Aromatic and Heterocyclic Chemistry
4 Lectures

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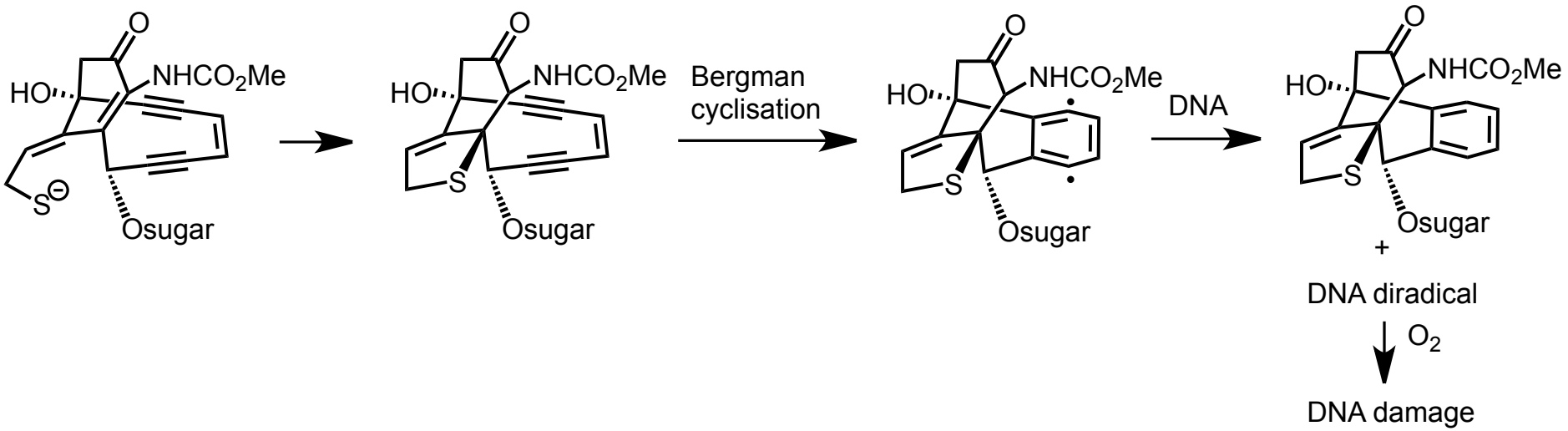
handout at: http://burton.chem.ox.ac.uk/teaching.html

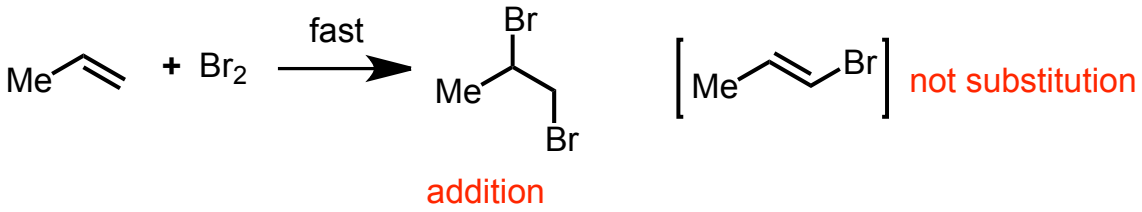


- *Advanced Organic Chemistry: Parts A and B*; Francis A. Carey, Richard J. Sundberg
- *Organic Chemistry*; Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers
- *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*; J. March
- *Frontier Orbitals and Organic Chemical Reactions*; I. Fleming
- *Heterocyclic Chemistry*; J. Joule, K. Mills, G. Smith
- *Aromatic Heterocyclic Chemistry*; D. Davies
- *Reactive Intermediates*; C. Moody and G. Whitham
- *Aromatic Chemistry*; M. Sainsbury
- *The Chemistry of C-C π-Bonds – Lecture notes*; Dr Martin Smith

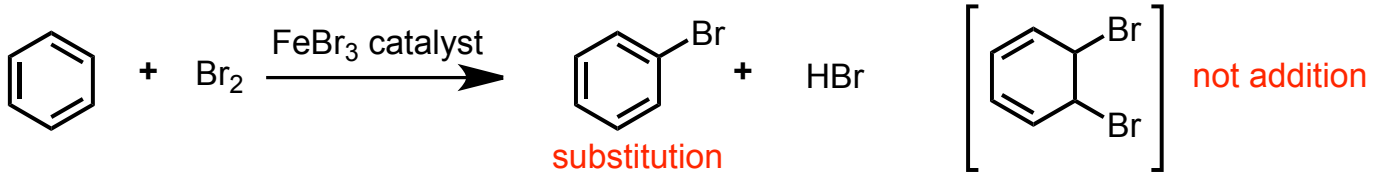
Synopsis

- The Origin of Aromaticity and General Characteristics of Aromatic Compounds
- Examples of Aromaticity
- Nucleophilic Aromatic Substitution
- Arynes
- Reactions with Metals: Ortho Metallation
- Introduction of Functional Groups
- Pyridine: Synthesis and Reactions
- Pyrrole, Thiophene and Furan: Synthesis and Reactions
- Indole: Synthesis and Reactions
- Reduction of Aromatics

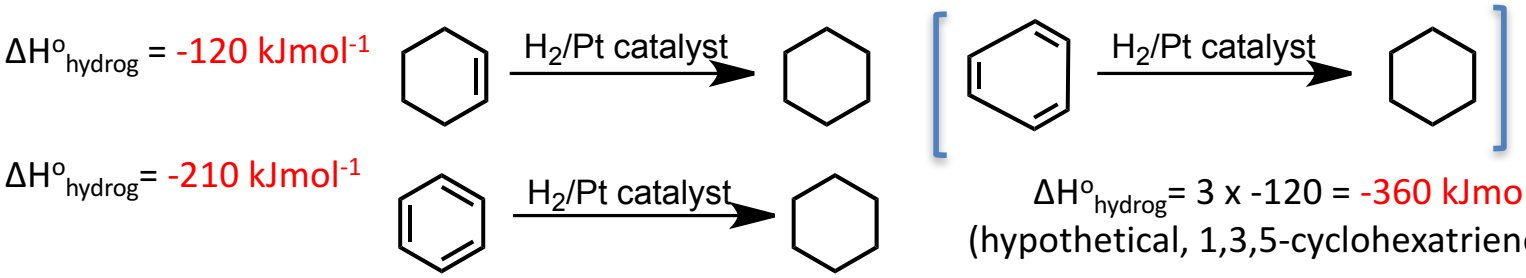
- typical reactions of alkenes



- typical reactions of benzene



- retains aromatic sextet of electrons in substitution reactions
- does not behave like a "normal" polyene or alkene
- benzene is both *kinetically* and *thermodynamically* very stable
- heats of hydrogenation



- benzene ≈150 kJmol^{-1} more stable than expected – (represents stability over hypothetical 1,3,5-cyclohextriene) – termed the *empirical resonance energy (values vary enormously)*
- we know that delocalisation is stabilising, but how much more stabilising is the delocalisation in benzene – should compare benzene with a real molecule – we will use 1,3,5-hexatriene
- require a theory which explains the stability of benzene

Understanding Aromaticity

- Hückel's Rule: *planar, monocyclic, completely conjugated hydrocarbons will be **aromatic** when the ring contains (4n +2) π-electrons (n = 0, 1, 2….positive integers)*

Corollary

- *planar, monocyclic, completely conjugated hydrocarbons will be **anti-aromatic** when the ring contains (4n) π-electrons (n = 0, 1, 2….positive integers)*

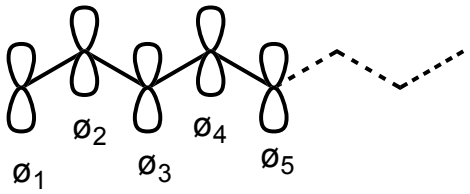
Hückel Molecular Orbital Theory (HMOT)

- applicable to conjugated planar cyclic and acyclic systems

- only the π-system is included; the σ-framework is ignored (in reality σ-framework affects π-system)

- used to calculate the wave functions (ψ_k) and hence *relative* energies by the LCAO method

i.e. $\psi_k = c_1\phi_1 + c_2\phi_2 + c_3\phi_3 + c_4\phi_4 + c_5\phi_5$ …..



- HMOT solves energy (E_k) and coefficients c_k
- there are now many more sophisticated methods for calculating the stabilisation energy in conjugated systems; however, HMOT is adequate for our purposes.

Understanding Aromaticity

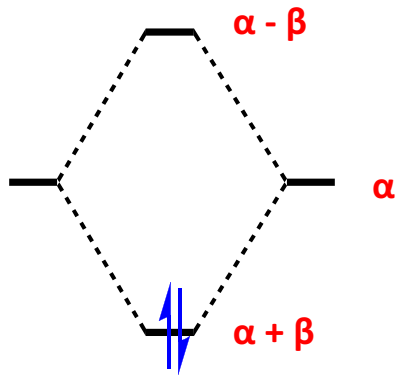
HMOT in Action

- For cyclic and acyclic systems: molecular orbital energies = $E_k = \alpha + m_j\beta$
- α = coulomb integral - energy associated with electron in an isolated 2p orbital (albeit in the molecular environment) – α is negative (stabilising) and is the same for any p-orbital in π-system
- β = resonance integral – energy associated with having electrons shared by atoms in the form of a covalent bond – β is negative (stabilising) and is set to zero for non-adjacent atoms.
- (all overlap integrals S assumed to be zero, electron correlation ignored)

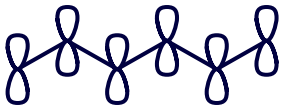
- linear polyenes $m_j = 2\cos[j\pi/(n+1)]$ j = 1, 2……n (n = number of carbon atoms in conjugated system)
- cyclic polyenes $m_j = 2\cos(2j\pi/n)$ j = 0, ±1, ±2……±[(*n*-1)/2] for odd *n*, ±*n*/2 for even *n*

Ethene

- two 2p atomic orbitals give 2π molecular orbitals
- $m_j = 2\cos(\pi/3)$ and $2\cos(2\pi/3)$ = 1 or -1 E = α ± β
- stabilisation energy $\mathbf{E_{stab}} = 2\alpha + 2\beta$

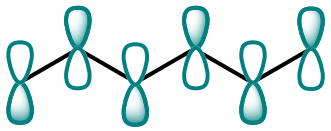
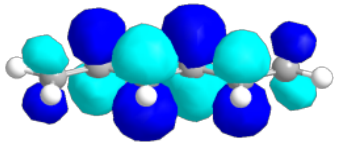
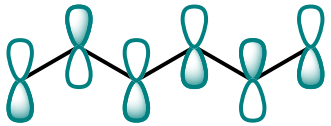
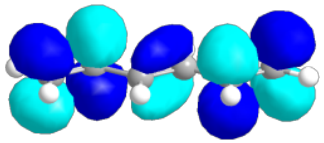
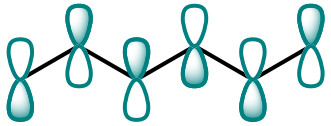
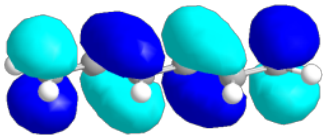
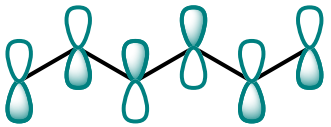
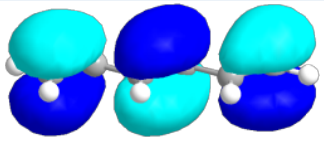
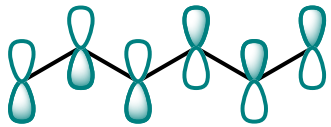
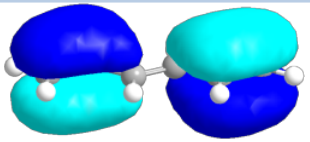
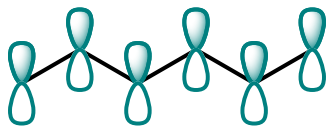
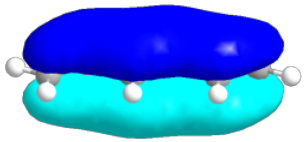


- 1,3,5-hexatriene vs benzene
- six 2p atomic orbitals give 6π molecular orbitals; *n* = 6, j = 1, 2, 3, 4, 5, 6



- m_j = 2cos(π/7) = 1.80 2cos(2π/7) = 1.25 2cos(3π/7) = 0.45.....
  and the corresponding negative values
- energy E = α + 1.80β α + 1.25β α + 0.45β α – 0.45β.....etc

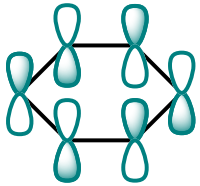
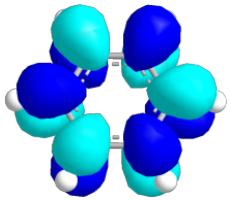
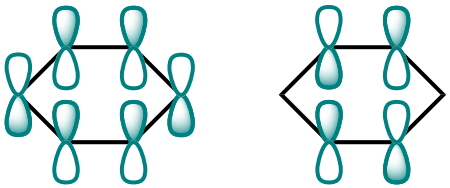
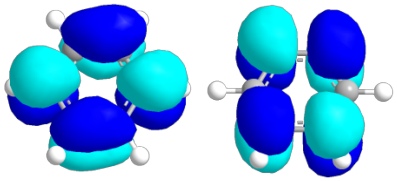
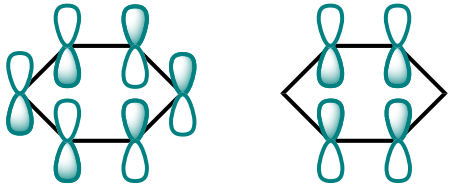
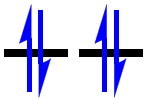
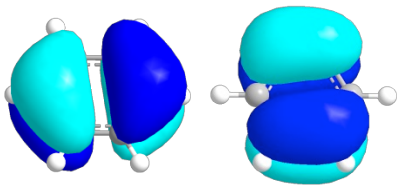
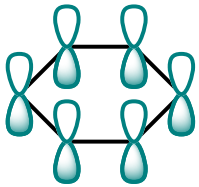
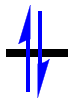
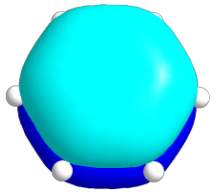
α

MO		no. nodes	energy		HMOT MO (calculated)
ψ_6		5	α - 1.80β	—	
ψ_5		4	α - 1.25β	—	
ψ_4		3	α - 0.45β	—	
ψ_3		2	α + 0.45β	↑↓	
ψ_2		1	α + 1.25β	↑↓	
ψ_1		0	α + 1.80β	↑↓	

- stabilisation energy = E_{stab}= 2(3α + 3.5β) **= 6α + 7β**
- stabilisation energy ethene = **2α + 2β**

- **Benzene** $m_j = 2\cos(2j\pi/n)$ $j = 0 \pm1, \pm[(n-1)/2]$ for odd n; $\pm n/2$ for even n
- six 2p atomic orbitals give 6π molecular orbitals; n = 6, j = 0 ±1, ±2, ±3
- $m_j = 2\cos(0) = 2$, $2\cos(\pm2\pi/6) = 1$, $2\cos(\pm4\pi/6) = -1$, $2\cos(\pm6\pi/6) = -2$
- energy E = α + 2β, α + β, α - β, α – 2β

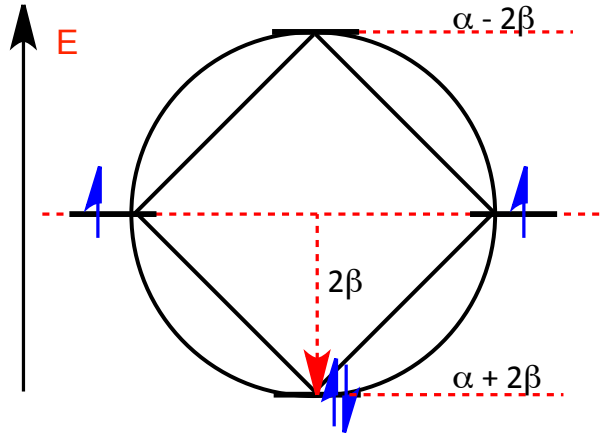
α

MO		no. nodes	energy		HMOT MO (calculated)
ψ_6		6	α - 2β		
$\psi_{4,5}$		4	α - β		
$\psi_{2,3}$		2	α + β		
ψ_1		0	α + 2β		

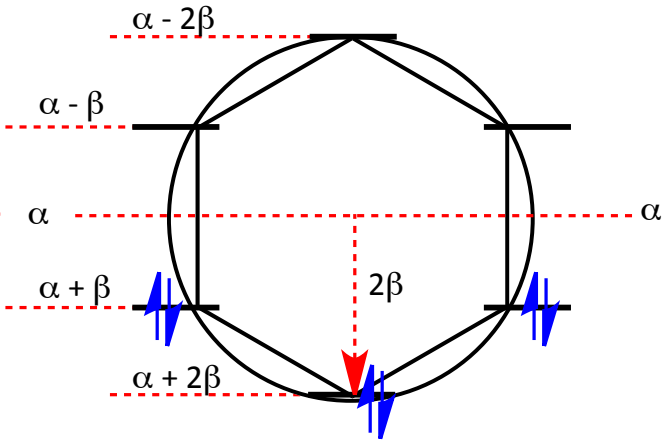
- stabilisation energy = E_{stab}= 2(α + 2β) + 4(α + β) **= 6α + 8β**; stabilisation energy w.r.t. 1,3,5-hexatriene **= β**
- HMOT predicts benzene is *more* stable than 1,3,5-hexatriene
- *aromatic compounds are those with a π-system lower in energy than that of acyclic counterpart*
- *anti-aromatic compounds are those with a π-system higher in energy than that of acyclic counterpart*

Frost-Musulin Diagram – Frost Circle

- simple method to find the energies of the molecular orbitals for an aromatic compound
- inscribe the regular polygon, with one vertex pointing down, inside a circle of radius 2β, centred at energy α
- each intersection of the polygon with the circumference of the circle corresponds to the energy of a molecular orbital



cyclobutadiene

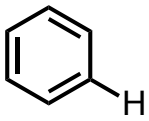


benzene

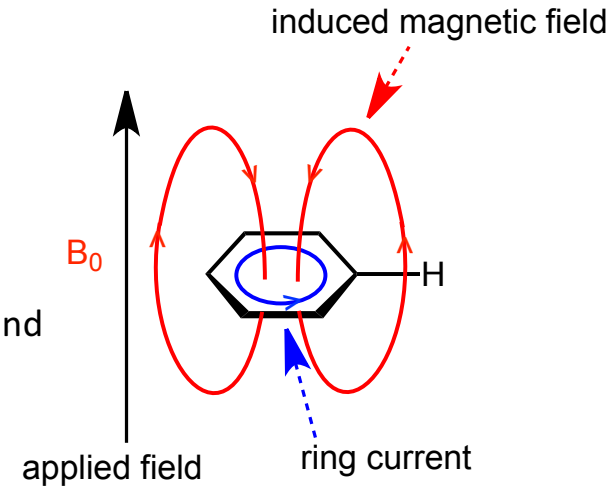
General Characteristics of Aromatic Compounds

- planar fully conjugates cyclic polyenes
- more stable than acyclic analogues
- bonds of nearly equal length i.e. not alternating single and double bonds
- undergo substitution reactions (rather than addition reactions)
- support a diamagnetic ring current - good test for aromatic character of a compound

δ_H = 5-6 ppm



δ_H = 7.26 ppm
aromatics δ_H = 7-8 ppm



Examples of Aromatic and Anti-Aromatic Compounds

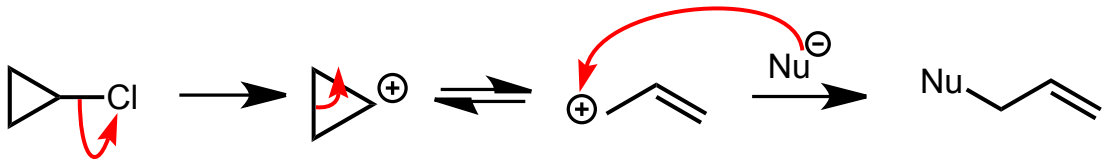
■ Hückel's rule [(4n +2) π-electrons for aromatic compounds [4n π-electrons for anti-aromatic compounds] holds for anions, cations and neutrals

Cyclopropenium cation

■ (4n +2), n = 0, 2π electrons; stabilisation energy = 2α + 4β – stabilisation energy of allyl cation = 2α + 2.8β

■ insoluble in non-polar solvents; 1 signal in ^{1}H NMR δ_H = 11.1 ppm - aromatic and a cation

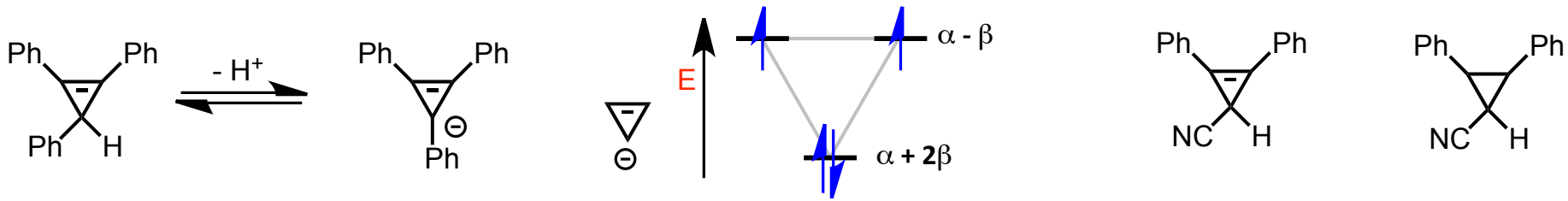
■ compare with cyclopropyl cation which is subject to rearrangement to the allyl cation



Cyclopropenium anion

■ (4n), n = 1, 4π electrons – anti-aromatic

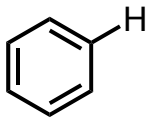
■ stabilisation energy E_{stab}= 4α +2β; stabilisation energy of allyl anion = 4α +2√2β



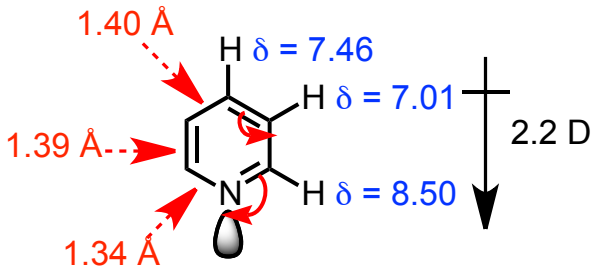
■ rate of proton exchange: cyclopropane/cyclopropene = 10000

Benzene

■ (4n +2), n = 1, 6π electrons δ_H = 7.26 ppm, planar molecule; bond length = 1.39 Å



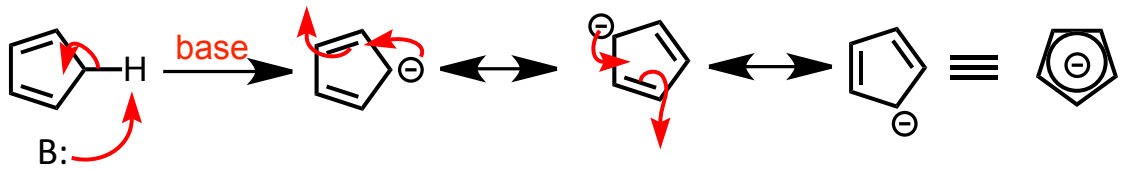
isoelectronic with pyridine

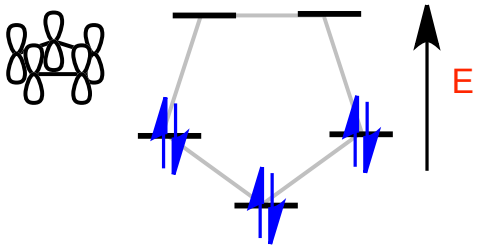


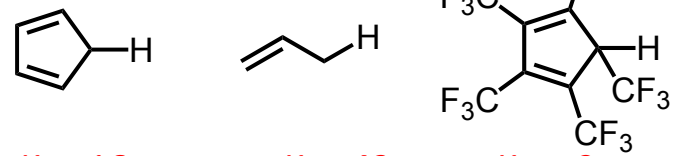
C-C	sp^3-sp^3	1.54 Å
C-C	sp^3-sp^2	1.50 Å
C-C	sp^3-sp	1.47 Å
C-C	sp^2-sp^2	1.46 Å
C-C	benzene	1.39 Å
C=C		1.34 Å
C≡C		1.21 Å

Cyclopentadienyl Anion

■ (4n +2), n = 1, 6π electrons







pK_a = 16 pK_a = 43 pK_a < -2

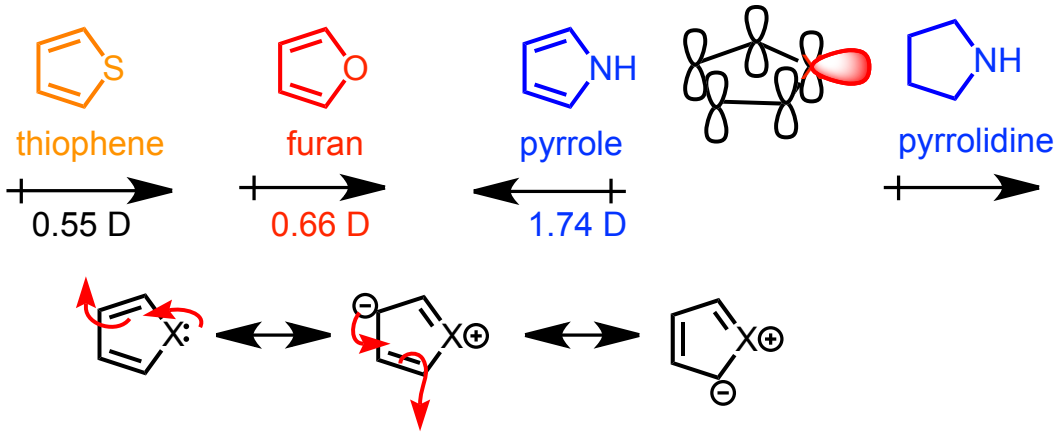
pK_a H_2O = 15.74 pK_a HNO_3 = -1.3

Examples of aromatic and antiaromatic compounds

- (4n +2), n = 1, 6 electrons
- cyclopentadienide anion is isoelectronic with furan pyrrole and thiophene

- in each case the (one of the) lone pair(s) is parallel to the p-orbitals and part of the π-system

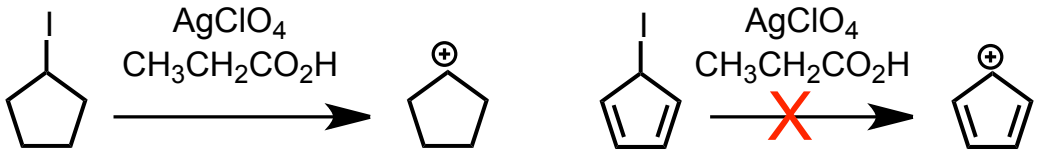
- all 3 are aromatic, show ring currents and undergo electrophilic aromatic substitution



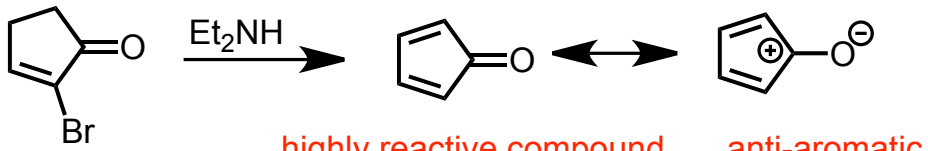
Examples of Aromatic and Anti-Aromatic Compounds

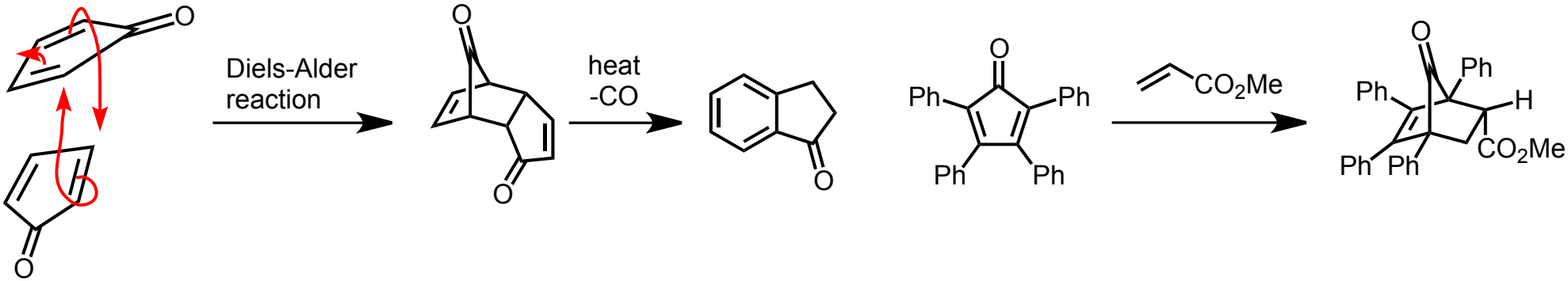
cyclopentadienyl cation

- (4n), n = 1, 4π electrons – anti-aromatic



cyclopentadienone

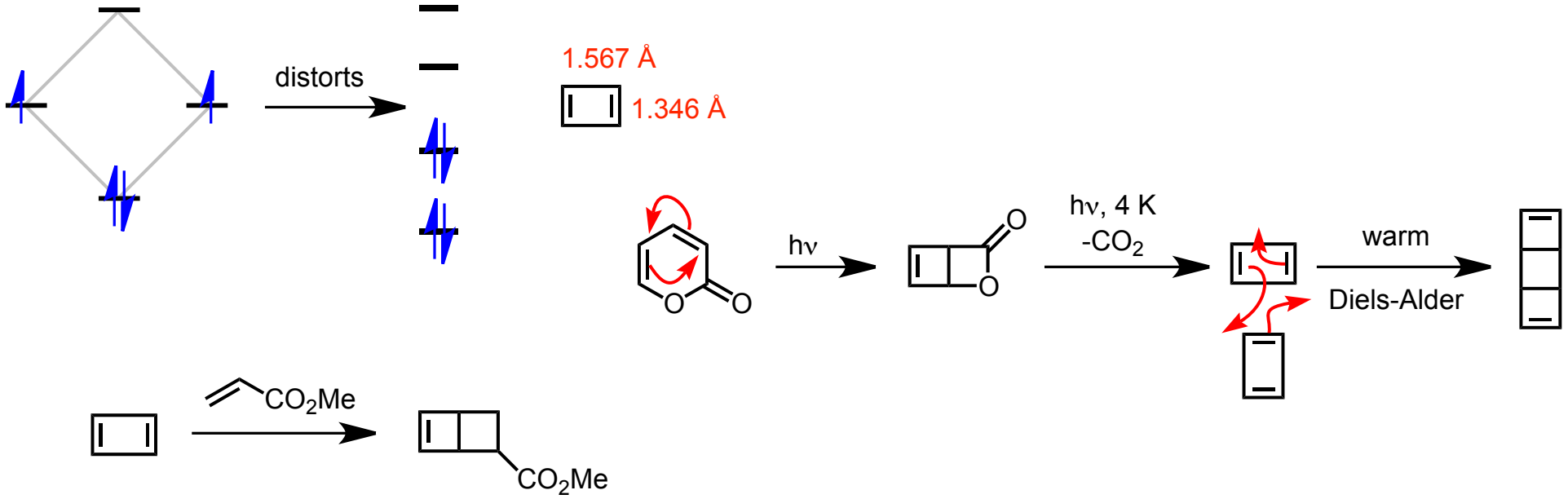




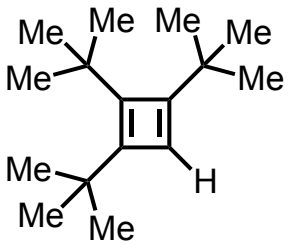
Examples of Aromatic and Anti-Aromatic Compounds

cyclobutadiene

- (4n), n = 1, 4π electrons – anti-aromatic
- HMOT predicts triplet ground state for cyclobutadiene – cyclobutadiene is actually a singlet ground state and is rectangular not square
- only possible to isolate at very low temperatures in an argon matrix



- cyclobutadiene can be stabilised with very bulky substituents
- stable up to 150 °C but very reactive towards O_2

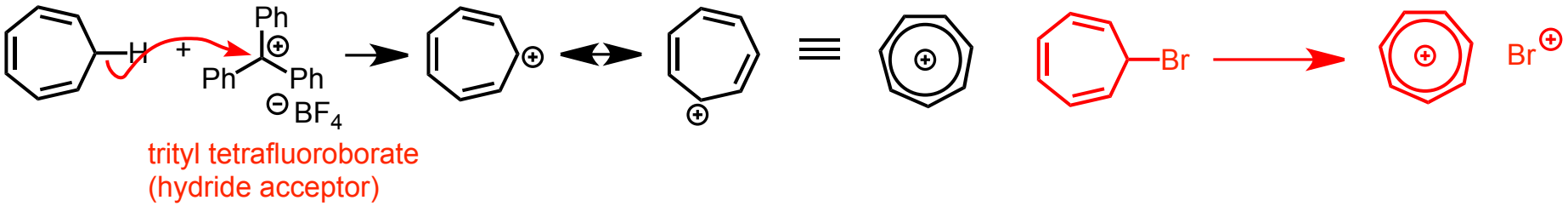


Examples of Aromatic and Anti-Aromatic Compounds

tropylium cation

- (4n +2), n = 1, 6π electrons – aromatic
- ionic compound mp 205 °C

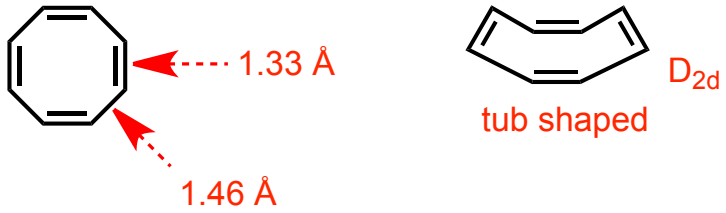
insoluble in non-polar solvents



trityl tetrafluoroborate
(hydride acceptor)

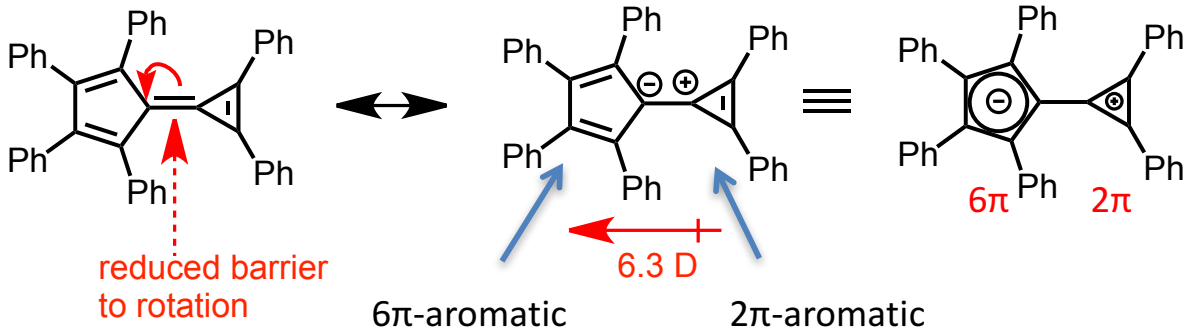
cyclooctatetraene

- non-aromatic, alternating bond lengths, distorts to avoid planar anti-aromatic conformation,
- normal reactivity of polyene

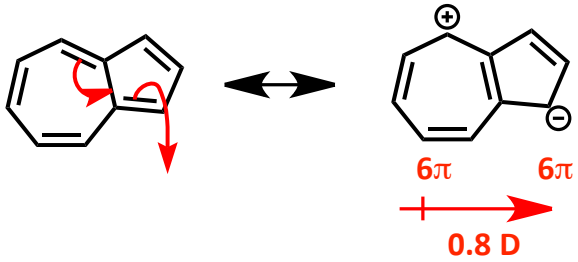


tub shaped

Examples of Aromatic and Anti-Aromatic Compounds



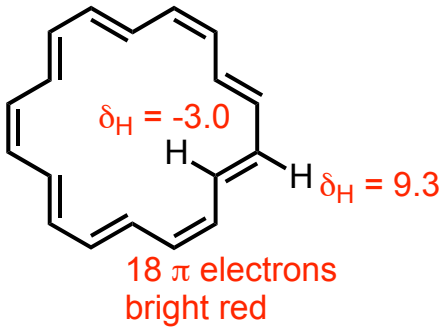
Azulene

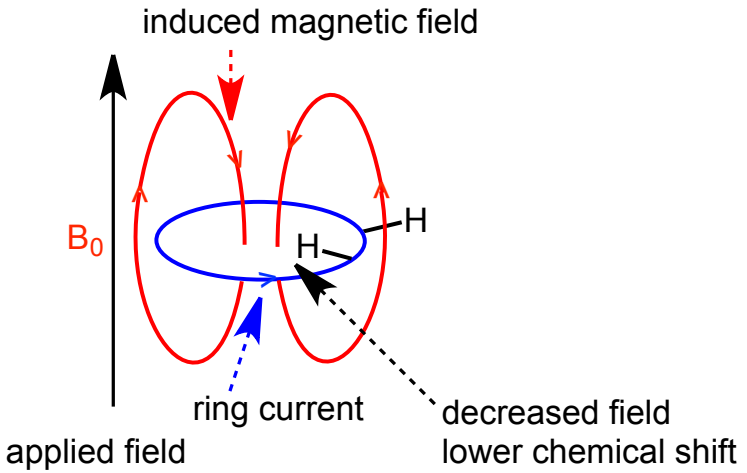


Lactarius indigo, the indigo milk cap

[18]-Annulene

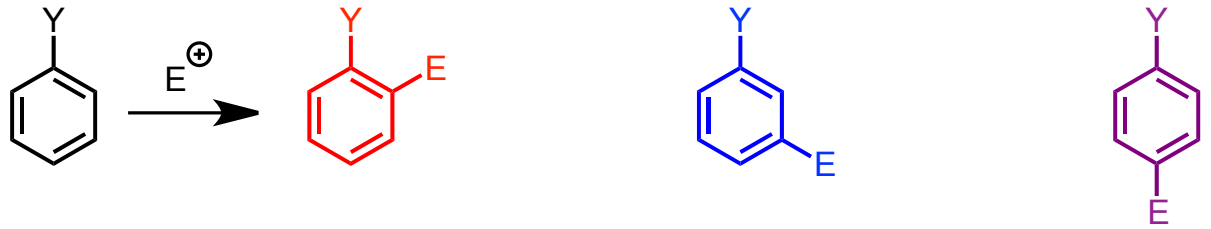
- (4n+2), n = 4, 18π electrons –aromatic
- ring large enough to be planar without steric congestion of inner protons
- 2 signals in ^{1}H NMR consistent with ring current





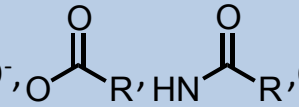
Electrophilic Aromatic Subsitution - Substituent Effects

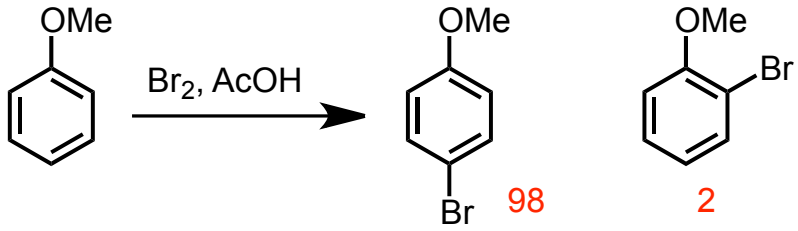
- substituent Y affects both the rate and regiochemistry of the reaction



- electron donating groups activate the aromatic ring (i.e. substrate reacts faster than benzene) *and* are *ortho* and *para* directing

ACTIVATING group means that the reaction of the substituted benzene is faster than that of benzene itself

Typical activating groups include: OH, O^-,  , OR, NH_2, NR_2, alkyl, Ph

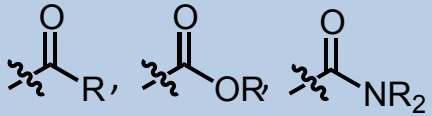


98 2

$k_{anisole} / k_{benzene} = 10^9$

- electron withdrawing groups deactivate the aromatic ring (i.e. substrate reacts slower than benzene) *and* are *meta* directing

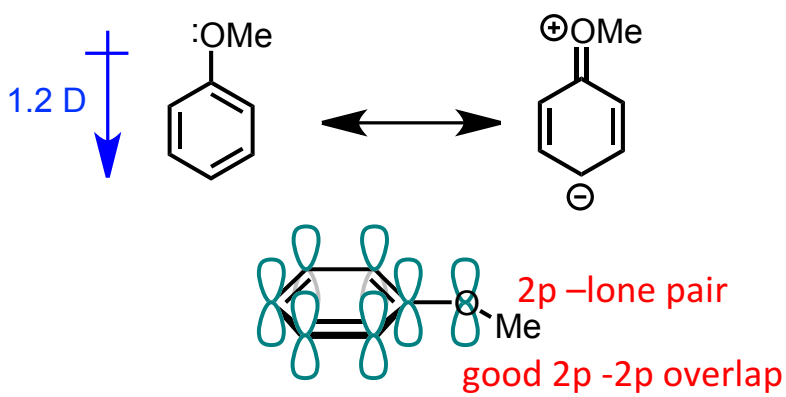
DEACTIVATING group means that the reaction of the substituted benzene is slower than that of benzene itself

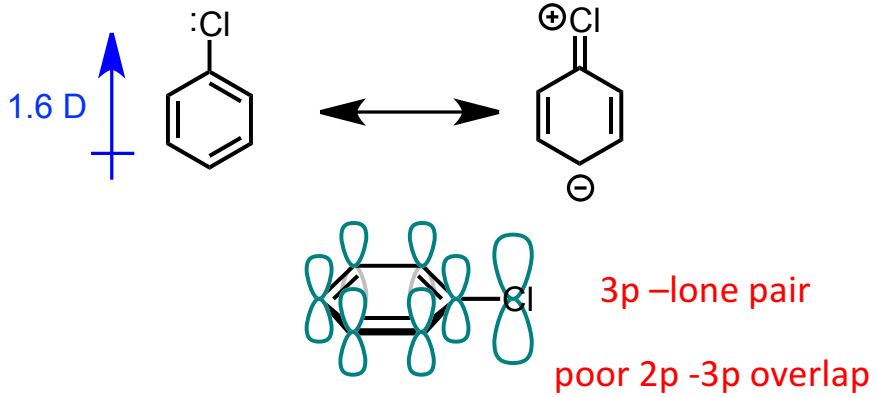
Typical deactivating groups include: R_3N^+, CF_3, NO_2, SO_3H, CN, O^-, 

- halogens are mildly deactivating and direct *ortho* and *para*

Halogens

- mildly deactivating as they are electronegative and withdraw electron density from the ring through the σ-framework (falls off with distance)
- halogens direct ortho and para as they have lone pairs in high energy orbitals which stabilise the intermediates for ortho/para attack





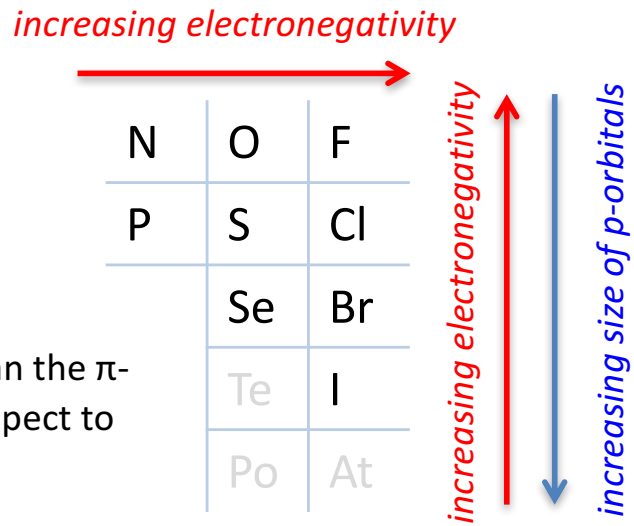
MeO – overall electron donating on benzene ring

Cl – overall electron withdrawing on benzene ring

- both oxygen and chlorine are electronegative

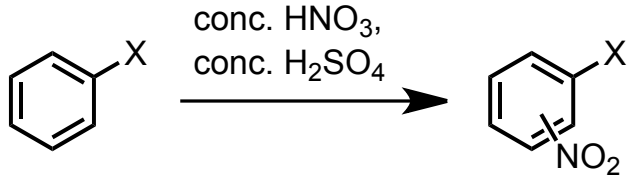
- with anisole the σ-electron withdrawing of the oxygen is less than the π-donation of the oxygen 2p lone pair and anisole is activated with respect to benzene

- with chlorobenzene the σ-electron withdrawing of the chlorine is greater than the π-donation of the chlorine 3p lone pair and chlorobenzene is deactivated with respect to benzene



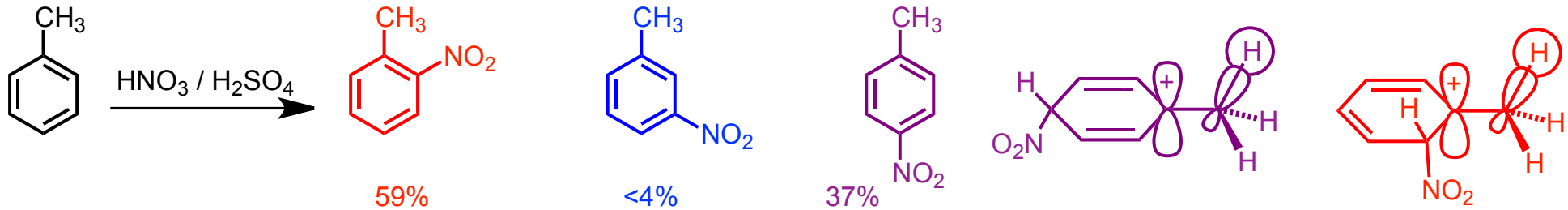
Nitration of halobenzenes

- why does fluorobenzene react faster than than the other halobenzenes?
- why does fluorobenzene give the largest amount of the *para* isomer?



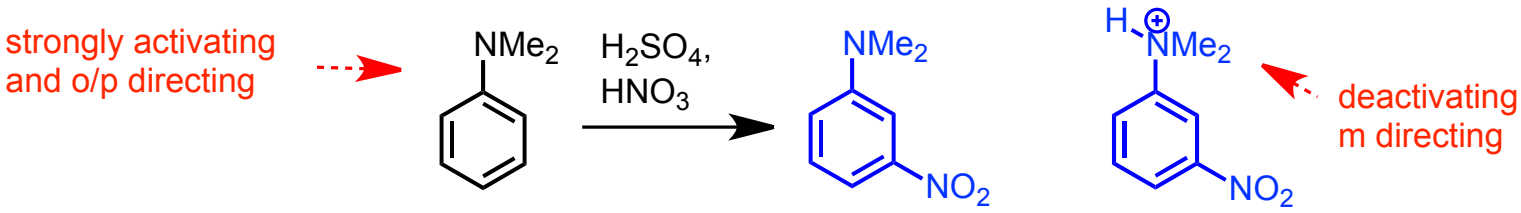
	product distribution %			$k_{ArX}/k_{benzene}$
	ortho	meta	para	
PhF	12	-	87	0.18
PhCl	30	0.9	69	0.064
PhBr	37	1.2	62	0.060
PhI	38	1.8	60	0.12

Nitration of toluene



- Me is an electron donating group and hence an activating group
- Wheland intermediate for *ortho* / *para* attack is stabilised by hyperconjugation – $\sigma_{CH} \rightarrow \pi$

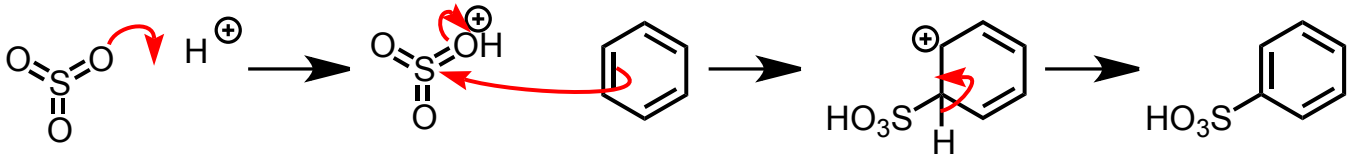
Nitration of dimethyl aniline



Ipso attack and reversible reactions

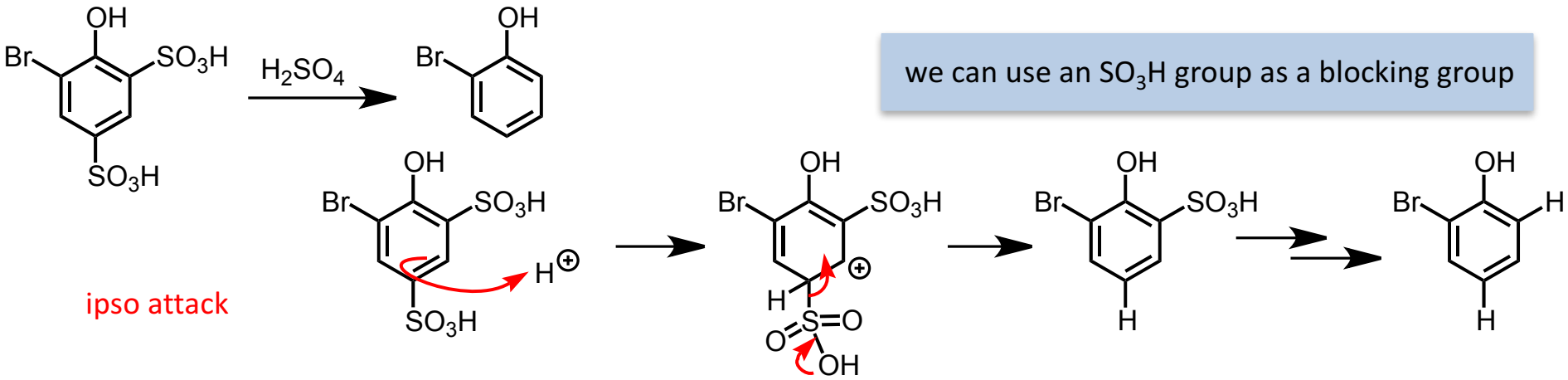
- electrophilic aromatic substitution is generally an irreversible process all of the above arguments with regard to *ortho*, *meta* and *para* ratios have been based on the irreversibility of the process
- i.e. the reactions are under kinetic control - but there are some exceptions
- not all electrophilic aromatic substitution reactions are under kinetic control
- sulfonation - usual reaction conditions: conc. H_2SO_4 with SO_3

sulfonyl group is electron withdrawing so we only have mono-substitution

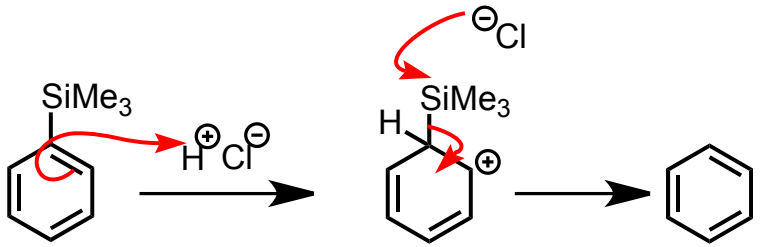


- at high temperatures with dilute H_2SO_4 – sulfonation is reversible
- attack by an electrophile at a position which already carries a non-hydrogen substituent is termed *ipso-substitution*

we can use an SO_3H group as a blocking group

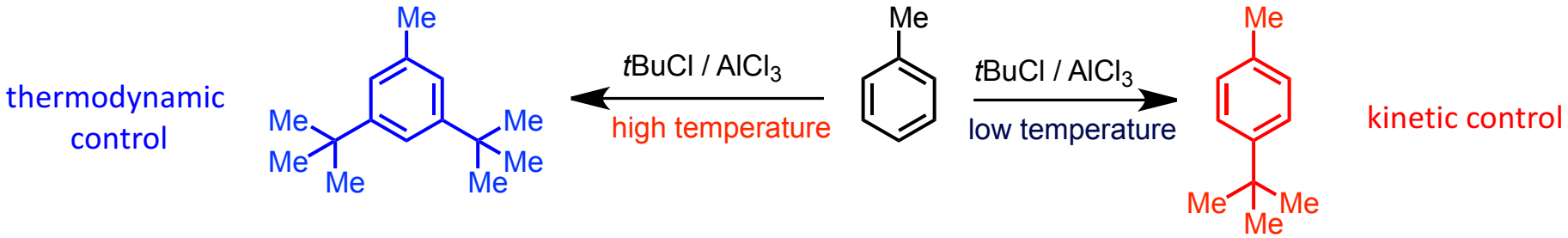


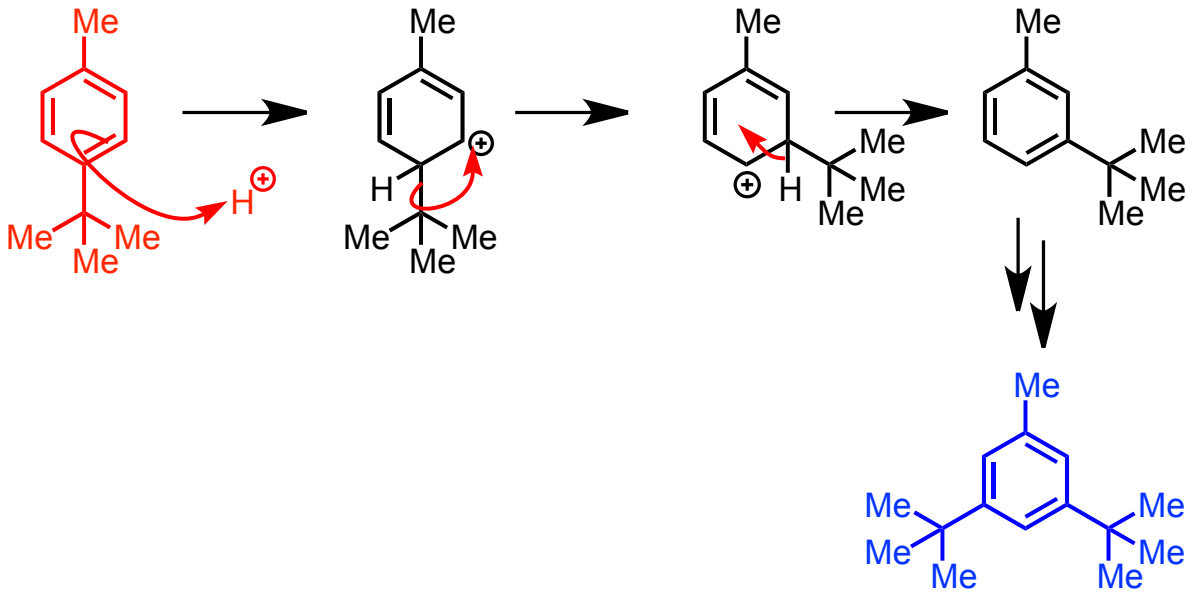
Ipso attack – *attack at position already carrying a substituent*



+ Me_3SiCl

10000 times faster than proton exchange in benzene
Si stabilises a β-cation – see organoelement course in Hilary

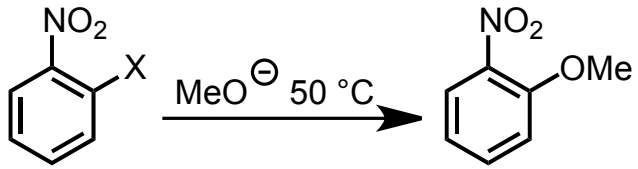




Nucleophilic Aromatic Substitution

S_NAr – Addition – Elimination Mechanism

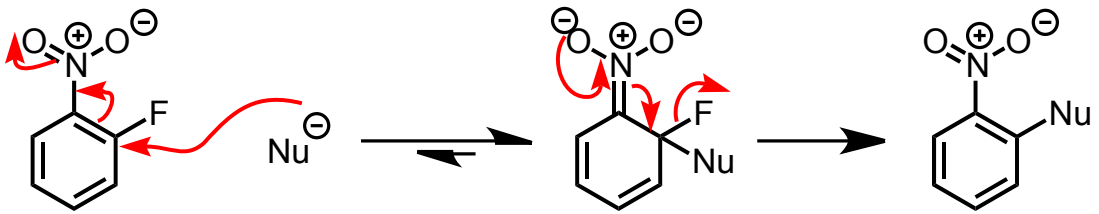
■ for halogens as leaving groups, rate of reaction usually follows $k_F > k_{Cl} > k_{Br}$ (c.f. rate of S_N2 reactions $k_I > k_{Br} > k_{Cl} > k_F$)



X =	F	Cl	Br	I
k_{rel}	2810	3.1	2.1	1

■ rate determining step is generally attack of nucleophile on aromatic ring therefore bond strength to leaving group is not so important in influencing the rate

■ fluorine is the most electronegative element and enhances the electrophilicity of the carbon being attacked increasing the rate of attack by the nucleophile



1st step usually rate determining

rate = k[substrate][nucleophile]

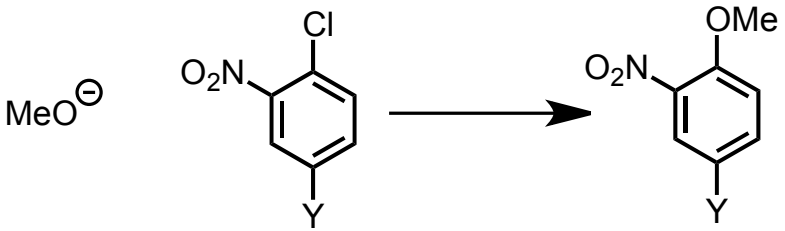
■ leaving group ability does depend on the nucleophile, nevertheless leaving groups can broadly be divided into three classes:

good: F, NO_2, Me_3N^+, OTs, Me_2S^+ medium: Cl, Br, I, OR, OAr, SR, SO_2R poor: NMe_2, H

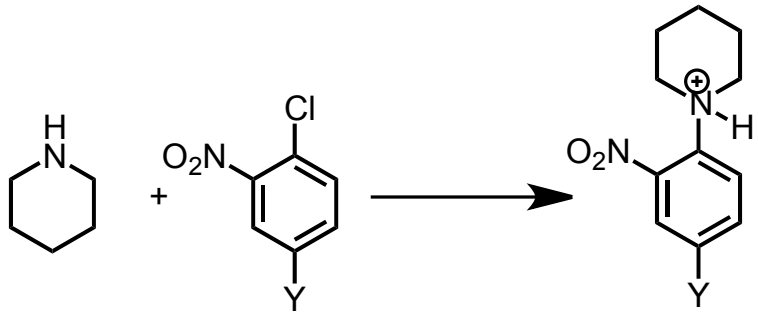
Nucleophilic Aromatic Substitution

- electron withdrawing groups ortho/para to leaving group enhance rate
- electron donating groups ortho/para to leaving group retard rate
- substituents meta to the leaving group have less influence

- the activating group

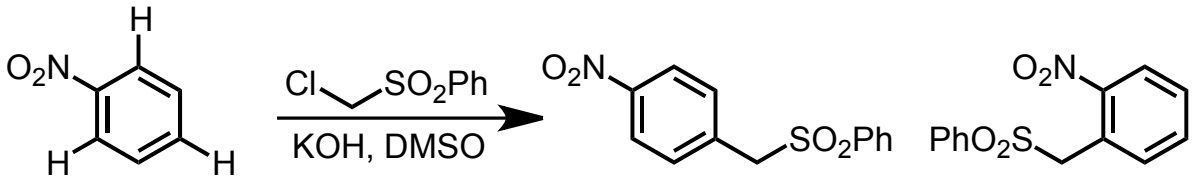


Y	NO_2	Me_3N^+	SO_2Ph	O=CPh	CF_3	H
k_{rel}	114000	2130	18400	2700	800	1

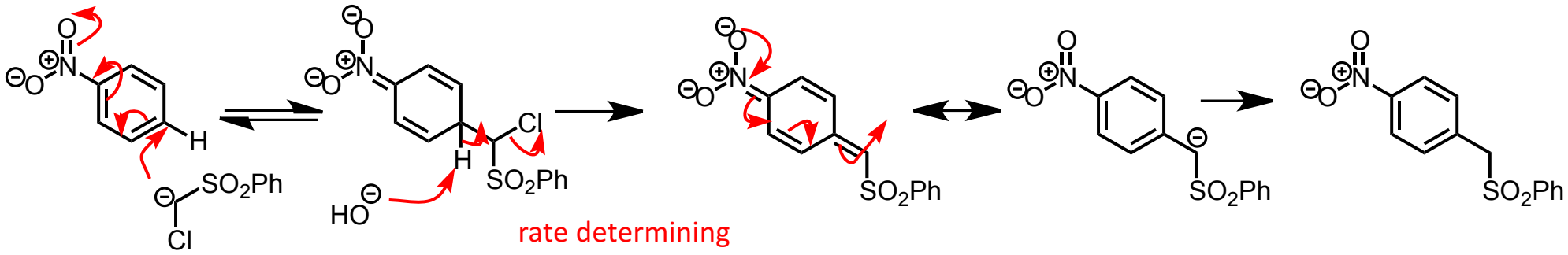


Y	CN	OMe	Br
k_{rel}	6000	0.25	10

- vicarious Nucleophilic Substitution - (nucleophilic substitution of hydrogen)

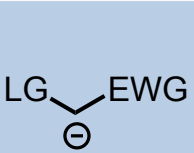


mechanism



rate determining step

- rate determining step is elimination of H-X (HCl) from σ-adduct

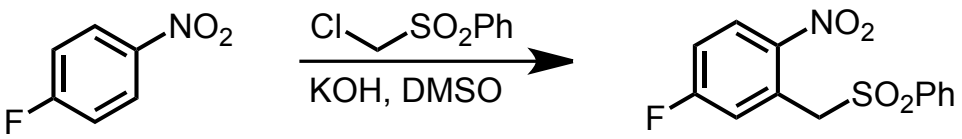


for VNS require a nucleophile which carries a leaving group

- LG = Cl, Br, PhO, PhS, RO^- etc; EWG = SO_2Ph, SO_2NR_2, SO_2OPh, $POPh_2$, CN, CO_2Et

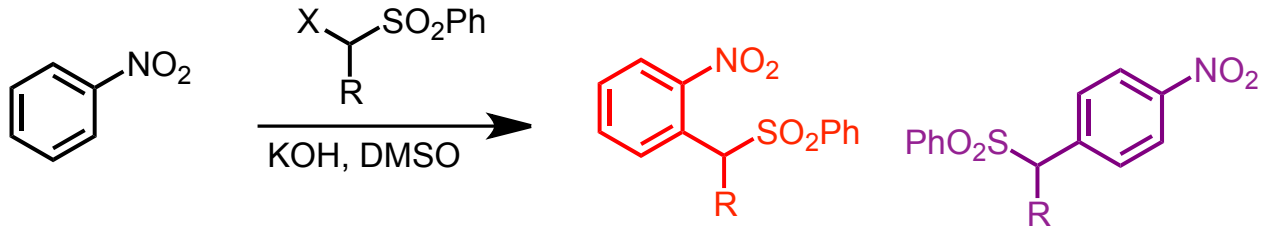
- Vicarious Nucleophilic Substitution

- orientation of addition depends on: structure of the carbanion; structure of the arene; reaction conditions



18% low yield due to competing S_NAr of fluoride

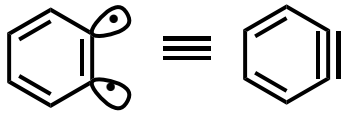
- for attack on nitrobenzene, as the bulk of the nucleophile increases the amount of *para* isomer increases



X	R	yield / %	*ortho*	*para*
F	H	63	74	26
Cl	H	75	53	47
Cl	Et	68		100
Cl	Ph	93		100

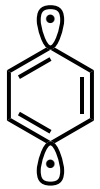
Arynes

■ removal of two hydrogen atoms from benzene leaving two electrons to be distributed between two orbitals gives rise to the various arynes



ortho-benzyne
(benzyne)
relative energy = 0 kJmol^{-1}

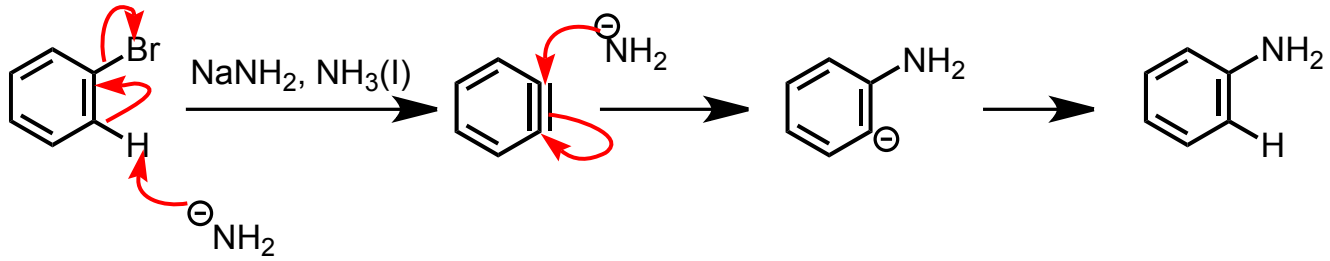
meta-benzyne
relative energy
ca. 64 kJmol^{-1}



para-benzyne
relative energy
ca. 130 kJmol^{-1}

ortho-benzyne

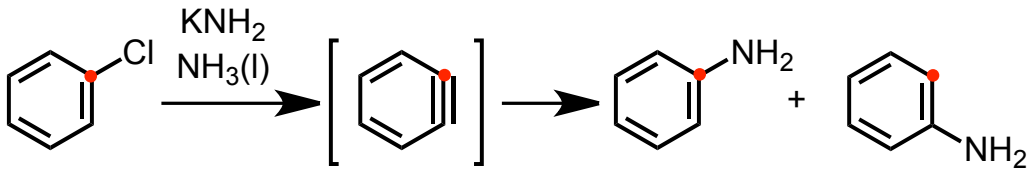
Synthesis



Evidence

■ IR spectrum of benzyne in an argon matrix shows C-C bond is 0.05 Å shorter than in benzene

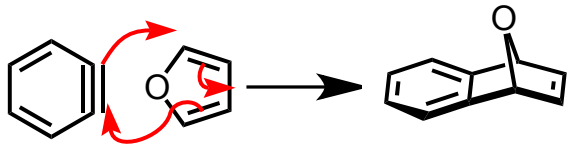
■ Roberts isotope labelling experiment – disproves direct substitution or S_NAr addition/elimination mechanism



1:1 mixture • = ^{14}C

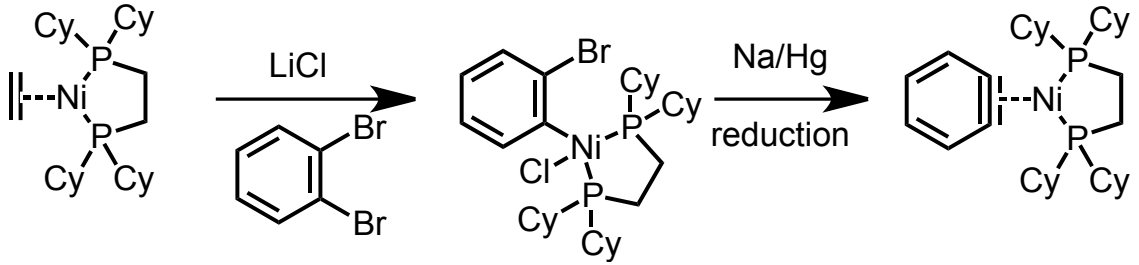
Arynes

- trapping experiments



Diels-Alder reaction

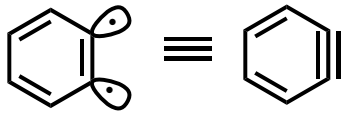
- isolation of complexes



oxidative addition
then ligand substitution

Structure of ortho-benzyne

- best represented as an alkyne with a very strained triple bond



- benzyne has a very small HOMO-LUMO gap (the “triple” bond is very weak)

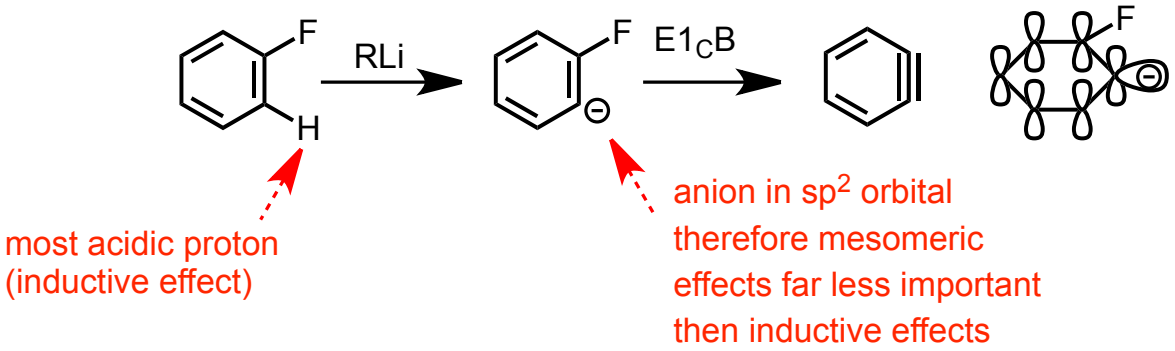
- the LUMO energy is very low and arynes are very electrophilic; they are uncharged their reactions tend to be dominated by orbital control (i.e. they are very “soft”)

- carbene like – two electrons in two orbitals

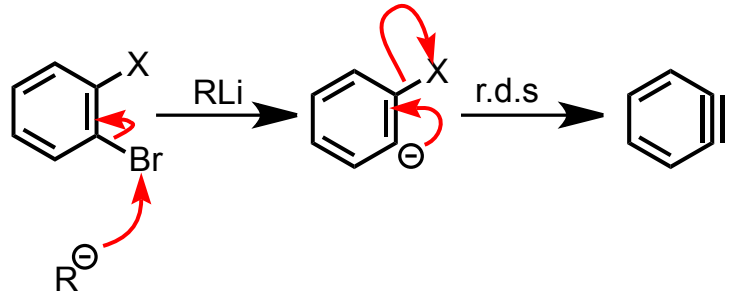
Arynes

Generation

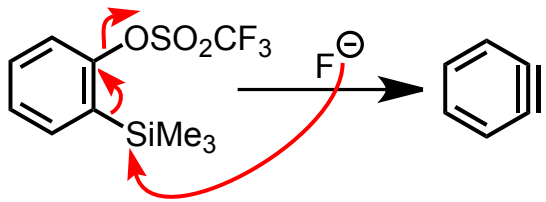
- relative reactivity for formation of benzyne with alkyl lithiums by deprotonation is F > Cl > Br > I; actual rate of generation of benzyne depends on solvent, base and leaving group

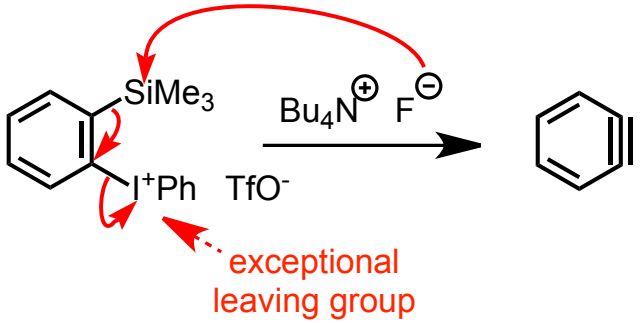


- lithium halogen exchange is very fast for Br and I and loss of X^- is r.d.s. hence rate is Br>Cl>F



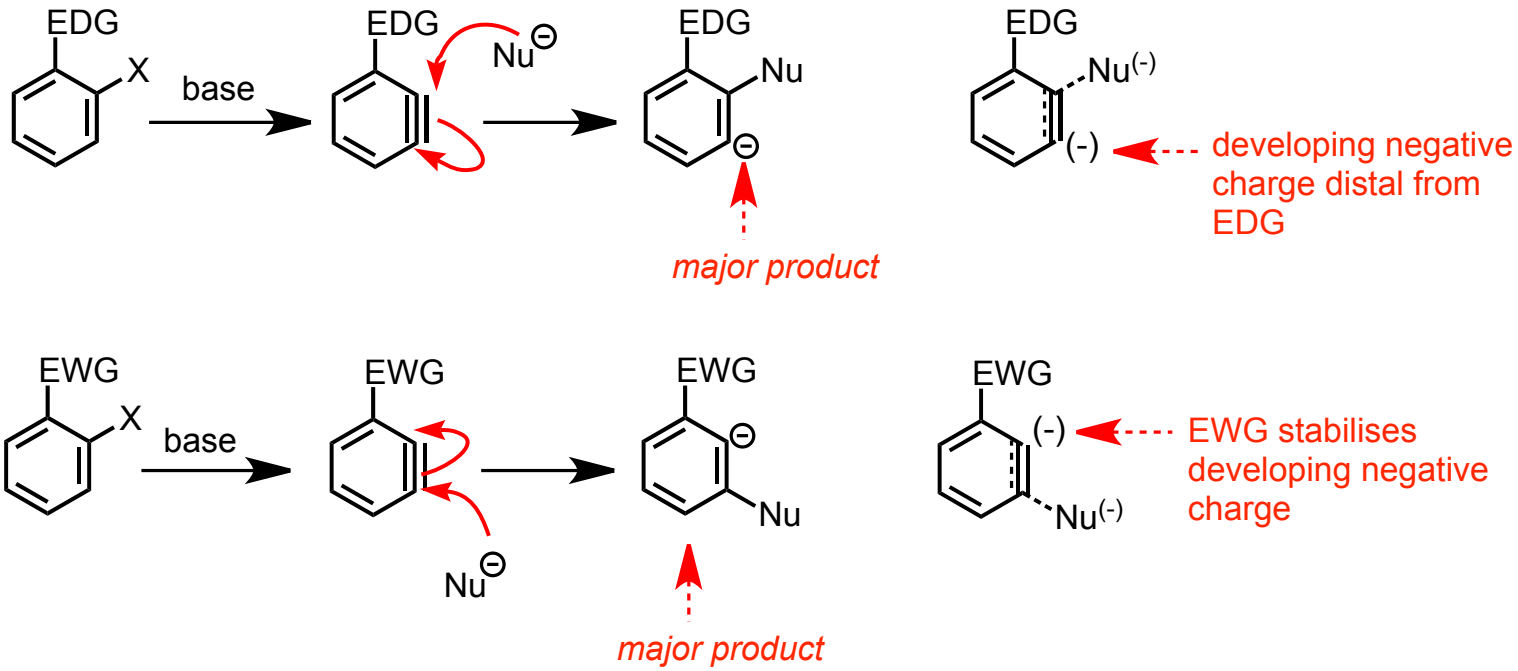
- mildest method of benzyne generation involves hypervalent iodine intermediate





Arynes

■ Orientation of attack on arynes from *ortho*-disubstituted substrates can be rationalised by a charge-control model – recently a more sophisticated model involving aryne distortion has been proposed.

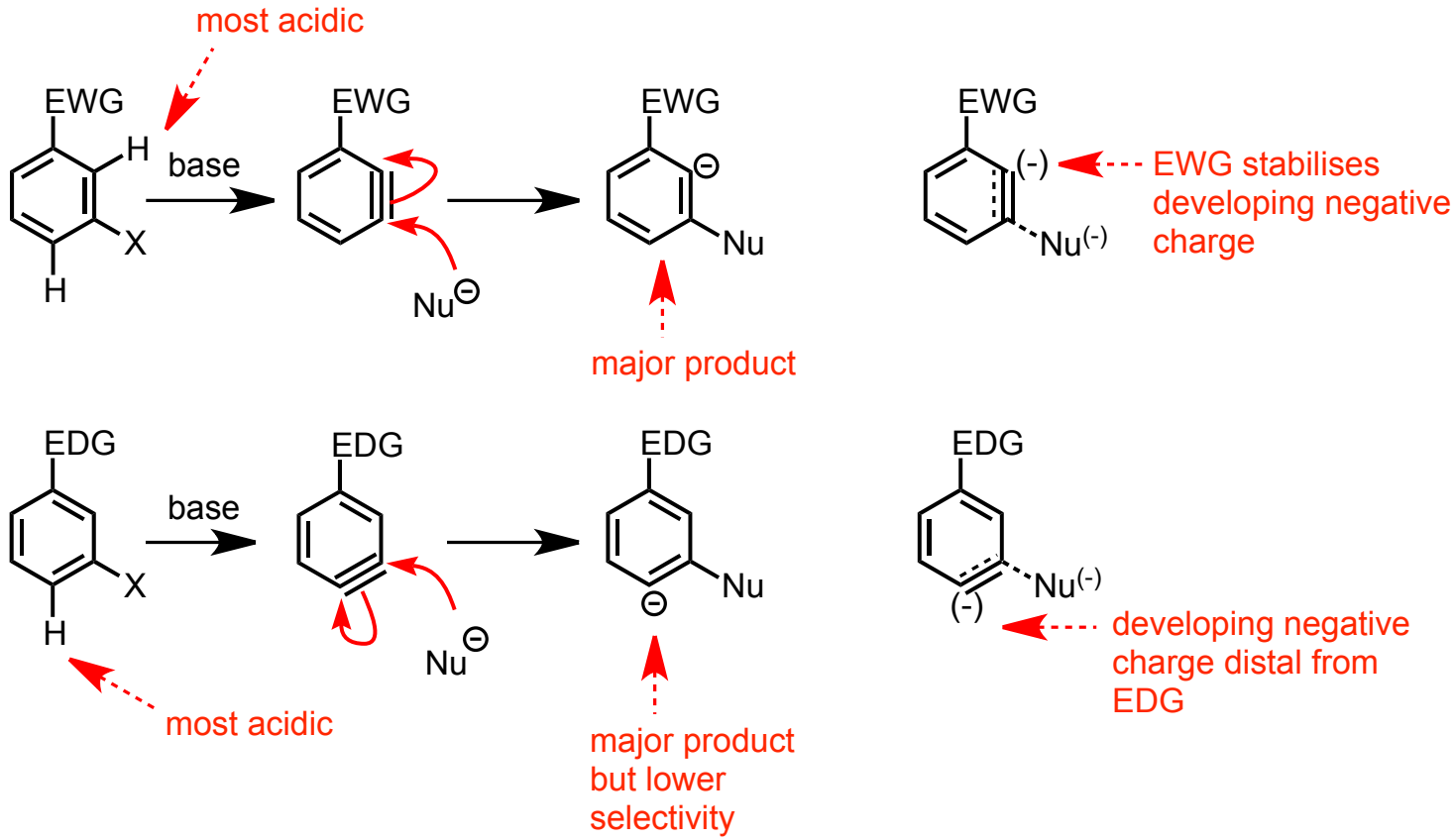


Note: EWG and EDG in the above examples refer to inductive effects

■ aryne orbitals are orthogonal to the aromatic π-system hence substituents exert influence inductively through σ-framework

Arynes

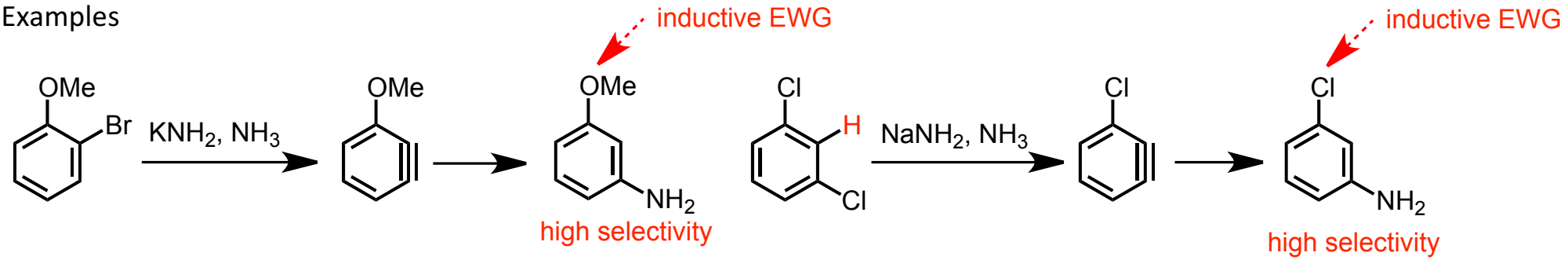
- Orientation of attack on arynes from *meta*-disubstituted substrates

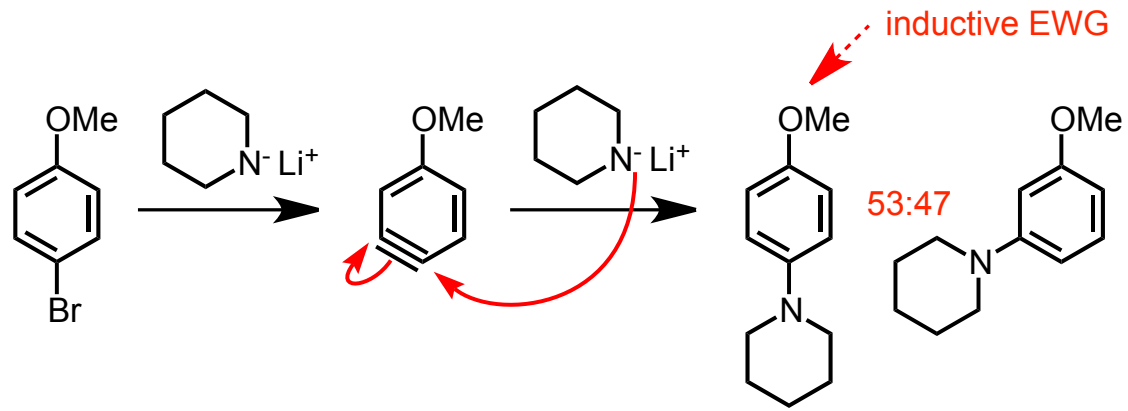


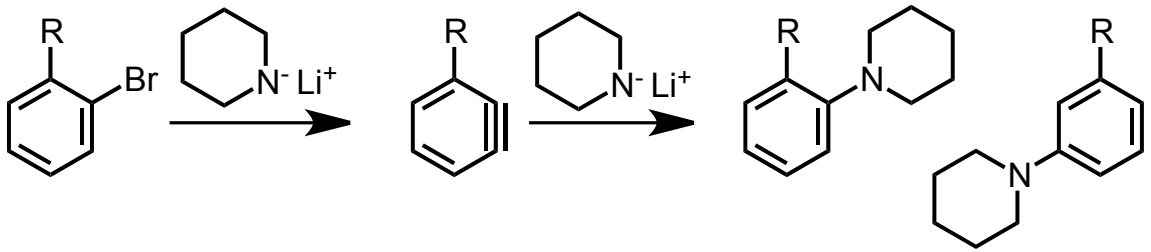
Note: EWG and EDG in the above examples refer to inductive effects

Arynes

Examples





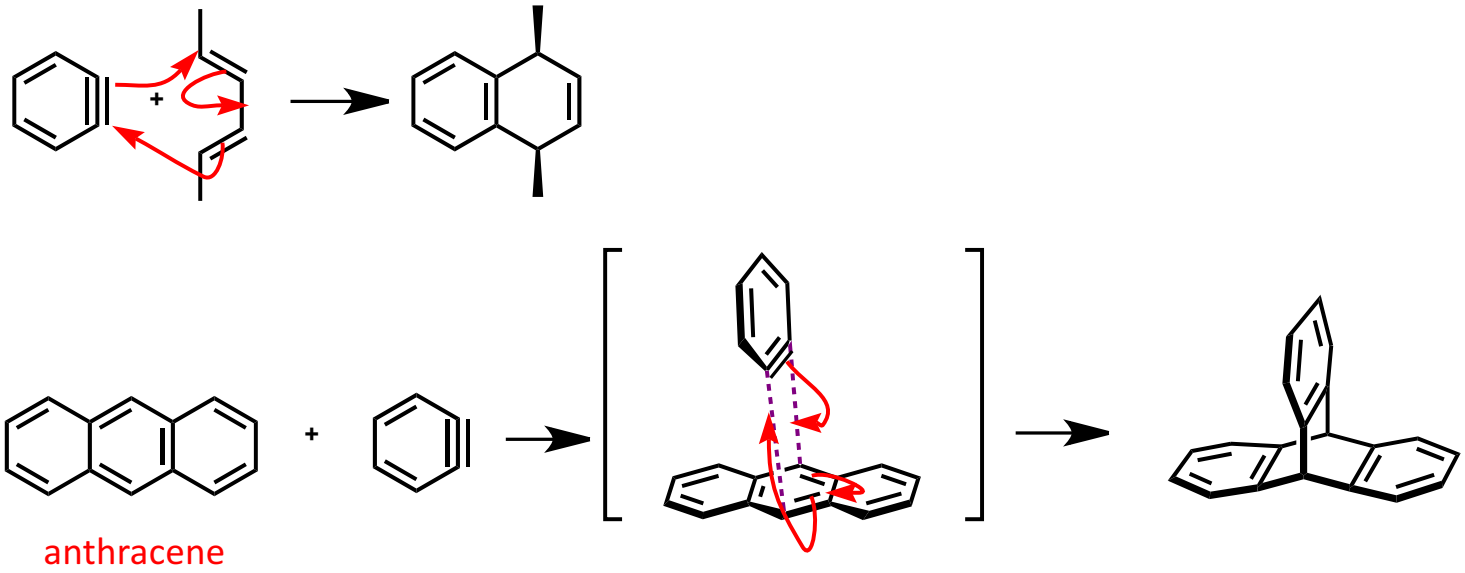


R = Me, 34:66
R = *i*Pr, 4:96

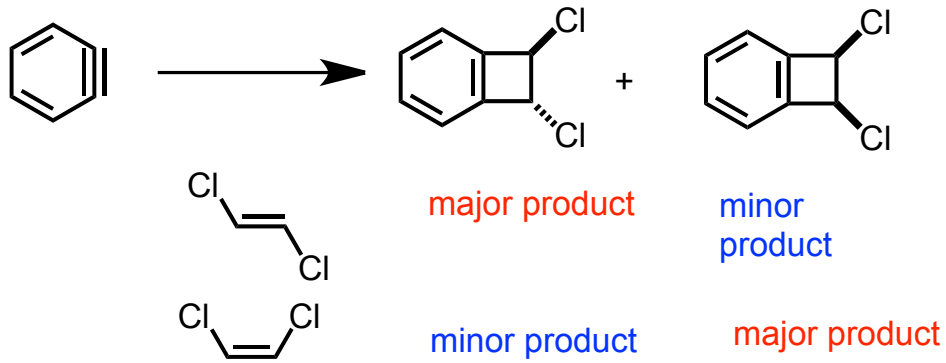
R = mild inductive EDG
but when R = *i*Pr, sterics win

Arynes

- Cycloaddition reactions of benzyne

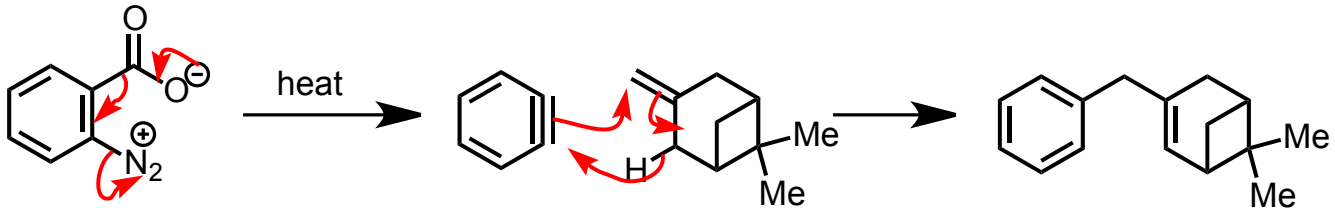


- 2+2 of benzyne is not completely stereospecific – probably a diradical mechanism



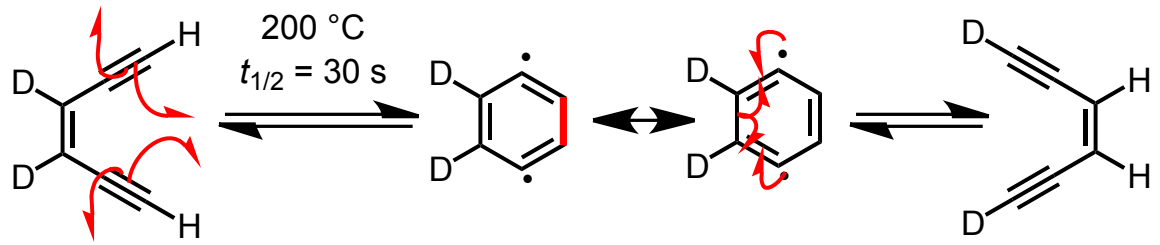
Arynes

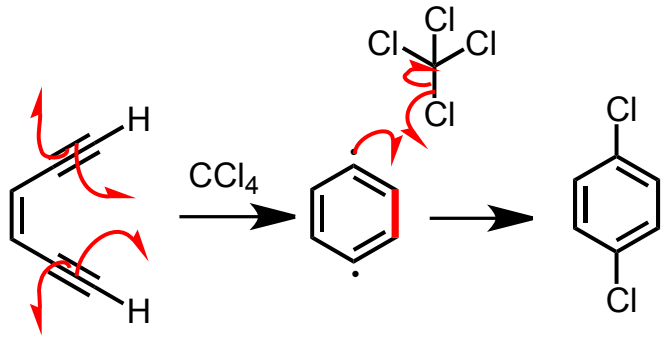
- ene reaction (a group transfer reaction)



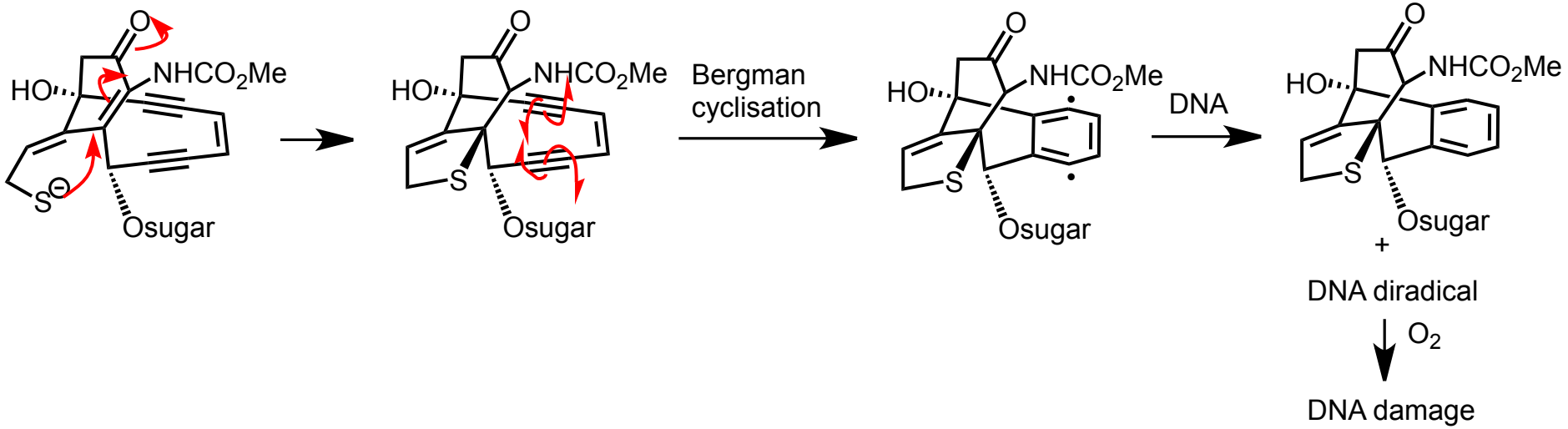
para-benzyne

- the Bergman cyclisation





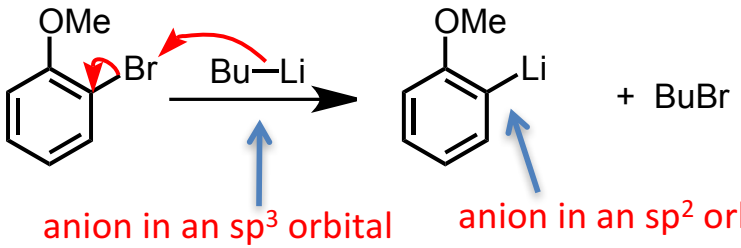
- mechanism of action of calicheamicin γ_1^I

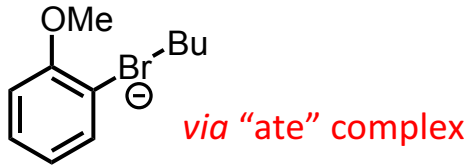


Aromatic organometallics

Ortho-directed electrophilic aromatic substitution

■ *ortho*-lithiation by lithium halogen exchange – faster then deprotonation **and** generally requires an organolithium base an aryl / alkenyl bromide or iodide.



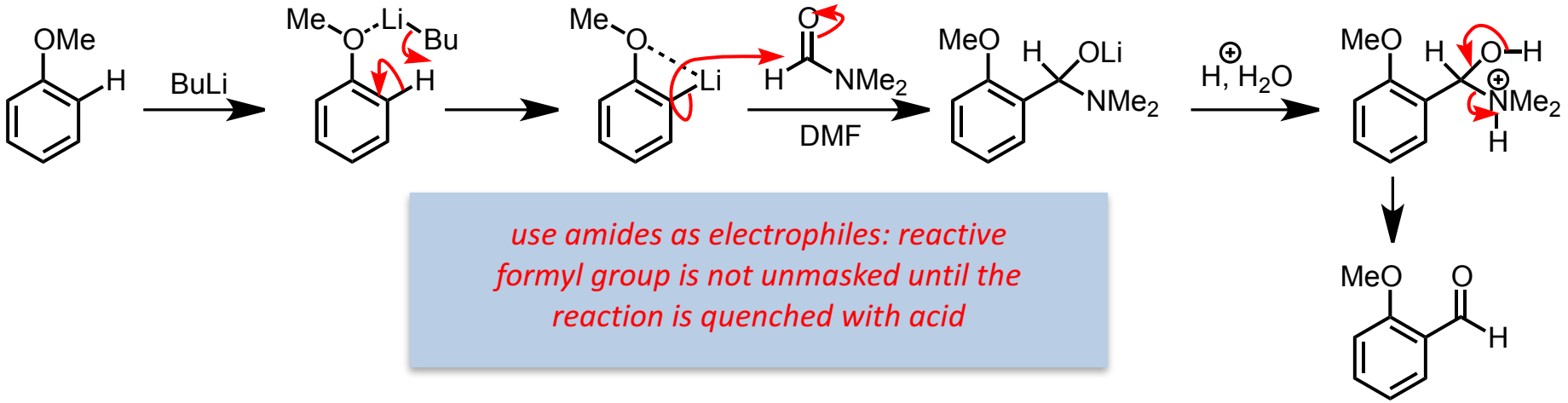


■ mechanism involves attack of alkyl lithium at the halogen *via* an intermediate “ate” complex

■ reaction is an equilibrium process which favours the more stable anion (remember, anion order is $sp^3>sp^2>sp$ – the stability of the anion is in the order of the pK_a of the corresponding hydrocarbon)

■ in the above example an sp^3 anion (butyl lithium) gives an sp^2 anion

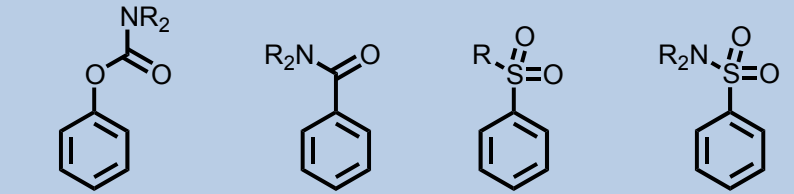
■ directed *ortho*-lithiation



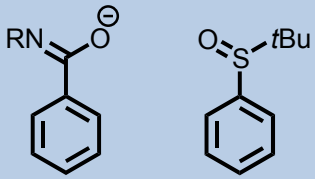
use amides as electrophiles: reactive formyl group is not unmasked until the reaction is quenched with acid

increasing ability to direct *ortho*-lithiation

condition dependent order

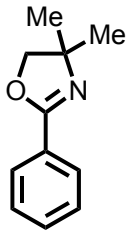


O-carbamates 3° amides sulfones sulfonamides

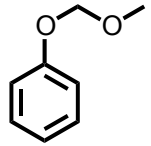


2° amides sulfoxides

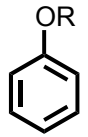
most powerful directors



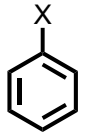
oxazloines



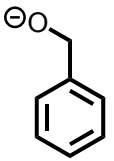
MOM ethers



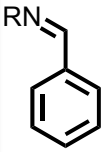
ethers



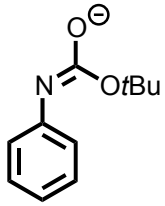
halogens



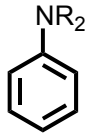
benzylic alkoxides



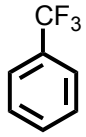
imines



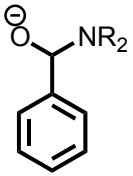
N-carbamates



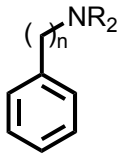
anilines



trifluoromethyl



aminomethyl



remote amines

-78 °C -78 °C -78 °C -78 °C -50 °C -20 °C 0 °C >0 °C >20 °C

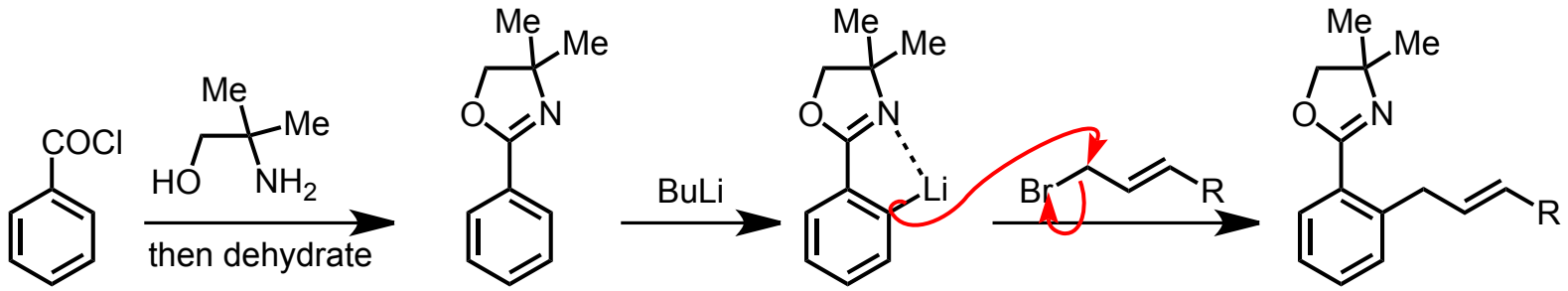
temperature (°C) of *ortho*-lithiation with RLi in THF or ether

Adapted from: J. Clayden in *"Organolithiums: Selectivity for Synthesis"*, Pergamon, Oxford 2002.

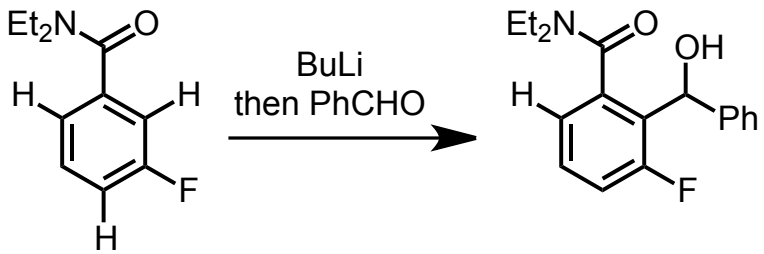
Aromatic organometallics

Directed *ortho*-lithiation

- application: *ortho*-allylation



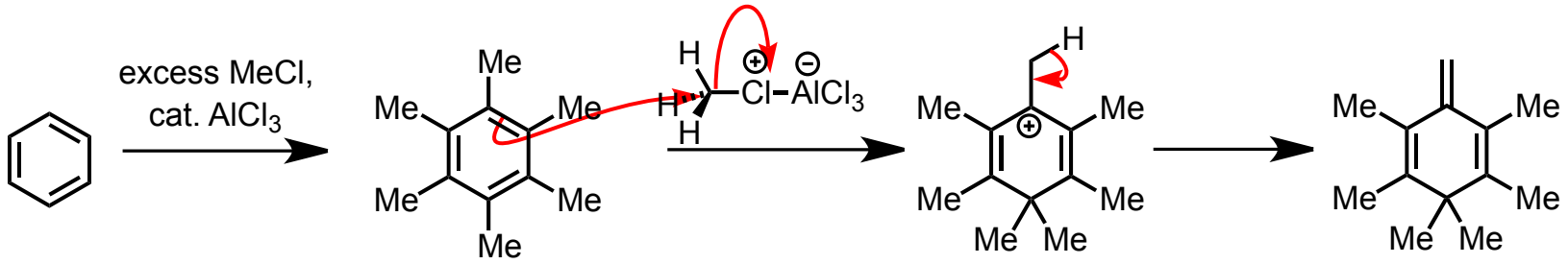
- cooperation between two *ortho*-directors



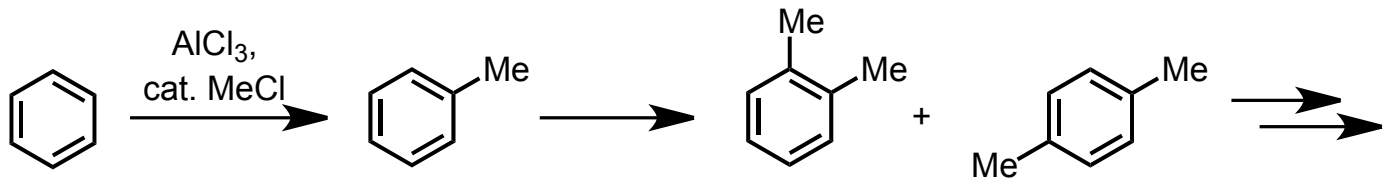
puts electrophile in most difficult position between two groups

Introduction of Functional Groups –Synthesis

- Friedel Crafts Alkylation
- polyalkylation and rearrangement predominate



- with one equivalent of alkylating agent mixtures of products result as the initially formed monoalkyl arene is more reactive than the unalkylated arene – alkyl groups are electron donating



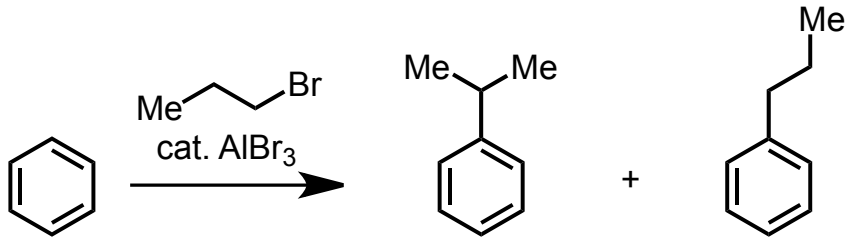
more reactive than benzene

more reactive than toluene

more reactive than toluene

Introduction of Functional Groups –Synthesis

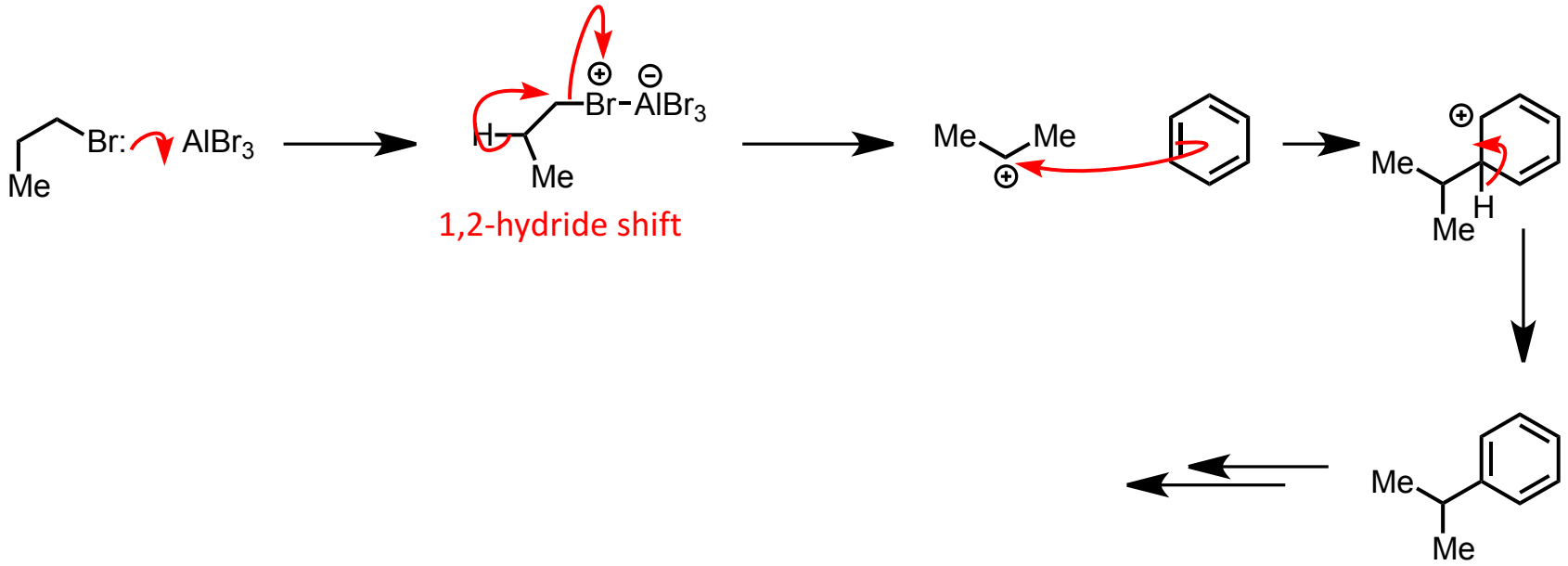
- Friedel Crafts Alkylation
- polyalkylation and rearrangement predominate
- with primary alkyl halides rearrangement occurs



major minor

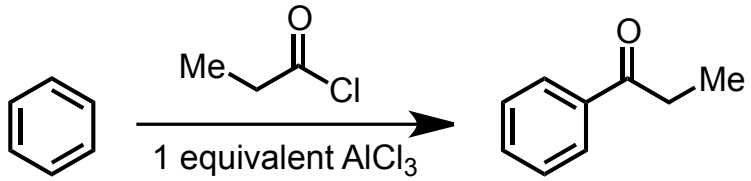
of monoalkylated products

primary carbocations are very unstable
rearrangement to the secondary carbocation occurs

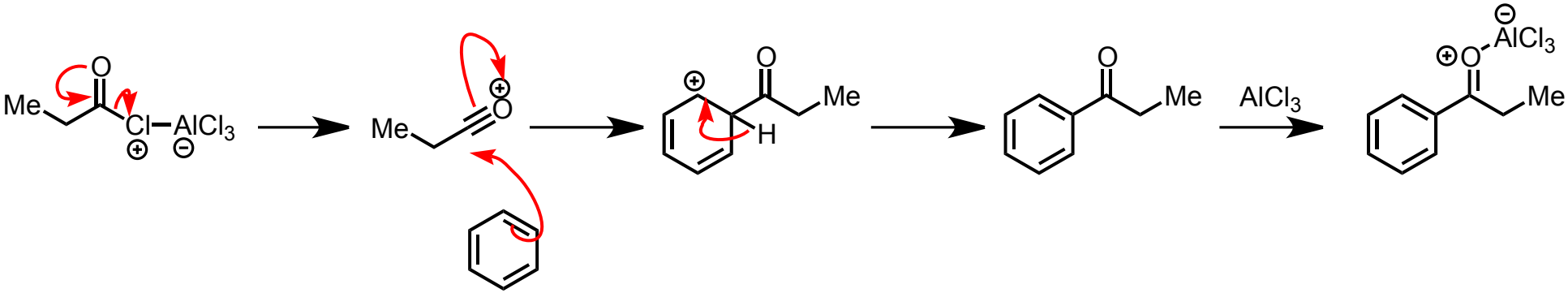


Introduction of Functional Groups –Synthesis

- Friedel Crafts Acylation
- requires a full equivalent of the Lewis acid
- mono-substitution predominates as introduced group is electron-withdrawing and deactivates aromatic ring

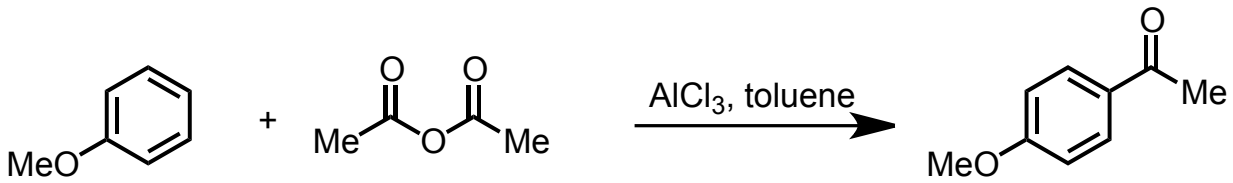


monosubstitution



- carbonyl group can then be removed if required (Clemensen reduction, Zn/HCl; Wolf-Kishner reduction, NH_2NH_2 then KOH, heat; dithiane than Raney Ni) giving products of a selective Friedel-Crafts alkylation

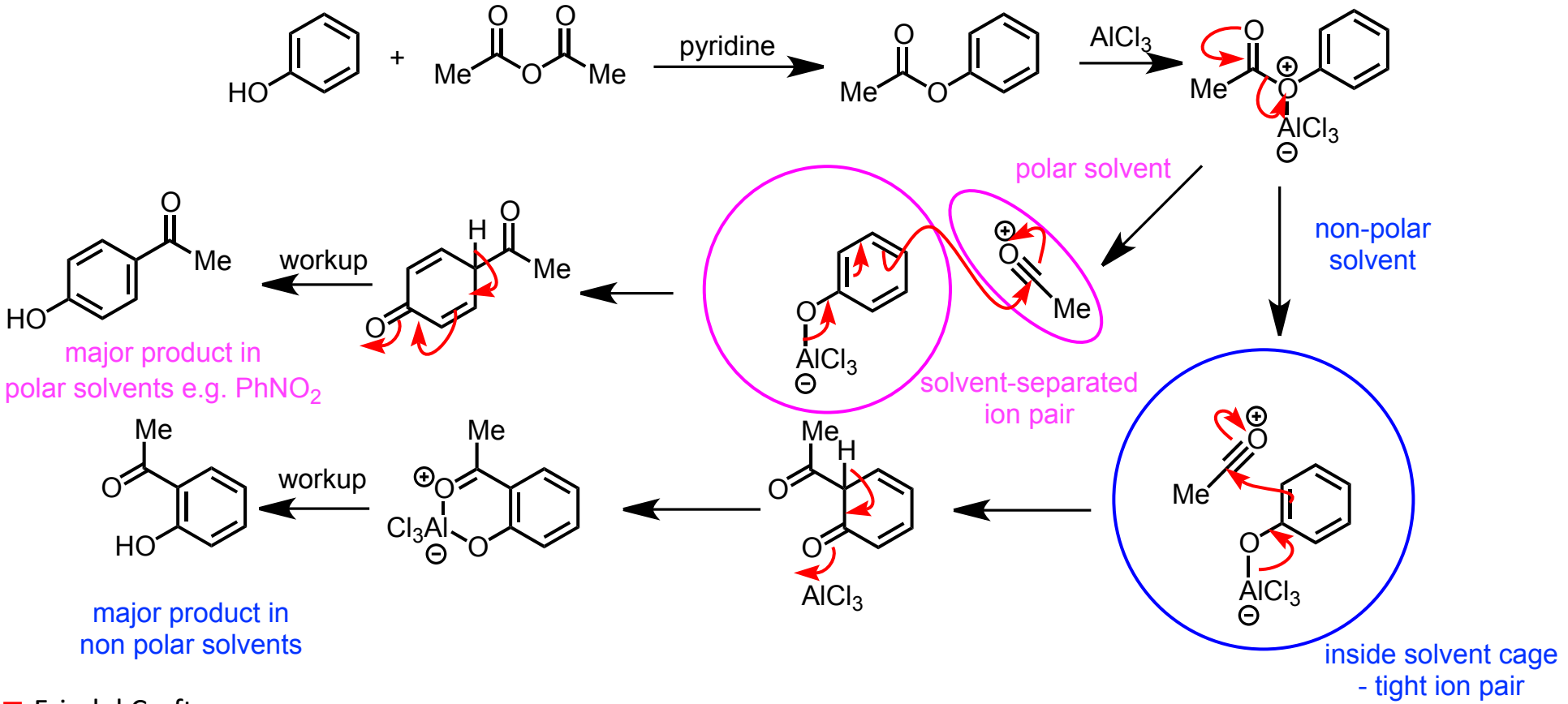
- *para*-isomer generally favoured by steric hindrance



93% yield

Introduction of Functional Groups –Synthesis

- Friedel Crafts Acylation
- Fries rearrangement can give access to either the *ortho*- or *para*-isomer



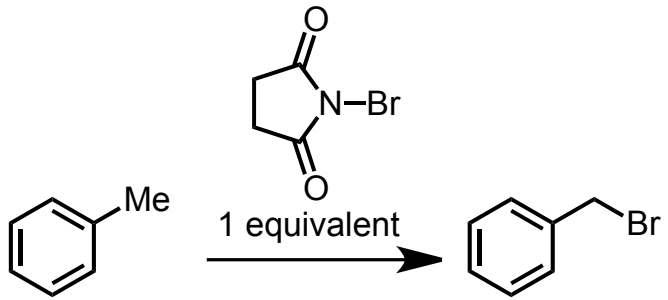
- Friedel Crafts summary

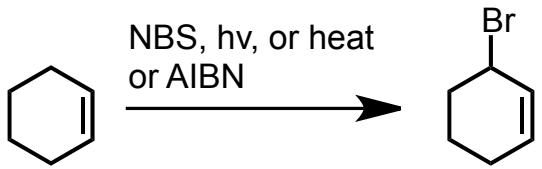
	Alkylation	**Acylation**
$AlCl_3$	*catalytic*	*stoichiometric*
Rearrangement	*possible*	*no, but loss of CO from R-C≡O⁺ if R⁺ stable, e.g. Ph_3C^+*
substitution order	*poly*	*mono*

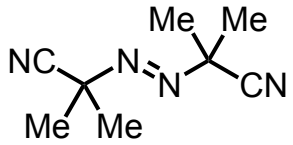
Introduction of Functional Groups –Synthesis

- Synthesis of benzyl halides

- free radical bromination



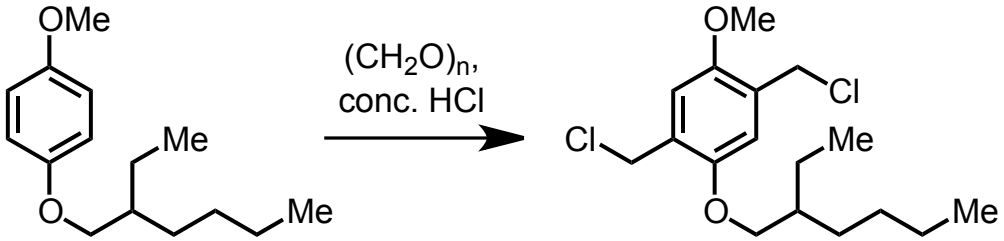




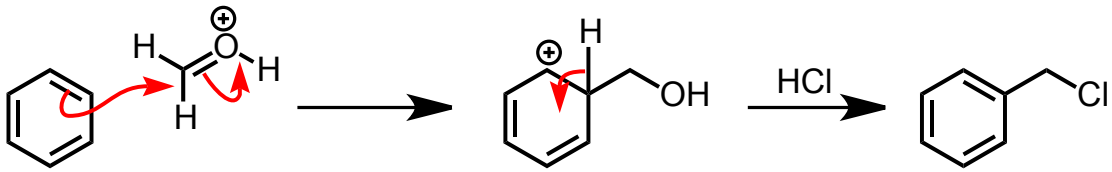
AIBN = **a**zobis**i**so**b**utyro**n**itrile

good radical initiator

- Blanc chloromethylation – related to Fiedel-Crafts reactions



- mechanism

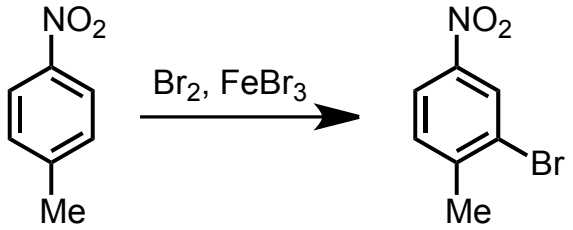


Introduction of functional groups

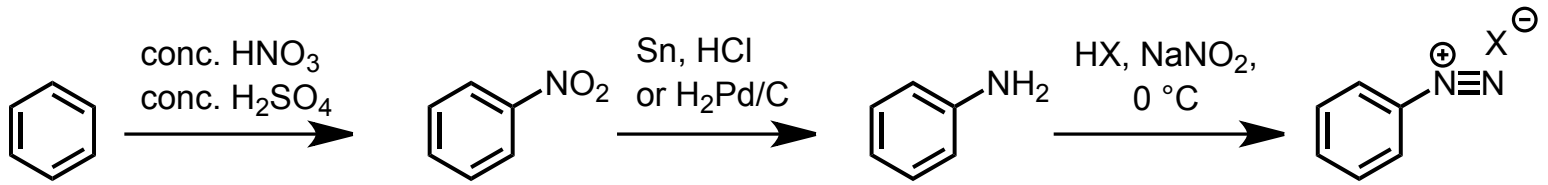
- halogenation – standard method is by electrophilic aromatic substitution using a source of positive halogen generally in the presence of a Lewis acid

- with activated aromatics Lewis acid activation of the electrophile is not required,

- with benzene and with deactivated aromatics Lewis acid activation of the electrophile is required

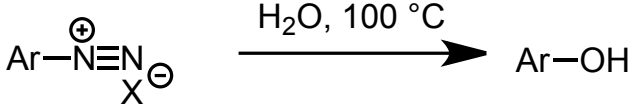


- halogenation can frequently be best achieved using Sandmeyer reactions (particularly good for introducing I and F as well as Cl, Br and CN)

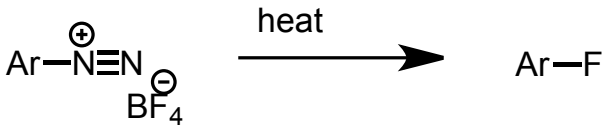


Introduction of Functional Groups –Synthesis

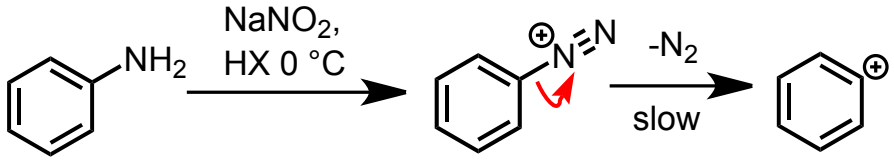
- diazonium salts - reactions



S_N1 reaction via carbenium ion

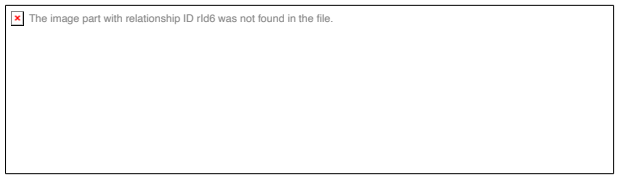


S_N1 reaction via carbenium ion – Balz Schiemann reaction

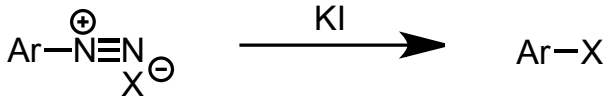


v. high energy intermediate, offset by the formation of N_2 carbenium not stabilised by π-system as is orthogonal to π-system

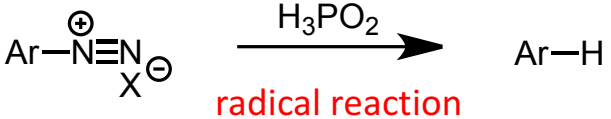
empty sp^2 orbital



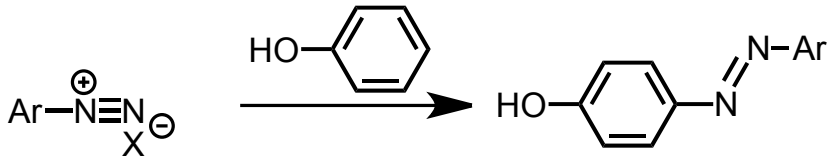
radical reaction



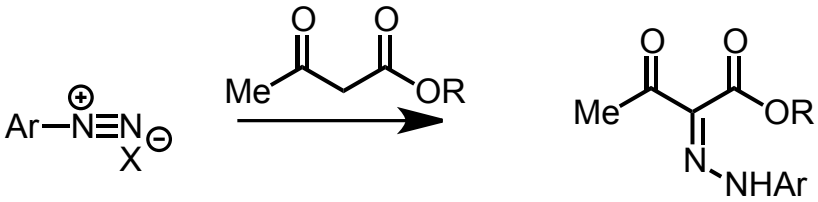
radical reaction



radical reaction



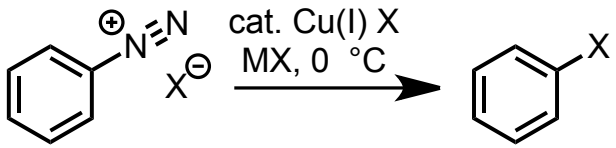
electrophilic aromatic substitution

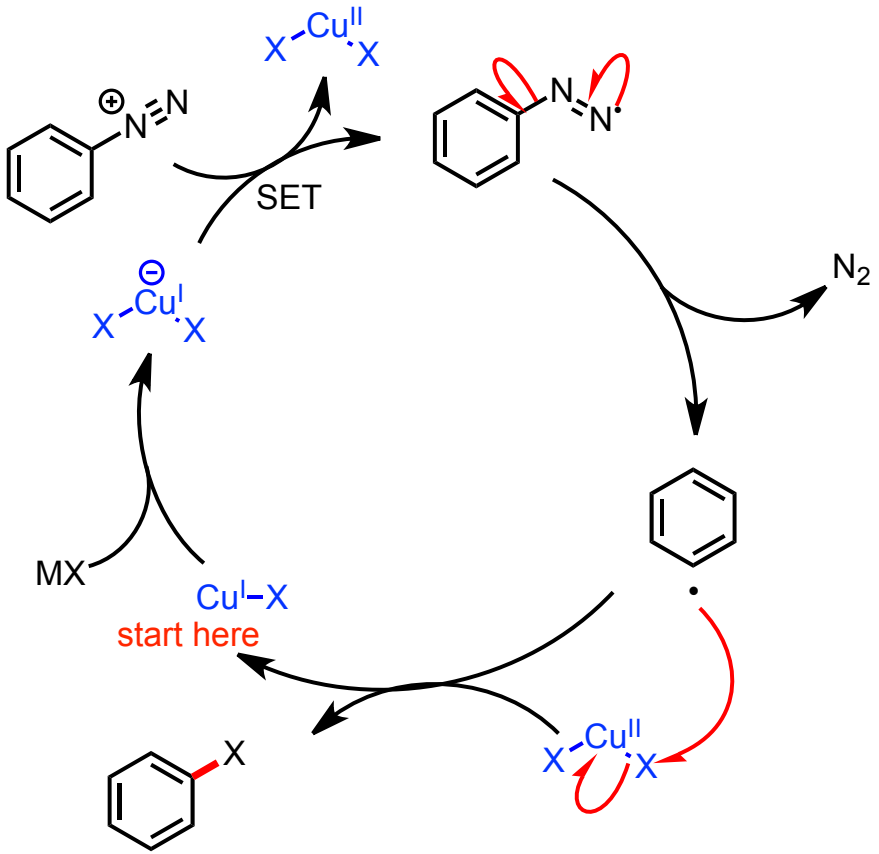


via enol

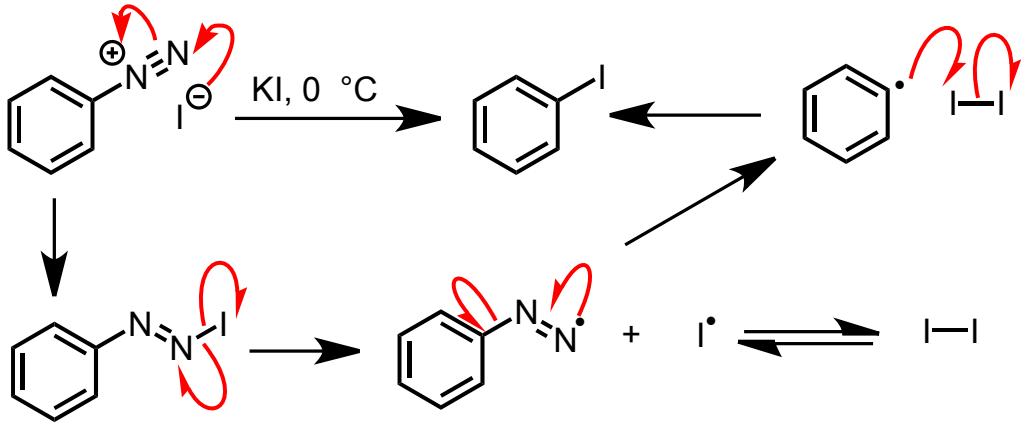
Introduction of Functional Groups –Synthesis

- Halogenation / cyanation Sandmeyer - X = Br, Cl, CN



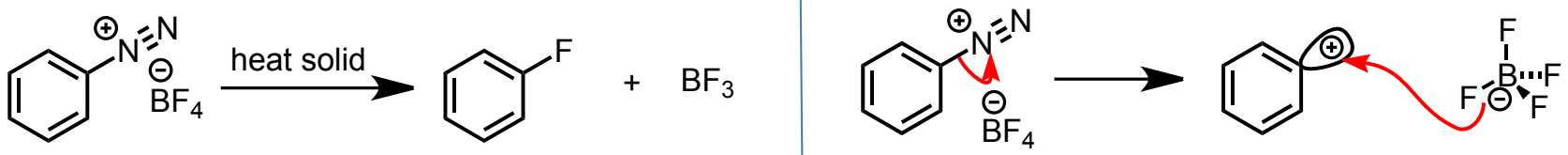


- Iodination Sandmeyer – no copper salt required



Introduction of Functional Groups –Synthesis

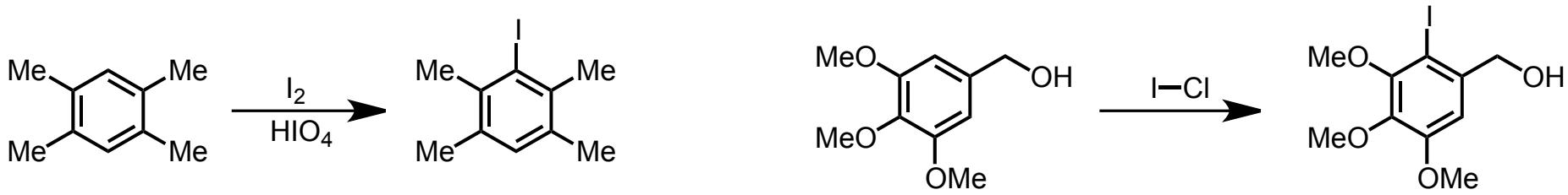
- Fluorination from diazonium salts – Baltz-Schimann reactions



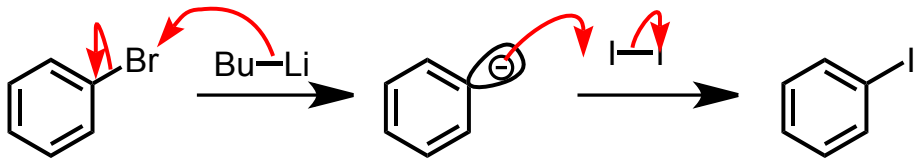
- Iodination other methods

- Iodine less reactive electrophile than bromine or chlorine, therefore require activated substrate or presence of an oxidising agent (maybe generating I^+), or more reactive interhalogen e.g. I-Cl

- examples

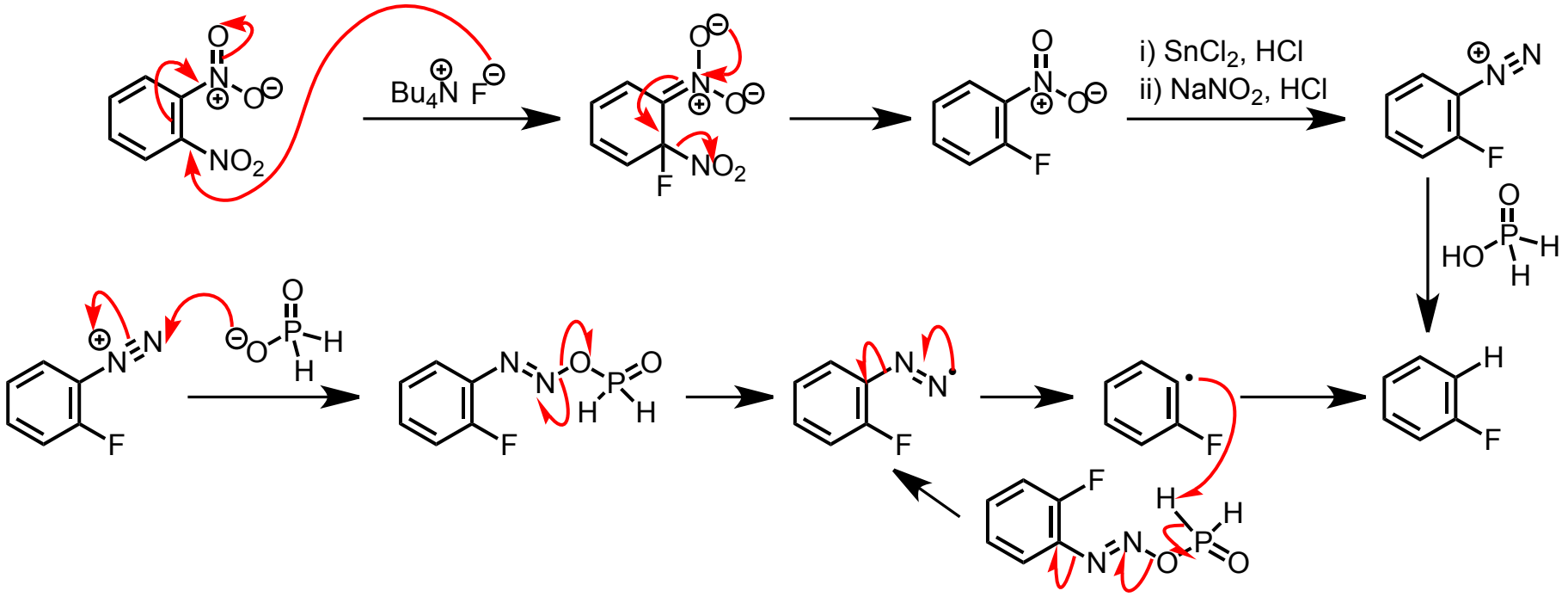


- metal halogen exchange

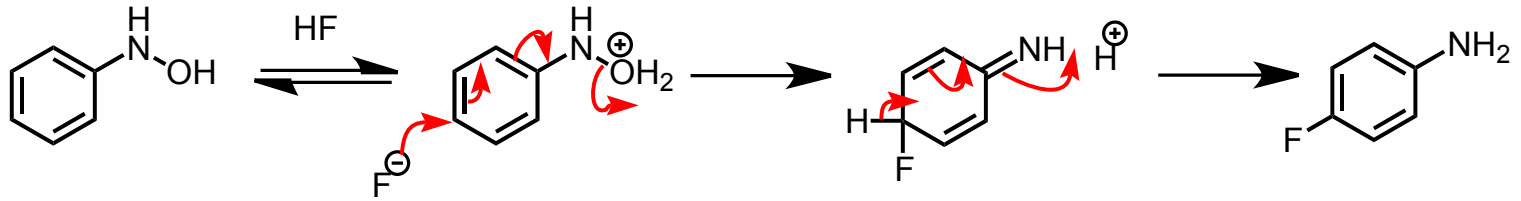


Introduction of Functional Groups –Synthesis

■ Fluorination – Halex reaction – S_NAr-type example

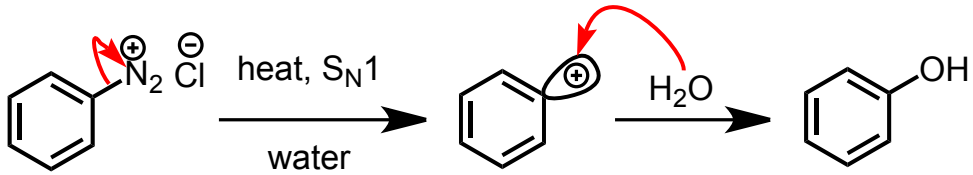


■ Bamberger reaction to give *para*-fluoroanilines

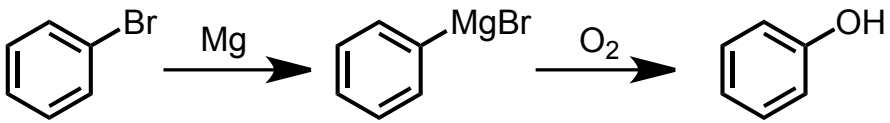


Introduction of Functional Groups –Synthesis

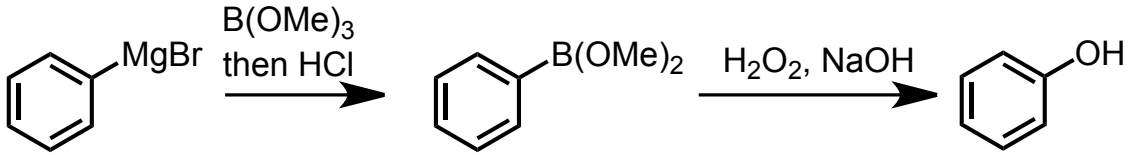
- Phenols
- Diazonium route



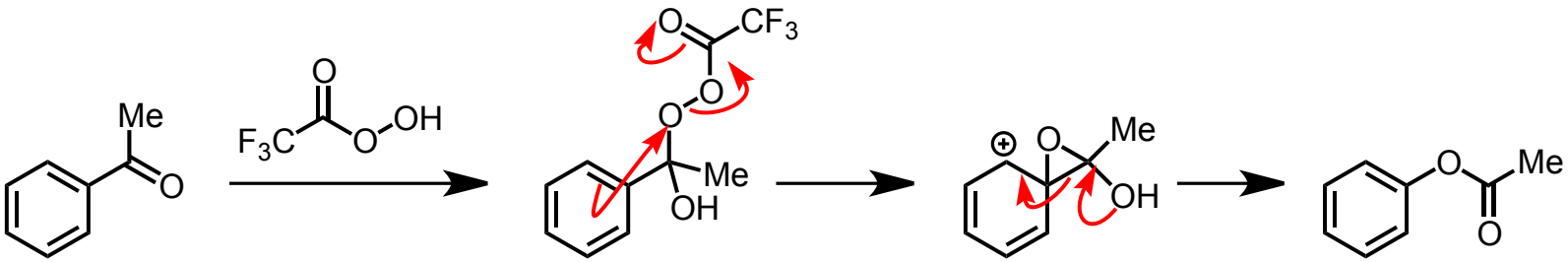
- Oxidation of Grignard reagents



- Oxidation of organoboranes

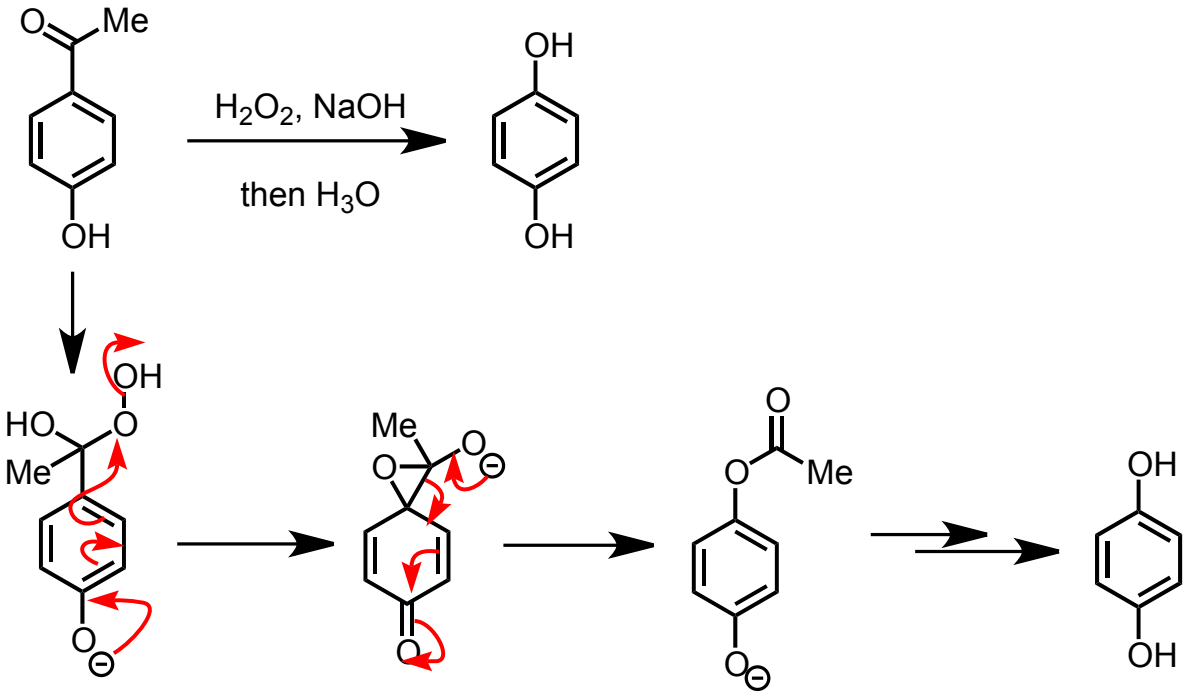


- Baeyer Villiger Oxidation

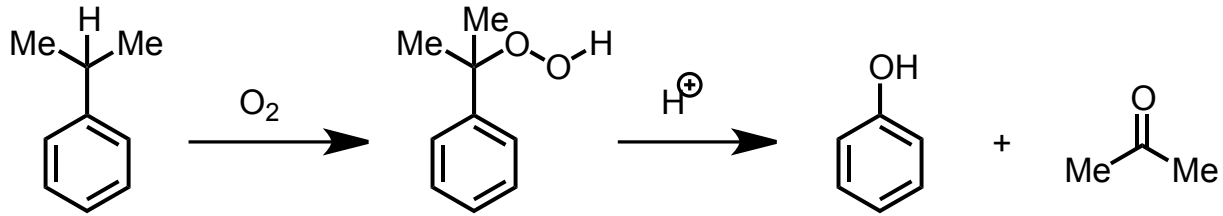


Introduction of Functional Groups –Synthesis

- Dakin reaction – usually used on phenolic substrates

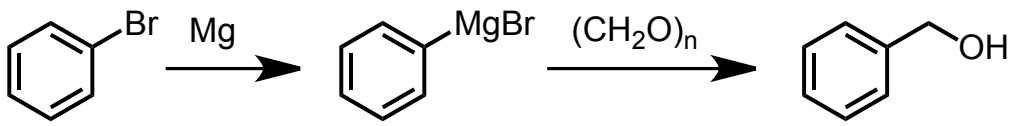


- Aerial oxidation of *iso*-propylbenzenes followed by cumenehydroperoxide rearrangement

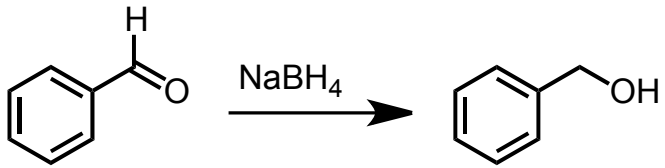


Introduction of Functional Groups –Synthesis

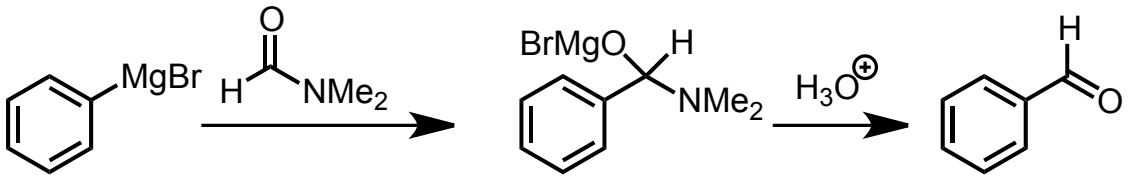
- Benzyl alcohols
- via Grignard reagents

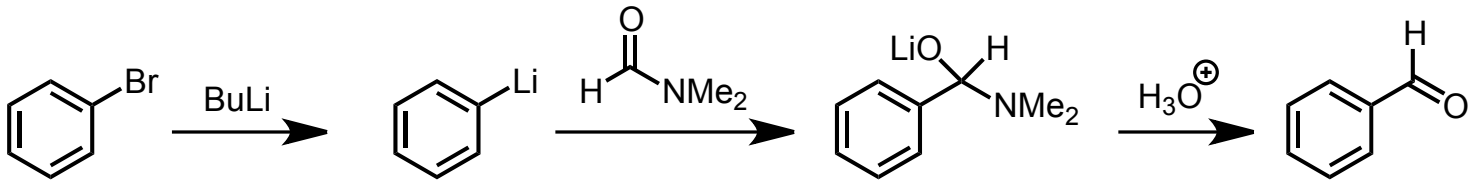


- reduction of benzaldehydes



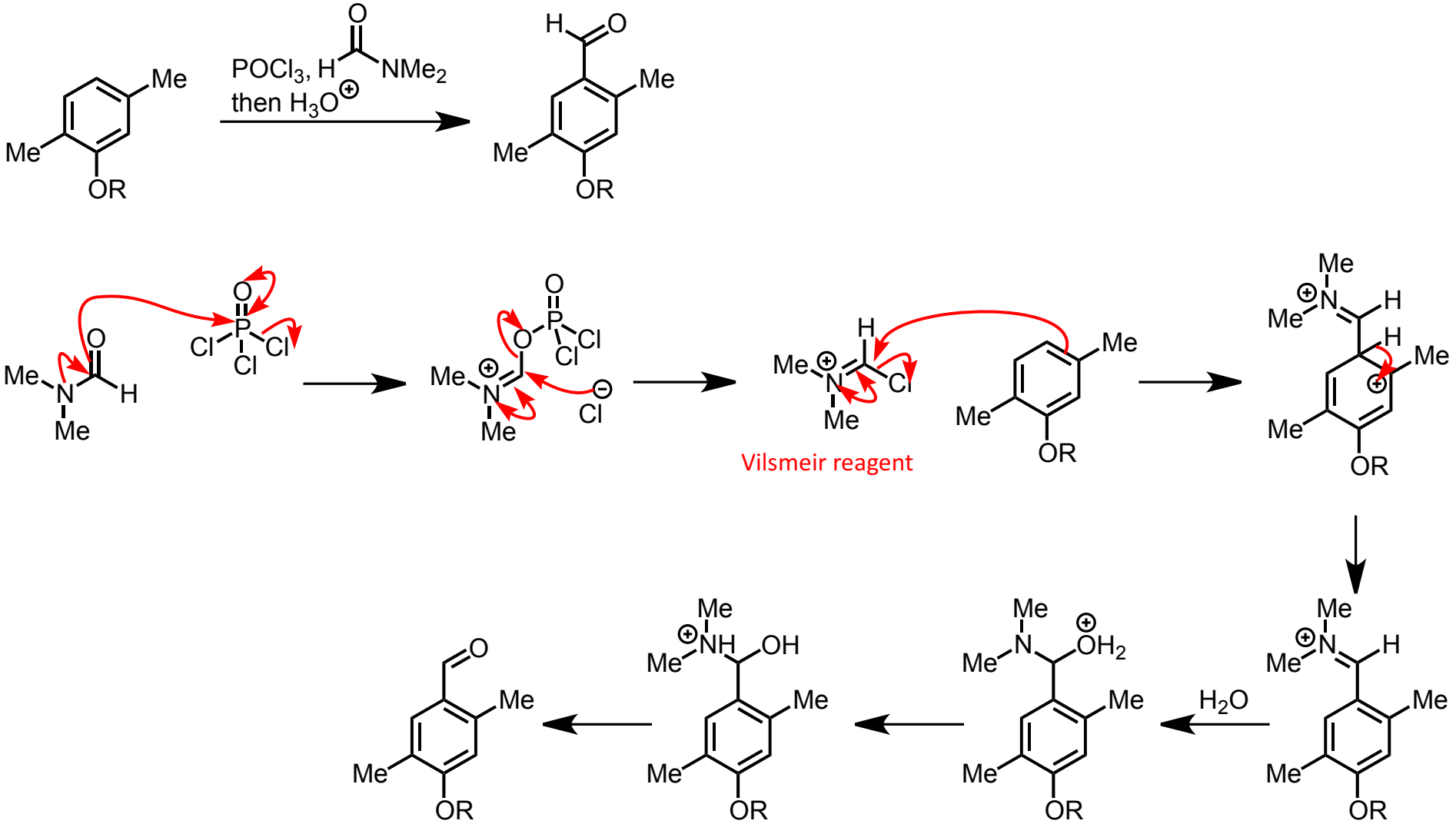
- Benzaldehydes
- Organometallic route





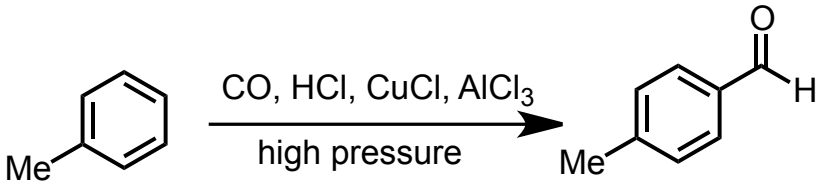
Introduction of Functional Groups –Synthesis

- Vilsmeir reaction – requires activated aromatics – very good with furan, thiophene, pyrrole and indole

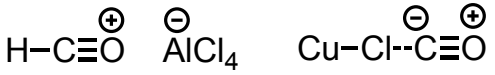


Introduction of Functional Groups –Synthesis

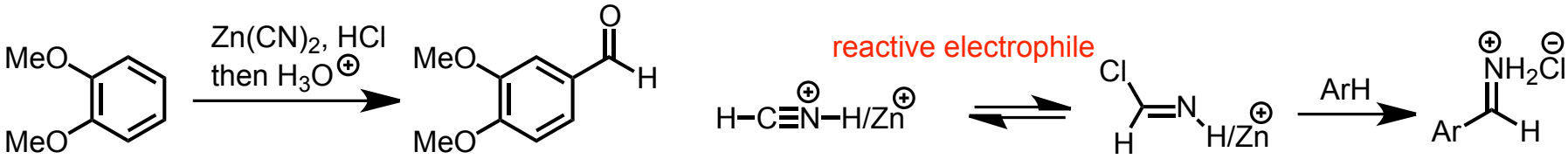
- formyl chloride is too unstable to partake in Friedel Crafts reactions as it readily decomposes to CO and HCl
- Gattermann-Koch formylation – good for alkyl benzenes, generally an industrial method



may involve intermediates such as

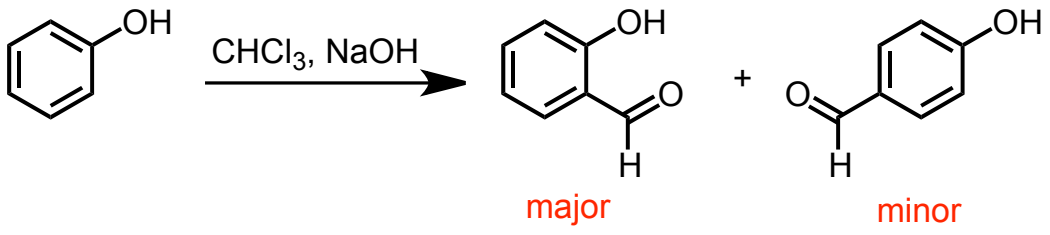


- Gattermann aldehyde synthesis
- Neither the Gattermann nor the Gattermann-Koch reactions can be used with aromatic amines

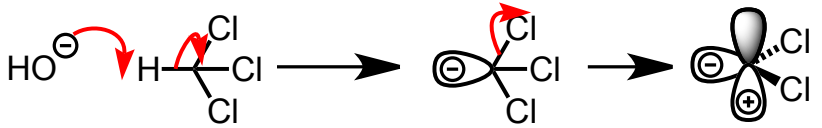


Introduction of Functional Groups –Synthesis

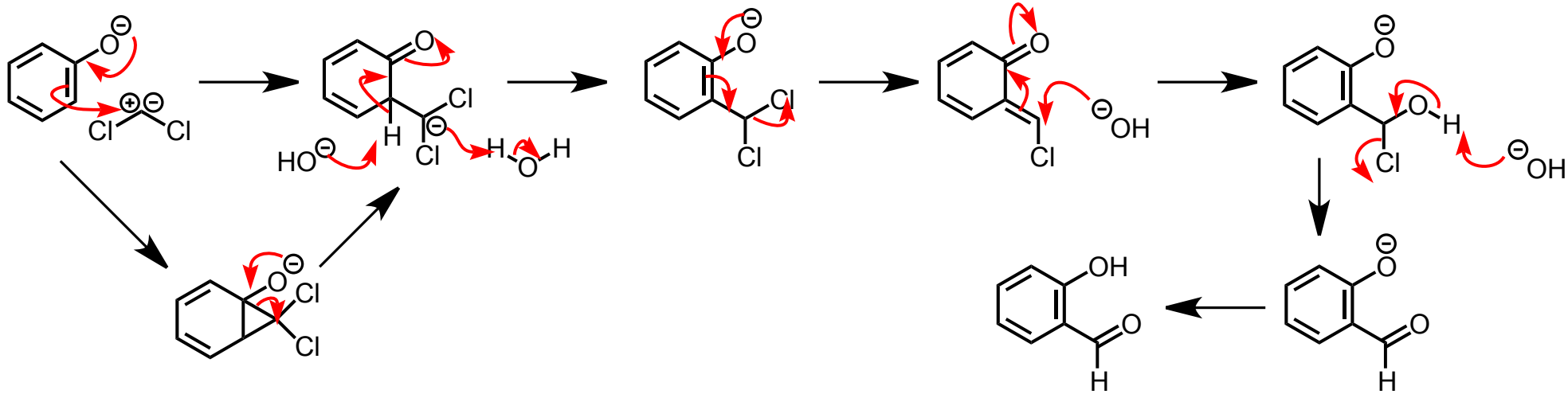
- Reimer-Tiemann Synthesis – requires a phenolic substrate



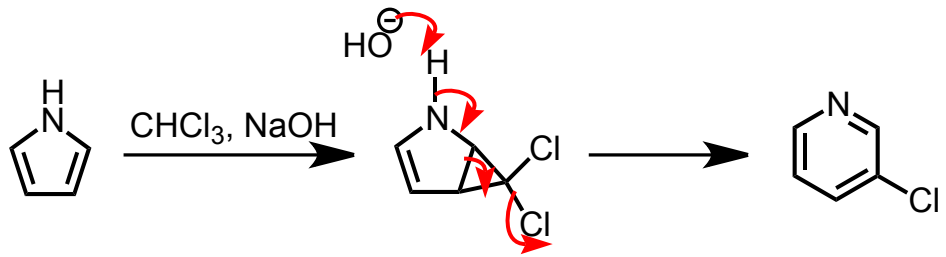
major minor



dichlorocarbene

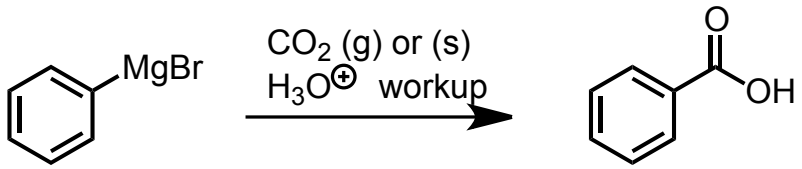


- Pyrrole gives 3-chloropyridine under Reimer-Tiemann reaction conditions

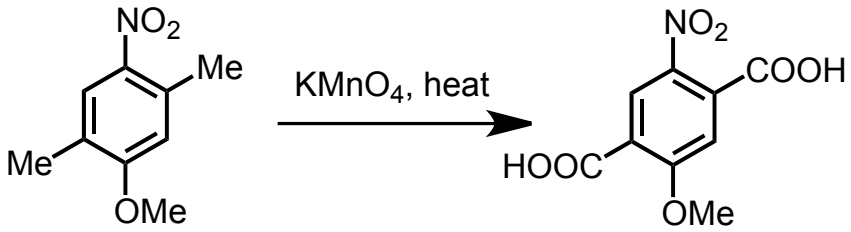


Introduction of Functional Groups –Synthesis

- Carboxylic acids
- Grignard route



- Oxidation of alkyl benzenes

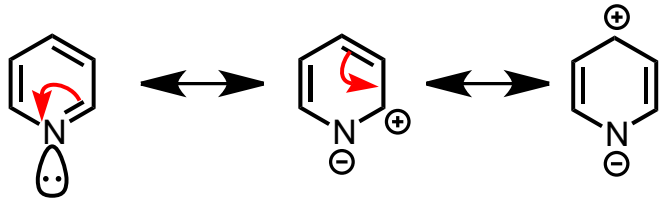


- Nitration
- standard nitrating mixture conc. sulfuric acid and conc. nitric acid is very harsh
- NO_2^+ BF_4^- is non-oxidizing and non-acidic – compatible with many more functional groups

- Sulfonation
- reversible process – sulfonated product formed with conc. H_2SO_4
- desulfonation can be achieved using dilute H_2SO_4

Hetroaromatics

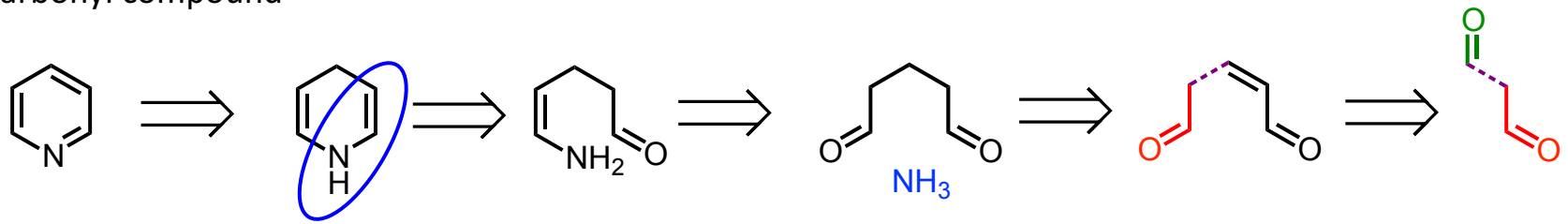
- Pyridine
- properties – pyridine is polarised by the presence of the nitrogen atom both through the π-system and σ-framework
- the lone pair on nitrogen is orthogonal to the π-system, and is the HOMO of pyridine; the LUMO of pyridine is an anti-bonding π-orbital
- pyridine is electron poor and undergoes EARS only very slowly



- pyridine is electron deficient at C-2 and C-4 and it is prone to attack by nucleophiles

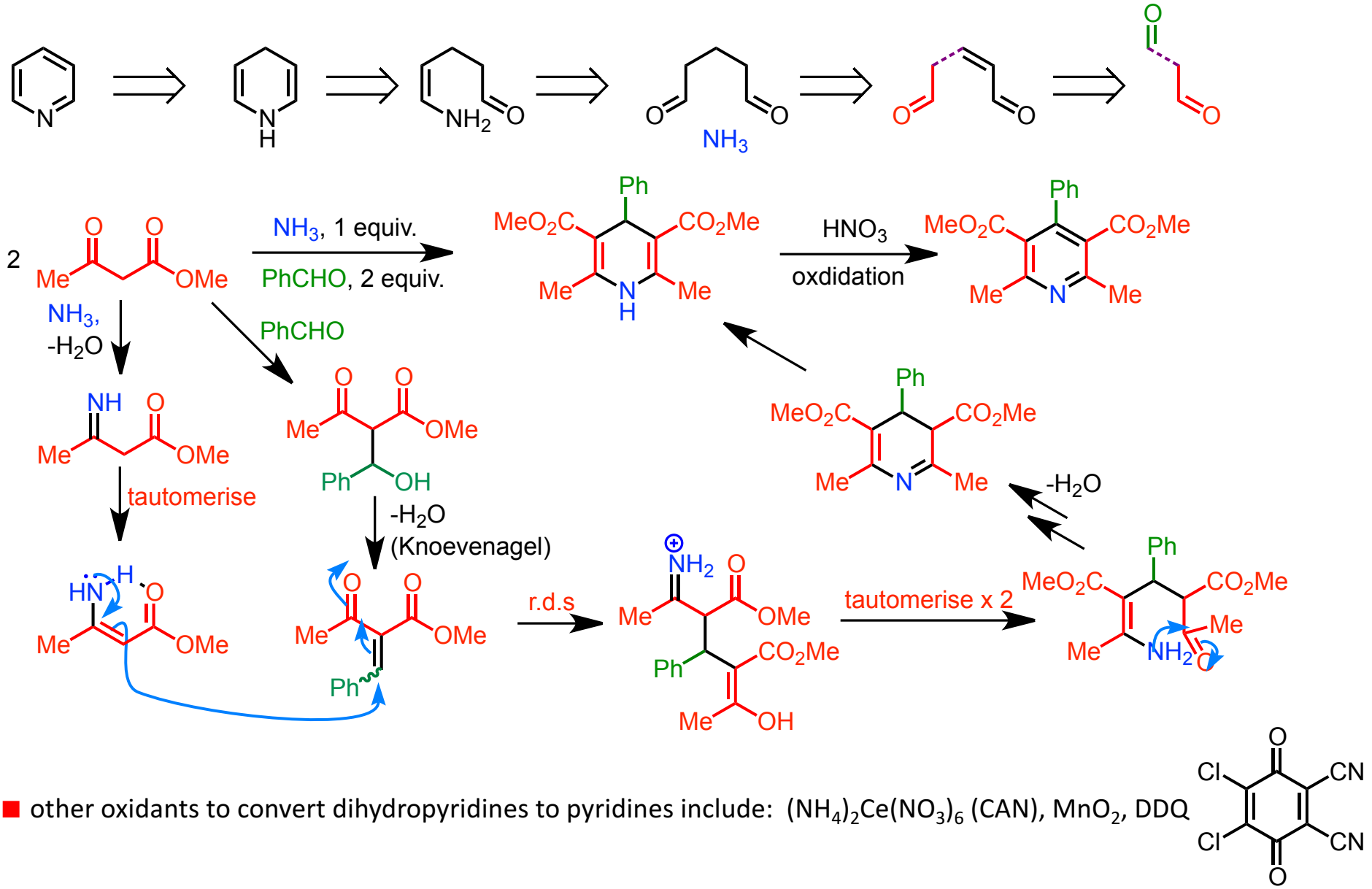
HOMO of pyridine is nitrogen lone pair in **sp^2 orbital**

- synthesis of pyridines and derivatives – generally aim to make dihydropyridine and then oxidise it to the corresponding pyridine
- dihydropyridines are readily prepared by the condensation of ammonia with 1,5-dicarbonyl compounds
- 1,5-dicarbonyl compounds are readily prepared by addition of an aldehyde or ketone to an α,β-unsaturated carbonyl compound



Heteroaromatics

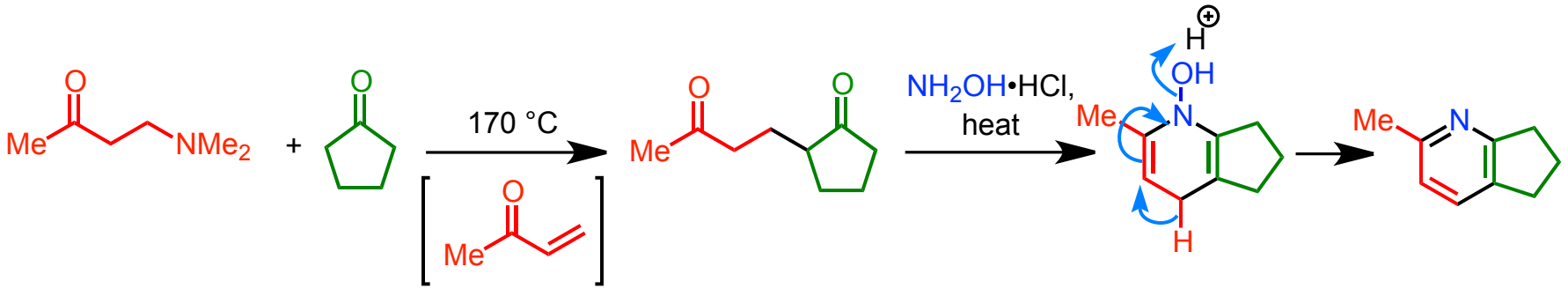
Hantzsch pyridine synthesis



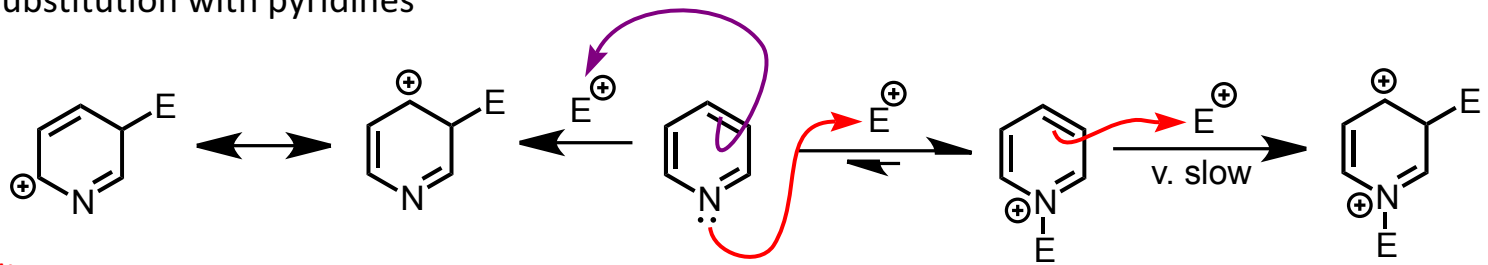
- other oxidants to convert dihydropyridines to pyridines include: $(NH_4)_2Ce(NO_3)_6$ (CAN), MnO_2, DDQ

Heteroaromatics

- Pyridine synthesis with hydroxylamine – no oxidant required



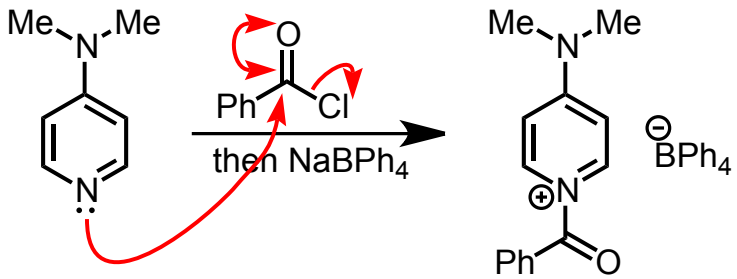
- Electrophilic substitution with pyridines



v. poor yielding
low concentration of free pyridine
meta-position least deactivated

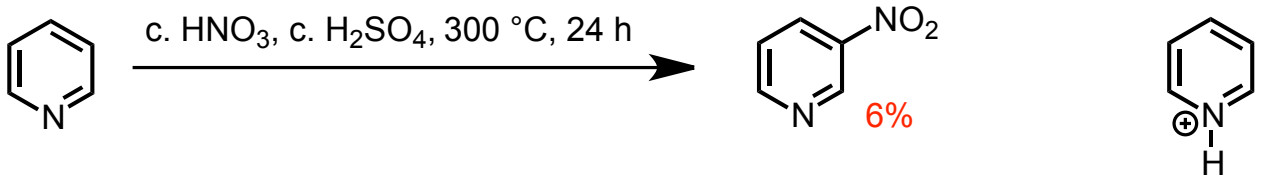
high energy intermediate
- electrophile reacting with positively charged nucleophile

- Pyridines are nucleophilic (on nitrogen)

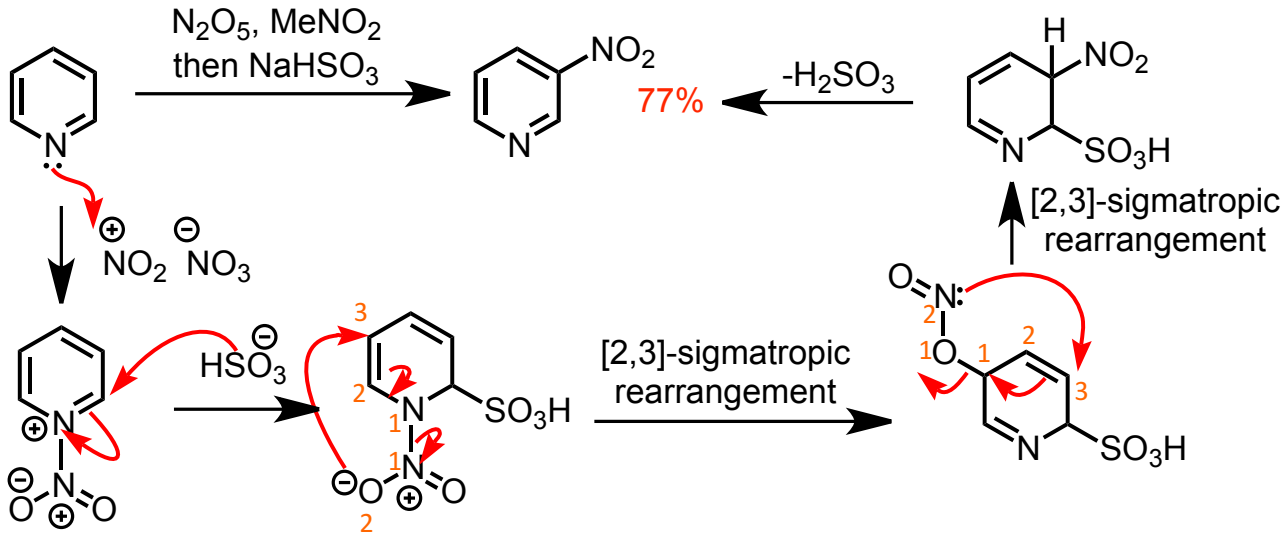


Heteroaromatics

- Nitration of pyridine

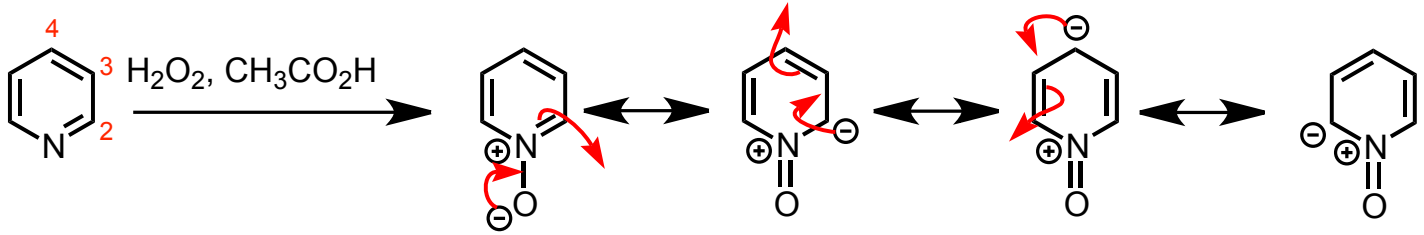


- nitration of pyridine with N_2O_5
- plausible mechanism

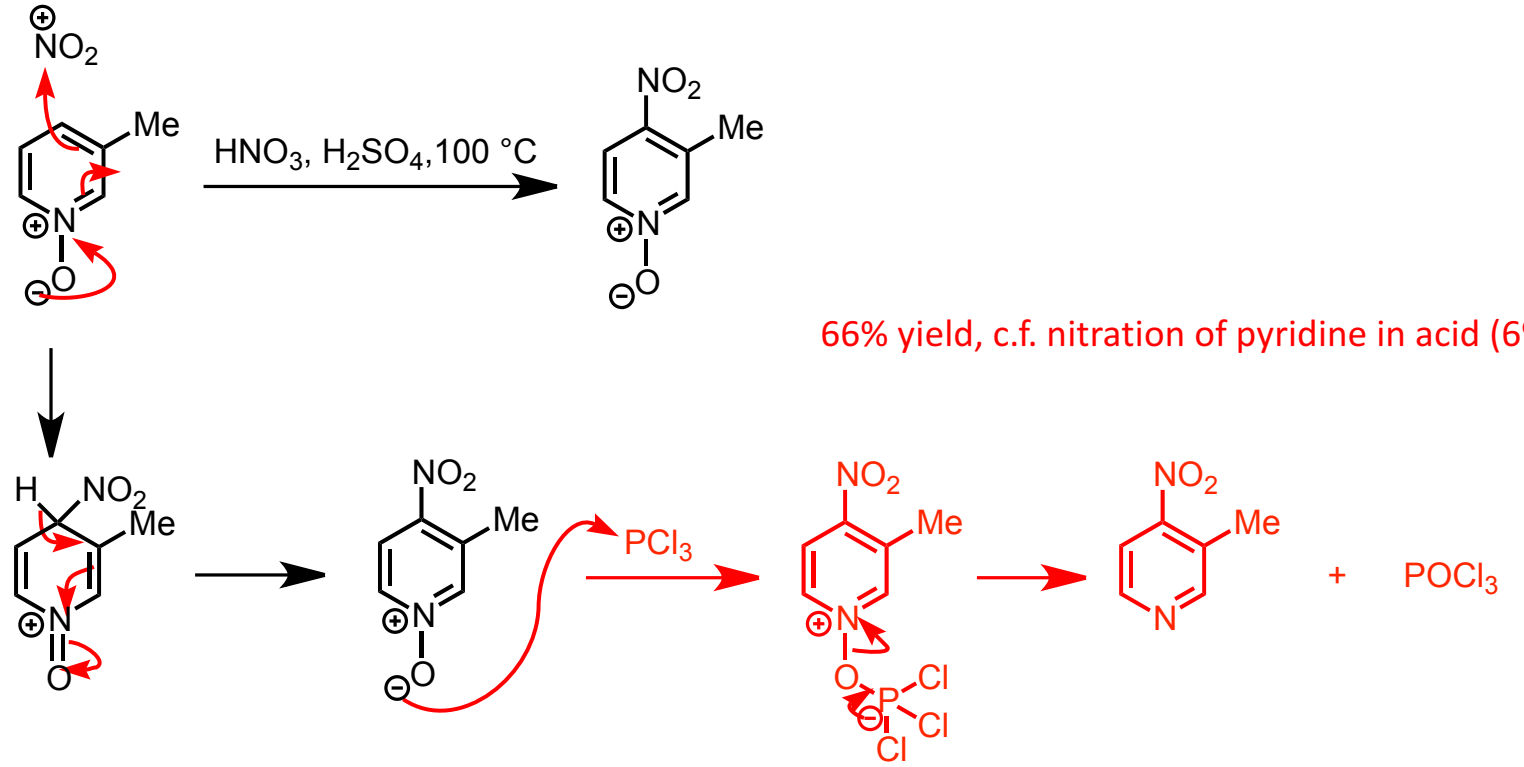


Heteroaromatics

■ pyridine *N*-oxides – much more susceptible to electrophilic attack at 2 and 4 positions (and to nucleophilic addition at 2 and 4 positions)

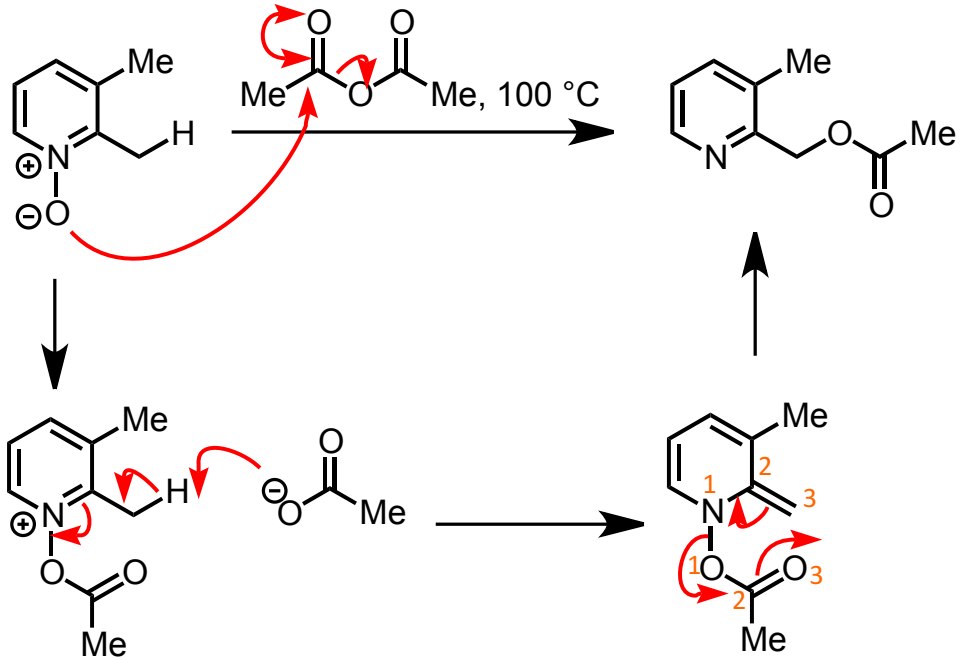


■ nitration of pyridine *N*-oxide

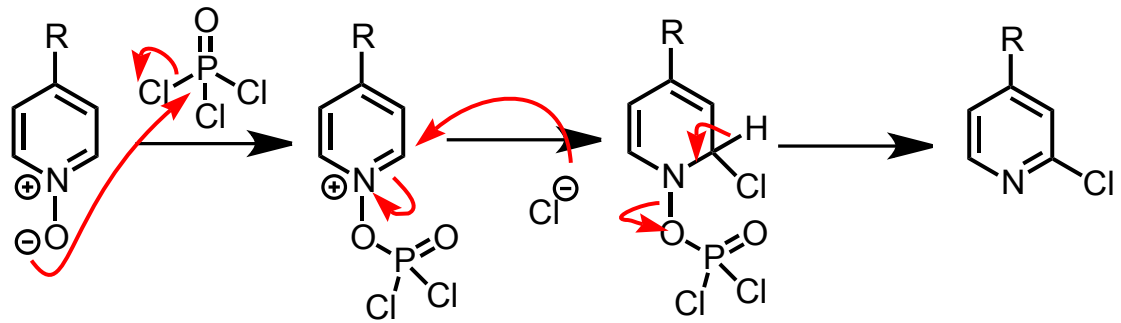


Heteroaromatics

- pyridine *N*-oxides – *N*-deoxygenation with rearrangement

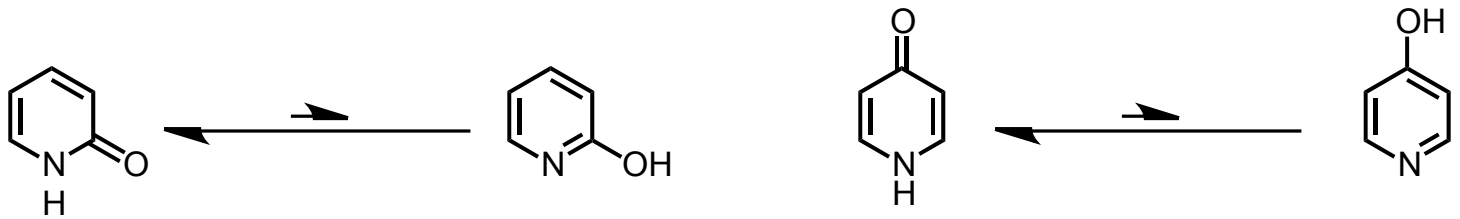


- pyridine *N*-oxides – conversion to chloro compounds

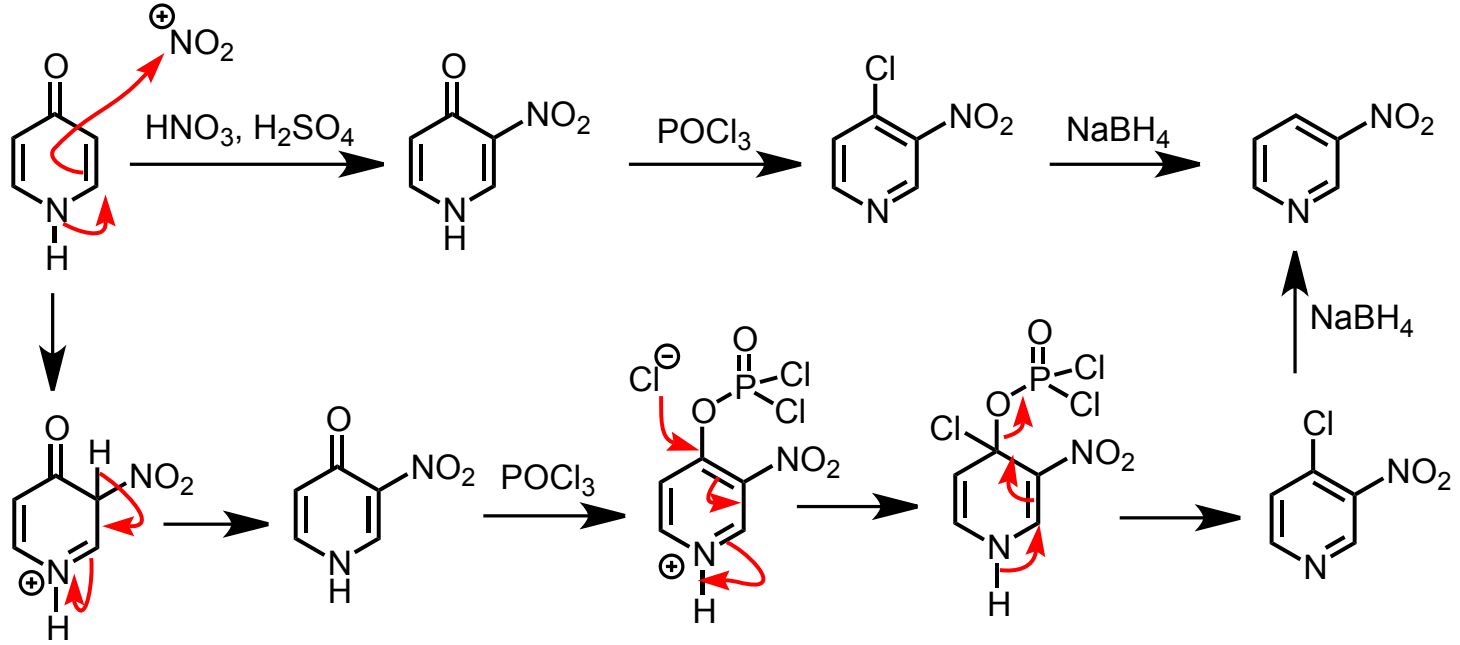


Heteroaromatics

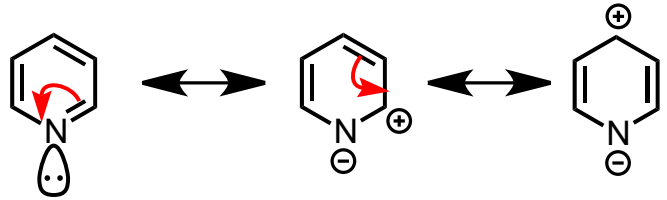
- pyridones



- nitration

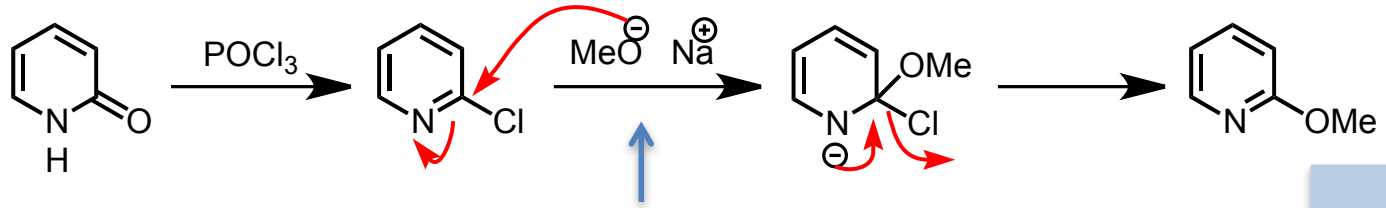


Heteroaromatics and Nucleophilic substitution



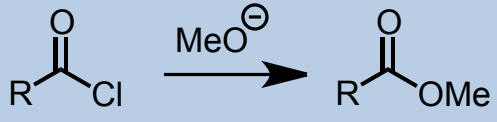
■ pyridine is electron deficient at C-2 and C-4 and is prone to attack by nucleophiles

HOMO of pyridine is nitrogen lone pair

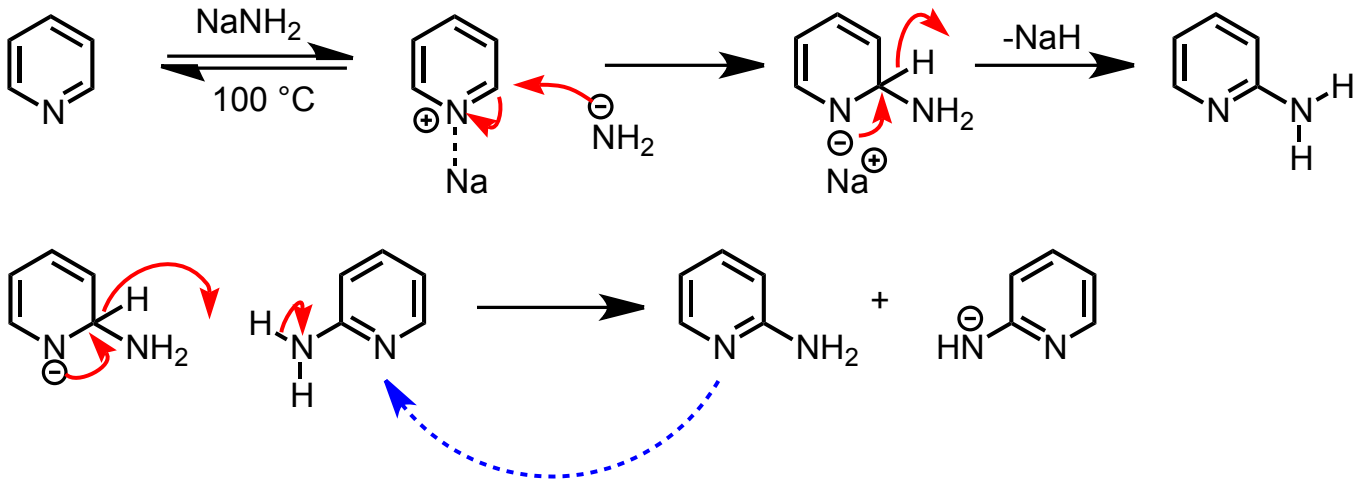


nucleophilic aromatic substitution

compare with



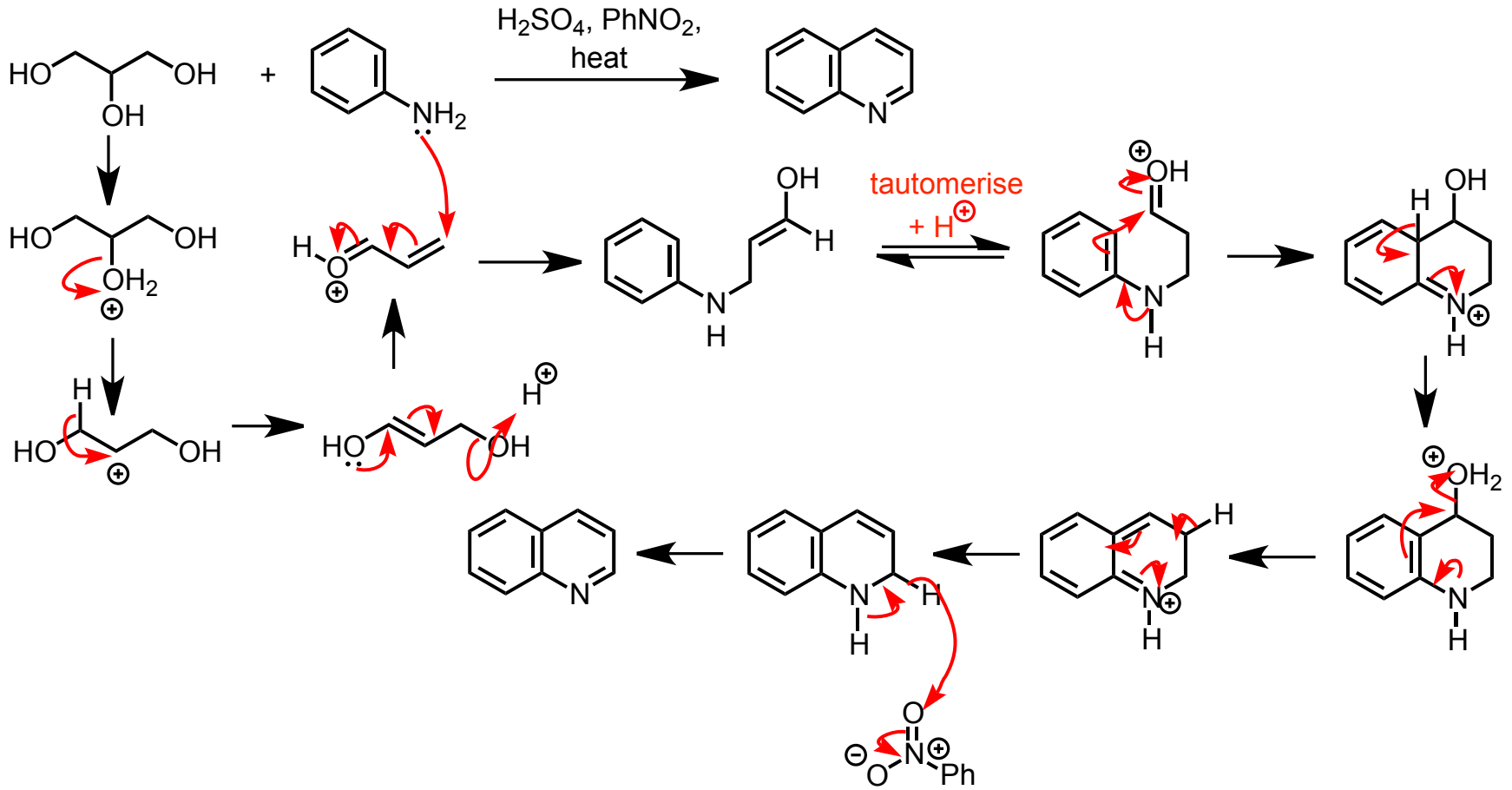
■ Chichibabin reaction



Heteroaromatics

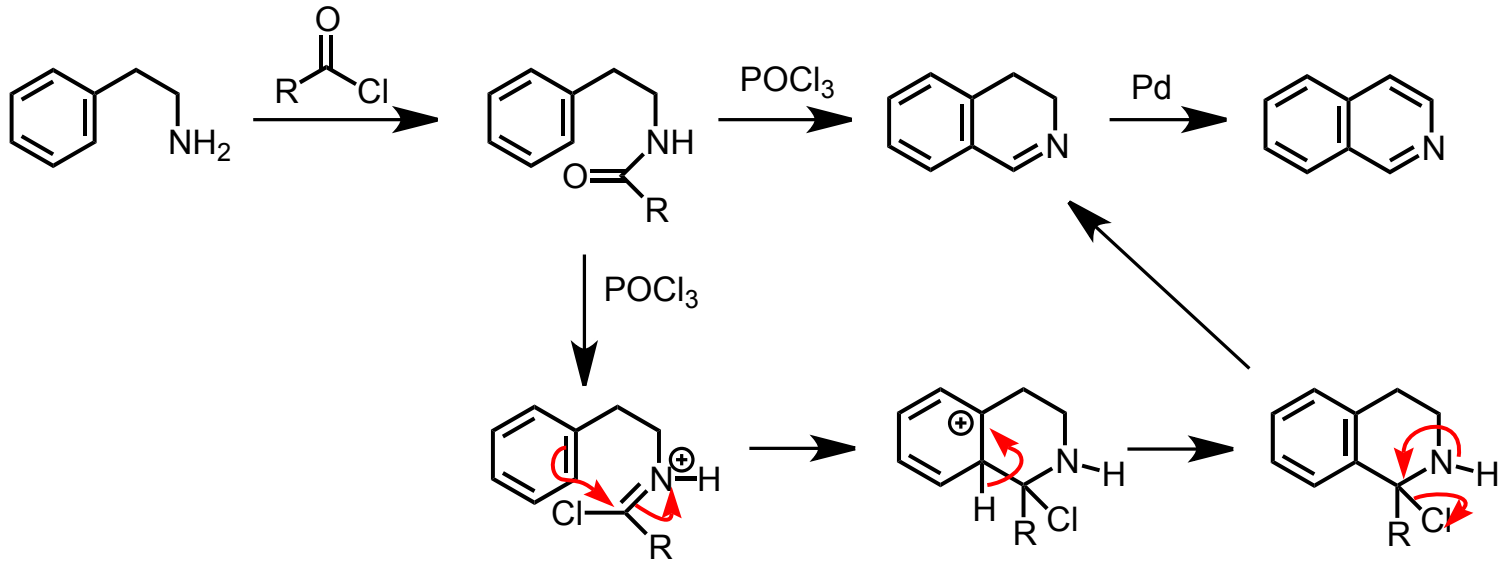
- quinolines and isoquinolines

- Synthesis – Skraup synthesis

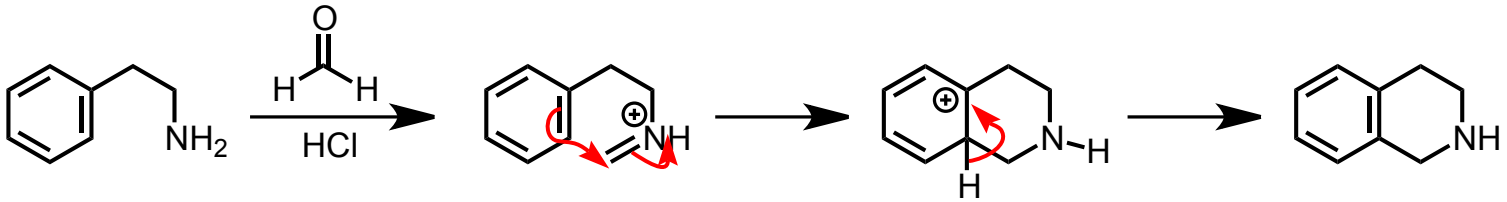


Heteroaromatics

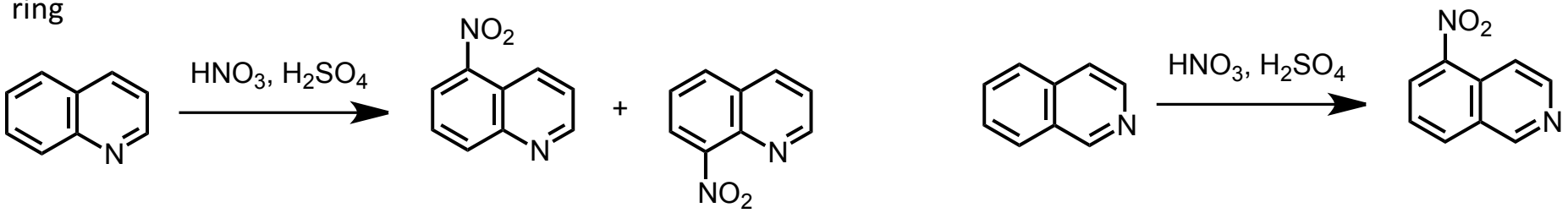
- synthesis of isoquinolines
- Bischler-Napieralski



- Pictet-Spengler

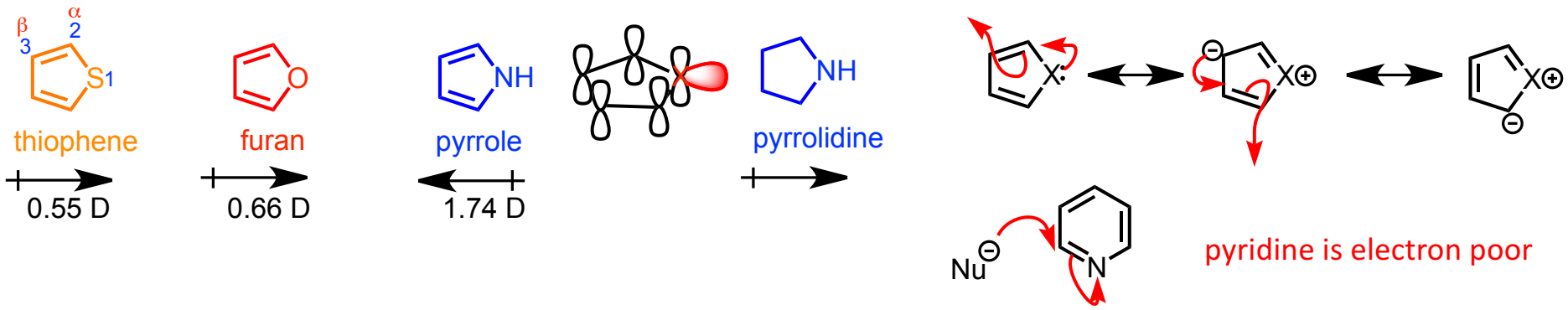


- quinoline and isoquinoline undergo EArS more readily than pyridine, with reaction occurring on the benzenoid ring



Heteroaromatics

- pyrrole, thiophene and furan
- all three have aromatic properties
- in each case the (one of the) lone pair(s) is parallel to the p-orbitals and part of the π-system
- the aromatic heterocycles are electron rich



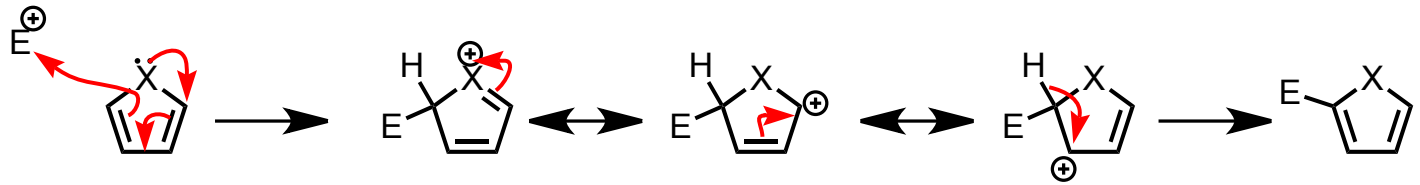
- order of aromaticity is: thiophene > pyrrole > furan (enol ether like)
- sulfur is the largest atom and hence is better matched for bonding to sp^2-hybridised carbon atoms in a 5-membered ring leading to thiophene being the most aromatic

Heteroaromatics

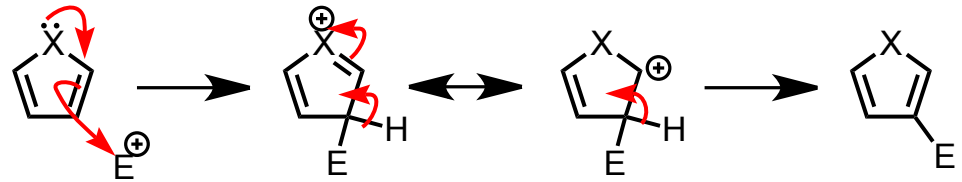
Reactions

- electrophilic substitution – kinetic reaction at the 2-position is favoured over reaction at the 3-position

- more reactive than benzene – e.g. pyrrole similar reactivity to aniline

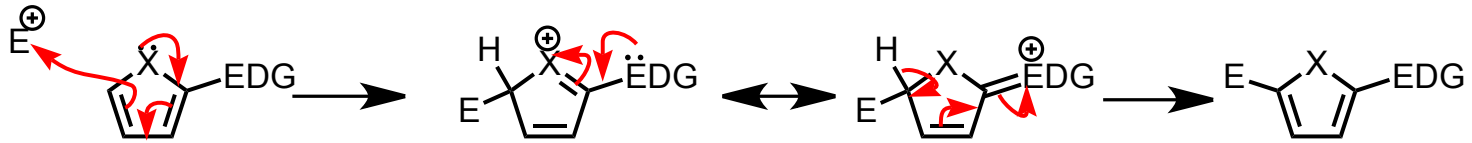


more delocalised intermediate ∴ more stable ∴ 2-substitution favoured

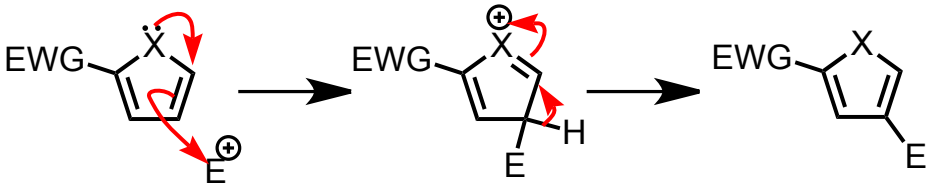


less delocalised intermediate ∴ less stable ∴ 3-substiution disfavoured

- substituents already present on the aromatic heterocycle exert less directing effect than the corresponding substituents in benzene



with EDG at α-position α'-substitution favoured

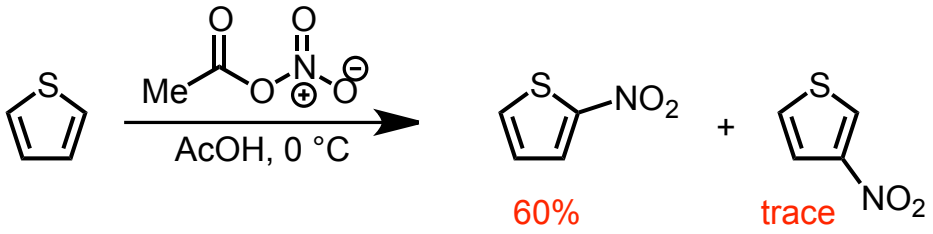


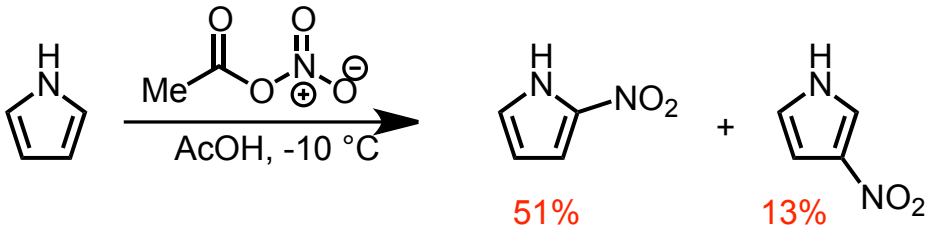
with EWG at α-position β'-substitution favoured

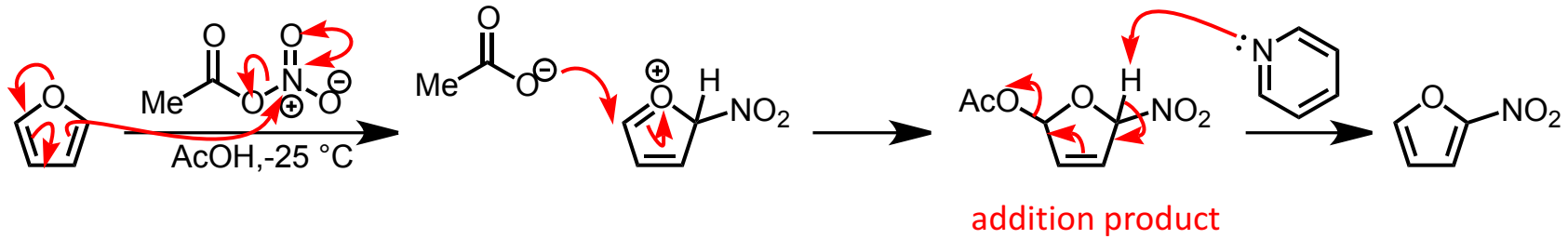
Heteroaromatics

Reactions

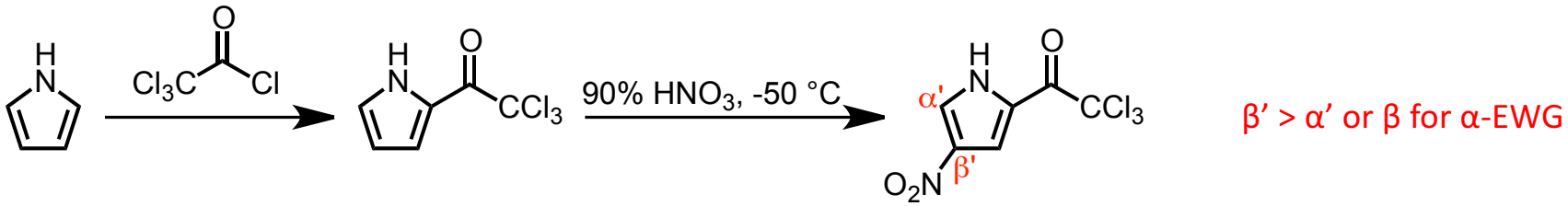
■ nitration

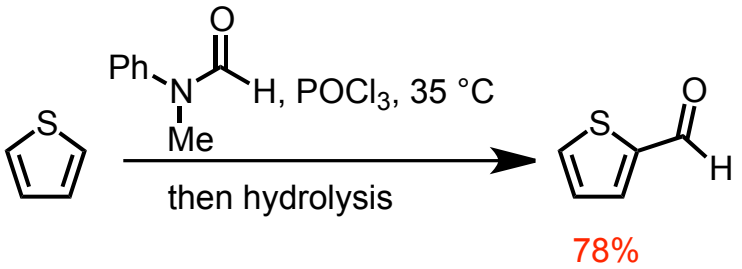


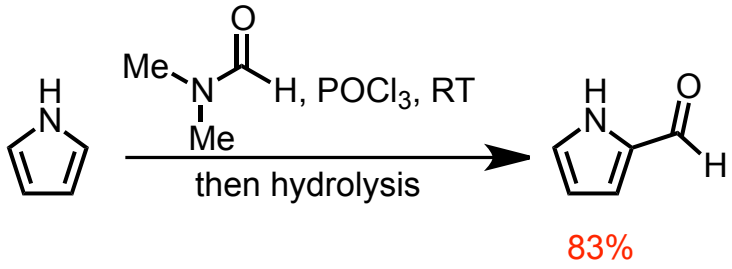




■ acylation and formylation







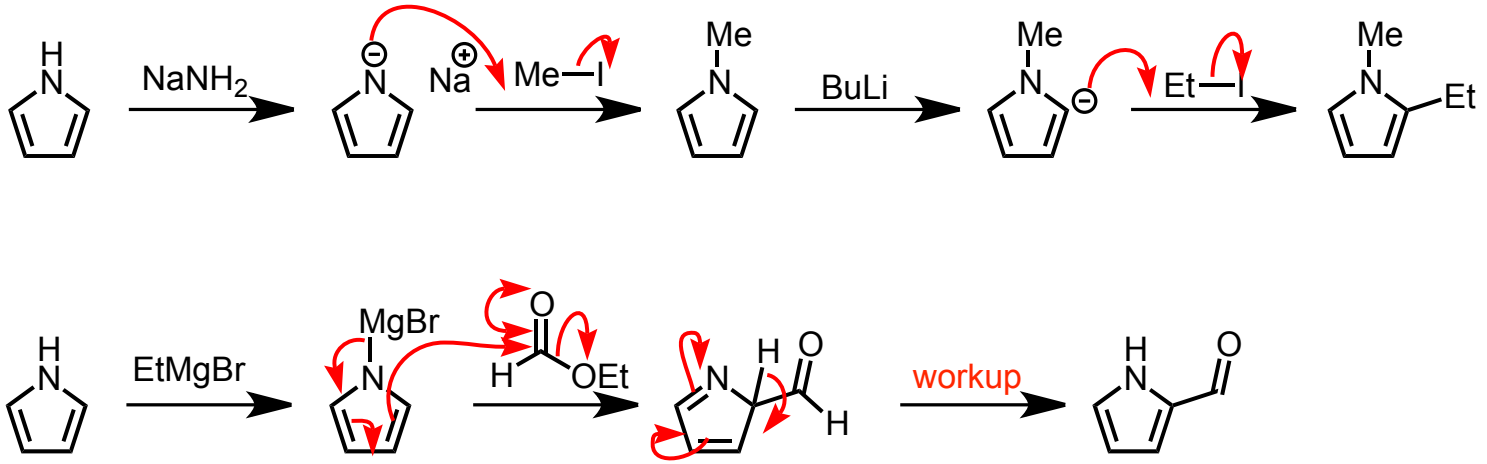
- lithiation of 5-membered heterocycles

- lithiation occurs preferentially α to the heteroatom due to inductive effect of heteroatom with, in some instances a DOM effect

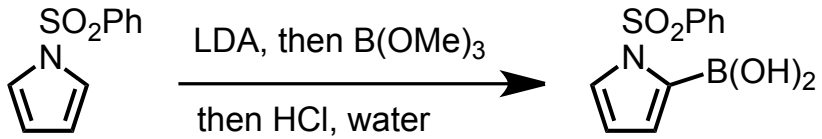
- furan and thiophene can be readily metalled α to the metal

- with pyrrole itself, the *N*-deprotonation occurs first – the more ionic the N-metal bond the greater the percentage attack at nitrogen

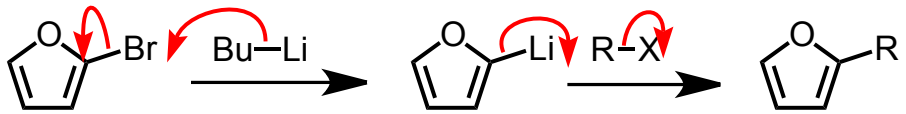
- with a more covalent N-M bond C-attack occurs.



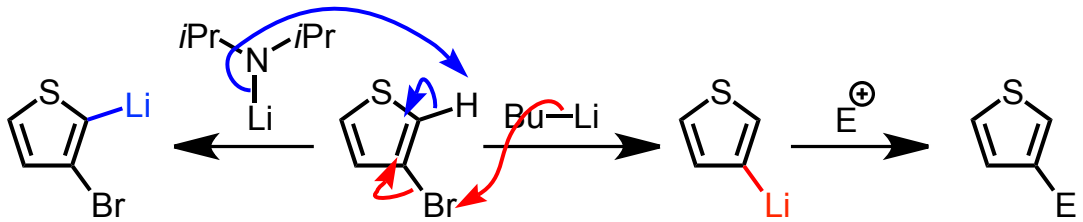
- with pyrroles bearing an *N*-EWG on nitrogen α-metallation occurs



- lithium halogen exchange occurs with aromatic heterocycles



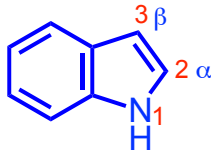
- selectivity can be achieved using LDA or butyllithium

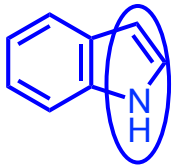


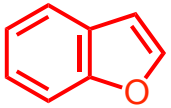
no lithium halogen exchange with LDA as would make weak N-Br bond most acidic proton removed by directed metallation

Heteroaromatics

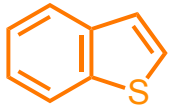
- indole







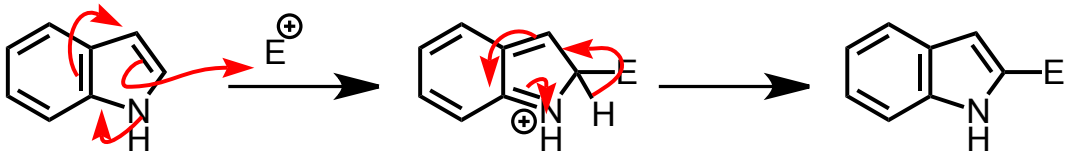
benzofuran



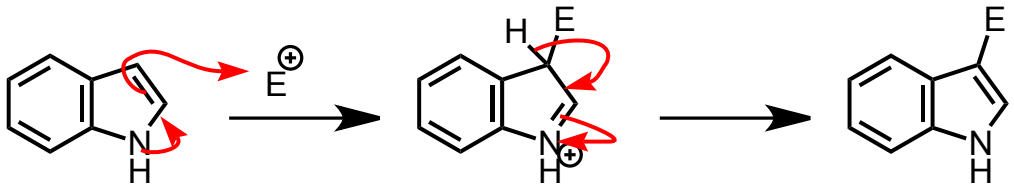
benzothiophene

- more enamine-like than pyrrole

- attack of electrophiles at the β position is the lowest energy pathway



minor

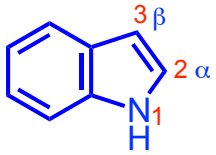


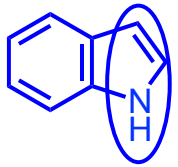
major

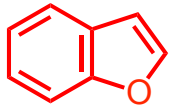
attack at β position retains aromatic sextet of benzenoid ring

Heteroaromatics

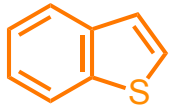
- indole







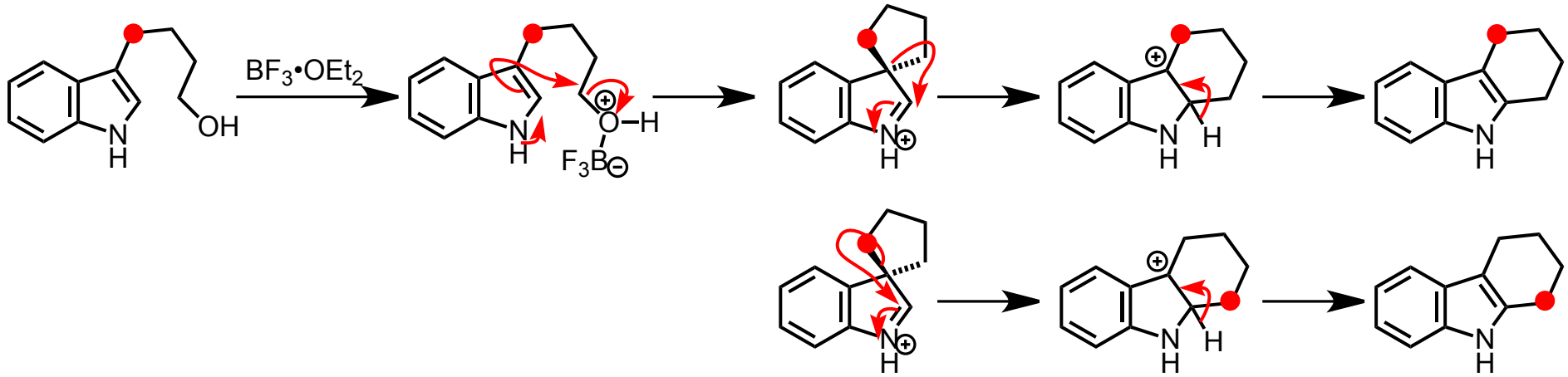
benzofuran



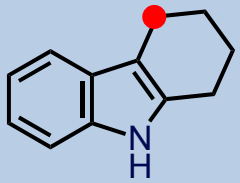
benzothiophene

- if the β-position is blocked α-attack occurs

- α-attack can occur *via* β-attack followed by rearrangement (● = CT_2 i.e. a tritiated methylene group)

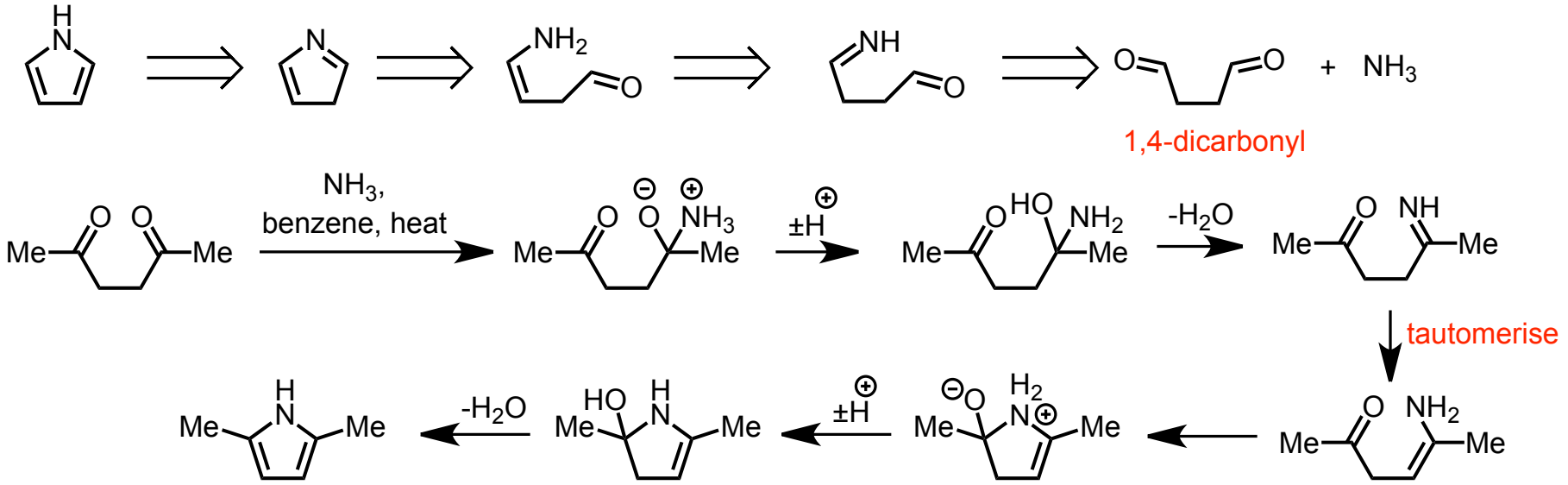


direct attack at α-position would give solely

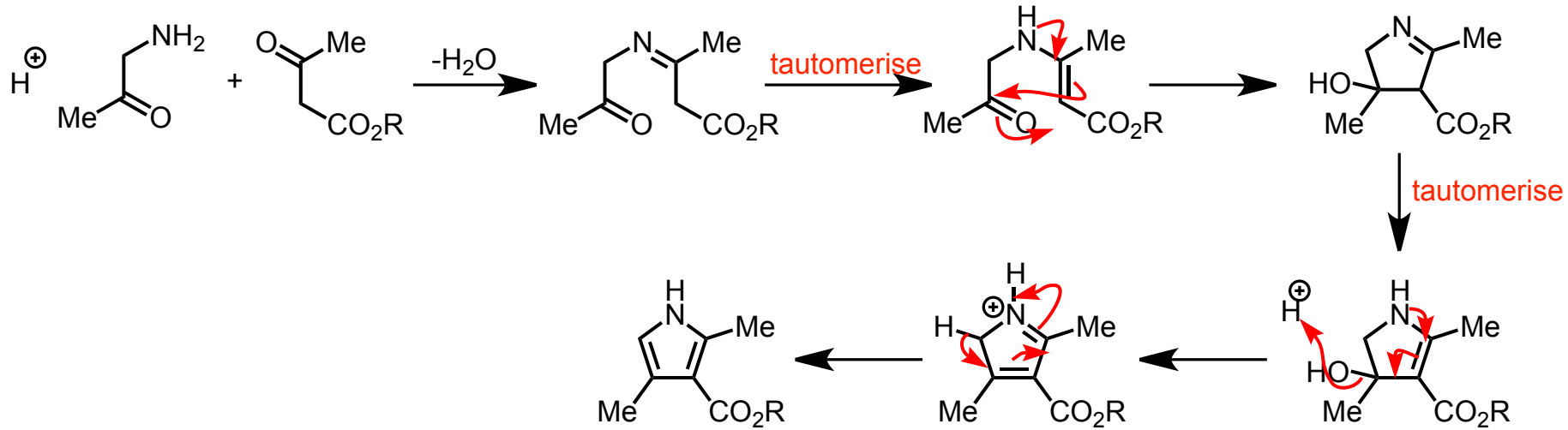


Heteroaromatics

- Synthesis
- pyrrole - synthesis from 1,4-dicarbonyls, Paal-Knorr synthesis

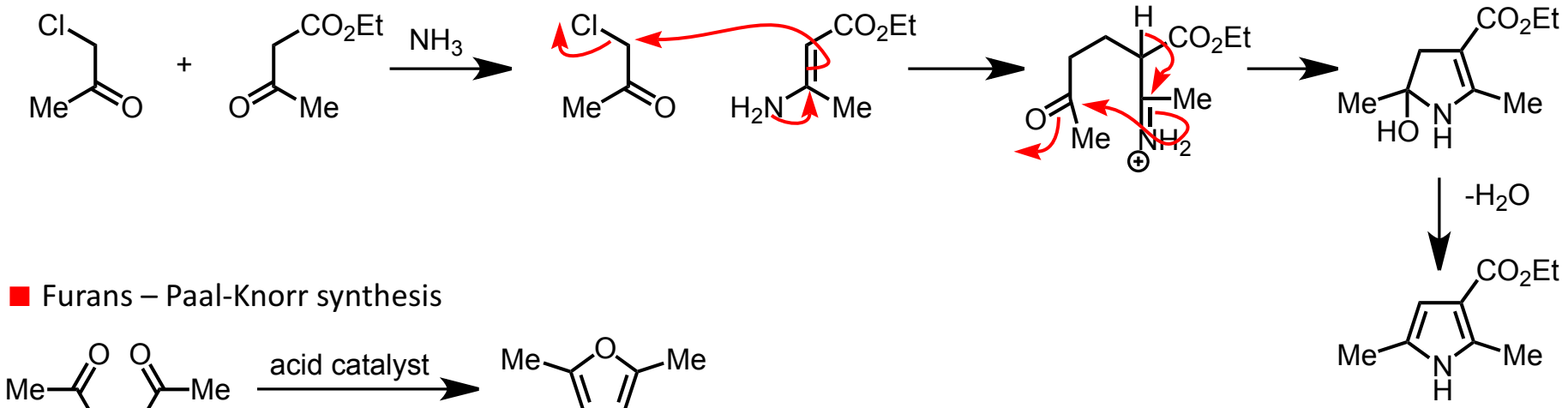


- from α-amino ketones and carbonyl compounds with activated α-methylene groups – Knorr synthesis



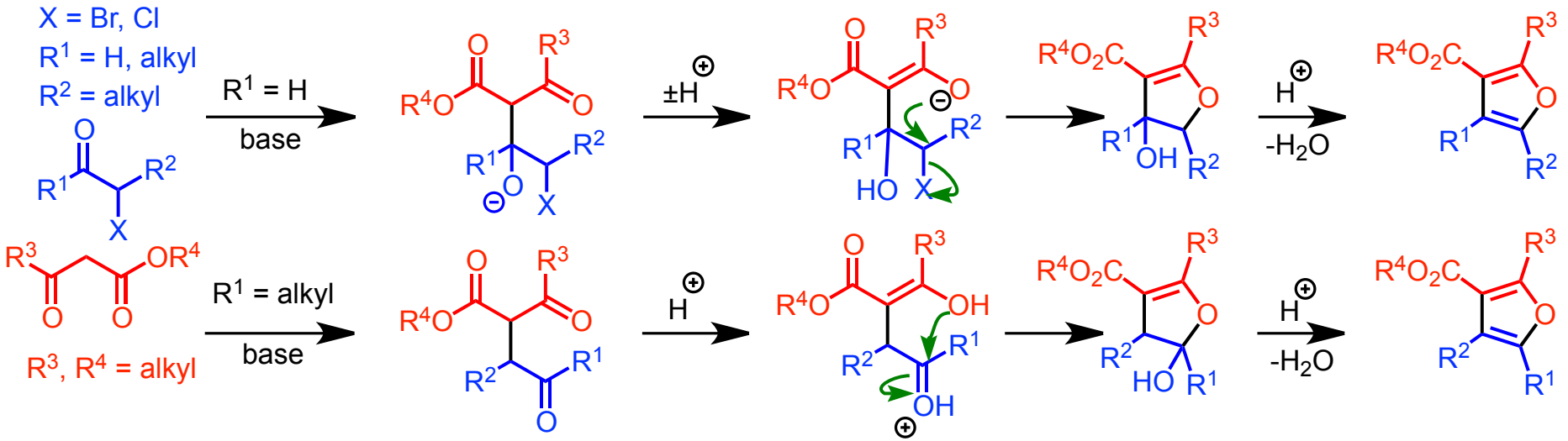
Heteroaromatics

■ Hantzsch pyrrole synthesis –from α-chloroketones and carbonyl compounds



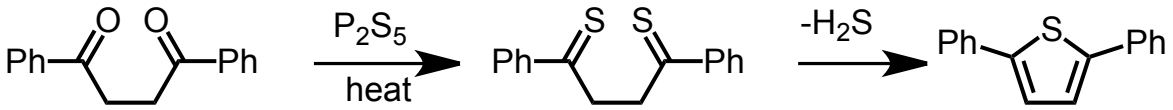
■ Furans – Paal-Knorr synthesis

■ Furans – from α-halocarbonyls and active methylene compounds

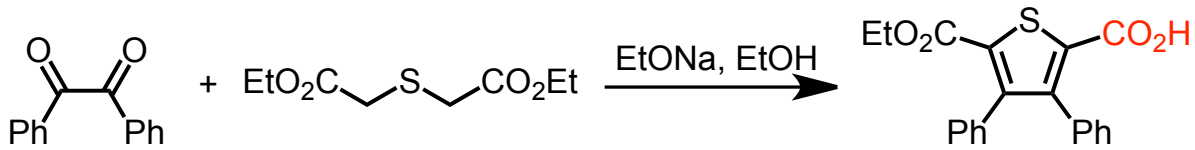


Heteroaromatics

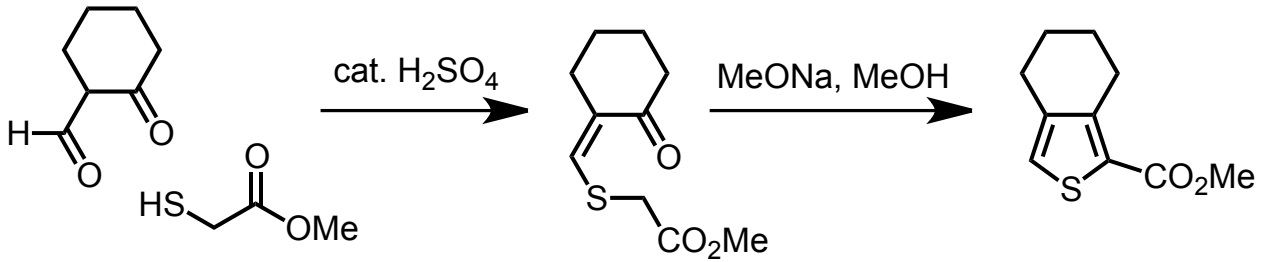
- thiophenes – from 1,4-dicarbonyl compounds



- from 1,2-dicarbonyl compounds – Hinsberg synthesis

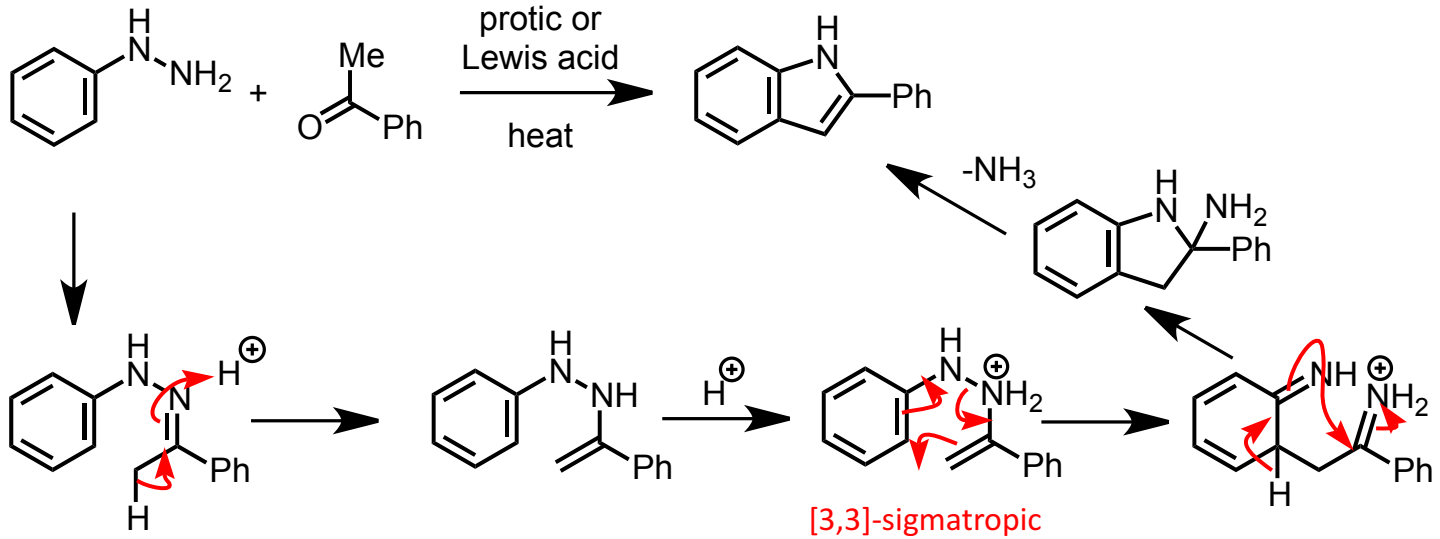


- from 1,3-dicarbonyl compounds

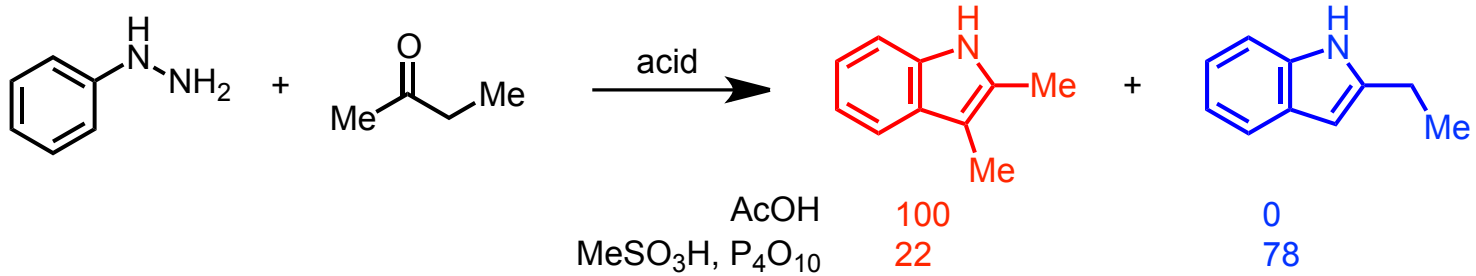


Heteroaromatics

■ Indoles – the Fischer indole synthesis

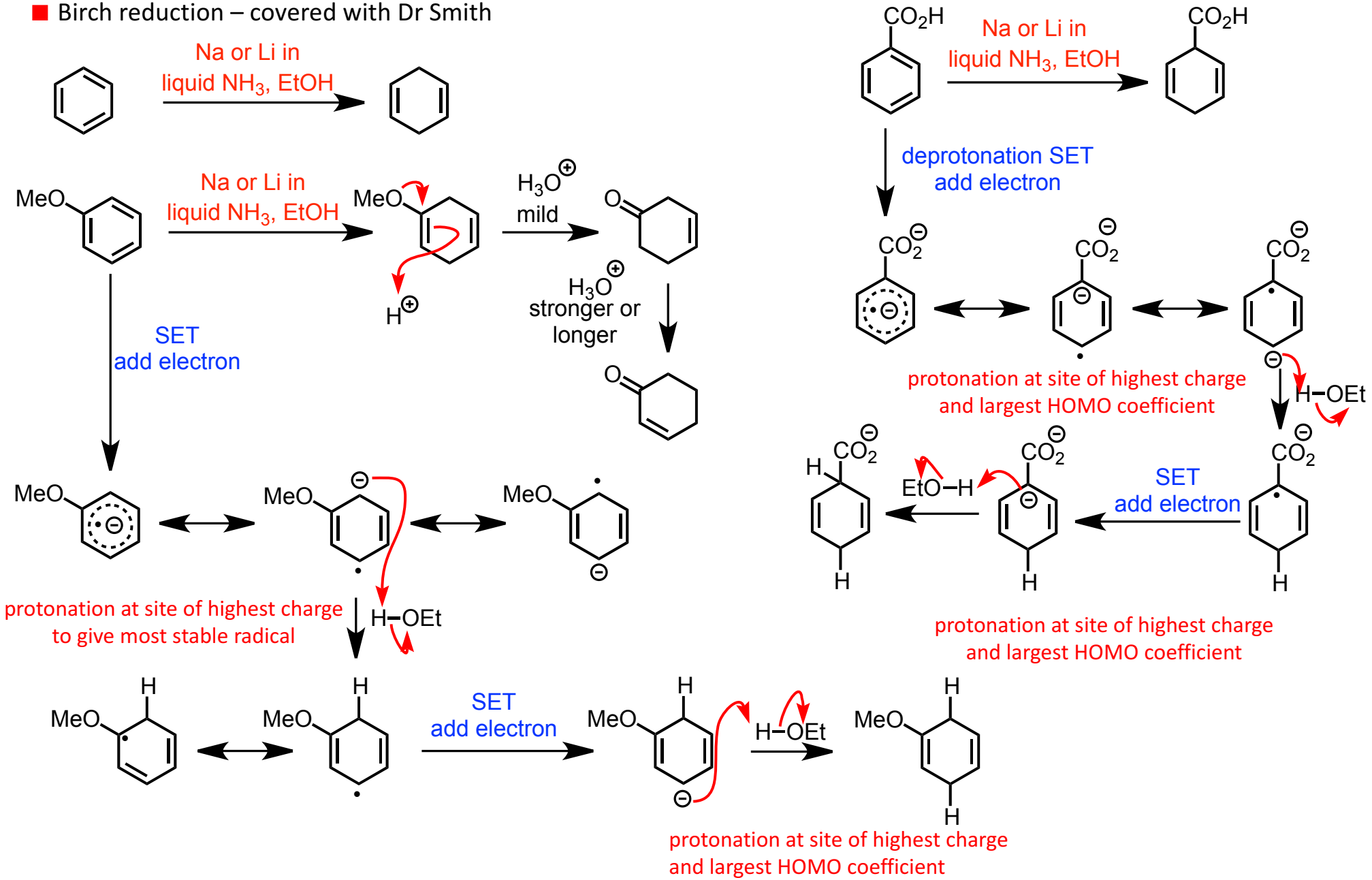


■ unsymmetrical ketones give mixtures of indoles: strong acids favour indole formation from the less substituted ene-hydrazine; weak acids favour indole formation from the more substituted ene-hydrazine



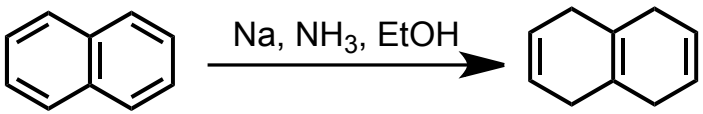
Reduction of Aromatics

- Birch reduction – covered with Dr Smith

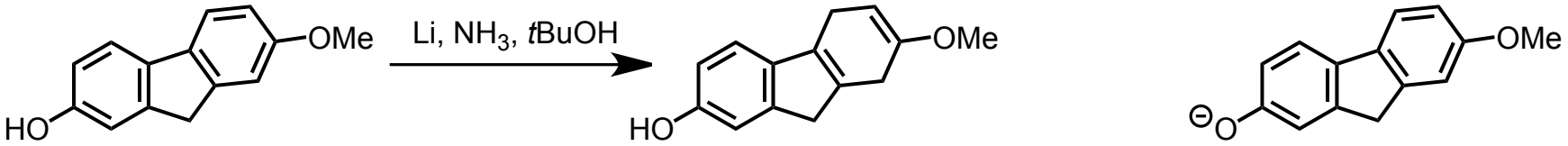


Reduction of Aromatics

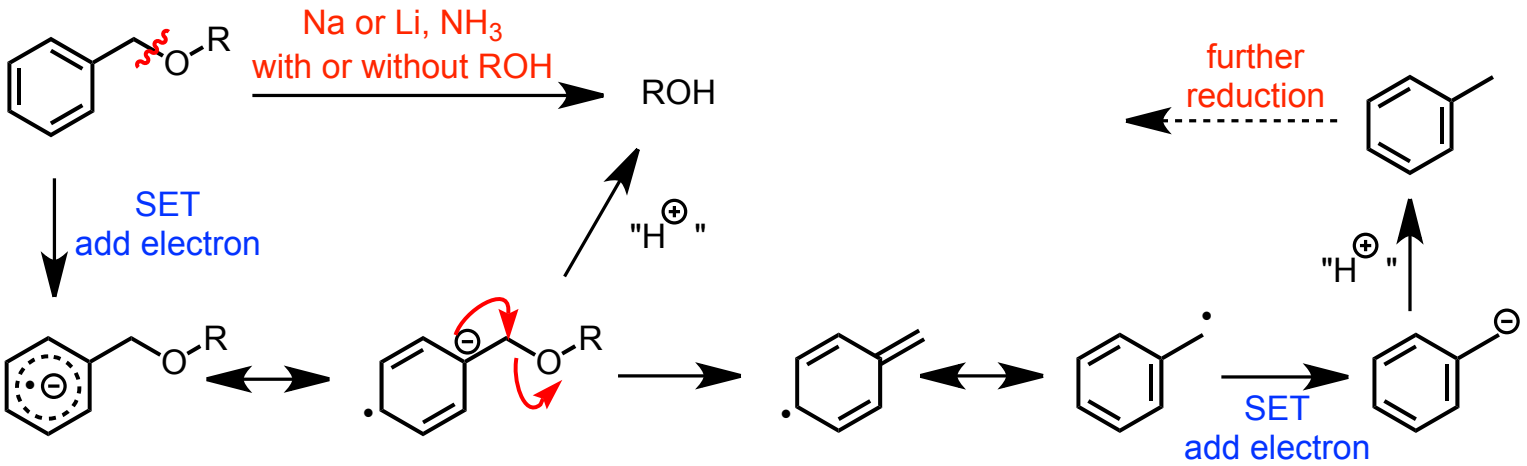
- Birch reduction examples

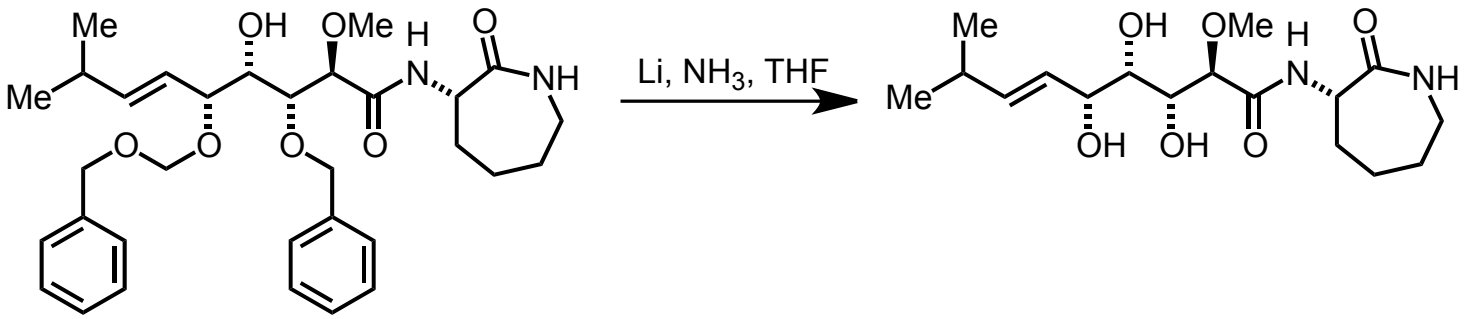


naphthalene



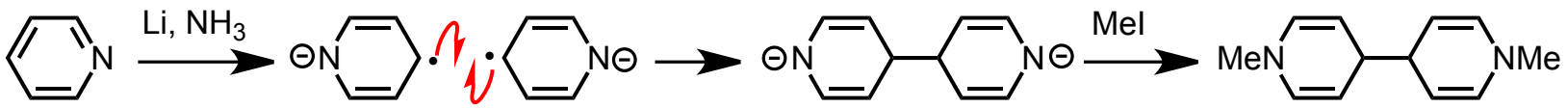
- Birch reduction with C-X bond cleavage



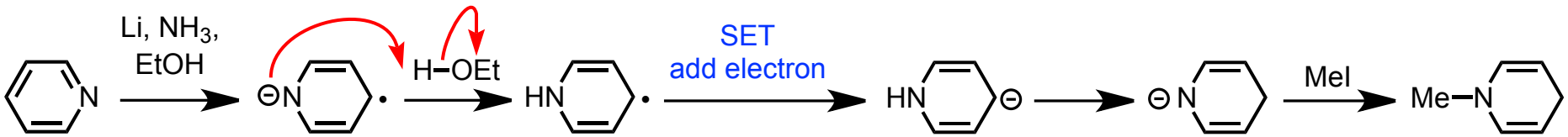


Reduction of Aromatics

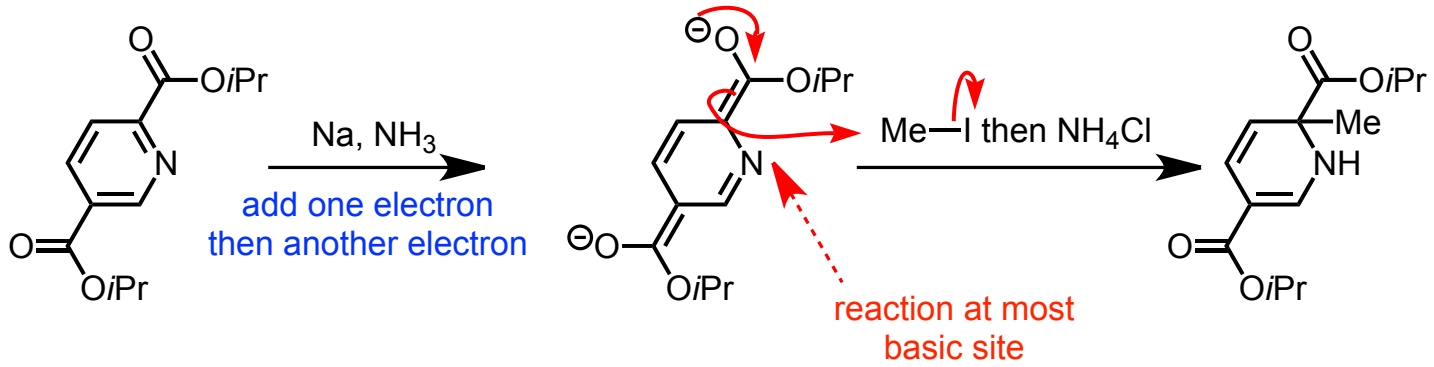
- Birch reduction – heteroaromatics
- pyridine - in the absence of added alcohol dimerisation of the intermediate radical anion occurs



- pyridine - in the presence of added alcohol dimers are not formed

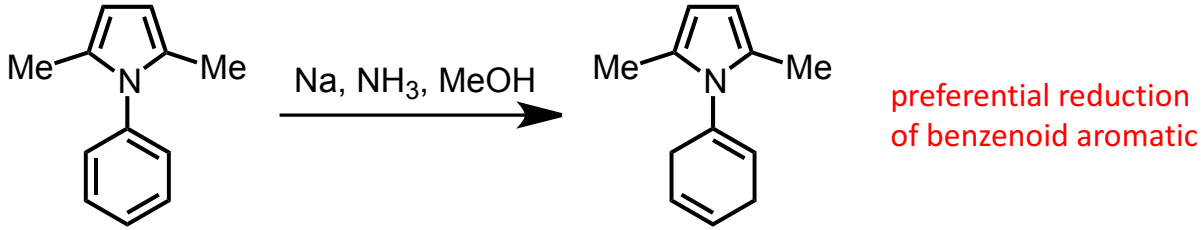


- with sufficient electron withdrawing groups, the addition of a further electron to the initially formed radical anion occurs to give a dianion



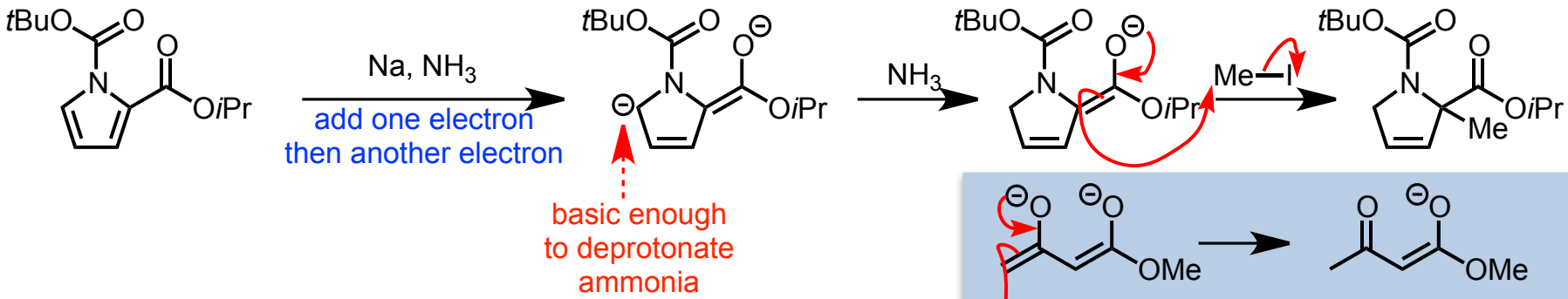
Reduction of Aromatics

- Birch reduction – pyrroles, furans, thiophenes
- electron rich and hence require an electron withdrawing group

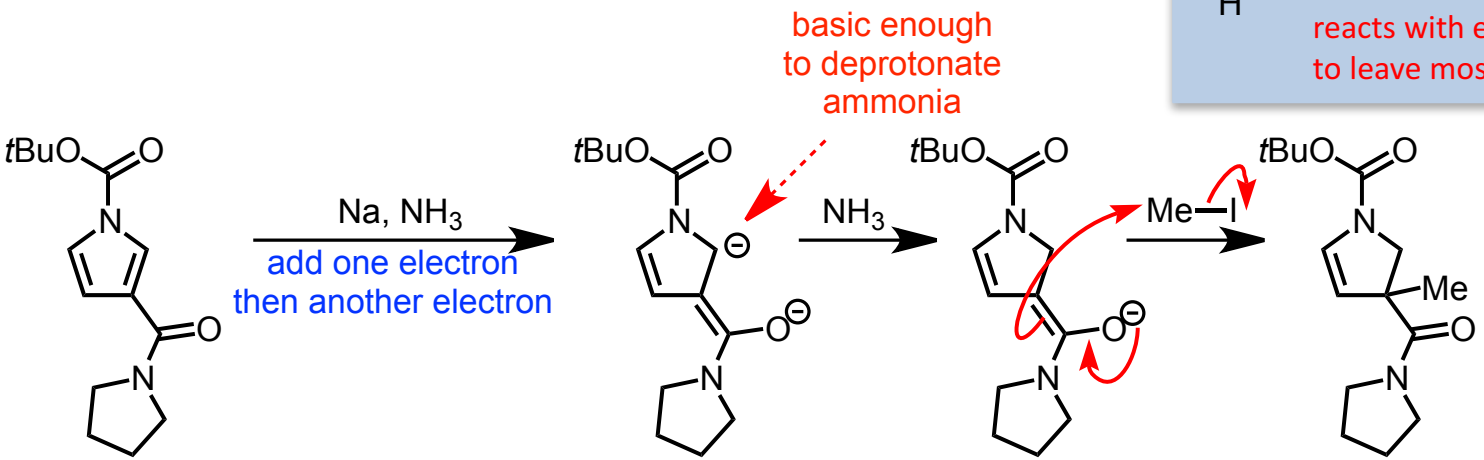


preferential reduction
of benzenoid aromatic

- with enough electron withdrawing groups further reduction of the intermediate radical anion occurs to give a dianion

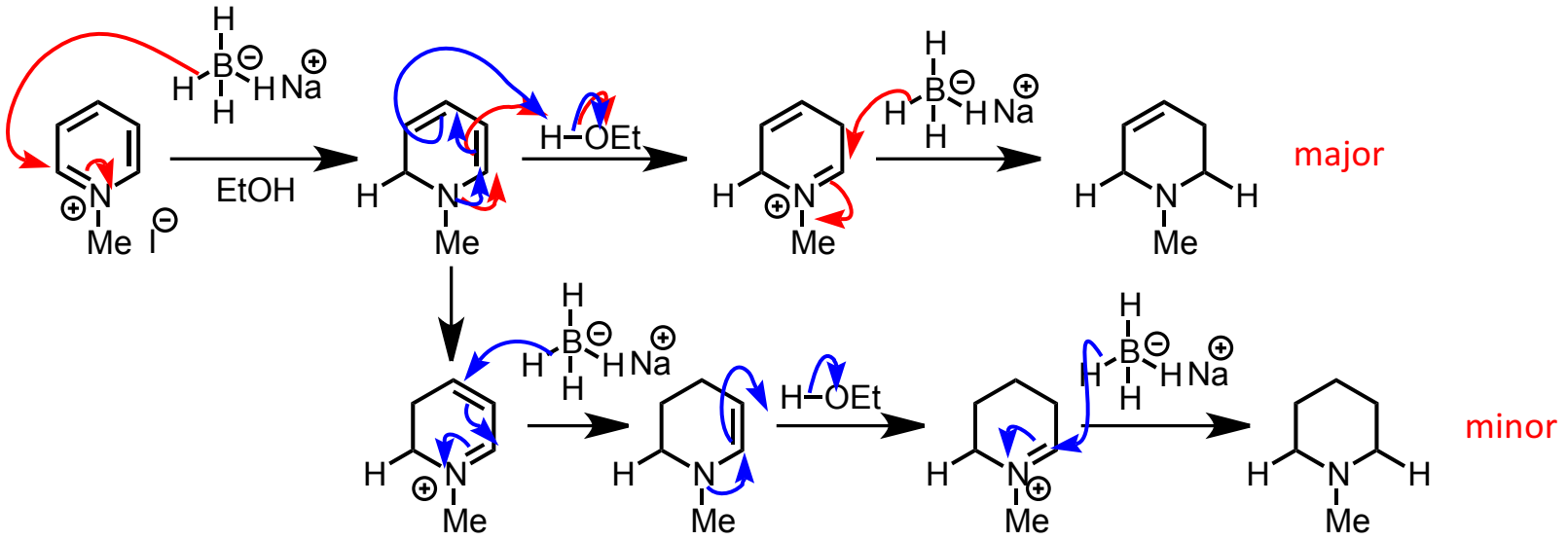


cf. dianion of alkyl acetoacetates
reacts with electrophiles at most basic site
to leave most stable, conjugated enolate

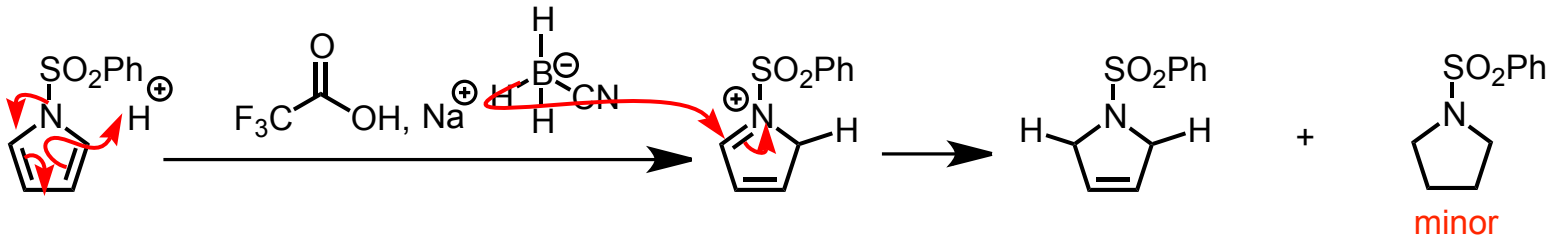


Reduction of Aromatics

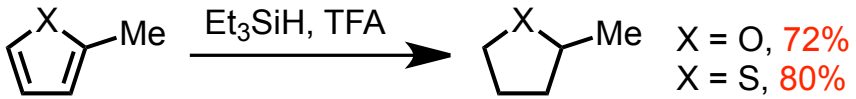
- Hydride reductions – pyridinium salts



- Simple pyrroles are only reduced by hydride reducing agents in the presence of acid



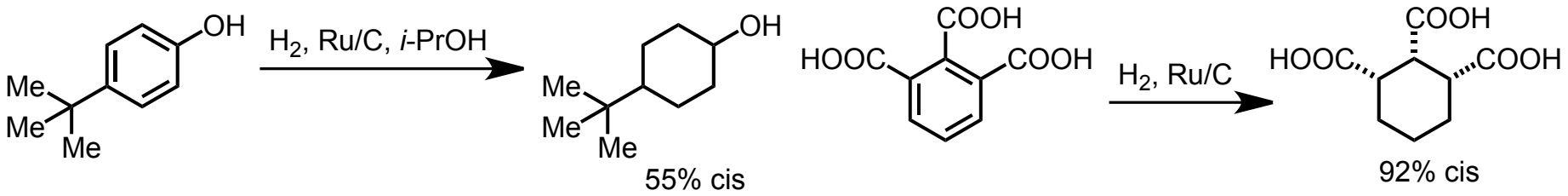
- "Ionic hydrogenation" of furan and thiophene gives the saturated derivatives



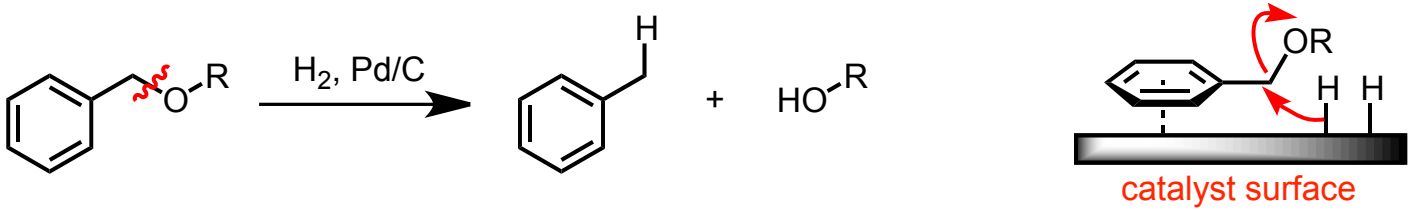
Reduction of Aromatics

- Hydrogenation – complete reduction of the aromatic ring
- hydrogenation of aromatic ring occurs most readily with Pt, Rh and Ru catalysts; Pd is less active

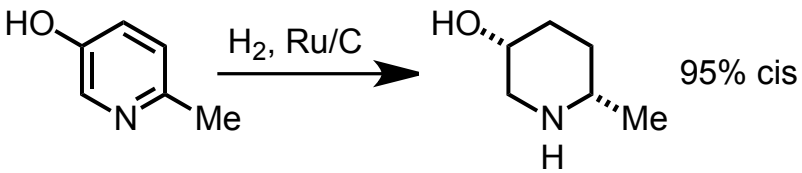
alkynes/alkenes and many other functional groups can be readily reduced in the presence of aromatic rings



- *Hydrogenolysis* of benzylic heteroatoms readily occurs under palladium catalysis; a cartoon mechanism is shown



- Pyridines are more easily hydrogenated than benzenoid aromatics



- hydrogenation of pyrrole and furan is relatively straightforward; hydrogenation of thiophene is complicated by catalyst poisoning and the hydrogenolysis of the C-S bond with complete removal of sulfur