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Chapter **6**

Aromatic and Heterocyclic Chemistry

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EXCHANGE REACTIONS:

Aryl halides, except fluorides, undergo metal-halogen exchange (1) 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 (2) attests to the preference for soft interaction.

The conversion of bromobenzene to benzene-d, by successive treatment with t-BuLi and D_2O is impractical. However, the reaction is improved by adding the organometallic reagent to the substrate in D_2O-saturated ether. Apparently the metal-halogen exchange proceeds much faster than the destruction of the reagent by D_2O.
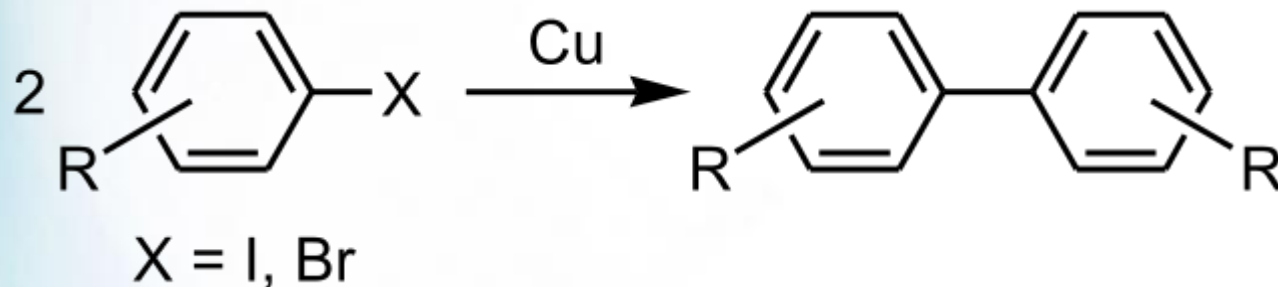
The presence of Me_3SiCl instead of heavy water in the medium allows for the preparation of trimethylsilylbenzene in good yield.

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.

Butyllithium attacks bromobenzene selectively to generate a harder base which reacts with the electrophile at a more leisurely pace.

The Ullmann biphenyl synthesis involves arylcopper intermediates.

The coupling is a typical soft-soft interaction. A useful extension to the generation of alkylarenes is by the reaction of dialkylcuprates with haloarenes.

$$2 \quad \text{R}\!-\!\!\langle\text{C}_6\text{H}_4\rangle\!-\!\text{X} \xrightarrow{\text{Cu}} \text{R}\!-\!\!\langle\text{C}_6\text{H}_4\rangle\!-\!\langle\text{C}_6\text{H}_4\rangle\!-\!\text{R}$$

X = I, Br

Metal-metal exchange between organometallic compounds may be effected in the presence of bromo substituents on the partners containing very soft metal atoms.

$$(p\text{-}BrC_6H_4)_2Hg + 2n\text{-}BuLi \longrightarrow 2p\text{-}BrC_6H_4Li + n\text{-}Bu_2Hg$$

ELECTROPHILIC SUBSTITUTIONS

When very hard substituents are present, the nucleophilicity of the π system is reduced. Pentafluorotoluene represents an extreme case which undergoes electrophilic substitution at the methyl group.

The Friedel-Crafts alkylation of aromatics with ω-haloalkyl fluorides always favors the formation of ω-haloalkylarenes. Symbiosis determines the selective C—X bond severance.

$$ArH + F(CH_2)_n X \xrightarrow{BF_3} Ar(CH_2)_n X$$

$$X = Cl, Br, I$$
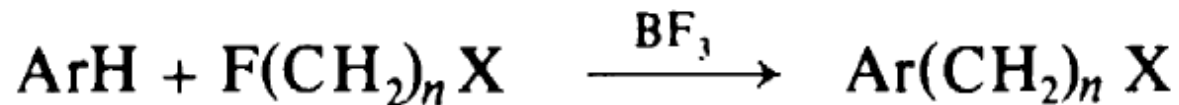
Similarly, the indene synthesis by alkylation of benzene with 1-bromo-l-fluorocyclopropanes is shown to proceed via an electrocyclic ionization of the hard F^-. This behavior is opposite to the trend of the uncatalyzed thermal heterolysis of halocyclopropanes.

Fluorination of aromatics is conveniently achieved by using fluoroxy compounds, e.g., $FOCF_3$. The fluorine in these reagents is a very soft acceptor.

Iodination of phenol involves an iodocyclohexadienone intermediate. The reversibility ratio for this process is larger than that for the corresponding reaction with 4-nitrophenol.

The nitro group evidently makes the corresponding dienone intermediate harder so that loss of a proton to the water solvent occurs more easily than the removal of I^+ by I^- in the former case.

Aromatic iodination via thallation has wide applicability. The iodine atom enters the same position as the thallium. Replacement of the hard trifluoroacetoxy groups of the thallium derivatives with iodide is favored because Tl(III) is soft.
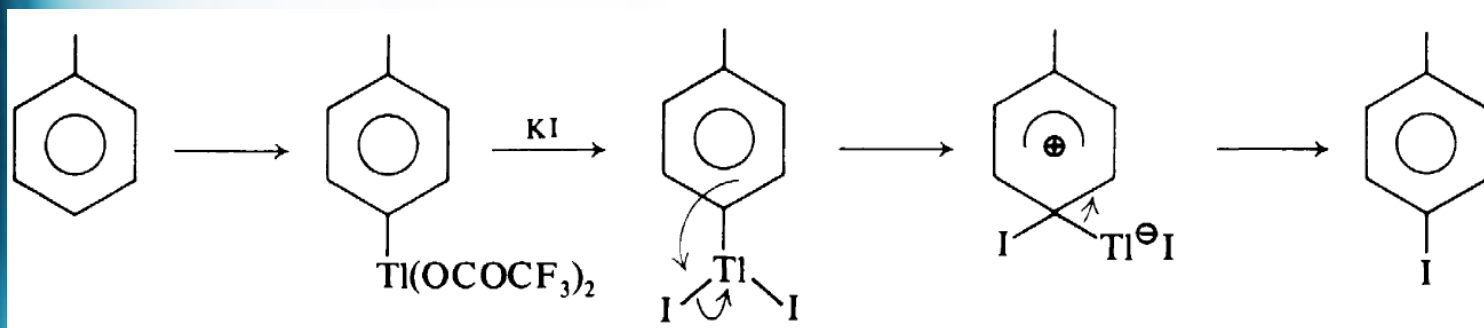
The relative rates of S_EAr reactions of alkylbenzenes are opposite to those expected from the electron release effect of the alkyl groups (Baker-Nathan effect). The rationalization of this phenomenon in terms of the HSAB principle is as follows.

The stability of the σ-complex intermediate may be analyzed by considering the R-C$^+$ fragment of the cross-conjugated canonical form. This fragment, as a carbene-carbenium ion pair [C: ──► R]$^+$, is more stable if R$^+$ is softer, i.e., Me$^+$ > Et$^+$ > i-Pr$^+$ > t-Bu$^+$, in agreement with the Baker-Nathan effect.
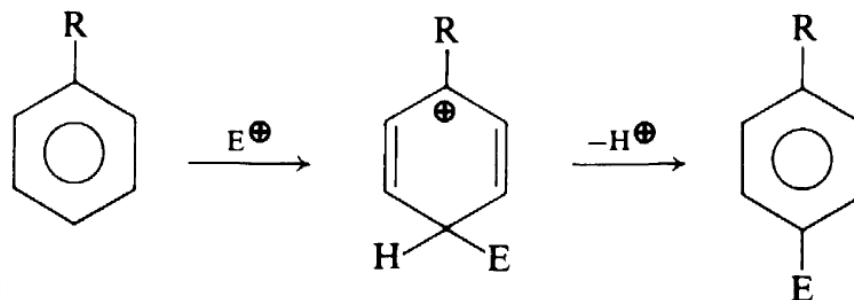
- In organic chemistry, the **Baker–Nathan effect** is observed with reaction rates for certain chemical reactions with certain substrates where the order in reactivity cannot be explained solely by an inductive **effect** of substituents. This **effect** was described in 1935 by John W. **Baker** and W. S. **Nathan**.

Hyperconjugation

R = Me 1.66
R = Et 1.40
R = i-Pr 1.35
R = t-Bu 1.34
R = H 1
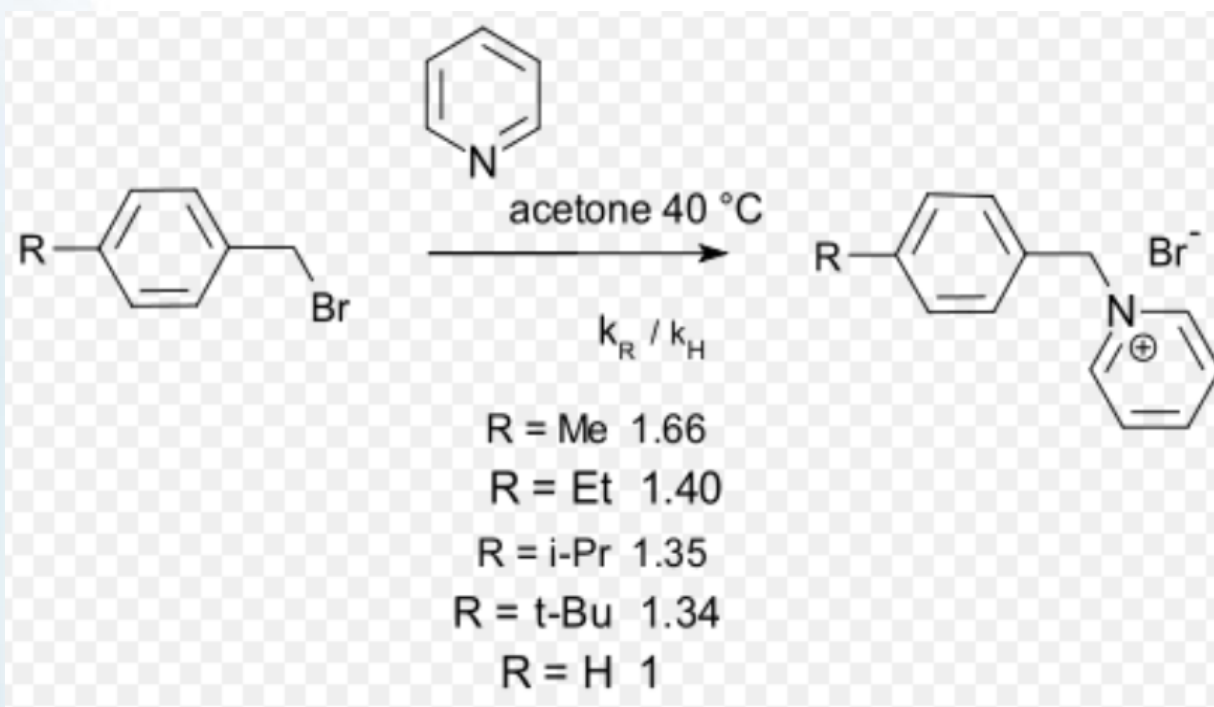
The stereochemical aspect of electrophilic substitution of metallocenes is intriguing. In acylation, the attack comes from the outside (anti to the metal) and the order of reactivities is ferrocene > ruthenocene > osmocene. On the other hand, during mercuration the electrophile approaches from the inside (syn to the metal).
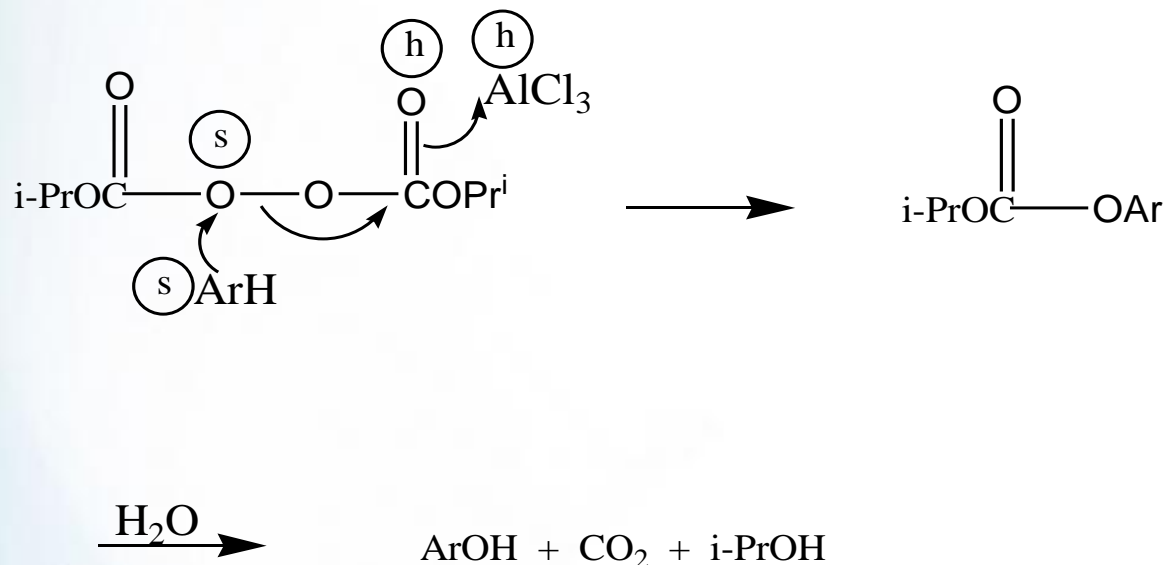
It is clear that (i) hard electrophiles align themselves farthest from the essentially soft metal in the transition states, and the charge controlled reactions (acylation) occur more readily with the harder metallocenes, and (ii) soft electrophiles (e.g., $Hg^{2+)}$ approach the aromatic ring from the same side as the metal which permits soft-soft interaction.
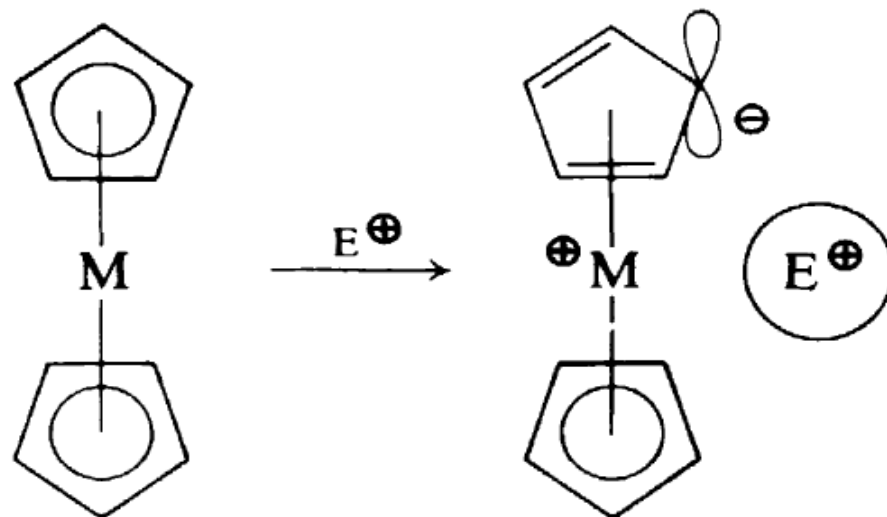
In the solvolysis of α-metallocenylmethyl acetates, the reactivity gradient osmocene> ruthenocene > ferrocene prevails. The ionization step may be envisioned as involving assistance from an electron pair of the ring. The geometry and electronic state of the metallocene moiety in the transition state must therefore resemble that in a substitution reaction by a soft acid.
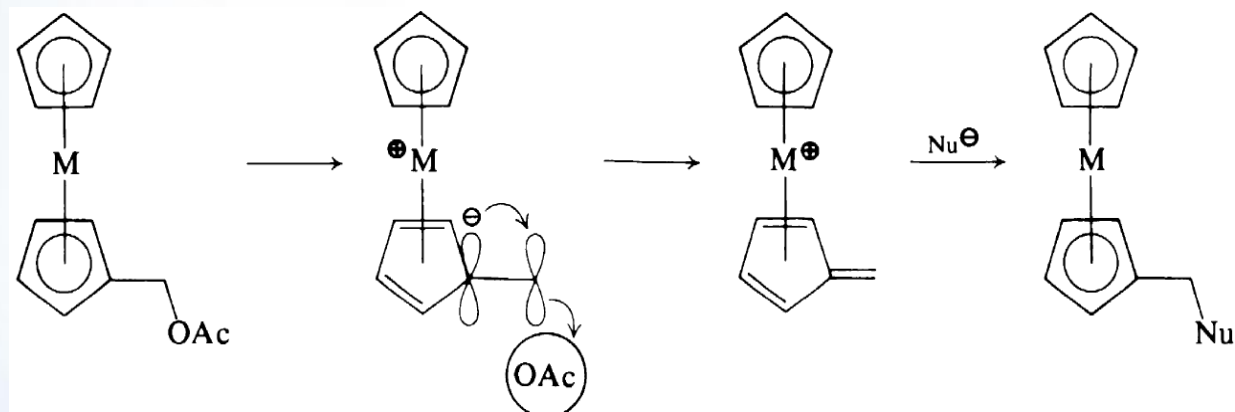
The oxygenation of aromatic compounds by Lewis acid-catalyzed decomposition of peroxydicarbonates may be formulated as indicated in the following reaction. Saville's rule is applicable to these reactions.


$$\text{i-PrOC} - O - O - \text{COPr}^i \xrightarrow{\text{AlCl}_3, \text{ArH}} \text{i-PrOC} - \text{OAr}$$

$$\xrightarrow{H_2O} \text{ArOH} + CO_2 + \text{i-PrOH}$$

Although the mechanism of the Dakin reaction given in many textbooks does not involve participation of the π electron of the aromatic ring, the mandatory presence of polar substituents (e.g., OH) in the ortho or para position to the formyl group suggests that an internal electrophilic substitution of the adduct intermediate is a better representation. The uncatalyzed $S_E Ar$ process is a soft-soft interaction.
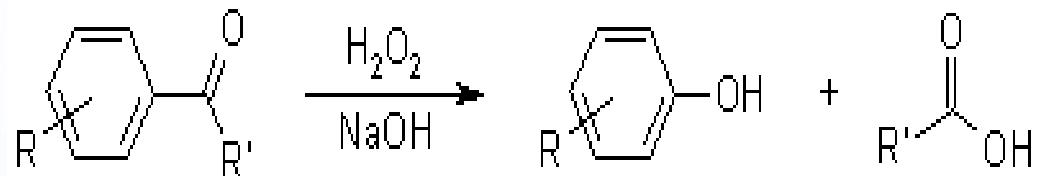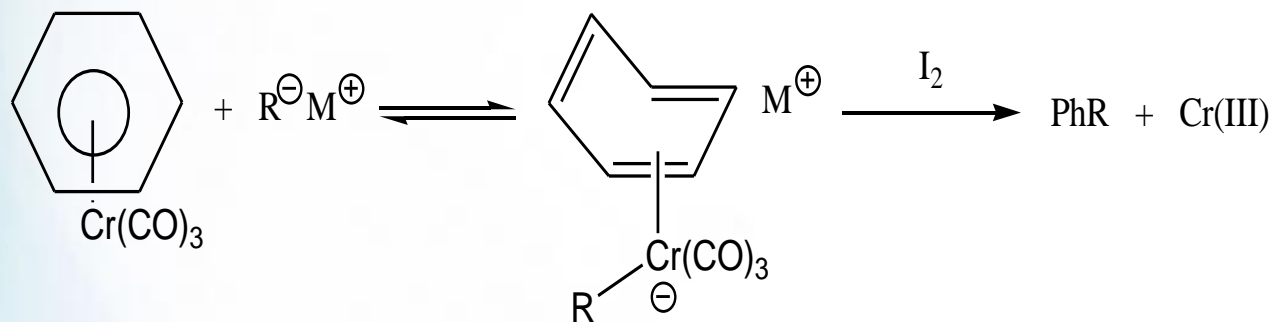
Dakin Oxidation or Dakin reaction
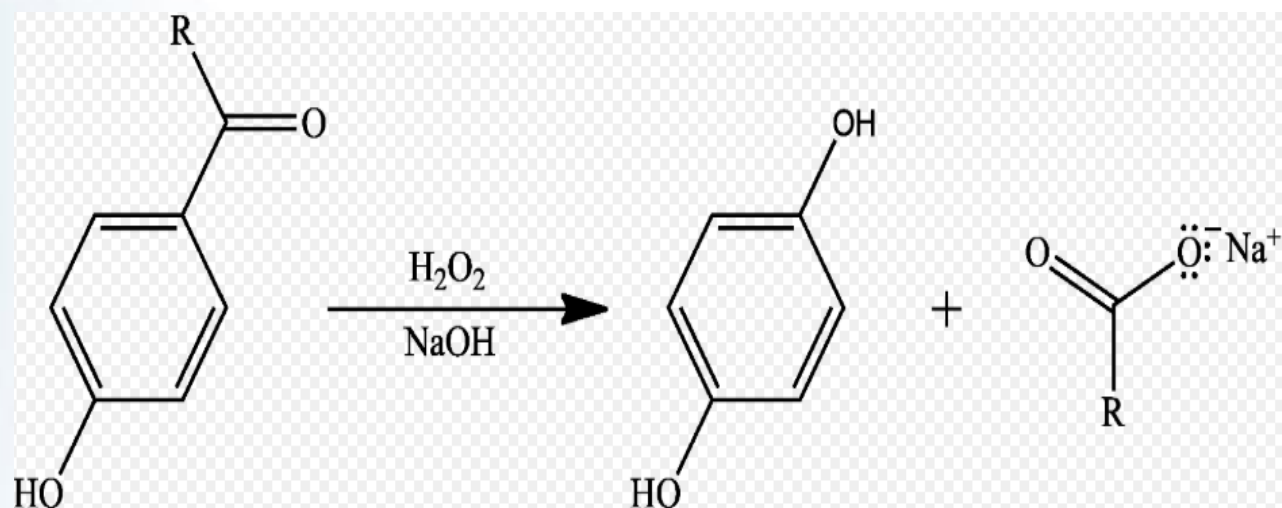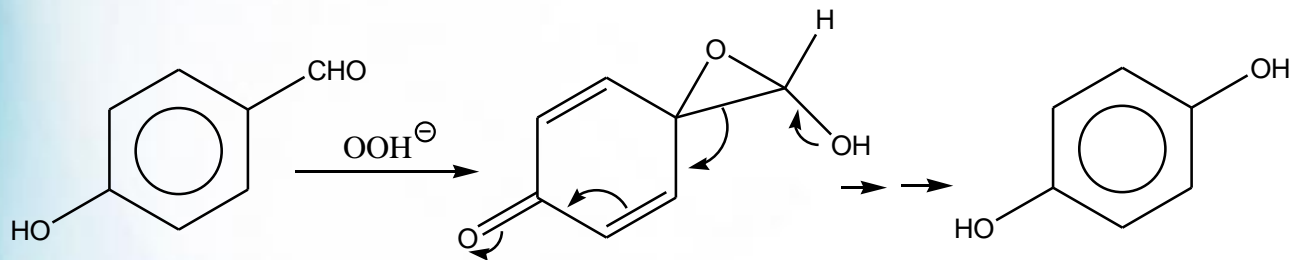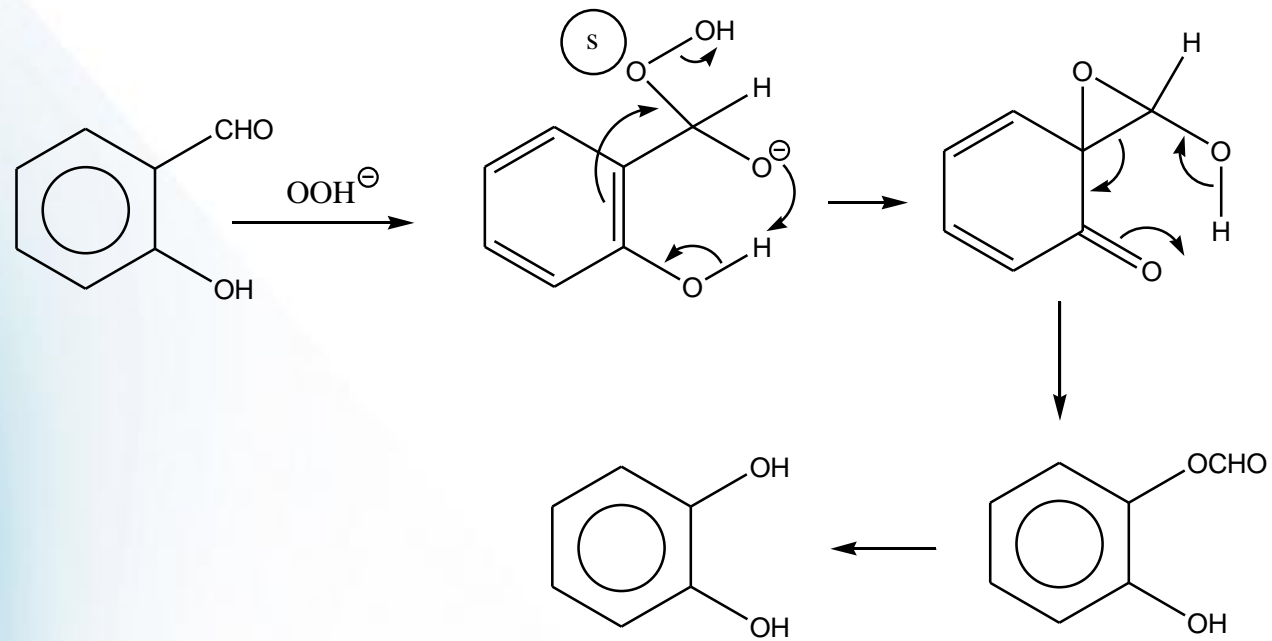
NUCLEOPHILIC SUBSTITUTION

Hydride ion can be formally displaced from the benzene ring of the chromium tricarbonyl complex. Evidence seems to be in favor of initial attack on the chromium atom which is also a soft-soft interaction.

The selective displacement of bromine from *o*-bromochlorobenzene (k_{Cl}/k_{Br} = 0.0030) by a soft Ni(O) complex has been demonstrated. In refluxing ethanol, nickel tetracarbonyl reacts with aryl iodides. Aryl bromides and alkyl halides are inert, the softness of the acceptor is thus of great importance.

Ni(0): $(Et_3P)_2Ni(C_2H_4)$
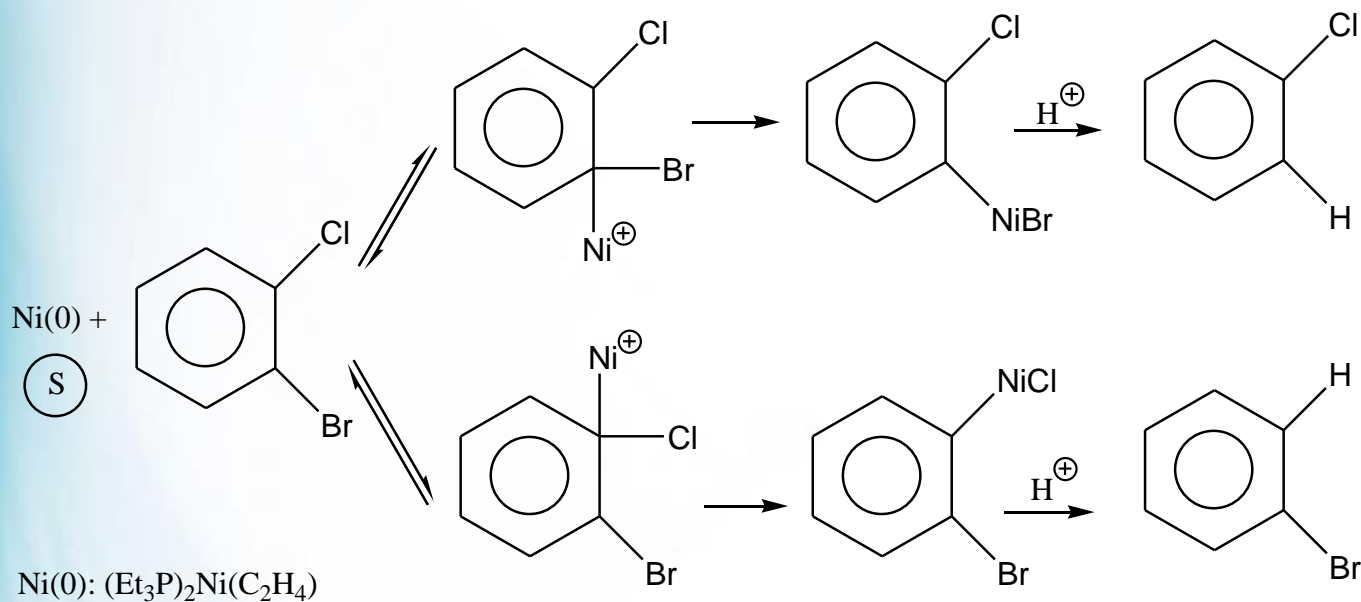
The mobility pattern for halonitrobenzenes is F > Cl > Br > I when they are displaced with nucleophilic atoms of the first row elements; the order is reversed when heavy atom bases are employed.

On the basis of the HSAB principle, initial attack by hard bases is favored when the leaving halogen is hard because the first transition state is symbiotically stabilized. The opposite is true for soft nucleophiles.

The expulsion of halogen from halonitrobenzenes by the nitrite ion always furnishes phenolic products. It has been shown by isotope labeling techniques that nitrogen attack is faster than oxygen attack when the leaving group is Cl, Br, or I, but the initial products are converted into the nitrite esters and then to the phenolates. Oxygen attack is faster if fluorine is being displaced.
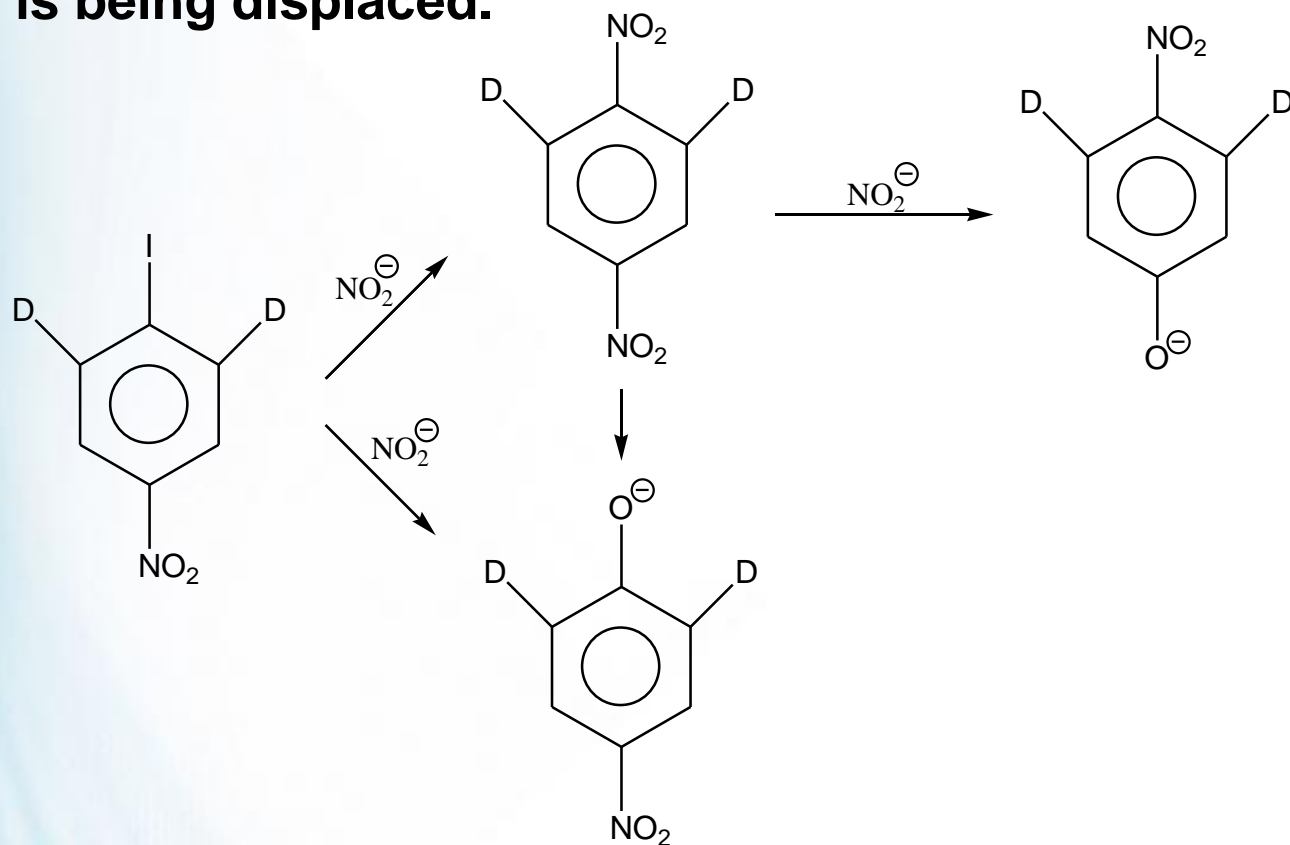
In the S_NAr reaction of polynitrophenyl derivatives (ArX) with the thiocyanate ion, the nature of the leaving group X has profound influence on the reaction rates. The rate ratio k_S/k_N has a 10^5 range (from X = pyridinium ion to X = I), with the iodo compound enormously favoring the attack by the soft S end of thiocyanate.

It was suggested that transition state symbiosis is much more reasonable in S_NAr reactions because the entering and leavingare much closer to each other than they are in the aliphatic S_N2 transition state

The S_NAr reaction of polyhalo aromatic compounds has been discussed. For the displacement of fluorine para to substituent R, the relative stability of the transition state appears to follow the order H ~ I > Br >C1 >F, in contrast to the normal electron-attracting influence exerted by the halogen.

The stability sequence is directly related to the chemical softness of the substituents. The fragment R-C⁻ may be regarded as a soft-soft combination [R⁻⟶ C··].
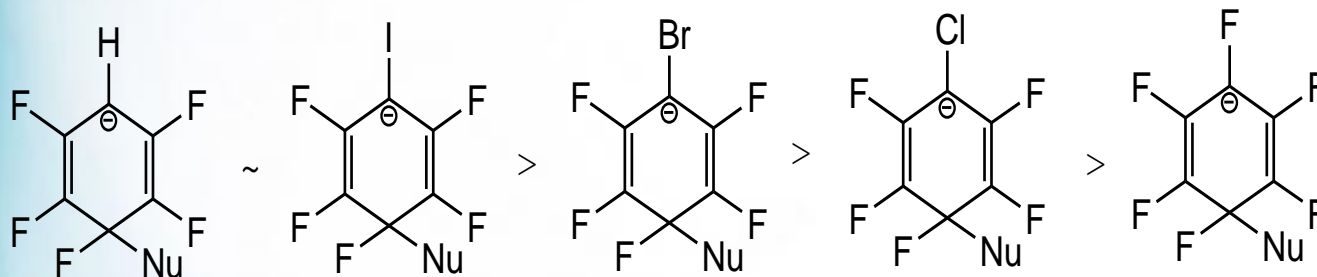
Variation of the substitution site according to the nature of the attacking base is known. The dichotomy may be the result of symbiotic stabilization of the transition state.
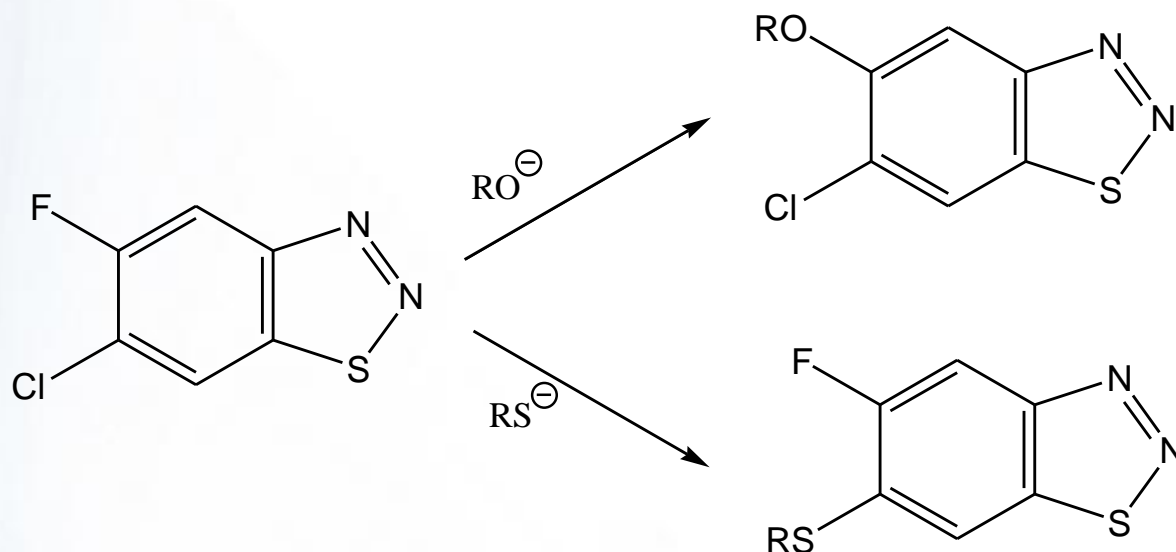
An interesting reaction involving an additive rearrangement of benzyne with alkylidenetriphenylphosphoranes is depicted as the following.
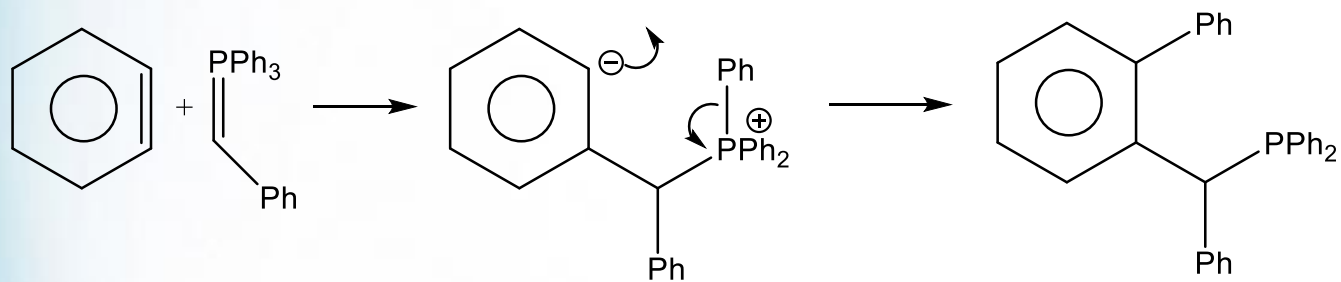
Benzyne displays greatly different reactivities toward I^-, Br^-, Cl^-, and ethanol. The strong hard bases (e.g., NH_2^-) cannot compete with the thiolate anions for benzyne, and the trapping efficiency for 9,10-dehydrophenanthrene is a function of donor softness:

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

3,4-Dehydropyridine (pyridyne) generated by dehydrohalogenation of 3- or 4-halopyridine with hard bases in the presence of methanethiol gives equimolar amounts of 3- and 4-methylthiopyridines predominantly.

2-Bromo-5-nitro-l,3,4-thiadiazole yields two different "monosubstituted" products from its reactions with sodium and silver benzenethiolates, respectively.

The counter ion in the nucleophile dictates the site of attack by the sulfide anion through the selective coordination with the leaving group more compatible in softness.

Thus, (s):(s) silver-bromine and (h):(h) sodium-oxygen (of the nitro group) pairings are responsible for the outcome.
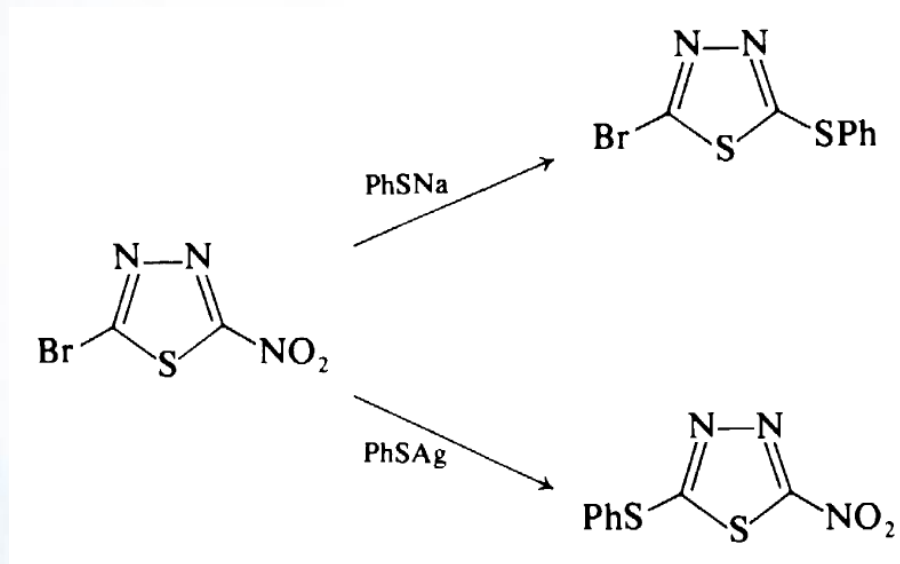
2-Bromo- and 2-iodoimidazoles are reductively dehalogenated by the sulfite ion. The corresponding chloro and fluoro compounds are stable to this soft reagent. It should be noted that the fluorine is easily replaced by hard bases via an S_NAr mechanism.
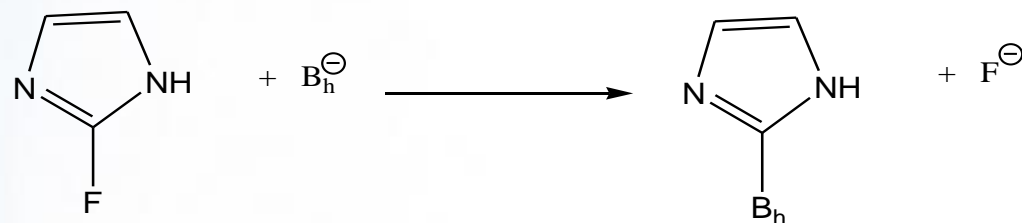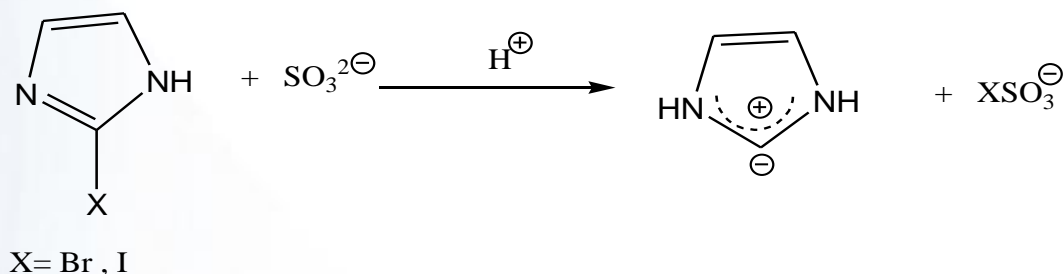
The hard nucleophiles (F^-, RO^-) displace the $MeSO_2$ groups in 3,5-dichloro-2,6-bis(methylsulfonyl)pyridine, whereas the softer CN^- and R_2NH species displace the chlorine atoms.

Dihydropyridine derivatives are obtained by the addition of nucleophiles to pyridinium salts. In general, the harder bases add to C-2, whereas the softer bases enter C-4, of the heterocyclic system

Quinoline is converted to the Reissert compound. In the competing process quinoline is released from the acyl appendage of the intermediate by the hard base.

Reissert compound

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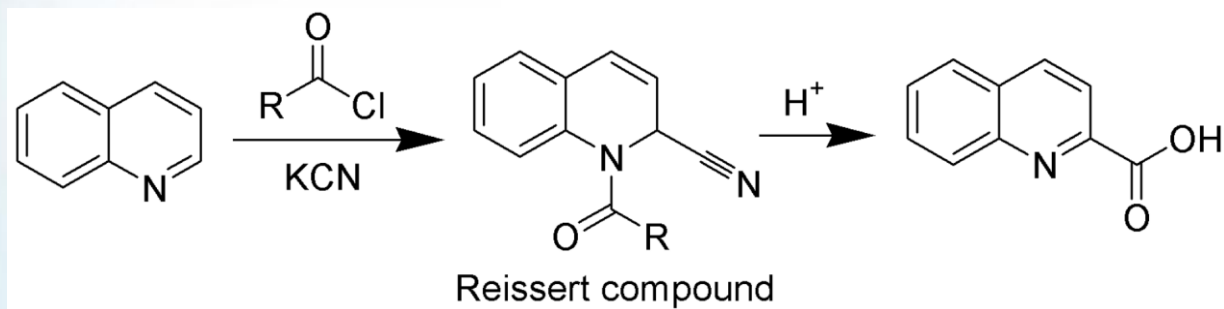
When quinoline is reacted with a combination of thiophosgene (Cl2C=S) and KCN, *o*-isothiocyanato-(E)-cinnamaldehyde (1) and 3-oxoimidazo[l,5-α]quinolone (2) are obtained according to Scheme 6.1. It should be noted that the chlorothiocarbonyl function, which is quite soft, reacts readily with cyanide ion in preference to hydroxide.

Scheme 6.1
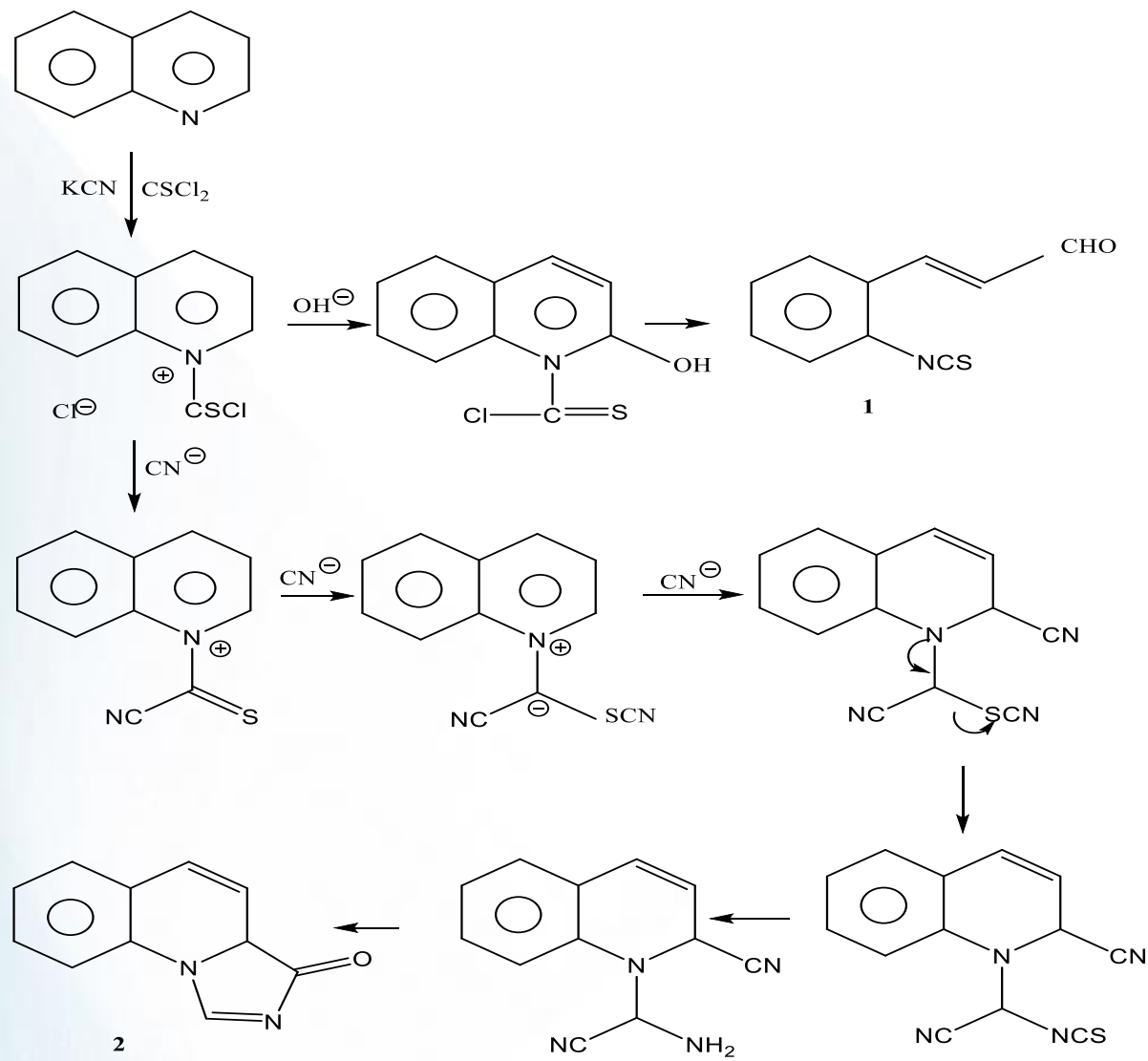
N-(*p*-**Nitrophenoxy**) **pyridinium salts aryloxylate methoxybenzenes and annelate with benzonitrile.**
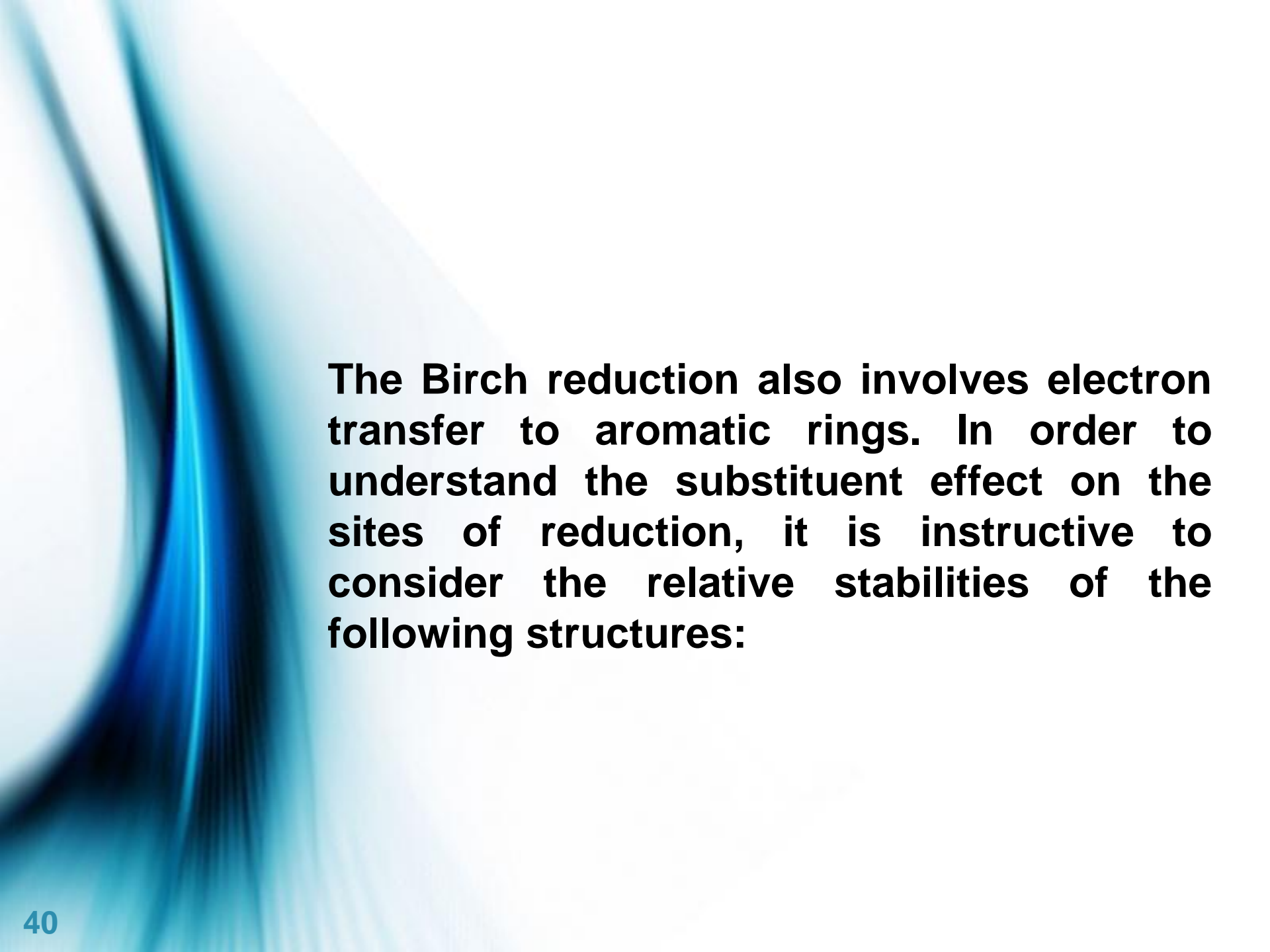
The oxygen site of the electrophiles is a softer acceptor than the ortho carbon, because as acids the core atoms belonging to the higher main groups are often softer (e.g., $O^+ > N^+ > C^+$).

It should be emphasized that for the same group the lighter electrophile atom would be softer,

e.g., C=O > C=S.

$$O^{\oplus} > N^{\oplus} > C^{\oplus}$$

RPh

$- C_5H_5NH^{\oplus} X^{\ominus}$

PhCN

$- C_5H_5N$

$- HX$
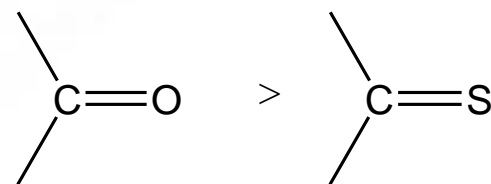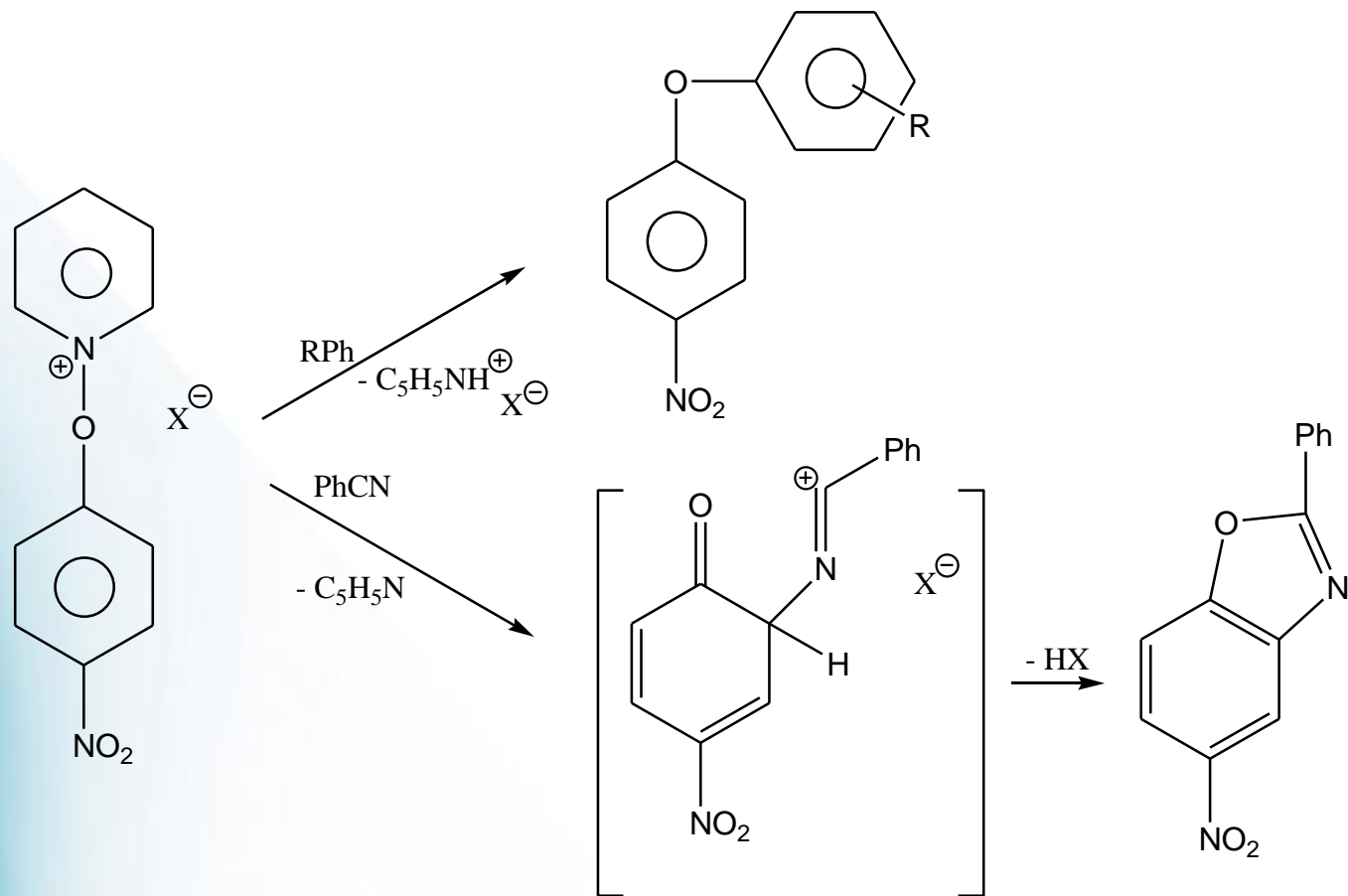
Metals supply a very soft electron to the C-4 of pyridines or pyridinium ions. Interestingly, viologens can be reduced by cyanohydrin anions.
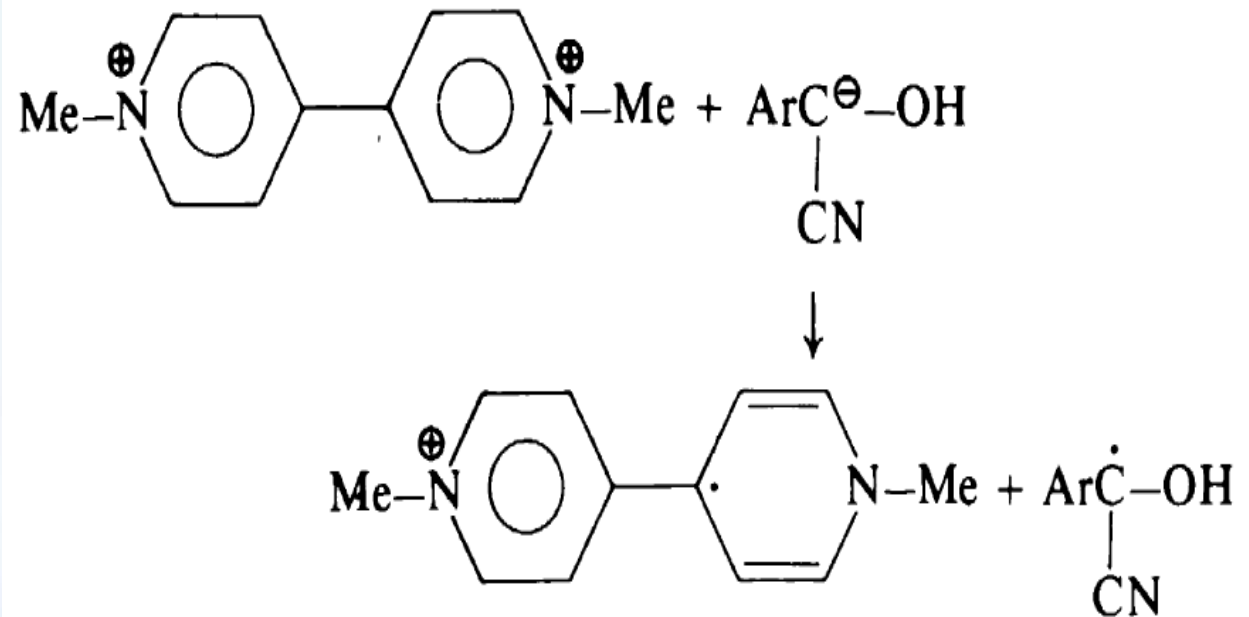
The Birch reduction also involves electron transfer to aromatic rings. In order to understand the substituent effect on the sites of reduction, it is instructive to consider the relative stabilities of the following structures:
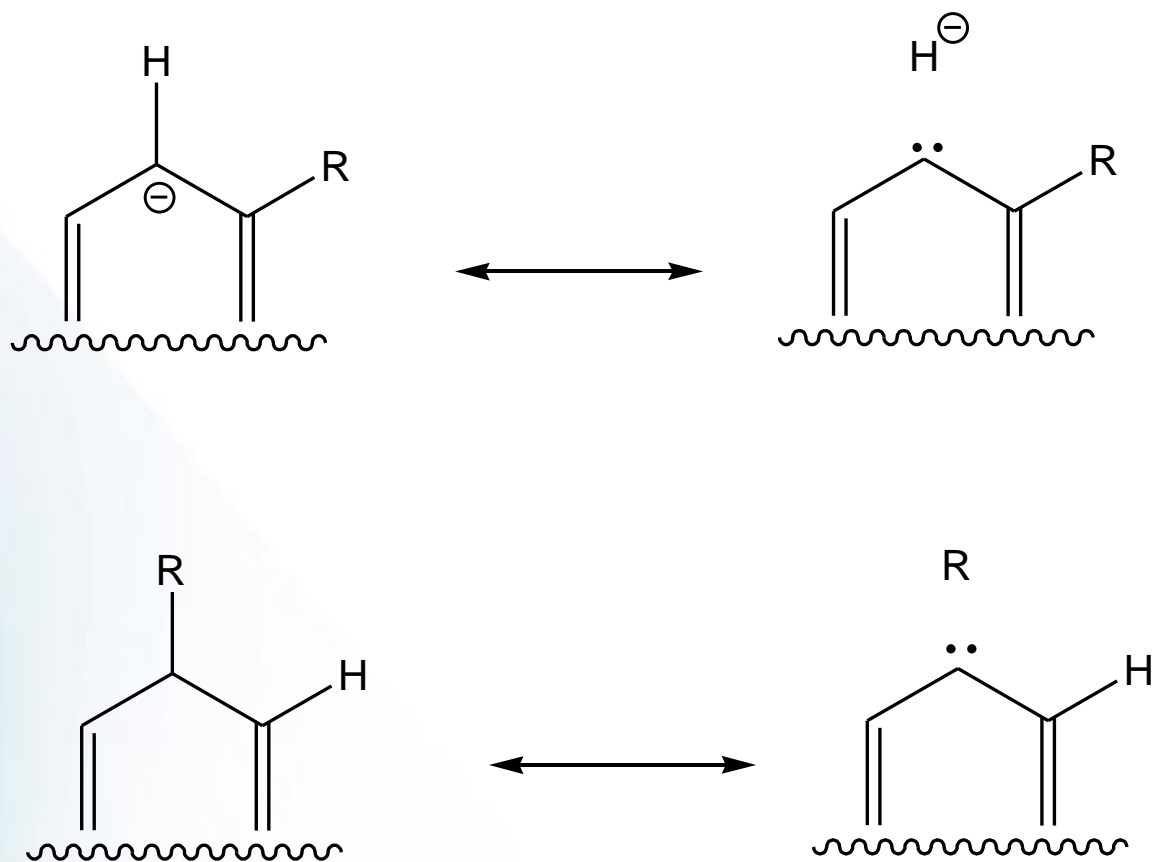
The disubstituted carbanion favored for the hydride-carbene complex is more stable than the carbanion-carbene complex corresponding to the tertiary carbanion.

The same influence on orientation is, however, not exerted by every type of substituent. For example, benzoic acid is reduced to 1,4-dihydrobenzoic acid, presumably owing to an initial electron transfer to the carbonyl oxygen.
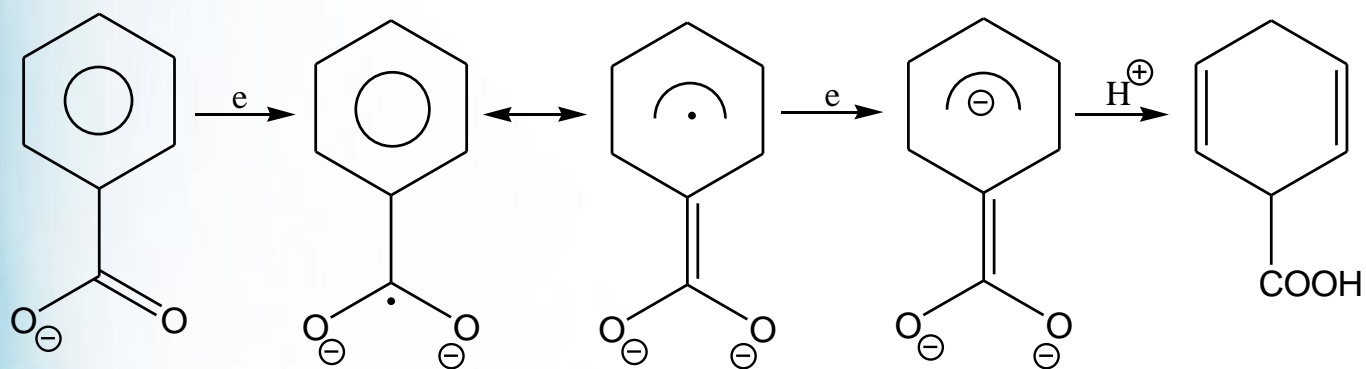
AMBIDENT BEHAVIOR OF HETEROCYCLIC COMPOUNDS

2-Pyridone anion undergoes *N*-alkylation in dimethylformamide (DMF) when the counter ion is Na^+. *O*-Alkylation is favored in a heterogeneous reaction using the Ag^+ salt in nonpolar solvents.

Acetylation of the thallium(I) salt of 2-pyridine at -40° provides up to 40% of the *N*-acetyl derivative, which on warming rearranges largely to the *O*-isomer. The Na salt of phenanthridinone reacts with benzoyl chloride at room temperature to afford only the less stable *O*-benzoylated product.

Thus, the use of the soft T1(I) salt diverts a portion of acetylation to the nitrogen site, even though the process is charge-controlled. In contrast, the hard Na salts of pyridone derivatives favor *O*-acylation.
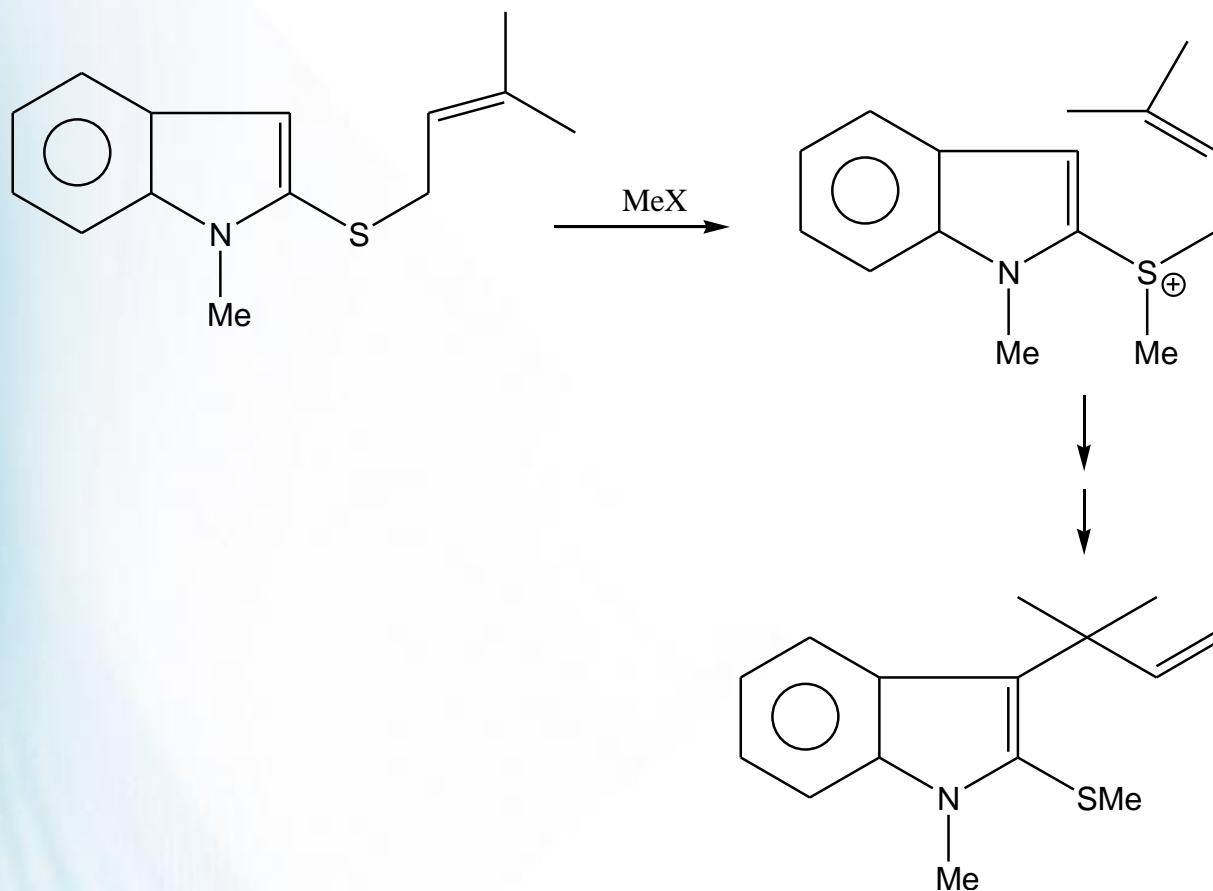
AROMATIC CLAISEN REARRANGEMENT

In the aromatic Claisen rearrangement, the ether-phenol transformation occurs at about 200°; S-C allyl shifts are more difficult to achieve.

As the formation of the dienone intermediates is rate-determining, the analysis of perturbance around the heteroatoms (X) leading to the intermediates should provide clues to the relative rates, for changes are the same elsewhere.

Thus, the crux of the problem involves only the net change of a Csp^3—X to a $Csp^2 - X$ bond. Such a change is favored with X = O rather than that with X = S because trigonal carbon is harder.
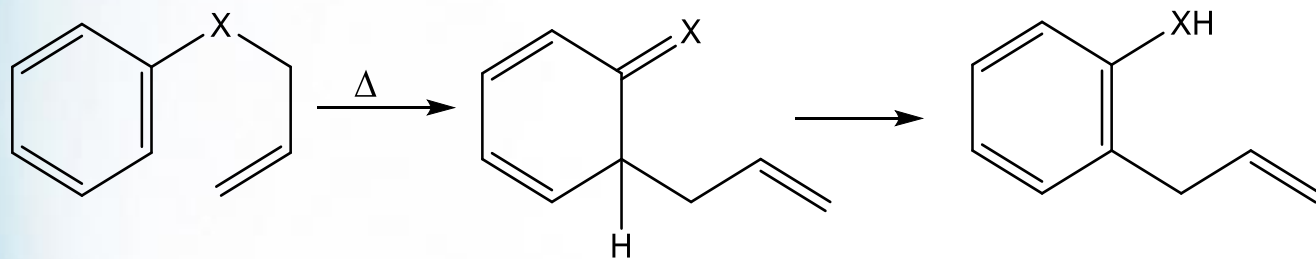
Since amino-Claisen rearrangement is facilitated by Lewis acids, it is therefore conceivable that the sulfonium salts derived from allyl aryl sulfides would undergo rearrangement at lower temperatures. Such an effect due to prehardening of sulfur atom has been observed

An interesting retro-thio-Claisen rearrangement has been reported. The driving force is the inherent instability of the C=S bond of the thioamide.
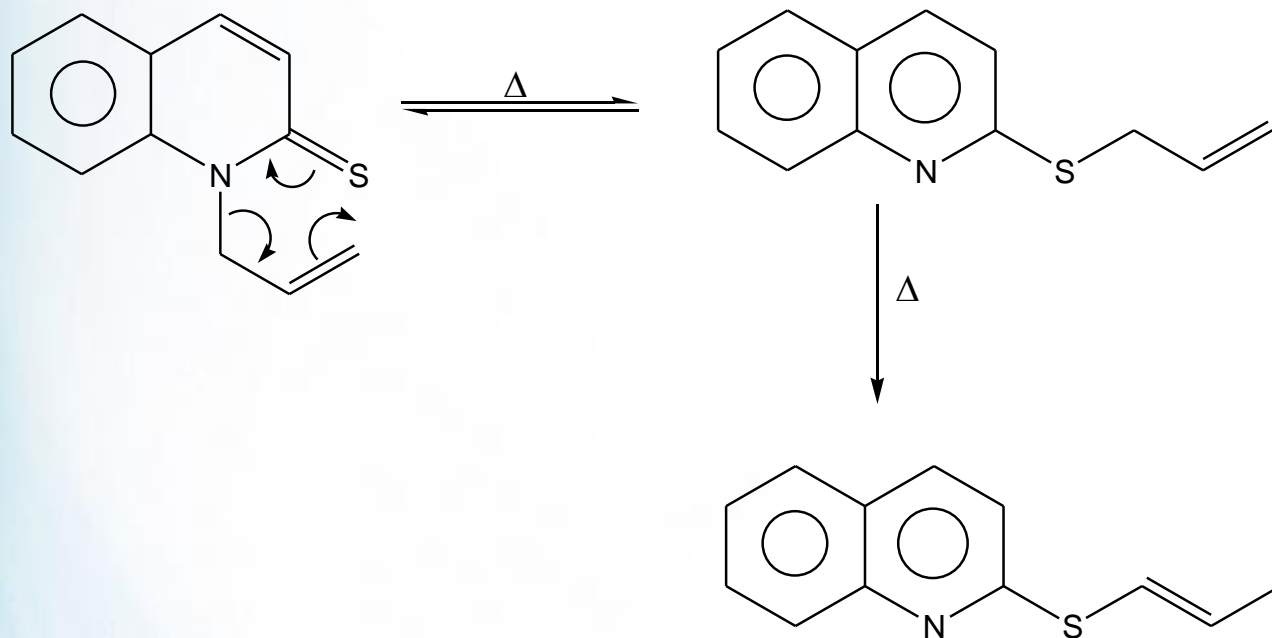
OXIDATIVE COUPLING OF PHENOLS

The oxidative coupling of phenols is biogenetically significant. This reaction can be performed *in vitro* by oxidants such as $FeCl_3$ and $K_3Fe(CN)_6$. Although both reagents are one-electron oxidants, disparate results often occur.

The oxidation of 2-naphthol by ferriccyanide occurs via an outer-sphere process in which no direct bonding between the substrate and the metal ion exists; the ensuing phenoxy radical is relatively free.

On the other hand, the complex having an ArO-Fe bond appears to intervene in the ferric chloride reaction. As the phenoxy radical remains coordinated to Fe, coupling can occur only at the carbon.