This section of the CH40206 unit deals with the chemistry of non-metallic heteroelements in organic synthesis. Over five lectures, we will cover the most important synthetic reactions of organic compounds based on boron, silicon, phosphorus, sulfur, and selenium. Due to time constraints, we will not discuss organohalogen chemistry, as this material is largely covered indirectly in other courses.

Each lecture in this course is accompanied by a workshop, in which we will run through exam-style problems.

Lecture & Workshop Timetable

[Bold highlighting indicates a change of 'usual' time or location]

Lecture 1 (Boron): Friday 10th Nov @ 09:15 in CB 5.1
Workshop 1 (Boron): Thursday 16th Nov @ 12:15 in CB 3.9
Lecture 2 (Silicon): Friday 24th Nov @ 09:15 in CB 5.1
Workshop 2 (Silicon): Thursday 30th Nov @ 12:15 in CB 3.9
Lecture 3 (Phosphorus): Friday 1st Dec @ 09:15 in CB 5.1
Workshop 3 (Phosphorus): Thursday 7th Dec @ 12:15 in CB 3.9
Lecture 4 (Sulfur): Friday 8th Dec @ 09:15 in CB 5.1
Workshop 4 (Sulfur): Thursday 14th Dec @ 12:15 in CB 3.9
Lecture 5 (Sulfur & Selenium): Thursday 14th Dec @ 16:15 in CB 4.16
Workshop 5 (Sulfur & Selenium): Friday 15th Dec @ 09:15 in CB 5.1

Recommended Texts

- Organic Synthesis: The Roles of Boron and Silicon (Oxford Chemistry Primer 1) (by Susan E. Thomas)
- Organosulfur Chemistry (Oxford Chemistry Primer 33) (by Gordon H. Whitham)
- Modern Organic Synthesis: An Introduction (by George S. Zweifel and Michael H. Nantz)
- Hans Reich's website (see https://www.chem.wisc.edu/areas/organic/index-chem)
**General Features**

- Boron is a somewhat borderline element, being slightly too electronegative to display metallic bonding in its elemental form or to give \( \text{B}^{3+} \) ions. It forms highly covalent bonds to carbon, and is often described as a **metalloid** rather than a metal.

- Boron’s electronic configuration is \( 1s^2, 2s^2, 2p^1 \). It therefore has only 3 electrons in it’s valence shell.

- Most boron compounds comprise three conventional 2-centre-2-electron bonds arranged in a **trigonal planar** structure, leaving a vacant p-orbital ready to accept a pair of electrons. Therefore many neutral boron species are **Lewis acidic** and are isoelectronic with carbocations:

- **Borane** (BH₃) tries to satisfy it’s electron-deficiency by dimerising to diborane (B₂H₆). The two bridging hydrogen atoms in diborane are part of non-classical 3-centre-2-electron bonds:

- Boron can satisfy its need for electrons more effectively by forming tetrahedral adducts with **Lewis bases**. Chemists typically use BH₃ complexes as reagents rather than diborane itself (a pyrophoric gas!), the most popular being BH₃·SMe₂ and BH₃·THF:

### Electronegativities

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### Borax (sodium borate)

Borax (sodium borate) is the natural source of boron and is used in household detergents.
Boron as a Lewis Acid in Organic Synthesis

- Although this lecture is focused primarily on organoboron reactants, it is important to note that boron compounds are also used extensively in organic synthesis as Lewis acid promoters.

- Boron trifluoride etherate (BF₃·OEt₂) is an easily-handled liquid that is frequently used to generate (stabilised) carbocations by C–O bond-cleavage. An unusual example (developed by Dr Cresswell in his PhD!) is the use of BF₃ as a fluorinating agent for aryl epoxides:

  ![BF₃·OEt₂ fluorination of aryl epoxide](image)

  - Another common use of boron Lewis acids is to activate carbonyl (C=O) groups to nucleophilic attack (i.e. by LUMO-lowering). Corey has developed a famous class of chiral, enantiopure boron Lewis acids that have been used to great effect in catalytic, enantioselective Diels-Alder reactions:
Classification of Organoboron Compounds

- For historical reasons, the nomenclature of organoboron compounds is somewhat muddled, as illustrated by use of the term "borate" to describe both neutral B(OR)₃ compounds and tetracoordinate boron anions of the form BX₄⁻:

  - borane
  - a trialkylborane
  - a borinic acid
  - a boronic acid
  - a boronic ester*
  - boric acid
  - trialkylborate
  - borate anion (or boronate anion**)

*Sometimes referred to as a "boronate ester", despite being neutral and tricoordinate. **Usually refers to tetracoordinate anions formed from boronic acids or esters.

- Certain organoboron compounds have found special significance in organic synthesis, particularly in terms of their utility in **Suzuki-Miyaura cross-coupling**:

  - 9-BBN borane
  - pinacol boronic ester (RBpin)
  - catechol boronic ester (RBcat)
  - MIDA boronate
  - organotrifluoroborate (RBF₃K)
  - a 'protecting group' for boronic acids

[Suzuki-Miyaura reaction]

\[ R-[B] + \text{Ar-}R' \xrightarrow{\text{Pd catalyst, base}} \text{Ar-R} \]
**Hydroboration:** The addition of boron hydrides to alkenes and alkynes

- A very important reaction, and one of the main ways for introducing boron into organic molecules.
- Involves the **concerted** addition of a B–H bond across an alkene (or alkyne):

  ![diagram of hydroboration reaction]

  2 B–H bonds still available

- Boron adds to the less-substituted end of the alkene - this is a combination of both electronic (major) and steric (minor) effects.
- The addition is **syn-stereospecific** – boron and hydrogen add to the same face of the double bond:

  ![diagram of stereospecificity]

- The hydroboration of 1-methylcyclohexene illustrates both of these features:
Borane itself can hydroborate up to 3 times. In many cases this multiple hydroboration is a disadvantage. Alternative hydroboration reagents are available which can react only once or twice.

These reagents are themselves made by the hydroboration of alkenes (can you work out which ones?):

- **thexyl borane (ThexBH for short)**
  2 B–H bonds available

- **9-borabicyclo-[3.3.1]-nonane (9-BBN for short)**
  1 B–H bond available

Bulky substituents on the borane enhance the regioselectivity of hydroboration:

Hydroboration is not restricted to alkenes – **alkynes** also undergo syn-additions:
Nucleophilic Borylation (*not examinable*)

- A modern development in the synthesis of alkylboron reagents has been to use diboron (B–B) reagents as formally nucleophilic sources of boryl groups.

- These reactions typically require transition metal catalysts and proceed via nucleophilic metal boryl intermediates. A wide variety of organic electrophiles can be used, including alkyl and aryl halides. The example below illustrates a conjugate addition reaction of nucleophilic boron to a Michael acceptor, catalysed by a copper(I) complex in the presence of NaO-t-Bu:

\[
\begin{align*}
\text{L}_n\text{CuCl (cat.), NaO-t-Bu} & \rightarrow \text{MeMeMeMeMeMeMeMe} \\
\text{L}_n\text{Cu-Bpin} & \rightarrow \text{MeMeMeMeMeMeMeMe} \\
\text{\(\alpha\)-bond metathesis} & \rightarrow \text{MeMeMeMeMeMeMeMe}
\end{align*}
\]

- Very recently, Varinder Aggarwal at Bristol has devised a way to convert (abundant) alkyl carboxylic acids into alkyl boronic esters, using visible light as a source of energy:

\[
\begin{align*}
\text{BocN} \text{OH} & \rightarrow \text{BocNMeMeMeMeMeMeMeMe} \\
\text{BocNMeMeMeMeMeMeMeMe} & \rightarrow \text{MeMeMeMeMeMeMeMe} \\
\text{(blue LED light)} & \rightarrow \text{91% yield}
\end{align*}
\]

*single electron reduction leads to fragmentation, with loss of CO\(_2\), to an alkyl radical (R-)*
C–H Borylation (not examinable)

One of the most significant recent breakthroughs in organic synthesis is the meta-selective C–H borylation of aromatic C–H bonds.

This iridium-catalysed reaction is based on steric effects and is most selective for 1,3-disubstituted benzenes:

The C–B bond introduced can then be used in cross-coupling or converted into a wide variety of heteroatom-based functions:

Strategically, this borylation-functionalisation approach can allow access to substitution patterns which are impossible using classical electrophilic aromatic substitution (S_EAr) chemistry:
Protonolysis of Organoboranes \([C-B \rightarrow C-H]\)

- Performed by heating with excess carboxylic acid (e.g. AcOH). Water, mineral acids (e.g. HCl) and alkali (NaOH) are all ineffective.
- Proceeds with **retention of configuration** on the organic group (R).
- Occasionally used in synthesis to effect net alkene hydrogenations, especially in the presence of sensitive functionality that would not survive Pd-catalysed hydrogenation (e.g. azides).

\[
\text{AcOH, heat} \quad \begin{array}{c}
\text{H-O-} \\
\text{Me} \\
\text{B} \\
\text{R} \\
\text{R} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{H-O-} \\
\text{Me} \\
\text{B} \\
\text{R} \\
\text{R} \\
\end{array}
\text{R-H + R', B-OAc}
\]

**Retention at R group**

Example

\[\text{D}_{\text{Bu}} \quad \text{D}_{\text{Ph}} \quad 1. \text{BH}_3\text{-THF} \quad 2. \text{AcOH, } \Delta \quad \text{H-H} \]

Halogenolysis of Organoboranes \([C-B \rightarrow C-Hal]\)

- Halogens \(\text{Br}_2\) and \(\text{I}_2\) are unreactive to neutral \(\text{R}_3\text{B}\), but reaction occurs readily in the presence of \(\text{NaOMe}\).
- For alkyl boranes, reaction proceeds with **inversion of configuration** on the organic group (R). [Note that for vinyl boranes, the stereochemical course depends upon the halogen used - see advanced texts, if interested].
- Combined with hydroboration, this is a useful way of effecting the **anti-Markovnikov** hydrohalogenation of alkenes.

\[
\text{NaOMe, I}_2 \quad \begin{array}{c}
\text{R} \\
\text{B} \\
\text{R} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{I} \\
\text{R} \\
\text{B} \\
\text{R} \\
\end{array}
\text{R-I + R', B-OMe}
\]

**Inversion at R group**

Example

\[\text{Me} \quad \text{Me} \quad \text{NaOMe, I}_2 \quad \text{Me} \quad \text{Me} \quad 97-98\% \text{ inversion} \]

\(\text{Br}_2\) gives \(3 \times \text{R-Br}\) (i.e. higher yield) but often lower levels of stereoinversion
For halogenolysis of alkenylboranes, the situation is more complicated – the stereochemical course depends on the halogen.

Alkenyl boronic acids are normally used to avoid competing migrations of $B-C_{\text{alkyl}}$ bonds in the halonium ion intermediates.

With iodine ($I_2$) and NaOH, the reactions proceed with retention to give (E)-alkenyl iodides:

With bromine ($Br_2$), initial reaction with the dihalogen leads to a 1,2-dibromide, then subsequent addition of NaOMe leads to an antiperiplanar elimination to give (Z)-alkenyl bromides. Thus, we get overall inversion:

*For iodine ($I_2$), addition to C=C bonds to give 1,2-diiodides is thermodynamically unfavourable, so this process only works with $Br_2$. 
**Oxidation of Organoboranes [C–B → C–O]**

- Performed using aqueous alkaline peroxide [or occasionally peracids, RCO₃H, or sodium perborate, NaBO₃].
- Proceeds with *retention of configuration* on the organic group (R).

![Reaction Scheme](reaction_scheme.jpg)

- The hydroboration-oxidation sequence provides for a net *anti-Markovnikov alkene hydration*.
- For alkynes, the product of this sequence is an enol, which immediately tautomerises to a *ketone* (or aldehyde for terminal alkynes).

```
1. BH₃·THF
2. NaOH, H₂O₂
```

- The oxidation of arylboron compounds allows for a convenient synthesis of *phenols*, with the C–B bond being readily installed by lithiation and trapping with a trialkylborate, B(OR)₃:

```
1. LDA, –78 °C
2. B(OMe)₃
```

```
65% over 3 steps
```

![Phenol Synthesis](phenol_synthesis.jpg)

![Retention at R group](retention_r_group.jpg)
**Amination of Organoboranes [C–B → C–NH₂]**

- For trialkylboranes, amination has classically been performed using chloramine (NH₂–Cl) under alkaline conditions or hydroxylamine-O-sulfonic acid (NH₂–OSO₃H). The latter reagent has the benefit of being commercially-available.
- Proceeds with retention of configuration on the organic group (R).
- Unfortunately the yields are fairly moderate (<66%), as only two of the three R groups on R₃B are able to react.

![Reagents and Reaction Scheme](image)

- James Morken at Boston has recently developed a superior procedure which can be used with (less reactive) alkyl boronic esters, greatly enhancing the synthetic utility of this process.
- His method relies on the use of methoxyamine (MeONH₂), which is first deprotonated with butyllithium (BuLi). The primary amines are typically protected in situ with Boc (tert-butyloxycarbonyl) protecting groups for ease of purification:

![Morken's Reaction Scheme](image)
C–C Bond Formation from Organoboranes

Both the oxidation and amination chemistry we have just seen is representative of a more general family of transformations involving the **insertion** of nucleophilic groups into C–B bonds. A necessary requirement is that the nucleophile (\( \text{Nu} \)) bears a leaving group (\( \text{X} \)):

\[
\begin{array}{c}
\text{B–R} \xrightarrow{\text{\text{Nu}} - \text{X}} \text{B–Nu} - \text{X} \\
\text{the nucleophilic group has formally inserted into the C–B bond}
\end{array}
\]

This concept can be extended to C–C bond formation by using **carbene equivalents** as nucleophiles:

**Darzens homologation with \( \alpha \)-halo esters**

**Carbonylation with carbon monoxide**

The **carbonylation** chemistry is actually more extensive than indicated here (see a textbook if interested).
Aggarwal Homologation of Organoboranes

- Varinder Aggarwal at Bristol has developed a huge amount of chemistry for the **stereospecific homologation of alkyl boronic esters**.
- The general concept is shown below, and it requires an enantiopure, configurationally-stable carbanion bearing an α-nucleofuge:

  ![Diagram of Aggarwal Homologation](image)

  - A **1,2-migration** of the purple carbon from boron to the green carbon
  - **Inversion** at green carbon
  - **Retention** at purple carbon

- The enantiopure carbanions used in this chemistry can be made by **enantioselective deprotonation** of carbamates. The chiral ligand **(--)-sparteine** is used with sec-BuLi (a very strong base) to selectively deprotonate the pro-S hydrogen:

  ![Diagram of Enantioselective Deprotonation](image)

  - **(--)-sparteine**
  - **Configurationally-stable** at low T

*It's enantiomer, (++)-sparteine is also available*
By telescoping a series of enantiopure (or achiral) carbanion additions to the boronic ester (the "growth phase"), followed by a final C–B bond functionalisation (the "termination step"), stereochemically-complex carbon chains can be built up in a one-pot process.

Aggarwal has termed this new concept "assembly line synthesis" (see *Nature* 2014, 513, 183):

Aggarwal has developed many other stereospecific C–B functionalisations that further increase the power of his homologation concept, including olefinations and arylations (see *Chem. Commun.* 2017, 53, 5481 for a recent review).
Allyl Boranes: Allyl anion equivalents that react cleanly with allylic rearrangement

- **Allyl boranes** react with carbonyl compounds via initial coordination of the carbonyl oxygen to the Lewis acidic boron atom, followed by attack via a 6-membered transition state:

  \[
  \text{RCHO} + \text{L}_2\text{B} = \text{OH} \xrightarrow{\text{initial coordination}} \left[ \begin{array}{c} \text{L} \text{L} \\ \text{B} \text{O} \end{array} \right] \xrightarrow{\text{attack}} \left[ \begin{array}{c} \text{O} \\ \text{B} \text{L}_2 \end{array} \right] \xrightarrow{\text{NaOH}} \text{R} \text{OH}
  \]

  \( \text{cyclic ("closed") TS} \)

- Using a chiral, enantiopure allyl borane reagent, it is also possible to render this process enantioselective. In the so-called Brown allylation, an allyl diisopinocampheylborane is freshly prepared from commercially available \( \alpha \)-pinene, which can be obtained in either enantiomeric form. Reaction with an aldehyde leads to enantioenriched homoallylic alcohols:

  - (+)-\( \alpha \)-pinene
  - (\(-\)Ipc)\(_2\)BOMe
  - (\(-\)Ipc)\(_2\)BAlyl

- It is also possible to transfer 'prenyl' groups in this type of process (a 'prenylation' reaction). Note that the mechanistic requirement for allylic inversion means that nucleophilic attack occurs from the more-substituted end of the reagent, giving an all-carbon quaternary centre:
Reactions with crotyl borane reagents are stereospecific, and the diastereoselectivity is highly predictable due to the chair-like nature of the transition states. The aldehyde R group displays a strong preference to sit in the pseudoequatorial position:

- (E)-crotyl borane reacts with aldehydes to give anti-homoallylic alcohols

- (Z)-crotyl borane reacts with aldehydes to give syn-homoallylic alcohols

This chemistry has been used extensively in natural products synthesis, and particularly for polyketides.
**Enol Boranes (Boron Enolates):** Enolate equivalents that react with high diastereoselectivity

- **Enol boranes** (AKA boron enolates) are analogous to allyl borane reagents in their reactivity with aldehydes, in that initial coordination of the carbonyl oxygen to the Lewis acidic boron atom is followed by attack via a 6-membered transition state.

- This is referred to as a **boron aldol reaction** and delivers β-hydroxy carbonyl compounds:

\[
\begin{align*}
\text{aldol addition product} & \quad \text{NaOH} \quad \text{H}_2\text{O}_2
\end{align*}
\]

As for crotylations (see previous slide), boron aldol reactions with substituted boron enolates are **stereospecific**, and the diastereoselectivity is predictable based on the **chair-like** nature of the transition states. Again, the aldehyde R group prefers to sit in the pseudoequatorial position:

- **(E)-boron enolates** react with aldehydes to give **anti-aldol products**

\[
\begin{align*}
\text{anti} & \quad \text{NaOH} \quad \text{H}_2\text{O}_2
\end{align*}
\]

- **(Z)-boron enolates** react with aldehydes to give **syn-aldol products**

\[
\begin{align*}
\text{syn} & \quad \text{NaOH} \quad \text{H}_2\text{O}_2
\end{align*}
\]
The advantage of boron enolates over lithium enolates other than the milder (neutral) reaction conditions is that the aldol reactions tend to exhibit much higher levels of diastereoselectivity. This is attributed to the fact that B–O bonds (1.36-1.47 Å) are significantly shorter than Li–O bonds (1.92-1.00 Å), and so the corresponding TSs are ‘tighter’. Also, the size of the groups on boron can be increased to enhance stereoselectivity:

For these reasons, it is important to have methods available to control the geometry of boron enolates.

Boron enolates are usually formed from a dialkylboron halide (or triflate), R₂B–X, and a tertiary amine base, R₃N. The stereoselectivity of enolisation is highly sensitive to the alkyl groups on boron, the leaving group on boron, and the identity of the base:

Don't worry about trying to make sense of these conditions, or committing them to memory. You just need to appreciate that recipes are available to control boron enolate geometry.
Radical Chemistry of Organoboranes

- Organoboron compounds have also found utility as precursors to **carbon-centred radicals**.
- The reaction of neutral, tricoordinate organoboron compounds with **heteroatom-centred radicals** (e.g. RO•, RO2S•) is uniquely effective in this regard, as the heteroatom lone pair can pre-coordinate to the empty B p-orbital:

\[
\begin{align*}
R'B-X &\rightarrow \Theta X\cdot \Theta B\cdot\Theta R' \quad (\beta \text{-scission}) \\
&\rightarrow X-BR_2 \\
&\rightarrow R^* \\
\end{align*}
\]

- This radical generation method has been used to effect a number of C–C bond-forming processes, including a 3-component **carboazidation** of simple alkenes:

- An alternative strategy for carbon radical generation from C–B bonds is to effect **single electron oxidation** of electron-rich, anionic borate species, such as **organotrifluoroborates**: