เคมีอินทรีย์สังเคราะห์

Organic Chemistry Synthesis

(Chem 451)

Semester 2/2564

อ.ดร. ปิยธิดา กล่ำภู่

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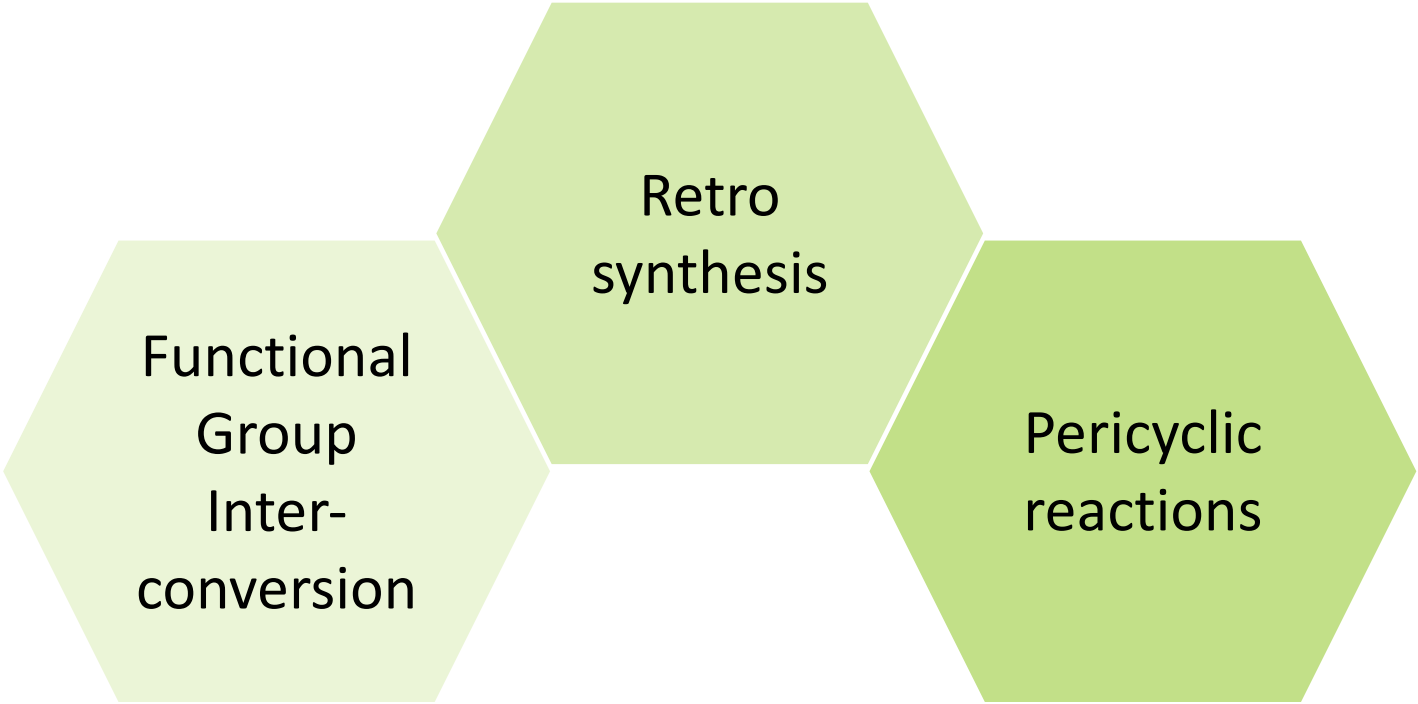
Course outline



Course syllabus

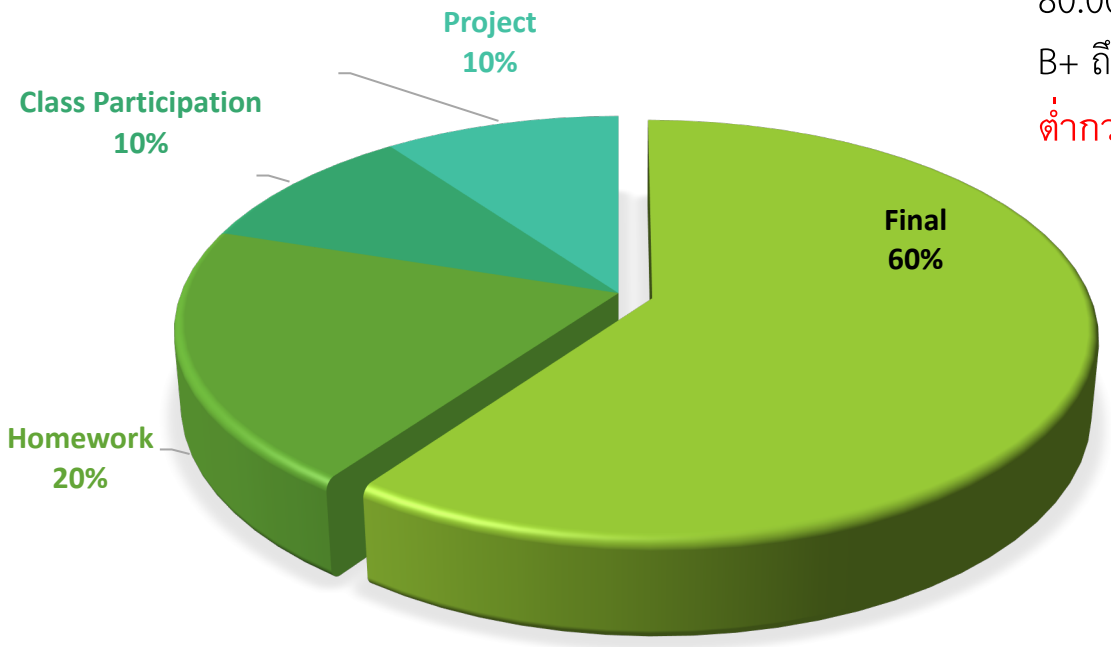
Week	Date	Topic	Note
1	22 พ.ย. 64	Class 1: Functional gr. Interconversion I	Introduction
	25 พ.ย. 64	Class 2: Functional gr. Interconversion II	
2	29 พ.ย. 64	Class 3: Functional gr. Interconversion III	
	2 ธ.ค. 64	Class 4: Functional gr. Interconversion III	
3	6 ธ.ค. 64	No class	Holiday
	9 ธ.ค. 64	Class 5: Retrosynthesis I	Exam I (Functn gr.)
4	13 ธ.ค. 64	Class 6: Retrosynthesis II	
	16 ธ.ค. 64	Class 7: Retrosynthesis III	
5	20 ธ.ค. 64	Class 8: Retrosynthesis III	
	23 ธ.ค.64	Class 9: Pericyclic reactions	Exam II (Retro syn)
6	27 ธ.ค. 64	Class 10: Electrocyclic reactions	
	30 ธ.ค. 64	No class	New Year Holiday
7	3 ม.ค. 65	Class 11: Cycloaddition reactions	
	6 ม.ค. 65	Class 12: Sigmatropic rearrangement	
8	10 ม.ค. 65	Project presentation	
	13 ม.ค. 65	Final Review	Exam3 III (Pericyclic)

Grading (Part1: 50% of final grade)

80.00 % ขึ้นไป ระดับคะแนน A

B+ ถึง D อิงกลุ่ม

ต่ำกว่า 38 % ระดับคะแนน F



List	Percentage (of 50%)	Total of final grade
Final exam	60%	30
Homework	20%	10
Class attendant	10%	5
Project	10%	5
Total	100%	50

Resources

Book

- บุญส่ง คงคาทิพย์, งามผ่อง คงคาทิพย์, **กลยุทธ์การสังเคราะห์สารอินทรีย์**, กรุงเทพ, พิมพ์ครั้งที่ 1, 2552.
- Francis A. Carey ,Richard J. Sunberg, **Advanced Organic Chemistry-Part B-Reactions and Synthesis**, 5th ed, 2007.
- Michael B. Smith, **Organic Synthesis**, 2nd ed, 2002.

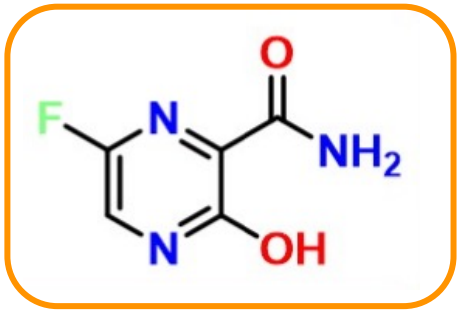
Reference websites

http://www.organic-chemistry.org
http://www.masterorganicchemistry.com
Sciencedirect, SciFinder

Course Webpage

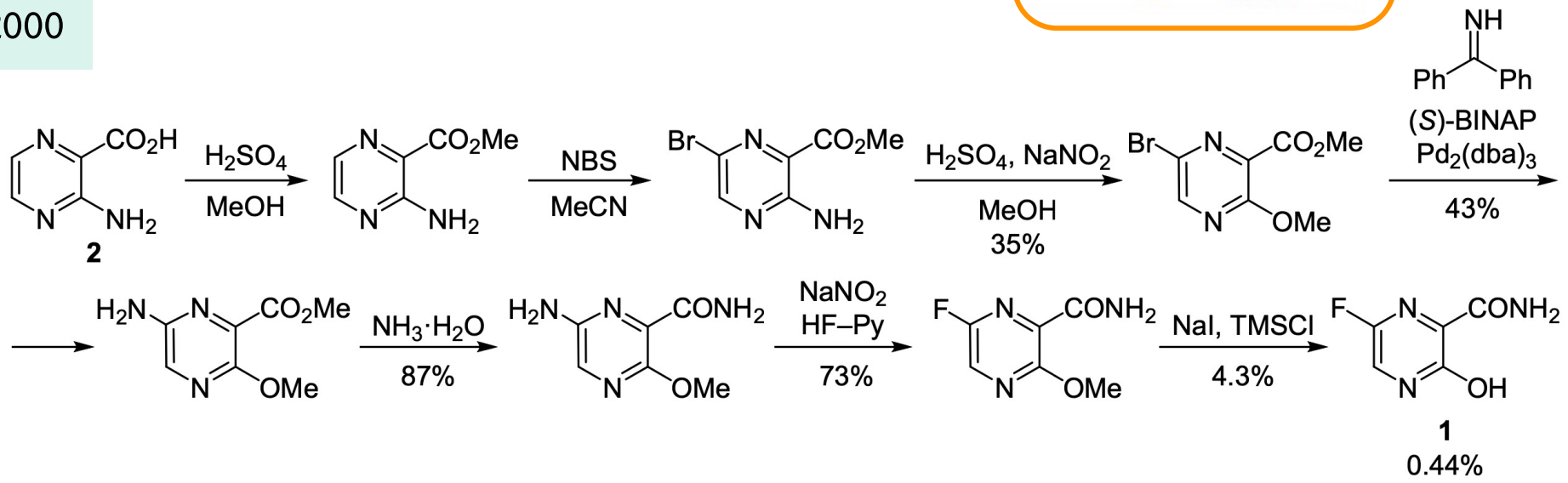
Microsoft team (CH451 Organic Chemistry Synthesis)

Multistep organic synthesis

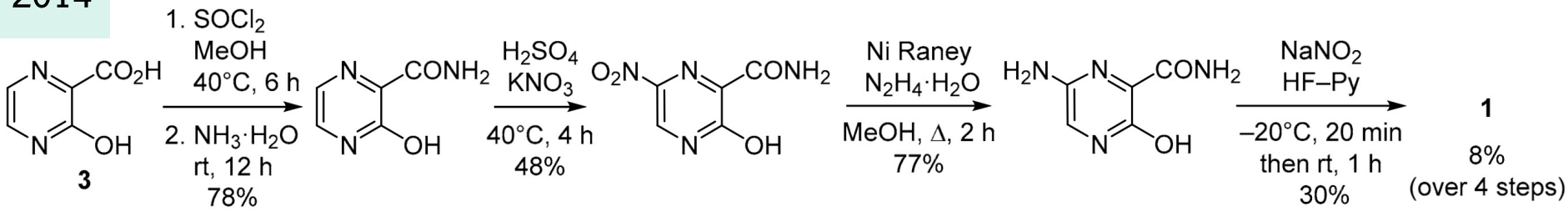


Favipiravir ยาต้านไวรัส ยารักษาโรคติดเชื้อโควิด-19

2000



2014

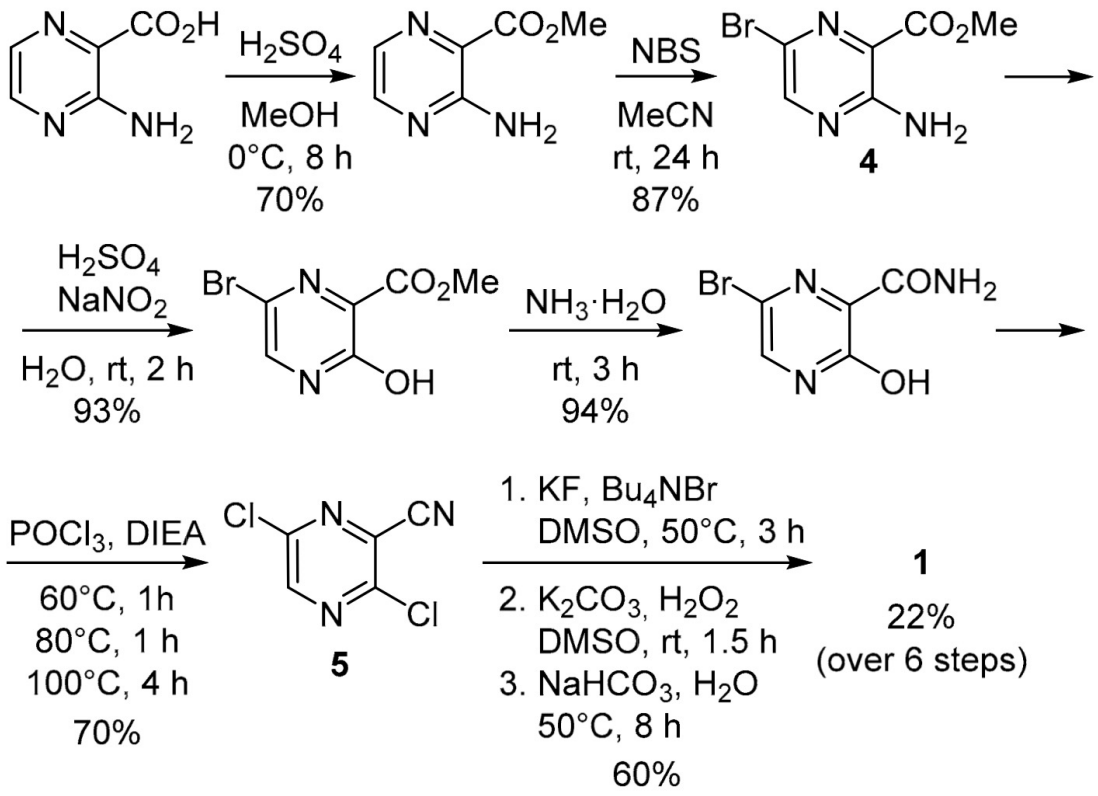


Multistep organic synthesis

Favipiravir ยาต้านไวรัส ยารักษาโรคติดเชื้อโควิด-19

2017

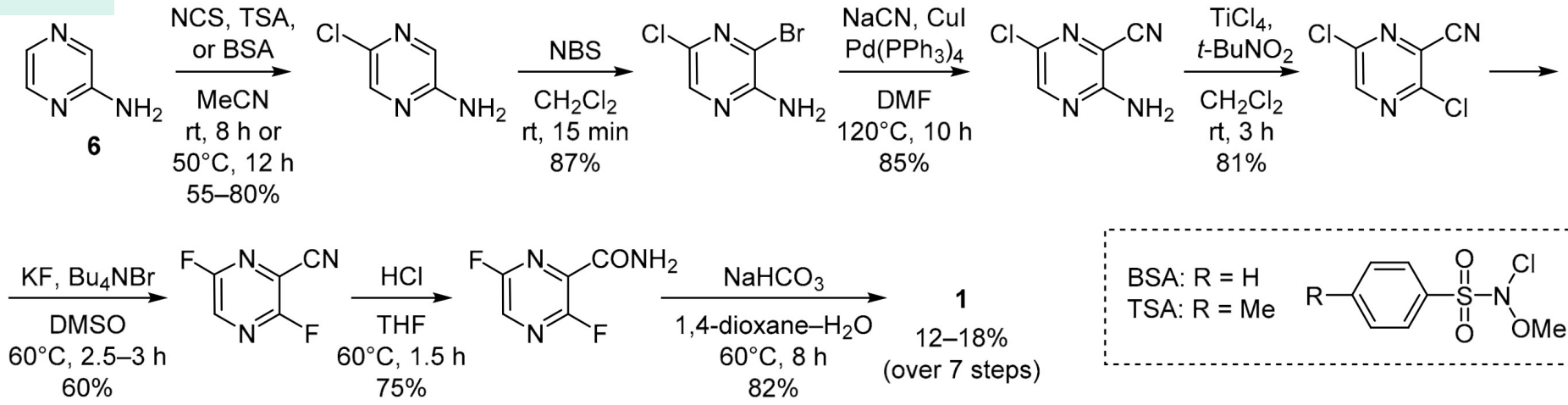
Scheme 3



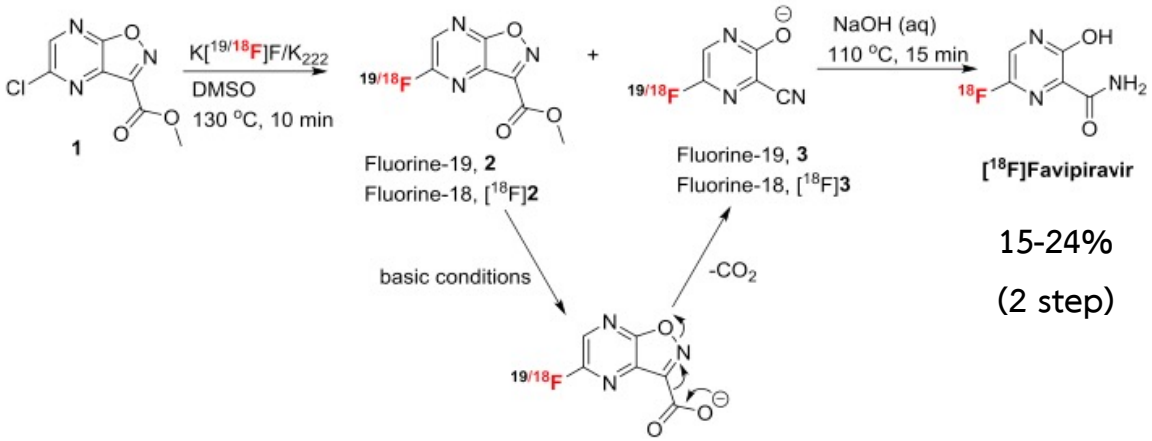
Multistep organic synthesis

Favipiravir ยาต้านไวรัส ยารักษาโรคติดเชื้อโควิด-19

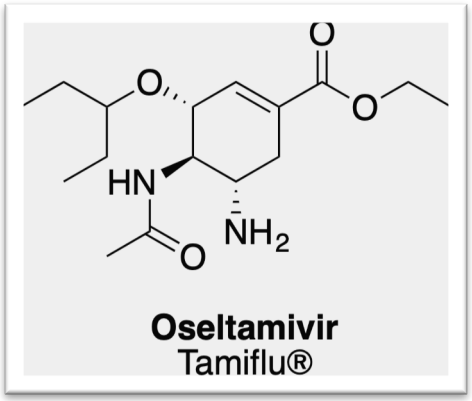
2019

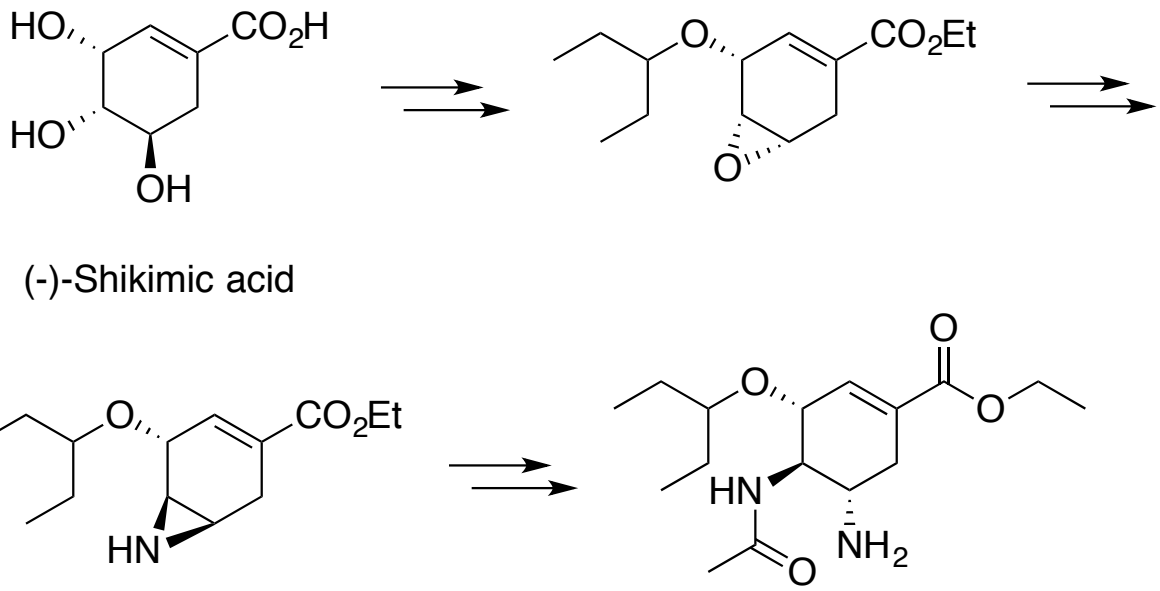


2019



Multistep organic synthesis





(-)-Shikimic acid

Oseltamivir
Tamiflu®

ยาต้านไวรัสไข้หวัดนก
และไข้หวัด 2009
ผลิตโดยบริษัท Roche

https://en.wikipedia.org/wiki/Oseltamivir#/media/File:A_Tamiflu_(oseltamivir)_capsule.jpg

Multistep organic synthesis

Multistep synthesis

Linear synthesis

A —90%→ B —90%→ C —90%→ D —90%→ E

Overall %yield = 90% x 90% x 90% x 90% x 90%
= **59%**

Convergent synthesis

A —90%→ X
Y —90%→ Z
X, Z —90%→ E

Overall %yield = 90% x 90% = **81%**

Retrosynthesis

The Nobel Prize in Chemistry 1990 was awarded to
Elias James Corey
"for his development of the theory and methodology of organic synthesis".

"Retrosynthetic analysis"

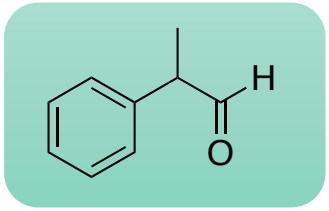
Past method Trials and errors

Retrosynthesis Logical and systematic

Target molecule (Desired product) $\Longrightarrow$ Building blocks) (Starting materials)

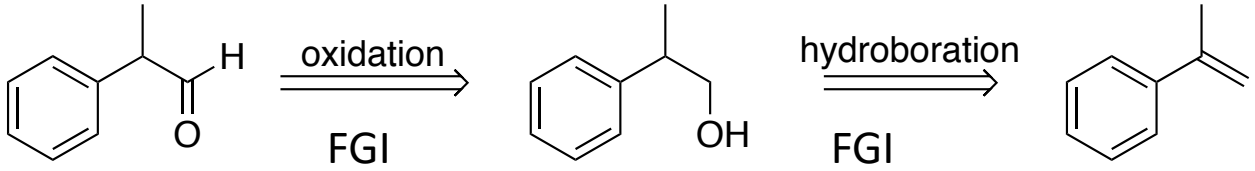
The 1990 Nobel Prize in Chemistry (http://www.nobel.se/chemistry/laureates/1990/ index.html)

Retrosynthesis

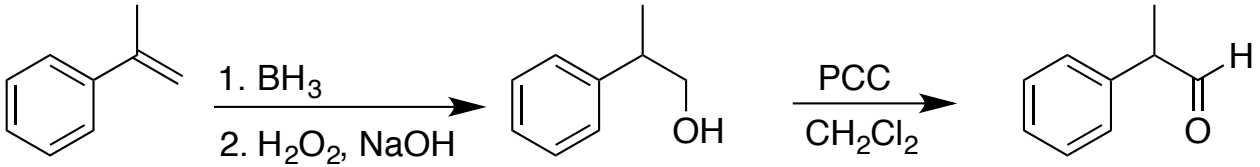


How to make this molecule?

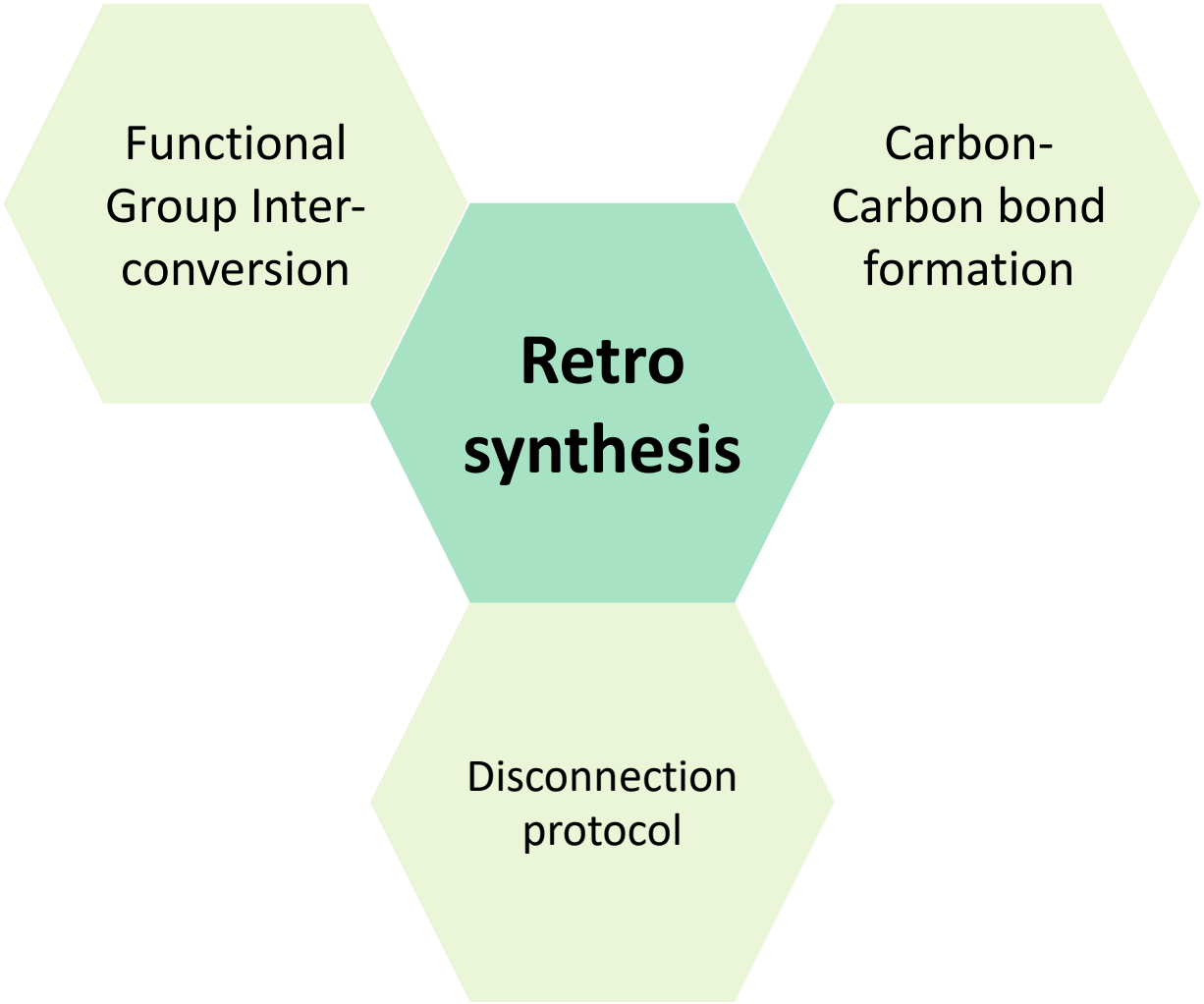
Retrosynthesis



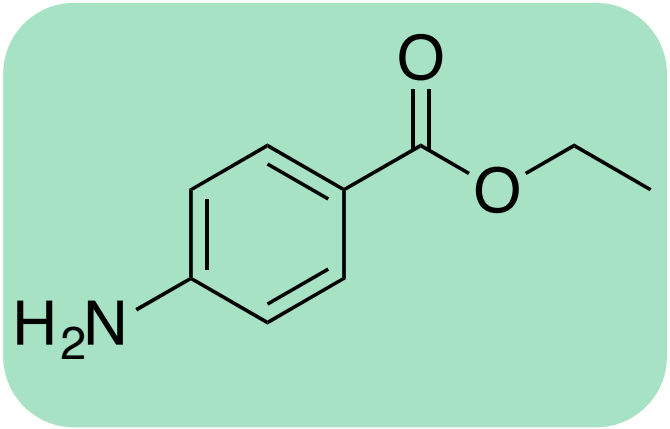
Forward direction



Retrosynthesis



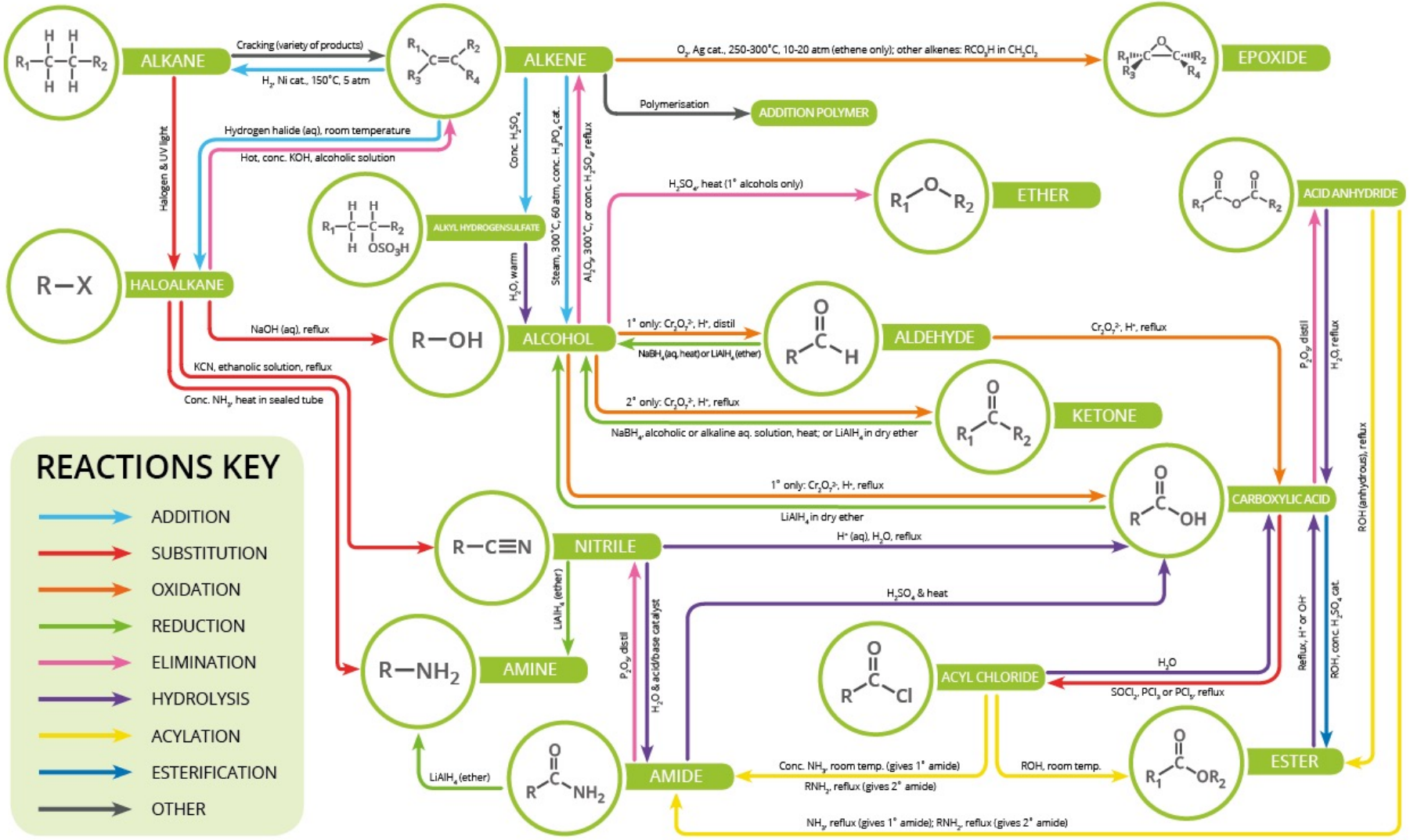
Molecule of the day



Benzocaine

(local anesthetics)

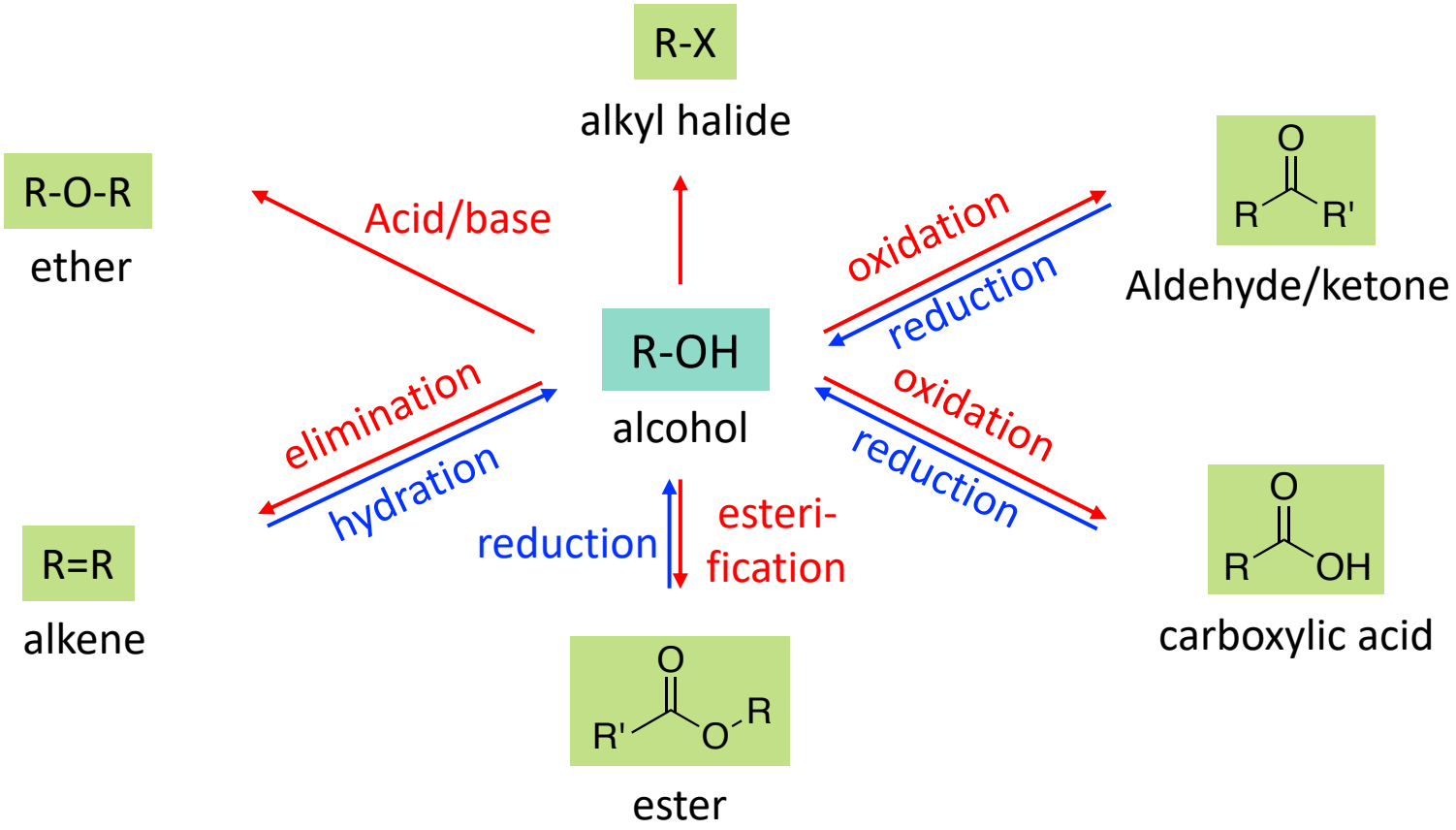
ORGANIC FUNCTIONAL GROUP INTERCONVERSIONS



Functional Group Interconversion (FGI)

- **Alcohols**
- Olefins
- Carboxylic acid and derivative
- Aromatic compounds
- Carbonyl compounds

FGI of alcohol

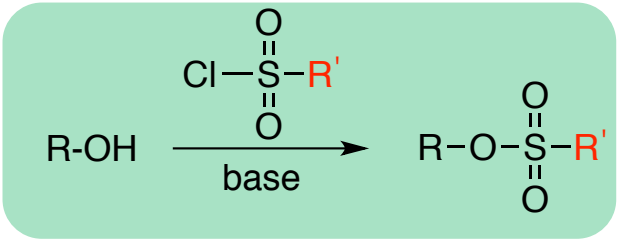


R-OH to R-X

Substitution reaction

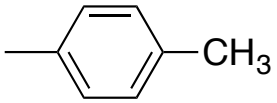
Sulfonate ester

Good leaving group

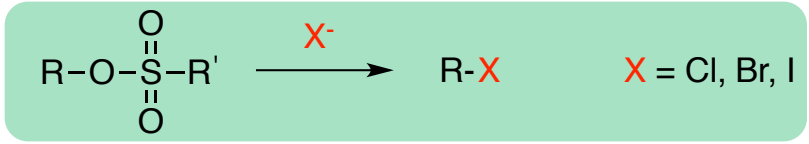


R' = —CH_3 (mesylate) mesylate Ms-

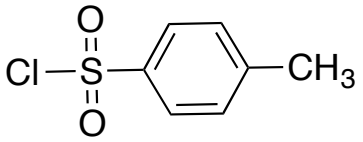
= —CF_3 triflate TfO-

=  CH_3 tosylate Ts-

Sulfonate ester to halide



$Ph_2C{=}CHCH_2CH_2OH$ → (1. tosyl chloride; 2. LiBr) → $Ph_2C{=}CHCH_2CH_2Br$ 89%



tosyl chloride

R-OH to R-X

Substitution reaction

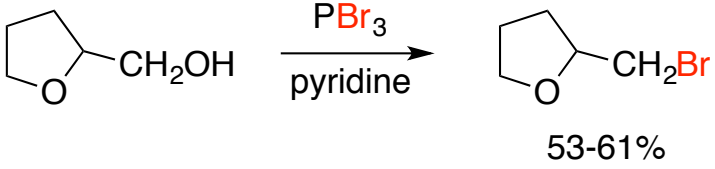
R-OH ⟶ R-X

Halides

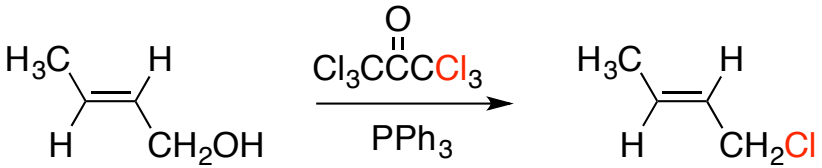
R-OH to R-Cl
- $SOCl_2$
- Ph_3P, CCl_4
- Ph_3P, Cl_2
- Ph_3P, $Cl_3CCOCCl_3$

R-OH to R-Br
- PBr_3, pyridine
- Ph_3P, CBr_4
- Ph_3P, Br_2

R-OH to R-I
- Ph_3P, DEAD, CH_3I
(Mitsunobu reaction)

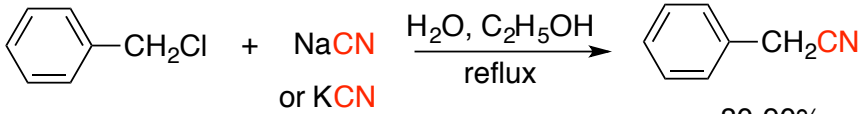


53-61%



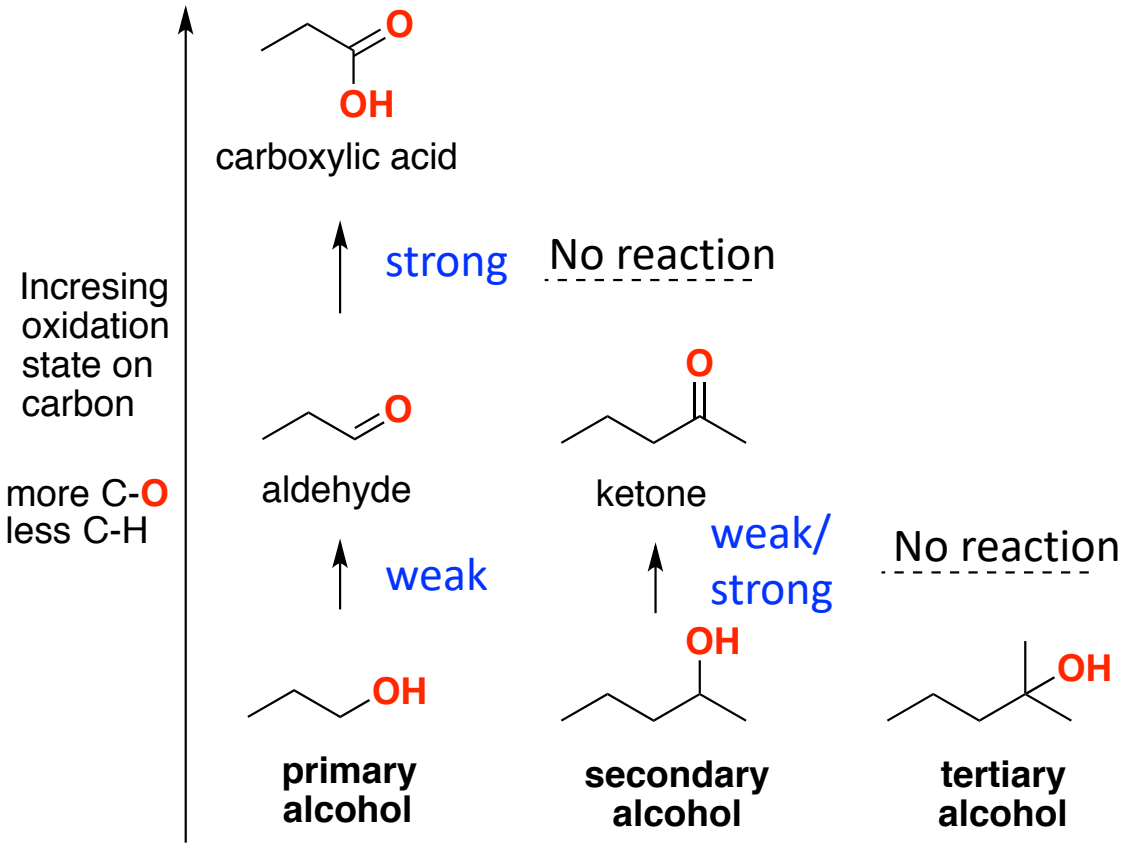
99%

Nitrile



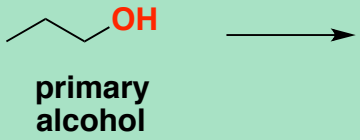
80-90%

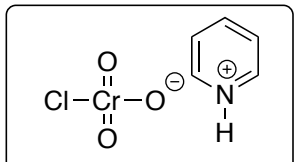
Oxidation of alcohol



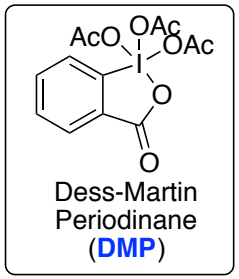
Oxidation

Weak oxidants





pyridinium chlorochromate (**PCC**)



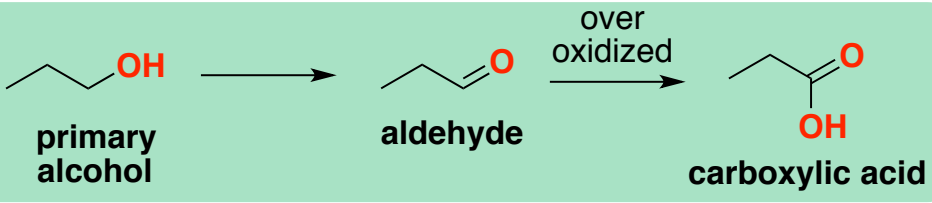
Dess-Martin Periodinane (**DMP**)

CrO_3, piridine
Collins reagent

1. $(COCl)_2$, DMSO
2. Et_3N

Swern oxidation

Strong oxidants



$KMnO_4$
potassium permanganate

H_2CrO_4
chromic acid

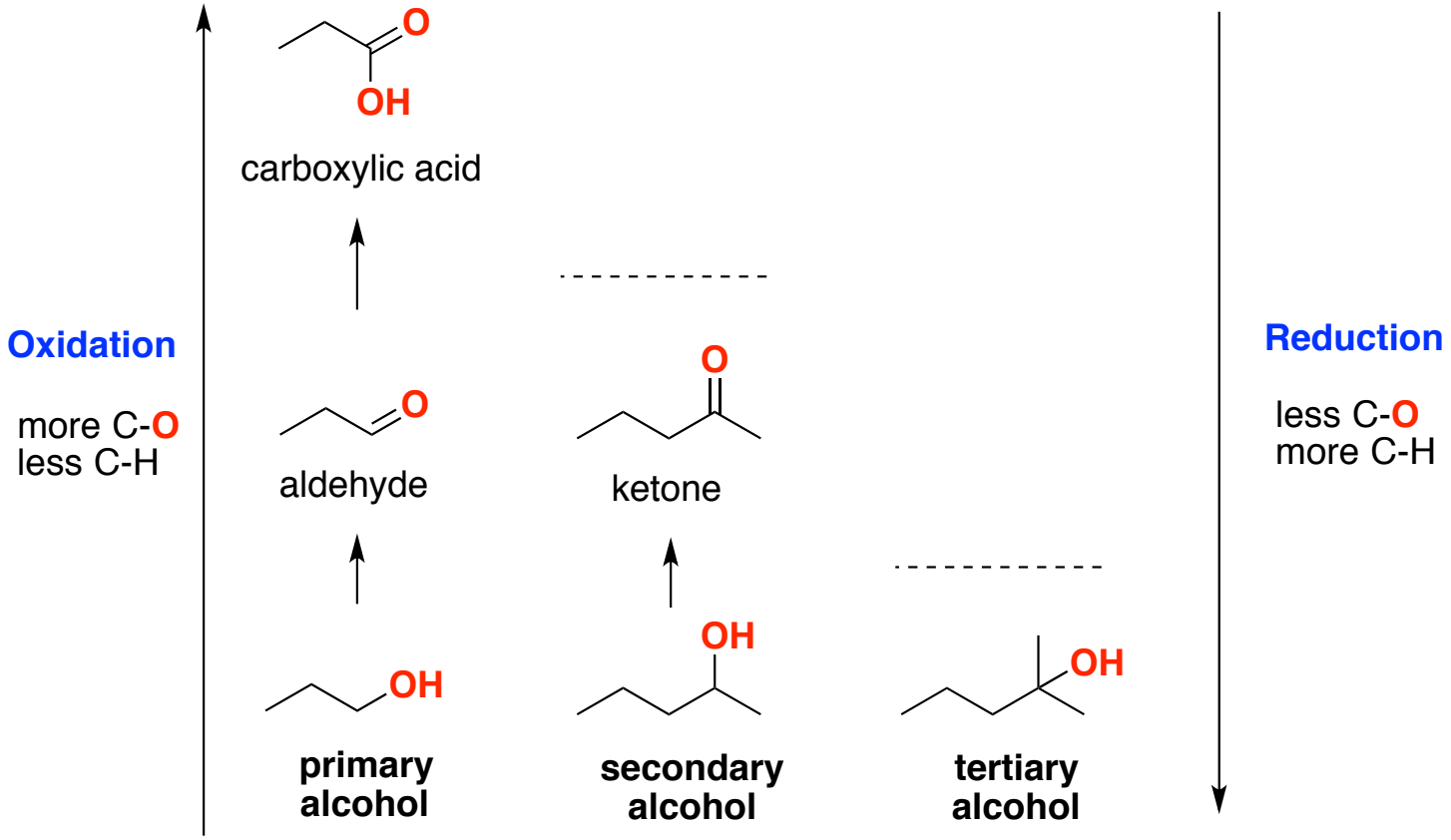
$K_2Cr_2O_7$, H_2SO_4
K_2CrO_4, H_2SO_4

CrO_3, H_2SO_4
Jones reagent

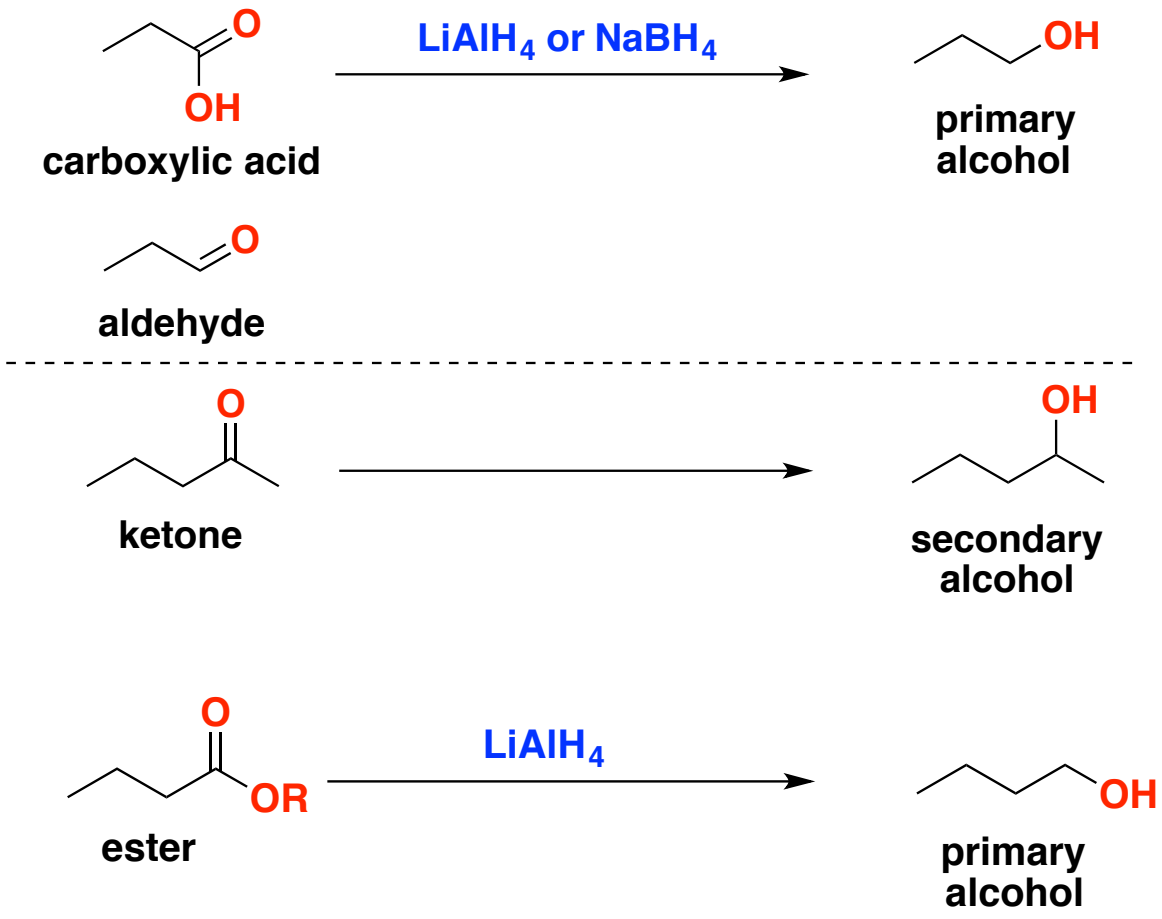
$Na_2Cr_2O_7$, H_2SO_4
Na_2CrO_4, H_2SO_4

CrO_3, H_3O^+

Reduction to alcohol

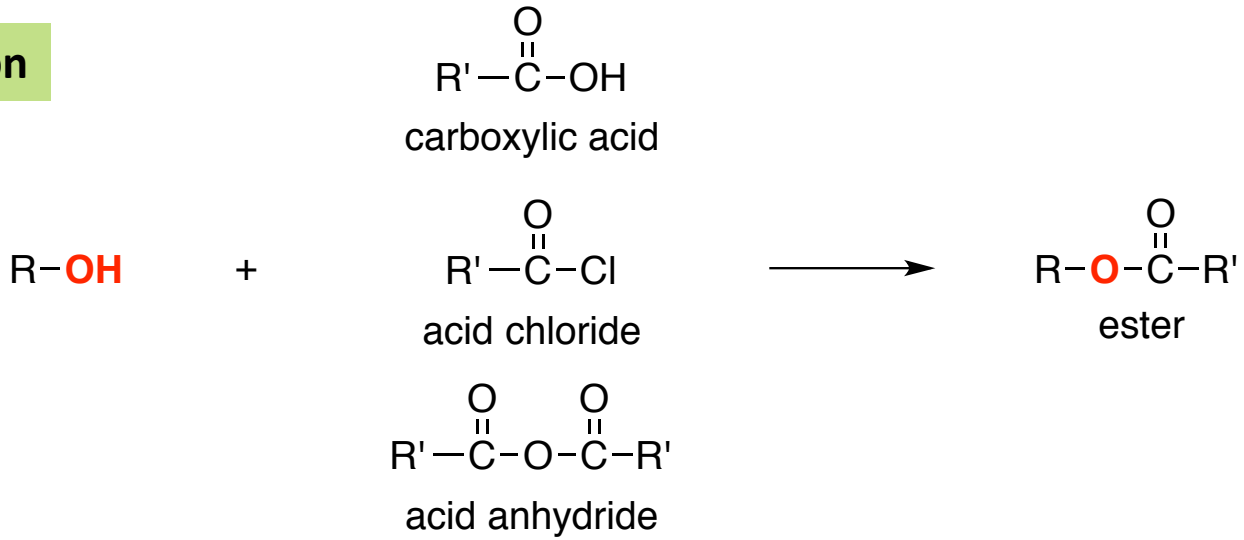


Reduction to alcohol

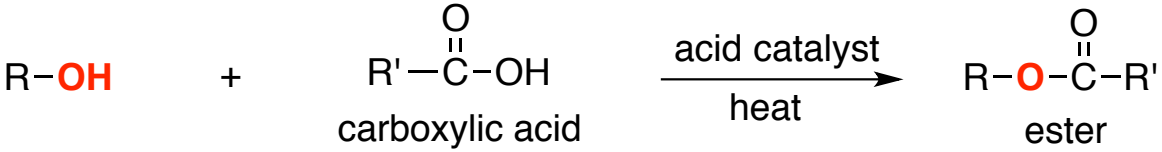


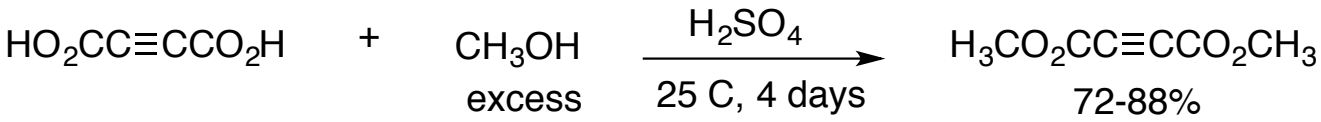
Alcohol to ester

Esterification



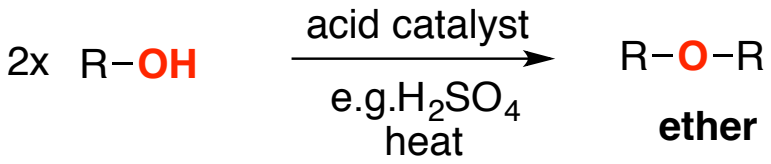
Fisher esterification





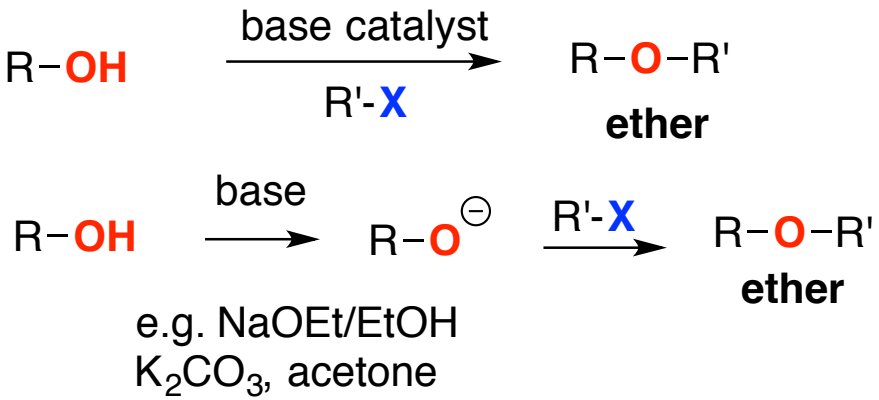
Alcohol to ether

Acid-catalyzed



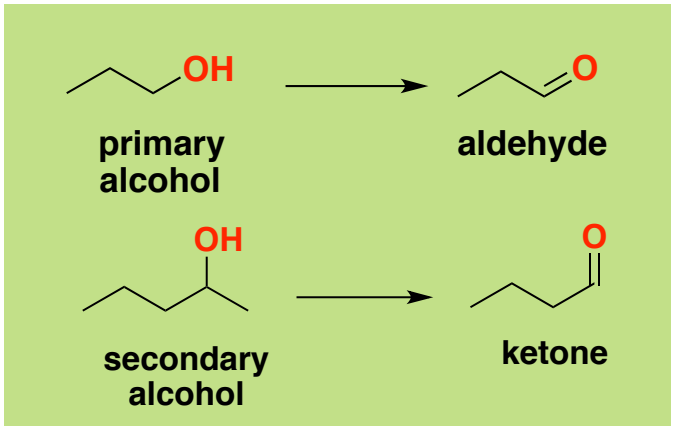
limit to synthesis of symmetrical ether

Williamson ether synthesis



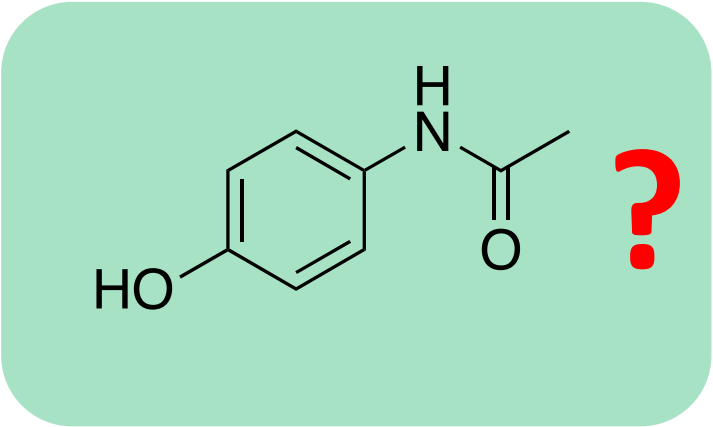
Take home

- Make 10 or more **flash cards**
- Finish **Homework 1** before next class

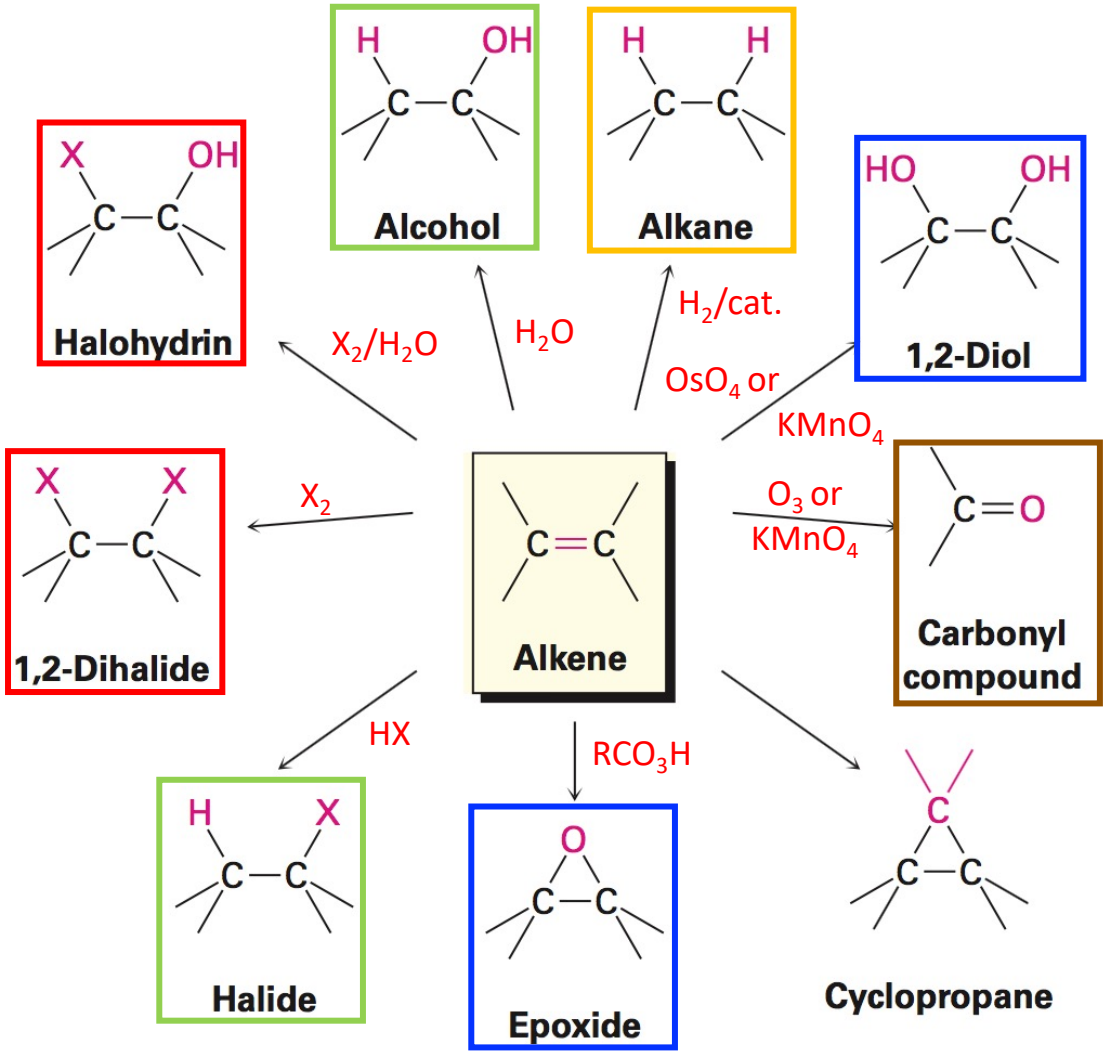


PCC
DMP
Collins reagent
Swern oxidation
$(COCl)_2$, DMSO, Et_3N

Molecule of the day

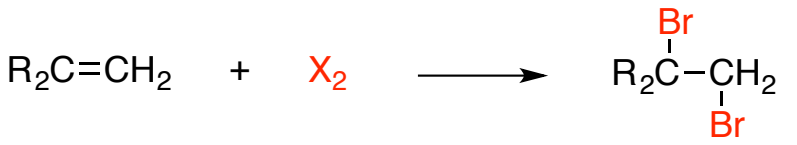


FGI of Alkene



FGI of Alkene-Alkyl halide

Halogenation

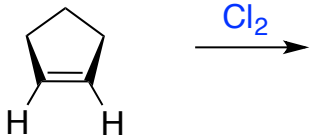


X= Br, Cl, I

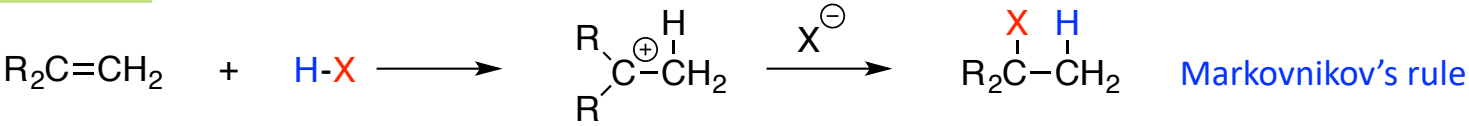
anti-addition

Halogen atoms are on the opposite site

Example



Hydrohalogenation

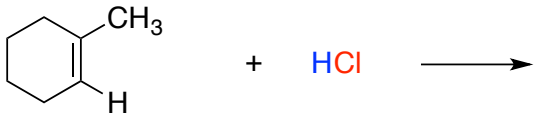


Markovnikov's rule

H-X = HBr, HCl, HI

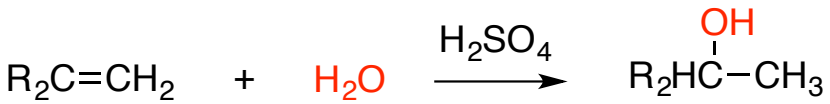
Nucleophile add to more stable carbocation

Example



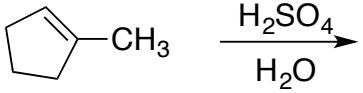
FGI of Alkene-Alcohol

Hydration

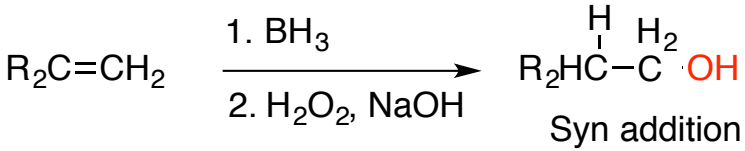


Markovnikov rule

Example

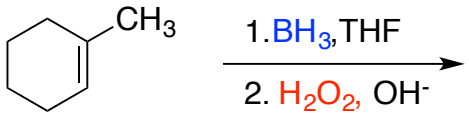


Hydroboration



Anti-Markovnikov rule

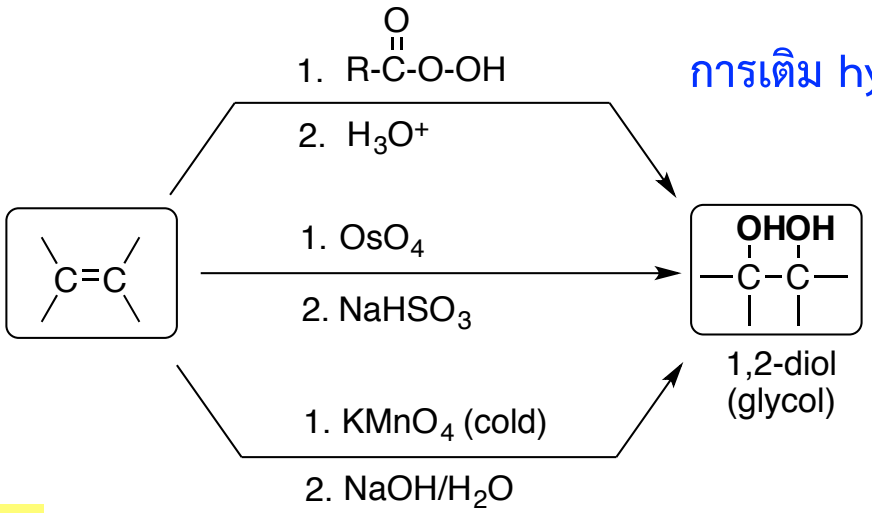
Example



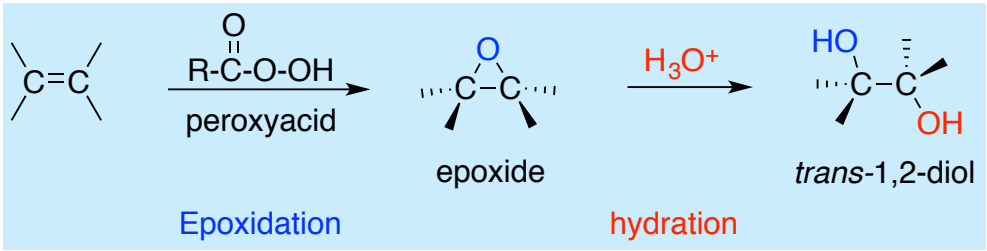
FGI of Alkene

การเติม hydroxyl group (2-OH)

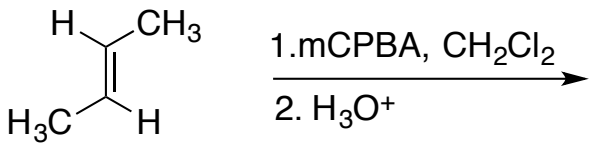
Hydroxylation



Epoxydation→hydration



Example



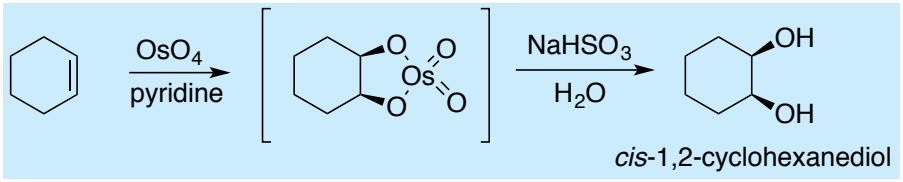
FGI of Alkene

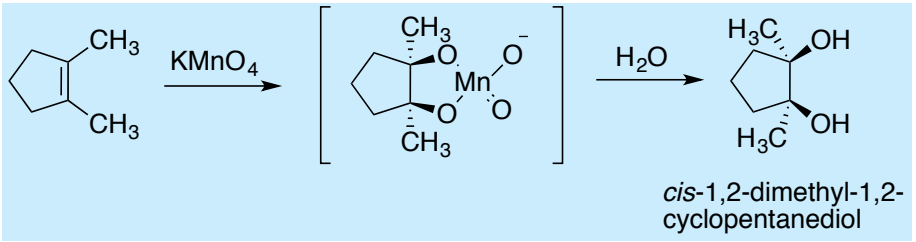
Hydroxylation

$OsO_4 \rightarrow NaHSO_3$

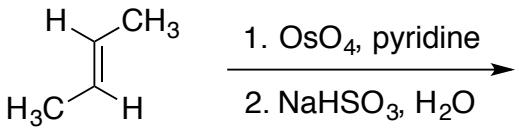
$KMnO_4 \rightarrow H_2O$

Example



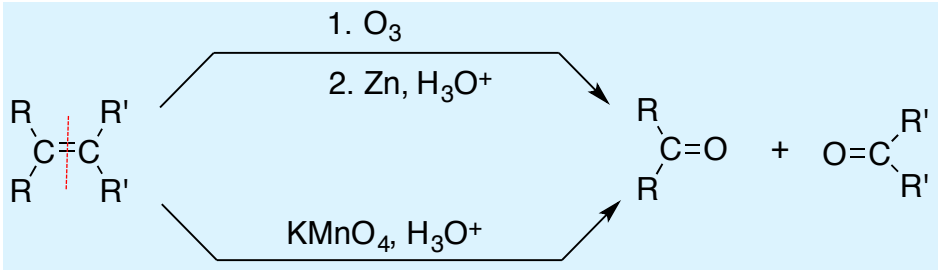


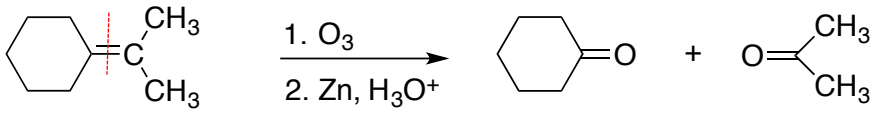
Example



FGI of Alkene

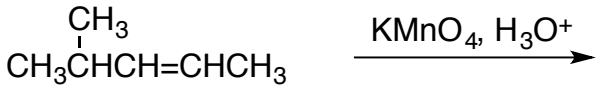
Oxidative cleavage การตัด Alkene → Ketone





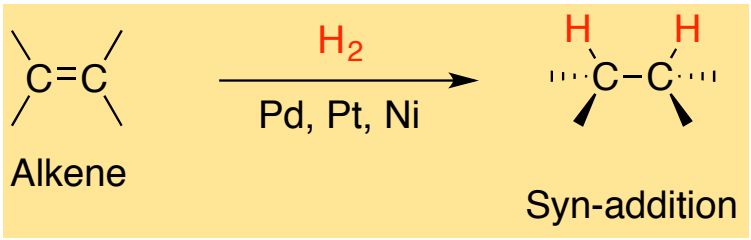
cleavage=cutting

Example

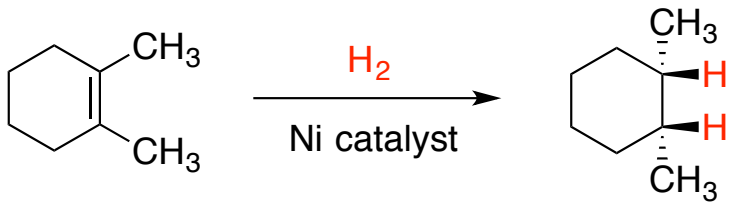


FGI of Alkene

Hydrogenation Alkene → Alkane

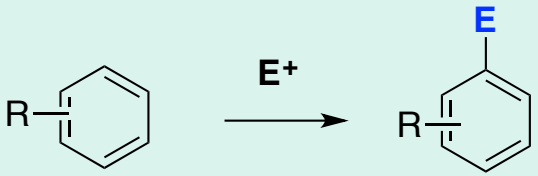


Example



FGI of aromatic

Electrophilic substitution

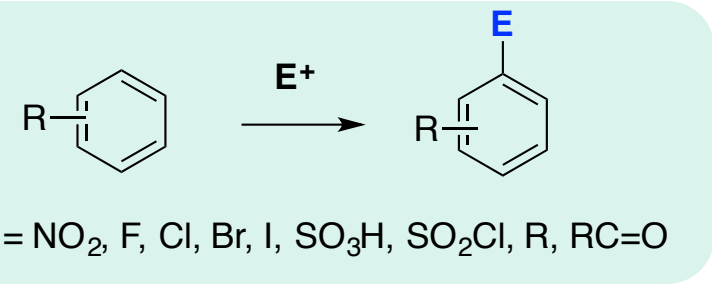


E = NO_2, F, Cl, Br, I, SO_3H, SO_2Cl, R, RC=O

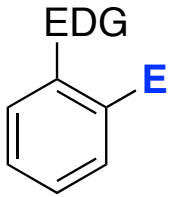
Electrophile (E)	Reagent	
NO_2	HNO_3/H_2SO_4	
Cl	Cl_2, $AlCl_3$	
	Cl_2, $FeCl_3$	
	NCS, $HClO_4$	
Br	Br_2, Fe	
	Br_2, HCl	
	NBS, CH_3CN	
I	I_2, HIO_4	
	ICl, HCl	
R(alkyl)	R-Br, $AlBr_3$	**Friedel-Crafts Alkylation**
	R-Cl, $AlCl_3$	
RC=O (acyl)	anhydride, $AlCl_3$	**Friedel-Crafts Acylation**
	acid chloride, $AlCl_3$	
CH_2Cl	CH_2O, HCl, $ZnCl_2$	**Chloromethylation**
CHO(formyl)	CO, HCl, $AlCl_3$	**Formylation**
	Me_2NCHO, $POCl_3$	**Vilsmeier-Haack formyaltion**

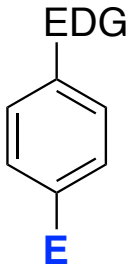
FGI of aromatic

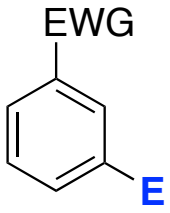
Electrophilic substitution



	R= EDG (Alkyl-, RO-, HO-, X-)	R= EWG (R-C=O, -NO_2)
Substitution Directing position	ortho-, para-	meta-



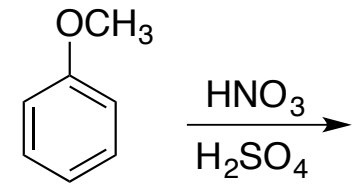


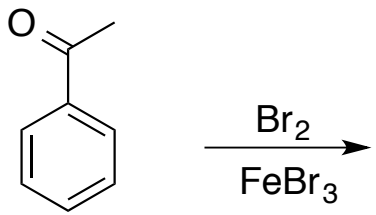


FGI of aromatic

Electrophilic substitution

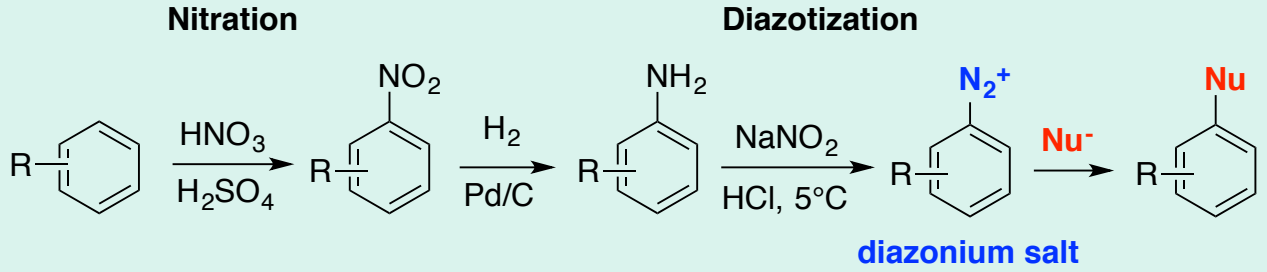
Example





FGI of aromatic

Nucleophilic substitution

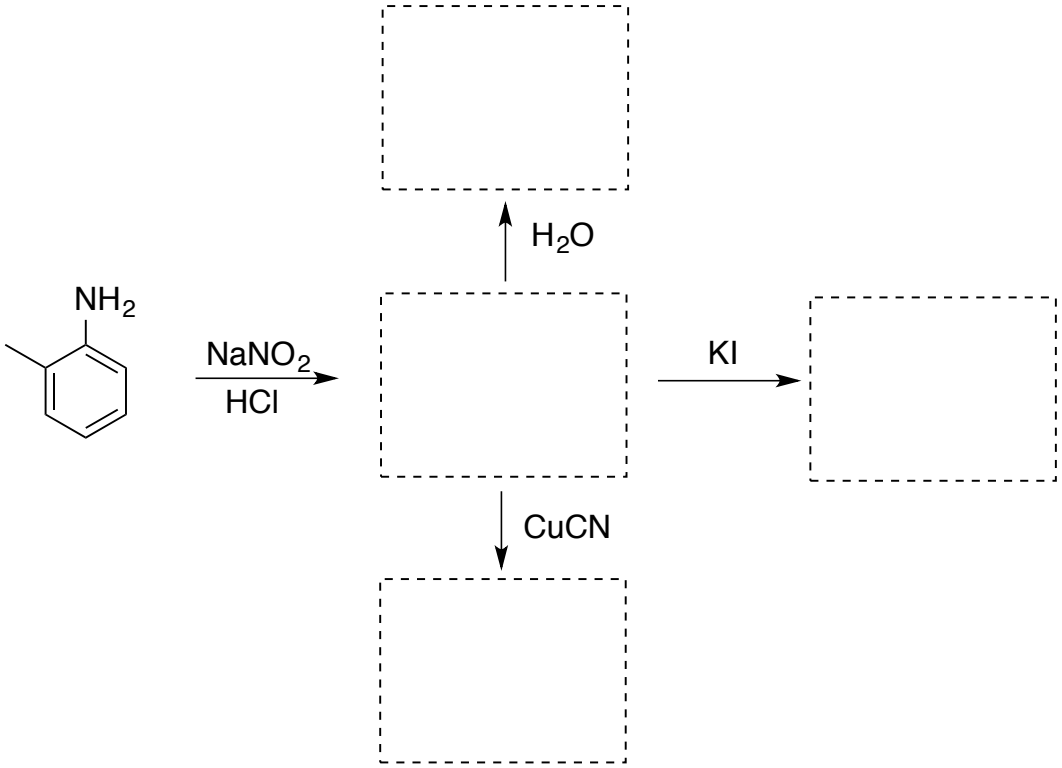


Nucleophile (Nu)	Reagent
HO	H_2O
RO	R-OH
CN	Cu(I)CN
Cl	Cu(I)Cl
Br	Cu(i)Br
I	KI
Ar	Ar-H
H	H_3PO_2
N_3	NaN_3

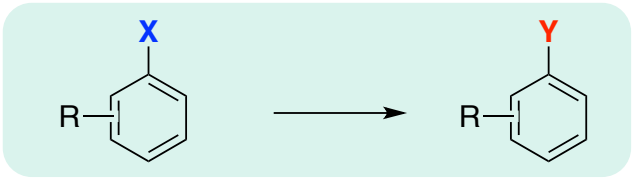
FGI of aromatic

Nucleophilic substitution

Example



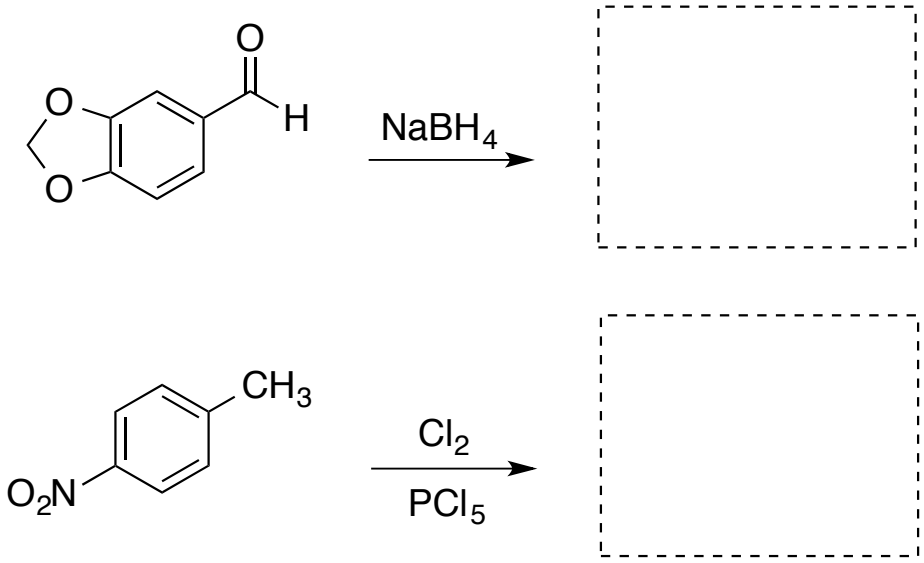
FGI of aromatic



	X	Reagent	Y
Reduction	$-NO_2$	H_2/Pd-C	$-NH_2$
	$-C(=O)-R$	$NaBH_4$	$-CH(OH)-R$
	$-C(=O)-R$	Zn/Hg, HCl	$-CH_2R$
Oxidation	$-CH_2Cl$	hexamethylenetetramine	$-C(=O)-H$
	$-CH_2R$ $-CH_3$	$KMnO_4$	$-C(=O)-OH$
	$-C(=O)-R$	$R'CO_3H$	$-C(=O)-OR'$
Substitution	$-CH_3$	Cl_2, PCl_5	$-CCl_3$
	$-CCl_3$	SbF_5	$-CF_3$
	$-CN$	OH^-, H_2O	$-C(=O)-OH$

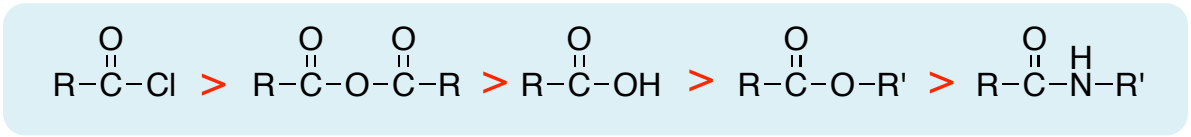
FGI of aromatic

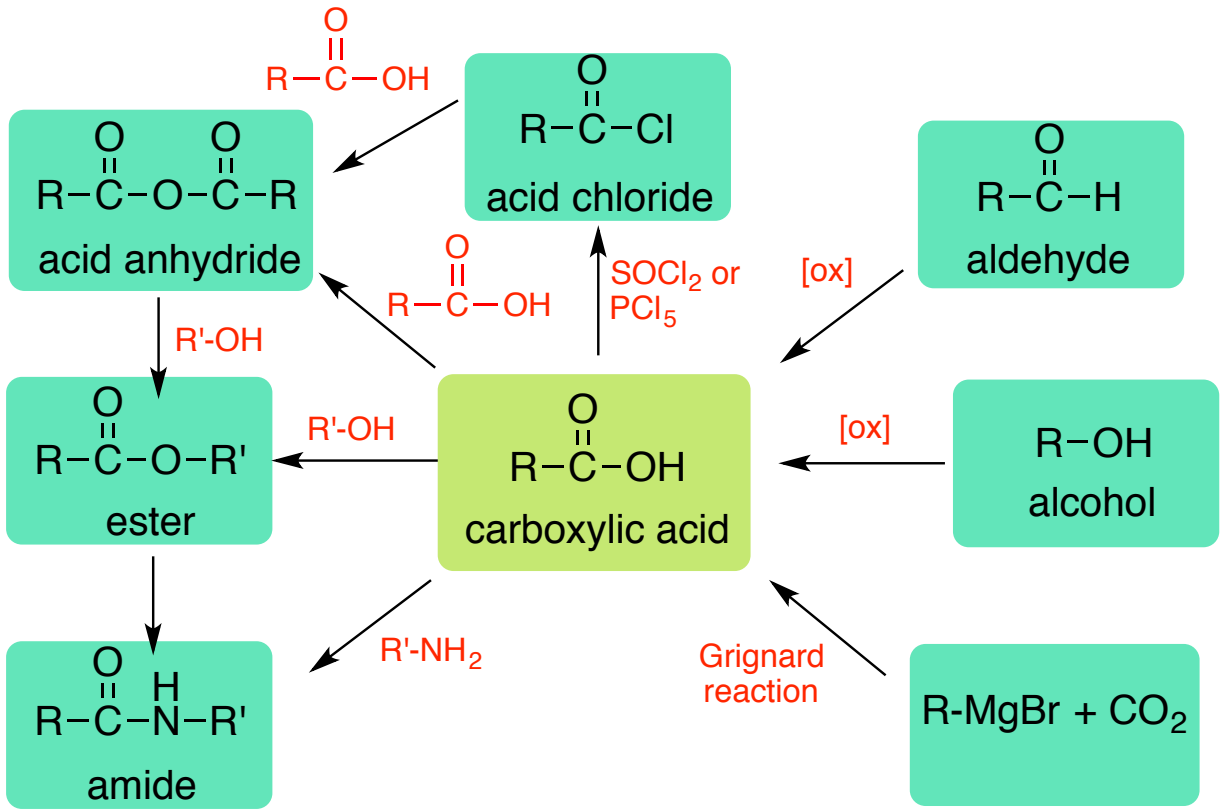
Example



FGI of carboxylic acid and derivatives

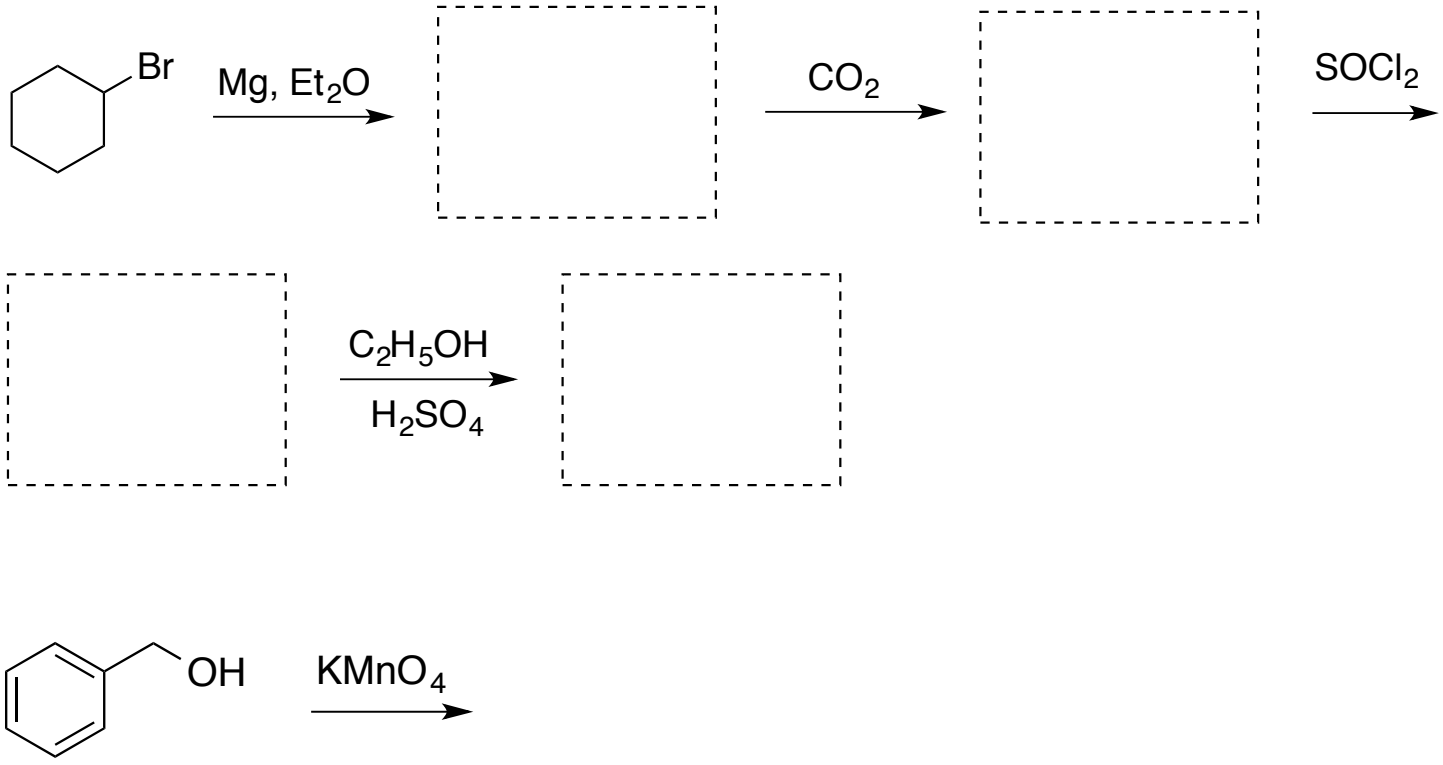
Reactivity



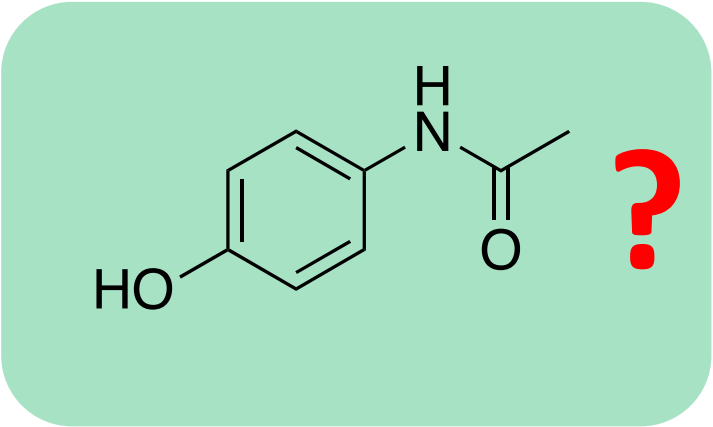


FGI of carboxylic acid and derivatives

Example



Molecule of the day



How to make this molecule?