Chirality

Chiral Molecules

- Dissymmetric Molecules.
- Molecules devoid of plane of symmetry, center of symmetry and alternating axis of symmetry.

Types of Chiral Molecules

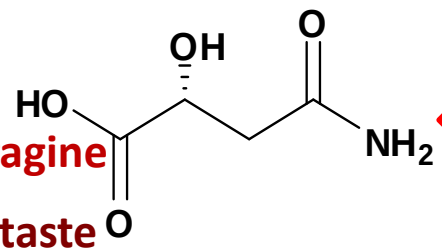
- Molecules with chiral centre.
- Molecules with chiral axis
- Molecules with chiral plane
- Helical molecules

CHIRALITY

- The term chiral is used to describe an object that is non-superimposable on its mirror image.
- Human hands are perhaps the most universally recognized example of chirality.
- The Left hand is a non-superimposable mirror image of the right hand; no matter how the two hands are oriented.

Why bother about chirality?

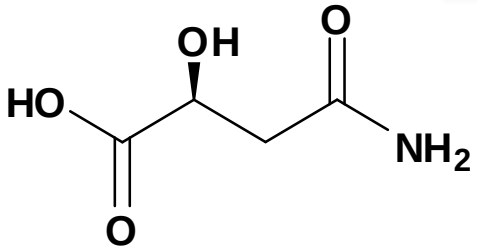
Chirality in Flavor & Fragrance



(*R*) Asparagine

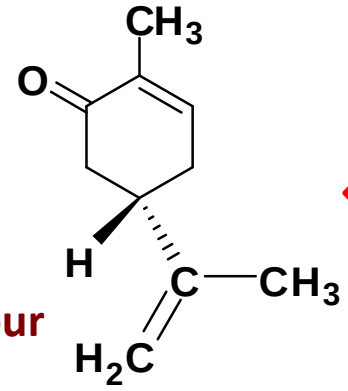
Sweet taste

Asparagine



(*S*) Asparagine

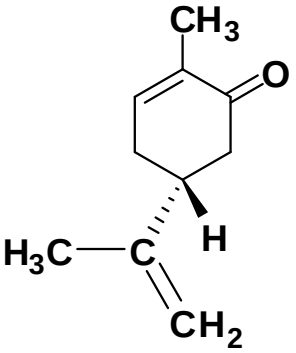
Bitter taste



S-Carvone

Caraway flavour

Carvone

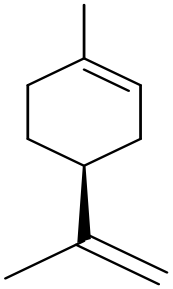


R-Carvone

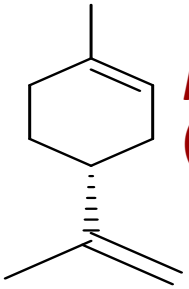
Spearmint flavour

S-limonene

(Lemon odour)



Limonene



R-limonene

(Orange odour)

Enantiomers are identical until they are placed in a chiral environment. Nature has chosen to make all its living structures from chiral molecules (amino acids, sugars) and has selected a single enantiomeric form of each.

Every amino acid in our body has the *S* and not the *R* configuration and sugars are in D-form.

The different smell and taste of the enantiomers is a result of the stereogenic interactions in the receptors in the nose and mouth as these are chiral.

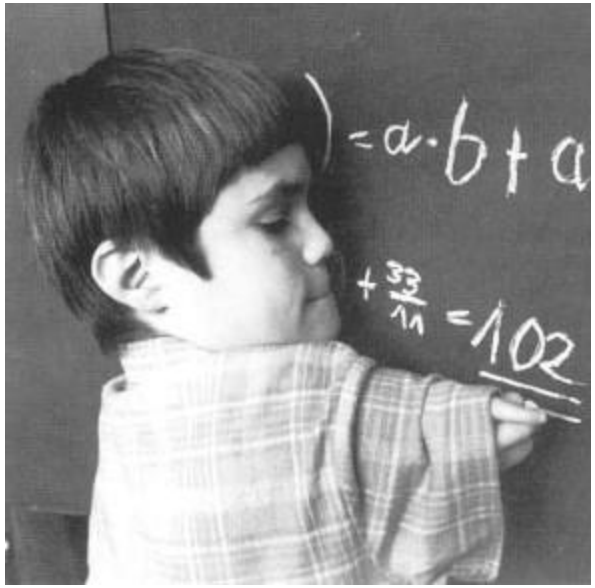
This behaviour is similar to fitting a key into a lock-only the key designed for a specific lock fits.

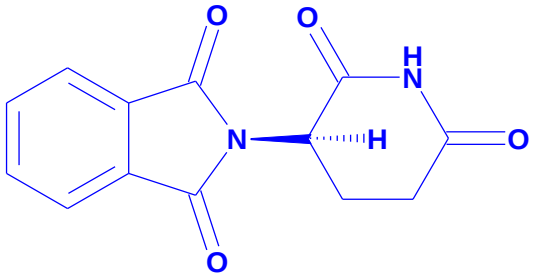
Likewise, the odour and and taste causing enantiomers fit only in the appropriately shaped odour and taste receptors in the nose and mouth.

For a flavour and fragrance manufacturer, the distinction between enantiomers of the same molecule is clearly of great importance.

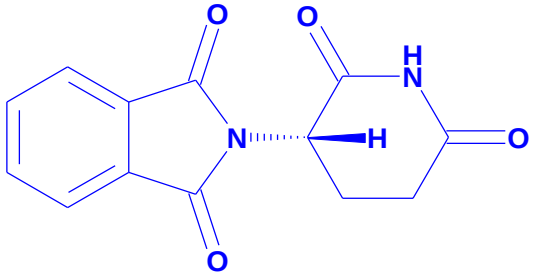
When it comes to drug molecules, providing the right enantiomer in pure form can be a matter of life and death.

Thalidomide-Tragedy





R-Thalidomide-Sedative



S-Thalidomide-Teratogen

When a chiral drug interacts with a biological system the following possibilities exist:

- I) The distomer shows no serious side effects.
- II) The distomer exhibits an undesirable side effect.
- III) Both isomers have independent therapeutic value.
- {Distomer is the enantiomer of a chiral compound that is less potent for a particular action} .

Chiral chemistry: Comparatively young branch of chemistry

- Till the early 1990s, about 90 % of synthetic chiral drugs were still racemic.

- Regulatory changes [after 1992] have a significant effect on the production of chiral chemicals, particularly those prepared for use in formulated pharmaceutical and agrochemical products.

- Henceforth, if molecule is chiral, only single enantiomers will be accepted.

Asymmetric synthesis

- Conversion of prochiral centre to a chiral centre with unequal formation of products.
- Prochiral centre can be enantiotopic or diastereotopic.
- Involvement of diastereomeric transition states is essential for asymmetric synthesis.

Asymmetric synthesis challenges

- The aim of enantioselective synthesis, or catalysis, is to produce chiral products (a single enantiomer as the ultimate goal) starting from achiral substrates.

- Three of the major approaches towards this goal are the use of chiral catalysts, the use of chiral reagents, and use of chiral auxiliaries.

- In ideal situations only two diastereomeric transition states can be desired, and formation of single enantiomer is achieved based on the difference in E_{act}.

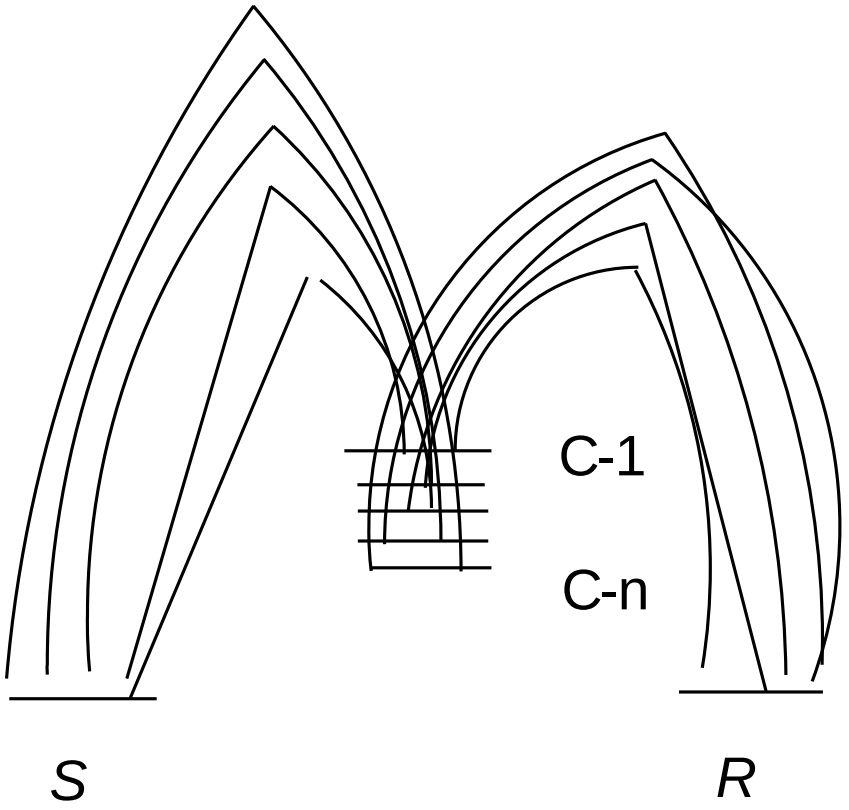
Asymmetric synthesis challenges

- Actually, the situation can be more complex: for instance, both the substrate and the reagent can exist as a mixture of conformational isomers, several conformations can be significantly populated, and they can also exist in different states of aggregation or solvation, with each of these species showing its own reactivity.

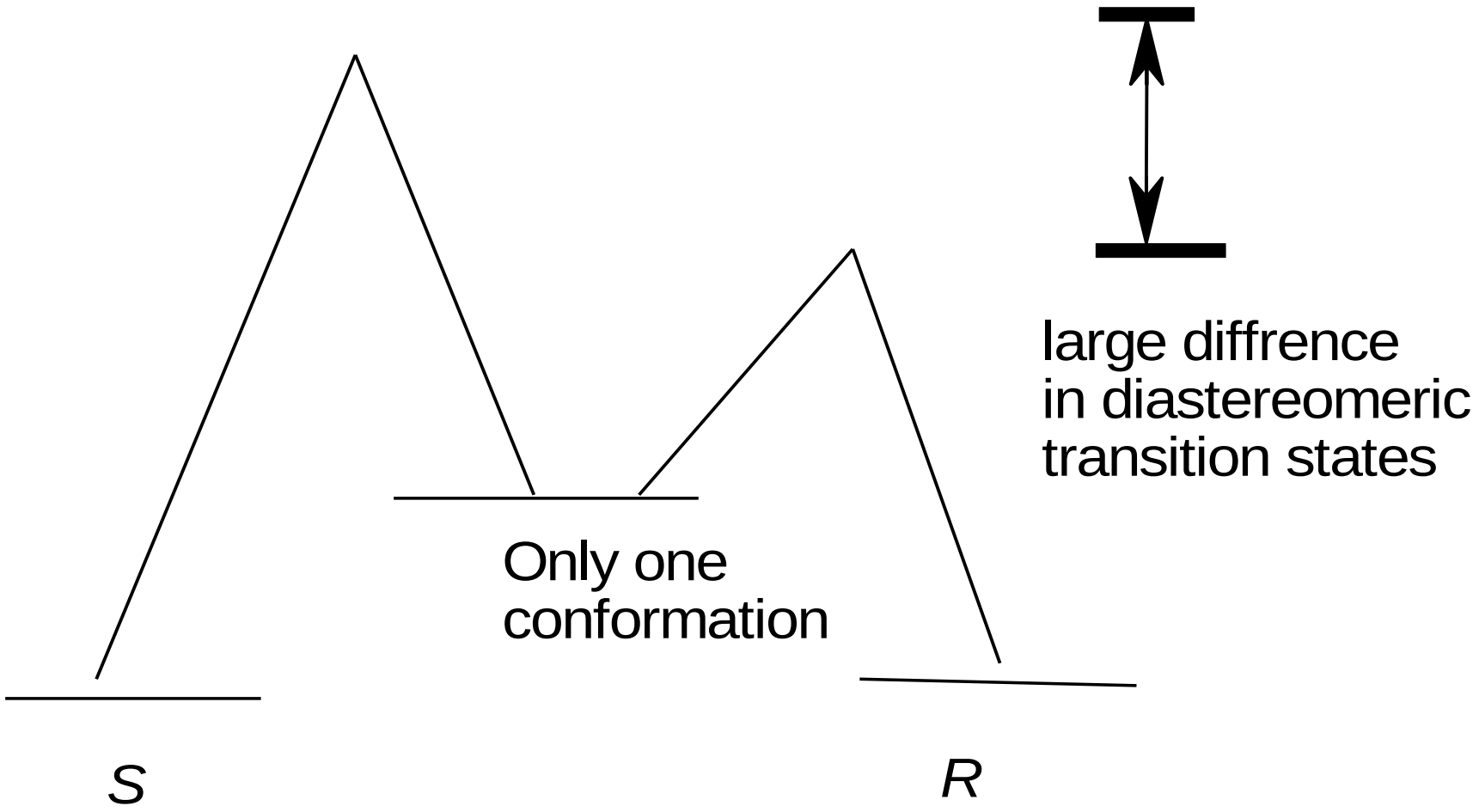
- The final result is a weighted average depending on the distribution and reactivity of the species involved, and a low stereoselectivity is generally obtained.

Asymmetric synthesis challenges

- Several conformations are usually present, with each capable of yielding both enantiomers.
- Several diasereomeric transition states co-exist leading to poor enantioselectivity.



Asymmetric synthesis challenges:
Desired situation



Asymmetric synthesis challenges

- A rational approach to the control of stereoselectivity is based on careful use of reaction parameters such as use of reagents or catalysts possessing only symmetry elements of pure rotation, presence of multiple ligating centers in the reagents, presence of appropriate bonding & non-bonding interactions between the substrate / reagent / catalyst etc.
- “Just as chemists of the Robinson generation worked without concern for stereochemical factors so we, in the early days, were working in ignorance of conformational considerations until Derek Barton showed us the light in 1950.”

- Barry Sharpless, Nobel Lecture, 2001.

- Till 1980s practical access to pure enantiomers relied largely on biochemical or biological methods.

- However, the scope of such methods using enzymes, cell cultures, or whole microorganisms is limited because of the inherent single-handed, lock-and-key specificity of biocatalysts.

2001 Chemistry Nobel Prize

- **K. Barry Sharpless**
  the Scripps Research Institute, La Jolla, California, USA

- **William S. Knowles**
  St Louis, Missouri, USA

- **Ryoji Noyori**
  Nagoya University, Chikusa, Nagoya, Japan,

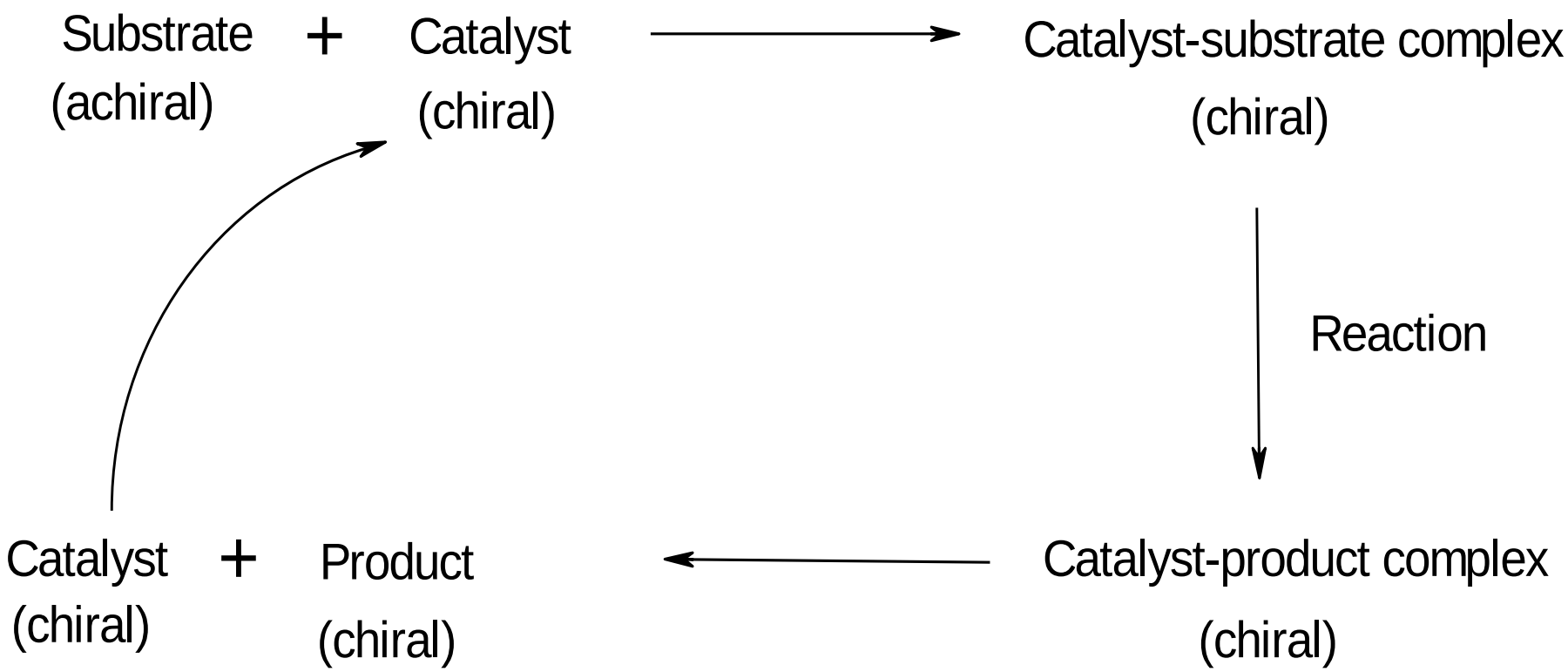
If we wish to catch up with Nature, we shall need to use the same methods as she does, and I can foresee a time in which physiological chemistry will not only make greater use of natural enzymes but will actually resort to creating synthetic ones.

Emil Fischer, 1902

Asymmetric synthesis: Use of chiral catalyst

- A chiral-substrate complex is formed initially.
- During the reaction, a stereocentre is created under the influence of chiral catalyst.
- This results in a catalyst-product complex, which then dissociates to product and catalyst.
- The catalyst is not affected by the reaction and is ready to catalyze the next transformation with a new substrate molecule.
- The catalytic cycle goes on until the reaction is complete or the catalyst becomes inactive due to catalytic poisoning.

Asymmetric synthesis: Use of chiral catalyst



Sharpless epoxidation

Oxidation of allylic alcohol with tert-butylhydroperoxide in presence of either (+) or (-) diethyl tartarate affords the corresponding asymmetric epoxide in high yield. Use of mol. Sieves recommended.

1) Very high enatioselection (>90% ee)

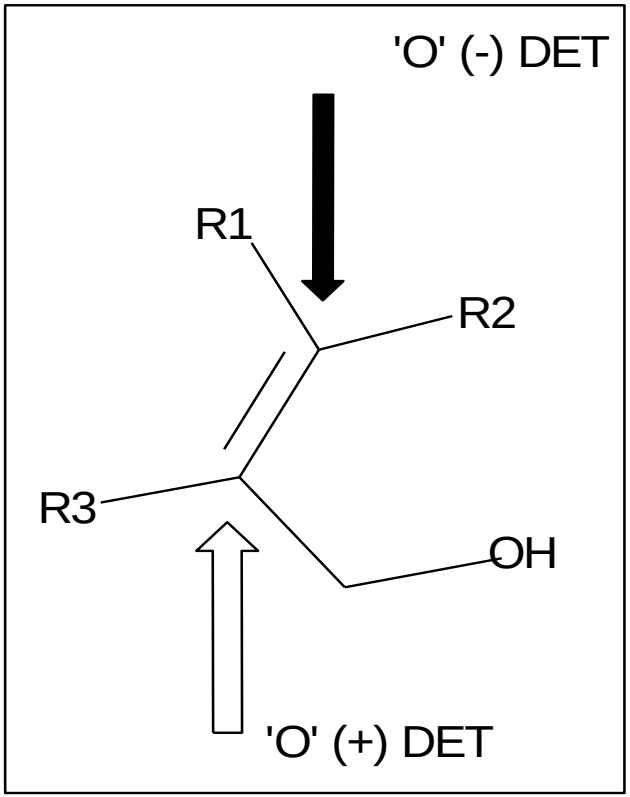
2) The absolute configuration of the epoxide produced can be predicted.

3) Gives uniformly high asymmetric induction throughout a range of substitution pattern.

4) Can be efficiently used for kinetic resolution.

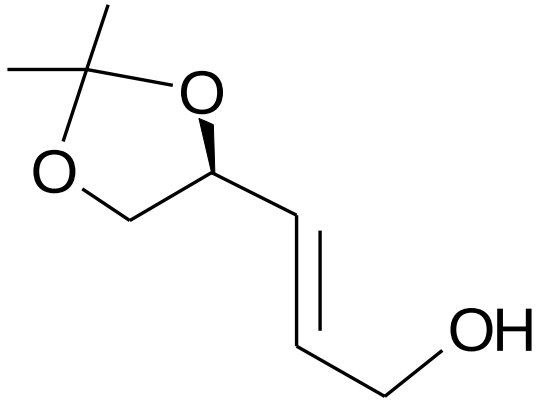
- (Z)-Substituted allylic alcohols react much more slowly than the corresponding (E)-substituted allylic alcohols.

Mnemonic for prediction of the stereochemical outcome



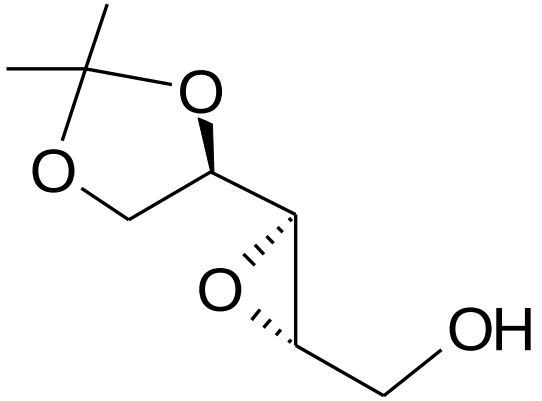
Relative insensitivity to pre-existing chiral centers

- In allylic alcohols with pre-existing chiral centers, the diastereofacial preference of the chiral titanium-tartarate catalyst is often strong enough to override diastereofacial preferences inherent chiral olefinic substrate.

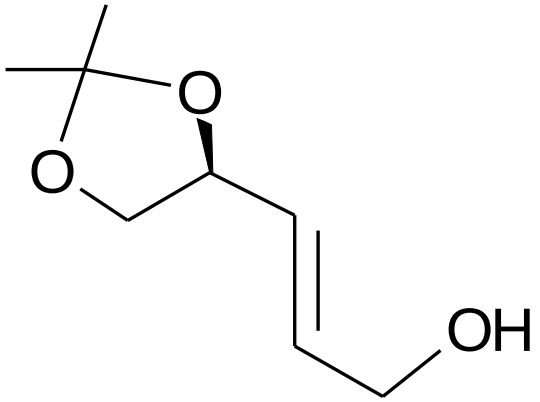


(+)-DET

> 20:1
15 hrs.

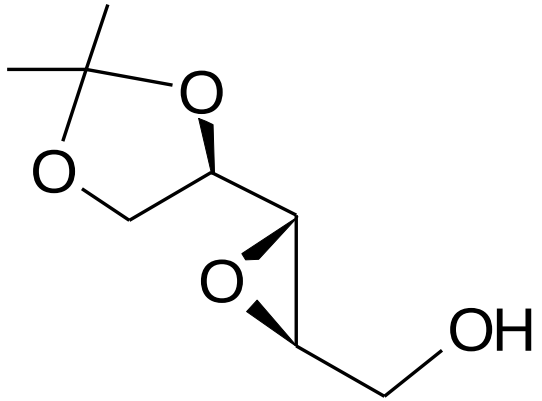


85%

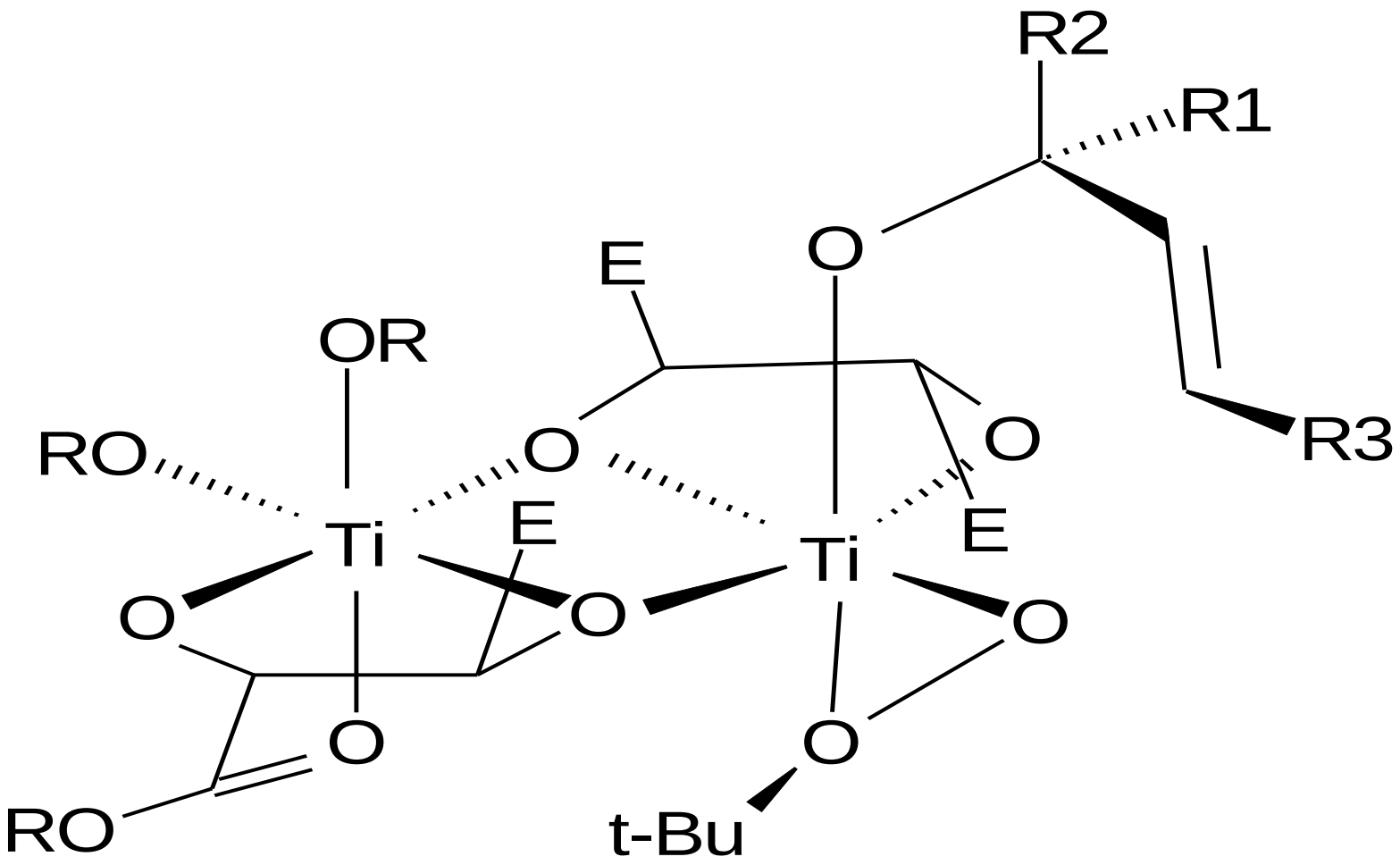


(-)-DET

> 20:1
15 hrs.

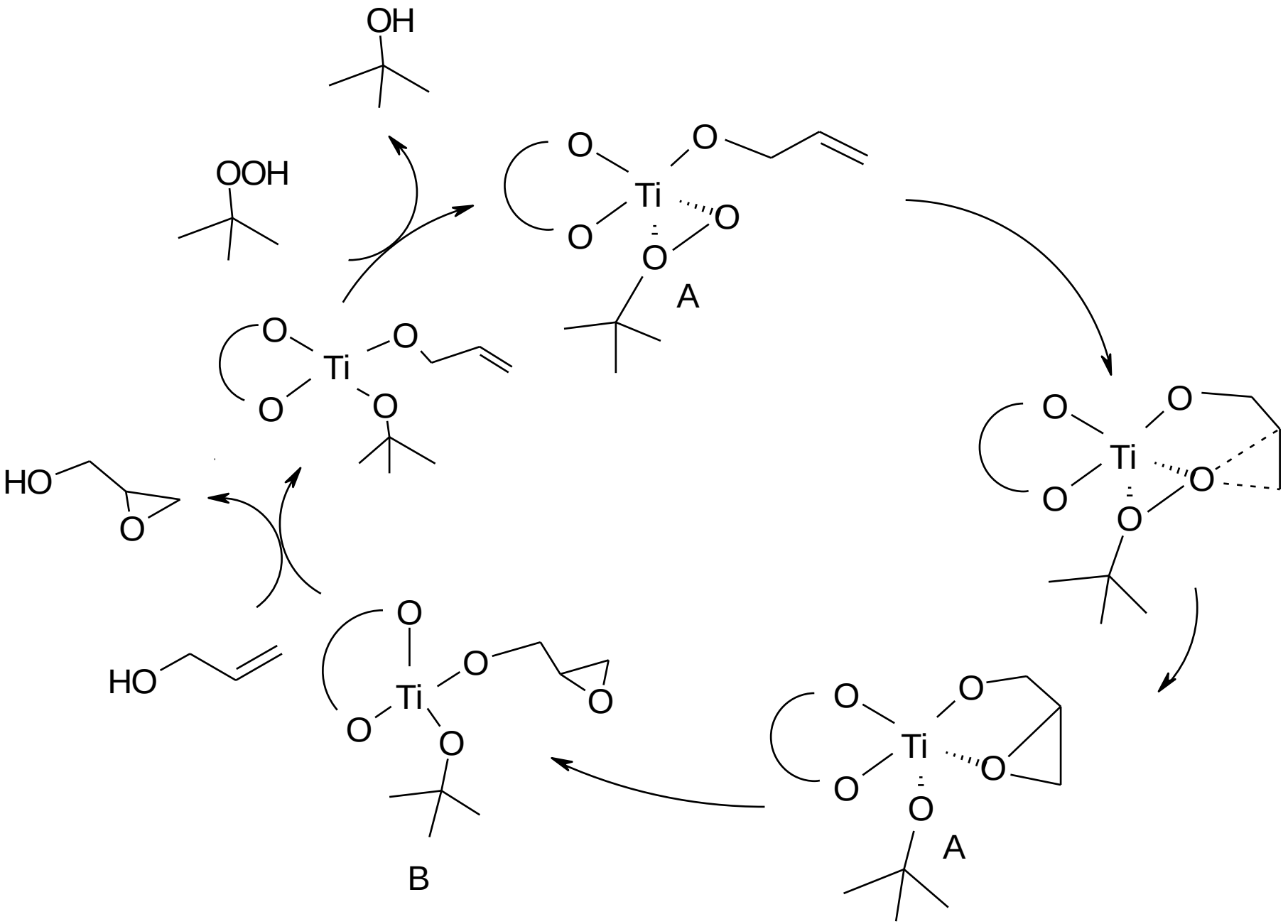


78%



E = COOR

- Presence of bimetallic titanium complex is suggested
- Ti aggregate with octahedral coordination complex.
- Oxidation proceeds at a single Ti center.
- The second Ti atom does not participate in the oxidation.


OH
OOH
O
O
Ti
O
O
A
HO
O
HO
B

Mechanism

- The reaction proceeds via a Ti(IV) mixed-ligand complex A bearing allyl alkoxide and TBHP anions as ligands.

- The alkyl peroxide is electrophilically activated by bidentate coordination to Ti(IV) center.

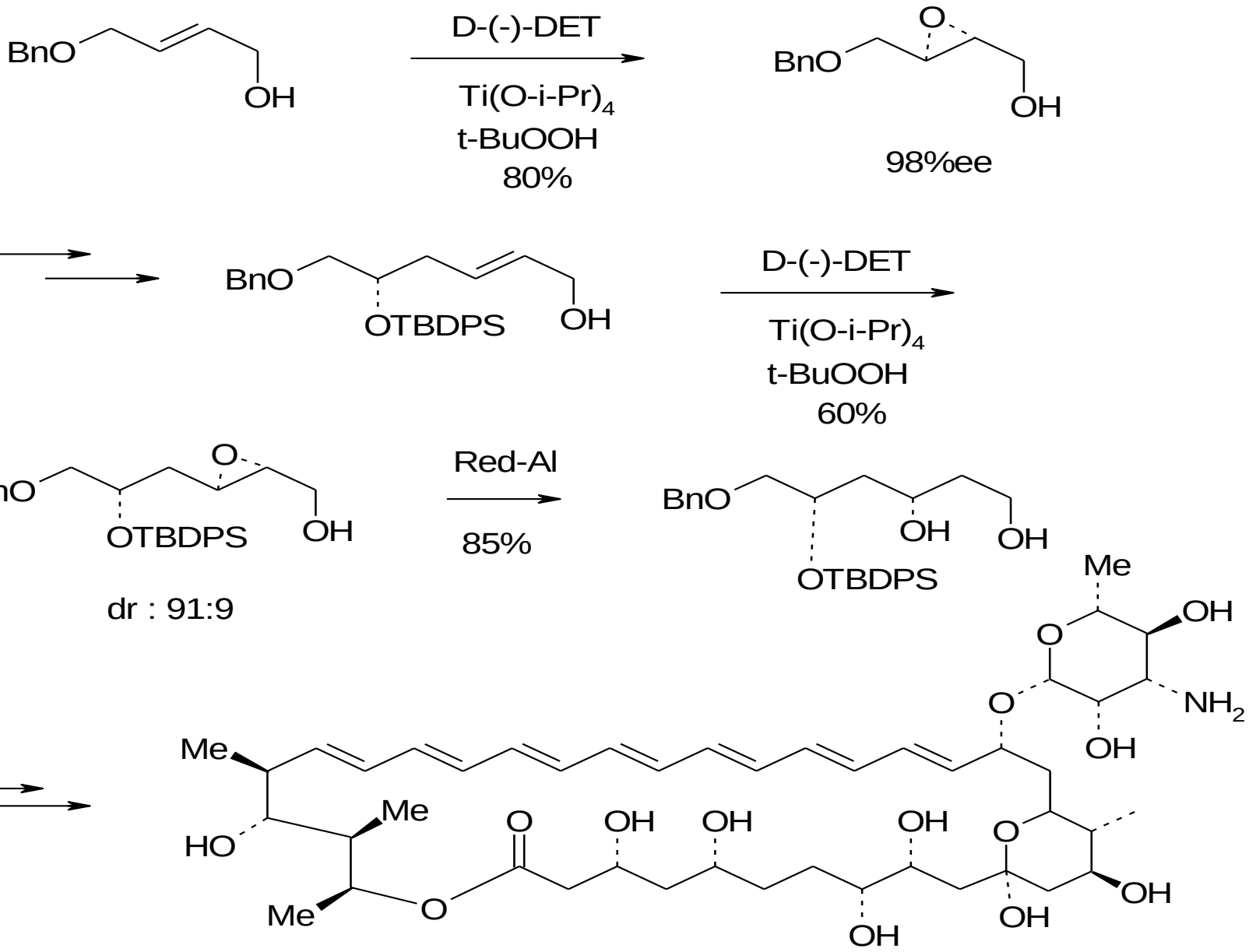
- Oxygen transfer to the olefinic bond occurs to provide the complex B, in which Ti(IV) is coordinated by epoxy alkoxide and t-butoxide.

- In complex B, alkoxide products are replaced by allylic alcohol and TBHP to regenerate A and complete the catalytic cycle.

- The Sharpless epoxidation reaction has been utilized widely in the total synthesis.

- Several advantages: high enantioseelectivity, unambiguous configurational assignments, and epoxide offers a versatile synthon which can be converted into great many products with predictable stereochemistry.

TOTAL SYNTHESIS OF AMPHOTERICIN B [ANTIFUNGAL AGENT]

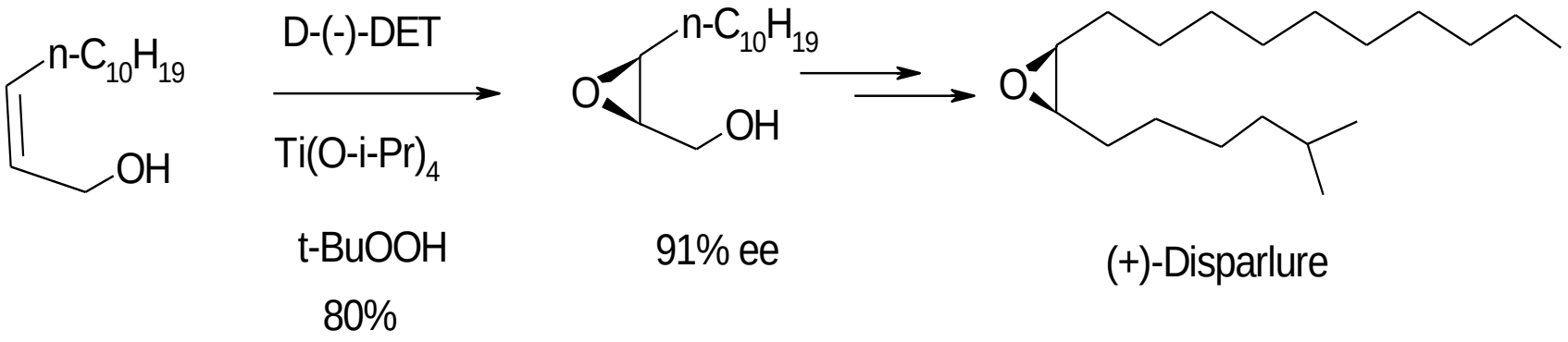


Amphotericin B
(Anti-fungal agent)

- Nicolaou, K. C., et. Al.

A. Chem. Comm., 1292-1293 (1982)
B. JACS, 109, 2205-2208 (1987).
C. JACS, 110, 4572-4685 (1988).
D. JACS, 110, 4685-4696 (1988).
E. JACS, 110, 4696-4705 (1988).

SYNTHESIS OF DISPARLURE, THE SEX ATTRACTANT OF THE GYPSY MOTH.



Rossiter, B. E., Kastuki, T. and Sharpless, K. B., JACS, 103, 464-465 (1981)

Enantioselective dihydroxylation of olefins

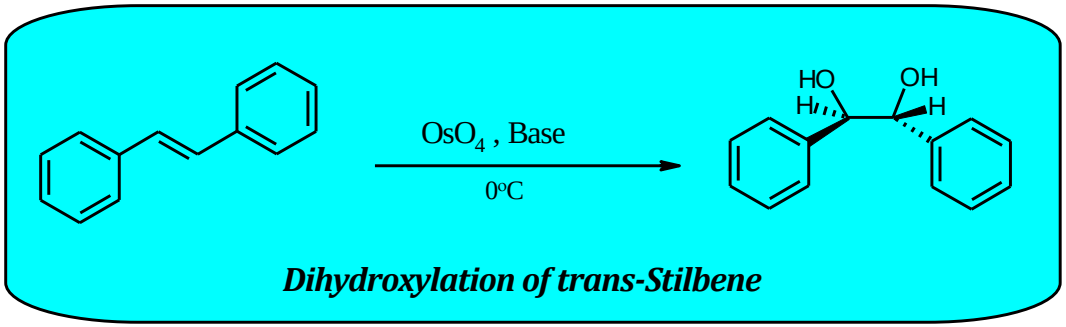
Gradual Development..

- Hoffmann in 1912 showed that osmium tetroxide could be used catalytically in the presence of a secondary oxygen donor for the cis-dihydroxylation.

- Criegee et al reported dramatic rate enhancement for the reaction by use of tert. Amines.

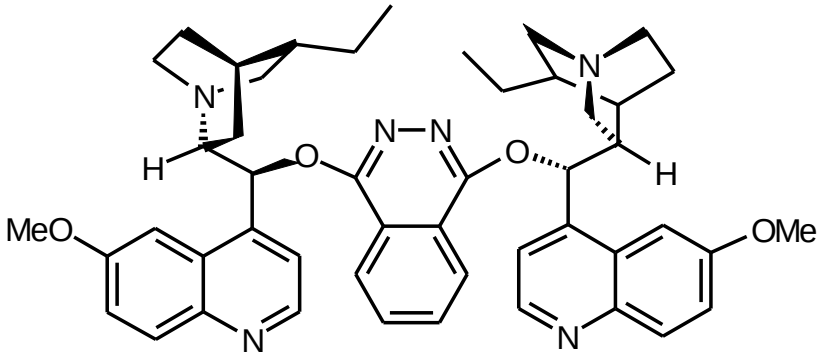
- Sharpless et al first attempted enantioselective dihydroxylation using (l)-2-(2-menthyl)pyridine as a chiral with low enatioselctivity (3-18% ee).

Classical Dihydroxylation

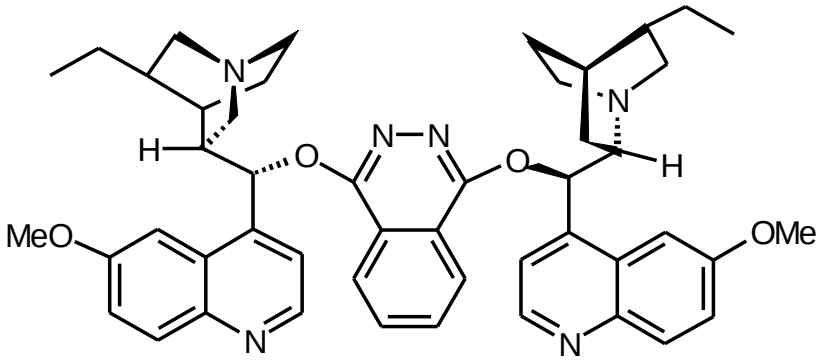


Dihydroxylation of trans-Stilbene

i) OsO_4 is Highly Toxic
ii) OsO_4 is reqiured in 1:1 Stoichiometry



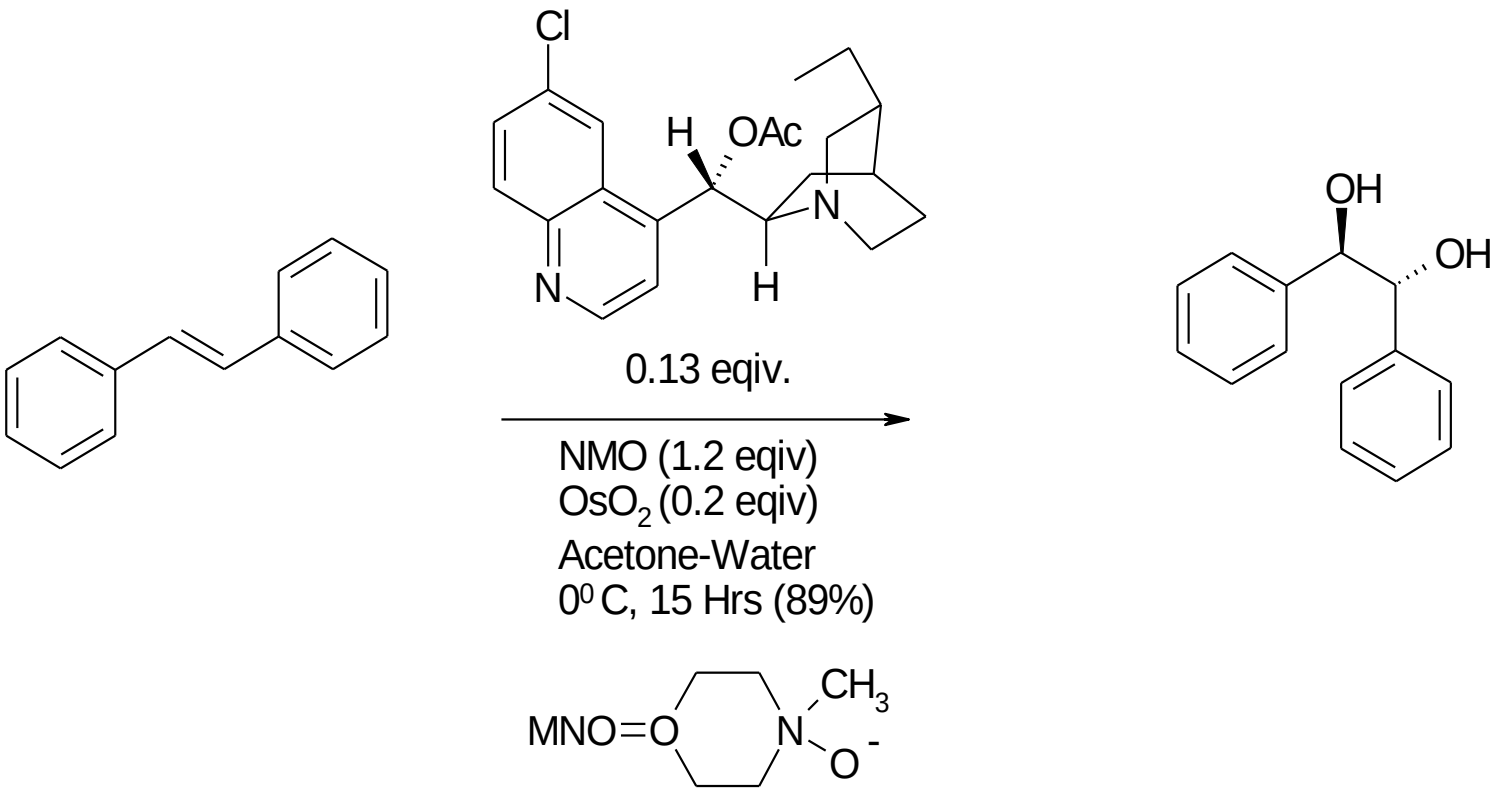
$(DHQD)_2$-PHAL
in AD-mix-β

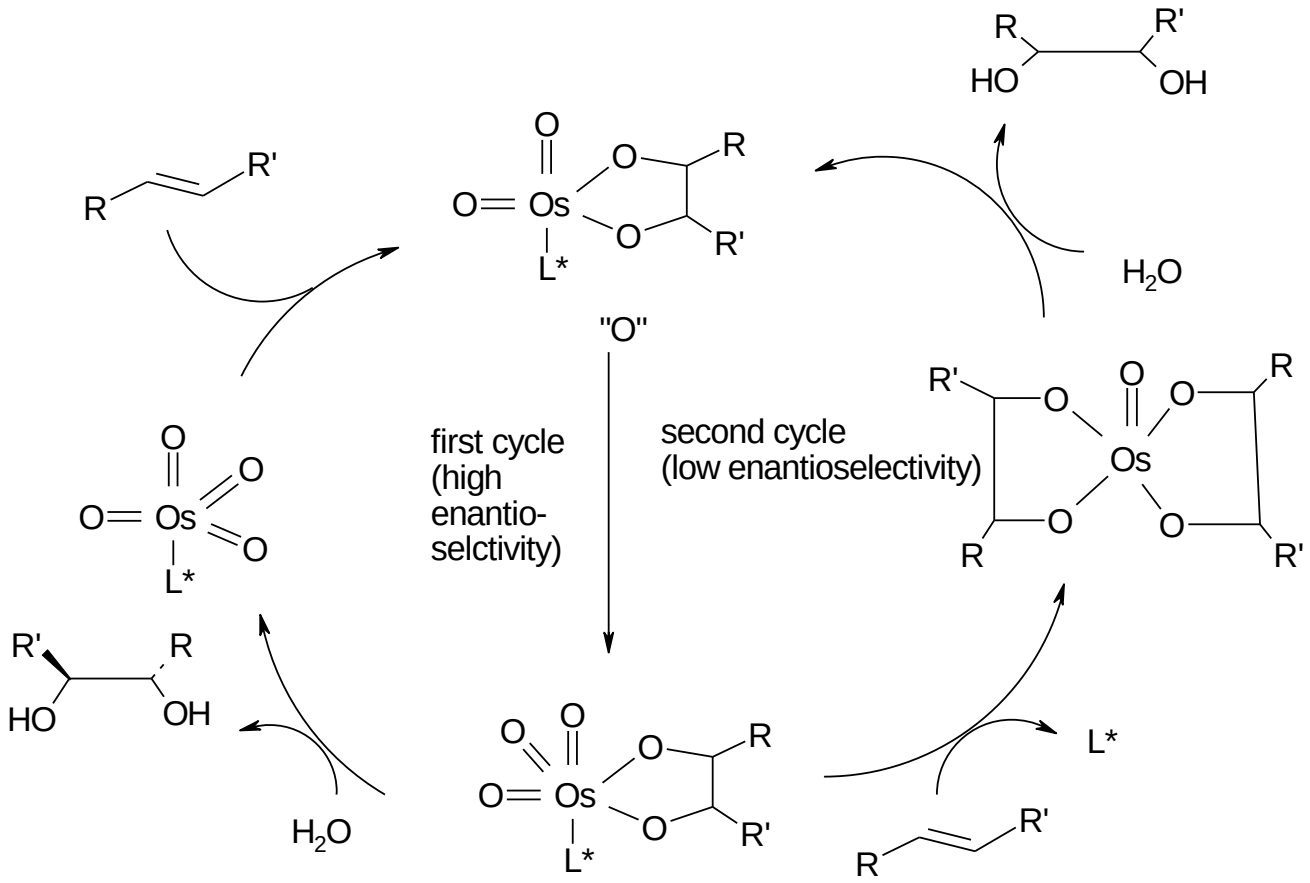


$(DHQ)_2$-PHAL
in AD-mix-α

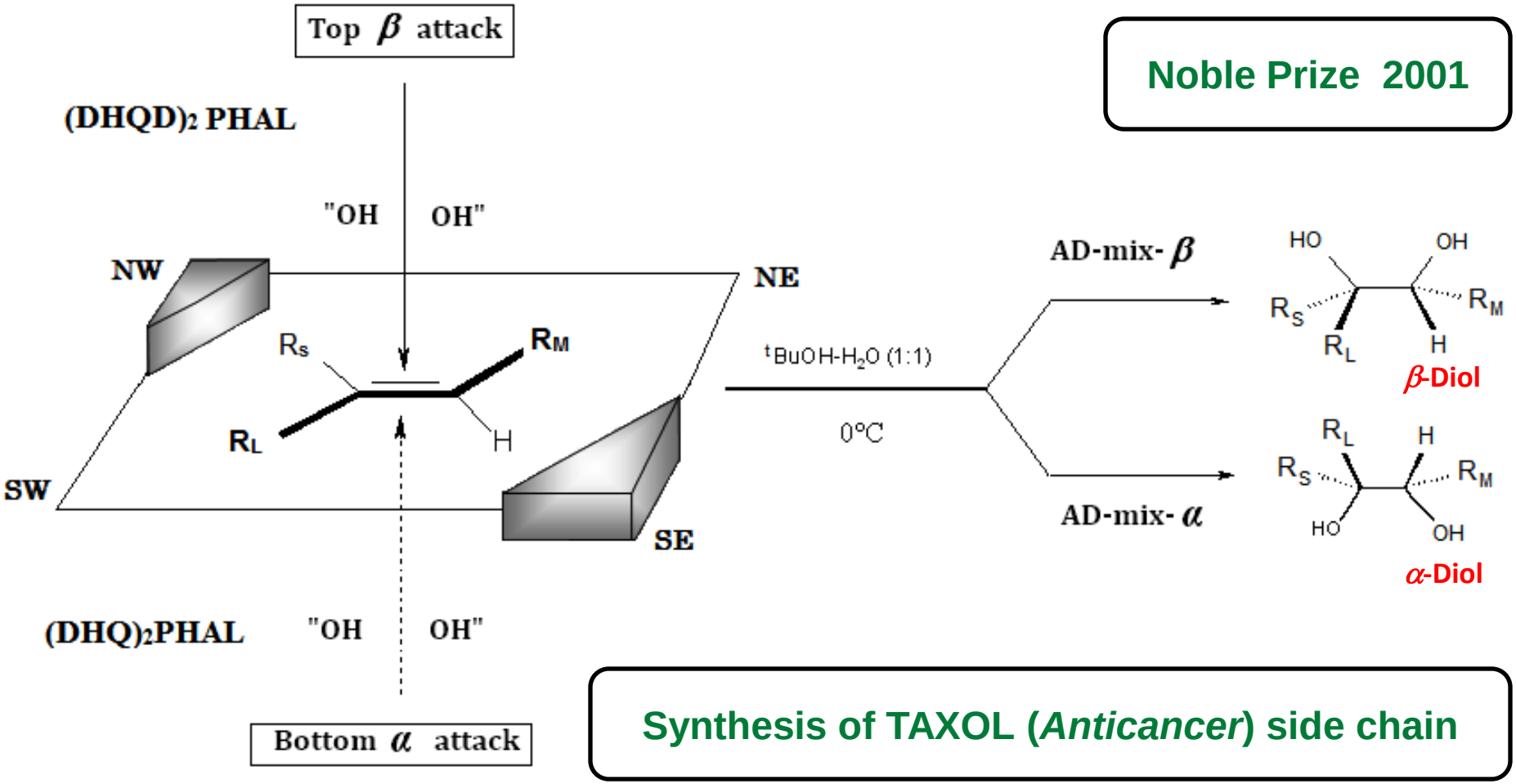
When OsO_4 is used in combination with enantiomeric ligands from plant alkaloid, the stiochiometry of OsO_4 was reduced to 0.2 -1 mole%.

Opposite sense of Stereochemical induction is achieved on switching between the ligands.


Cl
H
OAc
N
N
H
0.13 eqiv.
NMO (1.2 eqiv)
OsO2 (0.2 eqiv)
Acetone-Water
00 C, 15 Hrs (89%)
MNO=O
N
CH3
O -
OH
OH


R
R'
O
Os
L*
"O"
R
HO
OH
H_2O
first cycle
(high
enantio-
selctivity)
second cycle
(low enantioselectivity)
L*

Sharpless' Asymmetric Dihydroxylation



Noble Prize 2001

Synthesis of TAXOL (*Anticancer*) side chain

The Mnemonic device for predicting the facial selectiviy during Asymmetric Dihydroxylation of Alkene

Sharpless, B.; Amberg, W.; Bennani, Y. *J.Org. Chem.* **1992**, *57*, 2768-2771

P-Stereogenic Ligands in Asymmetric Synthesis

“We felt strongly that, if one wanted to get high ee values, the asymmetry would have to be directly on the phosphorous. That is where the action is.”

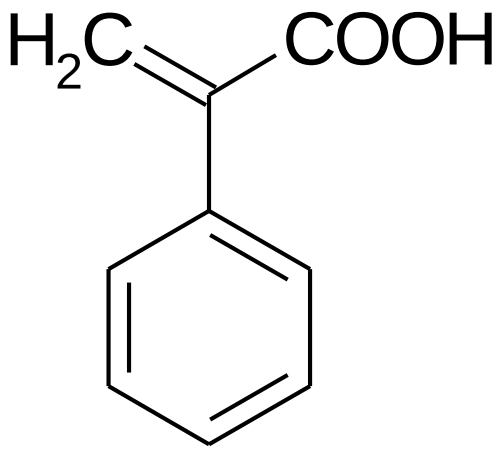
William S. Knowles, Nobel Lecture (December 8th, 2001)

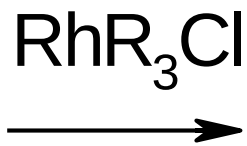
Gradual Development…

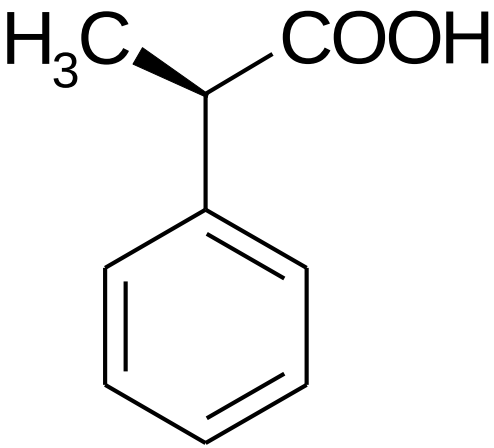
- In 1965 Wilkinson and co-workers reported that a soluble Rh(I) complex, [$RhCl(PPh_3)_3$], was an excellent pre-catalyst for alkene hydrogenation under mild conditions.

- The research groups led by Knowles [Chem. Commun., 1968, 1445] and Horner [Angew. Chem. Int. Ed. 1968, **7**, 942]independently replaced the achiral triphenyl phosphine ligands in the Wilkinson's catalyst by optically enriched P-stereogenic phosphines.

- In the initial experiments the optical yields were low, but proved that enantioselective homogeneous hydrogenation was feasible



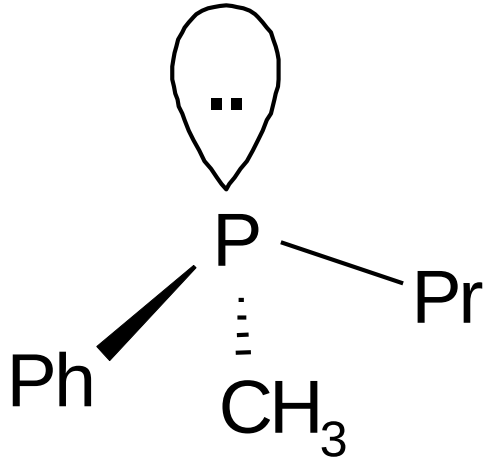




Aryl acrylic acid

15% ee

R =



Nobel lecture:

- While grouping in this area another seemingly unrelated development appeared, which played an important role in our project. This was the discovery that a fairly massive dose of L-DOPA was useful in treating Parkinson's disease.

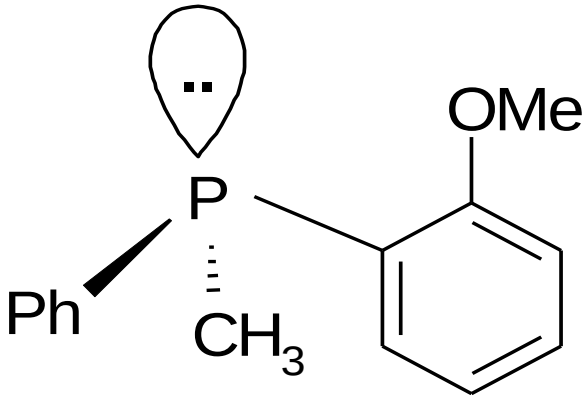
- It created a sizeable demand for this rare amino acid.

- "Story of a heavy infusion of 'naivety' [a lack of experience / wisdom]. Frequently it is not the experts that do the inventing, but they are the ones who, that once the lead is established, come in and exploit the area. Our work is an excellent illustration of this phenomenon."

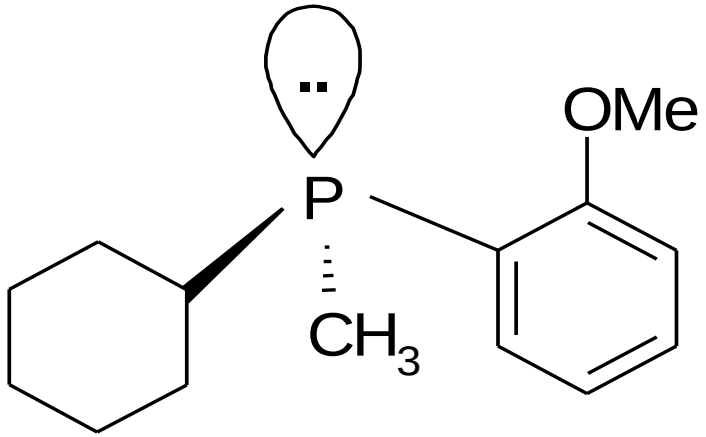
- Wilkinson's catalyst first major step.

- Development of methodology for making chiral phosphines by Mislow and also by Horner, laid the platform.

Mosanto modifications
Enhanced enantioselectivity



PAMP

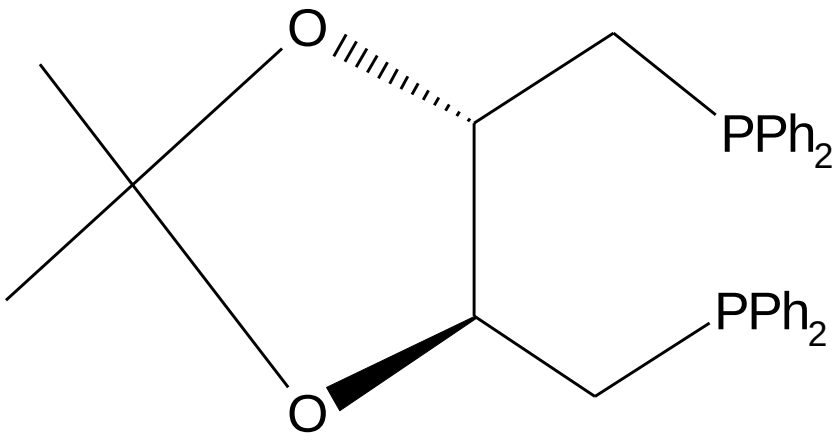


CAMP

Nobel lecture: Knowles

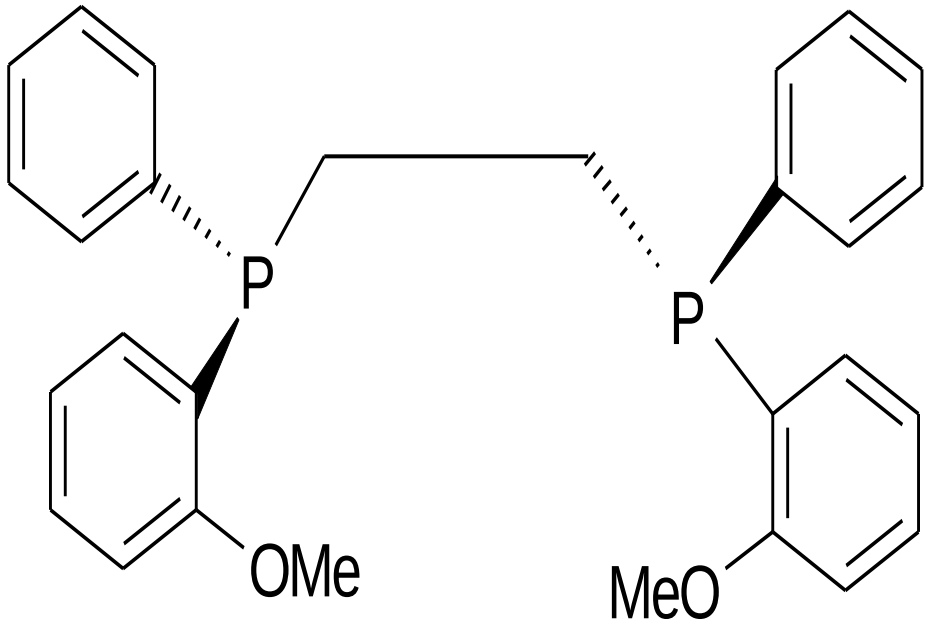
- We had hypothesized that to get good results one needed chirality directly on the phosphorous atom. It made sense, but Professor Kagan showed us to be totally wrong.

- Kagan’s discovery of DIOP was the wave of the future for a whole series of bisphosphine ligands with asymmetry on the chiral backbone.

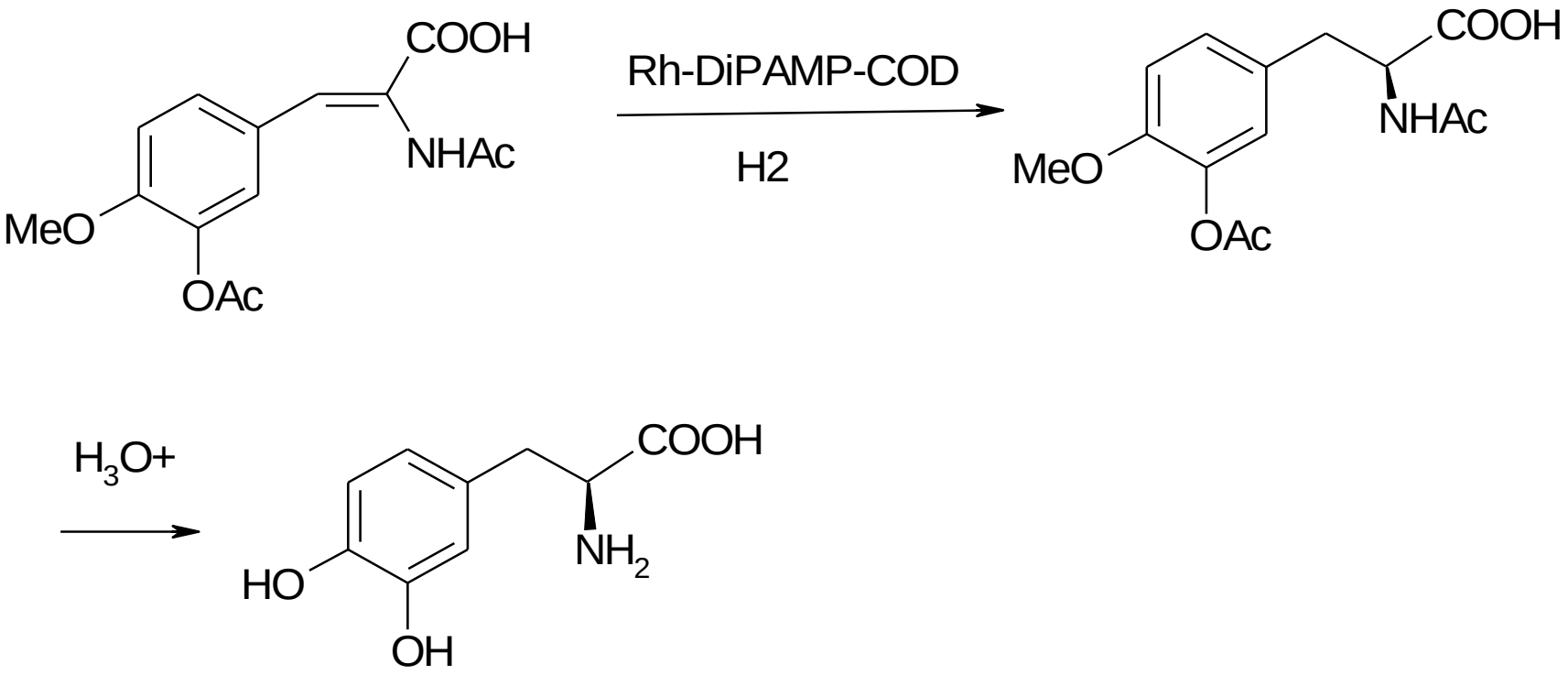


Kagan's DIOP

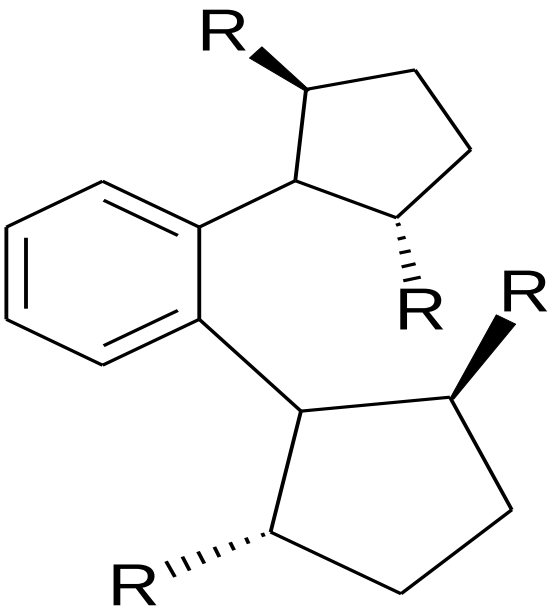
(R,R)-DiPAMP



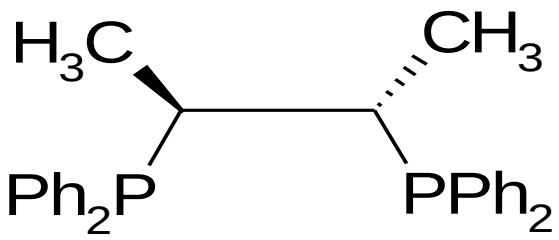
Mosanto L-DOPA Synthesis



Efficient C_2 symmetric diphosphines



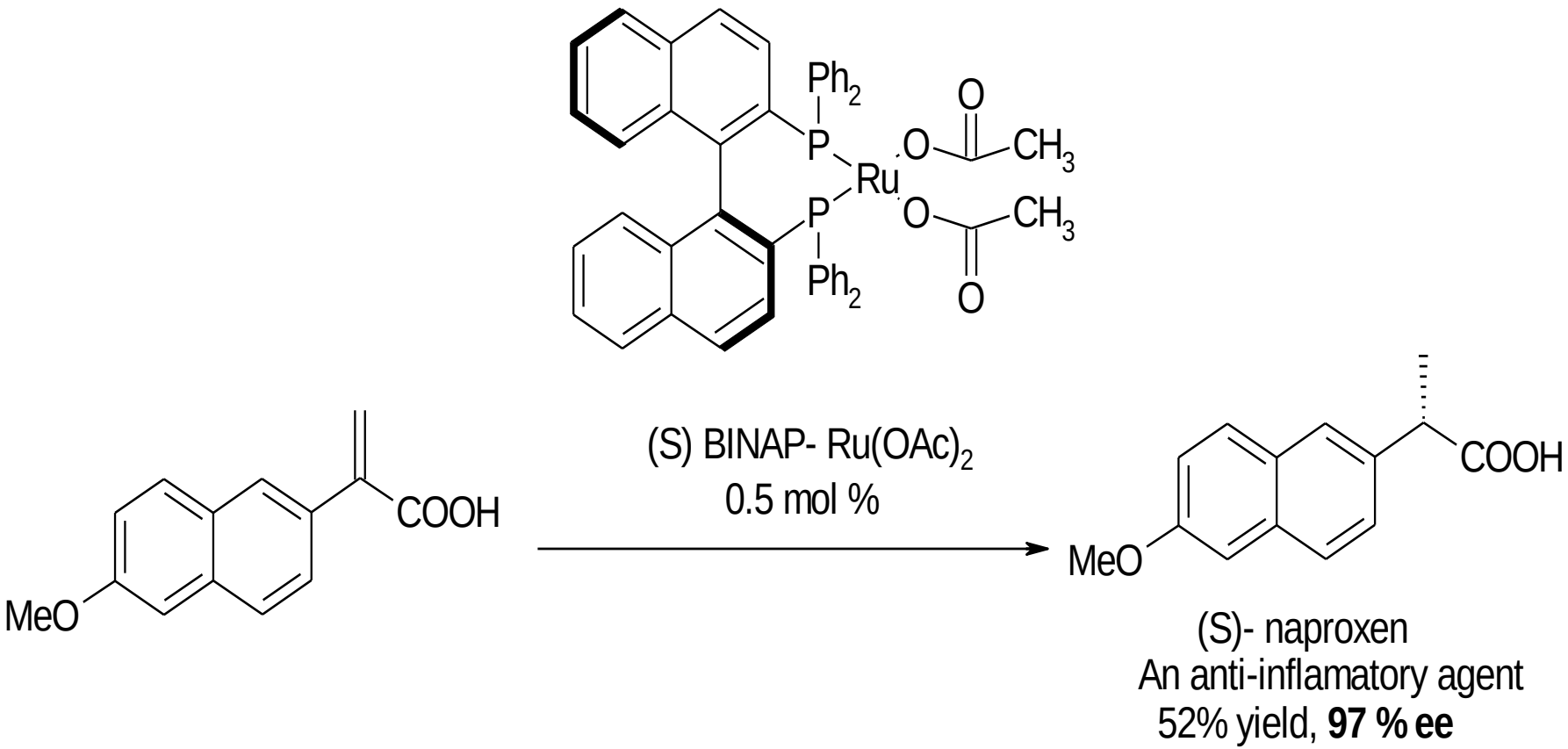
DuPhos



ChiraPhos

Nobel lecture: Knowles

One system which did not work well in our system was our original model, α-phenylacrylic acid. A number of these aryl propionic acids have value as non-steroidal anti-arthritics. Here, as is the usual case, only one enantiomer is active and thus a process to make one isomer directly was needed. We tried hard to solve this problem even using ruthenium-ligand systems but without success. It took Professor Noyori with his BINAP-Ruthenium complex to solve this problem.



(S)- naproxen
An anti-inflamatory agent
52% yield, **97 % ee**

Reference: R. Noyori, Inorg. Chem, 27, 566 (1988).

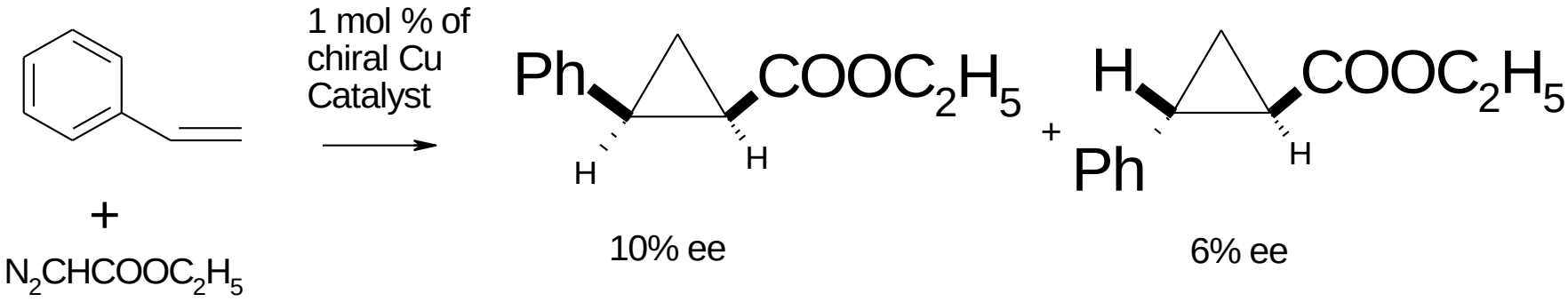
Nobel Lecture: Noyori

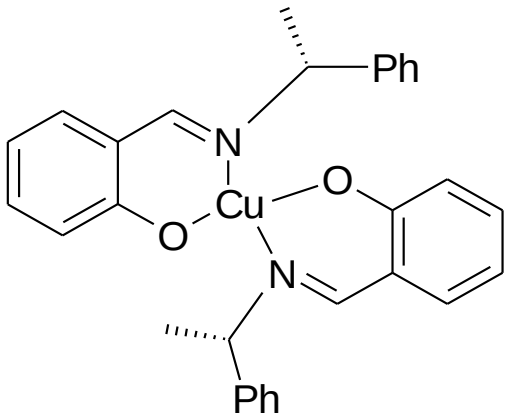
- In 1956, S. Akabori at Osaka reported that metallic Pd drawn on silk catalyzes asymmetric (heterogeneous) hydrogenation of oximes and oxazolones [S. Akabori*, S. Sakurai, Y. Izumi, Y. Fujii, *Nature* ***1956, 178, 323.***].

- This pioneering work, though not effective synthetically, was already well known throughout Japan.

- In 1968, two years after our asymmetric cyclopropanation in 1966, W. S. Knowles (fellow Nobel laureate in 2001) and L. Horner reported independently the first homogeneously catalyzed asymmetric hydrogenation of olefins with chiral monodentate tertiary phosphine–Rh complexes, albeit in 3–15% optical yield[16].

Noyori, Nozaki at Kyoto: First catalytic organometallic asymmetric synthesis





Chiral Cu catalyst

Industrial asymmetric synthesis of (-)-menthol

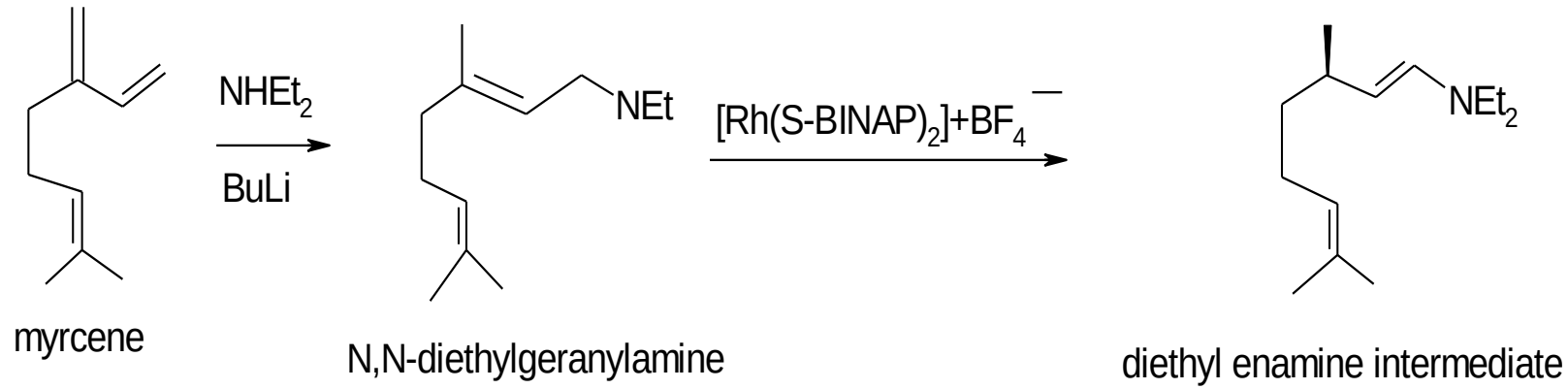
- Menthol is used in many consumer products such as toothpaste, chewing gum, cigarettes, and pharmacutical products, with an estimated worldwide consumption estimated at 4500 tons per year.

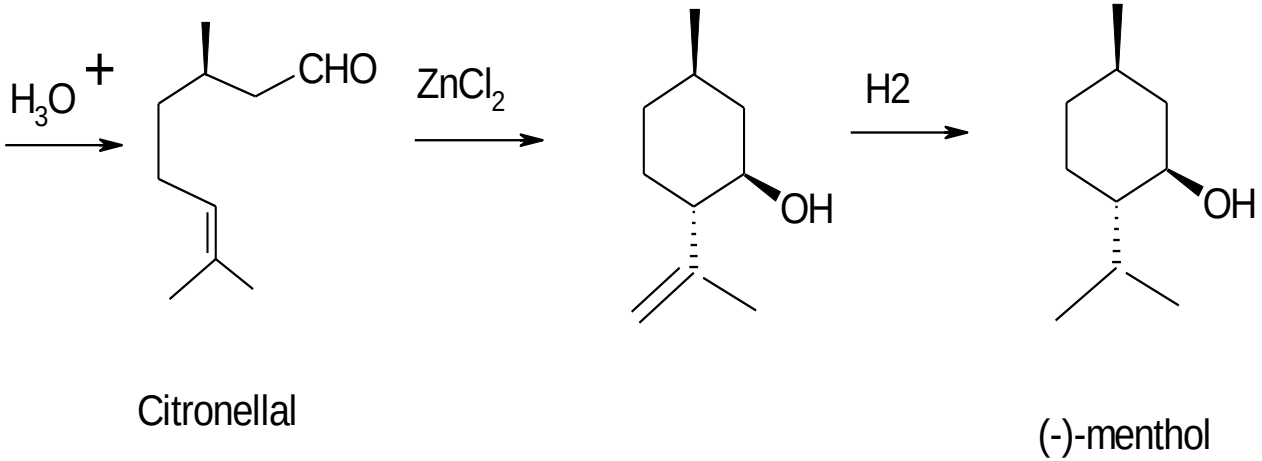
- The key step in the process is the asymmetric isomerization of N,N-diethylgeranylamine catalysed by $[Rh(S\text{-}BINAP)2]^{+}BF4^{-}$ to the diethyl enamine intermediate in 96-99% ee.

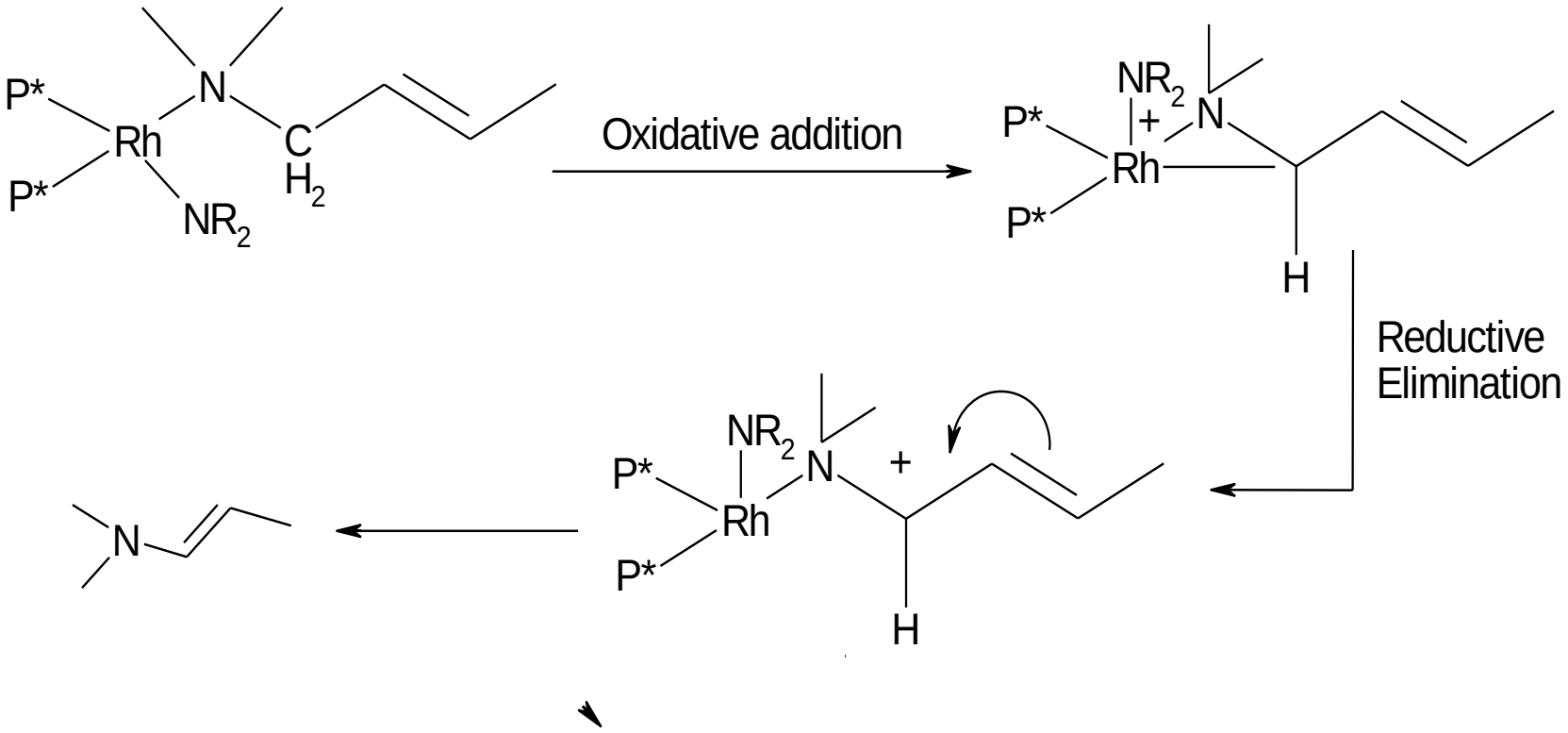
- Citronellal is obtained in 100% ee after hydrolysis; natural citronellal has an optical puity of 80%.

- The TON is improved to 4,00,000 through catalyst recycle.

Industrial asymmetric synthesis of (-)-menthol





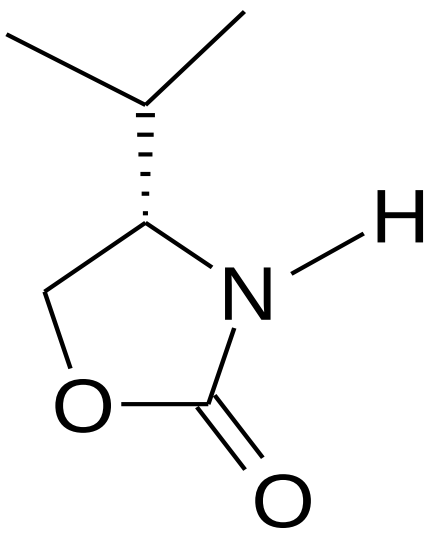

P*
Rh
P*
N
C
H2
NR2
Oxidative addition
NR2
+
N
P*
Rh
P*
H
Reductive
Elimination
NR2
N
+
P*
Rh
P*
H
N

Optically active terpenoids produced by asymmetric isomerization of allylamines

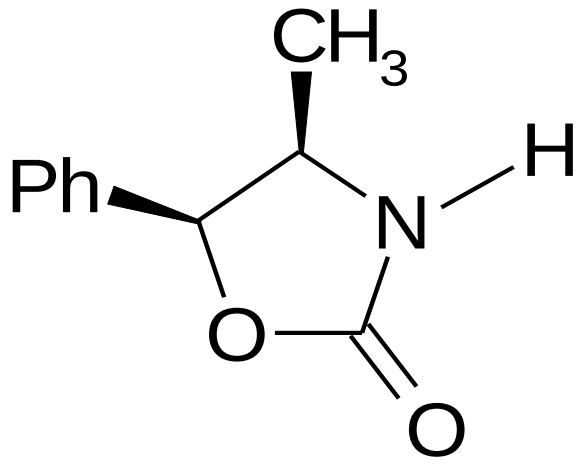
Name	Usage	EE%	Production (tons/year)
(-)-Citronellal	Intermediate	96-98	1500
(-)-menthol	Pharmaceuticals, Tobaco, Household products	100	1000
(-)-Citronellol	Fragrances	98	20
(+)-Citronellol	Fragrances	98	40
S-7-Methoxy-citronellal	Insect growth regulator	98	10
S-3,7-dimethyl-1-octanal	Insect growth regulator	98	7

CHIRAL AUXILIARIES

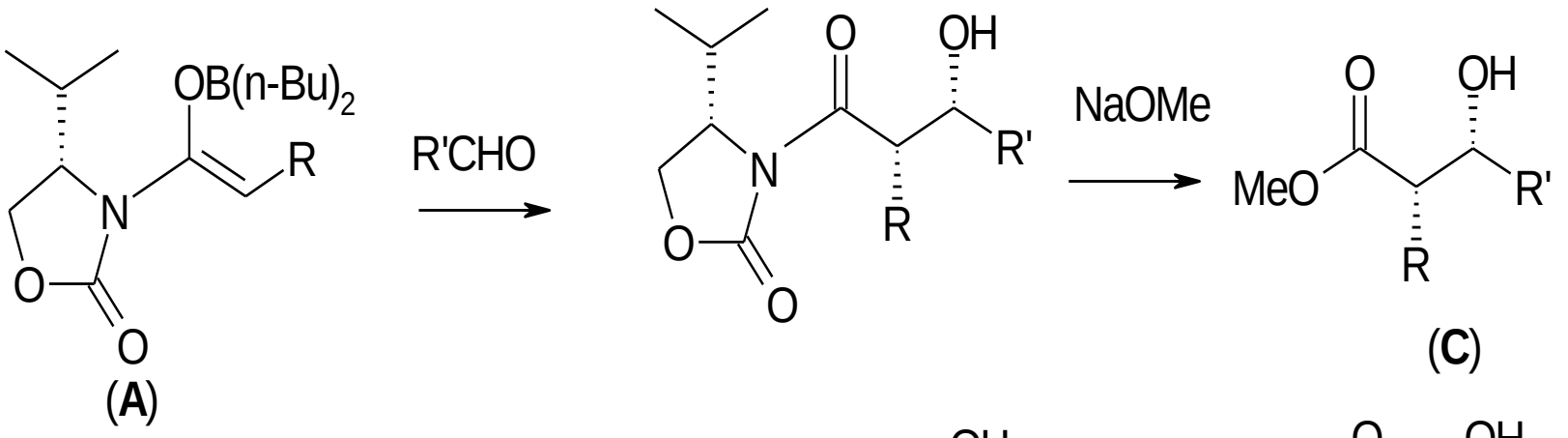
Chiral oxazolidines



A

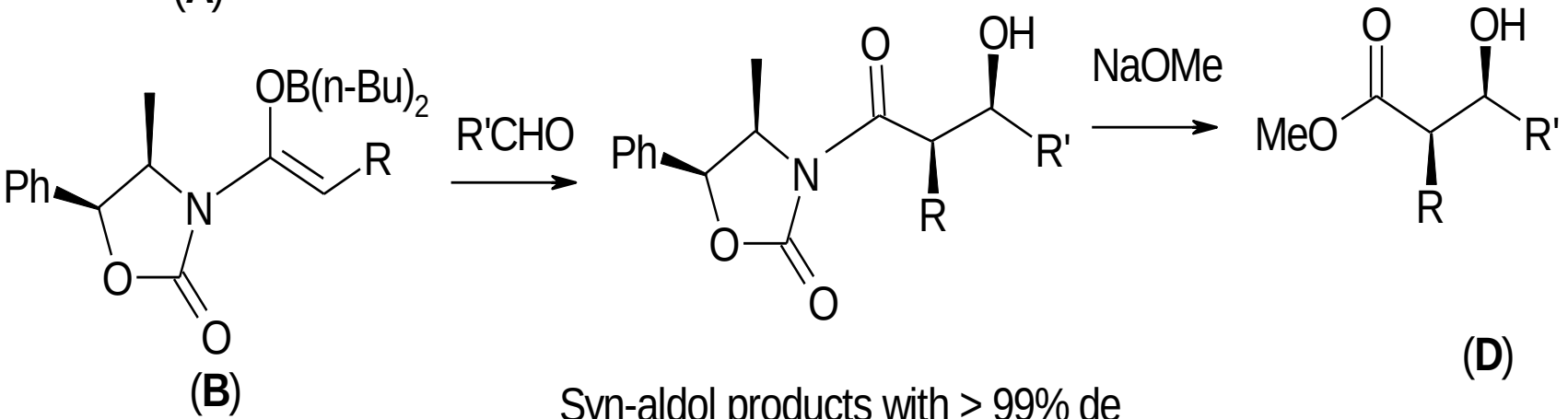


B



(**A**)

(**C**)



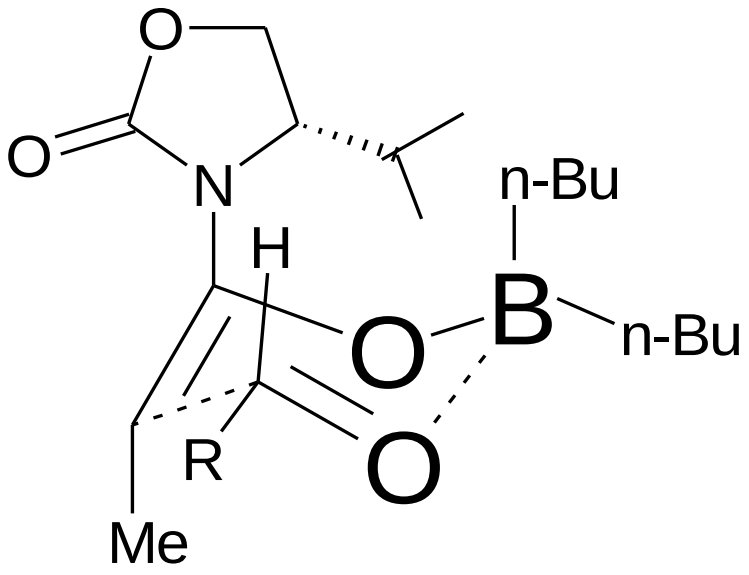
(**B**)

(**D**)

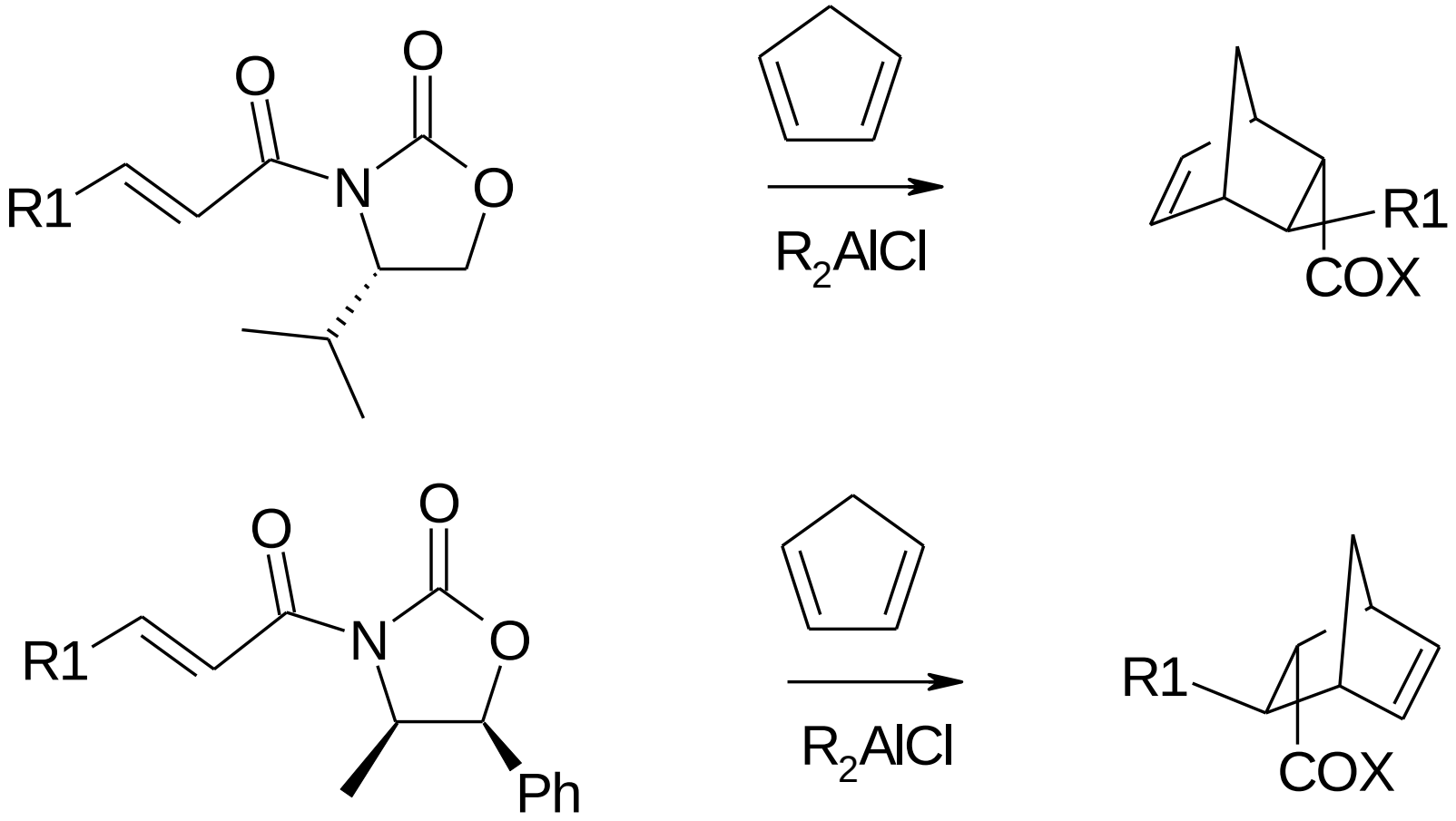
Syn-aldol products with > 99% de
Use of **A** and **B** results in the
formation of enantiomeric products **C** and **D**

Asymmetric Aldol

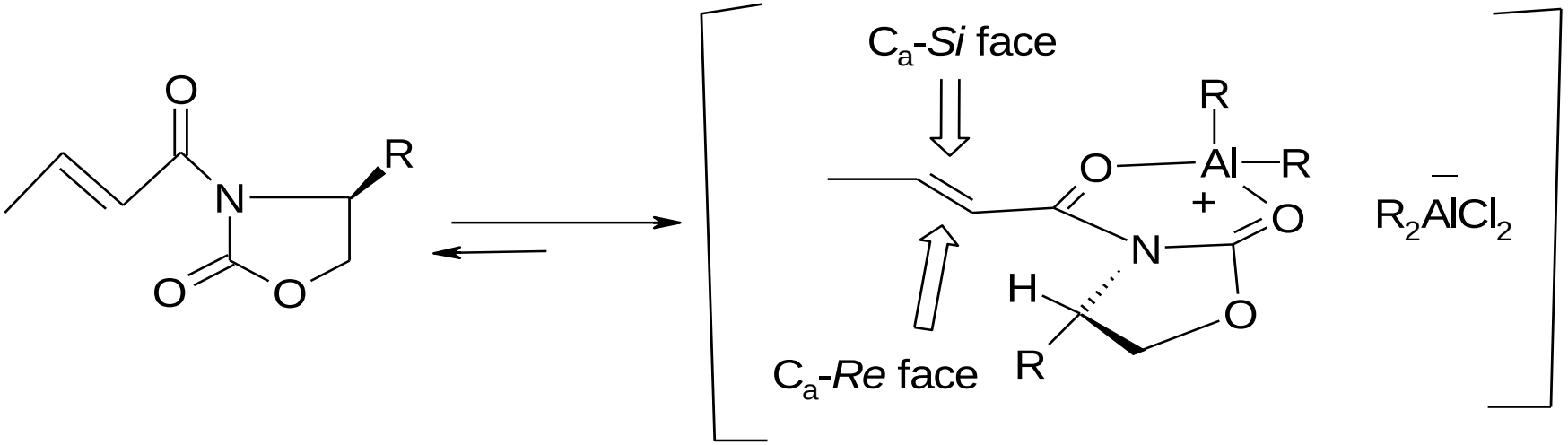
- Z-enolates are used [prepared by using di-n-butylboron & TEA]
- Stereoselectivity results from bidentate chelation of the boron via a chair-type transition state

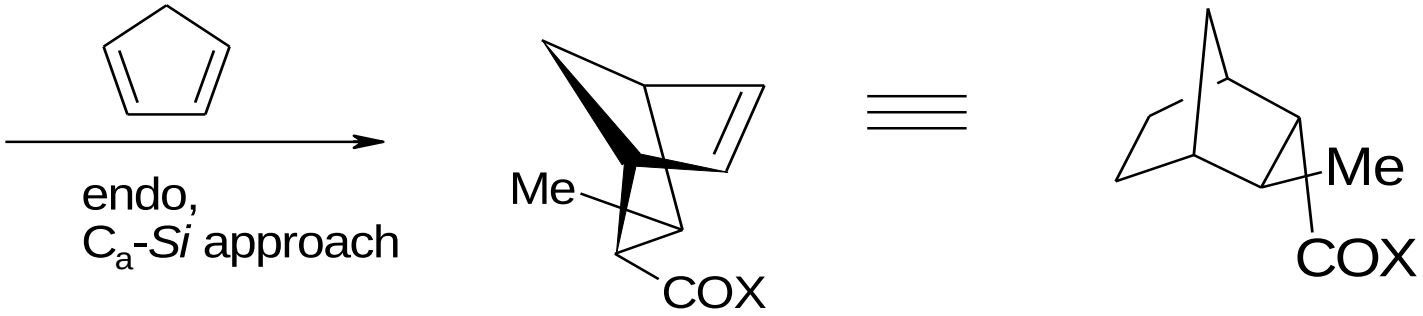


CHIRAL OXAZOLIDINONES AS CHIRAL AUXILIARIES FOR ASYMMETRIC DIELS –ALDER REACTIONS



Evans, D. A.; Chapman, K. T.; Bisaha, J., JACS, 1988, 110, 1238



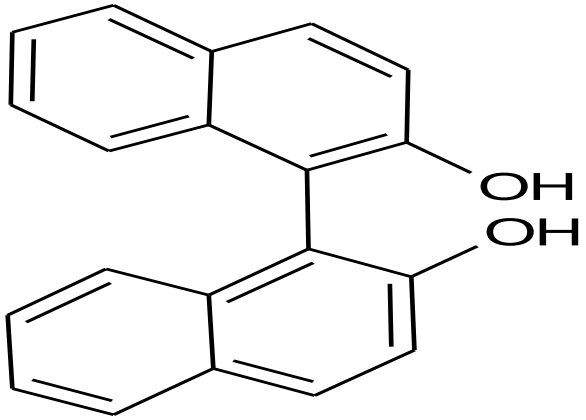


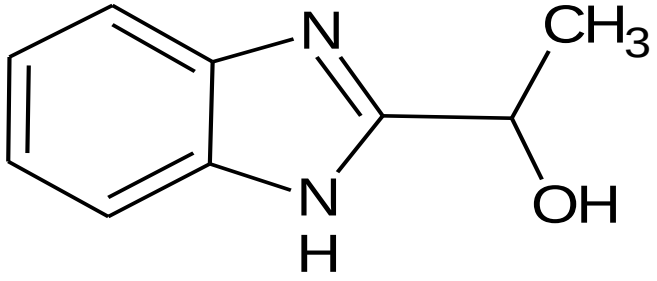
Evans, D. A.; Chapman, K. T.; Bisaha, J., JACS, 1988, 110, 1238

Research Area Of Our Group ….

We focus on synthesizing novel chiral molecules and to study their application various chiral discriminating processes.

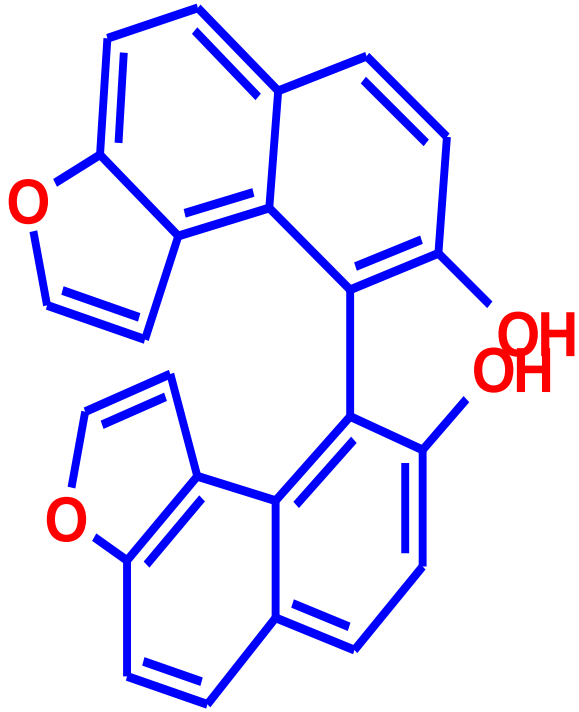
Hetero-atoms such as Oxygen and Nitrogen are two important legating sites in our molecules.



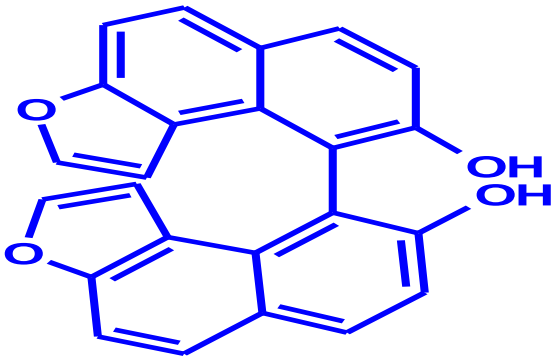


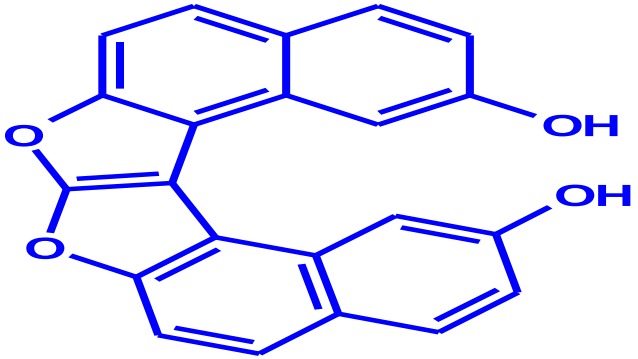
Furo fused Binol …..

- In 2007, our group publishd first report of synthesis and application of furo fused binol and its crown.
- Publications…..

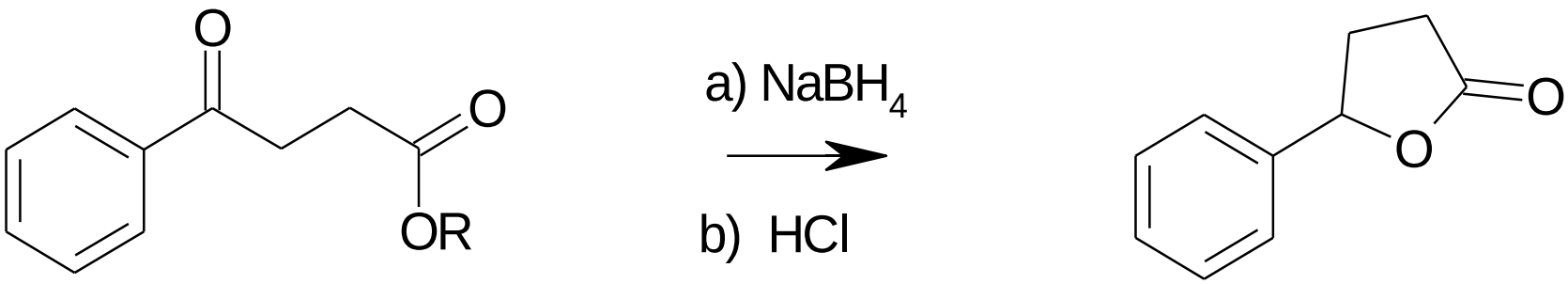


Moving ahead .. in target Oriented Research

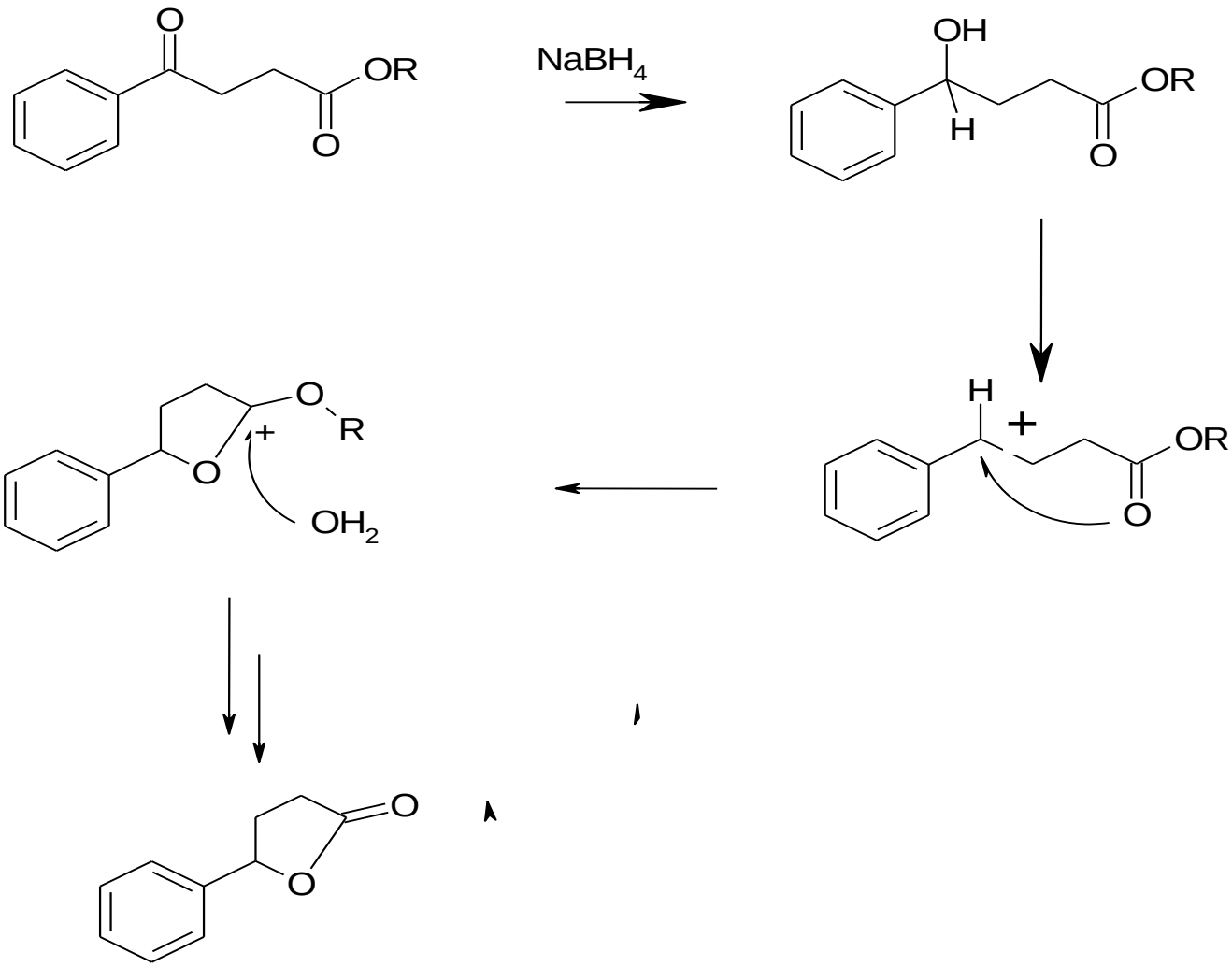




- With the success of furo fused Binol , we extended our interest in synthesizing a new hetero-helicene molecule.
- BINOL to HELICENE …. Just a transfer of chirality
- DST, India gave us the financial support to our group to carry out this challenging research project.


O
O
OR
a) NaBH4
b) HCl
O
O

Following mechanism was considered possible for the above conversion:



The reaction with l-menthol and (-)borneol, chiral maximum % ee was 99%,

New J. Chem., 2004, 28, 1420-1422.

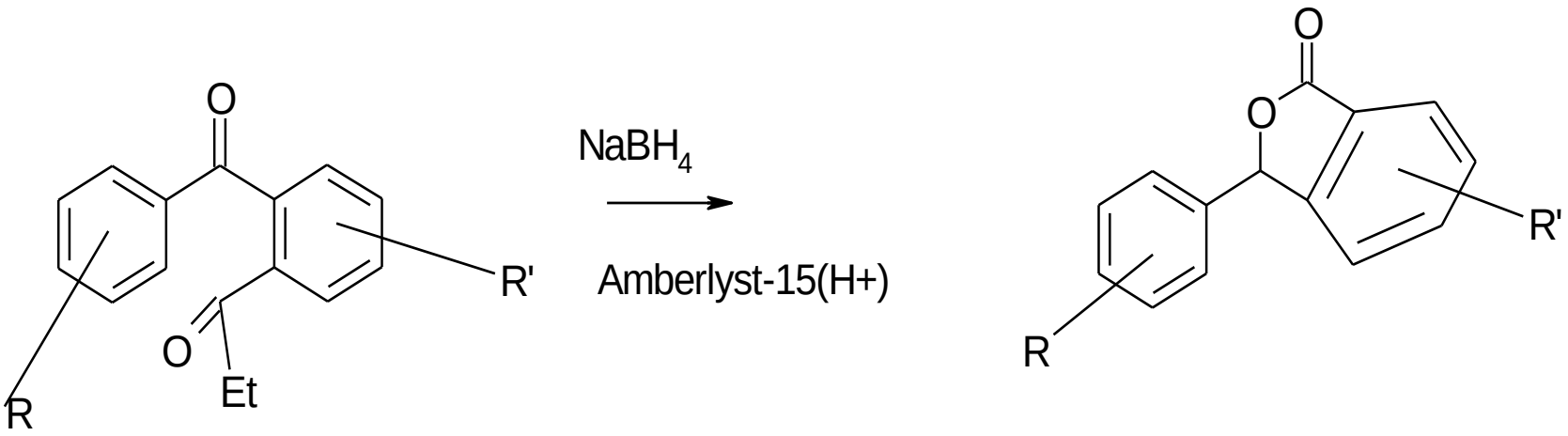
- Secondary alcohols, especially with aryl substituent, generate carbocation on treatment with acid, this can be attacked by an internal nucleophile.

- This Concept was used for some important schemes

Cascade synthesis of racemic 3–arylphthalides

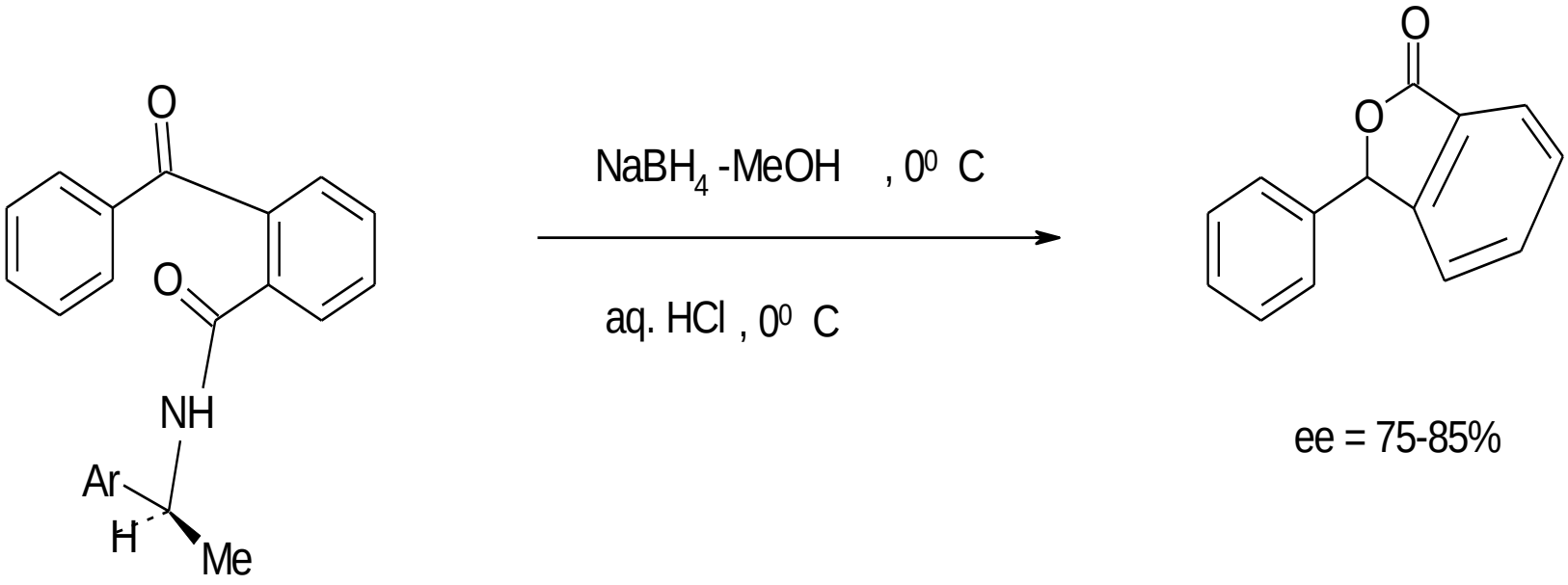
Sudhir Patil

Indian J. Chem., 46B, 2007, 710-712



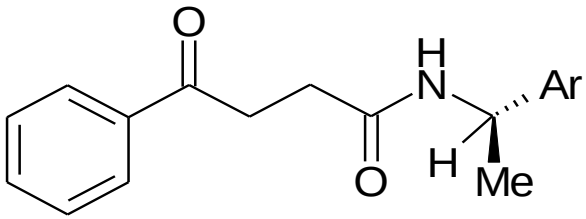
Cascade Enantioselective synthesis of 3-arylphthalides using chiral auxiliary route

Suchitra Kamath, Synthesis, 2008, 1832-1834

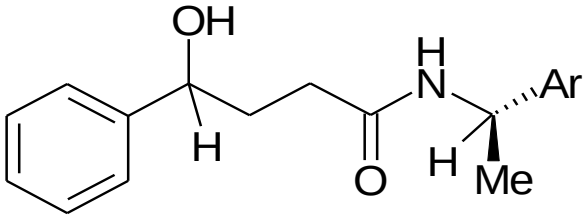


Cascade Enantioselective synthesis of γ-aryl- γ-butyrolactone with a delayed steroselective step
Suchitra Kamath, Tetrahedron, 64, 2008, 2992-2996

- It was established with HPLC data that the reduction step was not stereoselective, the further cyclization occurs with diastereo-selectivity.

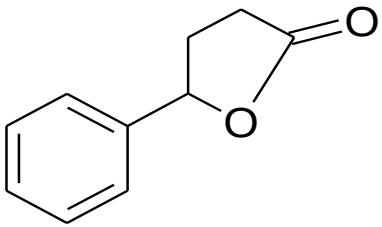


$NaBH_4$



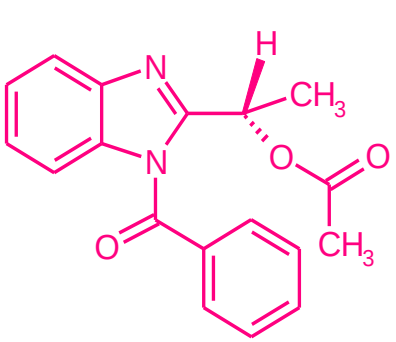
No diastereoselective reduction based on HPLC analysis

- 5^0 C - 0^0 C
6M HCl



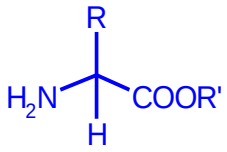
ee = 67 - 73 %

Kinetic Resolution Of Amino Esters



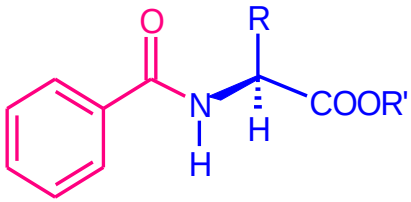
"Benzimidazolide"

2



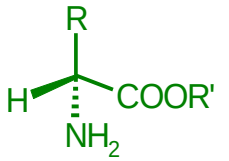
THF

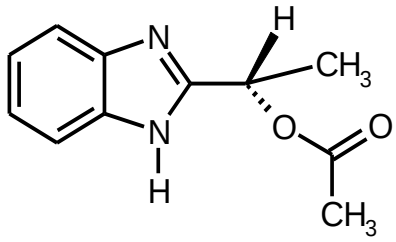
-10 °C , 12 hrs



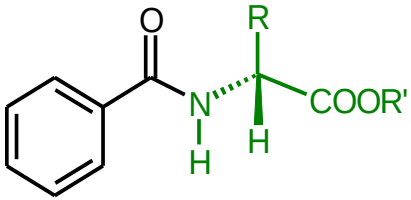
(*S*)- Isomer

ee = 89-92%





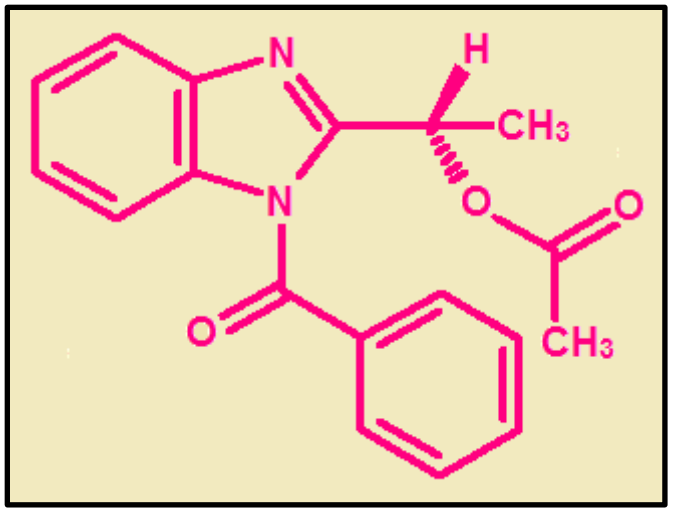
PhCOCl,
Pyridine
0° C



(*R*)- Isomer

Unreacted aminoester
converted to N-Benzoyl amino ester

Benzimidazolide : A successful Chiral Auxilliary for Kinetic Resolution of Amioesters (2005-2008)



The above chiral benzimidazolide was used for enantioselective benzoylation of chiral racemic amines and amino esters with ee ≤ 90%

- ✓ Kamath, S. S. & Karnik, A. V., *J. Org. Chem*, **2007**, *72*, 7435-7438.
- ✓ Kamath, S. S. & Karnik, A. V., *Tetrahedron Asymmetry* **2008**, *19*, 45-48.