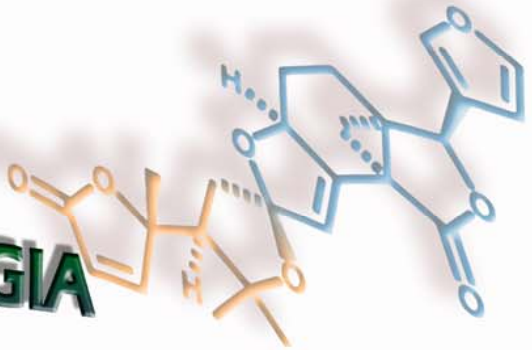
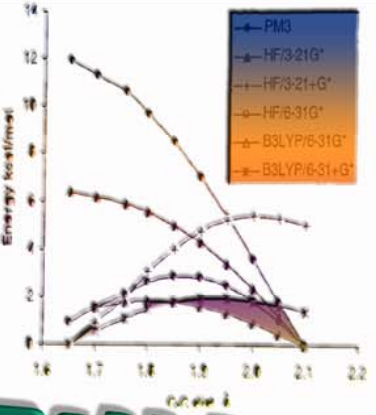
Kem-4.450 Asymmetric Synthesis

Prof. Ari Koskinen

Laboratory of Organic Chemistry



SYNTEETTINEN ORGAANINEN KEMIA

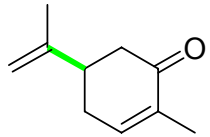


Organometallikatalyysi
Organokatalyysi
Vihreä kemia

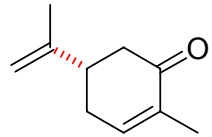
KEMIA
BIOLOGIA
FYSIIKKA

Chirality and Differing Properties

Carvone

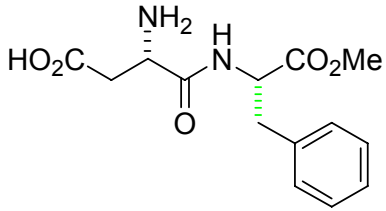


spearmint odor

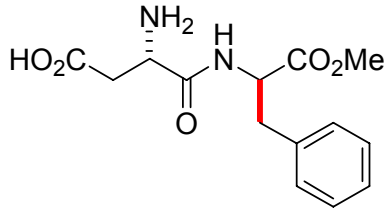


caraway

Aspartame (Nutrasweet)

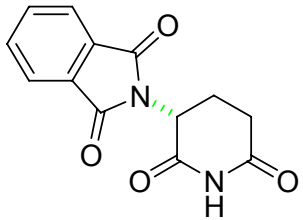


sweet

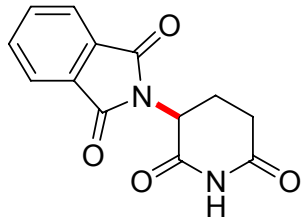


bitter

Thalidomide



sedative, hypnotic



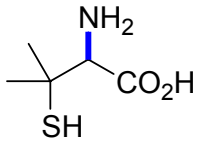
teratogenic

Pharmaceuticals

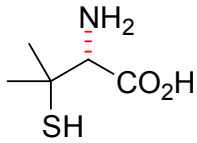
- Growing need for enantiopure compounds
- Enantiomers/diastereomers may have adverse effects
- Diastereomers usually easier to separate
- Enantiomers: FDA required

Pharmaceuticals

Penicillamine:

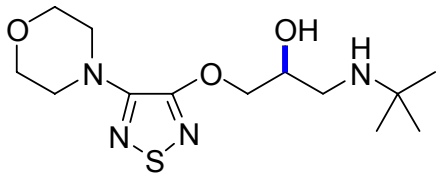


antidote for Pb, Au, Hg

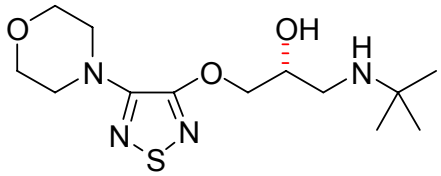


can cause optic atrophy => blindness

Timolol:



adrenergic blocker



ineffective

Sales of Enantiomeric Drugs and Intermediates

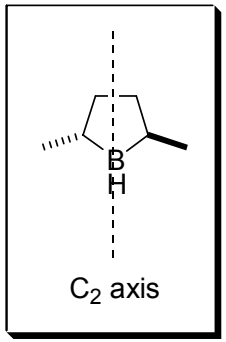
	ENANTIOMERIC INTERMEDIATES			BULK ENANTIOMERIC DRUGS		
$ MILLIONS	1999	2000	2005	1999	2000	2005
Anti-inflammatory/analgesics	$150	$156	$168	$200	$223	$241
Antiviral	794	830	1,643	983	1,180	2,054
Cancer	892	1,073	1,297	1,783	2,146	2,593
Cardiovascular	1,133	2,281	3,269	1,889	3,802	5,449
Central nervous system	1,038	1,142	1,821	1,483	1,632	2,602
Dermatology	82	85	106	164	170	212
Gastrointestinal	251	331	649	413	567	1,082
Ophthalmic	238	284	401	340	405	573
Respiratory	576	656	914	1,151	1,511	2,287
Other	140	170	356	315	426	891
TOTAL	$5,294	$7,008	$10,624	$8,721	$12,062	$17,984
SOURCE: Technology Catalysts International						

Chem. Eng. News **2001**, *79* (40), 79-97.

Asymmetric Induction - Definitions

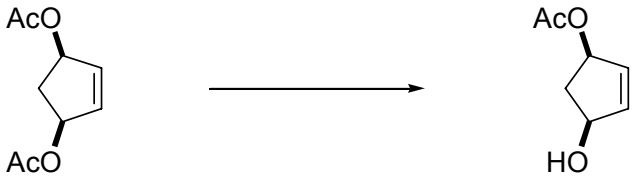
Chirality - handedness
Asymmetry - lacking all symmetry (except E)
Dissymmetry - lacking some element of symmery

NB!!! Molecules can be chiral but not asymmetric! *e.g.*



Asymmetric Induction (A.I.) - process that breaks (local) mirror symmetry

A.I. if not 1:1



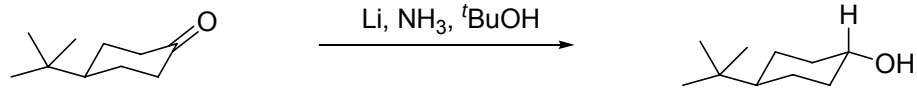
Prostaglandin synthesis intermediate
Danishefsky, S.J. *JACS* **1989**, *111*, 3456.

Specificity vs *Selectivity*

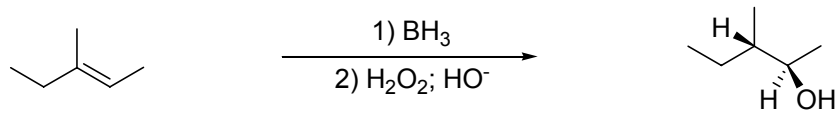
SPECIFICITY - non-statistical outcome of reaction
- **mechanism based**

SELECTIVITY - product determined by thermodynamics (product stability OR rates)

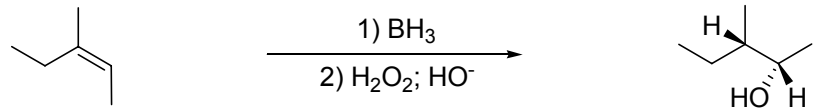
SELECTIVE PROCESS:



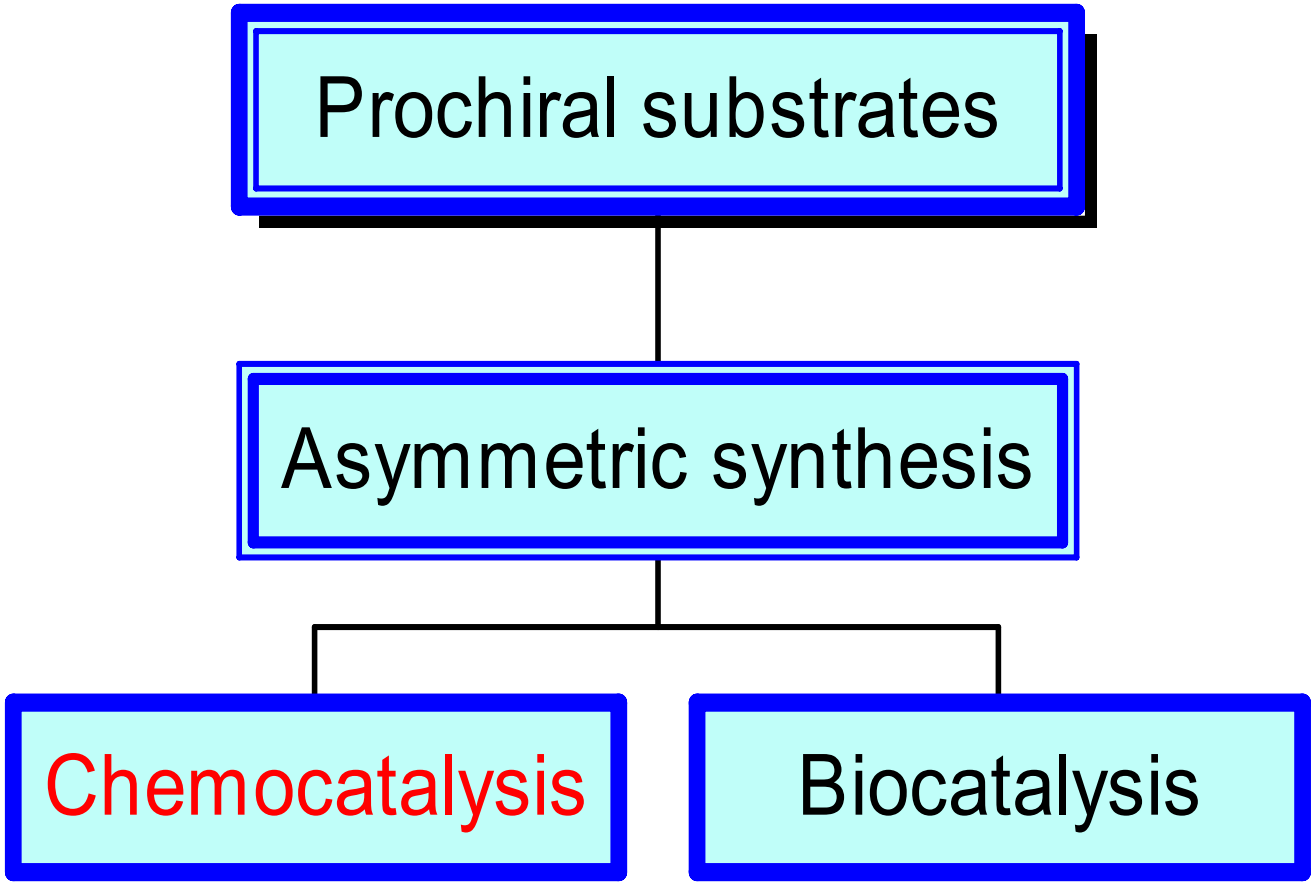
SPECIFIC PROCESS:



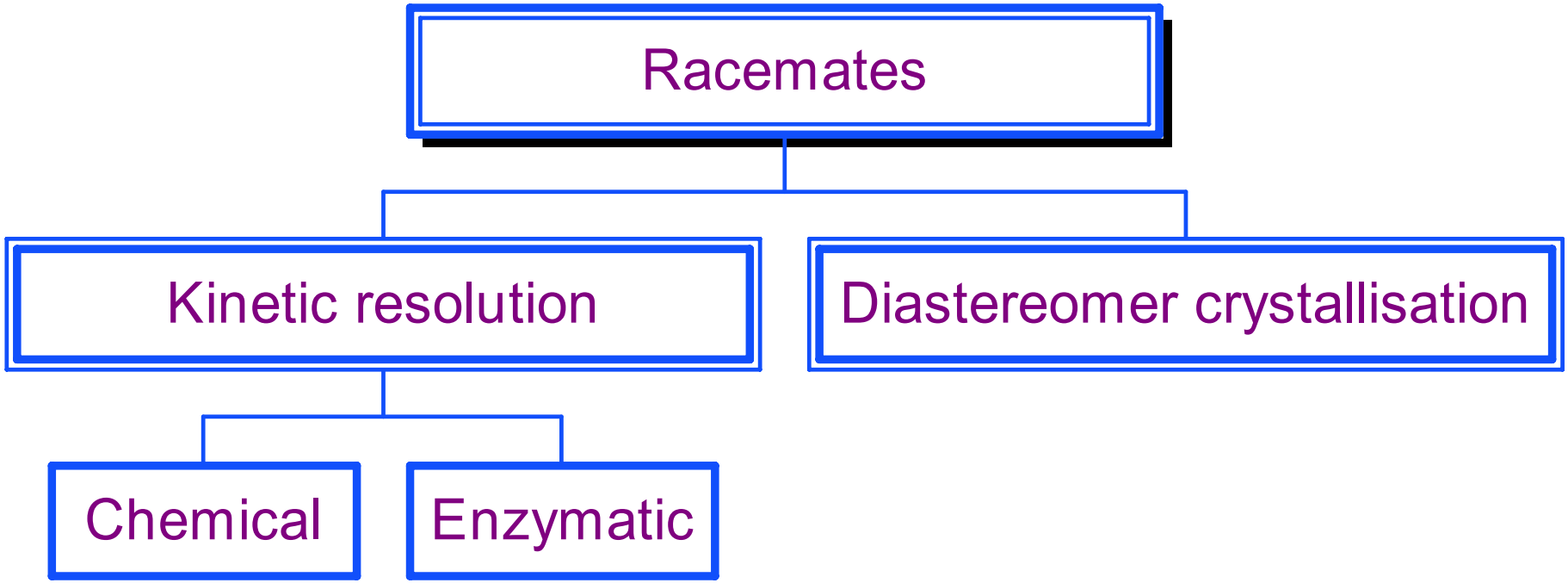
ALL *specific reactions* ***must*** *be selective, but not necessarily vice versa*
Two reactions must be carried out to determine if a process is specific



Optically Active Substances



Optically Active Substances



Enantioselective Synthesis

- **Purpose:**
  - to create single enantiomer
  - to control stereochemistry at remote sites

- **Methods:**
  - resolution
    - requires separation
    - loss of material
  - chiral pool
    - additional operations
  - asymmetric transformations (rare)
  - Asymmetric induction

Enantioselective Synthesis

For A.I. to be practical

- > 99% ee
- Access both configurations
- General transformations
- Control agent readily available
- NO added steps
- Catalysis:

Speed
Selectivity
Stability
Safety
\+ **S**ustainability

$$\frac{1}{\$}$$

Methods for Obtaining Enantiopure Compounds

- Purchase directly from a commercial supplier
- Isolate from natural sources
- Resolution
  - direct crystallization
  - diastereomeric derivatives
  - chiral chromatography
- Asymmetric Transformations
- Asymmetric Induction (AI)
  - internal a.i. (chiral SM)
  - relayed a.i. (chiral AUX)
  - external a.i. (chiral RGT)

Morrison, J.D. *Asymmetric Synthesis* vol 1, 1983, 1.

Methods for Obtaining Enantiopure Compounds

- Purchase directly from a commercial supplier

Problems: Availability, price, purity, ...

A growing number of small companies sell tailor-made specialty chemicals.

Applicable also in industry: contractors.

Methods for Obtaining Enantiopure Compounds

- Isolate from natural sources

Ideally a nearly unlimited source of new structures.

Tedious!!!

Finding the source!!!

May require vast amounts of purification, structure identification and labor.

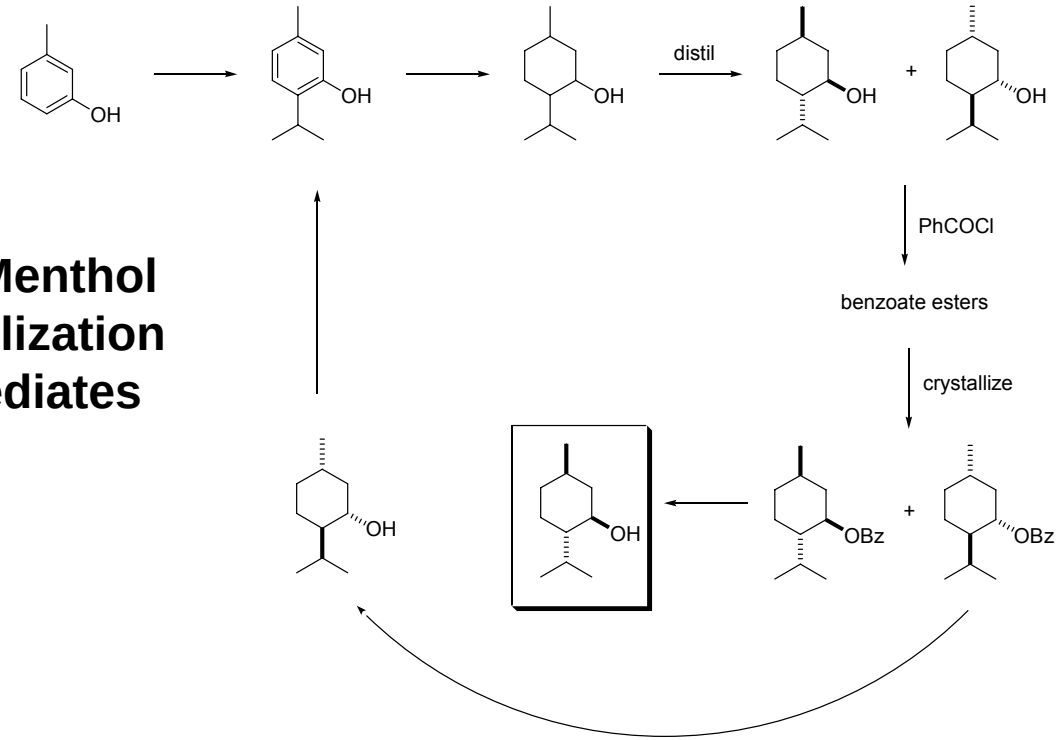
Semisynthetic derivatives (e.g. penicillins).

NB!!! NOT ALL NATURAL PRODUCTS ARE ENANTIOPURE!!!

Methods for Obtaining Enantiopure Compounds

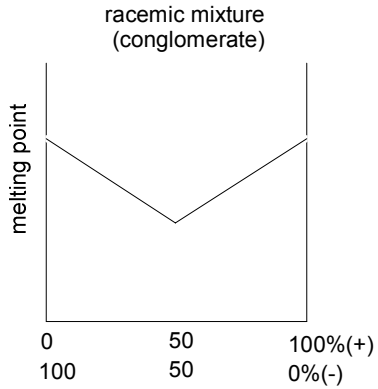
- Resolution
  - direct crystallization

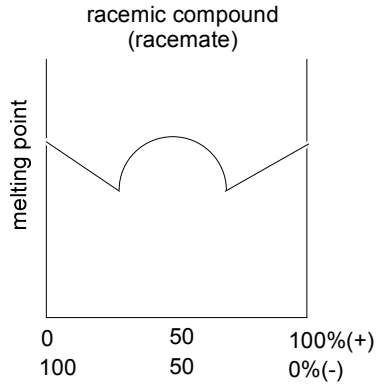
Industrial production of Menthol through fractional crystallization of benzoate ester intermediates

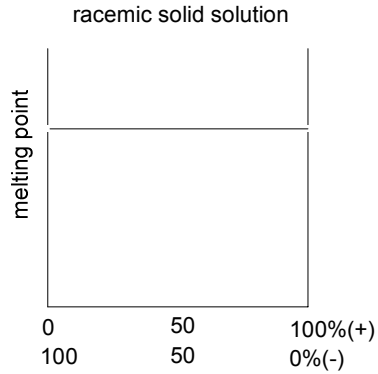


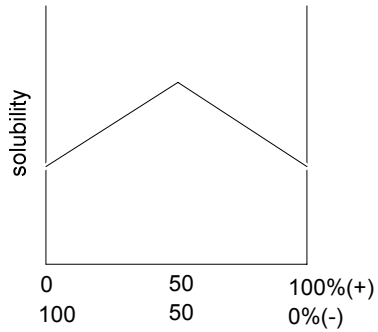
Haarmann & Reimer

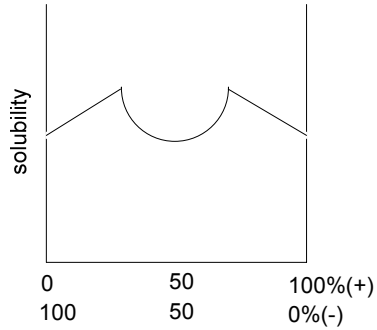
Solubility and melting point diagrams



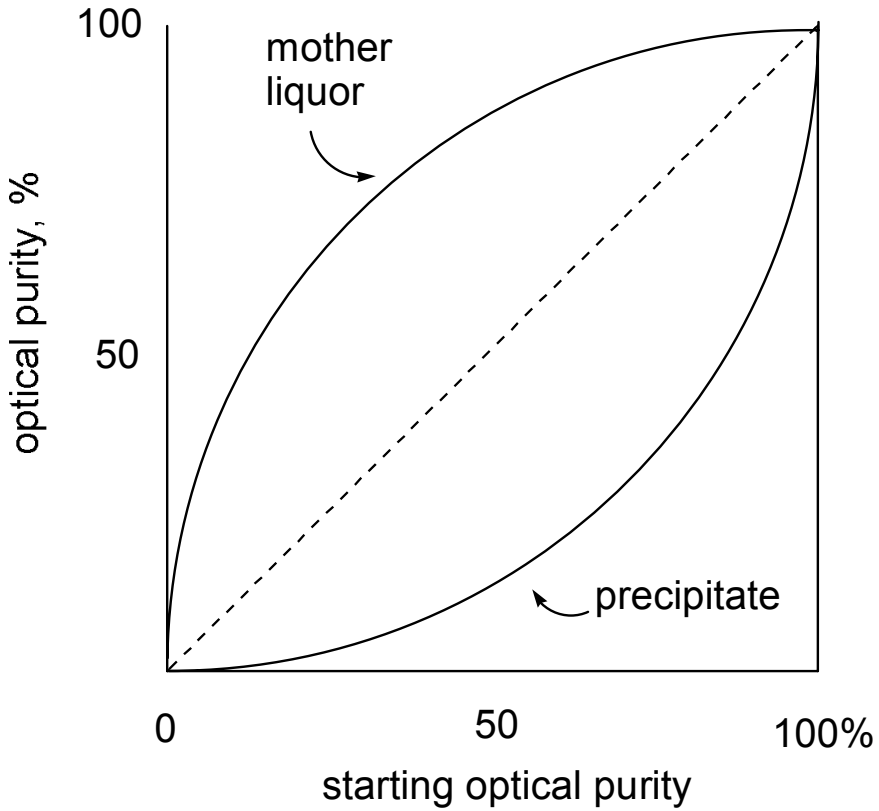


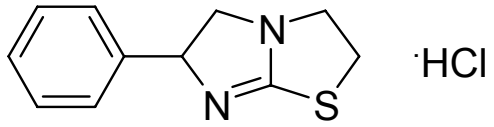




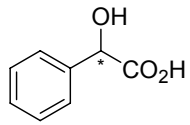


Optical purity during titration with aq NaOH

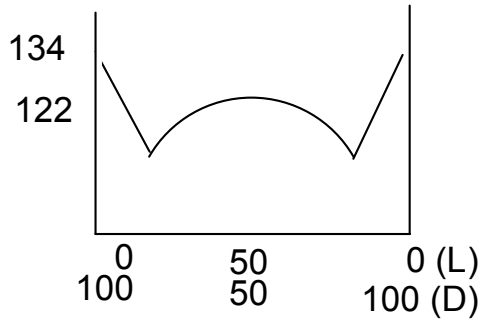




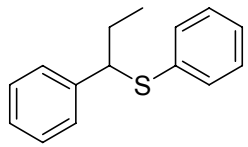
Fractional Sublimation of L-Mandelic Acid



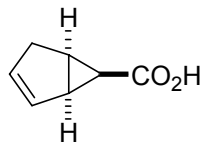
Sample	enantiomeric purity	% of L-isomer
Stg material	20.7	60.3
Fraction 1	37.2	68.6
Fraction 2	31.5	65.7
Fraction 3	25.2	62.6
Fraction 4	16.0	58.0
Fraction 5	4.7	52.3
Stg material	60.2	80.1
Fraction 1	52.5	76.3
Fraction 2	62.0	81.0
Fraction 3	64.1	82.1
Fraction 4	74.3	87.1



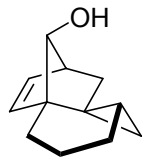
Other related examples:



6 %ee ----> 74 %ee



40 %ee ----> 64 %ee



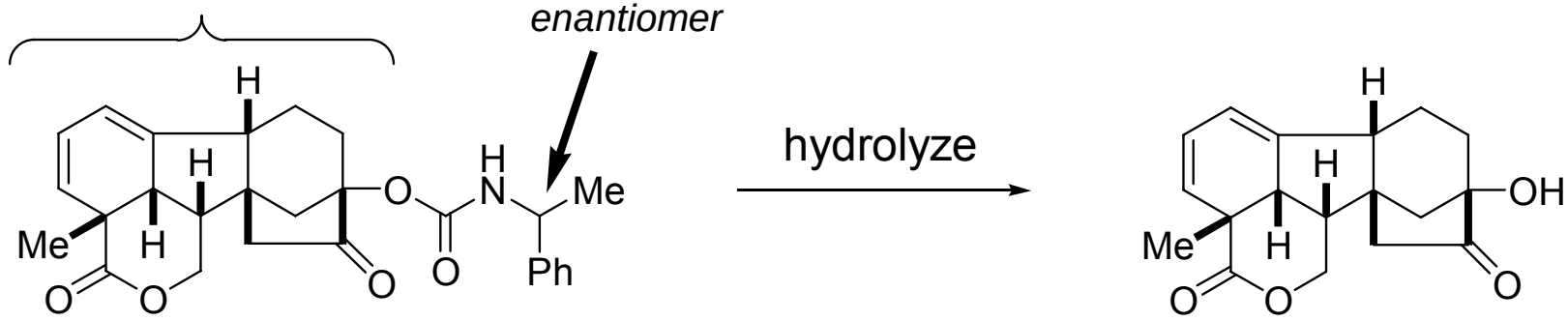
racemic ----> non-racemic

Methods for Obtaining Enantiopure Compounds

- Resolution
  - diastereomeric derivatives

NB! Both enantiomers of this half

single enantiomer



Separate 1:1 mixture of diastereomers by column chromatography

Corey, E.J. *et al. J. Am. Chem. Soc.* 1970, *92*, 396.

Methods for Obtaining Enantiopure Compounds

- Resolution
  - chiral chromatography

Chiral Stationary Phase
or
Chiral Mobile Phase Additive

Several applications, both analytical and preparative.

Price!

Columns available 'on request'.

Pirkle, W.H.; Finn, J. *Asymmetric Synthesis*, vol. 1, 1983, 87.

Methods for Obtaining Enantiopure Compounds

- Asymmetric Transformations
  - first order
  - second order

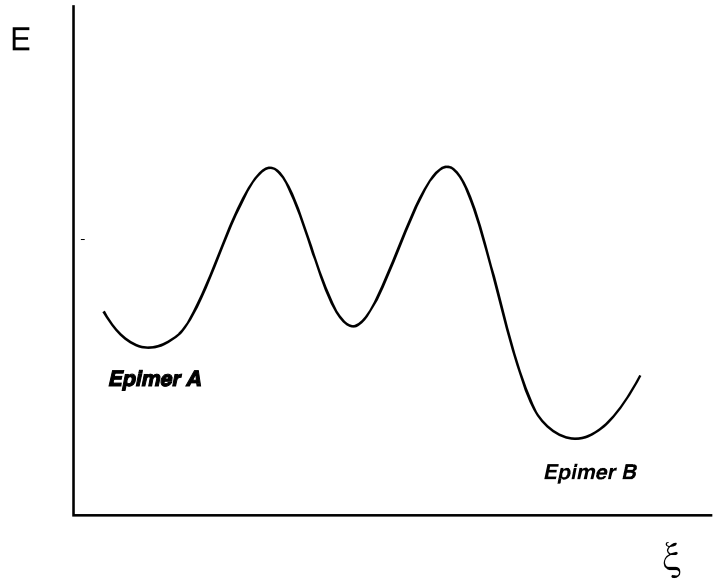
Thermodynamical control

Equilibrium between enantiomers or epimers is set up to favour one or the other of the products.

Methods for Obtaining Enantiopure Compounds

- Asymmetric Transformations
  - first order

Conditions set up so as to favor
e.g. crystallisation of one anantiomer.

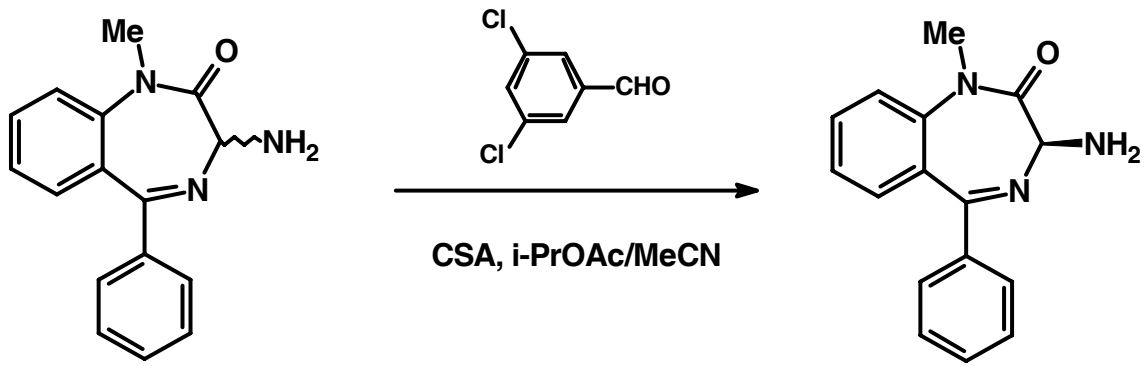


Classical example: *spontaneous* crystallisation of NaClO4 from aqueous solution. 844 trials, 51.3 % left handed, 48.7 % right handed crystals.

Soret, C.H. *Z. Krystallogr. Mineral.* 1901, *34*, 630.

Methods for Obtaining Enantiopure Compounds

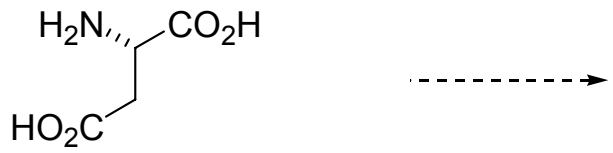
- Asymmetric Transformations
  - second order



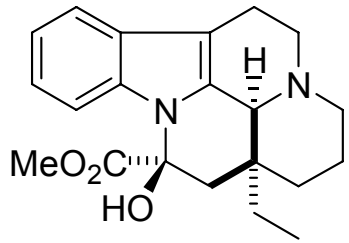
Reider, P.J. *et al. J. Org. Chem.* 1987, *52*, 955.

Methods for Obtaining Enantiopure Compounds

- Asymmetric Induction (AI)
  - internal a.i. (chiral SM)



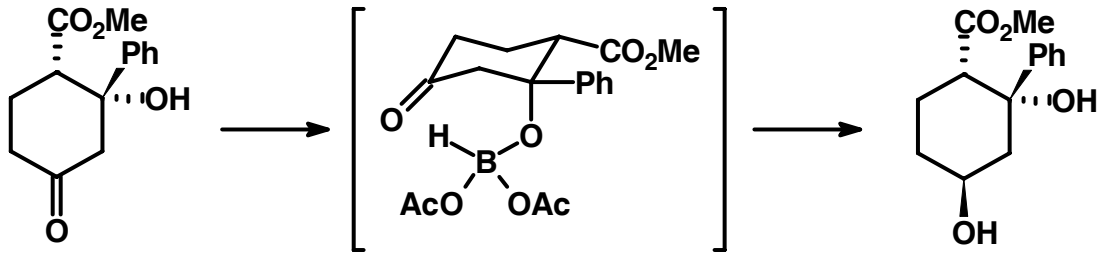
Aspartic acid



Vincamine

Rapoport, H. *et al. J. Org. Chem.* 1990, *55*, 3068.

Internal AI



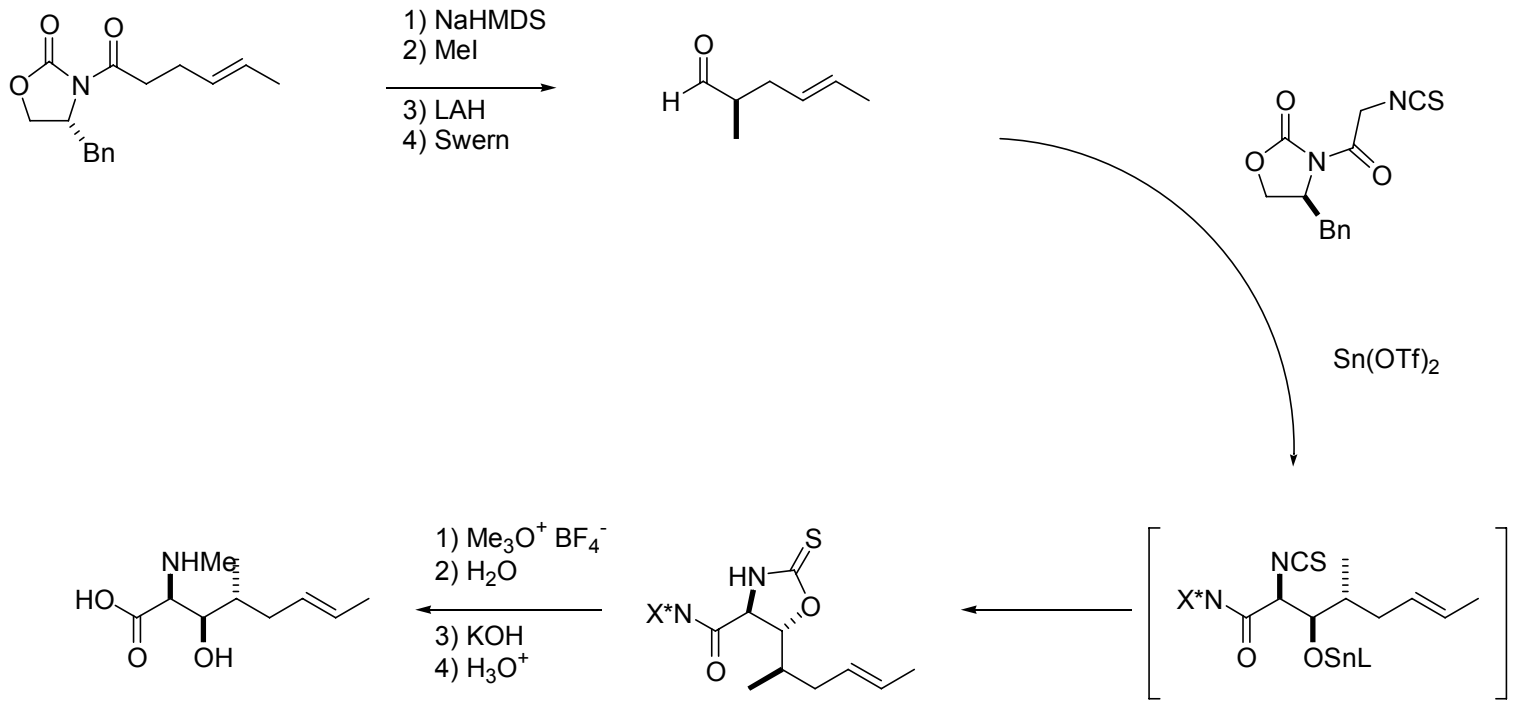
Chelation controls selectivity

(Saksena, A.K.; Mangiaracina, P. *Tetrahedron Lett.* 1983, *24*, 273.)

Turnbull, M.D. *et al. Tetrahedron Lett.* 1984, *25*, 5449.

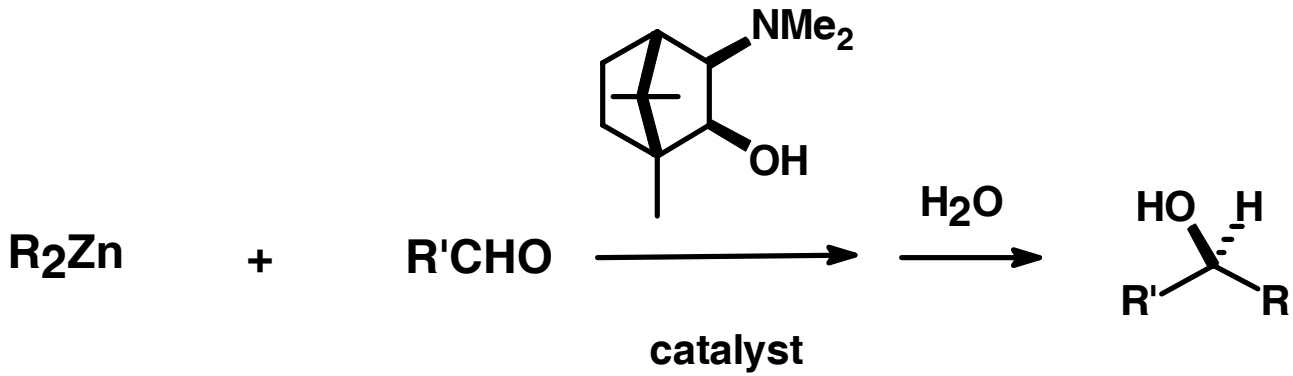
Methods for Obtaining Enantiopure Compounds

- Asymmetric Induction (AI)
  - relayed a.i. (chiral AUX)



Methods for Obtaining Enantiopure Compounds

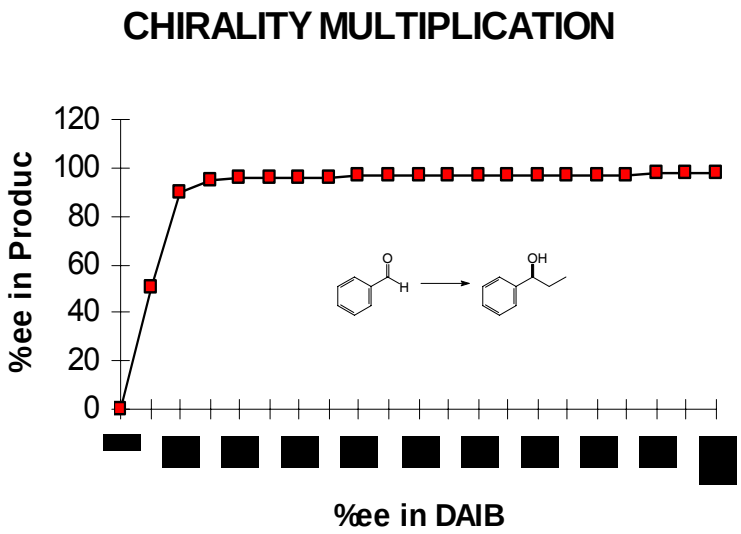
- Asymmetric Induction (AI)
  - external a.i. (chiral RGT)

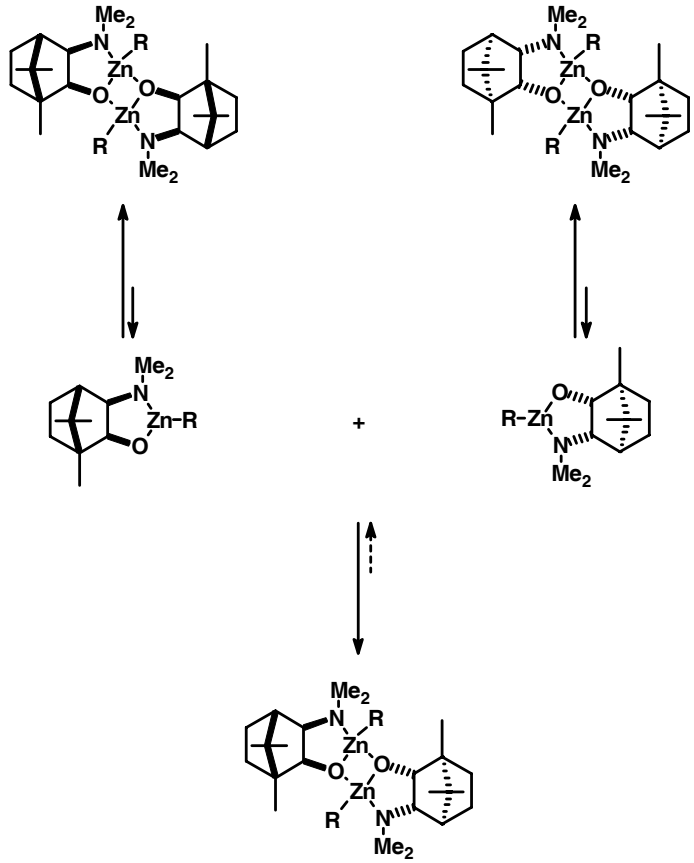


Noyori, R. *Science* 1990, *248*, 1194.
Angew. Chem., Int. Ed. Engl. 1991, *30*, 49.

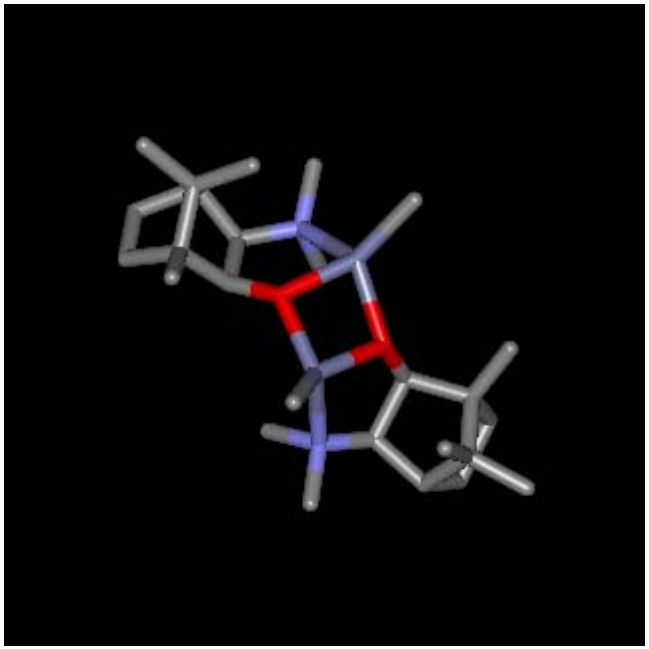
Methods for Obtaining Enantiopure Compounds

- Asymmetric Induction (AI)
  - external a.i. (chiral RGT)

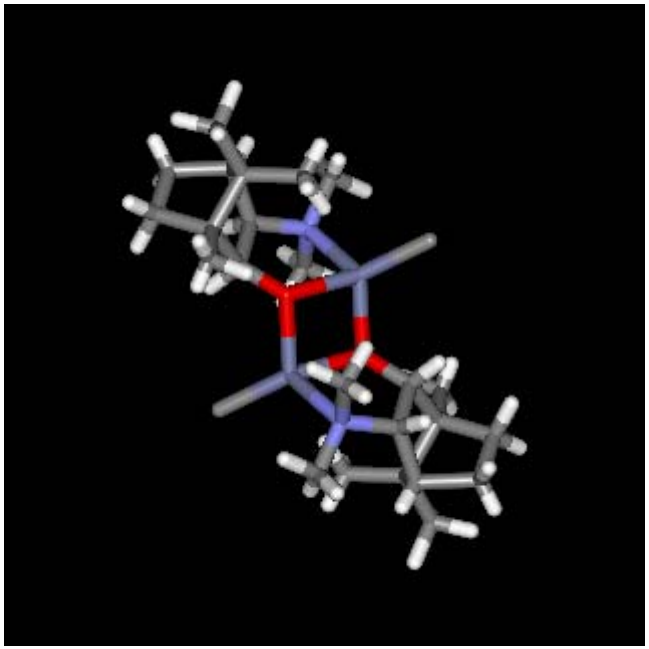




DAIB-Zn X-ray structures

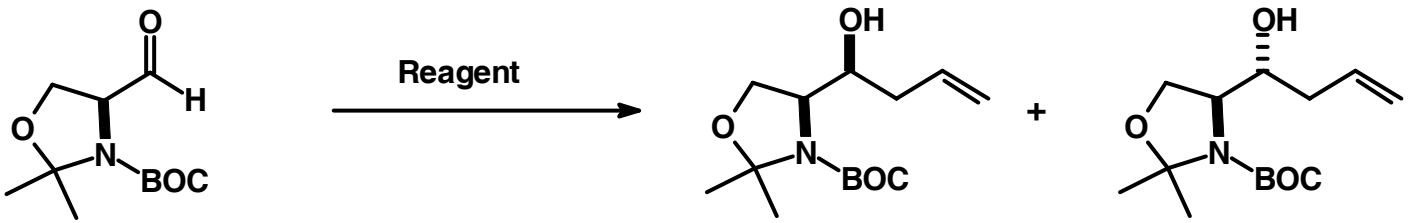


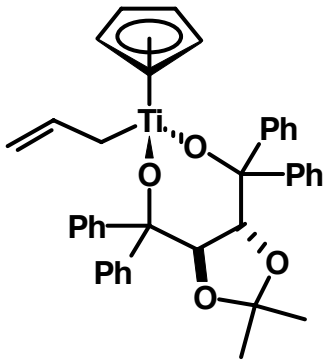
JAMYAX



JAMYEB

Reagent Control in Double Stereodifferentiation





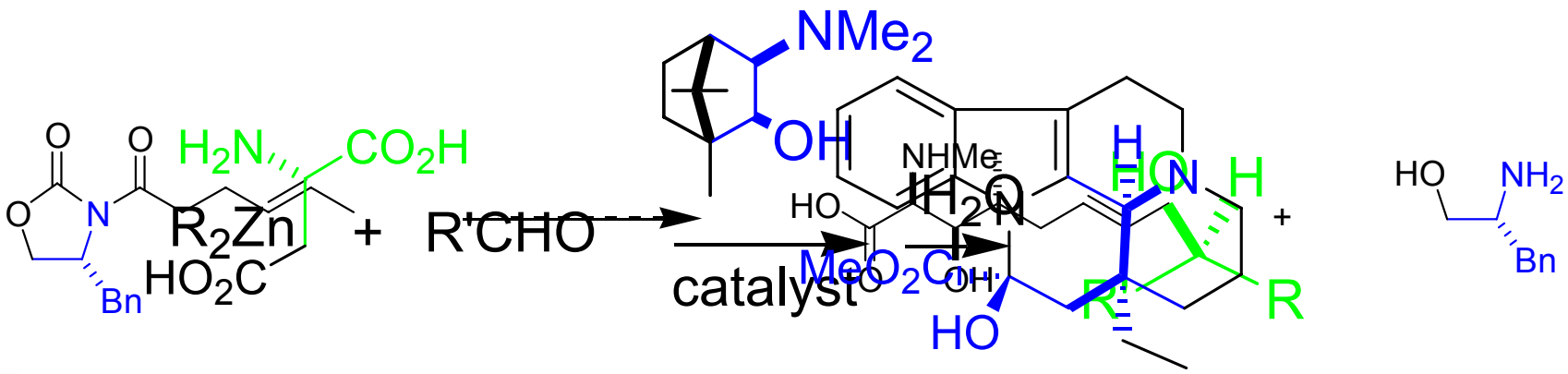
***R,R*-reagent**

Allyl-MgCl	**55.1 %**	**44.9 %**
***R,R*-reagent**	**98.1 %**	**1.9 %**
***S,S*-reagent**	**0.5 %**	**99.5 %**

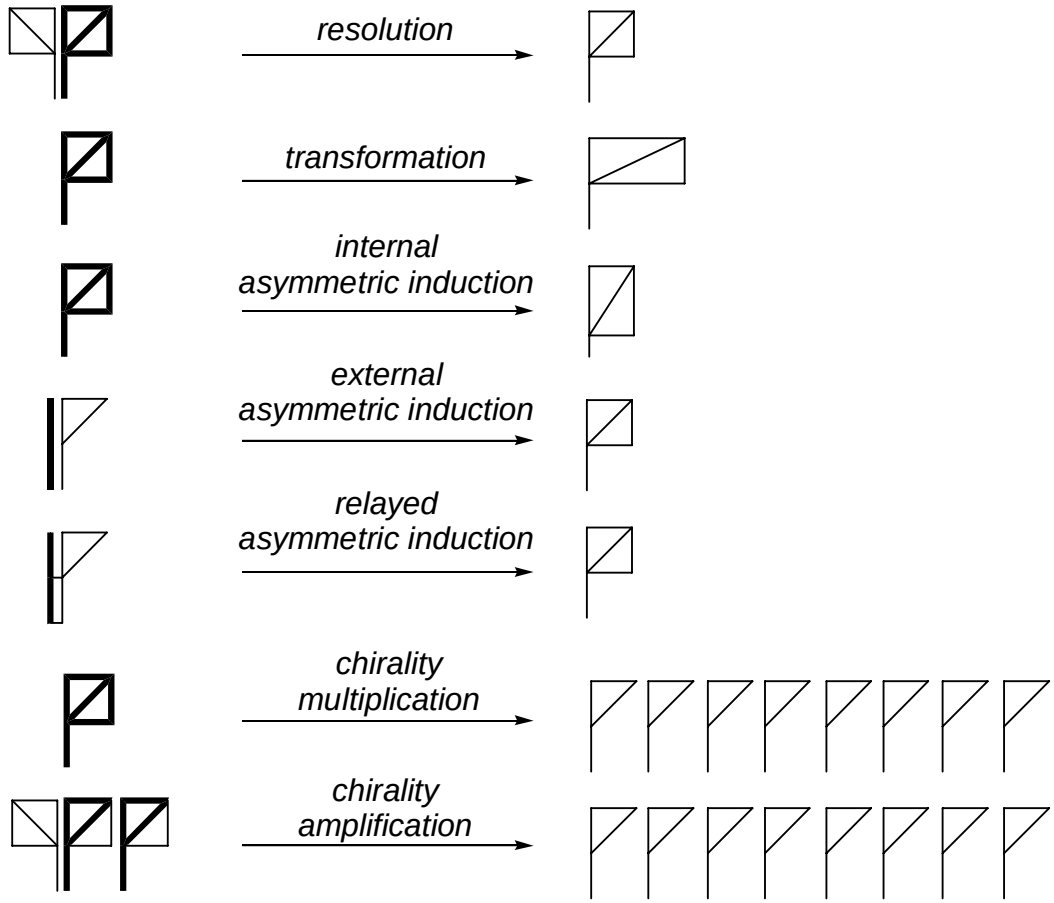
Duthaler, R.O. *et al. J. Am. Chem. Soc.* 1992, *114*, 2321.

Asymmetric Induction - Economy?

- internal (chiral SM)
  - Chirality incorporated (and multiplied) in product
  - Re-usable (?)



Modes of Access to Enantiopure Compounds



Noyori, *ACIEE* **2001**, 40.

Polarimetry

$$[\alpha]_\lambda = \frac{\alpha}{l \cdot c}$$

$$\% \text{ o.p.} = \frac{[\alpha]_{obs}}{[\alpha]_{max}}$$

Precautions:

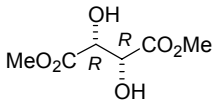
- longest path, large diameter
- strained glass (=distorted glass) polarized beam; use center filled tubes
- particles; rotate cell, measure again
- air bubbles - refract light
- colored sample

Enantiopurity

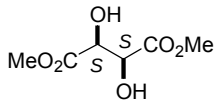
- **%ee**
  - ee = enantiomeric excess

$$\%ee = \frac{|\%R - \%S|}{|\%R + \%S|} * 100$$

  - e.g. mixture 80 % R, 20 % S
    - %ee = |80 - 20| = 60 %ee

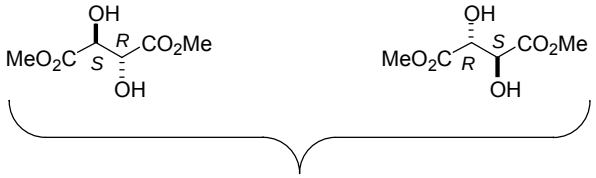


60 %



20 %

$$\%ee = \frac{60 - 20}{60 + 20} * 100 = 50\ \%ee$$

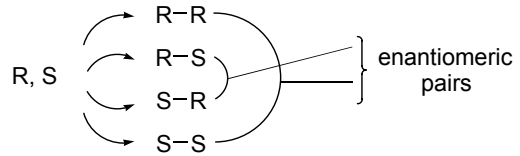


20 %

Enantiomeric Excess

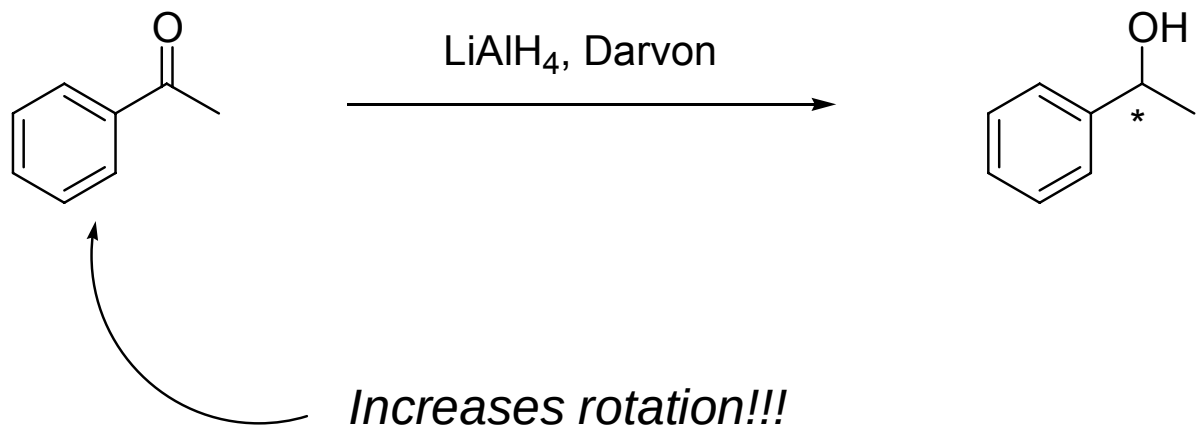
Often %e.e. = % o.p., but sources for error

- $[\alpha]_{max}$ must be known
- solvent, concentration and temperature
  - reproduction of literature concentration
  - e.g. $CHCl_3$ - how much EtOH?
  - EtOH - ?
- rotation not necessarily linear with %ee because of association phenomena
- $[\alpha]$ not constant for all molecules in solution (impurities with large $[\alpha]$)



Optical Rotation vs. *Enantiomeric Excess*

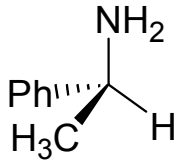
Achiral impurity can affect optical rotation:



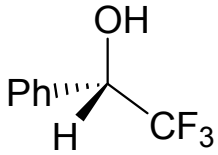
Yamaguchi, S.; Mosher, H.S. *J. Org. Chem.* **1973**, *38*, 1870.

Practical Determination: NMR

- Optically active solvent



ROH, α-OH acids

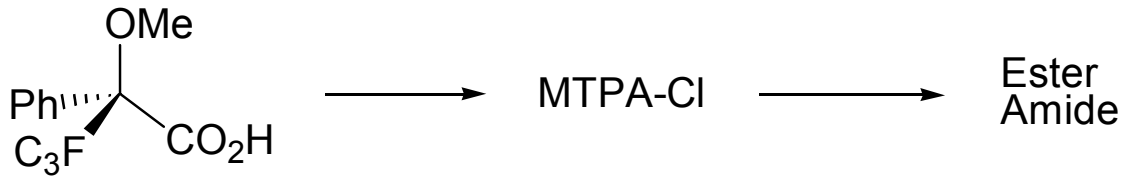


RNH_2, amino acids

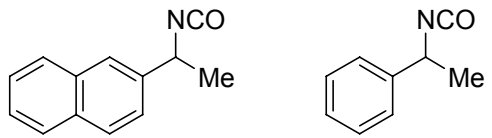
  - use either as sole solvent or more generally as additive
  - often requires optimization of mol fractions

Practical Determination: NMR

- Diastereomers
  - **different physical properties**
  - **α-methoxy-α-trifluoromethyl phenylacetic acid (MTPA = Mosher's acid; Dale Mosher *J. Am. Chem. Soc.* 1973, 512)**

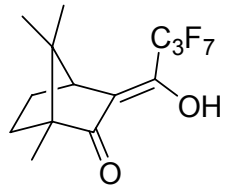


  - others: e.g. isocyanates



Practical Determination: NMR

- Chiral shift reagent
  - **need not make anything**
  - **add more & more until peaks split**
    - **Whitesides, G. *J. Am. Chem. Soc.*** 1974**, 1038.**
    - **Sullivan *Top. Stereochem.*** 1977**, *10*, 287.**



$Eu(hfc)_3$

hfc = heptafluorocamphorato

  - **always use dry solvents**
  - **always confirm with racemic material! (peak positions)**

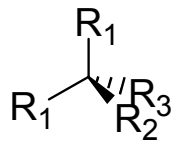
Practical Determination: HPLC

- Make diastereomeric derivatives
  - same restrictions as in NMR
- Chiral columns
  - BY FAR the most reliable method
  - columns available nearly tailor-made

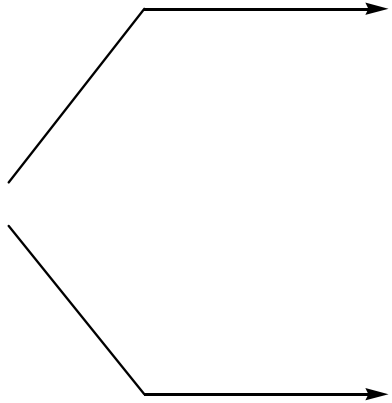
Creation of Stereocenters

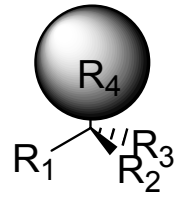
Enantiotopic differentiation

$sp^3 \longrightarrow sp^3$

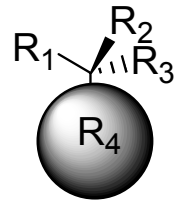


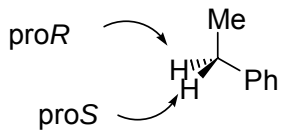
prochiral sp^3 center





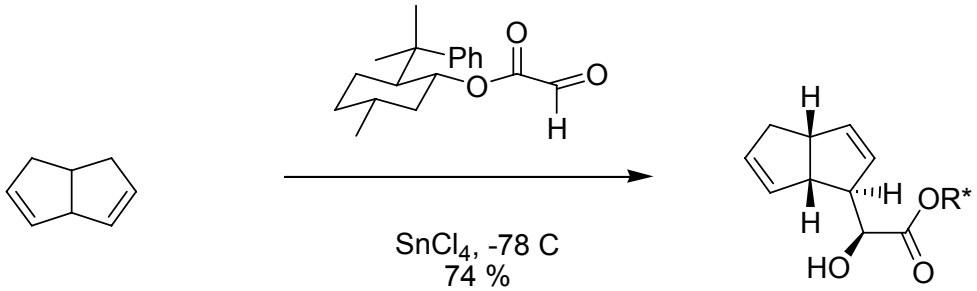
mirror





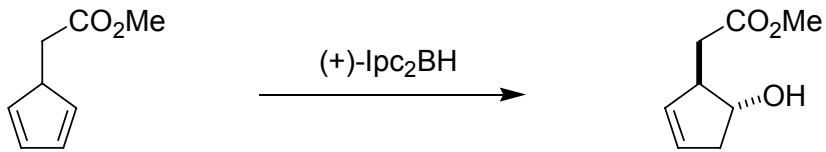
Hanson *J. Am. Chem. Soc.* **1966**, *88*, 2731.
Tetrahedron **1974**, *30*, 3649.

Enantiotopic differentiation



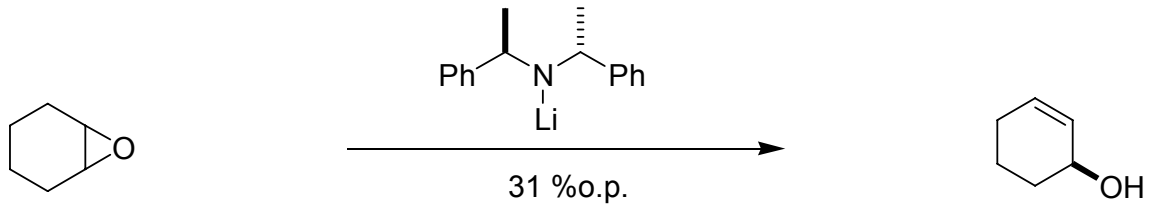
single diastereomer

Whitesell, J.K. *J. Org. Chem*. **1985**, *50*, 3025.

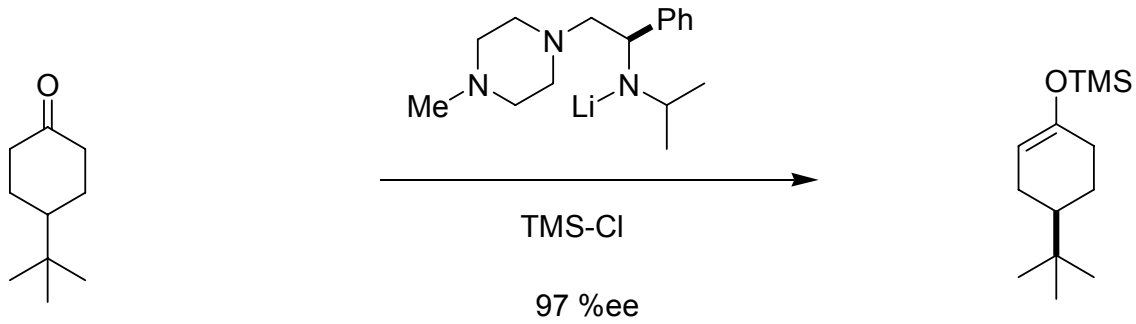


Uskokovic, M. *J. Am.Chem. Soc.* **1973**, *95*, 7171.

Enantiotopic differentiation



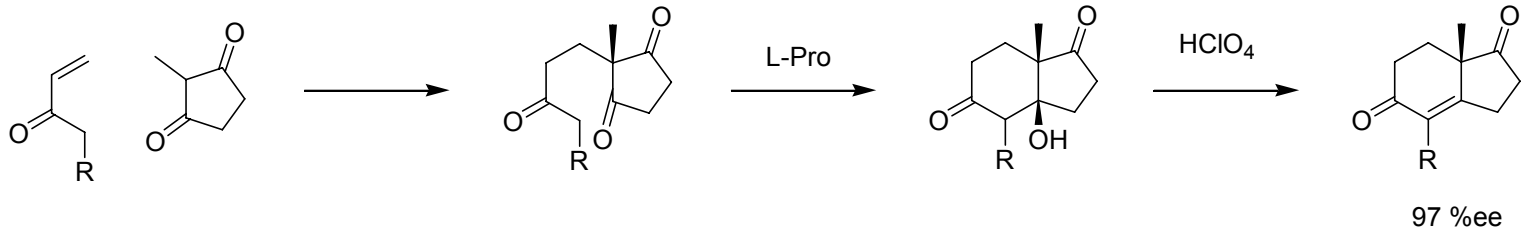
Whitesell, J.K. *J. Org. Chem.* **1980**, *45*, 755.



Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 542.

Enantiotopic differentiation

HAJOS-EDER-WIECHERT PROCESS



- Natural amino acid => natural steroid configuration
- amide, ester not as efficient; need bifunctional catalyst
- amino acid can be used catalytically
- polar aprotic solvent => aldol product
- mineral acid present => enone
- rather insensitive to temperature (120 °C: 64 %ee)

Cohen *Accts. Chem. Res.* **1976**, 412.

Synthetic Considerations

- Mechanism
- Molecular structural requirements
- Rxn limitations (pH, pK_a, temp, $h\nu$, etc)
- Rxn conditions compatibility
- Yield
- Operational points

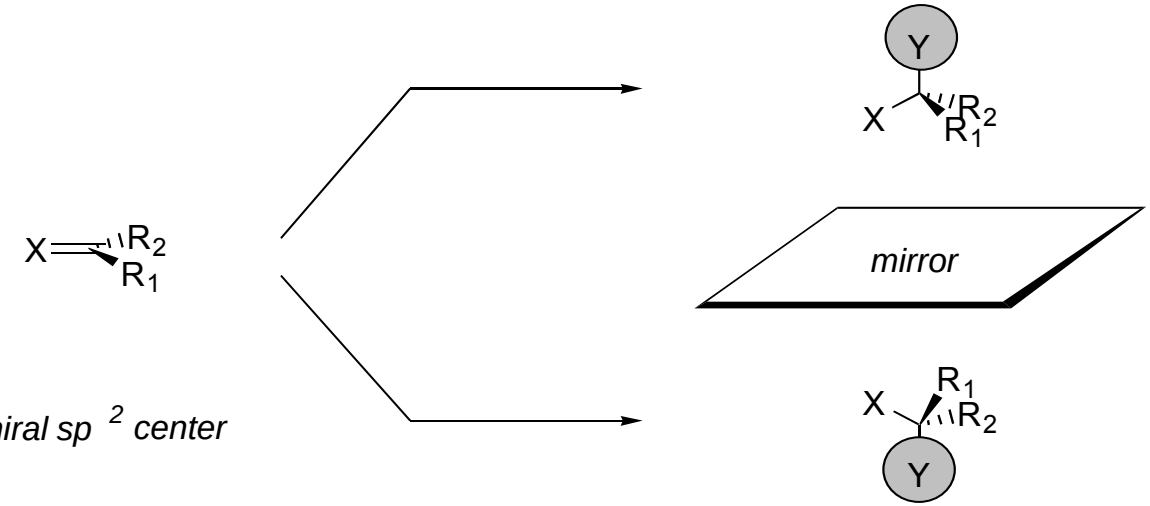
Further Considerations

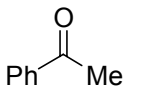
- Efficiency of overall scheme (Y, %ee)
- SM's: price, availability
- Selectivity:
  - chemo
  - regio
  - stereo
- Add to general knowledge of TGT
- FGI reagents (often serendipitous)

Creation of Stereocenters

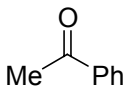
$sp^2 \longrightarrow sp^3$

Enantiofacial differentiation





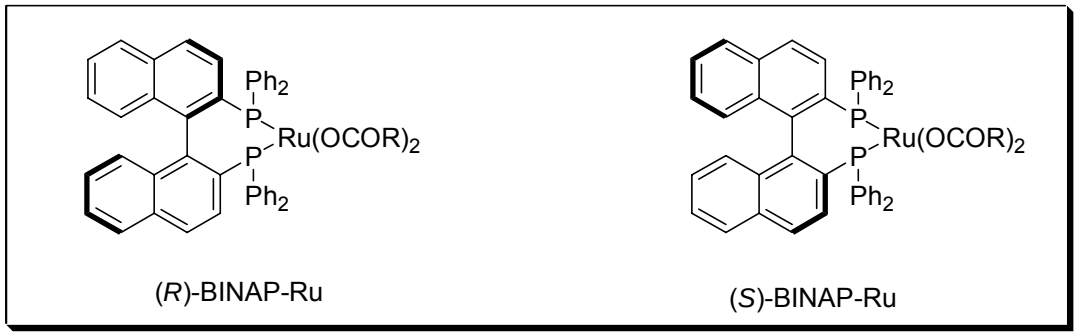
si

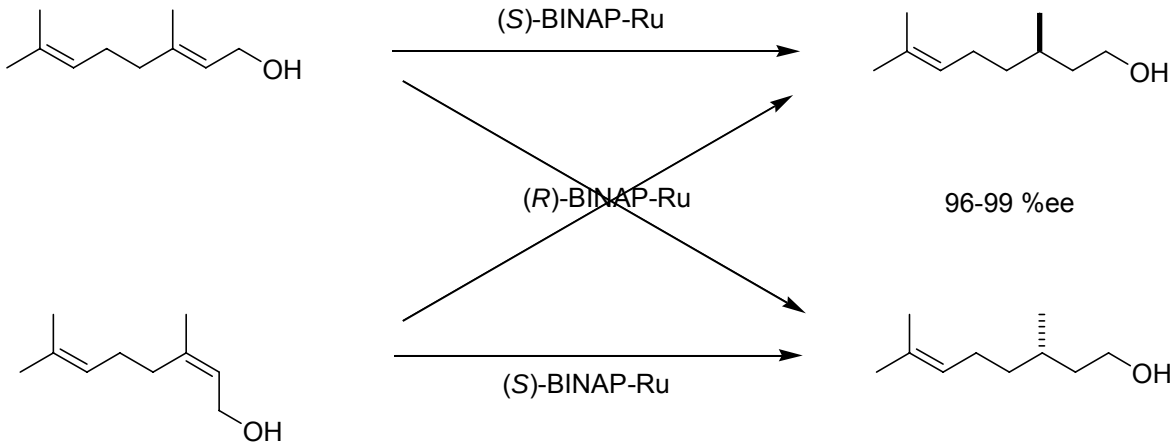


re

Hanson *J. Am. Chem. Soc.* **1966**, *88*, 2731.
Tetrahedron **1974**, *30*, 3649.

Enantiofacial differentiation

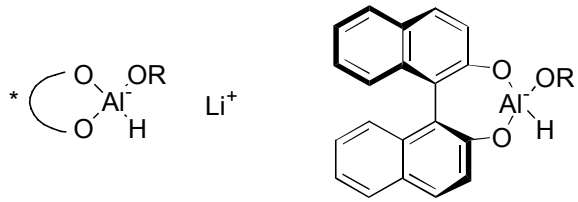




Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.
Accts. Chem. Res. **1990**, *23*, 345.

Methods for Asymmetric Induction

1) Reagent modification



Advantages:

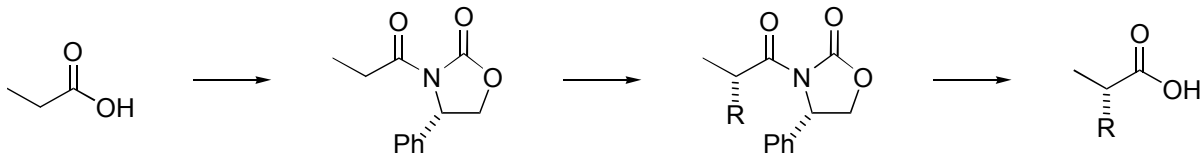
- ***no separate reactions on substrate***
- ***possibility for catalysis***
- ***can be designed (if TS known)***

Disadvantages:

- ***well defined TS for bimolecular rxns rare***
- ***analysis of results difficult***

Methods for Asymmetric Induction

2) Substrate modification



Advantages:

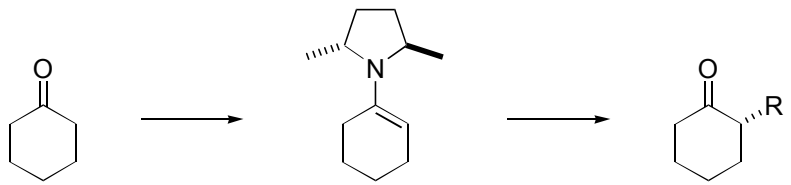
- ***fixed interaction between auxiliary/substrate***
- ***products diastereomers: analysis simple***

Disadvantages:

- ***two extra steps***
- ***cannot be catalytic***

Methods for Asymmetric Induction

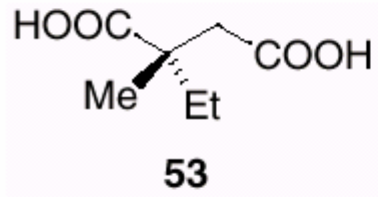
2) Substrate modification
   b) Weak bond
   a) Strong bond



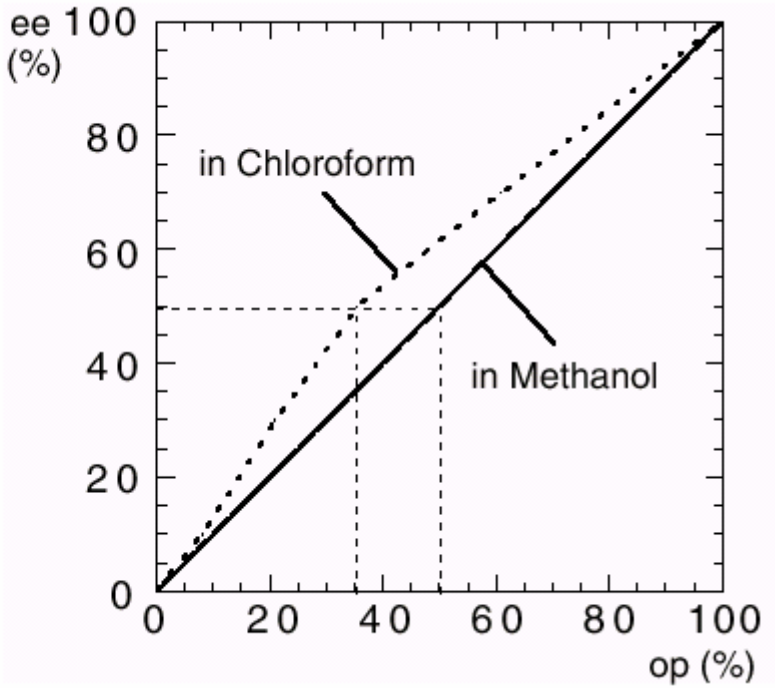
Advantages: ***•rxns for attachment/removal easier***
•possibility for catalysis

Disadvantages: ***➢combination of rgt modification and strong bond***

op = ee?

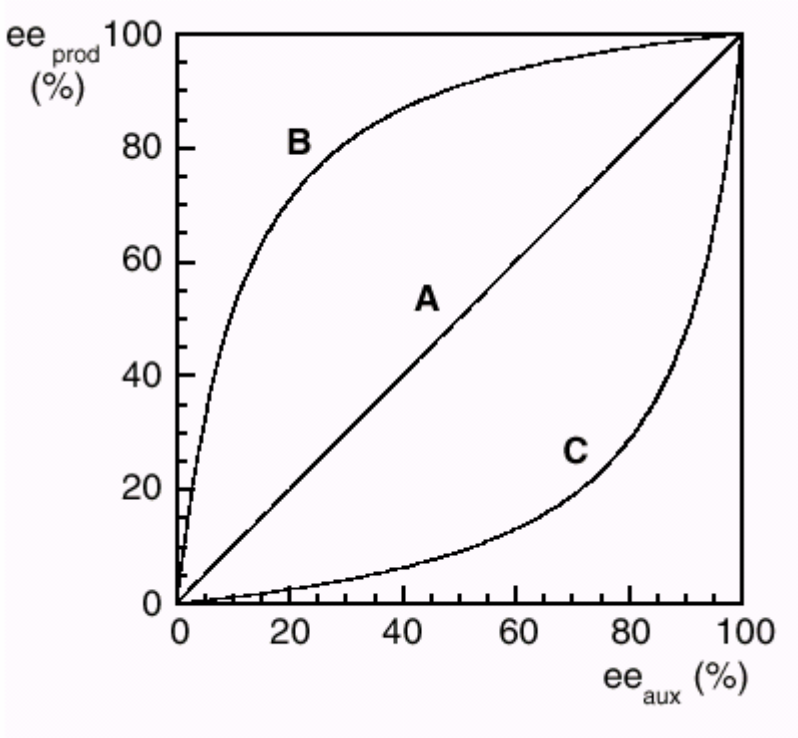


53



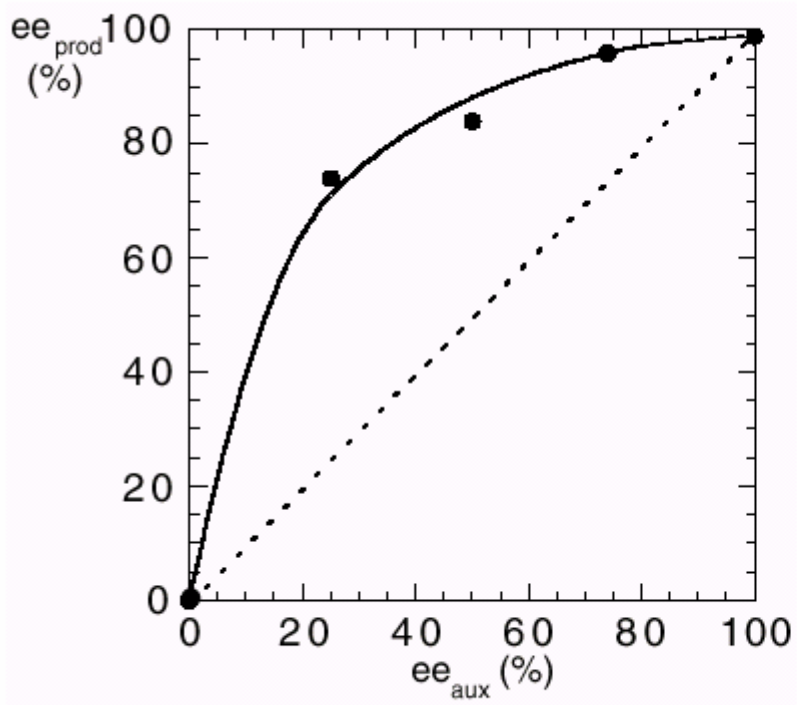
Horeau, A. *Tetrahedron Lett.* **1969**, *36*, 3121-3124.

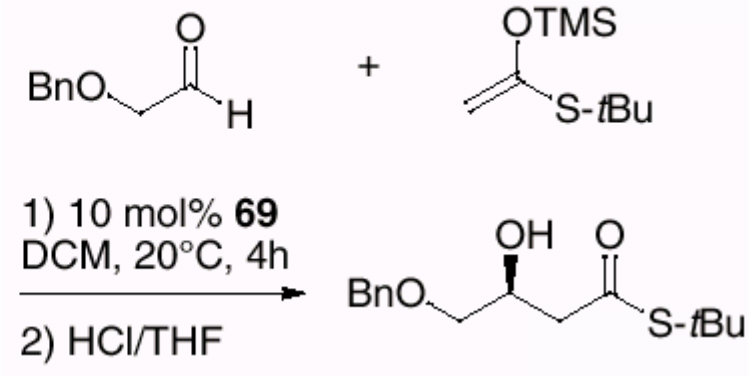
Non-linear effects

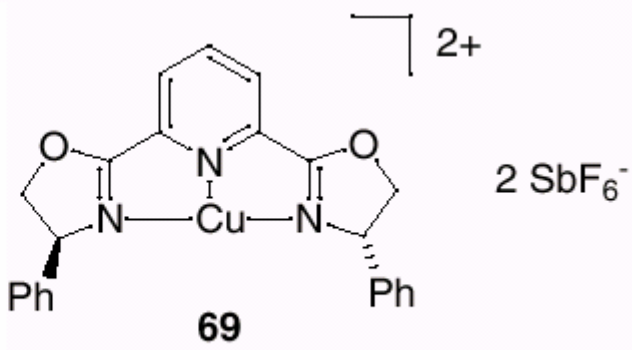


Line A: No effect
B: Positive non-linear effect
C: Negative non-linear effect

Non-linear effect in aldol

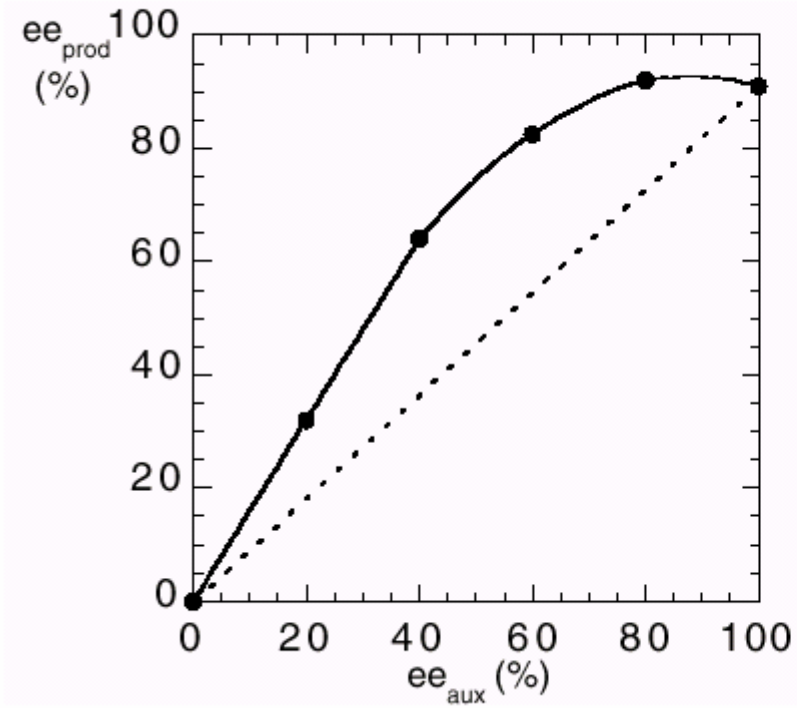


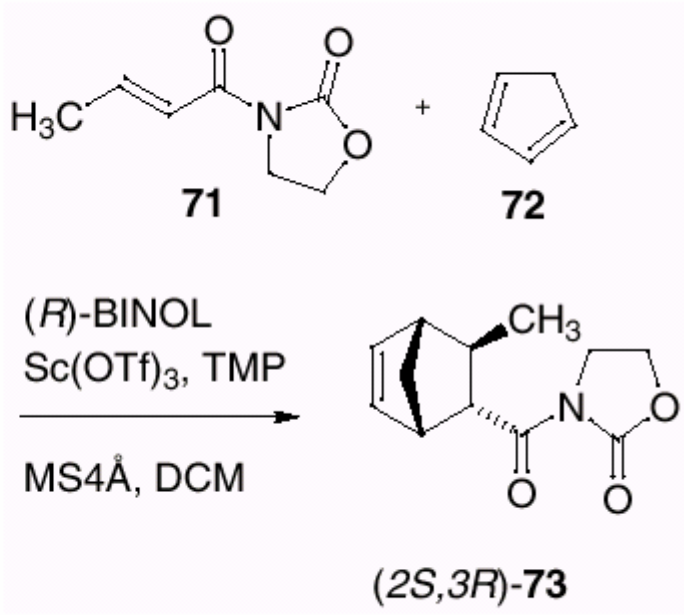




Evans, D.A. *et al. J. Am. Chem. Soc.* **1999**, *121*, 669-685.

NLE in Diels-Alder





Kobayashi, S. *et al*. *Tetrahedron Lett.* **1994**, *35*, 6325-6328.