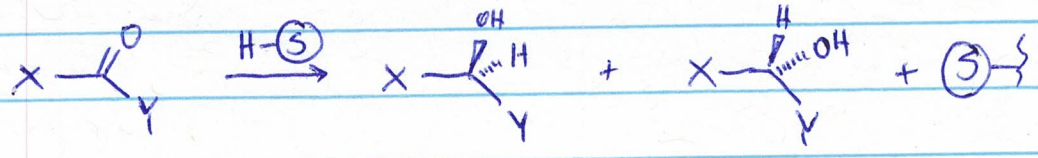
Lecture XXXII: Enantioselective Synthesis

04-20-2020

Enantioselective synthesis aims to create a single enantiomer of a chiral product. It is also called asymmetric synthesis (even though the products can still have a symmetry element) or asymmetric induction.

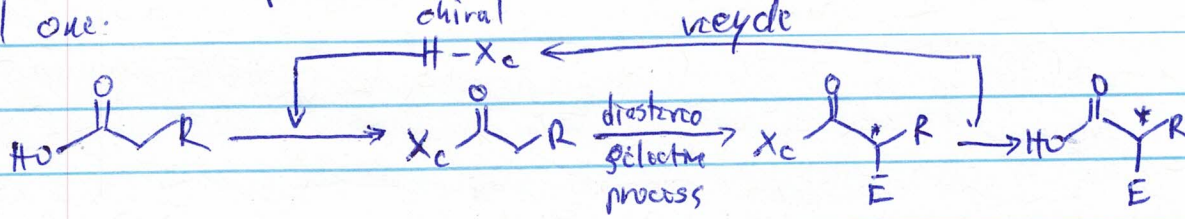


During the course of an enantioselective synthesis, a chiral reagent can be regenerated (although often they are not) or can completely lose its chirality. Mislow called the latter phenomenon immolative asymmetric synthesis.

In stoichiometric enantioselective synthesis, chiral reagents are used in stoichiometric amounts, or are attached to the molecule as chiral auxiliaries. Alternative which is much more elegant is asymmetric catalysis which has been growing explosively over the past decade (Nobel Prize 2001). We will talk about it today and next time.

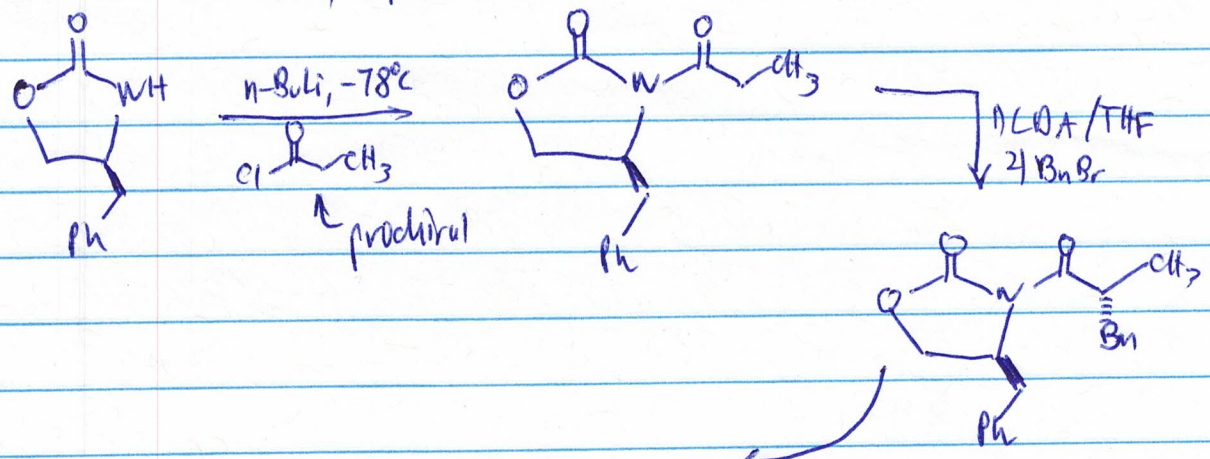
Chiral Auxiliaries

Temporarily employed to convert a prochiral substrate into a chiral one:



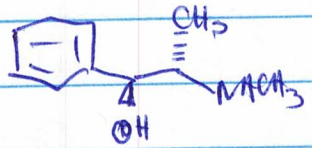
First introduced by EJ Corey and Barry Trost in the late 1970s. However they were difficult to prepare. More useful auxiliaries

were introduced by David Evans. They were based on oxazolidinones which can be easily prepared from chiral amino acids:

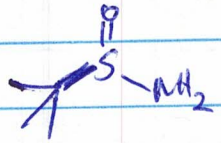


Removal can proceed under oxidative conditions to give ~~an aldeh~~ carboxylic acid, reductive to give an alcohol, and amides, esters and thioesters can be generated as well.

camphorsultam, popularized by Oppolzer



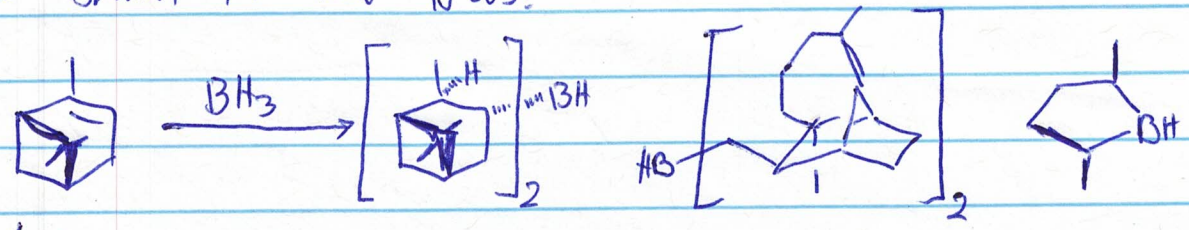
pseudoephedrine; useful but regulated



S-chiral t-butanesulfinamide, Ellman

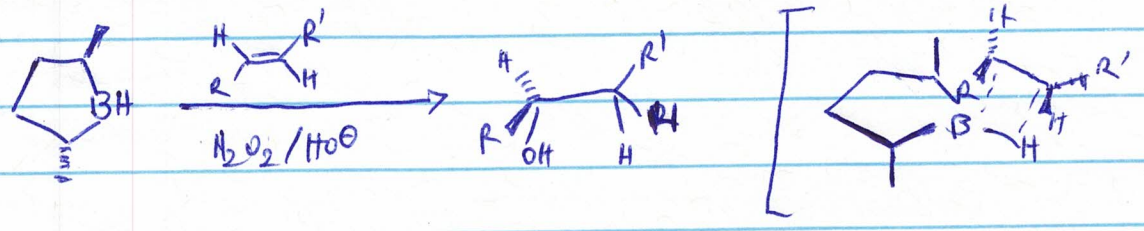
First industrial synthesis of drugs Tipranavir (HIV) and Lipitor (cholesterol lowering) were conducted using chiral auxiliaries, even though they are not used in today's synthesis.

Auxiliaries temporarily make our precursor chiral. Alternatively, chiral reagents can be used. Chiral boranes were popularized by HC Brown in the 1970s:

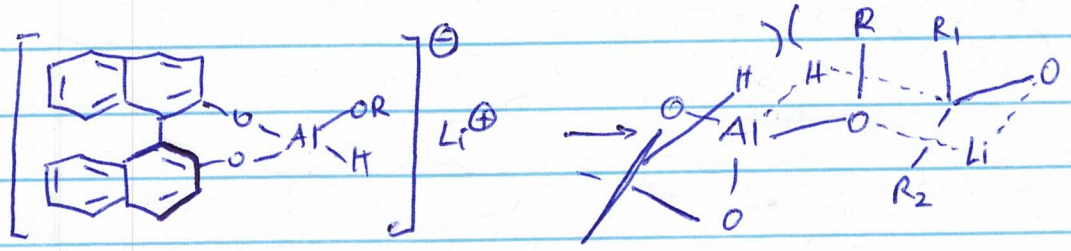


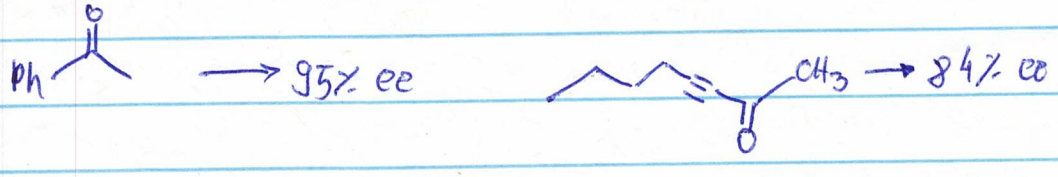
α-pinene

These species can then be used for chiral hydroboration of other alkenes, and from there other stereocenters can be set:

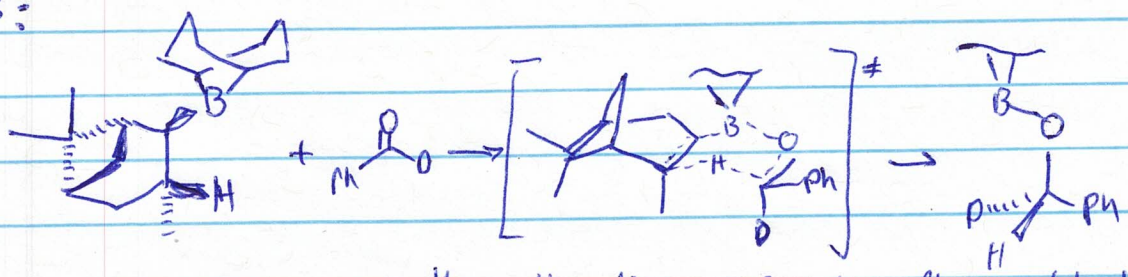


Ketone and aldehyde reductions with chiral complex hydrides:



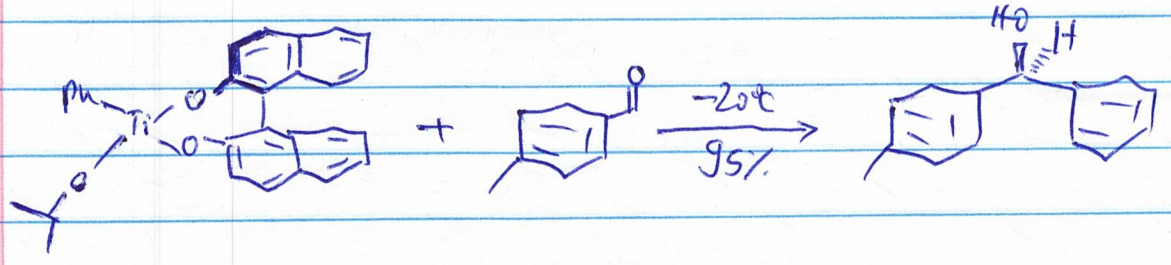


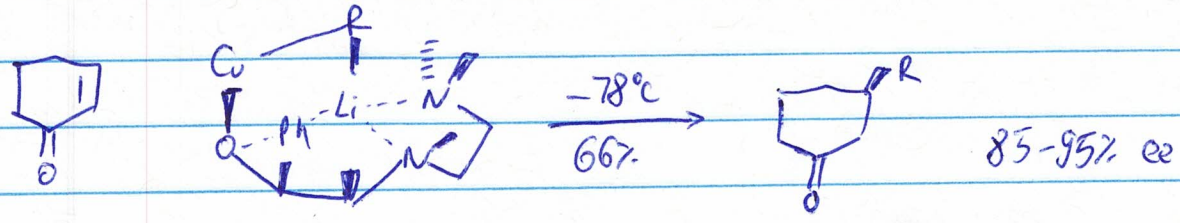
Chiral boranes can be once again used here as reducing agents:



in this alternative conformation Ph would bump into

Chiral auxiliaries can also be easily integrated into organometallic ~~reaction~~ reagents. Examples:





In modern synthesis, the use of stoichiometric chiral reagents is diminishing in importance. They used to be readily available, cheap, and relatively rigid so that they can suitably transfer chirality onto the substrate.

Enantioselective catalysis is a lot more efficient in transferring chirality from a single molecule of catalyst onto a very large number of substrate molecules. These chiral catalysts can be either natural or synthetic:

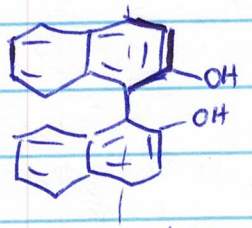
- enzymes
  - highly selective, often times too selective
  - can not work too well outside of aqueous environments
  - sometimes not too thermally stable

"Asymmetric Organic Synthesis with Enzymes", Wiley, 2008

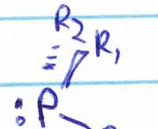
- synthetic catalysts
  - transition metal based
  - organocatalysts
    - chiral acids
    - chiral bases
    - chiral hydrogen bonds donor/acceptors

The two categories are not entirely dissimilar. Enzymes often have metals in their structures, and TM catalysts are often modeled on the binding pockets of enzymes.

Transition metal catalysts need to be chiral. Rarely, they create a chiral metal center (but see Gladysz tutorial). Instead their chirality starts from a chiral ligand, and these ligands are often not based on a chiral carbon either:



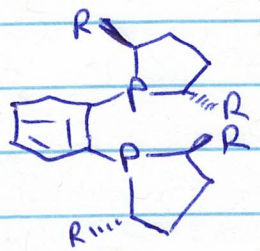
axial chirality



chiral phosphorus (early examples)

Additionally, these ligands are rarely completely lacking symmetry elements. Very commonly, they are C_2-symmetric. This creates two equivalent binding sites, lowers the flexibility of the transition states, and ultimately increase ee's. They are called privileged ligands:

BINOL.



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