NMR Spectroscopy for Studying Chirality

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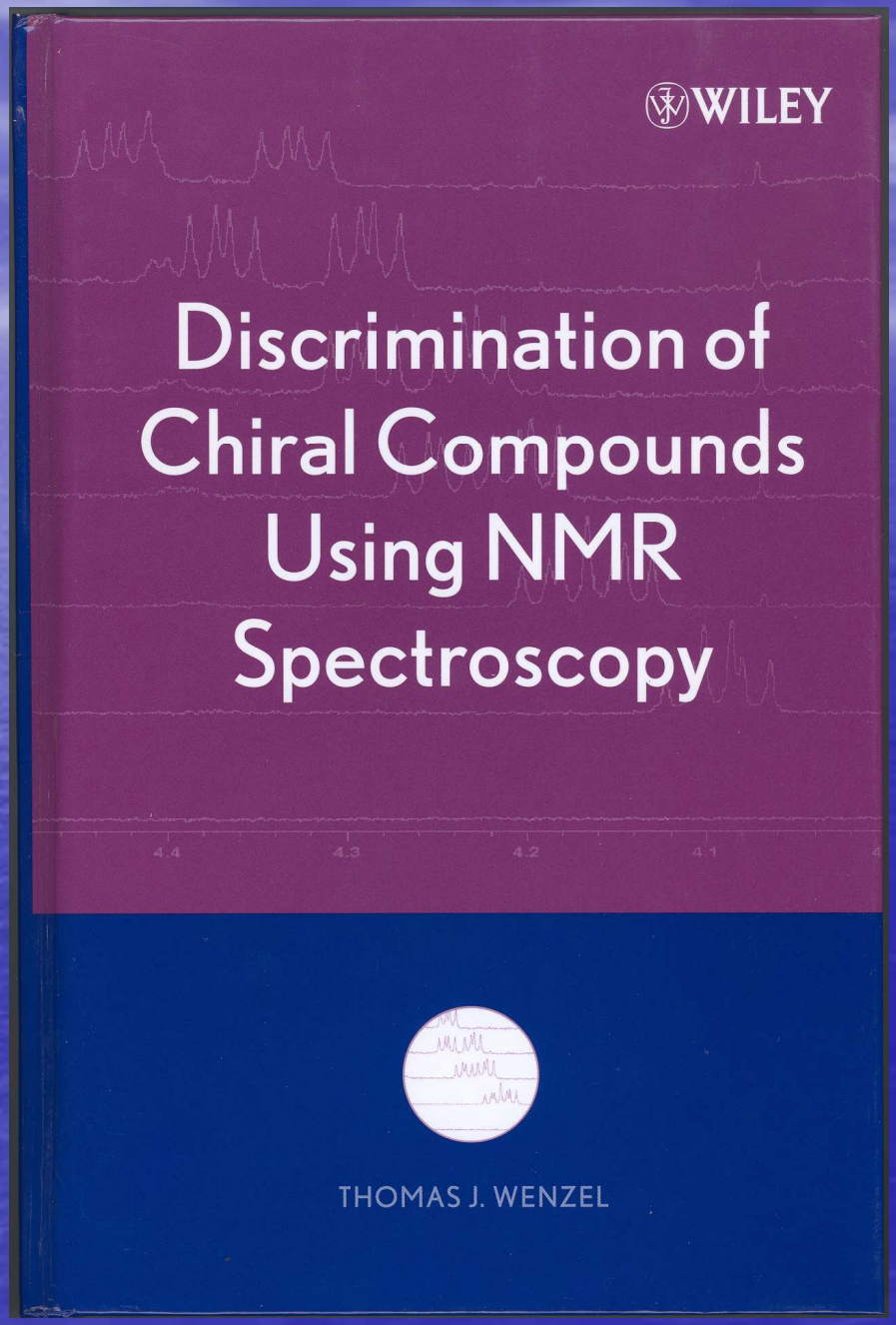

WILEY
Discrimination of Chiral Compounds Using NMR Spectroscopy
4.4
4.3
4.2
4.1
THOMAS J. WENZEL

Chiral Discrimination NMR Spectroscopy

- Chiral derivatizing agents
- Chiral solvating agents
- Metal complexes
- Liquid crystals

Chiral Derivatizing Agents

- Form a covalent bond between an optically pure reagent and the compound of interest

CDA + (*R*)-Sub = CDA-(*R*)-Sub

CDA + (*S*)-Sub = CDA-(*S*)-Sub

- Resulting compounds are diastereomers

Chiral Discriminating Agents

- No racemization
- No kinetic resolution
- Need 100% optical purity of the reagent if using for the determination of enantiomeric excess

Chiral Solvating Agents

- Form non-covalent interactions between an optically pure reagent and the compound of interest

CSA + (*R*)-Sub = CSA-(*R*)-Sub
CSA + (*S*)-Sub = CSA-(*S*)-Sub

- Resulting compounds are diastereomers

- K_R and K_S are likely different – causes different time-averaged solvation environments

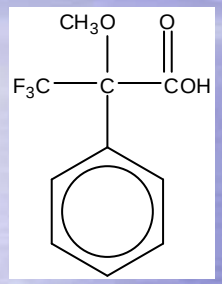
Chiral Solvating Agents

- Preferable to have fast exchange
- High concentration of CSA usually leads to larger discrimination
- Often see enhanced enantiomeric discrimination at lower temperatures

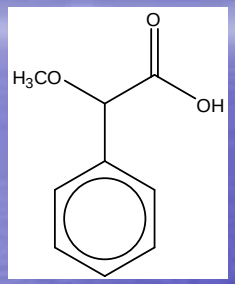
Assigning Absolute Stereochemistry

- Mechanism of discrimination is understood and characteristic shifts occur in the spectrum
  - More common with certain families of chiral derivatizing agents
  - Possible with some chiral solvating agents
- Empirical trend
  - Best if use known model compounds as close as possible in structural features to the unknown

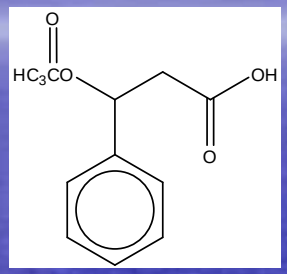
Aryl-containing Carboxylic Acids -Alcohols and Amines



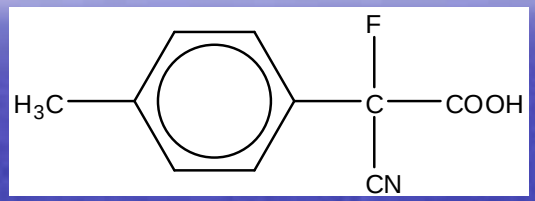
MTPA



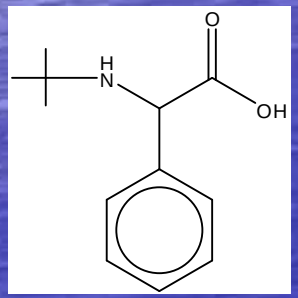
MPA (O-MMA)



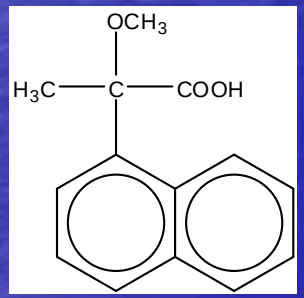
O-AMA



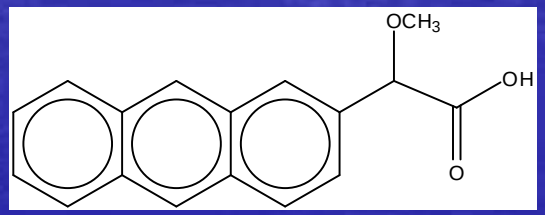
CFTA

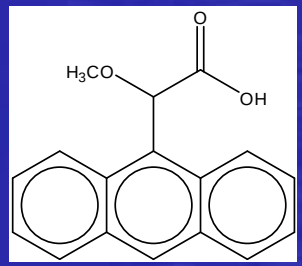


N-Boc PG



MαNP





2-AMA/9-AMA

Aryl-containing Carboxylic Acids

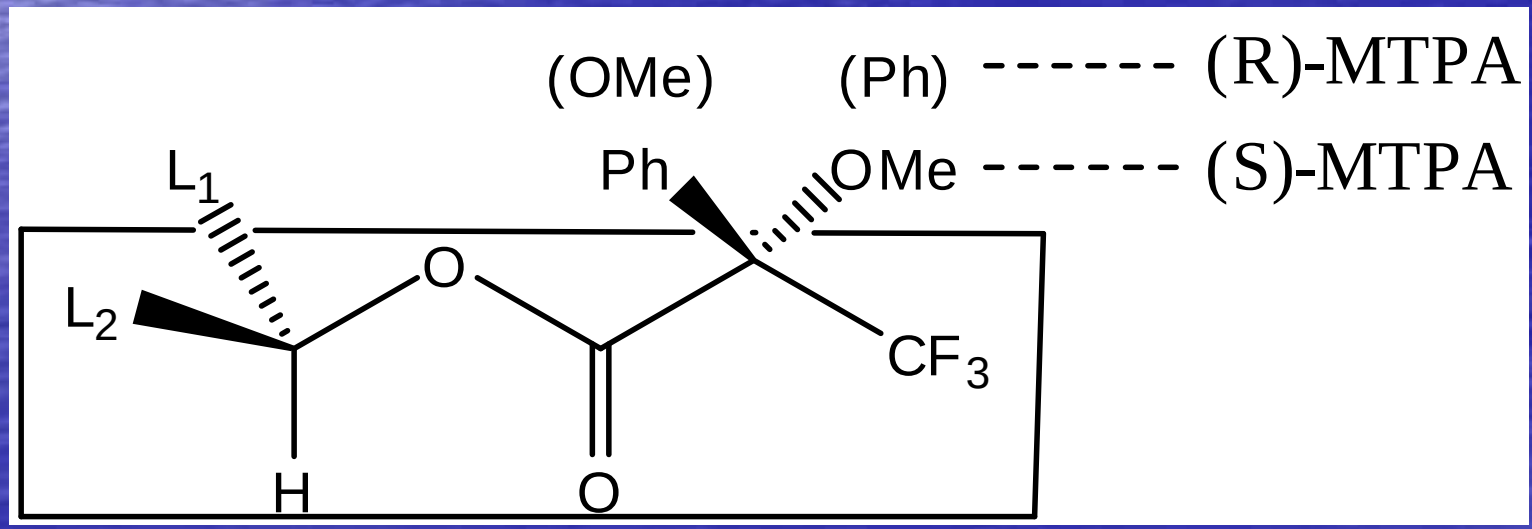
- MTPA = α-methoxy-α-trifluoromethylphenylacetic acid
- MPA = α-methoxyphenylacetic acid
- O-AMA = *O*-acetyl mandelic acied
- CFTA = α-cyano-α-fluoro-*p*-tolylacetic acid
- *N*-Boc PG = *N*-boc phenylglycine
- MαNP = 2-methoxy-2-(1-naphthyl)propionic acid
- 2-/9-AMA = α-(2-anthryl)-α-methoxyacetic acid

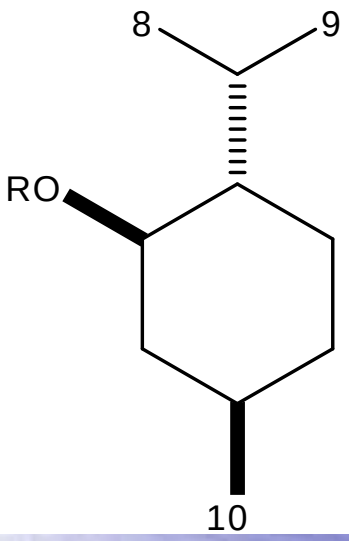
Mosher Method/Modified Mosher Method

-Prepare derivatives with (R)- and (S)-forms of the reagent

-*Syn-periplanar* arrangement of HC-O-C(O)-C atoms (secondary alcohols)

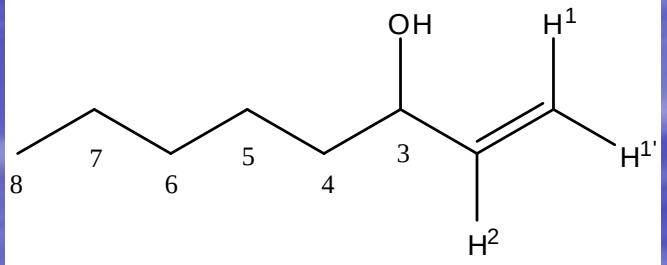
-Calculate $\Delta\delta^{RS}$ values – negative for L_1, positive for L_2





$\Delta\delta^{RS}$

	Me(10)	Me(8)	Me(9)
MTPA	0.07	-0.017	-0.04
MPA	0.05	-0.021	-0.26



Position	MTPA	MPA	PPA
1	0.07	0.19	0.43
1'	0.03	0.12	0.20
2	0.09	0.14	0.18
3	0.04	0.02	0.03
4	0.03	0.07	0.14
4'	0.03	0.06	0.13
8	0.03	0.04	0.10

PPA = α-phenyl-propionic acid

$\Delta\delta^{RS}$ depends on:

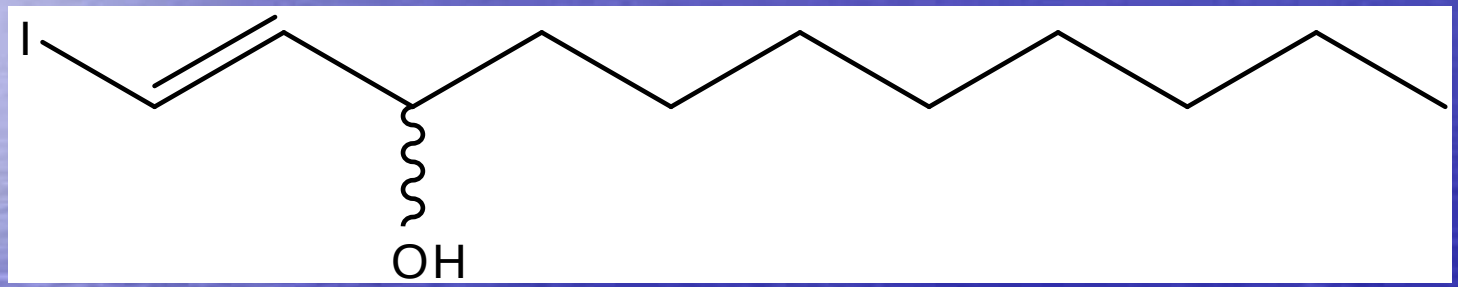
-Degree of conformational preference/how it influences the shielding

-Size of the shielding (anthryl > naphthyl > phenyl)

Secondary Alcohols

- MPA > MTPA (conformational preference that produces greater difference in shielding)
- MPA – early synthetic procedures – high degree of racemization
- Better procedures for MPA derivatization now exist
- Mix and shake method

MPA derivative

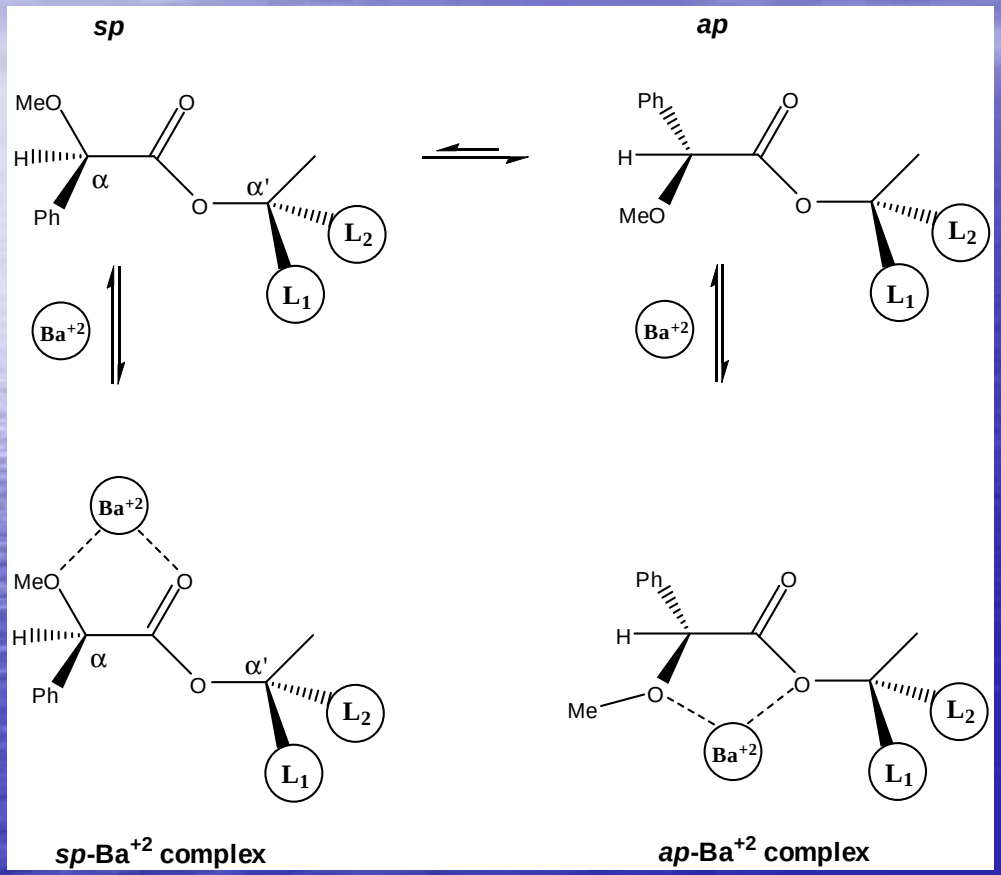


2.7 Hz differential shielding for the methyl group
9-bonds removed From the chiral center

Effect of temperature

- For MPA derivatives of secondary alcohols, lowering the probe temperature by about 100 K (to 175-200K) approximately doubles the $\Delta\delta^{RS}$ values
- Alters conformational preference further toward the *sp* form
- Can measure $\Delta\delta_{T_1T_2}$ values as a confirmation of stereochemical assignment
- Effect not as pronounced with MTPA or AMA

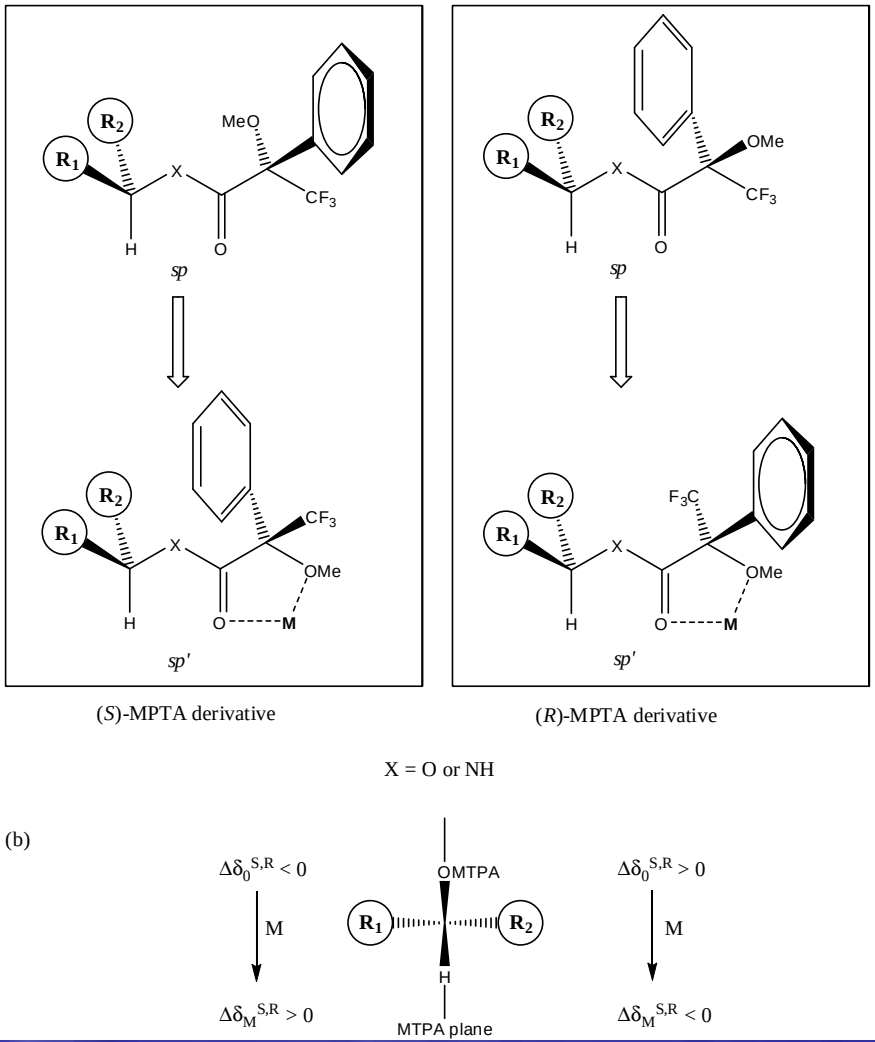
Barium Method
MPA/secondary alcohols



Barium binds in a chelate manner with the ester and alters the conformation preference toward the *sp* conformer.

Leads to enhancement in the shielding and get larger $\Delta\delta^{RS}$ values.

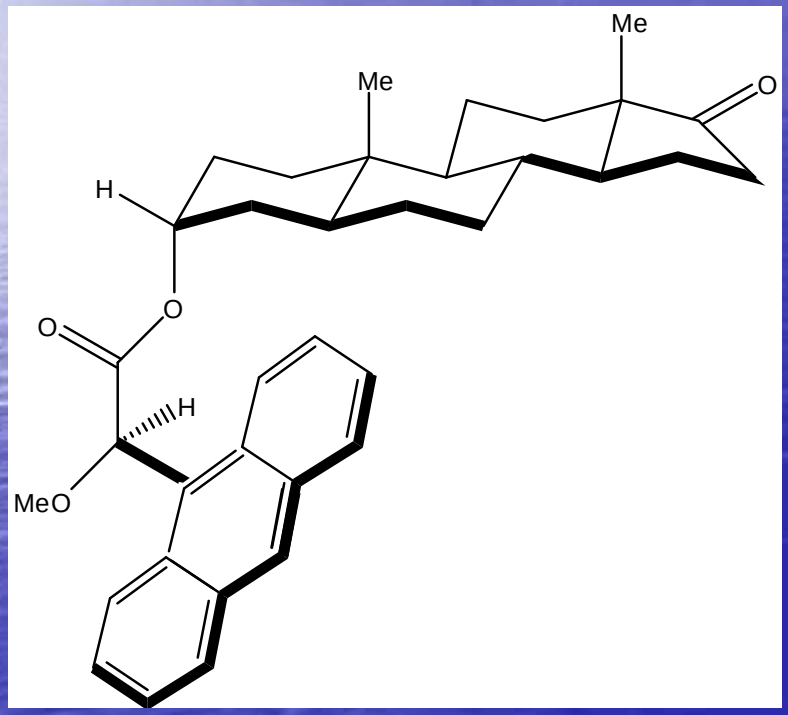
$La(hfa)_3$ method with MTPA Secondary alcohols

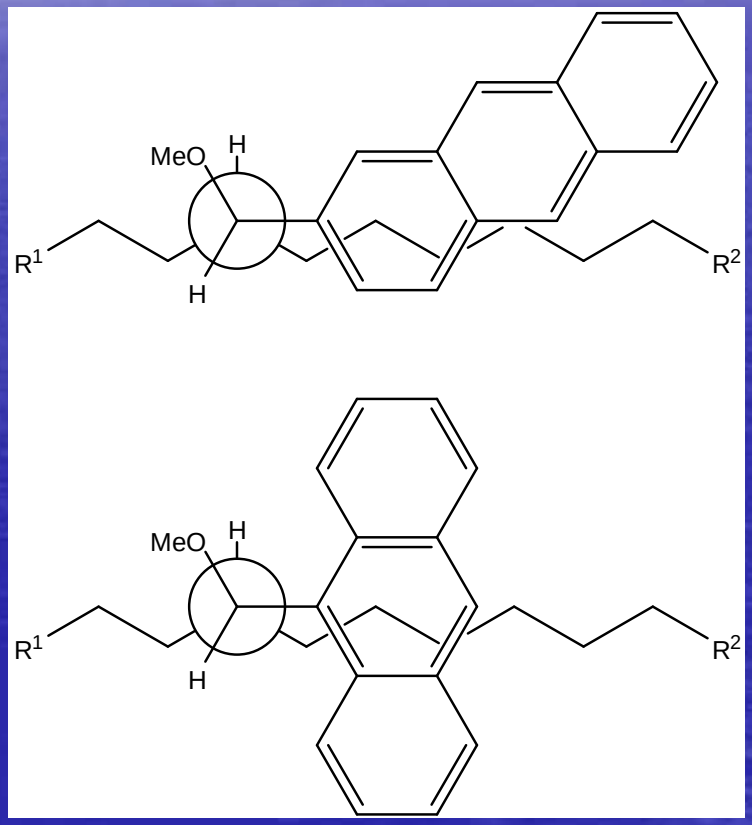


Chelate bonding of the La reverses the orientation of the phenyl ring and the shifts of the hydrogen resonances

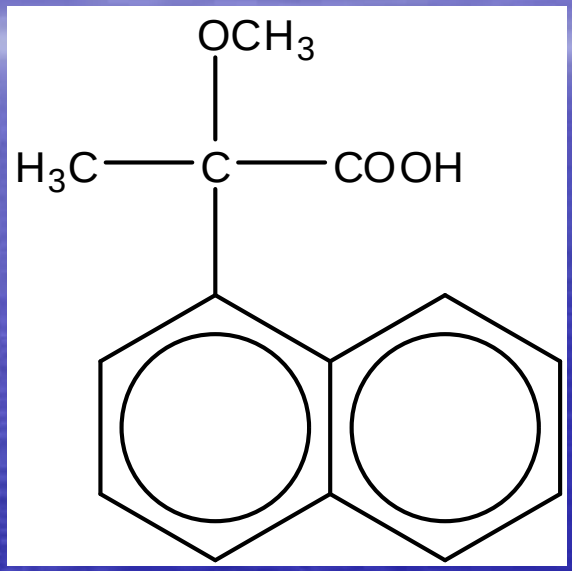
This reversal in shifts can be used to confirm the stereochemical assignment

2-AMA/9-AMA – Linear vs cyclic secondary carbinols





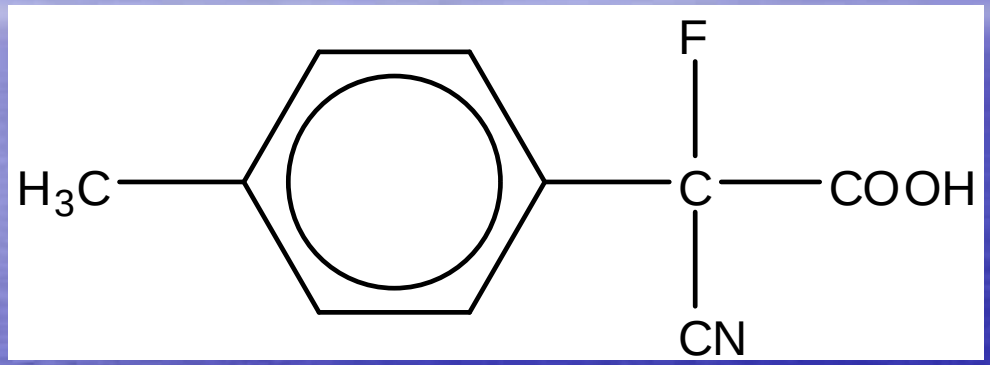
MαNP (secondary alcohols)



-$\Delta\delta^{RS}$ about 4-times greater than with MTPA

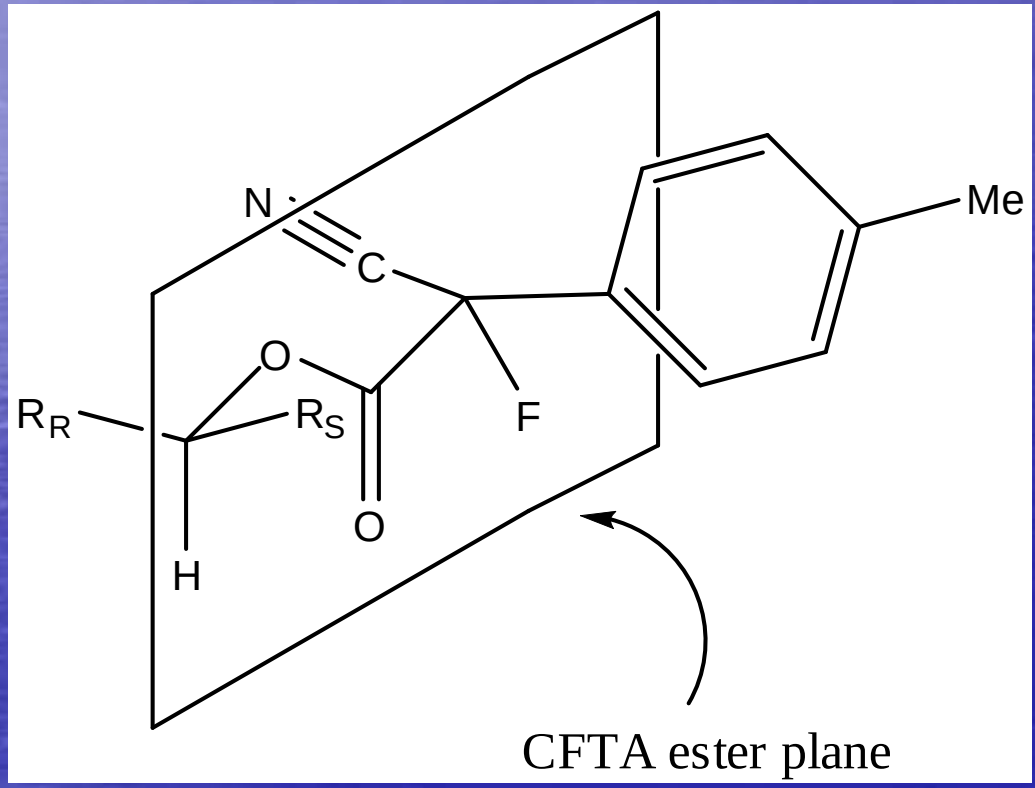
-Less prone to racemization with methyl group on chiral carbon

CFTA (secondary alcohols)



- The $\Delta\delta^{RS}$ values are typically 2-times greater than MTPA
- Much faster reaction than MTPA with hindered compounds
- ^{1}H and ^{19}F NMR can be used

CFTA - Conformational Preference
syn-periplanar arrangement



Secondary Diols and Polyols

- If groups are far enough apart, can determine the configuration of each group independently
- If groups are close together, bound reagent may influence the shielding or deshielding at more than one site

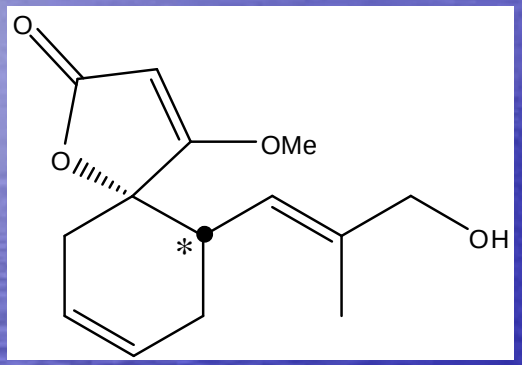
MPA for Diols

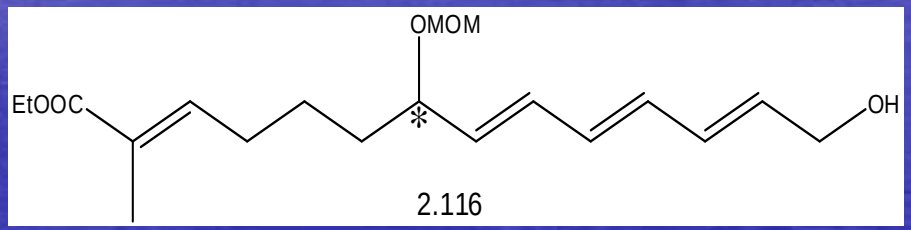
- Analysis of (*syn* and *anti*):
  - 1,2-
  - 1,3-
  - 1,4-
  - 1,5-diols with known configurations

- Observe reproducible trends that can be applied to compounds with unknown configurations

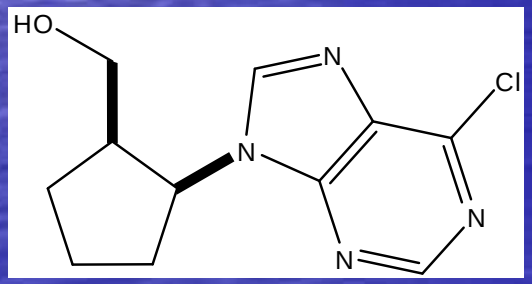
Primary Alcohols

- MTPA – C_2 chiral
- CFTA

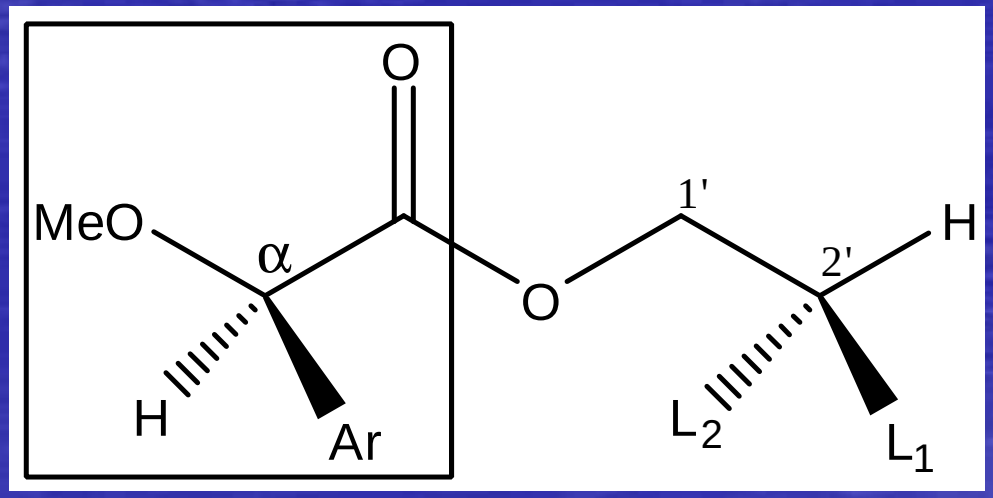




- 9-AMA



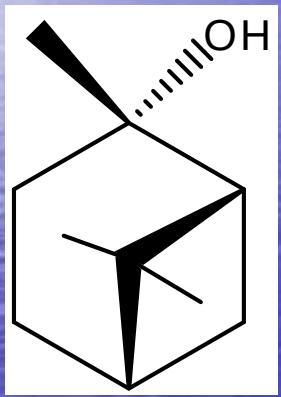
MPA - Unreliable

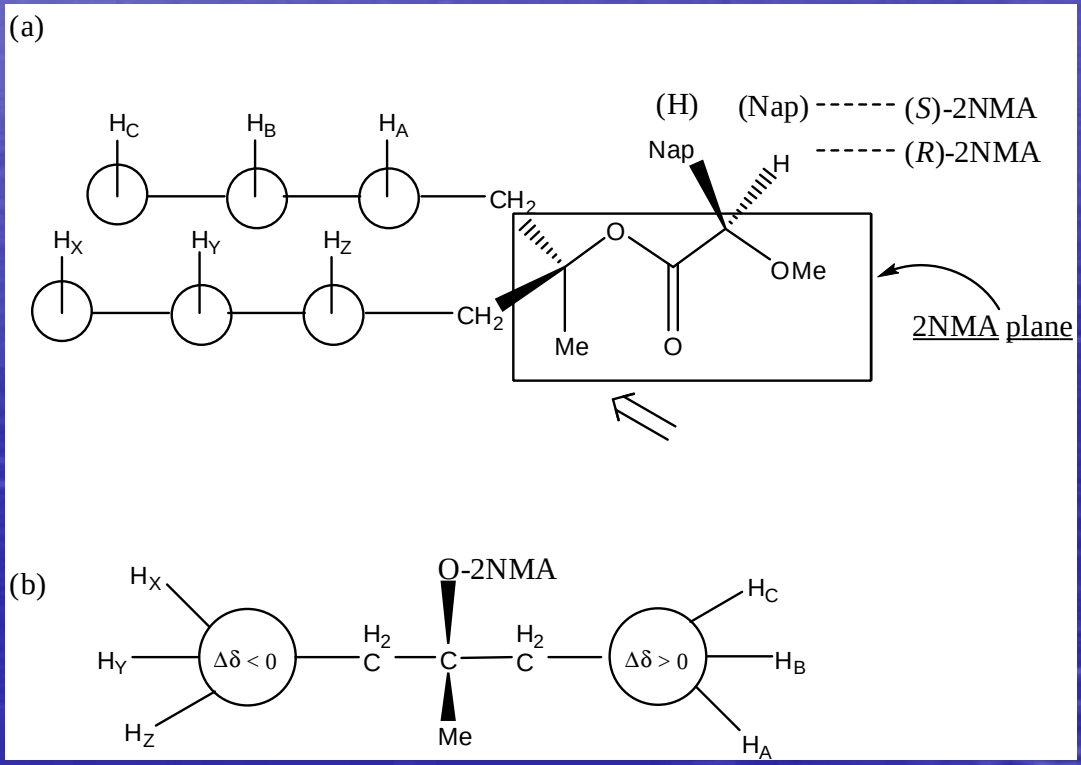


Tertiary Alcohols

2-NMA

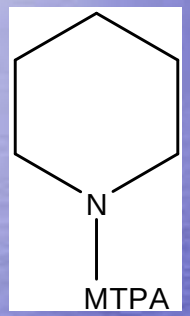
MTPA

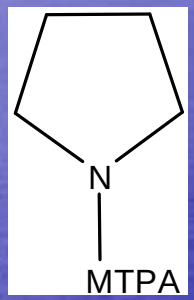


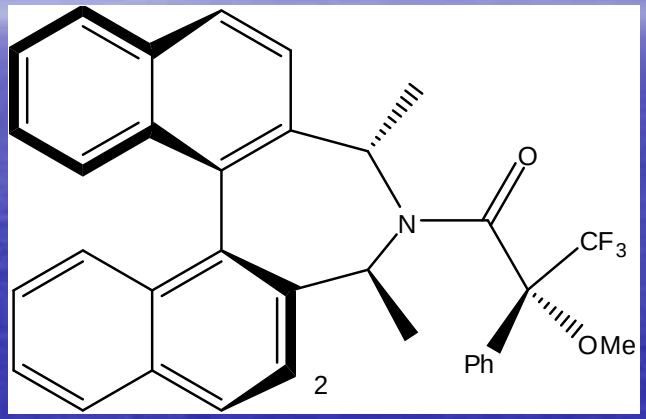


Secondary Amines

- MTPA





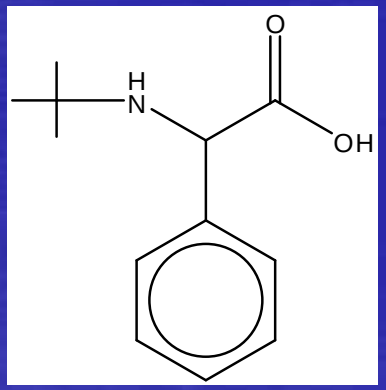


- H_2 had a $\Delta\delta^{RS}$ of 2.44 ppm!
- Values so large only need one MTPA derivative (use (*R*)-acid chloride since more reactive than (*S*)-acid chloride)

Primary Amines – α-substituted

- MTPA gives larger $\Delta\delta^{RS}$ values than MPA or 9-AMA - MTPA amides have greater preference for the *sp* conformer than observed with esters.

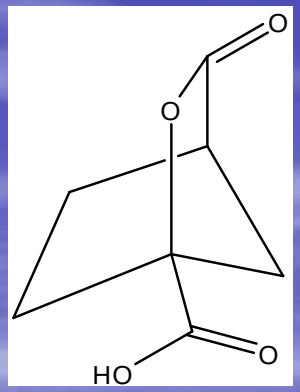
- BPG – preference for *ap* conformer – typical $\Delta\delta^{RS}$ values are 2- to 3-times larger than with MTPA



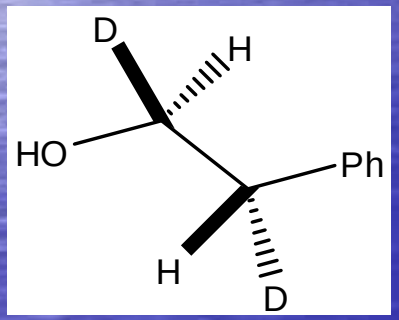
Aryl Methoxy Reagents - Summary

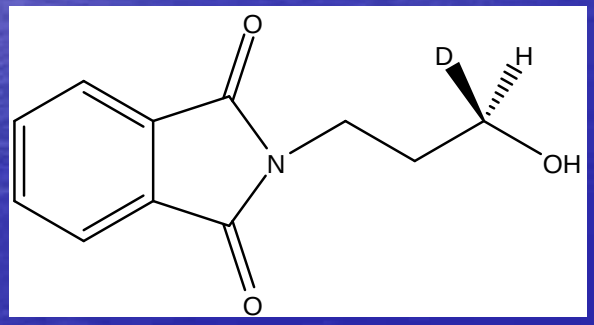
- Want larger $\Delta\delta^{RS}$ values – either through high conformational preference or larger aromatic ring (shielding)
- Values should all be positive for one substituent (L_1) and negative for the other (L_2)
- Need resonances in both substituents

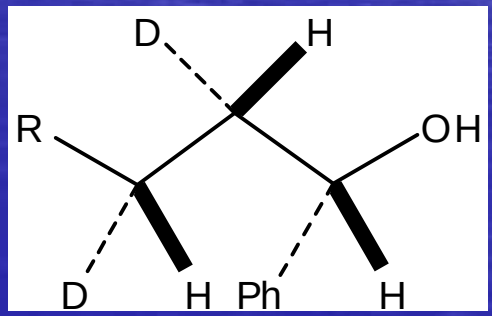
Camphanic Acid



- *pro*-(*R*) and *pro*-(*S*) positions of α-deuterated primary and secondary alcohols

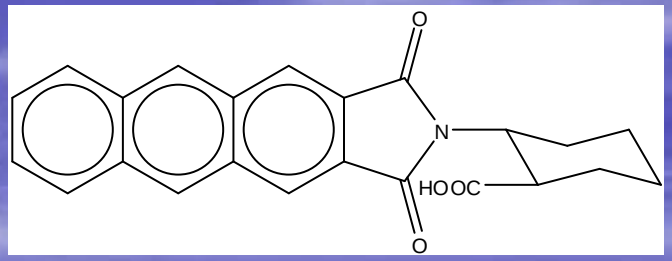




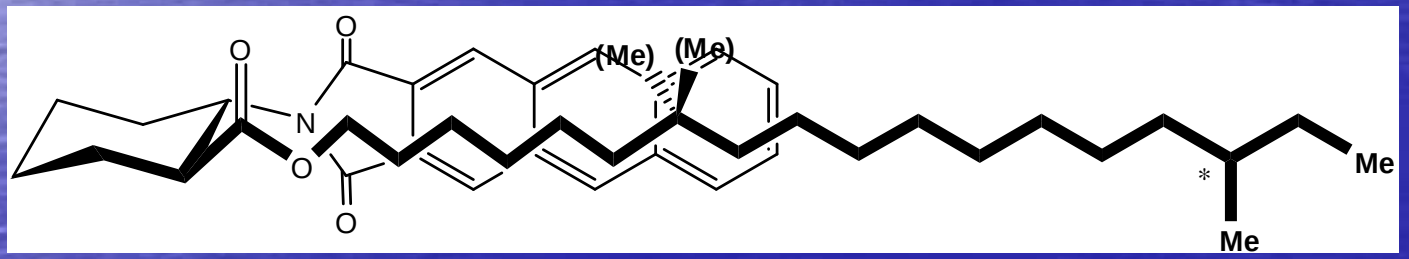


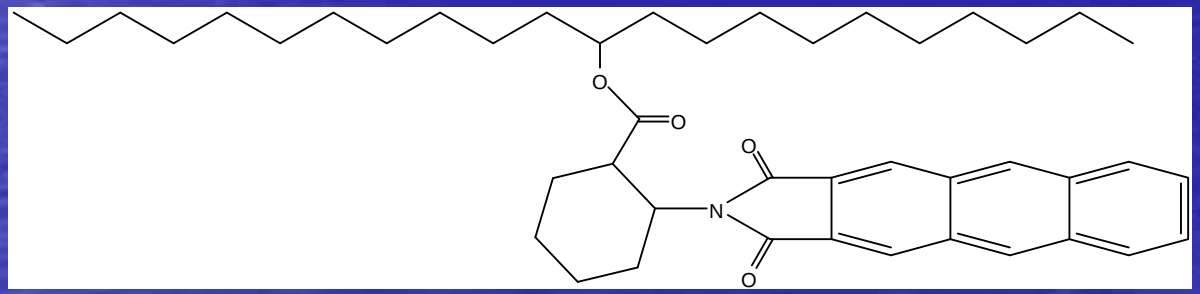
- Primary amines as well

2-(2,3-Anthracenedicarboximido)-cyclohexane carboxylic acid

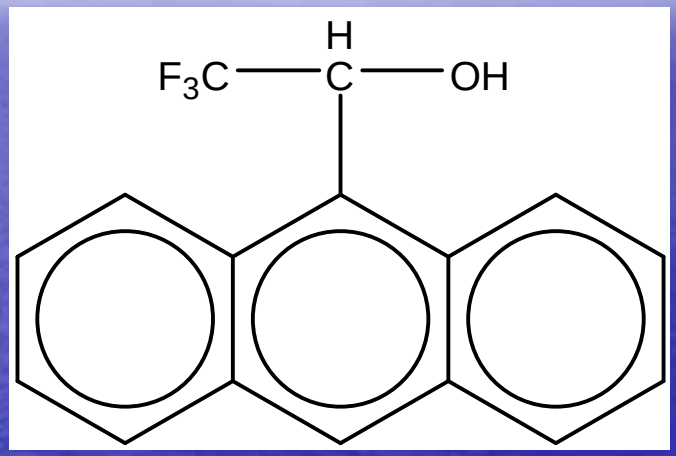


Analysis of primary and secondary alcohols – especially effective for compounds with remotely disposed chiral centers





2,2,2-Trifluoro-1-(9-anthryl)ethanol (TFAE) (Pirkle's Alcohol)



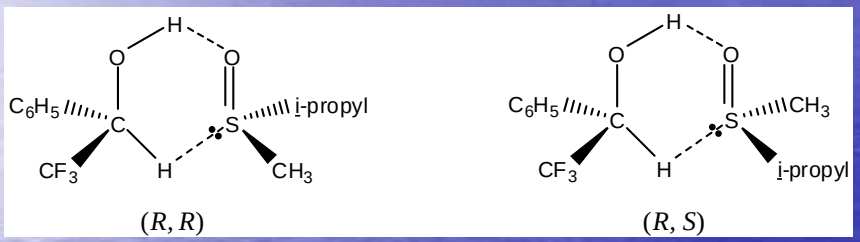
Versatile chiral solvating agent

-Can determine optical purity

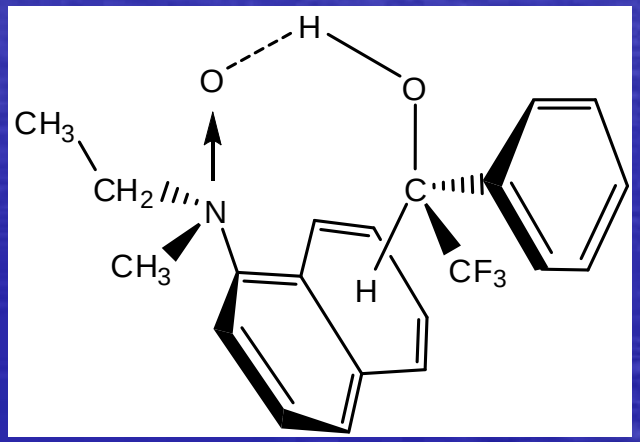
-Can assign absolute configurations for certain classes of compounds

Absolute Configurations - TFAE

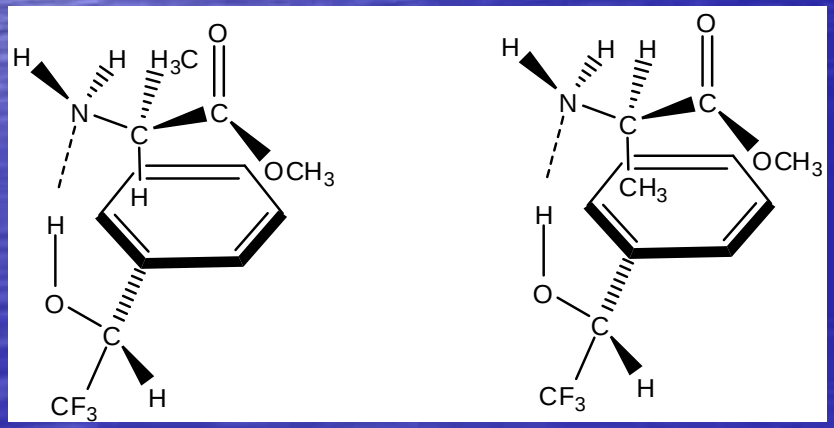
Sulfoxides



N-oxides



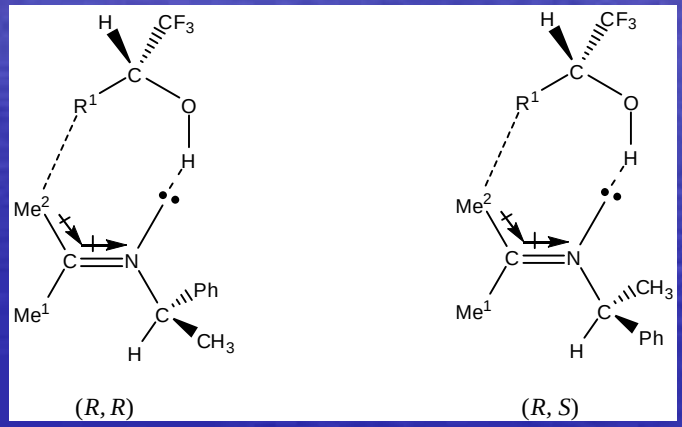
Amino Acids



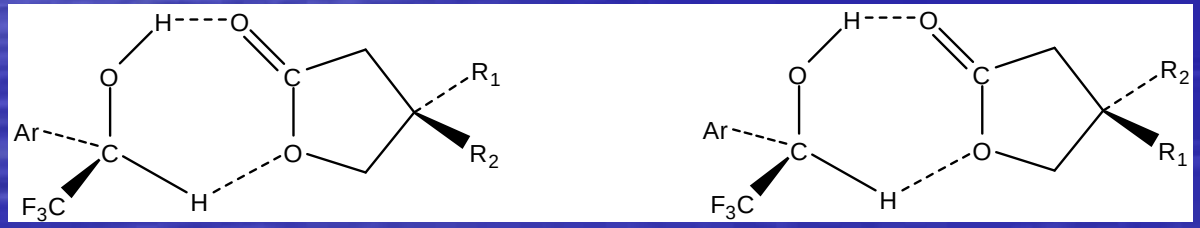
Absolute Configurations - TFAE

Oxaziridines

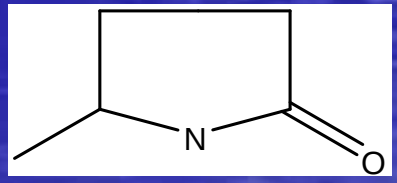
Imines



Lactones

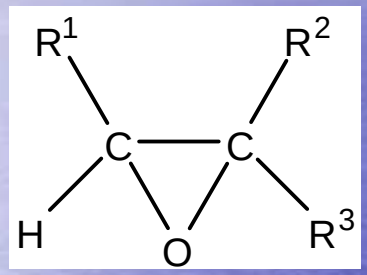


Lactams

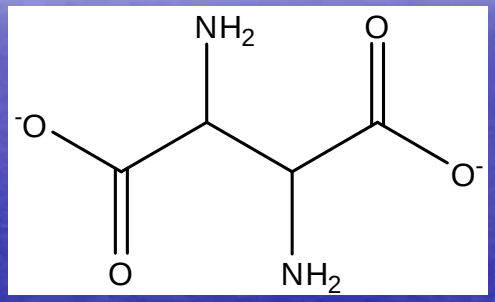


TFAE – Enantiomeric Purity

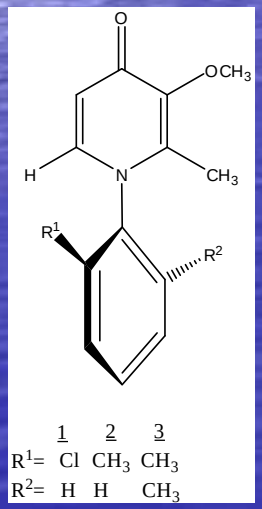
Epoxides



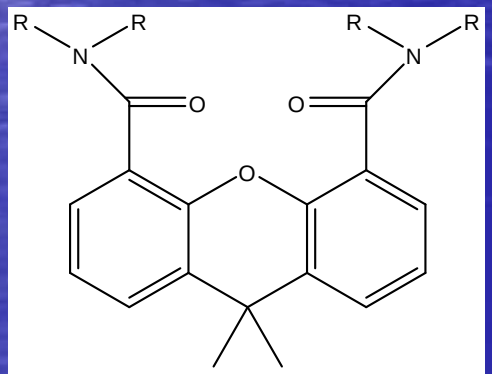
2,3-diamino succinate – methine signals for *meso* versus *dl*-isomers



Axial Chiral Compounds



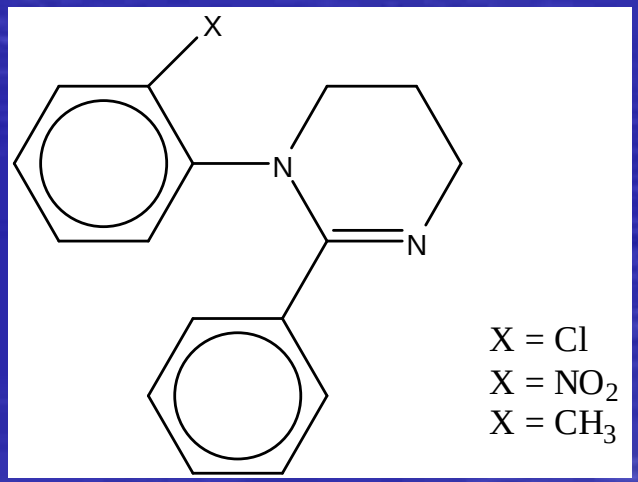
	1	2	3
R^1=	Cl	CH_3	CH_3
R^2=	H	H	CH_3



a (R = *i*-Pr)

b (R = Et)

Slow Rotation



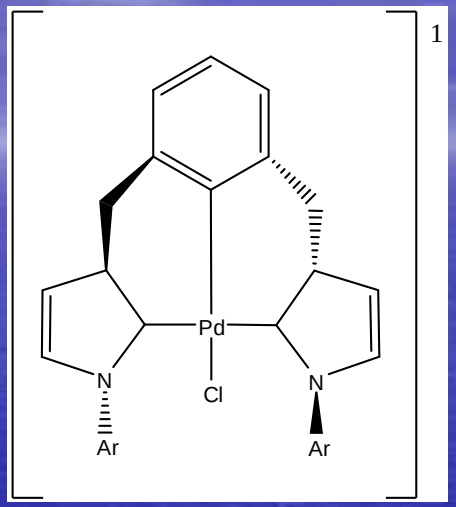
X = Cl

X = NO_2

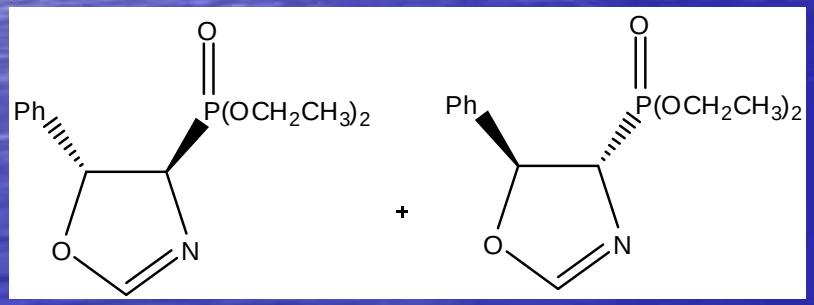
X = CH_3

TFAE – Enantiomeric Purity

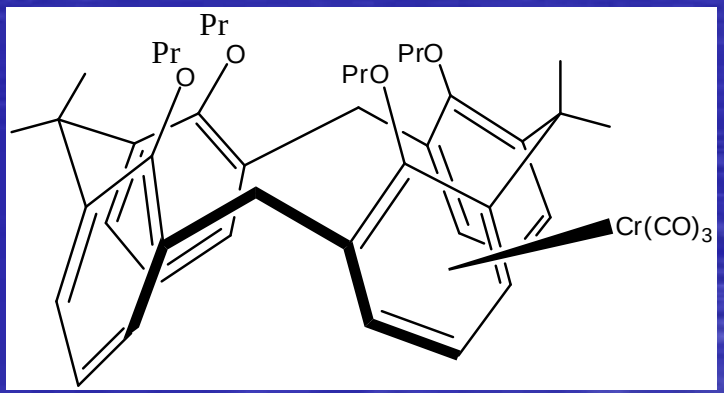
Metal Complexes



Phosphine Oxides

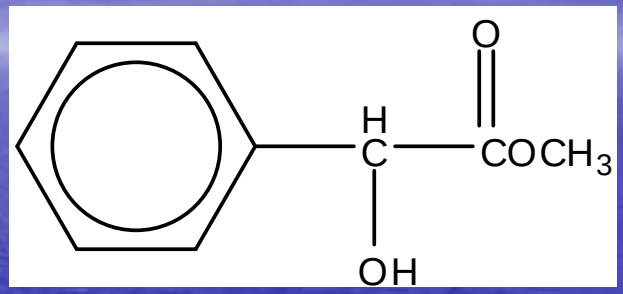


Calixarenes

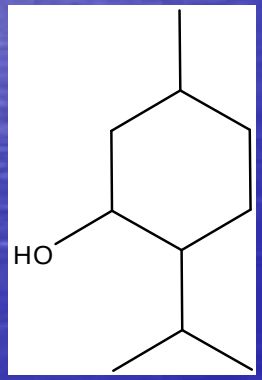


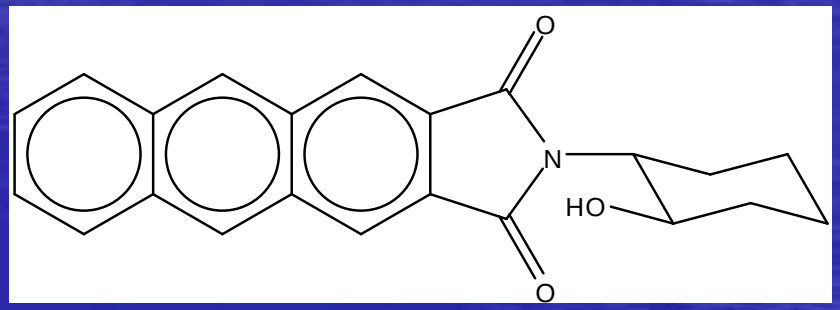
Alcohols as CDAs for Carboxylic Acids

- Methyl mandelate



- Menthol



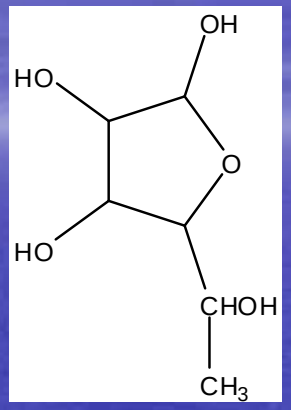


- 2-(2,3-anthracenedicarboximido)-1-cyclohexanol

Glycosidation Shifts

- React secondary alcohol with D-glucose or D-mannose
- Pronounced differences in the ^{13}C NMR spectrum that correlate with absolute configuration – see trends in both sugar and alcohol resonances
- Also see differences in the ^{1}H NMR spectrum of secondary alcohols with tetra-*O*-acetylglucose

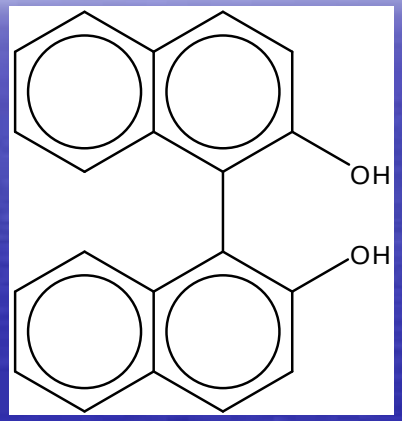
β-D- and β-L-Fucofuranoside and Arabinofuranoside

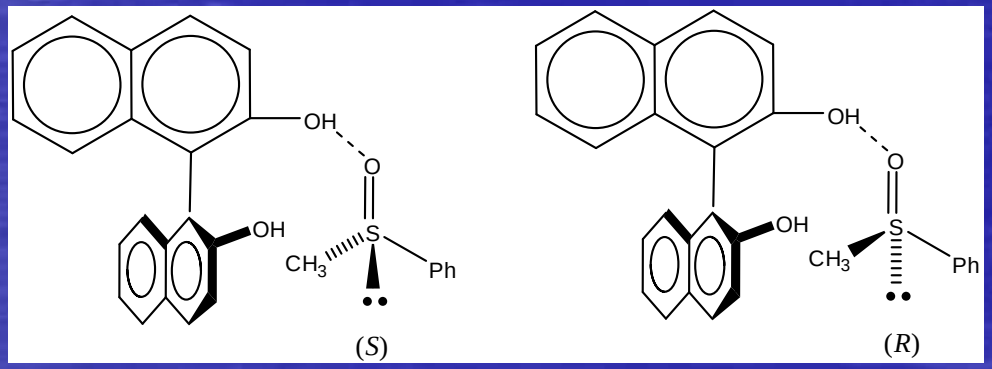


- Use tetraacetate derivative of sugar (arabino easier to prepare)
- React with secondary or tertiary alcohol
- Also works with 1,2-glycols
- Alkaline hydrolysis of acetate groups
- See differences in the ^{1}H and ^{13}C spectra of product that correlate with absolute configuration

2,2'-Dihydroxy-1,1'binaphthalene (BINOL)

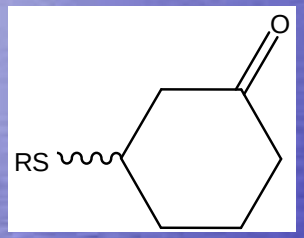
- Potential chiral solvating agent for several classes of substrates including alcohols, sulfoxides, selenoxides, amines, ketones, amides, and amino alcohols

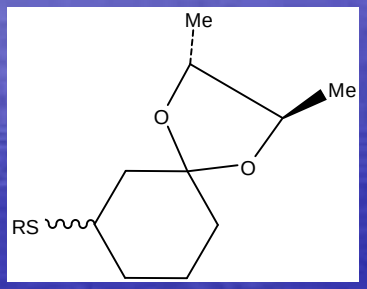




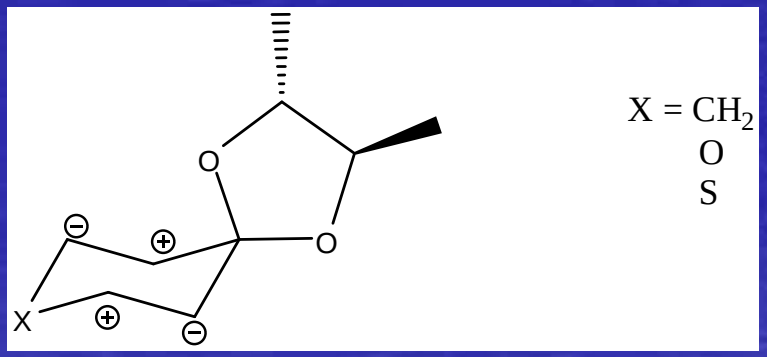
Butane-2,3-diol/Butane-2,3-thiol

- Chiral derivatizing agent for the analysis of chiral ketones – produce diastereomeric ketals

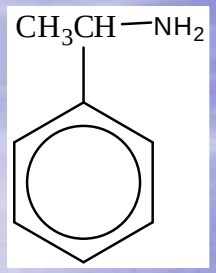


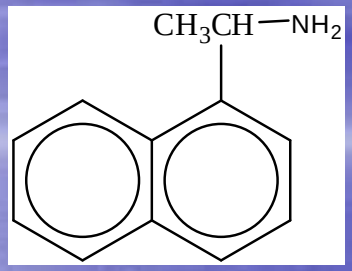


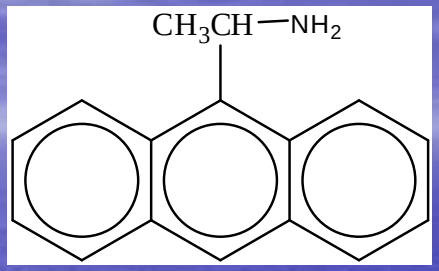
- For cyclohexanones in the chair conformation, the ^{13}C shifts correlate with absolute stereochemistry



PEA, NEA and AEA



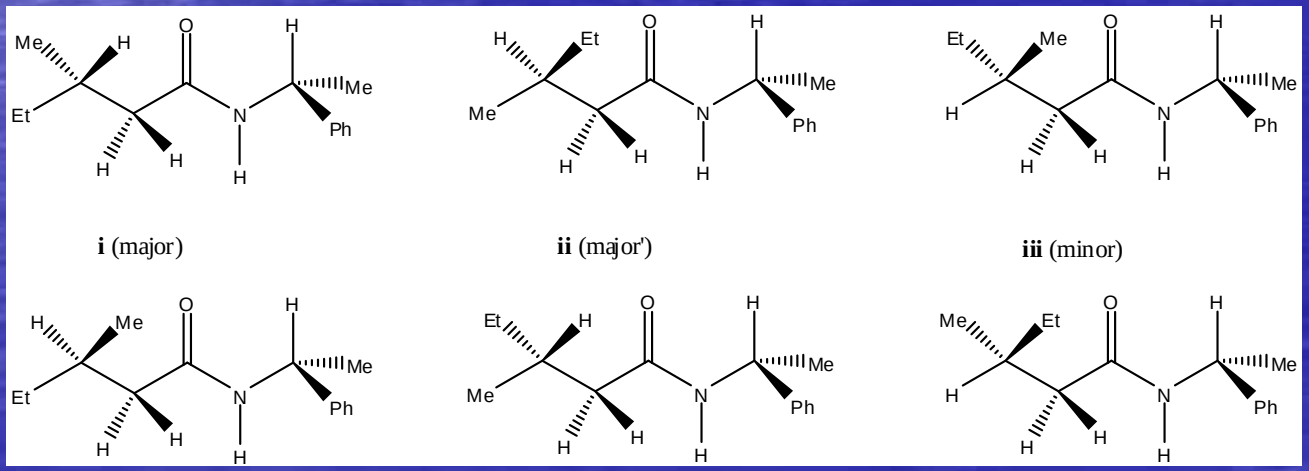




Useful with carboxylic acids

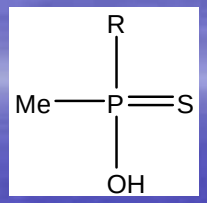
-chiral solvating agent – formation of diastereomeric salts

-chiral derivatizing agent – formation of amides – can assign absolute stereochemistry with certain compounds

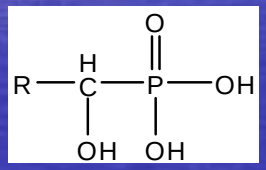


PEA, NEA and AEA

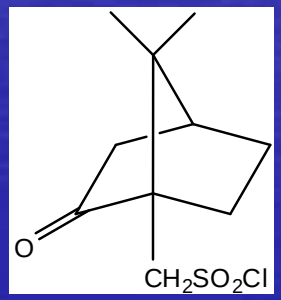
- Phosphorus thioacids



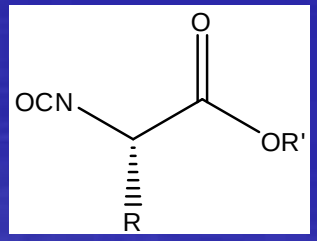
- Phosphonic acids



- Sulfonyl chlorides



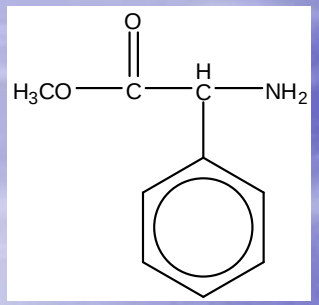
- Isocyanates



PEA, NEA and AEA - Ketones

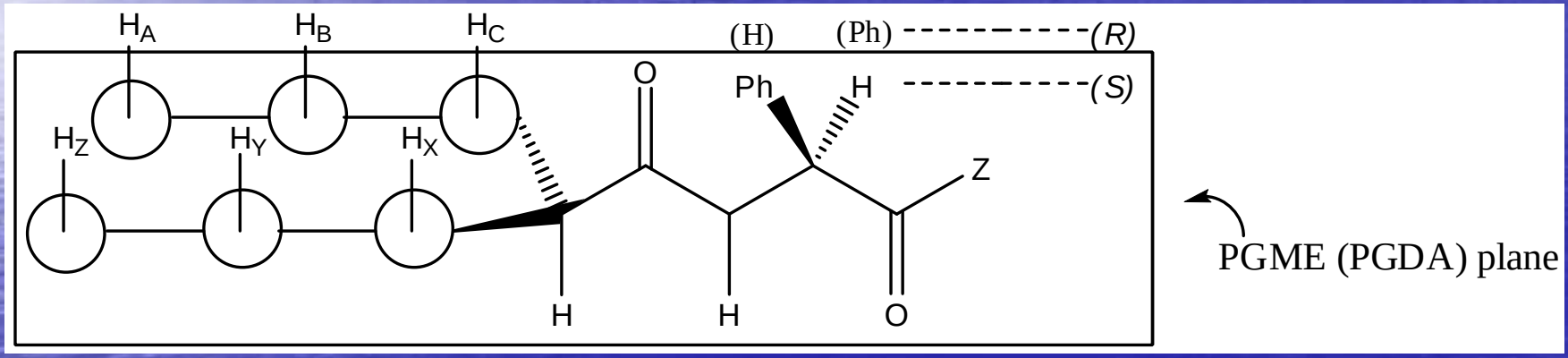
- Method 1
  - Convert to acid oxime using NH_2OCH_2COOH
  - Add NEA to form salt – see discrimination
- Method 2
  - Reductively aminate the enone with PEA perchlorate – see discrimination in products

Phenylglycine methyl ester and dimethyl amide (PGME)

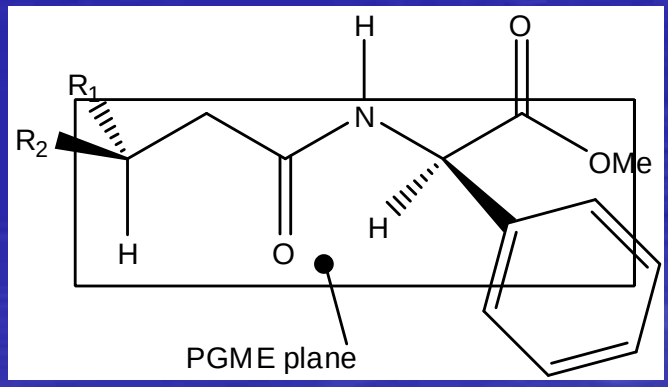


Absolute configuration of carboxylic acids – $\Delta\delta^{RS}$ values

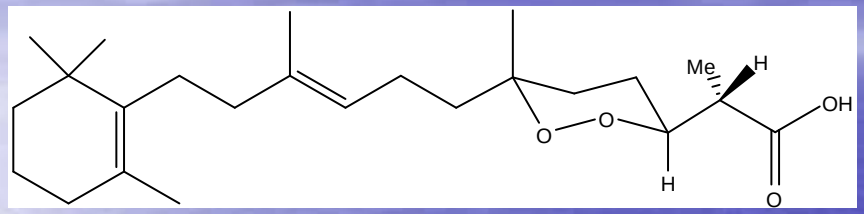
α-Substituted

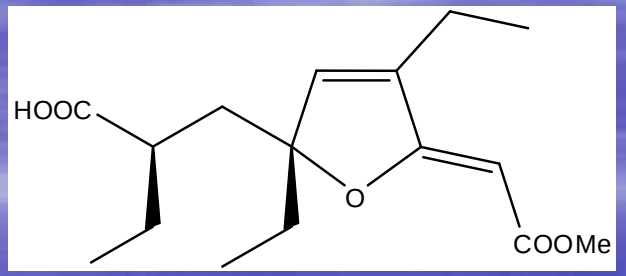


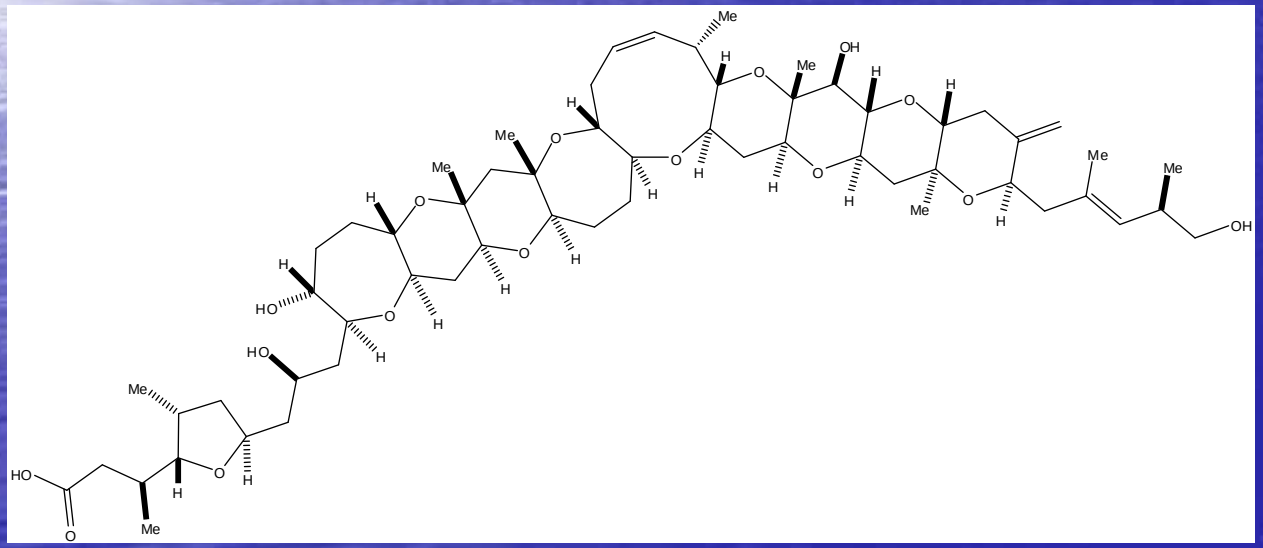
β,β-substituted acids

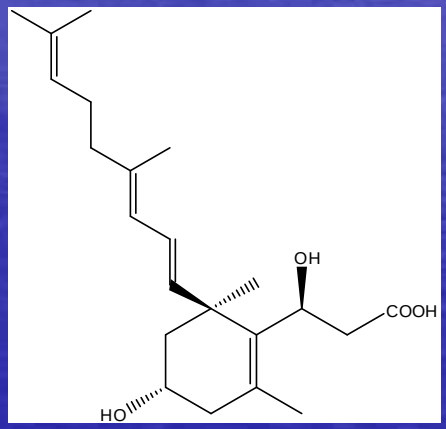


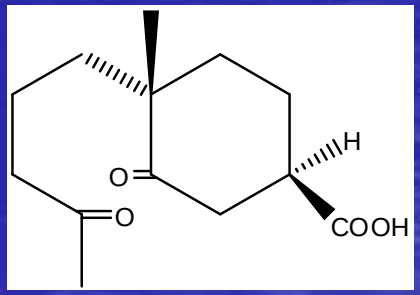
PGME - examples



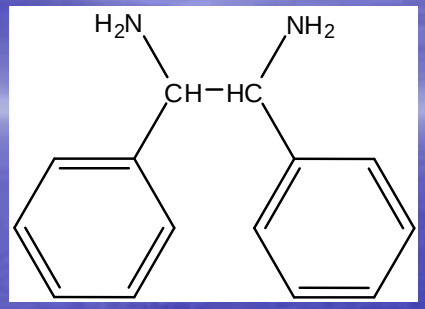




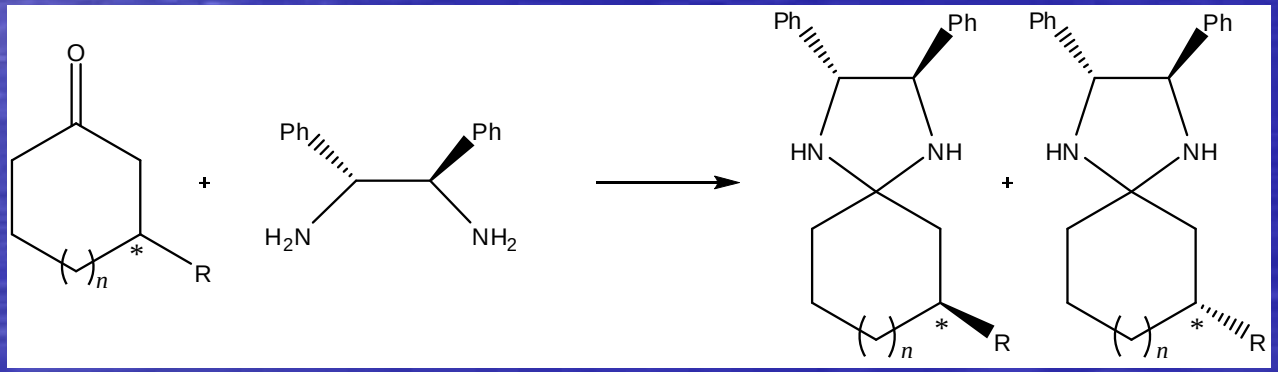




1,2-Diphenyl-1,2-diaminoethane



3-substituted cyclohexanones and cyclopentanones
-forms the corresponding aminal
-can determine enantiomeric purity

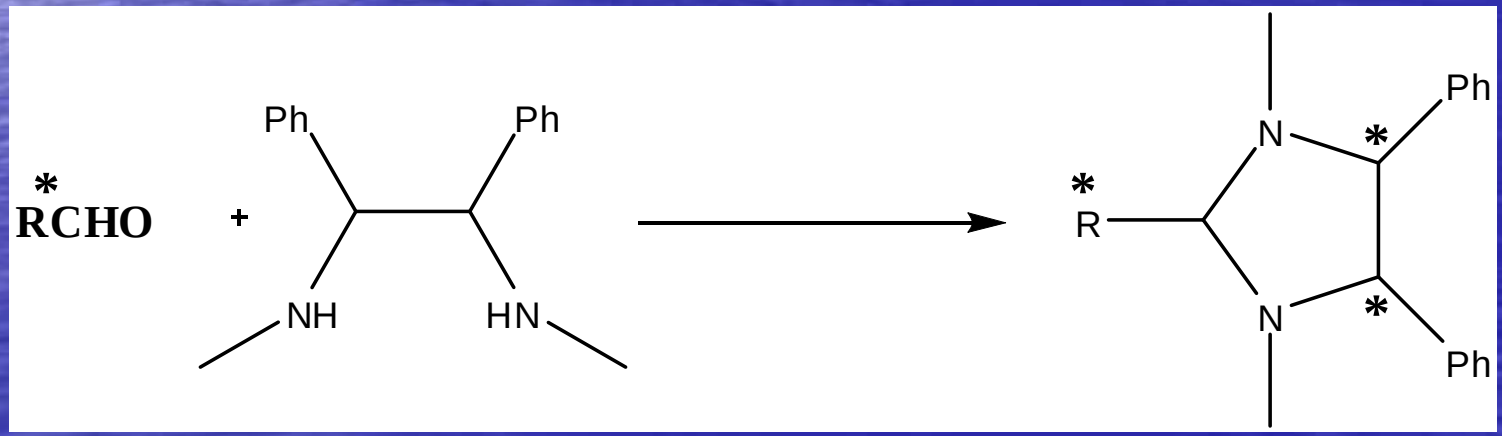


N,N-Substituted 1,2-diphenyl-1,2-diaminoethane

Reacts with Aldehydes

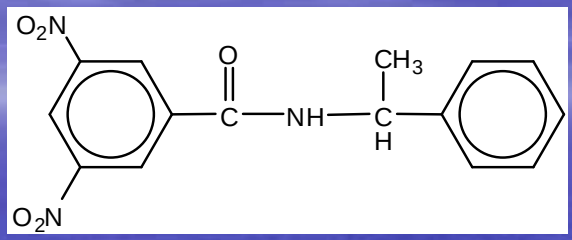
-forms the corresponding imidazolidine

-can be used to determine enantiomeric purity

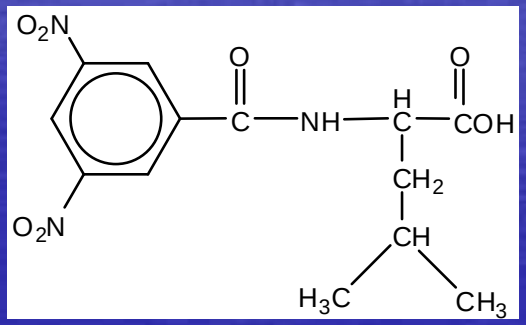


Amides as Chiral Solvating Agents
Soluble Pirkle LC Phases

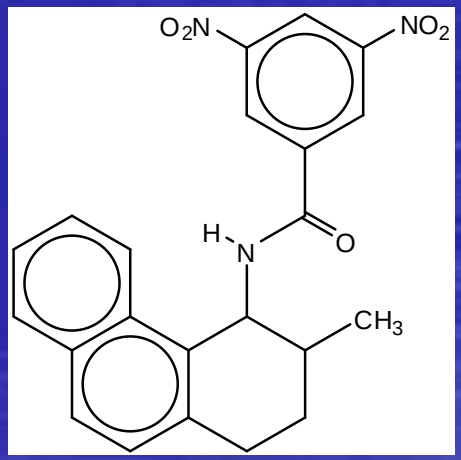
N-(3,5-Dinitrobenzoyl)-
1-phenylethylamine (DNB-PEA)



N-(3,5-Dinitrobenzoyl)-L-leucine
(DNB-Leu)



N-(3,5-Dinitrobenzoyl)-4-amino-
3-methyl-1,2,3,4-tetrahydrophen-
Anthrene (Whelk-O-1)



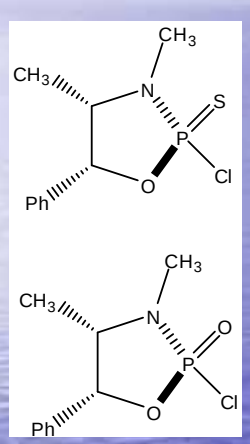
Phosphorus-based Reagents

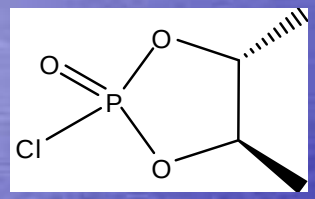
- P(V) reagents (P=O or P=S) group
- P(III) reagents

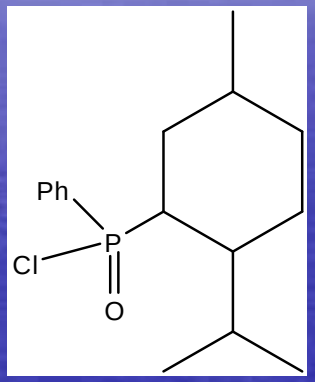
- P(V) reagents are more stable than P(III) reagents but usually have smaller enantiomeric discrimination

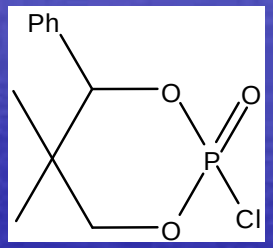
- ^{31}P signal usually monitored – splits into two singlets for the two diastereomers for derivatizing agents

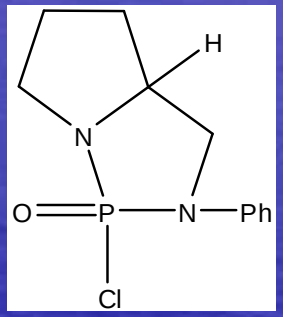
P(V) Reagents - Examples







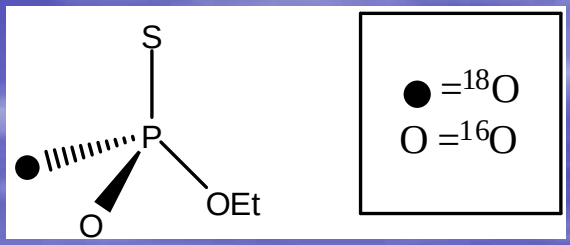


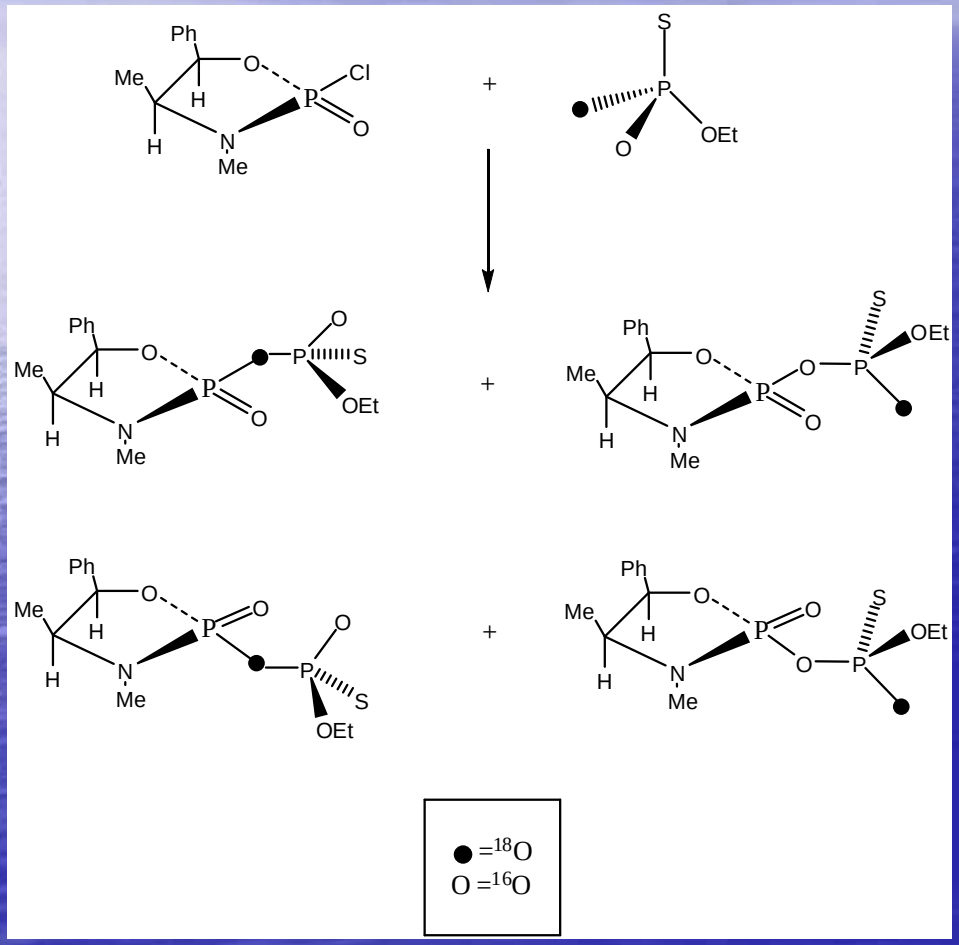


-Alcohols and amines react at the chlorine atom

-Primarily used for determining enantiomeric purity

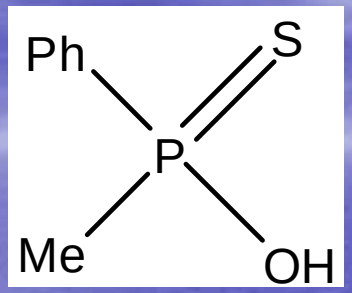
Configurational analysis of thiophosphate monoester that is chiral by virtue of different oxygen isotopes

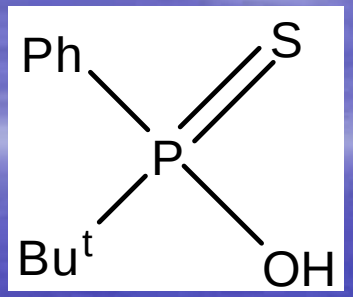


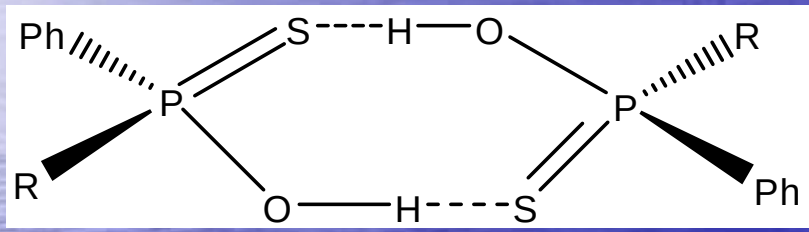


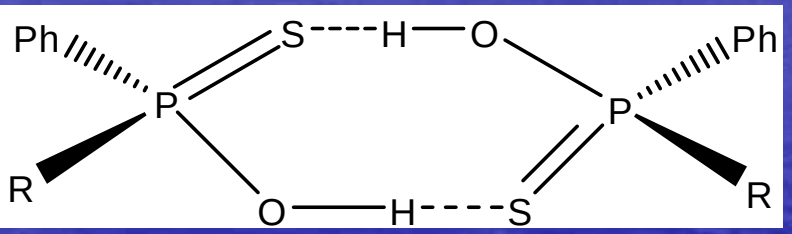
^{18}O and ^{16}O in the bridging position have different effects on the shift of the phosphorus resonance

Phosphinothioic Acids







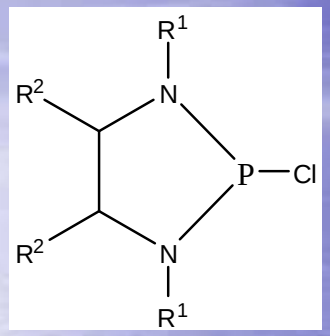


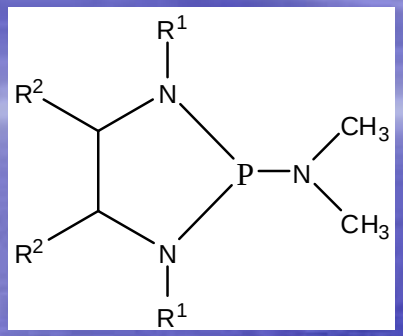
Effective chiral solvating agents for:

-Phosphine oxides
-Phosphonates
-Sulfoxides
-Amine oxides

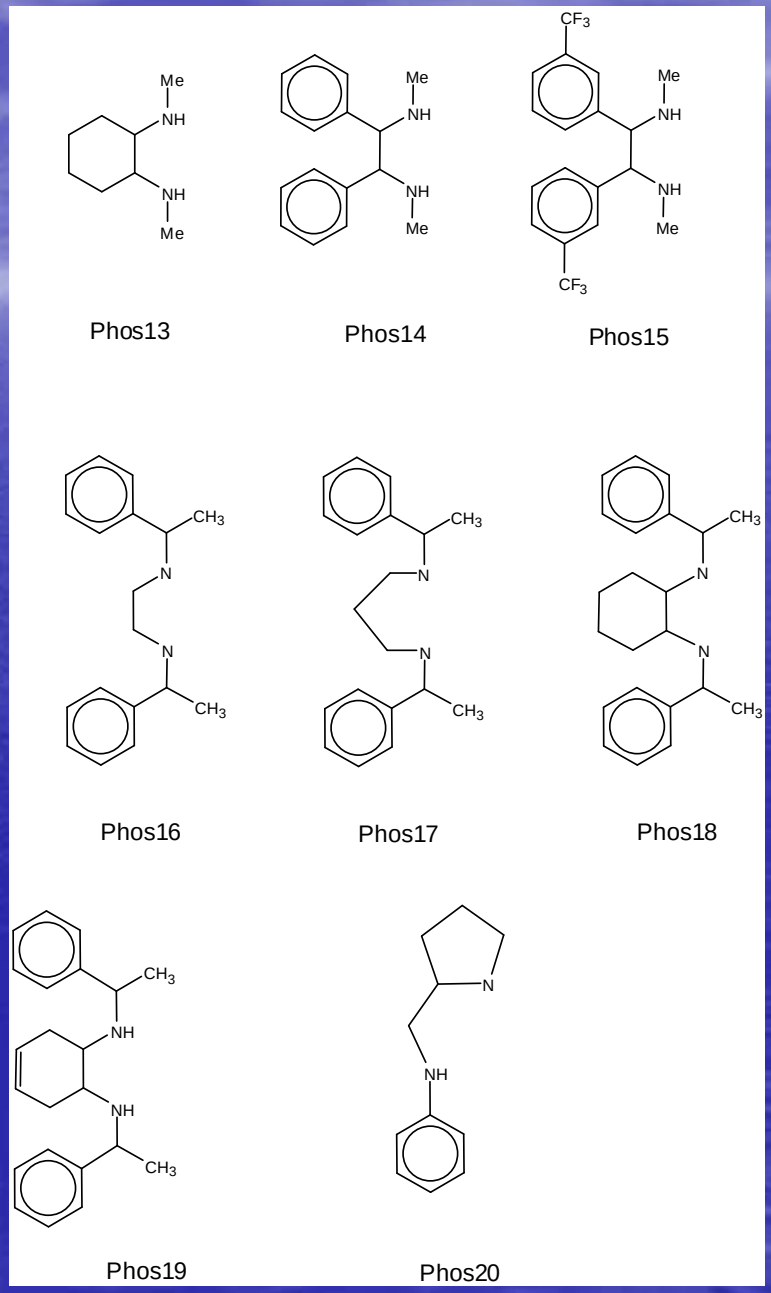
-Alcohols/Diols
-Amines
-Thiols
-Amino alcohols

P(III) Reagents

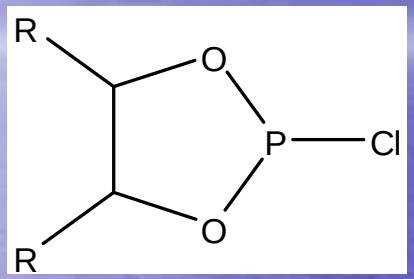




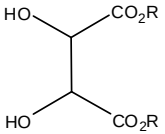
-Primary, secondary and tertiary alcohols
-Thiols
-Carboxylic acids
-α-hydroxyphosphonates



P(III) Reagents

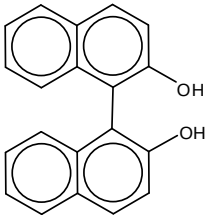


-Primary, secondary and tertiary alcohols
-Primary amines
-Carboxylic acids

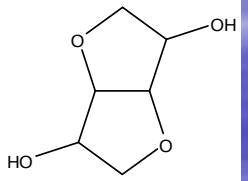


R = Et or *i*Pr

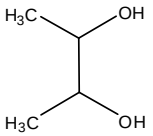
Phos21



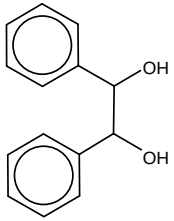
Phos22



Phos23



Phos24



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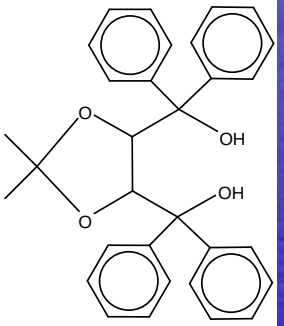
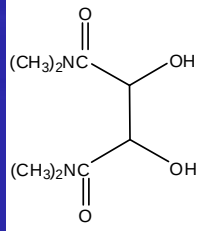
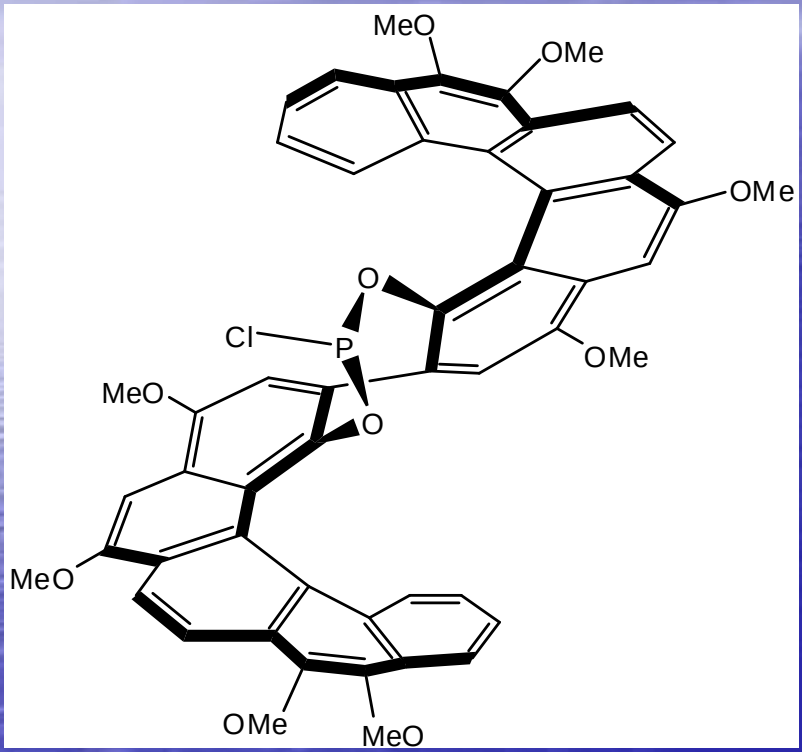


Phos26

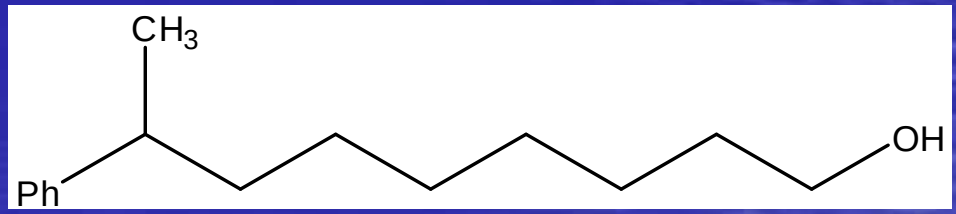


Phos27

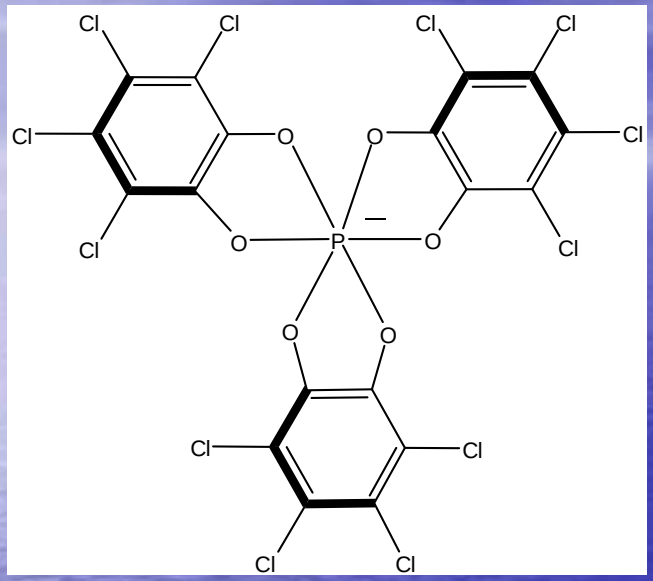
[5] HELOL Phosphite

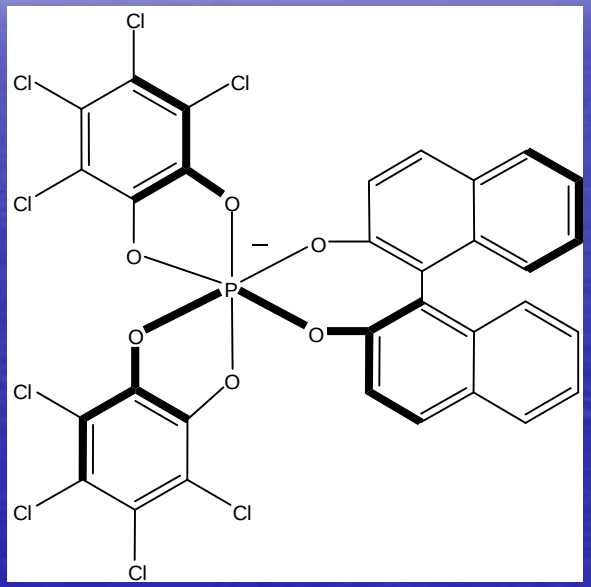


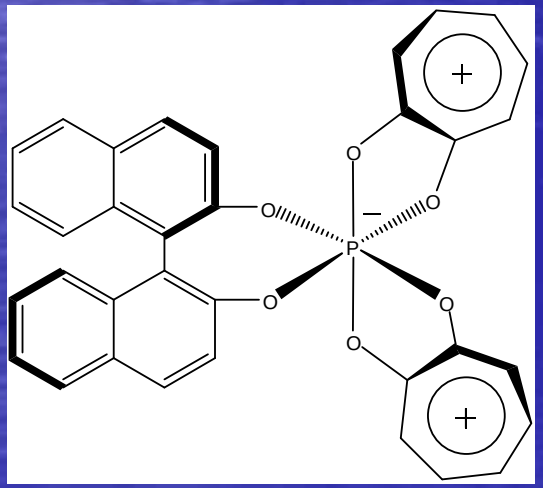
-Primary and secondary alcohols
-Phenols
-Amines
-Carboxylic acids after coupling to 2-aminophenol



TRISPHAT, BINPHAT, BINTROP

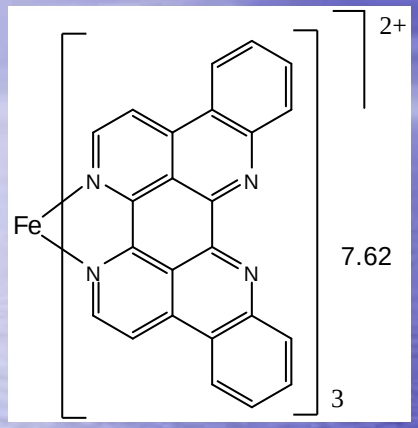


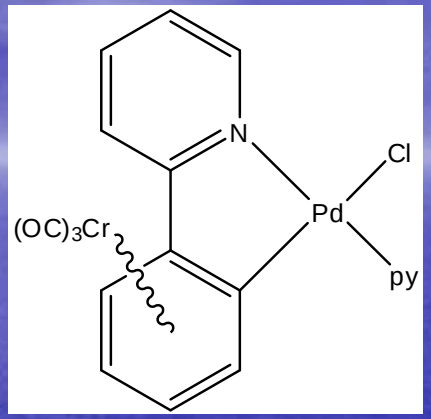


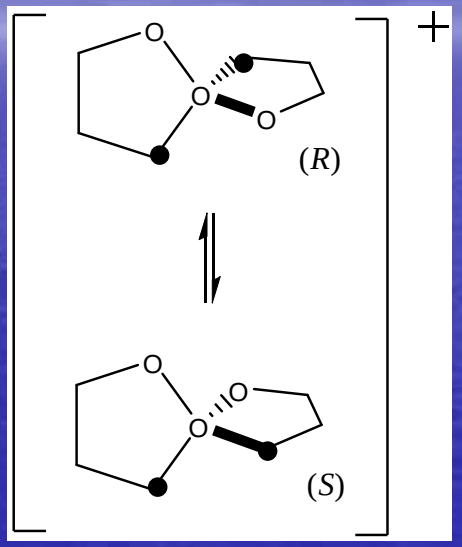


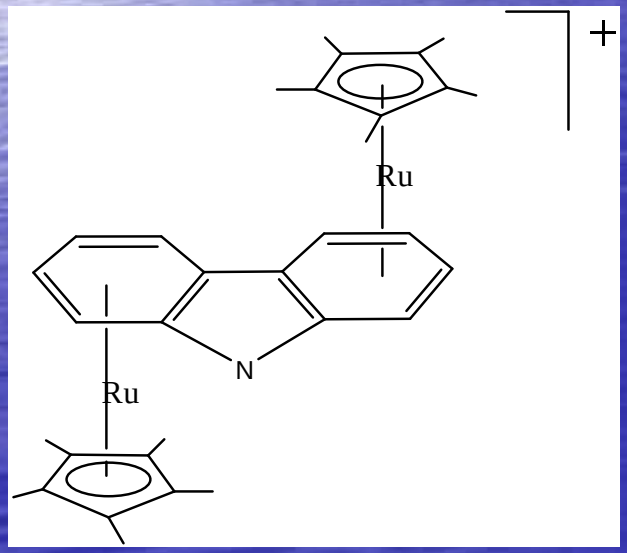
Useful for ionic compounds

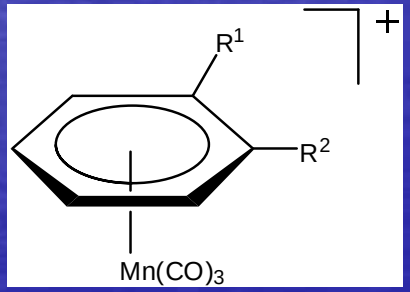
TRISPHAT – Metal Complexes

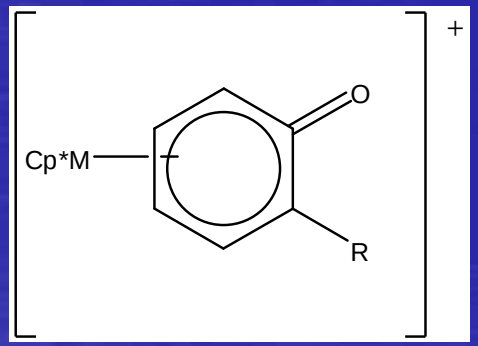


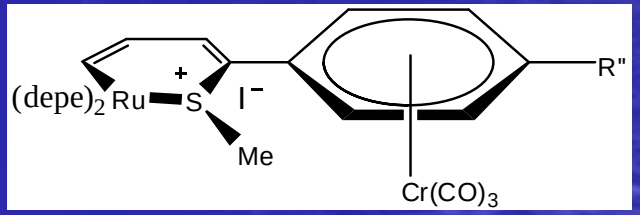




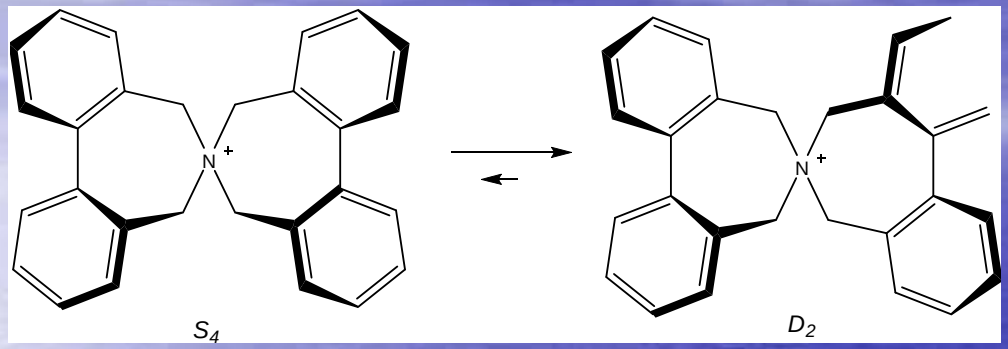


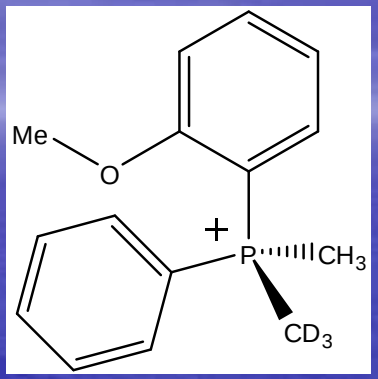


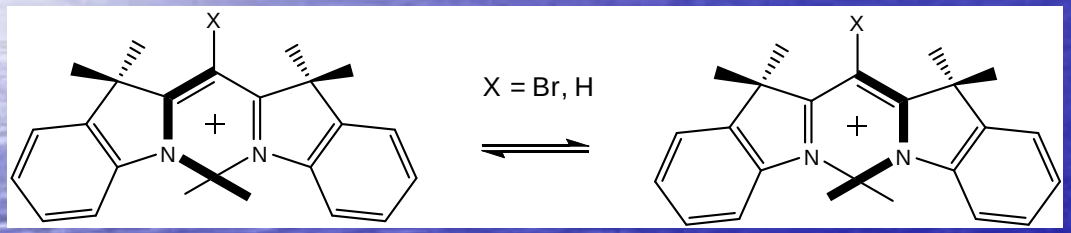


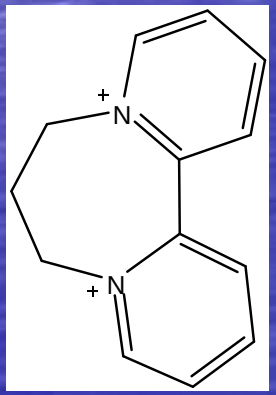


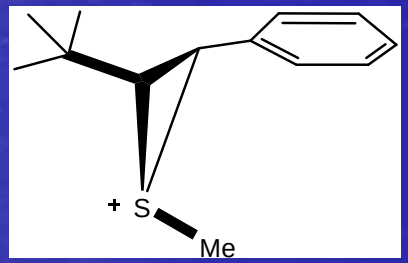
TRISPHAT, BINPHAT – Other Cations

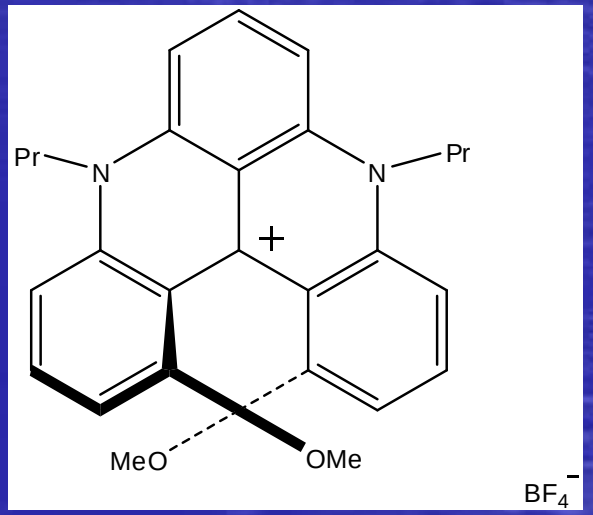




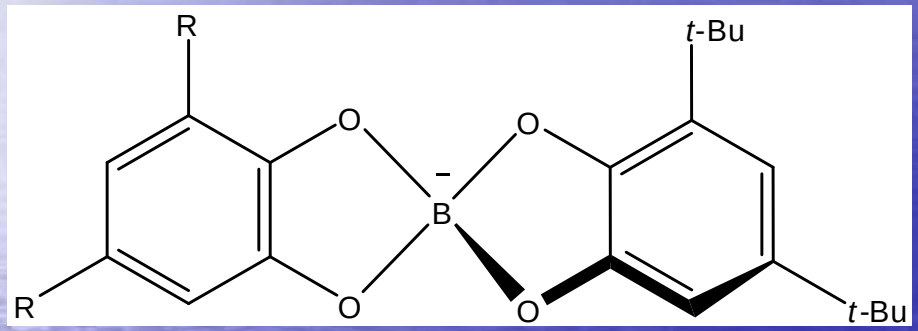


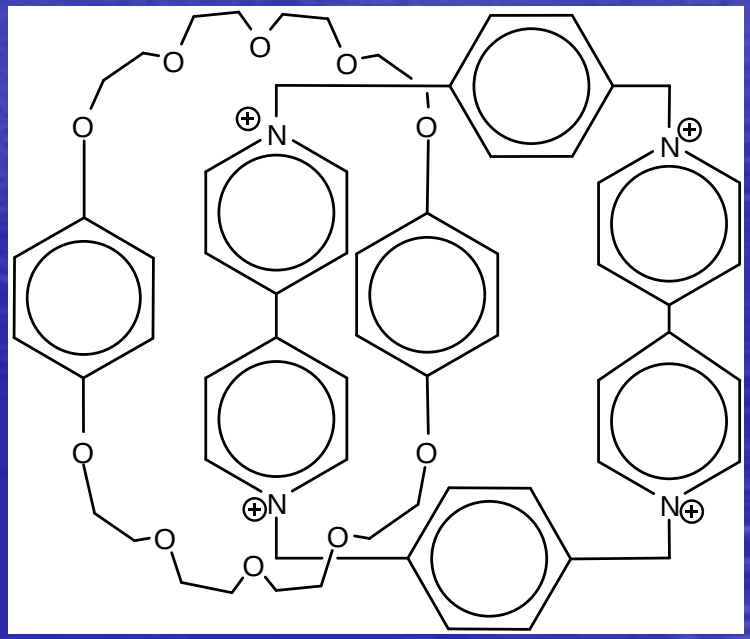






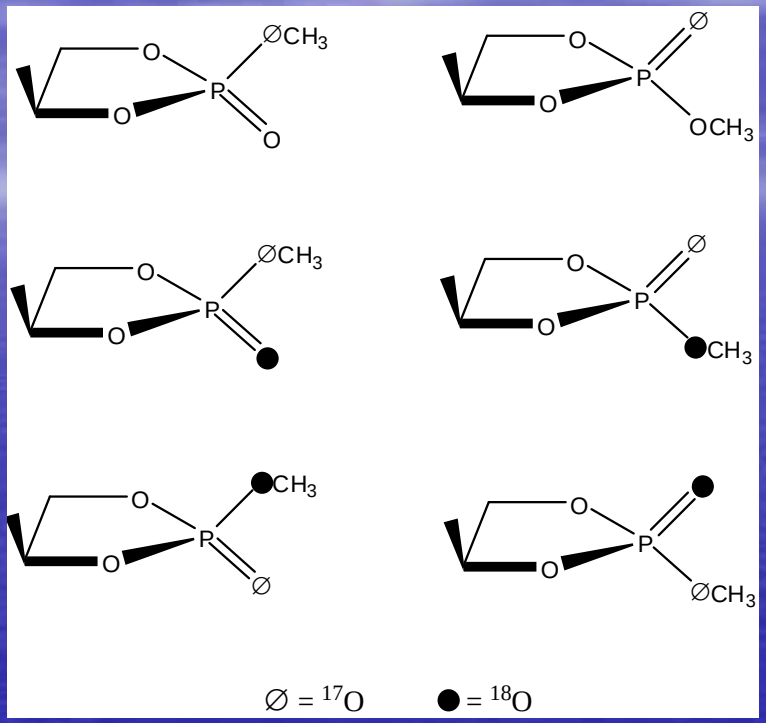
BINTROP
– Limited studies on anions



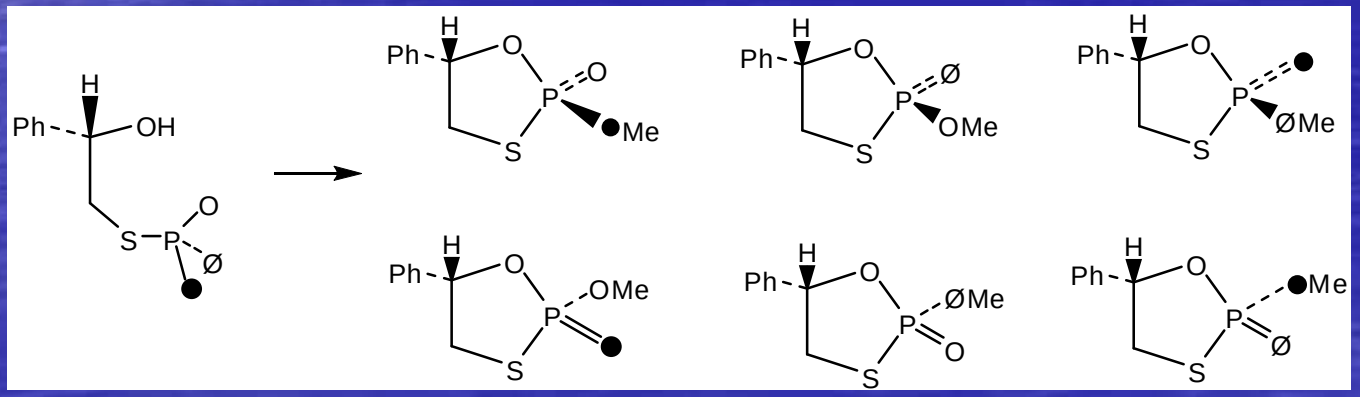


Configuration of Phosphates

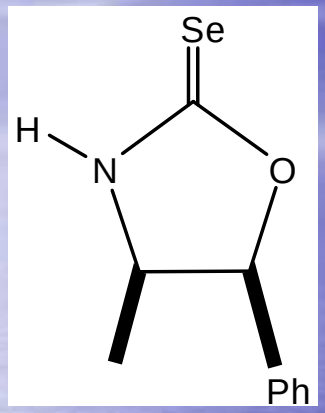
- React (cyclize) with propane-1,2-diol



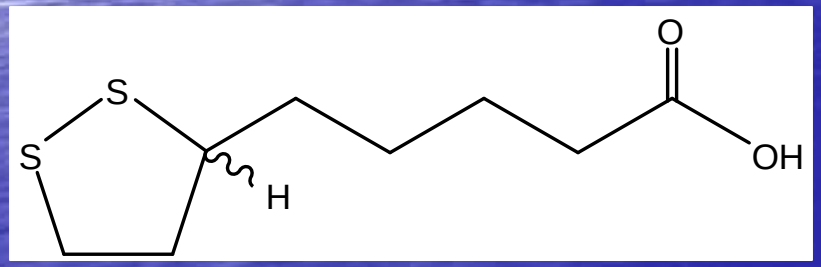
- React (cyclize) with (S)-2-iodo-1-phenylethanol

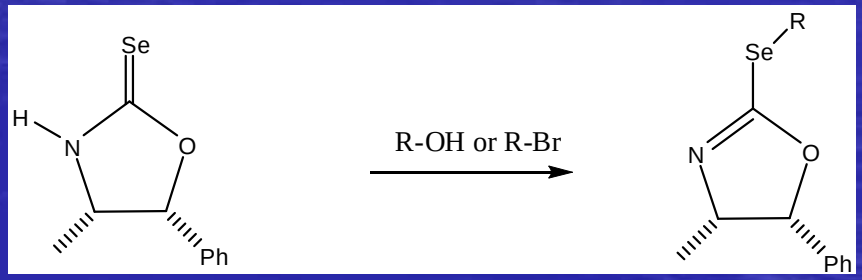


Selenium-containing Reagent
^{77}Se NMR



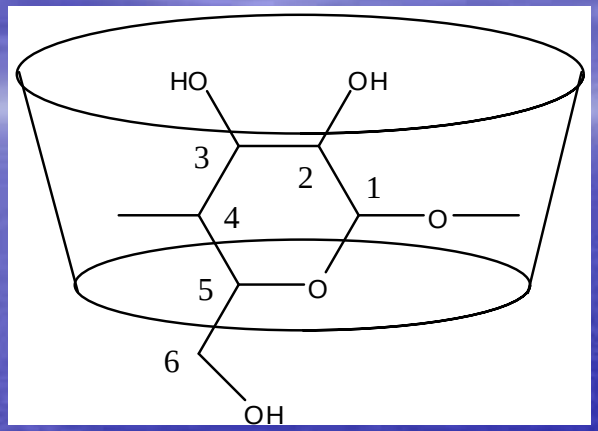
-Carboxylic acids – react at NH group
-Alcohols and alkyl halides react at selenium atom
-Amines with triphosgene react at the NH group





Effective for compounds with remotely disposed chiral centers – because of shift range of ^{77}Se NMR

α-, β- and γ-Cyclodextrins



Native – underivatized

-Water-soluble

-Effective for water-soluble substrates

-Determination of enantiomeric purity

-Substrates usually contain an aromatic ring (phenyl or bicyclic)

Cyclodextrins

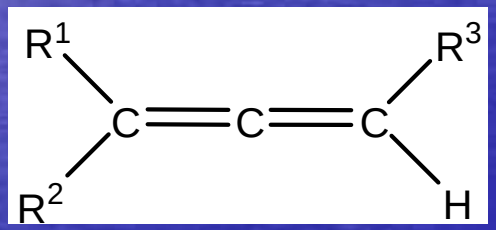
Permethylated cyclodextrins

-β-Derivative is more water-soluble than native β-CD

-Organic-soluble as well

-Broadly applicable for determining enantiomeric purity

-Especially useful for the analysis of allenes



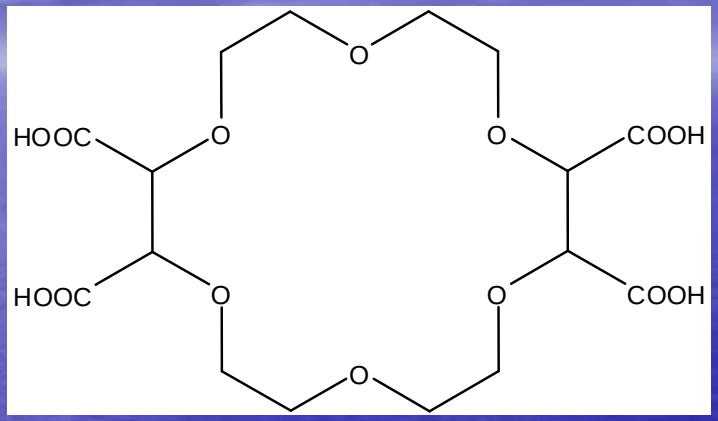
Carboxymethylated (-$CH_2CO_2^-$) cyclodextrins - Anionic

-Especially useful for organic cations

-Can add paramagnetic lanthanides – these associate at the carboxy group and cause shifts in the spectra that enhance the enantiomeric discrimination

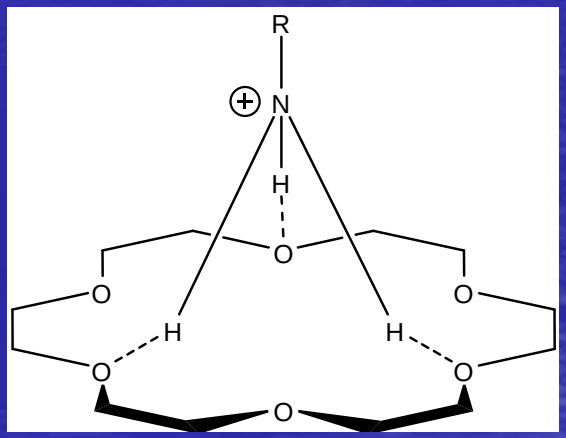
Crown Ethers

(18-Crown-6)-2,3,11,12-tetracarboxylic acid



Useful for primary amines

- -As hydrochloride salts
- -As neutral amines (neutralization reaction with crown ether)
- -In methanol, acetonitrile, or water (usually best in methanol)



Crown Ethers

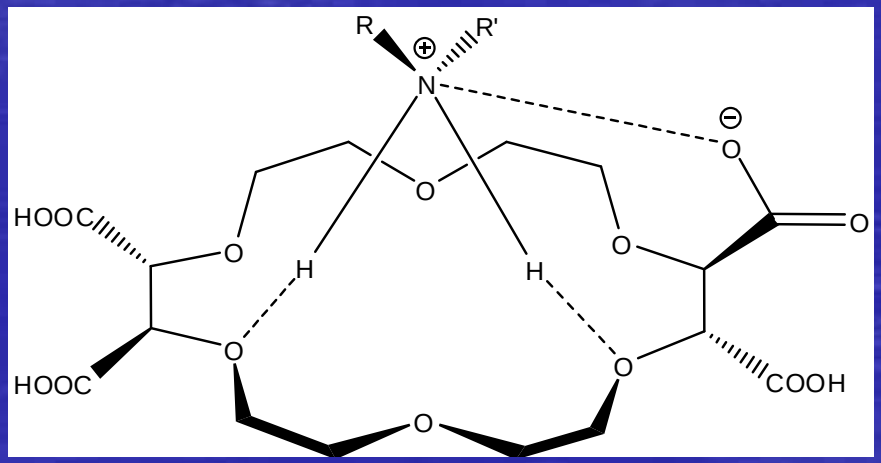
(18-Crown-6)-2,3,11,12-tetracarboxylic acid

Useful for secondary amines

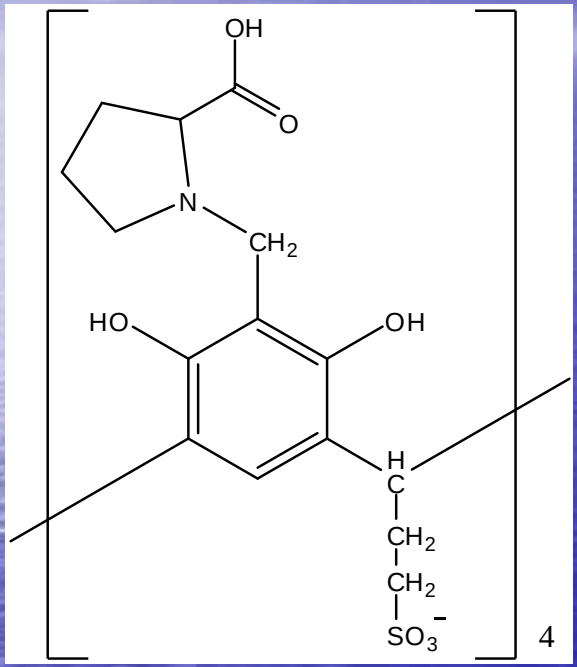
-As neutral amines (neutralization reaction with crown ether)

-In methanol

-Effective for pyrrolidines, piperidines, piperazines, alkyl aryl amines



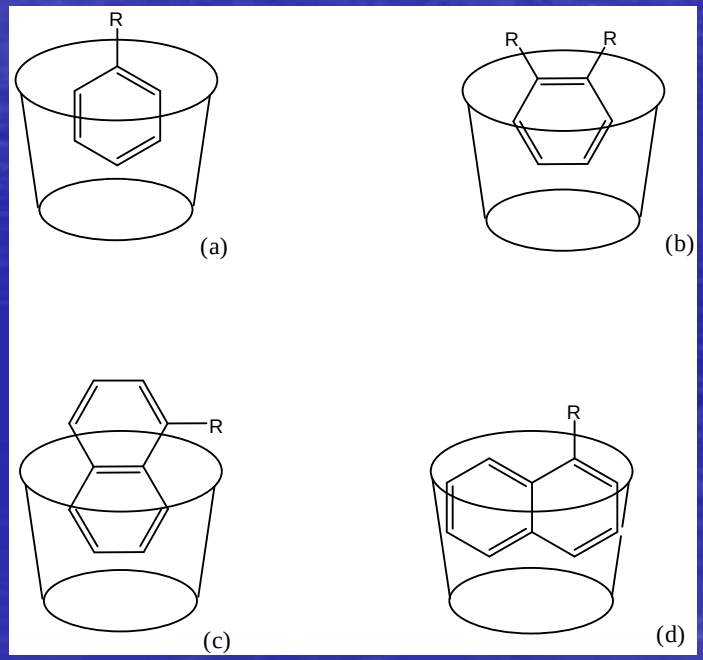
Calix[4]resorcarenes



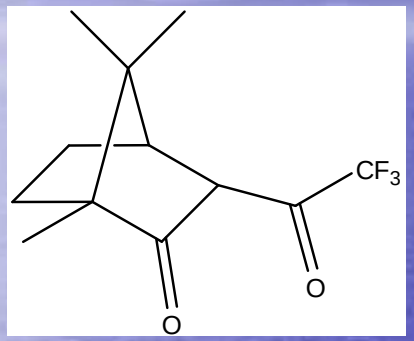
Sulfonated analog with L-proline groups

-Water-soluble

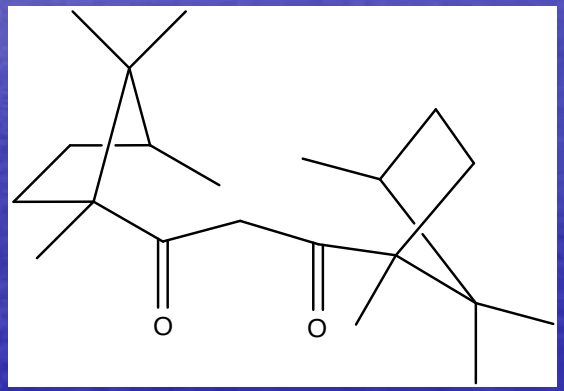
-Effective for mono or bicyclic aromatic compounds – singly or ortho-substituted



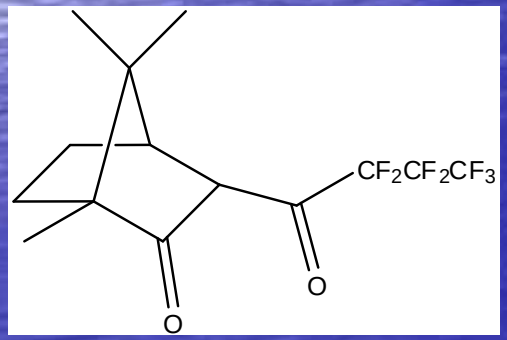
Lanthanide *tris*(β-diketonates)



tfc



dcm



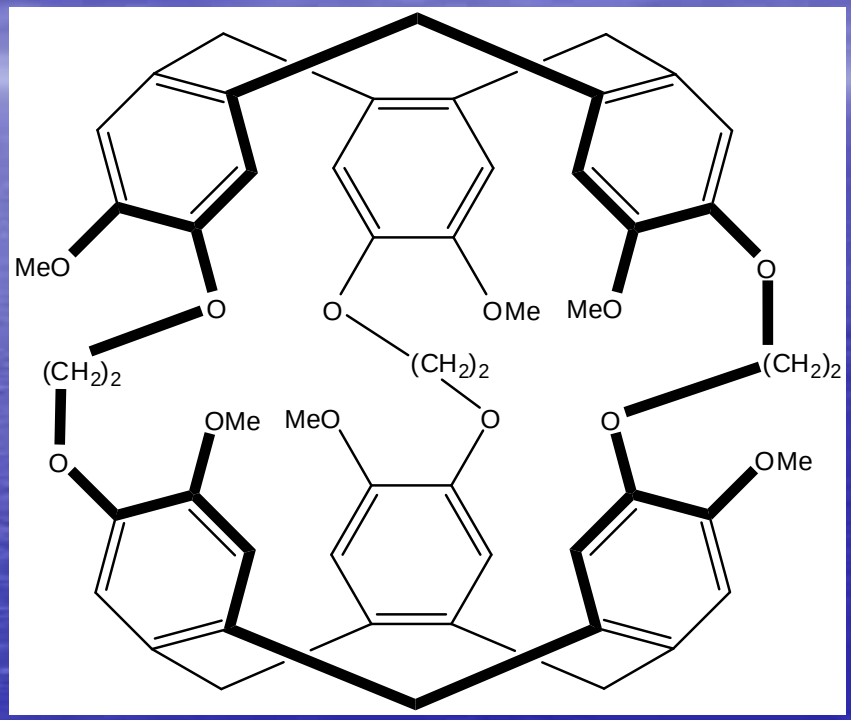
hfc

Organic-soluble

- Suitable for a wide range of hard Lewis bases – oxygen- and nitrogen-containing compounds – metal complexes with binding groups in ligands

- Paramagnetism of lanthanide ions does cause broadening – worse at higher field strengths
  - Use a lower field instrument (300 MHz or lower)
  - Run ^{13}C spectra
  - Use Sm(III) chelates
  - Use a polar solvent
  - Warm the sample (50-75^{o}C)

"Chiralization" of Xenon



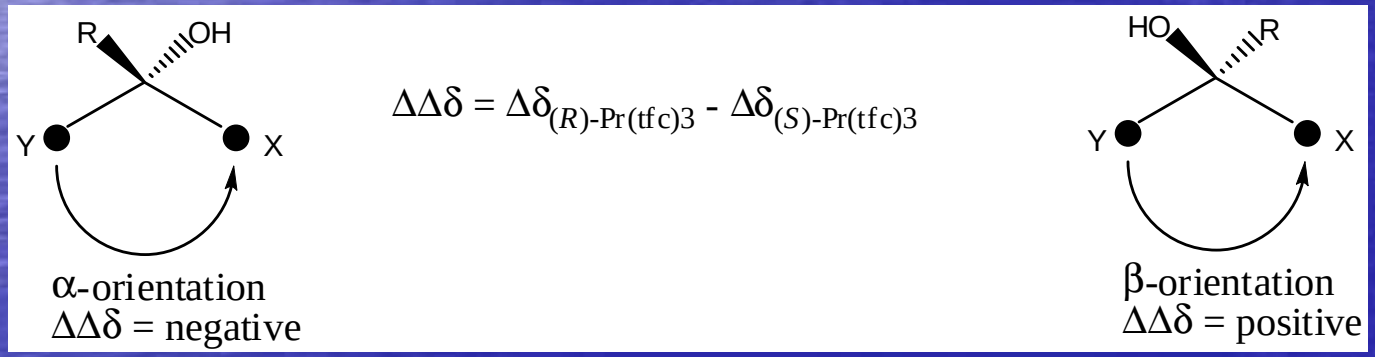
-Racemic cryptophane binds xenon in the cavity
-Addition of $Eu(hfc)_3$ causes the appearance of two ^{129}Xe signals

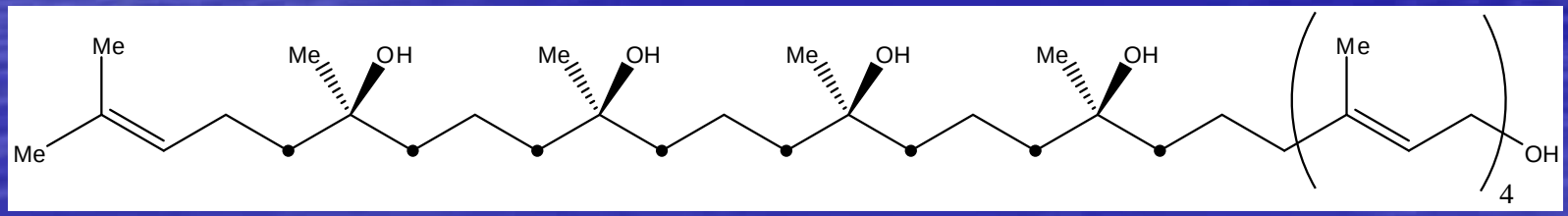
Lanthanides - Absolute Configuration Empirical Trends

- Alkyl aryl carbinols
- Benzhydrols
- 2-Aryloxypropionyl derivatives
- Amino acid methyl esters
- Menthyl butanoates
- *N*-phthaloyl-α-methylcyanoglycinates
- Lactones
- Epoxides and arene oxides

Secondary and Tertiary Carbinols

- Use $Pr(hfc)_3$
- Measure ^{13}C NMR spectrum
- Examine shifts of neighboring carbons
- Works for diols as well if separated by two or more carbons





Binuclear Lanthanide-Silver Reagents

$$Ln(\beta\text{-dik})_3 + Ag(\beta\text{-dik}) = [Ln(\beta\text{-dik})_4]Ag$$

- Effective for soft Lewis bases
  - Olefins
  - Aromatics
  - Alkynes
  - Phosphines
  - Halides (iodide and bromide)

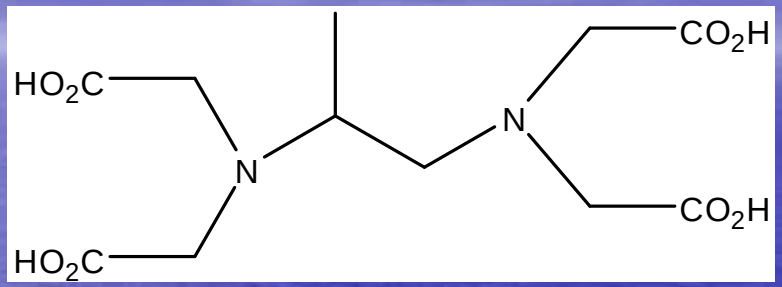
Binuclear Lanthanide-Silver Reagents – Organic Salts

$$[Ln(\beta\text{-dik})_4]Ag + R^+X^- = [Ln(\beta\text{-dik})_4]R + AgX(s)$$

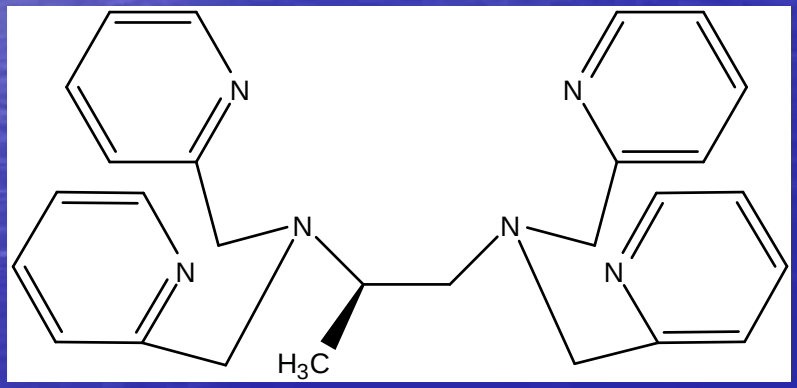
- Ammonium salts
- Isothiouronium salts
- Sulfonium salts

Lanthanide Complexes Water-soluble

- Chelates of pdta (anionic ligand)

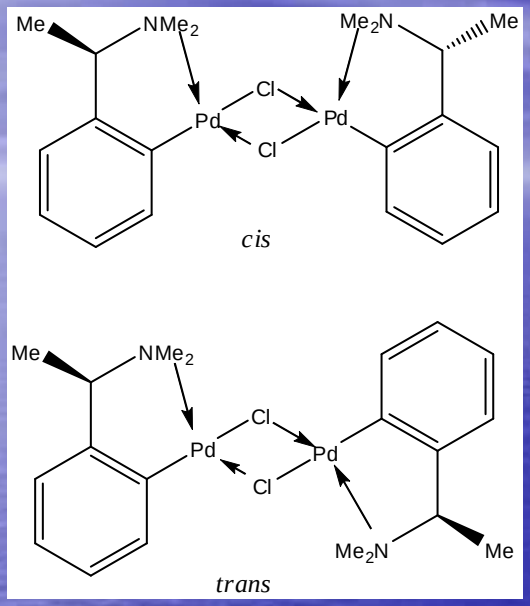


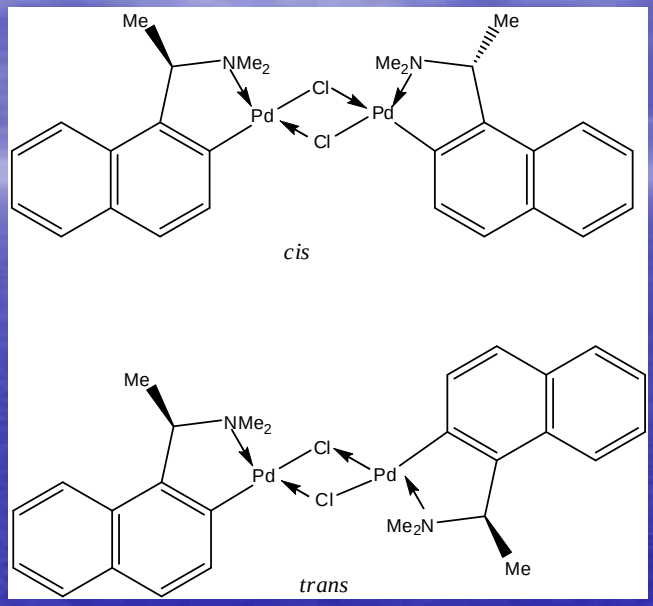
- Chelates of tppn (neutral ligand)



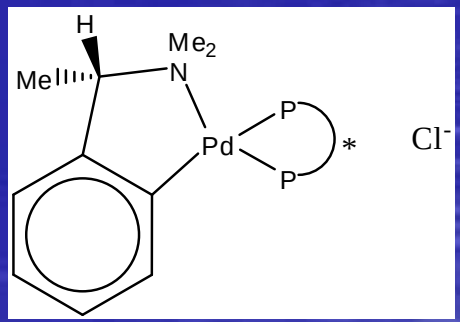
- Effective for carboxylic acids – absolute configurations of amino acids

Palladium-Amine Dimers

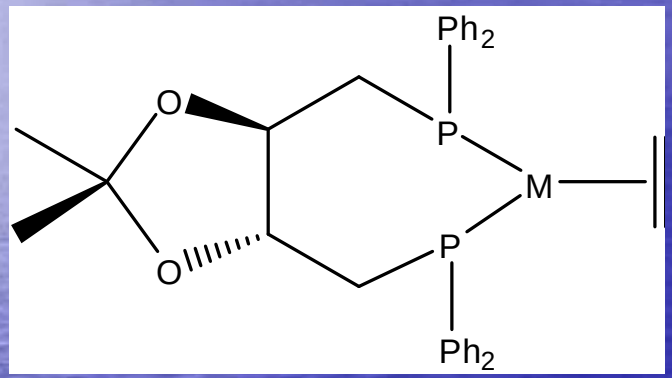


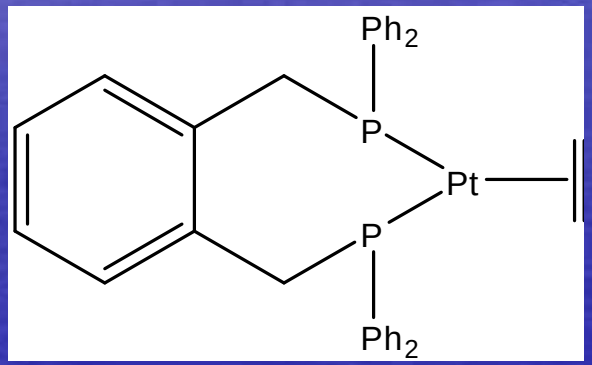


-Mono- and diphosphines bind to the palladium
-Can use for enantiomeric purity and absolute configuration (often with NOE data)



Palladium/Platinum Complexes

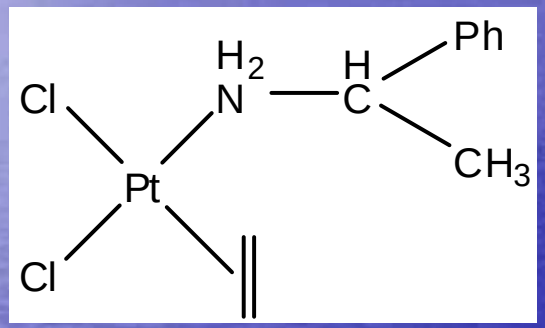


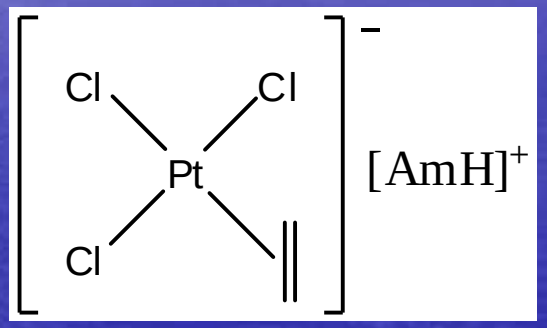


-Alkenes and alkynes can displace the ethylene ligand

-Enantiomeric purity

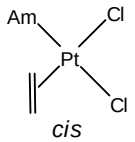
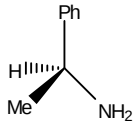
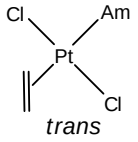
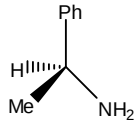
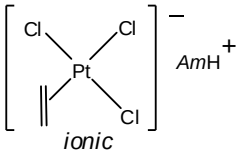
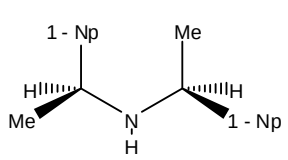
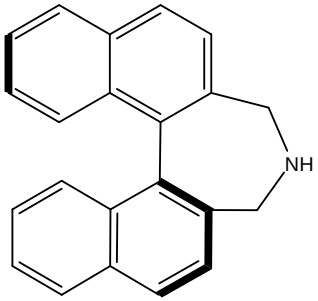
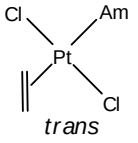
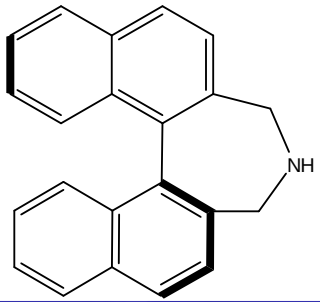
Platinum-Amine Complexes Covalent and Ionic



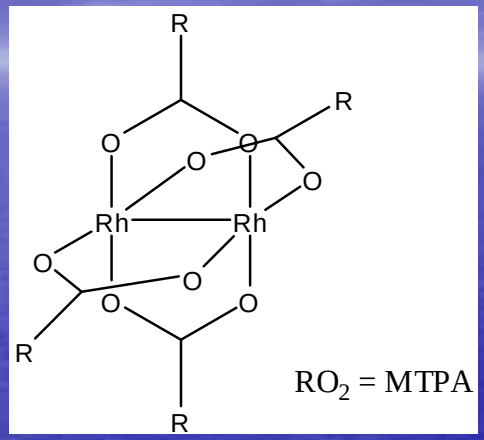


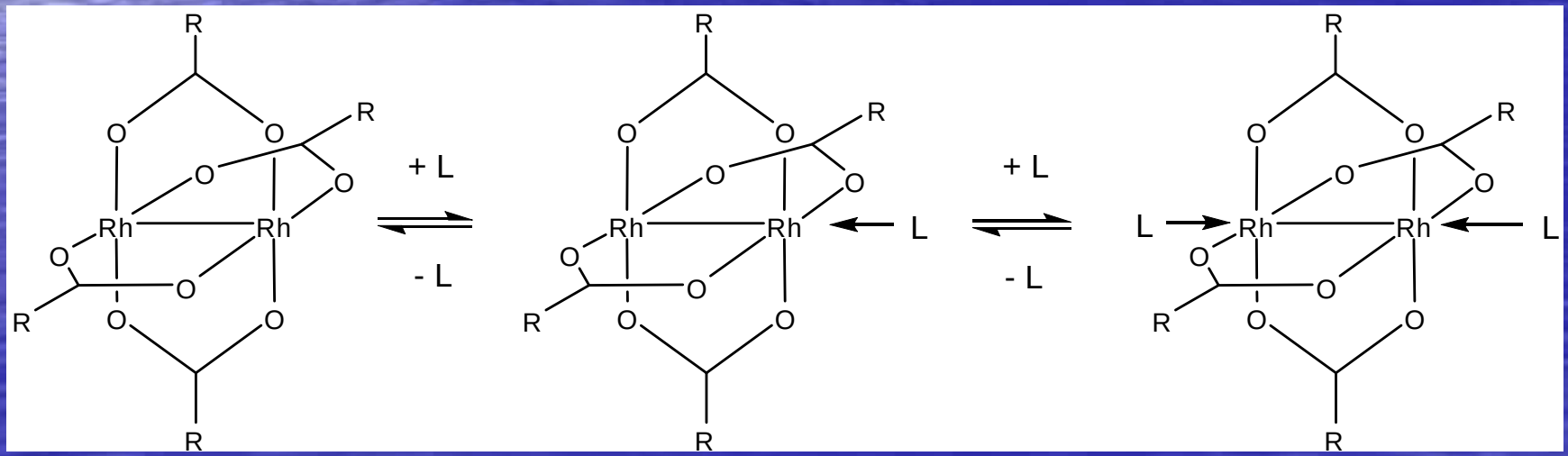
-Olefins and allenes displace the ethylene group
-Measure ^{195}Pt signal - used for enantiomeric purity
-Substrates have two prochiral faces
  -If only one face binds – two ^{195}Pt signals
  -If both faces bind – four ^{195}Pt signals

Platinum-Amine Complexes

CDA	*Am*	enantiodiscriminated substrates
 *cis*		unsaturated ethers
 *trans*		selected cases of allenes
 *ionic*		allenes, olefins, vinyl and allyl ethers
		β-olefins
 *trans*		α-olefins

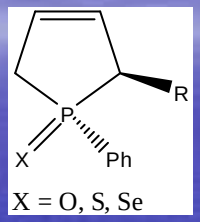
Rhodium Dimer with MTPA

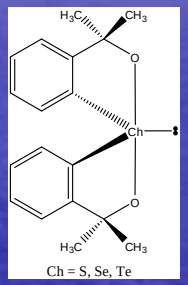


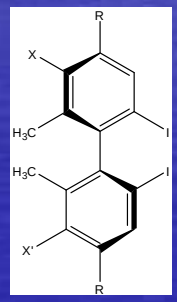


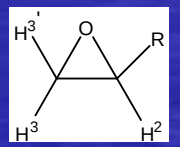
Rhodium Dimer with MTPA

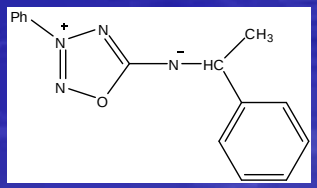
- Olefins
- Phosphines
- Aryl alkyl selenides
- Phosphine selenides (P=Se)
- Phosphorus thionates (P=S)
- Phospholene and phospholane chalcogenides
- Spirochalcogenuranes
- Alkyl iodides, diiodobiphenyls
- Nitriles
- Oxiranes
- Oxatriazoles, thiatriazoles, tetraazoles



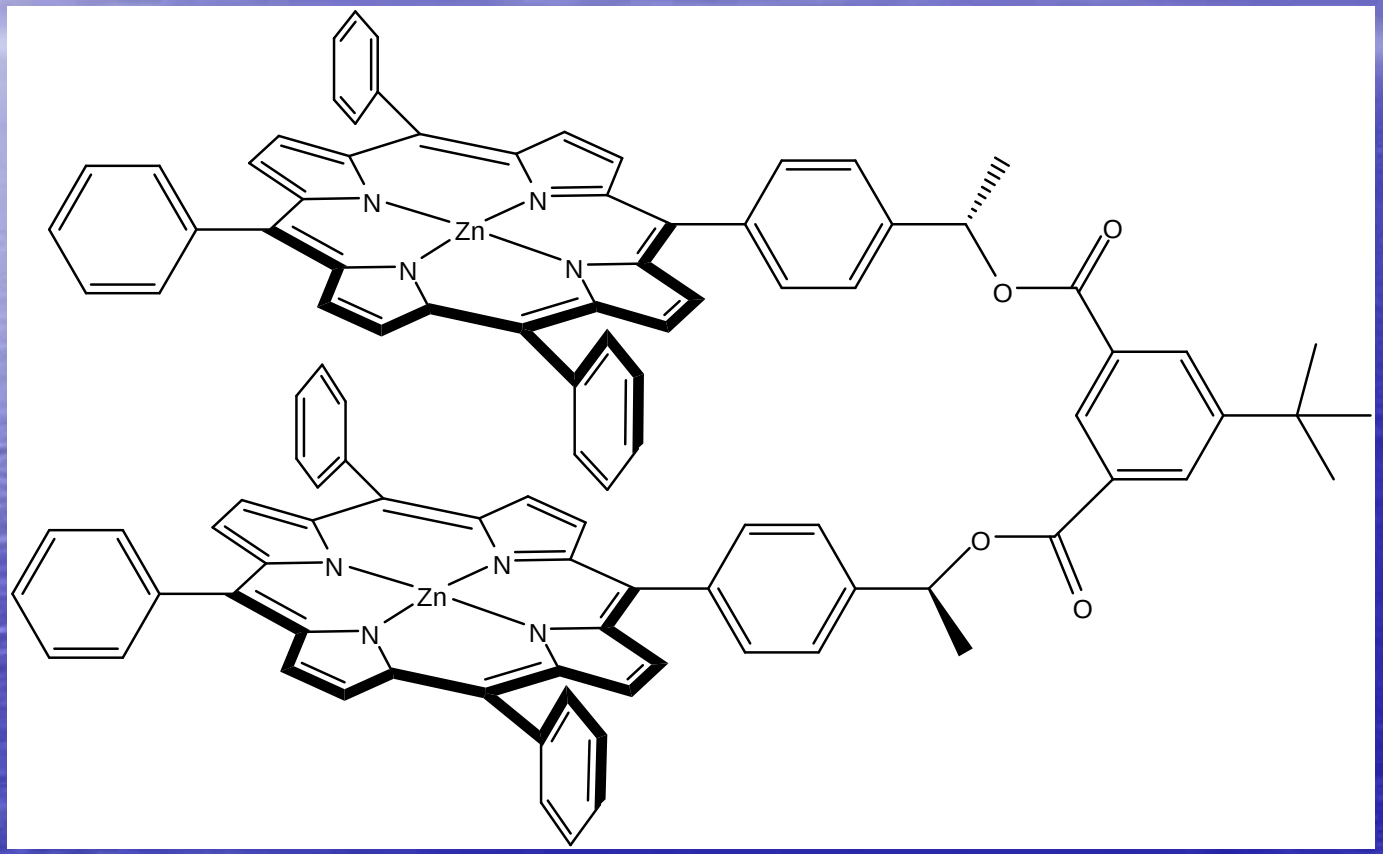








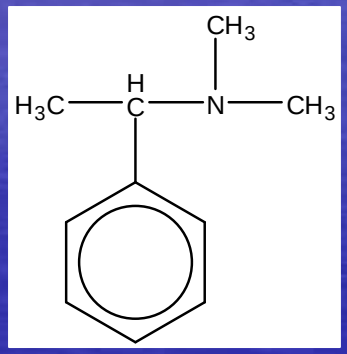
Zinc Porphyrins (Tweezer)



Especially effective for bifunctional substrates (diamines)

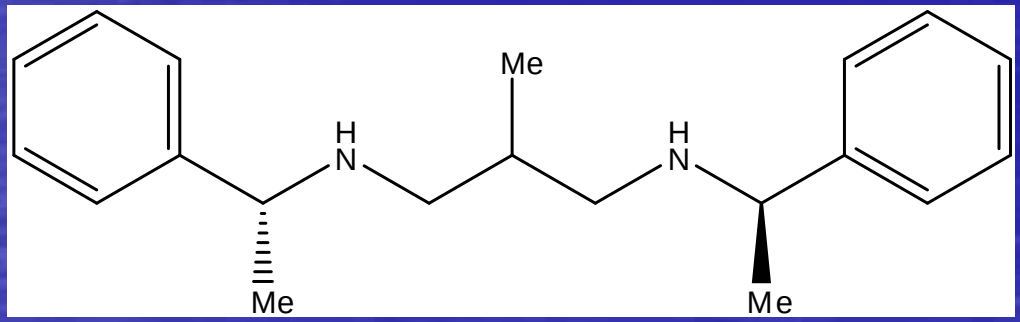
Database Techniques

- ^{13}C or ^{1}H shifts

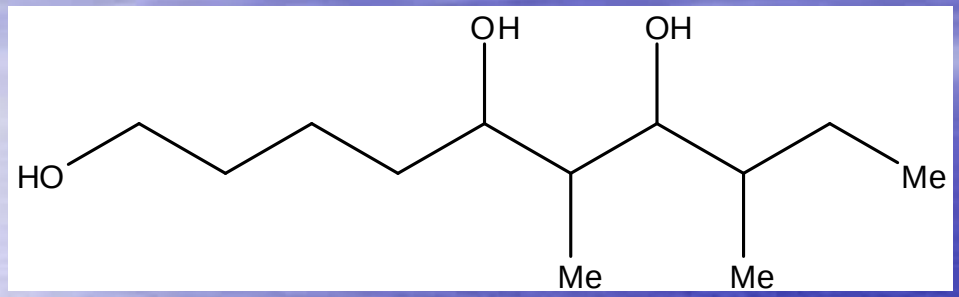


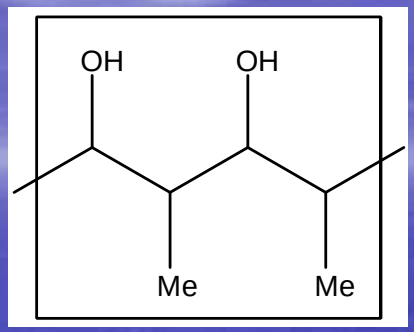
- *N*,α-Dimethylbenzylamine (DMBA)

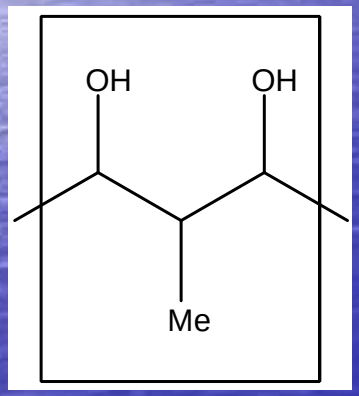
- Bis-1,3-methylbenzylamine-2-methylpropane (BMBA-pMe)

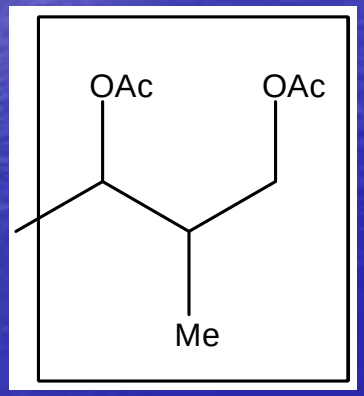


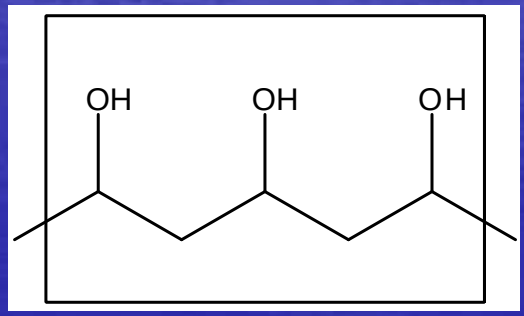
Structural Motifs

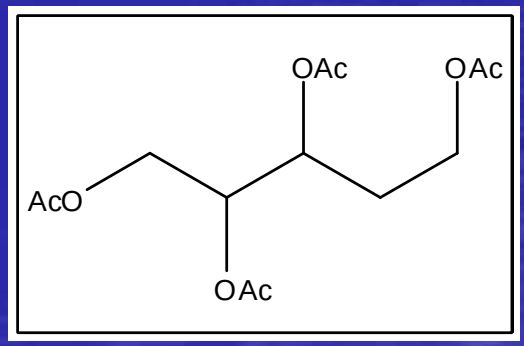






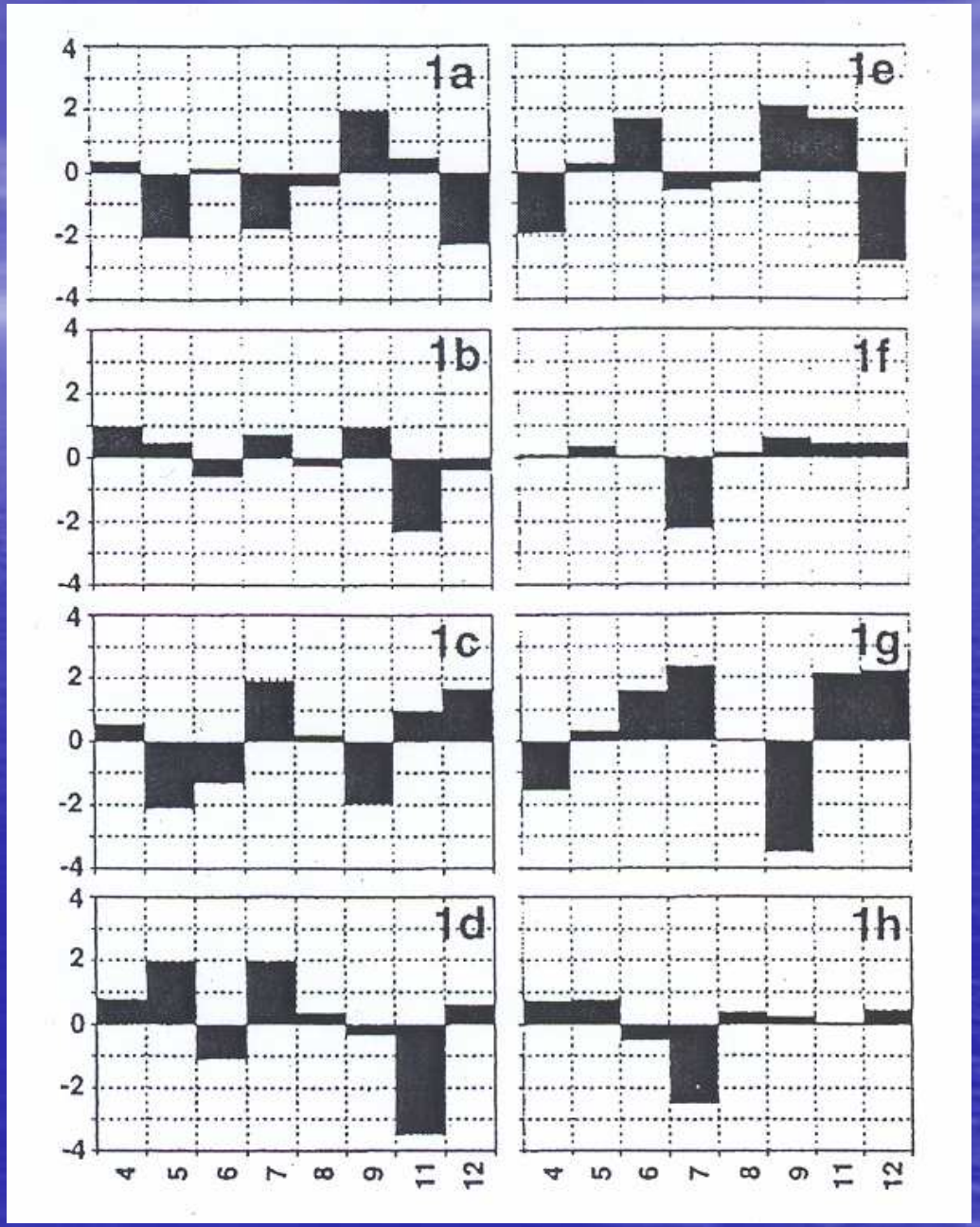




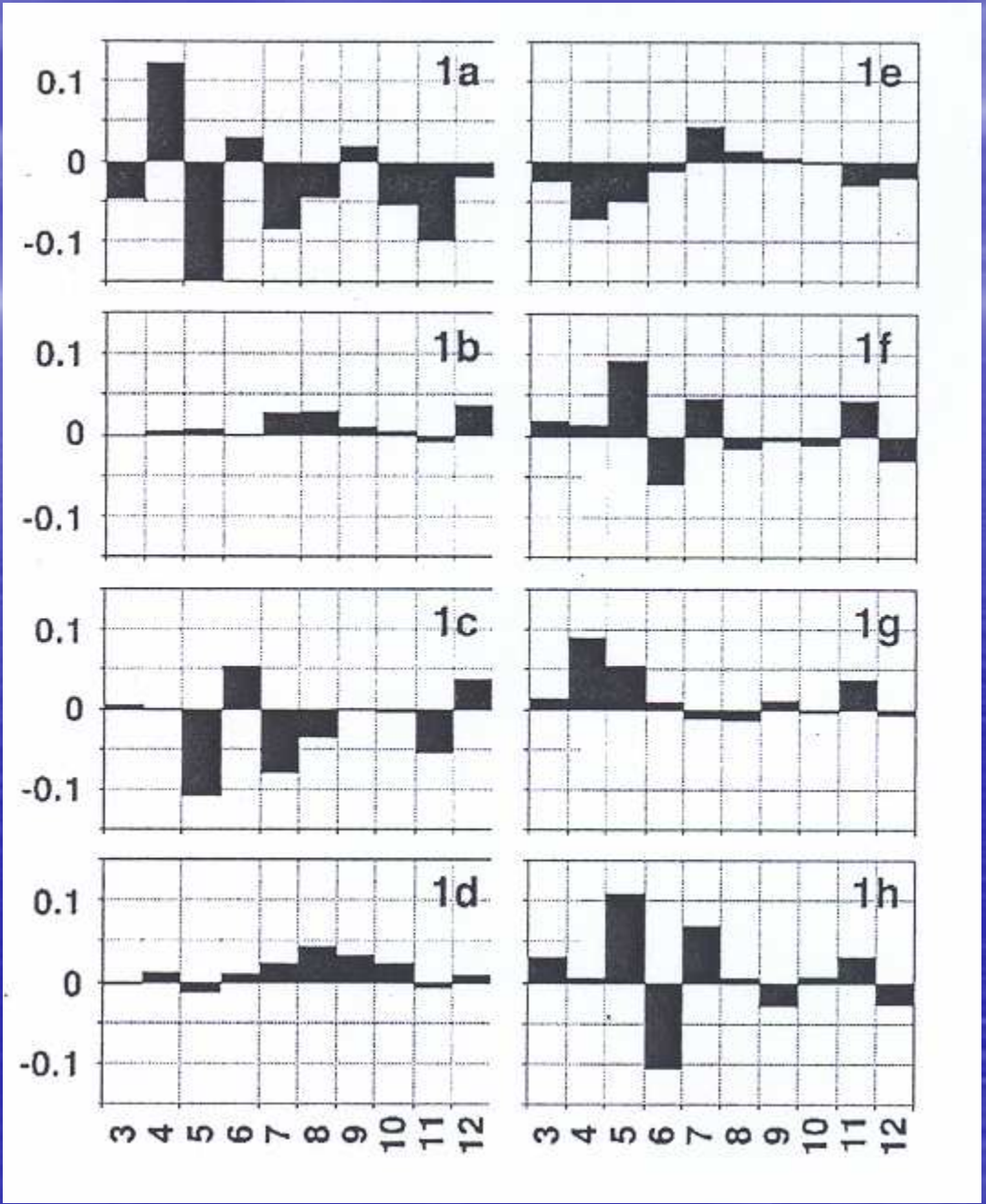


Prepare and examine all possible stereoisomers

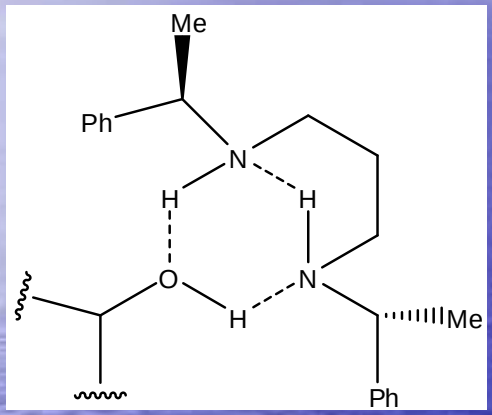
^{13}C or ^{1}H Database - subtract chemical shift of particular nucleus in one stereoisomer from average of value in all eight



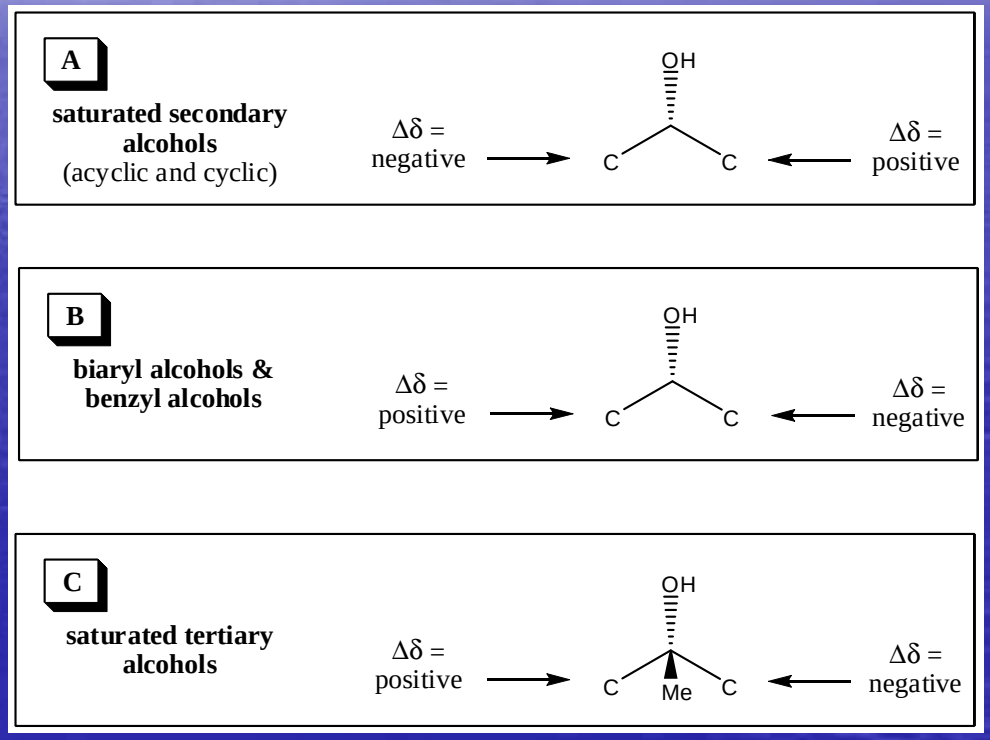
DMBA database
-Difference in ^{13}C shifts between (*R*)- and (*S*)-DMBA



BMBA-pMe – For assigning the stereochemistry of secondary and tertiary alcohols



Binding of BMBA-pMe to a secondary alcohol



Observed trends

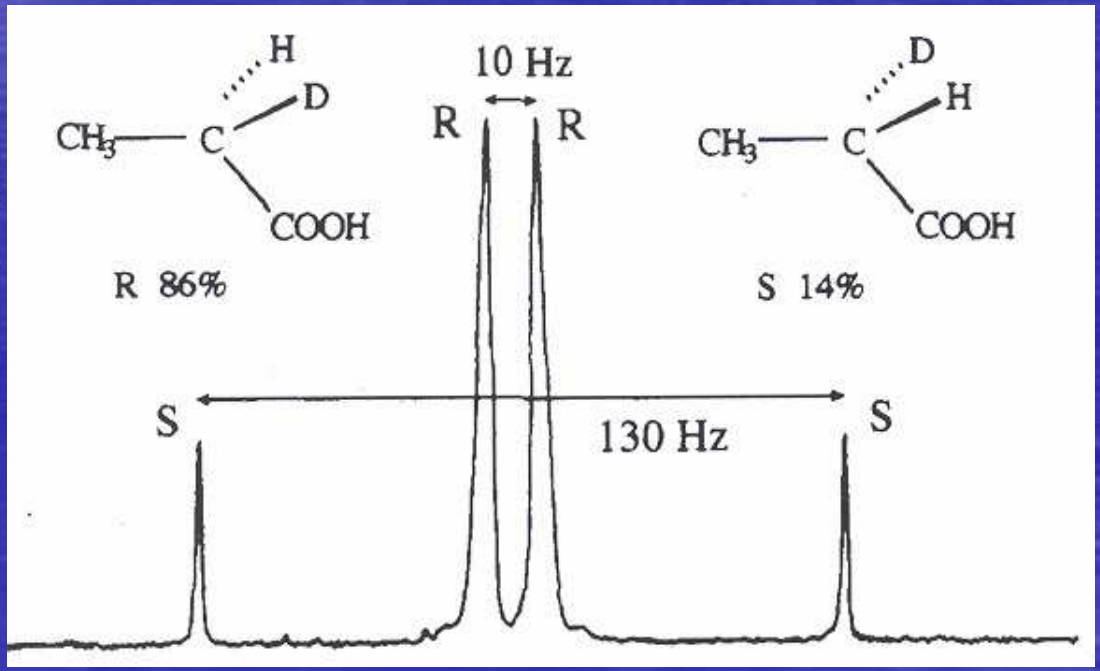
Liquid Crystals poly(γ-benzyl-L-glutamate) (PBLG)

- Forms ordered material in a magnetic field
- Pair of enantiomers have different molecular orientations in PBLG
- Three discrimination mechanisms
  - Chemical shift anisotropy (least useful)
  - Different dipolar coupling constants (^{1}H-^{13}C)
  - Differences in quadrupolar splitting (^{2}H) (most useful)

Quadrupolar Splitting

- Not observed in solution because of rapid tumbling
- Observed in ordered media and extent of splitting depends on orientation relative to the applied magnetic field

Proton-decoupled deuterium NMR spectrum



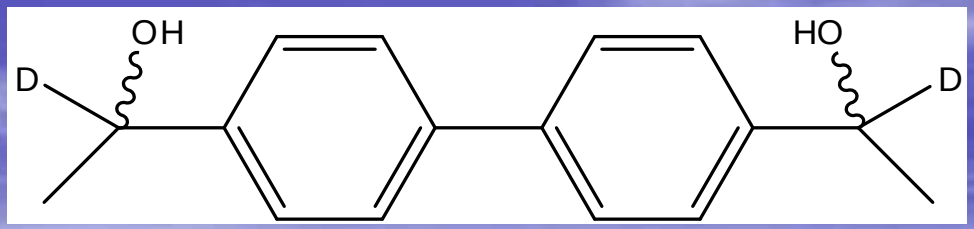
PBLG - Incredible Versatility

- Only need different packing orders
- Do not need specific interactions between the substrate and the liquid crystal
- Effective for virtually any class of compound
  - Includes aliphatic hydrocarbons
- Especially effective for resonances of nuclei remote to the chiral center

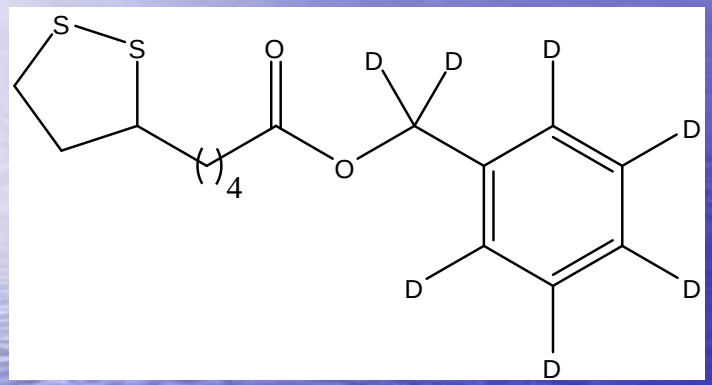
Deuterium Labeling

- Only need deuterium as a signal – better to use achiral reagents so no concern about kinetic resolution or racemization
  - Convert CO_2H to CO_2CD_3
  - Add perdeutero benzoyl group (have o-, m- and p-protons as potential probes
- Provides a single, strong signal (or a few easily assigned signals) for the analysis

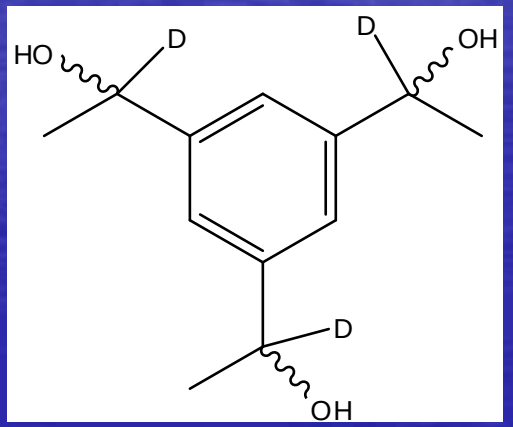
Examples



(*R*,*R*)-, (*S*,*S*)- and (*R*,*S*)-(*meso*)-isomer distinguished



-Remote chiral center
-^{2}H signal for the *para*-position showed different quadrupolar splitting



Can distinguish (*R*,*R*,*R*)-, (*R*,*R*,*S*)-, (*S*,*S*,*R*)- and (*S*,*S*,*S*)-isomers

Perdeuterated/Natural Abundance ^2H

- Complicated spectra
  - each ^2H signal is a doublet
  - each ^2H signal may be two doublets if the enantiomers have different quadrupolar splitting
  - can't predict a priori the magnitude of the quadrupolar splitting
- Procedures have been devised to aid in the assignment of ^2H spectra