Synthetic methods in molecular chemistry

Introduction

Teaching team

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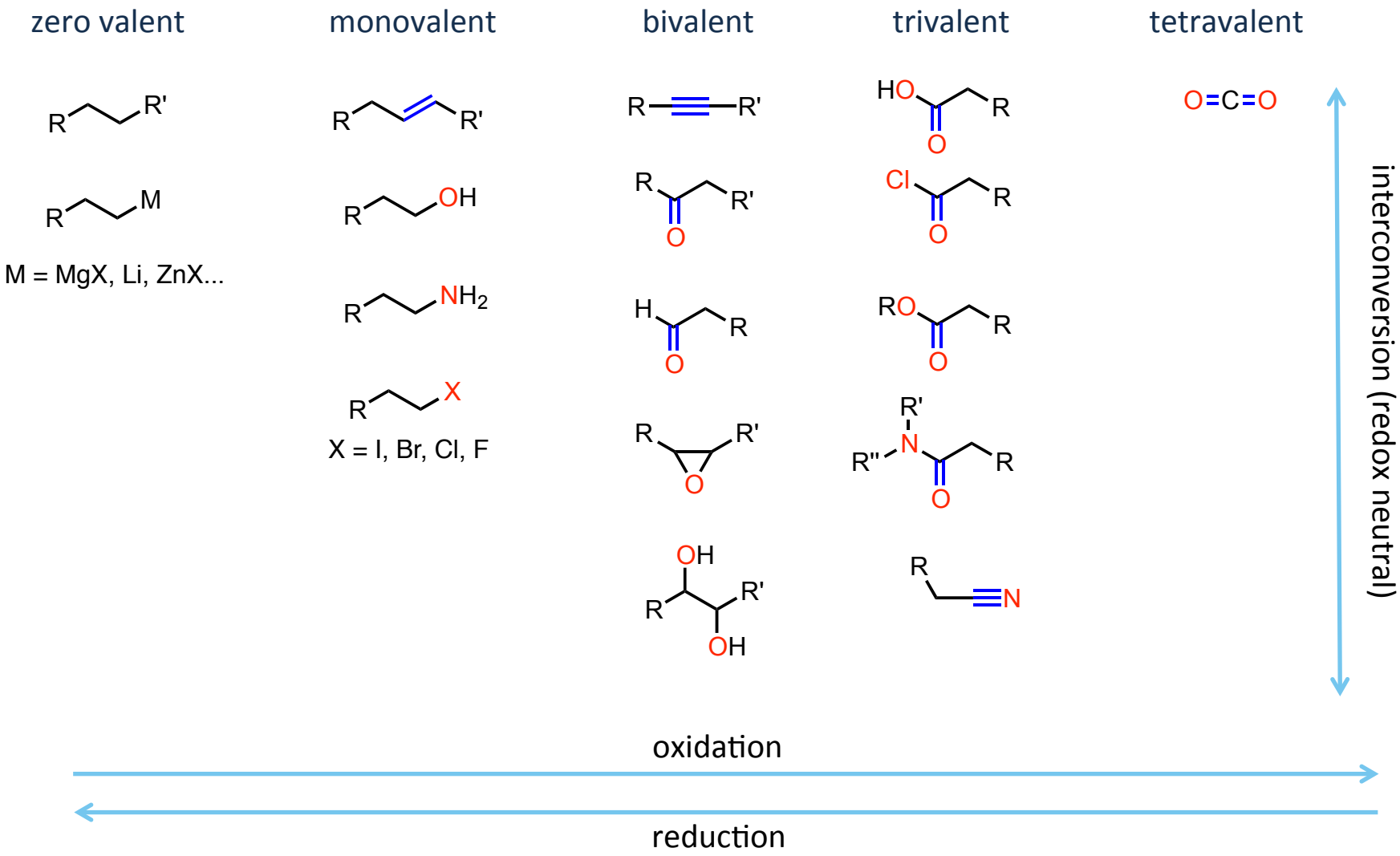
Functional groups – valence table



valence = number of H_2 molecules required to access a saturated compound + C-Heteroatom bonds

Synthetic methods in molecular chemistry – Table of contents

I- Oxidations

- oxidation of alcohols
- epoxidation
- dihydroxylation
- rearrangements

II- Reductions

- carbonyl, alkene and alkyne reduction
- stereoselective reductions
- deoxygenations
- C-X bonds reductions

III- Functional groups interconversion

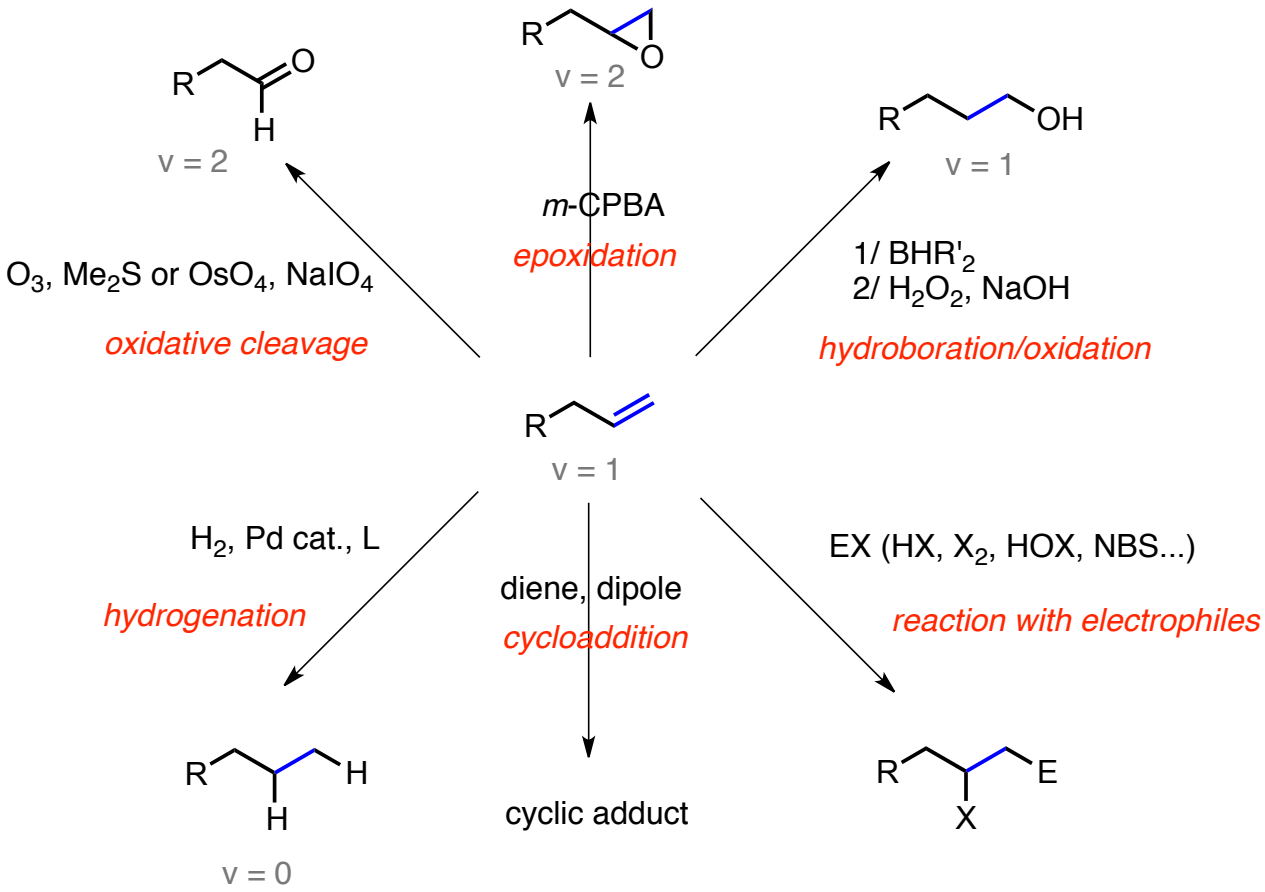
- conversion of alcohols into leaving groups
- S_N2 reactions
- Mitsunobu reaction
- interconversion of carboxylic acid derivatives

IV- C-C bonds formation

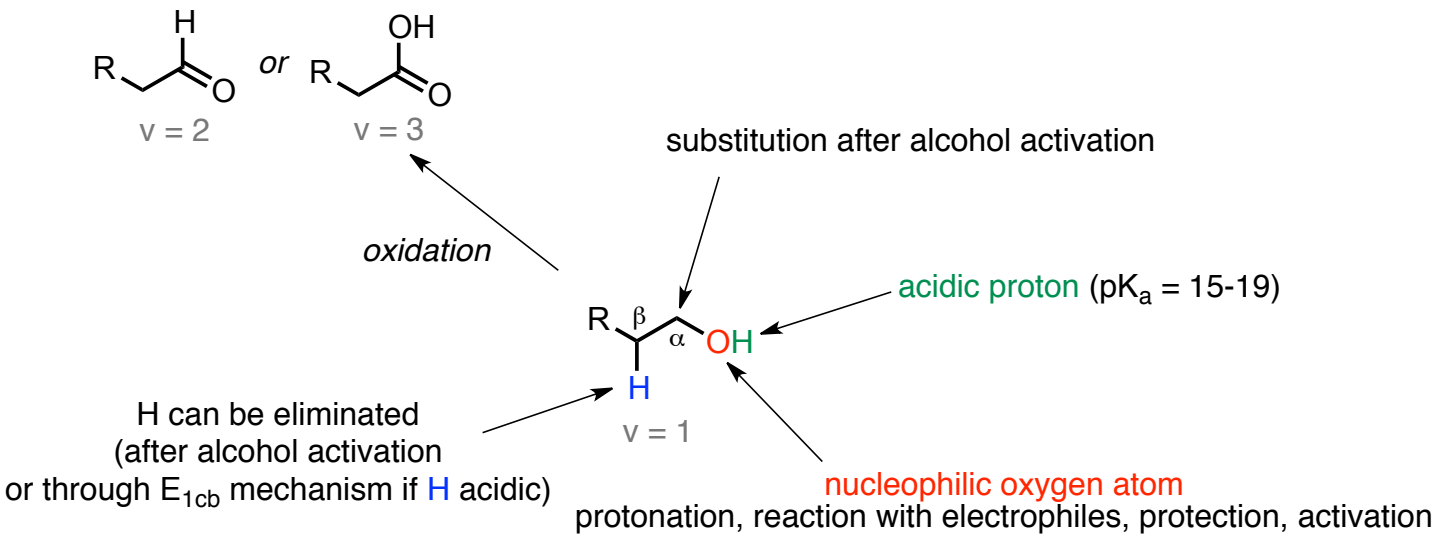
- olefination reactions
- organometallics
- metal-catalyzed cross-coupling

General reactivity profiles

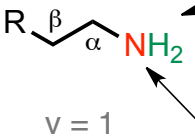
Alkenes


R
O
H
v = 2
R
O
v = 2
R
OH
v = 1
O_3, Me_2S or OsO_4, $NaIO_4$
oxidative cleavage
m-CPBA
epoxidation
1/ BHR'_2
2/ H_2O_2, NaOH
hydroboration/oxidation
R
v = 1
H_2, Pd cat., L
hydrogenation
diene, dipole
cycloaddition
EX (HX, X_2, HOX, NBS...)
reaction with electrophiles
R
H
H
v = 0
cyclic adduct
R
E
X

Alcohols


R
H
O
v = 2
or
R
OH
O
v = 3
oxidation
substitution after alcohol activation
acidic proton (pKa = 15-19)
R
β
α
OH
H
v = 1
H can be eliminated
(after alcohol activation
or through E1cb mechanism if H acidic)
nucleophilic oxygen atom
protonation, reaction with electrophiles, protection, activation

Amines



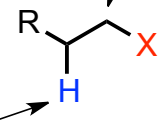
v = 1

poorly acidic protons ($pK_a \approx 35$)
strong base needed to deprotonate

nucleophilic nitrogen atom
protonation, imine formation, reductive amination
alkylation, amide formation...

Halides

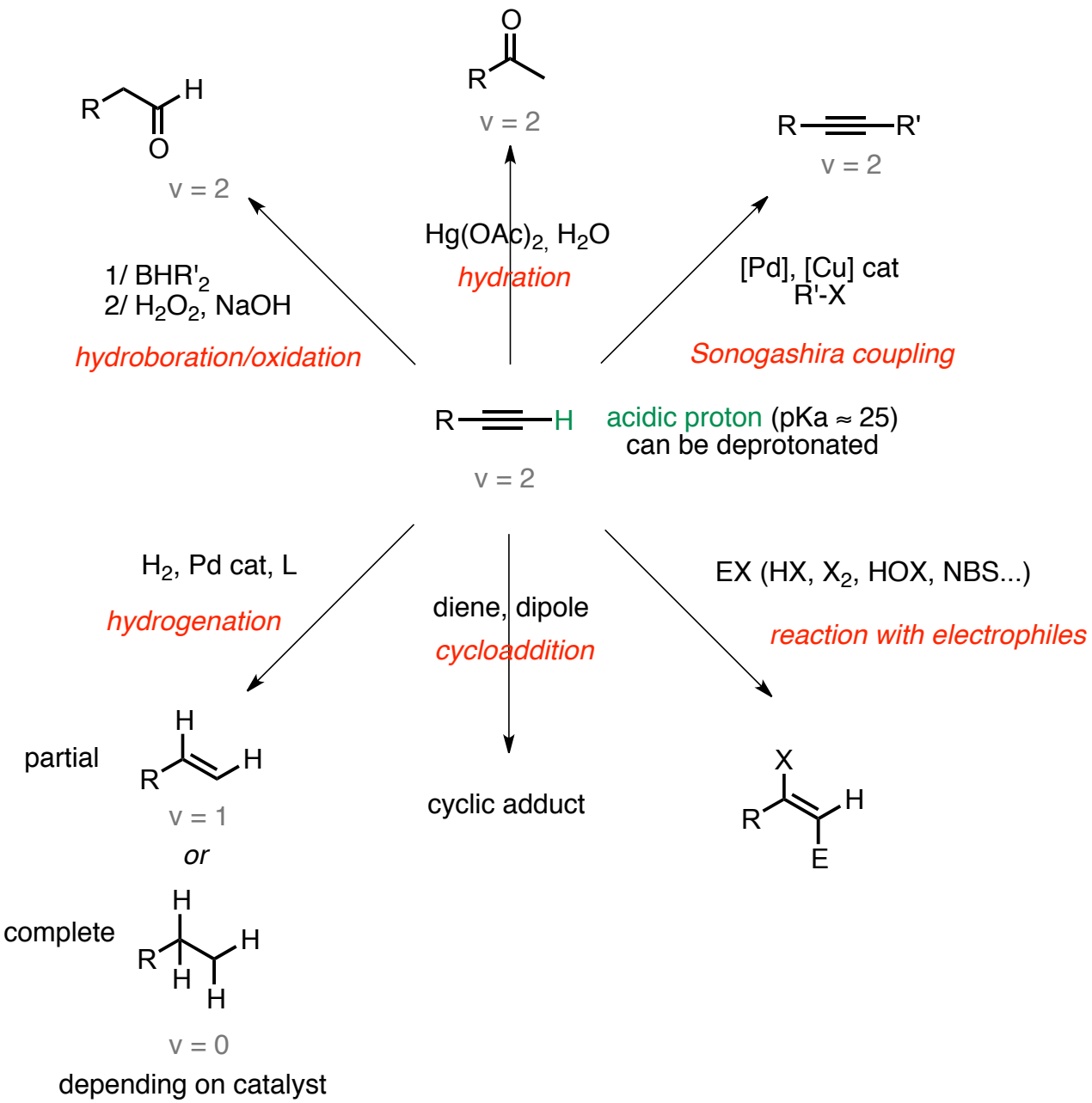
substitution (X = good leaving group)
S_N2 or S_N1 mechanism depending on substrate /conditions



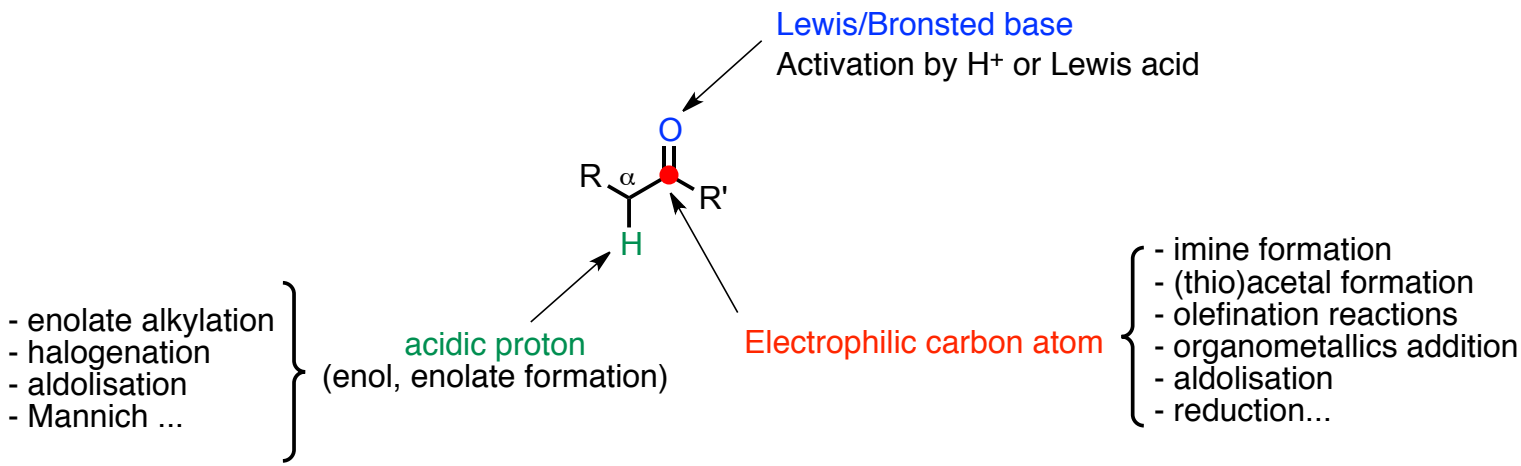
X = I, Br, Cl

H can be eliminated
E_2 or E_1 mechanism

Alkynes

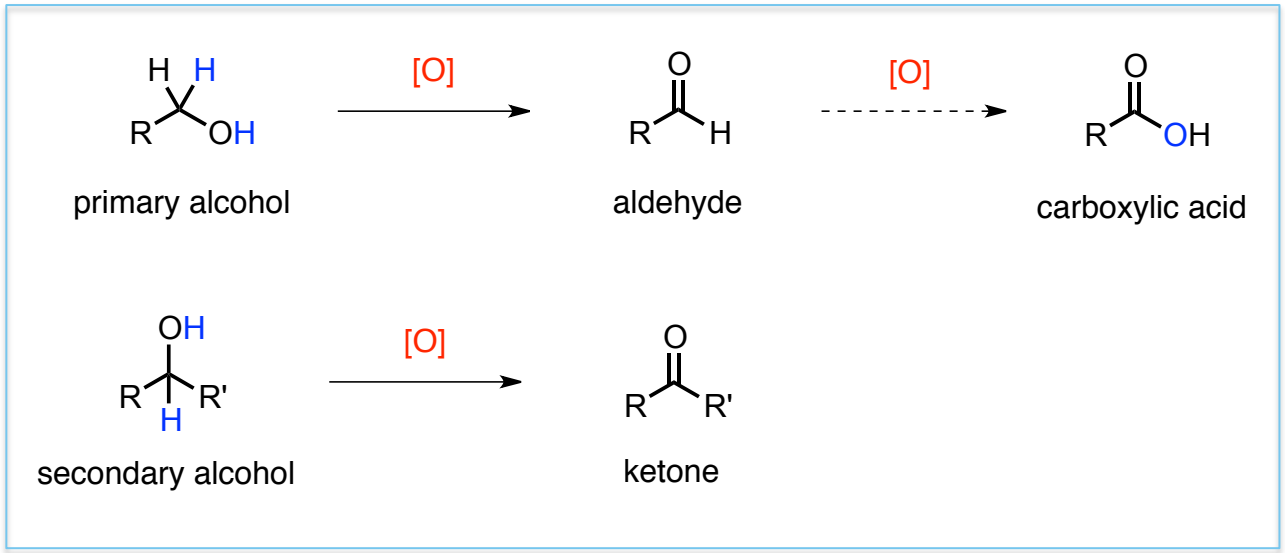

v = 2
Hg(OAc)2, H2O
hydration
v = 2
1/ BHR'2
2/ H2O2, NaOH
hydroboration/oxidation
v = 2
[Pd], [Cu] cat
R'-X
Sonogashira coupling
acidic proton (pKa ≈ 25)
can be deprotonated
v = 2
H2, Pd cat, L
hydrogenation
diene, dipole
cycloaddition
EX (HX, X2, HOX, NBS...)
reaction with electrophiles
partial
v = 1
or
complete
v = 0
depending on catalyst
cyclic adduct

Aldehydes and ketones



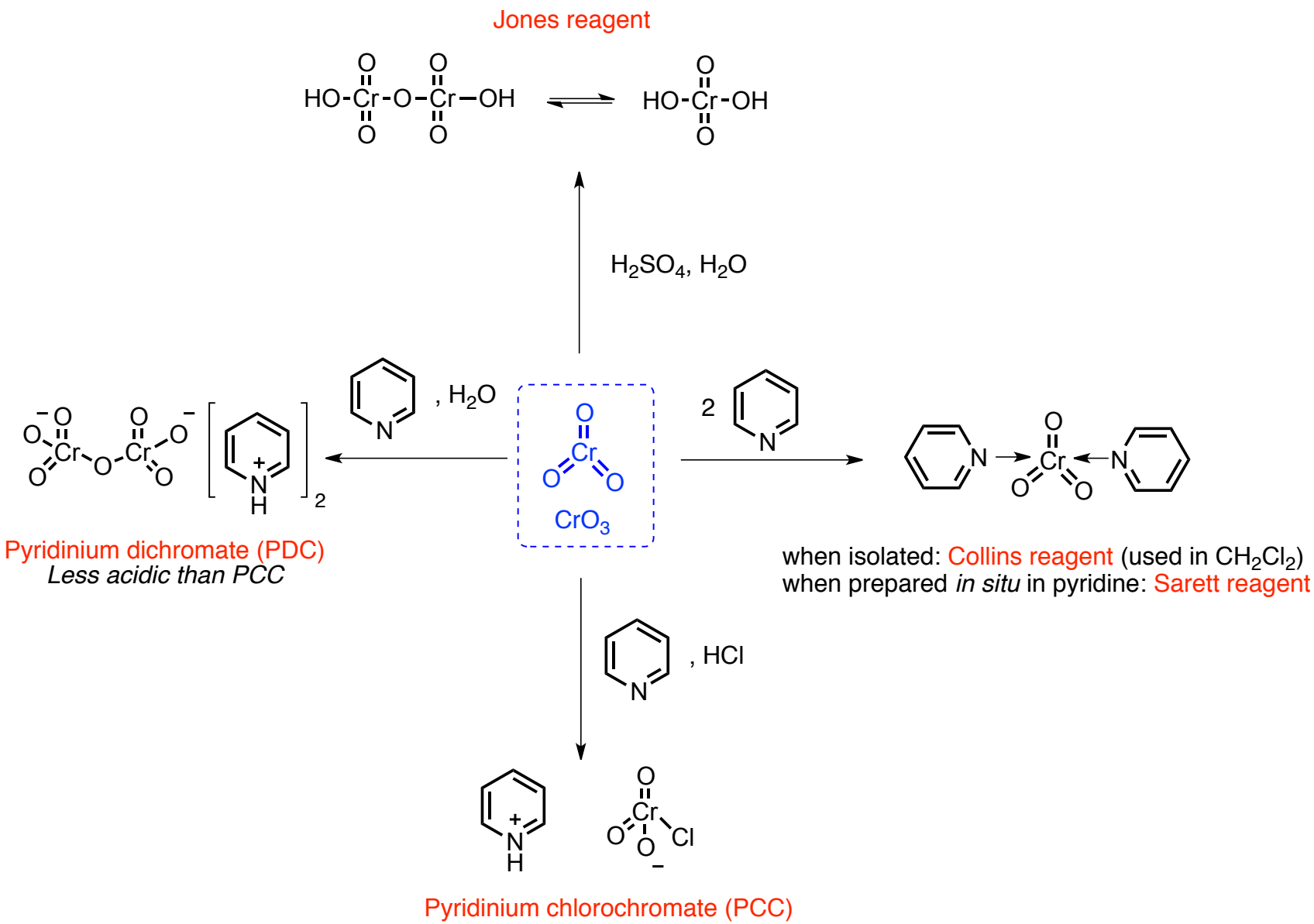
1- Oxidations

Oxidation of alcohols



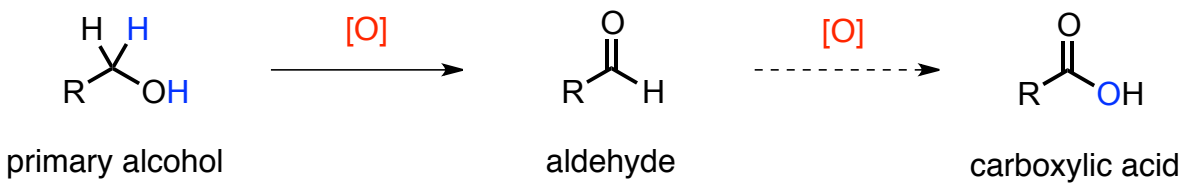
Oxidation with chromium based reagents

Preparation of Cr(VI) compounds derived from CrO_3



Oxidation of primary alcohols with Cr(VI) based reagents

Selectivity



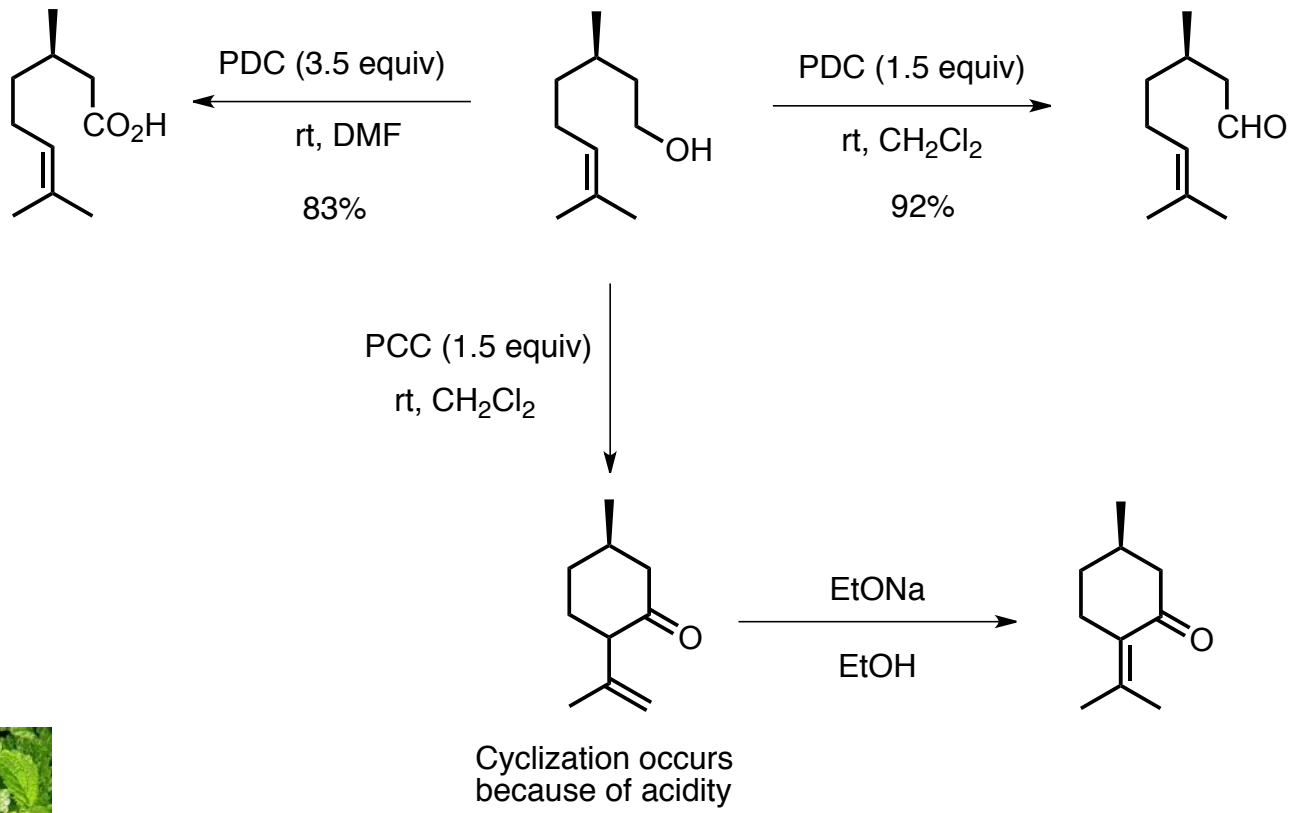
Jones	✗	✔
Collins/Sarett	✔	✗
PCC	✔	✗
PDC in CH_2Cl_2	✔	✗
PDC in DMF	✗	✔

Oxidation of primary alcohols with Cr(VI) based reagents

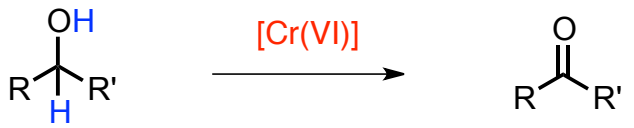
Mechanisms

Oxidation of primary alcohols with Cr(VI) based reagents

Example: oxidation of citronnelol



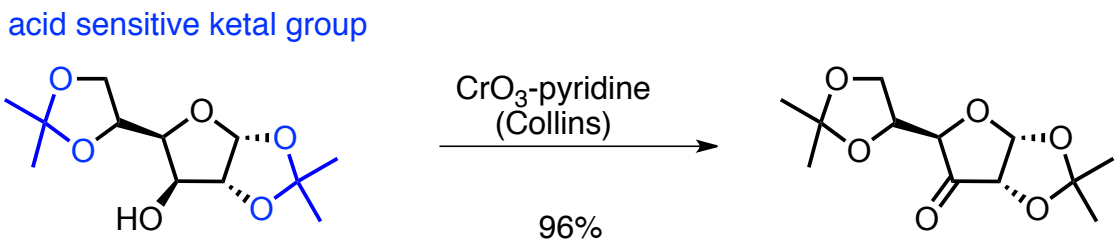
Oxidation of secondary alcohols with Cr(VI) based reagents

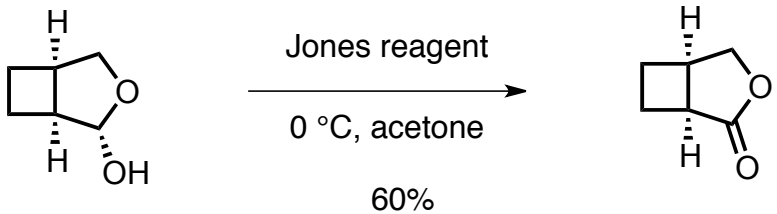


secondary alcohol ketone

All the previously mentionned Cr(VI) reagents able to oxidize secondary alcohols in ketones

Examples

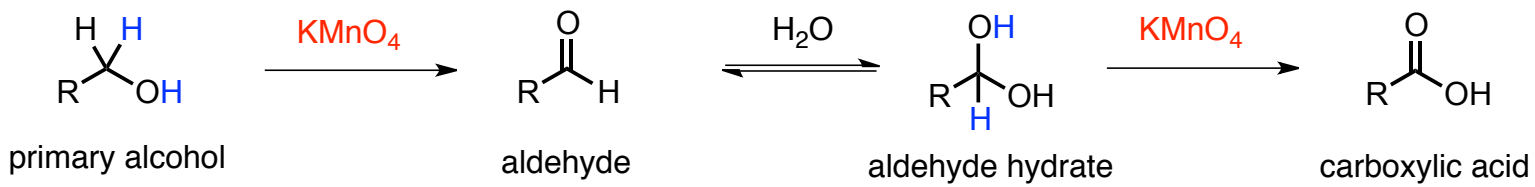




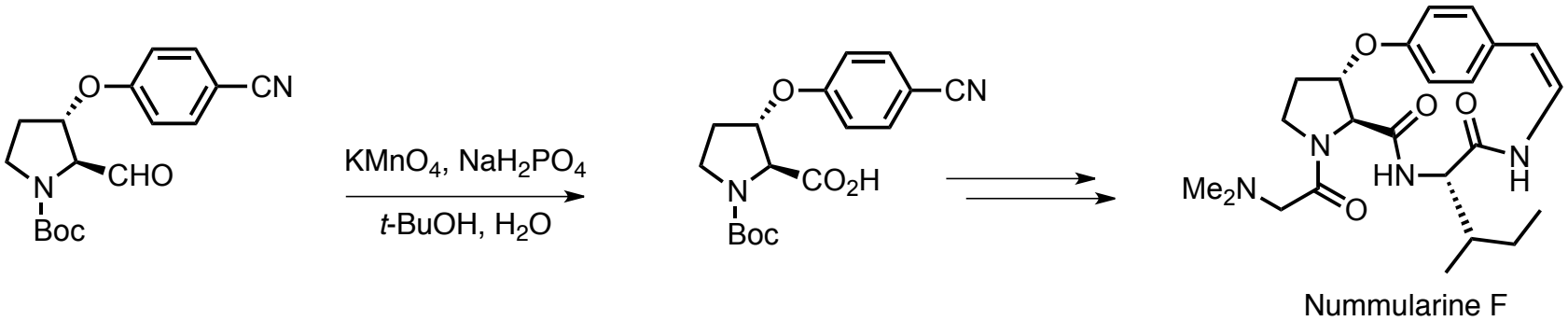
lactol lactone

Oxidation with manganese based reagents

- Potassium permanganate



- Primary alcohols or aldehydes can be used as starting material
- Reactions performed in aqueous solution (solubility of $KMnO_4$)
- Not compatible with the presence of double bonds
- Not widely used in synthesis, generally not the first option tested

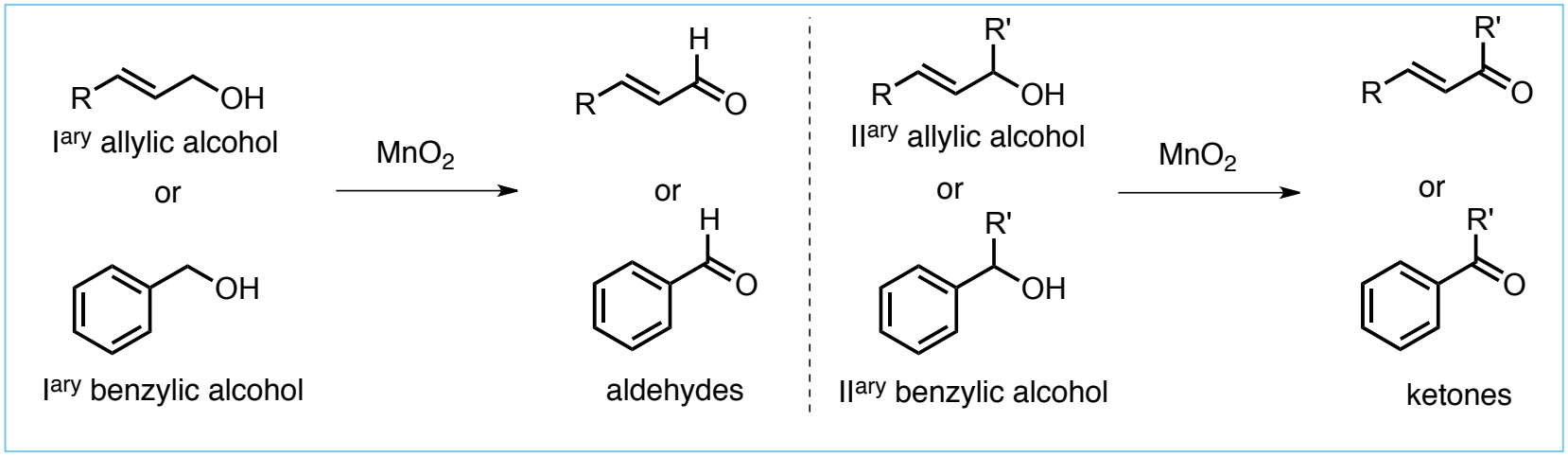


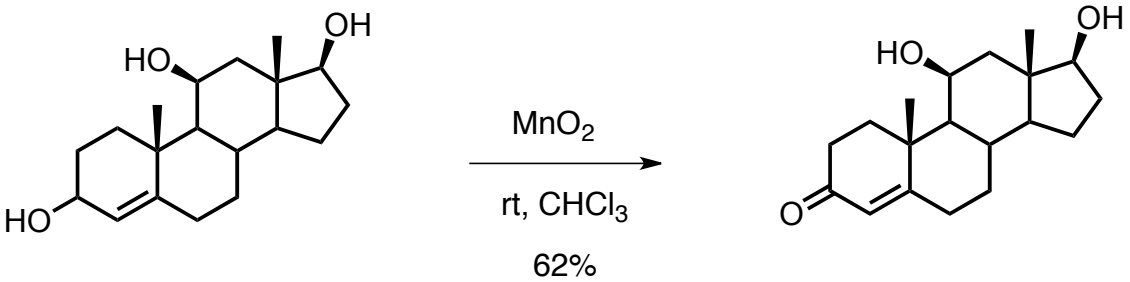
NaH_2PO_4 as a buffer, t-BuOH to favor the solubility of the substrate in water

Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181.

Oxidation with manganese based reagents

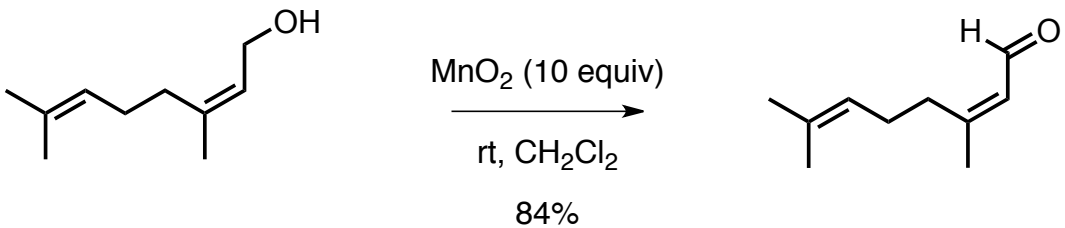
- Manganese dioxide





selective reagent

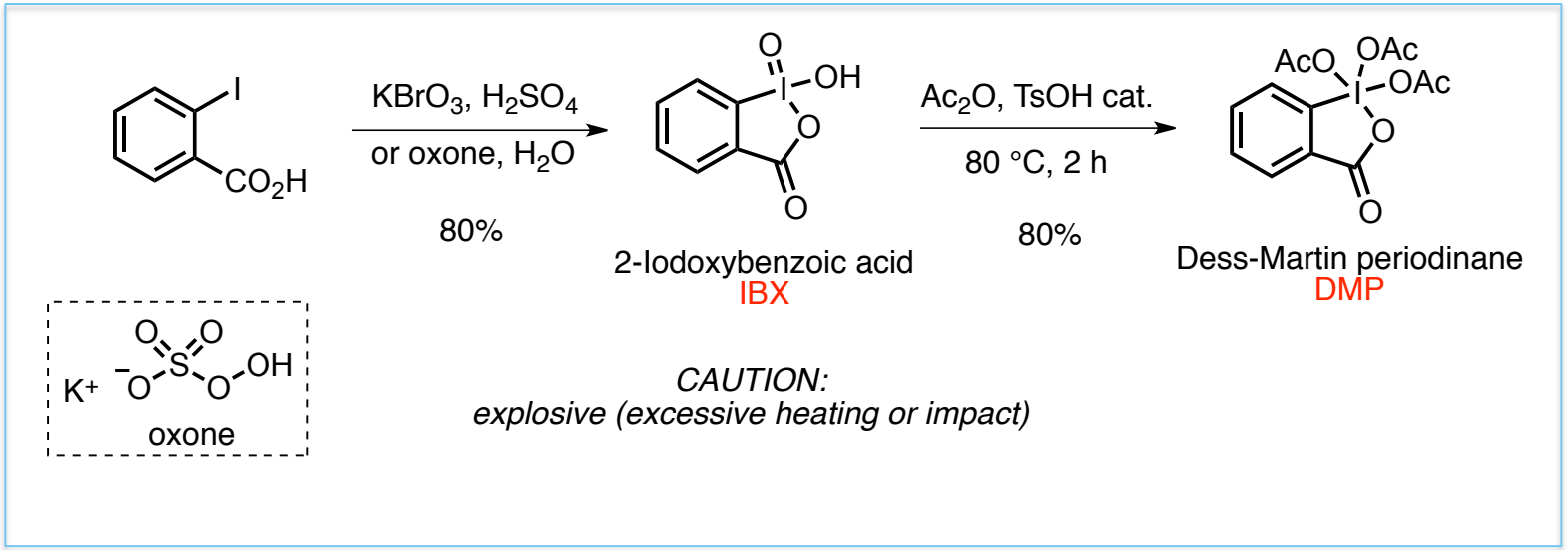
Rosenkranz et al. *J. Am. Chem. Soc.* **1955**, *77*, 4145.

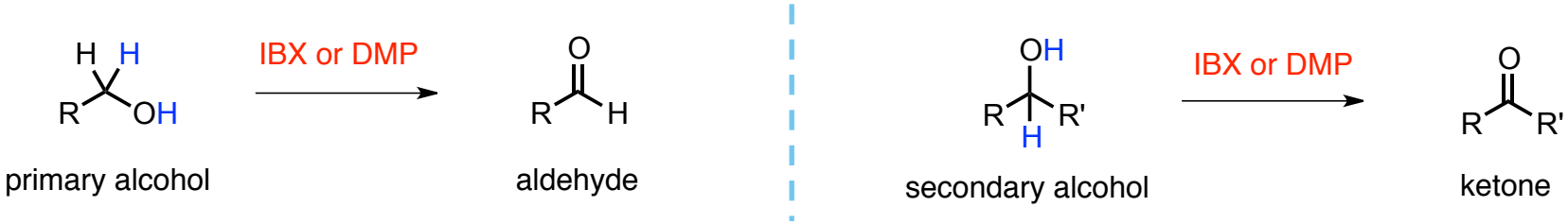


- mild conditions (no isomerization of alkenes)
- excess generally required

Taylor, R. J. K. et al. *Acc. Chem. Res.* **2005**, *38*, 851.

Hypervalent iodine based reagents





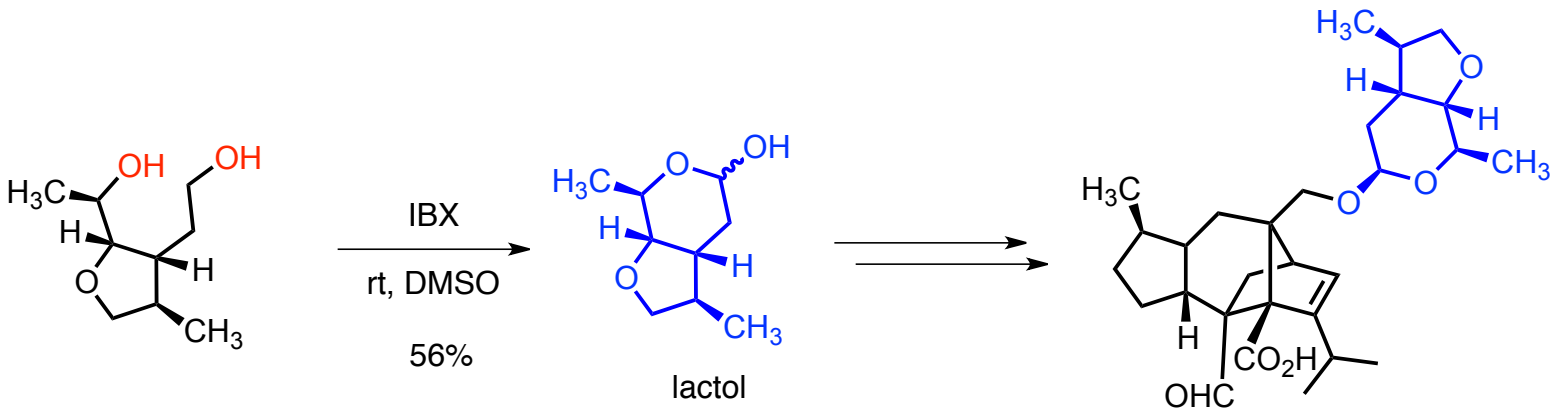
- Mild and chemoselective reagents
- IBX cheaper than DMP but potentially explosive and poorly soluble in organic solvents (DMSO generally used)
- DMP commercially available, widespread use in total synthesis of complex molecules. Buffer pH 7 or bases sometimes added to reduce the acidity of the medium (AcOH released)

Review: Kita, Y. *et al Adv. Synth. Catal.* **2004**, 346, 111.

Hypervalent iodine based reagents

Mechanisms

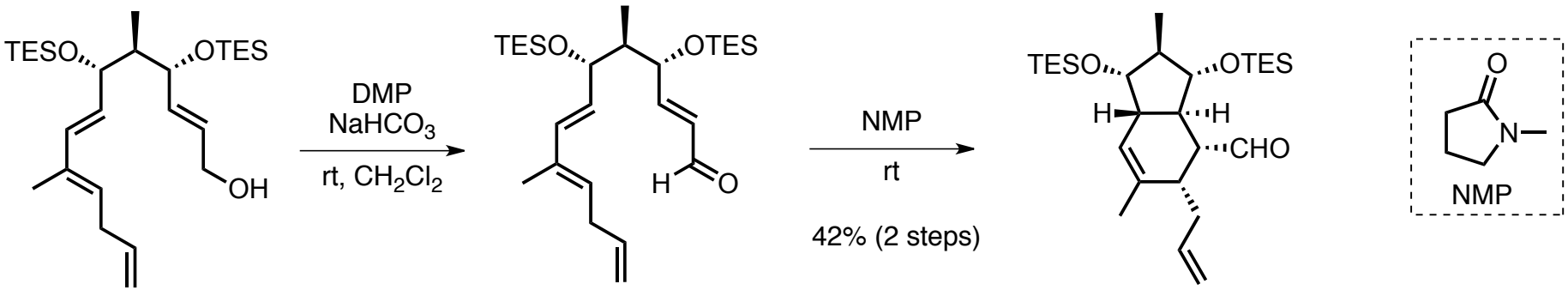
Hypervalent iodine based reagents



Selective [o] of the I^ary alcohol

GM222712
Antifungal agent

Chiara, J. L. *et al Tetrahedron Lett.* **2000**, *41*, 4379.



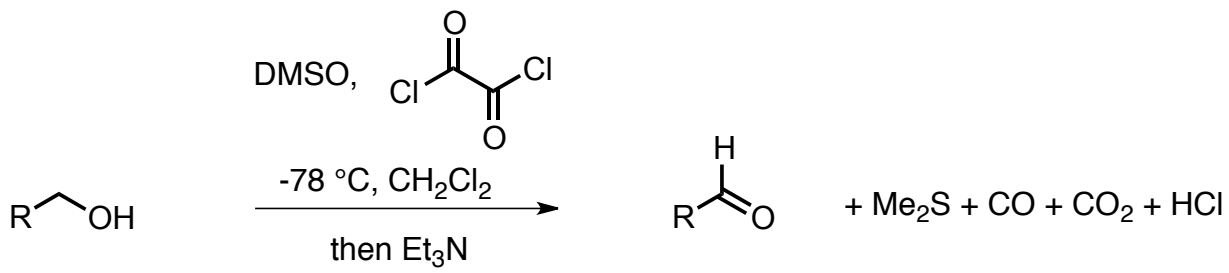
Oxidation
$NaHCO_3$ added to avoid alcohol deprotection

Diels-Alder

Key fragment in the synthesis
of a microtubuke-stabilizing agent

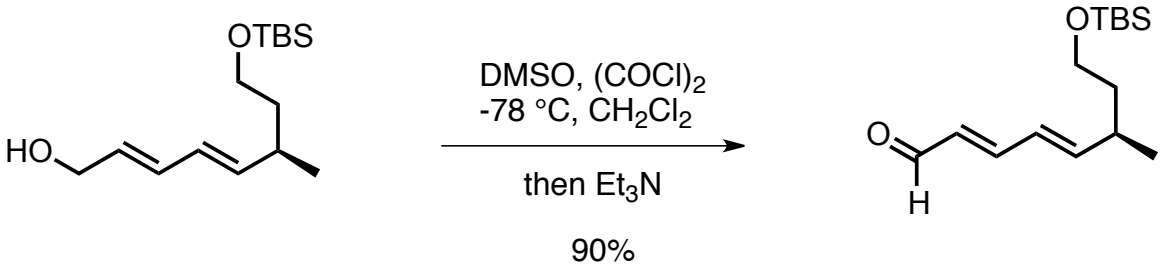
Sorensen, E. J. *et al J. Am. Chem. Soc.* **2003**, *125*, 5393.

Swern oxidation

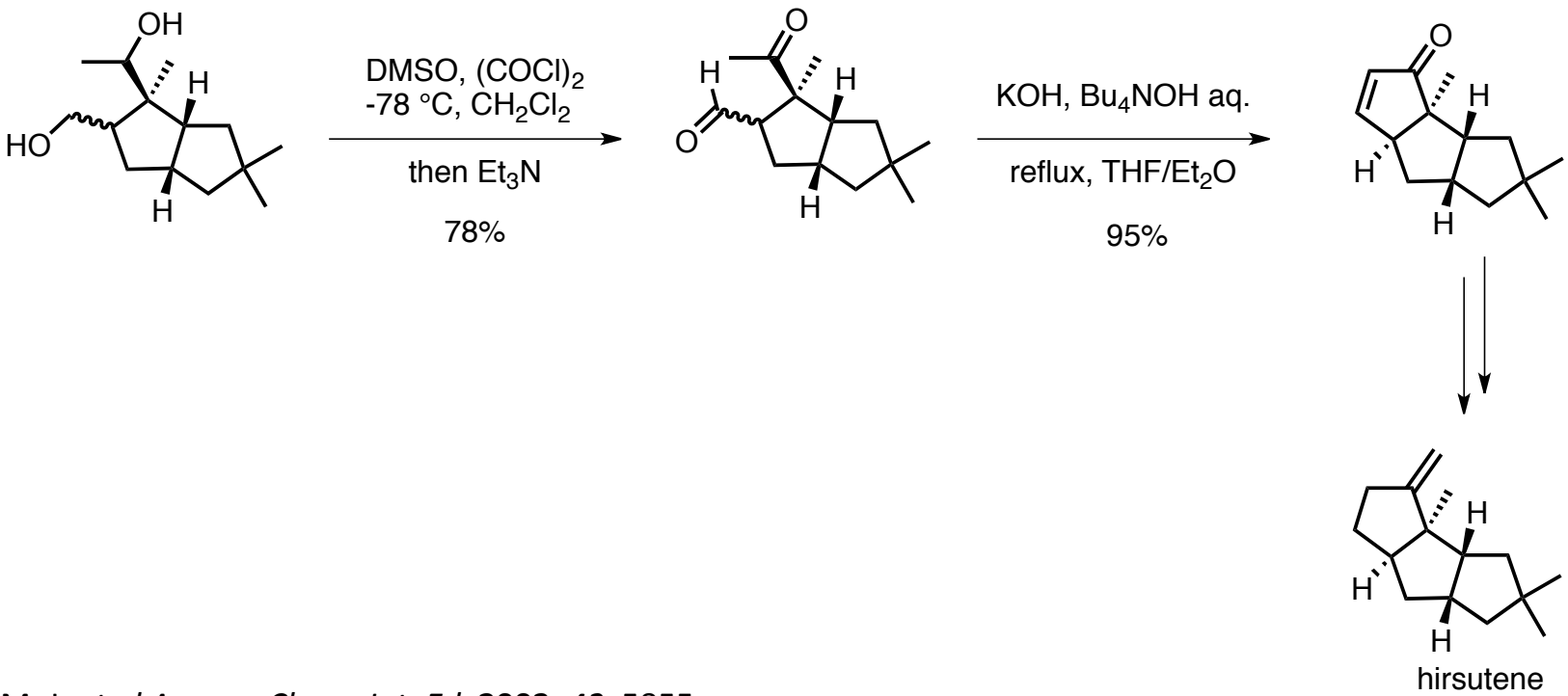


- Mild conditions, well adapted to sensitive substrates and unstable aldehydes
- Primary alcohols selectively oxidized into aldehydes, oxidation of secondary alcohols leads to ketones
- Me_2S is released: smelly reaction if successful !
- Mechanism:

Swern oxidation

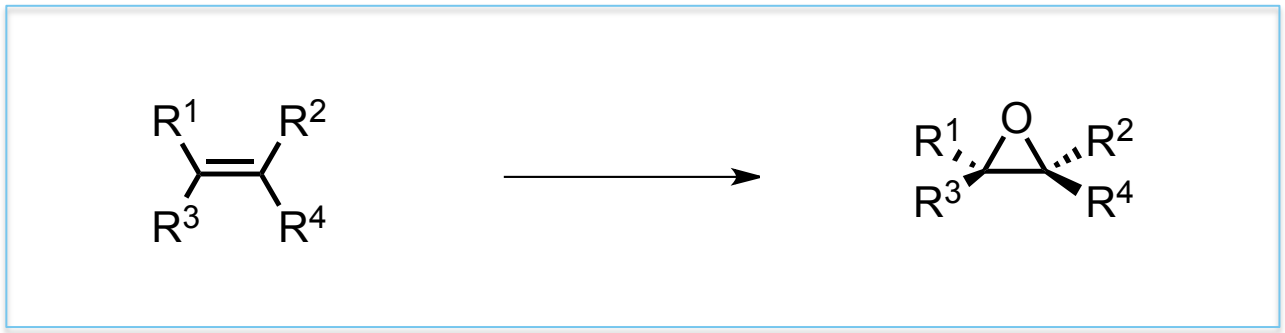


Smith, A. B. *et al J. Org. Chem.* **2000**, *65*, 3738.



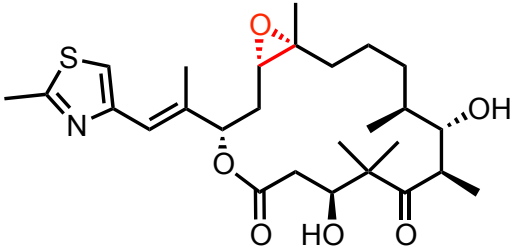
Krische, M. J. *et al Angew. Chem. Int. Ed.* **2003**, *42*, 5855.

Epoxidation of alkenes



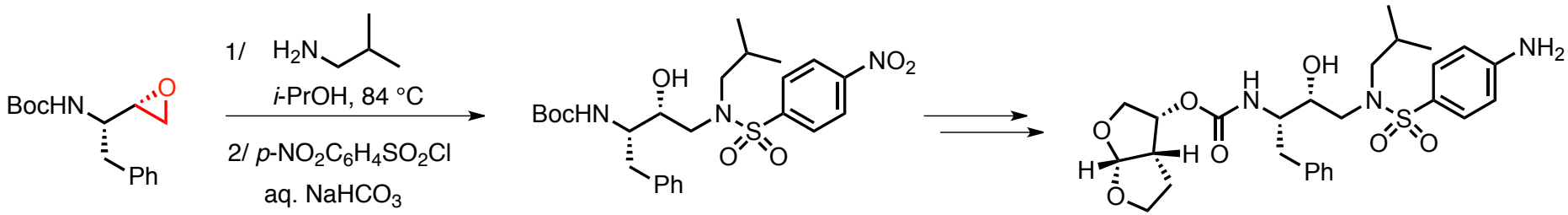
Epoxides

- Naturally occuring



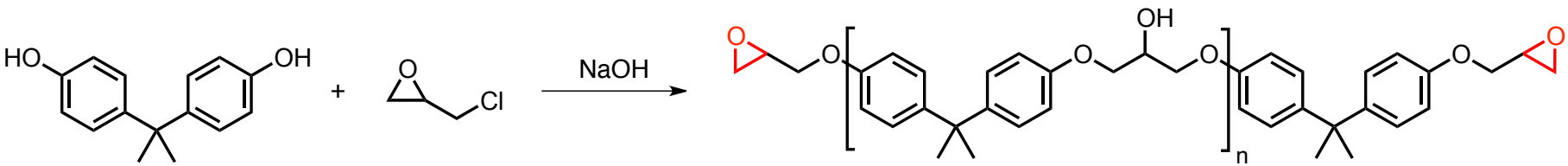
Epothilone B

- Useful synthetic intermediates



Darunavir (HIV treatment)

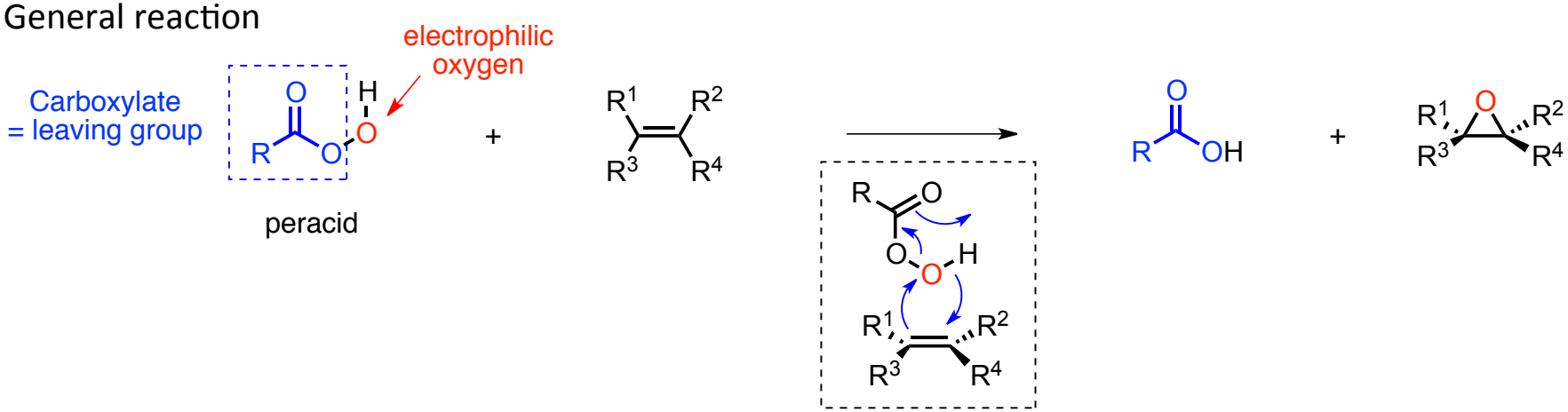
- Important use in materials



epoxy resin

Epoxidation of alkenes with peracids

- General reaction

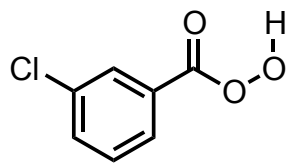


- Reactivity of peracids

R =	C_6H_5	*m*-ClC_6H_4	H	*p*-$NO_2C_6H_4$	CF_3
pK_a (RCO_2H/RCO_2^-)	4.2	3.9	3.8	3.4	0

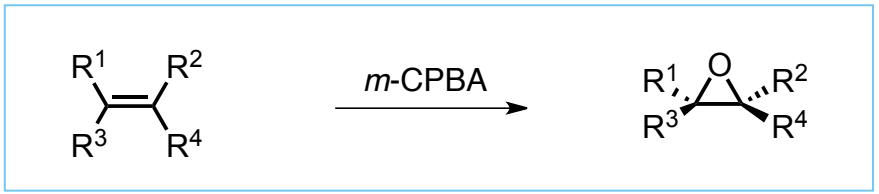
The lower the pK_a, the better the leaving group, the greater the reactivity

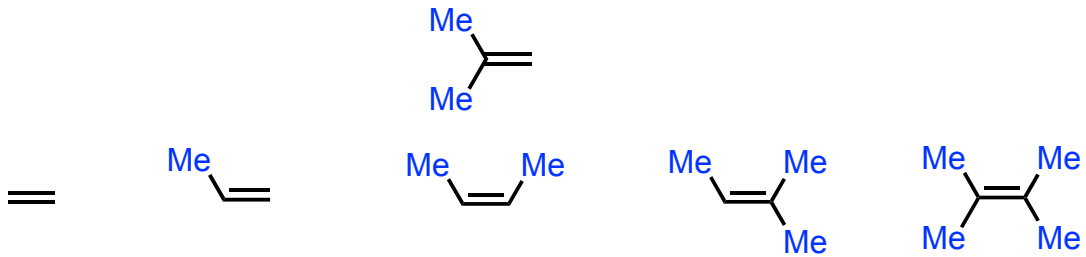
- Good compromise between stability (commercially available) and reactivity



m-chloroperoxybenzoic acid (mcpba)

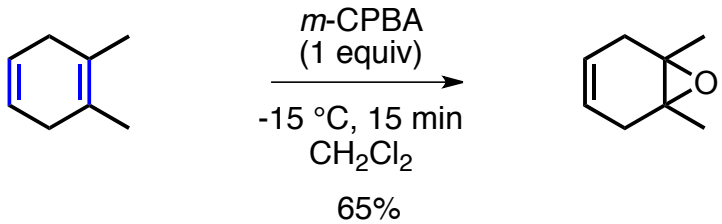
Alkenes compared reactivity



alkene					
relative reaction rates	1	24	500	6500	> 6500

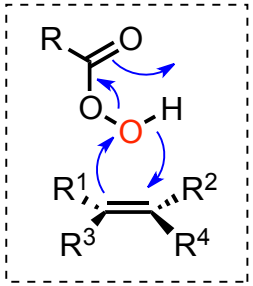
More substituted (= electron-rich) alkenes react faster with *m*-CPBA

Consequence = regioselectivity



Sureshkumar, D. *et al J. Org. Chem.* **2006**, *71*, 1653.

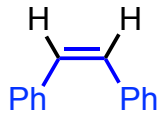
Stereospecificity



2 C-O bonds formed on the same face of alkene according to a concerted process

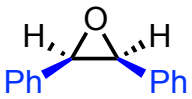
alkene geometry (*E*) or (*Z*) ⟷ epoxide stereochemistry *cis*- or *trans*-

= stereospecific reaction

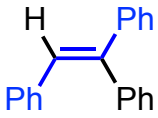


(*Z*)-stilbene

m-CPBA →



cis-epoxyde



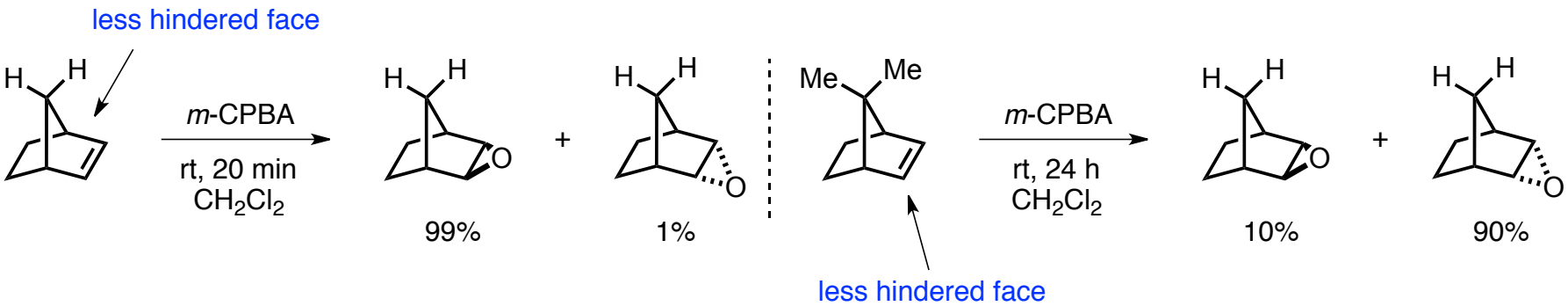
(*E*)-stilbene

m-CPBA →

trans-epoxyde

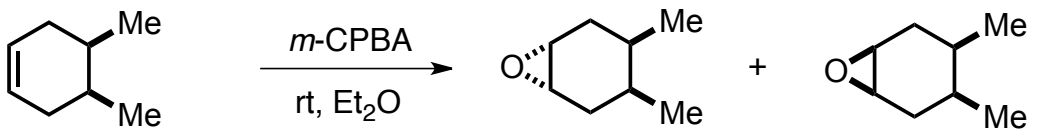
Diastereoselectivity in the absence of directing group

- Bicyclic systems

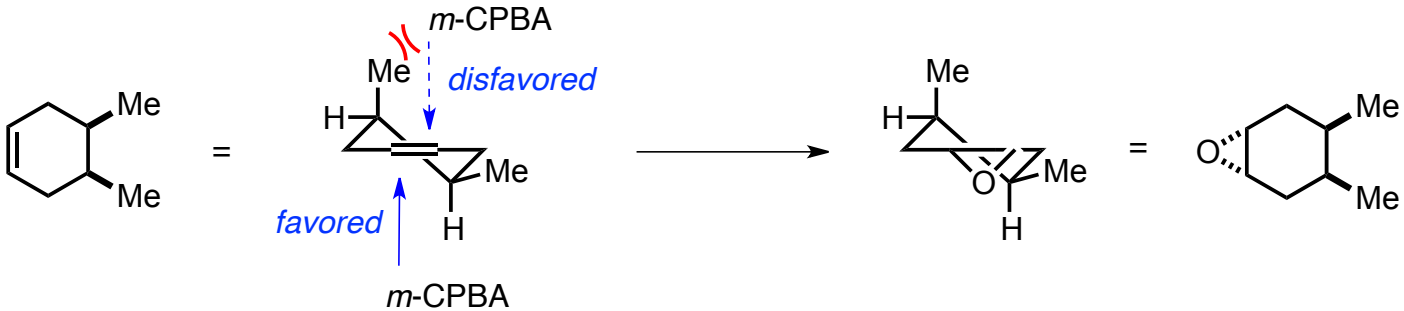


Brown J. *J. Am. Chem. Soc.* **1970**, 92, 6914.

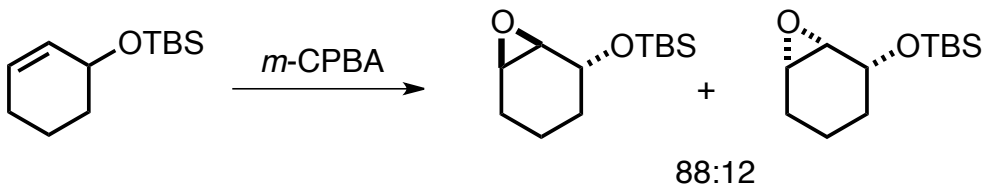
- Endocyclic olefins

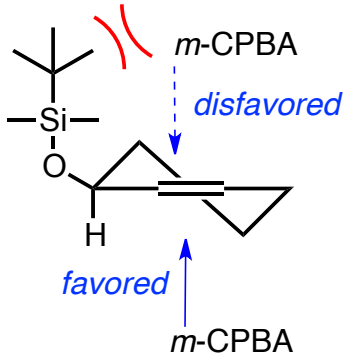


87:13 ratio between the 2 diastereomers

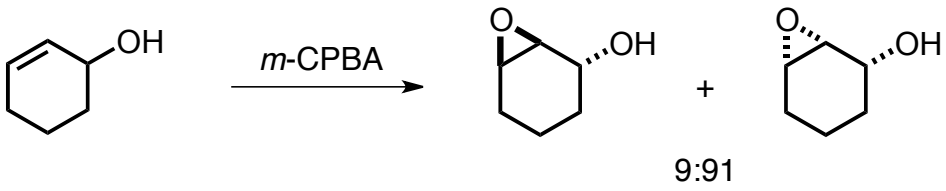


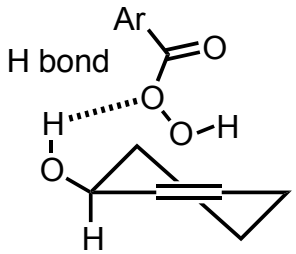
Diastereoselectivity: directing effect





but



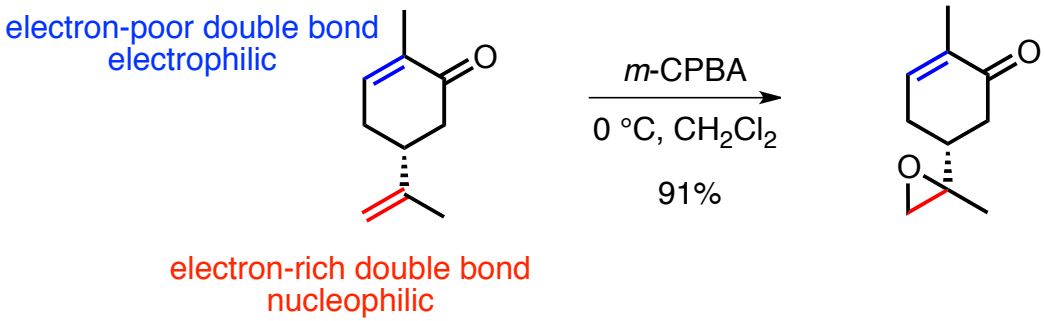


H bonding between the allylic alcohol and the peracid:

- epoxyde formed on the same face as OH group
- acceleration of the reaction

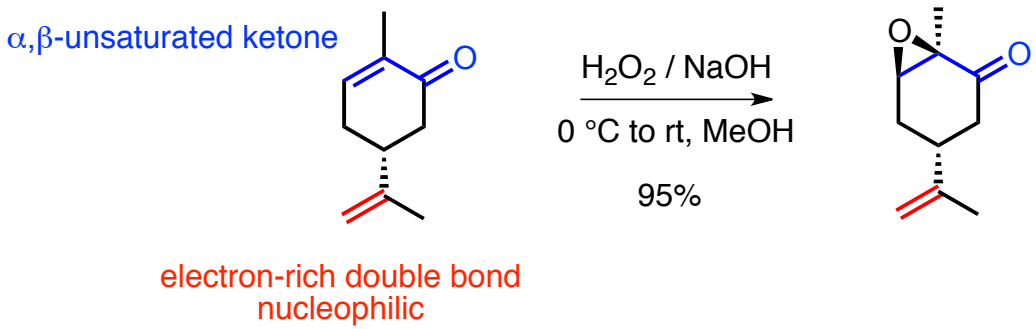
Electron-poor olefins

- Regioselective epoxidation of carvone with *m*-CPBA



The electron-rich double bond acts as a nucleophile and reacts selectively with *m*-CPBA.
Double bonds that are conjugated with electron-withdrawing groups are unreactive under these conditions.

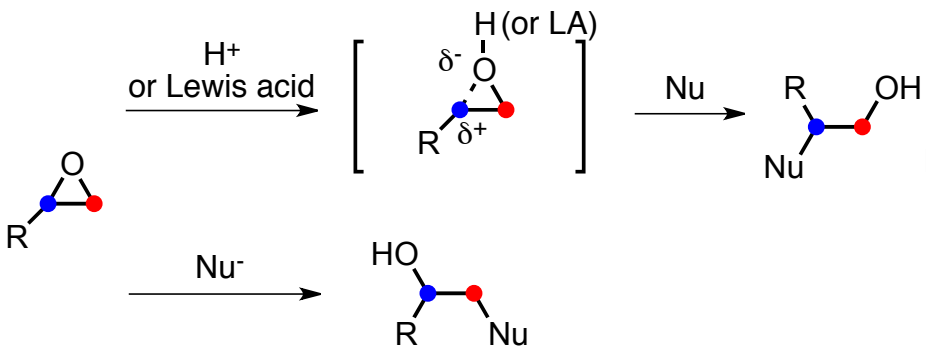
- Regioselective epoxidation of carvone with H_2O_2/NaOH



1,4-addition of HOO- on the α,β-unsaturated ketone followed by cyclization.
The double bond acts as an electrophile.

Mak, K. K. W. *et al J. Educ. Chem.* **2006**, *83*, 1058.

Nucleophilic addition on epoxides

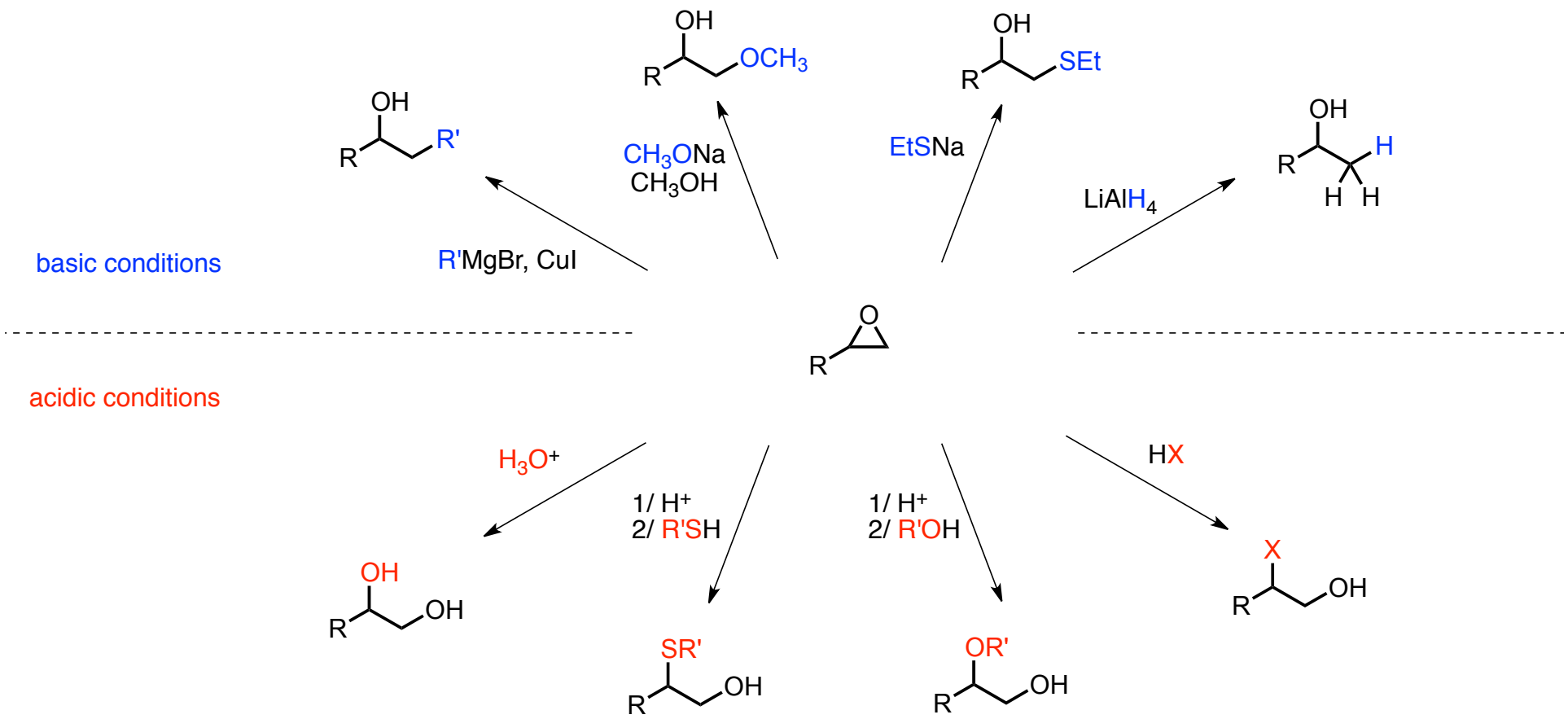


Addition to the more substituted carbon
(=more stable partial cation)
Loss of stereochemistry if pure S_N1 mechanism

S_N2 type reaction
Addition to the less hindered carbon
Nu = H^-, RO^-, RS^-, CN^-, R_2NH, N_3^-, R-M
Stereospecific

Regioselectivity of the nucleophilic attack depends on the conditions/nucleophiles

Ring opening through nucleophilic attack



Very useful intermediates in synthesis

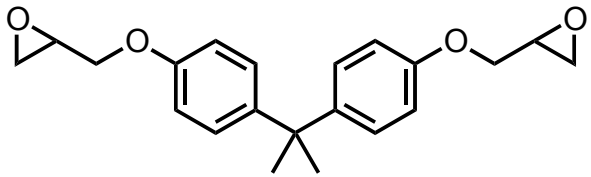
Ring opening through nucleophilic attack - examples

Epoxy glue

HARDENER

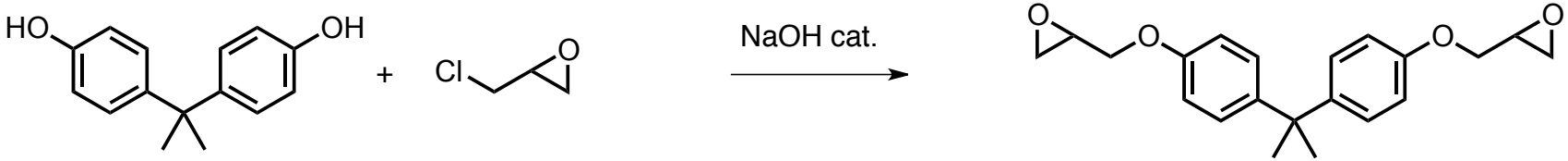
diamine

RESIN



Bisphenol A diglycidyl ether
DGEBA

Resin synthesis



Bisphenol A

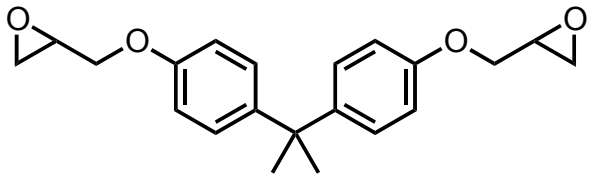
Epichlorhydrin

Epoxy glue - curing

HARDENER

diamine

RESIN

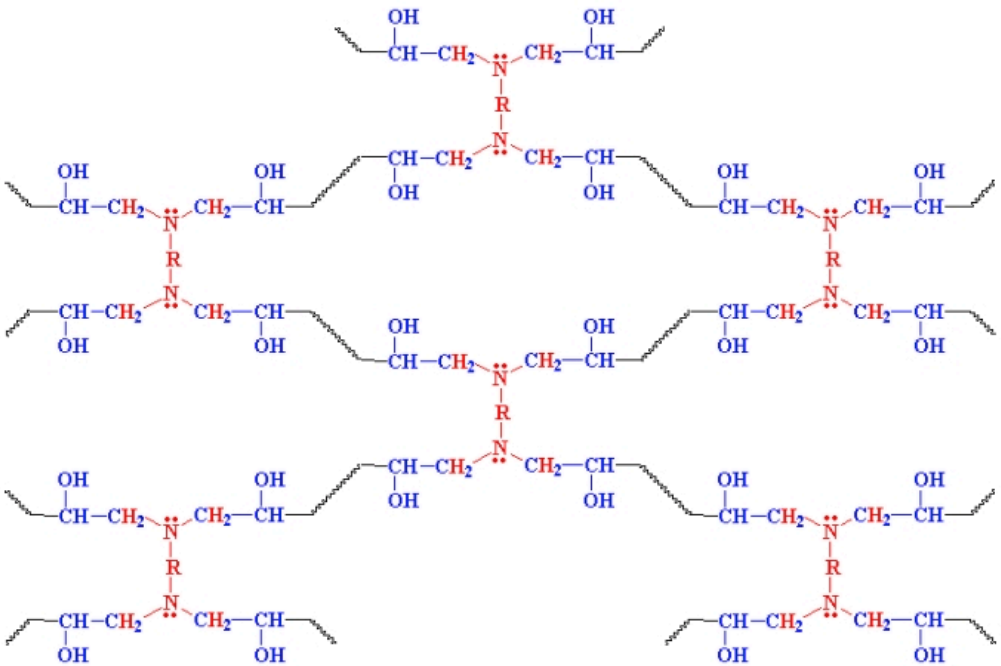


Bisphenol A diglycidyl ether
DGEBA

+

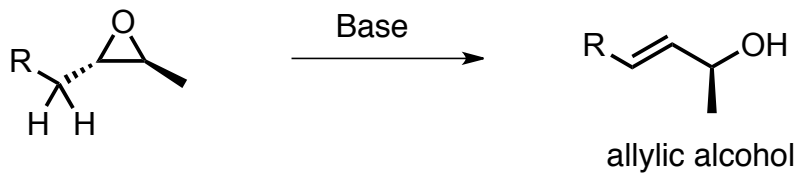
$H_2N-R-NH_2$

Curing →



Mixing the two components results in reticulation (cross-linked network)

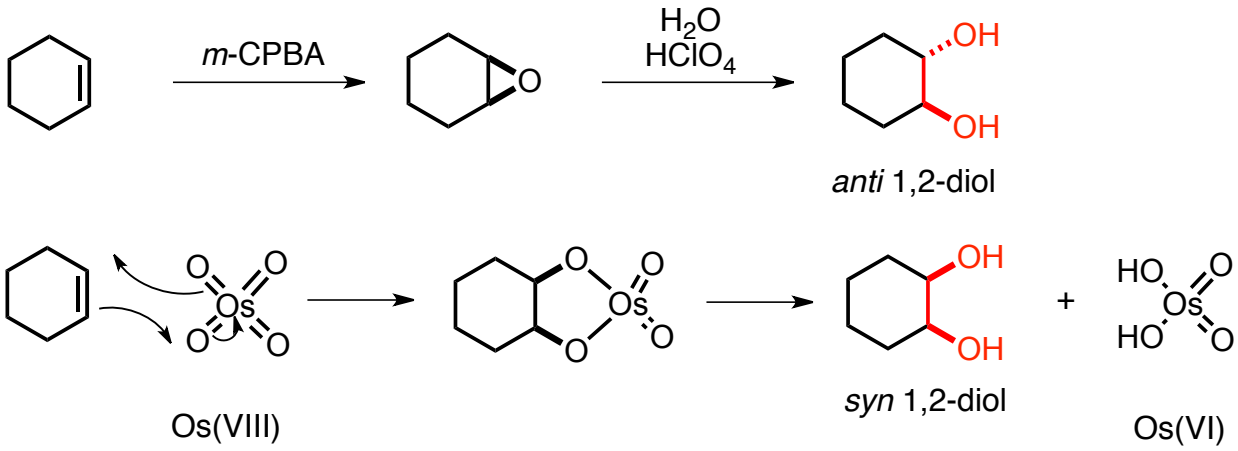
Elimination



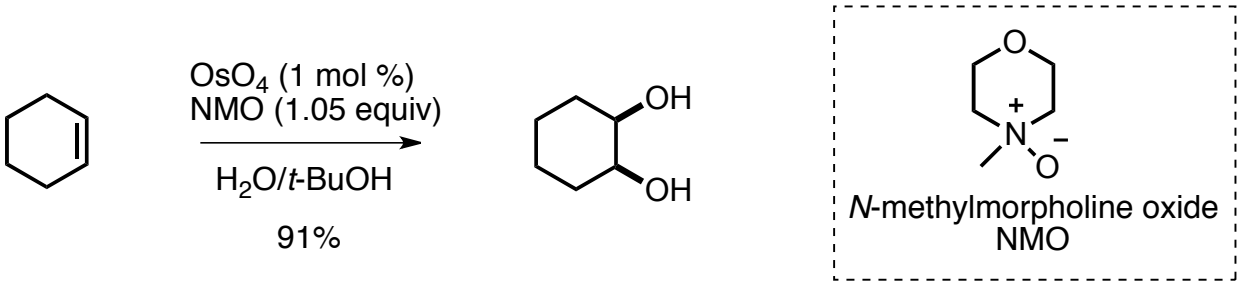
Choice of base depends on R groups that affect the pK_a

Dihydroxylation

- *Anti and syn* 1,2-diols



- Catalytic conditions

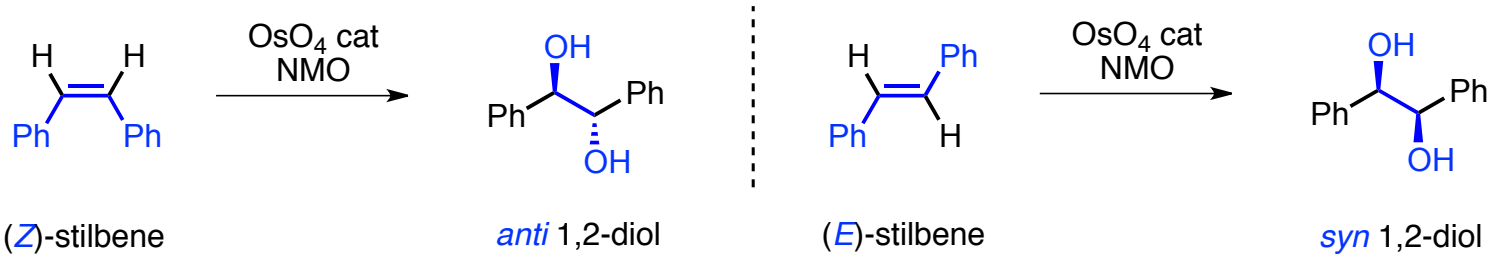


Used to reoxidize Os(VI) into Os(VIII)

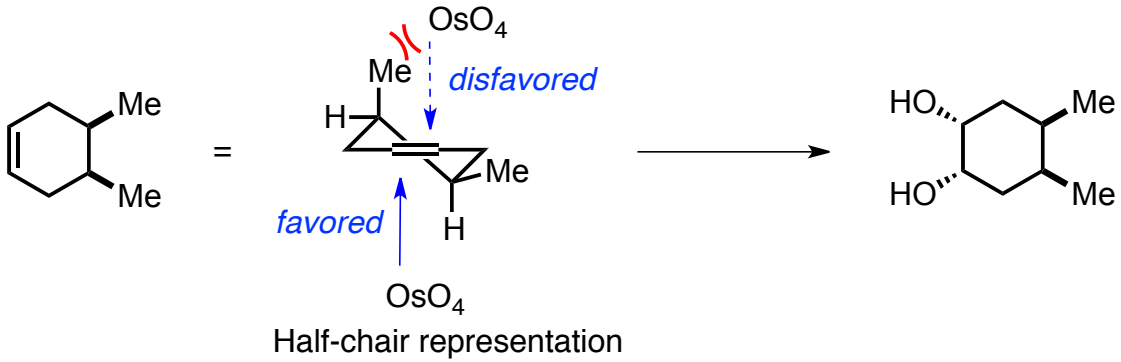
CAUTION: OsO_4 is highly toxic

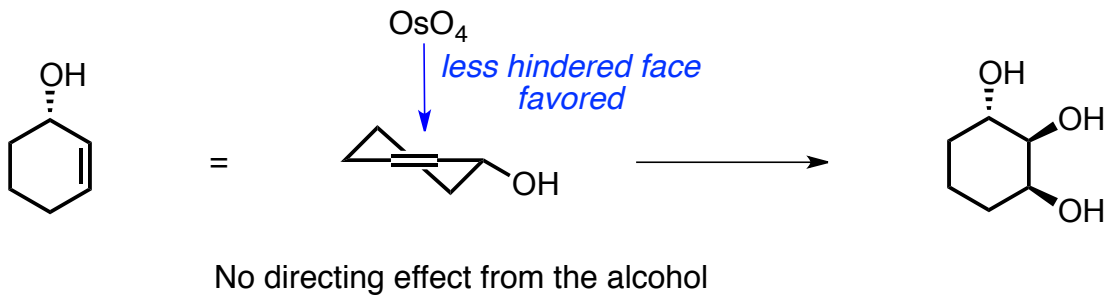
Diastereoselectivity

- Diastereospecificity



- In cyclic systems

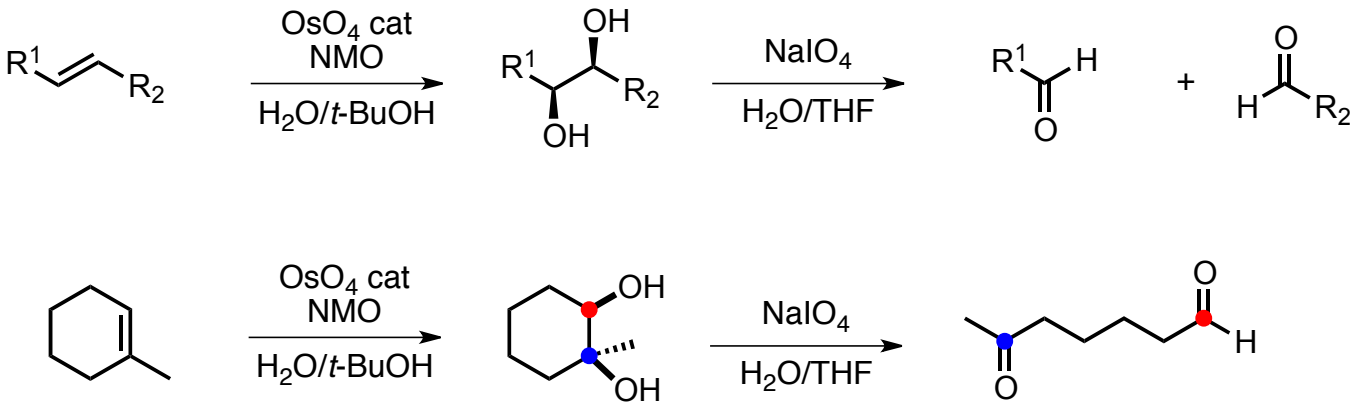




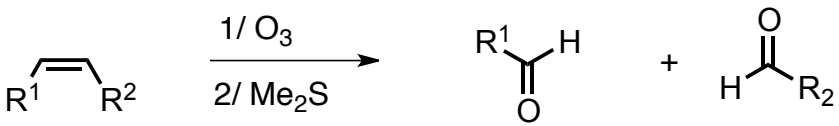
No directing effect from the alcohol

Oxidative cleavage

- Reaction of diols with periodate



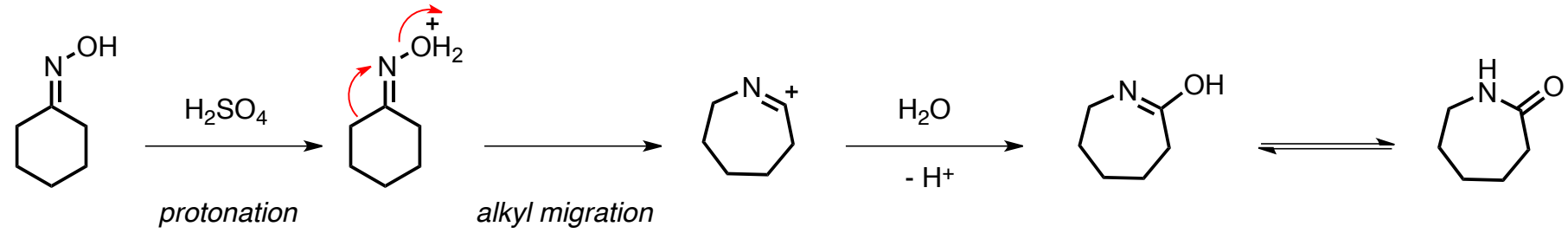
- Alternative: ozonolysis

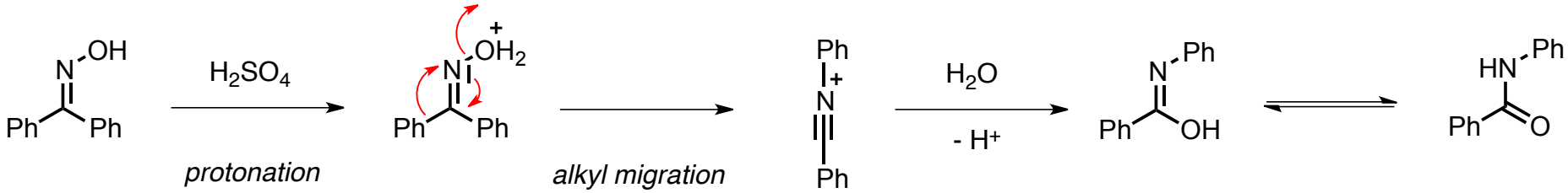


Ozone is less expensive and less toxic that OsO_4
but OsO_4 more chemoselective with polyfunctionalized molecules

Beckmann rearrangement

- Symmetrical oximes

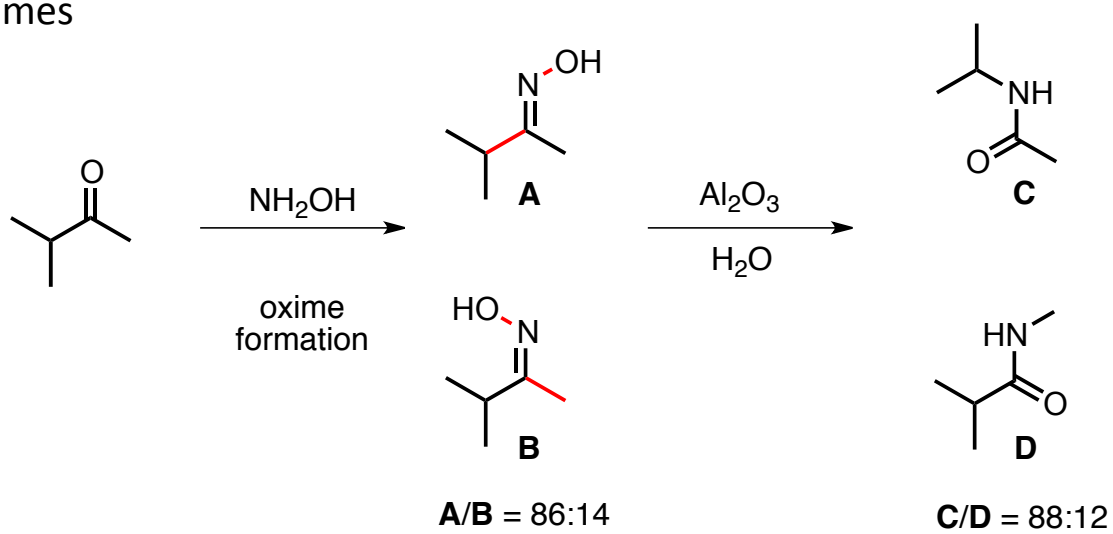




- Cationic species = nitrilium ion in the acyclic case
- Other ways than protonation to convert the alcohol into a leaving group are possible (Ac_2O, PCl_5, $SOCl_2$, RSO_2Cl…)

Beckmann rearrangement

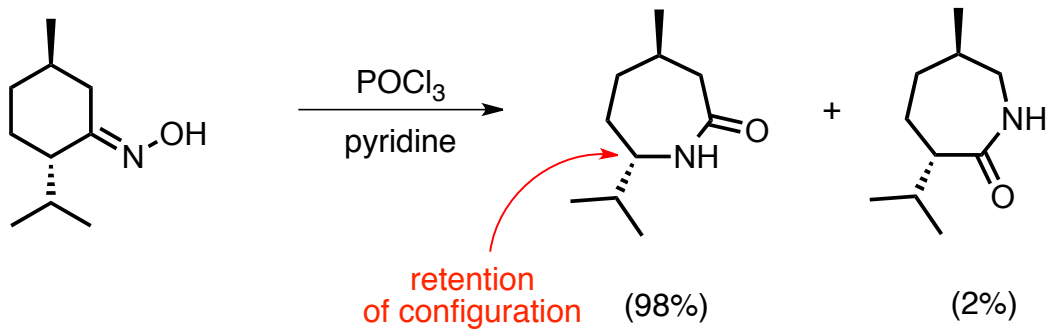
- Unsymmetrical oximes



A, **B** geometrical isomers

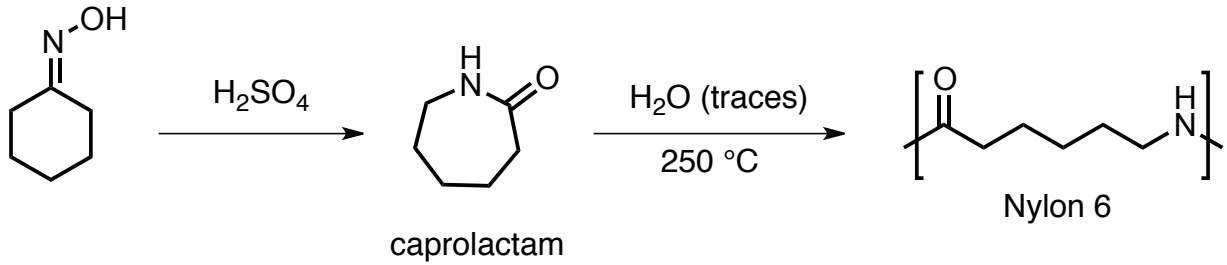
- Alkyl groups *trans* to the OH migrates
- Ratio of products reflects the ratio of geometrical isomers of the oxime = reaction is stereospecific

- Alkyl groups migrate with retention of configuration



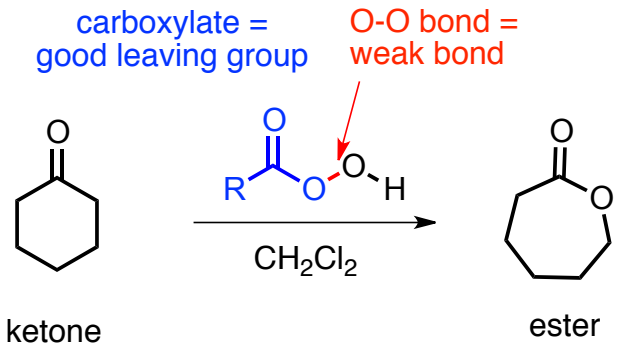
Beckmann rearrangement: application

Large-scale production of Nylon 6



Baeyer-Villiger rearrangement

- General scheme

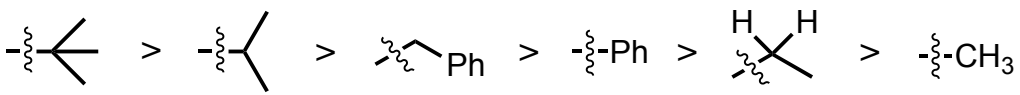


- *m*-CPBA most frequently used peracid, H_2O_2-NaOH can be used with reactive ketones

- Mechanism

Selectivity in alkyl group migration

- In general, the more electron rich (more substituted) alkyl group migrates preferentially



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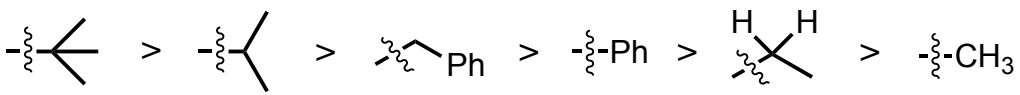
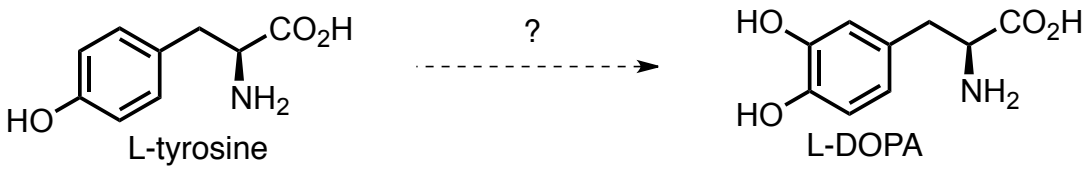


- Example: synthesis of L-dopa (Parkinson's disease)



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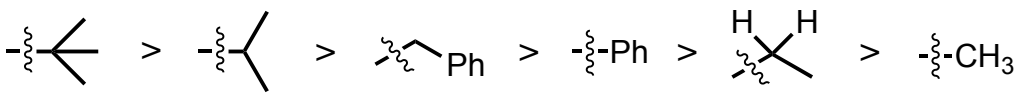

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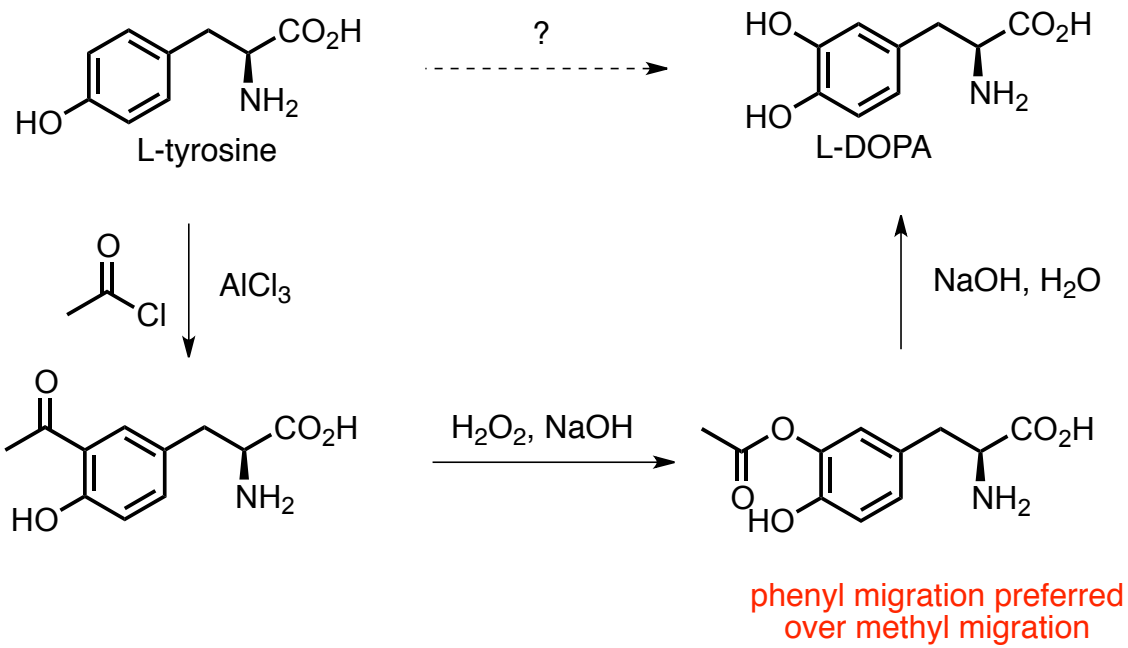
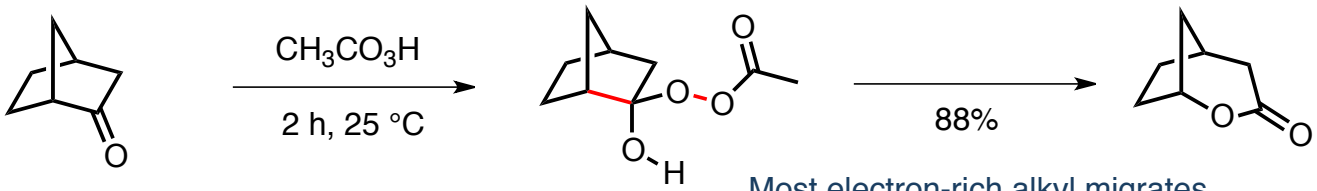


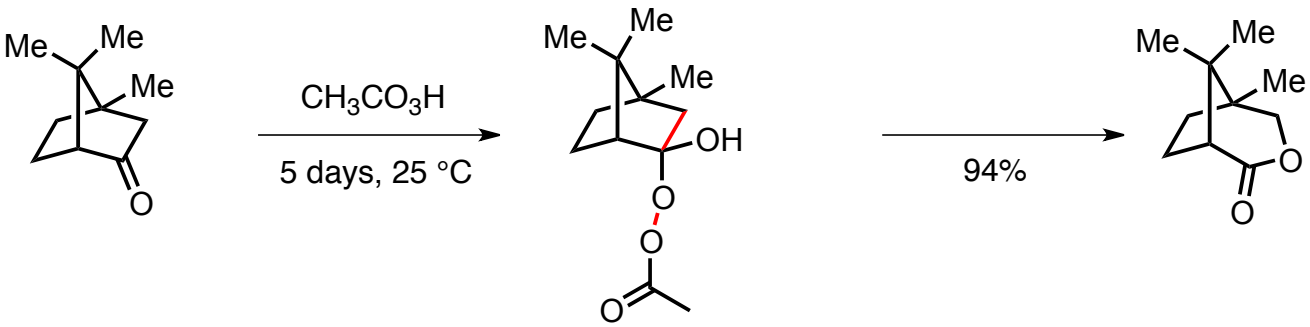
Selectivity in alkyl group migration

- But migrating C-C bond and O-O bond must be *trans*-antiperiplanar



Nucleophilic attack
on the least hindered *exo* face

Most electron-rich alkyl migrates
and C-C/O-O bonds *trans*-antiperiplanar

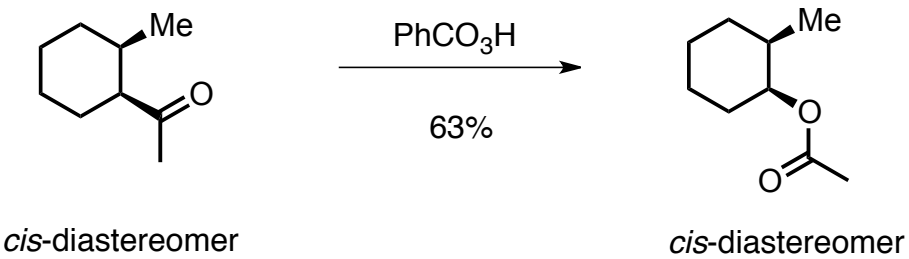


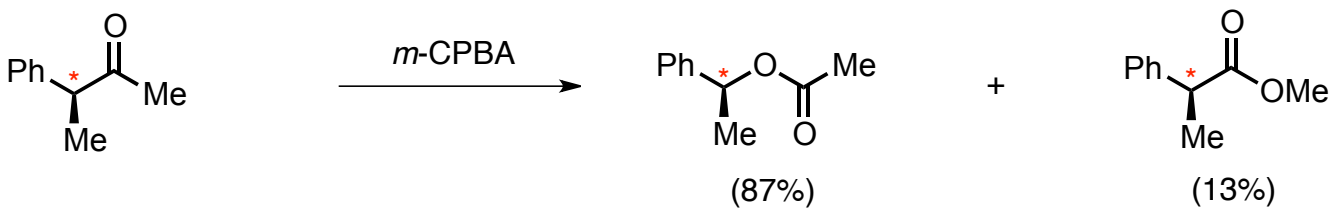
Nucleophilic attack
on the least hindered *endo* face
(steric hindrance due to the methyl groups)

Least electron-rich alkyl migrates
because C-C/O-O bonds must be *trans*-antiperiplanar

Selectivity in alkyl group migration

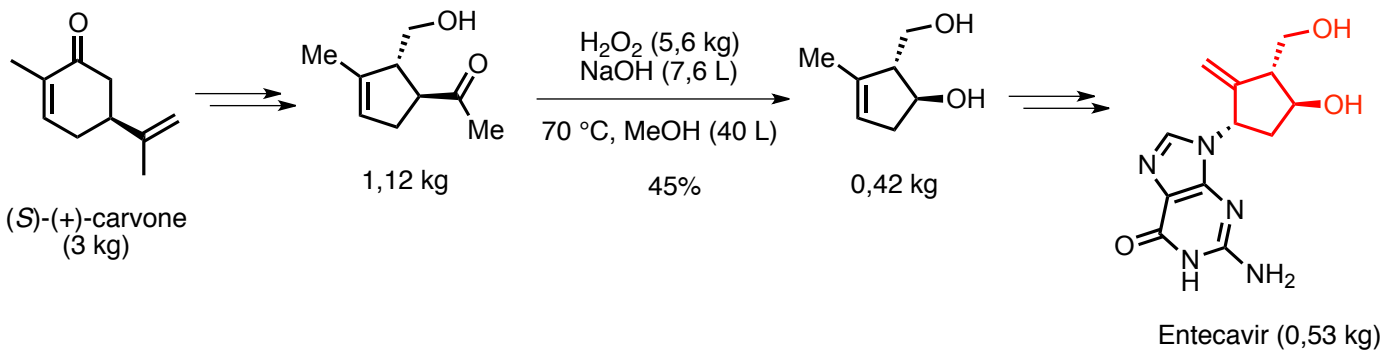
- Alkyl groups migrates with retention of configuration

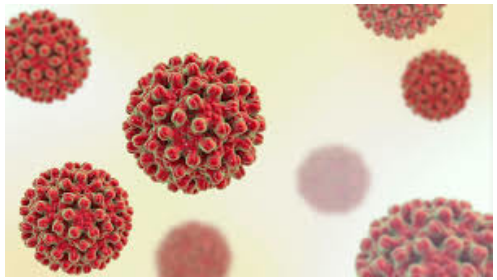




Baeyer-Villiger rearrangement: application

- Large scale synthesis of a drug for the treatment of hepatitis B virus

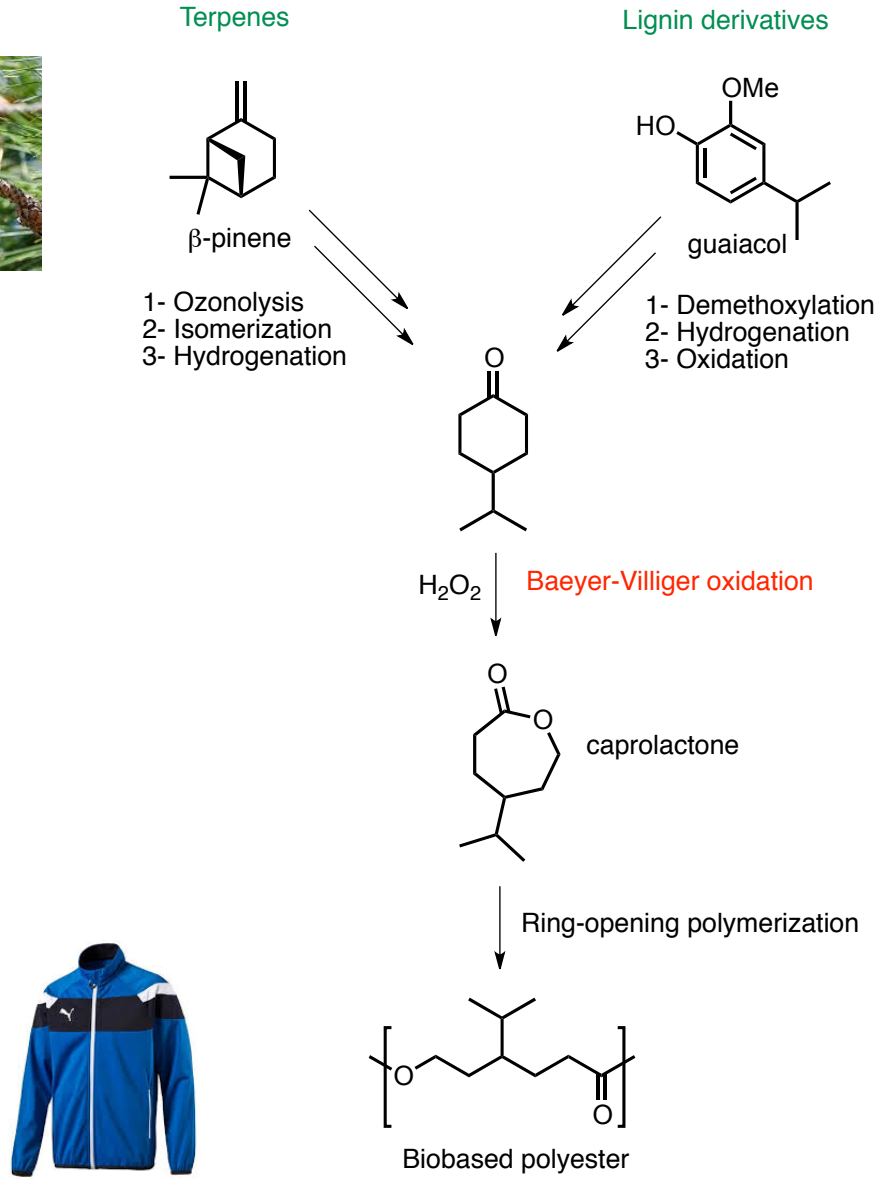




Jin, Y. *et al. Org. Process. Res. Dev.* **2018**, *22*, 377.

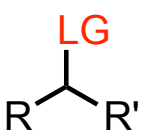
Baeyer-Villiger rearrangement: application

- Production of biorenewable lactone monomers for polyester synthesis



Hammond, C. *et al. ChemSusChem.* **2017**, *10*, 3652.

II- Functional group interconversion



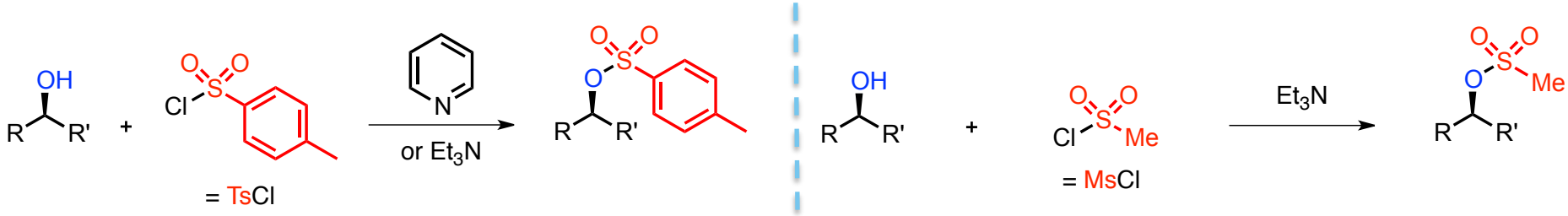
LG = leaving group

Conversion of alcohols into sulfonate esters

R'' = Me (mesylate)
R'' = *p*MeC$_6$H$_4$ (tosylate)

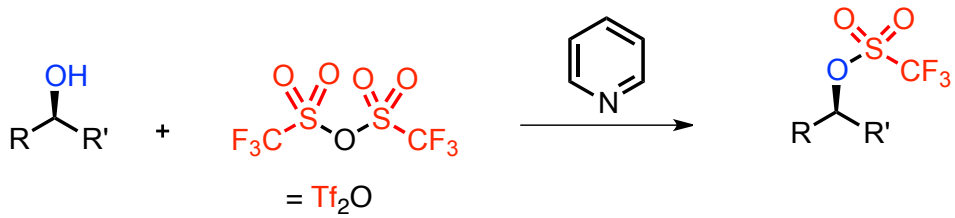
Formation of sulfonate esters from alcohols

- Tosylates and mesylates



- TsCl and MsCl most commonly used reagents
- Retention of configuration
- Be careful, two different mechanisms are operating
- Don't forget that Et_3N is not able to deprotonate alcohols

- Triflates

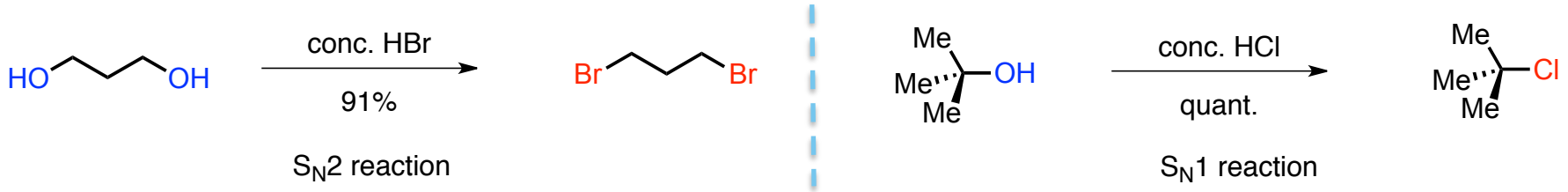


- Excellent leaving group
- Retention of configuration

Conversion of alcohols into halides

X = **I**, **Br**, Cl

Using strong acids



- Efficient for simple, non-functionalized alcohols
- Harsch conditions, not compatible with acid sensitive groups on the alcohol
- Generally avoided for the synthesis of halides on complex molecules

Using halides of nonmetalic elements (P, S)

- Reaction with thionyl chloride

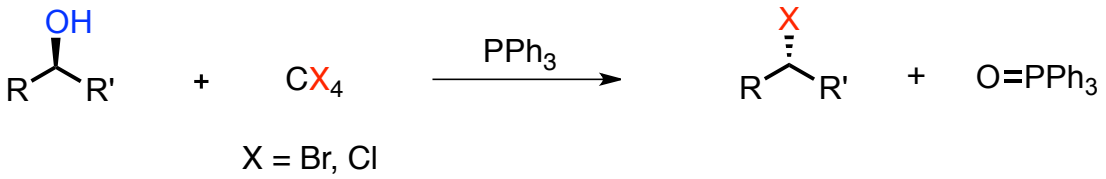
- gas release
- Acid generation: limited to acid-stable molecules
- Mechanism and stereochemistry depend on conditions

- Reaction with phosphorus tribromide

- S_N2 reaction : inversion of configuration
- Acid generation: limited to acid-stable molecules

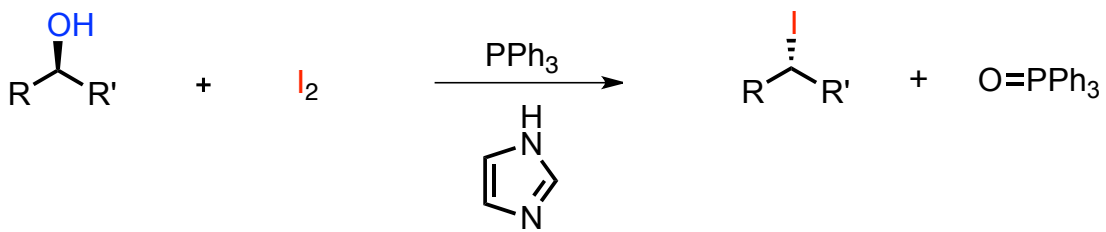
Appel reaction

- Alkyl bromides/chlorides

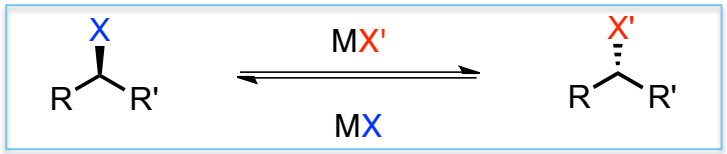


- Proceeds generally with high yields
- S_N2 reaction : inversion of configuration
- Driving force = formation of a strong P=O bond
- Formation of triphenylphosphine oxyde as a by-product

- Alkyl iodides

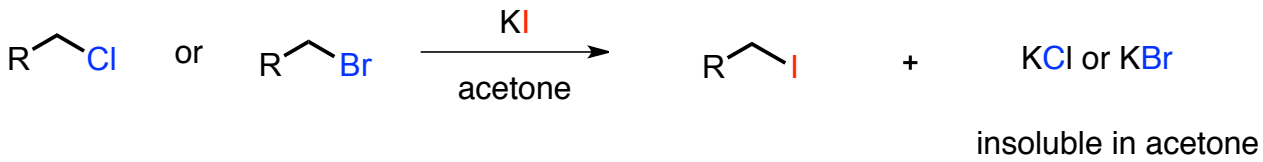


Finkelstein reaction



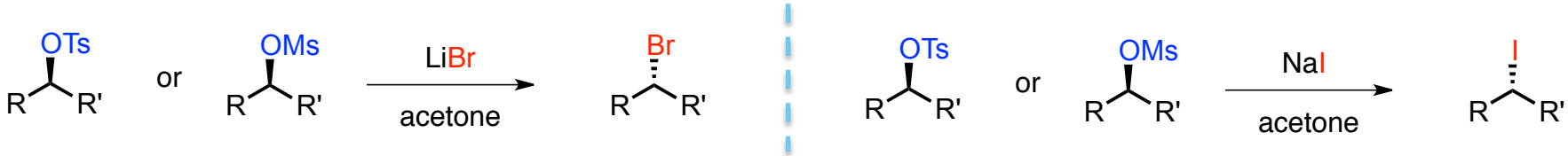
- S_N2 reaction : inversion of configuration
- Reaction in equilibrium

- Halide interconversion



- Solvent choice is crucial, , low solubility of KCl and KBr in acetone drives the equilibrium
- NaI can also be used
- Secondary alkyl halides show low reactivity, tertiary alkyl halides are unreactive

- From sulfonate esters

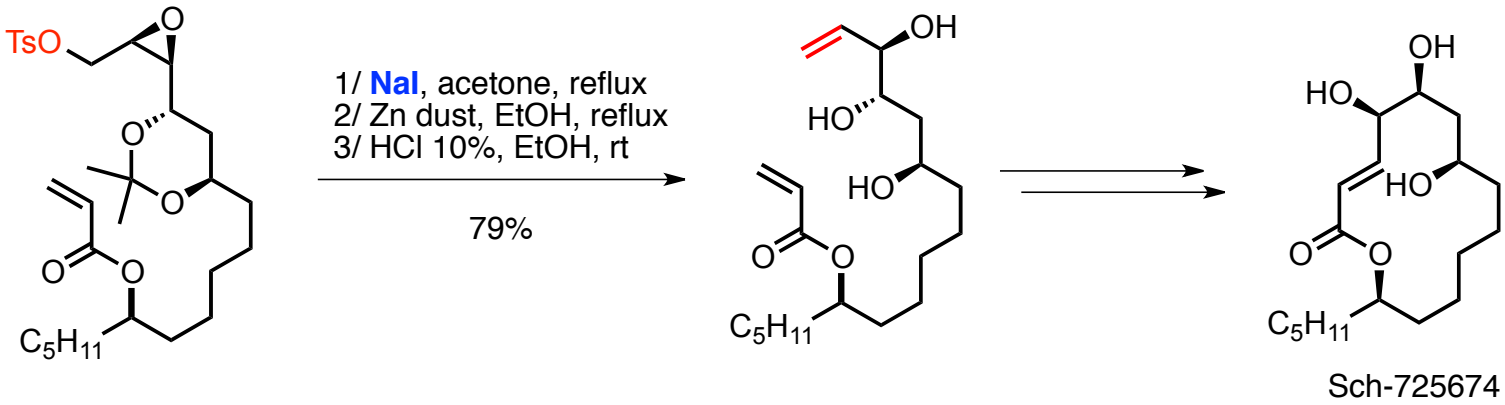


- Excess of MX generally used to shift the equilibrium toward the halide

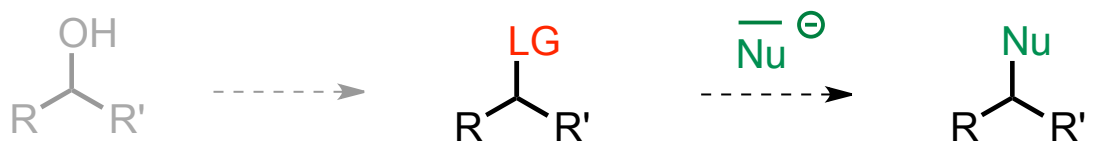
Finkelstein reaction : application

Total synthesis of Sch-725674

Antifungal macrolide



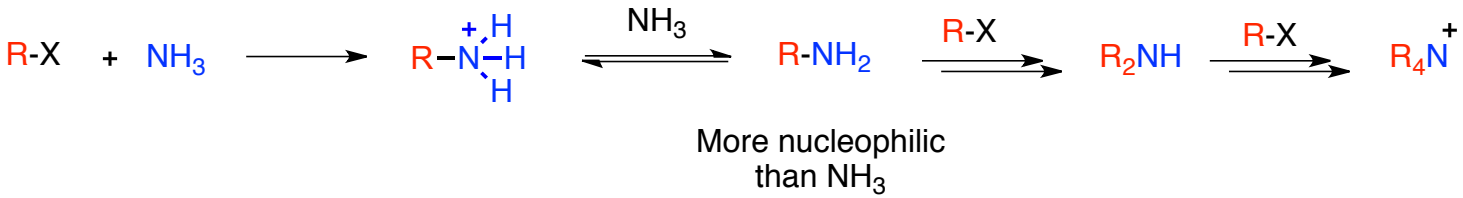
Transformation using S_N2 reactions



LG = leaving group

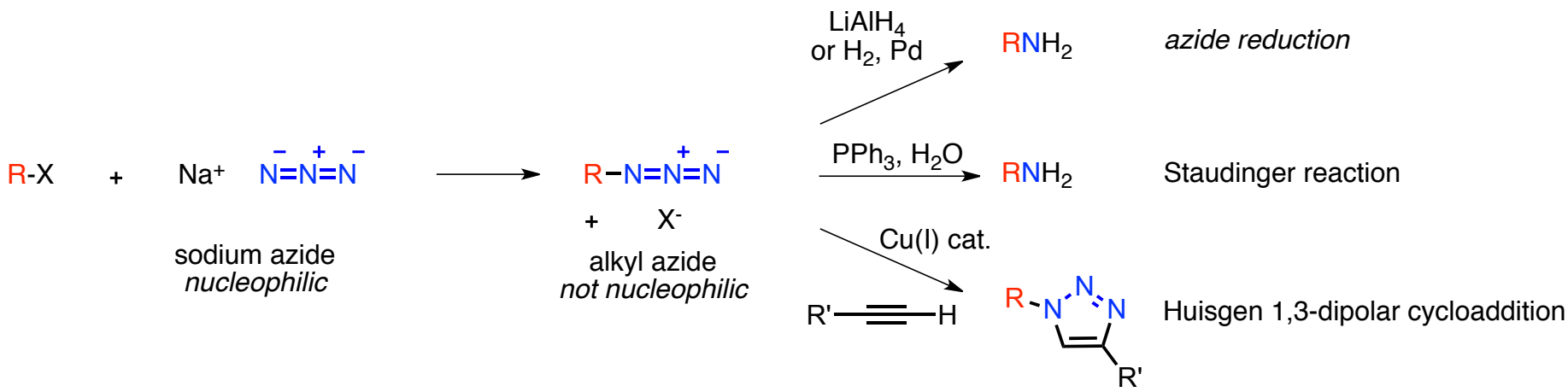
S_N2 reactions with nitrogen nucleophiles

- With ammonia or amines



- Problem : product formed by alkylation are more and more nucleophilic = mixture of compounds
- Not a good reaction for the clean preparation of primary, secondary or tertiary amine

- With sodium azide



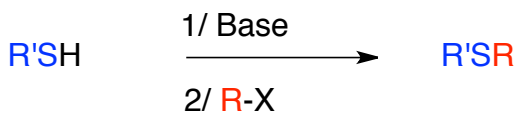
S_N2 reactions with O- and S- nucleophiles

- With alcohols

ether synthesis

- NaH generally used

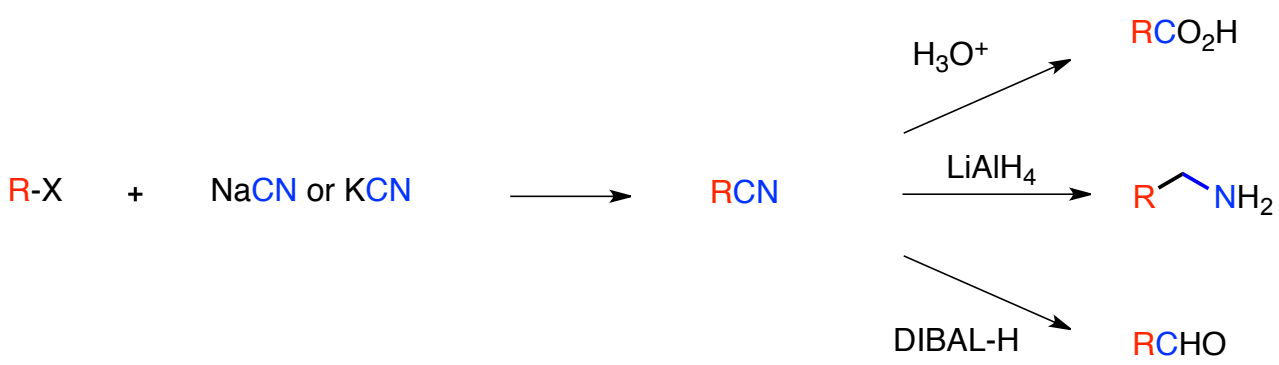
- With sulfur nucleophiles



thioether synthesis

- pK_a RSH/RS^- is 9-10, NaOH is sufficient

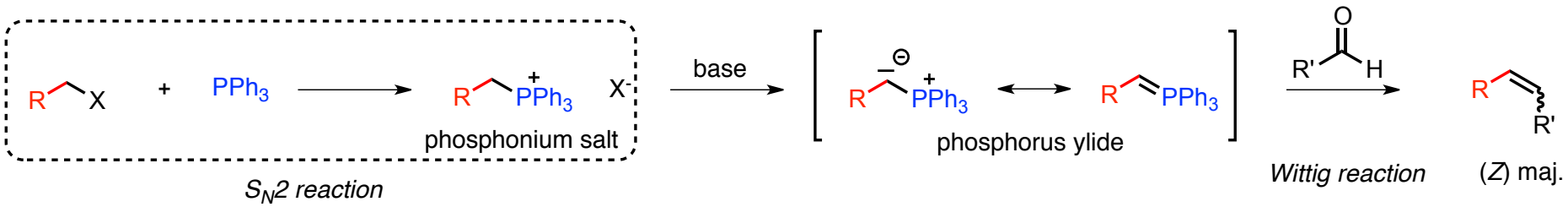
S_N2 reactions with nitriles



- Homologation of one carbon
- Nitriles are precursors of carboxylic acids, amines or aldehydes

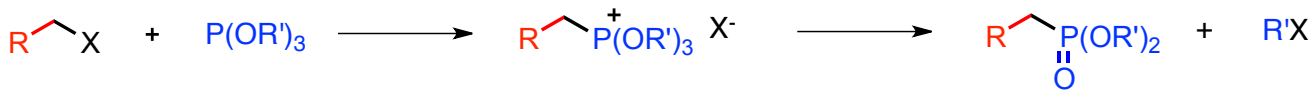
S_N2 reactions with phosphorus nucleophiles

- With triphenylphosphine

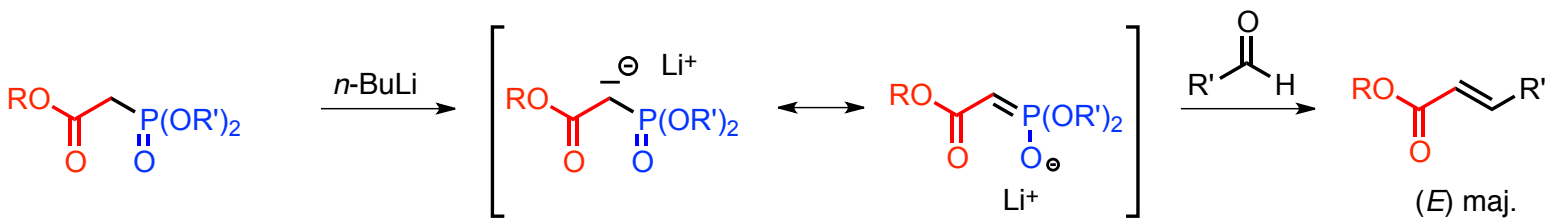


- With phosphite esters

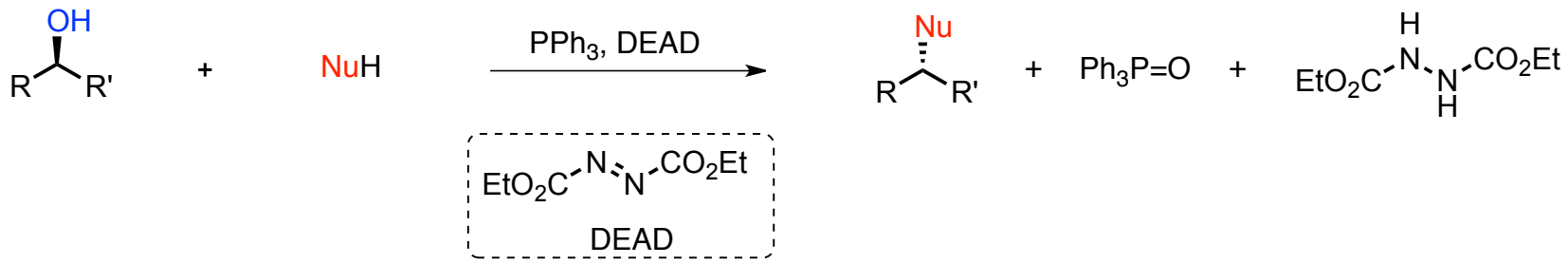
Michaelis-Arbuzov reaction



Horner-Wadsworth-Emmons reaction

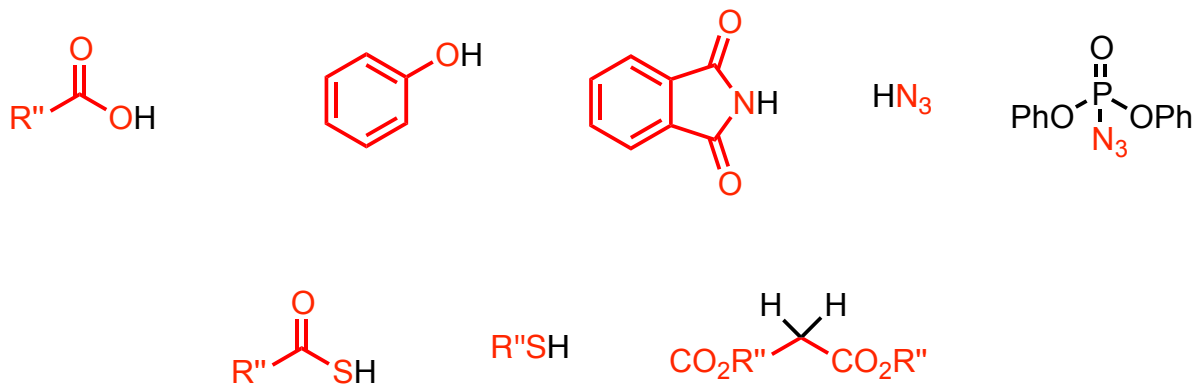


One-step conversion of alcohols: Mitsunobu reaction



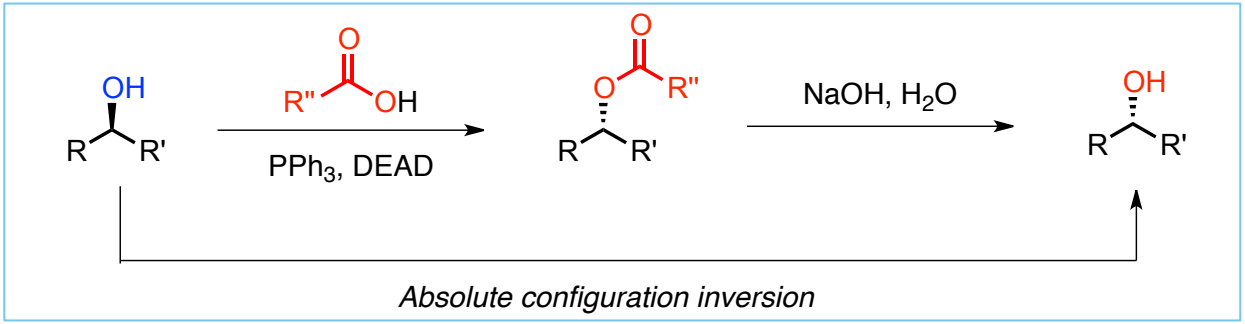
- All the reactants mixed in one-pot
- Phosphine oxide and reduced DEAD (hydrazine) formed as by-products
- Acidic nucleophiles (NuH) are needed, some examples are listed below:

NuH =

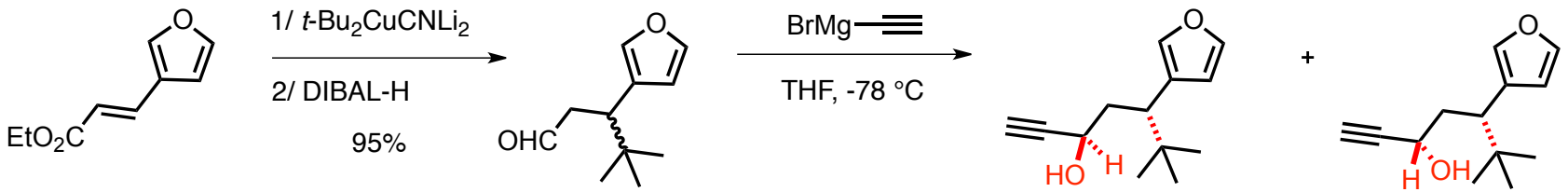


Kumara Swamy, K. C. *et al. Chem. Rev.* **2009**, *109*, 2551.

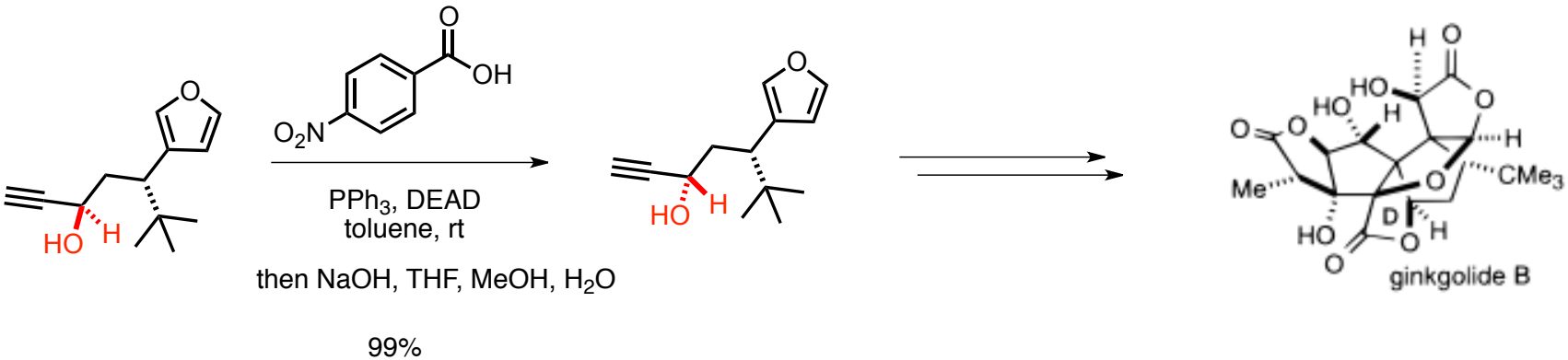
Mitsunobu reaction: alcohols inversion



Example : synthesis of (±)-Ginkgolide B

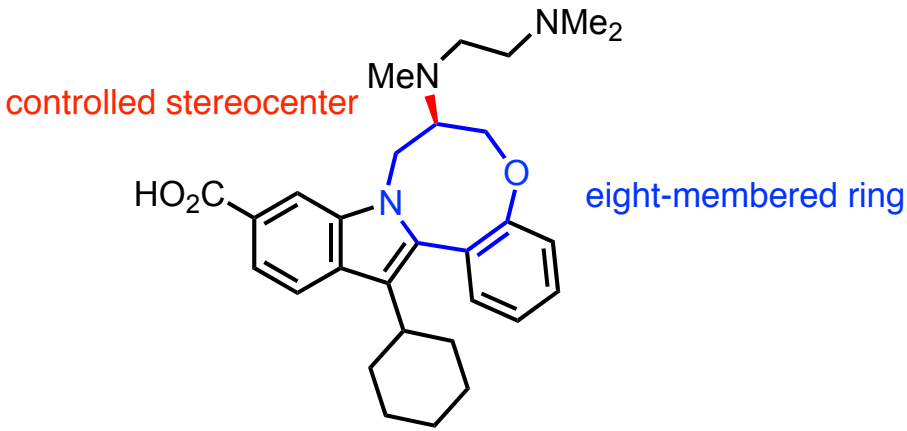


Mixture of diastereoisomers
anti / *syn* = 1:1.2
Separation using column chromatography



Crimmins, M. T. *et al. J. Am. Chem. Soc.* **1999**, *121*, 10249.

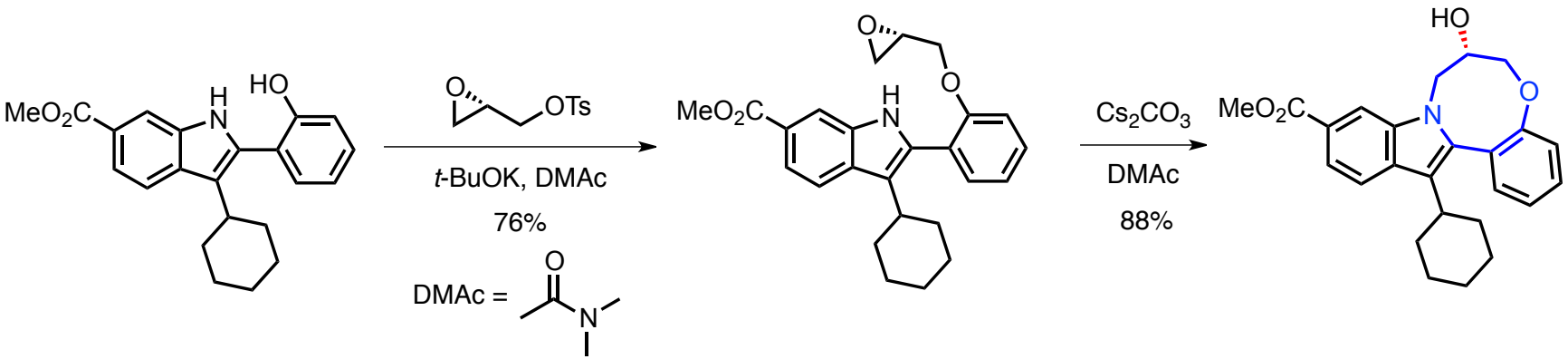
Mitsunobu reaction: application to a multikilogram synthesis



Drug candidate for the treatment of hepatitis C
Multikilogram synthesis required for preclinical and clinical evaluation

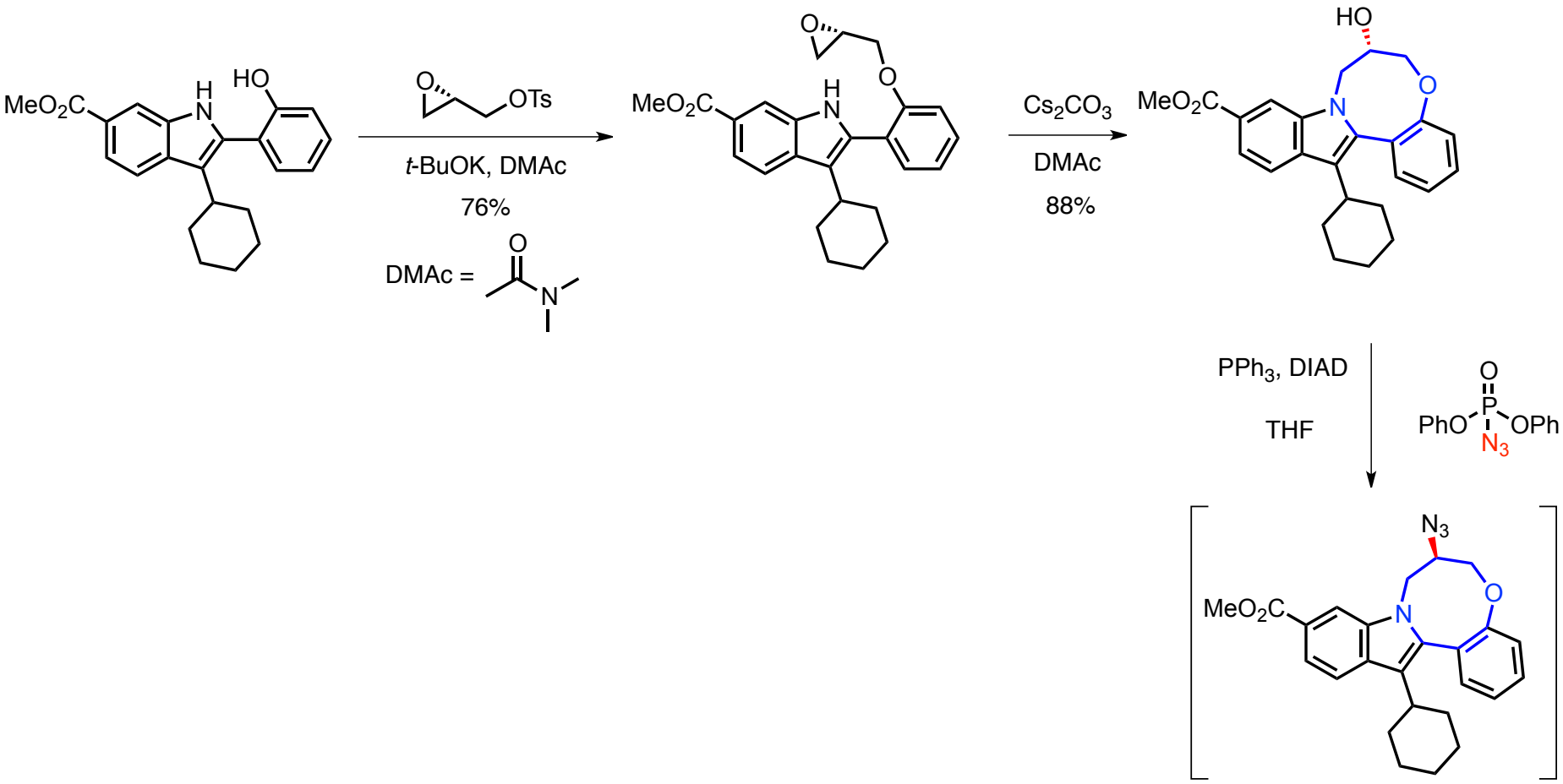
Scott, J. P. et al. *Org. Process. Res. Dev.* **2011**, *15*, 1116

Mitsunobu reaction: application to a multikilogram synthesis

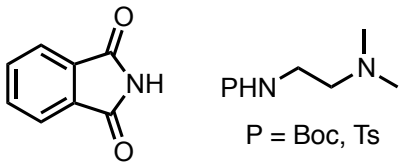


Scott, J. P. et al. *Org. Process. Res. Dev.* **2011**, *15*, 1116

Mitsunobu reaction: application to a multikilogram synthesis

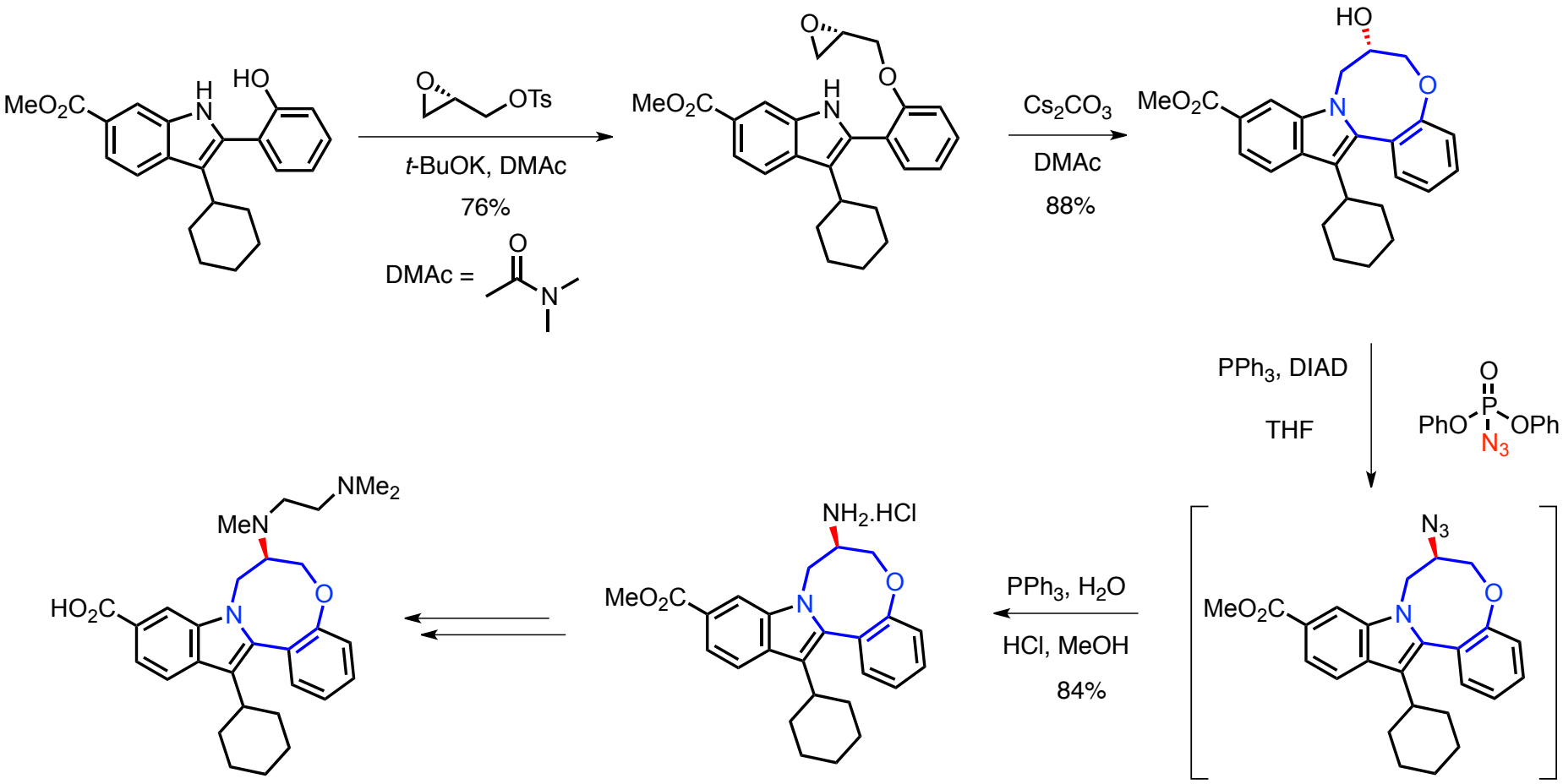


Other nucleophiles tested



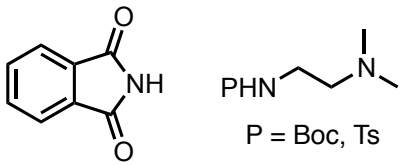
Scott, J. P. et al. *Org. Process. Res. Dev.* **2011**, *15*, 1116

Mitsunobu reaction: application to a multikilogram synthesis



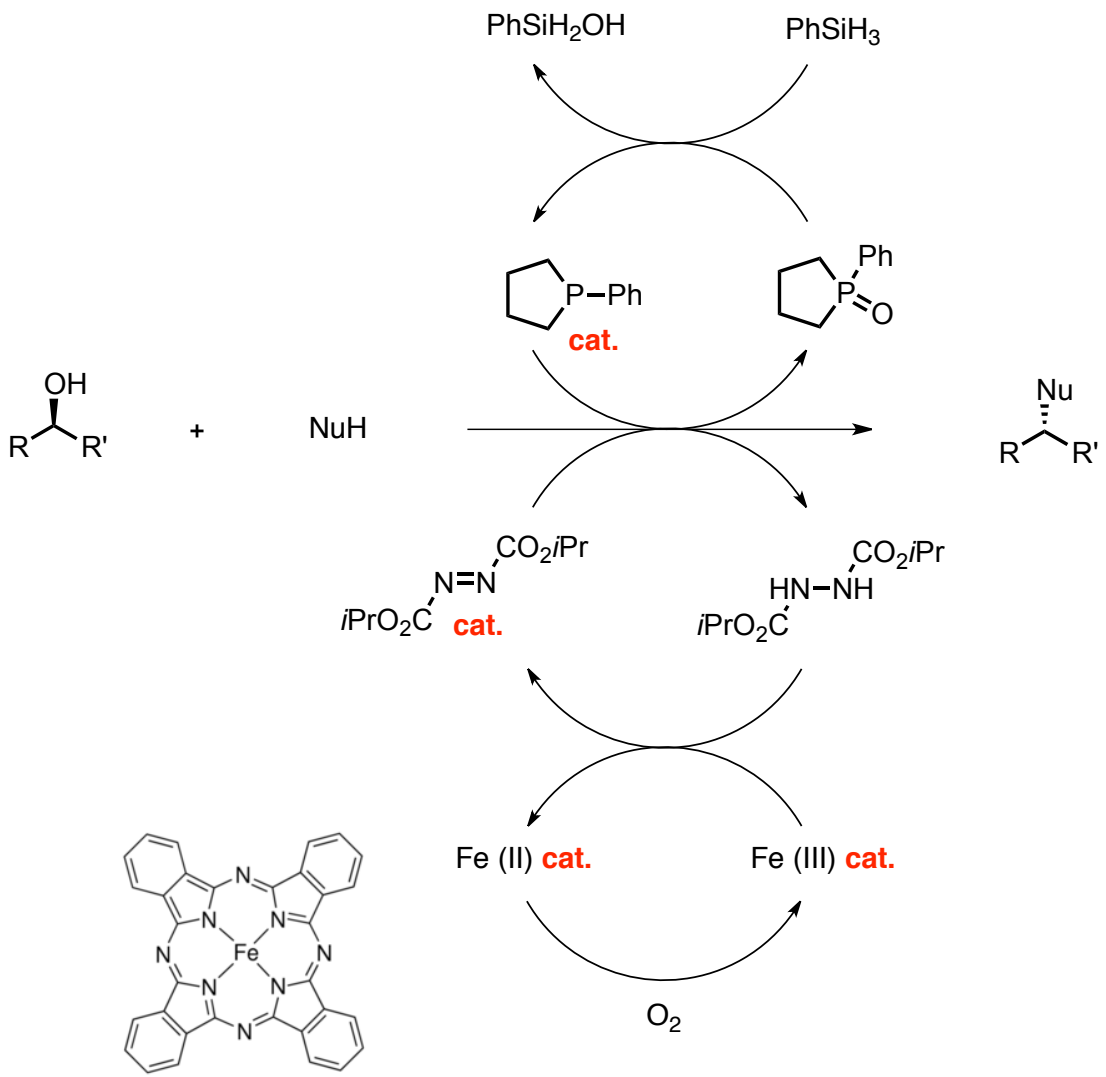
32% overall yield
Preparation of more than 3 kg

Other nucleophiles tested



Scott, J. P. et al. *Org. Process. Res. Dev.* **2011**, *15*, 1116

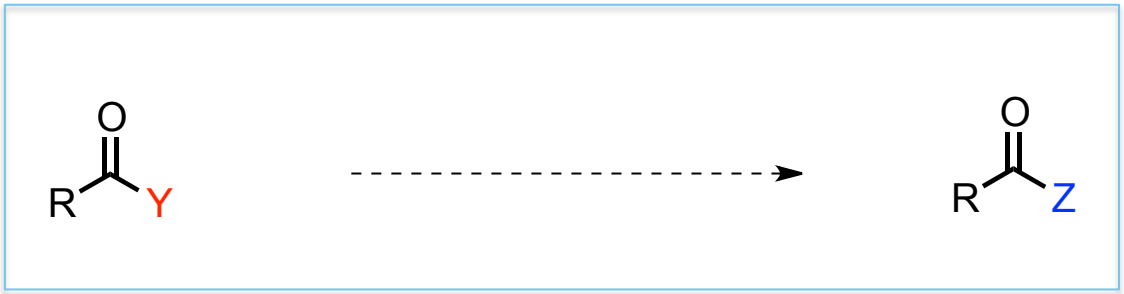
Mitsunobu reaction: development of a catalytic process



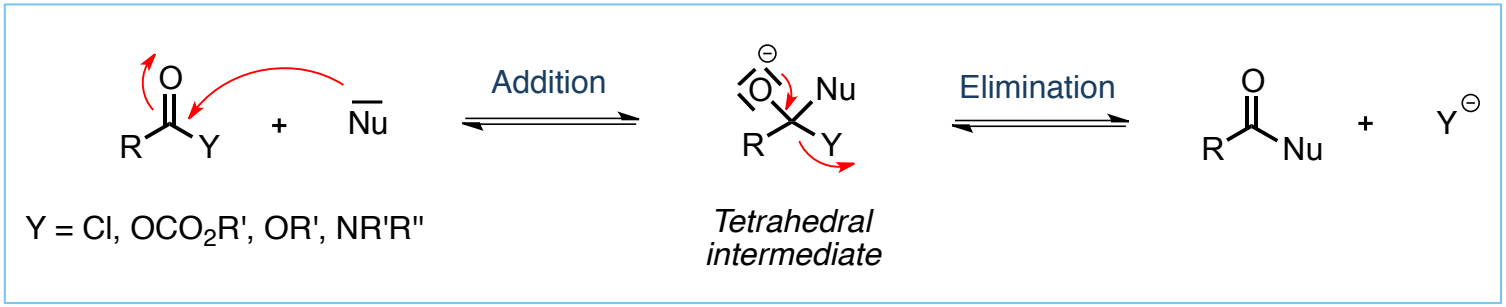
Phosphine oxide is reduced and hydrazine oxidized in situ

Aldrich, C. C. et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 13041.

Interconversion of carboxylic acid derivatives



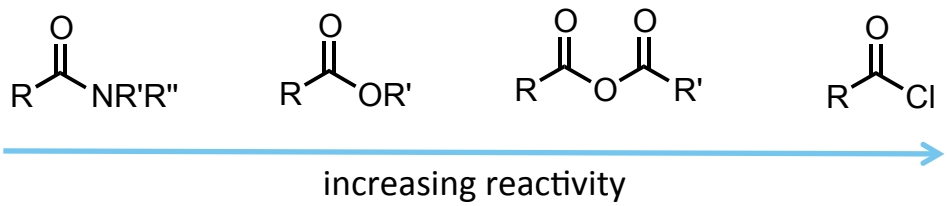
General scheme



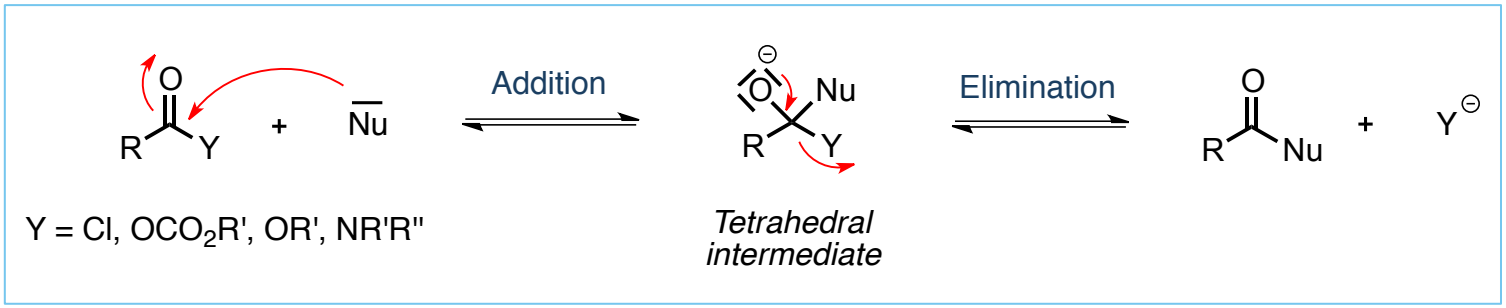
Reactivity of acid derivatives both linked to the addition step (*electrophilicity of the carbonyl moiety*) and to the elimination step (*leaving group ability of Y*)

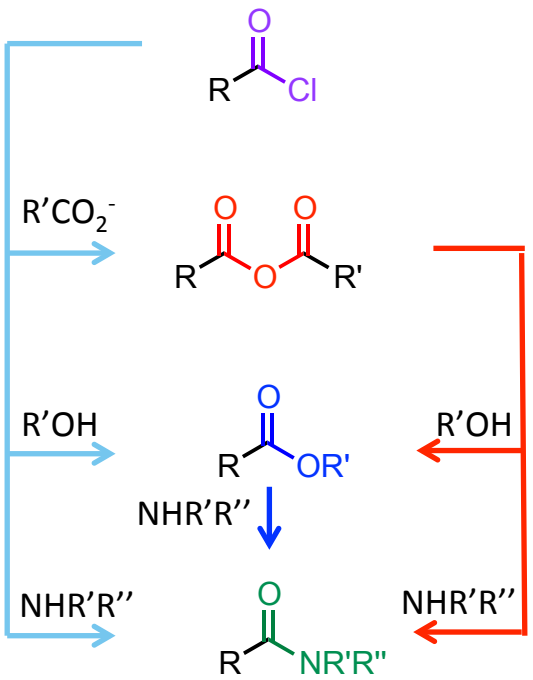
Leaving group ability linked to the pK_a of HY/Y^-

	amide	*ester*	*anhydride*	*acid chlorides*
HY/Y^-	**NH_3/NH_2^-**	**ROH/RO^-**	**RCO_2H/RCO_2^-**	**HCl/Cl^-**
pK_a	35	16	5	-7
LG	Very bad	Bad	Good	Very good



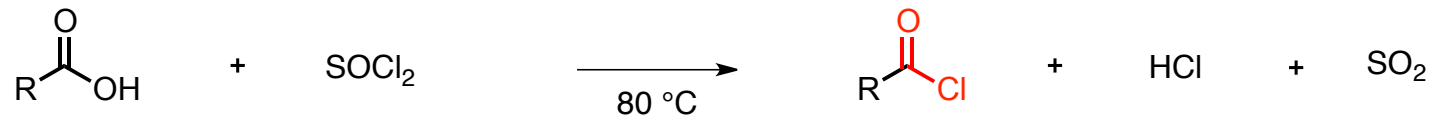
Interconversion of acid derivatives



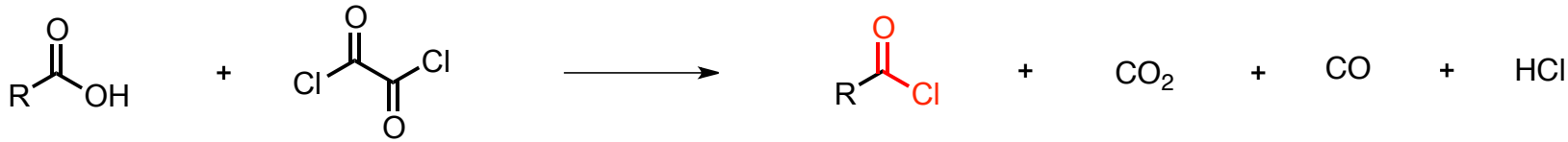


Acid chlorides and anhydrides formation

- Acid chlorides synthesis

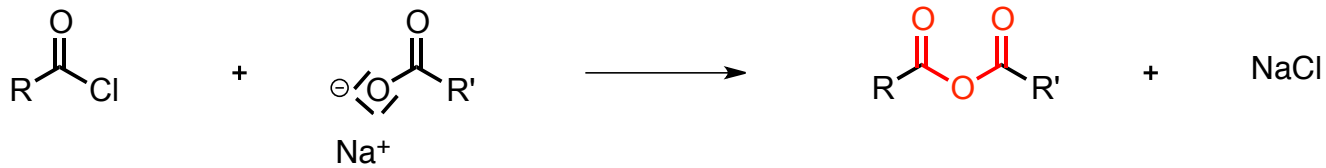


Caution: gaz release



- PCl_5 can also be used as chlorinating agent
- With oxalyl chloride $(COCl)_2$, DMF can be used as a catalyst

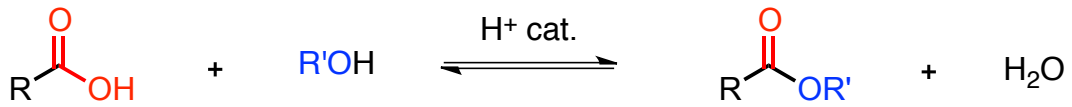
- Anhydride synthesis



- Symmetrical or mixte anhydrides can be prepared

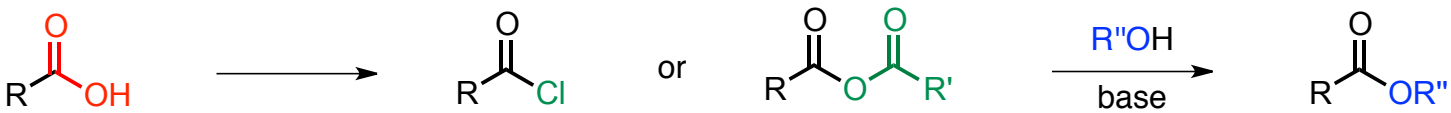
Ester synthesis

Fischer esterification



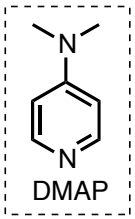
- Slow reaction, under equilibrium
- To draw the equilibrium toward ester formation: excess of one reactant or water removing (Dean-Stark, drying agent)
- Only with primary and secondary alcohols

Using acid chlorides or anhydrides



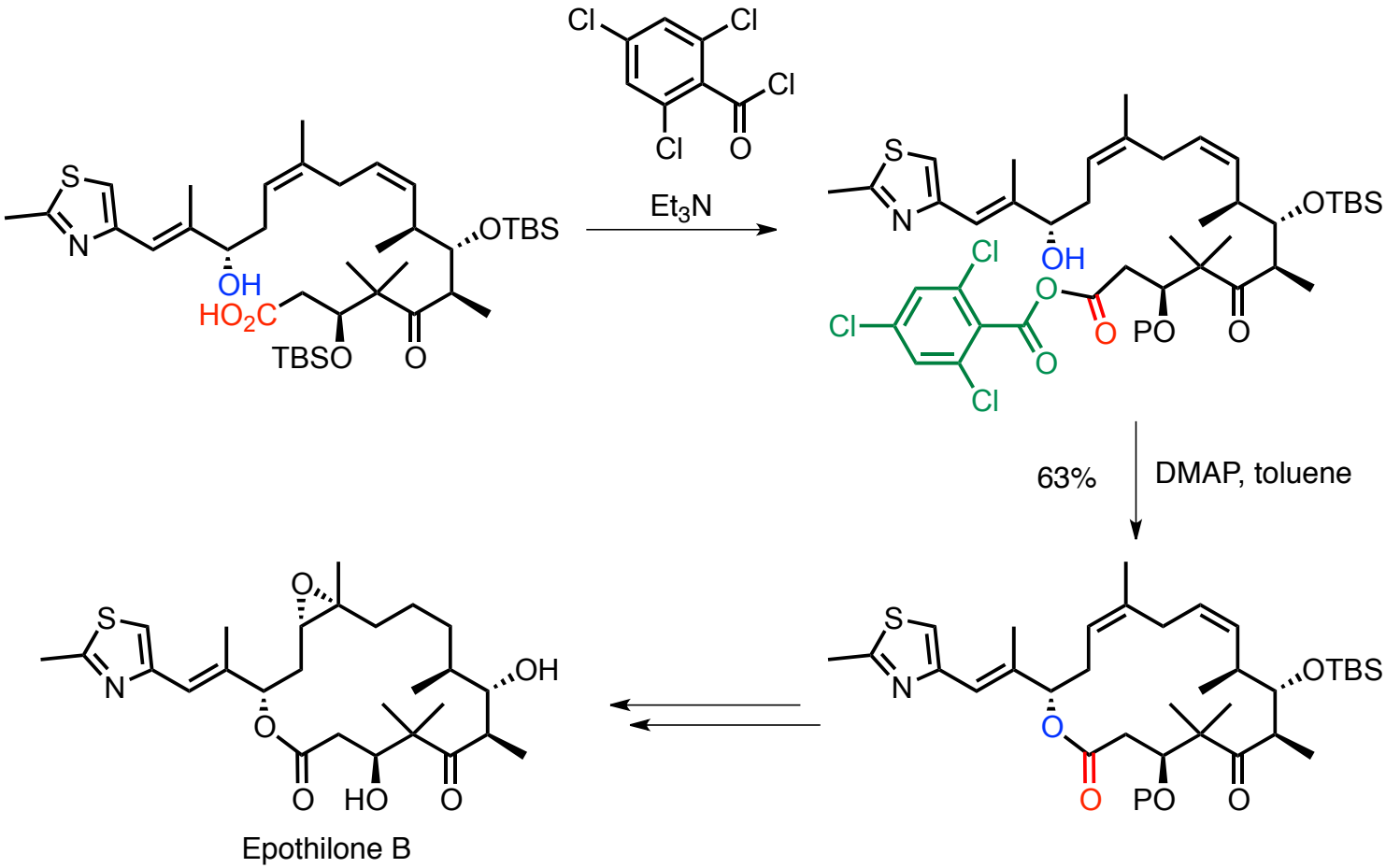
Activated forms of carboxylic acids

- Anhydrous conditions
- Weak base required to trap HCl or R'CO_2H (pyridine, Et_3N)
- Pyridine can also act as a nucleophilic catalyst but DMAP is better.



Important application: macrolactonisation using Yamagushi's reaction

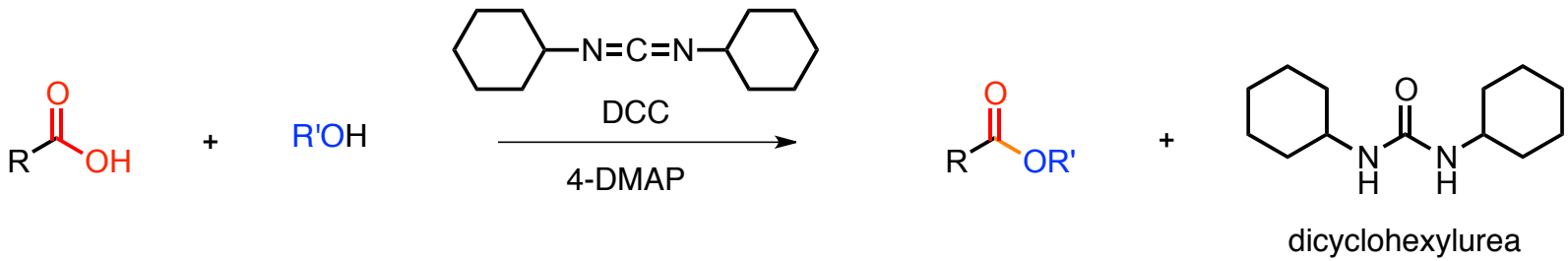
Yamagushi macrolactonisation



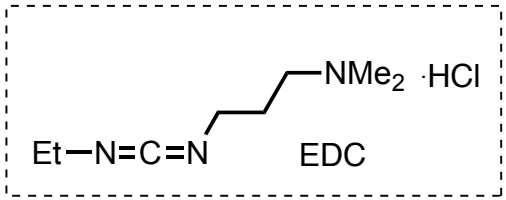
- Macrolactones are ubiquitous in biologically active natural products
- Yamagushi esterification = key step in numerous macrolactone total synthesis
- A mixte anhydride is prepared, regioselectivity of the hydroxyl addition required
- High dilution necessary to avoid intermolecular reactions
- Epothilone B = cytotoxic compound, clinical tests under progress

White *et al. J. Am. Chem. Soc.* **2001**, *123*, 5407.

Esterification using a coupling agent : DCC

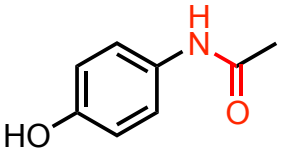


- In situ activation of the carboxylic acid through addition on the diimide (DCC = dicyclohexylcarbodiimide)
- DMAP = nucleophilic catalyst
- Stœchiometric formation of dicyclohexylurea (purification issues)
- Alternative : 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC). Advantage : corresponding urea is water soluble, can be separated during the work up (aqueous phase)



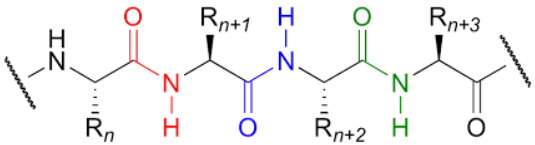
Amides are everywhere

Drugs

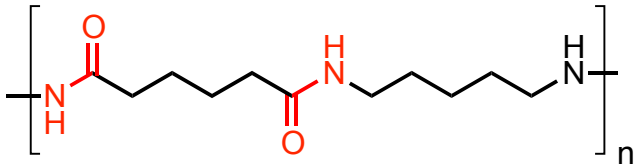


paracétamol

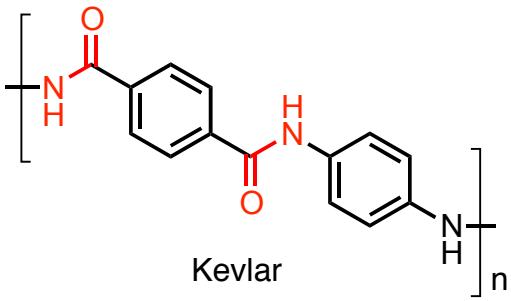
Life



Materials



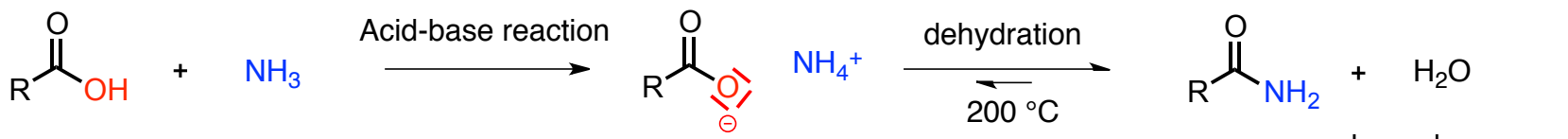
Nylon 6,6



Kevlar

Amide formation - Strategies

- From carboxylic acid

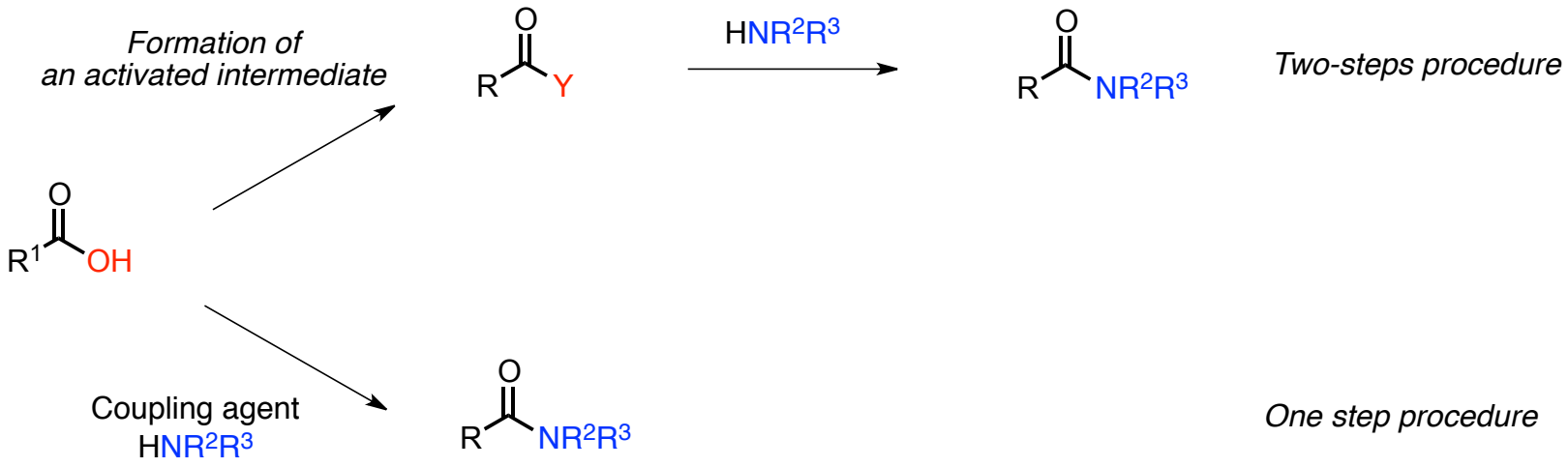


pK_a ($RCO_2H/RCOO^-$) ≈ 5
pK_a (NH_4^+/NH_3) ≈ 9

ammonium salt

Very difficult, very high temperature required

- Alternatives



Amide formation - Strategies

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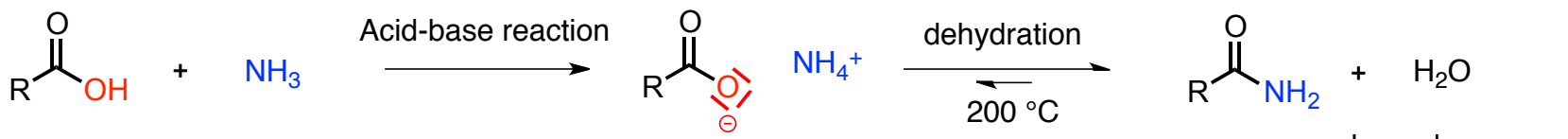

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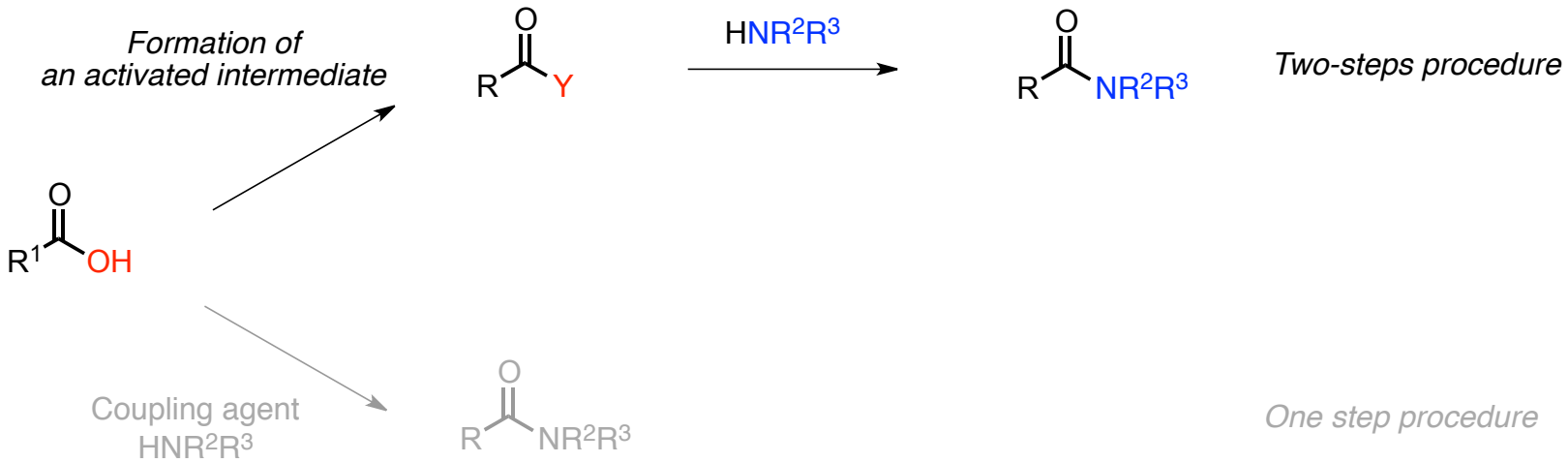
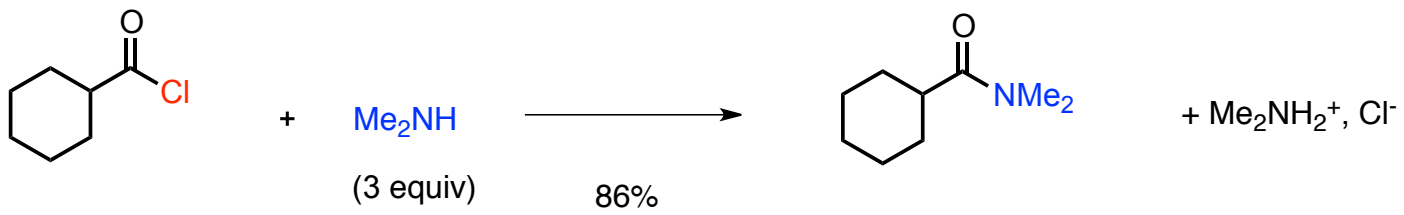


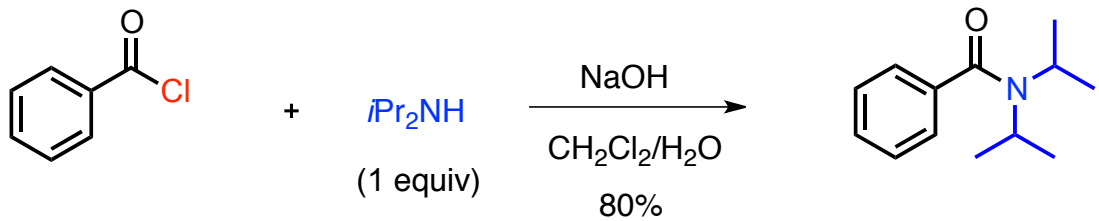
Amide formation – Using an acid chloride

- Using an excess of amine



- One equivalent of HCl produced, need for a second equivalent of amine to neutralize it.
- Can be problematic if the amine is precious

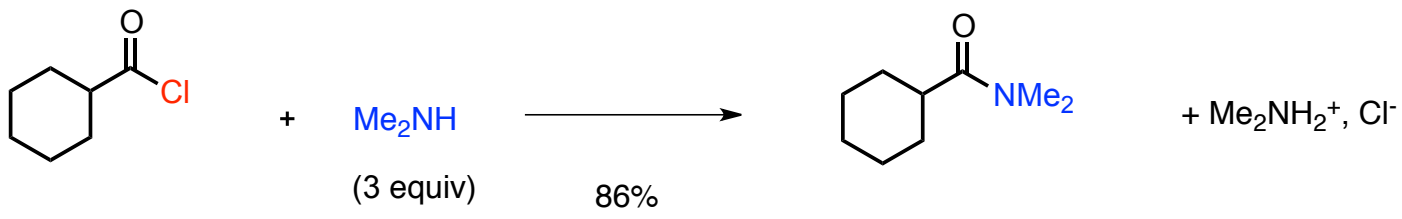
- Using Schotten-Baumann conditions



- Biphasic reaction medium: acid chloride and amine in the organic phase (CH_2Cl_2), NaOH in aqueous phase.
- No addition of OH- on the acid chloride.
- HCl can dissolve in water where it is neutralized by NaOH.
- Only one equivalent of amine consumed.

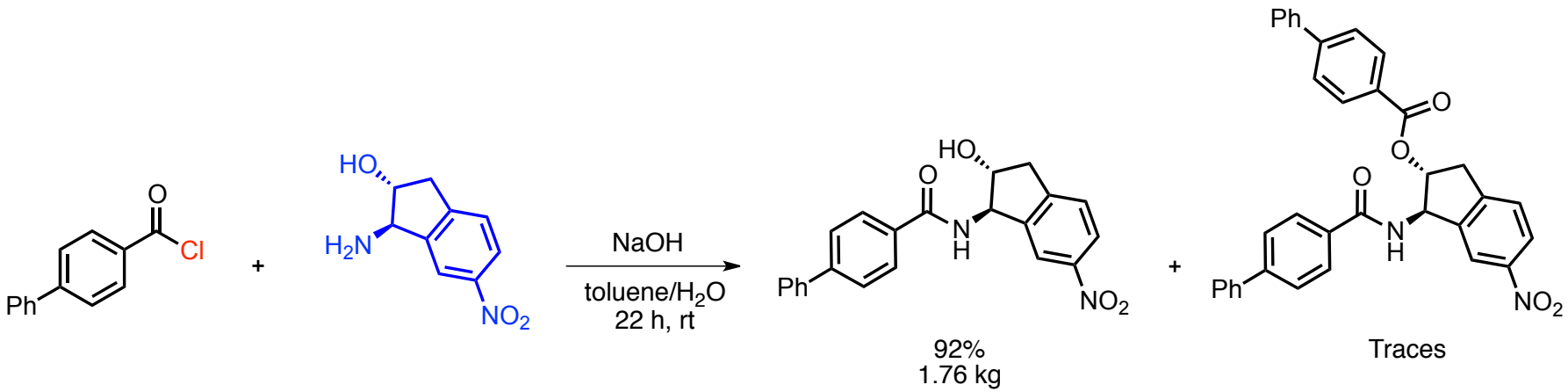
Amide formation – Using an acid chloride

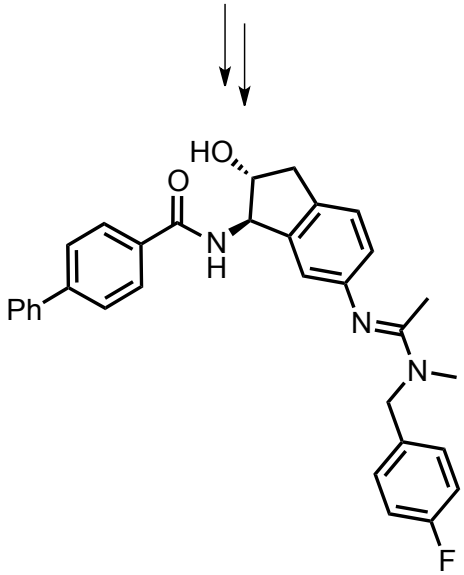
- Using an excess of amine



- One equivalent of HCl produced, need for a second equivalent of amine to neutralize it.
- Can be problematic if the amine is precious

Schotten-Baumann synthesis: application



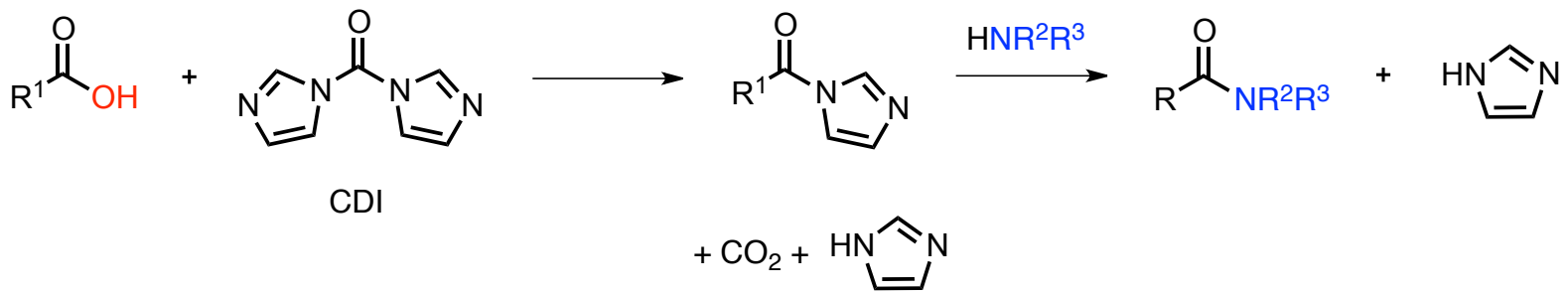


M1 muscarinic receptor agonist
Receptors involve in cognitive processing
Potential target in Alzheimer treatment

Hansen, M. M. et al. *Org. Process. Res. Dev.* **2009**, *13*, 198.

Amide formation – Other activated intermediate

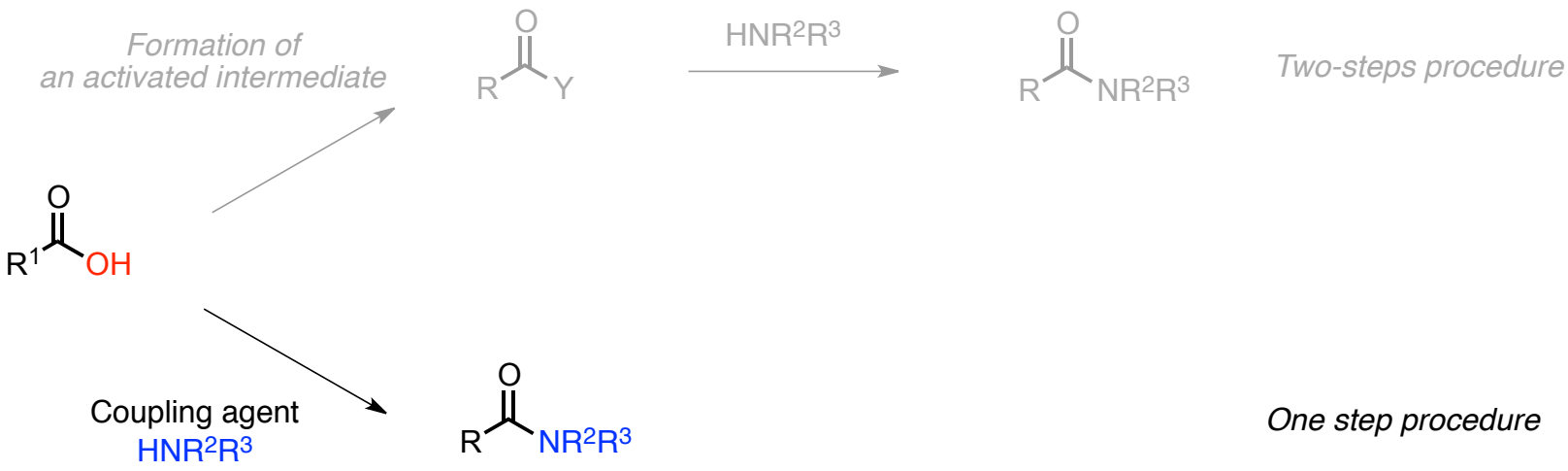
- Acyl imidazole



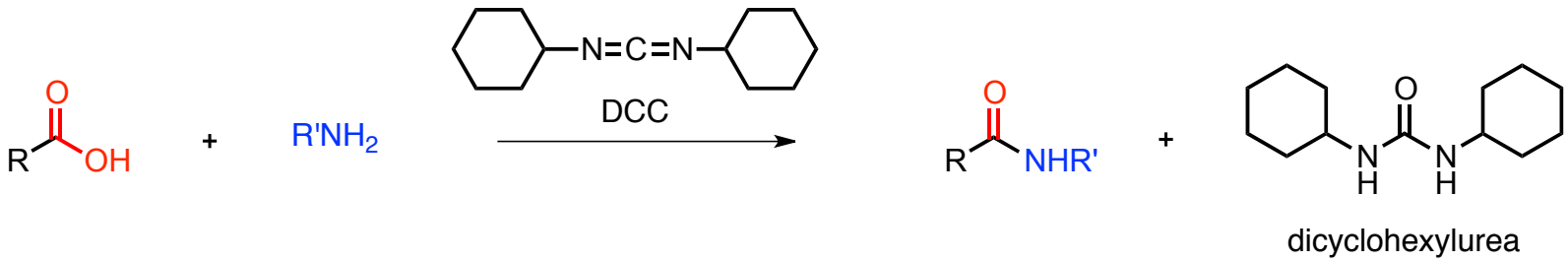
- Alternative to the intermediate formation of acyl chloride
- Formation of innocuous side-products (CO_2, imidazole)
- Be careful, amine can add on CDI if introduced in excess to form the corresponding urea

- Activated ester

Amide formation – One step procedure



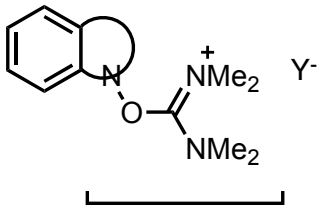
In the presence of a diimide



- Same mechanism of esterification (*in situ* activation of the carboxylic acid)
- 4-DMAP not mandatory as amines more nucleophilic than alcohols
- Several diimide reagents available, several applications

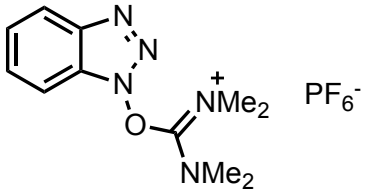
In the presence of uronium salts

- General structure

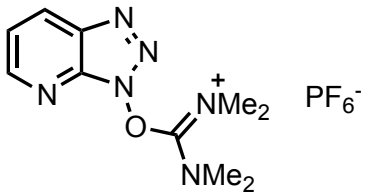


N-oxide guanidinium

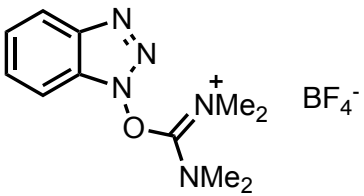
- Popular examples



O-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HBTU



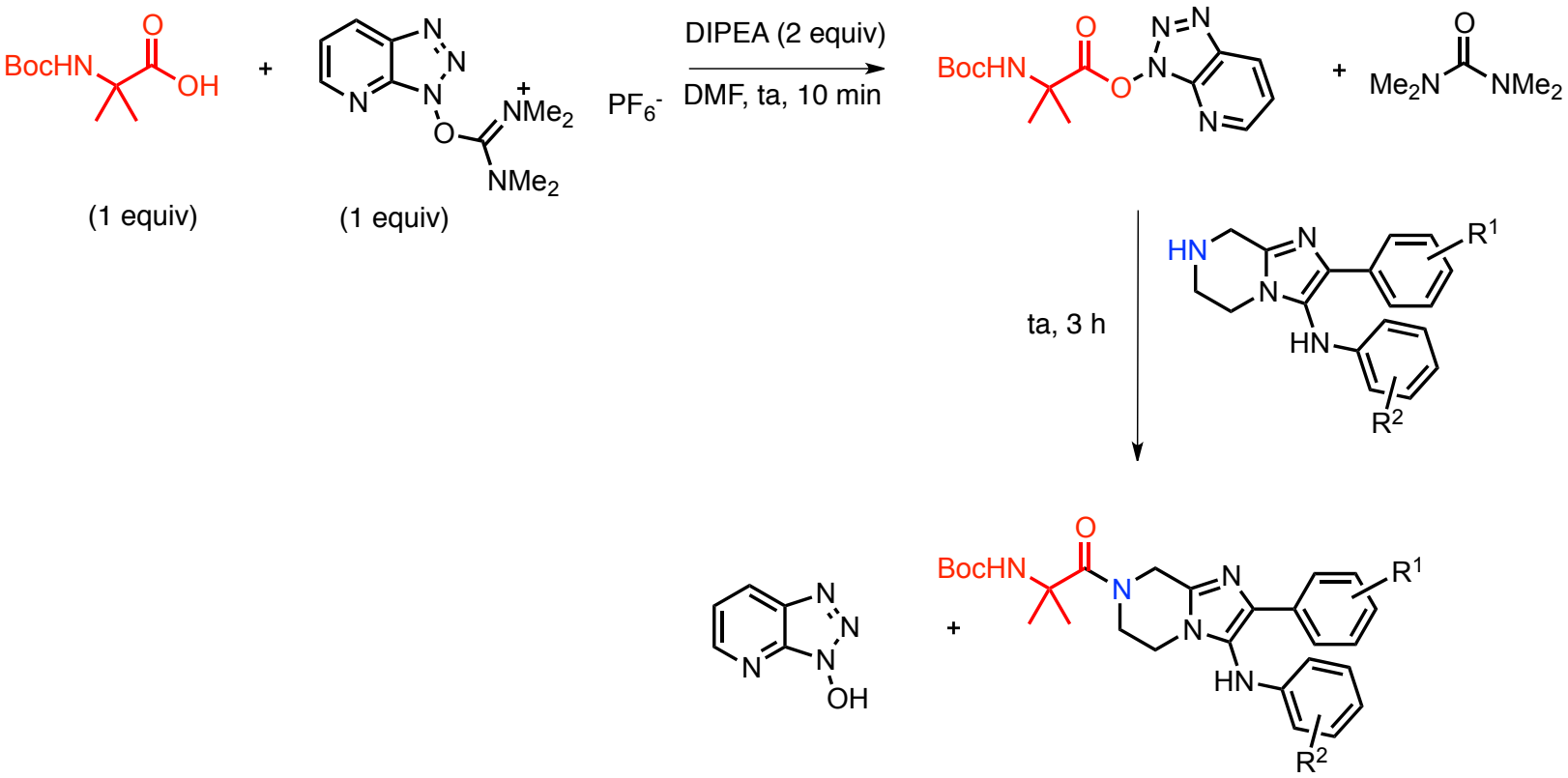
O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HATU



O-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TBTU

In the presence of uronium salts - examples

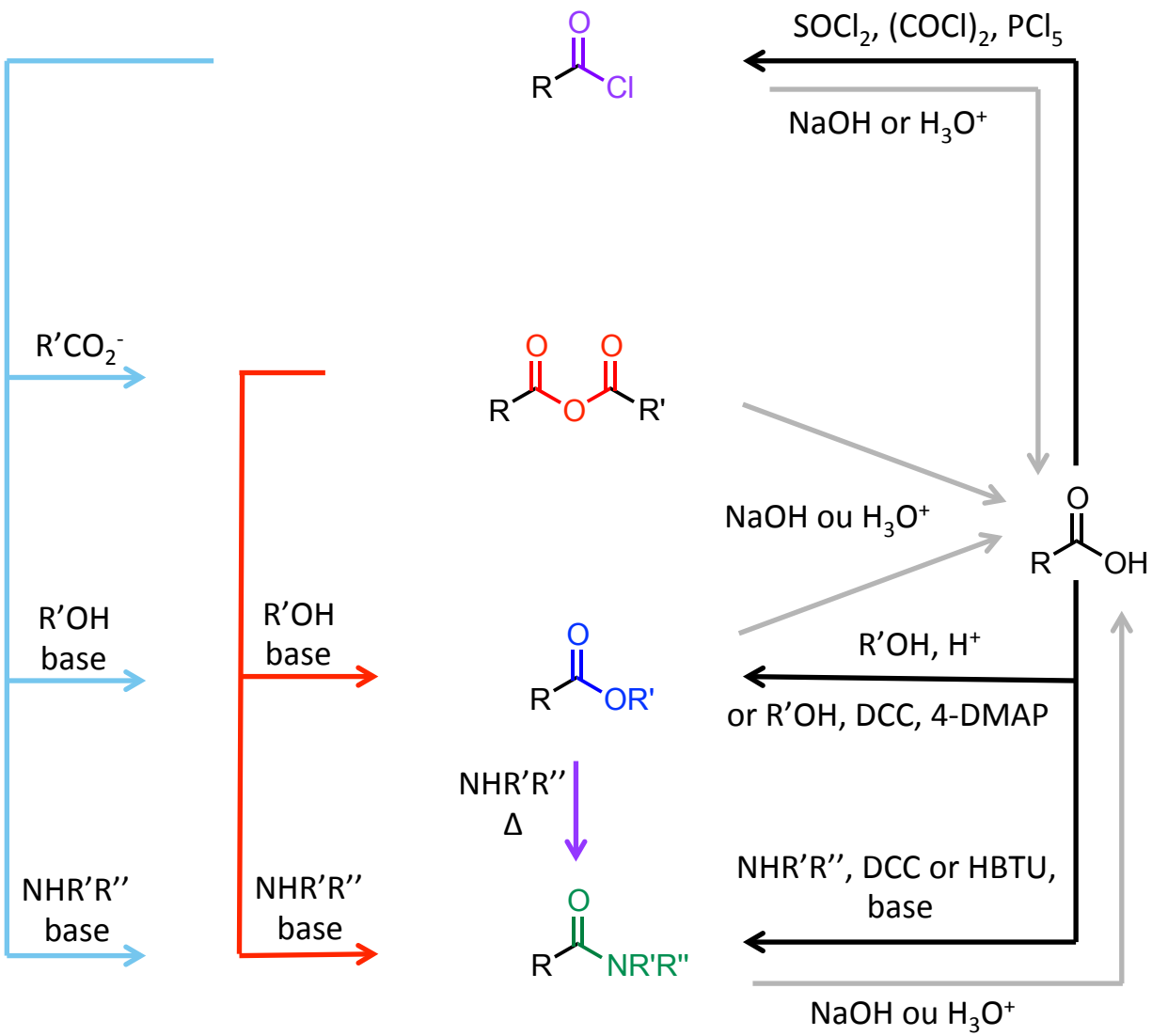
Synthesis of a library of potent antimalarial agents



- *In situ* formation of an activated ester
- Preliminar treatment of the acid with HATU important (avoid the direct addition of amide on the guanidinium)

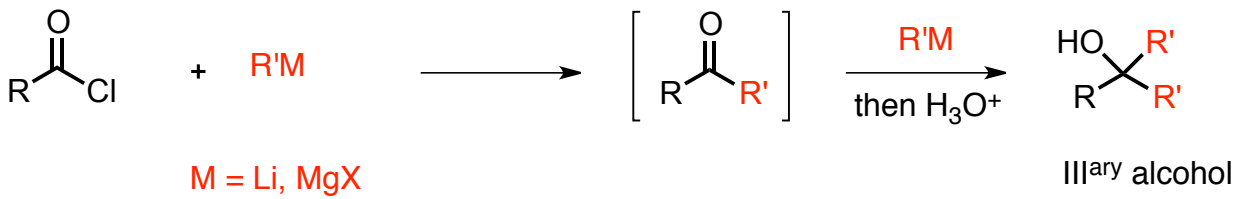
Chatterjee, A. K. et al. *J. Med. Chem.* **2011**, *54*, 5116.

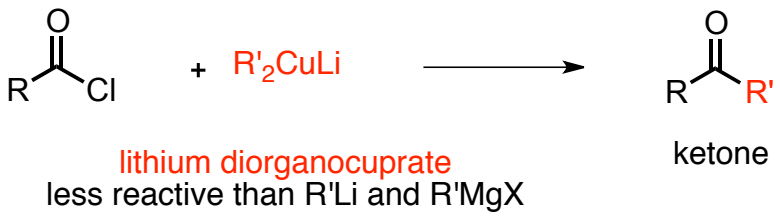
Interconversion of acid derivatives - Summary



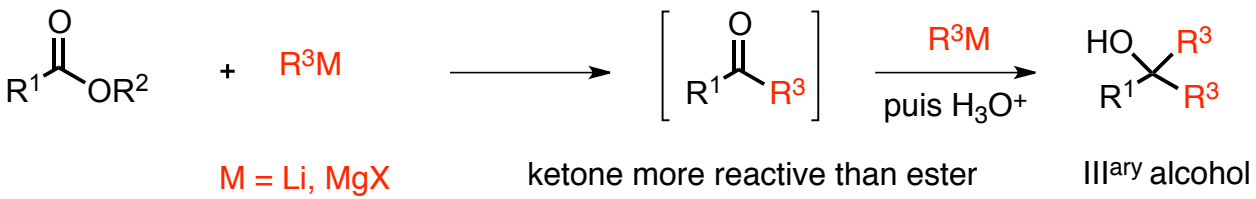
Reaction with organometallic derivatives

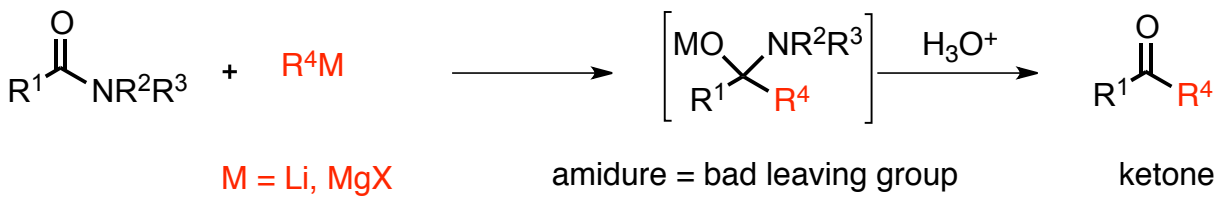
- Reactivity of acid chlorides



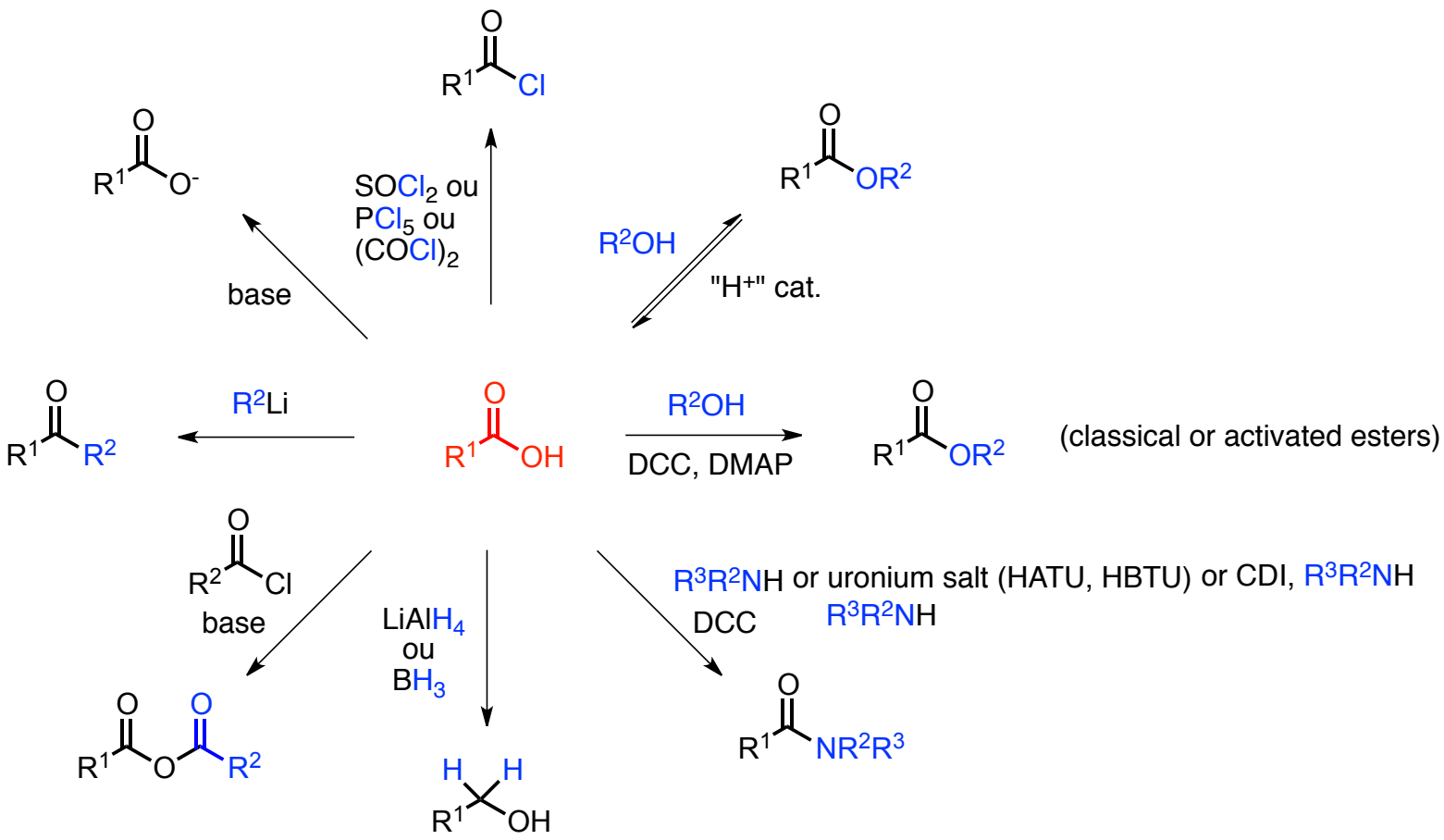


- Reactivity of esters and amides

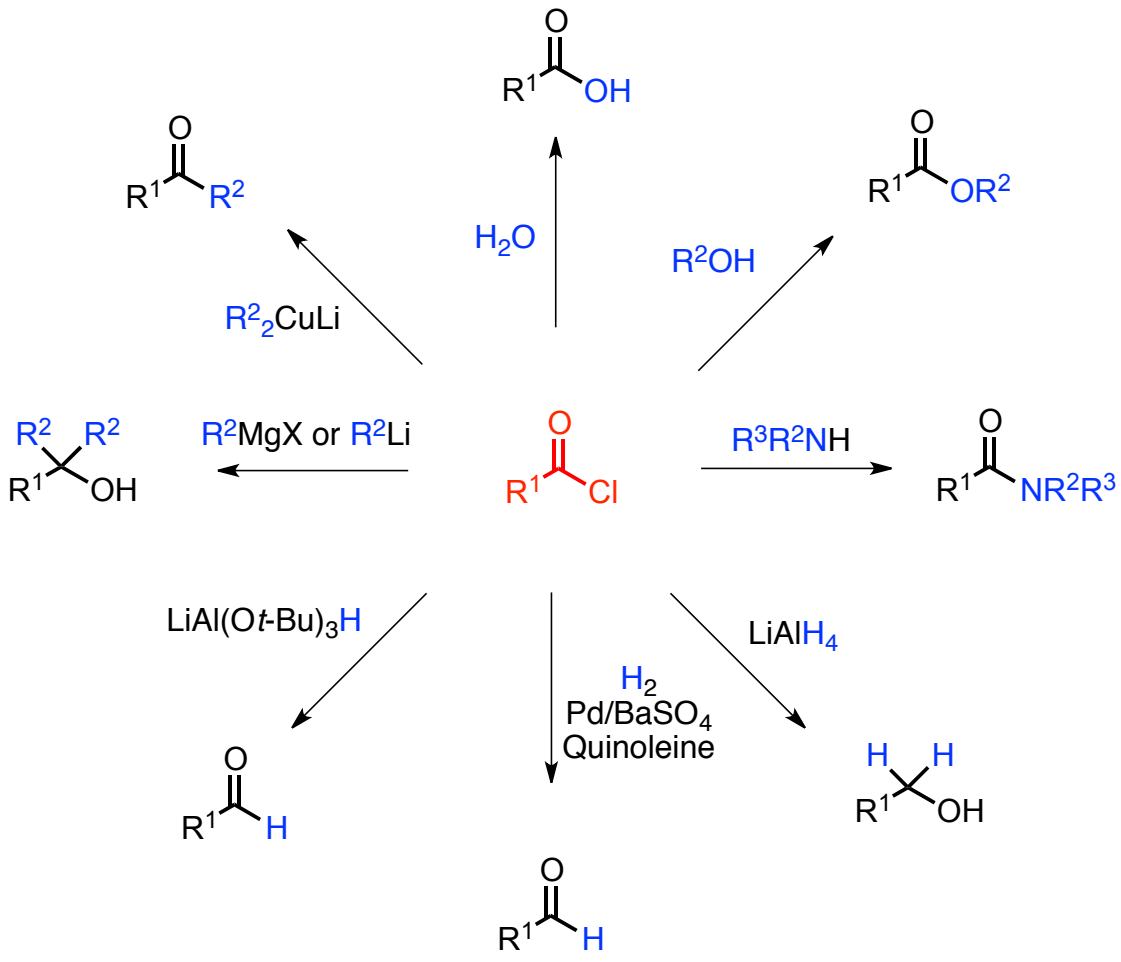




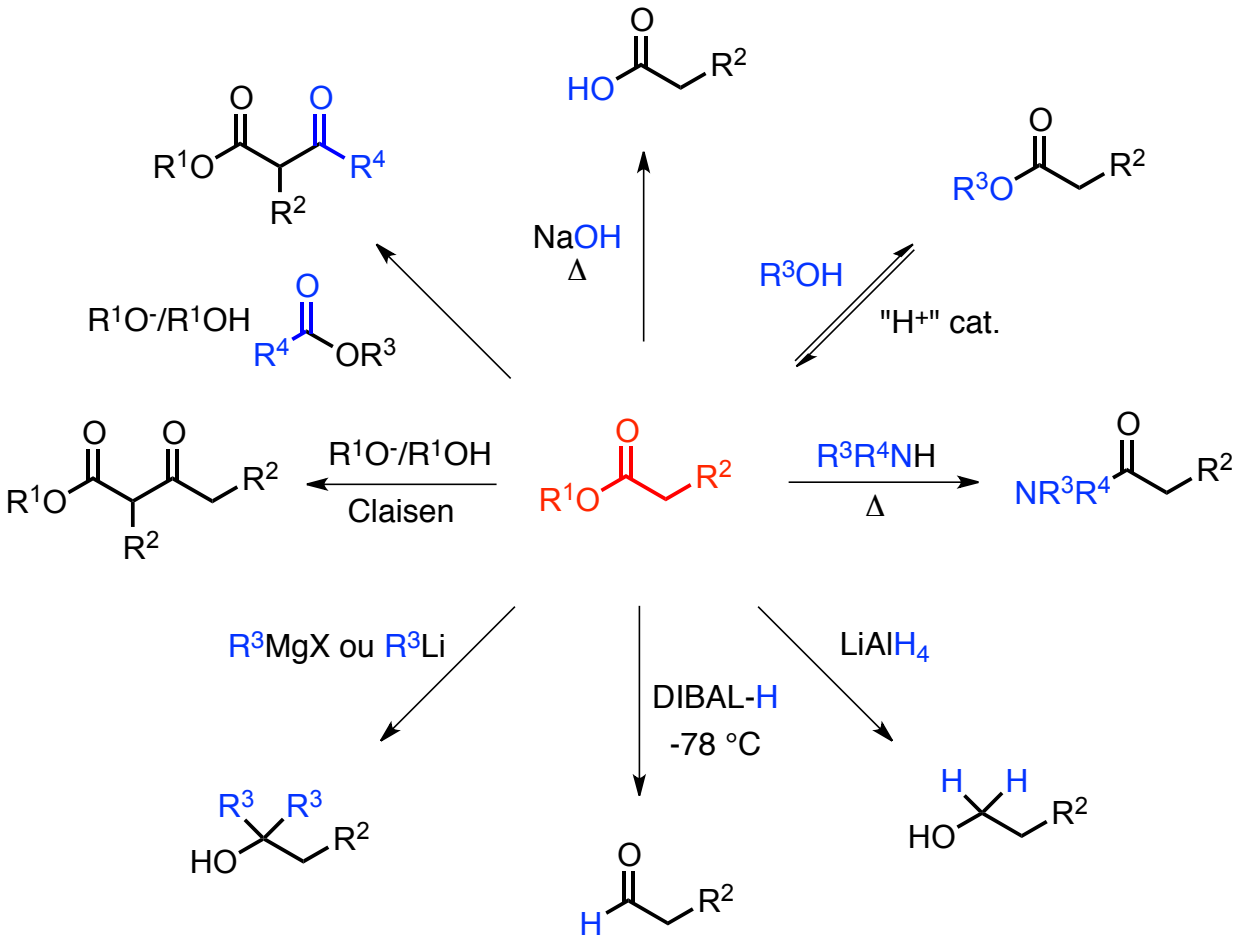
Carboxylic acids: summary



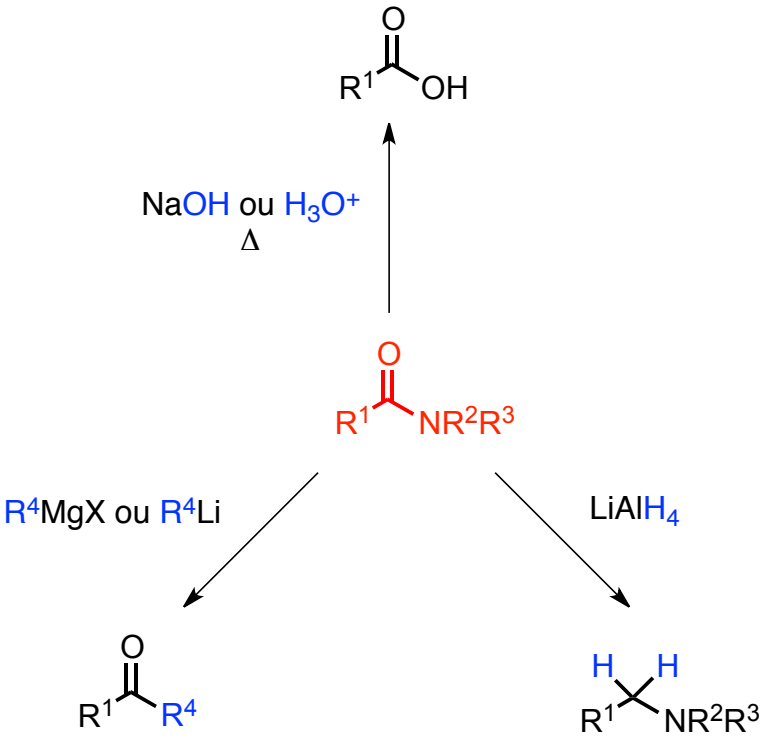
Acid chlorides: summary



Esters: summary



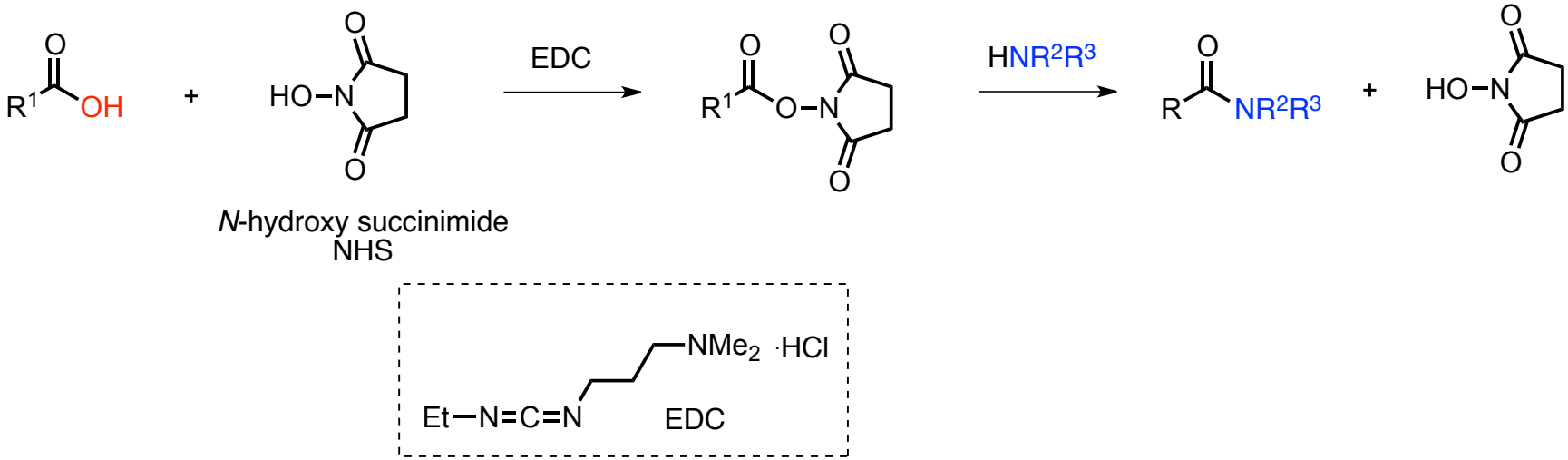
Amides: summary



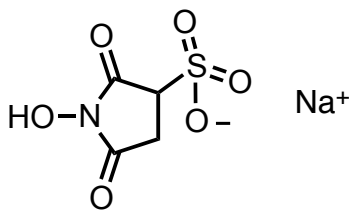
Formation of amides - Illustrations

Amide formation – Other activated intermediate

- Activated ester - NHS



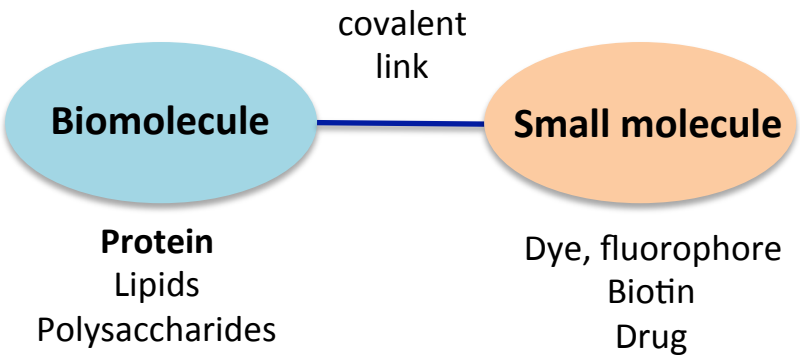
- Can be performed in water in the presence of EDC
- More water soluble version of NHS: sulfo-NHS



- Numerous applications in chemical biology or biology.

Bioconjugation - Introduction

Bioconjugation = covalent link between 2 molecules, at least one of which being a biomolecule



Biomarkers (imaging)

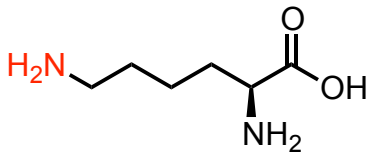
Drug vectorization

Nanotechnology

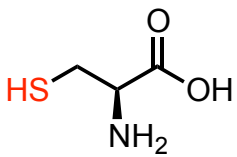
Bioconjugation - Strategies

Covalent linkage between a protein (antibody) and a small molecule

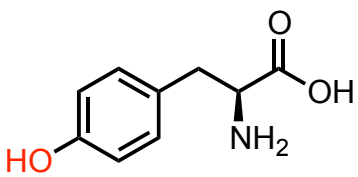
- One simple strategy: using selective reactions directly involving the functionalities present in amino acids of the protein.
- Generally, 4 nucleophilic amino-acids are targeted: lysine, cysteine, tyrosine, tryptophan



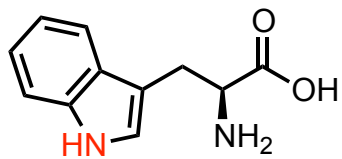
Lys



Cys



Tyr



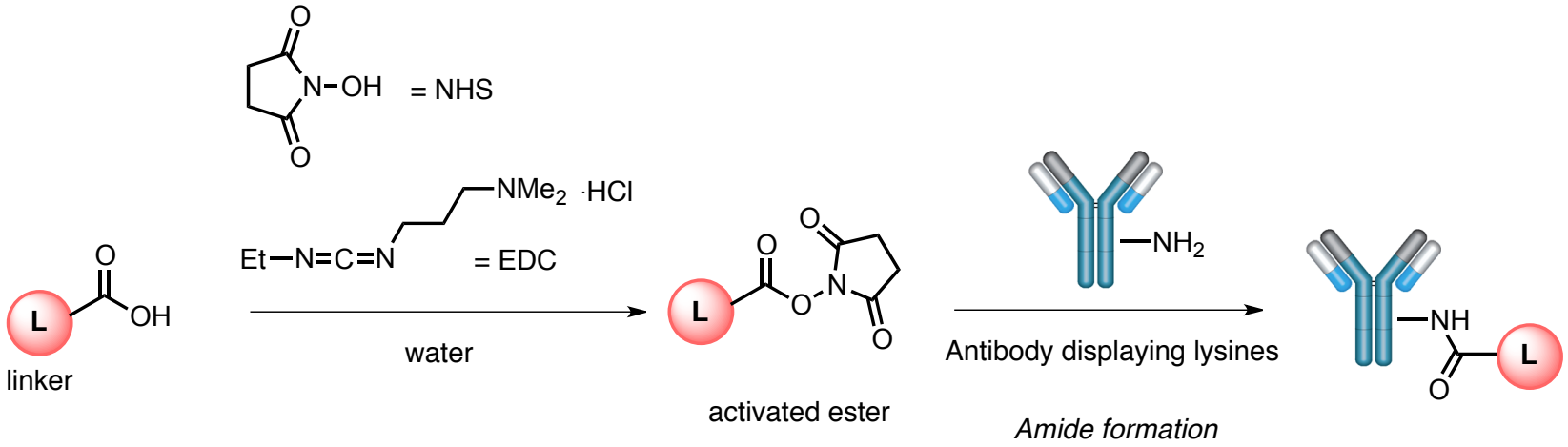
Trp

- Nucleophilic functions more accessible than the « internal » $-NH_2$, expressed at the surface of antibody.
- Need for very efficient, selective, « physiological friendly » reactions.

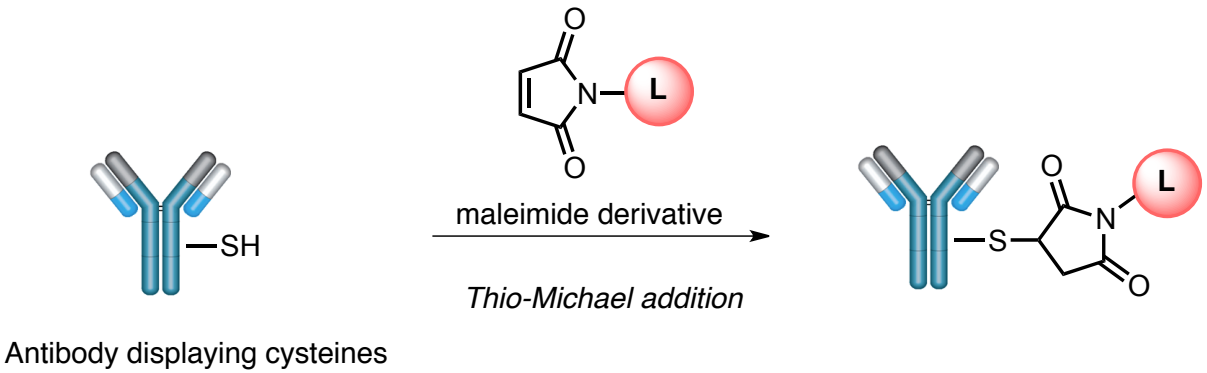
Bioconjugation - Strategies

Focus on two reactions used in bioconjugation

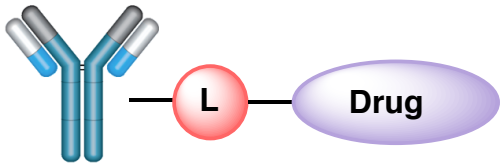
- Involving lysine residues



- Involving cysteine residues



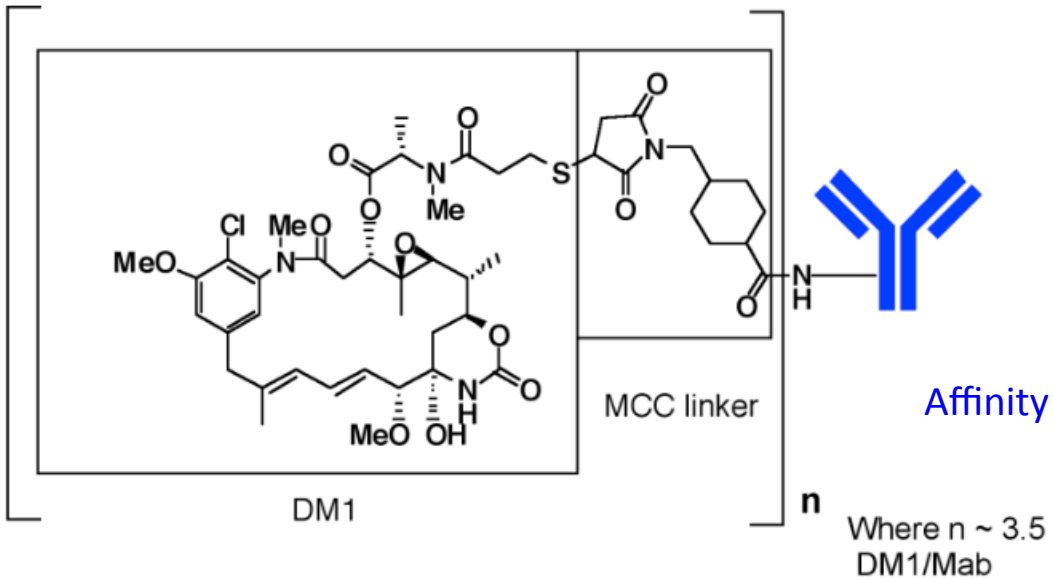
Antibody-drug conjugates (ADCs)



- Antibody: vectorization of the bioactive drugs towards a well-defined targets (ex: tumor). Antibody selectively binds to tumor cell surface antigens.
- Cytotoxic drug, able to kill cancer cells.
- Linker can be cleavable to deliver the drug or not.
- Particularly attractive in anticancer therapies with the aim of reducing side effects of treatments.
- Extensive research over the past 10 years, 2 FDA approved ADC therapeutics, 40 ADCs under clinical trials.

Antibody-drug conjugates (ADCs)

Example: Kadcyla® (Genentech)

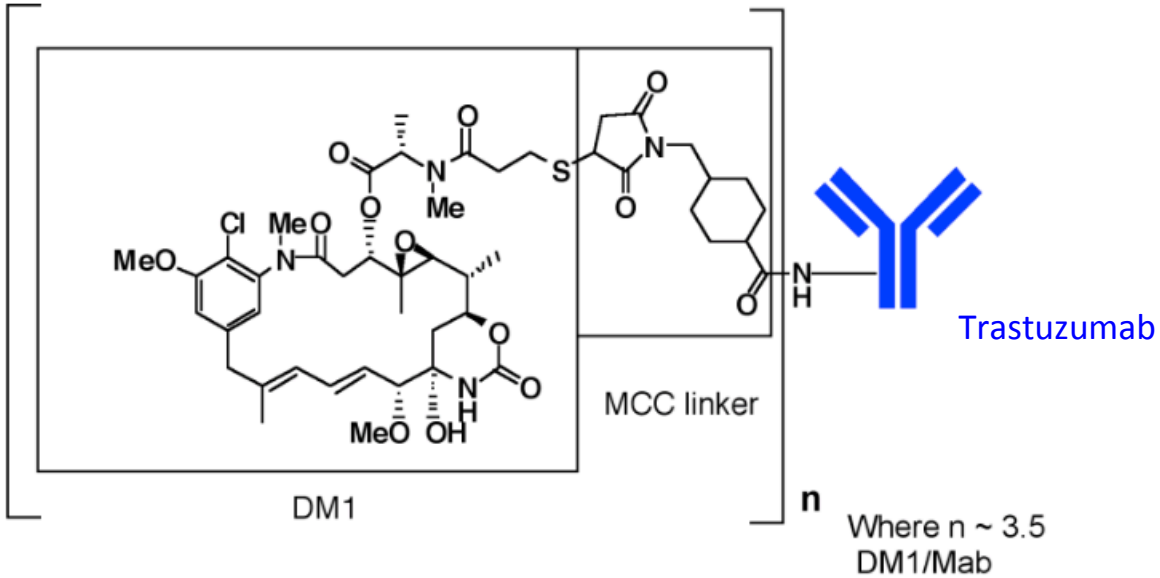


Maytansine
Cytotoxic agent

Trastuzumab
Affinity with HER2 receptors

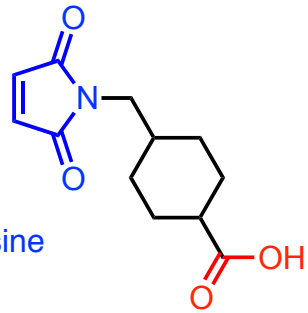
- Antibody: trastuzumab. Cells overexpressing HER2 receptors targetted. Concern HER2-positive metastatic breast cancers.
- Maytansine: cytotoxic drug, able to kill tumor cells (microtubule targeting).
- FDA-approved in 1998.
- Heterogeneous distribution of the cytotoxic agent on the antibody (0 to 8 molecules per antibody, average ratio around 3.5)

Structure of Kadcyla®



Maytansine

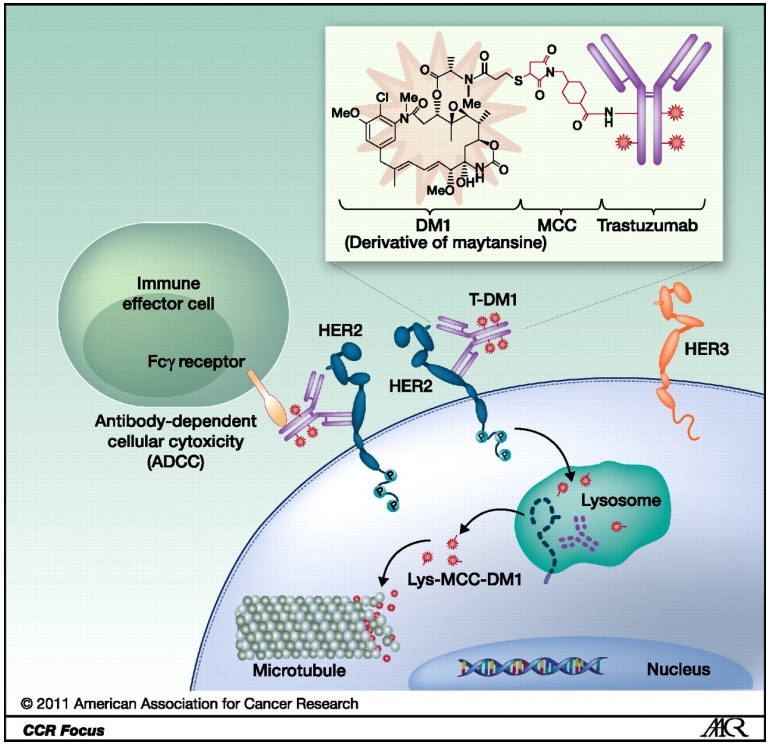
- Bifunctional linker



Maleimide
Reaction with a thiol present on Maytansine

Carboxylic acid
Reaction with lysine residues of trastuzumab after activation with EDC/NHS

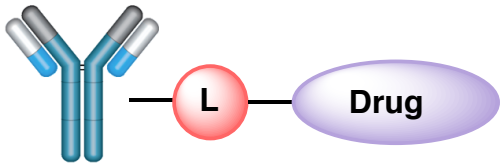
Mechanism of action



- Binding of the ADC to HER2 receptors on the surface of the tumor cell.
- Internalization into the cell of the HER2/ADC complex.
- Lysosomal degradation: intracellular release of the cytotoxic drug.
- Drug binds to tubulin and prevent microtubule polymerization and mitosis.

P. M. LoRusso et al. *Clin. Cancer Res*. **2011**, *17*, 6437.

Antibody-drug conjugates (ADCs)



Pros

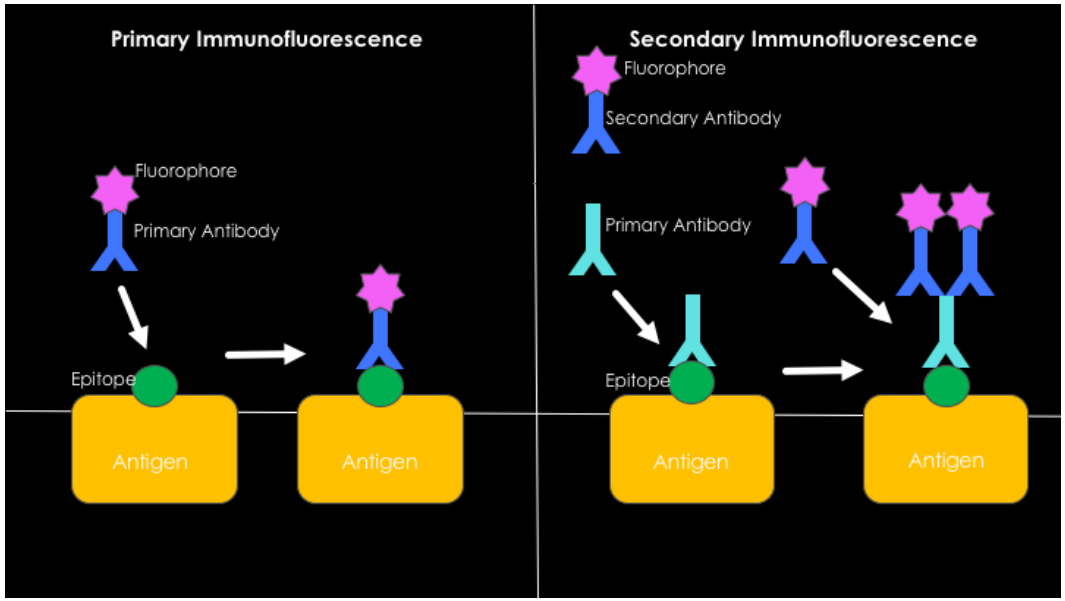
- Improved efficiency and selectivity
- Towards the development of personalized treatments.

Cons

- Heterogeneity (variation of the number of cytotoxic molecules per antibody). Variability of the stability, activity and pharmacokinetics.
- Huge compounds, difficulty to penetrate solid tumors
- Very high cost (for one patient, Kadcyla costs ca. 100 k€)

Immunofluorescence

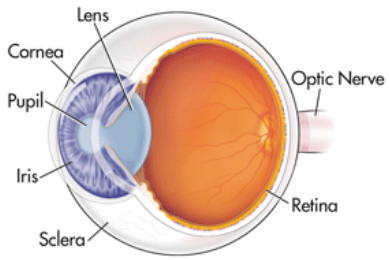
- Same chemical reactions can be used to link together an antibody and a fluorophore, principle of immunofluorescence.



- Numerous applications:
- diagnostic (detection of bacteria, of virus…)
- fundamental research (observation of cellular events)

Tissue engineering for cornea repair

- Cornea: protection of the inner part of the eyes.
- Some trauma or diseases can cause decrease of cornea transparency.
- Corneal affection = 2nd cause of vision loss.
- Possible treatment: *in vivo* repair of cornea using engineered tissue as corneal substitute.



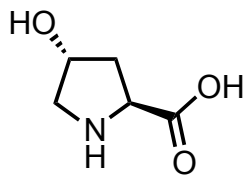
Anatomy of the Eye

Tissue engineering → cell sources

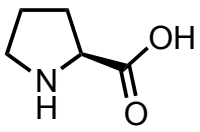
Tissue engineering → scaffold/matrix to promote cell growth

- Scaffolds: generally hydrogels with natural origin (hyaluronic acid, chitosan, collagen, gelatin).
- Important parameters: biocompatibility, biodegradability, mechanical and rheological properties, optical property (transparency in the case of cornea).

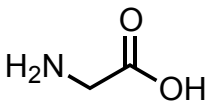
Gelatin and collagen hydrogels



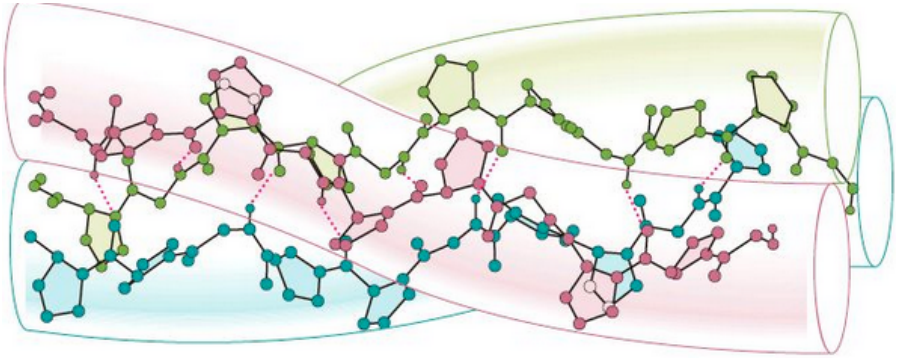
hydroxyproline



proline



glycine



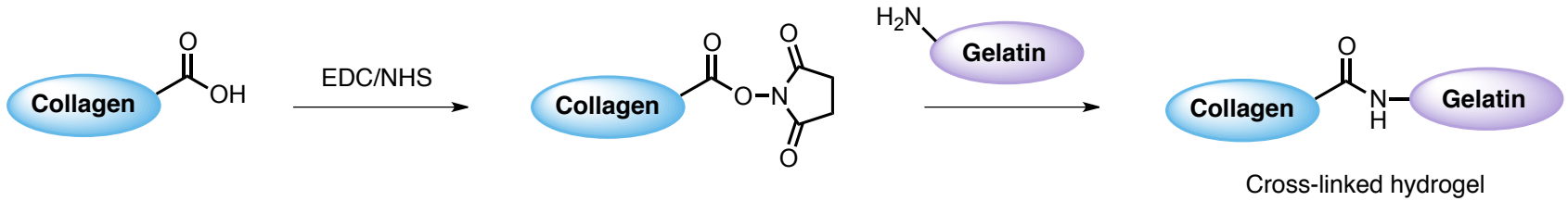
Collagen triple helix, ca. 1000 AA per helix

- Collagen (Col): primary molecule in native cornea = suitable biomaterial.
- Problem: pure collagen hydrogels not strong enough (too high water content) and degrade rapidly.
- Strategy to increase mechanical properties: cross-linking, hybrid synthesis by mixing with other hydrogel.
- Gelatin (Gel) formed by partial degradation of collagen, contains same amino-acids, transparent, biocompatible = also a good candidate for cell growing support.
- Topic of the article: synthesis and study of an hybrid Col/Gel hydrogel cross-linked with EDC/NHS method.

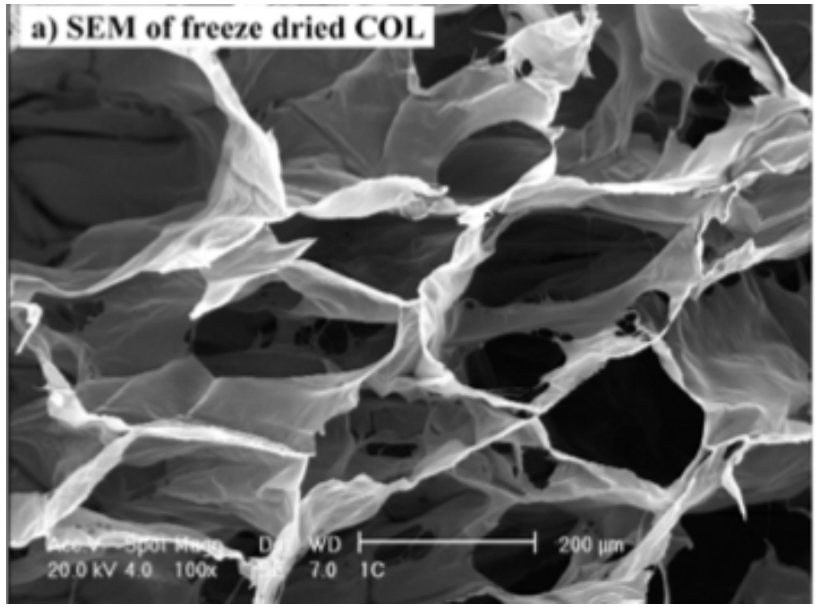
H. Aghamollaei et al. *Int. J. Biol. Macromol.* **2019**, *126*, 620.

Hybrid Col/Gel hydrogel synthesis

Preparation of a Col (1) / Gel (10) hybrid hydrogel, cross-linked with EDC/NHS procedure



- Scanning electron microscope (SEM) imaging.
- Porous structure with interconnected pores: important for cell proliferation and migration.

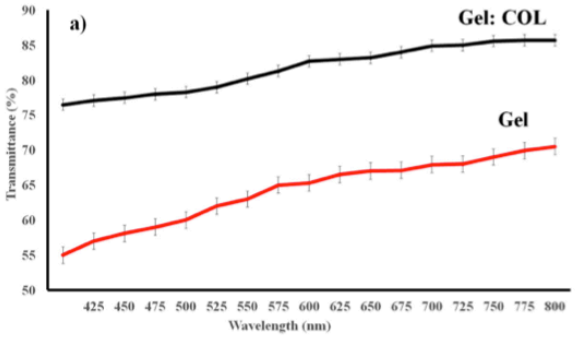


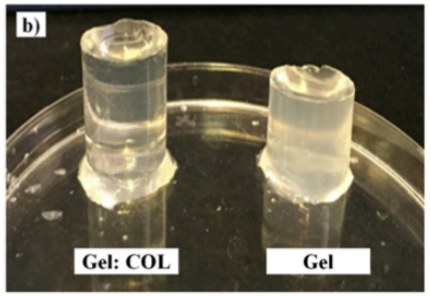
H. Aghamollaei et al. *Int. J. Biol. Macromol.* **2019**, *126*, 620.

Hybrid Col/Gel hydrogel properties

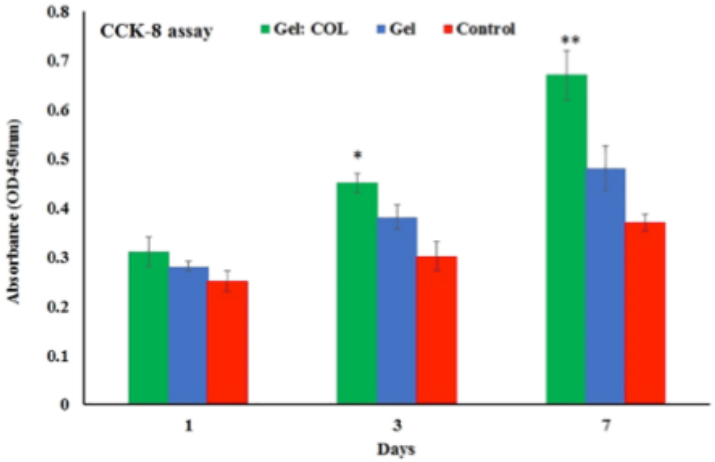
Comparison of Col/Gel properties with pure Gel

- Improved mechanical and rheological properties. Col/Gel more resistant to strain, more elastic.
- Good biodegradability in the presence of collagenase (important for a possible degradation *in vivo* after the implantation of the tissue).
- Higher transparency, important for corneal application.





- Higher cell survival and proliferation, tests realized with one of the existing cell source for corneal regeneration: human bone mesenchymal stem cells.



H. Aghamollaei et al. *Int. J. Biol. Macromol.* **2019**, *126*, 620.

Organic Process Research & Development

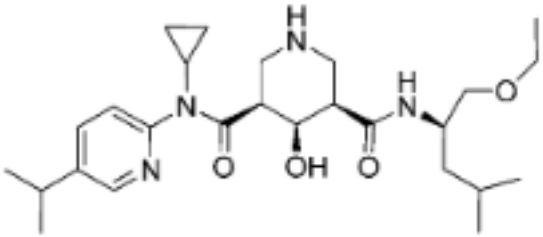
Article

pubs.acs.org/OPRD

Development of a Total Telescoped Synthesis of a Renin Inhibitor Containing 3,4,5-Substituted Piperidine with Sterically Hindered Amide Bonds

Wen-Chung Shieh,* Zhengming Du, Hongyong Kim, Yugang Liu, and Mahavir Prashad

Chemical and Analytical Development, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936, United States



1

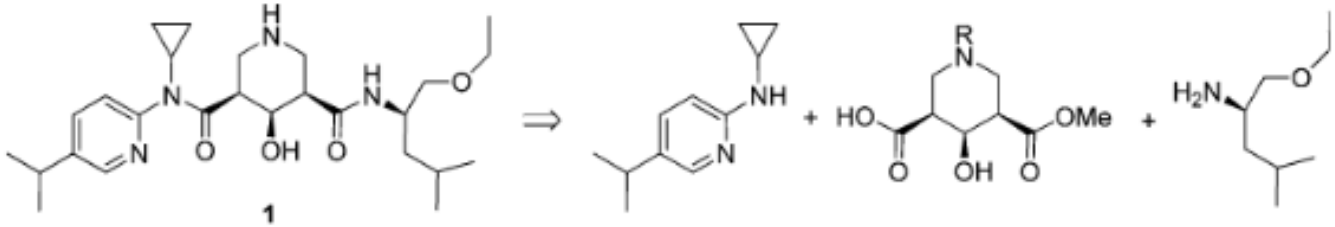
Figure 1. A renin inhibitor.

- Targeted molecule **1**: hypertension treatment
- Clinical trials: need for a synthesis allowing the production of several kilograms

Org. Process. Res. Dev. **2014**, *18*, 1339.

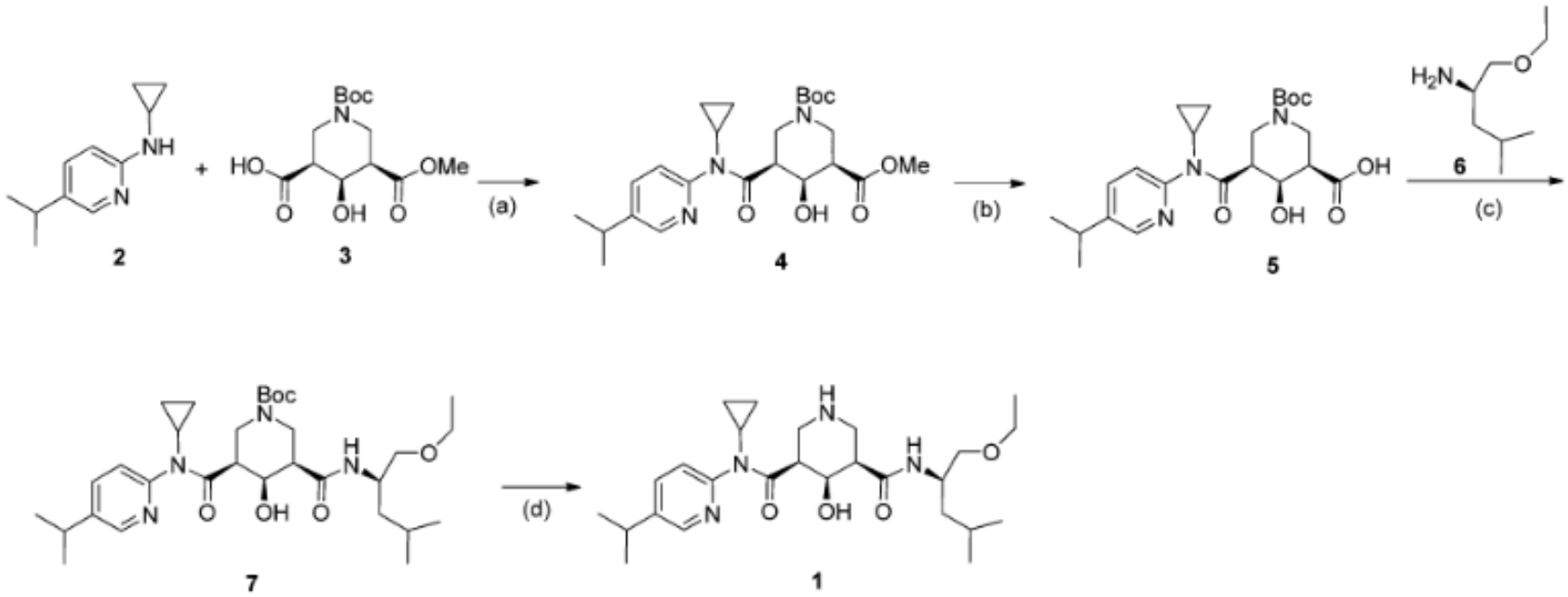
Retrosynthetic approach

Scheme 1. Retrosynthetic analysis of 1



- Strategy used by the medicinal chemists in the first synthesis of **1**.
- Challenge: formation of 2 sterically hindered amide bonds

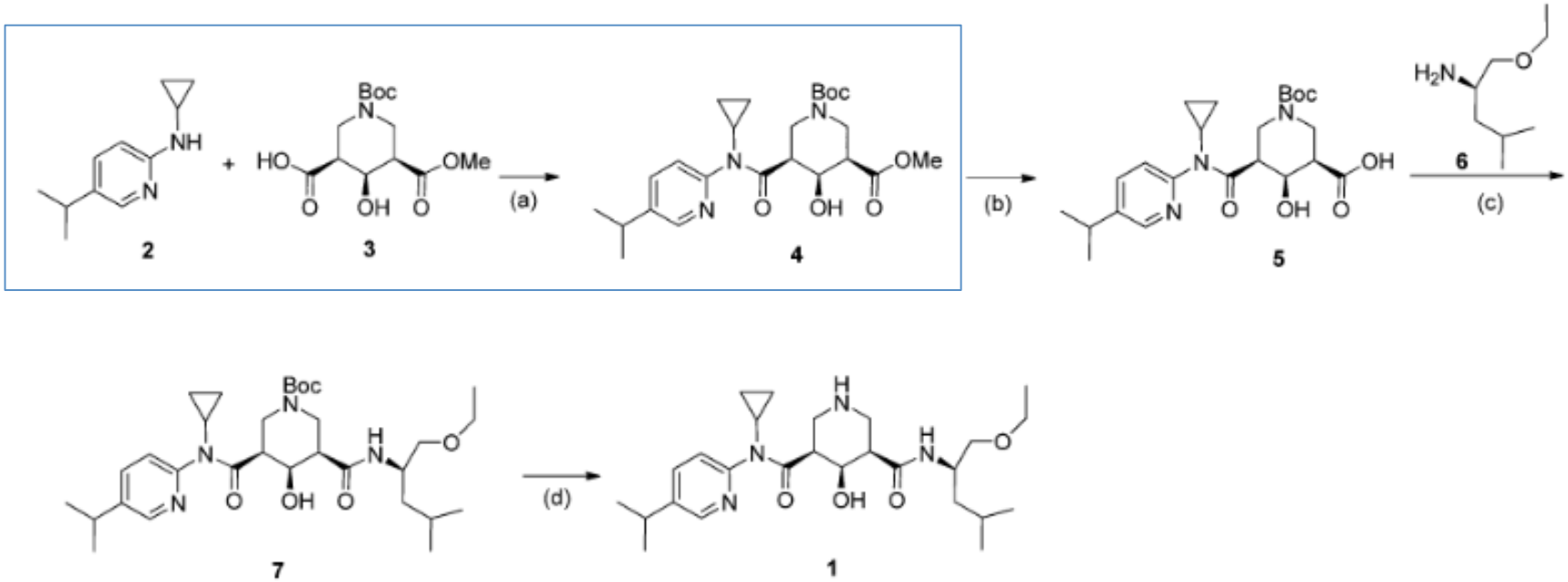
Initial research synthesis



[a]Reagents and conditions: (a) Ghosez reagent, CH_2Cl_2, 0–25 °C, chromatography; (b) 2.5 equiv of LiOH, THF, 0 °C, chromatography; (c) EDC–HCl, HOAt, Et_3N, CH_2Cl_2, 25 °C, chromatography; (d) 4 *N* HCl, dioxane, 25 °C.

- Four steps: 1st amide formation, selective ester saponification, 2nd amide formation, deprotection.
- Problem: purification by chromatography needed for **4**, **5** and **7** (non-crystalline intermediates), not suitable for scale up of the synthesis.
- To keep the same synthetic strategy: development of a telescoped synthesis ie no purification process.
- Need for very efficient and selective reactions (acceptable level of impurity level after each steps)

Optimization – First amidation



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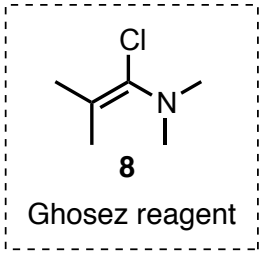
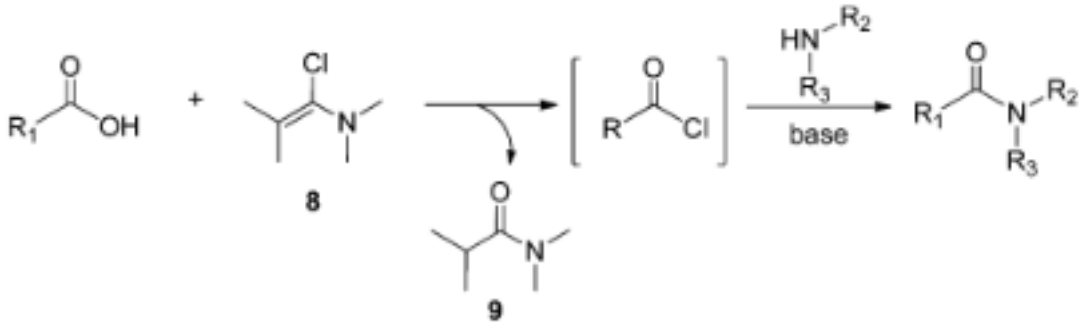
- Need for an efficient method to form the first amide bond.

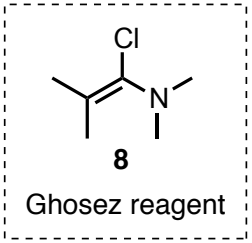
Optimization – First amidation

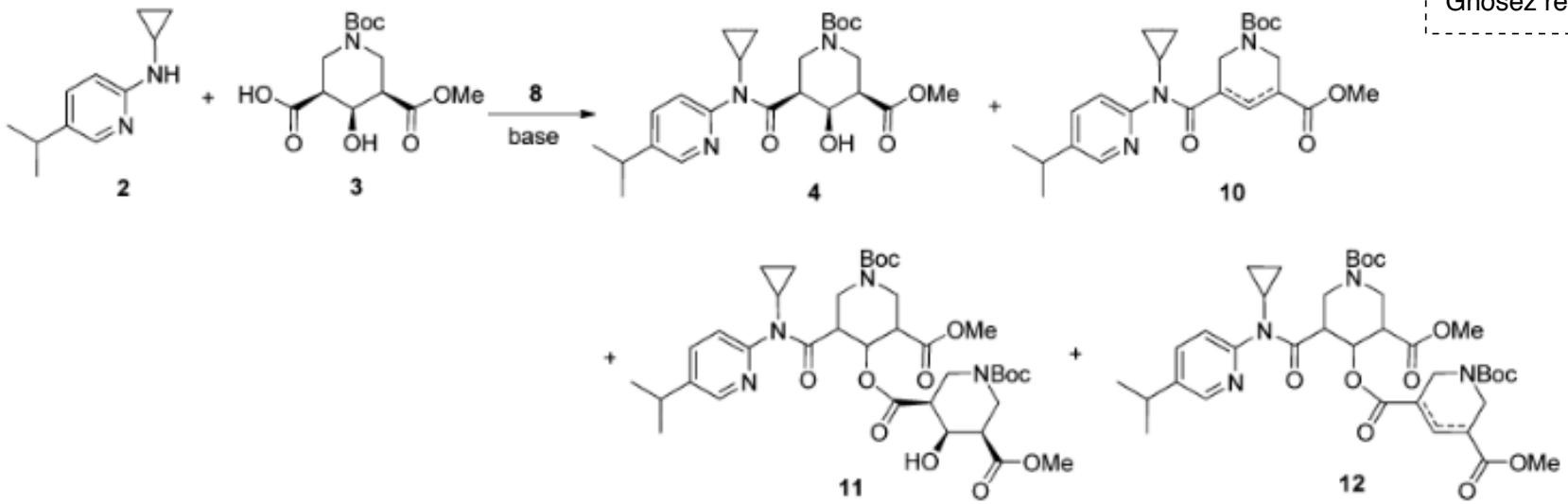




- *In situ* formation of the acyl chloride from the carboxylic acid.
- Side product: *N*,*N*-dimethylisobutyramide. Water soluble, easily removed by simple aqueous work-up.
- Ghosez reagent well adapted to the formation of sterically hindered amides
- Non-expensive and commercially available reagent.

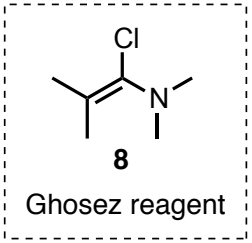
Optimization – First amidation



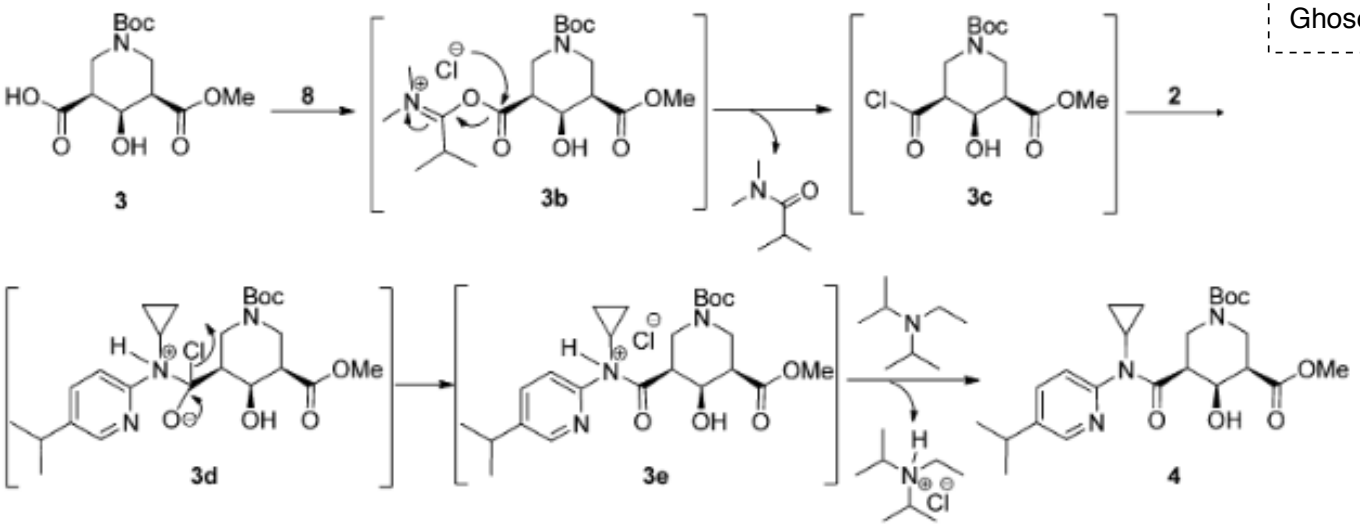


- First base tested: *N*,*N*-diisopropylethylamine (pK_a : 10.89), formation of 3 impurity observed resulting in ca. 70% yield in **4** (not acceptable for the telescoped synthesis)
- No impurity observed when **3** and **8** mixed without base nor amine (clean formation of the acyl chloride)

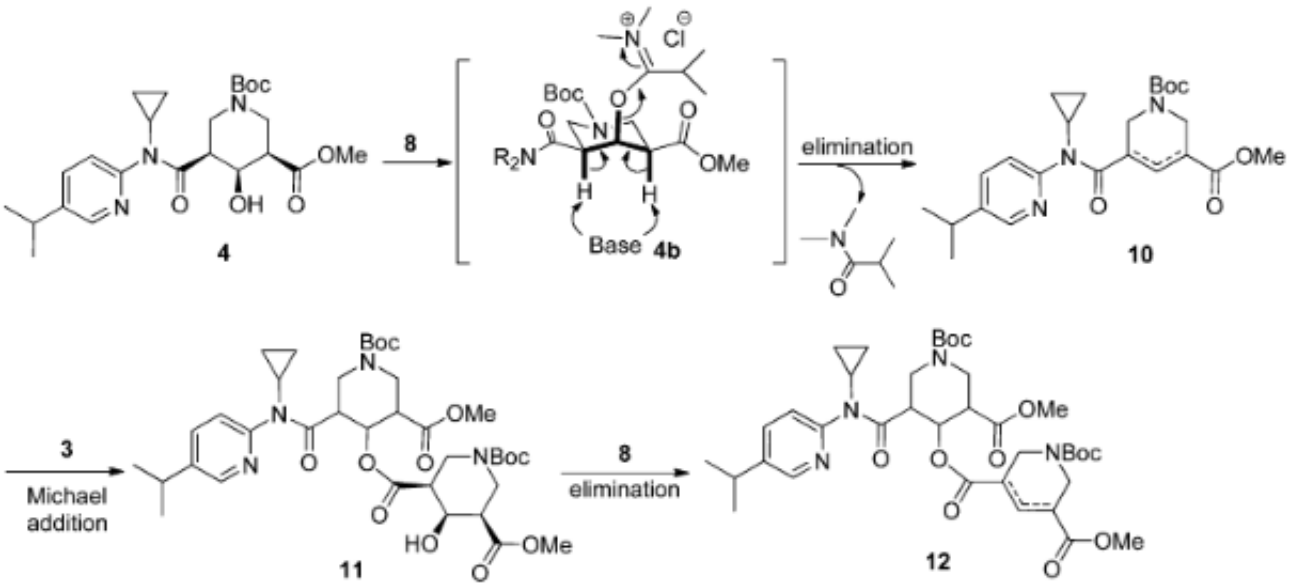
Optimization – First amidation



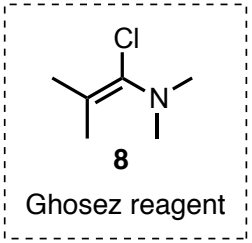
- Amidation mechanism

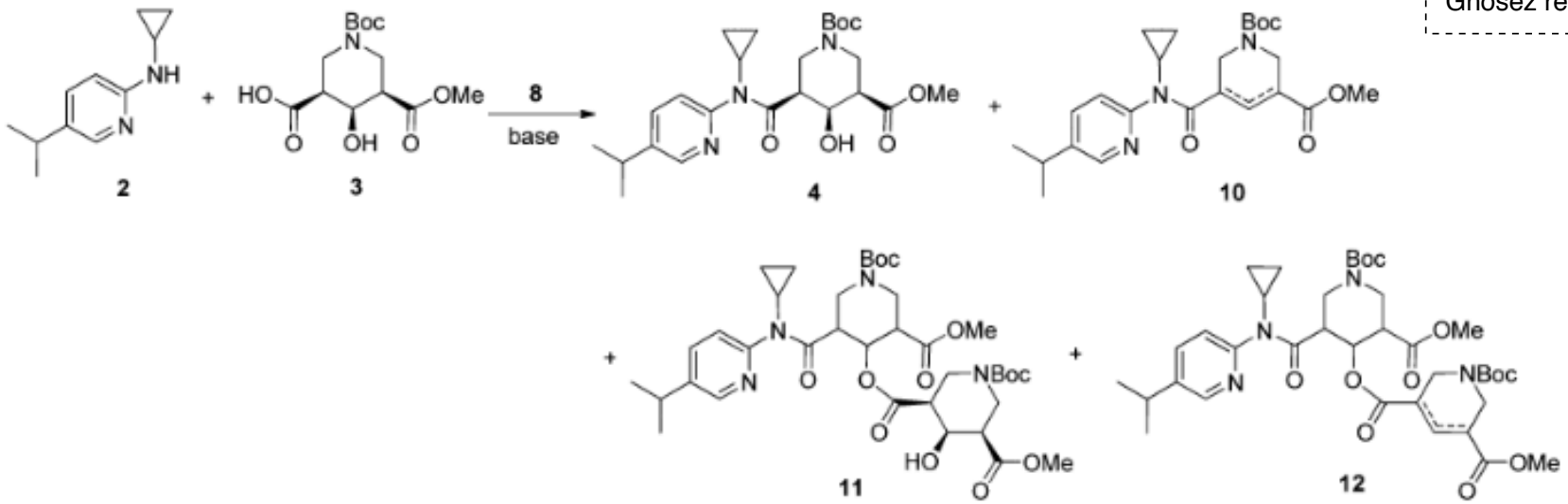


- Hypothesized mechanism for impurities formation



Optimization – First amidation

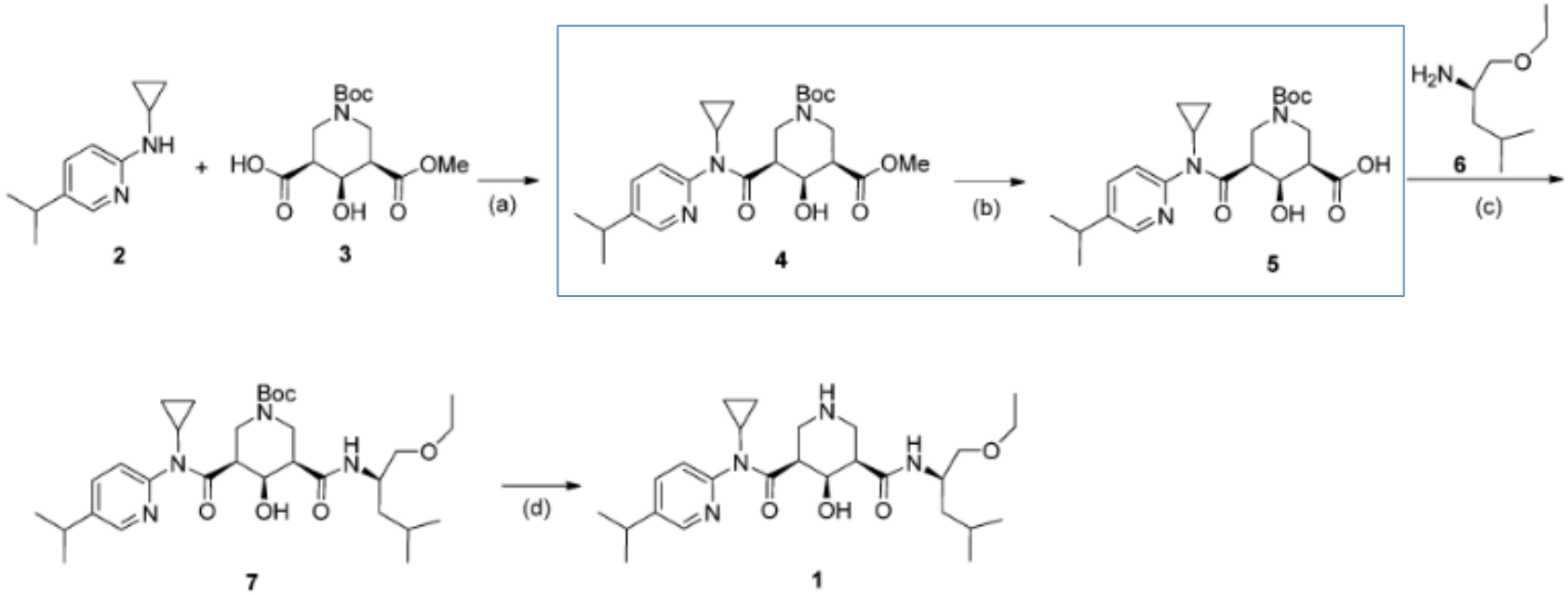




- Hypothesis: use of a weaker base than DIPEA (pK_a : 10.89) to avoid elimination reactions:
  - with N-methylmorpholine (pK_a : 7.58), 87% yield in **4**
  - with 2-*N*,*N*-dimethylaminopyridine (pK_a : 7.04), 98.4% yield in **4**

- Optimized conditions: **3**, Ghosez reagent in CH_3CN then **2** and 2-*N*,*N*-dimethylaminopyridine
- No need for purification.

Optimization – Chemoselective hydrolysis

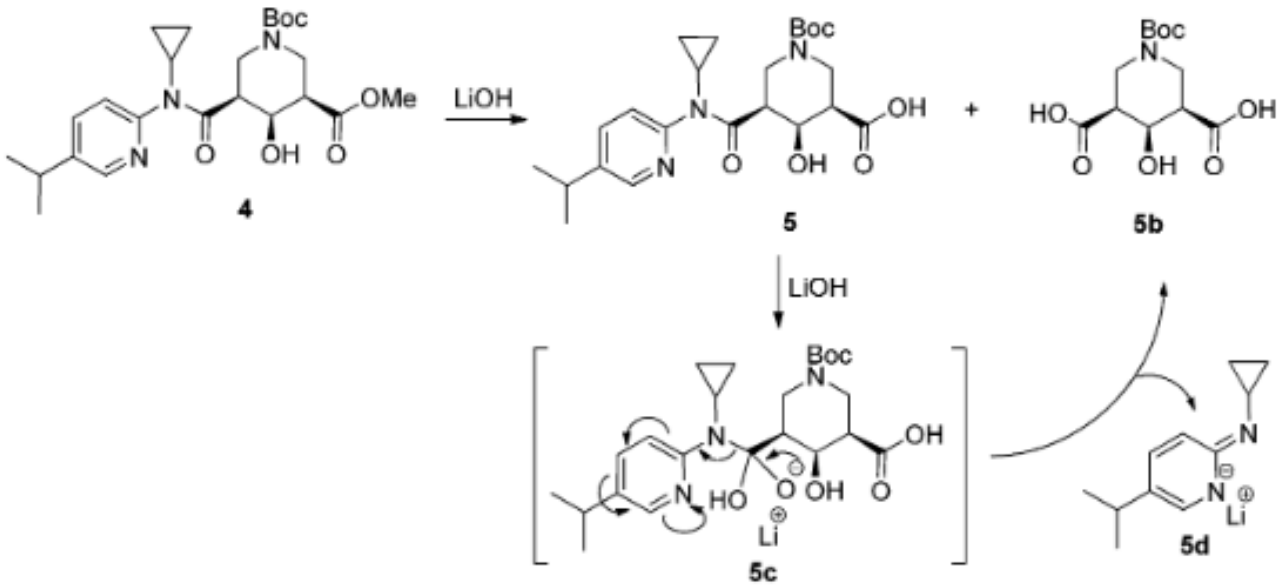


[a]Reagents and conditions: (a) Ghosez reagent, CH_2Cl_2, 0–25 °C, chromatography; (b) 2.5 equiv of LiOH, THF, 0 °C, chromatography; (c) EDC–HCl, HOAt, Et_3N, CH_2Cl_2, 25 °C, chromatography; (d) 4 *N* HCl, dioxane, 25 °C.

- Need to find conditions to selectively hydrolyze the ester without touching the amide linkage.

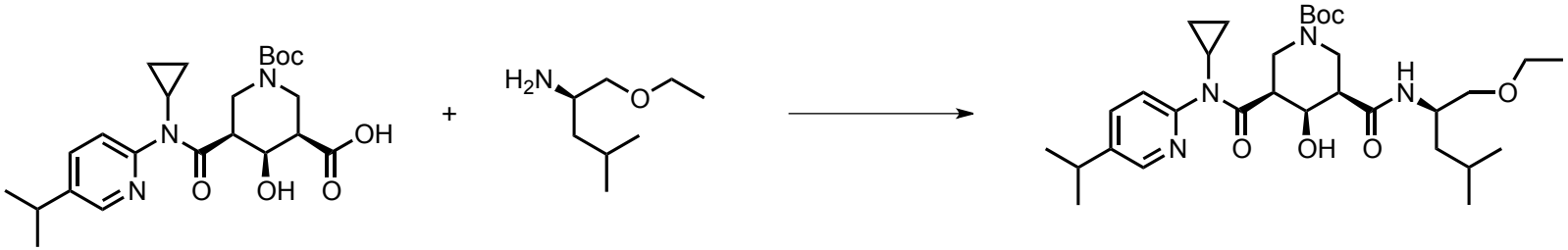
Optimization – Chemoselective hydrolysis

- First try: LiOH (1 equiv) in THF/H_2O. Problem: undesired diacid product formed (because of partial non-desired hydrolysis of the amide)

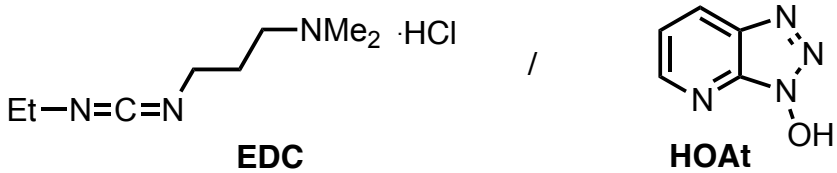


- Alternative: Karlsson procedure (Et_3N, LiBr in CH_3CN with 5 equiv of water). Slow generation of LiOH at low concentration supposed. In this case, mono-acid obtained in 99% yield, no more amide hydrolysis.
- Required a careful monitoring of the reaction (6 h).

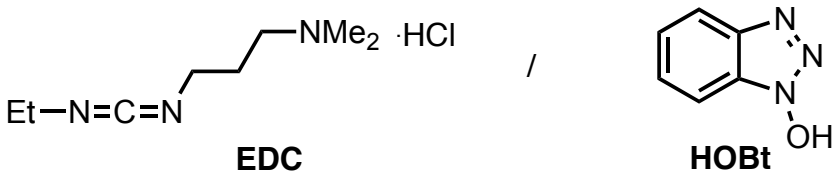
Optimization – Second amidation



- Medicinal chemists: formation of an activated ester with HOAt and EDC (urea side product water-soluble). Problem: HOAt hazardous (potential explosive).

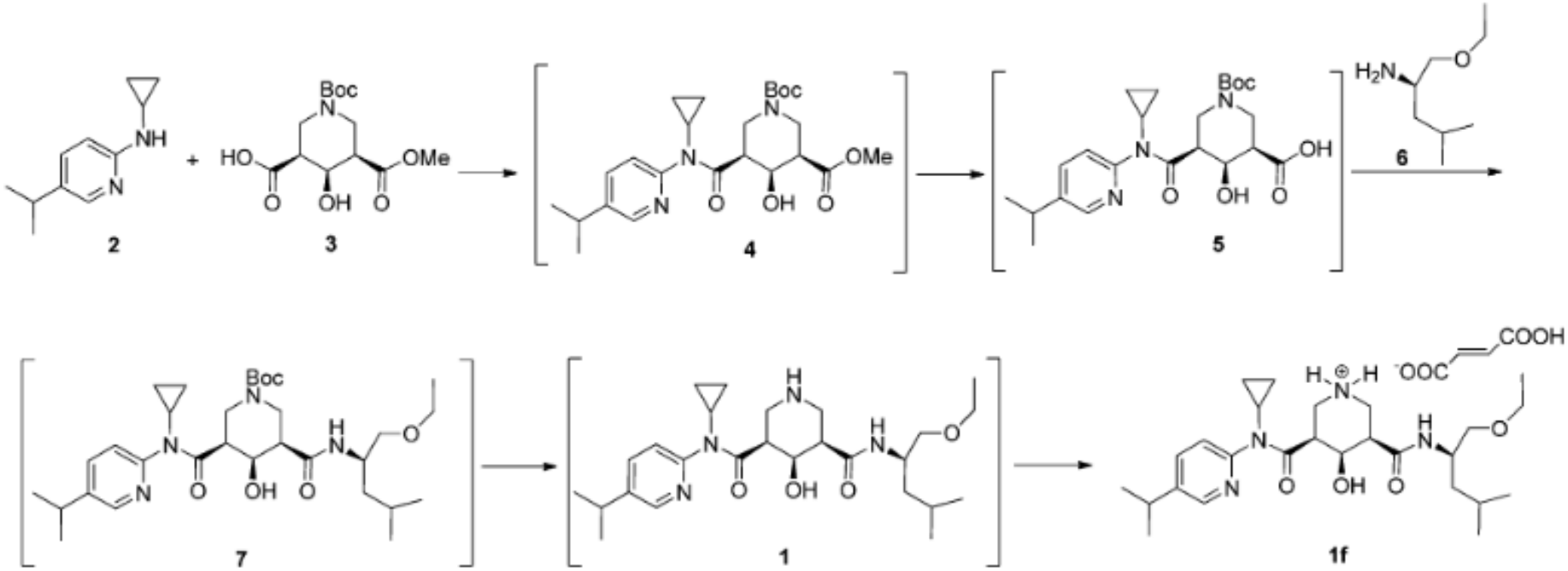


- Pilot: EDC was kept but HOAt was changed for the safer HOBt, already used in the pilot plant.



- Obtention of the amide in 99% yield with purity >98%.

End-game: telescoped synthesis



- Final Boc cleavage with 6 M aqueous solution of HCl (99% yield).
- Preparation of the fumarate salt (active pharmaceutical), isolated by filtration.
- Synthesis of 33.5 kg of the **A**ctive **P**harmaceutical **I**ngredient (API) with 99% purity in 54% overall yield from 31.5 kg of **3** in the plant.

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SYNTHETIC METHODS IN MOLECULAR CHEMISTRY (SMMC)

Outline

- **Reduction reactions**

  Reagents, products, selectivity issues

- **Formation of C=C bonds**

  Olefination reactions

  Metathesis reactions

- **Formation of C–C bonds**

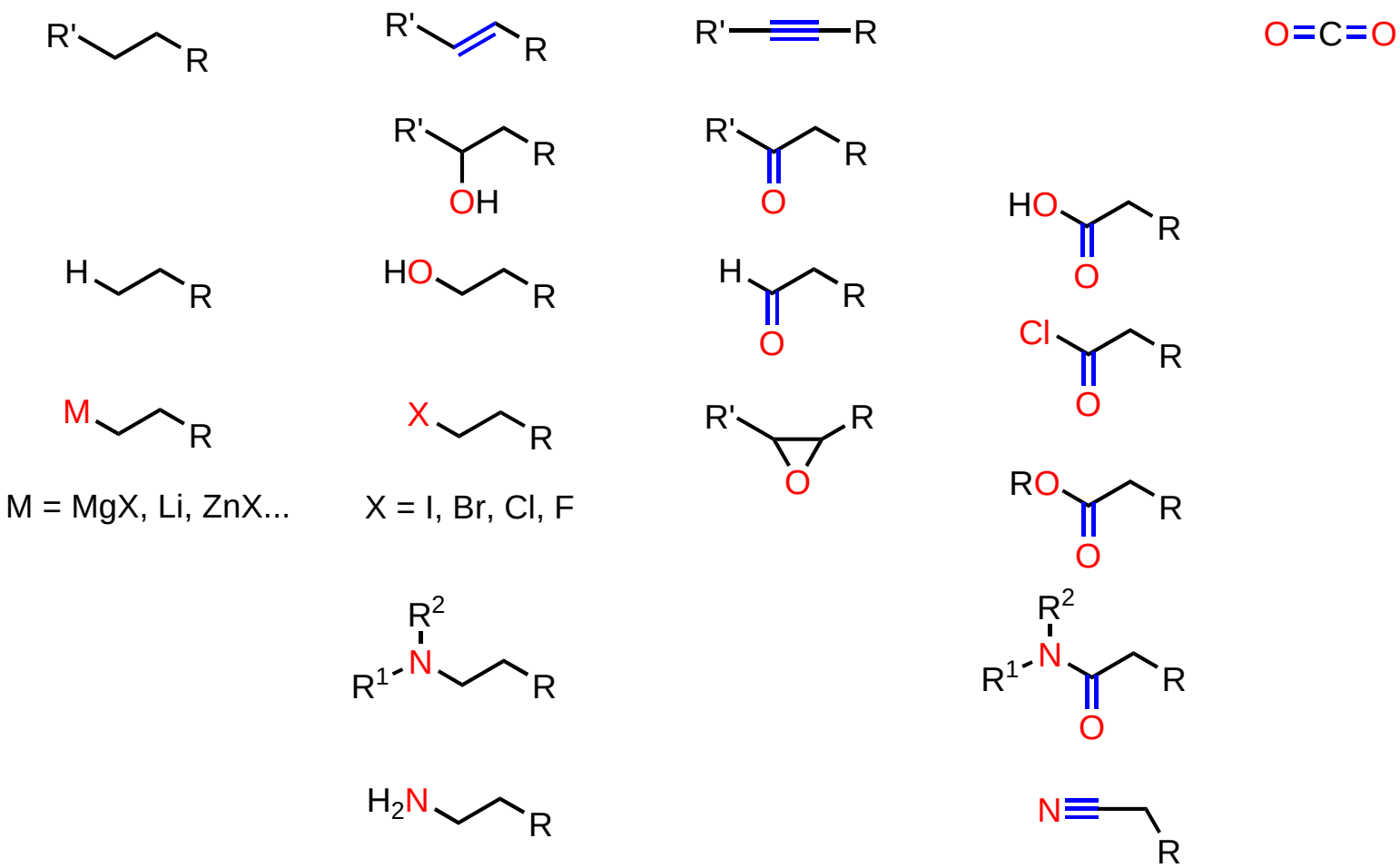
  Stabilized nucleophiles

  Main group organometallic reagents

  Transition metal-catalyzed cross-coupling reactions

2019

Functional groups - Valence table



Reduction reactions

Reducing agents

H_2

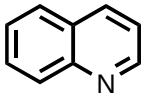
Heterogeneous catalysis

Metals : Pd, Pt, Ni, Rh, Ru

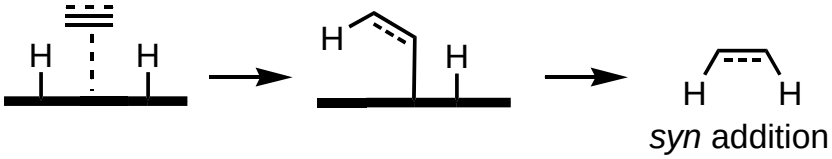
Supports : charcoal, alumina, silica, $CaCO_3$, $BaSO_4$

Solvents: usually protic (MeOH, EtOH, AcOH), EtOAc...

Easy separation of catalyst (filtration)

Activity can be modulated with poisons : Pb, 

(quinoline), sulfur compounds



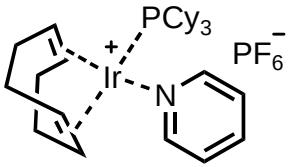
Homogeneous catalysis

Transition metal complex (Rh, Ru, Ir, ...)

Chiral ligands can be used (enantioselective hydrogenations)

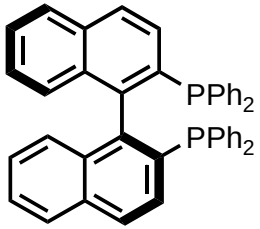
$RhCl(PPh_3)_3$

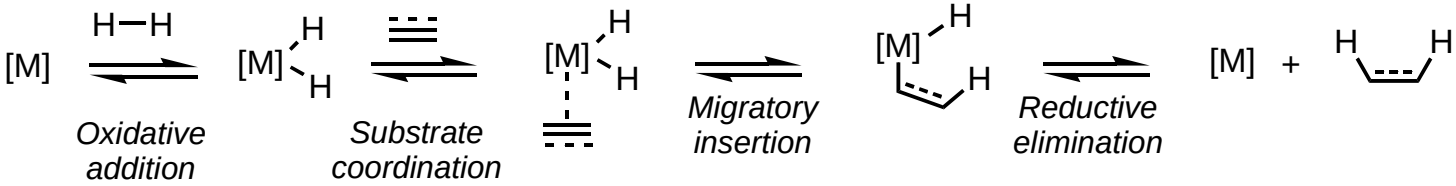
Wilkinson's catalyst



Crabtree's catalyst

(a*R*)-(+)-BINAP





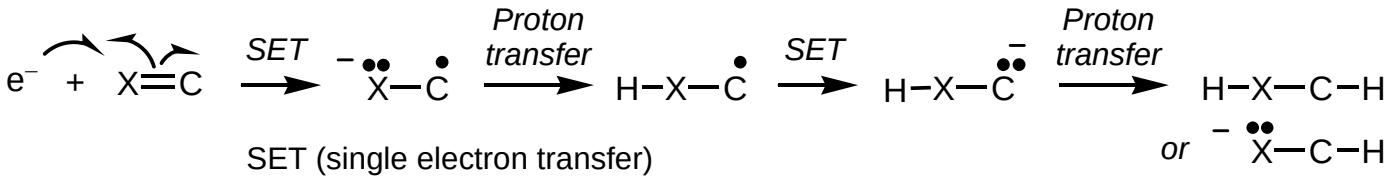
(or the reverse order)

Reducing agents

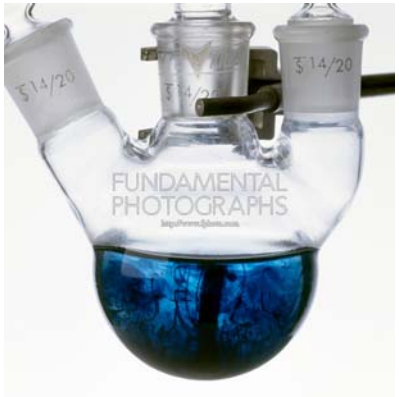
e^-

"Dissolving metal reductions"

$$M \xrightarrow[\text{liq. } NH_3]{} \underset{\text{blue solution}}{M^+ + e^-(NH_3)_n} \xrightarrow[\text{cat. } Fe(NO_3)_3]{} MNH_2 + 1/2\ H_2$$



SET (single electron transfer)

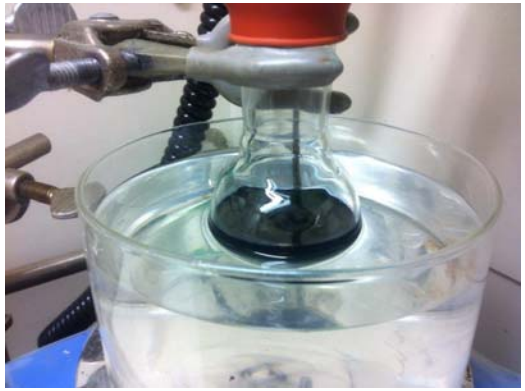


https://www.fphoto.com/

Reducing metals : Mg, Fe, Zn, Sn, Al ...(usually under acidic conditions)

Metal amalgams : Na(Hg), Mg(Hg), Al(Hg)

https://twitter.com/hubertmuchalski/



Reducing inorganic metal salts : $CrCl_2$, **SmI_2** ("Kagan's reagent")

$$2\ Sm + 3\ I_2 \longrightarrow 2\ SmI_3$$

$$2\ SmI_3 + Sm \longrightarrow 3\ SmI_2$$

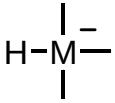
blue solution
(0.1 M in THF)

$$Sm + I(CH_2)_2I \longrightarrow SmI_2 + \ =$$

Reducing agents

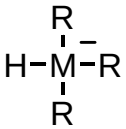
M−H Metal hydrides

M = B, Al	χ (H) = 2.20
(group IIIA)	χ (B) = 2.04
	χ (Al) = 1.61

Nucleophilic hydride donors 

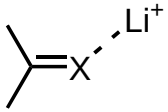
$LiAlH_4$ reacts violently with water, alcohols...
solvents: anhydrous THF or Et_2O
must be handled with care
powerful reducing agent (not chemoselective)

$NaBH_4$ easy to use
solvents: MeOH, EtOH, even wet organic solvents
mild reducing agent (chemoselective)

Reactivity of  M'^+ depends on:

- the metal Al > B
- the substituents

- the counter-cation (M'^+) : $Li^+ > Na^+$



(X = O, N)

If R has a +I effect : reactivity increases ($LiBH_4$ versus $LiEt_3BH$ = " Super hydride® ")

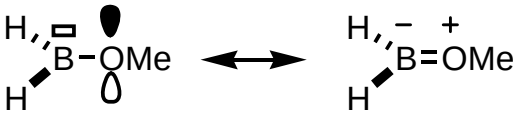
If R has –I effect : reactivity decreases ($LiAl(OEt)_3$ versus $LiAlH_4$ and $NaBH_3(CN)$ versus $NaBH_4$)

but if R = alkoxy group, +M effect also has to be considered

$NaBH_3(OMe)$ is more reactive than $NaBH_4$

$$NaBH_4 \xrightarrow[\text{MeOH}]{} NaBH_3(OMe) + H_2$$

releases a hydride more efficiently than $NaBH_4$



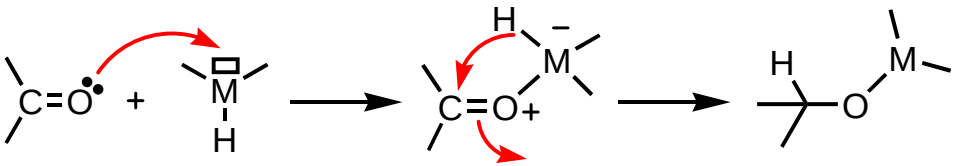
(B, O are on the same period unlike Al)

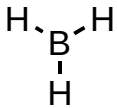
Reducing agents

M−H **Group III A metal hydrides** (M = B, Al)

Electrophilic metal hydrides

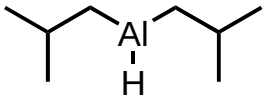
Lewis acidic metal





Borane

solutions of BH_3.THF or BH_3.SMe_2 in THF
commercially available

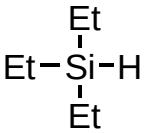


DIBAL-H (Diisobutylaluminum hydride)

solutions in CH_2Cl_2, toluene, hexane
commercially available

Group IVA metal hydrides (M = Si, Ge, Sn)

Silicon hydrides (silanes)

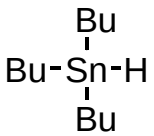


reduces only reactive species
(carbocations)

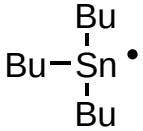
(Si and Sn are not significantly
Lewis acidic in these species)

Tin hydrides : widely used in radical reactions

(toxic reagents)



weak Sn-H bond
BDE = 78 kcal/mol



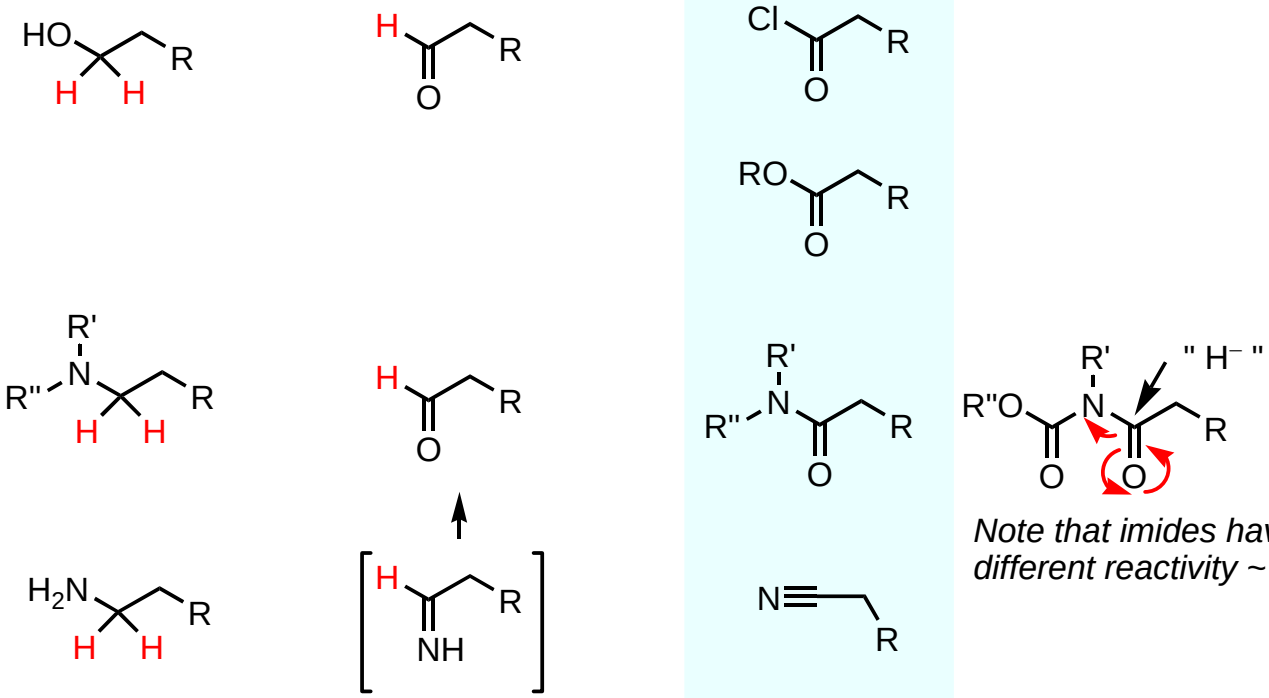
tin-centered radical has a strong
affinity for halides, sulfur, selenium

Reduction of carboxylic acid derivatives

Aldehydes are more reactive toward reducing agents than carboxylic acid derivatives

"Full" reduction to alcohols/amines

"Partial" reduction to aldehydes

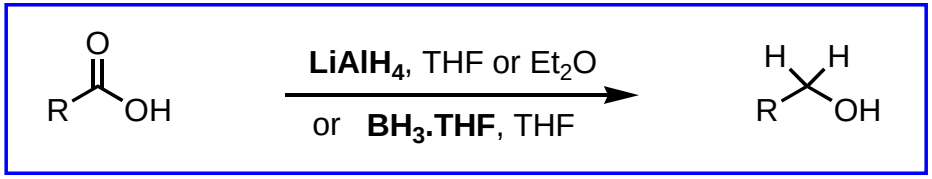


Reactivity depends on the reducing agent (carboxylate formed)

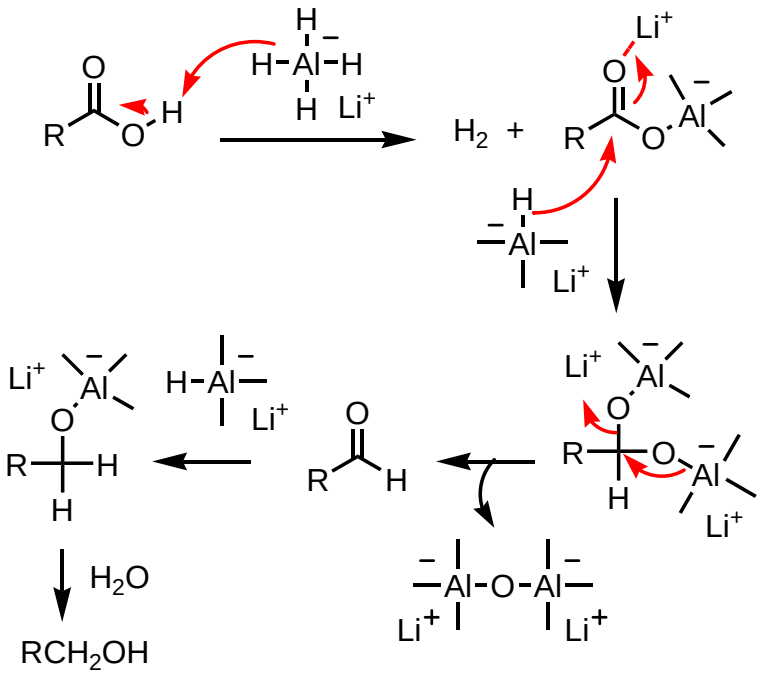
Note that imides have a different reactivity ~ esters

Reduction

Reduction of carboxylic acids



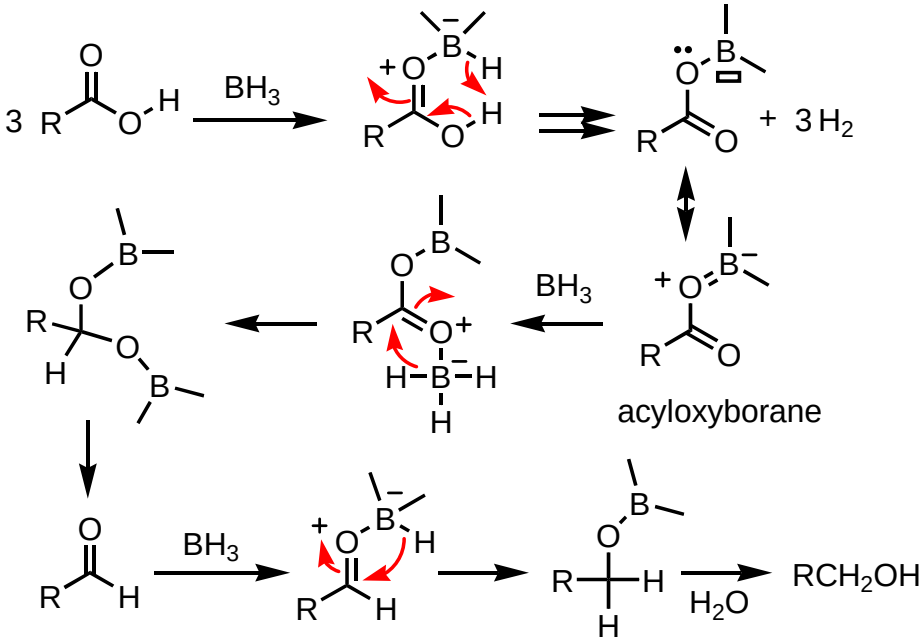
With $LiAlH_4$



$LiAlH_4$ will reduce all carboxylic acid derivatives

C=C are not reduced

With BH_3

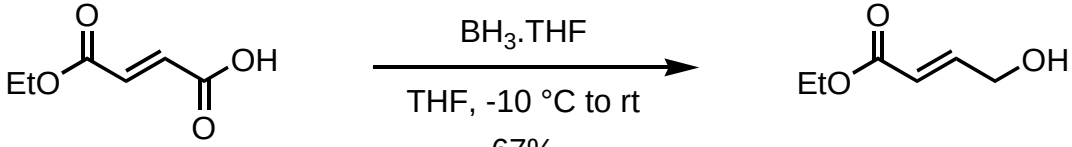


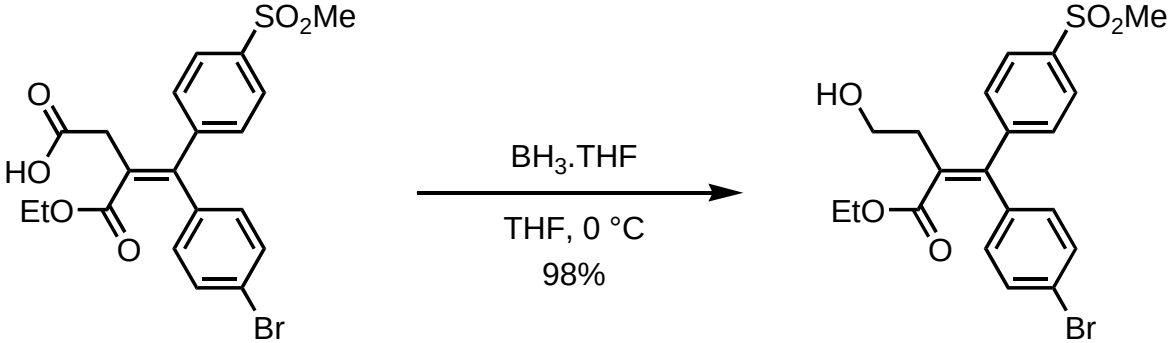
$RCONR^1R^2$ also reduced (slow)

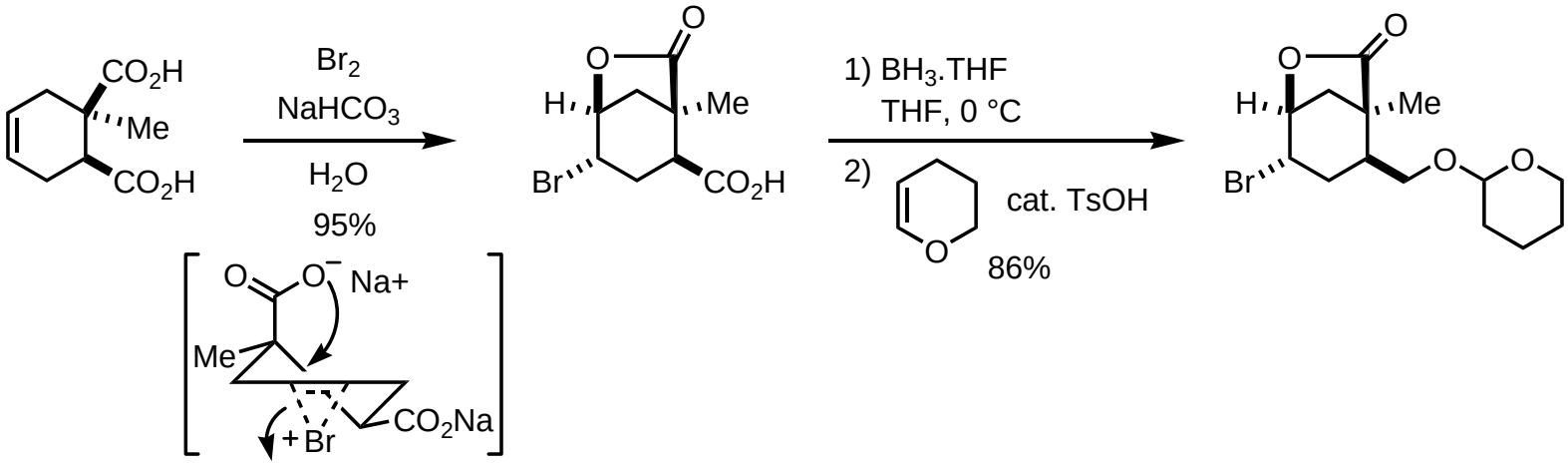
RCOCl, RCO_2R', RCN, reduced at a much slower rate

C=C usually incompatible (hydroboration)

Reduction of carboxylic acids

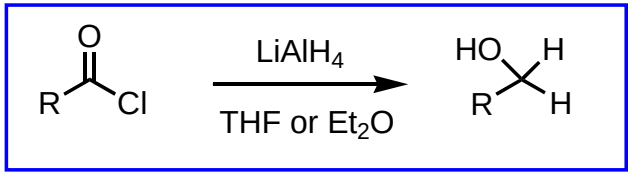




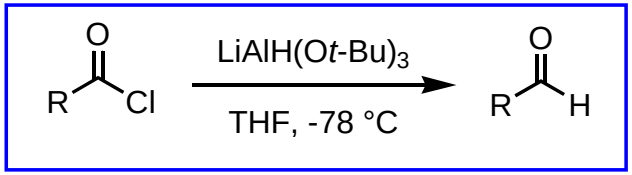


Org. Proc. Res. Dev. **2004**, *8*, 1072; *J. Org. Chem.* **1975**, *40*, 579

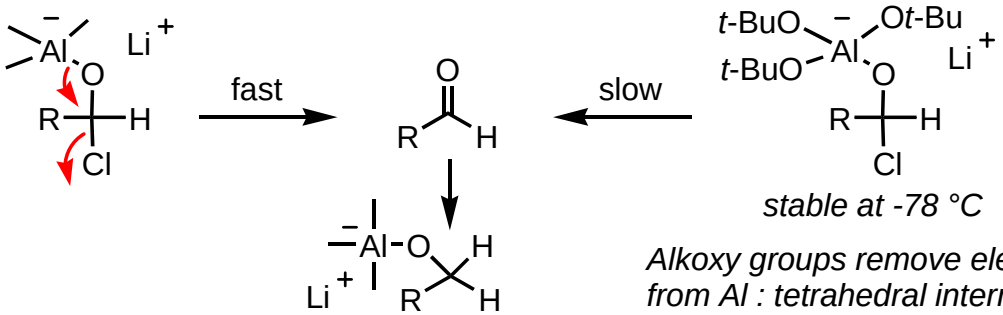
Reduction of acid chlorides



Usually the carboxylic acid itself is reduced



Other acid derivatives are usually preferred to access aldehydes by partial reduction

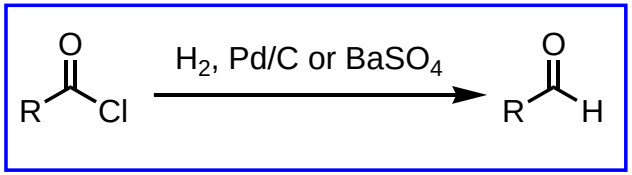


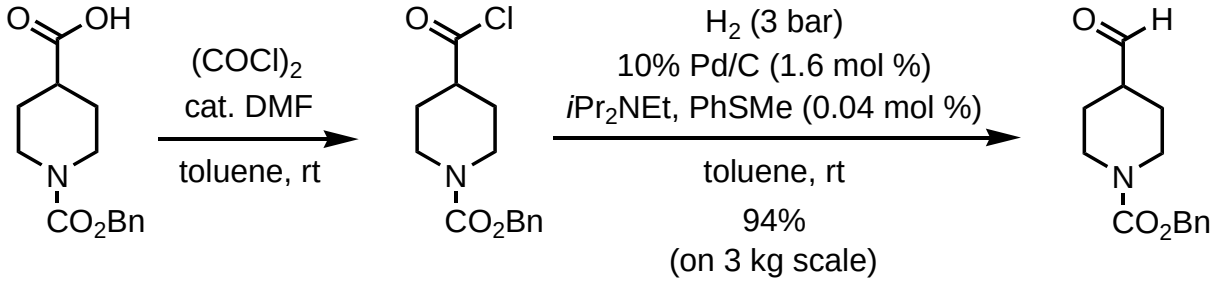
stable at -78 °C

Hindered reagent :
RCHO, RCOR', RCOCl reduced
esters/amides usually tolerated

Alkoxy groups remove electron density from Al : tetrahedral intermediate more stable

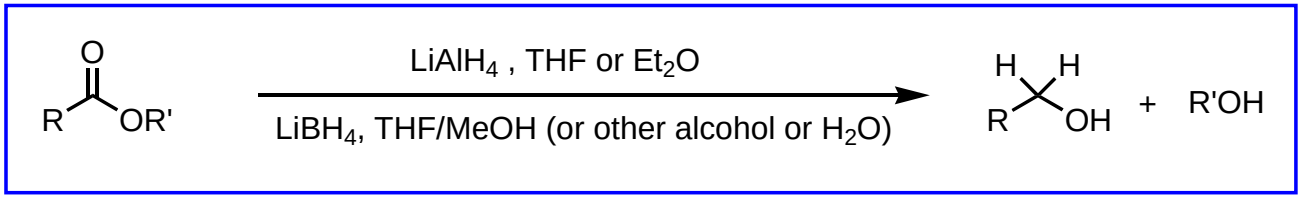
Old but useful alternative:
Rosenmund reaction



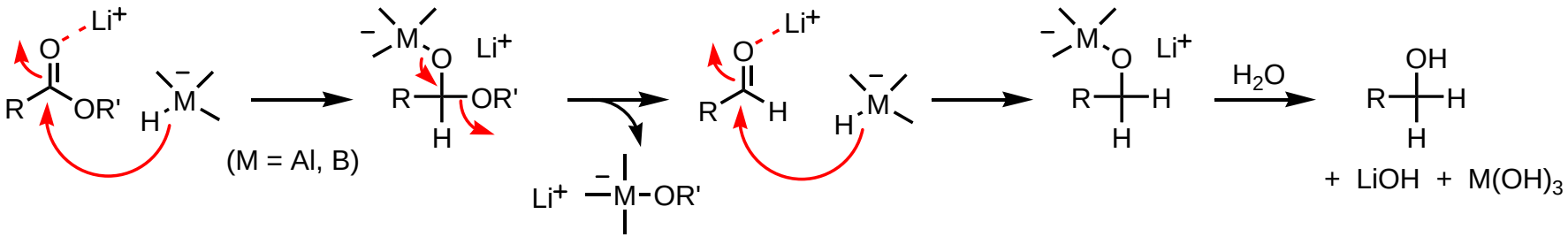


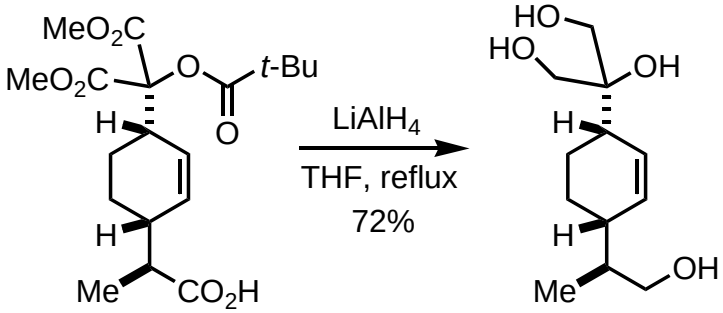
JACS **1958**, *80*, 5372; *Tetrahedron* **1997**, *53*, 10983

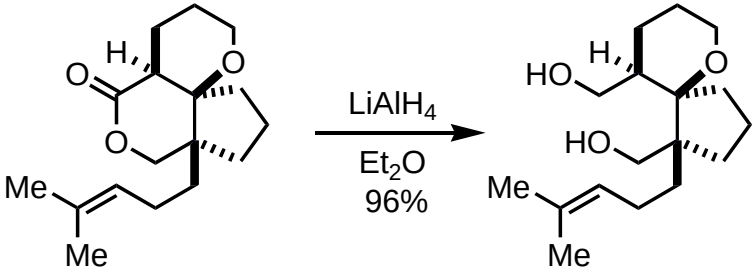
Reduction of esters to alcohols

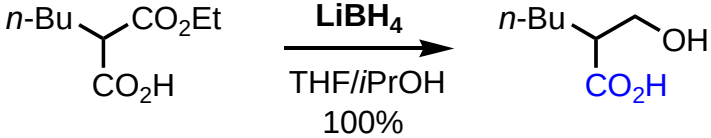


$LiBH_4$ more chemoselective than $LiAlH_4$ (RCO_2H, RCONR'R", RCN are tolerated)



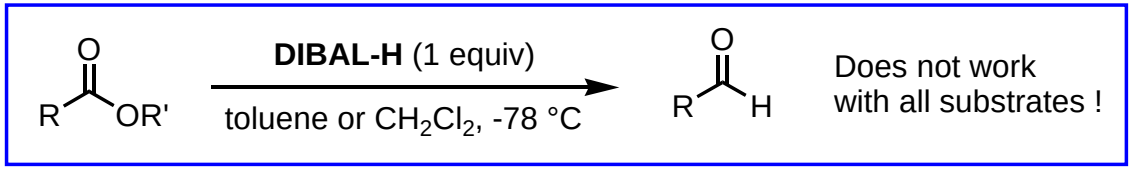




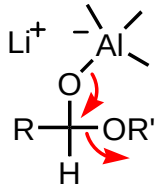


J. Org. Chem. **1992**, *57*, 3578; *J. Org. Chem.* **2000**, *65*, 5072; *Org. Proc. Res. Dev.* **2007**, *11*, 90

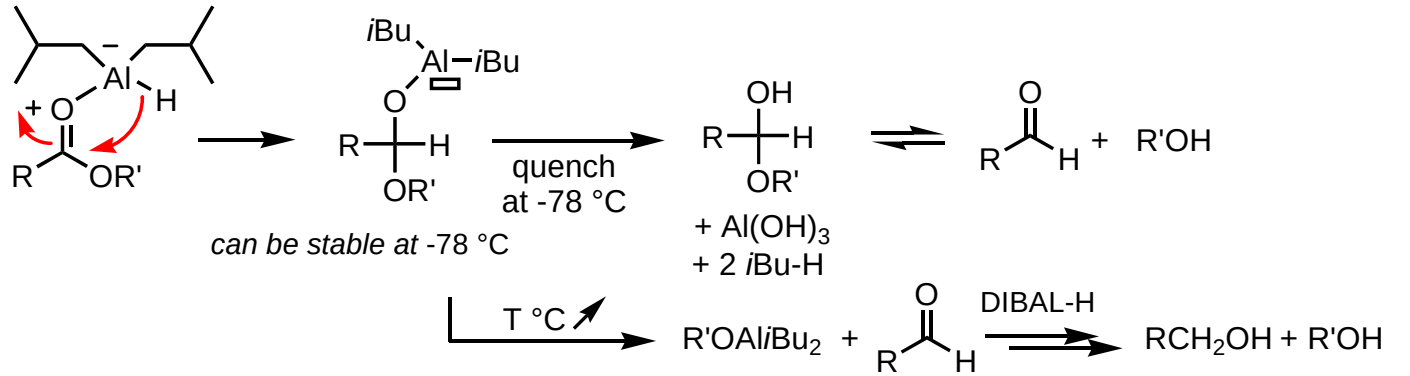
Partial reduction of esters to aldehydes



With $LiAlH_4$

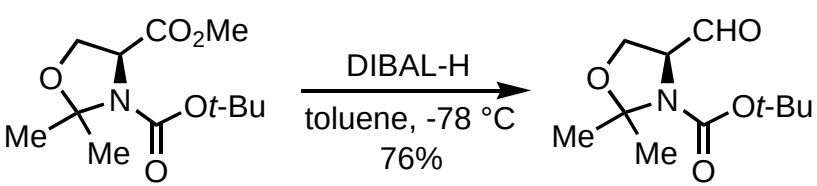


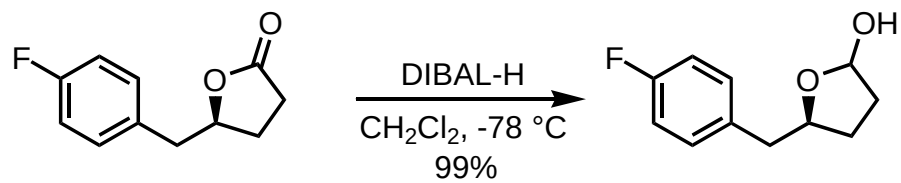
unstable tetrahedral intermediate

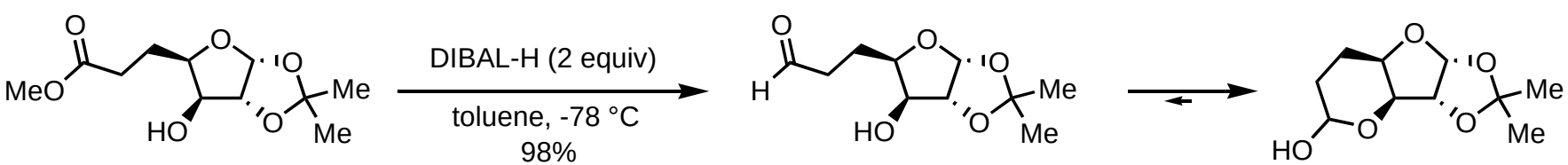


can be stable at -78 °C

With 2 equiv of DIBAL-H and without careful control, RCH_2OH + R'OH are obtained

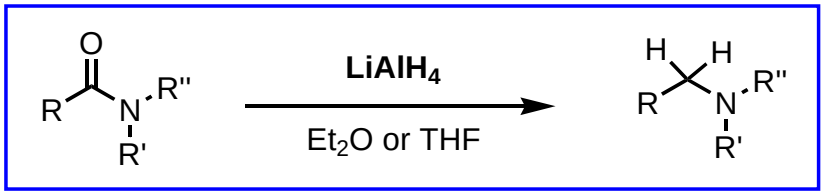




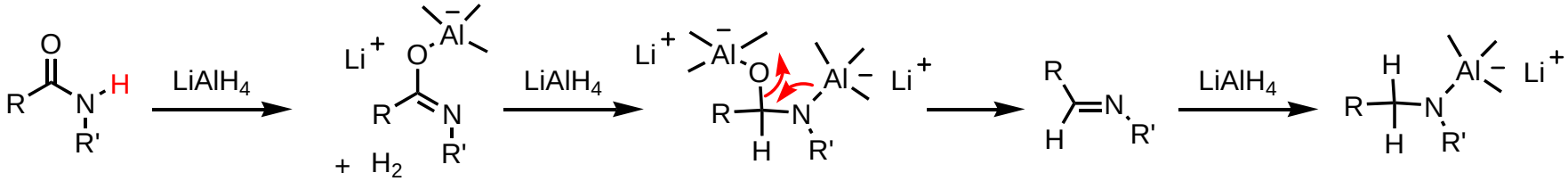


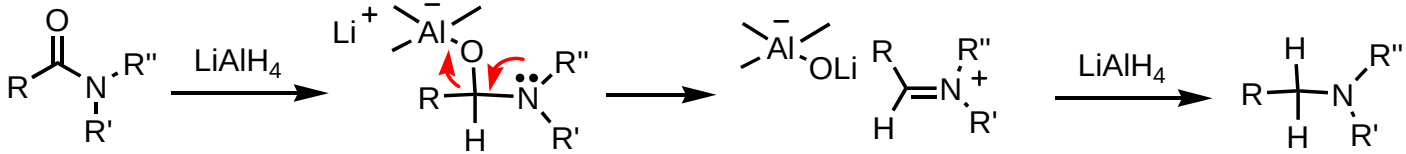
Org. Synth. **1991**, *70*, 18; *Org. Proc. Res. Dev.* **1999**, *3*, 76; *Tetrahedron* **1993**, *49*, 6669

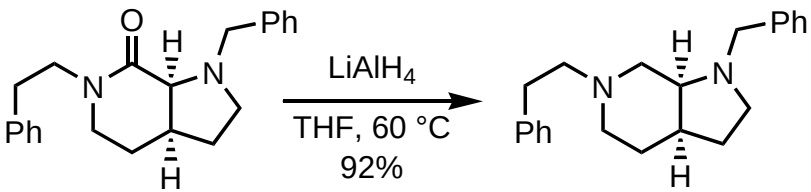
Reduction of amides to amines

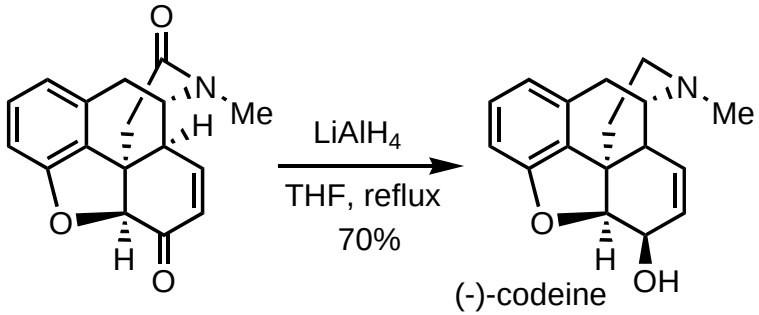


Alternative reagent:
BH_3.THF, THF
(slower than $LiAlH_4$)
but can tolerate esters



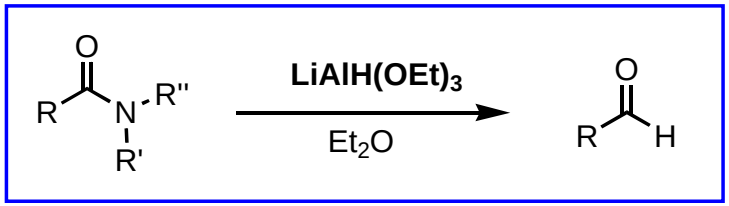


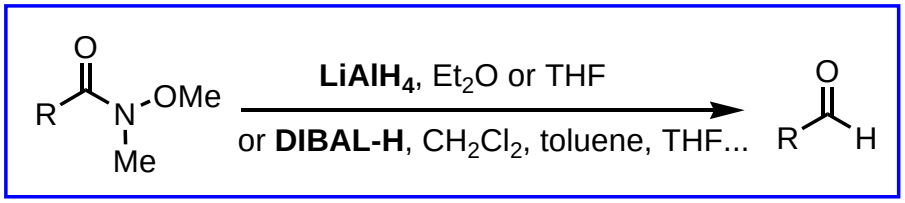


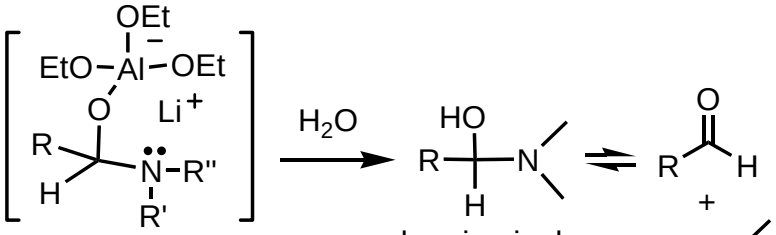


Org. Proc. Res. Dev. **2007**, *11*, 711; *J. Org. Chem.* **1999**, *64*, 7871

Partial reduction of amides to aldehydes



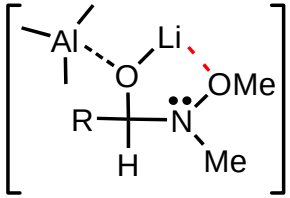




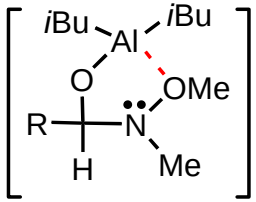
More stable tetrahedral intermediate

Weinreb amides

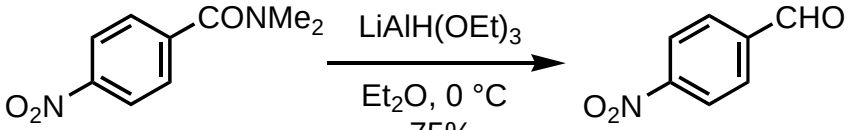
with $LiAlH_4$

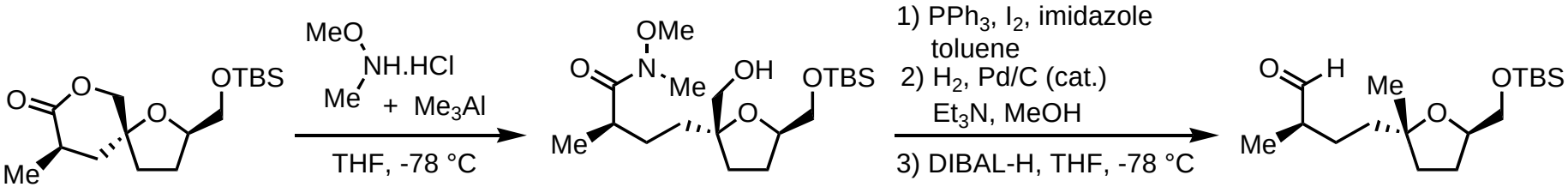


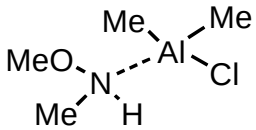
with DIBAL-H



Stabilization by chelation



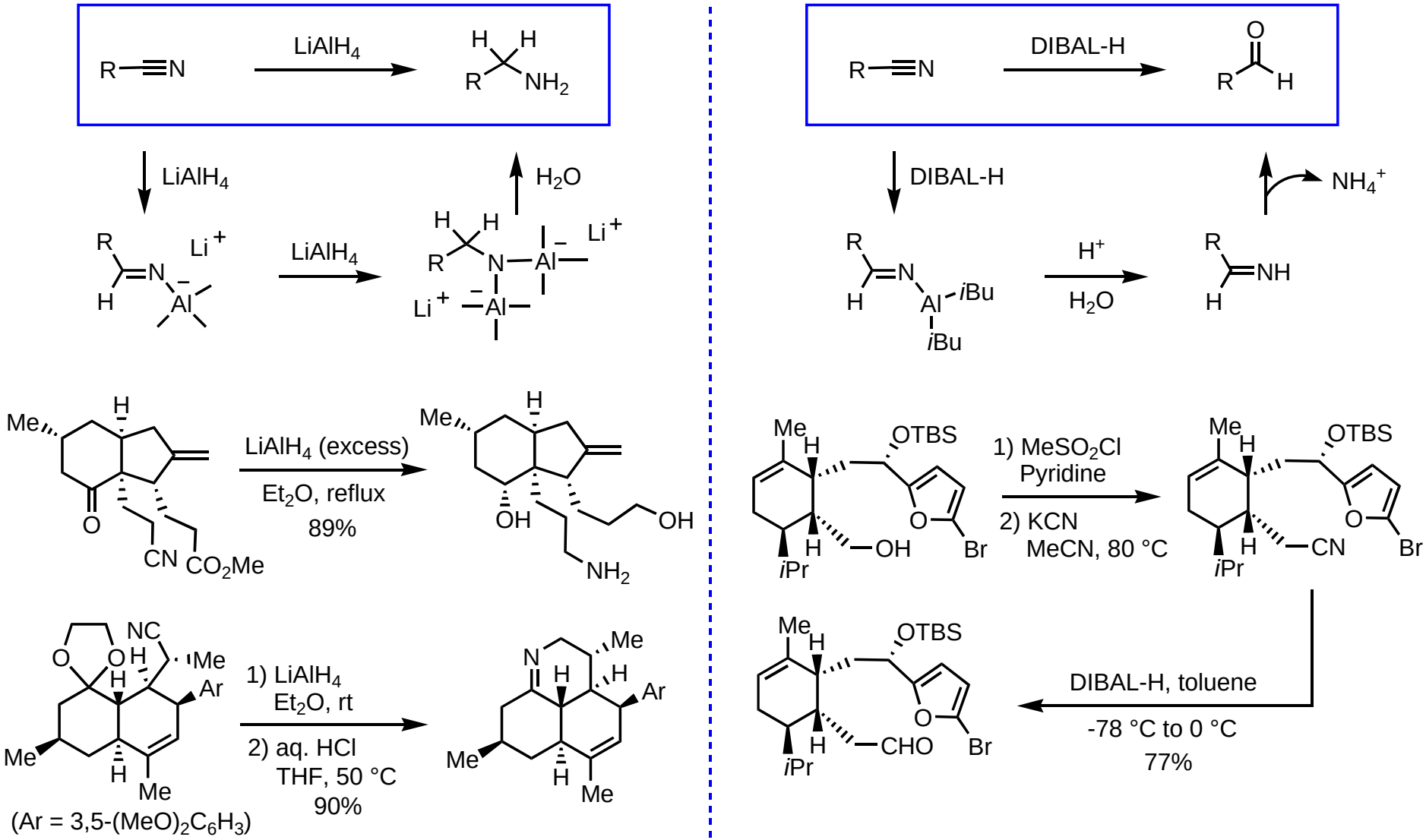




generated *in situ*

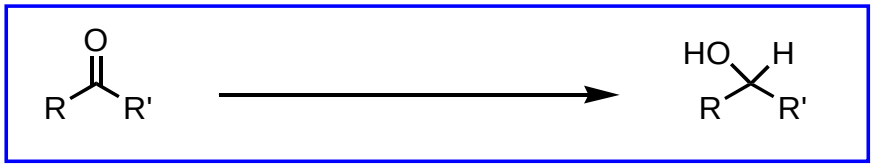
Weinreb amides: Tetrahedron Lett. **1981**, *22*, 3815, application: *Angew. Chem. Int. Ed.* **2017**, *56*, 14883

Reduction of nitriles



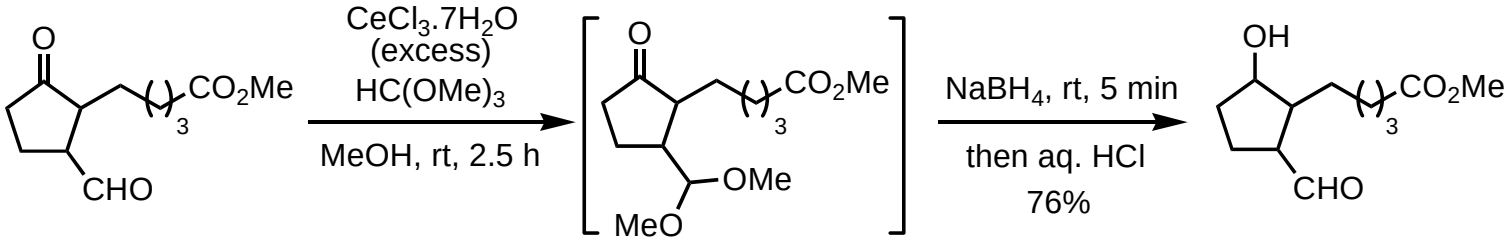
J. Org. Chem. **1989**, *54*, 1548; *Org. Lett.* **2007**, *9*, 1461; *JACS* **1999**, *121*, 6563

Reduction of aldehydes and ketones



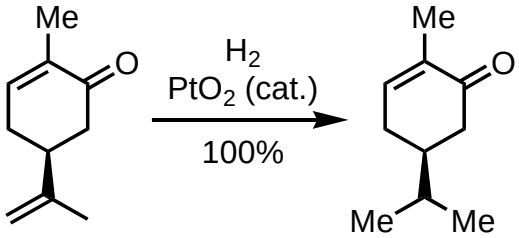
Facile reaction with almost all hydrides: $NaBH_4$, $LiBH_4$, $LiAlH_4$, $LiAlH(OR)_3$, DIBAL-H, BH_3 (slow with ketones)

Reagent of choice for chemoselective reductions

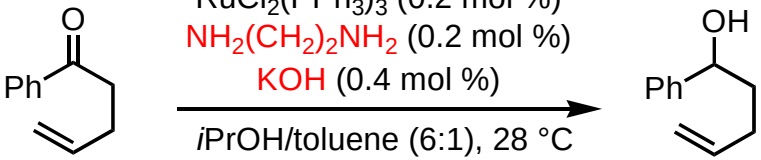


Catalytic hydrogenation: often Pt and Ru

C=C C≡C C=N C≡N are usually more reactive



Homogeneous catalysis

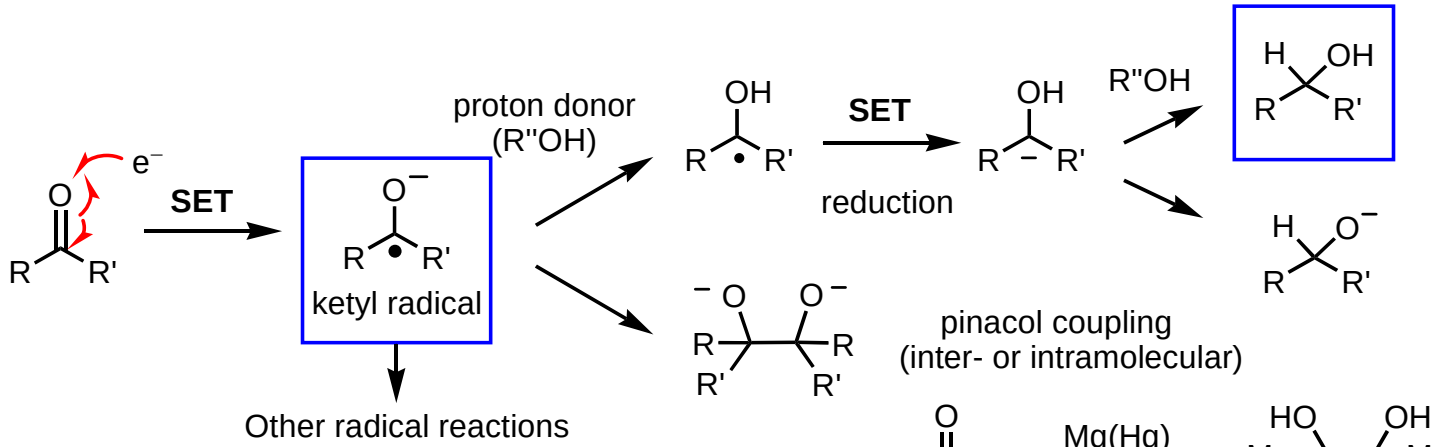


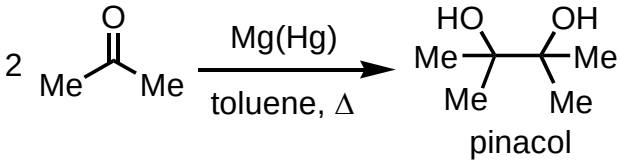
A ternary catalytic system allows for chemoselective hydrogenation of the carbonyl

Can. J. Chem. **1990**, *68*, 127

JACS **1995**, *117*, 10417

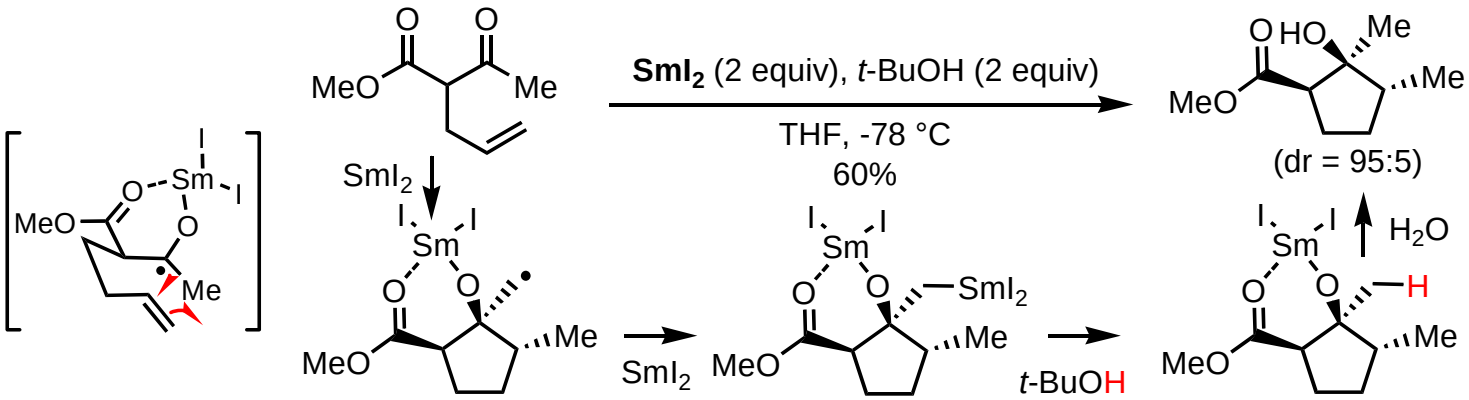
Reduction of aldehydes and ketones by electron transfer





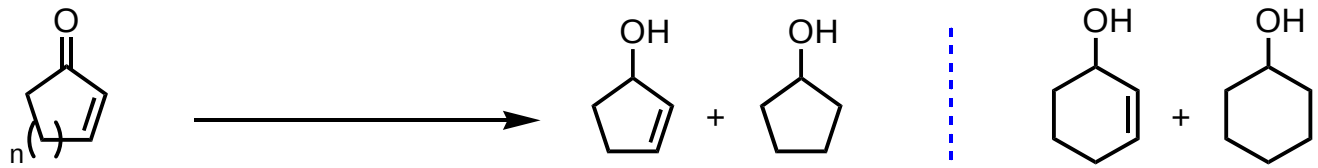
Reagents

Li, Na or K in liquid NH_3, THF/*t*-BuOH
SmI_2, THF/MeOH (or *i*PrOH, *t*-BuOH)
photoinduced electron transfer : hν (254 nm)/Et_3N



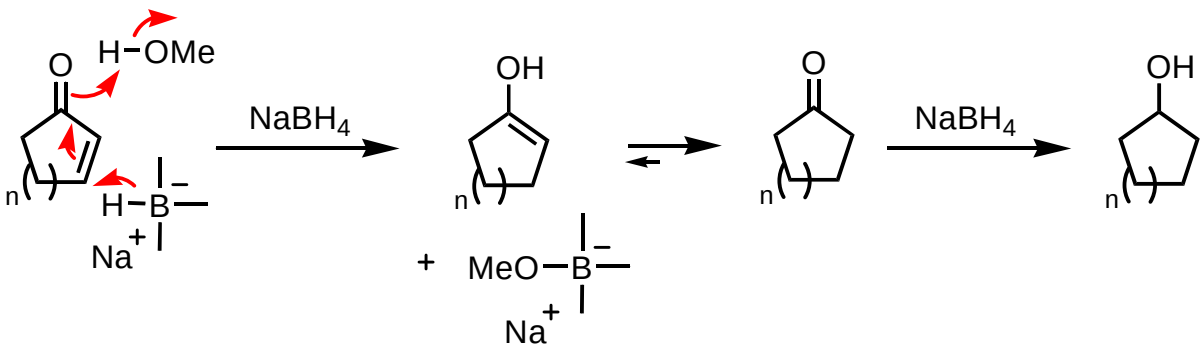
JACS **1989**, *111*, 8236; *Angew. Chem. int. Ed.* **2009**, *48*, 7140 (review)

Reduction of α,β-unsaturated aldehydes and ketones



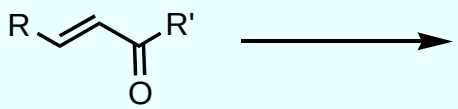
$LiAlH_4$, Et_2O	85	:	15	94	:	6
DIBAL-H, CH_2Cl_2	98	:	2	98	:	2
$NaBH_4$, MeOH	0	:	100	60	:	40
$NaBH_4$, $CeCl_3$, MeOH	**> 99**	:	**< 1**	**> 99**	:	**< 1**

Luche reduction: $NaBH_4$, $CeCl_3.7H_2O$, MeOH (1,2-addition)

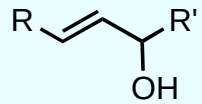


J. Org. Chem. **1979**, *44*, 4187; *JACS* **1978**, *100*, 2226; **1981**, *103*, 5454

Reduction of α,β-unsaturated aldehydes and ketones



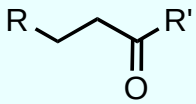
1,2-reduction



Reagents : $NaBH_4$, $CeCl_3$, MeOH

DIBAL-H, CH_2Cl_2

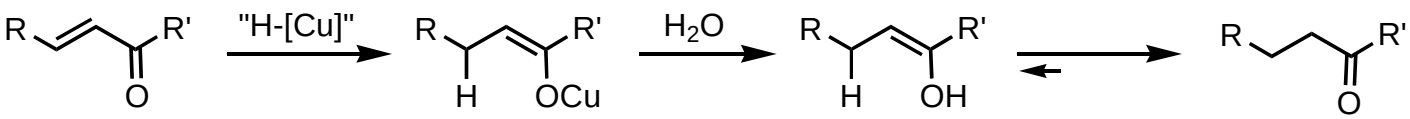
1,4-reduction

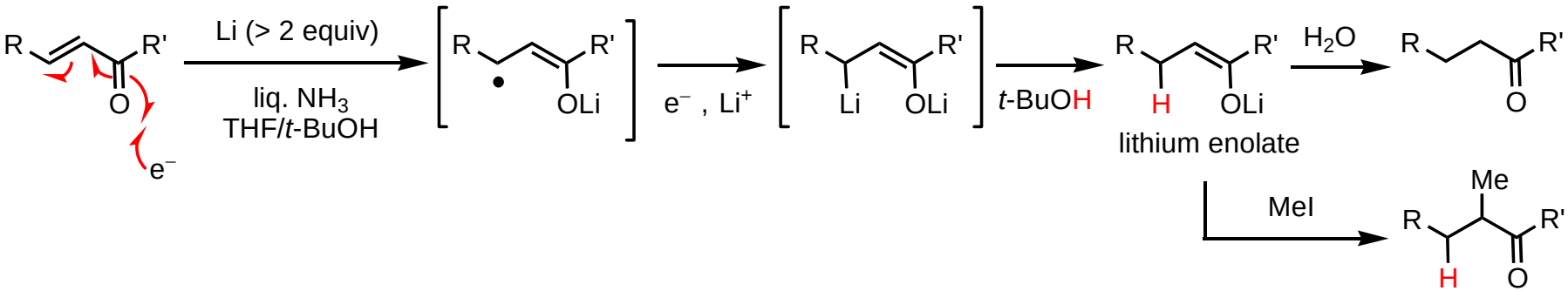


H_2, Pd/C (cat.), EtOH or PtO_2 (cat.), EtOAc

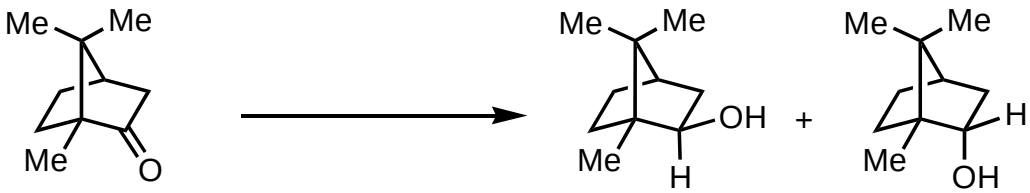
$[(Ph_3P)CuH]_6$, toluene/H_2O (Stryker's reagent)

Li, liq. NH_3, THF/*t*-BuOH

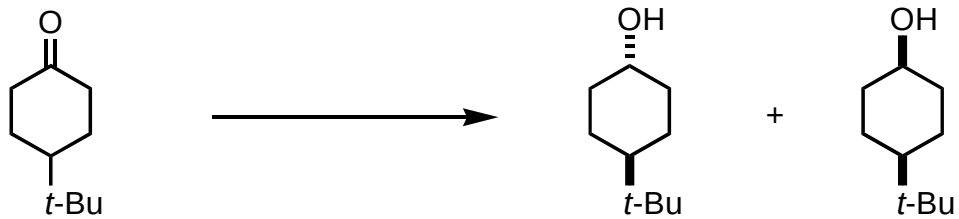




Stereoselective reduction of aldehydes and ketones

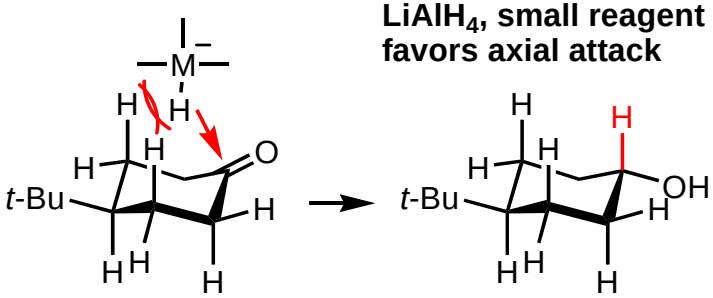


$NaBH_4$, MeOH	86	:	14
$LiAlH_4$, THF	92	:	8

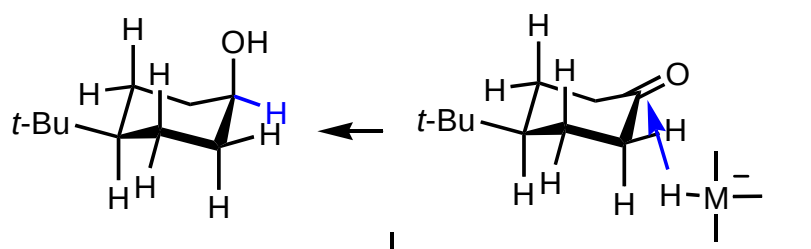


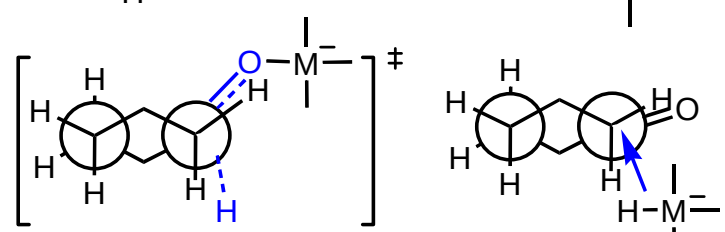
$LiAlH_4$, THF	92	:	8
s-Bu_3BHLi, THF	7	:	93

$LiAlH_4$, small reagent favors axial attack



L-Selectride, large reagent favors equatorial attack



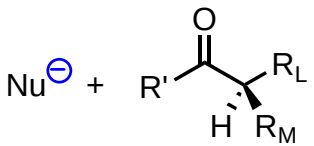


eclipsed conformation

axial attack : sensitive to the size of the reagent (1,3-diaxial interactions)

equatorial attack : disfavored by torsonial strain but less sensitive to the size of the nucleophile

Stereoselective reduction of aldehydes and ketones

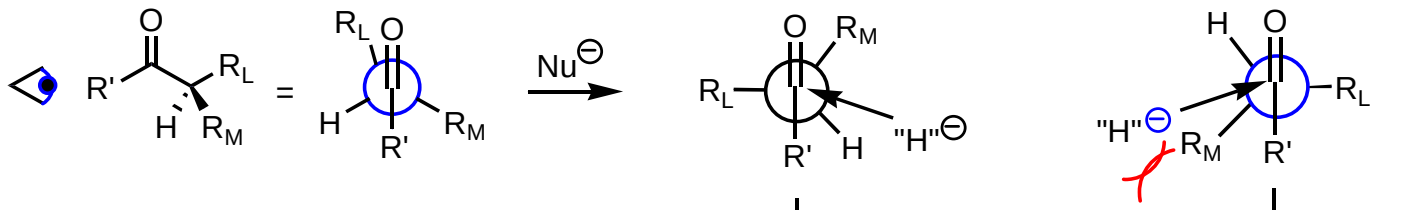


The substituents are ranked on the basis of their steric demand (L, M, S = H)

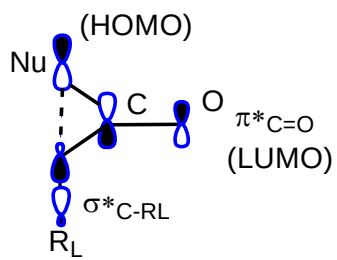
Exhothermic reaction: TS ressembles to reactant

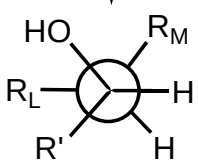
Felkin-Anh model

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

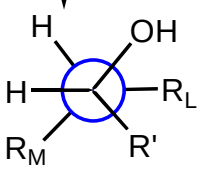


Best acceptor orbital $\sigma^*_{C\text{-}RL}$ and forming bond adopt antiperiplanar orientation

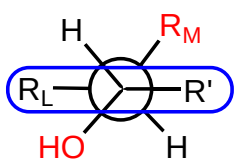


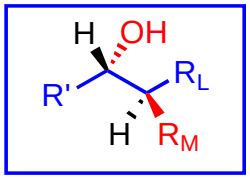


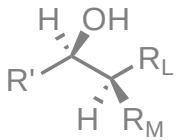
Major



Minor

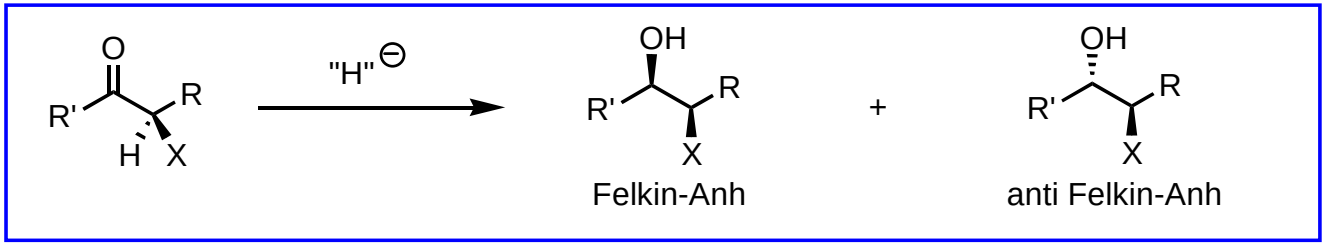






Chem. Rev. **1999**, *99*, 1191

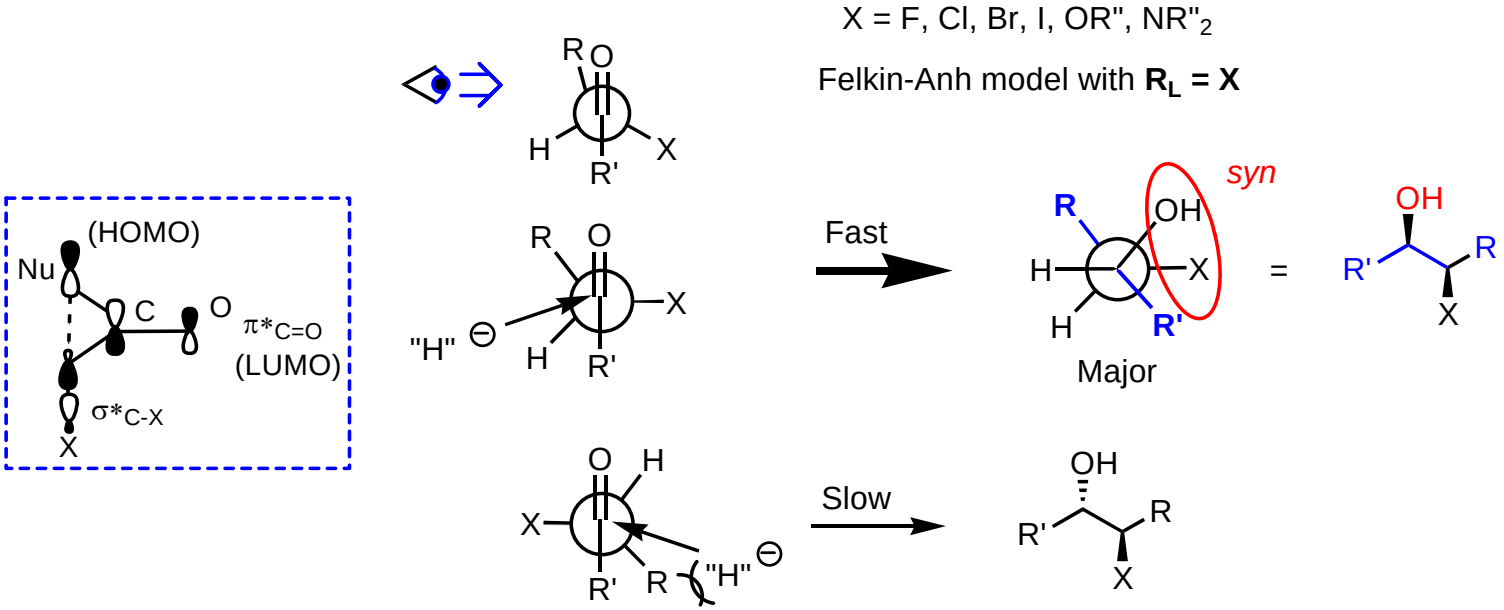
Stereoselective reduction of aldehydes and ketones



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

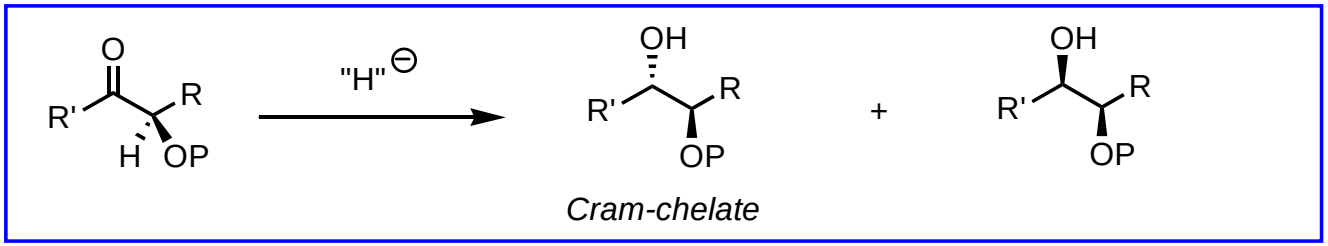
X = F, Cl, Br, I, OR", NR"$_2$

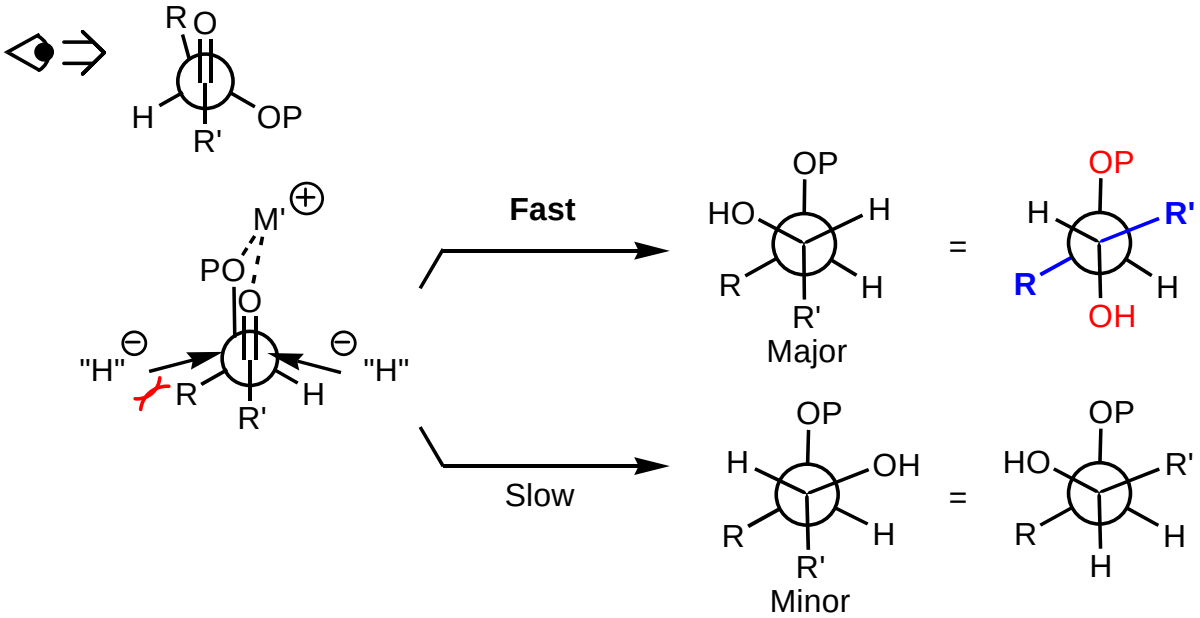
Felkin-Anh model with $\mathbf{R_L = X}$



Stereoselective reduction of aldehydes and ketones

An heteroatom (O, N, S) at the α position can coordinate the metallic counter-cation of the nucleophile : Nucleophilic addition preferentially proceeds on the less-hindered face of the carbonyl group on the resulting chelated intermediate

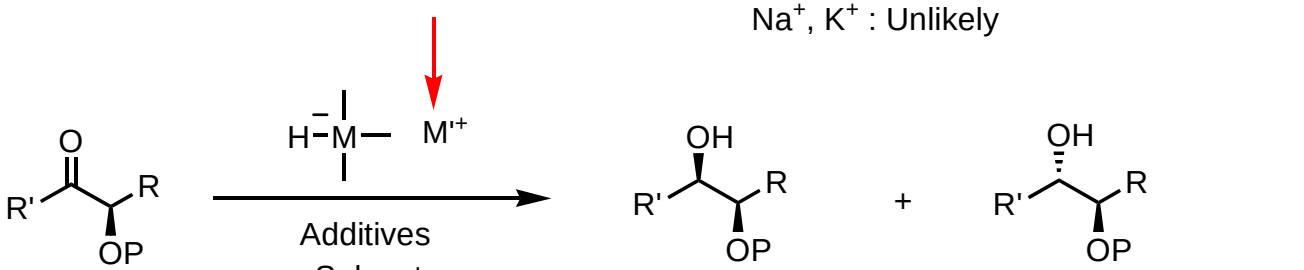




Stereoselective reduction of aldehydes and ketones

Is the metal singificantly Lewis acidic to induce the formation of a chelate?

Zn^{2+}, Mg^{2+} : Likely
Li^{+} : Intermediate
Na^{+}, K^{+} : Unlikely



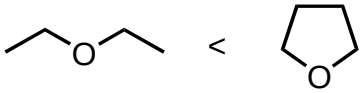
Felkin

anti-Felkin or Cram-Chelate

Is this oxygen atom able to induce the formation of a chelate ?

Coordinating ability of the solvent ?

Hydrocarbons : No



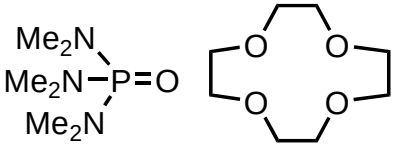
ether THF

OP = $OSiMe_3$, $OSiEt_3$, $OSiMe_2$*t*-Bu, $OSiPh_2$*t*-Bu..... No (in general)

OP = OMe, OBn, OCH_2OMe, OTHP... Likely

Lewis basic additives ?

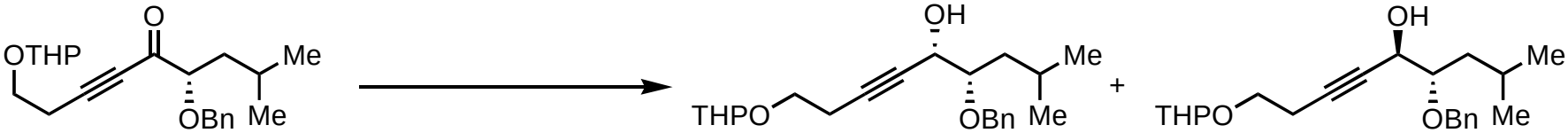
Lewis acid additives ?

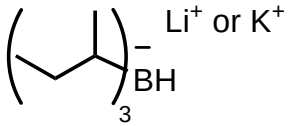


HMPA 12-crown-4

Zn^{2+}, Mg^{2+}, Ca^{2+}

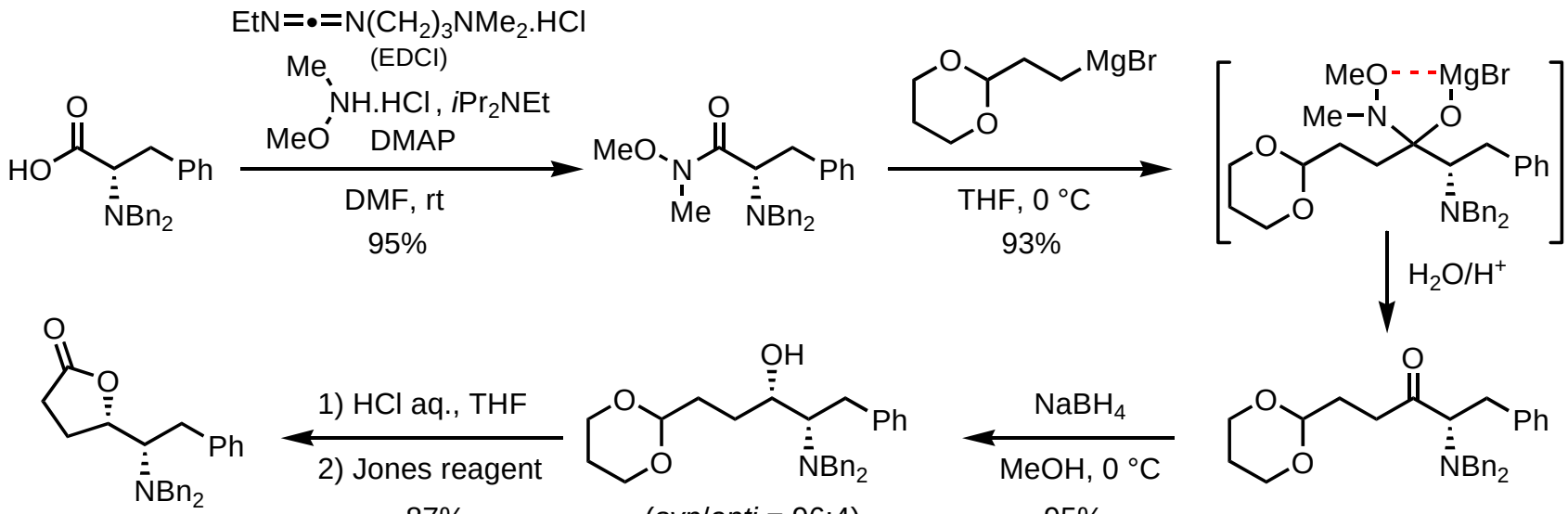
Stereoselective reduction of aldehydes and ketones





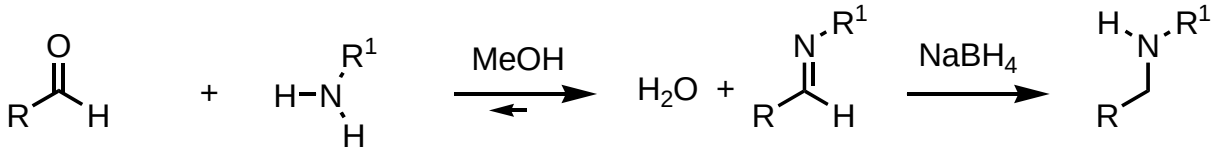
L- or K-Selectride®

$Zn(BH_4)_2$, Et_2O, -78 °C	**5** :	**95**
$LiAlH_4$, THF, -30 °C	32 :	68
L-Selectride, THF, -78 °C	73 :	27
K-Selectride, THF, -78 °C	85 :	15
K-Selectride, THF, -95 °C	**90** :	**10**
	Felkin-Anh control	*Chelation control*



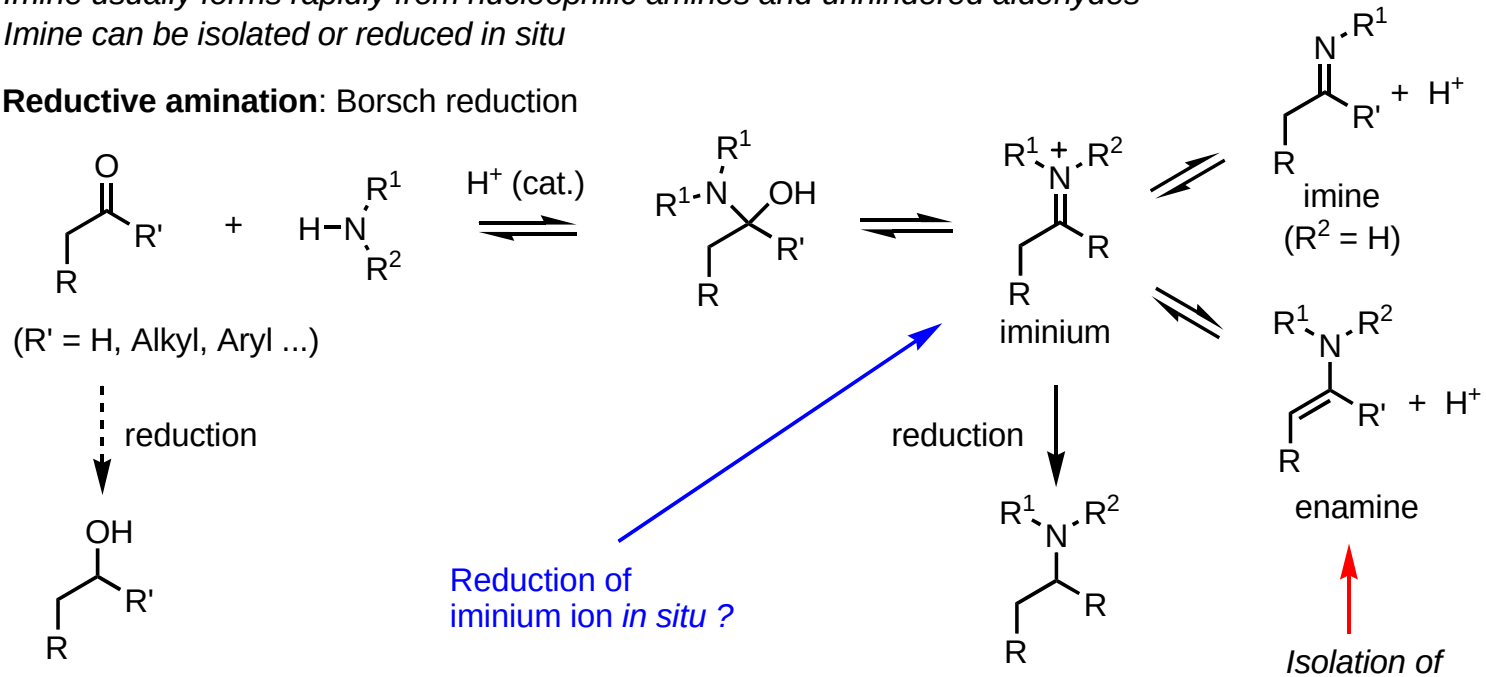
Tetrahedron Lett. **1985**, *26*, 5139; **1993**, *34*, 6169;

Reductive amination



Imine usually forms rapidly from nucleophilic amines and unhindered aldehydes
Imine can be isolated or reduced in situ

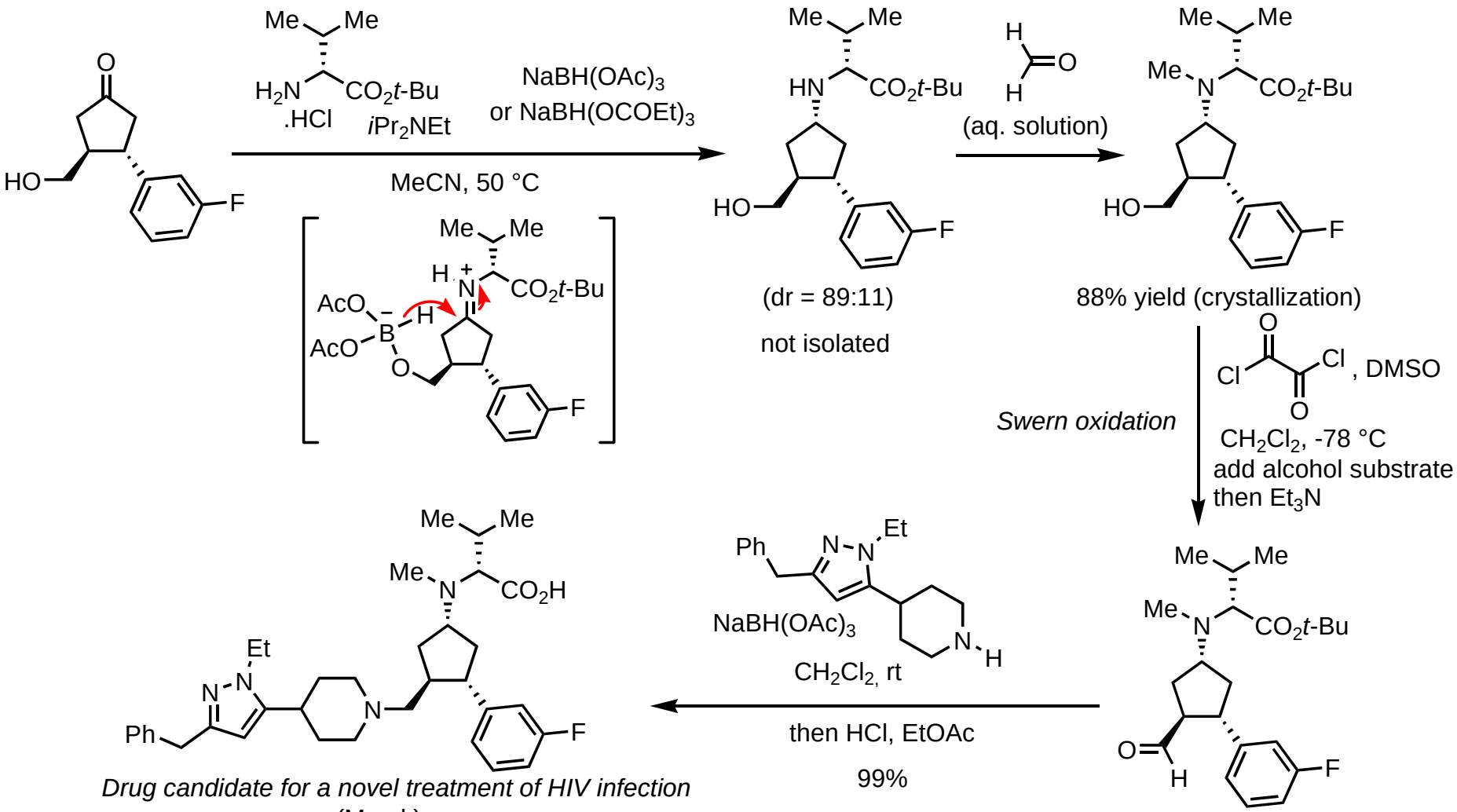
Reductive amination: Borsch reduction



$NaBH_3CN$: less reactive than $NaBH_4$ (pb: toxicity of cyanide)
stable under acidic conditions
at pH ~ 6-8 reduces iminium ions more quickly than aldehydes/ketones
at pH ~ 3-4 reduces aldehydes/ketones (C=O starts to be protonated)

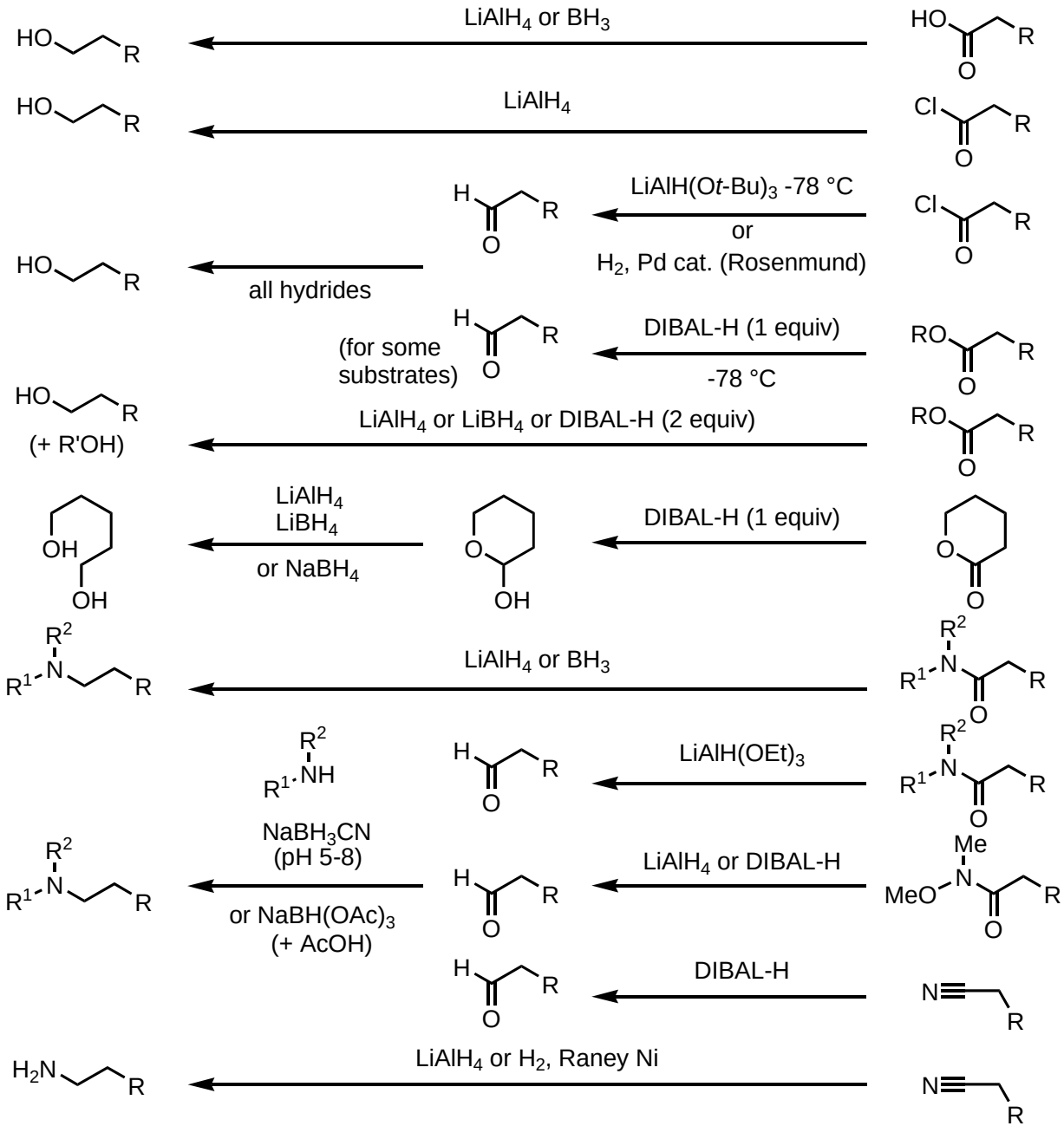
$NaBH(OAc)_3$: less reactive than $NaBH_4$ and $NaBH_3CN$
stable under acidic conditions, soluble in aprotic solvents
reduces iminium ions rapidly, also aldehydes but not ketones

Reductive amination : importance in medicinal chemistry

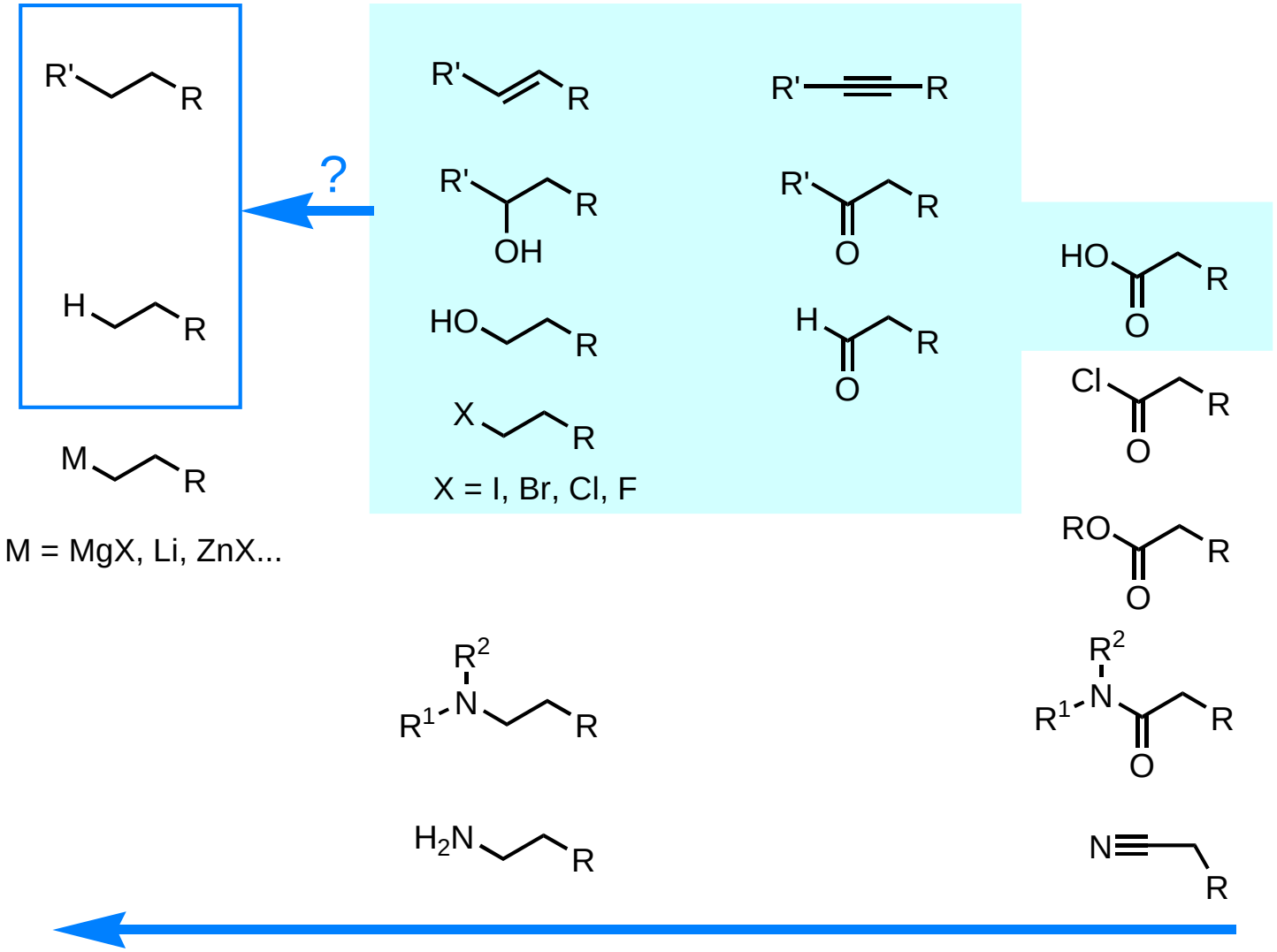


Chirality **2005**, *17*, S149; *Org. Proc. Res. Dev.* **2006**, *10*, 971 (review)

Summary: Reduction of carbonyl compounds



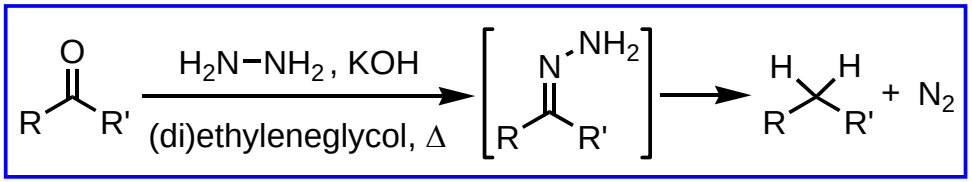
Functional groups - Valence table

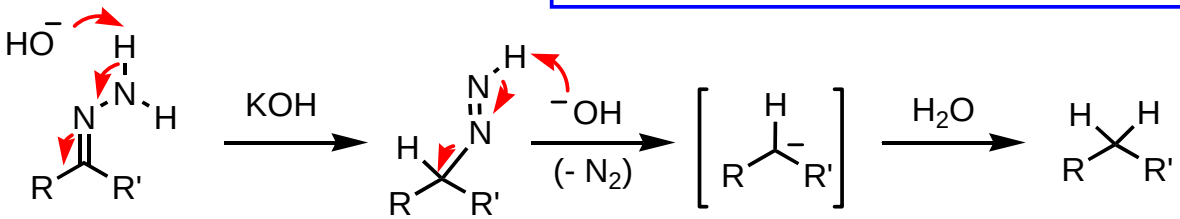


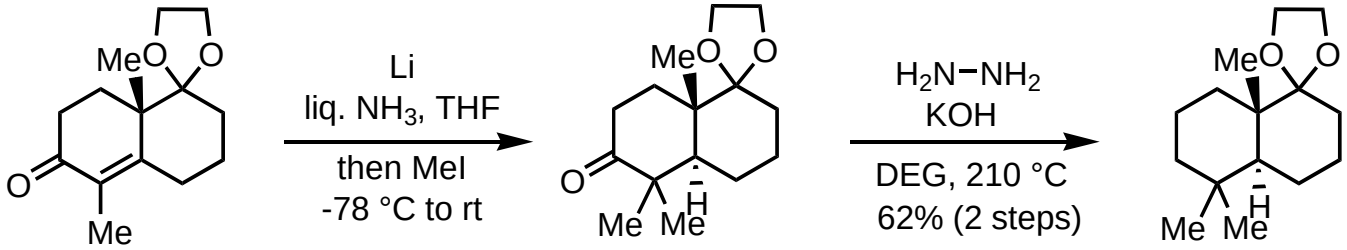
Reduction of ketones/aldehydes to alkanes

Wolff-Kishner reduction

Harsh alkaline conditions
Limited functional group compatibility

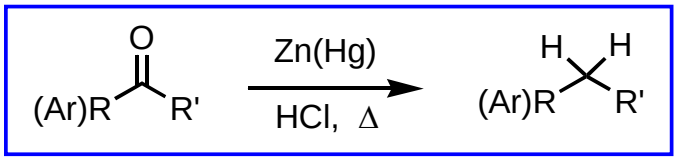




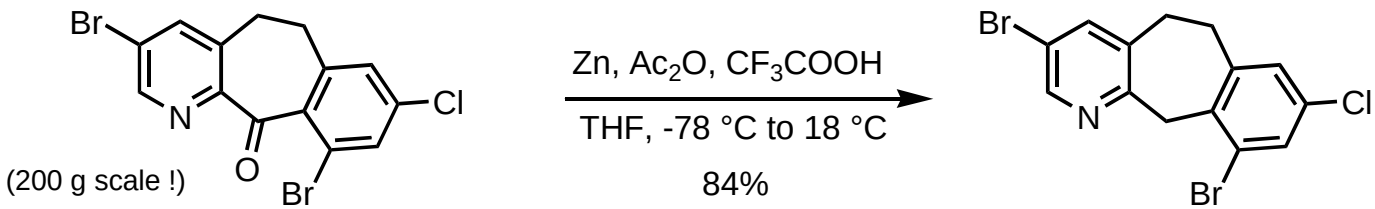


Clemmensen reduction

Strongly acidic conditions
Limited functional group compatibility
Scope essentially restricted to aryl ketones



Original conditions can be modified

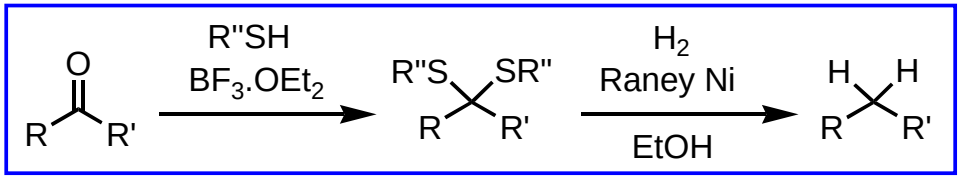


Org. React. **1948**, *4*, 378; *J. Org. Chem.* **1994**, 59, 3902; *J. Org. Chem.* **2003**, *68*, 4984

Reduction of ketones/aldehydes to alkanes

Thioketal desulfurization

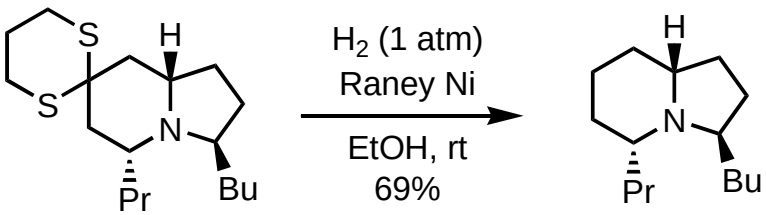
Mild conditions but requires dithiane formation
C=C bonds are often hydrogenated under these conditions



(by-products: NiS, 2 R"H)

Dry Raney Ni is pyrophoric !

Overlay (wet) catalyst with inert gas



Org. Lett. **2004**, *6*, 1493

N_2 or Ar

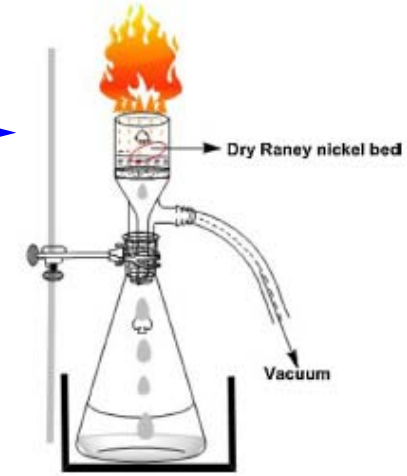
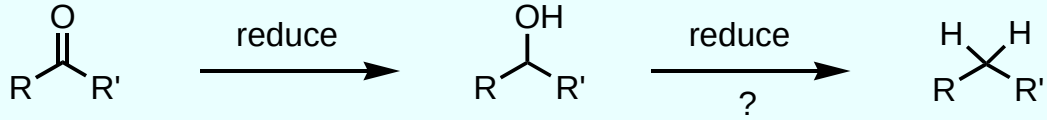


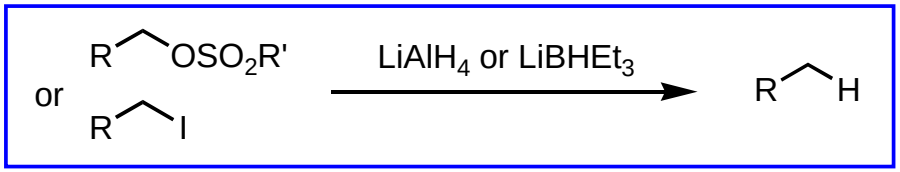
Figure 14. Catalyst fire during filtration.

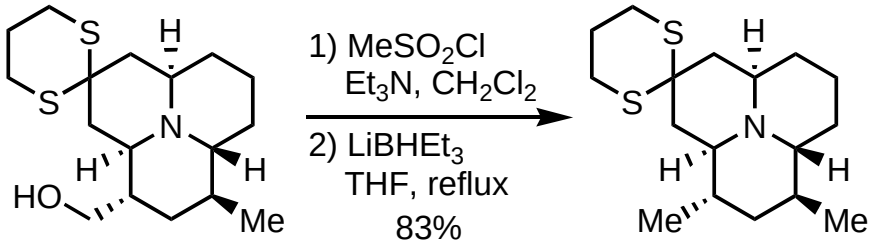
J. Chem. Health & Safety **2016**, 16

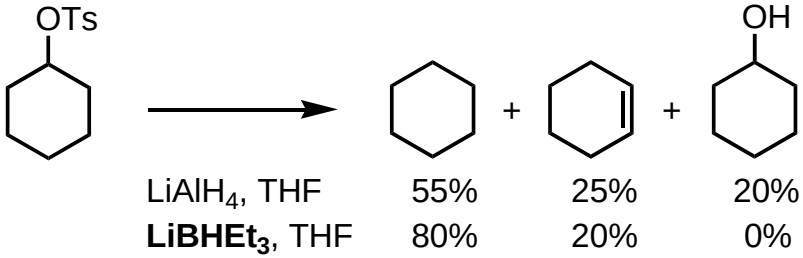
Alternative strategy

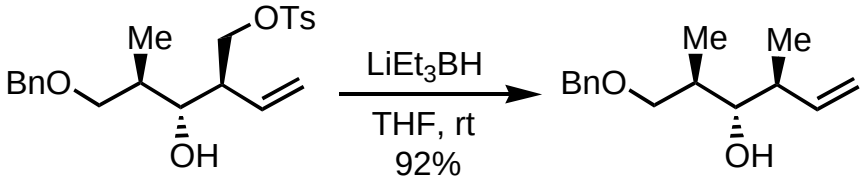


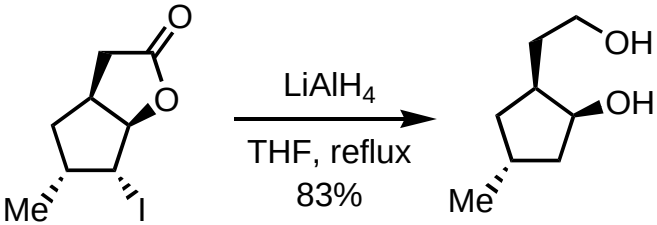
Reduction of halides/sulfonates







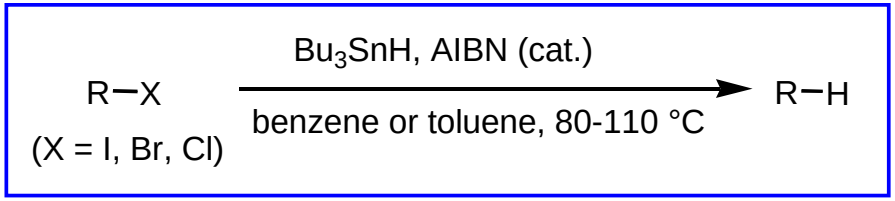




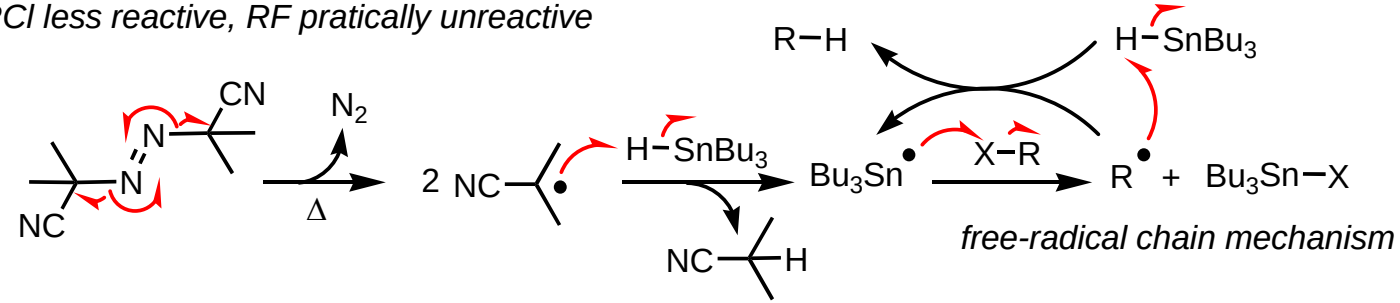
For iodides a radical mechanism seems to be involved

J. Org. Chem. **1976**, 41, 3064*; JACS* **1990**, *112*, 5290*; Org. Lett.* **2005**, *7*, 3247*; J. Org. Chem.* **2013**, *78*, 9

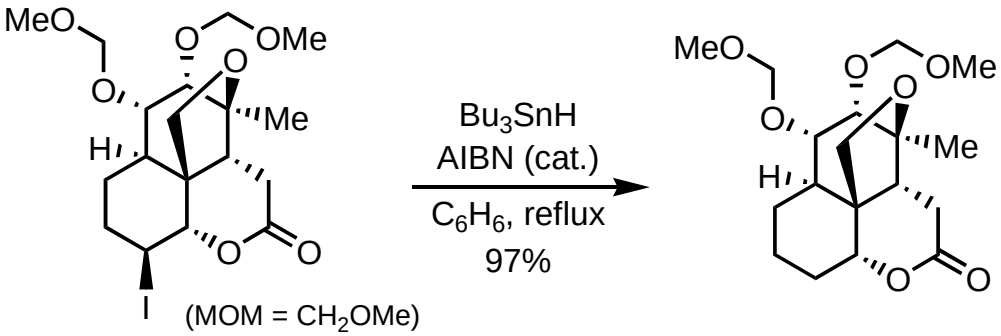
Radical reduction of halides

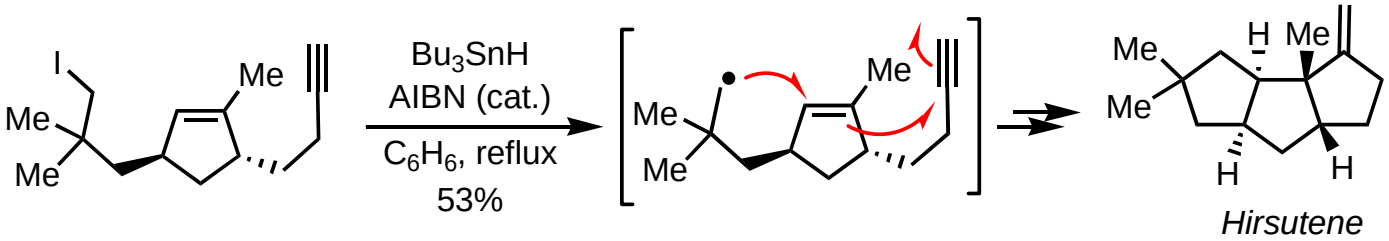


RCl less reactive, RF pratically unreactive



free-radical chain mechanism

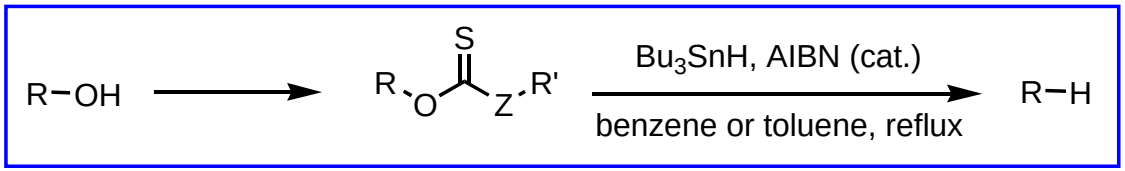


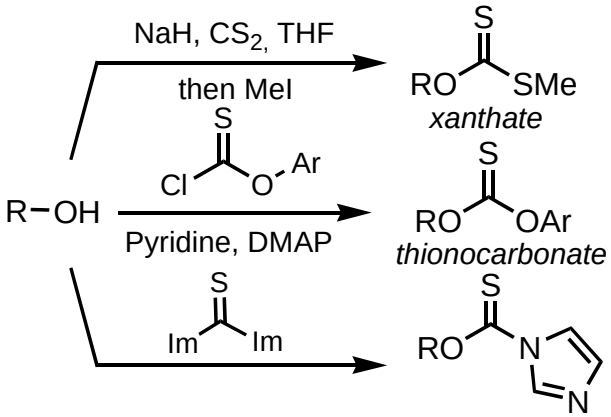


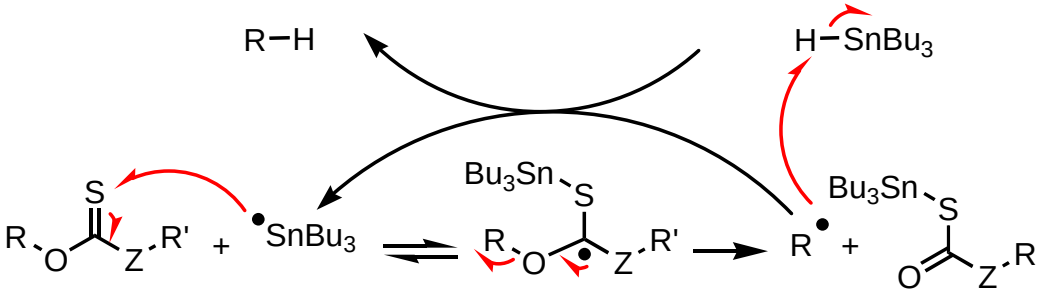
Hirsutene

Synthesis **1987**, 665; *J. Org. Chem.* **1987**, *52*, 3346; *JACS* **1985**, *107*, 1448

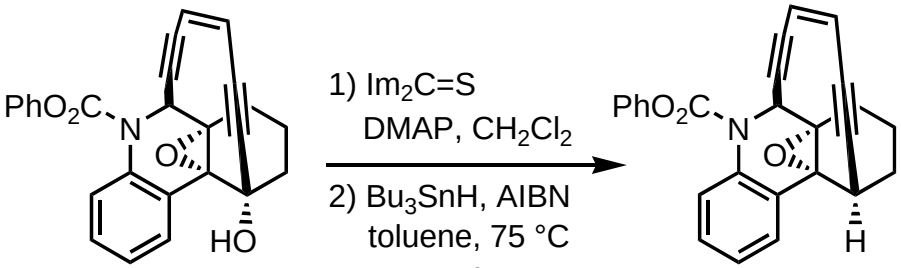
Radical deoxygenation of alcohols (Barton-McCombie reaction)

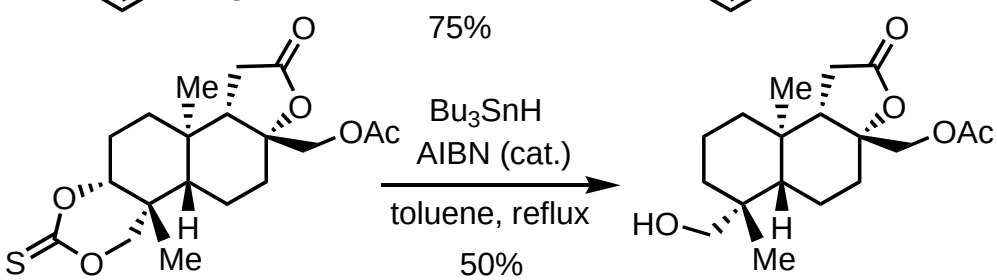


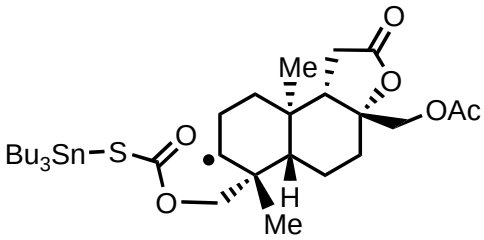




Fragmentation should preferentially generate R• (not R' •)



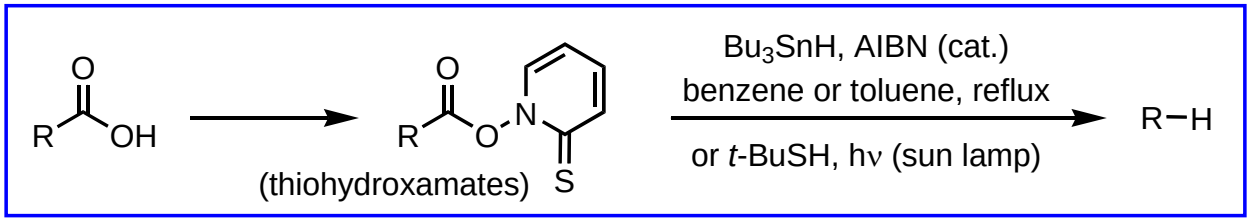


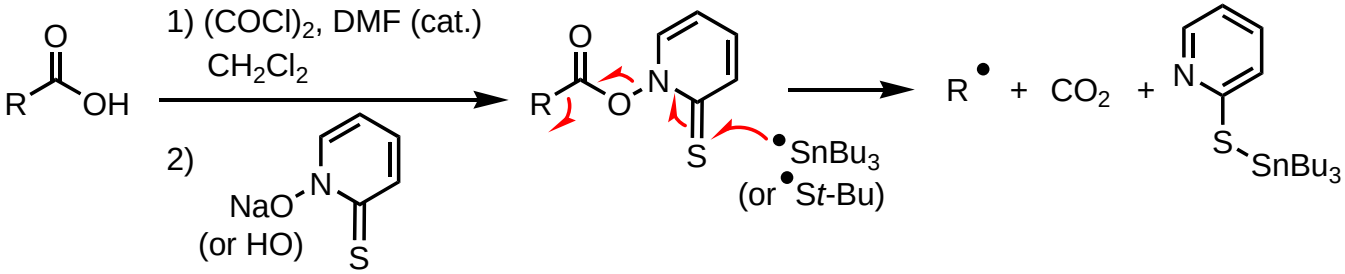


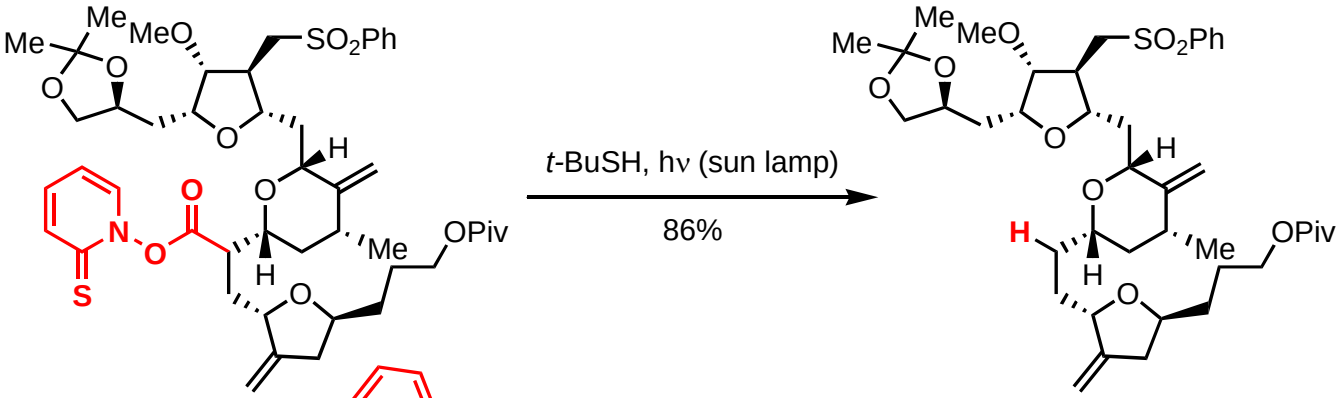
major product arises from 2^ary radical

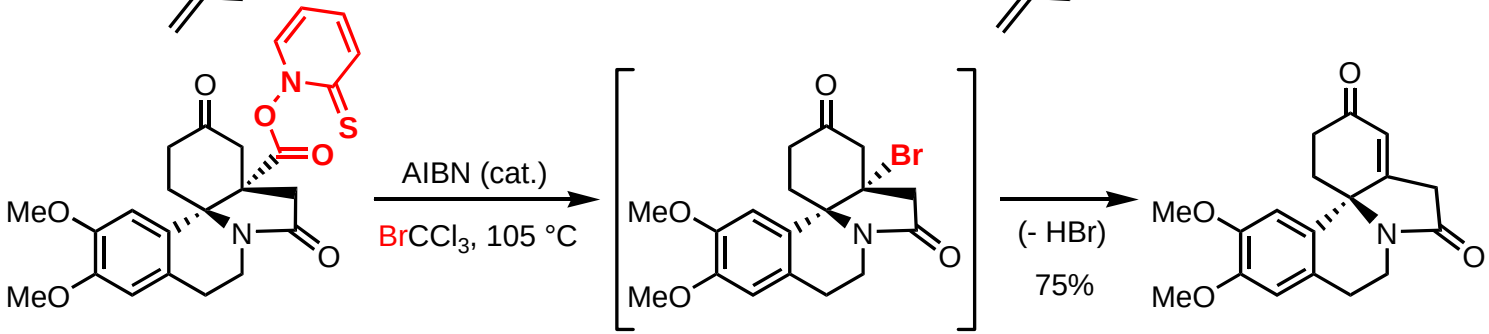
J. Chem. Soc., Perkin Trans 1 **1975**, *89*, 1574; *Tetrahedron Lett.* **1990**, *31*, 4681;*Tetrahedron* **1991**, *47*, 8669
JACS **1990**, *112*, 7416; *Eur. J. Org. Chem.* **2018**, 477

Radical decarboxylation of acids (Barton reaction)



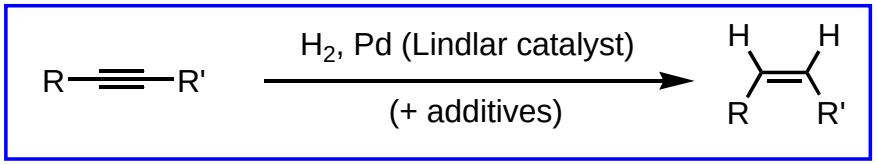






J. Chem. Soc., Chem. Commun. **1983**, 939; *Tetrahedron* **1987**, *43*, 2733; *JACS* **2009**, *131*, 15642; *Org. Lett.* **2006**, *8*, 601

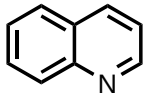
Reduction of alkynes



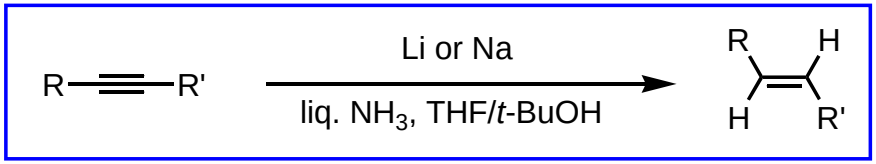
Good functional group tolerance

Lindlar catalyst : Pd(5%) / $CaCO_3$ poisoned with lead (Pb salts)

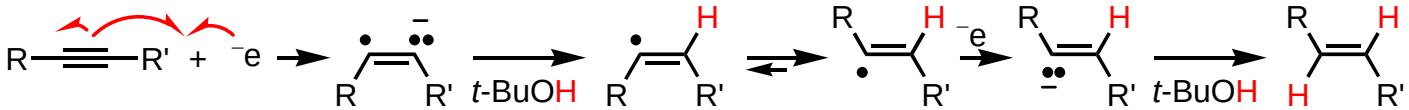
Additives : quinoline often used



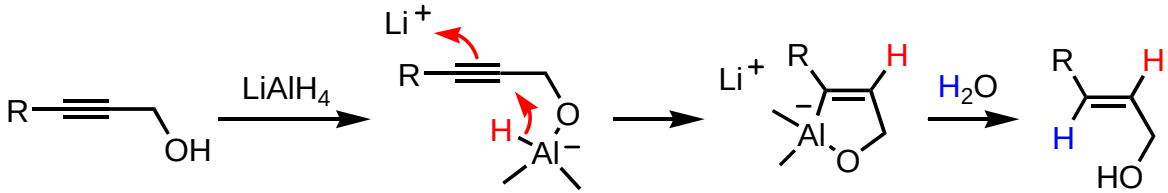
Solvents : in general, not the best for alkene hydrogenation
toluene (benzene), hexane, EtOAc



Strongly reductive conditions
Limited functional group compatibility



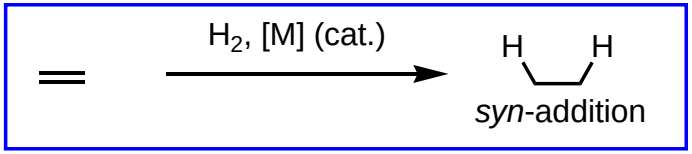
$LiAlH_4$ does not reduce alkynes in general except propargyl alcohols



Alternative reagent : $NaAlH_2(OCH_2CH_2OMe)_2$ "Red-Al"

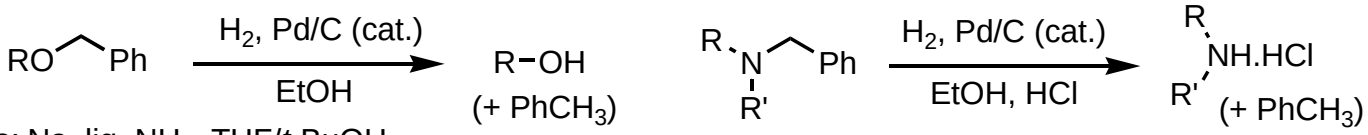
J. Org. Chem. **1974**, *39*, 968; *J. Org. Chem.* **1982**, *47*, 4595

Reduction of alkenes by hydrogenation



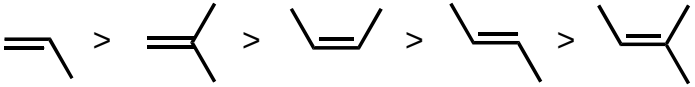
Usually carried out with **heterogeneous catalysts** (often Pd/C)

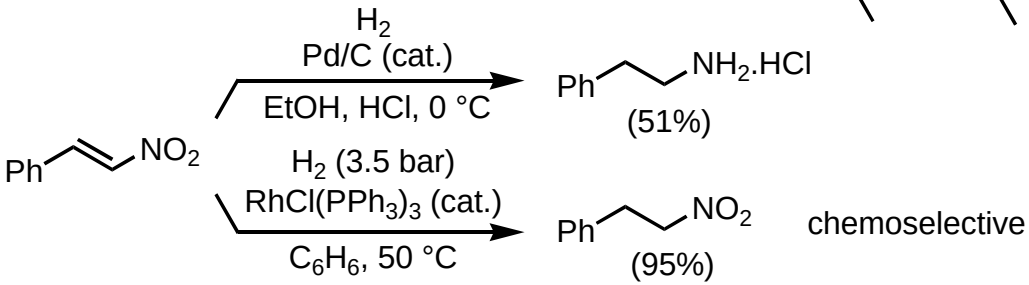
Benzyl ethers/carbamates
Benzylamines also cleaved



alternative conditions: Na, liq. NH_3, THF/*t*-BuOH

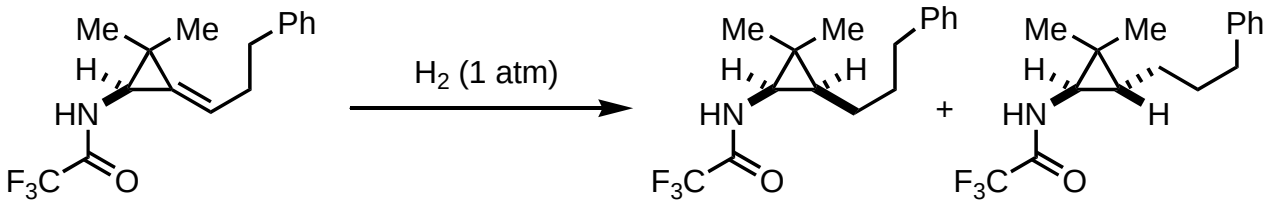
Homogeneous catalysts can also be employed

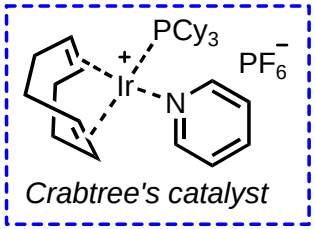




chemoselective

Directed reactions (coordination of the metal by a Lewis base)

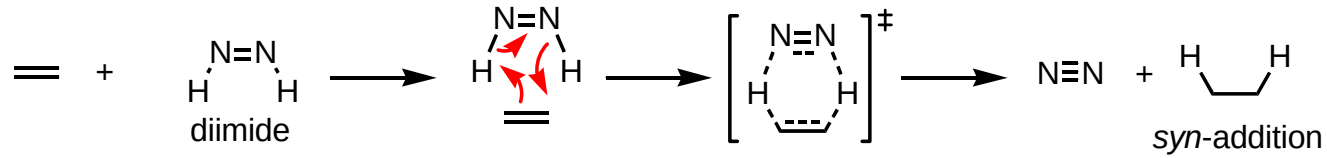


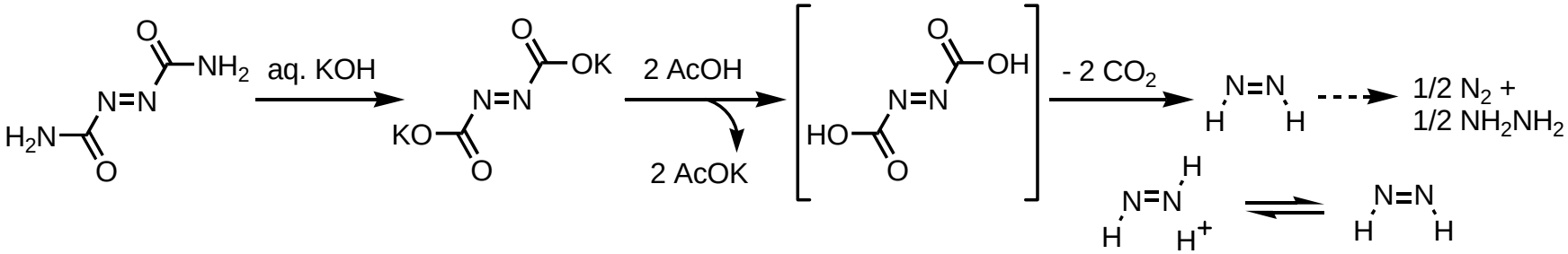


Pd/C (5 mol %), MeOH, rt	**92**	:	**8**	(97%)
Crabtree's cat. (6 mol %), CH_2Cl_2, rt	**10**	:	**90**	(92%)

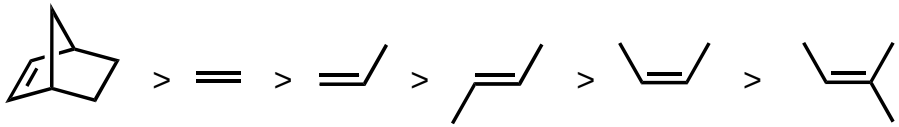
JACS **1983**, *105*, 1072; *J. Org. Chem.* **1986**, *51*, 2655; *Chem. Eur. J.* **2018**, *24*, 15104

Reduction of alkenes with diimide



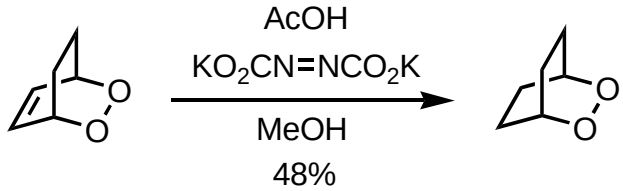


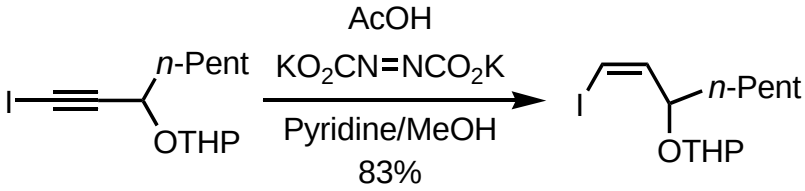
Relative rates



Other methods of generation
NH_2NH_2 + Cu(II) or H_2O_2
$TsNHNH_2$, AcONa, Δ

C–Br, C–I, C=O, O–O, S–S, S=O, N–O, NO_2 *are stable*





Alkynes are hydrogenated to alkanes, except iodoalkynes which led to (Z)-alkenyl iodides

Org. React. **1991**, *40*, 91

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Main group organometallic chemistry

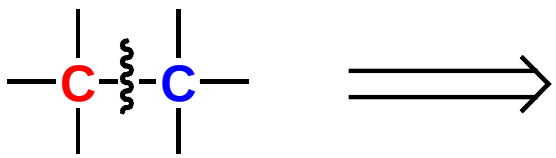
(R–M, M = Li, Mg, Zn, Cu)

SYNTHETIC METHODS IN MOLECULAR CHEMISTRY (SMMC)

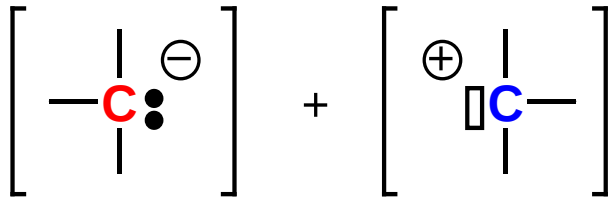
2019

Formation of carbon-carbon bonds

Retrosynthetic analysis



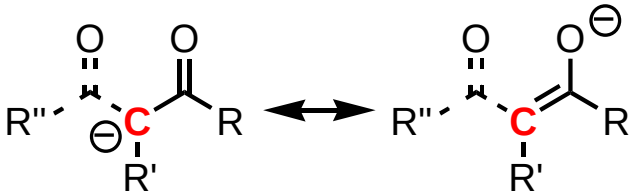
"Synthons"



Nucleophile *Electrophile*

Real synthetic equivalents ?

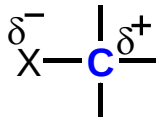
" Stabilized nucleophiles "



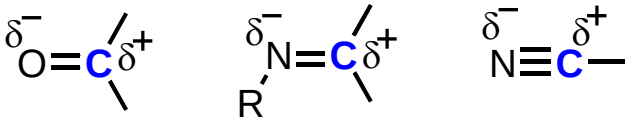
- Acetoacetic/Malonic synthesis
- Enolate *C*-alkylation
- Michael addition

Classical electrophiles

Polarized carbon-heteroatom bonds

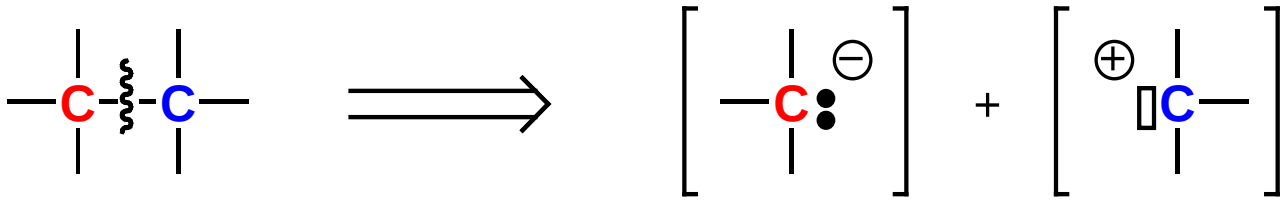


X = leaving group
(I, Br, Cl, OSO_2R)



Formation of carbon-carbon bonds

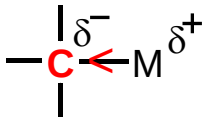
Retrosynthetic analysis *"Synthons"*



Nucleophile *Electrophile*

Real synthetic equivalents ?

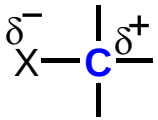
Organometallic reagent



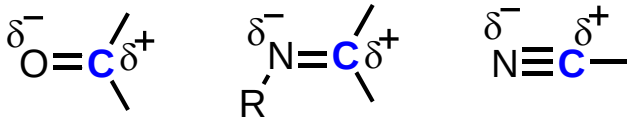
M = electropositive metal

Classical electrophiles

Polarized carbon-heteroatom bonds

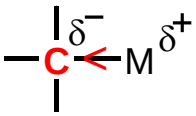


X = leaving group
(I, Br, Cl, OSO_2R)



Reactivity of organometallic reagents

Organometallic reagent

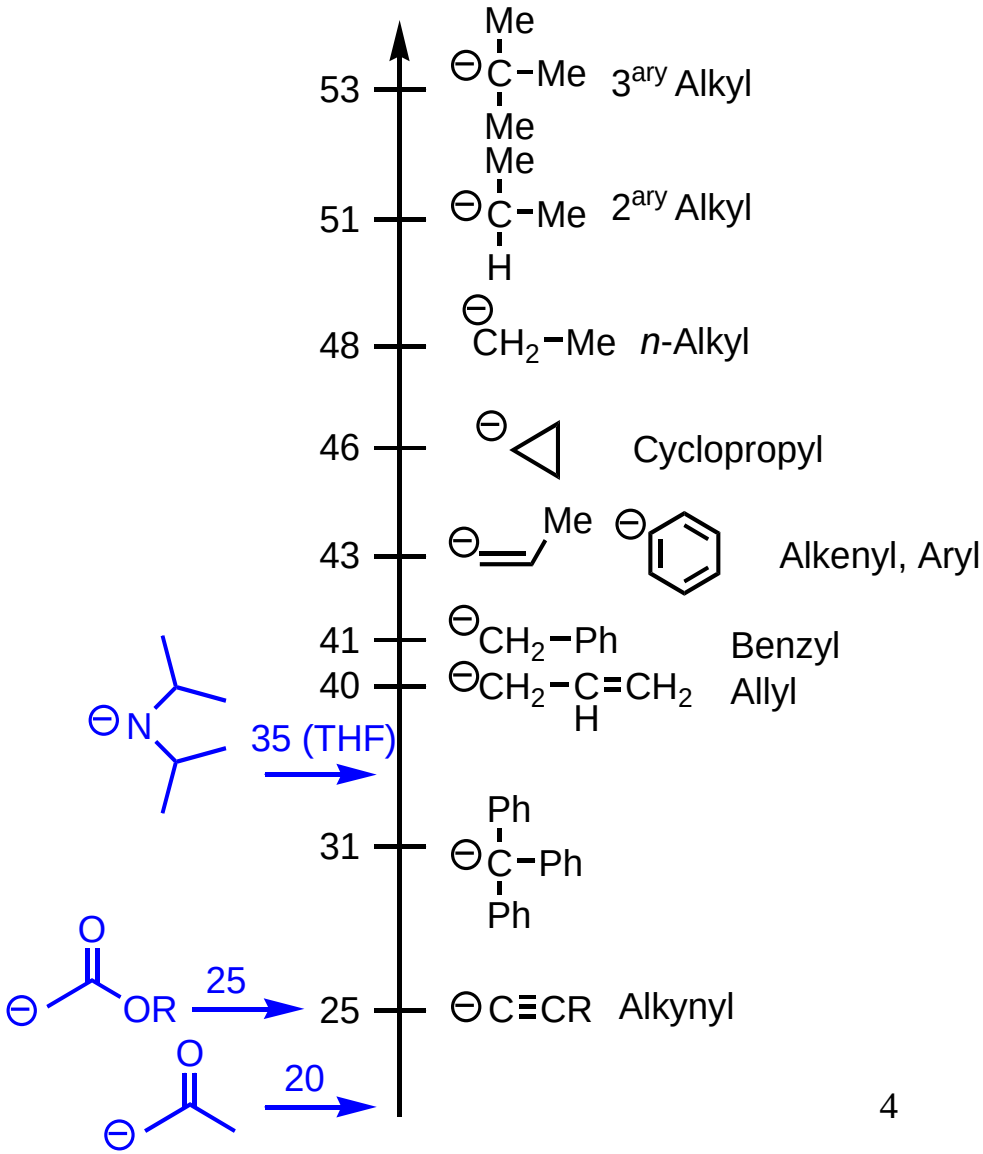


% of ionic character of the C-M bond

Reactivity ↗

51	C—K
47	C—Na
43	C—Li
35	C—Mg
22	C—Al
15	C—Zn
12	C—Cu
11	C—Sn
6	C—B

pK$_A$ (R$^-$/RH) *(H$_2$O, by extrapolation)*



Main methods of preparation of organometallic reagents

1) By reaction with the metal

$R-X + 2\,M \longrightarrow R-M + M-X$ *with monvalent metals* M = Li

$R-X + M \longrightarrow R-MX$ *with divalent metals* M = Mg, Zn

2) By halogen metal-exchange reactions

$R-X + R'-M \rightleftharpoons R-M + R'-X$

X = I, Br (M = Li or MgX or ZnR')

Equilibrium shifted toward the more stable organometallic reagent (= corresponding to the more stable carbanion)

3) By deprotonation reactions ("hydrogen-metal exchange")

$R-H + R'-M \rightleftharpoons R-M + R'-H$

(M = Li or MgX)

Equilibrium shifted toward the more stable organometallic reagent (= corresponding to the more stable carbanion)

There are many other useful exchange processes (Sn/Li, Se/Li, Sulfoxide/Li or Mg ...)

4) By transmetalation reactions

$R-M + M'-X \rightleftharpoons R-M' + M-X$

(M = Li or MgX)

Equilibrium shifted toward the more covalent (less ionic) organometallic reagent

Grignard reagents

$$\overset{\delta^+}{R}\text{—}\overset{\delta^-}{X} + Mg \xrightarrow[\text{(anhydrous)}]{\text{Ethereal solvent}} \overset{\delta^-}{R}\text{—}\overset{\delta^+}{MgX}$$

X = I, **Br**, **Cl**

R = Alkyl, Aryl, Alkenyl

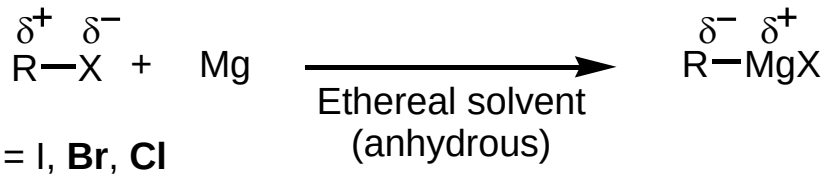
Inversion of polarity

« Umpolung »

Philippe Barbier (1848-1922)
Organomagnesium reagent
generated in the presence of the
electrophile (ketone)

Victor Grignard (1871-1935)
RMgX (1900)
Nobel prize (1912)

Preparation and structure of Grignard reagents



X = I, **Br**, **Cl**
R = Alkyl, Aryl, Alkenyl

Pure Mg turnings, reaction started with I_2 (cat.) or $BrCH_2CH_2Br$ (---> $H_2C{=}CH_2 + MgBr_2$)

Solvents

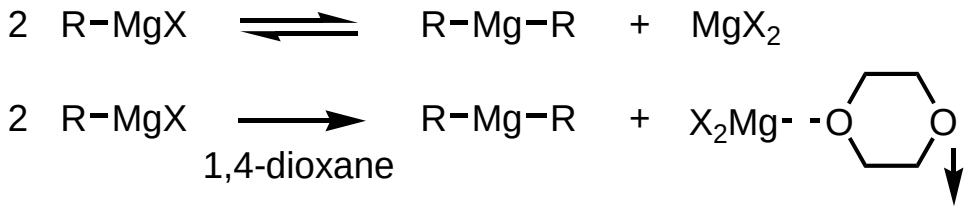
Diethyl ether ("ether")
(ε_r = 4.3)

absolutely required if R = Alkenyl
(H. Normant, 1954)

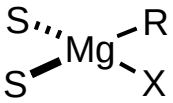
Tetrahydrofuran (THF) more coordinating than ether
(ε_r = 7.5)

Structure

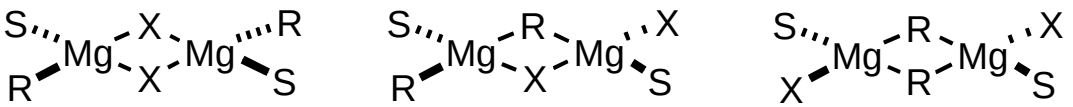
Schlenk equilibrium



Structure depends on the coordinating solvent (S), halide, R and the concentration



monomeric structure



Dimeric structures

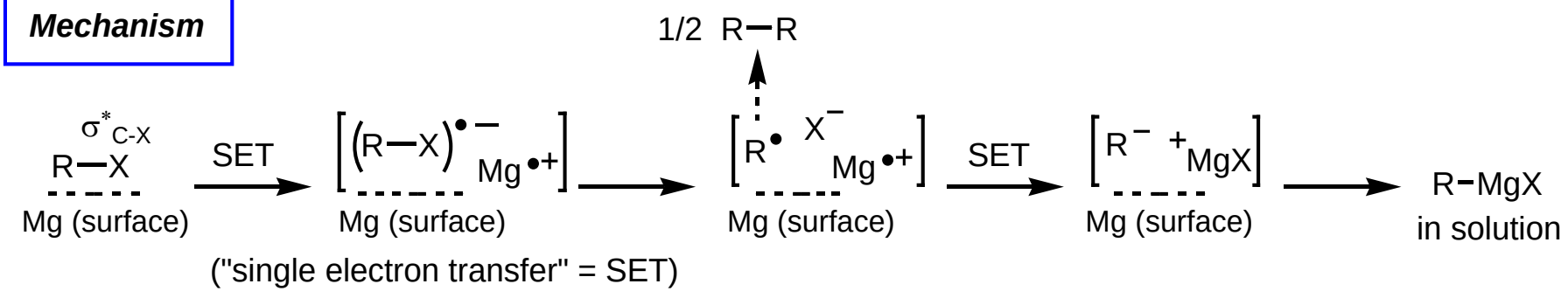
Preparation of Grignard reagents

$$\overset{\delta^+}{R}-\overset{\delta^-}{X} + Mg \xrightarrow[\text{(anhydrous)}]{\text{Ethereal solvent}} \overset{\delta^-}{R}-\overset{\delta^+}{MgX}$$

X = I, **Br**, **Cl**

R = Alkyl, Aryl, Alkenyl

Mechanism



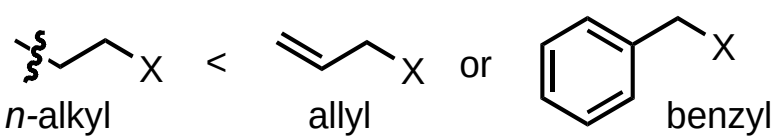
Substrates Higher yields with bromides and chlorides compared to iodides

Side reaction :
Würtz coupling

$$2\ R-X + Mg \longrightarrow R-R + MgX_2$$

$$R-X + R-MgX \longrightarrow R-R + MgX_2$$

Problematic reaction for halides able to react rapidly by an S_N2 reaction



Slow addition of a solution of R-X in Et_2O or THF : low concentration of [R-X] in solution

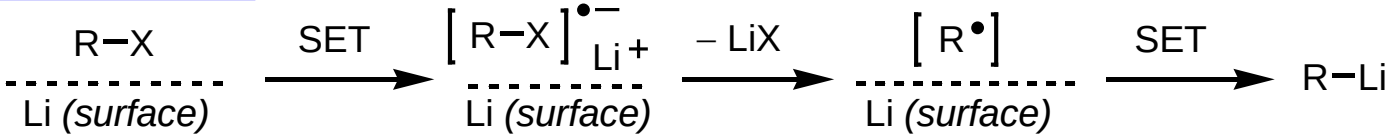
Preparation of organolithium reagents

$$R{-}X + 2\ Li \longrightarrow R{-}Li + LiX$$

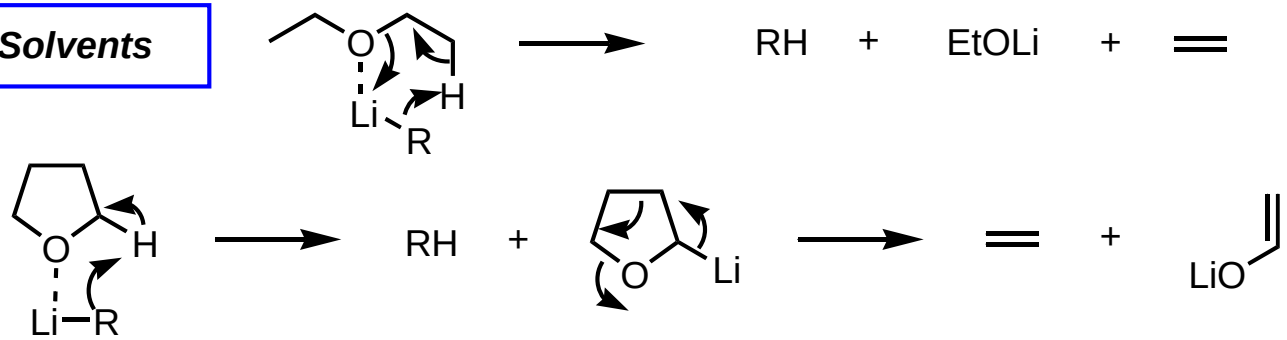
(Li containing 1-3% Na, anhydrous conditions, inert atmosphere = Ar rather than N_2)

Wilhelm Schlenk
RLi (1917)

Mechanism



Solvents



	half-life	
$CH_3(CH_2)_3Li$ (*n*-BuLi)	Et_2O, 20 °C	150 h
	Et_2O, 35 °C	31 h
	THF, 35 °C	30 min
$(CH_3)_3CLi$ (*t*-BuLi)	Et_2O, 0 °C	40 min
	THF, -20 °C	1 h

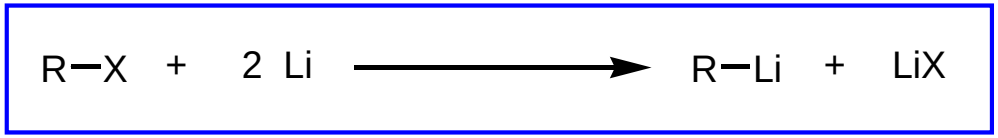
Hydrocarbons preferred/mandatory as solvents (but Li salts are insoluble)

LiCl : poorly soluble in Et_2O, LiBr soluble

Commercially available solutions

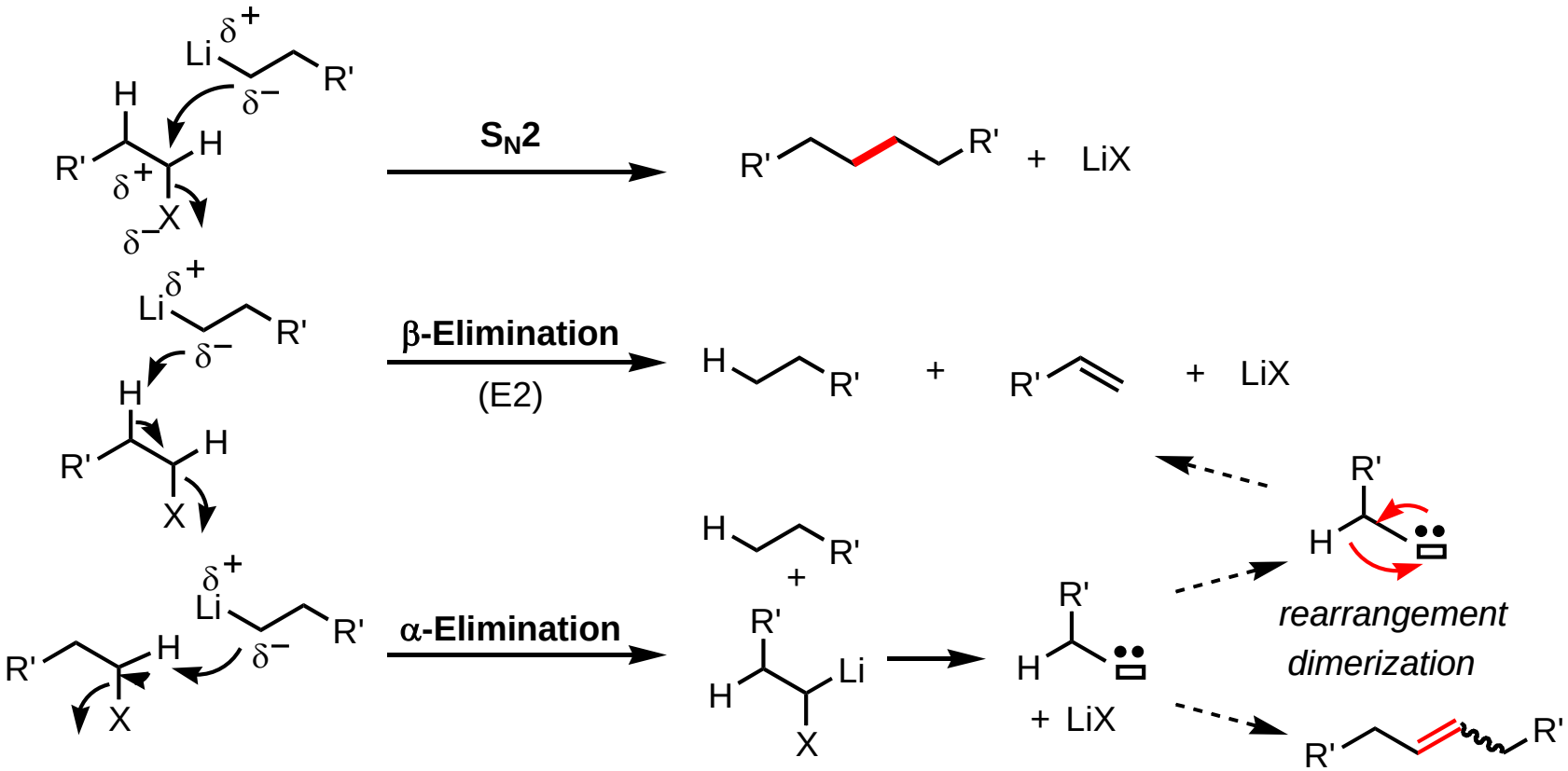
n-BuLi / hexanes (1.6M, 2.5M or 10M)
t-BuLi / pentane (1.7M)
MeLi,LiBr or MeLi / ether (1.4M ou 1.6M)

Preparation of organolithium reagents



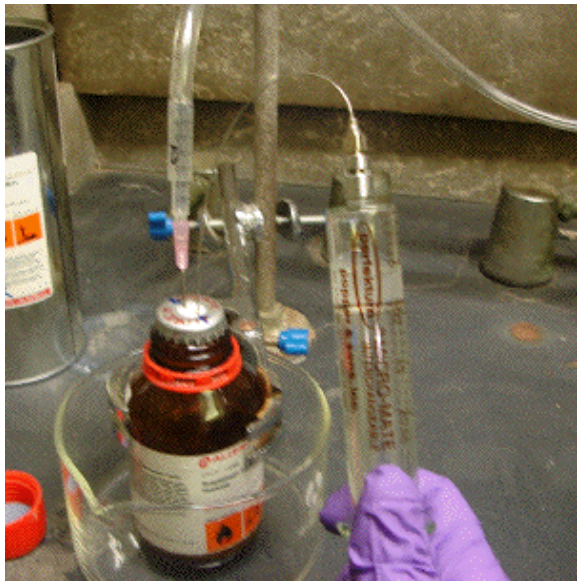
Substrates

Slow addition of the halide (R-X)
Less side-reactions with chlorides (X = Cl)



Handling organolithium reagents

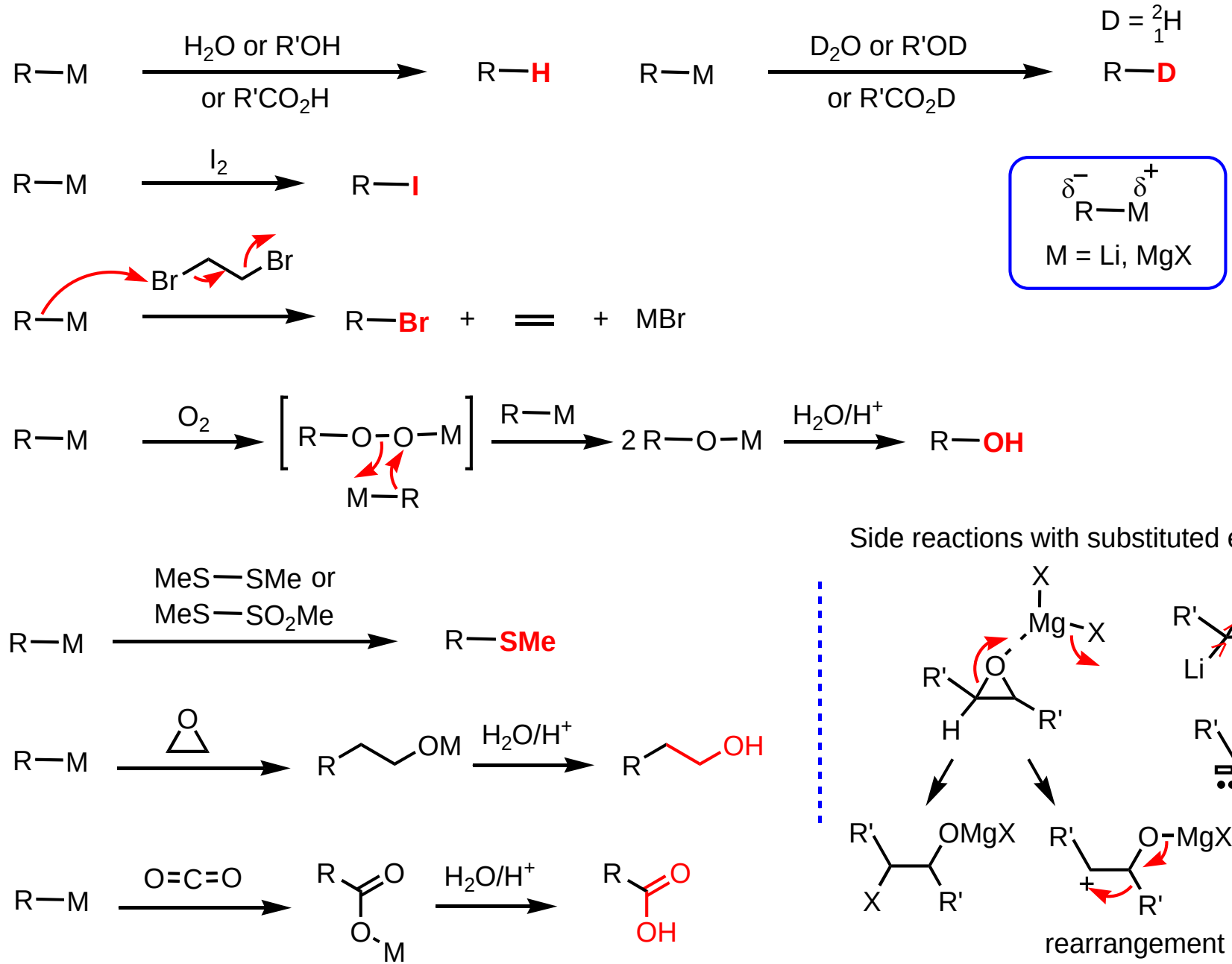
Organolithium reagents are pyrophoric. They are widely used both in academic laboratories and industrially but great care should be exercised!



Taking out a solution of an organolithium from a a bottle under inert atmosphere

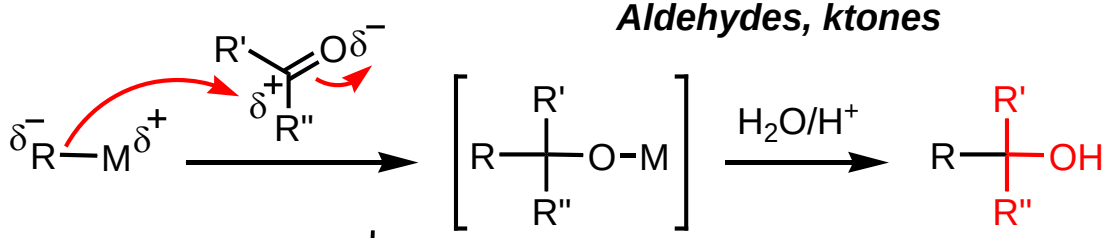
Solution of *tert*-butylithium exposed to air

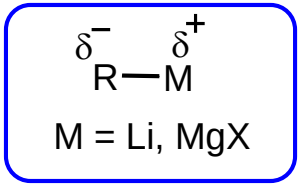
Reactivity of organomagnesium/organolithium reagents

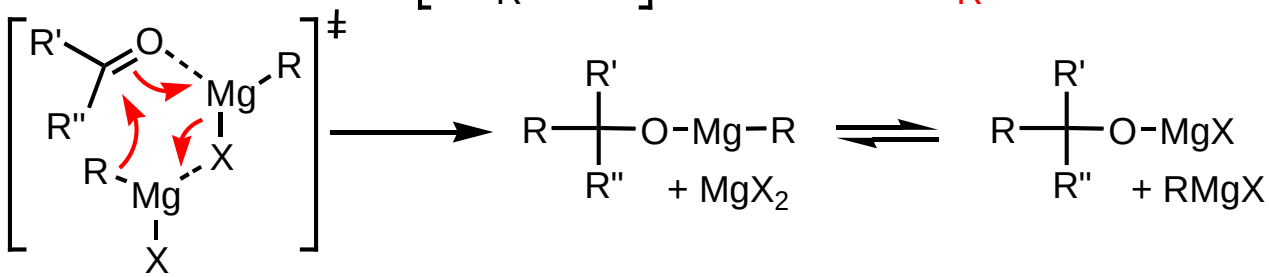


Reactivity of organomagnesium/organolithium reagents

Aldehydes, ktones

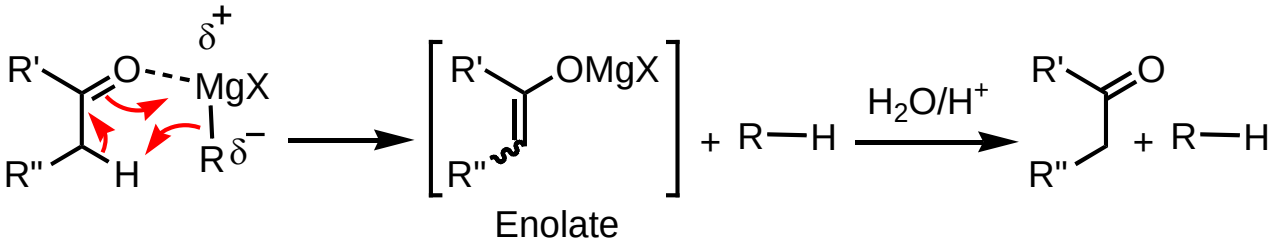




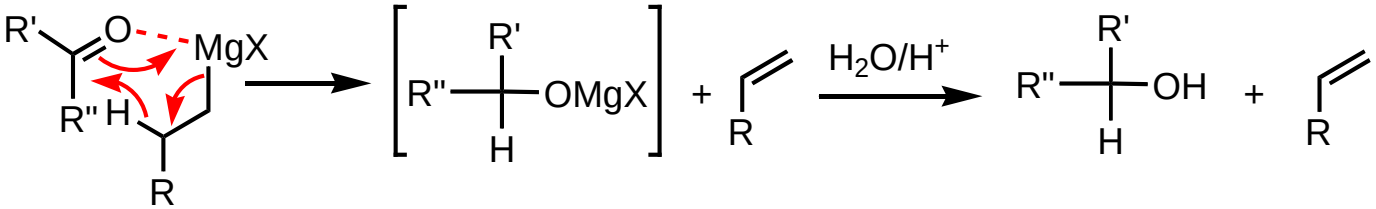


Possible side-reactions (with Grignard reagents, hindered ketones)

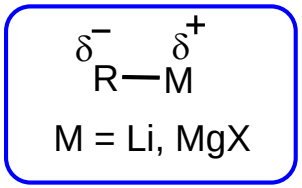
Enolization



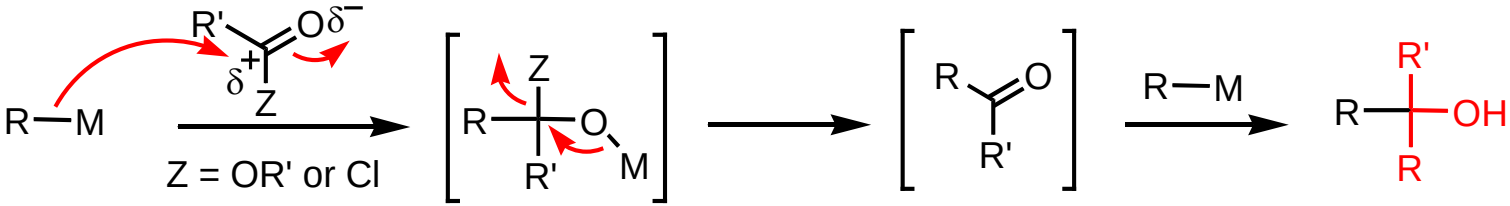
Reduction (Grignard reagent possessing β hydrogen(s))



Reactivity of organomagnesium/organolithium reagents

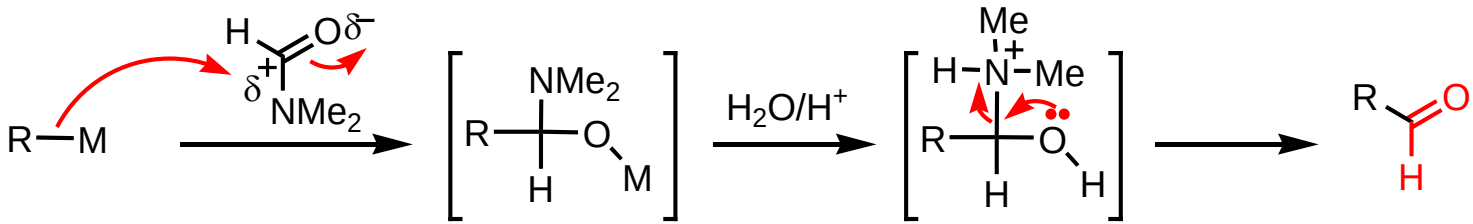


Carboxylic acid derivatives



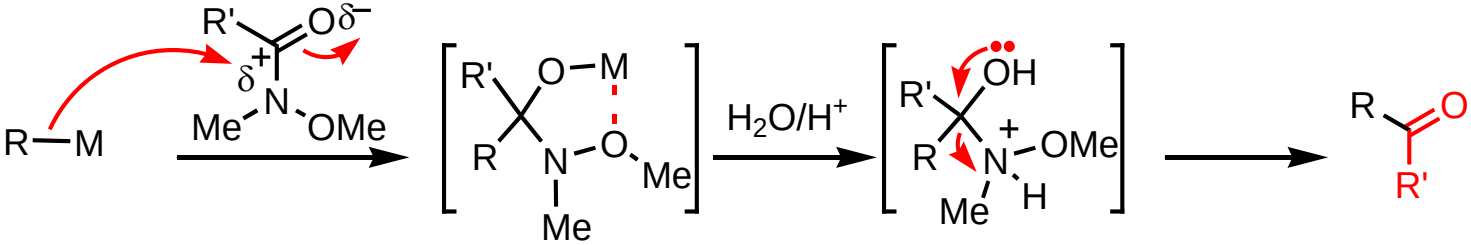
usually unstable
can be trapped in some cases (Me_3SiCl)

Dimethylformamide (DMF) can be used as a formylating agent



relatively stable

Weinreb amides are excellent acylating agents



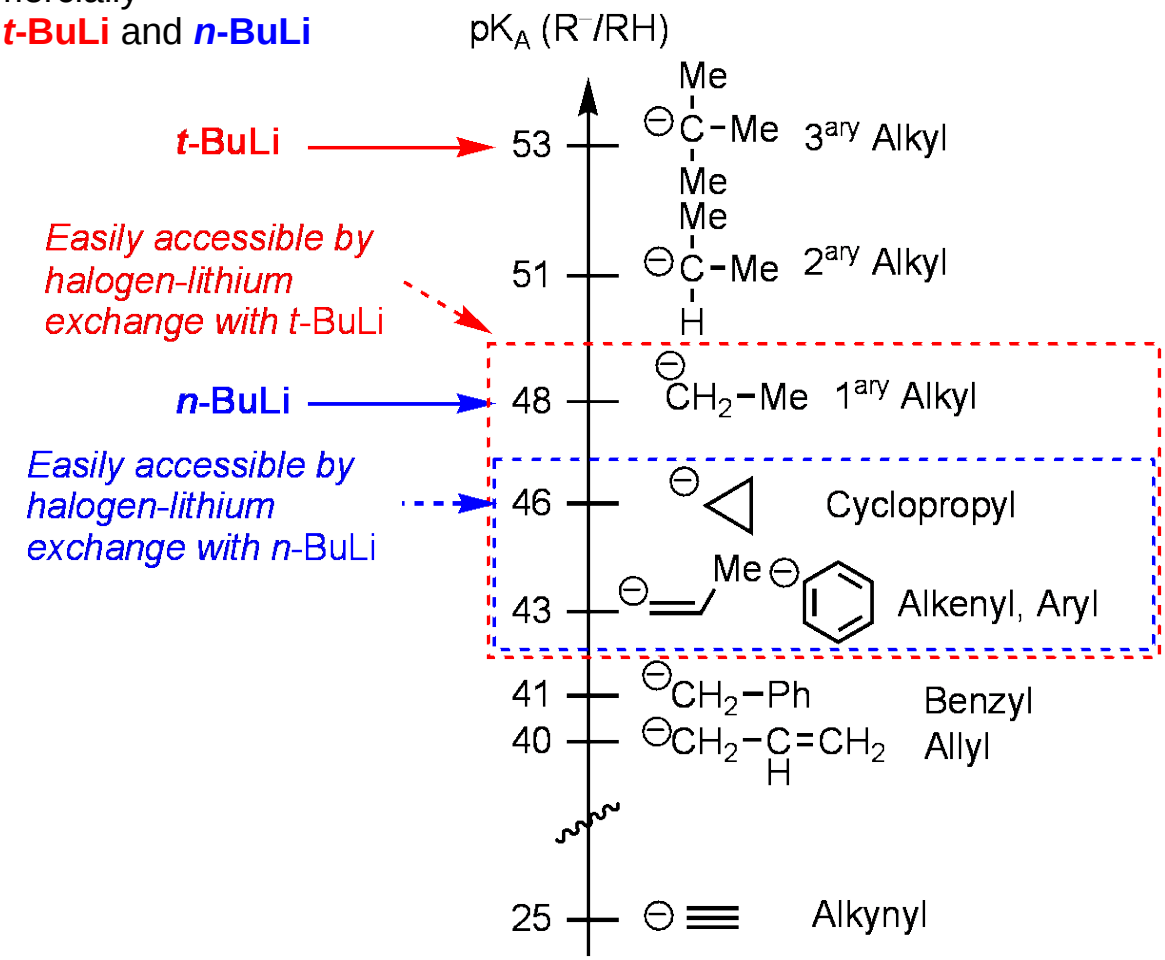
Preparation of organolithium reagents by lithium-halogen exchange

$$R{-}X + Li{-}R' \rightleftharpoons R{-}Li + X{-}R'$$

X = **I**, **Br**, Cl (rare)

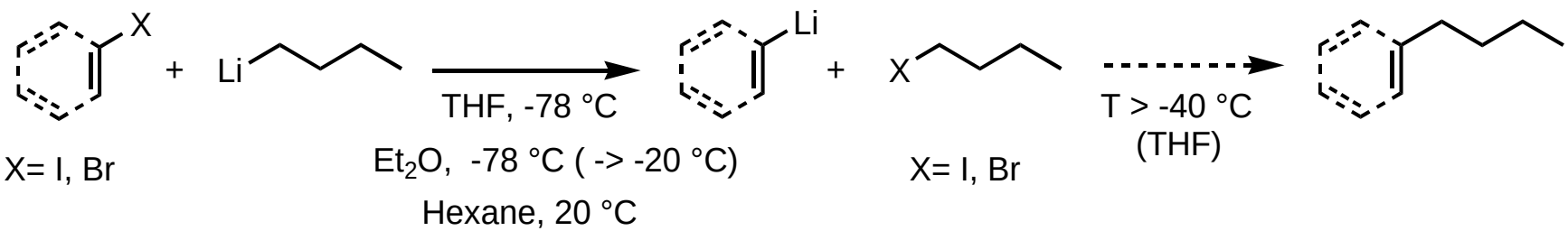
Equilibrium shifted toward the organolithium reagent corresponding to the more stable carbanion

with commercially available ***t*-BuLi** and ***n*-BuLi**



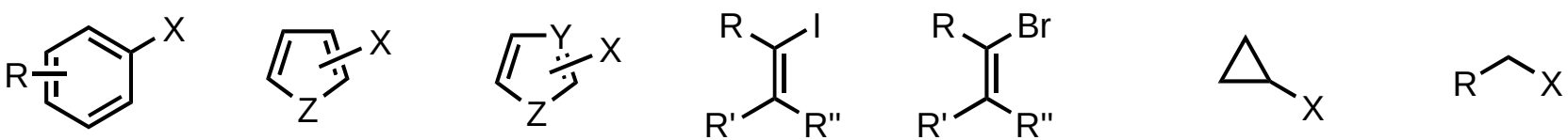
Halogen-lithium exchange with n-BuLi

$$R{-}X + n\text{-}Bu{-}Li \rightleftharpoons R{-}Li + n\text{-}Bu{-}X \quad \textit{via} \left[R{-}\bar{X}{-}Bu \;\; Li^{+} \right]$$



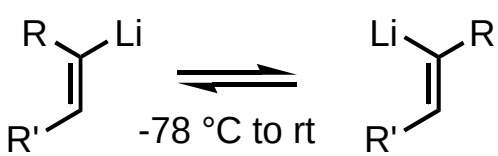
Substrates

Stereospecific reaction
(retention of configuration)



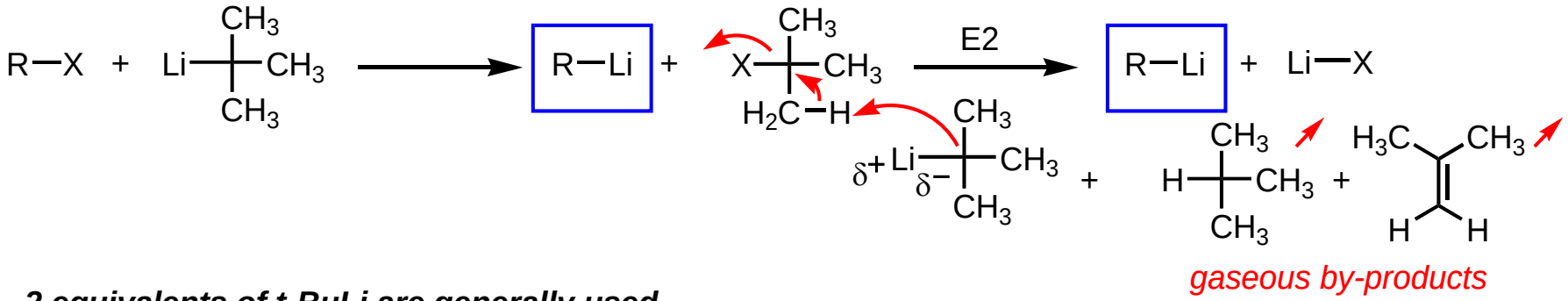
X= I, Br	X= I, Br	X= I, Br			X= I, Br	X= I, Br
+	+	+	+	— **in general*** + (some cases)	+	—

* *Side-reactions: elimination reactions*



Only for R = Aryl or $SiMe_3$

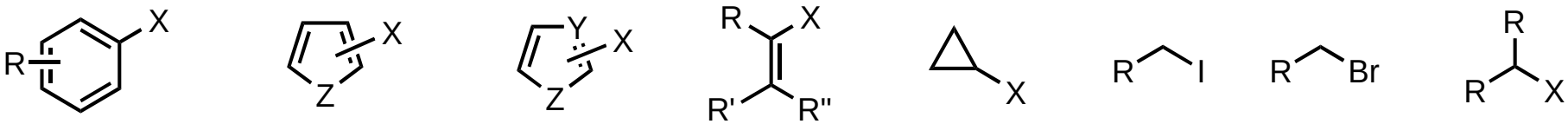
Halogen-lithium exchange with t-BuLi



2 equivalents of t-BuLi are generally used

Solvant : Ether/pentane (min 10% ether), Ether, THF

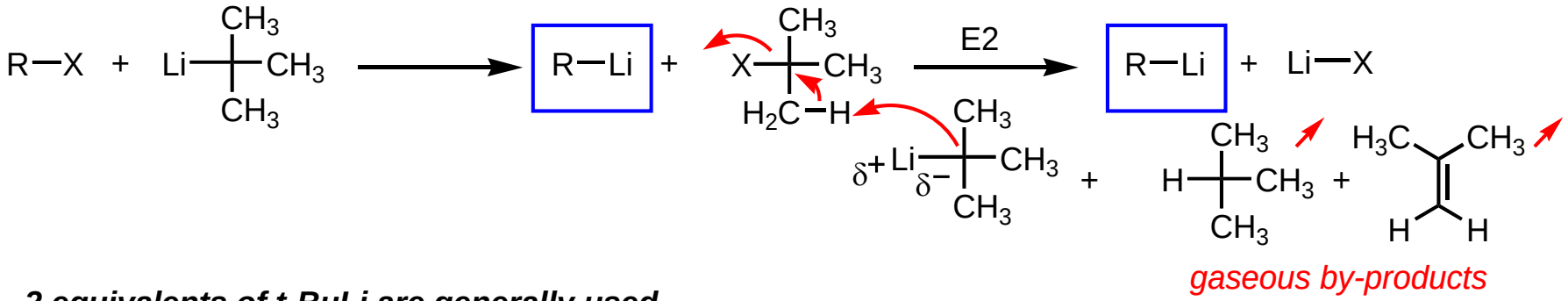
Substrates



+	+	+	+	+	+	–/+	–/+

special conditions

Halogen-lithium exchange with t-BuLi

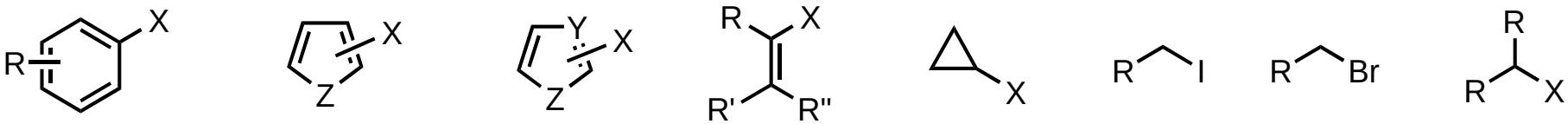


gaseous by-products

2 equivalents of t-BuLi are generally used

Solvant : Ether/pentane (min 10% ether), Ether, THF

Substrates

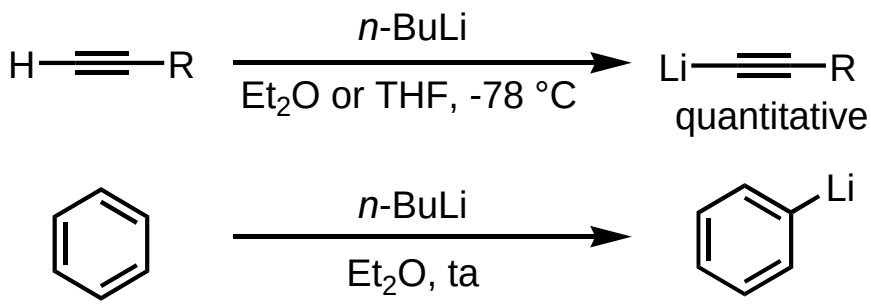


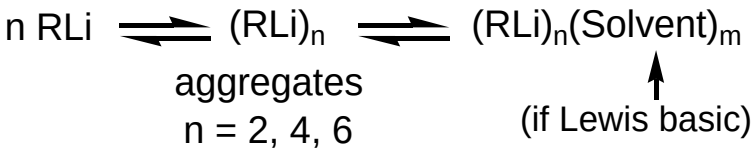
X= I, Br	X= I, Br	X= I, Br	X= I, Br	X= I, Br			X= I, Br
+	+	+	+	+	+	–/+	–/+

$CH_3(CH_2)_9CH_2I$ —*t*-BuLi (2 equiv), Pentane/ether (3:2), CH_3O**D** (10 equiv)→ $CH_3(CH_2)_9CH_2$**D** (> 90% deuterium)

What does this experiment tell us ?

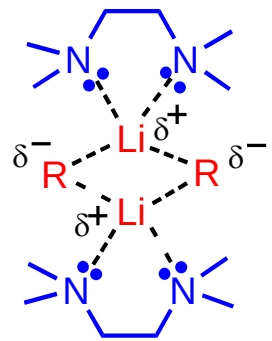
Preparation of organolithium reagents by deprotonation



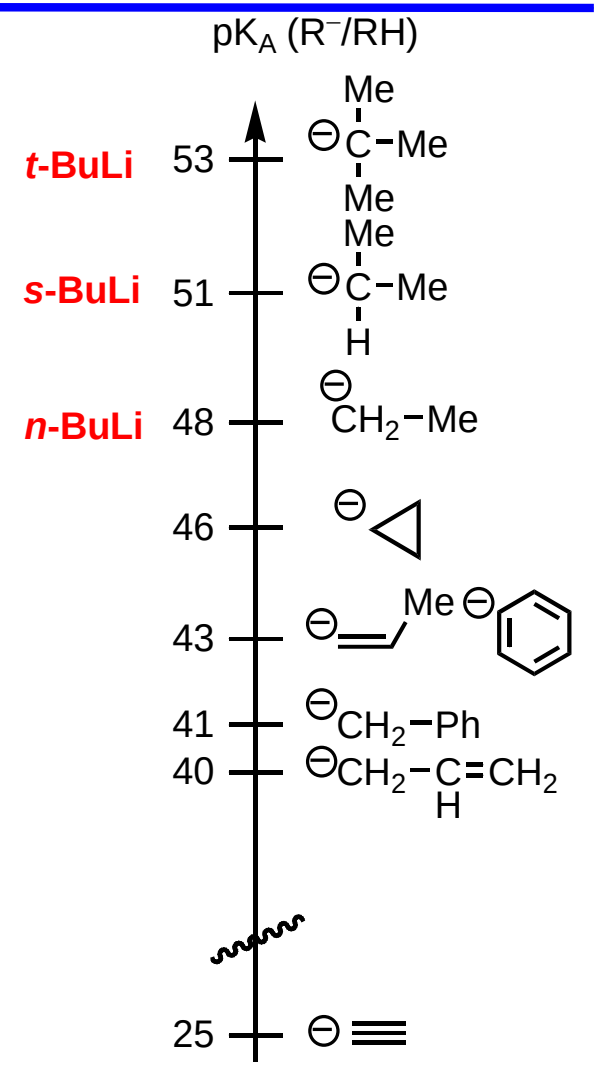


Reactivity of RLi ↑ if n ↓

n-BuLi	Cyclohexane	n = 6
	Ether	n = 4
	THF	n= 2, n = 4
t-BuLi	Cyclohexane	n = 4
	Ether	n = 2
	THF	n = 1

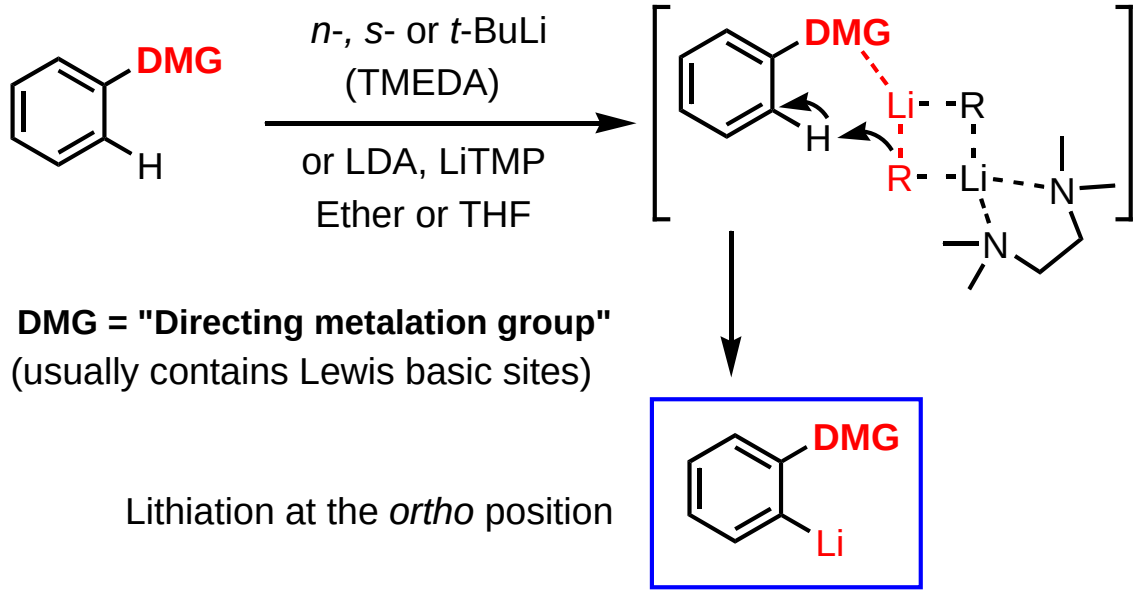


Coordination of Li increases the reactivity of RLi (nucleophilicity and basicity)



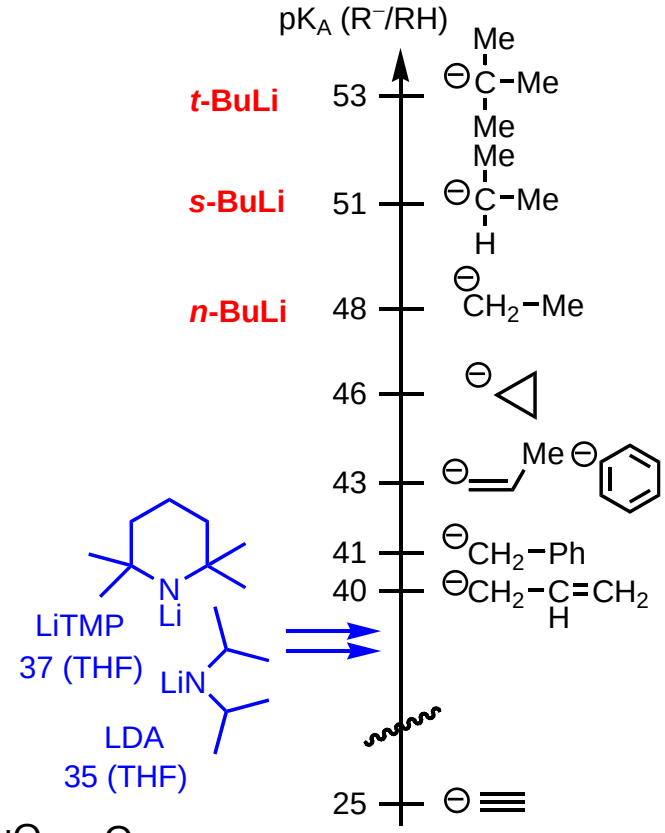
The rate efficient species is usually the monomer (or occasionally the dimer)

Directed ortholithiation of arenes

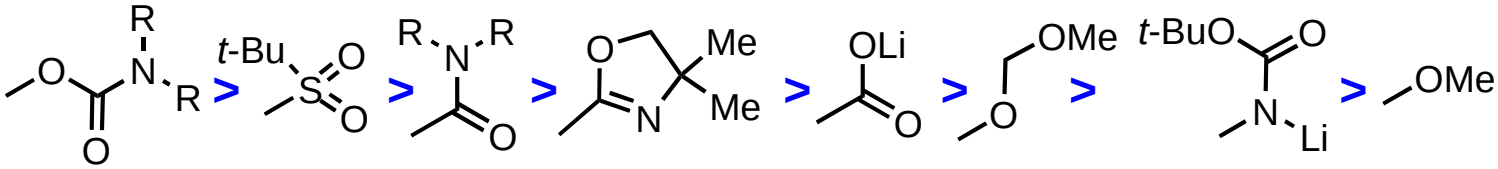


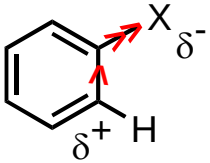
DMG = "Directing metalation group"
(usually contains Lewis basic sites)

Lithiation at the *ortho* position



Directing metalation groups

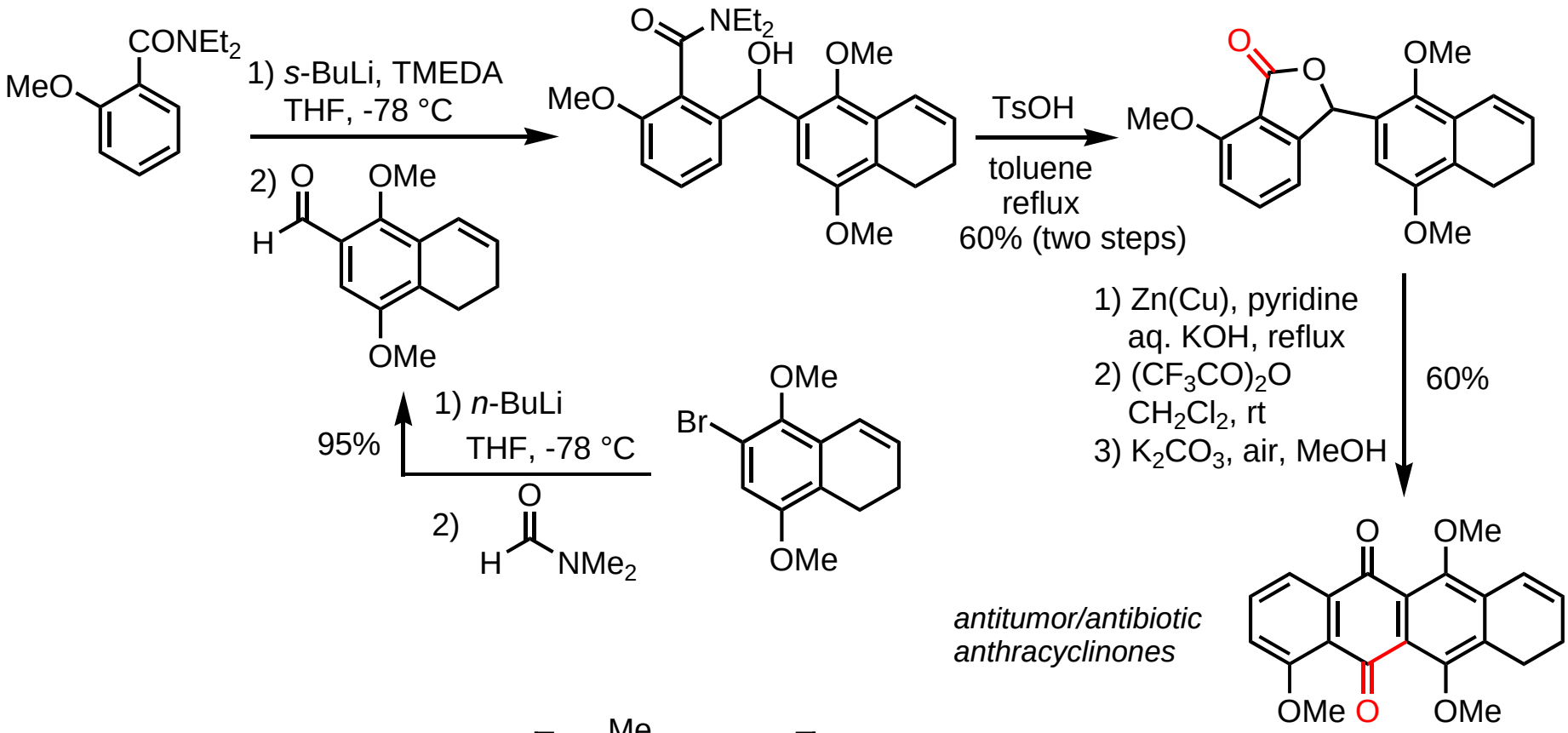


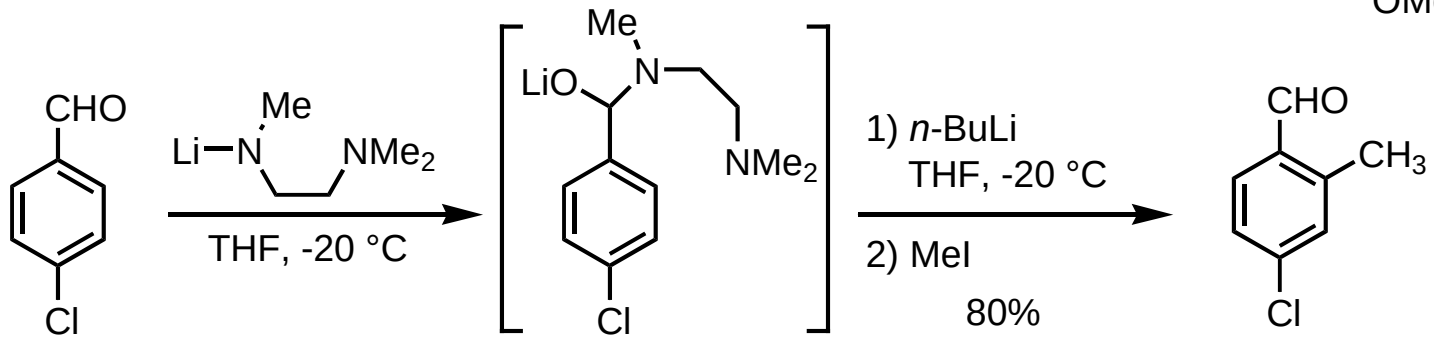


Which experiments would you perform to compare the power of these DMGs ?

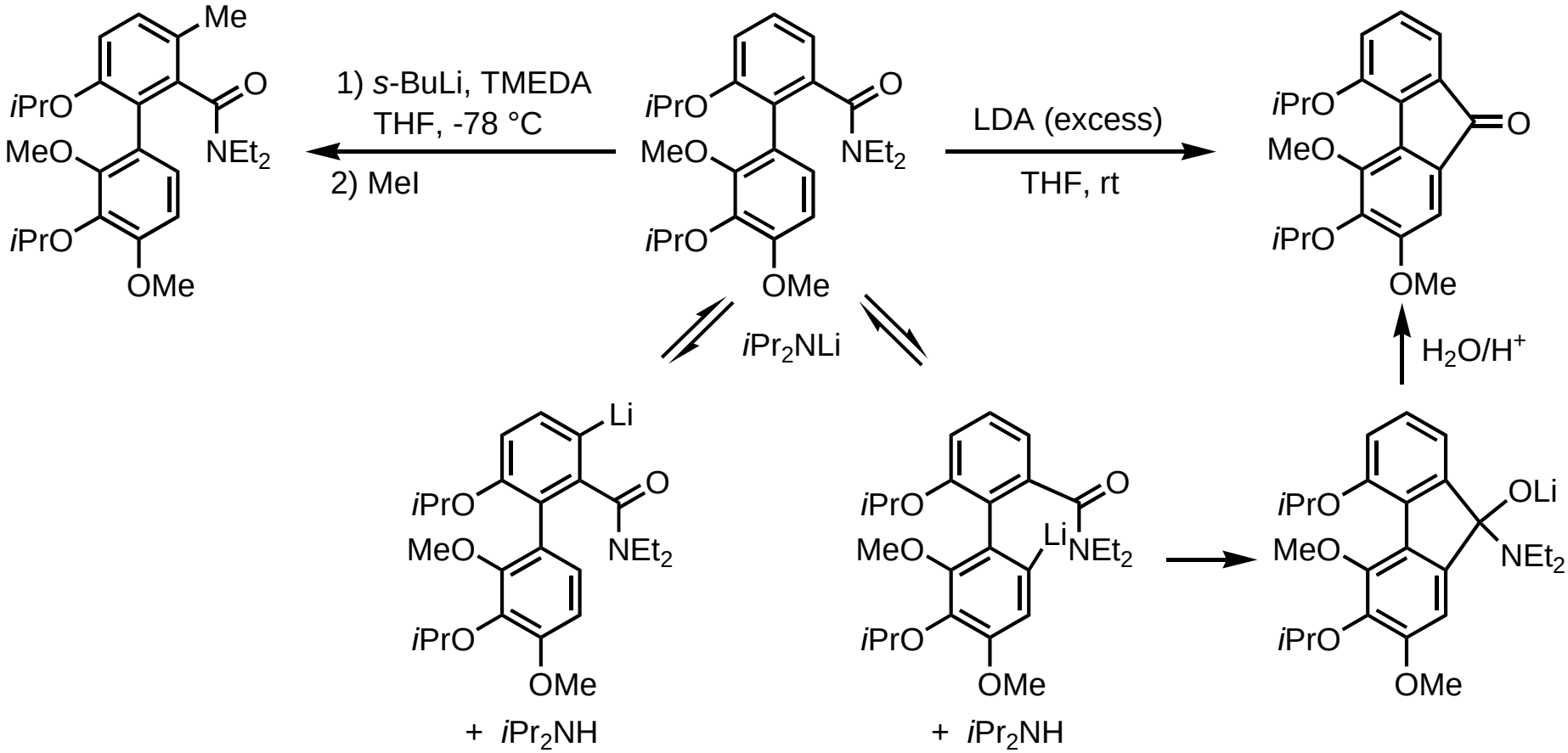
Georg Wittig
Ortholithiation of
PhOMe (1940)
Nobel Prize (1979)

Directed ortholithiation of arenes : Applications



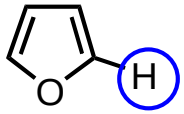


Directed ortholithiation of arenes : Applications

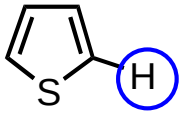


Preparation of organolithium reagents by deprotonation

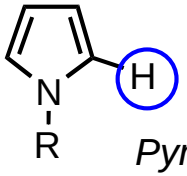
Heterocycles (*n*-BuLi, *t*-BuLi ou LDA)



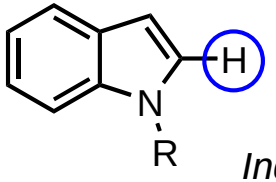
Furan



Thiophene

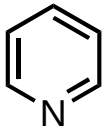


Pyrrole



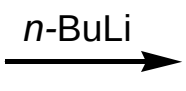
Indole

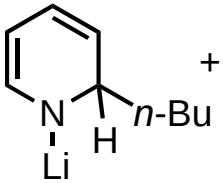
R = Alkyl, CO_2*t*-Bu, SO_2Ar



Pyridine

side reaction : addition





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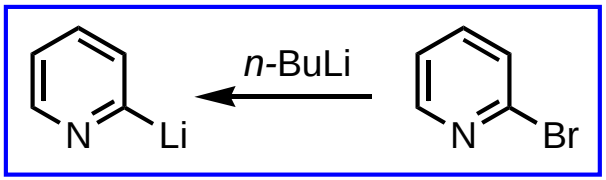
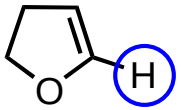
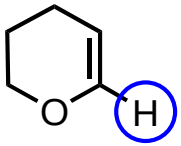


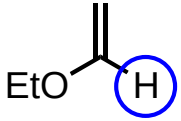
The solution : Br/Li exchange



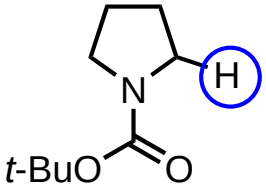
Dihydrofuran
(*t*-BuLi)



Dihydropyran
(*t*-BuLi)

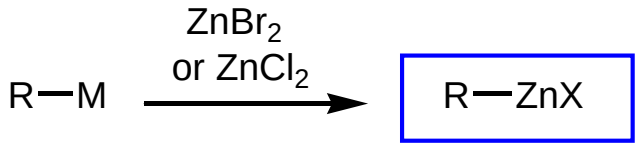


Ethyl vinyl ether
(*s*-BuLi, TMEDA)
(*t*-BuLi)



N-Boc pyrrolidine
(*s*-BuLi, TMEDA)

Organozinc reagents



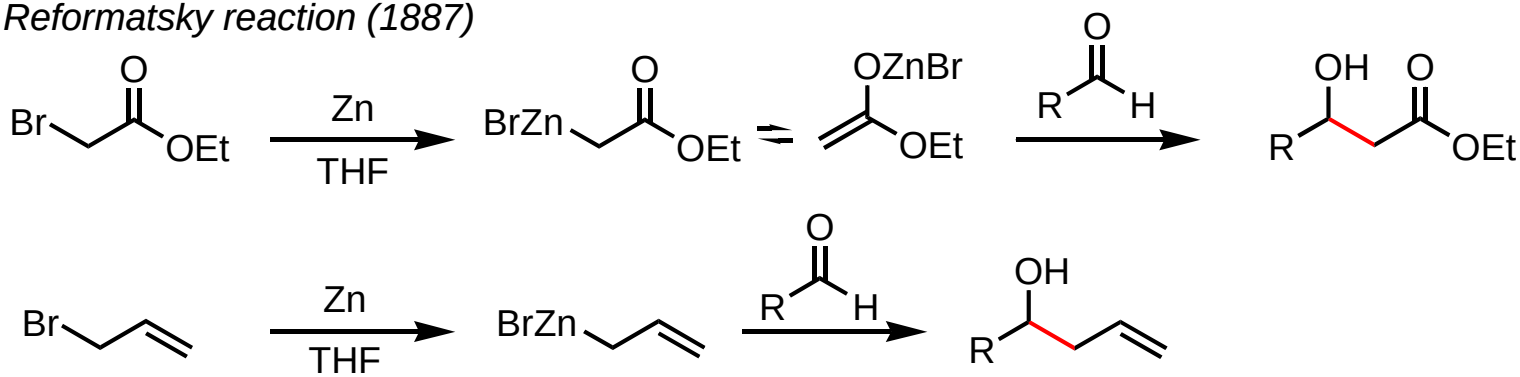
(Schlenk equilibrium : 2 R-ZnX ⇌ R_2Zn + ZnX_2)

M = Li, MgX

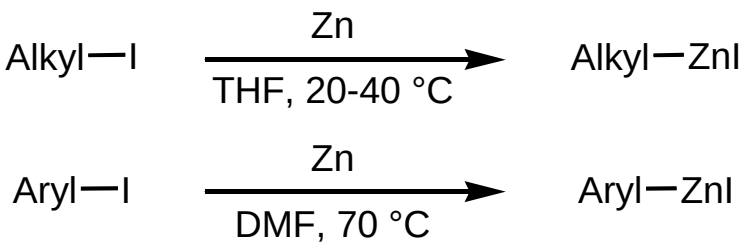
Organozinc

For some substrates, formation of the organozinc reagent by reaction with the metal is also possible

Reformatsky reaction (1887)



Y = O, CH_2



Those organozinc only react with powerful electrophiles (H^+, I_2, O_2)

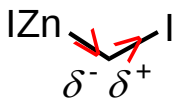
Edward Frankland
Et_2Zn (1848)

→ **High functional group tolerance**

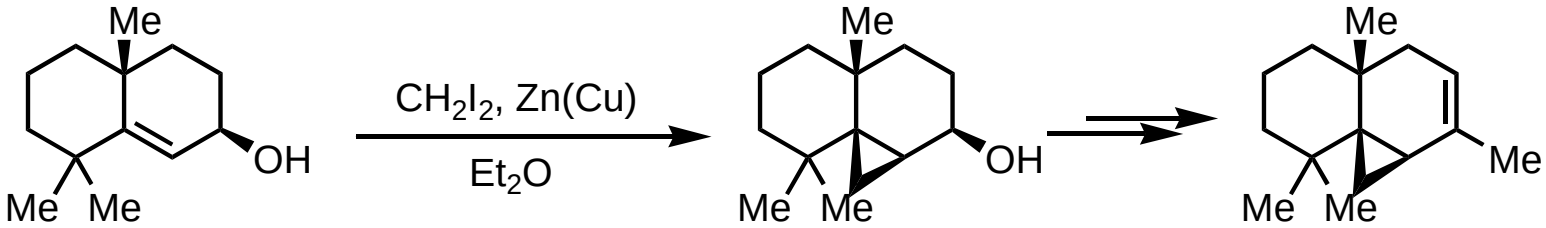
→ **Opportunity to catalyze the reaction with other electrophiles**

Simmons-Smith cyclopropanation of olefins

$I\text{-}CH_2\text{-}I$ + Zn(Cu) $\xrightarrow[Et_2O \text{ or } THF]{}$ **$I\text{-}CH_2\text{-}ZnI$** Simmons and Smith (1958)



carbenoid reagent ⇔ CH_2



(dr > 95:5) Thujopsene

Preparation of zinc carbenoids by iodine-zinc exchange

Furukawa (1963), Denmark (1991)

$I\text{-}CH_2\text{-}I \xrightarrow[CH_2Cl_2]{Et_2Zn}$ **$I\text{-}CH_2\text{-}ZnEt$** (+ EtI) $\xrightarrow[CH_2Cl_2]{I\text{-}CH_2\text{-}I}$ **$I\text{-}CH_2\text{-}Zn\text{-}CH_2\text{-}I$** (+ EtI)

The zinc carbenoids can be generated *in situ* and allowed to react with the olefin

Reviews: Org. React. **2001**, *58*, 1; *Chem. Rev.* **2003**, *103*, 977

Organocopper reagents

$$R{-}Li + CuX \xrightarrow[Et_2O \text{ or } THF]{} R{-}Cu + LiX \xrightarrow{R{-}Li} R_2CuLi \xrightarrow{R{-}Li} R_3CuLi_2$$

CuI or
$CuBr.SMe_2$

Organocopper
insoluble and poorly reactive

R_2CuLi
(soluble)
Organocuprate
"Gilman cuprate"

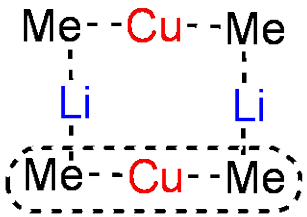
"Higher-order cuprate"

$CuI.PBu_3$ soluble

$RCu.PBu_3$ soluble/reactive

Thermally unstable reagents

Me_2CuLi, Ph_2CuLi (limit 0 °C)
n-Bu_2CuLi (limit -30 to -40 °C)
t-Bu_2CuLi (limit -50 °C)



Structure of Me_2CuLi

Henry Gilman
RCu (1936)
R_2CuLi (1952)

With Grignard reagents

$RCu.MgX_2$ ($RMgX + CuX$)

$R_2CuMgX.MgX_2$ magnesium organocuprates ($2\ RMgX + CuX$)

RMgX + CuX catalytic generates *in situ* magnesium organocuprates (lower/higher order)

Organocuprates

$$R_2CuLi \xrightarrow[\text{electrophilic reagent}]{\text{" } E^+ \text{ "}} R{-}E + RCu + Li^+ \xrightarrow[H_2O\ (air)]{NH_4Cl/NH_4OH} R{-}E + R{-}H + Cu(NH_3)_4^{2+}$$

Cuprate

Not reactive

In general, a single R group can be transferred to the electrophilic reagent

Solution : use of mixed organocuprate $R\text{-}\overset{-}{Cu}\text{-}R'\ Li^+$
with a non transferable R' group

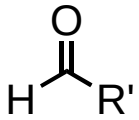
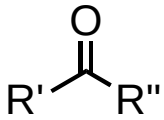
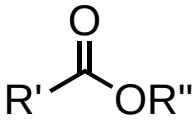
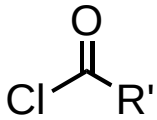
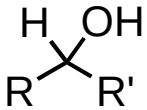
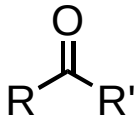
Cyanocuprates are also useful reagents

$$R{-}Li + CuCN \xrightarrow[\text{ether or THF}]{} RCu(CN)Li \xrightarrow{R{-}Li} R_2Cu(CN)Li_2$$

Cyanocuprate

Higher order cyanocuprate

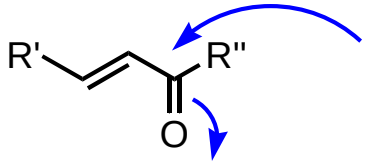
Reactivity of organocopper reagents

R_2CuLi + Electrophiles				
Product		no reaction	no reaction	

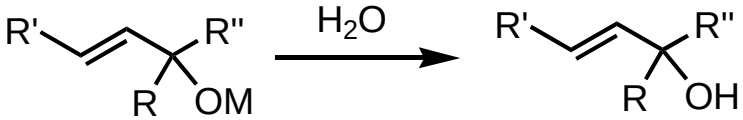
Chemoselectivity

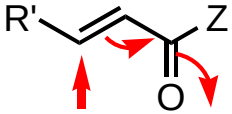
Organocopper reagents are soft nucleophiles ⇨ Unique reactivity profile

Conjugate addition *(1,4-addition)*



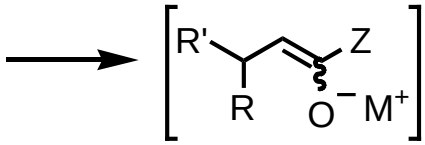
R-Li, R-MgX
1,2-addition



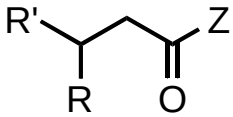


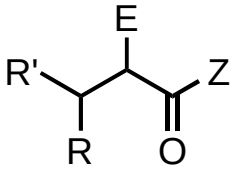
R_2CuLi
$R_2Cu(CN)Li_2$

RMgX + cat. CuX



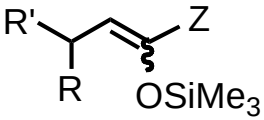
M = CuRLi, $CuR(CN)_2Li$, OMgX





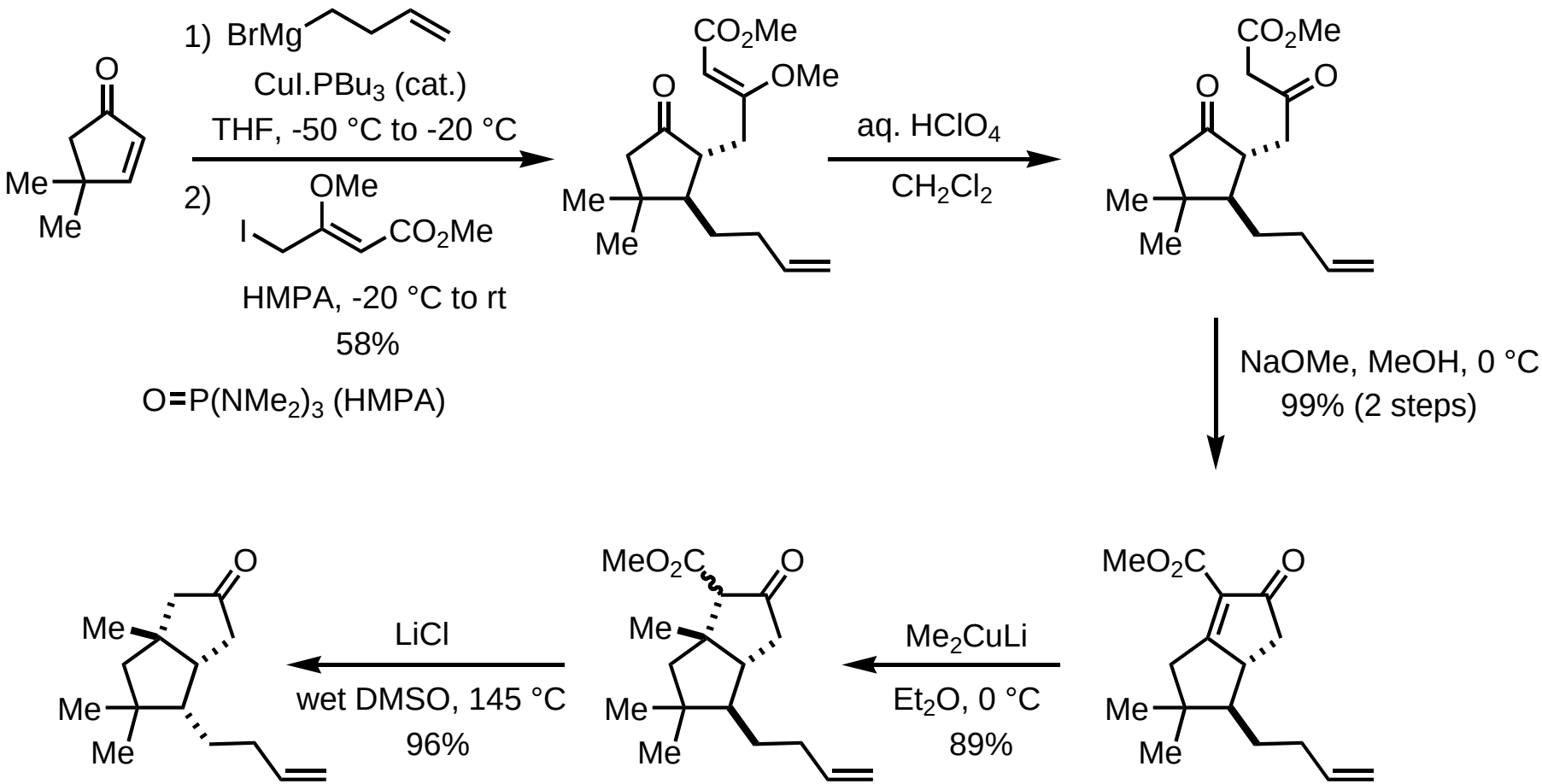
with alkylating agents

CH_3I, $H_2C{=}CHCH_2Br$,
$PhCH_2Br$, MeO_2CCH_2Br



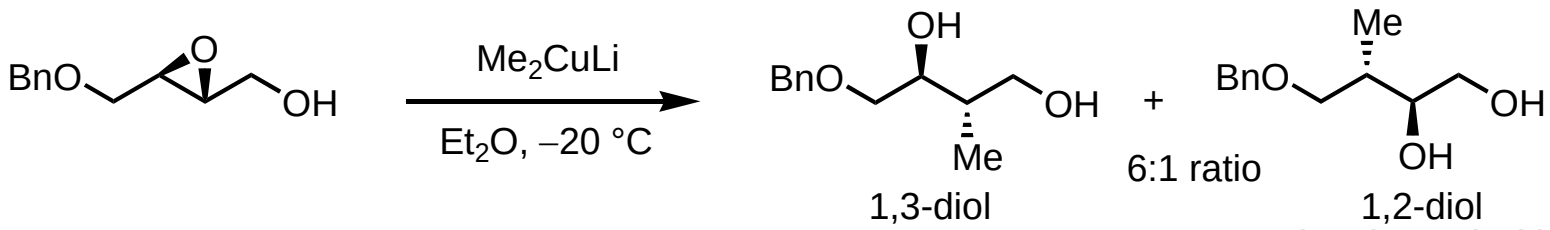
with Me_3SiCl

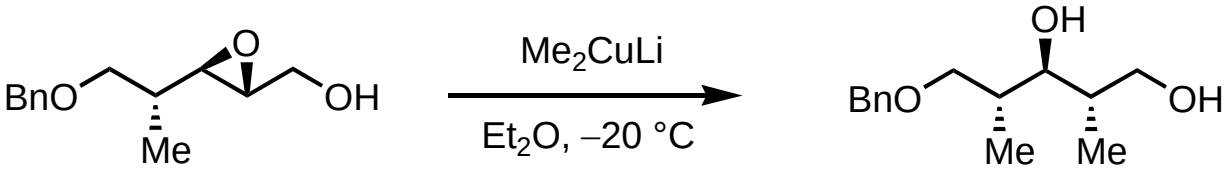
Reactivity of organocopper reagents : 1,4-Addition

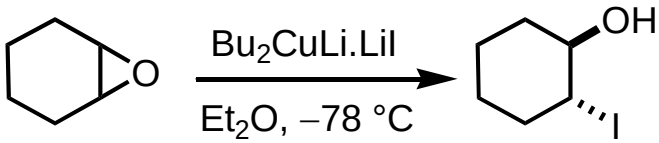


JACS **1986**, *108*, 3435

Reactivity of organocopper reagents: Ring-opening of epoxides

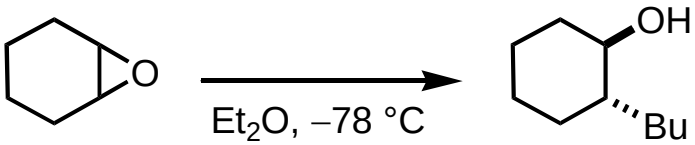






12%

Disubstituted epoxides are poorly reactive

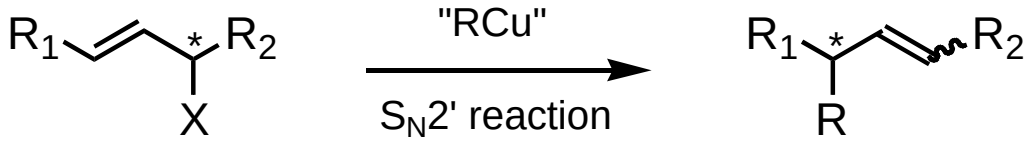


$Bu_2CuLi.LiBr + BF_3.OEt_2$ 80%

$Bu_2Cu(CN)Li_2 + BF_3.OEt_2$ 88%

Cuprates compatible with BF_3 (up to -40 °C)

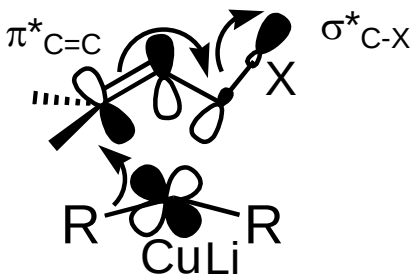
Reactivity of organocopper reagents: S_N2' Reactions



X = Halide (I, Br, Cl), OSO_2R', OCO_2R', $OP(=O)(OR')_2$, OCOR', OR', OCONHR

Although S_N2' is generally favored, S_N2 often competes

RCu(CN)Li and **$R_2Cu(CN)Li_2$** or **RMgBr + cat. CuCN**
Best reagents for high S_N2' regioselectivity

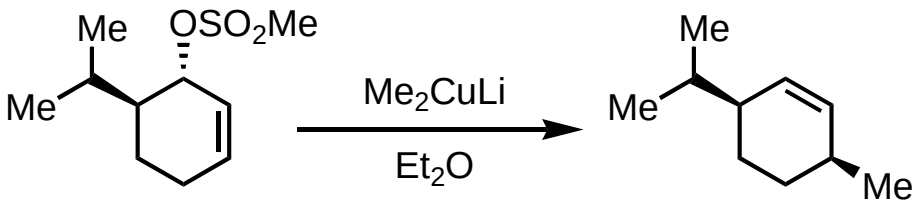


3 orbital overlap: d_{xz}(Cu) - $\pi^*_{C=C}$ - σ^*_{C-X}
anti S_N2' displacement of X

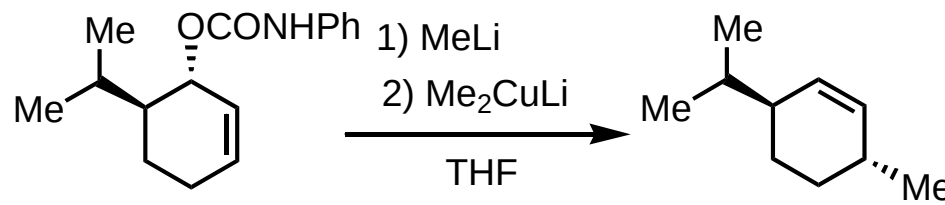
Unlike S_N2, S_N2' reactions can also involve a *syn* process

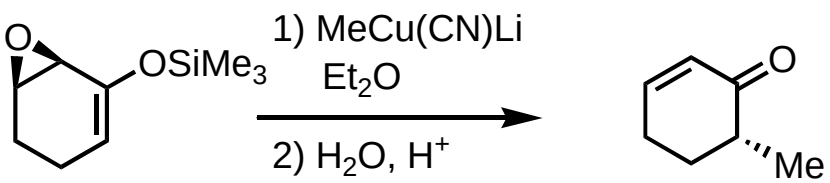
syn S_N2' occurs if X is able to coordinate the organocopper reagent

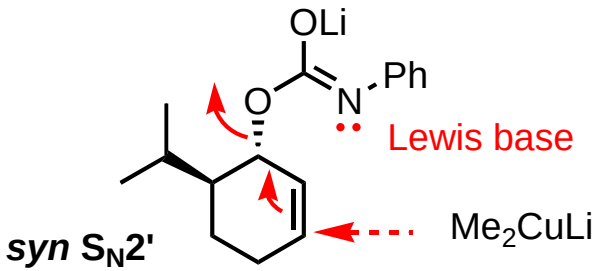
Reactivity of organocopper reagents: S_N2' Reactions



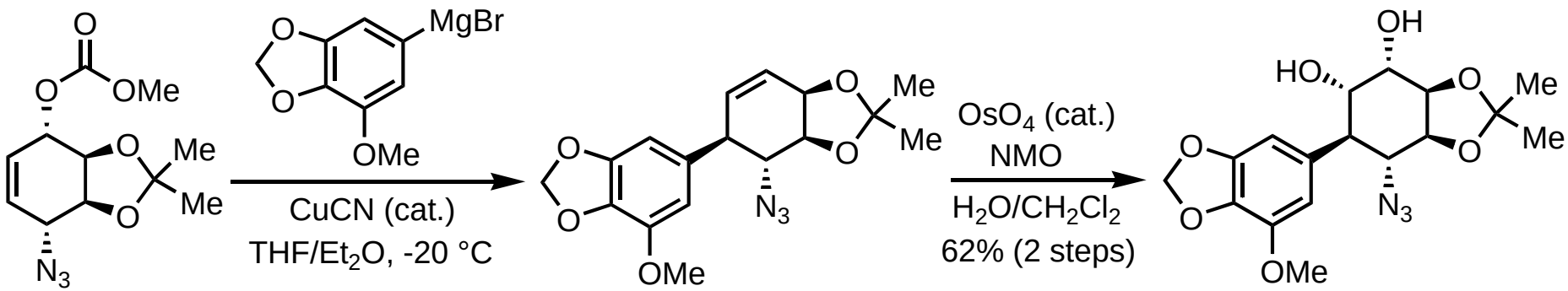
***anti* S_N2'**



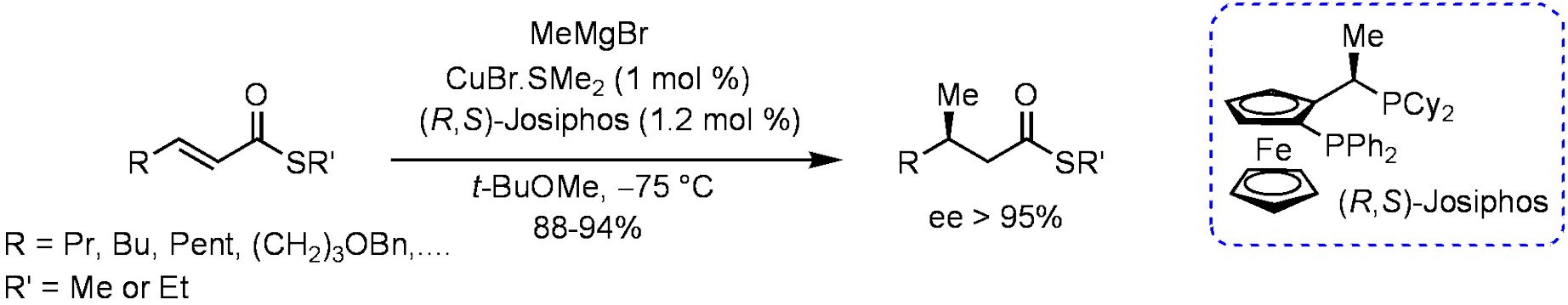




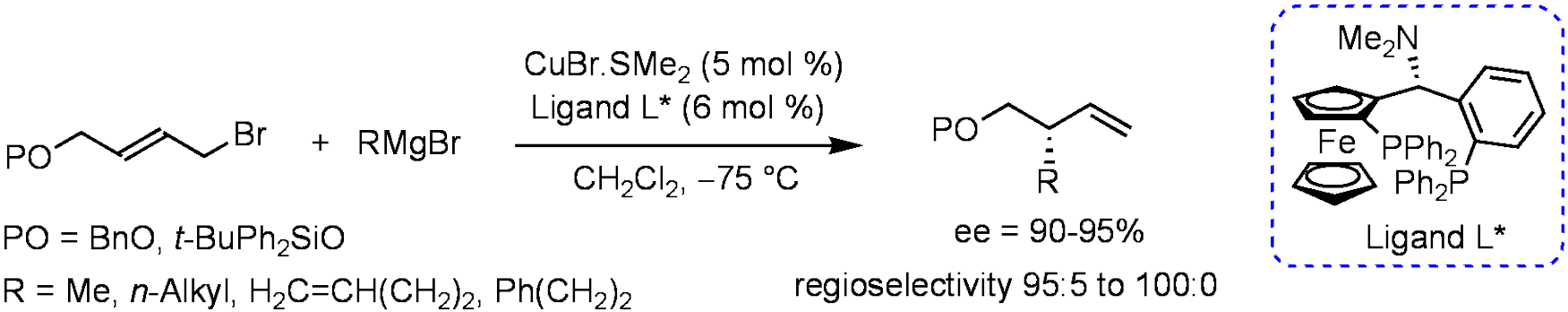
***syn* S_N2'**



Catalytic enantioselective reactions of organocopper reagents



Feringa, B. *Acc. Chem. Res.* **2007**, *40,* 179



Feringa, B. *J. Org. Chem.* **2007**, *72,* 2558

Bernard L. Feringa
Nobel Prize (2016) for molecular machines
with J. P. Sauvage and J. F. Stoddart

Transmetalation reactions

$$R{-}M_1 + M_2{-}X \rightleftharpoons R{-}M_2 + M_1{-}X$$

Equilibrium shifted toward the most covalent organometallic reagent

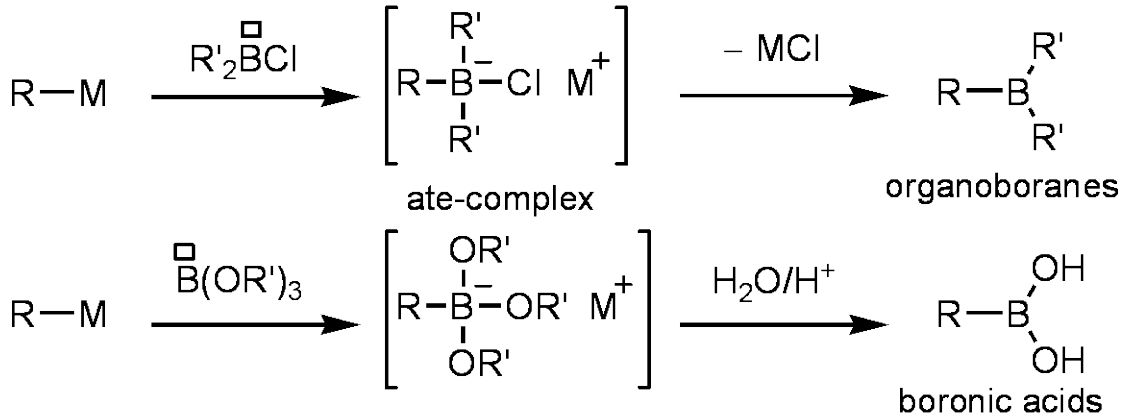
$$R{-}M \xrightarrow{Me_3SiCl} R{-}SiMe_3$$

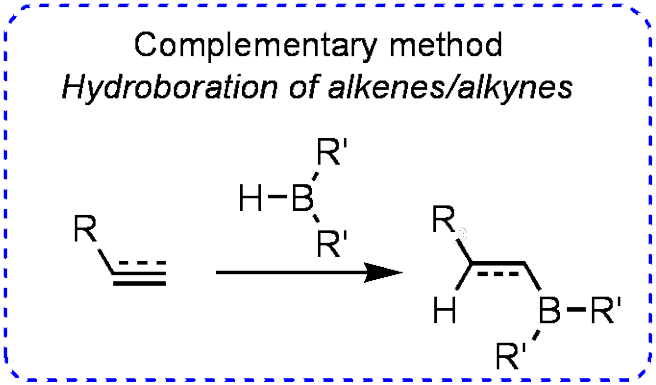
Organosilanes

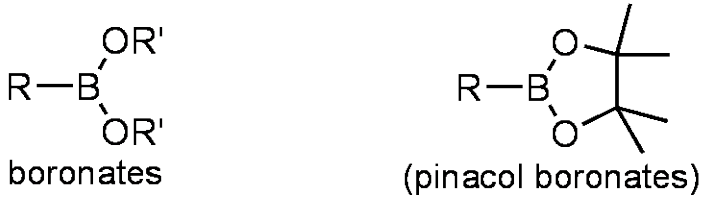
$$R{-}M \xrightarrow{n\text{-}Bu_3SnCl} R{-}SnBu_3$$

Organostannanes

These covalent organometallic reagent can be purified by chromatography







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An Overview of Palladium-Catalyzed Cross-Coupling Reactions

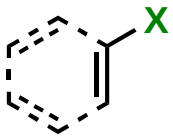
SYNTHETIC METHODS IN MOLECULAR CHEMISTRY (SMMC)

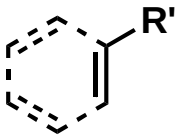
2019

Palladium-catalyzed cross-coupling reactions

Richard F. Heck Ei-ichi Negishi Akira Suzuki

Nobel Prize in Chemistry (2010) for palladium-catalyzed coupling reactions



+ **M—R'** $\xrightarrow{\text{cat. Pd(0)}}$ 

+ M—X

X = I, Br, Cl, OTf (OSO_2CF_3)

M = **MgX**	*Corriu-Kumada*
M = **ZnX**	*Negishi*
M = **SnR''$_3$**	*Stille (-Kosugi-Migita)*
M = **BR''$_2$**	*Suzuki-Miyaura (+ base)*
M = **SiR''$_3$**	*Hiyama (+ base/fluoride sources)*
Cu—C≡CR''	*Sonogashira*

Metal-Catalyzed Cross-Coupling Reactions

Stang, P. J.; Diederich, F. Eds. Wiley (1996)
De Meijere, A.; Diederich, F. Eds. Wiley (2004)

Palladium complexes

Pd

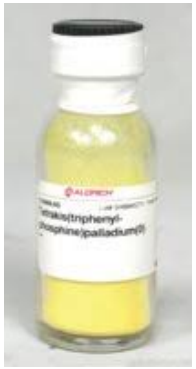
Z = 46 $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 4s^2\ 3d^{10}\ 4p^6\ 5s^2\ 4d^8\ 5p^0$

$(n\text{-}1)d^x\ ns^y$ indicated as "d^{x+y}" Pd(0) d^{10} and Pd(II) d^8

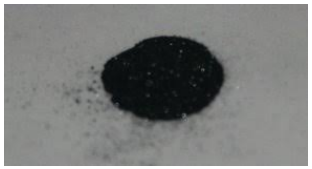
Electronegativity (Pauling) = 2.2 (C 2.5) : C-Pd bond is not engaged in polar chemistry

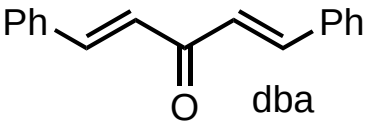
Pd(0) complexes

$Pd(PPh_3)_4$



$Pd(dba)_2$ or **$Pd_2(dba)_3.CHCl_3$**

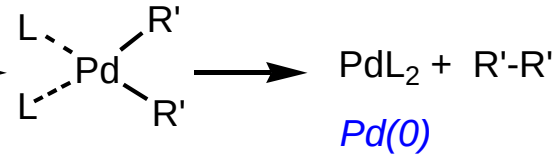




displaced by more coordinating ligands

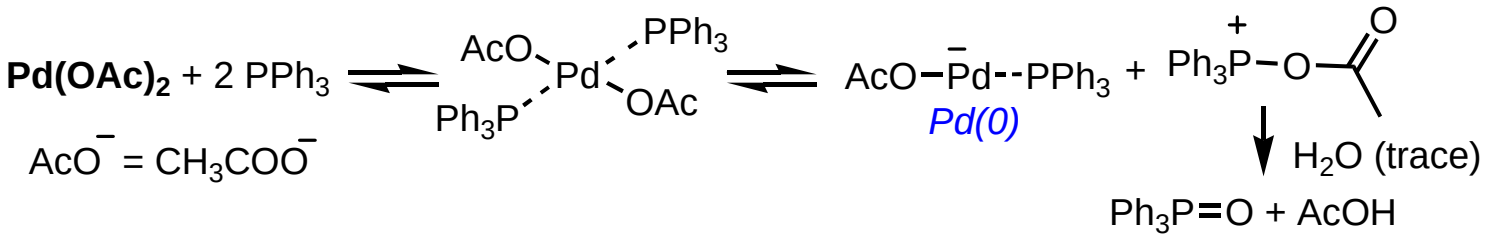
Pd(II) complexes

reduced *in situ*



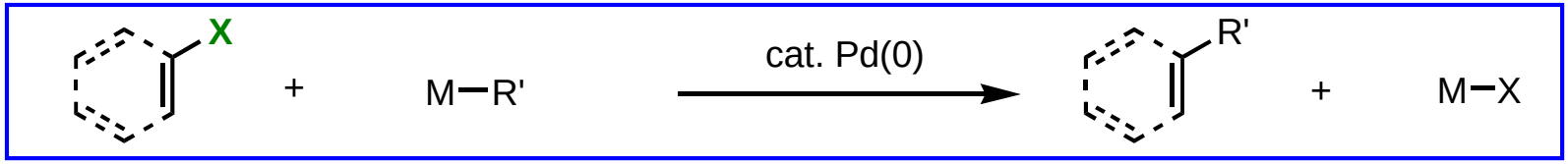
(L = PPh_3, MeCN...)

$Pd(OAc)_2$



$AcO^- = CH_3COO^-$

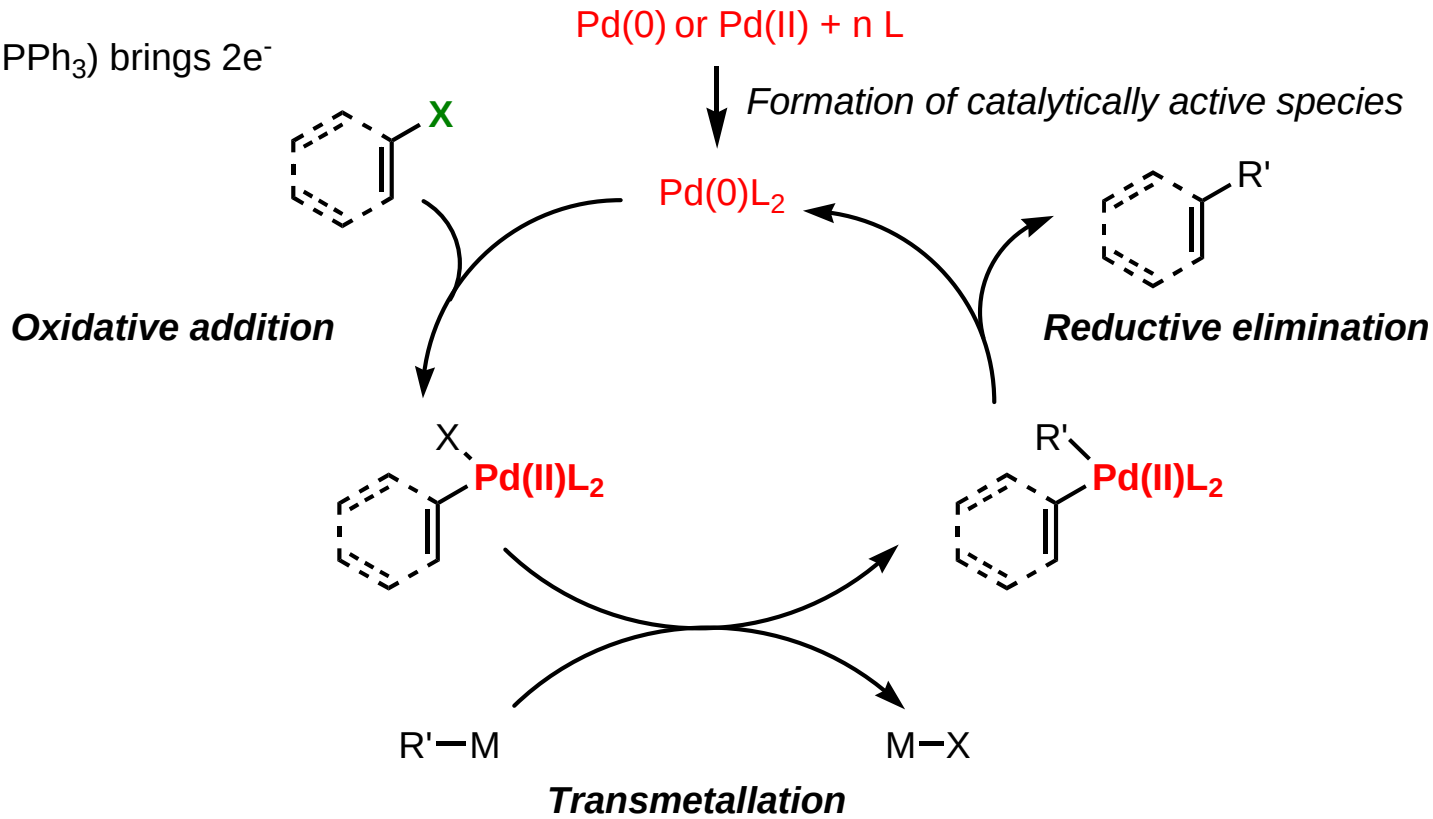
Catalytic cycle



X = I, Br, Cl, OTf (OSO_2CF_3)

Simplified general mechanism

Pd(0) d^{10}
L ligand (ex: PPh_3) brings $2e^-$



Metal-Catalyzed Cross-Coupling Reactions

Stang, P. J.; Diederich, F. Eds. Wiley (1996)
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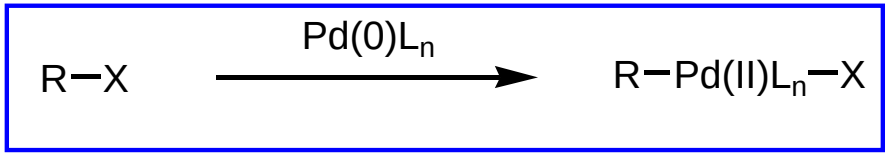
Oxidative addition



$Pd(0)L_n$ should be **coordinatively unsaturated** : n = 2 (14 e^-) or even better n = 1 (12 e^-)
.... but black Pd may precipitate

Favored by **electron-rich Pd(0) complexes** (*ie* with **strongly electron-donating ligands**)

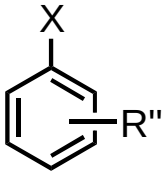
Favored by **mono-coordinated Pd(0) complexes** (n = 1) (steric reasons)

$P(Alkyl)_3$ is a better σ-donating ligand than $P(Aryl)_3$

I > Br > OTf >> Cl
in general

E dissociation (kcal/mol)

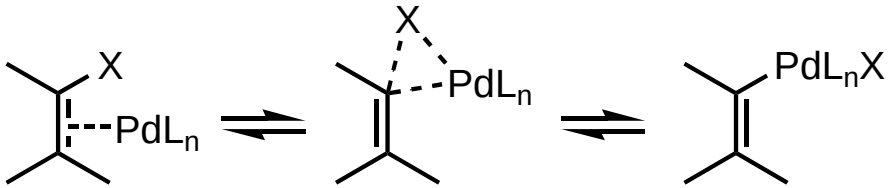
C-I	65
C-Br	80
C-Cl	95



Electron-withdrawing R'' group accelerates OA
Electron-releasing R'' group slows down OA

concerted (3-centered TS)

Most common mechanism



Aryl/vinyl halides are more reactive than alkyl halides

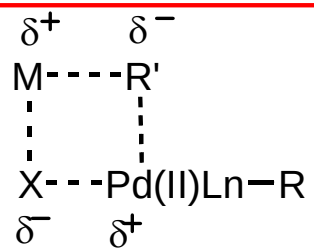
Transmetalation

$$R-Pd(II)L_n-X \quad + \quad R'-M \longrightarrow R-Pd(II)L_n-R' \quad + \quad M-X$$

Oxidation state of the metal does not change

Favored by **an electrophilic Pd(II)** center in $RPd(II)L_nX$

Favored by the nucleophilic character or R'-M



σ bonds metathesis

$R'ZnX > R'SnBu_3 > R'B(OH)_2$

Slow transmetalation
Additive LiCl (X = OTf)

Mandatory additive : Base

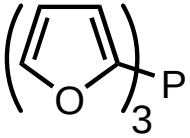
For RZnX, $RSnBu_3$

Step favored by

Poor electron-donating ligand
accelerates transmetalation

Ph_3As soft ligand

and/or



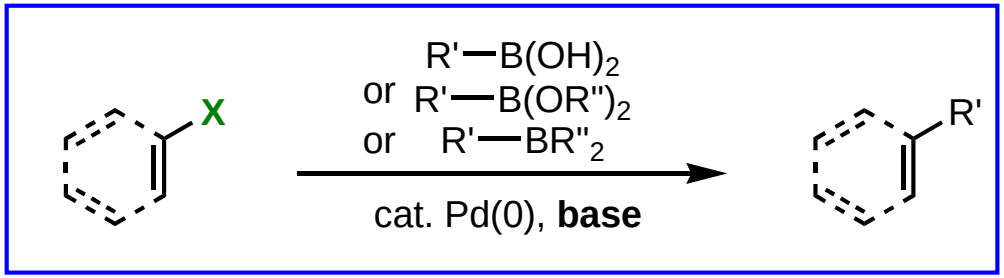
less σ donor than PPh_3 and more π acidic

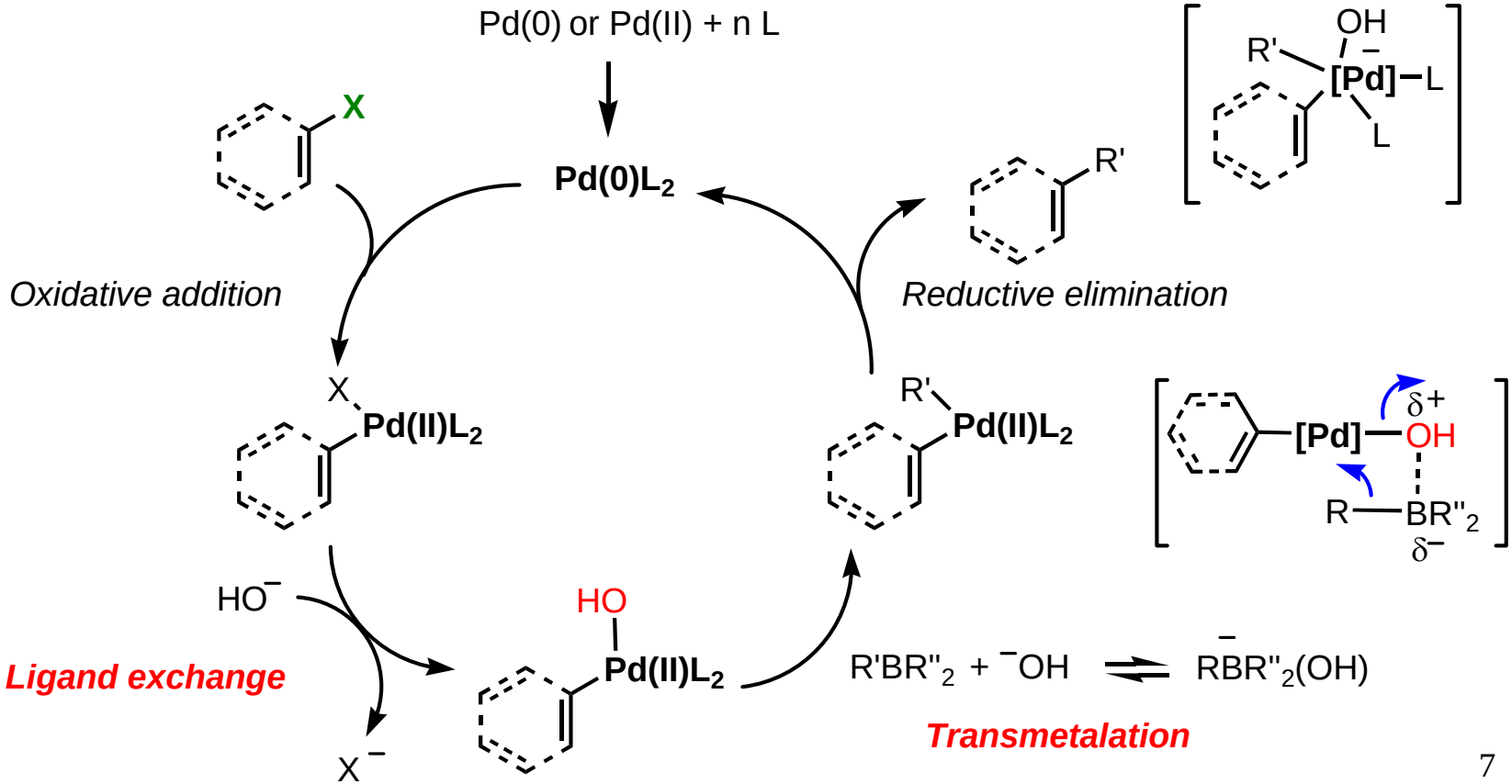
A mono-coordinated Pd(II) complex (n = 1)

Mono-coordination favors the approach of the reactants

Less ligands on Pd(II)

Transmetalation in Suzuki-Miyaura coupling reactions





Reductive elimination

$$R{-}Pd(II)L_n{-}R' \longrightarrow Pd(0)L_n + R{-}R'$$

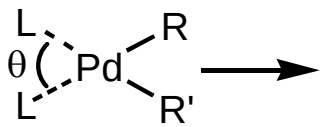
Relative rates of R.E. $C(sp^2)$-$C(sp^2) > C(sp^2)$-$C(sp^3) > C(sp^3)$-$C(sp^3)$

Step favored by

Low electron density on Pd(II) (Pd(II) destabilized, formation of Pd(0) favored)

Dissociation of a ligand on Pd(II) (n = 1): **sterically hindered ligand**

or **bidentate ligands with large bite-angles**



$\longrightarrow PdL_2 + R\text{-}R'$ (θ ↗ : rate acceleration)

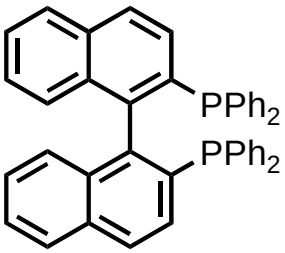
Bite angle (diphosphines)

$Ph_2P(CH_2)_nPPh_2$

dppe (n = 2) θ = 85°

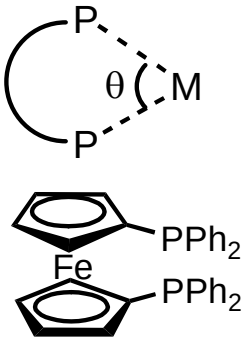
dppp (n = 3) θ = 91°

dppb (n = 4) θ = 98°



Binap

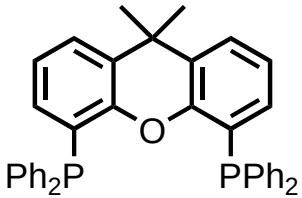
θ = 85°



dppf

θ = 99°

average
P-Rh length 2.315 Å

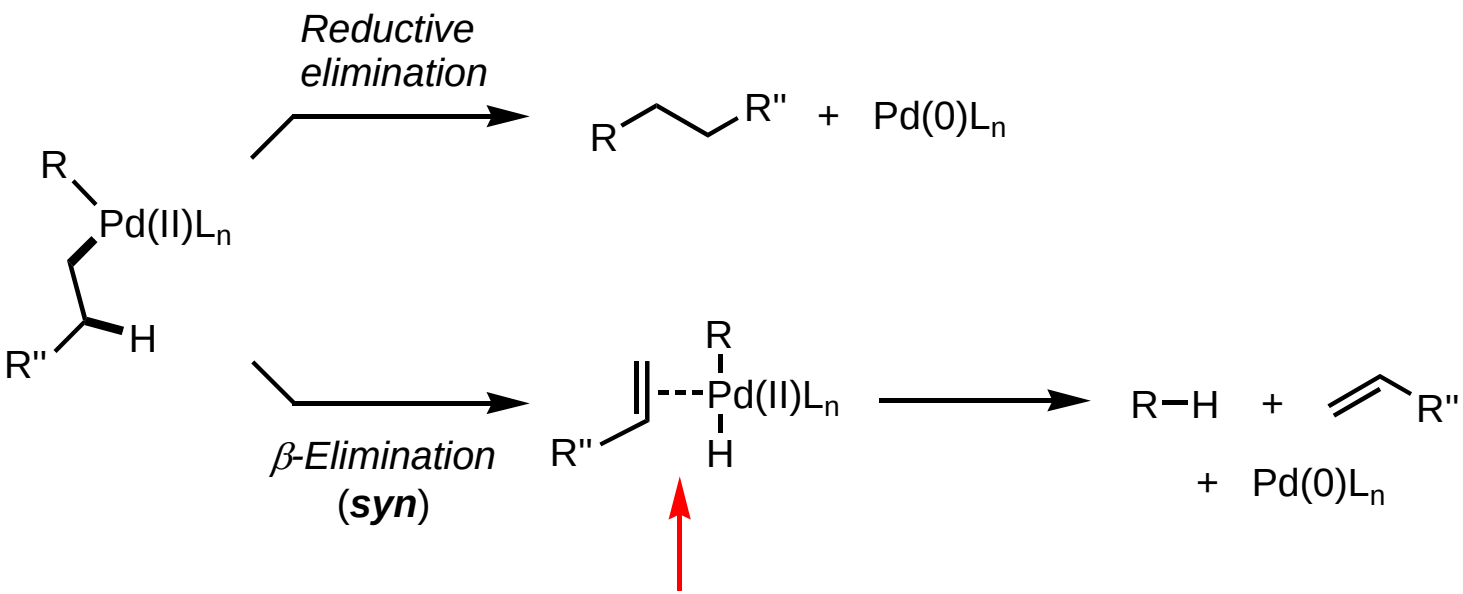


XantPhos

θ = 111°

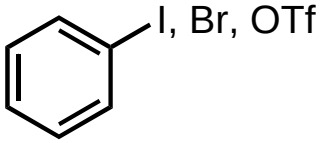
Reductive elimination and competitive β-H elimination

A competitive reaction when hydrogen atoms are present at the β position of Pd(II)

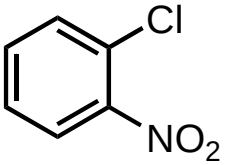


Coordination number of Pd(II) increases:
Disfavored by hindered and/or bidentate ligand

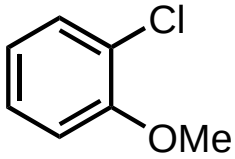
Expanding the substrate scope : The search for efficient ligands



usually not
difficult substrates



OA in C-Cl bond
favored by NO_2



very difficult substrate
(OA difficult step)

For many years, aryl chlorides could not be used as substrates because no efficient catalytic system was available. The critical step: oxidative addition

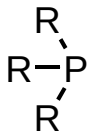
For high efficiency: not a single step of the catalytic cycle should be accelarated if the others remained slow under the same conditions

	Oxidative addition	Transmetalation	Reductive elimination
Electron-rich ligand	+	–	–
Mono-coordinated Pd	+	+	+

→ Electron-rich and sterically hindered ligands solved the problem

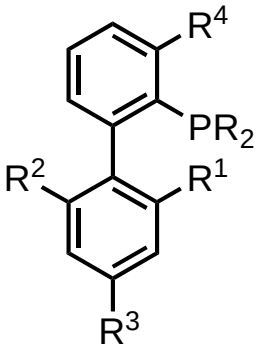
Efficient ligands in Pd-catalyzed cross-coupling reactions

Trialkylphosphines
(Fu)



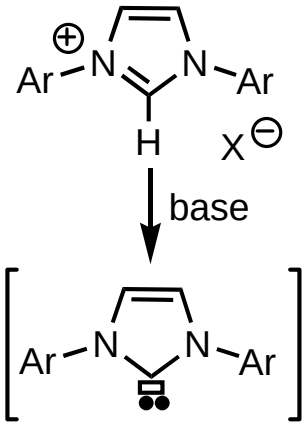
R = Cyclohexyl (Cy)
R = *t*-Bu

Biaryldialkylphosphines
(Buchwald)

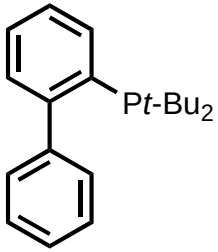


R = Cyclohexyl (Cy)
R = *t*-Bu

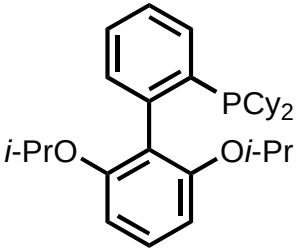
NHC (*N*-heterocyclic carbenes)
(Nolan)



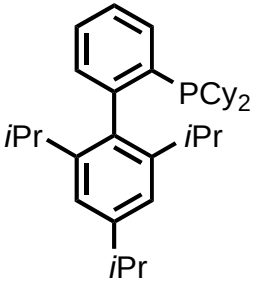
Excellent
σ-donor
ligand



JohnPhos



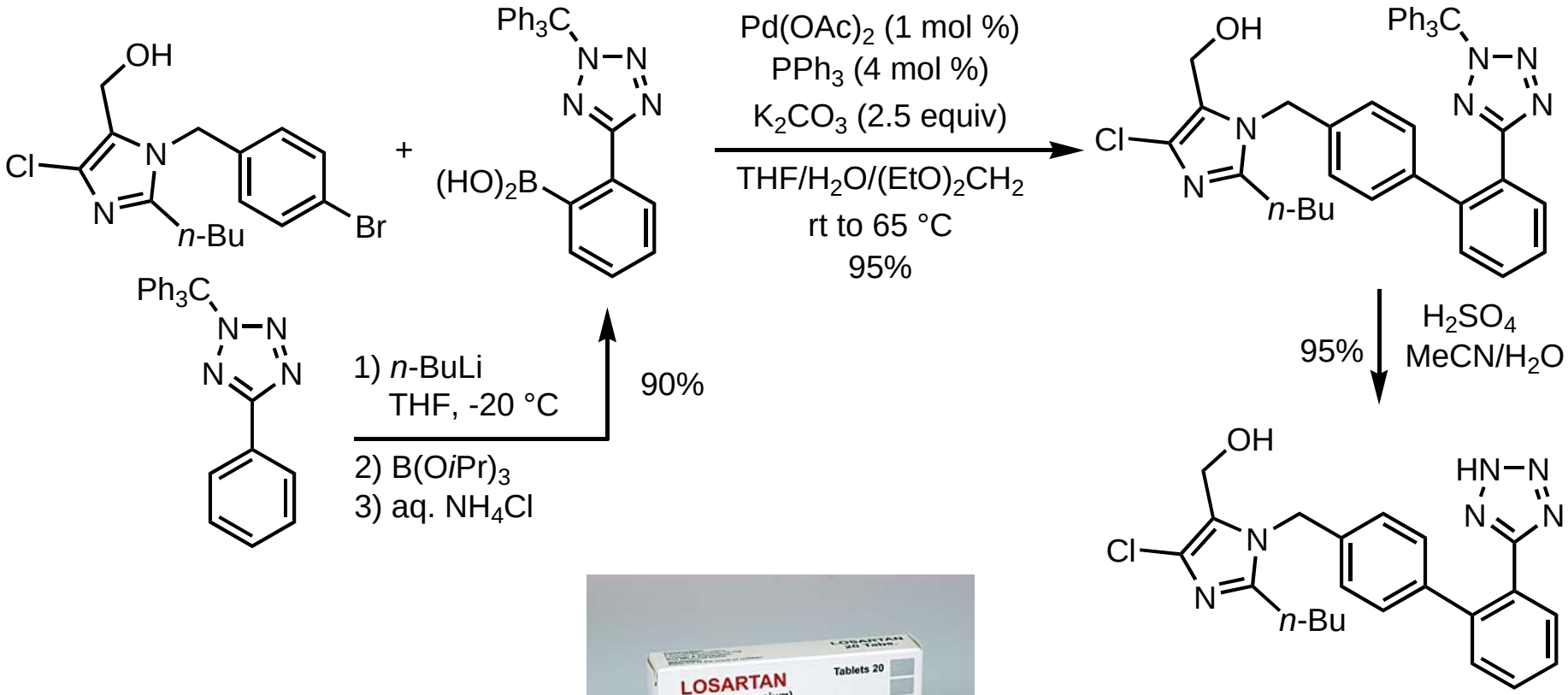
Ru-Phos



XPhos

Acc. Chem. Res. **2008**, *41*, 1440, 1455 and 1461

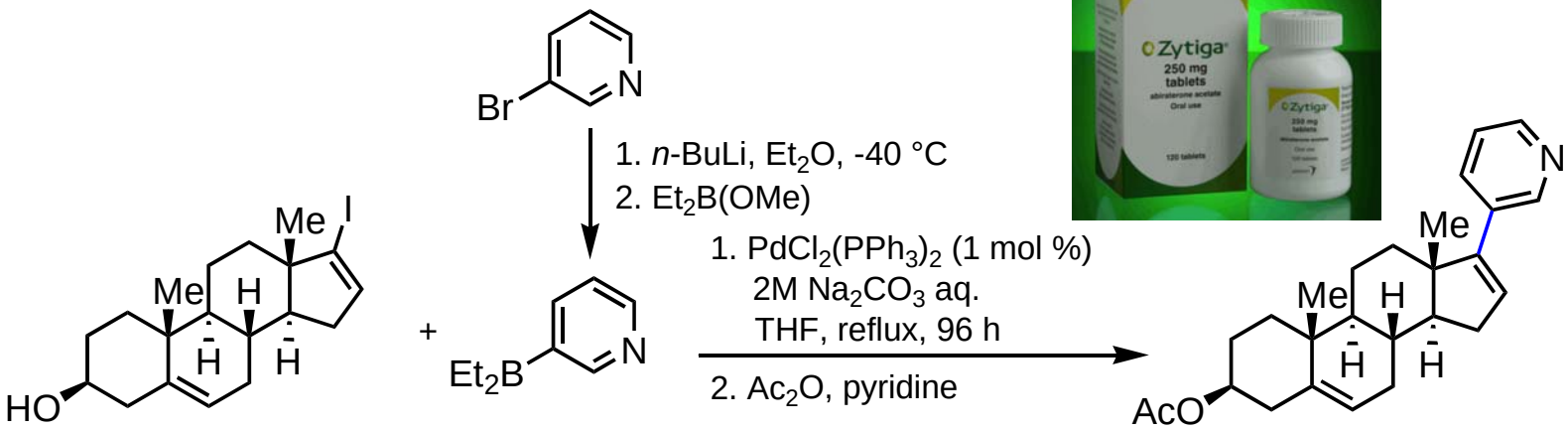
Suzuki-Miyaura coupling : Application



Losartan (Merck)
ACE II inhibitor – hypertension

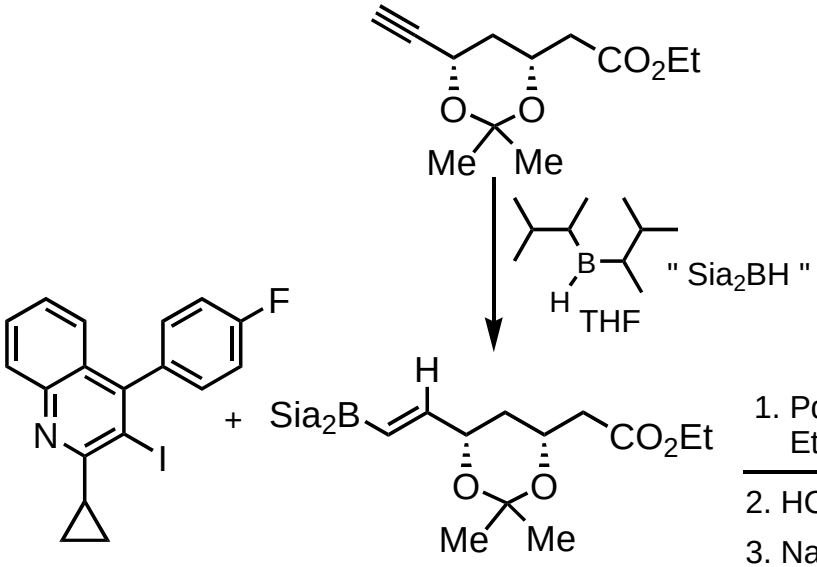
J. Org. Chem. **1994**, *59*, 6391

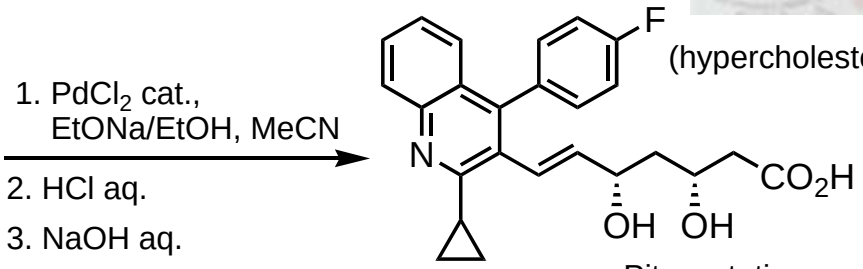
Suzuki-Miyaura coupling : Application



Abiraterone acetate
(prostate cancer)

Potter, G. A.; Hardcastle, I. R.; Jarman, M. *Org. Prep. Proced. Intl.* **1997**, *29*, 123-134



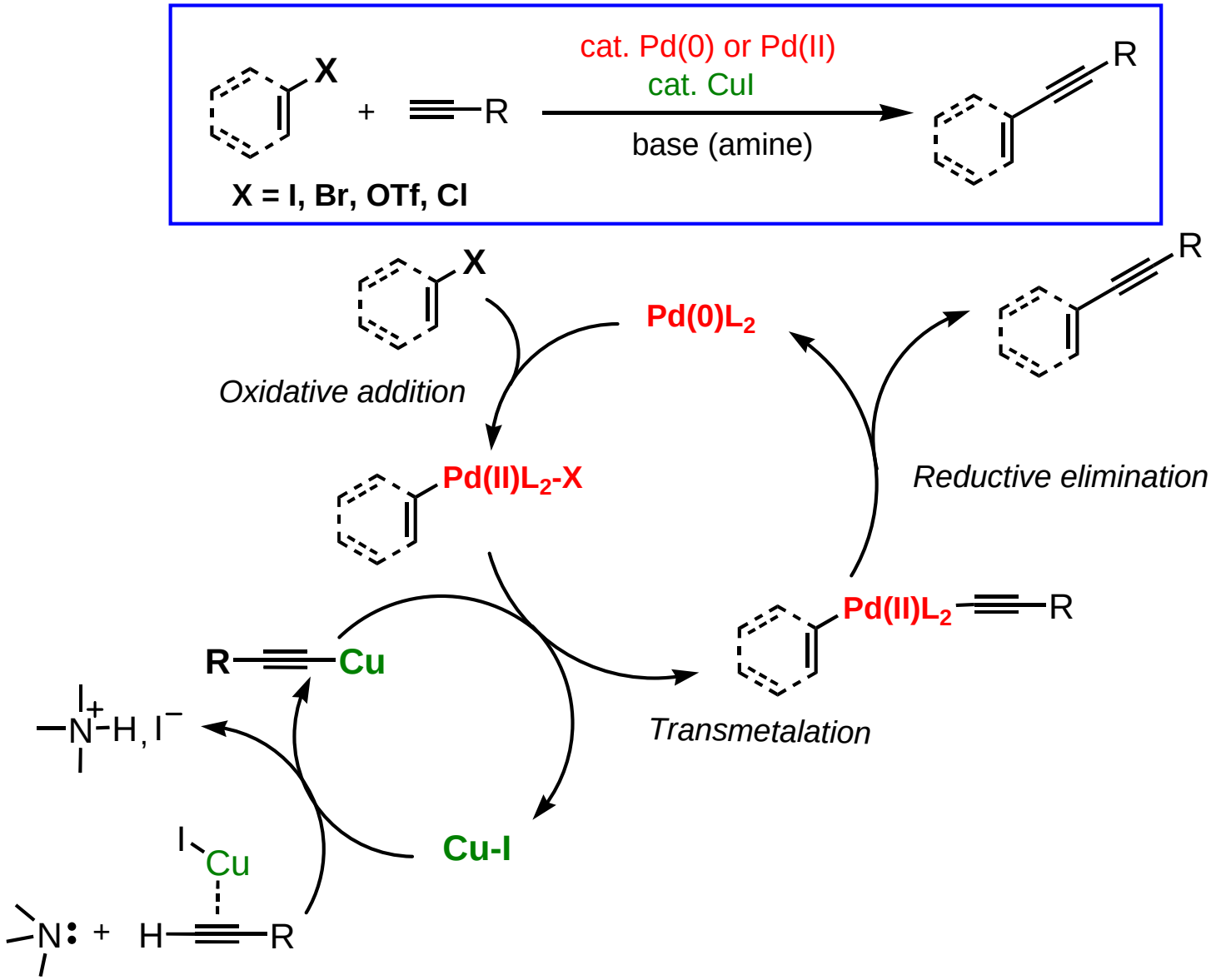


(hypercholesterolemia)

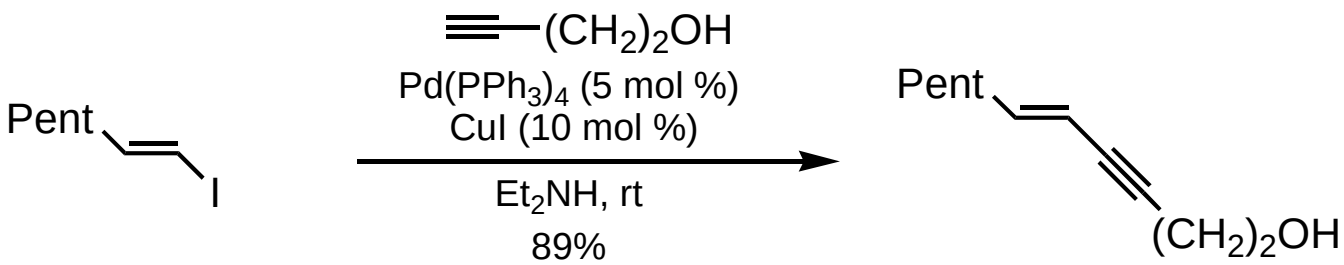
Pitavastatine

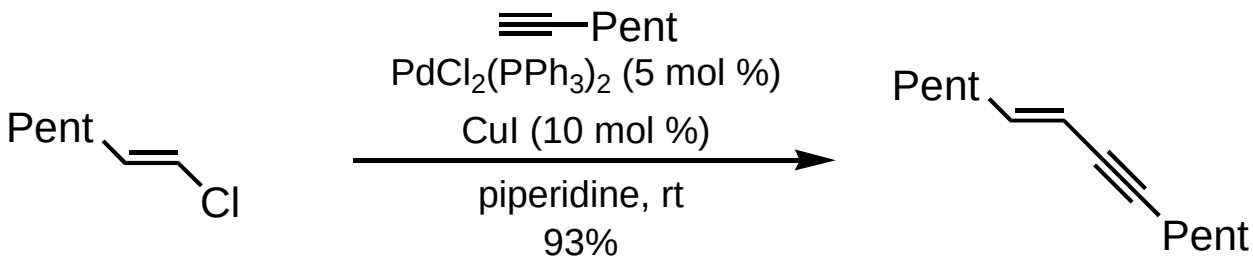
Miyachi, N. *et al. Tetrahedron Lett.* **1993**, *34*, 8267

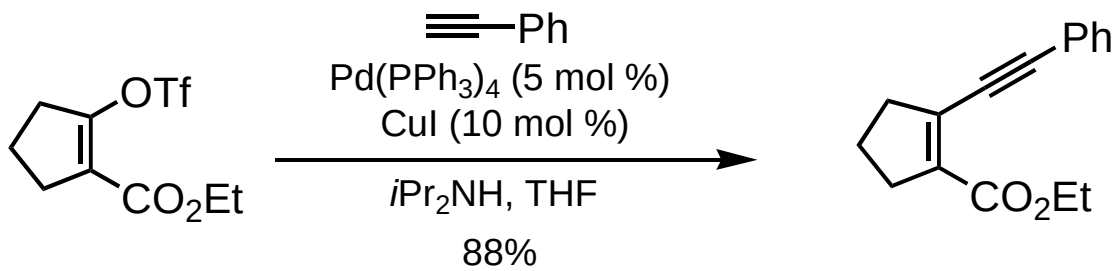
Sonogashira coupling



Sonogashira coupling



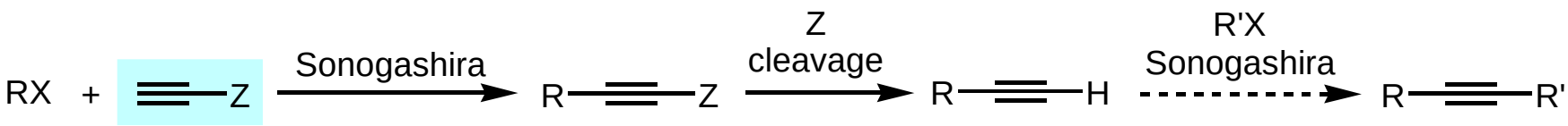




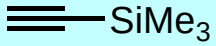
Vinyl triflates : prepared from the corresponding ketones

Acetylene surrogates in Sonogashira coupling

Acetylene :
gaseous alkyne



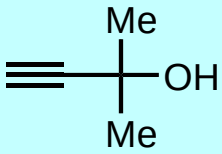
Trimethylsilylacetylene
(Ethynyltrimethylsilane)

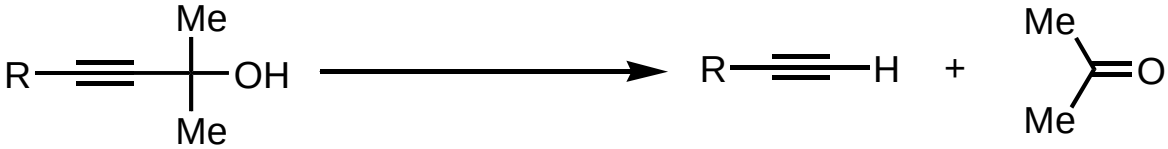


Stable towards acids
but base sensitive

- *n*-Bu_4NF, THF
- KF, DMF
- K_2CO_3 or KOH, MeOH
- $AgNO_3$ then NaCN/EtOH

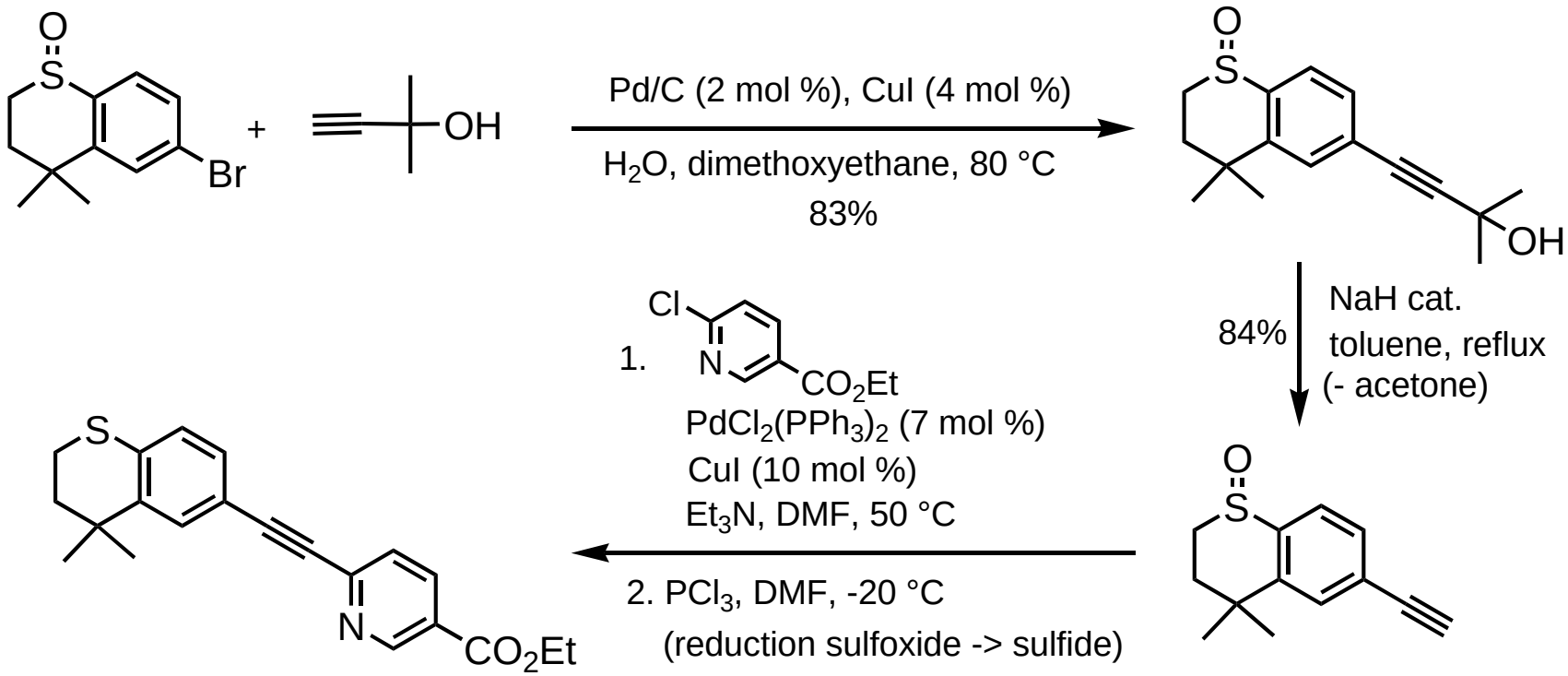
2-Methylbut-3-yn-1-ol



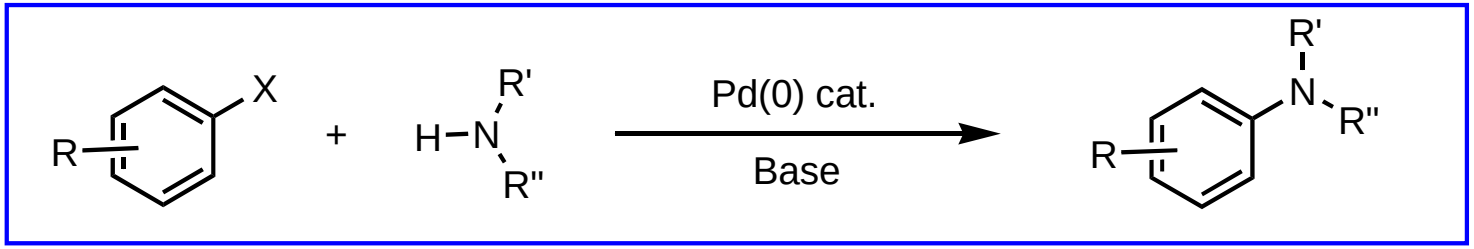
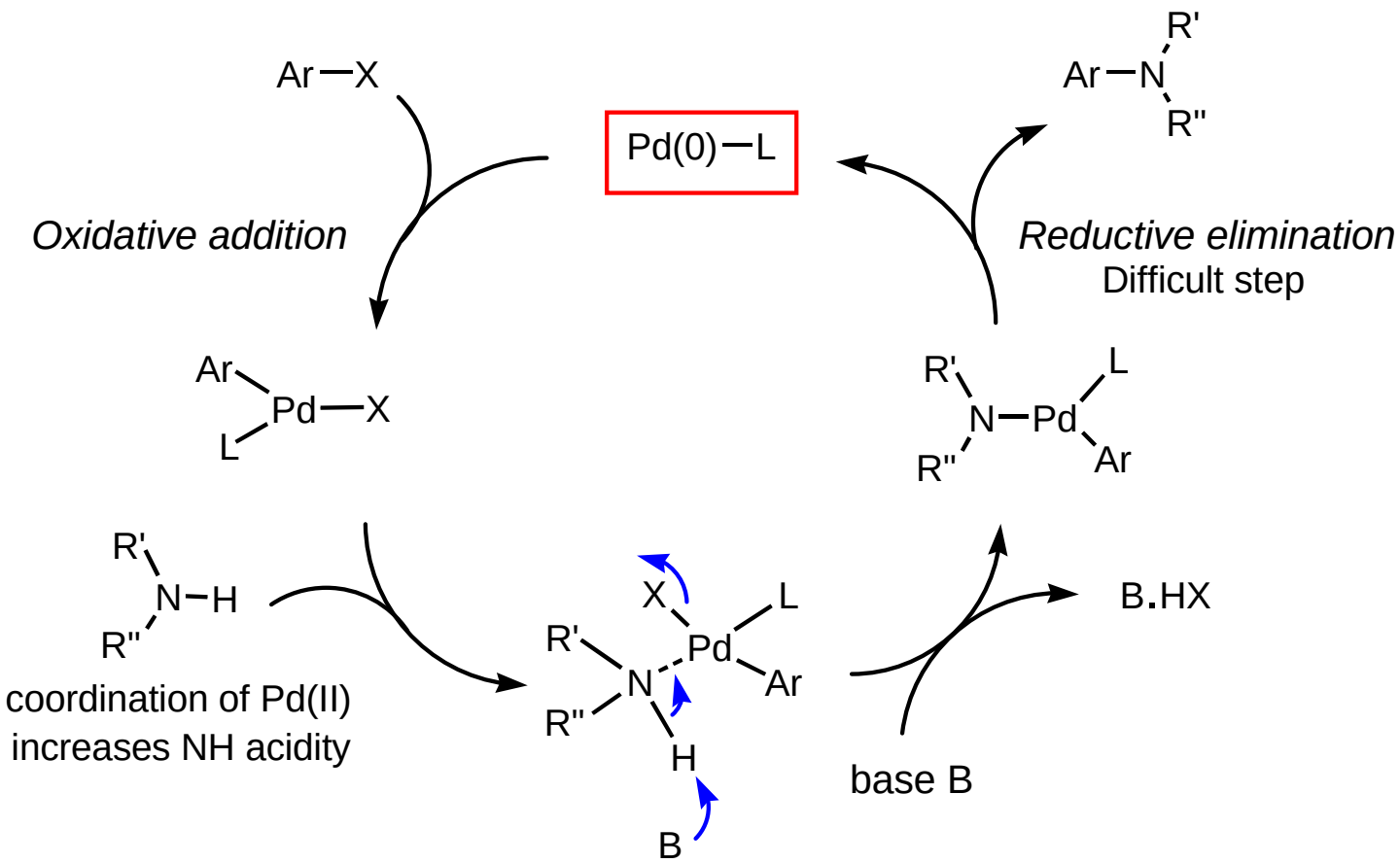


- K_2CO_3, 18-crown-6, toluene, reflux
- NaOH, KOH ou *t*-BuOK, heating at 80-100 °C

Sonogashira coupling : Application



Tazarotene (Allergan)
psoriasis, acne

Org. Proc. Res. Dev. **2005**, *9*, 646

Hartwig-Buchwald amination : The principle