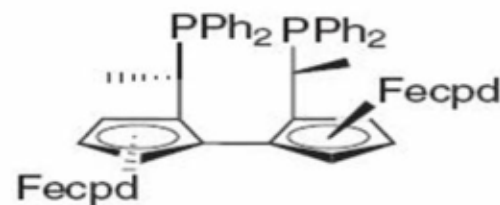
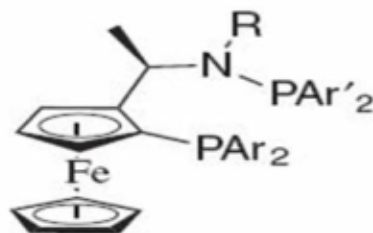
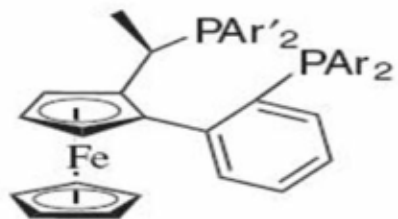
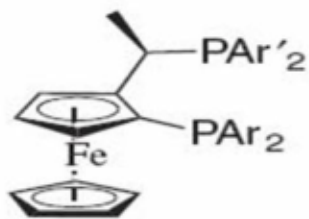
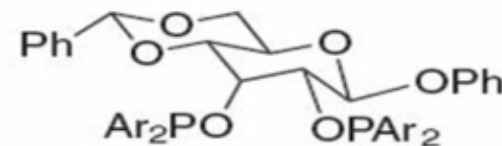
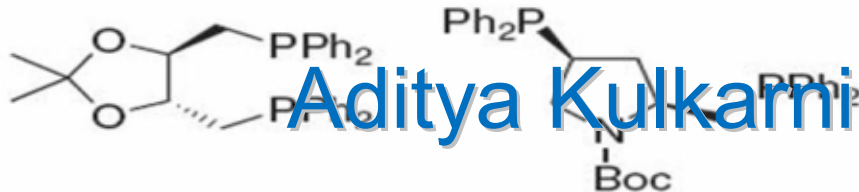
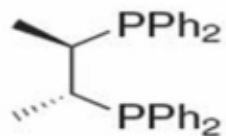
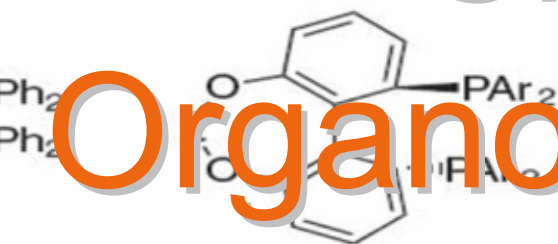


Chiral Organocatalysis

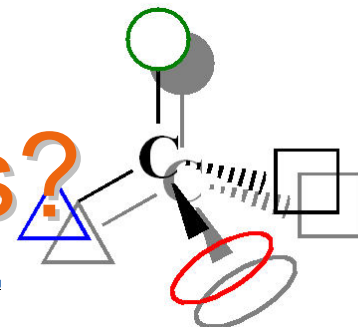


Aditya Kulkarni

Outline

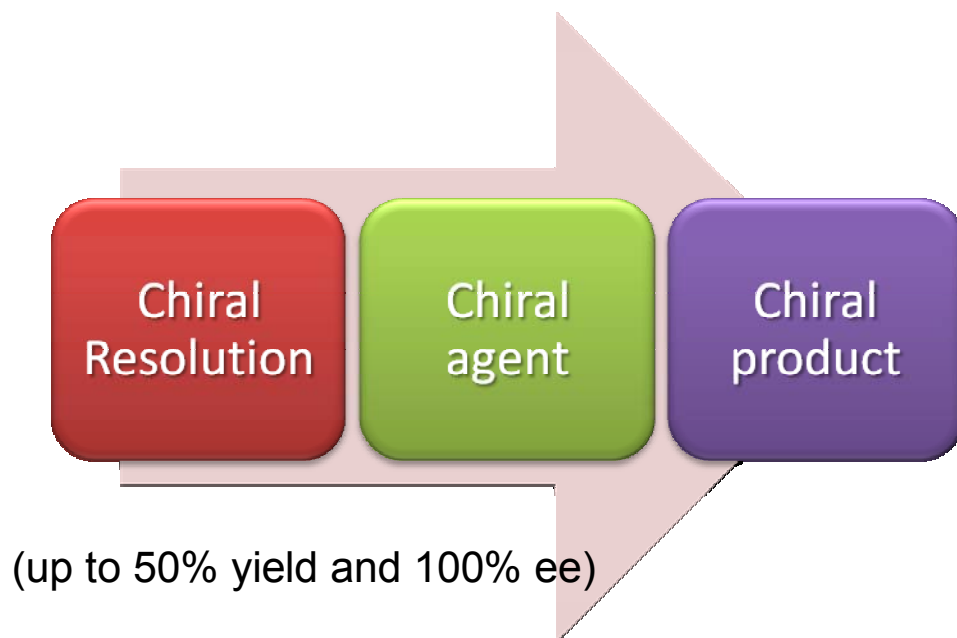
- Importance of asymmetric synthesis
- Organocatalysis and organocatalysts
- Comparison with conventional catalysis
- Advantages of organocatalysts
- Large scale organocatalytic reaction processes

Why asymmetric synthesis?

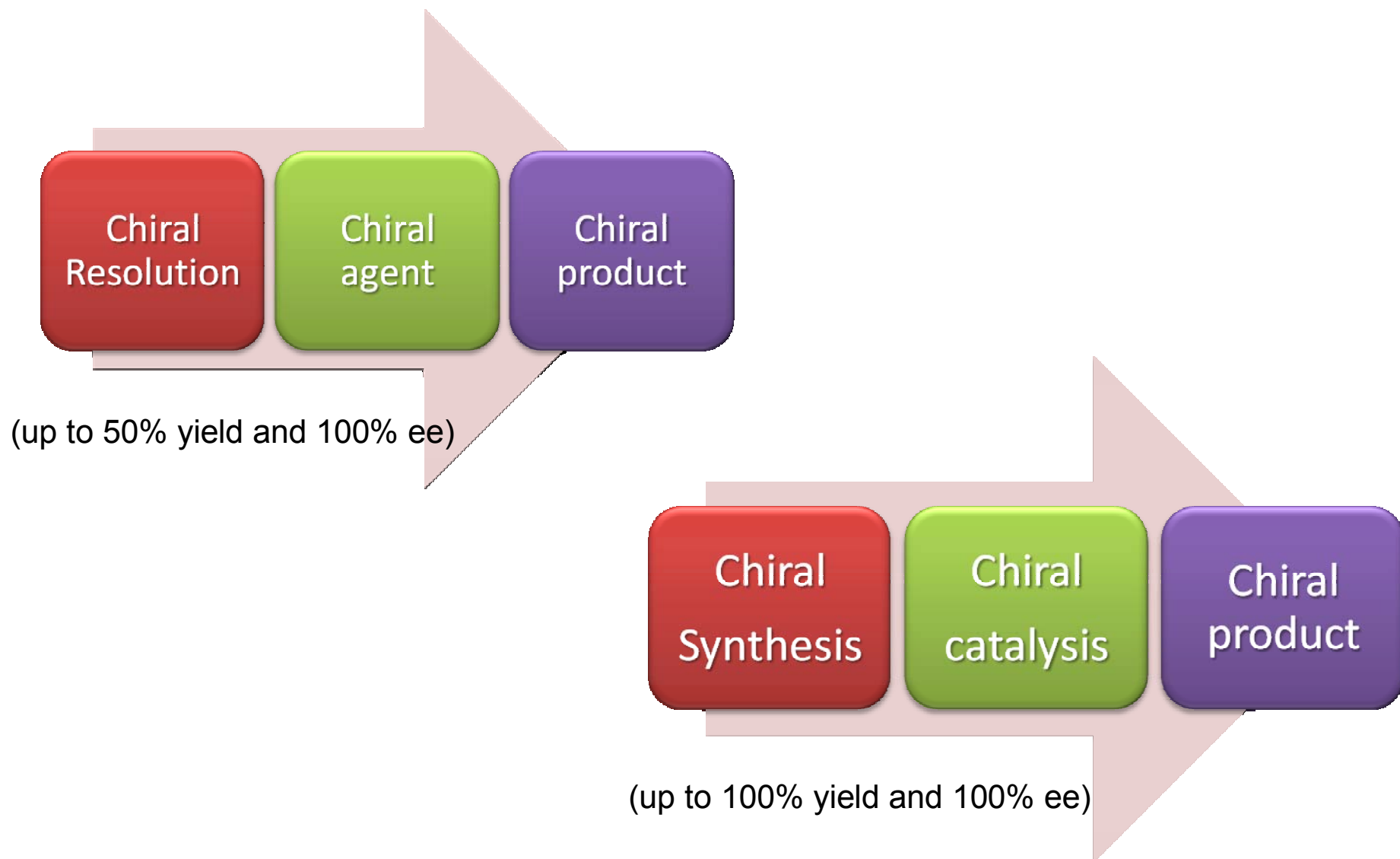


- Different enantiomers or diastereomers of a molecule often have different biological activity
- Synthesis of chiral drugs - \$18 billion annually (growing @ 9.04% p.a.)
- Predicted that 75% of the drugs will be sold as single enantiomers in the coming years

Why asymmetric synthesis?



Why asymmetric synthesis?



Asymmetric catalysis

- Organometallic catalysis

- Enzyme catalysis



organocatalysis

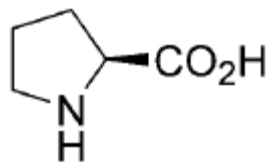
What is Organocatalysis?

- A concatenation of the terms “organic” and “catalyst”
- In organic chemistry, the term Organocatalysis refers to a form of catalysis, whereby the rate of a chemical reaction is increased by an organic catalyst consisting (mainly) of carbon hydrogen, sulfur, nitrogen, oxygen and phosphorus.
- “Metal free catalysis”

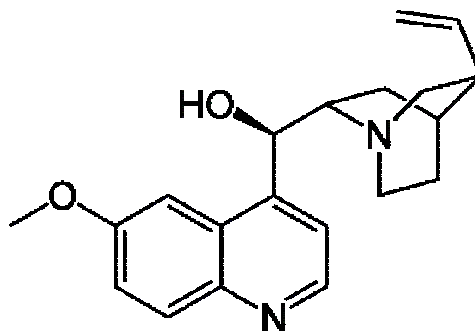
What is an Organocatalyst?

- An organocatalyst is an organic molecule that does not contain a metal which in substoichiometric amounts accelerates the reaction
- Usually a low molecular weight compound
- Two types:
 - Achiral
 - Chiral

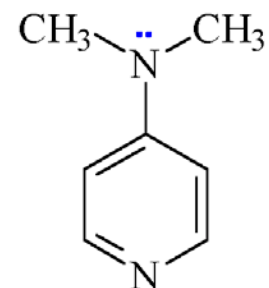
Few examples..



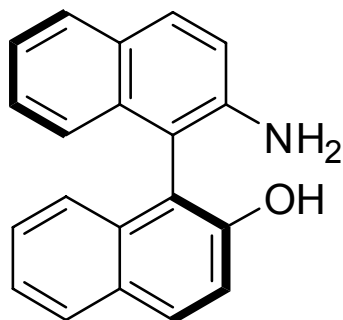
L-proline



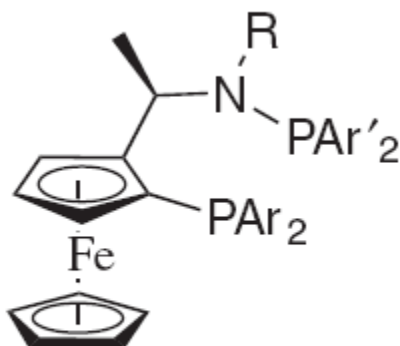
quinine



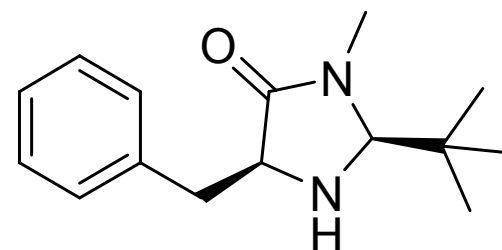
DMAP



Nobin

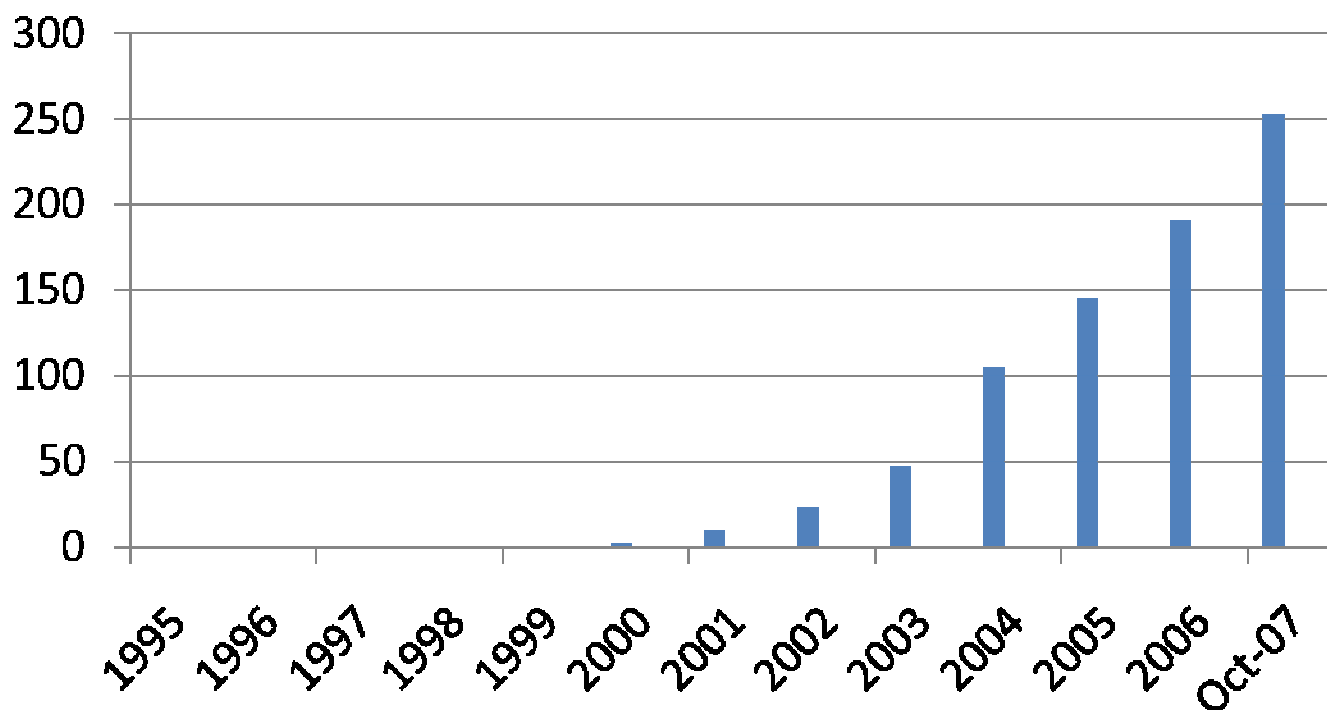


BOPHOZ



Macmillan's catalyst

Increasing popularity



Number of articles per year focusing on number of the use of organocatalytic concept

Primary attractions of organocatalysis

- Usually robust
- Inexpensive
- Readily available
- Non-toxic
- Able to bring about transformations that were not known earlier

Primary attractions of organocatalysis

- Inertness towards moisture and oxygen
- Demanding reaction conditions (inert atmospheres, low temperatures, absolute solvents etc.) are usually not required
- Absence of transition metals – attractive for synthesis of pharmaceutical products

Comparison with conventional catalysis

Type	Advantage	Disadvantage
Organometallic catalysis	Wide substrate scope high catalytic activity	Tedious process, potential heavy metal pollution
Enzyme catalysis	High selectivity & catalytic activity	Limited substrate scope Usually single enantiomer
<i>Organocatalysis</i>	Simple structure, inexpensive, natural molecules, nontoxic.	

Pharmaceutical Roundtable

ACS Green Chemistry Institute Pharmaceutical Roundtable



Mission:

To catalyze the implementation of green chemistry and engineering in the pharmaceutical industry globally.

Brainstorm Output

•Organocatalysis

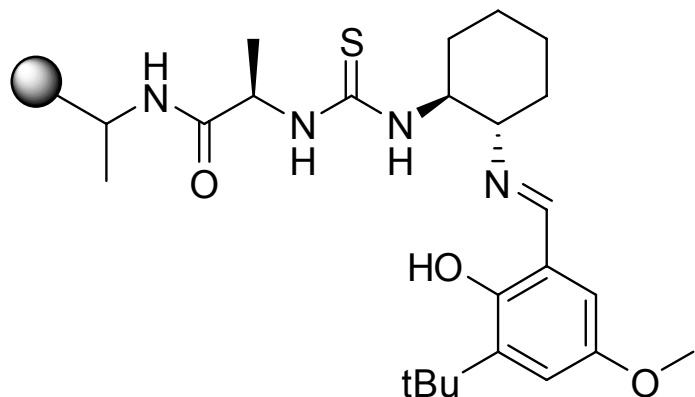
- Asymmetric Hydrocyanation
- Aldehyde or Ketone + NH_3 + "X" to give a chiral amine
- N-Centred chemistry avoiding azides hydrazines etc
- Asymmetric Hydrolysis of nitriles
- Asymmetric Hydrogenation of unfunctionalised olefins/enamines/imines
- Asymmetric Hydroformylation
- C-H activation of aromatics
- C-H activation of alkyl groups
- New Green Fluorination Methods
- Oxygen Nucleophiles with high reactivity
- Green sources of electrophilic Nitrogen
- Asymmetric Hydroamination of olefins
- Green Mitsunobu Reactions
- Reduction of amides avoiding LAH and Diborane
- Bromination Reactions
- Sulfonation reactions
- Amide Formation avoiding poor atom economy reagents
- Nitration reactions
- F/C Reactions on unactivated substrates
- Demethylation Reactions
- Ester Hydrolysis
- OH activation for nucleophilic substitution
- Epoxidation
- Oxidation
- Wittig Chemistry without Ph_3PO
- Radical Chemistry without Bu_3SnH

Large –scale Organocatalytic Reaction Processes

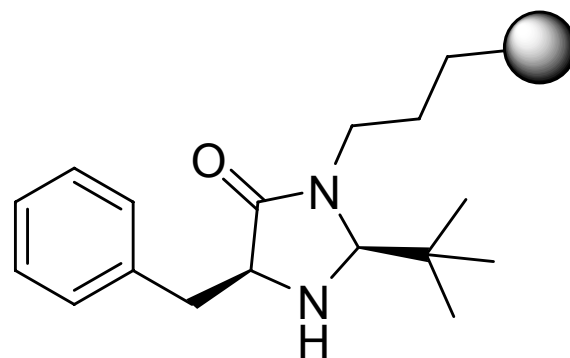
- General considerations:
 - Economy of the catalyst (Price and availability)
 - Readily available from nature's "Chiral pool" or their derivatives
 - Cheap
 - Stability of the catalysts and handling issues
 - Not moisture sensitive (serious issue for chiral metal complexes)
 - No special equipments for handling not required
 - Enantioselectivity, conversion and catalyst loading

Large –scale Organocatalytic Reaction Processes

- General considerations:
 - Recycling: Immobilization of Organocatalysts
 - Leaching problems do not occur due to covalent bonding with the support unlike metal complexes



Very efficient over 10 reaction cycles
Yield: 96-98% ee: 92-93%

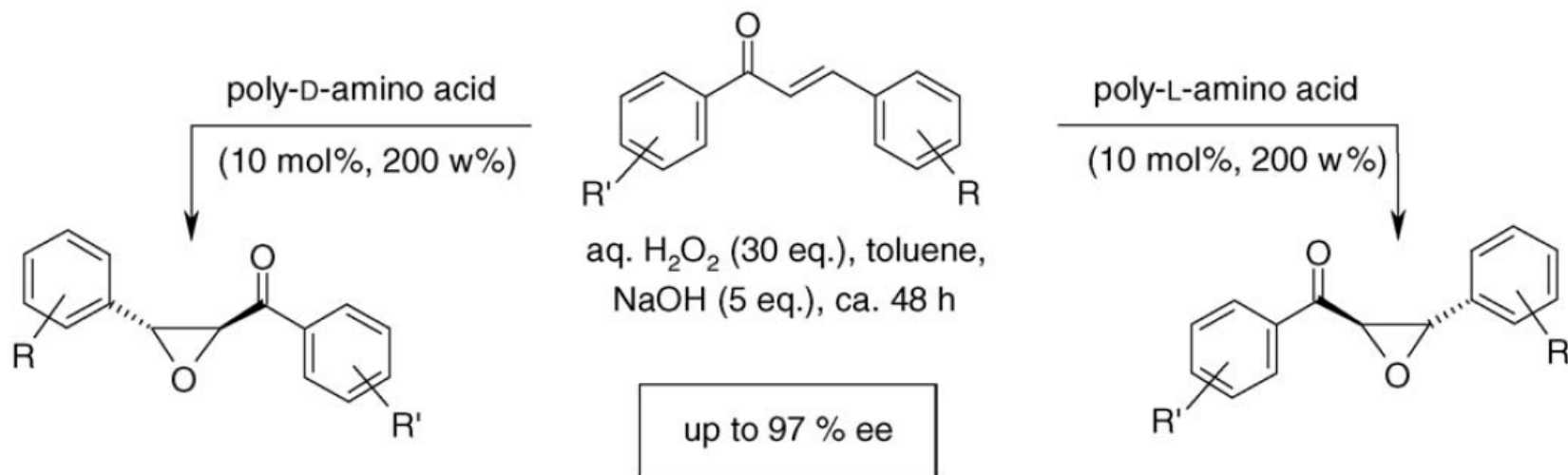


Results superior to those obtained with
analogous “free” solution-phase
catalyst

Large –scale Organocatalytic Reaction Processes

- Epoxydation of Chalcones
- Alkylation of Cyclic Ketones

Epoxydation of Chalcones



Advantages

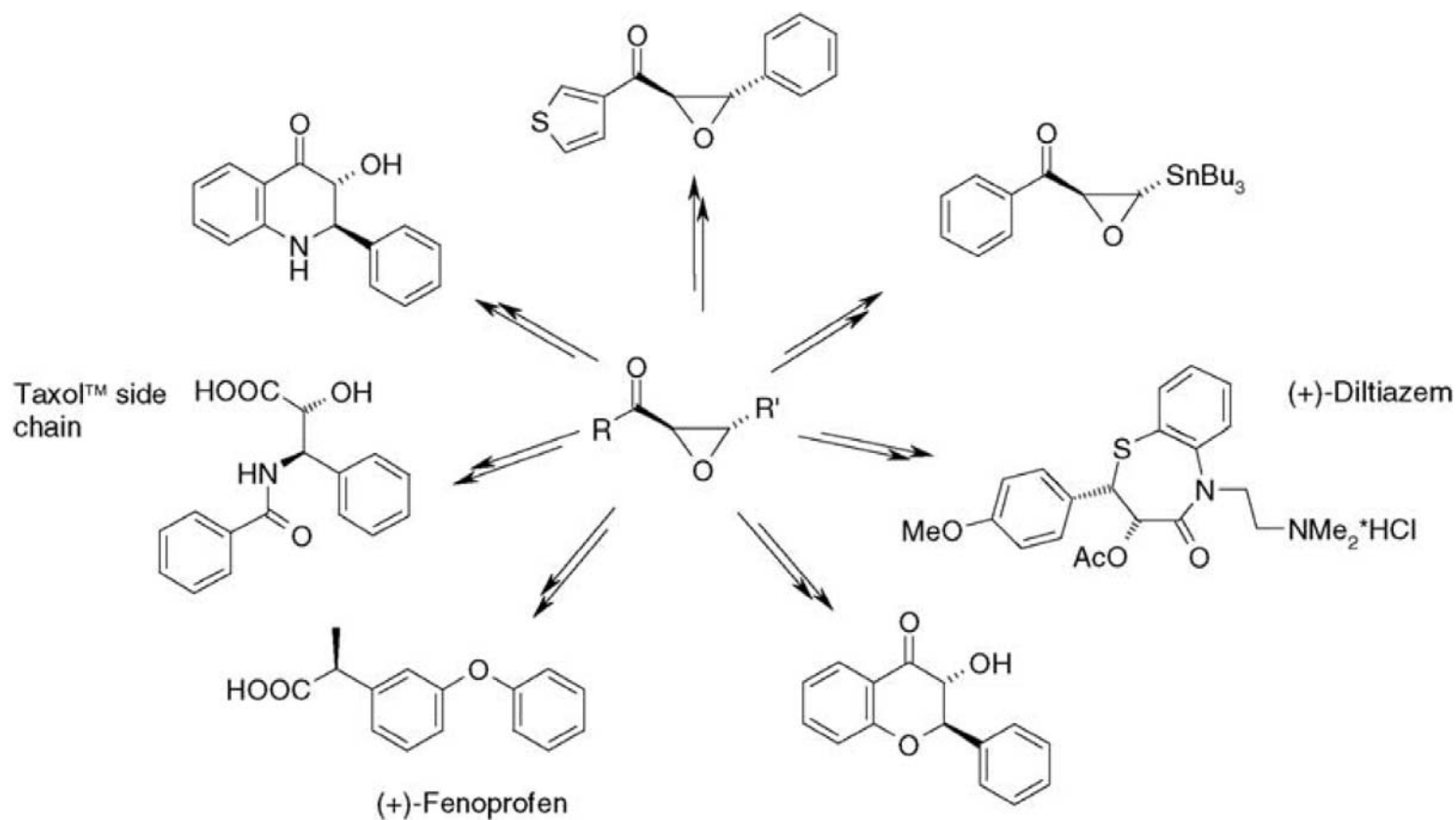
- Use of H_2O_2
- Use of organocatalyst
- Recyclability of catalyst
- High enantioselectivity

Disadvantages

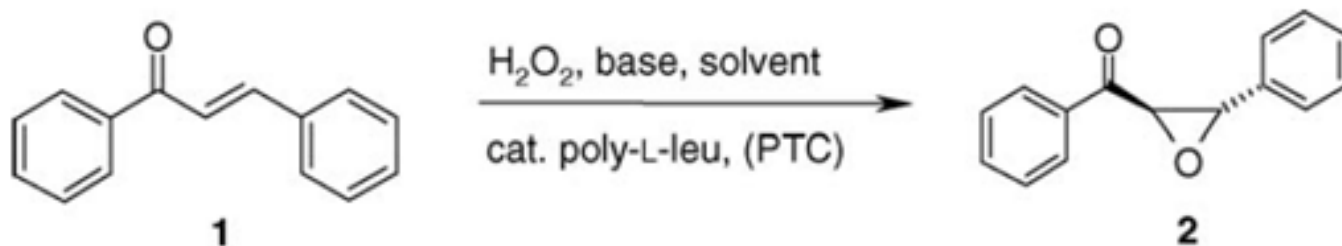
- Large excess of catalyst (up to 200%)
- Preactivation of catalyst needed (6hrs)
- Long reaction times (1-5 days)

Epoxydation of Chalcones

- Potential applications

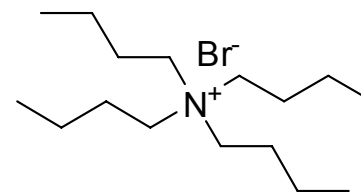
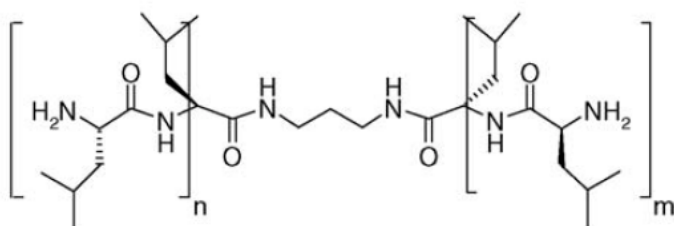


Epoxydation of Chalcones



H_2O_2 : 1.3 eq, NaOH: 1.3eq, cat: 0.35-0.7mol%, PTC: 11mol% at room temperature

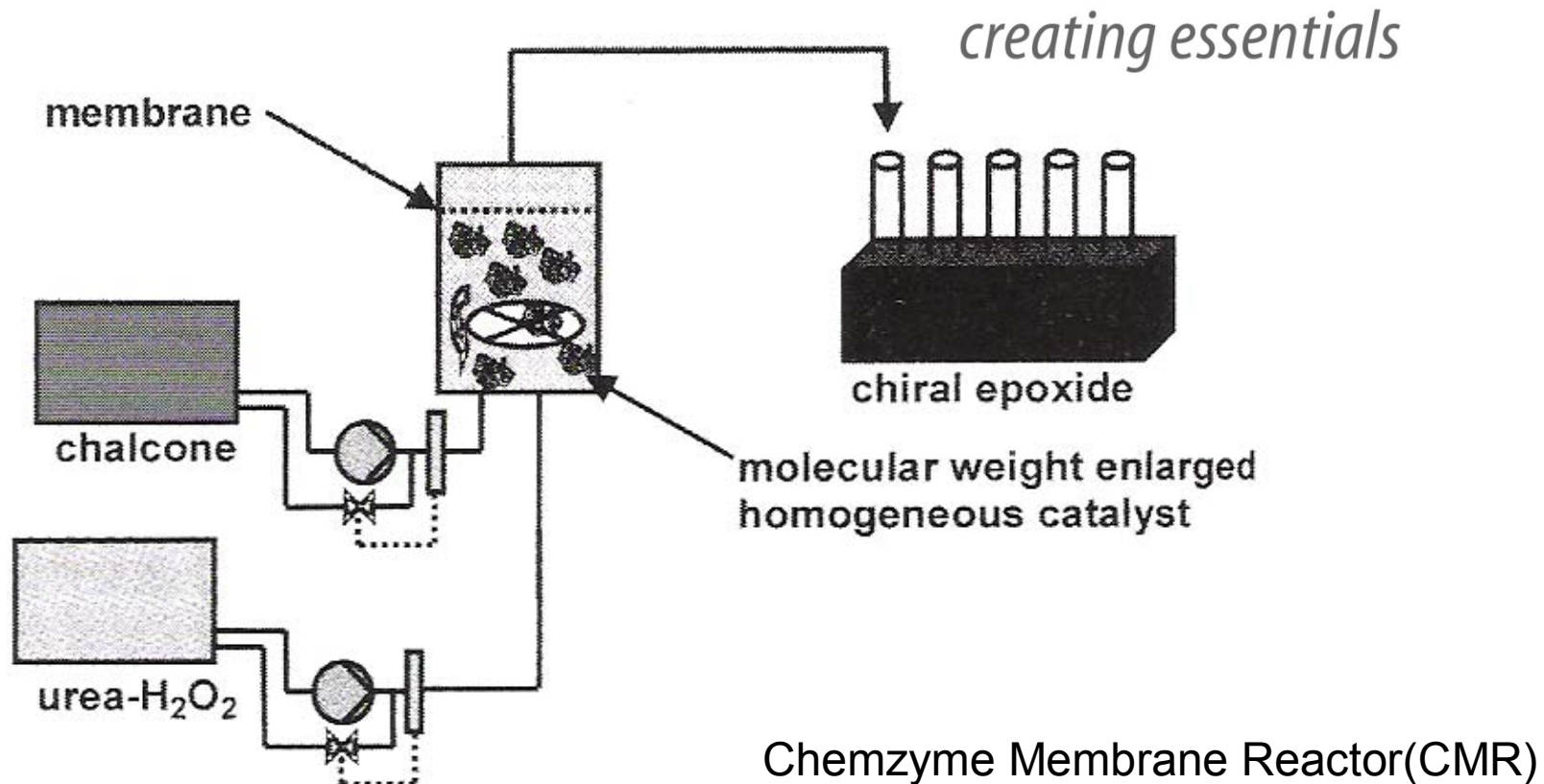
Entry	Catalyst	Time (min)	Result
1	Standard poly-L-leu	90	2% conversion, ee not evaluated
2	ht-Poly-L-leu	90	59% conversion, ee = 91%
3	ht-Poly-L-leu + TBAB	7	>99% conversion, ee = 94%



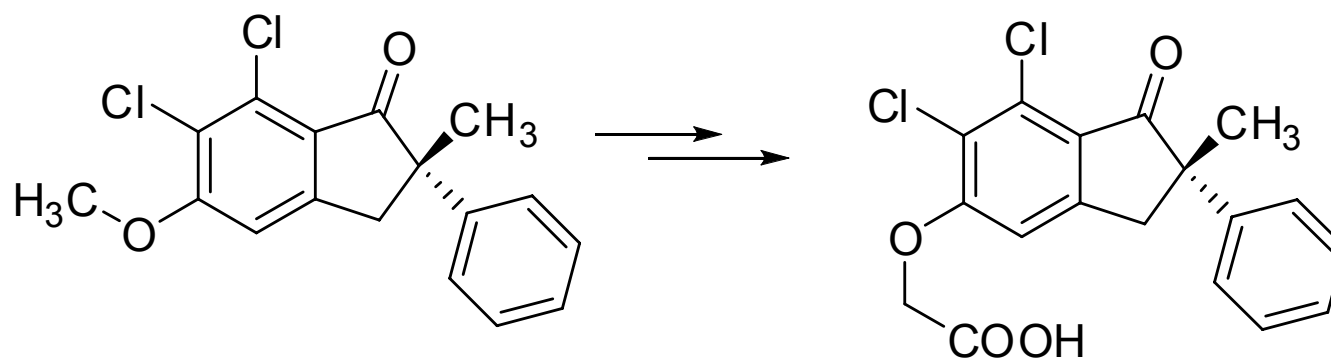
tetrabutylammonium bromide

Epoxydation of Chalcones

degussa.

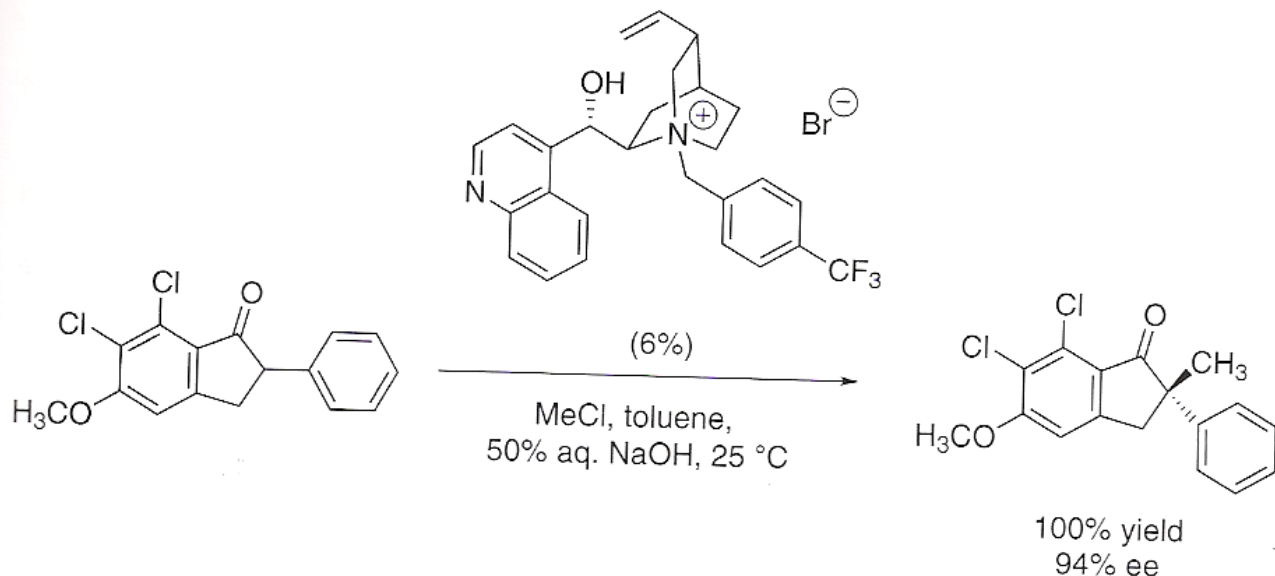


Alkylation of Cyclic Ketones



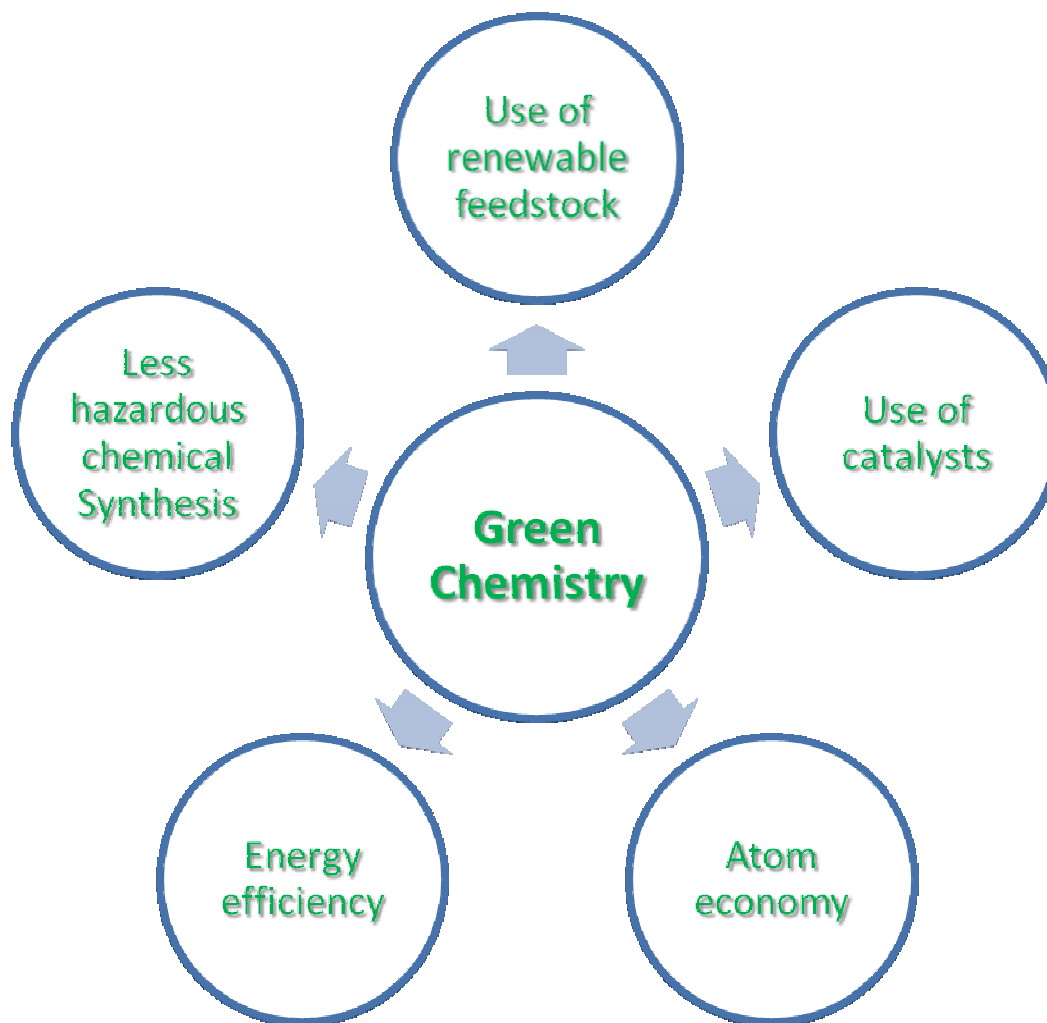
- Synthesis of Indacrinone

Alkylation of Cyclic Ketones



- First highly asymmetric PTC-catalyzed alkylation
- First organocatalytic synthesis applied on a large scale
- Highly efficient (100% yield, 94% ee)

Green Chemistry



Conclusion

- Asymmetric organocatalysis has matured in the recent few years into a very powerful, practical and broadly applicable third methodological approach in the catalytic asymmetric synthesis.
- Process development and scale up already achieved for several organocatalytic reactions have shown that organocatalysis can be a valuable tool for industrial-scale solutions.
- Broad variety of efficient syntheses will contribute to an increasing number of organocatalytic large-scale reactions in the future.

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Thank you!