction with bases of intermediary softness.[277]

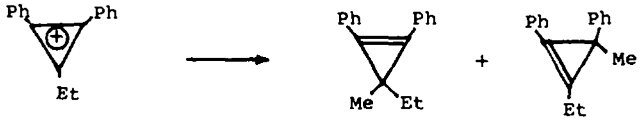
Similar manifest of site discrimination is found in the cleavage of β-propiolactone with heterostannanes.[278] A hard hetero group (OR, NR_2) is directed to bond with the acyl carbon, while soft groups (SR, Hal, PR_2) effect the formation of tin carboxylates.



Hardness of the organometallic reagents dictates the regiochemistry upon their reaction with N-carbethoxyaziridine.[279]

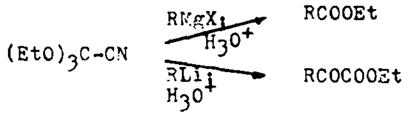


The reaction of 1,2-diphenyl-3-ethylcyclopropenium salts with organometallics appears to give more products in which C–C bond formation takes place at the ethylated carbon atom, as the reagent becomes softer.[280]

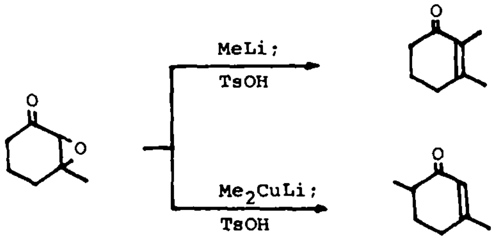


MeLi	67%	33%
MeMgI	80	20
Me_2CuLi	80	20

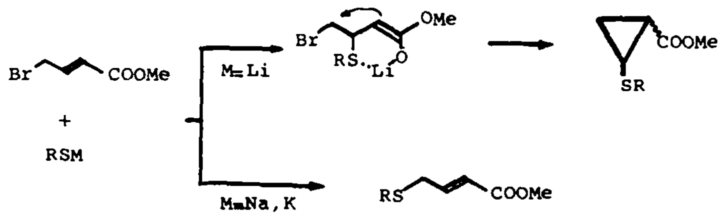
Triethoxyacetonitrile undergoes a formal S_N2 reaction with Grignard reagents, but it is attacked by organolithiums at the harder nitrile group.[281]



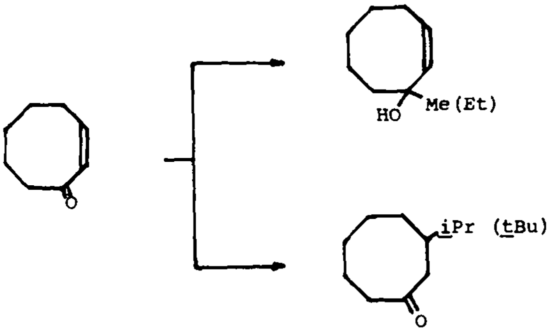
Very interesting deoxygenative methylation reactions of 3-methyl-2,3-epoxycyclohexanone have been observed.[282] Apparent S_N2 attack at C-2 by MeLi and dehydration of the *β*-ketol intermediate lead to 2,3-dimethyl-2-cyclohexenone. On the other hand, the softer lithium dimethylcuprate induces enolization and then effects an S_N2' substitution to give an isomeric ketol intermediate.



In the reaction of methyl 4-bromocrotonate with thiolate anions, the site of the initial attack is determined by the counterion of the nucleophile.[283] The hard Li^+ favors chelation with the oxygen atom of the ester group which is manifested in the Michael addition by the base prior to extrusion of the bromide ion. On the other hand, softer cations (Na^+, K^+) do not tend to restrain the thiolate ion to the vicinity of the ester function and allow the latter to effect a direct substitution at the terminal C atom.

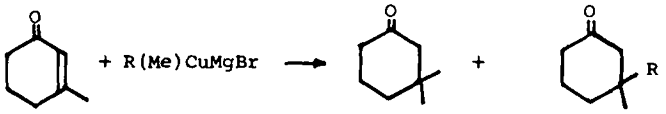


Conjugate carbonyl compounds contain acid centers of different hardness (hard carbonyl and soft *β*-C), and consequently they respond to subtle changes in hardness of the attacking nucleophiles. It is particularly interesting to note the behavior of 2-cyclooctenone toward a series of Grignard reagents.[284] The results are only readily rationalized in terms of HSAB concept. The hardness of RMgX falls according to R = Me > Et > i-Pr > t-Bu.



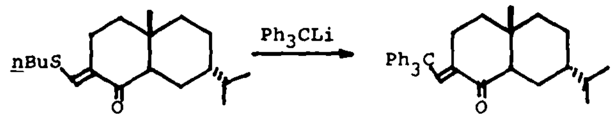
It has been claimed that α-chloro ester carbanions and Grignard reagents derived from t-butyl α-haloalkanoates are pyramidal and hard. They tend to attack the enone carbonyl. However, carbanions of α-chlorophenylacetates are planar, delocalized and soft, and they behave as Michael donors.[285]

The very soft cuprates 1,4-add to α,β-enones. The reactions involving mixed alkyl methylcuprates R(Me)CuMgBr (note: Ashby *et al.* have recently determined that the Normant reagents do not contain halide) show selective group transfer[286] according to the relative softness of R, e.g. $CH_2{=}CHCH_2CH_2CH_2 > CH_2{=}CHCH_2CH_2 > EtOCH(Me)OCH_2CH_2CH_2 > Me > CH_2{=}CHCH_2$.



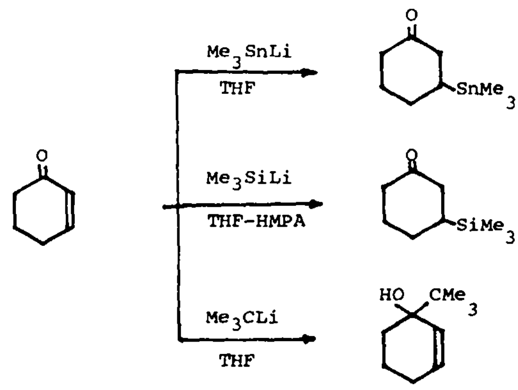
R= $CH_2{=}CH(CH_2)_3$-	6%	76%
$EtOCH(Me)O(CH_2)_3$-	18%	56%
$CH_2{=}CHCH_2$-	75%	0%

Tritylmetals are strong bases which have been used traditionally to deprotonate ketones. However, their softness (owing to charge dispersion) is manifested in the conjugate addition to 5,5-dimethyl-2-cyclohexenone[287] and 2-(butylthio)methylene-7α-isopropyl-10β-methyl-α-decalone.[288]



It has been claimed[289] that the trends of Group IVA metal anion addition to 2-cyclohexenones contrast the predictions based on HSAB principle.

However, the reported kinetic 1,2-addition of trimethylstannyllithium is on 3-butyl-2-cyclohexenone and not the unsubstituted ketone. Furthermore, there is no data for the addition of Me_3SiLi to 2-cyclohexenone in tetrahydrofuran alone. It is therefore moot to make direct comparison of reactions involving Me_3SnLi and Me_3SiLi. No violation of the HSAB principle is evident from inspection of the results outlined below.

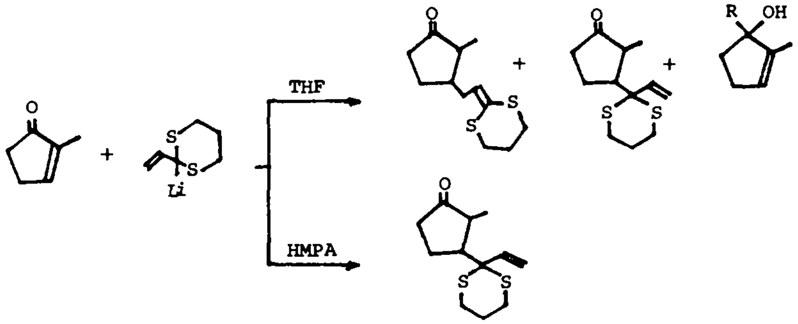


It should also be emphasized that softness of a base increases enormously when cation-solvating compounds such as HMPA are present in the reaction media.

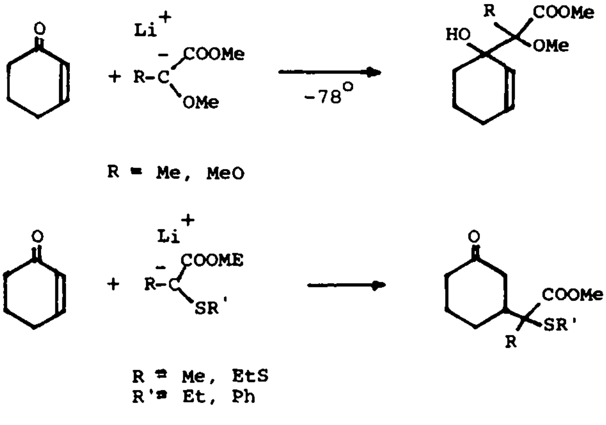
2-Lithio-1,3-dithianes are known to elicit 1,2-attack on α,β-unsaturated ketones.[39] However, the addition of HMPA induces a regiochemical change to afford conjugate adducts.[290]

Cation solvation by HMPA allows rehybridization of the carbanion center ($sp^3 \rightarrow sp^2$) so that electron overlap with the adjacent S atoms is possible. The change alters the softness of the anion as higher *p* character results and the charge is more dispersed.

Thioallyllithiums add mainly to the carbonyl group of 2-cyclopentenone in tetrahydrofuran. In the presence of one equivalent of HMPA, almost exclusive α/1,4 addition takes place.[291] Similarly, dithianylidene anions (Li^+ as counterion) add to enones in a γ/1,4 fashion. Strong favor of the α/1,4 mode can be achieved by addition of HMPA or $CuI \cdot P(OMe)_3$.[292] The α-C is softer.



The kinetic adducts of 2-cyclohexenone with α-alkoxyacetic esters are the tertiary alcohols,[293] those with α-alkylthioacetic esters are 3-substituted cyclohexanones.[294]



The results reflect the hardening and softening effects of alkoxy and thioalkoxy groups, respectively, on the metallated acetic esters.

The carbonyl group of α,β-unsaturated aldehydes is usually softer than that of α,β-enones. Consequently, allylic alcohols are the predominant products from Grignard reactions. This is especially true when harder reagents are employed.[295]

$$RCH{=}CHCHO + CH_2{=}CHMgX \rightarrow RCH{=}CHCH(OH)CH{=}CH_2$$

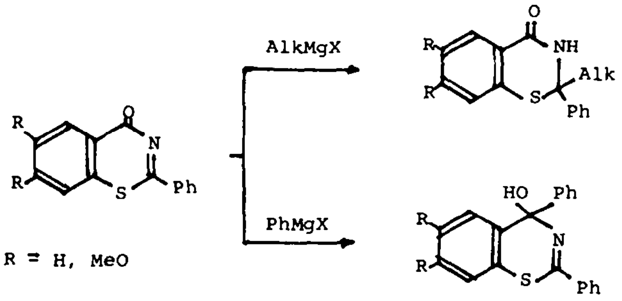
$$RCH{=}CHCHO + C_nF_{2n+1}MgX \rightarrow RCH{=}CHCH(OH)C_nF_{2n+1}$$

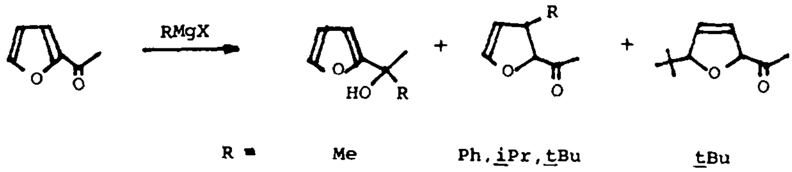
Crotonamides add Grignard reagents to give 1,4-adducts.[296] On the other hand, n-BuLi attacks crotonoylpyrrolidine at both the carbonyl group and C-3, as a result of the enhanced hardness of the Li compound.[297]

Interestingly, α,β-unsaturated thioamides react with organolithiums,[297] Grignard reagents, and lithium enolates[298] exclusively at C-3. Grignard and Gilman reagents add in 1,4- and 1,6-senses, respectively, to N,N-diethylsorbamide.[299]

Selective 1,2-addition of organoytterbium iodides to α,β-unsaturated carbonyl compounds has been noted.[299a] The results are due to the great hardness of such organometallic species as compared to Grignard reagents. Lanthanoids are very hard acids.

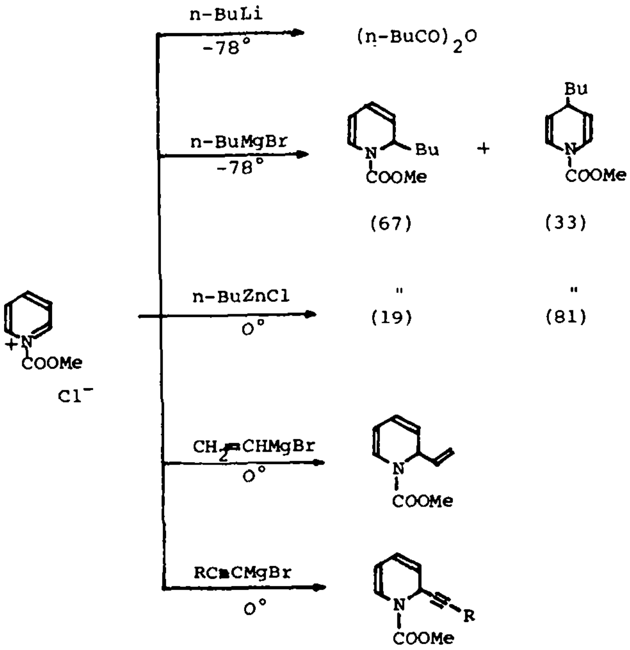
Although the hardness gap among various Grignard reagents is relatively slight, the regioselectivity pattern often changes dramatically with different reagents. The following equations are some examples of heterocyclic substrates.[300]





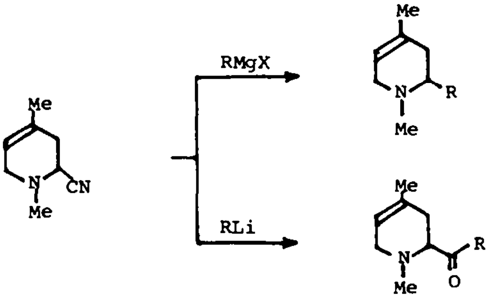
3-Cyanoquinoline has two soft acid centers, C-4 being the softer. While only 4-methylated product is obtained when it is exposed to MeMgI, a small amount of 2-phenyl-3-cyano-1,2-dihydroquinoline is also produced from the reaction with the harder phenyl reagent.[301]

N-Methoxycarbonylpyridinium chloride has three electrophilic sites of differing hardness. It reacts in a very selective manner with organometallics. The hardest reagents seek out the carbonyl function, relatively hard reagents enter the heterocycle at C-2, and soft reagents prefer reaction at C-4.[302]

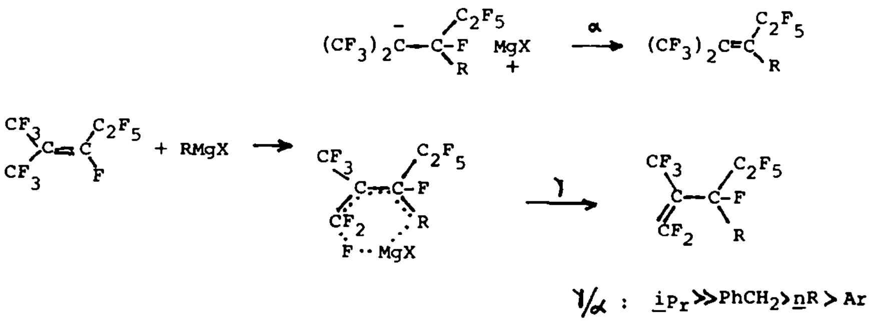


1-Acylpyridinium salts react with phenylmagnesium halides and diphenylcadmium to furnish 2-phenyl-1-acyl-1,2-dihydropyridine.[303] It is known that phenyllithium adds to the carbonyl group predominantly.

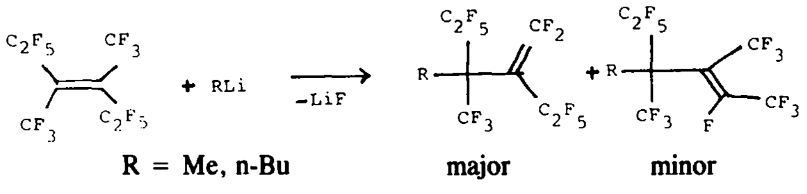
This sort of hard–soft discrimination is also evident in the reaction of 1,4-dimethyl-2-cyano-1,2,3,6-tetrahydropyridine with organometallics.[304]



Displacement of an F atom from C-3 of perfluoro-2-methyl-2-pentene with Grignard reagents[305] follows two pathways. The S_N2' route becomes more significant as the Grignard reagent is softer. A homopolar transition state is preferred.



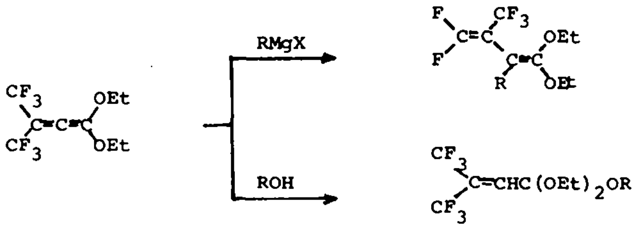
Equally interesting results have emerged from a study of alkyllithium reaction with the more symmetrical homolog, perfluoro-3,4-dimethyl-3-hexene.[306a] As F^- ex CF_3 is harder than that from the CF_2 group, its preferential coordination with the Li ion and thence acting as the leaving group is expected.



The observation that enolate anions choose to displace the allylic fluorine atom on the secondary C atom may indicate an "allo" symbiotic effect in operation.

Notably this perfluoroalkene does not react with hard bases without rearranging into an isomer which contains a harder acid center.[306b,c]

1,1-Bis(trifluoromethyl)-3,3-diethoxyallene undergoes similar S_N2' reaction. However, it is converted to ortho esters by alcohols (hard bases).[307]



α-Haloketones undergo Favorskii rearrangement[308] on exposure to metal alkoxides. However, thioalkoxide bases effect displacement of the halogen.[309]

Complex metal hydride reduction of α,β-unsaturated ketones has been examined from the HSAB viewpoint.[310] Softer hydrides (more covalent M–H bond) favor conjugate reduction, whereas hard hydrides tend to convert enones to allylic alcohols.

It is possible to modify the hardness of a given hydride reagent by replacing some of the hydride ions with hetero substituents. For example, the proportion of 1,2- vs 1,4-reduction of cyclopentenone varies from 14:86 using $LiAlH_4$ to 90:9.5 using $LiAl(OMe)_3H$.[311] *In situ* generation of such harder metal hydrides is demonstrated by the reduction of α,β-unsaturated esters to allylic alcohols with $LiAlH_4$ in the presence of ethanol.[312]

Analogous effect of the hard alkoxy group is found also in borohydride reduction. Cholestenone gives more 1,2-reduction product from reaction with $NaB(OMe)_3H$ than with sodium borohydride (98:2 vs 74:26).[313]

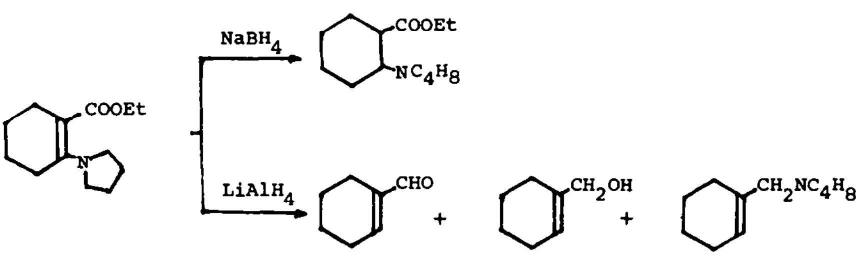
Dramatic enhancement of carbonyl reduction by borohydride is achieved by complexation of the substrates with a very hard lanthanide ion.[314] A significant role in modifying the substrate frontier orbital energy through such chelation must be played by the cations, as is recognized for the alkali metal ions.[315]

-	0%	100%
$CeCl_3$	97%	3%

In $LiAlH_4$ and $LiBH_4$ reduction of 2-cyclohexenone, the addition of cryptands reverses regioselectivity, resulting in predominant conjugate reduction.[318] Sequestration of the cation exposes the intrinsic softness of MH_4^-.

The more highly covalent B–H bond than Al–H bond means that borohydrides are softer than the corresponding aluminum hydrides. The different softness of the reagents provides an explanation for their behavior toward protic solvents (hard H^+ sources).

Another example illustrating the chemoselectivity of alumino- and borohydrides is found in the reduction of β-enamino-α,β-unsaturated esters.[319] The results are in accord with the HSAB principle.



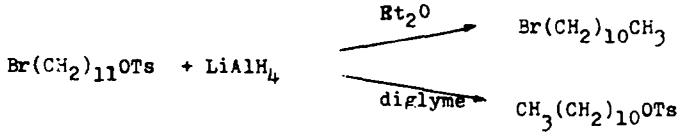
Metal hydrides in which the metal atoms do not bear a formal negative charge are harder. Thus aluminum hydride AlH_3[311] and diisobutylaluminum hydride[320] attack enones at the carbonyl group.

Organotin hydrides are softer than those based on Al, and B. The major reaction course of which with enones follows the 1,4-mode.[321]

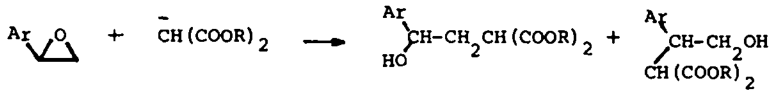
Table 3. Conjugate reduction by metal hydrides

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

A remarkably chemoselective reduction of 11-bromoundecyl tosylate by $LiAlH_4$ as controlled by solvents has been discovered.[322] Strong solvation of the Li ion in diglyme renders AlH_4^- much softer, consequently the displacement of the Br is facilitated. In more weakly solvating solvents such as diethyl ether, the Li ion may coordinate with the tosyloxy function, making it a better leaving group. Also the harder nature of the reducing nature is quite compatible with the tosylate (symbiosis).

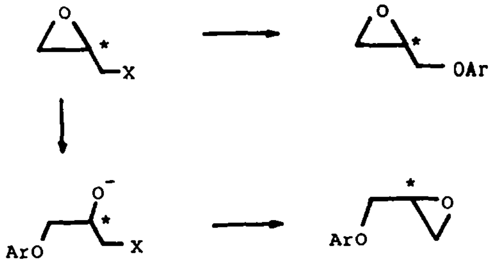


The reactivity of styrene oxides toward malonate anion varies according to the aromatic substituent.[323] Softening and hardening of the benzylic position by electron-donating and -withdrawing groups, respectively, are directly responsible for the regiochemistry.



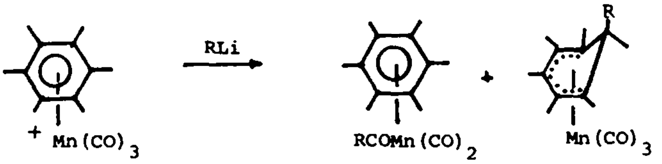
Ar = 4-$MeOC_6H_4$	0%	100%
C_6H_5	40	60
4-$O_2NC_6H_4$	100	0

Three electrophilic centers are present in glycidyl derivatives. The substitution reaction of the chiral substrates with phenolate anions has yielded results indicating that direct displacement is favored by the presence of a hard leaving group (x = OTf > OMs > Cl). For compounds with softer leaving groups the reaction proceeds to a large extent via epoxide opening.[324] Symbiosis is in operation.



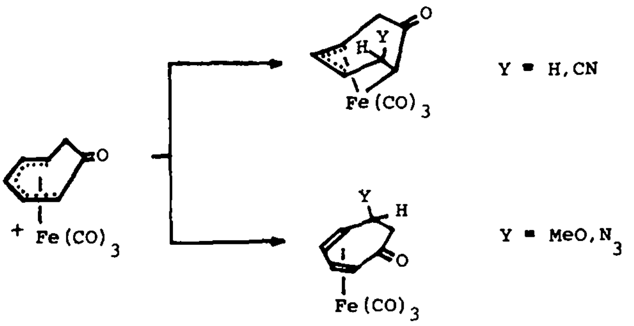
The formation of 2,2,2-trifluoroethyl phenyl sulfide from the displacement reaction of the trifluoroethyl iodide is well anticipated. On HSAB ground the distinct reaction profile which appears when sodium phenoxide is used as nucleophile[325] is not surprising either. Besides $PhOCH_2CF_3$, products arising from F substitution and elimination processes such as $PhOCF_2CH_2I$, $PhOCF{=}CHI$, $(PhO)_2C{=}CHI$ are obtained also.

The profile of organolithium reaction with hexamethylbenzenetricarbonylmanganese cation has been ascribed to steric effects.[326] However, the hard–soft discrimination trend is also apparent.

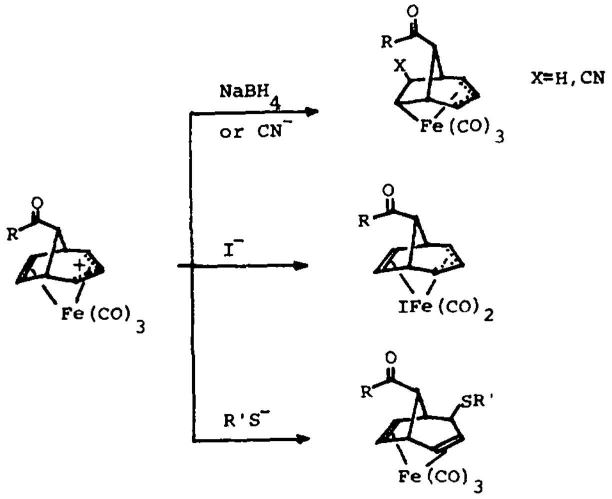


R=H(AlH_4)	8% (RCO-Me)	17%
Me	33%	trace
Ph	47%	4%

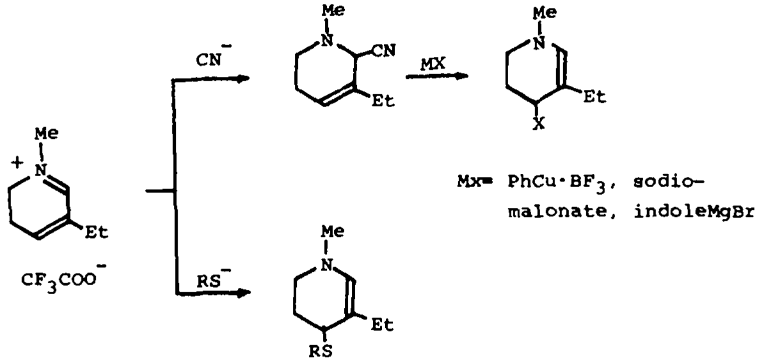
The tricarbonyliron cation complexes with protonated tropone form different types of products on reaction with nucleophiles.[327] The allylic complexes containing a σ C–Fe bond are obtained when conjugate addition by soft bases prevails. On the other hand, complexed dienones result upon neutralization by harder bases at the end of the pentadienyl system.



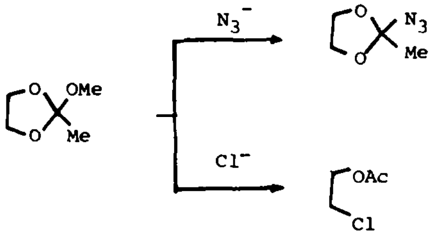
Addition of nucleophiles to η^3-[8-acyl-bicyclo(3.2.1)octa-2,6-dienyl]irontricarbonyl cation shows a high degree of regioselectivity.[328] The very soft bases attack C-2 or effect a ligand exchange, whereas somewhat harder species add onto C-6 with simultaneous formation of a C–Fe σ bond.



5,6-Dihydropyridinium salts react with thiolate ions at C-4 and with cyanide ion at C-2. The cyano group of the aminonitrile adducts is displaceable by an S_N2' process using soft bases.[329]



It is difficult to determine the relative hardness of acids and bases in the borderline region. For example, chloride and azide ions cannot be ranked with confidence. However, the following reactions indicate N_3^- is a harder base than Cl^-.[330]

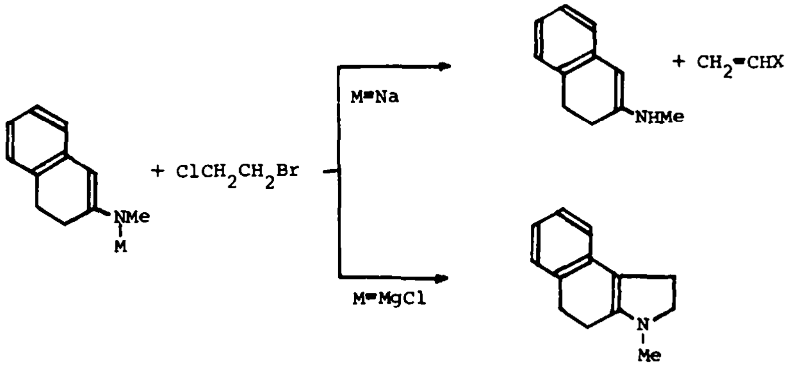


C *vs* H. Treatment of alkyl halides with bases can lead to either alkenes or substitution products, or both. Hard bases always favor elimination (by attacking the hard proton at the carbon) whereas soft donors prefer S_N2 processes.

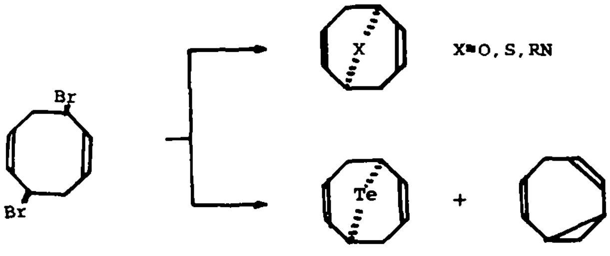
$$ClCH_2CH_2Cl \xrightarrow{RO^-} CH_2{=}CHCl \qquad ClCH_2CH_2Cl \xrightarrow{PhS^-} PhSCH_2CH_2SPh$$

Ethoxide and malonate anions have virtually identical proton affinity,[331] but significantly diverse hardness. Consequently, ethoxide promotes elimination of 2-bromopropane, while malonate effects substitution.

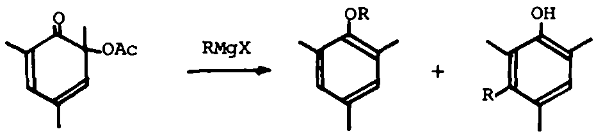
A change in the counterion sometimes has profound effect on the reaction course. Thus N-sodio-2-methylamino-3,4-dihydronaphthalene induces dehydrohalogenation of 1,2-bromochloroethane, and the softer chloromagnesium enamide effects a double displacement.[332]



Although 9-heterabicyclo[3.3.1]nona-2,6-dienes are the sole products from the double displacement of (*Z, Z*)-*cis*-3,7-dibromocycloocta-1,5-diene with oxa-, aza-, and thia-bases,[333] the very soft sodium telluride also effects a concurrent cycloelimination by attacking at the halogen.[334]

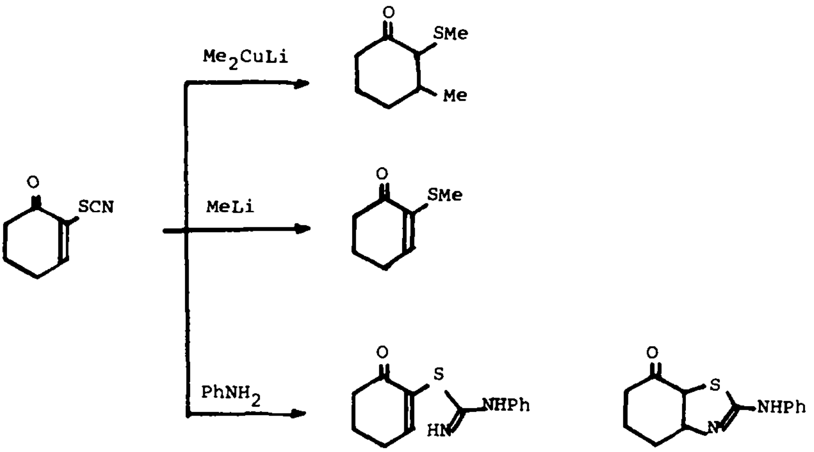


C *vs* O. A dichotomy exists for the Grignard reaction of *o*-quinol acetates.[335] O-Alkylation arises from reaction with soft Grignard reagents such as $PhCH_2MgCl$ and t-BuMgBr via cage collapse of the phenoxy–alkyl radical pair. Harder primary alkylmagnesium halides (EtMgBr, MeMgBr) favor conjugate addition at the β position. The softer dialkylmagnesiums may effect O-alkylation even if the alkyl groups are primary.[336]



C *vs* S. The nucleophilic substitution on 4-methylbenzyl thiocyanate is interesting for there are three different electrophilic sites. It has been shown that PhS^- and CN^- attack preferentially the sulfur atom, MeO^- reacts with the cyano carbon, and amines with the benzylic carbon.[337] These observations are in total harmony with the HSAB expectation.

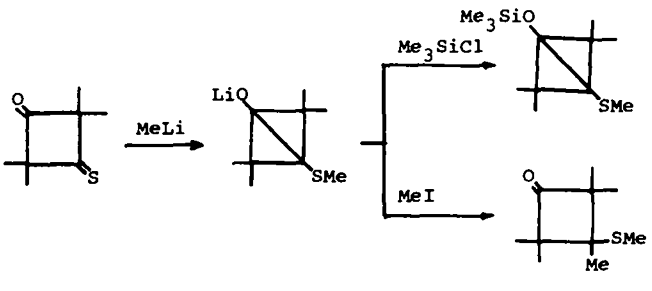
The reactivity patterns of 2-thiocyanato-2-cyclohexenone[338] are also consistent with the hardness compatibility of the reagents.



The thione group behaves in many ways differently from the carbonyl. Thus in contrast to the well-known addition reaction of organometallics to the latter function, the S atom of the thione is usually involved in bond formation with the attacking carbon base. Although it has been demonstrated that Grignard reactions with thiones proceed via free radical mechanisms, they certainly obey the HSAB principle.

Correlation of the hardness of the organometallic reagent with thiophilicity may be found in the literature. For example, MeMgI gives 55% of the adduct with thiobenzophenone, MeMgBr, 23%, but the harder MeLi attacks the carbon end of the thione group also.[339] Similarly, a dependence of the yield of thiophilic adduct on the softness of Grignard reagents from their reaction with dithiocarboxylic esters has been observed.[340]

Since most organometallic reagents are soft bases, it is not surprising that their reaction with the carbonyl function is generally overwhelmed by the thione counterpart which is present in the same molecule. The following examples are most fascinating.



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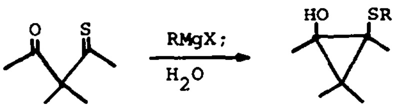
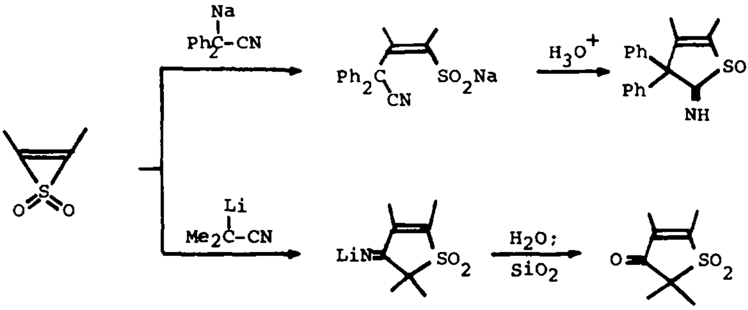


(342)

Exclusive thiophilic addition of Grignard reagents to α-thioketoesters is also known.[343]

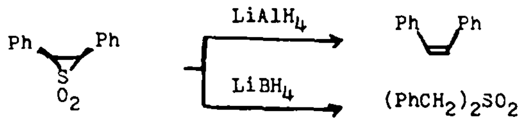
$$\mathrm{Me_3CC({=}S)COOEt} \xrightarrow[\mathrm{H_2O}]{\mathrm{RMgX;}} \mathrm{Me_3CCH(SR)COOEt}$$

In the sulfone state the S atom is a hard acid. 2,3-Dimethylthiirene dioxide reacts with slightly different α-metallated nitriles leading to different heterocyclic products.[344]

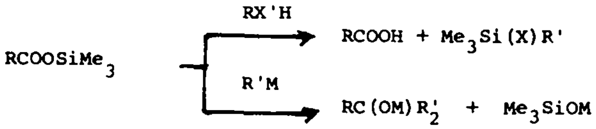


In the initial step the softer base chooses to add across the double bond, however, the harder base attacks the S.

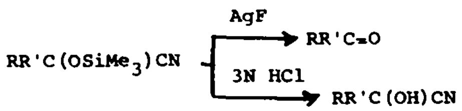
cis-1,2-Diphenylethylene episulfone is reduced to *cis*-stilbene with $LiAlH_4$, but to dibenzyl sulfone with the softer reagent, $LiBH_4$.[345]



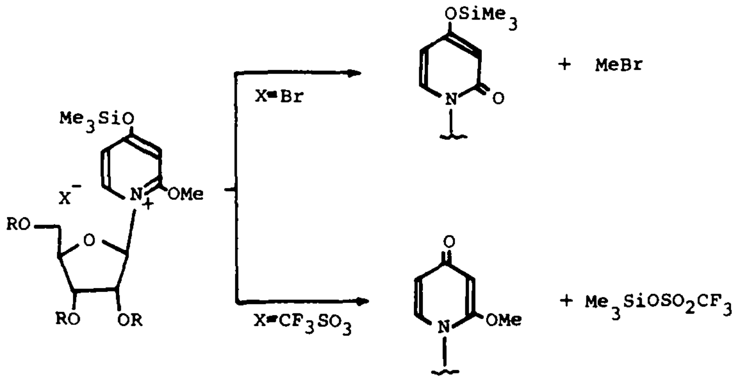
C *vs* Si. Si is a harder acid center than C, therefore the reaction of acyloxysilanes with hard bases (ROH, RO^-, RNH_2) results in the release of carboxylic acids, and the attack by organometallics on these substances gives alcohol products.[346]



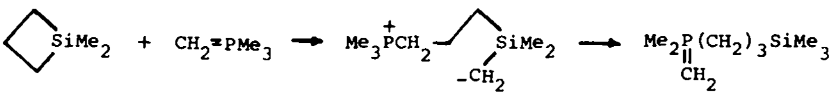
Carbonyl compounds are liberated from α-cyanohydrin silyl ethers on treatment with silver fluoride.[347] While this reagent is a perfect Saville-type catalyst, a protic acid (e.g. HCl) effects the hydrolysis of the silyl ether only, unless more drastic conditions are applied. The difference of the two reactions is the presence or absence of a soft acid to bind with the cyanide.



The Hilbert–Johnson reaction with 2-methoxy-4-trimethylsiloxypyridine can give rise to either a 2- or 4-pyridone product.[348] The determining factor is the counterion involved in the cleavage step. Dealkylation occurs with soft Br^-, and desilylation with hard species as the triflate ion.



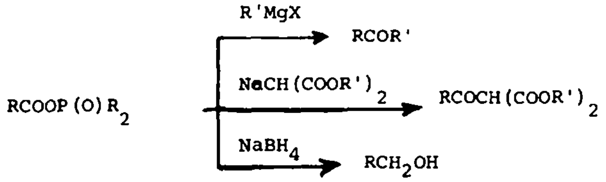
Silacyclobutanes suffer attack by hard bases at the silicon. Soft bases such as Wittig reagents can cause rupture of a cyclic C–Si bond.[349]



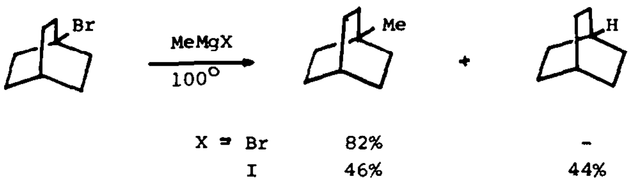
While hard bases prefer reaction at the Si center of α-iodoalkyl trimethylsilyl ethers to effect the regeneration of aldehydes, cuprate reagents tend to substitute the iodide.[350]

$$\text{RCH(I)OSiMe}_3 \xrightarrow{\text{R}'_2\text{CuLi}} \text{RR}'\text{CHOSiMe}_3$$

C vs P. The mixed anhydrides of carboxylic and phosphonic acids are very reactive toward various nucleophiles. The reaction takes place with most of these bases at the carbonyl site, except oxy bases.[351] The phosphorus center is too hard to be compatible.



C vs Hal. Although 1-bromobicyclo[2.2.2]octane is impervious to S_N2 attack for steric reasons, its reaction with methylmagnesium halides still affords homologous hydrocarbon. Reduction also occurs with the MeMgI.[352]



3-Bromopropyne surrenders the Br to the soft base sodium diphenylphosphide which is generated in liquid ammonia.[353] The significance of this reaction is that the rather facile ammonolysis involving $S_N2(C)$ is completely superceded.

$$\text{Ph}_2\text{PNa} + \text{BrCH}_2\text{C}{\equiv}\text{CH} \rightarrow \text{Ph}_2\text{PBr} + \text{NaCH}_2\text{C}{\equiv}\text{CH} \xrightarrow{\text{NH}_3} \text{Ph}_2\text{PNH}_2 + \text{MeC}{\equiv}\text{CH} + \text{NaBr}$$

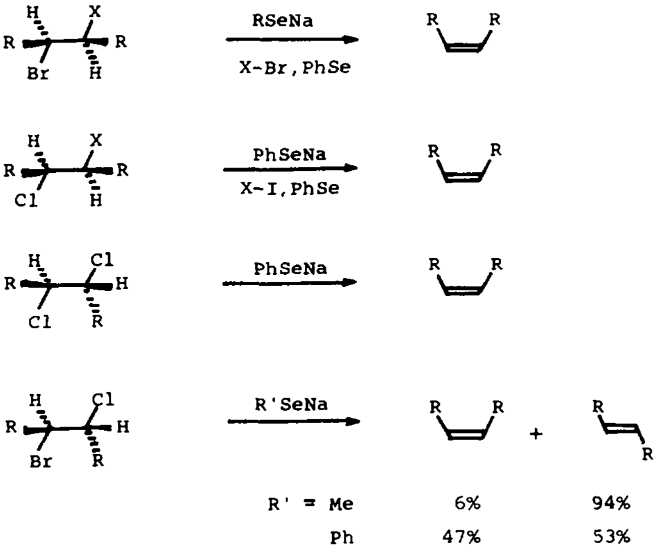
1,2-Dibromoalkanes are readily debrominated by treatment with P compounds. The reaction of 1,2-dibromoethane with lithium dicyclohexylphosphide produces ethylene.[354] However, the slightly harder diphenylphosphide anion elects to attack via an $S_N2(C)$ process.

Interestingly, the diphenylphosphide ion also promotes the debromination of 1,2-dibromoethene.[355] On the other hand, it rather attacks carbon (π system) when only harder halogen (Cl) atoms are present.[356]

$$\mathrm{BrCH{=}CHBr + Ph_2PLi \rightarrow CH{\equiv}CH}$$

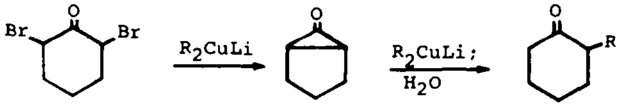
$$\mathrm{ClCH{=}CHCl + P_2PLi \rightarrow Ph_2PCH{=}CHPPh_2}$$

Vicinal dihalides and β-haloselenides react with sodium alkylselenides to give alkenes. The stereochemical courses of the reductive elimination have been delineated.[357]

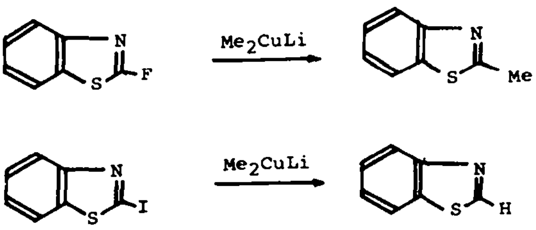


In the first two cases a concerted elimination process initiated by attack on the soft heteroatom X is indicated. For the third case, a single S_N2 displacement followed by E2 attack on the newly introduced seleno group leads to a formal syn-elimination. In the last case the softness of the nucleophile is important in determining the reaction pathway. While softer bases can still cause a concerted reaction, dual pathways are open, and the S_N2–E2 tandem becomes competitive.

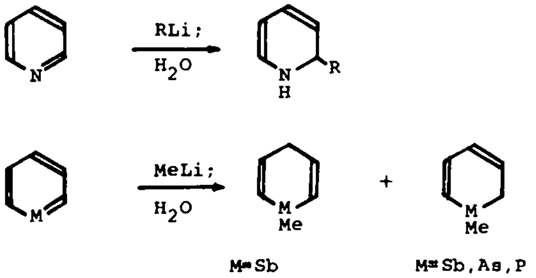
On treatment with Grignard or organolithium reagents, α-haloketones are converted to the conjugate bases of halohydrins as initial products, dehalogenation occurs when lithium dialkylcuprates are used. Most interestingly, the cuprate reaction with α,α'-dibromoketones affords cyclopropanones as the primary products.[358]



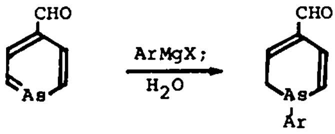
Depending on the softness of the halogen in 2-halobenzothiazoles, the reaction of these substances with lithium dimethylcuprate can take different courses (carbophilic vs halophilic).[359]



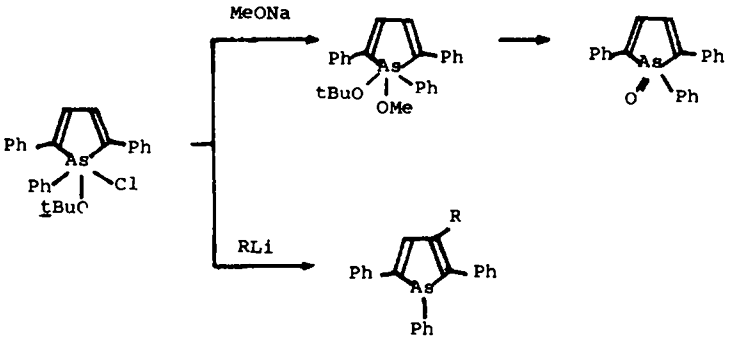
C *vs* E_{VA}. Heterabenzenes are susceptible to attack by organolithium reagents. It is noteworthy that except for pyridine, the favored locale of reaction is the heteroatom (Group V_A elements).[360]



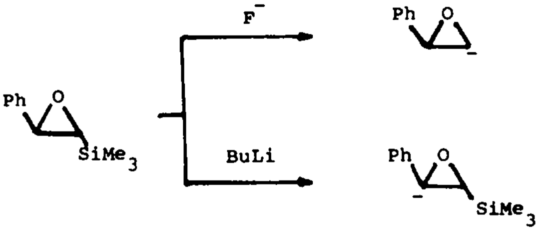
Arsabenzene-4-aldehyde behaves in the same manner, and the carbonyl group may be retained without protection.[361]



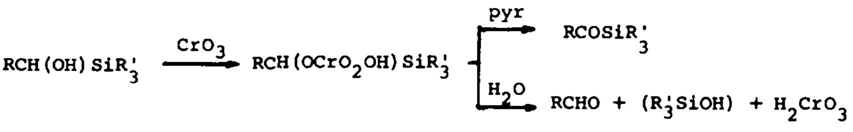
In the t-butyl hypochlorite adduct of 1,2,5-triphenylarsole two electrophilic centers are present. Consequently, attacks on C-3 and As are favored by soft and hard bases, respectively.[362]



H *vs* Si. The relative hardness of carbon bound hydrogen and Si is reflected in the formation of different carbanionic intermediates from β-trimethylsilylstyrene oxide on its reaction with fluoride ion[363a] and with butyllithium.[363b]



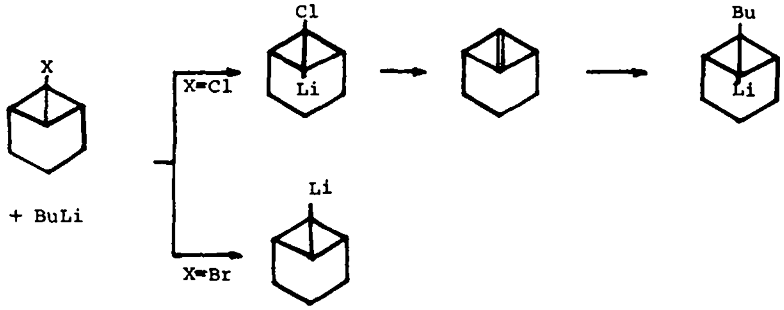
Chromic oxidation of silylcarbinols gives rise to silyl ketones. When water is present in the oxidation media, much aldehyde is produced.[364] Desilylative fragmentation of the chromate ester intermediates is readily triggered by hard bases.



Hal *vs* H, S. It has been reported that potassium n-butylthiolate attacks the sulfur center of bromomethylthiirane instead of pursuing a substitution of the Br.[365]

$$\underline{n}\text{-BuSK} + \overset{S}{CH_2\text{-}CH}\text{-}CH_2Br \longrightarrow \underline{n}\text{-BuS-}SCH_2CH{=}CH_2 + KBr$$

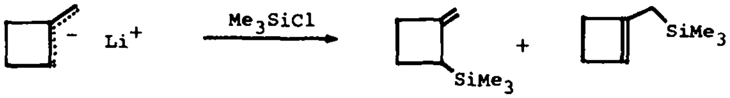
1-Halotricyclo(4.1.0.0^{2,7})heptanes may undergo either deprotonation or metal-halogen exchange with n-butyllithium,[366] depending on whether the halogen is the harder Cl or the softer Br, respectively.



Nucleophiles (bases, donors)

C *vs* C. Unsymmetrically substituted allyl carbanions are ambident. The CCl_2 terminus of *gem*-dichloroallyl anion,[367] with its inductively electron-withdrawing Cl atoms to delocalize the negative charge, is softer. Phenylated allyl carbanions,[368] and the electronically less biased 3-methyl-3-ethylallyllithium[369] show regioselectivities in alkylation reactions corresponding to the hardness of the attacking reagent. The rationalization that serves best to account for these studies, therefore, involves the HSAB concept.

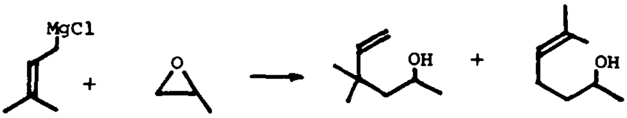
While nucleophilic attack on the silicon center of trimethylsilyl derivatives is rarely subject to steric effects, the different ratios of isomers produced by reaction of halotrimethylsilanes with cyclobutenylmethyllithium likely reflect a hard-soft selection of the two nucleophilic sites.[370a] The side-chain carbon should have a higher *p* character than the small ring carbon, and is softer.



X = Cl	50%	50%
Br	25	75
I	25	75

Methallylation of the anion[370b] gives the ring and side-chain homologs in an 85 : 15 ratio.

Isomeric allyl alcohols are produced on the reaction of prenylmagnesium halide with epoxides, depending on whether a copper salt is present.[371] Because the epoxide ring opening is essentially a soft-soft interaction, and, the magnesium-linked carbon atom is the harder base, γ attack is favored. When an allylcopper is the reactive species, the α-C spearheads the attack on account of its softness imparted by Cu.

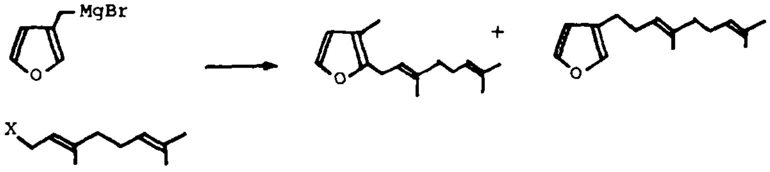


-	99%	1%
10% CuI	3%	97%

3-Furylmethylmagnesium bromide reacts with hard acids (CO_2, HCHO) at C-2,[372] because this site is connected to an O atom. Consistent with this observation sesquirosefuran is the major product when the Grignard reagent is coupled with geranyl phosphate.[373]

In the presence of cuprous iodide, the attacking nucleophile is a soft cuprate species. The reaction becomes more under frontier control, resulting in a direct union to give dendrolasin.

A more moderate changeover is observed using geranyl bromide as the alkylating agent. This is due to the fact that the softer acid is more compatible with the benzylic-type base. Addition of CuI reverses the regiochemistry to a smaller extent. It can only be speculated that a free radical pathway emerges.

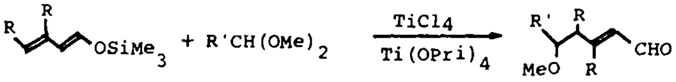


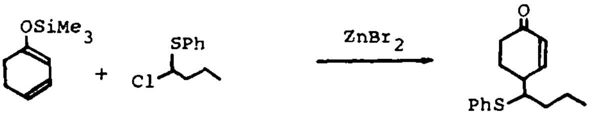
X = $(EtO)_2\overset{O}{P}O$ 70(0)% 16(79)%

Br 45(6)% 22(68)%

Yields in parentheses are from Cu-catalyzed reactions

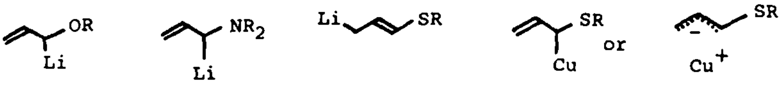
Although the kinetic electrophilic attack on dienolate anions occurs mainly at the α-C, silyl dienol ethers strongly favor γ-attack.[374] In the anionic species, the α-C is the softest center for interaction with (soft) electrophiles. On the other hand, in the Lewis acid-catalyzed alkylation of silyl ethers, the involvement of a harder acid/base pair is logical.





Heteroatom substituted allyl anions are ambident bases. The regioselectivity of their reactions with electrophiles is determined by a number of factors, among which the most important one appears to be the hardness compatibility of the acid and base, if extreme steric congestion is not encountered.

The heteroatoms impart either hardness or softness to the neighboring carbon, thereby determining the location of the C–metal bond. The following formulae should approximate the bonding situations in several of the allylmetals.



The opposite regioselectivities exhibited by oxallyl and thioallyl lithiums become apparent. The Cu reagents are somewhat different: Cu atom, using *d* orbitals for bonding, must demand the softest orbital available from the bonding partner, and a structure similar to a π-complex with an allyl group is preferred.

Nitrogen substitution hardens the α-C, therefore alkylation at the γ-position is generally observed for allylamines.[375] Exceptions are found in lithiated allyl nitrosoamines.[376]

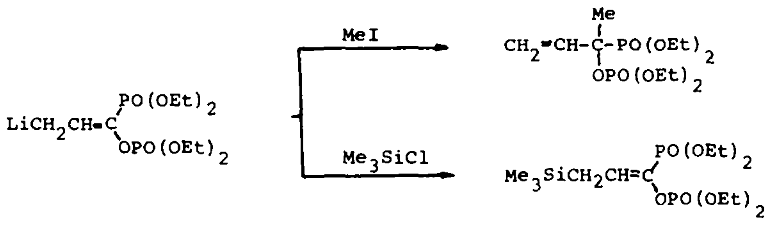
Metallated allyl ethers react with 1-iodopropane and cyclohexanone to give two regioisomers (α,γ) whose ratios are opposite.[377] The trends are in accord with the HSAB principle.

Table 4. Alkylation of $Li^+(Ch_2CHCHOR)^-$: product ratios

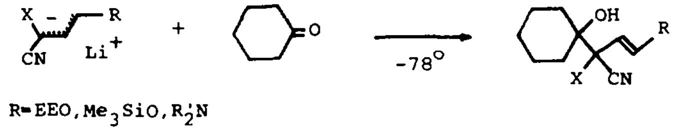
Lithiated allyl ether	Alkylating agent	
	1-Iodopropane	Cyclohexanone
R	α : γ	α : γ
Ph	37 : 63	76 : 24
Et	25 : 75	70 : 30
tBu	11 : 89	73 : 27

When the counterion is Zn^{2+}, a high degree of reaction at the α position results. The cause of this phenomenon is the softening of the anion.

Lithiated 1-phosphonato enolphosphates have a soft base center at the hetero substituted C, owing to the strong influence of the phosphonyl group. Accordingly, methylation at this center and silylation at the allylomeric position are observed.[378]



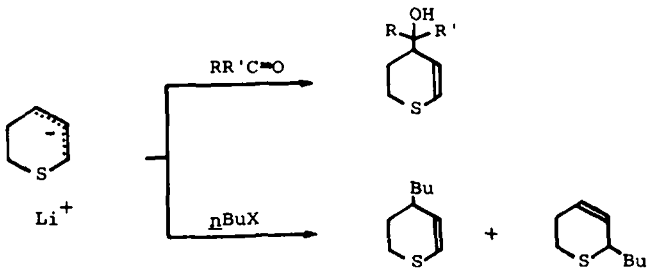
Metallated α-hetero-β,γ-unsaturated nitriles form α-adducts with carbonyl compounds at −78°. However, the reaction is reversible.[379]



The regioselectivity of thioallyl anion alkylation is opposite to that of the oxallyl counterpart. The soft influence of S atom on the ipso C is evident. The high α:γ ratio for alkylation with alkyl halides[380] decreases dramatically when HMPA is added.[380b] Under such conditions, there is a tendency for the anion to change to a more delocalized structure.

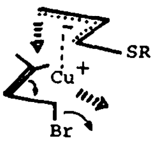
Similar ambidoselectivity has also been observed with lithiated allyl N,N-dimethyldithiocarbamates.[381]

Reagent discrimination in the alkylation of lithiodihydrothiopyran[382] reflects the HSAB trend. It should be noted that dihydropyranyllithium silylates at C-2 exclusively.[383] Here the C-2 is linked to a hard element.

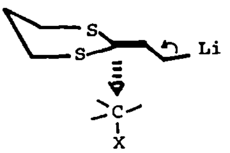


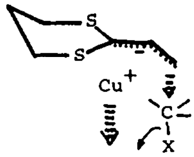
X=Cl	1.3%	68.5%
Br	6.5%	72.5%
I	29.5%	70.5%

Exclusive γ-allylation of alkylthioallylcopper with transposition (S_N2') has been reported.[384] If the base is an η^3-type complex, the transition state is sandwich-like, then a bonding process starting at the remote ends of the two allyl moieties should be more favorable. As the Cu^+ ion slides out of the interstitial cavity toward the halide and the S atom, the system would gain stability through soft–soft interaction.

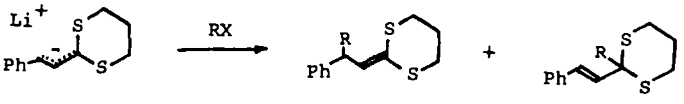


Lithio ketene thioacetals undergo alkylation at α-position with alkyl halides.[385] This regioselectivity is reverted in favor of the γ-site by the addition of cuprous salts.[386] Carbonyl substrates direct a predominant γ-attack even in the absence of Cu.[387]



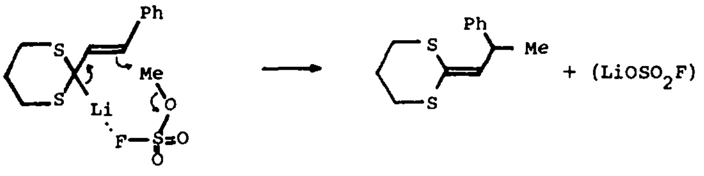


2-(*E*-α-styrenyl)-1,3-dithian-2-yllithium protonates and silylates at the α-C. The reaction at this position diminishes as the alkylating agent becomes softer,[388] i.e. $(RO)_2SO_2$ > ROTs > RCl > RBr > RI. The softening effect of the phenyl substituent is probably so great that the benzylic center surpasses the thioacetal carbon in softness.

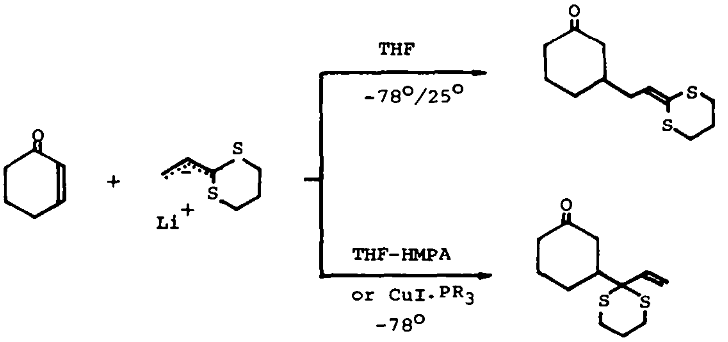


By varying the counterion, it has been noted that γ-alkylation is favored as covalency of the C–M bond is removed.[389] This finding is consistent with the HSAB principle, as allylic "anion" is experiencing a softening transition from sp^3 to p.

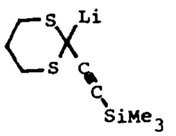
A few discrepancies have also been uncovered. While the soft sulfenyl groups enter C-2 can be explained by symbiosis, the pronounced γ-methylation (52% of total) with the very hard $MeOSO_2F$ in comparison with an almost exclusive α-methylation with dimethyl sulfate is perplexing.[389] However, the situation may be a special one owing to the possibility of the fluorine atom acting as an auxiliary base to coordinate with the metal. Model examination showed colinearity of the πC··C··O segment in an 8-membered transition state

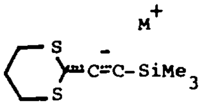


It must be emphasized that both the α- and the γ-positions of 2-vinyl-1,3-dithian-2-ylmetals are soft, their difference being a matter in degree. The addition of such species to α,β-enones readily shows their soft nature.[390]



By comparing the limiting structures of 2-trimethylsilylethynyl-1,3-dithian-2-yllithium, it is immediately evident that the one with the lithium attached to an sp^3-hybridized C-2 is a harder base. In the γ-lithiated structure, further rehybridization of the carbanionic center to gain overlap with the adjacent C is likely. This would result in having a p-type orbital to associate with the metal.





It should be stressed that in the totally ionic form the two ends of the allyl anion are identical except for the influence by the directly linked groups. Thus in the present case the α-C is softened by the S atoms, whereas the γ-C is hardened by Si, and on this basis the regiochemistry of alkylation with araldehydes is understandable.

Dependence of the hardness of the alkylating agent in the reaction of dithioketene imine anions has been revealed.[391]

$$PhCH_2N=C(SMe)_2 \xrightarrow[RX]{t\text{-}BuOK} PhCH(R)N=C(SMe)_2 + PhCH=NC(SMe)_2R$$

RX = $PhCH_2Br$	9	1
EtI	4	6

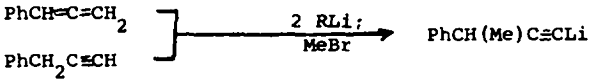
Perlithiopropyne C_3Li_4 has a softer propargylic site and a harder acetylenic site, and is very selective in derivatization.[392] It does not silylate unless three alkyl groups are incorporated first. The subsequent silylation is at the sp C.

The hardness of the propargylic position of MeC_3Li_3 is increased and may undergo silylation, although not as readily as ethylation. For $Me_2C_3Li_2$, propargylic ethylation and silylation become competitive. Addition of HMPA to the THF solution of the anions tends to increase the proportion of allene products.

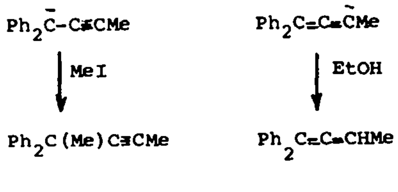
$$C_3Li_4 \xrightarrow[THF]{Et_2SO_4,\ Me_3SiCl} Et_3CC\equiv CSiMe_3 + Et_2C(SiMe_3)C\equiv CSiMe_3 + EtC(SiMe_3)C=C=C(SiMe_3)Et$$

10 1 1

A same dianion obtained by deprotonation of phenylallene[393] or 3-phenylpropyne[394] is methylated to give an acetylene. The reaction takes place at the soft base center (benzylic position).



The ambident anion derived from Na–K alloy cleavage of 1-methoxy-1,1-diphenyl-2-butyne protonates at the harder end, leading to an allene, whereas it undergoes methylation at the softer C.[395]

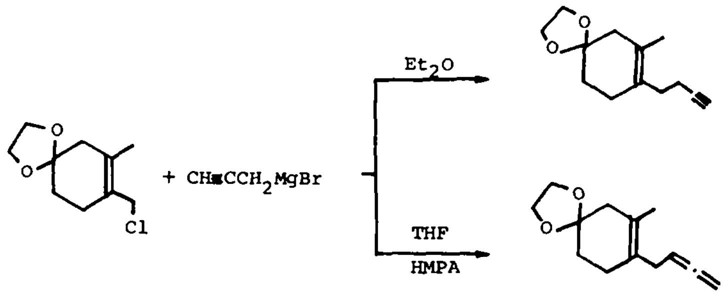


The methoxylated allene anion also appears to follow the same pattern.[396]

$$C_5H_{11}C\equiv CCH_2OMe \rightarrow C_5H_{11}\bar{C}=C=CHOMe \xrightarrow{Me_3SiCl} C_5H_{11}C(SiMe_3)=C=CHOMe$$

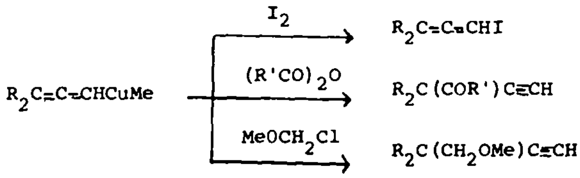
2-Ethynyl-1,3-dithian-2-yllithium undergoes selective alkylation according to the hardness of the reagent.[390b] Thus, methylation occurs at C-2 only, while silylation at the acetylenic terminus. A minor amount of silylallene product is also formed.

Coupling of propargylmagnesium bromide with an allyl chloride in ether gives the substituted acetylene.[397] The reaction in THF–HMPA leads to an allene product.[398]

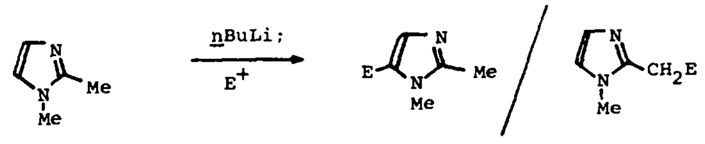


It appears that in the presence of HMPA, the Grignard reagent becomes softer and less compatible with the relatively hard acid center. Reaction takes place instead employing the harder allene anion.

Allenylcoppers iodinate with retention of the unsaturation pattern. On the other hand, propargyl derivatives are obtained when harder acids are involved.[399]



Lithiation of 1,2-dimethylimidazole may occur at the C-methyl group or at C-5. However, the nature of the product depends mainly on the hardness of the quenching electrophile.[400] Thus, harder acids (D_2O, R_3SnCl, Me_3SiCl) give rise to C-5 substituted analogs, whereas mixture of two different products results on treating the lithioimidazole with soft reagents such as dimethyl disulfide.



C *vs* N. The most well-known C,N-ambident bases are the enamines, whose reactions are outside the scope of this article. Metallated enamines/imines also partake regioselective reactions with various acids. Thus, alkyl groups may be introduced into the β position of the indole nucleus by interacting the halomagnesium salts of the indoles[401] with alkyl halides. N-Alkylation occurs by merely changing the counterion to the harder Na^+ or K^+. Treatment of alkali metal salts of 2-phenylindole with dibenzoyl peroxide furnishes only the 3-benzoyloxy derivative.[402] The reaction course is thus completely governed by the soft acceptor characteristic of the peroxide.

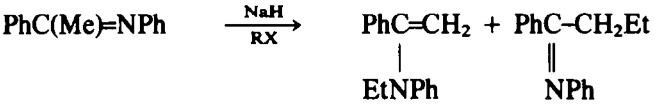
The pyrrole anion behaves similarly. Moreover, the fraction of N-allylation increases when allyl tosylate is used instead of the softer allyl bromide.[403]

Acylation of pyrrolylmagnesium halides gives rise to various amounts of C/N products, depending on the hardness of the carbonyl substrate.[404] Substituent effects on this C indicate a hardness order of O > CO > Cl ~ Me ~ SEt ~H. The softer thiocarbonyl group of diethyl thiocarbonate forces the reaction at C, which is contrary to the overwhelming N-acylation with diethyl carbonate and carbodiimides.

The halogen of the Grignard reagent also exerts certain influence on the extent of C,N-ambidoselectivity in a predictable fashion, i.e. softer halogen, more C-acylation.

The ambident 4-pyridylmethide ion can be trapped on the nitrogen with ethyl chloroformate.[405] The homolog ion forms spiro derivatives on treatment with hard organo halides. However, it is not known whether C-alkylation would occur with softer alkyl halides.

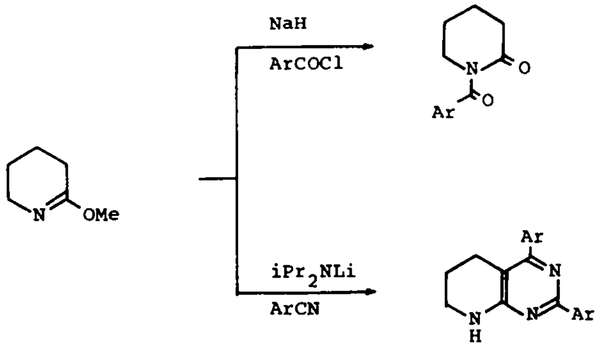
Imine anions attack alkylating agents[406] in accordance with the HSAB principle. The selectivity is very similar to that displayed by the isoelectronic enolate anions.



$$PhC(Me){=}NPh \xrightarrow[RX]{NaH} \underset{EtNPh}{PhC{=}CH_2} + \underset{NPh}{PhC{-}CH_2Et}$$

RX =	EtI	0.1	1
	Et_2SO_4	1.2	1
	$Et_3O^+BF_4^-$	22	1

Imides are formed when O-methyl-δ-valerolactim reacts with aroyl chlorides in the presence of sodium hydride. When the lithiated imine is exposed to softer aroylating agents (aryl cyanides) piperidino-fused 1,3-diazine derivatives are obtained.[407] These heterocyclic substances apparently arise from an initial C–C bond forming process.

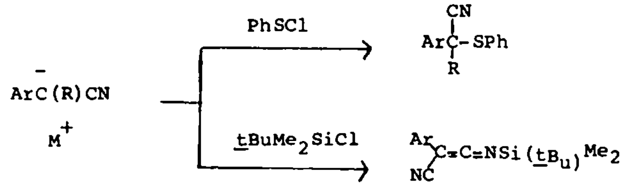


Metallated imines undergo N-silylation[408a] as expected on the basis of the HSAB principle. The aberration of silylation at the β-C when the N carries a t-Bu substituent must be due to steric reasons.[408] Remarkably, even N-t-butylimines react at N with the extremely hard trimethylsilyl triflate, in the presence of triethylamine.[409]

Reaction of phenylhydrazone and oxime dianions with one equivalent of alkyl halide takes place at the C.[410]

The ambident anion of a 1,3-bisphenylmalondiamidine undergoes either C- or N-methylation exclusively, depending on whether the counterion is Li^+ or Na^+, respectively.[411]

α-Cyano carbanions alkylate and silylate at different sites.[412] Such chemoselectivity is again observable in the reactions of arylacetonitrile anions.[413]



Metal cyanides are ambident bases. Displacement of alkyl halides with alkali cyanides represents the simplest way to prepare alkyl cyanides. Isonitrile formation is promoted by using Ag ion to polarize the C–halogen bond thereby rendering the electrophilic C harder, and receptive to attack by the N end of CN^-.

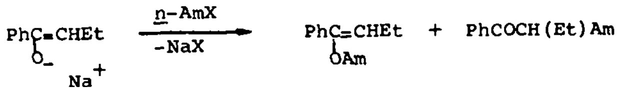
Both trityl chloride and trityl perchlorate furnish the same product ratio from their reaction with tetraphenylarsonium cyanide, indicating the same electrophilic species that undergoes reaction.[414] The preponderance of nitrile over isonitrile (9:1) must mean that trityl cation is soft.

The reaction of acylating agents with the cyanide ion yields acyl isocyanides.[415]

C vs O. Because of the synthetic importance of reactions involving enolization of carbonyl substances, the C,O-ambident behavior of enolates has been encountered most frequently.

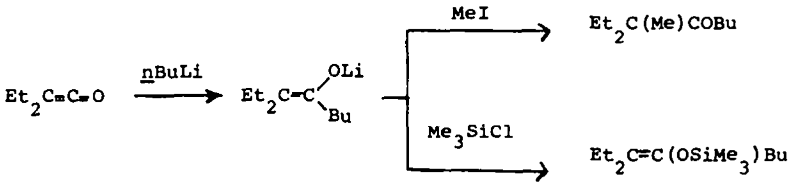
O-Alkylation of enolates is typified by the reaction with halosilanes.[203,204] Alkyl halides usually react with the softer carbon base of an enolate ion. For example, 4-t-butylcyclohexanone lithium enolate reacts with ethyl iodide to yield solely the 2-Et homolog.[416] However, up to 17% enol ether is produced when triethyloxonium fluoroborate is the alkylating agent.

Acetophenone anion is alkylated at O and C in the following ratios: 0.1, 3.5 and 4.9, depending on whether the reagent is EtI, Me_2SO_4, or $Et_3O^+BF_4^-$, respectively.[417] Amylation of butyrophenone enolate in dimethyl sulfoxide with reference to halide variation has been studied.[418] The lesser amount of enol ether corresponds to a softer halide.



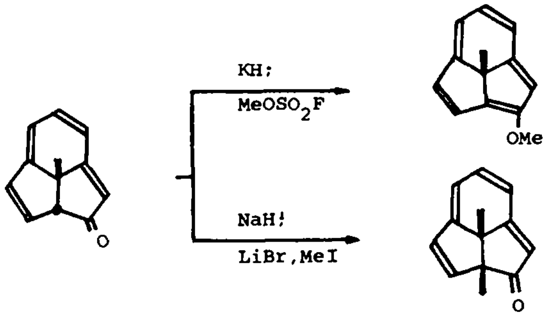
X		
Cl	1.2	1
Br	0.64	1
I	0.23	1

The enolate generated by the addition of n-butyllithium to diethylketene reacts with iodomethane and chlorotrimethylsilane to give a ketone and an enol ether, respectively.[419]

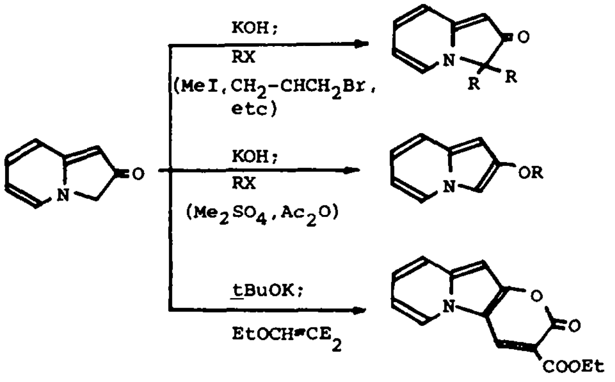


The "naked" enolate of phenylacetone generated from its silyl enol ether undergoes exclusive C- or O-attack on iodomethane or acetic anhydride.[420] Again, a clear discrimination according to hardness diversity is manifested.

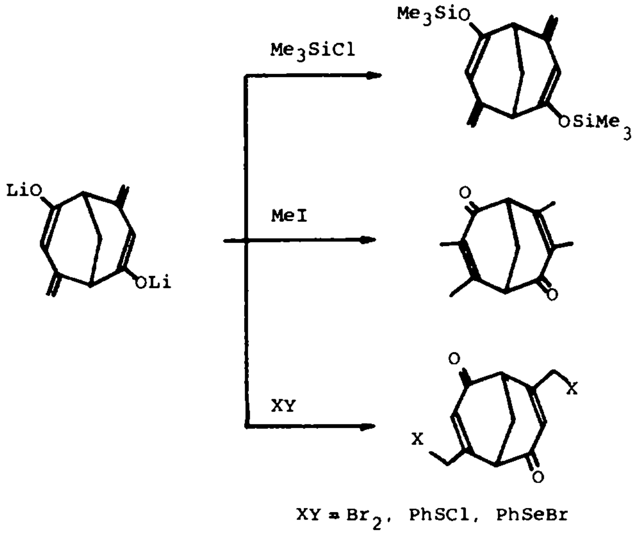
Methylation of a phenol "hückelog" can be effected on either C or O as desired, by judicious choice of conditions. Exclusive O-silylation is also observed.[421]



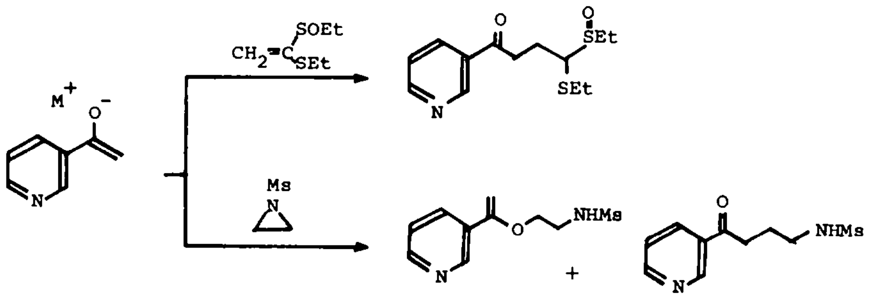
2,3-Dihydroindolizin-2-one derivatives show ambidoselectivity in their reactions with electrophiles in accordance with the HSAB prediction.[422]



Regioselective reactions at the three different sites of the bisdienolate of bicyclo[3.3.1]nona-3,7-diene-2,6-dione have been observed.[423] The results correlate well with the HSAB dictum.



The enolate ion of 3-acetylpyridine accommodates the electrophile in the way it reacts.[424] It is interesting to learn that N-mesylaziridine shows a borderline hardness.



Anthrone displays considerable chemoselectivity in its alkylation, producing 9-alkoxyanthracenes with alkyl sulfonates, and 10-alkyl-/10,10-dialkylanthrones with alkyl halides.[425] Although benzoins form enediol derivatives readily (e.g. with chloral), exclusive C-alkylation with alkyl halides[426] proceeds as expected.

An interesting symbiosis occurs that determines the C/O-ambidoselectivity in the acylation of lithium 4-methoxy-1,3-butadien-2-oxide. Acylating agents with oxy leaving groups but not others, attack the anion to form enol derivatives.[427]

$$CH_2{=}C(OLi)CH{=}CHOMe + RCOX \rightarrow CH_2{=}C(OCOR)CH{=}CHOMe + RCOCH_2COCH{=}CHOMe$$

X = Cl, imidazolyl	–	+
$(EtO)_2P(O)O$, i-BuOCOO	+	–

Of special interest is the reaction of benzophenone dianion $Ph_2\bar{C}{-}O^-$) with methylating agents.[428] Despite the unusual arrangement of two negative charges on adjacent atoms, no exception to the general rule of leaving group dependence of reaction site is noted. The C/O ratios for the few methylating agents are: 7.7 (MeI), 4.2 (MeBr), 2.7 (Me_2SO_4), and 0 (MeOTs).

Solvent effects play an important role in the alkylation of ketones. In protic solvents C-alkylation of 9-benzoylfluorene[429] predominates. On the other hand, O-alkylation becomes significant in HMPA, presumably owing to strong solvation of the cations thus exposing the hard oxynucleophile.

This phenomenon is also discernible during acylation of ketone enolates. The results of acylation of the bromomagnesium salt which is generated by conjugate addition of Grignard reagents to benzalacetone[430] indicate a great enhancement of the O-acylation in the presence of HMPA.

$$\mathrm{Ph_2CHCH{=}C(Me)OMgBr} \rightarrow \mathrm{Ph_2CHCH{=}C(Me)OCOR} + \mathrm{Ph_2CHCH(COMe)COR}$$

α-Mercurioketones and solvent-separated metal enolate ion pairs undergo kinetic acylation mainly at the hard O site. The amount of C-acylation is increased when the metal enolate exists as contact ion pair in which the hardness of the O atom is diminished. The HSAB pattern is also conformed on reagent variation. Thus when the metal cation and solvent are kept constant, more C-acetylation takes place with acetyl halides than with acetic anhydride or ketone.[431]

Phenols are permanently enolized cyclohexadienones. Claisen *et al.*[432] have shown that metal phenoxides react with active alkyl halides (e.g. allyl and benzyl bromides) in nonpolar solvents to afford *o*-alkylphenols. Cyclohexadienones may be prepared in this manner starting from 2,6-disubstituted phenols.[433] It has been suggested[434] that only C-alkylation occurs under completely heterogeneous conditions and only O-alkylation in homogeneous media.

Correlation of reaction sites of phenolates with electrophiles is as valid as in ketone enolates. Thus, only methyl ethers are produced from the reaction of sodium 2,6-dimethylphenoxide with methyl brosylate,[435] and sodium 2-naphthoxide with dimethyl sulfate.[436] Analysis of aroylation of 2-naphthoxides in hexane[437] indicates that (i) softer (more covalent) lithium enolate gives higher C/O ratios than the sodium enolate, and (ii) more C-acylation occurs with aroyl chlorides of softer nature.

The thallium(I) salt of 2-hydroxythiophene is methylated mainly at C-3 with iodomethane,[438] as a consequence of the softness of the nucleophile.

Considerable attention has been paid to the elucidation of the ambidoselectivity of β-dicarbonyl compounds. The HSAB principle proves very useful in rationalizing the massive results.

As expected, the nature of the electrophile is of crucial importance in governing the ambidoselectivity in alkylation and acylation of such bases. For example, O-methylation of ethyl sodioacetoacetate in dimethyl sulfoxide increases progressively with harder methyl halide: 6% (MeI), 26% (MeBr), 43% (MeCl).[439] A similar trend also emerges by changing only the hardness of the acid center for O-alkylation: EtBr 26%, n-PrBr 47%, i-PrBr 62%.

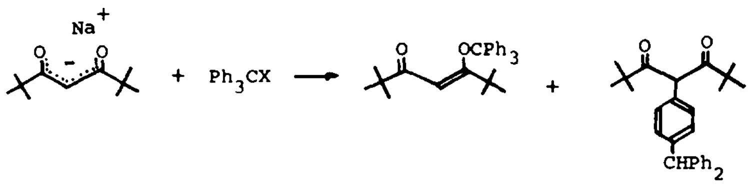
Rate variation according to the leaving group of the alkylating agent, k_c/k_o, is in the order I > Br > Cl > OTs, and it is very large for MeX, but negligible for s-BuX.[440] As changing from tosylate to iodide, k_c increases by 10^3, whereas k_o changes by a factor of 10 only. These results demonstrate the sensitivity of soft–soft interactions to subtle changes in reagent softness as contrasted to the hard–hard interactions which are dominated by electrostatic forces.

Alkylation of sodioacetoacetates with chloromethyl methyl sulfide leads to substitution at C.[441] It should be compared with the exclusive O-alkylation of β-dicarbonyl compounds with chloromethyl alkyl ethers.[442] The electrophilic ethers are very hard, and they behave in a manner similar to that of acyl halides.[443] Sodioacetoacetate ion also reacts with $\mathrm{Et_3O^+BF_4^-}$ to provide an enol ether,[444] but C-alkylated products result with $\mathrm{R_3S^+BF_4^-}$.[445]

Acylation is charge-controlled. Even so, variation of the hardness of the acylating agents is often reflected in a corresponding shift in ambidoselectivity. There is an increasing tendency for 2-carbethoxycycloalkanones toward O-acylation along the series,[446] $\mathrm{ClCOOEt} < \mathrm{ClCOCH_2Cl} < \mathrm{ClCOMe} < \mathrm{O_3ClOCOMe}$.

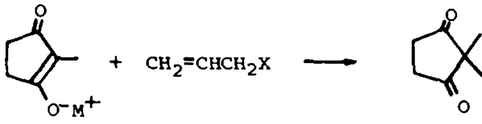
Phosphorylation of β-keto esters gives rise to enolphosphates exclusively.[447] Sulfonylation of aroylmalonates also leads to the enol derivatives.[448] Phosphoryl and sulfonyl halides are harder than acyl halides.

Alkylation of acetylacetone enolates falls into the same pattern as acetoacetates.[449] Interestingly, sodiodipivaloylmethane reacts with trityl halides to give different ratios of C- and O-alkyl products by using either the chloride or the bromide.[450] The C-alkylated product is abnormal because steric hindrance around the nonaromatic carbon of the trityl group is too great for C–C bond formation.



X = Cl	64-88%	5-25%
Br	47-72%	25-48%

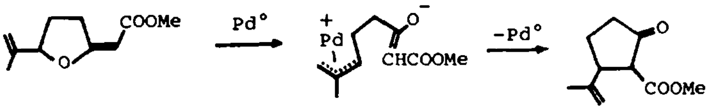
1,3-Cyclopentanedione is notorious for yielding high ratios of O-alkylation products.[451] Recently it has been found that practically exclusive C-allylation may be achieved by a Pd(0)-catalyzed reaction using allyl acetate as the electrophile.[452]



X = Br	30%	
OAc	94%	(Pd° -catalyzed)

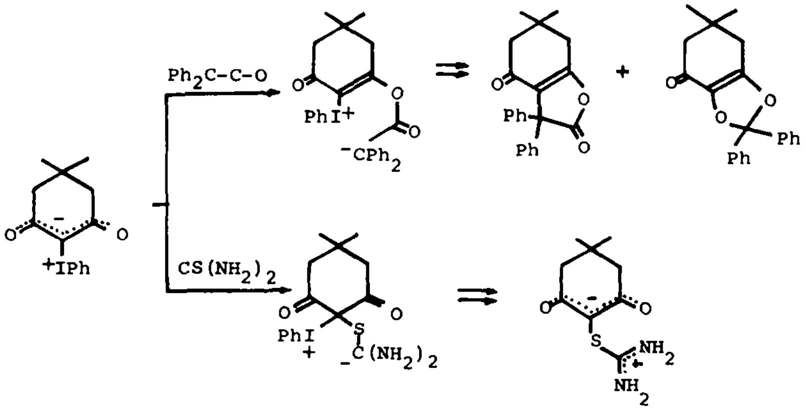
The electrophile is in fact an η^3-allylpalladium species which is substantially softer than allyl bromide because the positive charge is located at the metal. The enolate ion interacts with the π orbital of the allyl group during the bond formation process.

The Pd(0)-catalyzed rearrangement of β-allyloxyacrylic esters[453] to β-keto esters is another example in which a soft acid directs the attack by a soft base.



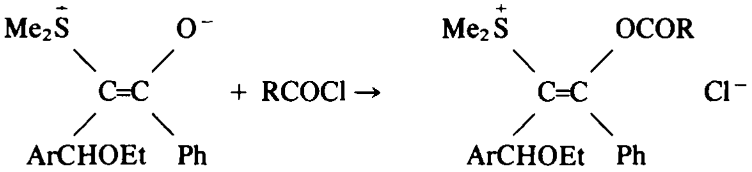
In the reaction of nitronates with 1-oxy-2-propenes, O-allylation is totally suppressed by using $(Ph_3P)_4Pd$ as catalyst.[454]

2-Phenyliodonium dimedone ylide adds to diphenyldiketene using the O site,[455] it attacks thiourea from the C base.[456] Undoubtedly the divergent reaction pathways are determined by HSAB factors.



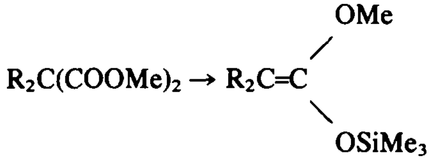
α-Alkoxy-β-oxosulfone anions form sulfonyl reductone derivatives on reaction with chloromethyl methyl ether or aroyl chlorides.[442b] It should be noted that C-alkylation of such bases with alkyl halides are known. Stabilized ylides are acylated at oxygen[457] in accordance with the HSAB principle:

$$Ph_3P{=}CHCOR + AcCl \rightarrow Ph_3\overset{+}{P}CH{=}C(OAc)R\ Cl^-$$



The α-carbanions of esters undergo C-alkylation regardless of the hardness of the alkylating agent. This is due to the great difference in thermodynamic stabilities between C- and O-alkylated substances. In light of this fact, it is significant to note that both C-silylation and enol silylation occur.[458] The O,α-dianions of carboxylic acids furnish bistrimethylsilyl enol ethers.[459]

Disubstituted malonic esters are dealkoxycarbonylated under the modified acyloin condensation conditions (Na–Me$_3$SiCl). The intermediary ester enolates undergo silylation at the O atom.

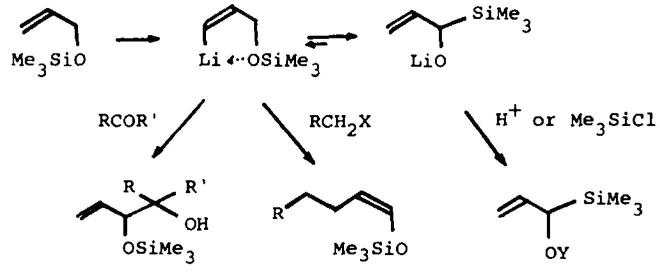


$$R_2C(COOMe)_2 \rightarrow R_2C{=}C(OMe)(OSiMe_3)$$

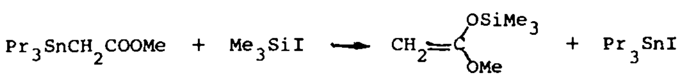
Trimethylsilylation of t-butyl lithio(α-trimethylsilyl)acetate occurs predominantly at the C center.[460] The observed reaction is favored by symbiosis.

For α-amination of the anion of methyl 9-fluorenecarboxylate with 2,4-dinitrophenoxylamine[461] the reaction proceeds normally via a soft–soft interaction.

Deprotonated allyl silyl ether exists in two equilibrated forms: silylallyloxide and O-silylallyllithium. When it is exposed to very hard acids (H$^+$, Me$_3$SiCl), the silylallyl oxide form reacts.[462] O-Silylallyllithium becomes the reactive species toward alkylating agents, and depending on the hardness of the latter, α- (with carbonyl compounds[463]) or γ-adducts (with alkyl halides[464]) may be obtained.

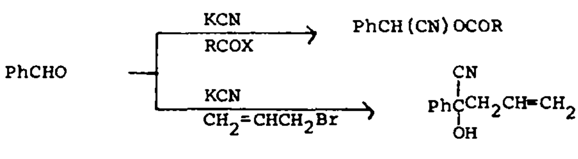


The group exchange reaction between α-stannylacetic esters and iodosilanes provides a method for synthesizing mixed silyl ketene acetals.[465] The harder silicon acid prefers bonding to the O atom.

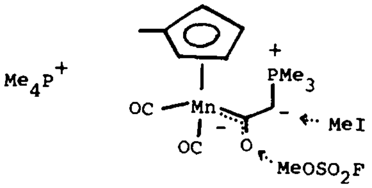


$$Pr_3SnCH_2COOMe + Me_3SiI \rightarrow CH_2{=}C(OSiMe_3)(OMe) + Pr_3SnI$$

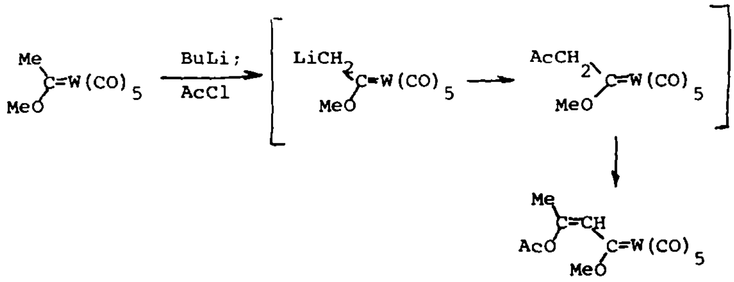
The anion of mandelonitrile is trapped by acyl halides, anhydrides, and chlorotrimethylsilane at the oxygen. With alkyl halides such as allyl and benzyl bromides, the reaction takes place at C.[466]



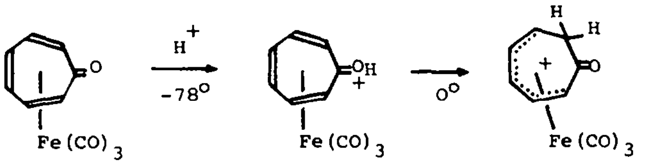
Tetraalkylphosphonium manganacylphosphorus ylides undergo methylation at C with iodomethane, at O with methyl fluorosulfate.[467]



The acetylation of a deprotonated tungsten carbene complex shows a preference for reaction at O in the second stage.[468] C-Acetylation at the beginning occurs because there is no other choice.

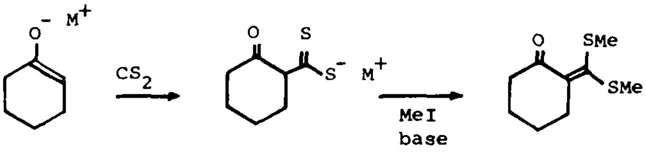


Kinetic protonation of tropone(tricarbonyl)iron appears at the O atom as is favored by the HSAB consideration. On warming it is isomerized into a more stable C-protonated complex.[469]

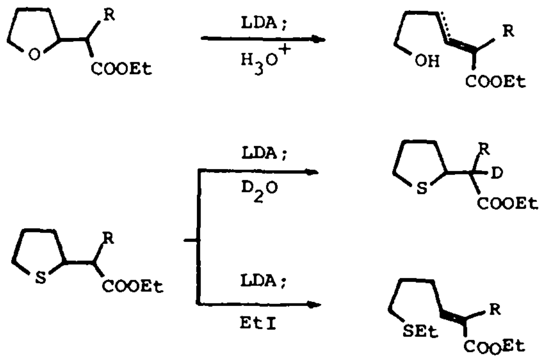


C *vs* S. Because sulfur is softer than carbon, the rate ratio of 1.7 for the ethylation of O,O-diethyl monothiomalonate anion in favor of sulfur is most reasonable.[470]

The treatment of a ketone enolate with carbon disulfide followed by quenching with iodomethane affords di(methylthio)methylene ketone.[471] Methylation occurs at both S atoms as contrasted to the alkylation of 2-carbomethoxycyclohexanone enolate which takes place at C.

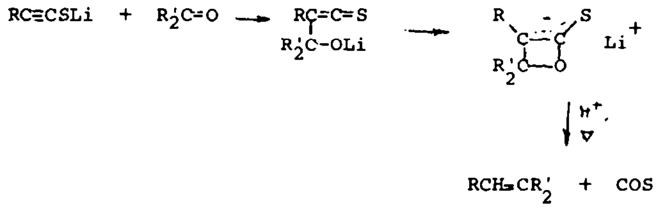


Deprotonation/protonation of 2-(tetrahydrofuranyl)acetic esters lead to open-chain tautomers. The heterocyclic system of the corresponding tetrahydrothiophene derivative remains intact upon similar treatment. However, evidence for the generation of acyclic intermediate has been obtained by trapping the anions with iodoethane.[472] Thus the difference between the two systems stems from their hardness characteristics. Selective protonation at the harder site available to each anion (O > C; C > S) is the sole reason.

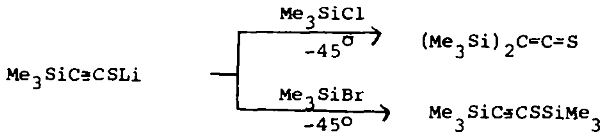


Lithium thioalkynolates give sulfide products on treatment with alkyl halides.[473] Their reaction with ketones affords trisubstituted olefins after protonation and mild pyrolysis.[474] The harder acids cause new bond formation at C instead of S, resulting in α-thiolactones which are readily decomposed into olefins.

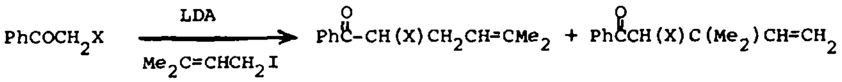
$$RC{\equiv}CSLi + R'X \longrightarrow RC{\equiv}CSR'$$



There is an apparent discrimination for the two sites of trimethylsilylethynylthiolate anion in the attack by the silylating agents Me_3SiCl and Me_3SiBr.[475] Such delicate chemoselectivity is really surprising, but not in conflict with the HSAB trend.



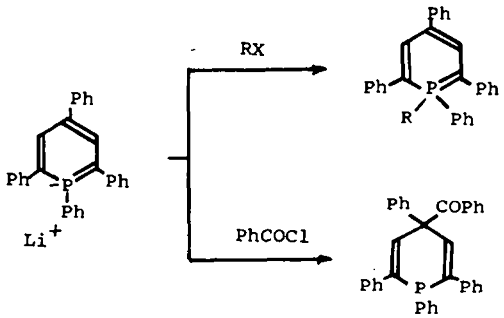
Prenylation of α-chalcogenated acetophenones gives abnormal products to the extent that is related to the softness of the heteroatom. An ylide mechanism is most likely involved in the formation of the abnormal products.[476] The softer Se is more prone to undergo alkylation in competition with the C base. Subsequently the ylide undergoes a [2,3] sigmatropic rearrangement to deliver the S_N2'-like product.



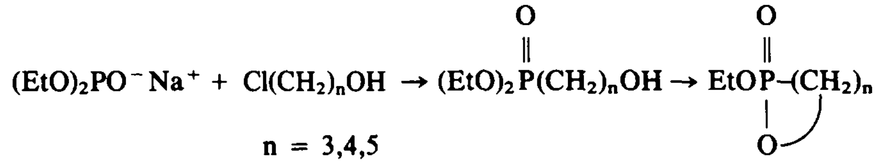
$$PhCOCH_2X \xrightarrow[Me_2C=CHCH_2I]{LDA} Ph\overset{O}{\overset{\|}{C}}-CH(X)CH_2CH=CMe_2 + Ph\overset{O}{\overset{\|}{C}}CH(X)C(Me_2)CH=CH_2$$

X= SPh	69	31
SePh	47	53

C *vs* P. The fact that phosphabenzenes fail to react with hard acids, but form σ complexes readily with soft metal compounds[477] suggest the very soft nature of P. The alkylation of 1,2,4,6-tetraphenylphosphabenzene anion at P and its acylation at C-4[478] agree with the HSAB principle.



O *vs* P, As. The sundrance in hardness between O and P can be shown by many reactions involving phosphite ions. For example, sodium diethylphosphonate combines with ω-chloroalkanols of appropriate chain length to yield cyclic phosphonates.[479] It is evident that a soft–soft interaction constitutes the first step and an internal displacement of an ethoxy group follows. It should be noted that the P atom changes roles from a soft base to a hard acid.



$$(EtO)_2PO^-Na^+ + Cl(CH_2)_nOH \rightarrow (EtO)_2\overset{\overset{O}{\|}}{P}(CH_2)_nOH \rightarrow EtO\underset{\underset{O}{|}}{\overset{\overset{O}{\|}}{P}}\text{–}(CH_2)_n$$

$$n = 3,4,5$$

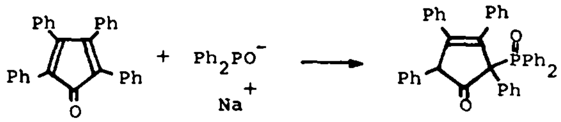
In the substitution of mesylates by sodium diethylphosphonate[480] considerable amounts of olefins and O-alkylation compounds are detected in polar solvents, in addition to the normal Michaelis–Becker products arising from P-alkylation. The mesyloxy group is more readily displaced by the oxy anion of the phosphonate than the softer halogen of alkyl halides. The olefin products are also derived from a hard process (via deprotonation).

A related report[481] reveals that phosphites are formed by the reaction of triarylchloromethanes with silver diisopropylphosphite. This reaction is charge-controlled.

$$(i\text{-}PrO)_2POAg + Ar_3CCl \rightarrow (i\text{-}PrO)_2P\text{–}OCAr_3 + AgCl$$

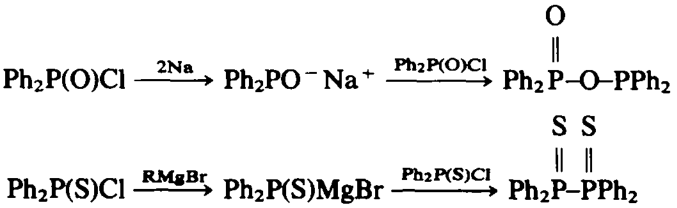
The photoinduced substitution ($S_{RN}1$) of aryl iodides with phosphite anions leads to aryl phosphonates.[482] However, the major products from the reaction of aryl triflates are the phosphate esters.[483] It seems clear that the leaving groups exert great influences on the selection of reaction pathways and the "nucleophiles".

The kinetic adduct of sodium diphenylphosphite and tetraphenylcyclopentadienone is an unconjugate ketone which indicates that the P base acts as a Michael donor.[484]



vic-Diphosphonates are easily prepared by a reaction of phosphonate anions with vinyl phosphonates.[485]

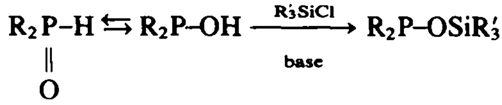
The reductive dimerization of diphenylphosphonyl chloride and the thiophosphonyl chloride[486] involve hard–hard and soft–soft interactions, respectively, between the anionic intermediates and the starting materials.



$$Ph_2P(O)Cl \xrightarrow{2Na} Ph_2PO^-Na^+ \xrightarrow{Ph_2P(O)Cl} Ph_2\overset{\overset{O}{\|}}{P}\text{–}O\text{–}PPh_2$$

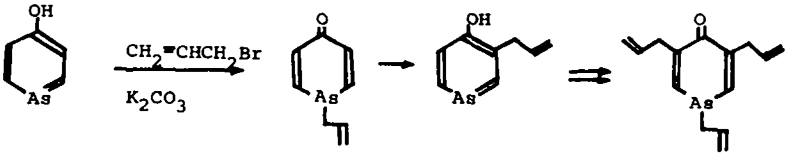
$$Ph_2P(S)Cl \xrightarrow{RMgBr} Ph_2P(S)MgBr \xrightarrow{Ph_2P(S)Cl} Ph_2\overset{\overset{S}{\|}}{P}\text{–}\overset{\overset{S}{\|}}{P}Ph_2$$

The valence tautomers of dialkylphosphine oxides are the unstable phosphinous acids. However, these compounds undergo silylation at the O atom.[487]



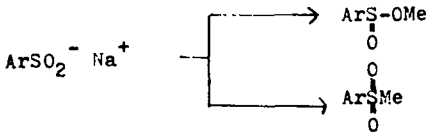
$$R_2\underset{\underset{O}{\|}}{P}\text{–}H \leftrightarrows R_2P\text{–}OH \xrightarrow[\text{base}]{R'_3SiCl} R_2P\text{–}OSiR'_3$$

As-Alkylation and O-acylation of 4-hydroxyarsabenzene[488] have been noted. The reactivity of ethylating agents increases according to softness: EtOTs < EtBr < EtI. Furthermore, during allylation an exceptionally facile hetero-Cope rearrangement occurs.[489]

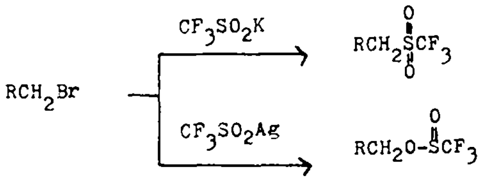


O *vs* S, Se. While both O and S belong to the same family of elements, the absence or presence of *d* orbitals/electrons in them makes tremendous differences in many reactions. Contrasting chemoselectivity is most apparent for the reactions involving O,S-ambident bases.

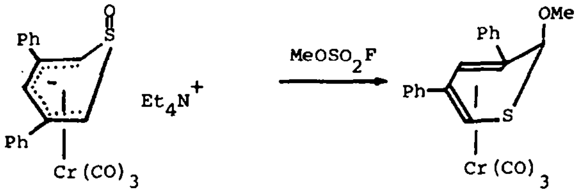
Methylation of sodium *p*-toluenesulfinate[490] gives rise to either a sulfinate ester or the sulfone. Hard methylating agents favor the formation of the ester because the nucleophilic center is the oxygen atom, soft methylating agents tend to attack the S base.



The product control can be achieved by varying the counterion of the sulfinate ion. Thus, the reaction of an alkyl bromide with potassium trifluoromethylsulfinate (triflinate)[491] furnishes a triflone. Close association of the hard cation to the O atoms of the sulfinate renders the S center available for an S_N2 displacement. On the other hand, the reaction with silver triflinate yields an alkyl triflinate.[492] The polarization of the C–Br bond of the alkyl bromide by Ag ion shifts the reaction toward S_N1-type. The harder acid selects the harder oxy base which is also more exposed because the Ag ion would bind more tightly to S in the nucleophile.

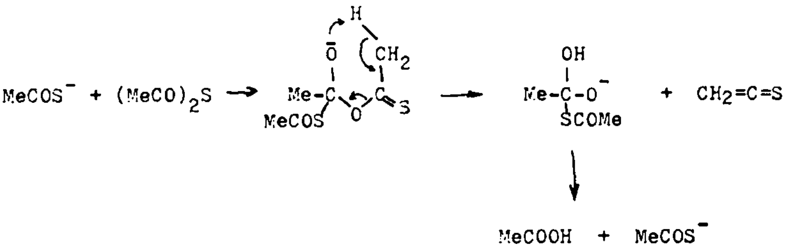


O-Alkylation of sulfoxides with hard acids is well known. There is no exception in the case of the anionic tricarbonylchromium complex of η5-3,5-diphenyl-1-thiacyclohexadienyl-1-oxide.[493] Although the alkylation is accompanied by an unusual Pummerer-type rearrangement

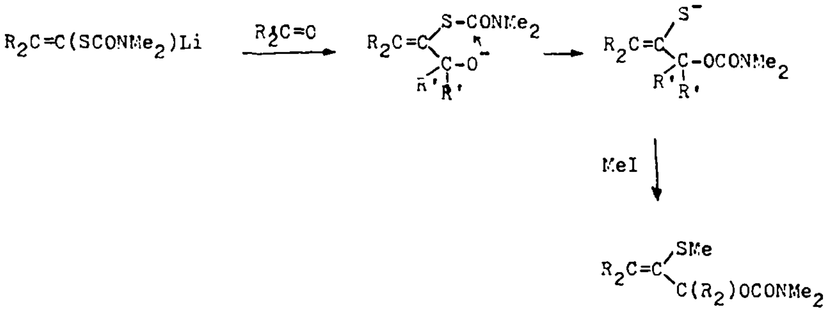


In analogy to the sulfinate alkylation, that involving arylsulfenate anions yields methyl arylsulfenates with either dimethyl sulfate or methyl fluorosulfate, and methyl sulfoxides with the softer iodomethane.

In an ion cyclotron resonance cell, the thioacetate anion reacts with thioacetic anhydride through its O end.[495] The adduct then undergoes a McLafferty rearrangement to give $MeCOS^-$.

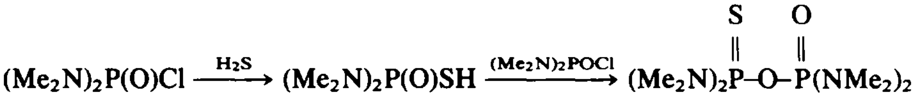


The sequential alkylation reactions of α-(carbamylthio)vinyllithium with carbonyl compounds and methyl iodide[496] demonstrate the occurrence of an S → O transamidation which is favored by the HSAB relationship.



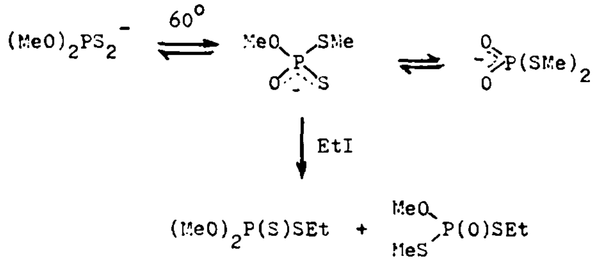
Phosphorothioate ions are also O,S-ambident. Their reactions with alkyl halides and sulfenyl chlorides occur at the softer S atom as expected.[497]

Treatment of N,N,N′,N′-tetramethylphosphorodiamidic chloride with hydrogen sulfide affords a mixed anhydride[498] indicating that the intermediary phosphorothioate is phosphorylated at the hard O atom.

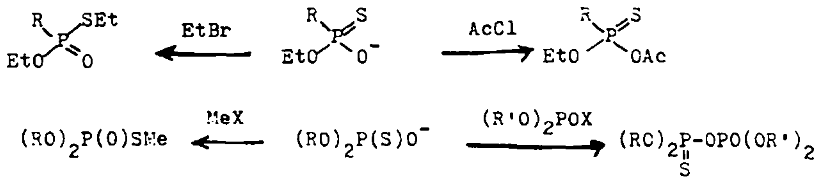


$$(Me_2N)_2P(O)Cl \xrightarrow{H_2S} (Me_2N)_2P(O)SH \xrightarrow{(Me_2N)_2POCl} (Me_2N)_2\overset{\overset{S}{\|}}{P}{-}O{-}\overset{\overset{O}{\|}}{P}(NMe_2)_2$$

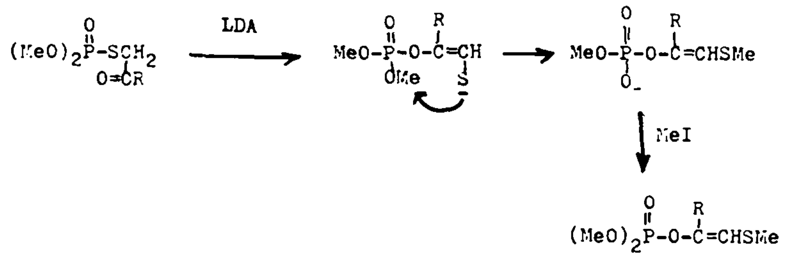
Sodium O,O-dimethylphosphorodithioate is gradually transformed into the O,S-isomer and then the S,S-isomer on warming.[499] The isomerizations improve the unfavorable bonding situation between the hard P and the soft S atoms. Single bonding between the two represents a better match. When the equilibrium mixture is allowed to react with ethyl iodide, only S-ethylation is observed.



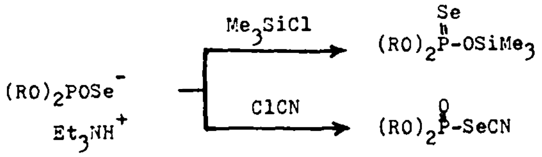
The chemoselective alkylation and acylation of phosphonothionate and phosphorothiolate ions[500] also conform to the HSAB principle.



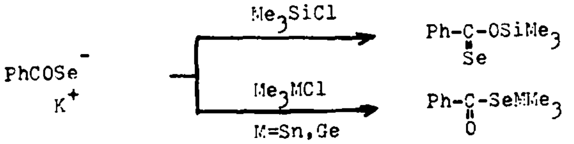
Base treatment of β-ketophosphorothiolates causes a rearrangement to the enolphosphates.[501] The process involves enolization, and a P–S to P–O and C–O to C–S bond exchange sequence. In so reacting, symbiosis is achieved for all the concerned elements.



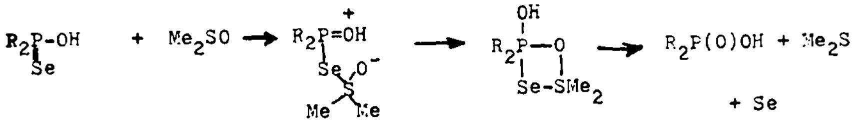
Ambidoselectivity concerning O and Se atoms is illustrated in the silylation and cyanation of phosphoroselenoate ions.[502]



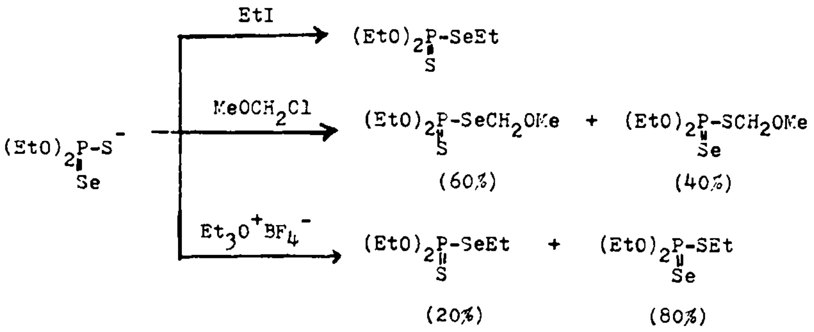
The esterification of potassium selenobenzoate with chlorides of Group IV elements is very enlightening.[503] O-Trimethylsilyl ester is produced even if the compounds containing C=Se bond are unstable. On the other hand, the salt reacts with chlorides of more polarizable metals and furnishes the seleno esters. The trimethylsilyl ester is sensitive to moisture owing to the presence of a hard Si acid. The stannoselenyl and germanoselenyl esters are quite stable toward hard bases.

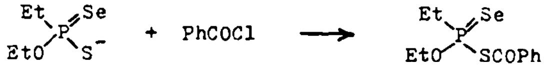


The deselenonation of phosphinoselenoic acids by dimethyl sulfoxide[504] proceeds exothermically, whereas the corresponding desulfurization of phosphinothioic acids requires heating at 100°. Apparently the reactivity index of the P=X bond is proportional to the softness disparity of the two adjoining atoms.



The competitive alkylation and acylation of phosphorus selenothio acids confirm the anticipated relative softness of the S and Se.[505]





N *vs* O, S. The ambifunctional nitrite ion can effect nucleophilic substitution with either the N or O base. Generally a mixture of alkyl nitrite and nitroalkane is produced on reacting an alkyl halide with alkali nitrite. The proportion of organic nitrite product is increased by using silver nitrite as the nucleophile, and in the case of harder alkyl halide such as benzyl bromide.[506] On the other hand, "naked" nitrite ion reacts with alkyl halides to give nitroalkanes only,[507] because the electrophiles are soft species.

$$Me_3CCl + NO_2^- \rightarrow Me_3C\text{–}ONO + Cl^-$$

$$MeI + NO_2^- \rightarrow MeNO_2 + I^-$$

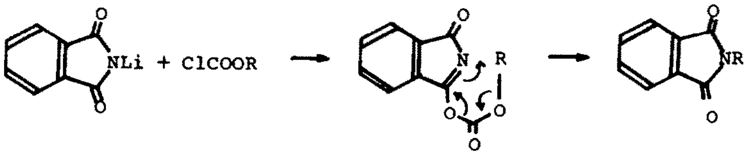
The benzylation of nitramine anions $RN(NO_2)^-$ occurs predominantly at the nitrogen site. The O/N ratio is raised to approximately unity when harder electrophiles such as chloromethyl ethers are involved.[508]

Sodium 9-fluorenone oximate, as dissociated ions,[509] is alkylated to the extent of 65% at O and 35% at N. When existing as ion pairs the oximate reacts to give 30% O-Me derivative. In the presence of a crown ether, the oximate ion undergoes almost exclusive (95–99%) O-methylation with methyl tosylate and O/N-methylation (65/35) with iodomethane.[510] The addition of sodium tetraphenylborate to suppress the dissociation of the sodium oximate reduces the alkylation with both methyl tosylate and iodomethane to nearly the same rate and gives essentially an identical ratio of the two products (O/N = 43/57). The hardness of the two different hetero atoms are about the same under such conditions.

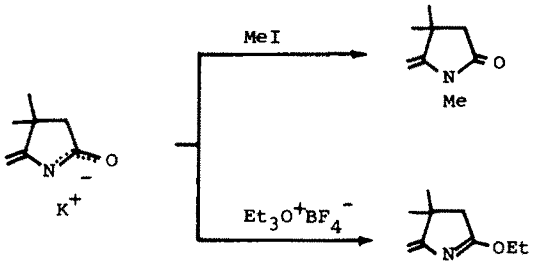
The salts of O-benzyl-benzohydroxamic acid is alkylated mainly at N.[511] Gradual increase in O-alkylation as the C-chain of the alkylating agent lengthens is indicative of a change in hardness of such reactant: MeI (100 N), EtI (100 N), n-PrI (75 N, 25 O), n-BuI (70 N, 30 O). The much harder diazomethane effects O-methylation of O-alkyl hydroxamates. In general, O-alkylation can be enhanced at the expense of N-alkylation by using dipolar aprotic solvents, and only O-alkylation is observed in a heterogeneous state.[512]

Benzohydroxamic acid is less reactive than its N–Me derivative toward alkyl tosylates[513] because $PhCON(Me)O^-$ is harder than $PhC(=NOH)O^-$.

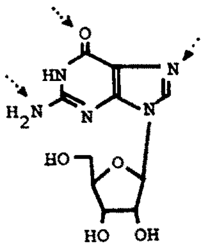
Imides are alkylated at the N atom only.[514] However, treatment of lithium phthalimide with an alkyl chloroformate leads to an enol carbonate which decomposes via an O–N alkyl transfer and decarboxylation to give the N-alkylphthalimide.[515] It is evident that hard acid chooses to react with the harder oxy base center.



Enamides are trident bases. It has been shown that the K salt of 4,4-dimethyl-5-methylenepyrrolidone reacts with iodomethane at N and gives an imino ether with Meerwein's reagent.[516]

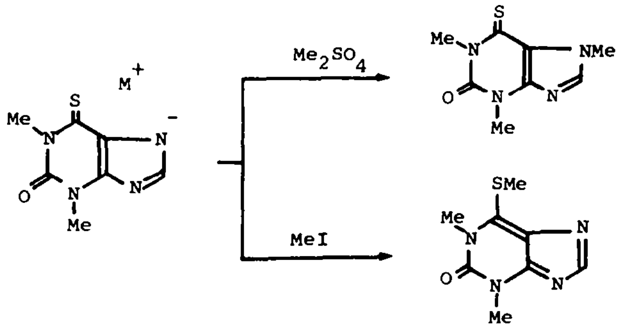


Three different products are obtained from benzylation of guanosine.[517] The product ratio of oxy- to amino-alkylation increases as the leaving group becomes harder.

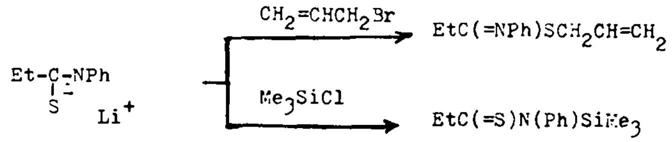


Selective triphenylmethylation of α-pyridone anion in acetonitrile with trityl chloride[518] can be controlled at the N or the O site by varying the gegenion from Li to Na.

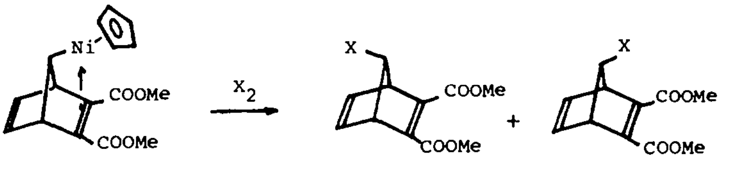
Replacement of a carbonyl group in purines with a thiocarbonyl counterpart changes their nucleophilic properties because the S atom is the softer base. A study of methylation reveals the pattern variation in chemoselectivity.[519]



The dependence of reaction sites of s-thioamide monoanions on the nature of alkylating agents[520] is most easily rationalized in terms of the HSAB principle.



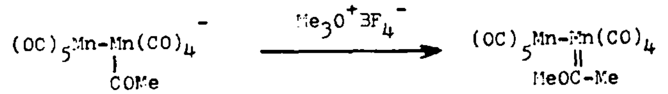
M *vs* C, O. Metal nucleophiles are generally very soft. In the reaction of the half-sandwich complex $CpCo(PMe_3)_2$ with methyl and ethyl iodides, C–Co bond formation results.[521] Interestingly, attack at the cyclopentadienyl ligand by isopropyl and t-butyl bromides has been documented.[522] Although steric effects may play a role in causing divergent pathways to be followed, there is no denying that the HSAB principle is also obeyed when harder acids become linked to the harder C nucleophile. Soft electrophilic agents effect cleavage of C–metal bonds with retention of configuration by attacking the metal atom. On the other hand, harder electrophiles tend to interact with the antibonding orbital of the C atom at the backside of the C–M bond. An example of this phenomenon is the halogenolysis of *syn*-(2,3-dicarbomethoxy-2,5-cycloheptadien-7-yl)(η^5-cyclopentadienyl)nickel.[523] Softer halogen favors the formation of the *syn*-halide.



X = Cl	10	1
Br	2.3	1
I	0	1

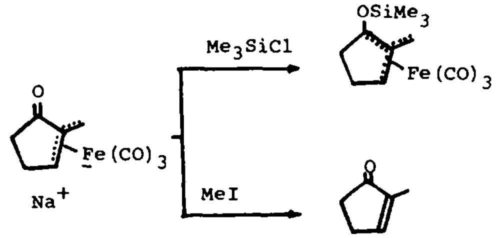
Acylferrocenes undergo protonation only at the carbonyl O under stable ion conditions.[524] The O atom is much harder than the Fe in these molecules (note: metallocenes can be protonated at the metal sites; the harder the metal the easier protonation, i.e. Fe > Ru > Os).

Hydroxycarbene complexes are obtained by protonation of the corresponding acylmetals.[525] Meerwein's salts also effect O-alkylation of acylmetals.[526]



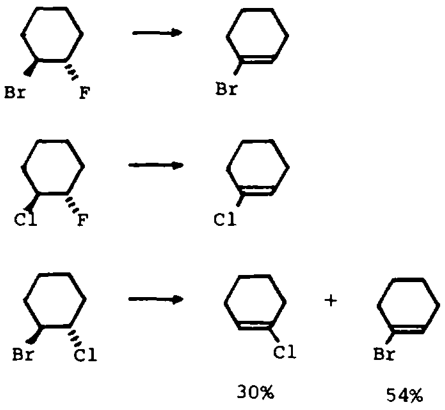
$$\underset{\text{COMe}}{(OC)_5Mn\text{-}Mn(CO)_4^-} \xrightarrow{Me_3O^+BF_4^-} \underset{\text{MeOC-Me}}{(OC)_5Mn\text{-}Mn(CO)_4}$$

The anionic $Fe(CO)_3$ complex of 2-methyl-2-cyclopentenone undergoes O-silylation, but it releases the organic ligand on reaction with an alkyl halide.[527]

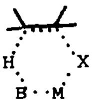


Although it is not clear whether a free radical (one-electron transfer) mechanism operates or a C–Fe bond formation is involved in the alkylation reaction, the HSAB-dependent pathways are followed faithfully.

Hal *vs* Hal. Although *vic*-dihalides can hardly be classified as bases, let alone ambident ones. However, it seems appropriate to mention here the unusual chemoselectivity which attends the *syn*-dehydrohalogenation processes using the complex base t-BuONa–$NaNH_2$.[528]



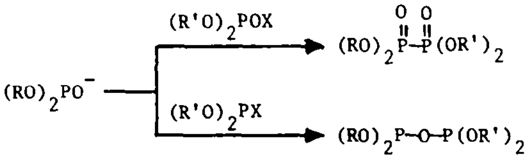
The preferential loss of the harder halogen leaving group must be due to a favorable interaction with the hard metal ion in the transition state.



EXCEPTIONAL CASES

The composite factors determining the hardness parameters as well as external influences such as reaction media necessarily complicate the reaction between an acid and a base. Violations of the HSAB principle are therefore anticipated.

As application of the HSAB principle to organic chemistry is concerned, perhaps the most problematical area is that dealing with ambidoselectivity. The contradictory behavior of phosphite ion toward phosphoryl and phosphinyl groups is not predictable on the HSAB basis. A knowledge of the transition state structure (Hammond's postulate) is required to provide a rationale.[529]



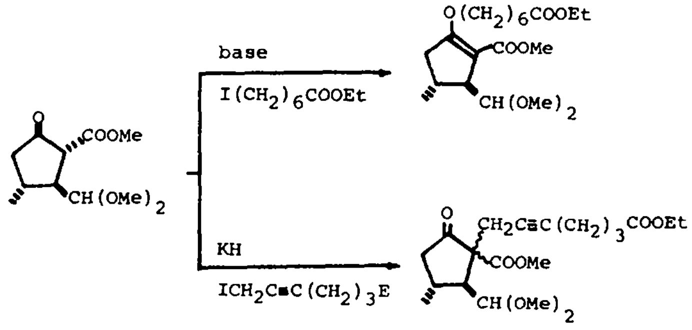
The monoanions of 1,2-cycloalkanediones undergo O-alkylation[530] whereas the dianions are C-alkylated.[531]

While the ambidoselectivity of most heteroatom substituted allyl anions are readily set in the HSAB context, there are cases in which either opposite trend or no selectivity is apparent.

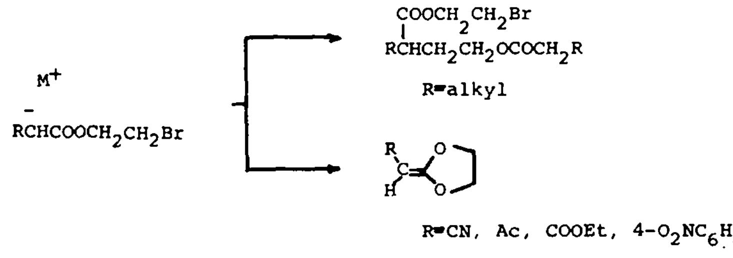
Thioacrolein dianion is alkylated preferentially at the γ carbon with electrophiles ranging from chlorosilanes, aldehydes, alkyl halides to disulfides.[532]

Allyl alanates couple with various alkylating agents (including carbonyl compounds) predominantly at the α-position, whether the hetero substituent is an alkoxy or alkylthio group.[533]

In a prostaglandin synthesis[534] the reaction of a β-keto ester with an alkyl iodide provided mainly the O-alkyl product. However, the alkylation with a propargyl iodide (harder!') occurs at C.

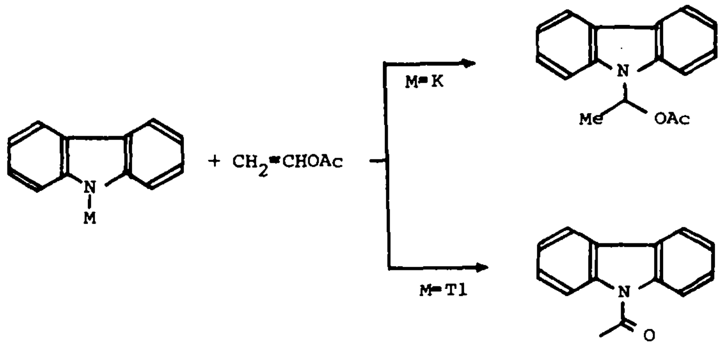


The self-alkylation of 2-bromoethyl carboxylates,[535] with respect to C- vs O-, intermolecular vs intramolecular, cannot be explained succinctly by the HSAB concept. The seemingly contradictory O-alkylation of the softer anion may have been coerced by steric factors.



Chemoselectivity is absent in the alkylation of α-carbanions of esters.[536] Exclusive C–C bond formation with MeI, Me_2SO_4, $MeOSO_2F$, and $Et_3O^+BF_4^-$ has been observed.

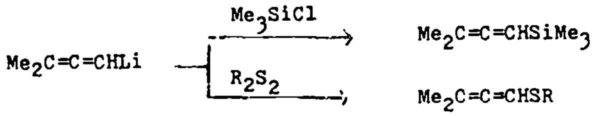
The very interesting reactions between metallocarbazoles and vinyl acetate[537] are not easily understandable. For N-acetylation of the Tl(I) derivative, the metal may be acting as a template to coordinate the vinyl group, bringing the N atom and the acetyl residue to within bonding distance.



Tl(I) salts of β-diketones in ether suspensions undergo O-acetylation with acetyl chloride at −78°, and exclusive C-acetylation with the harder acetyl fluoride at ambient temperature.[538]

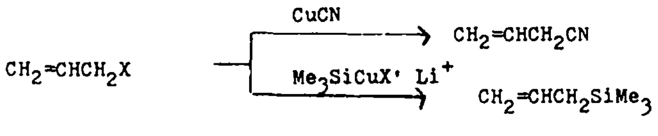
Alkynylthiolate ions react with aroyl halides to furnish S-acyl derivatives.[539] Perhaps the acylation product at the harder ambido center, acylthioketene, is too unstable that it may revert to the educts or act as acylating agent itself.

3,3-Dimethyl-1,2-butadienyllithium attacks both hard and soft bases alike.[540] No propargyl-type products are detected.



The softness of organocopper reagents is indisputable. Their preference for displacing alkyl tosylates[91] to halides is perplexing.

In the substitution reactions involving hard acids, soft bases are generally poor partners. However, if such bases are further softened by coordination with soft ligands, the substitution process improves. Examples include the conversion of allyl halides to cyanides[541] and silanes.[542]



The anomaly is also witnessed in certain cases of soft acid/soft base interactions. Thus the conjugate addition of 3-carbomethoxy-α-pyrone with ethylmagnesium bromide is inhibited by the presence of a cuprous salt.[543] Presumably electron transfer processes emerge as the favorite.

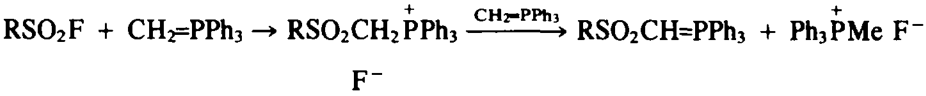
There is an unexpected reversal of solvent dependence for the addition of α-thio- and α-selenoalkyllithiums to chalcone.[544] In the presence of HMPA, a predominant attack at the carbonyl site results. On the other hand, in pure tetrahydrofuran much higher degree of conjugate addition is observed. It is suspected that chalcone represents a special case in that the reaction might involve electron transfer, and the 1,2-adducts originate from radical pair combination.

Hydride reduction using $Zn(BH_4)_2DMF$ and $Cd(BH_4)_2DMF$ complexes[545] cannot be rationalized easily with the HSAB principle, although no serious violation is found. Both reagents are soft, the cadmium reagent being more so. Reduction of benzoyl chloride with the Zn complex leads to benzyl alcohol, whereas benzaldehyde is produced when the cadmium reagent is used. These results indicate Zn^{2+} but not Cd^{2+} is capable of polarizing the carbonyl group of the aldehyde, which is necessary for the second stage reduction.

The low reactivity of these soft hydrides toward reduction of activated double bonds (of enones, for example) is disconcerting. Steric hindrance and/or change of strength factors arising from complexation of the borohydride with Zn ion may figure importantly in these reductions.

The *cine* substitution of di(*m*-anisyl)cadmium with acyl derivatives to give *p*-acylanisoles[546] is thought to proceed via a complex in which the Cd is associated with the leaving group. No correlation of the leaving group softness with the degree of the rearrangement can be found.

While sulfonyl chlorides react with Wittig reagents in accordance with the HSAB principle, i.e. at the soft Cl atom, sulfonyl fluorides suffer attack at the hard acid center.[547]



$$RSO_2F + CH_2{=}PPh_3 \rightarrow \underset{F^-}{RSO_2CH_2\overset{+}{P}Ph_3} \xrightarrow{CH_2{=}PPh_3} RSO_2CH{=}PPh_3 + Ph_3\overset{+}{P}Me\ F^-$$

In this case, the S–F bond is so polarized that the only available acid center is the S atom.

CONCLUDING REMARKS

As expected, the HSAB principle triumphs in dealing with organometallic reactions. There are exceptions, and definitely more than the few I have listed, because the equally or even more important strength factors with which the hardness parameters share the responsibility of governing a chemical reaction have not been always taken into account. Oftentimes exception rears its head when the two factors oppose each other. With "absolute hardness" recently defined, and the anticipated development in this direction, a better understanding of the HSAB principle and hence its multifacet application are exciting prospects to contemplate.

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