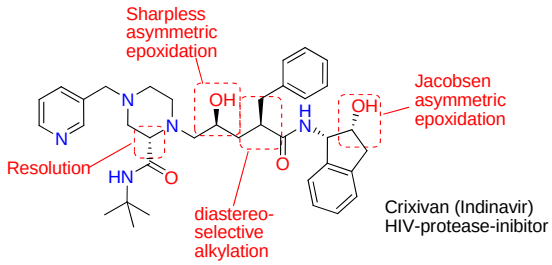
Asymmetric (stereoselective) synthesis



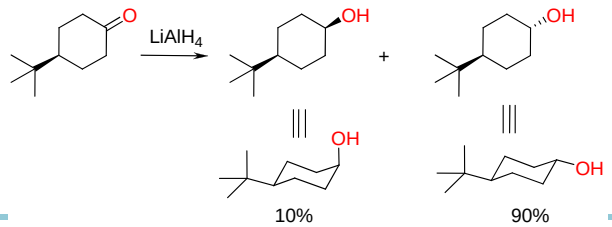
Drug synthesis II
Tapio Nevalainen
2012

UNIVERSITY OF EASTERN FINLAND

UNIVERSITY OF EASTERN FINLAND

Streoselectivity

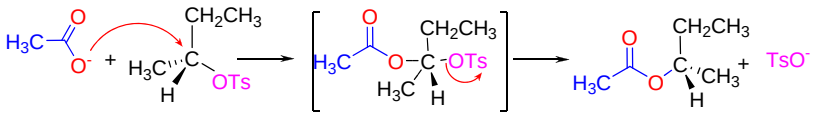
- **Stereoselective reactions** — reactions where one stereoisomer of product is formed predominantly because the reaction has a choice of pathways, and one pathway is more favourable than the other
- Selective reduction of 4-tert-butylcyclohexanone (I) to a 10:1 mixture of trans- and cis-4-tert-butylcyclohexanol by LiAlH4 is an example of diastereoselectivity, reflecting a preference for hydride attack at the more hindered axial face of the carbonyl group.



UNIVERSITY OF EASTERN FINLAND

Stereospecificity

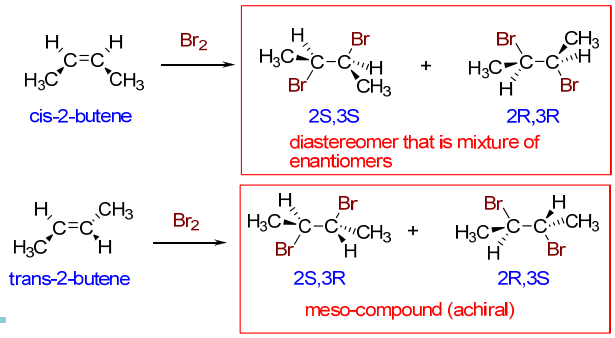
- **Stereospecific reactions** — reactions where the mechanism means that the stereochemistry of the starting material determines the stereochemistry of the product and there is no choice involved
- S_N2 reactions are stereospecific: they proceed with inversion so that the absolute stereochemistry of the starting material determines the absolute stereochemistry of the product



UNIVERSITY OF EASTERN FINLAND

Stereospecific reactions

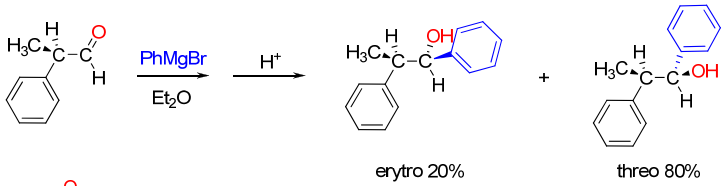
- Electrophilic addition of bromine to alkenes is stereospecific and leads to anti addition across a double bond. For example cis-2-butene gives the anti dibromide (mixture of 2S,3S and 2R,3R isomers) and trans-2-butene the syn dibromide (2R,3S isomer = meso-compound)
- The geometry of the starting material determines the relative stereochemistry of the product



UNIVERSITY OF EASTERN FINLAND

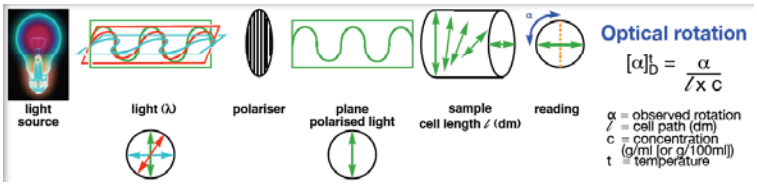
Asymmetric induction

- Asymmetric induction describes the preferential formation in a chemical reaction of one enantiomer or diastereoisomer over the other as a result of the influence of a chiral feature present in the substrate, reagent, catalyst or environment.
- When 2-phenylpropionaldehyde (1, racemic but (R)-enantiomer shown) was reacted with the phenylmagnesiumbromide, 1,2-diphenyl-1-propanol (2) is produced as a mixture of diastereomers, predominantly the threo isomer.
- The preference for the formation of the threo isomer can be explained by having the nucleophile attacking the carbonyl group from the least hindered side.



Optical purity and enantiomeric excess

- Enantiomers rotate plane of polarised light in opposite directions



- Optical purity:

$$optical\ \ purity = \frac{[\alpha]_{measured}}{[\alpha]^{pure}_{enantiomer}} \times 100\%$$

- Enantiomeric excess (*e.e.*)

$$e.e. = \frac{[R]-[S]}{[R]+[S]} \times 100\%$$

[*R*] = concentration of the R-isomer

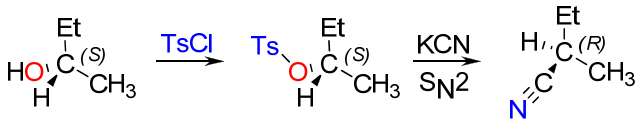
[*S*] = concentration of the S-isomer

UNIVERSITY OF EASTERN FINLAND

Absolute and Relative Configurations

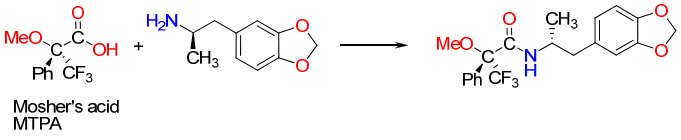
The relative configurations of optically active compounds can be measured by interconverting them to known compounds

– The reaction of an alcohol with TsCl is known to occur with retention of configuration (stereogenic center has not been altered). The reaction of the tosylate with nitrile occurs with inversion (the stereogenic center has been altered). ***The absolute configuration of the parent is known while only the relative configurations of the tosylate and the nitrile are known.***



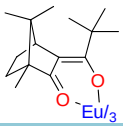
Resolution of enantiomers by NMR

- Chiral derivatising agents for NMR
  - The one most commonly used is MTPA or Mosher's acid
  - ^{19}F NMR gives one signal for each diastereoisomer



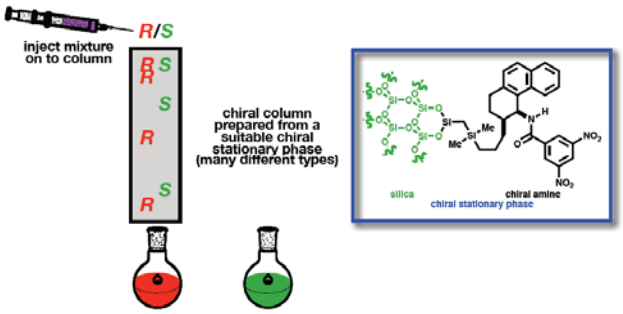
Mosher's acid
MTPA

  - Chiral shift reagents: paramagnetic lanthanide complexes can bind reversibly to certain chiral molecules via the metal centre
  - Two diastereomeric complexes are formed on coordination; these may have different NMR signals



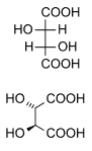
Resolution of enantiomers by chiral chromatography

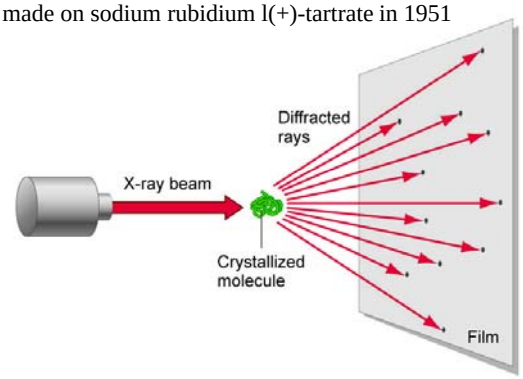
- Normally HPLC or GC
- A racemic solution is passed over a chiral stationary phase
- Compound has rapid and reversible diastereotopic interaction with stationary phase: matched S-enantiomer travels slowly whereas mis-matched R-enantiomer is readily eluted



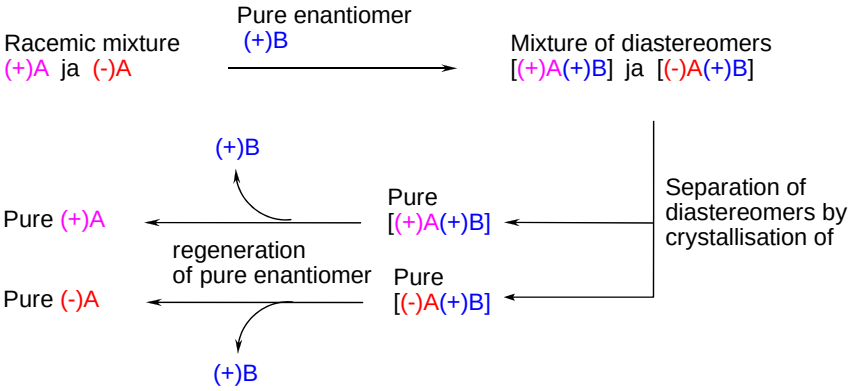
The Use of X-ray Crystallography to Determine Absolute Configuration

- **X-ray crystallography** is a method of determining the arrangement of atoms within a crystal, in which a beam of X-rays strikes a crystal and causes the beam of light to spread into many specific directions
- The first determination of an absolute configuration by anomalous dispersion of X-rays was made on sodium rubidium l(+)-tartrate in 1951



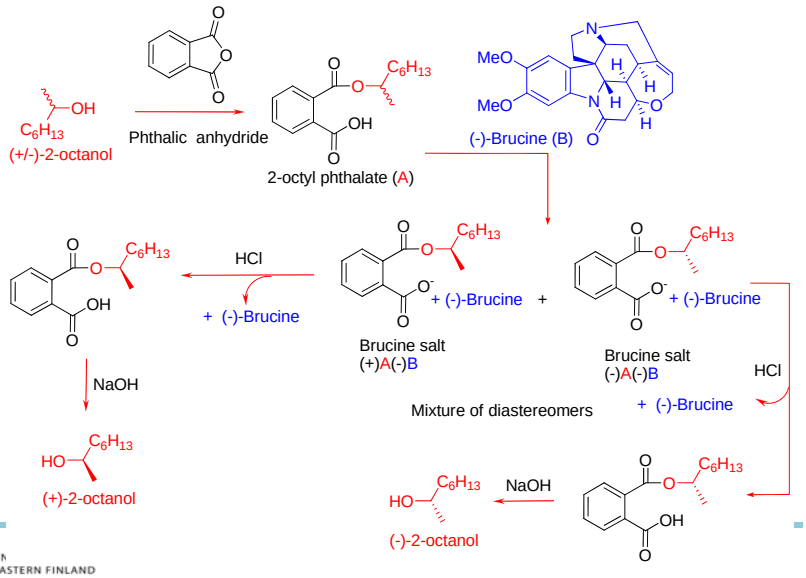


Resolution can be used to separate enantiomers



UNIVERSITY OF EASTERN FINLAND

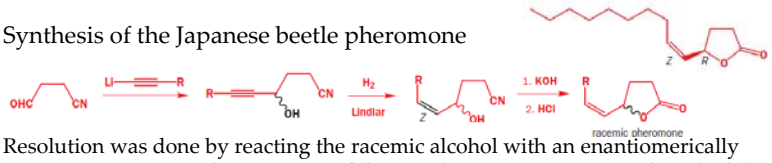
Example of resolution: 2-octanol



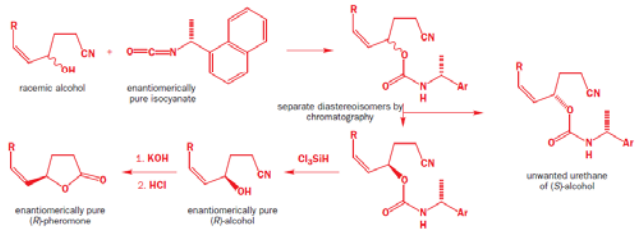
UNIVERSITY OF EASTERN FINLAND

Resolution of Japanese beetle pheromone

- Synthesis of the Japanese beetle pheromone

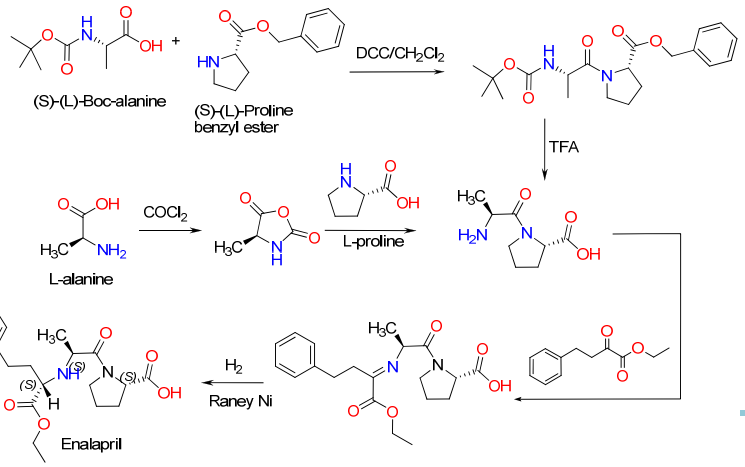


- Resolution was done by reacting the racemic alcohol with an enantiomerically pure isocyanate to make a mixture of the two diastereoisomeric amides which he then separated by chromatography. The resolving agent was removed from one of the diastereoisomers to give a single enantiomer of the alcohol, which could be cyclized to the natural (R)-pheromone using base and then acid.



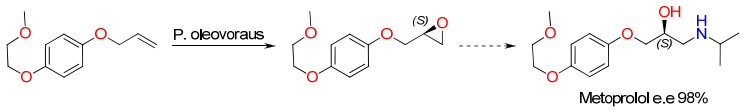
Use of an enantiomerically pure natural products as starting materials

- Enalapril is prepared by a diastereoselective reductive amination between ethyl-2-oxo-4-phenylbutyrate and alanyl-proline favoring the desired (S,S,S)-enantiomer (17:1)

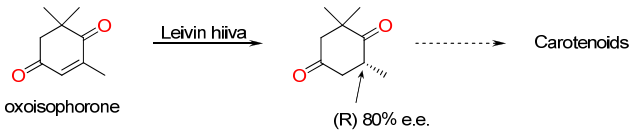


Enzymatic resolution

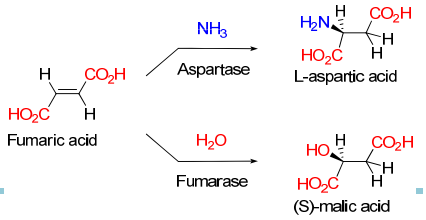
- **Oxidation:**



- **Reduction:**

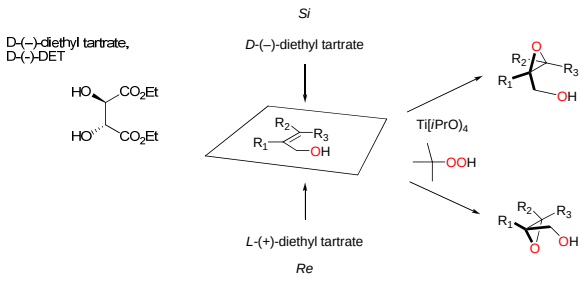


- **Addition** of ammonia (by aspartase) to fumaric acid to form L-aspartic acid or addition of water (by fumarase) to (S)-malic acid

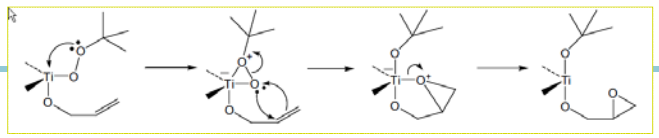


Kinetic resolution

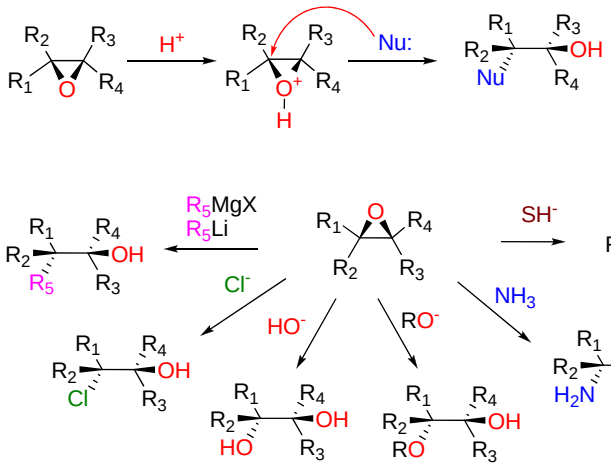
- Sharpless Asymmetric Epoxidation
  - Racemic allylic alcohols are treated with a half equivalent of terr-butyl hydroperoxide in the presence of chiral catalysts, titanium tetraisopropoxide complexed with D- or L-ethyl tartrate.



Mechanism

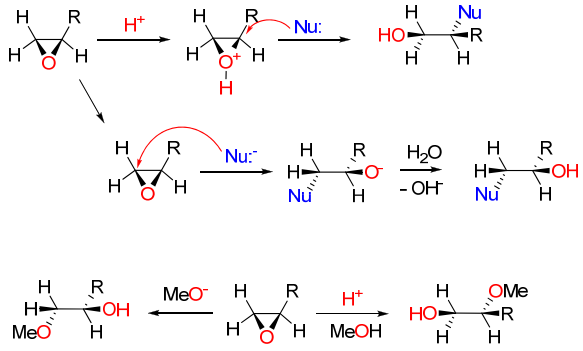


Epoxide Reactions:

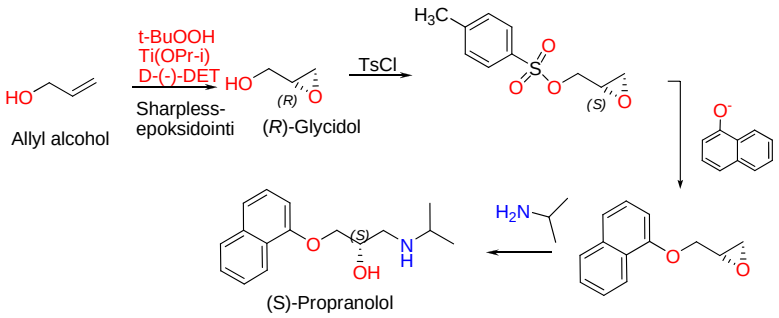


Epoxide Reactions:

- Under acidic conditions, the nucleophile attacks the carbon that will form the most stable carbocation, i.e. the *most substituted* carbon (SN1 like). Under basic conditions, the nucleophile (usually with reactive anions like RMgX, RLi, $LiAlH_4$, HO-, RO-) attacks the *least substituted* carbon (SN2 like).



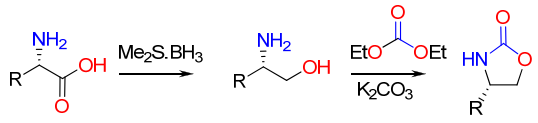
Synthesis of (*S*)-propranolol by Sharpless epoxidation



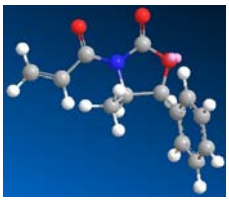
Klunder, J. M.; Ko, S. Y.; Sharpless, K. B.
J. Org. Chem. 1986, 51, 3710

Asymmetric synthesis via chiral auxiliaries

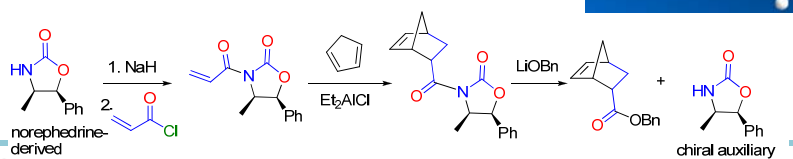
- The oxazolidinone chiral auxiliaries were developed by David Evans at Harvard University
- Synthesized from amino acid or norephedrine



R= i-Pr (valine), Bn (phenylalanine)



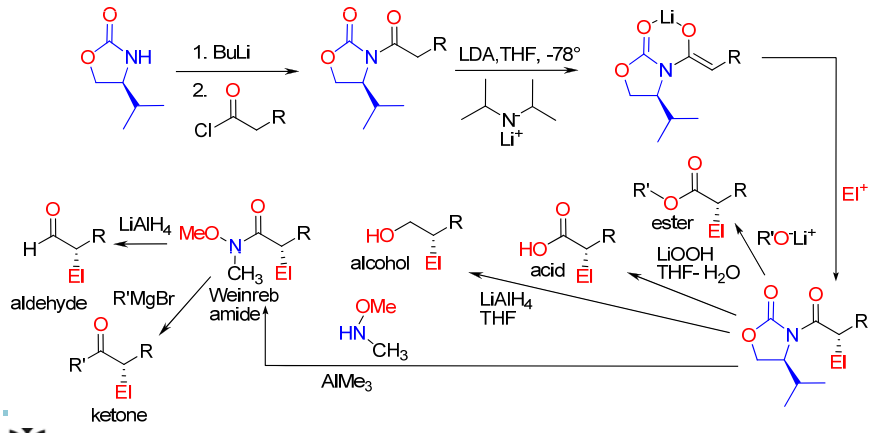
- Asymmetric Diels–Alder reaction



Evans, D. A. *Aldrichimica Acta* 1982, 15, 23)

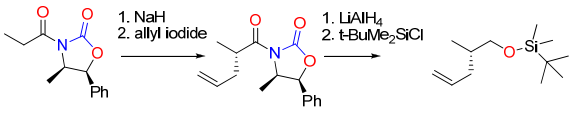
Evans's oxazolidinone chiral auxiliary

- Treatment with base (usually LDA) at low temperature produces an enolate, which is attacked by electrophiles on only one face of the enolate
- Many methods are available for the cleavage of the auxiliary

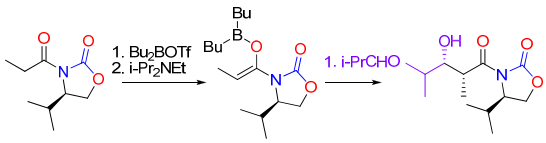


Evans's oxazolidinone chiral auxiliary

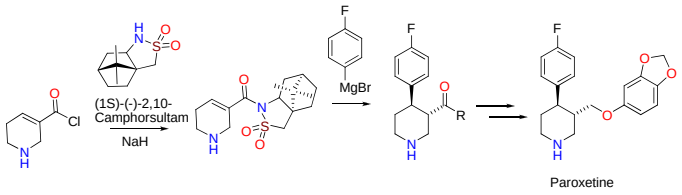
- For the synthesis of antibiotic X-206 is needed chiral alcohol, which is made by a chiral-auxiliary-controlled alkylation, followed by reduction to give the alcohol.



- Aldol reactions of chiral borinate enols

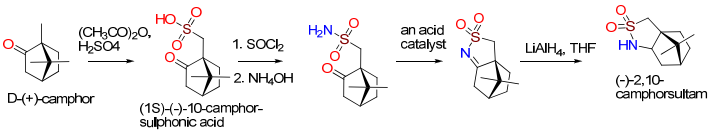


Asymmetric synthesis of paroxetine using Oppolzer's camphor sultam



Tetrahedron Letters 44(28), 5355-5358

- Synthetic Route to Oppolzer's Camphor Sultam

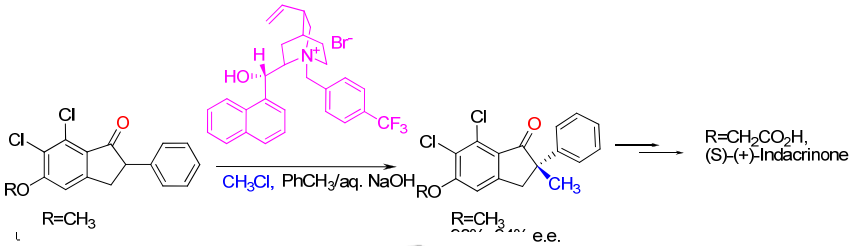


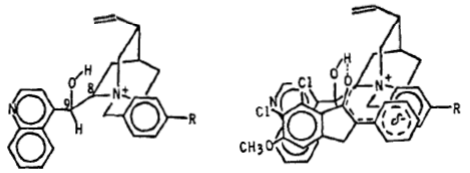
UNIVERSITY OF EASTERN FINLAND

16.2.2012

Asymmetric Alkylation of Enolates

- Merck's synthesis of (+)-Indacrinone: first efficient phase-transfer catalysed asymmetric enolate alkylation based on a quaternary ammonium salt derived from a naturally occurring cinchona alkaloid.





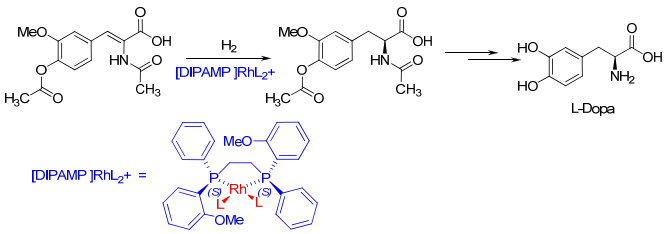
Chem. Rev. **2003**, *103*, 3013-3028
J. Am. Chem. Soc. **1984**, *106*, 446-447

Figure 1. Ion pairing between indanone anion and benzyl cinchoninium cation.

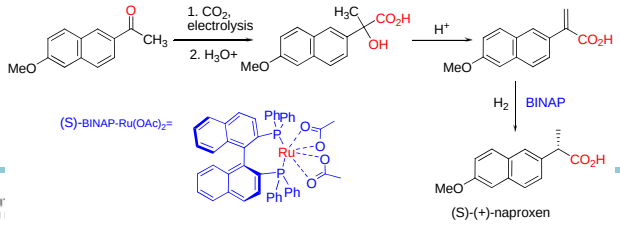
EASTERN FINLAND

Asymmetric reductions

- The Monsanto synthesis of L-DOPA using catalytic asymmetric hydrogenation.



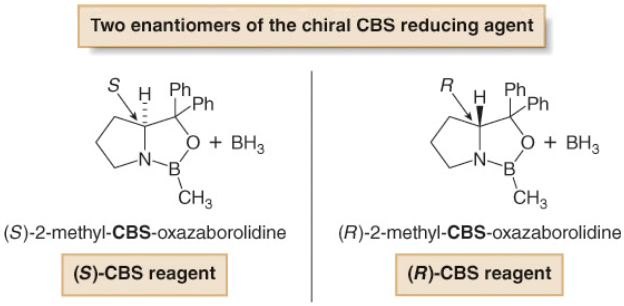
- *(S)*-Naproxen is produced in high yield and high enantiomeric excess using Noyori's BINAP-catalyst



UNIVERSITY OF EASTERN

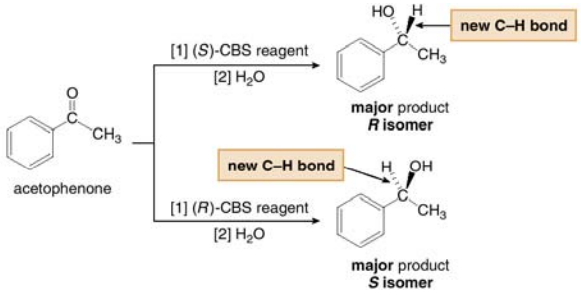
Enantioselective Carbonyl Reductions

- An example of chiral reducing agents are the enantiomeric CBS reagents



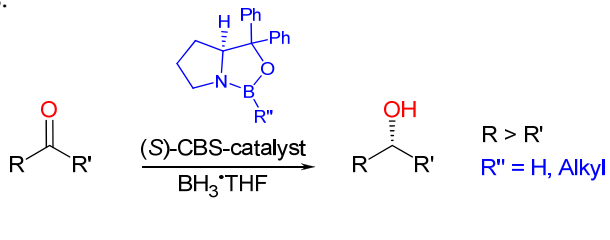
Enantioselective Carbonyl Reductions

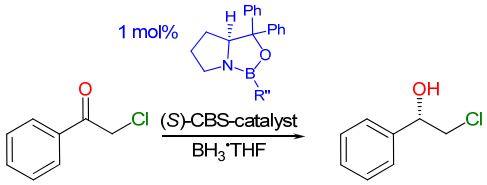
- The (*S*)-CBS reagent delivers H:- from the front side of the C=O. This generally affords the R alcohol as the major product.
- The (*R*)-CBS reagent delivers H:- from the back side of the C=O. This generally affords the S alcohol as the major product.



Corey-Bakshi-Shibata Reduction

- The enantioselective reduction of ketones using borane and a chiral oxazaborolidine as catalyst (CBS Catalyst). Used also for imines and oximes.

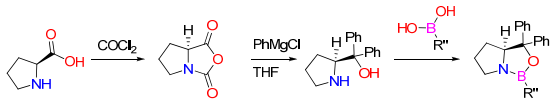




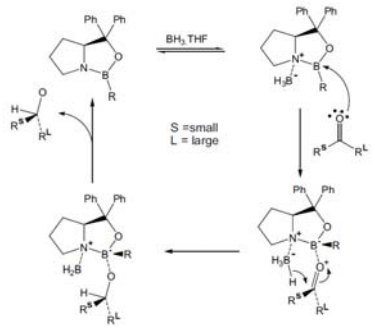
E. J. Corey, S. Shibata, R. K. Bakshi, J. Org, Chem., 1988, 53, 2861-2863

Preparation and mechanism of CBS Catalyst

- Oxazaborolidine is derived from the proline in two steps by reacting the prolinol with an alkylboronic acid [$RB(OH)_2$]

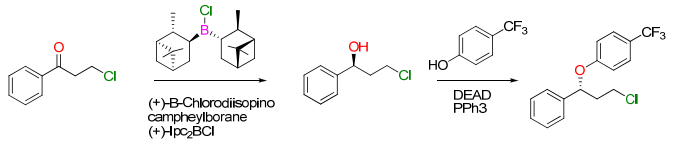


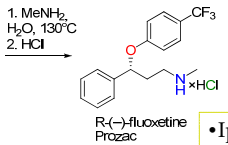
Mechanism:

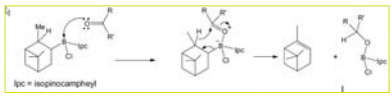


Synthesis of R-(–)-fluoxetine

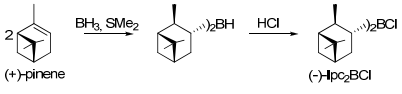
- **Diisopinocampheylchloroborane (Ipc_2BCl) as a chiral reducing reagent for the synthesis of halo alcohols.**







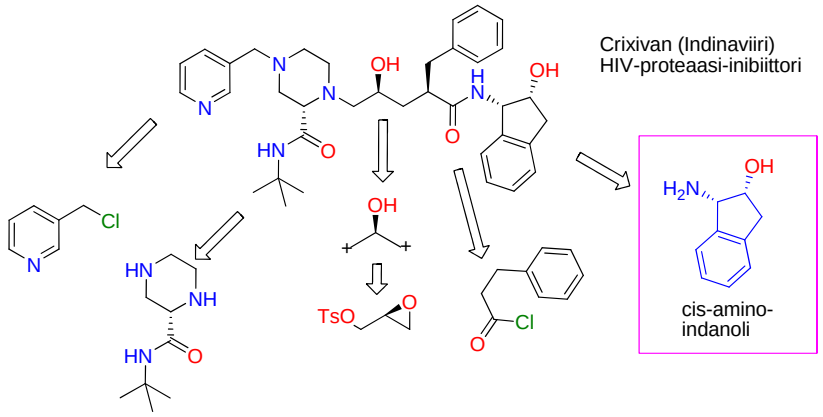
•Ipc_2BCl can be synthesized from pinene



M. Srebnik, P.V. Ramachandran & H.C. Brown, *J. Org. Chem.*, ***1988, 53, 2916***

Synthesis of Indinavir

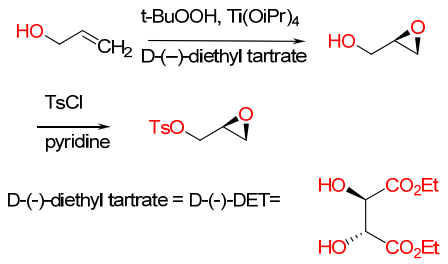
- Retrosynthesis



UNIVERSITY OF EASTERN FINLAND

Synthesis of Indinavir

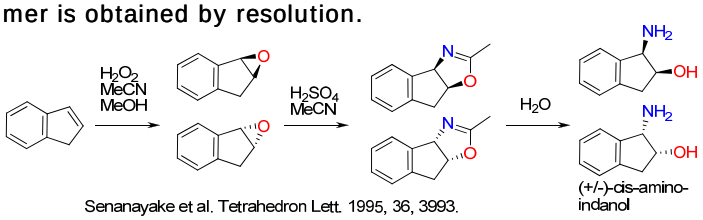
- The central epoxide carrying a tosylate leaving group can easily be made from the epoxyalcohol, which is made by **Sharpless asymmetric epoxidation** of allyl alcohol.



UNIVERSITY OF EASTERN FINLAND

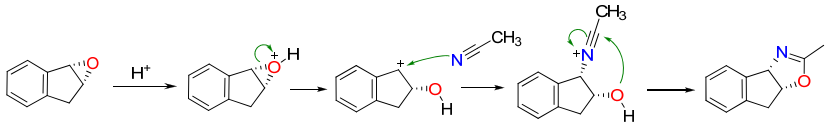
Synthesis of Indinavir

- **Synthesis of cis-aminoindanol** from indene epoxide with MeCN gives a cis product (Ritter reaction). The (1S, 2R)-isomer is obtained by resolution.



Senanayake et al. Tetrahedron Lett. 1995, 36, 3993.

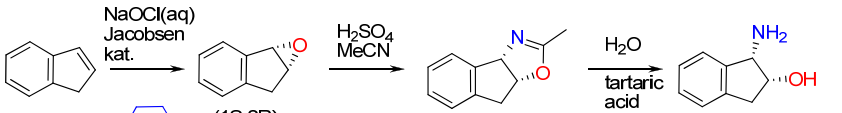
- Mechanism of Ritter reaction

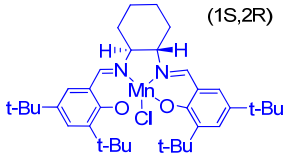


UNIVERSITY OF EASTERN FINLAND

Synthesis of Indinavir

- Jacobsen chiral epoxidation, the (salen)Mn-catalyzed epoxidation yield the (1S, 2R)-isomer





Jacobsen catalyst

Jacobsen et al. J. Am. Chem. Soc. 1991,113, 7063-7064.

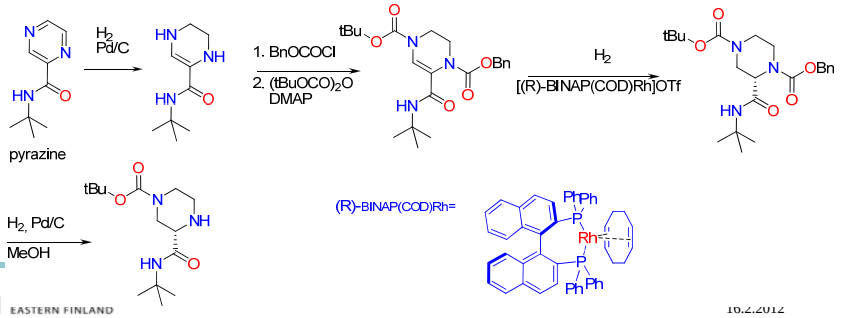
Organic Syntheses, Vol. 76, 46

UNIVERSITY OF EASTERN FINLAND

16.2.2012

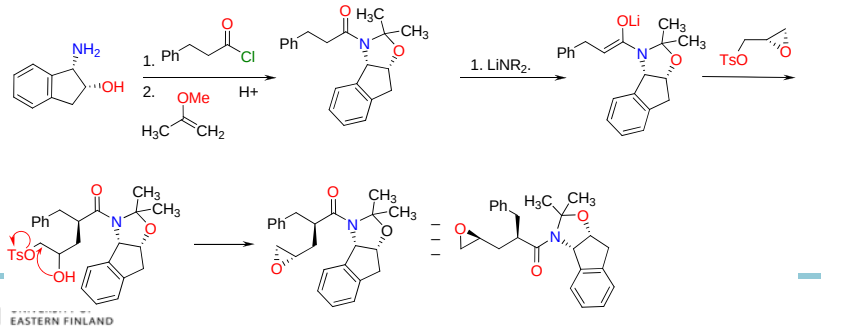
Synthesis of Indinavir

- The piperazine fragment has two nucleophilic nitrogen atoms, which will both need different protecting groups: the more nucleophilic nitrogen was protected with benzyl chloroformate Cbz and the less reactive nitrogen with a Boc group, using DMAP as a nucleophilic catalyst.
- Single enantiomer is made by enantioselective hydrogenation using BINAP–metal complex. A further hydrogenation step allowed selective removal of the Cbz group.



Synthesis of Indinavir

- Amino-alcohol function as a chiral auxiliary and is acylated with the acyl chloride
- The amide was protected as a acetonide by treating with 2-methoxypropene (the methyl enol ether of acetone).
- The enolate of this amide reacts highly diastereoselectively with the epoxy-tosylate
- The more electrophilic epoxide is opened first giving an alkoxide, which closes again to give a new epoxide.



Synthesis of Indinavir

- The protected piperazine react with the epoxide, and the product was treated with acid to deprotect both the second piperazine nitrogen and the acetonide group. The amine was alkylated with the 3-chloromethyl pyridine.