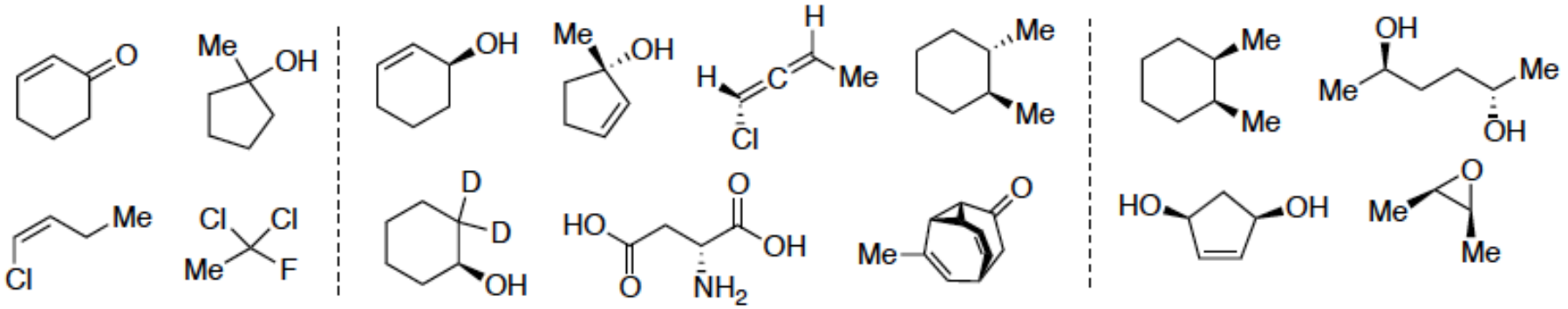
Key stereochemical terminology

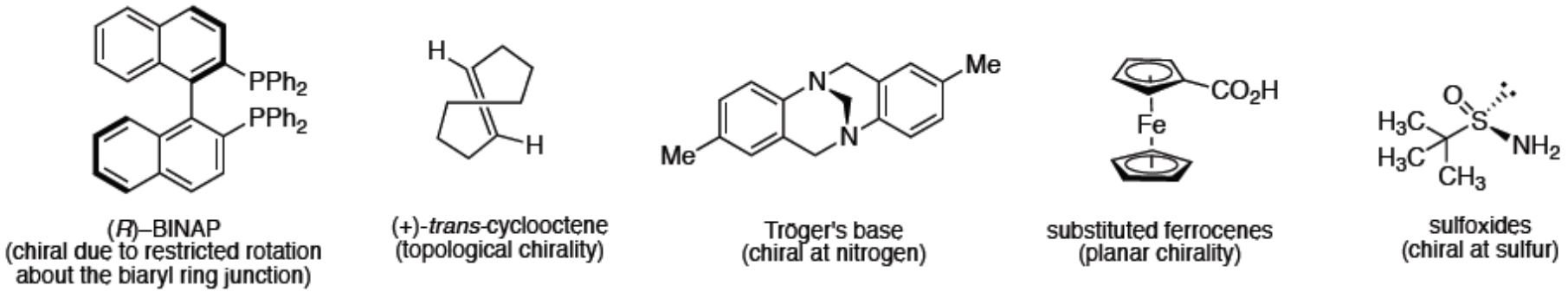
Stereochemical terminology in organic chemistry can refer to structure of a molecule or to properties of a physical sample of the molecule. It is very important to recognize the distinction and use the correct terminology.

Properties of a molecule



Absolute configuration, Cahn-Ingold–Prelog

Planar, axial, topological chirality and chirality at atoms other than carbon

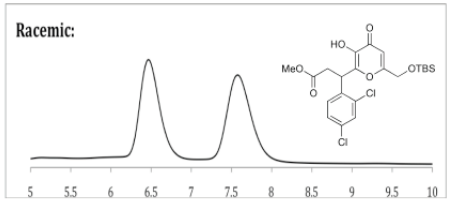


Properties of a sample (racemic, scalemic {enantioenriched, enantiomerically pure, optically pure})

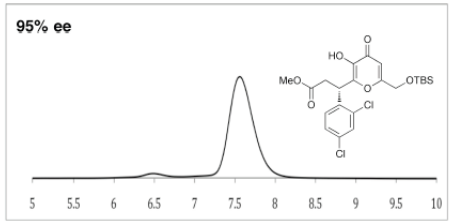
racemic – a 50/50 mixture of two enantiomers
scalemic – a sample with a non-racemic mixture of enantiomers, which can be:
enantiomerically enriched (optically active) – a sample that contains both enantiomers, one in excess
enantiomerically pure (optically pure) – a sample that contains only one enantiomer (>99.5% ee)

Determination of Enantiopurity
Enantiomers cannot be differentiated by most analytical methods (NMR, UV, IR, MS, melting point) as enantiomers have identical physical properties. The ratio of enantiomers can be determined by:
1) Optical rotation (less accurate and requires an enantiopure reference sample)
2) NMR with chiral shift reagents (formation of transient diastereomeric complexes)
3) Separation of enantiomers by chromatography on chiral solid supports [High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), Super Critical Fluid Chromatography (SFC)]

Racemic HPLC/SFC trace



Enantioenriched trace



The **ratio of enantiomers** (er) is most often expressed as **% enantiomeric excess**:

calculation of enantiomeric excess (% ee)

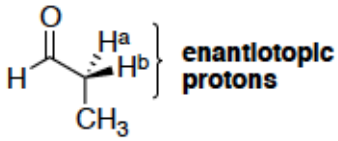
$$\% \text{ ee} = 100 \times \frac{(\text{enantiomer A} - \text{enantiomer B})}{(\text{enantiomer A} + \text{enantiomer B})}$$

example: for a sample that has an enantiomeric ratio (er) = 66:22

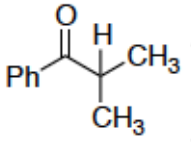
$$\% \text{ ee} = 100 \times \frac{(66 - 22)}{(66 + 22)} = \frac{44}{88} \times 100 = 50\% \text{ ee}$$

Prochirality

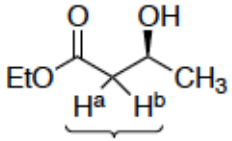
A prochiral proton or group is one that leads to a chiral center when substituted or modified.



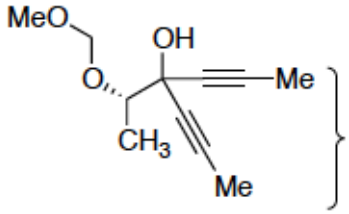
enantiotopic protons



enantiotopic groups

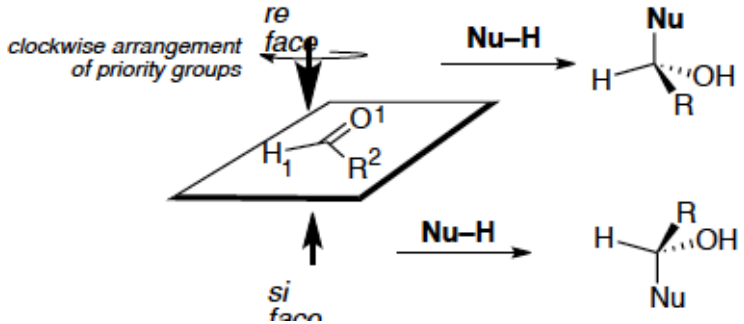


diastereotopic protons



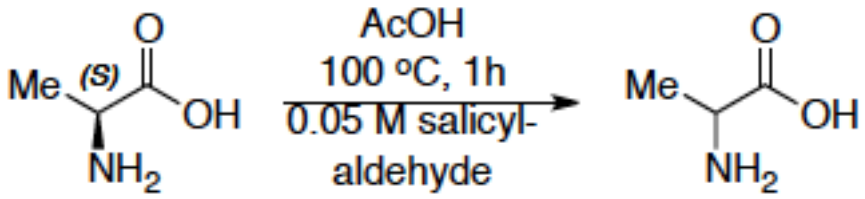
diastereotopic groups

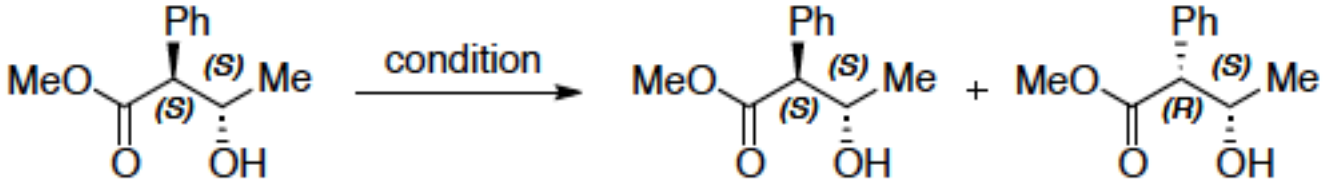
sp^2 hybridized compounds have prochiral faces, often referred to as the ***re*** and ***si*** faces.

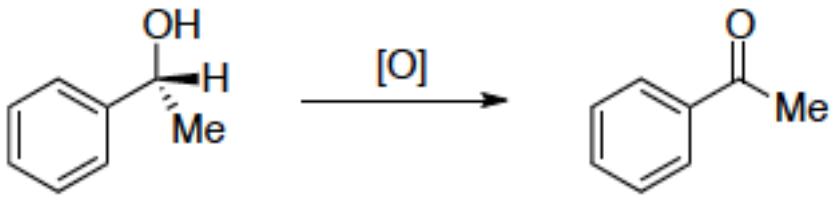


Stereochemisty of reactions

Loss of stereochemistry (Racemization, Epimerization, Loss of chirality)

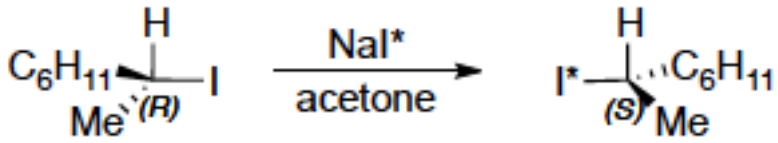


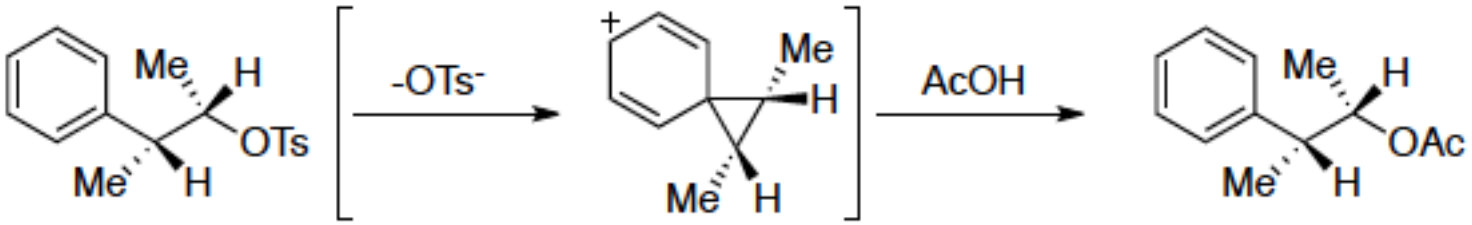




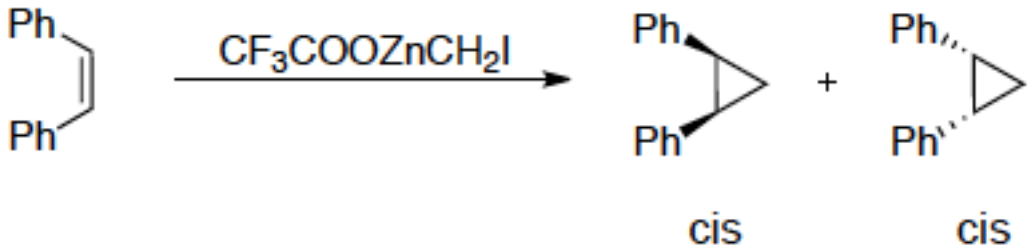
Stereospecific reactions

In stereospecific reactions, the stereochemistry of the starting material determines the stereochemistry of the product. For a reaction to be stereospecific,
the stereochemical transfer mustbe perfect. If it is not, it is a stereoselective reaction





Many reactions of alkenes are stereospecific and give the products as a single diastereomer

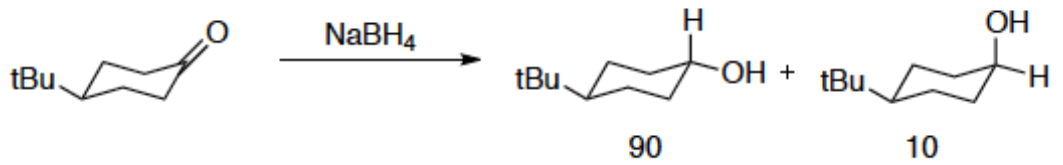


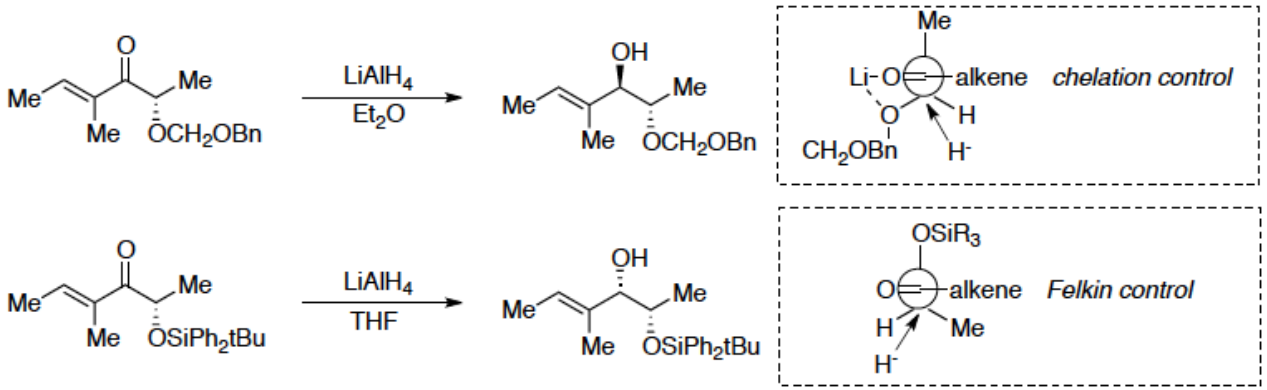
Diastereoselective reactions

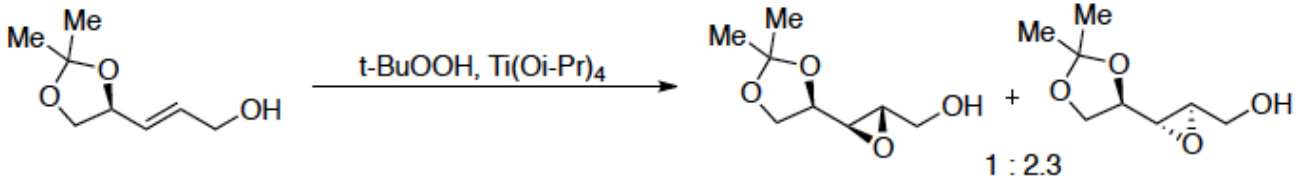
Substrate controlled diastereoselective reactions

Cyclic stereocontrol,

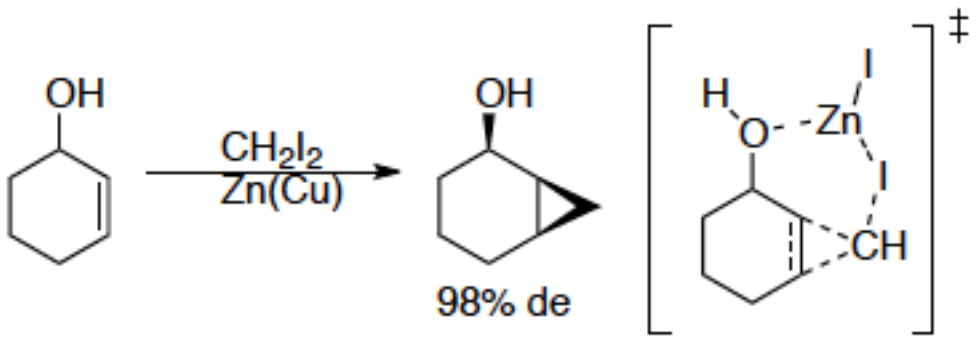
Acyclic stereocontrol (i.e. Felkin addition, chelation control, etc)





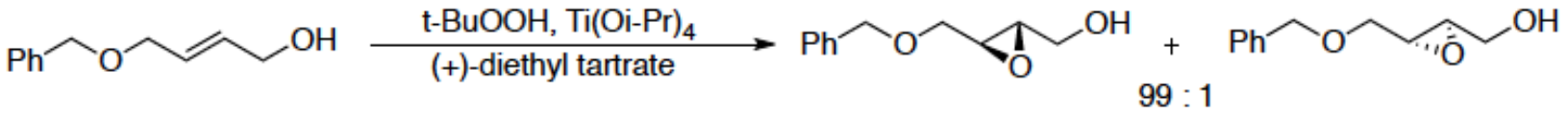


Directed reactions

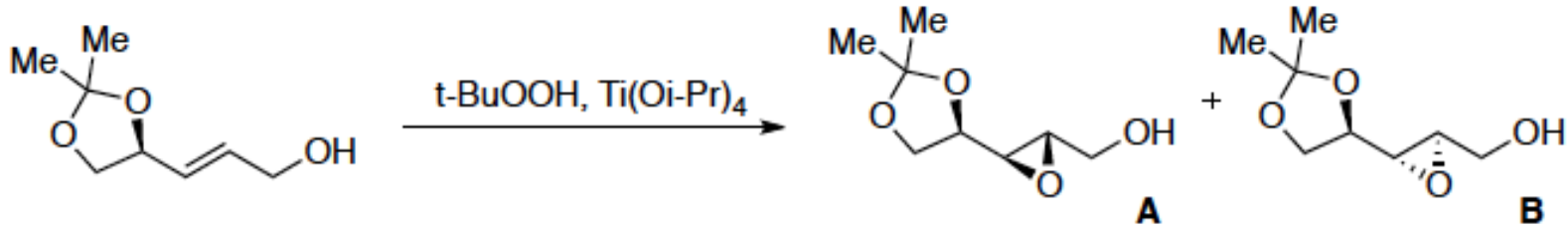


Hoveyda and Evans Chem. Rev. 1993, 93, 1307

Reagent/ligand control



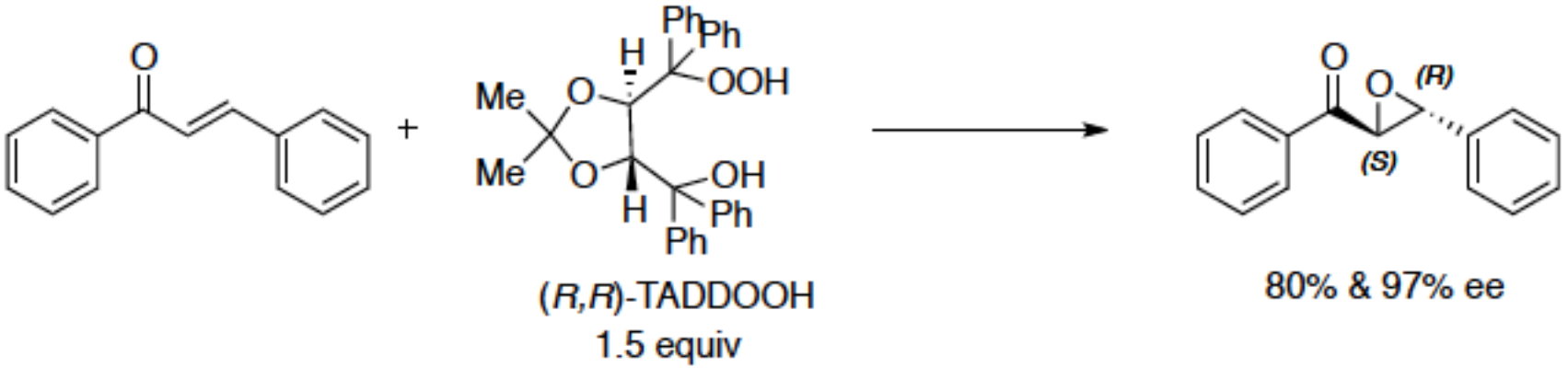
Match/mismatch



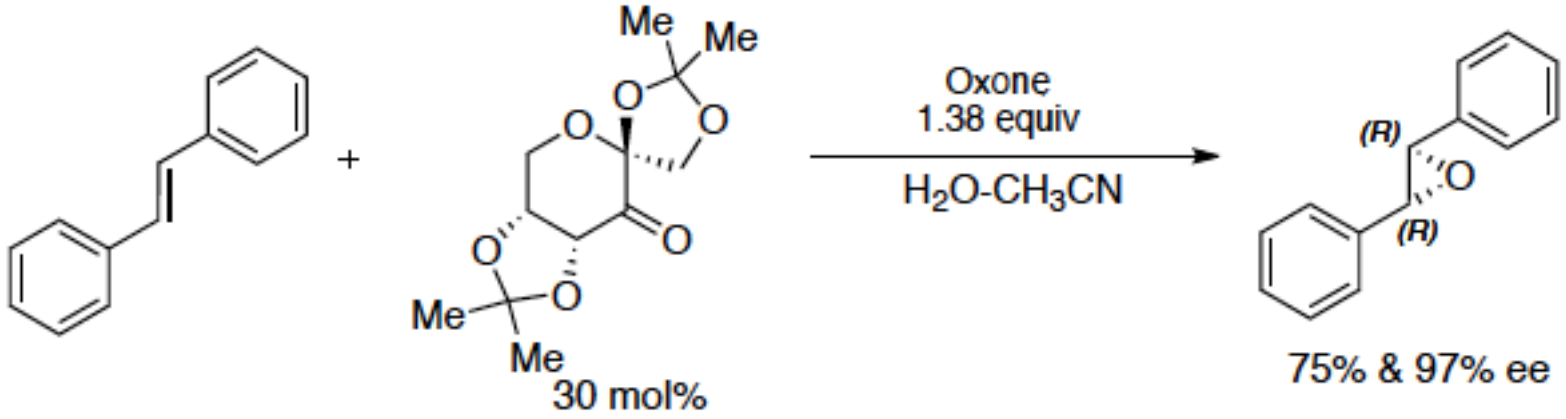
Condition	Ratio of A to B
no tartrate	1 : 2.3
(+)-diethyl tartrate	22:1 (mismatched)
(-)-diethyl tartrate	1:90 (matched)

Enantioselective reactions

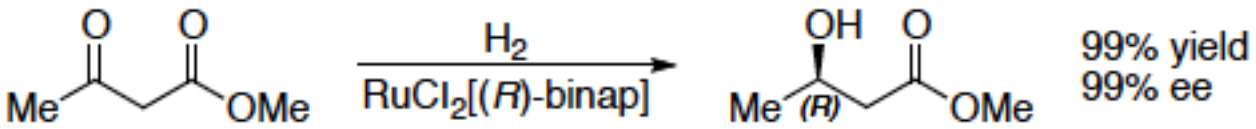
Stoichiometric reagents

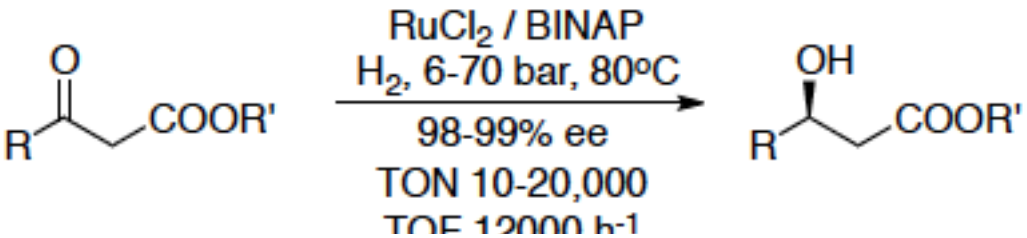


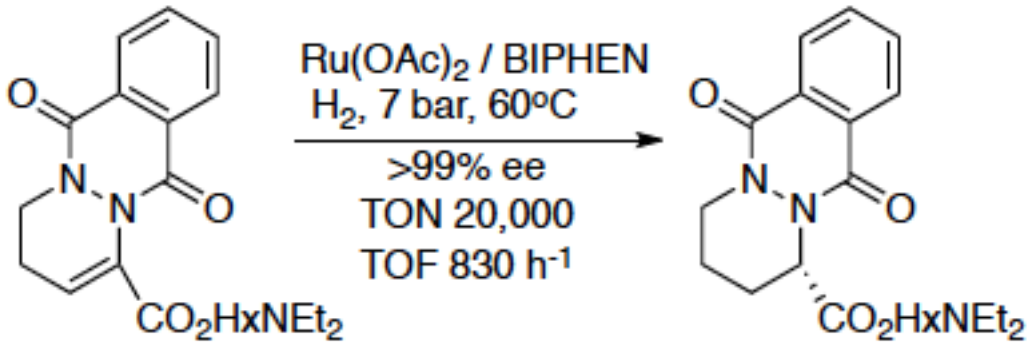
Catalytic asymmetric synthesis

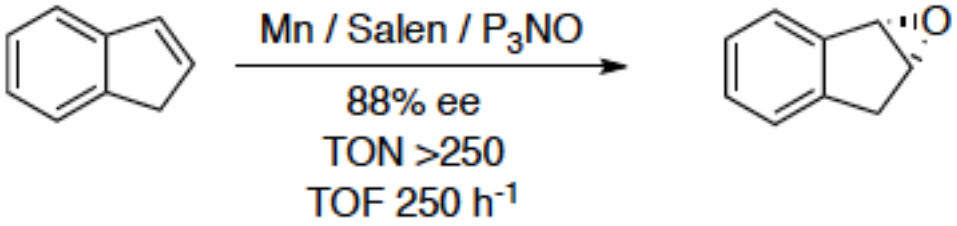


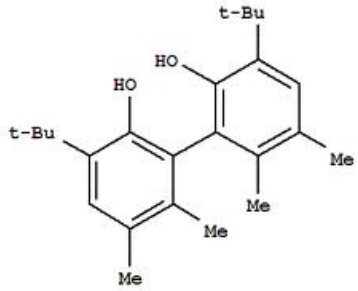
Industrial catalytic enantioselective processes

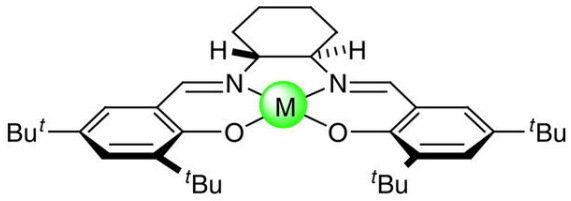






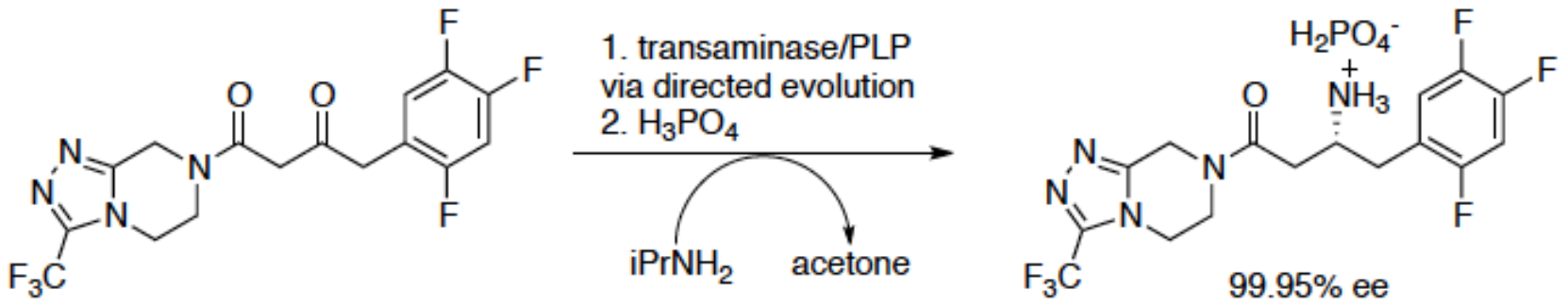






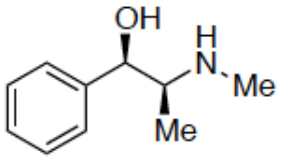
1: M = Cr–Cl
2: M = Al–Cl
3: M = Co
4: M = Mn–Cl

Enzymes often make excellent enantioselective catalysts and are commonly used by the pharmaceutical industry. A limitation is that only one enantiomer of enzymes are available and only one enantiomer of the product may be produced.

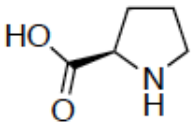


Importance of asymmetric catalysis
All enantioenriched molecules derived from natural sources

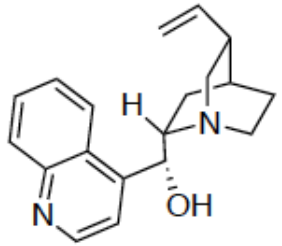
Enantiomerically enriched chiral substance can only be generated from other chiral starting materials or by enantioselective reactions using chiral, enantiomerically enriched reagents or catalysts. The natural world is enantiomerically enriched: all genetically encoded amino acids are L-configured (usually (S)) and most natural sugars D-configured. Until the advent of asymmetric catalysis, very few methods to prepare chiral compounds were available. The chiral pool is now greatly expanded due to advances in asymmetric catalysis and biocatalysis. Some readily available, naturally derived chiral compounds include:



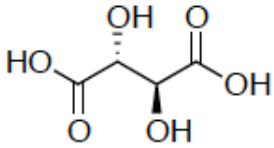
ephedrine



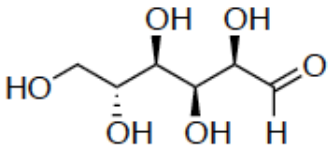
proline



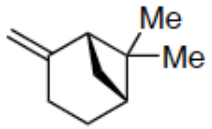
cinchona alkaloid



tartaric acid



glucose

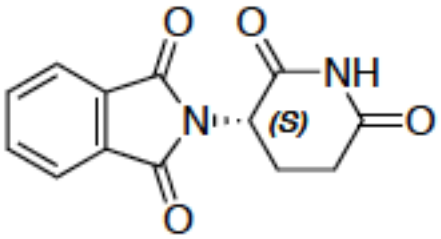


pinene

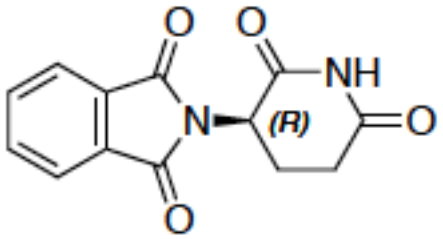
All new pharmaceuticals must be single enantiomer

In 1992, the US Federal Drug Administration (FDA) decreed that all new molecular entities (drugs) be approved as single enantiomers.

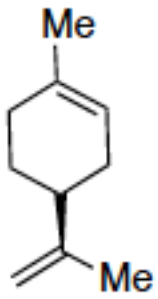
Previously, mixtures of enantiomers were sold even though the two enantiomers often had completely different biological activities.



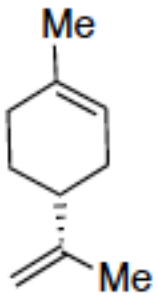
(*S*)-thalidomide
teratogenic



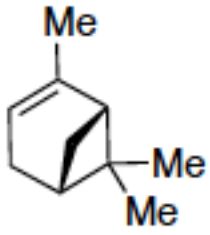
(*R*)-thalidomide
effective against
morning sickness



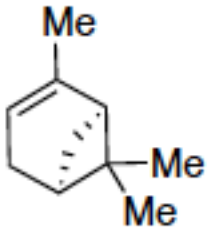
(-)-Limonene
pine-like odour



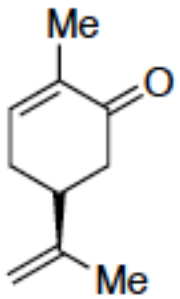
(+)-Limonene
orange-like odour



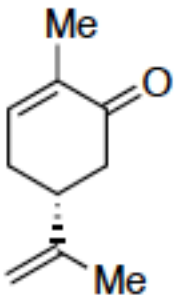
(+)-Pinene
pine-like odour



(-)-Pinene
pine-like odour



(+)-Carvone
carraway odour



(-)-Carvone
spearmint odour

Historical and contemporary names in catalytic, enantioselective synthesis
(selected names)
Early days (1950–1985): Kagan, Sheehan, Knowles, Noyori, Sharpless, Mukaiyama

Lewis acid catalysis: Mukaiyama, Yamamoto, Corey, Evans, Mikami, Carreira, Shibasaki, many others

Transition metal catalysis: Trost, Overman, Backval, Pfaltz, Togni, Hayashi, Sigman, Stoltz, Doyle, Davies, Hoveyda, Feringa, Kundig, many others

Oxidation: Sharpless, Jacobsen, Katsuki, Shi

Reduction: Knowles, Noyori, Backvall, Corey, Pfaltz, Zhang

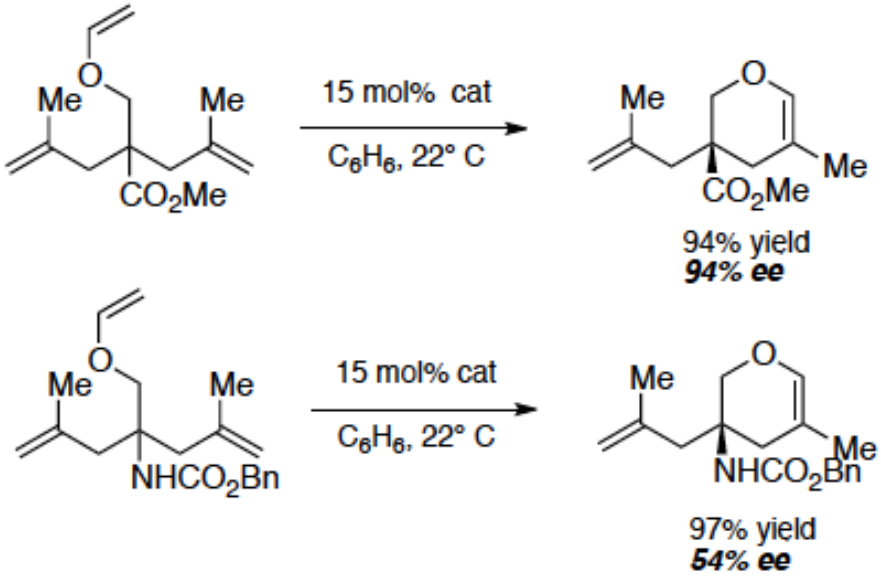
Organocatalysis: Vedejs, Fu, List, Barbas, Jacobsen, Miller, Macmillan, Jorgensen, Enders, Akiyama, Terada, Bode, Reuping, Maruoka, Hayashi

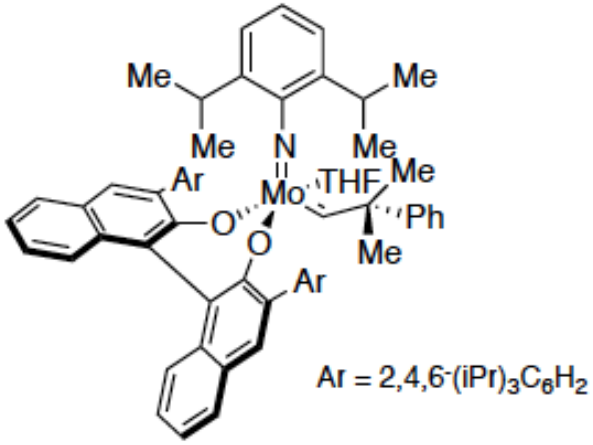
Biocatalysis: many

Problems with enantioselective catalysis

Catalyst generality

A major problem with catalytic enantioselective synthesis is the fact that in many cases, small changes in the substrates dramatically change the results. The search for “general” catalysts is an important topic but is probably unobtainable.



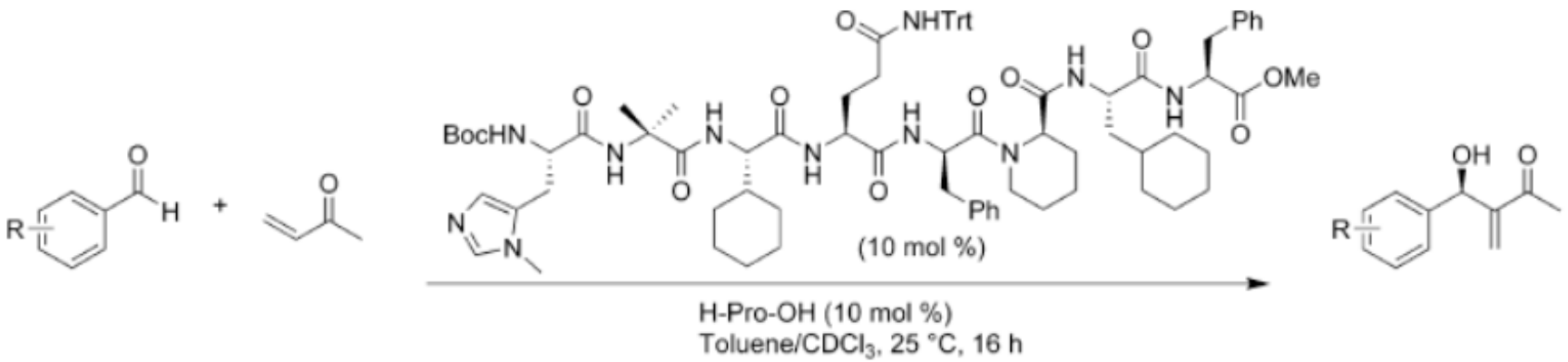


mw = 1165

Catalyst identification

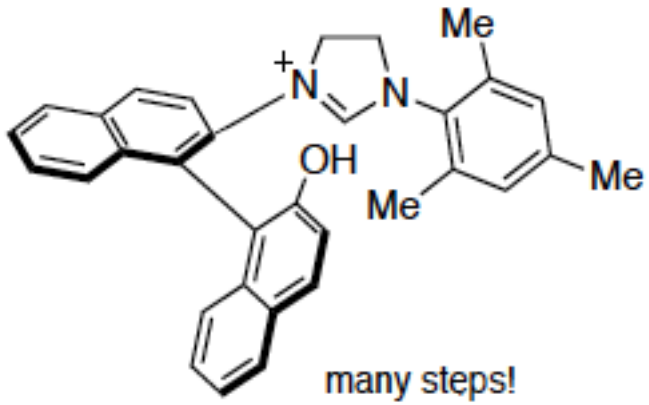
It is often very difficult to identify the best ligand or metal ligand-combination for a given transformation. Most major pharmaceutical and related companies now have entire units dedicated to screening catalysts for enantioselective reactions. Each substrate often requires extensive optimatization. Strategies that allow rapid generation and optimization of enantioselective catalysts are in great demand.

Example: this peptide catalyst for Morita-Baylis-Hillman reactions was selected first from a random library of 105 peptides and then subjected to further optimization.

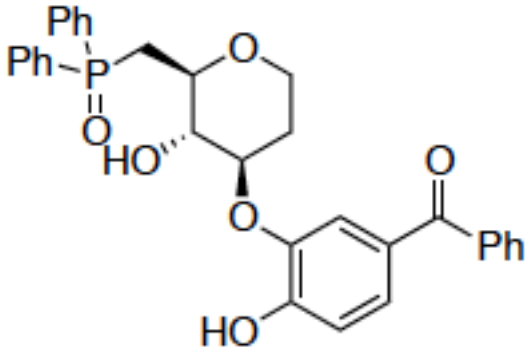


Preparation of chiral catalysts and ligands

Many good chiral catalysts require multiple synthetic steps and are very expensive to produce.
The cost of the catalyst is often prohibitive.



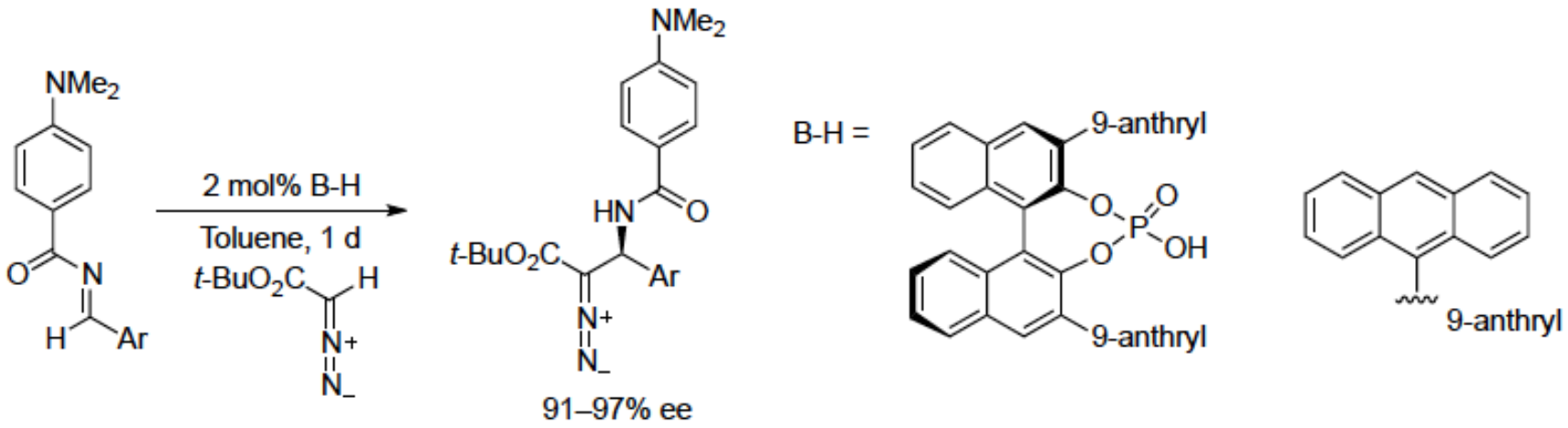
many steps!



12+ steps
only one enantiomer
available

Substrate scope

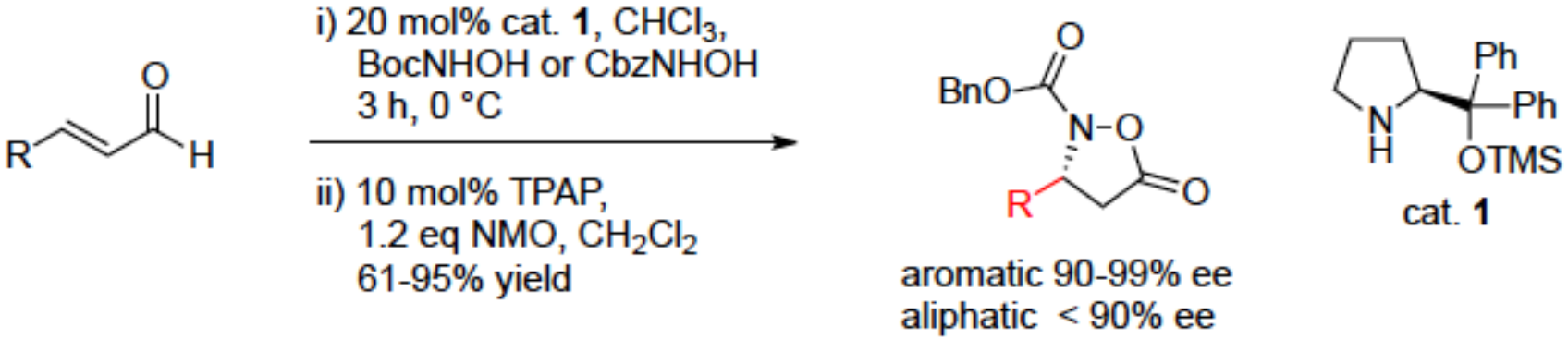
Many catalytic enantioselective reactions are severely limited in substrate scope. Often only substrates with aryl groups are tolerated, and the process is useless for other substrates.



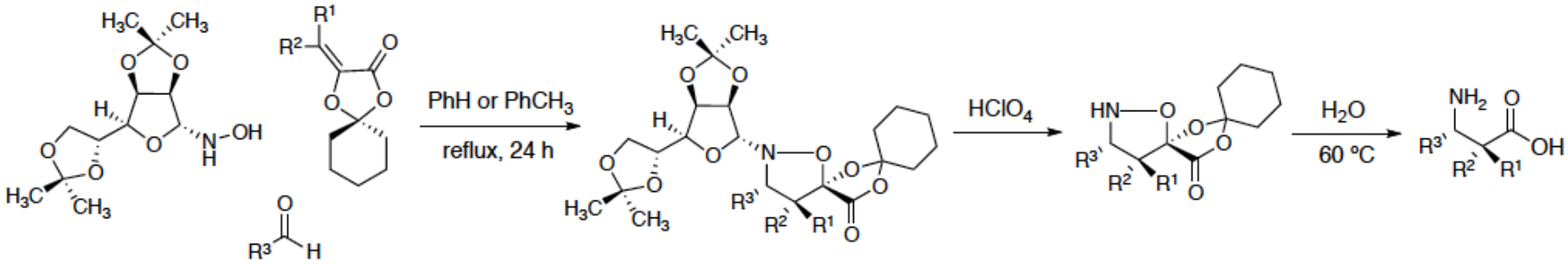
This is a very nice reaction, but it works only for a few aryl groups.
Aliphatic or other functionalities are not tolerated.

Sub-optimal enantioselectivities

Although it is sometimes possible to crystallize products with modest enantiomeric excess to enantiopurity, this is often difficult and requires extensive optimization. Many powerful enantioselective reactions are not used because they deliver sub-optimal enantioselectivities.

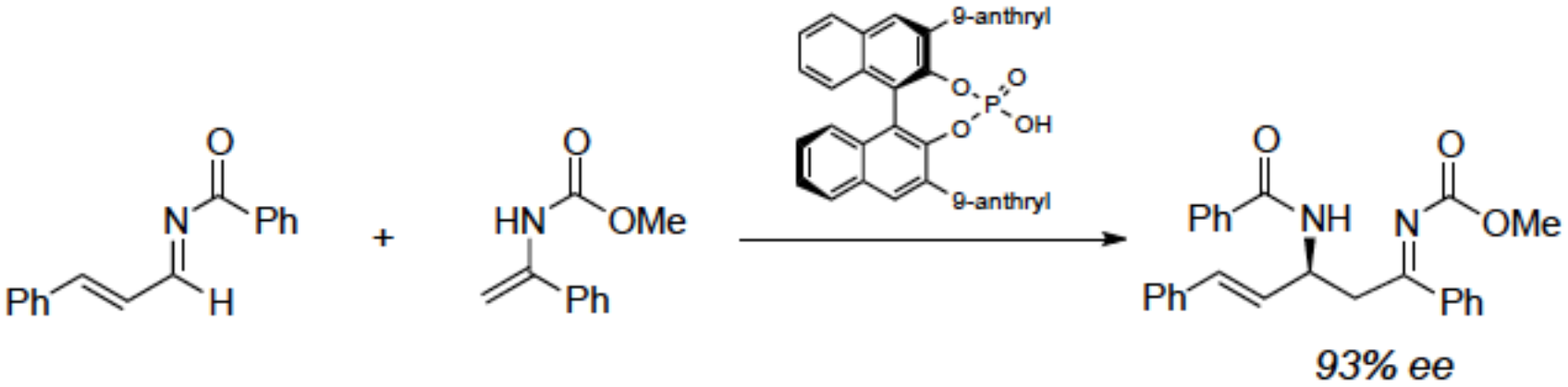


Although this chemistry was perfect for preparing monomers for beta3-peptide synthesis, the sub-optimal enantioselectivity forced researchers to adopt a longer, less efficient route using a chiral auxiliary. The chiral auxiliary approach, however, allowed the preparation of a number of monomers in high enantiomeric excess.



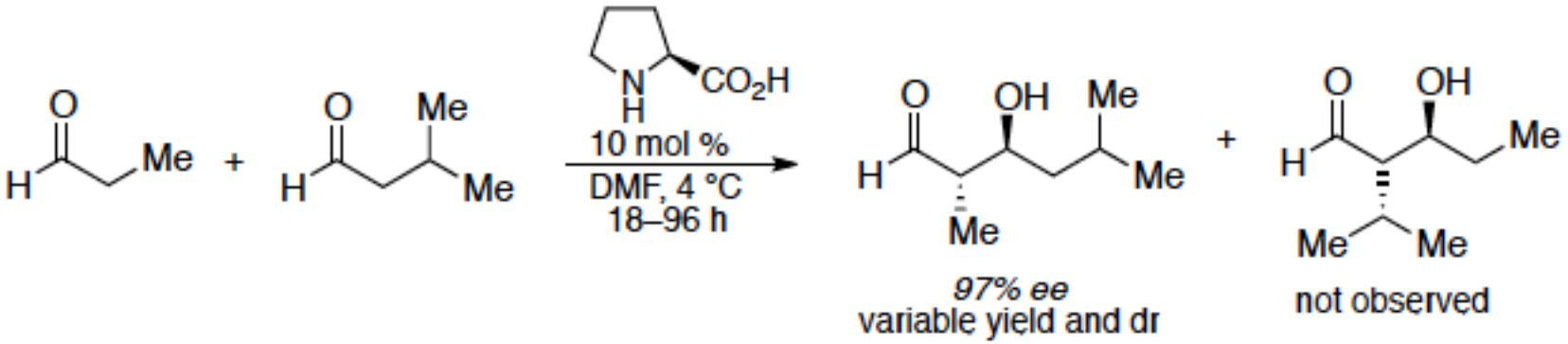
Non-standard protecting groups

In many cases, protecting groups are selected for compatibility with the catalytic enantioselective reactions rather than their utility in the resulting products. This leads to catalytic enantioselective reactions that give products that cannot be further elaborated due to the lack of methods to remove the “protecting groups”. For example, despite the importance of enantiopure beta-amino acids, few in any catatylic enantioselective routes are actually used to make the monomers.



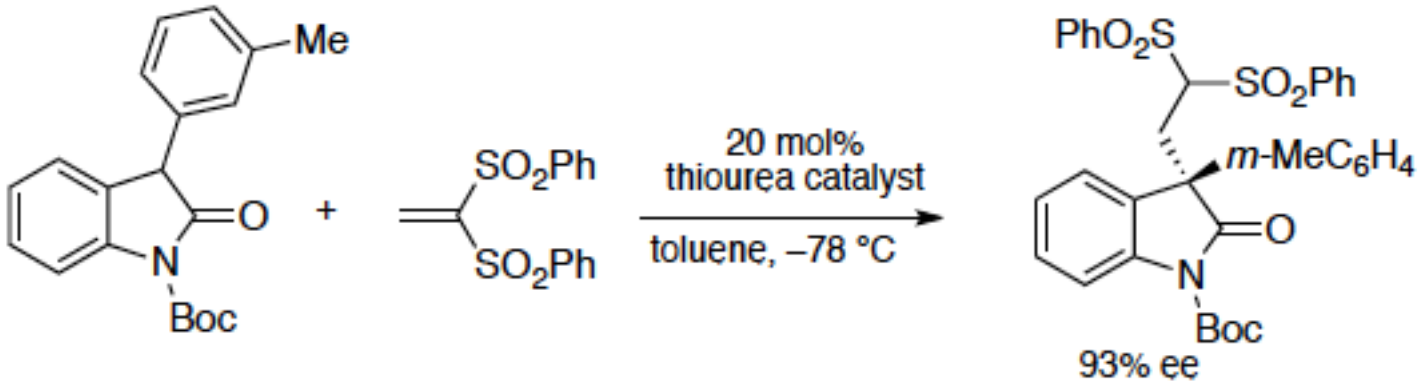
Complicated and sensitive reaction conditions

Many catalytic enantioselective reactions suffer from very sensitive and delicate reaction conditions. This makes repeating the reactions very difficult, often leading to frustration. For example, the following reaction is very useful and simple to set up, but often difficult to execute.



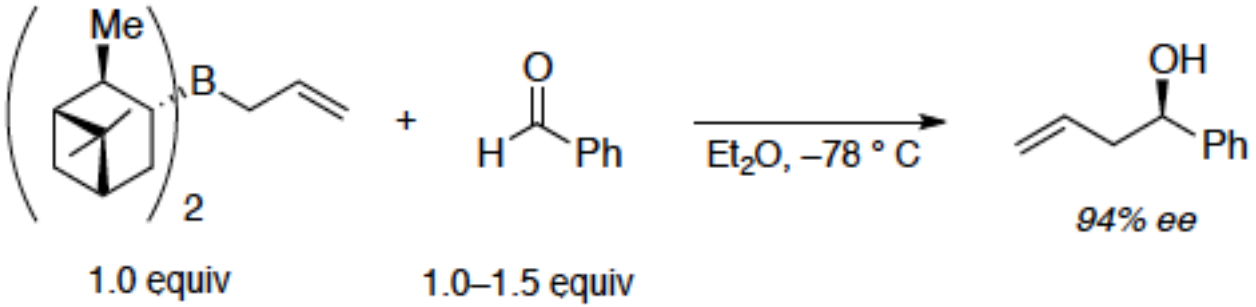
Good ee vs. useful transformations

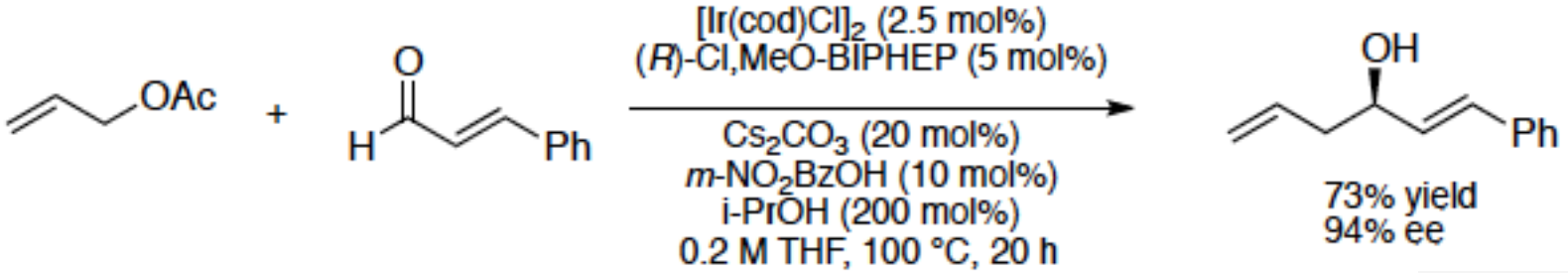
In recent years, academic scientist have focused more on enantioselectivity than on the usefulness of a given transformation. This has led to a large body of highly enantioselective reactions of limited utility and with poor substrate scope that are published only due to high ee. Often, more interesting reactions reported for the first time in racemic form are overlooked. In contrast, the early days of the field were focused on developing enantioselective reactions of the most useful processes such as hydrogenation, expoxidation, and ketone reduction.

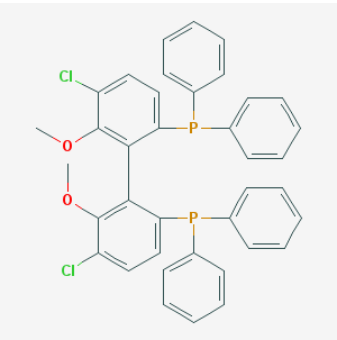


Cost vis-à-vis traditional methods

Very often, traditional methods such as resolution by salt formation are simple cheaper than even a good catalytic enantioselective process. This is particularly true of transition metal catalyzed reactions employing palladium, rhodium, iridium or other expensive metals. The few catalytic enantioselective processes used in industry with these metals are extremely effective and use very low catalyst loadings.

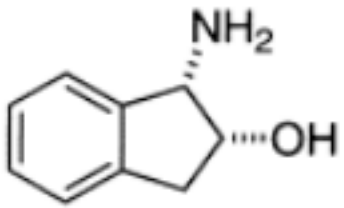




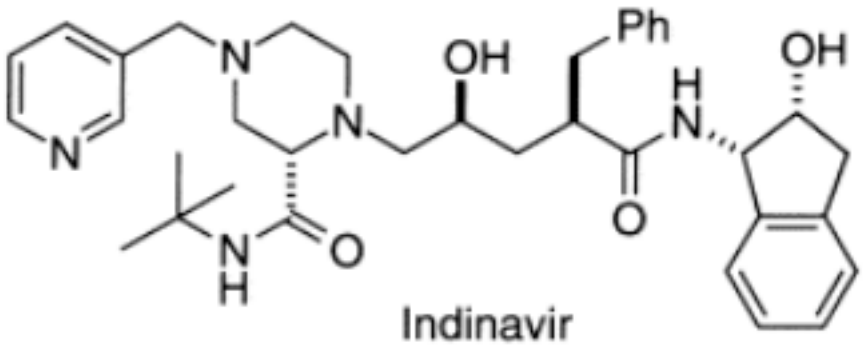


Patents and licensing

There have been numerous cases where demands for royalties to use a catalytic enantioselective reaction in the preparation of an important molecule prevented its eventual adoption. An excellent case is the preparation of chiral amino indanol, which was needed for the synthesis of an anti-HIV drug. A method using Jacobsen's epoxidation was owned by Sepracor. Merck instead contracted a company to produce it by a biotechnological approach. Olefin metathesis using Grubb's catalysts suffers from similar problems, as the company that owns the license demands large royalties for its use. This has led to new variants from companies and other group that get around the intellectual property.



(1*S*, 2*R*)-**1**



Indinavir

Asymmetric vs. racemic synthesis

In a racemic synthesis, a target molecule is produced as a 50-50 mixture of enantiomers. If the target has multiple chiral centers, the correct diastereomer (with the correct relative configuration) is produced.

Asymmetric synthesis is the preparation of only one of the two possible enantiomers of the final product.
This can be accomplished by a number of techniques, including:

1) **chiral pool (chiral starting materials)** – at least one of the stereocenters derives from an enantioenriched starting material such as a sugar or an amino acid.
2) **resolution** – a mixture of enantiomers is separated by chemical, chromatographic, or catalytic (often enzymatic) resolution. This can be done at any stage of the synthesis.
3) **chiral auxiliaries** – an enantiopure appendage is used to introduce new stereocenters in a defined relative configuration. This appendage is later removed and often recycled.
4) **enantioselective synthesis** – new stereocenters are introduced by reagent control from a chiral reagent that does not itself become part of the product. When substoichiometric quantities of the chiral reagent are used, it is known as catalytic, enantioselective synthesis.