Selective Organic Synthesis

KD 2390 (9 hp)

Christina Moberg

The advent of organic chemistry shaped the world

- *Biology is dependent on organic synthesis*
- *Organic synthesis is the foundation for biotechnology, nanotechnology, pharmaceutical industry, and material industry*

About the course:

- *Disposition:* lectures, exercises, lab, workshop
- *Course book:* Clayden, Greeves and Warren Organic Chemistry, Oxford University Press, 2012 (ISBN 978-0-19-927029-3) [or Clayden, Greeves, Warren and Wothers: Organic Chemistry, Oxford University Press, 2001 (ISBN 0 19 850346 6)] and distributed material
- *Examination:* oral exam, lab work (lab and workshop compulsory)

After the course the student should be able to:

- Describe basic stereochemical concepts
- Describe principles for stereoselective synthesis, in particular for enantioselective synthesis
- Explain the stereochemistry observed in chemical reactions
- Suggest methods for stereoselective synthesis of simple organic compounds containing stereogenic elements
- Identify suitable reagents for stereoselective transformations
- Use retrosynthetic analysis for the construction of synthetic routes for simple organic compounds
- Prepare organic compounds using advanced synthetic methodology

Contents

- Fundamental stereochemical concepts
- Synthetic strategy and principles for stereoselective, in particular enantioselective, chemical transformations
- Transition metal catalysis
- Applications of frontier orbital theory
- Retrosynthetic analysis
- Advanced organic synthesis

Marcellin Pierre Eugène Berthelot (1827 - 1907)

"La Chimie crée ses objets"

"This is an important point: neither biology nor chemistry would be served best by a development in which all organic chemists would simply become biological such that, as a consequence, research at the core of organic chemistry and, therefore, progress in understanding the reactivity of organic molecules, would dry out. Progress at its core in understanding and reasoning in not only essential for organic chemistry itself, but for life sciences as a whole. Life science needs Organic Chemistry that remains strong."

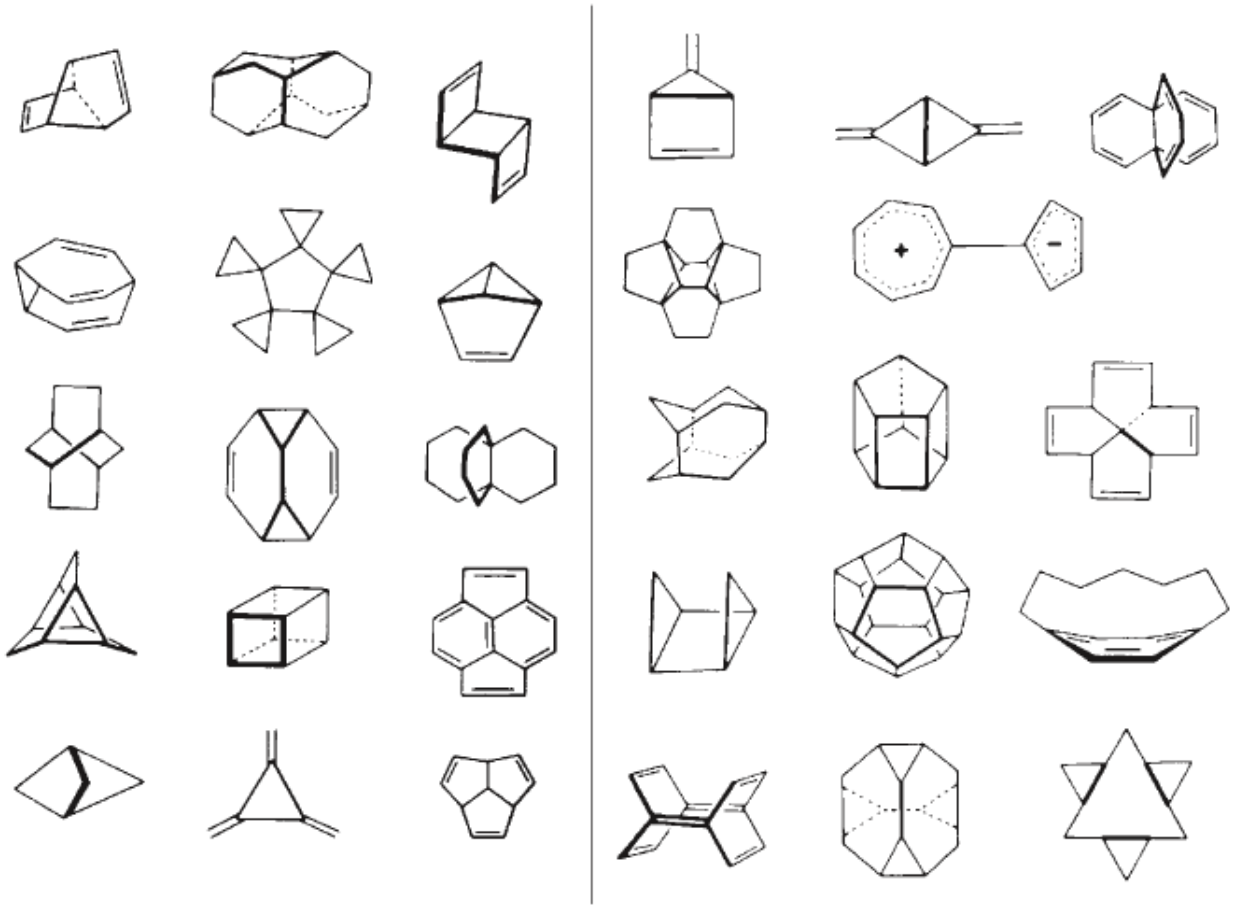
Axel Eschenmoser (2008)

"Without the possibility of synthesis on the molecular level, efforts in reconstructing or engineering life are certainly bound to fail"

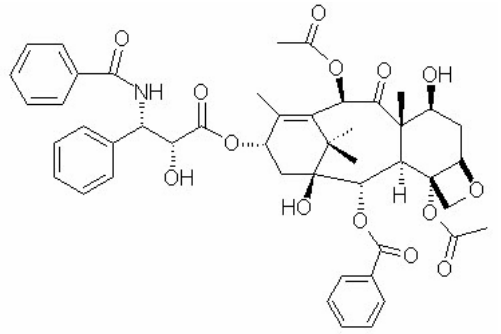
P. Schwille, Angewandte Editorial 2013

Why are new molecules synthesized?

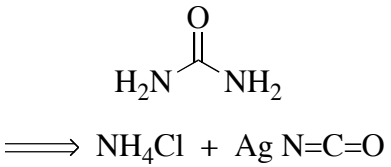
Verify structure
Curiosity
Challenge
Understand properties
Function



Cram's and Hammond's challenge to hydrocarbon chemists.



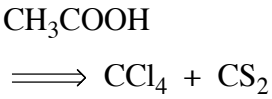
Paclitaxel (Taxol)



Urea
Wöhler 1828

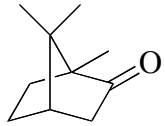
first organic compound

"I can no longer, so to speak, hold my chemical water and must tell you that I can make urea without needing a kidney, whether of man or dog; the ammonium salt of cyanic acid is urea."

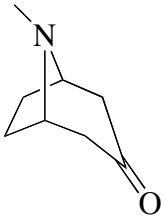


Acetic acid
Kolbe 1847

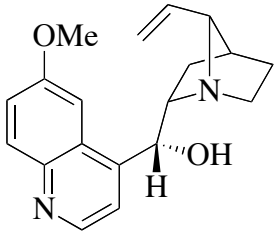
first C-C bond



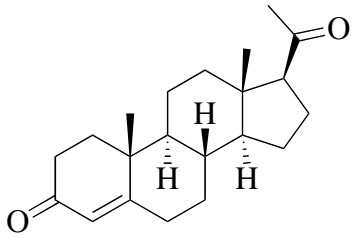
Camphor
Komppa1903



Tropinone
Robinson 1917

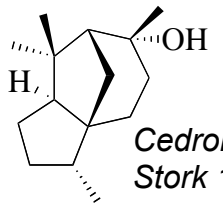


Quinine
Woodward & Doering 1944

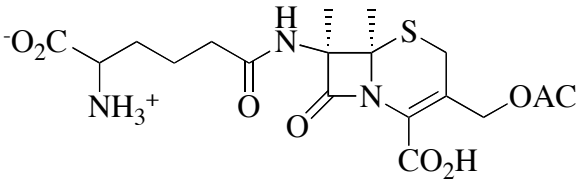


Progesterone
Djerassi 1951

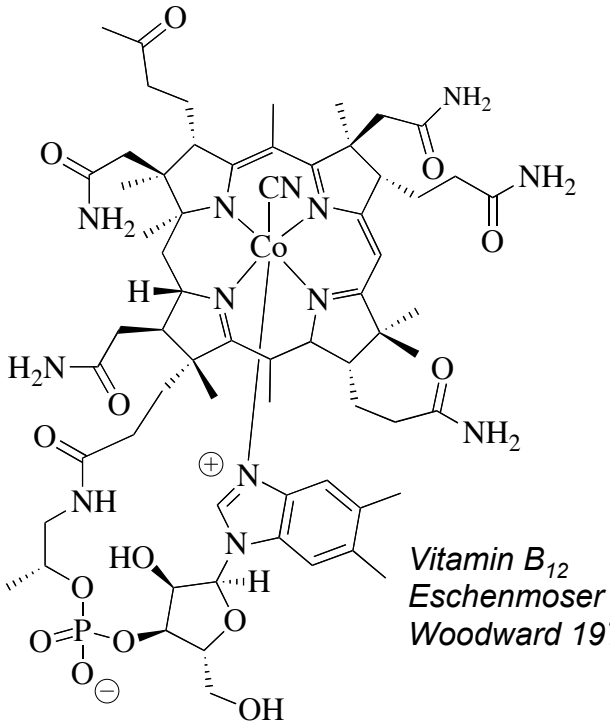
…it is in the course of attack of the most difficult problems, without consideration of applications, that new fundamental knowledge is most certainly generated.



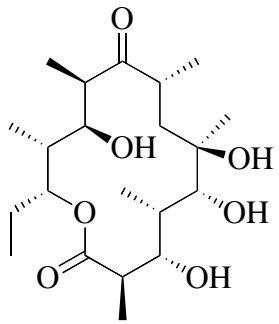
Cedrol
Stork 1955



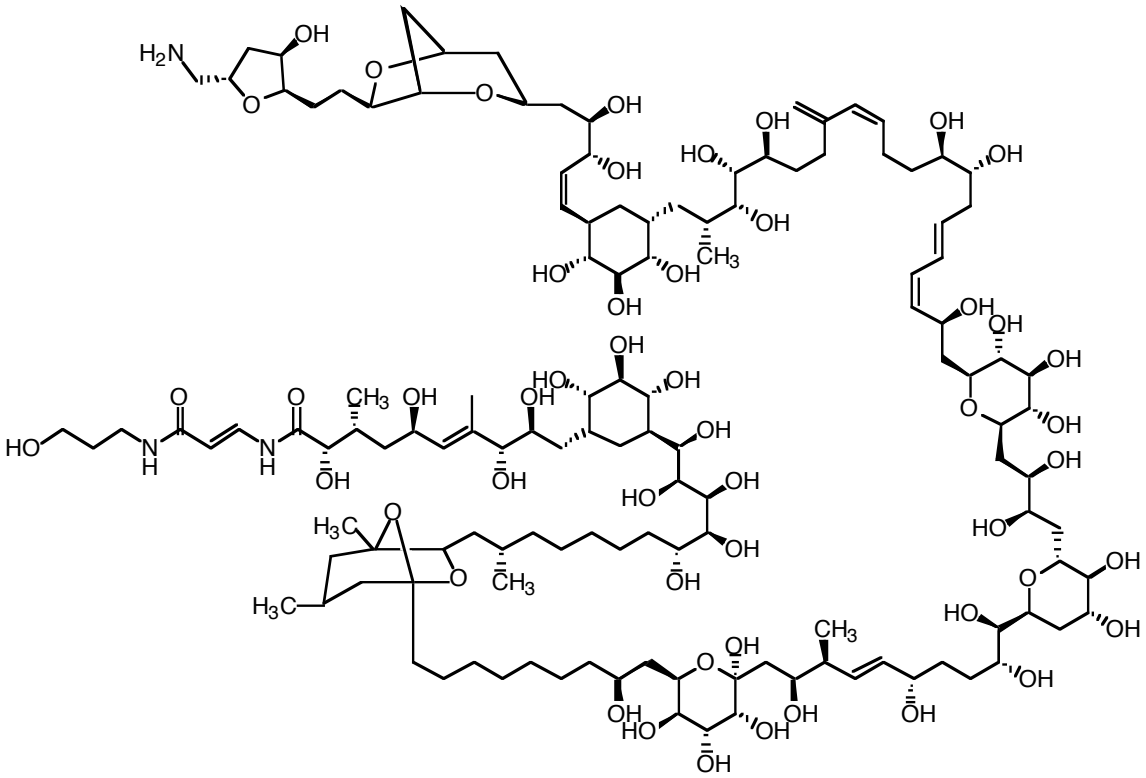
Cephalosporin
Woodward 1966



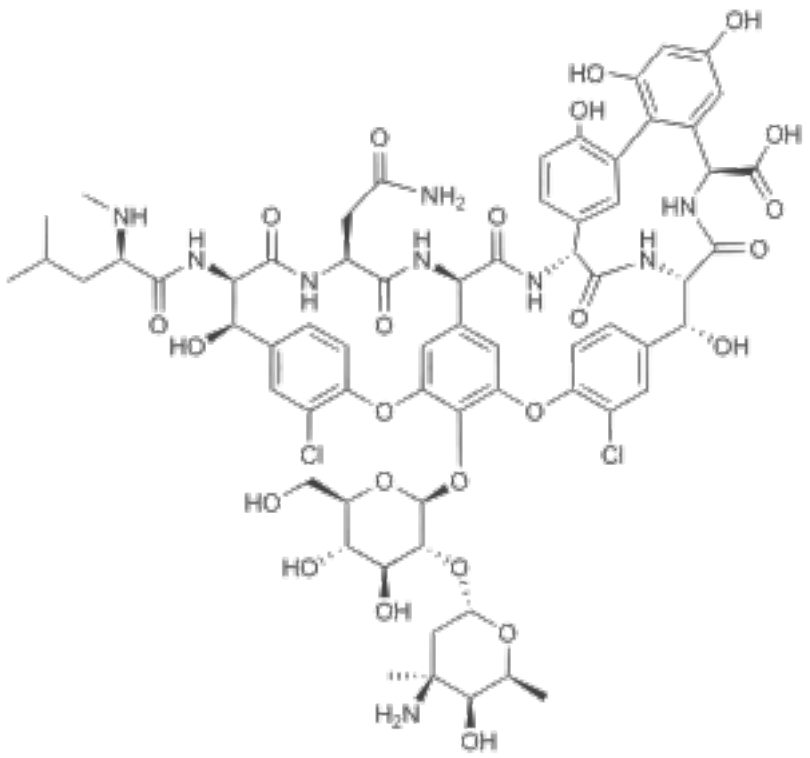
Vitamin B_{12}
Eschenmoser &
Woodward 1973



Erythronolide
Corey 1978

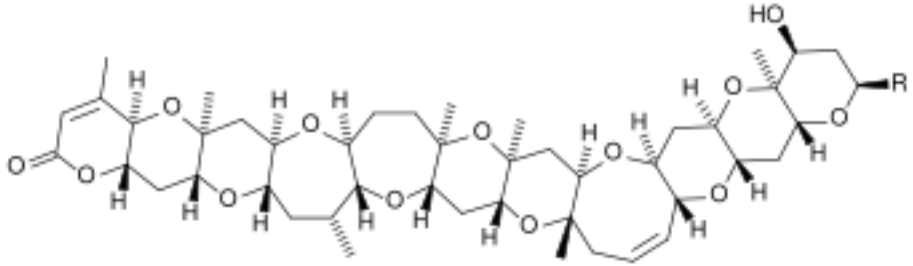


Palytoxin
Kishi 1994



Vancomycin
Nicolau 1998

Brevetoxin B

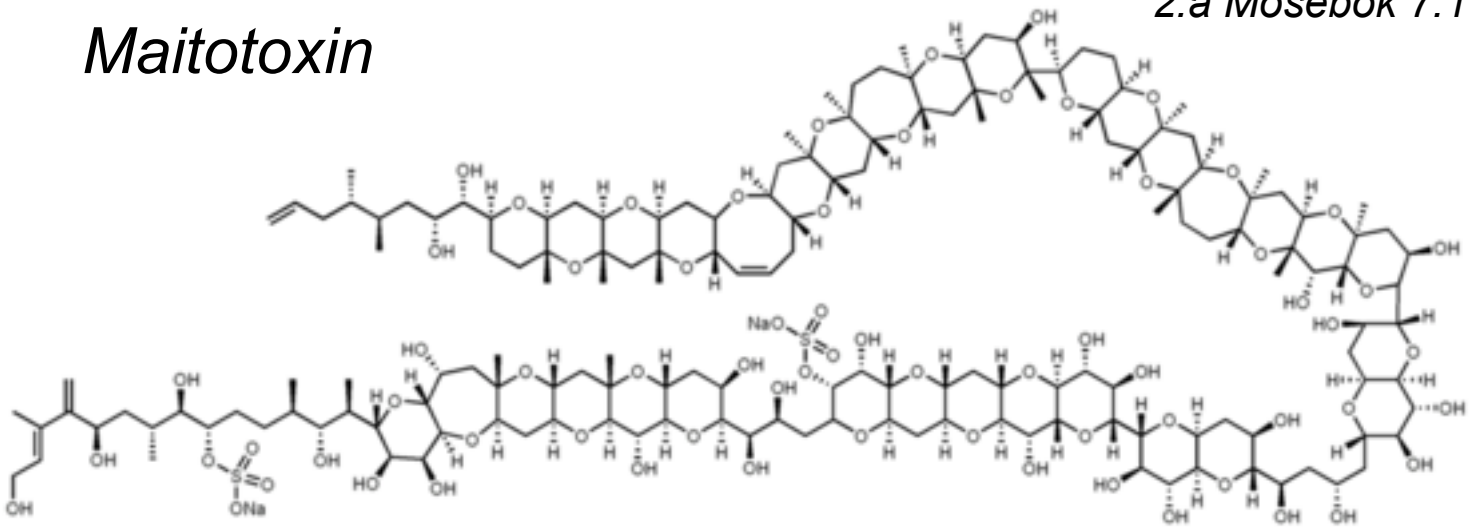


Därför säger nu Herren så: "Härav skall du förnimma att jag är Herren: se, med staven som jag håller i min hand vill jag slå på vattnet i Nilfloden, och då skall det förvandlas till blod.

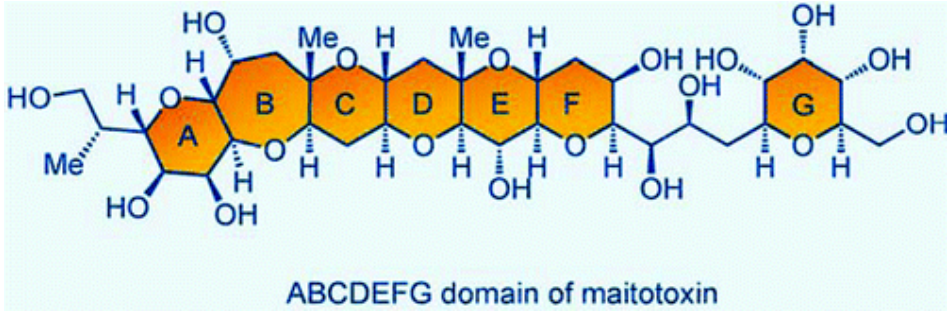
Och fiskarna i floden skola dö, och floden skall bliva stinkande, så att egyptierna skola vämjas vid att dricka vatten ifrån floden."

2:a Mosebok 7:17-18

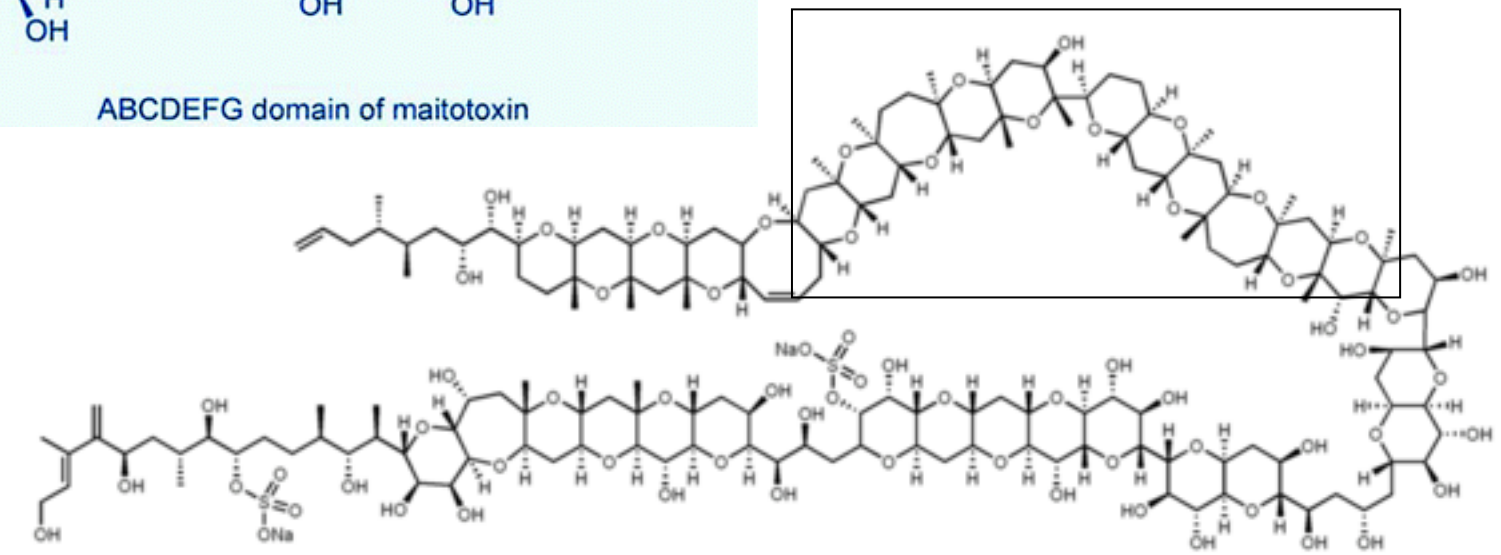
Maitotoxin

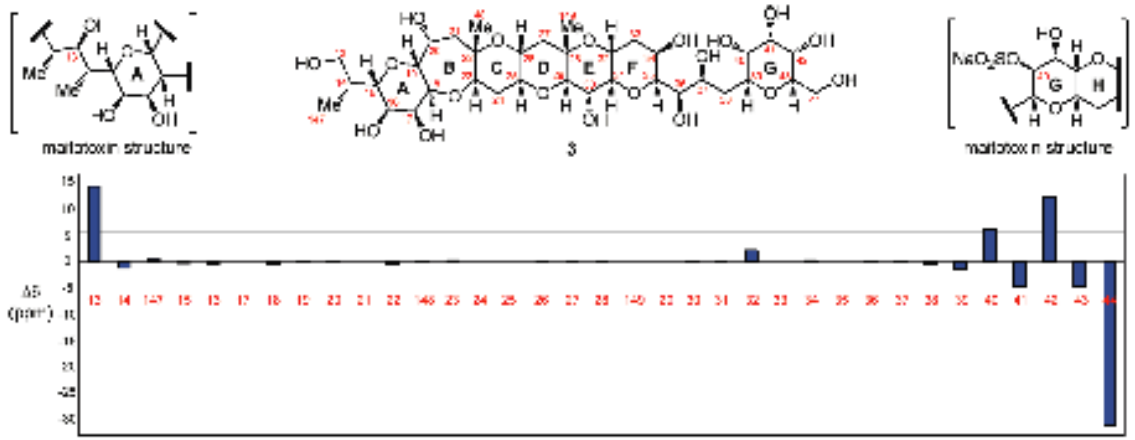


Isolated 1971 from ciguateric fish (svart kirurgfisk)
LD_{50}: 50 ng/kg - 1 mg can kill 1 million mice



98 stereogenic centers



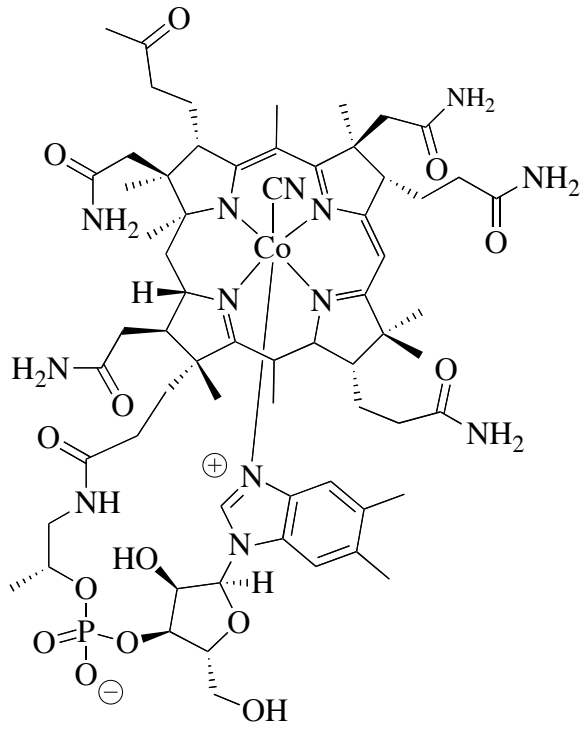


11 rings
26 stereogenic centers

Figure 3. Graphically depicted ^{13}C chemical shift differences ($\Delta\delta$, ppm) for each carbon between C_{13} to C_{44} and C_{147} to C_{149} for maitotoxin (1) and ABCDEFG ring system 3.

Structure determination -

You need to know which molecule to synthesize



Vitamin B_{12}
Dorothy Crowfoot Hodgkin 1956

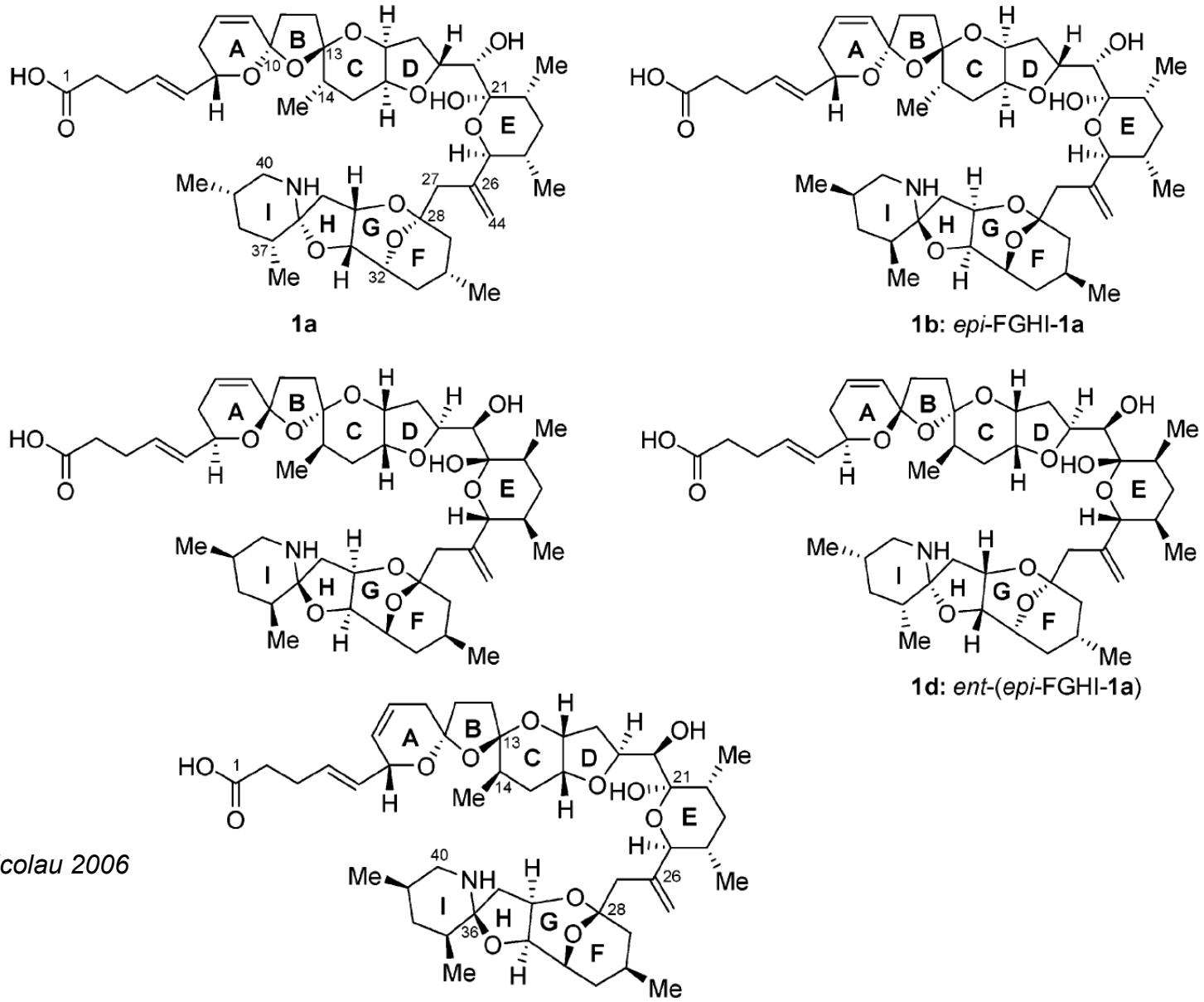
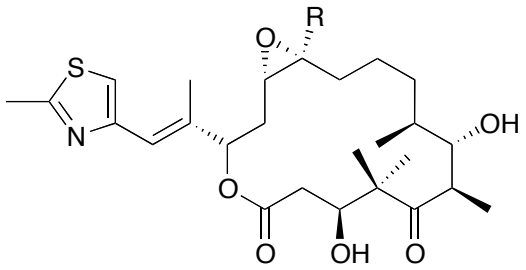
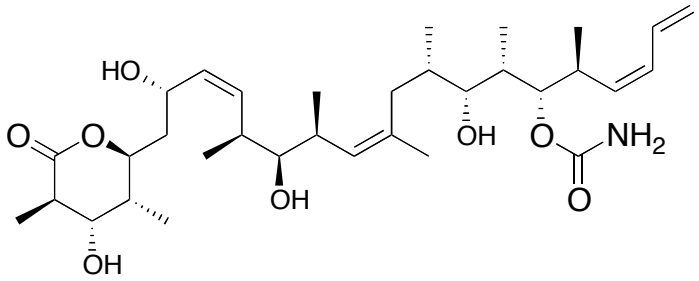


Figure 2. Revised structure of azaspiracid-1 (**1**).

Epothilone A (anticancer)

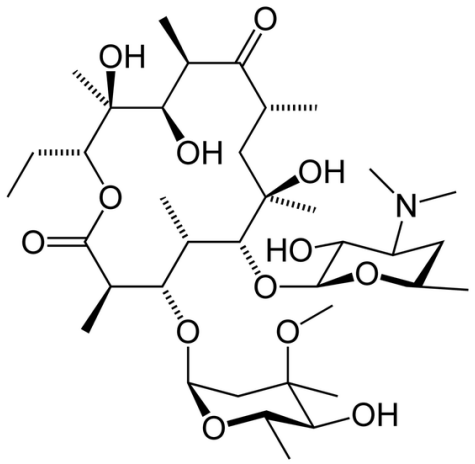


Discodormelide



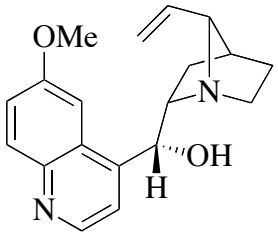
first isolated in 1990 from the Caribbean marine sponge *Discodermia dissoluta*

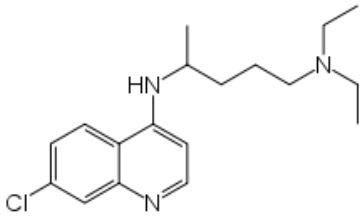
Erythromycin (antibiotic)



Malaria

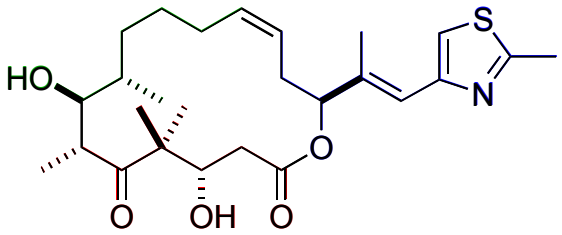
Malaria kills two children every minute





Strategy

Retrosynthesis



epothilone C

and methodology:

chemoselectivity

regioselectivity

stereoselectivity

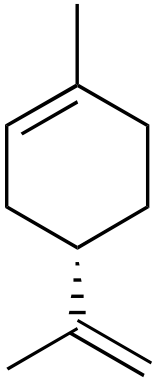
yield

Chirality - Asymmetric synthesis

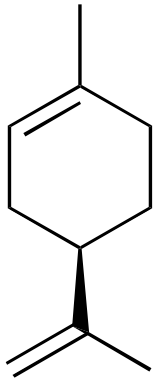
A compound which is not identical to its mirror image is chiral
A chiral compound is not identical to its mirror image

A compound which is identical to its mirror image is not chiral

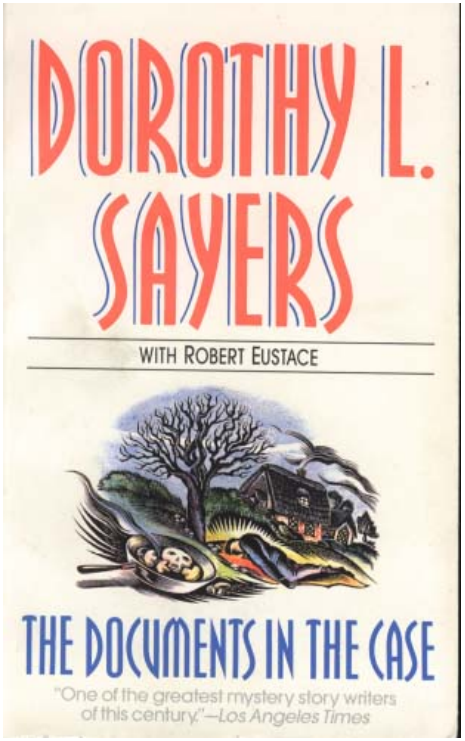
A compound which is not chiral is identical to its mirror image

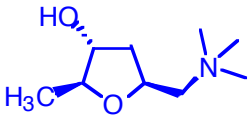


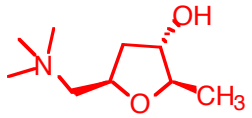
S-(-)-limonene



R-(+)-limonene

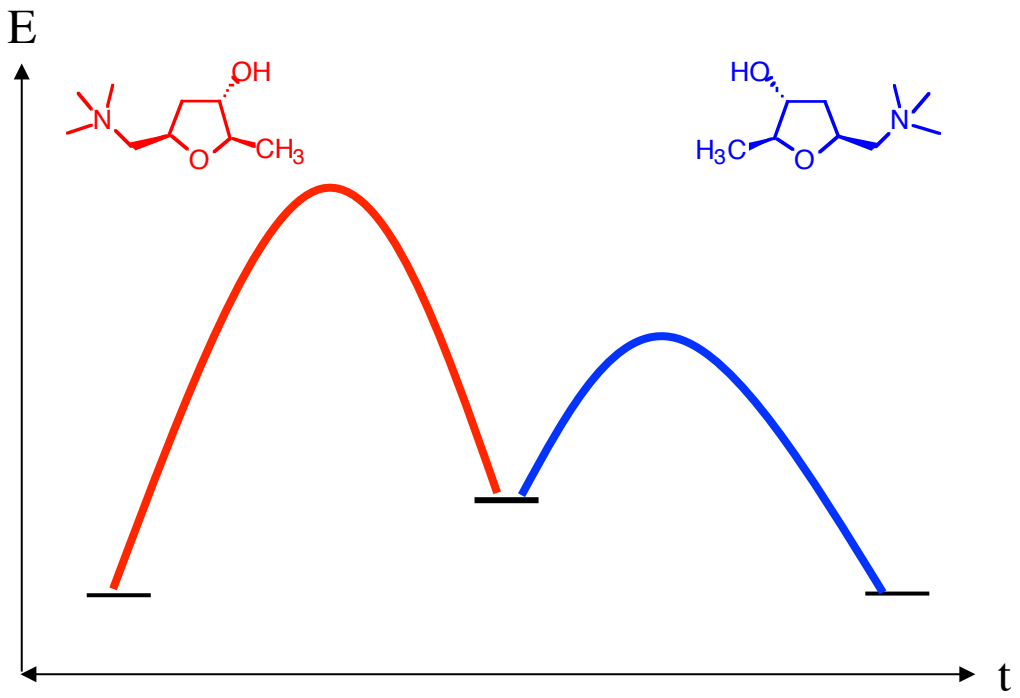

DOROTHY L.
SAYERS
WITH ROBERT EUSTACE
THE DOCUMENTS IN THE CASE
"One of the greatest mystery story writers of this century."—Los Angeles Times

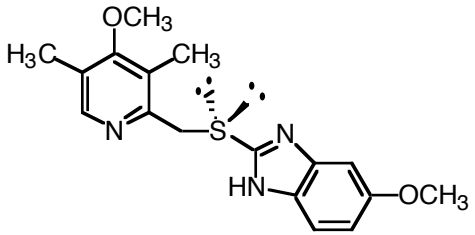

HO
H3C
O
N

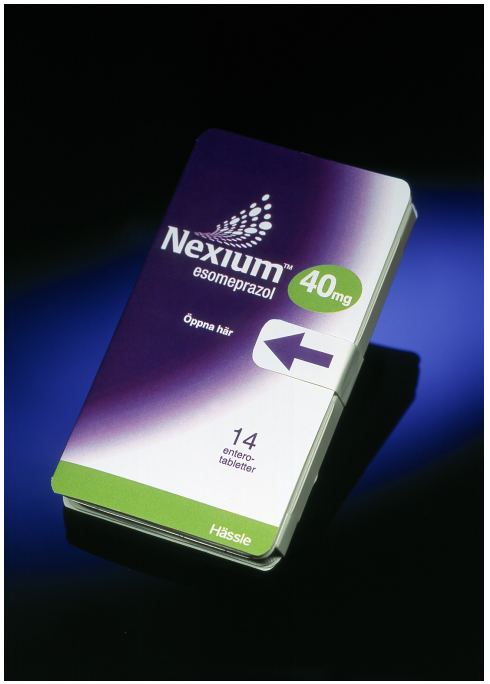

OH
N
O
CH3

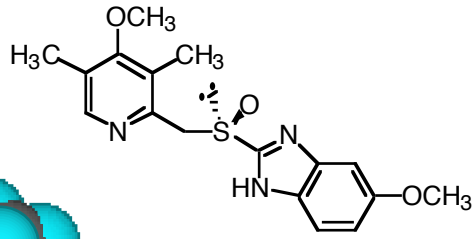
Muskarin

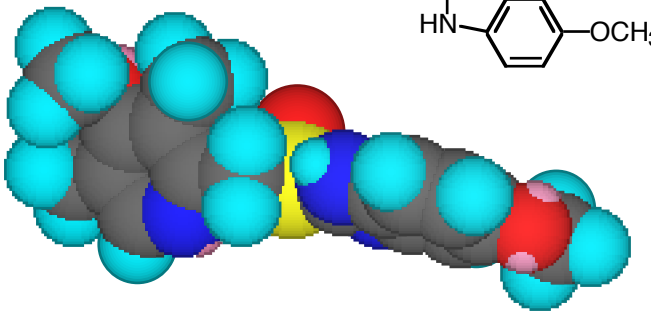
"Lorsqu'il se forme un corps dissymmétrique dans une réaction ou l'on n'a mis en présence les uns des autres que des corps symmetriques, il y aura formation dans la meme proportions des deux isomères de symétrie inverse… Il n'en est pas nécessairement de meme composés dissymétriques formés en présence de corps actifs euxmemes ou traversés de la lumière polarisée circulairement…" J.-A. LeBel 1874

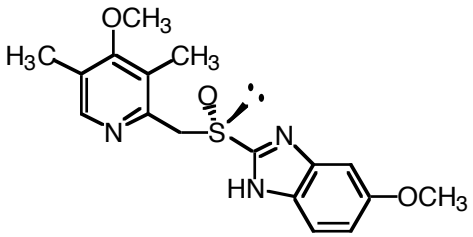


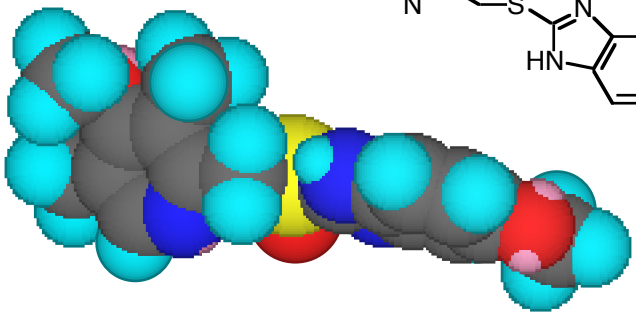

OCH3
H3C
CH3
N
S
N
HN
OCH3

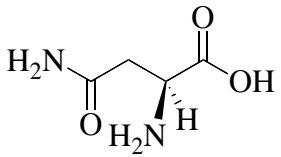

Nexium
esomeprazol
40mg
Öppna här
14
entero-tabletter
Hässle


OCH3
H3C
CH3
N
S
O
N
HN
OCH3



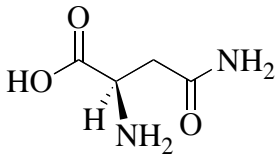

OCH3
H3C
CH3
N
S
O
N
HN
OCH3



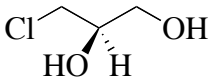


bitter taste

Aspargine

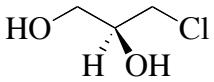


sweet taste

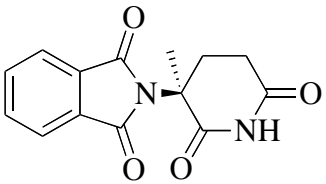


poison

1-Chloro-2,3-propanediol

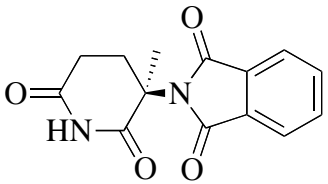


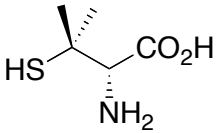
pharmaceutical



teratogenic

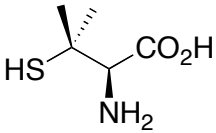
Thalidomide





Pharmaceutical against artrite

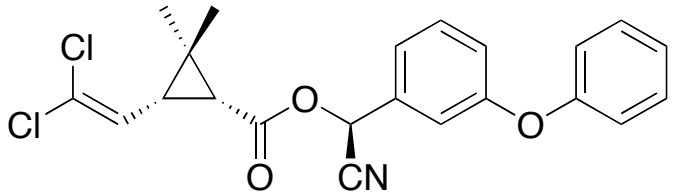
Penicillamine

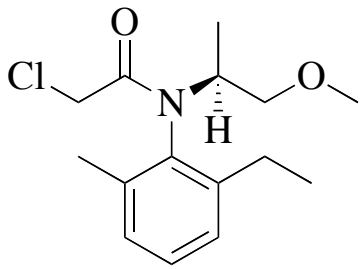


poison

In 2006, 80% of small-molecule drugs approved by FDA were chiral and 75% were single enantiomers.

The field of asymmetric synthesis is expanding rapidly.

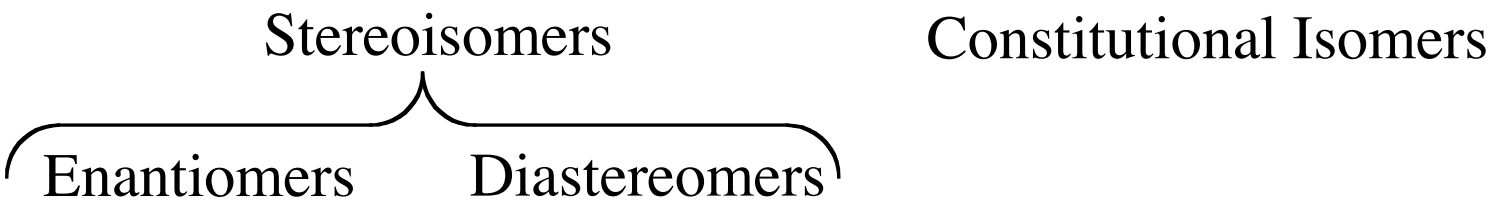

Cl
Cl
O
O
O
CN



S-Metolachlor *herbicide*

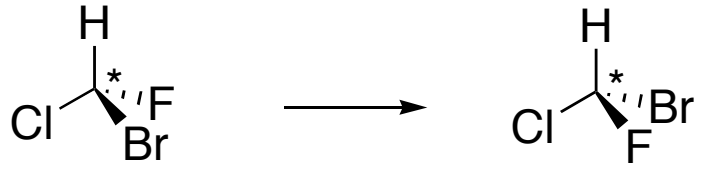
Largest asymmetric metal-catalyzed process in the world (via hydrogenation of the imine using an Ir catalyst)

Classification of isomers

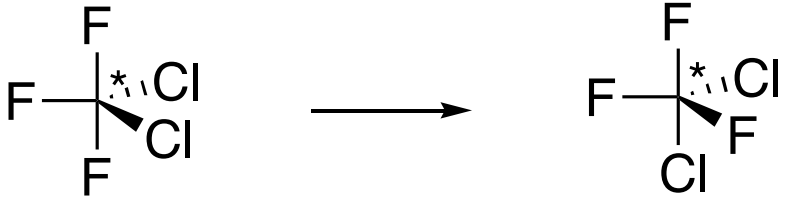


Stereogenic center

Interchange of two ligands at a stereogenic center leads to a stereoisomer.



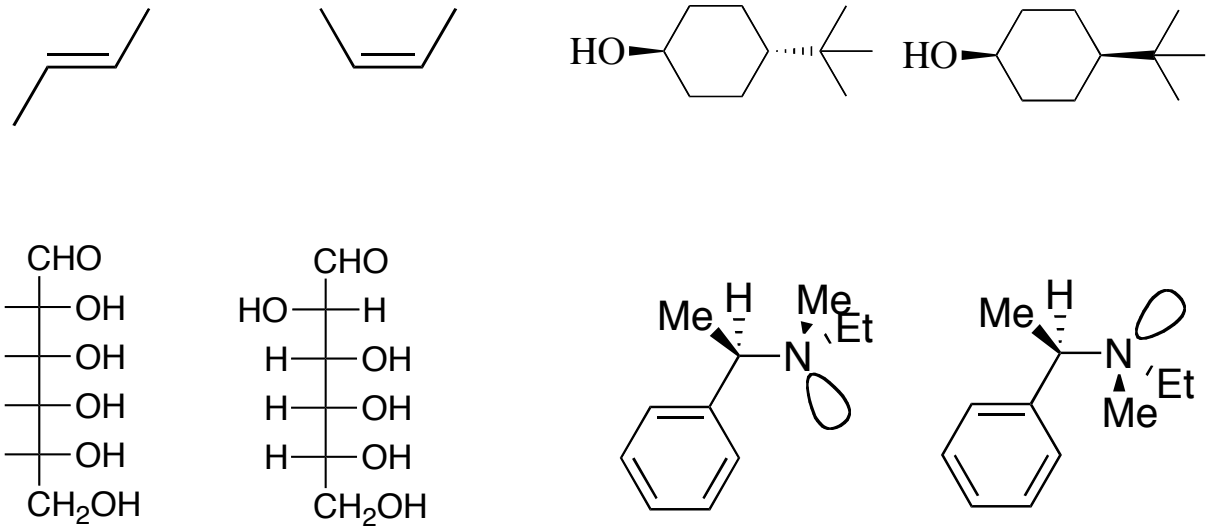
For the tetrahedral carbon atom the interchange
leads to an enantiomer



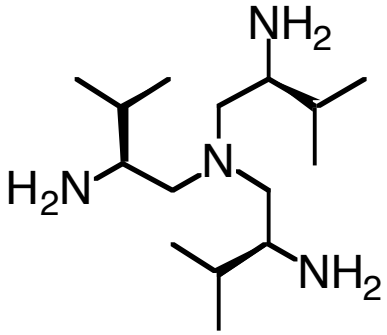
This is not necessarily the case for molecules with other geometries

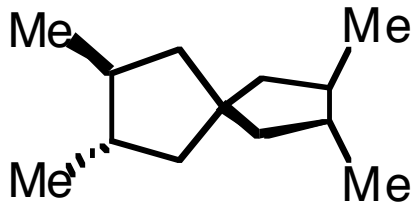
A stereogenic center may or may not be chiral, but all chiral centers are stereogenic.

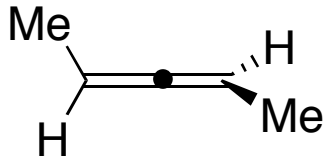
Diastereomers

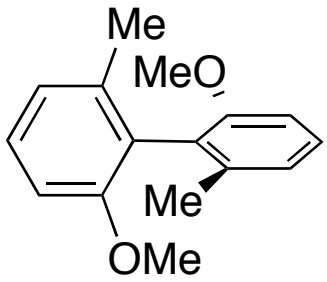


Chiral?



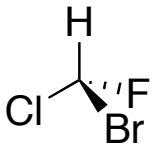


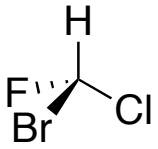




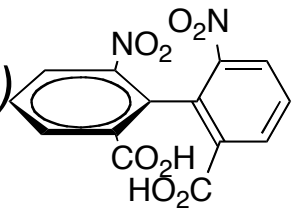
Chiral (or stereogenic) elements

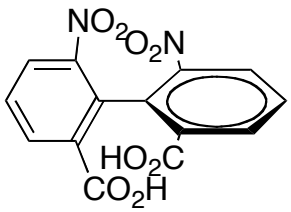
- *Chiral (stereogenic) center*

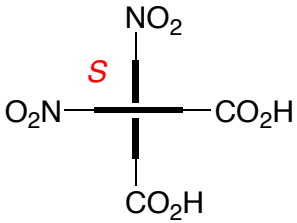




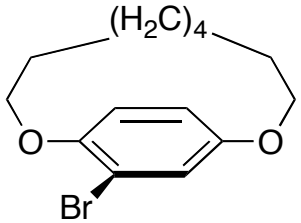
- *Chiral (stereogenic) axis*

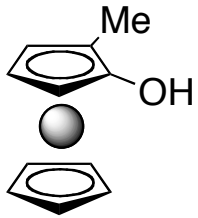


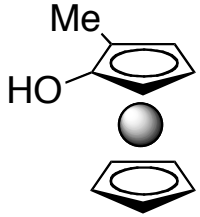




- *Chiral (stereogentic) plane*

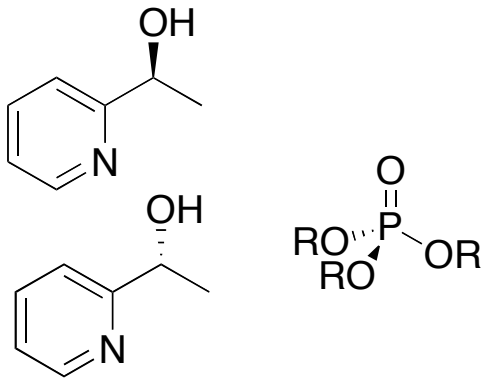






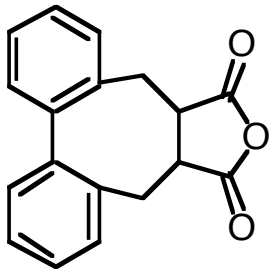
Exercise

Racemic 2-(1-hydroxyethyl)pyridine reacts with $POCl_3$ to yield a phosphoric ester, $OP(OR)_3$. Describe the methyl part of the ^1H NMR spectrum of the product mixture, assuming a statiscial ratio of isomers



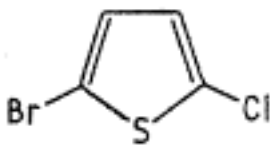
Exercise

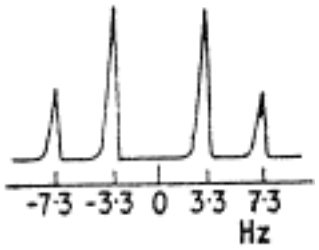
Draw all stereoisomers of the anhydride **1**.
Which isomers are chiral? Are there any symmetry elements? The optical rotation of two of the isomers approaches zero after standing at room temperature. Which are these isomers? Explain the phenomenon.



1

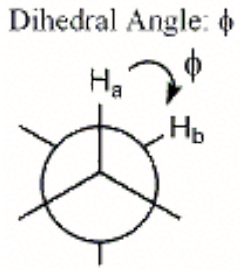
AB-spectrum

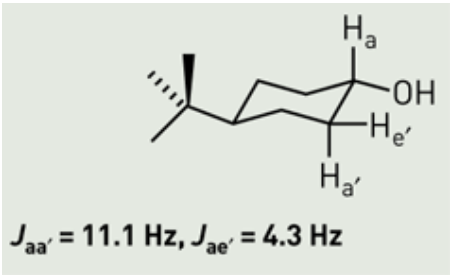


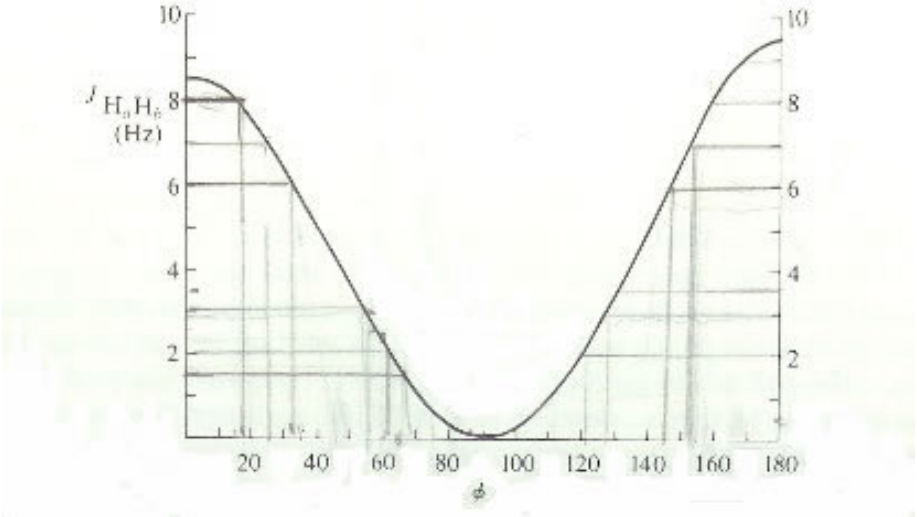


http://micro.magnet.fsu.edu/electromag/java/nmr/abspectrum/

Karplus' equation





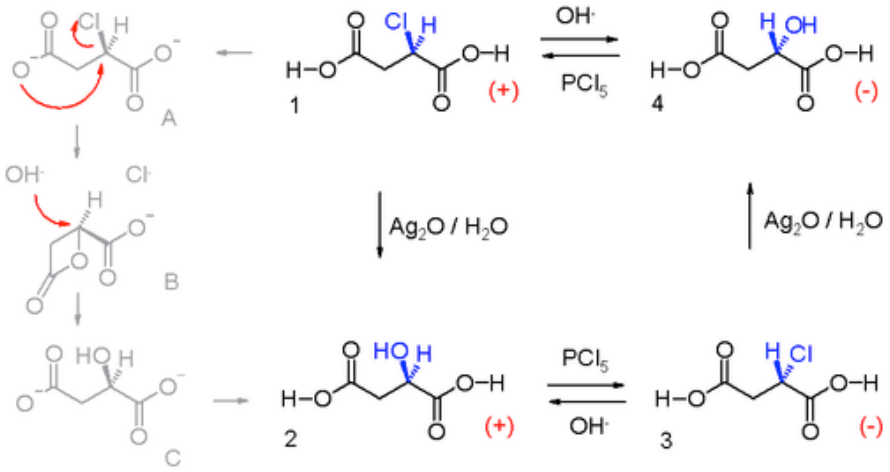


J. Chem. Phys. **1959**, *30,* 11
J. Am. Chem. Soc. **1963**, *85*, 2870

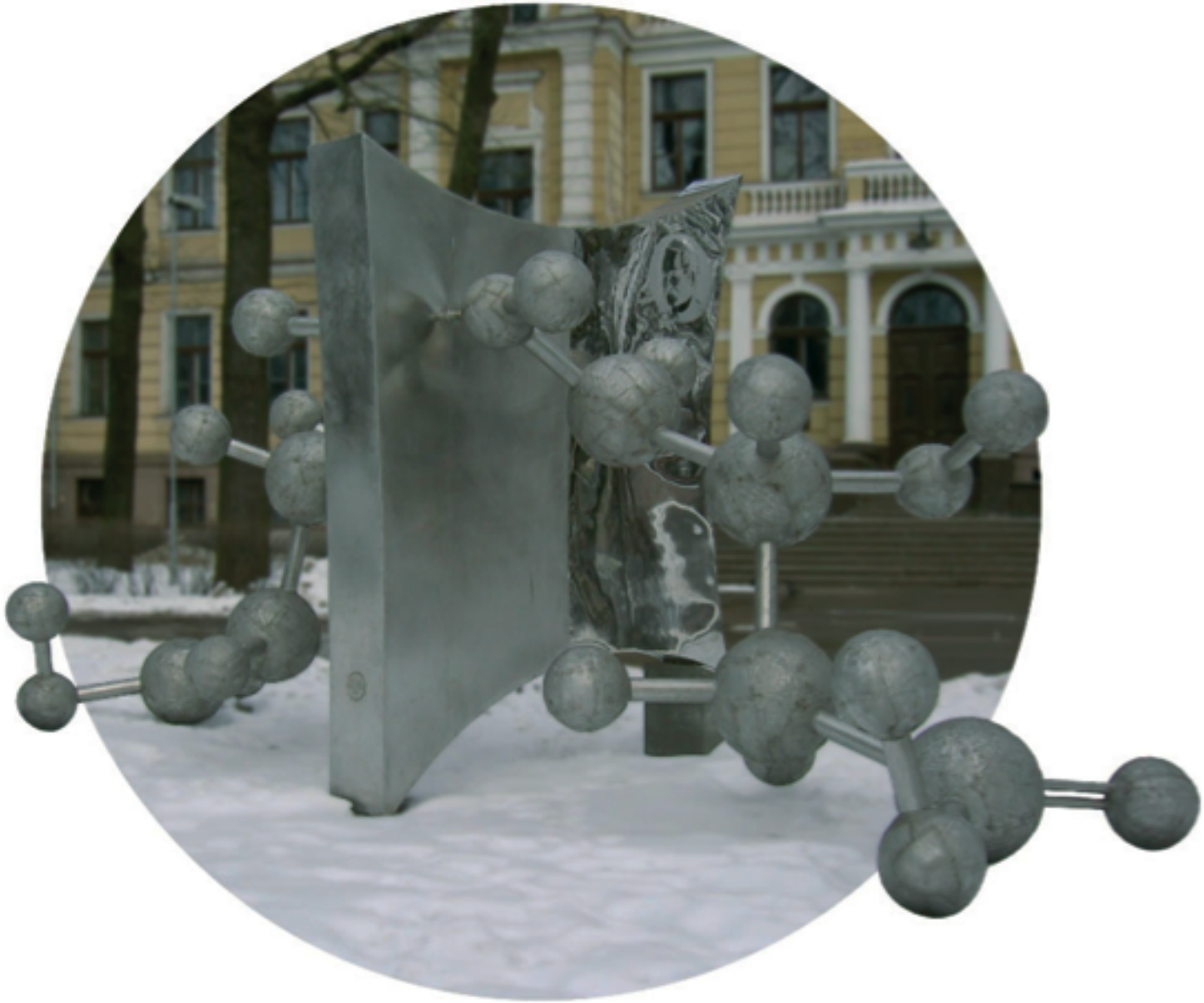
How to get chiral enantioenriched molecules?

- The chiral pool
- Separation of enantiomers
- Kinetic resolution (dynamic kinetic resolution)
- Stereoselective synthesis

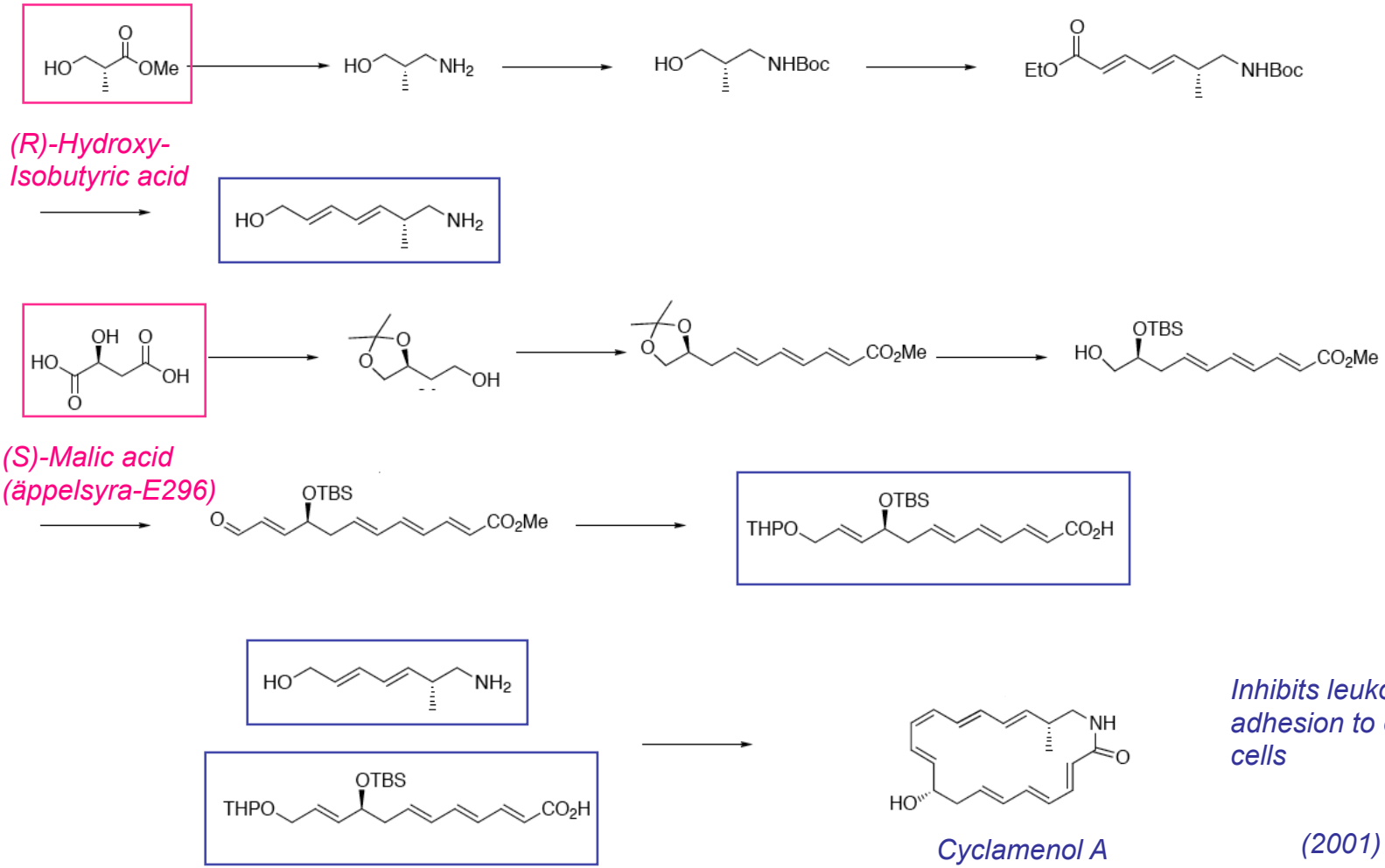
"Life depends on chiral recognition, because living systems interact with enantiomers in decisively different manners" (R Noyori)



Paul Walden

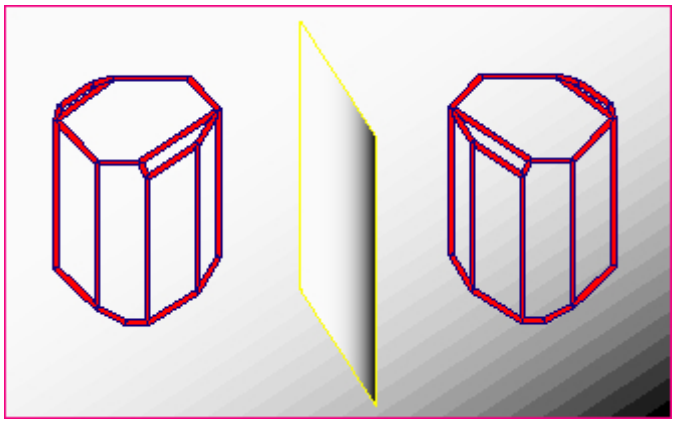


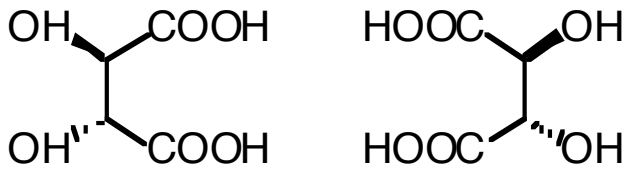
The Chiral Pool - Kirala poolen



Inhibits leukocyte adhesion to endothelial cells

(2001)




OH
COOH
OH
COOH

HOOC
OH
HOOC
OH

Asymmetric synthesis: De novo synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other.

Molecules which contain at least one chiral element: lack of agreement; use

Stereoselective synthesis
Enantioselective synthesis
Diastereoselkective synthesis

Methods for stereoselective (asymmetric) synthesis

–Diastereoselective reaction with chiral substrate

–Use of chiral auxiliary

–Use of chiral reagent

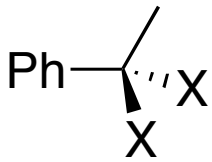
–Asymmetric catalysis

- •Chiral metal catalyst
- •Enzymatic catalysis
- •Catalytic antibodies
- •Organocatalysis

Catalysis has a key role to play in the development of Green Chemistry - not only for replacement of old stoichiometric reactions, but also for the development of new reactions.

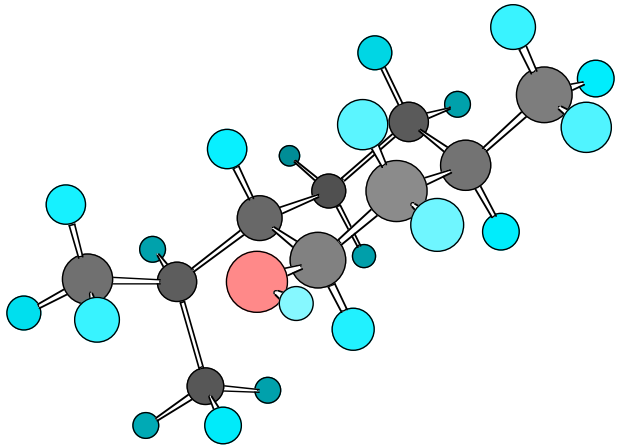
Chiral induction in catalytic reactions

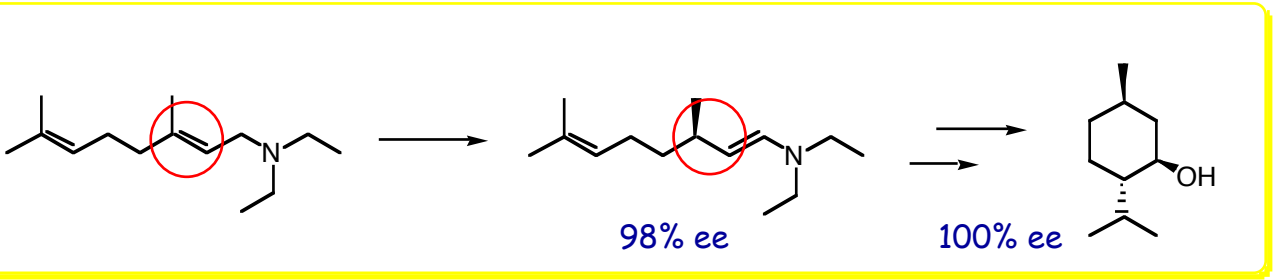
Enantiotopic faces



Enantiotopic groups

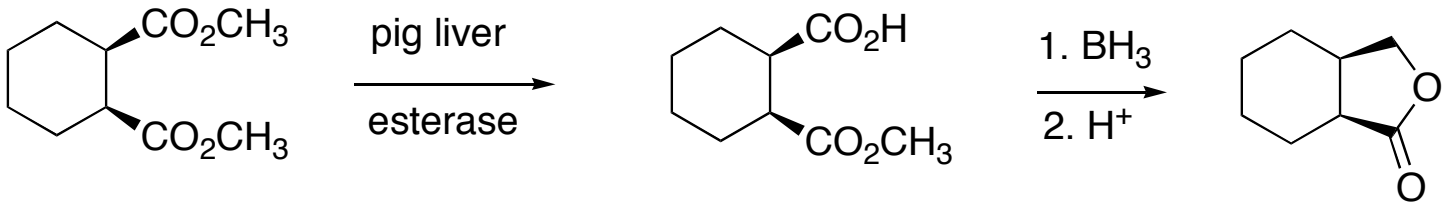
(-)-Menthol
20 000 ton/year



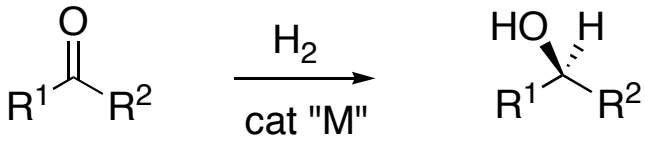


TOF = 50 000

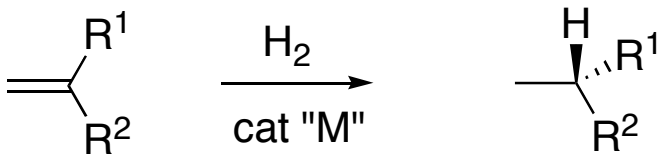
Enzymatic hydrolysis



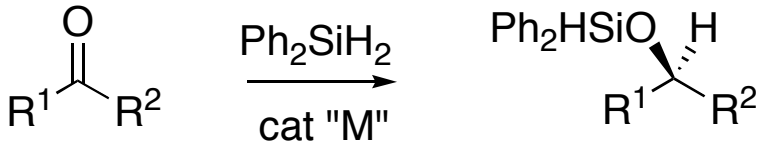
Examples of additions to enantiotopic faces



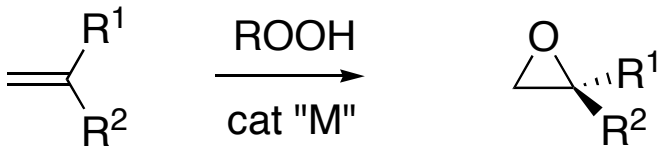
hydrogenation



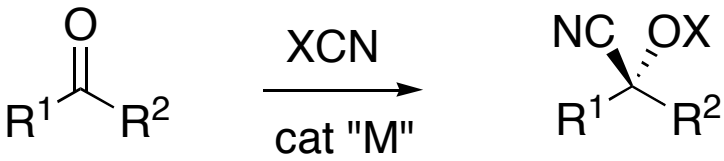
hydrogenation



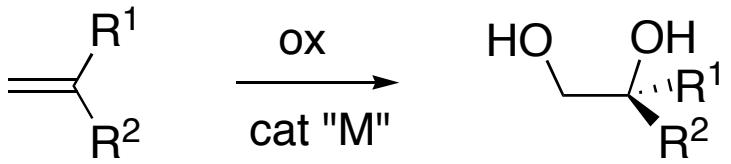
hydrosilylation



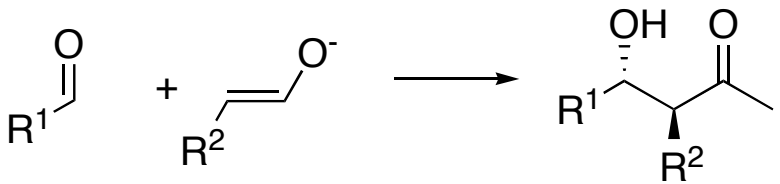
epoxidation



hydrocyanation

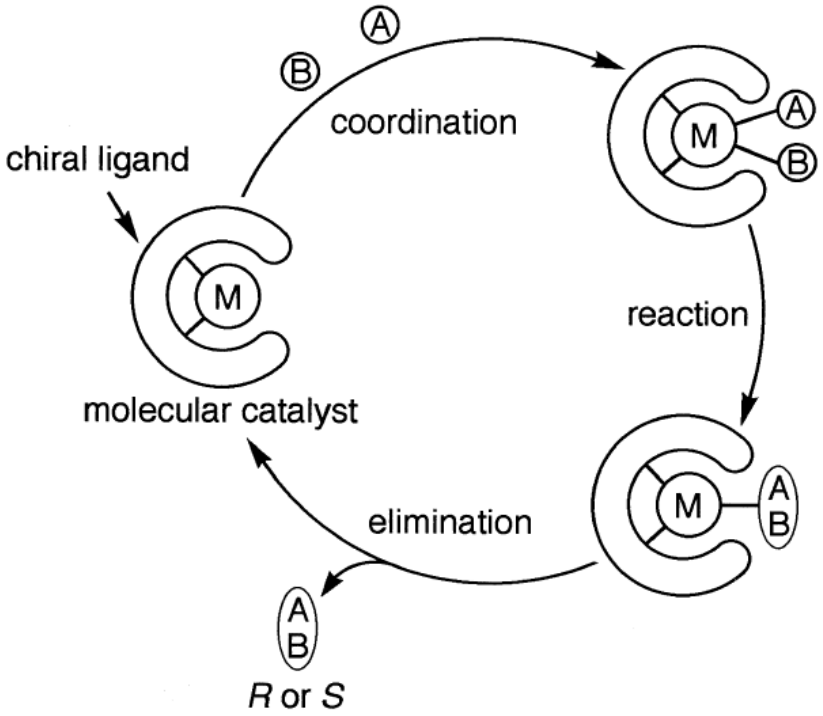


dihydroxylation

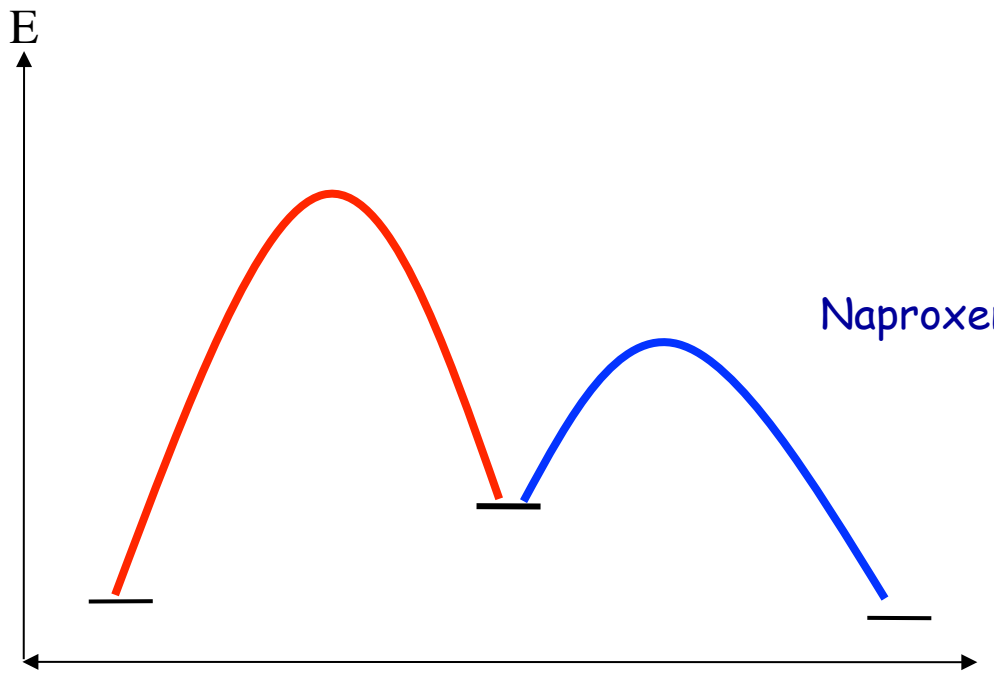


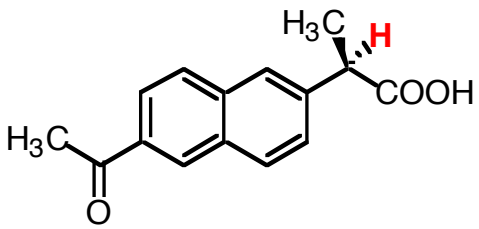
aldol condensation

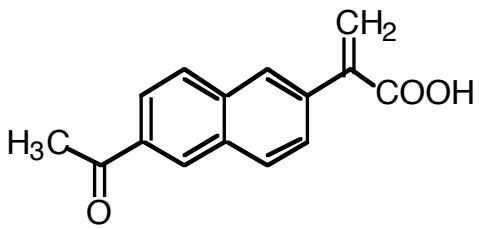
Catalytic cycle

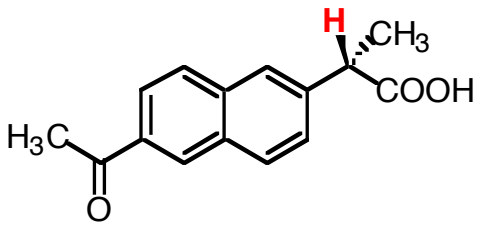


Catalytic hydrogenation

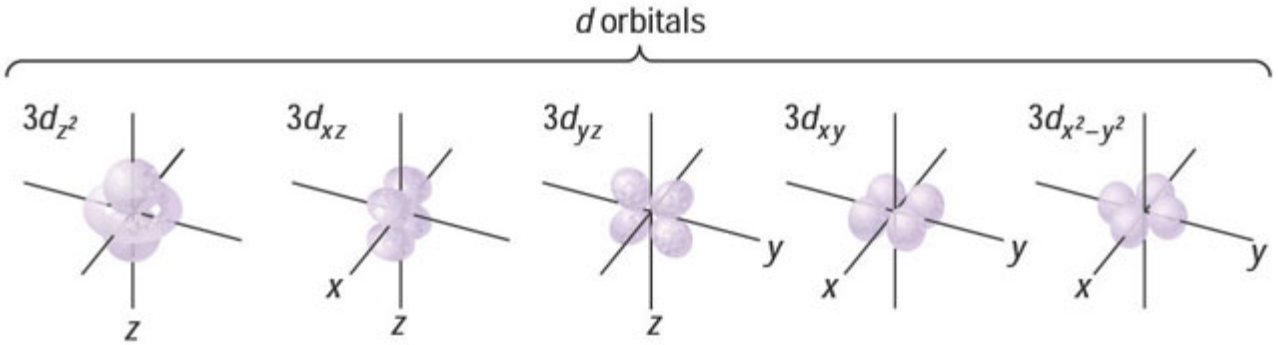




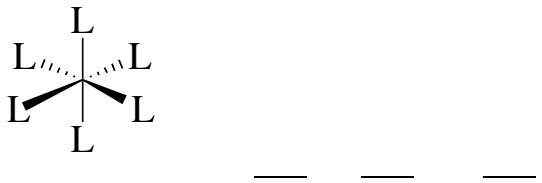




Bonding in transition metal complexes

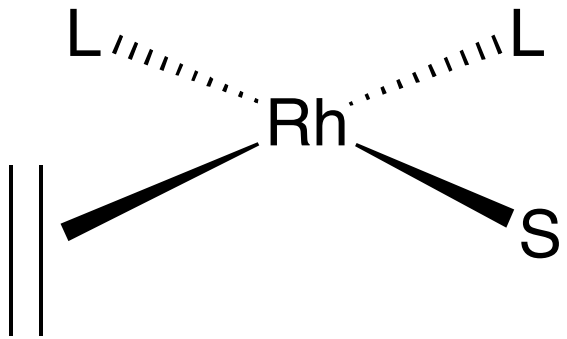


Octahedral complex

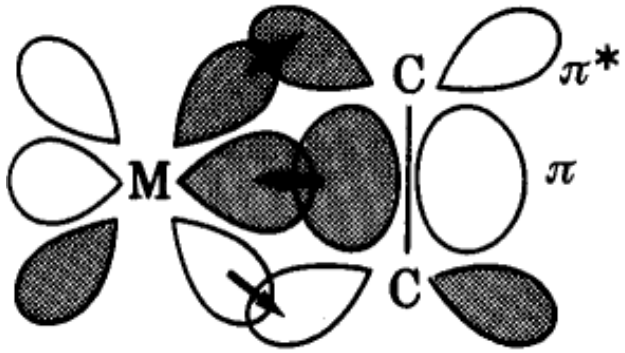


Square planar complex

Square planar Rh(I) complex
Two coordination sites available for the olefin

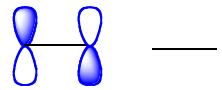


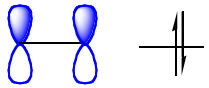
The Dewar-Chatt-Duncanson model

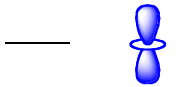


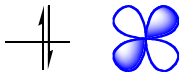
olefin

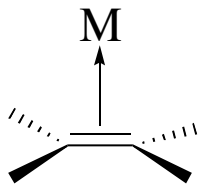
metal











Pd(II)

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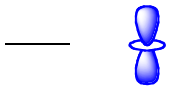
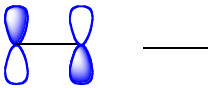
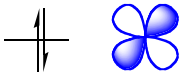
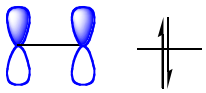
olefin

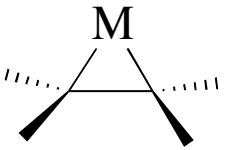
metal





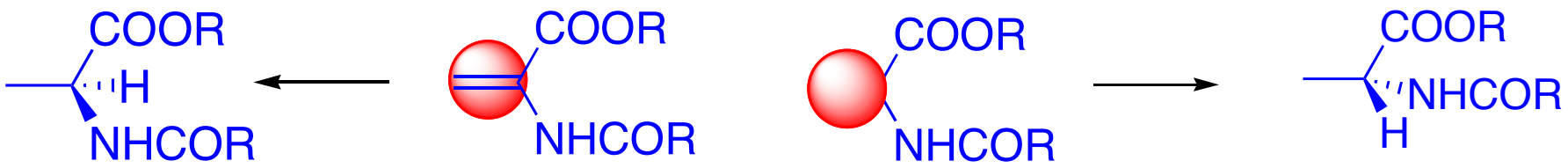






Pd(O)

Determination of stereochemistry



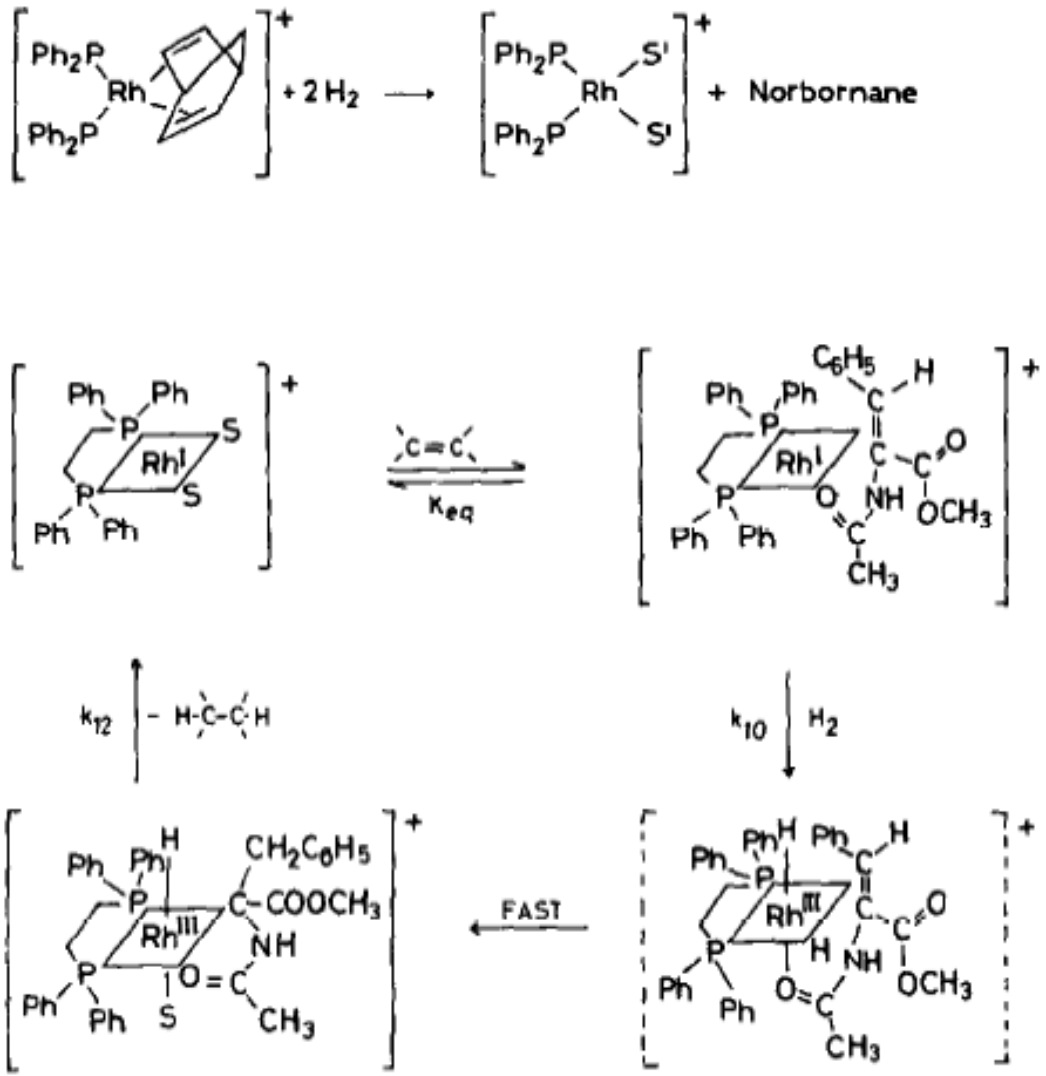
Diastereomeric complexes

Inorganica Chimica Acta, 50 (1981) 11–19

Mechanistic Aspects of Homogeneous Catalytic Hydrogenation and Related Processes

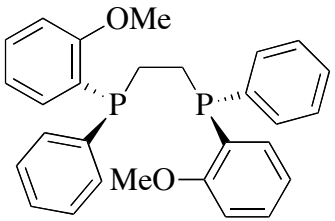
JACK HALPERN

Department of Chemistry, The University of Chicago, Chicago, Ill. 60637, U.S.A.

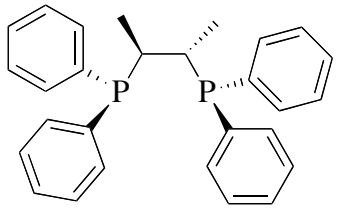


Mechanism of the $[Rh(DIPHOS)(MeOH)_2]^+$-catalyzed hydrogenation of MAC. (S = MeOH)

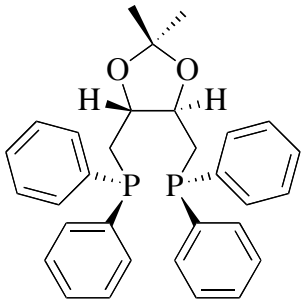
Chiral ligands



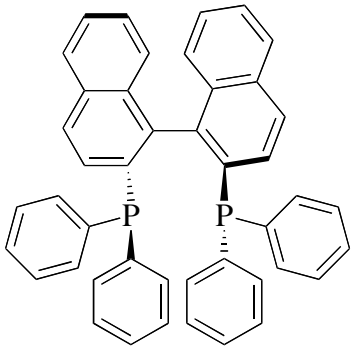
(R,R)-DIPAMP



(S,S)-CHIRAPHOS

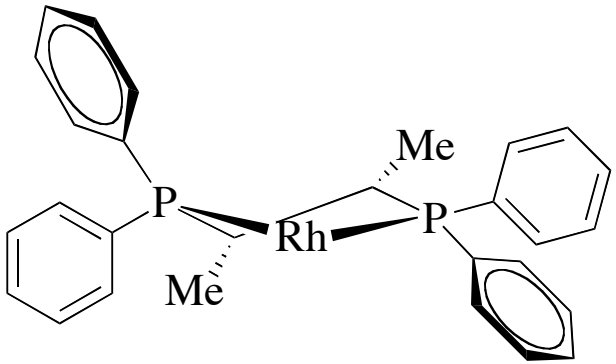


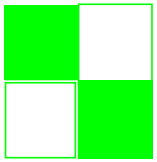
(R,R)-DIOP

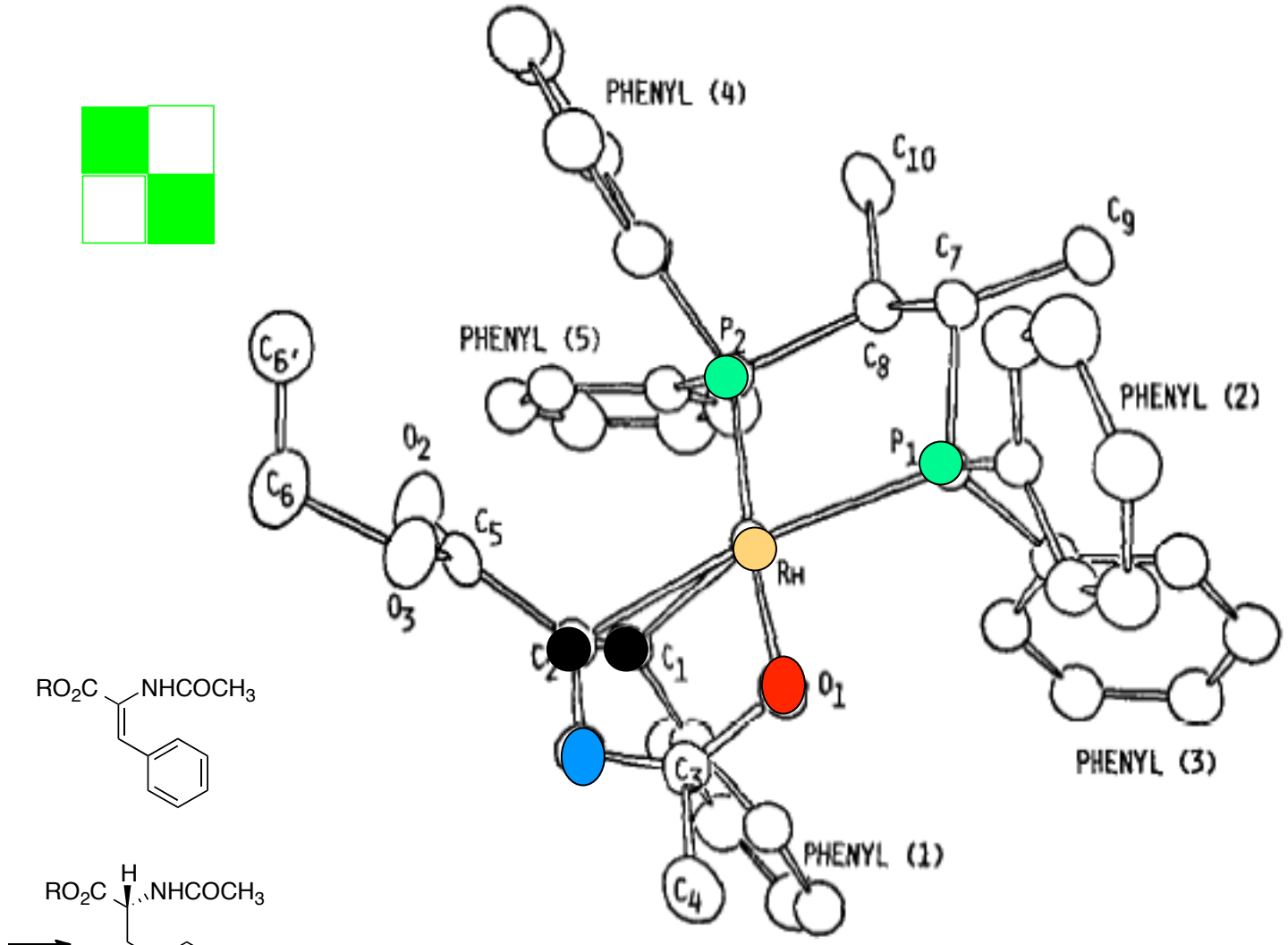


(a*R*)-BINAP

Conformation (S,S)-Chiraphos

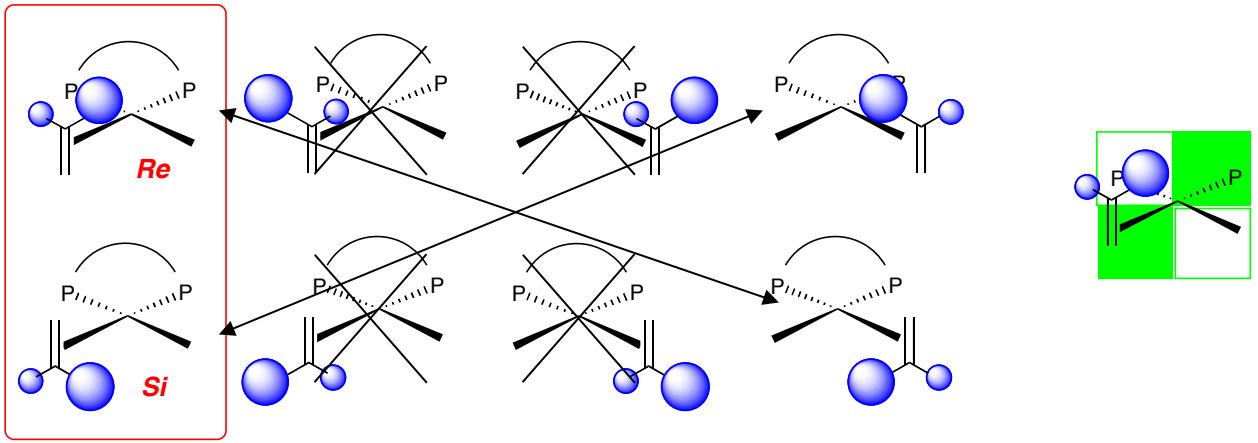


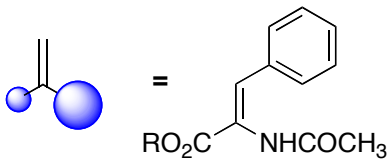




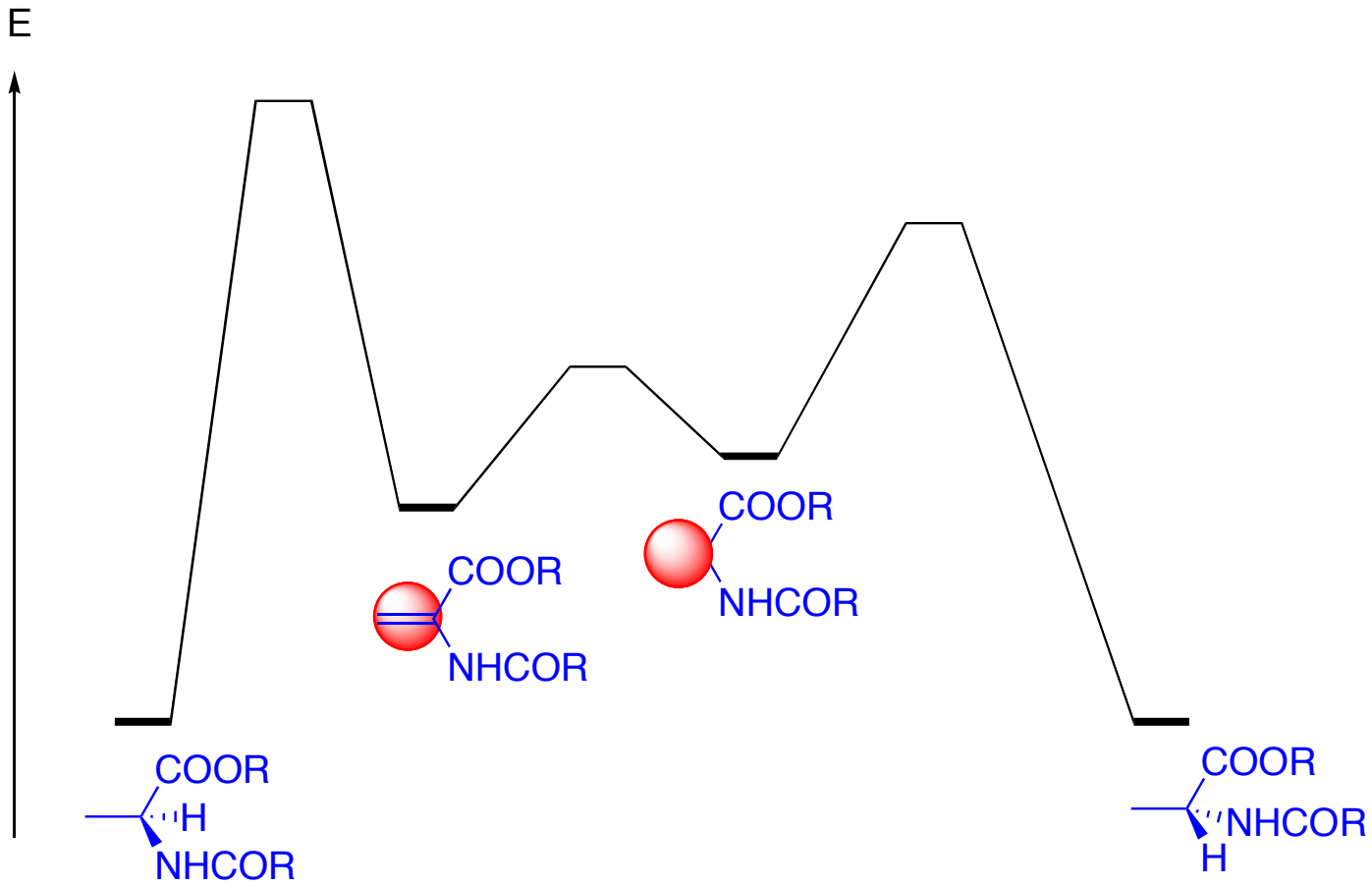
Structure of [Rh(S,S-CHIRAPHOS)(EAC)]⁺.

Rh(I)-olefinkomplex

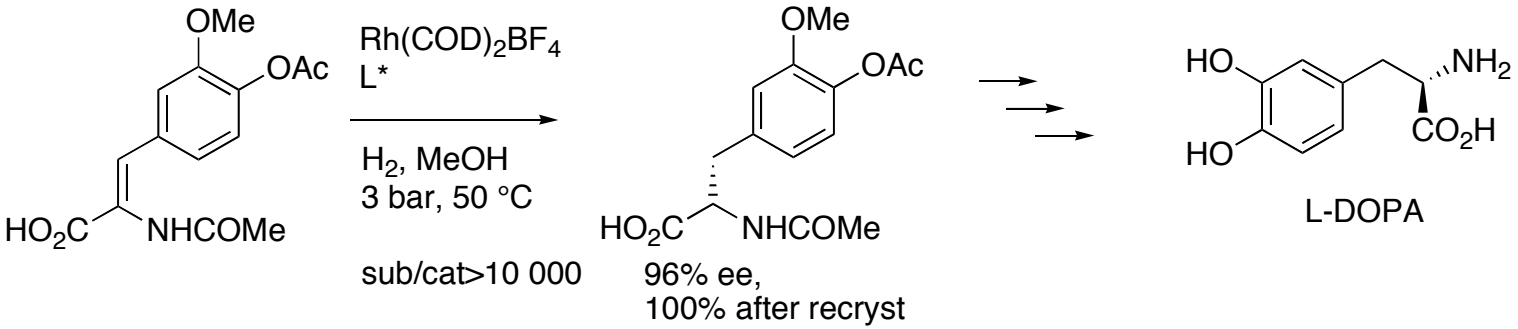




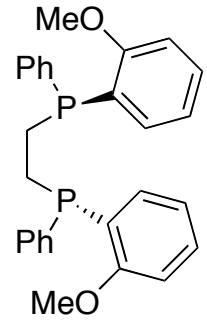
Curtin Hammet principle

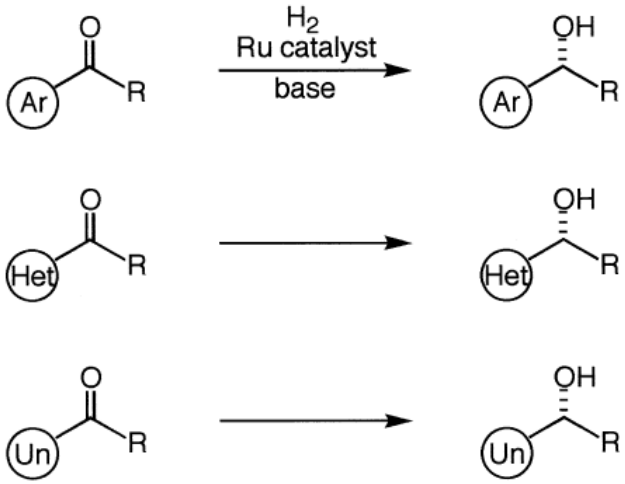


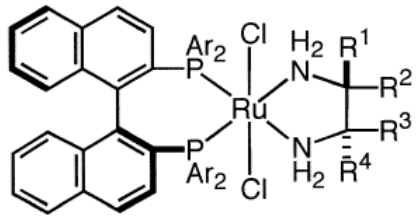
Preparation of L-Dopa



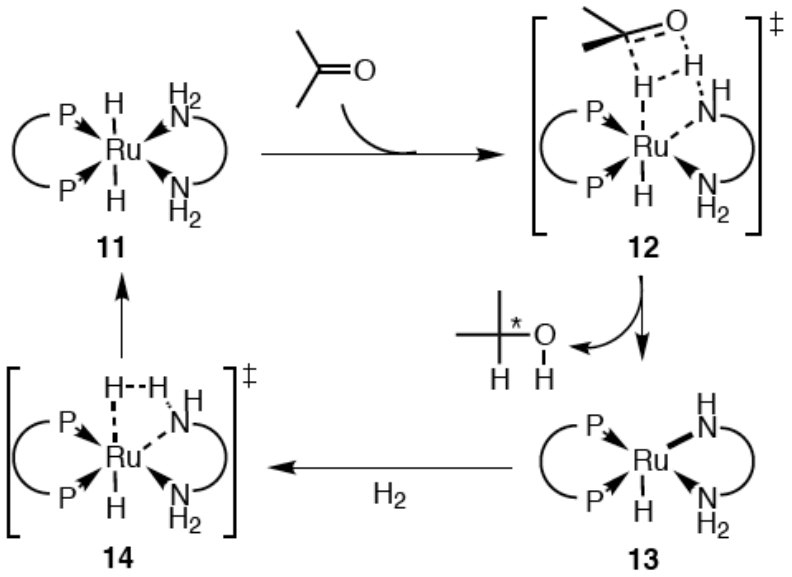
L* =



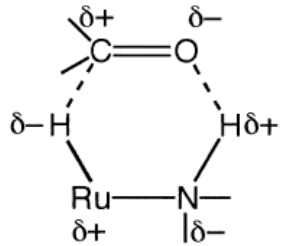


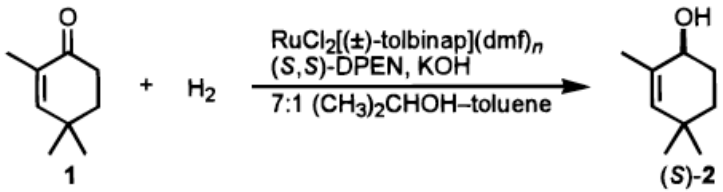


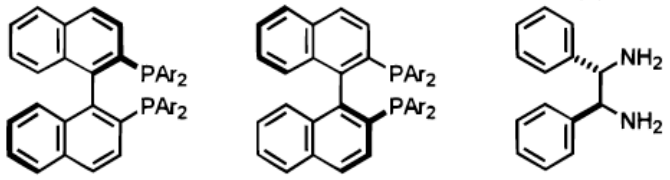
(*S*)-BINAP/(*S*)-diamine–Ru(II) catalyst

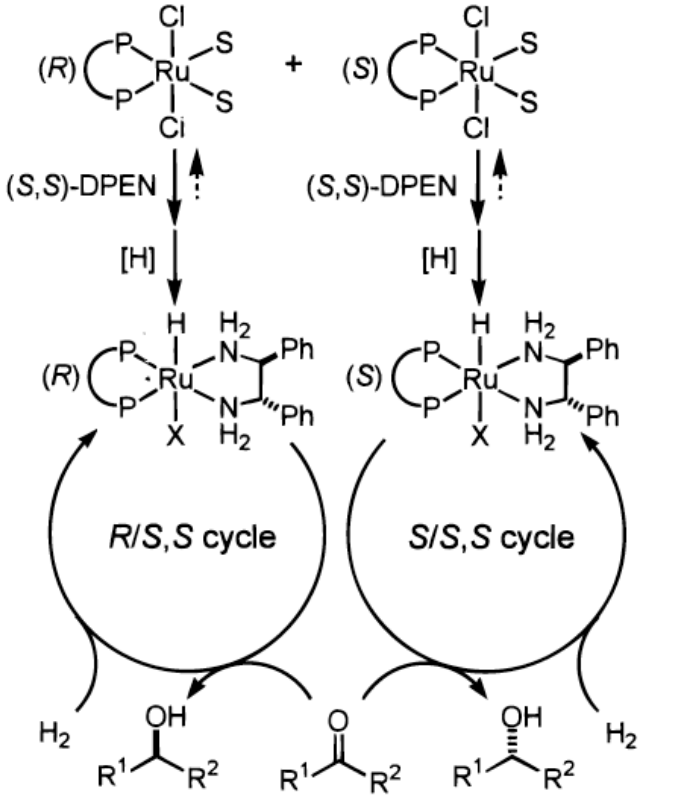


Scheme 1. The catalytic mechanism of asymmetric hydrogenation of ketones.

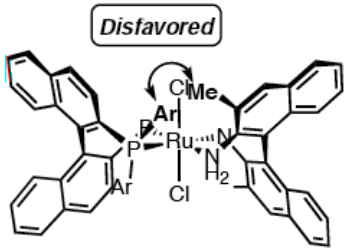




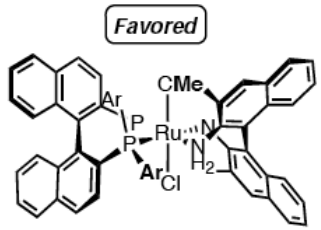




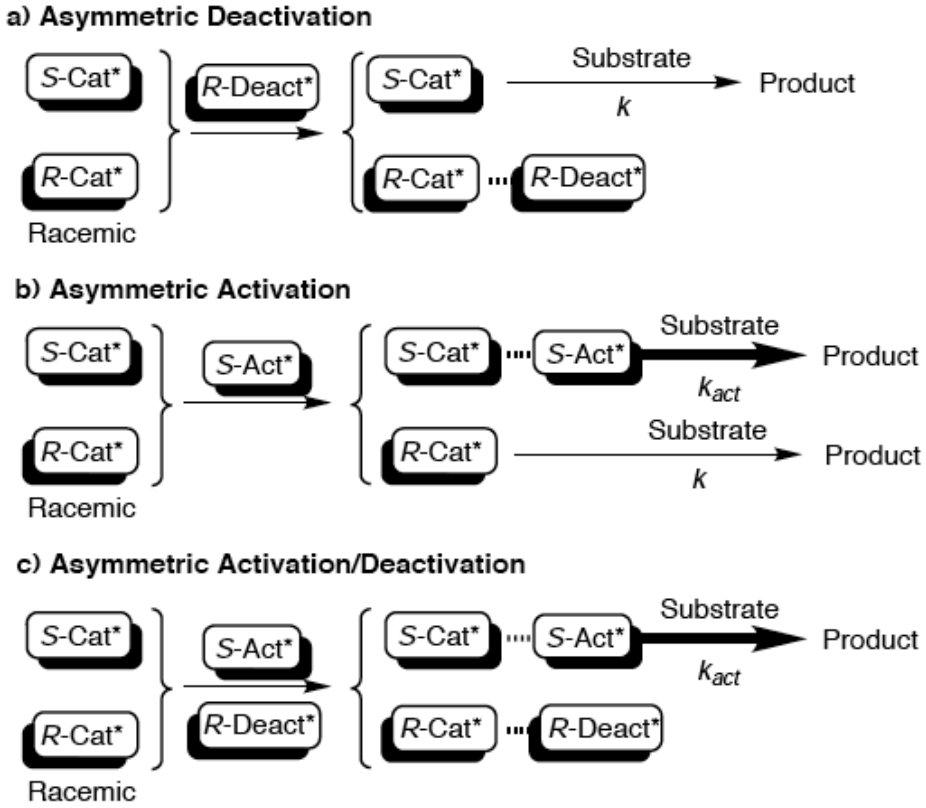
P–P = (*R*)- or (*S*)-TolBINAP; S = DMF or other ligands; X = Cl, H, etc.

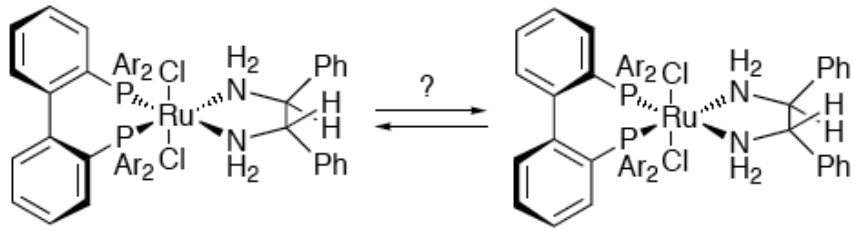


(*R*)-BINAP-Ru(II)Cl_2/(*S*)-DM-DABN

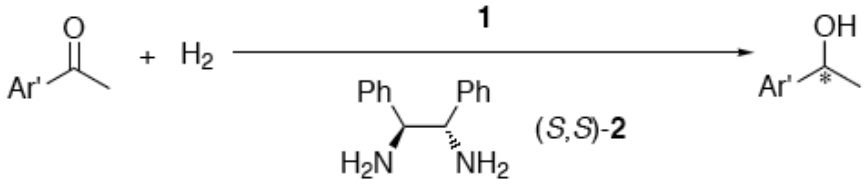


(*S*)-BINAP-Ru(II)Cl_2/(*S*)-DM-DABN

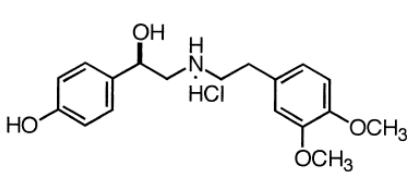

a) Asymmetric Deactivation
S-Cat*
R-Cat*
Racemic
R-Deact*
S-Cat*
R-Cat*
R-Deact*
Substrate
k
Product
b) Asymmetric Activation
S-Cat*
R-Cat*
Racemic
S-Act*
S-Cat*
S-Act*
Substrate
k_act
Product
R-Cat*
Substrate
k
Product
c) Asymmetric Activation/Deactivation
S-Cat*
R-Cat*
Racemic
S-Act*
R-Deact*
S-Cat*
S-Act*
Substrate
k_act
Product
R-Cat*
R-Deact*


Ar2
P
Cl
Ru
P
Ar2
Cl
H2
N
N
H2
Ph
H
H
Ph
?
Ar2
P
Cl
Ru
P
Ar2
Cl
H2
N
N
H2
Ph
H
H
Ph

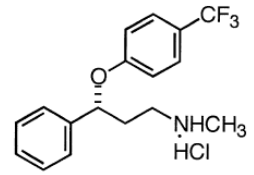
(*S*)-**1** / (*S*,*S*)-**2** (*R*)-**1** / (*S*,*S*)-**2**


O
Ar'
+ H2
1
Ph
Ph
H2N
NH2
(S,S)-2
OH
Ar'
*

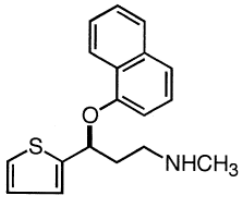
$RuCl_2$-BINAP-diamine-catalyzed reduction of ketones



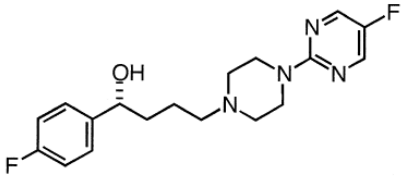
denopamine hydrochloride
β_1-receptor agonist



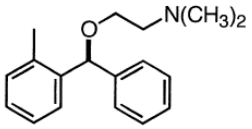
fluoxetine hydrochloride
antidepressant agent



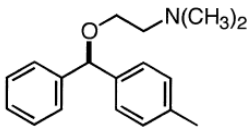
duloxetine
inhibitor of serotonin and
norepinephrine



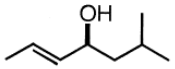
BMS 181100
antipsychotic agent



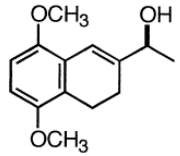
orphenadrine
antihistaminic and
anticholinergic agent



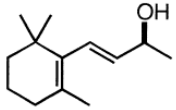
neobenodine
antihistaminic agent



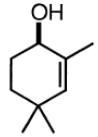
precursor of
α-tocopherol



precursor of
anthracyclins



β-ionol



precursor of
α-damascone

Industrial-Scale Synthesis and Applications of Asymmetric Hydrogenation Catalysts

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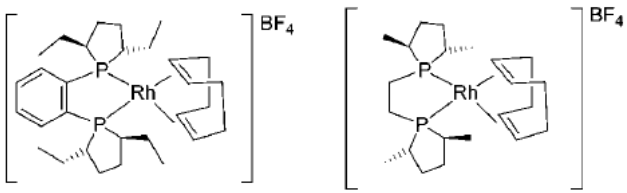
Acc. Chem. Res. **2007,** *40,* 1291–1299



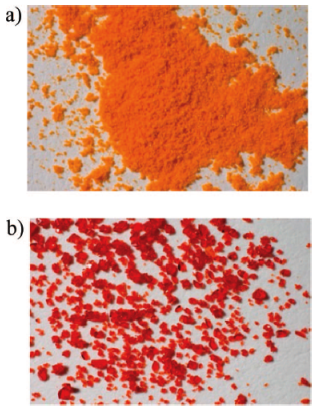
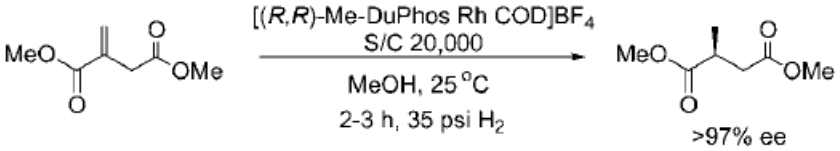
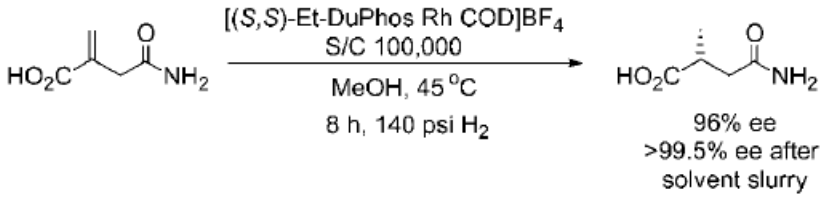


FIGURE 4. Precatalyst made by (a) first-generation synthesis and (b) optimized synthesis.

Scheme 3. Asymmetric Hydrogenation of Dimethyl Itaconate



Scheme 4. Asymmetric Hydrogenation of Methylene Succinamic Acid



Asymmetric Hydrogenation of Itaconates. Enantiomerically enriched two-substituted succinic acids are used as peptidomimetics in several drug candidates and can be made using asymmetric hydrogenation. Rhodium DuPhos catalysts have been shown to be extremely active and selective for the asymmetric hydrogenation of itaconates,[18] and we have manufactured in excess of 1 metric ton of (*S*)-dimethyl methylsuccinate (Scheme 3) using such a process. An extremely good molar substrate to catalyst (S/C) loading of 20,000 (4,800, wt/wt was achieved), thus making the asymmetric hydrogenation of a low-molecular-weight substrate viable. Furthermore, the pro-

Hydrogenation Processes in the Synthesis of Perfumery Ingredients

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Firmenich SA, P.O. Box 239, CH-1211 Geneva 8, Switzerland

Acc. Chem. Res. **2007,** *40,* 1309–1319

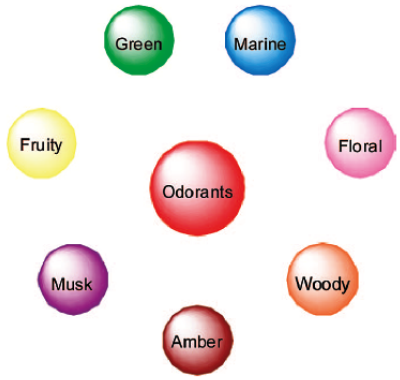
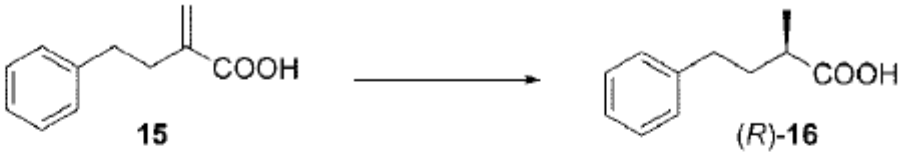
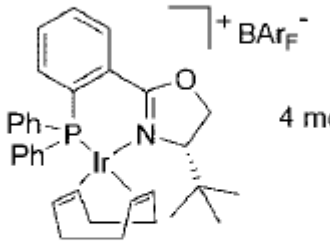


FIGURE 1. Odorant families.

Scheme 3

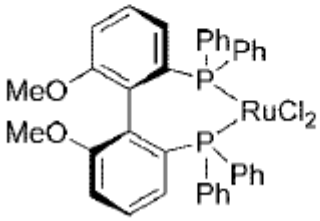


15 (*R*)-**16**



17

4 mol% **17**, 2 bar H_2, CH_2Cl_2, 0°C — 100% conv., 80% ee



18

0.6 mol% **18**, 100 bar H_2, Et_3N, MeOH, 0°C — 100% conv., 96% ee

Hydrogenation Processes in the Synthesis of Perfumery Ingredients

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Synthesis, Corporate R&D Division,
Firmenich SA, P.O. Box 239, CH-1211 Geneva 8, Switzerland

Acc. Chem. Res. **2007,** *40,* 1309–1319

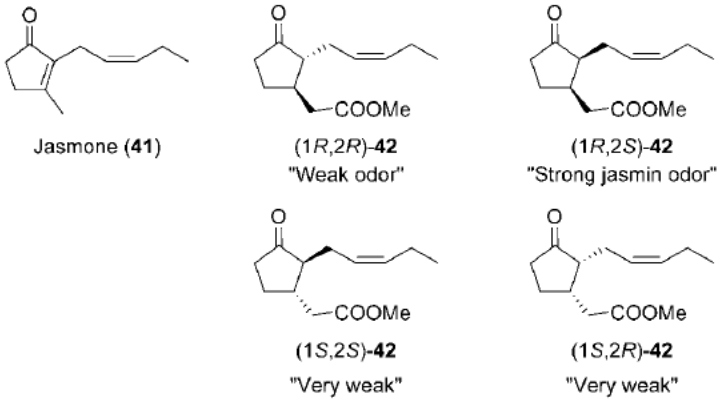
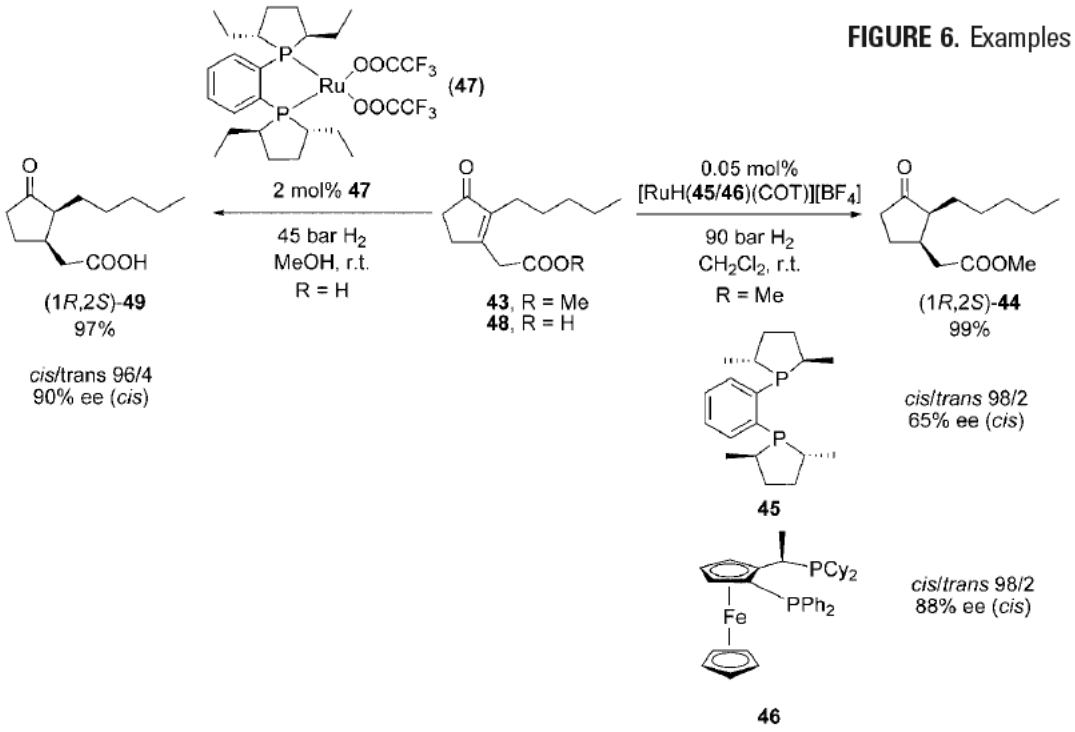


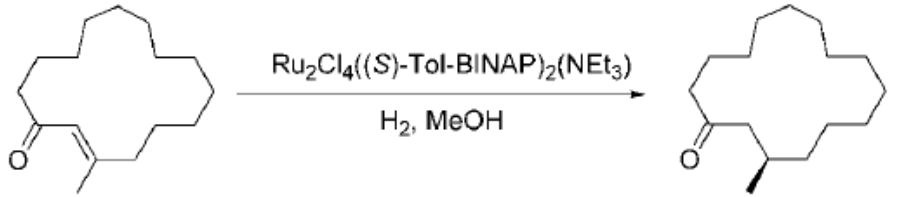
FIGURE 6. Examples of jasmin odorants.



Hydrogenation Processes in the Synthesis of Perfumery Ingredients

LIONEL A. SAUDAN*
Synthesis, Corporate R&D Division,
Firmenich SA, P.O. Box 239, CH-1211 Geneva 8, Switzerland

Acc. Chem. Res. **2007,** *40,* 1309–1319

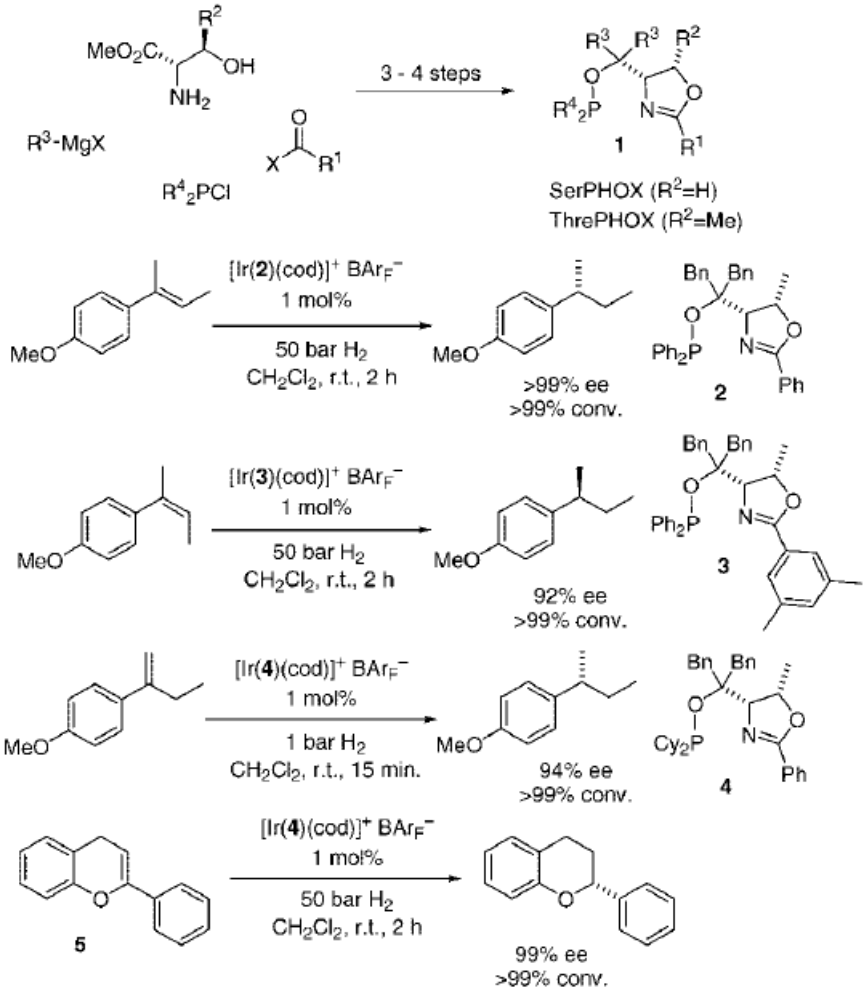


(*E*)-**71** (*R*)-Muscone ((*R*)-**72**)
99% *ee*

Iridium-Catalyzed Asymmet Hydrogenation of Olefins

STEPHEN J. ROSEBLADE AND
ANDREAS PFALTZ*
Department of Chemistry, University of Basel, St Johanns-Ring 19, 4056 Basel, Switzerland

Acc. Chem. Res. **2007,** *40,* 1402–1411



Iridium-Catalyzed Asymmet Hydrogenation of Olefins

STEPHEN J. ROSEBLADE AND
ANDREAS PFALTZ*
Department of Chemistry, University of Basel, St Johanns-Ring 19, 4056 Basel, Switzerland

Acc. Chem. Res. **2007**, *40*, 1402–1411

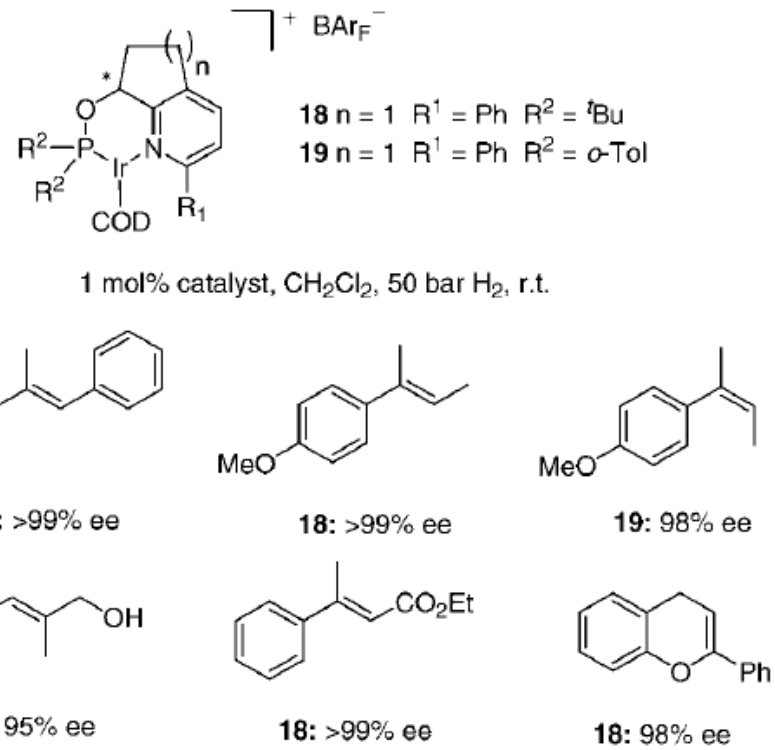
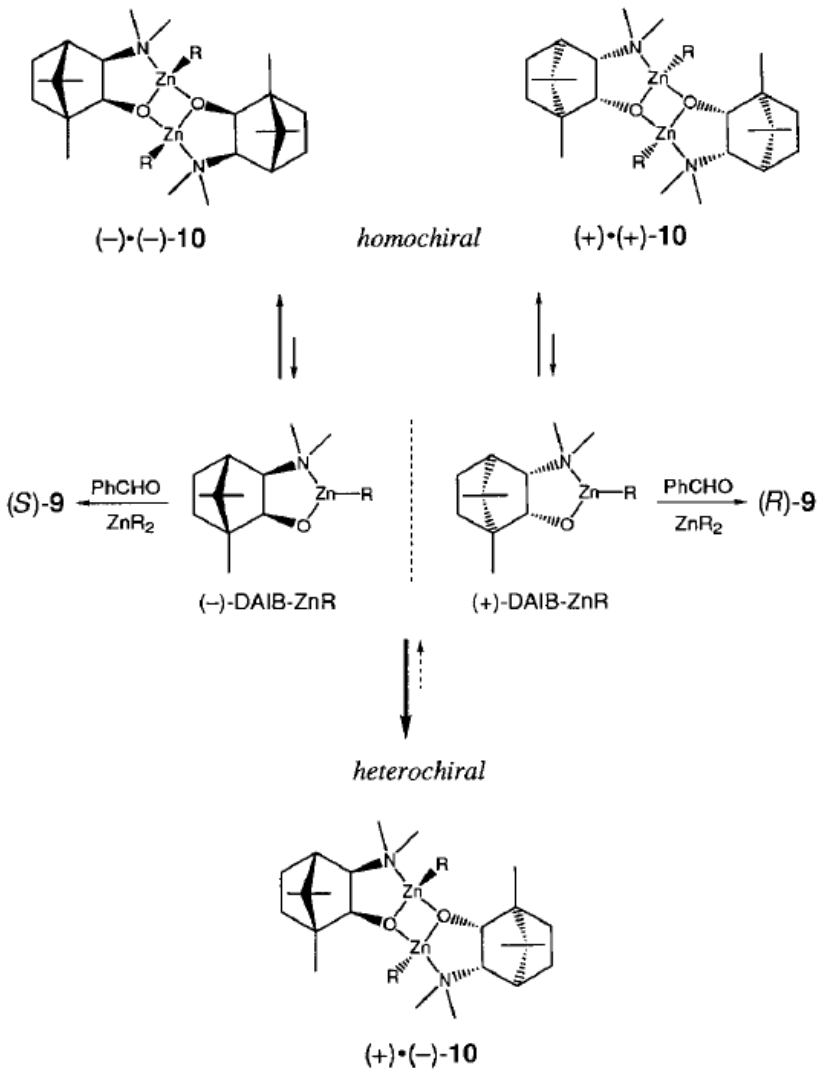


FIGURE 1. Hydrogenation with catalysts **18** and **19**.


(–)•(–)-10
homochiral
(+)•(+)-10
(S)-9
PhCHO
ZnR2
(–)-DAIB-ZnR
(+)-DAIB-ZnR
PhCHO
ZnR2
(R)-9
heterochiral
(+)•(–)-10

Nonlinear effects

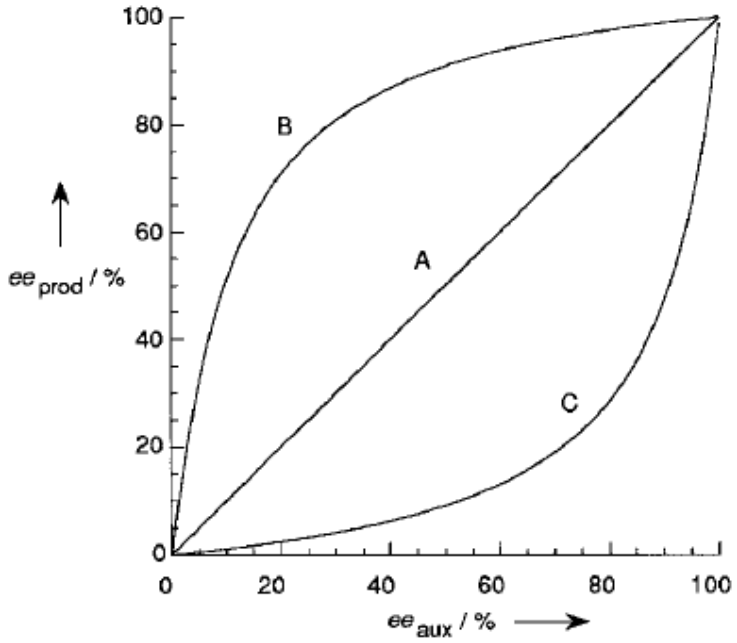
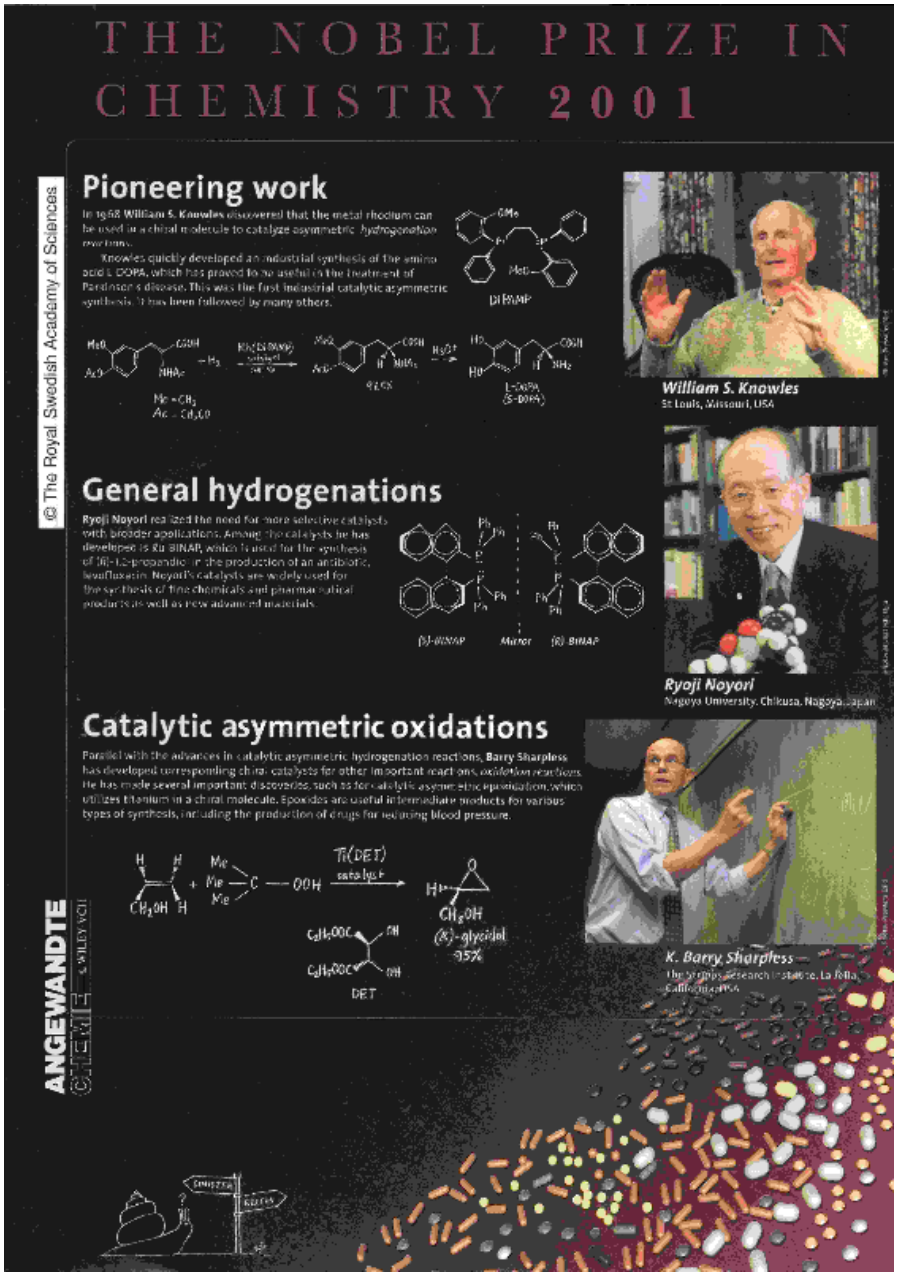
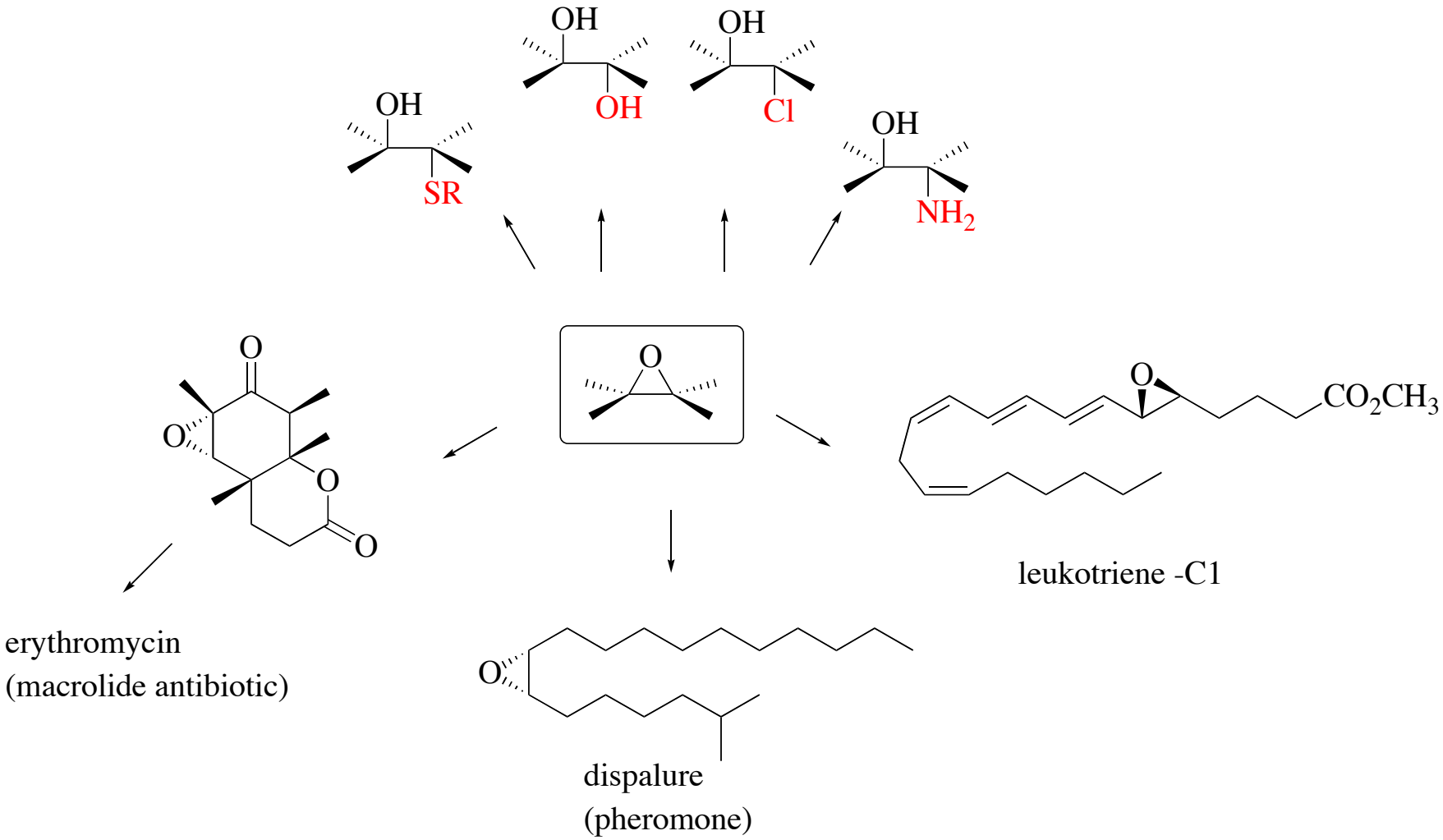


Figure 1. Typical curves for positive (B) and negative (C) nonlinear effects.

Enantioselective reductions and oxidations



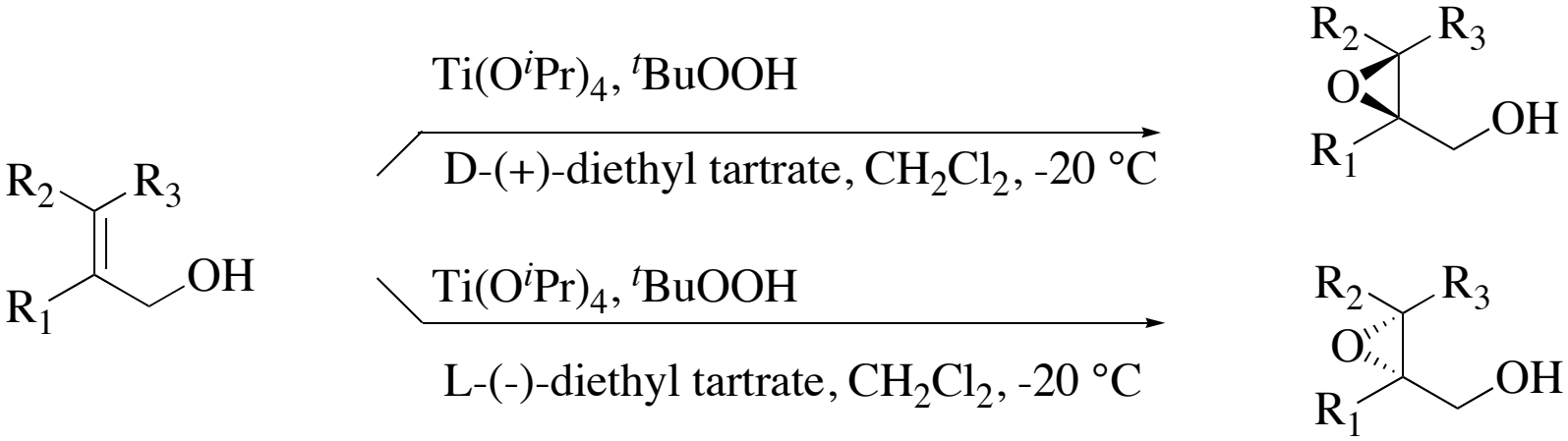
Epoxide Reactions



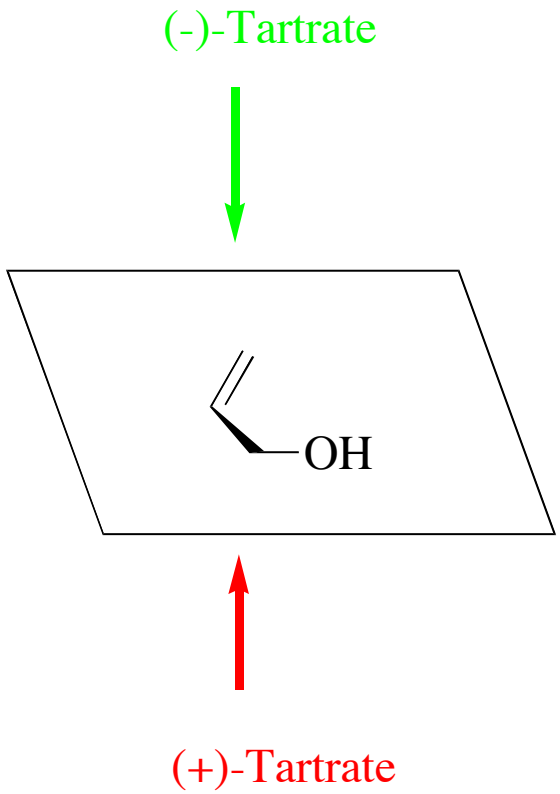
Sharpless Epoxidation

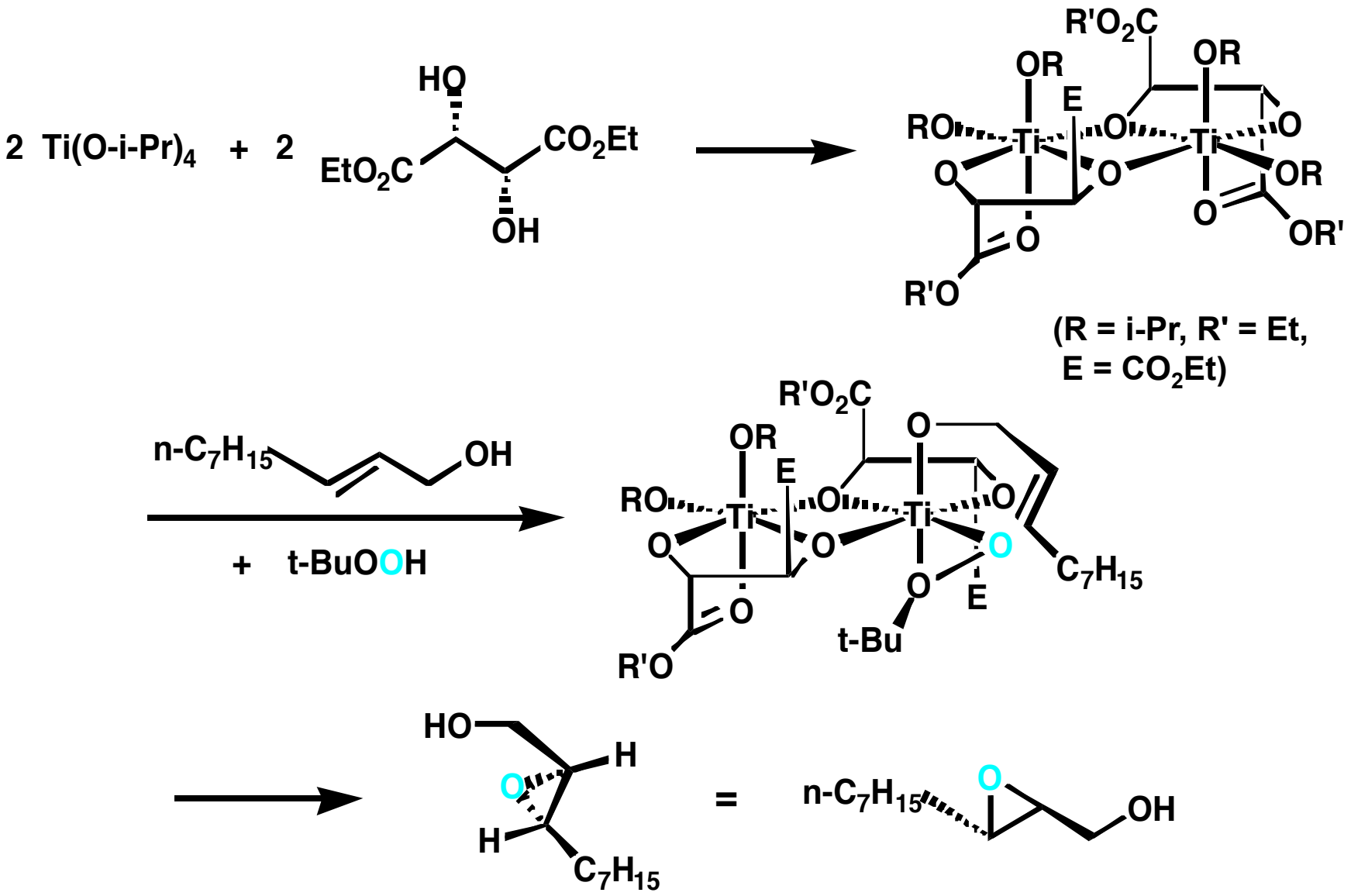
- *Enantioselective epoxidation of allylic alcohols*
- *Reagents involved are*
  - *Tert-butyl hydroperoxide (oxidant)*
  - *Titanium tetraisopropoxide (Lewis acid)*
  - *(+) or (-) dialkyl tartrate (source of chirality)*
- *Double bond adjacent to the OH bearing C is epoxidized*

Sharpless Epoxidation

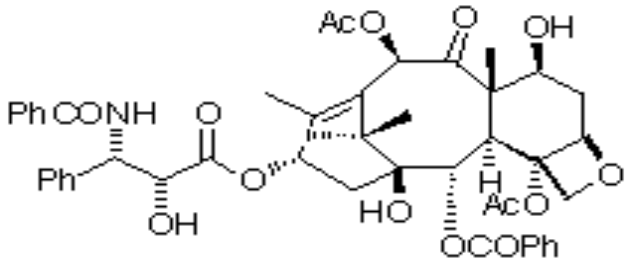


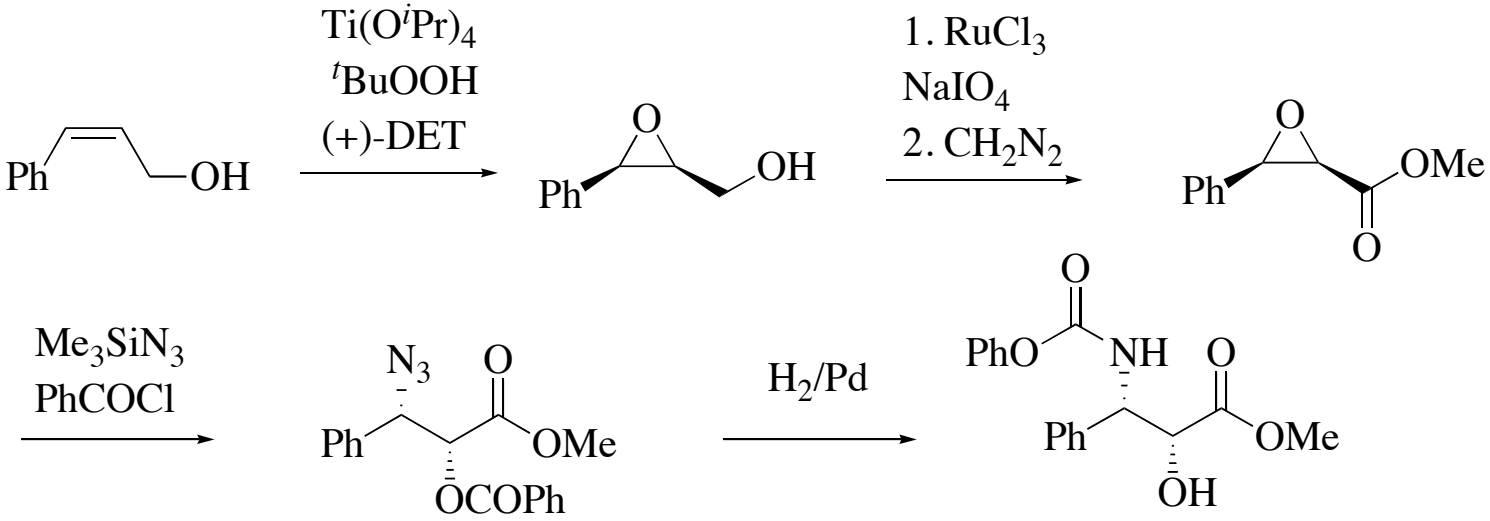
Model for predicting the product



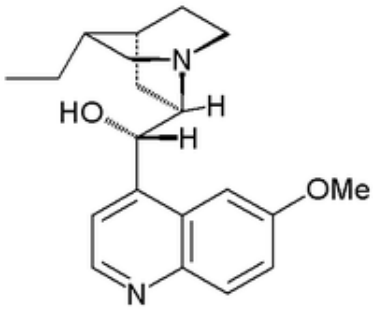

2 Ti(O-i-Pr)4 + 2
HO
EtO2C
CO2Et
OH
R'O2C
OR
OR
E
RO
Ti
O
Ti
O
O
O
O
OR
O
OR'
R'O
(R = i-Pr, R' = Et,
E = CO2Et)
n-C7H15
OH
+ t-BuOOH
R'O2C
O
OR
E
RO
Ti
O
Ti
O
O
O
O
C7H15
O
E
t-Bu
R'O
HO
H
O
H
C7H15
=
n-C7H15
O
OH

Taxol Synthesis

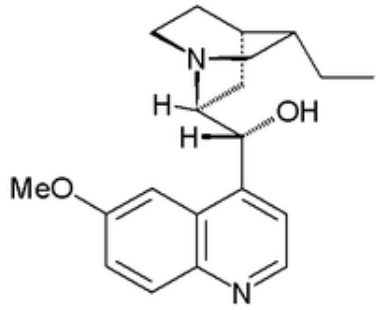




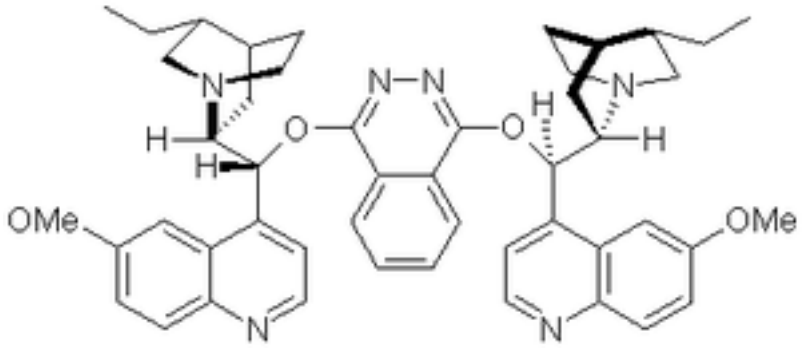
Ligands for Asymmetric Dihydroxylation

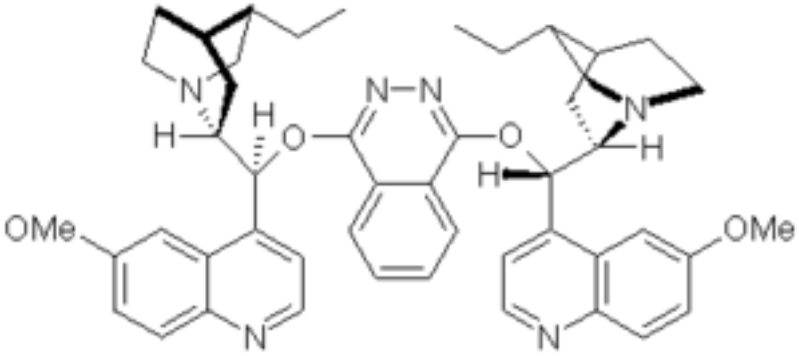


Dihydroquinidine (DHQD)

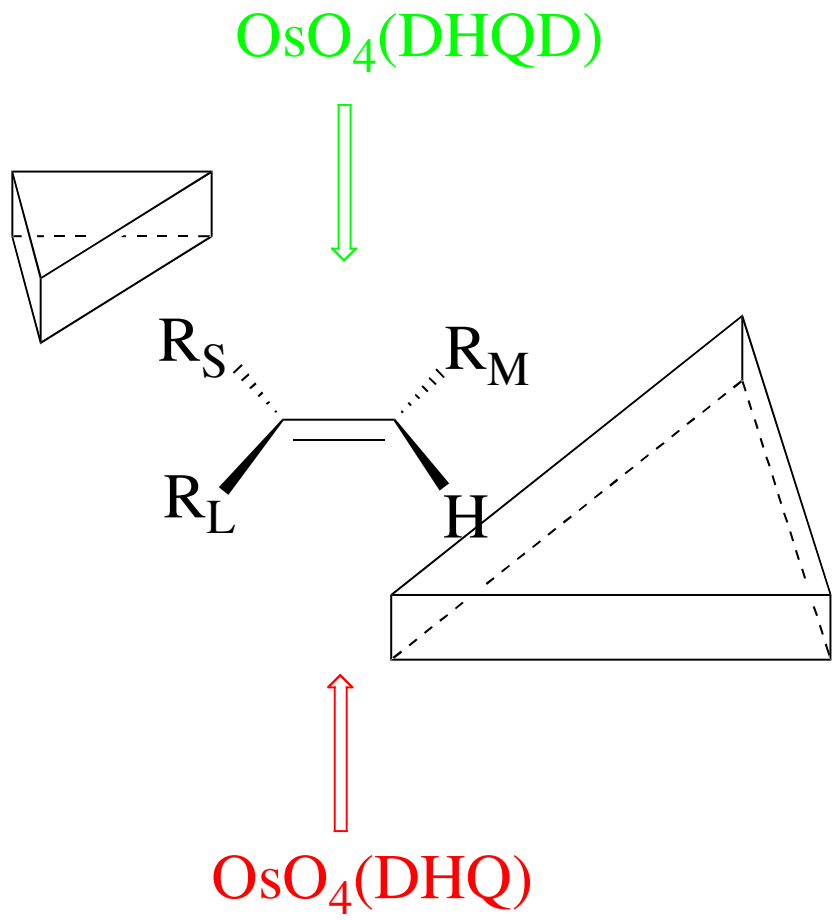


Dihydroquinine (DHQ)

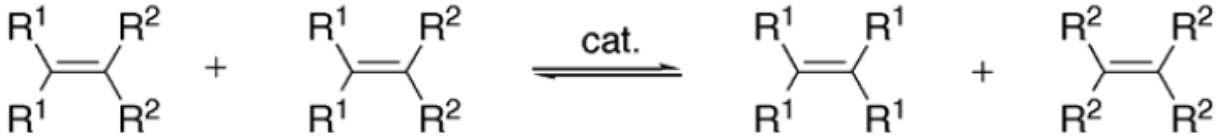




Model for predicting the product



Methathesis



Nobel price in Chemistry 2005

"för utveckling av metates-metoden inom organisk syntes"

Yves Chauvin

Institut Français du Pétrole
Rueil-Malmaison, France

b. 1930

Robert H. Grubbs

California Institute of Technology (Caltech)
Pasadena, CA, USA

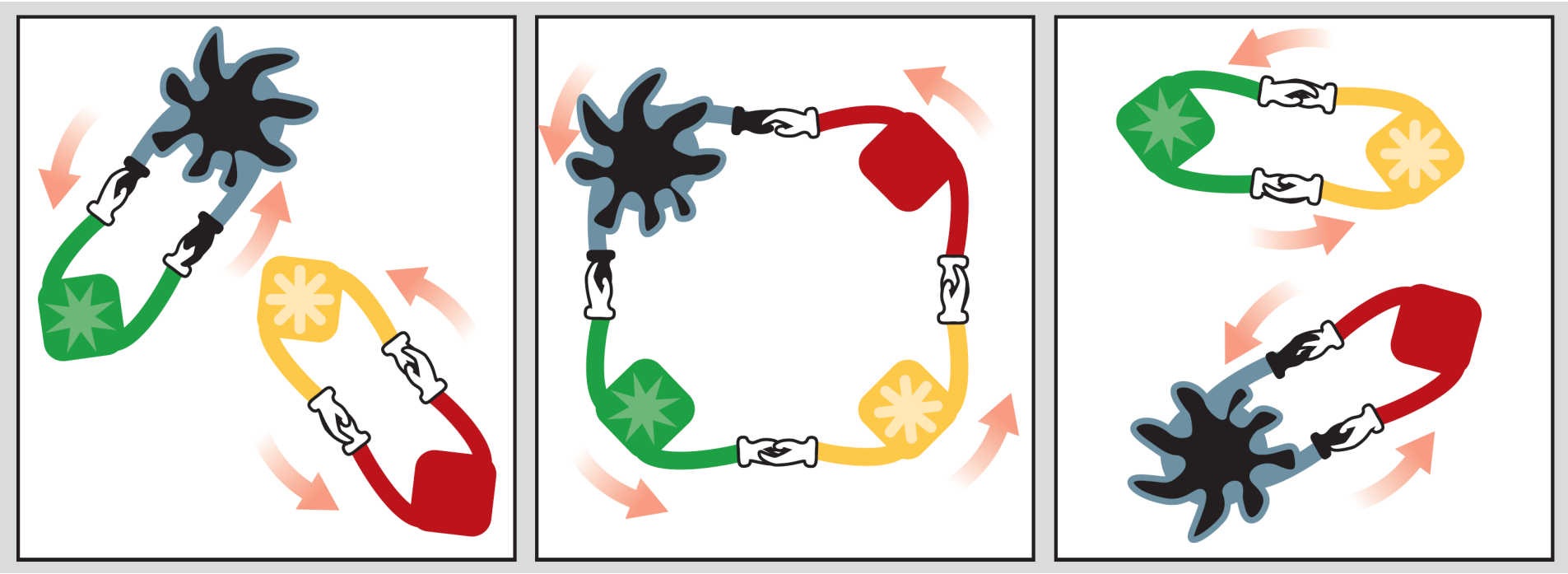
b. 1942

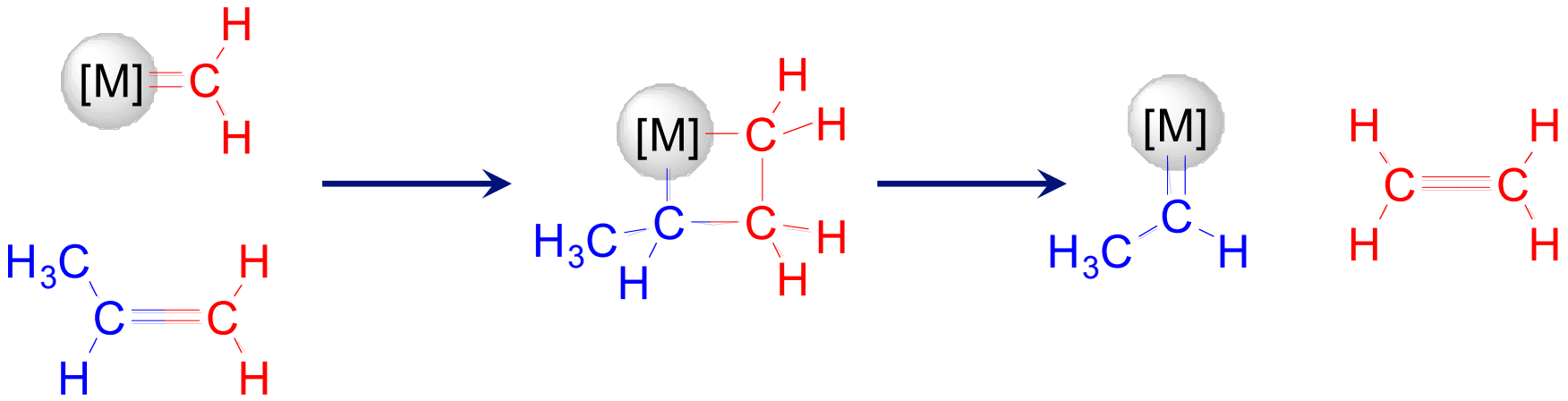
Richard R. Schrock

Massachusetts Institute of Technology (MIT)
Cambridge, MA, USA

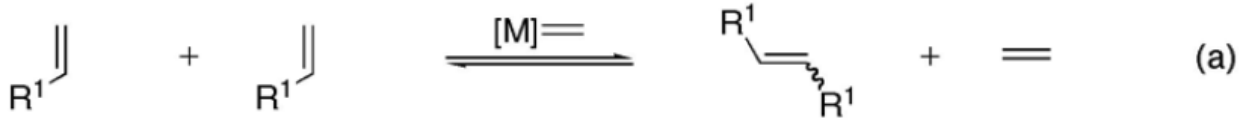
b. 1945

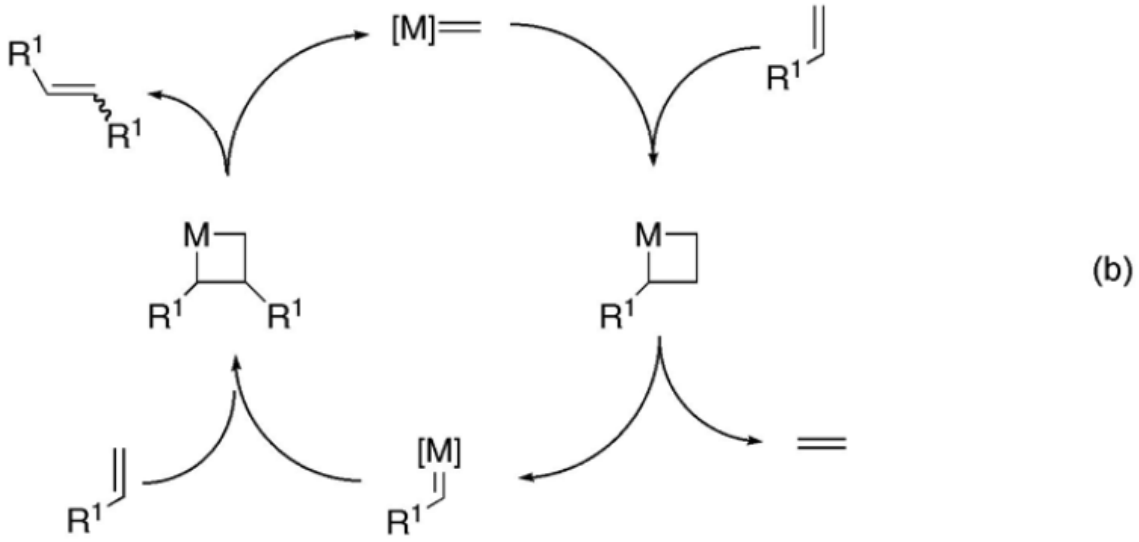
Mekanismen kan beskrivas som en pardans





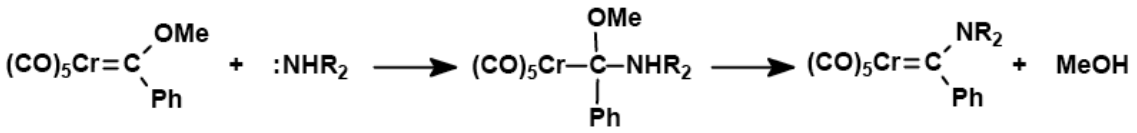
Metates, mekanism





Metal Alkylidene Bonds

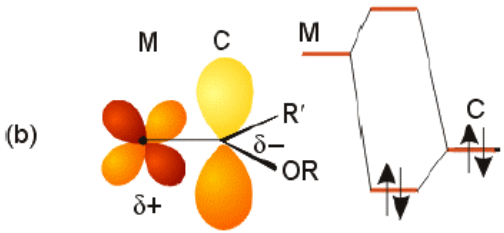
- electrophilic Fischer carbenes react with a nucleophiles



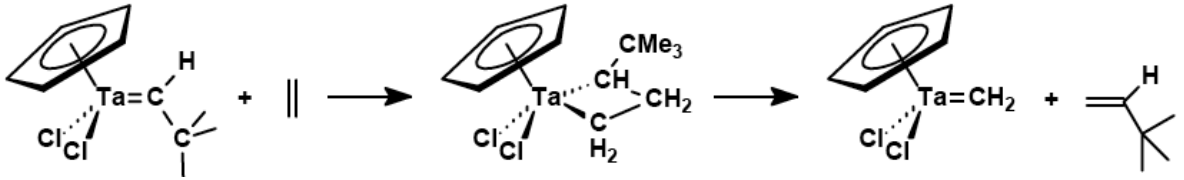
Schrock Carbenes

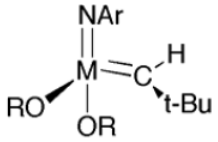
- Early transition metal carbenes
- filled carbon p_z orbital lower in energy than d-π orbitals

=> Schrock carbene C is nucleophilic

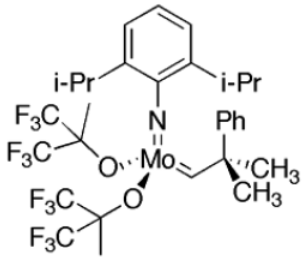


- Schrock carbenes are catalysts for the alkene metathesis reaction

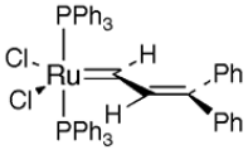




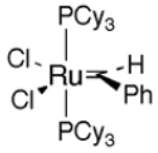
General formula of the family of Schrock's metathesis catalysts (M= Mo or W; R and Ar are bulky substituents)



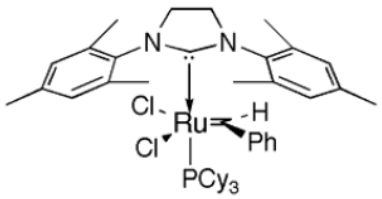
Schrock catalyst commercially available



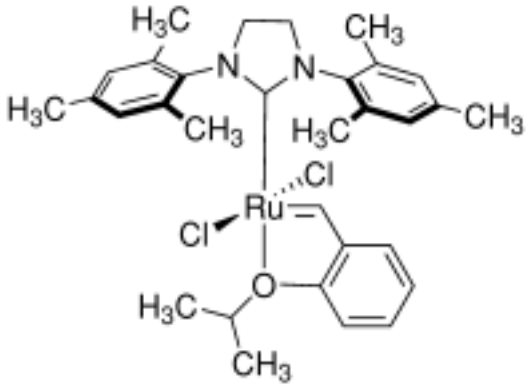
Grubbs,1992



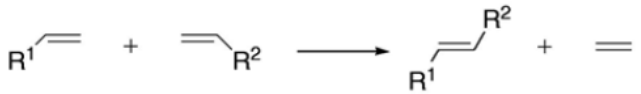
Grubbs, 1995
1st generation Grubbs
commercially available



Grubbs,1999
2nd generation Grubbs
commercially available

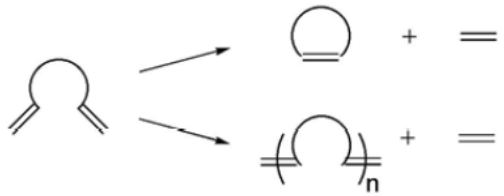


Cross metathesis (CM)

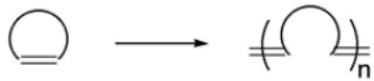


Ring-closing metathesis (RCM)

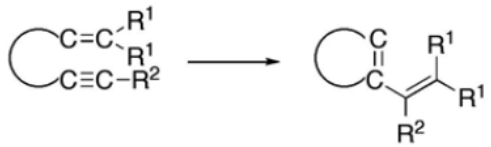
Acyclic diene metathesis polymerization (ADMEP)



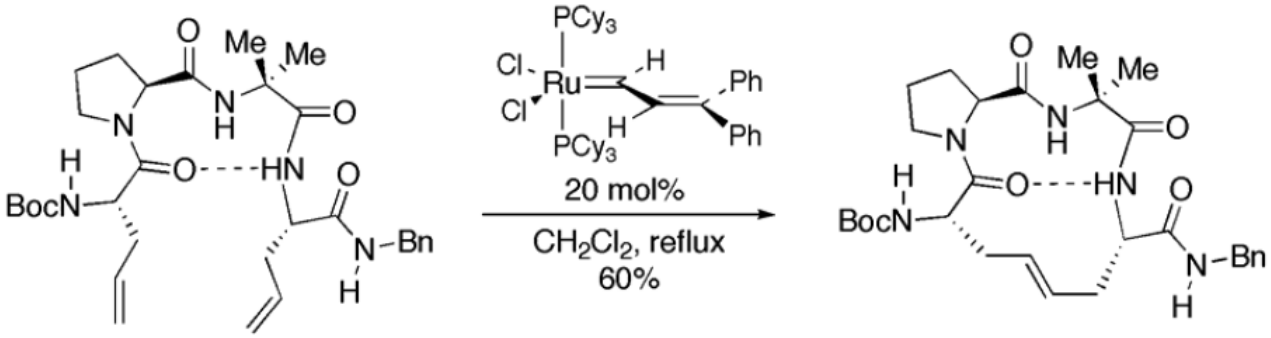
Ring-opening metathesis polymerization (ROMP)

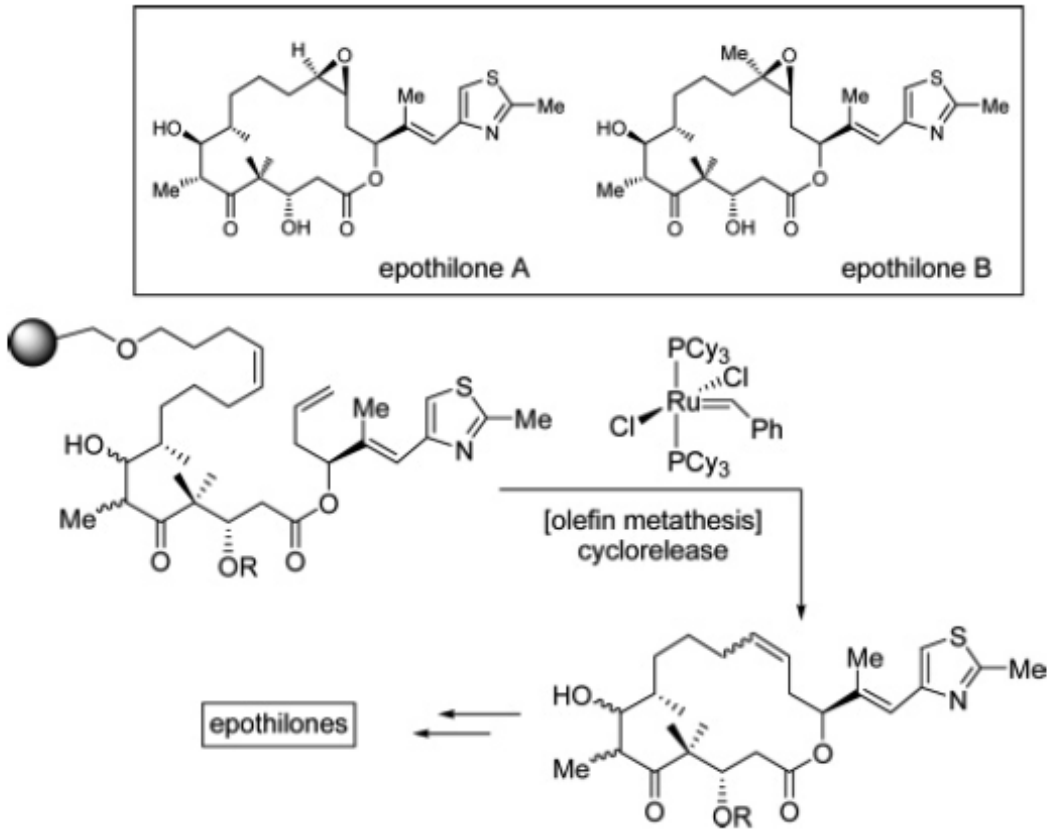


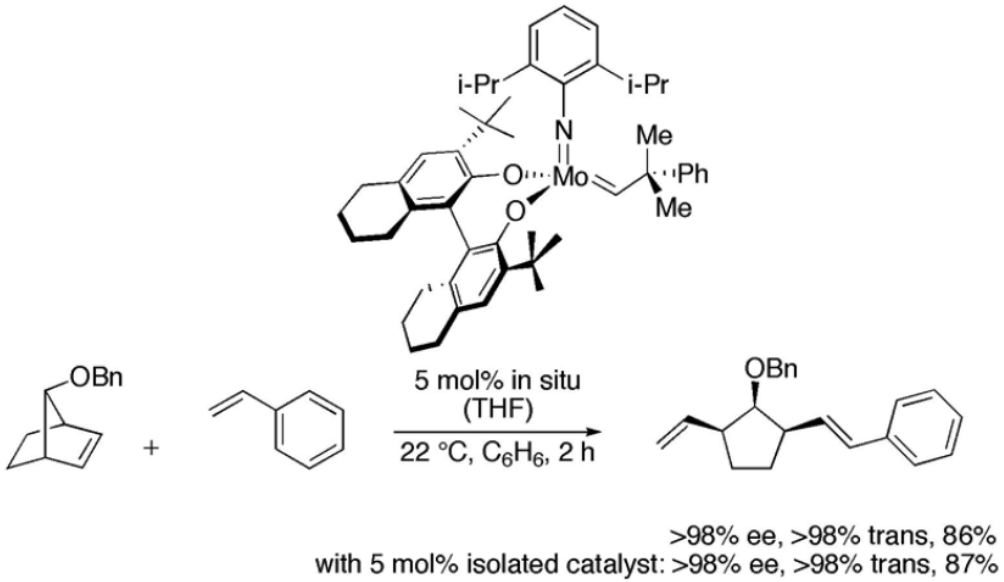
Enyne metathesis (EYM)



Ring-opening cross metathesis (ROCM)

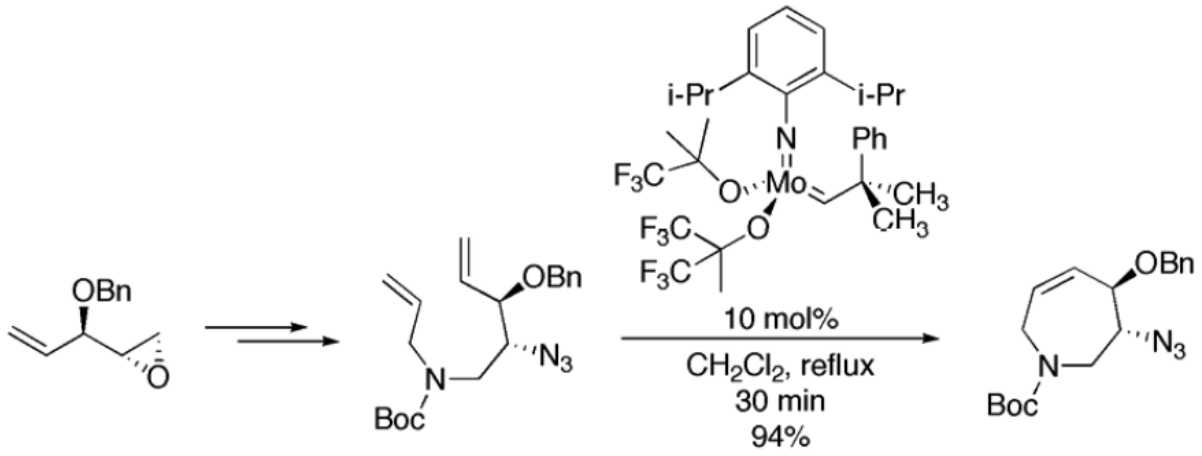

PCy3
Cl
Ru
H
Ph
Cl
H
Ph
PCy3
20 mol%
CH2Cl2, reflux
60%
O
Me
Me
N
H
O
N
H
O
O
HN
O
BocN
N–Bn
H
H


epothilone A
epothilone B
[olefin metathesis]
cyclorelease
epothilones



Scheme 11. An efficient stereoselective CM using *in situ* prepared and isolated chiral catalyst, respectively developed by Hoveyda and Schrock.[14]

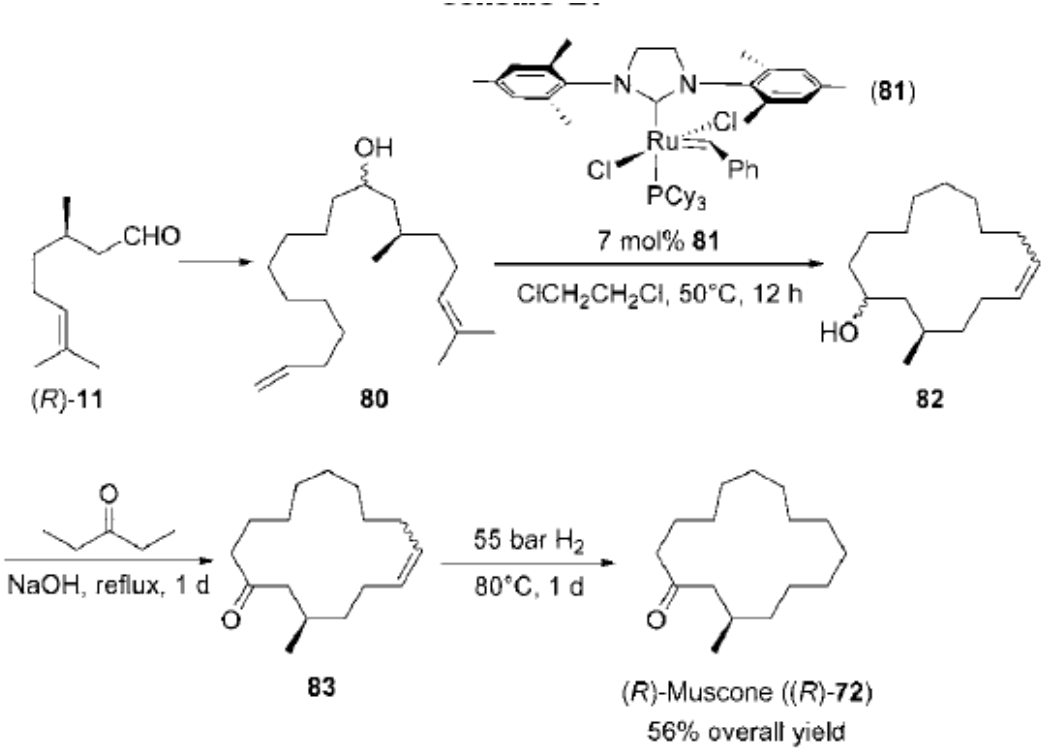
Fürstner: Synthesis of Balanol



Hydrogenation Processes in the Synthesis of Perfumery Ingredients

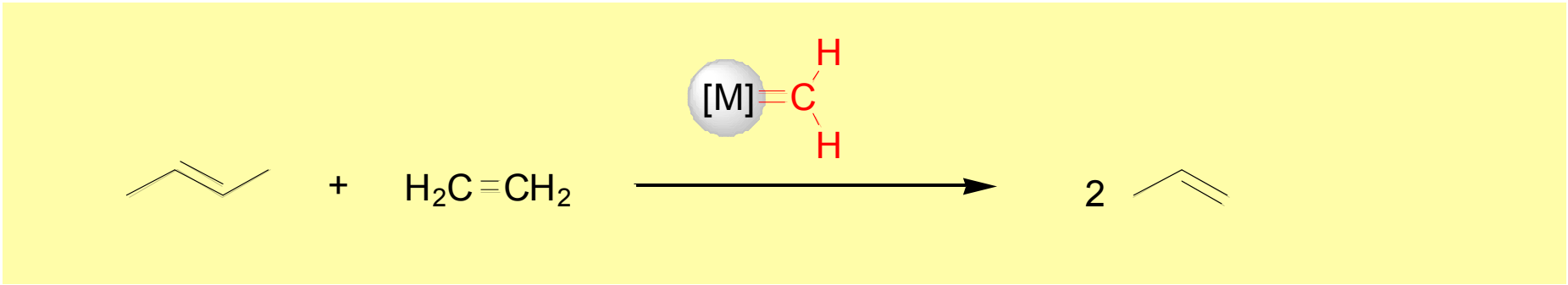
Acc. Chem. Res. **2007,** *40,* 1309–1319

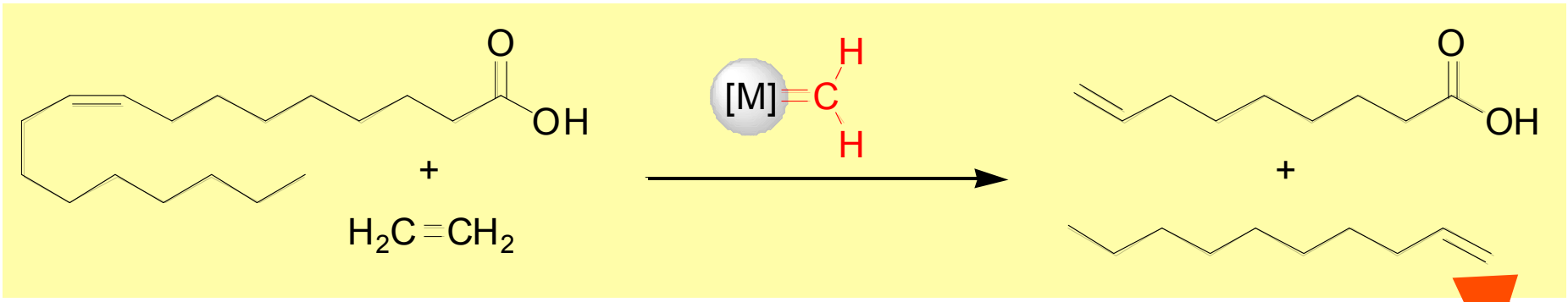
LIONEL A. SAUDAN*
Synthesis, Corporate R&D Division,
Firmenich SA, P.O. Box 239, CH-1211 Geneva 8, Switzerland



Large scale production

Cross-metathesis (CM) for preparation of propene

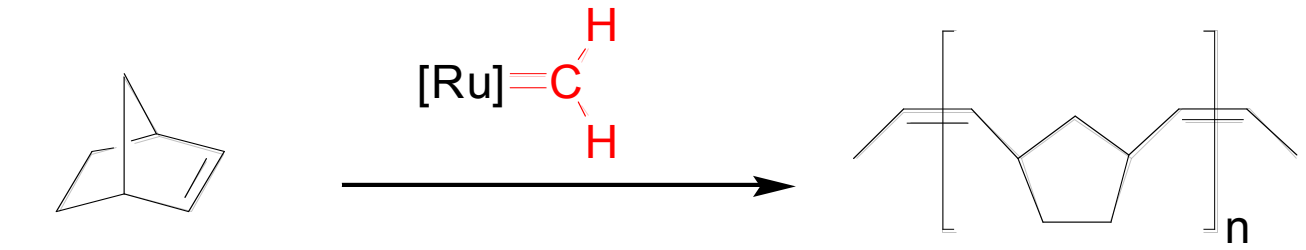


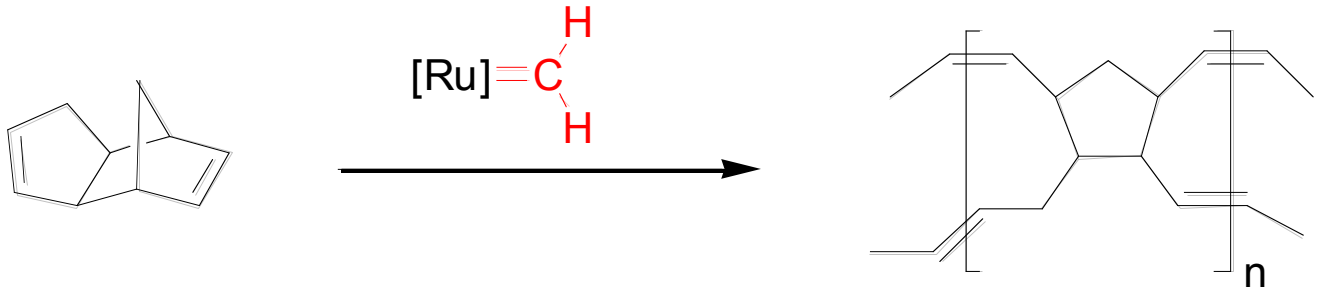


Cross-metathesis (CM) for cleavage of oleic acid

Fuel of the future?

Ring opening polymerization (ROMP)

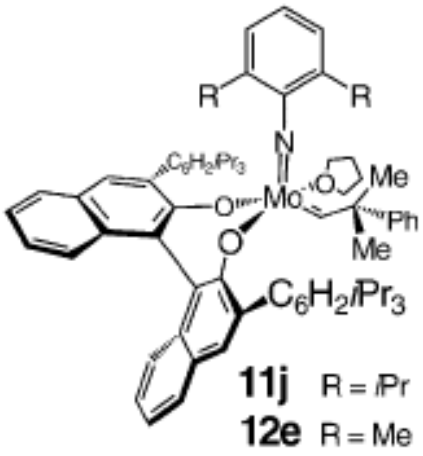


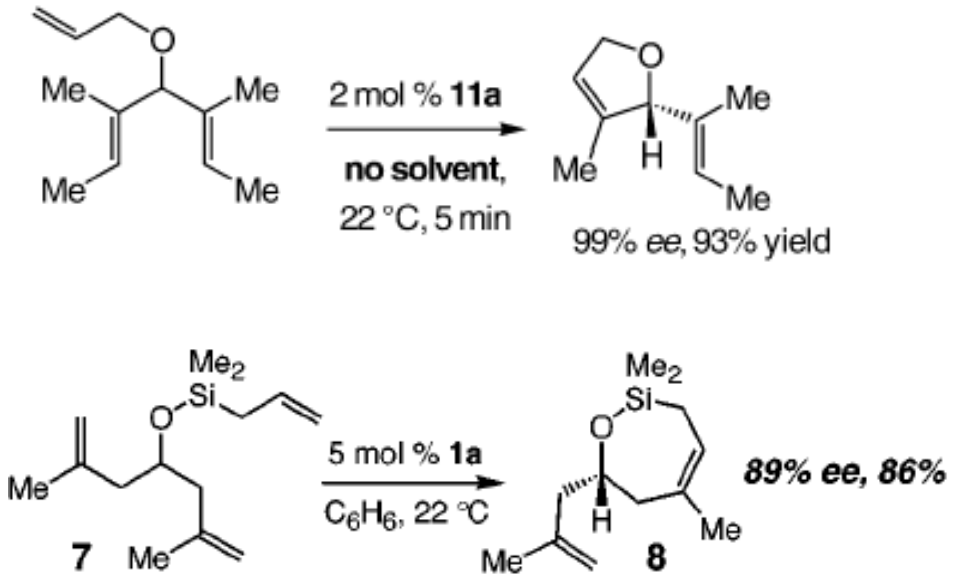


Bulletproof plastics (stops 9-mm bullets)

"Unbreakable" baseball racket

Asymmetric Ring-Closing Metathesis (ARCM)

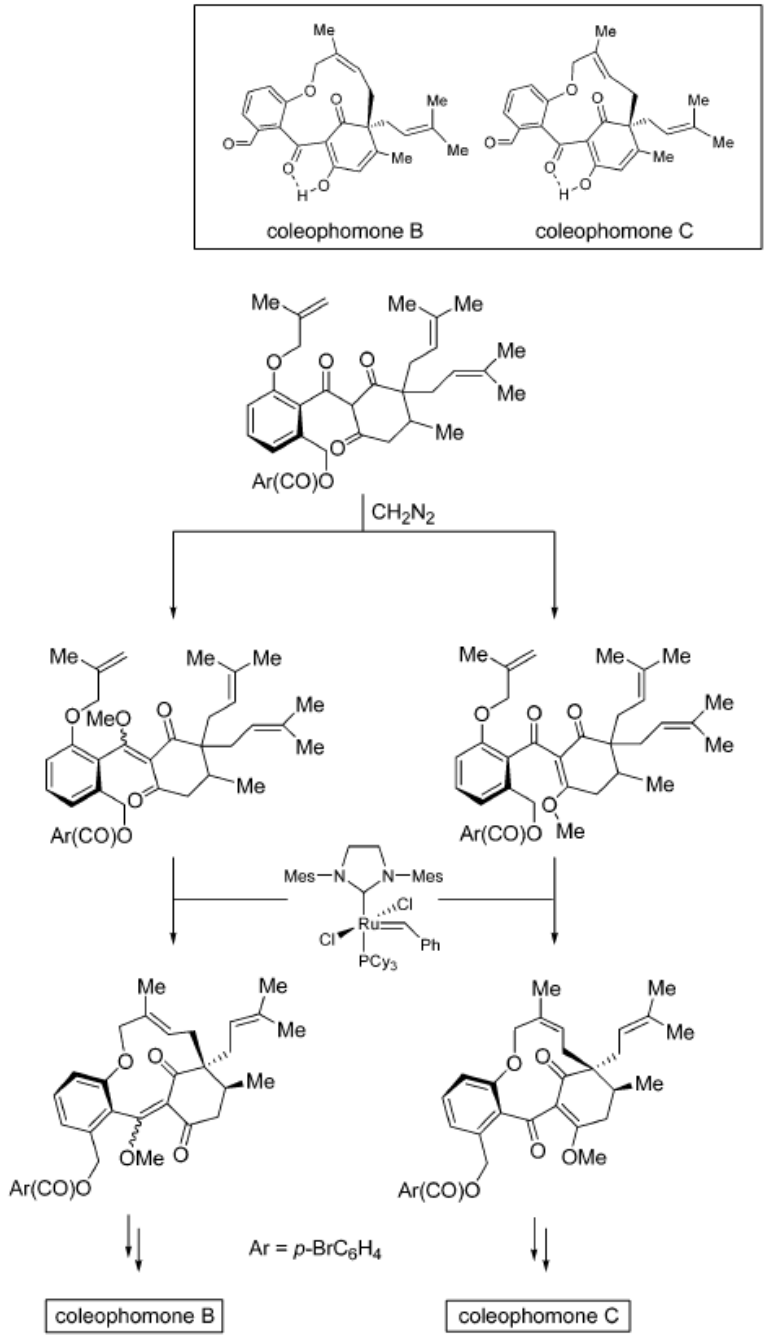




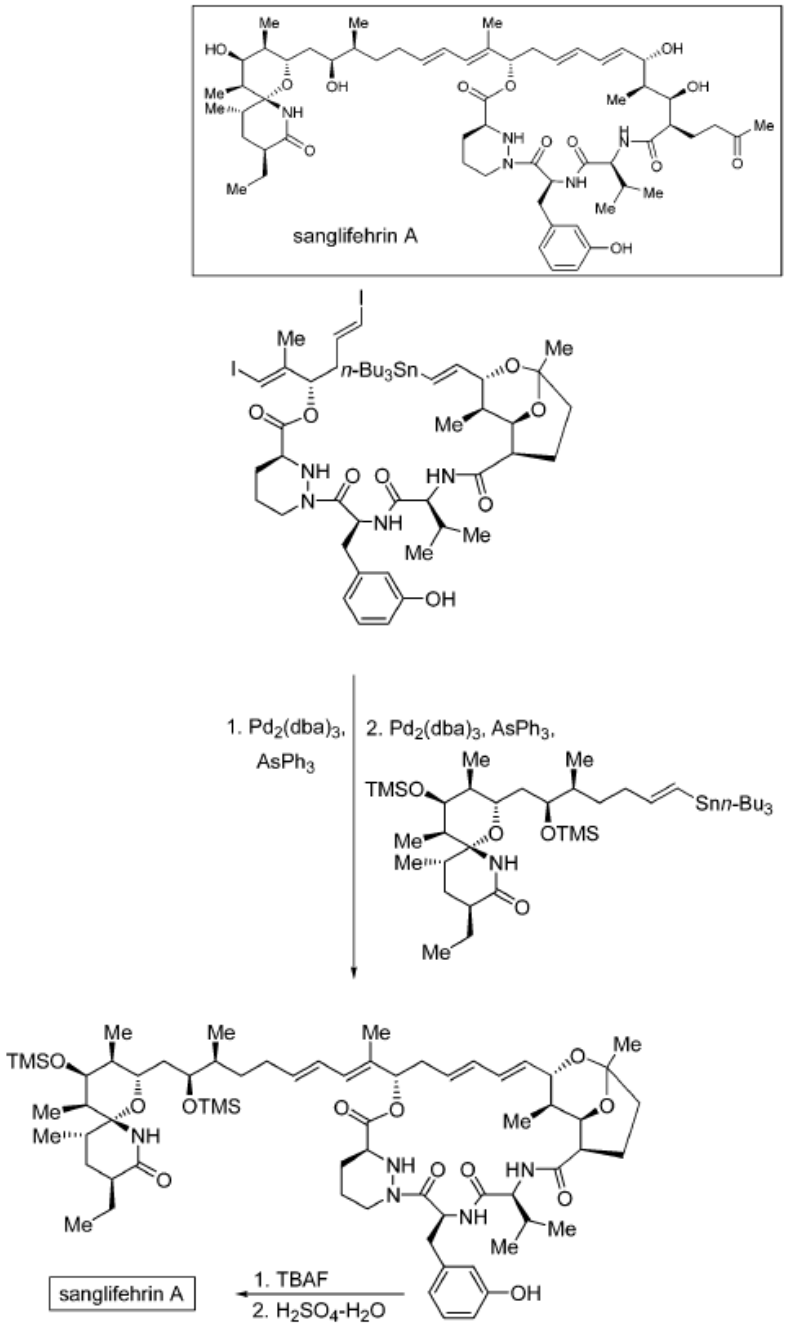
Desymmetrization of a meso-Substrate with a chiral Metathesis catalyst.

Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868-2869

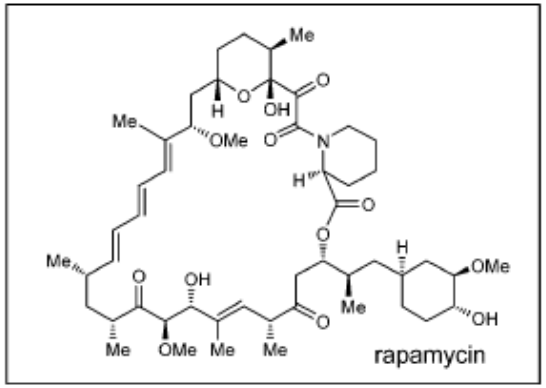
Enantioselective methathesis reaction

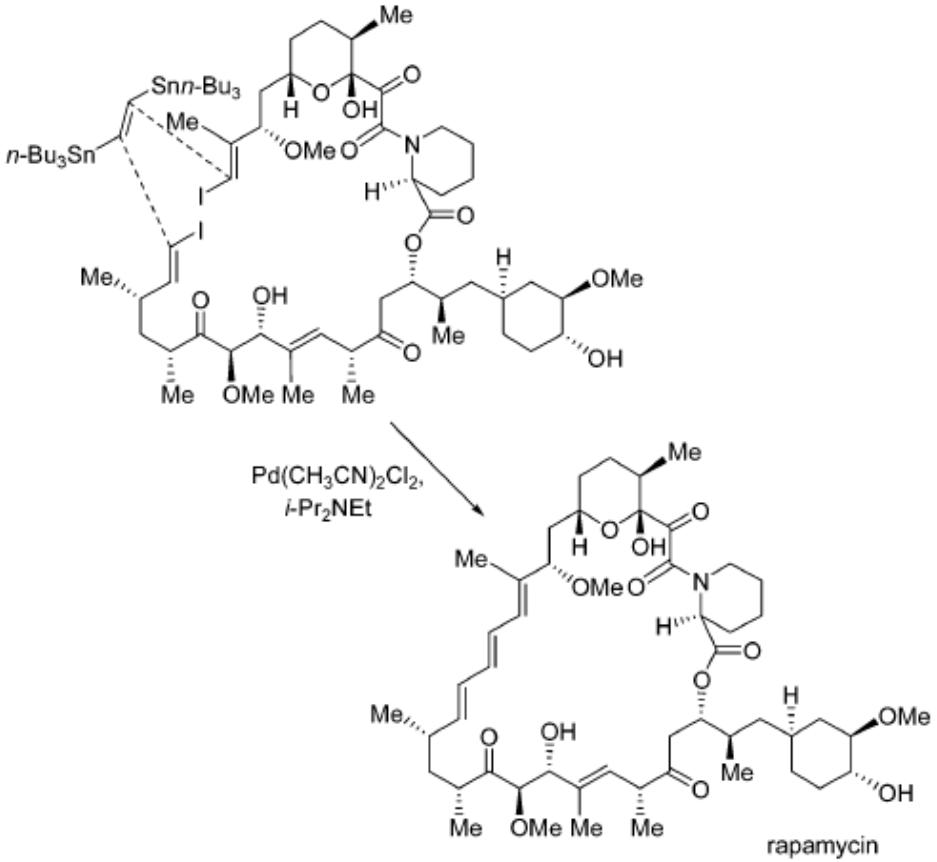


Stille couplings

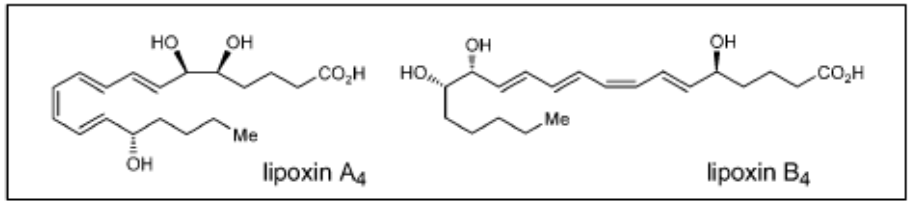


Stille couplings

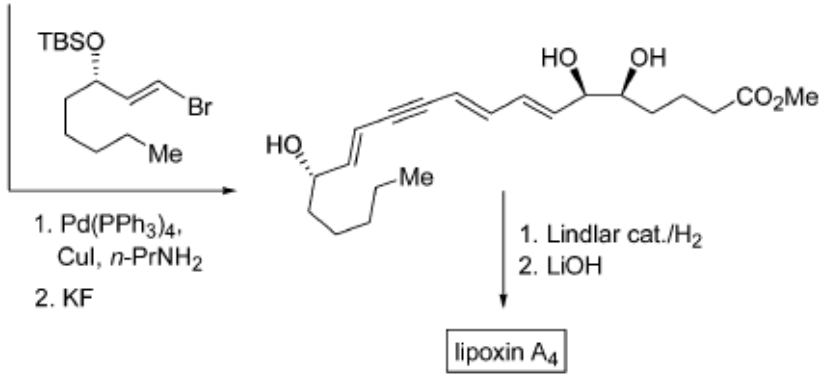


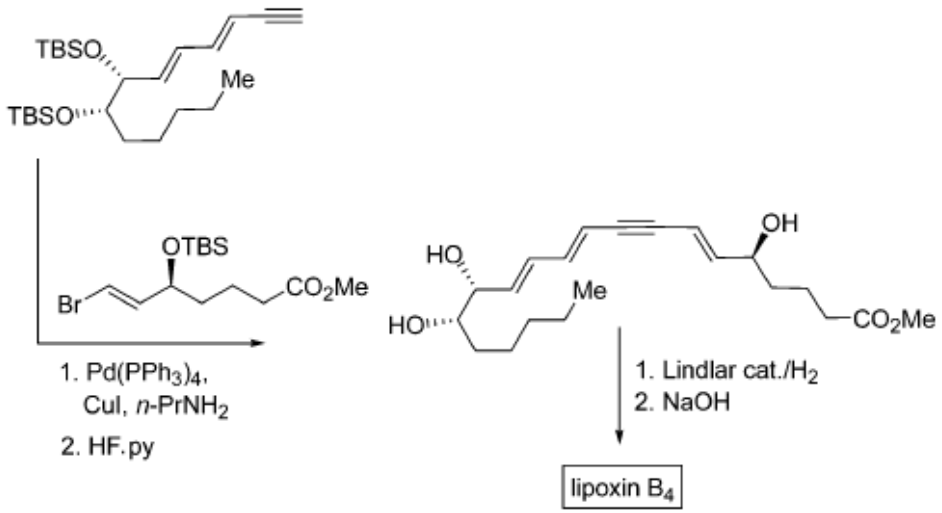


Sonogashira couplings

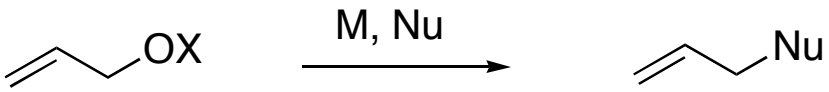


The stereoselective palladium-catalyzed total syntheses of lipoxin A_4 and lipoxin B_4 (Figure 6) is illustrative of our strategy toward the linear eicosanoids,[23–25] molecules that became important in the 1970s and 1980s. These syntheses represent some of the earliest applications of palladium-catalyzed cross-coupling reactions in complex molecule construction, a trend that was to become one of today's most influential themes in total synthesis.[26]





Metal Catalyzed Asymmetric Allylic Alkylations (*AAA*)



M = Pd, Mo, Ir, W, Cu, Ni, Pt, Ru, Rh, Co, Fe

X = $COCH_3$, COOR, $PO(OR)_2$

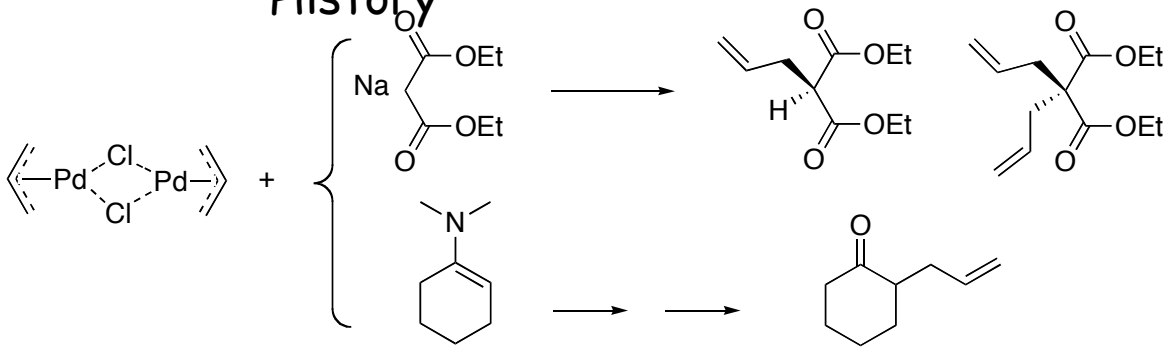
1 1A												13 3A	14 4A	15 5A	16 6A	17 7A	18 8A
1	1 H 1.00794	2 2A															2 He 4.00260
2	3 Li 6.941	4 Be 9.01218										5 B 10.811	6 C 12.011	7 N 14.0067	8 O 15.9994	9 F 18.9984	10 Ne 20.1797
3	11 Na 22.9898	12 Mg 24.3050	3 3B	4 4B	5 5B	6 6B	7 7B	8	9 8B	10	11 1B	12 2 B	13 Al 26.9815	14 Si 28.0855	15 P 30.9738	16 S 32.066	17 Cl 35.4527	18 Ar 39.948
4	19 K 39.0983	20 Ca 40.078	21 Sc 44.9559	22 Ti 47.88	23 V 50.9415	24 Cr 51.9961	25 Mn 54.9381	26 Fe	27 Co	28 Ni	29 Cu	30 Zn 65.39	31 Ga 69.723	32 Ge 72.61	33 As 74.9216	34 Se 78.96	35 Br 79.904	36 Kr 83.80
5	37 Rb 85.4678	38 Sr 87.62	39 Y 88.9059	40 Zr 91.224	41 Nb 92.9064	42 Mo	43 Tc (98)	44 Ru	45 Rh	46 Pd	47 Ag 107.868	48 Cd 112.411	49 In 114.818	50 Sn 118.710	51 Sb 121.75	52 Te 127.60	53 I 126.904	54 Xe 131.29
6	55 Cs 132.905	56 Ba 137.327	57 *La 138.906	72 Hf 178.49	73 Ta 180.948	74 W	75 Re 186.207	76 Os 190.23	77 Ir	78 Pt	79 Au 196.967	80 Hg 200.59	81 Tl 204.383	82 Pb 207.2	83 Bi 208.980	84 Po (209)	85 At (210)	86 Rn (222)
7	87 Fr (223)	88 Ra 226.025	89 †Ac 227.028	104 Rf (261)	105 Ha (262)	106 Sg (263)	107 Ns (262)	108 Hs (265)	109 Mt (266)	110 (269)	111 (272)	112 (272)						

58 Ce 140.115	59 Pr 140.908	60 Nd 144.24	61 Pm (145)	62 Sm 150.36	63 Eu 151.965	64 Gd 157.25	65 Tb 158.925	66 Dy 162.50	67 Ho 164.930	68 Er 167.26	69 Tm 168.934	70 Yb 173.04	71 Lu 174.967
90 Th 232.038	91 Pa 231.036	92 U 238.029	93 Np 237.048	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (260)

C-C, C-O, C-N, C-S bond formation

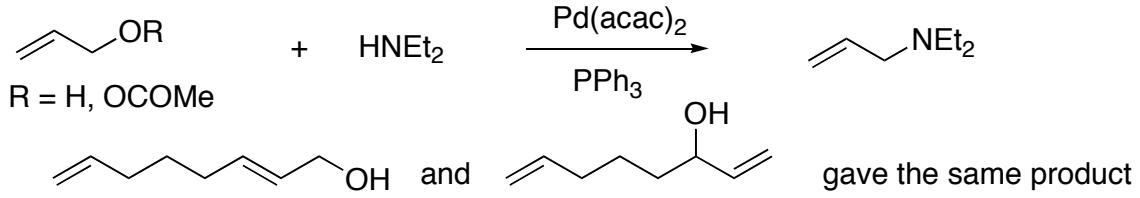
History

First allylic alkylation:



Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett*. **1965**, 4387

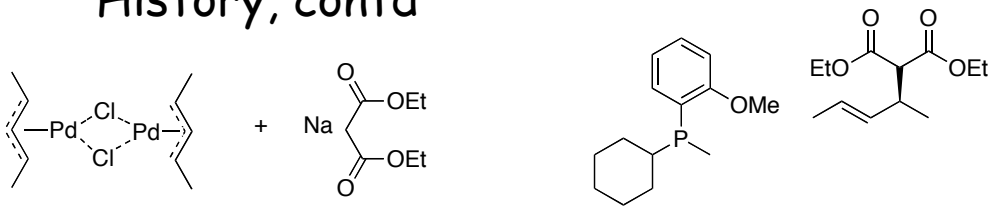
First catalytic reaction:



Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett*. **1970**, 3821

History, contd

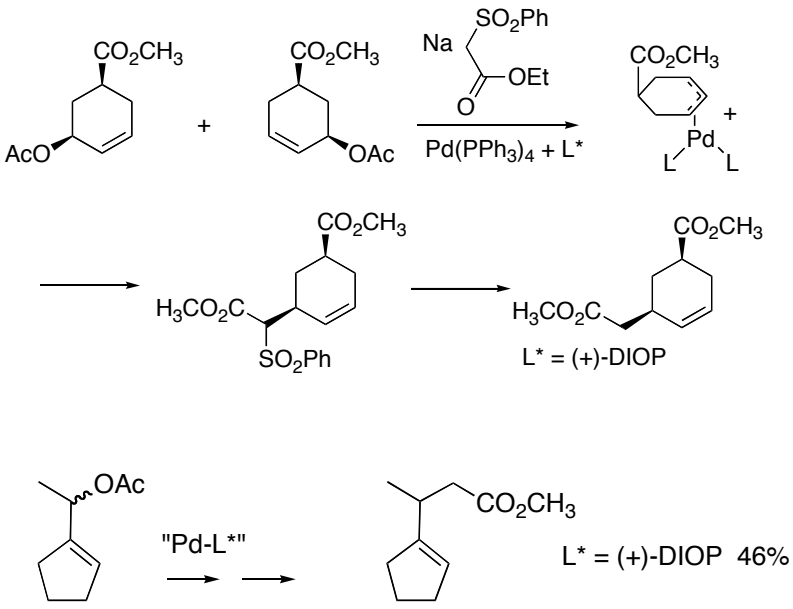
First asymmetric reaction



24% ee, corrected for 80% optical purity of ligand!
optical yield

Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc*. **1973**, *95*, 8200

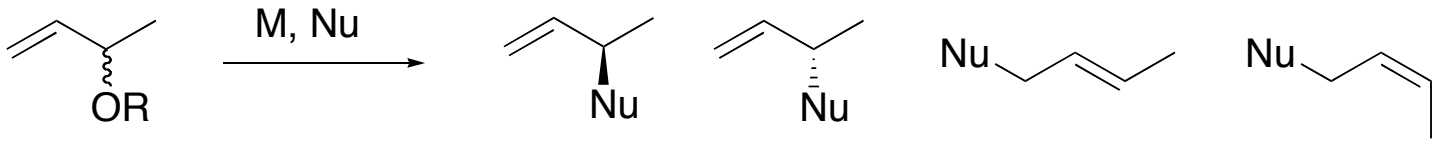
First catalytic asymmetric reactions



"Optical yields of this magnitude for carbon-carbon bond forming reactions at normal temperatures (70-80 °C) in a catalytic process are among the highest seen and suggest this approach as an exciting solution to asymmetric induction in carbon-carbon bond forming reactions."

Trost, B. M.; Strege, P.E. *J. Am. Chem. Soc*. **1977**, *99*, 1649

Asymmetric Allylic Alkylations, AAA

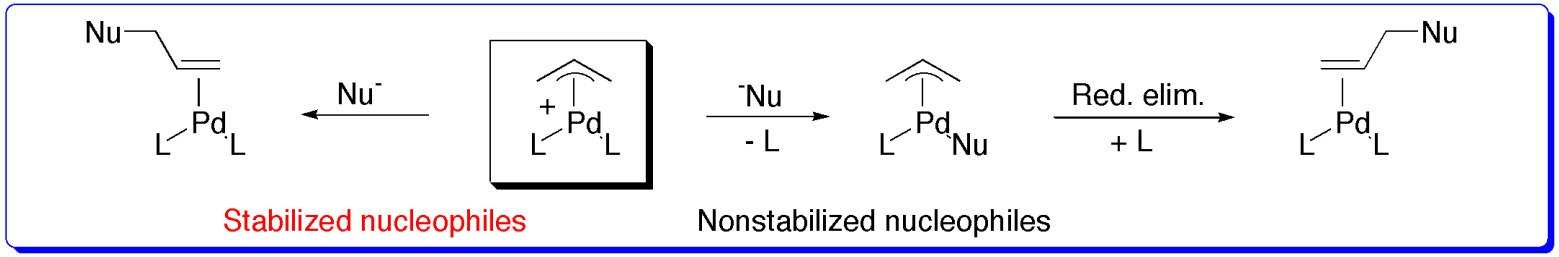


R = OAc, OCOOMe, $OPO(OEt)_2$ M = Pd, Mo, W, Ir, Rh, Co, F, Ru, Ni, Pt, Cu

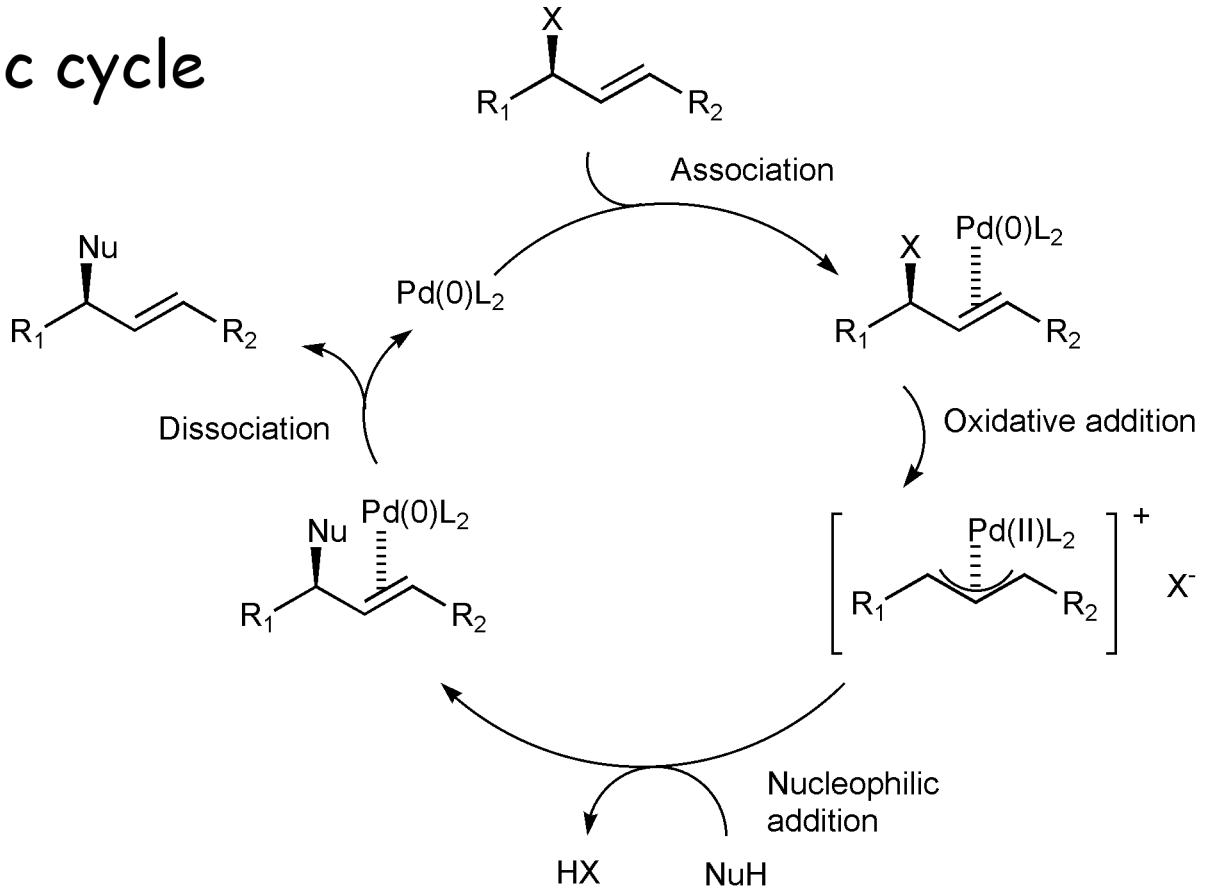
stereoselectivity regioselectivity

The selectivity is a function of many factors:

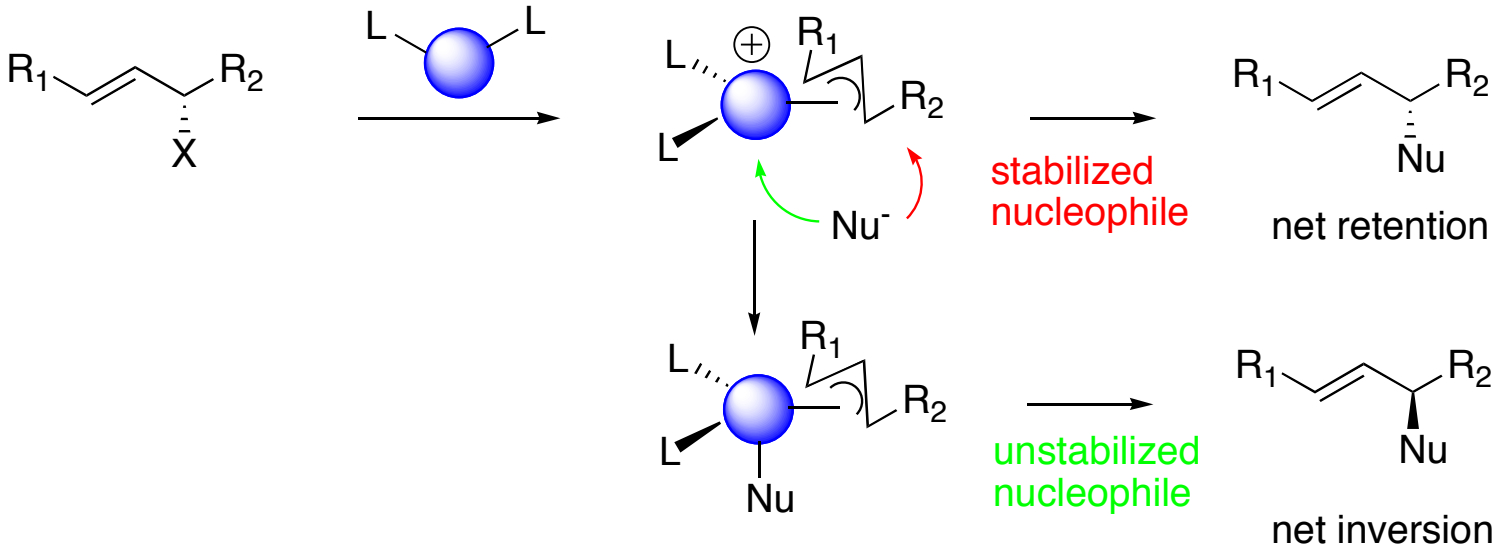
- The metal ion
- The ligand
- The nucleophile
- The substituents of the allyl system



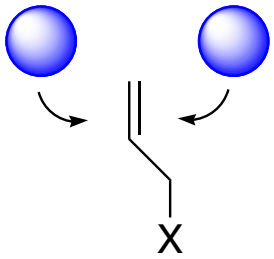
Catalytic cycle



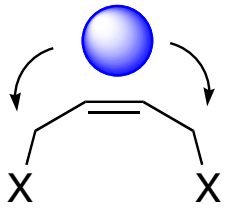
Stereochemistry



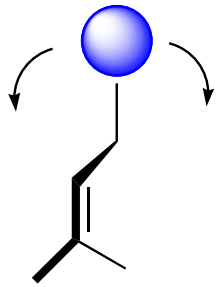
Sources of enantiodiscrimination in transition metal catalyzed allylic alkylations



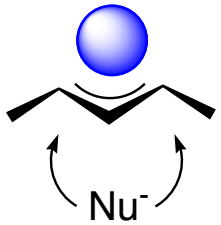
enantiotopic faces
of the olefin

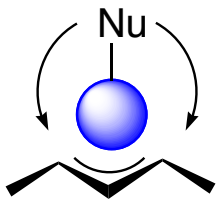


enantiotopic
leaving groups

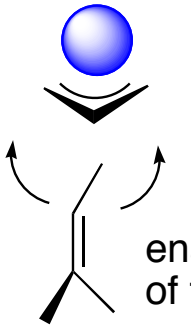


enantiotopic faces
of the allyl





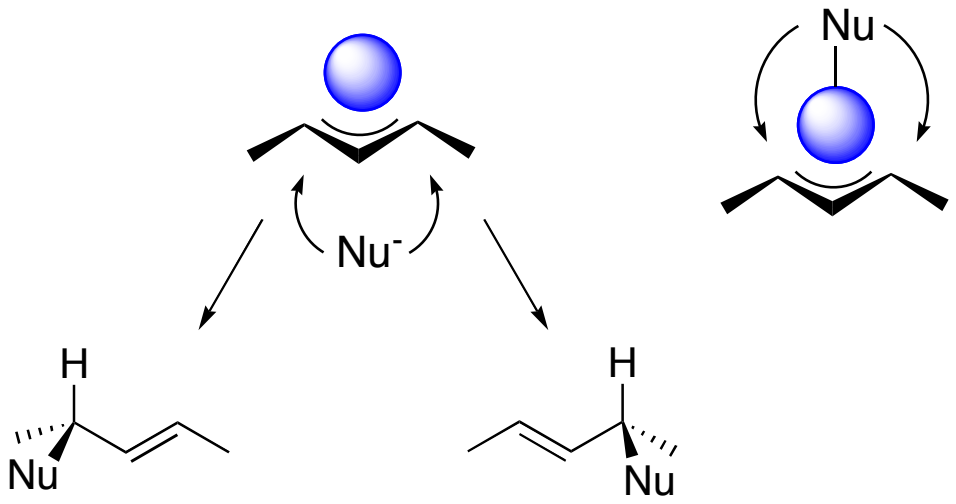
enantiotopic termini of the allyl



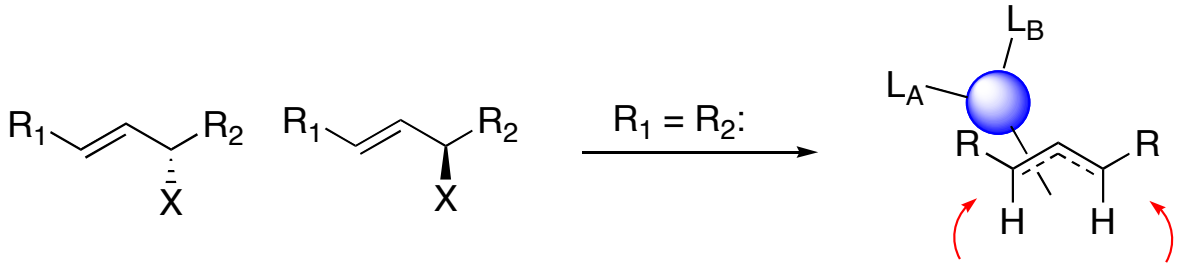
enantiotopic faces
of the nucleophile

Sources of enantiodiscrimination in transition metal catalyzed allylic alkylations

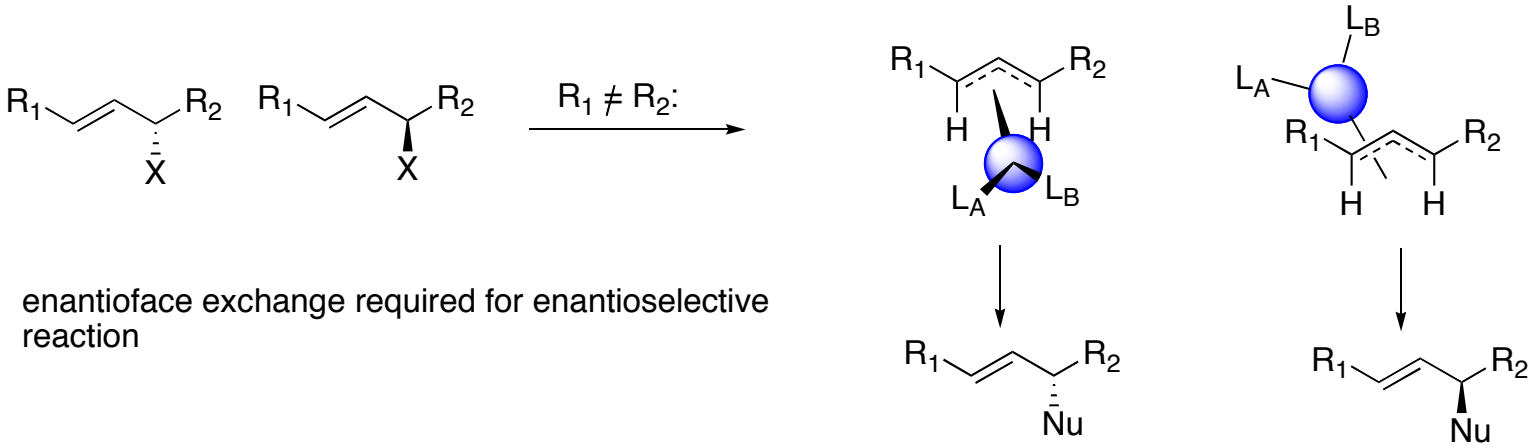
enantiotopic termini of the allyl



Enantioface exchange

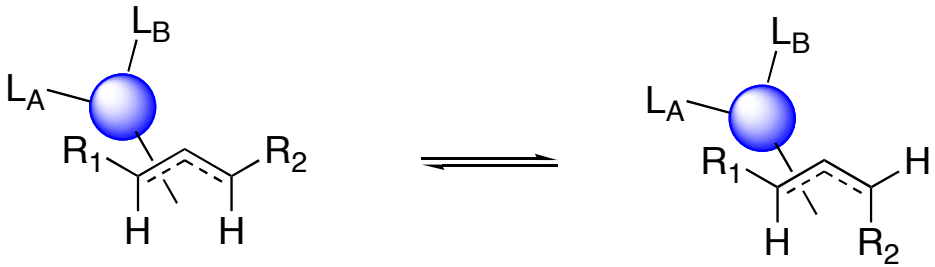


regiochemistry of nucleophilic attack enantiodetermining

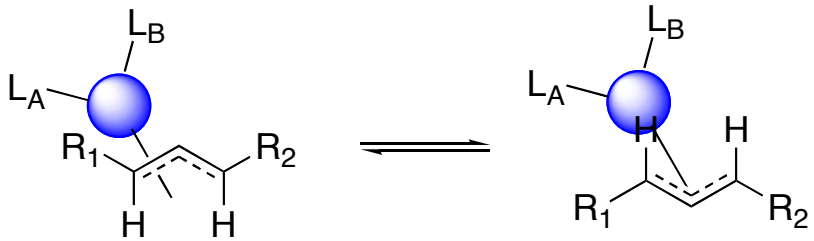


enantioface exchange required for enantioselective reaction

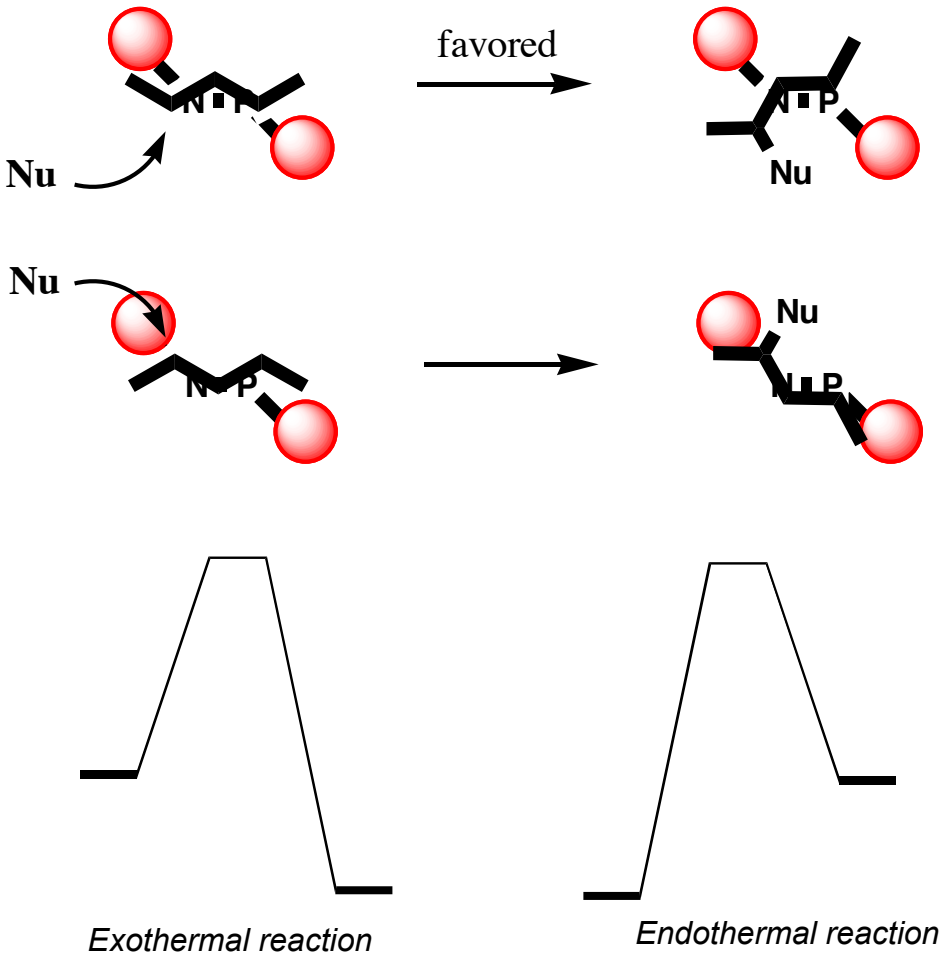
Syn-anti isomerization



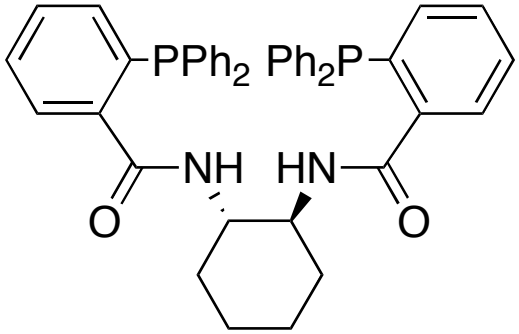
Apparent allyl rotation

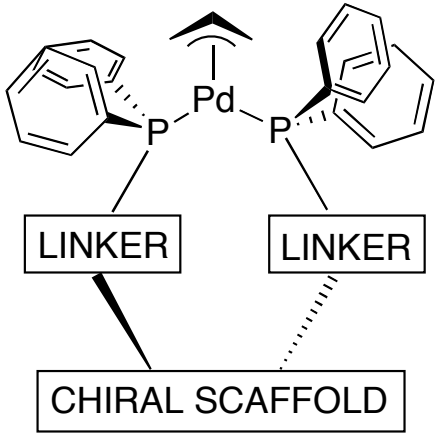


Prediction of enantioselectivity

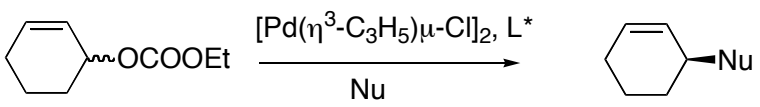


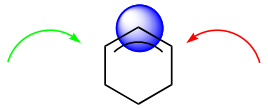
"Trost ligand"



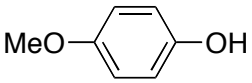


Trost' s ligand in catalytic reactions
symmetric substrate

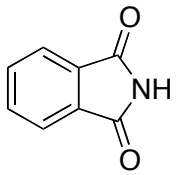




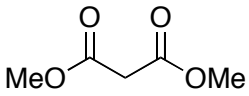
regiochemistry of nucleophilic attack enantiodetermining



1 min, 96% yield, 95% ee

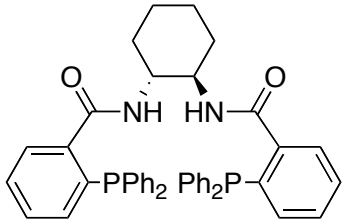


4 min, 79% yield, 97% ee



1.5 min, 83% yield, >95% ee

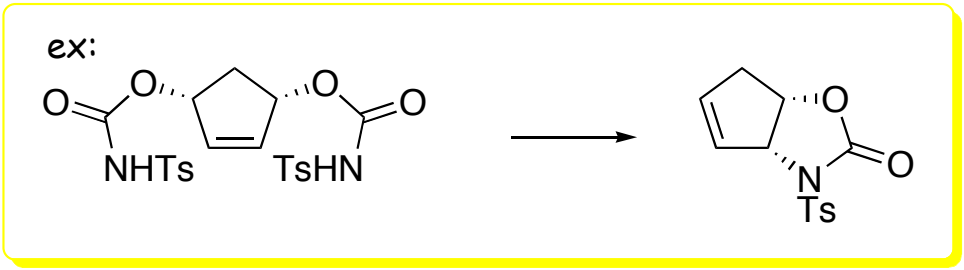
L* =

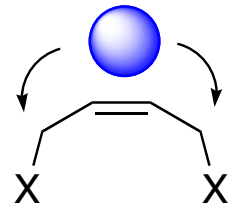


Biotage

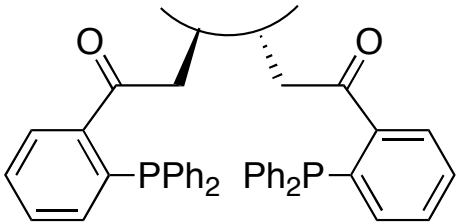
Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *J. Org. Chem*. **1999**, *64*, 1082

Enantiotopic leaving groups

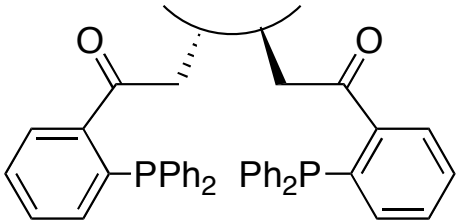


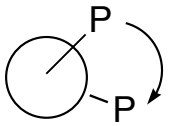


enantiotopic
leaving groups

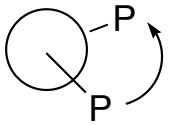


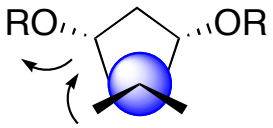
ligand



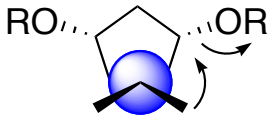


side view





preferred motion



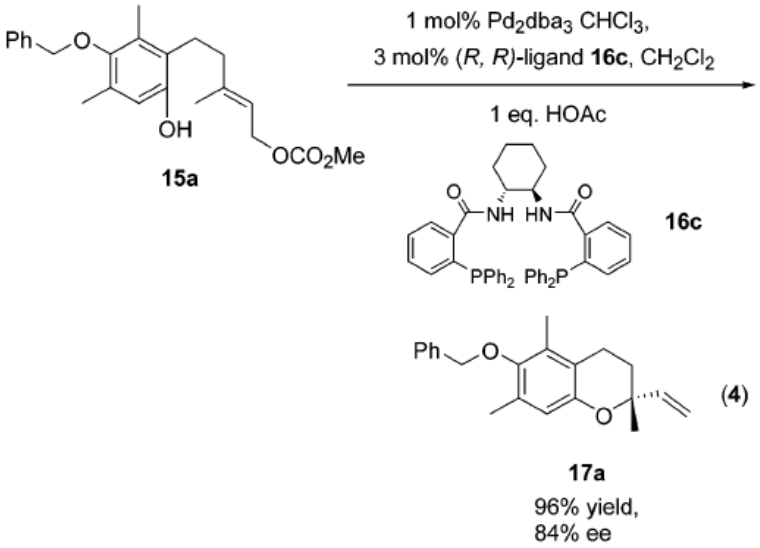
J|A|C|S
ARTICLES
Published on Web 09/03/2004

Synthesis of Chiral Chromans by the Pd-Catalyzed Asymmetric Allylic Alkylation (AAA): Scope, Mechanism, and Applications

Barry M. Trost,* Hong C. Shen, Li Dong, Jean-Philippe Surivet, and Catherine Sylvain

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

J. AM. CHEM. SOC. 2004, *126*, 11966−11983



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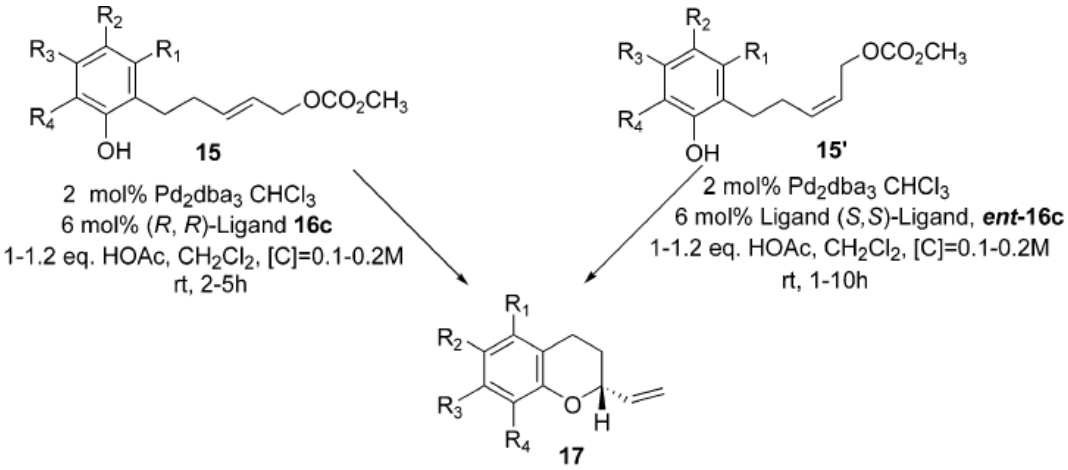
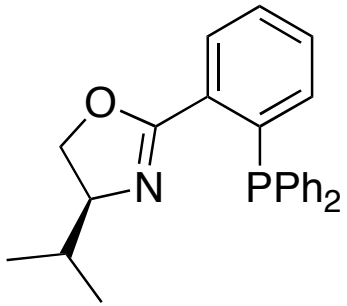
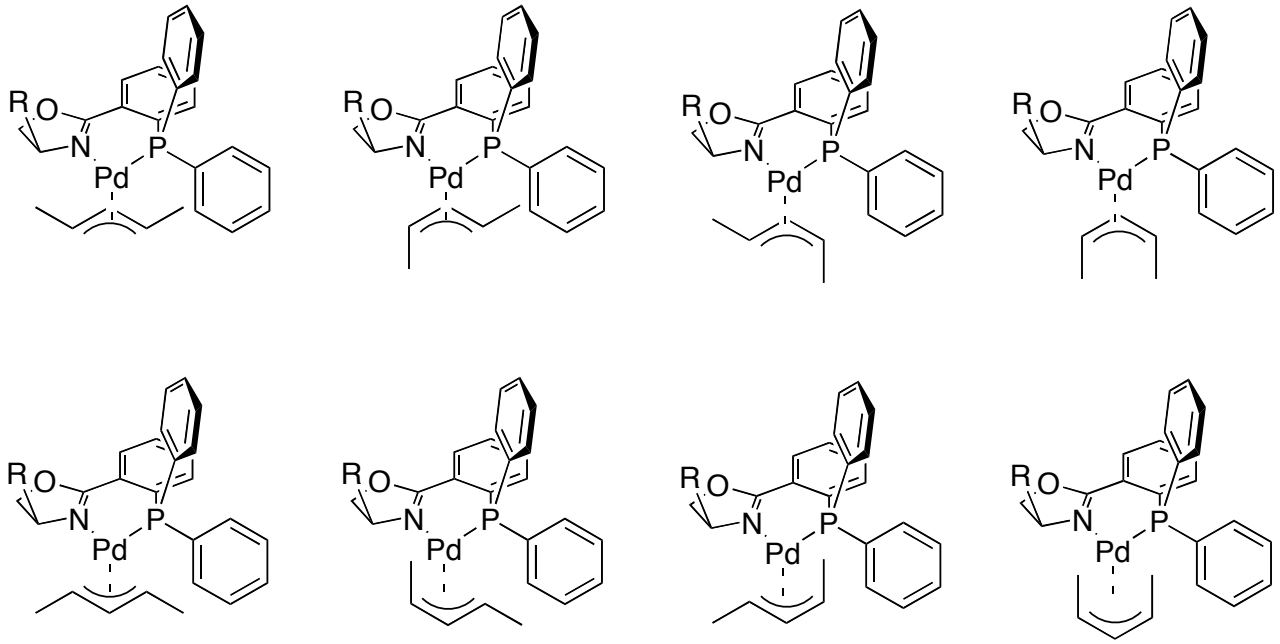


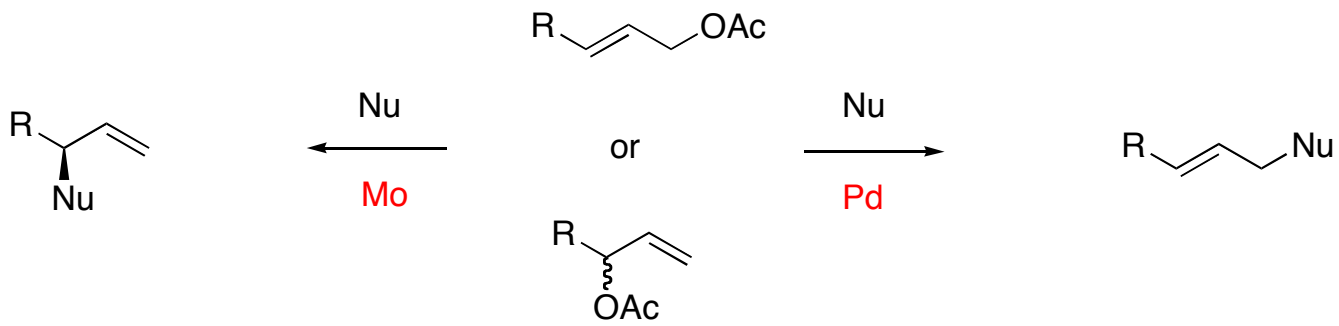
Complexes with phosphineoxazoline



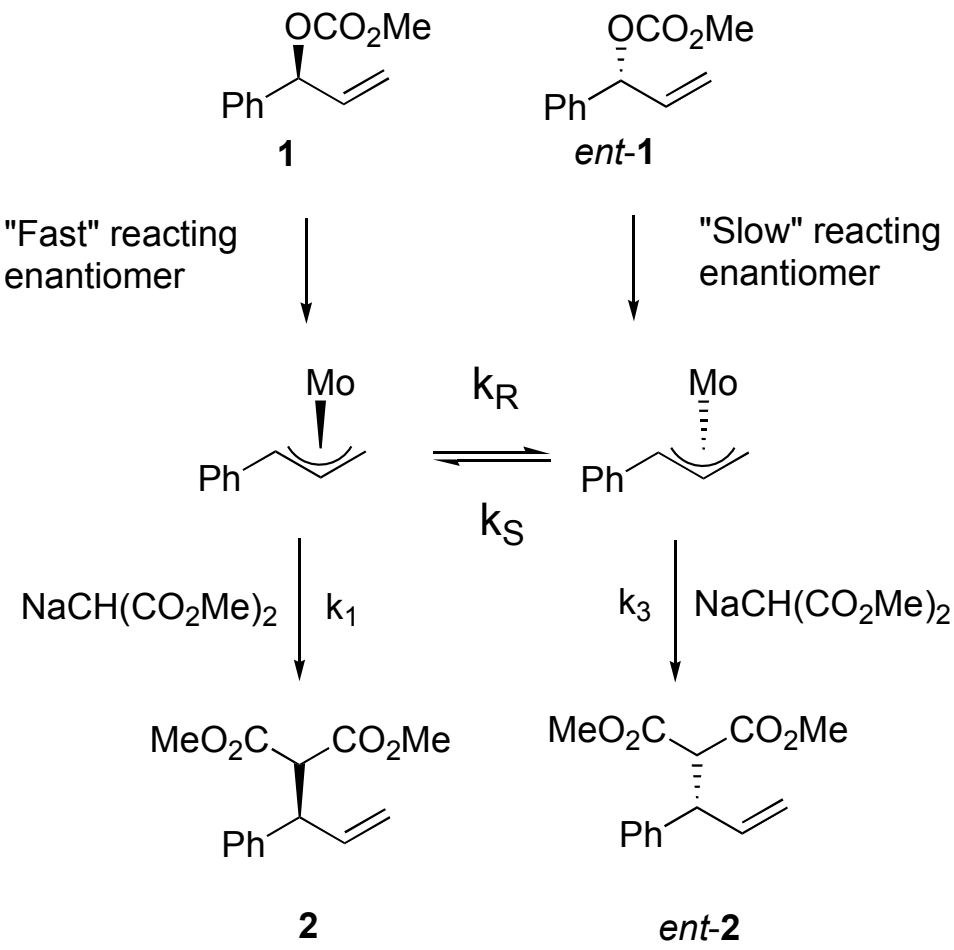
Complexes with phosphineoxazoline



Regioselectivity

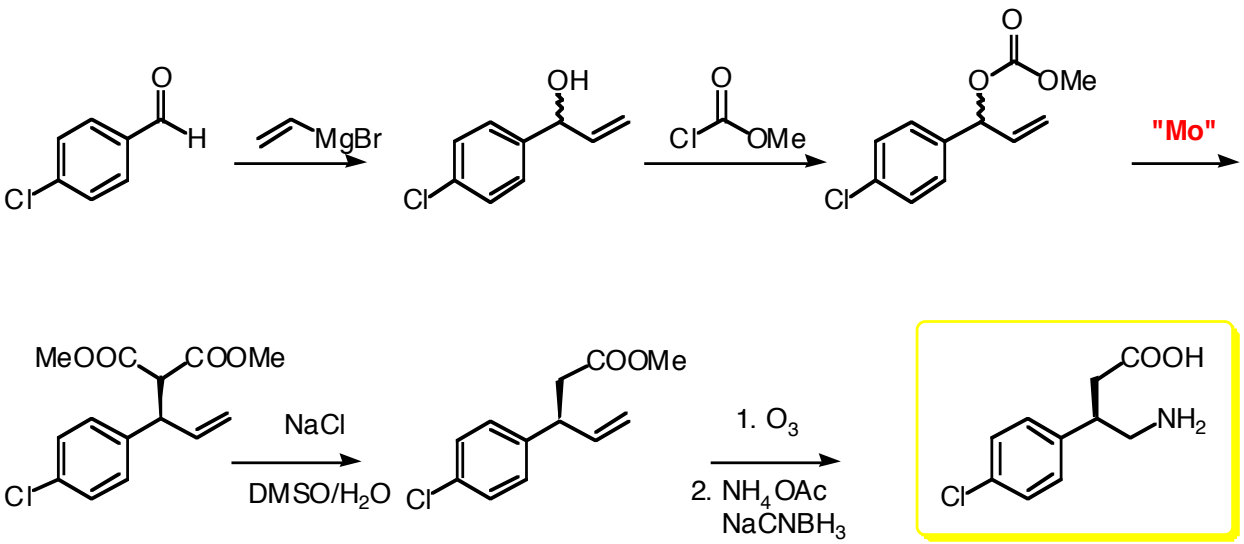


Isomerization



Fast equilibrium: k_R and k_S >> k_1, k_2

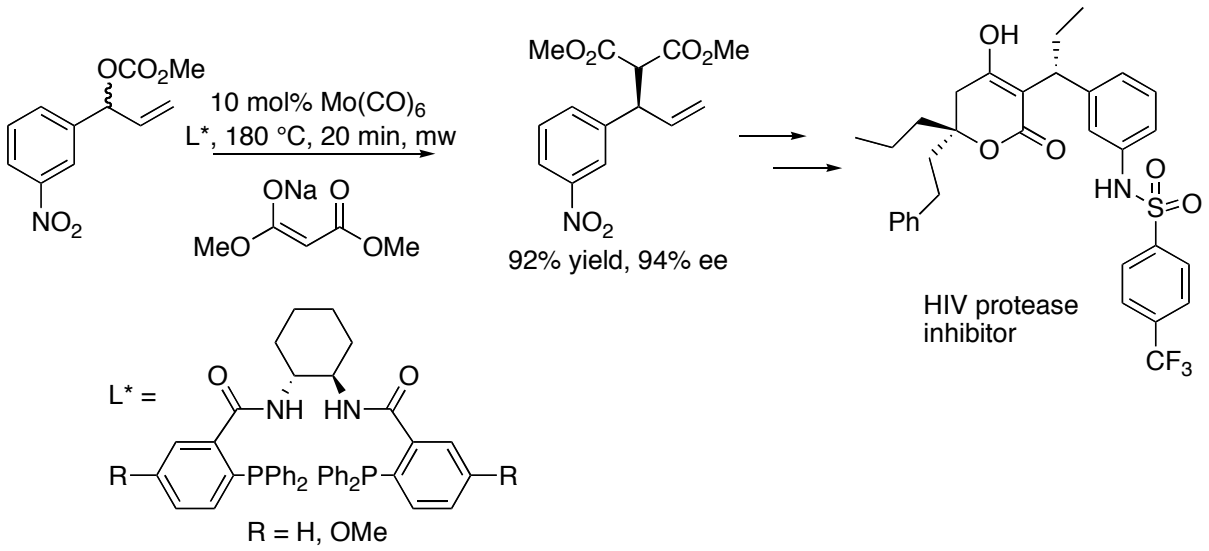
Synthesis of (*R*)-baclofen



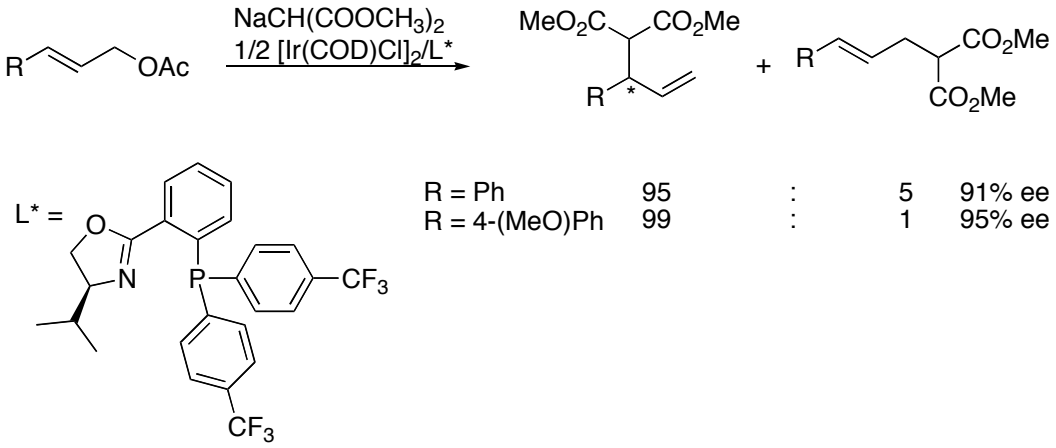
Homogeneous cat: 160 °C, 6 min, 78% yield, b:l 26:1, 96% ee
Polymeric cat: 160 °C, 30 min, 76% yield, b:l 25:1, 89% ee

Belda, O.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275-2278.

Synthesis of Tipranavir



First enantioselective Ir-catalyzed allylation

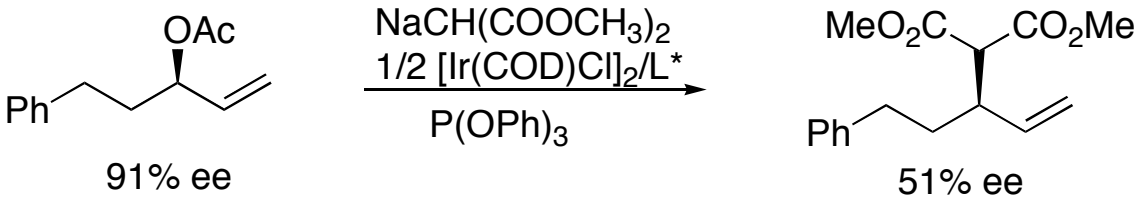


R = Ph	95	:	5	91% ee
R = 4-(MeO)Ph	99	:	1	95% ee

Takeuchi and Kashio had demonstrated the high regioselectivity using an achiral catalyst

Janssen, J. P.; Helmchen, G. *Tetrahedron Lett*. **1997**, *38*, 8025-8026.

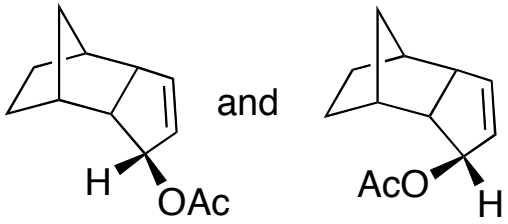
Memory effect



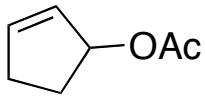
memory of stereochemistry of starting material:

$\sigma-\pi$ isomerization is slow

retention of configuration - shown to be double inversion

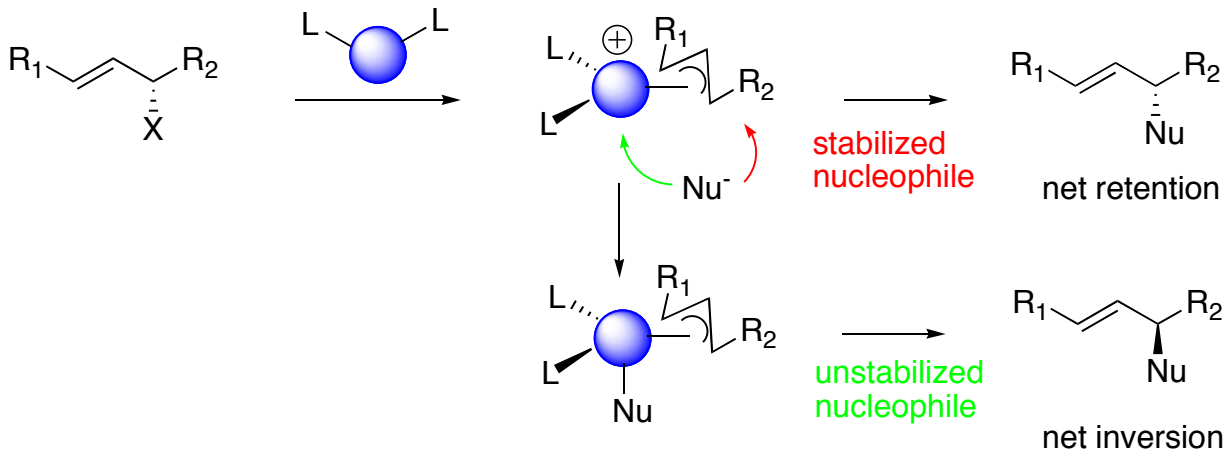


give no product, while

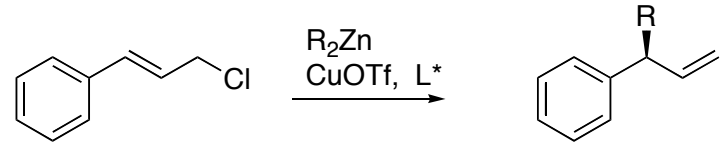


does

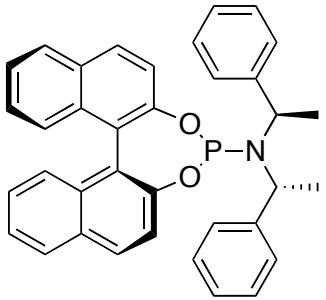
Nickel catalysts have been used for allylations using stabilized as well as non-stabilized nucleophiles. Good selectivities have been obtained only in a few cases.



Cu-catalyzed *AAA*



L* =



R	regioselectivity	yield (%)	ee (%)
Et	93:7	74	86
^{i}Pr	97:3	94	88

Van Zijl, A. W.; Arnold, L. A.; Minnard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2004**, *346*, 413-420.

Summary

Pd catalysts have been most deeply explored. High enantioselectivity with different types of allylic substrates. React wide a wide range of nucleophiles.

Mo and W and catalysts show different regioselectivity. Higher enantioselectivity with Mo.

Ir catalysts show the same regiochemistry as Mo and W. React wide a wider range of nucleophiles.

Rh: regiochemistry of starting allylic substrate largely conserved during reaction

Ru catalysts less explored, but seem to have promising properties.

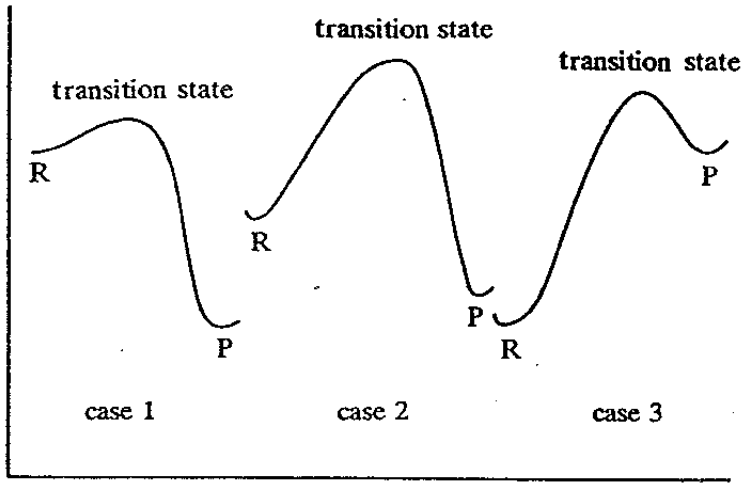
Ni catalysts have been used for allylations using stabilized as well as non-stabilized nucleophiles. Good selectivities have been obtained only in a few cases.

Cu catalysts react with non-stabilized nucleophiles with high enantioselectivity.

FRONTIER ORBITALS AND THE "HARD-SOFT" CONCEPT

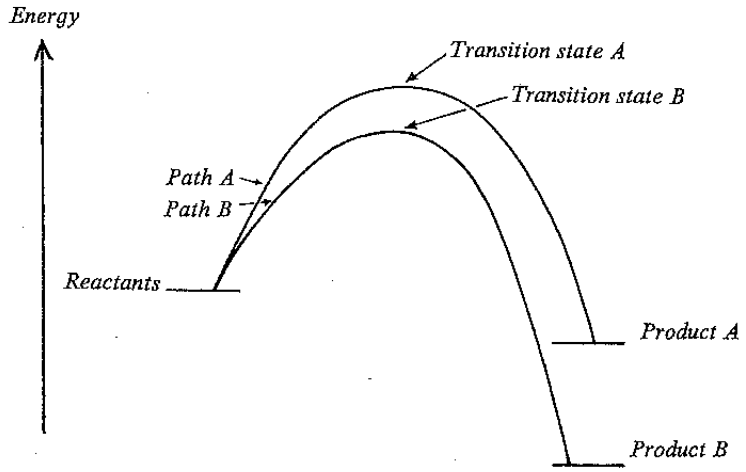
How to estimate the energy of the transition state?

Hammond's postulate: The transition state resembles the reactants in exothermic reactions (case 1) and the products in exothermic reactions (case 3).



Some typical potential energy diagrams that illustrate the application of Hammond's postulate.

Which path, A or B, is favored?



The energy along two possible reaction coordinates

The frontier orbitals can be used to estimate the slope of an early part of the reaction path.

The Equation for Estimating Chemical Reactivity

Using perturbation theory, Klopman[14] and Salem[15] derived an expression for the energy (ΔE) gained and lost when the orbitals of one reactant overlap with those of another. Their equation has the following form:

$$\Delta E = \underbrace{-\sum_{ab}(q_a + q_b)\beta_{ab}S_{ab}}_{\textit{first term}} + \underbrace{\sum_{k<l}\frac{Q_kQ_l}{\varepsilon R_{kl}}}_{\textit{second term}} + \underbrace{\sum_{r}^{\text{occ.}}\sum_{s}^{\text{unocc.}} - \sum_{s}^{\text{occ.}}\sum_{r}^{\text{unocc.}} \frac{2(\sum_{ab} c_{ra}c_{sb}\beta_{ab})^2}{E_r - E_s}}_{\textit{third term}} \qquad 2\text{-}7$$

q_a and q_b	are the electron populations (often loosely called electron densities) in the atomic orbitals a and b.
β and S	are the resonance and overlap integrals mentioned on p. 14.
Q_k and Q_l	are the total charges on atoms k and l.
ε	is the local dielectric constant.
R_{kl}	is the distance between the atoms k and l.
c_{ra}	is the coefficient of atomic orbital a in molecular orbital r, where r refers to the molecular orbitals on one molecule and s refers to those on the other.
E_r	is the energy of molecular orbital r.

Table 3-1 Some hard and soft acids (electrophiles) and bases (nucleophiles)

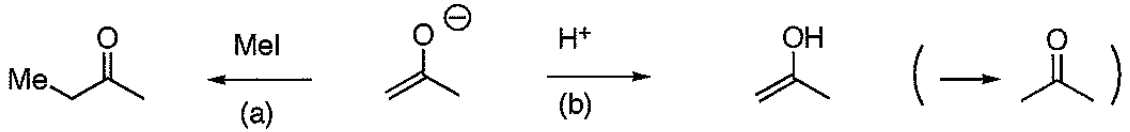
Bases (Nucleophiles)	Acids (Electrophiles)
Hard	*Hard*
H_2O, OH^-, F^-	H^+, Li^+, Na^+, K^+
$CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-}	Be^{2+}, Mg^{2+}, Ca^{2+}
Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-	Al^{3+}, Ga^{3+}
ROH, RO^-, R_2O	Cr^{3+}, Co^{3+}, Fe^{3+}
NH_3, RNH_2, N_2H_4	CH_3Sn^{3+}
	Si^{4+}, Ti^{4+}
	Ce^{3+}, Sn^{4+}
	$(CH_3)_2Sn^{2+}$
	$BeMe_2$, BF_3, $B(OR)_3$
	$Al(CH_3)_3$, $AlCl_3$, AlH_3
	RPO_2^+, $ROPO_2^+$
	RSO_2^+, $ROSO_2^+$, SO_3
	I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+}
	RCO^+, CO_2, NC^+
	HX (hydrogen bonding molecules)
Borderline	*Borderline*
$C_6H_5NH_2$, C_5H_5N, N_3^-, Br^-, NO_2^-, SO_3^{2-}, N_2	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, $B(CH_3)_3$, SO_2, NO^+, R_3C^+, $C_6H_5^+$
Soft	*Soft*
R_2S, RSH, RS^-	Cu^+, Ag^+, Au^+, Tl^+, Hg^+
I^-, SCN^-, $S_2O_3^{2-}$	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, CH_3Hg^+, $Co(CN)_5^{2-}$
R_3P, R_3As, $(RO)_3P$	Tl^{3+}, $Tl(CH_3)_3$, BH_3
CN^-, RNC, CO	RS^+, RSe^+, RTe^+
C_2H_4, C_6H_6	I^+, Br^+, HO^+, RO^+
H^-, R^-	I_2, Br_2, ICN, etc.
	trinitrobenzene, etc.
	chloranil, quinones, etc.
	tetracyanoethylene, etc.
	O, Cl, Br, I, N, $RO^{\cdot}$, $RO_2^{\cdot}$
	M^0 (metal atoms)
	bulk metals
	CH_2, carbenes

Nucleophilicity of Inorganic Ions towards Organic Electrophiles

By using only the HOMO of a nucleophile and the LUMO of an electrophile, we can simplify equation 2-7 to equation 3-1. This will be a good approximation, because the interactions of the other orbitals all have much larger $E_r - E_s$

$$\Delta E = \underbrace{-\frac{Q_{nuc.}\, Q_{elec.}}{\varepsilon R}}_{\substack{The \\ Coulombic \\ term}} + \underbrace{\frac{2(c_{nuc.}\, c_{elec.}\, \beta)^2}{E_{HOMO\,(nuc.)} - E_{LUMO\,(elec.)}}}_{The\ frontier\ orbital\ term}$$

Ex: enolate anion



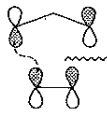
why?

Frontier orbital control (a):
Electrophile reacts at the center having the largest coefficient of the HOMO

Charge control (b):
Electrophiles reacts at the center having the largest negative charge

(a) [π2s + π2s]

Frontier orbitals:



LUMO *of an allyl cation*

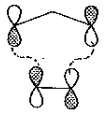
antibonding

HOMO *of an olefin*

There are no known examples of a pericyclic reaction of an allyl cation with an olefin.

(b) [π4s + π2s]

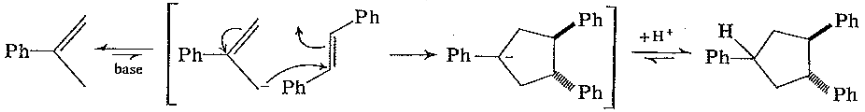
Frontier orbitals:



HOMO *of an allyl anion*

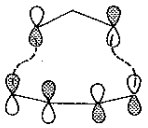
LUMO *of an olefin*

An example:[122]



(c) [π4s + π2s]

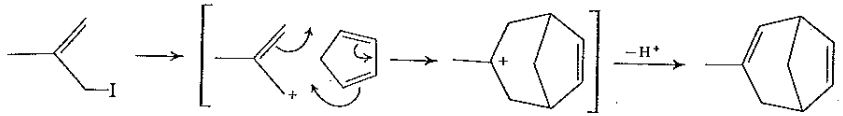
Frontier orbitals:



LUMO *of an allyl cation*

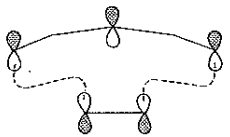
HOMO *of a diene*

An example:[123]



(d) [π4s + π2s]

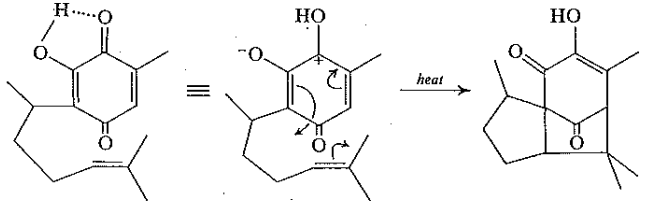
Frontier orbitals:



LUMO *of a pentadienyl cation*

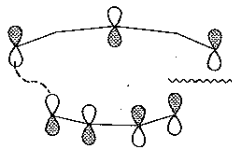
HOMO *of an olefin*

An example:[124]



(e) [π4s + π4s]

Frontier orbitals:

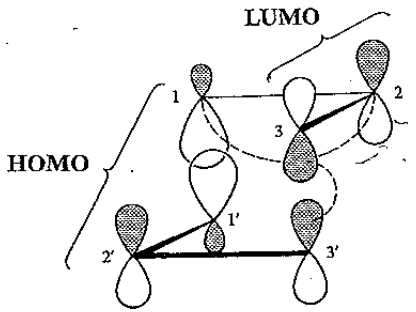


LUMO *of a pentadienyl cation*

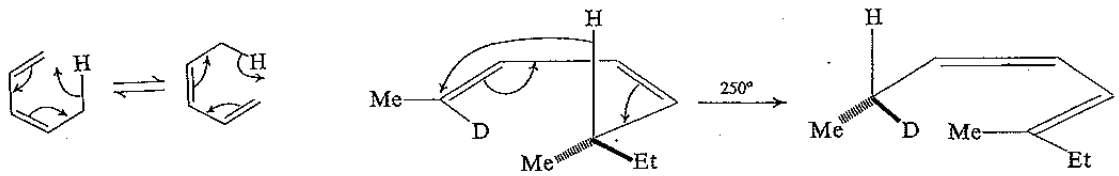
antibonding

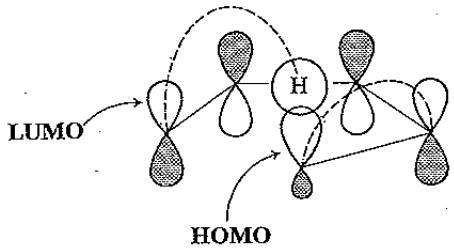
HOMO *of a diene*

There are no known examples of a pericyclic reaction of a pentadienyl cation with a diene.



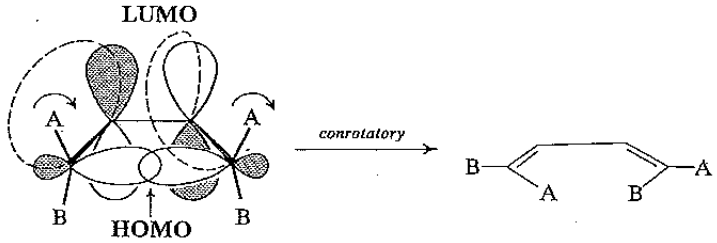
Frontier orbitals for a Cope rearrangement

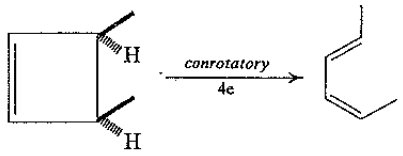


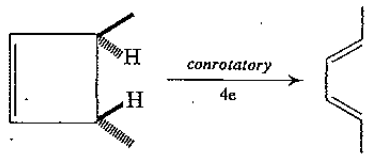


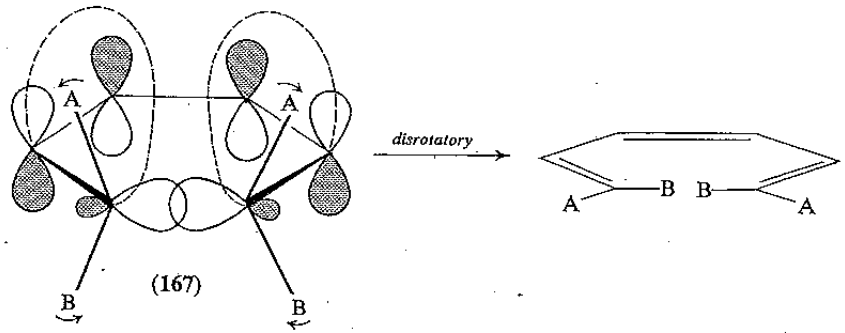
Frontier orbitals for suprafacial [1,5] sigmatropic rearrangement of hydrogen

Electrocyclic reactions

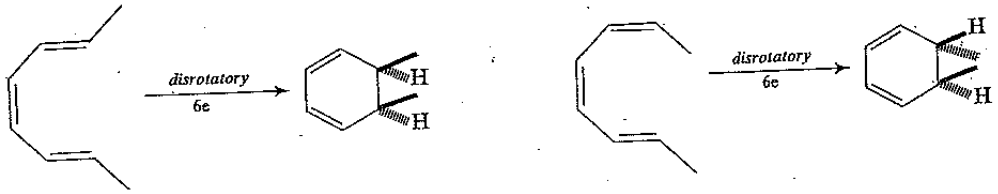






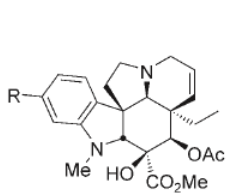


(167)

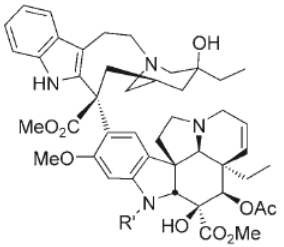


Total Synthesis of (−)- and *ent*-(+)-Vindorosine: Tandem Intramolecular Diels–Alder/1,3-Dipolar Cycloaddition of 1,3,4-Oxadiazoles**

Vindorosine (**1**) is among the most complex, highly functionalized, and stereochemically rich natural products within a family of more than 90 alkaloids isolated from the Madagascan periwinkle (*Catharanthus roseus* (L.) G. Don).[1] The related C16-methoxy derivative vindoline (**2**) constitutes the

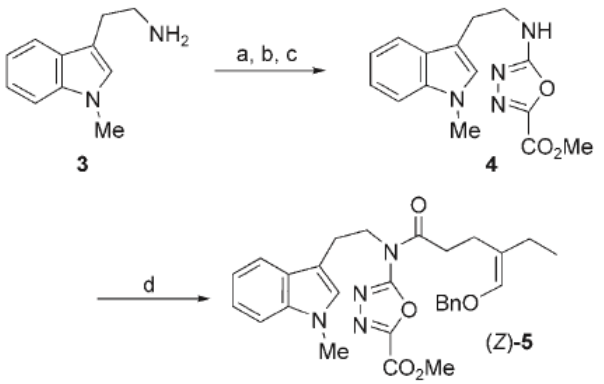


R = H: vindorosine (**1**)
R = OMe: vindoline (**2**)

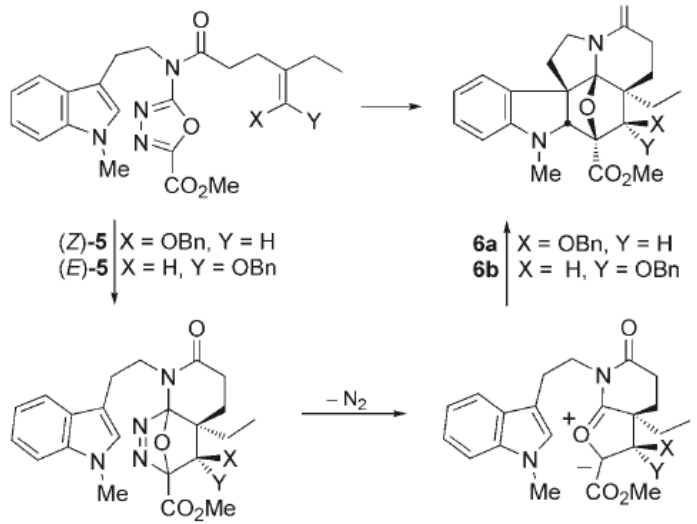


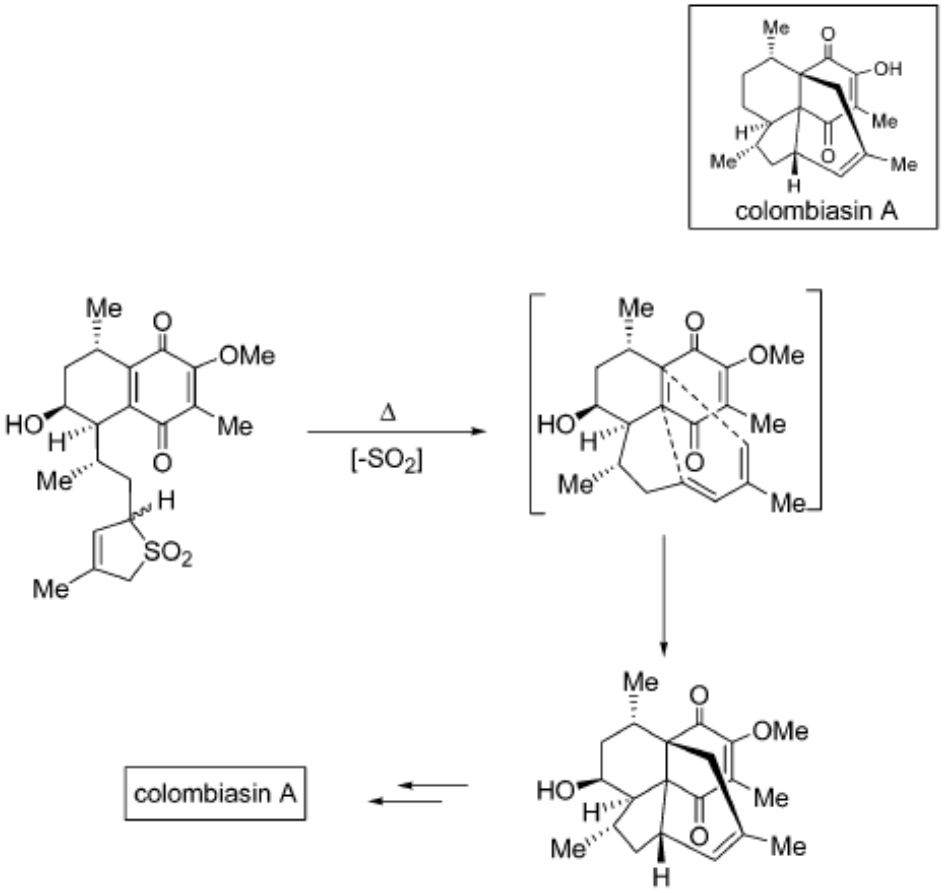
R' = CH_3: vinblastine
R' = CHO: vincristine

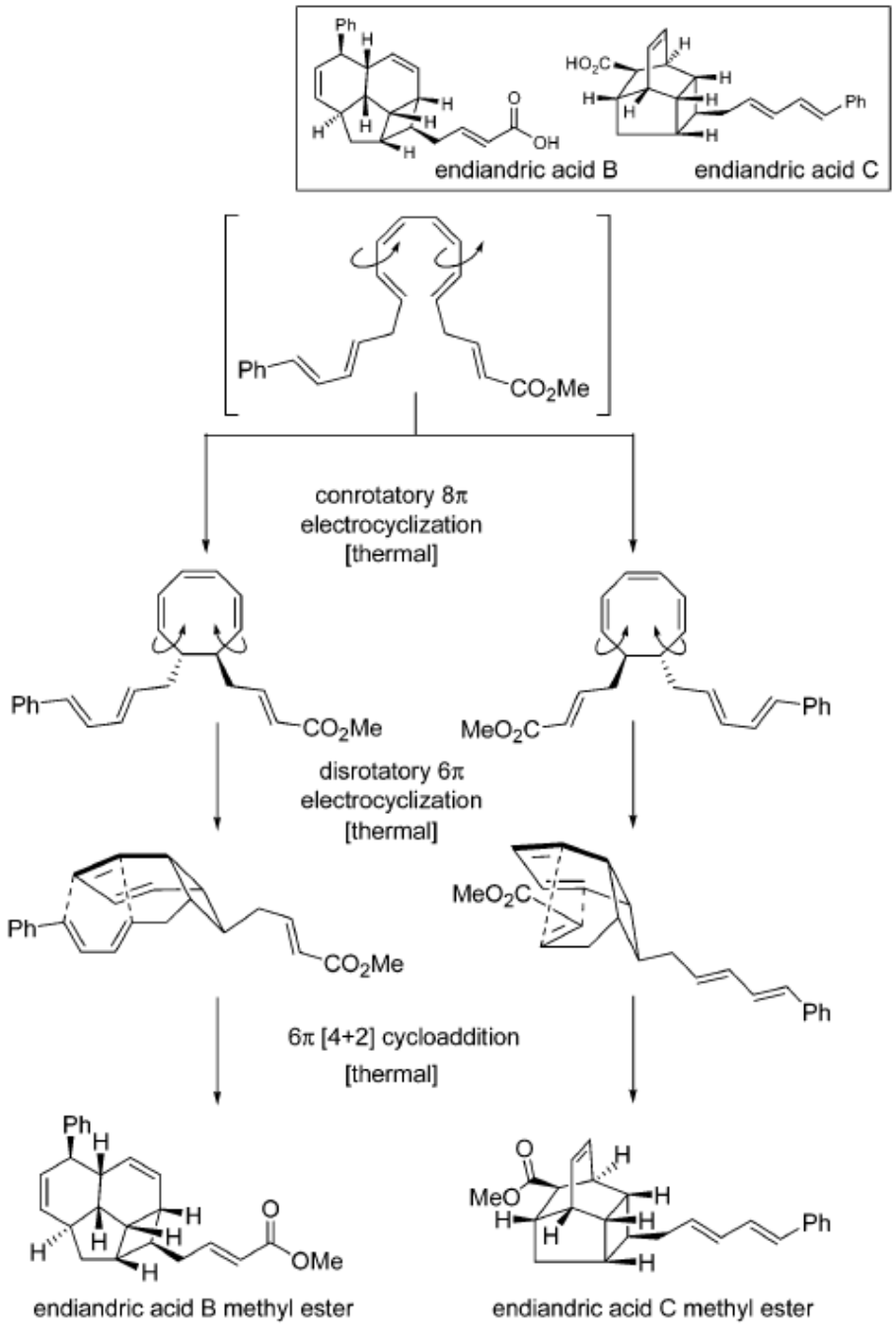
lower portion of vinblastine, which together with vincristine represent an important class of clinically effective anticancer therapeutics.[2]



Scheme 1. Reagents and conditions: a) CDI, THF/CH_2Cl_2, 23 °C, 89%; b) methyl oxalylhydrazide, AcOH, THF, 40 °C, 93%; c) TsCl, Et_3N, CH_2Cl_2, 23 °C, 83%; d) (*Z*)-5-benzyloxy-4-ethylpent-4-enoic acid, EDCI, DMAP, CH_2Cl_2, 0–23 °C, 96%. Bn = benzyl, CDI = 1,1-carbonyldiimidazole, Ts = *p*-toluenesulfonyl, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, DMAP = 4-(dimethylamino)pyridine.




colombiasin A
Δ
[-SO2]
colombiasin A


endiandric acid B
endiandric acid C
conrotatory 8π
electrocyclization
[thermal]
disrotatory 6π
electrocyclization
[thermal]
6π [4+2] cycloaddition
[thermal]
endiandric acid B methyl ester
endiandric acid C methyl ester

THE END