*Sky and Water I*
*Maurits Cornelis Escher, 1938*

Universitat de Barcelona

Dr. Pere Romea
Department of Organic Chemistry

# 6. Functional Group Interconversion

Organic Synthesis 2014-2015 Autumn Term

*The synthesis of an organic compound must pay attention to ...*

*Carbon backbone* ⟷ *Functional groups*

*(Chapters 2–4 )*

*Functional Group Interconversion (FGI)*

*I. Nucleophilic Substitutions*

*Electrophilic Additions to C=C*

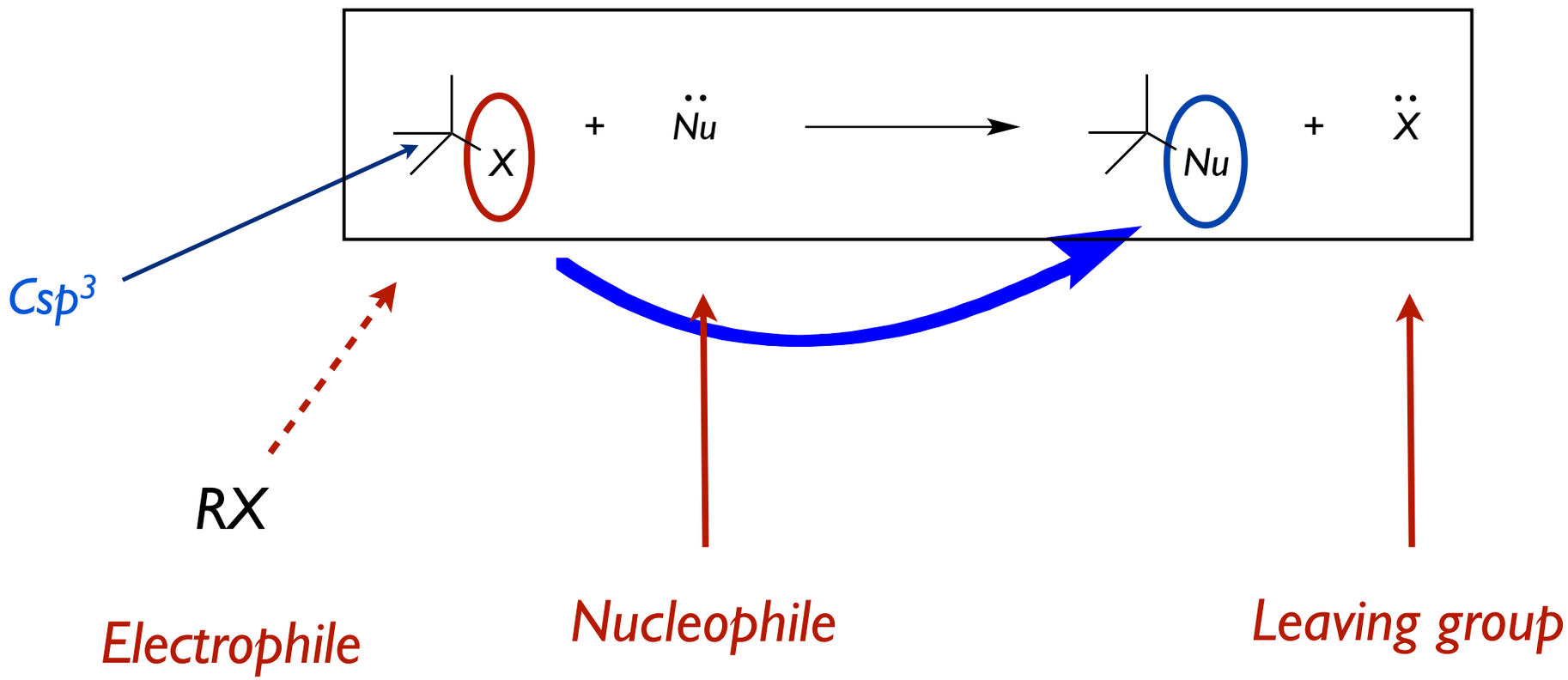
*Addition-Eliminations on Carboxylic Acids and Derivatives*

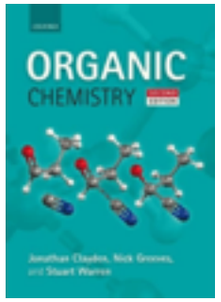
*II. Reductions*

*III. Oxidations*

***Mechanism!!!***

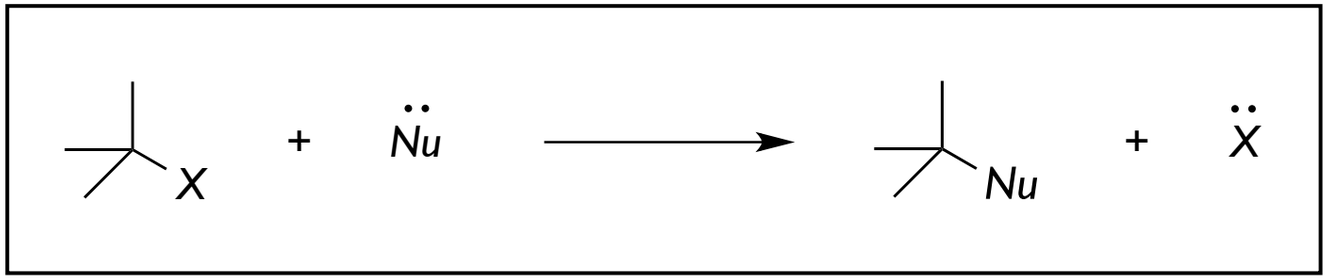
- *The **nucleophilic substitutions** involve the interconversion of functional groups bound to **sp³ carbonis***



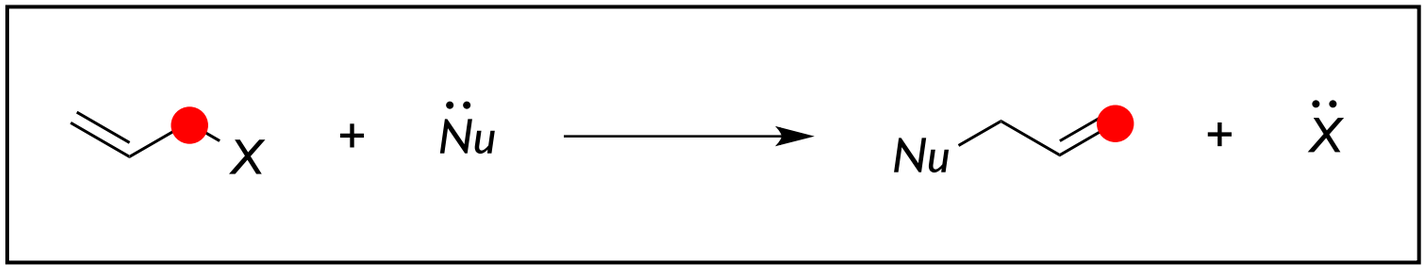

*Chap. 15*

- *Two model mechanisms, called $S_N1$ i $S_N2$, are used to explain the nucleophilic substitutions*




*Unimolecular ($S_N1$) or bimolecular ($S_N2$) nucleophilic substitution?*

- *A slightly different model, called $S_N2'$, may be useful in substitutions on allylic substrates*



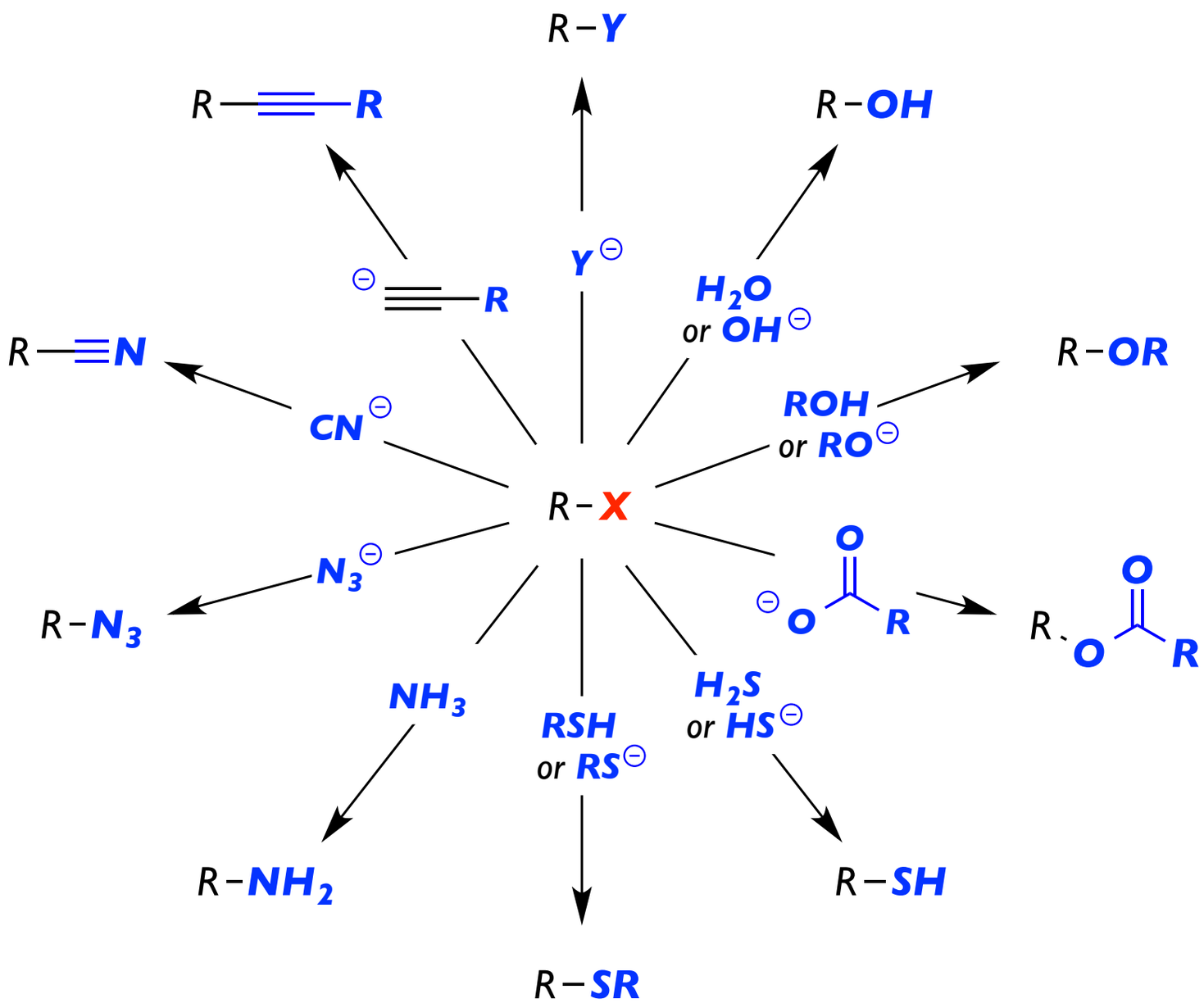
*There are three main sources to carry out FGI through nucleophilic substitutions: sulfonates, alcohols, and alkyl halides*

*Sulfonates* $R–OSO_2R' \xrightarrow{Nu} R–Nu$

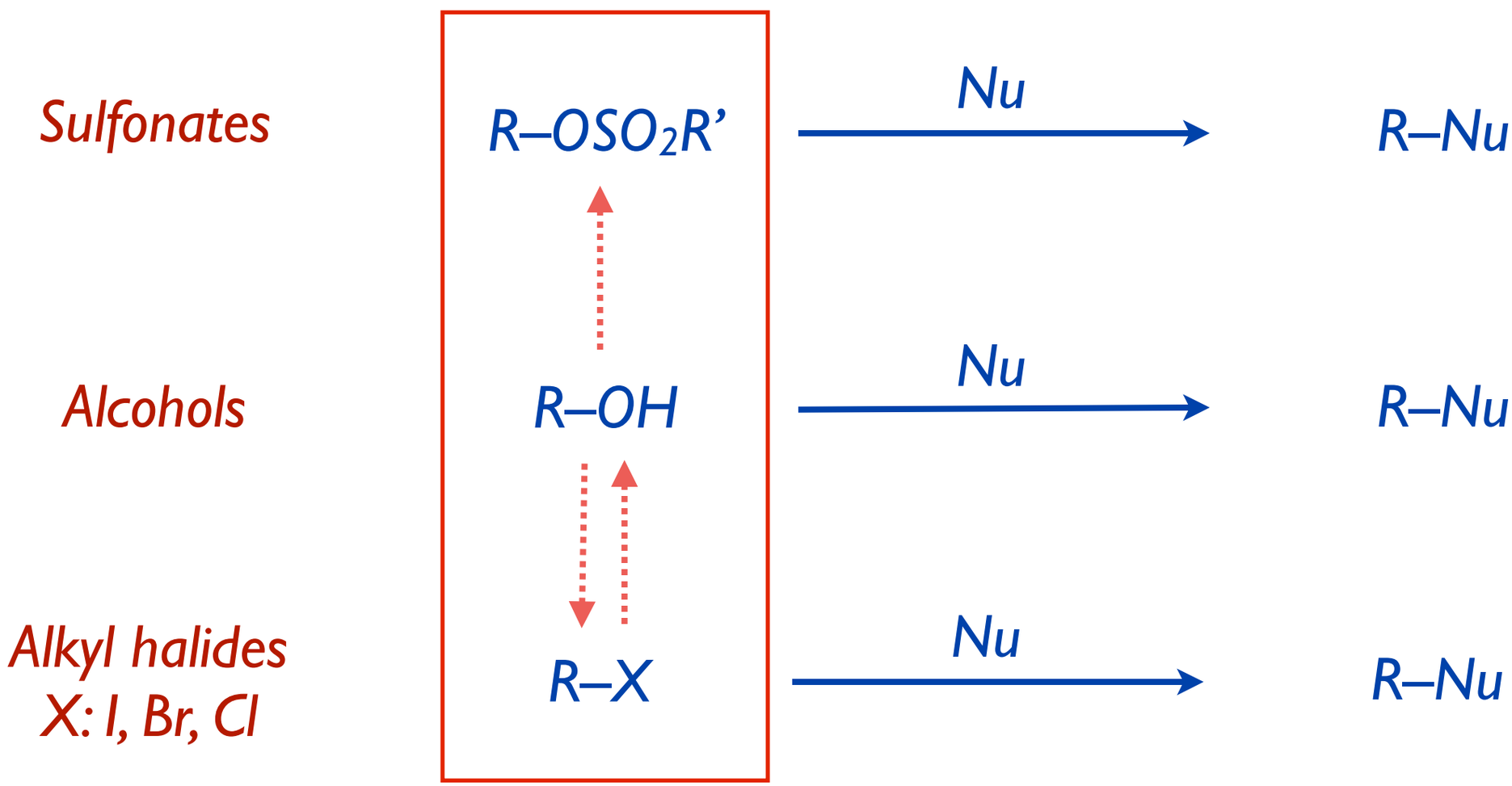
*Alcohols* $R–OH \xrightarrow{Nu} R–Nu$

*Alkyl halides*
*X: I, Br, Cl* $R–X \xrightarrow{Nu} R–Nu$

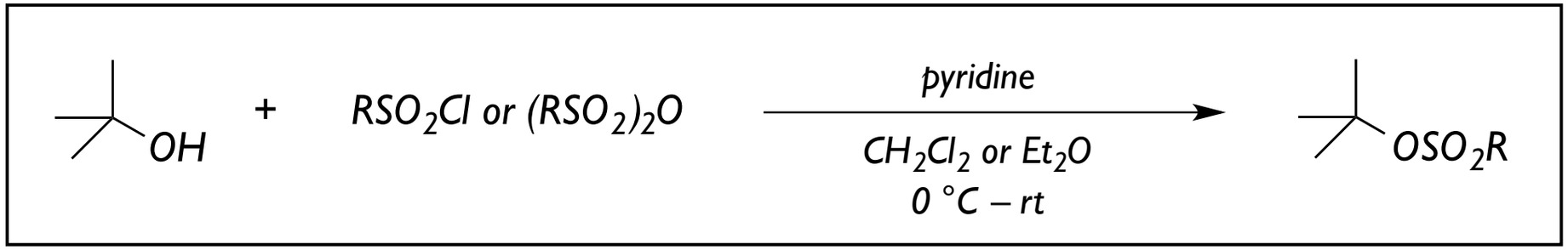
*A wide array of structures can be synthesized from sulfonates and alkyl halides through nucleophilic substitution of X = $OSO_2R$, I, Br, Cl in C–C bond forming reactions and FGI*



*How easy is to interconvert sulfonates, alcohols, and alkyl halides?*

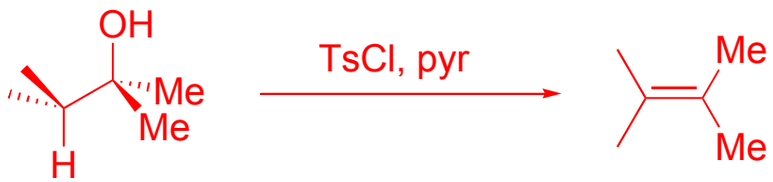


## Conversion of alcohols into sulfonic esters




| | | | |
|---|---|---|---|
| Mesyl chloride | **Ms**Cl | $MeSO_2Cl$ | Mesylate |
| Tosyl chloride | **Ts**Cl | p-$MePhSO_2Cl$ | Tosylate |
| Triflic Anhidride | **Tf**$_2$O | $(CF_3SO_2)_2O$ | Triflate |

– Primary and secondary ROH OK, but the reaction is sensitive to steric hindrance

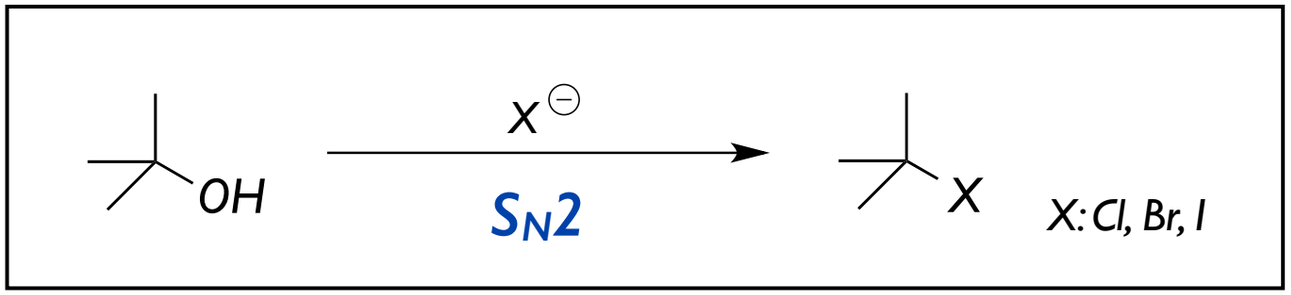


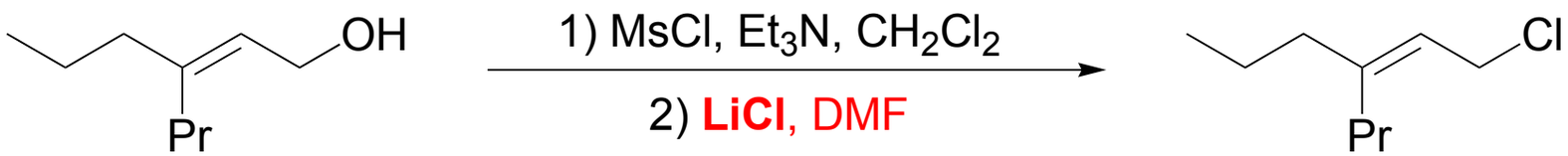

– The reaction does not affect the C–O bond: the configuration of the carbon remains the same

– Mesylates and tosylates are largely employed. Triflates are the most reactive sulfonates

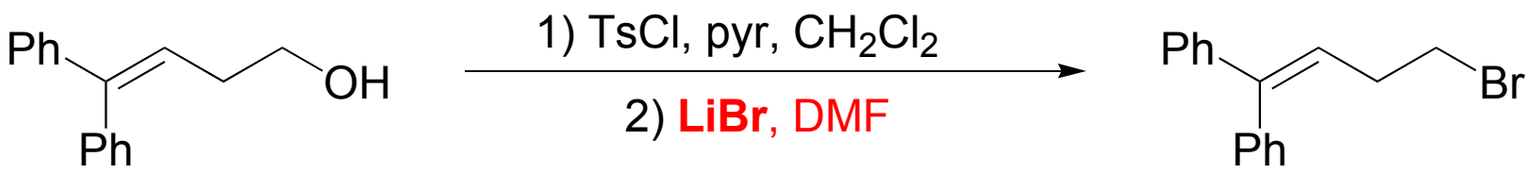
– Rearrangements of the carbon backbone are not frequent

## *Conversion of sulfonate into alkyl halides*

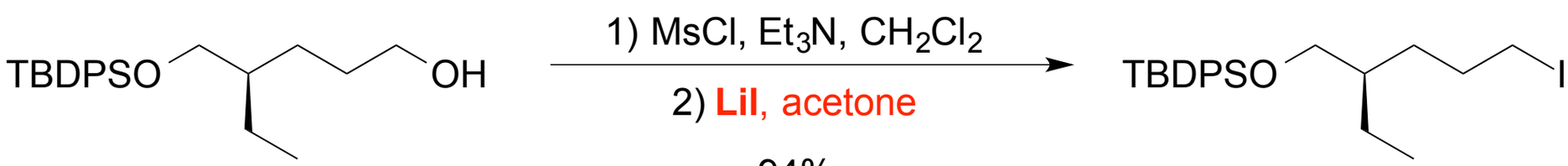



83%

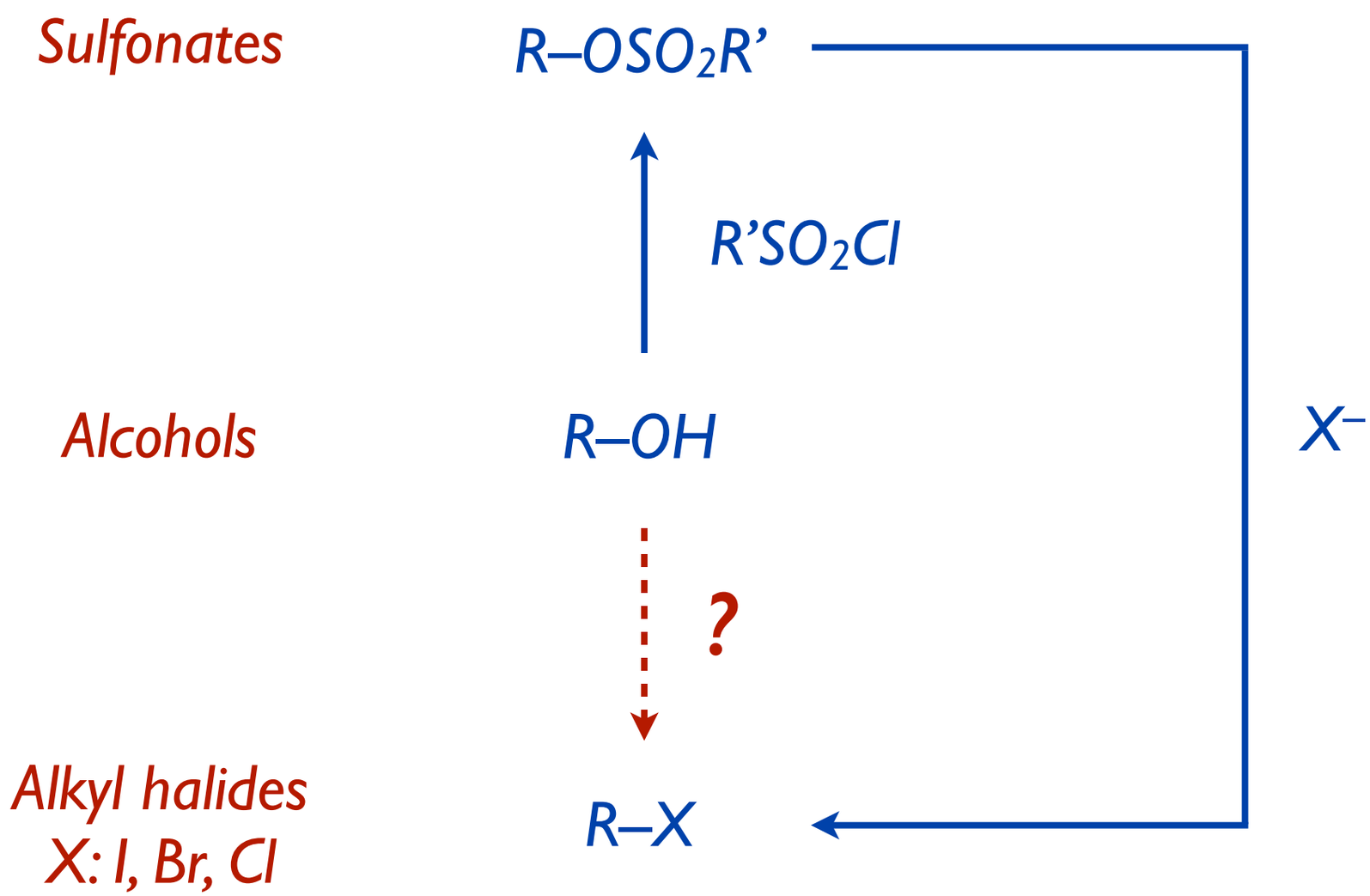



89%

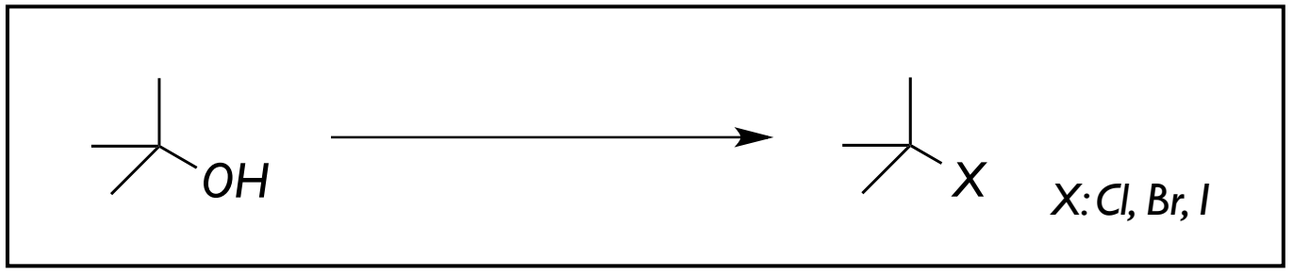



94%

## Conversion of alcohols into alkyl halides

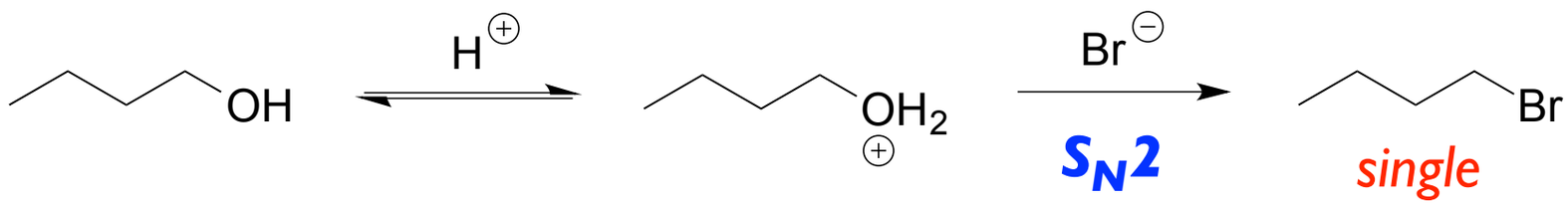


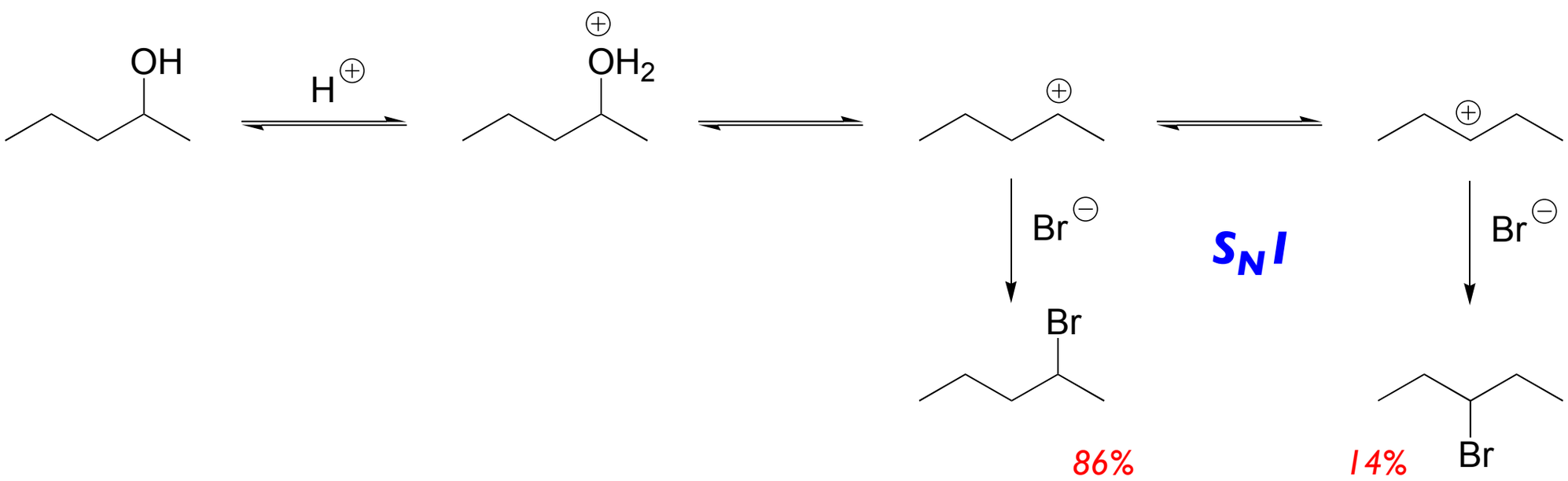
## Conversion of alcohols into alkyl halides

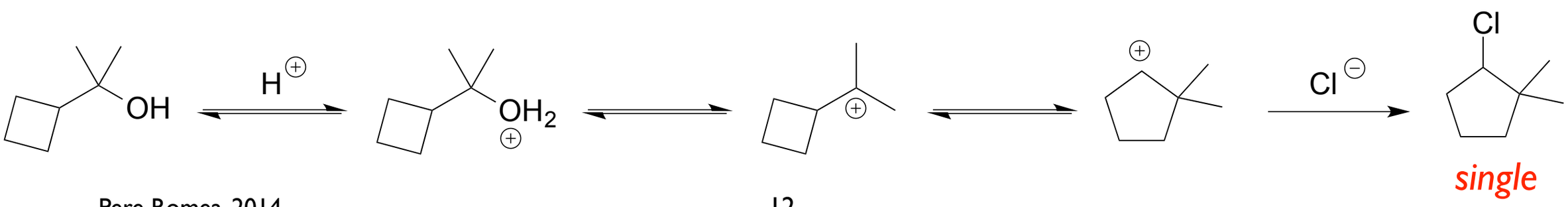



| Reagents & Conditions | Alcohols | Mechanism |
|---|---|---|
| HCl conc | Tert | $S_N1$ (racemization) |
| $HCl/ZnCl_2$ (Lucas reagent) | Prim & Sec | $S_N2$ (inversion) |
| $PCl_3$ | Prim & Sec | $S_N2$ (inversion) |
| $SOCl_2$, 1,4-dioxane | Prim & Sec | $S_N2$ + $S_N2$ (retention) |
| $SOCl_2$, non nucleophilic solvent | Prim & Sec | $S_N2$ (inversion) |
| HBr conc | Tert | $S_N1$ (racemization) |
| HBr conc, Δ | Prim | $S_N2$ |
| $PBr_3$ | Prim & Sec | $S_N2$ (inversion) |
| $P/I_2$ | Prim & Sec | $S_N2$ (inversion) |

## *Problem! Too harsh experimental conditions: mixture of mechanisms and transpositions*

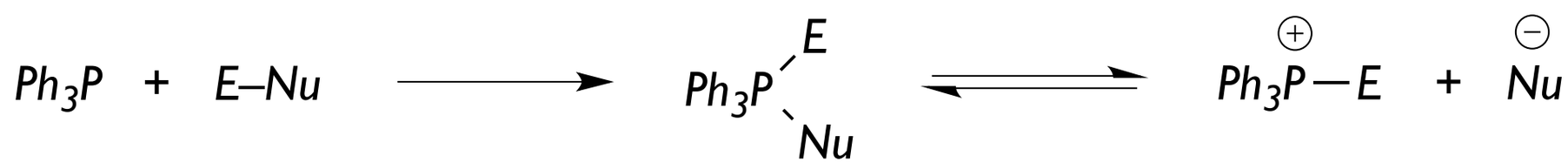


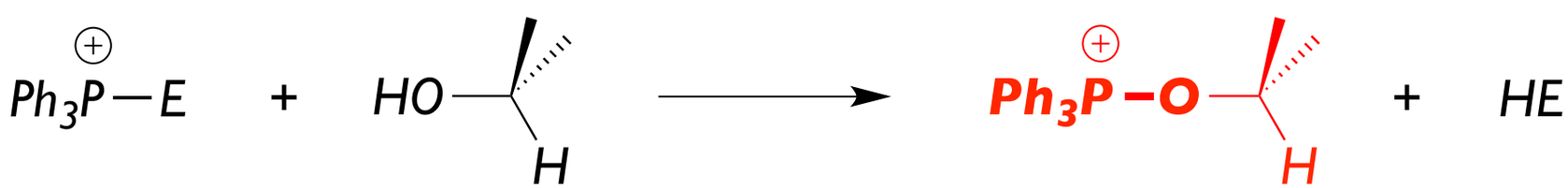



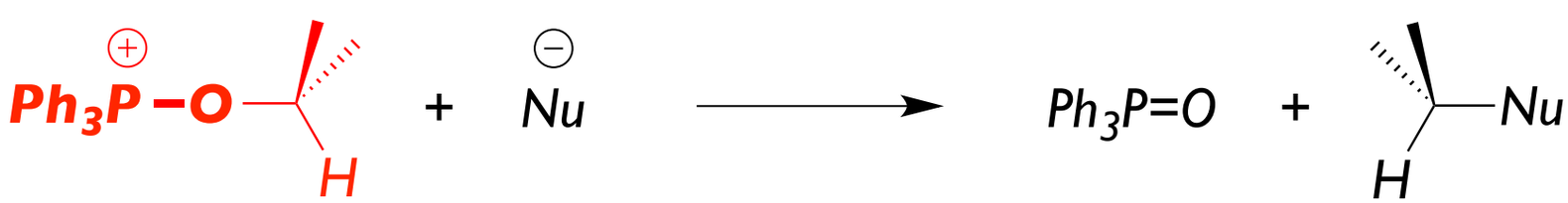
## *More selective transformations are required …*

*The most used options are based on the conversion of alcohols into **alkoxyphosphonium salts**, highly reactive in $S_N2$ substitutions*



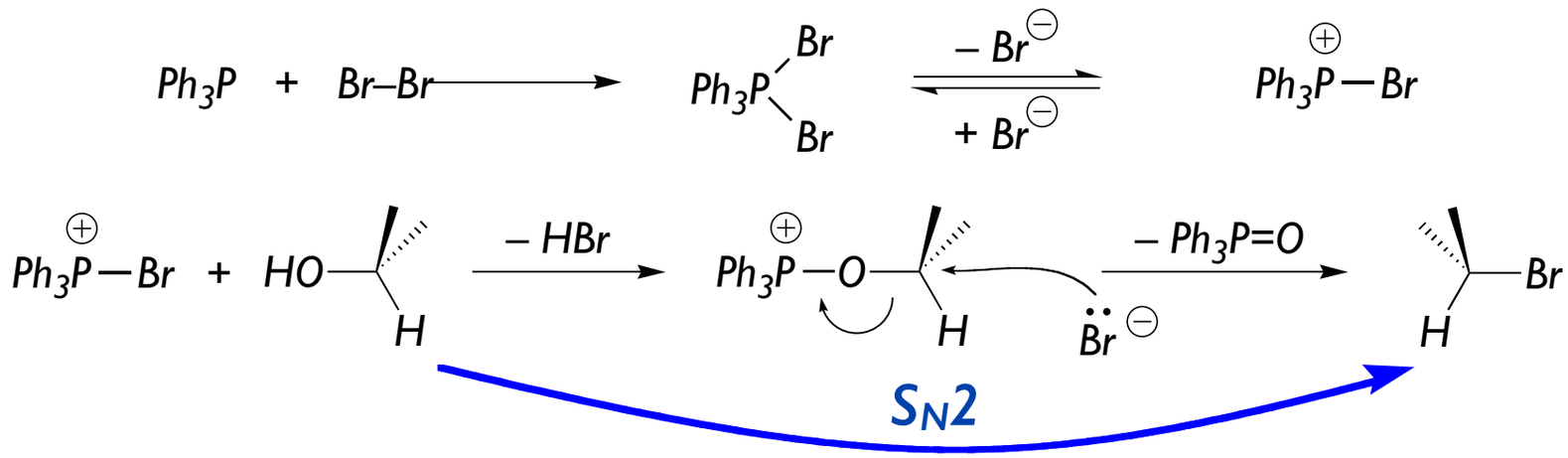




*Alkoxyphosphonium salt*

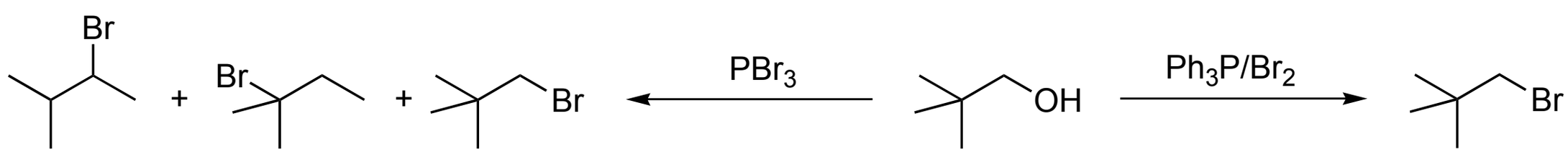



*Alkoxyphosphonium salt*

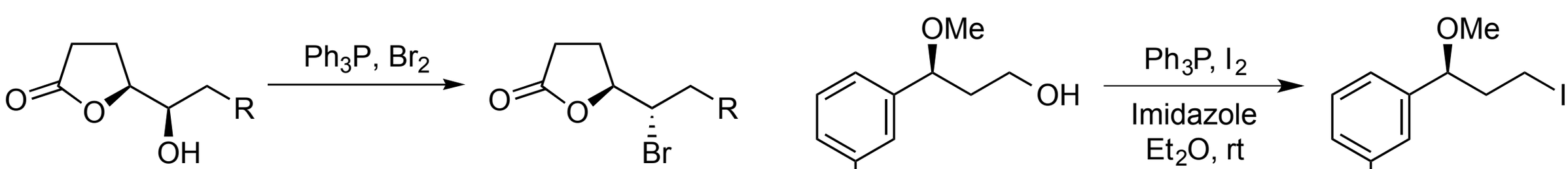
## $Ph_3P$ / $X_2$ : $Ph_3P$ / $I_2$, $Ph_3P$ / $Br_2$, $Ph_3P$ / $Cl_2$




*This transformation is very useful for secondary alcohols and those systems that easily produce transpositions, as neopentylic alcohols*
*The control on the configuration is very good.*

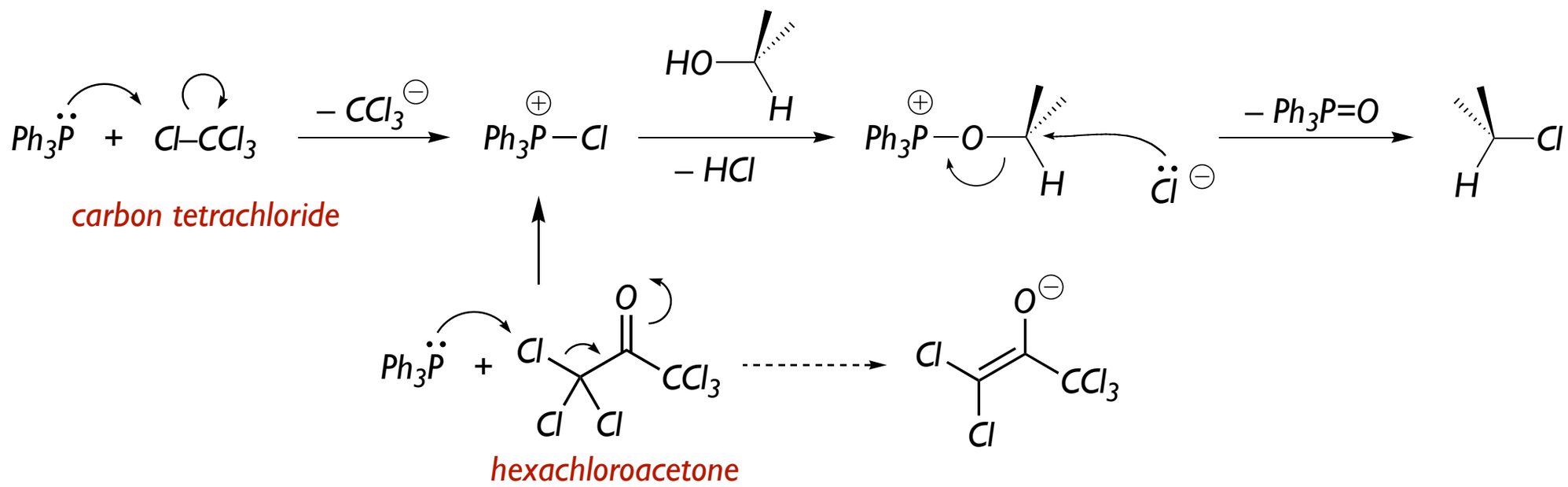


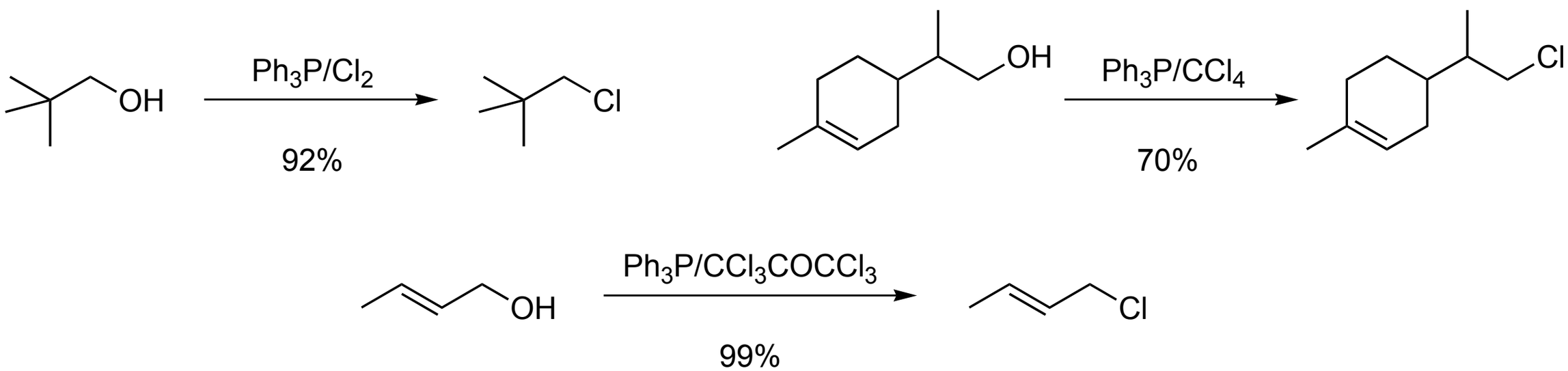

11% 26% 63% 90%

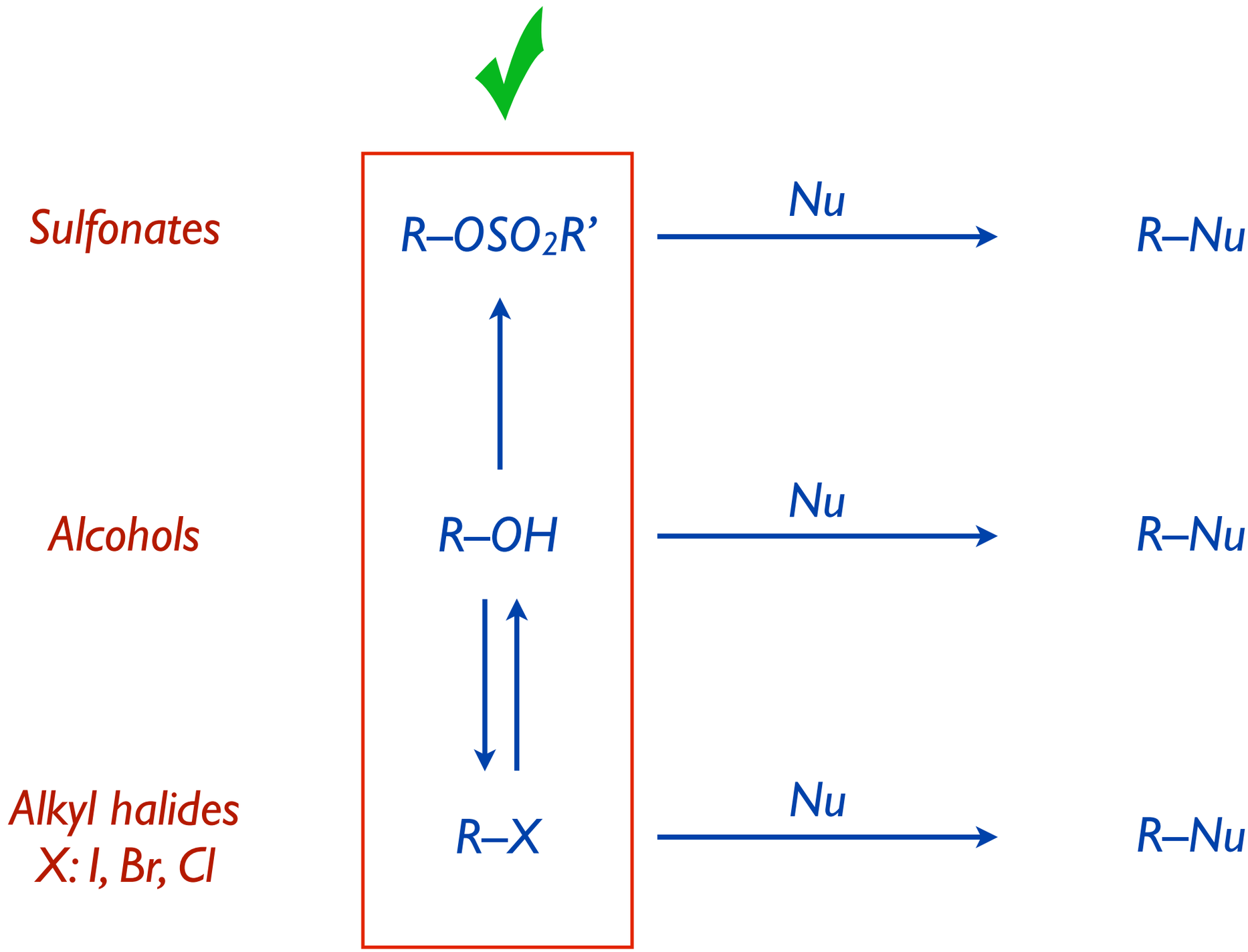


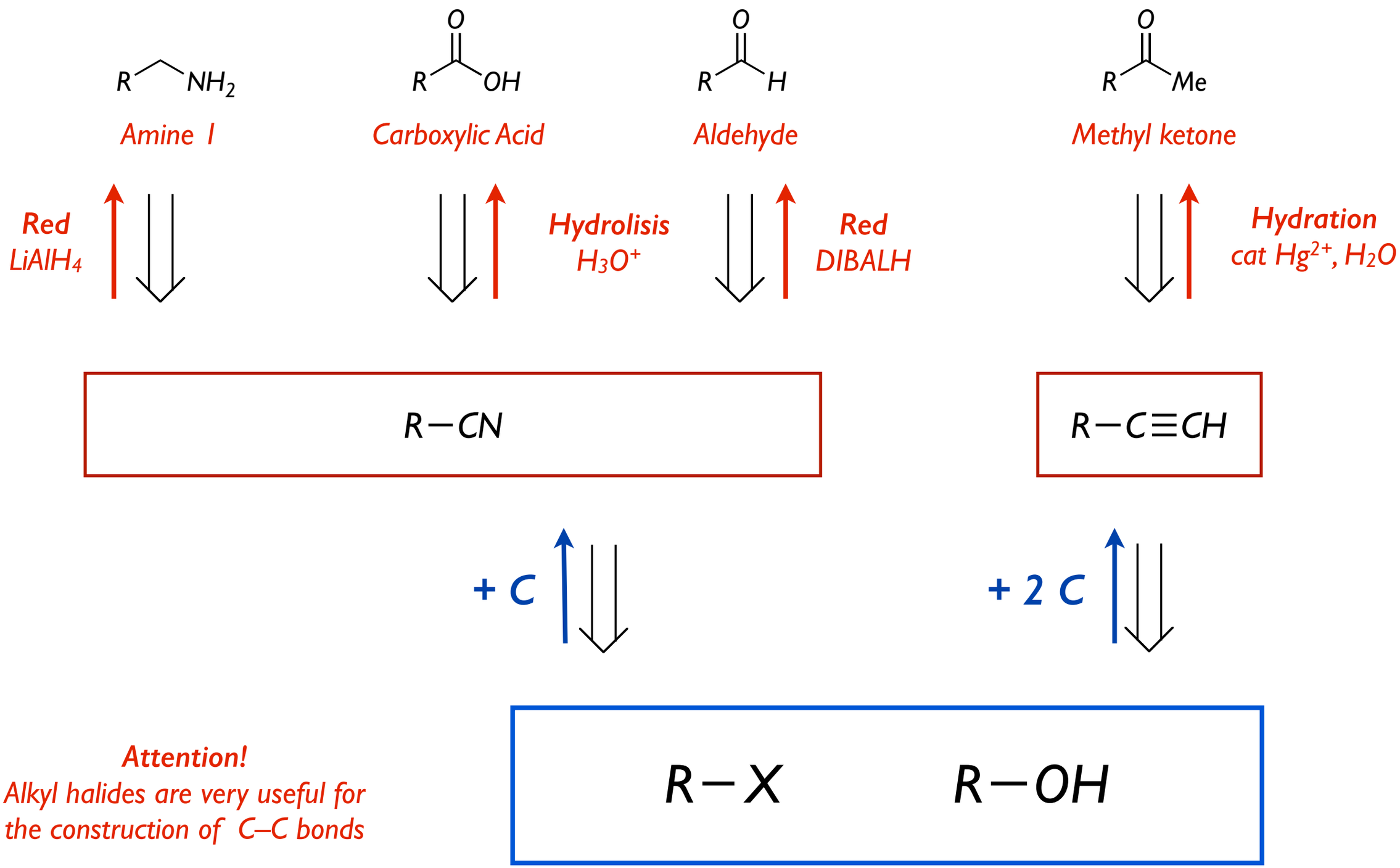

85% 96%

## *Since chlorine ($Cl_2$) is a gas difficult to handle ....*




Sulfonates
R–OSO2R'
Nu
R–Nu
Alcohols
R–OH
Nu
R–Nu
Alkyl halides
X: I, Br, Cl
R–X
Nu
R–Nu




***Attention!***
*Alkyl halides are very useful for the construction of C–C bonds*

## *The alkylation of ammonia, $NH_3$, is not easy ...*

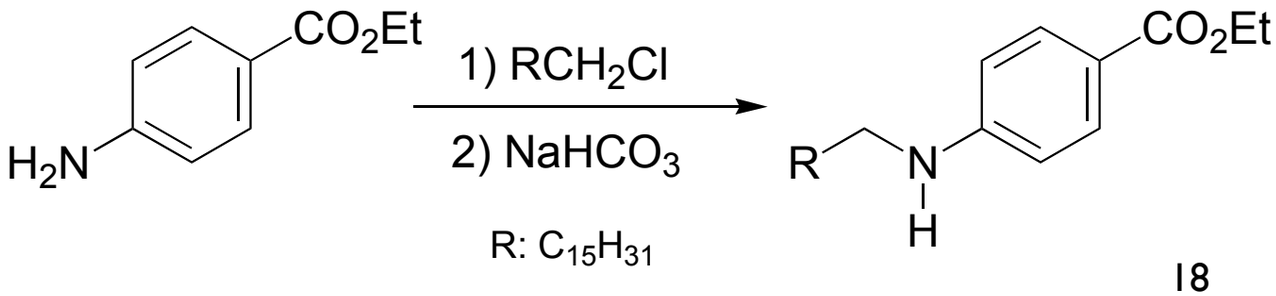
$$NH_3 \xrightarrow{R-X} R-\overset{\oplus}{N}H_3\ X^{\ominus} \underset{+\,HX}{\overset{-\,HX}{\rightleftharpoons}} R-NH_2$$ *Primary Amine*

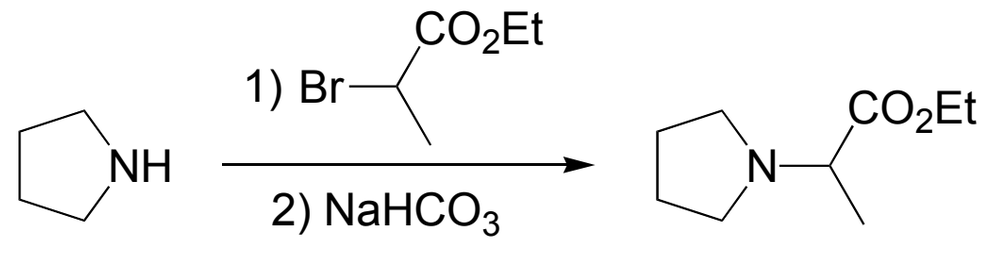
$$R-NH_2 \xrightarrow{R-X} R_2-\overset{\oplus}{N}H_2\ X^{\ominus} \underset{+\,HX}{\overset{-\,HX}{\rightleftharpoons}} R_2-NH$$ *Secondary Amine*

$$R_2-NH \xrightarrow{R-X} R_3-\overset{\oplus}{N}H\ X^{\ominus} \underset{+\,HX}{\overset{-\,HX}{\rightleftharpoons}} R_3-N$$ *Tertiary Amine*

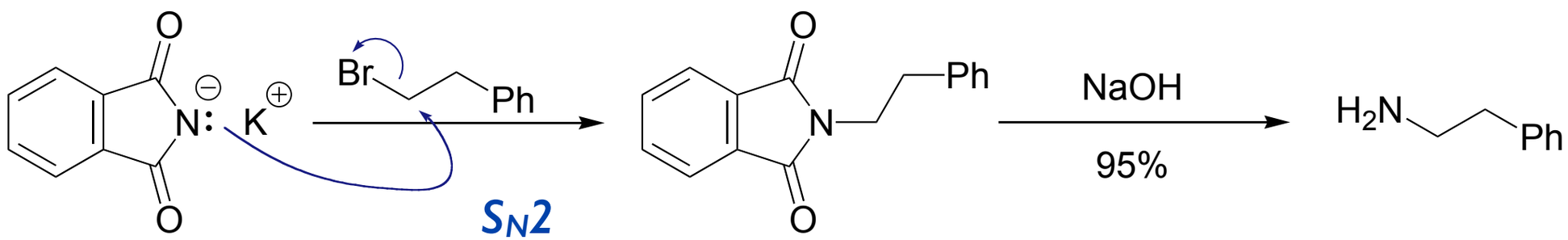
$$R_3-N \xrightarrow{R-X} R_4-\overset{\oplus}{N}\ X^{\ominus}$$ *Ammonium Salt*

*Such an alkylation only becomes efficient when the resulting amine is much less nucleophile than the initial one, for steric or electronic reasons*



## *Potassium phthalimide, PhthNK*



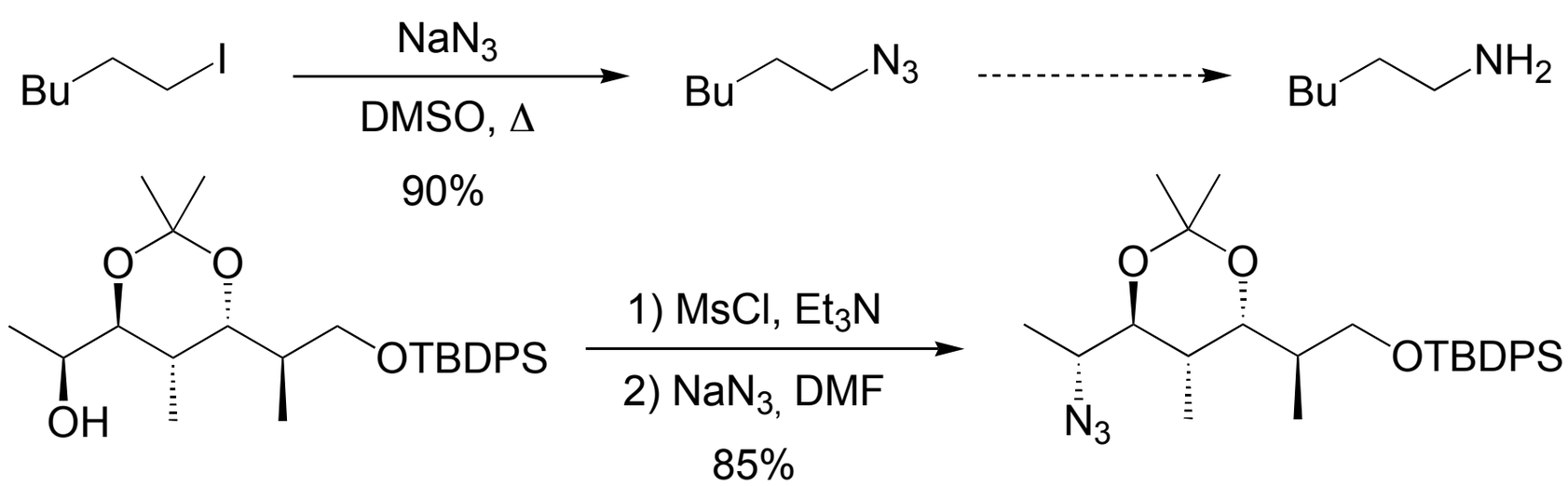

*Potassium phthalimide, pKa 8.3*

***Gabriel synthesis of amines***

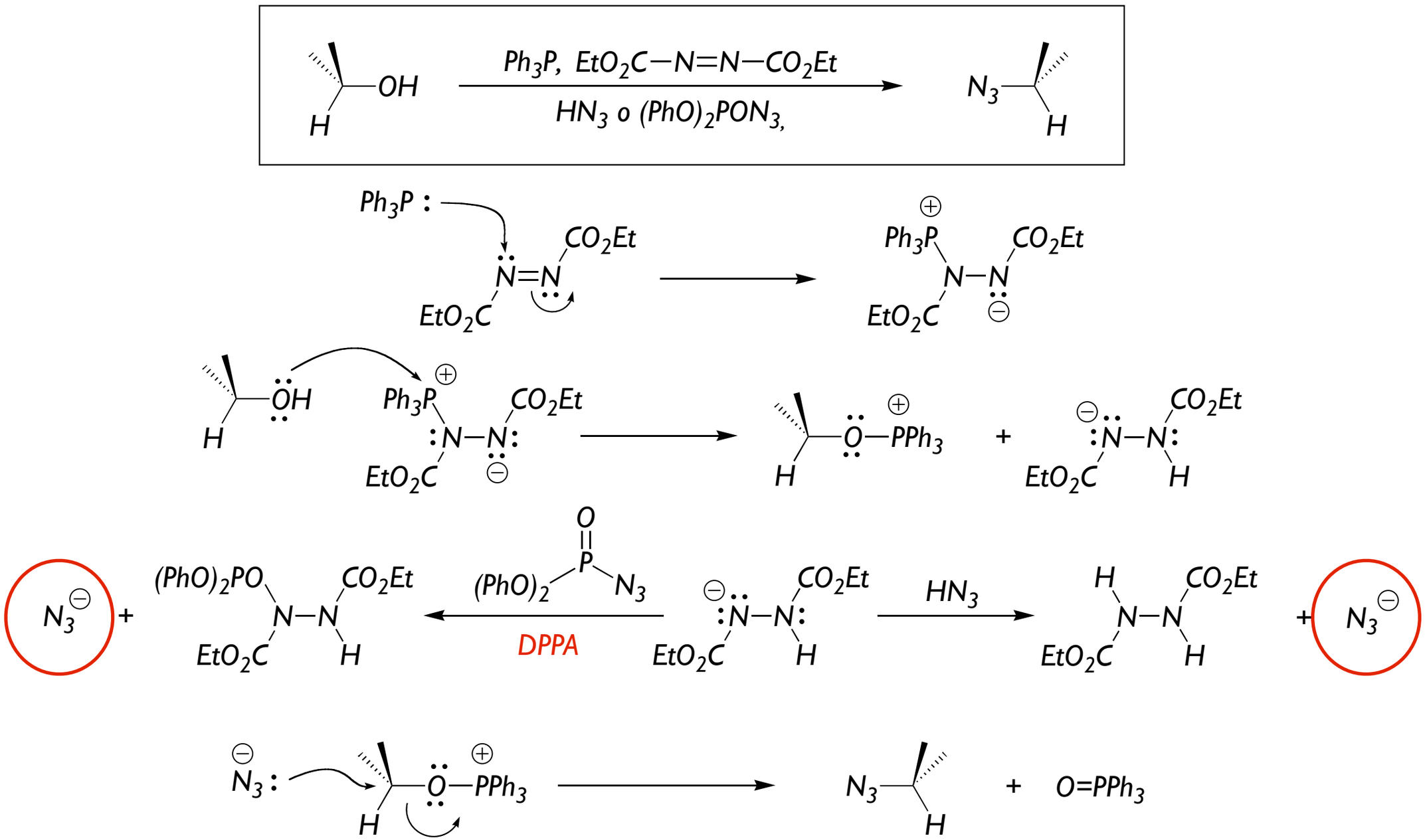
## *Azide, $N_3^-$*

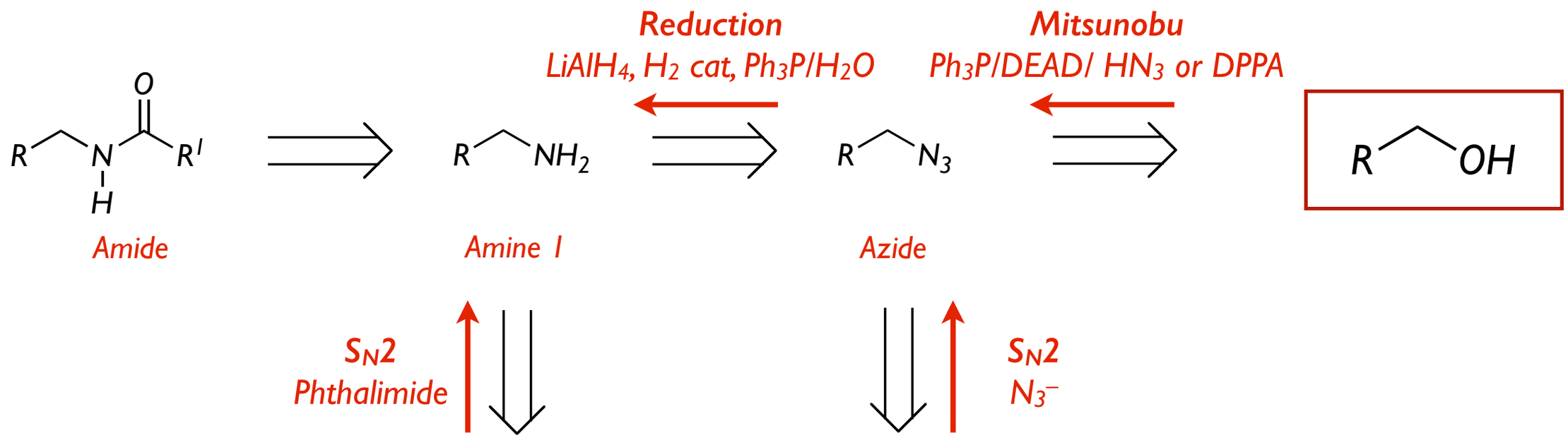
*The azide anion is an excellent nucleophile that participates in a large number of $S_N2$ processes*

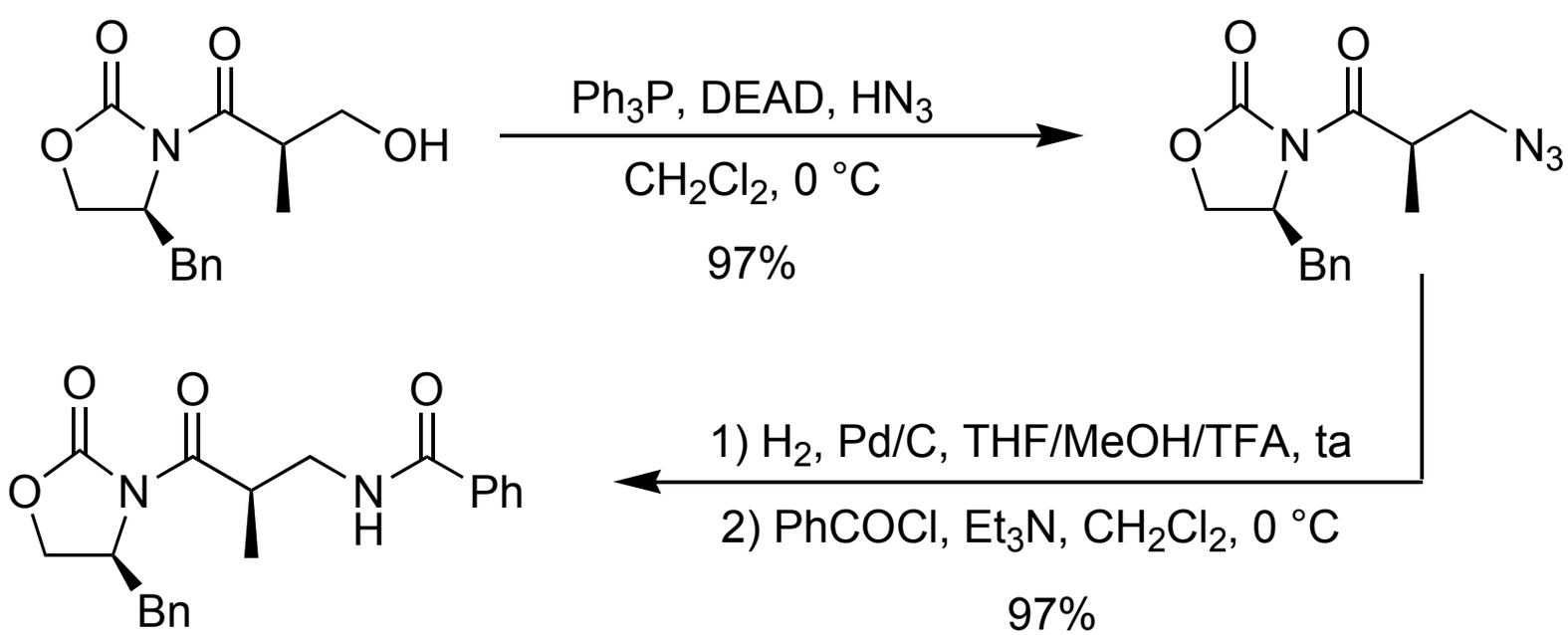
***The reduction of the azide group affords a primary amine***



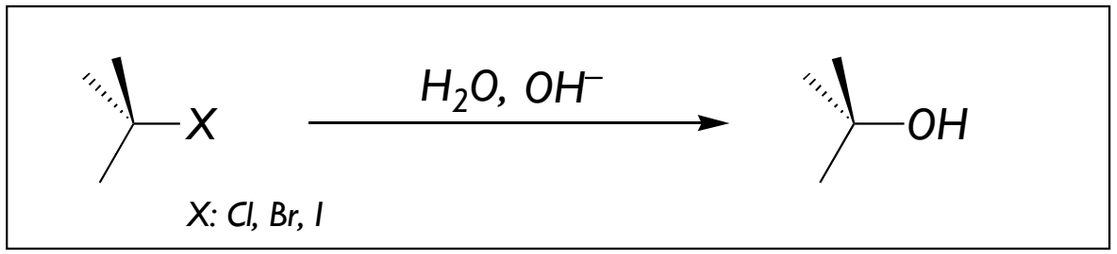
## *Mitsunobu conditions: $Ph_3P$ / DEAD / $HN_3$ or DPPA [$(PhO)_2PON_3$]*




Reduction
LiAlH4, H2 cat, Ph3P/H2O
Mitsunobu
Ph3P/DEAD/ HN3 or DPPA
Amide
Amine I
Azide
SN2
Phthalimide
SN2
N3−


Ph3P, DEAD, HN3
CH2Cl2, 0 °C
97%
1) H2, Pd/C, THF/MeOH/TFA, ta
2) PhCOCl, Et3N, CH2Cl2, 0 °C
97%

## *The most simple nucleophile: $H_2O$ / $OH^-$*



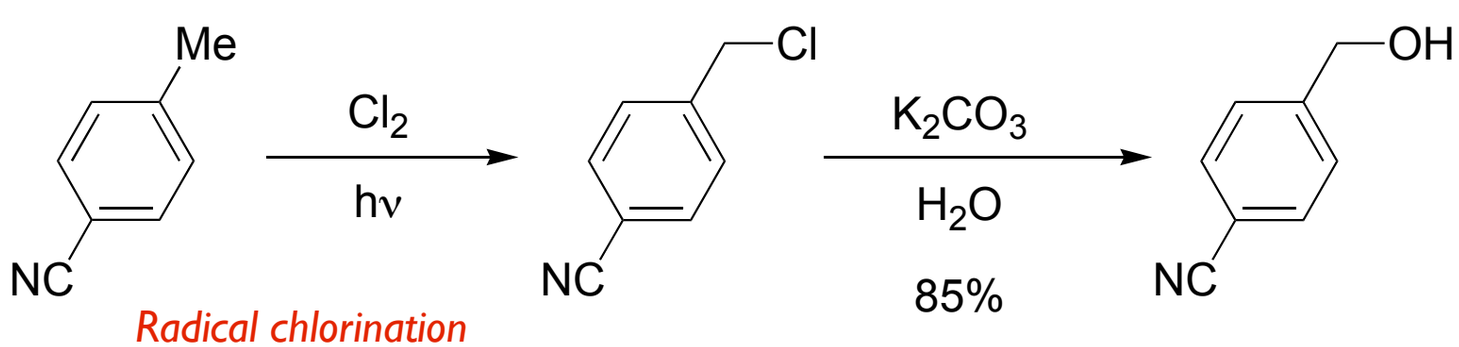

*This is a rare transformation in which...*

*... tertiary halides, $R_3C–X$, react with $H_2O$ (solvolysis) through $S_N1$ and*

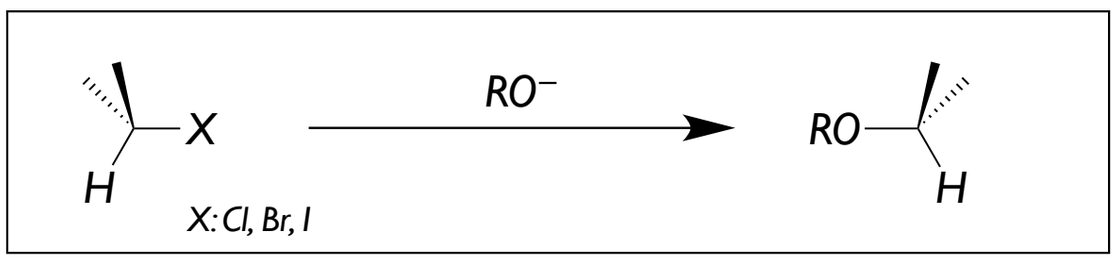
*... the secondary and primary ones, $R_2CH–X$ i $RCH_2–X$, with $OH^-/H_2O$ through $S_N2$*

*In both situations E1 and E2 eliminations are competing reactions*

*No eliminations can occur at this benzylic position*



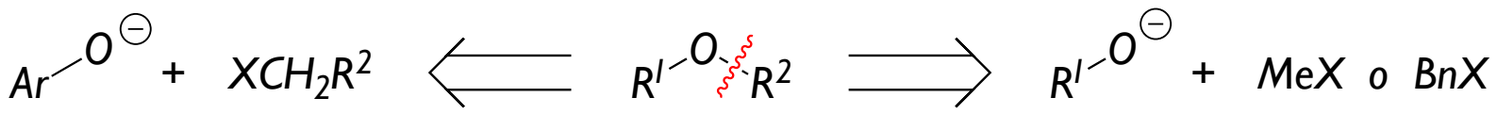
## *Alkoxydes, $RO^-$: Williamson Synthesis*

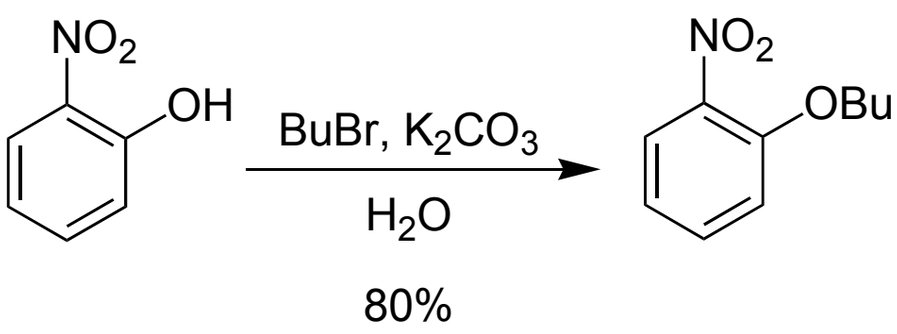


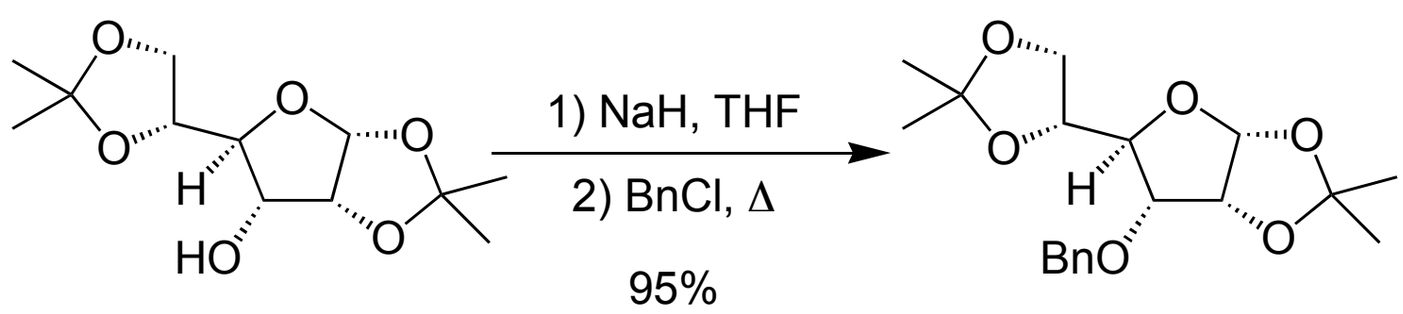

$S_N2$

*Only on 1ary substrates to avoid E2 eliminations*

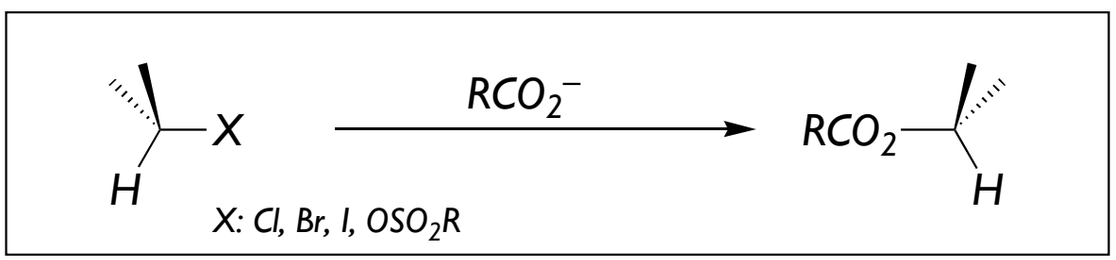
*... and the most successful deconnections are applied to activated systems*



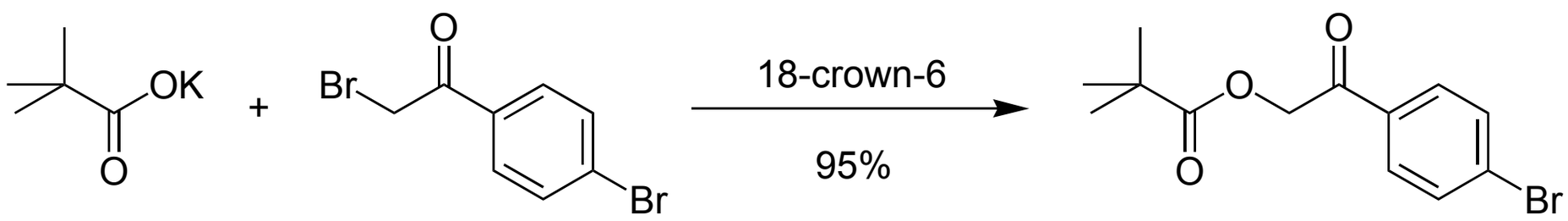



## *Carboxilates, $RCO_2^-$*

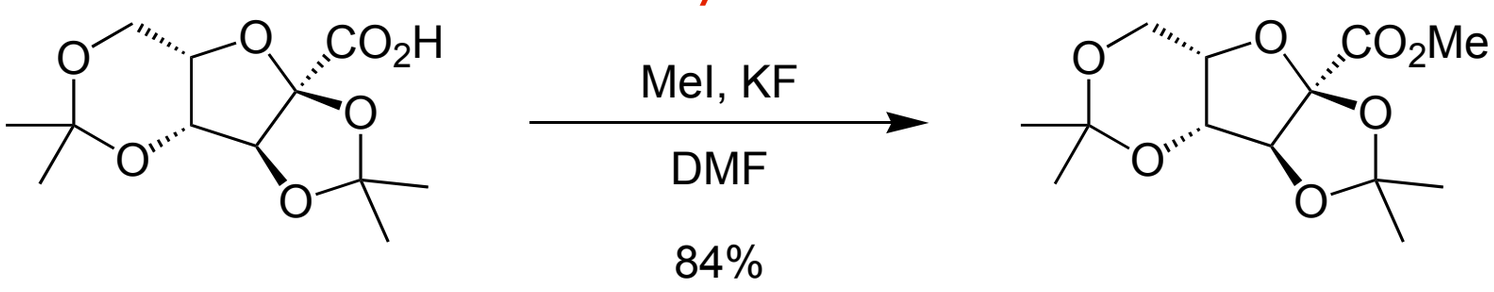



$S_N2$

*They are usually applied to 1ary substrates to avoid E2 eliminations*

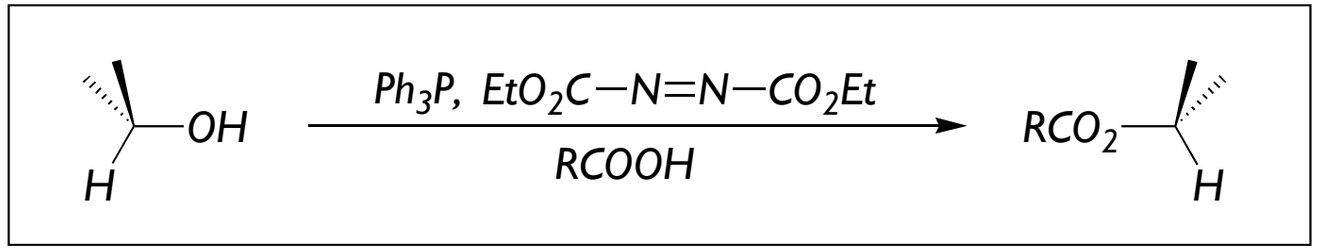



*why KF?*

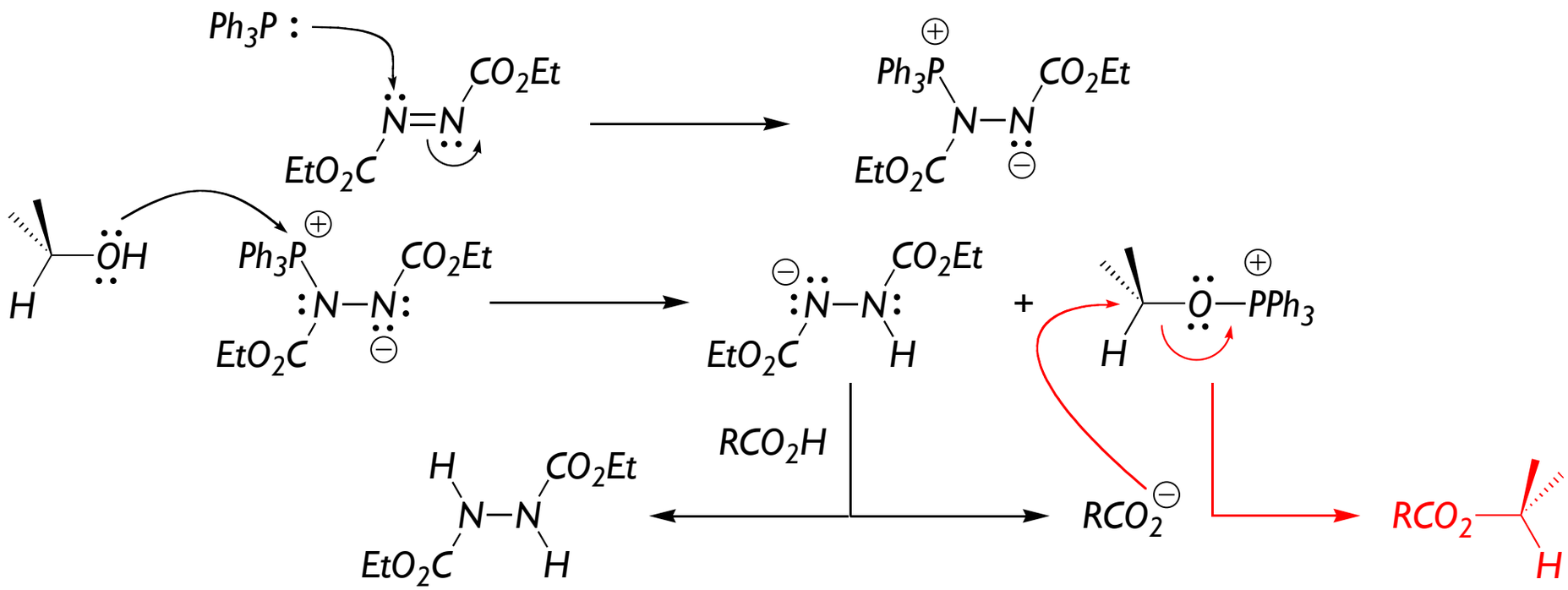


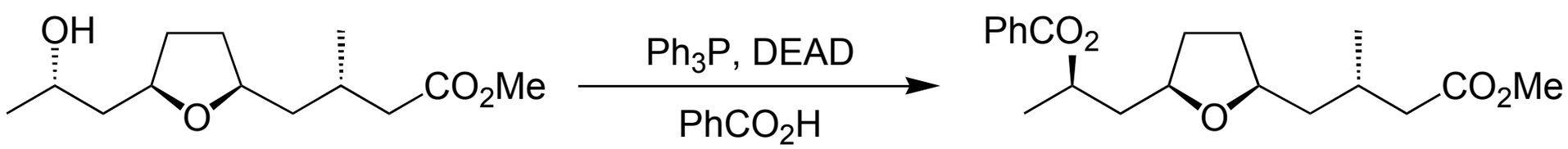

*Attention: interconversion of carboxílic acids and derivatives*

## *Mitsunobu conditions: $Ph_3P$ / DEAD / $RCO_2H$*



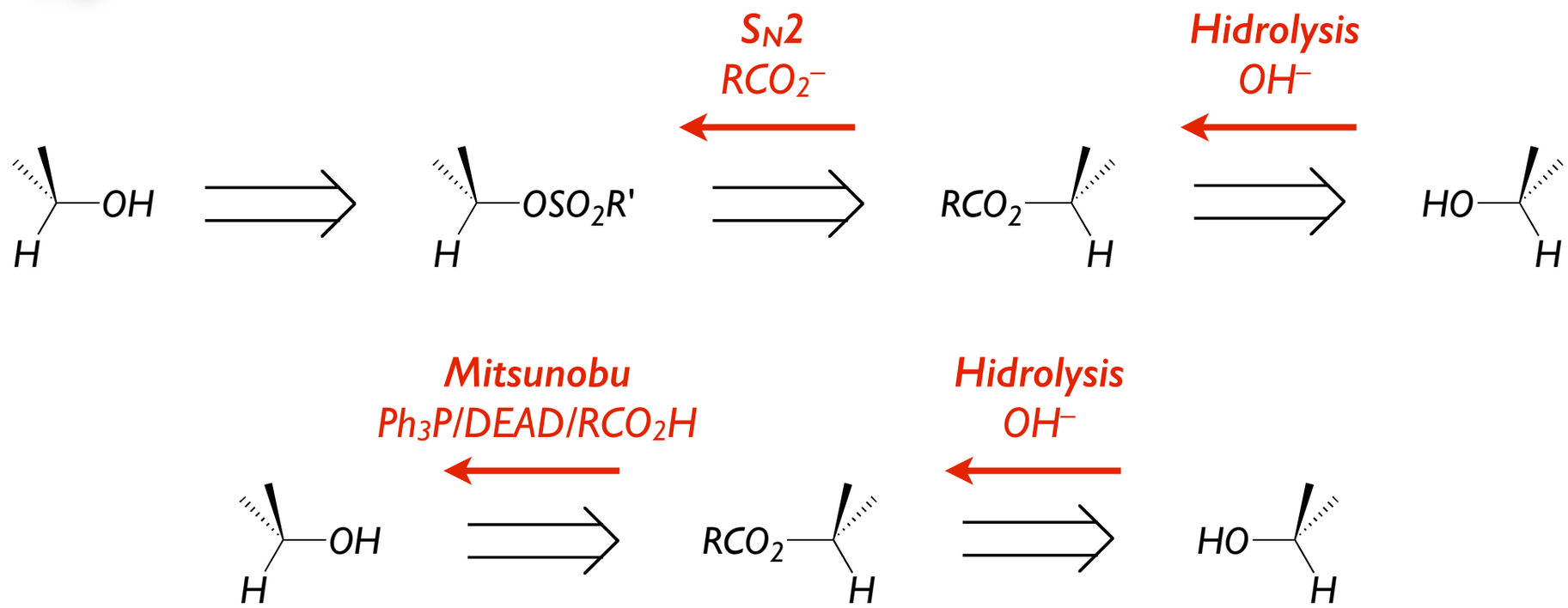

$S_N2$

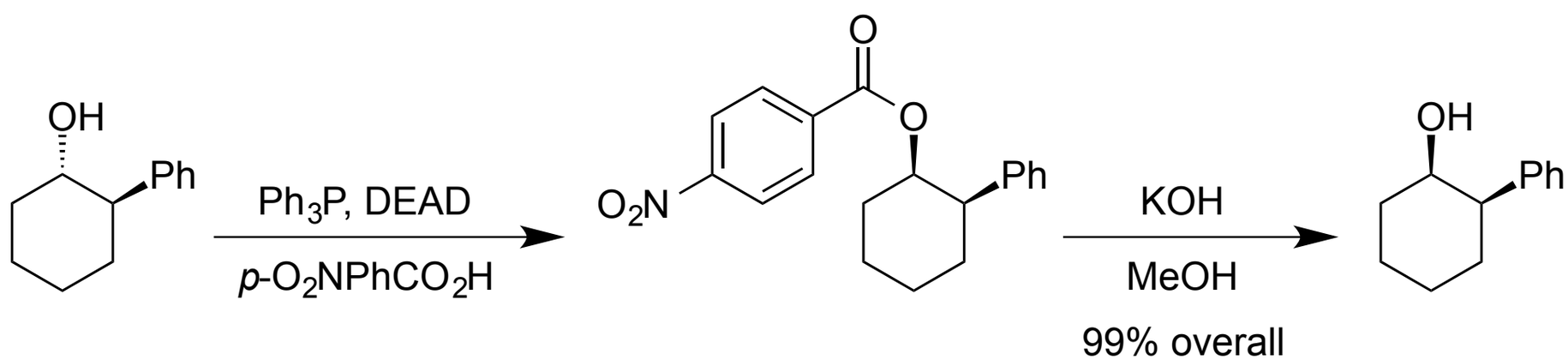


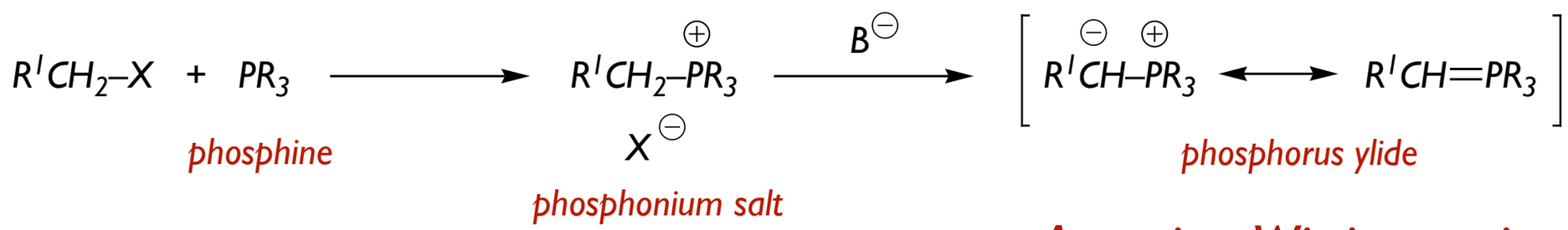

89%

## Configuration inversion

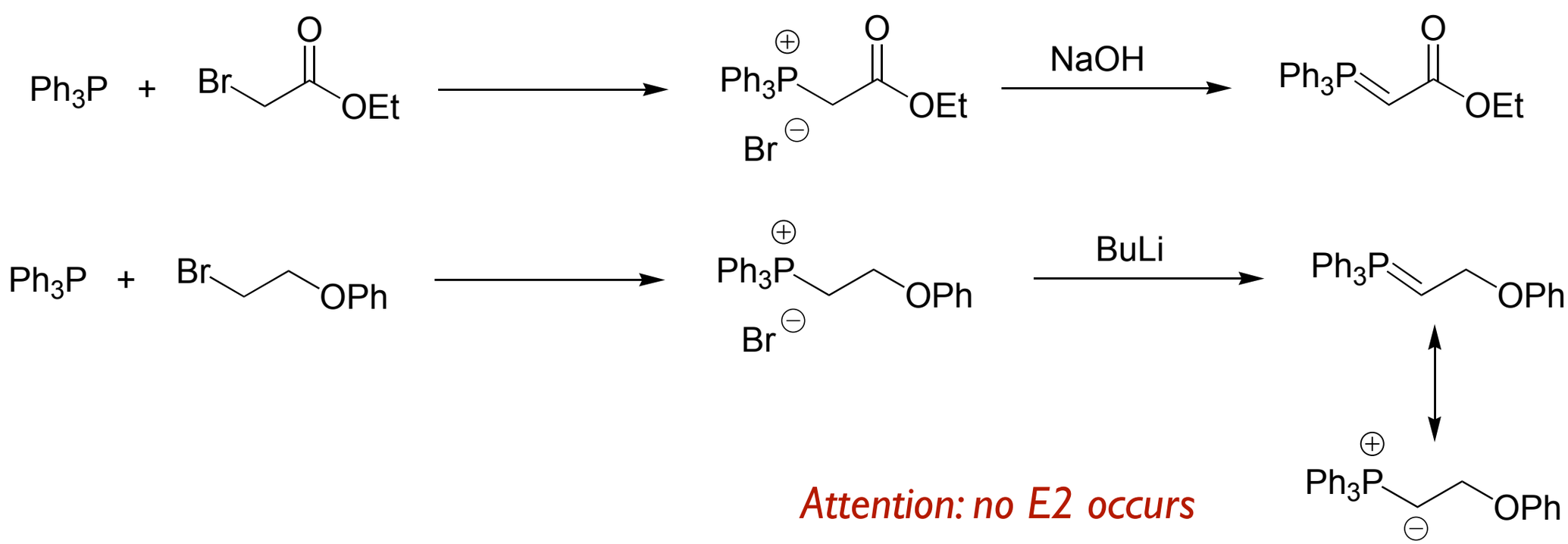


- *Phosphines are excellent nucleophiles because they are less basic than amines and the phosphorus atom is very polarizable. Moreover, E2 reactions do not compete with $S_N2$ because they are weak bases*



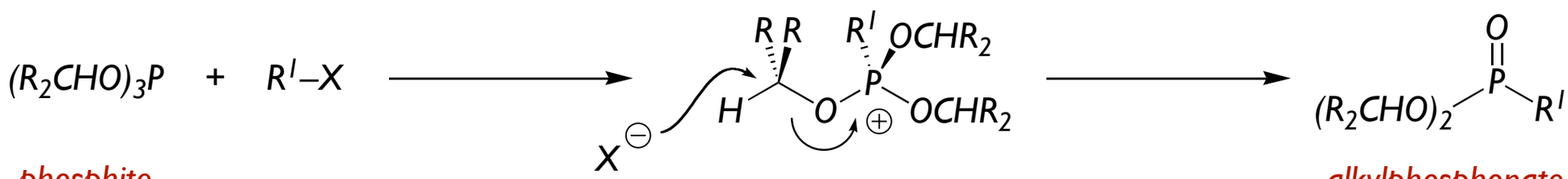

*Attention: Wittig reaction*




*Attention: no E2 occurs*

- *Phosphites are also good nucleophiles and react with alkyl halides:*

  ***Michaelis-Arbuzov reaction***

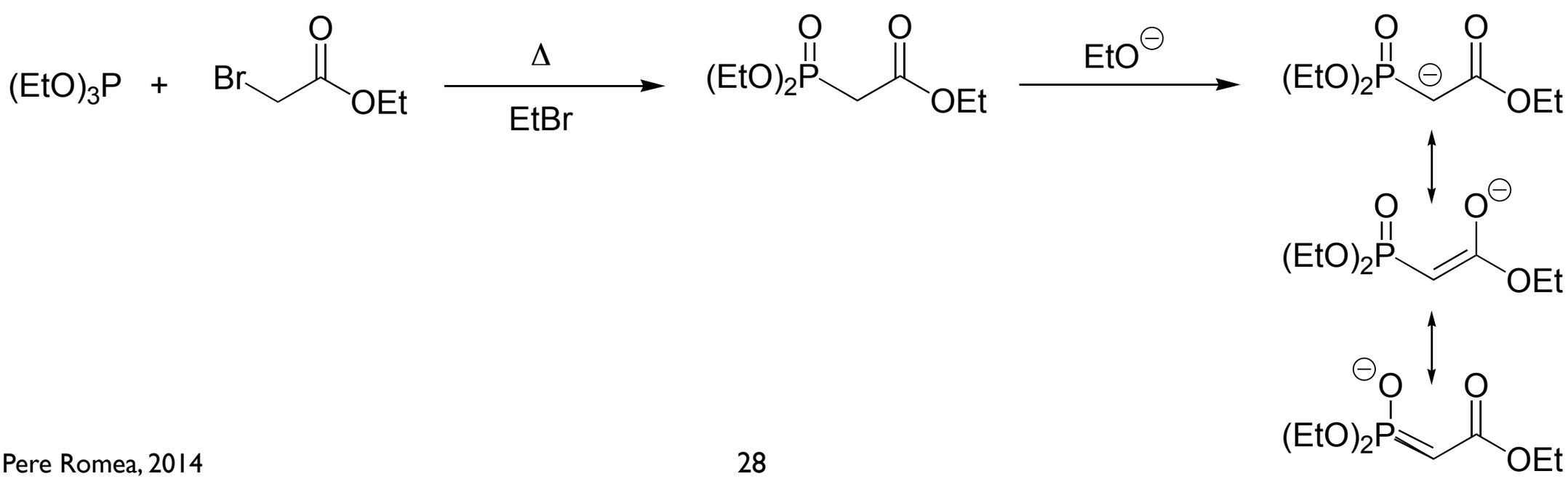



*phosphite*

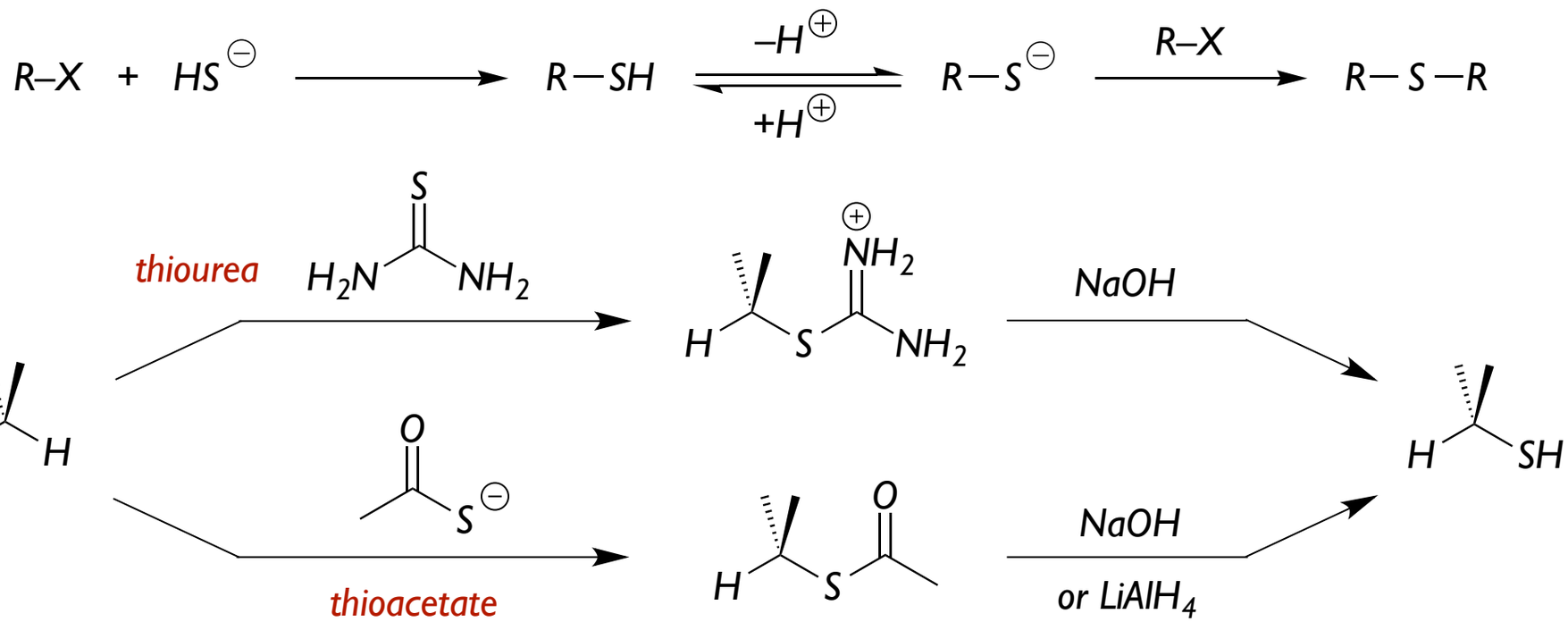
*alkyltrialkoxyphosphonium halide*

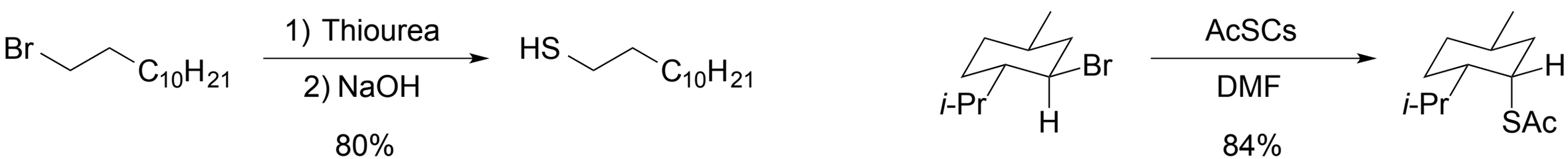
*alkylphosphonate*

***Attention:***
***Horner-Wadsworth-Emmons reaction***

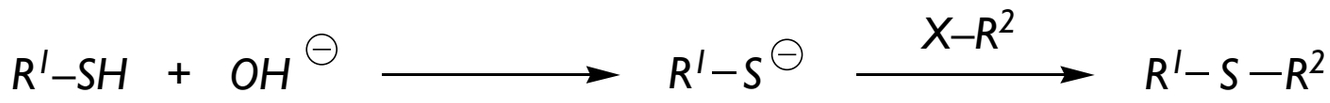


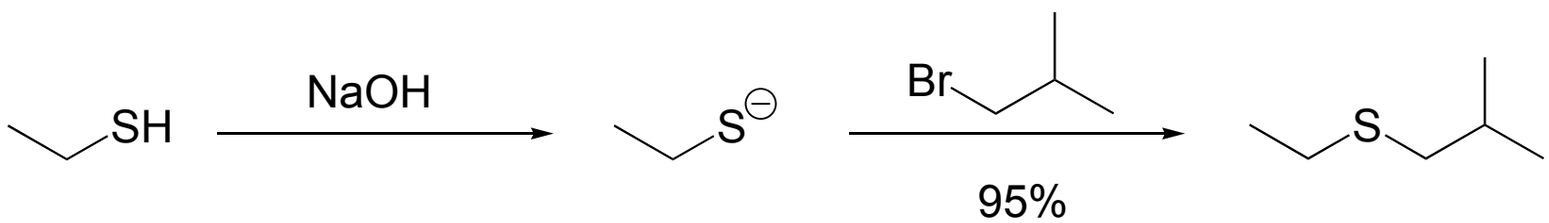
## *The easiest option is troublesome ...*

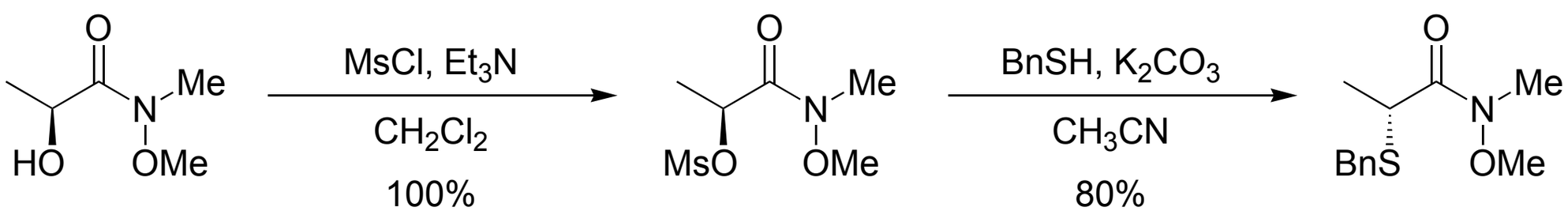


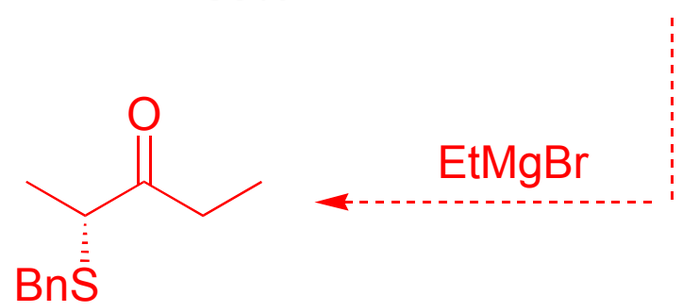
- *Thiolates are the best option since they are excellent nucleophiles ...*




*Weinreb Amide*

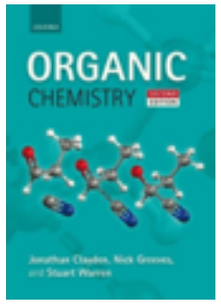


*The synthesis of an organic compound must pay attention to ...*

*Carbon backbone* ⟷ *Functional groups*

*(Chapters 2–4 )*

*Functional Group Interconversion (FGI)*




*Chap. 19*

*I. Nucleophilic Substitutions*

*Electrophilic Additions to C=C*

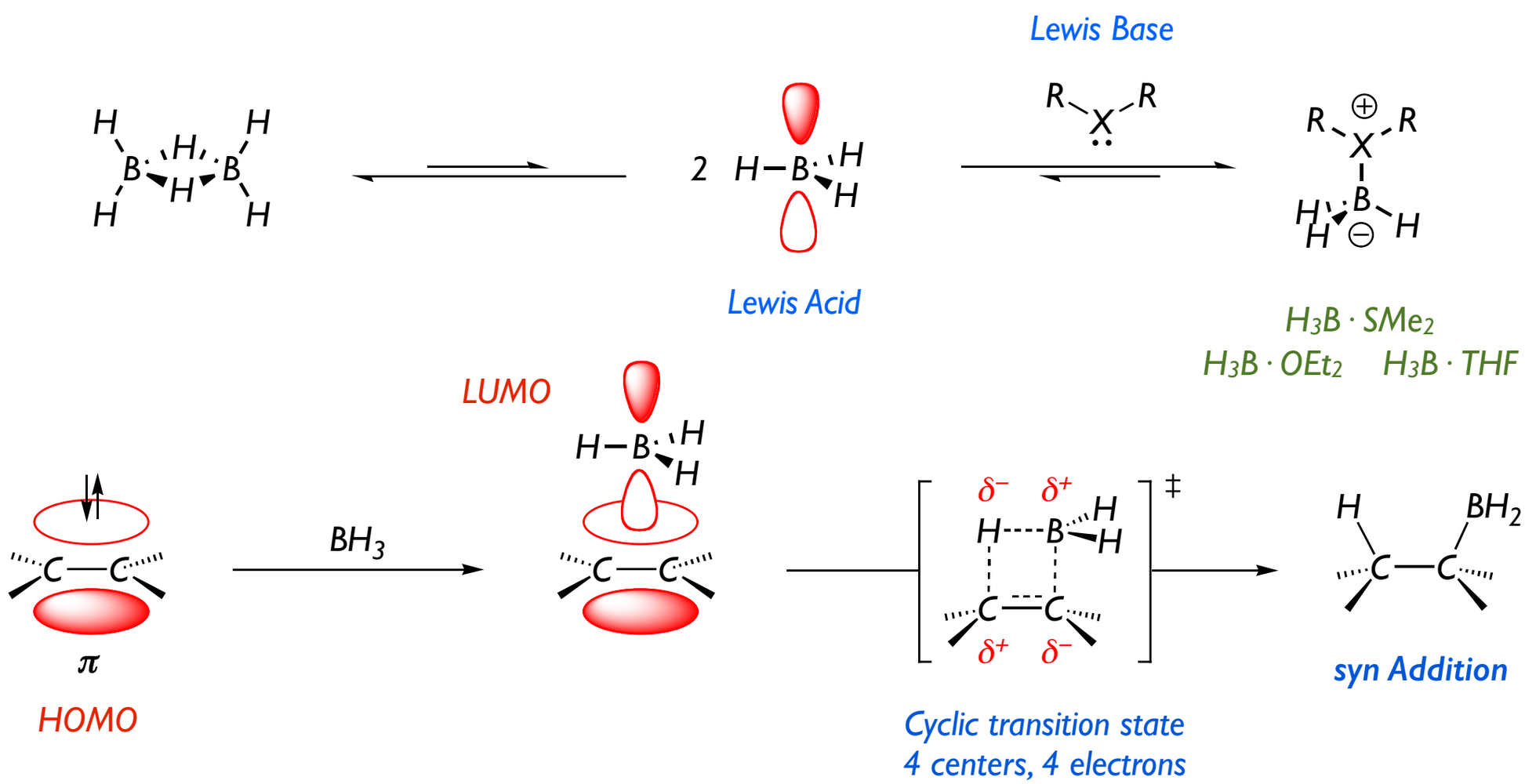
*Addition-Eliminations on Carboxylic Acids and Derivatives*

*II. Reductions*

*III. Oxidations*

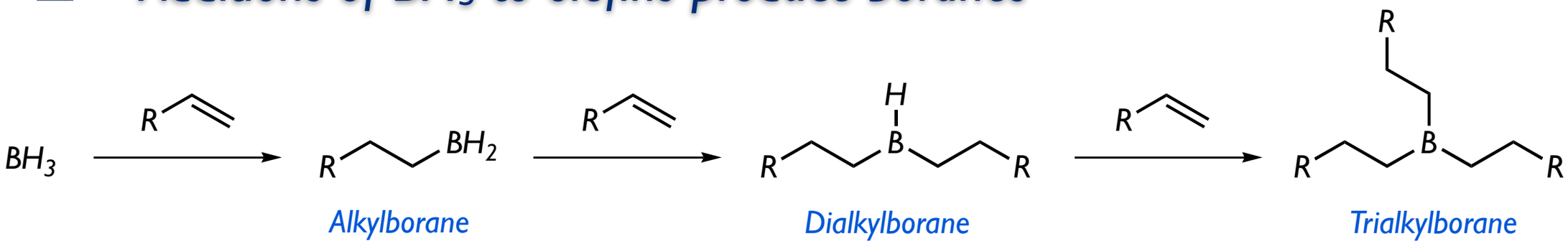
***Mechanism!!!***

## *Borane, $BH_3$, as a reacting species*

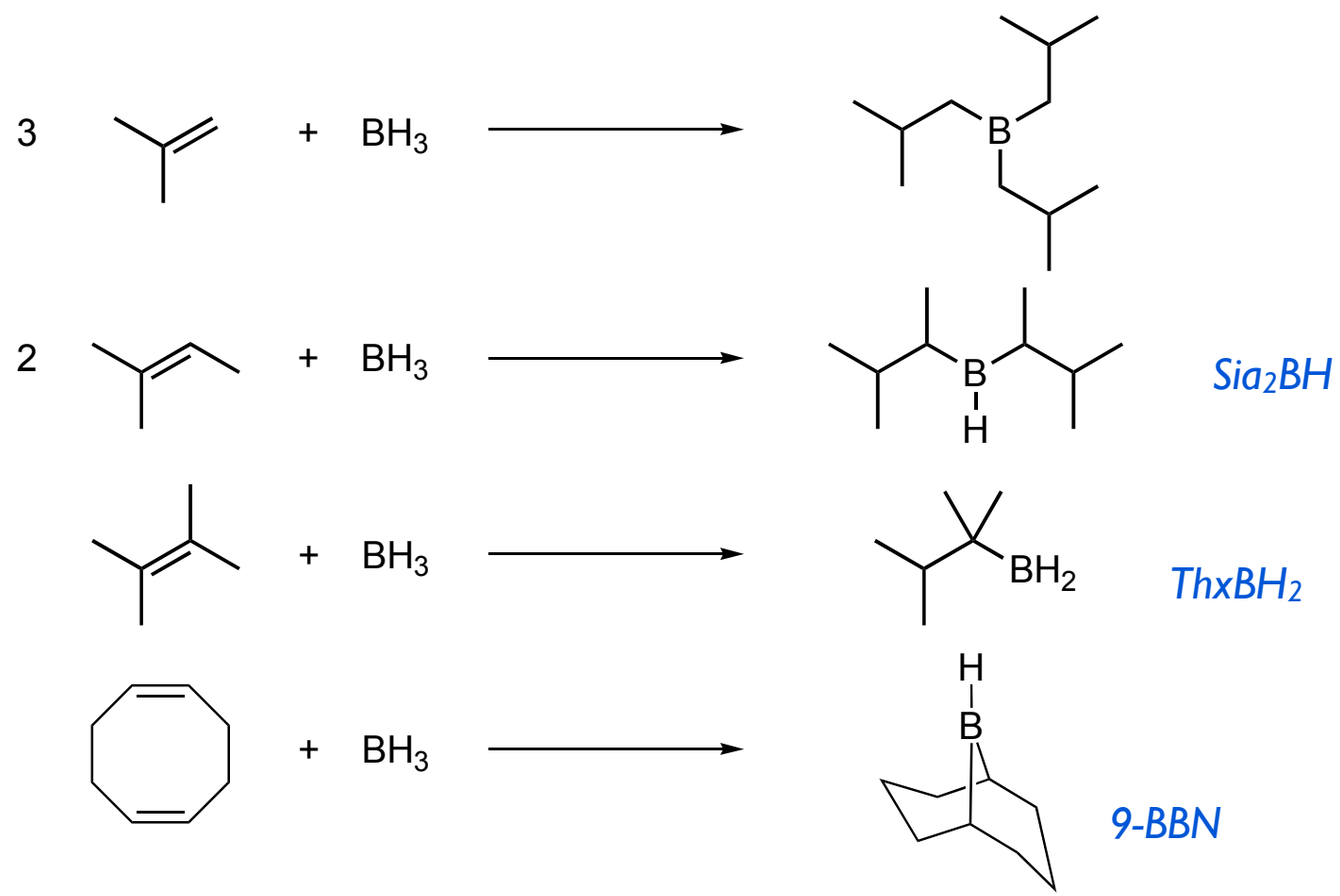



*The **regiochemistry** for the addition of $BH_3$ to an olefin is controlled by steric as well as electronic factors: the boron atom binds to the less substituted carbon atom*

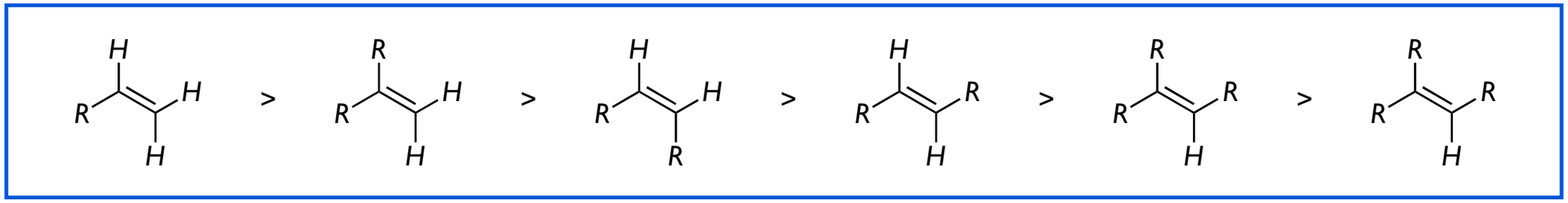
## *Additions of $BH_3$ to olefins produce boranes*



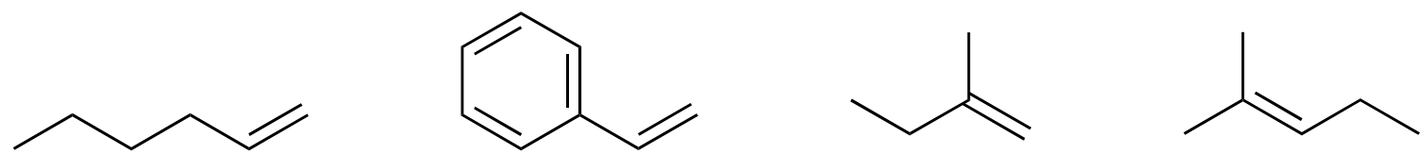

*– The appropriate choice permits to obtain a wide array of alkylboranes*



## – Steric effects rule the reactivity



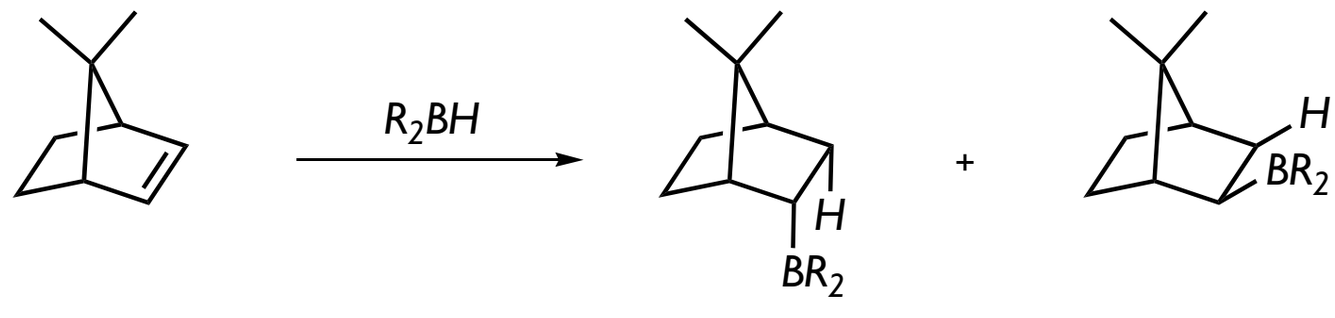
## ... the regioselectivity,



| | | | | |
|---|---|---|---|---|
| **$BH_3$** | 94 | 80 | 99 | 57 |
| **$Sia_2BH$** | 99 | 98 | | 97 |
| **9-BBN** | 99.9 | 98.5 | 99.5 | 99.8 |

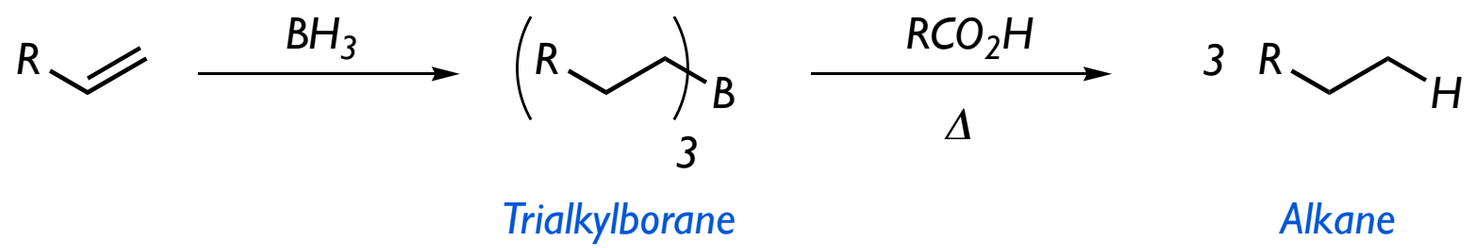
% atack B to the less substituted carbon atom

## ... and the stereoselectivity

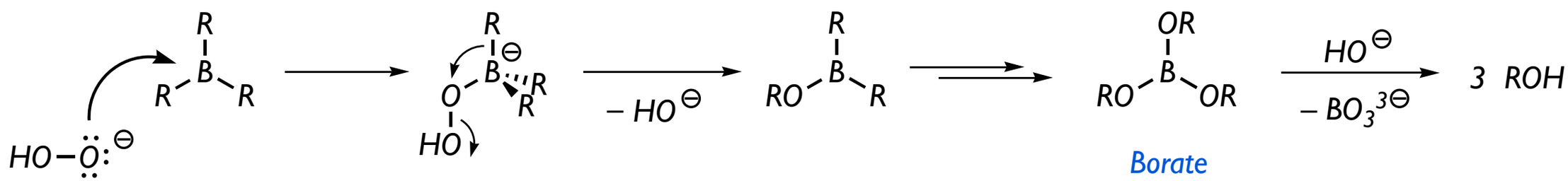



| | | |
|---|---|---|
| $BH_3$ | 72 | 28 |
| 9-BBN | 97 | 3 |

## *Protonolysis: synthesis of alkanes*

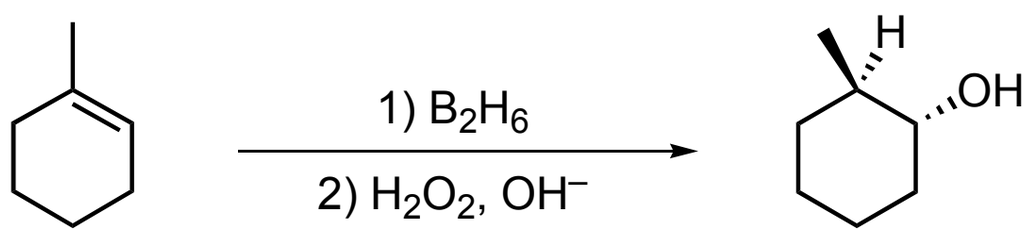



## *Conversion of trialkylboranes into alcohols: $H_2O_2$/NaOAc, ...*




*– The migration does not produce the inversion of the configuration*

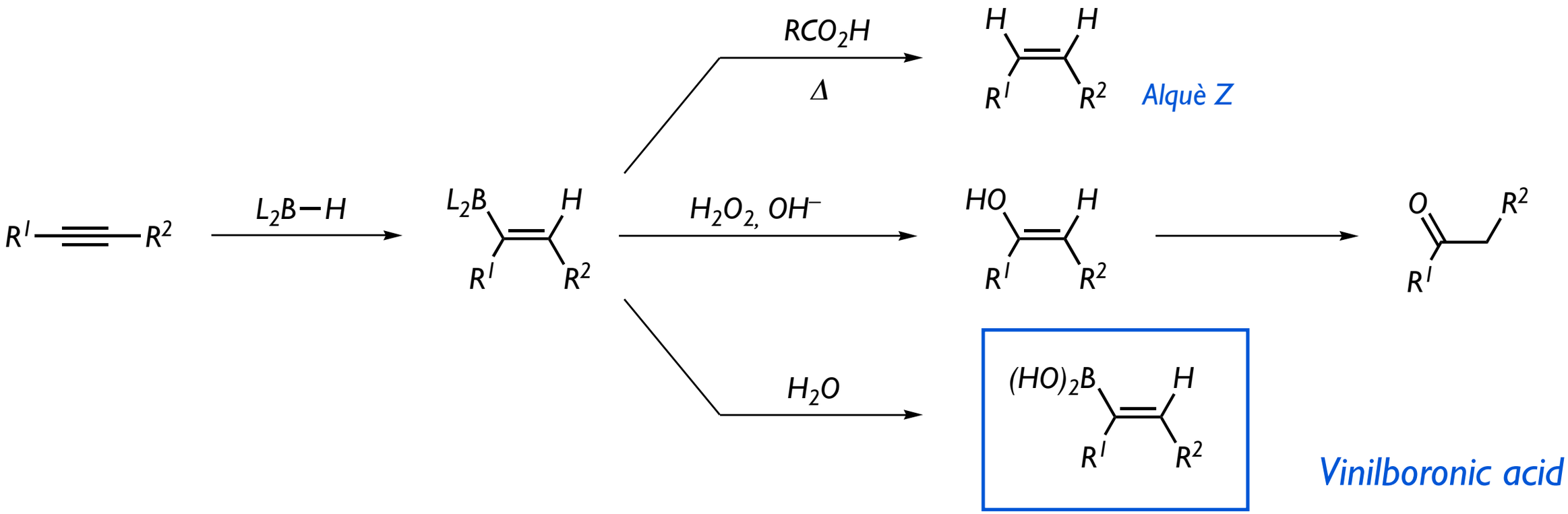
*Hidrolysis*

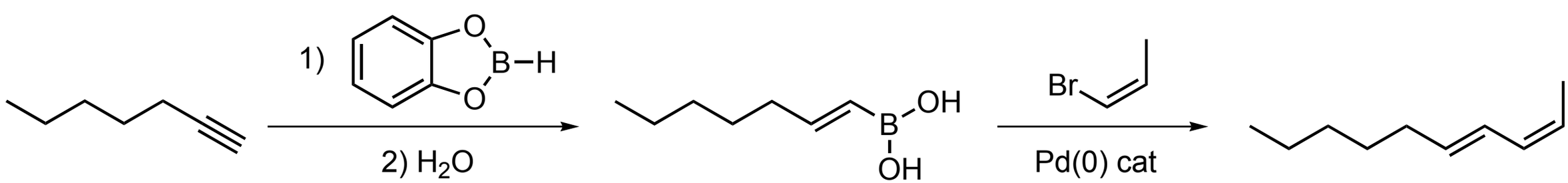



85%

*It looks like an anti-Markovnikov hydration with a syn stereochemistry*

## Hidroboration of alkynes




Suzuki Coupling

*The moneychanger and his wife*
*Marinus Claesz van Reymerswaele, 1539*

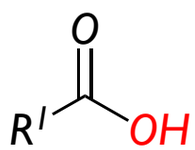
Universitat de Barcelona

Dr. Pere Romea
Department of Organic Chemistry

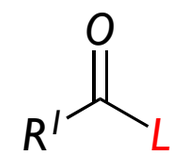
# 6. Functional Group Interconversion

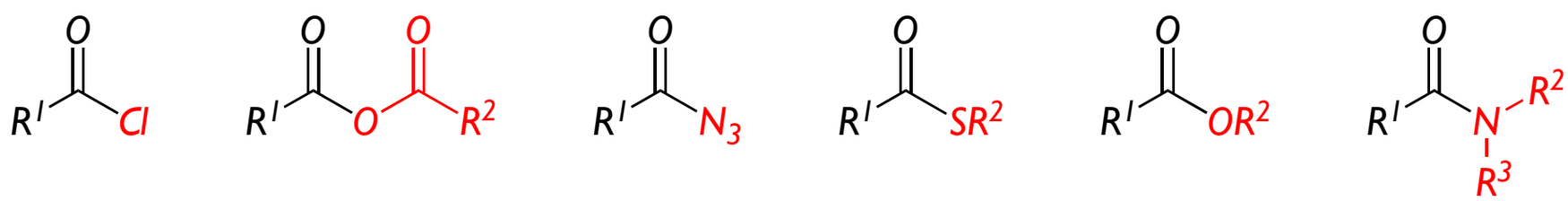
Organic Synthesis 2014-2015 Autumn Term

## Carboxylic acids



## Derivatives of carboxylic acids



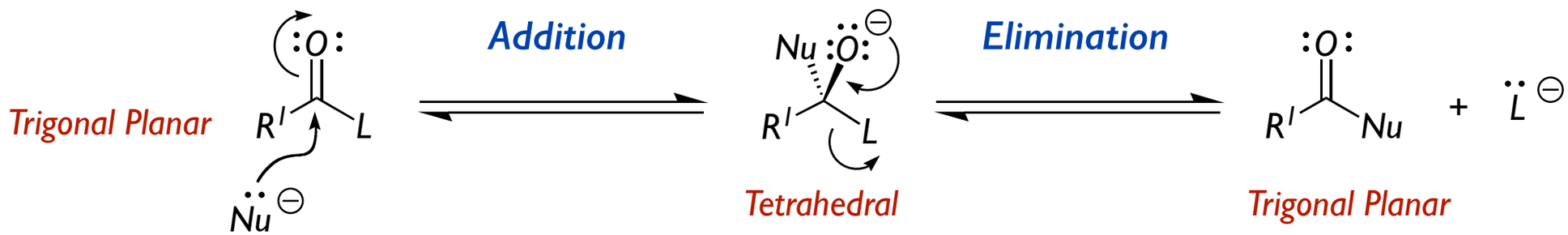


Acid chloride | Anhydride | Acyl azide | Thioester | Ester | Amide

Nitrile

***All these FG participate in reactions that can be understood using the **addition-elimination mechanism***

## Addition-elimination mechanism




*The requirements for a smooth process are …*

*a) RCOL must be a good electrophile,*

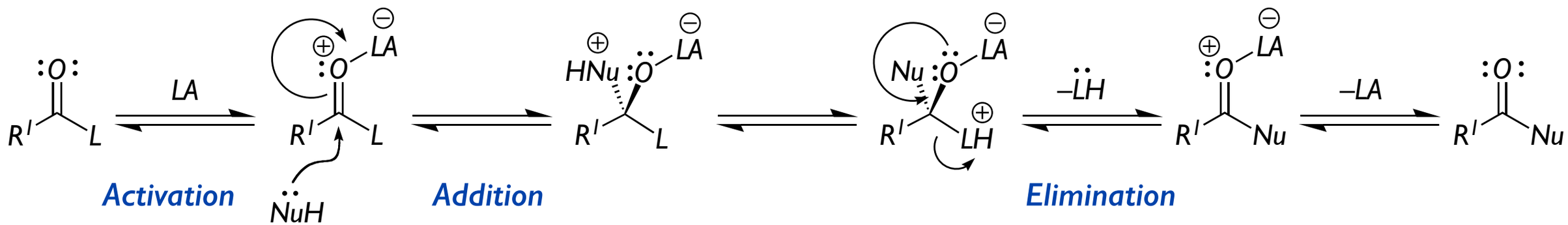
*b) Nu must be a good nucleophile,*

*c) L must be a better leaving group than Nu*

*Remember: "The lower the pKa (HL), the better the leaving group"*

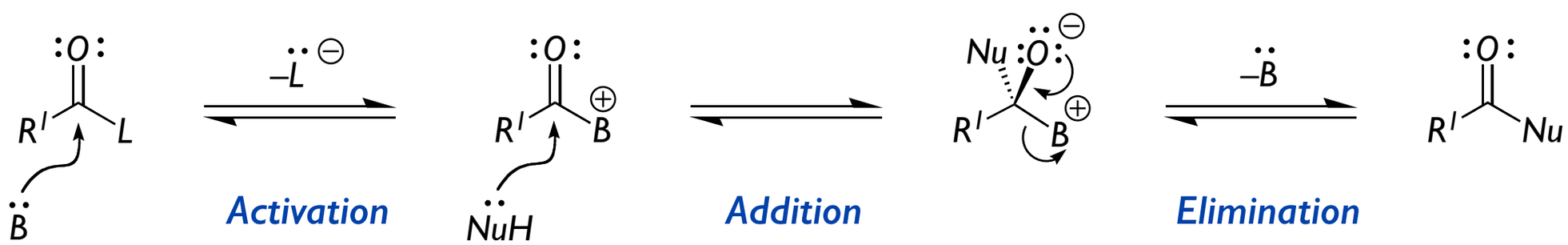
***If the system is not reactive enough, it must be activated ...***

## Activation with a Lewis Acid, LA, ...



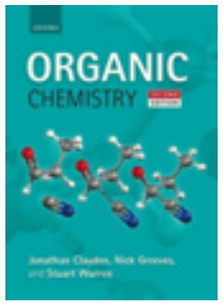

**Remember:** *Fischer esterification*

## Activation with a Lewis Base, B, ...

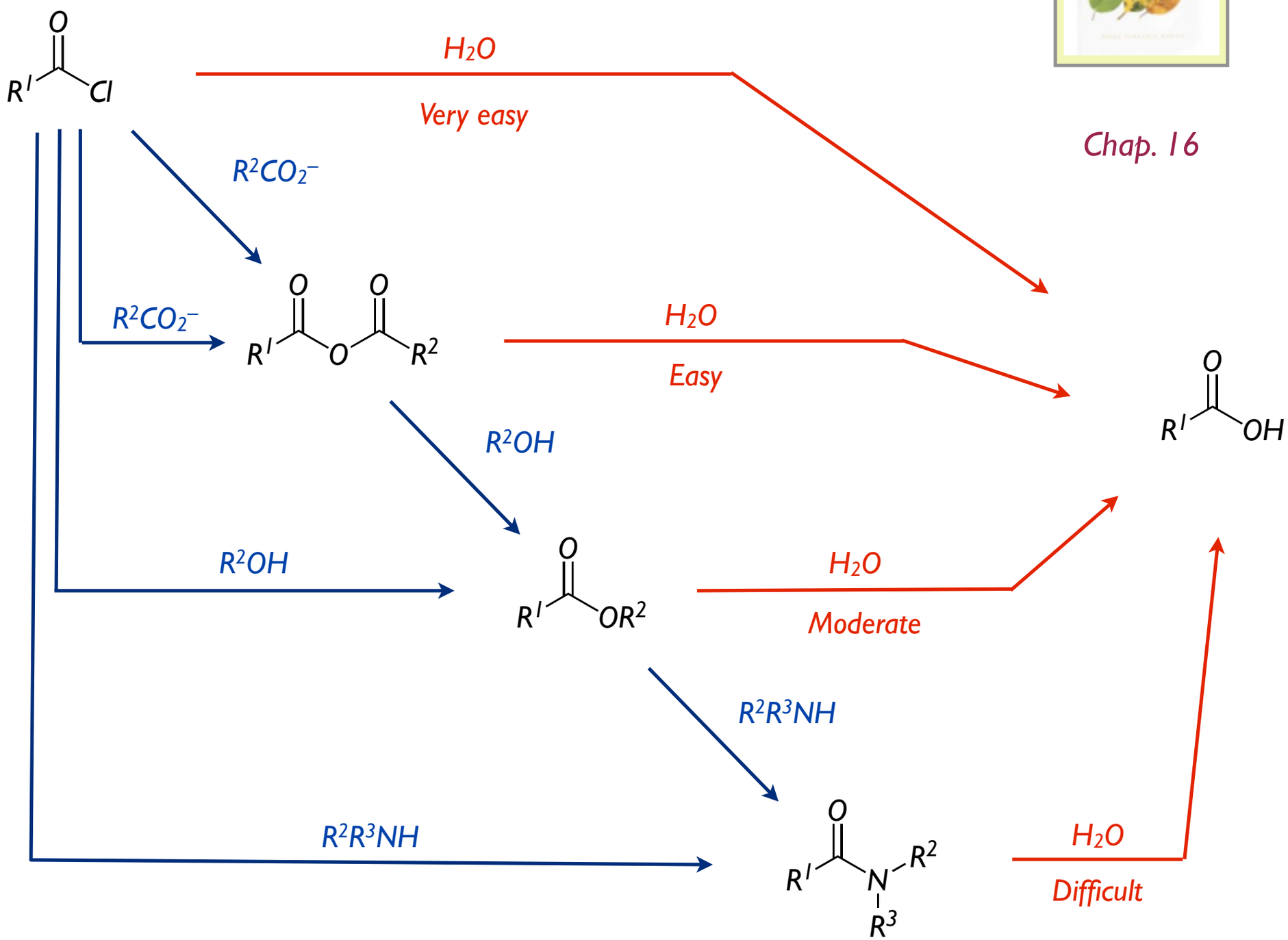



**Remember:** *synthesis of esters by addition of alcohols to acid chlorides in the presence of DMAP*

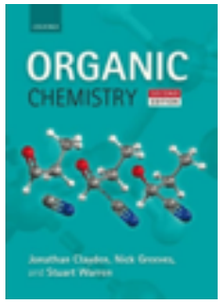
Chap. 16



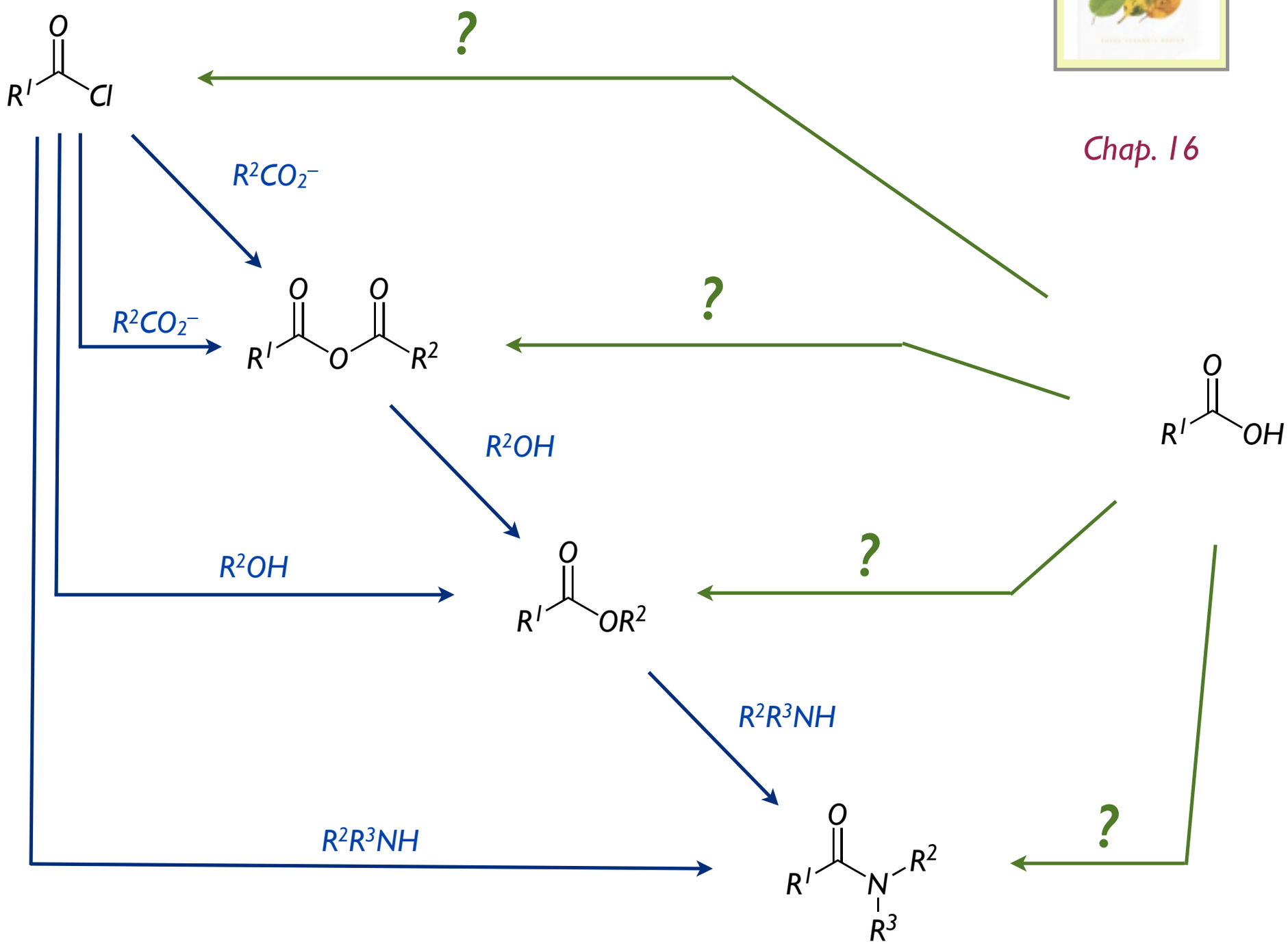

Chap. 10



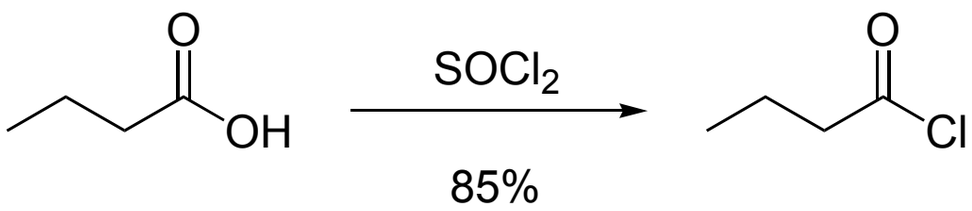
Chap. 16

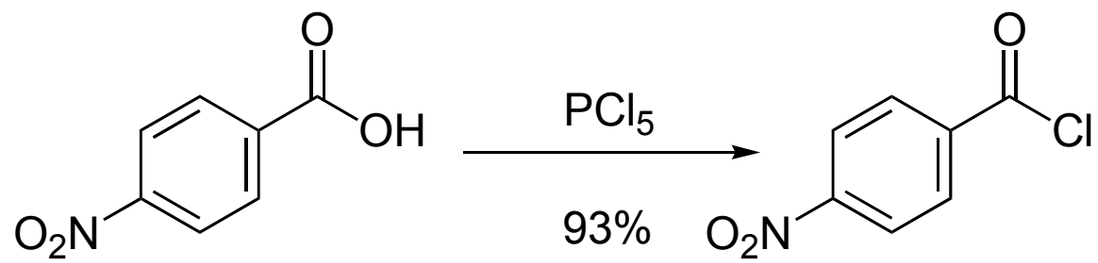



Chap. 10



## *Via $SOCl_2$ o $PCl_5$*

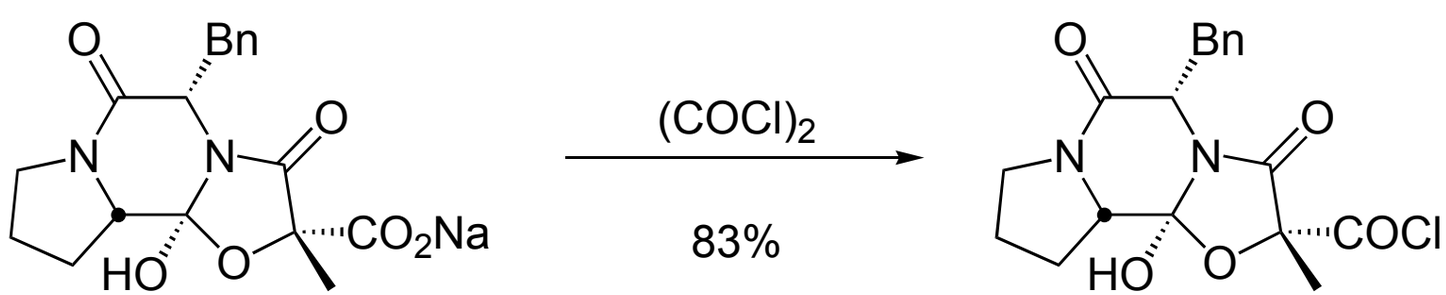



## *Via $(COCl)_2$*

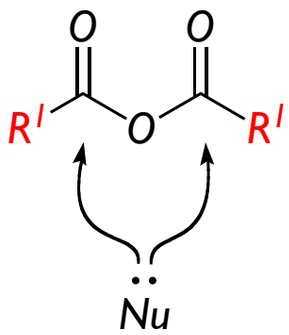
*Useful for systems sensitive to acid media.*

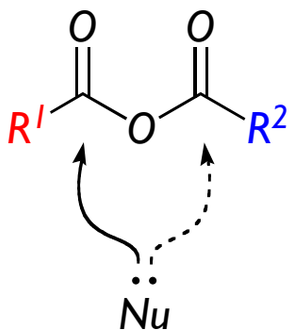
*It is usually used with the sodium salt (neutral media) or with catalytic amounts of DMF.*



## Regioselectivity in the nucleophilic attacks to anhydrides

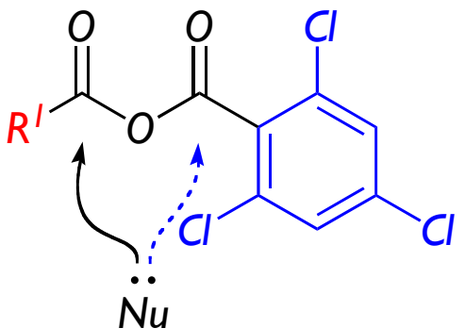
*Regioselectivity is not a problem for the symmetric anhydrides*

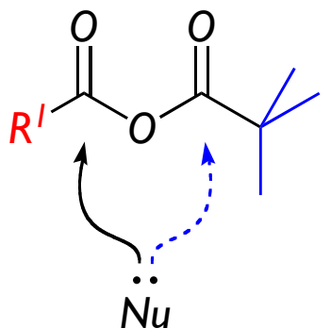


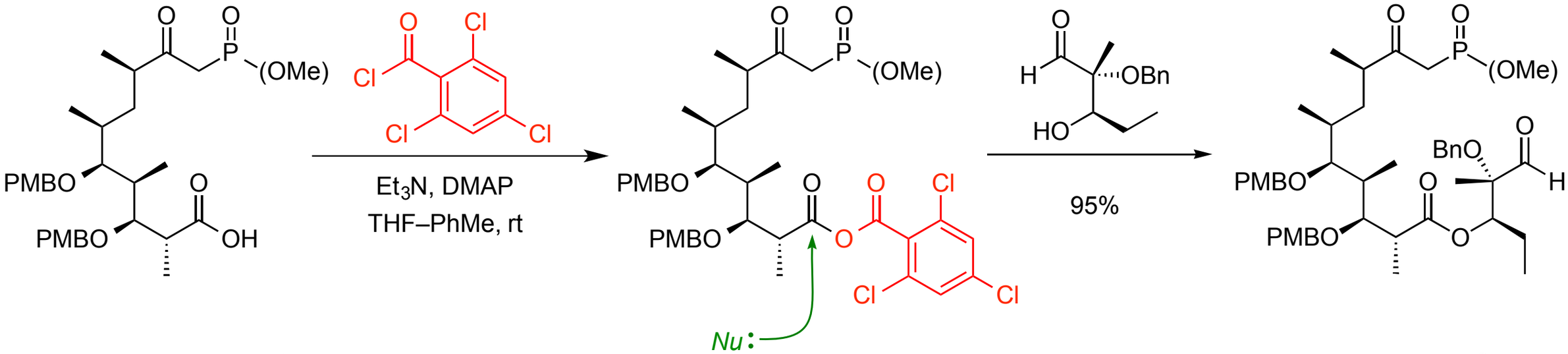

*In **mixed anhydrides** the **R²** group must prevent the nucleophilic attack*

*The mixed anhydrides are usually prepared quantitatively from acid chlorides or other anhydrides. They are not isolated.*

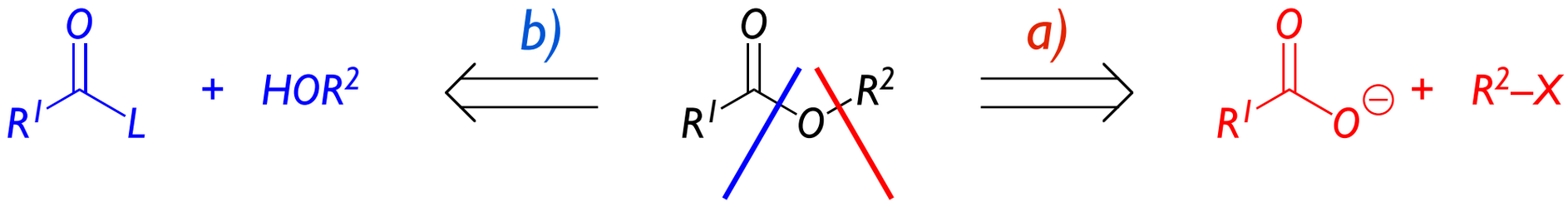



*Yamaguchi Method*



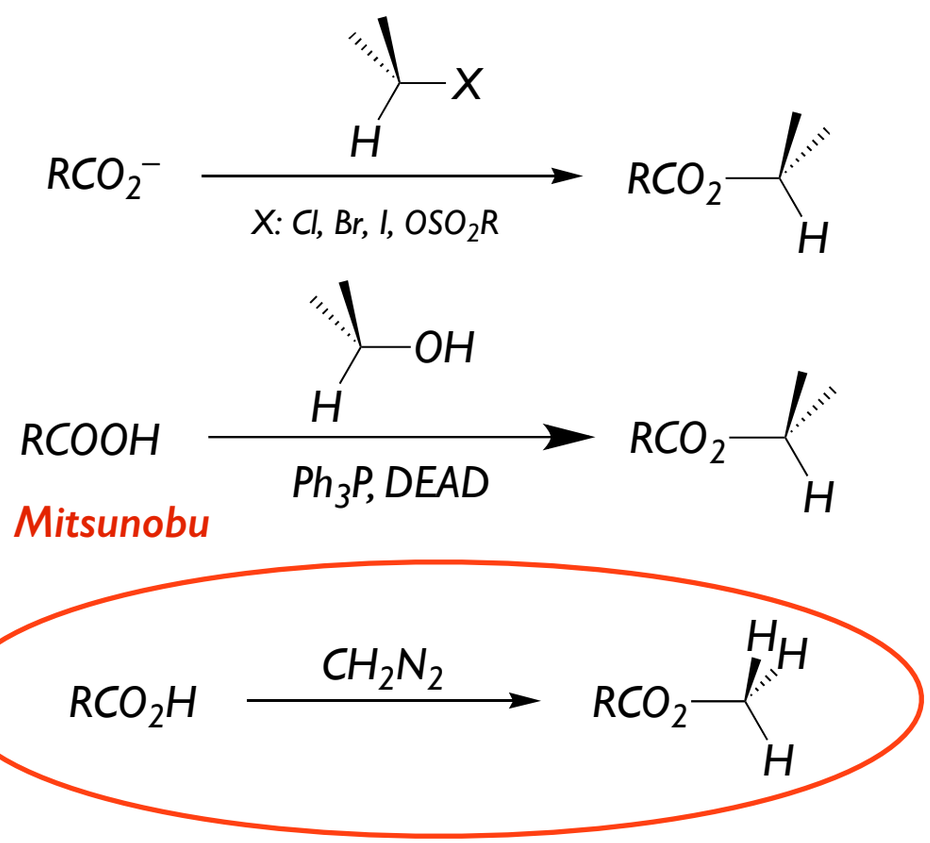
- *The retrosynthetic analysis shows two ways of deconnecting the ester group ...*




## Addition-elimination Processes

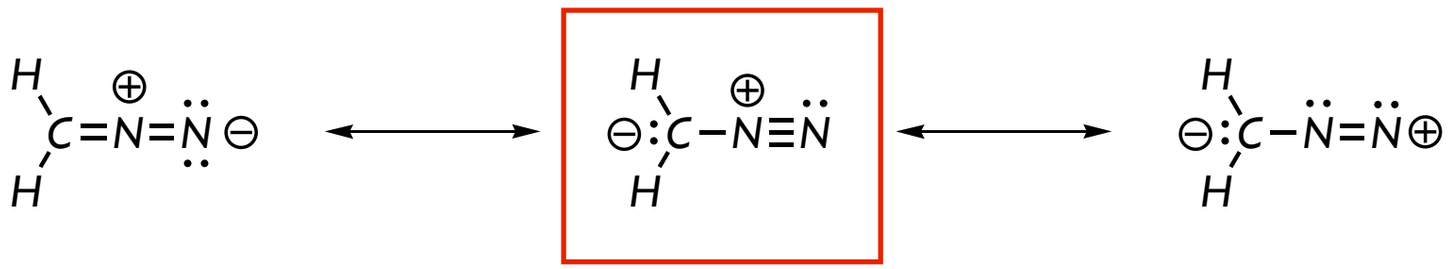
- *Fischer Esterification*
- *Using coupling agents as carbodiimides*
- *Acylation with acid chlorides or anhydrides*

## $S_N2$ Processes

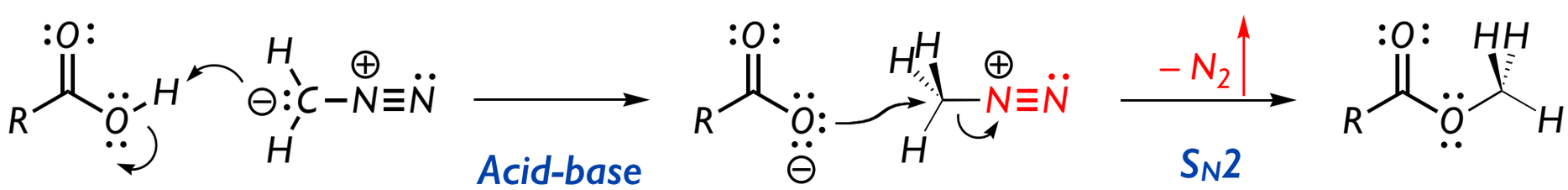


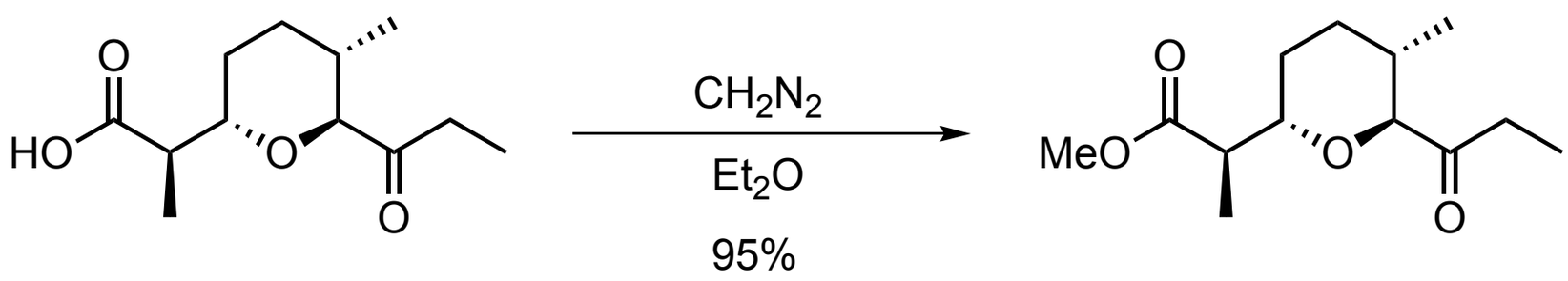
## *Synthesis of methyl esters by reaction with diazomethane*

*Diazomethane is a highly volatile (it must be handled in etherial solutions), toxic, and explosive compound ...*



*The best leaving group*



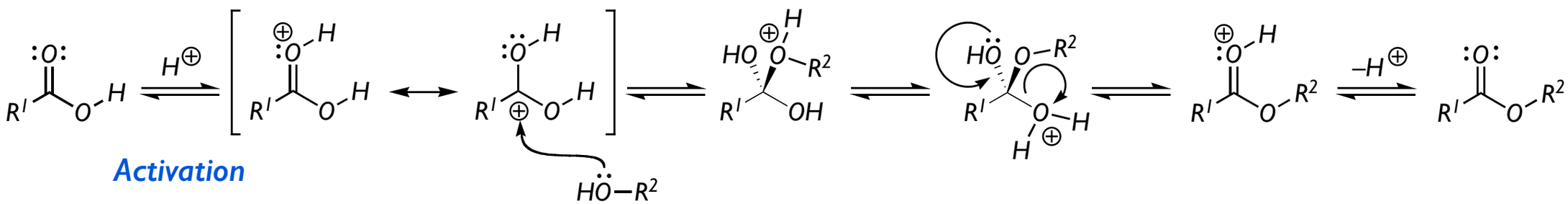

*pKa 10*

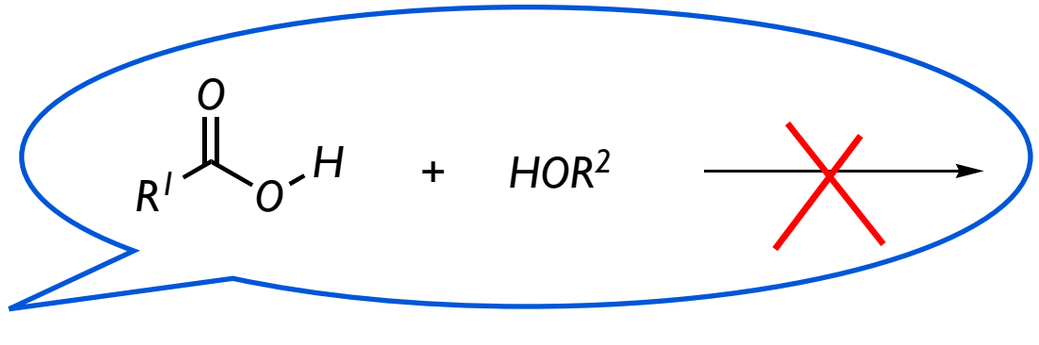
$PhOH + CH_2N_2 \longrightarrow PhOMe$

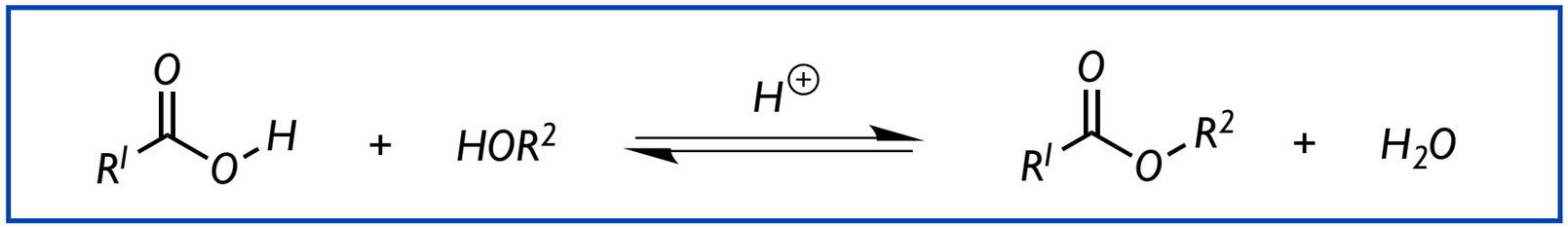
*pKa 16*

$PrOH + CH_2N_2 \not\longrightarrow PrOMe$

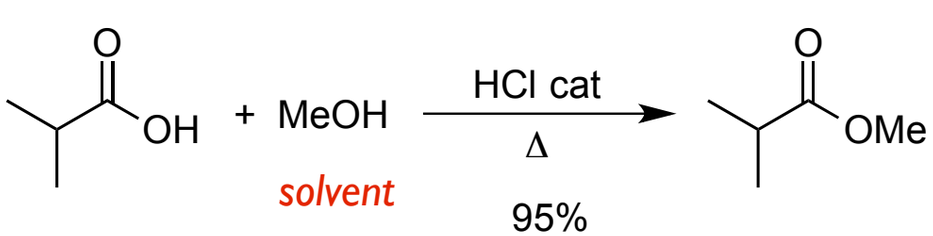
## Fischer esterification

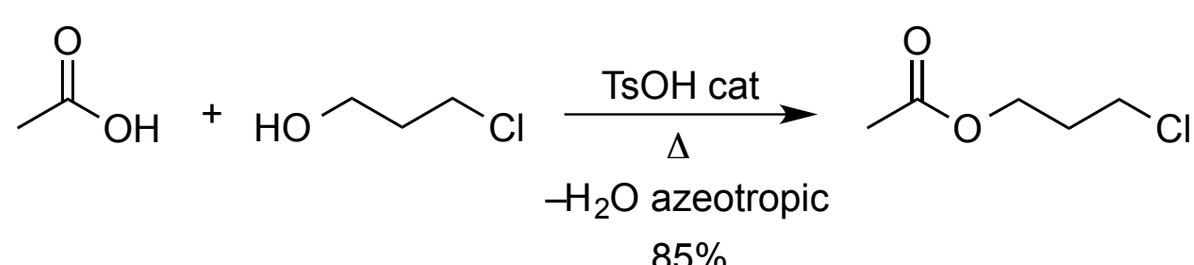



- *Reversible reaction catalyzed by $H^+$*
- *Excess of $R^2OH$ or removal of $H_2O$ are necessary to obtain esters in high yields*

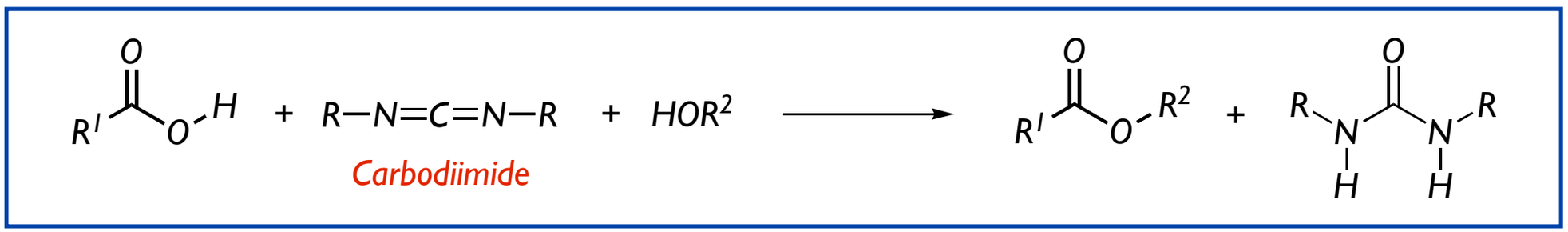


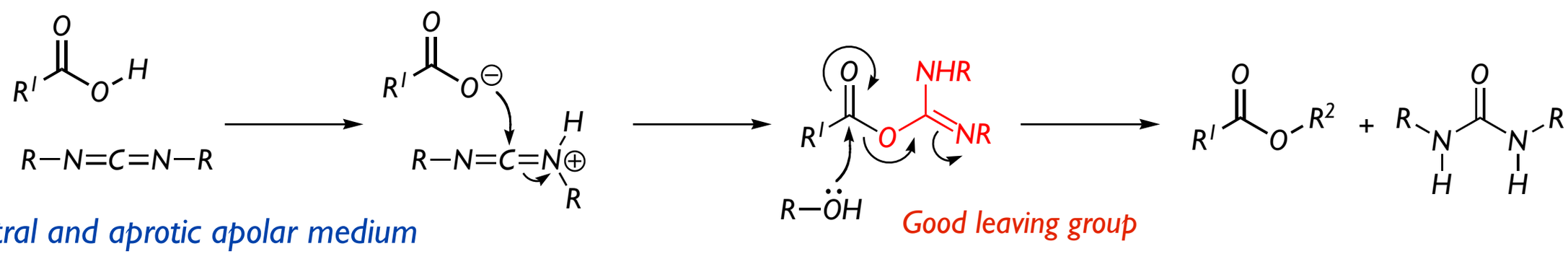





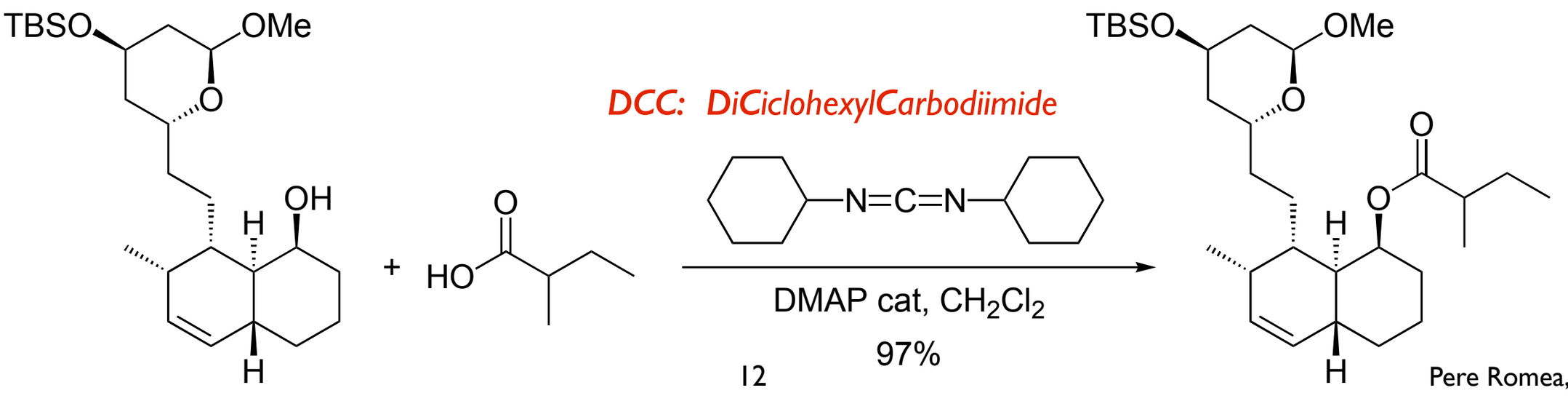

Pere Romea, 2014

## Esterification with carbodiimides



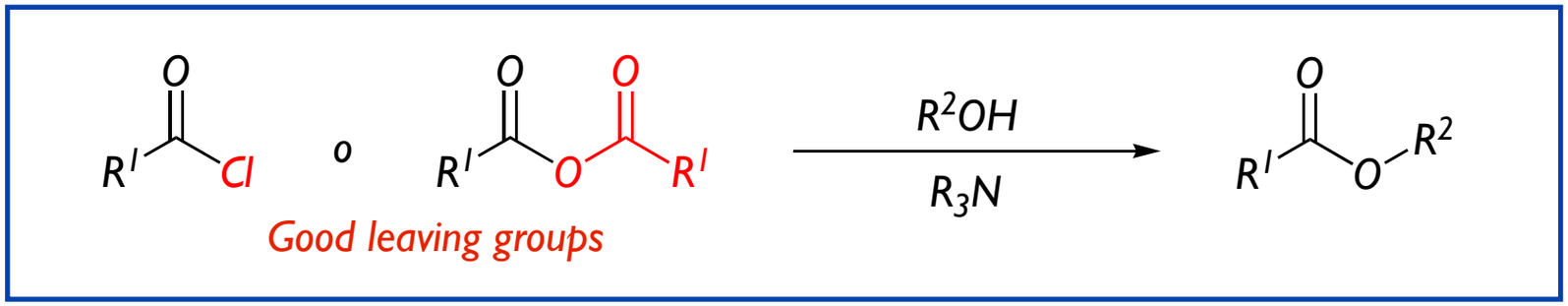

- Neutral and aprotic apolar medium
- DMAP is usually used as catalyst

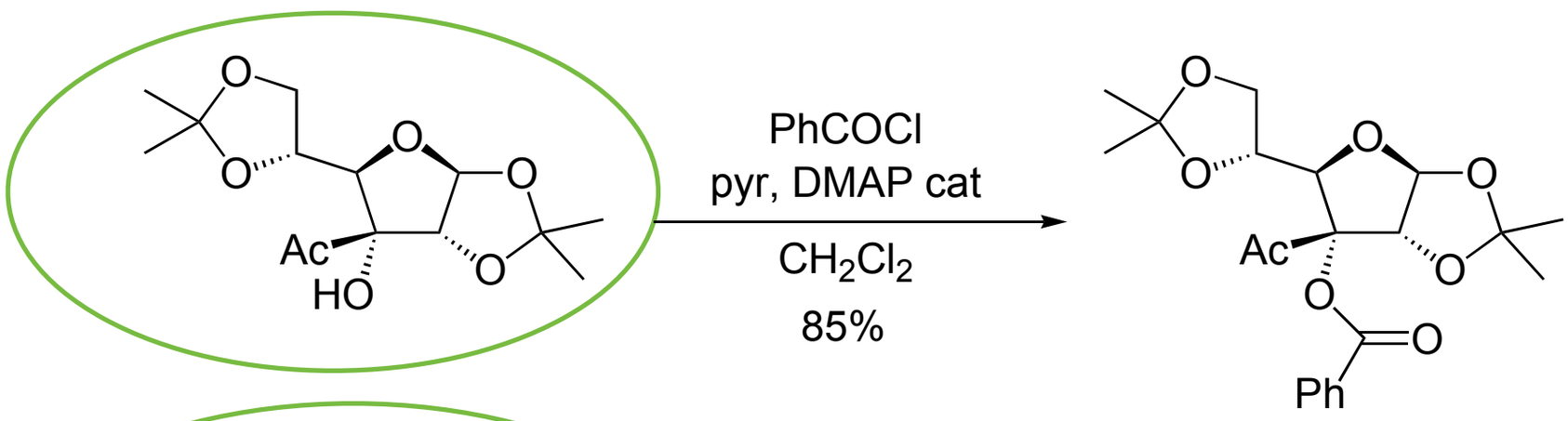


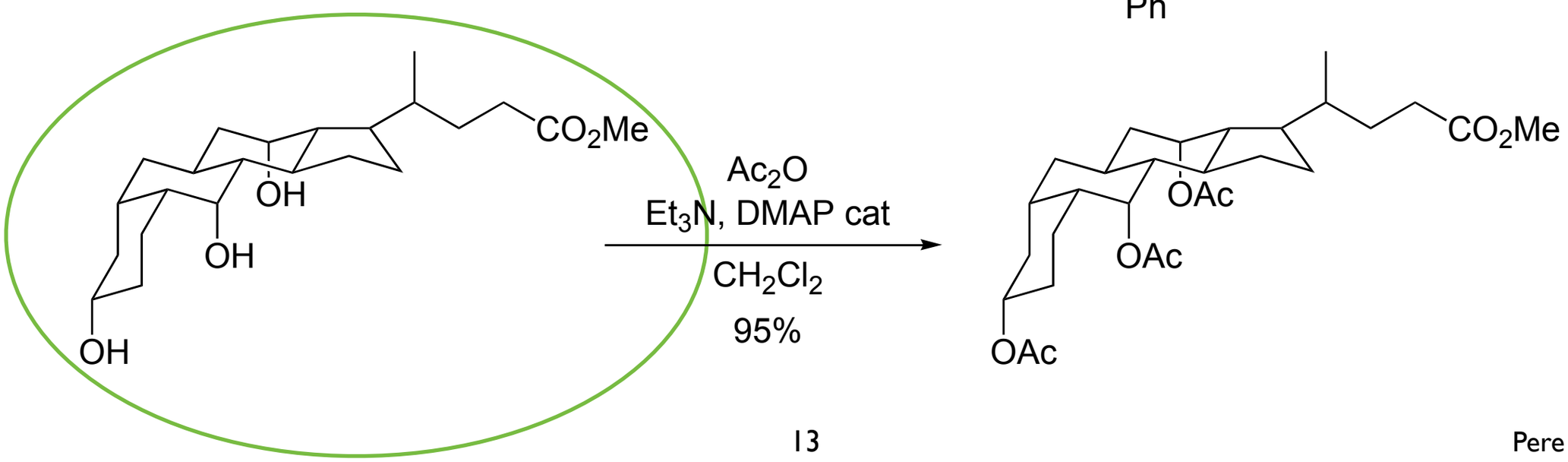



Pere Romea, 2014

## Acylation with acid chlorides and anhydrides

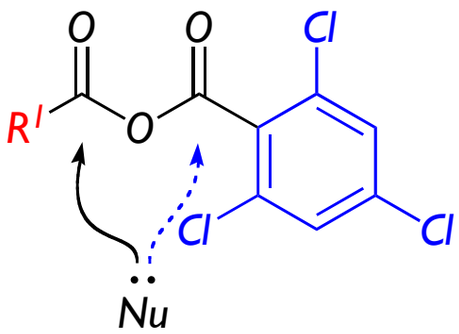


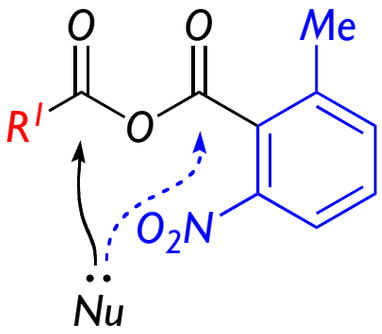



## Acylation with mixed anhydrides

*Mixed anhydrides are usually prepared quantitatively from acid chlorides or other anhydrides.*
*They are not isolated.*

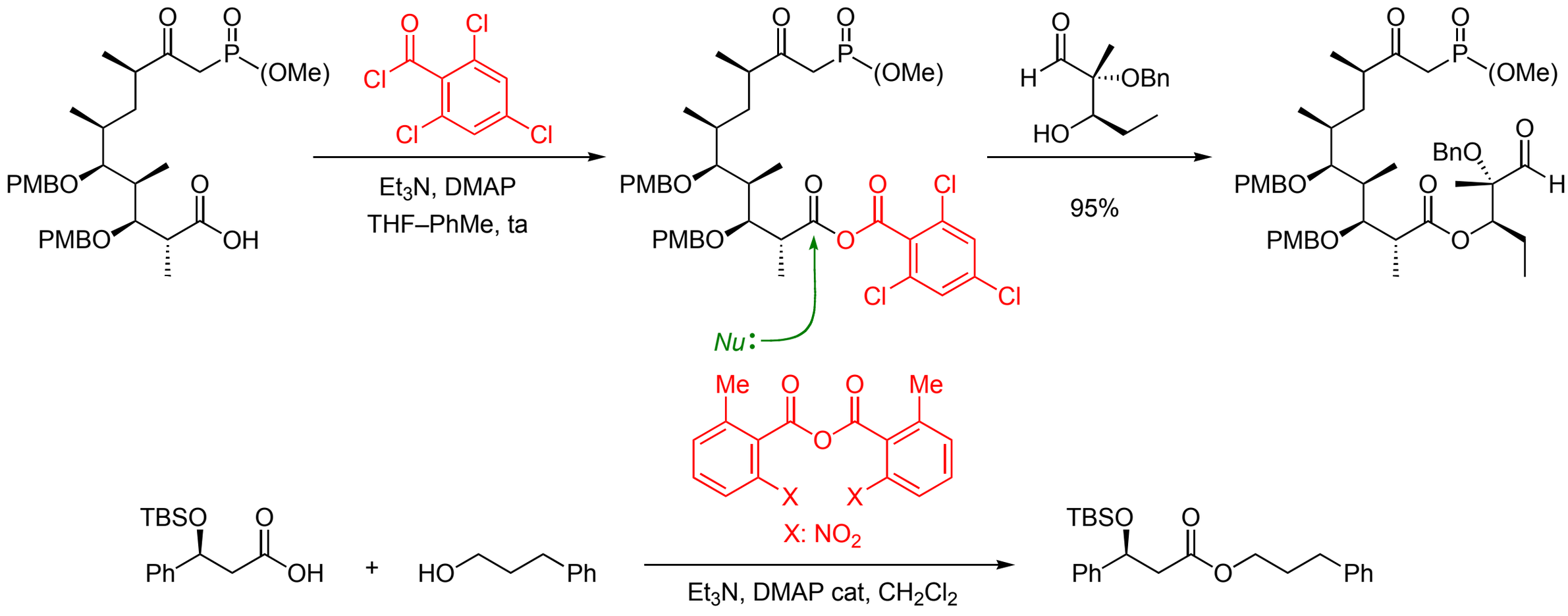



*Yamaguchi Method*

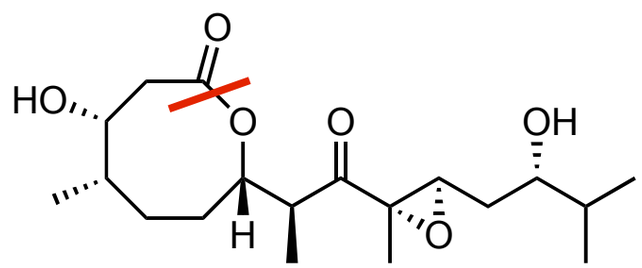



*Shiina Method*

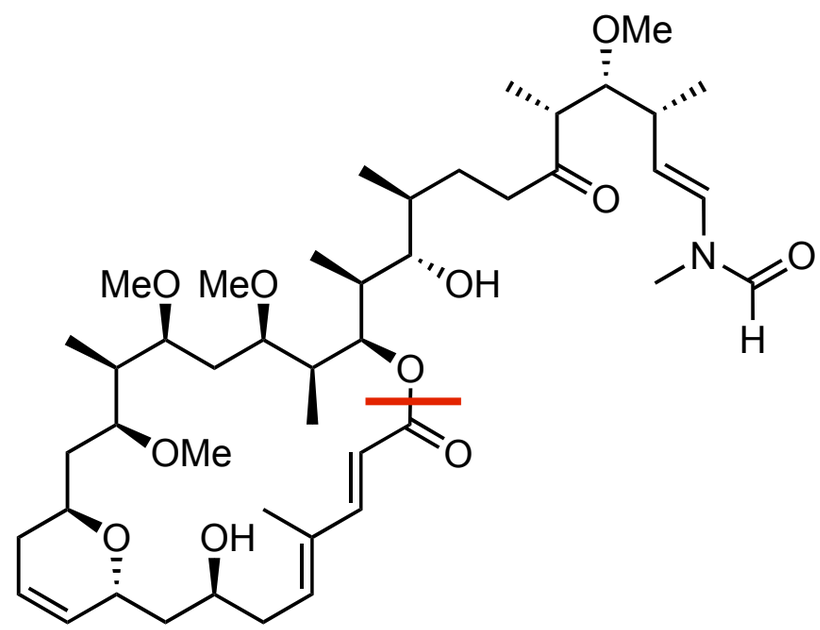
*J. Org. Chem.* **2004**, *69*, 1822



## *Lactones (cyclic esters) are a common structural motif in natural products*

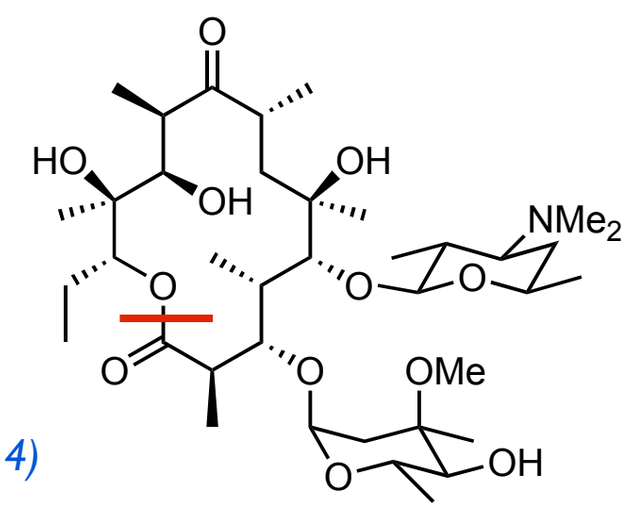



*Octalactin A (8)*

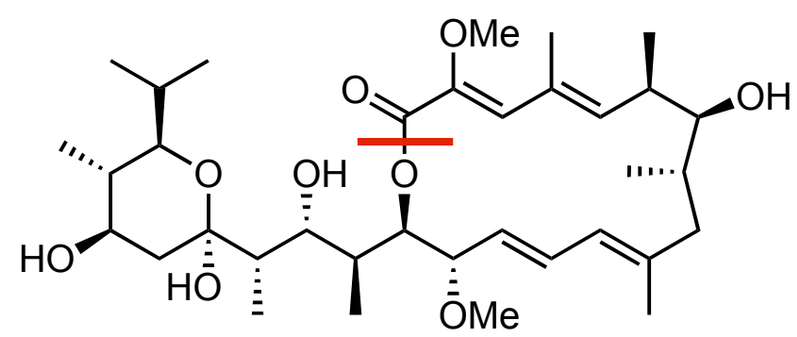


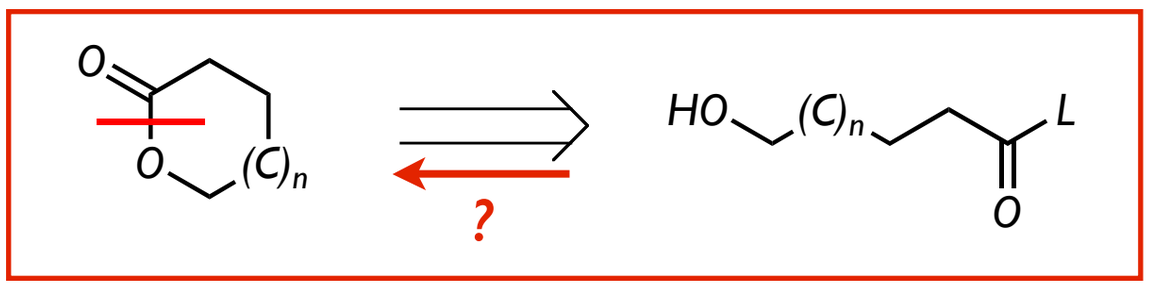

*Scytophycin C (20)*

*Bafilomycin A (16)*




*Erythromycin A (14)*

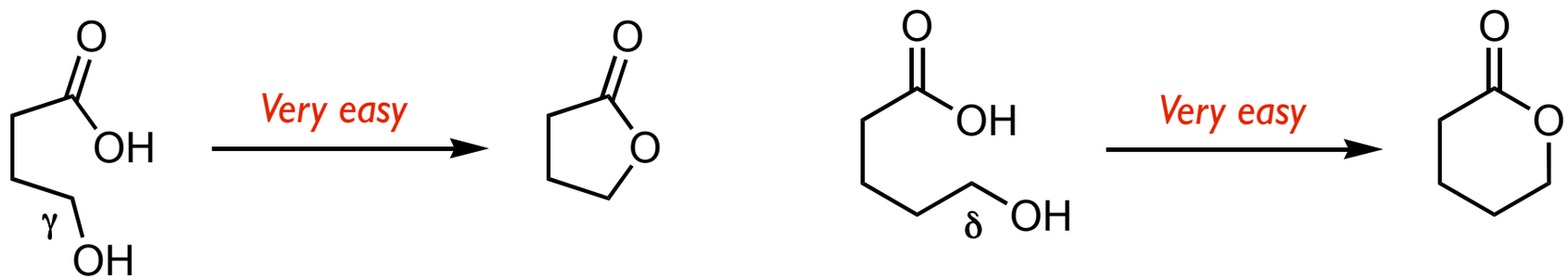



Campagne, J. -M.
*Chem. Rev.* **2006**, *106*, 911 & **2013**, *113*, PR1

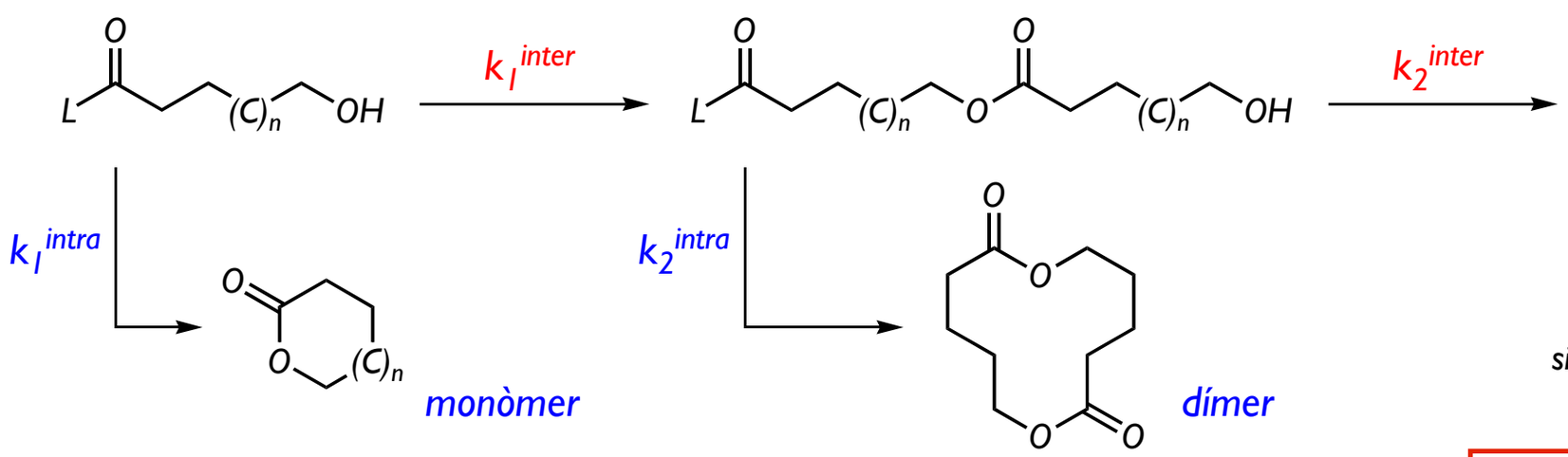
## *The size of the ring determines the synthetic method ...*

- *Cyclization of γ- and ∂-hydroxy acids is straightforward …*




*For 5- and 6-membered rings, both enthalpy and entropy OK !!!*

- *... but as the size of the ring increases, the cyclization mets the **selectivity problem***




$v_{intra} >> v_{inter}$

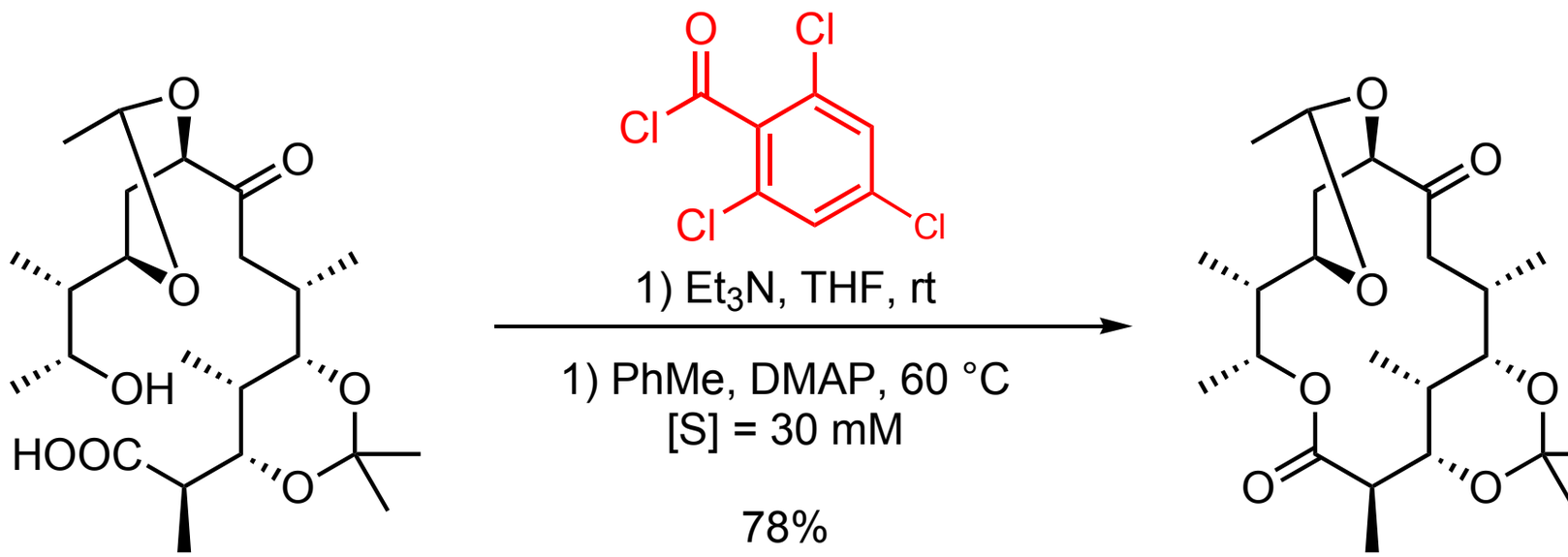
$v_{intra} = k_1^{intra}\,[S]$ $\quad v_{inter} = k_1^{inter}\,[S]^2$

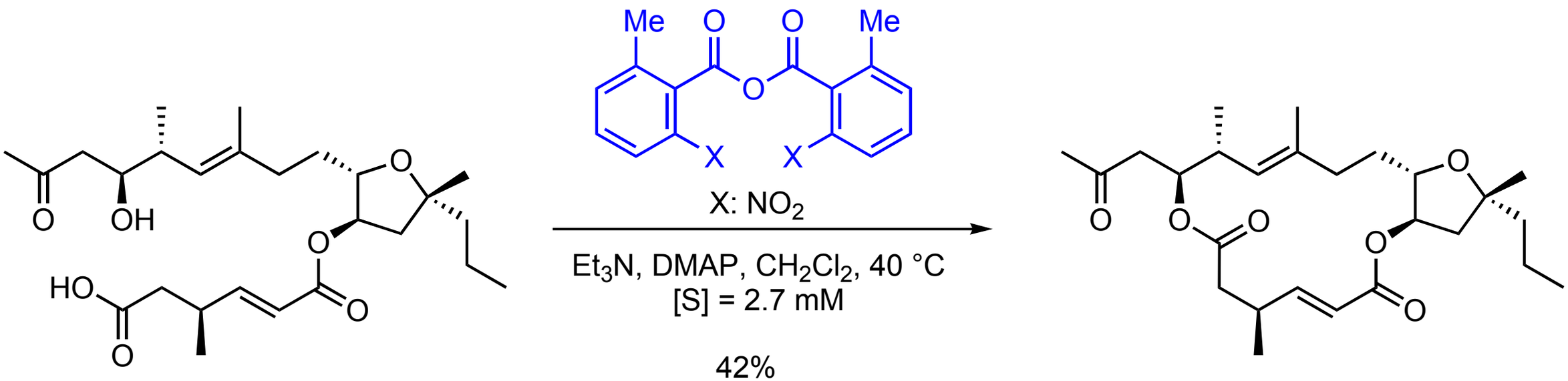
si $k_1^{intra} \square k_1^{inter}$ $\quad \dfrac{v_{intra}}{v_{inter}} = \dfrac{1}{[S]}$

Per a $v_{intra} >> v_{inter}$ $\quad [S] \longrightarrow 0$

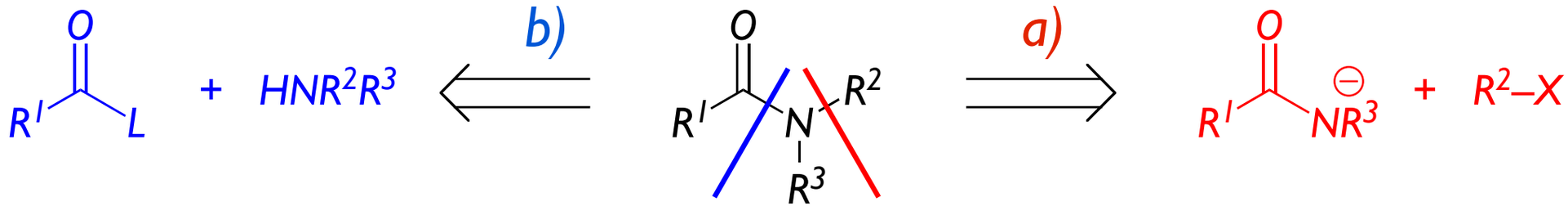
*High dilution conditions are required as well as activation of the carboxylate group compatible with the OH group*

*Mixed anhydrides (**Yamaguchi** and **Shiina** methods) met these conditions*



- *The retrosynthetic analysis of amides also shows two options …*



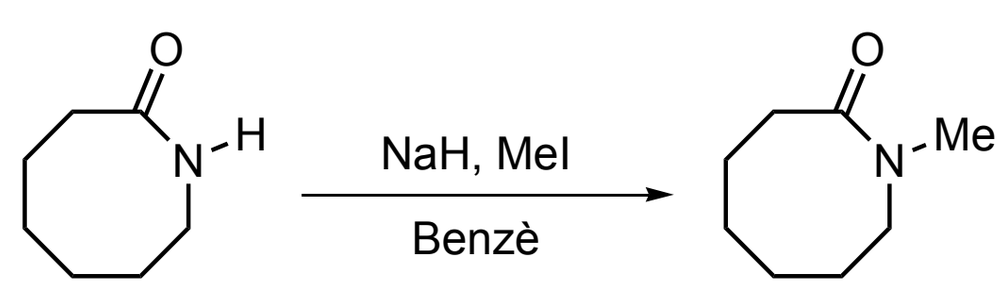

***Addition-elimination** processes*

- *Acylation with acid chlorides and anhydrides*
- *Via coupling agents: carbodiimides, HATU*

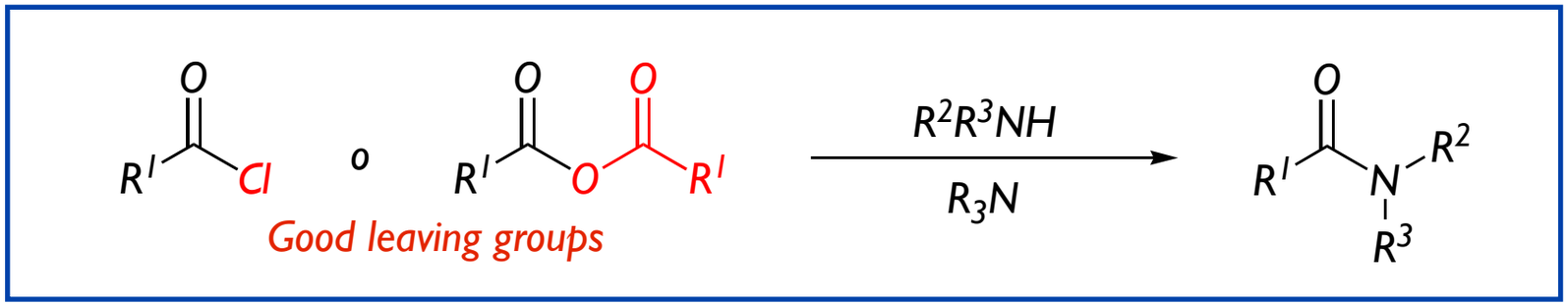
***$S_N2$** Processes*

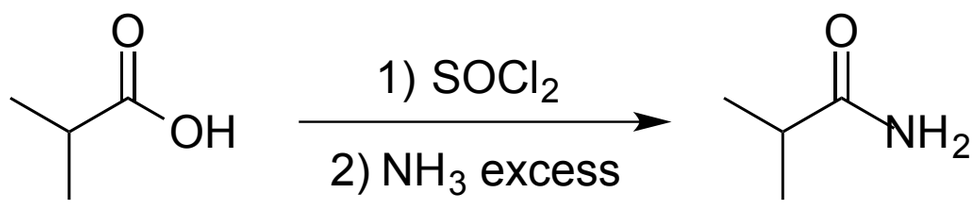
*No very common, but N-substitutions using sterically unindexed alkyl halides are useful options.*

***Attention with E2***

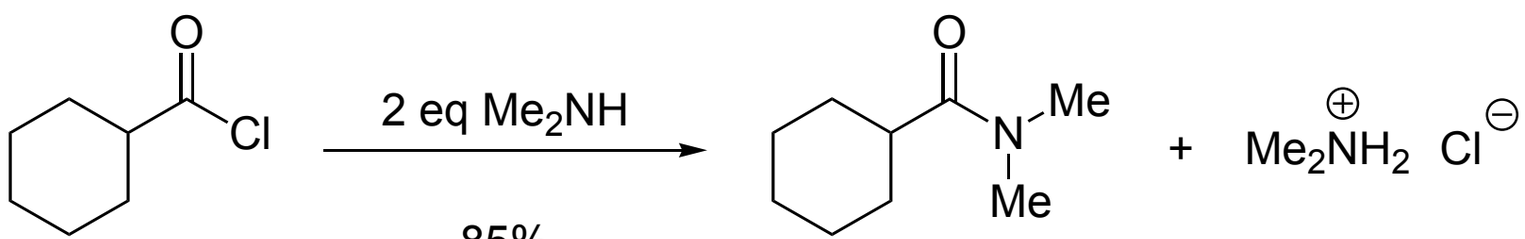


## Acylation with acid chlorides and anhydrides

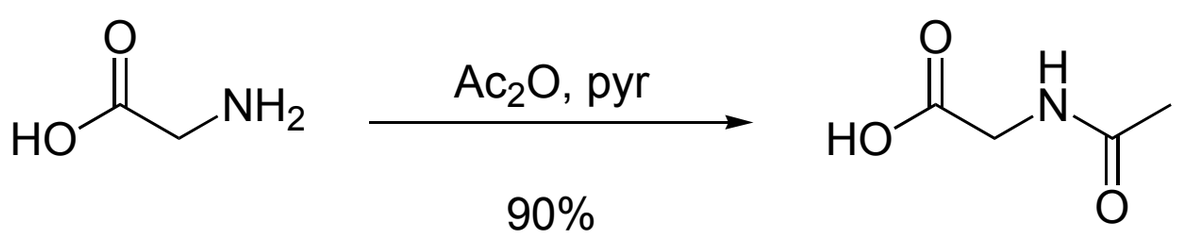



70%

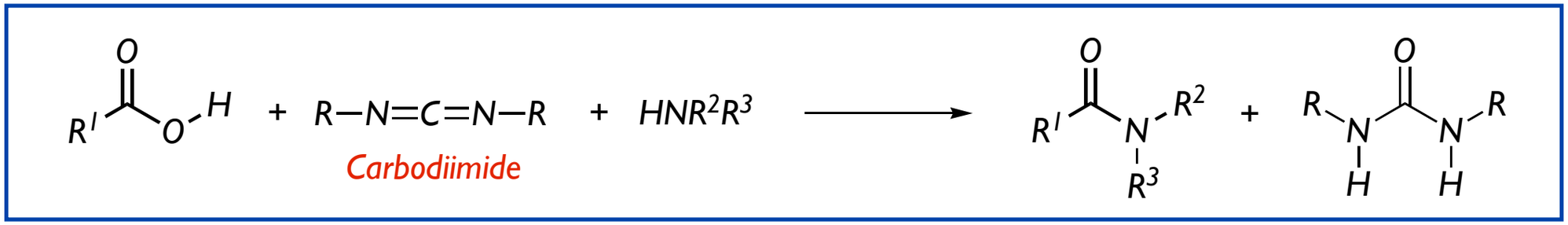


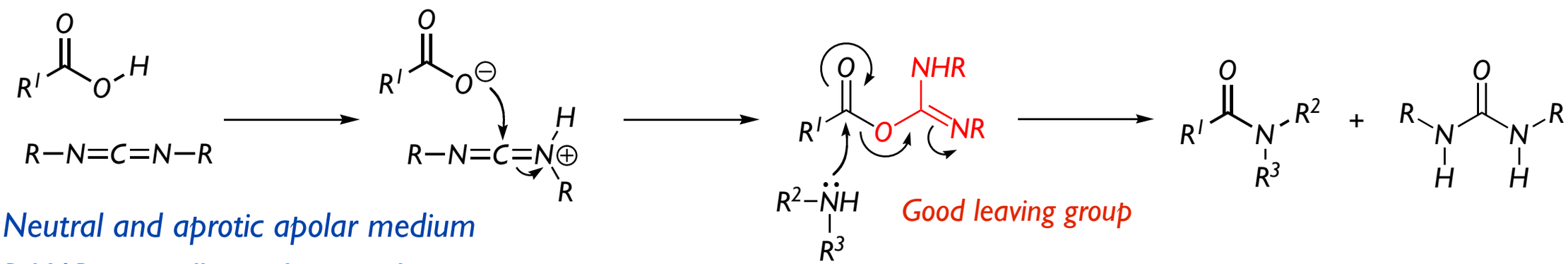

85%




90%

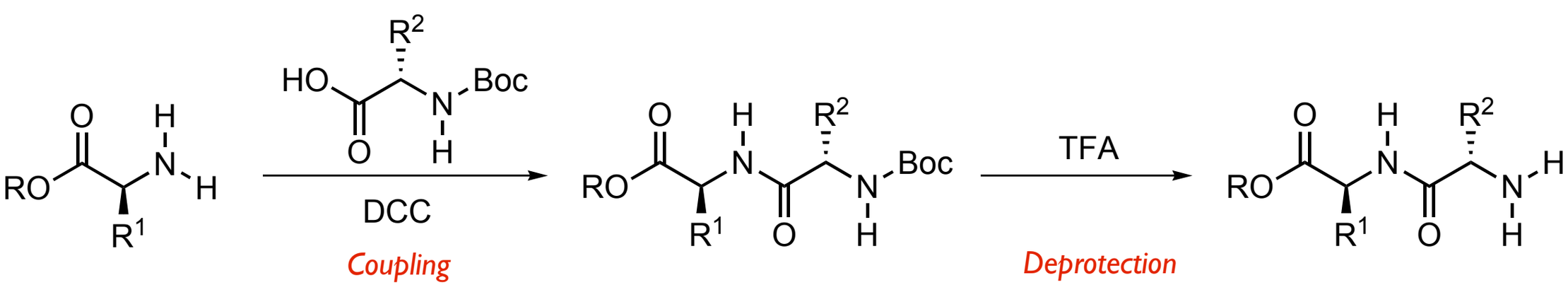
## Synthesis of amides by using carbodiimides



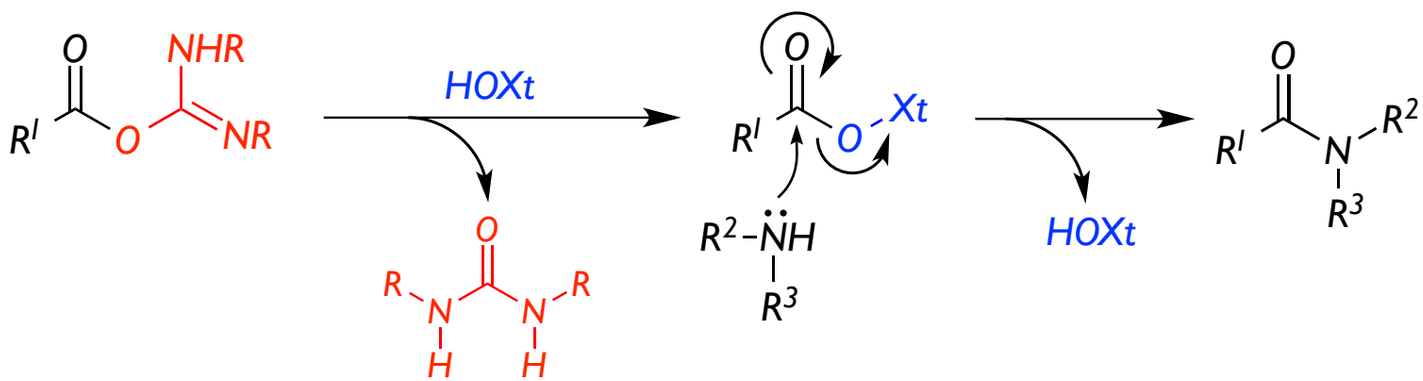
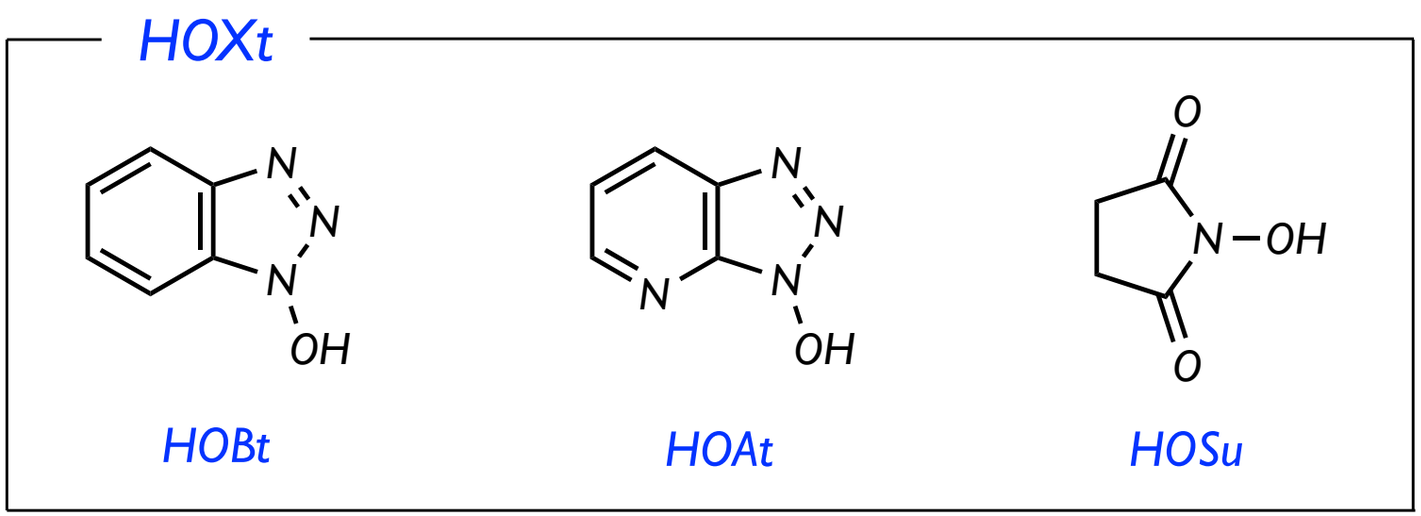




– Neutral and aprotic apolar medium

– DMAP is usually used as catalyst




Peptide synthesis

# Amides through Addition-Elimination Transformations

*Occasionally, O-acylisourea intermediates are not stable enough or produce the epimerization of the Cα center.*
*Then, the addition of N-hydroxy derivatives transforms such intermediates into less reactive active esters with a beneficial effect on the overall efficiency*