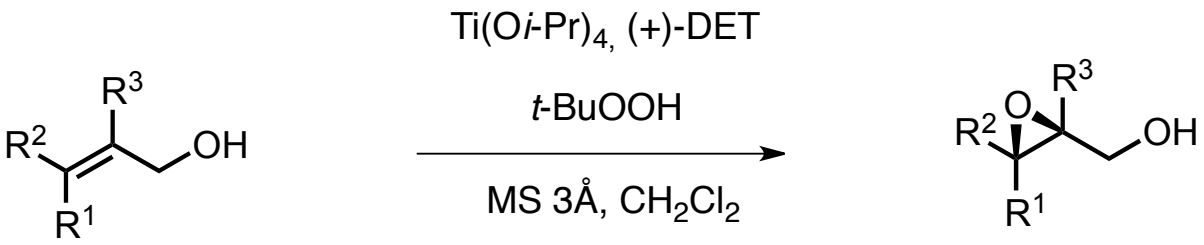
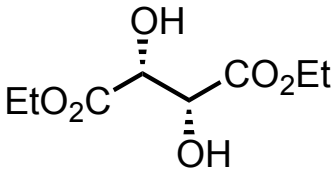
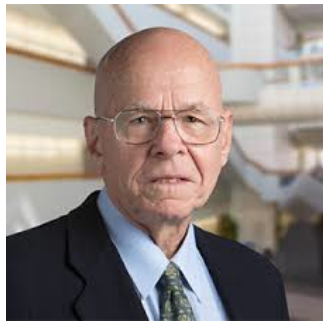
Asymmetric oxidation reactions

Sharpless asymmetric epoxidation reaction



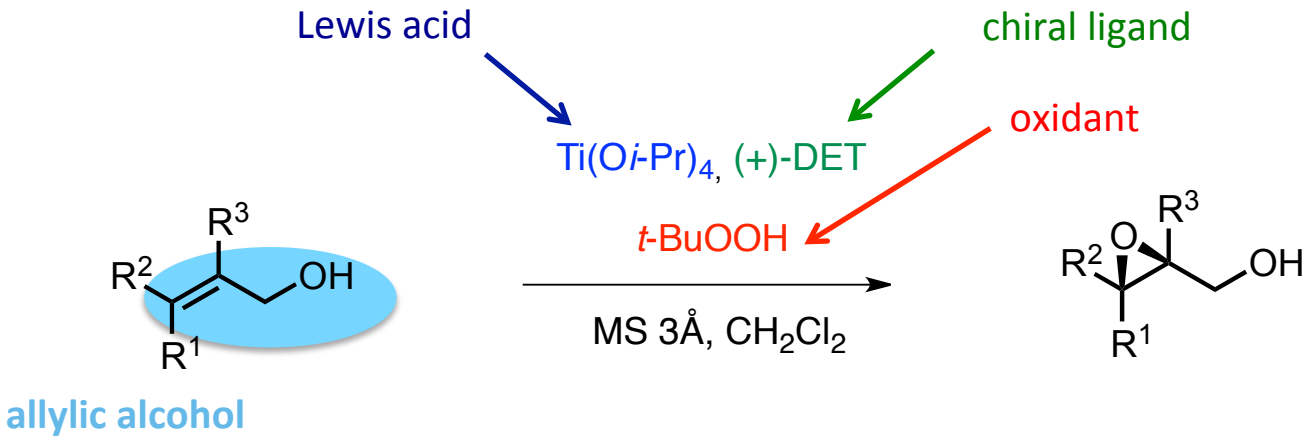
(+)-DET = 

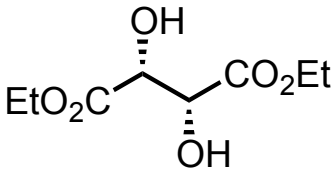
- Enantioselective reaction
- Works only with allylic alcohols
- (+)-DET and (-)-DET available and non-expensive
- Ti(Oi-Pr)$_4$ can be used in catalytic amount



Barry Sharpless
Chemistry Nobel Prize 2001

Sharpless asymmetric epoxidation reaction



(+)-DET = 

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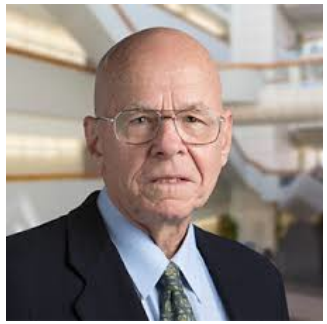
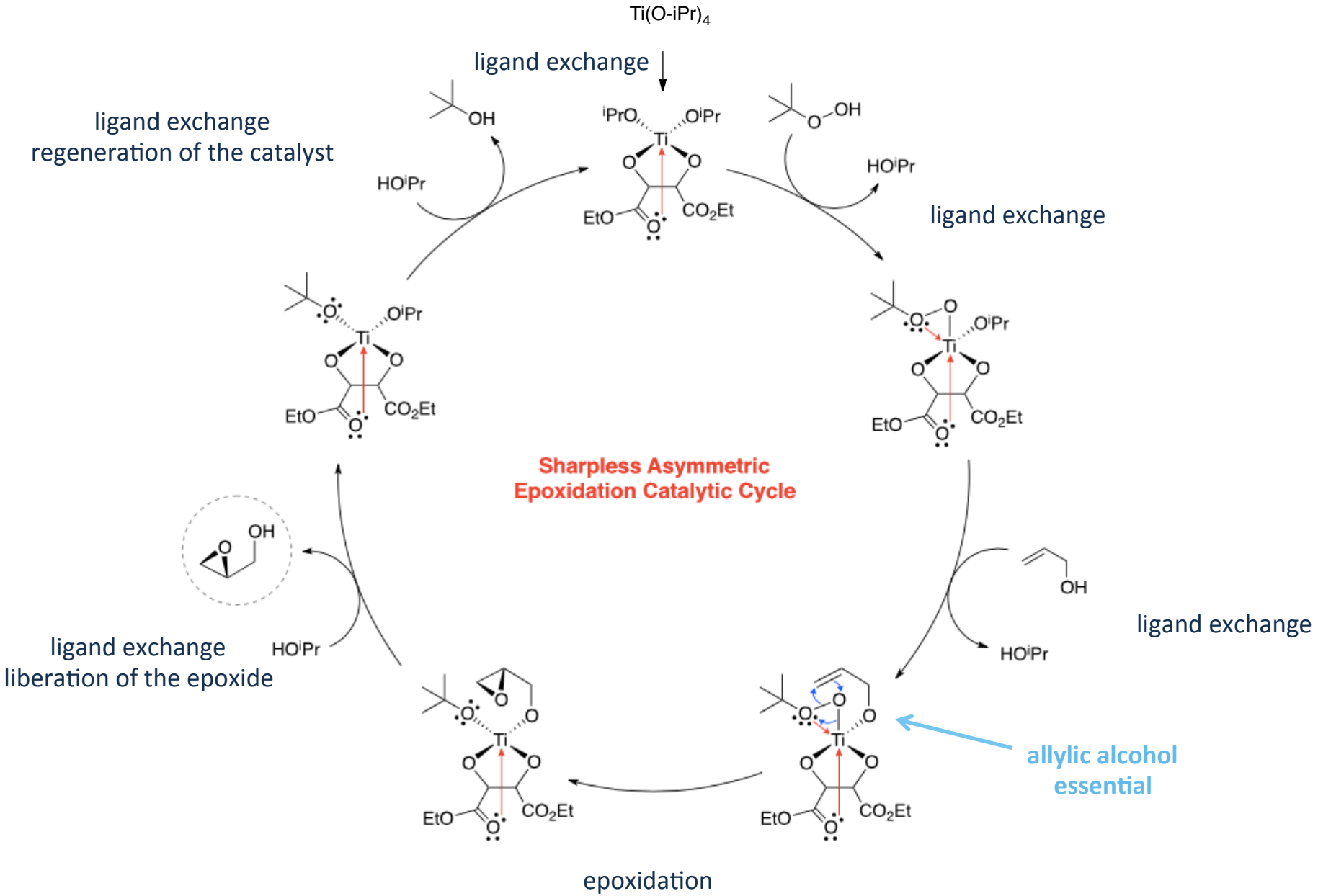


Barry Sharpless
Chemistry Nobel Prize 2001

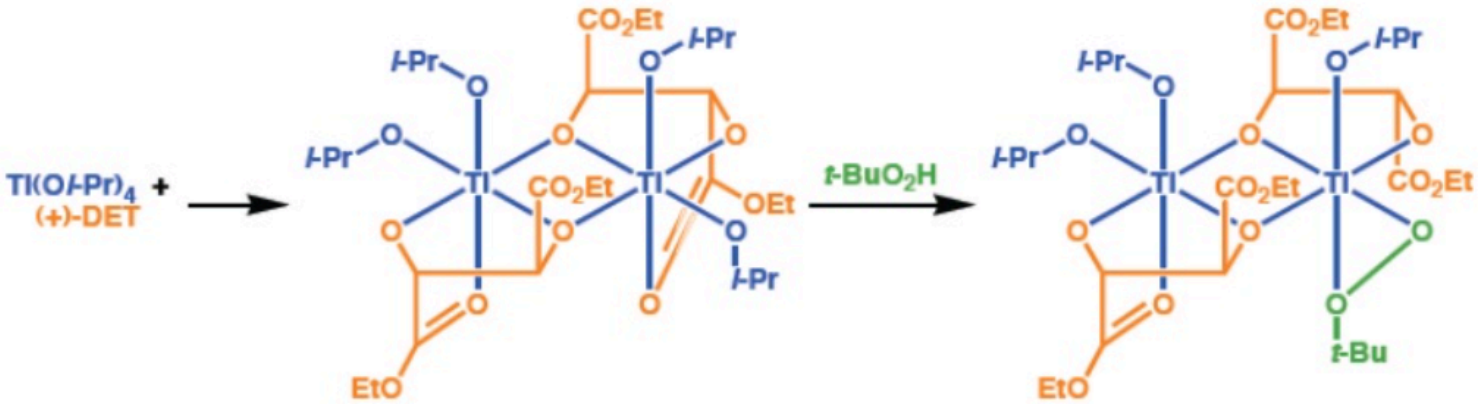
Simplified catalytic cycle



From www.name-reaction.com

Origin of selectivity

Formation of a dimeric titanium complex incorporating DET ligand and oxidant



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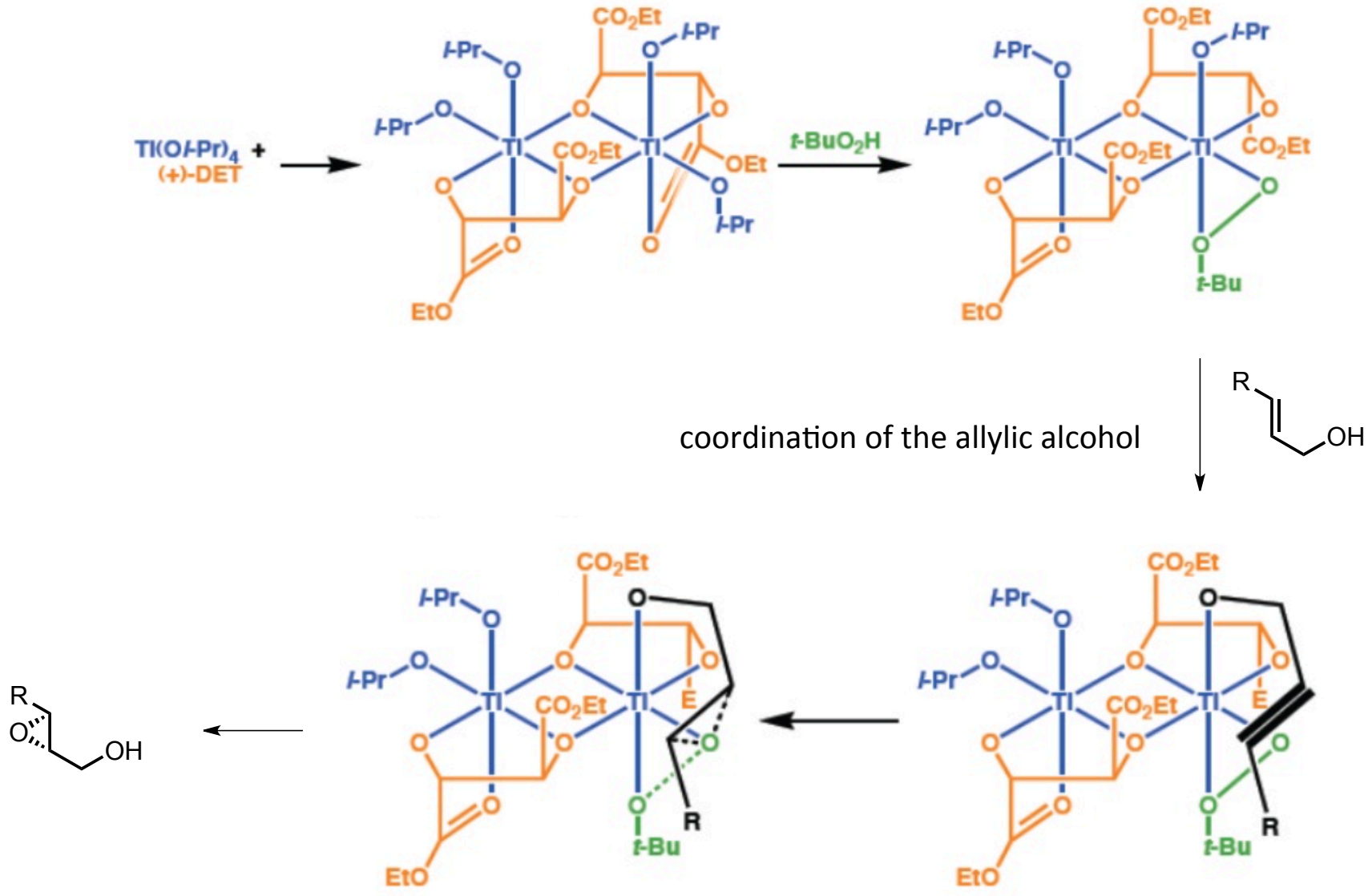
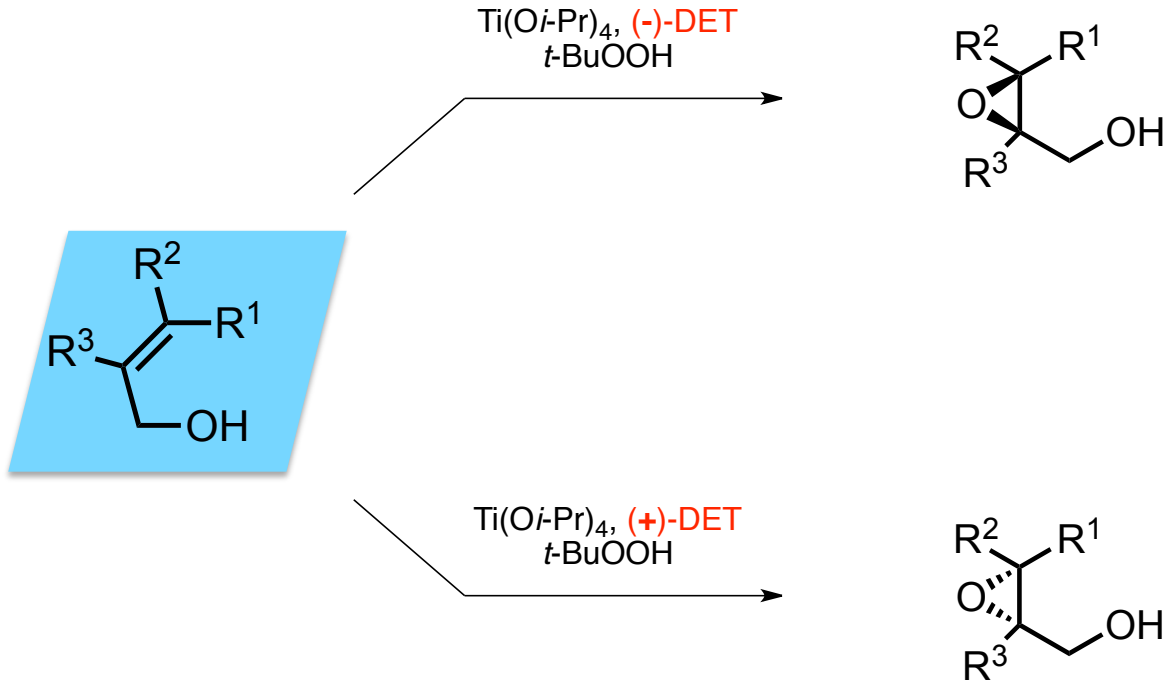
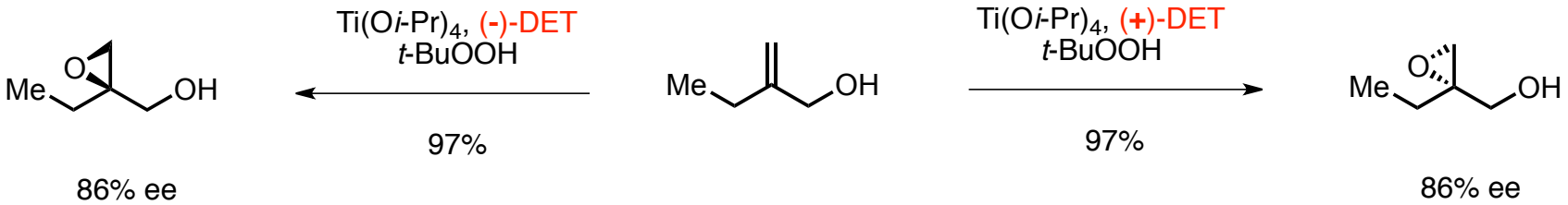


Mnemonic

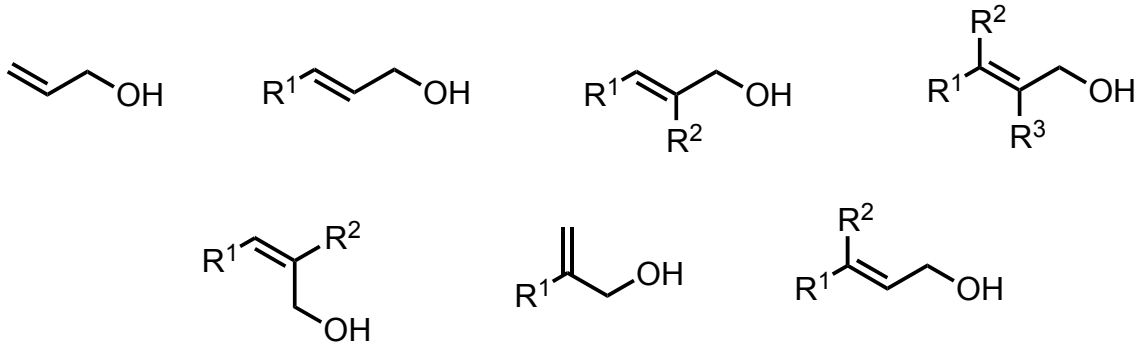


Example:

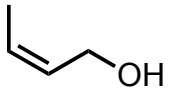


Substitution patterns tolerated

- Works well with

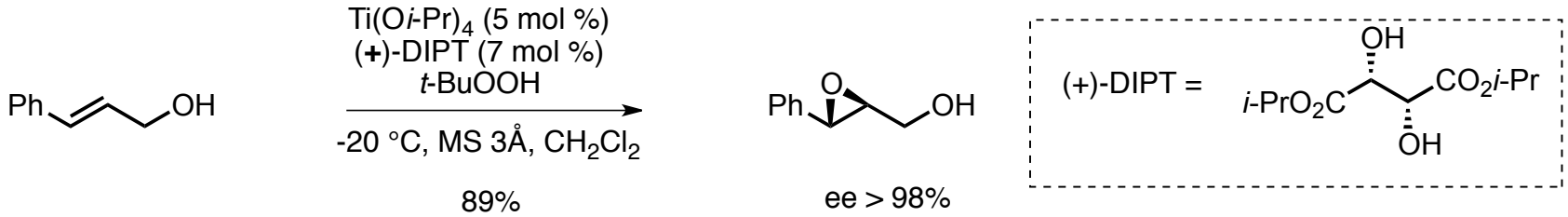


- Less efficient and selective with (Z)-disubstituted olefins

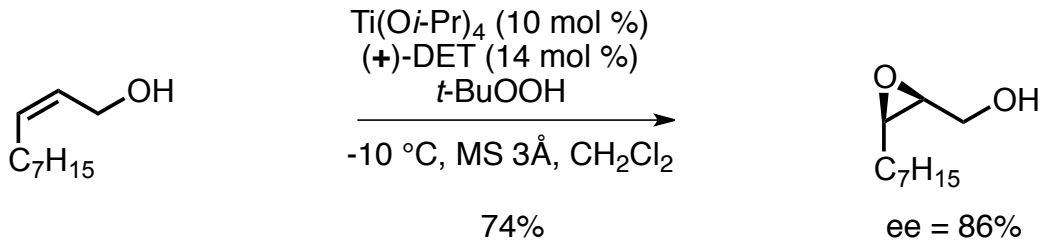


Examples

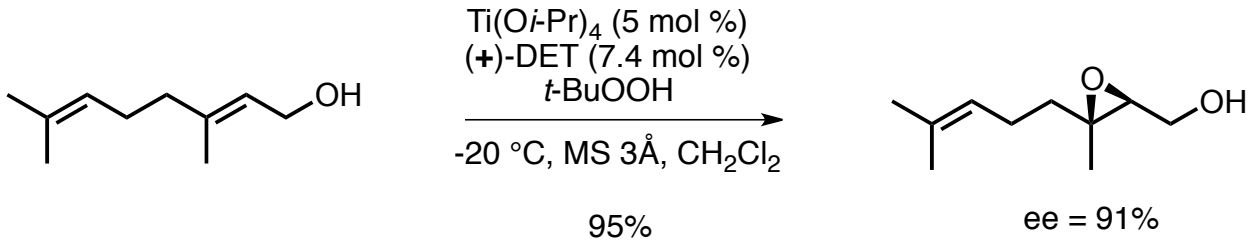
- Styrenyl derivative



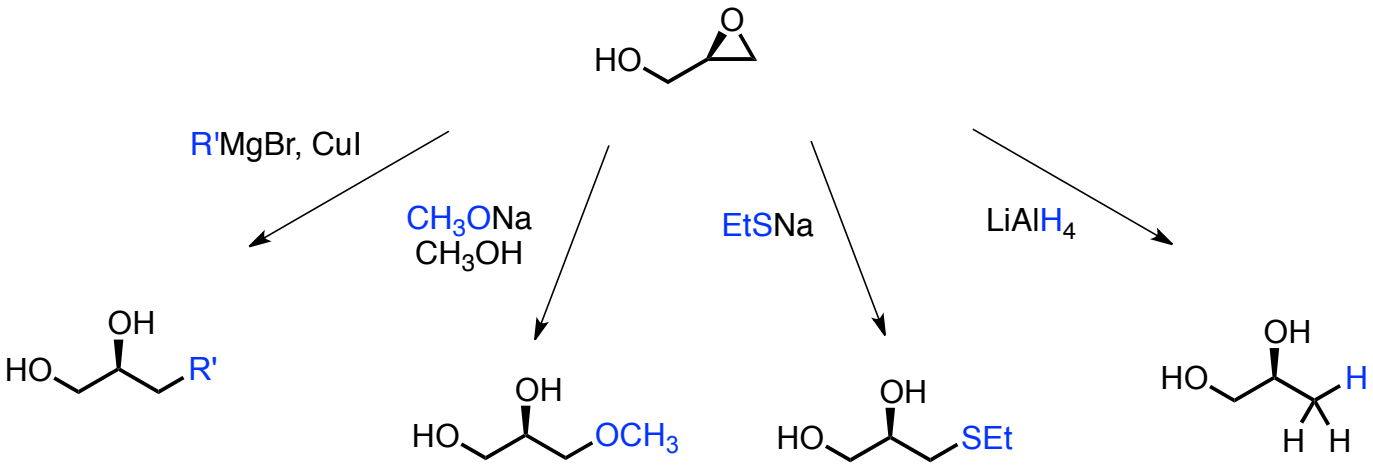
- (*Z*)-olefin



- Regioselectivity



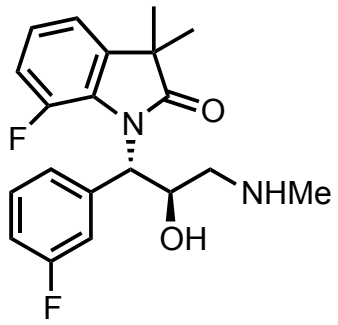
Epoxides as useful intermediates



Numerous applications in total synthesis of biologically active molecules

Application : pharmaceutical industry

Kilogram scale synthesis of a bioactive molecule (Wyeth drug company)



WAY-315193
treatment of mental disorders

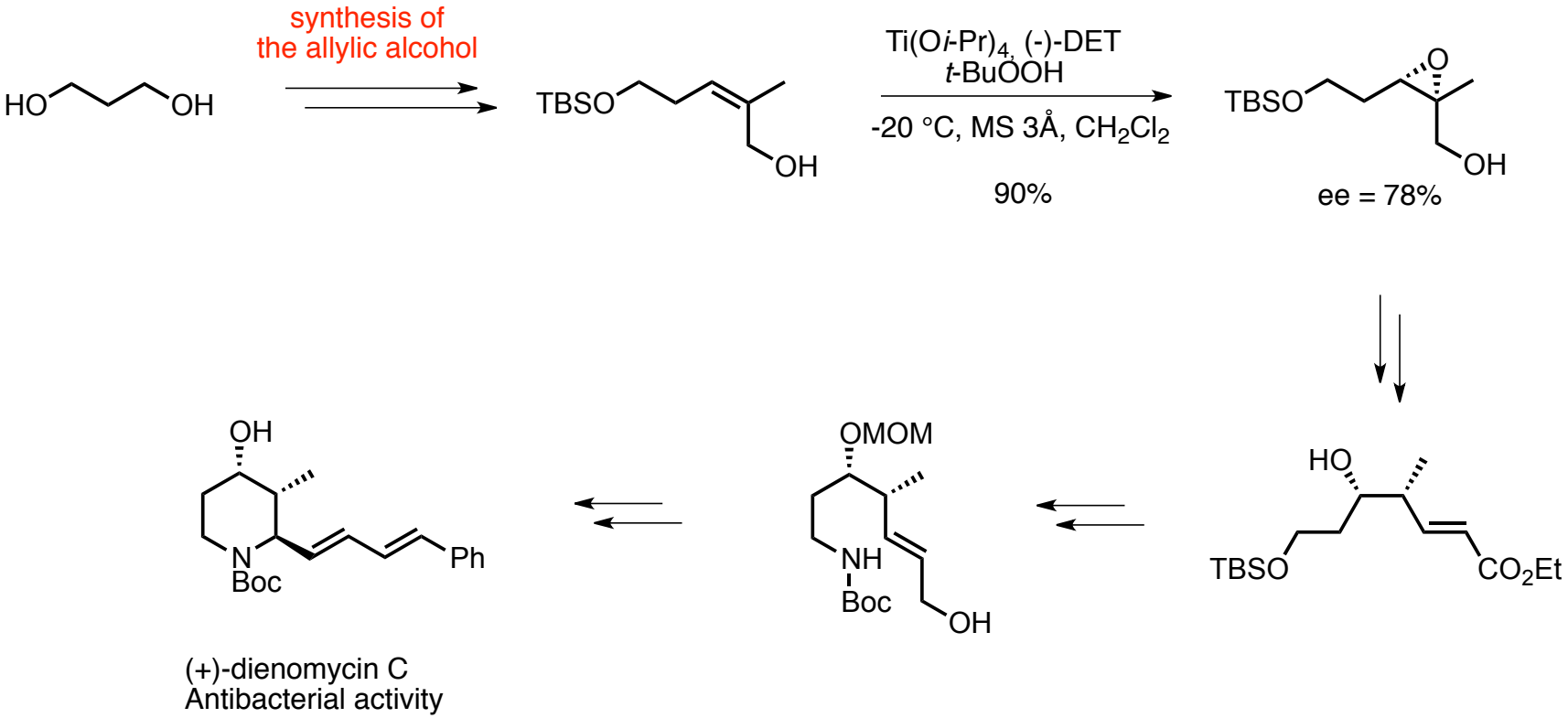
A. Alimardanov *et al. Org. Process. Res. Dev.* **2009**, *13*, 880

Application : pharmaceutical industry

Kilogram scale synthesis of a bioactive molecule (Wyeth drug company)

A. Alimardanov *et al. Org. Process. Res. Dev.* **2009**, *13*, 880

Application : synthesis of a bioactive alkaloid



Y. Hirai *et al. Tetrahedron* **2010**, *66*, 8458.

Kinetic resolution

- Operating when secondary allylic alcohols are used

racemic mixture

49%
ee > 99%

(*S*)-enantiomer reacts faster

48%
ee > 99%

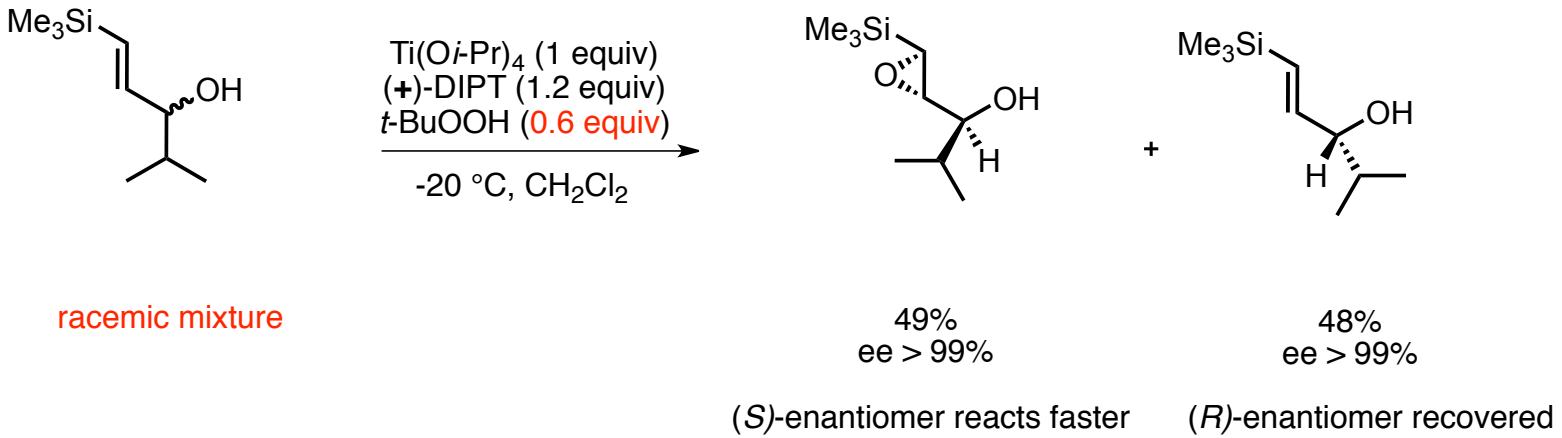
(*R*)-enantiomer recovered

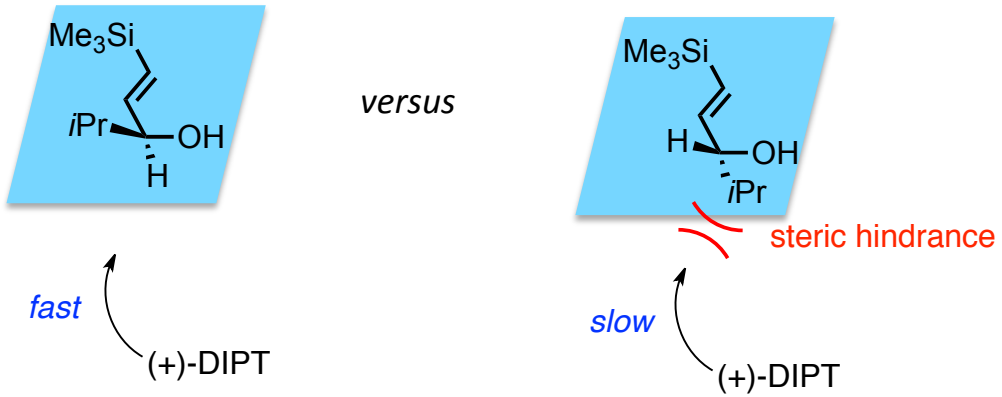
Kinetic resolution = the two enantiomers of the initial racemic mixture are differentiated because one reacts with an higher reaction rates than the second

High ee can be obtained for both the epoxide and the recovered alkene but yields are limited to 50%.

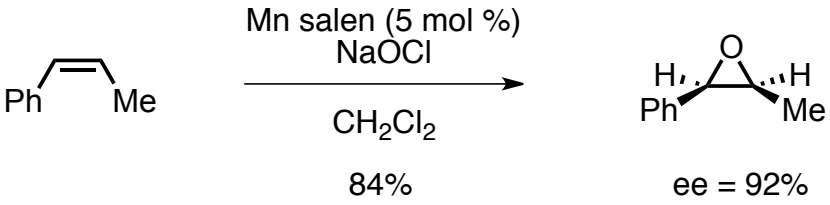
Kinetic resolution

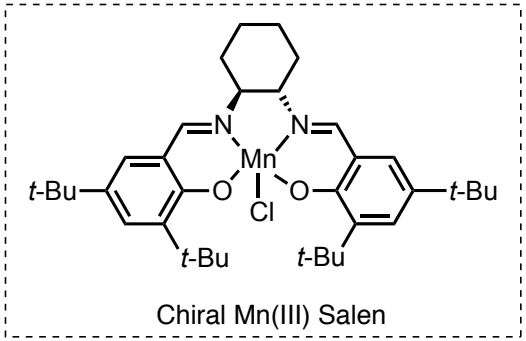
- Operating when secondary allylic alcohols are used



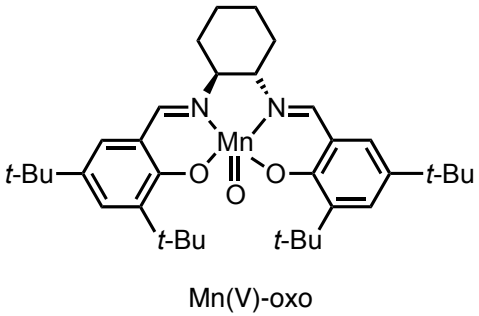


Jacobsen epoxidation

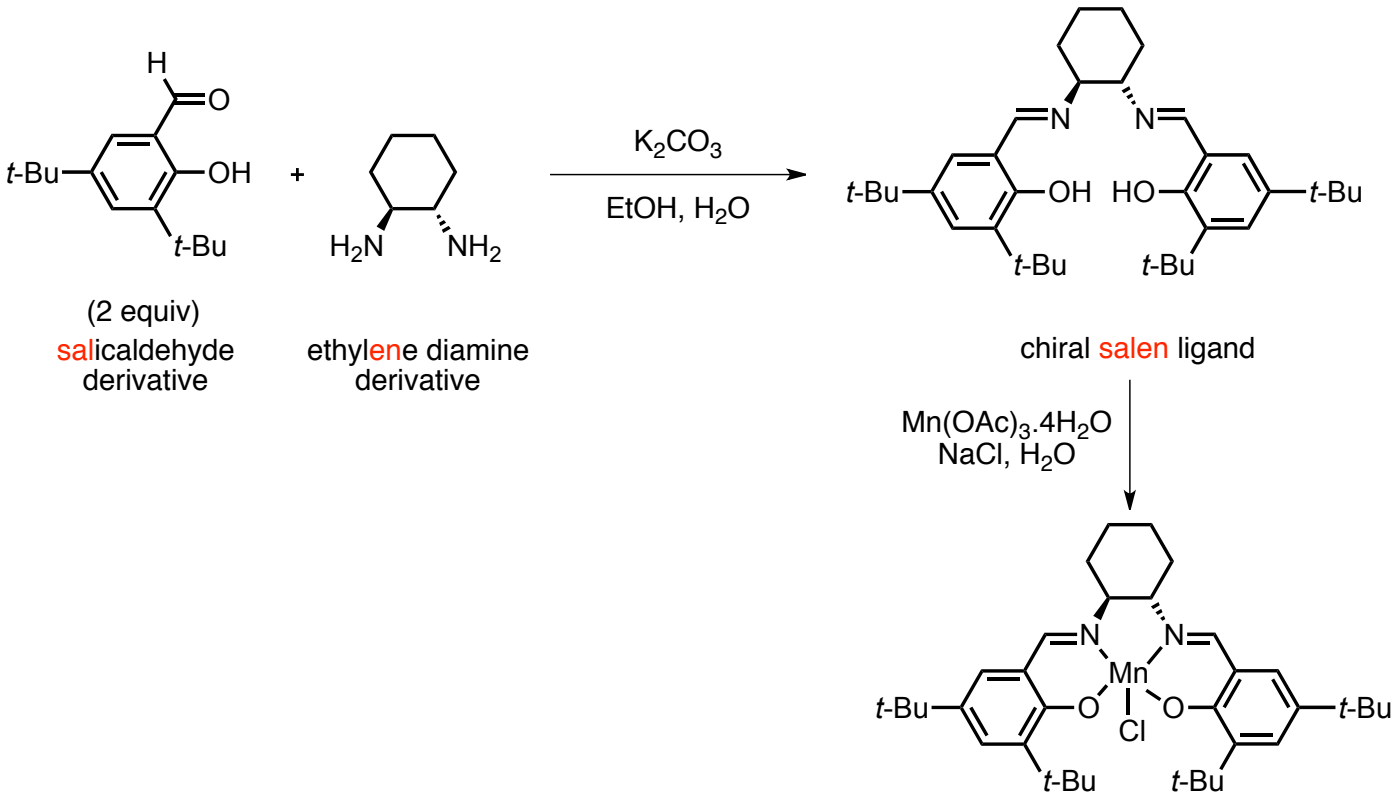




- Sodium hypochlorite generally used as an oxidant
- Works on unactivated alkenes, better with (Z)-olefins
- Mechanism not fully understood, oxo-Mn(V) species probaly involved



Jacobsen epoxidation – ligand synthesis

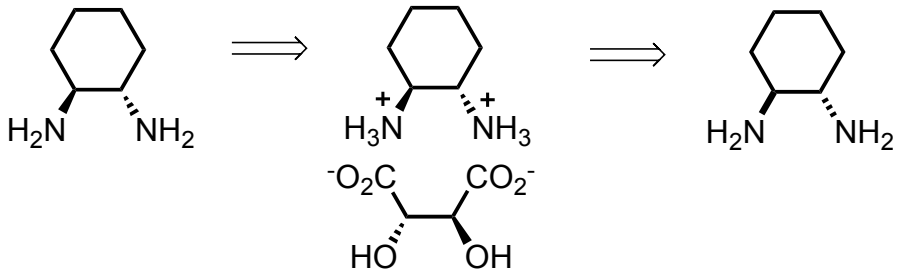


(2 equiv)
salicaldehyde derivative

ethylene diamine derivative

chiral salen ligand

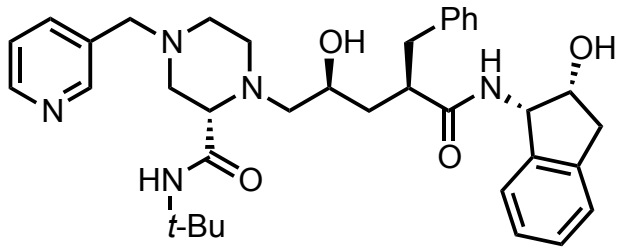
Optically active diamine obtained by resolution



tartric acid

Jacobsen epoxidation – application

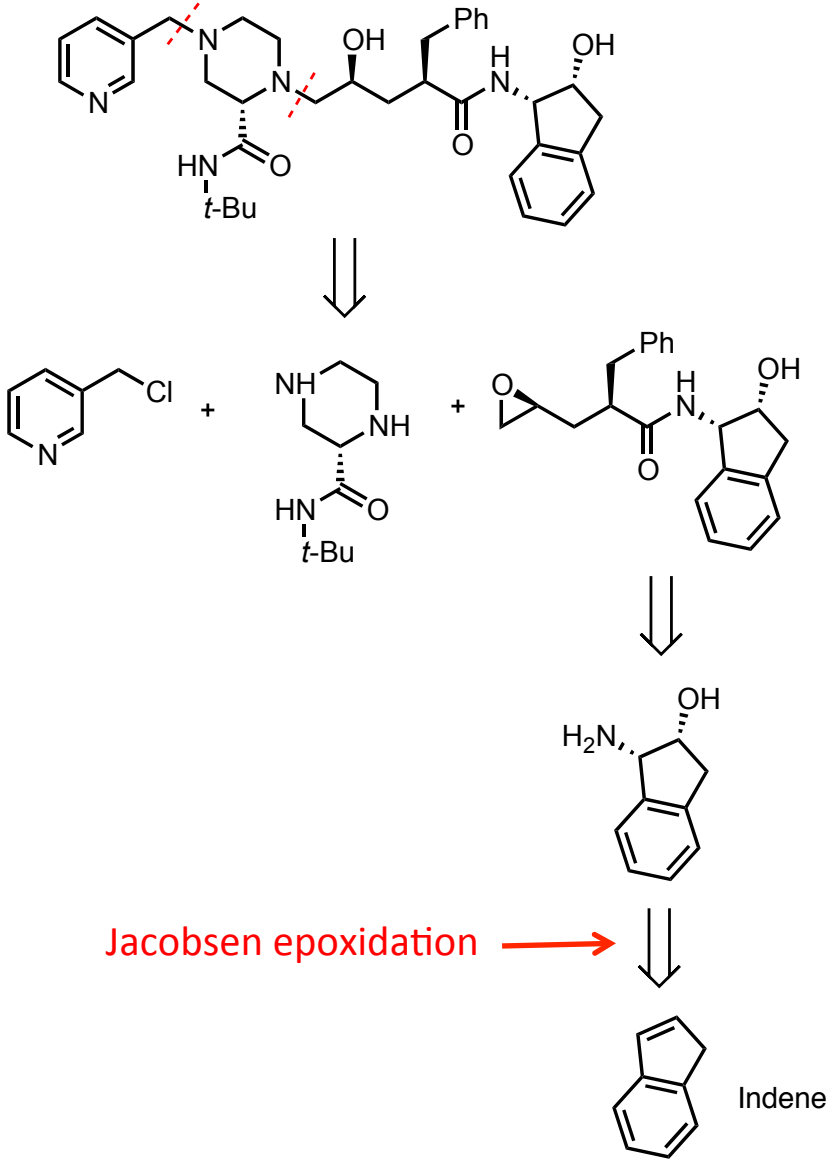
Synthesis of Indinavir



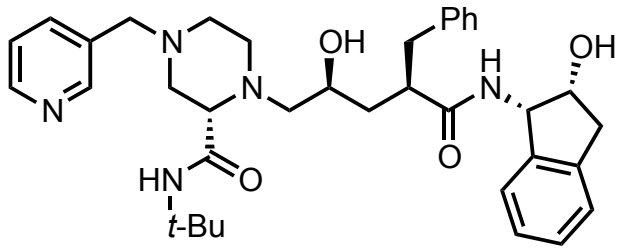
- HIV protease inhibitor
- Used in combination with antiviral agents AZT and Lamivudine (tritherapy)
- This combination reduces the amount of virus to undetectably low levels
- 3 g per day dose needed in Indinavir (1 kg per year per patient) = need for very efficient synthesis
- Complex structure with 5 stereocenters

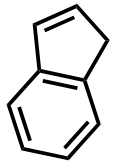
Jacobsen epoxidation – application

Retrosynthesis



Jacobsen epoxidation – application

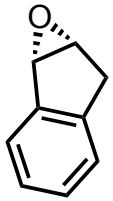




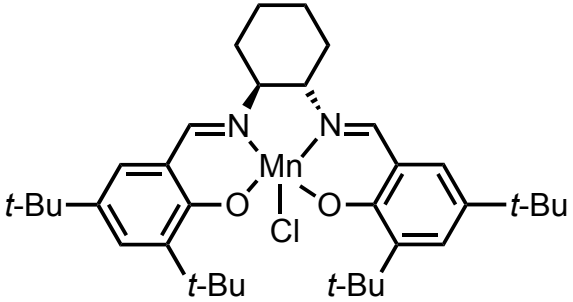
Mn salen (5 mol %)
NaOCl

CH_2Cl_2

79%

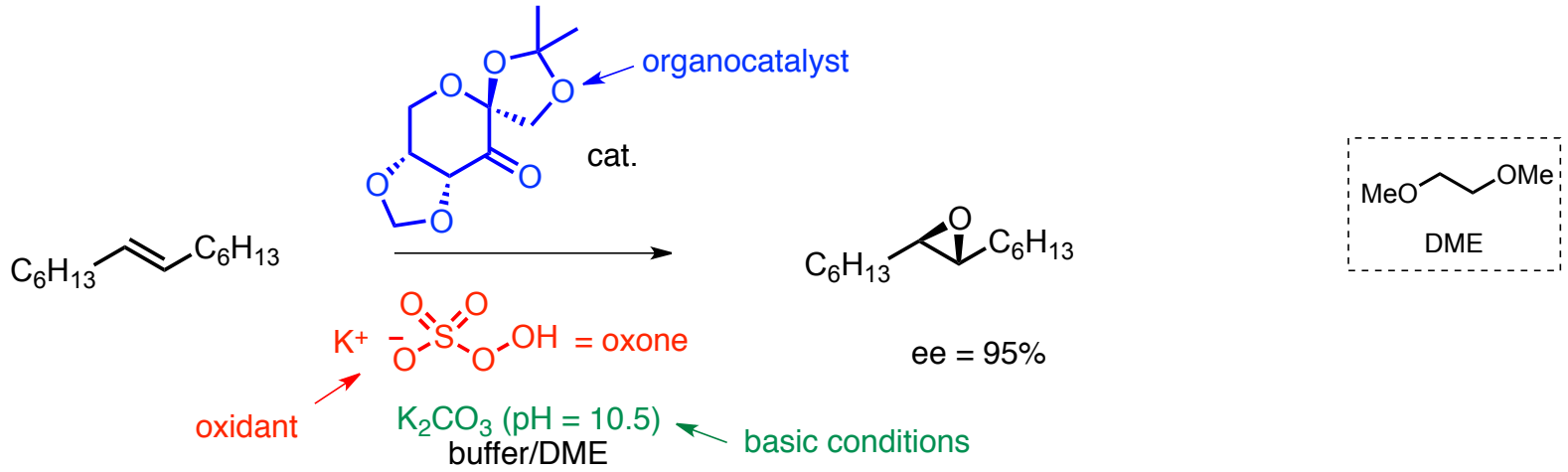


ee = 84%

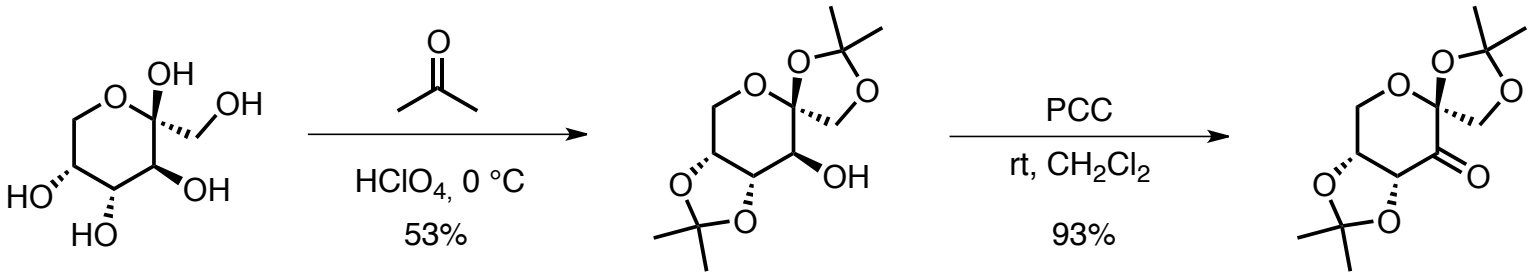


Chiral Mn(III) Salen

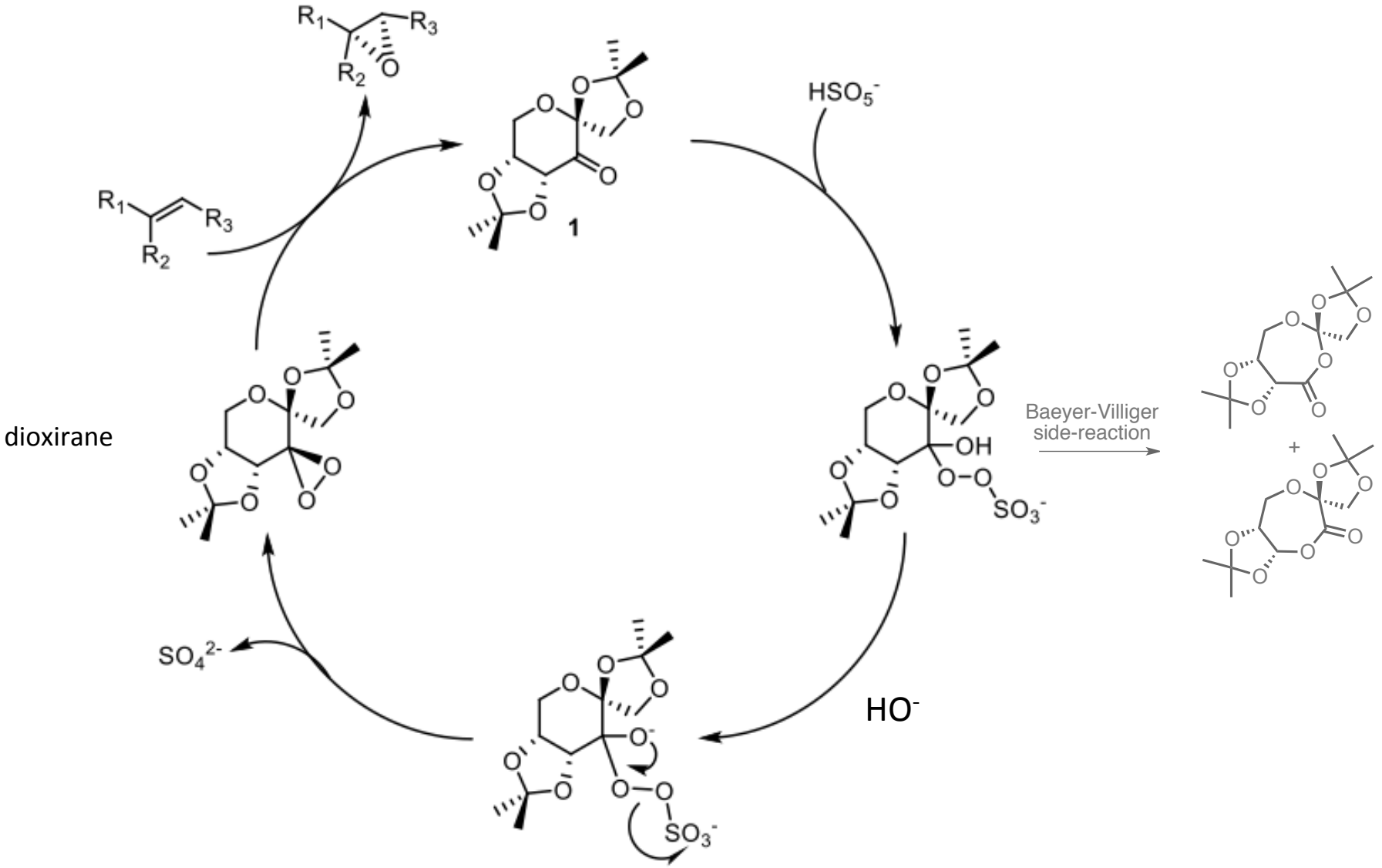
Shi epoxidation



- General asymmetric epoxidation of (*E*)- and (*Z*)-olefins
- Organocatalyst prepared from (*D*)-fructose

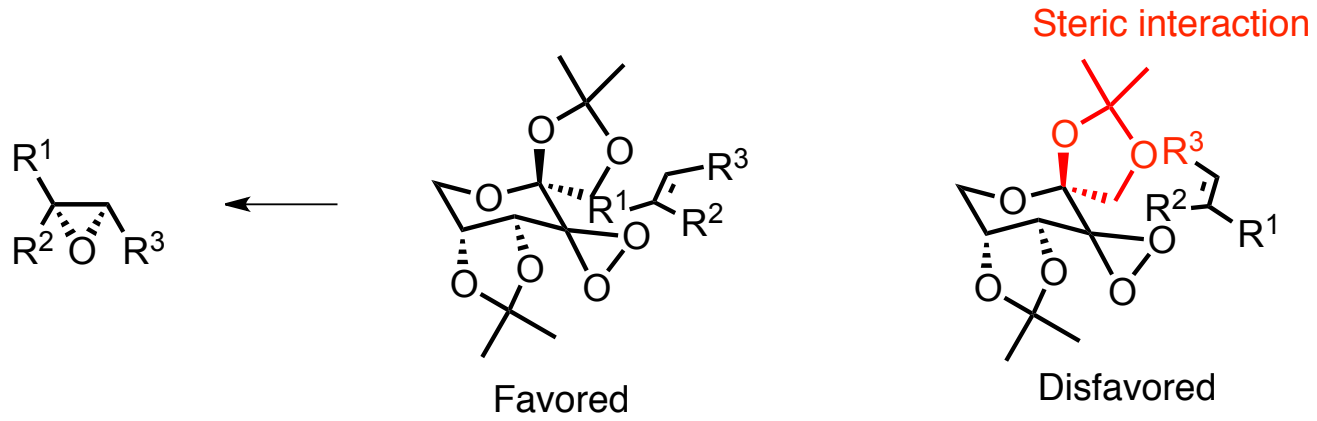


Shi epoxidation - mechanism



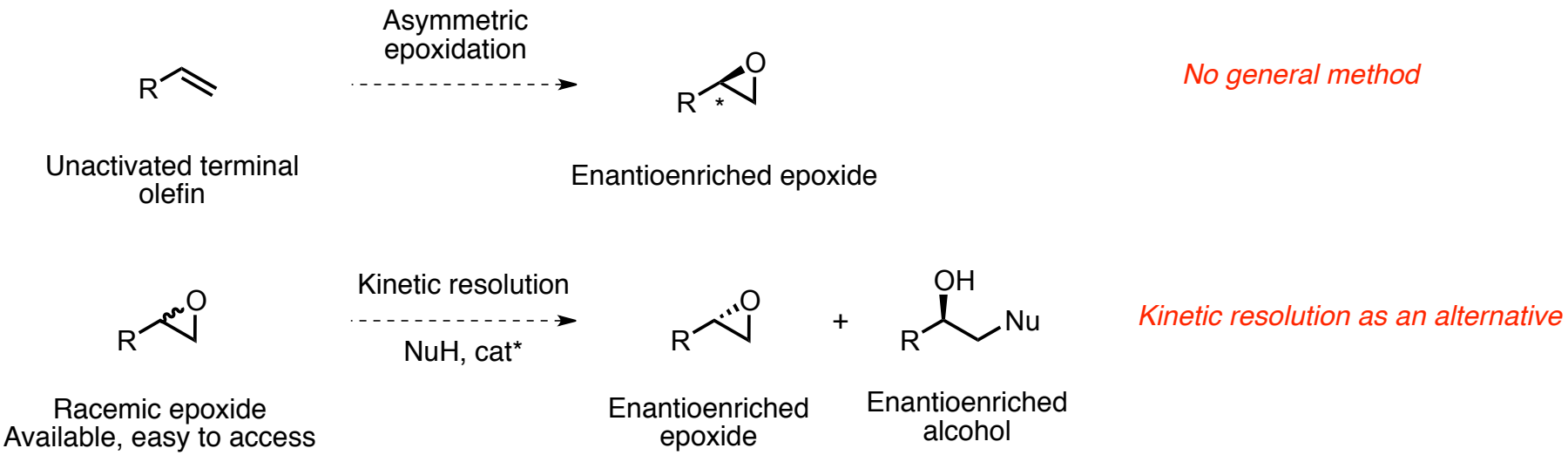
Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *19*, 11224–11235.

Shi epoxidation - rationalization

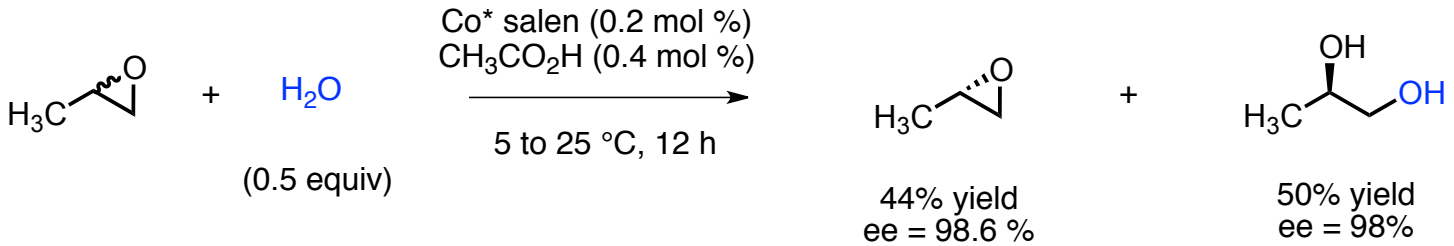


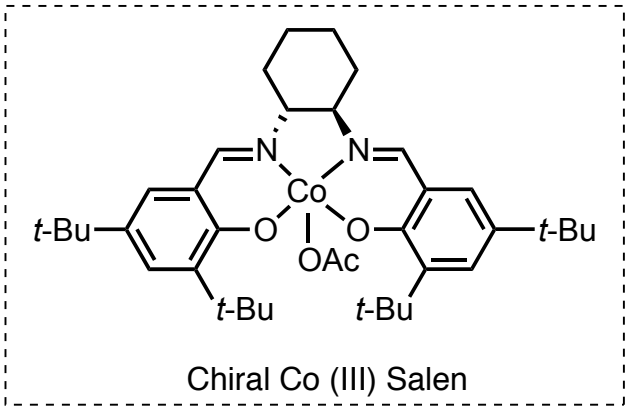
- Spiro approached is proposed
- Selective epoxidation of one face of the alkene due to steric interaction with the acetal moiety.
- Good selectivity with di- or tri-substituted olefins, terminal alkene are not good substrates.

Kinetic resolution of terminal epoxides



Hydrolytic kinetic resolution of terminal epoxides





Chiral Co (III) Salen

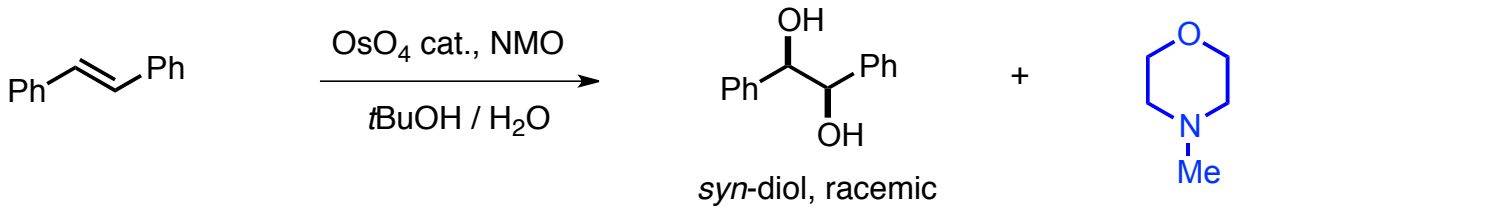
- High difference of rate between the two enantiomers of the epoxide ($k_{rel} > 400$).
- Both enantioenriched epoxide and diol are valuable compounds.
- Yields limited to 50% in both products.
- Extensions to other Nu have been developed (ex = $TMSN_3$, NH_2Boc…)

E. N. Jacobsen *et al. Science* **1997**, *277*, 936.

Kinetic resolution of terminal epoxides - examples

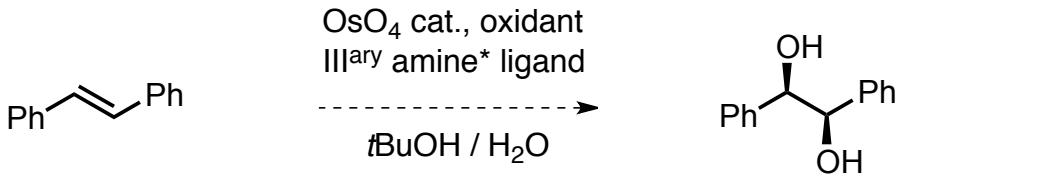
E. N. Jacobsen *et al. Science* **1997**, *277*, 936.

Asymmetric Sharpless dihydroxylation - hypothesis



syn-diol, racemic

N-methylmorpholine
By-product of the reaction
Accelerate the rate of the dihydroxylation
(good ligand for Os)



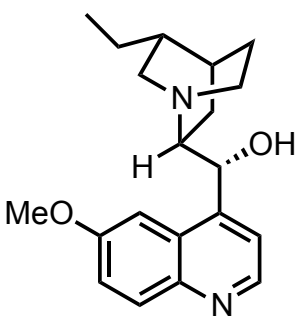
syn-diol, enantioenriched

Screening of chiral tertiary amines and particularly natural alkaloids (Sharpless)

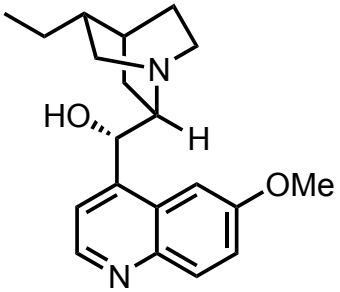
Asymmetric dihydroxylation - ligands

- Identification of two *cinchona* alkaloids

not enantiomers



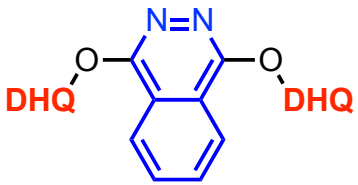
dihydroquinine
DHQ



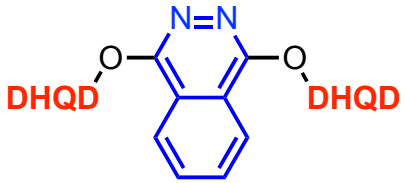
dihydroquinidine
DHQD

- High selectivity in asymmetric dihydroxylation when attached to an aromatic group

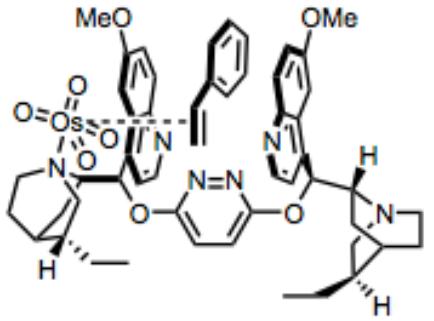
phthalazine ligands



DHQ_2PHAL

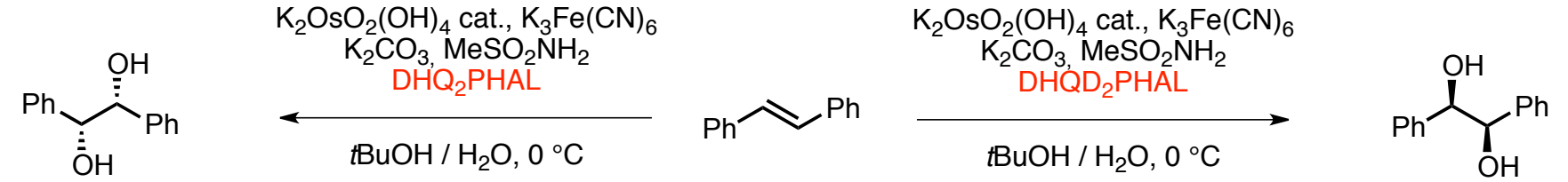


$DHQD_2PHAL$



U-shaped binding pocket

Asymmetric dihydroxylation - conditions



ee > 99.5 %

ee = 99.8 %

$K_2OsO_2(OH)_4$ = non-volatile source of OsO_4 generated *in situ*
$K_3Fe(CN)_6$ = oxidant
K_2CO_3, $MeSO_2NH_2$ = additives facilitating the regeneration of the catalyst

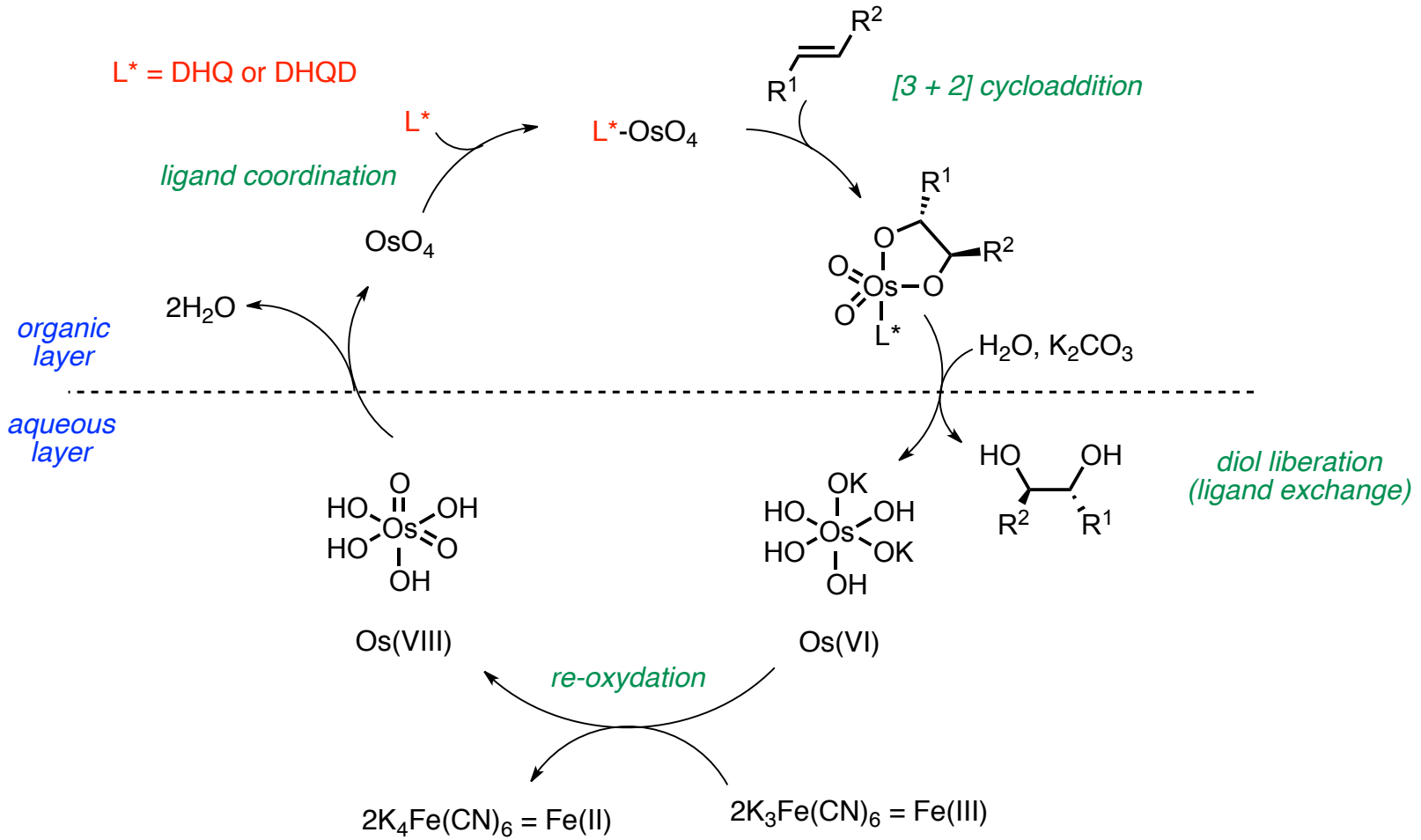
- Pre-formed mixture commercially available, ready to use

$K_3Fe(CN)_6$ (3 equiv)
K_2CO_3 (3 equiv), Lig-PHAL (1 mol %)
$K_2OsO_2(OH)_4$ (0.2 mol %)

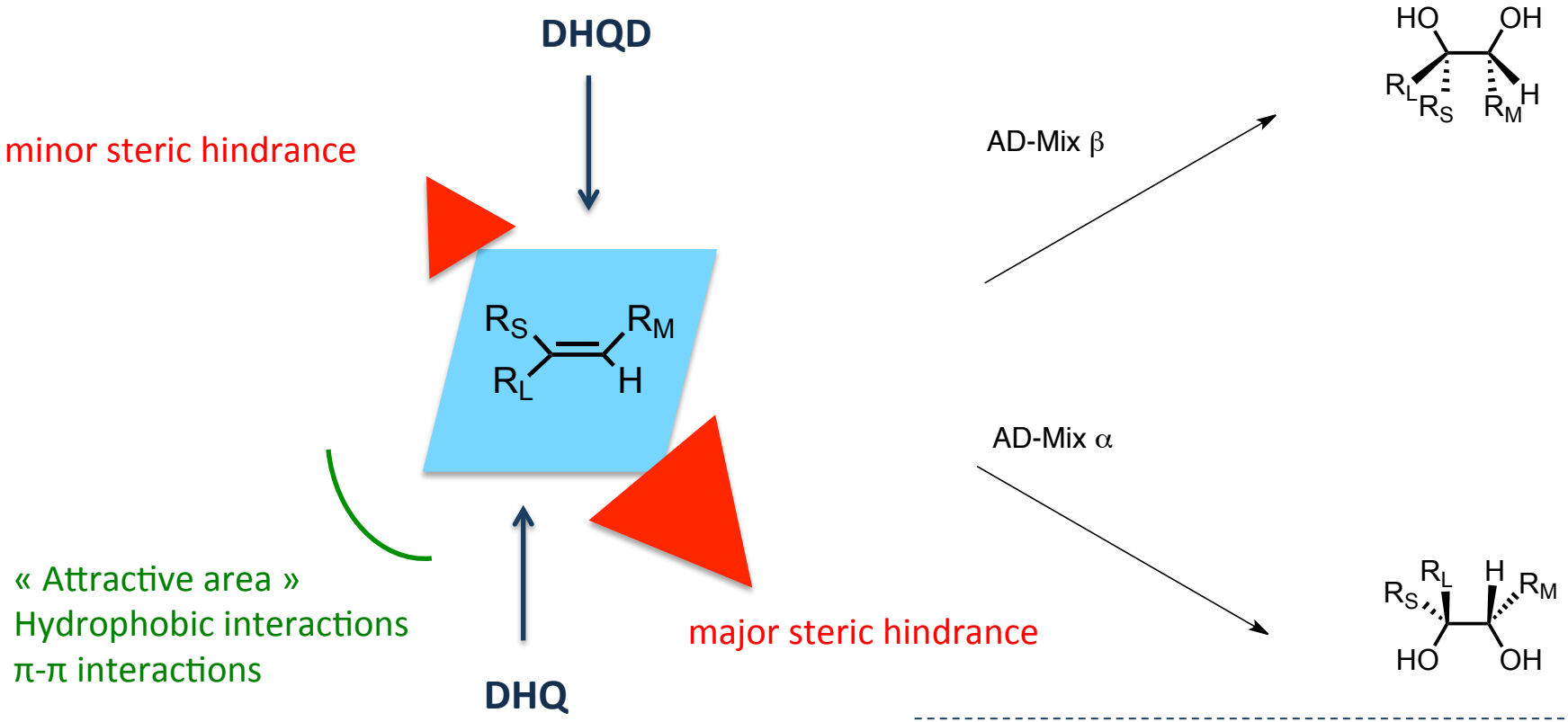
AD-Mix α (Lig = DHQ)
AD-Mix β (Lig = DHQD)

« This alternative asymmetric oxidation is probably the best asymmetric reaction of all »
(in Organic Chemistry, J. Clayden)

Asymmetric dihydroxylation - mechanism



Asymmetric dihydroxylation – mnemonic

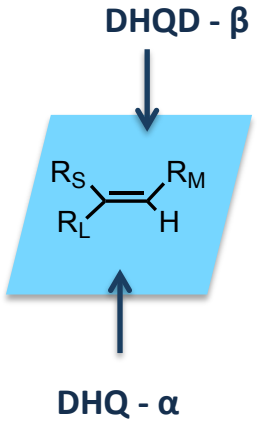


S = small
M = medium
L = large

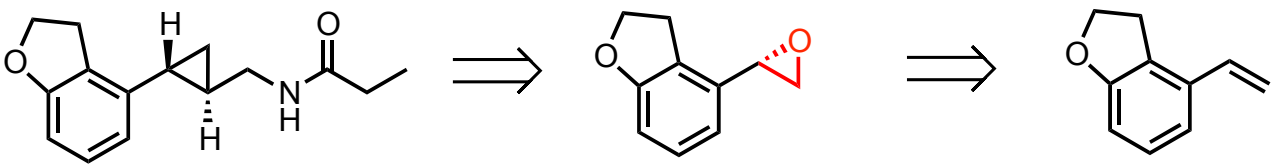
Works well with

Poor selectivity with

Asymmetric dihydroxylation – Application of mnemonic

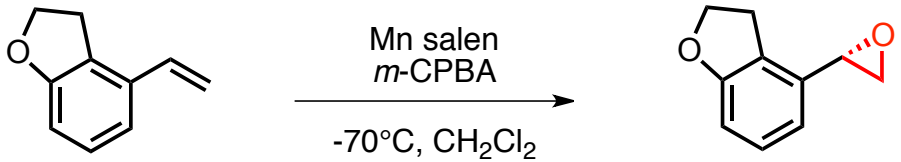


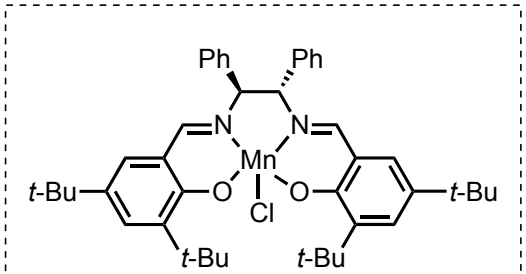
Application – medicinal chemistry



Melatonin agonist | Key intermediate | Available and cheap starting material

- Option 1: Jacobsen epoxidation





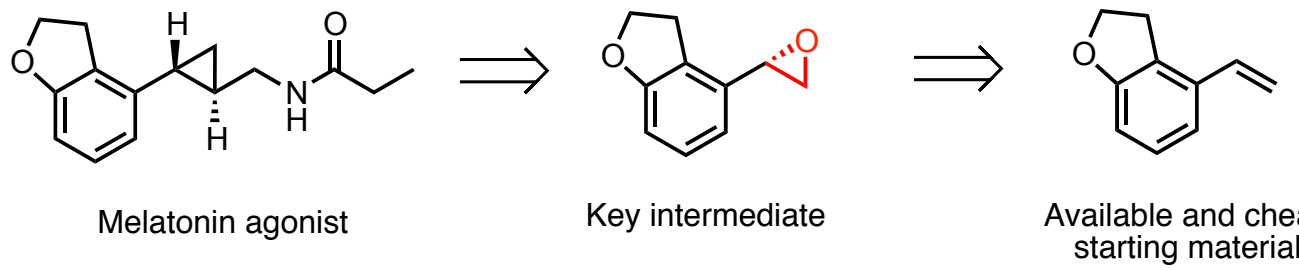
Chiral Mn(III) Salen

Moderate yield and ee, *m*-CPBA hazardous on large scale (shock sensitive, potentially explosive)

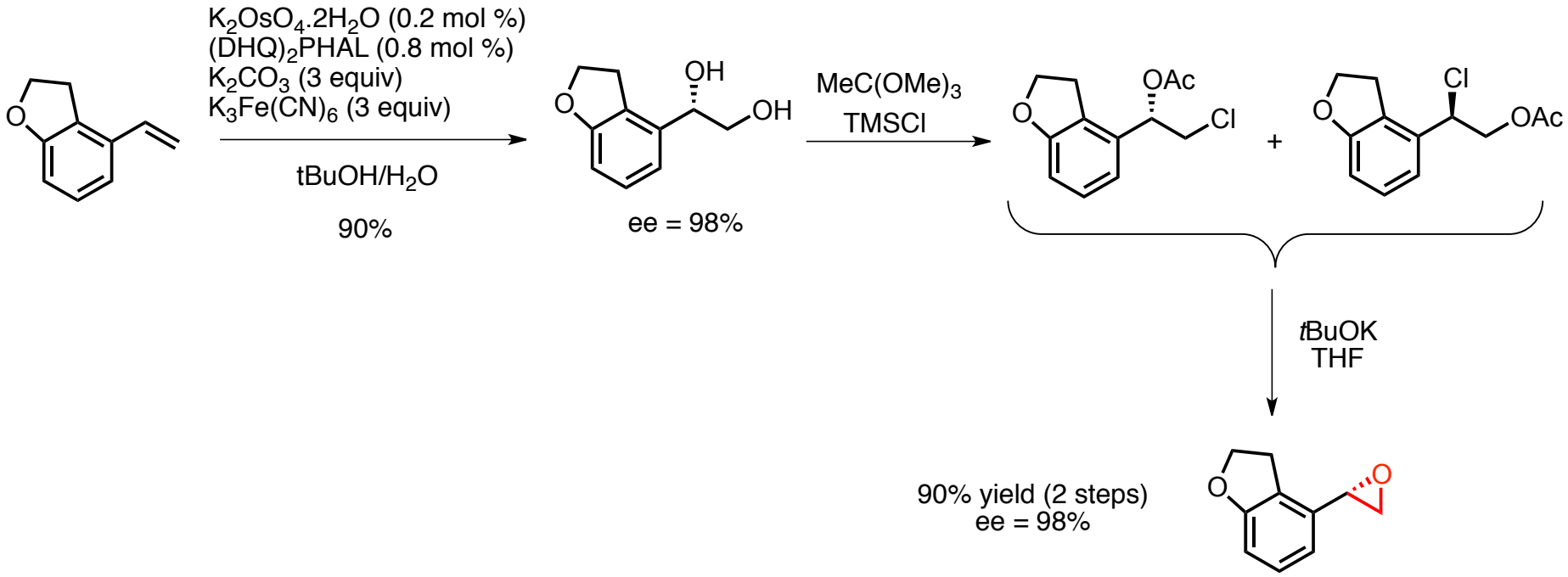
Not suitable on a preparative scale

J. S. Prasad *et al. Org. Process. Res. Dev.* **2003**, *7*, 821.

Application – medicinal chemistry

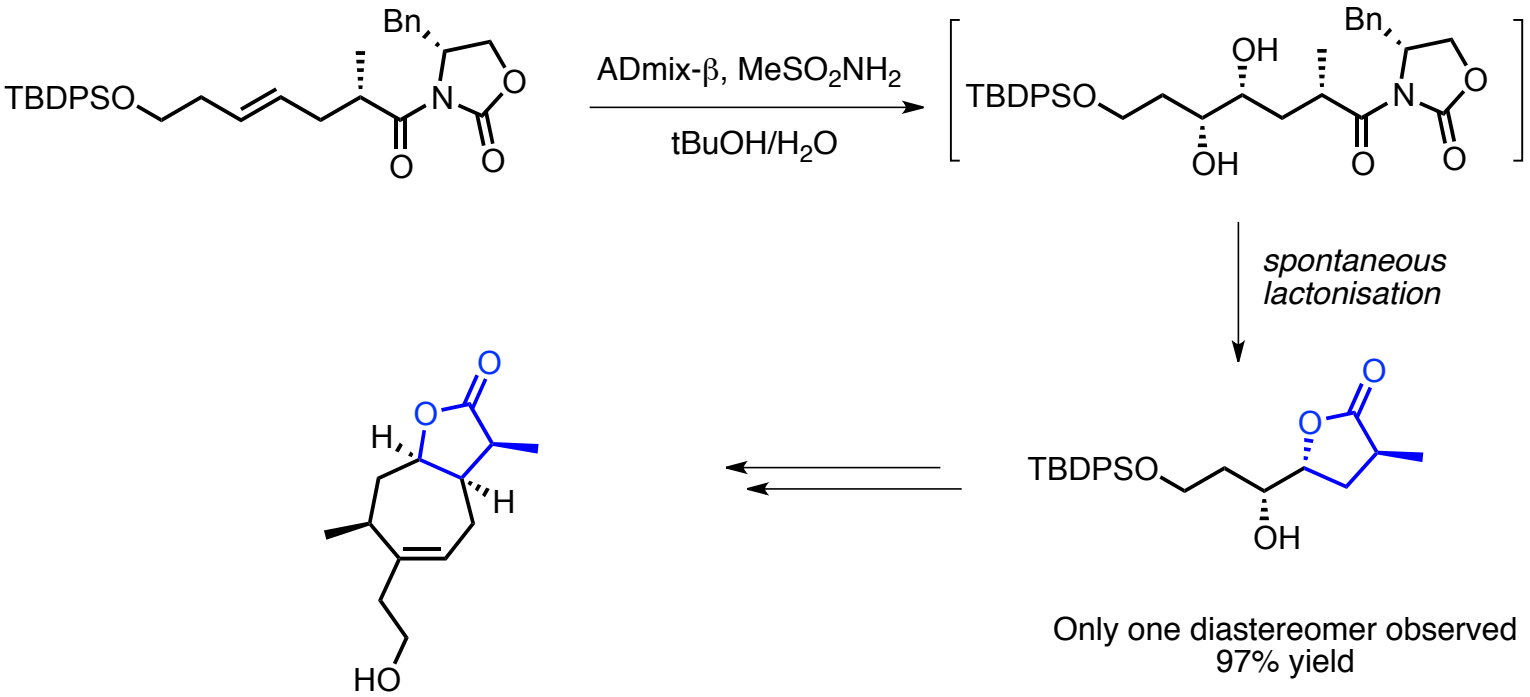


- Option 2: Sharpless asymmetric dihydroxylation



J. S. Prasad *et al. Org. Process. Res. Dev.* **2003**, *7*, 821.

Application – total synthesis of a natural product



(-)-Sundiversifolide
Potent naturally occurring herbicide

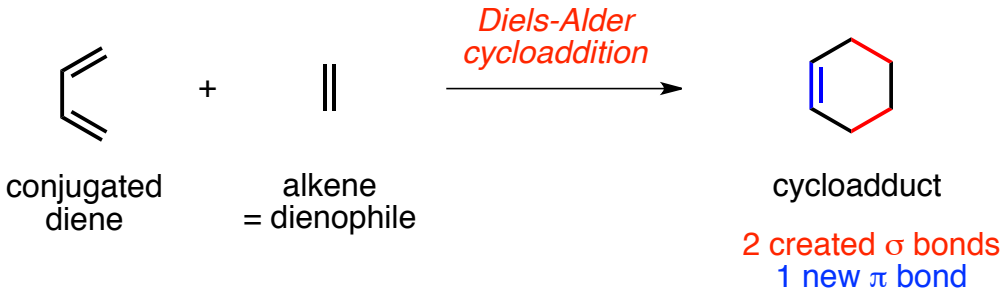
Only one diastereomer observed
97% yield

M. Shindo *et al. Org. Lett.* **2008**, *10*, 1247.

Pericyclic reactions

Diels-Alder cycloadditions

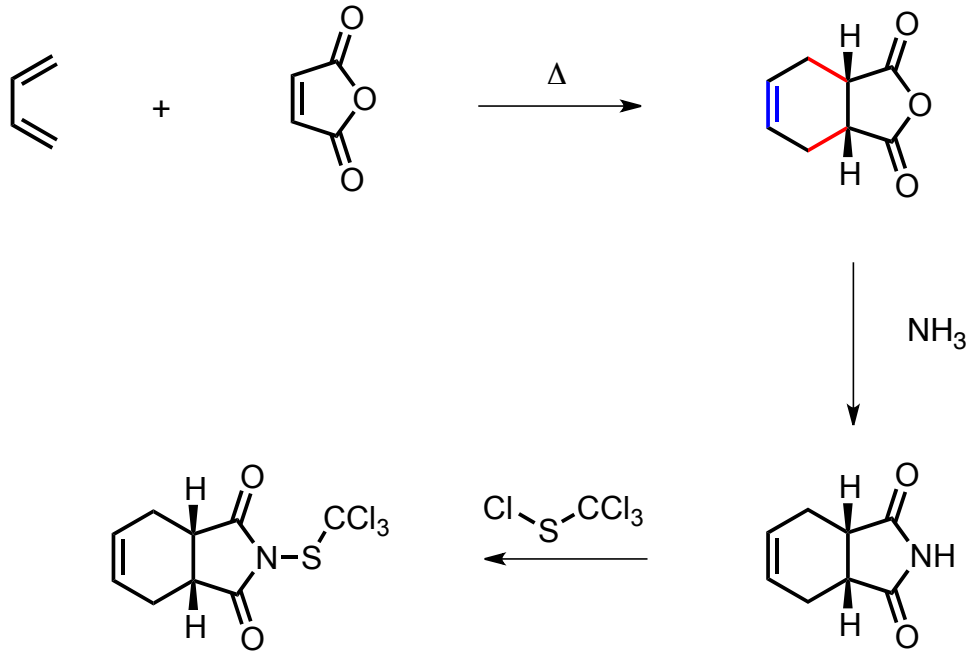
Diels-Alder cycloaddition - generalities



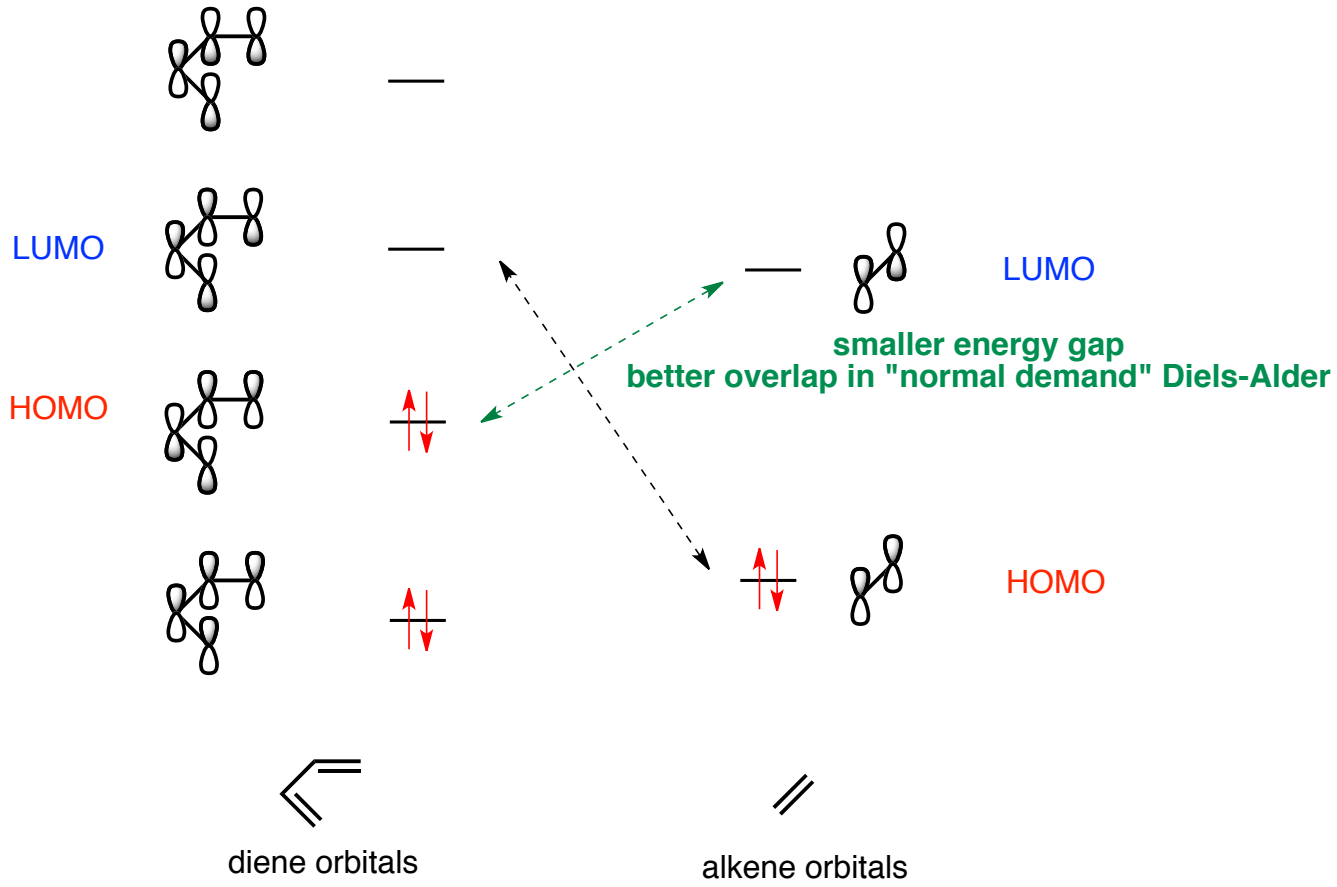
- Discovered in 1928 by Otto Diels (1876-1954) and Kurt Alder (1902-1958) at Kiel University, Nobel Prize in 1950.
- Involves a conjugated diene and an alkene (dienophile), results in the formation of a 6-membered ring.
- 3 bonds formed, 3 bonds broken.
- Alkynes and allenes are also good dienophiles in Diels-Alder cycloaddition.
- Concerted mechanism, [4+2] cycloaddition.
- One of the most used synthetic tools.

Diels-Alder cycloaddition – simple example

Synthesis of Captan, an agricultural fungicide



Molecular orbital interactions

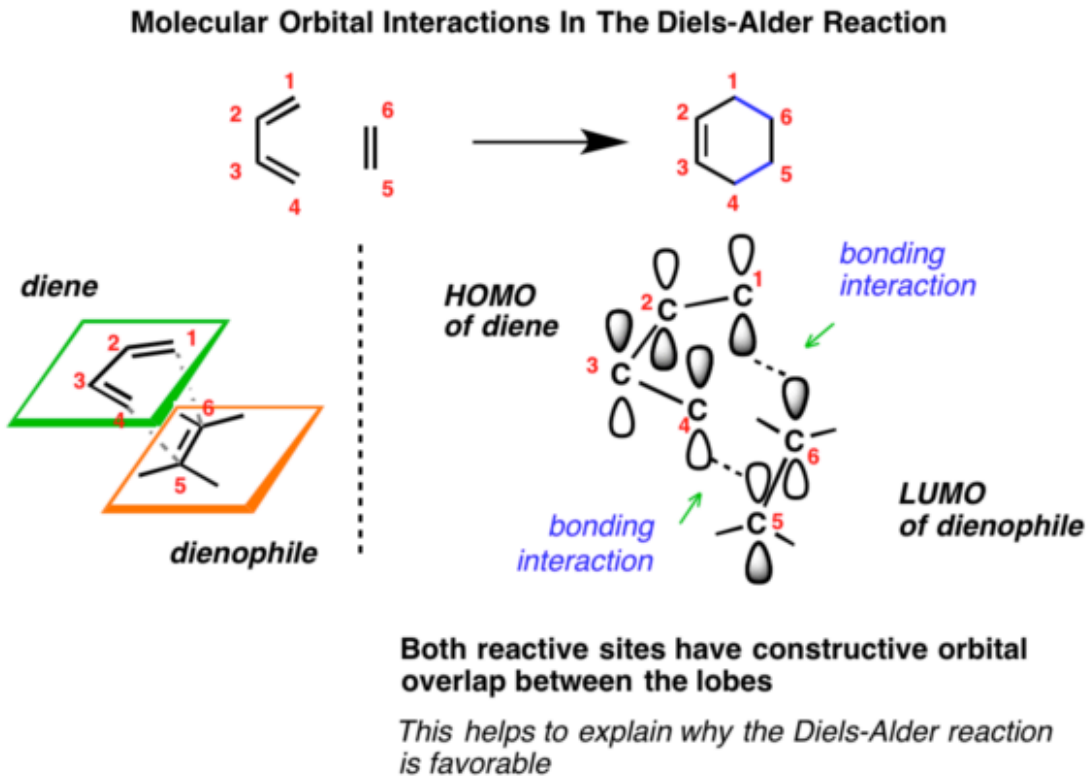


- Normal demand Diels-Alder: electron-rich diene (HOMO high in energy) with electron-poor alkene (LUMO low in energy)
- Reverse demand Diels-Alder: electron-poor diene (LUMO low in energy) with electron-rich alkene (HOMO high in energy)

From Organic Chemistry, J. Clayden.

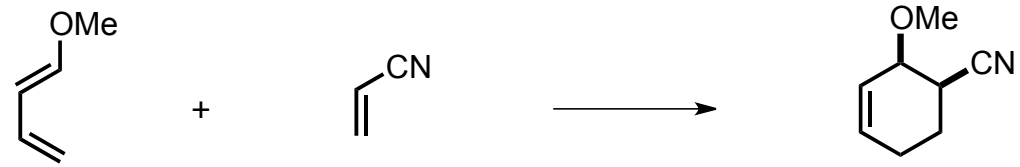
Molecular orbital interactions

- Orbital overlap in a normal demand Diels-Alder reaction



From masterorganicchemistry.com.

Examples of normal/reverse demand D-A

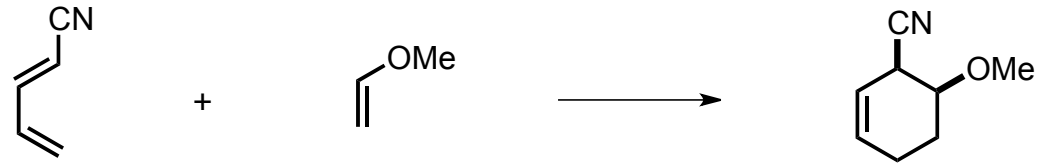


OMe: +M
electron-rich diene

CN: -M
electron-poor alkene

normal demand Diels-Alder

versus



CN: -M
electron-poor diene

OMe: +M
electron-rich alkene

reverse demand Diels-Alder

From masterorganicchemistry.com.

The diene

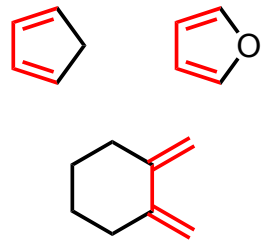
- Diene must be conjugated.
- Diene can be acyclic or cyclic.
- Acyclic diene can adopt s-*trans* or s-*cis* conformations:

s-*trans* conformation
More stable but not reactive in D-A

s-*cis* conformation
Less stable but reactive in D-A

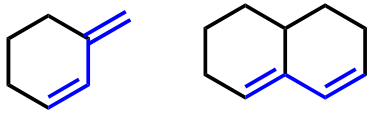
To be able to react in Diels-Alder reaction, diene *must be able to adopt s-cis conformation*.

Excellent partners in D-A



s-*cis* conformation
is blocked

Unreactive partners in D-A

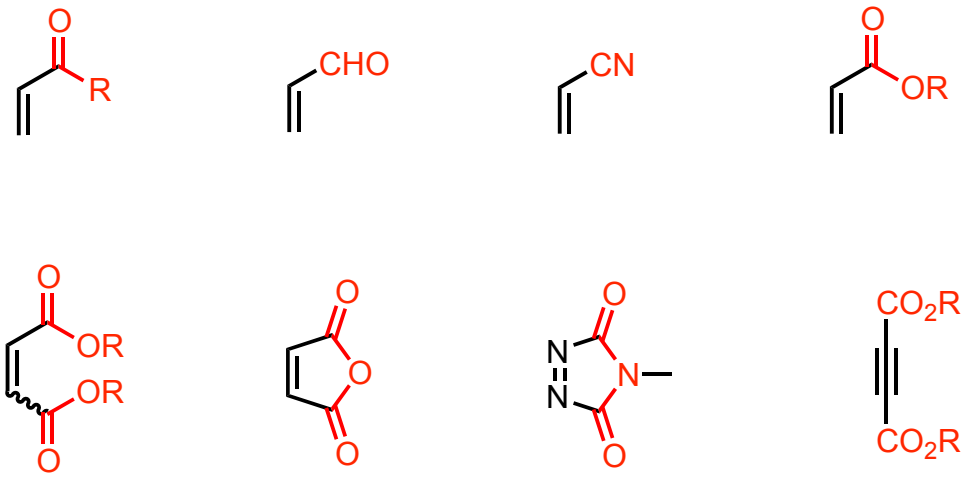


Unable to adopt a s-*cis* conformation

- In normal demand Diels-Alder, electron-rich substituents (alkyl, O- or N-substituents) facilitate the reaction.

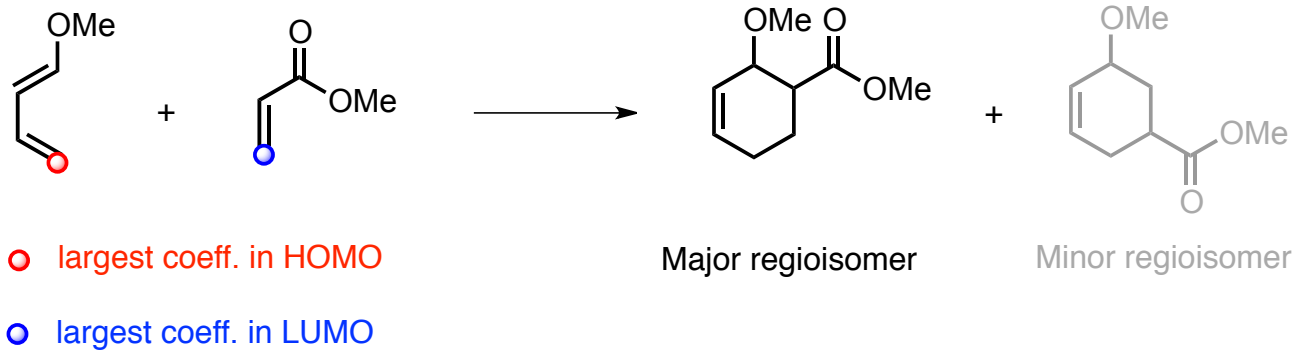
The dienophile

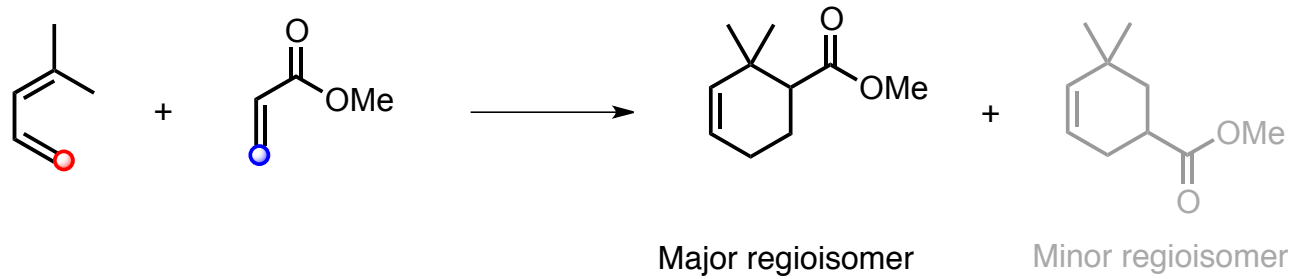
- In normal demand Diels-Alder, electron-poor substituents (generally π-acceptor groups) accelerate the rate of the Diels-Alder.
- Common dienophiles:



Regioselectivity (normal demand D-A)

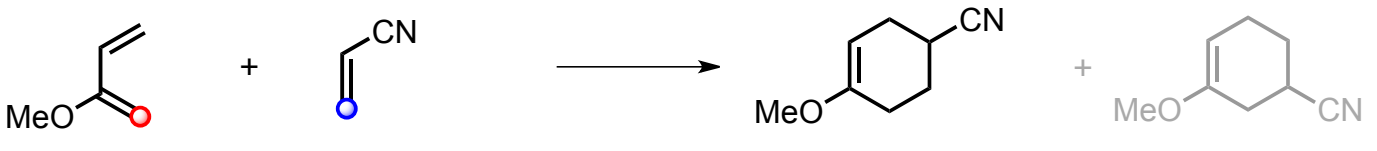
- Substituents on diene/dienophile affect the coefficient in HOMO/LUMO orbitals. Bond created between the two atoms possessing the largest coefficients in HOMO/LUMO.
- Case 1: 1-substituted diene





Regioselectivity (normal demand D-A)

- Case 1: 2-substituted diene

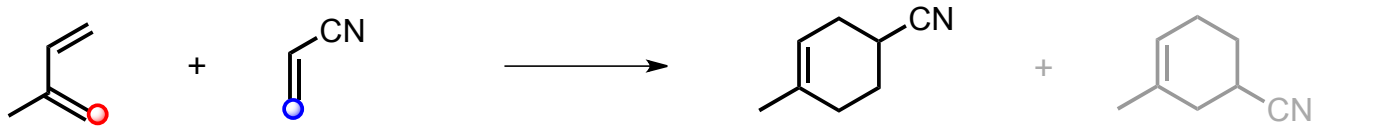


largest coeff. in HOMO

largest coeff. in LUMO

Major regioisomer

Minor regioisomer

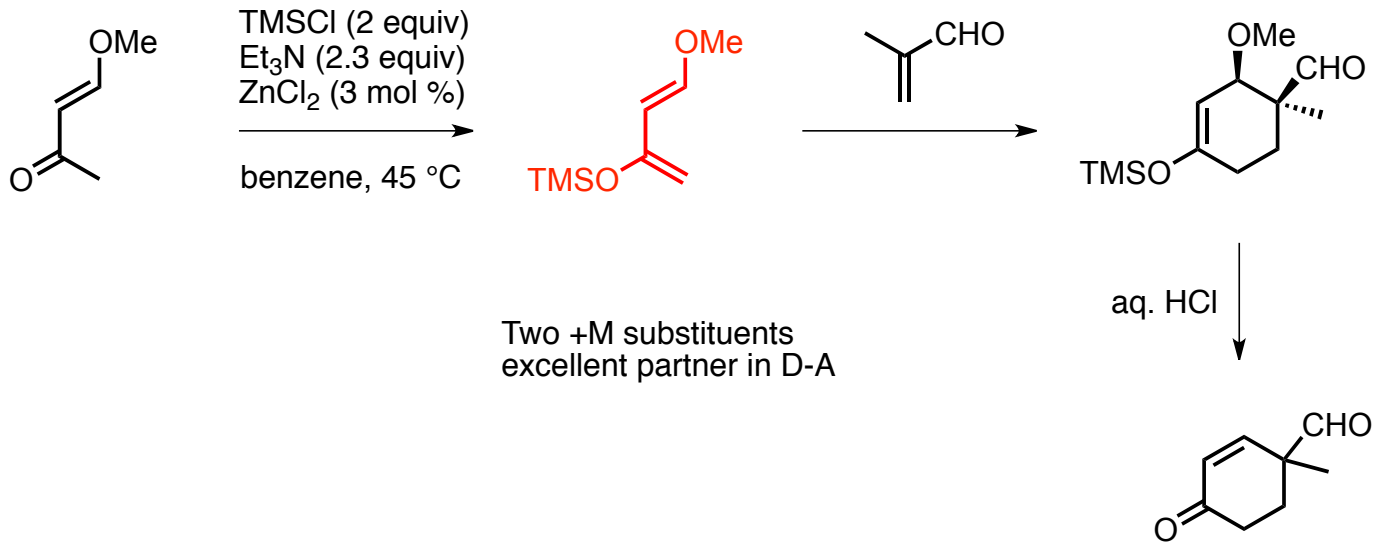


Major regioisomer

Minor regioisomer

Danishefsky diene

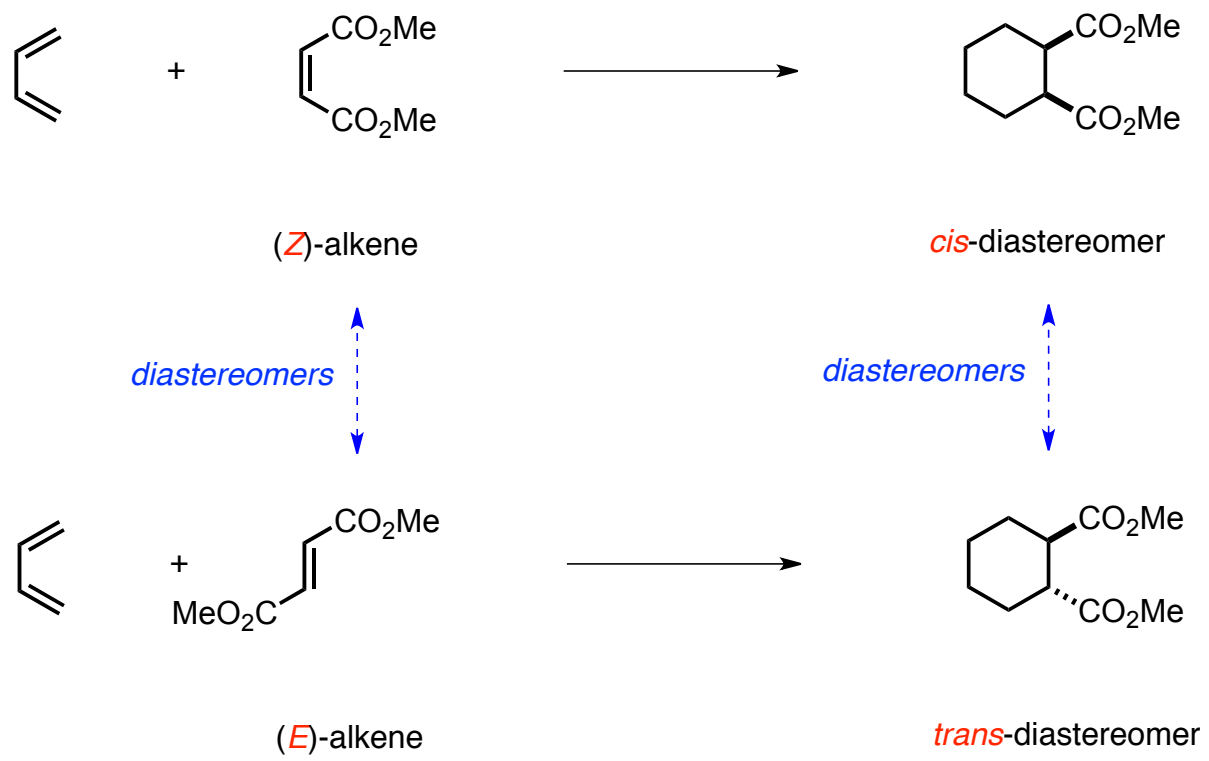
- Normal demand Diels-Alder



Two +M substituents
excellent partner in D-A

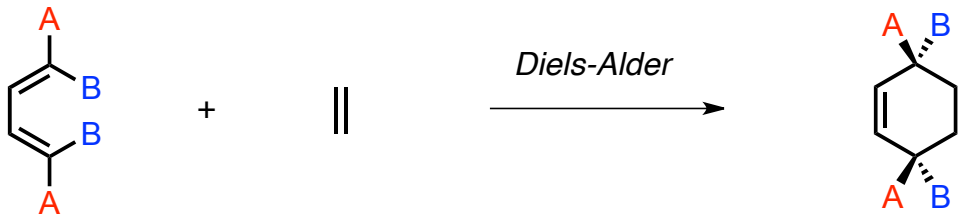
- Hetero Diels-Alder

Stereoselectivity – disubstituted alkene



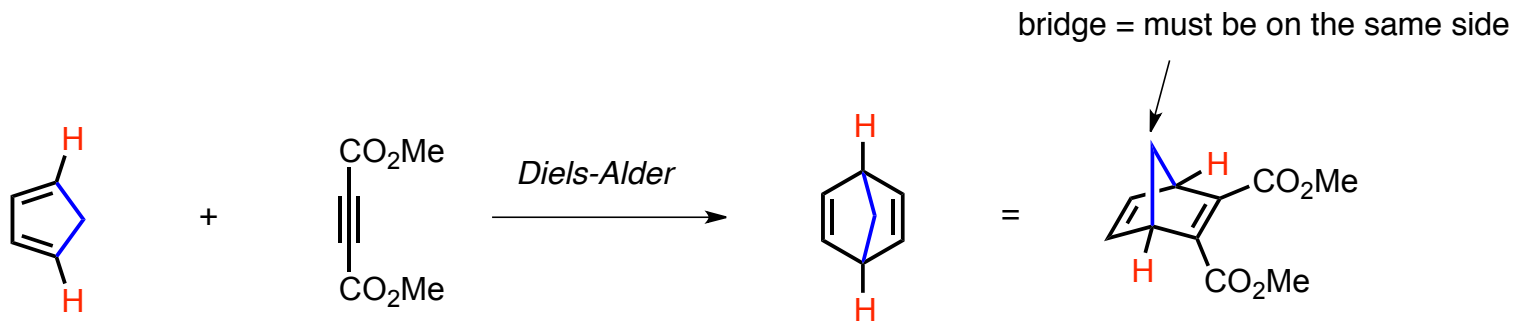
Diels-Alder is **diastereospecific**

Stereoselectivity – disubstituted diene



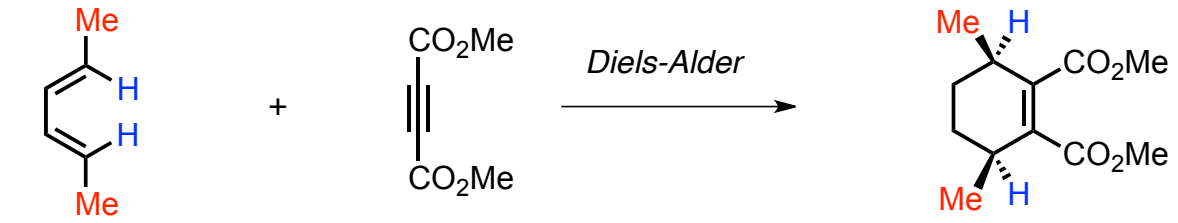
A: outside substituents
B: inside substituents

Easier to see with cyclic diene:



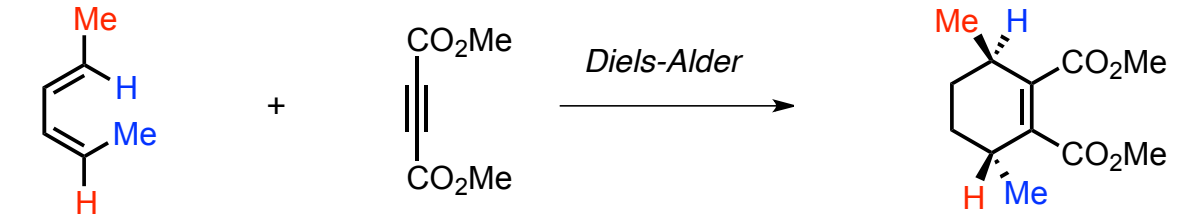
Stereoselectivity – disubstituted diene

Examples with acyclic dienes:



(*E*, *E*)-diene

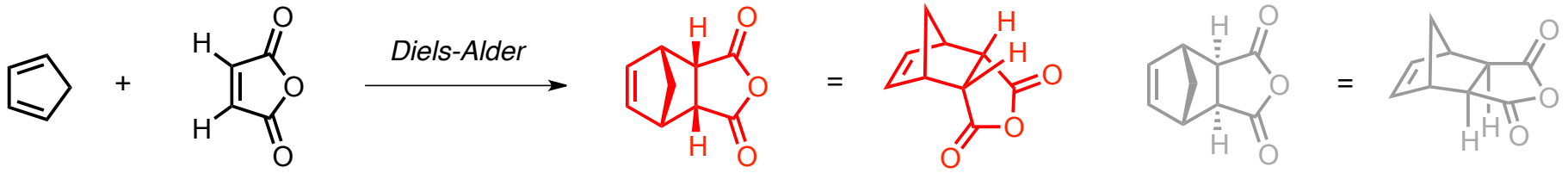
cis Me substituents



(*E*, *Z*)-diene

trans Me substituents

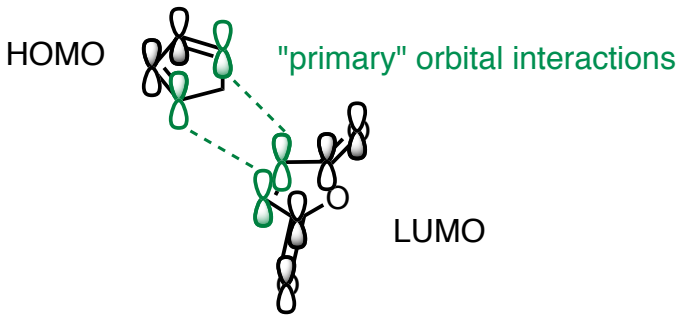
Stereoselectivity – endo rule (1)



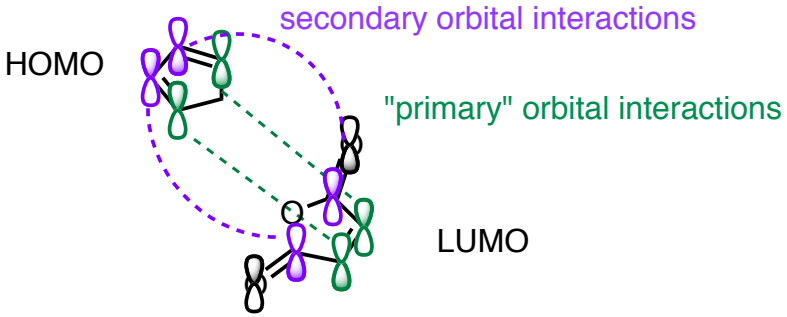
endo adduct, major
less stable, kinetic product

exo adduct, minor
more stable

- Under kinetic control (irreversible D-A), less stable *endo* adduct is formed preferentially
- Explained by secondary orbital interactions between HOMO of diene and LUMO of dienophile



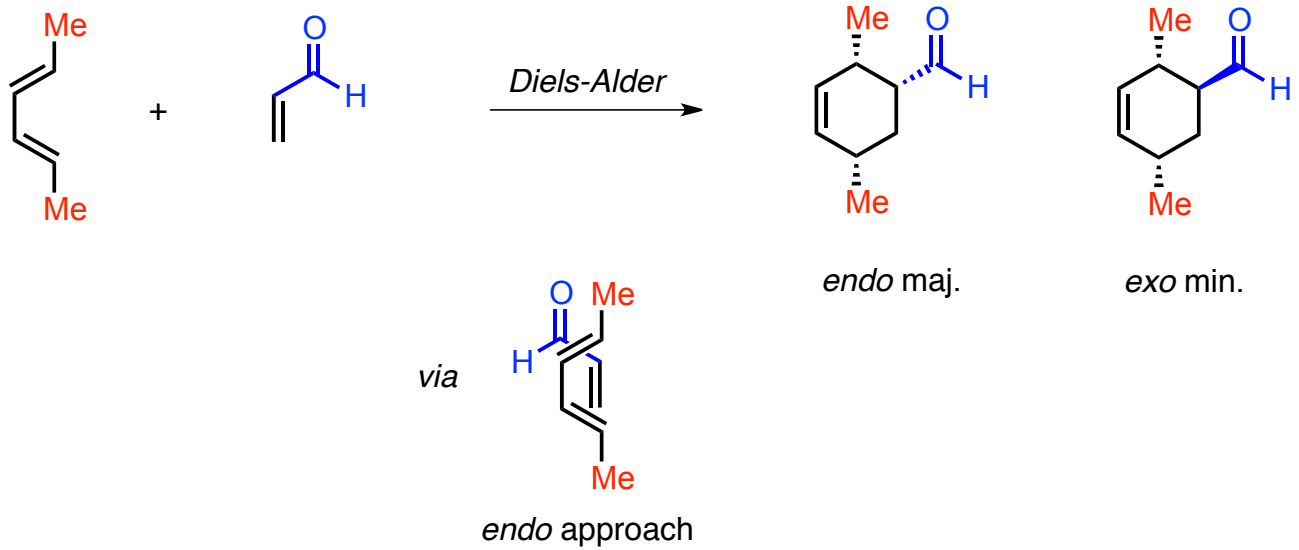
exo transition-state



endo transition-state
Lower in energy because of secondary orbital interactions

Stereoselectivity – endo rule (2)

- With acyclic diene/dienophile:

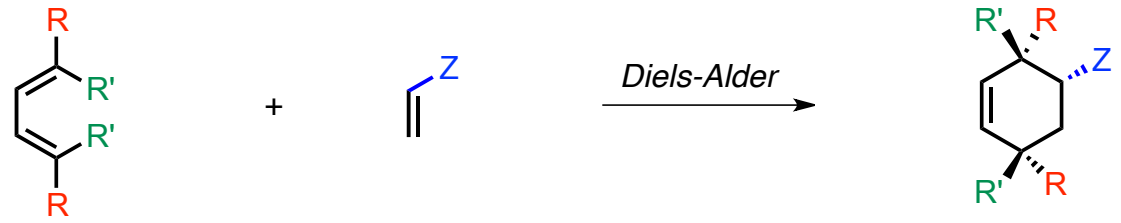


endo maj.

exo min.

endo approach

- Mnemonic:



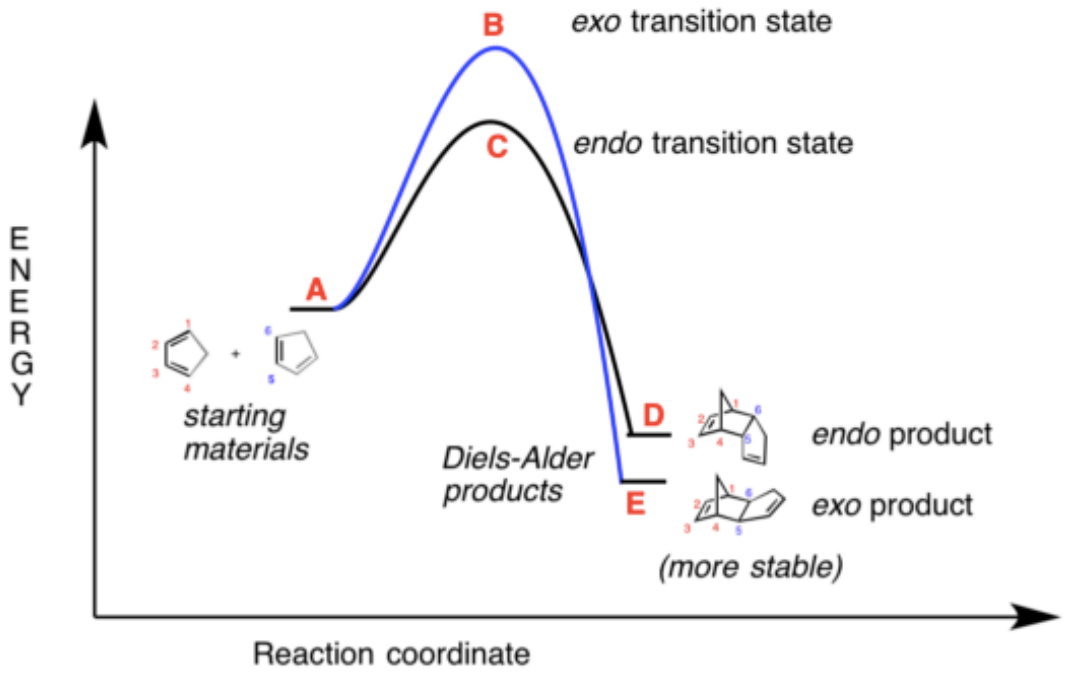
R: outside substituents
R': inside substituents

Z: EWG

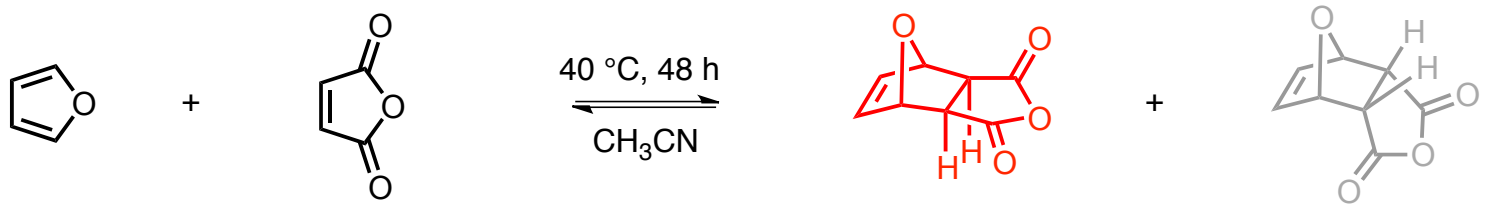
endo maj.
Z *cis* to outside substituents

Kinetic versus thermodynamic control

- *Endo* product is the **kinetic product**. Under kinetic control, the distribution between *endo* and *exo* products reflects the **difference in energy** between the *endo* and *exo* **transition states**.
- Kinetic control is operating when Diels-Alder reaction is **irreversible**. Depending on diene and conditions (temperature), retro Diels-Alder can occur, rending the cycloaddition **reversible**. Under such conditions, reactants and products are in equilibrium resulting in a thermodynamic control. The most stable *exo* adduct is formed preferentially and the distribution between *exo* and *endo* products reflects the **difference in energy (stability)** between the *exo* and *endo* **products.**



Reversible Diels-Alder - example



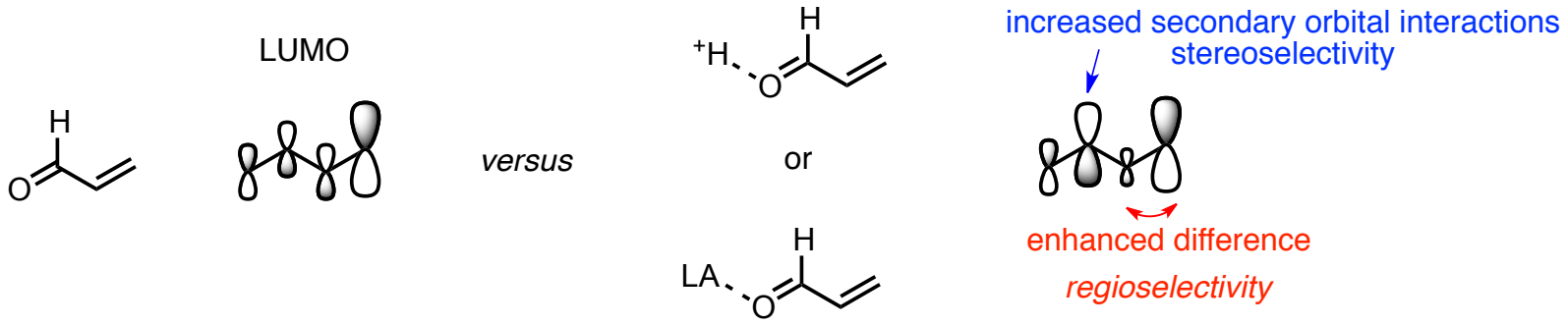
exo adduct, only product isolated
more stable

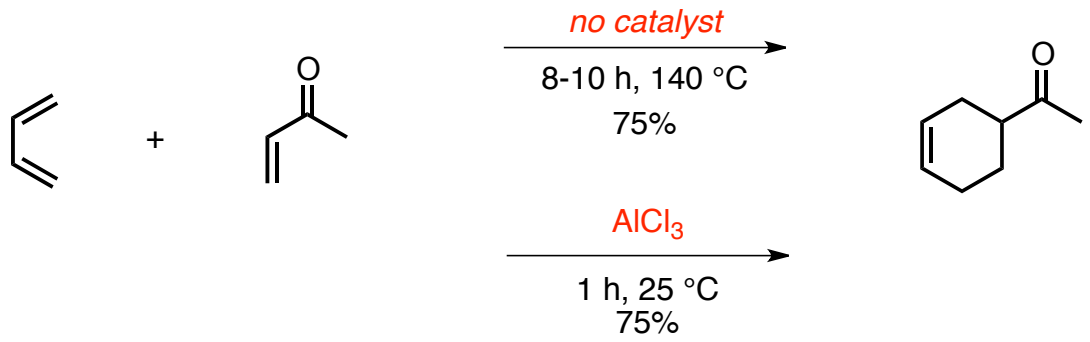
endo adduct
less stable

- D-A disrupts the aromaticity of furan, retro Diels-Alder easier than with other dienes (ie possible at much lower temperatures).
- *Endo* product formed 500 times faster than *exo* but quickly reverts to starting materials. 1.9 kcal/mol of difference in energy between *endo* and *exo* products.

Lewis/Bronsted acid catalyzed Diels-Alder

- The presence of Lewis or Bronsted acid significantly increases the rate of D-A reactions by lowering the LUMO of the dienophile (factors as large as 10^6). It modified the coefficients in the LUMO orbital improving regioselectivity (by increasing the difference in magnitude between coefficients of the 2 carbons) and *endo* stereoselectivity (by increasing secondary orbital interactions).

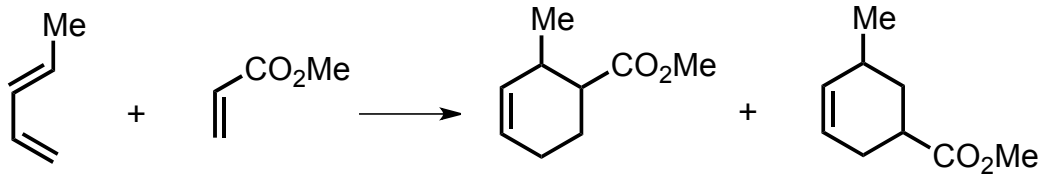




Lewis/Bronsted acid catalyzed Diels-Alder

- Simple examples

Regioselectivity



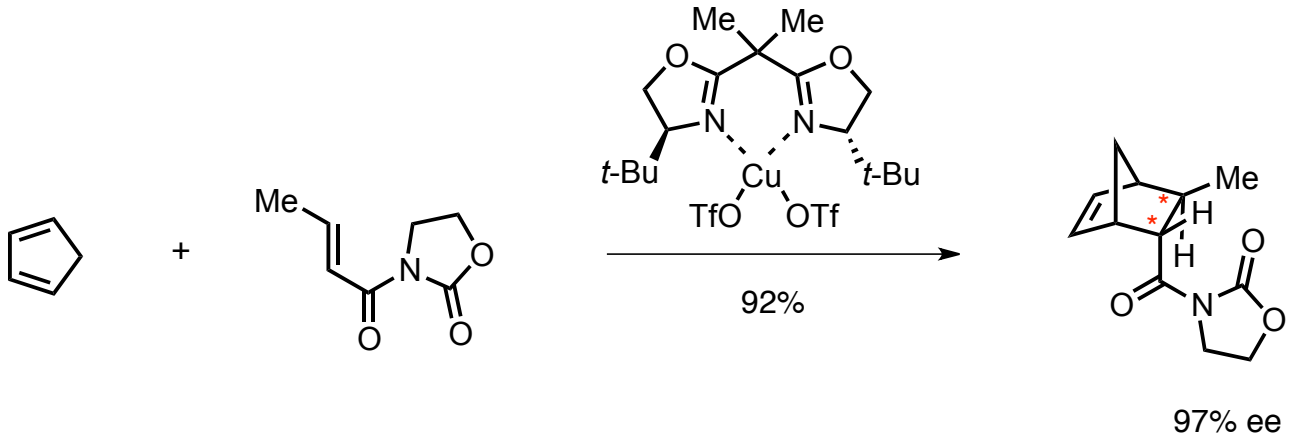
thermal	90	10
$AlCl_3$ cat.	98	2

Stereoselectivity

endo *exo*

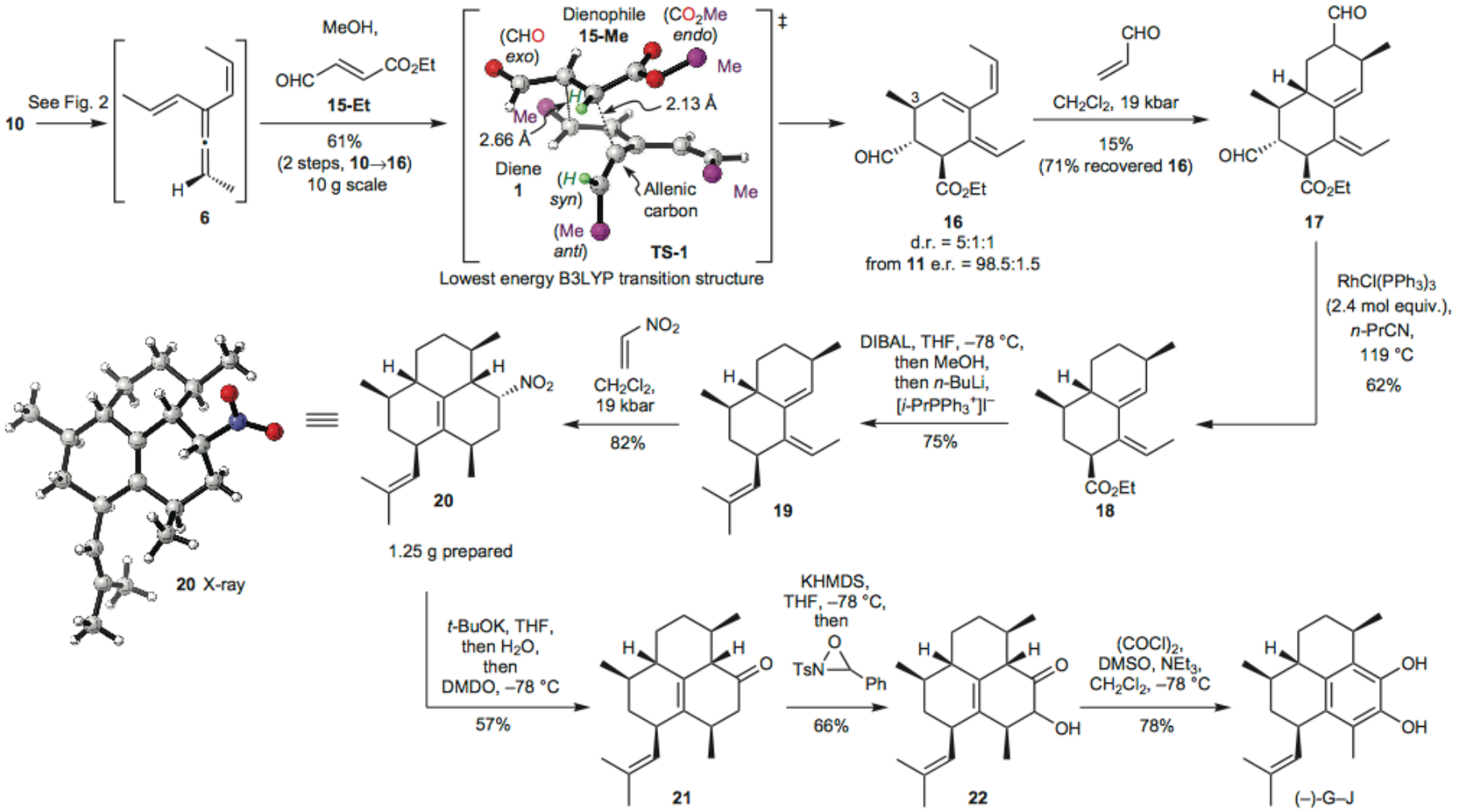
thermal	82	18
$AlCl_3$ cat.	99	1

Enantioselective Diels-Alder



- Chiral bis(isoxazoline) ligand hindered one face of the dienophile rendering the reaction enantioselective.

Diels-Alder application – Total Synthesis



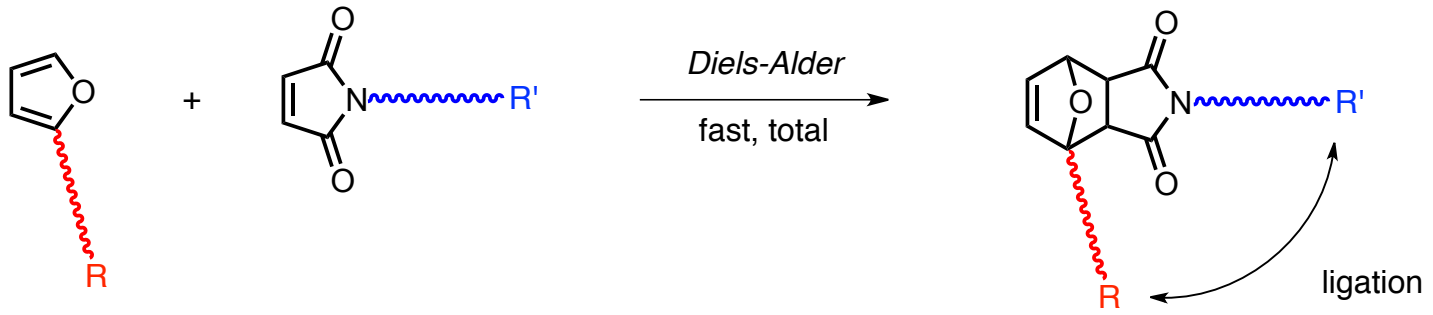
Pseudopterosin : family of diterpene marine natural products with anti-inflammatory and analsegic properties

M. S. Sherburn *et al. Nature Chem.* **2015**, *7*, 82.

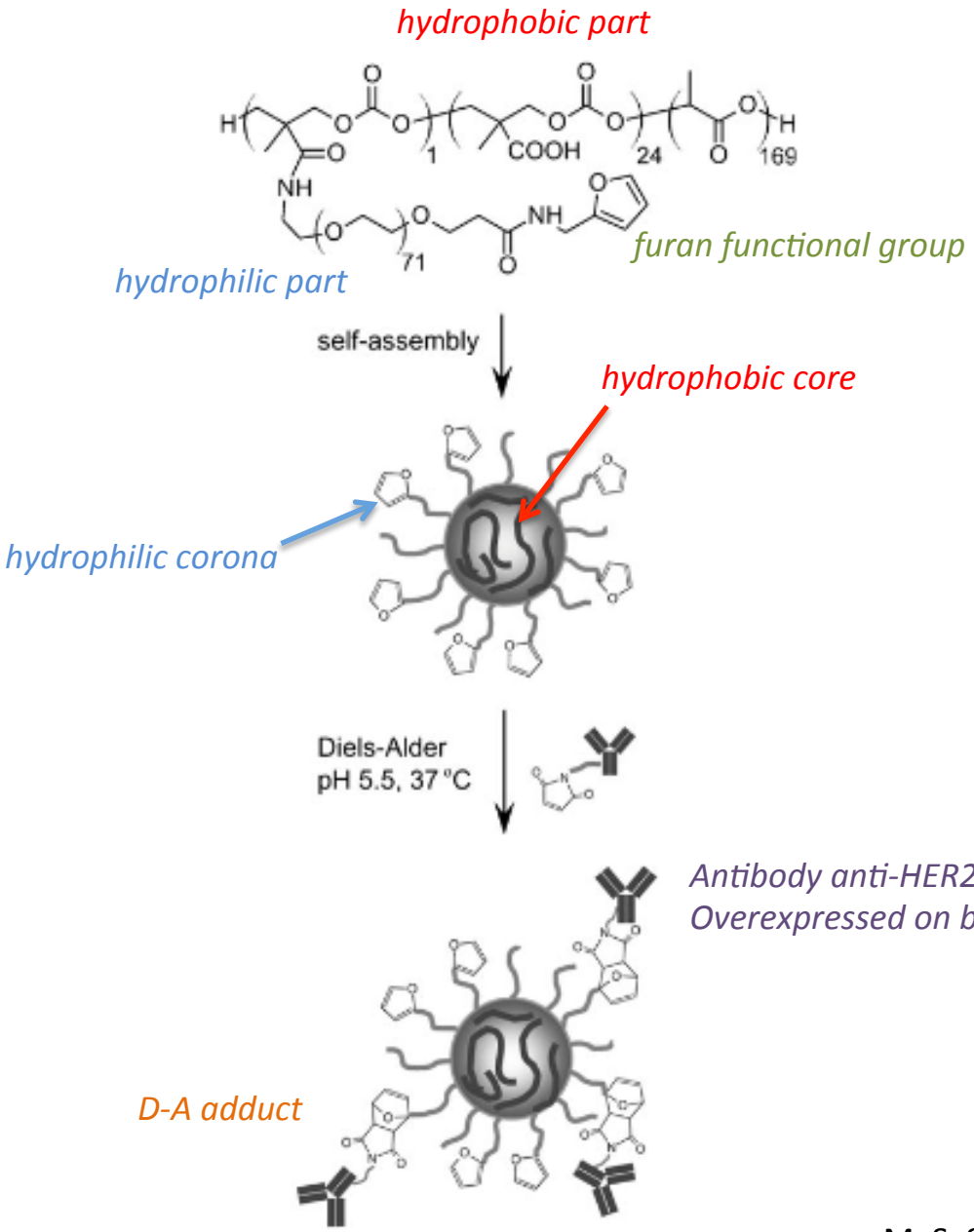
Diels-Alder application in biotechnology

- Advantages of Diels-Alder reaction for biomedical applications:
  - proceeds readily in water
  - with well chosen partners, can go to completion at room temperature without any catalyst

- Partners of choice : furan and maleimide



Nanoparticles for intracellular anticancer drug delivery



Amphiphilic copolymer

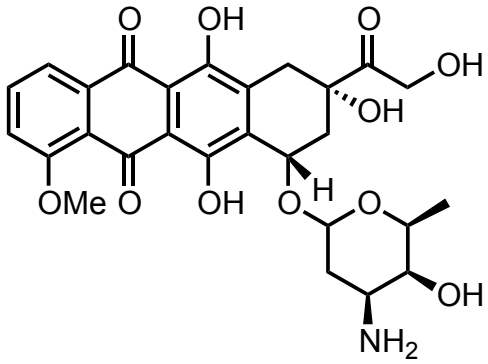
Self-assembly of nanoparticles (NPs) in water

Antibody anti-HER2
Overexpressed on breast and ovarian cancer cell surfaces

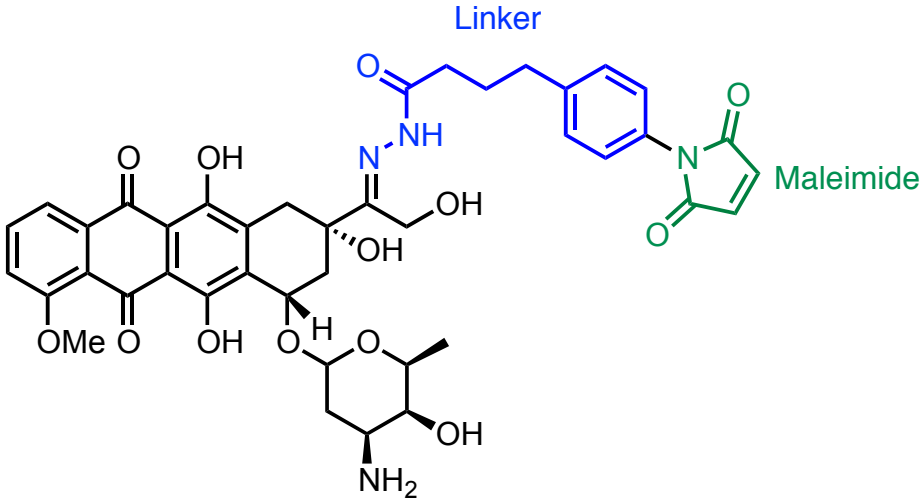
Grafting of NPs with an antibody using D-A

M. S. Shoichet *et al. Adv. Funct. Mater.* **2009**, *19*, 1689.

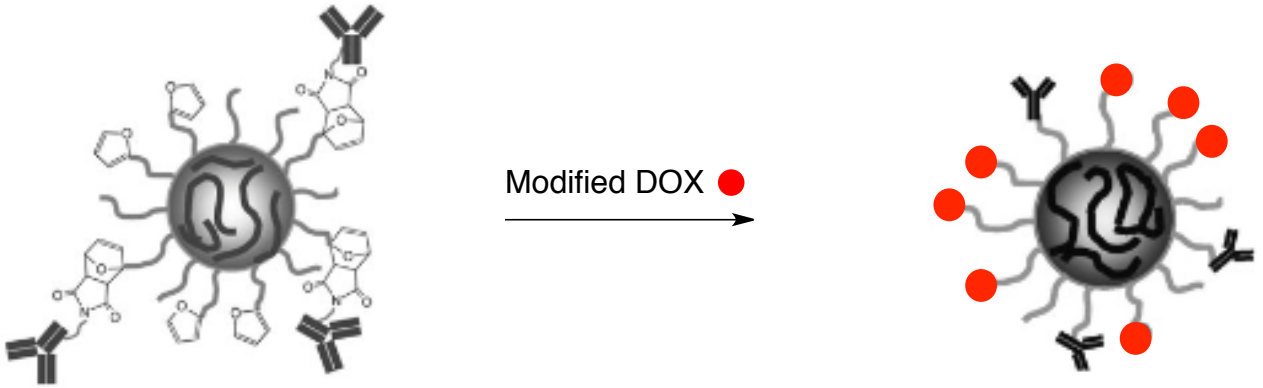
Nanoparticles for intracellular anticancer drug delivery



Doxorubicin (DOX)
One of the most effective chemotherapeutic anticancer drugs
(acute leukemia, malignant lymphoma, breast cancer)

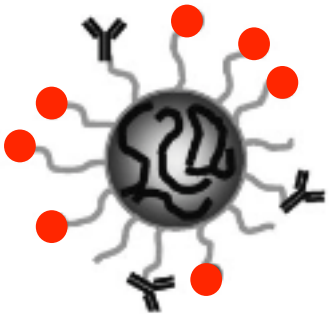


Modified Doxorubicine



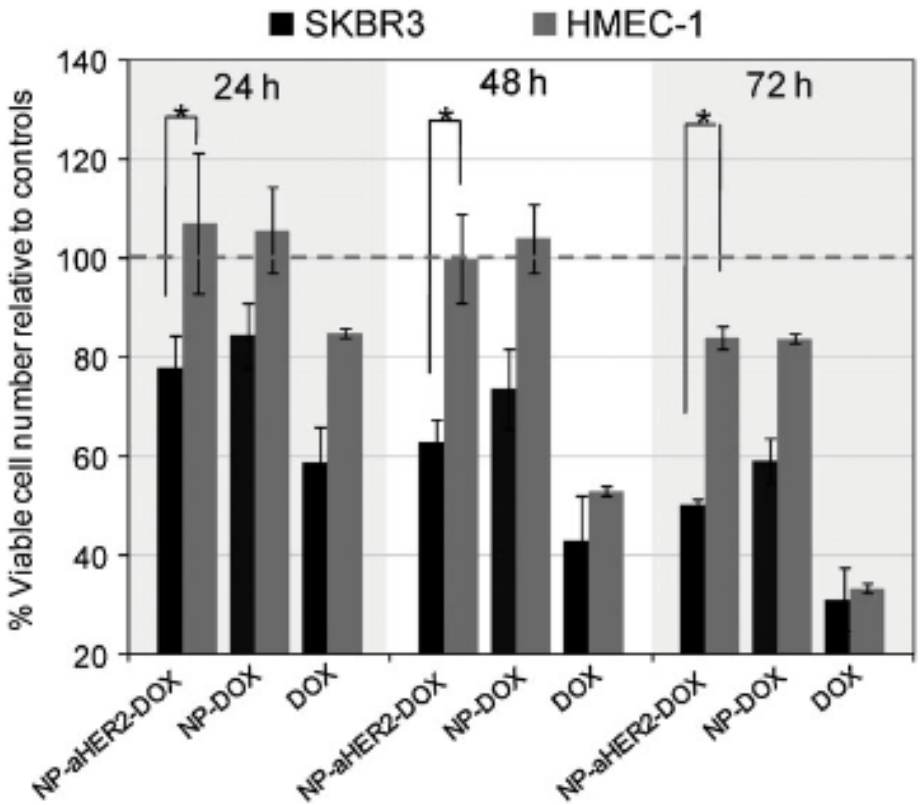
Objective: intracellular delivering of DOX selectively in cancer cells

Nanoparticles for intracellular anticancer drug delivery



NP-anti HER2-DOX

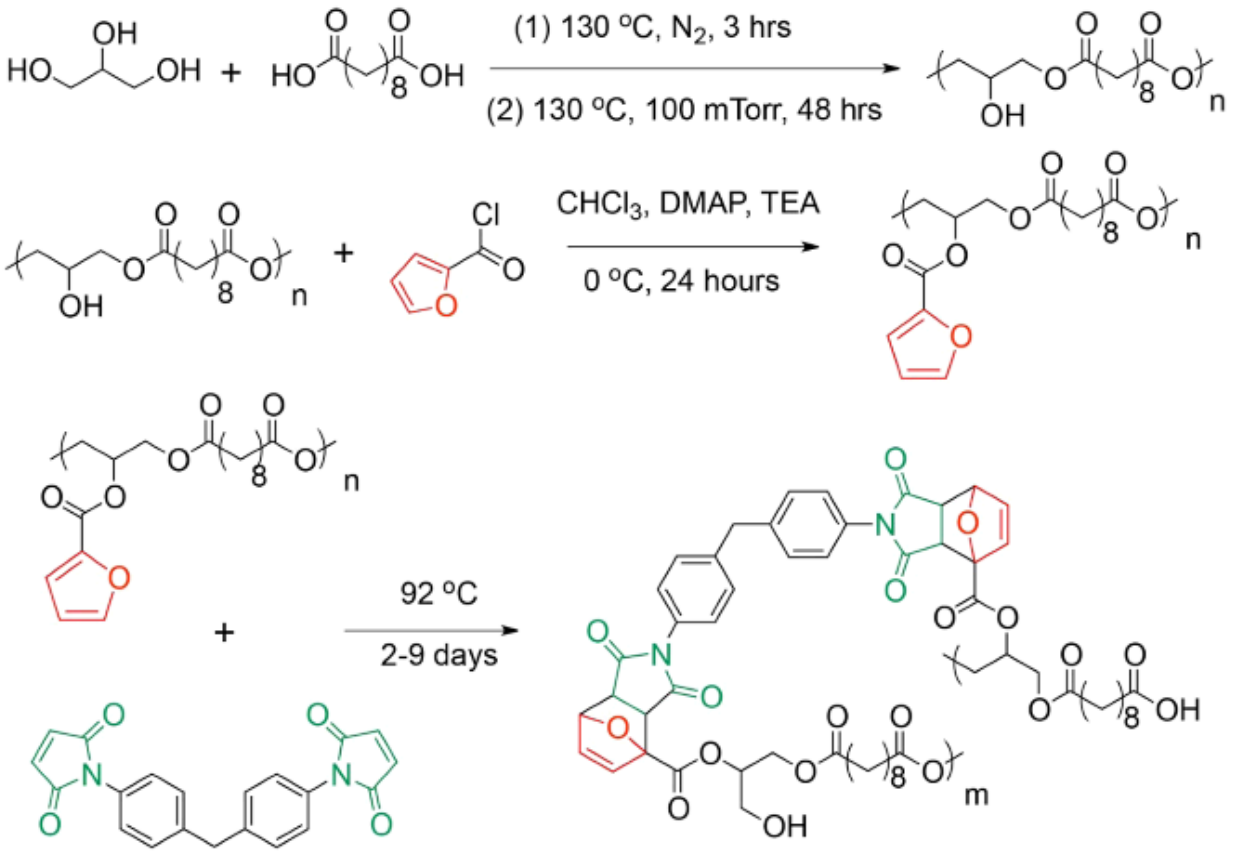
SKBR3 = cancer cells
HMEC-1 = normal cells



- Free DOX cytotoxic towards both cancer and normal cells (= side effects)
- NP-anti HER2-DOX more selective towards cancer cells
- NP-anti HER2-DOX more cytotoxic than NP-DOX (enhanced intracellular uptake and apoptosis)

M. S. Shoichet *et al. Adv. Funct. Mater.* **2009**, *19*, 1689.

Shape-memory elastomers



synthesis of a pre-polymer

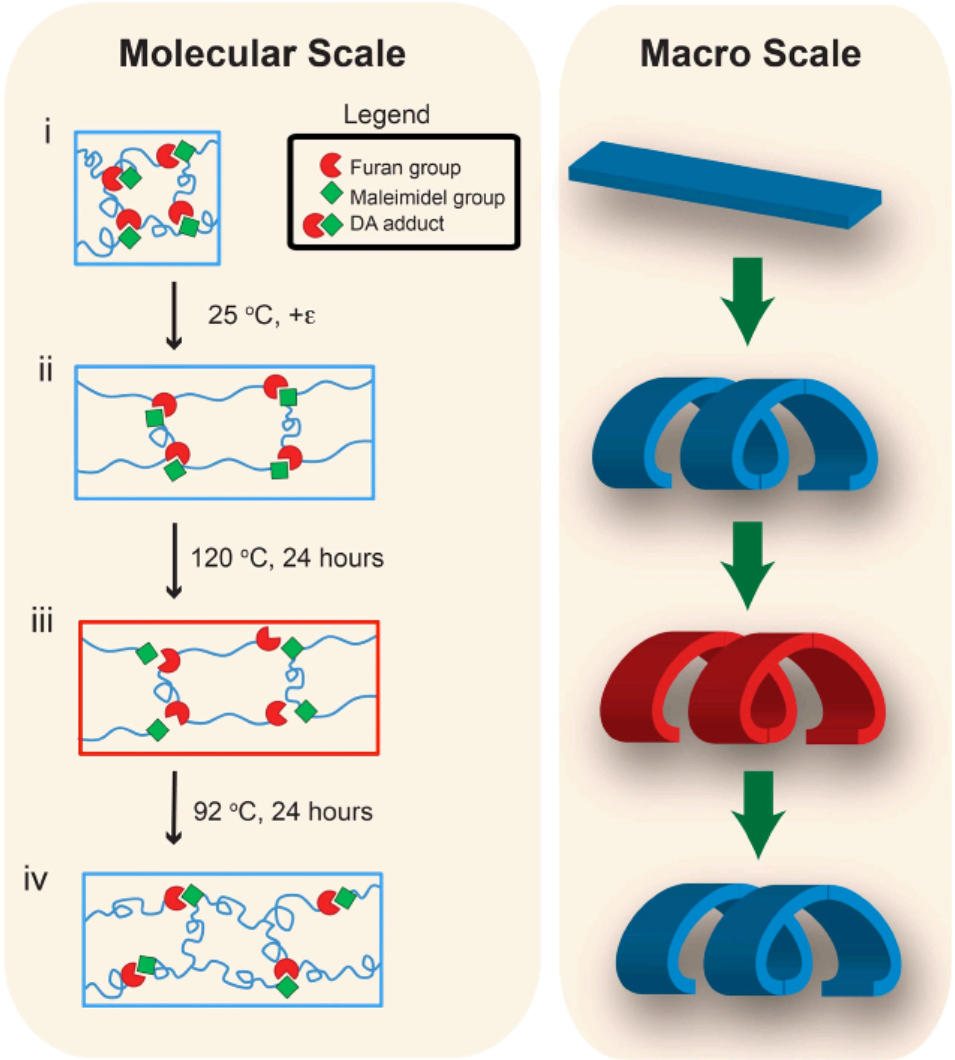
functionalization with furan groups

cross-linking through D-A

Final covalent adaptable network

C. J. Bettinger *et al. Biomacromolecules* **2013**, *14*, 2162.

Shape-memory elastomers



Initial state - linear

Elastomer shaped into helical structure at rt
Residual stresses induced in the polymeric network

Heating at 120 °C, retro D-A favored
Cross-link temporary lost, stress released

Temperature decreased to 92 °C, D-A favored
Cross-linked network recovered

The whole process reprogramms the network into a permanent helical geometry

C. J. Bettinger *et al. Biomacromolecules* **2013**, *14*, 2162.

Shape-memory elastomers

- T < Tg : material can be reshaped, shape is arbitrarily fixed (ex = linear)
- Once T > Tg, the material returns to its permanent programmed shape (helical)

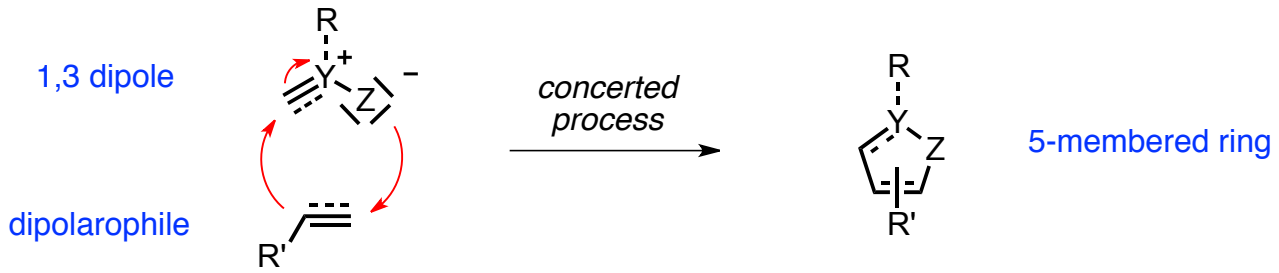
See the video !

Very interesting for biomedical application

C. J. Bettinger *et al. Biomacomolecules* **2013**, *14*, 2162.

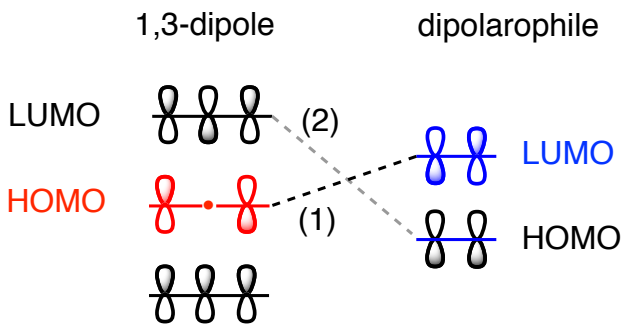
1,3-dipolar cycloadditions

1,3-dipolar cycloaddition - generalities



- Formation of 5-membered rings by cycloaddition = need for an unsaturated compound (= alkene, alkyne) and for a 3 atoms, 4 electrons molecule (= 1,3-dipole).
- Concerted mechanism, [3+2] cycloaddition.
- Common 1,3-dipoles: see the table.
- In this course: nitrones, azomethine ylides, azides, nitrile oxides, diazoalkanes.

Frontier molecular orbital



Two modes of interaction are possible:

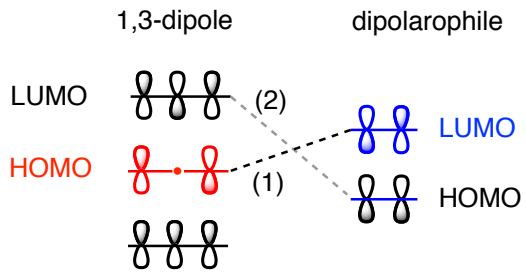
(1) HOMO (dipole) / LUMO (dipolarophile)

(2) LUMO (dipole) / HOMO (dipolarophile)

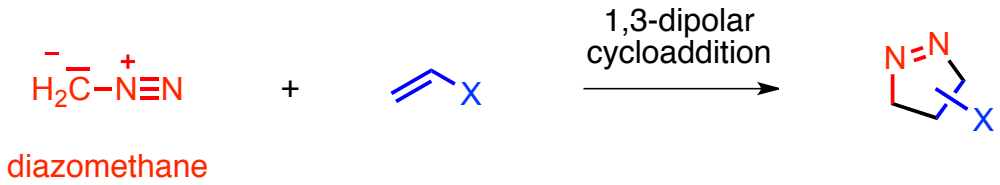
Will depend on the nature of the reactants, 3 mains cases

Frontier molecular orbital – Case 1

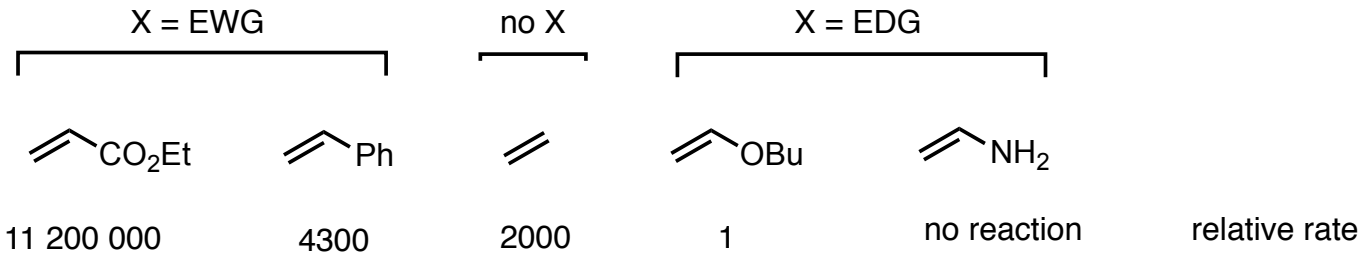
Case 1: dipoles with HOMO of high energy level
« HOMO-controlled dipoles » or nucleophilic dipoles



- HOMO (dipole) / LUMO (dipolarophile) interaction is predominant
- Nucleophilic dipoles: azomethine ylides, carbonyl ylides, nitrile ylides, diazoalkanes.
- Reaction is faster with EWG groups on the dipolarophile (decrease of the LUMO energy level).
- Example:

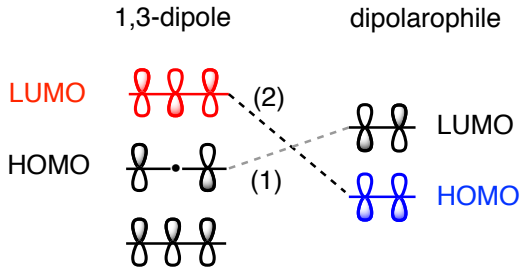


diazomethane

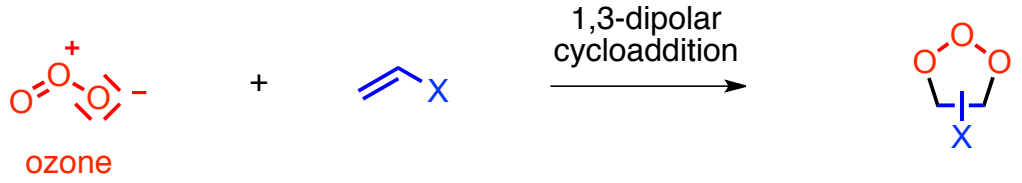


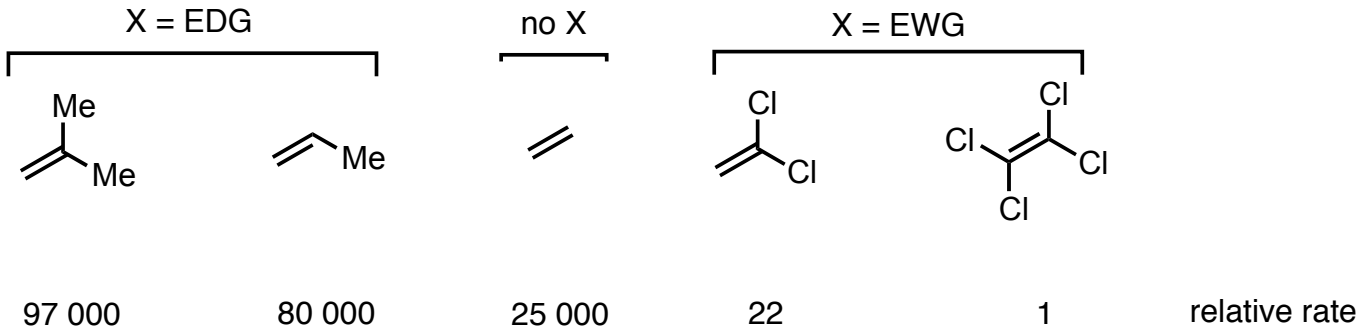
Frontier molecular orbital – Case 2

Case 2: dipoles with LUMO of low energy level
« LUMO-controlled dipoles » or electrophilic dipoles



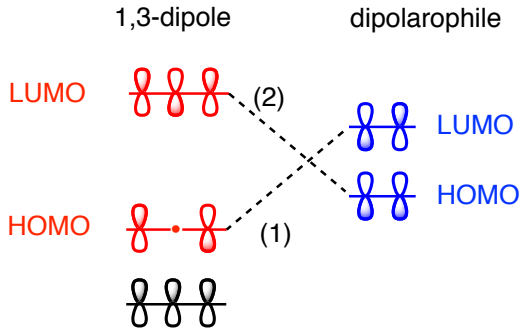
- LUMO (dipole) / HOMO (dipolarophile) interaction is predominant
- Electrophilic dipole: ozone.
- Reaction is faster with EDG groups on the dipolarophile (increase of the HOMO energy level).
- Example:





Frontier molecular orbital – Case 3

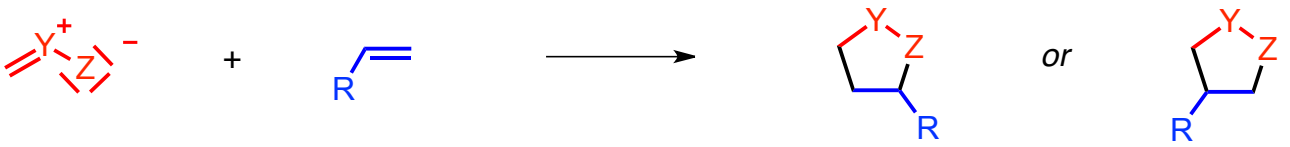
Case 3: dipoles with HOMO and LUMO of medium energy level
ambiphilic dipoles



- Ambiphilic dipoles: nitrile imides, nitrones, carbonyl oxides, nitrile oxides, azides.
- Ambiphilic dipoles can interact with dipolarophiles either through their HOMO or their LUMO depending on the electronic nature of the dipolarophile.
- Electron-poor dipolarophiles: HOMO (dipole) / LUMO (dipolarophile)

  Electron-rich dipolarophiles: LUMO (dipole) / HOMO (dipolarophile)
- Any substituent on the dipolarophile will accelerate the reaction.

Regioselectivity



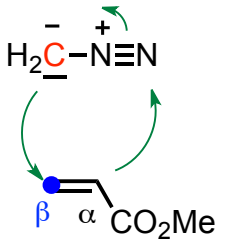
mono-substituted alkene

Two regioisomers can be envisioned

- Essential to know the nature of frontier orbital interaction to determine the regioselectivity.
- Generally, atoms with the larger coefficients in HOMO and LUMO which are involved to form one of the two new bonds.
- Example:

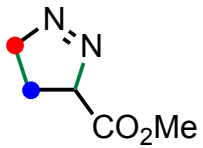
diazomethane
nucleophilic dipole
(HOMO)

methyl acrylate
(LUMO)



carbon has the largest coefficient in HOMO

β–carbon has the largest coefficient in LUMO



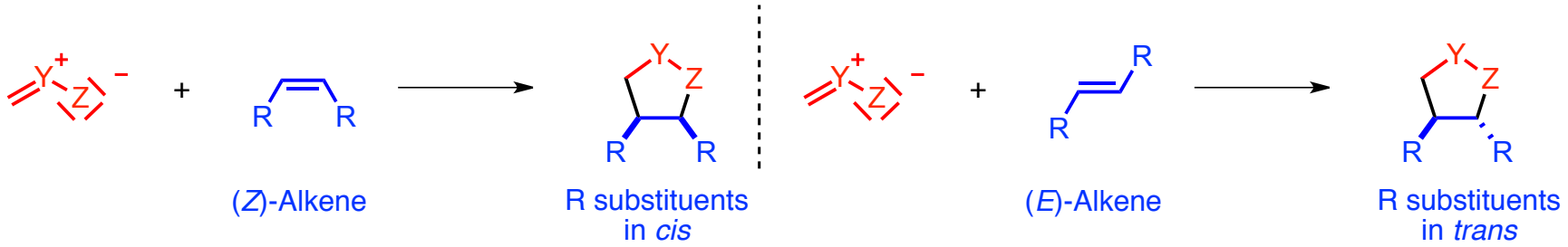
major regioisomer obtained

Regioselectivity

- Be careful, steric effect can compete:

	Regioisomer predicted with orbital frontier intercations	Other regioisomer
R = H	100	0
R = Me	63	37
R = *i*Pr	19	81
R = *t*Bu	0	100

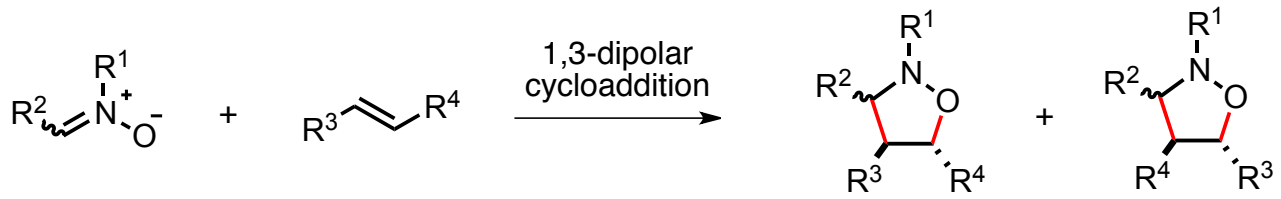
Stereospecificity



- When disubstituted alkenes are used, geometry of the double bond totally reflected in the relative stereochemistry of the two substituents in the product.
- Reaction is stereospecific.

1,3-dipolar cycloadditions with nitrones

General scheme



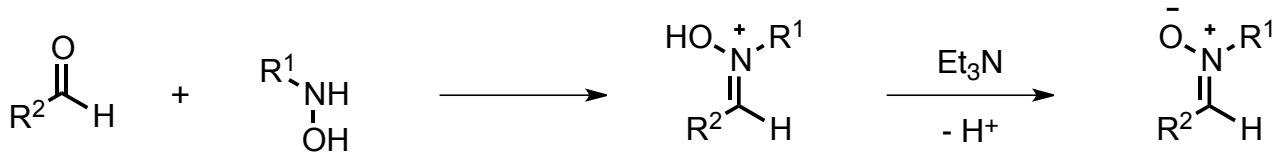
2 created bonds
3 stereocenters

- Formation of substituted isoxazolidines
- (*E*) and (*Z*) nitrones generally under equilibrium through isomerization process.
- Consequence: isoxazolidines generally formed as a mixture of 2 diastereomers.
- Stereospecific with respect to the geometry of the double bond.

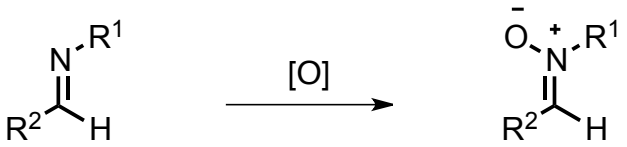
1,3-dipolar cycloadditions with nitrones

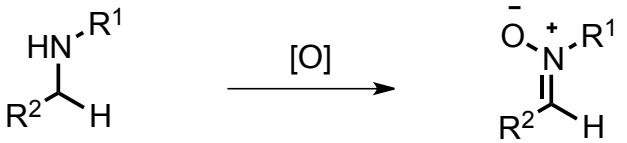
Synthesis of nitrones

- From reaction between aldehyde and hydroxylamine



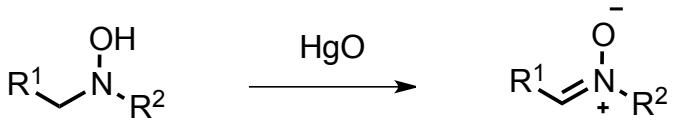
- From oxidation of imines or amines





Common oxidative agents: $MeReO_3$-H_2O_2-urea, oxone, $KMnO_4$

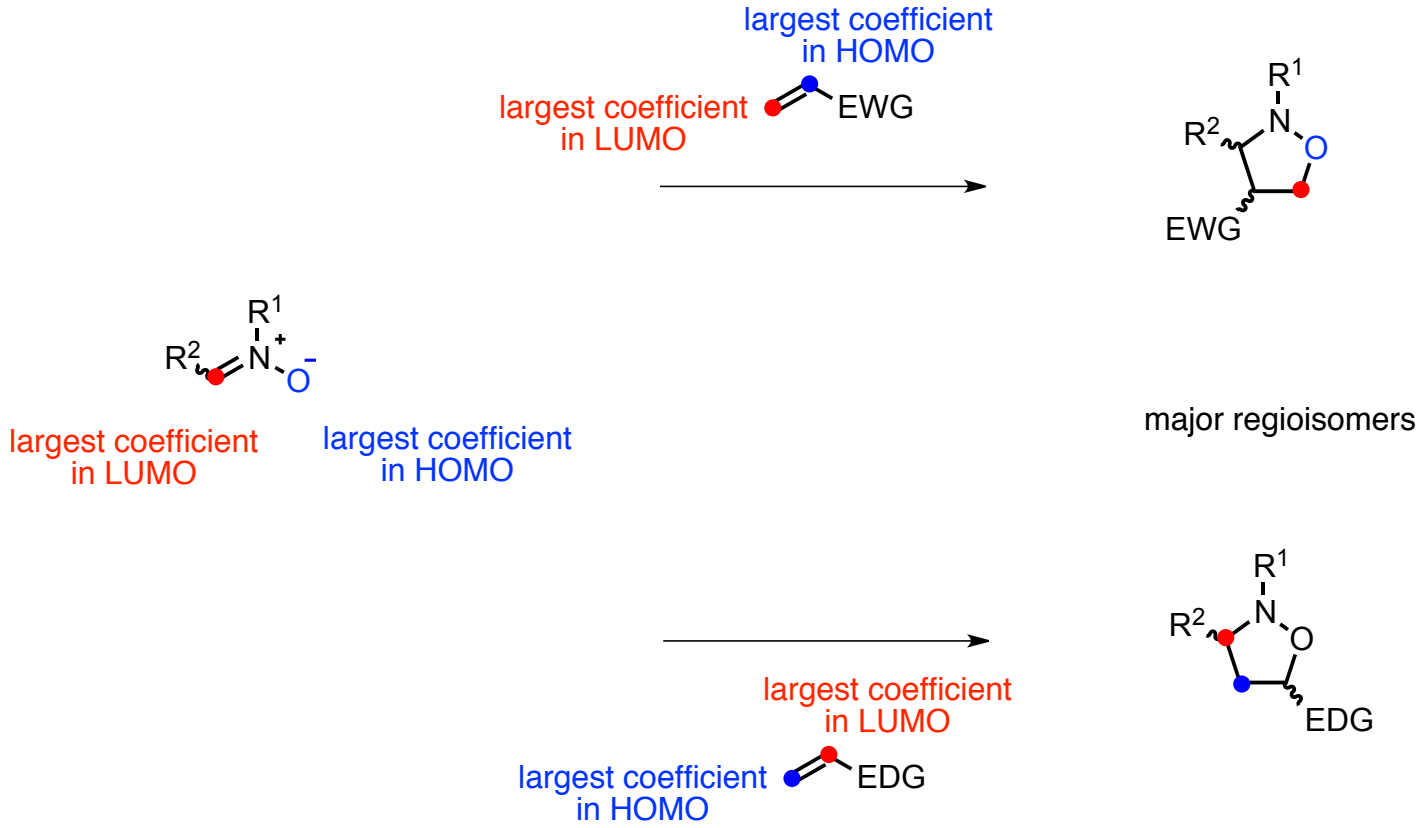
- From oxidation of hydroxylamines



1,3-dipolar cycloadditions with nitrones

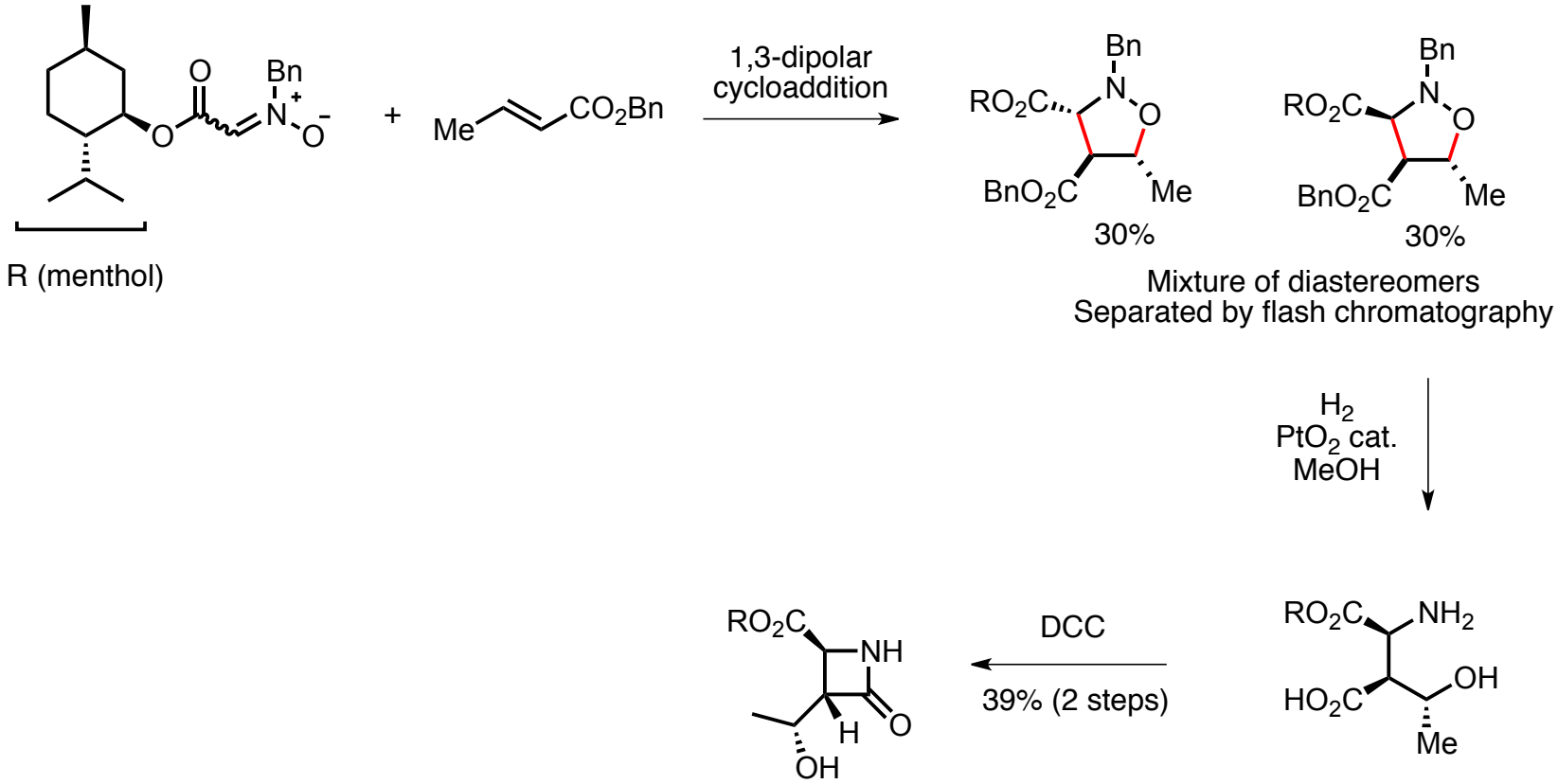
Regioselectivity

- Regioselectivity directed by the dominant frontier orbital interaction.
- Nitrones = amphiphilic dipoles so regioselectivity highly dependent on the nature of dipolarophile



1,3-dipolar cycloadditions with nitrones

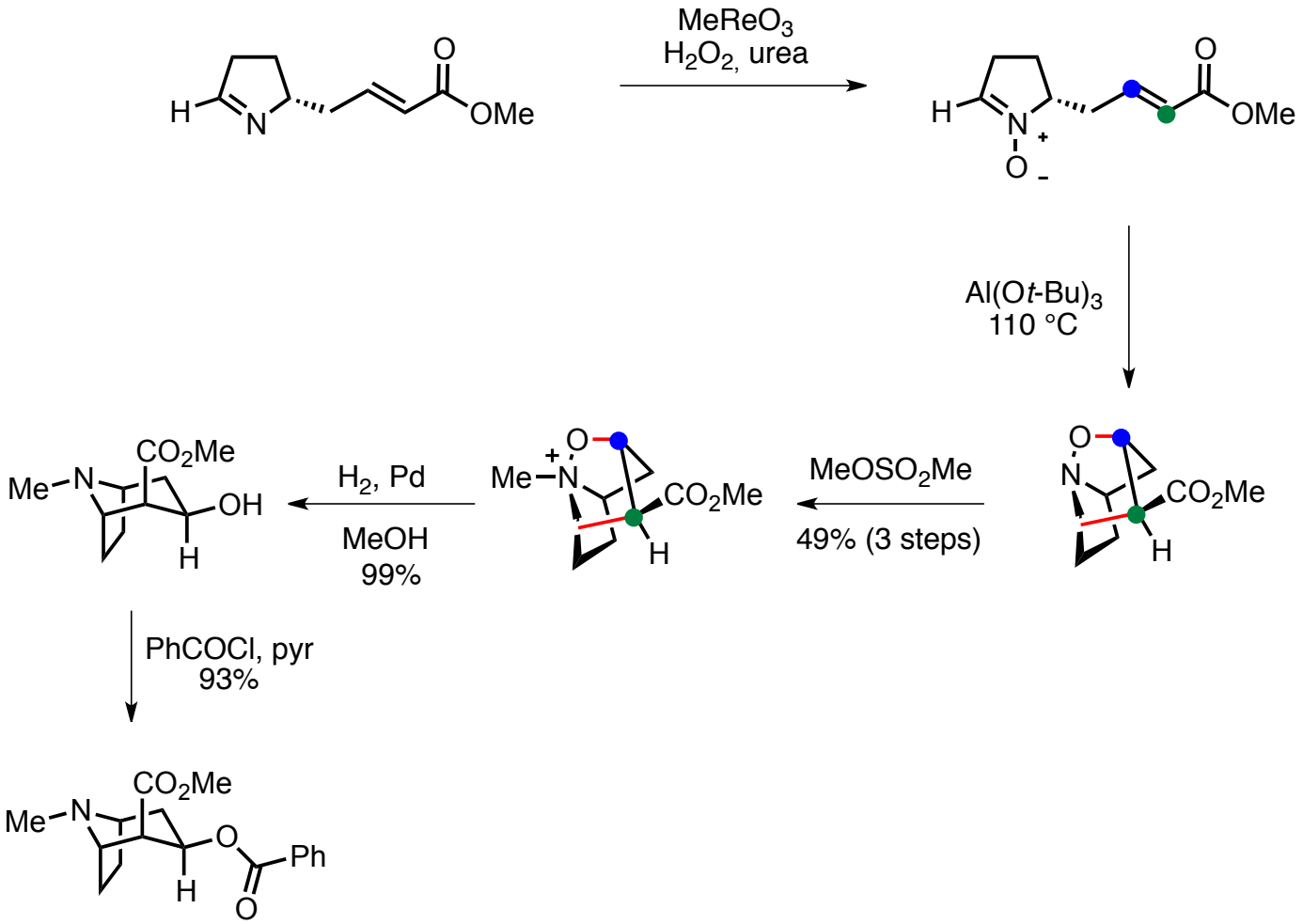
Application: access to 1,3-amino alcohols



- N-O = weak bond, can be cleaved to give amino-alcohols ($LiAlH_4$, Zn/AcOH, H_2/Ni or Pt or Pd cat)

1,3-dipolar cycloadditions with nitrones

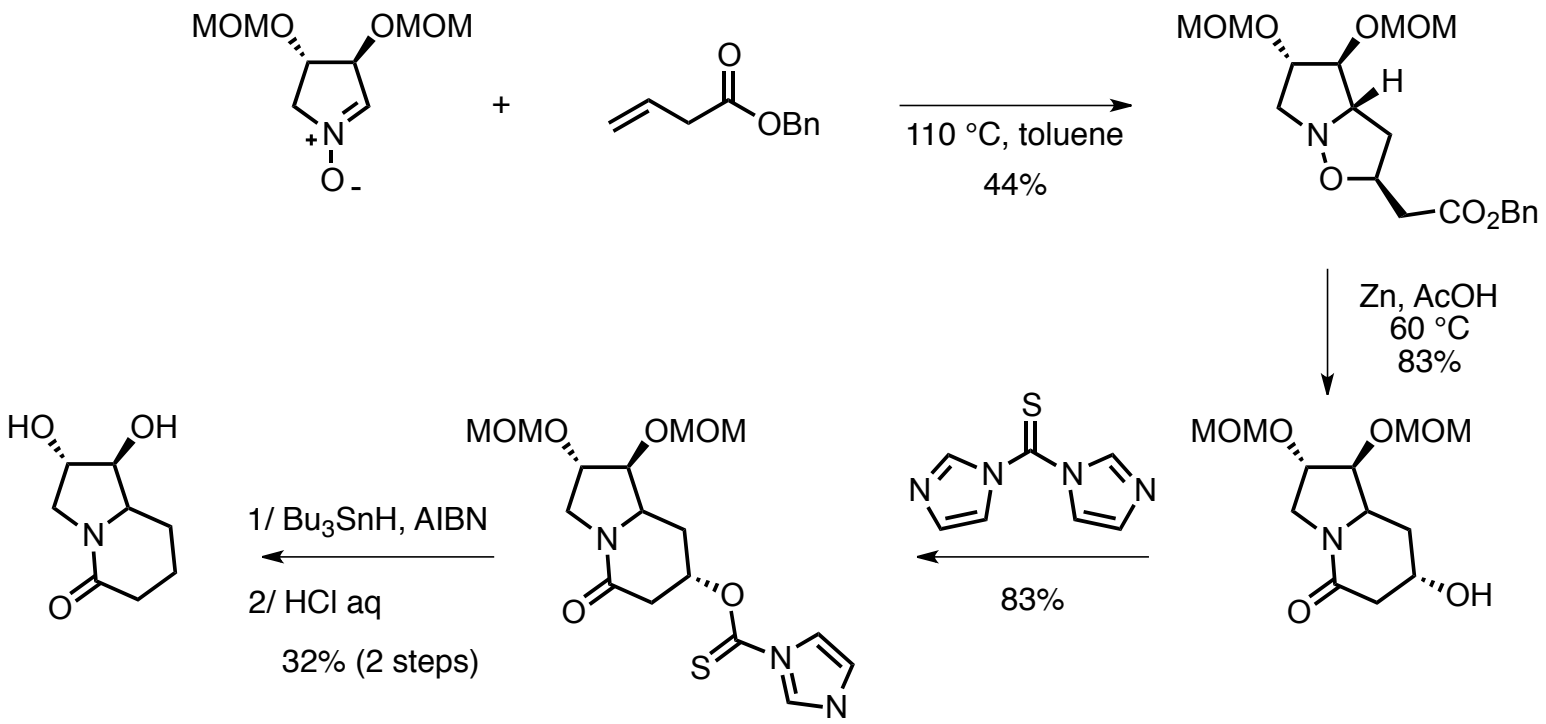
Application: intramolecular cycloaddition



F. A. Davis et al. *Org. Lett.* **2010**, *12*, 4118.

1,3-dipolar cycloadditions with nitrones

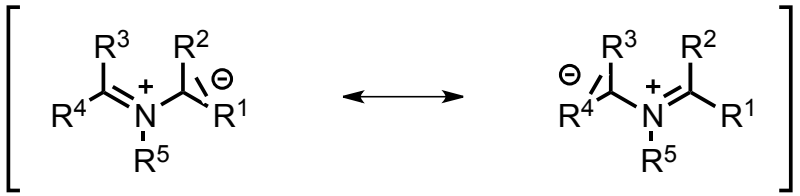
Application: cyclic nitrone



A. E. McCaig et al. *Tetrahedron* **1998**, *54*, 9429.

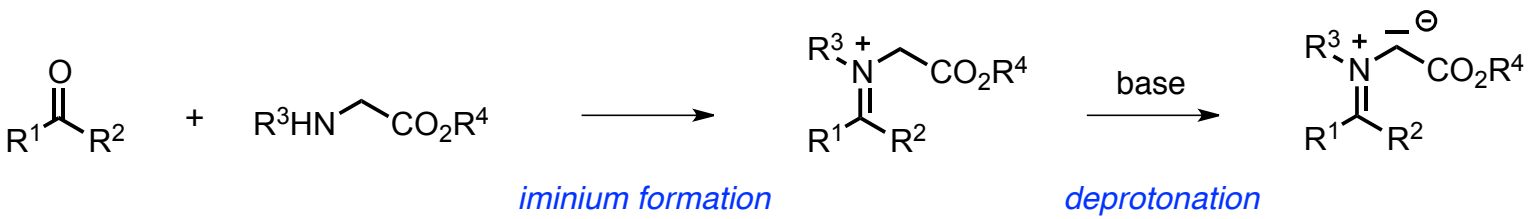
1,3-dipolar cycloadditions with azomethine ylides

- Resonance forms of azomethine ylides

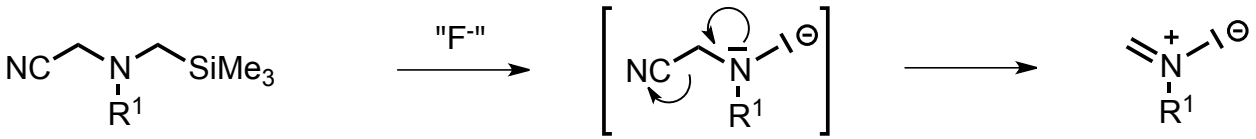


- Preparation of azomethine ylides

- through iminium formation and deprotonation



- from α-cyanoaminosilanes



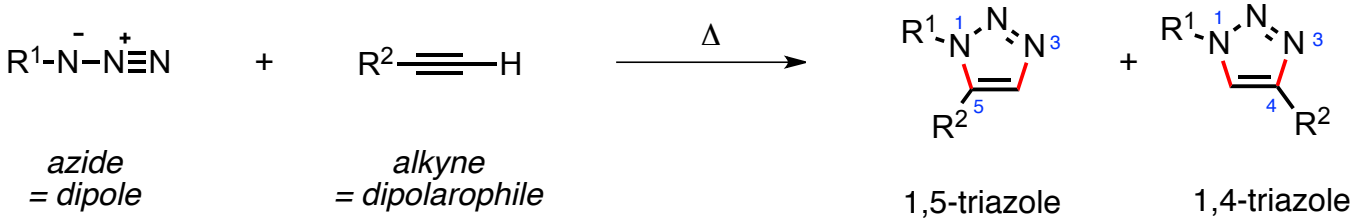
Generation of azomethine ylides has to be done *in situ*, in the presence of the dipolarophile

1,3-dipolar cycloadditions with azomethine ylides

- Access to substituted pyrrolidines
- Azomethine ylides = nucleophilic dipoles, will interact through the HOMO, reaction favored with EWG groups on the alkene (especially when intermolecular)
- Regioselectivity depends on the nature of R^1 and R^3 : one σ bond formed between carbon atom with the highest coefficient in HOMO of the ylide and carbon and carbon atom with the highest coefficient in the LUMO of alkene.
- Stereoselectivity depends on the conformation of the azomethine ylide.

1,3-dipolar cycloadditions between azides and alkynes

General scheme – Thermal conditions



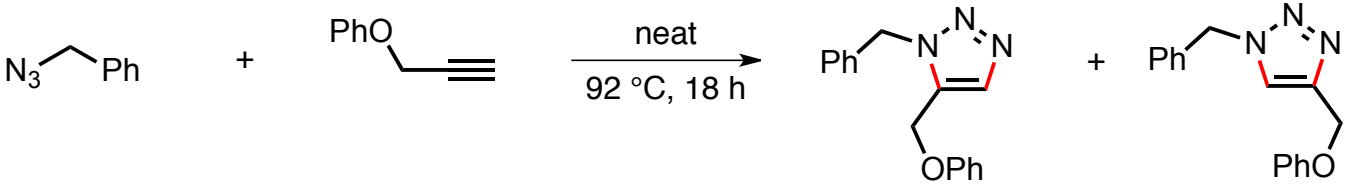
azide = dipole

alkyne = dipolarophile

1,5-triazole

1,4-triazole

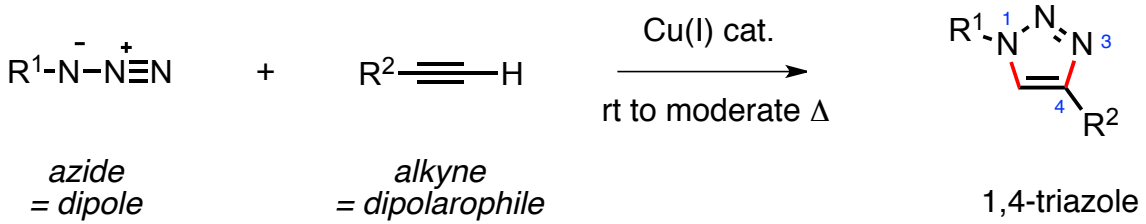
- Reaction is slow: prolonged reaction time, high temperature required
- Lack of selectivity: both regioisomers obtained, difficult to separate



1:1.6 ratio

1,3-dipolar cycloadditions between azides and alkynes

Copper (I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC)



- Tremendous acceleration of the reaction rate: 10^7 to 10^8
- Reactions can be run at rt or under moderate heating
- Perfect regioselectivity towards the formation of 1,4-triazoles
- Easy work-up (filtration, extraction), no need for chromatography
- Tolerant towards a wide array of functional groups
- Compatible with water as solvent, broad range of pH tolerated (4-12)
- Limited to terminal alkynes (see the mechanism)

K. B. Sharpless et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

Click reaction

Click reaction = connexion of 2 building-blocks to furnish a more complex molecule

High yield

High selectivity

No purification

Wide scope

Simple

Atom economy

Fast

Benign solvents
including water

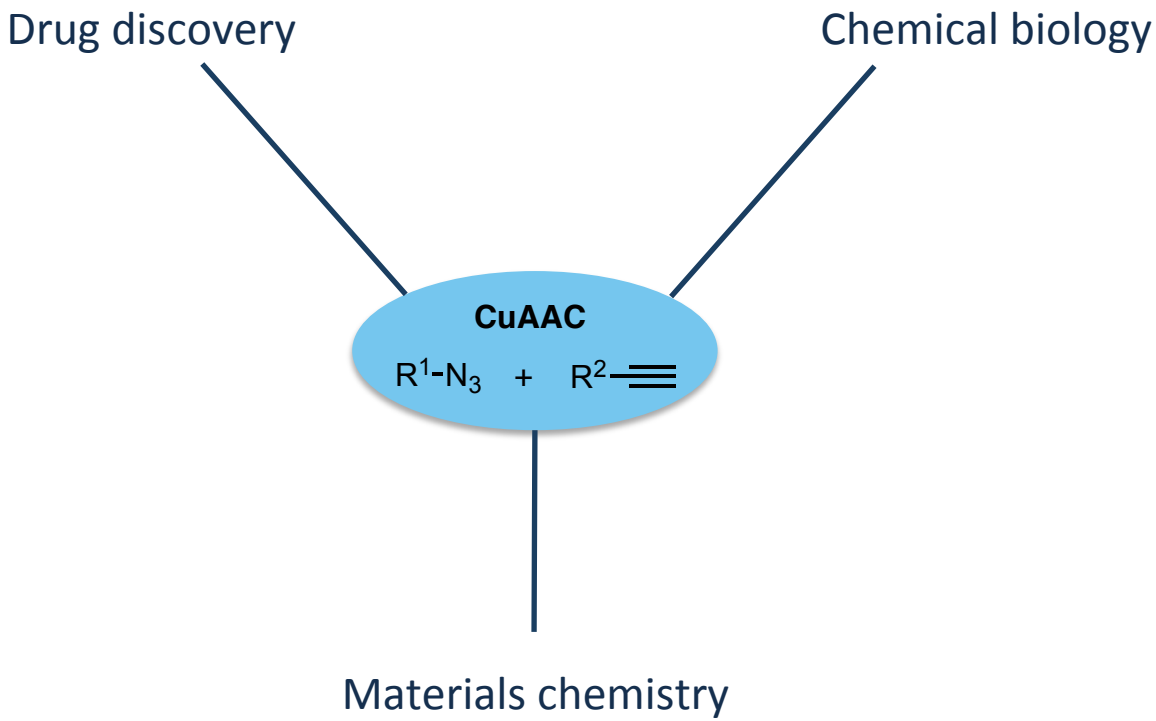
Compatible with
physiological conditions

Mild conditions

B. Sharpless: « CuAAC is the premier example of click reaction »

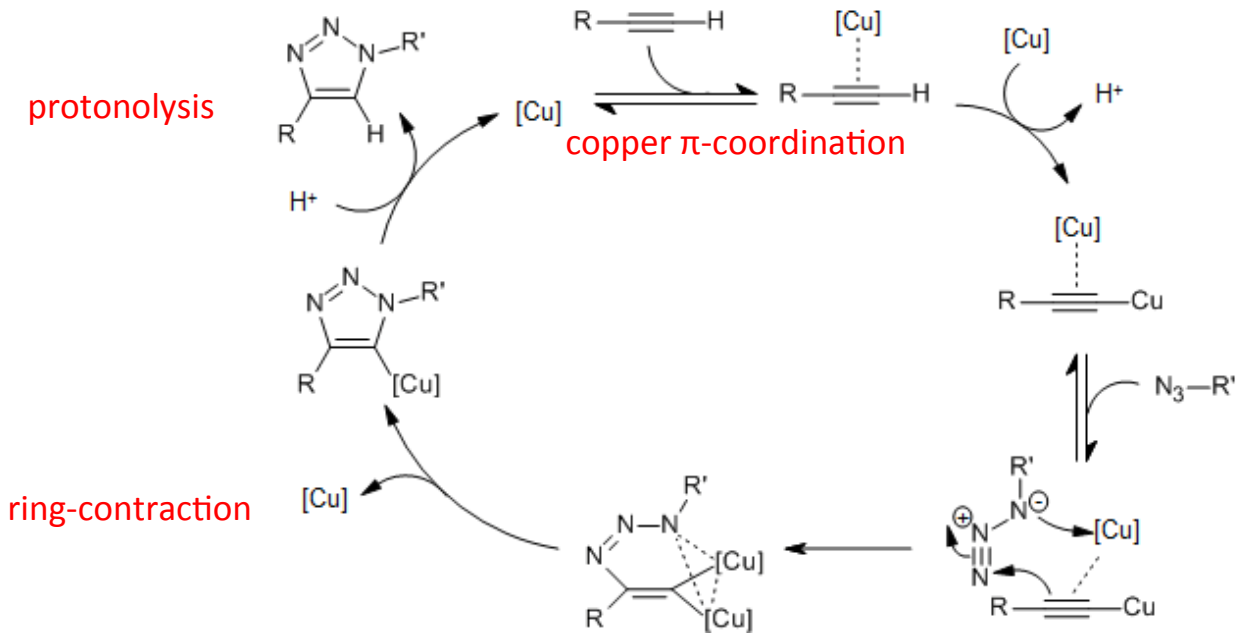
K. B. Sharpless et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

Application of CuAAC



Alkyne/Azide: available materials. Bioorthogonal functions.

CuAAC - Mechanism



- Cu(I) generally generated from Cu(II) salts in the presence of sodium ascorbate as a reductive agent.
- Different from thermal 1,3-cycloaddition, step-wise mechanism (not concerted)
- Established based on calculations, bi-nuclear copper intermediates isolated

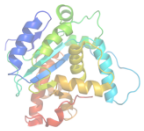
V. V. Fokin et al. *Science* **2013**, *340*, 457.

From www.organic-chemistry.org

Application of CuAAC: chemical biology

Identification of cellular targets of bioactive molecules

Most of the marketed drugs have unidentified cellular target and/or mechanism



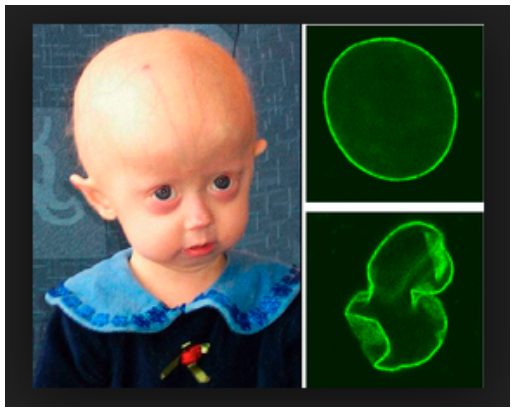
Cellular target identification

- Better understanding of activity
- Synthesis of more active molecules
- Original target discovery
- Innovative therapeutic strategy

- Identification of undesired targets
- Synthesis of more selective molecules
- Decrease of side-effects
- Less toxic treatment

Application of CuAAC: chemical biology

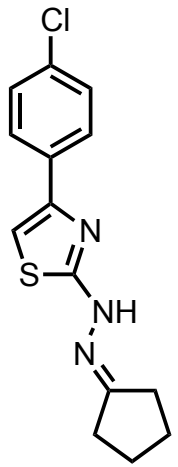
Hutchinson-Gilford progeria syndrome

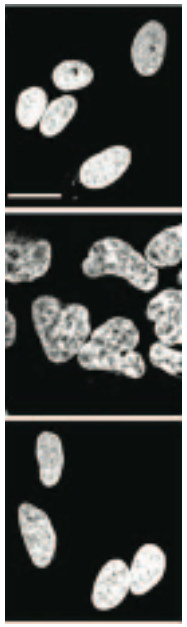


- Extremely rare genetic disease causing an accelerated aging of children.
- Due to a mutation of LMNA gene encoding for lamin A and C.
- The mutation causes misshapen nuclei and altered chromatin organization.
- No effective existing treatment, average age of death is 13 years old.

Application of CuAAC: chemical biology

Identification of an active compound





treated abnormal cells

untreated abnormal cells

normal cells

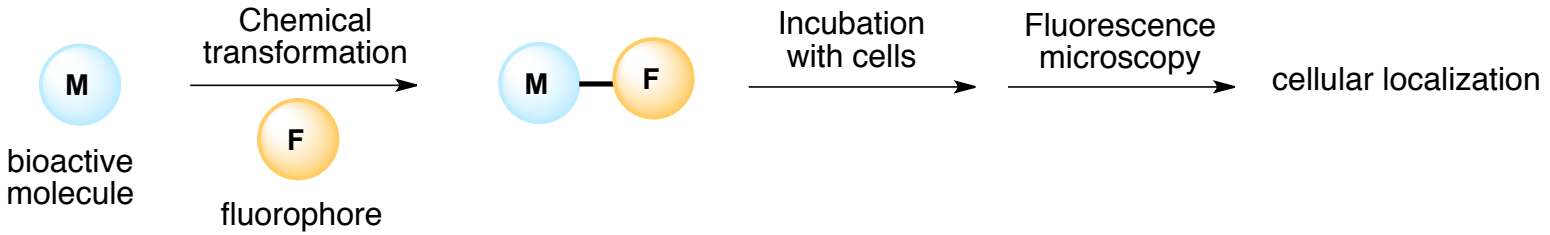
- Extensive screening: identification of an active molecule.
- Restoration of nuclear circularity.
- Complete nuclear-shape rescue after 12 h of treatment without affection of the cell cycle.
- But mode of action and cellular target both unknown.

R. Rodriguez *et al. Science* **2014**, *344*, 527.

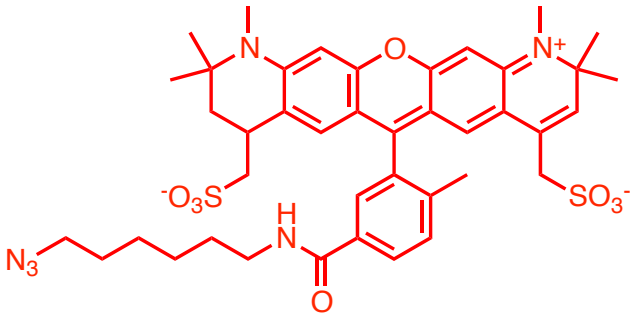
Application of CuAAC: chemical biology

Towards the identification of the cellular target

- Option 1: localization of the bioactive molecule through direct labelling



- Problem: fluorophore are big molecules displaying various functional groups.
- Will modify the cellular behaviour of the active molecule.
- Lack of fiability for the observed results.



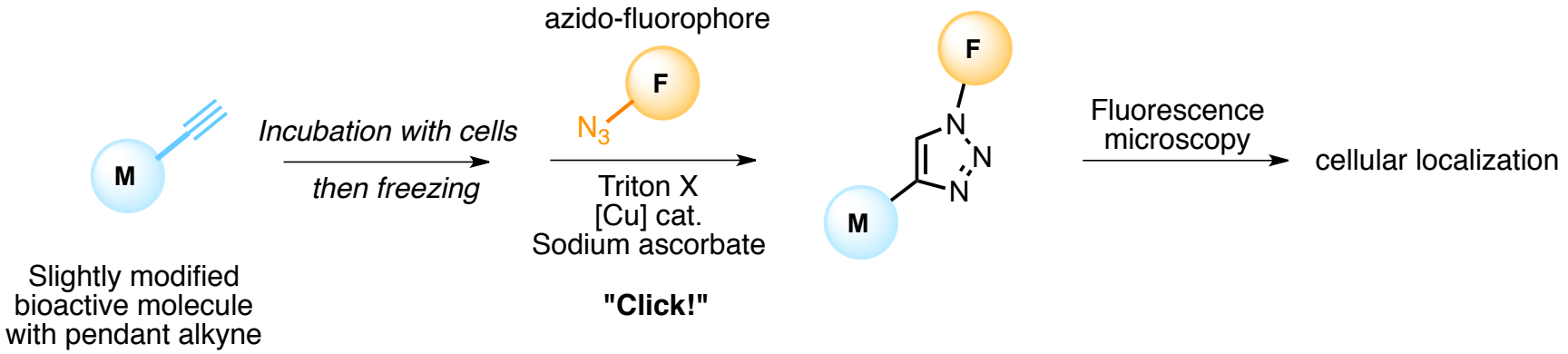
Alexa Fluor 594 Azide

R. Rodriguez *et al. Nat. Rev. Chem.* **2018**, *24*, 202.

Application of CuAAC: chemical biology

Towards the identification of the cellular target

- Option 2: *in cellulo* labelling through *in cellulo* click reaction



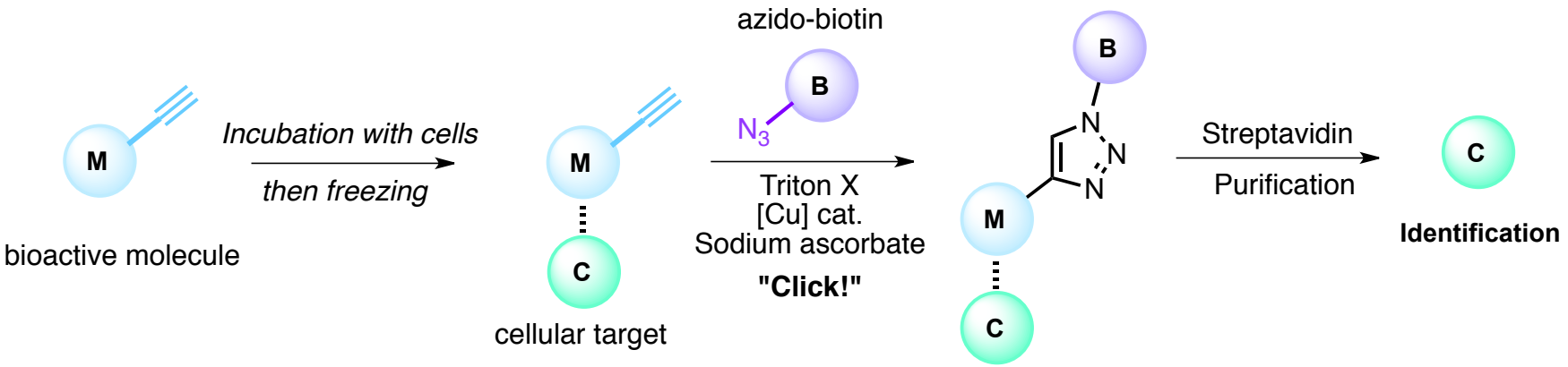
- Labelling occured after the incubation, bioactivity and localization of the molecule not disturbed by the presence of the fluorophore.
- Alkyne = small function that generally does not affect the bioactivity of the molecule (have to be checked).
- Alkyne and azide not present in living cells (= bioorthogonal functions), click reaction is selective.
- Cellular localization gives some clue about the target and biological mechanism.

R. Rodriguez *et al. Nat. Rev. Chem.* **2018**, *24*, 202.

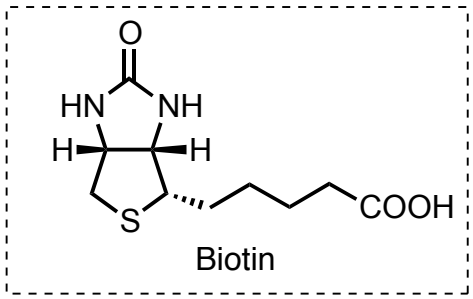
Application of CuAAC: chemical biology

Towards the identification of the cellular target

- Pull-down experiment: how to fish the cellular target?



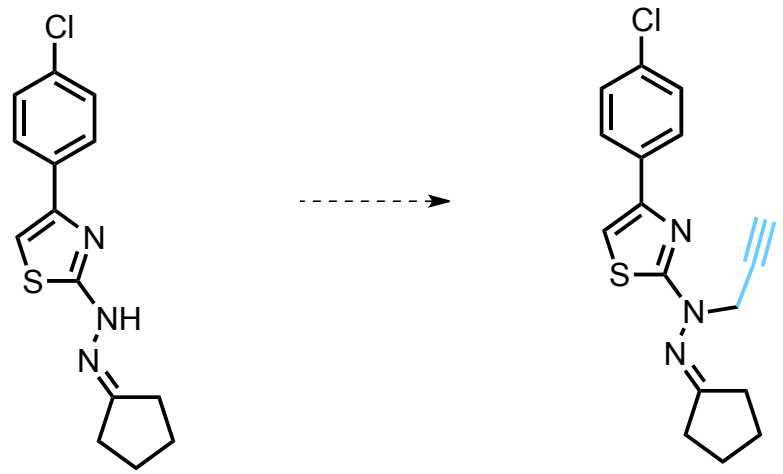
- Based on the strong biotin/streptavidin interaction.
- Most of cellular targets are proteins. Can be identified through mass spectrometry (generally associated to liquid chromatography, LC/MS)



R. Rodriguez *et al. Nat. Rev. Chem.* **2018**, *24*, 202.

Application of CuAAC: chemical biology

Synthesis of a clickable analog

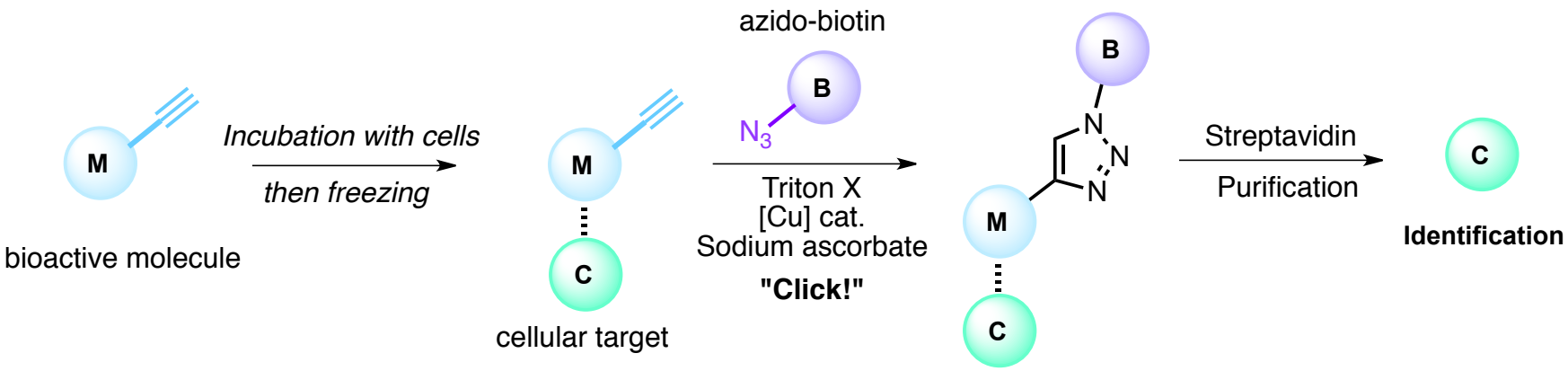


- Alkyne introduction does not affect the bioactivity towards abnormal cells.
- Excellent candidate for pull-down and imaging experiments.

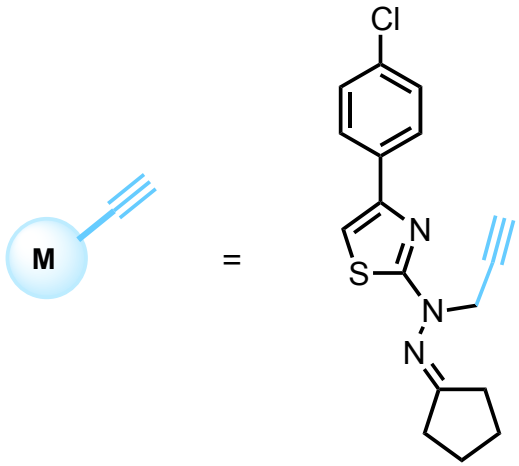
R. Rodriguez *et al. Science* **2014**, *344*, 527.

Application of CuAAC: chemical biology

Pull-down experiment



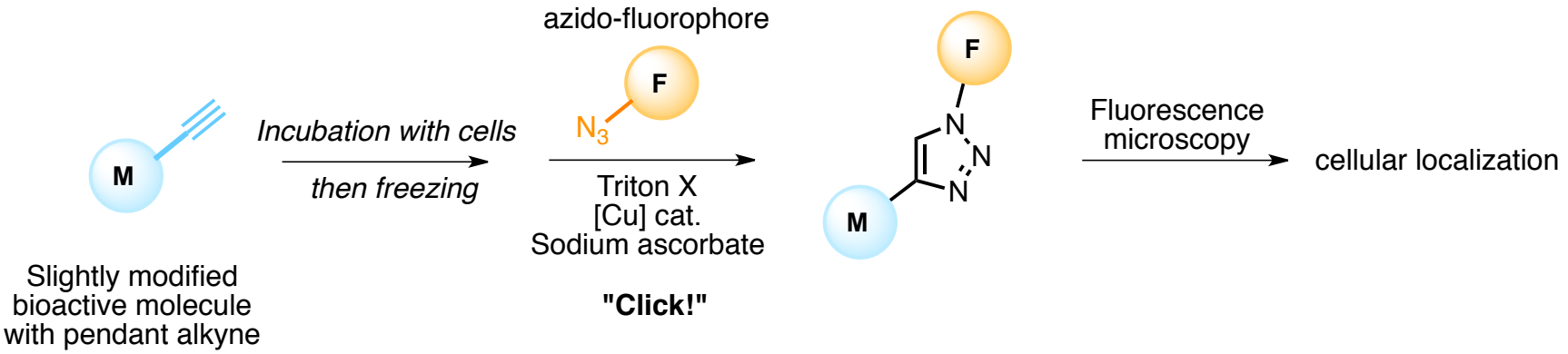
- Identification of a protein target: NAT10 by (LC/MS)/MS

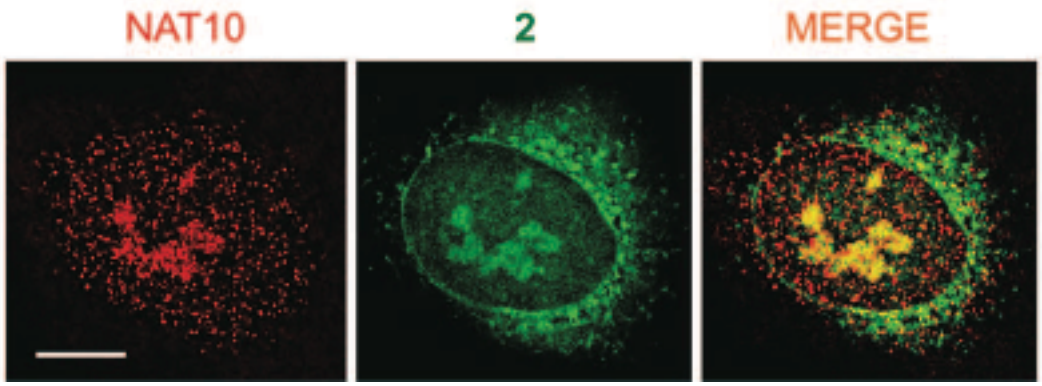


R. Rodriguez *et al. Science* **2014**, *344*, 527.

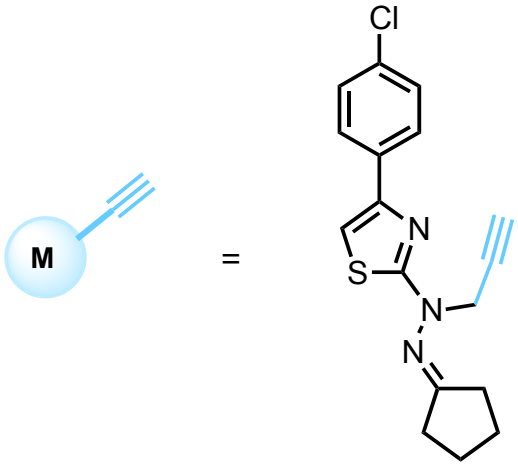
Application of CuAAC: chemical biology

Imaging experiment





Red = NAT10 Green = labelled M Yellow = colocalization of M and NAT10



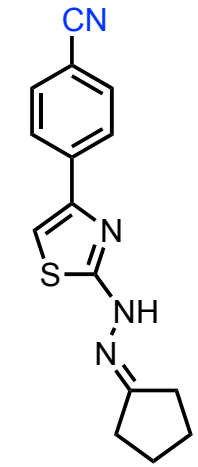
- NAT10 targetting confirmed (+ complementary experiments)

R. Rodriguez *et al. Science* **2014**, *344*, 527.

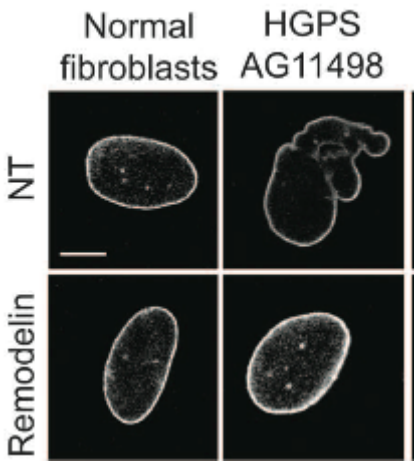
Application of CuAAC: chemical biology

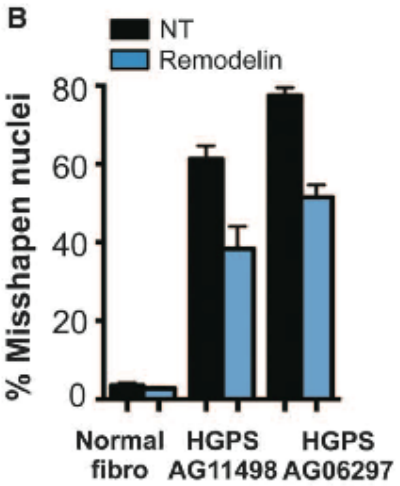
Towards innovative therapeutic strategies

- Identification of the protein target open the way towards new therapeutic strategies against Hutchinson-Gilford syndrome



More active analog
Remodelin

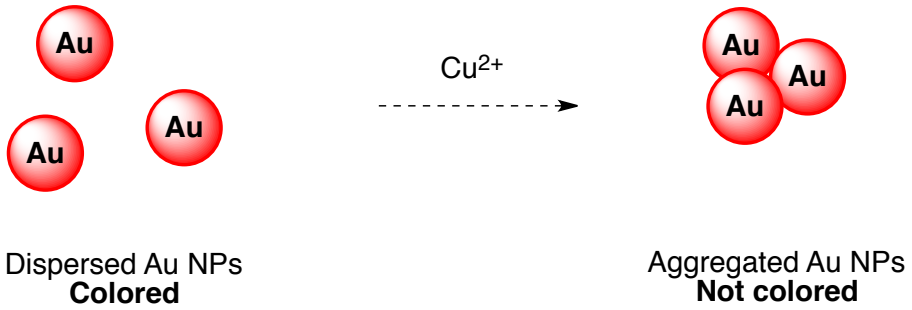




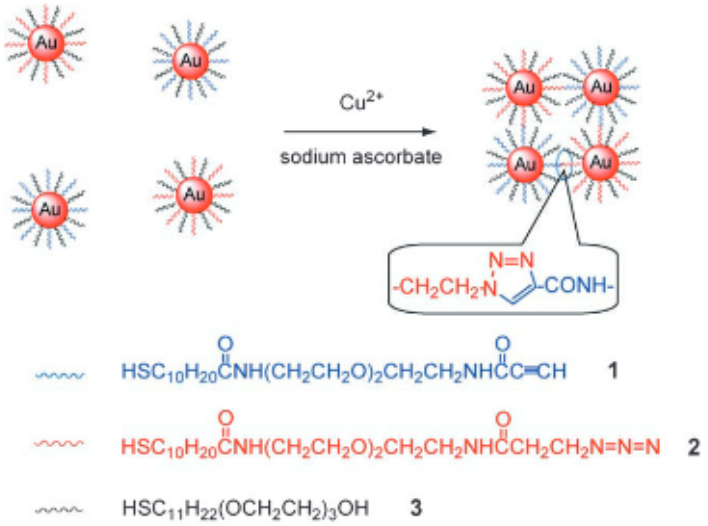
R. Rodriguez *et al. Science* **2014**, *344*, 527.

Application of CuAAC: Cu(II) detection

- Copper: transition metal essential to life but highly toxic if present in excess in the body
- Liver damage in children exposed to high dose of copper suspected.
- Need for efficient and practical analytical methods for the measurement of Cu^{2+} ions in environmental and biological samples.
- Colorimetric methods are attractive, particularly if the presence of Cu can be detected by the naked eye.
- Concept: exploit gold nanoparticles that are colored at very low concentrations (nanomolar) when dispersed but lose their color upon aggregation.



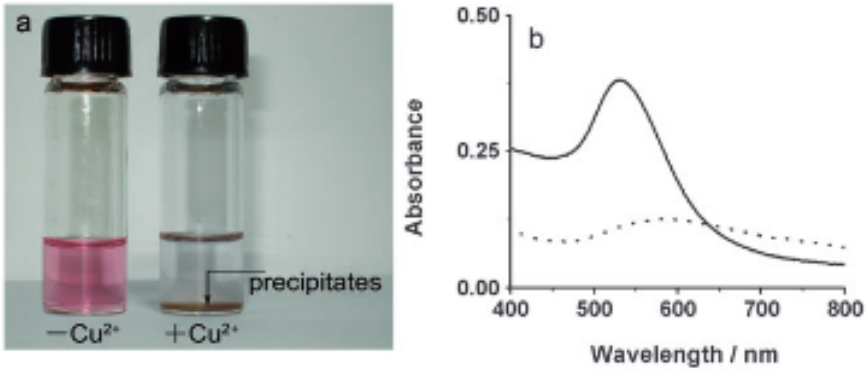
Application of CuAAC: Cu(II) detection



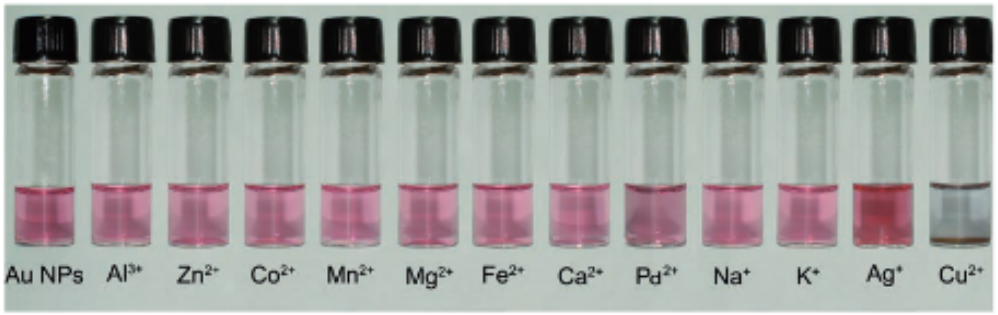
- Preparation of 3 thiols (S has a high aurophilicity):
- **1**: alkyne functionalized thiol
- **2**: azide functionalized thiol
- **3**: stabilizer and spacer
- Preparation of 2 families of Au NPs by ligand exchange (Alkyne Au NPs and Azide Au NPs)
- In the presence of sodium ascorbate (reductive agent) and Cu^{2+}, aggregation of the Au NPs caused by click reaction occuring between alkyne and azide functions.

X. Jiang et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 7454.

Application of CuAAC: Cu(II) detection

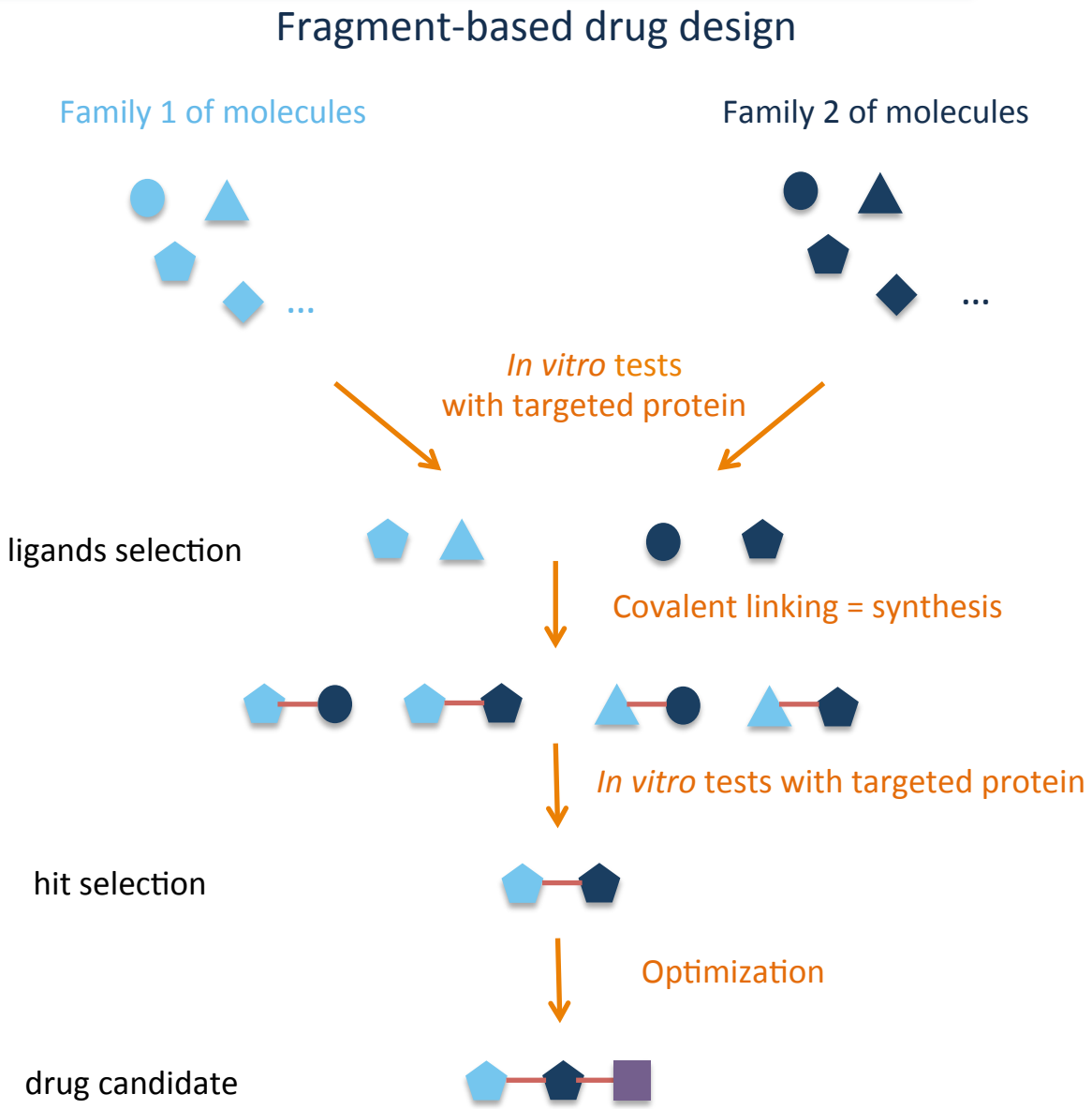


- In the absence of Cu^{2+}: pink solution while in the presence of Cu^{2+} the solution turned colorless.
- Easy to monitor by the naked eye but also with UV/Vis spectra.
- Limit of detection is ca. 50 µM (cannot compete with methods using sophisticated instruments but very interesting for detection by the naked eye alone).
- Very selective towards the detection of copper ions, method can be applied in complex mixtures.

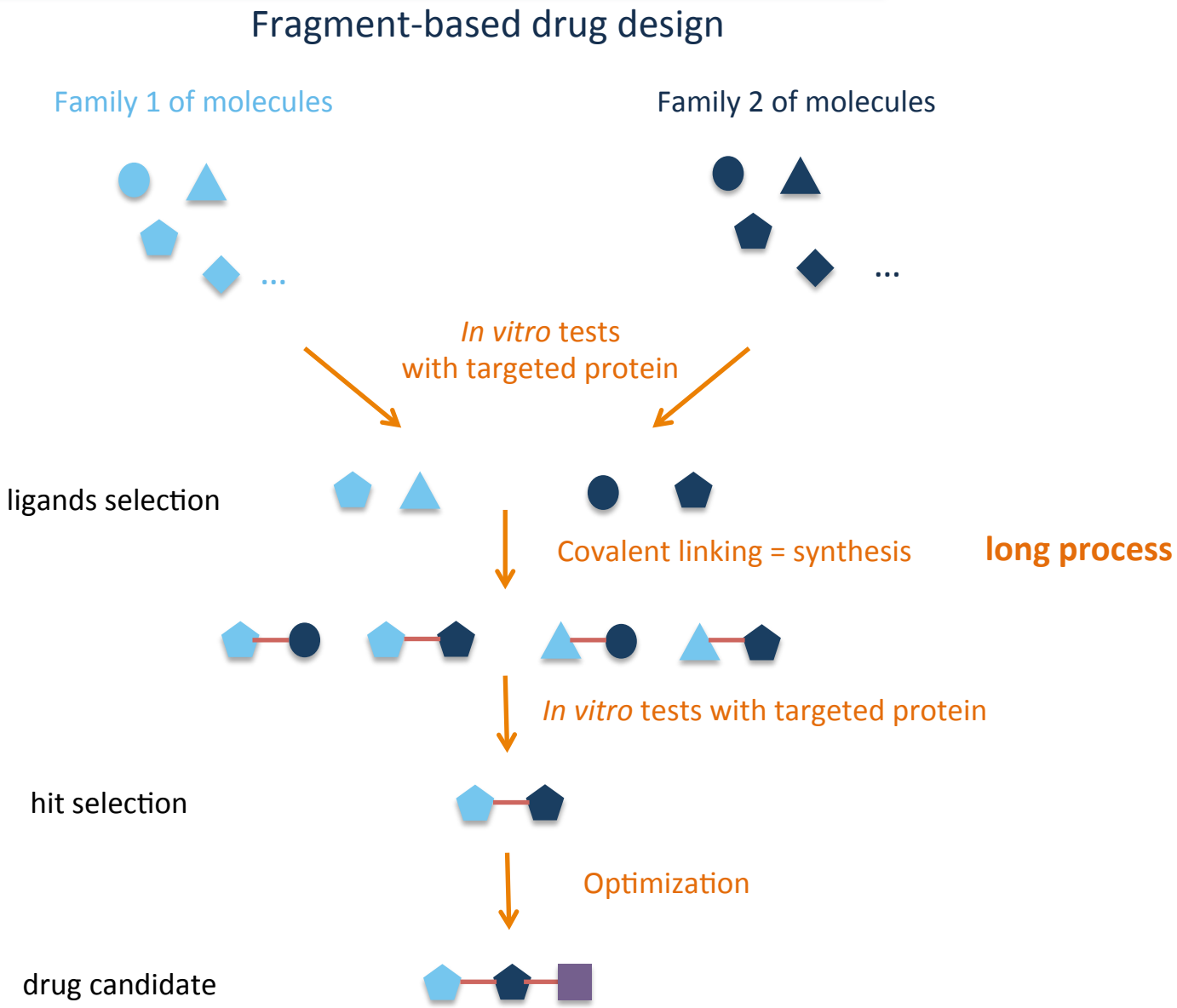


X. Jiang et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 7454.

Application of click reaction: drug discovery

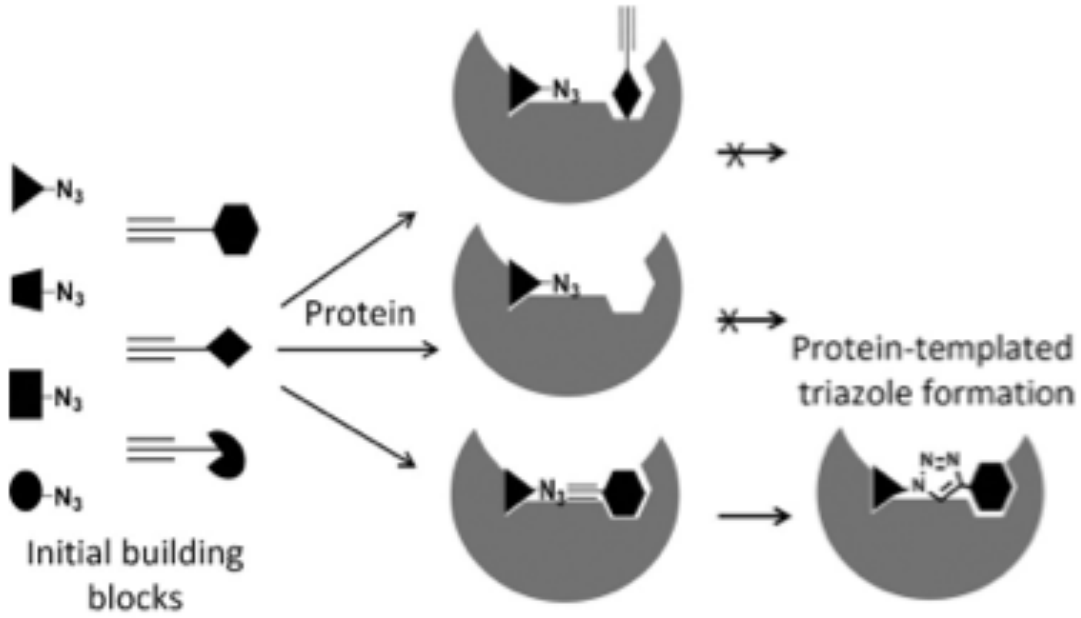


Application of click reaction: drug discovery



Application of click reaction: drug discovery

Protein-templated click chemistry



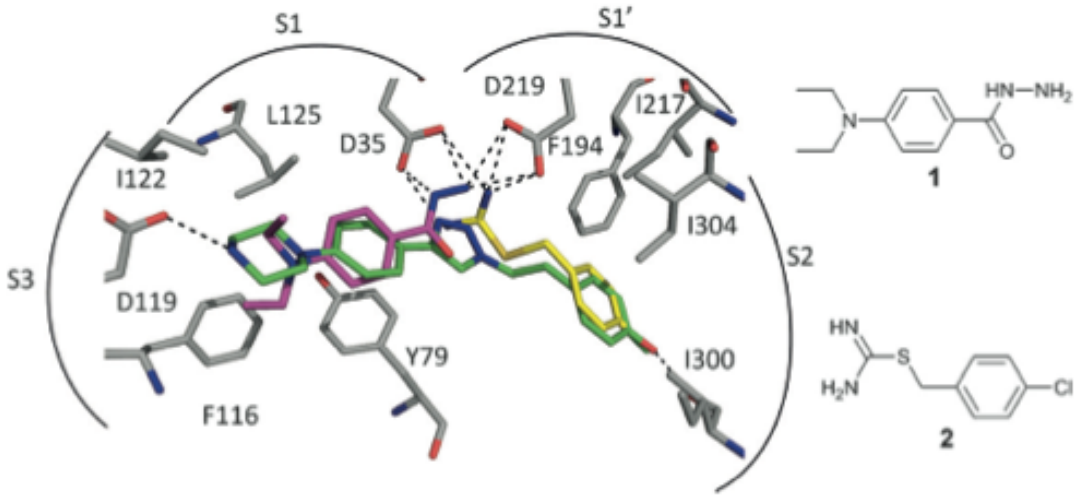
- Two families of ligands prepared: azide-ligands and alkyne-ligands.
- Targeted protein acts as a template to bring close to each other azide-ligand and alkyne-ligand with high affinity for different but closed binding sites.
- If the orientation of the two molecules is appropriated, click reaction occurs without any Cu(I) catalyst.
- Isolation of the formed triazoles (1,4 or 1,5) leads to identification of hits.

A. K. H. Hirsch *et al. Chem. Eur. J.* **2016**, *22*, 14826.

Application of click reaction: drug discovery

Example: Inhibition of endothiapepsin (pepsin-like aspartic protease)

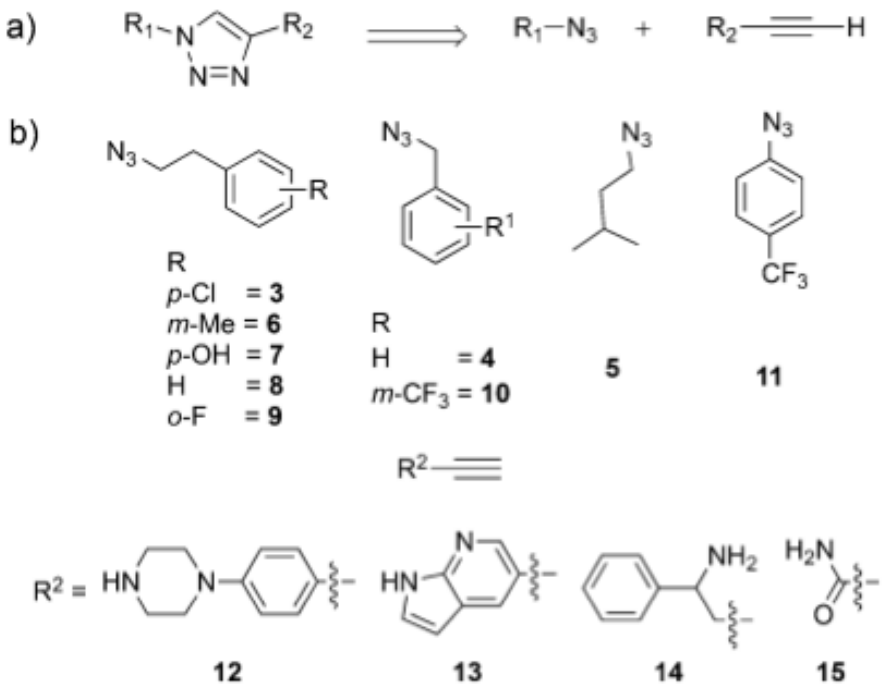
- Aspartic protease: role in several diseases (Alzheimer, hypertension, AIDS).
- Endothiapepsin = good model (high degree of similarity, high stability over time at rt)
- Molecular modeling and docking based on a X-Ray structure of the protein (cristallized in the presence of small molecules 1 (purple) and 2 (yellow))
- In silico screening of various triazoles (green) to design the libraries of azide and alkynes.



A. K. H. Hirsch *et al. Chem. Eur. J.* **2016**, *22*, 14826.

Application of click reaction: drug discovery

Protein templated click reaction

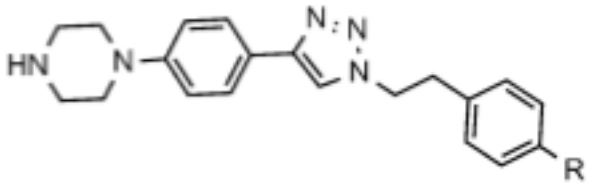


- Azides prepared from the bromo-derivatives.
- Alkynes prepared through Sonogashira reaction.
- Incubation of 13 molecules with the protein (2 weeks).
- LC/MS monitoring to identify the formed triazoles

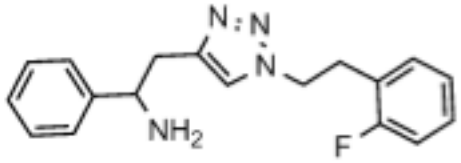
A. K. H. Hirsch *et al. Chem. Eur. J.* **2016**, *22*, 14826.

Application of click reaction: drug discovery

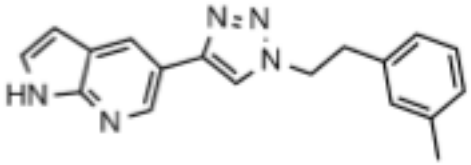
Hit selection and biological activity test



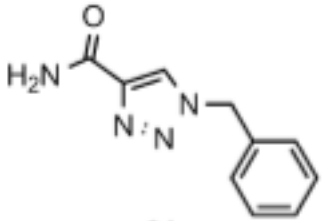
R = OH, **17**
= Cl, **19**



18



20



21

- Four triazoles formed **17**-**20** (**21** = negative control for the end of the study)
- Synthesis of these molecules through CuAAC.
- IC_{50} measurement (inhibitory activity against endothiapepsin):

Inhibitor	**17**	**18**	**19**	**21**
IC_{50} (µM)	43	94	121	no inhibition

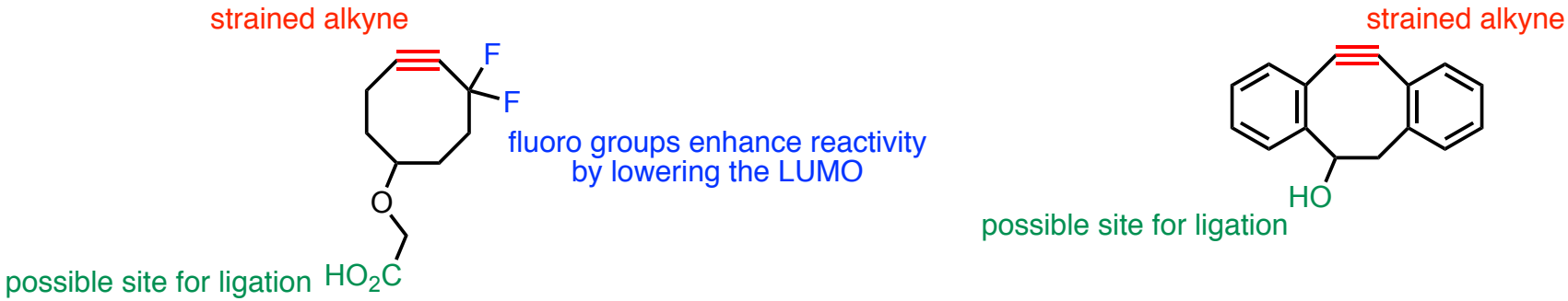
A. K. H. Hirsch *et al. Chem. Eur. J.* **2016**, *22*, 14826.

Copper-free click reaction

- Main drawback of CuAAC: toxicity of copper salts.
- Examples: - exposition of zebra fish to 1 mM $CuSO_4$ + 1 mM sodium ascorbate let to embryos death in less than 15 minutes

  - incubation of Escherichia coli with 100 µM CuBr for 16 h stops the cell division
- Detrimental for the use of CuAAC for *in vivo* bio-imaging.

- Alternative strategy: use highly strained and consequently reactive alkynes to facilitate copper-free 1,3-dipolar cycloaddition with azides.

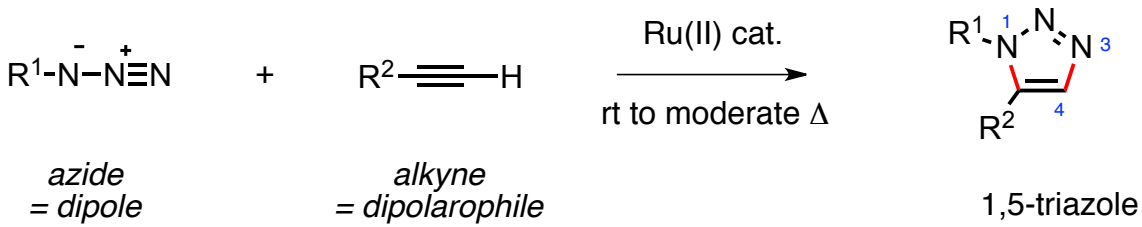


- Mixture of triazoles obtained (generally not a problem for biological applications)
- Synthesis of the cyclooctyne needed

C. R. Bertozzi *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 6974.

1,3-dipolar cycloadditions between azides and alkynes

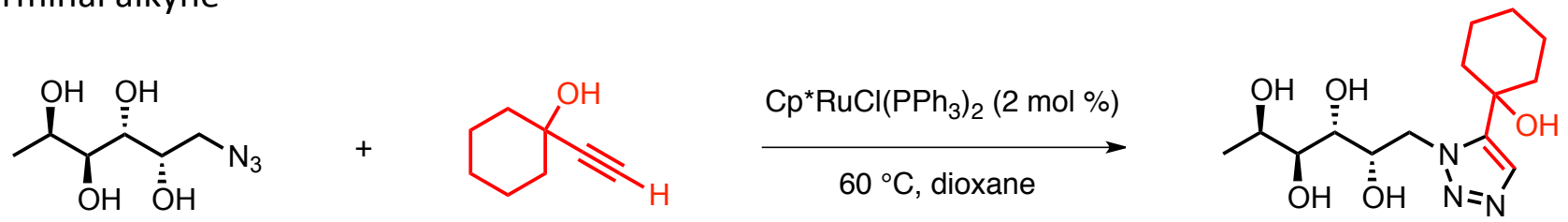
Ruthenium (II)-catalyzed Azide-Alkyne Cycloaddition (RuAAC)



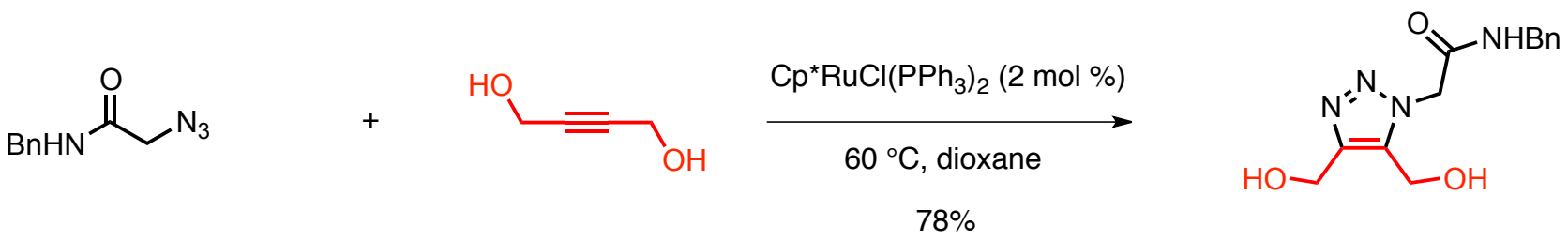
- [Cp*RuCl] are efficient catalysts
- 1,5-triazoles obtained regioselectively (complementarity with CuAAC)
- Compatible with internal alkynes (mechanism different from CuAAC, no Ru-acetylide formed)

RuAAC - Examples

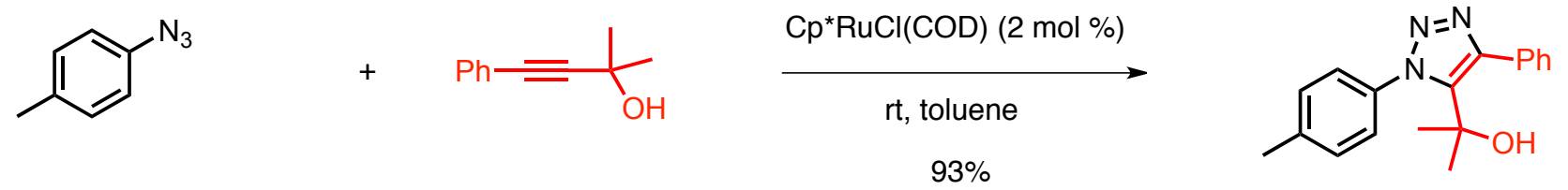
- Terminal alkyne



- Internal symmetrical alkyne



- Internal non-symmetrical alkyne

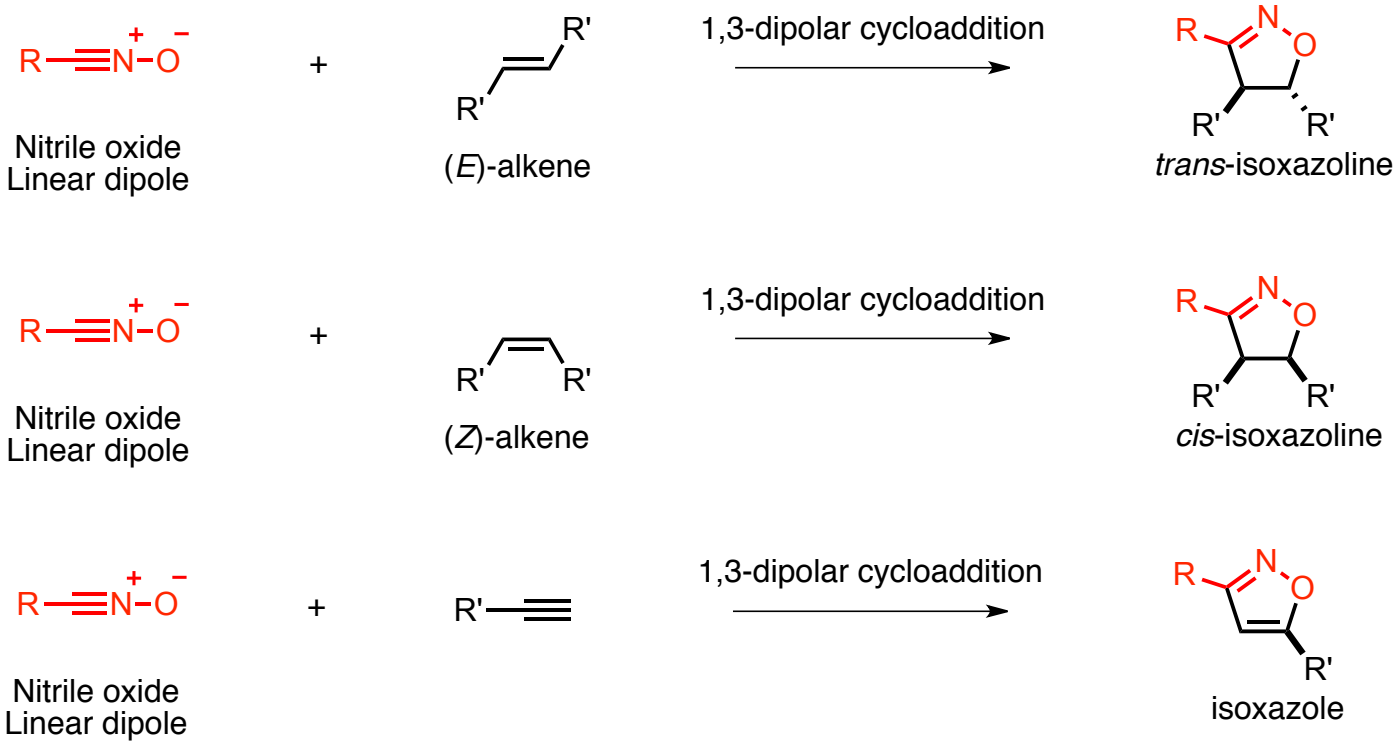


More electronegative and less sterically hindered carbon of the alkyne reacts with terminal nitrogen on the azide

V. V. Fokin et al. *J. Am. Chem. Soc.* **2008**, *130*, 8923.

1,3-dipolar cycloadditions with nitrile oxides

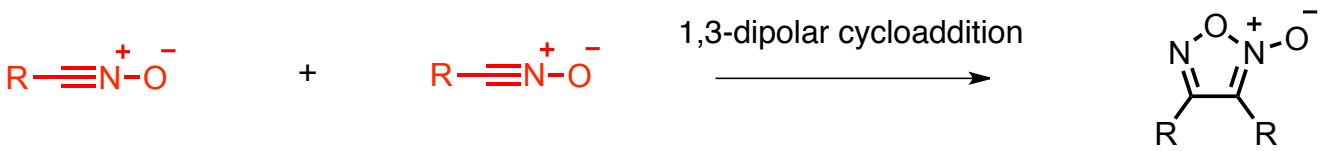
General scheme



- Interaction HOMO (dipolarophile) / LUMO (nitrile oxide) generally favored.

1,3-dipolar cycloadditions with nitrile oxides

Dimerization

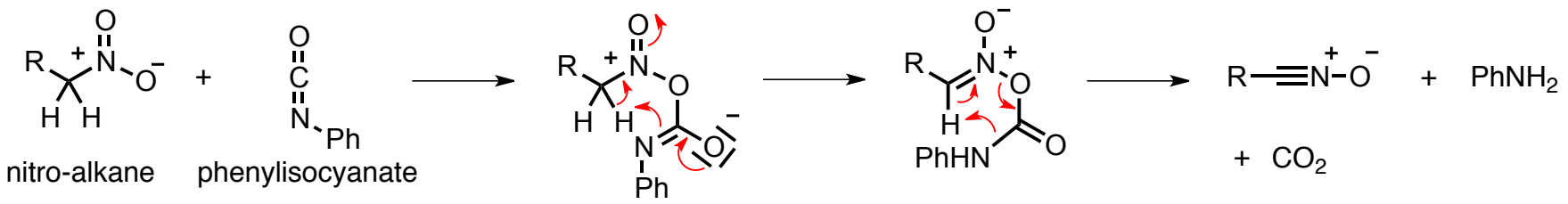


- Side reaction occuring with unhindered nitrile oxides.
- Resulting heterocycles are called furoxans, can be cracked to regenerate nitrile oxides under extreme conditions.
- Hindered nitrile oxides (R = *t*-Bu, Mesityl) stable enough to be isolated.
- Due to this lack of stability, nitrile oxides often generated *in situ* from stable precursors.

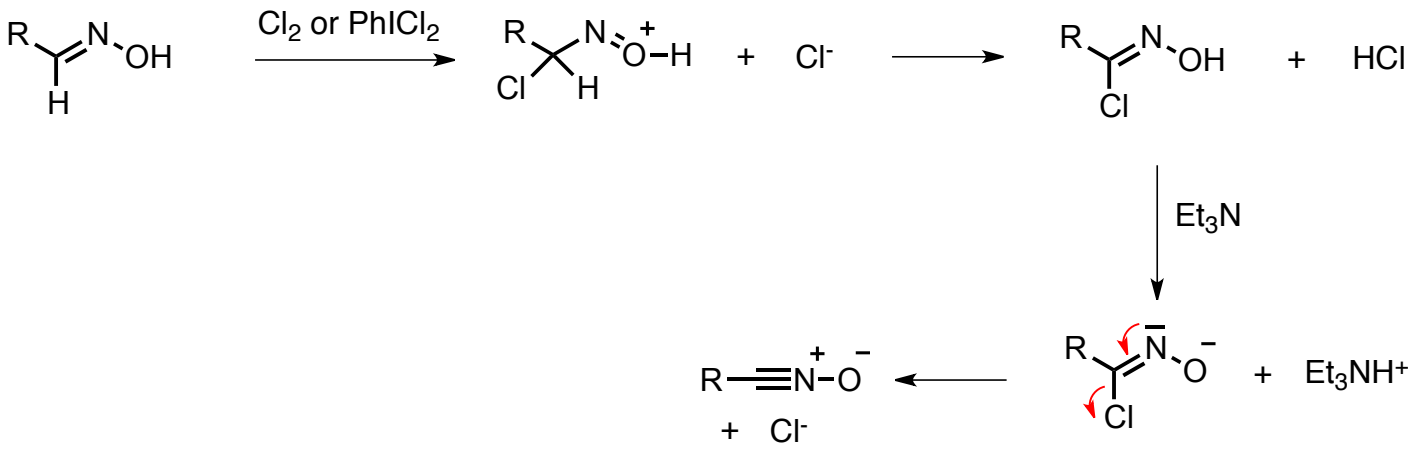
1,3-dipolar cycloadditions with nitrile oxides

Synthesis of nitrile oxides: 2 main methods

(1) From nitro-alkane dehydration



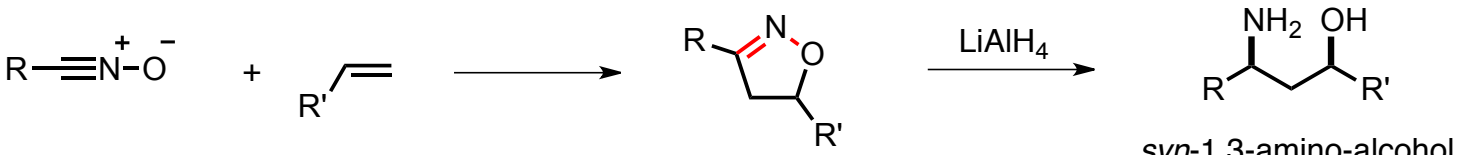
(2) From oxime oxidation



1,3-dipolar cycloadditions with nitrile oxides

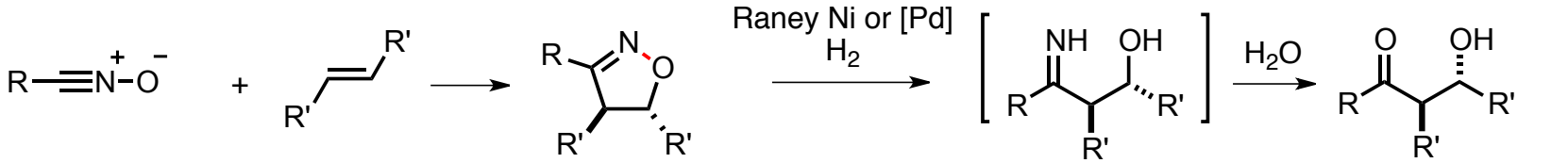
Application: ring-opening of isoxazolines

- Isoxazoline complete reduction: access to 1,3-amino alcohols

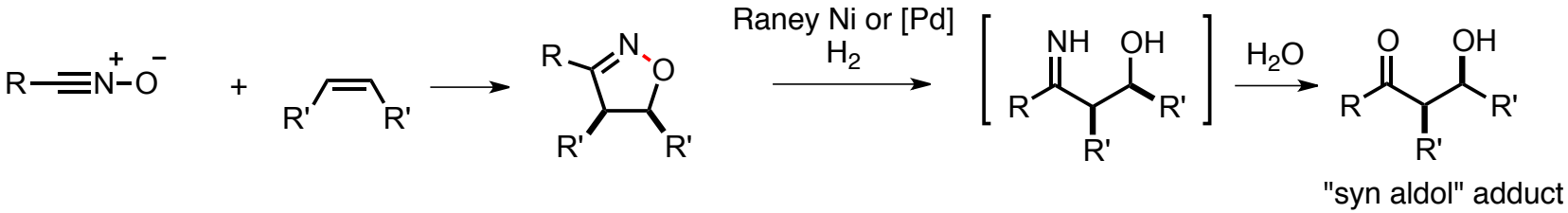


C=N and N-O reduction

- Isoxazoline partial reduction: access to aldol type products

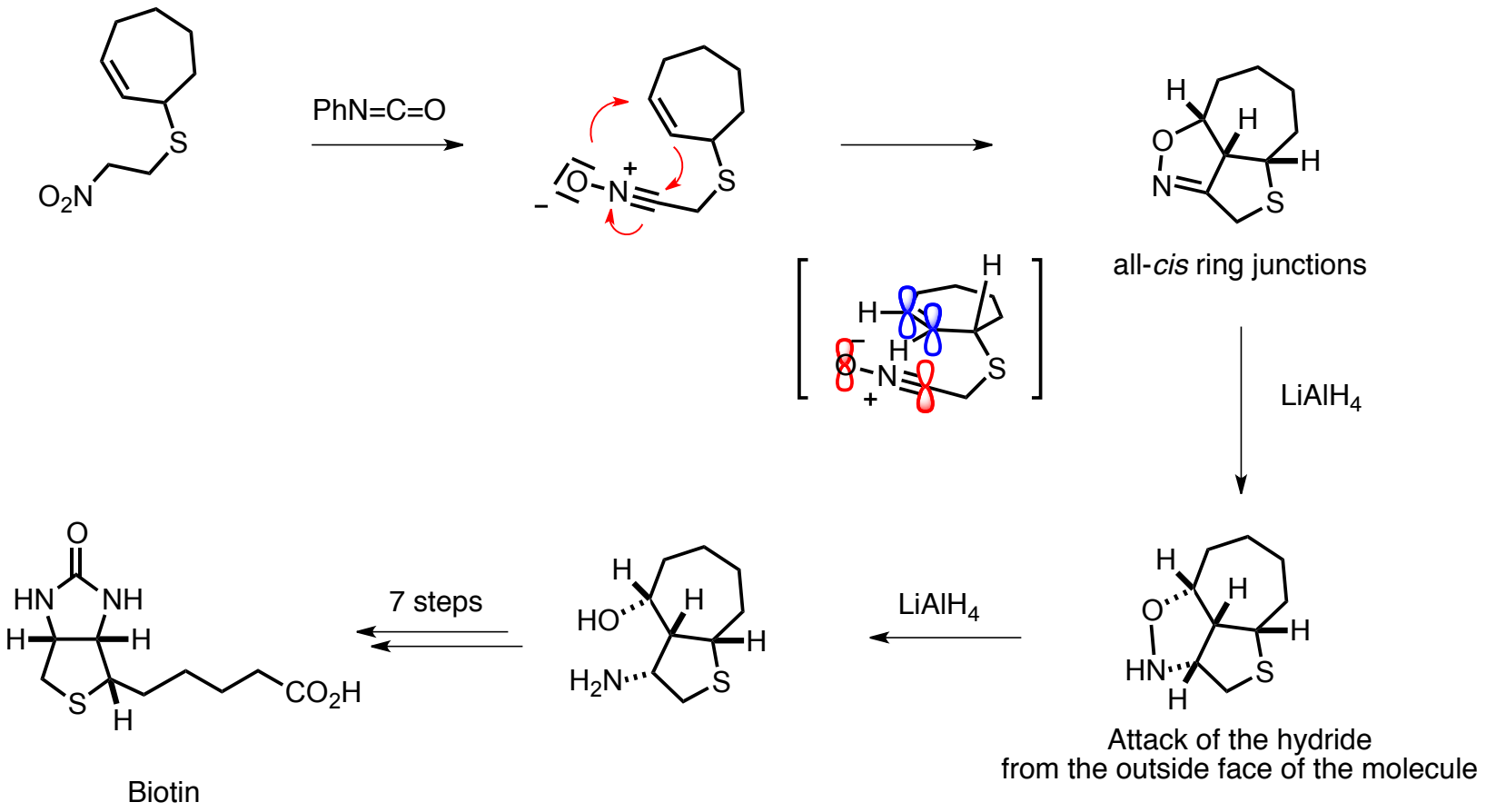


selective N-O reduction



1,3-dipolar cycloadditions with nitrile oxides

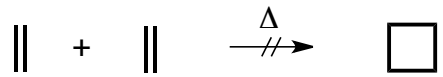
Application: intramolecular reaction in the synthesis of Biotin

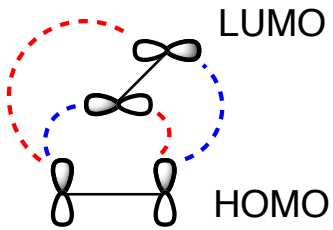


[2+2] thermal cycloaddition

Thermal [2+2] cycloadditions: generalities

- Reaction is not possible between two « classical » alkenes under simple heating



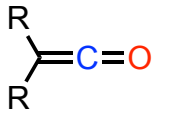


--- bonding interaction
--- antibonding interaction

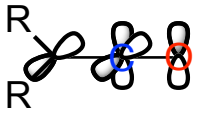
2 bonding interactions, 2 antibonding interactions = no reaction

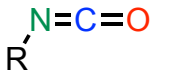
Thermal [2+2] cycloadditions: generalities

- Reaction possible with peculiar alkenes possessing 2 double bonds on the same carbon

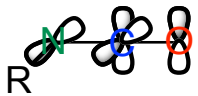


ketene

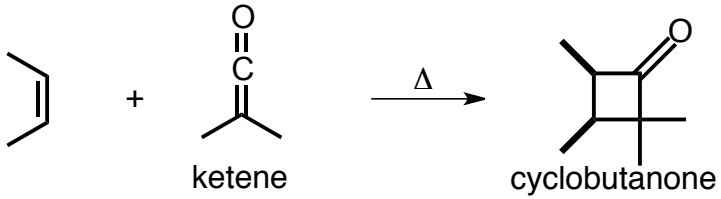




isocyanate

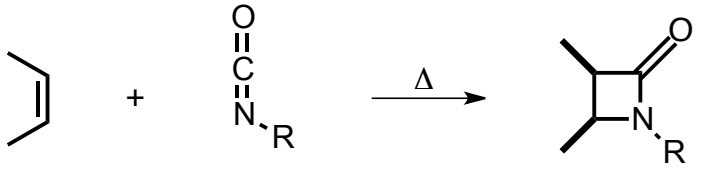


2 π bonds at 90 °



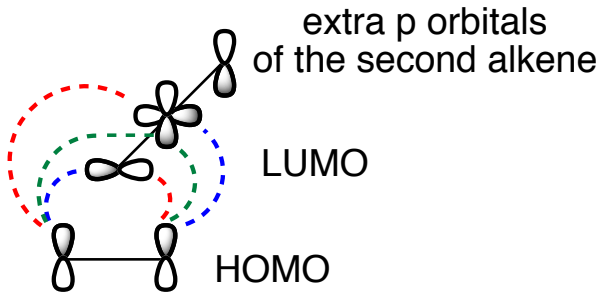
ketene

cyclobutanone



isocyanate

β-lactam



--- bonding interaction

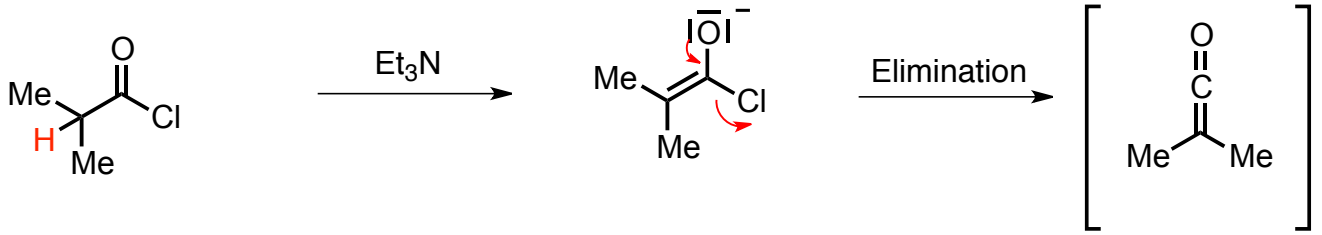
--- extra-bonding interaction

--- antibonding interaction

Additional presence of the p orbital of the second alkene offers 2 extra-bonding interactions, making the reaction possible.

Cyclobutanone synthesis – formation of ketenes

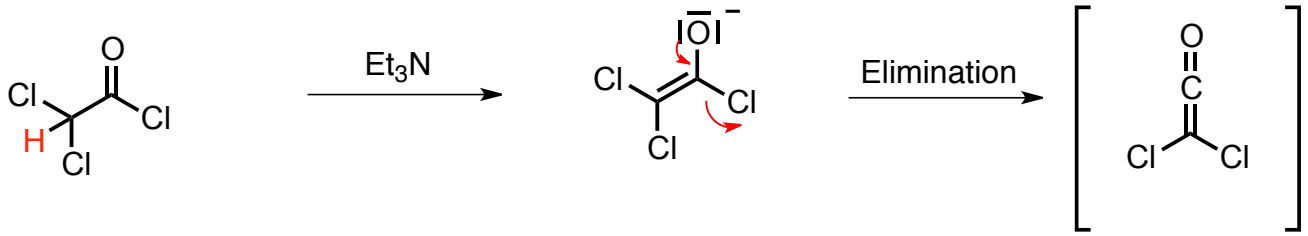
- From acyl chloride



Acidic proton

ketene

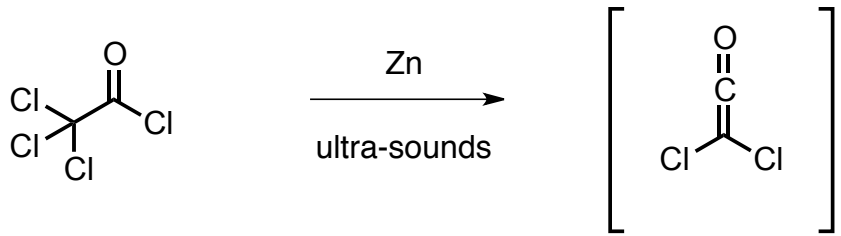
- From dichloroacetyl chloride



Very acidic proton

dichloroketene

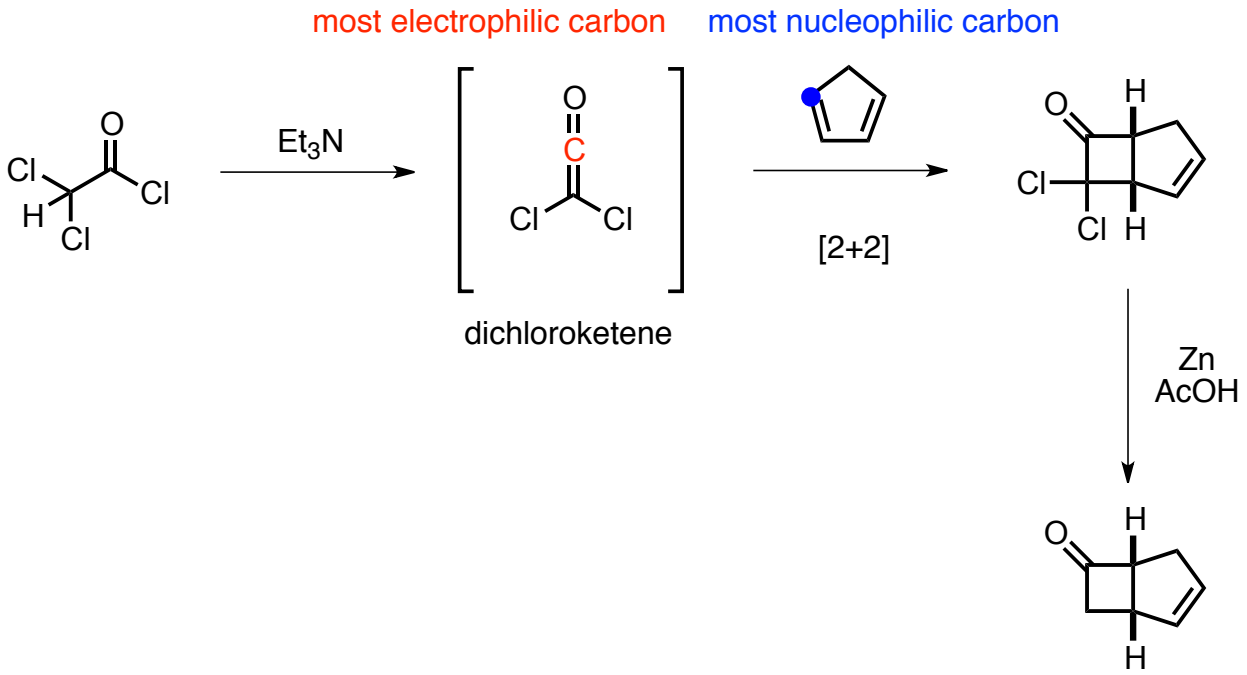
- From trichloroacetyl chloride



dichloroketene

Ketenes are generated *in situ*, risk of dimerization.

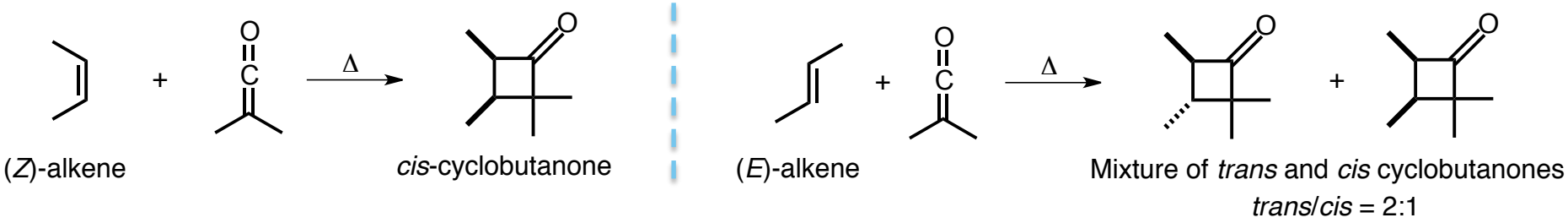
Cyclobutanone synthesis – Regioselectivity



- The most nucleophilic carbon of the alkene adds on the most electrophilic carbon of the ketene (regioselectivity).
- The two chloride atoms can be removed by reduction using Zn in AcOH.

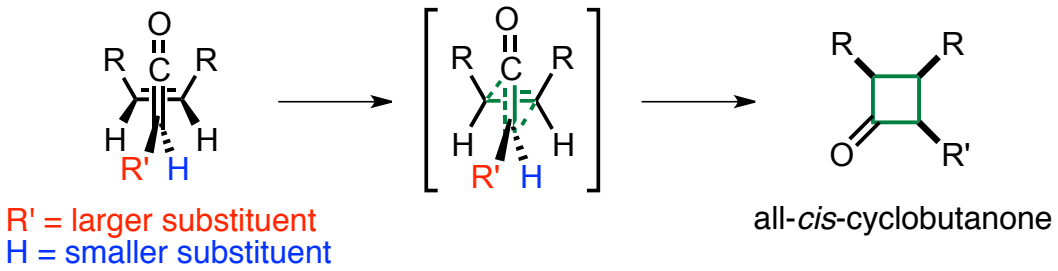
Cyclobutanone synthesis – Diastereoselectivity

- Alkene geometry



- Exclusive formation of *cis*-cyclobutanone from (*Z*)-alkenes but mixture of diastreomers obtained starting from (*E*)-alkenes.
- Isomerization in favor of a stepwise mechanism.

- Unsymmetrical disubstituted ketenes

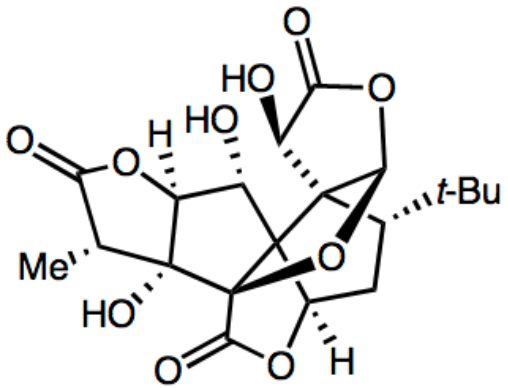


- Approach of ketene and alkene from the least hindered direction results in the formation of all-*cis* cyclobutanone.

Cyclobutanone synthesis – Application

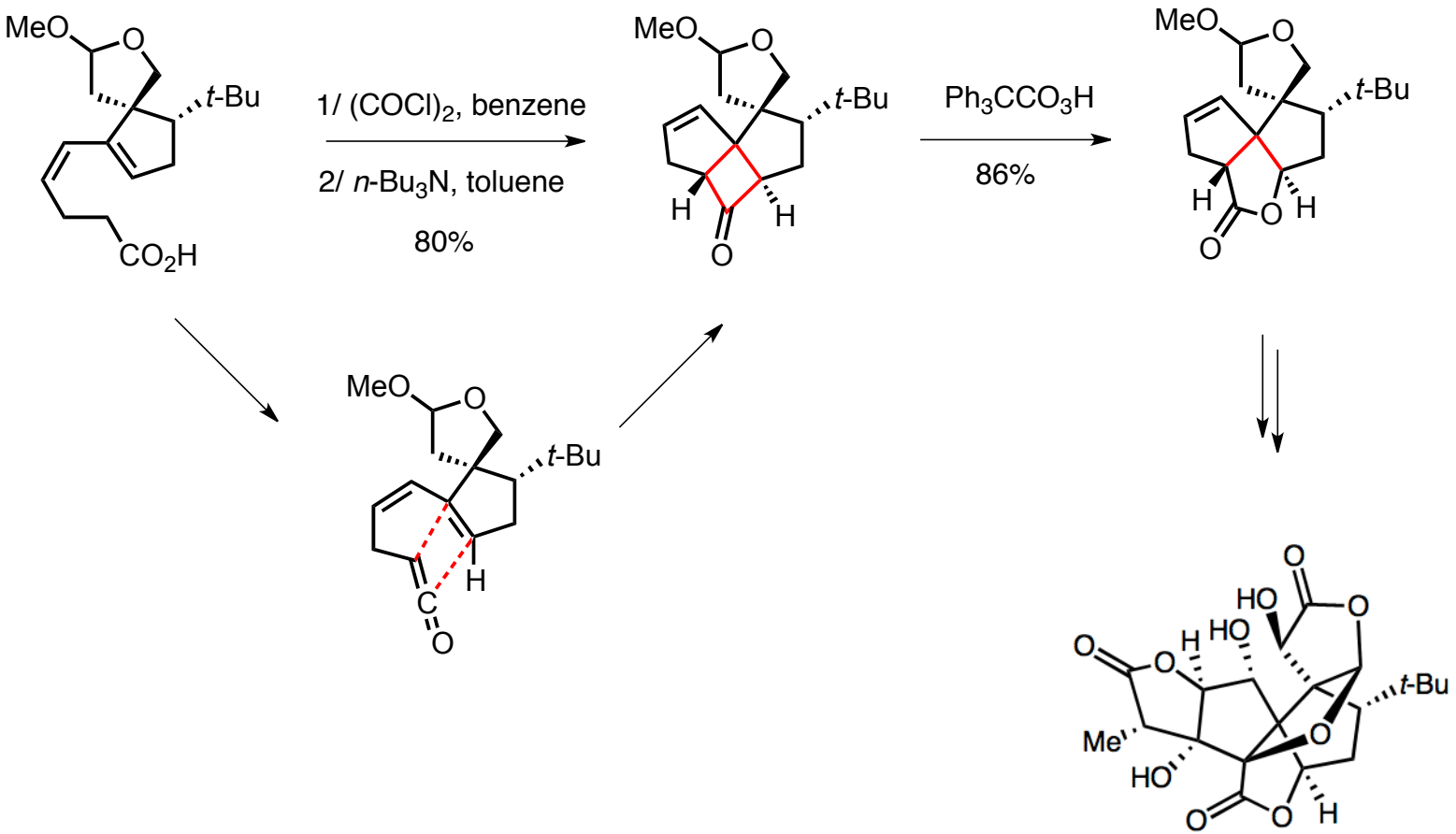
Total synthesis of Ginkgolide B

- Extracted from the root bark of Ginkgo biloba.
- Anti-inflammatory effect, improves blood circulation.
- Polycyclic molecules, cage structure, 11 stereogenic centers.
- Several total syntheses described, first one was reported by Corey et al. in 1988.



Cyclobutanone synthesis – Application

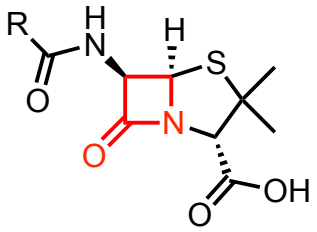
[2+2] ketene cycloaddition in the total synthesis of Ginkgolide B



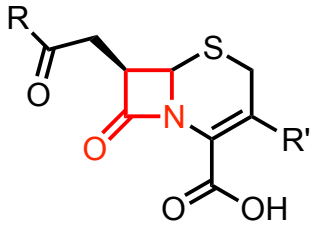
E. J. Corey *et al. J. Am. Chem. Soc.* **1988**, 110, 649.

Synthesis of β-lactams

β-lactams = key motif in a several antibiotics

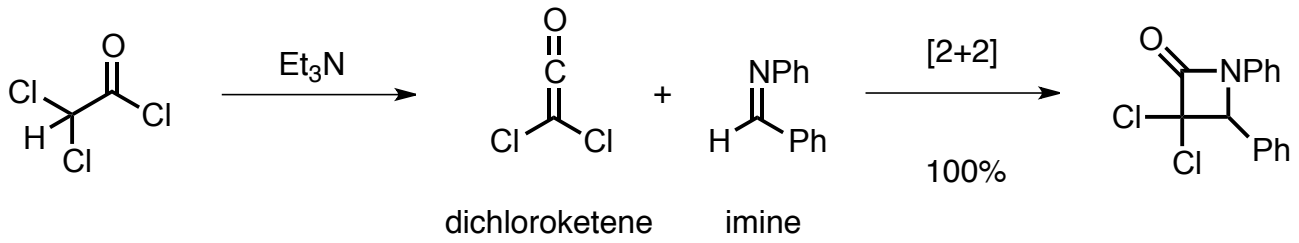


Core structure of penicillins

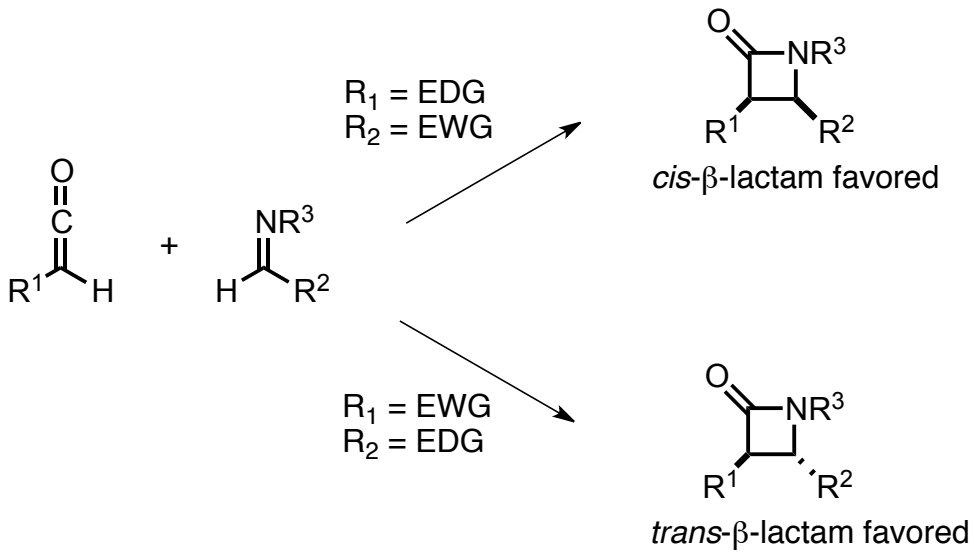


Core structure of cephalosporins

Synthesis of β-lactams – Staudinger synthesis

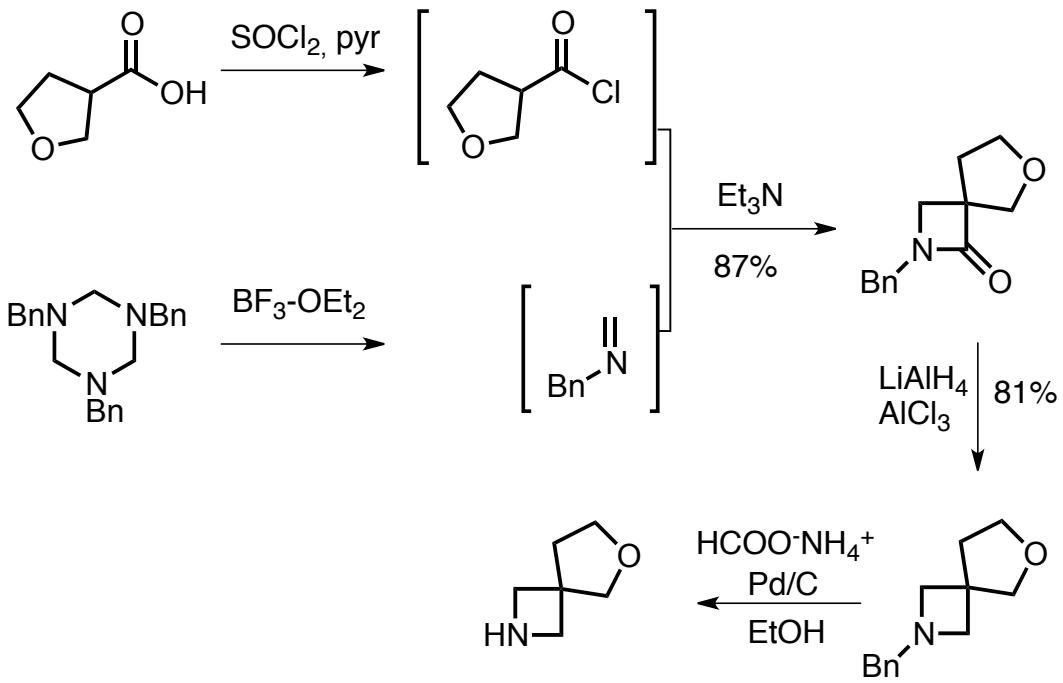


- Often with N-aryl imines (stability)
- Stepwise mechanism is generally proposed.
- Nucleophilic attack of the nitrogen to the C=O electrophilic carbon to form an iminium as the first step followed by ring closure by intramolecular addition of the enolate to the iminium
- When disubstituted unsymmetrical ketenes are used, diastereoselectivity depends on the nature of the substituents on ketene and imine (depends on the rate of the ring-closure).



Synthesis of β-lactams – Staudinger synthesis

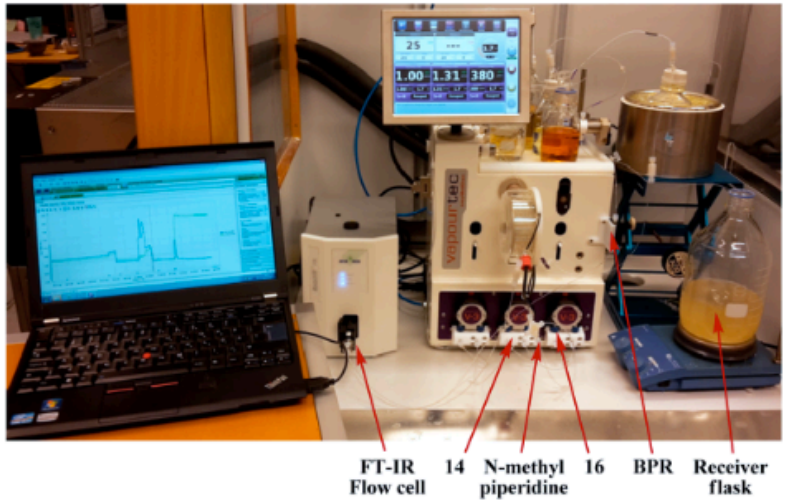
Synthesis of a spirocyclic pharmacophore
Classical batch method

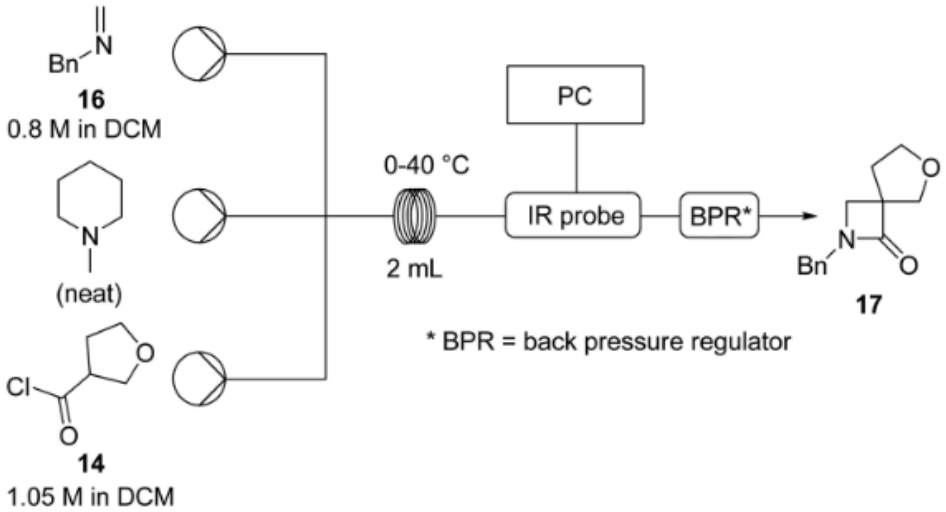


H. Sorensen *et al. Org. Process. Res. Dev.* **2015**, *19*, 2067.

Synthesis of β-lactams – Staudinger synthesis

Synthesis of a spirocyclic pharmacophore
Flow method



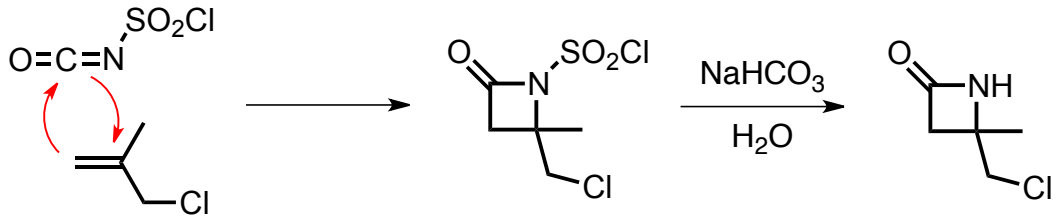


H. Sorensen *et al. Org. Process. Res. Dev.* **2015**, *19*, 2067.

Synthesis of β-lactams

- What about another disconnection?

- [2+2] cycloaddition between alkene and isocyanate also leads to β-lactams.
- As alkenes are not strong nucleophiles, a strong EWG is required on the N-isocyanate to reinforce its electrophilicity.
- R = SO_2Cl often used (commercial availability of the isocyanate, easy to remove after the cycloaddition).
- Mechanism is concerted with « neutral » alkenes: HOMO alkene / LUMO isocyanate interaction. Bond is formed between the terminal carbon of the alkene and the C=O carbon of the isocyanate)



- Stepwise mechanism favored with electron-rich alkenes such as enol ethers or enol thioethers.

ESPCI PARIS | PSL

ADVANCED SELECTIVE ORGANIC SYNTHESIS (ASOS)

Amandine GUERINOT
Assistant Professor - ESPCI Paris

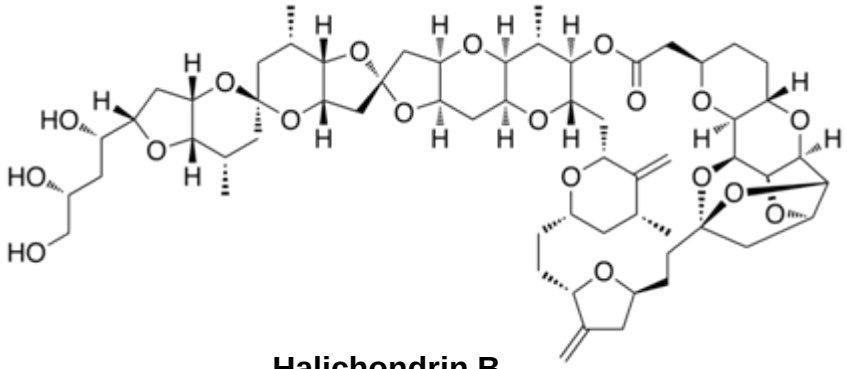
Christophe MEYER
Research Director - CNRS

Outline

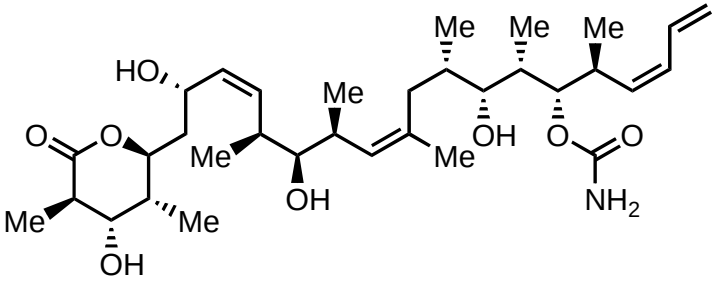
- Asymmetric synthesis of substituted carbonyl compounds (CM)
- Stereoselective aldol and allylation reactions (CM)
- Enantioselective oxidation reactions (AG)
- Enantioselective reduction reactions (CM)
- Pericyclic reactions (Sigmatropic rearrangements, cycloadditions) (CM, AG)
- Examples of total syntheses of bioactive compounds (AG, CM)

2019

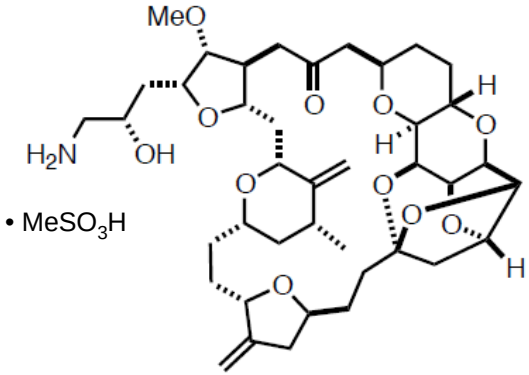
Challenges with structurally complex bioactive compounds



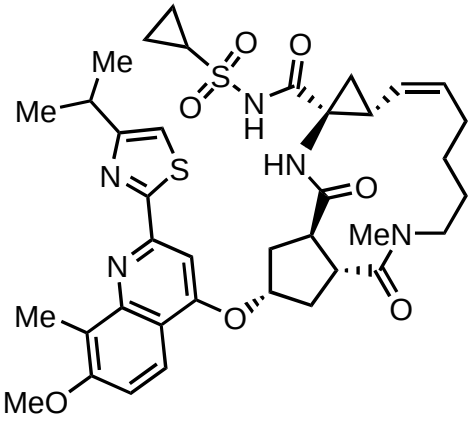
Halichondrin B
From extracts of a marine sponge (*Halichondria okadai*)
antitumor agent
Total synthesis: Kishi, Y. *et al. JACS* **1992**, *114*, 3162



Discodermolide
From extracts of a marine sponge (*Discodermia dissoluta*)
Immunosuppresant, antitumor agent
(60 g produced by total synthesis – Novartis)
Clinical trials stopped (pneumotoxicity)



Eribulin mesylate (Halaven®)
A simplified analog of halichondrin B produced by total synthesis (62 steps!)
Anticancer agent (breast cancer, liposarcome)



Simeprevir (Olysio®)
Inhibitor of hepatitis C virus NS3/4A protease

Structural complexity
Multiple functional groups
Multiple stereocenters

⇌

Efficient and selective synthetic tools

Regioselectivity

A regioselective reaction is one in which one direction of bond making or breaking occurs preferentially over all other possible directions

IUPAC definitions (http://goldbook.iupac.org)

Chemoselectivity

Chemoselectivity is the preferential reaction of a chemical reagent with one of two or more different functional groups

IUPAC definitions (http://goldbook.iupac.org)

Stereoselectivity

The preferential formation in a chemical reaction of one stereoisomer over another.

When the stereoisomers are **enantiomers**, the phenomenon is called **enantioselectivity**.

When they are diastereoisomers (**diastereomers**), it is called **diastereoselectivity**.

Enantioselective reaction : from an **achiral substrate**
Diastereoselective reaction: **introduces one (or more) new stereocenter(s)**

A process is termed **stereospecific** if starting materials differing only in their configuration are converted into stereoisomeric products

IUPAC definitions (http://goldbook.iupac.org)

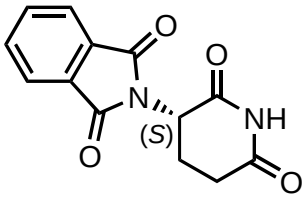
Chiral drugs: Importance of enantioenriched compounds

The asymmetry of bio(macro)molecules allows for a differentiation between the enantiomers of a substrate:

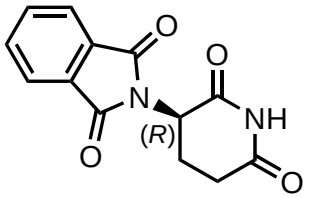
Enantiomers have different affinities at receptor sites, rates of metabolism (and metabolic pathways) and pharmacokinetic properties

The tragedy of thalidomid

Thalidomid was sold as a racemate
Thalidomid racemizes *in vivo* anyway



Sedative, hypnotic
(used to alleviate morning sickness for pregnant women)



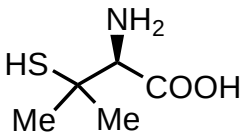
Teratogenic action
(by inhibition of angiogenesis)

Chiral drugs (50%) are not always marketed as “enantiopure” compounds but the biological properties of enantiomers (or stereoisomers if appropriate) has to be carefully evaluated

In recent years, most chiral drugs approved (by the FDA) were produced as enantiomerically pure compounds

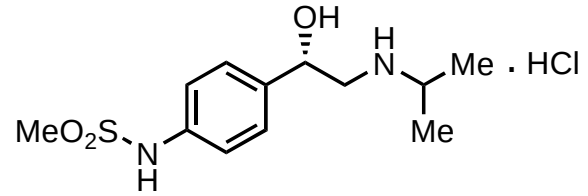
Some drugs previously sold as racemates are also developed as *de novo* enantiomerically pure compounds

Examples of chiral drugs



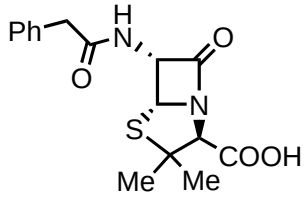
D-Penicillamine

(chelating agent used to treat Wilson's disease – Cu^{2+})
The (*S*) enantiomer is toxic (optic neuritis)

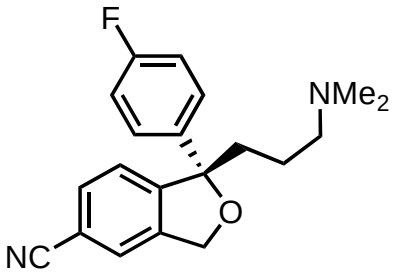


Sotalol

(*S*) and (*R*) enantiomers both have antiarythmic activity
but only the (*S*) acts as a β-adrenergic antagonist

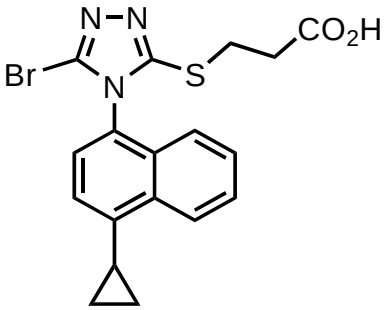


Penicillin G



Escitaprolam

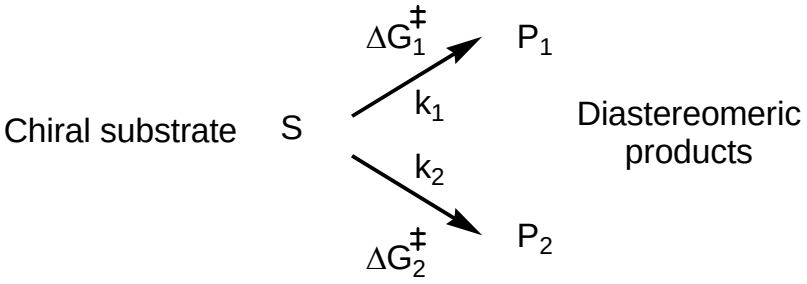
(used for treating depression, obsessive/compulsive disorders)
reformulated as a single enantiomer since 2014 (fewer side effects claimed)



Lesinurad

(used for gout treatment)
marketed as a racemate

Diastereoselective synthesis

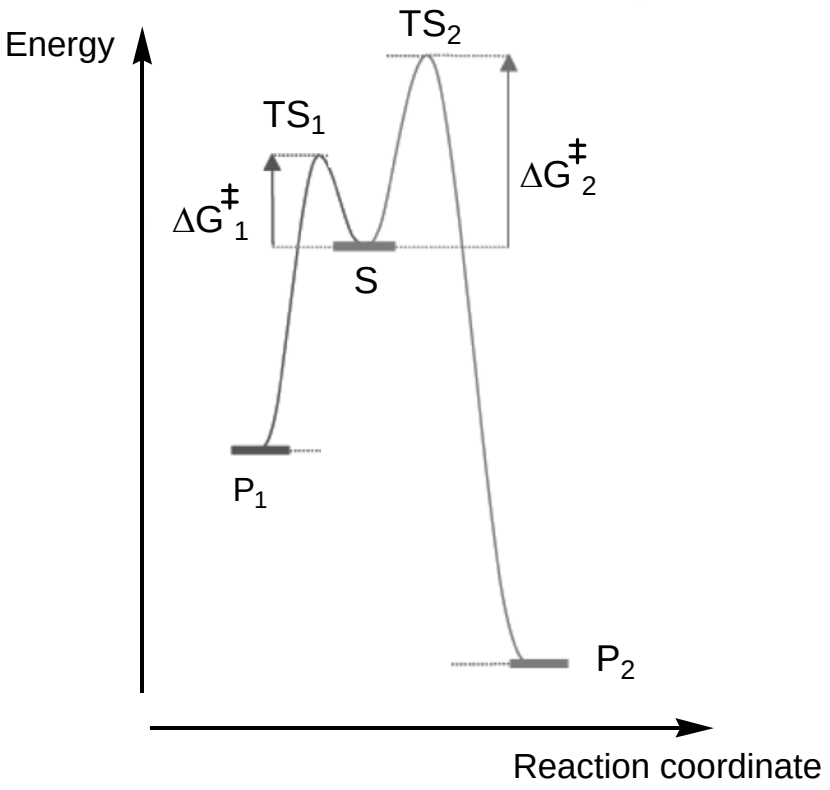


Eyring equation $k = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$

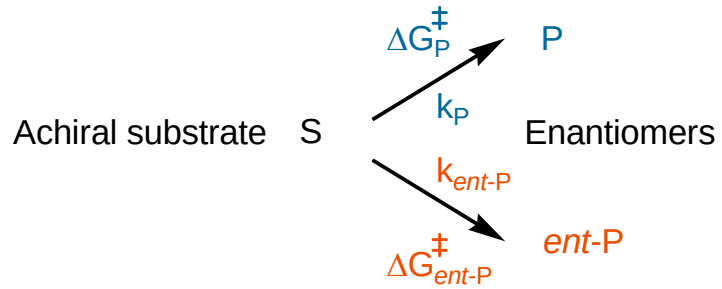
Diastereomeric transition states TS1 and TS2

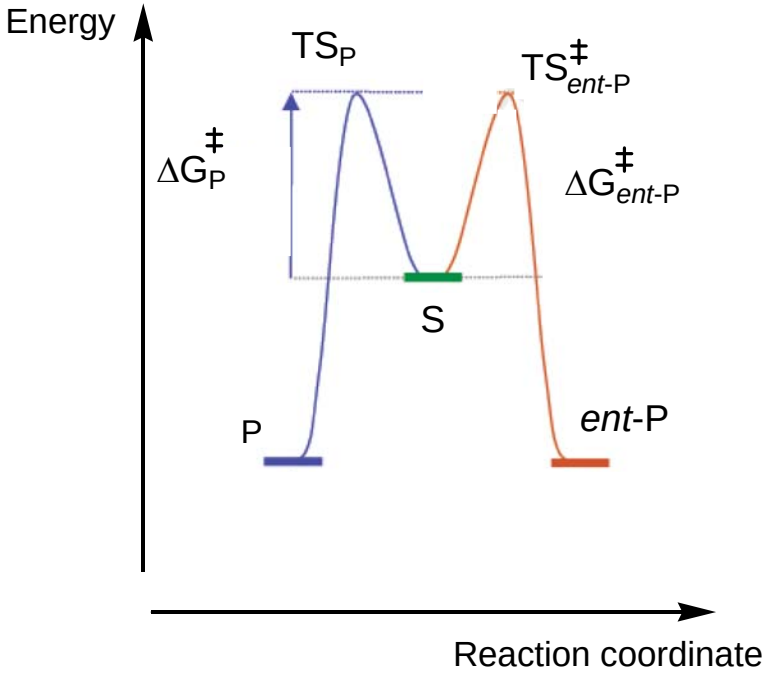
Under kinetic control (assuming first order reaction) the selectivity factor depends on $\Delta(\Delta G^{\ddagger})$

$s = [P_1]/[P_2] = \exp(-(\Delta G^{\ddagger}_1 - \Delta G^{\ddagger}_2)/RT)$



Enantioselective synthesis



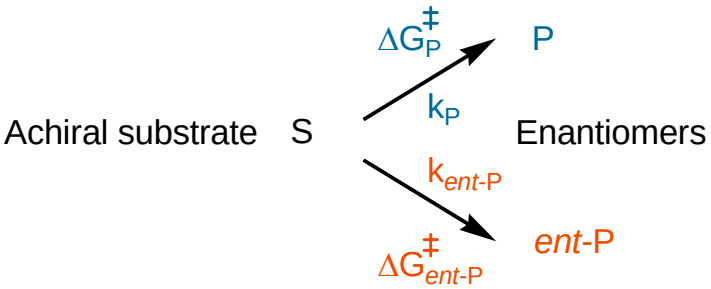


With **achiral reagents** -> **enantiomeric transition states**

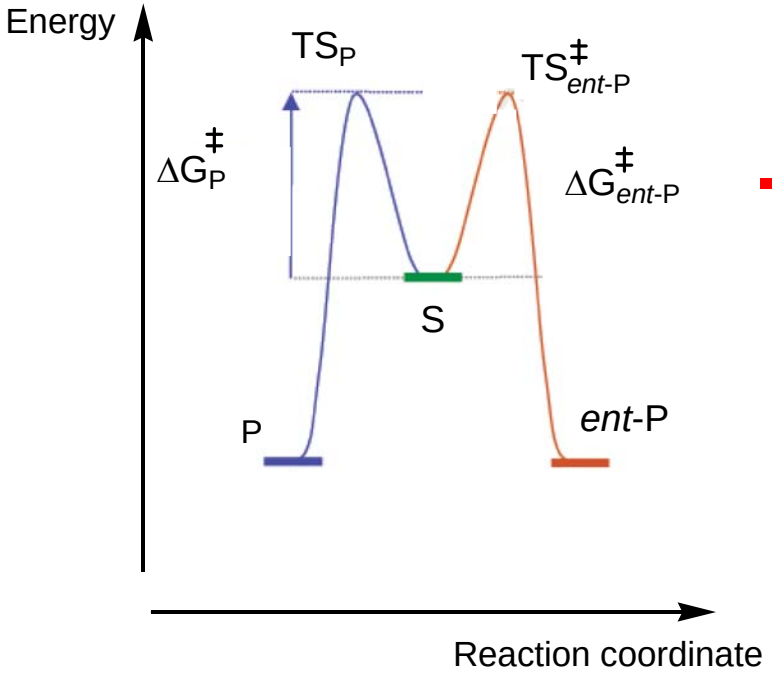
P and *ent*-P are formed at the same rate ($k_P = k_{ent\text{-}P}$)

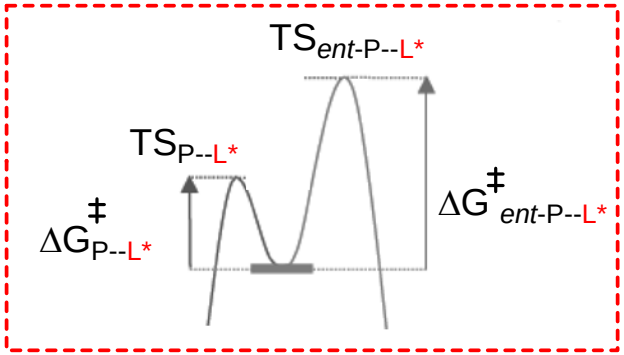
The racemate is obtained

Enantioselective synthesis



Enantioselective synthesis *requires a* ***source of asymmetry*** *(chiral reagent/catalyst : L*) to generate* ***diastereomeric transition states***





P and *ent*-P not formed at the same rate

[P] > [ent-P]

Enantiomeric ratio

$$er = \frac{[P]}{[ent\text{-}P]}$$

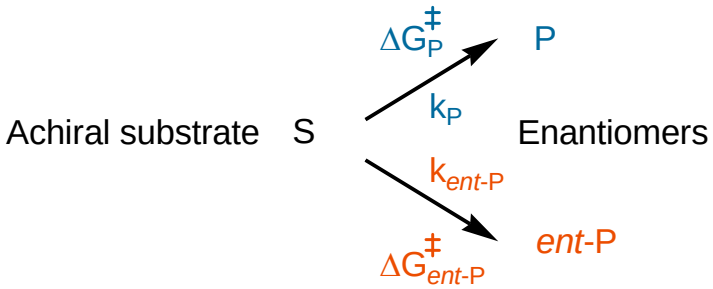
er = 90:10

Enantiomeric excess

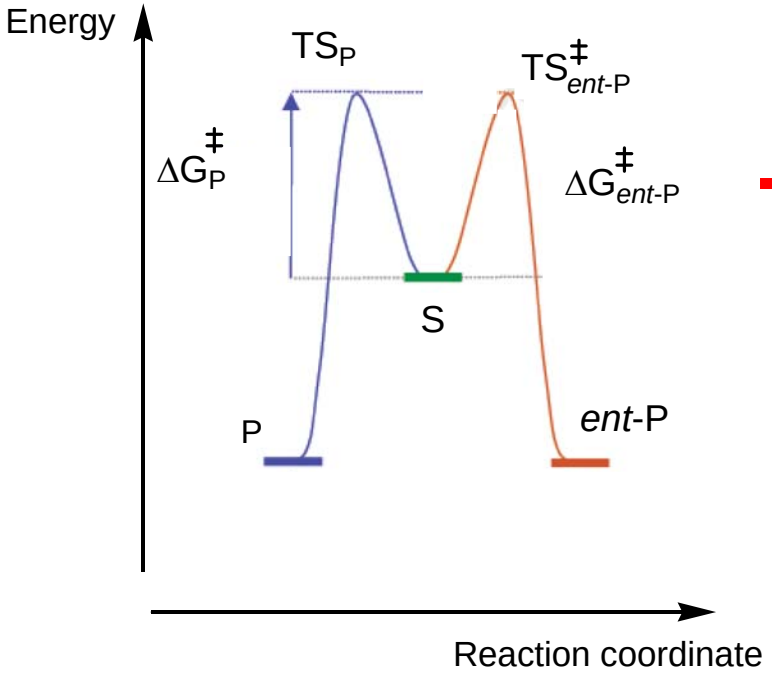
$$ee\ (\%) = \frac{|[P]-[ent\text{-}P]|}{[P]+[ent\text{-}P]} \times 100$$

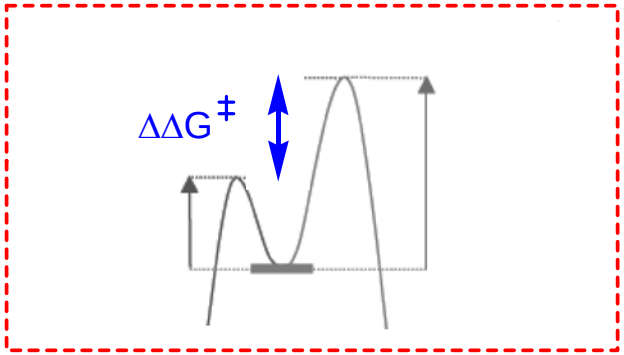
ee = 80%

Enantioselective synthesis



Enantioselective synthesis *requires a* ***source of asymmetry*** *(chiral reagent/catalyst : L*) to generate* ***diastereomeric transition states***





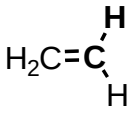
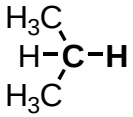
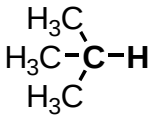
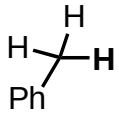
$\Delta(\Delta G^{\ddagger})$ (kcal/mol)	Product ratio*
0	50:50
0.5	70:30
1.0	85:15
1.5	93:7
2.0	97:3
3.0	99.5:0.5

*at 293K (20 °C)

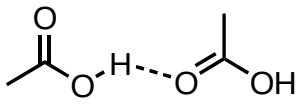
← at -20 °C, 73:27
at -80 °C, 79:21

Typical energy values

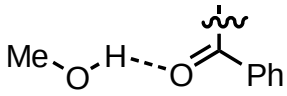
Bond dissociation energies (kcal/mol)

$HC{\equiv}CH$	(231)	$HC{\equiv}C{-}H$	(133)
$C{\equiv}N$	(213)		(110)
$H_2C{=}CH_2$	(174)		
$C{=}O$	(179)	$Ph{-}H$	(108)
$C{=}N$	(147)	$H_3C{-}H$	(104)
$H_3C{-}F$	(108)	$CH_3CH_2{-}H$	(101)
$H_3C{-}OH$	(91)		(99)
$H_3C{-}CH_3$	(90)		
$H_3C{-}NH_2$	(87)		(96)
$H_3C{-}Cl$	(84)		
$H_3C{-}Br$	(70)		(85)
$H_3C{-}I$	(56)		

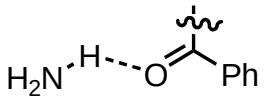
Hydrogen bonding (wide range of energies 0.2-40 kcal/mol)



(7.4)



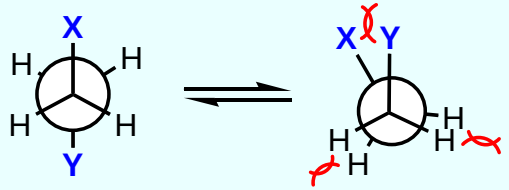
(3.2)

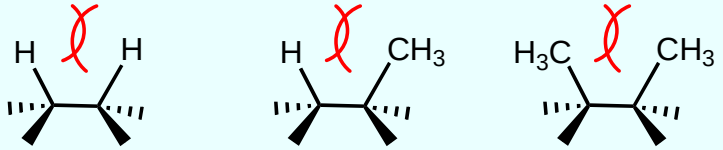


(2.2)

Steric interactions

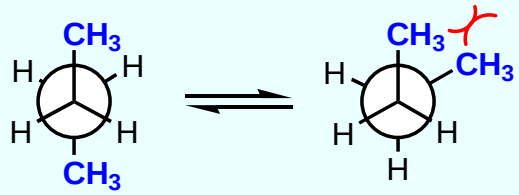
Eclipsing interactions





(1.0) (1.4) (3.1)

Gauche interaction

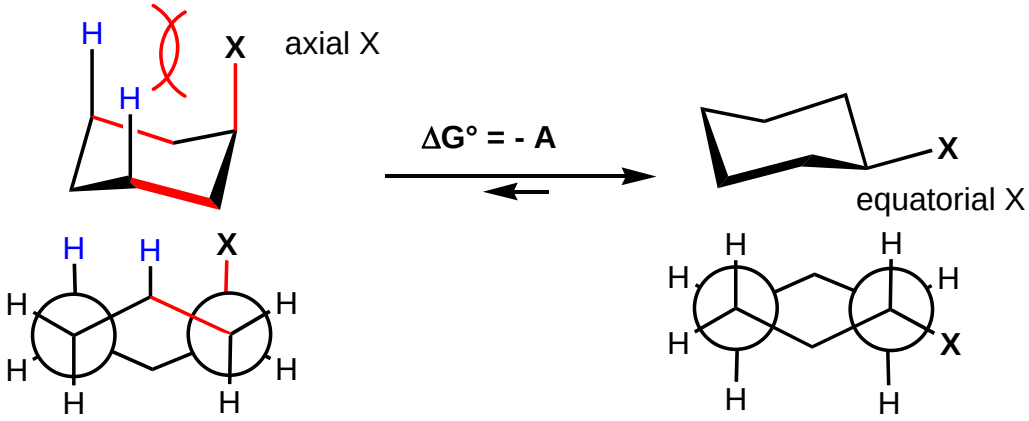


(0.0) (0.9)

(in kcal/mol)

Typical energy values

Steric interactions

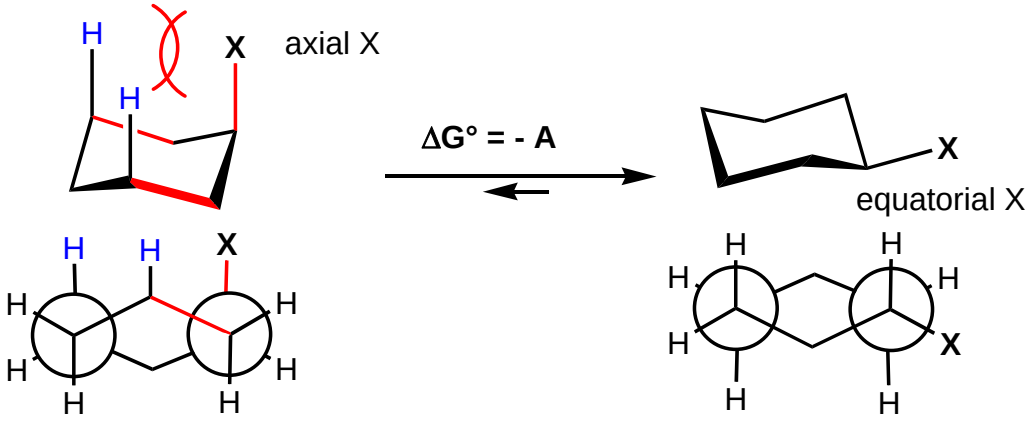


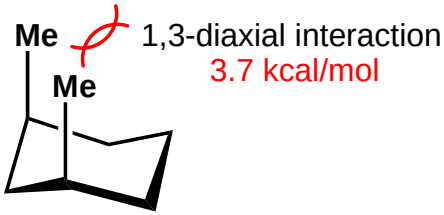
A values (Eliel values)

X	A (kcal/mol)
CN	0.20
F	0.25
C≡C−H	0.41
Cl	0.50
OMe	0.75
COOEt	1.1
NO_2	1.1
$HC{=}CH_2$	1.7
Me	1.8
Et	1.9
*i*Pr	2.1
SO_2Ph	2.5
Ph	3.0
t-Bu	5.0

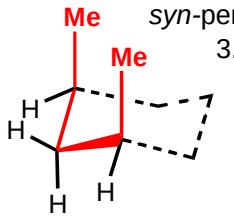
Typical energy values

Steric interactions





1,3-diaxial interaction
3.7 kcal/mol



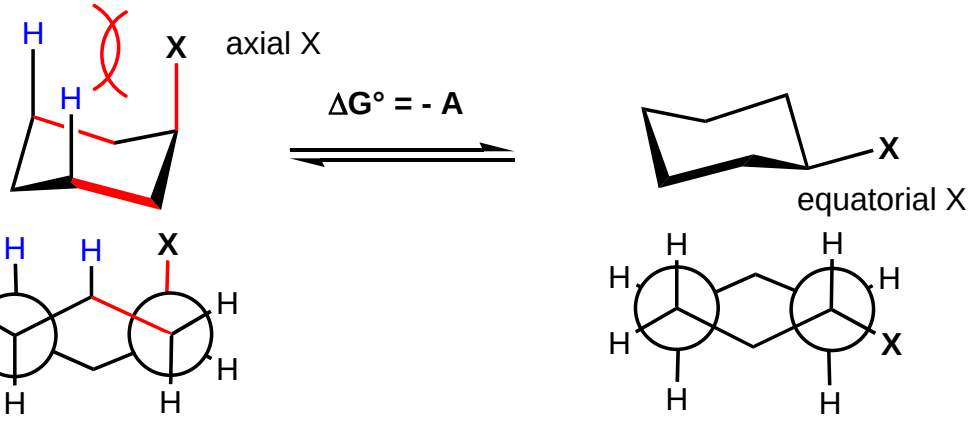
syn-pentane interaction
3.7 kcal/mol

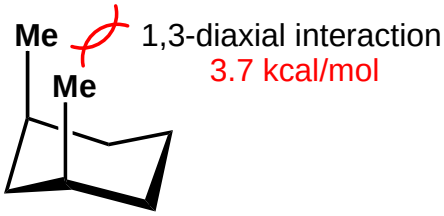
A values (Eliel values)

X	A (kcal/mol)
CN	0.20
F	0.25
C≡C−H	0.41
Cl	0.50
OMe	0.75
COOEt	1.1
NO_2	1.1
HC=CH_2	1.7
Me	1.8
Et	1.9
*i*Pr	2.1
SO_2Ph	2.5
Ph	3.0
t-Bu	5.0

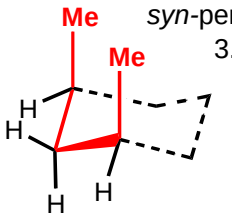
Typical energy values

Steric interactions



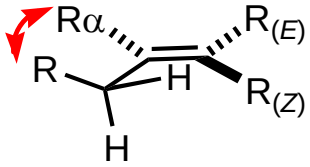


1,3-diaxial interaction
3.7 kcal/mol



syn-pentane interaction
3.7 kcal/mol

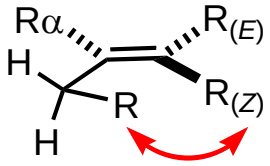
Allylic strain



Allylic 1,2-strain ($A^{1,2}$)

If R = Me and R_α = Me

3.0 kcal/mol



Allylic 1,3-strain ($A^{1,3}$)

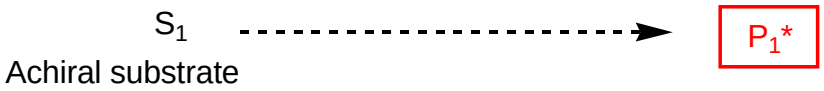
If R = Me and $R_{(Z)}$ = Me

3.9 kcal/mol

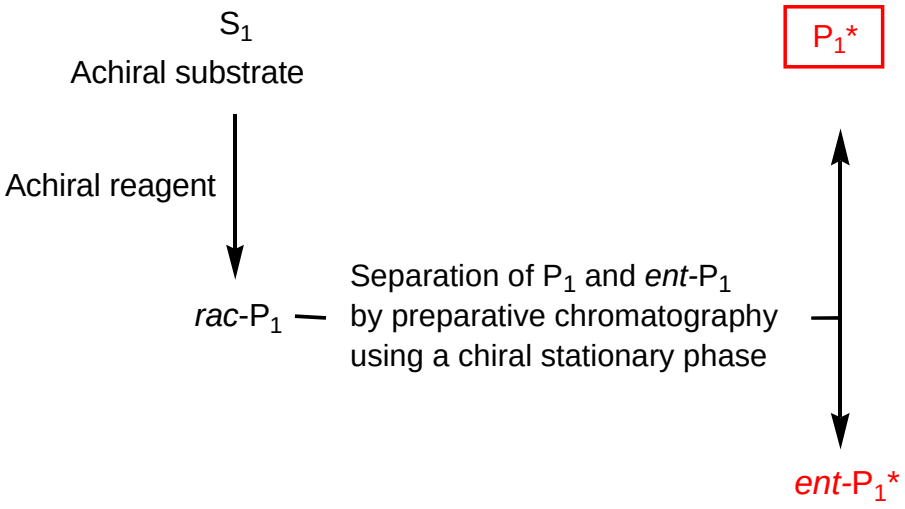
A values (Eliel values)

X	A (kcal/mol)
CN	0.20
F	0.25
C≡C−H	0.41
Cl	0.50
OMe	0.75
COOEt	1.1
NO_2	1.1
$HC{=}CH_2$	1.7
Me	1.8
Et	1.9
*i*Pr	2.1
SO_2Ph	2.5
Ph	3.0
t-Bu	5.0

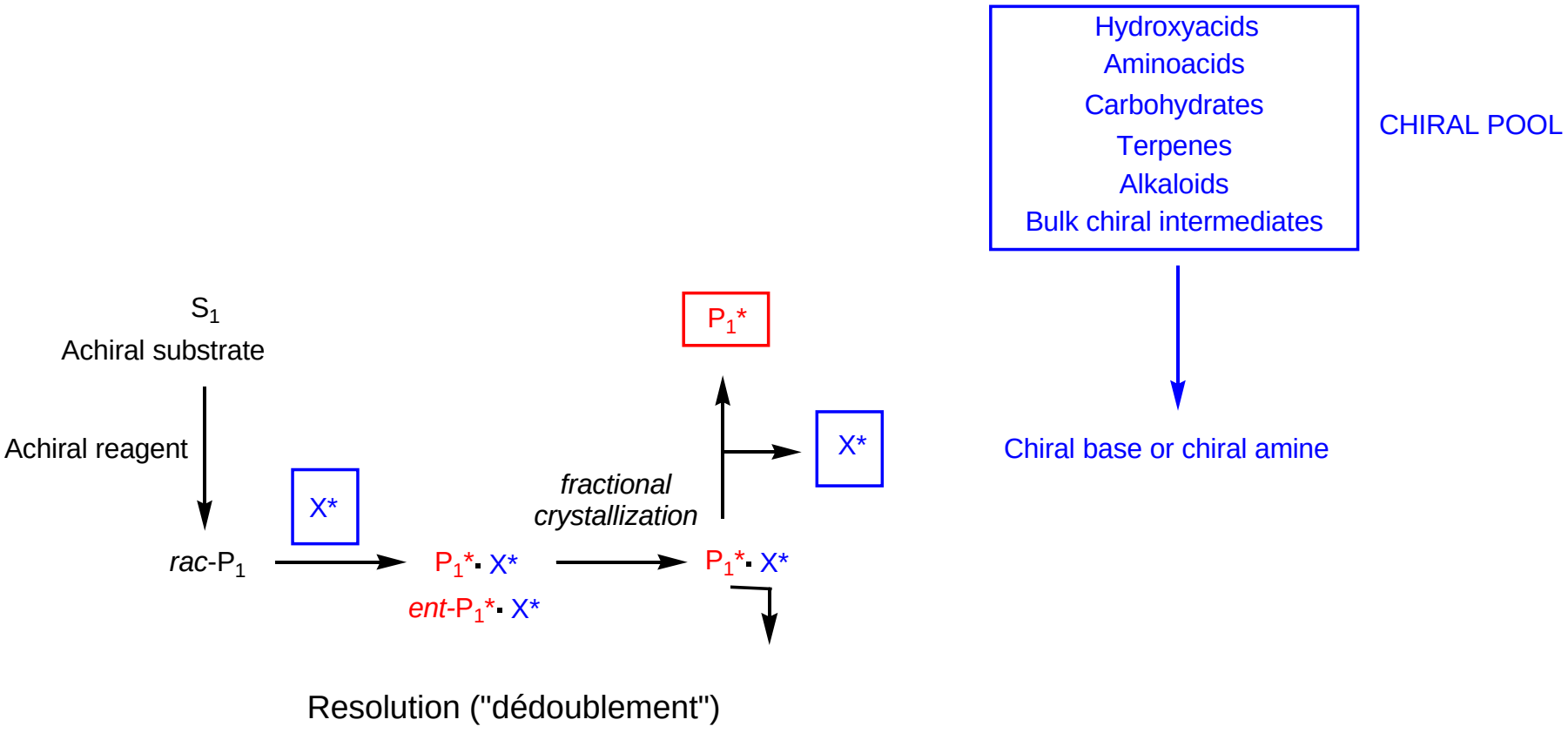
Access to enantioenriched compounds



Access to enantioenriched compounds

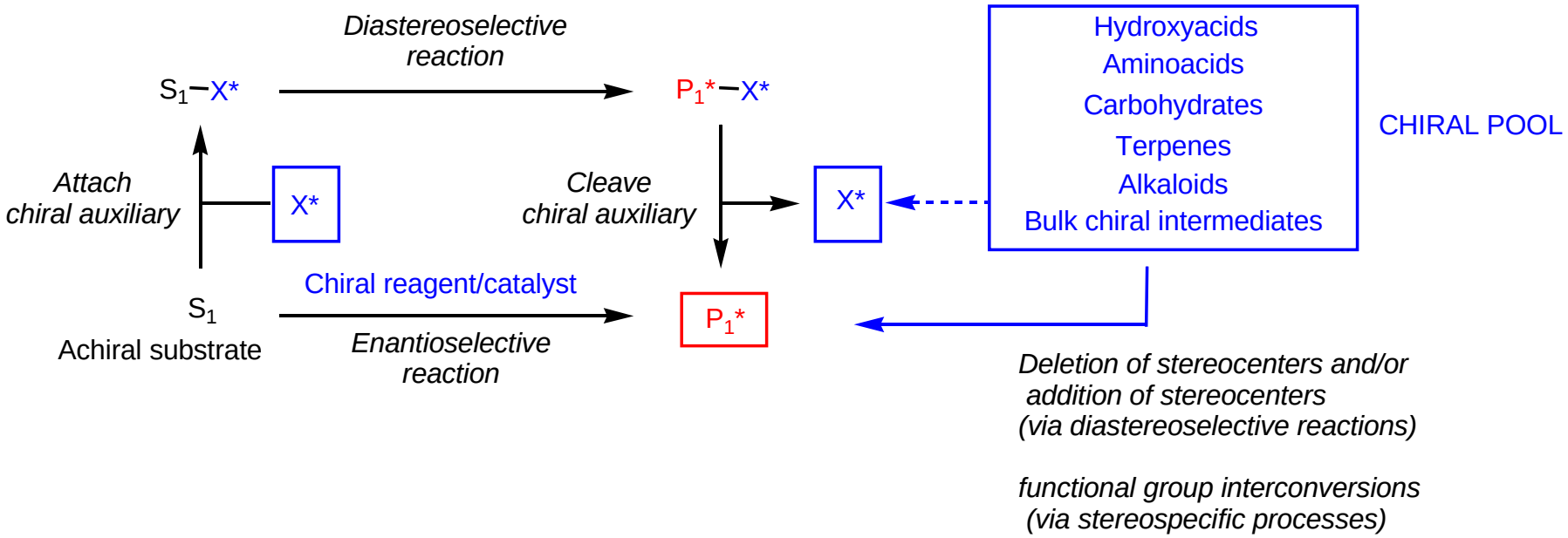


Access to enantioenriched compounds

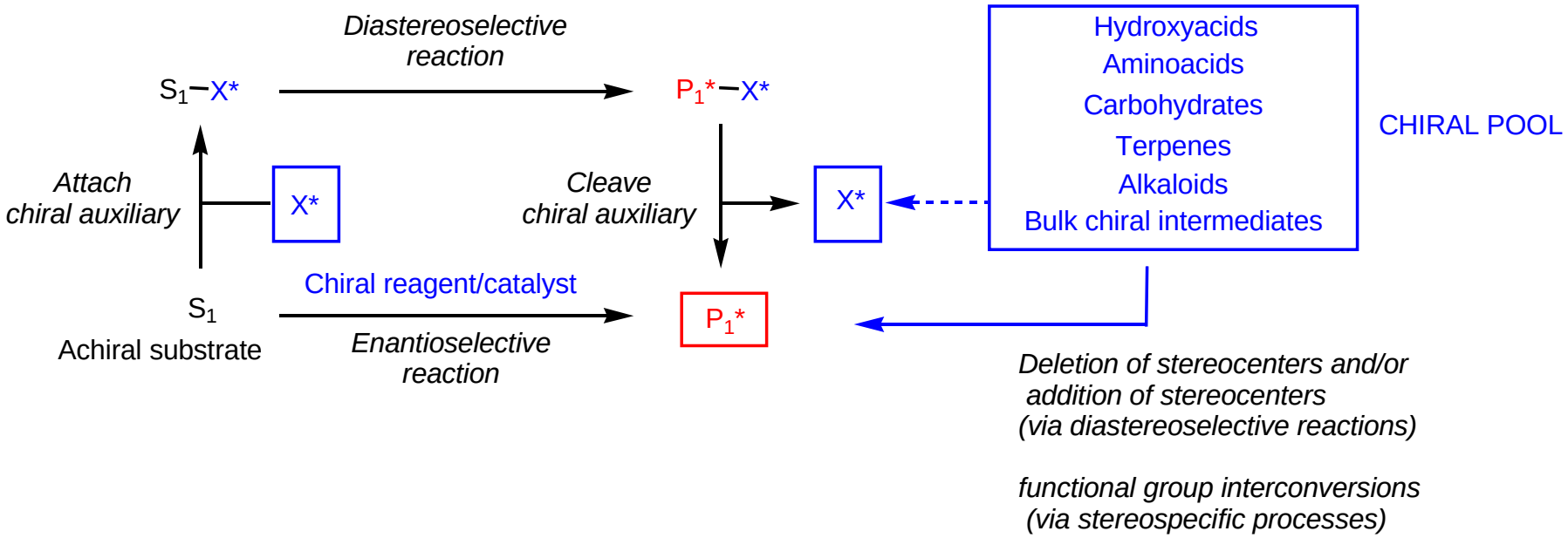


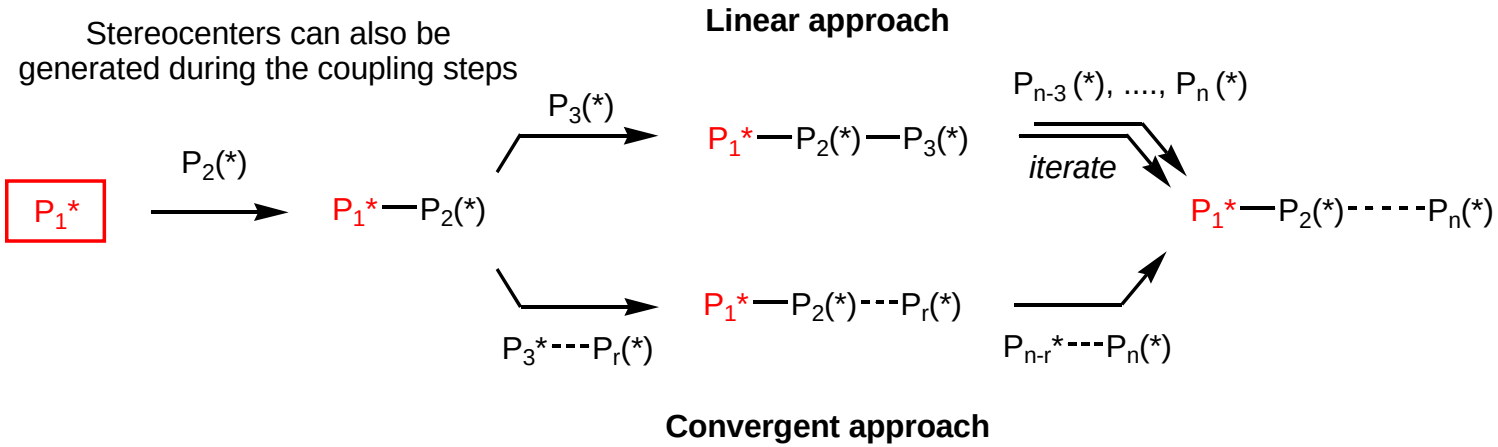
Resolution ("dédoublement")

Asymmetric synthesis



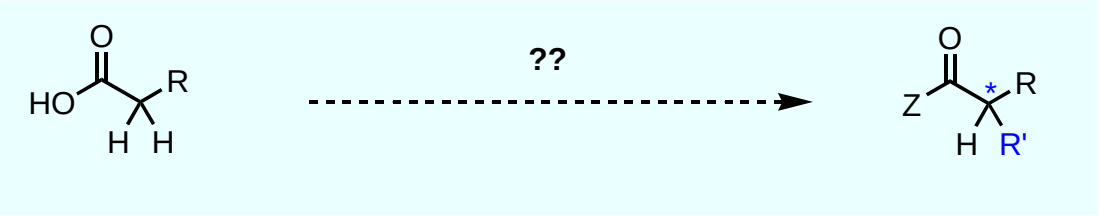
Asymmetric (multi-step) synthesis





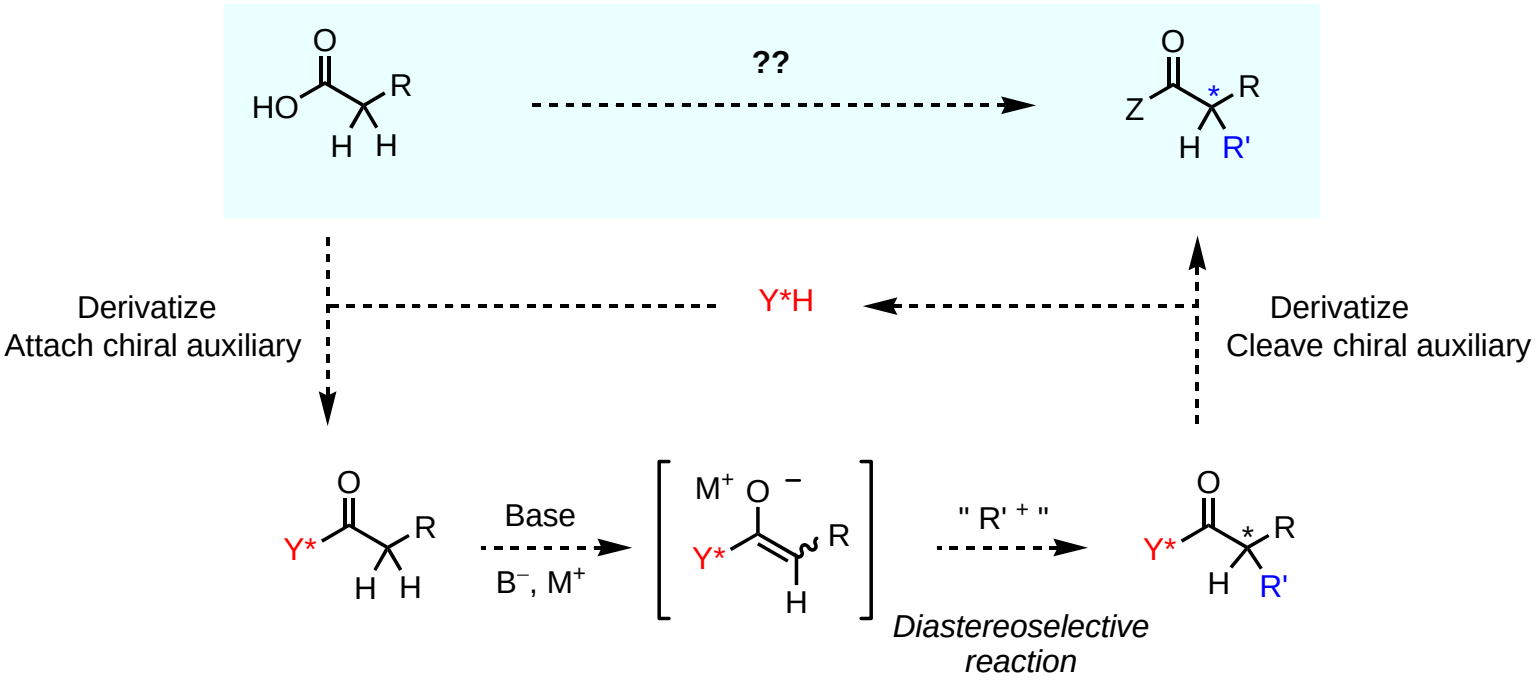
Synthesis of chiral α-substituted carbonyl compounds

Problem



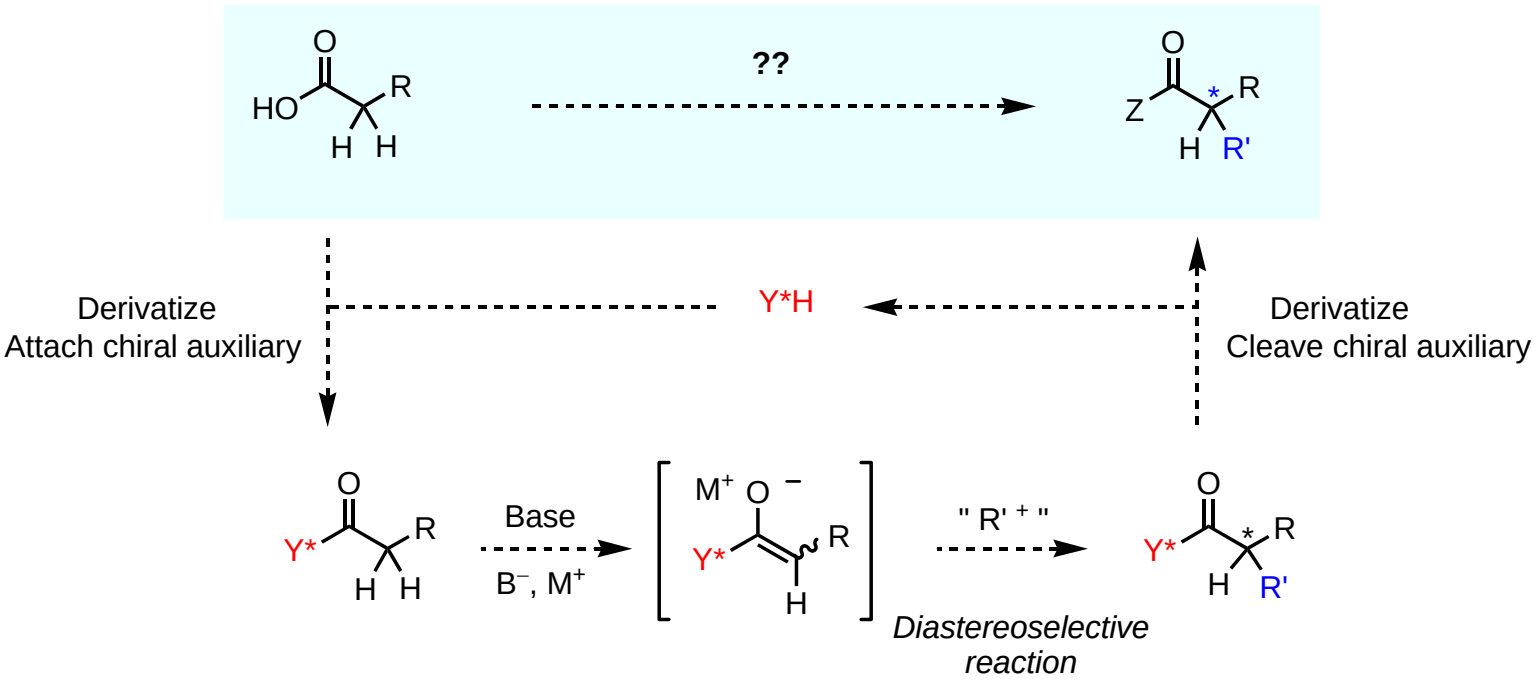
Synthesis of chiral α-substituted carbonyl compounds

Problem



Synthesis of chiral α-substituted carbonyl compounds

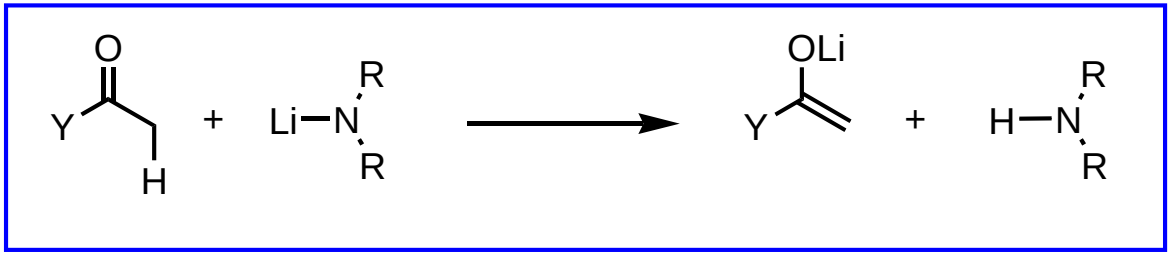
Problem



Issues

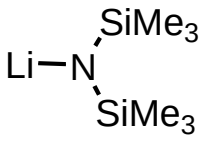
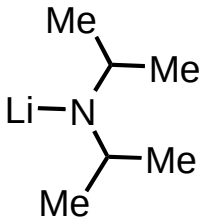
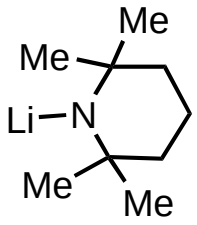
- Which type of derivative should we form ?
- Choice of chiral auxiliary (accessibility, structural features) ?
- How can we generate the enolate and control its configuration ?
- Regioselectivity of electrophilic trapping ?
- Control of the diastereoselectivity ?
- Cleavage of the auxiliary (derivatization reactions) ?
- Racemization of the product ?

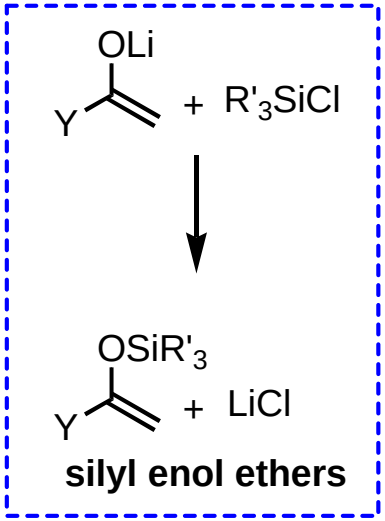
Enolization of carbonyl compounds with amide bases



"Hard enolization" with lithium amide bases

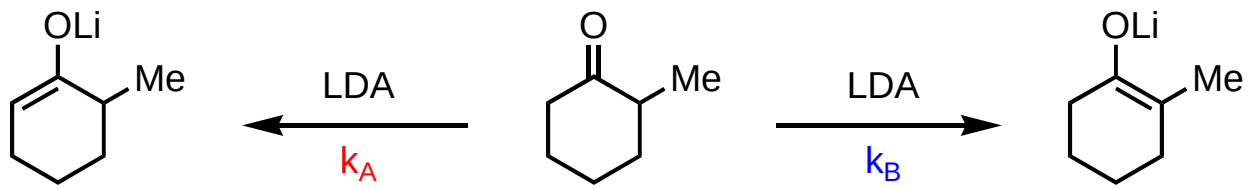
Y	Me	O*t*-Bu	NEt_2
pKa	**19-20** (H_2O) 26.5 (DMSO)	**24.5** (H_2O) 30.3 (DMSO)	**30** (H_2O) 35 (DMSO)

			
	LiHMDS	**LDA**	**LiTMP**
pKa	**26** (THF) 30 (DMSO)	**36** (THF)	37 (DMSO)



Stable and isolable enolate equivalents

Regioselective enolization with amide bases

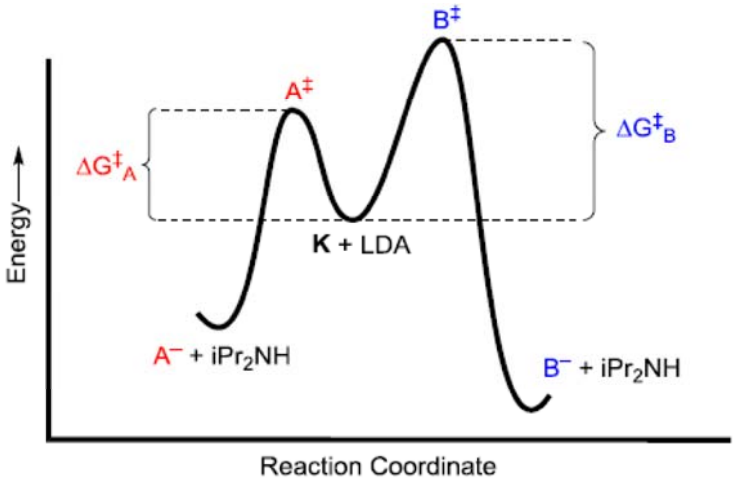


Enolate A^-
Kinetic enolate

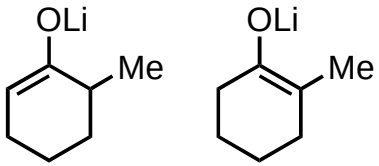
Differences in the rate of proton removal by the base $k_A > k_B$

Enolate B^-
Thermodynamic enolate

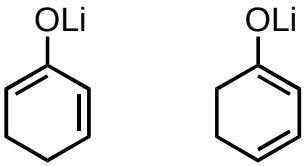
Regioselective deprotonation under non-equilibrating conditions



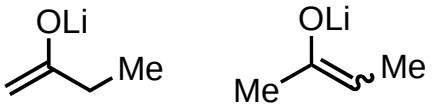
Kinetic/thermodynamic enolates



(Kin) 99:1
(Th) 10:90

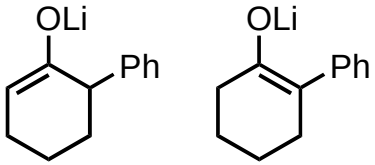


(Kin) 99:1

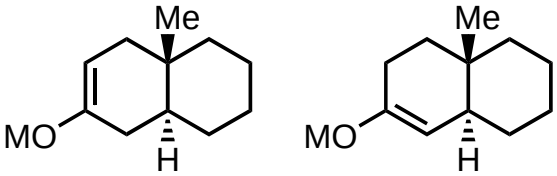


(Kin) 71:29

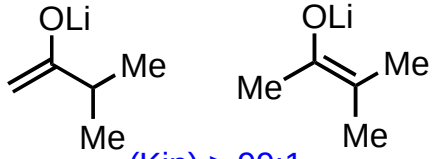
(Kin) 84:16
(Th) 13:87



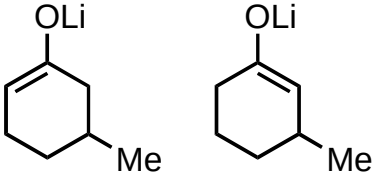
(Kin) 99:1



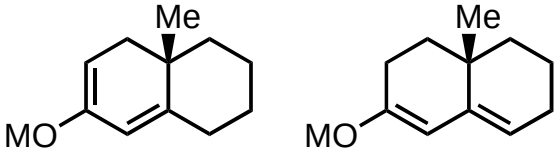
(M = Li) (Kin) 87:13
(M = K) (Th) 47:53
(*t*-BuOK/*t*-BuOH)



(Kin) > 99:1

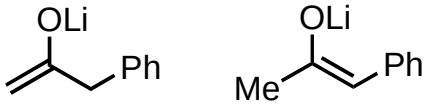


(Kin) 90:10



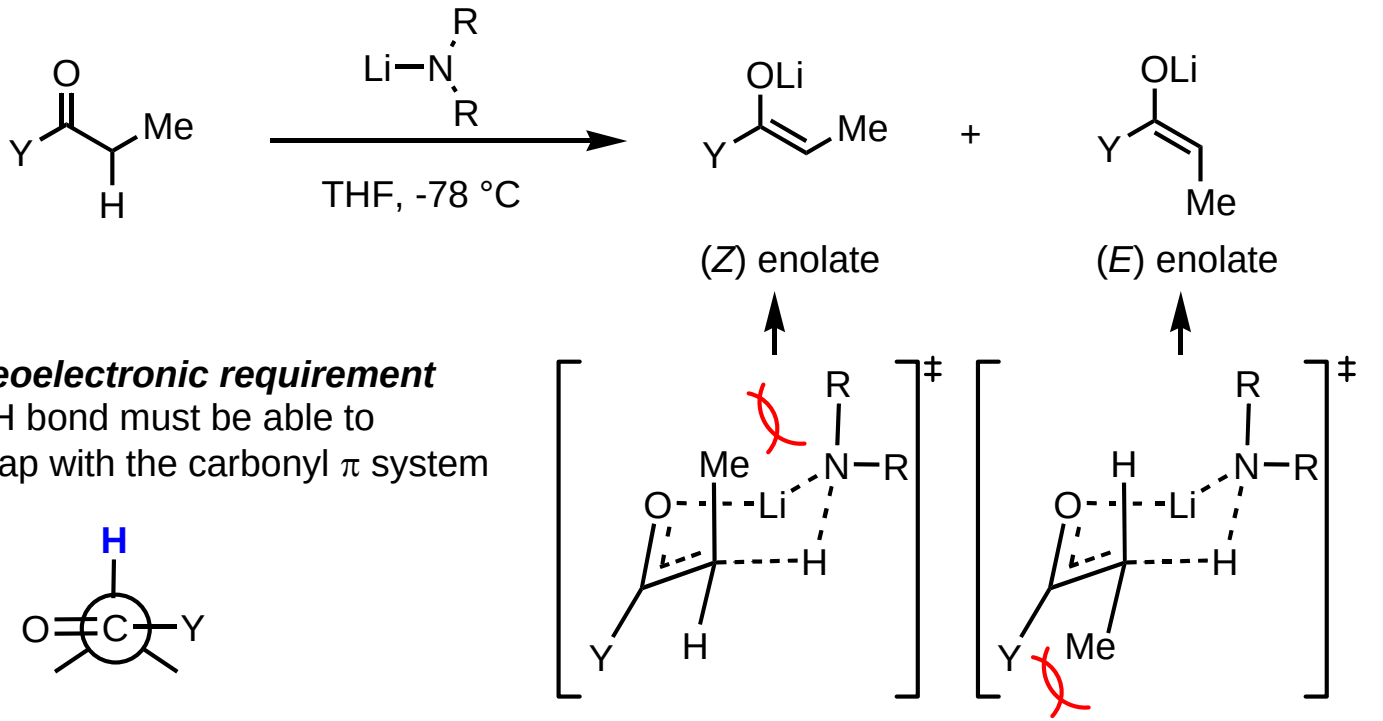
Only enolate with LDA (Kin) 99:1

Only enolate with *t*-BuOK/*t*-BuOH



(Kin) 14:86
(Th) 1:99

Stereoselective enolization with amide bases



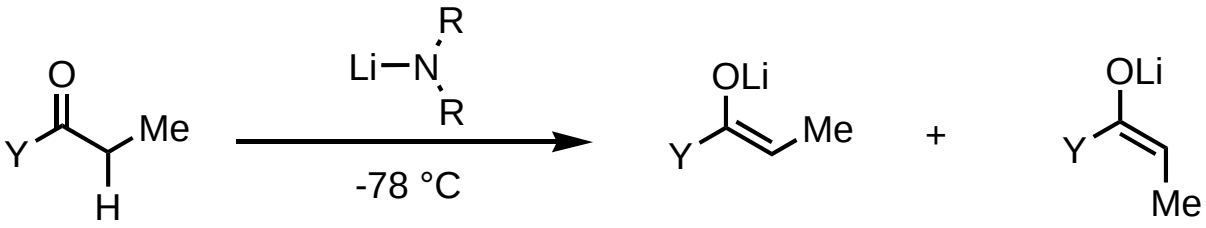
Stereoelectronic requirement
α C-H bond must be able to overlap with the carbonyl π system

Cyclic transition state (**Ireland model**)

Y	***with LDA***	(*Z*)		(*E*)
OMe, O*t*-Bu		**5**	**:**	**95**
S*t*-Bu		**5**	**:**	**95**
Et		23	:	77
*i*Pr		40	:	60
t-Bu		100	:	0
Et_2N		**100**	:	**0**

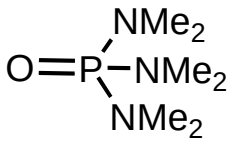
JACS **1976**, *98*, 2868; *J. Org. Chem.* **1991**, *56*, 650

Stereoselective enolization with amide bases



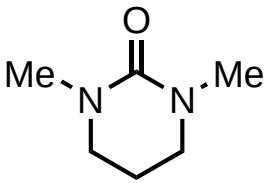
Y	Base, Solvent	(*Z*)		(*E*)
MeO	**LDA, THF**	**5**	**:**	**95**
MeO	LDA, THF/HMPA (77:23)	85	:	15
MeO	LDA, THF/DMPU (55:45)	**93**	**:**	**7**

Ireland, R. E. *et al. JOC* **1991**, *56*, 650



Hexamethylphosphoramide

HMPA



N,*N*′-Dimethylpropyleneurea

DMPU

Oxazolidinones derived from chiral 1,2-aminoalcohols

David A. Evans
(Harvard University)

Aminoacids

(both enantiomers available)

R = *i*Pr (valine)

R = CH_2Ph (Phenylalnine)

R = Ph (Phenylglycine) (non natural)

Norephedrine

$COCl_2$, base
or $(EtO)_2C=O$, Δ

Evans oxazolidinones

n-BuLi, THF, -78 °C

$SOCl_2$ or

HCONMe$_2$
(DMF) (cat.)

CH_2Cl_2

t-Bu Cl (PivCl)
Et_3N

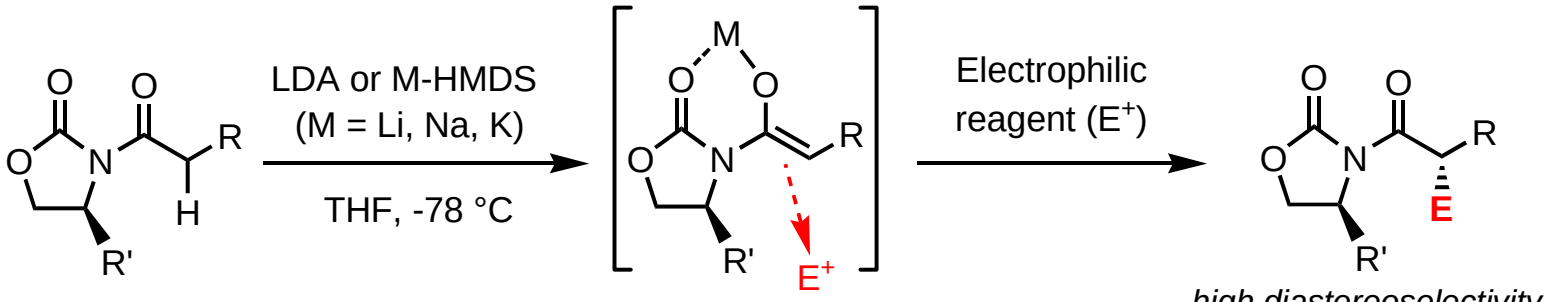
THF

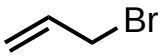
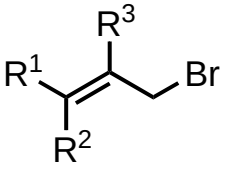
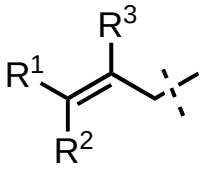
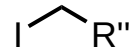
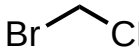
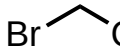
-78 °C to rt

-78 °C to rt

acidity ~ ketone

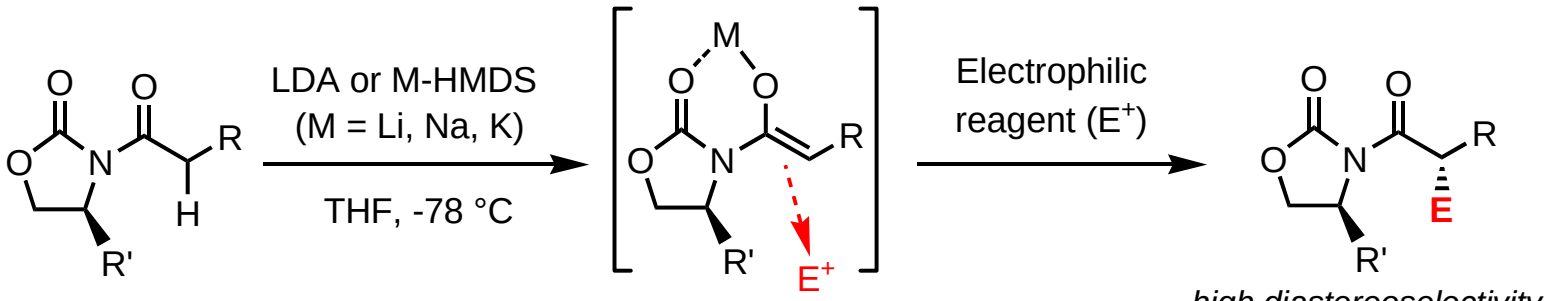
Evans oxazolidinones : Alkylation reactions

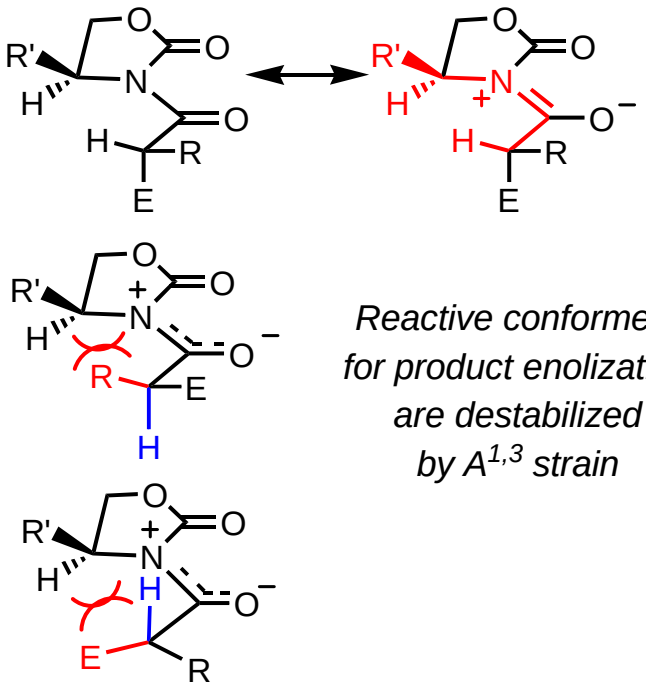


Electrophilic agent E^+	**E**
MeI	Me
$PhCH_2Br$ (BnBr)	Bn
$BnOCH_2Br$	CH_2OBn
	Allyl
	
Moderate yields in general 	CH_2R''
	CH_2CN
	CH_2CO_2R''

Evans, D. A. *et al. JACS* **1982**, *104*, 1737; review: Heravi, M. M. *et al. RSC Adv.* **2016**, *3*, 30498

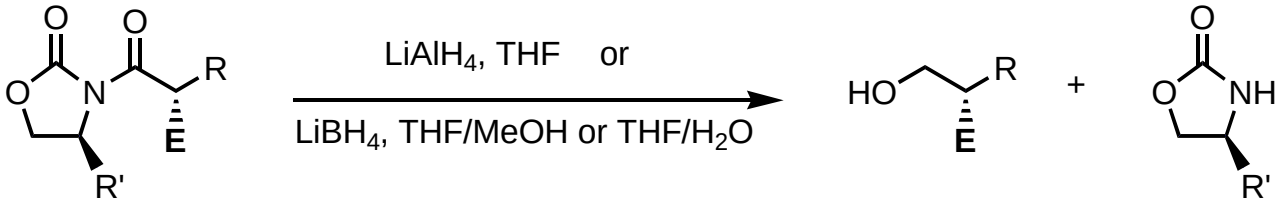
Evans oxazolidinones : Alkylation reactions



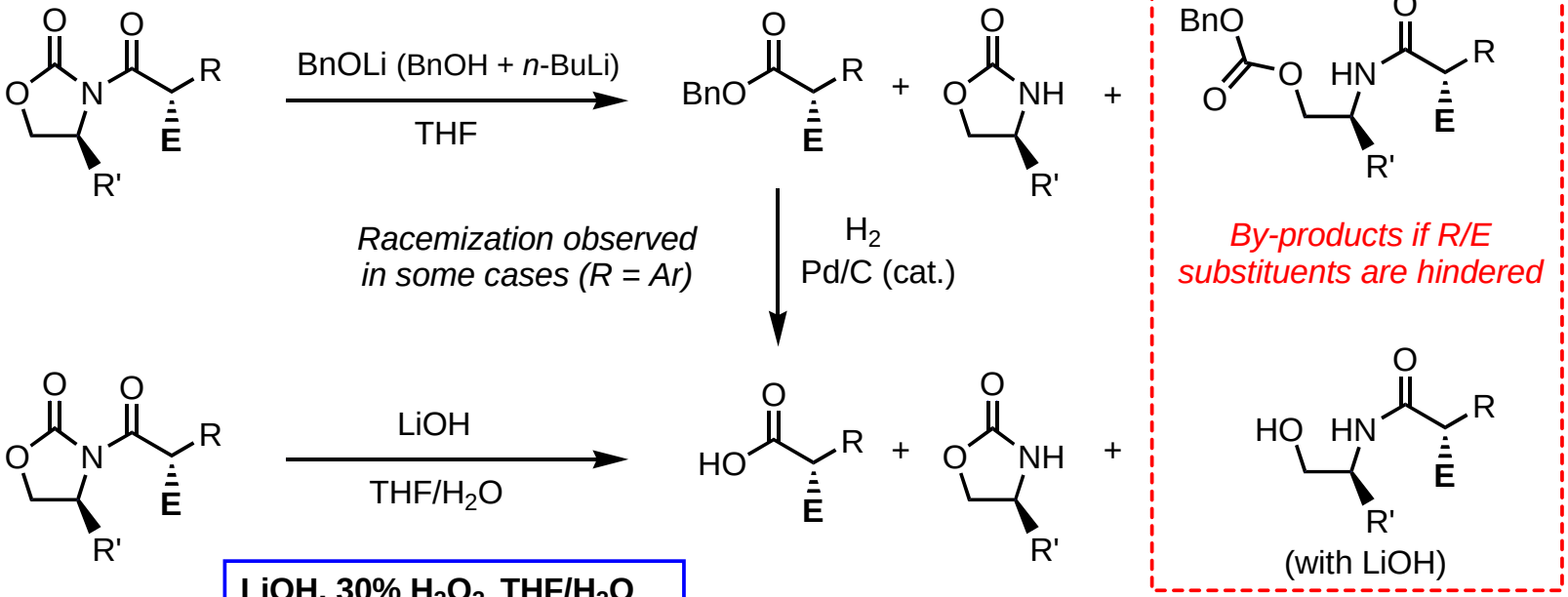


Reactive conformers for product enolization are destabilized by $A^{1,3}$ strain

Evans oxazolidinones : Cleavage of the chiral auxiliary



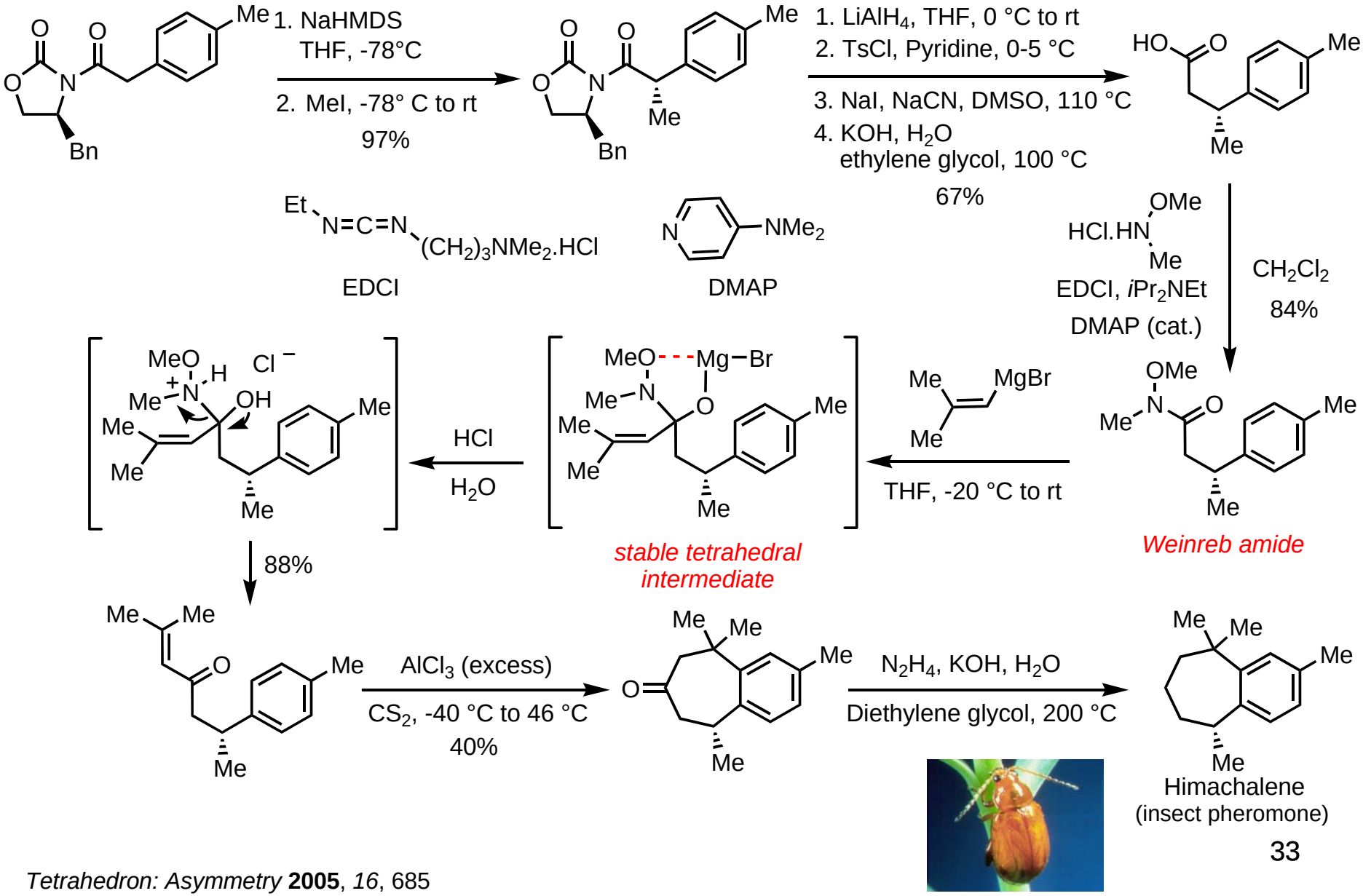
Examples also reported with $NaBH_4$ in THF/H_2O



LiOH, 30% H_2O_2, THF/H_2O
- no racemization
- attack of the exocyclic C=O

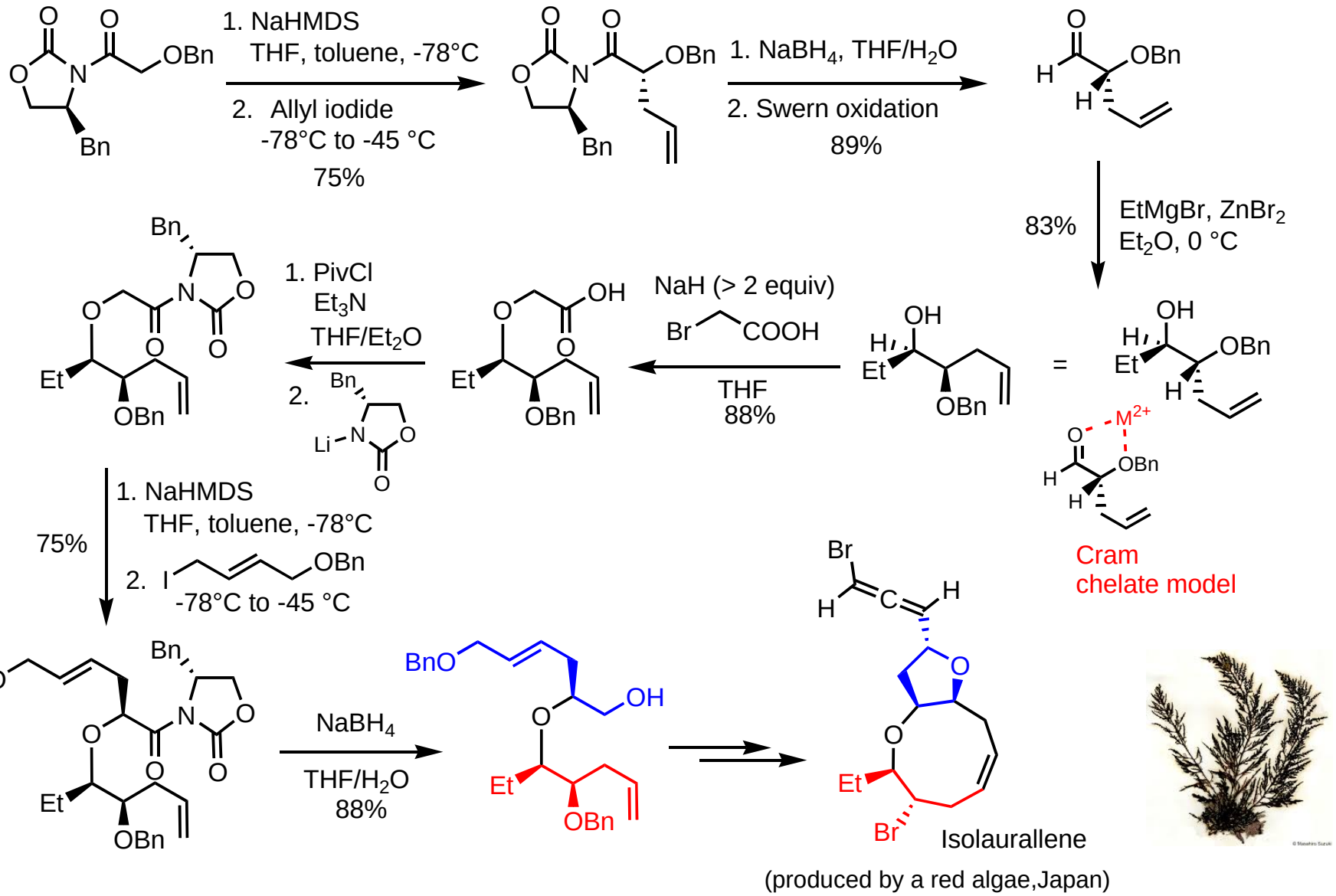
Evans, D. A. *et al. JACS* **1982**, *104*, 1737; *Tetrahedron Lett.* **1987**, *28*, 6141

Alkylation of Evans oxazolidinones : Applications



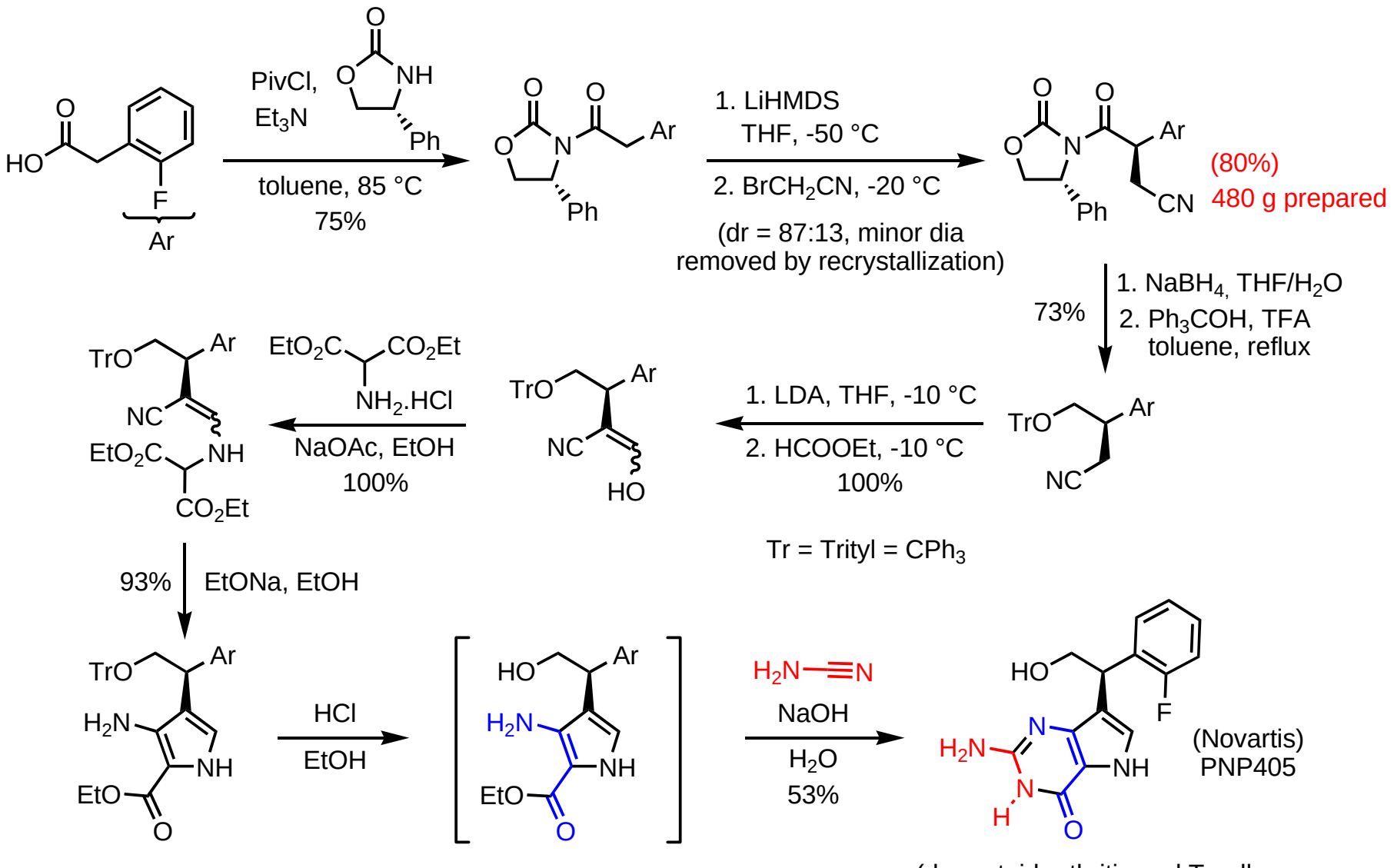
Tetrahedron: Asymmetry **2005**, *16*, 685

Alkylation of Evans oxazolidinones : Applications



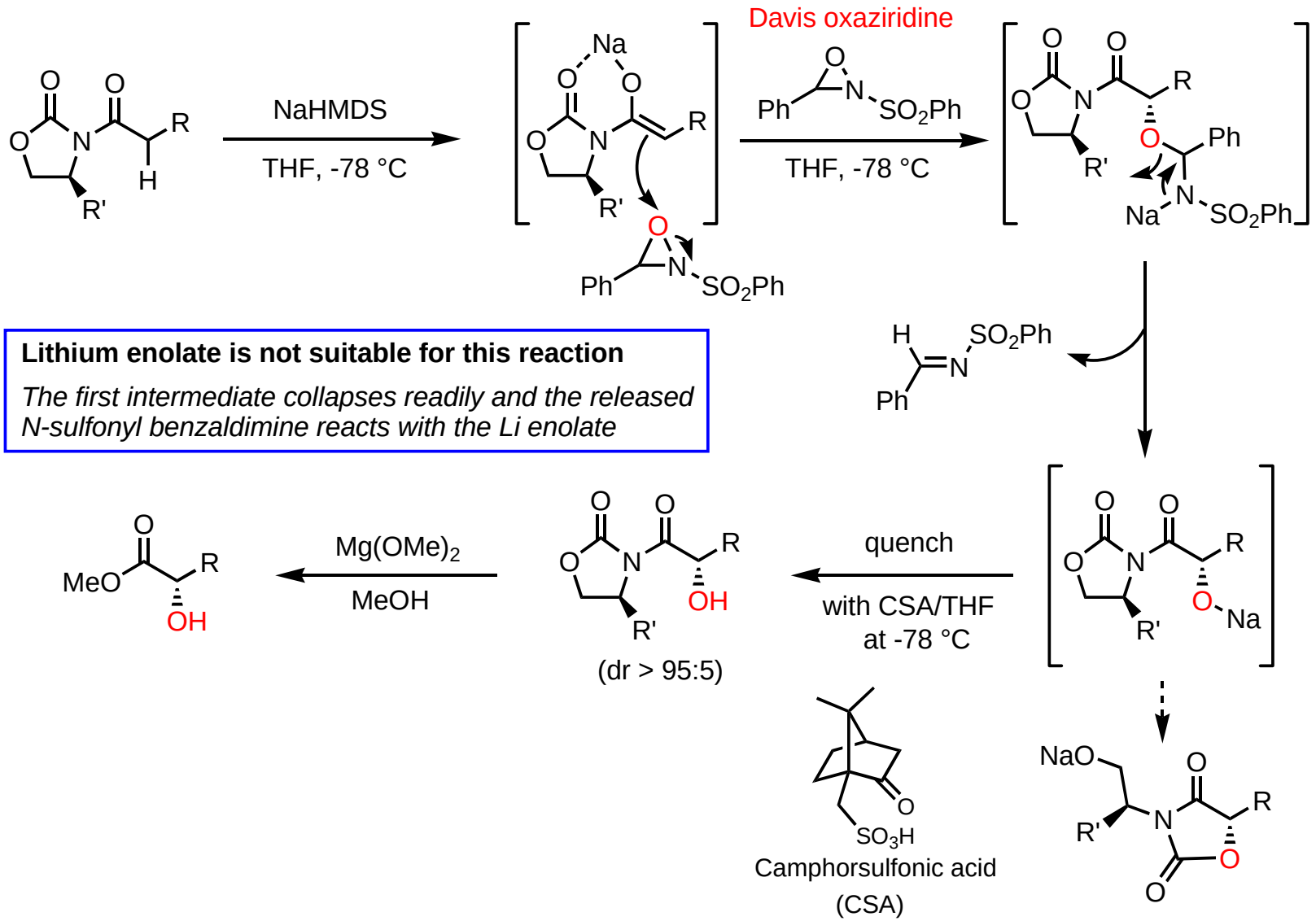
Tetrahedron **2002**, *58*, 1817

Alkylation of Evans oxazolidinones : Applications



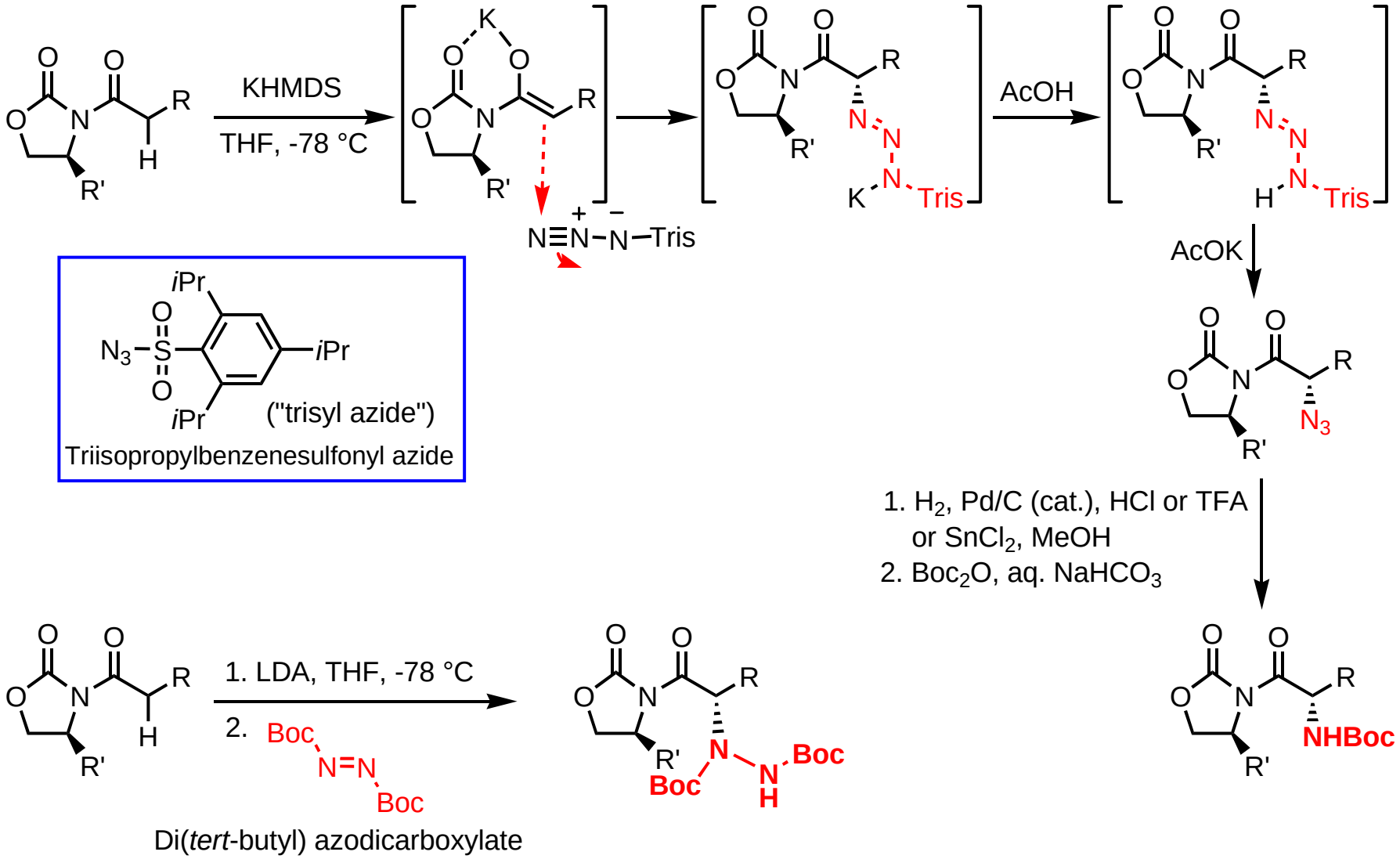
J. Org. Chem. **2002**, *67*, 6612

Evans oxazolidinones : Hydroxylation



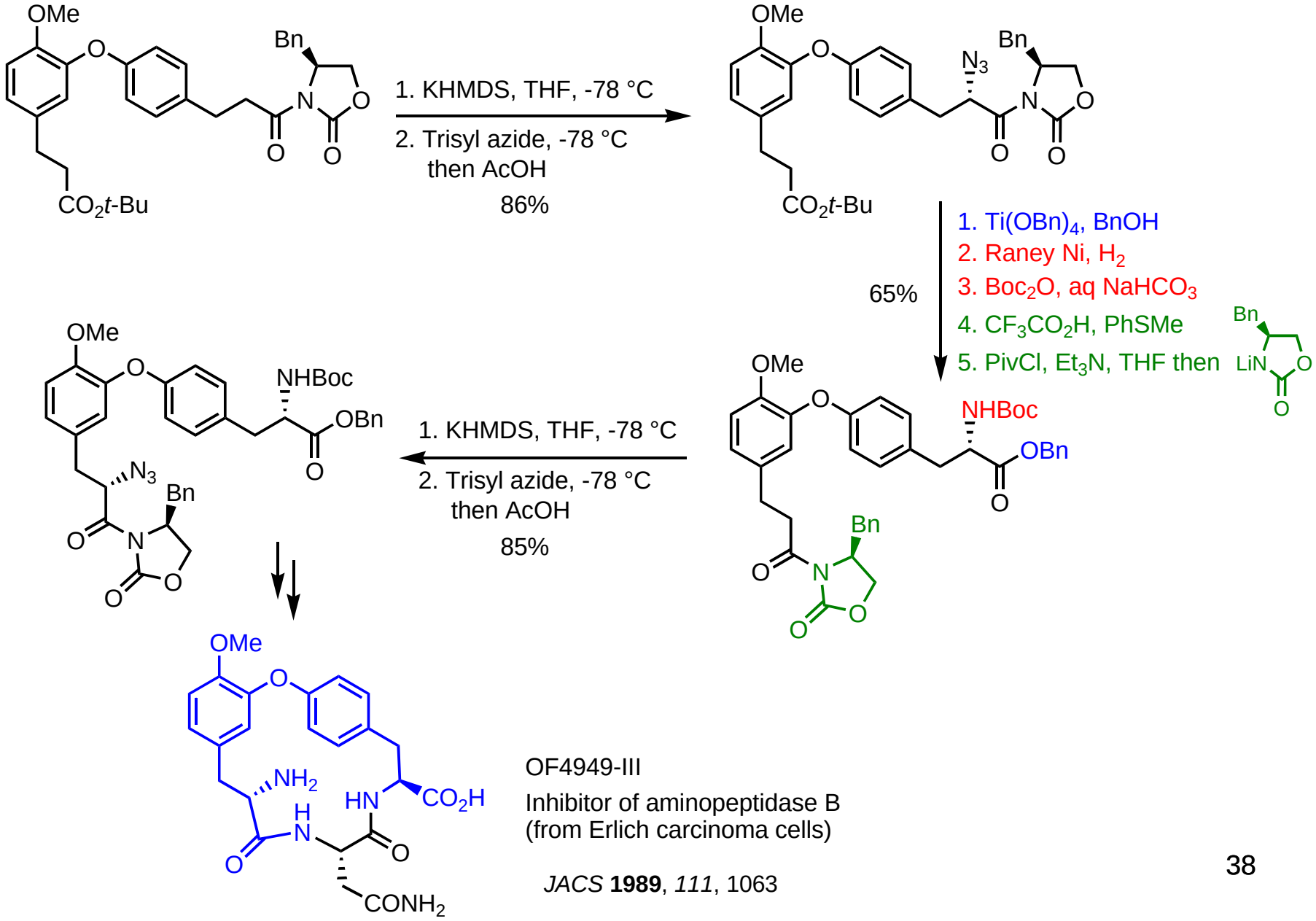
JACS **1985**, *107*, 4346

Evans oxazolidinones : Amination



JACS **1986**, *108*, 6395; **1987**, *109*, 6881; **1990**, *112*, 4012

Amination of Evans oxazolidinones : Applications

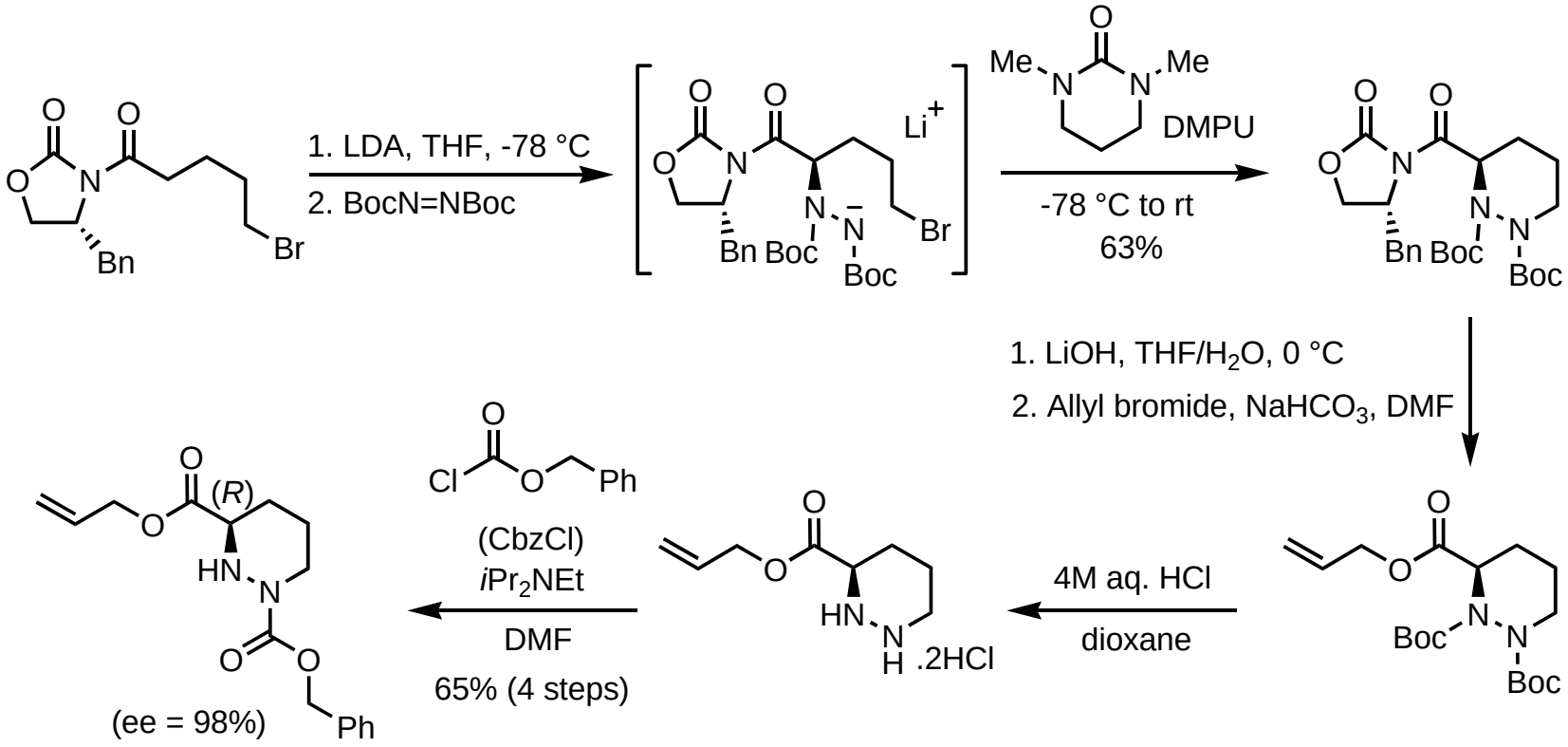


OF4949-III

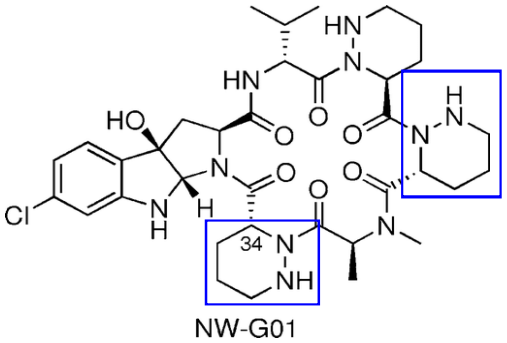
Inhibitor of aminopeptidase B
(from Erlich carcinoma cells)

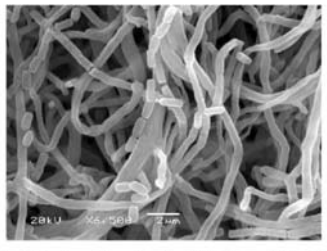
JACS **1989**, *111*, 1063

Amination of Evans oxazolidinones : Applications



Key intermediate in the synthesis of antibiotic NW-G101

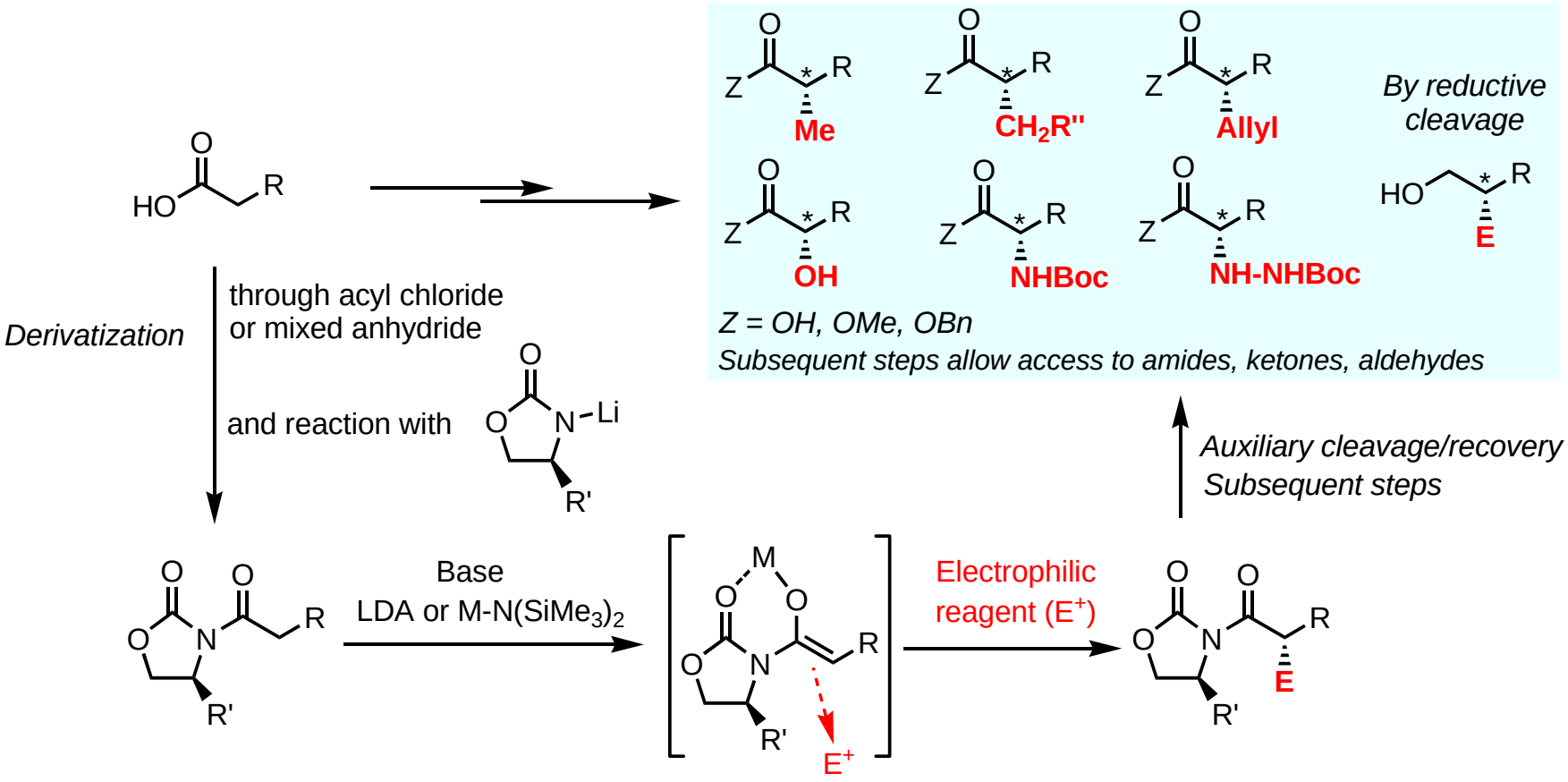




Org. Lett. **2011**, *13*, 4700

Produced by *Streptomyces alboflavus*
Active against *Staphylococcus aureus*

Evans oxazolidinones : Useful chiral auxiliaries

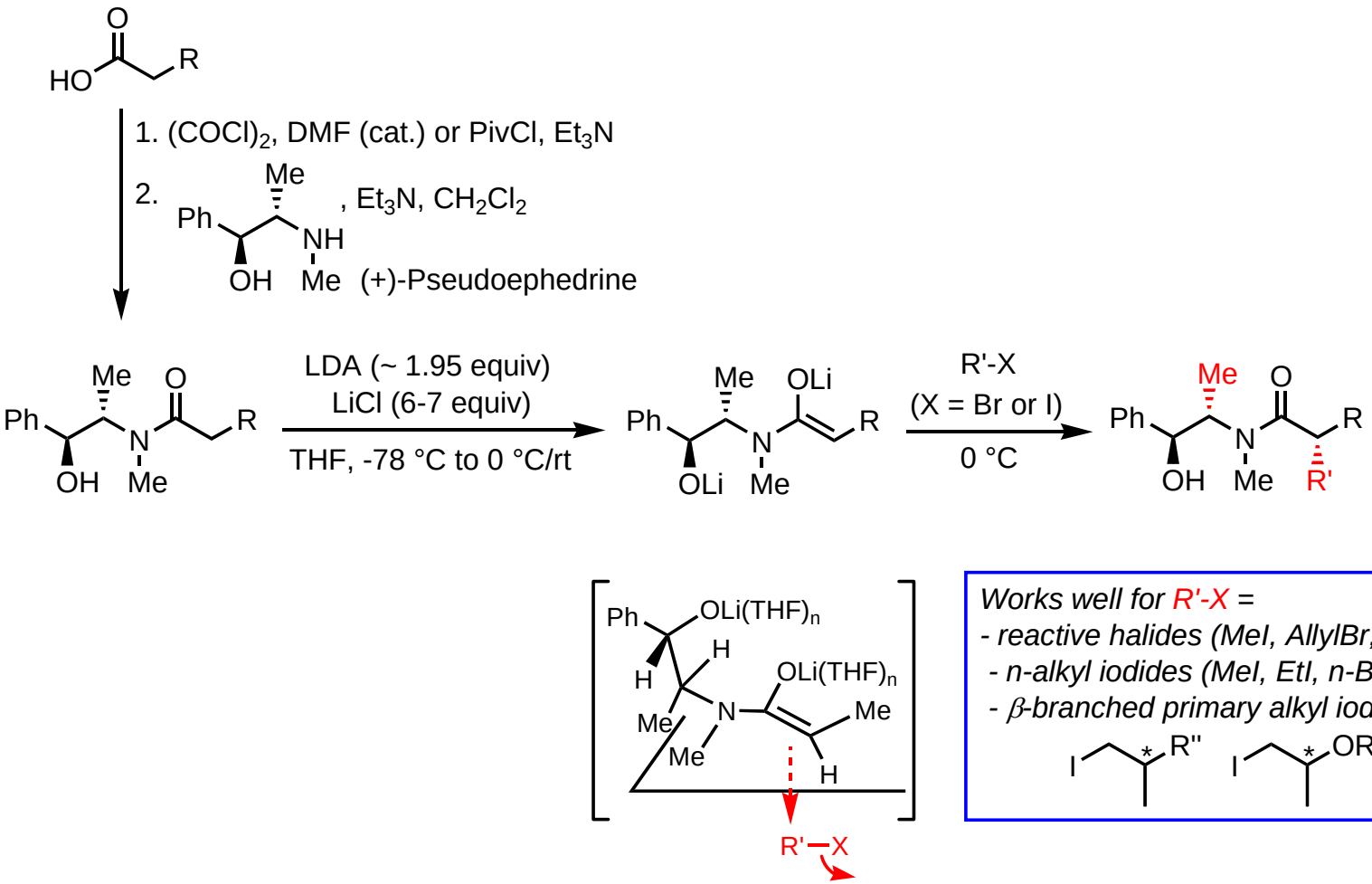


Reliable reaction which has found many applications in industry
Broad substrate scope (R substituent) and high diastereoselectivities

Alkylation reaction limited to reactive halides (MeI, Allylic bromides, Benzylic bromides)
β-branched primary iodides ($ICH_2CHR^1R^2$) are poor substrates, secondary iodides not suitable

Cleavage of the auxiliary sometimes difficult (when R is relatively hindered)
Direct access to ketones with concomittant auxilary cleavage (addition of RLi or RMgX) is not possible

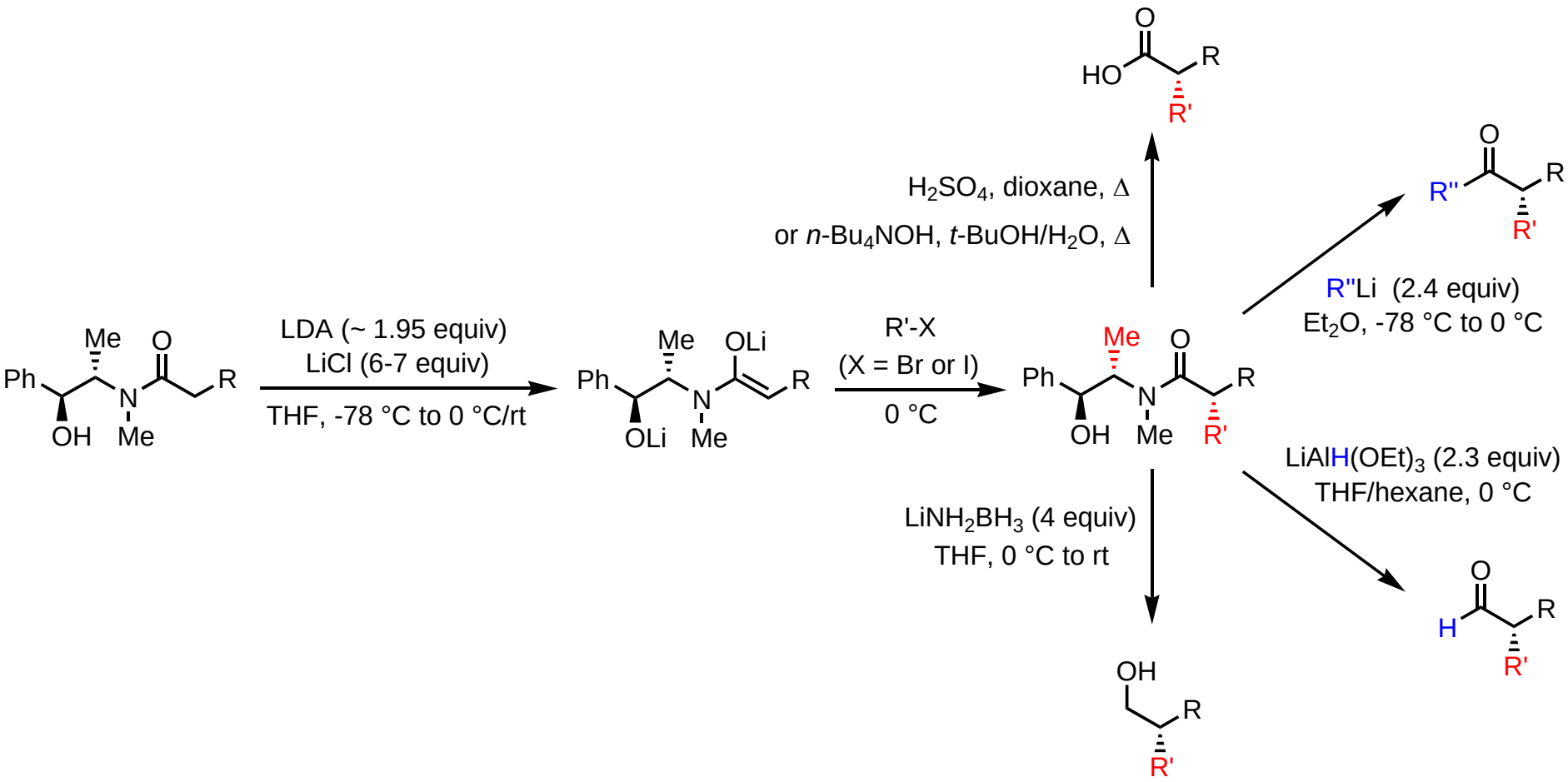
Myers alkylation (pseudoephedrine amides)



Works well for R'-X =
- reactive halides (MeI, AllylBr, BnBr...)
- n-alkyl iodides (MeI, EtI, n-BuI...)
- β-branched primary alkyl iodides

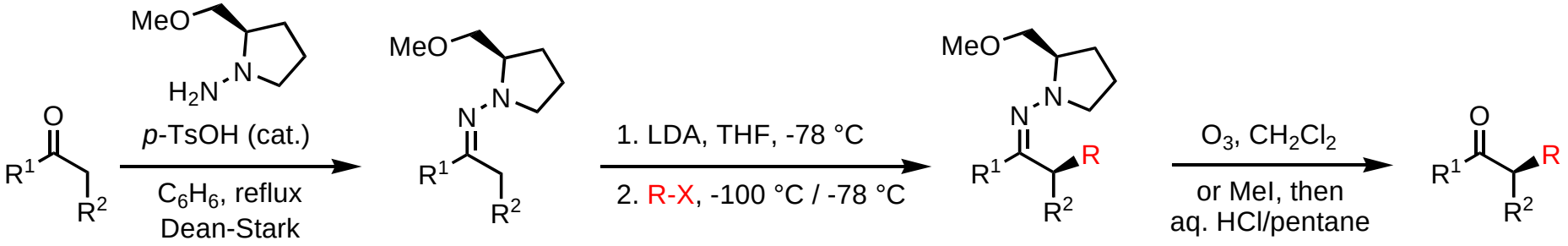
Myers, A. G. *et al. JACS* **1997**, *119*, 6496

Myers alkylation (pseudoephedrine amides)



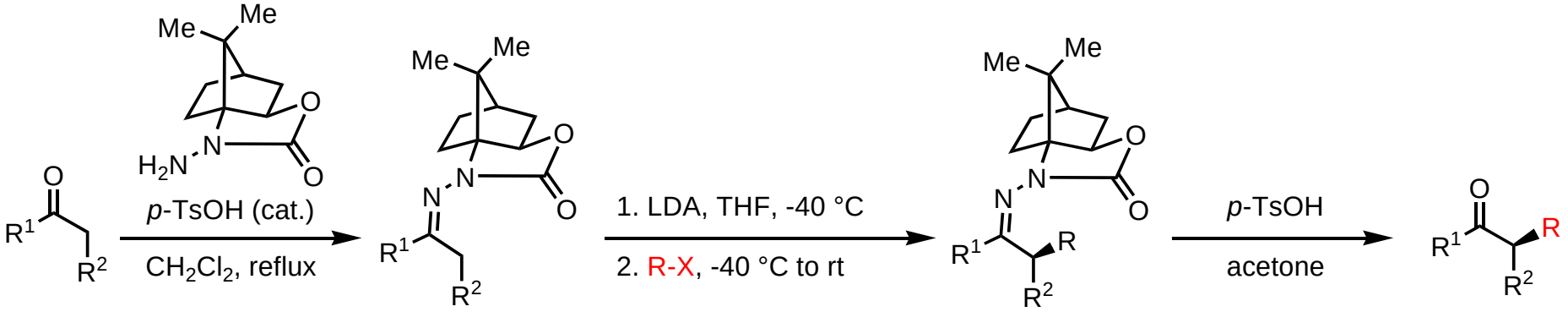
Myers, A. G. *et al. JACS* **1997**, *119*, 6496

Other useful auxiliaries for ketone alkylation reactions



R-X = MeI, alkyl iodides, AllylBr, BnBr, $BrCH_2CO_2t$-Bu

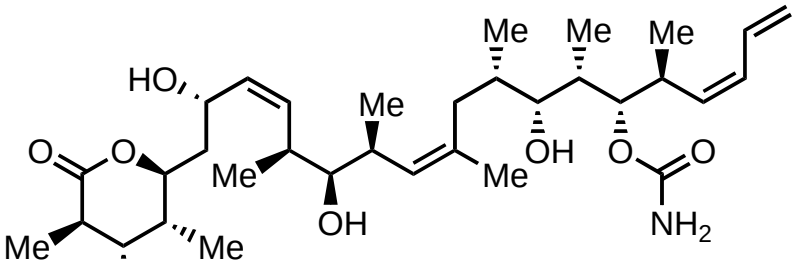
RAMP/SAMP hydrazones: Enders, D. *et al. Tetrahedron* **2002**, *58*, 2253



R-X = MeI, alkyl iodides, *i*PrI, AllylBr, BnBr

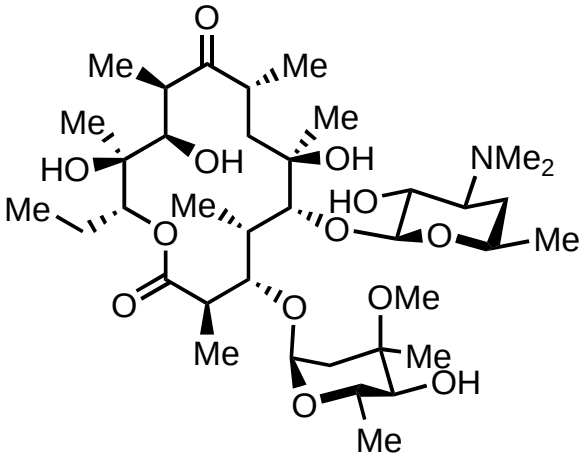
N-Amino cyclic carbamates: Coltart, D. M. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 5207; *J. Org. Chem.* **2010**, *75*, 8578

Bioactive polyketides

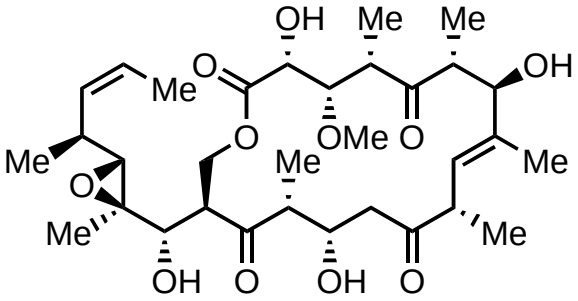


Discodermolide (marine origin)

(immunosuppresant, antitumor agent)

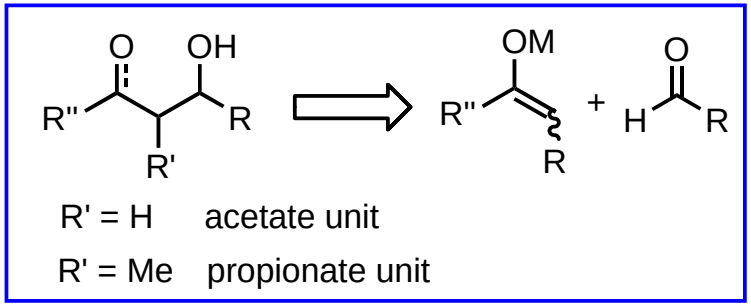


Erythromycin A (from a strain of *actinomyces*)
(antibiotic)

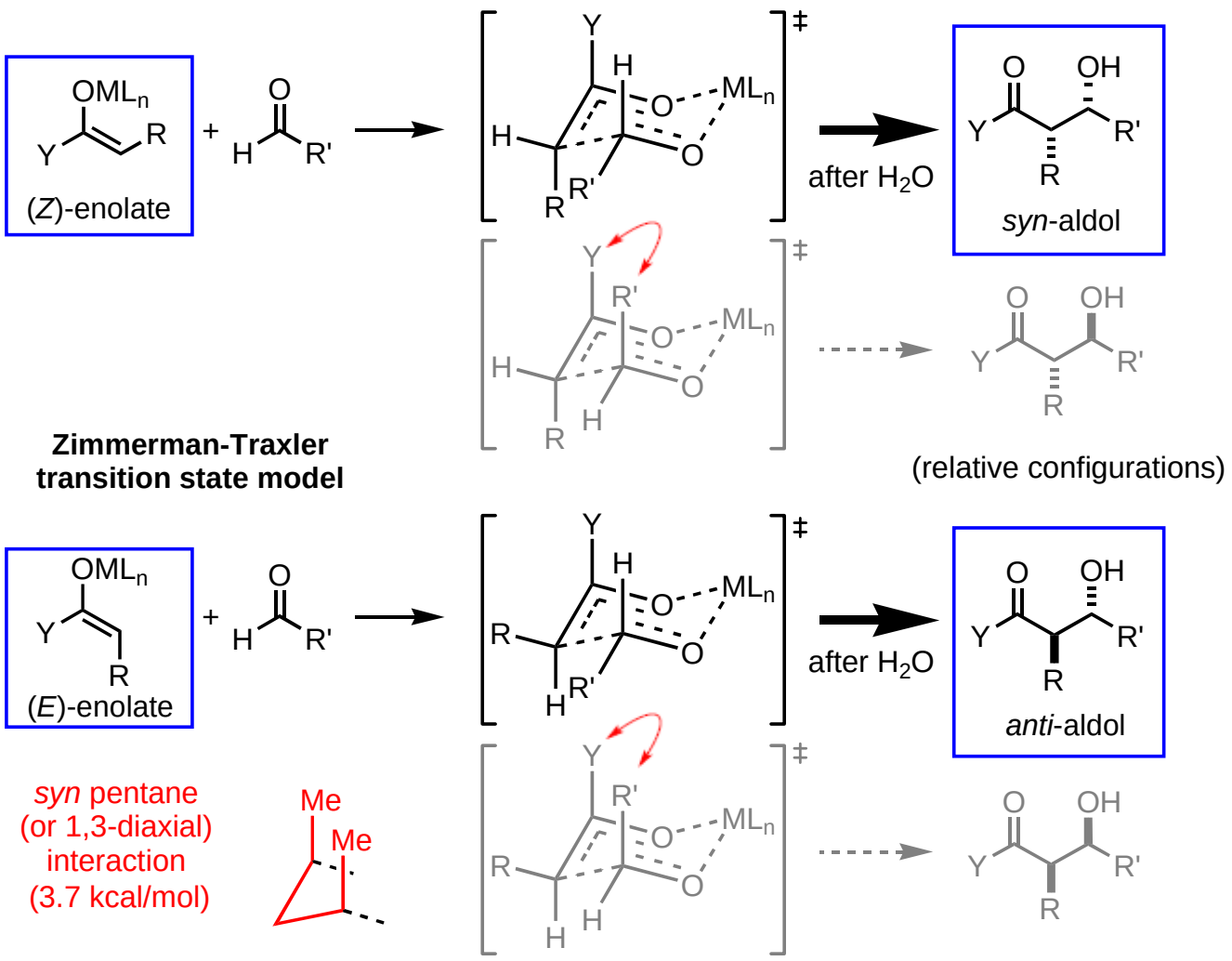


Tedanolide (marine origin)

(cytotoxic activity)



Enolate geometry and diastereoselectivity of the aldol reaction



Zimmerman, H. E.; Traxler, M. D. *JACS* **1957**, *79*, 1920; Heathcock, C. H. *et al. JOC* **1980**, *45*, 1066

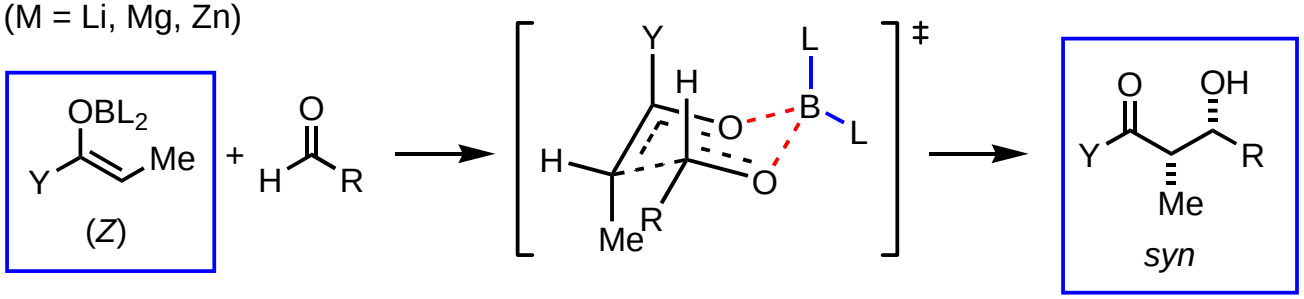
Interest of boron enolates in aldol reactions

Short O–B and C–B bonds

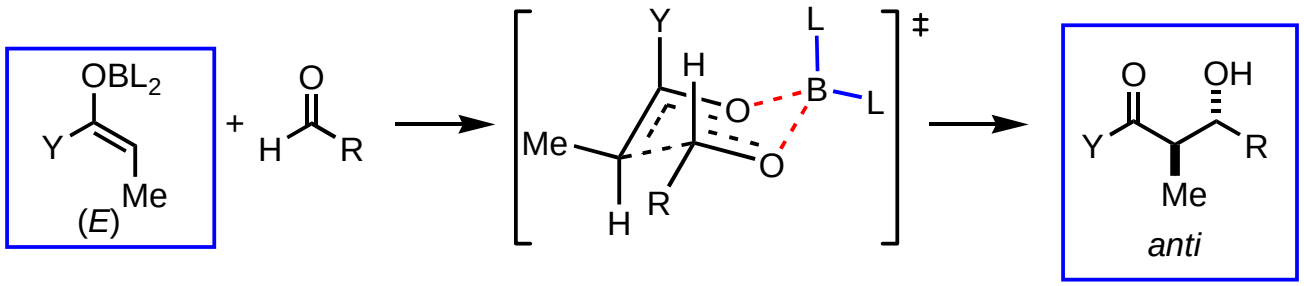
O–M 1.6-2.2 Å **O–B 1.4-1.5 Å**

C–M 1.9-2.3 Å C–B 1.5-1.6 Å

(M = Li, Mg, Zn)

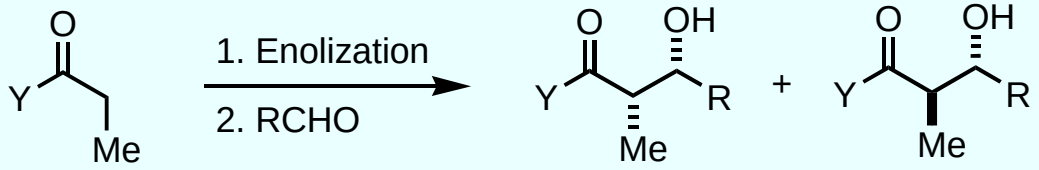


Products are usually isolated after an oxidative hydrolytic work-up
(aqueous pH = 7 buffer / MeOH / 30% H_2O_2)



Evans, D. A. *et al. JACS* **1979**, *101*, 6101; *JACS* **1983**, *103*, 3099

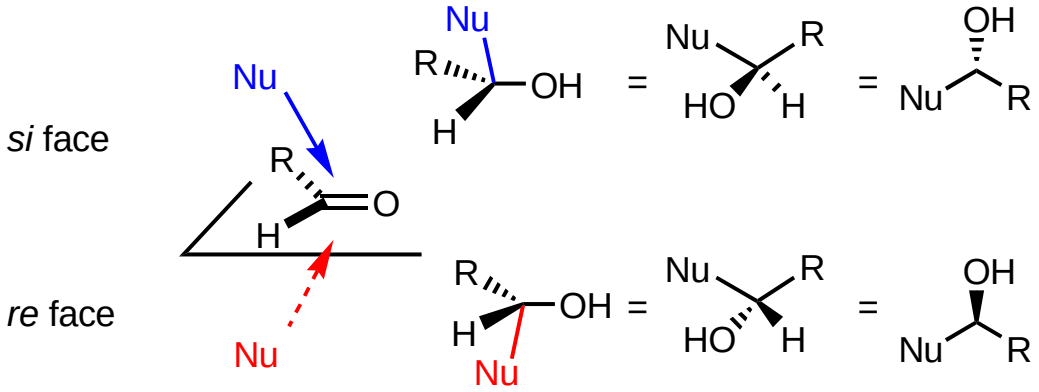
Control of the enolate face selectivity



How can one product stereoisomer be formed selectively ?

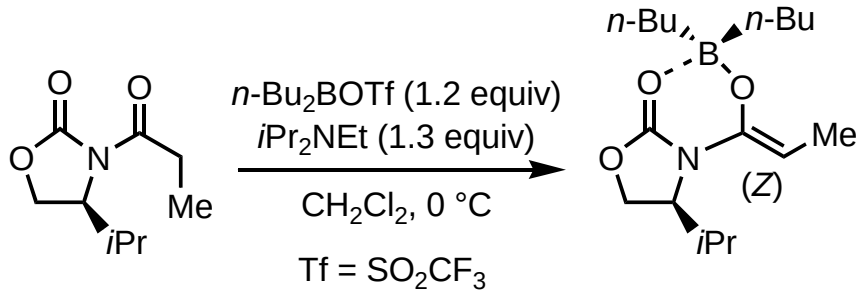
- Control geometry of enolate
- Control facial selectivity of enolate : Use of a chiral auxiliary (Y*)

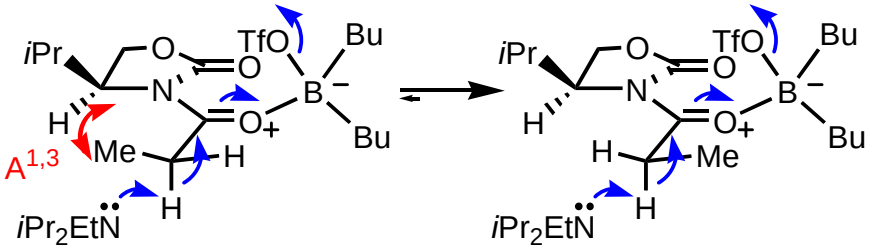
Addition onto *si* face



Addition onto *re* face

Control of the enolate face selectivity : Aldol reaction

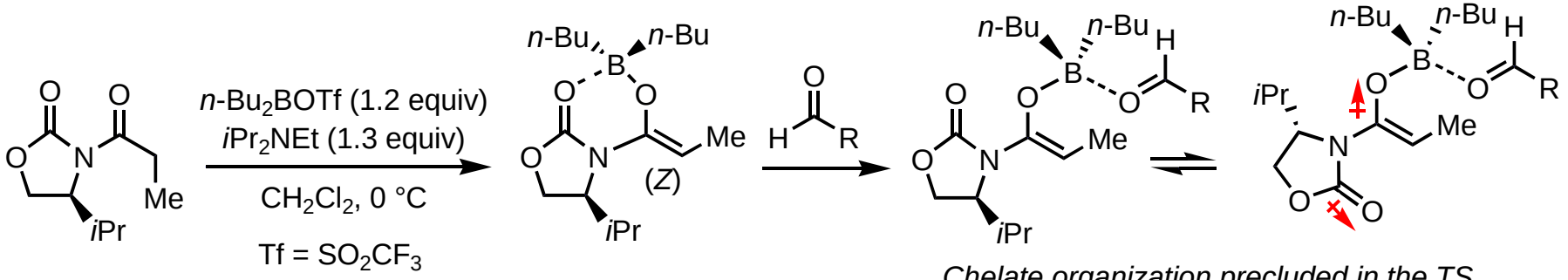


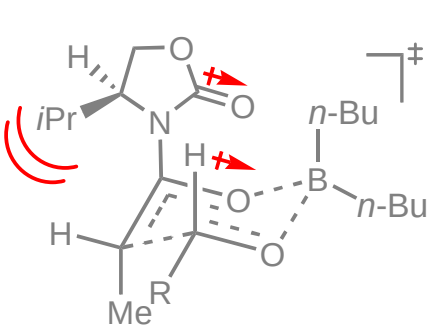


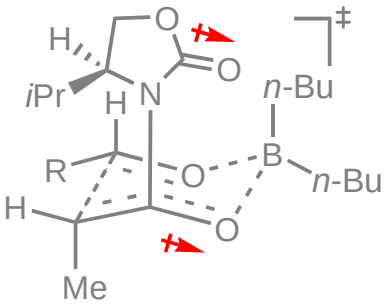
more stable and reactive conformer

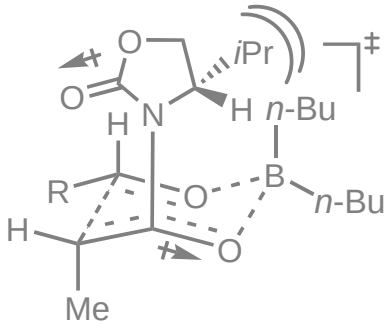
Open transition state for enolization

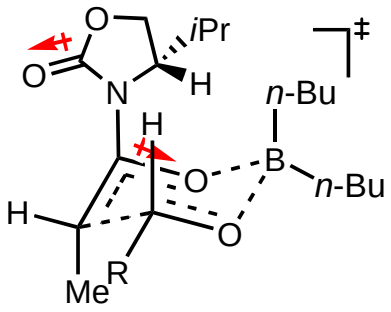
Control of the enolate face selectivity : Aldol reaction

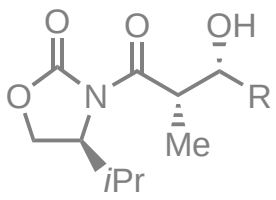


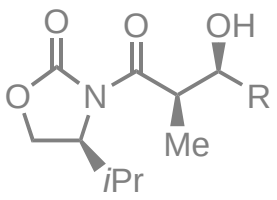


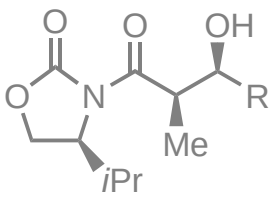


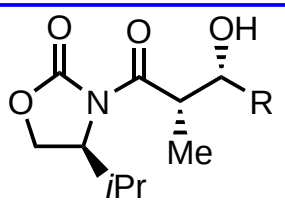








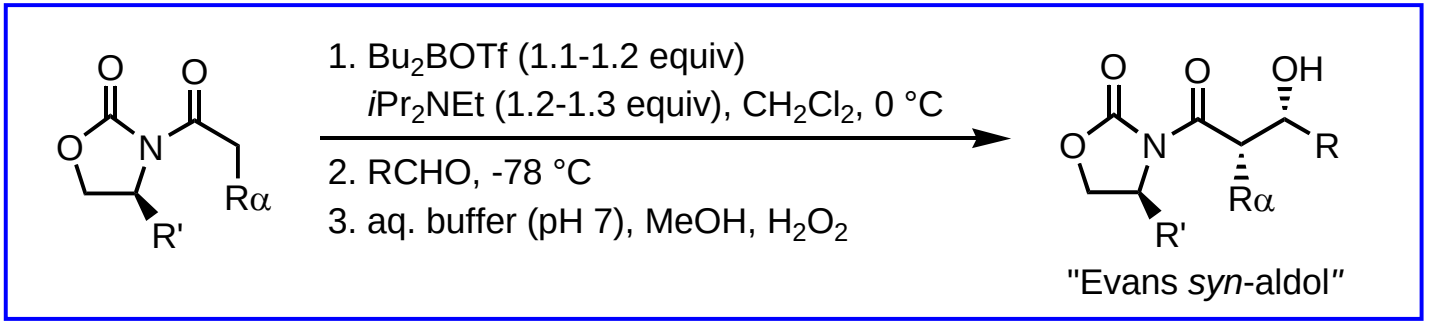


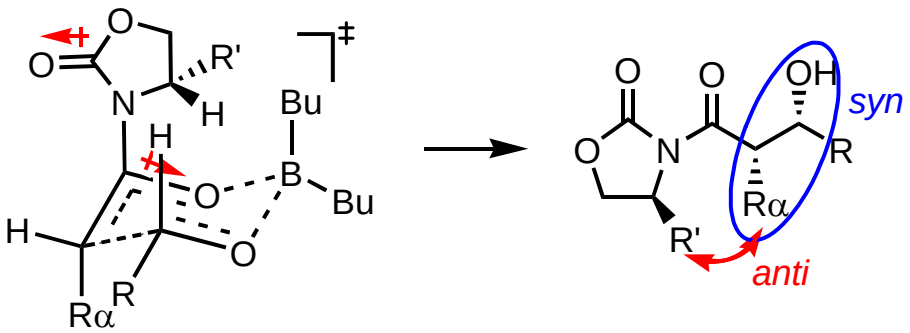


major, dr > 99:1 (up to 99.9:0.1)

Steric interactions between oxazolidinone group (iPr) and RCHO and dipole-dipole interactions are minimized in the favored TS

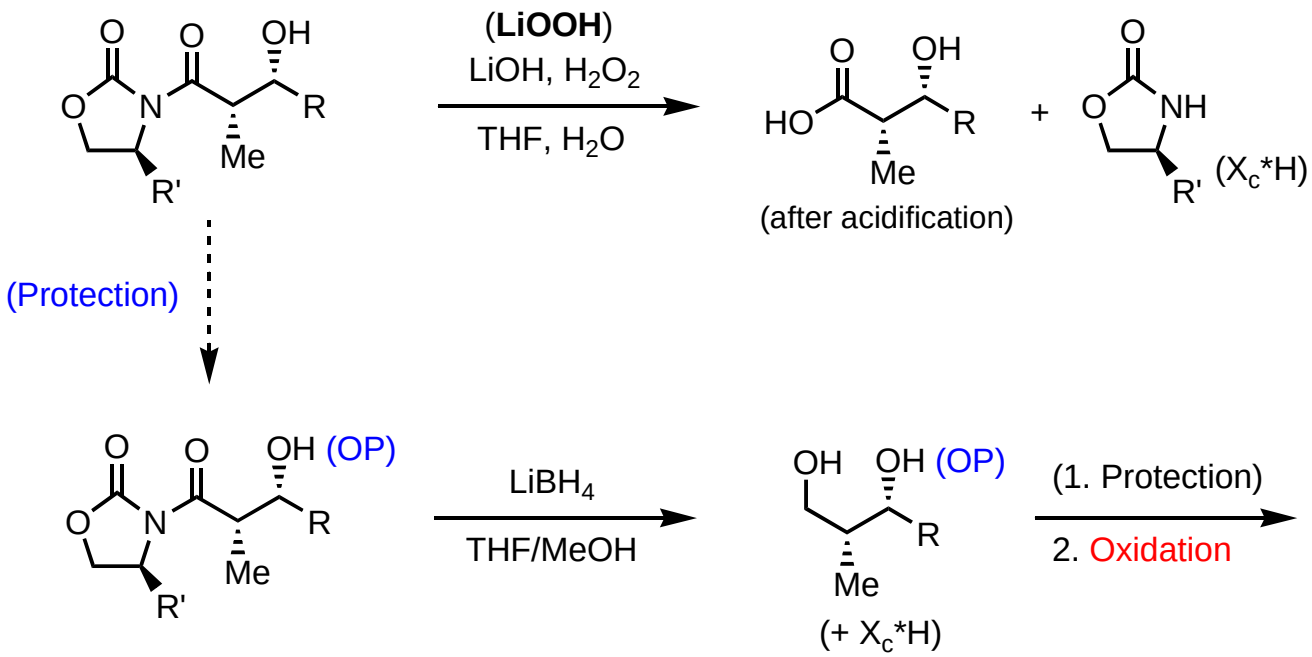
Evans aldol reaction





- High diastereoselectivities controlled by the oxazolidinone (even if R includes stereocenters)
- Broad scope of aldehydes and Rα substituents (**but not Rα = H**)
- Reliable process which has been used industrially
- Only *syn* aldols are accessible by this method

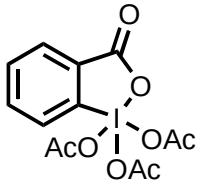
Cleavage of the auxiliary



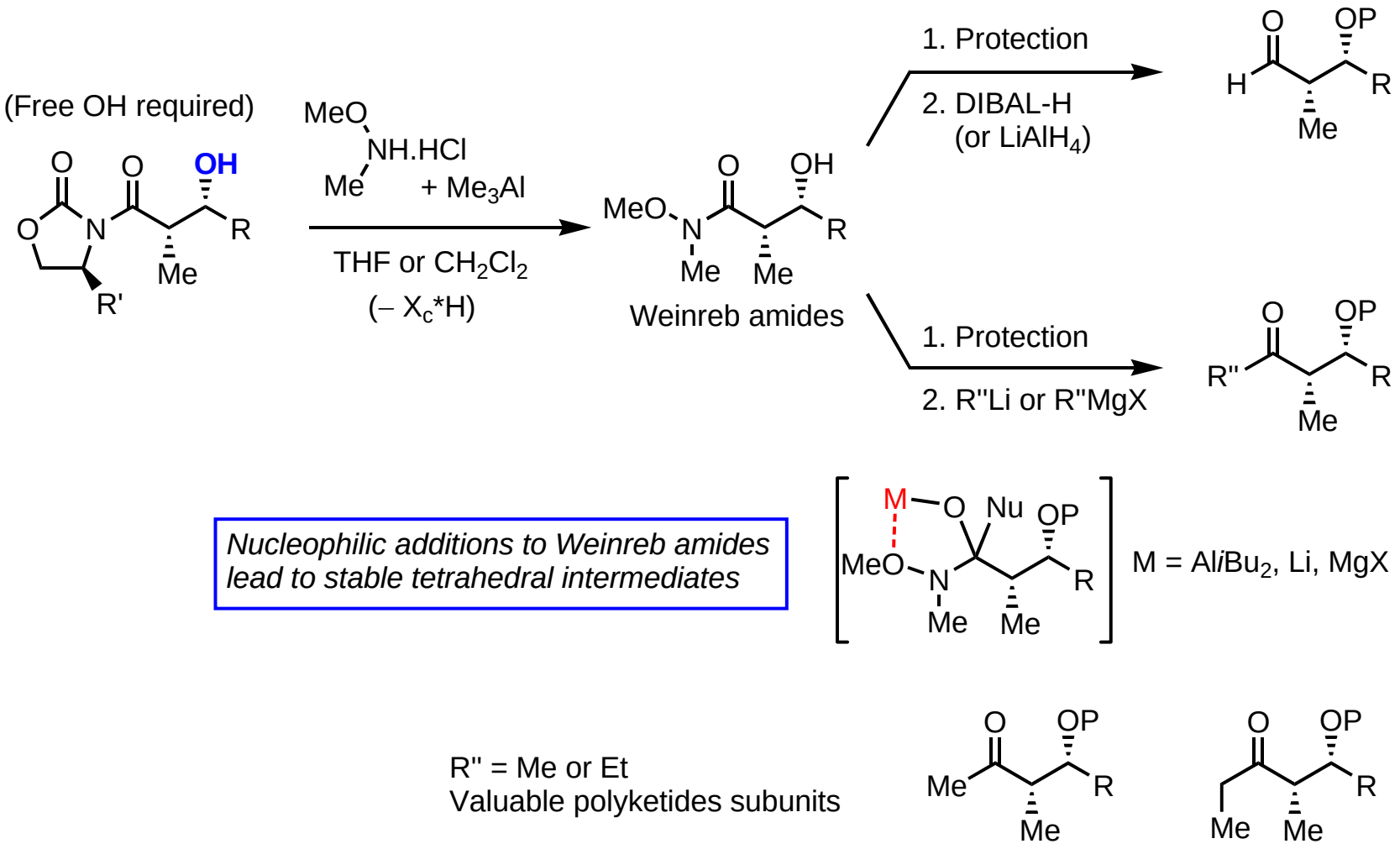
Silyl ethers ofter used as protecting groups
OH -> OTBS (TBS = $SiMe_2tBu$)
TBSCl, imidazole, DMF
or more often
TBSOTf, 2,6-lutidine (= 2,6-dimethylpyridine), CH_2Cl_2

Swern oxidation
i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C
ii) add acohol substrate, -78 °C
iii) Et_3N, -78 °C to rt

Dess-Martin oxidation
DMP (pyridine or $NaHCO_3$)
CH_2Cl_2, 0 °C to rt

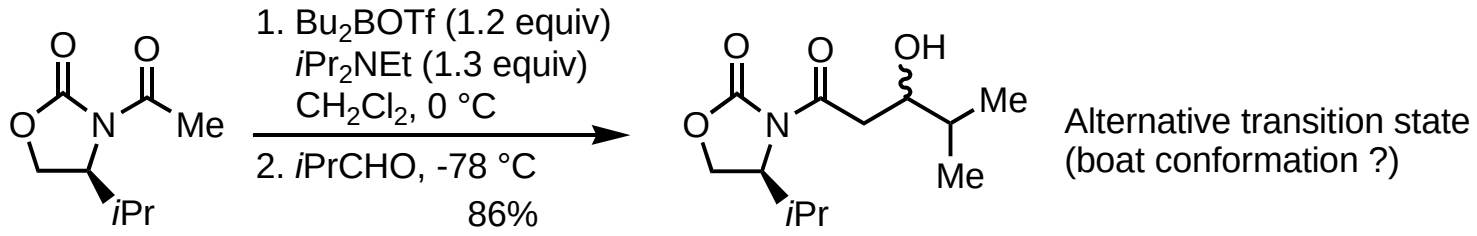


Cleavage of the auxiliary : transamidation to Weinreb amides

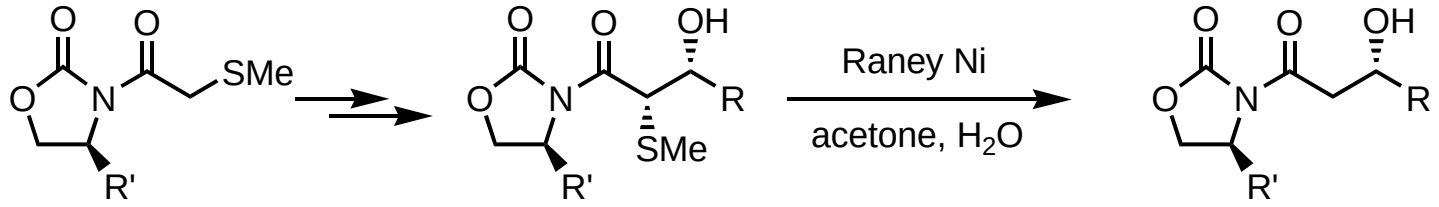


Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815
Review on Weinreb amides: *Synthesis* **2008**, 3707

Evans aldol reaction : limitations and potential solutions

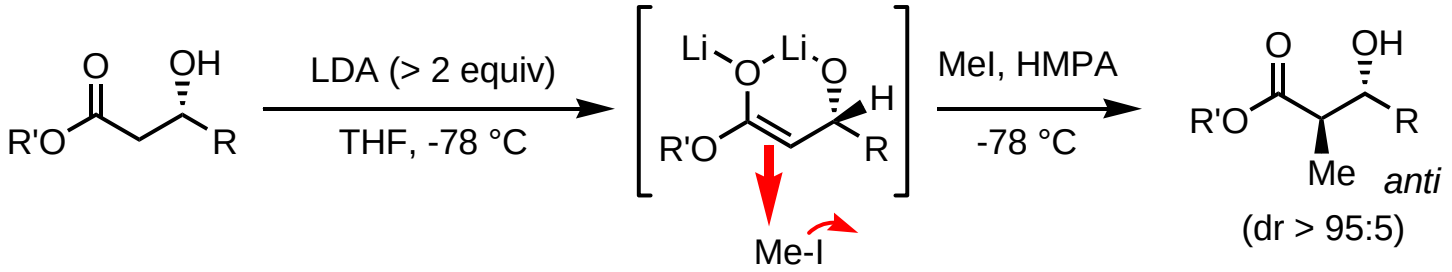


One solution to acetate aldol reactions



JACS **1981**, *103*, 2127

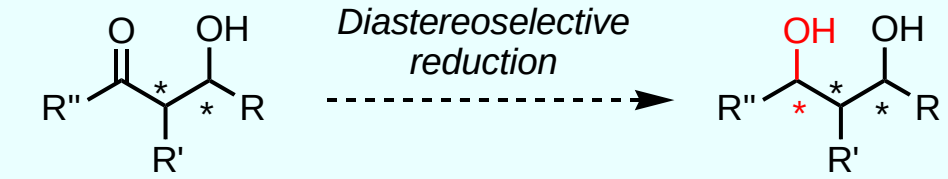
One entry toward anti propionate aldol subunits : Frater-Seebach alkylation



(other halides can be used: AllylBr, BnBr)

Helv. Chem. Acta **1979**, 2825; **1980**, *63*, 197; *Tetrahedron Lett.* **1984**, *40*, 1269

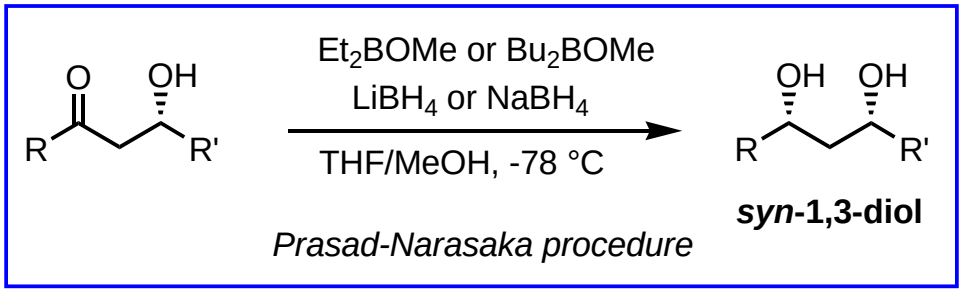
Diastereoselective reduction of β-hydroxy ketones



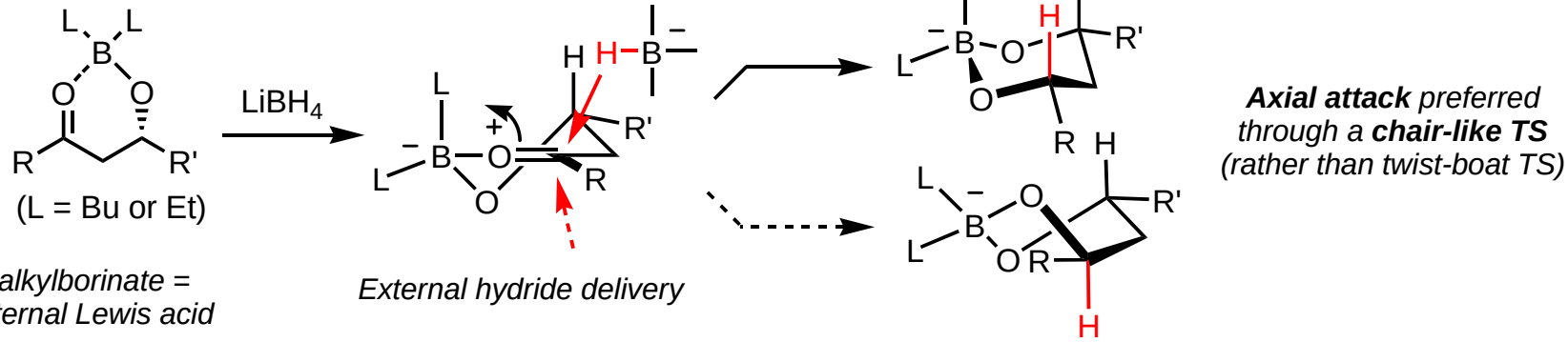
β-Hydroxy ketone

1,3-Diol

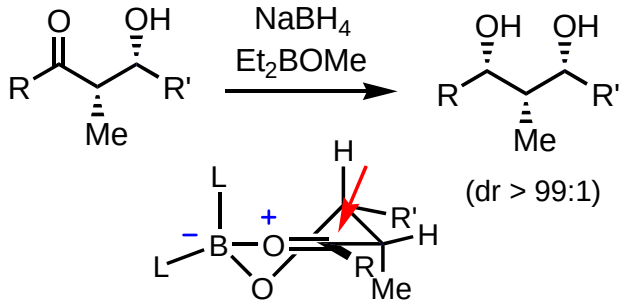
Diastereoselective reduction of β-hydroxy ketones : syn-1,3-diols

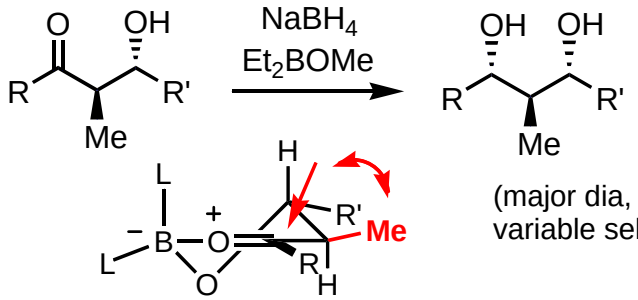


Alternative reagent
$Zn(BH_4)_2$



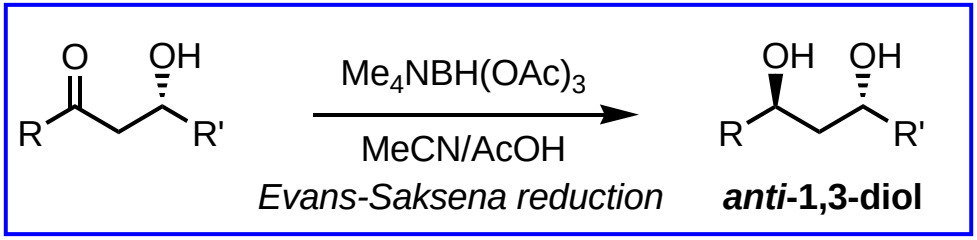
***Axial attack** preferred through a **chair-like TS** (rather than twist-boat TS)*





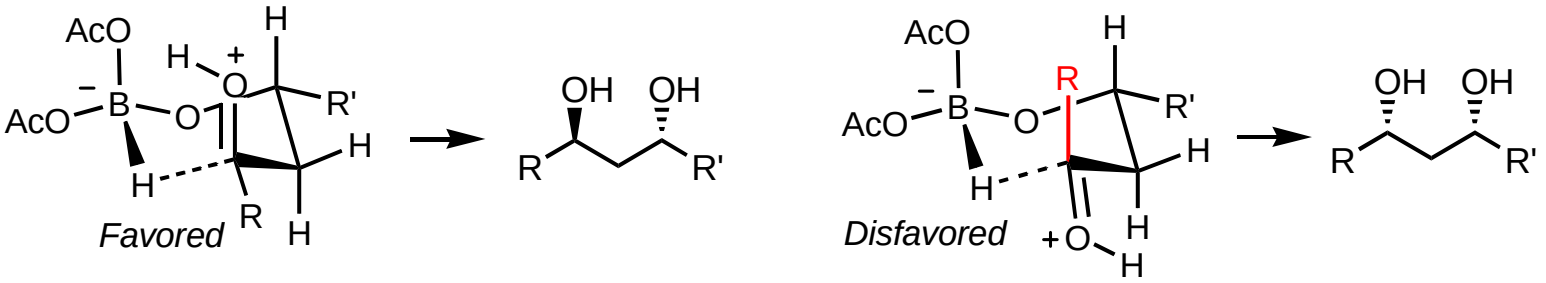
Chem. Lett. **1980**, 1415; *Tetrahedron* **1984**, *40*, 2233; *Tetrahedron Lett.* **1987**, *28*, 155

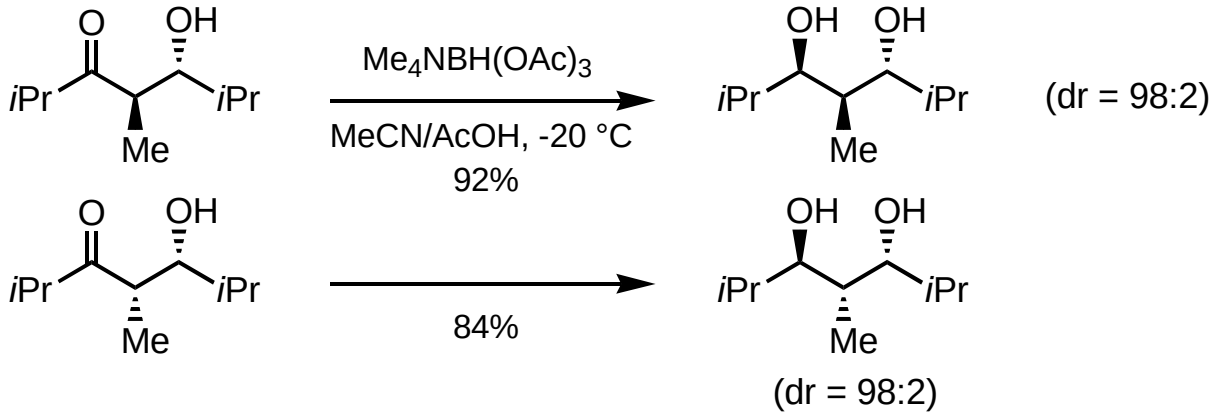
Diastereoselective reduction of β-hydroxy ketones : anti-1,3-diols



$Me_4NBH(OAc)_3$: poorly reactive reducing agent

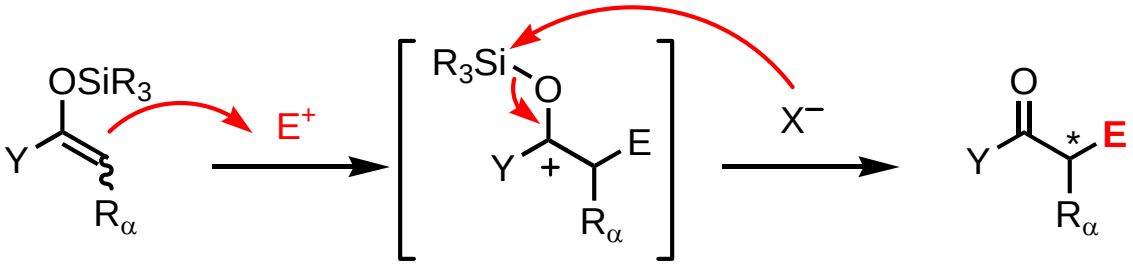
Ligand exchange on boron + intramolecular hydride delivery





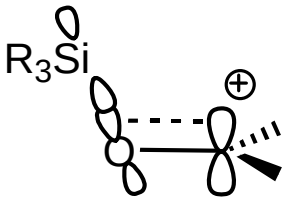
Evans, D. A.; Chapman, K. T.; Carreira, E. M. *JACS* **1988**, *110*, 3560

Enoxysilanes (silyl enol ethers) as nucleophiles



β effect of silicon

Silicon stabilizes carbocations at the β position (hyperconjugation)

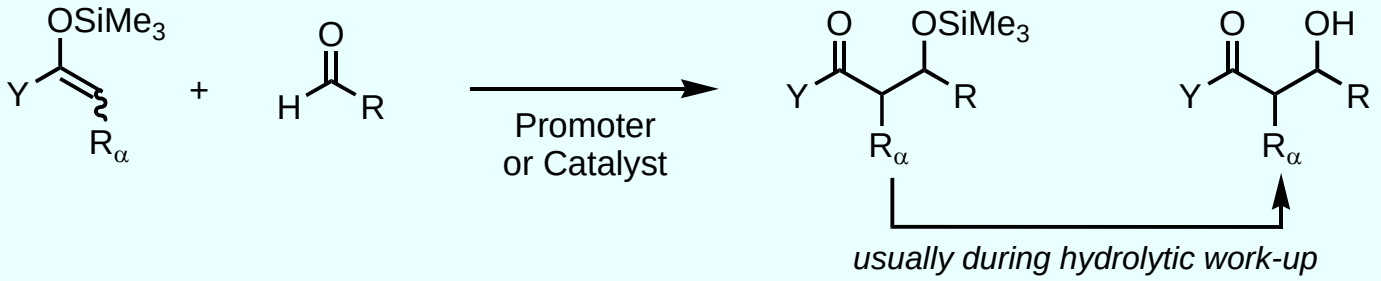


Filled σ_{Si-O} -> vacant p orbital

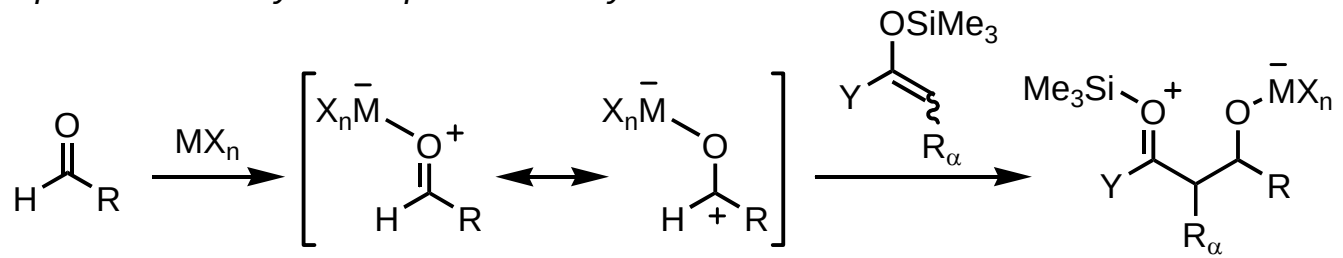
Examples of electrophiles: halogenating agents, enones and aldehydes (activated by Lewis acids)

(Nomenclature note) : Enoxysilanes (general), silyl enol ethers (more suitable for ketones/aldehydes)
Y = OR' (silyl ketene acetals), Y = NR'$_2$ (silyl ketene aminals)

Mukaiyama aldol reaction

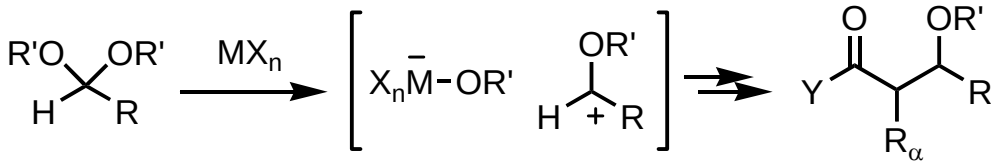


- *Reaction discovered by Mukaiyama (1973)*
- ***Trialkylsilyl enol ethers are unreactive toward aldehydes***
- *A promoter / catalyst is required : usually a* ***Lewis acid***



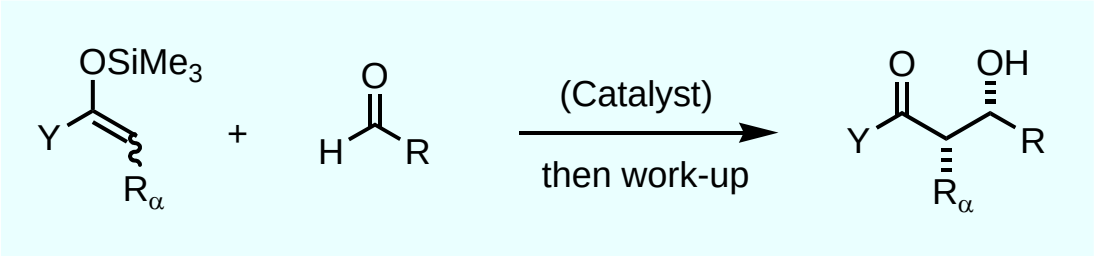
MX_n = $BF_3.OEt_2$, $TiCl_4$, $SnCl_4$...

- *Acetals can be used instead of aldehydes*

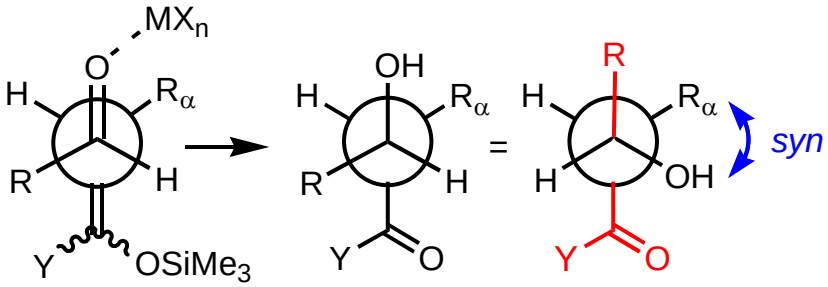


Angew. Chem. Int. Ed. **2013**, *52*, 9109

Mukaiyama aldol reaction : Diastereoselectivity

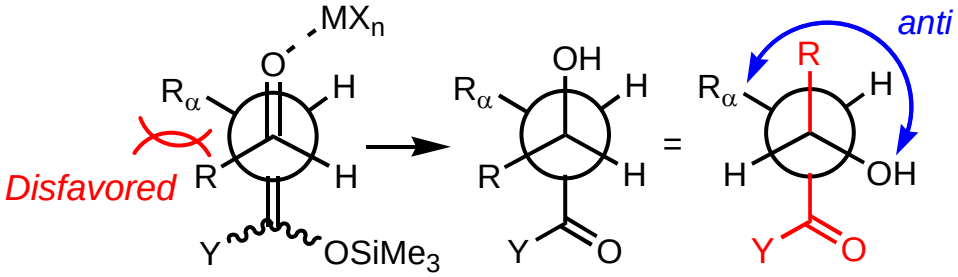


The reaction proceeds through an open TS



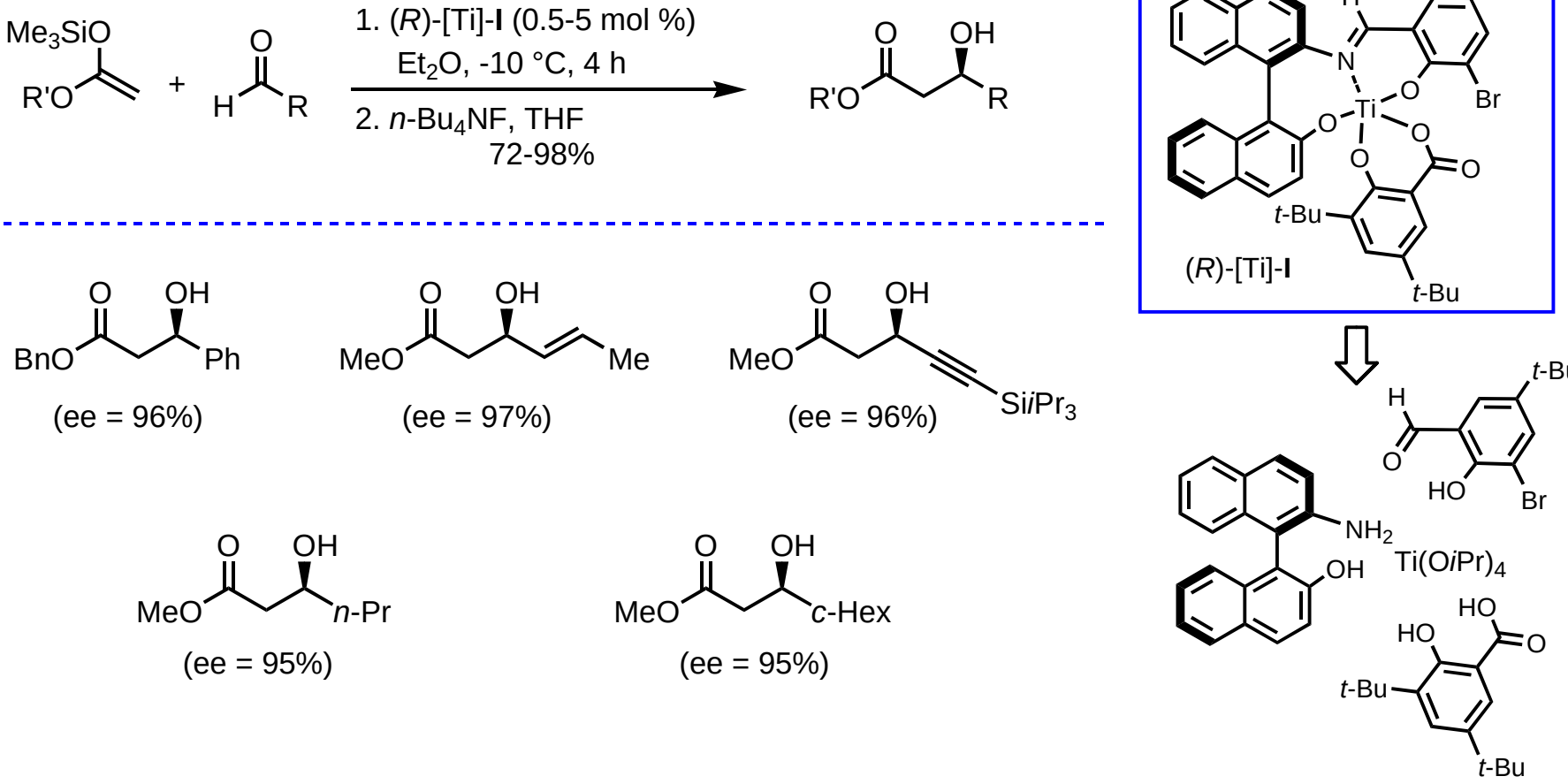
Antiperiplanar approach

syn
major diastereomer
regardless of enoxysilane geometry



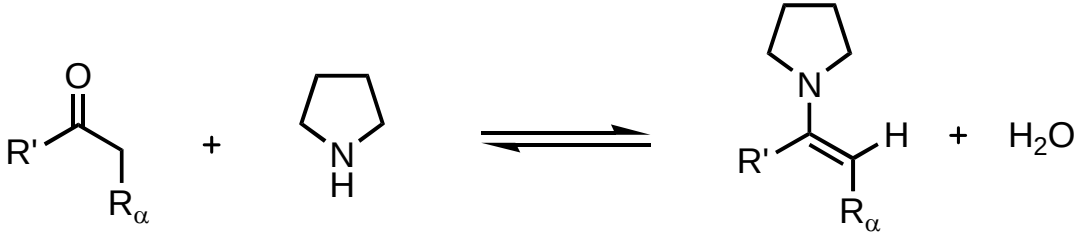
Note that this is nevertheless an oversimplified analysis

Example of catalytic enantioselective Mukaiyama aldol reaction

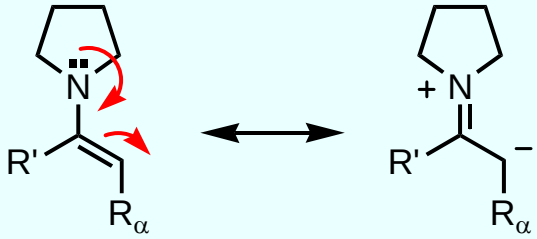


Carreira, E. M. *et al. JACS* **1994**, *116*, 8837; **1995**, *117*, 12360

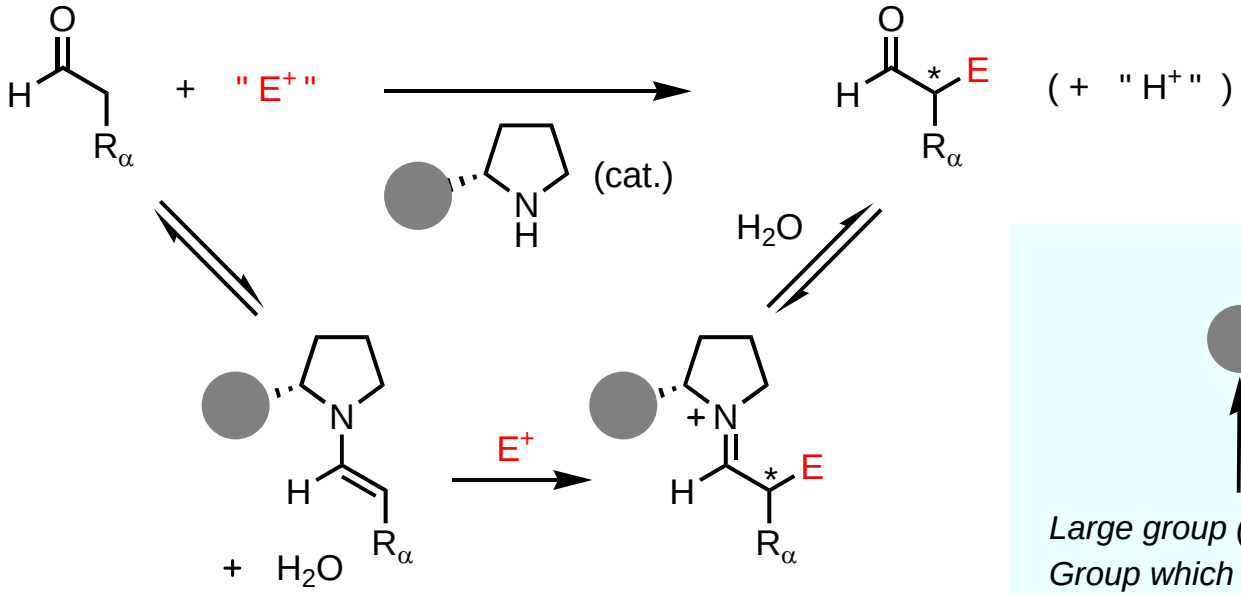
Enamines as nucleophiles : Organocatalyzed reactions

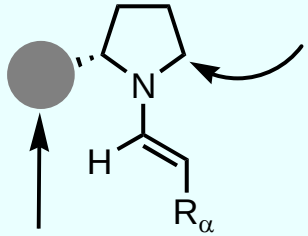


Enamine
(more nucleophilic than a silyl enol ether)



Organocatalysis : Use of (small) organic molecules as catalysts



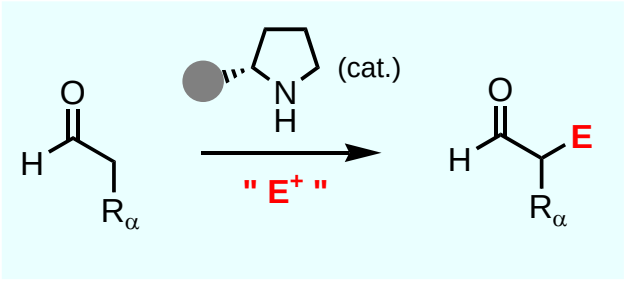


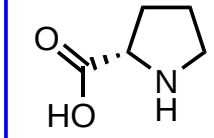
additional substituent can also be present at this position

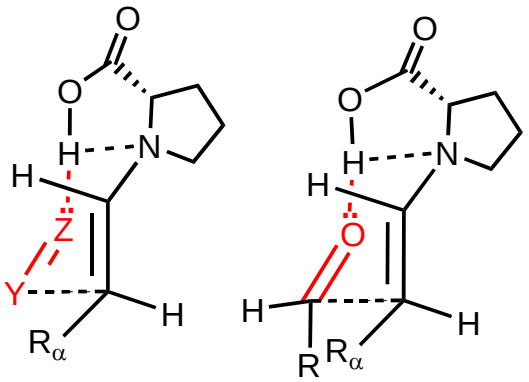
Large group (steric effect) or
Group which can interact with E^+ (directing effect)

Organocatalyzed α-functionalization of aldehydes

α-Functionalization of aldehydes

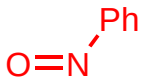



(*S*)-Proline

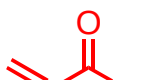

Y, Z = O, N

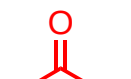
Bifunctional activation

Electrophile

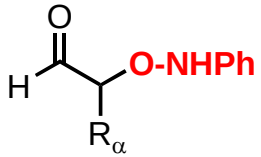


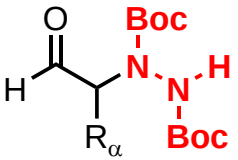
BocN=NBoc

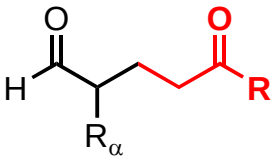


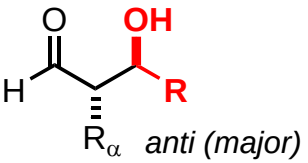


Product

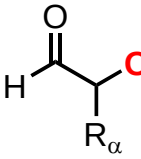






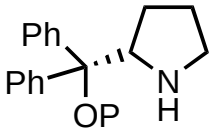


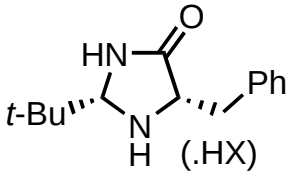
anti (major)

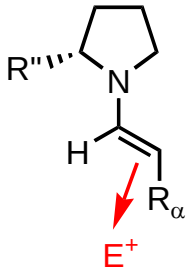


(after treatment with $CuSO_4$/MeOH)

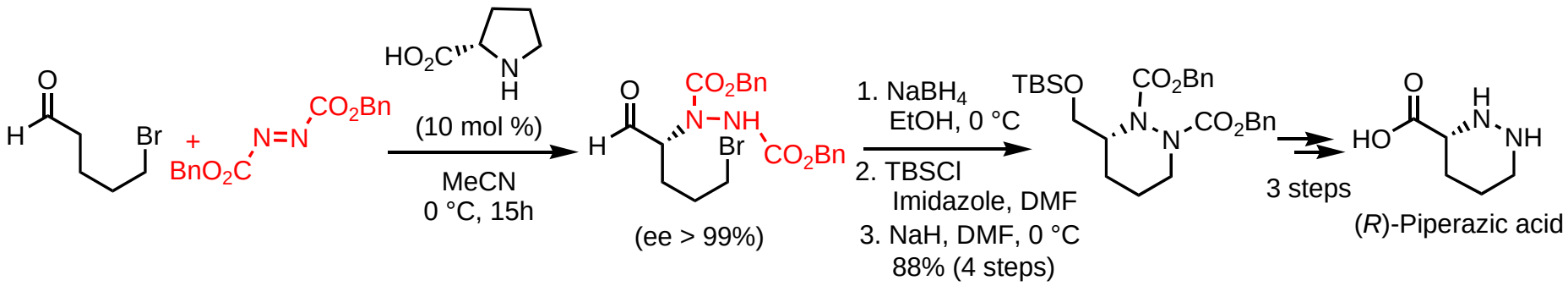
Enamine should not form with RCHO or at least very slowly
R = Aryl, α- or β-branched Alkyl


Hayashi-Jorgensen
(diphenylprolinol ethers)

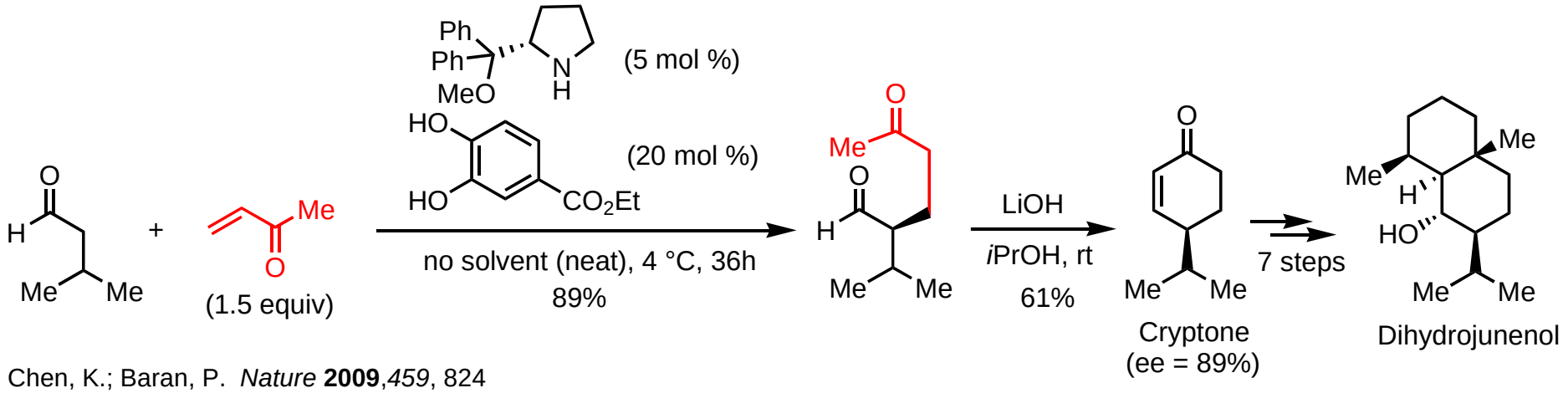

MacMillan
(imidazolidinones)



Organocatalyzed α-functionalization of aldehydes



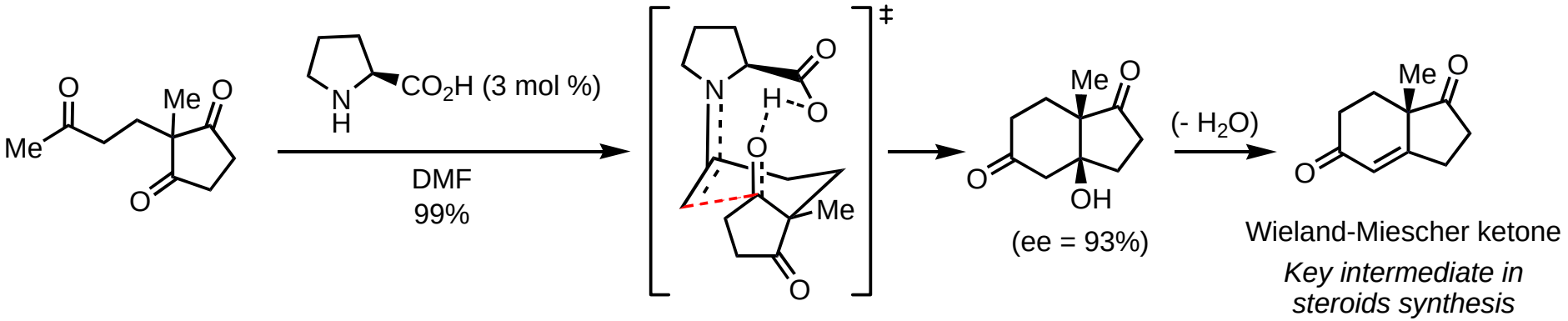
Hamada, Y. *et al. Tetrahedron: Asymmetry* **2004**,*15*, 3477



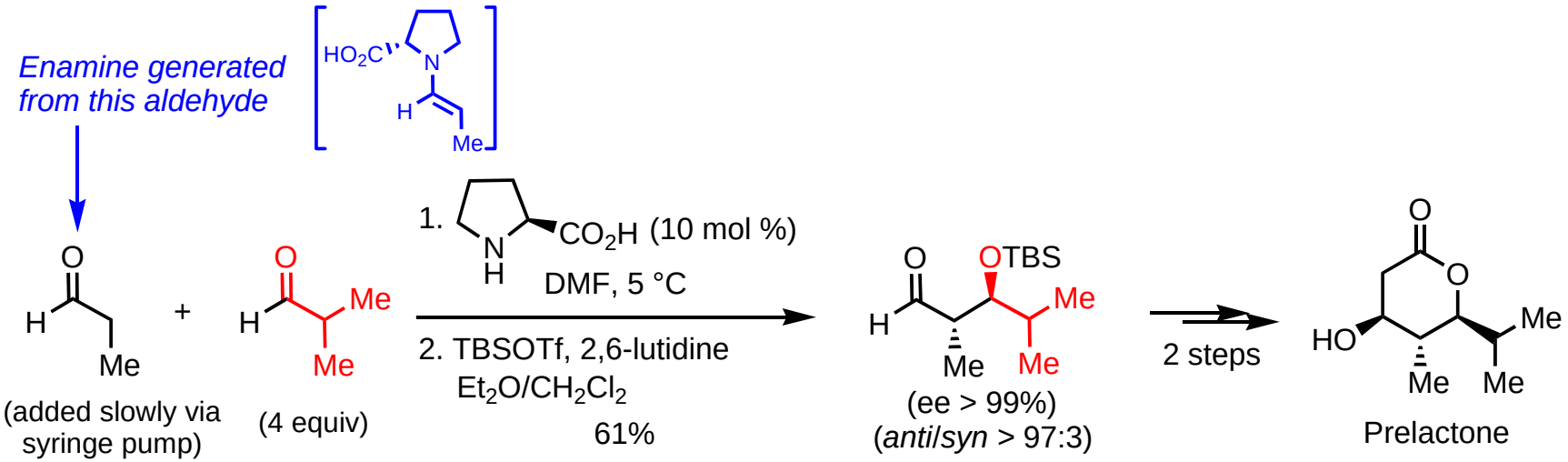
Chen, K.; Baran, P. *Nature* **2009**,*459*, 824

Proline-catalyzed aldol reactions

Hajos-Parrish-Eder-Sauer-Wiechert aldol reaction : a major breakthtough in organocatalysis



J. Org. Chem. **1973**, *38*, 3239; **1974**, *38*, 1615; *Angew. Chem., Int. Ed. Engl.* **1971**, *40*, 496

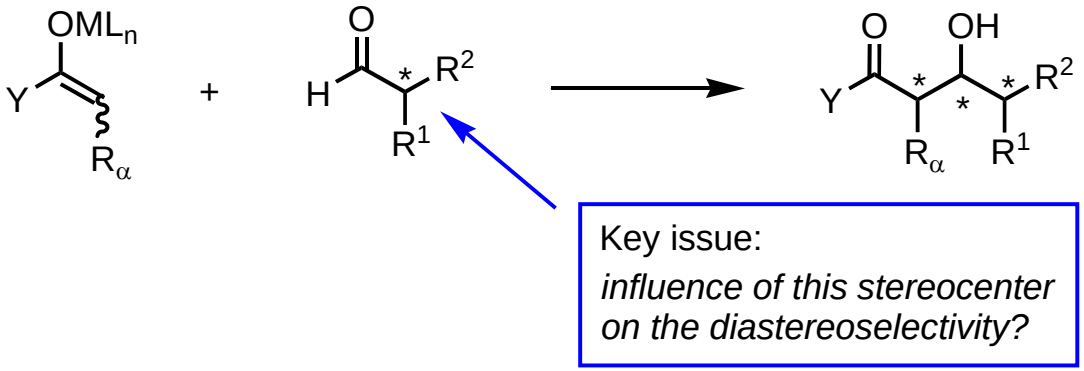


Tetrahedron Lett. **2006**, *44*, 7607

Aldehyde cross-aldol reaction: Northrup, A. B.; MacMillan, D. W. C. *JACS* **2002**, *124*, 6798

Aldol reactions involving chiral aldehydes

So far, we have considered **reagent-controlled** aldol reactions: chiral enolate/nucleophile + achiral aldehyde



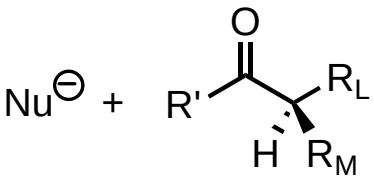
- **Achiral enolate** : **Substrate-controlled** aldol reactions with chiral aldehydes ?

- **Chiral enolate + chiral aldehyde** : **Double stereodifferentiating** aldol reactions

Stereocontrol by the enolate and the aldehyde can be **cooperative** : **Matched case**
Excellent diastereoselectivities will be observed

Stereocontrol by the enolate and aldehyde can be opposite : **Mismatched** case
Diastereoselectivities can be high but depends on the partners

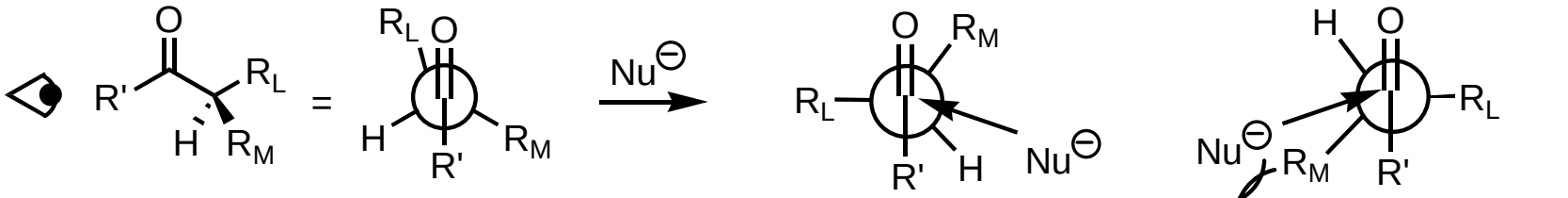
Nucleophilic addition to carbonyl compounds : Felkin-Anh model



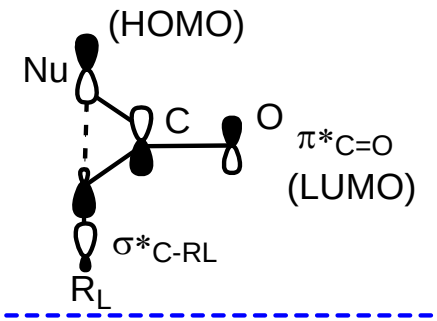
The substituents are ranked on the basis of their steric demand (L, M, S = H)

Felkin-Anh model

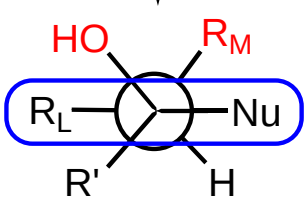
- Reactive conformers $R_L \perp$ C=O group
- Attack of the nucleophile: Bürgi-Dunitz trajectory angle 109°



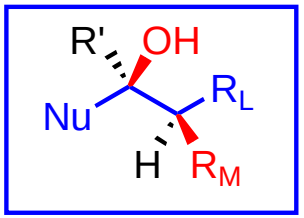
Best acceptor orbital $\sigma^*_{C\text{-}RL}$ and forming bond adopt antiperiplanar orientation



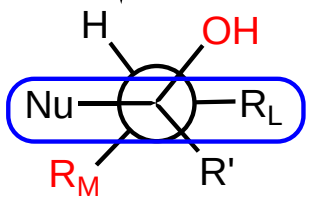
fast



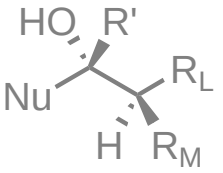
Major



slow



Minor

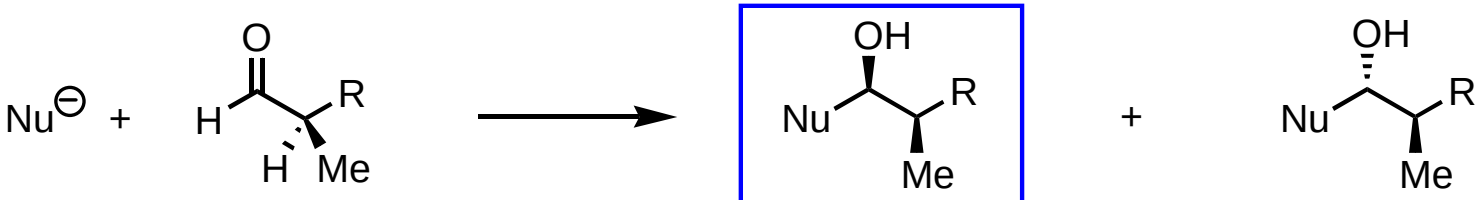


OH and R_M *syn*
in major diastereomer

Nucleophilic addition to carbonyl compounds : Felkin-Anh model

Assuming that the R (large) group does not exert any particular effect ...

Addition to α-methyl aldehydes

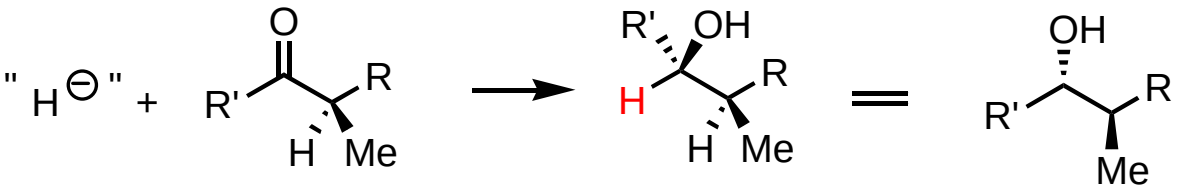


(R larger than Me)

major diastereomer
"Felkin-Anh"

minor diastereomer
"anti Felkin-Anh "

*For the **reduction of α-methyl substituted ketones**:*



major diastereomer

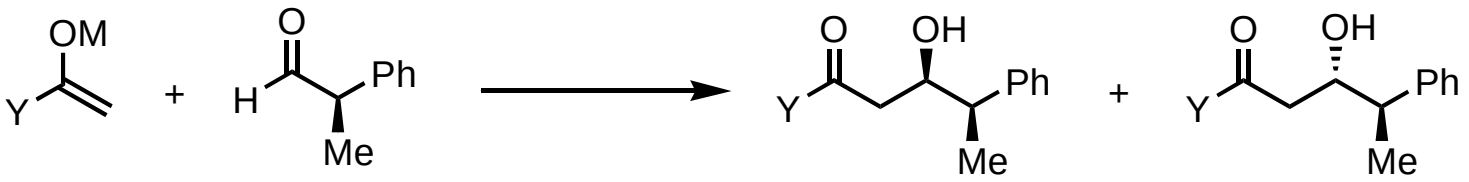
"Felkin"
diastereomer

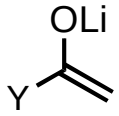
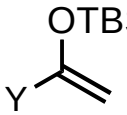
Nu = H

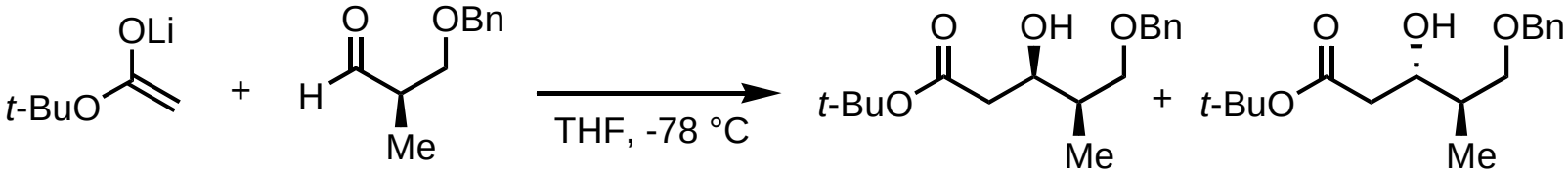
When Nu = H, the zig-zag has to be redrawn to extend the longest carbon chain

Review: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191

Examples with α-unsubstituted enolates/enoxysilanes



	Conditions	Y	*syn*/*anti*
	THF, -78 °C	Me	75:25
		MeO	75:25
		t-BuO	80:20
	$BF_3.OEt_2$ CH_2Cl_2, -78 °C	Me	**91:9**
		t-BuO	**97:3**

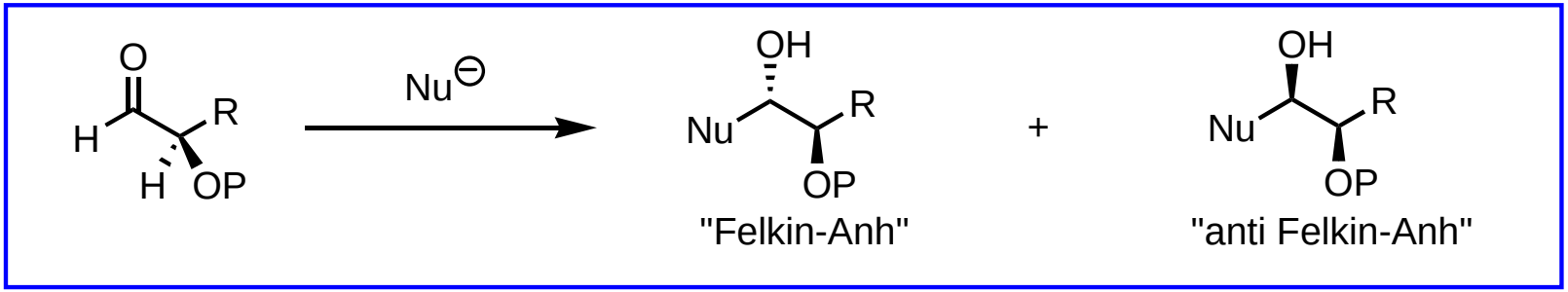


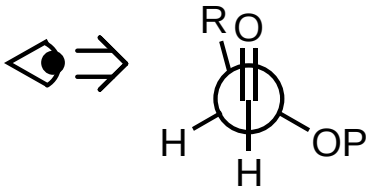
(*syn*/*anti* = 50:50)

Tetrahedron Lett. **1985**, *26*, 973; *Org. Lett.* **2008**, *10*, 2059

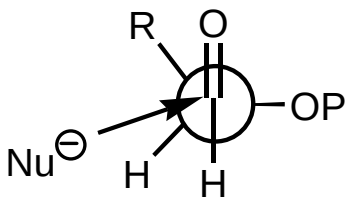
Felkin-Anh model for α-heterosubstituted aldehydes

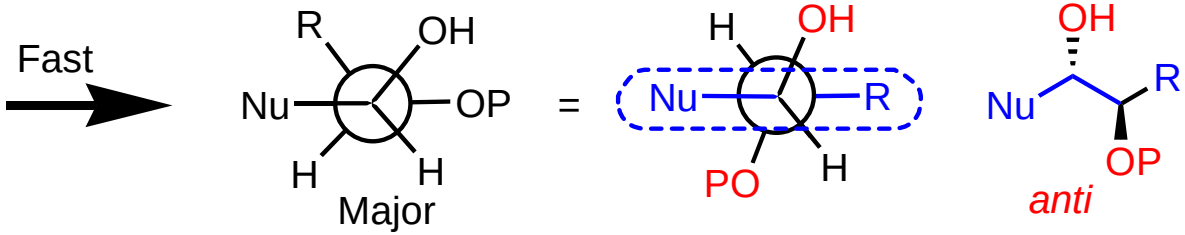
Electron-withdrawing substituents at the α position of the C=O group play the role of the large substituent R_L in the Felkin-Anh model for stereoelectronic reasons (low lying $\sigma^*_{C\text{-}OP}$ orbital overlaps with $\pi^*_{C=O}$ and also $\sigma_{C\text{-}Nu}$ in the TS)

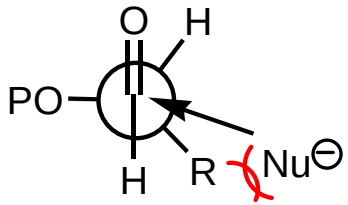


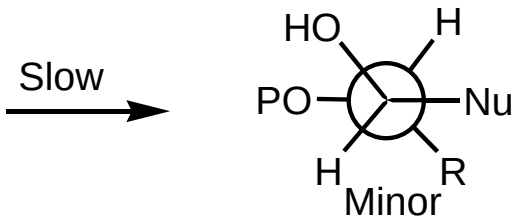


Felkin-Anh model with R_L = OP



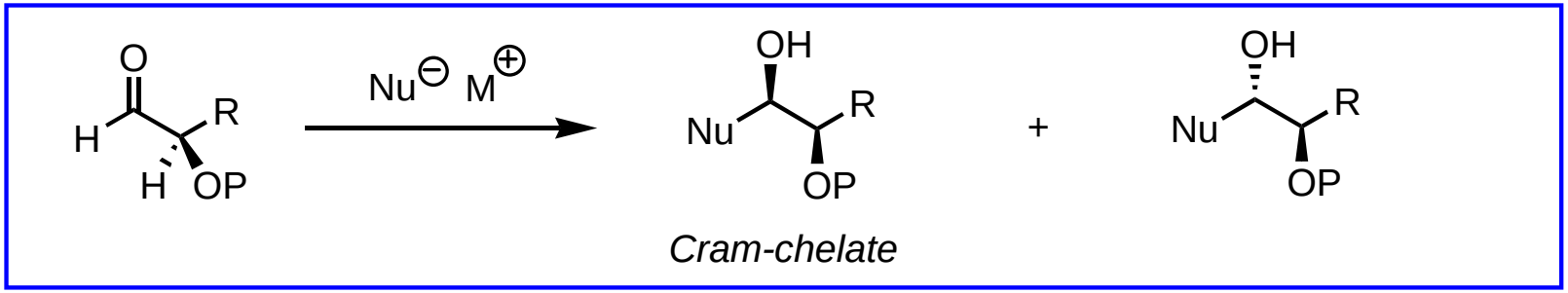


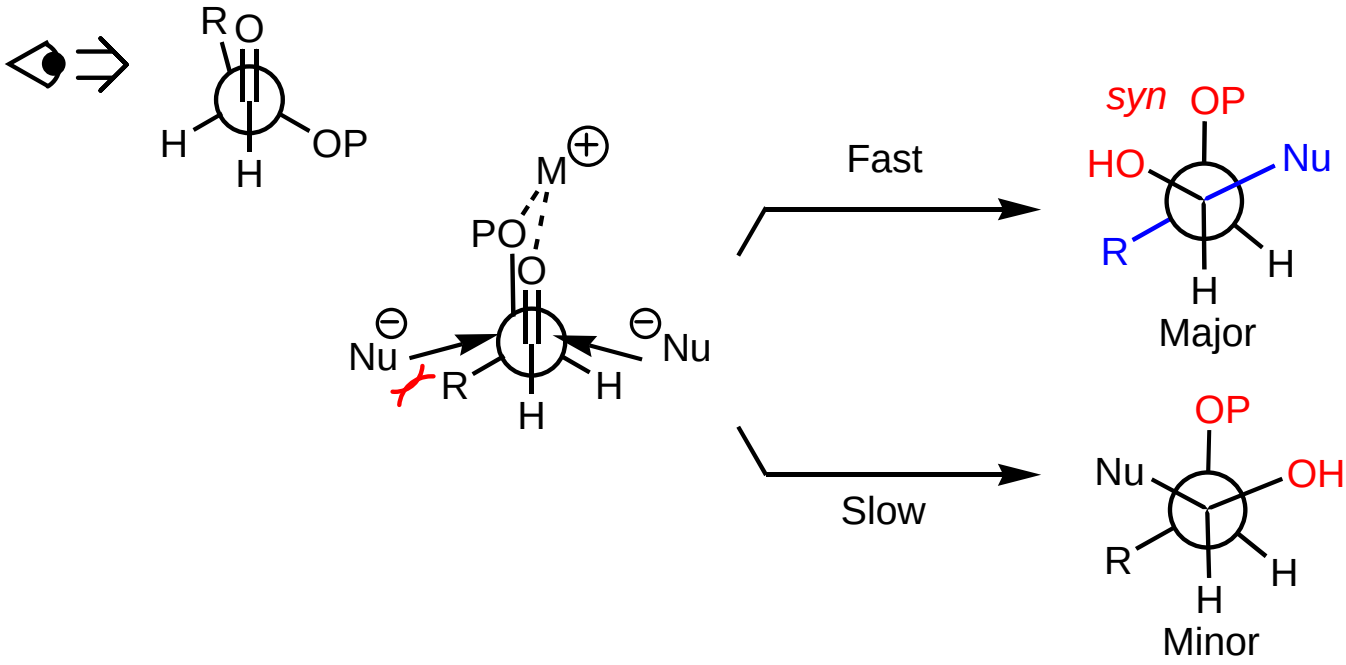




Cram chelate model for α-heterosubstituted aldehydes

An heteroatom at the α position can coordinate M^+ : Nucleophilic addition preferentially proceeds on the less-hindered face of the carbonyl group on the resulting chelate





Felkin-Anh versus Cram-chelate model for α-alkoxy aldehydes

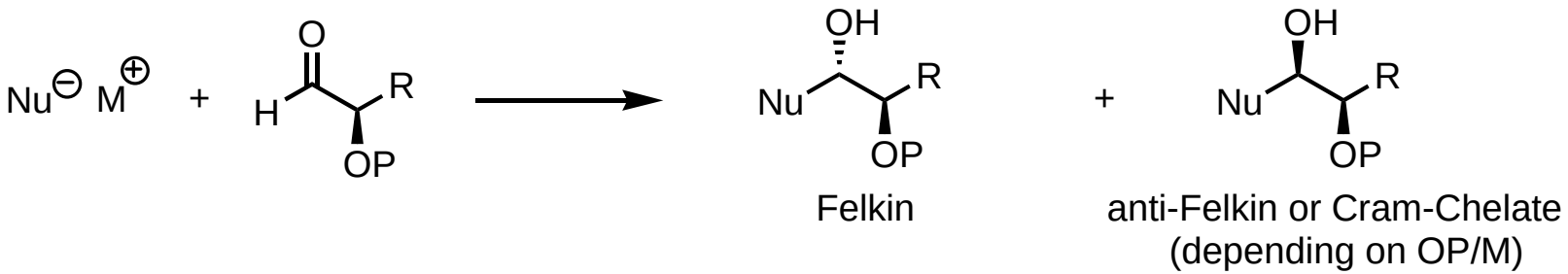
OTMS, $OSiMe_2t$-Bu, $OSiPh_2t$-Bu, $OSiiPr_3$
(OTBS) (OTBDPS) (OTIPS)

OP = OMe, OBn, OCH_2OMe (OMOM)

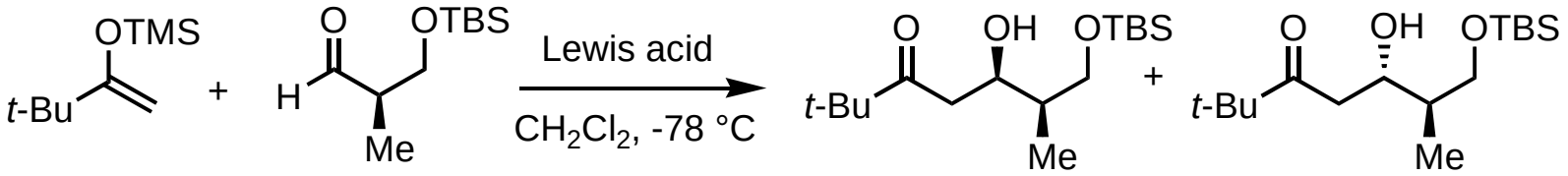
No chelation (in general)

Chelation depends on M^+,
the conditions (solvent), the presence
of additives (Lewis acids/bases)

- **The ability of M^+ to be chelated (or not) and its Lewis acidity should be considered**



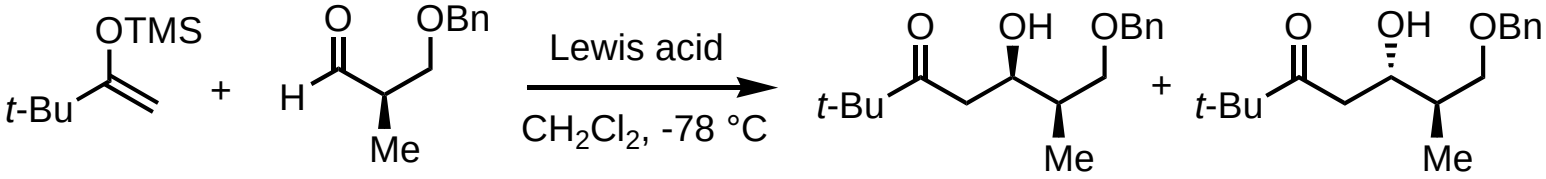
Influence of a β-alkoxy group

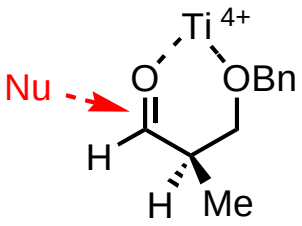


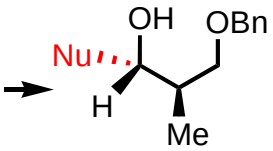
Felkin-Anh diastereomer

$BF_3.OEt_2$	91	:	9
$TiCl_4$	93	:	7

No chelation with OTBS (except in rare cases)



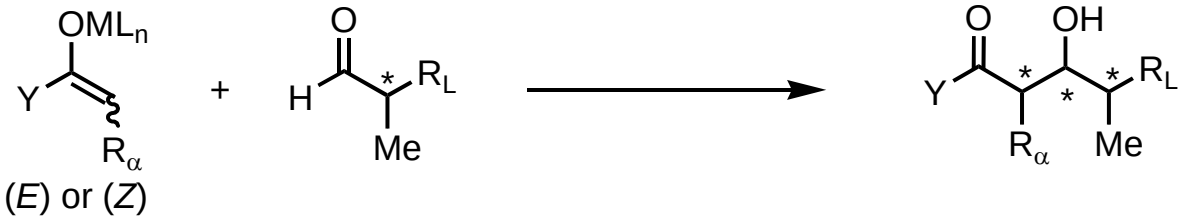




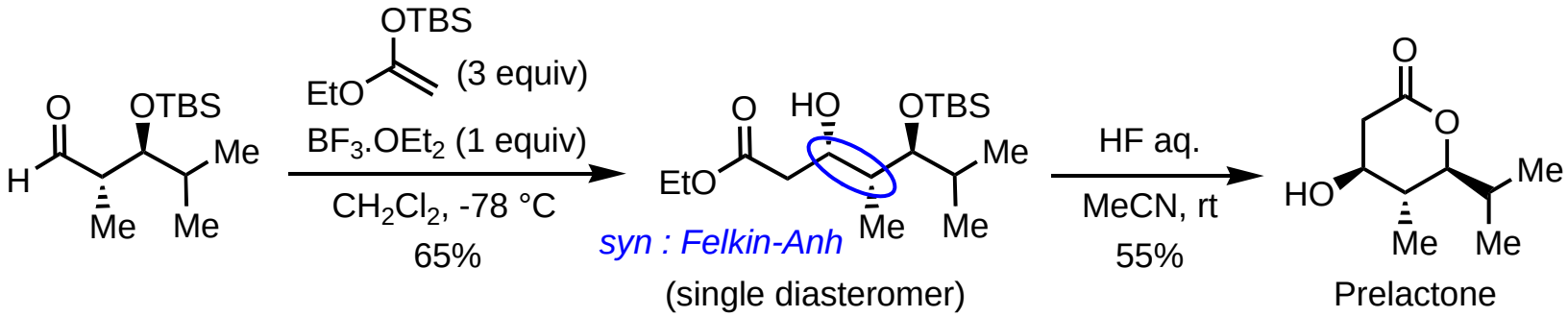
$BF_3.OEt_2$	74	:	26
$TiCl_4$	3	:	**97**

Chelation of Ti(IV) with β-OBn

Felkin-Anh model and aldol reactions



The Fekin-Anh/Chelate models apply well to Mukaiyama aldol reactions (open transition state)

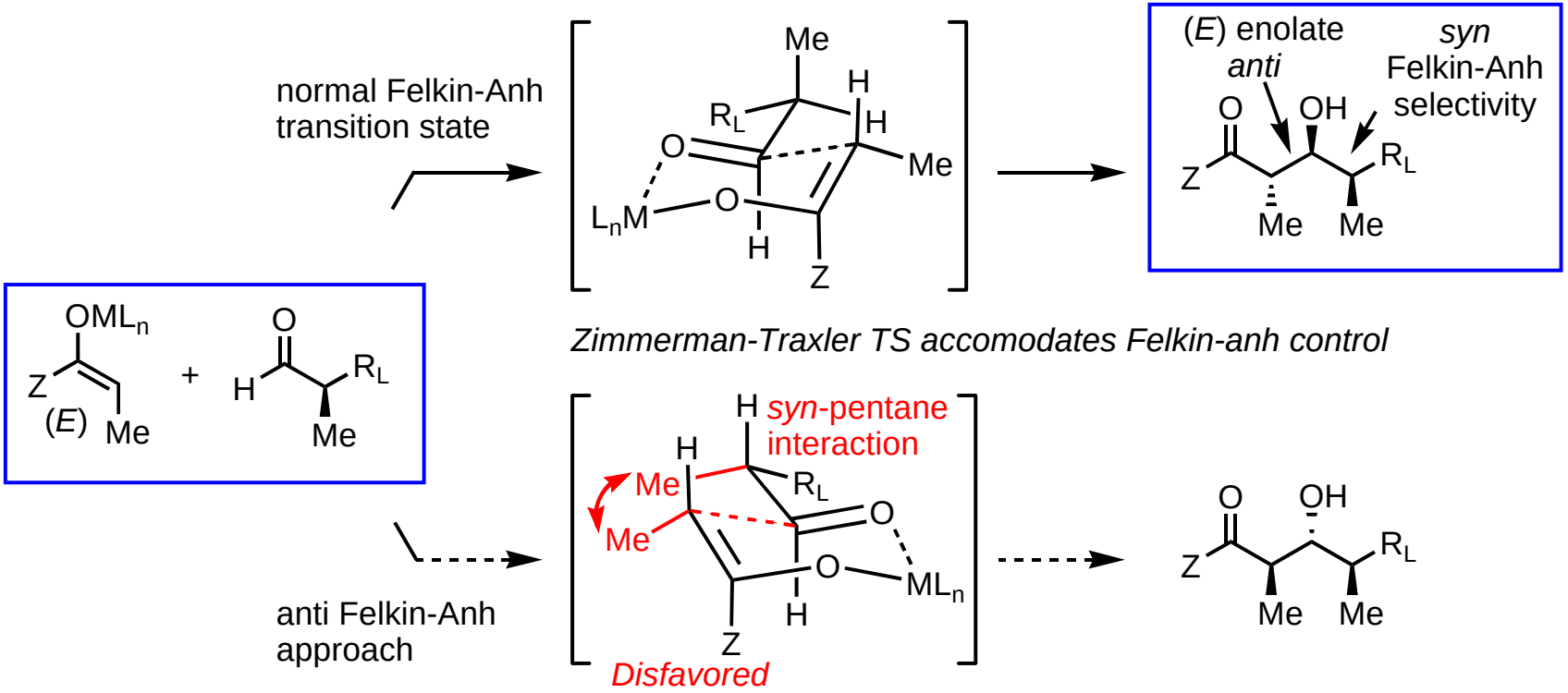


Tetrahedron Lett. **2003**, *44*, 7607

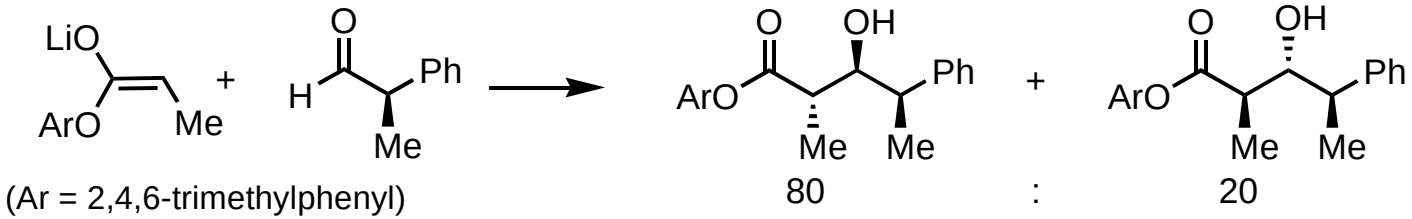
However the Felkin-Anh model does not consider the case of nucleophilic additions proceeding through an ordered (cyclic) transition state (ex: Zimmerman-Traxler transition state)

How do the Felkin-Anh and Zimmerman-Traxler transition state merge ?

Zimmerman-Traxler and Felkin-Anh models



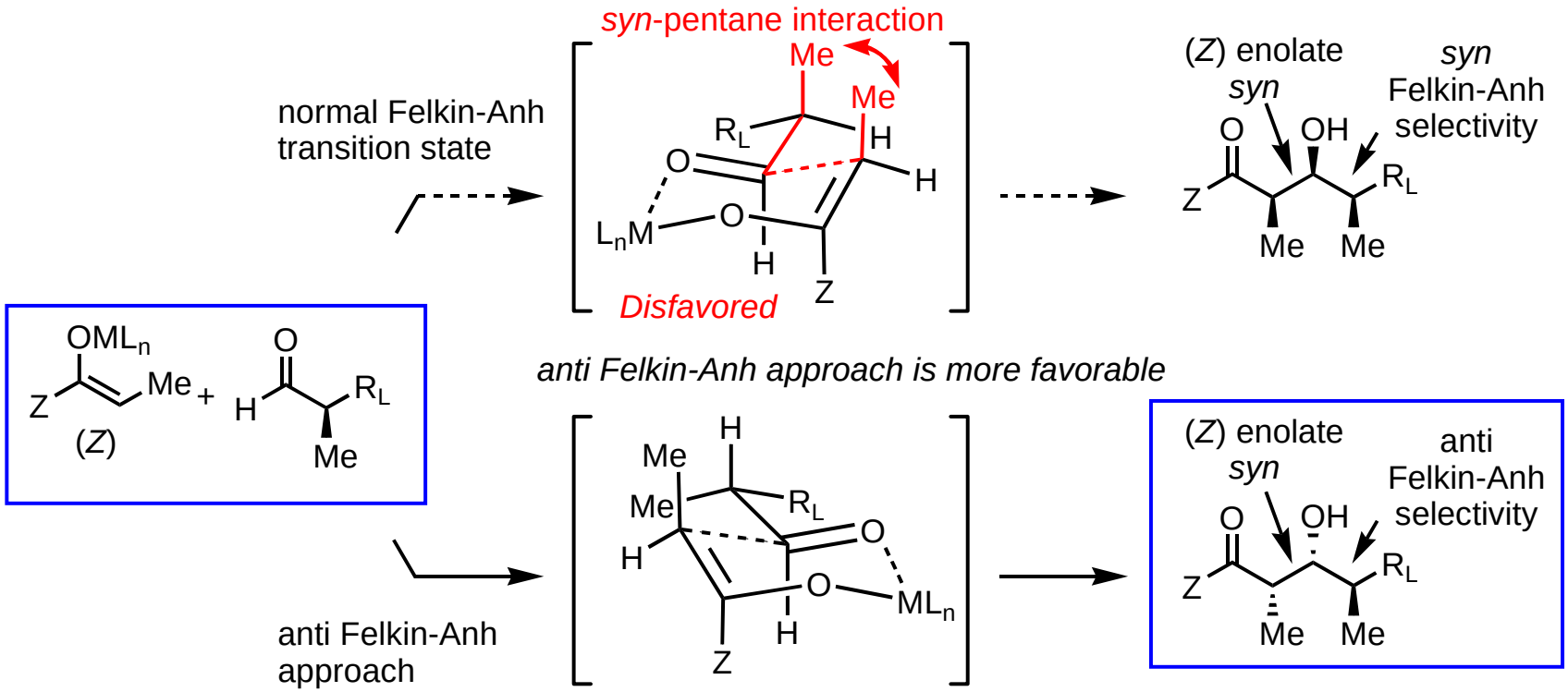
(E) enolates favor the Felkin-Anh diastereomers



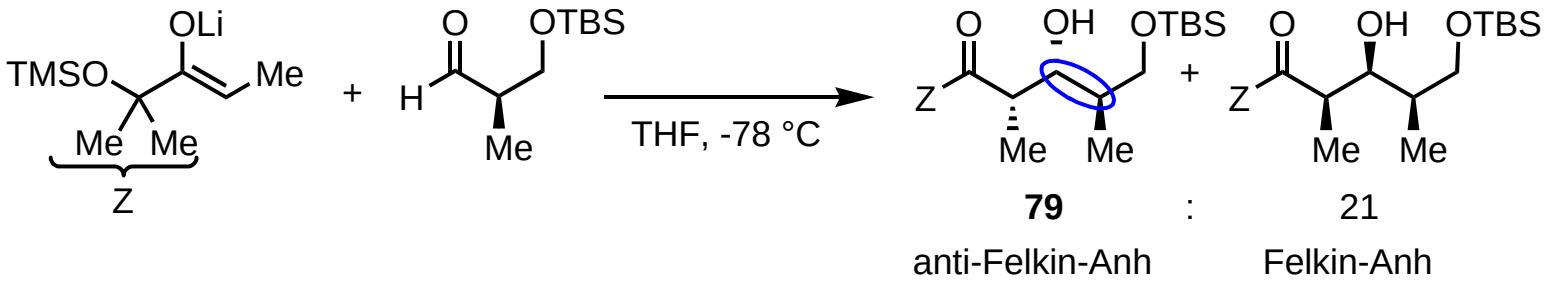
(Ar = 2,4,6-trimethylphenyl)

Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151

Zimmerman-Traxler and Felkin-Anh models

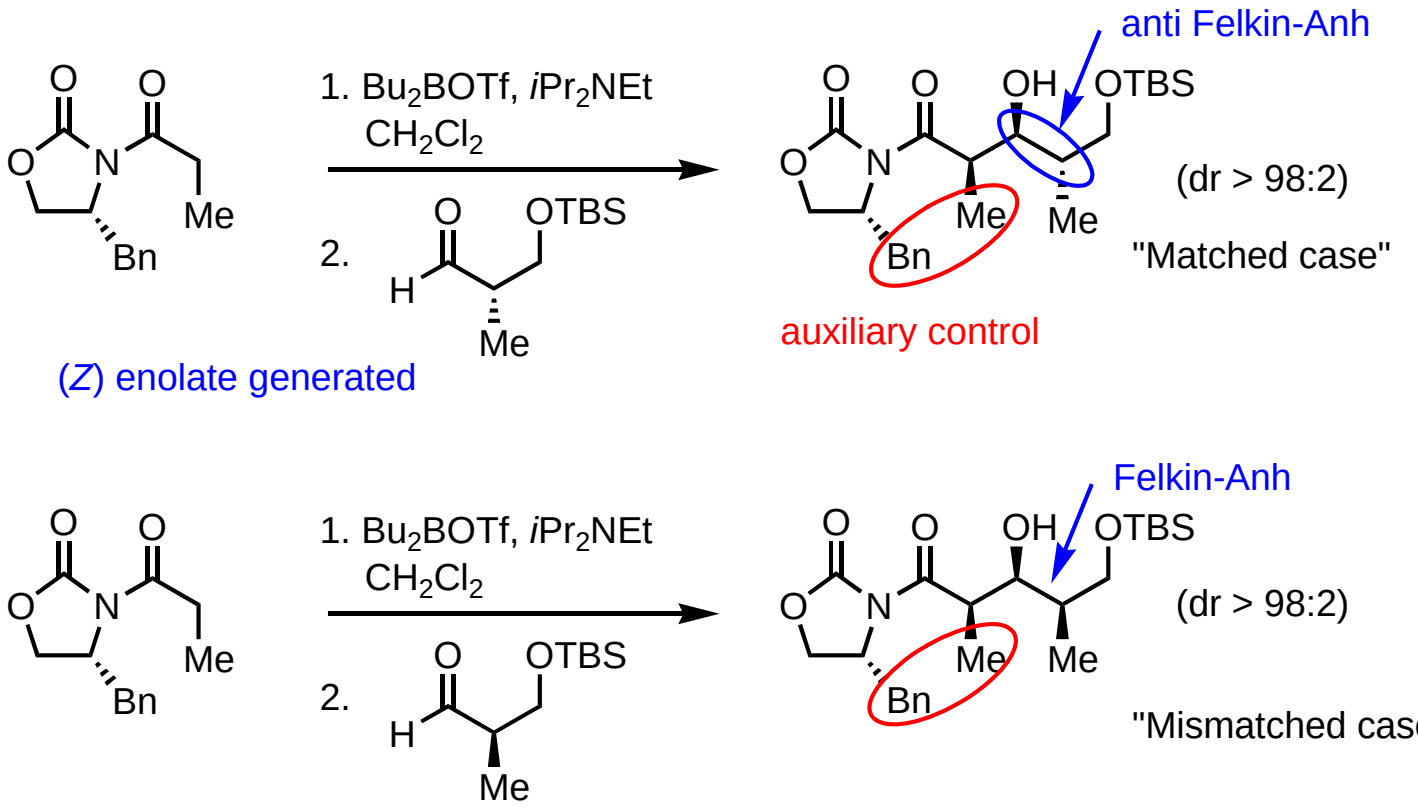


(Z) enolates favor the anti Felkin-Anh diastereomers



Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151

Double stereodifferentiating aldol reactions



Excellent diastereoselectivity (reagent-controlled) in both situations

Facial bias imposed by the reagent (oxazolidinone (Z)-boron enolate) overrides substrate control

Org. Lett. **2014**, *16*, 548; *Org. Lett.* **2002**, *4*, 4443; *JOC* **1993**, *58*, 5878

What needs to be remembered

Regioselectivity, **chemoselectivity** and **stereoselectivity** issues in a chemical reaction

Enantiomerically enriched α-substituted carbonyl compounds

*** Enolization of carbonyl compounds**

"Hard" enolization = deprotonation with amide bases (**typical pK_A values**)

Regioselectivity (**kinetic versus thermodynamic enolate**)

Stereoselectivity : **Ireland-Model** *Under kinetic control: Amides -> (Z) enolates, esters -> (E) enolates*
For esters, reversal of selectivity -> (Z) enolates in THF/HMPA or THF/DMPU

***O*-silylation of enolates**

*** Evans oxazolidinones : Alkylation, hydroxylation, azidation and hydrazination reactions**

Reagents *(alkylating halides, Davis oxaziridine, trisyl azide and BocN=NBoc)*

You should be able to explain the ***stereochemical outcome of these reactions***

Cleavage of the auxiliary (LiOH, LiOOH, reduction: $LiAlH_4$, THF; $LiBH_4$, THF/MeOH or $NaBH_4$, THF/H_2O)

Alternative auxiliary for alkylations: Myers pseudoephedrine propionamide (*Only the principle not the stereochemical control*)

*** Aldol reactions**

Zimmerman-Traxler model: (*Z*)-enolates -> *syn* aldols, (*E*)-enolates -> *anti* aldols

Interest of boron enolates (tighten the transition state)

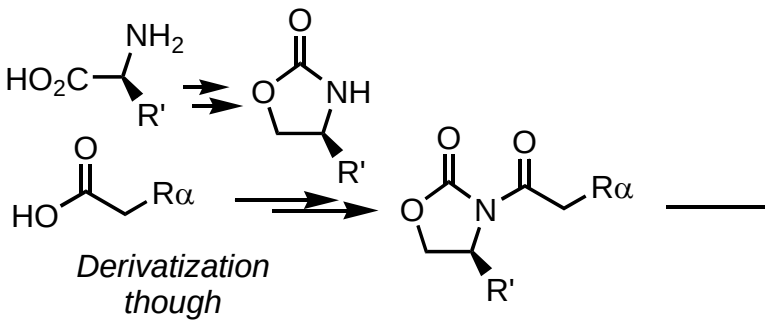
Evans aldol reaction

Conditions (soft enolization), formation of a (*Z*) boron enolate

You should be able to explain the ***stereochemical outcome of these reactions***

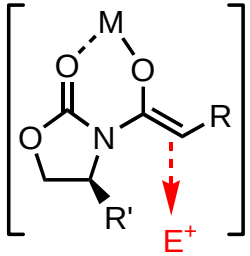
Cleavage of the auxiliary : LiOOH, reduction, transamidation to Weinreb amides and interest of Weinreb amides

What needs to be remembered



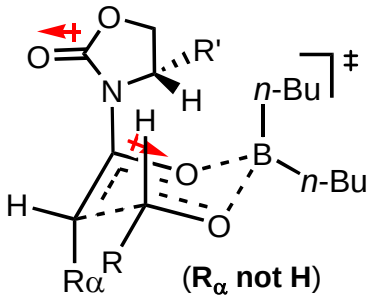
Derivatization though acyl chloride or mixed anhydride

(Z) chelated enolate



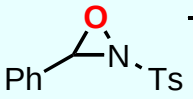
(*Z*) boron enolate

Zimmerman-TraxlerTS
dipole-dipole +
steric interactions minimized



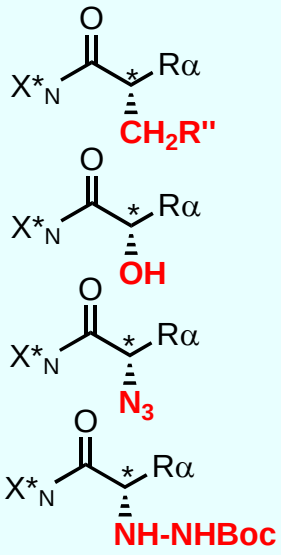
LDA or LiHMDS, or NaHMDS, THF, -78 °C — **$R''CH_2Br$** or **$R''CH_2I$**

NaHMDS, THF, -78 °C (quench with H^+ at -78 °C)



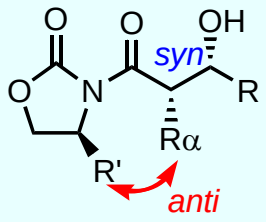
KHMDS, THF, -78 °C (quench with H^+ at -78 °C) — **N_3-SO_2Ar** (trisyl azide)

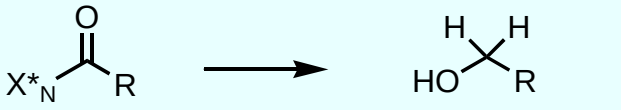
LDA or LiHMDS, THF, -78 °C — **BocN=NBoc**



Evans aldol reaction

1. *n*-Bu_2BOTf (1 equiv), *i*Pr_2NEt, CH_2Cl_2
2. RCHO, -78 °C
3. Work-up with H_2O_2, pH 7 buffer, MeOH





Cleavage reactions of oxazolidinones

$LiAlH_4$, THF, $LiBH_4$, THF/MeOH or $NaBH_4$, THF/H_2O

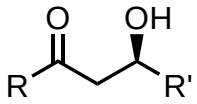
LiOH, THF/H_2O
better: LiOH, 35% aq. H_2O_2 H_2O/THF (LiOOH)

In some cases NaOMe, $Mg(OMe)_2$ $Ti(OBn)_4$

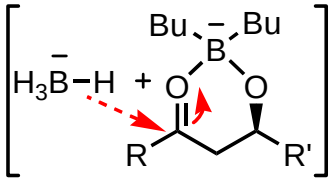
For aldols (*free OH required*) Me(MeO)NH.HCl, Me_3Al THF or CH_2Cl_2

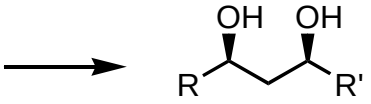
What needs to be remembered

Diastereoselective reduction of β-hydroxyketones

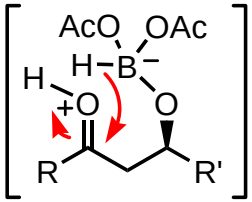


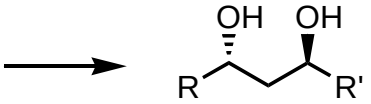
$Bu_2B(OMe)$ or $Et_2B(OMe)$
$LiBH_4$ or $NaBH_4$, THF/MeOH
or $Zn(BH_4)_2$, Et_2O





$Me_4N^+ {}^-BH(OAc)_3$
MeCN/AcOH





*You should know the **reagents** and the principle of these diastereoselective reductions*
(chelation/external hydride delivery or ligand exchange/intramolecular hydride delivery on protonated carbonyl group)

Mukaiyama aldol reactions

Enoxysilanes (silyl enol ethers) as partners: **a Lewis acid promoter/catalyst** is required (general mechanism)

*You should be aware that those reactions proceed through **an open TS***
(syn diastereoselectivity regardless of enoxysilane geometry)

Enantioselective versions have been developed using chiral Lewis acid catalysts (principle only)

Organocatalyzed α-functionalization of aldehydes

With *in situ* generated **enamines** as nucleophiles (general mechanism)

Examples of catalysts (proline, prolinol derivatives, imidazolidinones)

Representative reactions: oxyamination (O=NPh)/hydroxylation, hydrazination, 1,4-addition, cross-aldol reactions

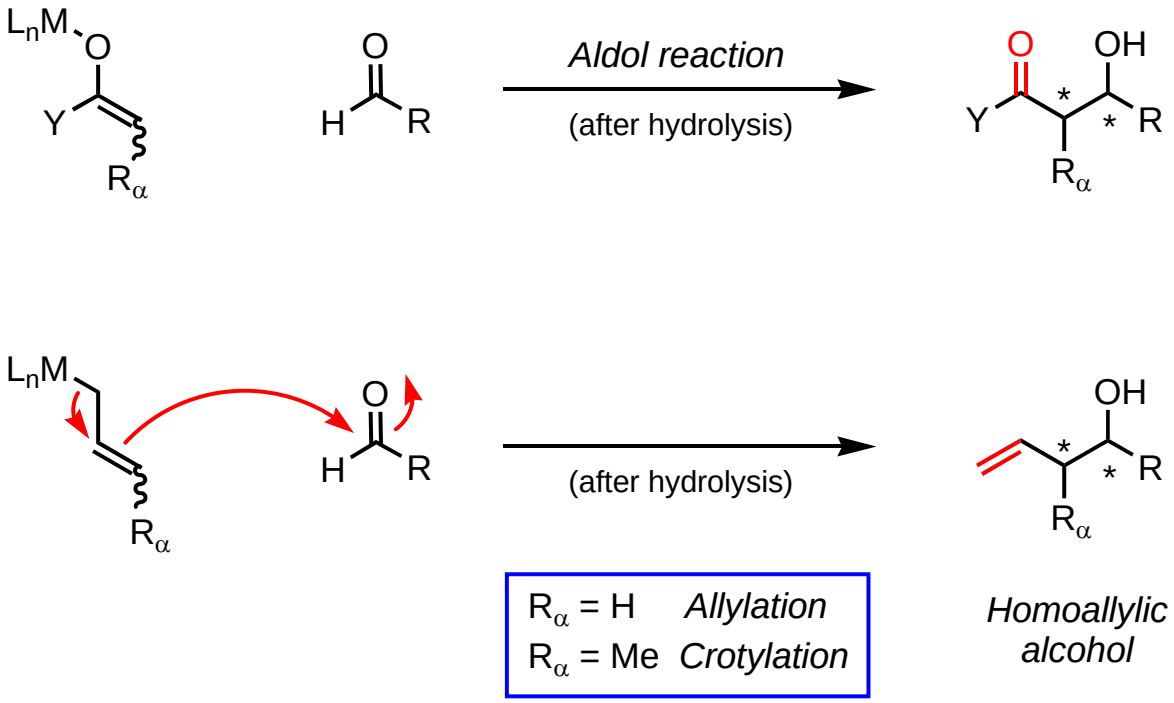
Addition to α-substituted carbonyl compounds

Felkin-Anh and Cram chelate models (α-heteromatom), β-chelation

*You should be able **to draw the models** and **predict/analyze the diastereoselectivity** of nucleophilic additions*

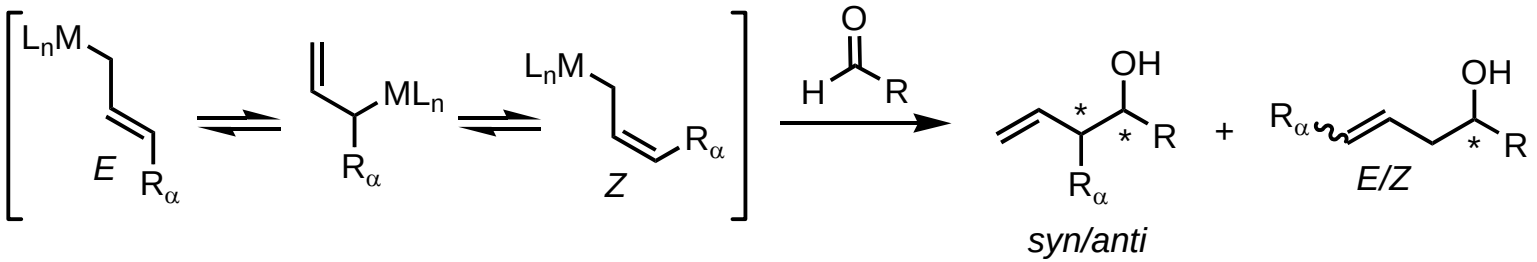
You should be aware that for aldol reactions proceeding through cyclic TS (Zimmerman-Traxler TS),
the stereochemical outcome depends on the geometry of the enolate (*E* : Felkin-Anh control, *Z*: anti-Felkin-Anh control)
but a detailed explanation does not need to be remembered at this stage

Allylation/Crotylation of aldehydes



Allylic organometallic reagents

Key issue : ***metallotropic equilibrium***



Three different types of allylic organometallic reagents

1. **Highly covalent C–M** bond and **M not significantly Lewis acidic**
   Configurationally stable
   Activation of **aldehyde by a Lewis acid required** (open TS)

   ML_n = $SnBu_3$, $SiMe_3$

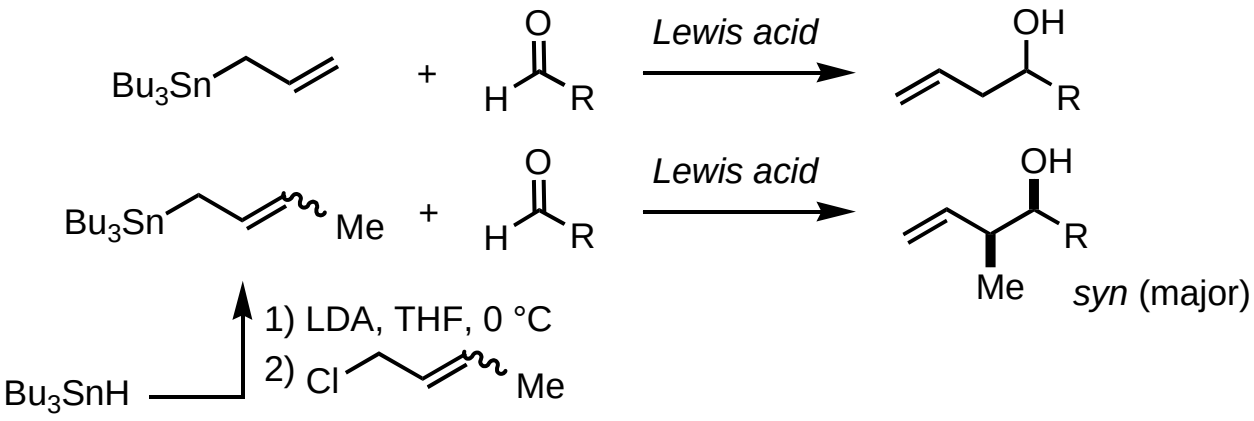
2. **Covalent C–M bond**, **M Lewis acidic**
   (Very) slow metallotropic equilibrium (**configurationally stable**)
   Addition occurred without a catalyst (through a cyclic TS)

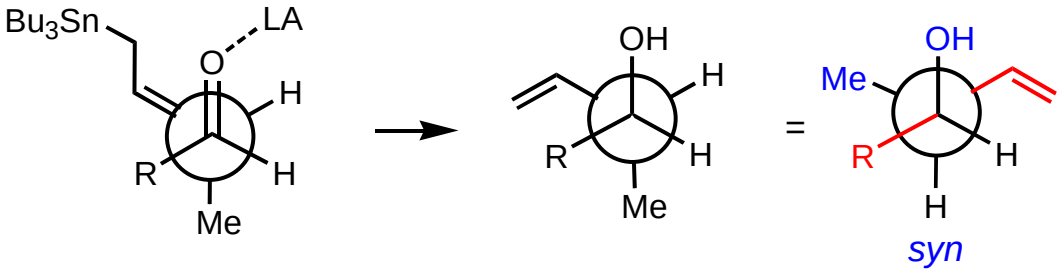
   ML_n = BR_2, $B(OR)_2$

3. **Ionic C–M bond**, **M Lewis acidic**
   Rapid metallotropic equilibrium, not configurationally stable
   Addition occurred without a catalyst (through a cyclic TS)

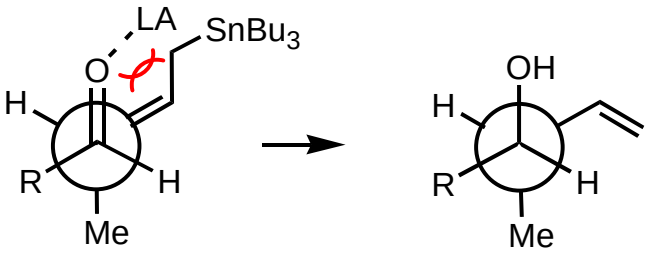
   ML_n = Ti(IV), Cr(III)

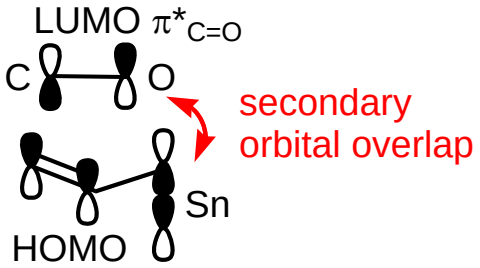
Addition of allyl- and crotylstannanes





(*E*) ***Open synclinal TS***

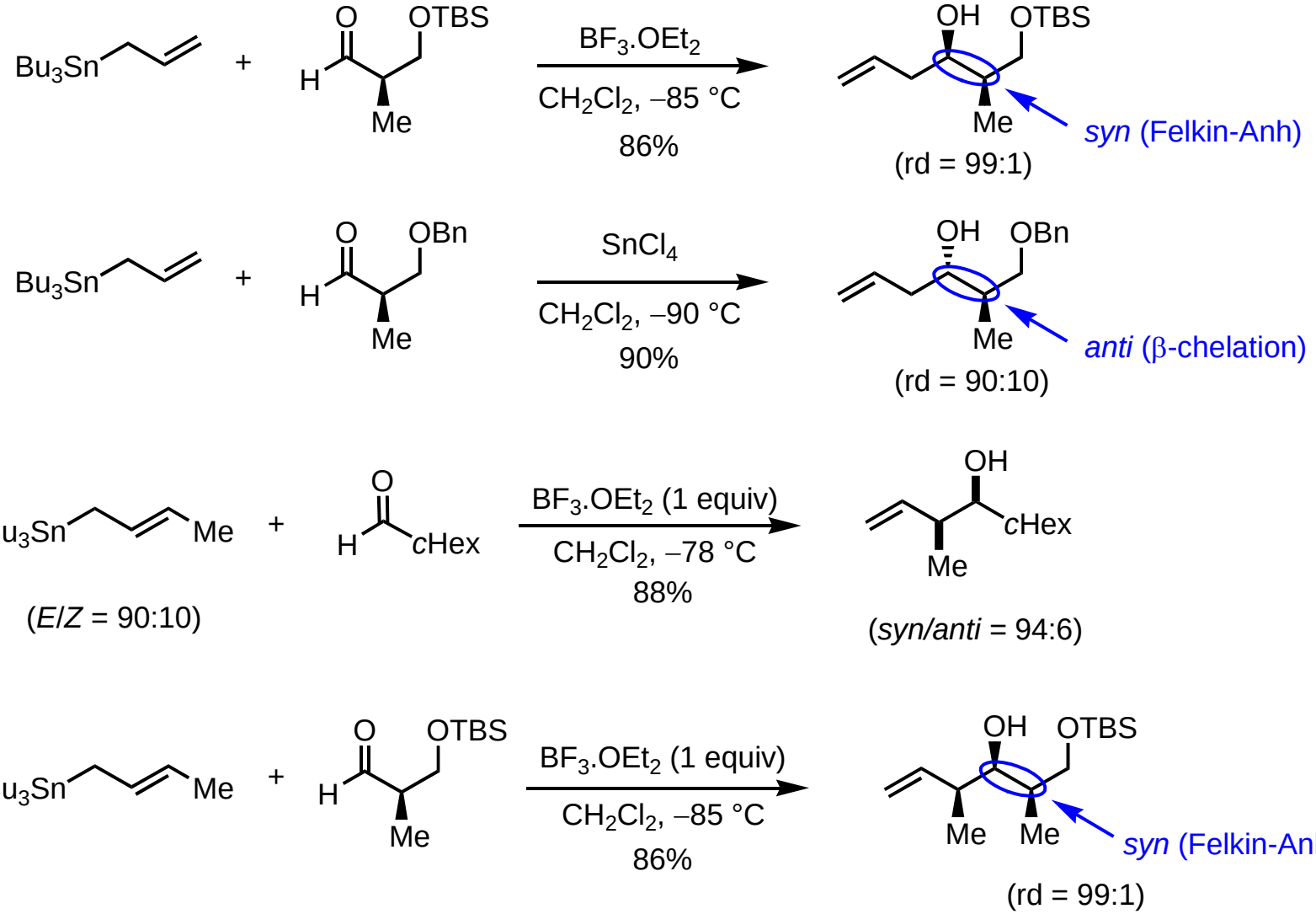




(*Z*) isomer much less selective than (*E*)

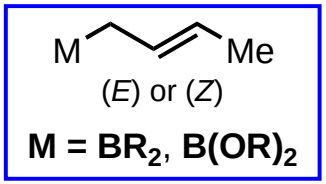
Denmark, S. E. *et al. JACS* **1988**, *110*, 984; Keck, G. E. *J. Org. Chem.* **1994**, *59*, 7889

Addition of allyl- and crotylstannanes

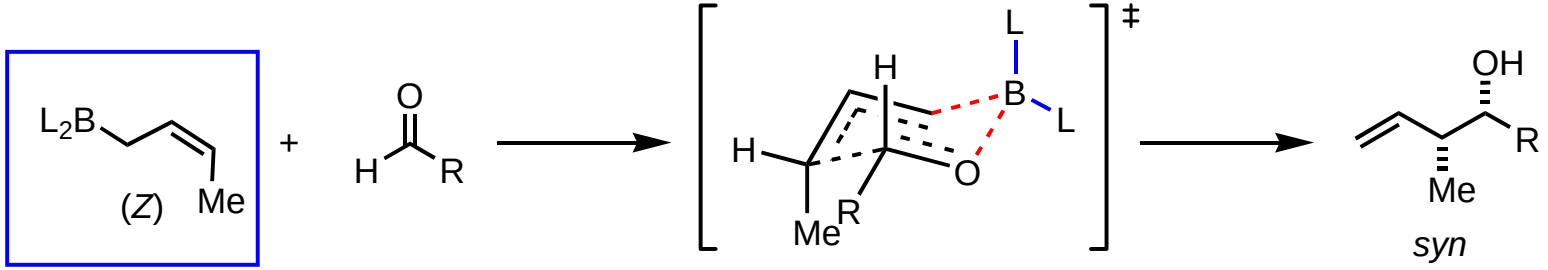


Keck, G. E. *Tetrahedron Lett.* **1984**, *25*, 1883; *J. Org. Chem.* **1994**, *59*, 7889

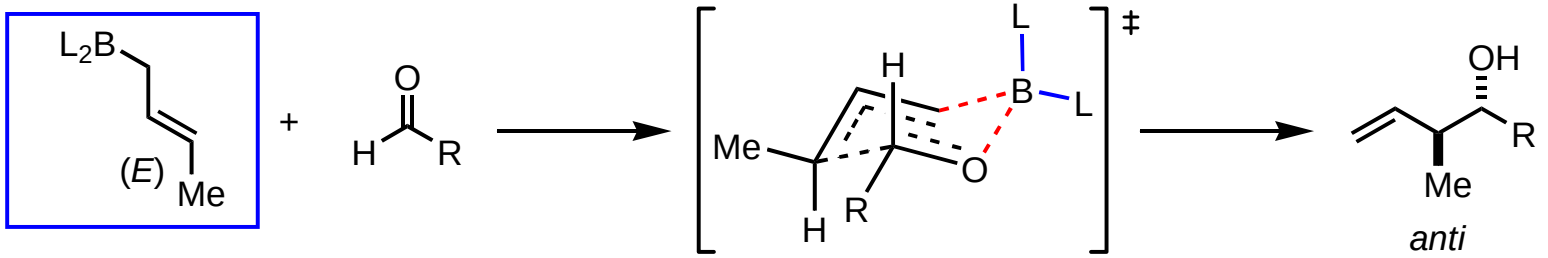
Addition of allyl- and crotylboranes/boronates



Very slow metallotropic equilibrium at least at low temperatures
(organoboronates more stable/less reactive than organoboron)

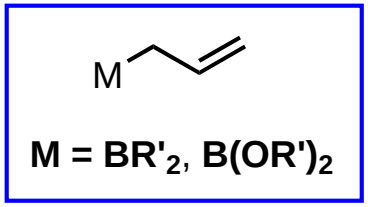


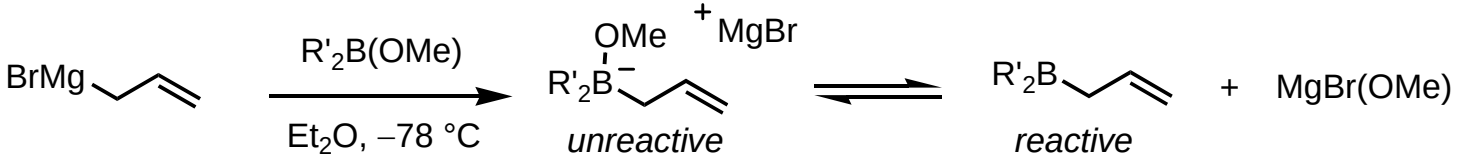
Zimmerman-Traxler transition state

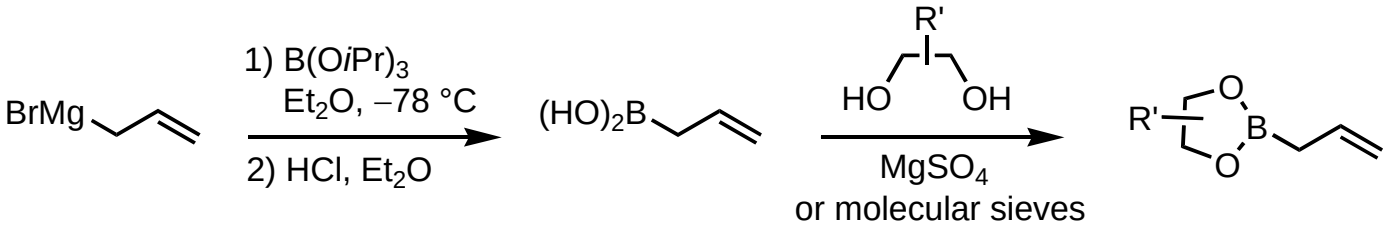


For allylic organoboron reagents, products are usually isolated after an oxidative hydrolytic work-up (NaOH, 30 % H_2O_2 or sometimes $NaBO_3$) (oxidation of C-B bonds of the ligands, B–L -> HO–L)
For allylic organoboronates (M = $B(OR)_2$), a standard hydrolytic (acidic) work-up can be used

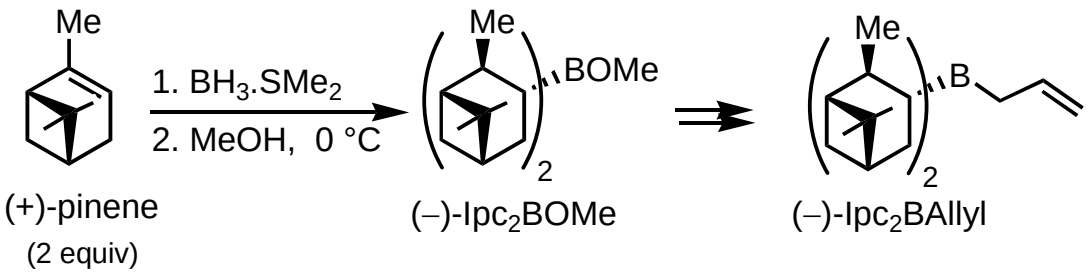
Preparation of allylboranes/boronates



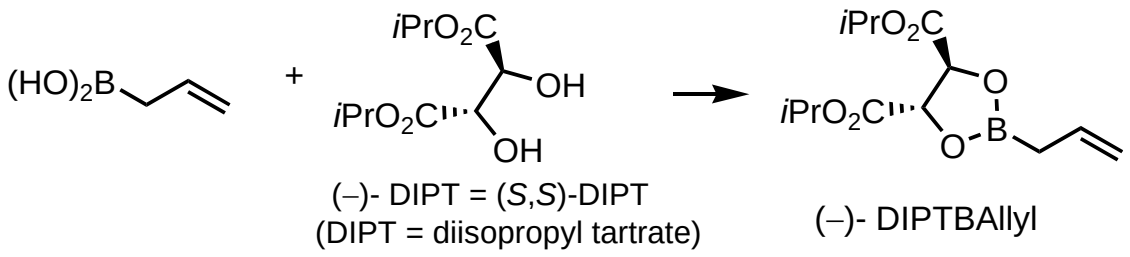




Chiral reagents

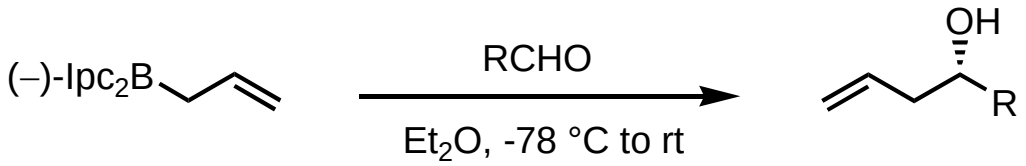


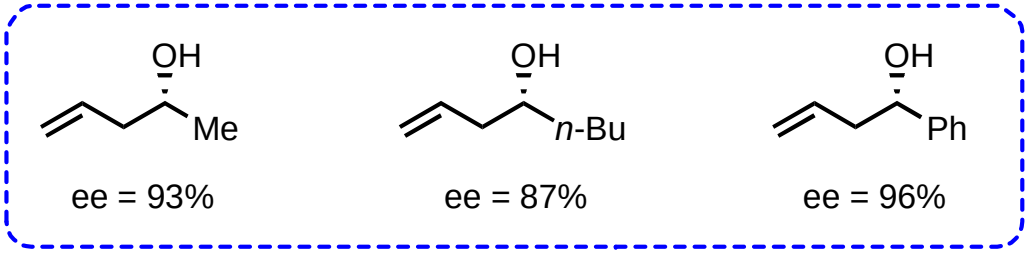
H.C. Brown

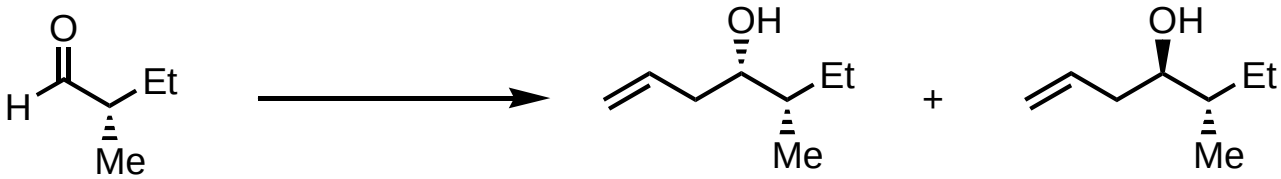


W. R. Roush

Allylboration of aldehydes

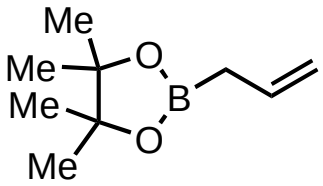






(-)-Ipc$_2$B	96	:	4
(+)-Ipc$_2$B	5	:	95
pinB	62	:	38

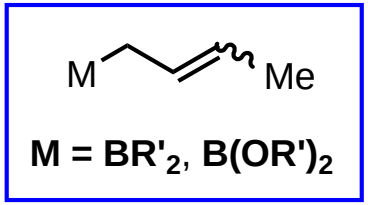
Reagent-controlled reactions

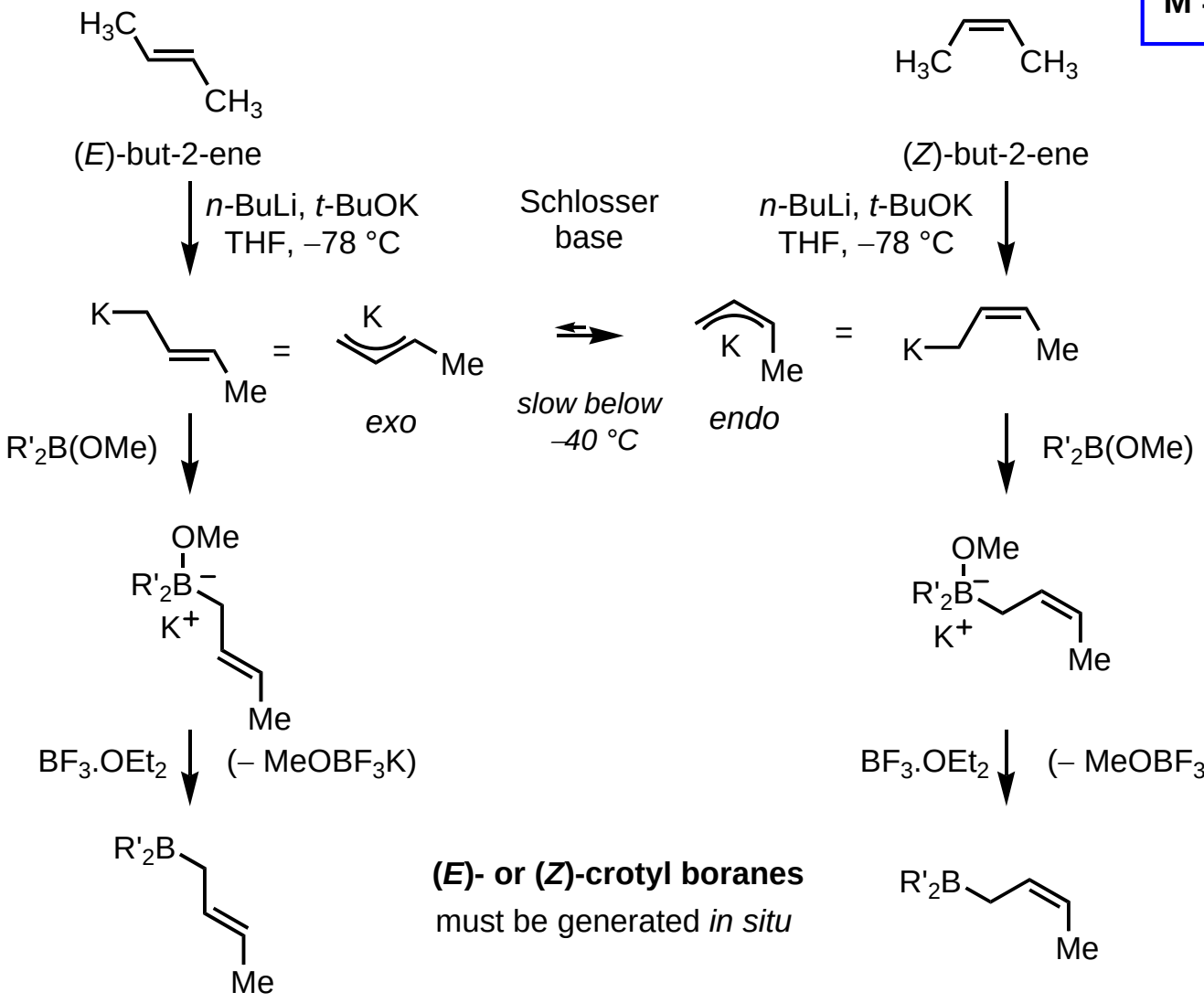


= *Achiral reagent*

Brown, H. C. *J. Org. Chem.* **1982**, *47*, 5065; **1984**, *49*, 945; **1986**, *51*, 432
JACS **1983**, *105*, 2092; **1986**, *108*, 5919; **1991**, *105*, 2092

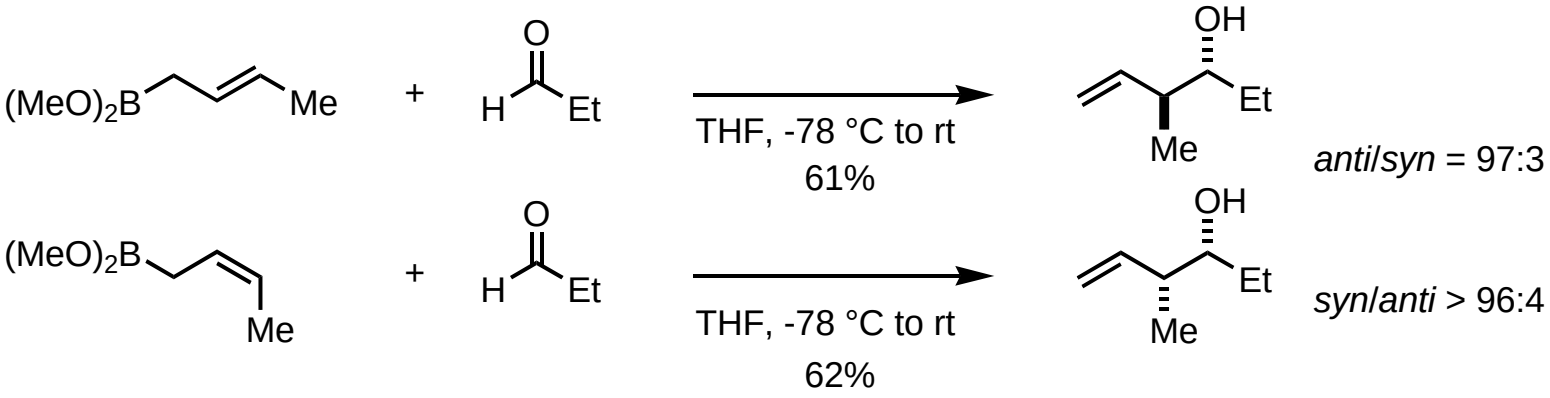
Preparation of crotylboranes/boronates



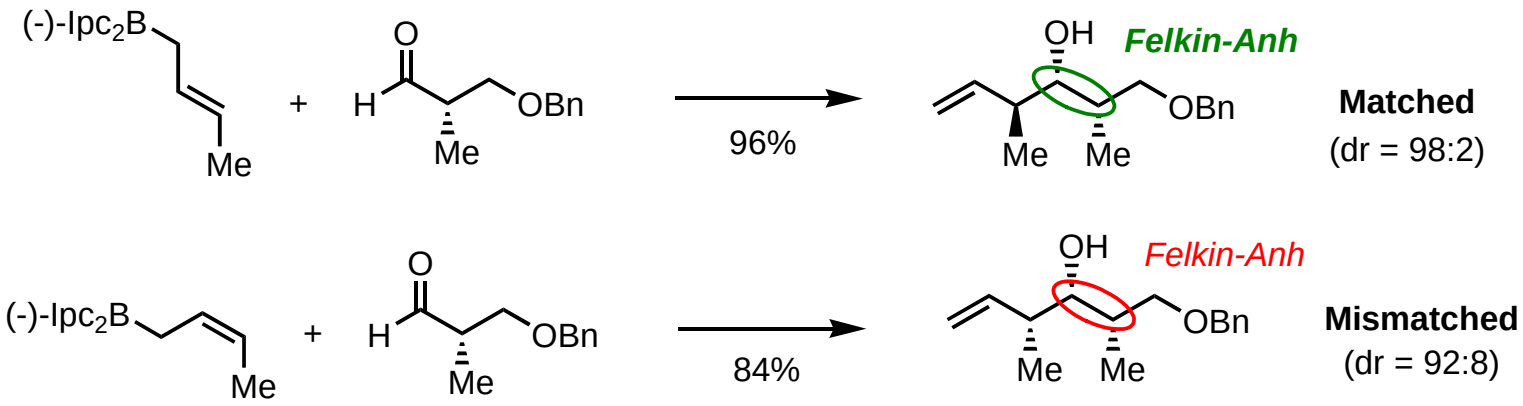


By using $B(OMe)_3$, $B(OiPr)_3$ instead of $R'_2B(OMe)$, it is possible to prepare (E)- or (Z)-crotylboronic acids/boronates

Crotylboration of aldehydes



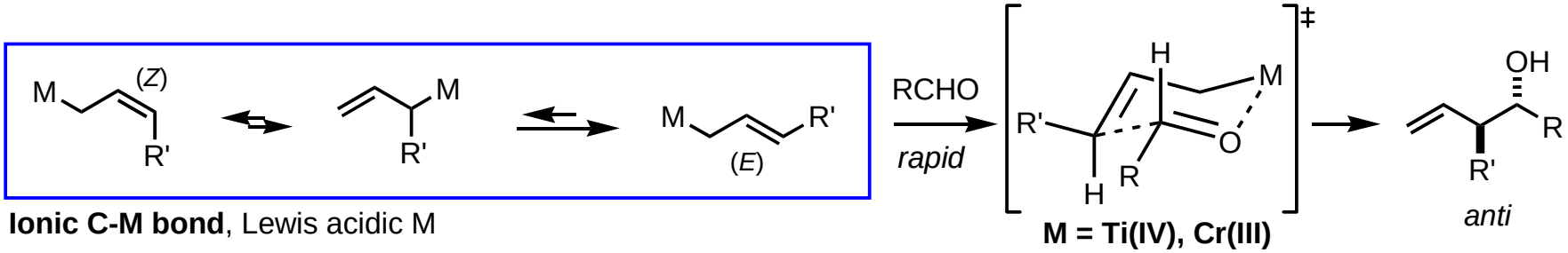
Crotylboranes add to aldehydes through a Zimmerman-Traxler transition state.
Normally (*E*) crotylborane -> Felkin-Anh selectivity and (*Z*) crotylborane -> anti Felkin-Anh selectivity



Reagent controlled diastereoselectivity

Brown, H. C. *et al.*
J. Org. Chem. **1982**, *47*, 5065; **1984**, *49*, 945; **1986**, *51*, 432
JACS **1983**, *105*, 2092; **1986**, *108*, 5919; **1991**, *105*, 2092

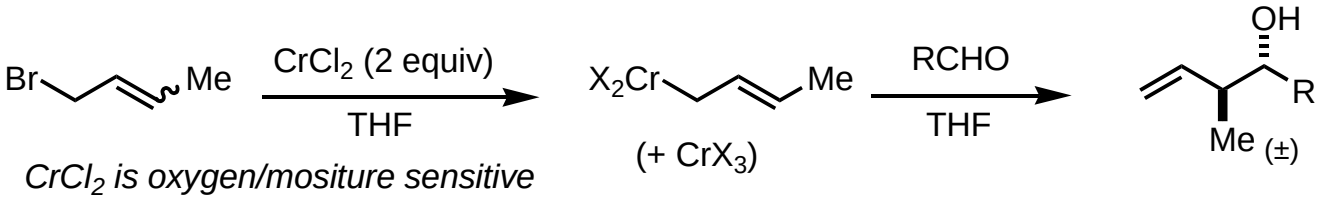
Addition of allyltitanium/allylchromium reagents



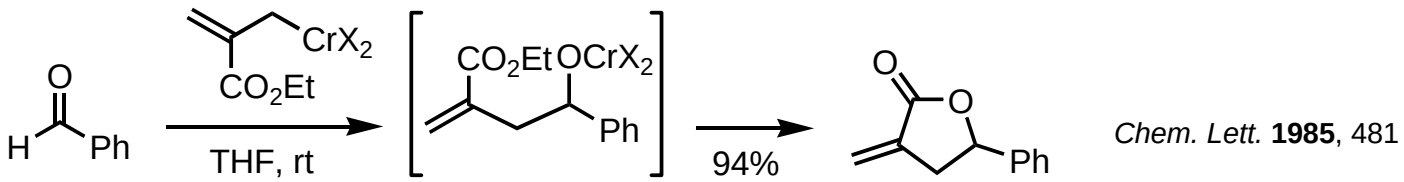
Ionic C-M bond, Lewis acidic M

M = Ti(IV), Cr(III)

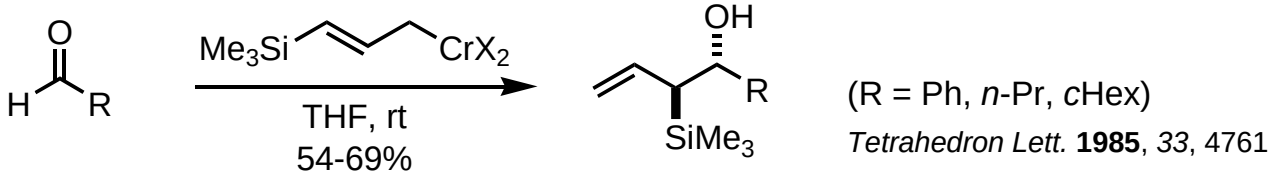
Rapid metallotropic equilibrium in favor of the (*E*) crotyl metal reagent which also adds more rapidly with an aldehyde through a close Zimmerman-Traxler TS



$CrCl_2$ is oxygen/mositure sensitive



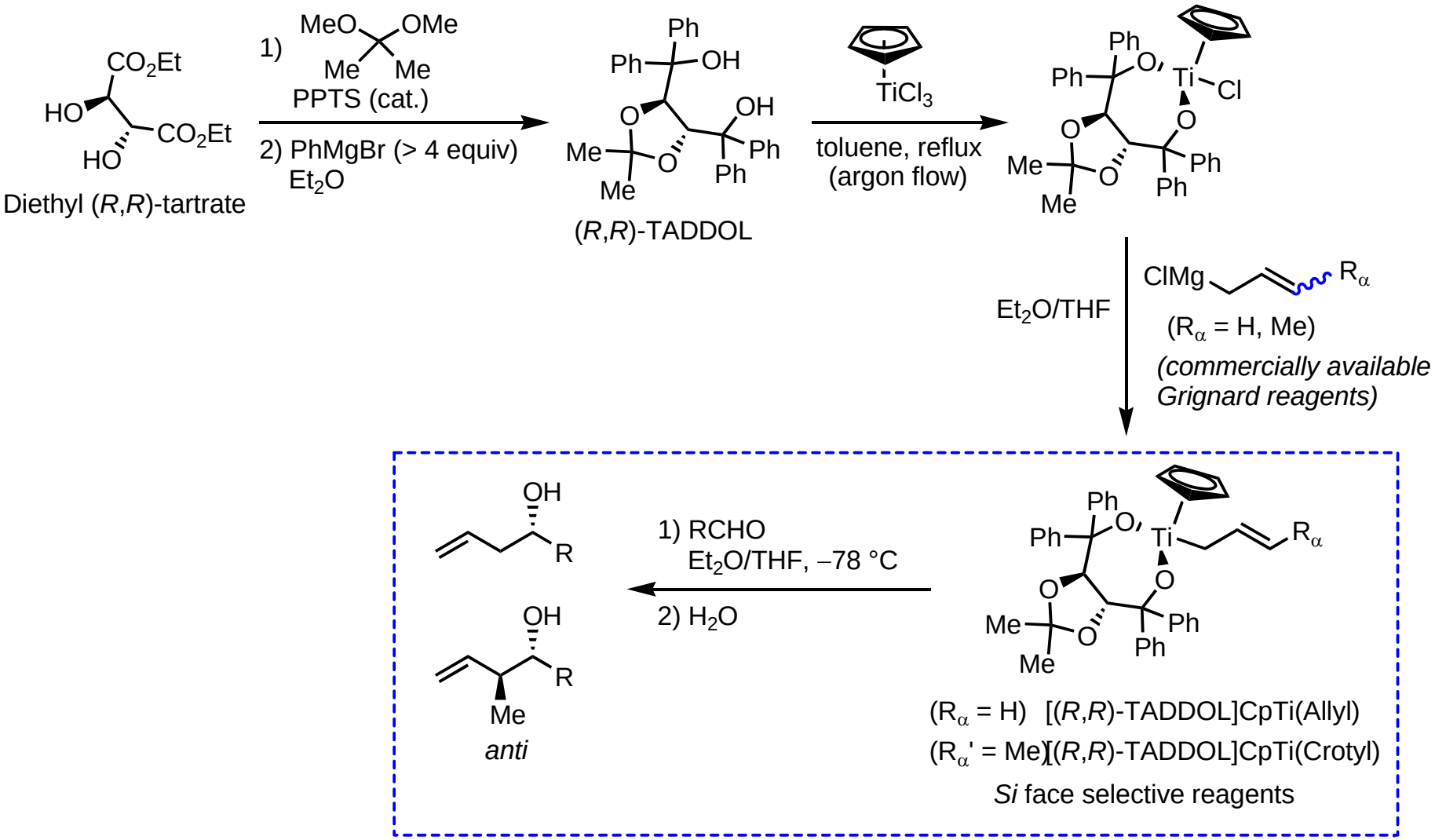
Chem. Lett. **1985**, 481



(R = Ph, *n*-Pr, *c*Hex)

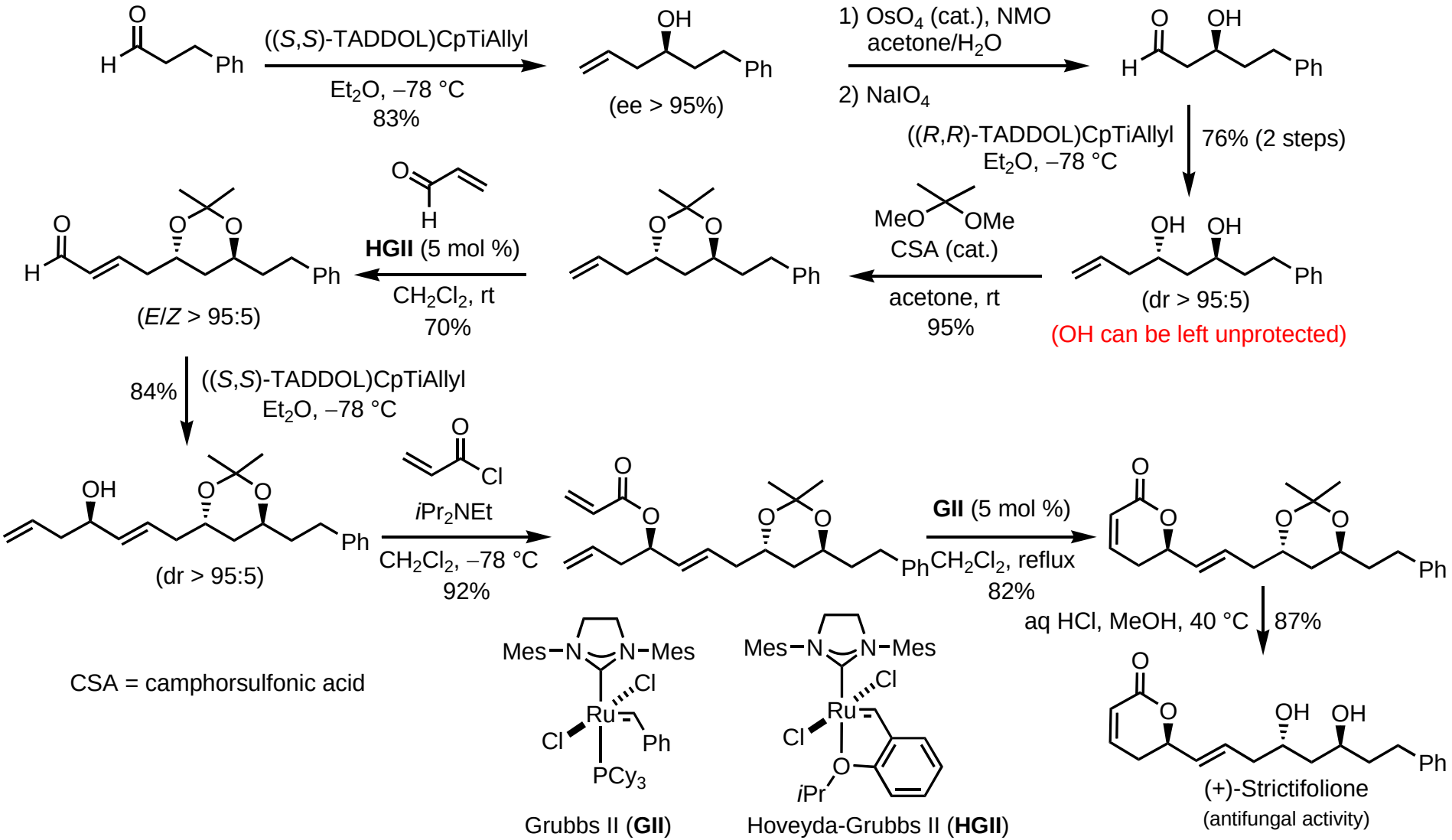
Tetrahedron Lett. **1985**, *33*, 4761

Duthaler-Hafner allyl/crotyltitanation



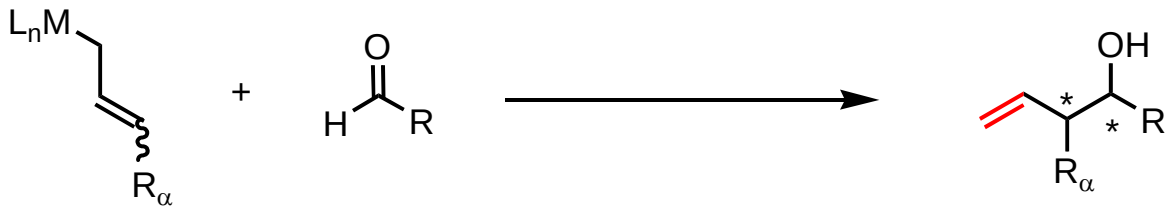
Hafner, A.; Duthaler, R. O. *et al. JACS* **2001**, *114*, 2321

Application to the synthesis of strictifolione



BouzBouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*,1995

What needs to be remembered



1. **Highly covalent C–M bond and M not significantly Lewis acidic**
   Configurationally stable
   Activation of aldehyde by a Lewis acid required (open TS)
   (ex: $BF_3.OEt_2$, $SnCl_4$, $TiCl_4$ ....)
   CrotylSnBu$_3$ leads to ***syn*** **homoallylic alcohols**
   For chiral α-substituted aldehydes : Felkin-Anh/Cram-chelate control applies

ML$_n$ = SnBu$_3$, SiMe$_3$

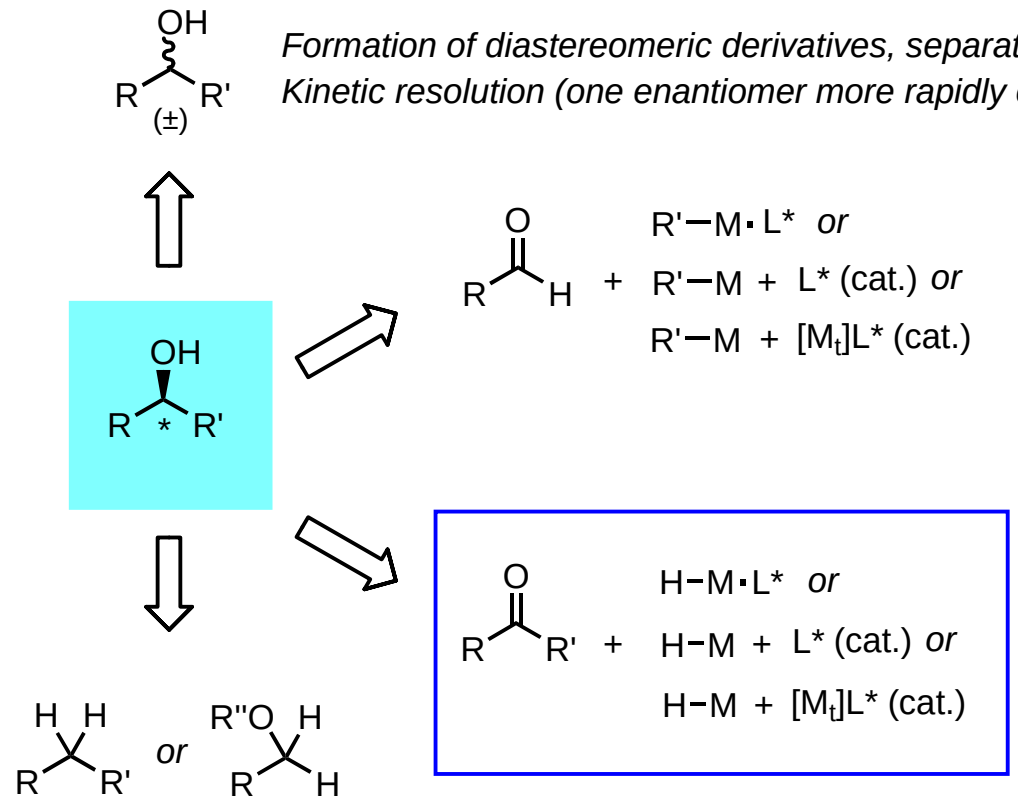
2. **Covalent C–M bond**, **M Lewis acidic**
   (Very) slow metallotropic equilibrium (**configurationally stable**)
   Addition occurred without a catalyst : **Zimmerman-Traxler transition state**
   (*E*)-Crotylboranes/boronates lead to ***anti*** **homoallylic alcohols**
   (*Z*)-Crotylboranes/boronates lead to ***syn*** **homoallylic alcohols**
   The synthesis of theses reagents from (*E*)- or (*Z*)-but-2-ene should be known
   You should be aware that the face-selectivity can be controlled by chiral ligands on boron

ML$_n$ = BR$_2$, B(OR)$_2$

3. **Ionic C–M bond**, **M Lewis acidic**
   Rapid metallotropic equilibrium, not configurationally stable
   Addition occurred without a catalyst : **Zimmerman-Traxler transition state**
   (*E*)- and (*Z*)-crotyl reagents both lead to ***anti*** **homoallylic alcohols**
   You should be aware that the face-selectivity can be controlled by chiral ligands on titanium

ML$_n$ = Ti(IV), Cr(III)

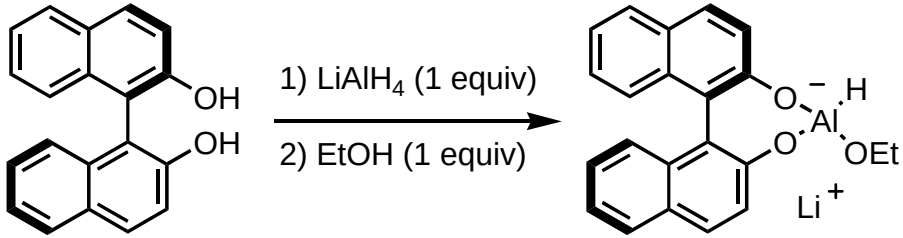
Enantioselective reduction of ketones : a brief overview



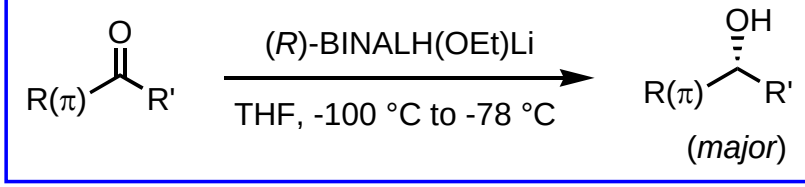
Asymmetric functionalization of C-H bonds
(challenging approach...not yet general !)

For catalytic asymmetric processes, the "background reaction"(uncatalyzed reaction leading to the racemate) should be slow: ***acceleration by the chiral catalyst/ligand should operate***

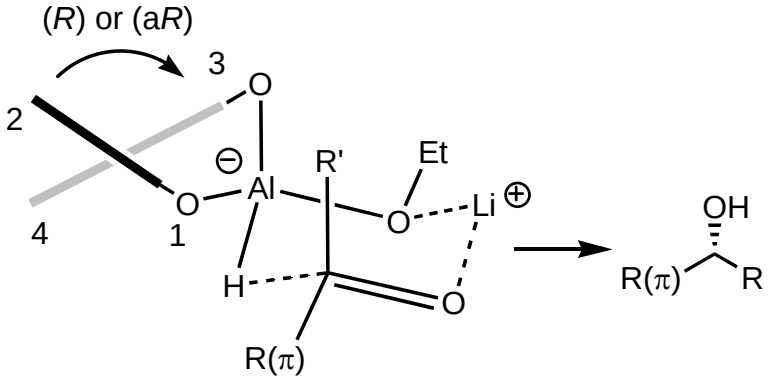
Enantioselective reduction of ketones: BINAL-H

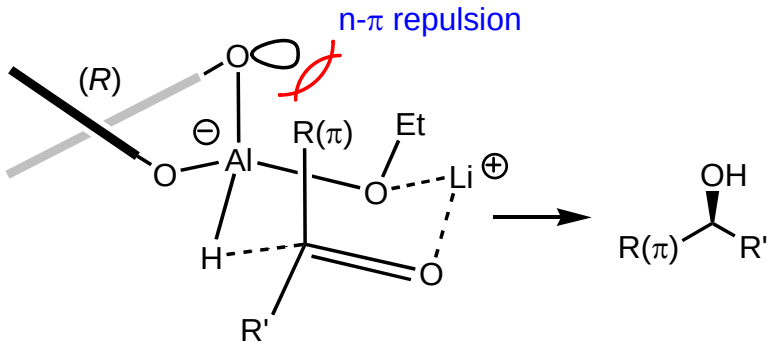


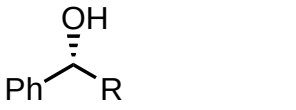
(*R*)-BINOL (*R*)-BINAL-H(OEt)Li



R(π) = π system = Aryl, Alkenyl, Alkynyl
R' = Alkyl

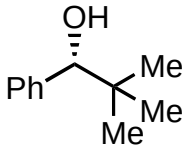




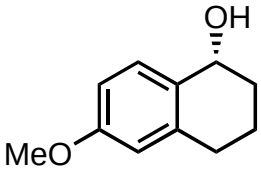


(R = Me, CH_2Br, Et, *n*-Pr, *i*Pr)

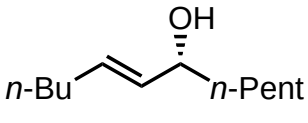
ee = 95-99%



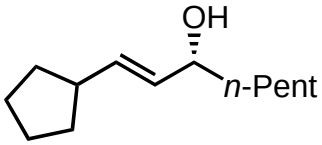
ee = 44%



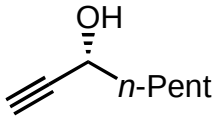
ee = 74%



ee = 91%



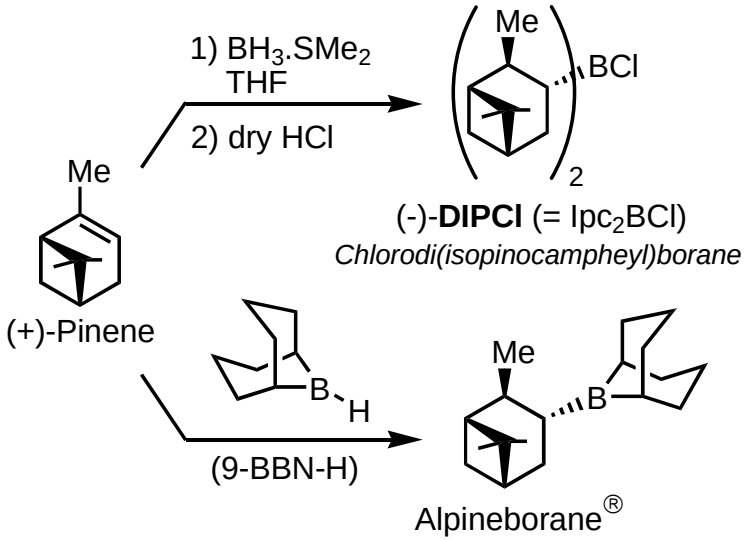
ee = 92%

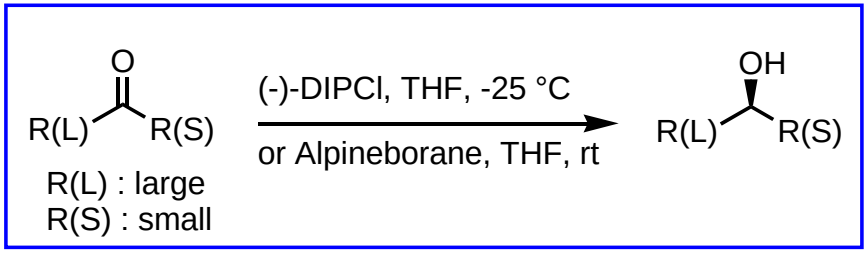


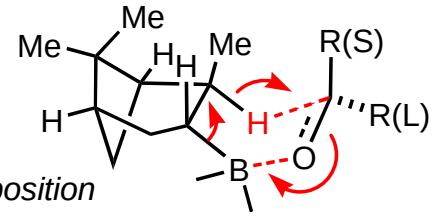
ee = 84%

Noyori *JACS* **1984**, *106*, 6709 & 6717, see also *Chem. Rev.* **2005**, *105*, 857

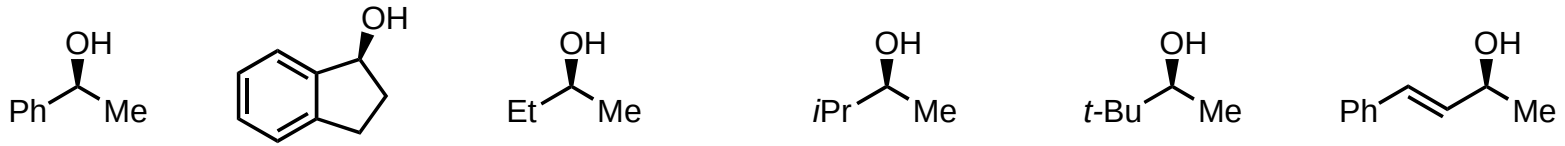
Enantioselective reduction of ketones : DIPCl and Alpineborane





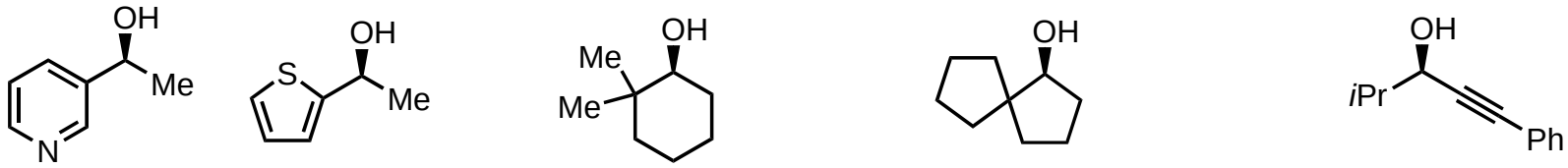


Hydrogen atom at the β position of boron is transferred



ee = 98% | ee = 97% | ee = 4% (43%*) | ee = 32% (66%*) | ee = 95% | ee = 81%

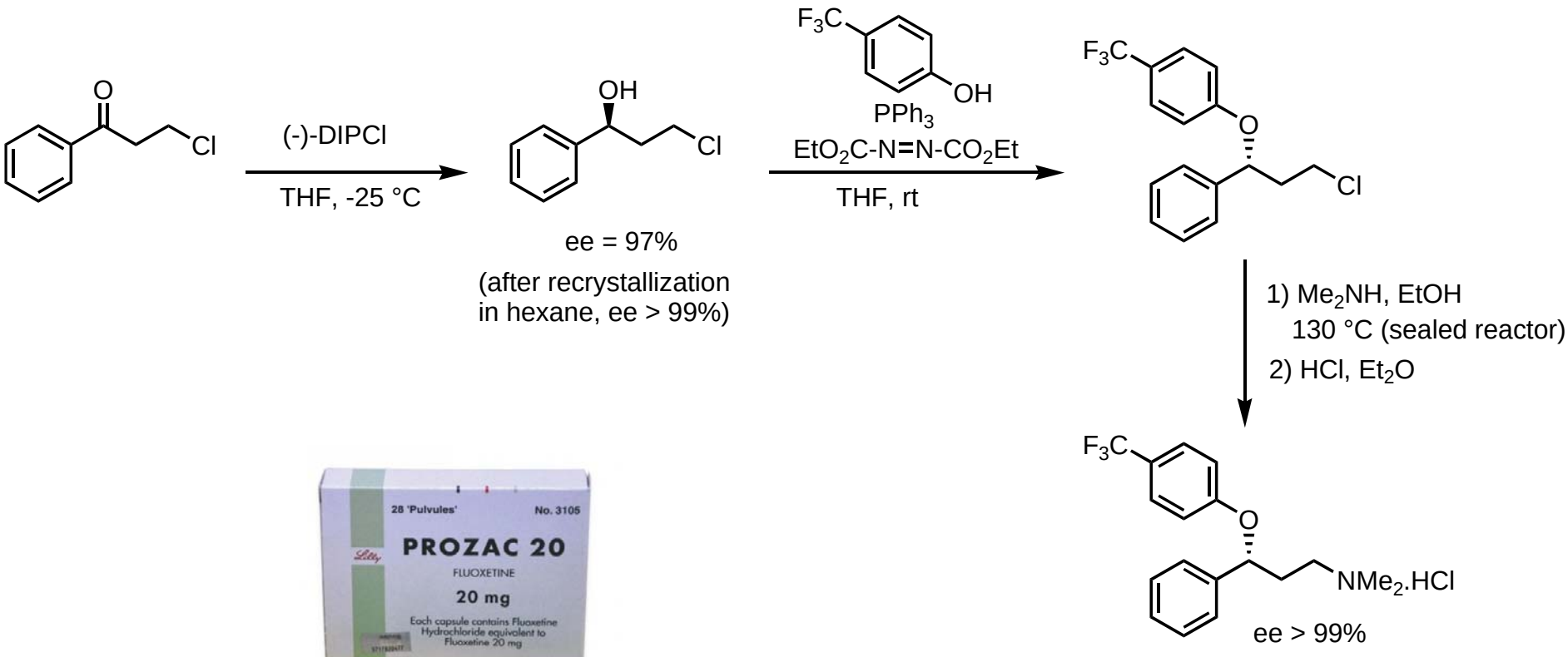
** with Alpineborane*



ee = 92% | ee = 91% | ee = 91% | ee = 95% | ee = 92%

Midland, M. M. *J. Organomet. Chem.* **1978**, *156*, 203; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 1384; **1986**, *51*, 3394 & 5446

Enantioselective reduction of ketones : DIPCl



(-)-Fluoxetine hydrochloride

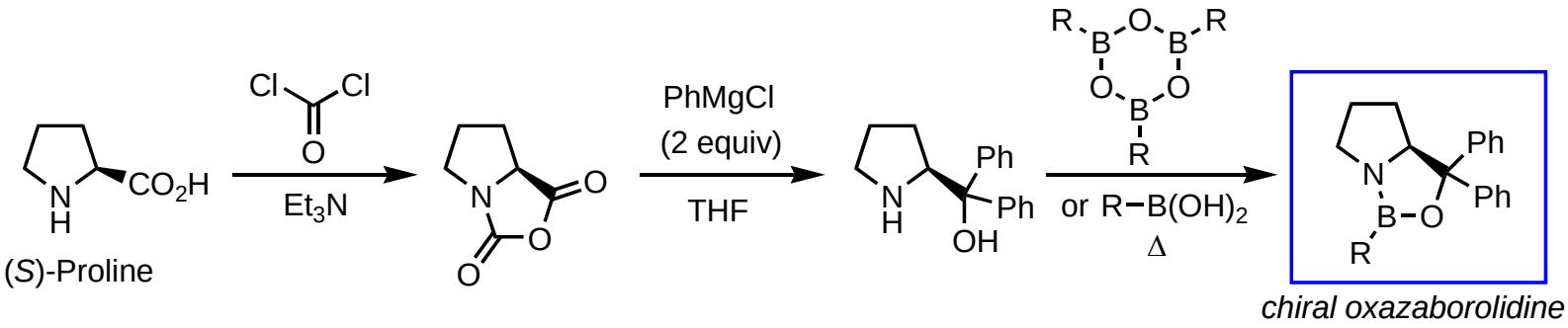
rac-Fluoxetine (Prozac®)

J. Org. Chem. **1988**, *53*, 2916

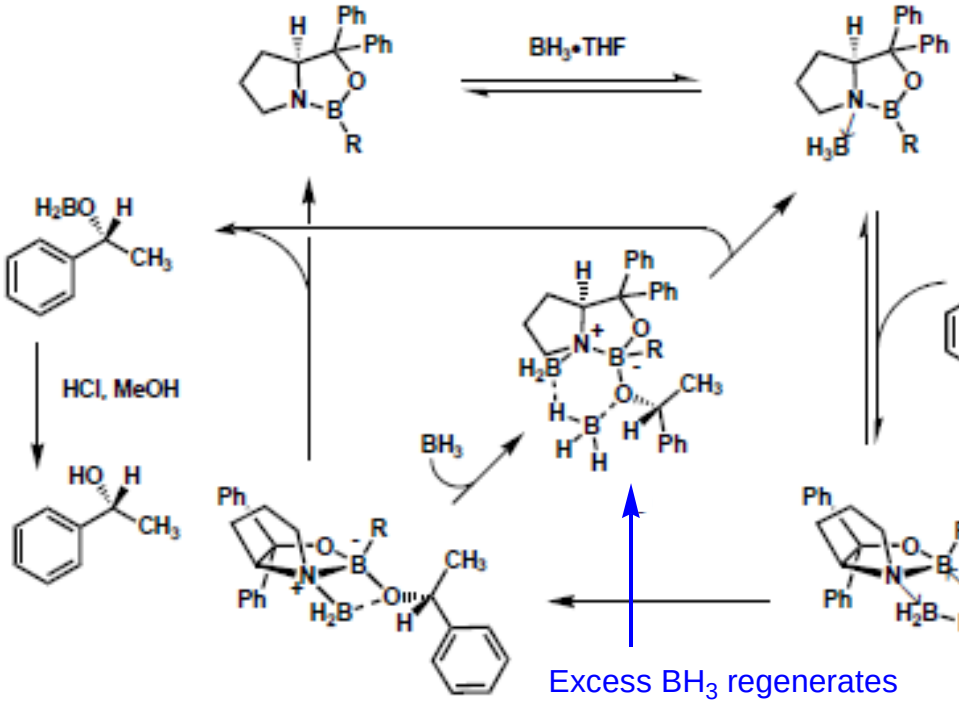
CBS enantioselective reduction of ketones

The reduction of ketones with BH_3•SMe_2 is slow : opportunity for asymmetric catalysis

Corey-Bakshi-Shibata (CBS) reduction : chiral oxazaborolidines as catalysts



chiral oxazaborolidine



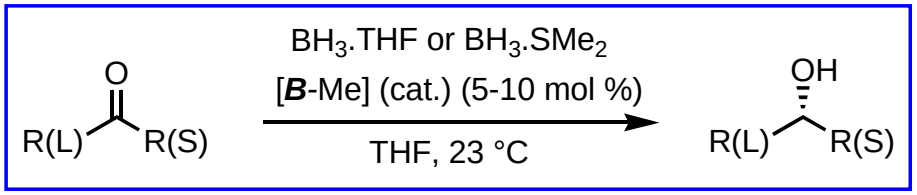
Complexation of BH_3 by N

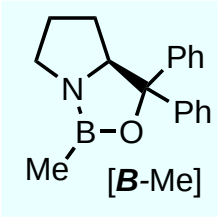
Lewis acidity of B in oxazaborolidine increases

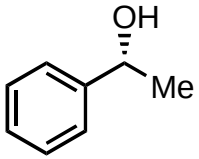
Dual activation (Lewis base/Lewis acid)

Angew. Chem. Int. Ed. **1998**, *37*, 1986

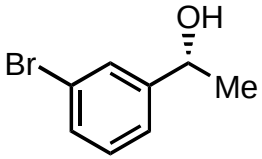
CBS enantioselective reduction of ketones



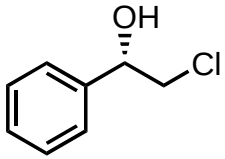




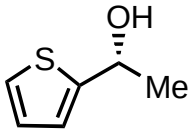
ee = 97%



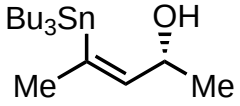
ee = 96%



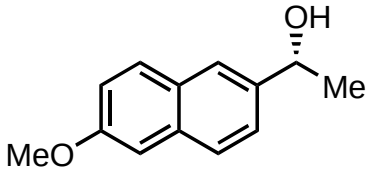
ee = 98%



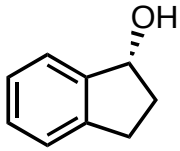
ee = 94%



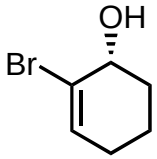
ee = 93% (-30 °C)



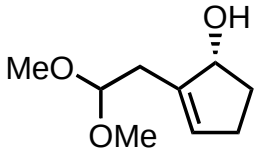
ee = 98%



ee = 98% (-20 °C)

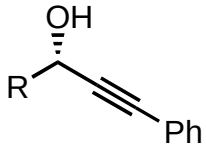


ee = 96% (-15 °C)



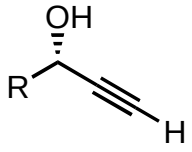
ee = 93% (10 °C)

With $BH_3.SMe_2$ *and* [***B***-Me] (2 equiv) (THF, -30 °C)



R = *n*-Alkyl, ee = 71-88%

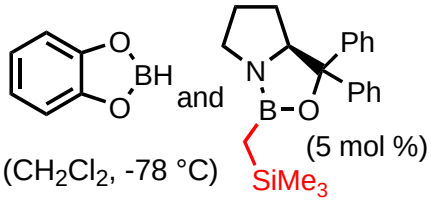
R = *s*-Alkyl, ee = 94-96%



R = *n*-Hexyl, ee = 95%

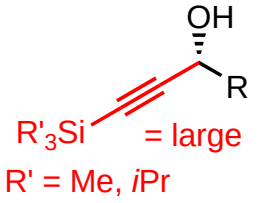
R = Cyclohexyl, ee = 98%

With



(5 mol %)

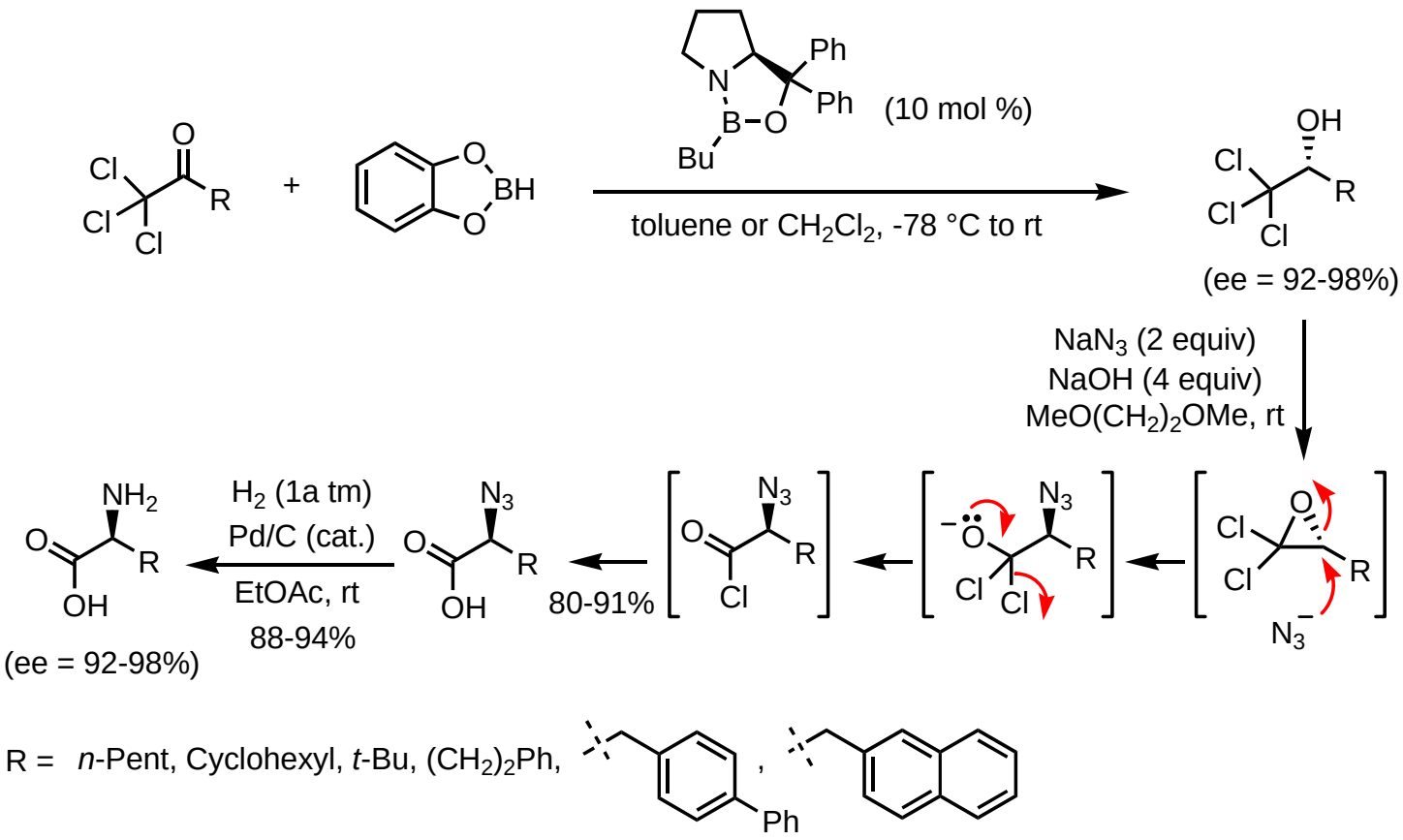
(CH_2Cl_2, -78 °C)



R = Me, *n*-Pentyl, CH_2Cl, $(CH_2)_2CO_2Et$, *i*Pr, ee = 83-97%

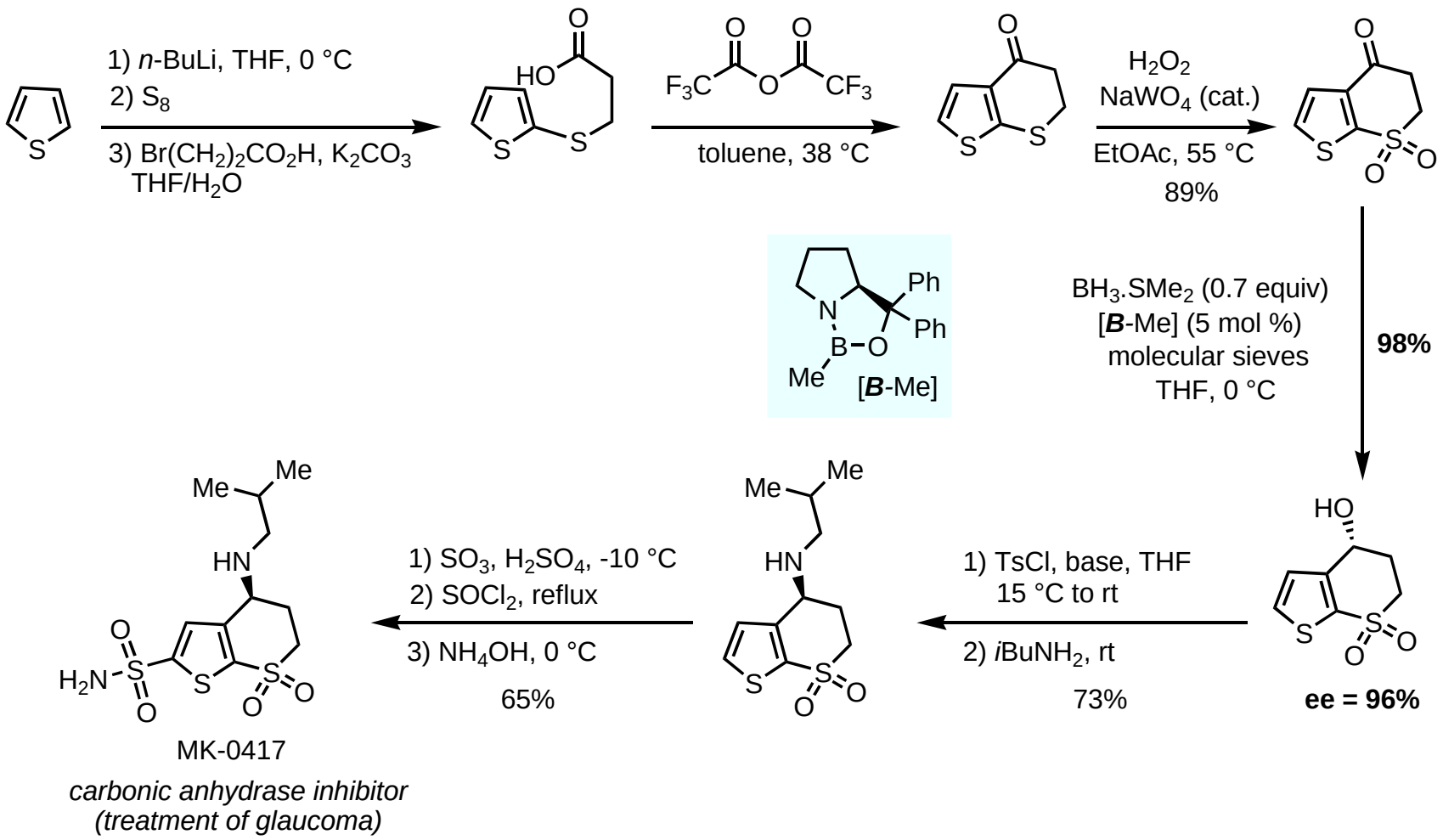
Angew. Chem. Int. Ed. **1998**, *37*, 1986

CBS enantioselective reduction of ketones: Application



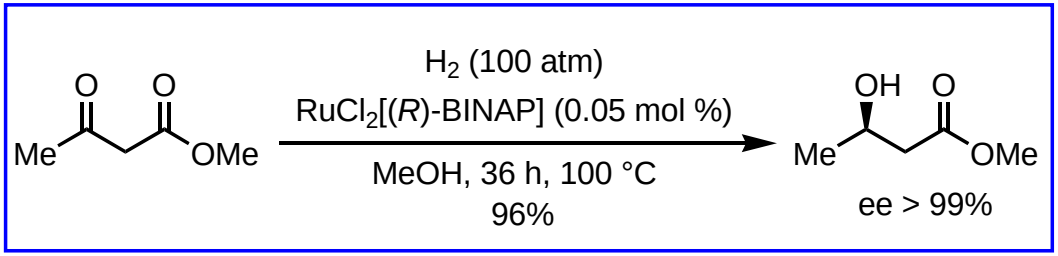
JACS **1992**, *114*, 1906

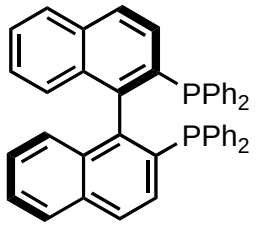
CBS enantioselective reduction of ketones: Application



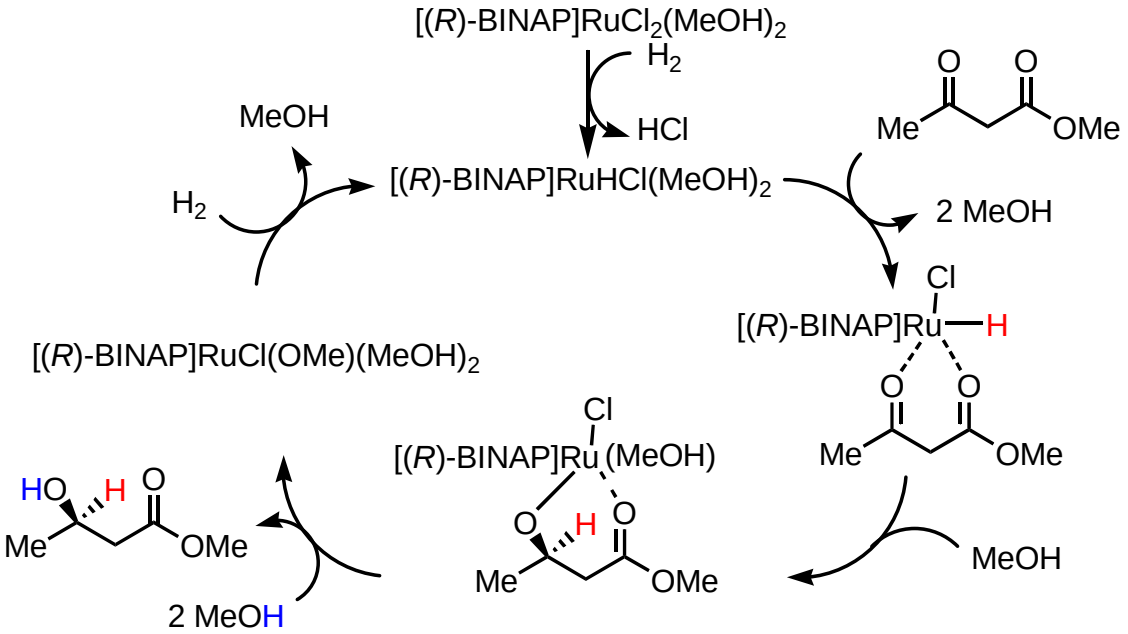
J. Org. Chem. **1991**, *56*, 763

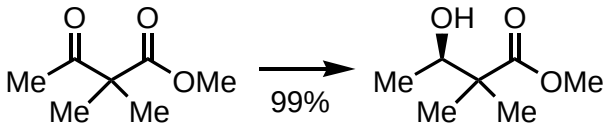
Noyori hydrogenation reaction: a brief overview





(*R*)-(+)-BINAP

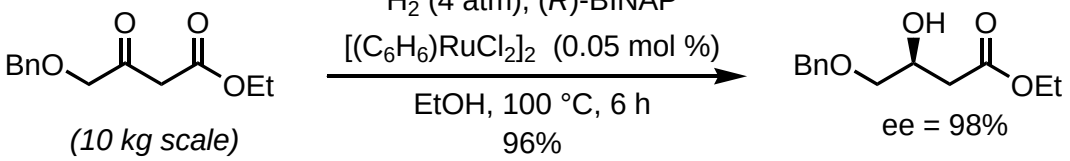




The C=O group is hydrogenated (not the enol)

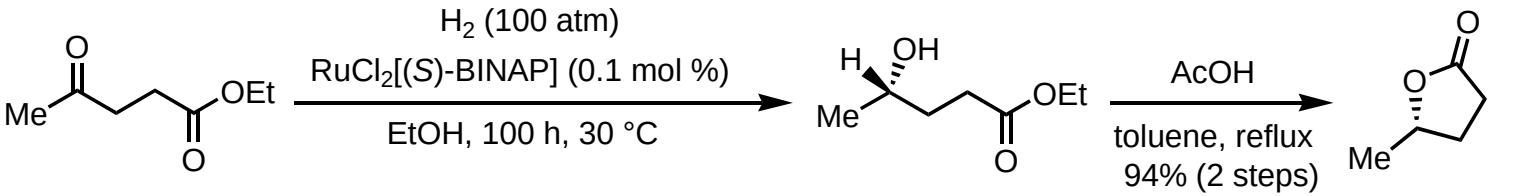
The presence of a second coordinating functional group is important

The catalyst can be generated in situ



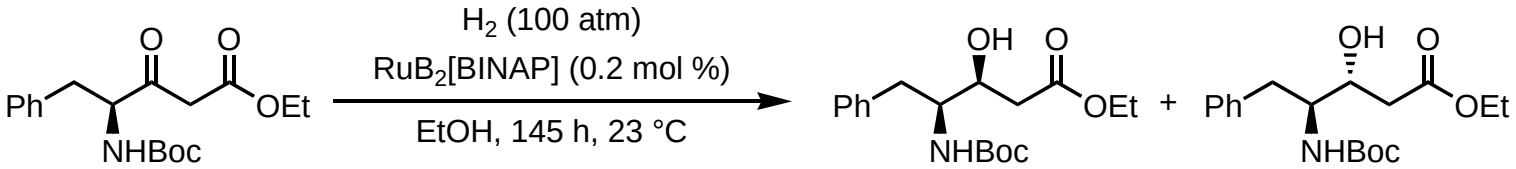
JACS **1987**, *109*, 5856
Angew. Chem. Int. Ed. **2001**, *40*, 40
Chem. Rev. **2003**, *103*, 3029

Noyori hydrogenation reaction: a brief overview

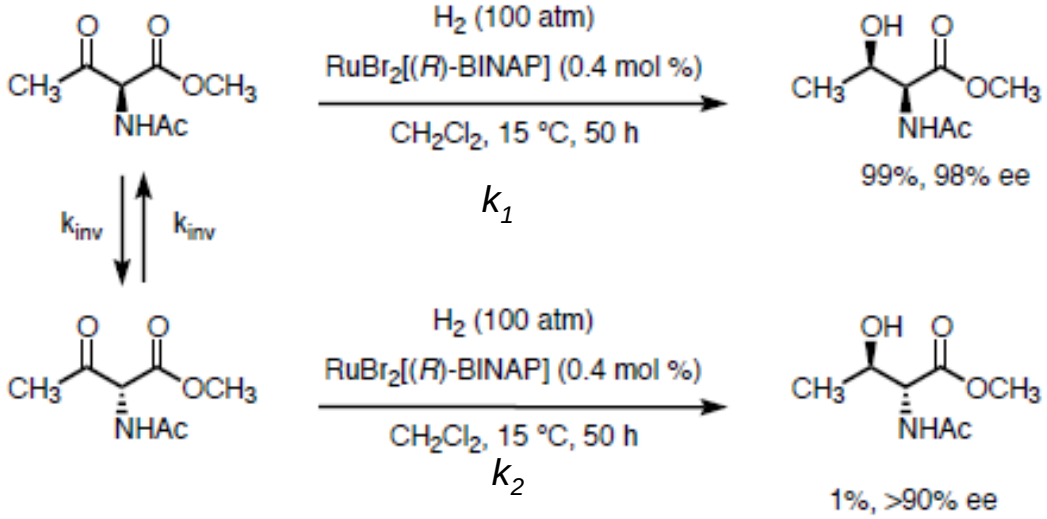


Tetrahedron Lett. **1990**, *31*, 5509

Catalyst controlled diastereoselectivity



with (*S*)-BINAP	9	:	91
with (*R*)-BINAP	> 99	:	< 1

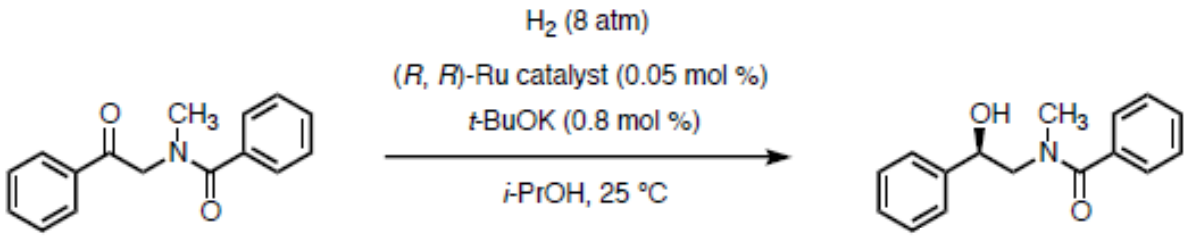


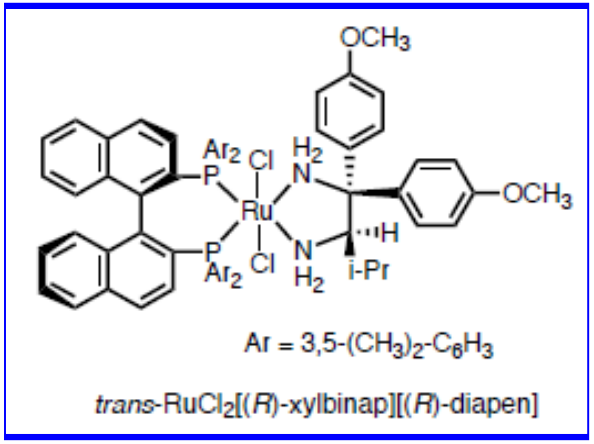
Dynamic kinetic resolution is observed for some substrates able to racemize

$K_{inv} > k_1$ *and* k_2

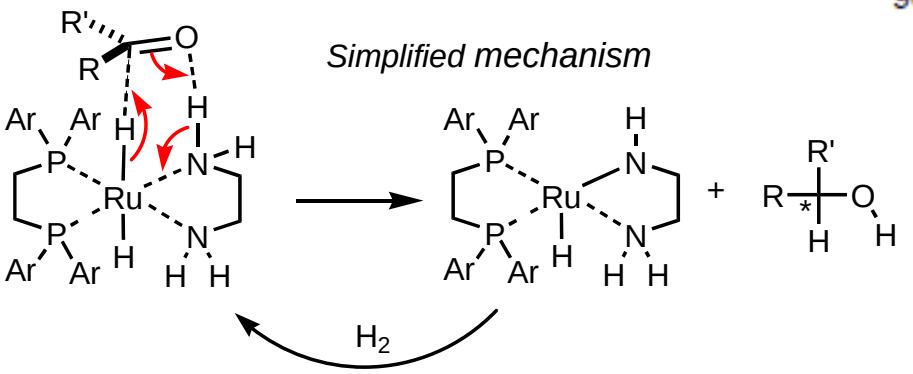
Tetrahedron Lett. **1988**, *29*, 6327; *JACS* **1989**, *111*, 8934

Noyori hydrogenation reaction: a brief overview

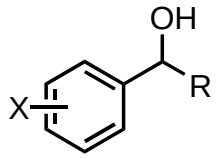


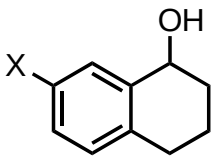


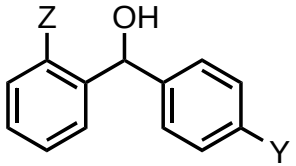
Simplified mechanism

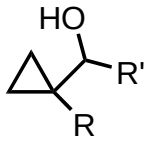


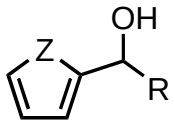
Chelation by another Lewis basic functional group is not required

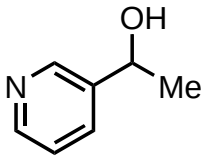

ee = 90-100%

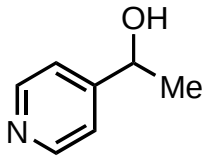

ee = 94-95%

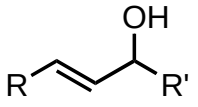

ee = 96-99%

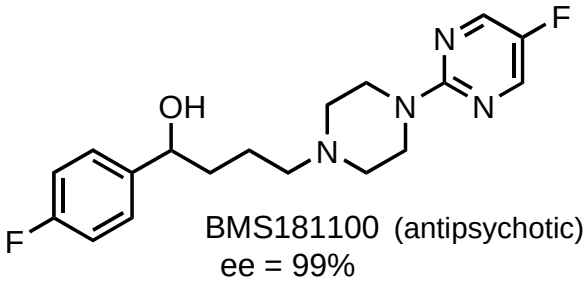

ee = 95-98%


ee = 97-99%
(Z = O, S, NTs)


ee > 99%

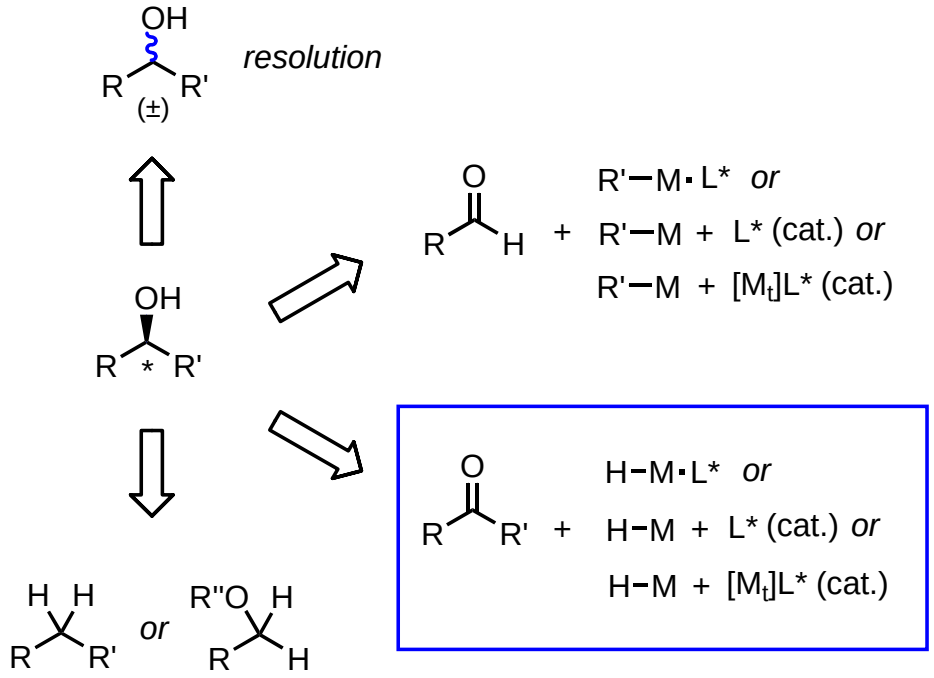

ee > 99%


ee = 86-99%



JACS **1998**, *120*, 13529; *Angew. Chem. Int. Ed.* **2001**, *40*, 40

Enantioselective reduction of ketones : a brief overview

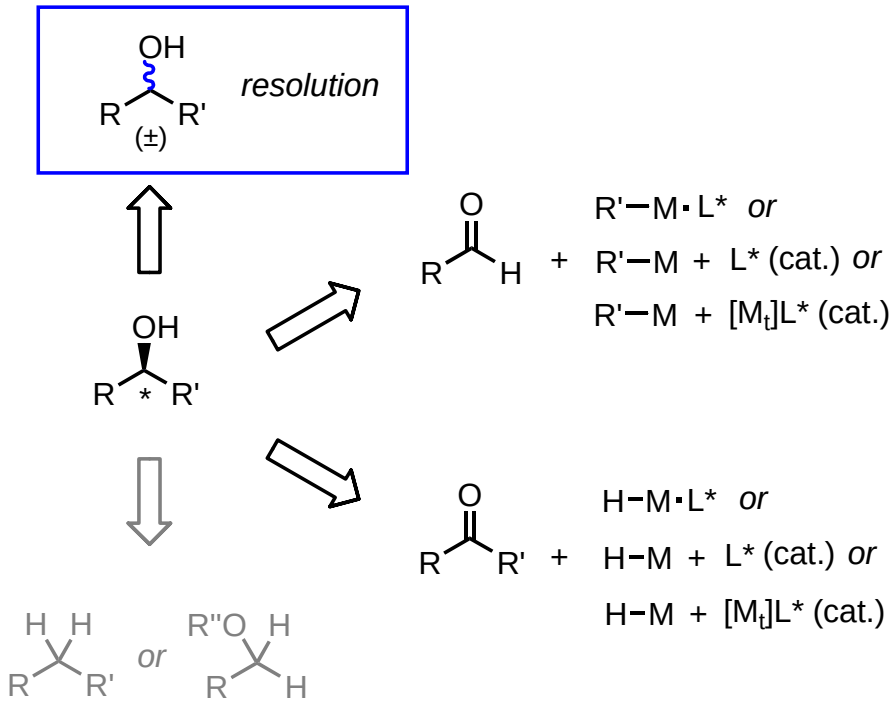


What needs to be remembered?

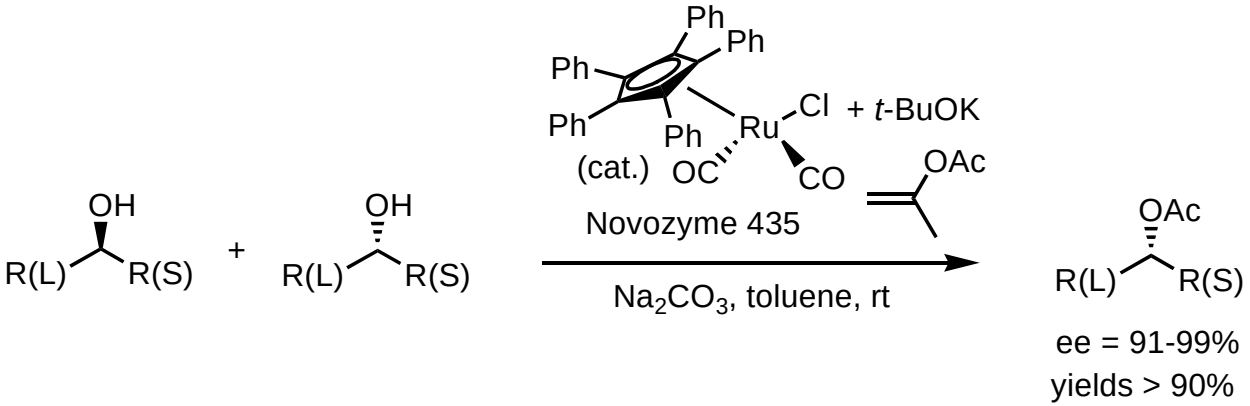
The principle *of the most classical enantioselective reduction of ketones (with BINAL(OEt)HLi, DIPCl, oxazaborolidines) should be known (but the sense of induction in each case need not be remembered).*

You should be aware that the enantioselective reduction of a wide variety of ketones possessing another coordinating group (typically β-ketoesters) or not (aryl/heteroaryl/alkenyl/alkynyl ketones) can be achieved by hydrogenation in the presence of a chiral ruthenium catalyst. BINAP or related substituted derivatives are classically used as chiral ligands.
Ru complexes possessing a chiral diphosphine and a chiral diamine as ligands lead to excellent results.

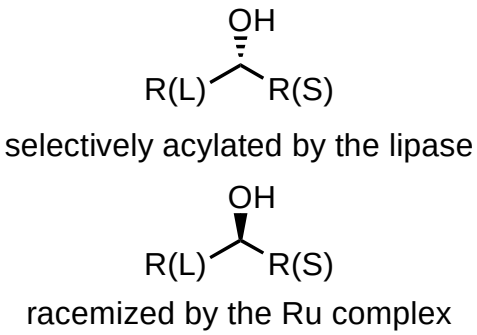
Optically enriched secondary alcohols

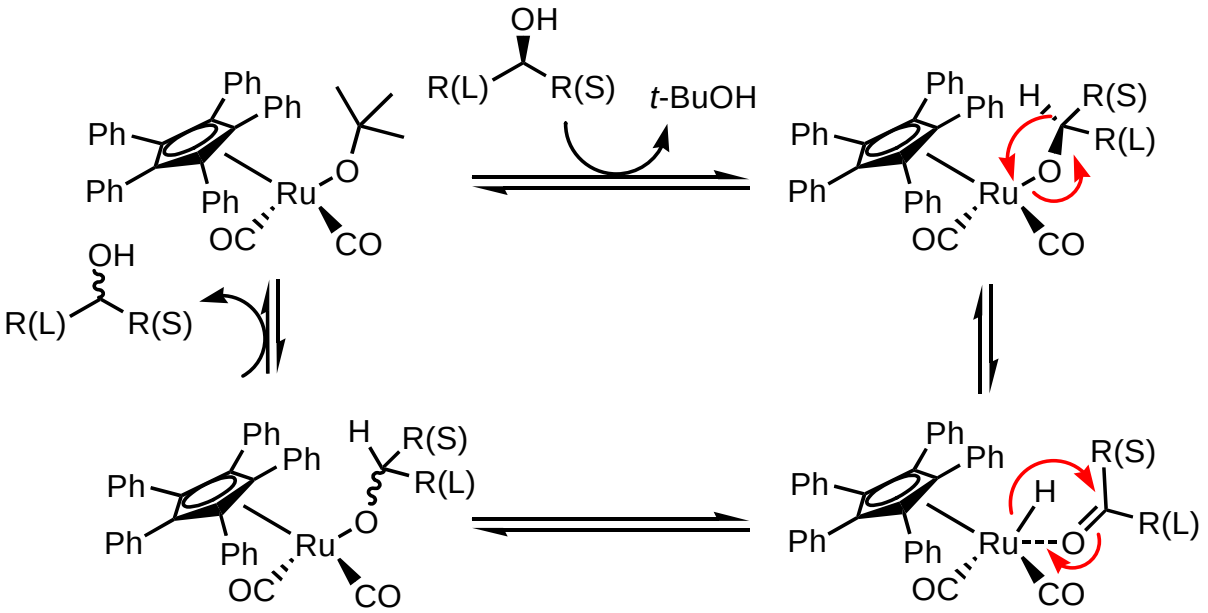


Bäckwall dynamic kinetic resolution : bio- and organometallic catalysis



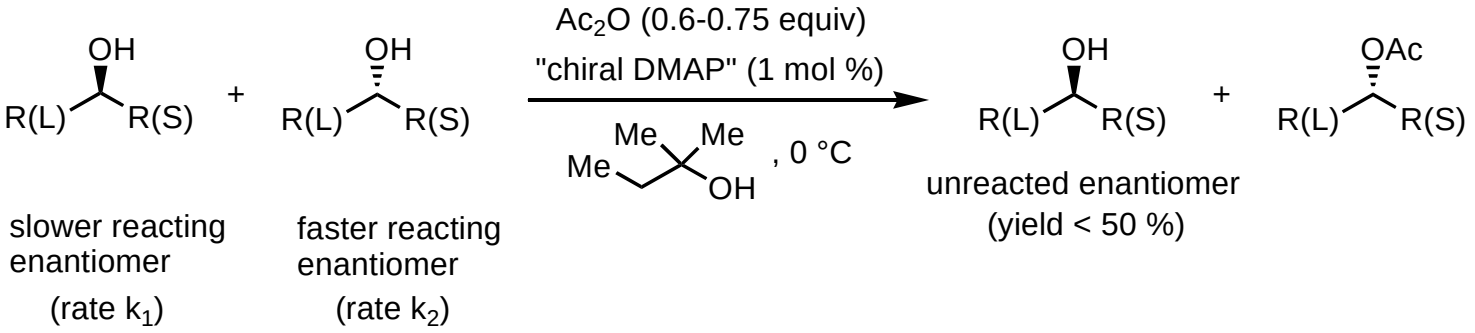
Novozyme 435 = *Candida Antartica lipase B immobilized on polystyrene (cross-likned with divinylbenzene)*





JACS **2005**, *127*, 8817

Fu's kinetic resolution with « chiral DMAP » analogs

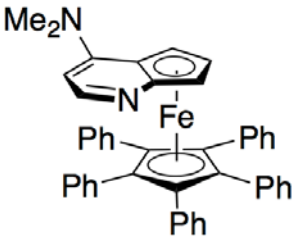


slower reacting enantiomer (rate k_1)

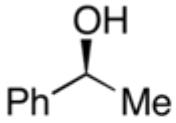
faster reacting enantiomer (rate k_2)

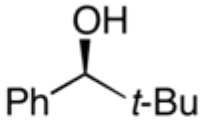
unreacted enantiomer (yield < 50 %)

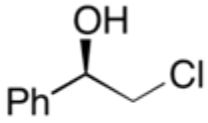
selectivity factor $s = k_2 / k_1$

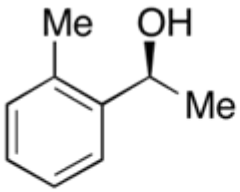


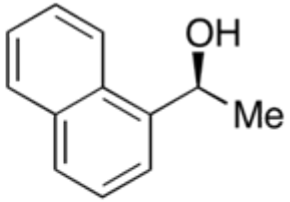
"chiral DMAP"







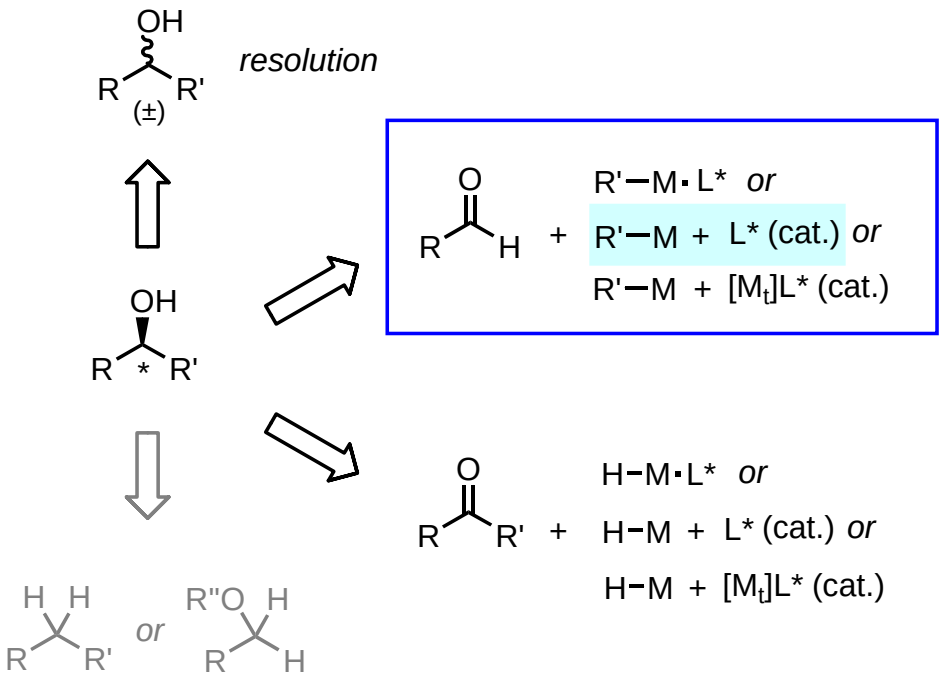




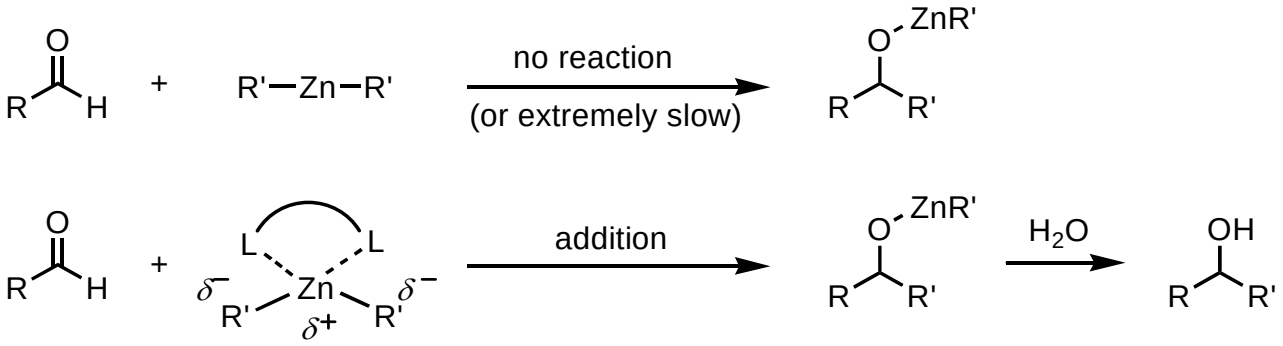
s	43	95	32	71	65
ee	99%	96%	98%	99%	95%
conv	55%	51%	56%	53%	52%

JACS **2005**, *127*, 8817

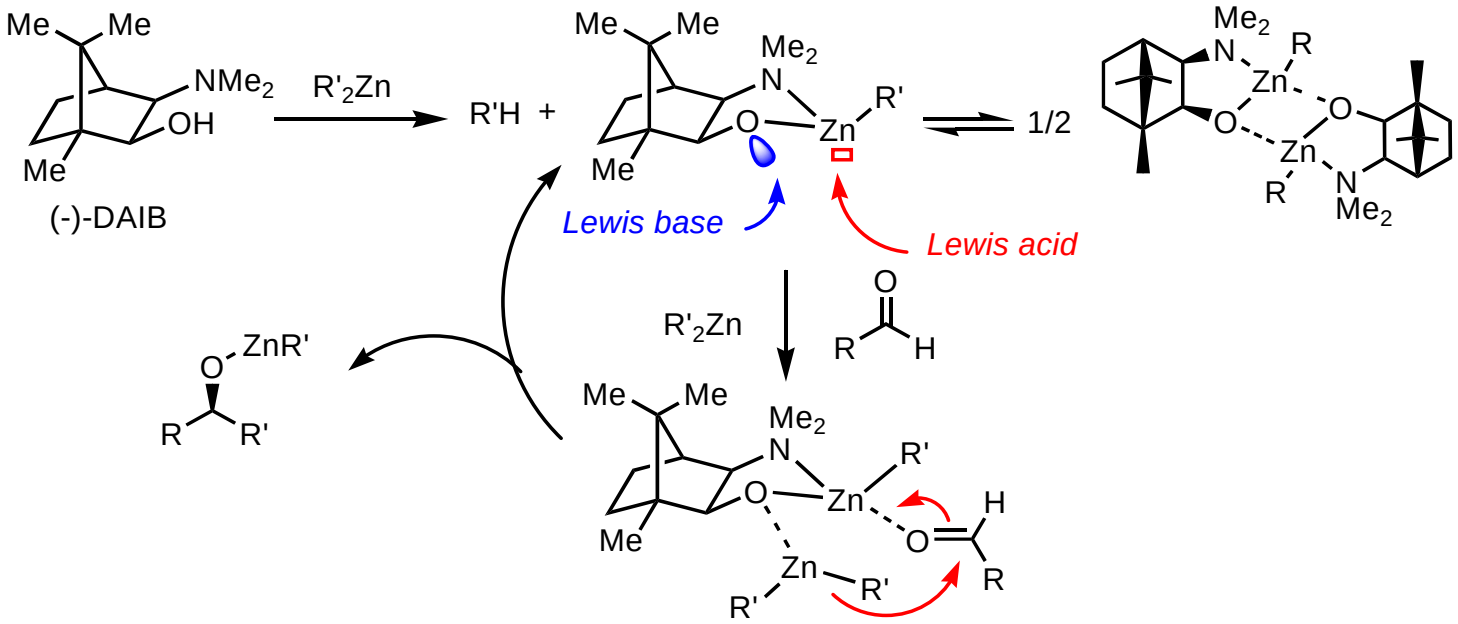
Optically enriched secondary alcohols



Nucleophilic addition of organozinc reagents to aldehydes



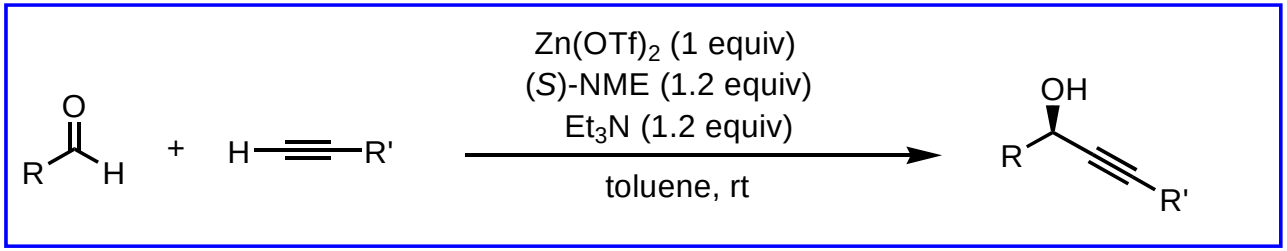
Chiral ligand : catalytic enantioselective addition



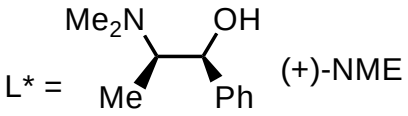
But few diorganozinc are commercially available (Et_2Zn, Me_2Zn*)*

Noyori *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49; Soai *Chem. Rev.* **1992**, *92*, 833

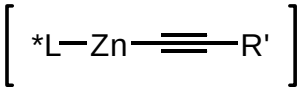
Carreira's enantioselective alkynylation of aldehydes



High ee's (ee > 90 %) for most aldehydes (alkyl, aryl)
Moderate yields for unbranched aliphatic aldehydes
Tolerates a wide variety of substituents on the alkyne



N-methylephedrine



Chiral zinc acetylide formed *in situ*

A catalytic version (with 20 mol % ligand) has also been reported (toluene, 60 °C)

Other catalytic enantioselective alkynylation reactions of aldehydes have been developed

JACS **2000**, *122*, 1806; *JACS* **2001**, *123*, 9687; *Acc. Chem. Res.* **2000**, *33*, 373

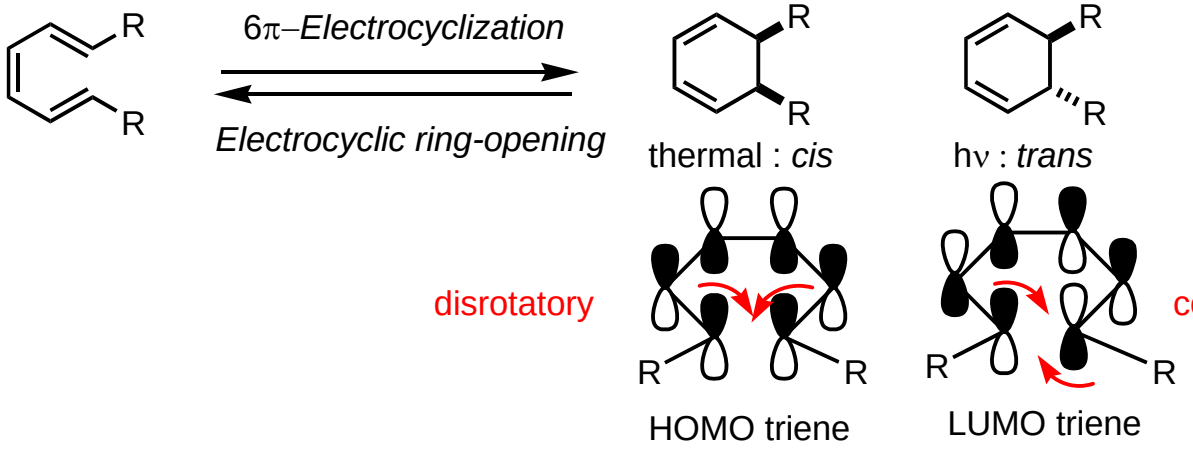
Pericyclic reactions : Definition and representative classes

Pericyclic reactions are **concerted processes** in which **bonds are formed/broken in a cyclic transition state** (with a cyclic movement of electrons)

(concerted process = single transition state from substrate to product without any reaction intermediate)

Electrocyclizations Conversion of conjugated polyenes into cyclic products

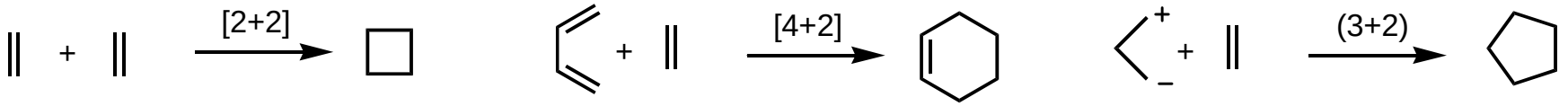
Can be achieved thermally of photochemically



Electrocyclization mode depends on
- the number of electrons (4n+2 or 4n)
- the activation method (Δ or hν)

"Woodward-Hoffmann rules"

Cycloadditions Two unsaturated compounds converted into a cyclic product in one step



often indicated as [3+2] althgouh this does not reflect the number of electrons

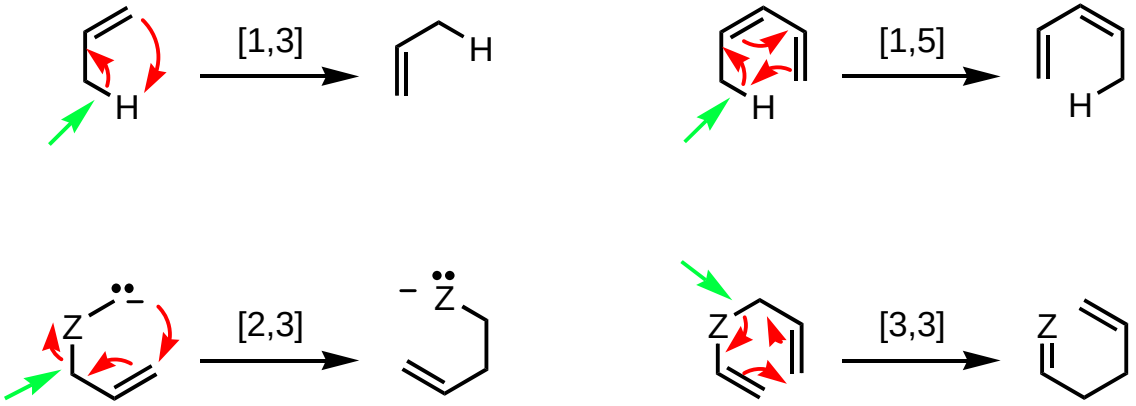
Pericyclic reactions : Sigmatropic rearrangements

Sigmatropic rearrangement

Concerted migration of an allylic σ bond with concomittant reorganization of the π system

A new σ bond is formed between atoms not linked previously and a σ bond is broken

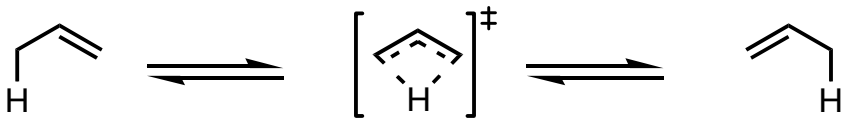
There is relocalization of π bonds in the product but the total of π and σ bond does not change



[n,m]	n and m correspond to the number of atoms on each side of the **broken σ bond** n < m by convention

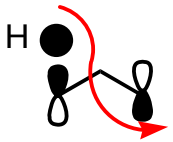
Hydrogen [1,n]-shift

[1,3]-shift

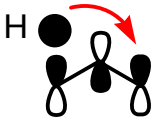


thermal activation | **photochemical activation**

HOMO (allyl radical)



antarafacial



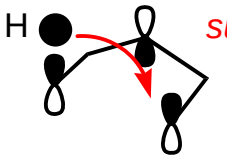
suprafacial

LUMO (allyl radical)

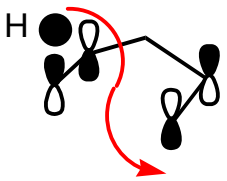
difficult to achieve thermally (forbidden process)

[1,5]-shift suprafacial (allowed) | antarafacial (difficult)

HOMO (pentadienyl radical)



suprafacial



LUMO (pentadienyl radical)

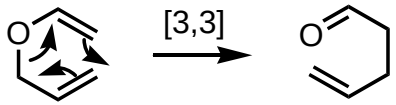
antarafacial

A similar analysis would lead to the following conclusion

[1,7]-shift antarafacial shift possible (enough flexibility) | suprafacial

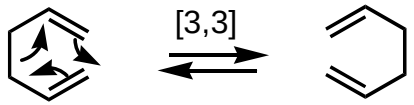
[3,3]-Sigmatropic rearrangements

Claisen rearrangement

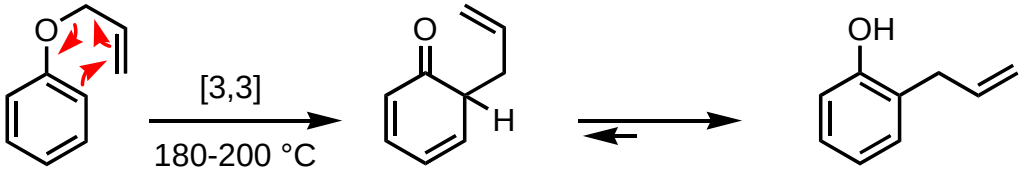


Discovered by Rainer Ludwig Claisen (1912)

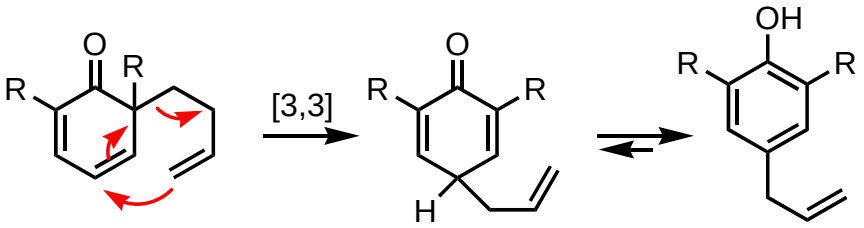
Cope rearrangement

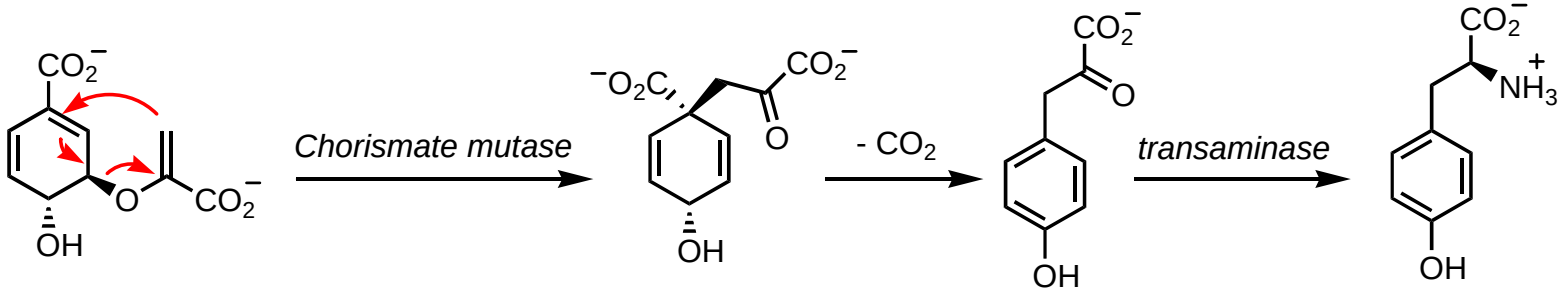


[3,3]-rearrangement of 1,5-dienes disclosed by Cope (1940)



minor pathway if R = H

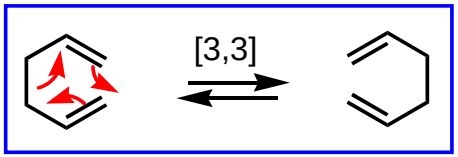




chorismate — prephenate — tyrosine

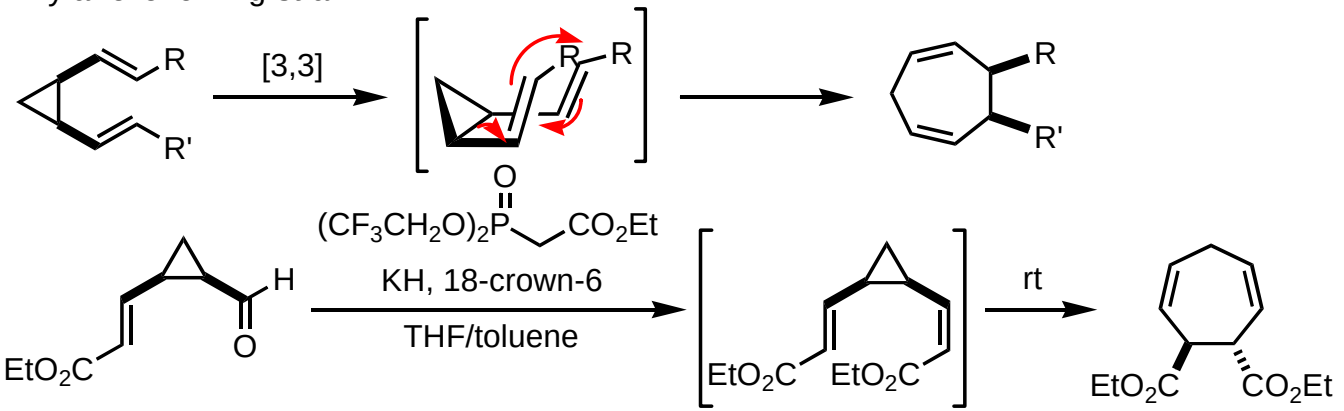
a key branched point intermediate in the biosynthesis of aromatic amino-acids in plants

Cope rearrangement



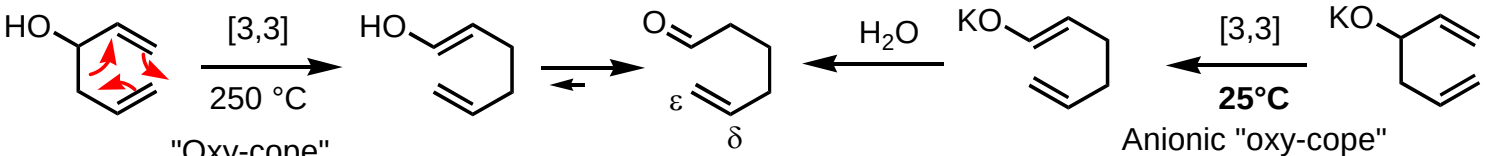
The equilibrium can be displaced:

- By a relief of ring-strain



(Still-Gennari olefination: *Tetrahedron Lett.* **1983**, *24*, 4404)

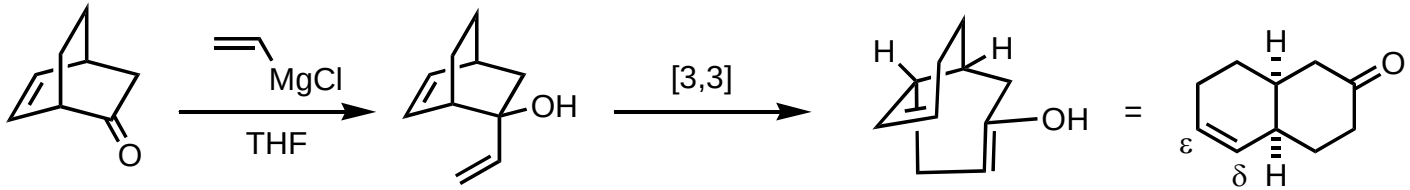
- By the presence of an alcohol/ alkoxide



"Oxy-cope"

Anionic "oxy-cope"

10^{10} to 10^{17} rate acceleration !



(dr = 70:30)

320 °C

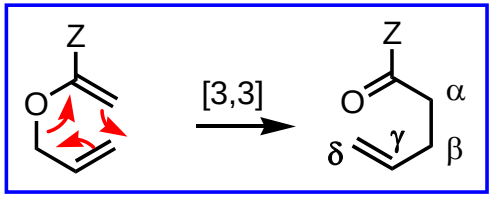
KH, 18-crown-6, DME, **25 °C**, 14 h

50%

85%

Org. Biomol. Chem. **2013**, *11*, 7587; *JACS* **1964**, *86*, 5019; *J. Org. Chem.* **1983**, *48*, 1000

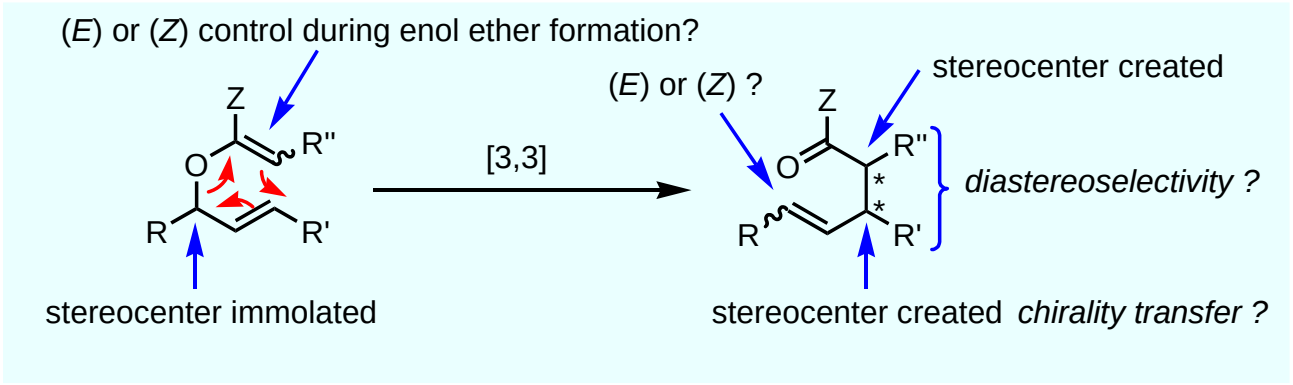
Claisen rearrangement

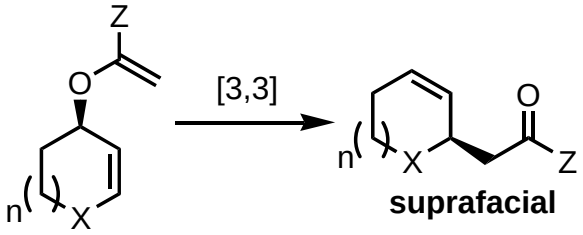


- Carbonyl compound more stable than vinylic ether (by *ca* 20 kcal/mol)
- Requires the generation of a vinylic ether from an allylic alcohol derivative (sometimes more difficult than the rearrangement itself)
- Extremely useful tool in organic synthesis (many applications)
- Several variants have been developed

Z = OR	Johnson-Claisen (1970)
Z = NR_2	Eschenmoser-Claisen (1964)
Z = $OSiR_3$	Ireland-Claisen (1972)

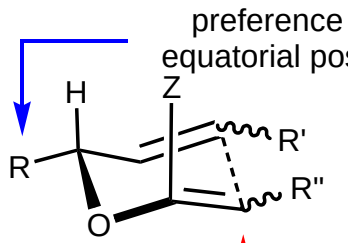
- Many opportunities for stereochemical control



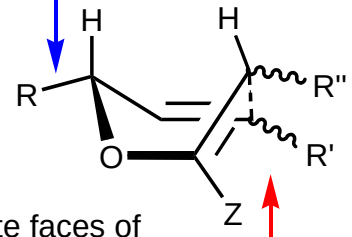


if X = CH, preference for chair-like TS
if X = O, preference for boat TS

chair-like TS (in most cases)

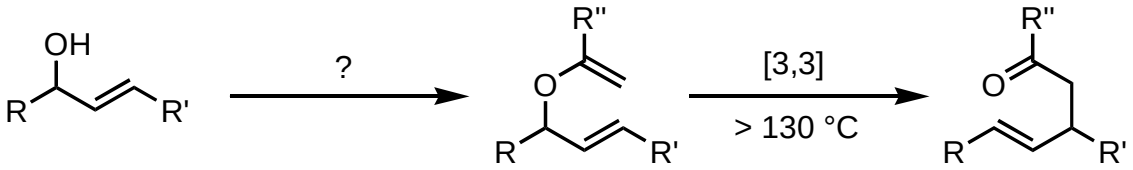


boat-like TS



opposite faces of
enol ether involved

Claisen rearrangement



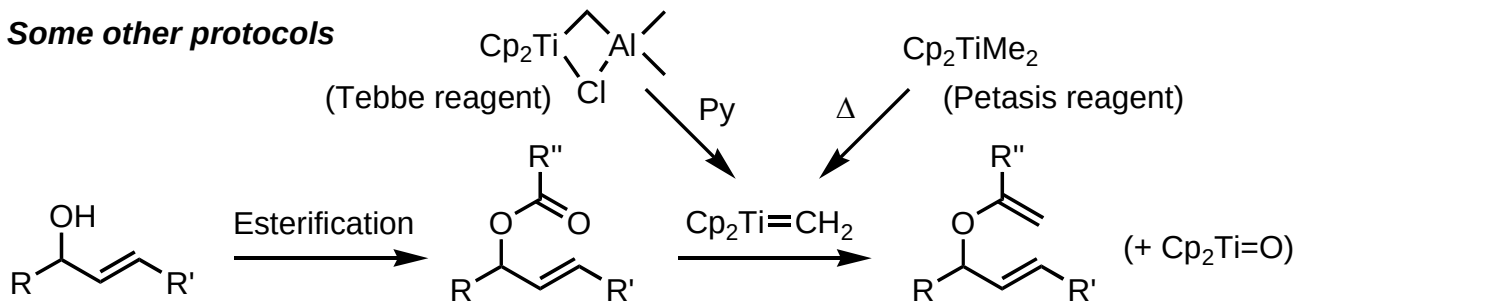
Generation of the vinyl ether : classical methods

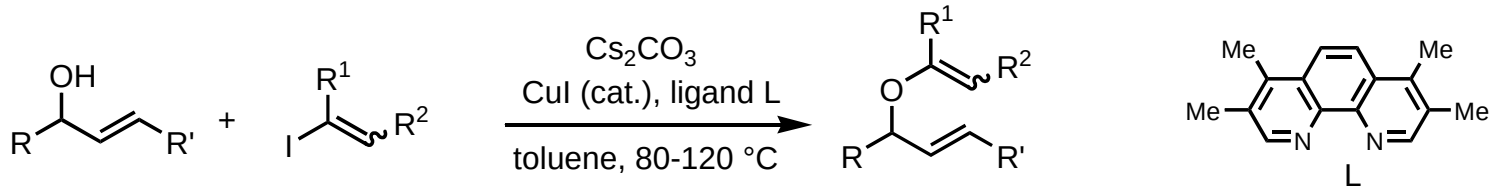
- EtO , $Hg(OAc)_2$ (cat.) transetherification

- KH, Ph S O then heating (enol ether rearranges under these conditions)

- Me MeO , TsOH (cat.) or H_3PO_4 "Saucy-Marbet conditions"

Some other protocols

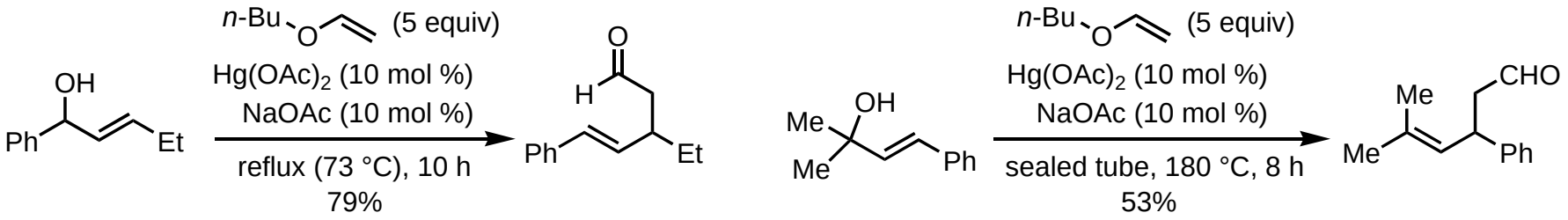


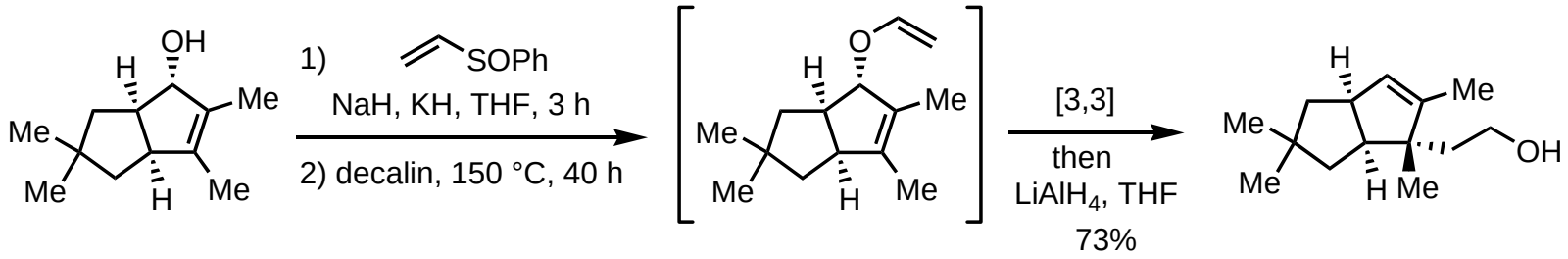


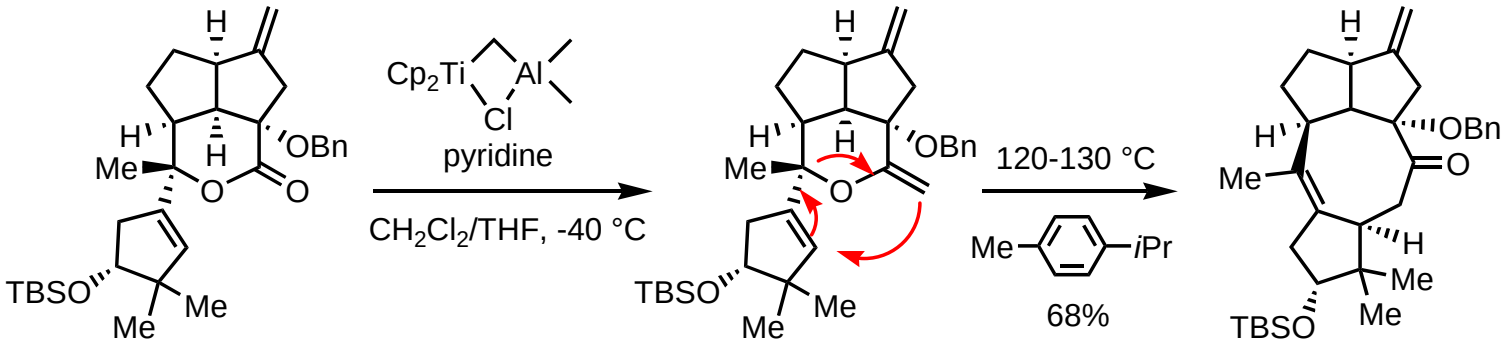
Ullman-type coupling (Buchwald)

(rearranges under the reaction conditions)

Claisen rearrangement : Examples

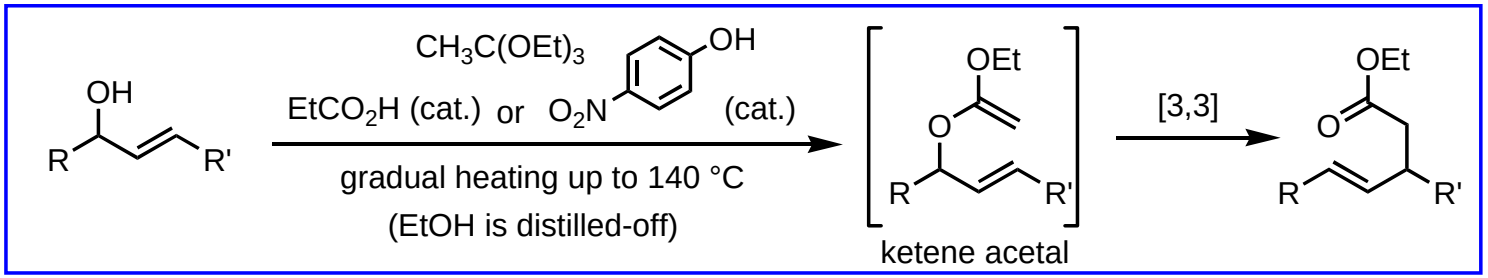




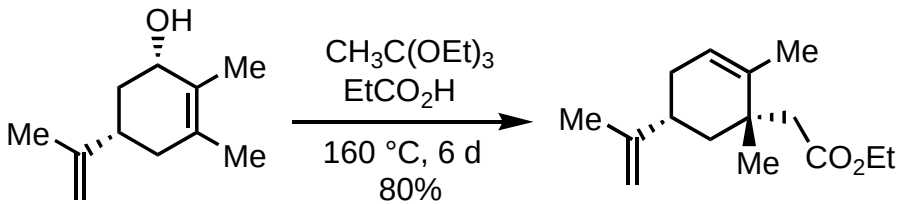


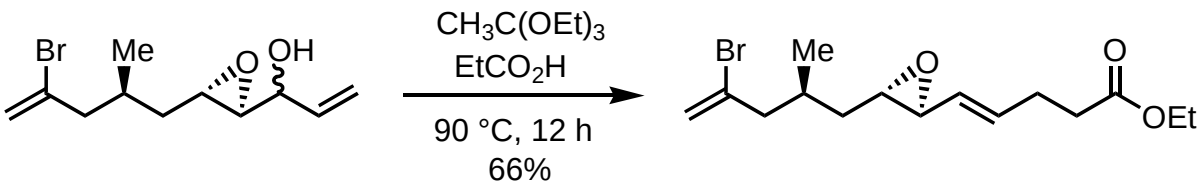
Synth. Commun. **2002**, *32*, 869*; Tetrahedron Lett.* **1995**, *36*, 15; *JACS* **1996**, *118*, 727

Johnson-Claisen rearrangement

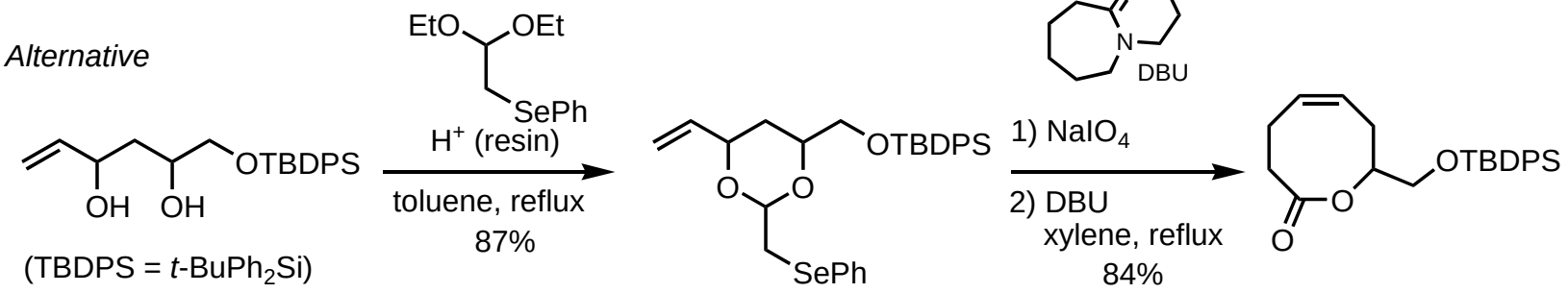


$CH_3C(OR)_3$: orthoacetates essentially used, limited stereocontrol for other orthoesters (but cyclic ones are useful)



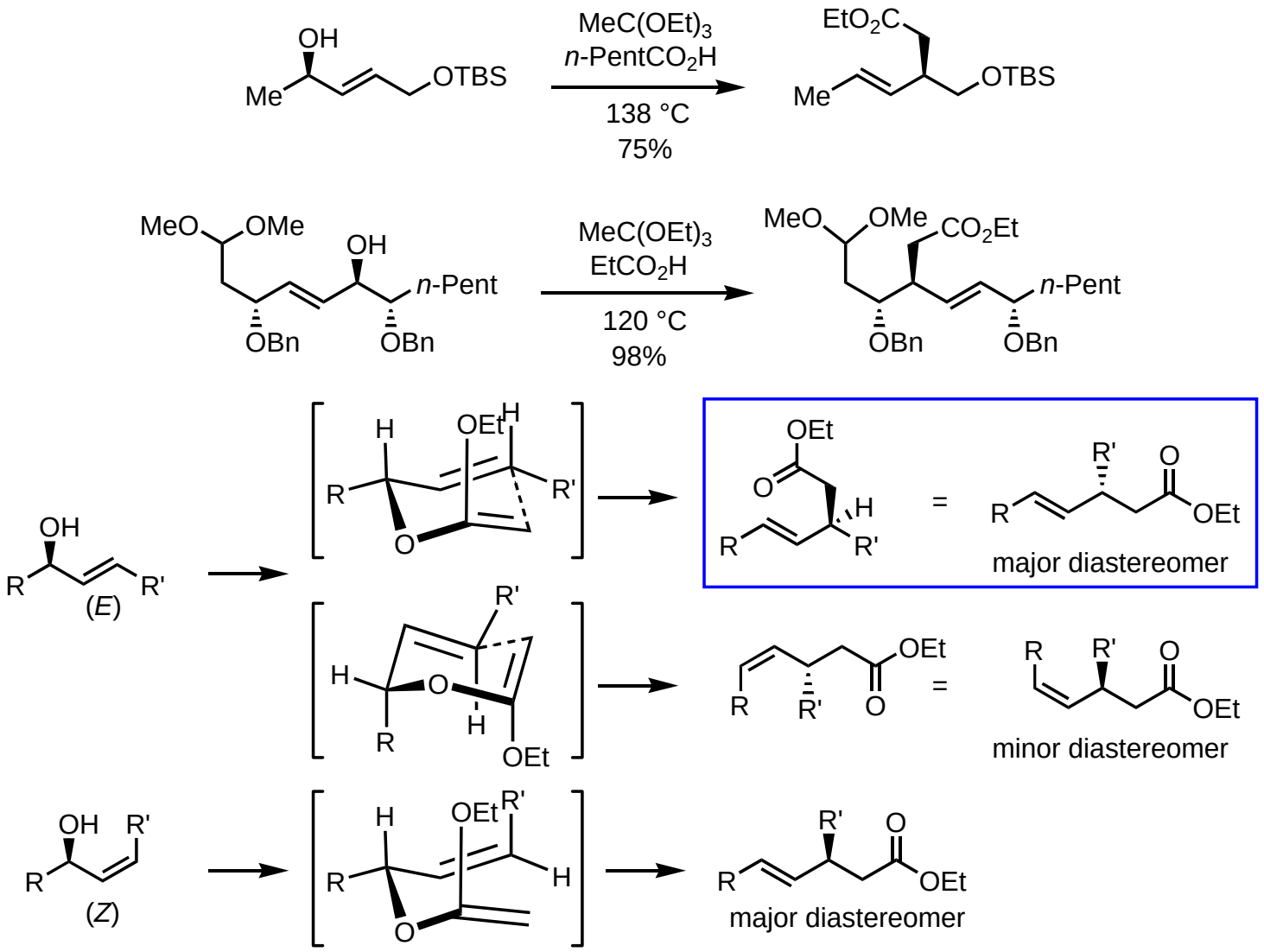


Alternative



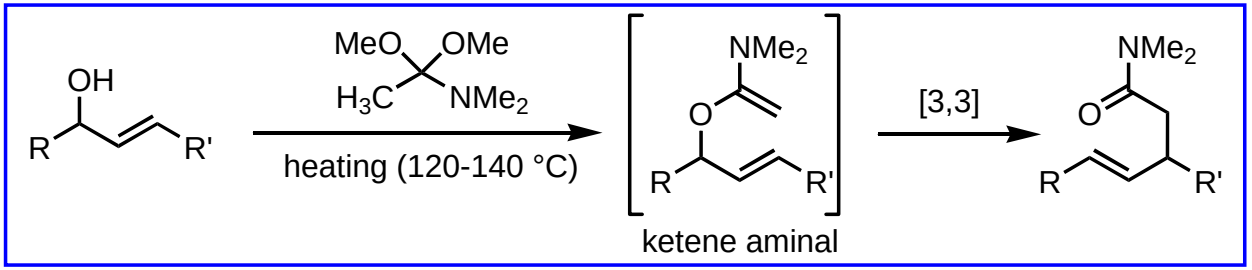
JACS **1970**, *92*, 741; *Tetrahedron Lett.* **1996**, *37*, 2863; *Tetrahedron Lett.* **1997**, *38*, 7909;
J. Chem. Soc., Chem. Commun. **1986**, 325; *Tetrahedron* **1991**, *47*, 7171

Johnson-Claisen rearrangement : stereoselectivity

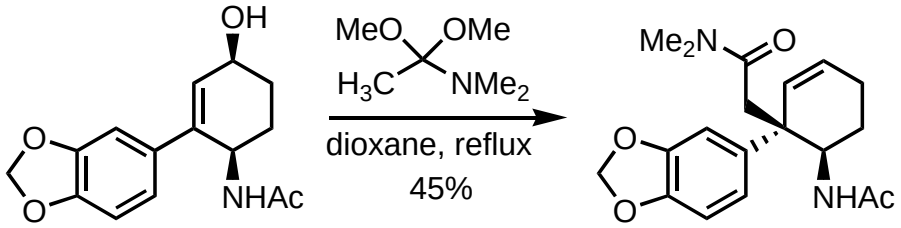


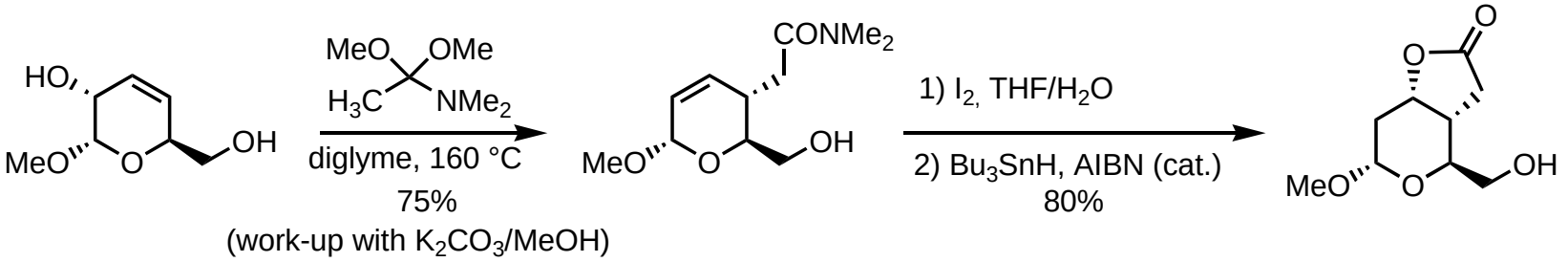
Synth. Commun. **2002**, *32*, 869*; Tetrahedron Lett.* **1995**, *36*, 15; *JACS* **1996**, *118*, 727

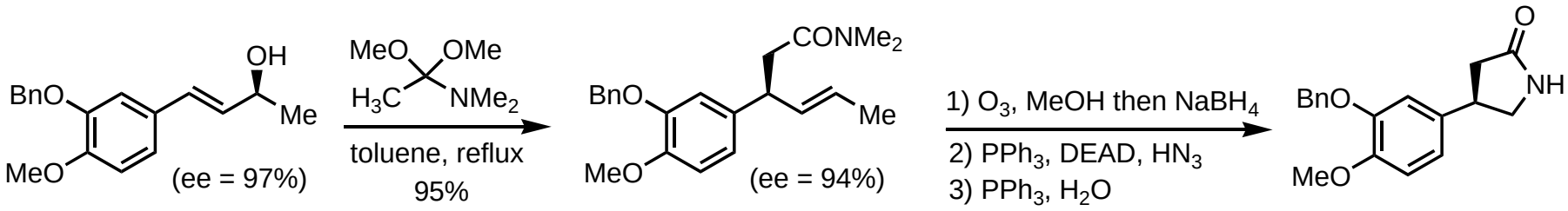
Eschenmoser-Claisen rearrangement



Acid catalyst not required (neutral conditions)

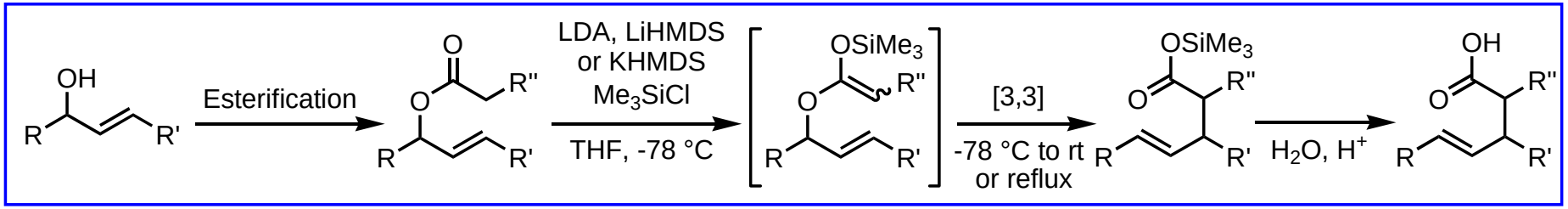






Helv. Chim. Acta **1964**, *47*, 2425; **1969**, *52*, 1030; *Tetrahedron Lett.* **1977**, *18*, 1625; *J. Prakt. Chem.* **1994**, *336*, 27

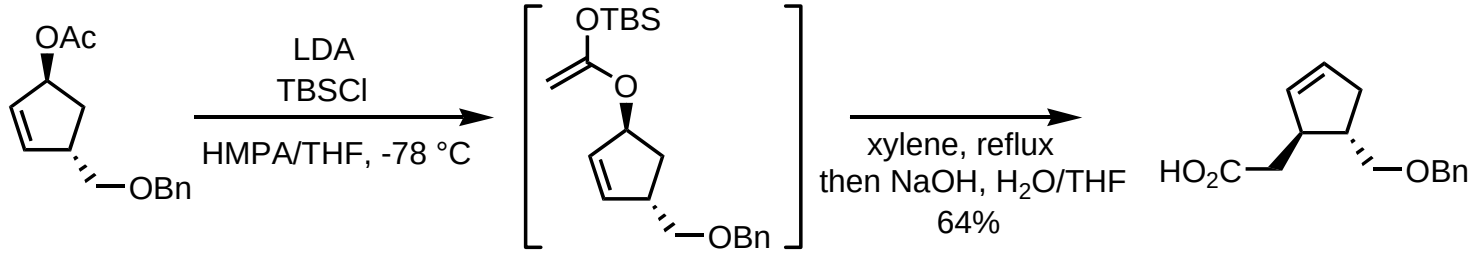
Ireland-Claisen rearrangement

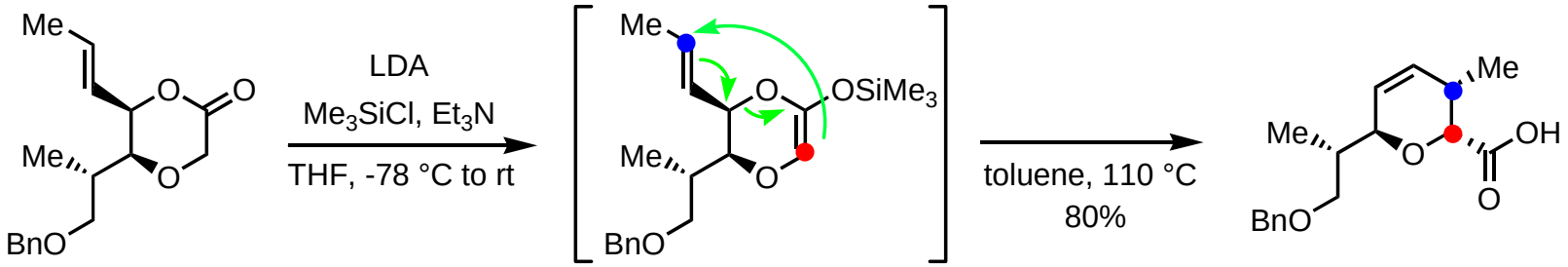


Esters precurors easily generated from allylic alcohols

Mild conditions for the generation of the ketene silyl acetal (-78 °C) and the rearrangement (in most cases)

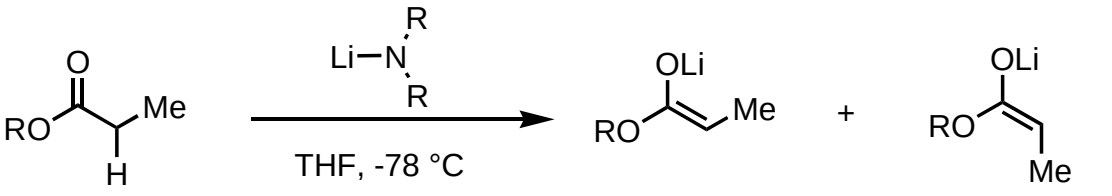
If R'' = H, C-silylation can be observed as a side reaction, TBSCl (*t*-BuMe_2SiCl) usually lead to better results



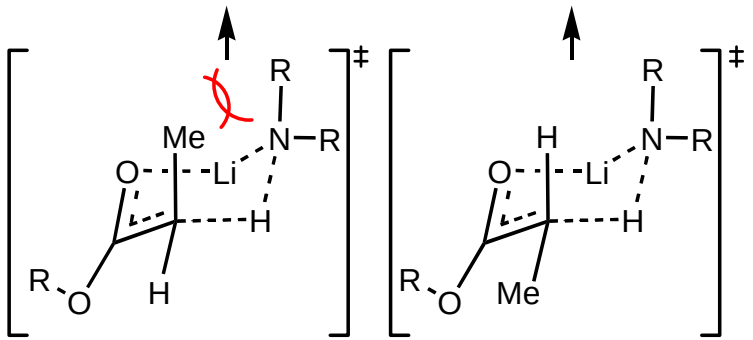


JACS **1972**, *94*, 5897; **1976**, *98*, 2868, *J. Org. Chem.* **1991**, *56*, 650 and 3572

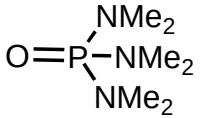
Control of the geometry of silyl ketene acetals



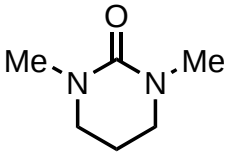
Cyclic transition state
(**Ireland model**)



		(*Z*)		(*E*)
OMe, O*t*-Bu	with LDA, THF	**5**	**:**	**95**
MeO	LDA, THF/HMPA (77:23)	85	:	15
MeO	LDA, THF/DMPU (55:45)	**93**	**:**	**7**

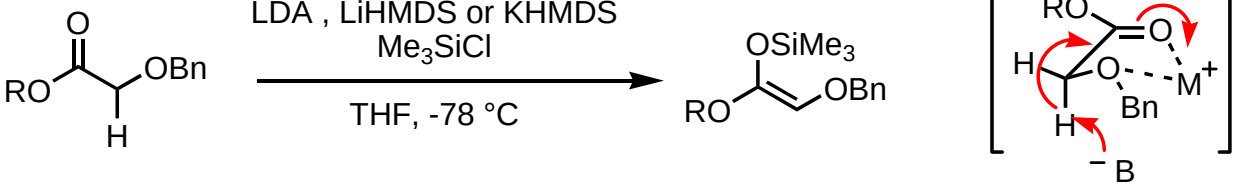


HMPA



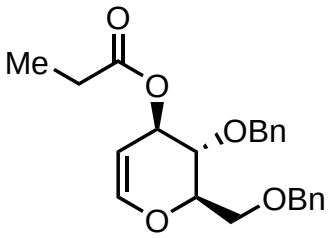
DMPU

reversal of
kinetic selectivity

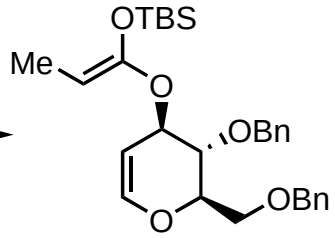


JACS **1976**, *98*, 2868; *J. Org. Chem.* **1991**, *56*, 650

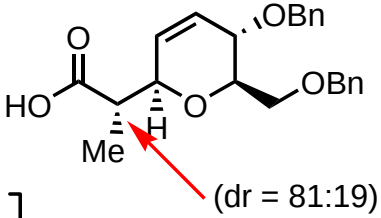
Ireland-Claisen rearrangement



LDA
TBSCl
HMPA
THF, -78 °C to rt

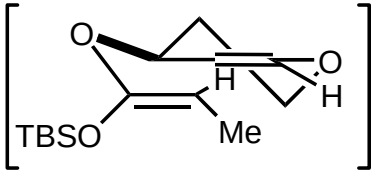


1) -78 °C to rt
2) NaOH, puis H^+
65%

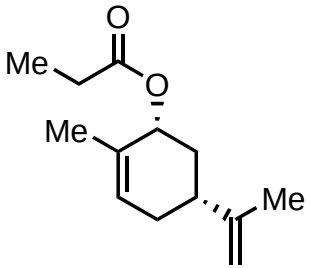


(dr = 81:19)

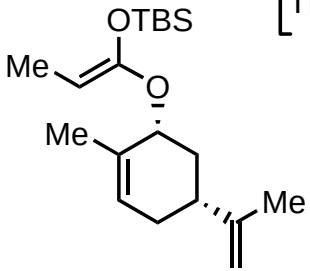
preference for boat TS
in this case (cyclic enol ether)



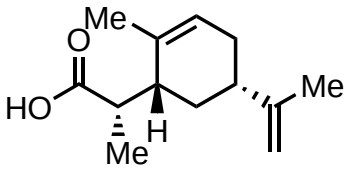
(sub. on pyran removed for clarity)

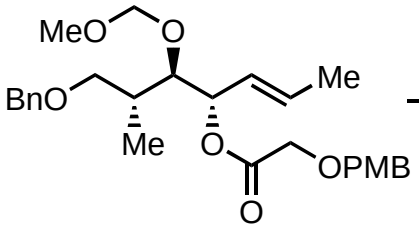


LDA
TBSCl
HMPA
THF, -78 °C to rt

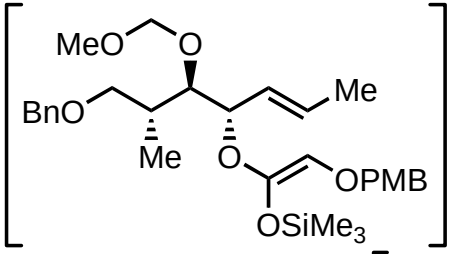


1) -78 °C to rt
2) NaOH, puis H^+
60%

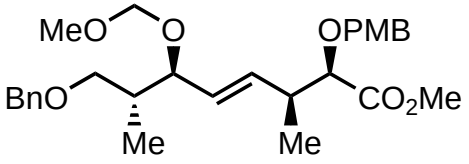




LDA
TMSCl
THF, -78 °C

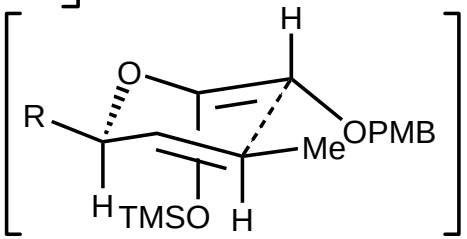


1) -78 °C to rt
2) H_2O/H^+
3) CH_2N_2, Et_2O
85%



single diastereomer

PMB = CH_2–OMe



JACS **1981**, *103*, 3205; *Synlett* **1997**, 657; *Tetrahedron Lett.* **1993**, *34*, 1103

What needs to be remembered ?

- The **main different types of pericyclic reactions** including sigmatropic rearrangements and what nomenclature [n,m] means

- **Cope rearrangement**, oxy-cope and anionic oxy-Cope versions

You should recognize these reactions and be able draw the structure of the product (all the stereochemical aspects not been discussed thoroughly in this course)

- **Claisen rearrangement and the different variants** (Johnson, Eschenmoser, Ireland)

Classical methods for the generation of the reactive enol ether

Generation of ketene acetal derivatives (from orthoesters, amide acetals)

Generation of silyl ketene acetals and stereochemical control (Ireland model, reversal of kientic selectivity with HMPA or DMPU, chelation control with glycolates)

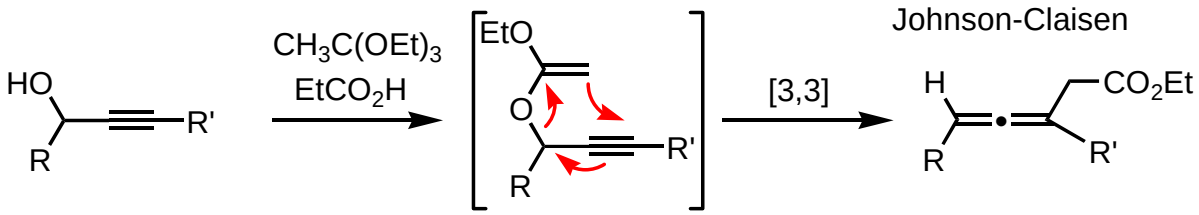
You should recognize these reactions and be able to draw the structure of the product

You should consider the use of Claisen rearrangements for the synthesis of γ,δ-unsaturated compounds

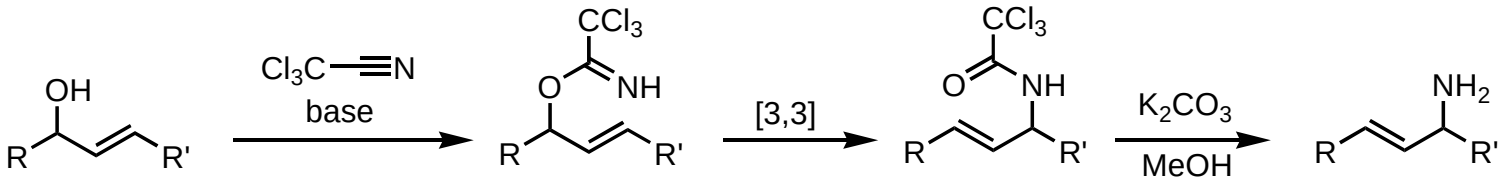
You should be able to draw a chair-like transition state and predict/understand the stereochemical outcome of a Claisen rearrangement (in simple cases, see slide 10 and slide 14 - last example)

A glimpse of other synthetically useful [3,3]-sigmatropic rearrangements

[3,3]-sigmatropic rearrangements applied to propargyl alohols

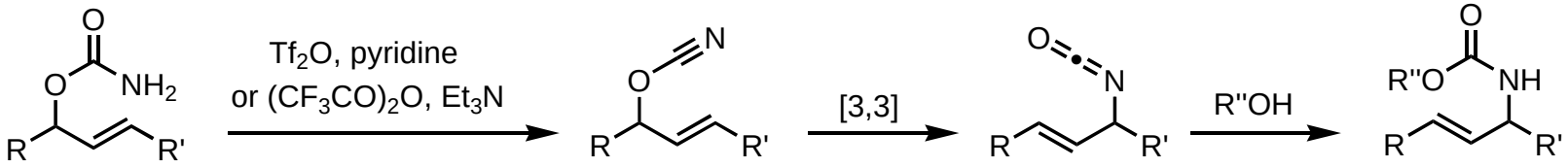


Overman rearrangement of allylic trichloroacetimidates



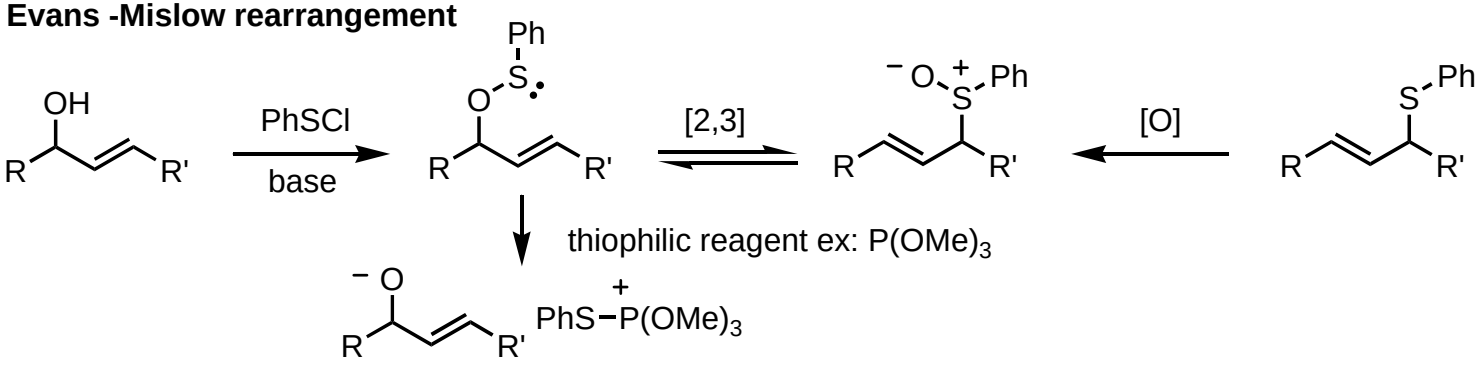
High temperatures (130 °C) are usually required but can be catalyzed (Pd(II) complexes)

Cyanate to isocyanate rearrangement

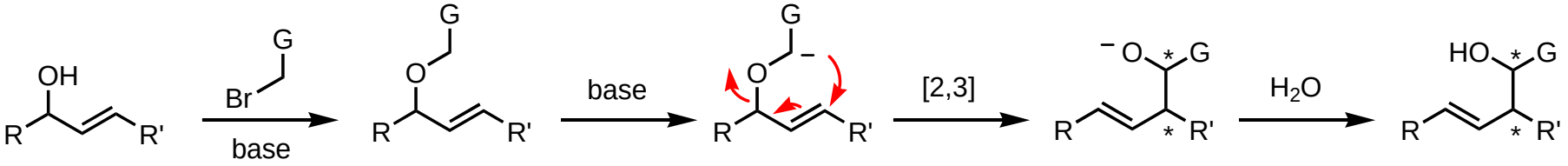


A glimpse of [2,3]-sigmatropic rearrangements

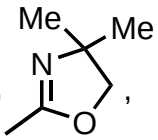
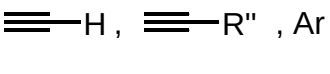
Evans -Mislow rearrangement



Wittig rearrangement

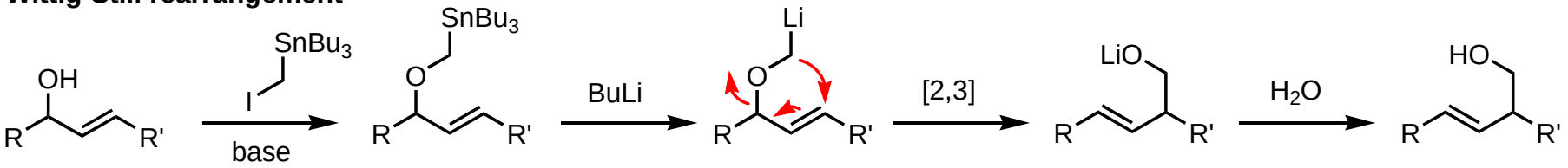


G = anion-stabilizing group

G = CONR"$_2$, COOH (CO_2^-),  , 

π-acceptors stabilizing groups π-donors stabilizing groups

Wittig-Still rearrangement



(- Bu_4Sn : tin-lithium exchange)

ADVANCED SELECTIVE ORGANIC SYNTHESIS (2019)

A. Guérinot, C. Meyer

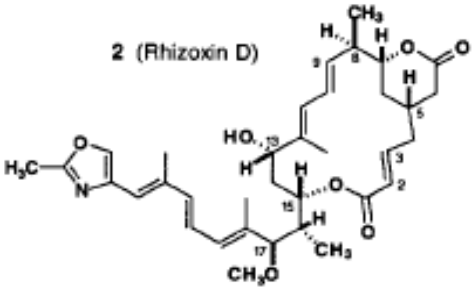
ESPCI PARIS
EDUCATION SCIENCE INNOVATION

Total Synthesis of Bioactive Natural Products

Total Synthesis of Rhizoxin D

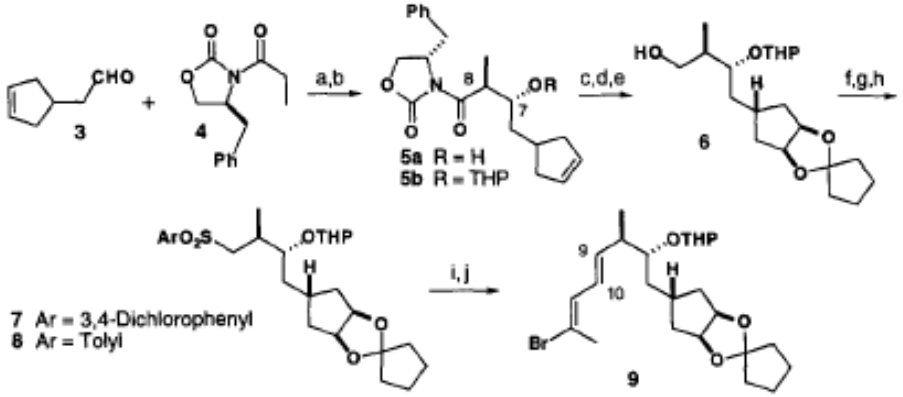
David R. Williams,* Kim M. Werner, and Bainian Feng

Tetrahedron Letters, Vol. 38, No. 39, pp. 6825-6828, 1997



The rhizoxins are a family of sixteen-membered macrolactones with exceptionally potent antitumor and antifungal activity.

Scheme I[a]



[a]Key: a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C to –78 °C then **3**, 95%; b) DHP, PPTs, CH_2Cl_2, 100%; c) OsO_4, NMO, Acetone/H_2O, 88%; d) cyclopentanone, PPTs, $HC(OEt)_3$, CH_2Cl_2, 92%; e) $LiBH_4$, MeOH, Et_2O, 0 °C, 91%; f) TsCl, Et_3N, CH_2Cl_2, 98%; g) ArSH, NaH, DMF/THF, 0 °C, 95%; h) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 98%; i)LDA, HMPA, THF, –78 °C then (*E*)-1,3-dibromo-2-butene, 88%; j) DBU, tol., 105 °C, 70%.

The authors observed that sulfone **7** gave a much higher yield of **9** in step j) (70%) than sulfone **8** (30% yield).

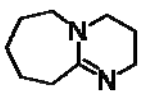
PPTS = Pyridinium *p*-toluenesulfonate

DHP = 3,4-Dihydro-2*H*-pyrane; THP = tetrahydropyran-2-yl

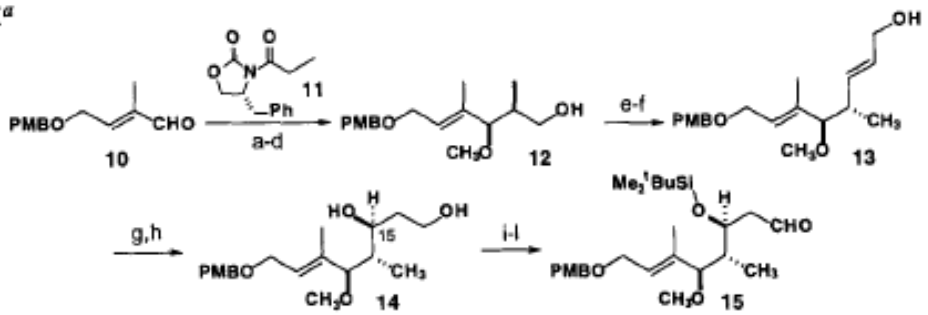
NMO = *N*-Methylmorpholine *N*-oxide

HMPA : $O=P(NMe_2)_3$

DBU =



Scheme II[a]



[a]Key: a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C to –78 °C then **10**, 87%; b) Bu_3B, $LiBH_4$, HOAc, THF, 77%; c) TBDMSCl, Imid., CH_2Cl_2, (100%); d) *i*. NaH, CH_3I, THF, *ii*. PPTs, EtOH, 66 °C, 97% (two steps); e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 22 °C, then $(C_6H_5)_3PCHCO_2CH_3$, 88%; f) DIBAL, CH_2Cl_2, 93%; g) $Ti(O^iPr)_4$, (–)-DET, ^tBuOOH, CaH_2, 4Å sieves, CH_2Cl_2, 93%; h) Red-Al, THF, –78 °C to 22 °C, 90%; i) Piv-Cl, pyr, CH_2Cl_2, 90%; j) $Me_2{}^tBuSiOTf$, collidine, CH_2Cl_2, 98%; k) DIBAL, CH_2Cl_2, –78 °C, 87%; l) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N, –78 °C to 22 °C, 92%.

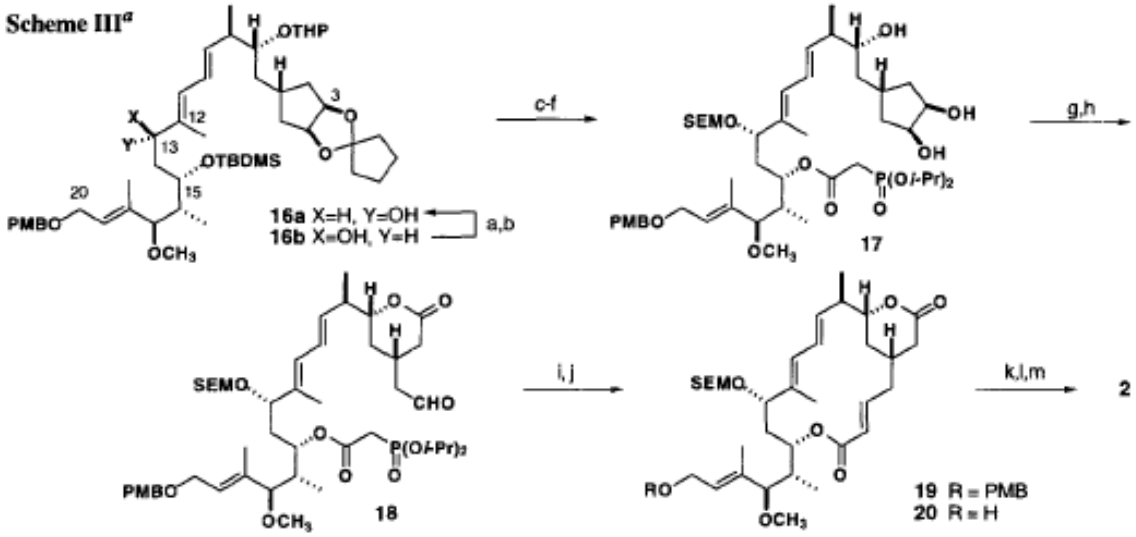
PMB = *p*-methoxybenzyl; (-)-DET = (-)-D-Diethyl tartrate; Piv = *t*-BuCO; Red-Al = $NaAlH_2(OCH_2CH_2OMe)_2$; collidine = 2,4,6-trimethylpyridine

Suggest a method for the preparation of aldehyde **10** from ethylene glycol $HO(CH_2)_2OH$ or glycerol $HOCH_2CH(OH)CH_2OH$ and *p*-methoxybenzylalcohol.

Assembly of the fragments:

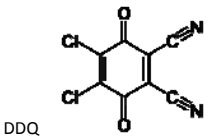
Linkage of our nonracemic fragments was achieved through halogen-metal exchange of **9** (^{t}BuLi, 2 equiv., THF/Et_2O/pentane (4:1:1) at –120 °C; warming to –90 °C) followed by addition of aldehyde **15** (–90 °C to –78 °C). The process afforded a mixture (1:1 ratio) of C_{13} alcohol diastereomers **16** in 77% yield (Scheme III).[18] Undesired isomer **16b** was readily separated by flash chromatography and effectively converted into **16a** via TPAP oxidation[19] and borohydride reduction using (*R*)-2-methyl-CBS-oxazaborolidine,[20] giving a 68% overall yield of the desired C_{13} alcohol.

Scheme III[a]



[a]Key: a) TPAP, NMO, 4Å sieves, CH_2Cl_2, 80%; b) (*R*)-2-methyl-CBS-oxazaborolidine, BH_3, THF, –10 °C, 85%; c) SEMCl, $^i Pr_2EtN$, CH_2Cl_2, 94%; d) TBAF, THF, 94%; e) diisopropylphosphonoacetic acid, 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide methyl-*p*-toluenesulfonate, DMAP, 4Å sieves, CH_2Cl_2, 97%; f) HOAc/H_2O (4/1), 48 h, 56%; g) $NaIO_4$, THF/H_2O; h) TPAP, NMO, 4Å sieves, CH_2Cl_2, 67%, 2 steps; i) DBU (2 equiv), CH_3CN, LiCl (15 equiv), 4.6×10^{-4} M, 84%; j) DDQ, H_2O, CH_2Cl_2, 98%; k) MnO_2, 70%; l) KHMDS, 4-[3-(diphenylphosphinoyl)-2-methylpropenyl]-2-methyloxazole, 44%; m) Me_2BBr, THF/CH_2Cl_2, 0 °C, 65%

TPAP = n-Pr_4N^+ RuO_4^-
SEM = CH_2-O-CH_2-CH_2-$SiMe_3$



DDQ

Completion of the total synthesis of **2** was realized by oxidation of the allylic alcohol **20**, and Wittig olefination (–78 °C, THF) with the carbanion generated from 4-[3-(diphenylphosphinoyl)-2-methyl-propenyl]-2-methyloxazole.[9] The all-*trans*-triene was obtained in 44% yield,[24] and deprotection of the C_{13} SEM ether afforded synthetic rhizoxin D, $[\alpha]_D^{24}$ + 293° (c 0.53, MeOH), with characterization data which were identical to the literature for the natural product.[2a]