Year 1 CHEM40006
Reactivity at Carbon Centres

LECTURE 13 - Reactivity at sp^2 Centres: Aromatic Compounds as Nucleophiles

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Format and scope of presentation

- ***Electrophilic aromatic substitution (S_EAr):***
  - Mechanism
    - Wheland intermediates
    - energy profile diagrams
    - deuterium isotope effects
  - Useful S_EAr reactions
    - nitration
    - sulfonylation
    - halogenation
    - Friedel-Crafts alkylation
    - Friedel-Crafts acylation

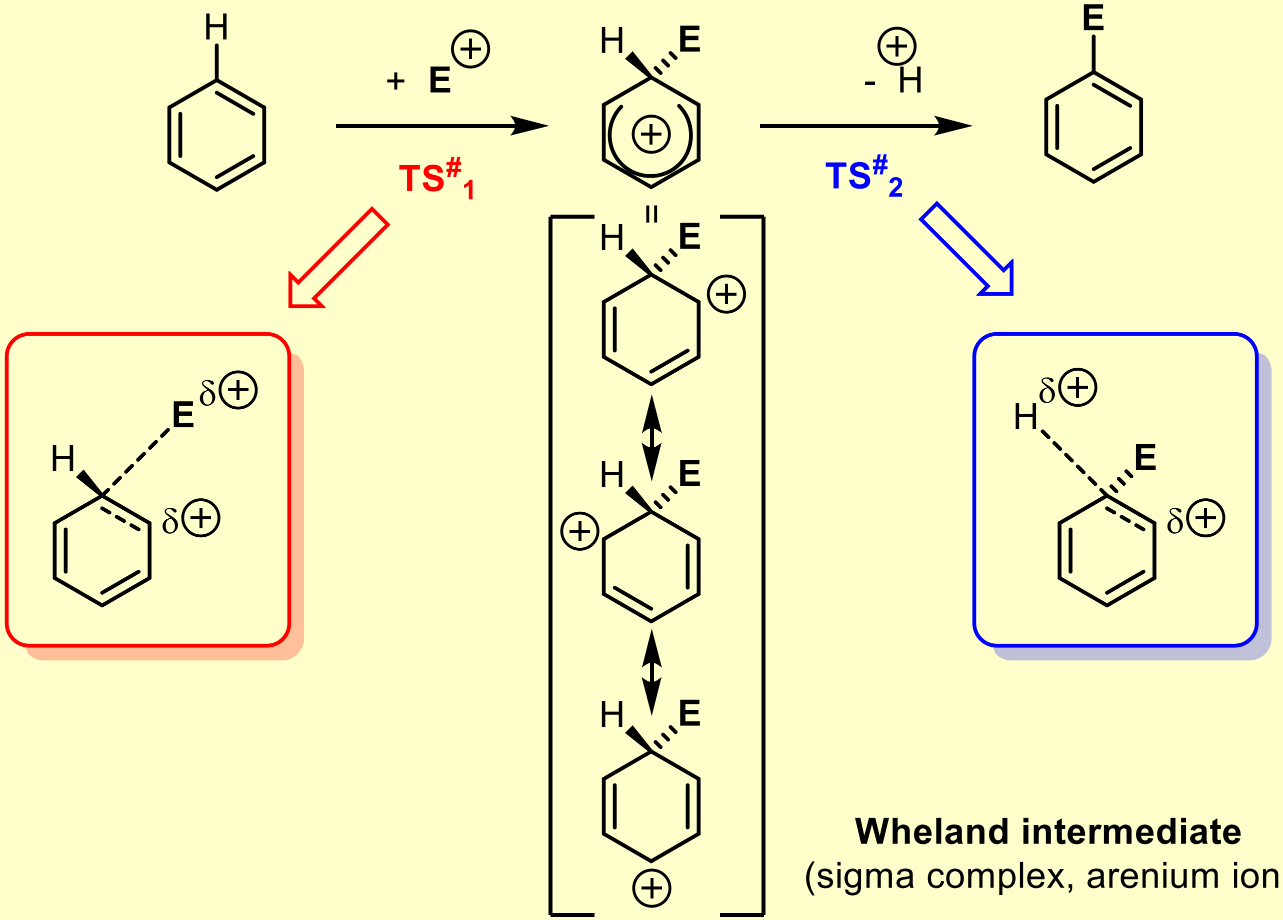
Key further reading: Clayden, Greeves & Warren, *Organic Chemistry*, 2nd Ed., Chapter 21
- *mechanism and examples* – pages 473 – 478
- *Friedel-Crafts alkylation & acylation* – pages 492 - 494

Electrophilic Aromatic Substitution (S_EAr) - *Mechanism*

- Comparison with electrophilic addition reactions of sp^2 centres in alkenes:

Electrophilic Aromatic Substitution: S_EAr

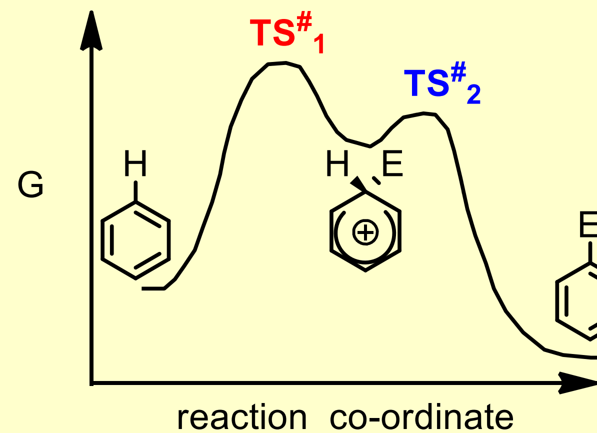
- Mechanism: ***addition-elimination***



Wheland intermediate
(sigma complex, arenium ion)

notes

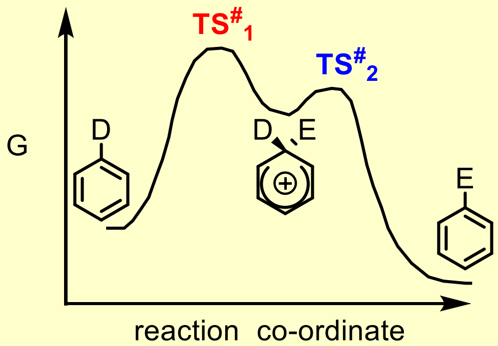
- *Intermediates*: energy minima
- *Transition states*: energy maxima
- Wheland intermediate is NOT aromatic but stabilised by delocalisation
- Generally under kinetic control

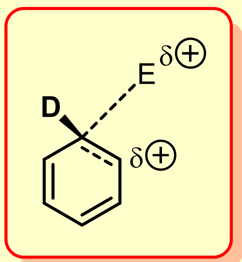


Evidence for addition-elimination

- ***Deuterium Isotope Effects***
  - *NB.* C-D bonds are slightly stronger than C-H bonds (due to difference in zero point energies)
    - See: http://www.princeton.edu/chemistry/macmillan/group-meetings/RRK-KIE.pdf

Case 1





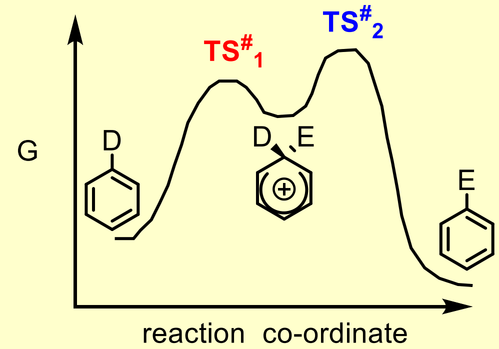
$TS^{\#}_{1}$ is the
***Rate Determining Step* (RDS)**

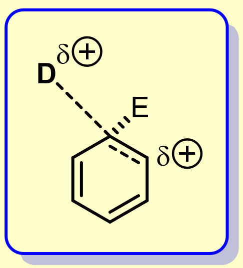
this DOES NOT involve C-D bond breaking

i.e. **NO Deuterium Isotope Effect**

This is the case for <u>almost</u> <u>ALL</u> S_EAr REACTIONS

Case 2





$TS^{\#}_{2}$ is the
***Rate Determining Step* (RDS)**

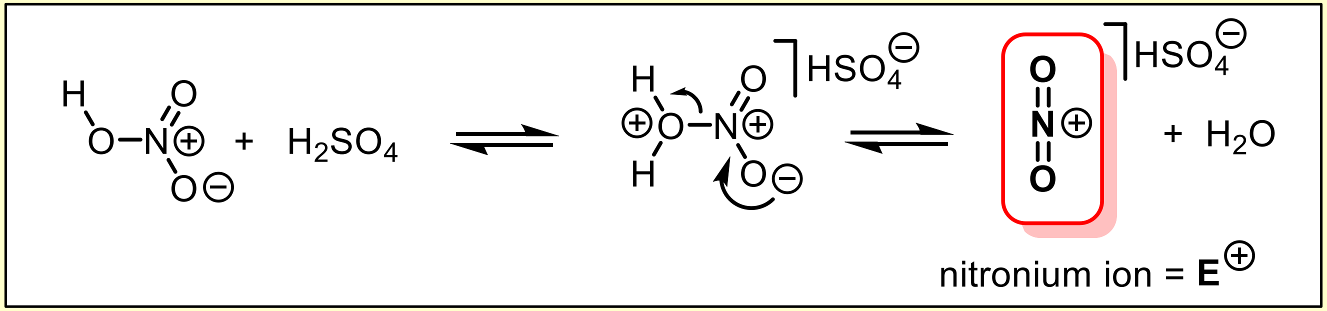
this DOES involve C-D bond breaking

i.e. **primary Deuterium Isotope Effect expected**

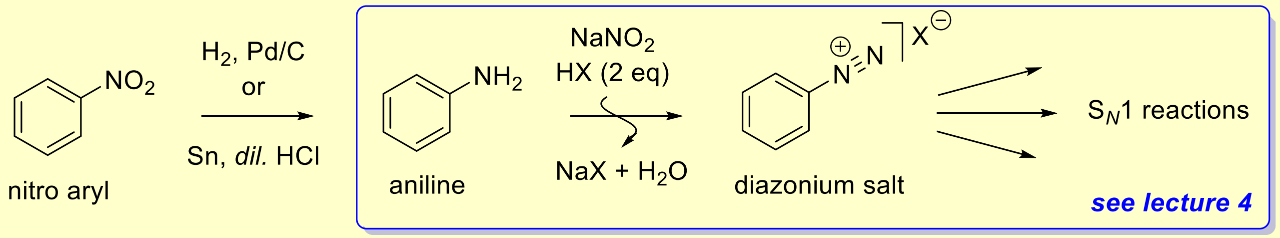
very <u>RARE</u> for S_EAr REACTIONS

Nitration

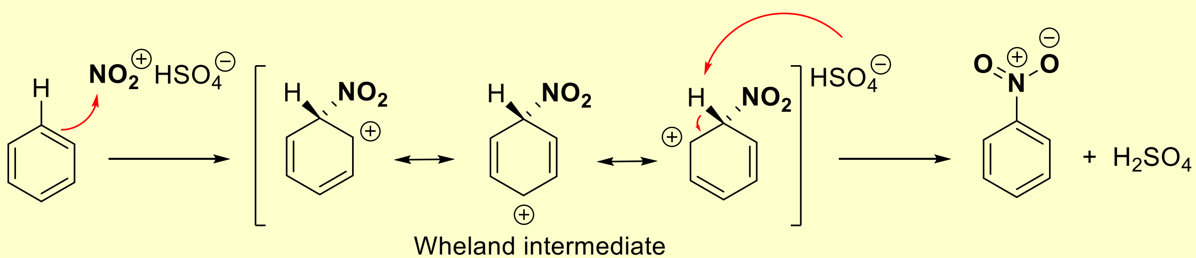
- ***Typical conditions:*** *c*.HNO_3/*c*.H_2SO_4 (1:1)



  – Nitro aryls can be selectively reduced to aryl amines (“anilines”), which in turn are very useful precursors to aryl diazonium salts and hence S_N1_{Ar} reactions (see lecture 4):

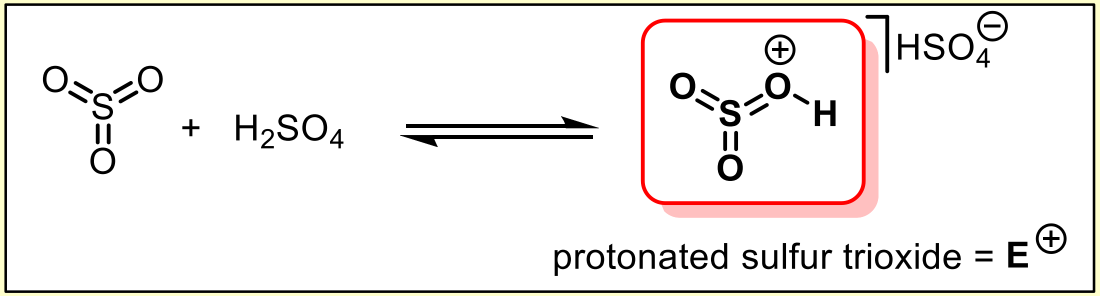


  – Overall, sulfuric acid is a *catalyst* in S_EAr nitration:

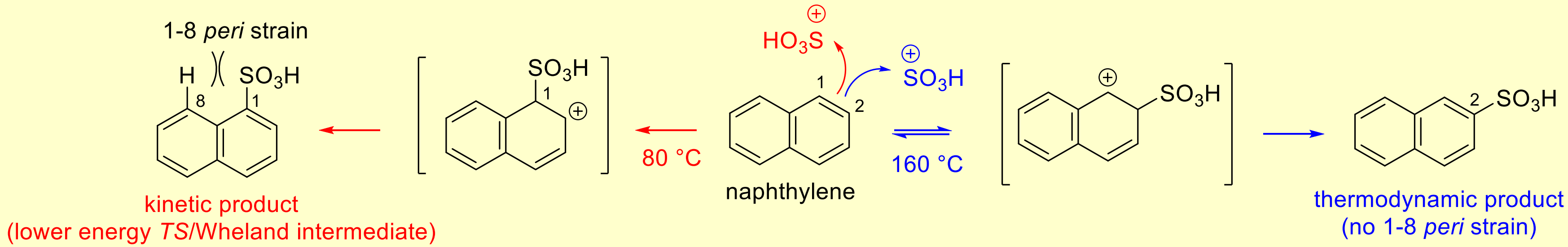


Sulfonylation

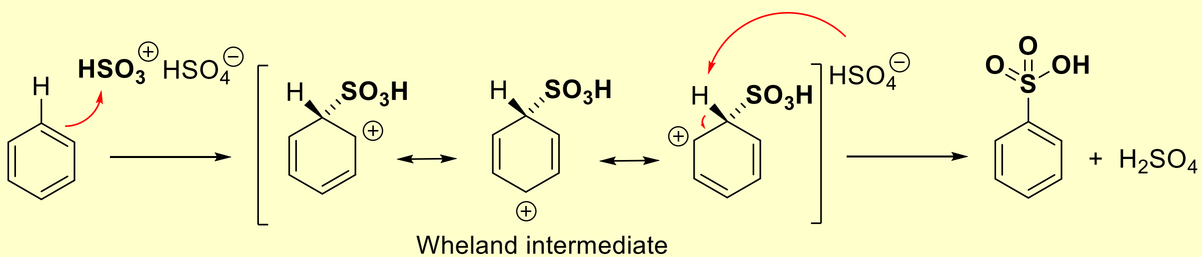
- ***Typical conditions:*** 'oleum', *i.e*. *c*.H_2SO_4 saturated with SO_3



  – Sulfonation is essentially irreversible below 80 °C (kinetic control), but becomes **reversible at higher temperatures** – allowing access to products of thermodynamic control. *e.g.*

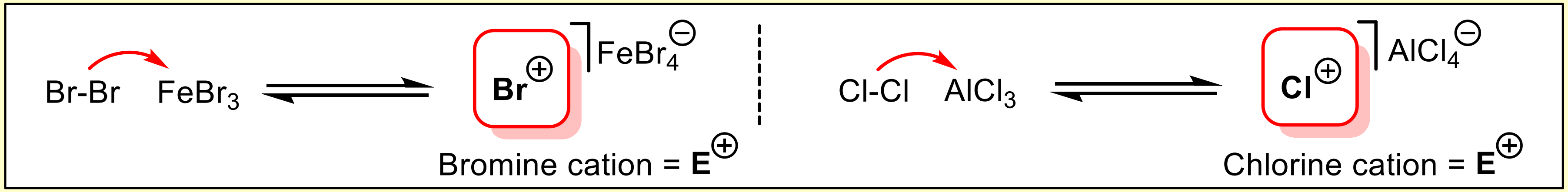


  – Overall, sulfuric acid is a *catalyst* in S_EAr sulfonylation:



Halogenation

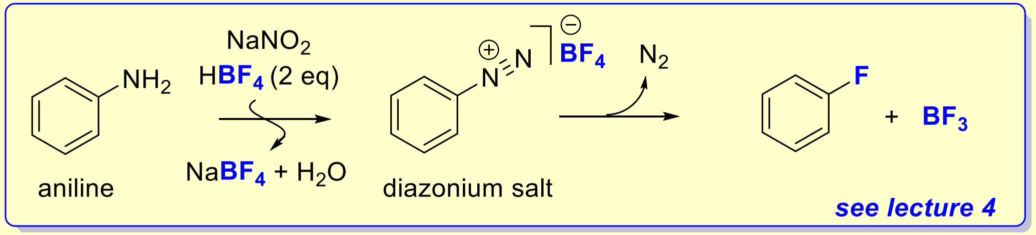
- ***typical conditions:*** Molecular halogen + Lewis acid



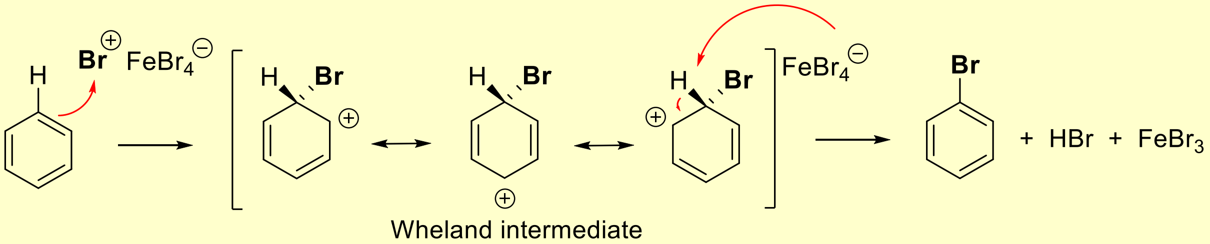
– ***bromine and chlorine:*** for activated aromatics (*i.e*. electron rich, *e.g.* phenols) no Lewis acid is required

– ***iodine:*** requires oxidising promoters, *e.g*. I_2 – Ceric Ammonium Nitrate (Ce^{4+}), or use of **I-Cl**

– ***fluorine:*** generally reacts explosively with aromatics. So, fluorine is best introduced by thermal rearrangement of a diazonium salt formed using HBF_4 (a S_N1_{Ar} reaction, see lecture 4):

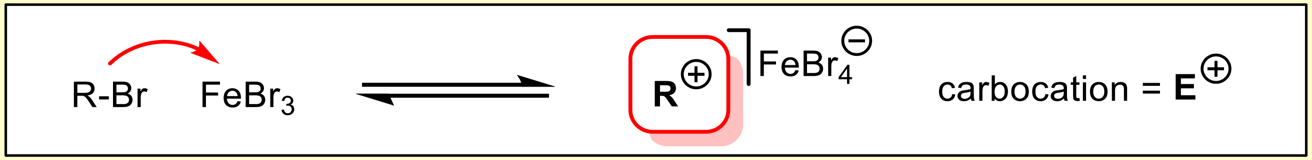


– Overall, the Lewis acid is a *catalyst* in S_EAr halogenation:

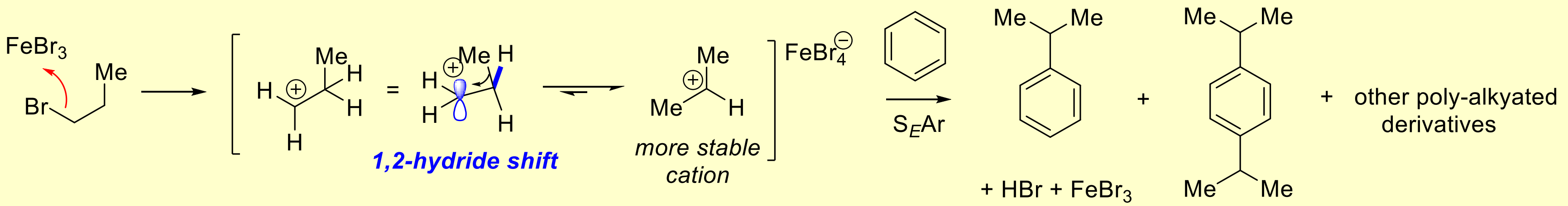


Friedel-Crafts alkylation

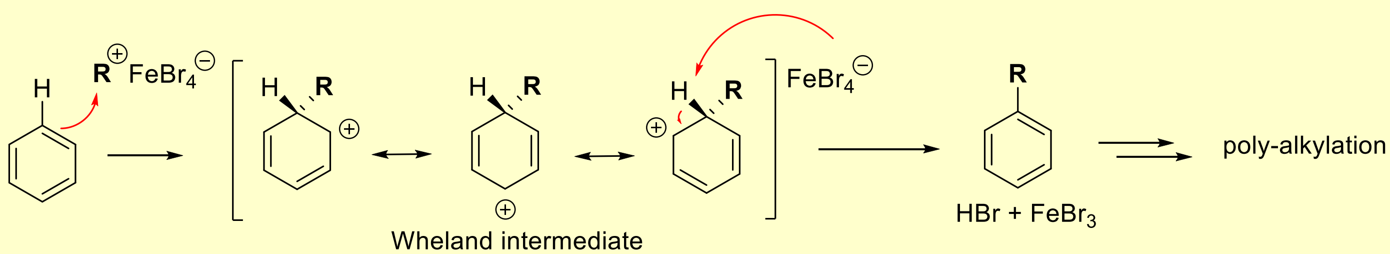
- ***Typical conditions:*** alkyl halide + Lewis acid



  - ***Limitation 1***: carbocations often rearrange by *e.g*. Wagner-Meerwein 1,2-hydride and alkyl shifts
  - ***Limitation 2:*** the products are activated (*i.e*. electron rich) relative to starting materials leading to poly-alkylation. *e.g.*

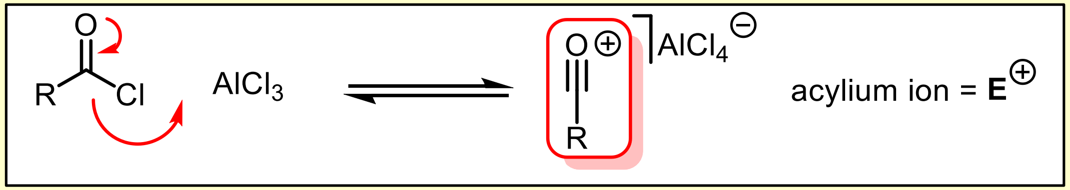


  - Overall, the Lewis acid is a *catalyst* in Friedel-Crafts alkylation:

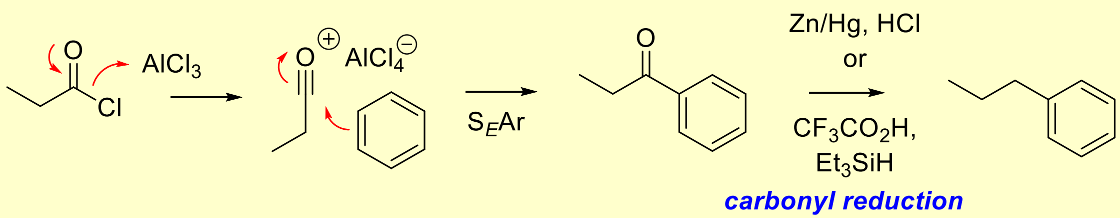


Friedel-Crafts acylation

- ***Typical conditions:*** acid chloride (or anhydride) + Lewis acid

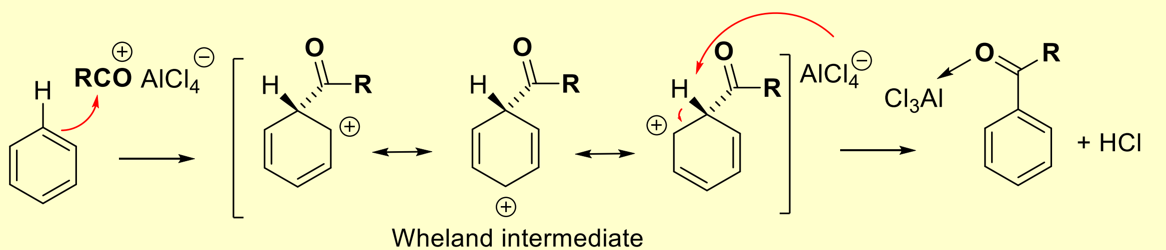


  - for activated aromatics (*i.e*. electron rich, *e.g.* phenols) no Lewis acid is required
  - Friedel-Crafts acylation followed by carbonyl reduction is a preferred alternative to any Friedel-Crafts alkylation reaction requiring a primary carbocation as it avoids rearrangements and over-alkylation*. e.g*.



NB. impossible to obtain efficiently *via* direct Friedel-Crafts alkylation (see previous slide)

  - although in theory the Lewis acid is a *catalyst* in Friedel-Crafts acylation, most Lewis acids complex to the product more strongly than to the acid chloride – so *stoichiometric* amounts are required



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