

Year 1 CHEM40006
Reactivity at Carbon Centres

***LECTURE 15 - Reactivity at sp^2 Centres: Aromatic
Compounds as Electrophiles***

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Feb 2020

Format and scope of presentation

- ***Nucleophilic aromatic substitution:***
 - S_NAr
 - mechanism (addition-elimination)
 - leaving group influence and examples
 - S_{N1Ar} & S_{RN}
 - diazonium salt formation
 - Sandmeyer-type reactions
 - Benzyne & arynes

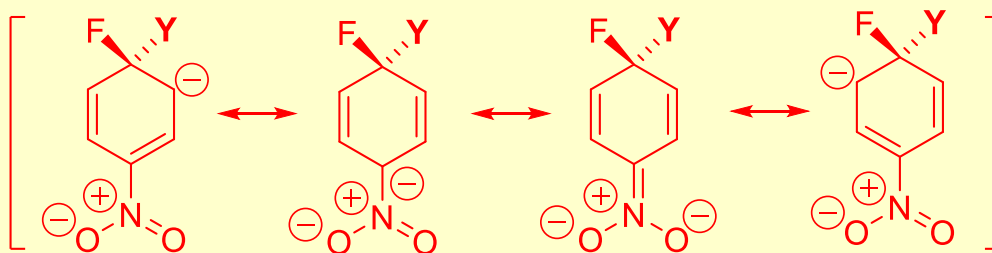
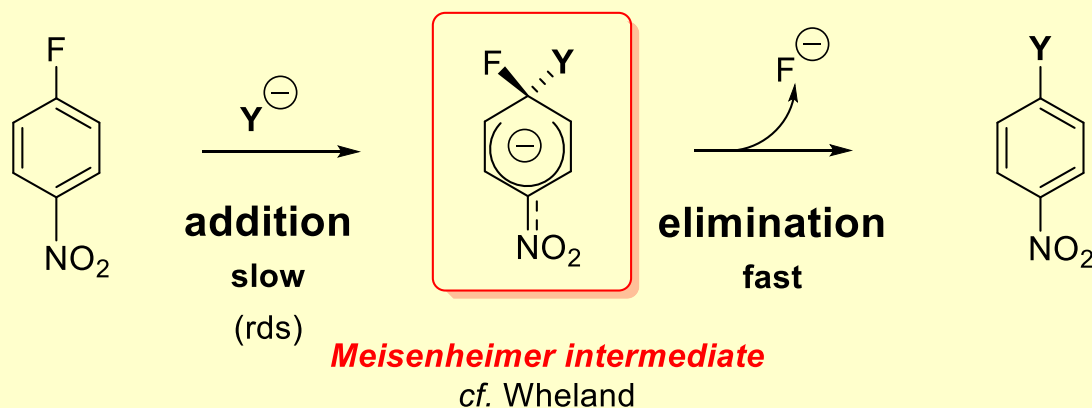
Key further reading: Clayden, Greeves & Warren, *Organic Chemistry*, 2nd Ed., Chapter 22

- S_NAr – pages 514 - 520
- S_{N1Ar} & benzyne – pages 520 - 525

Nucleophilic Aromatic Substitution - S_NAr

- **Mechanism:** addition-elimination

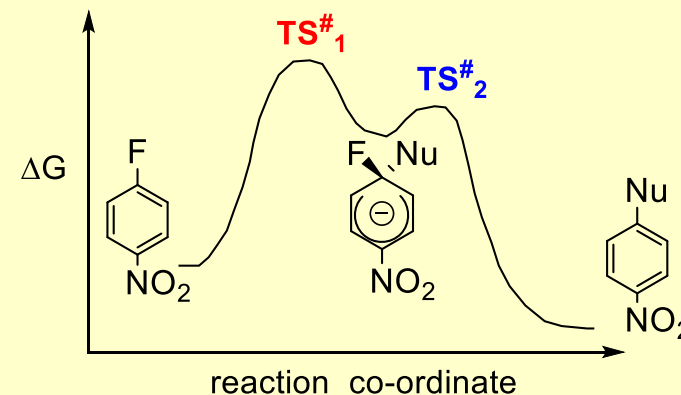
- Rate = $k[\text{ArX}][\text{Y}^-]$; bimolecular but rate determining step does *NOT* involve departure of leaving group (cf. S_N2)
- e.g. 4-fluoro nitrobenzene:



- only efficient for electron deficient benzene derivatives (i.e. those having an electron withdrawing/anion stabilising group at *ortho* or *para* position relative to leaving group)

notes

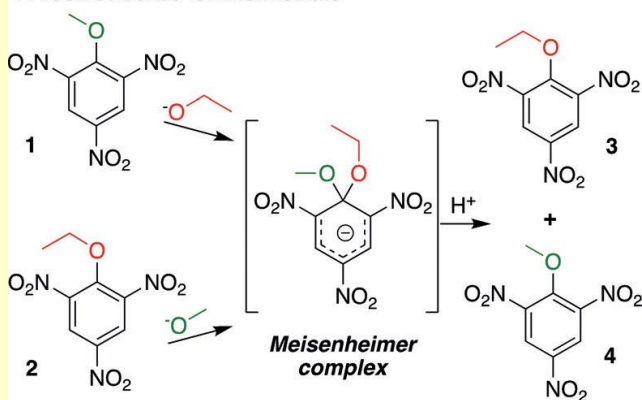
- *Intermediates:* energy minima
- *Transition states:* energy maxima
- Meisenheimer intermediate is NOT aromatic but stabilised by delocalisation
- Generally under kinetic control



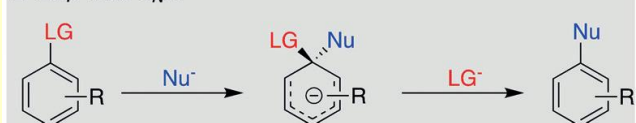
Nucleophilic Aromatic Substitution - S_NAr

- **Mechanism:** recent studies by Jacobsen indicate these reactions can also be *concerted*
 - Jacobsen *Nat. Chem.* **2018**, *10*, 917 ([DOI](#)) & Lennox *Ang. Chem. Int. Ed. (Highlight)* **2018**, *57*, 14686 ([DOI](#))
 - Use of Singleton natural abundance ¹²C/¹³C Kinetic Isotope Effects measured *via* ¹⁹F NMR satellites from carbon *ipso* to fluorine leaving group:

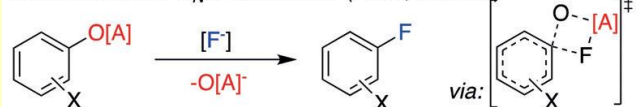
A 1902 evidence for intermediate



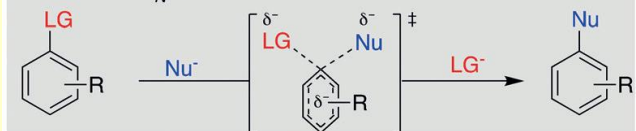
B Step-wise S_NAr



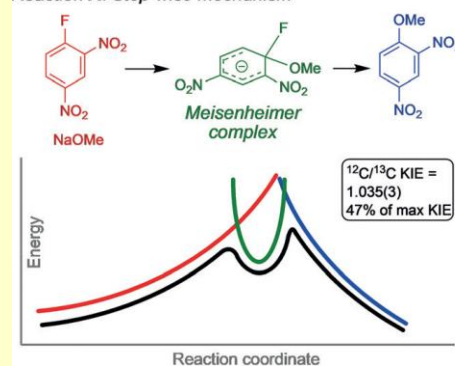
C Intramolecular S_NAr fluorination (Ritter, Sanford)



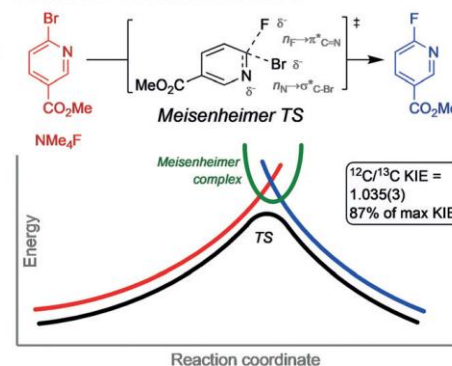
D Concerted S_NAr



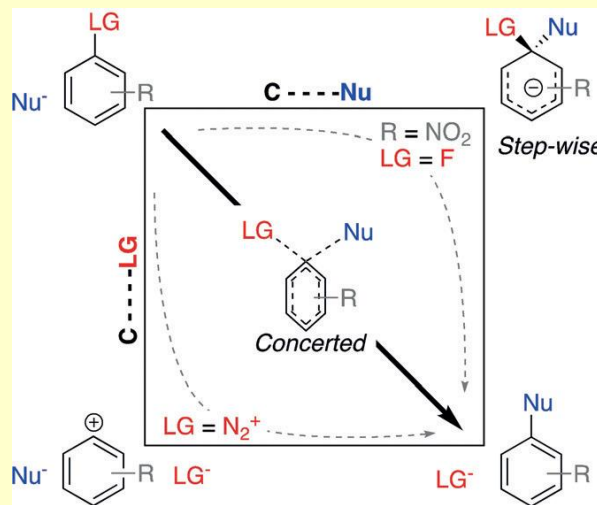
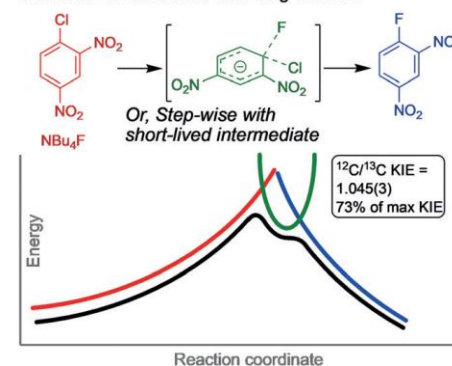
Reaction A: Step-wise mechanism



Reaction B: Concerted mechanism



Reaction C: Concerted with long-lived TS



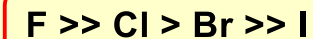
More O'Ferrall-Jencks plot for S_NAr reactions

CONCLUSION:

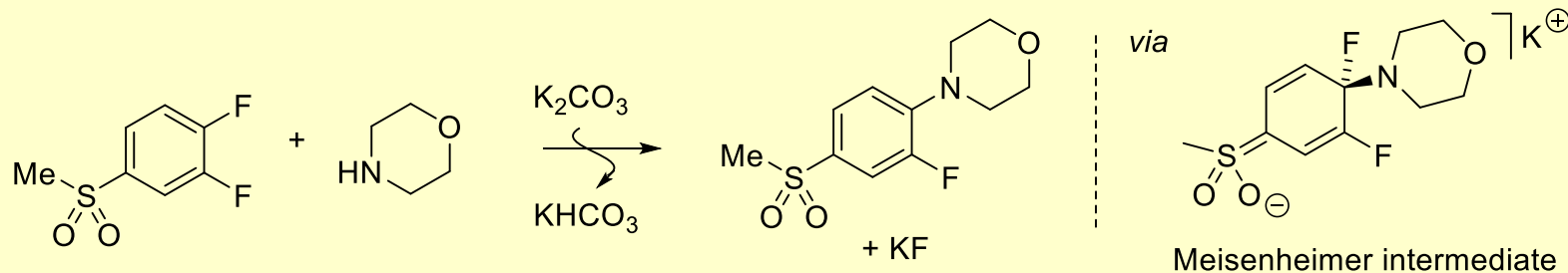
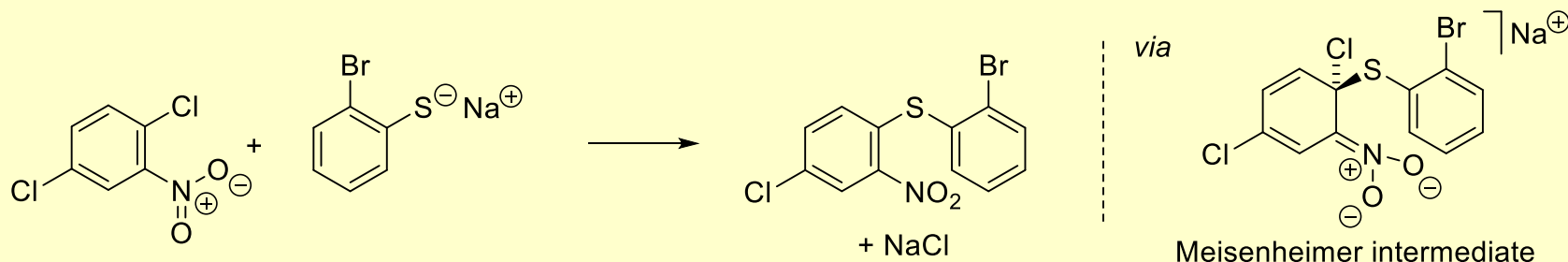
There is a mechanistic continuum between S_N2 Ar and S_N1_{Ar}. When employing fluoride as a nucleophile with a Cl or Br leaving group on a very electron deficient aryl the process can be concerted, *i.e.* 'mid-way' between the two mechanistic extremes

S_NAr - Leaving group influence & examples

- **Halides:** ease of substitution mirrors electronegativity (“**element effect**”)
 - Sugiyama *Chem. Lett.*, **1999**, 7, 691 ([DOI](#))
 - *Fluorides* are often difficult to prepare and unstable so *chlorides* are generally used



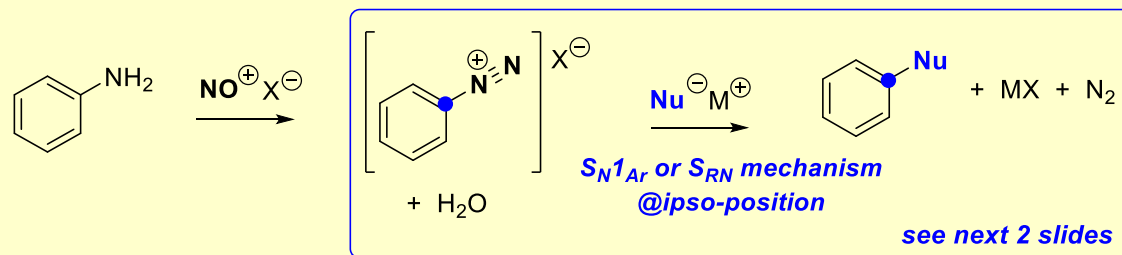
- **Activation by an anion-stabilising group at the ortho or para position is required:**



Nitrosation & the formation of diazonium salts

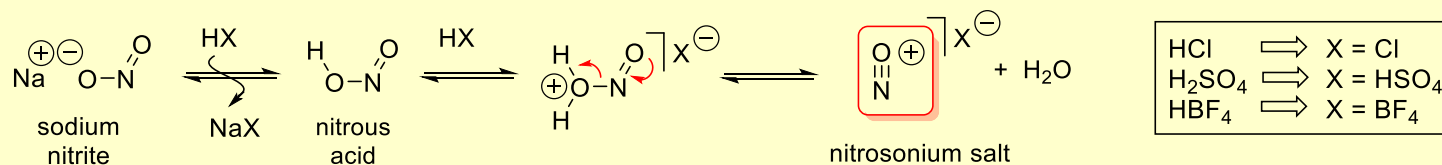
- **Reactions of anilines with nitrosonium salts give diazonium salts**

- These are versatile substrates for nucleophilic substitution reactions but NOT *via* the S_NAr mechanism...

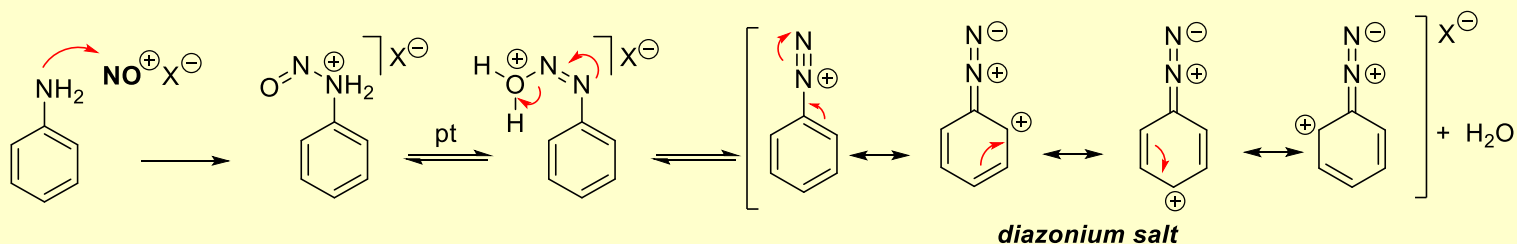


- **Typical conditions for nitrosonium salt formation**

- formed *in situ* from sodium nitrite and a mineral acid (e.g. HCl, H_2SO_4 or HBF_4)



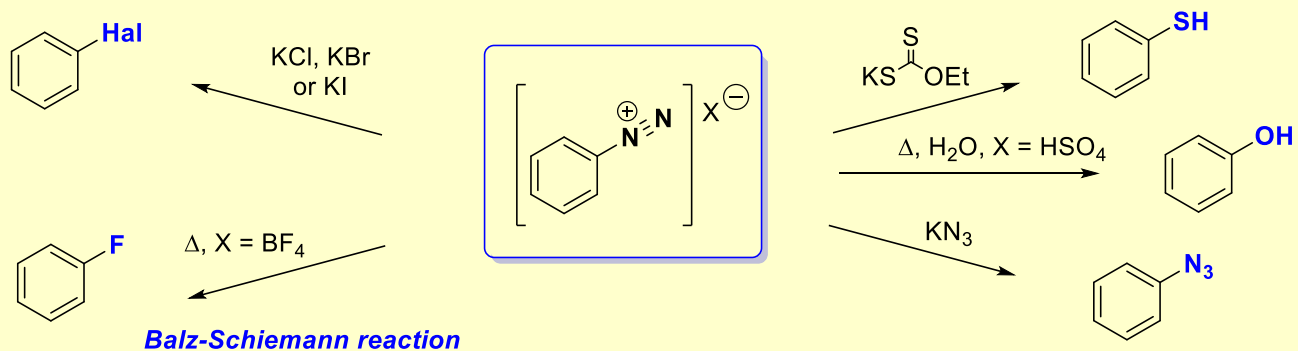
- **The nitrosonium ion reacts with the nitrogen lone pair (NOT the aryl ring ipso/para positions):**



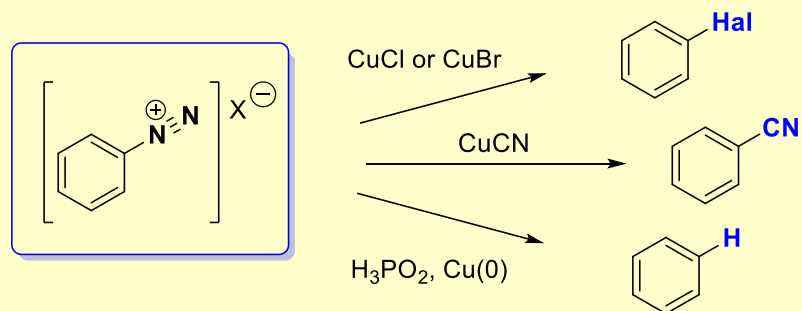
S_{N1Ar} & S_{RN} (Sandmeyer) reactions of diazonium salts

- S_{N1Ar} reactions:

- *ipso*-substitution with loss of nitrogen gas:

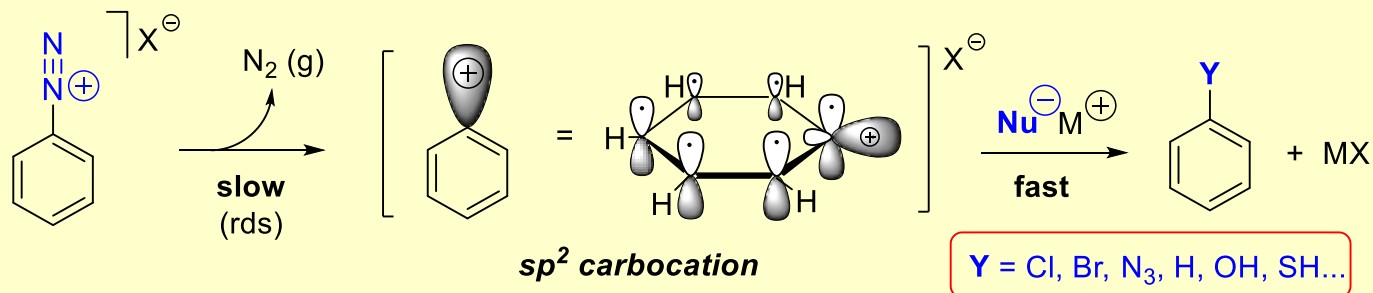


- S_{RN} (Sandmeyer reactions):

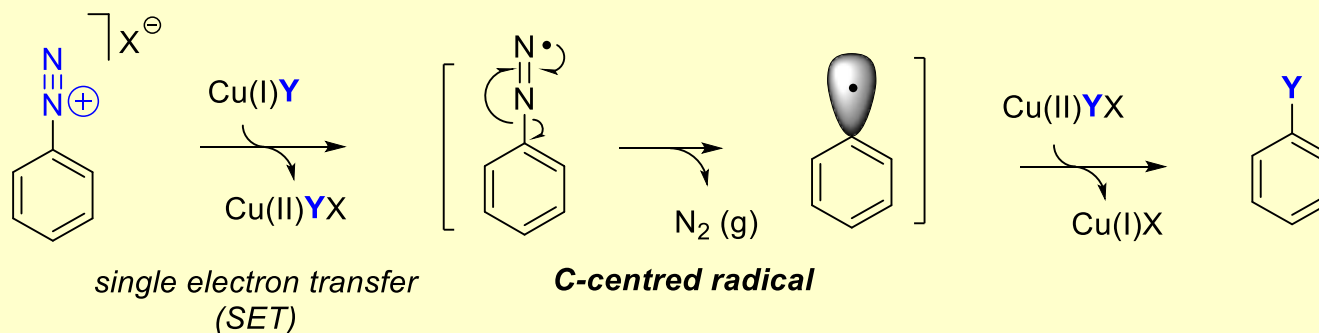


Aromatic S_N1_{Ar} & S_{RN} reaction mechanisms

- **Diazonium salts** can react *via* either S_N1_{Ar} or S_{RN} mechanisms:
 - NB. No activating anion stabilising groups are required (*cf.* S_NAr)
- **In absence of Cu salts - S_N1_{Ar} :**



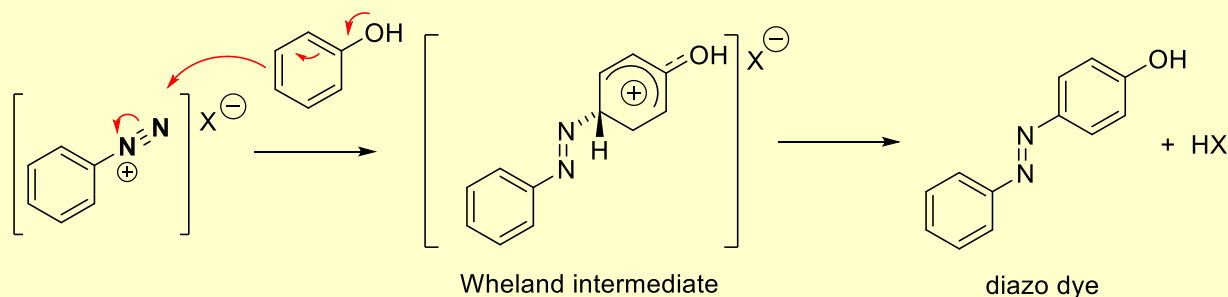
- Rate = $k[ArN_2^+]$ (unimolecular)
 - Driving force is loss of N_2 ($\Delta G = \Delta H - T\Delta S$)
 - Aryl cation is still aromatic BUT high s-character of sp^2 hybrid orbital (~33%; *cf.* p-orbital!) → high energy carbocation
- **Using copper(I) salts (*i.e.* Sandmeyer reactions) - S_{RN}**



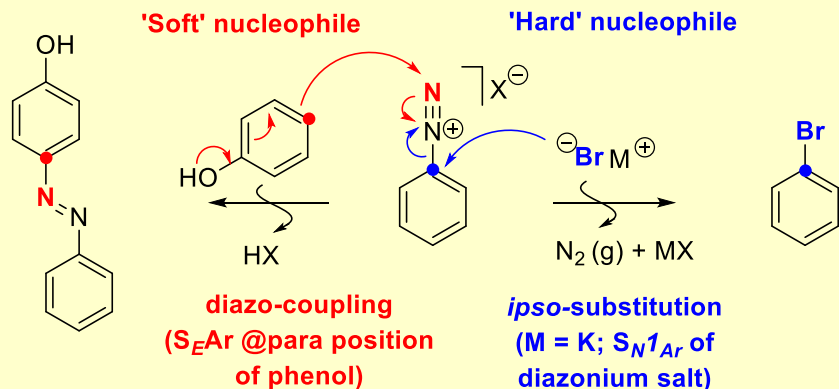
- **Review:** Bunnett *Acc. Chem. Rev.* **1978**, 11, 413 ([DOI](#))

Alternative/competing reactions of diazonium salts – *diazo coupling*

- **Certain 'soft' nucleophiles react at the terminal nitrogen of diazonium ions** (cf. 'hard' nucleophiles at the *ipso*-carbon as in S_N1_{Ar} and S_{RN} reactions)
 - e.g. synthesis of diazo dyes using **phenols** as C-nucleophiles:

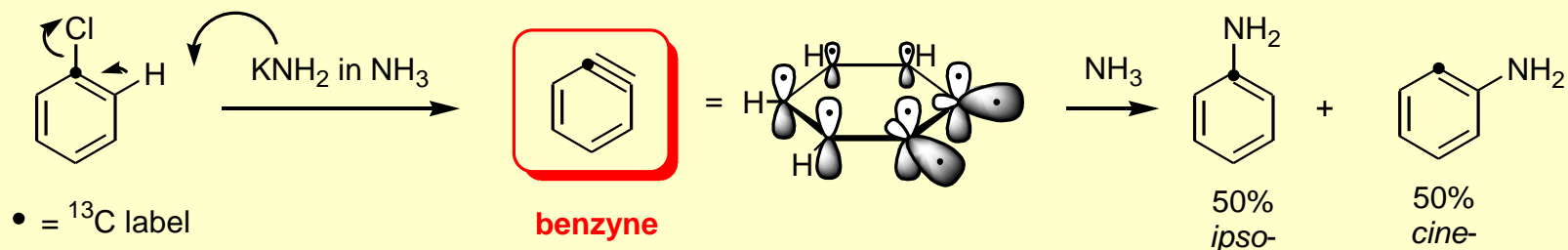


- **Diazonium salts are therefore 'ambident' electrophiles:**



Benzynes and arynes - preparation

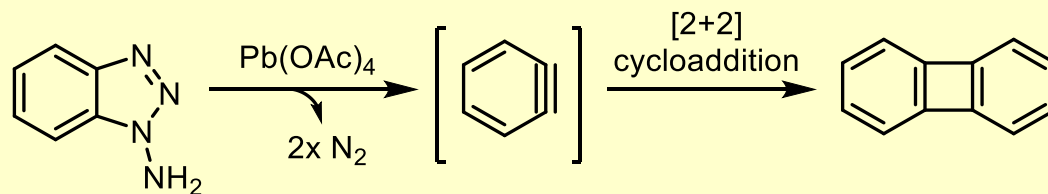
- **Mechanism:** Elimination-addition:



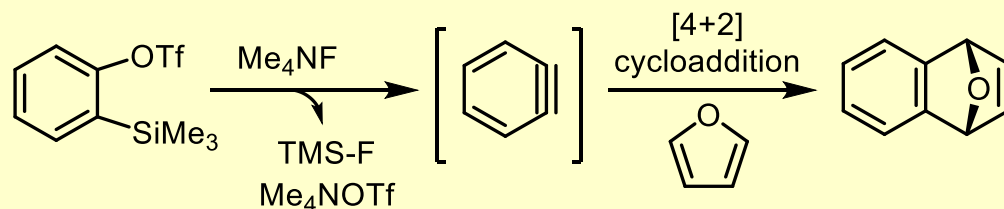
- **Evidence:** ^{13}C labelling (see above) & 2 x *ortho*-substituents \rightarrow no reaction

- **Preparation** - other methods:

- Oxidation of aminobenzotriazoles with LTA: Rees *J. Chem. Soc. C.* **1969**, 5, 742 ([DOI](#)):



- Treatment of 1,2-silyltriflates with fluoride @ low temperature: Kobayashi *Chem. Lett.* **1983**, 12, 1211 ([DOI](#)), see also: Garg *Org. Lett.* **2020**, 22, 1665 ([DOI](#)):



Arynes in synthesis – [4+2]-cycloaddition

- **Review:** Pellissier *Tetrahedron* **2003**, 59, 701 ([DOI](#))
- **Review** of the effect of strain on aryne regiochemistry, Garg, *J. Am. Chem. Soc.* **2014**, 136, 15798 ([DOI](#))
- e.g. Guitian *Eur. J. Org. Chem.* **2001**, 4543 ([DOI](#))

