Advanced Organic Chemistry/ Organic Synthesis – CH 621

Asymmetric Synthesis

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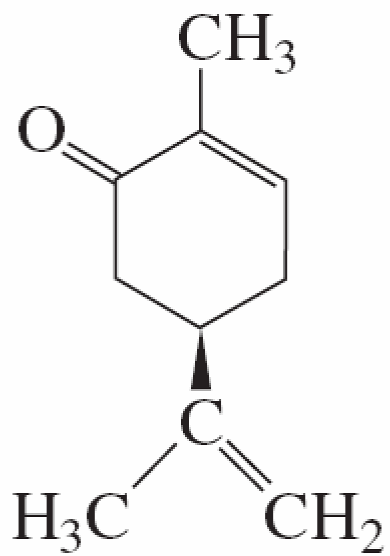
Introduction

<u>Major Goal</u>

Synthesis of Chiral Compounds

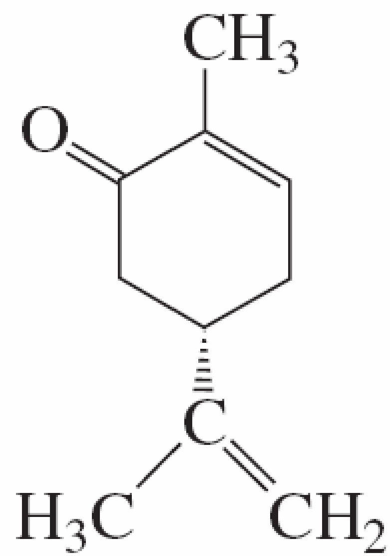
- Importance of chiral compounds (pharmaceuticals, non-linear optical devices, biochemical processes, molecular recognition)

Introduction



(*R*)-(–)-carvone
spearmint oil

$[\alpha]_D^{20\,°C} = -62.5$

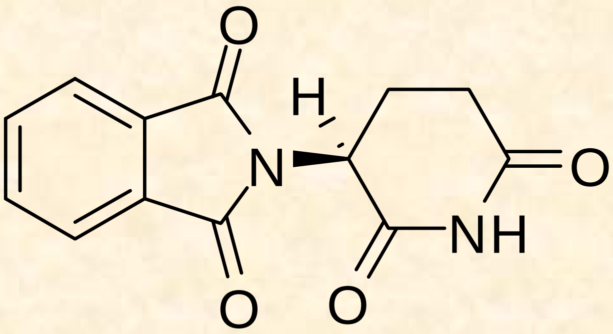


(*S*)-(+)-carvone
caraway seed oil

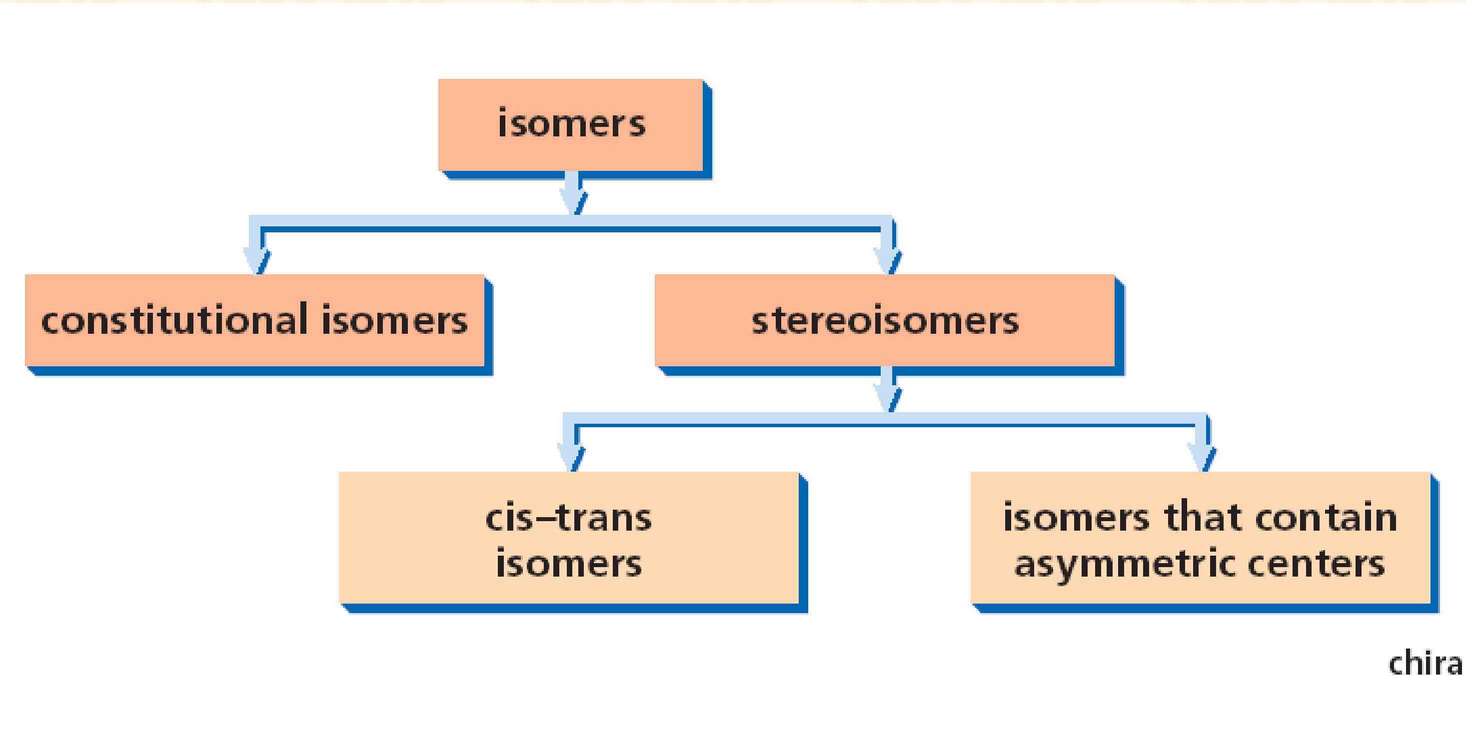
$[\alpha]_D^{20\,°C} = +62.5$

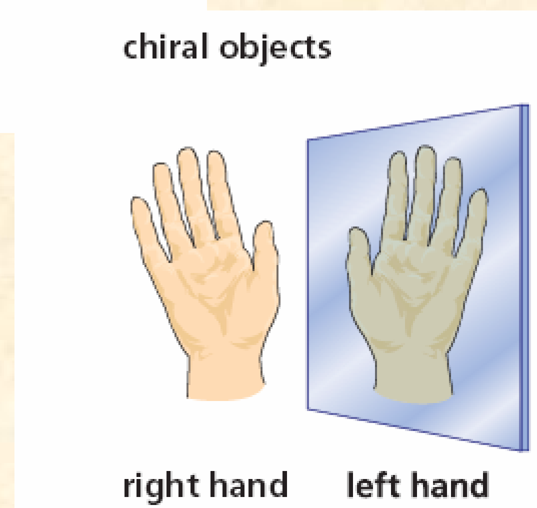
Introduction

Thalidomide



Introduction





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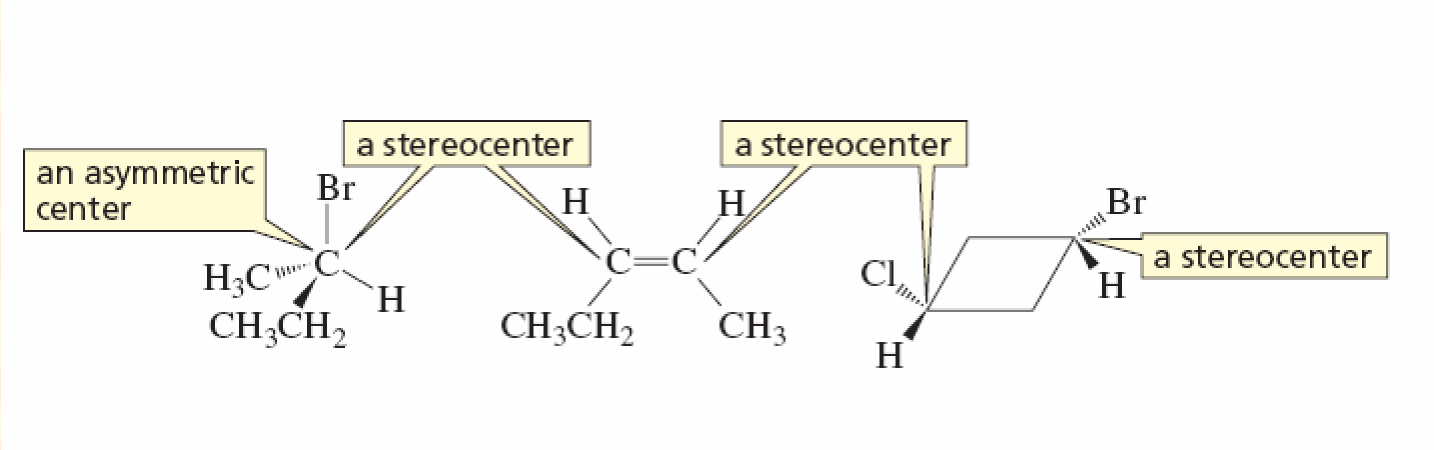
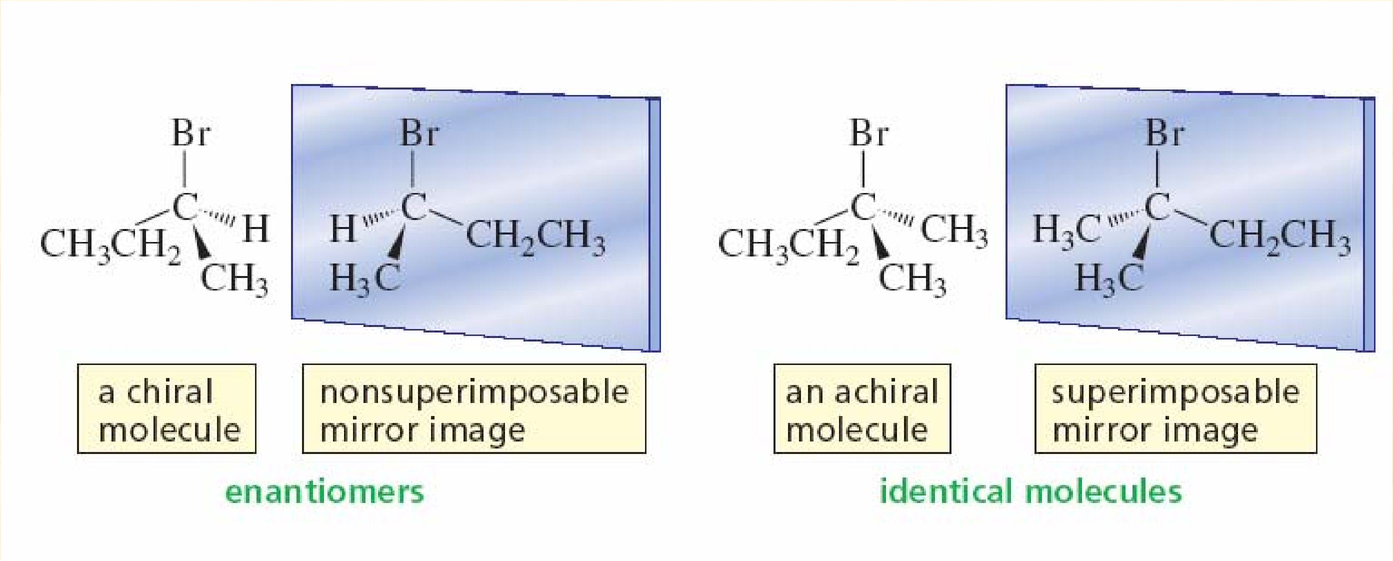
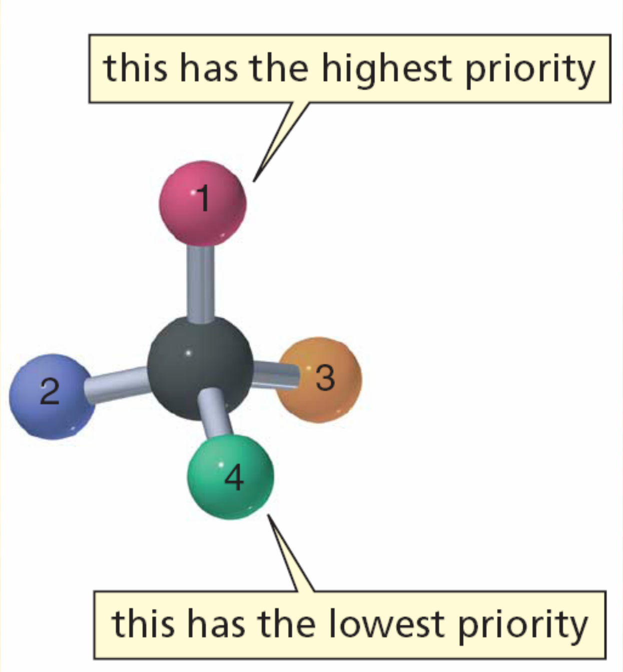
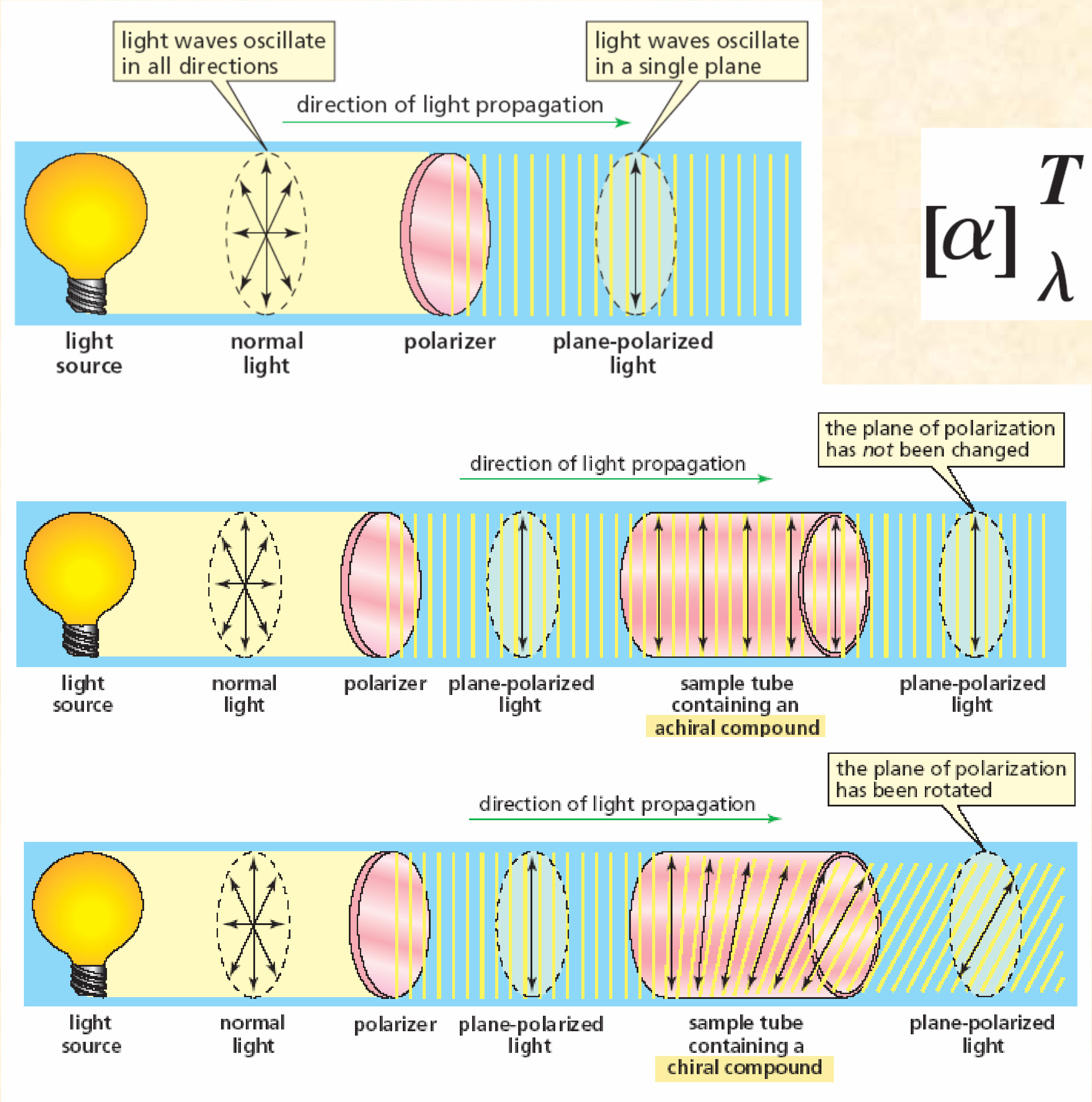




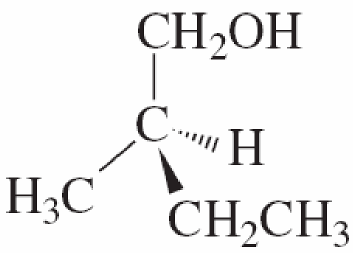
Introduction



Introduction



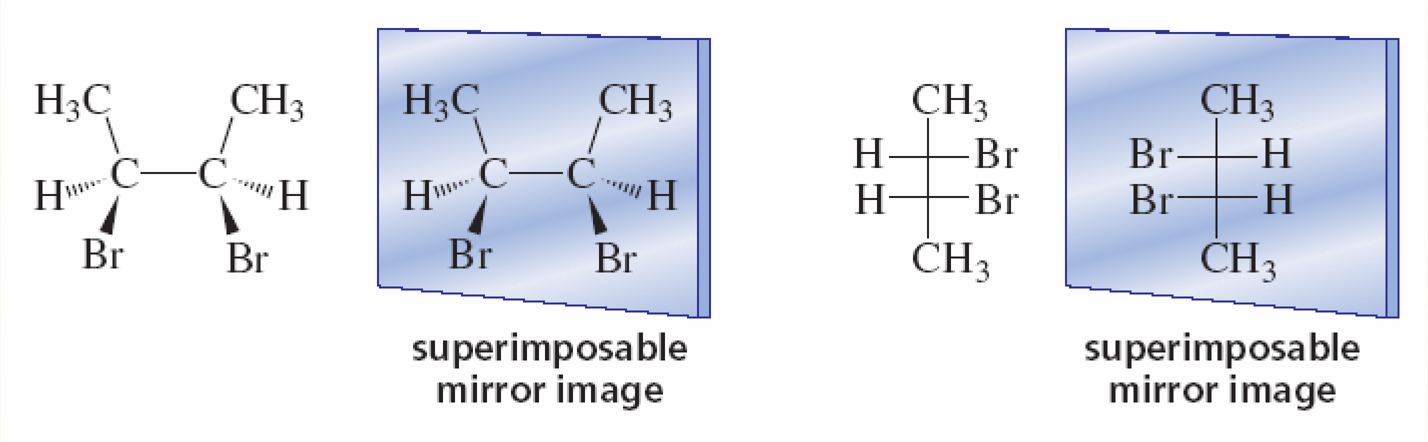
$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \times c}$$

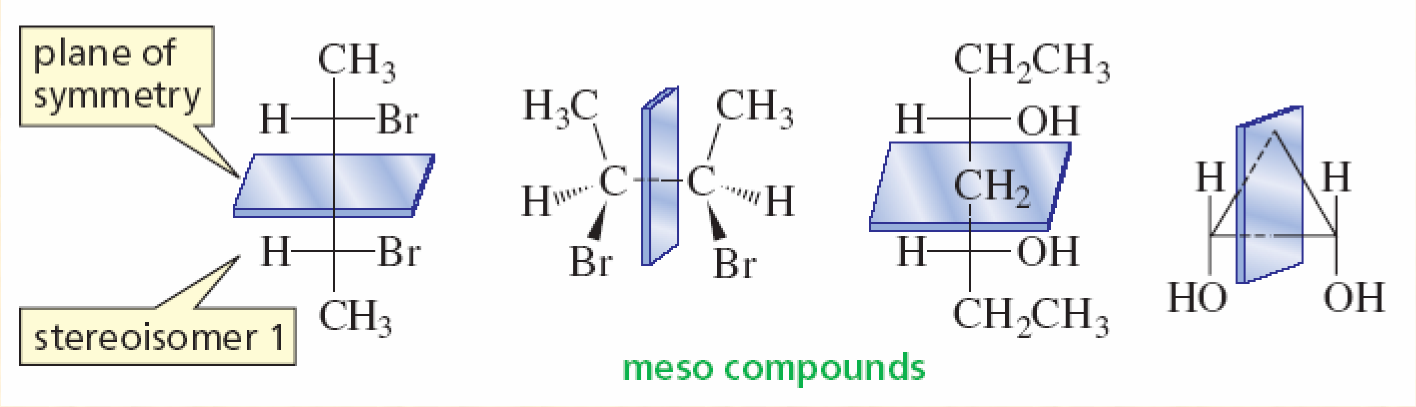


(*R*)-2-methyl-1-butanol

$$[\alpha]_{D}^{20\ °C} = +5.75$$

Introduction

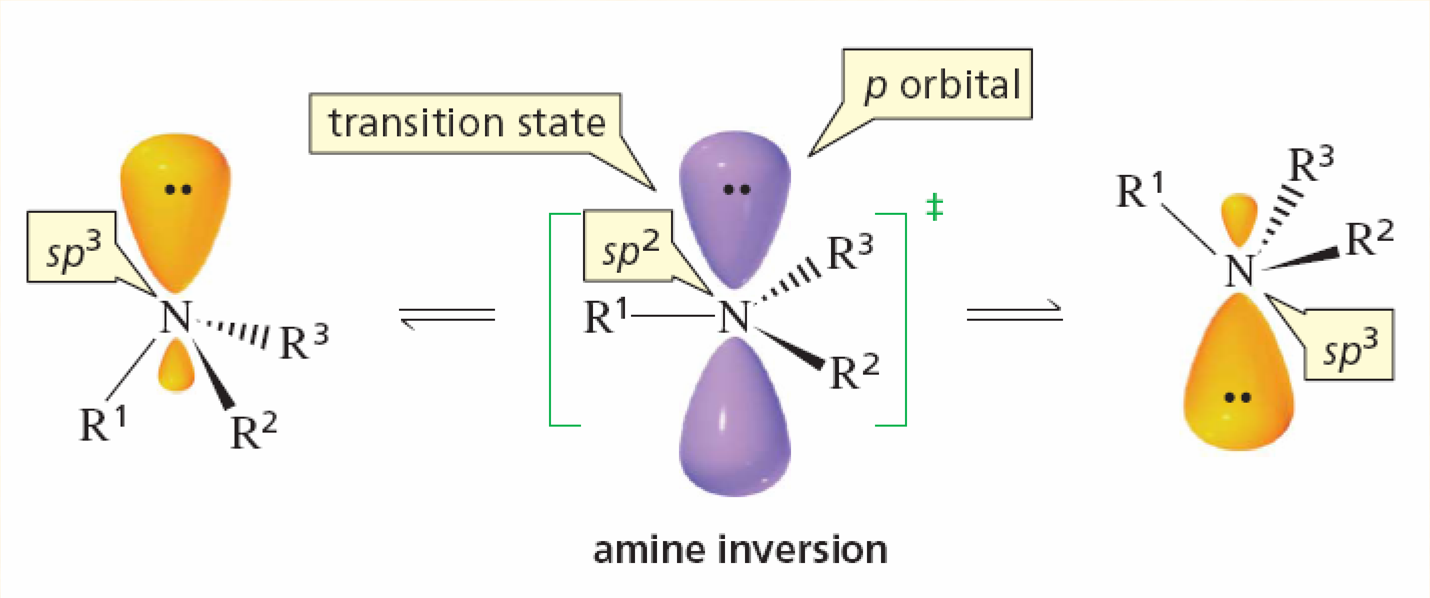




Introduction

Other elements with Central Chirality

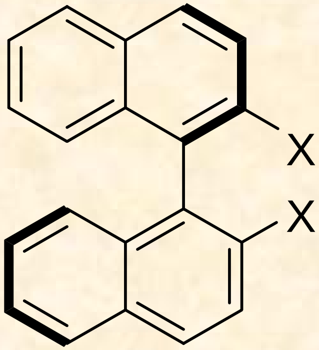
Si, Ge, P, N, S



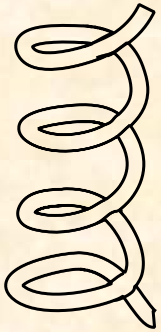
Introduction

Other types of Chirality

Planar (or axial)

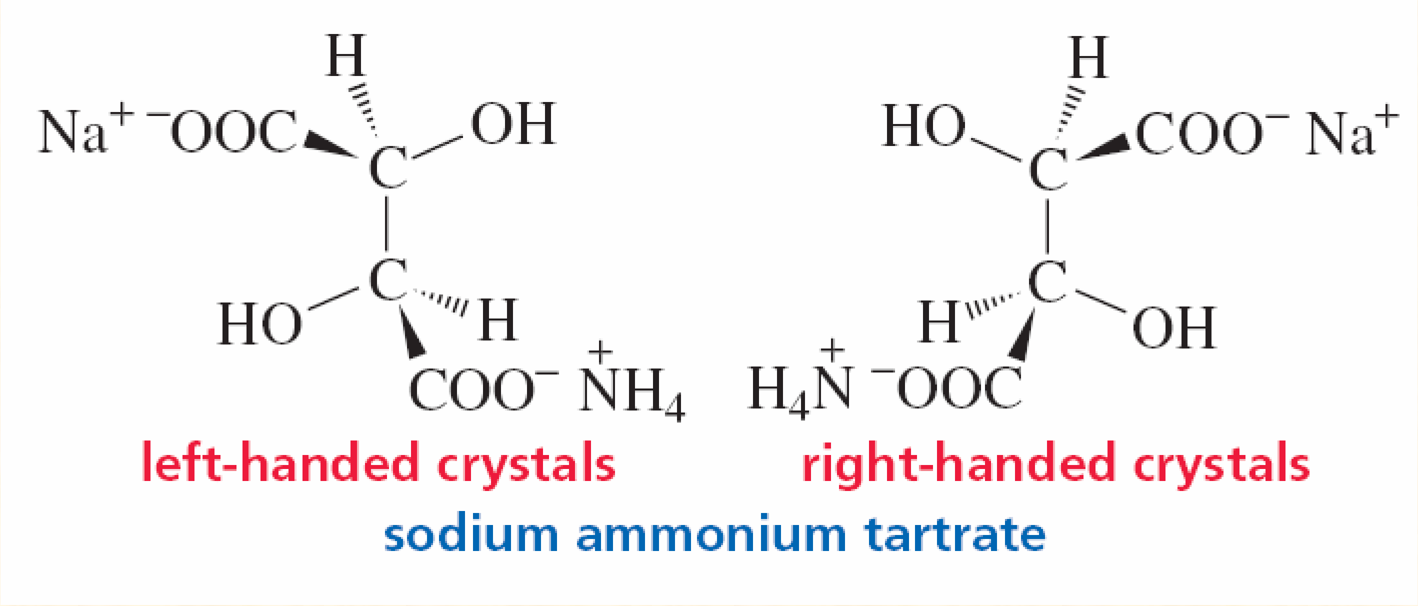


Helical



Separation of Chiral Compounds

[Pasteur]



Separation of Chiral Compounds

Diastereomer pair formation

Most important preparative method

Separation of Chiral Compounds

Chiral Chromatography

GC

HPLC

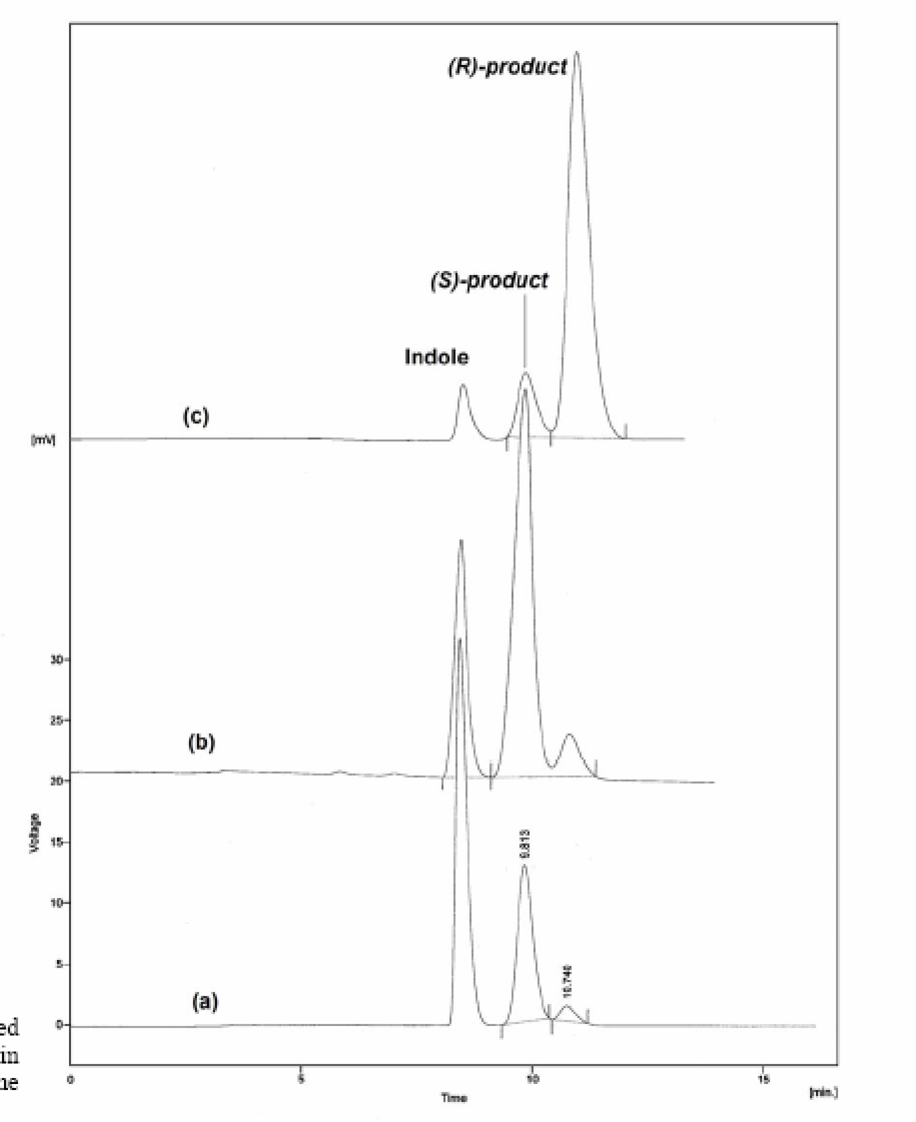
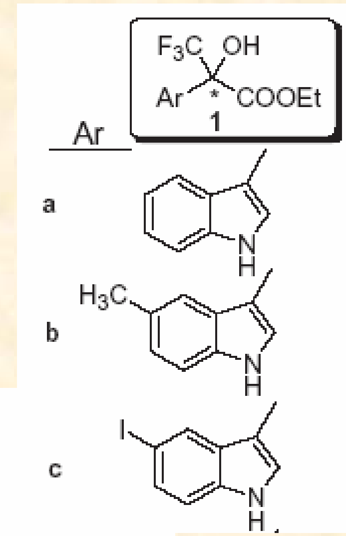


Figure 1.
Assignment of 3, 3, 3-trifluoro-2-hydroxy-2-(indol-3-yl)-propionic acid ethyl ester enantiomers based on a comparison with an authentic sample: starting material (indole) and reaction products obtained in the reaction of indole and ethyl 3,3,3-trifluoropyruvate catalyzed by (a) $Cu(OTf)_2$-bisoxazoline (authentic sample), (b) cinchonidine and (c) cinchonine

Separation of Chiral Compounds

NMR Spectroscopy

- Chiral Reagents (Mosher's chloride, shift reagents)
- Chiral Solvation



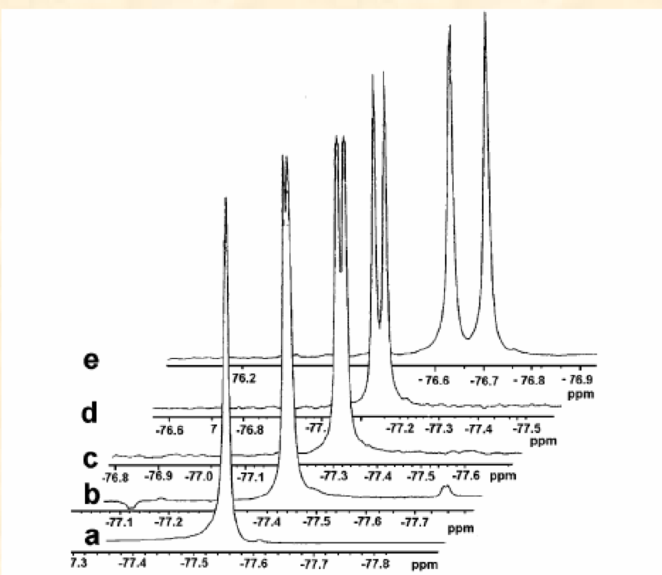


Figure 1. [19]F NMR resonances of CF_3 fluorines in **1c** in the presence of cinchona alkaloids: (a) no alkaloid, (b) cinchonine, (c) cinchonidine, (d) quinine, (e) quinidine (376 MHz, $CDCl_3$, 25 °C).

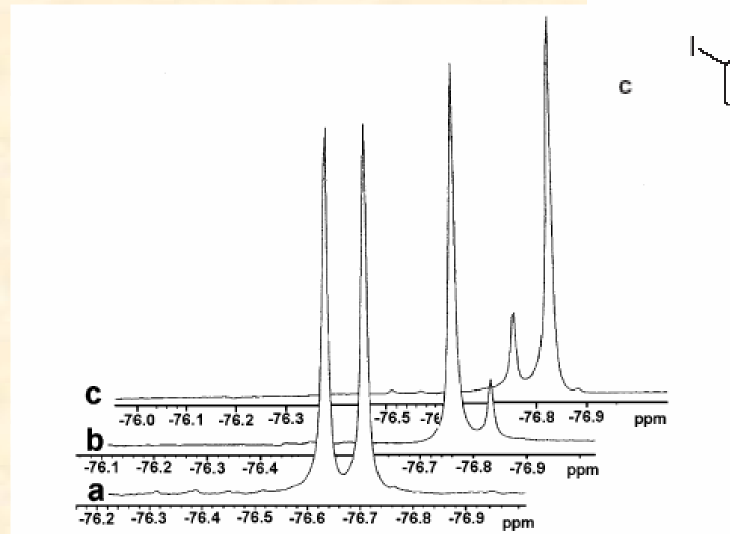
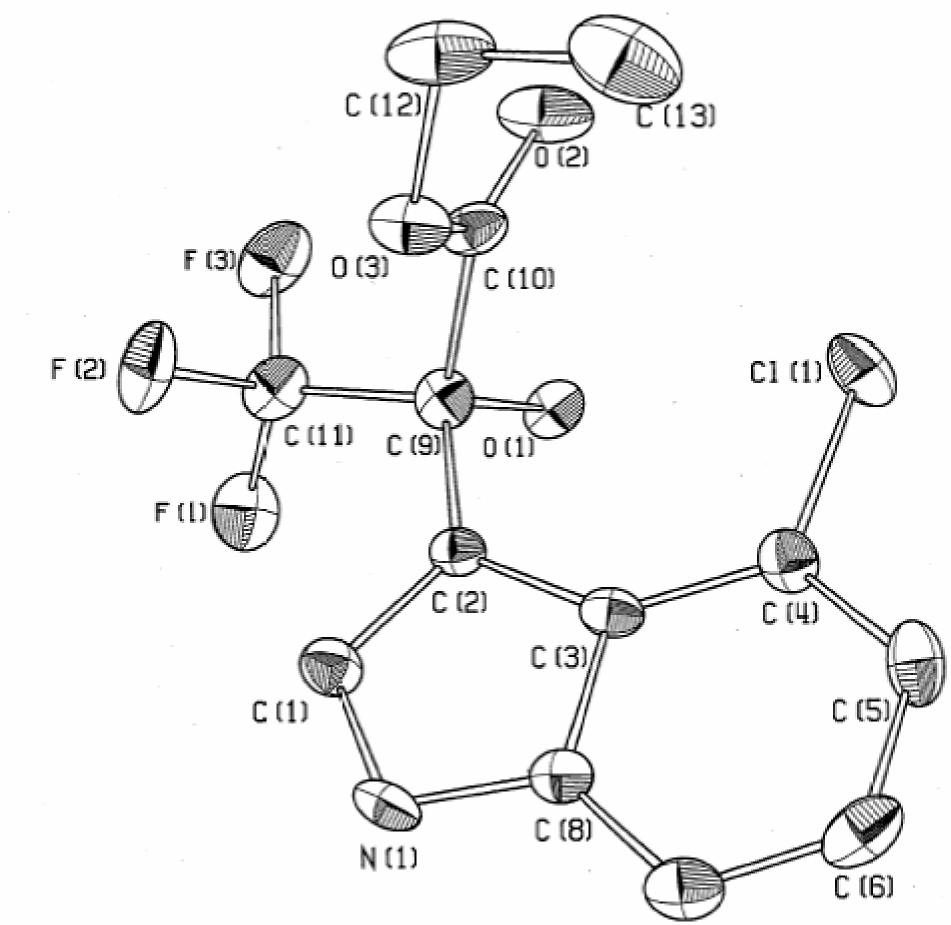


Figure 2. [19]F NMR resonances of CF_3 fluorines in **1c** in the presence of quinidine (QD): (a) racemic sample, (b) (*S*)-isomer in excess, (c) (*R*)-isomer in excess (376 MHz, $CDCl_3$, 25 °C).

Introduction

X-ray crystallography



Synthesis of Chiral Compounds

Routes to chiral compounds

Chiral Resolution	Chiral Synthesis
⇓	⇓
Chiral derivatization agent	Stoichiometric and Catalytic Methods
⇓	⇓
Chiral Product	Chiral Product
(up to 50% yield and 100% ee)	(up to 100% yield and 100% ee)

enantiomer

diastereoisomers

ee – enantiomeric excess (ee % = $\frac{|[R] - [S]|}{[R] + [S]}$ x 100)

diastereomeric excess (d.e.)

Synthesis of Chiral Compounds

Strategy and classification of methods

The main classes of natural product

(i) amino acids (and their reduction products, e.g. amino alcohols);
(ii) other amines and amino alcohols, including alkaloids;
(iii) hydroxy acids (lactic, tartaric, mandelic, etc.);
(iv) terpenes, such as α-pinene, camphor, etc.;
(v) carbohydrates;
(vi) enzymes and other proteins.

“0” generation method

Synthesis of Chiral Compounds

(i) *'First-generation' or substrate-controlled methods.*

$$S{-}X^* \xrightarrow{R} P^*{-}X^*$$

(ii) *'Second-generation' or auxiliary-controlled methods.*

$$S \xrightarrow{A^*} S{-}A^* \xrightarrow{R} P^*{-}A^* \xrightarrow{-A^*} P^*$$

(iii) *'Third-generation' or reagent-controlled methods.*

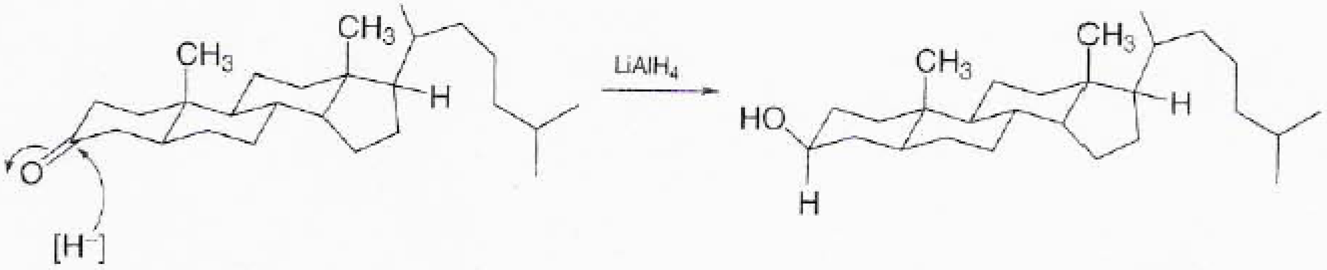
$$S \xrightarrow{R^*} P^*$$

(iv) *'Fourth-generation' or catalyst-controlled methods.*

$$S \xrightarrow[\text{cat.}^*]{R} P^*$$

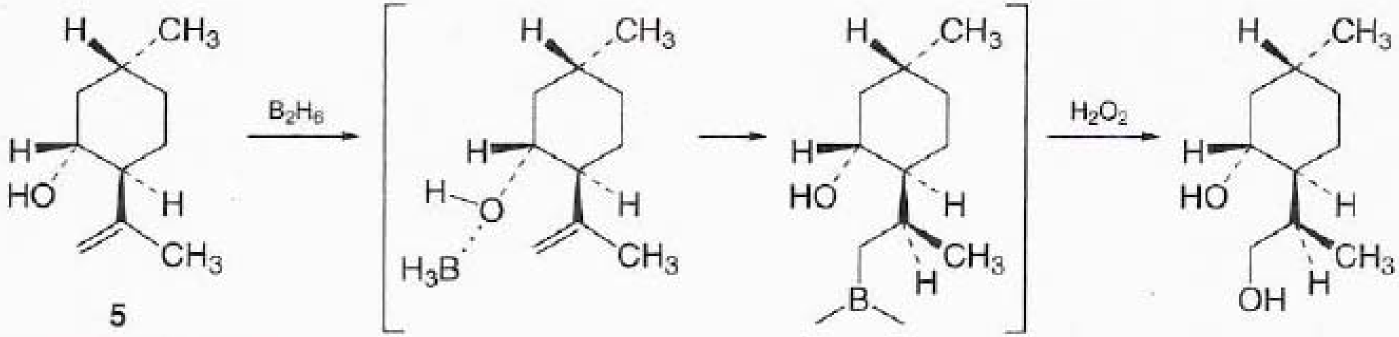
Synthesis of Chiral Compounds

First-generation methods: the use of chiral substrates



3 Cholestan-3-one

4 (95% yield; 83% d.e.)

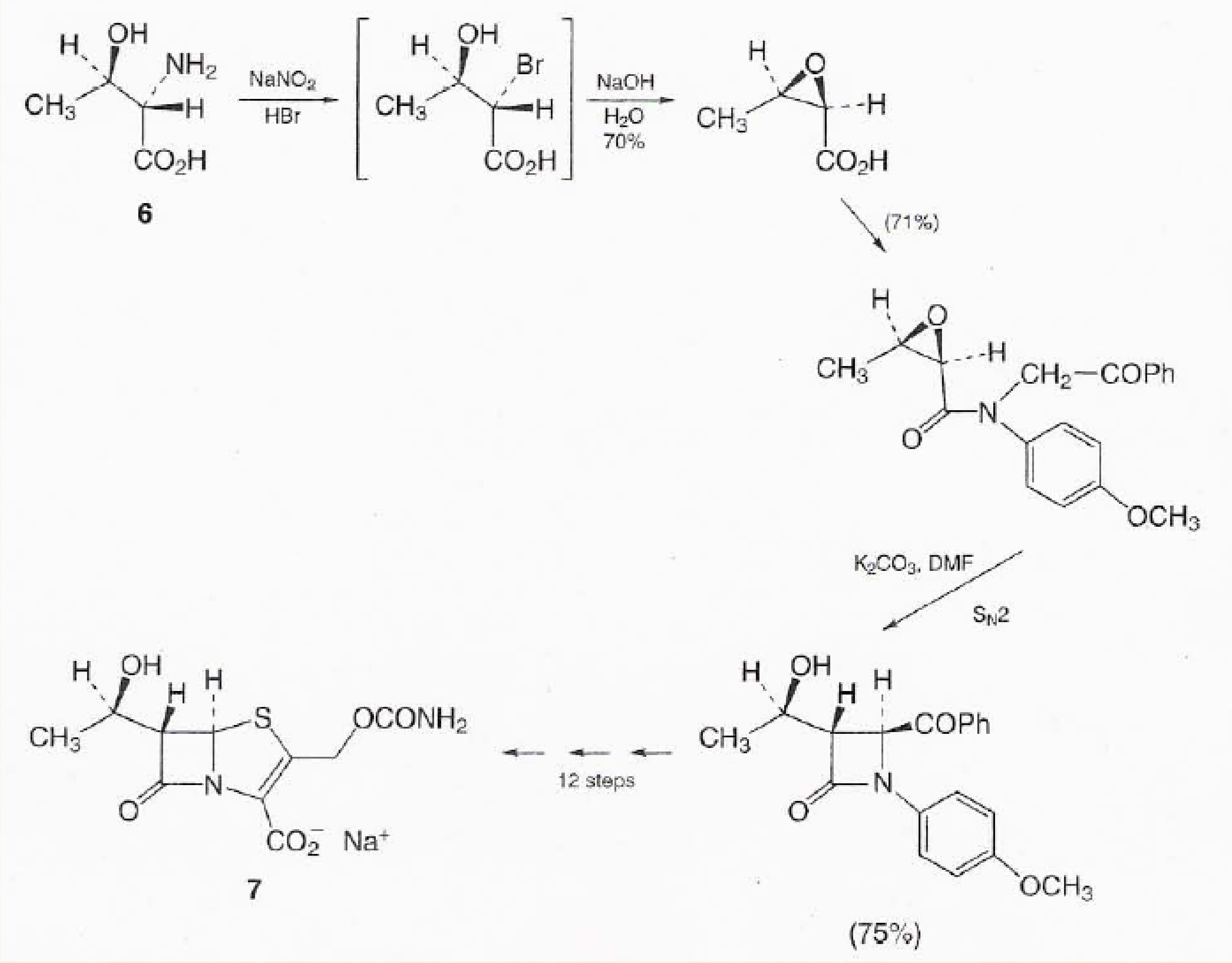


5 (–)-isopulegol

(94% yield; 90% d.e.)

Synthesis of Chiral Compounds

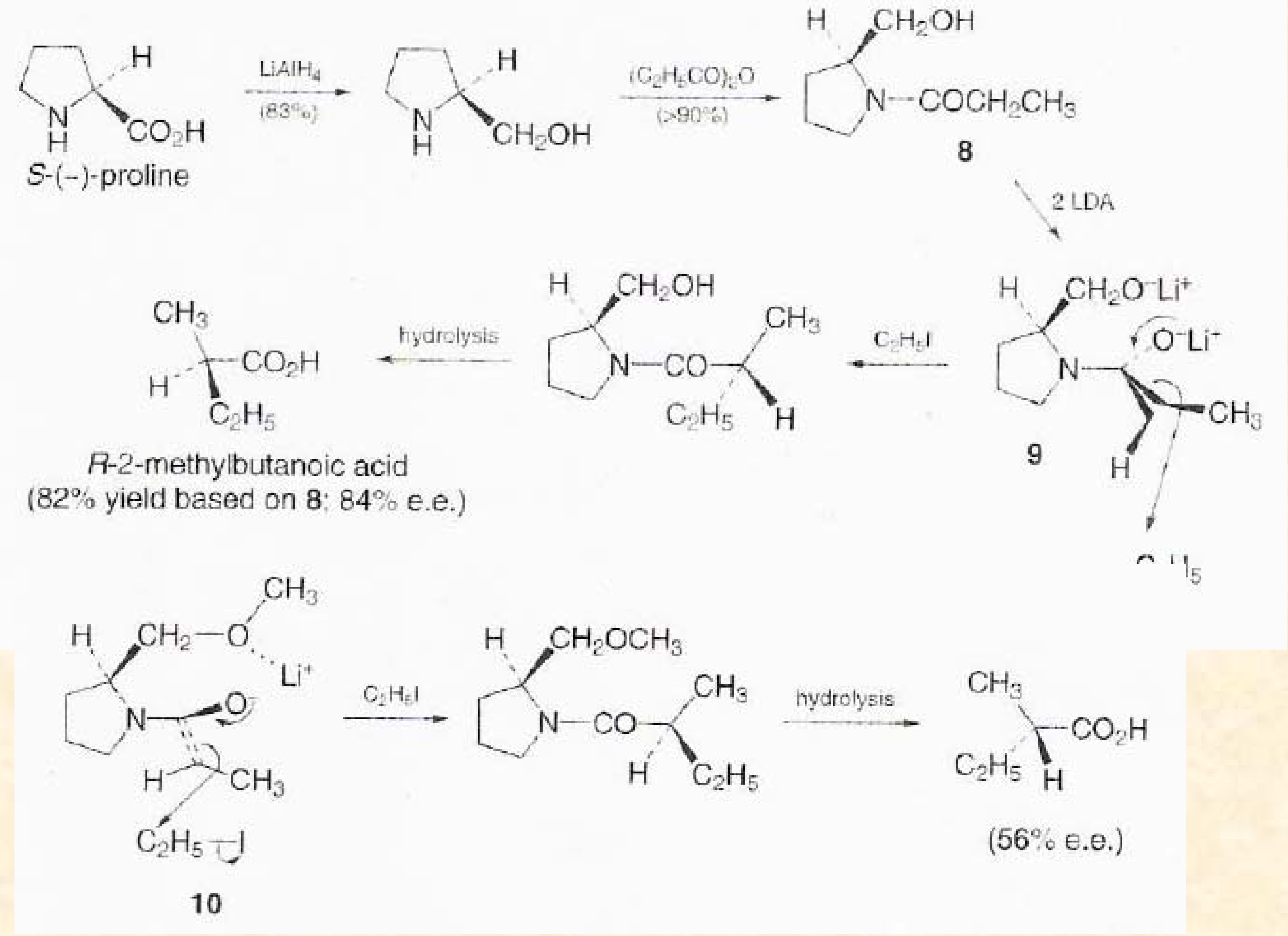
First-generation methods: the use of chiral substrates



Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

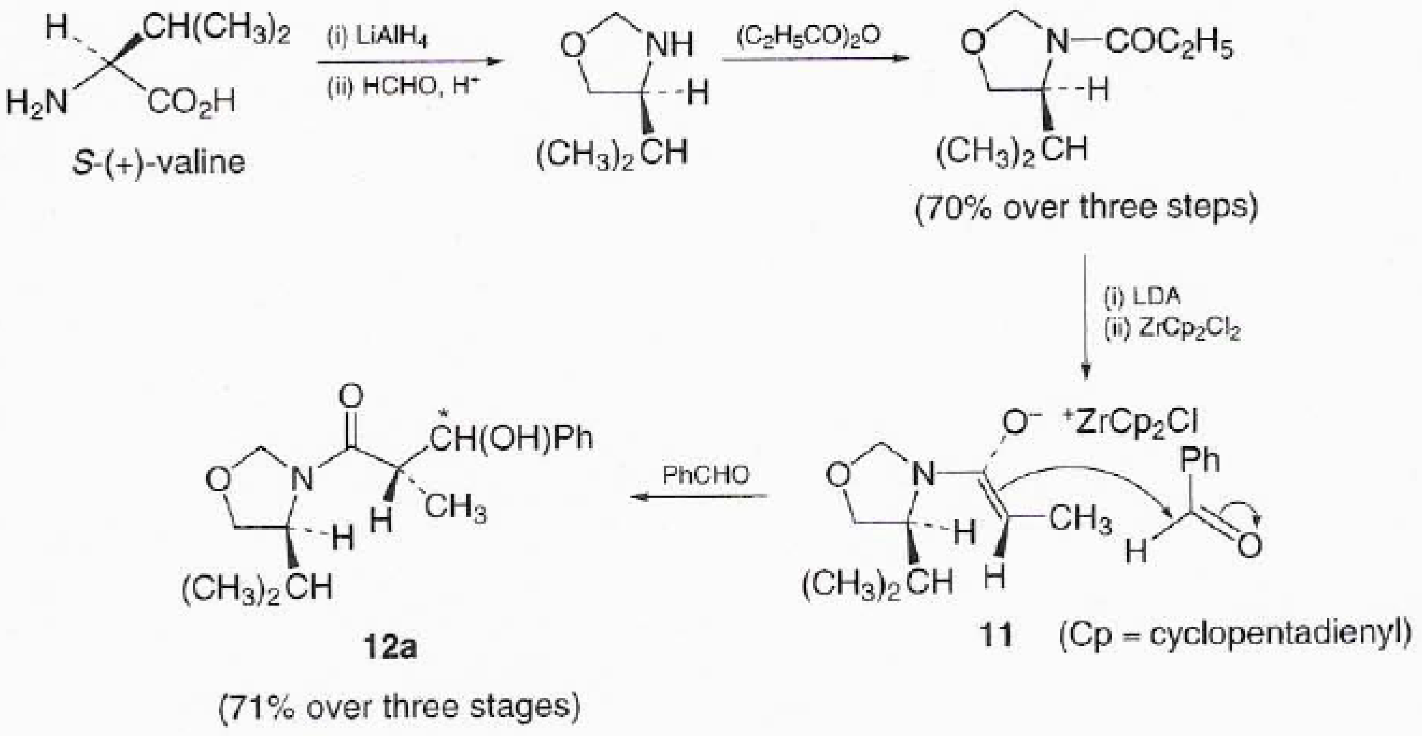
Alkylation of chiral enolates



Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

asymmetric aldol reaction,



Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

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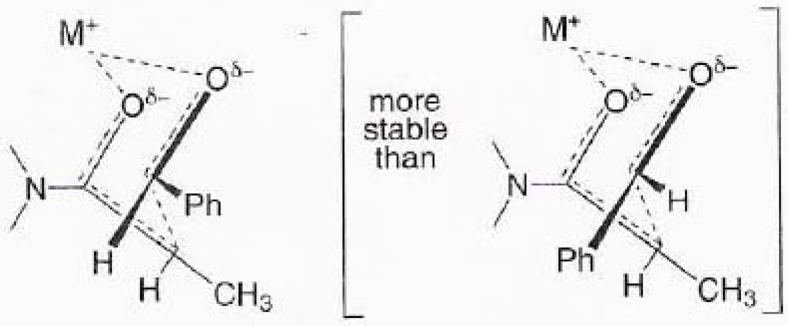

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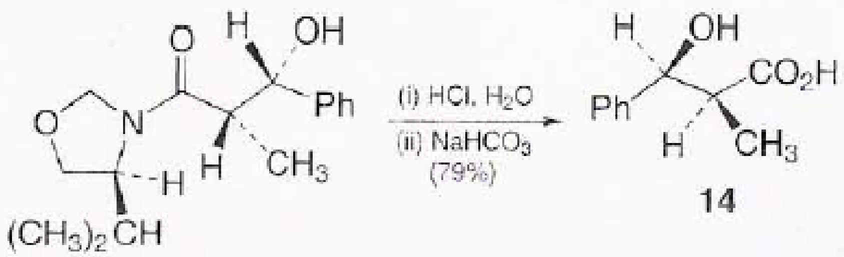

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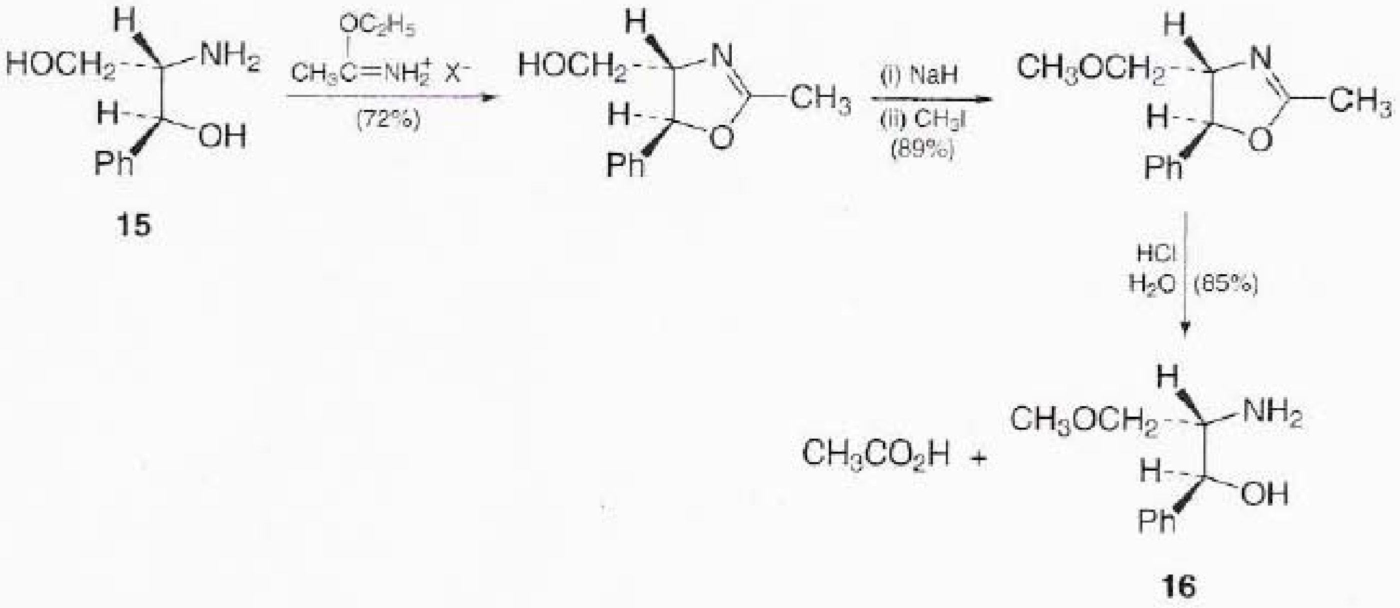
Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

Chiral aza-enolates



Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

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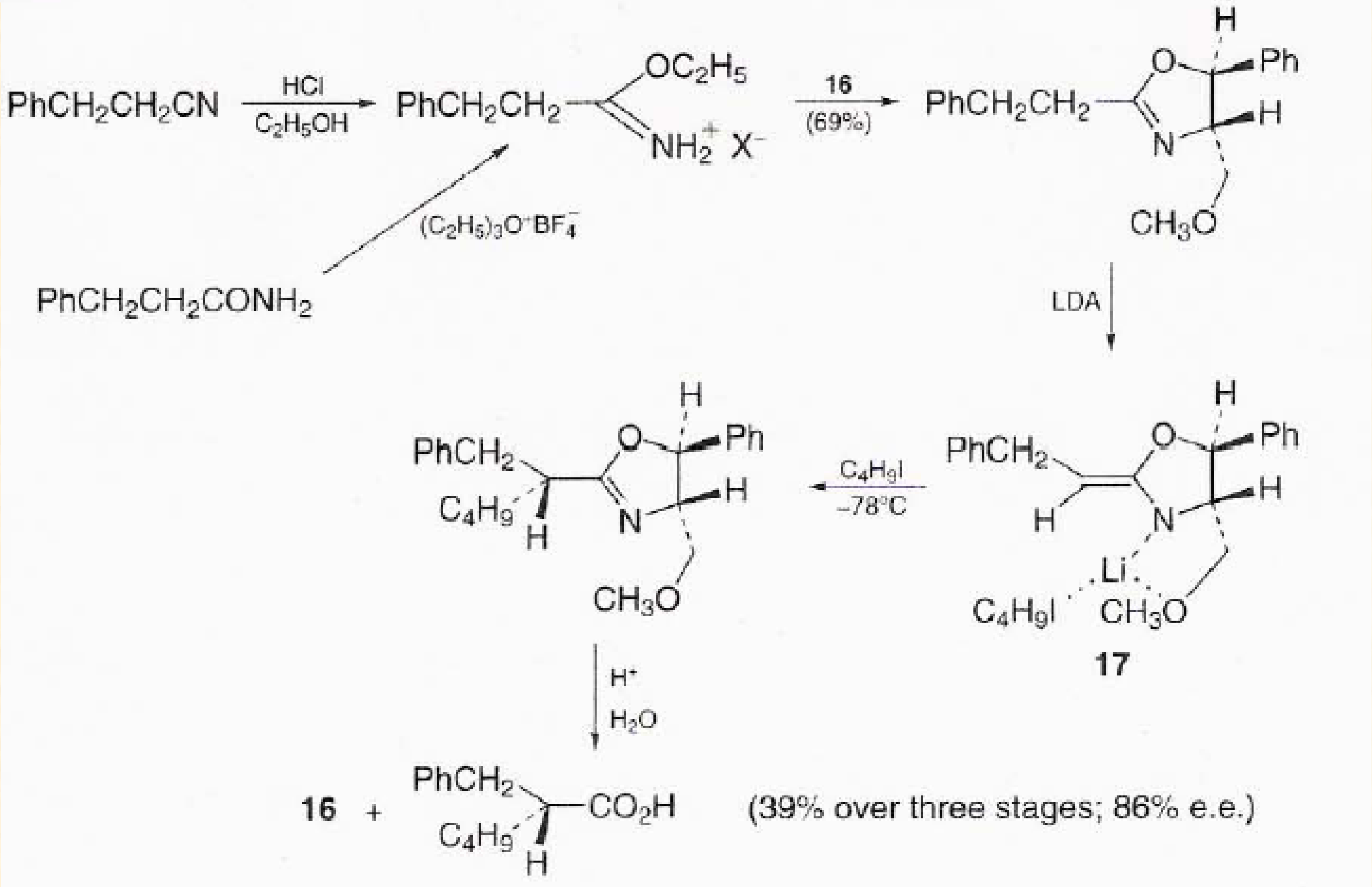

Synthesis of Chiral Compounds

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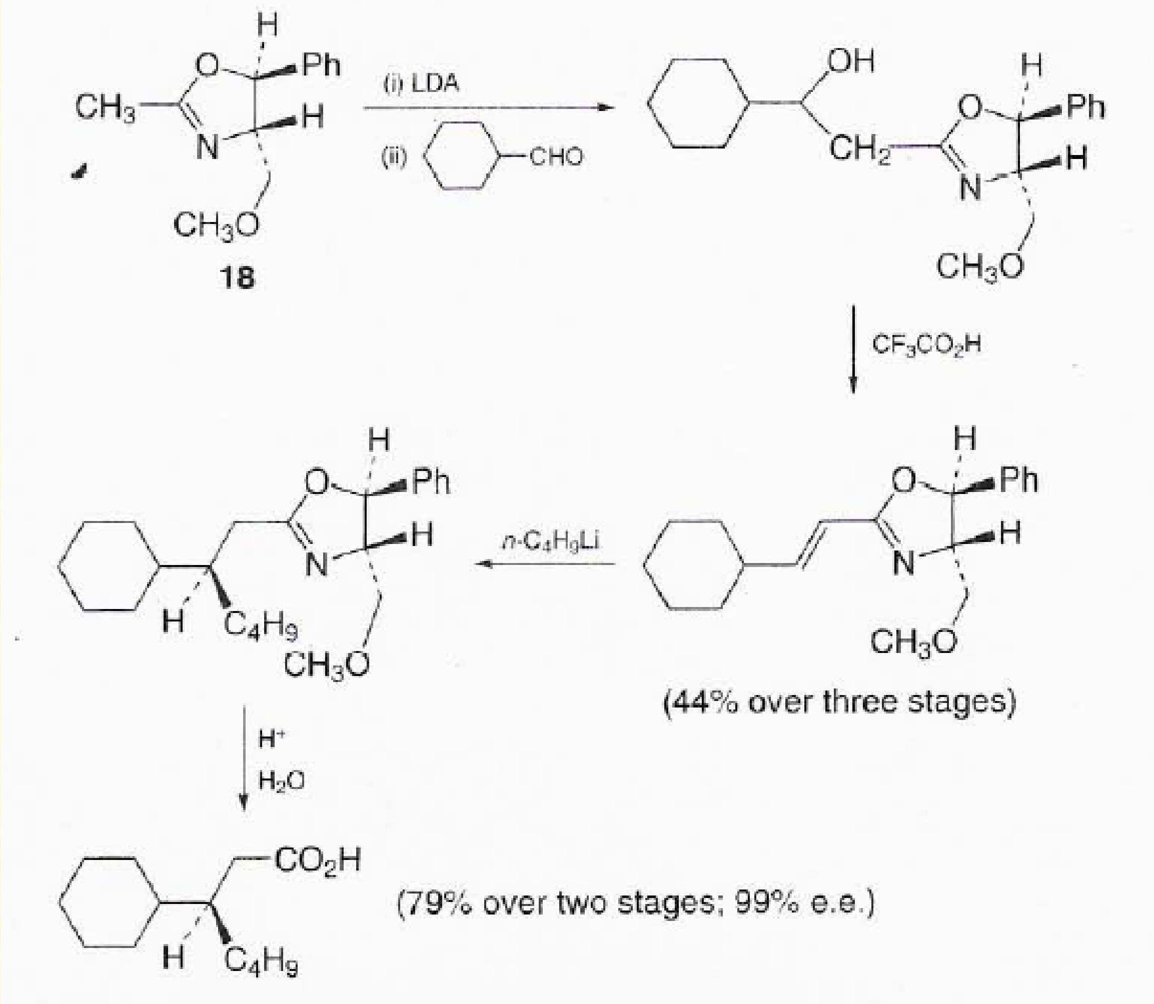

Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

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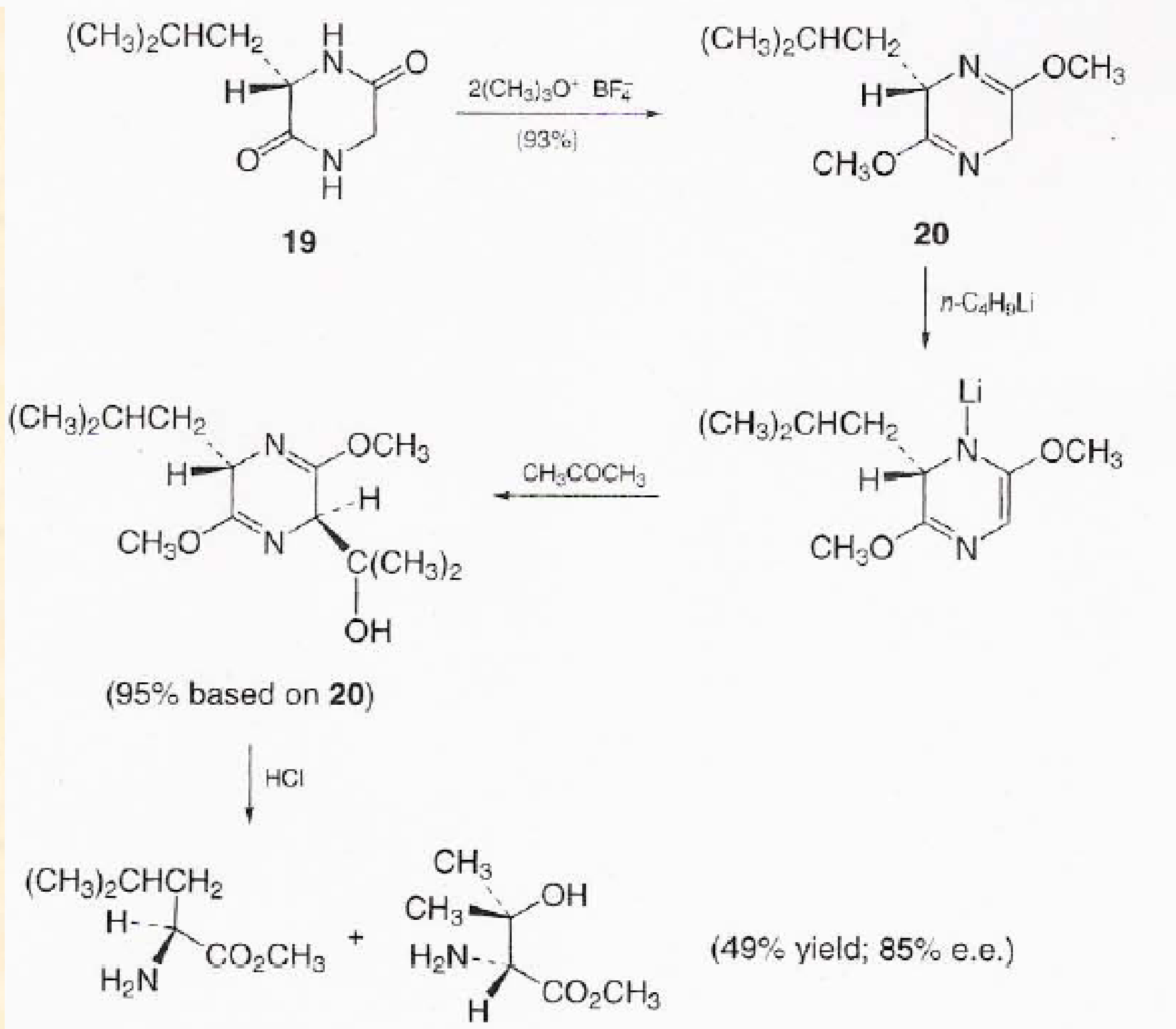

Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

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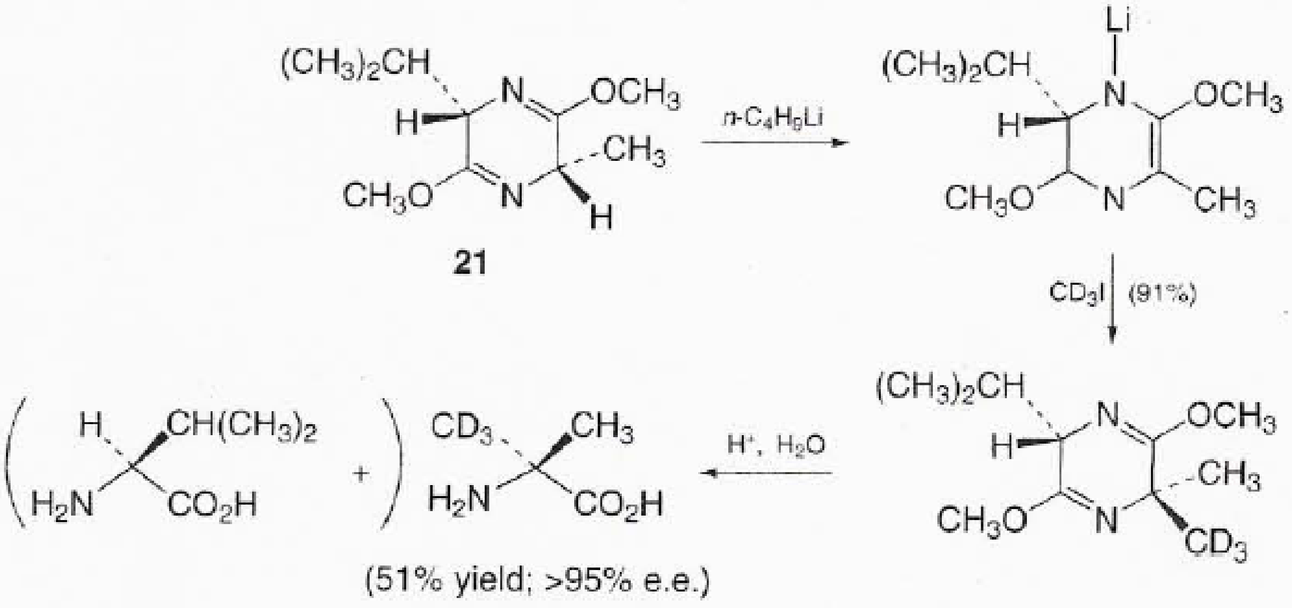
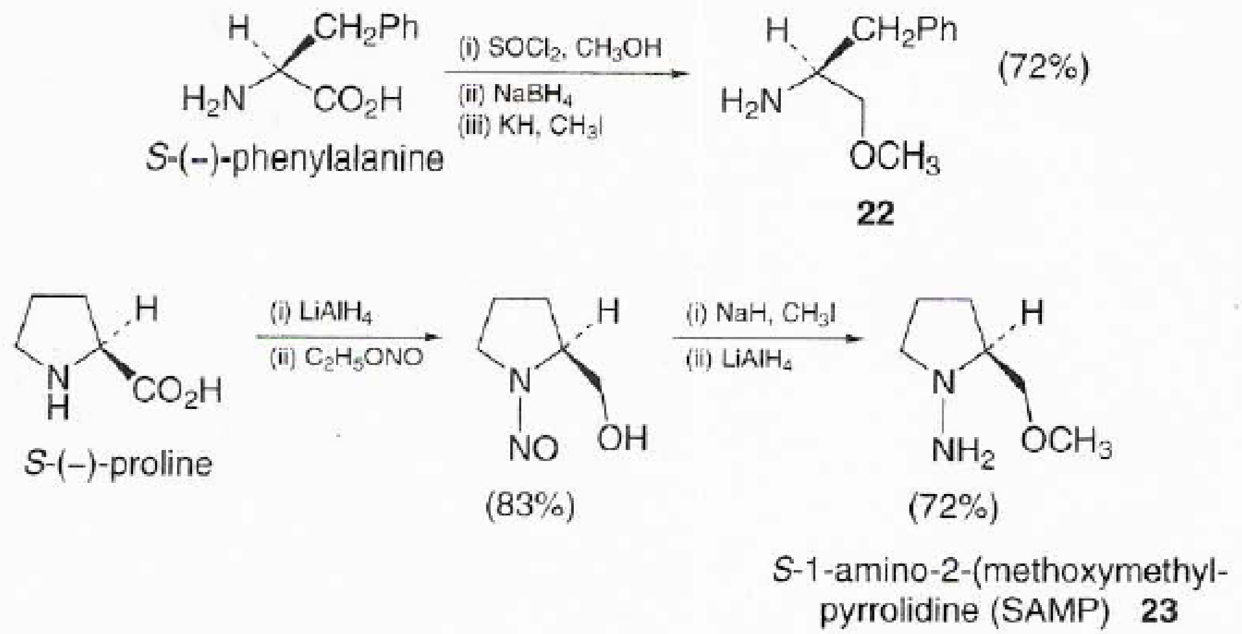


Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

Alkylation of chiral imines and hydrazones



Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

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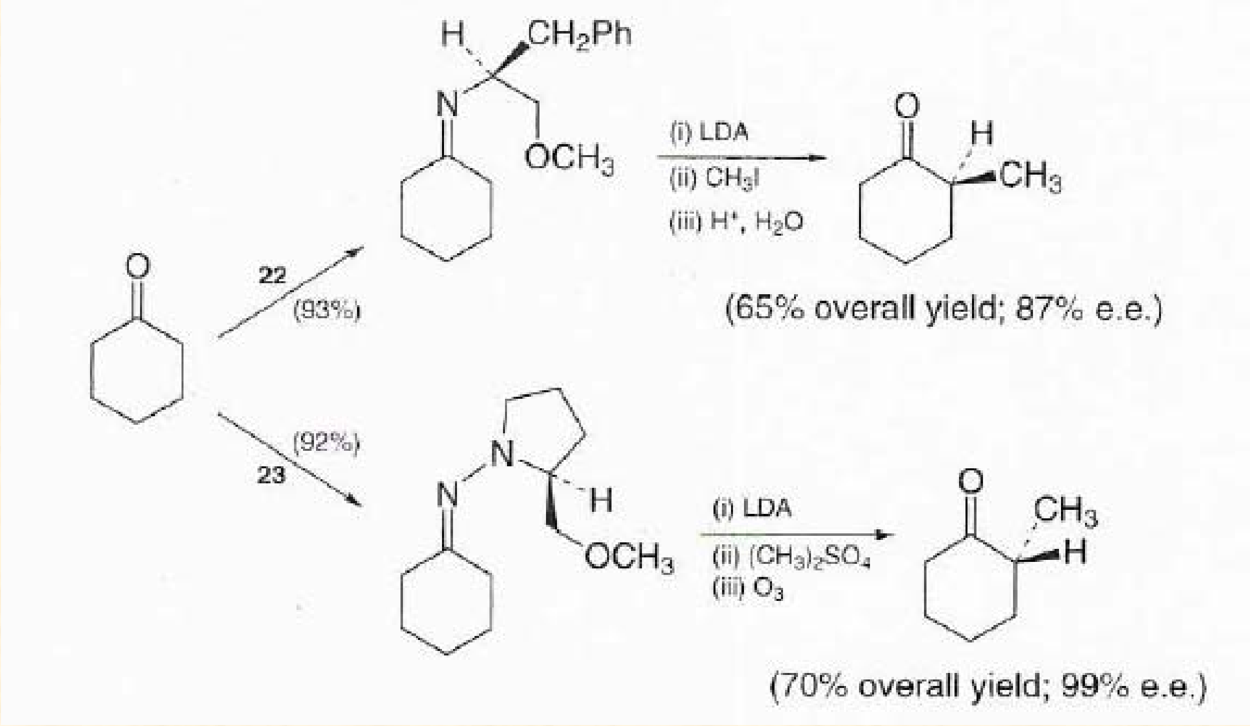

Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

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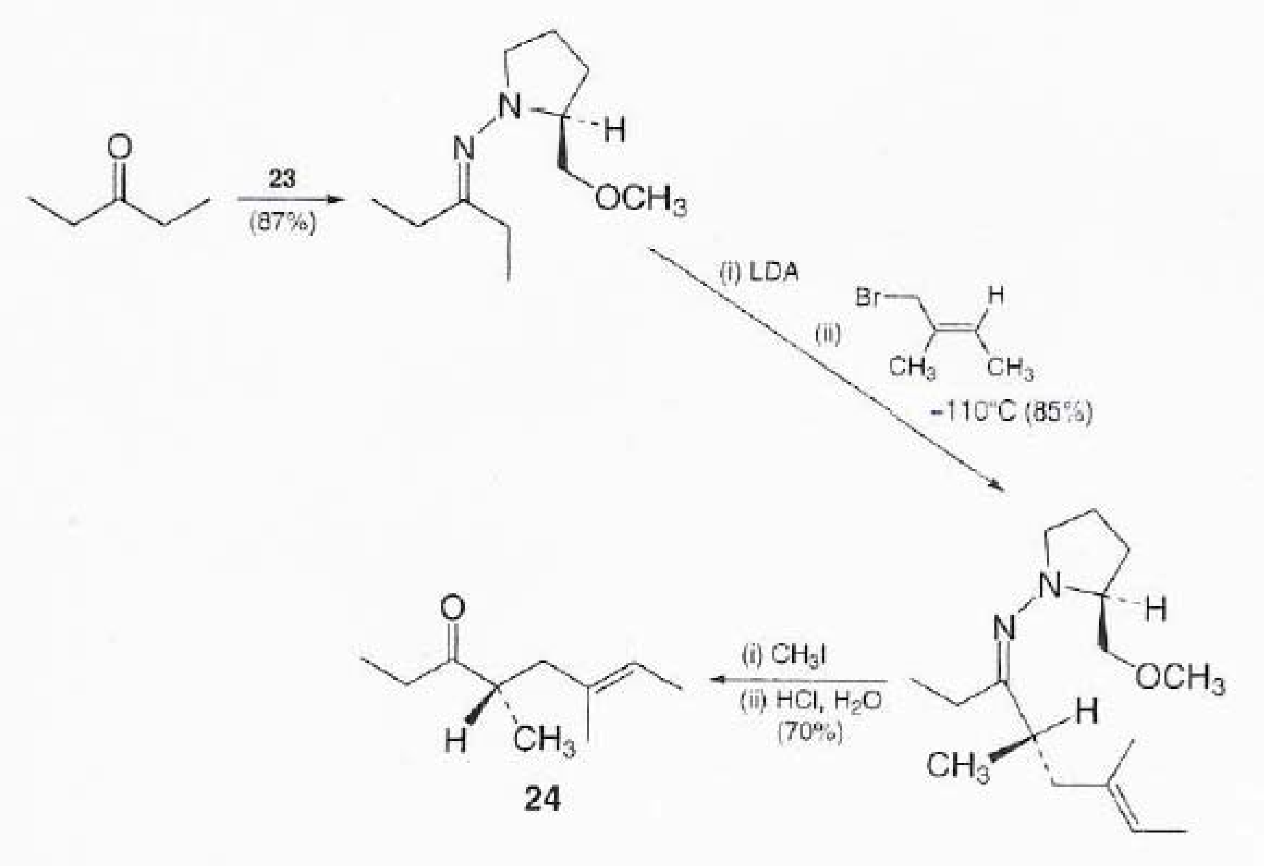
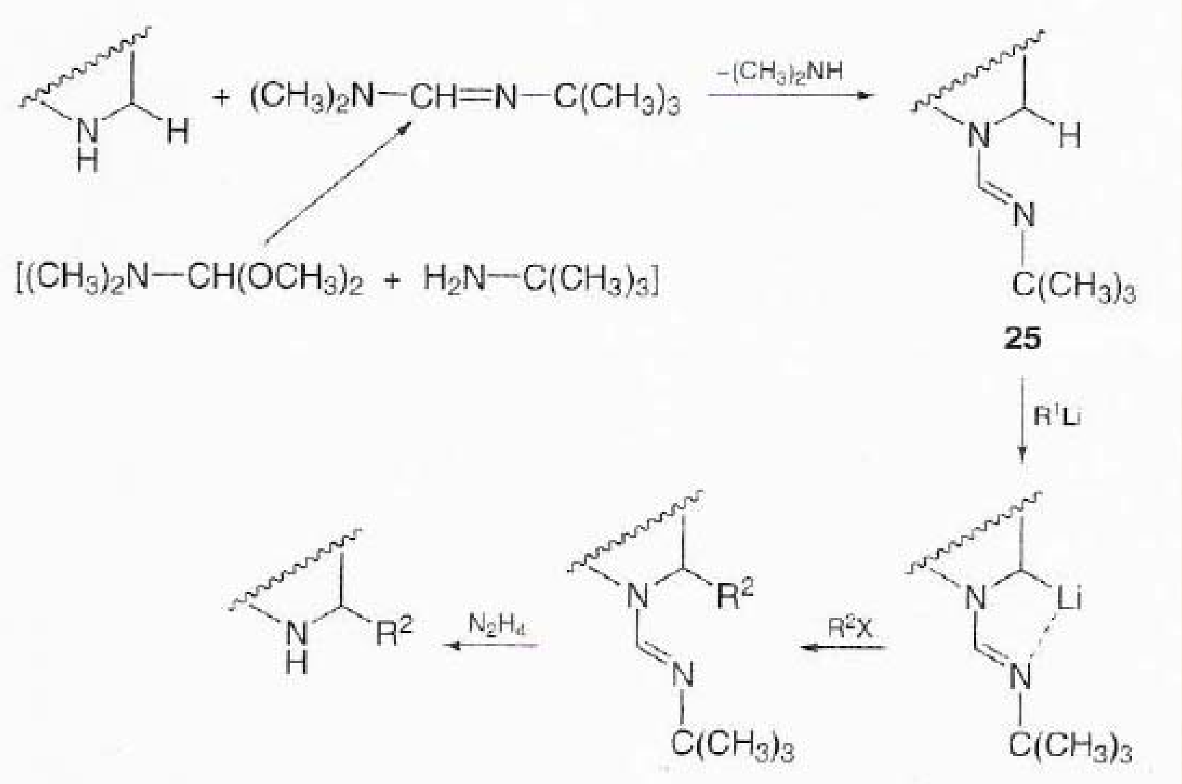


Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

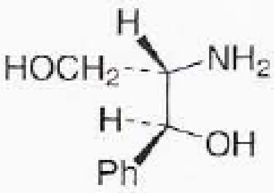
Alkylation α to nitrogen: chiral formamidines



Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

Alkylation α to nitrogen: chiral formamidines



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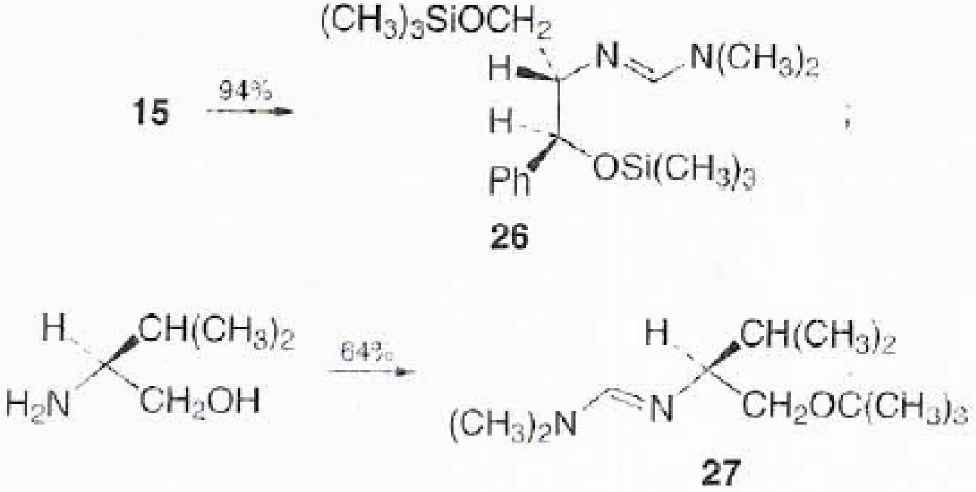
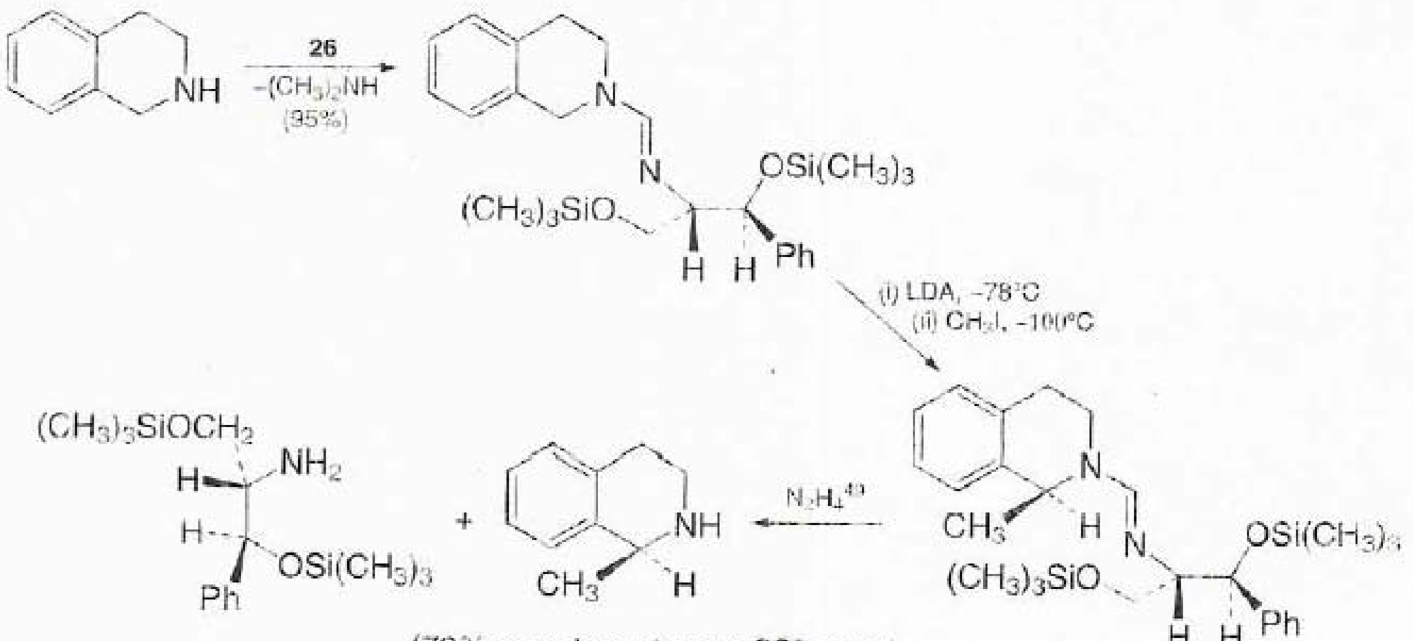


Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

Alkylation α to nitrogen: chiral formamidines

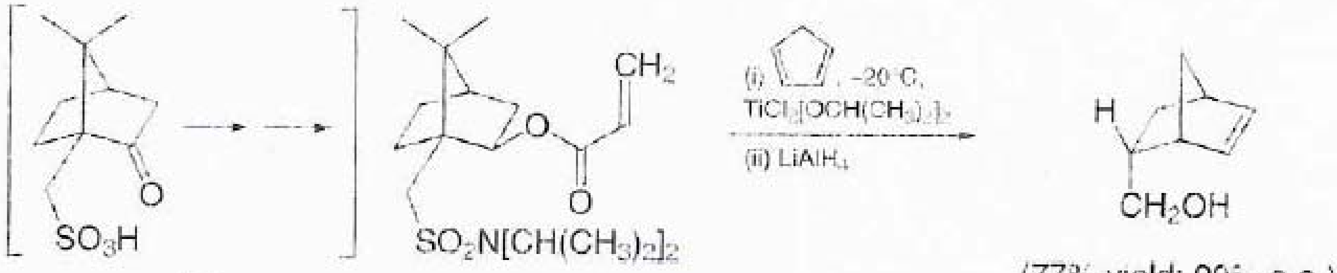


(79% over two stages; 99% e.e.)

Synthesis of Chiral Compounds

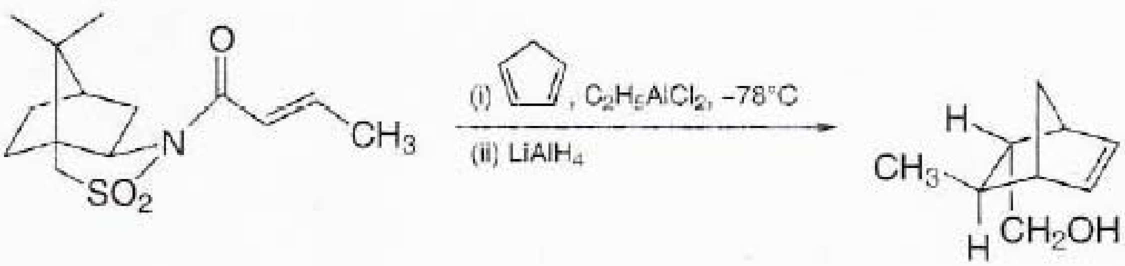
Second-generation methods: the use of chiral auxiliaries

Asymmetric Diels–Alder reactions



28 29

(77% yield; 99% e.e.)



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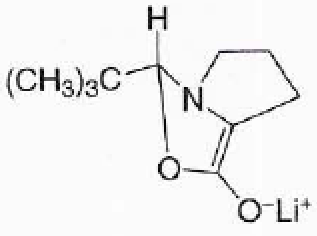
(91% yield; 98% e.e.)

Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

Self-regeneration of stereogenic centres



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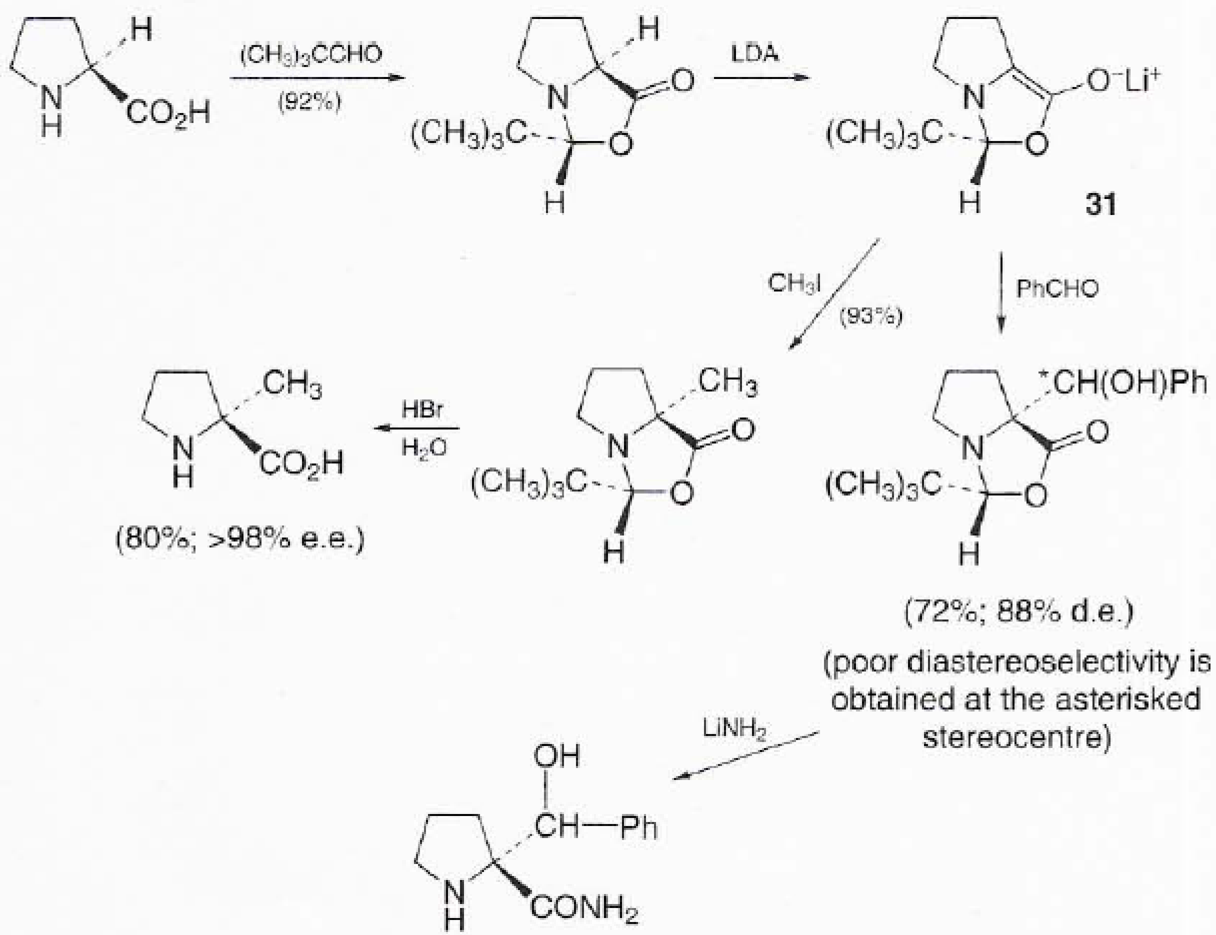
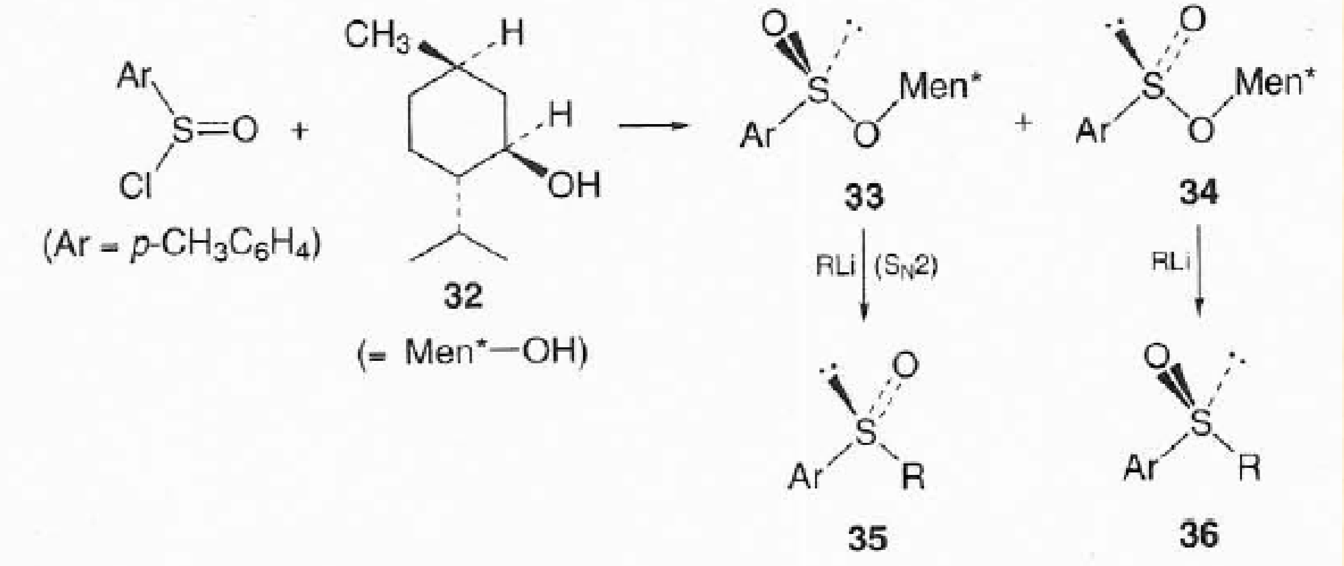


Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

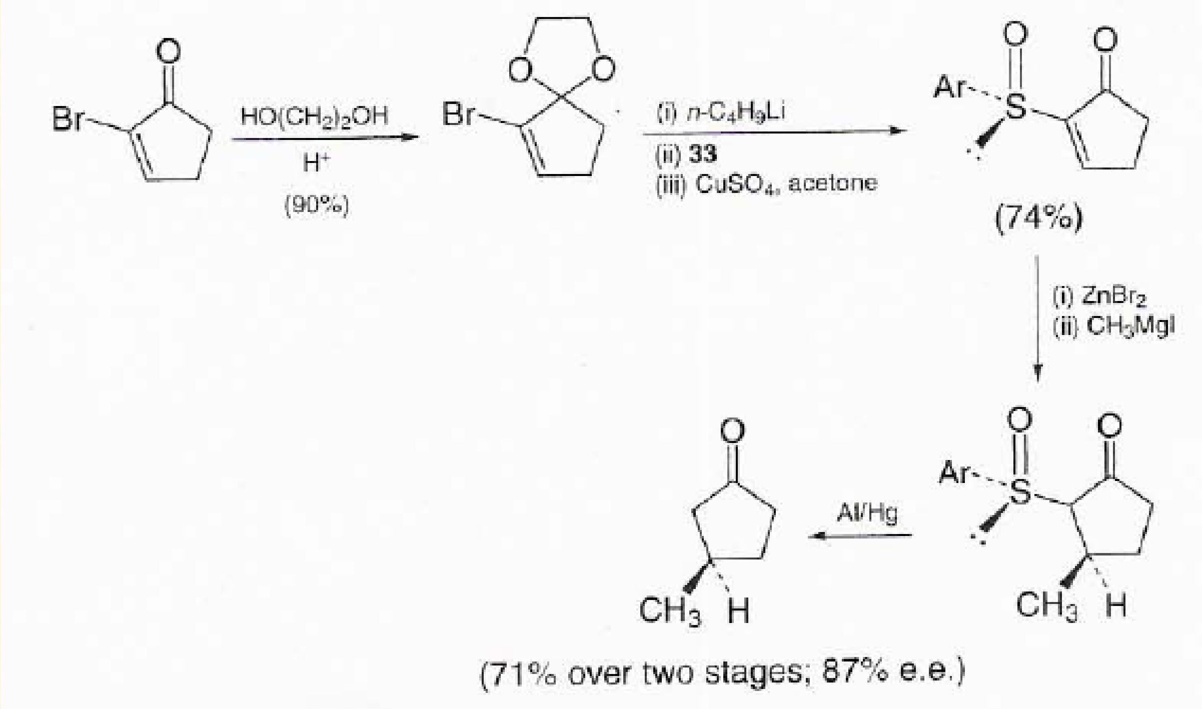
Chiral sulfoxides



Synthesis of Chiral Compounds

Second-generation methods: the use of chiral auxiliaries

Chiral sulfoxides

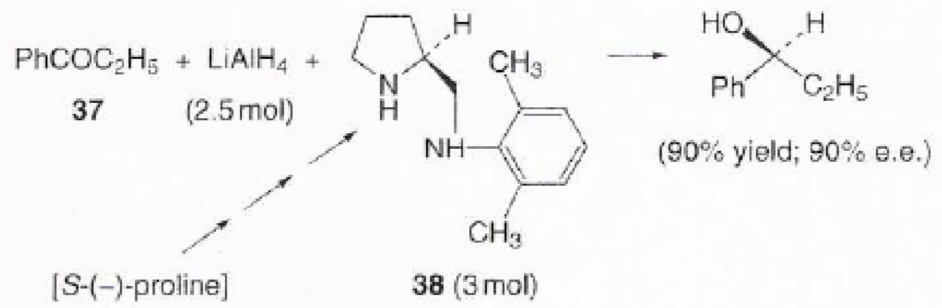


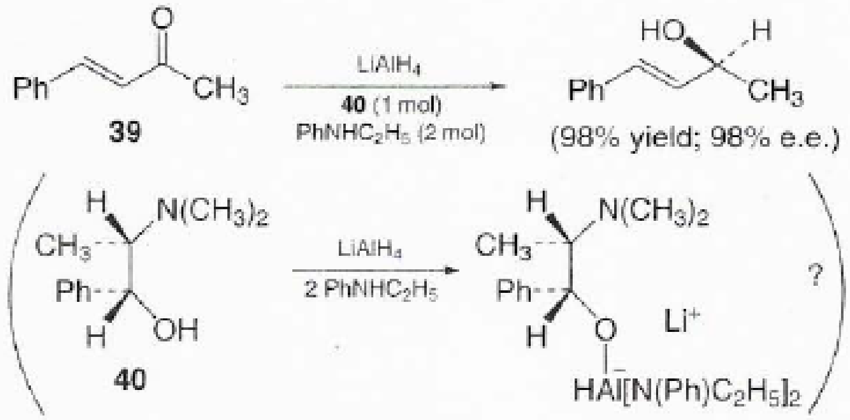
Synthesis of Chiral Compounds

Third-generation methods: the use of chiral reagents

Asymmetric reduction using lithium aluminium hydride

$LiAlH_4 + 3(CH_3)_3COH \rightarrow LiAlH[OC(CH_3)_3]_3$

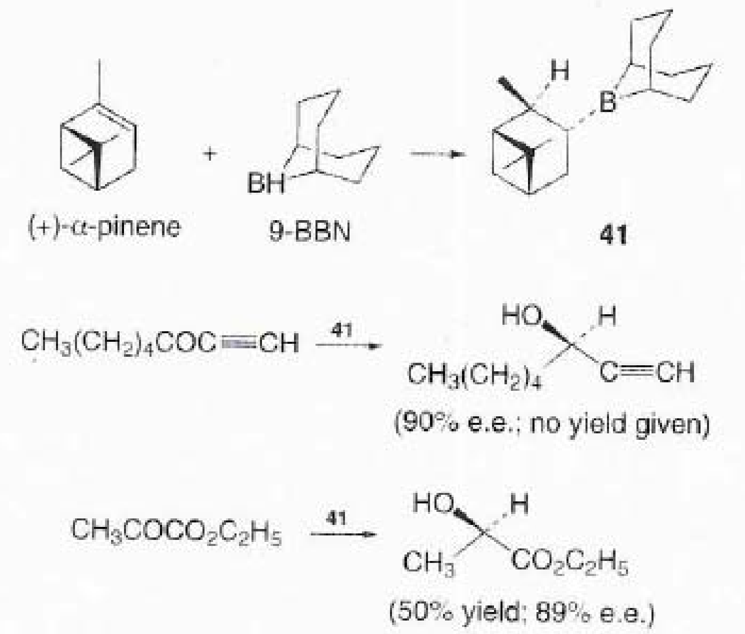


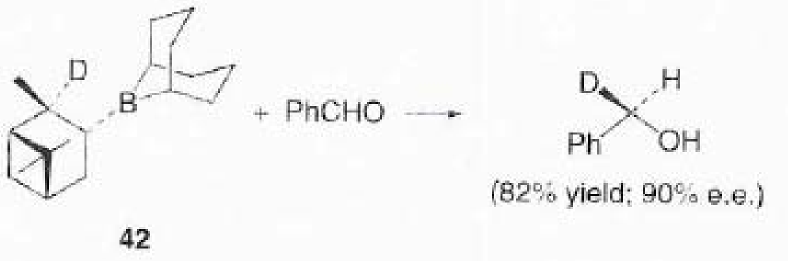


Synthesis of Chiral Compounds

Third-generation methods: the use of chiral reagents

Asymmetric reduction using boron reagents

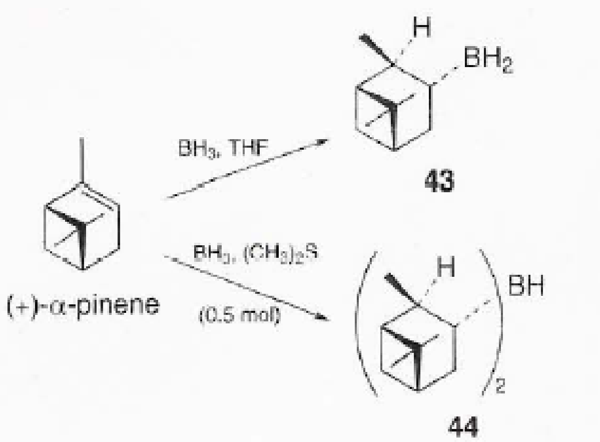


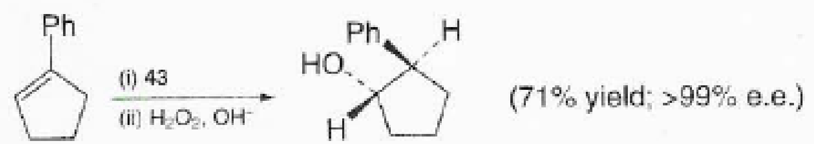


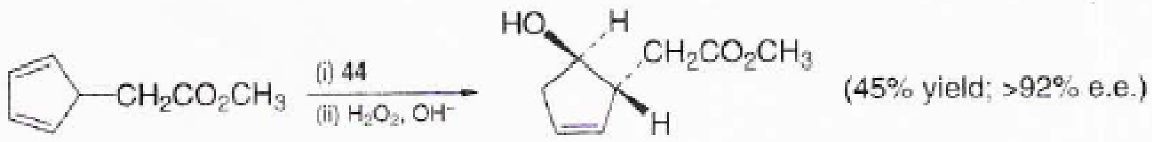
Synthesis of Chiral Compounds

Third-generation methods: the use of chiral reagents

Asymmetric hydroboration



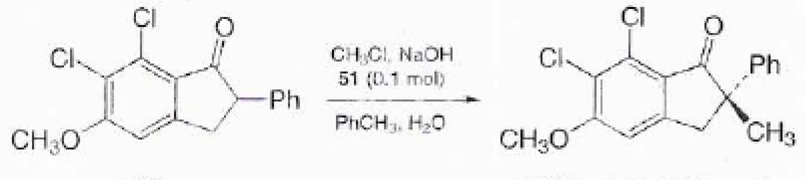


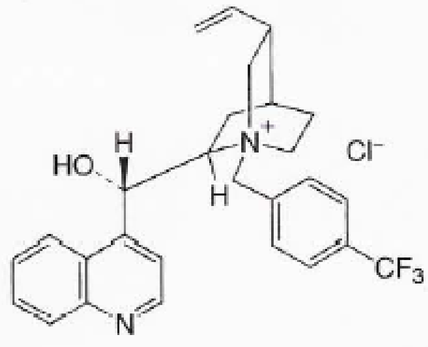


Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Catalytic asymmetric alkylation





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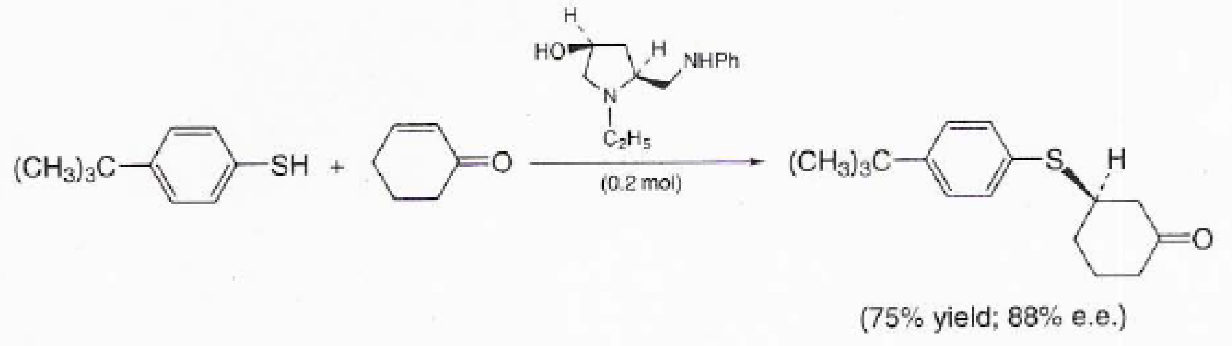
Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

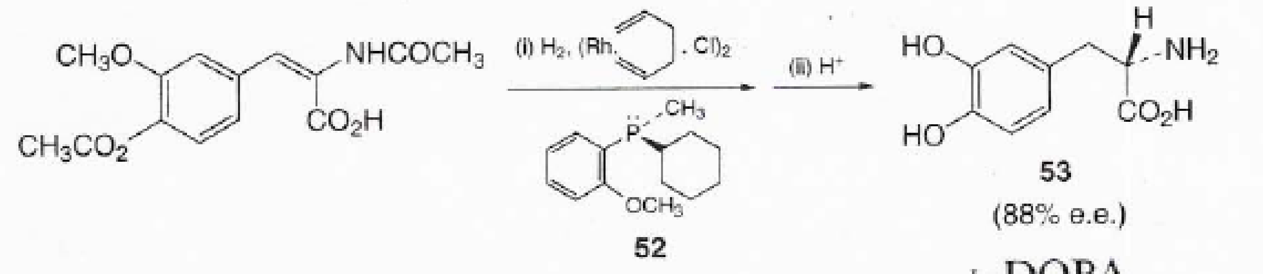
Catalytic asymmetric conjugate addition



Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Catalytic asymmetric hydrogenation

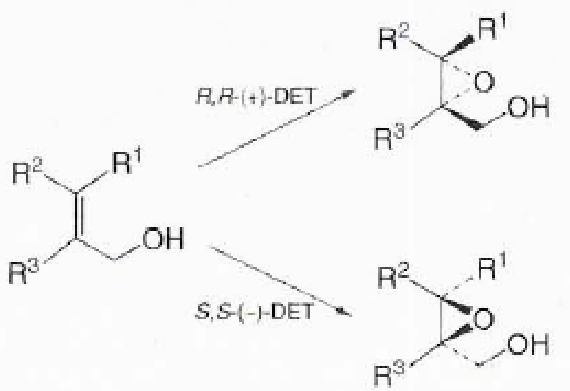


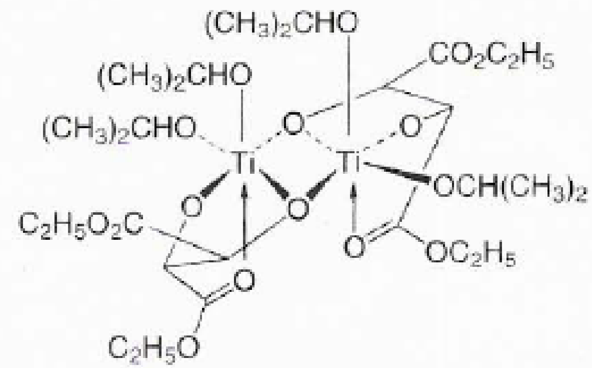
L-DOPA

Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Asymmetric oxidations





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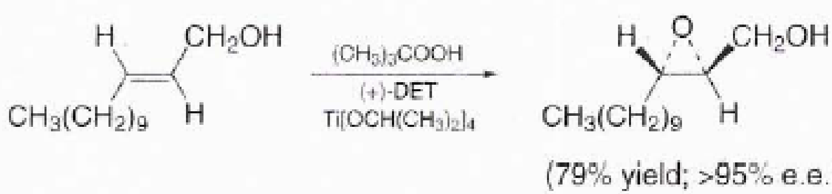
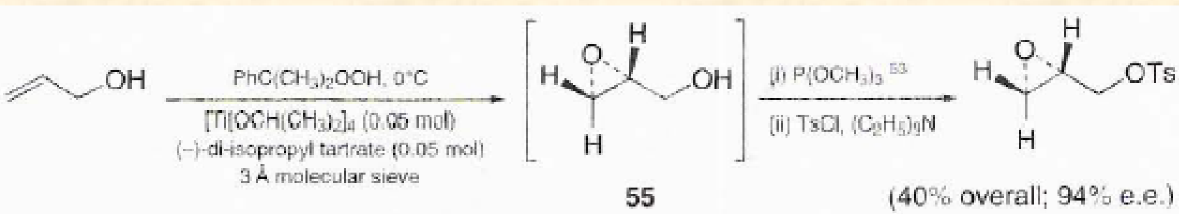
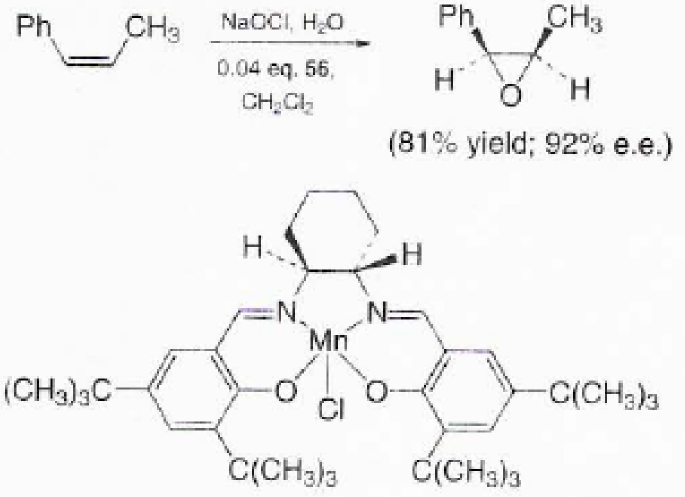




Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Asymmetric oxidations



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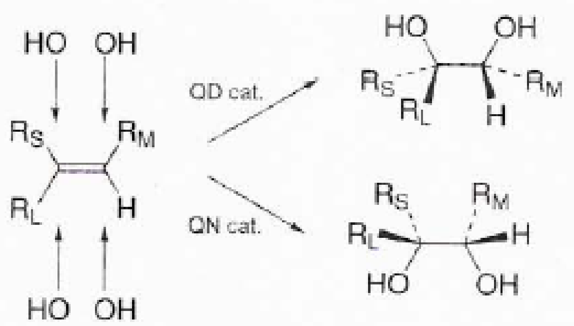
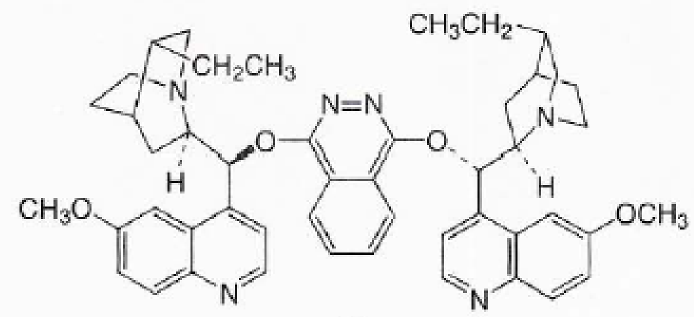
Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Asymmetric oxidations





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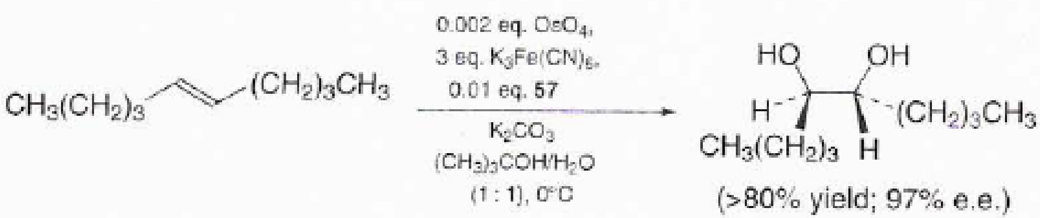
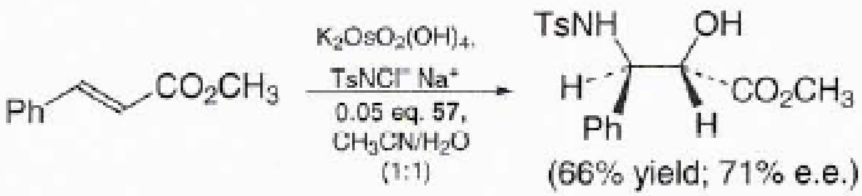


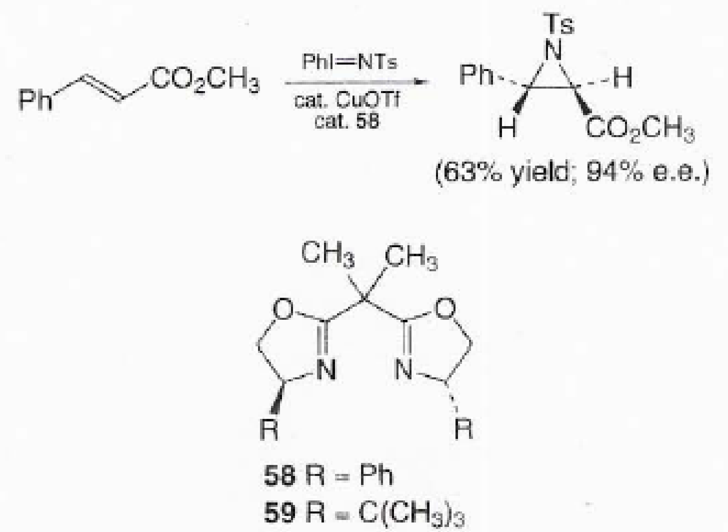


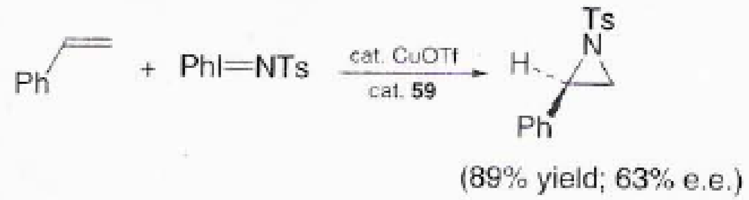
1,2-aminohydroxylation

Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Asymmetric aziridination and cyclopropanation

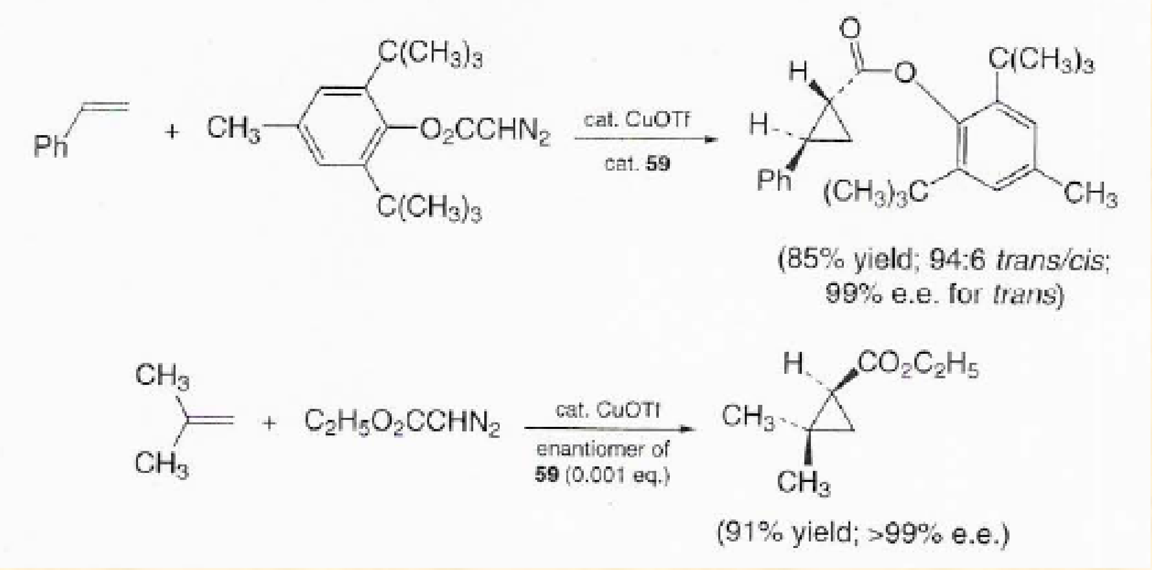




Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Asymmetric aziridination and cyclopropanation

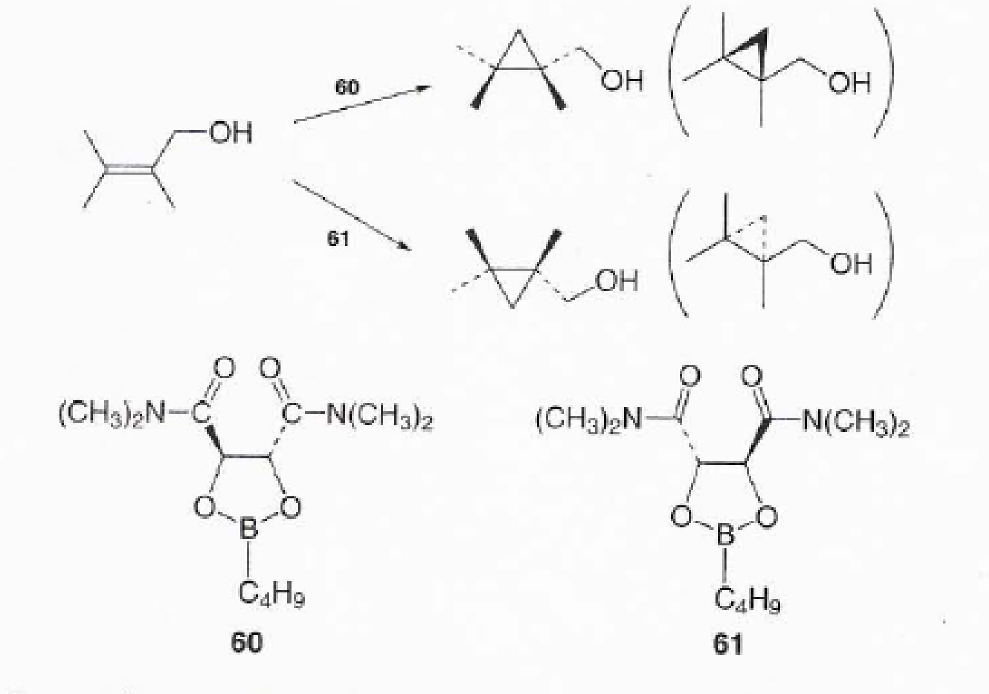


Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Asymmetric aziridination and cyclopropanation

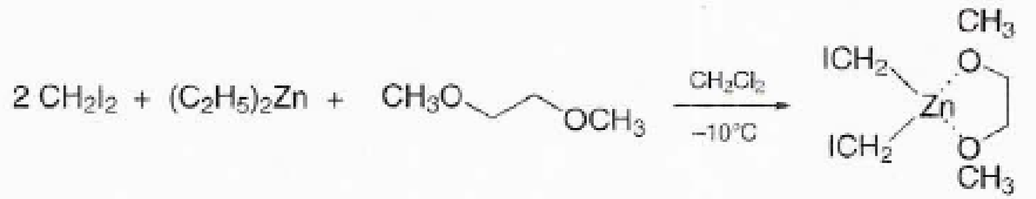
Simmons–Smith reaction



Synthesis of Chiral Compounds

Fourth-generation methods: asymmetric catalysis

Asymmetric aziridination and cyclopropanation



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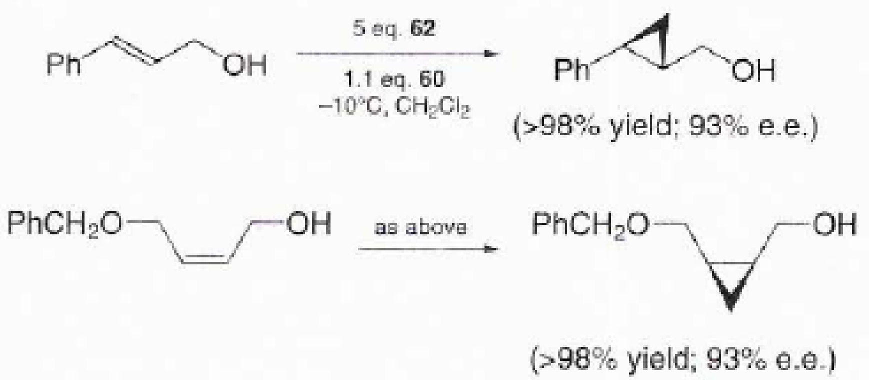


Synthesis of Chiral Compounds

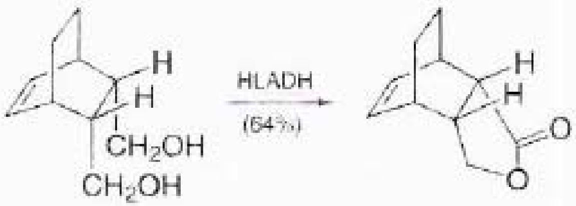
Fourth-generation methods: asymmetric catalysis

Reactions catalysed by enzymes and other proteins

Thermoanaerobium brockii

63: R = CH_3
64: R = C_2H_5

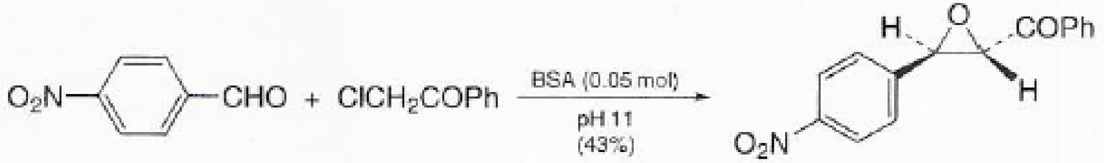
horse liver alcohol dehydrogenase



65 **66**

(>97% e.e.)

bovine serum albumin,



(100% d.s.; 62% e.e.)