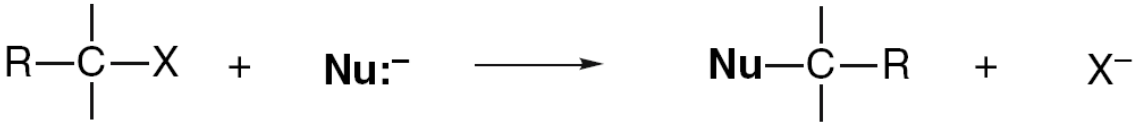
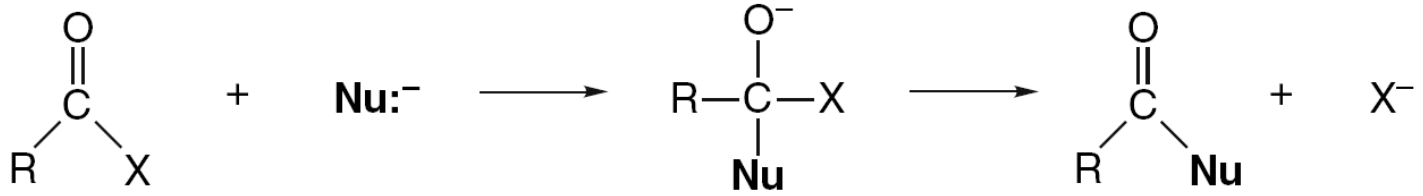
Functional Group Interconversion

- substitution
- S_N2 – $C(sp^3)$
- addition-elimination – $C(sp^2)=O$

Substitution at saturated carbons



Substitution at carbonyl groups



FG Interconversion

(1) conversion of ROH to reactive alkylating agents
(2) S_N2 reactions (various FG transformations)
(3) cleavage of C−O bonds in ethers and esters by S_N2 and S_N1 reactions
(4) carbonyl substitution reactions
(5) protective groups reactions („summer part of OS“)

Functional Group Interconversion

(1) Conversion of Alcohols to Alkylating Agents

A. Sulfonate esters

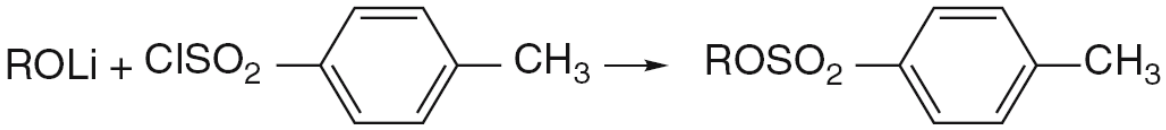
- OH poor leaving group

- preparation of SE:
  primary, secondary ROH → ROZs
  (tertiary ROH → alkenes)

- standard methods:
  TsCl/py, MsCl/py,
  Tf_2O/py-CH_2Cl_2

- alternative method:

Leaving group	k_{rel}
$CF_3SO_3^-$ (triflate)	1.4×10^8
p-Nitrobenzensulfonate (nosylate)	4.4×10^5
p-Toluenesulfonate (tosylate)	3.7×10^4
$CH_3SO_3^-$ (mesylate)	3.0×10^4
I^-	91
Br^-	14
$CF_3CO_2^-$	2.1
Cl^-	1.0
F^-	9×10^{-6}
p-Nitrobenzoate	5.5×10^{-6}
$CH_3CO_2^-$	1.4×10^{-6}



Functional Group Interconversion

(1) Conversion of Alcohols to Alkylating Agents

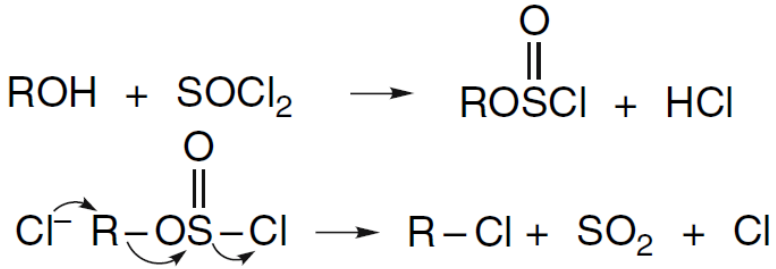
B. Halides

- ROH most common precursores

Preparation of RX:

1) harsh conditions (HX)
unsubstituted primary ROH → RBr (hot HBr), S_N2
unsubstituted primary ROH → RCl (HCl-$ZnCl_2$), S_N2
unsubstituted tertiary ROH → RX (HX) S_N1
(for non-acid-sensitive ROH, rearrangements)

2) non-metallic halides ($SOCl_2$, PCl_3, PBr_3) S_N2
non-participing solvents (chlorinated solvents, pyridine)



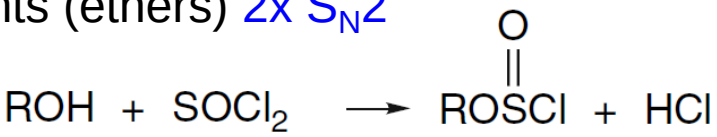
Functional Group Interconversion

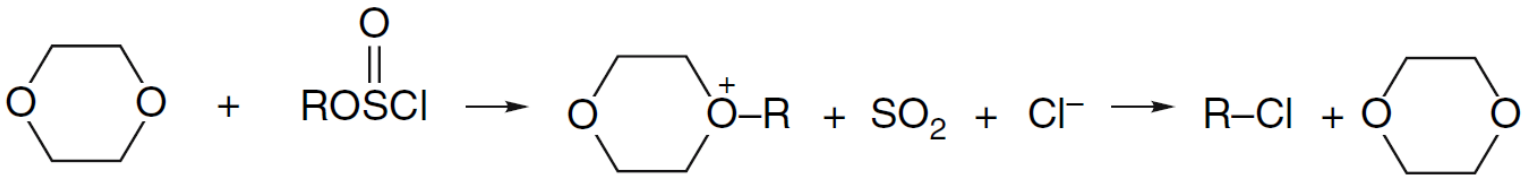
(1) Conversion of Alcohols to Alkylating Agents

B. Halides

Preparation of RX:

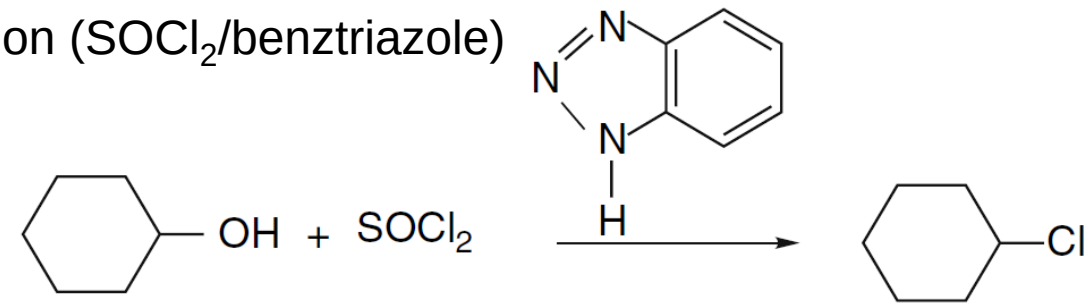
2) non-metallic halides ($SOCl_2$, PCl_3, PBr_3)
participiing solvents (ethers) 2x S_N2





retention

modification ($SOCl_2$/benztriazole)



92%

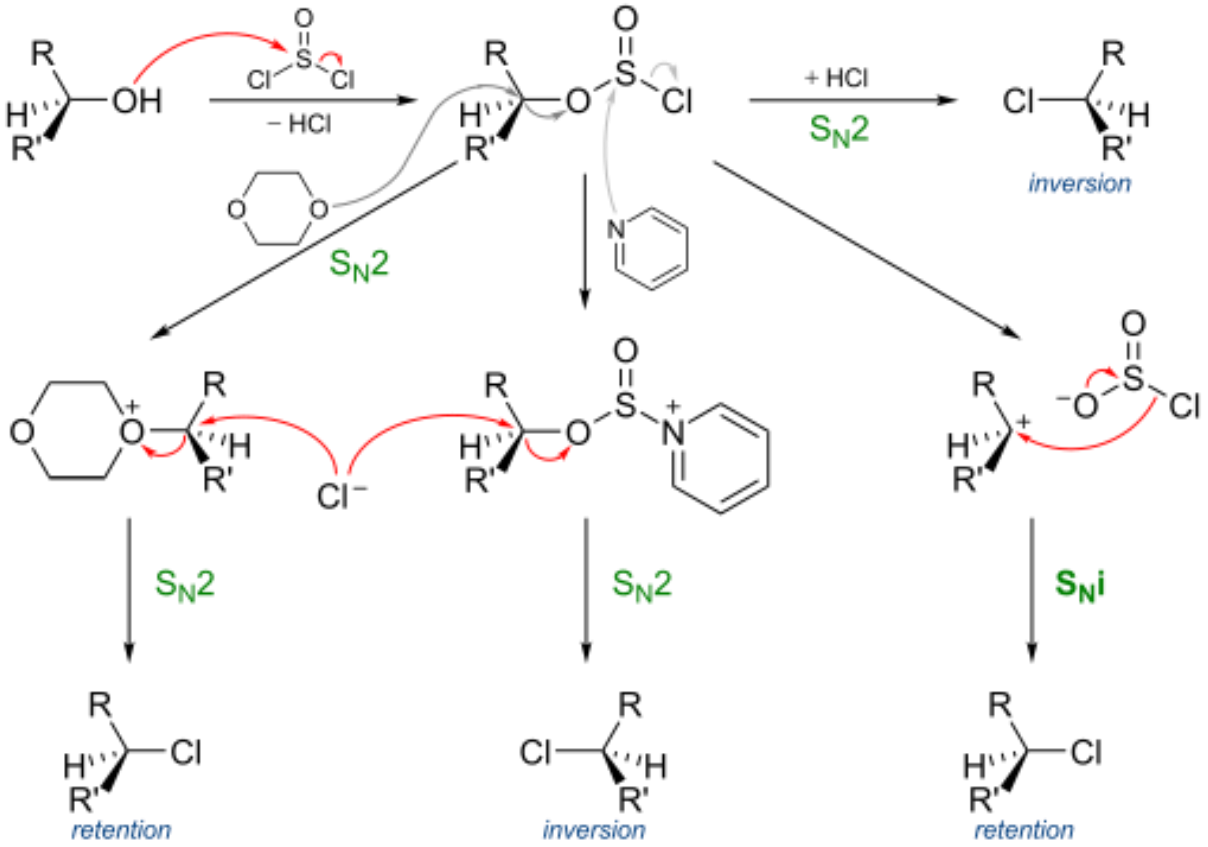
Functional Group Interconversion

(1) Conversion of Alcohols to Alkylating Agents

B. Halides

Preparation of RCl (summary):

- all possibilities (S_Ni - internal nucleophilic substitution, DCM)



Functional Group Interconversion

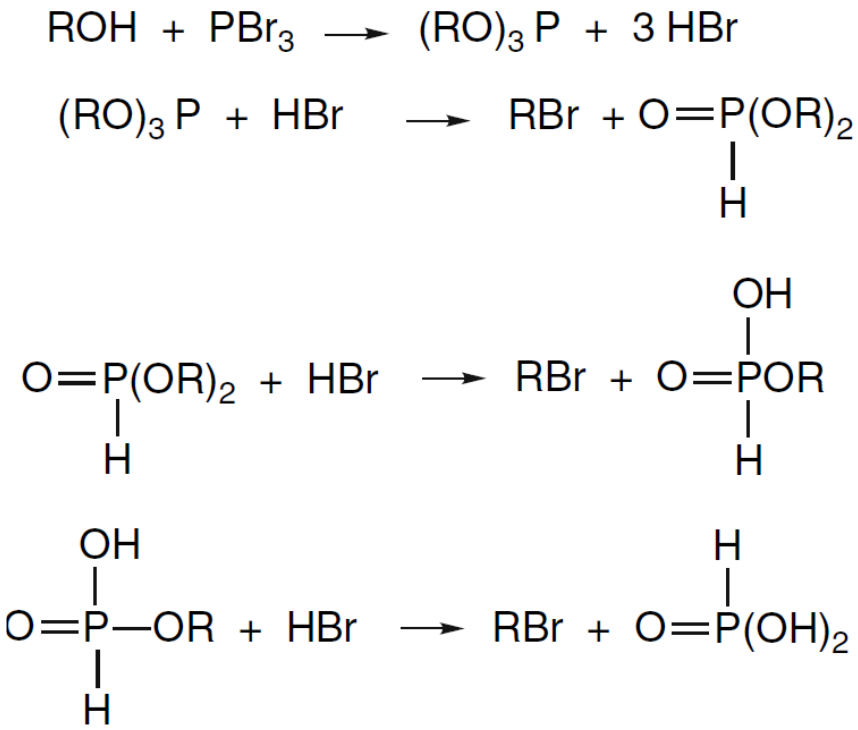
(1) Conversion of Alcohols to Alkylating Agents

B. Halides

Preparation of RX:

2) non-metallic halides ($SOCl_2$, PCl_3, PBr_3)

PBr_3



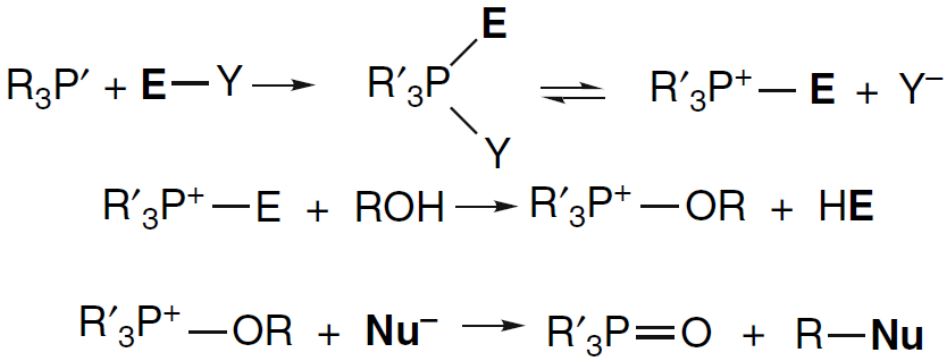
Functional Group Interconversion

(1) Conversion of Alcohols to Alkylating Agents

B. Halides

Preparation of RX:

3) *via* alkoxyphosphonium ions (P(III)-electrophile)



Electrophiles: halogens, positive halogen sources, DEAD

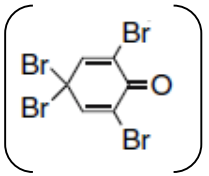
Functional Group Interconversion

(1) Conversion of Alcohols to Alkylating Agents

B. Halides

Preparation of RBr:

3) *via* alkoxyphosphonium ions (Ph_3P/Br_2) inversion

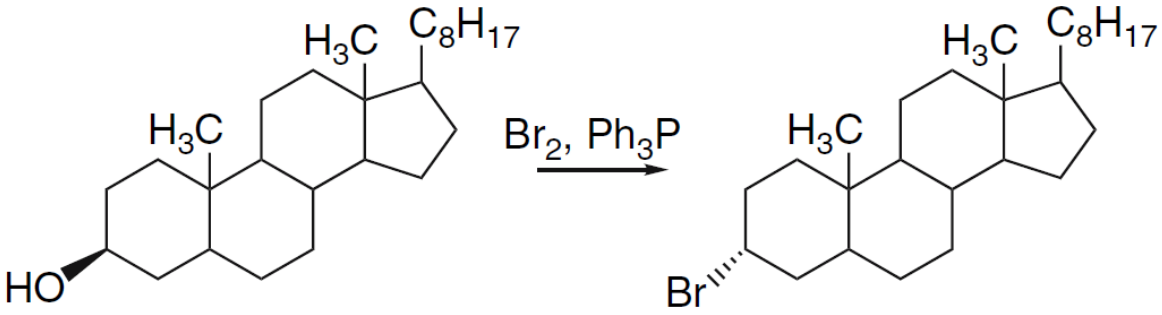


$$PPh_3 + Br_2 \longrightarrow Br_2PPh_3$$

$$Br_2PPh_3 + ROH \longrightarrow ROP^+Ph_3Br^- + HBr$$

$$Br^- + ROP^+Ph_3 \longrightarrow RBr + Ph_3P{=}O$$

Example



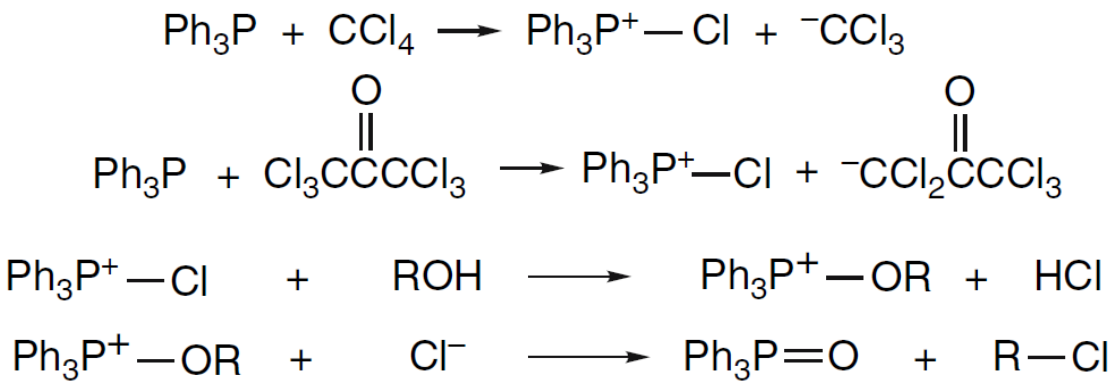
Functional Group Interconversion

(1) Conversion of Alcohols to Alkylating Agents

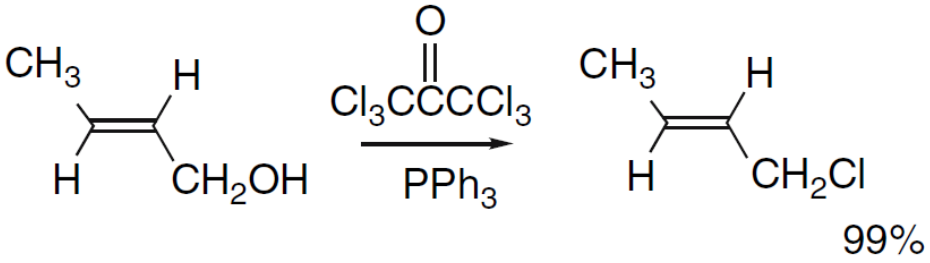
B. Halides

Preparation of RCl:

3) *via* alkoxyphosphonium ions (Ph_3P/Cl_2 or CCl_4, $Cl_3CCOCCl_3$)



Example



Functional Group Interconversion

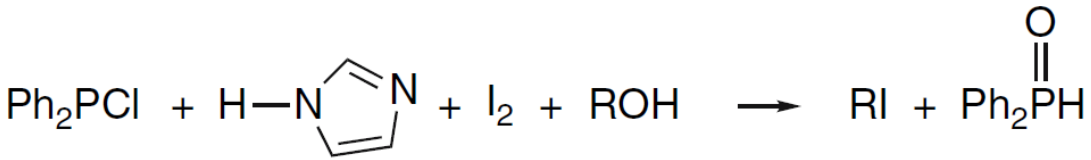
(1) Conversion of Alcohols to Alkylating Agents

B. Halides

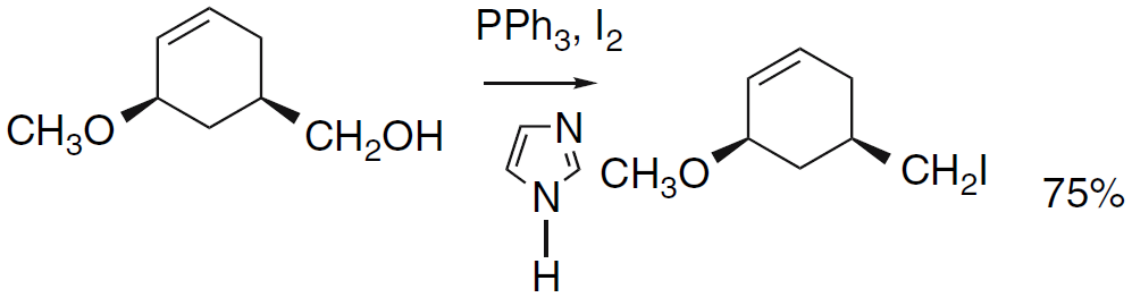
Preparation of RI:

3) *via* alkoxyphosphonium ions (*modifications*)

- imidazole
- work-up (base)



Example



Functional Group Interconversion

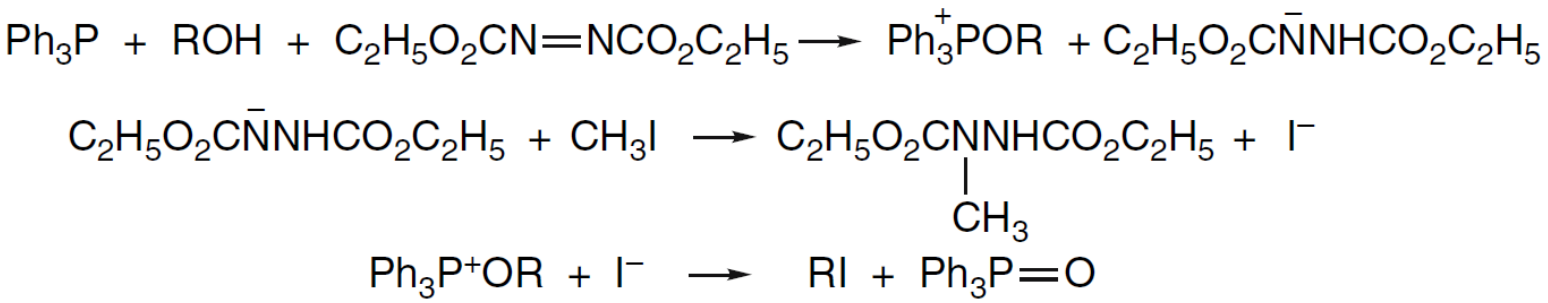
(1) Conversion of Alcohols to Alkylating Agents

B. Halides

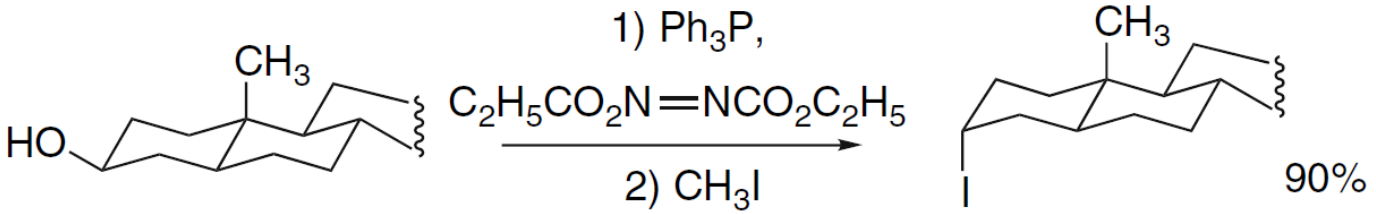
Preparation of RX:

3) *via* alkoxyphosphonium ions – *Mitsunobu reaction (DEAD)*

- very mild conditions
- with different types of nuclephiles (RI, RCOOH, RCONHR, ArOH, ArSH, etc.)



Example



Functional Group Interconversion

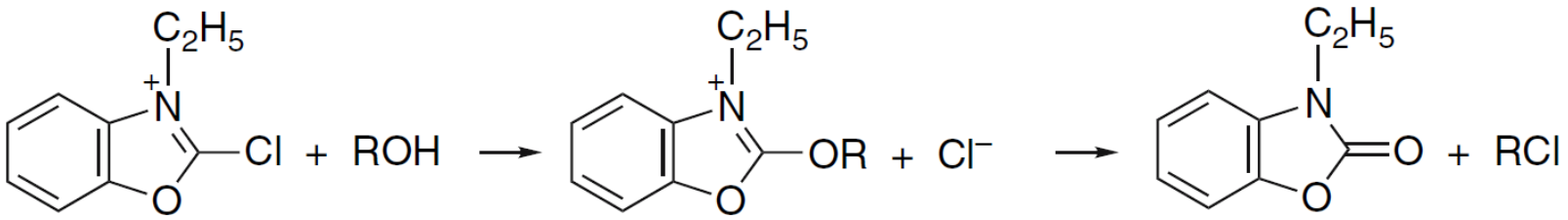
(1) Conversion of Alcohols to Alkylating Agents

B. Halides

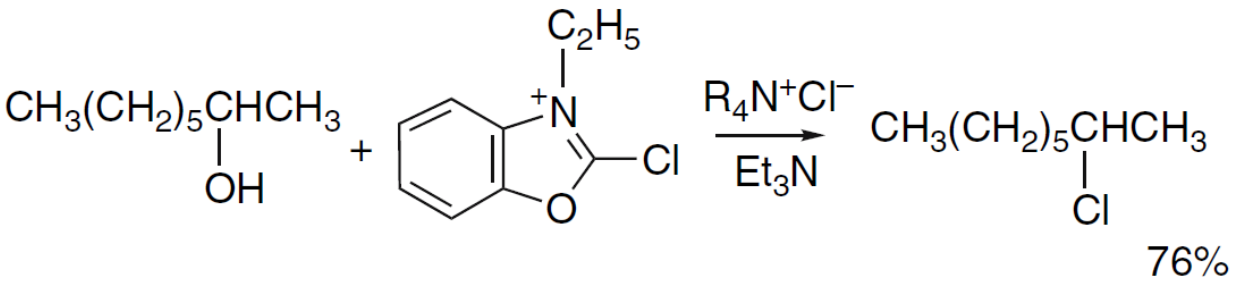
Preparation of RX:

4) *via* benzoxazolium cations

- very mild conditions
- preparation of RCl and RBr



Example



Functional Group Interconversion

(1) Conversion of Alcohols to Alkylating Agents

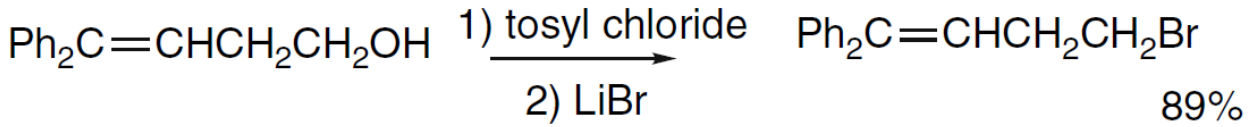
B. Halides

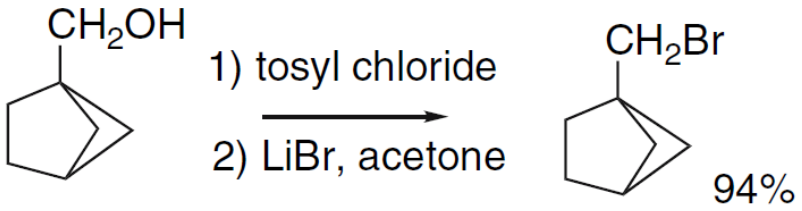
Preparation of RX:

5) double conversion *via* sulfonates

- allylic alcohols
- preparation of RCl and RBr (LiCl, LiBr)
- solvents: DMF, acetone

Example



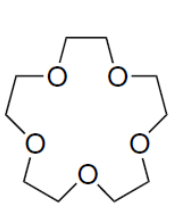


Functional Group Interconversion

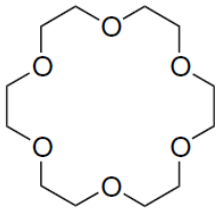
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

General

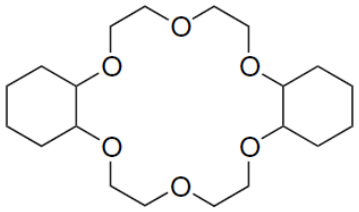
- S_N2 preffered (to avoid carbocations)
- LG: $RSO_3^- \geq I^- > Br^- > Cl^-$
- RCl (allylic, benzylic)
- important solvent effects:
  1) hydrocarbons, halogenated solvents, ethers – unsuitable
  2) acetone, acetonitrile – more polar, low solubility of ionic compounds
  3) alcohols – good solubility, nucleophility of hard anions low (solvation)
  4) polar aprotic solvents (DMF, DMSO, HMPA, *N*,*N*-dimethylacetamide, *N*-methylpyrrolidone) – good solvents for salts, selective cation solvation, anions usually show enhanced nucleophilicity
- crown ethers, PTC



15-crown-5



18-crown-6



dicyclohexano-18-crown-6

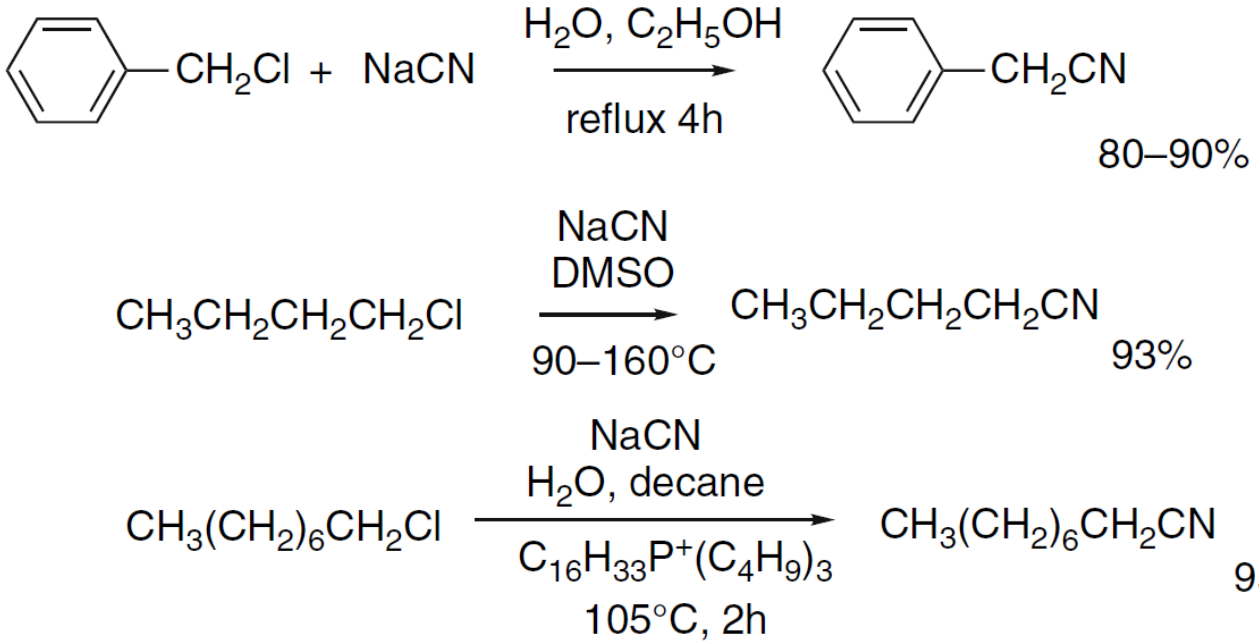
Functional Group Interconversion

(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Nitriles

- RX, RSO_3R' + CN^-
- solvents: ROH/H_2O
- Na, K, Ag salts

Examples



Functional Group Interconversion

(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

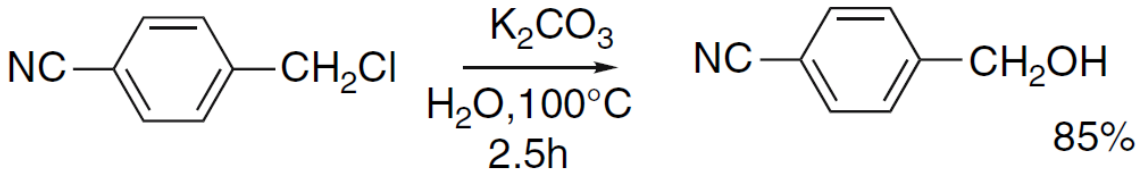
Oxygen Nucleophiles

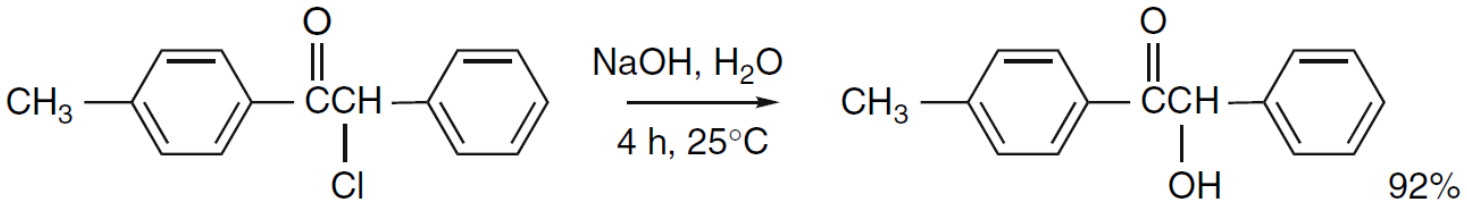
- H_2O, RO^-, $RCOO^-$
- nucleophile x base (substitution x elimination)
- Na, K, Ag salts

ROH from RX

- not frequently used
- BnX $\rightarrow$ BnOH

Examples





Functional Group Interconversion

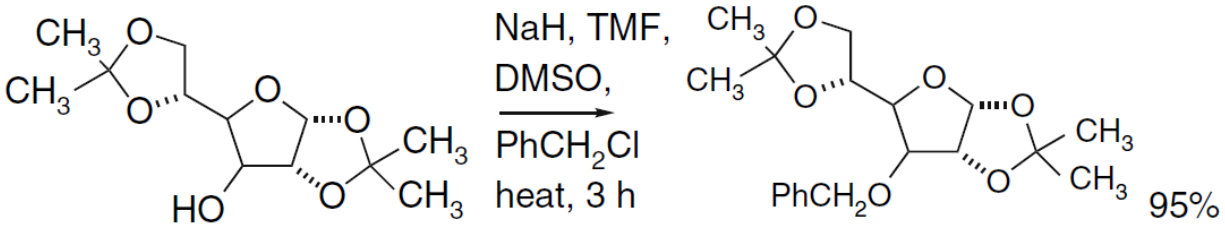
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

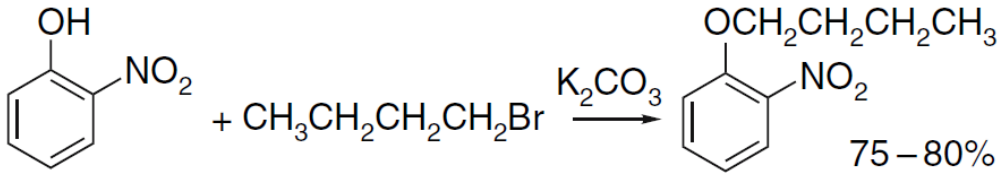
Oxygen Nucleophiles

ROR´ from RX

- wide synthetic importance
- alkoxides (phenoxides)
- *Williamson ether synthesis*

Examples





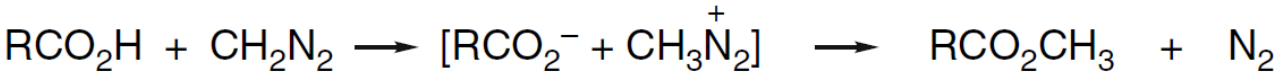
Functional Group Interconversion

(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

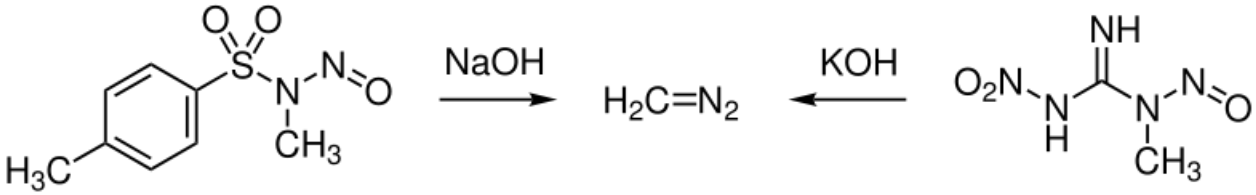
Oxygen Nucleophiles

RCOOR´ from RCOOH

- *via* diazocompounds (R´´CH_2N_2)
- fast, clean, reactive alkyldiazonium intermediate
- toxic, explosive (TMS-diazocompounds)



- preparation of CH_2N_2



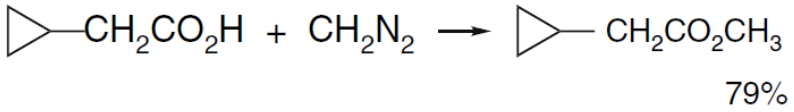
Functional Group Interconversion

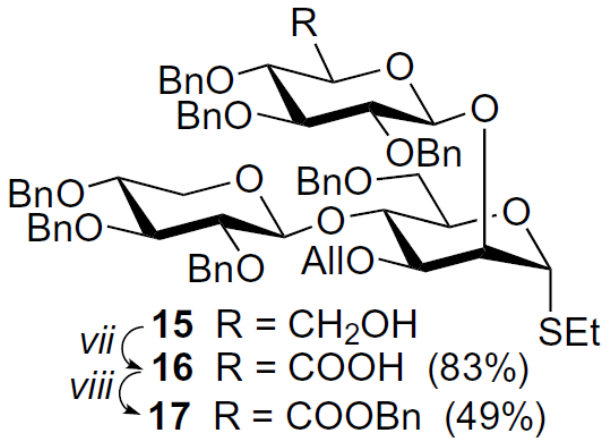
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Oxygen Nucleophiles

RCOOR´ from RCOOH

Examples





(vii) TEMPO, BAIB, CH_2Cl_2/H_2O; (viii) $PhCHN_2$, EtOAc.

Functional Group Interconversion

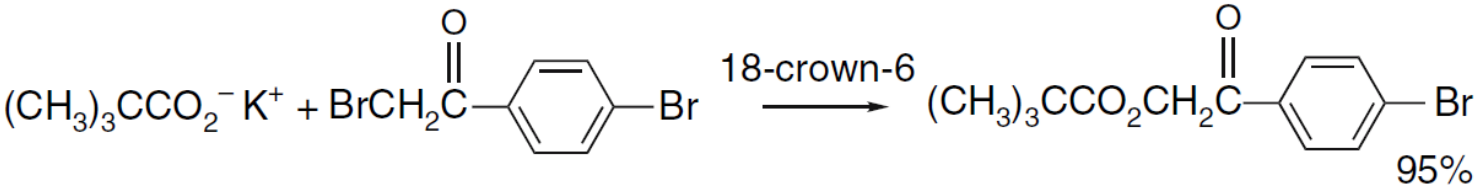
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Oxygen Nucleophiles

RCOOR´ from $RCOO^-$ and R´X

- RX or RSO_3R''
- carboxylate anions not very reactive nucleophiles
- solvents: DMF, acetone (R´I)
- reactivity order for carboxylate salts: $Na^+ < K^+ < Rb^+ < Cs^+$
- Cs^+ (minimum ion pairing, high solubility)
- even for hindered esters (not available *via* *Fisher esterification*)

Example

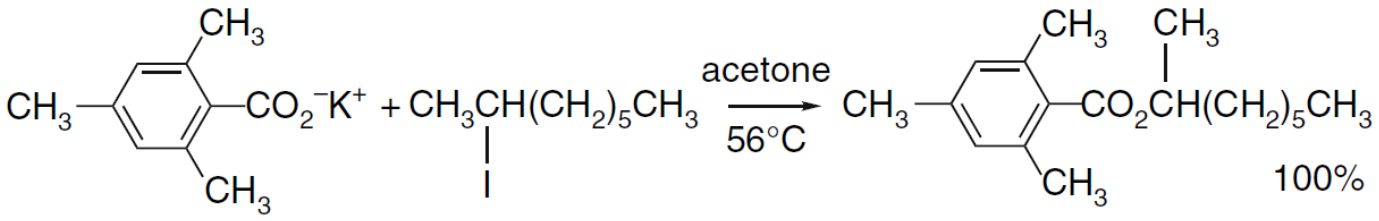


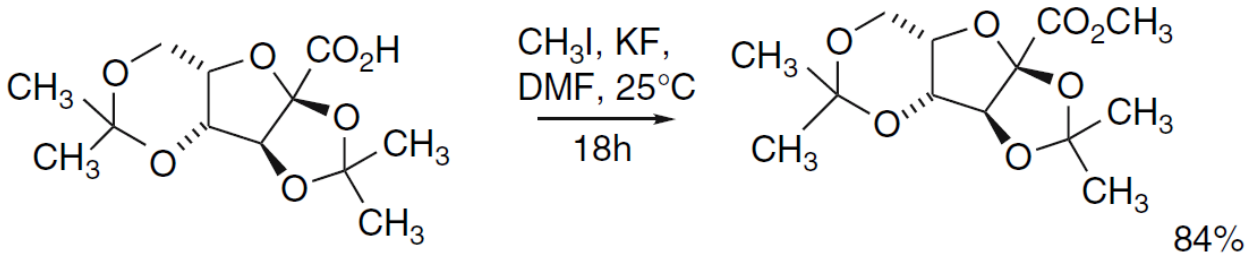
Functional Group Interconversion

(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Oxygen Nucleophiles

Examples





Functional Group Interconversion

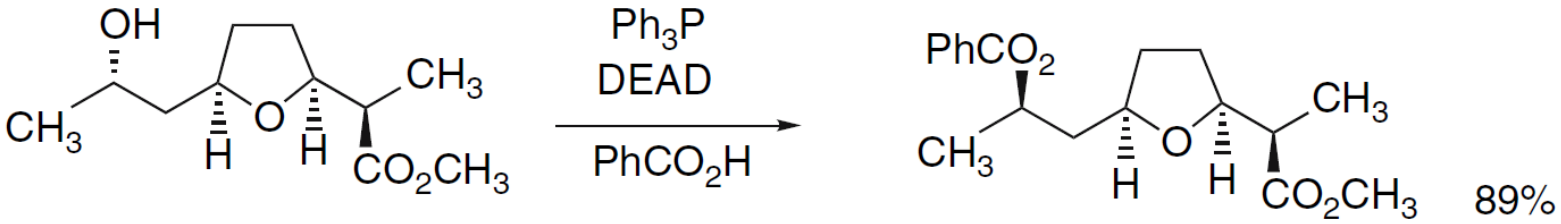
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

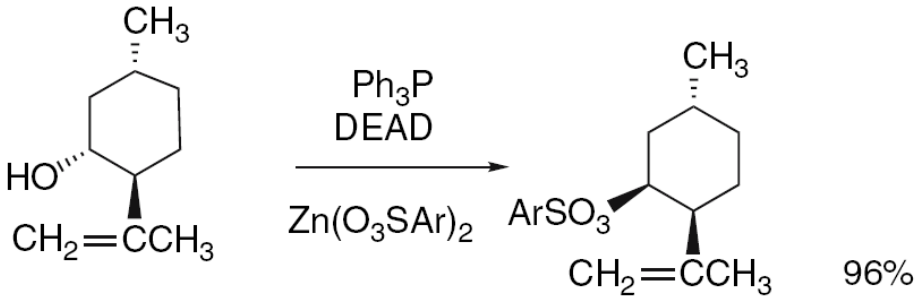
Oxygen Nucleophiles

RCOOR´ from ROH *via* Mitsunobu reaction

- mild conditions

Examples





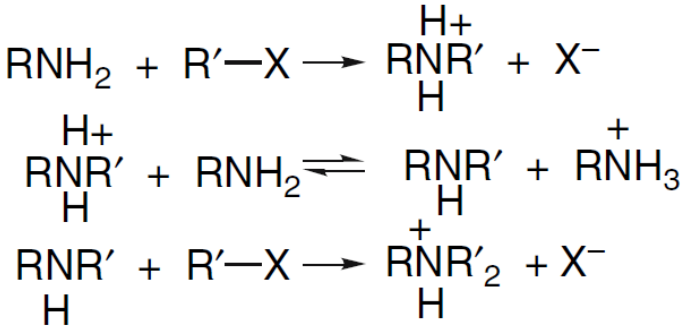
Functional Group Interconversion

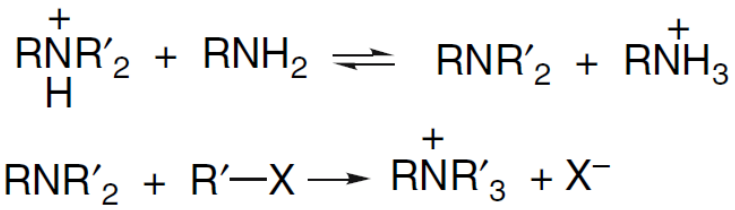
(2) Introduction of FG by Nucleophilic Substitution (C-sp³)

Nitrogen Nucleophiles

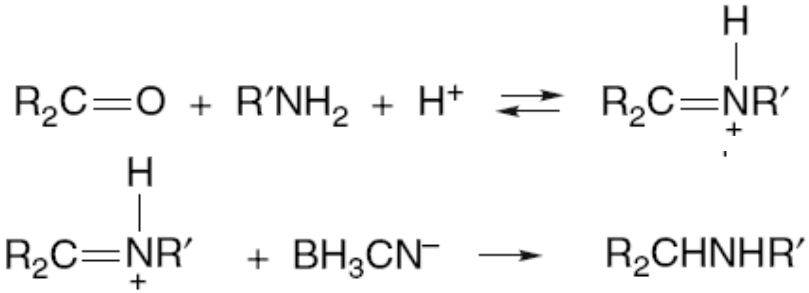
1) Direct alkylation of neutral amines by R´X

- complications (multiple alkylation)
- usefull for $R'_4N^+ X^-$





- preparation of RR´NH/RNH_2 (*reductive amination*)

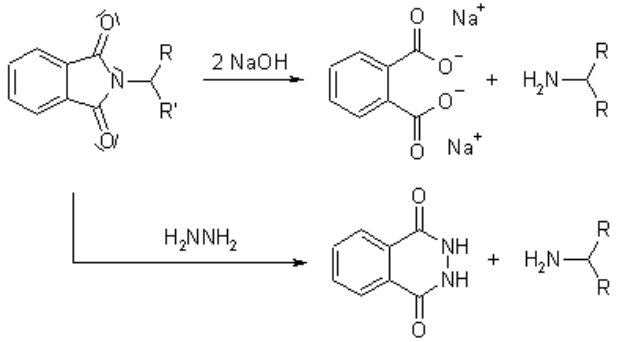


Functional Group Interconversion

(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Nitrogen Nucleophiles

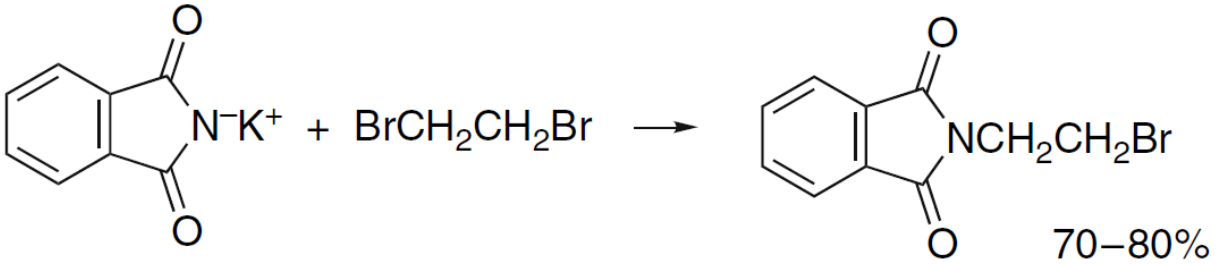
2) Gabriel synthesis



- „imidation“ with stabilized PhthN$^-$
- amides (less nucleophilic)
- deprotection (N_2H_4/ROH)

- various heterocycles (indole, benzimidazole, succinimide, etc.)
- solvents: DMF, ionic liquids

Example



Functional Group Interconversion

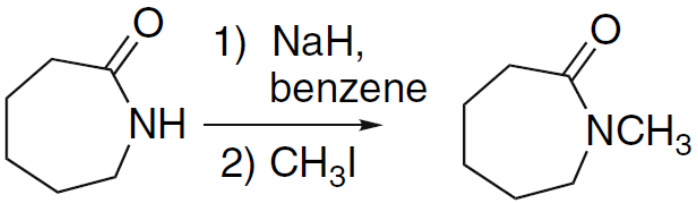
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Nitrogen Nucleophiles

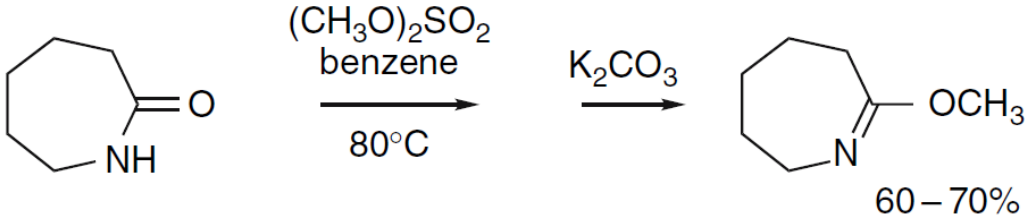
Watch out!

Examples

N-alkylation



O-alkylation



Functional Group Interconversion

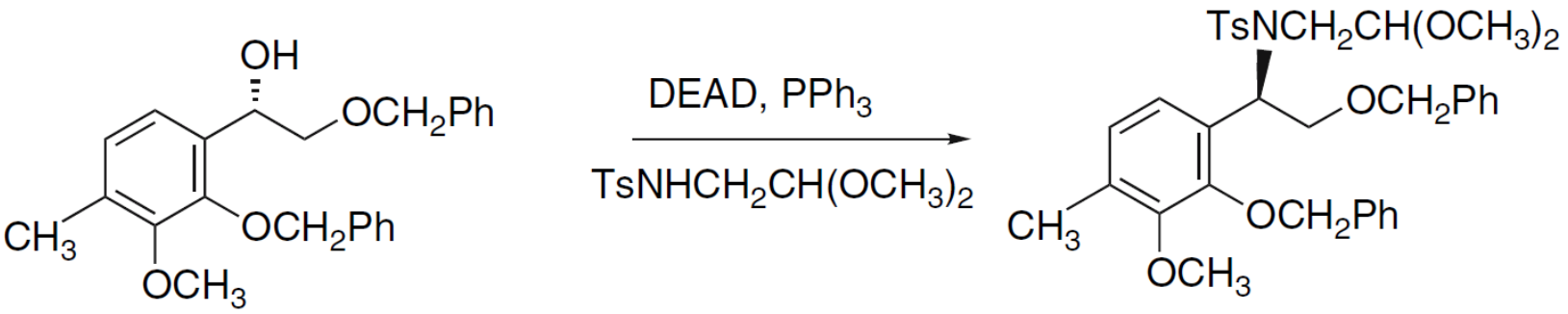
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Nitrogen Nucleophiles

3) Nucleophiles used in Mitsunobu reaction

a) sulfonamides
b) carbamates
c) various heterocycles (indoles, etc.)
d) azides

Example



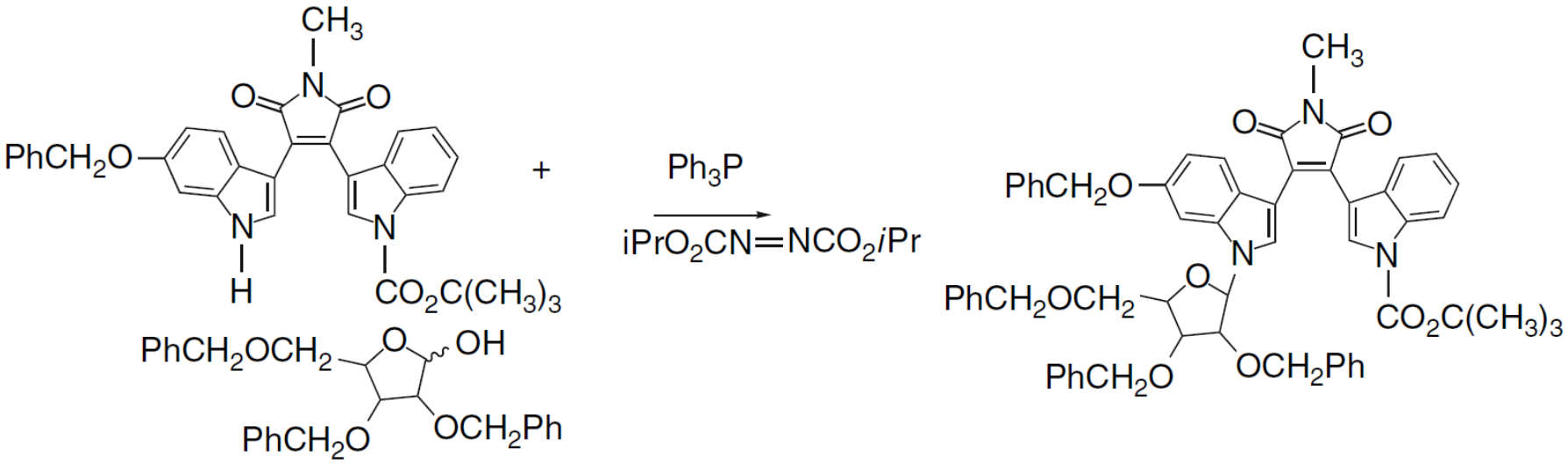
Functional Group Interconversion

(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Nitrogen Nucleophiles

3) Nucleophiles used in Mitsunobu reaction

Example



Functional Group Interconversion

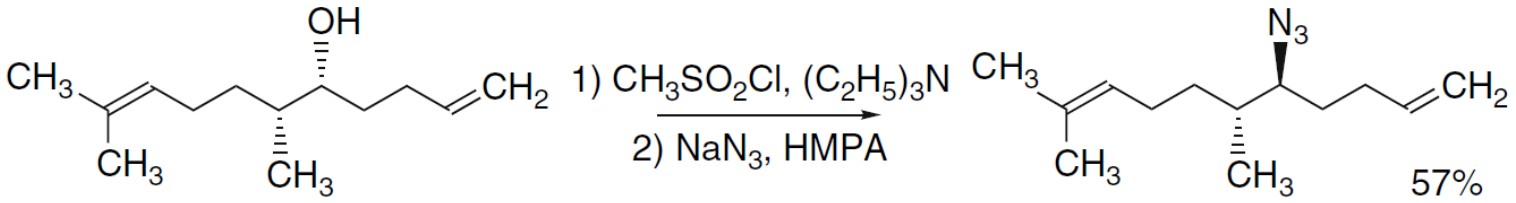
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

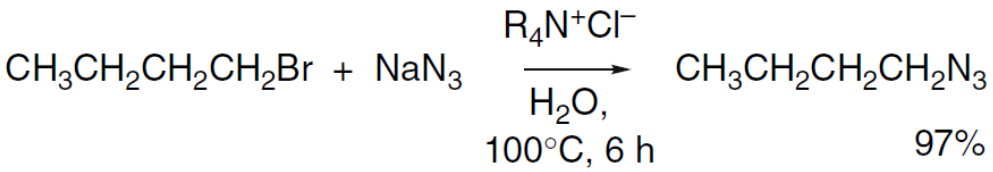
Nitrogen Nucleophiles

4) N_3^-

- Na^+, Li^+
- S_N2 mechanism
- solvents: DMF, DMSO, alcohols
- PT conditions

Examples





Functional Group Interconversion

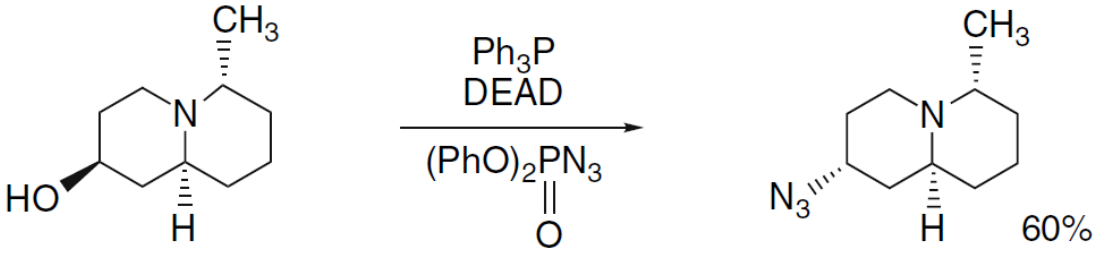
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Nitrogen Nucleophiles

4) N_3^-

- Mitsunobu conditions
- diarylphosphoryl azides

Examples



Functional Group Interconversion

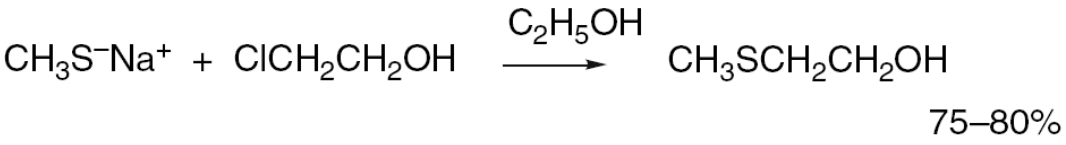
(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

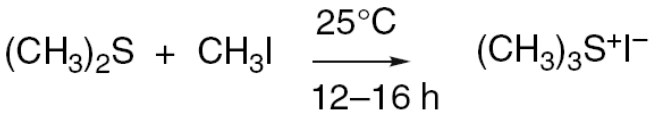
Sulfur Nucleophiles

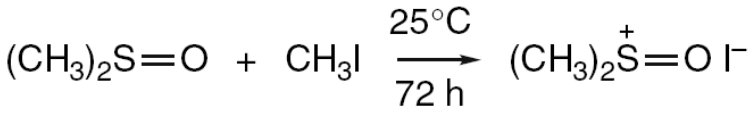
Thiolates (RS^-)

- strong nucleophiles
- negative x neutral sulfur compounds (sulfides, thioamides, even sulfoxides etc.)

Examples





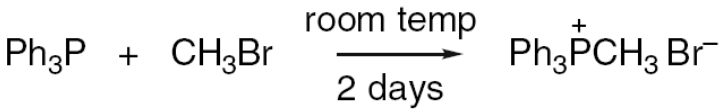


Functional Group Interconversion

(2) Introduction of FG by Nucleophilic Substitution (C-sp^3)

Phosphorus Nucleophiles

- trivalent P
- good nucleophiles (neutral, anionic)



- *Michaelis-Arbuzov reaction*
- phosphite esters (*via* unstable trialkoxyphopsphonium intermediate)