CHIRASKOOL

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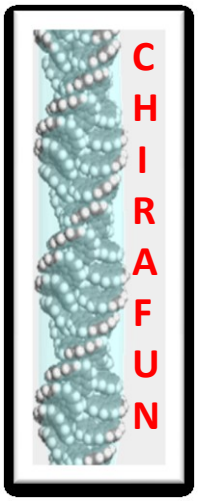


Historical aspects and properties of enantiomers

Definitions

Symmetry aspects

- Symmetry point groups for achiral molecules
- Symmetry point groups for chiral molecules

Molecules with stereogenic centers

- Asymmetric carbon, chiral amines, sulfoxides, phosphines, …
- Half-sandwich complexes, metallocenes
- Tetrahedral or spiro-type complexes
- Octahedral Complexes

Molecules displaying axial chirality

- Examples of allenes
- Atropoisomerism and axial chirality

Planar chirality

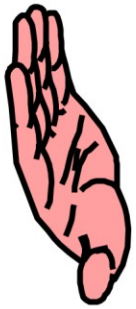
Inherent chirality

- Helicenes, fullerenes
- Trefoil knots and topological chirality

Selected examples: stereochemistry of helicene derivatives

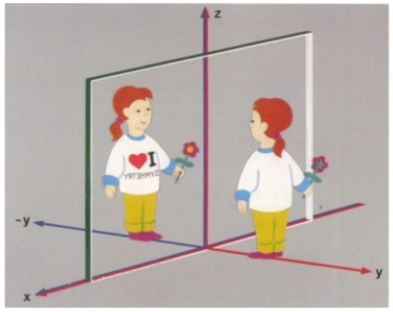
Chirality

Cheir « Χηειρ »
means Hand in Greek

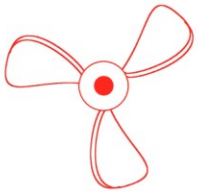


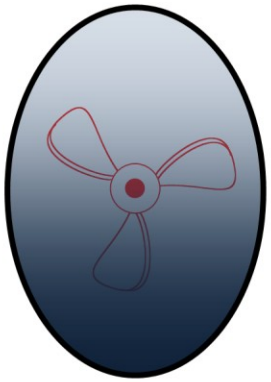
Left hand

Right hand



Chiral objects





Achiral objects

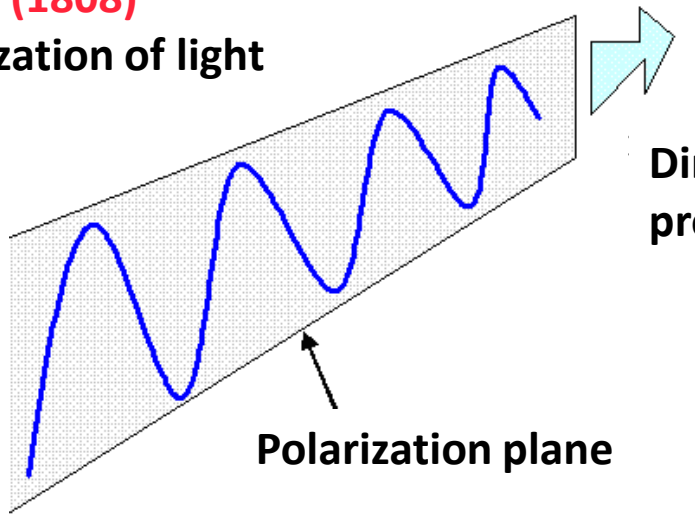
Œuf, brique

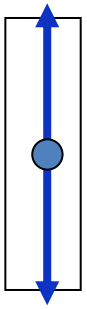
Some (simplified) history…

Bartholin (1669) birefringence Iceland Spar – Spath d'Islande ($CaCO_3$)

Malus (1808)

Polarization of light





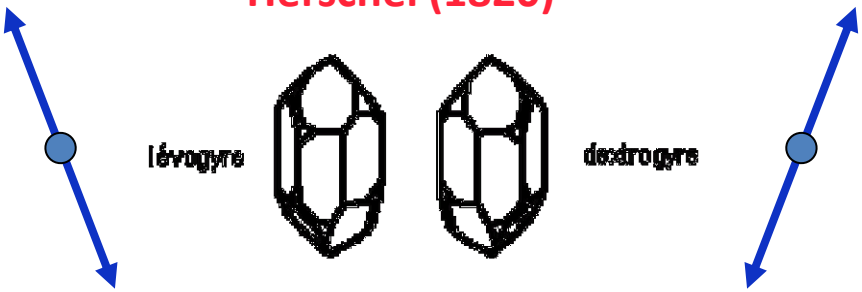
Wave seen by the observer

Abbey Haüy (1809) modern crystallography, hemihedry

Mitscherlich (1819) polymorphism

Arago (1811)

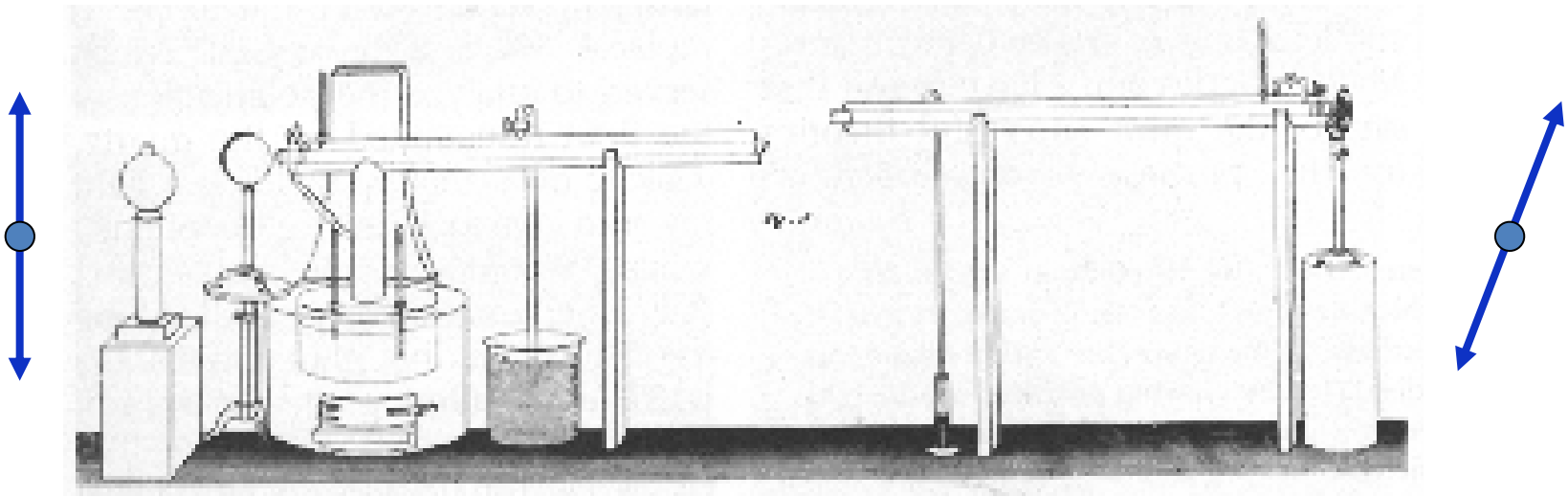
Herschel (1820)



Hemihedral crystals of quartz

They 'turn the light' : they have a rotatory power

The Biot's polarimeter (1815)



Solutions of camphor, glucose, tartaric acid

They 'turn the light' : they have a rotatory power (optical rotation)

Camphor tree

Grapes (tartaric acid)

The tartrates by Pasteur (1848)

1820 Kessler (Alsacian chemist)

Synthesis of a mysterious acid after refining the potassium acid tartrate from vinification

Was named paratartaric acid or racemic (Gay-Lussac 1828)

Berzelius : same composition as tartaric acid but different crystals (isomerim)

Mitscherlich (1844) : the crystals of double salts of sodium and ammonium of tartaric acid and of racemic acid are identical!

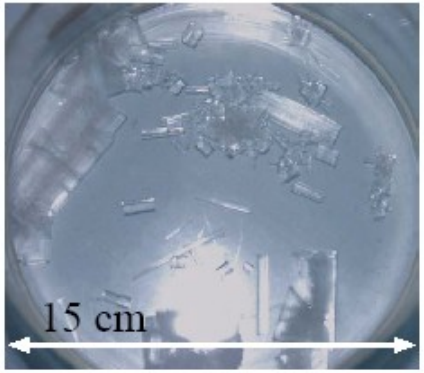
Biot ‘s polarimeter: optical rotation was zero

The tartrates by Pasteur (1848)

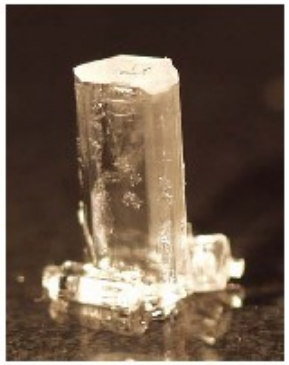
168 years ago!

Louis PASTEUR
1822-1895

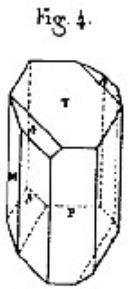
Tartrate
In alcohol

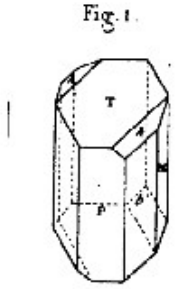


1848 Pasteur : hemihedral crystals (microscope)

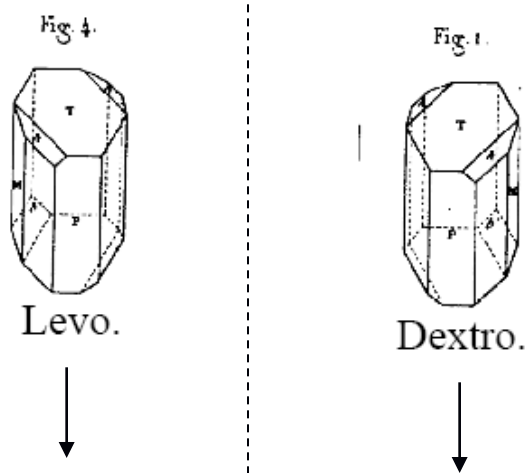


First spontaneous resolution !





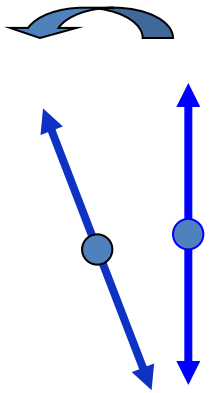
Pictures given by Dr. Thierry RUCHON (CEA)

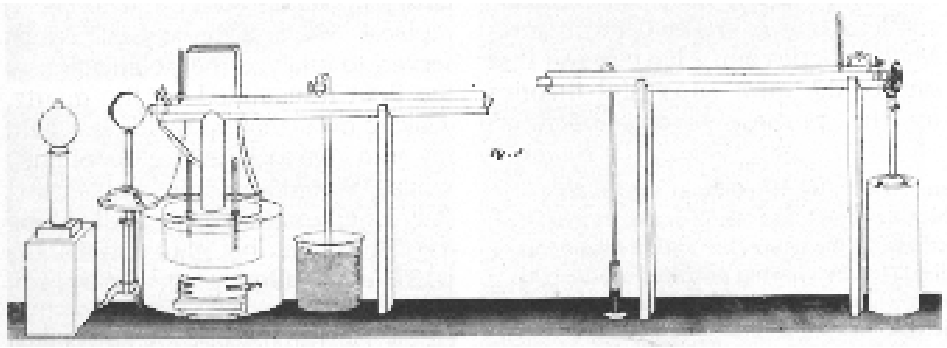


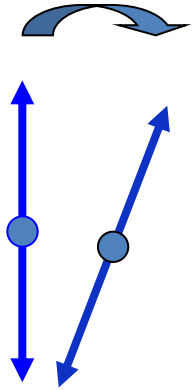
Tartrate 'Left'

Tartrate 'right'

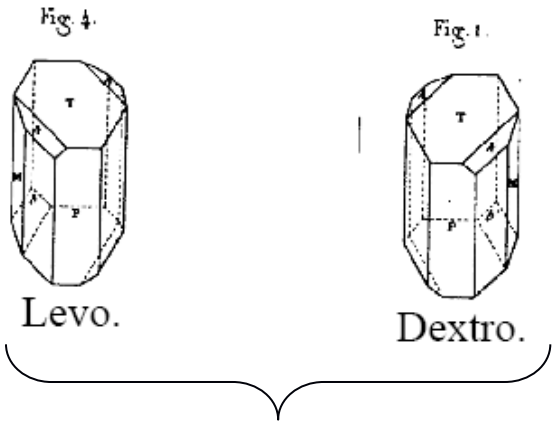
Tartrate solutions



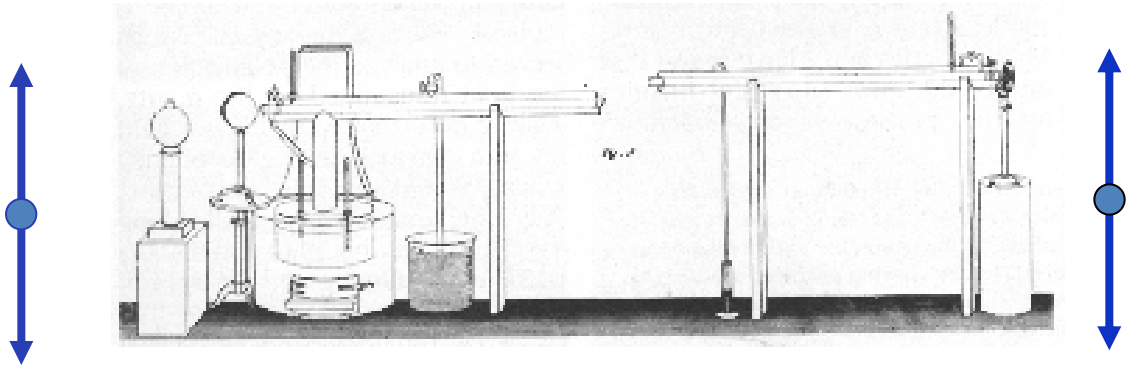




They 'turn the light' : they have an optical rotation



Solutions of racemic tartrate



Optical rotation: zero

Link between crystal and substance (molecule)!

INSTITUT DE FRANCE.

ACADÉMIE DES SCIENCES.

Extrait des *Comptes rendus des séances de l'Académie des Sciences*, tome XXXI, séance du 28 octobre 1850.

RAPPORT

Sur un Mémoire présenté à l'Académie, par M. L. Pasteur, *ayant pour titre :* Nouvelles recherches sur les relations qui peuvent exister, entre la forme cristalline, la composition chimique, et le pouvoir rotatoire moléculaire.

Commissaires, **MM. Chevreul, Dumas, Regnault, Balard, Biot** rapporteur.

Le Bel and van't Hoff (1874)
Theory of the asymmetric carbon

Joseph Achille LE BEL
(1847-1930)

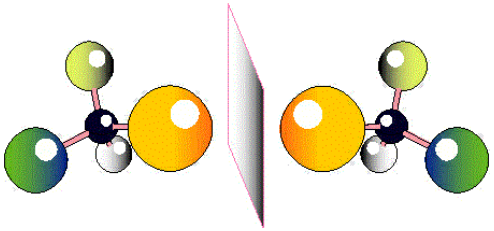
« Sur les relations qui existent entre les formules atomiques des corps organiques et le pouvoir rotatoire de leur dissolution »

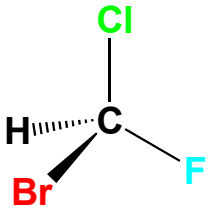
Jacobus Henricus VAN'T HOFF
(1852-1911)

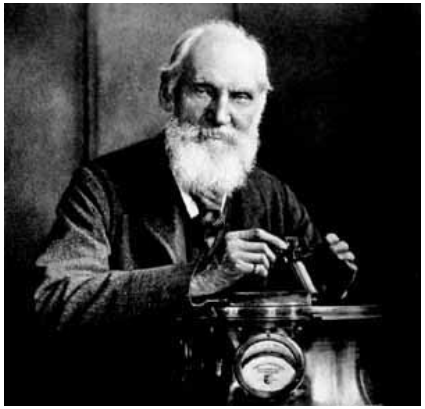
« La chimie dans l'espace »

First Nobel prize in chemistry (1901)

There exist two products corresponding to a tetrasubstituted methane







Lord Kelvin (Sir William Thompson)

Baltimore Lectures, 1884

I call any geometrical figure, or group of points, **chiral**, and say that it has **chirality**, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.

« J'appelle **chiral** toute figure géométrique ou tout ensemble de points qui n'est pas superposable à son image dans un miroir. Je parle alors de **chiralité** ».

Laurence Barron (1980's)

A more recent physical definition: True and False chirality

True chirality is shown by systems existing in two distinct enantiomeric states that are **interconverted by space inversion, but not by time reversal** combined with any proper spatial rotation.

Pointing **the role of time reversal symmetry** in optical activity and pointed out that time-even pseudoscalar observables are the hallmark of genuine chirality.

Circularly polarized light: true chiral influence
B.**k**: true chiral influence
Only **B**: cannot induce an enantiomeric excess

Absolute asymmetric synthesis under physical fields: facts and fictions.
Chem. Rev. **98**, 2391-2404.

« L'univers est dissymétrique »

Pasteur (1883)

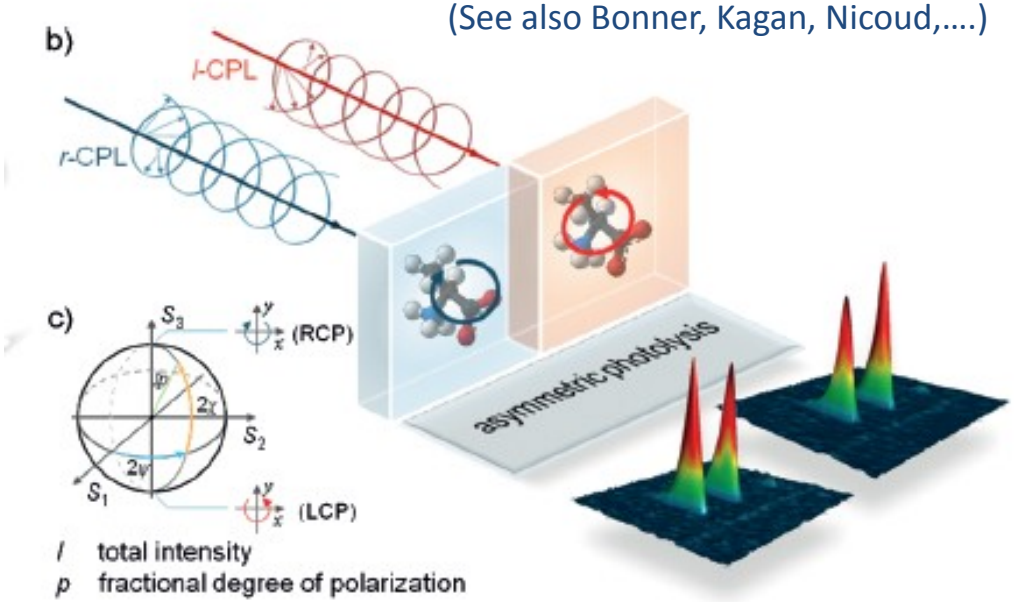
Louis PASTEUR
1822-1895

« Me demanderez-vous : quelles sont les forces dissymétriques qui président à l'élaboration des principes immédiats naturels? … les forces cosmiques dissymétriques…. Un des liens entre la vie à la surface de la terre et le cosmos…. »

Recent results

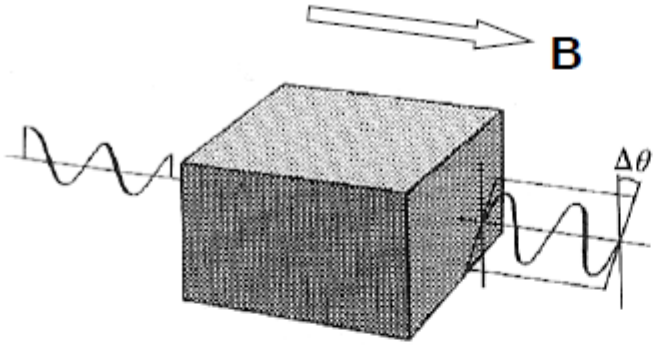
Photon energy-Controlled Symmetry Breaking with Circularly Polarized Light

L. Nahon **(GDR),** U. Meierhenrich, *Angew. Chem.* **2014**, *53*, 210
(See also Bonner, Kagan, Nicoud,….)



Synchrotron wavelength at 200 nm
CPL light on an amorphous film
Alanine with ***ee* up to 4.2 %**

A. Fresnel (1817) Circular birefringence



Natural and Magnetic Optical Rotation

- A collection of chiral molecules (*e.g.* a tartaric acid solution) shows **natural optical rotation**. The mirror-image molecules show equal but opposite rotation (Pasteur 1848).

- A static magnetic field **B** parallel to the incident light beam induces **magnetic optical rotation** in a collection of achiral molecules (the Faraday effect, 1846). Reversing the magnetic field direction reverses the sense of optical rotation.

A. Cotton (1895) Circular Dichroism (Cotton effect), then Magnetic CD

Chirality, magnetism and light, L. D. Barron, *Nature* **2000**, 405, 895

Magneto-optical properties of chiral systems

Breaking of parity symmetry by chirality leads to **optical activity**.

Breaking of time reversal symmetry by a magnetic field leads to the **Faraday effect**.

Breaking both symmetries leads to an **additional** new effect: **magnetochiral anisotropy**.

Dielectric constant for CPL:

$$\varepsilon(\omega,\mathbf{k},\mathbf{B})_{\pm}^{D/L} = \varepsilon(\omega) \pm \alpha(\omega)^{D/L} k \pm \gamma(\omega) B + \Omega(\omega)^{D/L} \mathbf{k}\cdot\mathbf{B}$$

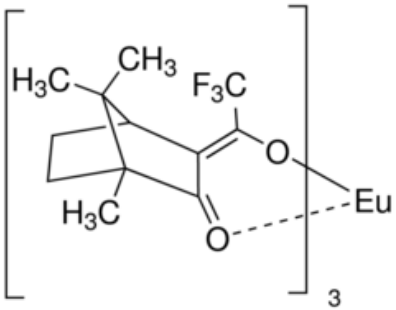
- dependent on relative orientation of light and field
- independent of polarization
- enantioselective: $\Omega^{D} = -\Omega^{L}$

$$g \equiv \frac{I(\mathbf{B}\uparrow\uparrow\mathbf{k}) - I(\mathbf{B}\uparrow\downarrow\mathbf{k})}{I(\mathbf{B}\uparrow\uparrow\mathbf{k}) + I(\mathbf{B}\uparrow\downarrow\mathbf{k})}$$

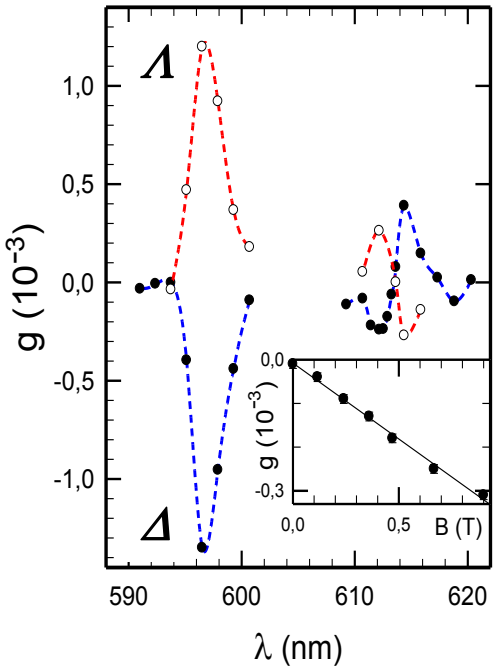
Rikken, Raupach,

Nature **1997**, *390*, 493

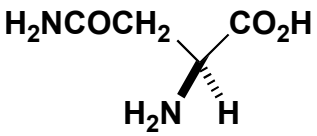
N. Avarvari, C. Train (GDR)



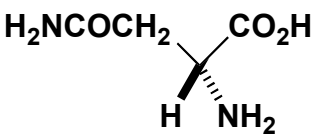
Luminescence of Eu(Δ/Λ)tfc$_3$



Tastes and odors

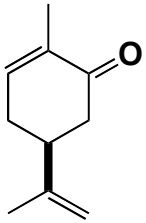


asparagine

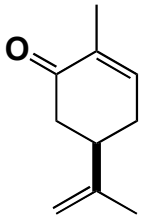


S amère

R sucrée

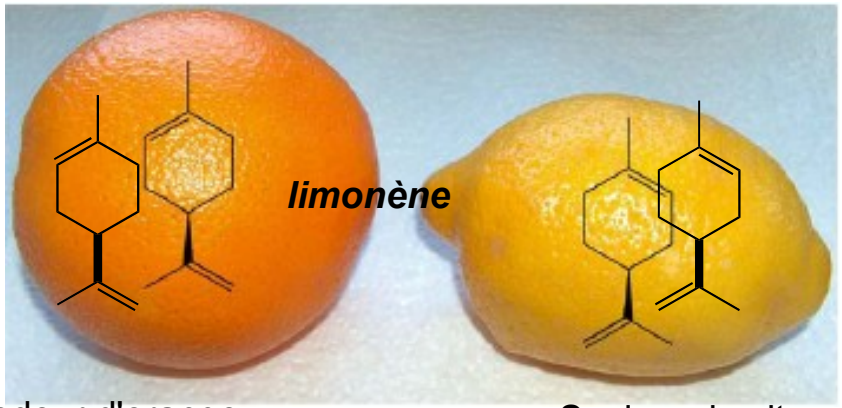


carvone



S odeur de cumin

R odeur de menthe verte

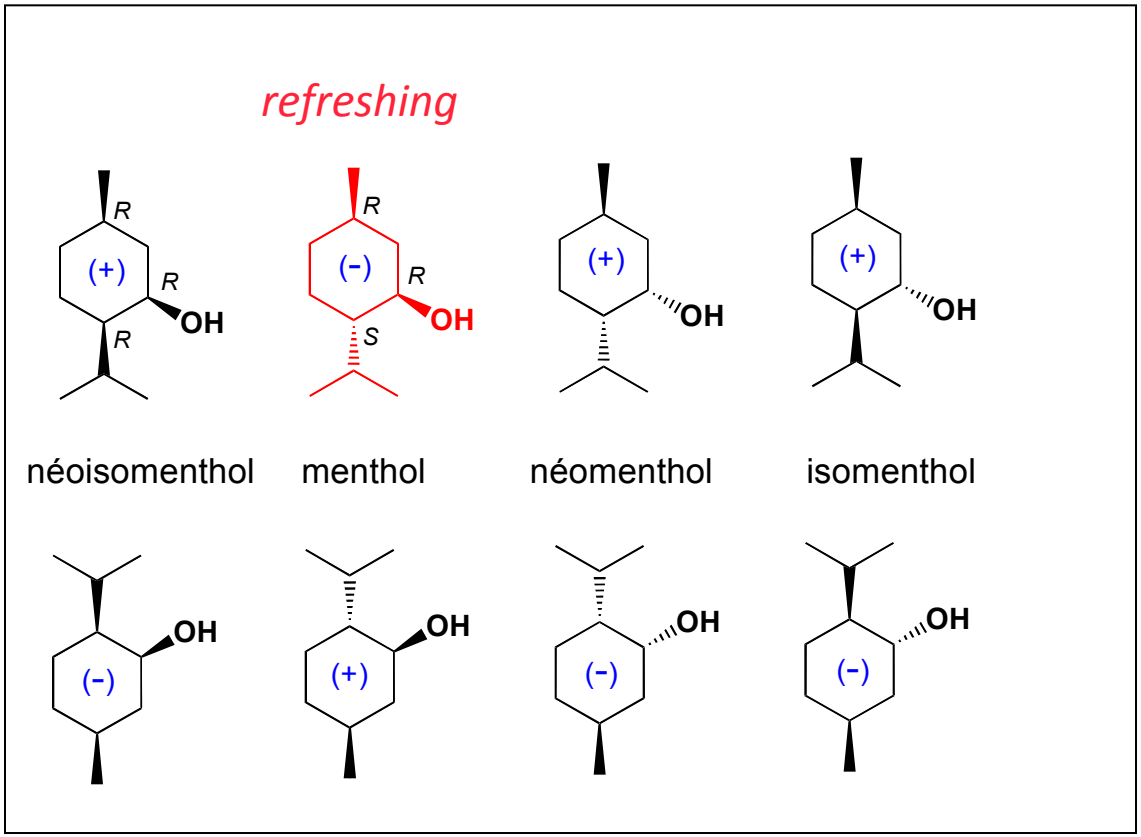


R odeur d'orange

S odeur de citron

Mint candies

Eight different forms (left and right-handed)



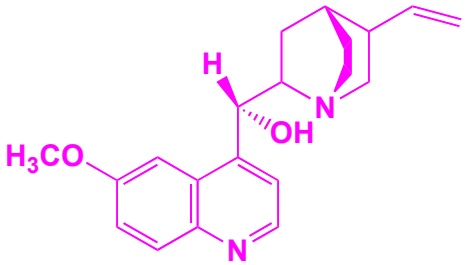
Different physical properties between racemates and enantiomers

see teaching course 2 (Laure Guy)

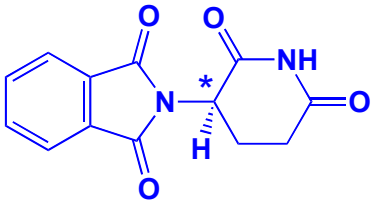
What about natural and medicinal compounds?

Different properties of enantiomers

Quinquina

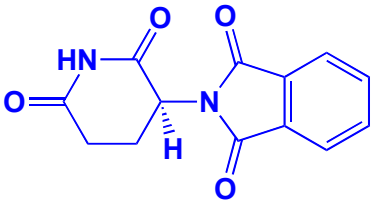


quinine



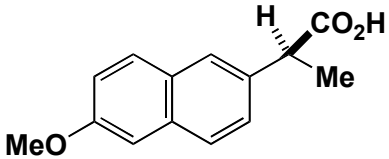
R-(+)-thalidomide

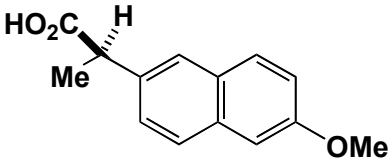
Anti-vomitive



S-(–)-thalidomide

teratogen





S naproxene: anti-inflamatory

R naproxene: inactive

Different pharmacodynamics and pharmacokinetics of enantiomeric pharmaceuticals

« L'univers est dissymétrique »

Pasteur (1883)

Louis PASTEUR
1822-1895

« Me demanderez-vous : quelles sont les forces dissymétriques qui président à l'élaboration des principes immédiats naturels? … les forces cosmiques dissymétriques…. Un des liens entre la vie à la surface de la terre et le cosmos…. »

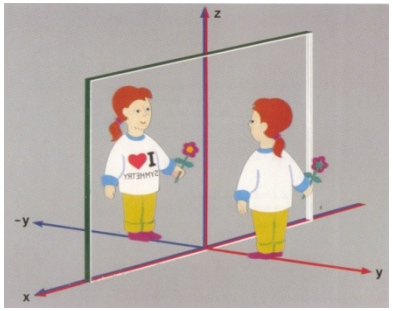
« J'ai fait vivre des petites graines de *penicillium glaucum*, de cette moisissure qu'on trouve partout, à la surface de cendres et d'acide paratartrique, et j'ai vu l'acide tartrique gauche apparaître. »

The firt enzymatic resolution!

"Most natural organic products, the essential products of life, are asymmetric and possess such asymmetry that they are not superimposable on their images."

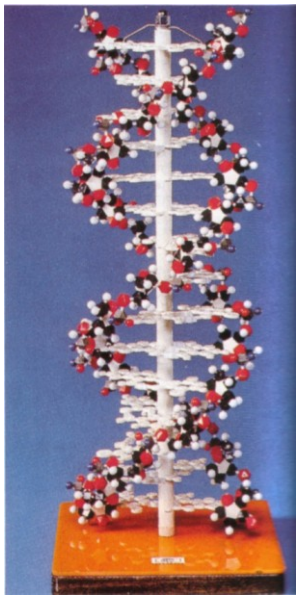
Why?

The Universe is dissymmetric



The 20 amino-acids essential for life are L

All natural sugars are D



DNA

What is its origin?

Extraterrestrial life
CPL in space (Orion)
Parity violation
(matter is intrinsically chiral)

Parity : a broken symmetry

Parity operation : $(x, y, z) \xrightarrow{P} (-x, -y, -z)$

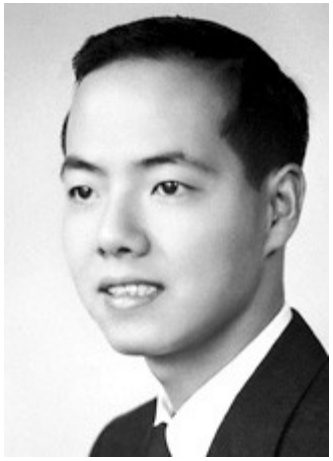
1956
Lee and Yang

Prediction of *Parity violation in weak interaction*

1957
Wu et al.

First experimental observation *in β-decay of cobalt 60*

Chen Ning Yang

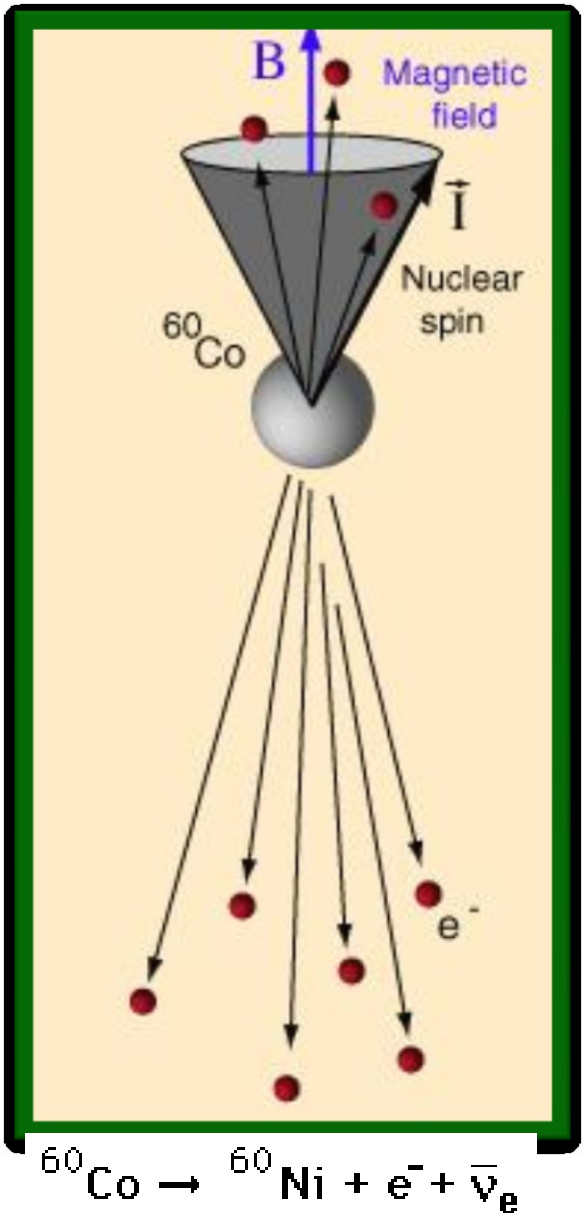


Tsung-Dao Lee

Chien-Shiung Wu

(Nobel prize in Physics 1957)

Wu experiment on beta decay of Cobalt-60.



1957 : Wu et al. – First experimental observation in β-decay of cobalt 60.

Beta emission is preferentially in the direction opposite to the nuclear spin … Wu 1957

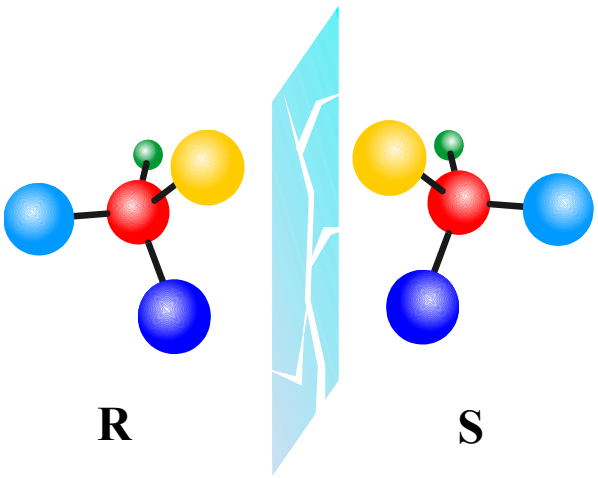
1974 : M.-A and C. Bouchiat – PV effects in highly forbidden transitions in cesium

1979 : Barkov and Zolotorev
Optical rotation in heavy metals vapors (Bi,Cs,Pb)

What about molecules?

Parity violation (PV) in molecules: a fundamental effect

The broken mirror



$\Delta E_{PV} = 2E_{PV}$

ΔE_{PV} c.a. 10^{-17}kT

A big challenge to measure it!

Comes from the weak nuclear interaction

(one of the four fundamental forces: electromagnetic, gravitational, weak and strong nuclear forces):

Interaction between elementary particles

A fundamental effect

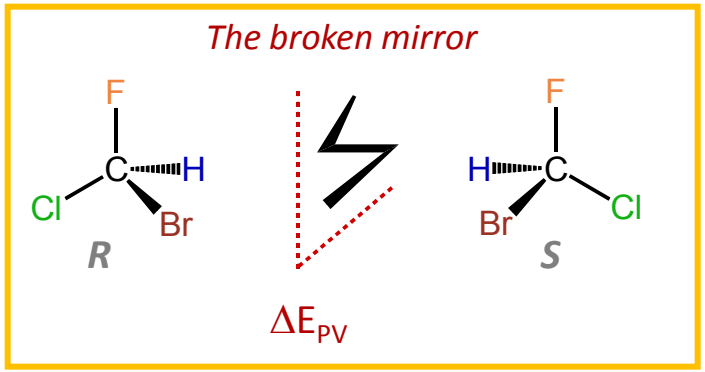
Provoques a spatial symmetry breaking between the right and the left-handed molecules

PV measurements by highly-accurate IR spectroscopy

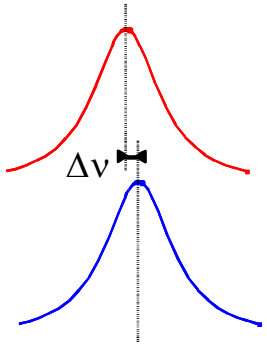
C. Chardonnet, C. Daussy, A. Amy-Klein, C. Bordé, B. Darquié…
Laboratoire de Physique des Lasers, Villetaneuse, Villetaneuse

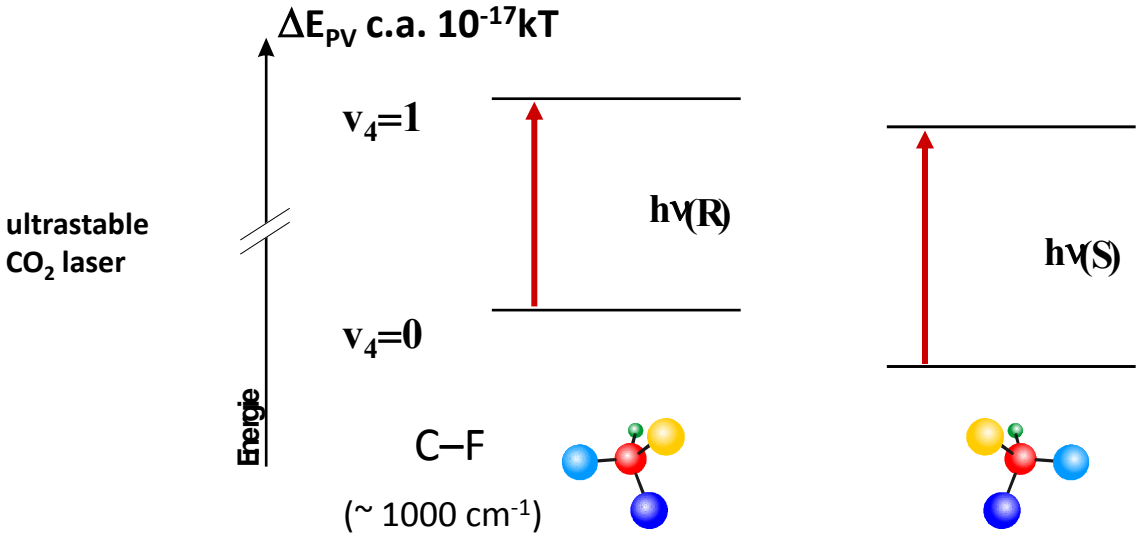
Chardonnet *et al., Phys. Rev. Lett.* **1999**, *83*, 1554
Review:
Crassous *et al., Org. Biomol . Chem*. **2005**, *3*, 2218

Simultanous measurement of transition frequencies
In the two enantiomers of CHFClBr



Due to parity violation two enantiomers do not have the same absorption spectrum
Letokhov, *Phys. Lett.* **1975**, *53A*, 275





Proposition to search for PV effect in CHFClBr spectrum
Kompanents *et al.*,
Opt. Commun. **1976**, *19*, 414

Upper limit : 10 Hz

New molecules for PV measurements

$E_{PV} \alpha Z^5$

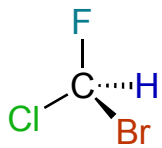
Theoretical calculations of PV effects :

relativistic calculations

Pr Schwerdtfeger, Aukland (New Zealand)

T. Saue, R. Bast, Université Paul Sabatier, Toulouse (France)

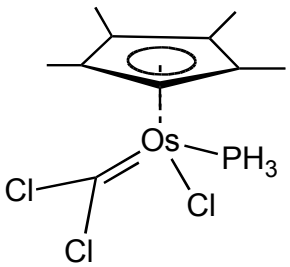
Z: atomic number



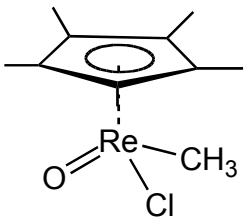
$\Delta\nu_{PNC}$ = 1.7 mHz
for C–F stretching

P. Schwerdtfeger, T. Saue, *et al., Phys. Rev. A* **2005**, *71*, 012103

P. Schwerdtfeger, R. Bast *J. Am. Chem. Soc.* **2004**, *126*, 1652



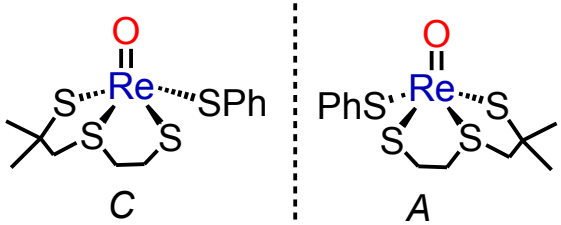
$\Delta\nu_{PNC}$ = 1,30 Hz
for Os=C stretching
at 901 cm^{-1}



$\Delta\nu_{PNC}$ = 1,09 Hz
for Re=O stretching
at 989 cm^{-1}

Large PV values
Intense Re=O stretching band accessible to the CO_2 laser

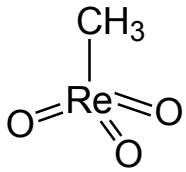
Chiral oxo-rhenium complexes



IR: $\nu_{Re=O}$: $\Delta\nu_{PV}$(calc) = 0.1-1 Hz

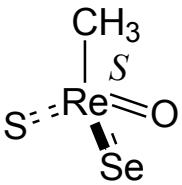
Inorg. Chem. **2006**, *45*, 10230

Chem. Comm. **2009**, 4841



méthyltrioxorhénium

MTO



Laure Guy, J. Crassous, B. Darquié *et al.* (GDR)

Phys. Chem. Chem. Phys. **2013**, *15*, 10952

Chirality: an economic reality!!!

enantiopure racemic achiral

Chiral drugs

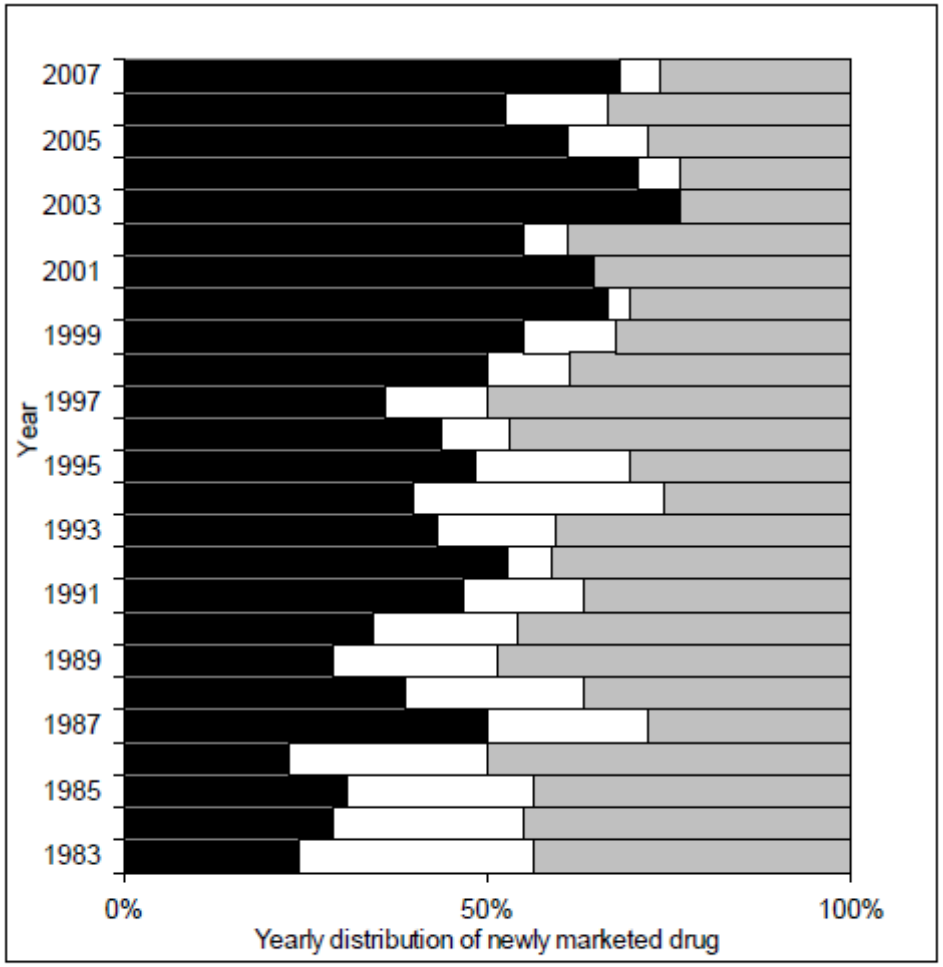


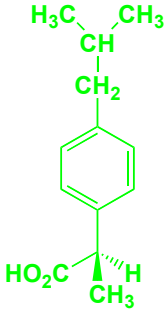
Figure 1-3. Yearly distribution of newly marketed drug from 1983 to 2007: ■ chiral drug marketed in optically pure form; □ chiral marketed in racemic form; ■ achiral drug.

Other markets:

agricultural chemicals, electronic chemicals, flavors and fragrances

Commercial patenting

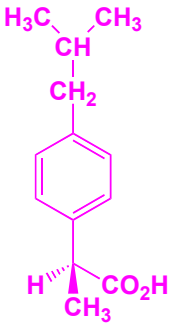
Anti-inflammatory



R-Ibuprofène

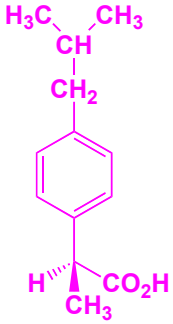
Racemic drug

-Invention, development, patents, Clinical studies, market
- 5 years exclusivity (USA)
- Side effects
- Expiration of patents



S-Ibuproféne

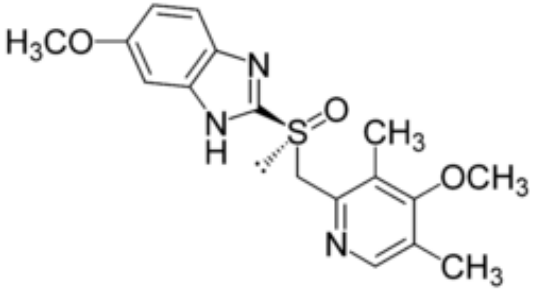
« Chiral Swich »



S-Ibuproféne

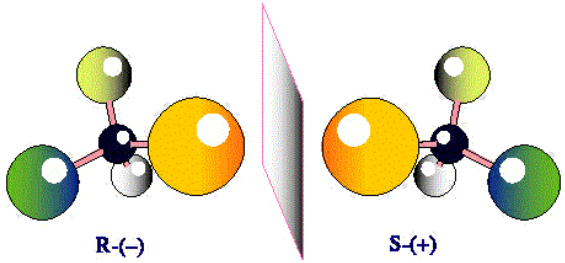
Pure enantiomer (+)

- Selected patent
- Better therapeutic properties
- Similar indications
- 3 years exclusivity (USA)

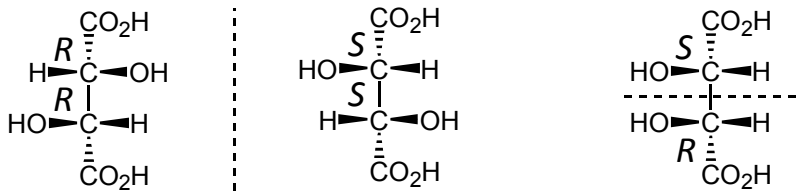


Other example: **Omeprazole** (racemic, anti-ulcer drug) became **Esomeprazole** (enantiopure, AstraZeneca, Nexium®) in 2002

Definitions



Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms (constitution), but that differ *only* in the three-dimensional orientations of their atoms in space.



meso form: a

In general: 2^n stereoisomers

(*Z* and *E* comprised)

Relative configuration

(*R*,*R*)* or *R**,*R** : *R*,*R* and *S*,*S*

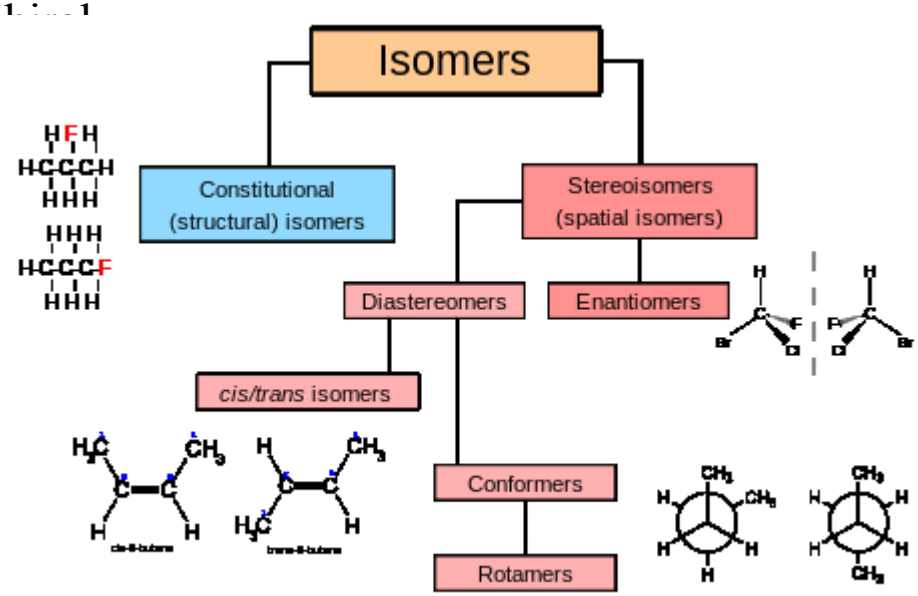
Absolute configuration

(*R*,*R*)-(+) and (*S*,*S*)-(-)

The two mirror images are called **enantiomers** from Greek ἐνάντιος *(enantíos)*, meaning "opposite", and μέρος *(méros)*, meaning "part")

Diastereoisomers (or diastereomers) : stereoisomers that are not enantiomers

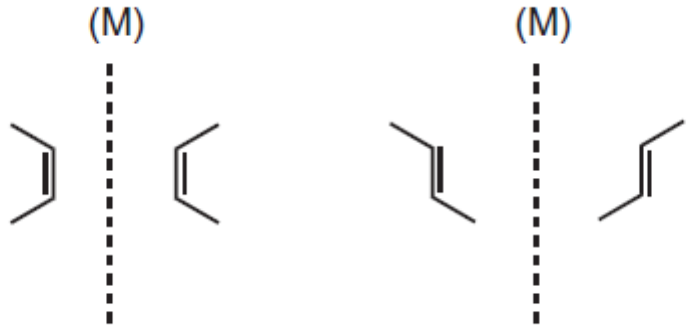
Conformers vs. stereoisomers



2D-Chirality and prochirality

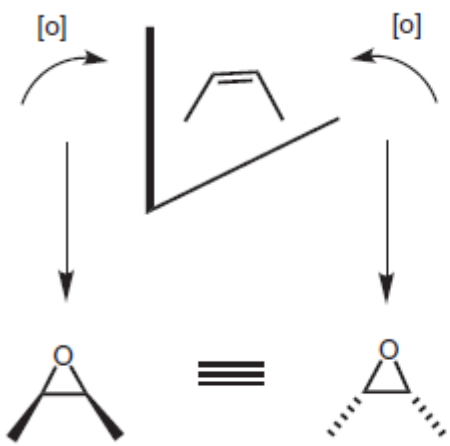
Prostereoisomerism in *cis* and *trans*-but-2-ene

2D-achiral



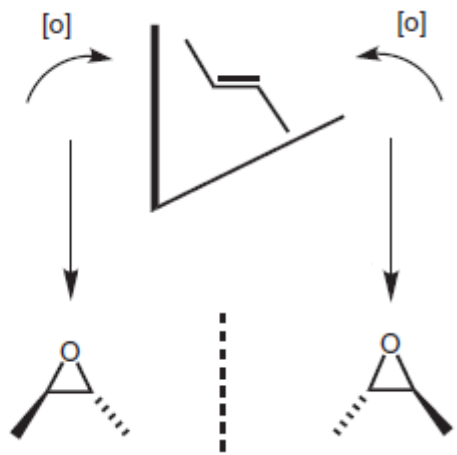
2D-chiral

Homotopic faces



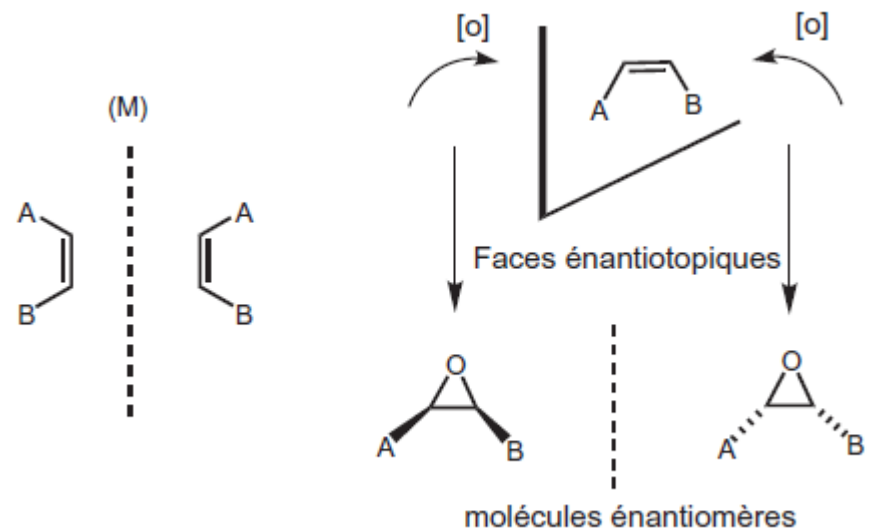
identical

Enantiotopic faces



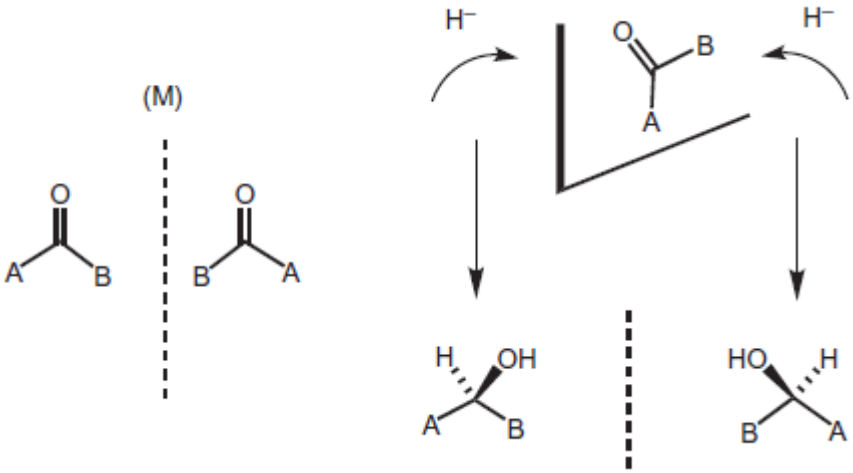
enantiomers

Enantiotopic faces in cis-olefines

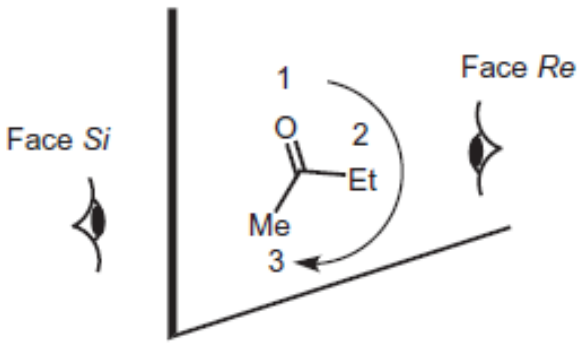


2D-Chirality and prochirality

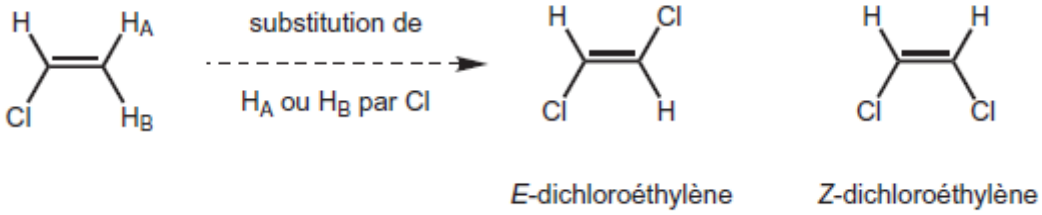
Enantiotopic faces in carbonyles



enantiomers



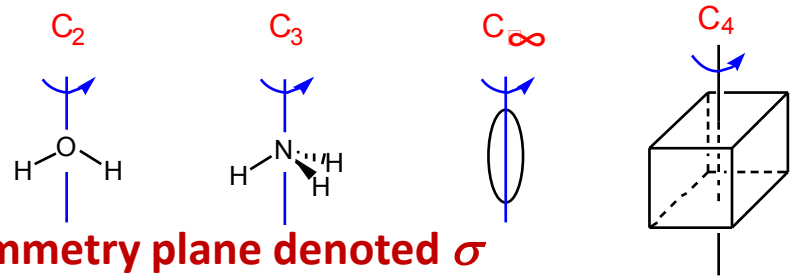
Prostereogenic elements in olefines



Symmetry operations

1. Identity *E*

2. Rotation C_n ($2\pi/n$ radians)

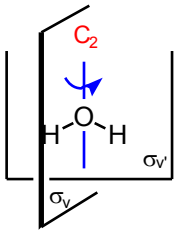


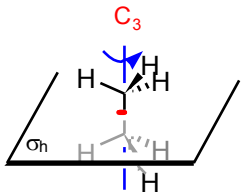
(principal axis)

Higher order

3. Reflexion over a mirror or a symmetry plane denoted *σ*

vertical



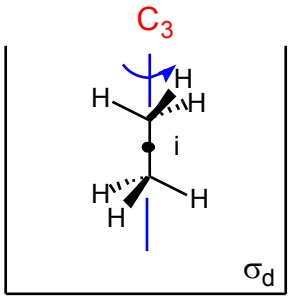


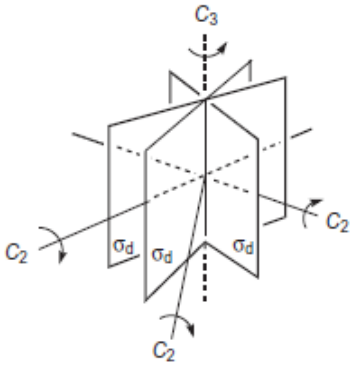
horizontal

4. Symmetry inversion, denoted *i*.

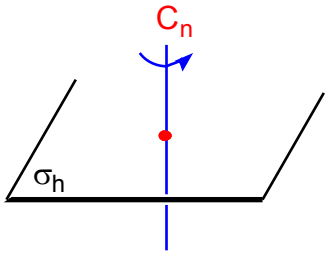
Staggered ethane, its inversion point, and its symmetry planes σ_d

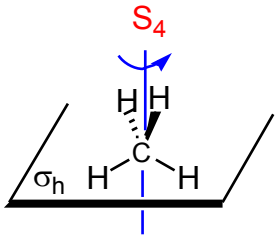
Overall symmetry: D_{3d}





5. Rotation-reflexion of order n, or improper rotation, denoted S_n (S_{2n})





$$S_n = C_n\sigma_h = \sigma_h C_n$$

Unique only if n is even

If n is odd: a combination of other operations

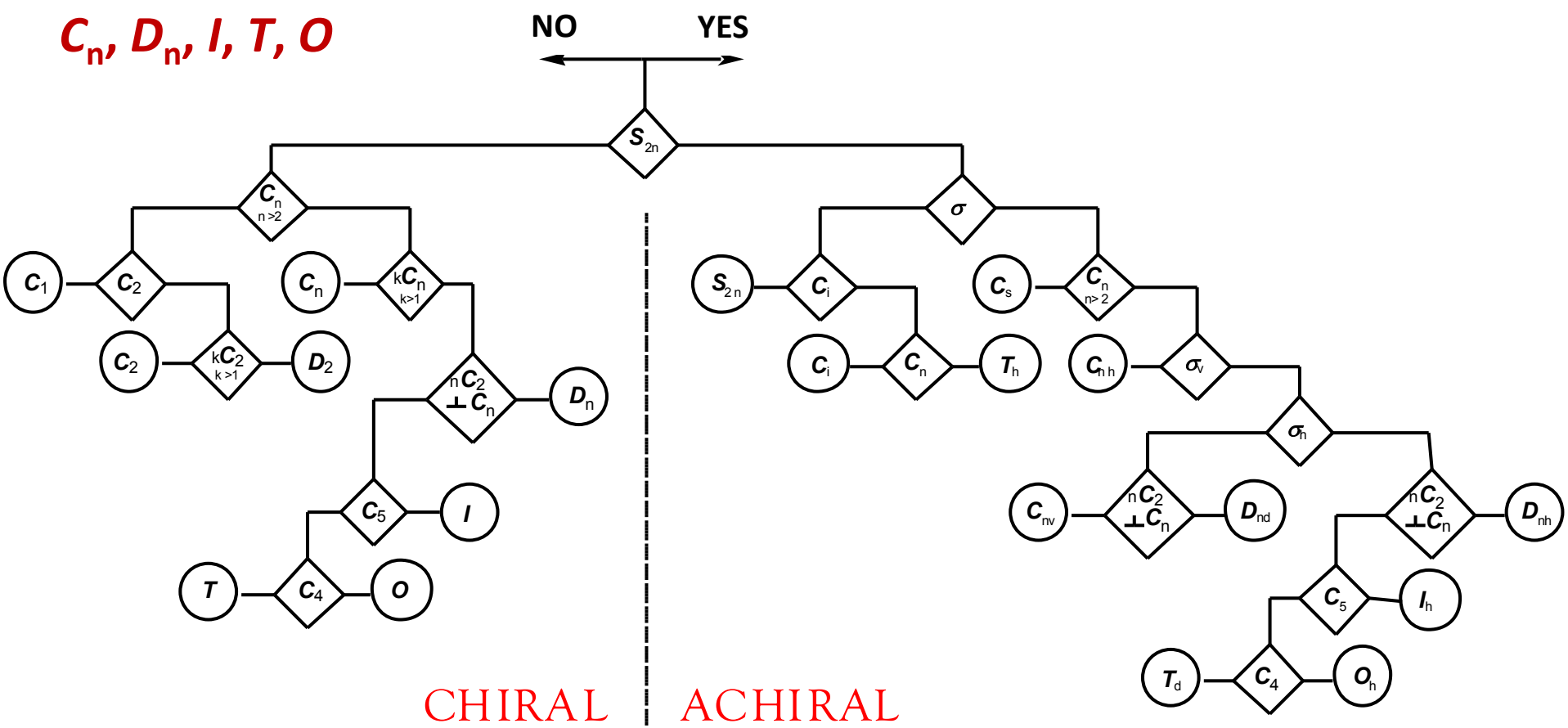
$$S_3 = C_3\sigma_h$$

Symmetry point groups

A molecule can be classified according to its symmetry point group: all its symmetry operations that keep it unchanged (axis, plane, centre).

It exists at least one fixed point that is invariant upon all the symmetry operations (point group symmetry) . Schoenflies notation is used here.

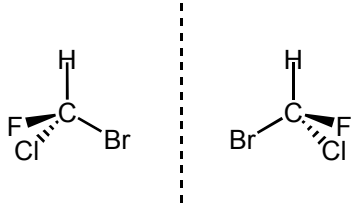
A molecule is chiral if it does not possess any improper axis S_n



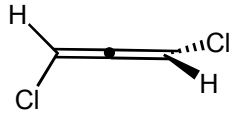
Symmetry point groups for chiral molecules

Chiral molecules belong to C_1, C_n ou D_n (or more rarely to T, O, I)

Which means point groups that have only proper rotation axes

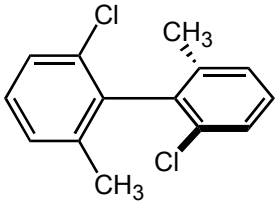


Group C_1



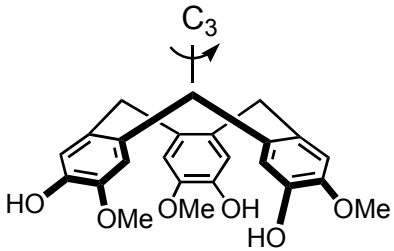
1,3-dichloroallène

Group C_2



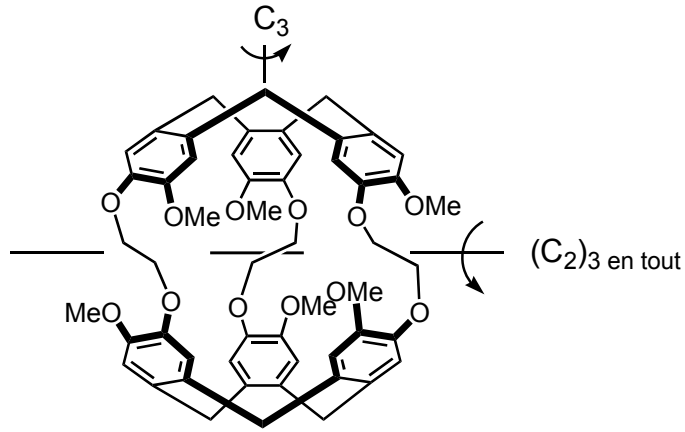
2,2'-dichloro-6,6'-diméthyl-biphényle

Group C_2



cyclotrivératrylène (CTV)

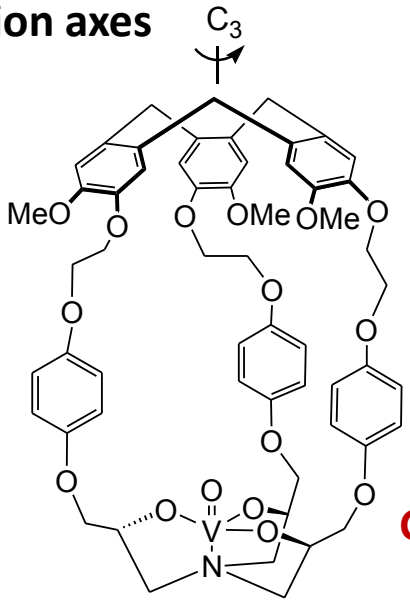
Group C_3



cryptophane-A

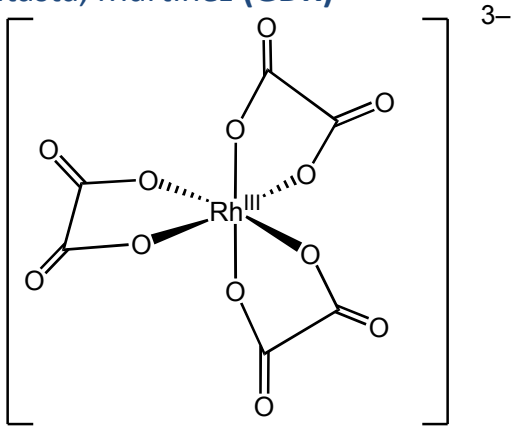
Group D_3

Collet, Brotin, Dutasta **(GDR)**



Group C_3

Dutasta, Martinez **(GDR)**



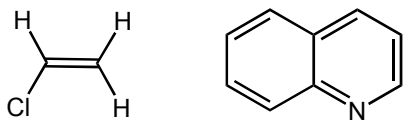
Group D_3

Symmetry point groups for achiral molecules

Contain improper symmetry S_n, with planes et centers of symmetry

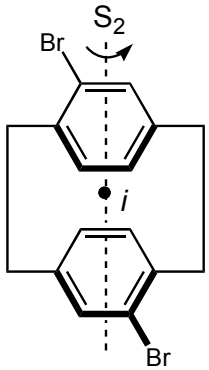
Examples

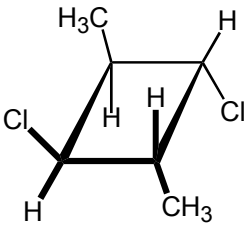
a)



groupe C_s

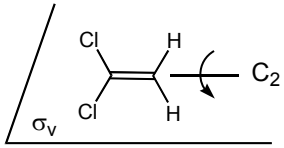
b)



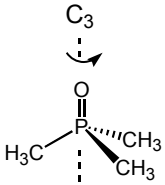


groupe C_i (= S_2)

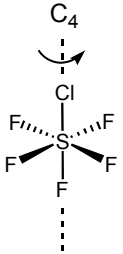
d)



groupe C_{2v}

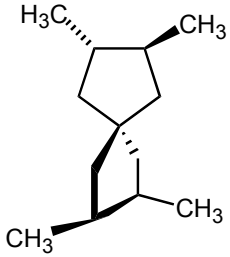


groupe C_{3v}



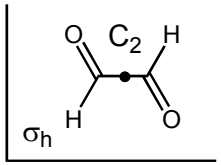
groupe C_{4v}

c)

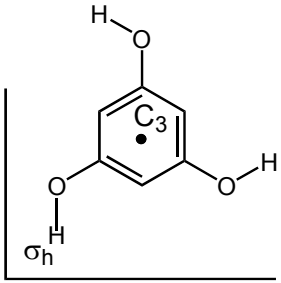


groupe S_4

e)



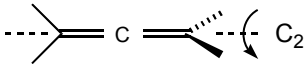
groupe C_{2h}



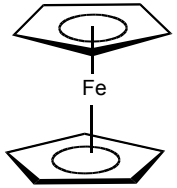
groupe C_{3h}

f)

groupe D_{2d}

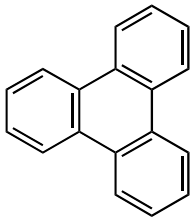


groupe D_{2d}

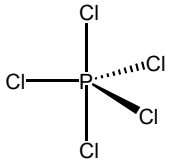


groupe D_{5d}

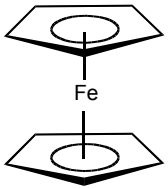
g)



groupe D_{3h}



groupe D_{3h}



groupe D_{5h}

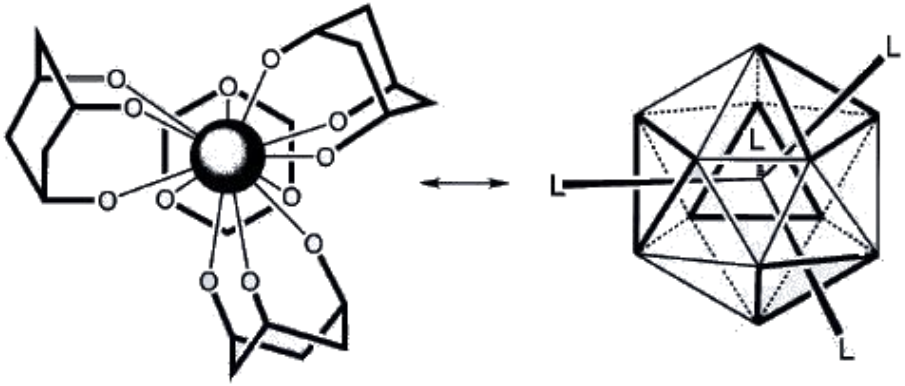
Molécules Chirales : Stéréochimie et Propriétés. Editions du CNRS. ISBN 2-271-06329-9
A. Collet, J. Crassous, J. -P. Dutasta, L. Guy **(GDR)**, 2006

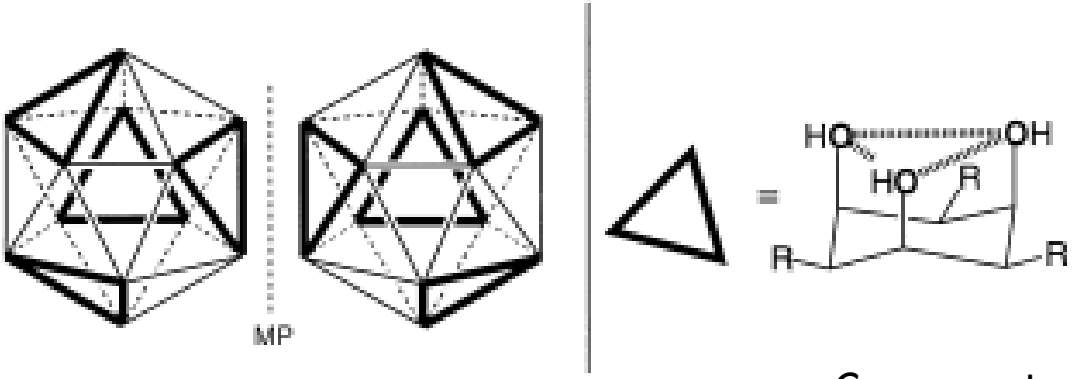
T, *O*, *I* groups

Cubic groups that have no symmetry planes but proper axes of symmetry of different orders. Very rare

group T A barium atom substituted with 4 cyclohexanetriols

B. Morgenstern et al.
Angew. Chem. Int. Ed., **2001**, *40*, 4179.





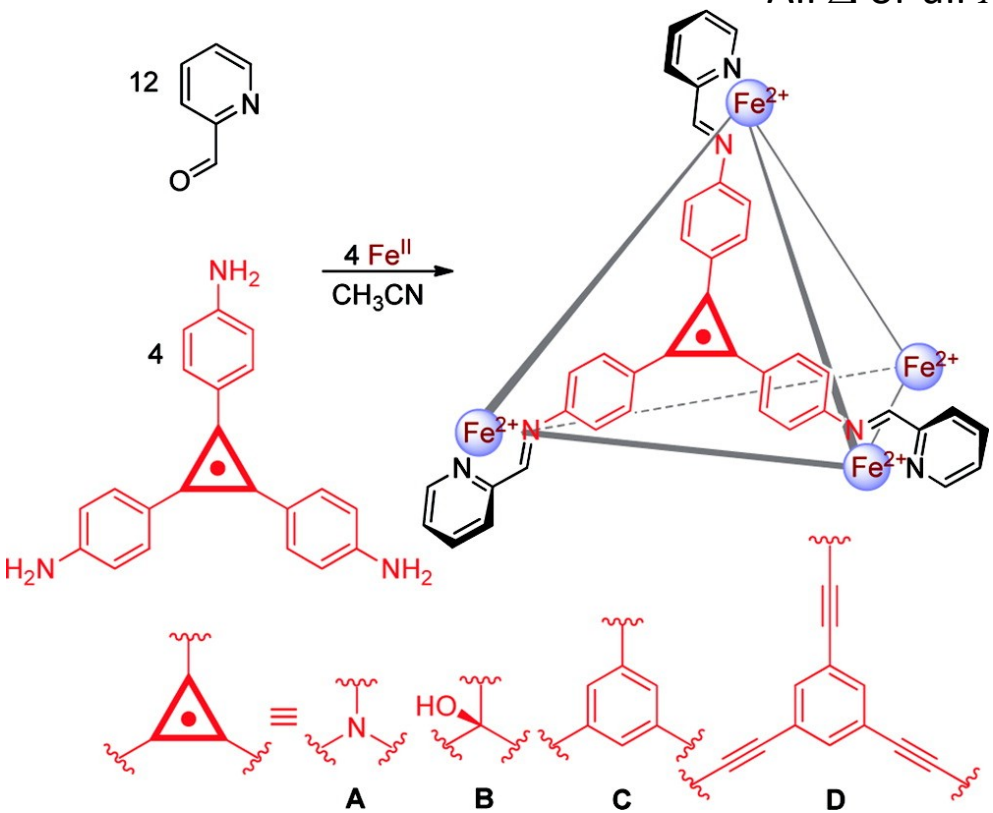
C_3 symmetry

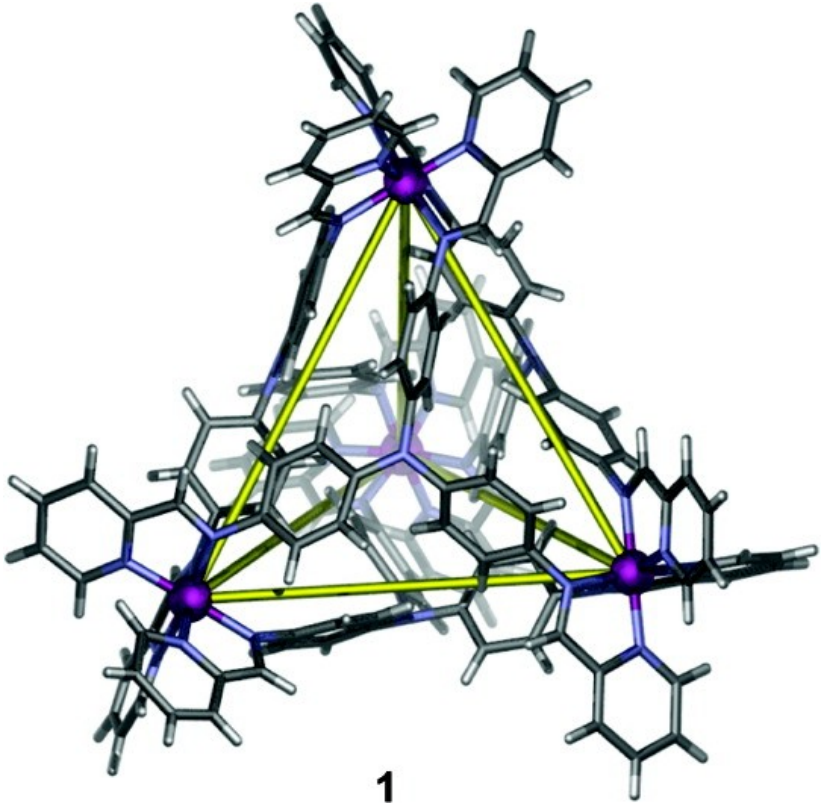
Other examples from cubic groups :

a) M. Farina, C. Morandi, *Tetrahedron*, **1974**, *30*, 1819 ;
b) L. R. MacGillivray, J. L. Atwood, *Angew. Chem. Int. Ed.*, **1999**, *38*, 1018 ;
c) A. Rassat, *Angew. Chem. Int. Ed.*, **2003**, *42*, 611.

A Self-Assembled $[Fe_4L_4]$ Capsule with a T symmetry (chiral)

All Δ or all Λ





J. R. Nitschke *et al., J. Am. Chem. Soc.* **2012,** 134, 5110

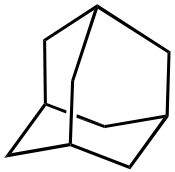
T_d, O_h, I_h. Achiral molecules with more than one principal symmetry axis

$\boldsymbol{T_d}$ group: principal symmetry axis of order 3 (CH_4, adamantane)

$\boldsymbol{O_h}$ group: principal symmetry axis of order 4

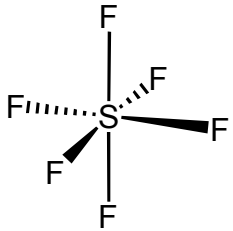
$\boldsymbol{I_h}$ group: principal symmetry axis of order 5

Principal axis: the one with the highest *n* in C_n



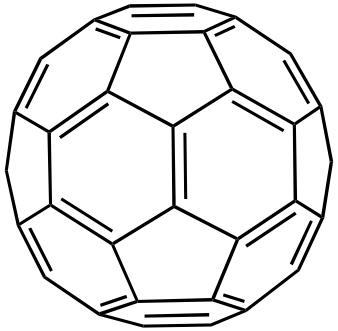
adamantane

groupe T_d



SF_6

groupe O_h



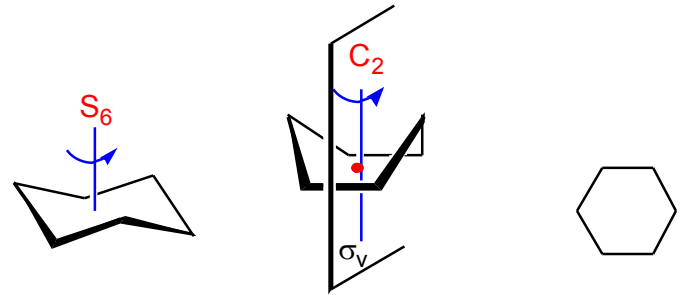
C_{60}

groupe I_h

A molecule is in general **flexible** and can adopt different **conformations**.
Each conformation has its own symmetry. In average, the symmetry can be higher.

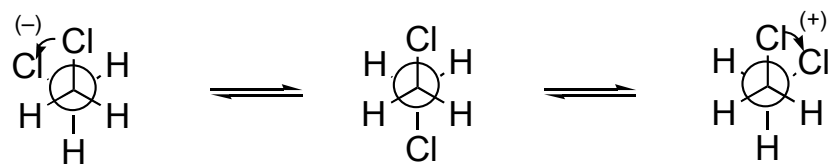
Cyclohexane

chair ***boat*** ***average***



S_6 C_{2v} D_{6h}

1,2-Dichloroethane

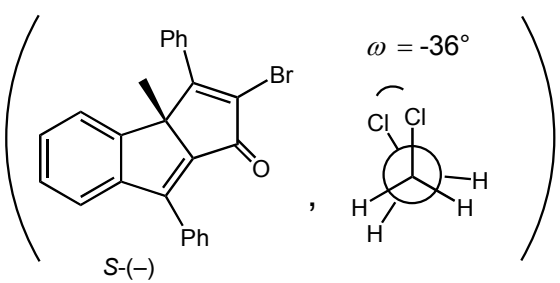


g^- a g^+

Gauche conformation
M configuration

Anti conformation
Achiral

Gauche conformation
P configuration



Blocked conformation in the solid state

F. Toda, K. Tanaka, R. Kuroda, *Chem. Commun.*, **1997**, 1227.

Molecules with stereogenic centers

Asymmetric carbon, chiral amines, sulfoxides, phosphines, …
Half-sandwich complexes, metallocenes
Tetrahedral or spiro-type complexes
Octahedral Complexes

Molecules displaying axial chirality

Examples of allenes
Atropoisomerism and axial chirality

Planar chirality

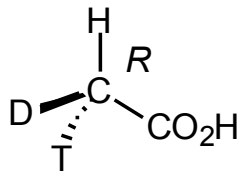
Inherent chirality

Helicenes, fullerenes
Trefoil knots and topological chirality

Selected examples: stereochemistry of helicene derivatives

Molecules with stereogenic centers

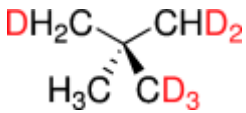
Isotopic chirality



R-[^{1}H,^{2}H,^{3}H]acetic acid

Arigoni, …

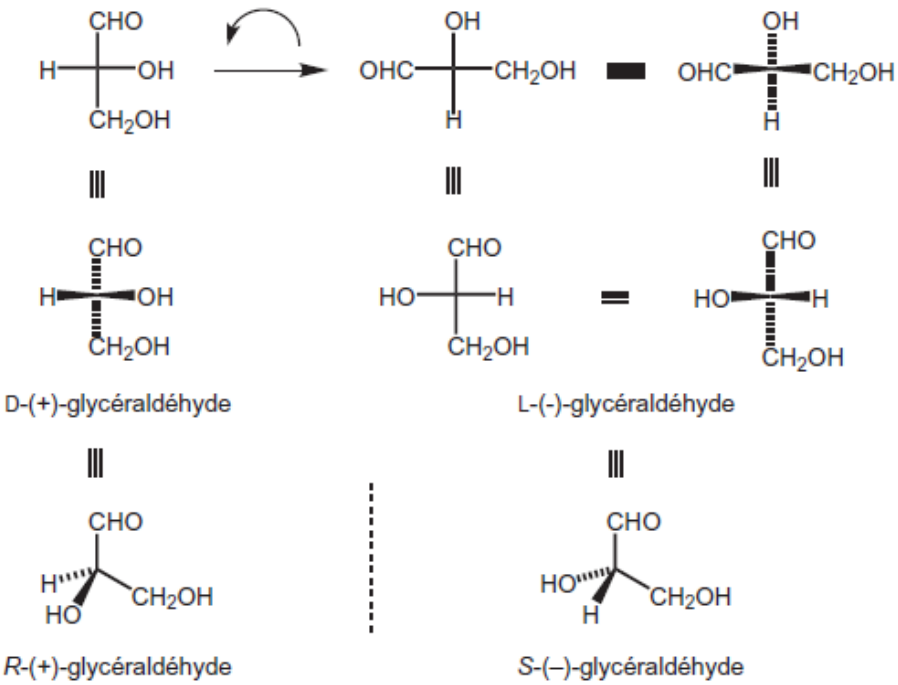
Cryptochiral neopentane

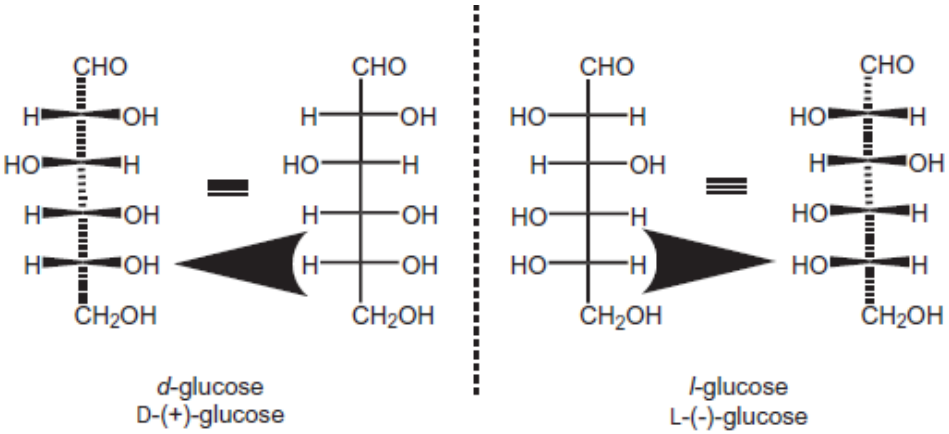


S

C. G. Bochet, W. Hug, et al. *Nature* **2007**, *446*, 526
I. Marek et al. *Angew. Chem.* **2015**, *54*, 13106

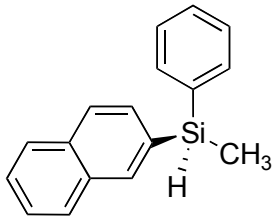
The D/L configuration in sugars
Emil Fischer (Nobel prize 1902)



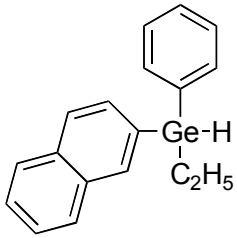


Molecules with stereogenic centers

Group 14 **Si, Ge, Sn, Pb**



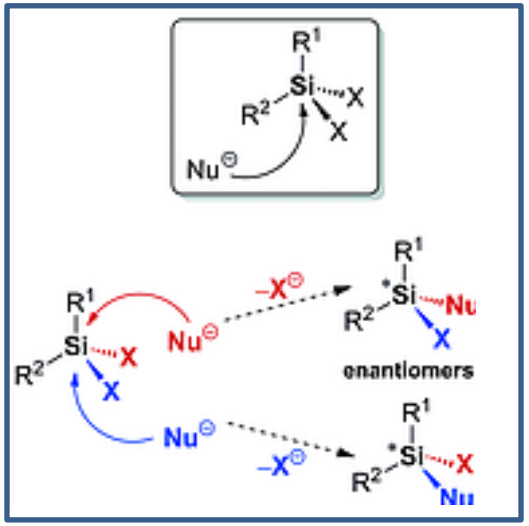
$[\alpha]_D$ = +33.4 (*C* 13.5, pentane)

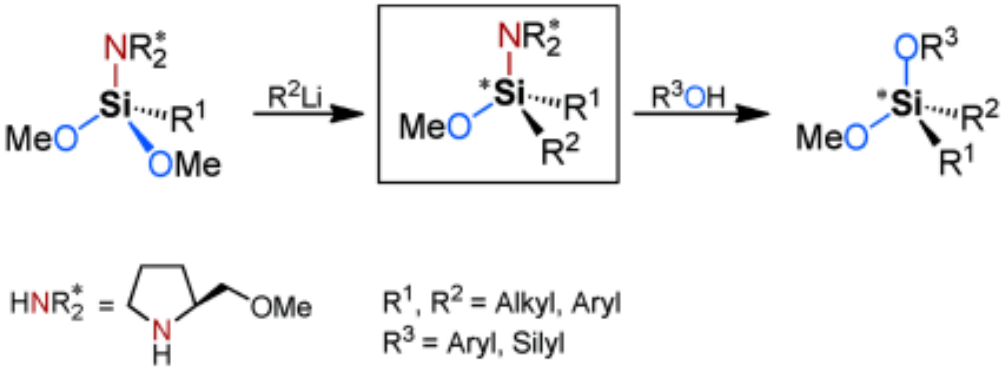


$[\alpha]_D$ = +23.6 (*C* 5.5, benzene)

Recent examples of silicon-stereogenic silanes

Enantiotopic X groups





J. O. Bauer, C. Strohmann,
Angew. Chem. Int. Ed. **2014**, 53, 720

Recent reviews:

J. O. Bauer, C. Strohmann, *EurJIC,* **2016**, *18*, 2868
L.-W. Xu et al. *Chem. Soc. Rev.,* **2011**, *40,* 1777

R. J. P. Corriu, C. Guerin, J. J. E. Moreau, in
The Chemistry of Organic Silicon Compounds, ed. S. Patai and Z. Rappoport,
John Wiley & Sons, New York, 1989, pp. 305–370.

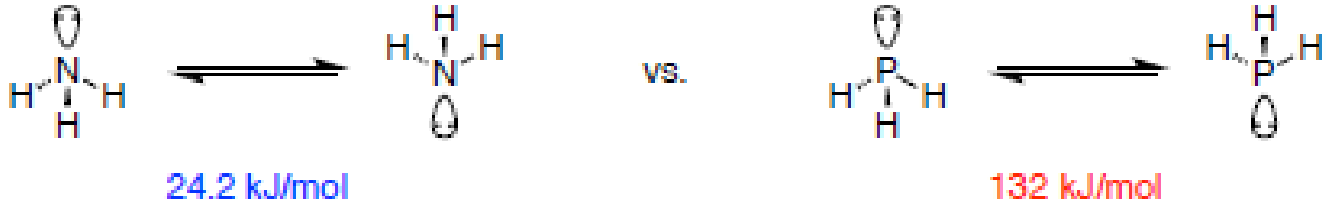
Group 15

N, P, As, Sb, Bi
Arsines and phosphines

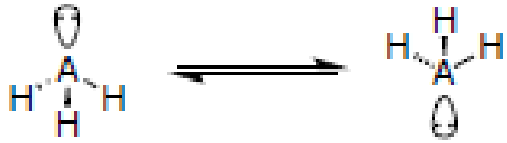
Molecules with stereogenic centers

Configurational stability

Ahlrichs *et al.*,
Theor Chim Acta **1991**, 82, 271



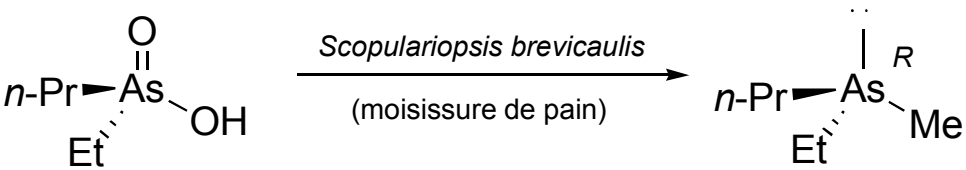
Inversion Energy Barriers

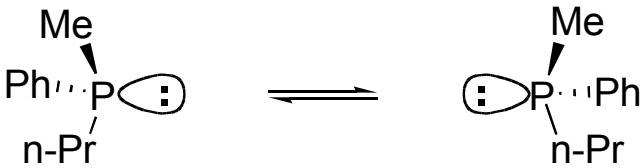


A = As 164 kJ/mol

A = Sb 184 kJ/mol

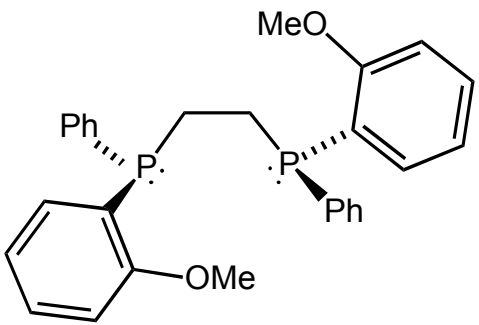
A = Bi 264 kJ/mol





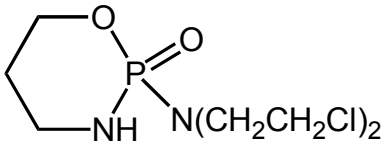
$t_{1/2}$ = 3 h 20 min in methylnaphtalene (130°C)

E_a (inversion) = 125-150 kJ mol^{-1} (tertiary phosphines)



(*R*,*R*)-DIPAMP

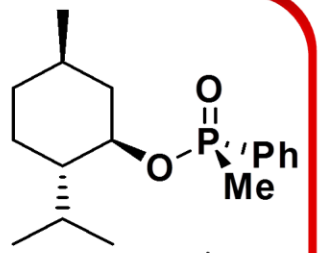
Chiral ligand for asymmetric catalysis



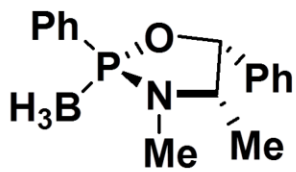
Cyclophosphamide
(antitumoral agent)

Preparation of P-Stereogenic monophosphines

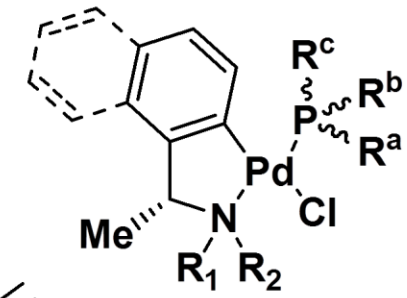
Stereoselective synthesis

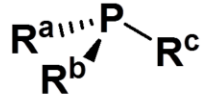


(–)-Menthol
(Mislow, Knowles, Imamoto)



(–)-ephedrine
(Jugé, Brown)

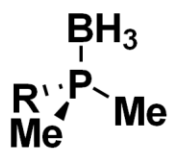


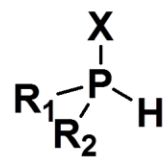


Resolution by crystallization or by chromatography

[Pd*], [Pt*], [Ru*]

Chiral base
(*s*-BuLi, spartéine)
(Evans, Imamoto, Jugé, Mezzetti, Ward, Muller)





Asymmetric catalysis
(Glueck, Helmchen, Bergman, Toste, Gaumont, Buono)

Muller *et al. Coord. Chem. Rev.* **2007**, 251, 25.

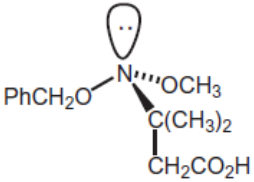
Molecules with stereogenic centers

Group 15

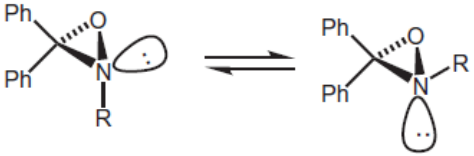
Chiral amines

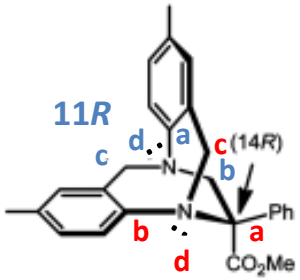
J. Lacour, J. -V. Naubron (**GDR**) *et al.*, *Angew. Chem. Int. Ed.* **2011**, *50*, 3677

amine chirale

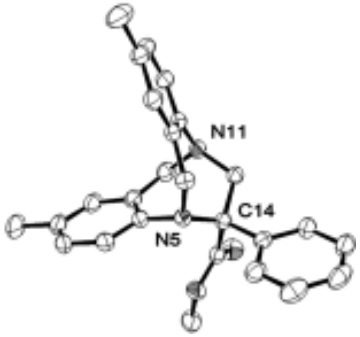


oxaziridine

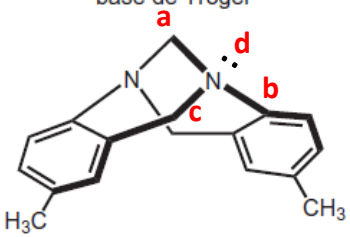




5*S*



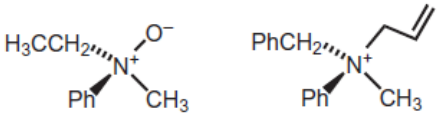
base de Tröger



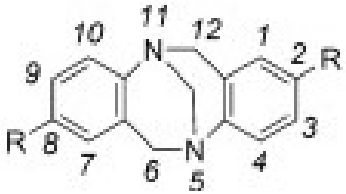
$(5S_N,11S_N)$-(+)

2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

amines quaternaires



CIP rules



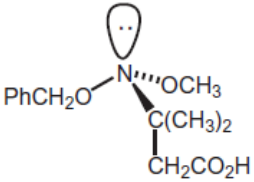
Molecules with stereogenic centers

Group 15

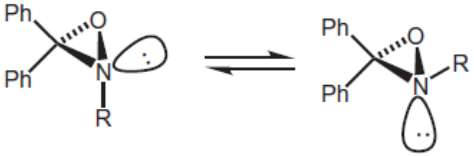
Chiral amines

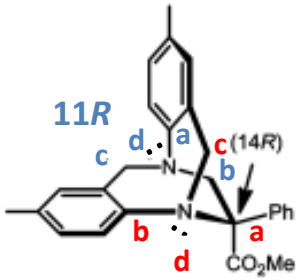
J. Lacour, J. -V. Naubron (**GDR**) *et al.*, *Angew. Chem. Int. Ed.* **2011**, *50*, 3677

amine chirale

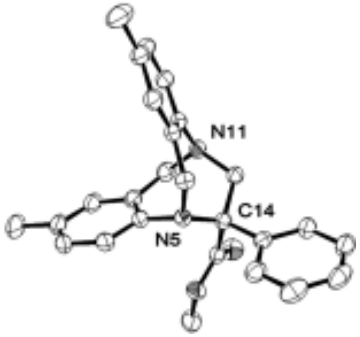


oxaziridine

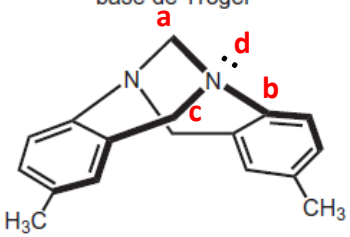




5*S*

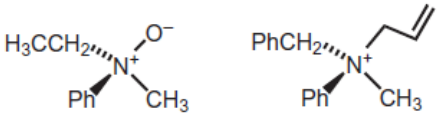


base de Tröger



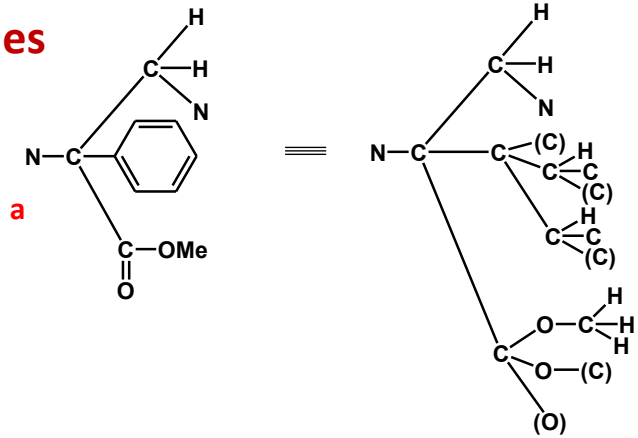
$(5S_N,11S_N)$-(+)

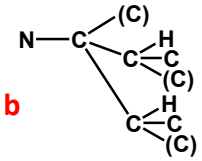
amines quaternaires



2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

CIP rules



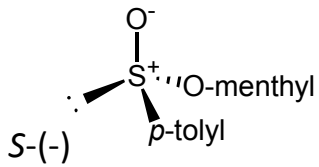


Molecules with stereogenic centers

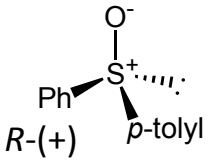
Group 16

Chiral sulfoxide

Menthyl sulfinate

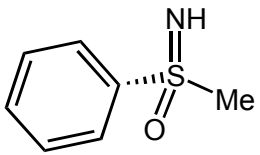


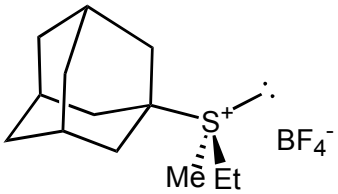
PhMgBr →



$[\alpha]_D^{25}$ = -199 (*C* 2, acetone)

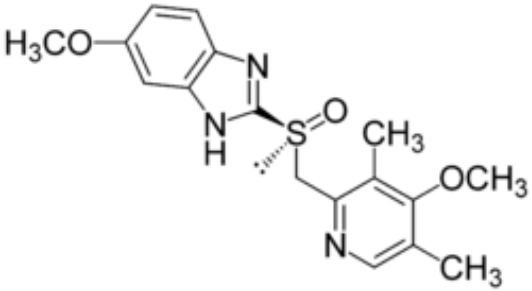
$[\alpha]_D^{25}$ = +22 (*C* 2, acetone)



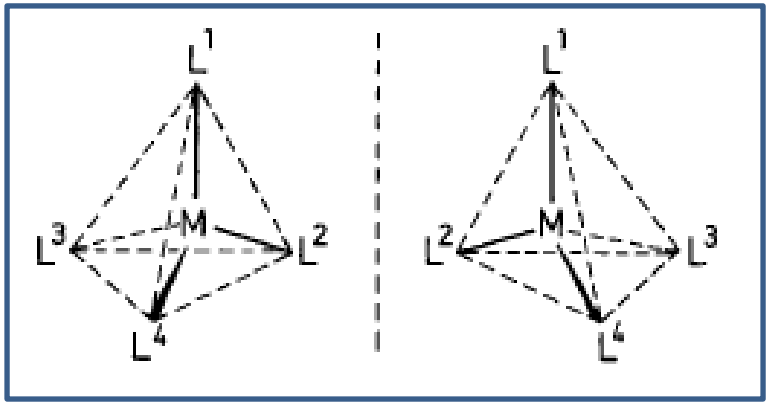


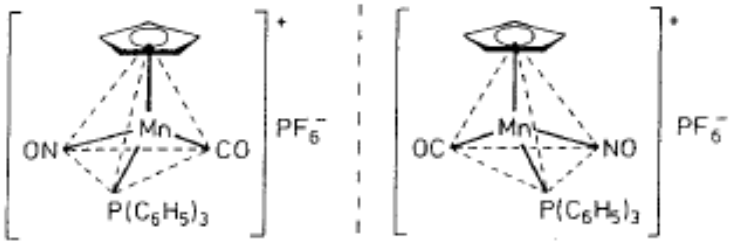
sulfoximine **sulfonium**

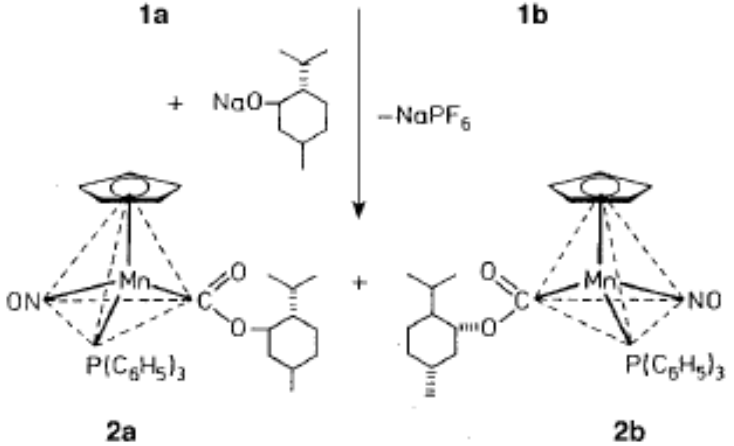
Esomeprazole



Transition metal complexes
« chiral at metal » half-sandwich complexes







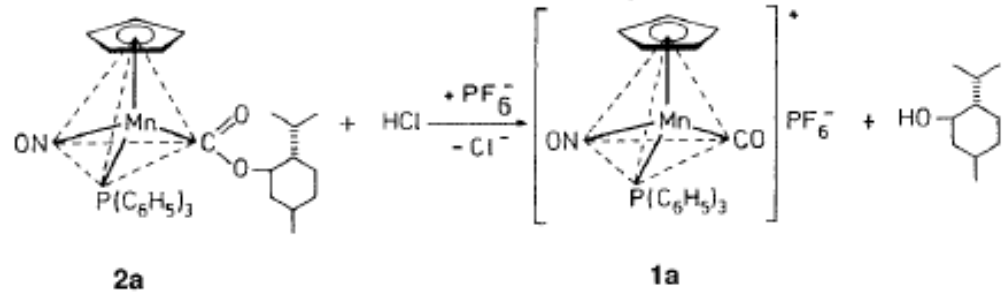
Resolution of diastereoisomers by crystallization

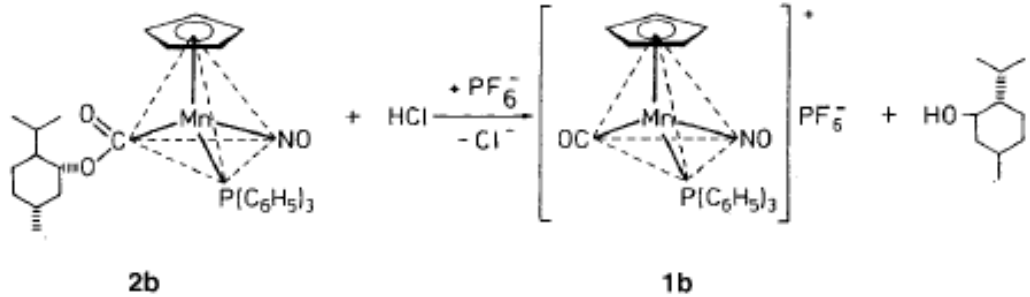
First resolution of a T4 organometallic complex

H. Brunner, *Angew. Chem. Int. Ed.* , **1969**, *8*, 382

Review: H. Brunner, *Angew. Chem. Int. Ed.* , **1999**, *38*, 1194

Chiral three-legged piano-stool





See also J. A. Gladysz et al. *Organometallics* **2001**, *20*, 3087

Chiral rhenium complexes

CIP rules for metallocenes

Configuration of chiral metallocenes at the tetrahedral metal center

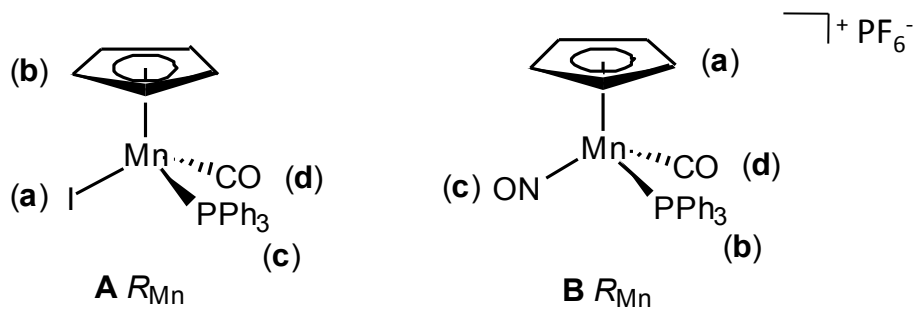
The Cahn, Ingold, Prelog* (CIP) system. Based on atomic numbers priority

Descriptors that describe the enantiomeric relationship (*R*/*S*, *M*/*P*, *C*/*A*, *Δ*/*Λ*, D/L), or diastereoisomerism (*E*/*Z*, *cis*/*trans*, *fac*/*mer*, *threo*/*erythro*, etc.).

η^5-cyclopentadiényle ligand **: ligand η^5-C_5H_5 is considered as a "pseudo-atom" with atomic number equal to the sum of atomic numbers of the linked atoms**,
i. e. $Z = 5 \times 6 = 30$

Therefore: I > η^5-C_5H_5 > PPh_3 > NO > CO

Similarly: ligands η^7-C_7H_7 , η^6-C_6H_6 and η^3-C_3H_5 the respective atomic numbers are 42, 36 and 18.



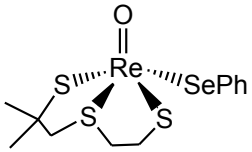
J. Tirouflet et al. *J. Organomet. Chem.*, **1974**, *73*, 67

See also: Eike B. Bauer, *Chem. Soc. Rev.*, 2012, **41**, 3153-3167

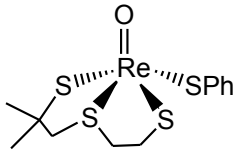
*Prelog: Nobel 1975

The *C*, *A* nomenclature

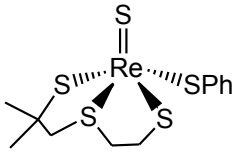
L. Guy, J. Crassous *et al.*
Chem. Comm. **2009**, 4841



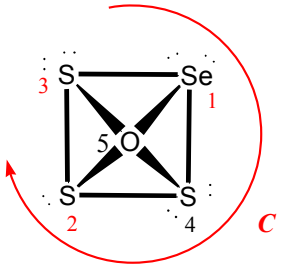
SPY-5-52-*C*



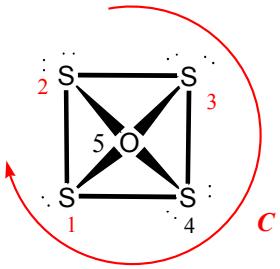
SPY-5-53-*C*



SPY-5-14-*C*



Clockwise



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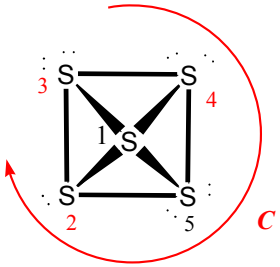
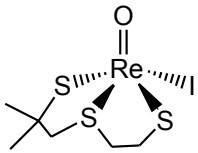


Clockwise

See also:
H. Amouri, M. Gruselle **(GDR)**
Chirality in Transition Metal Chemistry: Molecules, Supramolecular Assemblies and Materials,
Wiley-VCH, **2009**.



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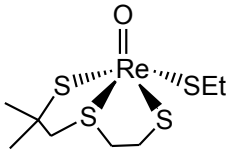
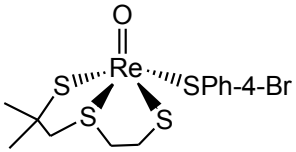
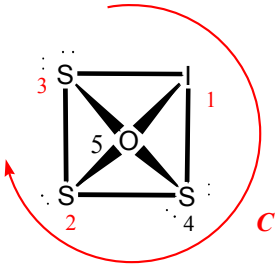


SPY-5-54-*C*



SPY-5-53-*C*



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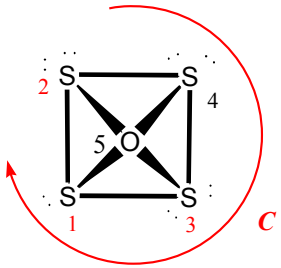

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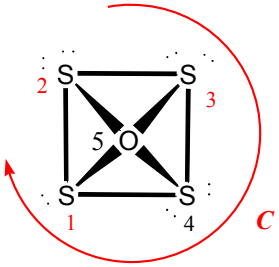
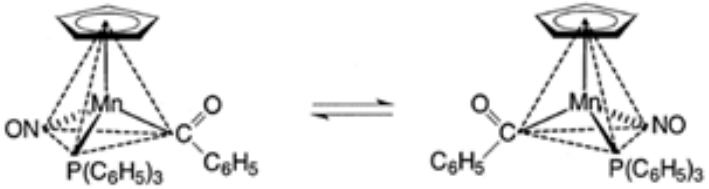


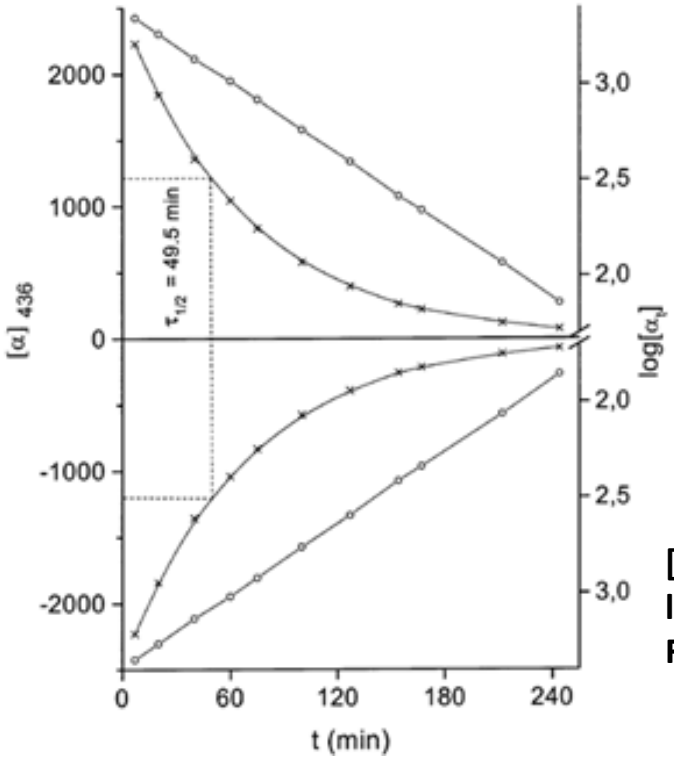
Clockwise

Configurational lability

Racemization

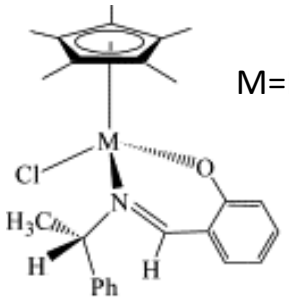


R_{Mn} S_{Mn}



$t_{1/2}$: 49.5 min in toluene at 20 °C

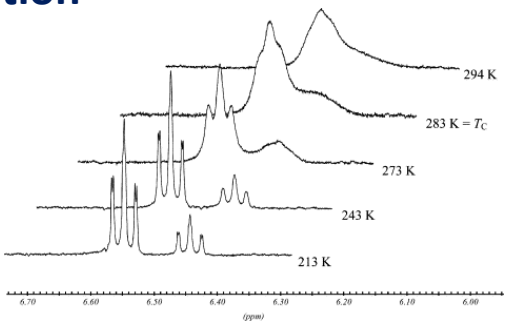
Epimerization



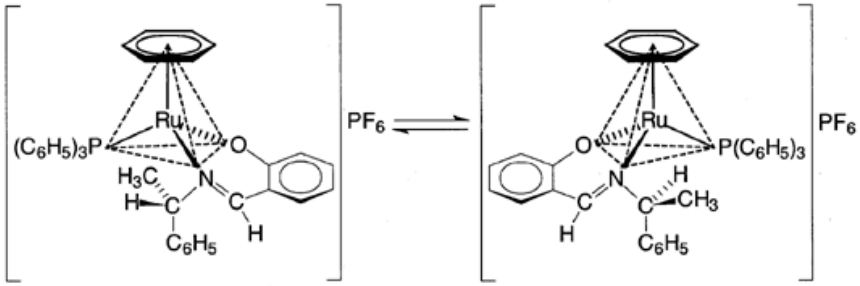
M=Rh, Ir

R_M, S_C and S_M, S_C

^{1}H NMR



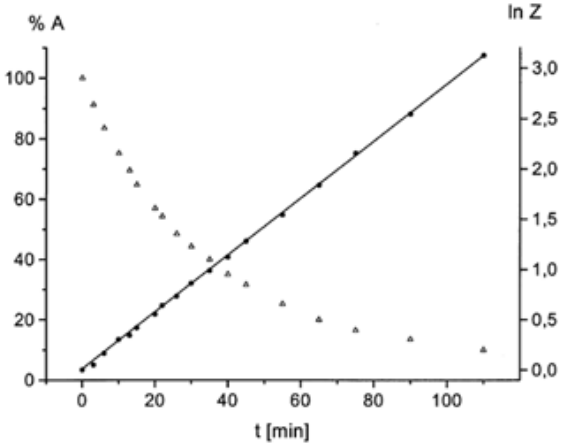
2 diastereomers, coalescence process



R_{Ru}, S_C S_{Ru}, S_C

$[A_t]$ by ^{1}H NMR integration;
$\ln Z = k.t$, $Z = ([A_o] - [A_\infty])/([A_t] - [A_\infty])$
First order kinetics

$t_{1/2}$: 25 min in $CDCl_3$ at 12 °C



Review: H. Brunner, *Eur. J. Inorg. Chem.* **2001**, 905

Tetrahedral or spiro-type Cu(I) complexes

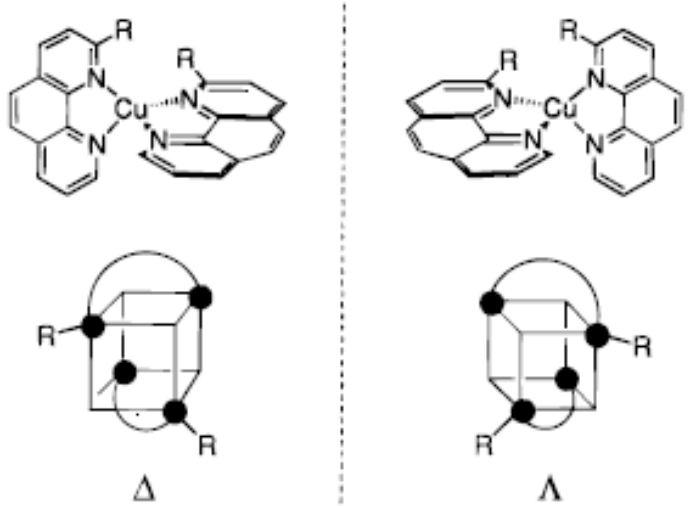
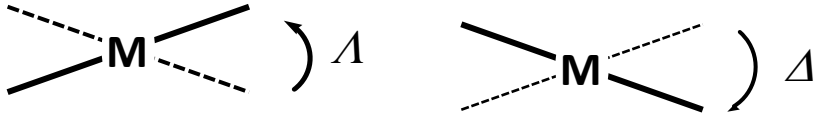
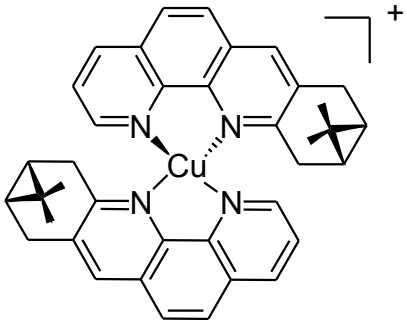


Figure 1. Chirality in $[Cu(2\text{-}R\text{-}phen)_2]^+$ complexes.



Configurational lability,
transfer of chirality from ligand to Cu



Δ-$[Cu(\mathbf{L})_2]^+$

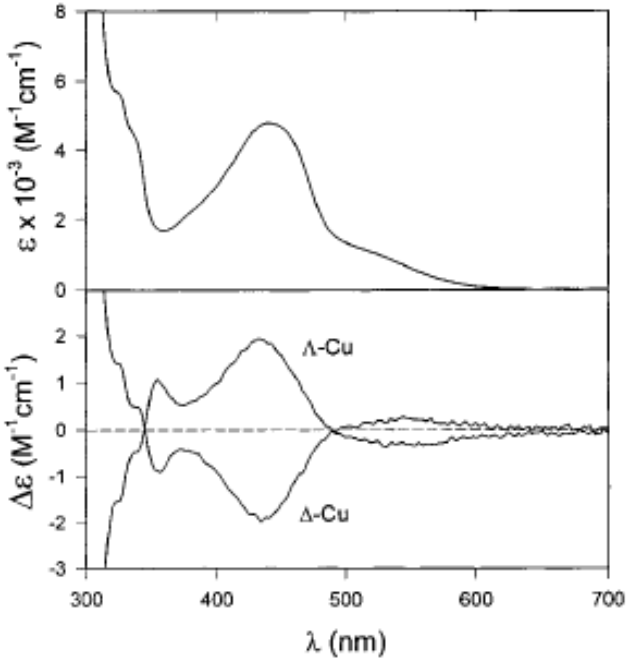
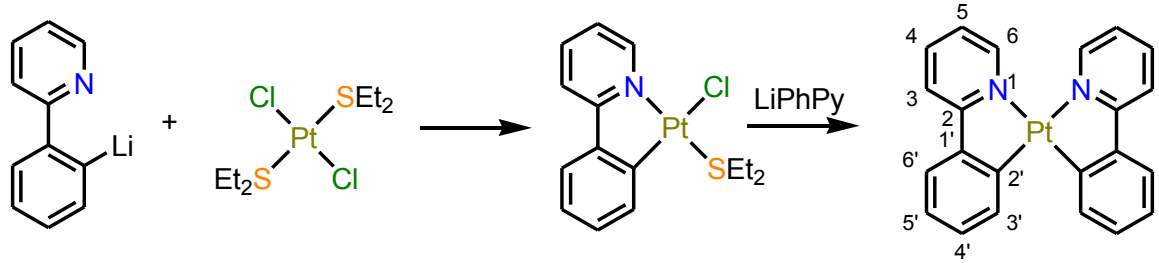


Figure 2. Absorption (top) and circular dichroism (bottom) spectra of Λ-Cu and Δ-Cu in CH_2Cl_2 solution at 298 K.

E. R. Riesgo, A. Credi, L. de Cola, R. P. Thummel, *Inorg. Chem.*, **1998**, *37*, 2145

Distorted square-planar (SP-4) complexes

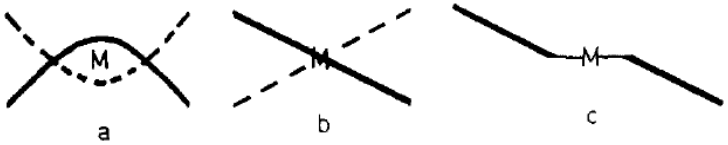
Phenyl-pyridine: bidentate C^N chelate ligand



C = *S > C1 > N in trans labilization*
Trans-effect

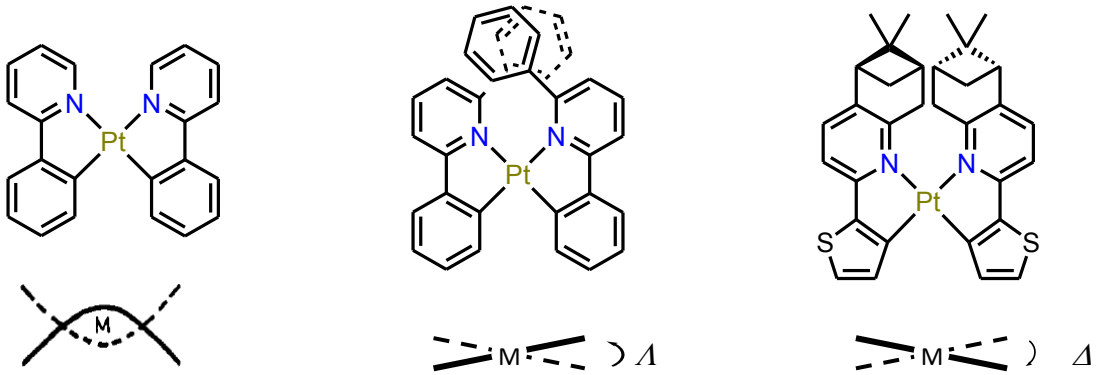
Cis-arrangement

Chassot, L.; Müller, E.; von Zelewsky, A.*Inorg. Chem.***1984**, *23*, 4249



Cis-biscycloplatinated complex exclusively

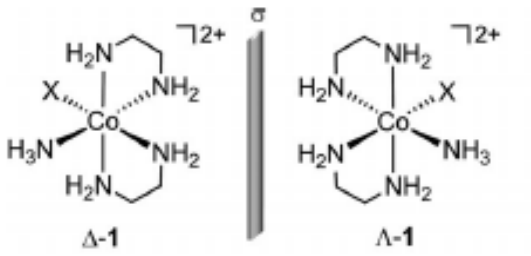
Because the steric problem coming from two hydrogen's, the square planar metal center will have three kinds of conformation.



Octahedral Coordination Complexes

Alfred Werner's discovery (1893)

First example of a chiral complex devoid of any carbon atoms

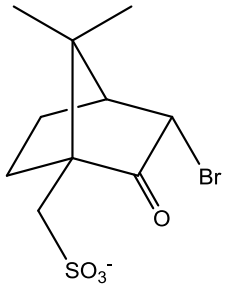


Alfred Werner (1866 – 1919)

Nobel prize 1913

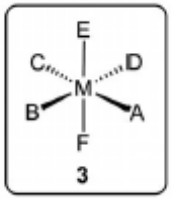
A. Werner, *Z. Anorg. Chem.* **1893**, 3, 267

X=Cl, Br
Resolution of cation $[Co(NH_3)(en)_2X]^{2+}$ by crystallization of diastereoisomeric salt of (+) or (-)-3-bromocamphre-9-sulfonate (1897)

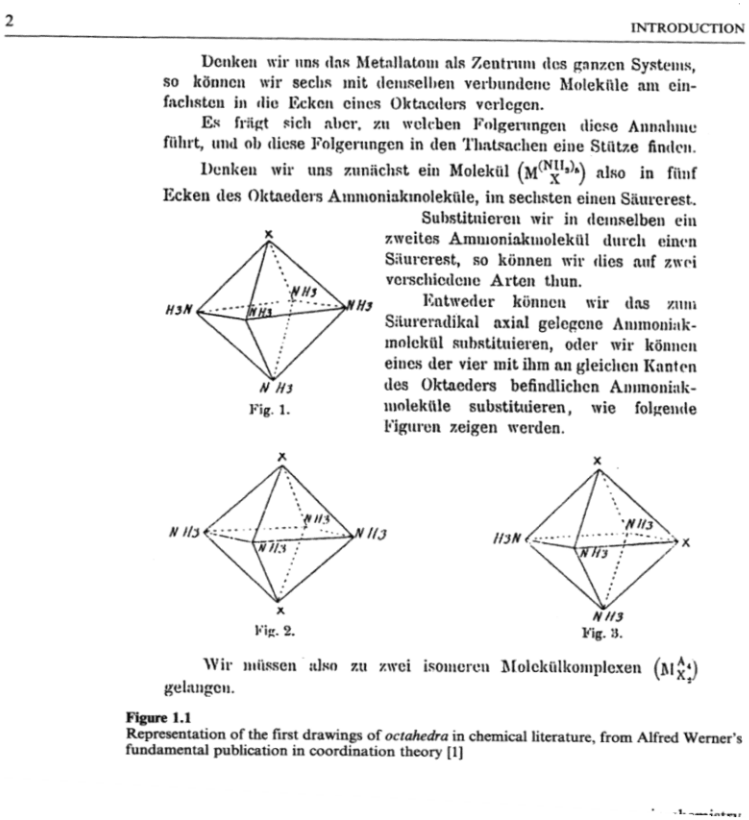


A. Werner, V. King, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1887.
I. Bernal, G. B. Kauffman, *J. Chem. Ed.* **1987**, *64*, 604.

E. Meggers, *Eur. J. Inorg. Chem.* **2011**, 2911.
E. C. Constable, *Chem. Soc. Rev.* **2013**, *42*, 1637.



30 stereosiomers, all chiral, and 15 pairs of enantiomers



2 INTRODUCTION

Denken wir uns das Metallatom als Zentrum des ganzen Systems, so können wir sechs mit demselben verbundene Moleküle am einfachsten in die Ecken eines Oktaeders verlegen.

Es frägt sich aber, zu welchen Folgerungen diese Annahme führt, und ob diese Folgerungen in den Thatsachen eine Stütze finden.

Denken wir uns zunächst ein Molekül $(M^{(NH_3)_5}_{X})$ also in fünf Ecken des Oktaeders Ammoniakmoleküle, im sechsten einen Säurerest.

Substituieren wir in demselben ein zweites Ammoniakmolekül durch einen Säurerest, so können wir dies auf zwei verschiedene Arten thun.

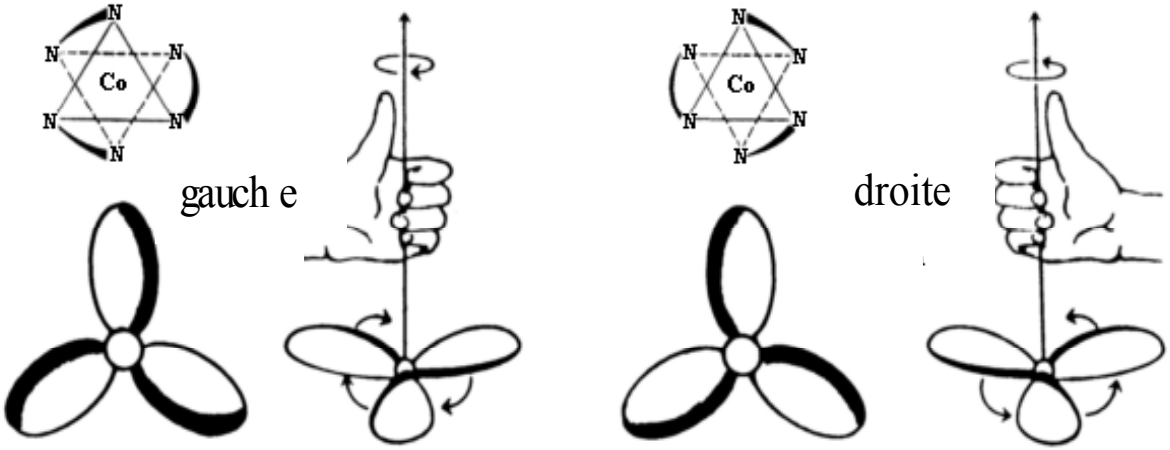
Entweder können wir das zum Säureradikal axial gelegene Ammoniakmolekül substituieren, oder wir können eines der vier mit ihm an gleichen Kanten des Oktaeders befindlichen Ammoniakmoleküle substituieren, wie folgende Figuren zeigen werden.

Fig. 1. Fig. 2. Fig. 3.

Wir müssen also zu zwei isomeren Molekülkomplexen $(M^{A}_{X_2})$ gelangen.

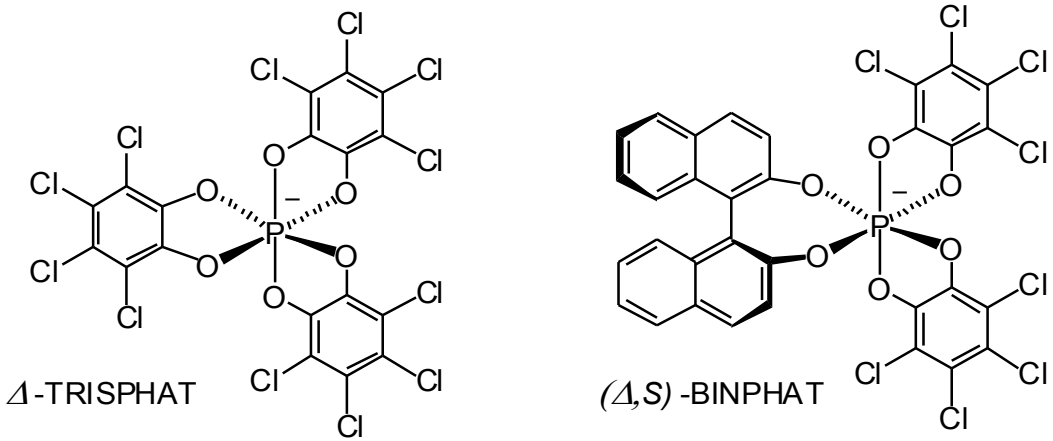
Figure 1.1
Representation of the first drawings of *octahedra* in chemical literature, from Alfred Werner's fundamental publication in coordination theory [1]

$[Co(en)_3]^{3+}$ (en = $NH_2CH_2CH_2NH_2$) has three bidentate ligands positioned like a three bladed propeller arrangement.



Left-handed Λ Right-handed Δ

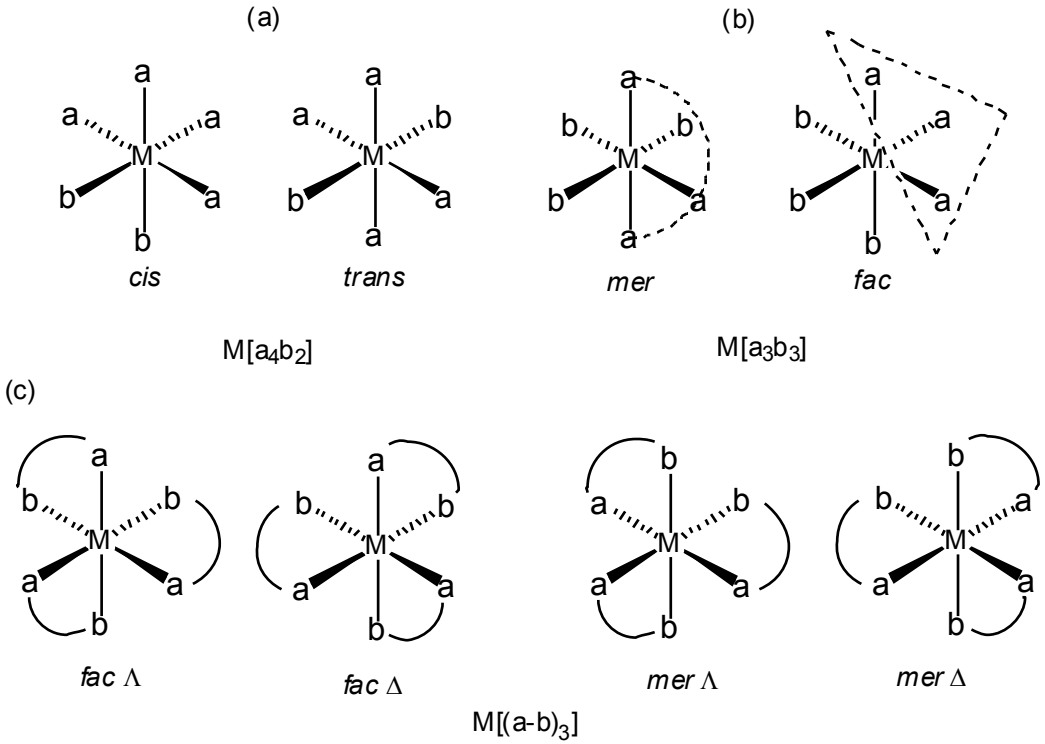
Chiral phosphorated anion

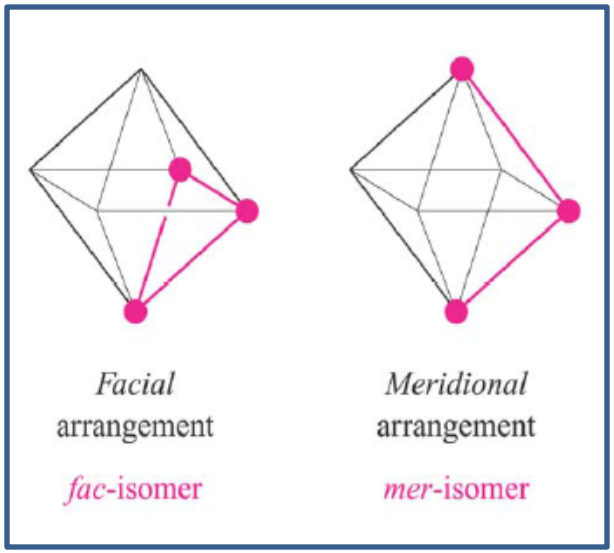


Cases with 2 types of different ligands ligands a and b

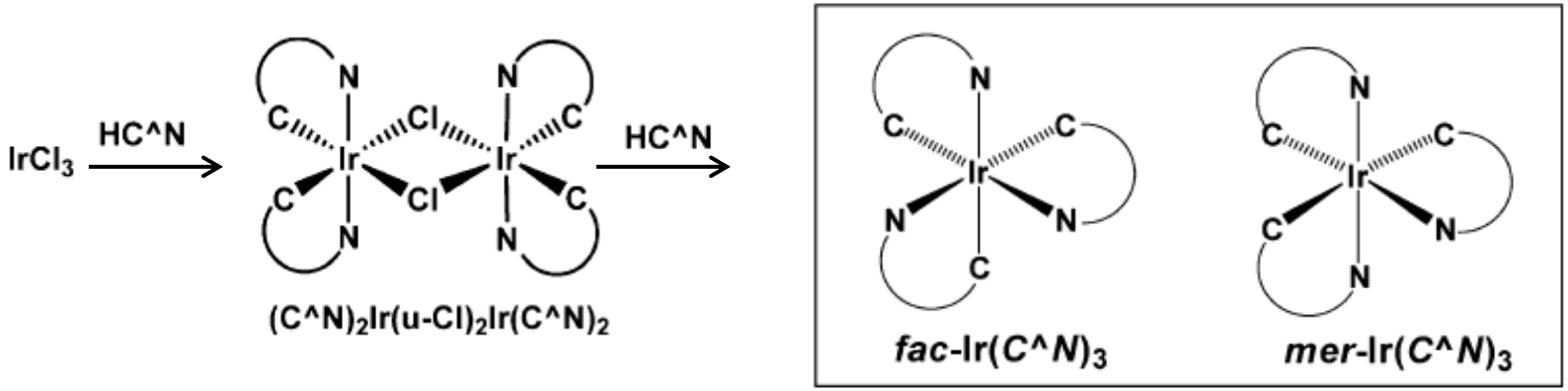
We define an isomerism *cis/trans* for complex $M[a_4b_2]$ and an isomerism *mer/fac* for complex $M[a_3b_3]$

The terminology *mer* comes from 3 ligands a (or b) arranged alond one « meridian » (the molecule is considered spherical).
Isomer *fac* has its three ligands on the same side.
With bidentate ligands, the configuration of each stereoisomer needs two descriptors .

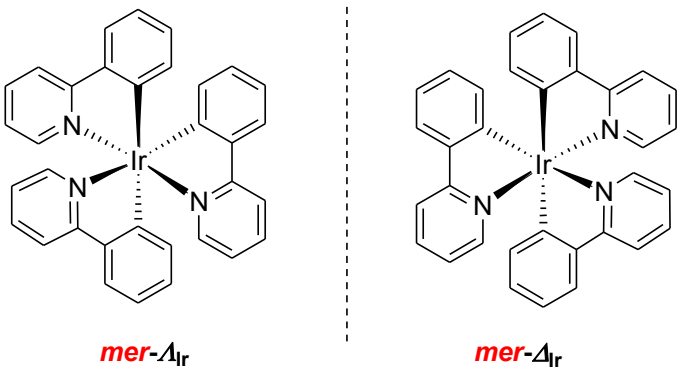




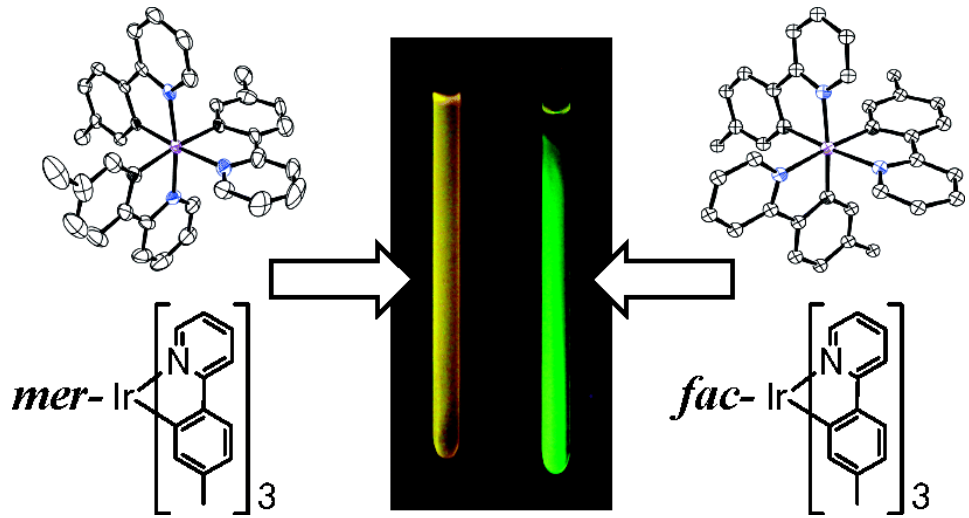
Phosphorescent chiral cyclometallated complexes



M. E. Thompson *et al., J. Am. Chem. Soc.* **2003**, *125*, 7377



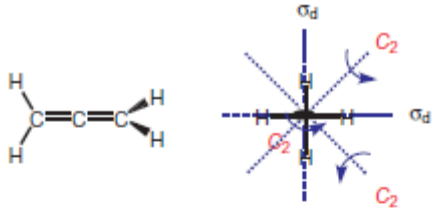
Idem for the *fac* isomer



Chiral OLEDs: J.-L. Zuo *et al., Scientific Reports* **2015**, *5*, 14912

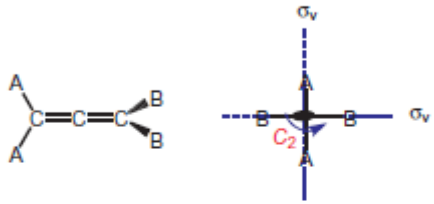
Molecules displaying axial chirality: examples of allenes

Point-group symmetry



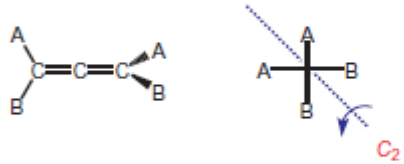
σ_d, C_2, 2 C_2 ⊥

D_{2d} symmetry
achiral

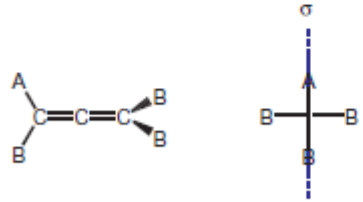


σ_v, C_2

C_{2v} symmetry
achiral

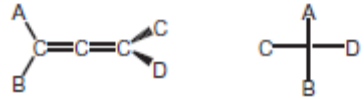


C_2 symmetry
chiral



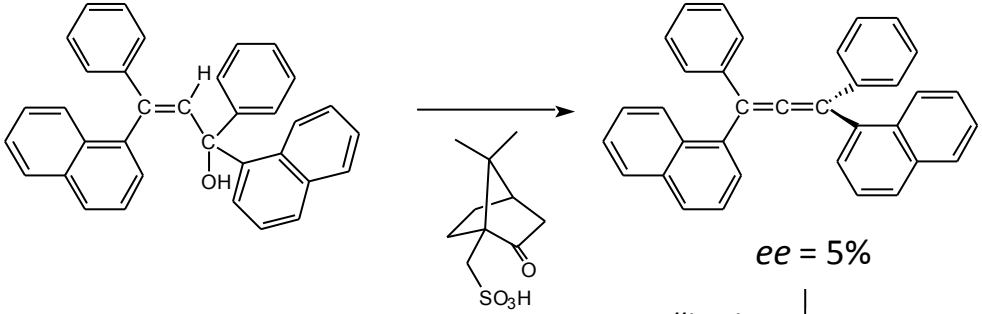
σ

C_s symmetry
achiral



C_1 symmetry
chiral

First optically active allene (1935)



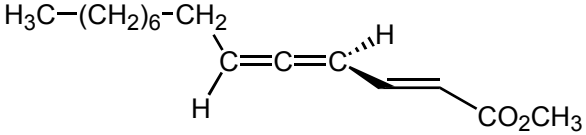
ee = 5%

recrystallization

ee = 100%

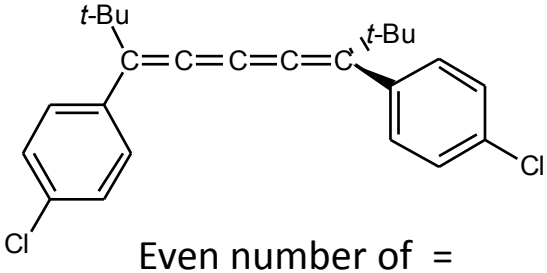
$[\alpha]^{17}_{546}$ = +437 (benzene)

A natural chiral allene: a pheromone



$[\alpha]^{23}_{D}$ = -128 (*C* 0.6, hexane)

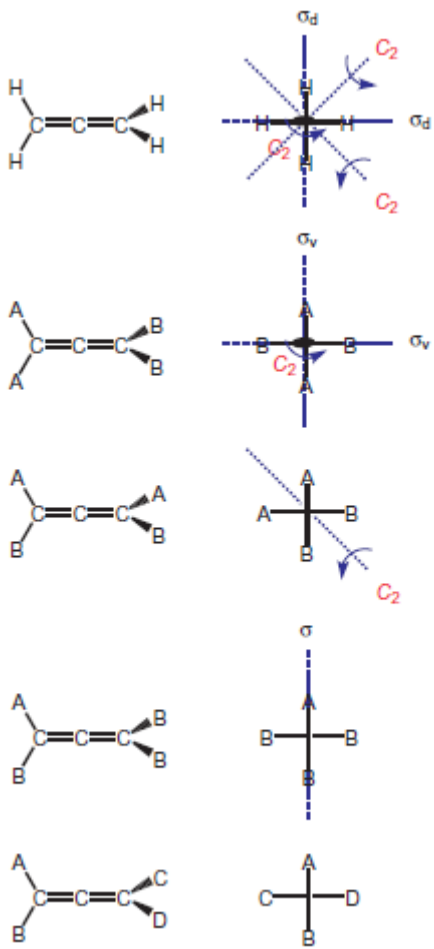
Example of a chiral cumulene



Even number of =

Molecules displaying axial chirality: examples of allenes

Point-group symmetry



σ_d, C_2, 2 C_2 ⊥

D_{2d} symmetry
achiral

σ_v, C_2

C_{2v} symmetry
achiral

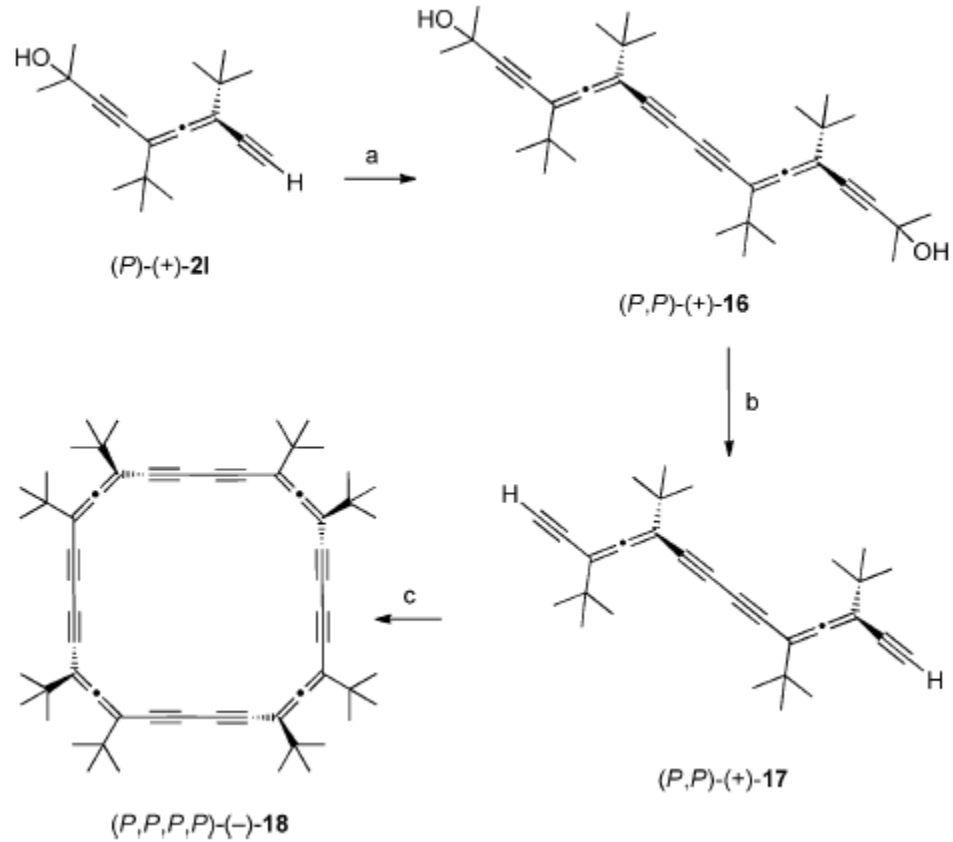
C_2 symmetry
chiral

σ

C_s symmetry
achiral

C_1 symmetry
chiral

Allenophanes



Cotton effects at 253 nm

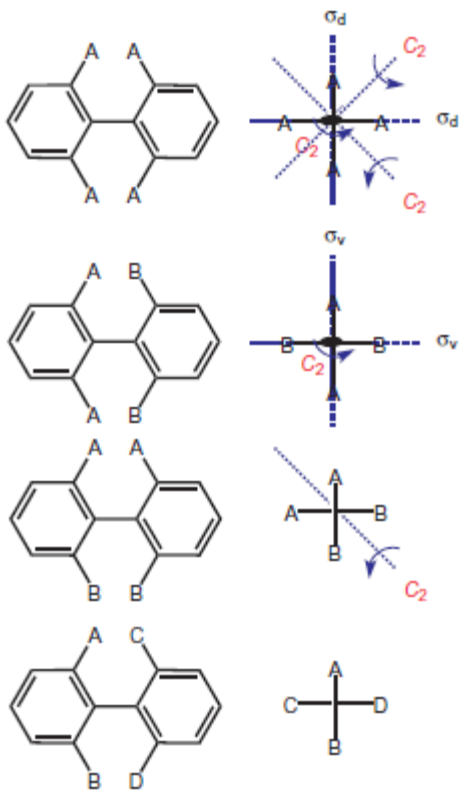
$\Delta\varepsilon$ =790 M^{-1} cm^{-1}

P. Rivera-Fuentes, F. Diederich,
Angew. Chem. Int. Ed. **2012**, *51*, 2818

Atropoisomerism and axial chirality

We can define it as **a conformational isomerism in which the conformers can be isolated** .
This concept **is tightly linked to the conformational barrier** and to the conditions in which the conformers can be isolated.
A conformational barrier $\Delta G^{\neq}$ around 92 kJ mol^{-1} at 300 K corresponds to a half-life time of 15 min.
Atropoisomerism can exist around single bonds of different types : **sp^3–sp^3, sp^3–sp^2, sp^2–sp^2.**

Biphenyle derivatives display such **atropoisomerism** (sp^2–sp^2).
For compounds non substituted in *ortho* position: very low inversion barrier, below 9 kJ mol^{-1} in the gas phase gazeuse, with torsion angle between aromatic rigns around 45°. In the solide state: a great proportion are planar.
Substituents in *ortho* position induces steric congestion and therefore atropoisomerism.
This is the case for tri and tetra-*ortho*-substituted compounds.

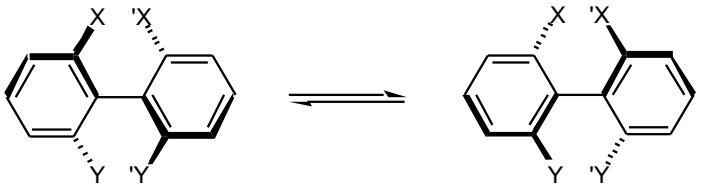


In average D_{2d} symmetry achiral

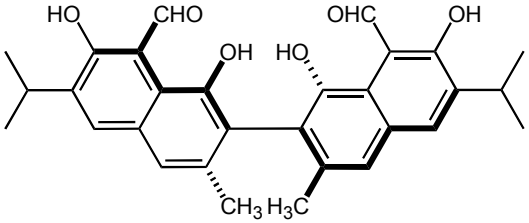
In average C_{2v} symmetry achiral

C_2 symmetry chiral

C_1 symmetry chiral



A natural binaphtyl derivative: gossypol



C. Wolf, *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, **2008**, RSC Publishing

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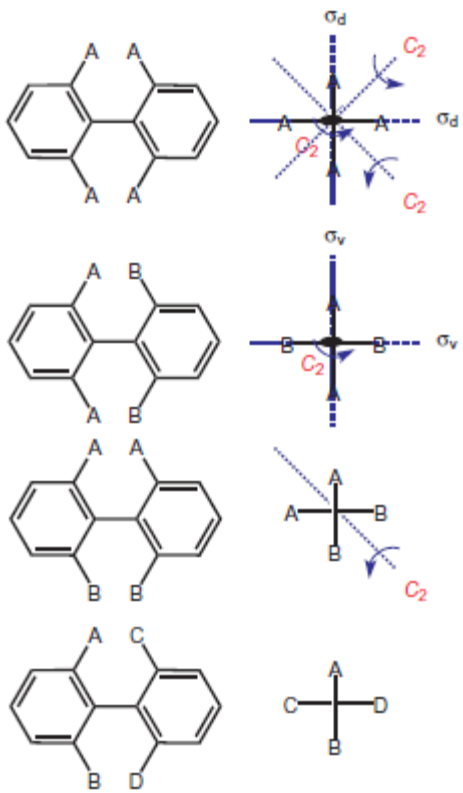


In average D_{2d} symmetry achiral

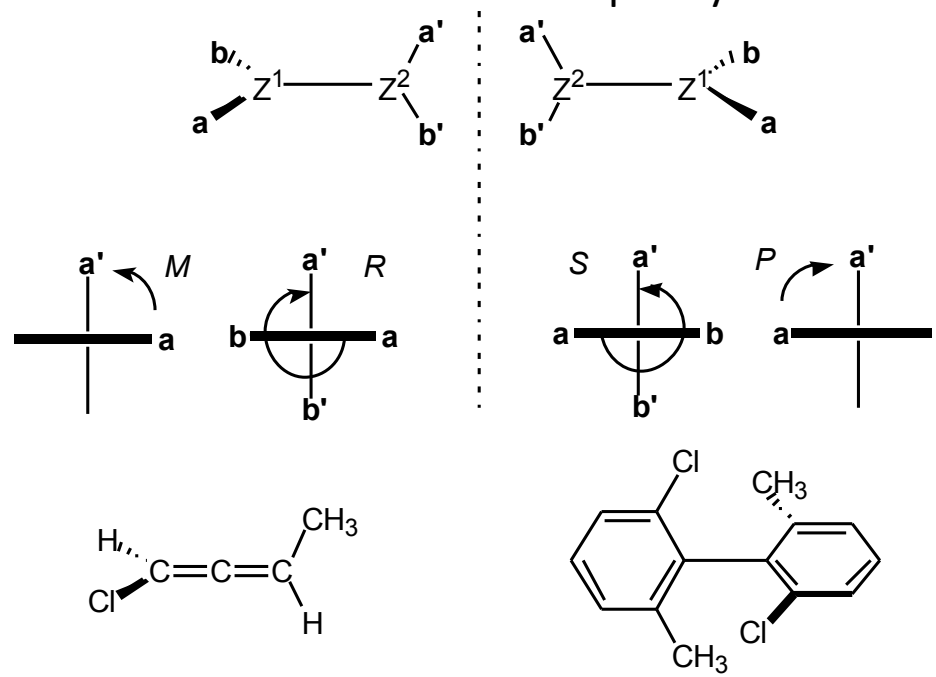
In average C_{2v} symmetry achiral

C_2 symmetry chiral

C_1 symmetry chiral

CIP nomenclature

allene | biphenyle



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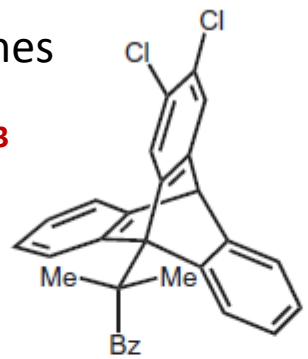
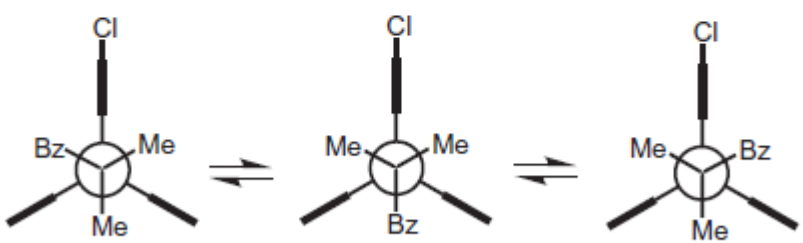
Triptycènes

sp^3–sp^3

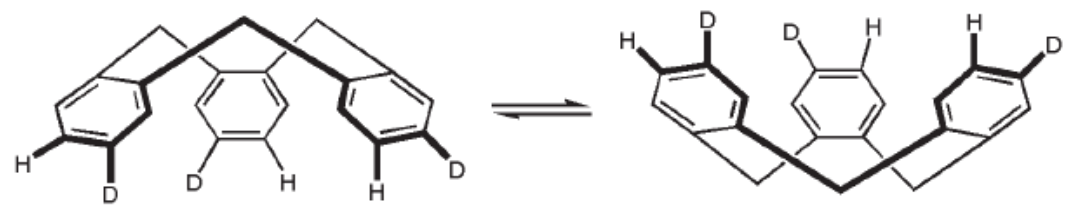




E_a = 153 kJ mol^{-1}

Cyclotrivératrylènes

sp^2–sp^3



M-(–) $\Delta G^{\neq}_{298}$ = 112,4 kJ mol^{-1} *P*-(+)

$[\alpha]^{25}$ = –2,3 (*c* 2,6 ; $CHCl_3$)

Brotin, Dutasta, Martinez, Châtelet **(GDR)**

C. Wolf, *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, RSC Publishing, **2008**.

Planar chirality

Such type of chirality mainly concerns cyclic alkenes, cyclophanes, metallocenes.

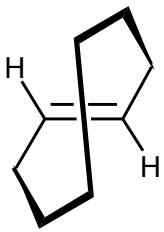
Planar chirality comes from the **arrangement of groups out of a plane called chiral plane.**

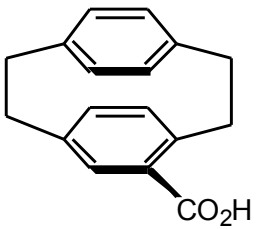
It is linked to the rest of the molecule and imposes a steric congestion so that it cannot be in a symmetry plane.

The chiral plane contains a maximum of atoms.

For example, in *trans*-cyclooctène, the chiral plane is the one which contains the double bond.

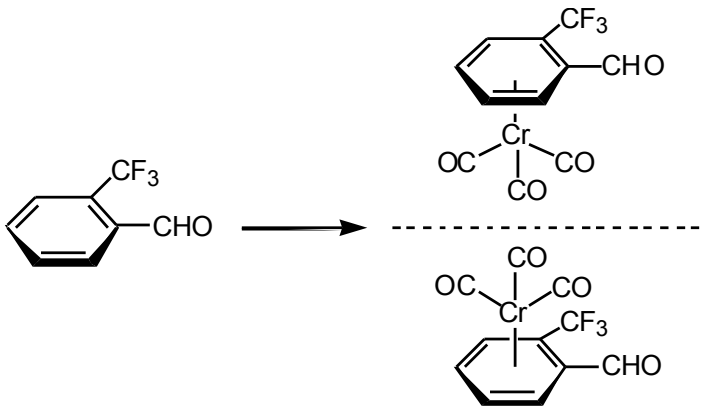
In [2,2]paracyclophane carboxylic acid , the chiral plane is the one with the acidic function.



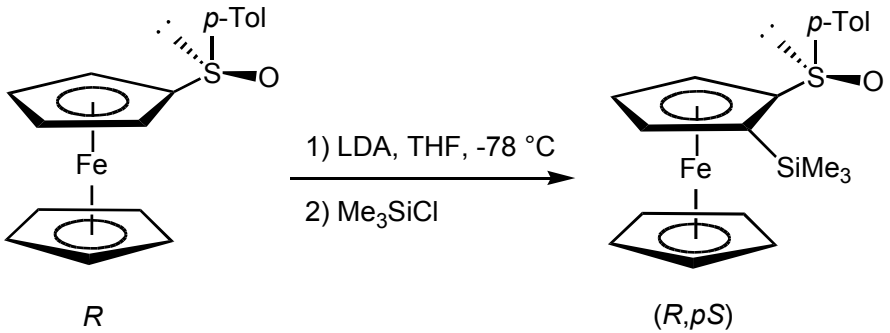


One can also define **planar chirality in terms of prostereoisomerism**. The labeling of the two enantiotopic faces of a prochiral plane makes it appear enantiomeric structures, such as in chiral chromium tricarbonyle complex.

Ferrocenes are other examples of chiral metallocenes when (for example) they display two different substituents in the same cyclopentadienyle.



$[\alpha]_D^{20}$ = ± 754 (*c* 1, $CHCl_3$)

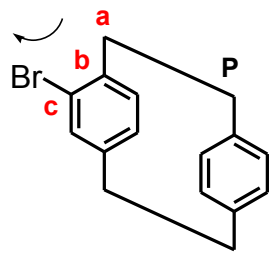


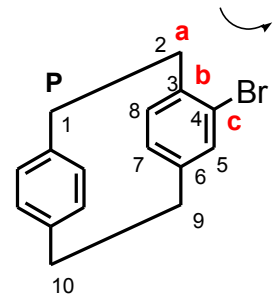
$[\alpha]_D^{20}$ = +333 (*c* 0.88, $CHCl_3$)

CIP rules for planar chirality

The atom of highest priority is the one that is directly bound to the chirality plane, but not a member of it, must first be found. This atom is then known as the **pilot atom** (**P**). In 4-bromo[2.2]paracyclophane, the pilot atom is the C bound to the methylene carbon atom that is located right next to the bromine atom in the aromatic ring. Aside from the pilot atom, the next three consecutive atoms of the chirality plane are labelled a, b, and c. If there is a branching, the atom of highest CIP priority is selected in each case. The configuration is called (p*S*) or *M* if the atom sequence P - a - b - c is arranged counterclockwise, while it is classified as (p*R*) or *P* if the atom sequence is arranged clockwise.

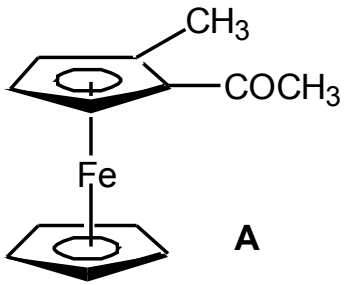
p*R* or *P*



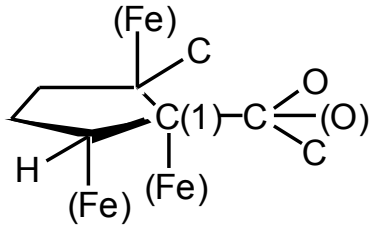


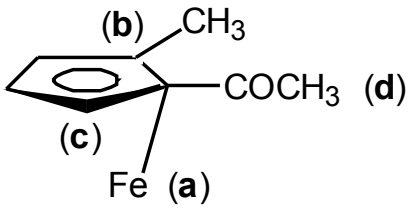
p*S* or *M*

For planar chirality in complexes it's more simple and clearer to use central chirality. In compound **A**, the chirality is due to the two different subtituent in the Cp. The configuration of the atom of higher priority (C(1)) is considered as a pseudo-tetrahedral center surrounded by four groups Fe (**a**), CCH_3 (**b**), CH (**c**) et $COCH_3$ (**d**). This unequivocally specifies the configuration.



A



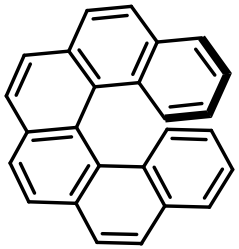


1*R*

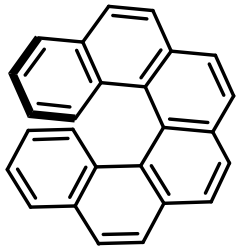
Inherent chirality

(no center, no axis, no plane of chirality)

Carbo[6]helicenes

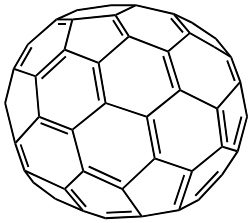


M-(-)

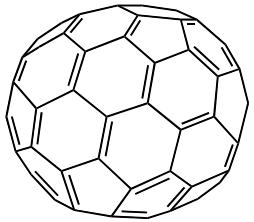


P-(+)

Chiral fullerenes

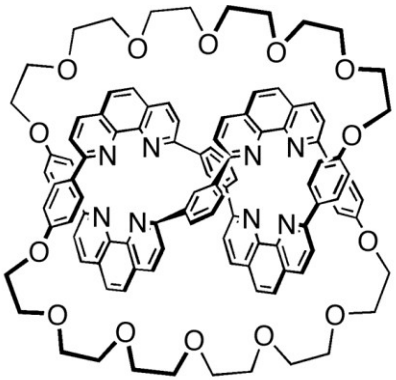


CD(-)282-(^{f}A)-C_{76}

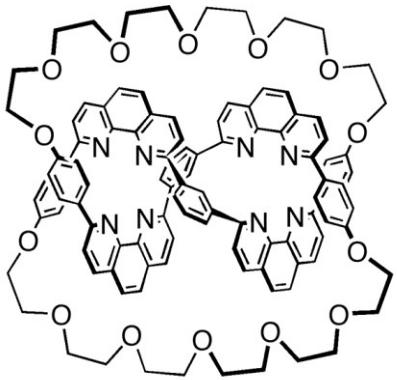


CD(+)282-(^{fC})-C_{76}

Trefoil knots

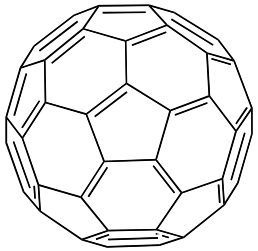


M-(+)



P-(-)

Carbon allotropes

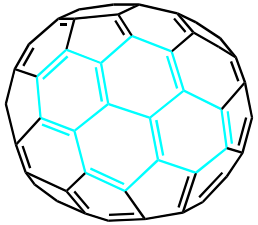


Footbalene or Buckminsterfullerene C_{60}

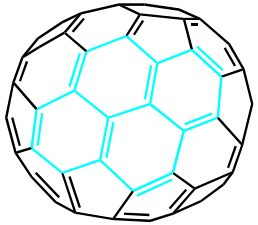
I_h Symmetry, achiral

Stereodescriptors

Schlegel diagrams

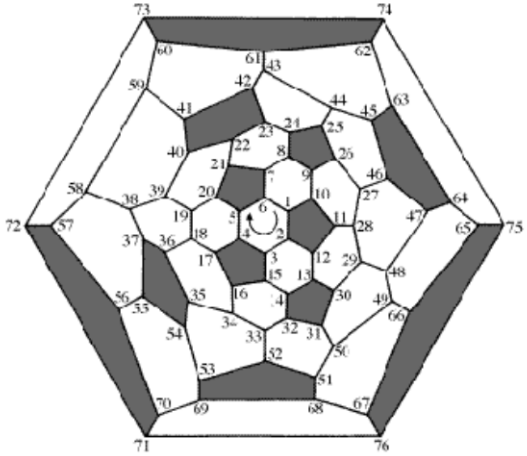


C_{76}

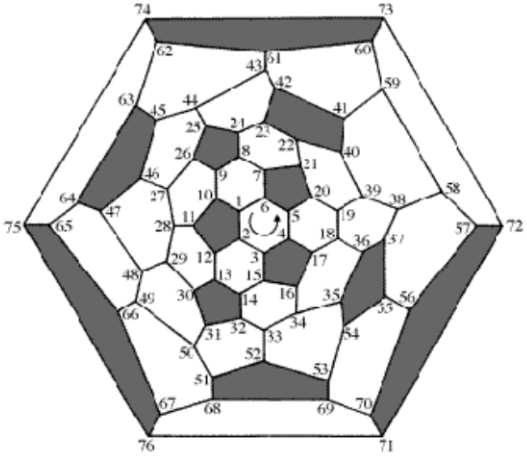


ent-C_{76}

D_2 Symmetry chiral



^1C

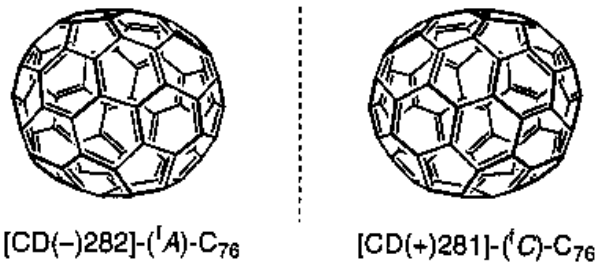


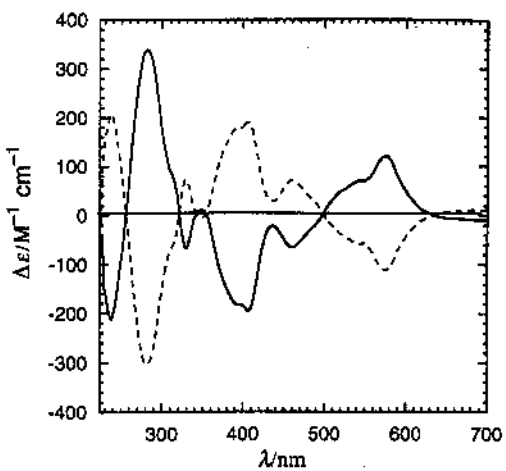
^1A

Review on chiral fullerenes: C. Thilgen, F Diederich, *Chem. Rev.* **2006**, *106*, 5049.

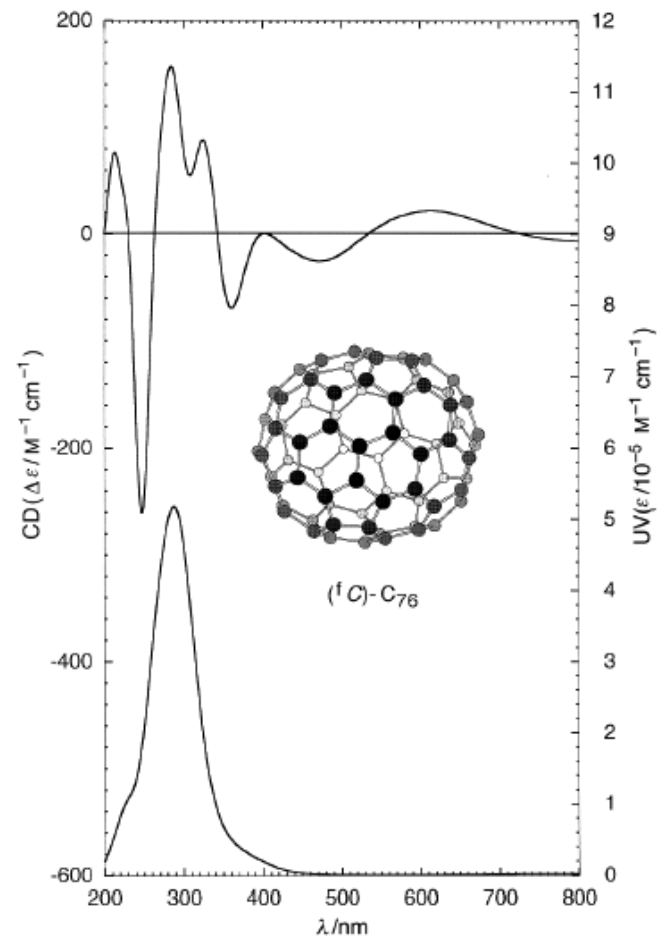
Theoretical calculation of circular dichroism of fullerenes
Absolute configuration

Collaboration with Prof. Nobuyuki Harada, Sendai (Japon)
SCF-CI-DV MO (self consistent field-configuration interaction-dipole velocity molecular orbital)



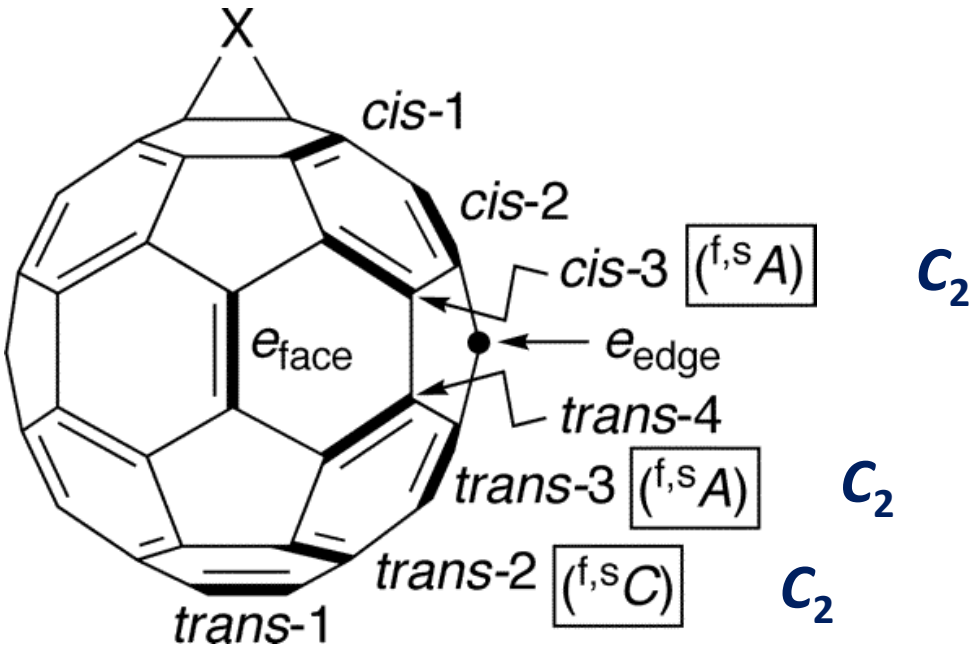


$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R$$



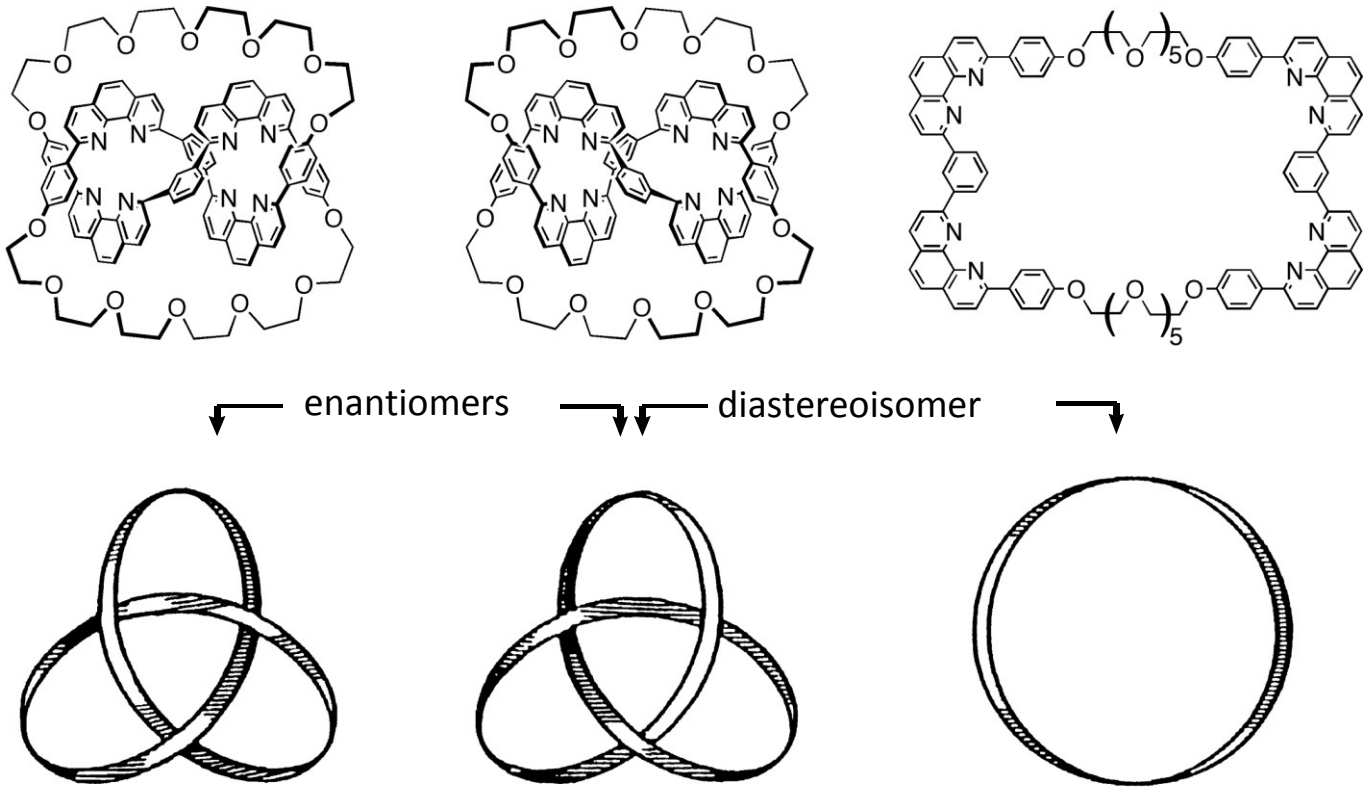
Crassous, Diederich et al.
Angew. Chem. Int. Ed. Engl. **1998**, *37*, 1919.
J. Chem. Soc., Perkin Trans. 2, **1998**, 1719.

Achiral adducts of C_{60}



The possible [60]fullerene bis-adduct isomers and the stereodescriptors for the highlighted inherently chiral addition patterns. If both addends are identical and C_{2v}-symmetric, the addition patterns *cis*-1, *cis*-2, *e*, and *trans*-4 are C_s-symmetric, *cis*-3, *trans*-3, and *trans*-2 are C_2-symmetric, and *trans*-1 is D_{2h}-symmetric.

Trefoil knots



G. Rapenne, C. O. Dietrich-Buchecker, J. -P. Sauvage, *J. Am. Chem. Soc.*, **1996**, *118*, 10932.

Topological chirality: Impossible to interconvert two topological enantiomers by a continuous deformation (i.e. without breaking a bond)

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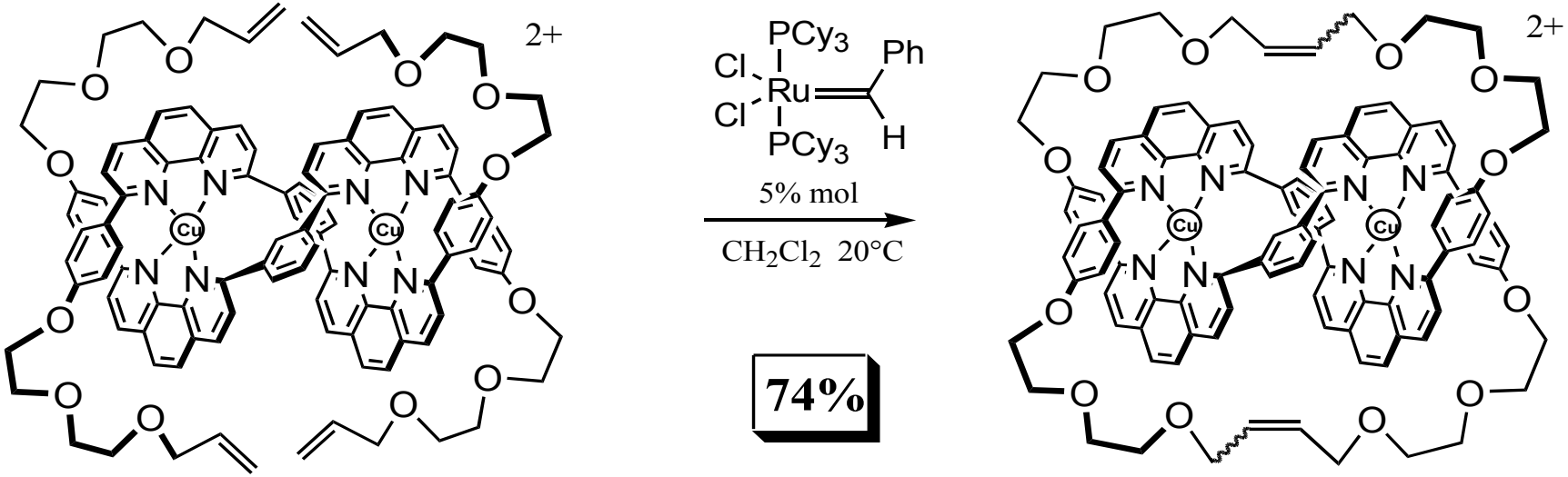
J.-C. Chambron, J.-P. Sauvage, *et al.*, *Chirality* **1998**, *10*, 125

Thèse : Un nœud obtenu avec 74% de rendement

- 1989 : First knot prepared with 3% de rendement
- **1997 : Cyclization by olefin metathesis**



Double helicate

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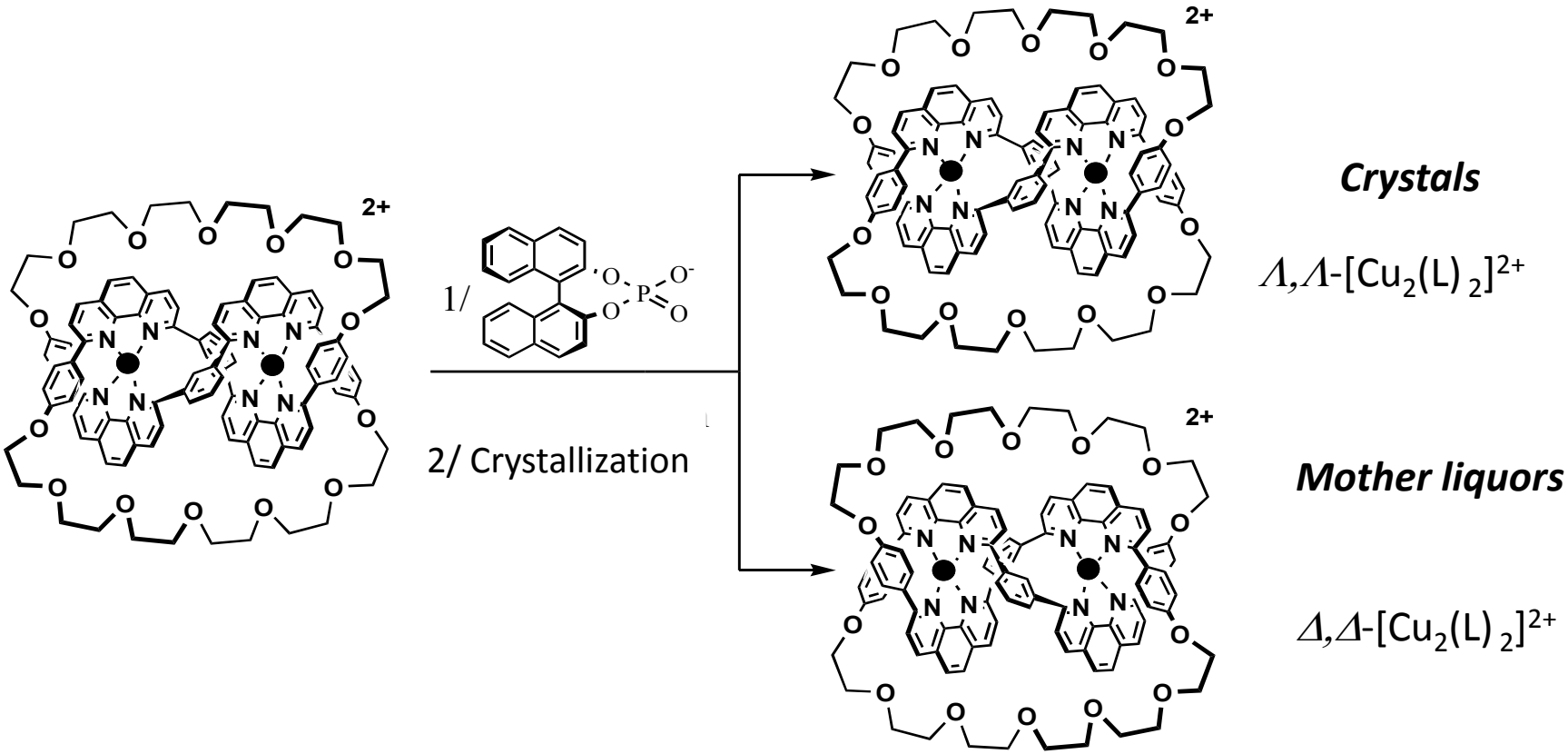
Resolution of a Cu(I) trefoil knot

Diastereoselective crystallization



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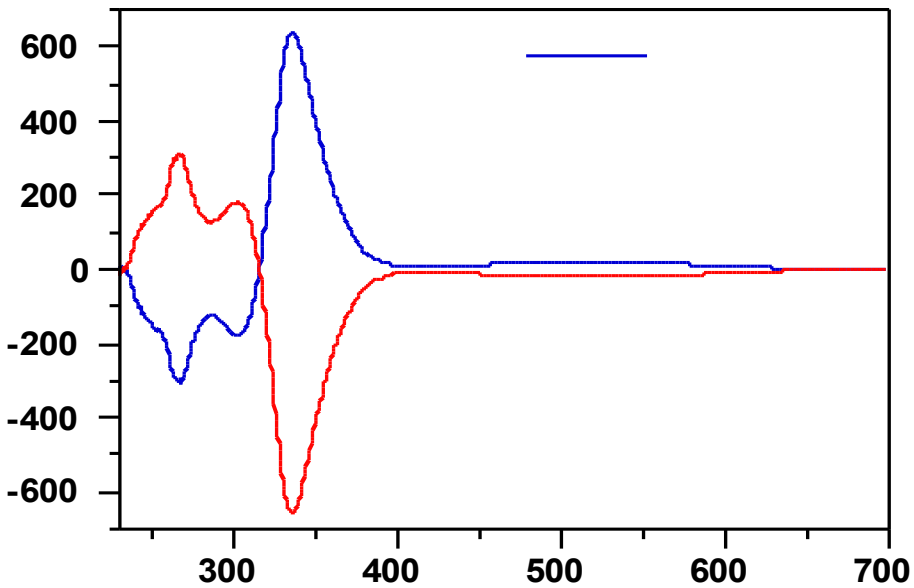
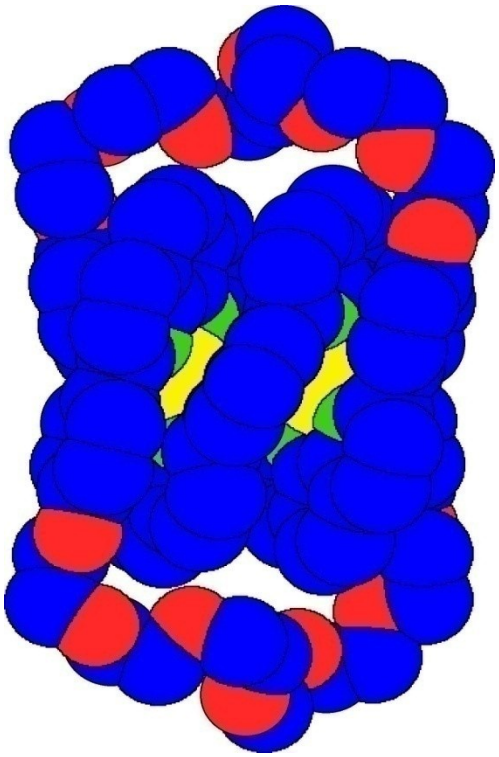
Chiroptical properties – Absolute configuration (X-Ray)

$[\alpha]_D = 4000\ °g^{-1}.ml.dm^{-1}$

Circular dichroism





(+)-Knot = Left-handed

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