Conjugate (1,4-) addition

- Nucleophilic attack on C=C bond normally requires electron deficient alkene
- Know as 1,4-addition or conjugate addition
- As enolate formed during reaction - possibility of forming two stereogenic centres
- **Substrate control** - initial addition to the least hindered face of enone
- Second addition normally occurs from opposite face
Substrate control in total synthesis

- Prostaglandins are technically hormones with very strong physiological effects.
- Prostaglandins have been utilised to prevent and treat peptic ulcers, as a vasodilator, to treat pulmonary hypertension and induce childbirth / abortion.
Diastereoselective conjugate additions

- Possible to use chiral auxiliary to control 1,4-nucleophilic addition
- Chelation of amide and sultam oxygens to Mg restricts rotation and favours cis conformation
- Addition occurs from most sterically accessible side
- Chiral auxiliary readily cleaved (& reused) to give enantiomerically pure compound via diastereoselective reaction
Chiral auxiliary to control two stereocentres

- It possible to utilise 1,4-addition to introduce **two** stereogenic centres
- The first addition (**BuMgBr**) occurs as before to generate an **enolate**
- The enolate can then be trapped by an appropriate **electrophile**
- Once again the sultam chiral auxiliary controls the face of addition (of **Me**)

**Scheme:**

1. **BuMgCl**
2. **Mel**

Electrophile approaches from bottom face

95% de
Alternative chiral auxiliaries I

A second chiral auxiliary is the oxazoline (5-membered ring) of Meyers’

It can be prepared from carboxylic acids (normally in 3 steps) or from condensation of the amino alcohol and a nitrile

As can be seen excellent enantiomeric excesses can be achieved via a highly diastereoselective reaction
Chiral auxiliary and radical conjugate addition

Radicals once thought to be too reactive to allow diastereoselective reactions
Clearly not true - oxazolidinone auxiliary
Rare-earth Lewis acids give superior results
Use of Et₃B & O₂ as radical initiator allows the use of low temperatures
Sulfoxide-based chiral auxiliary (& total synthesis)

- **Sulfoxide** is a good chiral auxiliary; not only does it introduce a stereocentre but it activates the alkene by addition of an extra electron-withdrawing group.
- **Sulfoxide** substituent blocks the bottom face & is readily removed.
- Simple substrate control instals aryl group on opposite face to *substituent*.
- (−)-Podorhizon is a member of the anticancer podophyllotoxin family of compounds.
Chiral auxiliaries and total synthesis

- L-CCG-I (L-carboxycyclopropylglycine-I) is a conformationally restrained analogue of L-glutamic acid (there are four possible stereoisomers of L-CCG).
- L-Glutamic acid is the most abundant excitatory neurotransmitter in our bodies; it is thought to be involved in cognitive functions like learning and memory in the brain and possibly with umami, one of the five basic human tastes.
Enantioselective catalytic conjugate addition

- Much effort has been expended trying to develop enantioselective catalysts for conjugate addition.
- Whilst many are very successful for certain substrates, few are capable of acting on a wide range of compounds.
- The system above gives excellent enantioselectivities for cyclohexenone but... no selectivity for cyclopentenone.

\[
\text{Et}_2\text{Zn, Cu(OTf)}_2 (2\%), \text{ lig. (4\%), tol, 3h, } -30^\circ\text{C}
\]
Enantioselective radical conjugate addition

Not unsurprisingly, once **stereoselective** conjugate radical additions with auxiliaries had been developed, the **enantioselective catalytic** variant rapidly followed.

Effectively, this is a **chiral Lewis acid** catalysed reaction.

Most work in this area has been pioneered by Sibi.
Organocatalysis

- New small molecule organic catalysts are now achieving remarkable results
- Enone is activated by formation of the charged iminium species
- The catalyst also blocks one face of the enone allowing selective attack
A range of reactions can be achieved, including enantioselective Friedel-Crafts.

Catalyst ensures that the enone reacts *via* one conformation.

Must use electron rich aromatic substrates.

Steric hindrance results in predominantly one conformation.
Organocatalysts III

- Possible to introduce two stereogenic centres with good diastereoselectivity and enantioselectivity
- An interesting reaction is the **Stetter** reaction - this is the conjugate addition of an **acyl** group onto an activated alkene and proceeds via **Umpolung** chemistry (the reversal of polarity of the carbonyl group)

\[
\text{Me} \quad \text{TMSO} \quad \text{H} \quad \text{Me} \\
\text{R} \quad \text{Me} \quad \text{H} \quad \text{Me} \\
\text{DCM} / \text{H}_2\text{O} \quad \text{cat. (20\%)} \\
-20 \text{ to } -70^\circ\text{C}, 11-30\text{h} \\
77\% \\
syn:anti = 1:31:1 \\
84-99\% \text{ ee}
\]

\[
\text{Me} \quad \text{H} \quad \text{Me} \\
\text{R} \quad \text{Me} \quad \text{H} \quad \text{Me} \\
\text{KHMDS (20\%)} \text{, 25°C, 24h} \\
80\% \\
97\% \text{ ee}
\]
The Stetter reaction is analogous to the activity of thiamine (vitamin B₁) in our bodies and the reaction is thus biomimetic.
Organocatalytic bifunctional catalysis

- The thio(urea) moiety acts as a **Lewis acid** via two hydrogen bonds
- The amine both activates the nucleophile and positions it to allow good selectivity

![Chemical reaction diagram](attachment:image.png)
Organocatalysis and total synthesis

- Beautiful example of enantioselective conjugate addition in total synthesis
- From the synthesis of a marine alkaloid from the Bryozoa, *Flustra foliacea* by Joel F. Austin, Sung-Gon Kim, Christopher J. Sinz, Wen-Jing Xiao, and David W. C. MacMillan, *PNAS* 2004, 101, 5482