Lecture three

C–X disconnections get more complex

Fenfluramine
neuroactive drug
N-unsubstituted imines are notoriously unstable.

Amide formation followed by reduction

**synthesis**

Amide formation followed by reduction
tryptophan ester

\[
\begin{align*}
\text{tryptophan ester} & \quad \xrightarrow{\text{amine formation}} \quad \text{amide formation} \\
\text{70\% three steps} & \quad J. Am. Chem. Soc. 2003, 125, 5628
\end{align*}
\]
Azides have a nasty habit of suddenly reverting to nitrogen gas when heated or, with the smaller examples, tapped with a metal spatula. In English, this means they can explode.

Tetrahedron 1987, 43, 3083

Tf = triflate = trifluoromethanesulfonate or F3CSO2−
two-group C–X disconnections

one-group disconnection

\[
\begin{align*}
R^1_1X_2R^2 & \quad \Rightarrow \quad R^1_1X_2^+R^2_2 \\
\end{align*}
\]

two-group disconnection

\[
\begin{align*}
R^1_1X_2R^2 & \quad \Rightarrow \quad R^1_1X_2^+R^2_2 \\
\end{align*}
\]
retrosynthesis

route A

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH} & \quad \text{Me} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH}
\end{align*}
\]
chemoselectivity

route B
route B: synthesis

Sn2 reaction of epoxides favours attack at the least hindered end.

One functional group gives two functional groups.
Retrosynthesis
Why do we get mono-alkylation of the amine? Its because of the electron withdrawing effect of the hydroxyl formed from opening the epoxide...

**Did you know?**

Cl is more electrophilic than chloride.
did you know?

OClNuc123Cl123NucO123NucO
does this make a difference?

does this make a difference?
yes!
1,3-diX

Ns = 2-nitrobenzenesulfonyl, a good nitrogen protecting group
retrosynthesis

\[
\text{Ph-S-S-Ph} \quad \text{C-X} \quad \text{Ph-S-S-Ph} \quad + \quad \text{Ph-S-S-Ph}
\]

\[
\text{Ph-SH} \quad \text{Br-CH-CH-OMe} \quad \text{?}
\]

retrosynthesis

\[
\text{Ph-S-S-Ph} \quad 1,3\text{-di-X} \quad \text{Ph-S-S-Ph} \quad + \quad \text{Ph-S-S-Ph}
\]

\[
\text{Ph-SH} \quad \text{=CH-CH-OMe} \quad \text{?}
\]
Proton can be replaced by other electrophiles to allow more complex molecules to be prepared.

1,3-diXRO RO123!
retrosynthesis

\[
\text{O} \quad \text{N} \quad \text{H}_2 \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{F} \quad \text{G} \quad \text{I} \quad \text{reduction} \quad \text{1,3-diX} \\
\text{O} \quad \text{N} \quad \text{H} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad 1,3\text{-diX} \quad \text{N} \quad \text{Ph} \quad \text{O} \\
\text{not just carbonyl groups}
\]

retrosynthesis

\[
\text{Ph} \quad \text{N} \quad \text{O} \quad \text{1,3-diX} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad \text{1,3-diX} \\
\text{not just carbonyl groups}
\]