Aromaticity & Electrophilic/Nucleophilic Aromatic Substitution

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Format and scope of presentation

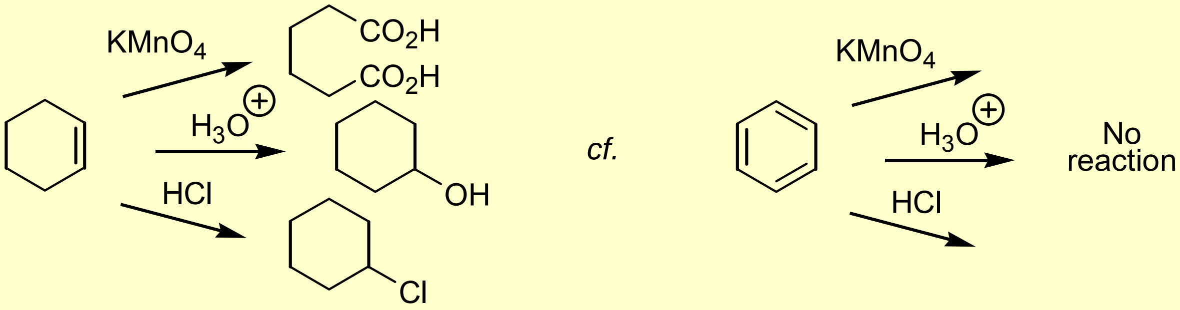
- ***Aromaticity:***
  - Historical perspective (Kekulé)
  - Characteristics, NMR ring currents
  - Valence bond & molecular orbital representations (Hückel's rule)
  - Anti-aromaticity

- ***Electrophilic aromatic substitution (S_EAr):***
  - Mechanism (Wheland intermediates, energy profile diagrams & kinetic isotope effects)
  - Nitration, sulfonylation, halogenation, Friedel-Crafts alkylation and acylation, nitrosation (diazonium salt formation & diazo-coupling, Sandmeyer reactions),
  - Directing effects (*ortho*-/*para*- ratios, *ipso*-substitution)

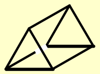
- ***Nucleophilic aromatic substitution:***
  - S_NAr
  - VNS (vicarious nucleophilic substitution)
  - S_N1 & $S_{RN}1$ (Sandmeyer reactions)
  - Benzyne & arynes

Aromaticity: historical perspective

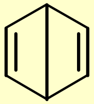
- *'Aromatic'* → *'aroma'* → *natural fragrances* e.g. *benzaldehyde (peaches)*
- *Unusual stability/unreactivity*



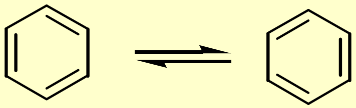
- *Late 1800's: benzene combustion analysis* → *molecular formula C_6H_6*



Ladenburg

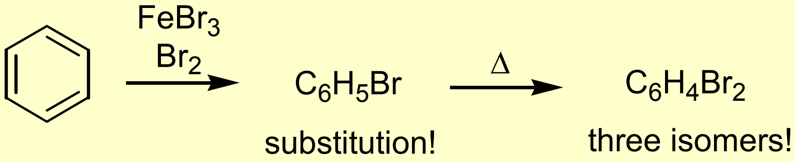


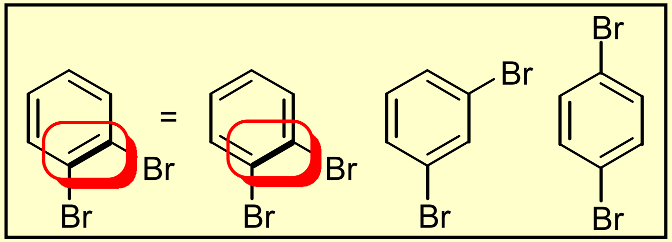
Dewar



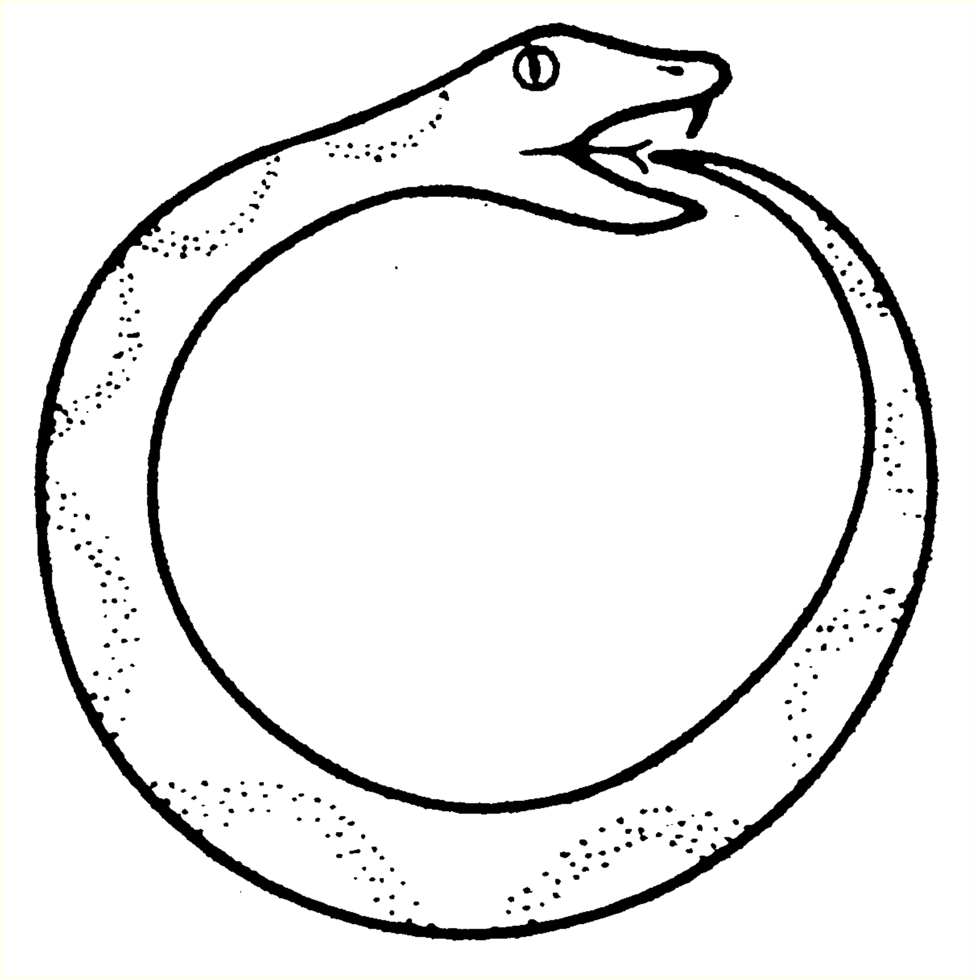
Kekulé

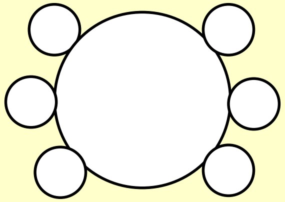
- *No-decolourisation of bromine water (addition of Br_2 across double bonds)*



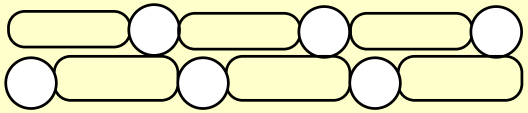


Kekulé and his dream of snakes...





Loschmidt 1861



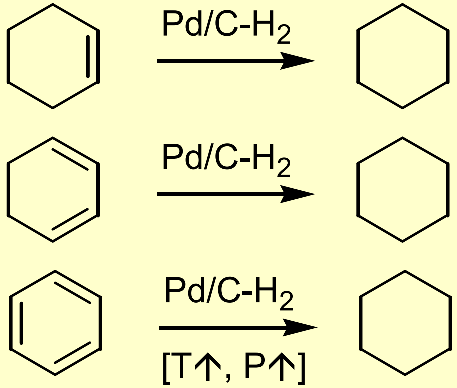
Kekulé 1861

Kekulé or Loschmidt?

- *'Facts are better than dreams'* Noe & Bader *Chem Brit*. **1993**, 126
- *'Waking up to the facts?'* Rocke *Chem. Brit.* **1993**, 401
- *'Crocker, Not Armit and Robinson, Begat the Six Aromatic Electrons'* Rzepa *Chem. Rev.* **2005**, *105*, 3436 (DOI)

Aromaticity: stability and bond lengths

- ***Quantification of unusual stability: heats of hydrogenation (calorimetry)***
  - see: Vollhardt *J. Am. Chem. Soc.* **2000**, *122*, 7819 (**DOI**)

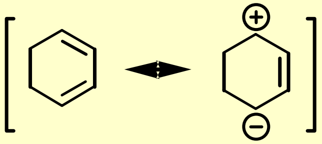


ΔH° = -120 kJmol^{-1}

N.B. 1 kcal = 4.18 kJ

ΔH° = -232 kJmol^{-1}

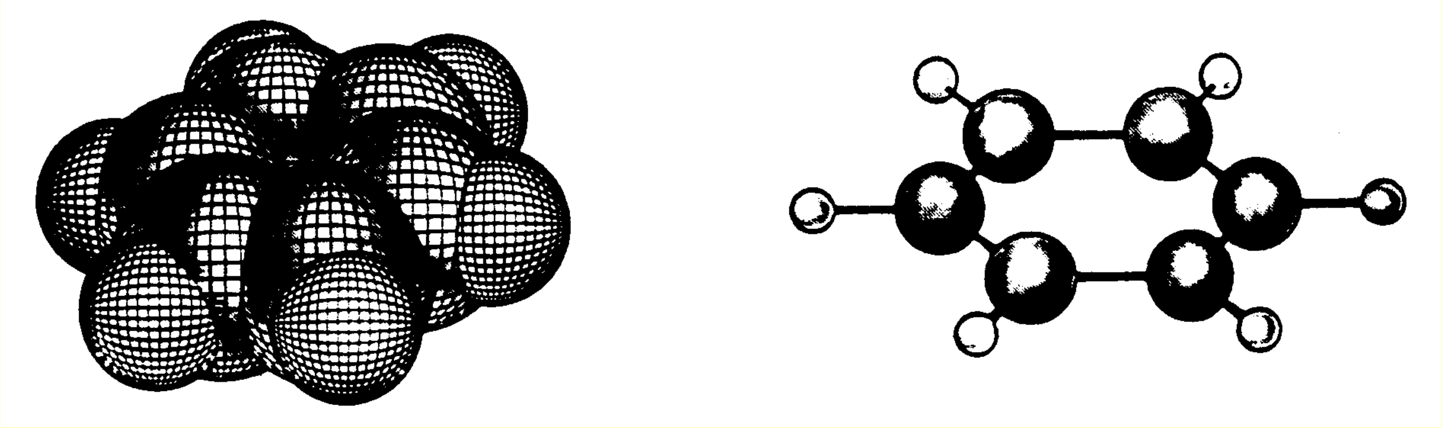
i.e. resonance 'worth' **~8 kJmol^{-1}**
[(2x120)-232]



ΔH° = -208 kJmol^{-1}

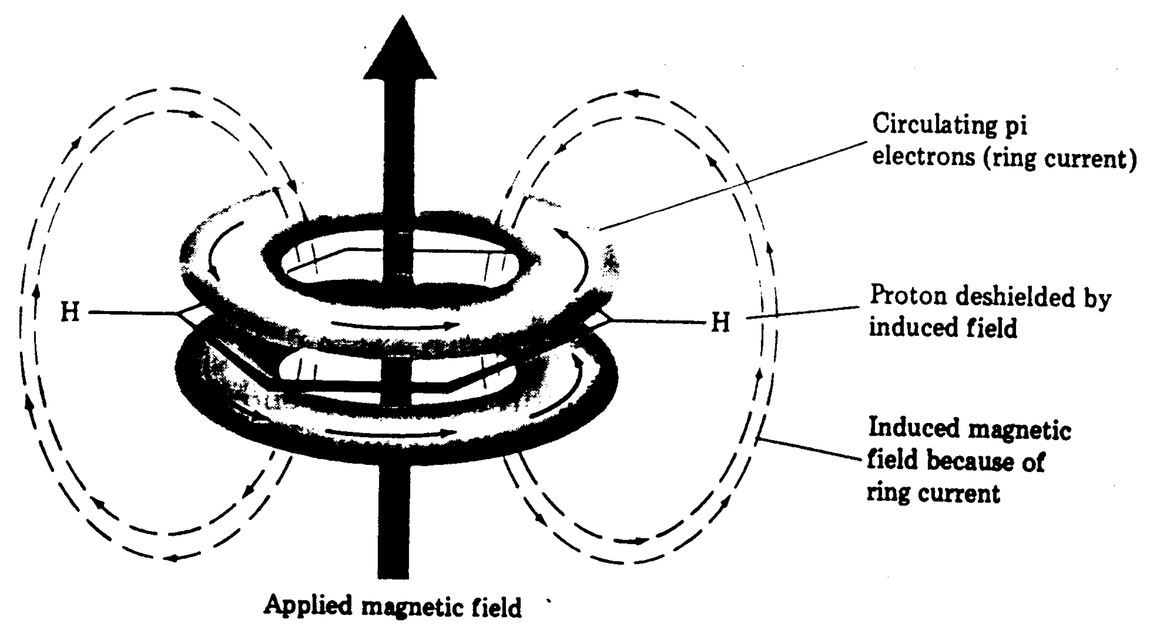
i.e. aromatic stabilisation 'worth' **~152 kJmol^{-1}**
[(3x120)-208]

- ***X-ray data show all bond lengths to be the same***
  - 1.39Å *cf.* ave C-C 1.54Å & ave C=C 1.34Å



Aromaticity: NMR ring currents

- ***Protons 'outside' ring experience deshielding (i.e → low field)***
- ***Protons 'inside' ring experience shielding (i.e. → high field)***

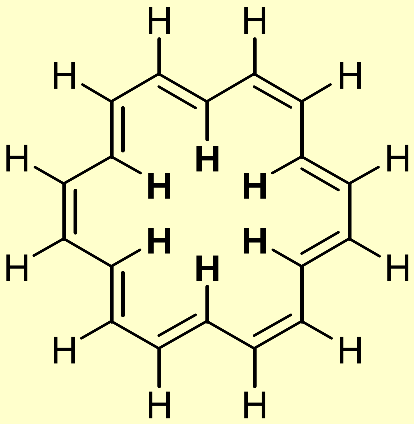


- ***BUT***: Schleyer *Org. Lett.* **2003**, *5*, 605 (**DOI**) '...there is no evidence for a special ring current influence'
- Zanasi *Org. Lett*. **2004**, *6*, 2265 (**DOI**) '...conventional interpretation...supported by large basis set QM calcs'

Aromaticity: NMR ring currents

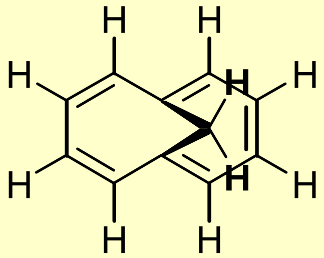
- ***Benzene gives a singlet at δ 7.27 ppm***
  - *i.e.* deshielding due to ring current (*cf.* δ 4.5-6.5 ppm for ave. vinylic protons)
  - *i.e.* singlet because all H's are in identical environment (C_6 symmetry)

- ***Higher aromatic systems have stronger ring currents resulting in dramatic shielding/deshielding:***



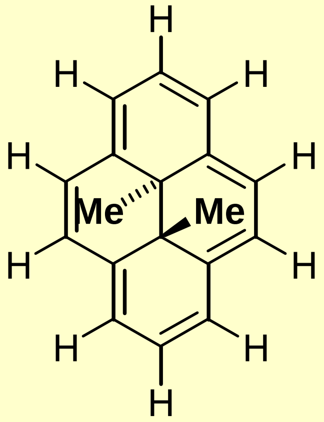
18-annulene
(18π electrons)

δ **-1.8** ppm **inside**
δ 8.9 ppm outside



Vogel's hydrocarbon
(10π electrons)

δ **-0.7** ppm **inside**
δ 7.1 ppm outside

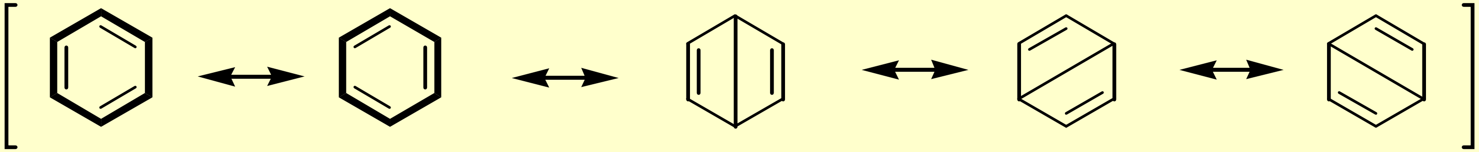


dimethyldihydropyrene
(14π electrons)

δ **-5.5** (Me) **inside**

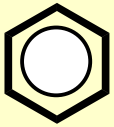
Benzene – Valence Bond and Molecular Orbital Representations of Aromaticity

- ***VALENCE BOND (VB) THEORY***
    - resonance hybrids - imaginary structures which differ only in position of electrons (atoms/nuclei do not move)
    - Not all resonance structures contribute equally - ‘real’ structure is weighted average of resonance structures



VB structure

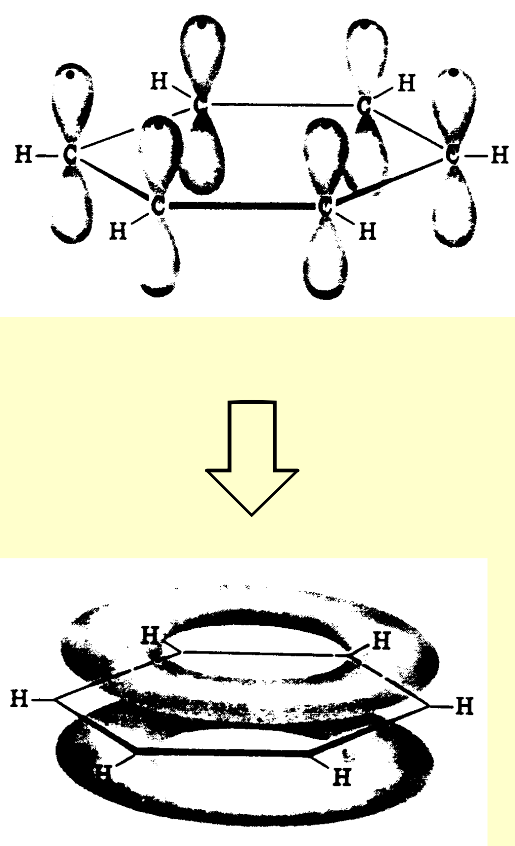
- ***MOLECULAR ORBITAL (MO) THEORY***
    - ***L***inear ***C***ombination of ***A***tomic ***O***rbitals (LCAO)
    - σ-bonding framework formed from sp^2 hybridised carbons
    - leaves p-orbital on each C atom *orthogonal* to ring
    - 6 atomic p-orbitals (AOs) → [LCAO maths] → 6 MOs
    - each MO capable of containing 2 electrons
    - 6 electrons available to occupy the 6 MOs
    - placed in 3 molecular orbitals of lowest energy: ***bonding orbitals***
    - 3 ***anti-bonding orbitals*** remain vacant

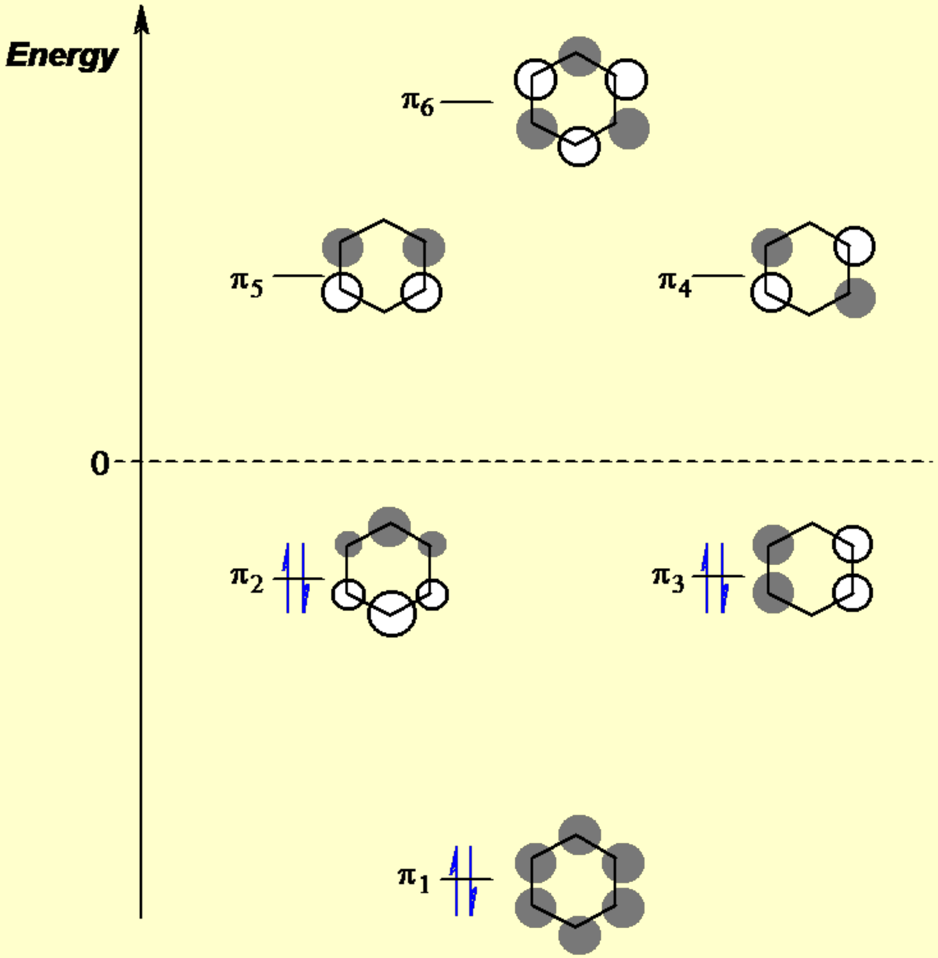


MO structure

Benzene - Molecular Orbital Description

- *Molecular orbital theory rationalises reactions and properties of benzene:*



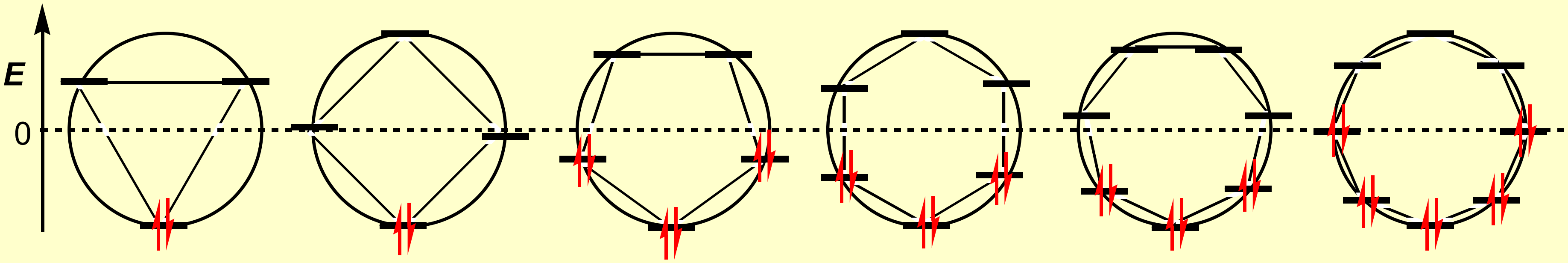


DEGENERATE

Musulin-Frost diagrams:
MO diagrams without the maths

- ***Graphical device for constructing MO energy diagrams:***
  - Frost & Musulin *J. Chem. Phys*. **1953**, *21*, 572 (**DOI**) & Zimmerman *J. Am. Chem. Soc*. **1966**, *88*, 1564 (**DOI**)

  - Draw appropriate regular polygon within a circle (with atoms touching circumference)
  - Ensure one atom is at lowest point → ring atom positions represent energy levels
  - Centre of circle is zero energy level (*i.e.* bonding orbitals below, anti-bonding above)



cyclopropenyl cation

2 π e's

cyclobutadienyl dication

2 π e's

cyclopentadienyl anion

6 π e's

benzene

6 π e's

cycloheptatrienyl (tropylium) cation

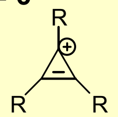
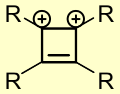
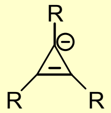
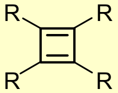
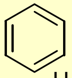
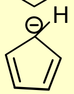
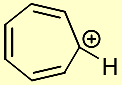
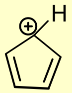
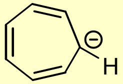
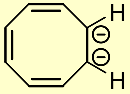
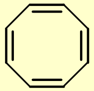
6 π e's

cyclooctatetraenyl dianion

10 π e's

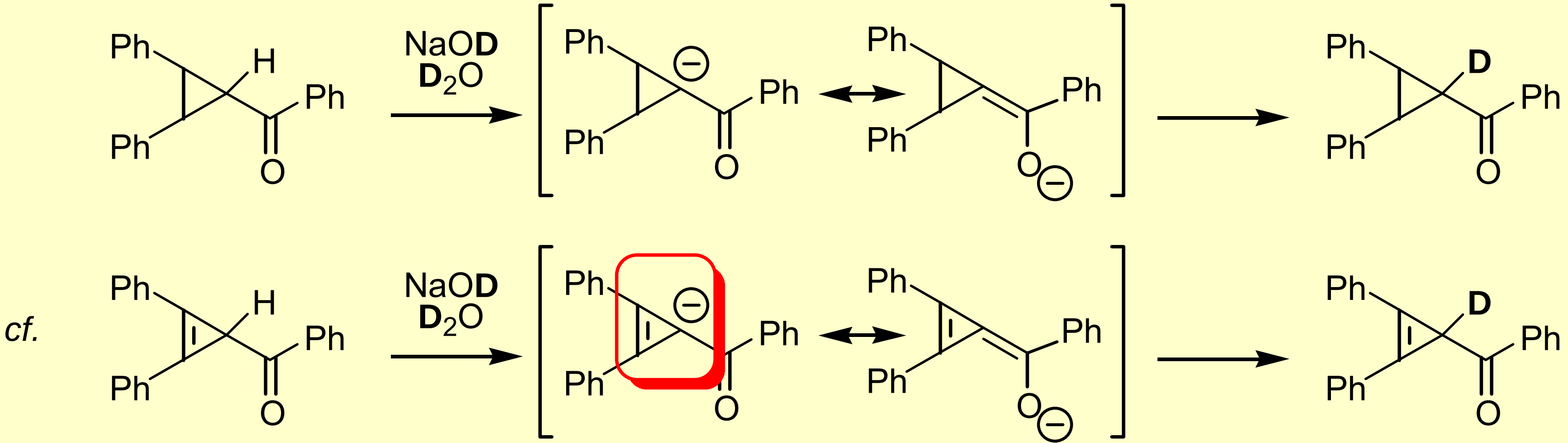
Hückel’s rule

- ***Empirical rule for aromaticity:***
  - Hückel *Z. Phys.* **1931**, *70*, 204; ***Review:*** Berson *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2750 (**DOI**)
  - For compounds which are planar & have a contiguous, cyclic array of p-orbitals perpendicular to plane of ring:
    - Those with 4n+2 p electrons display special stabilisation: *i.e.* **aromatic**
    - Those with 4n p electrons display special instability: *i.e.* **anti-aromatic**:

4n+2 π electrons (aromatic)	**4n π electrons** (antiaromatic or non aromatic)
n = 0  cyclopropenyl cation  cyclobutadienyl dication	 cyclopropenyl anion  cyclobutadiene
n = 1  benzene  cyclopentadienyl anion  cycloheptatrienyl cation (tropylium cation)	 cyclopentadienyl cation  cycloheptatrienyl anion
n = 2  cyclooctatetraenyl dianion	 cyclooctatetraene

Evidence for anti-aromaticity

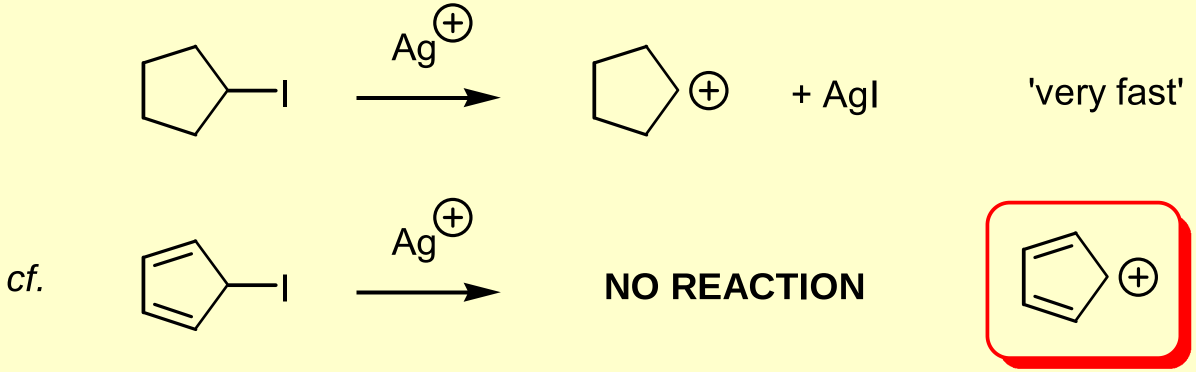
- ***Deprotonation of cycloprop(en)yl ketones***



4 π electrons
anti-aromatic

6000 times
slower!

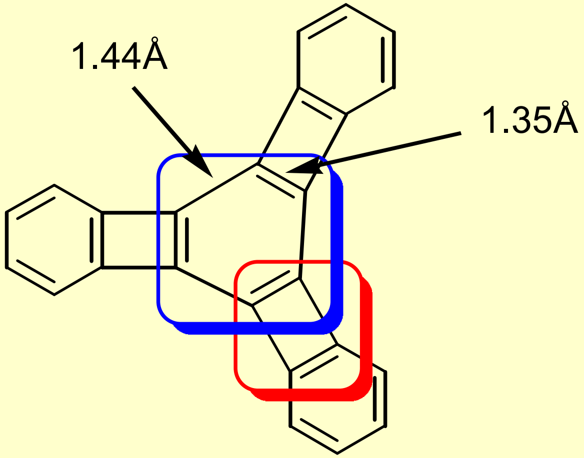
- ***Silver assisted solvolysis of cyclopent(adien)yl iodides***



4 π electrons
anti-aromatic

Vollhardt's cyclohexatriene

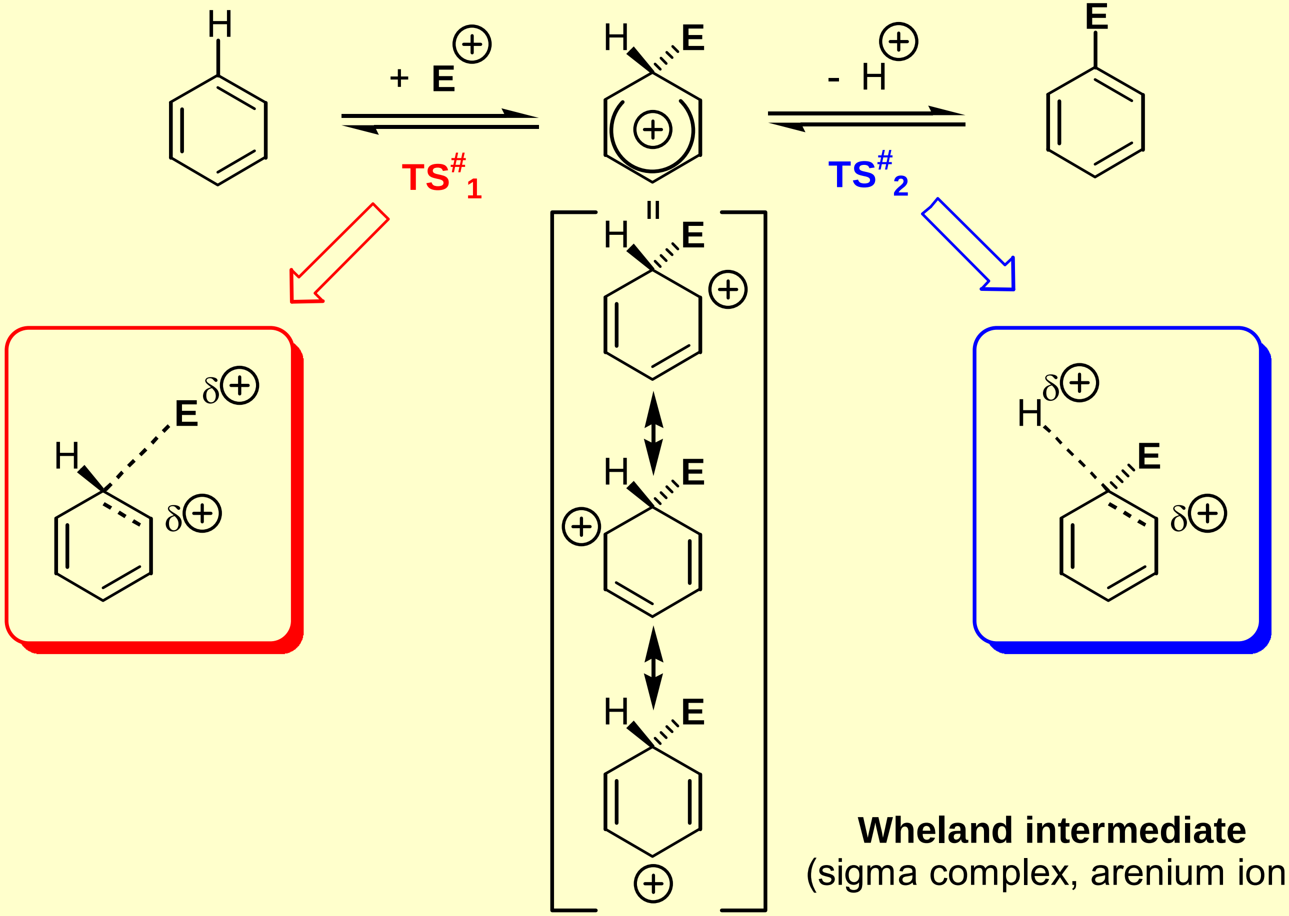
- Vollhardt *J. Am. Chem. Soc.* **1986**, *108*, 3150 (**DOI**)
- Rouhi *Chem. Eng. News* **1996**, April, 27 & Chem. Eng. News **2001**, March, 55 (**DOI**)



- Destabilisation afforded by 3 x antiaromatic cyclobutadiene units apparently outweighs stabilisation of 1x aromatic benzenoid ring
- Vollhardt *J. Am. Chem. Soc.* **2000**, *122*, 7819 (**DOI**)

Electrophilic Aromatic Substitution: S_EAr

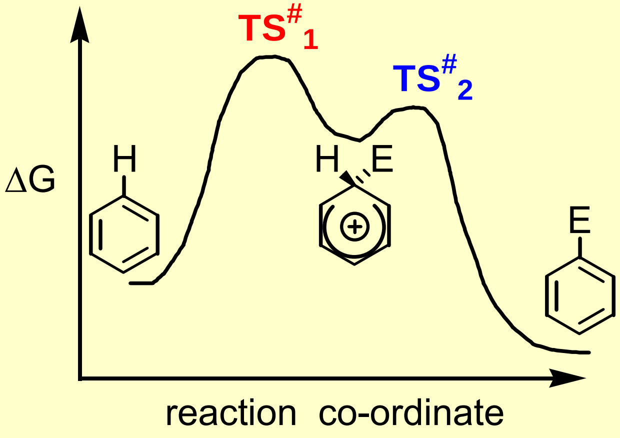
- Mechanism: ***addition-elimination***



Wheland intermediate
(sigma complex, arenium ion)

notes

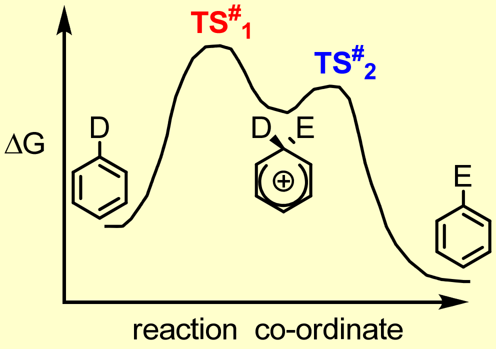
- *Intermediates*: energy minima
- *Transition states*: energy maxima
- Wheland intermediate is NOT aromatic but stabilised by delocalisation
- Generally under kinetic control

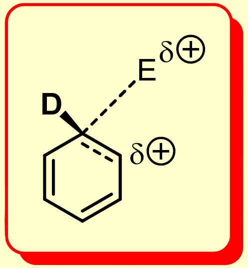


Evidence for addition-elimination

- ***Kinetic Isotope Effects (KIE's)***

Case 1





$\text{TS}^{\#}_{1}$ is the

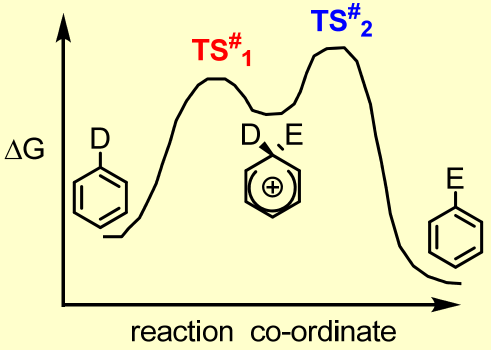
***Rate Determining Step* (RDS)**

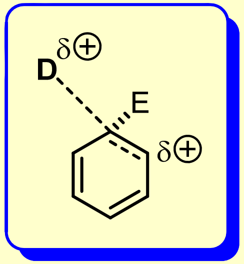
this DOES NOT involve C-D bond breaking

i.e. **NO *Kinetic Isotope Effect* (*KIE*)**

<u>MOST</u> S_EAr REACTIONS e.g. Nitration

Case 2





$\text{TS}^{\#}_{2}$ is the

***Rate Determining Step* (RDS)**

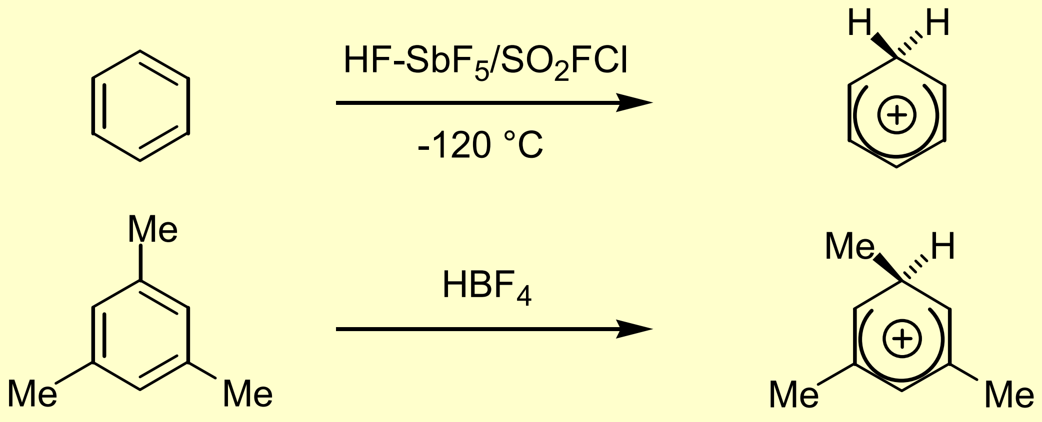
this DOES involve C-D bond breaking

i.e. **primary *Kinetic Isotope Effect* (*KIE*) expected**

<u>RARE</u> for S_EAr REACTIONS, but e.g. nitrosation shows small KIE possibly due to partitioning effects

Further evidence

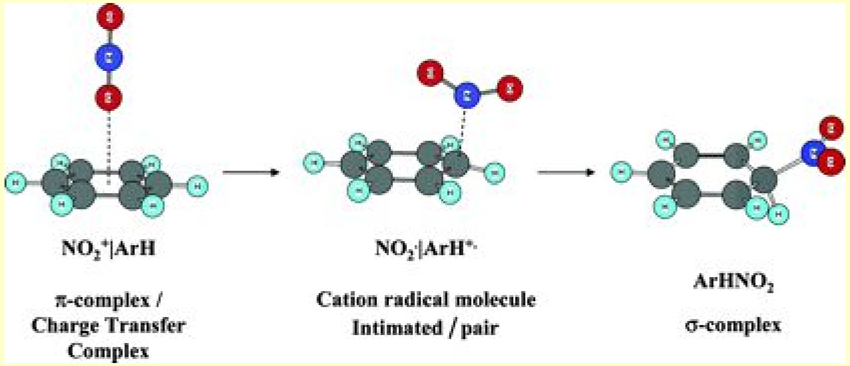
- ***Direct observation/isolation of Wheland intermediates:***



^{1}H NMR

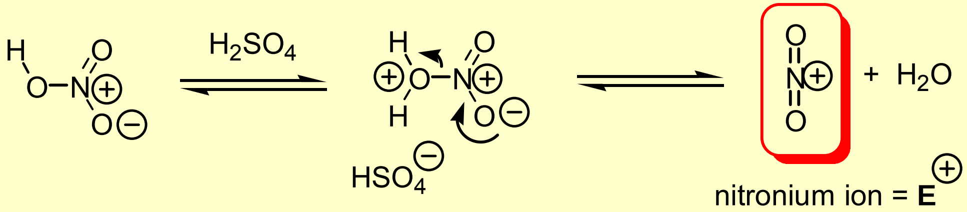
white isolable solid

- ***Detailed mechanistic studies on NITRATION:***
  - Electrophilic vs charge-transfer processes: Tanaka *J. Org. Chem*. **2000**, *65*, 2972 (**DOI**)
  - Femtosecond UV of Wheland intermediates: Kochi *J. Am. Chem. Soc*. **2000**, *122*, 8279 (**DOI**)
  - Full energy profile for benzene nitration including full historical background and development of understanding – recommended reading:
  - Olah *J. Am. Chem. Soc*. **2003**, *125*, 4836 (**DOI**)

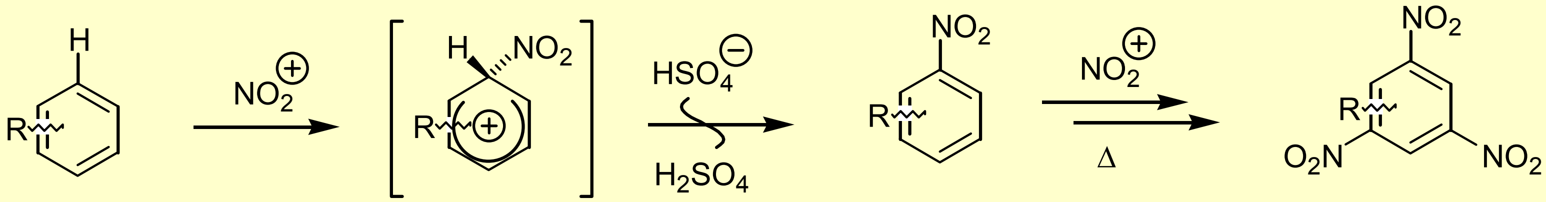


Nitration

- ***Review:*** Albright *ACS Symposium Series* **1996**, *623*, 1
- ***Typical conditions:*** *c*.HNO_3/*c*.H_2SO_4 (1:1) or *c*.HNO_3 in AcOH



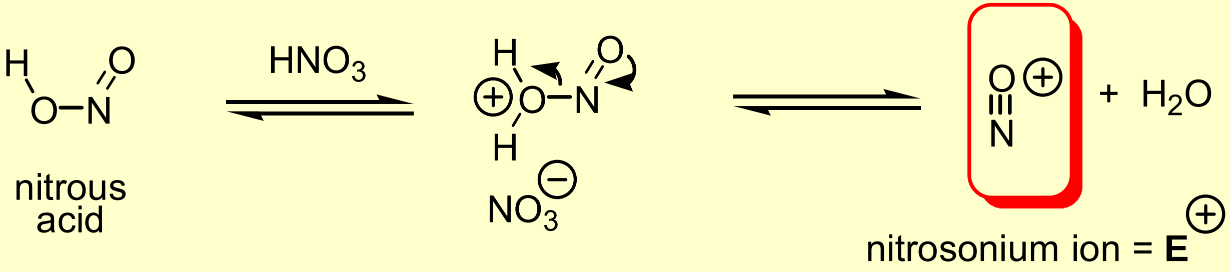
  - Can also use NO_2BF_4, NO_2ClO_4, NO_2PF_6, $NO_2CF_3SO_3$, N_2O_4, or N_2O_5 in organic solvents
  - Useful method for introduction of nitrogen (*e.g.* Ar-NO_2 → Ar-NH_2 → Ar-N_2^+ → *etc.*)
  - The process is catalytic in sulfuric acid (or whichever acid used to protonate nitric acid)



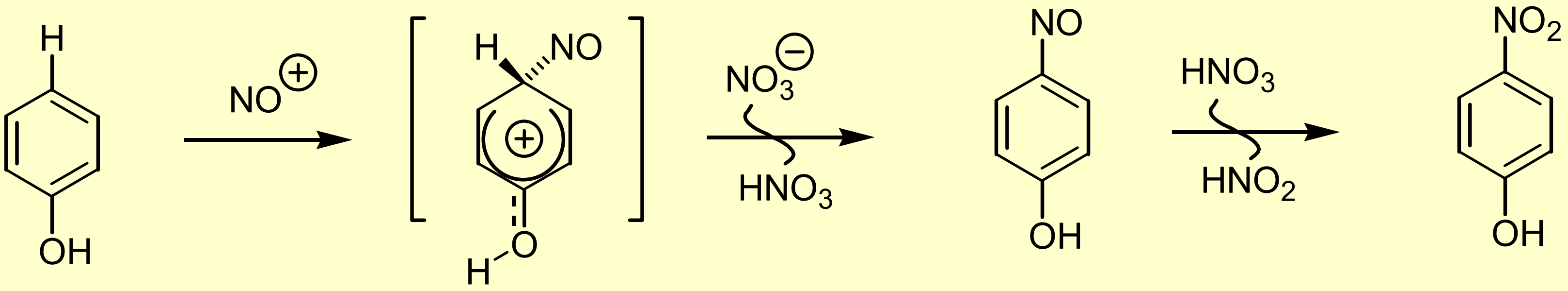
- ***Recent developments:***
  - *Microwave assistance* (NR_4NO_3-Tf_2O)*:* Shackleford *J. Org. Chem.* **2003**, *68*, 267 (**DOI**)
  - *Lanthanide(III) triflate catalysis*: Waller *Chem. Commun.* **1997**, 613 (**DOI**); Barrett *Green Chemistry* **2001**, 26 (**DOI**)
  - *In ionic liquids*: Laali *J. Org. Chem.* **2001**, *66*, 35 (**DOI**)
  - *Using* $Bi(NO_3)_3 \cdot 5H_2O$: Yin *J. Org. Chem*. **2005**, *70*, 9071 (**DOI**)

Nitration of activated aromatics

- ***Typical conditions:*** dilute HNO_3 in water, acetic acid or acetic anhydride

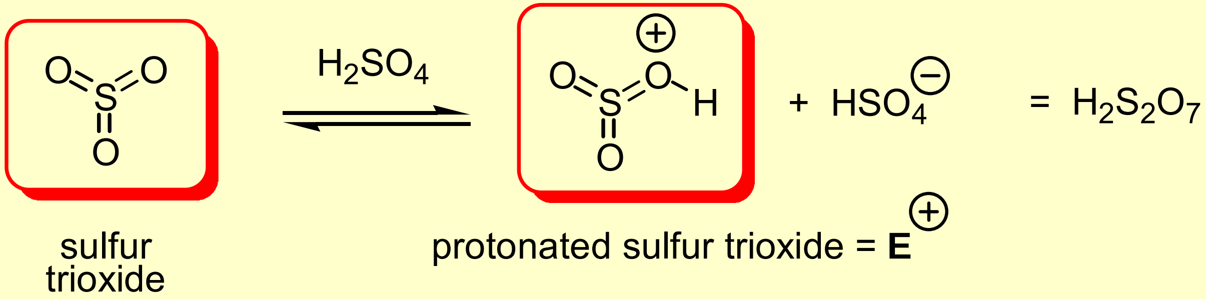


  - The nitrosonium ion is a less powerful electrophile than the nitronium ion
  - Dilute nitric acid always contains traces of nitrous acid
  - The intermediate nitrosoarene can sometimes be isolated without oxidation
  - Autocatalytic: oxidation of the nitrosoarene to the nitroarene by nitric acid produces nitrous acid

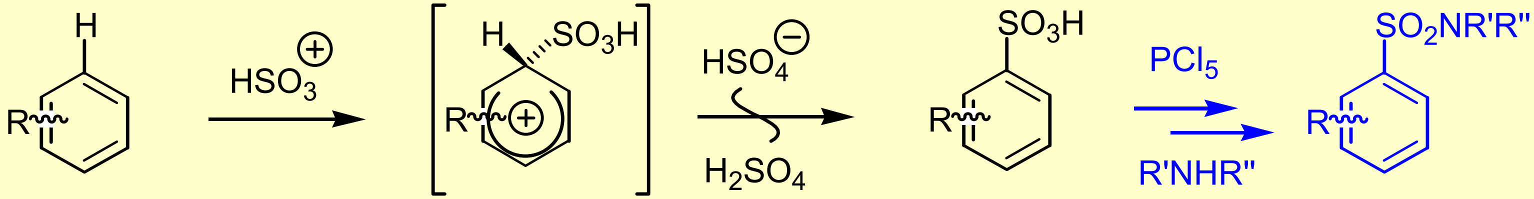


Sulfonylation

- ***Typical conditions:*** oleum (*c*.H_2SO_4 saturated with SO_3)



  - The electrophile is either SO_3 or HSO_3^+ depending on the conditions
  - Can also use SO_3 in aprotic solvents (here, the electrophile is SO_3)
  - Virtually all aromatic systems can be sulfonated under appropriate conditions
  - Sulfonation is substantially **reversible at high temperatures** but essentially irreversible at 0 °C
  - Useful entry to ***sulfonamides*** in medicinal chemistry:



  - *NB*. recent use of pentafluorophenyl (pfp) sulfonates for sulfonamide construction:
  - Caddick *J. Am. Chem. Soc.* **2004**, 126, 1024 (**DOI**)

Halogenation

- ***typical conditions: Molecular halide ±Lewis acid (LA) catalyst in the dark.***

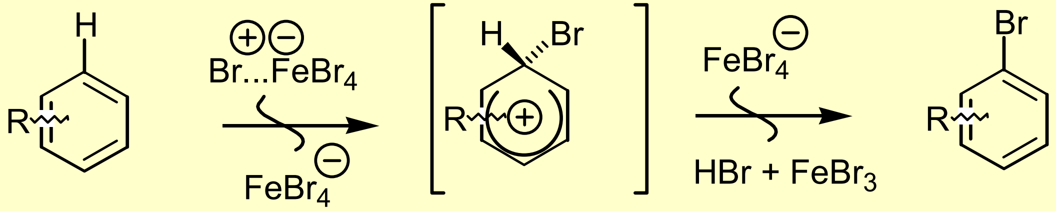
$$Br_2 \underset{}{\overset{FeBr_3}{\rightleftharpoons}} \boxed{\overset{\oplus\,\ominus}{Br...FeBr_4}}$$

Halogen-Lewis acid complex = $\mathbf{E}^{\oplus}$

  – ***bromine and chlorine:*** activated hetero-aromatics do NOT require LAs
    - hypohalous acids: HO-Cl, HO-Br, & *N*-halosuccinimides (NBS & NCS) also useful
    - *e.g.* NCS in 2-propanol see: Zanka *Synlett* **1999**, 1984 (**DOI**)

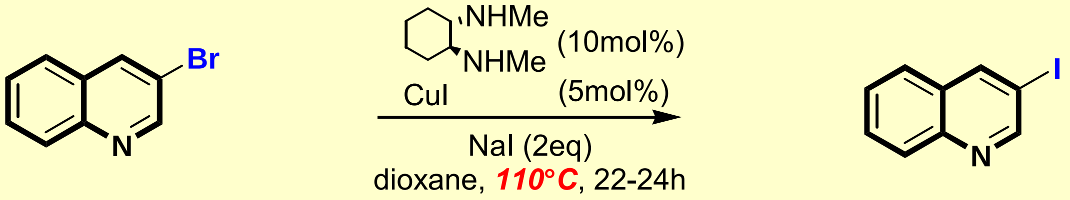
  – ***iodine:*** requires oxidising promotors, *e.g.* I_2 -CAN: Antequera *Tetrahedron Lett.* **2001**, *42*, 863 (**DOI**)
    - iodine better introduced by (i) ICl, (ii) lithiation/I_2 quench, (iii) diazonium/KI, (iv) thallation/KI
    - ***review:*** Merkushev *Russ. Chem. Rev. (Engl. Trans.)* **1984**, *53*, 583

  – ***fluorine:*** generally reacts explosively with aromatics:
    - fluoride best introduced by ***Bälz-Schiemann*** reaction: HBF_4^-diazonium/Δ
    - ***Review:*** Silvester *Aldrichchimica Acta* **1991**, *24*, 31 (**DOI**); ***review:*** Moilliet *Chim. Oggi* **2001**, 41

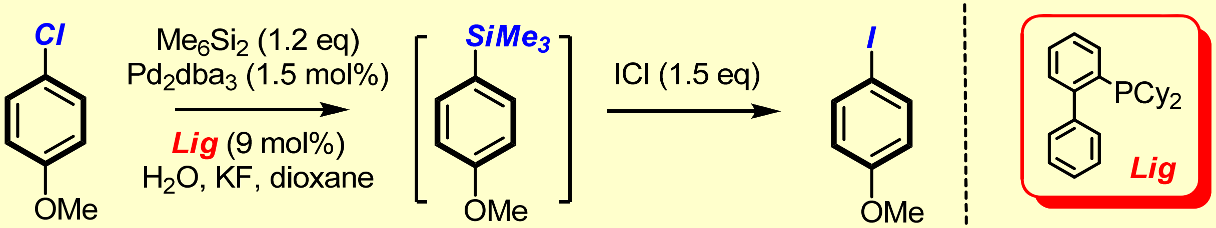


Aromatic Finkelstein reactions

- ***Br → I exchange - Cu catalysis:***
  - Buchwald *J. Am. Chem. Soc.* **2002**, *124*, 14844 (**DOI**)

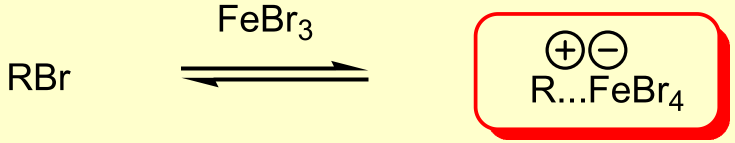


- ***Cl → I exchange via silylation:***
  - Buchwald *Org. Lett.* **2007**, *9*, 3785 (**DOI**)



Friedel-Crafts alkylation

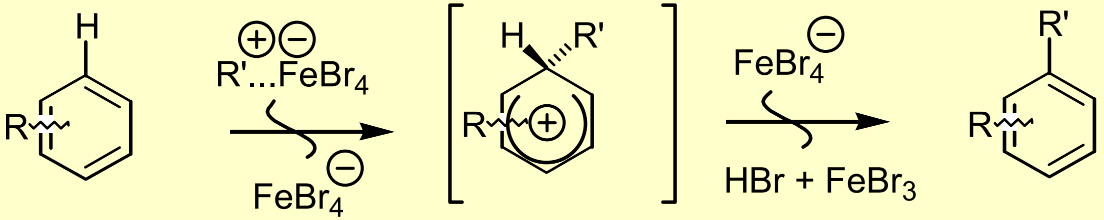
- ***Typical conditions:*** alkyl halides in the presence of Lewis acid promotors



$$RBr \xrightleftharpoons{FeBr_3} \boxed{\overset{\oplus\ominus}{R...FeBr_4}}$$

alkyl halide-Lewis acid complex = $\mathbf{E}^{\oplus}$

  - Plagued by rearrangements (Wagner-Meerwein 1,2-proton shifts)
  - Substantially reversible and therefore can de-alkylate!
  - Products are activated relative to starting materials hence extensive poly-alkylation
  - Alkyl halide-Lewis acid complex is a weak electrophile and deactivated aromatics do not react
  - The Lewis acid is a catalytic promotor

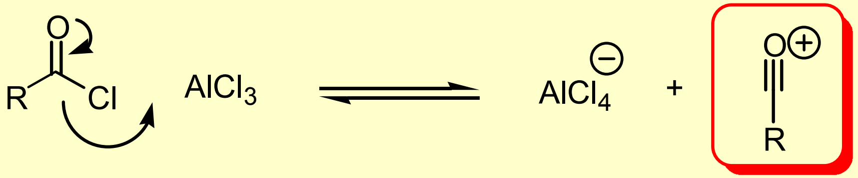


Order of Lewis acid effectiveness: $AlCl_3 > FeCl_3 > BF_3 > TiCl_3 > ZnCl_2 > SnCl_4$

  - *NB.* 1) useful method for introduction of *t*-Bu groups via DoM/sulfinylation: Clayden *Chem. Commun.* **2006**, 1393 (**DOI**); 2) ionic liquids as solvents; Kantam *Synlett* **2008**,1449 (**DOI**)

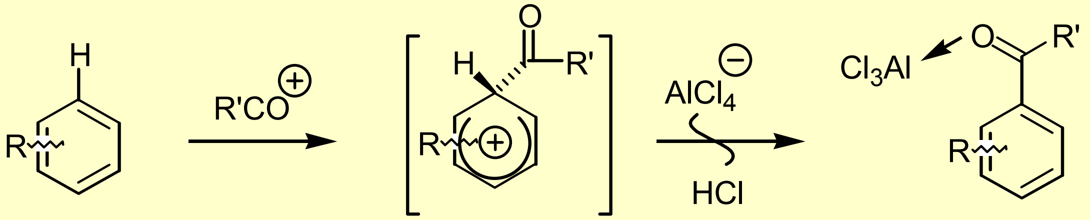
Friedel-Crafts acylation

- ***Reviews:***
  - *Stoichiometric* classical LAs: Olah *Friedel-Crafts & related reactions,* Wiley, **1964**, *vol 3*, pt1
  - *Catalytic* lanthanide LAs: Collin *Co-ord. Chem. Rev.* **1998**, *180*, 117 (**DOI**)
- ***Typical conditions:*** acid chlorides or anhydrides (also sulfonyl chlorides) ± LA promotor :



acylium ion = **E**$^+$

  - LA not required for activated aromatics
  - ***stoichiometric LAs**:* $AlCl_3$ > $FeCl_3$ > BF_3 > $TiCl_3$ > $ZnCl_2$ > $SnCl_4$
    - Generally can't be recycled *via* aqueous extraction
  - ***catalytic LAs**:* lanthanide(III) halides/triflates *e.g.* $GaCl_3$, $InCl_3$, $Hf(OTf)_4$; aqueous recycling possible
    - Mikami *Synlett* **1999**, 1990 (**DOI**); Kobayashi *Synlett* **2000**, 403 (**DOI**); Furstner *Org. Lett.* **2001**, *3*, 417 (**DOI**); Shiina *Tetrahedron Lett.* **2002**, *43*, 6391 (**DOI**); Marks *J. Org. Chem.* **2008**, *73*, 4004 (**DOI**)

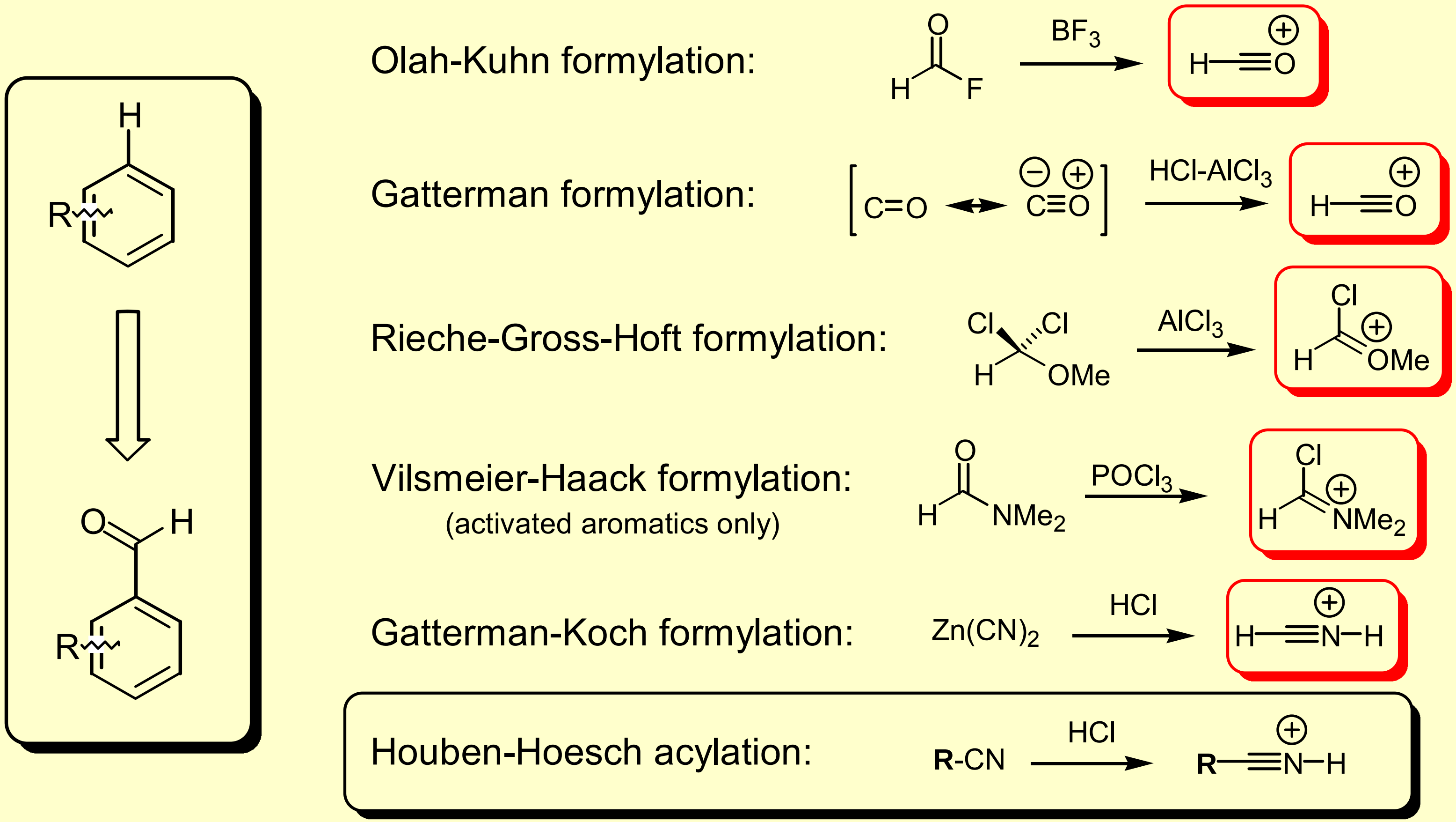


N.B. NOT
catalytic in
Lewis acid
because it
complexes to
product ketone

- ***Synthetic alternative*** – aryne insertion into an acid chloride → *ortho*-chloroarylketone:
  - *e.g.* Yoshida *Chem. Commun.* **2007**, 2405 (**DOI**)

Formylation

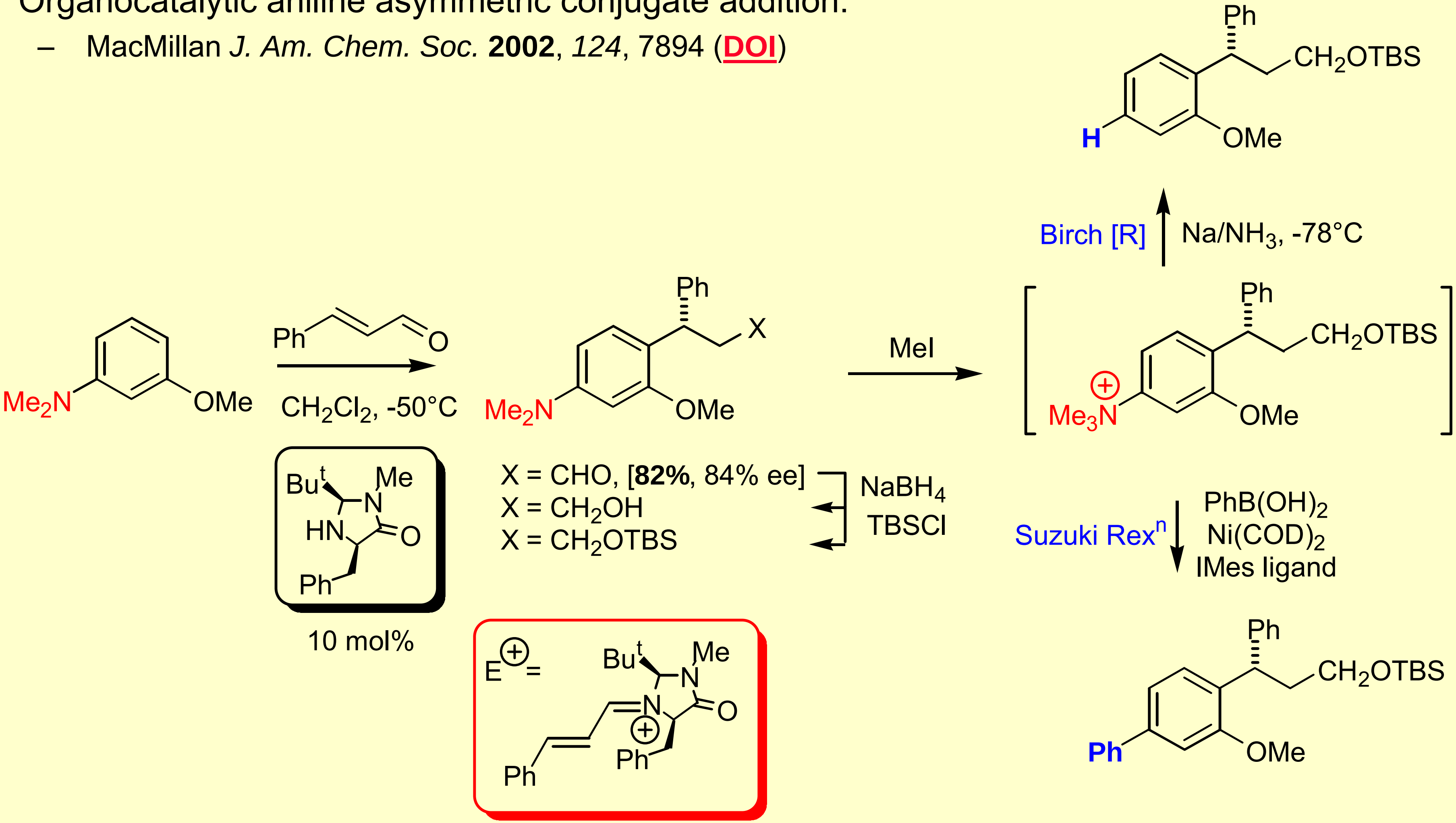
- ***Review:*** Aldabbagh *Comp. Org. Funct. Group Transform. II* **2005**, *3*, 99



- For a powerful alternative approach from (hetero)aryl bromides using Pd(0) cat. CO(g)/H_2(g):
  - Beller *Angew. Chem. Int. Ed.* **2006**, *45*, 154 (**DOI**)

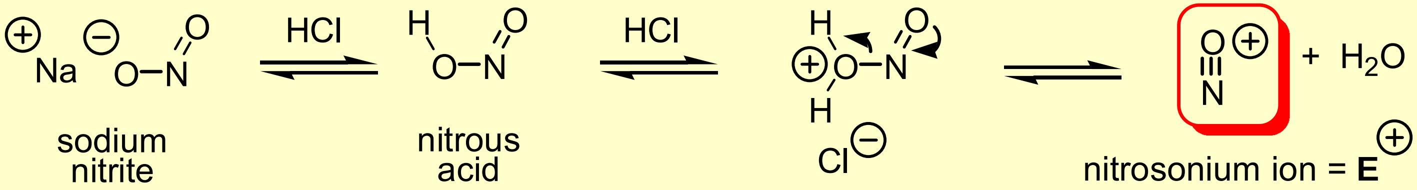
Organocatalytic FC-type conjugate addition

- Organocatalytic aniline asymmetric conjugate addition:
  - MacMillan *J. Am. Chem. Soc.* **2002**, *124*, 7894 (**DOI**)



Nitrosation

- ***Typical conditions:*** sodium nitrite and hydrochloric acid

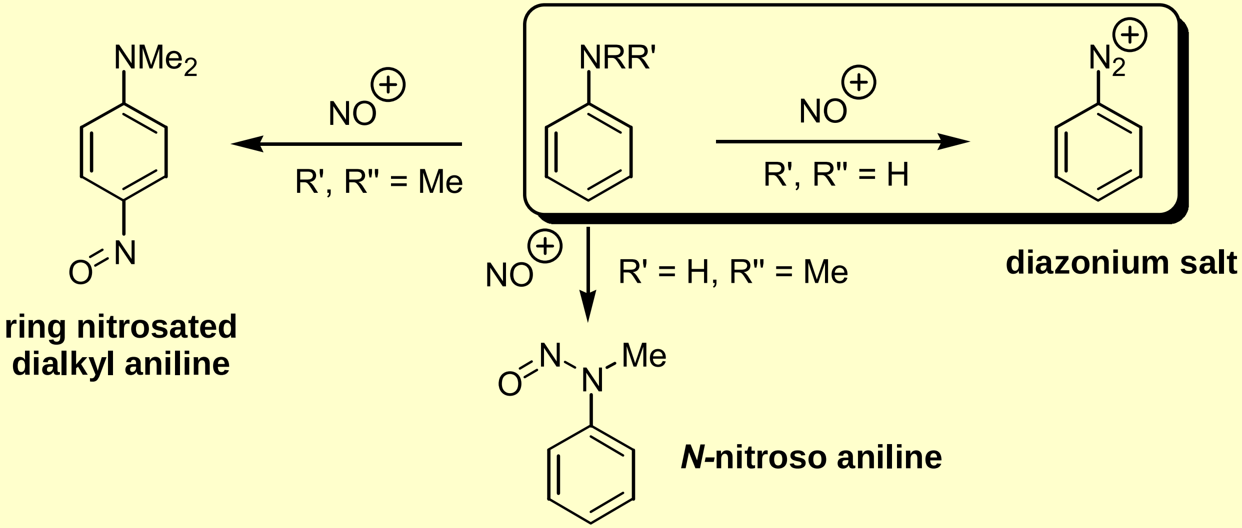


sodium nitrite

nitrous acid

nitrosonium ion = **E**$^{+}$

  - Nitrosonium ion is weak electrophile: only ring nitrosates activated aromatics (*e.g.* phenols)
  - *N*-Alkyl anilines give *N*-nitroso anilines (*i.e. N*-nitrosation not ring nitrosation)
  - *N*-Nitroso anilines can undergo Fischer-Hepp rearrangement on heating to ring nitrosated products
  - Anilines give diazonium salts *via* initial *N*-nitrosation



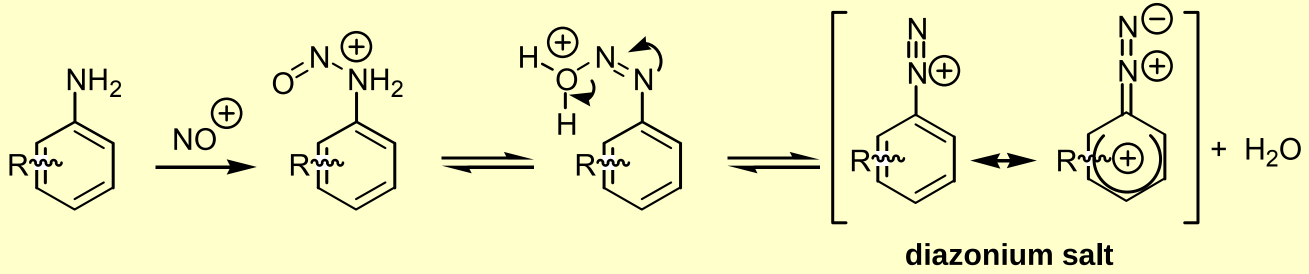
ring nitrosated dialkyl aniline

diazonium salt

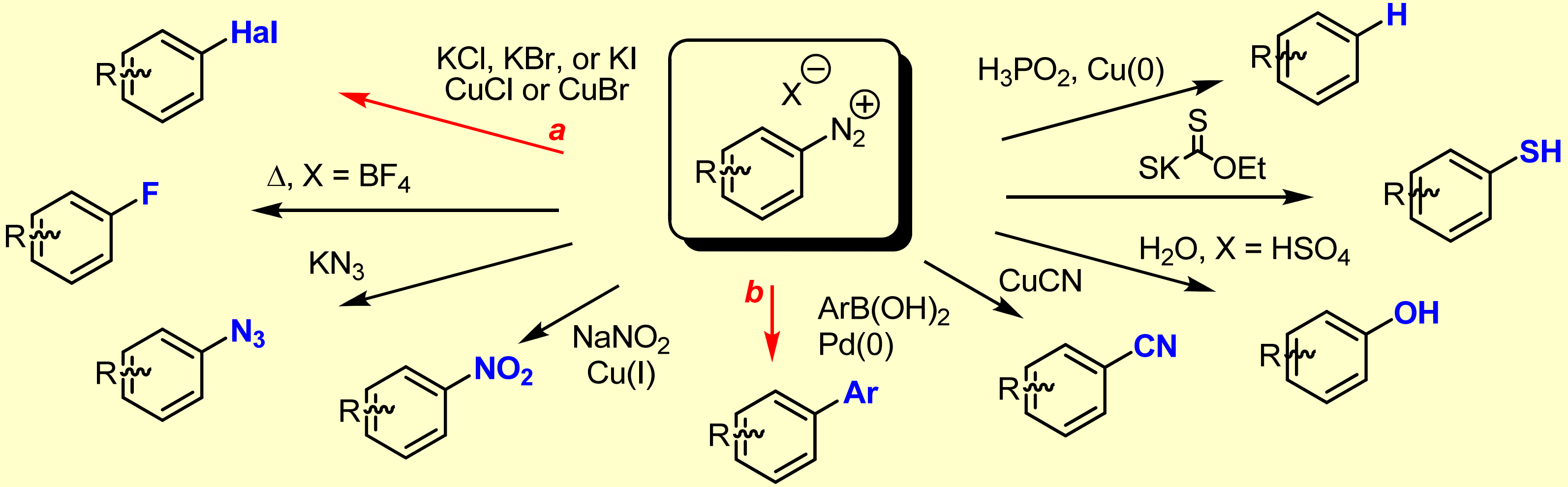
***N*-nitroso aniline**

Diazotisation & Sandmeyer reactions

- ***Mechanism of formation:***



- ***Nucleophilic* ipso-*substitution (Sandmeyer reactions):***

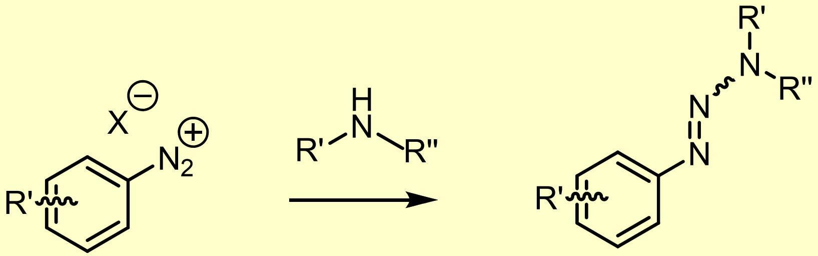


a) Chi Synthesis **2008**, 185 (**DOI**) - one-pot diaotisation/iodination

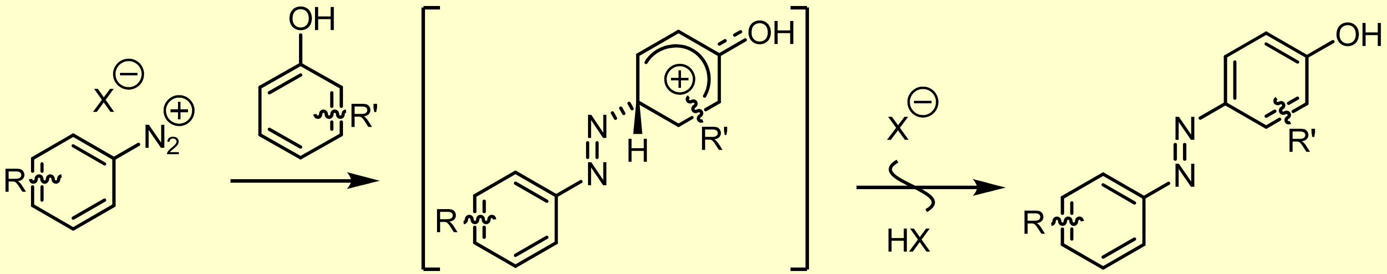
b) Sengupta *J. Org. Chem*. **1997**, *62*, 3405 (**DOI**)

Diazotisation & diazo-coupling

- ***Nucleophilic attack can also occur at the terminal nitrogen of diazonium ions*** (*cf.* at the ipso-carbon in Sandmeyer reactions)
  - *e.g.* triazine synthesis using ***amines*** as nucleophiles:

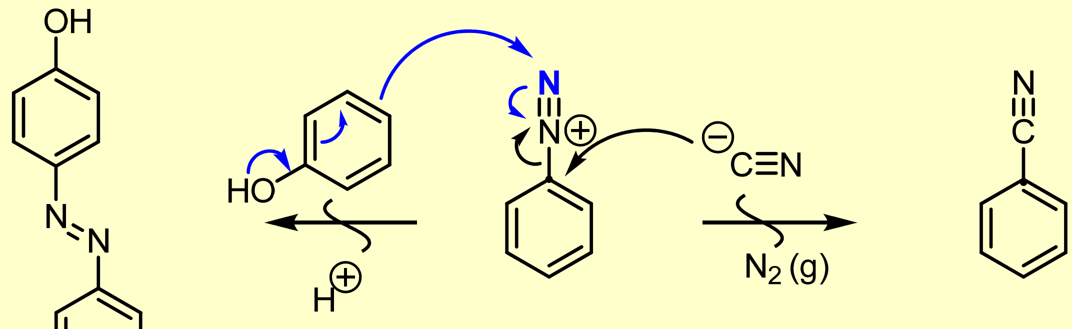


  - *e.g.* diazo-compound synthesis (dyes) using ***phenols*** as *C*-nucleophiles:



Aromatics as ambident nucleophiles

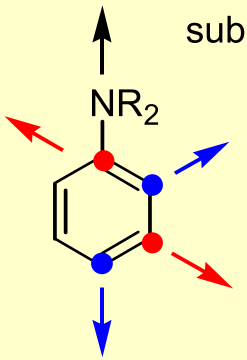
- cf. ***Aryl diazonium ions as ambident electrophiles:***



diazo-coupling

***ipso*-substitution**

- ***Aromatics as ambident nucleophiles ('directing effects'):***



substituent (e.g. *N*-) as nucleophile

ipso-carbon
as nucleophile

ortho-carbon as nucleophile

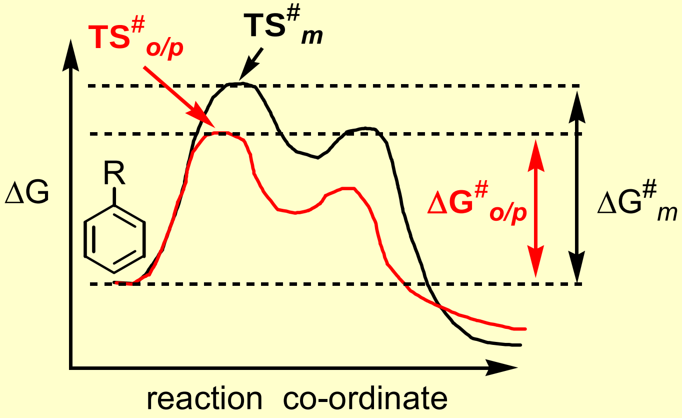
meta-carbon as nucleophile

para-carbon as nucleophile

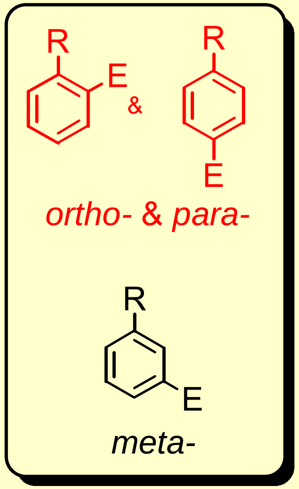
What governs position of reactivity?

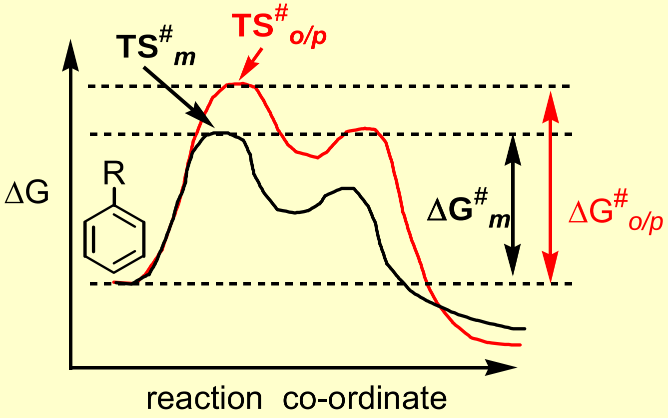
Directing effects

- ***Electrophilic substitution is under kinetic control -*** **i.e.** ***fastest formed product predominates***
- ***The fastest formed product will be formed*** **via** ***the lowest energy transition state:***



ortho-/para-**directing**



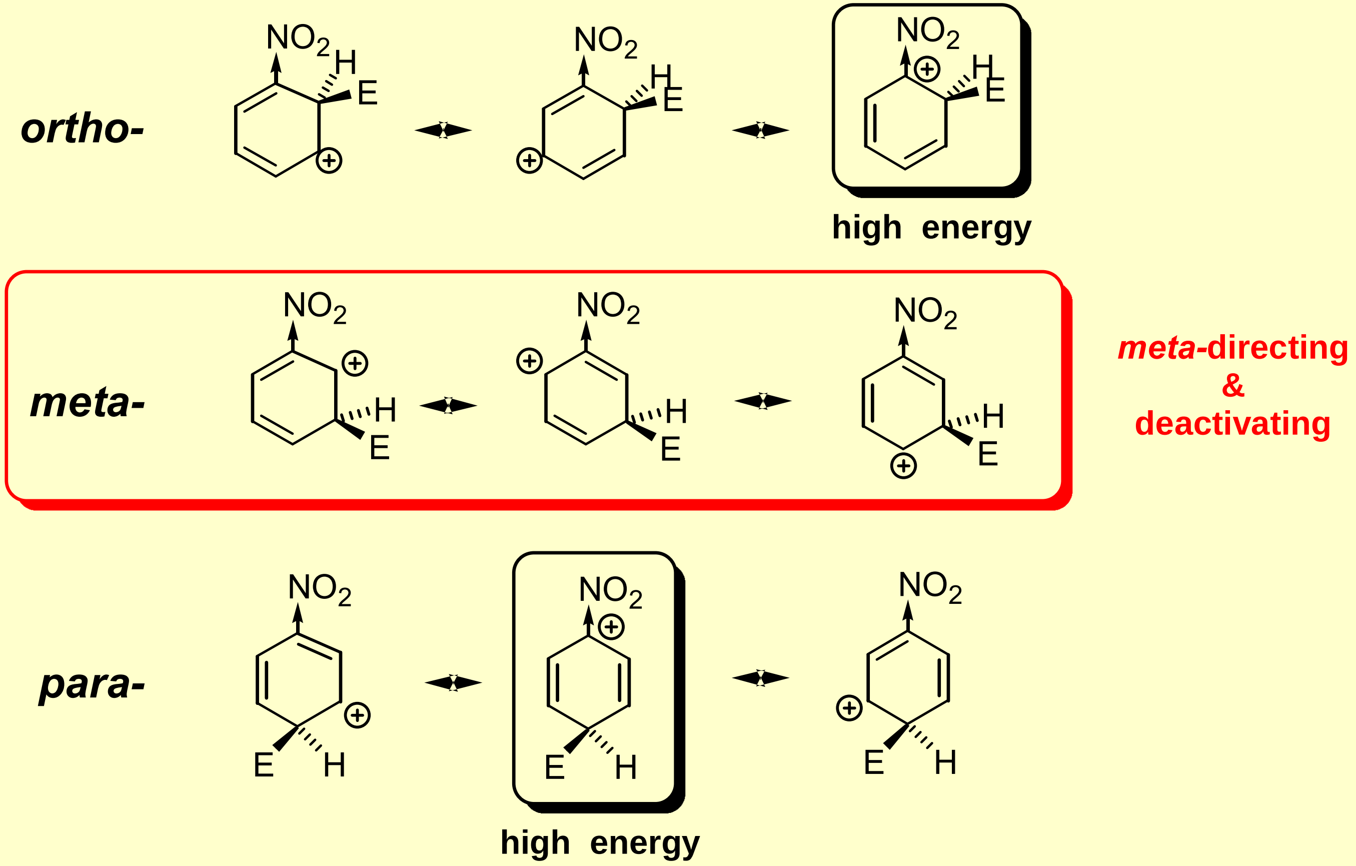


meta-**directing**

- ***How can we estimate which transition state has lowest energy?***
- *HAMMONDS POSTULATE:* ***‘energy of $TS^{\#}$ will resemble that of Wheland intermediate more closely than the starting materials or products’***
- ***We can estimate the energies of the Wheland intermediates from their resonance forms...***

meta-Directing groups (deactivating)

- ***NR_3^+, NH_3^+*** (deactivating by induction only)
- ***NO_2, CN, SO_3H, SO_2R, CHO, COR, CO_2R, CO_2H*** (deactivating by induction and resonance)
- ***Triflates*** are meta-directing groups: Kraus *Tet. Lett*. **2002**, *43*, 7077 (**DOI**)



ortho-

high energy

meta-

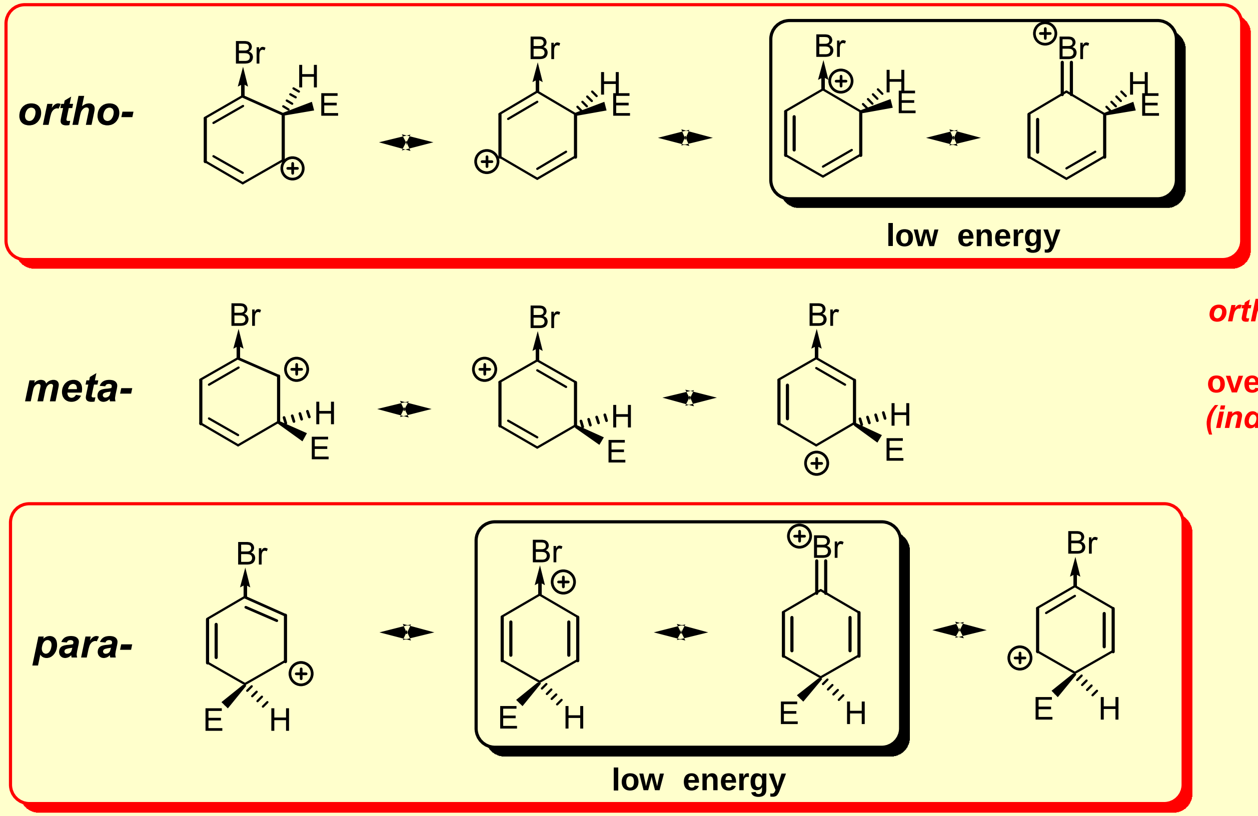
***meta*-directing**
&
deactivating

para-

high energy

*ortho-/para-*Directing (deactivating)

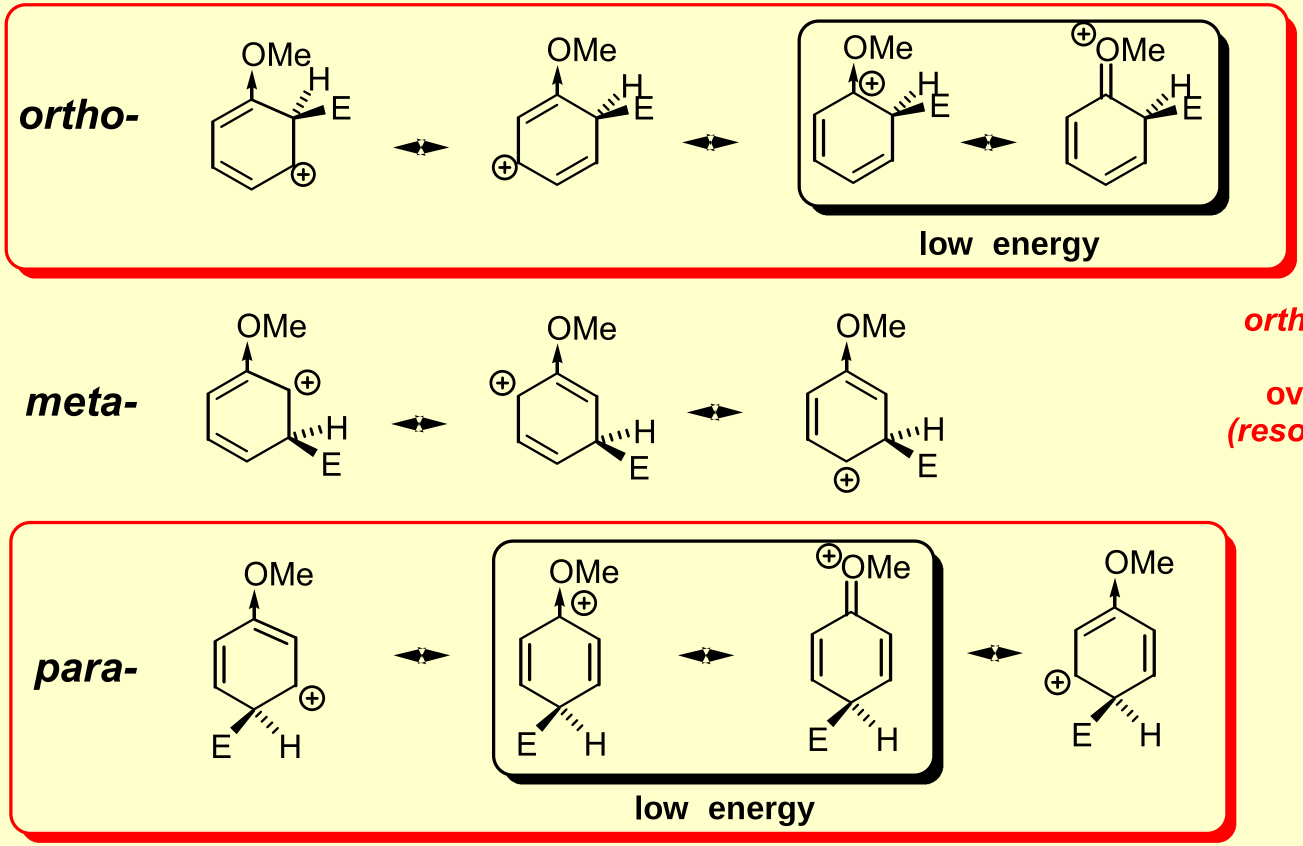
- ***I, Br, Cl, NO (deactivating by induction which overrides resonance)***



*ortho-/para-*directing
&
overall deactivating
(induction outweighs resonance)

*ortho-/para-*Directing (activating)

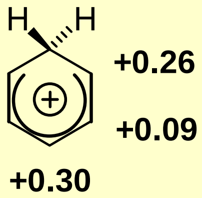
- ***NR_2, NH_2, OH, OR, NHCOR, OCOR*** (activating by resonance which overrides induction)
- ***Alkyl*** (activating by hyperconjugation)
- ***Aryl*** (activating by resonance)



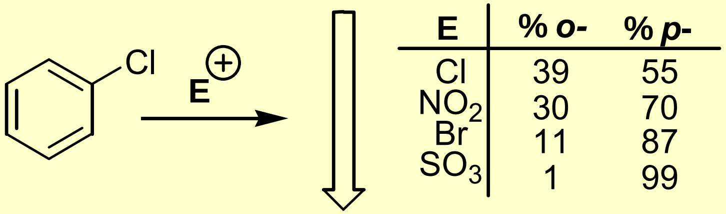
***ortho-/para-*directing**
&
overall activating
(resonance outweighs
induction)

*ortho-/para-*Ratios

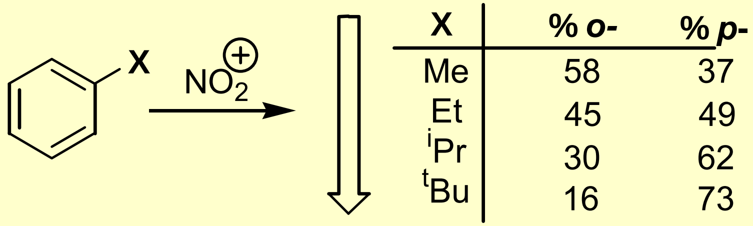
- ***Statistically we expect ~2:1*** **ortho- : para-**
- ***Theoretical charge density studies favour the*** **para-*:***



- ***Steric effects (large E⁺ or directing substituent or both) disfavour the*** **ortho-**

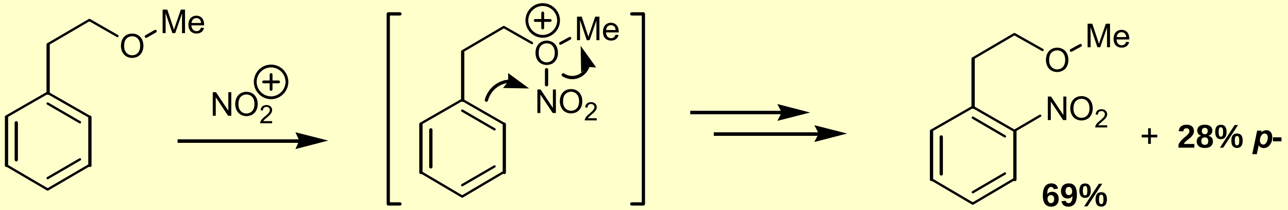


E	% *o-*	% *p-*
Cl	39	55
NO_2	30	70
Br	11	87
SO_3	1	99



X	% *o-*	% *p-*
Me	58	37
Et	45	49
^{i}Pr	30	62
^{t}Bu	16	73

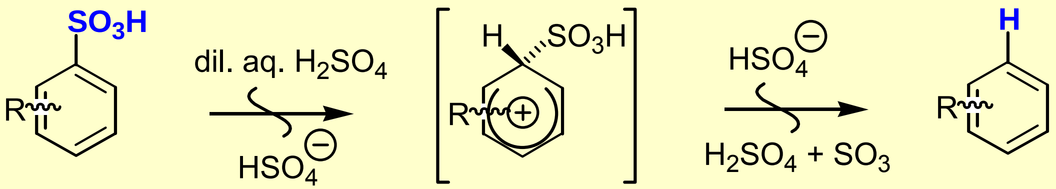
- ***Complexation (chaperone) effects can favour the*** **ortho-**
  - Strazzolini *J. Org. Chem*. **1998**, *63*, 952 (**DOI**)



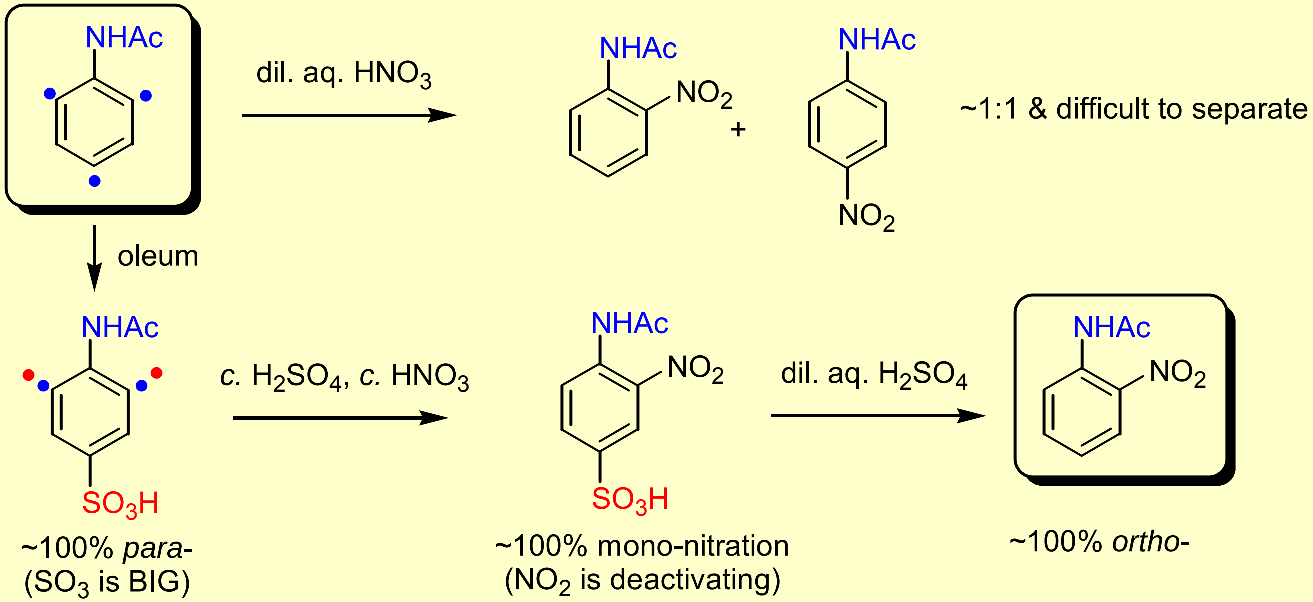
- ***Solvent effects are difficult to predict***

ipso-Substitution

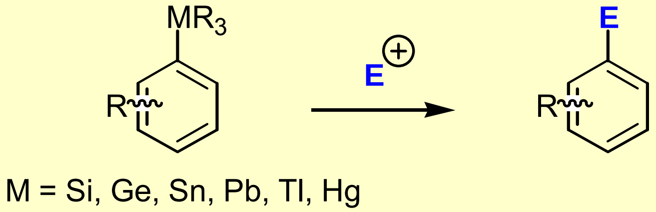
- ***Proto-desulfonylation:***



- ***Utility of SO_3H as temporary directing group***



- ***Desilylation, degermylation & destannylation:***
  - ***Review:*** Eaborn *J. Organometal. Chem.* **1975**, *100*, 43 (**DOI**)

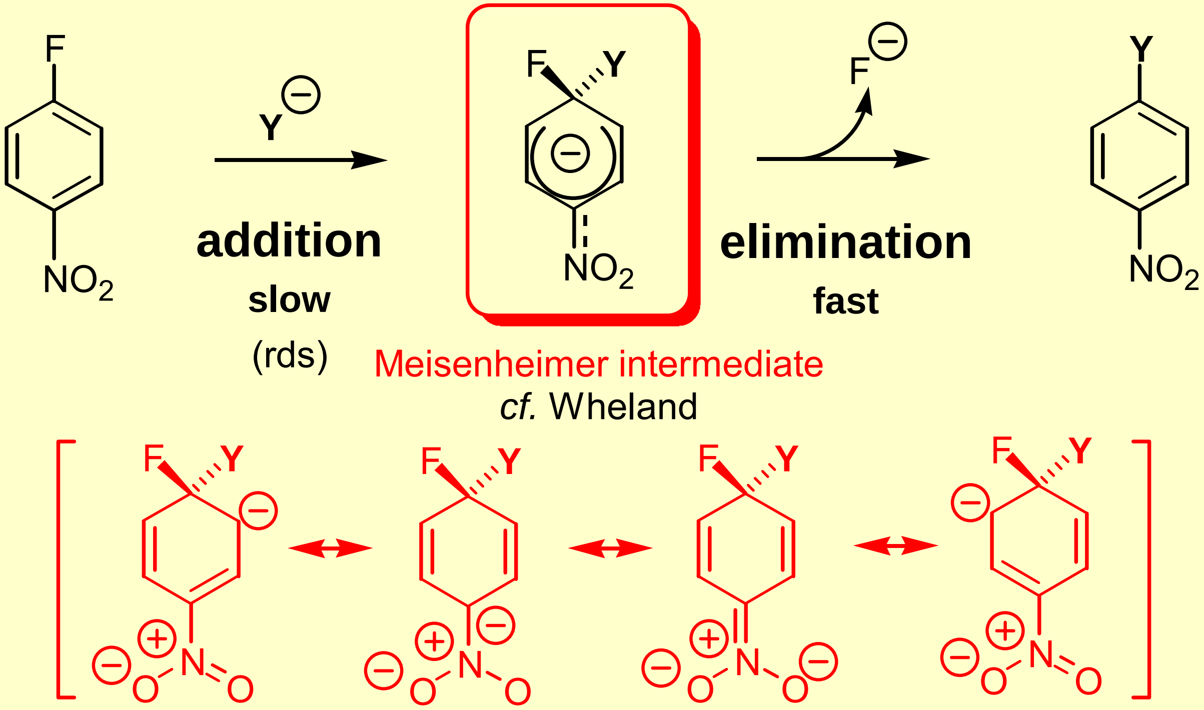


Synthetic ‘check list’ for S_EAr

- ***Will E^+ react at ring carbon or elsewhere*** **(e.g.** ***at amine substituent)?***
- ***Is the E^+ sufficiently reactive to react with a ring carbon?***
- ***If reaction at a ring carbon is expected, what orientation relative to existing groups (i.e. directing effects)?***
  - *ortho-*/*para*- or *meta*- or *ipso*-?
  - If *ortho-*/*para*- …which?
  - Use a temporary directing group to get desired orientation?
- ***Mono- or multiple substitution?***
  - Will introduction of E activate or deactivate the ring relative to the starting material?
  - Which directing effects dominate ‘second’ electrophilic substitution?

Nucleophilic Aromatic Substitution: S_NAr

- ***Mechanism:*** addition-elimination
  - Rate = k[ArX][Y^-] (bimolecular but rate determining step does *NOT* involve departure of LG (*cf.* S_N2)
  - *e.g.* 4-fluoro nitrobenzene:



addition

slow

(rds)

elimination

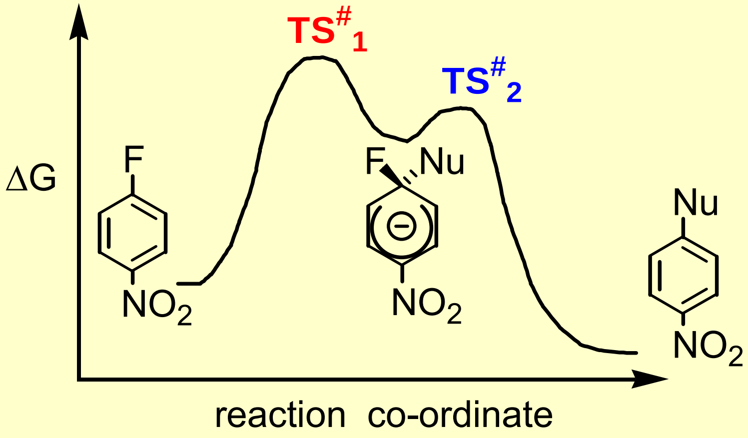
fast

Meisenheimer intermediate

cf. Wheland

notes

- *Intermediates*: energy minima
- *Transition states*: energy maxima
- Meisenheimer intermediate is NOT aromatic but stabilised by delocalisation
- Generally under kinetic control

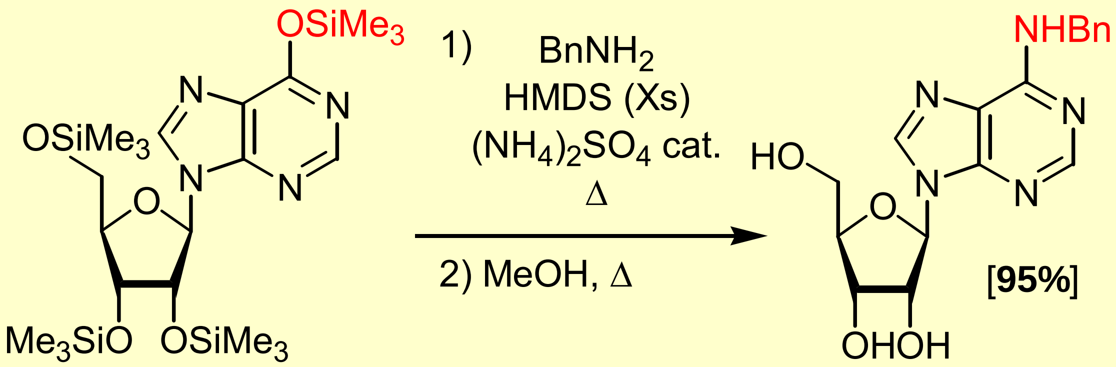


- only efficient for electron deficient benzene derivativess and azines
- relative rates for azines see: Shephard *Adv. Het. Chem*. **1965**, *4*, 145

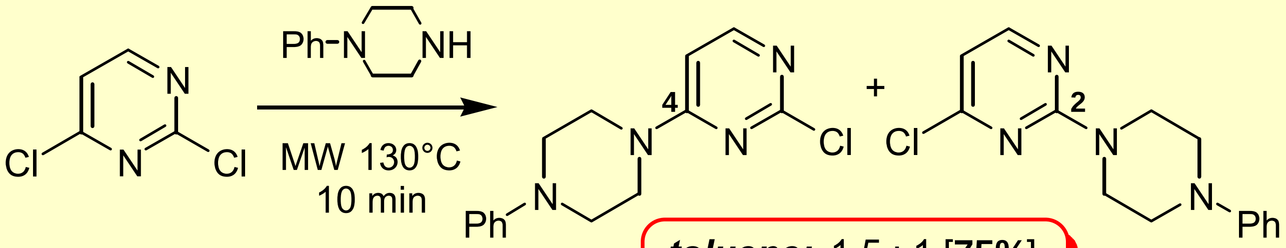
Leaving group influence: S_NAr

- ***Halides:*** ease of substitution follows the ***element effect:***
  - Sugiyama *Chem. Lett.,* **1999**, *7*, 691 (**DOI**)
  - *Fluorides* are often difficult to prepare and unstable so *chlorides* are generally used
- ***NO_2 and OTMS groups:*** also good leaving groups for S_NAr:
  - ***review:*** Vorbruggen *Acc. Chem. Res.* **1995**, *28*, 509 (**DOI**)

F > Cl > Br >> I



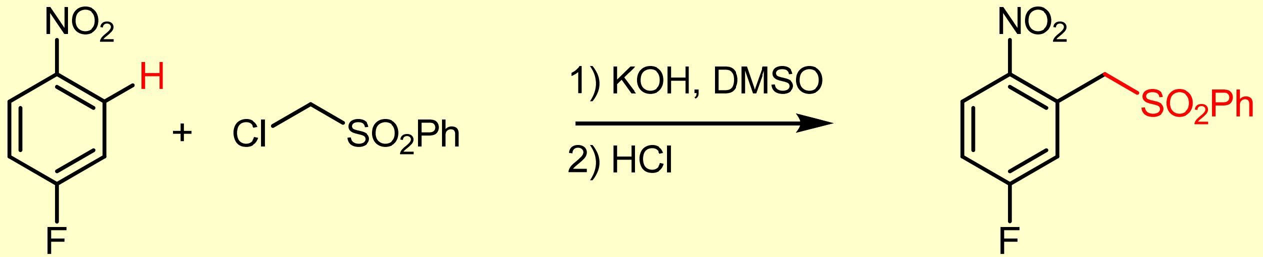
- ***Ionic liquid media:*** *e.g.* Welton *Org. Lett.* **2007**, *9*, 5247 (**DOI**)
- ***Microwave acceleration:*** *e.g.* Luo *Tet. Lett.* **2002**, *43*, 5739 (**DOI**)



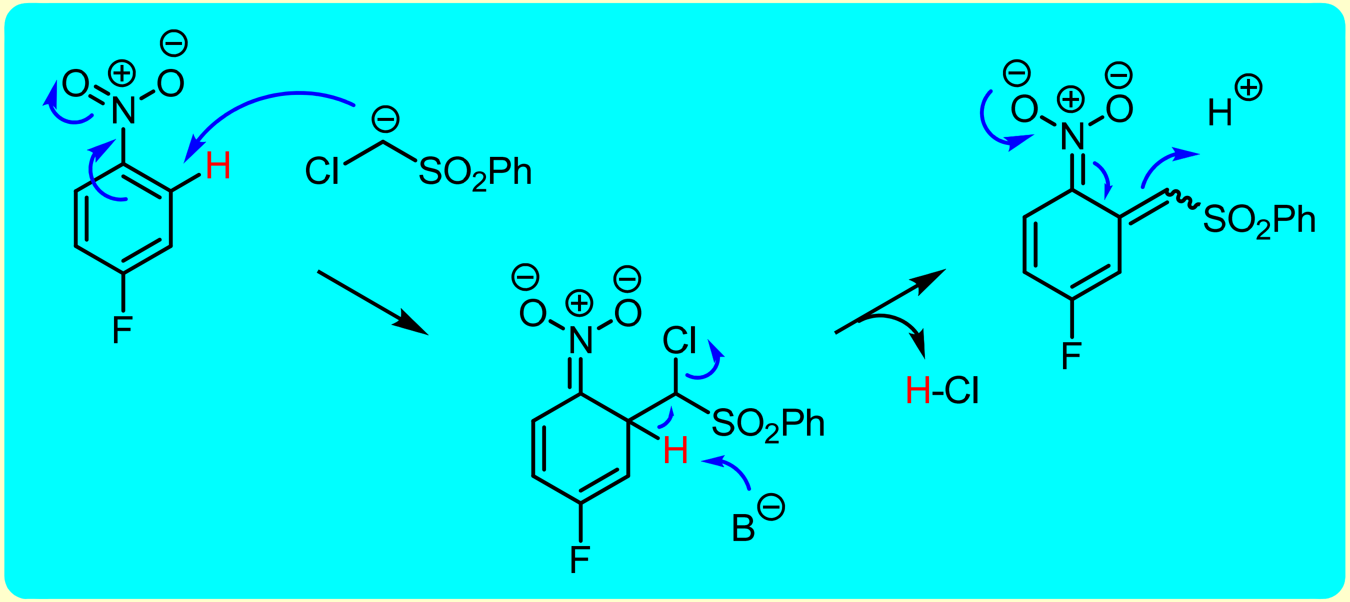
toluene: 1.5 : 1 [**75%**]
IPA: 5.5 : 1 [**81%**]

Vicarious Nucleophilic Substitution: VNS

- *Nucleophilic replacement of* ***HYDROGEN*** *ortho and para to* $\textbf{NO}_\textbf{2}$ *groups*
  - ***Review:*** Makosa *Acc. Chem. Res*. **1987**, *20*, 282 (**DOI**)
    - Exploits the fact that nucleophile *addition* to hydrogens @ C2 and C4 relative to a nitro group is more rapid even than to halogens at these positions (the addition is reversible, so in standard S_NAr reactions of these substrates S_NAr of the halogens eventually ensues)
  - *e.g.*

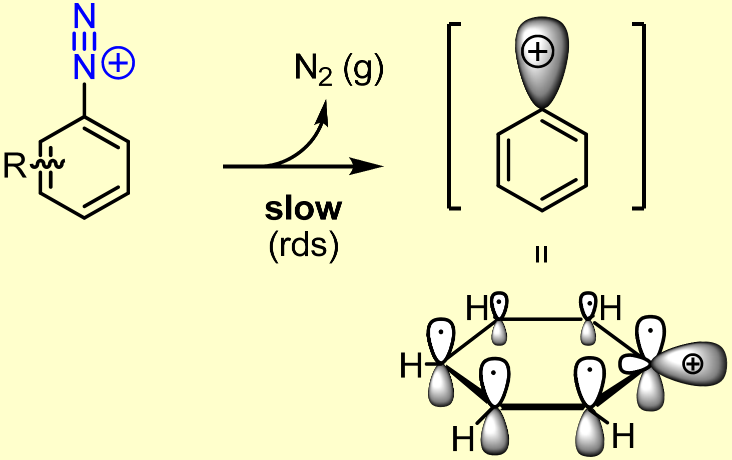


via



Aromatic S_N1 & $S_{RN}1$ reactions

- ***Diazonium salts*** do NOT react via S_NAr but either by ***S_N1*** or ***$S_{RN}1$*** mechanisms:
- ***In absence of Cu salts - S_N1***:



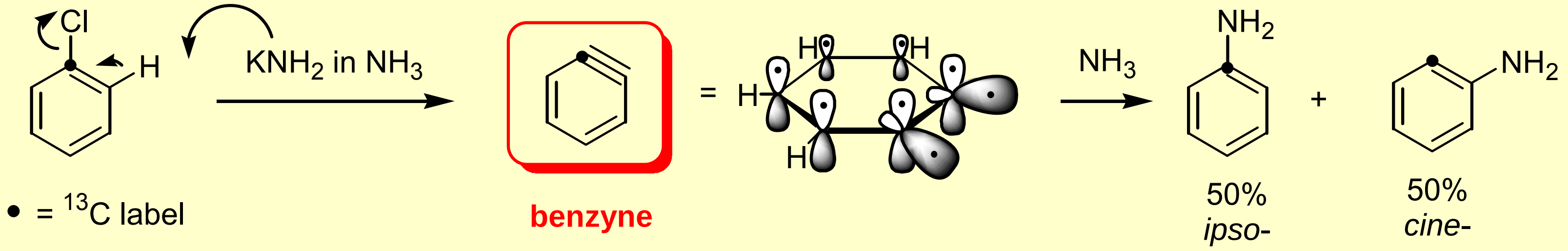
Y = CN, F, Cl, Br, N_3, H, OH, SH...

  - Rate = $k[ArN_2^+]$ (unimolecular)
  - accelerated by photolysis: Albini *J. Org. Chem.* **2005**, *70*, 603 (**DOI**)
  - Driving force is loss of N_2 ($\Delta G = \Delta H - T\Delta S$)
  - Aryl cation is still aromatic

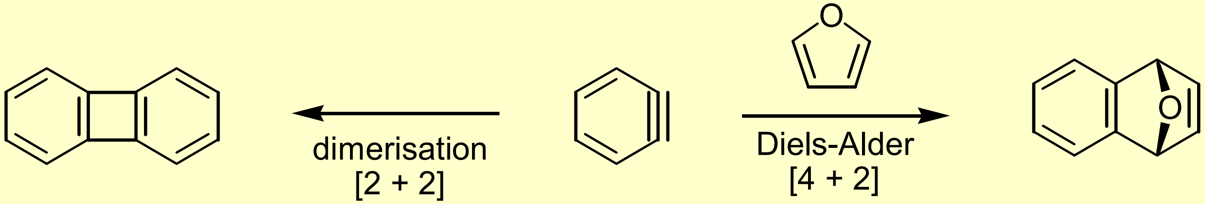
- ***Using copper salts (i.e. Sandmeyer reactions) - $S_{RN}1$***
  - ***Review:*** Bunnett *Acc. Chem. Rev.* **1978**, *11*, 413 (**DOI**)
  - Single Electron Transfer mechanism - *see workshop*
  - VERY USEFUL SYNTHETIC REACTIONS – SEE EARLIER SLIDE

Benzynes and arynes

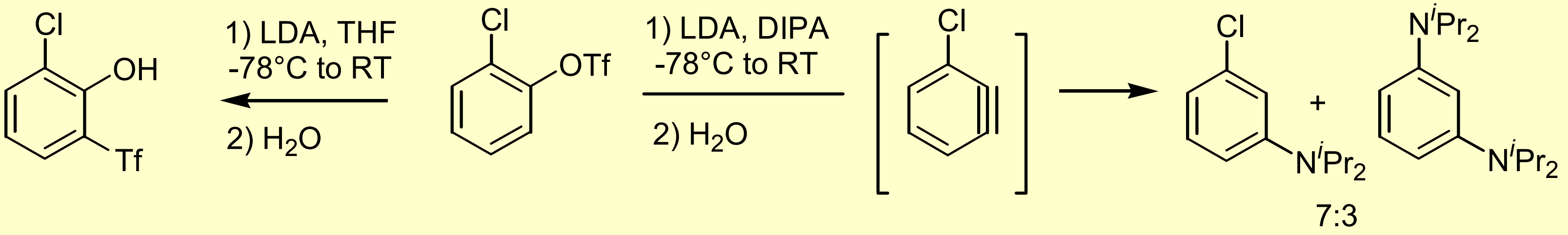
- ***Mechanism:*** Elimination-addition:



- ***Evidence:*** ^{13}C labelling (see above) & 2 x *ortho*-substituents → no reaction
- Benzyne is still aromatic but VERY reactive towards *e.g.* cycloadditions:

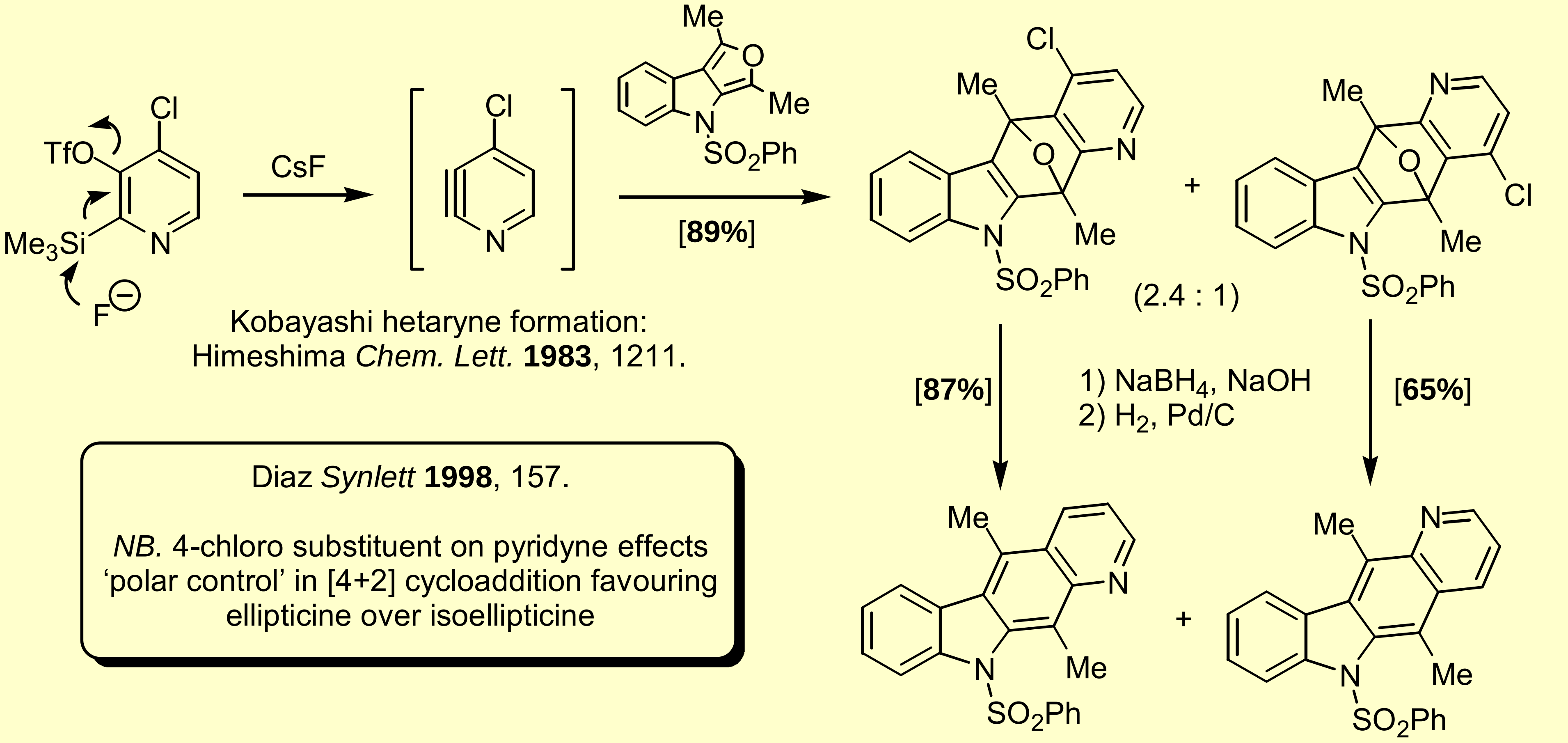


- Triflates suffer competitive thia-Fries rearrangement:
  - Lloyd-Jones *Chem. Comm*. **2003**, 380 (**DOI**)



Arynes in synthesis

- ***Review:*** Pellissier *Tetrahedron* **2003**, *59*, 701 (**DOI**)



Kobayashi hetaryne formation:
Himeshima *Chem. Lett.* **1983**, 1211.

Diaz *Synlett* **1998**, 157.

NB. 4-chloro substituent on pyridyne effects ‘polar control’ in [4+2] cycloaddition favouring ellipticine over isoellipticine

ellipticine

isoellipticine

Summary

- ***Aromaticity:***
  - Historical perspective (Kekulé)
  - Characteristics, NMR ring currents
  - Valence bond & molecular orbital representations (Hückel's rule)
  - Anti-aromaticity

- ***Electrophilic aromatic substitution (S_EAr):***
  - Mechanism (Wheland intermediates, energy profile diagrams & kinetic isotope effects)
  - Nitration, sulfonylation, halogenation, Friedel-Crafts alkylation and acylation, nitrosation (diazonium salt formation & diazo-coupling, Sandmeyer reactions),
  - Directing effects (*ortho*-/*para*- ratios, *ipso*-substitution)

- ***Nucleophilic aromatic substitution:***
  - S_NAr
  - VNS (vicarious nucleophilic substitution)
  - S_N1 & $S_{RN}1$ (Sandmeyer reactions)
  - Benzyne & arynes