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 (SEAr):**
  – 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:**
  – $S_{N}Ar$
  – VNS (vicarious nucleophilic substitution)
  – $S_{N}1$ & $S_{RN}1$ (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 $C_6H_6$

- No-decolourisation of bromine water (addition of $Br_2$ across double bonds)
Kekulé and his dream of snakes...

Kekulé or Loschmidt?

- ‘Facts are better than dreams’ Noe & Bader Chem Brit. 1993, 126
Aromaticity: stability and bond lengths

- **Quantification of unusual stability: heats of hydrogenation (calorimetry)**

\[
\text{Pd/C-H}_2 \quad \Delta H^\circ = -120 \text{ kJmol}^{-1}
\]

\[
\text{Pd/C-H}_2 \quad \Delta H^\circ = -232 \text{ kJmol}^{-1}
\]

\[
\text{Pd/C-H}_2 \quad \Delta H^\circ = -208 \text{ kJmol}^{-1}
\]

\[\text{[T} \uparrow, \text{P} \uparrow\text{]}\]

\[\text{i.e. resonance 'worth' } \sim 8 \text{ kJmol}^{-1}\]

\[\text{[(2x120)-232]}\]

\[\text{i.e. aromatic stabilisation 'worth' } \sim 152 \text{ kJmol}^{-1}\]

\[\text{[(3x120)-208]}\]

- **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 $\delta 7.27$ ppm
  – i.e. deshielding due to ring current (cf. $\delta 4.5$-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:

  \[
  \begin{array}{c}
  \begin{array}{c}
  H \\
  H \quad H \quad H \quad H \\
  H \quad H \quad H \quad H \\
  H \quad H \quad H \quad H \\
  H \quad H \quad H \quad H \\
  H \quad H \quad H \quad H \\
  H \quad H \quad H \quad H \\
  H \quad H \quad H \\
  \end{array} \\
  18\text{-annulene} \\
  (18\pi \text{ electrons}) \\
  \delta -1.8 \text{ ppm inside} \\
  \delta 8.9 \text{ ppm outside}
  \\
  \begin{array}{c}
  \begin{array}{c}
  H \\
  H \quad H \quad H \\
  H \quad H \quad H \\
  H \quad H \quad H \\
  H \quad H \quad H \\
  \end{array} \\
  \text{Vogel’s hydrocarbon} \\
  (10\pi \text{ electrons}) \\
  \delta -0.7 \text{ ppm inside} \\
  \delta 7.1 \text{ ppm outside}
  \\
  \begin{array}{c}
  \begin{array}{c}
  \text{Me} \\
  \end{array} \\
  \text{dimethyldihydropyrene} \\
  (14\pi \text{ electrons}) \\
  \delta -5.5 \text{ (Me) inside}
  \end{array}
  \end{array}
  \]
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

\[ \text{VB structure} \]

- **MOLECULAR ORBITAL (MO) THEORY**
  - *Linear Combination of Atomic Orbitals (LCAO)*
  - $\sigma$-bonding framework formed from sp$^2$ hybridised carbons
  - leaves p-orbital on each C atom orthogonal to ring
  - 6 atomic p-orbitals (AOs) $\rightarrow$ [LCAO maths] $\rightarrow$ 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

\[ \text{MO structure} \]
Benzene - Molecular Orbital Description

- Molecular orbital theory rationalises reactions and properties of benzene:

![Diagram of benzene with molecular orbitals and energy levels]
Musulin-Frost diagrams: MO diagrams without the maths

- **Graphical device for constructing MO energy diagrams:**
  - 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)

![Musulin-Frost diagrams](image-url)
Hückel’s rule

- **Empirical rule for aromaticity:**
  - 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**:

<table>
<thead>
<tr>
<th>4n+2 $\pi$ electrons (aromatic)</th>
<th>4n $\pi$ electrons (antiaromatic or non aromatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 0</strong></td>
<td></td>
</tr>
<tr>
<td>cyclopropenyl cation</td>
<td>cyclopropenyl anion</td>
</tr>
<tr>
<td>cyclobutadienyl dication</td>
<td>cyclobutadiene</td>
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<tr>
<td><strong>n = 1</strong></td>
<td></td>
</tr>
<tr>
<td>benzene</td>
<td>cyclopentadienyl cation</td>
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<tr>
<td>cyclopentadienyl anion</td>
<td>cycloheptatrienyl anion</td>
</tr>
<tr>
<td>cycloheptatrienyl cation (tropylium cation)</td>
<td>cycloheptatrienyl cation</td>
</tr>
<tr>
<td><strong>n = 2</strong></td>
<td></td>
</tr>
<tr>
<td>cyclooctatetraenyl dianion</td>
<td>cyclooctatetraene</td>
</tr>
</tbody>
</table>
Evidence for anti-aromaticity

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

  ![Deprotonation reaction diagram](image)

  - 4 π electrons anti-aromatic
  - 6000 times slower!

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

  ![Silver assisted solvolysis reaction diagram](image)

  - 4 π electrons anti-aromatic

  - 'very fast'
Vollhardt’s cyclohexatriene


- 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: $S_{E}Ar$

- Mechanism: *addition-elimination*

\[ \text{Wheland intermediate (sigma complex, arenium ion)} \]

**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**

1. **TS\(\text{#}_1\)** is the *Rate Determining Step (RDS)*
2. this DOES NOT involve C-D bond breaking
3. i.e. **NO Kinetic Isotope Effect (KIE)**

**Case 2**

1. **TS\(\text{#}_2\)** is the *Rate Determining Step (RDS)*
2. this DOES involve C-D bond breaking
3. i.e. primary **Kinetic Isotope Effect (KIE)** expected

*MOST S\(_E\)Ar REACTIONS* e.g. Nitration

*RARE for S\(_E\)Ar REACTIONS, but e.g. nitrosation shows small KIE possibly due to partitioning effects*
Further evidence

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

  
  ![Chemical diagram]

  
  - Femtosecond UV of Wheland intermediates: Kochi *J. Am. Chem. Soc.* **2000**, 122, 8279 ([DOI](https://doi.org/))
  - 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](https://doi.org/))
**Nitration**

- **Review:** Albright ACS Symposium Series *1996*, 623, 1
- **Typical conditions:** c.HNO₃/c.H₂SO₄ (1:1) or c.HNO₃ in AcOH

Can also use NO₂BF₄, NO₂ClO₄, NO₂PF₆, NO₂CF₃SO₃, N₂O₄, or N₂O₅ in organic solvents
- Useful method for introduction of nitrogen (e.g. Ar-NO₂ → Ar-NH₂ → Ar-N₂⁺ → etc.)
- The process is catalytic in sulfuric acid (or whichever acid used to protonate nitric acid)

- **Recent developments:**
  - *Using Bi(NO₃)₃·5H₂O*: Yin *J. Org. Chem.* 2005, 70, 9071 (DOI)
Nitration of activated aromatics

- **Typical conditions**: dilute HNO₃ 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.\(\text{H}_2\text{SO}_4\) saturated with \(\text{SO}_3\))

\[
\begin{align*}
\text{sulfur} & \quad \text{trioxide} \\
\text{protonated sulfur} & \quad \text{trioxide} = E
\end{align*}
\]

- The electrophile is either \(\text{SO}_3\) or \(\text{HSO}_3^+\) depending on the conditions
- Can also use \(\text{SO}_3\) in aprotic solvents (here, the electrophile is \(\text{SO}_3\))
- 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:

\[
\begin{align*}
\text{R} & \quad \text{H} \\
\text{SO}_3\text{H} & \quad \text{HSO}_3^- \\
\text{R'}\text{NHR''} & \quad \text{SO}_2\text{NR'}\text{R''}
\end{align*}
\]

- *NB.* recent use of pentafluorophenyl (pfp) sulfonates for sulfonamide construction:
- Caddick *J. Am. Chem. Soc.* 2004, 126, 1024 ([DOI](https://doi.org/))
Halogenation

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

\[
\begin{align*}
\text{Br}_2 & \quad \xrightarrow{\text{FeBr}_3} \quad \text{Br...FeBr}_4 \\
& \quad \text{Halogen-Lewis acid complex } = E
\end{align*}
\]

- **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 promoters, 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

- **fluorine:** generally reacts explosively with aromatics:
  - fluoride best introduced by Bälz-Schiemann reaction: HBF\(_4\) diazonium/Δ
Aromatic Finkelstein reactions

- **Br → I exchange - Cu catalysis:**

  \[
  \text{Br} \rightarrow I \\
  \text{CuI (5mol%)} \\
  \text{Nai (2eq)} \\
  \text{dioxane, 110°C, 22-24h}
  \]

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

  \[
  \text{Cl} \rightarrow I \\
  \text{Me_3Si_2 (1.2 eq)} \\
  \text{Pd_2dba_3 (1.5 mol%)} \\
  \text{H_2O, KF, dioxane} \\
  \text{LiCl (1.5 eq)} \\
  \text{Lig (9 mol%)}
  \]
Friedel-Crafts alkylation

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

\[
\text{alkyl halide-Lewis acid complex} = E
\]

- 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

\[
\begin{align*}
\text{Order of Lewis acid effectiveness: } & \\
\text{AlCl}_3 > \text{FeCl}_3 > \text{BF}_3 > \text{TiCl}_3 > \text{ZnCl}_2 > \text{SnCl}_4
\end{align*}
\]

Friedel-Crafts acylation

- **Reviews:**

- **Typical conditions:** acid chlorides or anhydrides (also sulfonyl chlorides) ± LA promotor:
  
  \[
  \begin{align*}
  R'CO & \quad \text{Cl} \quad \text{AlCl}_3 \quad \text{AlCl}_4 \quad \text{acylium ion} = E^+ \\
  R'' & \\
  \end{align*}
  \]

  - LA not required for activated aromatics
  - *stoichiometric LAs*: \( \text{AlCl}_3 > \text{FeCl}_3 > \text{BF}_3 > \text{TiCl}_3 > \text{ZnCl}_2 > \text{SnCl}_4 \)
    - Generally can’t be recycled *via* aqueous extraction
  - *catalytic LAs*: lanthanide(III) halides/triflates e.g. \( \text{GaCl}_3, \text{InCl}_3, \text{Hf(OTf)}_4 \); aqueous recycling possible

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

---

\( N.B. \) NOT catalytic in Lewis acid because it complexes to product ketone
Formylation


Olah-Kuhn formylation: $\text{HCl-AlCl}_3 \rightarrow \text{H} \equiv \text{O}$

Gatterman formylation: $\text{HCl-AlCl}_3 \rightarrow \text{H} \equiv \text{O}$

Rieche-Gross-Hoft formylation: $\text{Cl} \text{H} \text{Cl} \text{H} \text{Me} \text{O} \text{Me} \rightarrow \text{H} \equiv \text{O}$

Vilsmeier-Haack formylation: $\text{POCl}_3 \rightarrow \text{H} \equiv \text{NMe}_2$

Gatterman-Koch formylation: $\text{Zn(CN)}_2 \rightarrow \text{H} \equiv \text{N-H}$

Houben-Hoesch acylation: $\text{R-CN} \rightarrow \text{R} \equiv \text{N-H}$

- 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](http://dx.doi.org/10.1002/anie.200600815))
Organocatalytic FC-type conjugate addition

- Organocatalytic aniline asymmetric conjugate addition:

\[
\text{Me}_2\text{N} - \text{Ph} - \text{OMe} \xrightarrow{\text{CH}_2\text{Cl}_2, -50^\circ\text{C}} \text{Me}_2\text{N} - \text{Ph} - \text{OMe} \xrightarrow{\text{MeI}} \text{Me}_3\text{N} - \text{Ph} - \text{OMe} \\
\]

\[
\xrightarrow{\text{Birch} [\text{R}] \text{Na/NH}_3, -78^\circ\text{C}} \xrightarrow{\text{Suzuki Rex}^n \text{PhB(OH)}_2, \text{Ni(COD)}_2, \text{IMes ligand}} \]

- X = CHO, [82%, 84% ee]
- X = CH$_2$OH
- X = CH$_2$OTBS

\[
\xrightarrow{\text{NaBH}_4 \text{TBSCl}} \]

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Nitrosation

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

\[
\begin{align*}
\text{sodium nitrite} & \quad \rightarrow \quad \text{nitrous acid} \\
\text{HCl} & \quad \rightarrow \quad \text{HCl} \\
\text{nitrosonium ion} & \quad = \quad \text{E}^+ \\
\end{align*}
\]

- 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
Diazotisation & Sandmeyer reactions

- **Mechanism of formation:**

  \[
  \begin{align*}
  &\text{NH}_2 \quad \text{NO}^+ \\
  &\text{R} \quad \text{R} \quad \text{N} \\
  &\text{R} \quad \text{R} \quad \text{N} \\
  &\text{H}_2\text{O} \\
  &\text{N} \\
  &\text{N} \\
  &\text{N} \\
  &\text{N} \\
  \\
  &\text{diazonium salt} + \text{H}_2\text{O}
  \end{align*}
  \]

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

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

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:

\[
\begin{align*}
\text{X}^-\text{N}_2\text{R'}\text{X}^+ & \rightarrow \text{R'}\text{H}^+ & \rightarrow \text{N}_2\text{N}^+\text{R'}\text{R''} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{X}^-\text{N}_2\text{R} & \rightarrow \text{R'O} & \rightarrow \text{N}_2\text{N}^+\text{R'} & \rightarrow \text{N}^-\text{R'} \quad \text{HX} \\
\end{align*}
\]
Aromatics as ambident nucleophiles

• cf. Aryl diazonium ions as ambident electrophiles:

\[
\begin{align*}
&\text{diazochlorination} \\
&\text{ipso-substitution}
\end{align*}
\]

• Aromatics as ambident nucleophiles (‘directing effects’):

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:

**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-/para-Directing (deactivating)**

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

---

### ortho-

- Low energy conformation

### meta-

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

### para-

- Low energy conformation
**ortho-/para-Directing (activating)**

- **NR₂, NH₂, OH, OR, NHCOR, OCOR** (activating by resonance which overrides induction)
- **Alkyl** (activating by hyperconjugation)
- **Aryl** (activating by resonance)
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-

\[
\begin{array}{c|c|c}
E & \% \text{o-} & \% \text{p-} \\
\hline
\text{Cl} & 39 & 55 \\
\text{NO}_2 & 30 & 70 \\
\text{Br} & 11 & 87 \\
\text{SO}_3 & 1 & 99 \\
\end{array}
\]

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

\[
\begin{array}{c|c|c}
X & \% \text{o-} & \% \text{p-} \\
\hline
\text{Me} & 58 & 37 \\
\text{Et} & 45 & 49 \\
^1\text{Pr} & 30 & 62 \\
^1\text{Bu} & 16 & 73 \\
\end{array}
\]

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

- **Proto-desulfonylation:**

  ![Reaction Scheme]

  - Utility of SO$_3$H as temporary directing group

    ![Reaction Scheme]

    - ~100% para-
      
      (SO$_3$ is BIG)

    - ~100% mono-nitration
      
      (NO$_2$ is deactivating)

- **Desilylation, degermylation & destannylation:**

  - **Review:** Eaborn J. Organometal. Chem. 1975, 100, 43 (DOI)
Synthetic ‘check list’ for $S_E\text{Ar}$

- **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: $S_{N}Ar$**

- **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:

- **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 derivatives and azines
Leaving group influence: $S_{N\text{Ar}}$

- **Halides**: ease of substitution follows the *element effect*:
  - *Fluorides* are often difficult to prepare and unstable so *chlorides* are generally used

- **NO$_2$ and OTMS groups**: also good leaving groups for $S_{N\text{Ar}}$:

- **Ionic liquid media**: e.g. Welton *Org. Lett.* **2007**, 9, 5247 (DOI)

- **Microwave acceleration**: e.g. Luo *Tet. Lett.* **2002**, 43, 5739 (DOI)

\[
\begin{array}{c}
\text{Me$_3$SiO OSiMe$_3$} \\
\text{OSiMe$_3$ (NH$_4$)$_2$SO$_4$ cat.} \\
\text{Δ} \\
\text{OH} \\
\text{[95%]}
\end{array}
\]
**Vicarious Nucleophilic Substitution: VNS**

- **Nucleophilic replacement of HYDROGEN ortho and para to NO₂ groups**
  - 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 SₐAr reactions of these substrates SₐAr of the halogens eventually ensues)
  - e.g.

![Reaction Mechanism Diagram](image-url)

\[
\text{NO}_2 \text{H} \quad + \quad \text{Cl} \text{SO}_2 \text{Ph} \quad \xrightarrow{1) \text{KOH, DMSO}} \quad 1) \quad \text{HCl} \rightsquigarrow \quad \text{NO}_2 \quad \text{SO}_2 \text{Ph}
\]
Aromatic $S_N1$ & $S_{RN1}$ reactions

- **Diazonium salts** do NOT react via $S_NAr$ but either by $S_{N1}$ or $S_{RN1}$ mechanisms:
- **In absence of Cu salts - $S_N1$:**

  - Rate $= k[ArN_2^+]$ (unimolecular)
  - 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) - $S_{RN1}$**
  - **Review:** Bunnett *Acc. Chem. Rev.* **1978**, *11*, 413 ([DOI](http://dx.doi.org/10.1021/ar500061f))
  - Single Electron Transfer mechanism - see workshop
  - VERY USEFUL SYNTHETIC REACTIONS – SEE EARLIER SLIDE
Benzynes and arynes

- **Mechanism:** Elimination-addition:

  \[
  \begin{align*}
  \text{Cl} & \quad \text{H} \quad \xrightarrow{\text{K} \text{NH}_2 \text{ in } \text{NH}_3} \quad \text{benzyne} \\
  \text{H} & \quad \text{Cl} \quad \xrightarrow{\text{label}} \quad \text{13C label}
  \end{align*}
  \]

  \[
  \text{NH}_3 \rightarrow \text{NH}_2 \quad \text{50% ipso-} \quad \text{50% cine-}
  \]

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

  \[
  \begin{align*}
  \text{[2 + 2]} & \quad \text{dimerisation} \\
  \text{[4 + 2]} & \quad \text{Diels-Alder}
  \end{align*}
  \]

- Triflates suffer competitive thia-Fries rearrangement:
Arynes in synthesis

- **Review:** Pellissier *Tetrahedron* 2003, 59, 701 ([DOI](https://doi.org/10.1016/S0040-4020(02)01292-5))


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


\[
\begin{align*}
\text{TsO} & \quad \text{Cl} \\
\text{Me}_3\text{Si} & \quad \text{Cl} \\
\text{F} & \quad \text{F}
\end{align*}
\]

\[
\begin{align*}
\text{NaBH}_4, \text{NaOH} & \quad [89\%] \\
\text{H}_2, \text{Pd/C} & \quad [65\%]
\end{align*}
\]

1) NaBH₄, NaOH
2) H₂, Pd/C

**ellipticine** and **isoellipticine**

Summary

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

• **Electrophilic aromatic substitution ($S_{E\text{Ar}}$):**
  – 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:**
  – $S_{N\text{Ar}}$
  – VNS (vicarious nucleophilic substitution)
  – $S_{N1}$ & $S_{RN1}$ (Sandmeyer reactions)
  – Benzyne & arynes