The Julia Olefination: An (E)-selective alternative to the Wittig reaction

- α-Metalated sulfones also react with carbonyl compounds to form β-hydroxysulfones. If the hydroxyl group is then converted into a better leaving group (by acetylation), a reductive desulfonylation can be performed to give an alkene. Overall, this multistep sequence is referred to as the Julia olefination:

\[
\begin{align*}
\text{PhSO}_2\text{Ph} & \underset{\text{BuLi}}{\rightarrow} \text{PhSO}_2\text{Li} \quad \text{HCO}_2\text{R'} \quad \text{Ac}_2\text{O} \quad \text{Na/Hg} \\
\end{align*}
\]

- Although it was originally thought that the sulfonyl group is reduced to an alkyl carbanion (c.f. previous slide), it is now believed that an initial E1cB elimination to a vinyl sulfone occurs. Reductive desulfonylation then proceeds to give a vinyl anion, which is protonated by the MeOH present (see *J. Org. Chem.* 1995, 60, 3194).

- In accord with this mechanism, use of MeOD instead of MeOH results in >90% deuterium incorporation into the final product:

"Why is a Vinyl Anion Configurationally Stable but a Vinyl Radical Configurally Unstable?" *Tetrahedron Lett.* 1992, 33, 3543
**Julia-Kocienski Olefination:** A popular modification of the classical Julia reaction

- The **Julia-Kocienski olefination** is an improved protocol that takes place in one step from the sulfone, and can give excellent (E)-selectivities [provided that potassium bases and polar (non-protic) solvents (e.g. 1,2-dimethoxyethane) are used].

- It uses specially-designed sulfones commonly referred to as **PT-sulphones** (PT = 1-phenyl-1H-tetrazol-5-yl):

$$\begin{align*}
\text{R} & \quad \text{X} \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{H} \\
\hline
\text{R} & \quad \text{H} \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\hline
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\hline
\text{R} & \quad \text{H} \\
\text{Ph} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\hline
\end{align*}$$

- Involves diastereoselective addition of the $\alpha$-sulfonyl anion to the aldehyde, **intramolecular (S$_{N}$Ar) transfer of the PT group** to the alkoxide, and fragmentation (with loss of SO$_2$):

$$\begin{align*}
\text{R} & \quad \text{R'} \\
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\hline
\text{R} & \quad \text{R'} \\
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\hline
\text{R} & \quad \text{R'} \\
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\hline
\text{R} & \quad \text{R'} \\
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\hline
\end{align*}$$

- **Origin of (E)-Selectivity** (for interest only):
  - Large M$^+$ ion (K$^+$)
  - Polar solvent
  - Closed transition state: (E)-selectivity

- Small M$^+$ ion (Li$^+$)
  - Apolar solvent
  - Open transition state: (Z)-selectivity

KHMDS is a strong, bulky amide base similar to LDA

$$\text{Me}_3\text{Si} \quad \text{N} \quad \text{SiMe}_3$$

**KHMD (potassium hexamethyldisilazide)**
Darren Dixon at Oxford has recently used the Julia-Kocienski olefination reaction to prepare an 8-membered cyclic alkene *en route* to the alkaloid natural product nakadomarin A:

1. $m$-CPBA
2. aq. HCl

Sometimes people use benzothiazolyl (BT) sulfones as alternatives to PT sulfones. The example below, taken from the total synthesis of iejimalide B, uses the Julia-Kocienski olefination on two different occasions to form 1,2-dienes:

$BT = \text{benzothiazolyl}$
Ramberg-Bäcklund Reaction: A Useful Way to Make Strained Alkenes

- The Ramberg-Bäcklund reaction is yet another popular method for the synthesis of alkenes.
- It involves the base-mediated conversion of $\alpha$-halo sulfones into episulfones via an intramolecular $S_N 2$ (similar to the Favorskii reaction in C=O chemistry). The episulfone intermediates are unstable, and decompose with loss of SO$_2$ to give alkenes:

  $$\text{R-SO}_2\text{R'} \xrightarrow{\text{KOH, CCl}_4} \text{R-SO}_2\text{Cl} \xrightarrow{[O]} \text{R-SO}_2\text{R'} \xrightarrow{t-$\text{BuOK or KOH}$} \text{episulfone} \xrightarrow{\text{mechanism still debated}} \text{alkene}$$

- The stereoselectivity of the reaction – whether an (E)- or (Z)-olefin is produced – depends on a number of factors, and we will not discuss those here.
- One of the main advantages of the R-B reaction over other methods for alkene synthesis is the ease with which it can make strained (or sterically-congested) alkenes (the loss of SO$_2$ providing a strong thermodynamic driving force):

  $$\text{Br-S-S-Br} \xrightarrow{\text{Na}_2\text{S}} \text{S-SR-SR'} \xrightarrow{1. \text{NCS}} \text{S-SR-SR'} \xrightarrow{2. \text{m-CPBA}} \text{Cl-S-SR-SR'} \xrightarrow{t-$\text{BuOK}$} \text{a cyclobutene}$$

  $$\text{NCS (N-chlorosuccinimide)}$$
Vinyl Sulfones as Micheal Acceptors for C–C Bond Formation

- Due to the anion-stabilising nature of the sulfonyl group, vinyl sulfones are electrophilic alkenes much like $\alpha,\beta$-unsaturated carbonyls (though not quite as reactive):

Vinyl sulfones are also effective partners in Diels-Alder cycloadditions. As we’ve already seen, the leftover sulfonyl group can be further reacted in a lithiation-alkylation-desulfonylation sequence:

strictly speaking 'vinyl' refers to the -CH=CH$_2$ group, but chemists often use it more generally to mean 'alkenyl'
Sulfonyl Protecting and (De)activating Groups

- The most common use of the sulfonyl group is as an electron-withdrawing protecting and/or (de)activating group for nitrogen and oxygen functionalities:

  - mesyl (Ms) \[\text{[methanesulfonyl]}\]
  - tosyl (Ts) \[\text{[p-toluenesulfonyl]}\]
  - nosyl (Ns) \[\text{[o-nitrobenzenesulfonyl]}\]
  - triflyl (Tf) \[\text{[trifluoromethanesulfonyl]}\]

*N Mesyl chloride (MsCl) actually reacts differently - goes via a 'sulfene' intermediate

- **Nitrogen protecting and/or (de)activating groups** in which the amine lone pair is strongly deactivated (like in an amide):

  - deactivated pyrroles (pyrrole itself is too reactive)
  - nosyl amines (for 2° amine synthesis)
  - activated aziridines
  - tosylhydrazones

- **Oxygen activating groups** to convert alcohols or related functions into good leaving groups. Note that the triflyl (Tf) group is much more electron-withdrawing than tosyl (Ts) or mesyl (Ms):

  - solid, organic-soluble alternative to \(\text{H}_2\text{SO}_4\)
  - extremely powerful acid \((\text{p}K_a = -14!\) for \(\text{S}_2\) substitution
  - activation of alcohols for cross-coupling
  - activation of enols for cross-coupling
  - activation of phenols for cross-coupling
  - powerful silylating agents
  - Lewis acidic metals
Sulfonyl Groups as Leaving Groups: Utility in both polar and radical chemistry

- A peculiar feature of the sulfonyl group is that it can not only stabilise \( \sigma \)-anions, but can also act as a **leaving group** in certain cases. This is because the C–S bond is fairly weak and the sulfanyl anion (\( \text{RSO}_2^- \)) [or sulfonyl radical (\( \text{RO}_2S^* \))] is resonance-stabilised.

- A good example is the **Caglioti reduction** of tosylhydrazones to alkanes using \( \text{NaBH}_4 \), which provides a mild alternative to the Wolff-Kishner reduction for \( \text{C}=\text{O} \rightarrow \text{CH}_2 \):

  ![Caglioti reaction diagram](image)

  The sulfonyl group is also an excellent leaving group in **radical chemistry** (to give sulfanyl radicals, \( \text{RO}_2S^* \)). For example, alkyl radicals react with **vinyl sulfones** by addition-elimination to afford vinylated products:

  ![Radical addition-elimination](image)

- A number of other groups can also be transferred to alkyl radicals in a similar manner by using sulfonlated reagents:
General Features

- Selenium is just below sulfur in Group 16, and much of its chemistry parallels that of its lighter congener.
- Selenium is generally very highly toxic, although it is present in the body as an essential trace element.
- Because of the toxicity issue, chemists are only motivated to use selenium because it can accomplish reactions which are not possible with sulfur, or which proceed under much milder conditions.
- The critical differences between selenium and sulfur are:

1. The C–Se bond is weaker than the C–S bond, so C–Se bond-breaking reactions occur under milder conditions.
2. Selenoate anions (RSe\(^-\)) are more powerful nucleophiles than thiolates.
3. Selenoxides are thermally unstable at ambient temperature (see later), in contrast to sulfoxides.
4. Higher oxidation states [i.e. Se(IV)] are more readily accessible.

Nucleophilic Selenation (or ‘Selenylation’)

- The starting point for most organoselenium chemistry is diphenyldiselenide (PhSeSePh), which is a commercially-available solid.
- Reduction of PhSeSePh with NaBH\(_4\) gives access to selenoate anions (RSe\(^-\)), which are powerful (‘soft’) nucleophiles.
- Reaction of these with alkyl halides (or other carbon electrophiles, such as Michael acceptors) gives alkyl selenides:
Alkyl Selenides as Radical Precursors

- Due to the weakness of C-Se bonds, alkyl selenides are excellent precursors to alkyl radicals using the tin hydride method.
- Using Bu$_3$SnH as a radical reducing agent and AIBN as an initiator, C-Se bonds can be reduced to C-H bonds under very mild conditions:

  \[
  \text{R} - \text{SePh} + \text{Bu}_3\text{SnH} \rightarrow \text{R}^\bullet \rightarrow \text{R} - \text{H}
  \]

  alkyl radical

As organotin residues are highly toxic, this chemistry is not attractive for large-scale applications.

- The radicals produced by this method can be engaged in 5-exo cyclisations prior to reduction, allowing the formation of 5-membered rings:

  \[
  \text{Initiation of the radical chain reaction}
  \]

  \[
  \text{AIBN} [\text{azobis(isobutyro)nitrile}]
  \]

- Note that free hydroxyl groups are tolerated in radical chemistry (unlike in carbanion chemistry).
Electrophilic Selenation

- The reaction of organometallics or stabilised anions (such as enolates) with PhSe–X electrophiles is another common entry to organoselenium compounds:

- Phenylselenyl halides (e.g. PhSeBr) are also superb reagents for the selenofunctionalisation of alkenes. The reactions proceed via electrophilic addition of PhSeX to the alkene to give a seleniranium ion intermediate, which is then ring-opened by nucleophiles.

- One of the most popular applications of this process is to carry out intramolecular nucleophilic trapping with alcohol or carboxylic acid nucleophiles, providing a facile synthesis of oxacycles.
**Syn-Elimination of Selenoxides: A very mild alkene synthesis**

- Perhaps the most common application of selenium in organic synthesis is the **syn-elimination of selenoxides** to make alkenes.
- **Selenoxides** are generated by oxidation of alkyl selenides and, if a $\beta$-H is available, they undergo spontaneous syn-elimination to deliver an alkene, along with PhSeOH as a by-product:

\[
\begin{align*}
\text{alkyl selenide} & \xrightarrow{\text{H}_2\text{O}_2 \text{ or NaIO}_4 \text{ or m-CPBA}} \text{selenoxide} \\
& \quad \xrightarrow{\text{syn-elimination}} \text{alkene} + \text{PhSeOH}
\end{align*}
\]

- This is one of the mildest methods of alkene synthesis known (no acids or bases!) and it is heavily used in natural product synthesis.
- It also provides a general solution to the $\alpha,\beta$-dehydrogenation of carbonyl compounds to $\alpha,\beta$-unsaturated carbonyls:

\[
\begin{align*}
\text{Me} & \xrightarrow{1. \text{LDA}} \text{Me} \\
\text{Me} & \xrightarrow{2. \text{PhSeBr}} \text{Me}
\end{align*}
\]

- When combined with selenofunctionalisation, it allows for the **allylic functionalisation** of alkenes:

\[
\begin{align*}
\text{Me} & \xrightarrow{\text{PhSeCl}} \text{Me} \\
\text{Me} & \xrightarrow{\text{H}_2\text{O}_2} \text{Me}
\end{align*}
\]

Actually, **sulfoxides** can undergo the same process, but strong heating is required (100-150 °C). With selenoxides, it takes place rapidly at room temperature or below.
A useful application of selenoxide chemistry is the **Grieco elimination**, which provides an extremely mild method for the **dehydration of primary alcohols to alkenes**:

![Reaction scheme showing Grieco elimination](image)

The mechanism for the formation of the selenide using PBu$_3$ as a reducing agent is very similar to that for the Appel halogenation of alcohols with PPh$_3$ and Br$_2$ (or CCl$_4$) (see lecture 3):

![Mechanism for Grieco elimination](image)

The mildness of this dehydration protocol, as well as its selectivity for **primary** alcohols, has proven valuable in complex molecule synthesis:

![Examples of Grieco elimination](image)
Selenium Dioxide as an Oxidant: Allylic oxidation of alkenes

- Another very commonly used reaction involving selenium is the allylic oxidation of alkenes with selenium dioxide (SeO₂).
- This reaction proceeds via two sequential pericyclic processes – an ene reaction followed by a [2,3]-sigmatropic shift (see pericyclics course for detail).
- Because both steps involve alkene transposition, the net result is that the alkene C=C bond always ends up back where it started:

  ![Reaction Diagram]

  Note that the sterically more accessible trans-methyl group is attacked - a general feature of SeO₂ oxidations

  The stage at which oxidation stops depends on the amount of SeO₂, the substrate, and the conditions

- If t-BuOOH is used as a stoichiometric oxidant, SeO₂ can be used in a catalytic amount, as the Se(II) by-product is re-oxidised to SeO₂ [Se(IV)]:

  ![Reaction Diagram]
Another Example of Selenium Catalysis... (not examinable)

- In 2015, Dr Cresswell (under the supervision of Prof. Scott Denmark, University of Illinois) reported the first ever example of an alkene difunctionalisation catalysed by selenium.

- This reaction was also the first catalytic, syn-stereospecific dichlorination of alkenes (note that Cl₂ itself, and similar reagents, give anti-addition).

- In this process, selenium is used as a catalyst. The PhSeSePh pre-catalyst [Se(I)] is first oxidised to PhSeCl₃ [Se(IV)], which carries out the dichlorination reaction.

- The PhSeCl by-product [Se(III)] is then re-oxidised back to PhSeCl₃ by the oxidant, which happens to be an electrophilic source of fluorine (an “F⁺⁺” equivalent).

- The silicon in this reaction (Me₃SiCl) serves to 'mop up' fluoride ion (F⁻) produced by the oxidant, as F⁻ ions were found to poison the Se catalyst.

This chemistry was developed to help address stereochemical challenges posed in the total synthesis of polychlorinated natural products:

mytilipin A