Chiral auxiliaries - allows enantioselective synthesis via diastereoselective reaction. Add chiral unit to substrate to control stereoselective reaction. Can act as a built in resolving agent (if reaction not diastereoselective). Problems - need point of attachment, adds additional steps, cleavage conditions must not damage product!
Chiral auxiliary and addition to the carbonyl group

- We have seen many examples of substrate control in nucleophilic addition to the carbonyl group (Felkin-Ahn & chelation control)
- If molecule does not contain a stereogenic centre then we can use a **chiral auxiliary**
- The chiral auxiliary can be removed at a later stage

![Reaction Scheme](image)

- Opposite diastereoisomer can be obtained from reduction of the ketone
- Note: there is lower diastereoselectivity in the second addition as the nucleophile, ‘H−’ is smaller

![Second Reaction Scheme](image)
Chiral auxiliary in synthesis

- The chiral auxiliary, 8-phenylmenthol, has been utilised to form the pheromone, frontal in.
- Aggregation pheromone of the Southern Pine Beetle - the most destructive beetle to pine forests in southeastern United States.
Stereoselective synthesis: chiral reagents

Chiral reagents

- **Chiral reagent** - stereochemistry initially resides on the reagent
- **Advantages** - No coupling / cleavage steps required
  - Often override substrate control
  - Can be far milder than chiral auxiliaries
- **Disadvantages** - Need a stoichiometric quantity (not atom economic)
  - Frequently expensive
  - Problematic work-ups
Chiral reagents

- Clearly, chiral reagents are preferable to chiral auxiliaries in that they function independent of the substrate's chirality or on **prochiral** substrates.
- A large number have been developed for the reduction of carbonyls.
- Most involve the addition of a chiral element to one of our standard reagents.

![Diagram](image_url)

- Proceedings via boat-like transition state.
- Selectivity governed by 1,3-diaxial interactions.
- Can be reused for subsequent reactions.
**Binol derivative of LiAlH₄**

- Reducing reagent based on BINOL and lithium aluminium hydride.
- Selectivity is thought to arise from a 6-membered transition state (surprise!!)
- Largest substituent ($R^L$) adopts the pseudo-equatorial position and the small substituent ($R^S$) is axial to minimise 1,3-diaxial interactions.
Chiral reagent in total synthesis

(+)-Ipc$_2$BCl is a more reactive, Lewis acidic version of Alpine-borane

Might want to revise the Mitsunobu reaction (step 2)

Chiral allyl boron reagents

- Allyl boron reagents have been used extensively in the synthesis of homoallylic alcohols.
- Reaction always proceeds via coordination of Lewis basic carbonyl and Lewis acidic boron.
- This activates carbonyl as it is more electrophilic and weakens B–C bond, making the reagent more nucleophilic.
- Funnily enough, reaction proceeds by a 6-membered transition state.

- Aldehyde will place substituent in pseudo-equatorial position (1,3-diaxial strain).
- Therefore alkene geometry controls the relative stereochemistry (like aldol rct).

\[
\text{CH}_2=CH-CH(OH) \quad \text{versus} \quad \text{CH}_2\text{CH}=\text{CH(OH)}
\]

\[
\text{E-alkene gives anti product} \quad \text{Z-alkene gives syn product}
\]
Chiral allyl boron reagents II

- Reagent is synthesized from pinene in two steps
- Gives excellent selectivity but can be hard to handle (make prior to reaction)

- Remember pinene controls absolute configuration
- Geometry of alkene controls relative stereochemistry
Other boron reagents

- A number of alternative boron reagents have been developed for the synthesis of homoallylic alcohols.
- These either give improved enantiomeric excess, diastereoselectivity or ease of handling / practicality.

- Ultimately, **chiral reagents** are wasteful - they need at least one mole of reagent for each mole of substrate.
- End by looking at **chiral catalysts**.
Chiral reagent in total synthesis

- Silicon reagent developed by J. Leighton
- Used in the synthesis of (+)-SCH 351448, a reagent for the activation of low-density lipoprotein receptor (LDLR) promoter (no I don't know what it means either!)
• **Chiral catalysis** - ideally a reagent that accelerates a reaction (without being destroyed) in a chiral environment thus permitting one chiral molecule to generate millions of new chiral molecules...
Catalytic enantioselective reduction

- An efficient catalyst for the reduction of ketones is Corey-Bakshi-Shibata catalyst (CBS)
- This catalyst brings a ketone and borane together in a chiral environment
- The reagent is prepared from a proline derivative
- The reaction utilises ~10% heterocycle and a stoichiometric amount of borane and works most effectively if there is a big difference between each of the substituents on the ketone
- The mechanism is quite elegant...
Mechanism of CBS reduction

- Interaction of amine & borane activates borane
- It positions the borane
- It increases the Lewis acidity of the endo boron

Catalyst turnover

Coordination of aldehyde activates aldehyde and places it close to the borane

Chair-like transition state

Largest substituent is pseudo-equatorial
Catalytic enantioselective nucleophilic addition

- There are now many different methods for catalytic enantioselective reactions
- Here are just a few examples...
- Many simple amino alcohols are known to catalyse the addition of dialkylzinc reagents to aldehydes
- Mechanism is thought to be bifunctional - one zinc becomes the Lewis acidic centre and activates the aldehyde
- The second equivalent of the zinc reagent actually attacks the aldehyde
- Once again a 6-membered ring is involved and 1,3-diaxial interactions govern selectivity

\[
\text{[Reaction Diagram]}
\]
Lewis acid catalysed allylation / crotylation

- Chiral Lewis acids can be used to activate carbonyl group with impressive results
- Allylation works very well with high e.e.
- Problem with crotylation - often hard to control d.e.
- Reason is that the reaction proceeds via an open transition state

\[
\text{PhCHO} + \text{SnBu}_3\text{SnBu}_3\text{SnBu}_3 \xrightarrow{(R)\text{-BINAP, AgOTf, THF, }-20^\circ\text{C}} \text{PhCHMe} = \text{CHMe}
\]

- 56% 70%de 94%ee
- 72% 70%de 91%ee
- 45% 70%de 94%ee
Catalytic chiral Lewis base mediated allylation

- An alternative strategy is the use of **Lewis bases** to activate the crotyl reagent.
- Reaction proceeds *via* the activation of the **nucleophile** to generate a hypervalent silicon species.
- This species coordinates with the aldehyde, thus **activating** the aldehyde and allowing the reaction to proceed by a highly ordered **closed transition state**.
- As a result, good **diastereoselectivities** are observed and the geometry of nucleophile controls the **relative** stereochemistry.
Lewis acid organocatalysis

- **Intermolecular hydrogen bond** acts as a Lewis acid and activates carbonyl
- **Intramolecular hydrogen bond** organises catalyst
- Catalyst derived from simple nature product, tartaric acid
- Clean, green and effective
Catalysis in total synthesis

- (R)-Muscone is the primary contributor to the odour of musk, a glandular secretion of the musk deer.
- A racemic, synthetic version is used in perfumes.