C–H Halogenations: A Brief Recap...

- You have already met the **radical chain halogenation** of C–H bonds with dihalogens, $X_2$ (Br$_2$ or Cl$_2$). This process is only useful for substrates lacking alkene functionality, because C=C bonds undergo rapid addition of $X_2$ by either a radical or an ionic mechanism.

  ![Radical Chain Halogenation](image)

- You have also met another radical chain process for C–H halogenation based upon *in situ* generation of Br$_2$ in low concentrations (from NBS). This is suitable for use with alkene-containing substrates, and is selective for the (weak) allylic C–H bond (**allylic bromination**).

  ![Allylic Bromination](image)

- The latter method can also be used for **benzylic** C–H bromination, if desired (as an alternative to handling dibromine, Br$_2$).
In general, there are two mechanistic processes by which alkyl radicals can be generated from C(sp$^3$)–H bonds: (1) hydrogen atom transfer (HAT) and (2) SET oxidation-deprotonation (typically encountered for amines in the presence of an SET oxidant).

Be careful to use the correct terminology when referring to hydrogen atom transfers - these are not deprotonations...

...and neither are they hydride transfers!

The subsequent examples in this lecture will all involve HAT processes, but you will see some examples of SET oxidation-deprotonation later in the course.

For many HAT C–H functionalisations, a chain reaction is operative (think back to halogenations) and this is shown on the left in a generalised form.

However, as we shall soon see, not all radical reactions proceed via a chain mechanism, and we will also meet examples of non-chain processes.
Factors Affecting Selectivity in HAT Reactions

- Almost all organic molecules have multiple C–H bonds in different chemical environments, so which are most active towards HAT?
- One important factor is **C–H bond strength**, as weaker C–H bonds (i.e., those that give the most stable C-based radicals) are easier to break.

\[
\begin{array}{cccc}
\text{t-BuO} & H - R & k_{rel} & 1 \\
\text{t-BuO} & H & 2,700 \\
\text{t-BuO} & H & 0 & 3,000 \\
\text{Bu}_3\text{Sn} - H & 700,000 \\
\end{array}
\]

- For very bulky radical abstractors, **steric effects** can also play a role, such that the most sterically-accessible C–H bonds are attacked.

"Reagent-dictated site selectivity in intermolecular aliphatic C–H functionalizations using nitrogen-centered radicals"

*Chem. Sci.* **2018**, *9*, 5360
Polarity effects (i.e., radical philicity) also play a major role in governing the rate (and thus selectivity) of HAT steps.

Whilst this can be rationalised by considering interaction of the SOMO of a radical A• with the HOMO and LUMO of an B–H bond (see handout 2), it is easier to explain here using the concept of resonance.

The transition state (TS) for the HAT can be considered to have contributions from four different resonance canonicals, two of which are neutral and two of which are ionic (i.e., have separated charges).

\[
\begin{align*}
A \overset{\cdots}{H} \overset{\cdots}{\rightarrow} A &= A^+ \overset{\cdots}{H} \overset{\cdots}{B} \\
\text{neutral contributions} &\quad \text{ionic contributions}
\end{align*}
\]

If one of the ionic canonicals can be considered to be a major contributor (i.e., both of the charges are well stabilised on the respective atoms, A and B) then the overall activation energy will be lower.

Looking at it another way, a HAT reaction is fastest when the starting and product radical possess an opposite sense of philicity (i.e., one is nucleophilic and the other is electrophilic). This is called polarity-matching.

Thus, because simple alkyl radicals are nucleophilic, the most effective hydrogen atom abstractors from most C–H bonds are electrophilic radicals such as RO•, R₂N•, F•, Cl•, or Br•.

The selectivity for more nucleophilic (higher HOMO) C–H bonds becomes more pronounced as the electrophilicity of the abstracting radical increases, and this can even override bond strength preferences.

For the example drawn in the scheme; see: Nature 2017, 547, 79
A number of different HAT C–H functionalisations have been developed with a range of stoichiometric oxidants.

You probably haven't seen any of these oxidants before, but can you figure out how each of these reactions work?
Draw a full mechanism for the following reaction, taken from the previous slide.
Draw a full mechanism for the following reaction, taken from the previous slide.

**Initiation:**

**Propagation:**
Radicals generated from C–H bonds by HAT can also be added across alkenes to form new C–C bonds (compare this to the Giese reaction from handout 2).

For nucleophilic radicals, additions are most efficient to **electrophilic alkenes** (**Michael acceptors**).

A classic example is the addition of (nucleophilic) **acyl radicals**, derived by HAT from aldehydes, across \( \alpha,\beta \)-unsaturated esters.

Again, this is a **chain process**, whereby the electrophilic radical formed upon addition to the Michael acceptor serves to abstract a H atom from the aldehyde.

With respect to the alkene, this process can be formulated as yet another example of an ATRA (**Kharasch-type**) reaction (see handout 2).

Draw a full mechanism for the following reaction. Why do you think such a large excess of alcohol and a high loading of initiator are needed here? Why is telomerisation (formation of short polymers) such a problem?

\[
\text{Me}_3\text{C}H\quad +\quad \text{C}_6\text{H}_{13}\text{C}H_2\quad \xrightarrow{125\ ^\circ\text{C}}\quad \text{Me}_3\text{CC}_6\text{H}_{13}\quad +\quad \text{telomers}\quad (44\%)\quad +\quad \text{Me}_3\text{C}H\quad (38\%)\quad +\quad \text{Me}_3\text{C}H\quad (38\%)\quad +\quad \text{Me}_3\text{C}H\quad (38\%)
\]
Draw a full mechanism for the following reaction. Why do you think such a large excess of alcohol and a high loading of initiator are needed here? Why is telomerisation (formation of short polymers) such a problem?

One of the propagation steps is a HAT that is polarity-mismatched, because both the starting and product radicals are nucleophilic. In other words, there is not a good ionic contribution to the TS that we can draw.

Because the HAT is relatively slow, further radical additions to alkene molecules can compete, leading to telomers.

Because one of the propagation steps is slow and inefficient, chain lengths are short (i.e., radicals can accumulate and terminate). Thus, a higher concentration of initiator is required to maintain an acceptable reaction rate [because reaction rate = chain length \times initiation rate].

It is possible to speed up slow, polarity-mismatched HAT steps in a chain reaction by adding a HAT catalyst, such as a thiol. Now there are two HAT propagation steps involved, but both are polarity-matched and fast, and so the chain is much more efficient.

This strategy even allows for the efficient addition of nucleophilic radicals to electron-rich alkenes; in fact, it works best in these cases!

Photoinduced HAT Catalysis: Ketones as More Widely-Applicable HAT Catalysts

- Thiols are not the most widely-applicable HAT catalysts, as thyl radicals (RS•) can only abstract H from relatively weak C–H bonds.
- Highly reactive alkoxyl radicals (RO•) would be more powerful H-abstractors, but they are hard to generate from strong O–H bonds, so simple alcohols are not viable HAT catalysts.
- However, some ketones, such as benzophenone, can be photoexcited to give biradicals that have alkoxyl radical character, and these can abstract H atoms from a wide range of C(sp³)–H bonds.

Because the resultant HO(Ph)₂C• radical is persistent, it has a reasonably long lifetime, and it can serve as an effective H• donor to other radicals (in a disproportionation-type process).

This H• transfer is fastest to electrophilic radicals, because the HOMO of the weakened O–H σ-bond is lower than normal, due to conjugation with the radical (try drawing an MO scheme for yourself).

Thus, it is possible to carry out HAT catalysis with ketones, provided that the reaction mixture is continuously irradiated with UV light.

Radical acceptors that produce electrophilic radicals are required for catalytic turnover, and this could involve addition of R• to a Michael acceptor or reaction of R• with a reagent X–Y to produce an electrophilic radical X•.

This ketone-catalysed C–H functionalisation is sometimes referred to as the Yang reaction.

The following reaction is a good example of photoinduced HAT catalysis using benzophenone, in which a fairly strong (2\(^{-}\)) C–H bond is functionalised by introducing a cyano group. Can you draw a mechanism?

\[
\text{Ph}_2\text{C}=\text{O} (100 \text{ mol\%}) \quad \text{h}_\nu \quad \text{(Hg lamp)} \quad \text{MeCN, rt, 10 h} \quad \text{Ts–CN} \quad \rightarrow \quad \text{Ph}_2\text{C}=\text{C}(-\text{CN}) \quad 87\%
\]

4-toluene-sulfonyl

Acetonitrile (MeCN) is a popular solvent in organic synthesis, and especially in radical chemistry because it is pretty unreactive to alkyl radicals.
The following reaction is a good example of photoinduced HAT catalysis using benzophenone, in which a fairly strong (2°) C–H bond is functionalised by introducing a cyano group. Can you draw a mechanism?

\[
\text{Ph}_2\text{C}=\text{O} \quad (100 \text{ mol\%}) \\
\text{h} \quad (\text{Hg lamp}) \\
\text{MeCN, rt, 10 h} \\
\rightarrow \quad \text{Ts–CN} \\
\rightarrow \quad \text{Ts} = \text{SO}_2\text{Ph} \\
\rightarrow \quad \text{87\%} \\
\]

Sulfonyl radicals can be drawn in two different resonance forms. The one on the left is more stable, but the right-hand one explains why the O atom can abstract hydrogen atoms (O–H very strong).

"Photoinduced Cyanation of C(sp^3)–H Bonds" *Synlett* 2013, 45, 874
Photoinduced HAT catalysis with benzophenone has been applied in a wide variety of C(sp³)–H functionalisations, including C–C and C–X bond formations. [Can you write mechanisms for both of the below transformations?]

Very recently, it has been merged with transition metal catalysis to effect C–H arylations (and even alkylations).

**HAT Catalysis: Other Catalysts for the Functionalisation of Strong C(sp^3)–H Bonds**

- The **decatungstate anion** has also proven popular in organic synthesis as a photoinduced HAT catalyst, behaving in a similar way to benzophenone.

\[
\begin{align*}
\text{hv} & \quad (\lambda = 365 \text{ nm}) \\
[W_{10}O_{32}]^{4-} & \quad \text{HAT catalysis} \\
\text{re-oxidation} & \quad \text{H}^+ [W_{10}O_{32}]^{5-}
\end{align*}
\]

- There is also a large amount of literature on the **aerobic C–H oxidation** of organic compounds (to give alcohols or ketones) catalysed by **N-hydroxyphthalimide (NHPI)**. The phthalimide N-oxyl (PINO) radical is the active hydrogen atom abstracting species, and a metal catalyst (e.g., Co^{II}) is also involved.* [Don't worry about the mechanism - it is rather complex...]

\[
\text{MeMe} \quad \text{NHPI (10 mol%)} \quad \text{Co(OAc)}_2 \quad (0.25 \text{ mol%}) \quad \text{air (O}_2) \quad \text{PhCN, 100 °C} \quad \text{MeMe} \quad \text{MeOH} \quad + \quad \text{MeCO} \quad 81\% \quad 14\%
\]

Intramolecular HAT Reactions: Radical Translocation for Remote C–H Functionalisation

- If the abstracting radical is part of the substrate itself, an intramolecular HAT reaction can occur.
- The advantage of this approach is that C–H selectivity is now restricted by proximity factors. When all else is equal, 1,5-HAT is the most kinetically facile process, as it allows for an almost ideal 180° X···H···C alignment in the TS, whilst minimising entropic cost.

\[
\begin{align*}
\text{1,5-HAT} & \quad \text{(X = O, N, S, C)} \\
\end{align*}
\]

- Other factors, such as C–H bond strength or polarity factors, also influence selectivity, and can sometimes favour 1,n-HAT reactions with n > 5.*

- This strategy is useful in organic synthesis for the 'directed' functionalisation of remote C–H bonds.** The following example illustrates an alkoxyl radical-mediated remote desaturation reaction (using Fe^{II} as an SET reductant and Cu^{II} as an oxidant).

**For a review, see: "Remote C–H Functionalization via Selective Hydrogen Atom Transfer" Synthesis 2018, 50, 1569

Remote C–H Functionalisation: The Hofmann-Löffler-Freytag Reaction for Azacycle Synthesis (1883)

- A classic example of a remote C–H functionalisation by 1,5-HAT is the Hofmann-Löffler-Freytag reaction, in which a nitrogen-centred radical (derived from an \(N\)-haloamine) serves as the hydrogen atom abstractor.
- This is chain reaction that leads to remote C–H halogenation. A basic work-up then causes cyclisation (\(S_N2\)) to a cyclic amine product.

\[
\begin{array}{c}
R \stackrel{\text{H}^+}{\longrightarrow} \text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{H} \text{H}
\end{array}
\]

initiation

\[
\begin{array}{c}
\text{H}
\end{array}
\]

propagation

\[
\begin{array}{c}
\text{H}
\end{array}
\]

Note that aminium radicals are more electrophilic and more reactive than neutral aminyl radicals, which is why the acid is needed.

The conditions employed in the classical HLF reaction are not always high-yielding, but the reaction has been used to prepare quite a diverse array of azacyclic compounds.

For a recent development, see: "An Iodine-Catalyzed Hofmann-Löffler Reaction" Angew. Chem. Int. Ed. 2015, 54, 8287
A modification of the HLF reaction has been applied by Baran et al. to the synthesis of 1,3-diols by C–H functionalisation. Can you draw a mechanism for the second step?
A modification of the HLF reaction has been applied by Baran et al. to the synthesis of 1,3-diols by C–H functionalisation. Can you draw a mechanism for the second step?

Note that an amidyl radical (i.e., bearing a carbonyl group on N) is reactive enough to perform C–H abstraction; there is no need for any strong Brønsted acid in this case.

"1,3-Diol Synthesis via Controlled, Radical-Mediated C–H Functionalization"

*J. Am. Chem. Soc.* **2008**, *130*, 7247

"Total synthesis of eudesmane terpenes by site-selective C–H oxidations"

Remote C–H Functionalisation: The Barton Nitrite Ester Reaction (1960)

Another classic example of a remote C–H functionalisation featuring 1,5-HAT is the **Barton nitrite ester reaction**, which involves photolytic homolysis of alcohol-derived nitrite esters to give oximes as products.

Unlike the HLF, this is a non-chain process that involves a radical-radical cross-coupling as the key step (more on this soon...).

![Diagram of the Barton Nitrite Ester Reaction](image)


Barton invented this reaction to solve a very specific problem: the synthesis of the steroid hormone **aldosterone**. At the time, there was a great deal of interest in the biological role of this steroid in mammals, but it was in extremely scarce supply.

![Diagram of steroid synthesis](image)


But why does this reaction work so well? Why is the radical-radical coupling selective? Why don't we get a statistical mixture of products?
The Persistent Radical Effect: Cross-Selective Radical-Radical Couplings

- The persistent radical effect (PRE) is a principle that explains the highly selective cross-coupling between a persistent (long-lived) radical and a transient radical, when both species are generated at equal rates.

- When radical-radical coupling reactions are responsible for product formation, it is usually because of the PRE.

- Because persistent radicals are slow to dimerise (due to kinetic stability), even a rudimentary statistical analysis shows that one would expect a reaction between a persistent and a transient radical to be cross-selective (if all coupling rates are identical).

<table>
<thead>
<tr>
<th>Dimerisation Reactions for Transient Radicals (T•)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_1^* + T_1^* \rightarrow T_1-T_1 ) 25%</td>
</tr>
<tr>
<td>( T_2^* + T_2^* \rightarrow T_2-T_2 ) 25%</td>
</tr>
<tr>
<td>( T_1^* + T_2^* \rightarrow T_1-T_2 ) 50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dimerisation Reactions Between a Transient Radical (T•) and a Persistent Radical (P•)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T^* + T^* \rightarrow T-T ) 33%</td>
</tr>
<tr>
<td>( P^* + P^* \rightarrow P-P )</td>
</tr>
<tr>
<td>( T^* + P^* \rightarrow T-P ) 66%</td>
</tr>
</tbody>
</table>

**Stability** (a thermodynamic effect) is not the same as **persistence** (a kinetic effect), and most stable radicals are not persistent. Most radical–radical reactions are so exothermic that it makes no difference to the rate whether the radicals involved are a little more or a little less stable.

- In practice, the selectivity is almost total, because the coupling rates are actually not identical.

- Initial fast homocoupling of \( T^* \) radicals creates a **concentration imbalance**, such that \([P^*]\) quickly becomes much higher than \([T^*]\).

- In this scenario, most subsequent radical-radical collisions involve either two persistent radicals (\( P^* + P^* \)), which forms no product, or the heterocoupling process (\( T^* + P^* \)).


The persistent radical effect (PRE) appears in many different guises, and below are a selection of radical-radical interactions that we have seen throughout this course. All of these are governed by the PRE.

- **transient radical**
  - ![Diagram](image1.png)
  - ![Diagram](image2.png)
  - ![Diagram](image3.png)
  - ![Diagram](image4.png)

- **persistent radical**
  - ![Diagram](image5.png)

- Trapping of transient radicals with TEMPO (often used as a mechanistic probe for radical intermediacy).
- The second HAT step in the Yang reaction (and same with decatungstate catalysis).
- The Barton nitrite ester reaction.
- Reactions of radicals with paramagnetic transition metal complexes [e.g., d⁵ Ru(III) in ATRA reactions]*.

*For another example, see: "Anodically Coupled Electrolysis for the Heterodifunctionalization of Alkenes" J. Am. Chem. Soc. 2018, 140, 2438
The photochemical nitrosation of cyclohexane forms part of the industrial process for the production of caprolactam, which is made on about 5 million tonnes a year as the precursor to Nylon-6. Can you draw mechanisms to explain how the synthesis of caprolactam works?

\[
\text{cyclohexane} \xrightarrow{\text{NOCl, } h_v} \xrightarrow{\text{conc. } \text{H}_2\text{SO}_4} \xrightarrow{260 \degree C} \text{caprolactam} \xrightarrow{} \text{Nylon-6}
\]
The photochemical nitrosation of cyclohexane forms part of the industrial process for the production of caprolactam, which is made on about 5 million tonnes a year as the precursor to Nylon-6. Can you draw mechanisms to explain how the synthesis of caprolactam works?
Revision Checklist

Revised?

- Generation of alkyl radicals from C–H bonds by: (1) hydrogen atom transfer (HAT) or (2) SET oxidation-deprotonation
- Factoring affecting selectivity in HAT reactions, including: (1) C–H bond strength, (2) steric effects, and (3) polarity effects
- Radical chain C–H functionalisations via HAT (e.g., halogenation, azidation, alkynylation) [no need to memorise new reagents]
- Radical chain addition of C–H bonds across alkenes via HAT (another Kharasch-type process); use of aldehydes in hydroacylation
- Polarity-matching issue in adding nucleophilic radicals to unactivated (or nucleophilic) alkenes, and telomerisation problems
- Use of HAT catalysts (e.g., thiols) for catalysing polarity-mismatched HAT processes (exemplified for hydroacylation)
- Photoinduced HAT catalysis with ketones for the functionalisation of C–H bonds (e.g., cyanation, alkylation, fluorination)
- Intramolecular HAT reactions as a strategy for radical translocation or remote C–H functionalisation; kinetic preference for 1,5-HAT
- The Hofmann-Löffler-Freytag (HLF) reaction, and the importance of Brønsted acid to generate a reactive aminium radical cation
- The Barton nitrite ester reaction
- The persistent radical effect (PRE) and its importance in controlling cross-selective radical-radical couplings