ASYMMETRIC SYNTHESIS

BY

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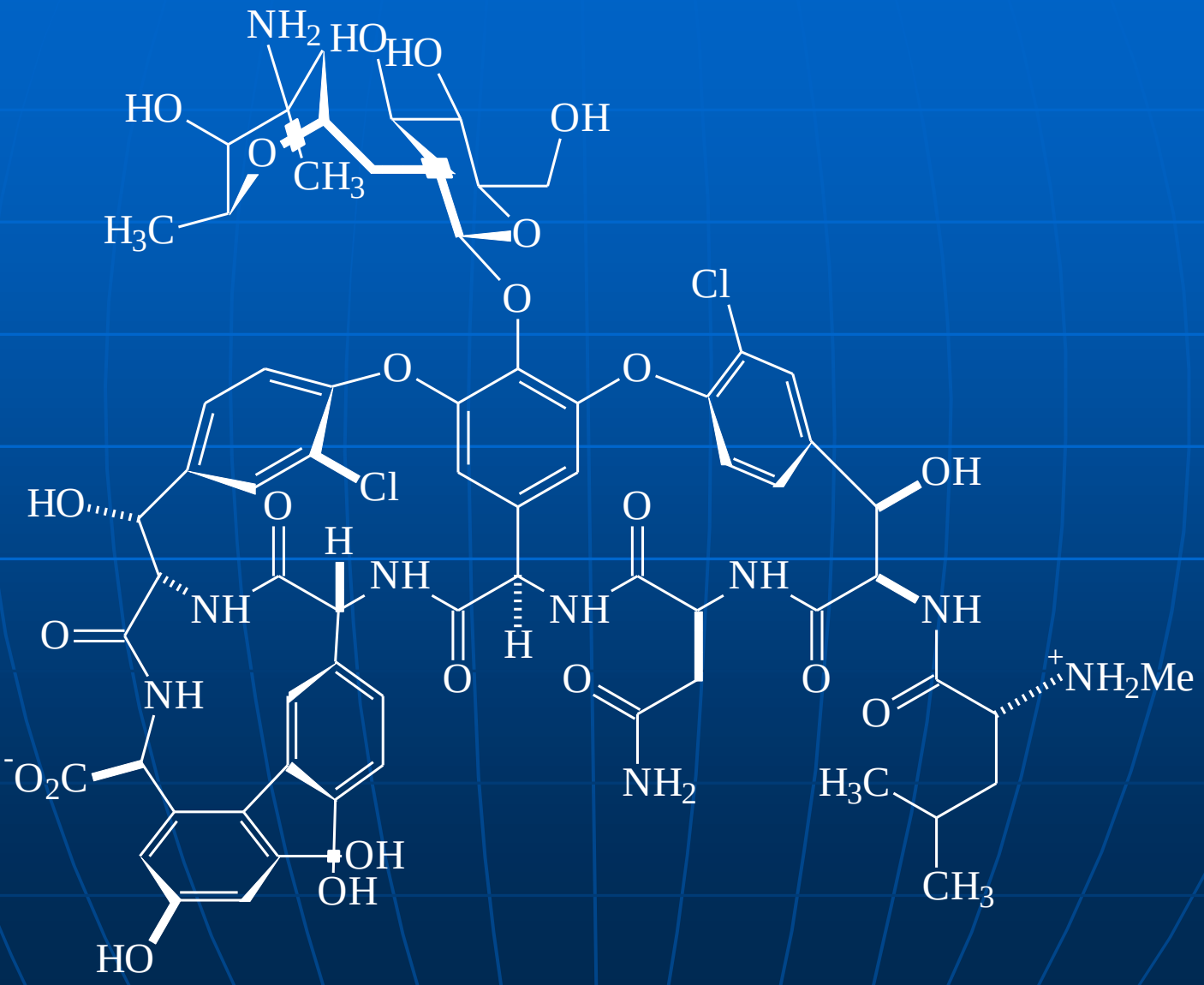
Asymmetric Synthesis

Introduction

Outline

- Introduction
- Principles
- Addition to carbonyl compounds
- α-Substitution using chiral enolates
- Asymmetric aldol reactions
- Additions to C=C bonds
- Reduction and oxidation
- Rearrangements
- Hydrolysis and esterification

Vancomycin


NH2
HO
HO
HO
OH
O
CH3
H3C
O
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Cl
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O
Cl
HO
OH
O
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H
NH
NH
NH
NH
NH
O
O
H
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NH
+
NH2Me
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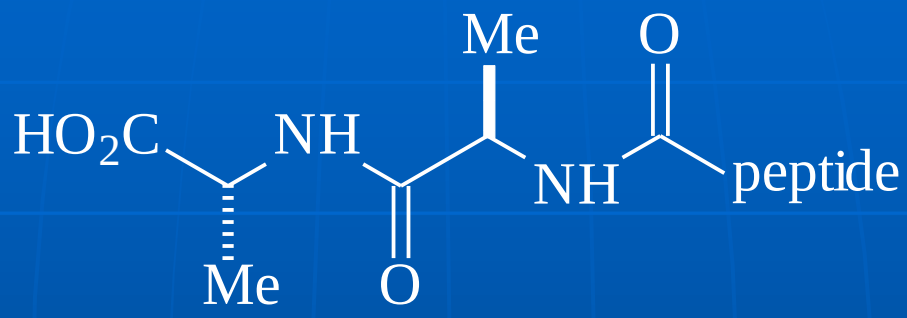
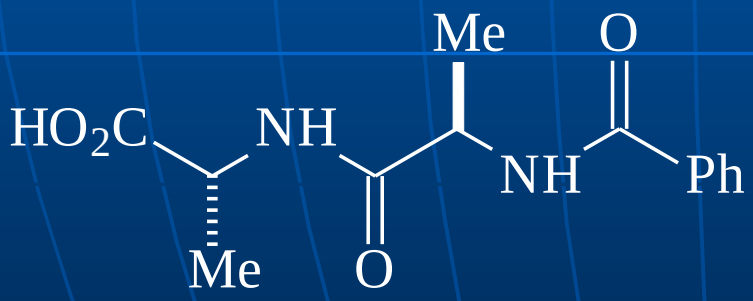
-
O2C
NH2
H3C
OH
OH
CH3
HO

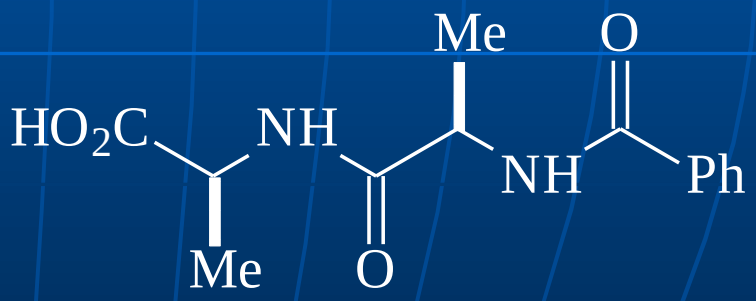
Vancomycin models



D-Ala-D-Ala terminus



D-Ala-D-Ala model



L-Ala-D-Ala model

Definitions

- Stereospecific reaction
  - A reaction in which the configuration of the substrate influences the configuration of the product, or
  - A reaction in which only a specific isomer reacts, in such a way that its configuration influences the configuration of the product.
- Stereoselective reaction
  - A reaction in which one specific isomer is formed to a greater extent than any other.
- Asymmetric synthesis
  - A synthesis in which the stereoisomers of a chiral molecule are formed in unequal quantities.

Stereodifferentiation

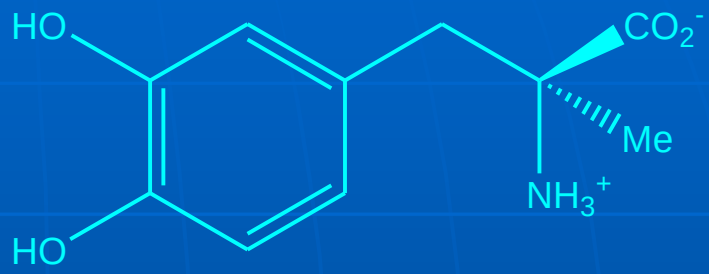
- Enantiodifferentiating reaction
  - Differentiation is provided by the reagent or reaction environment, and refers to the reagent's ability to differentiate between enantiofaces, enantiotopes, or enantiomers.
- Diastereodifferentiating reaction
  - Reactions are influenced by chirality in the substrate and form diastereomers in unequal quantities. May differentiate between diastereofaces, diastereotopes, or diastereomers.

Introduction

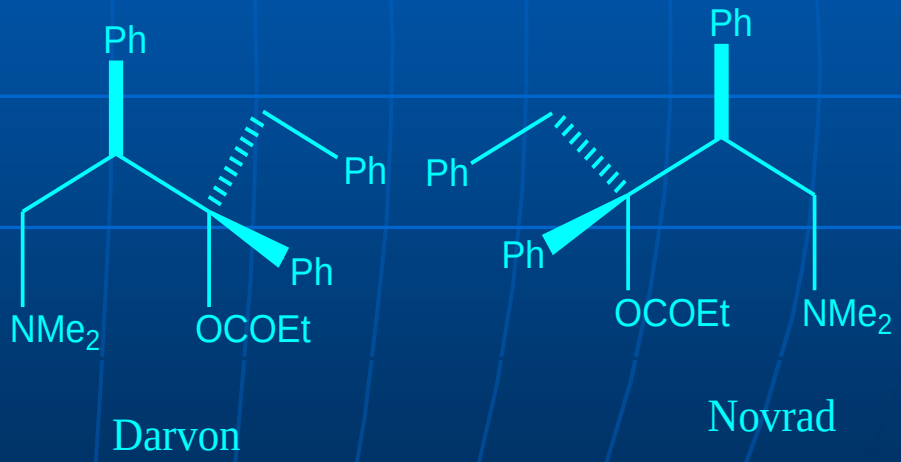
- Biologically active molecules are also chiral
- Enantiomers possess different types of activity
  - Both are active, have different potencies
  - Both have similar activity
  - Both are active but type of activity is different.
  - Only one enantiomer is active, other is devoid of activity

Examples

- Hypertensive agent L-Methyldopa



- Propoxyphene – both enantiomers are biologically active. D isomer is an analgesic while L isomer has antitussive property



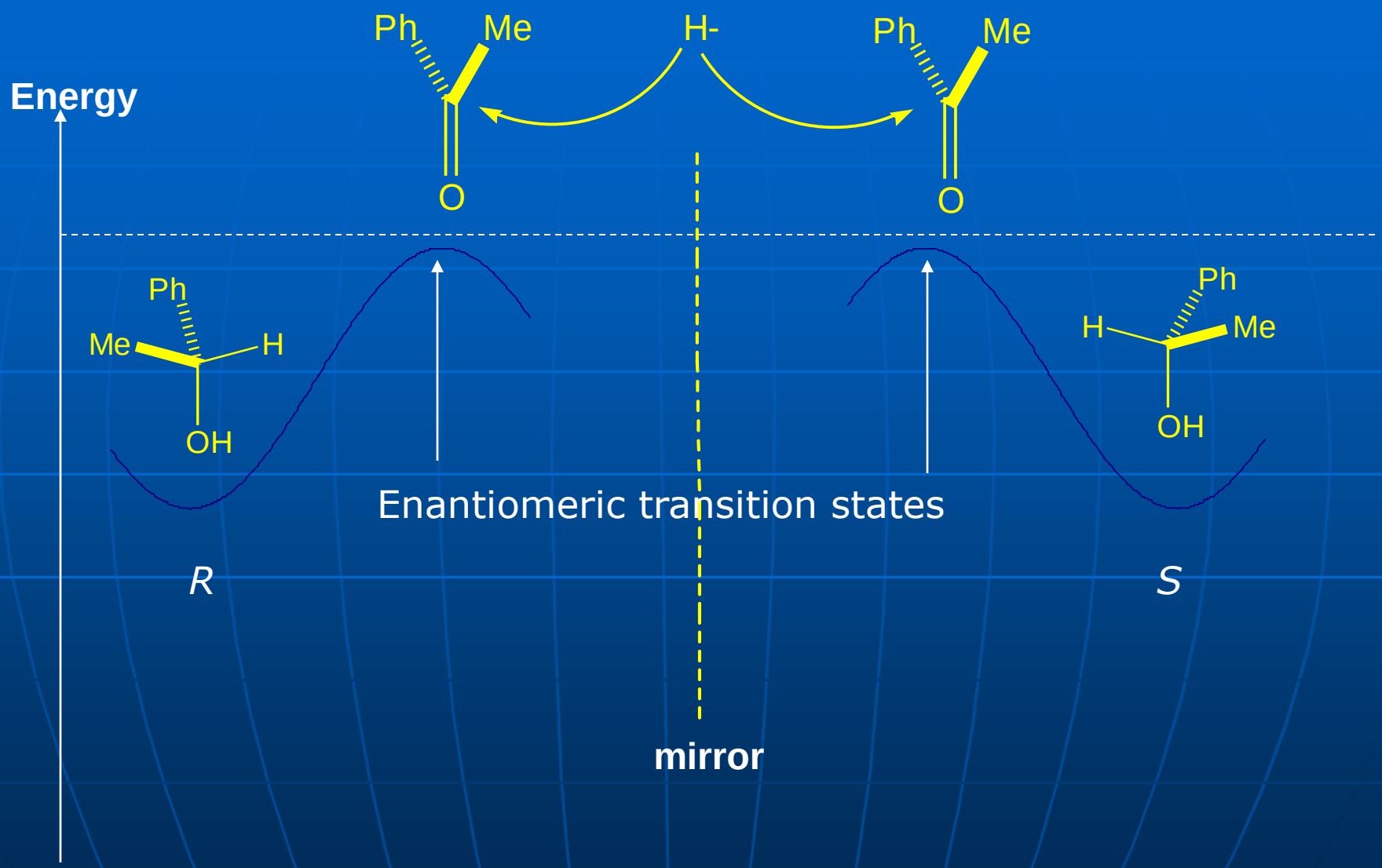
Potential Problems of Enantiomers & their Solution

- In the racemic mixture
  - only half may have beneficial result so the dosage must be increased to reach the therapeutic window
  - one enantiomer may have adverse effect when taken
- To get pure enantiomers
  - Resolution of the racemate or intermediate in the synthetic route – expensive & introduces disposal of other enantiomer
  - Use of enantiomerically pure starting material – must be readily available

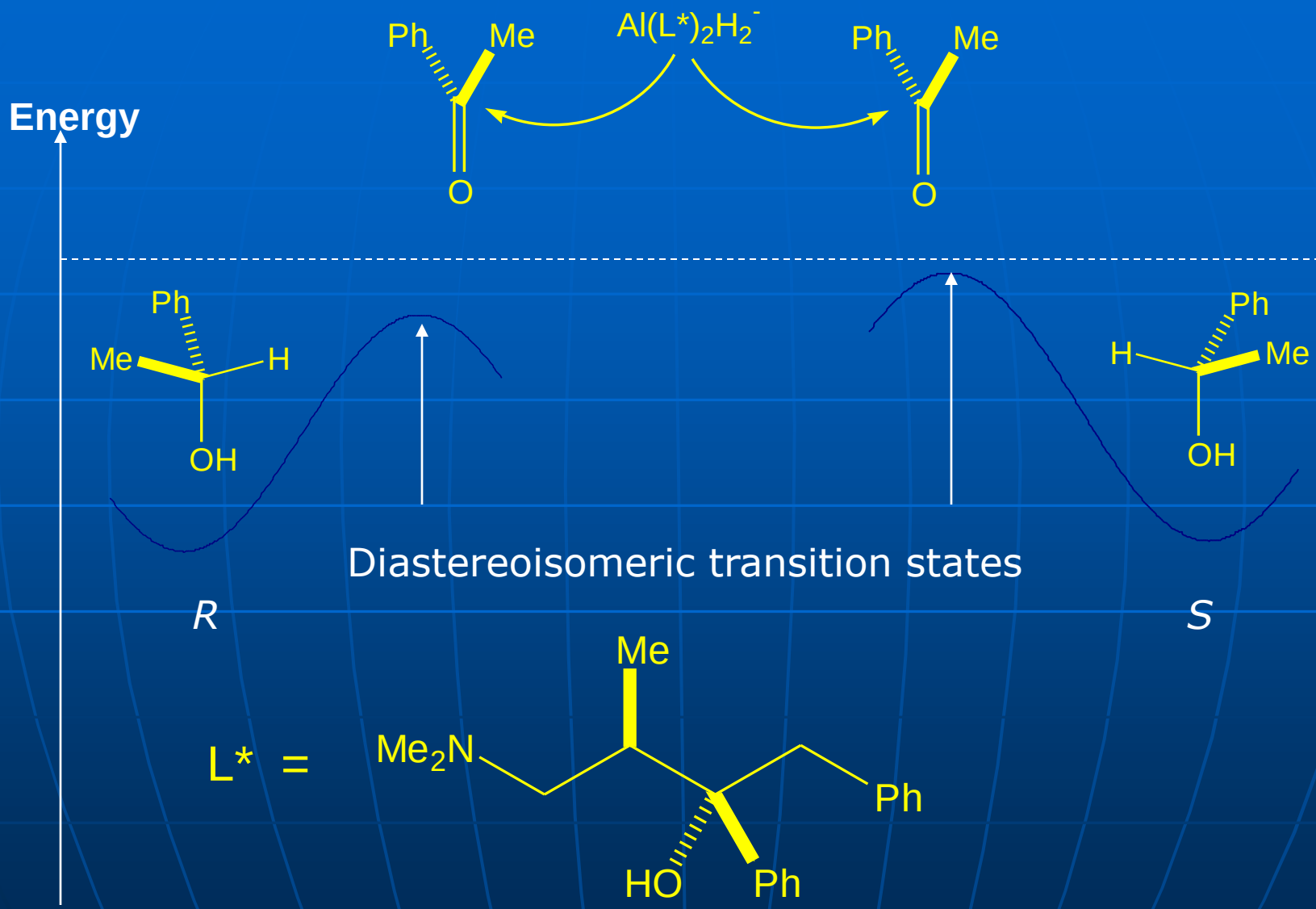
Asymmetric Synthesis

- An array of synthetic methods which result in the desired transformation and control the absolute stereochemistry of chiral centres created as a result of the synthetic operations is called *asymmetric synthesis*
- In order to achieve asymmetric synthesis one or more components of the reaction must be chiral, or chiral auxiliaries (stoichiometric or catalytic amounts) or catalysts can be used
- Chiral components could make the possible enantiomeric transition states diastereomeric, different energies

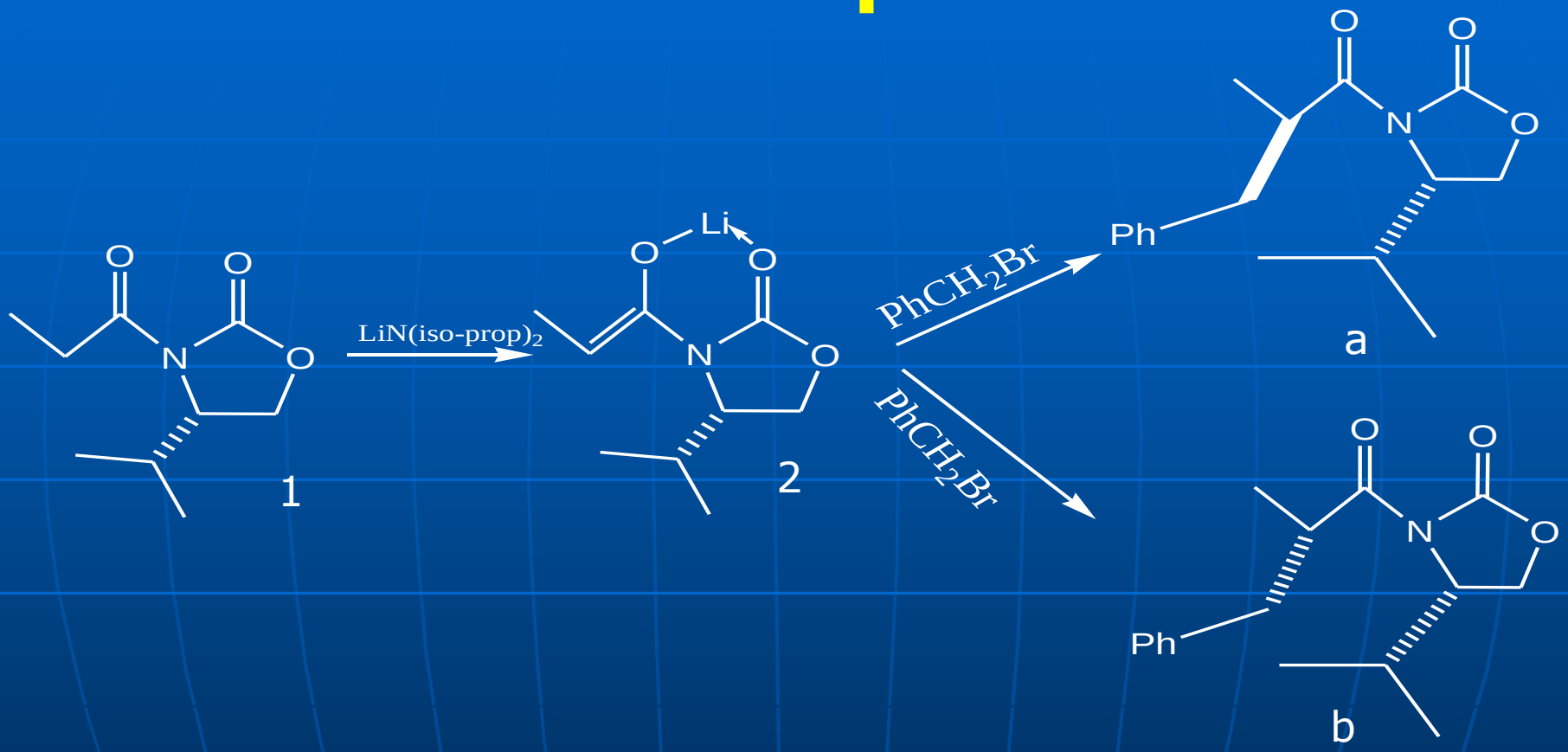
Enantiomeric Transition States



Diastereomeric Transition States



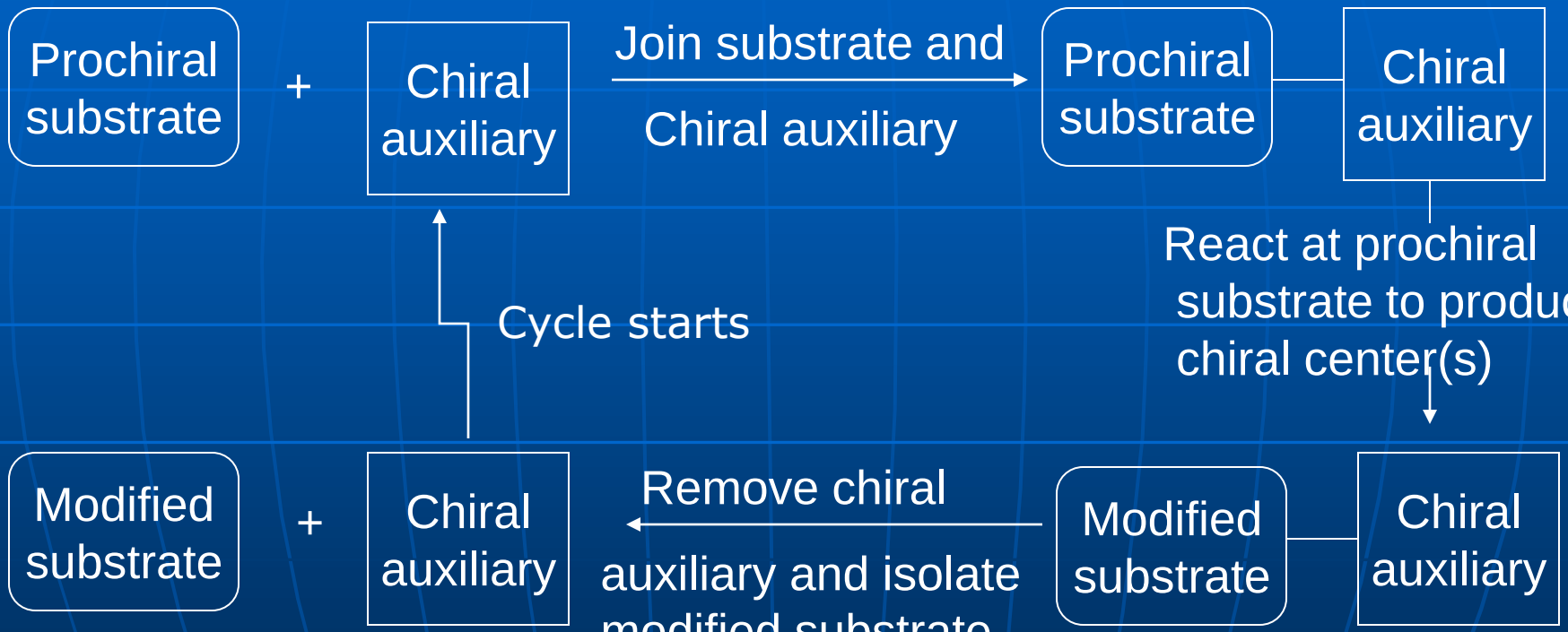
Example



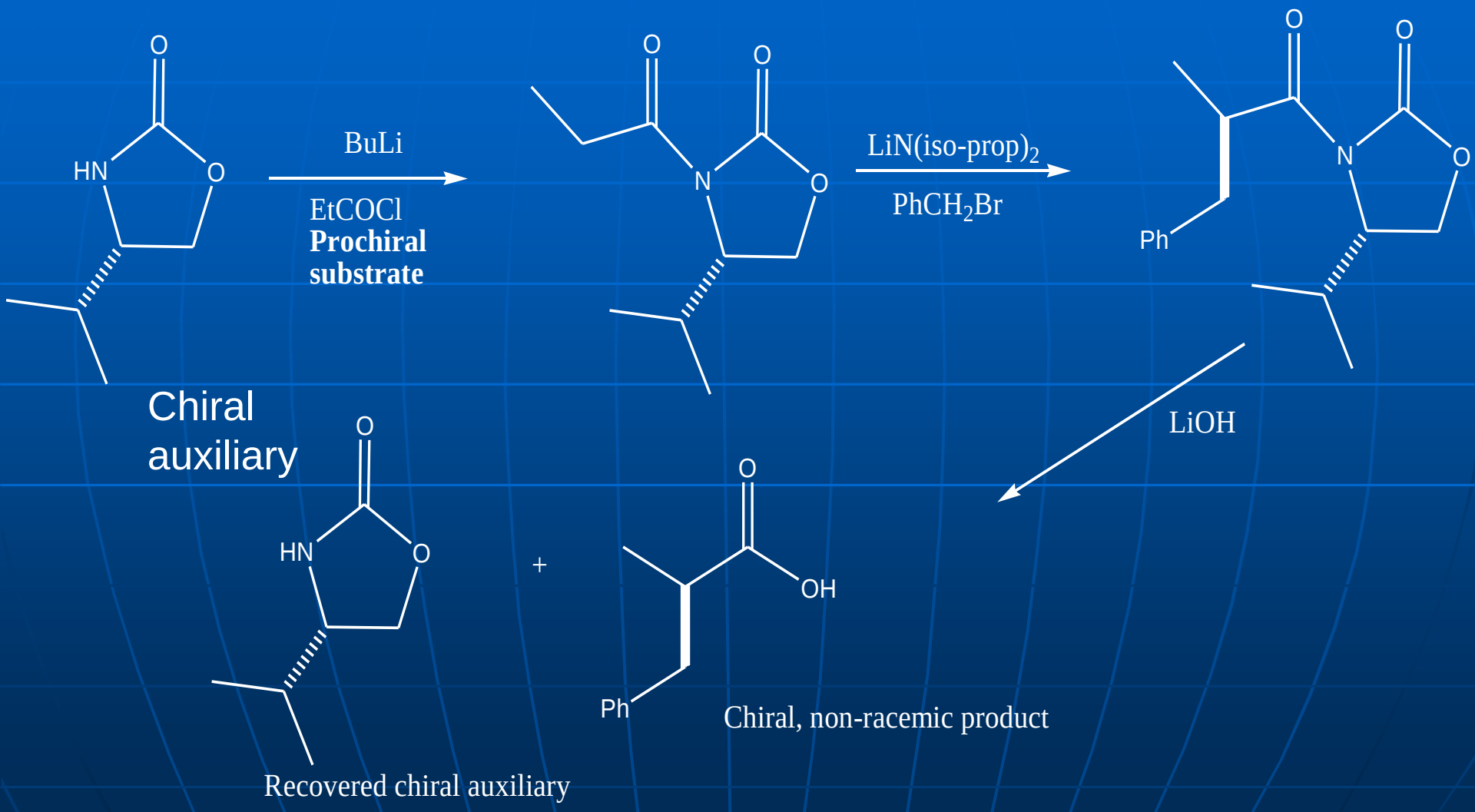
Diastereomeric excess (d.e.) = (major diastereomer(%) – minor diastereomer (%))

= (% a - % b) = 99-1 = 98%

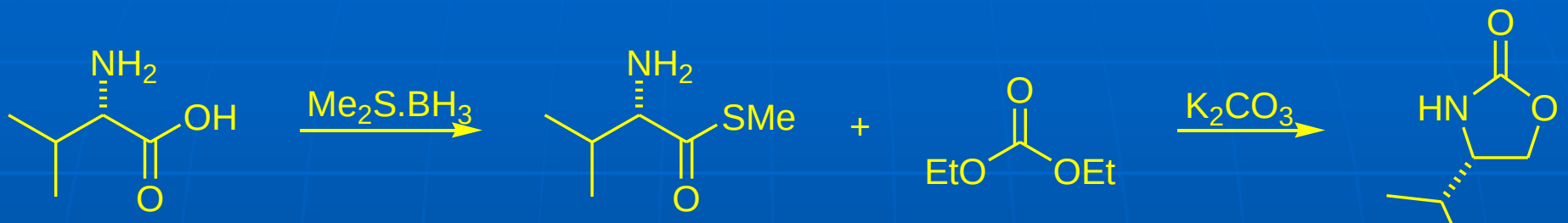
Use of Chiral Auxiliary



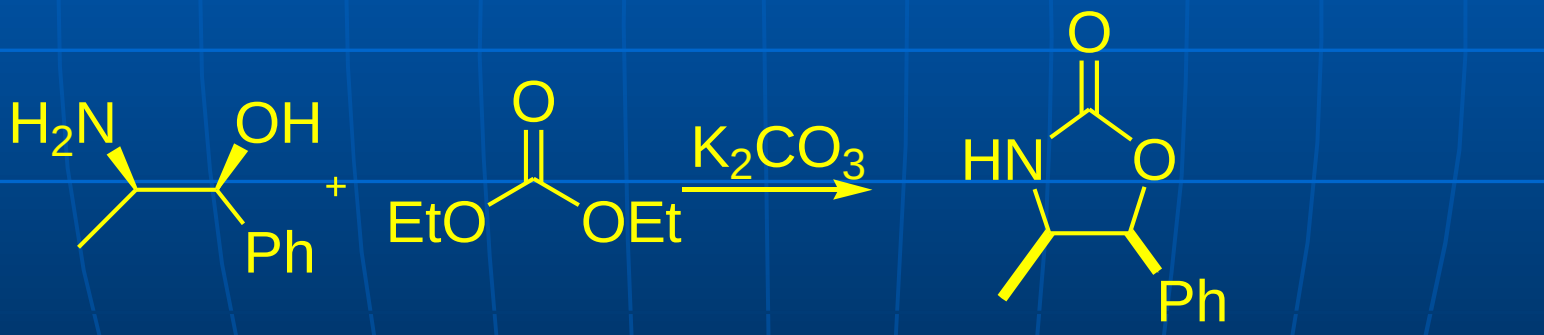
Example of chiral auxiliary



Evans Auxiliary



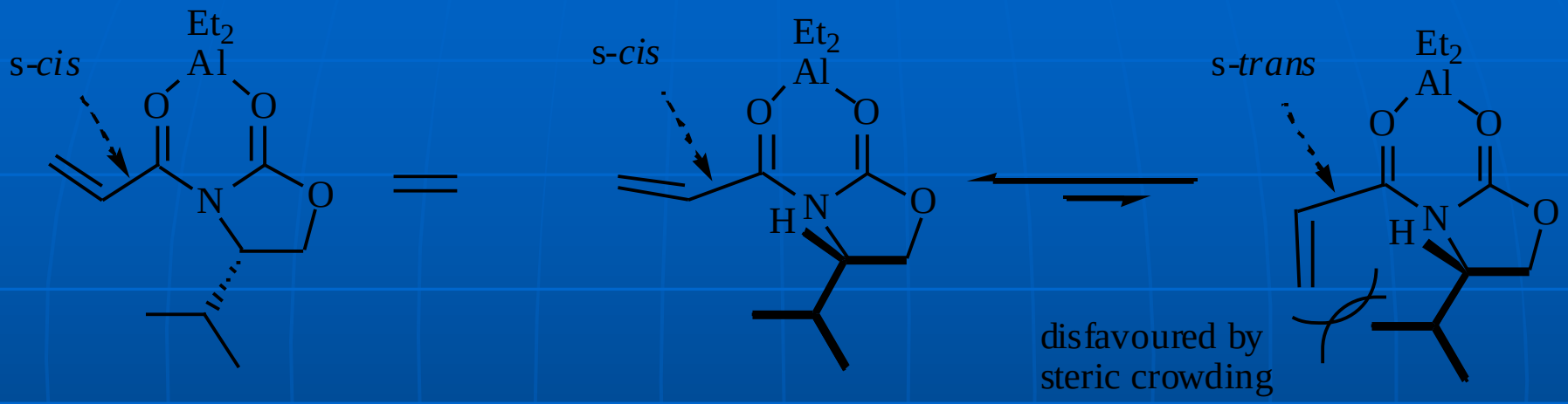
(*S*)-Valine



Norephedrine

Norephedrine-derived auxiliary

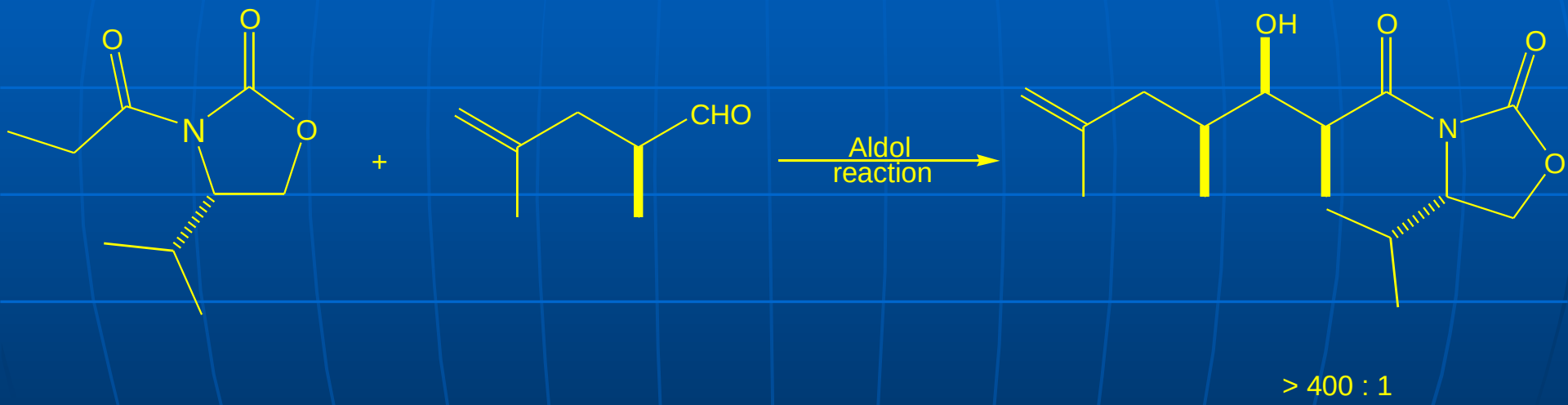
Why does it work?



Requirements for Chiral Auxiliaries

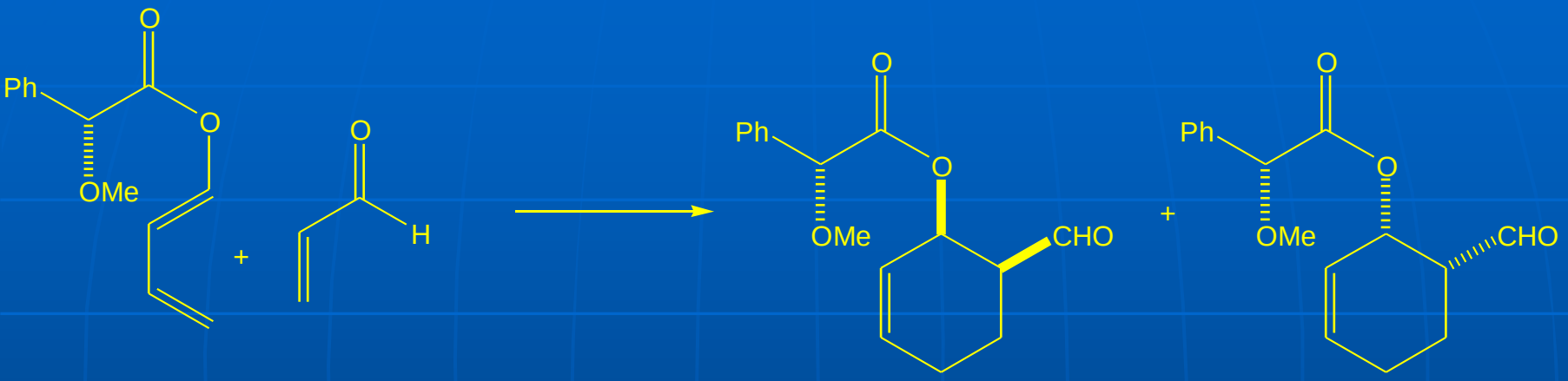
- Enantiomerically pure
- Cheap and easy to obtain in quantity
- Easy to attach to substrate
- High and predictable control of stereoselectivity
- Easy purification of diastereomers
- Easy removal without loss of purity
- Easy separation and recovery

Two chiral components (1)

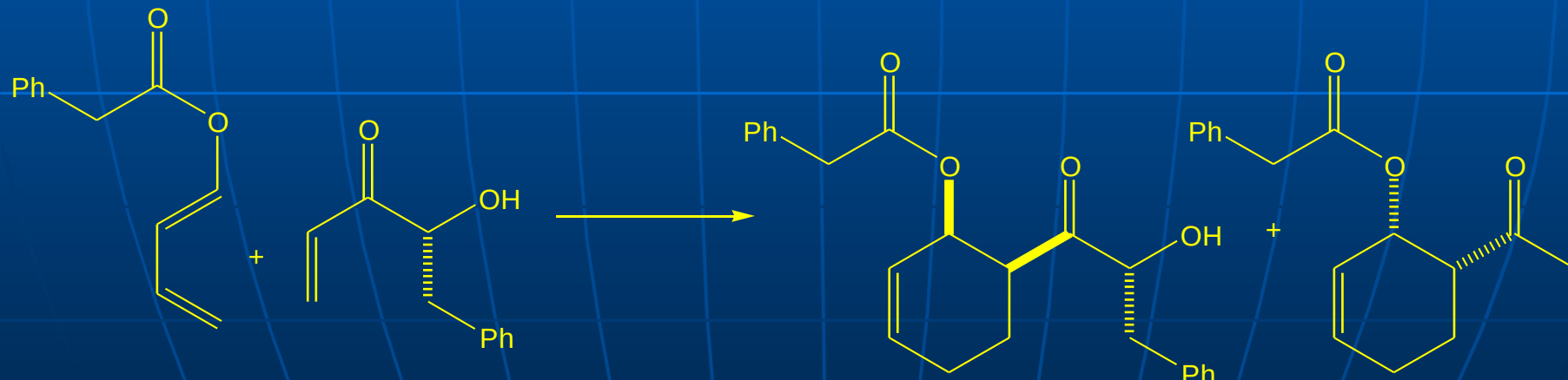


> 400 : 1

Two chiral components (2)

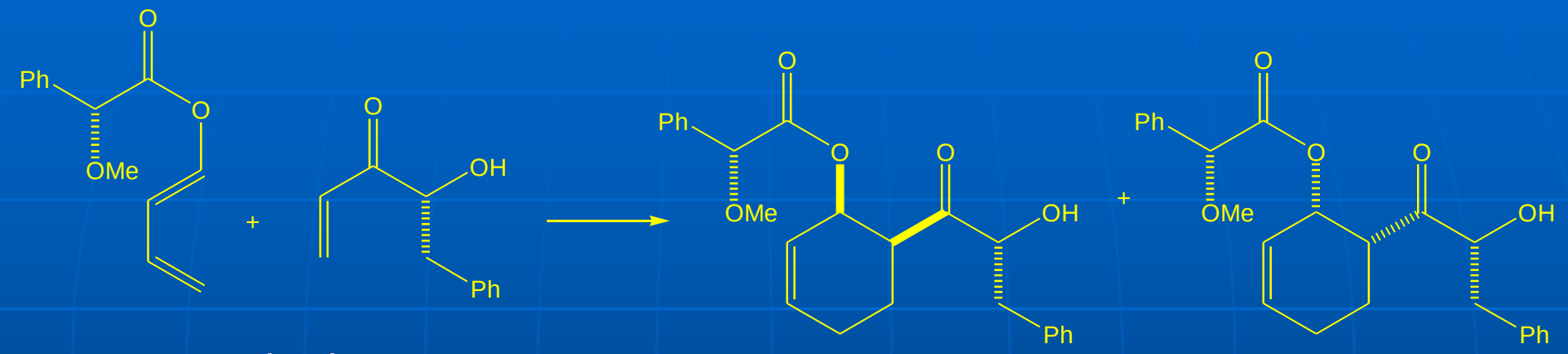


4.5 : 1



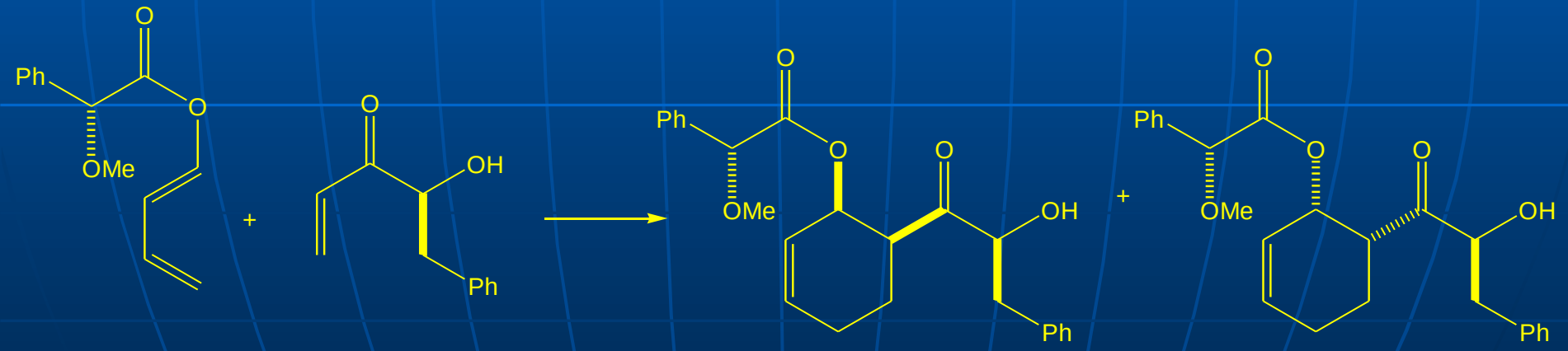
8 : 1

Two chiral components (3)



Matched pair

40 : 1

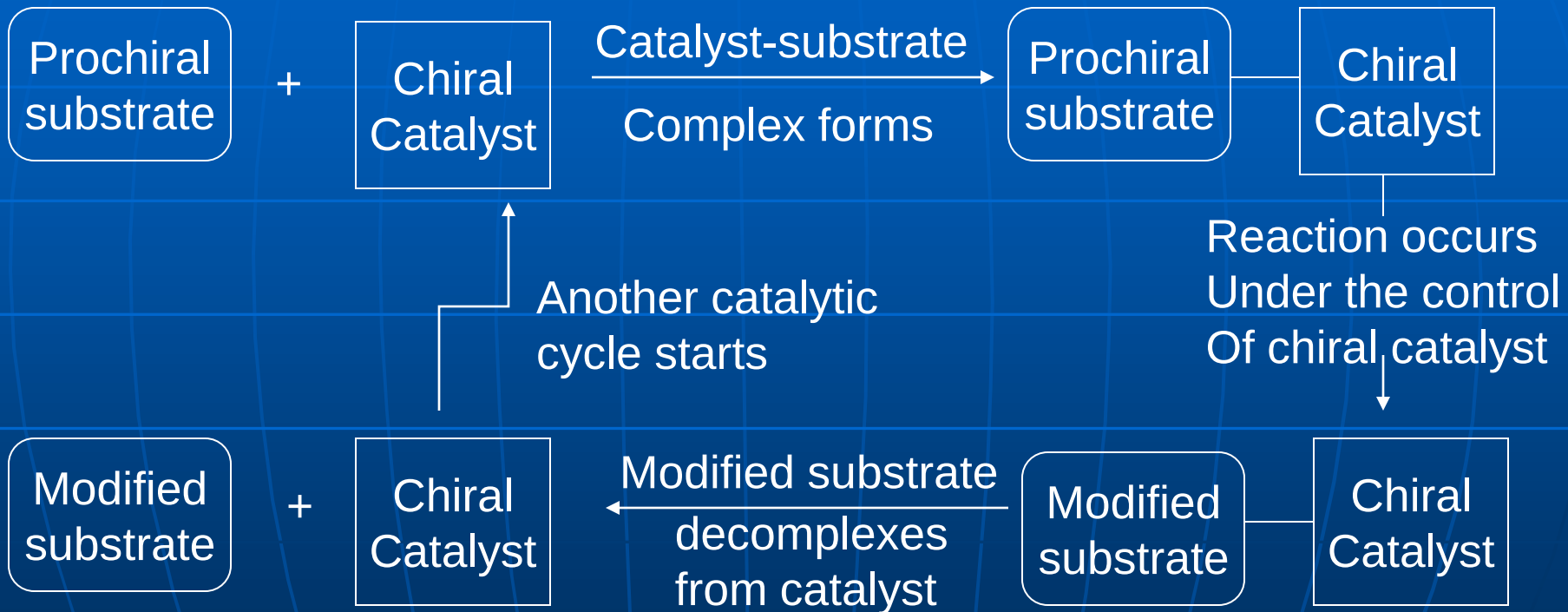


Mismatched pair

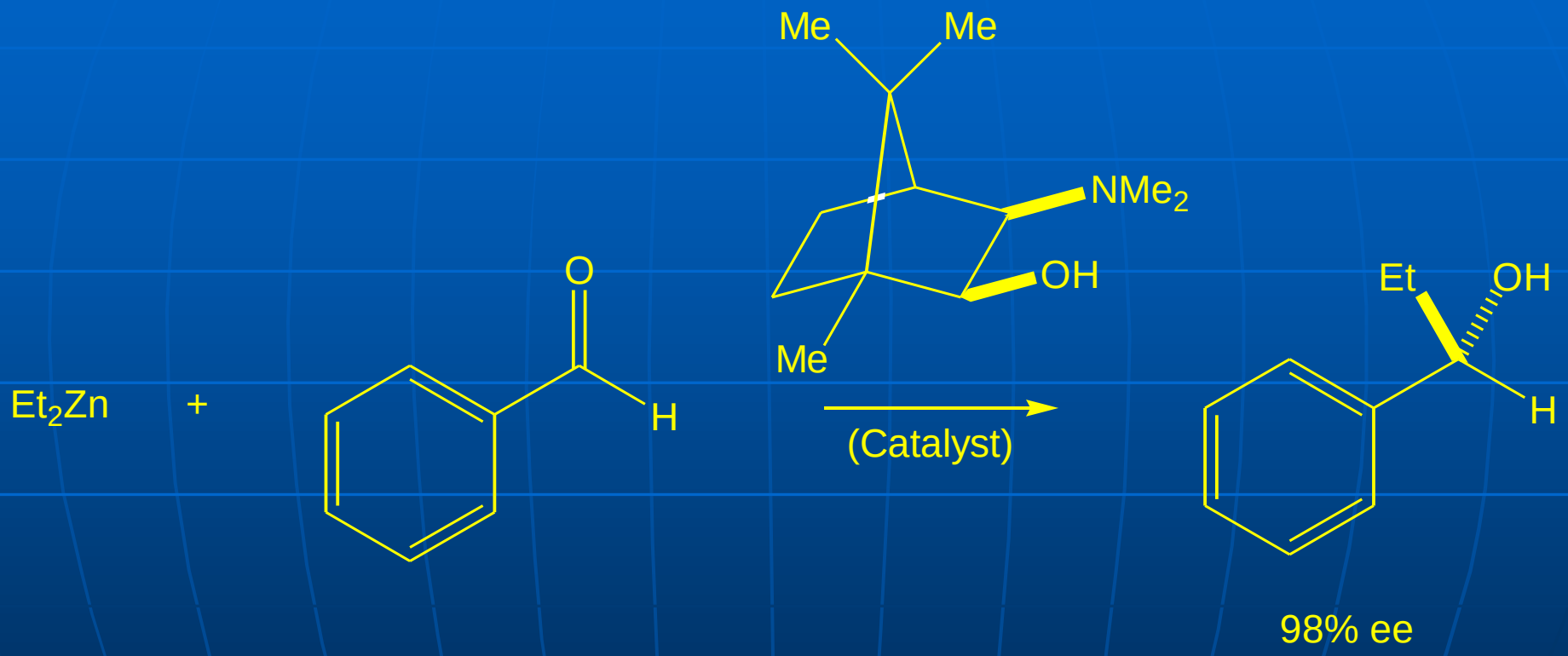
1 : 2

Double asymmetric induction

Schematic Representation of Asymmetric Catalysis



Example of chiral catalyst



Methods for asymmetric synthesis

- *Chiral reagent:* No manipulations required, but lacks generality.
- *Chiral solvent:* No practically useful procedures.
- *Chiral solvating agent:* As chiral reagent.
- *Chiral auxiliary:* Predictable, reliable, recycled.
- *Chiral catalyst:* Ideal, but few catalysts give high ee and accept wide substrate range, and enantiomer mixtures are obtained.