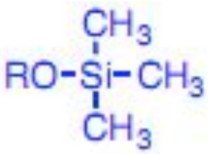
ЗАЩИТНЫЕ ГРУППЫ

для спиртов

Силильная защита спиртов

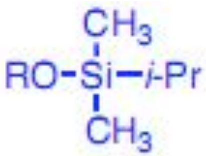


$$\mathrm{RO-\underset{CH_3}{\overset{CH_3}{Si}}-CH_3}$$

Trimethylsilyl (TMS)

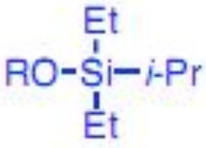
$$\mathrm{RO-\underset{Et}{\overset{Et}{Si}}-Et}$$

Triethylsilyl (TES)



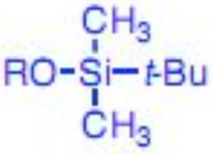
$$\mathrm{RO-\underset{CH_3}{\overset{CH_3}{Si}}-\mathit{i}\text{-}Pr}$$

Dimethylisopropylsilyl (IPDMS)



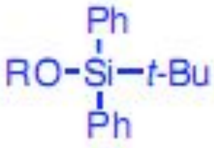
$$\mathrm{RO-\underset{Et}{\overset{Et}{Si}}-\mathit{i}\text{-}Pr}$$

Diethylisopropylsilyl (DEIPS)



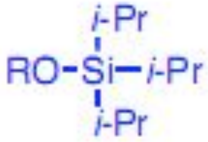
$$\mathrm{RO-\underset{CH_3}{\overset{CH_3}{Si}}-\mathit{t}\text{-}Bu}$$

t-Butyldimethylsilyl (TBS)



$$\mathrm{RO-\underset{Ph}{\overset{Ph}{Si}}-\mathit{t}\text{-}Bu}$$

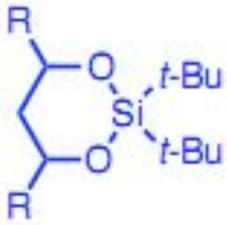
t-Butyldiphenylsilyl (TBDPS)



$$\mathrm{RO-\underset{\mathit{i}\text{-}Pr}{\overset{\mathit{i}\text{-}Pr}{Si}}-\mathit{i}\text{-}Pr}$$

Triisopropylsilyl (TIPS)

Tetraisopropyldisilylene (TIPDS)



Di-*t*-butyldimethylsilylene (DTBS)

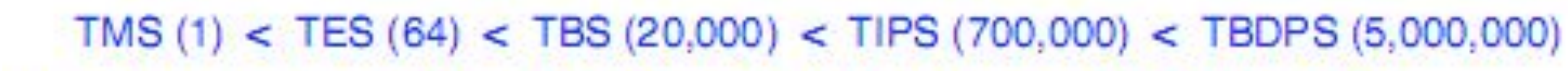
Основная методика синтеза эфиров из спиртов

$$\mathrm{ROH} \xrightarrow[\text{imidazole, DMF}]{\mathrm{R'_3SiCl}} \mathrm{ROSiR'_3}$$

$$\mathrm{ROH} \xrightarrow[\text{2,6 lutidine, } \mathrm{CH_2Cl_2}]{\mathrm{R'_3SiOTf}} \mathrm{ROSiR'_3}$$

Устойчивость защитных групп к кислотным и основным средам

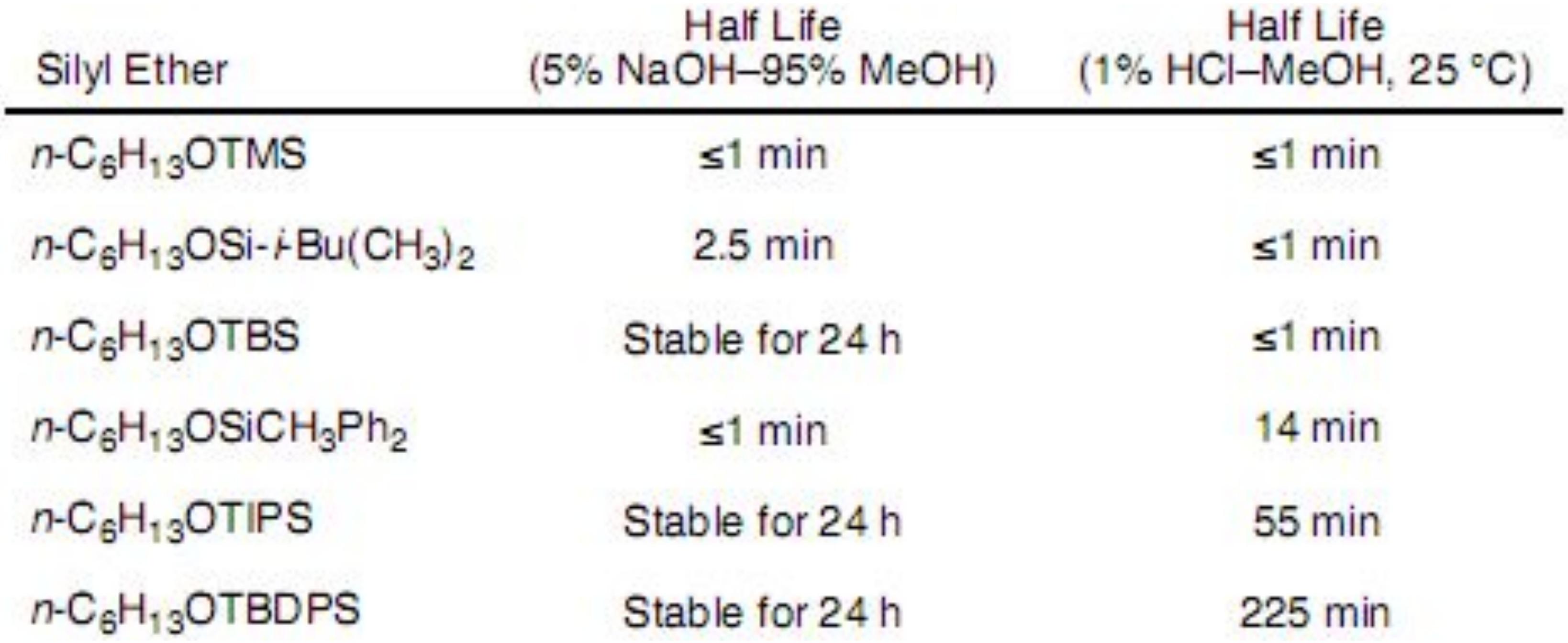
Устойчивость эфиров к кислым средам
изменяется в следующем ряду



TMS (1) < TES (64) < TBS (20,000) < TIPS (700,000) < TBDPS (5,000,000)

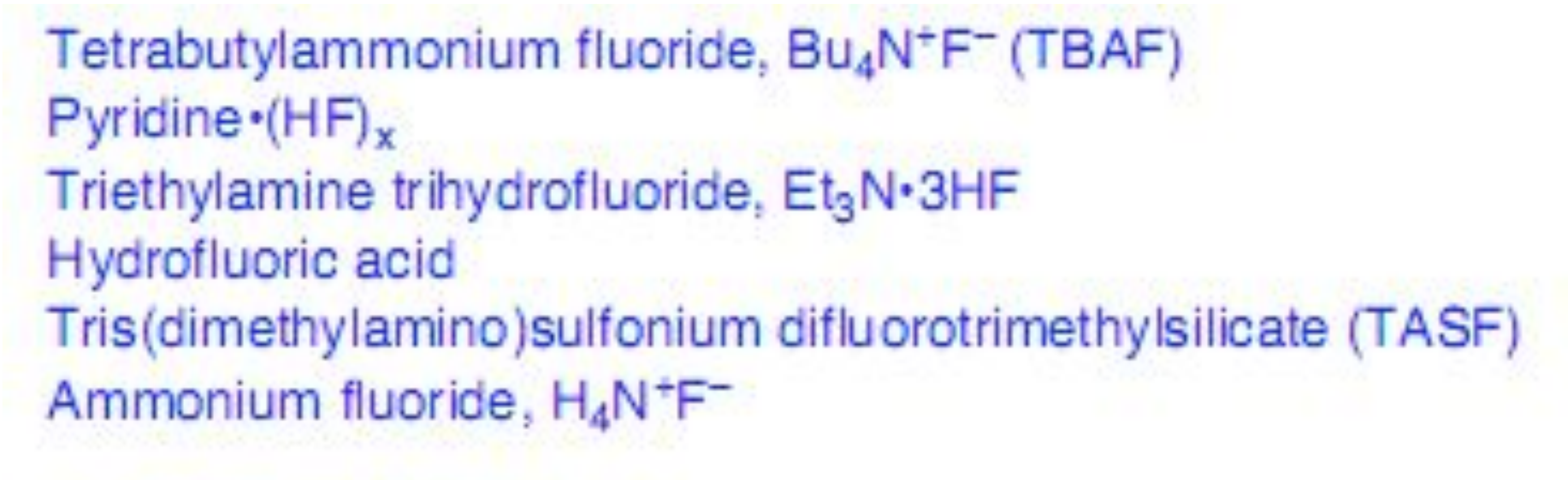
Устойчивость эфиров
к основным средам
изменяется в следующем ряду

TMS (1) < TES (10-100) < TBS ~ TBDPS (20,000) < TIPS (100,000)



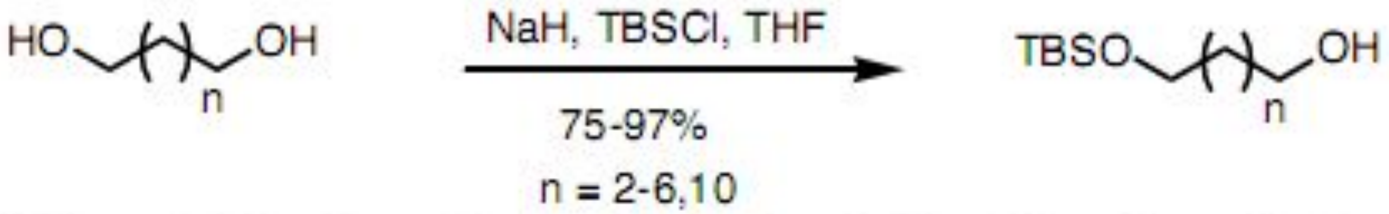
Silyl Ether	Half Life (5% NaOH–95% MeOH)	Half Life (1% HCl–MeOH, 25 °C)
$n\text{-}C_6H_{13}OTMS$	≤1 min	≤1 min
$n\text{-}C_6H_{13}OSi\text{-}i\text{-}Bu(CH_3)_2$	2.5 min	≤1 min
$n\text{-}C_6H_{13}OTBS$	Stable for 24 h	≤1 min
$n\text{-}C_6H_{13}OSiCH_3Ph_2$	≤1 min	14 min
$n\text{-}C_6H_{13}OTIPS$	Stable for 24 h	55 min
$n\text{-}C_6H_{13}OTBDPS$	Stable for 24 h	225 min

Защиту силильными группами, как правило, снимают с использованием реагентов с фторид-ионом. Сила связи Si-F на 30 ккал / моль сильнее связи Si-O.

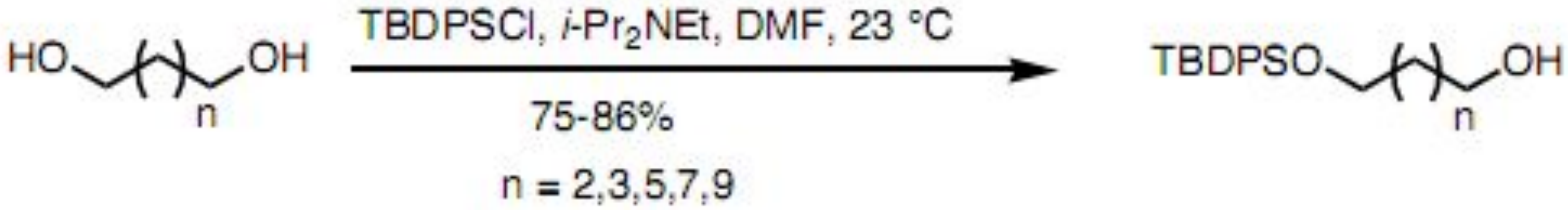


Tetrabutylammonium fluoride, $Bu_4N^+F^-$ (TBAF)
Pyridine•$(HF)_x$
Triethylamine trihydrofluoride, $Et_3N\cdot 3HF$
Hydrofluoric acid
Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)
Ammonium fluoride, $H_4N^+F^-$

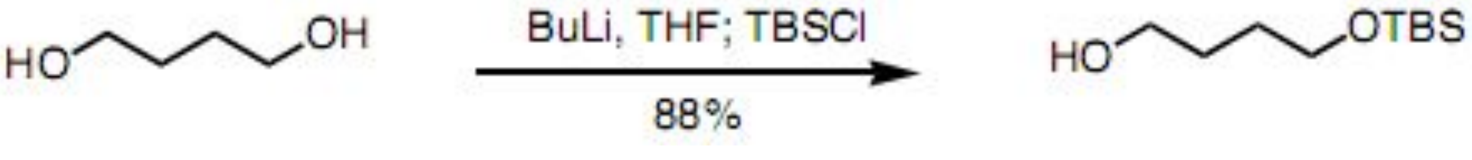
МОНО-силильная защита
Примеры.
Хорошие результаты даже для симметричных диолов



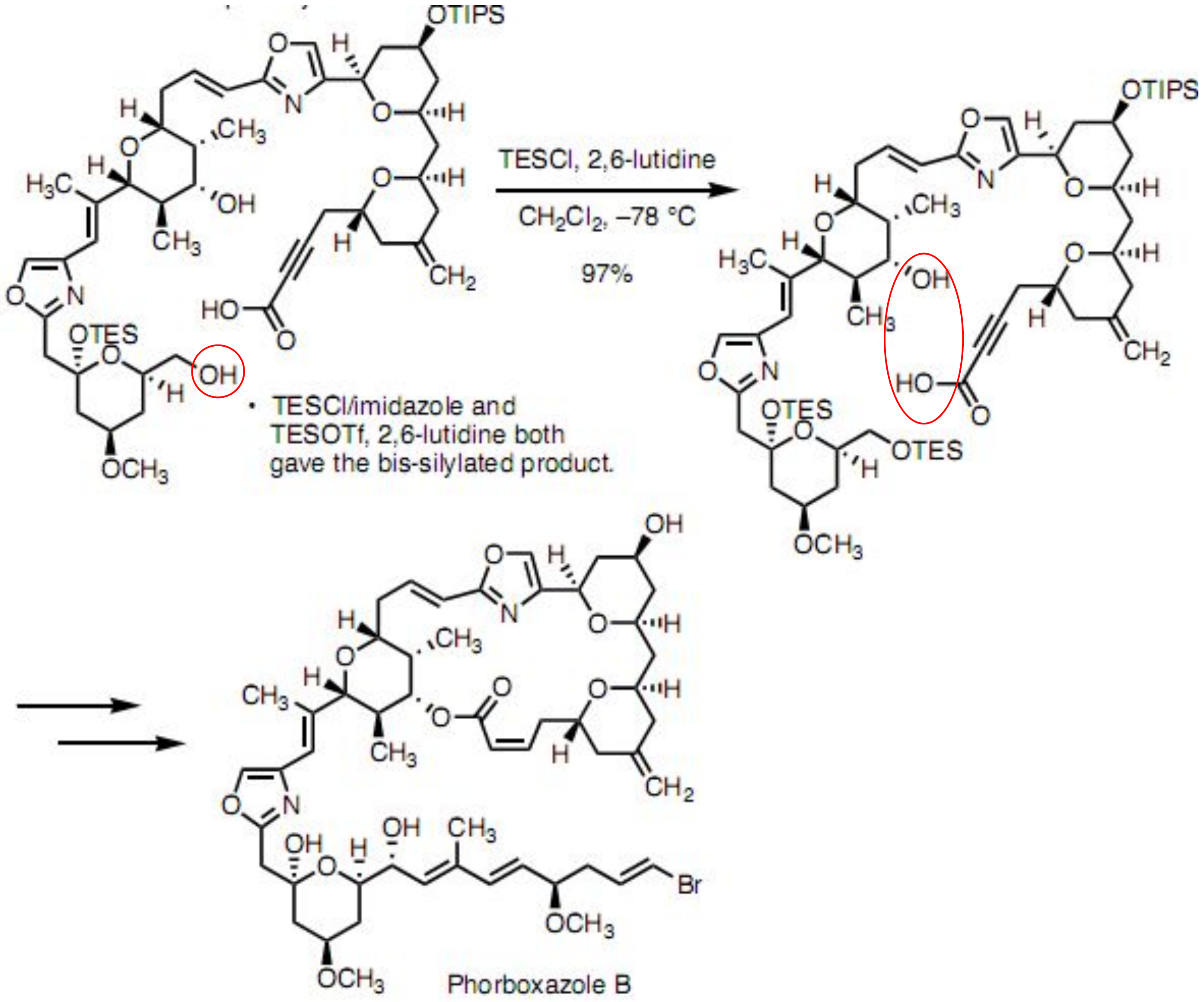
McDougal, P.G.; Rico, J.G.; Oh, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.



Hu, L.; Liu, B.; Yu, C. *Tetrahedron Lett.* **2000**, *41*, 4281.



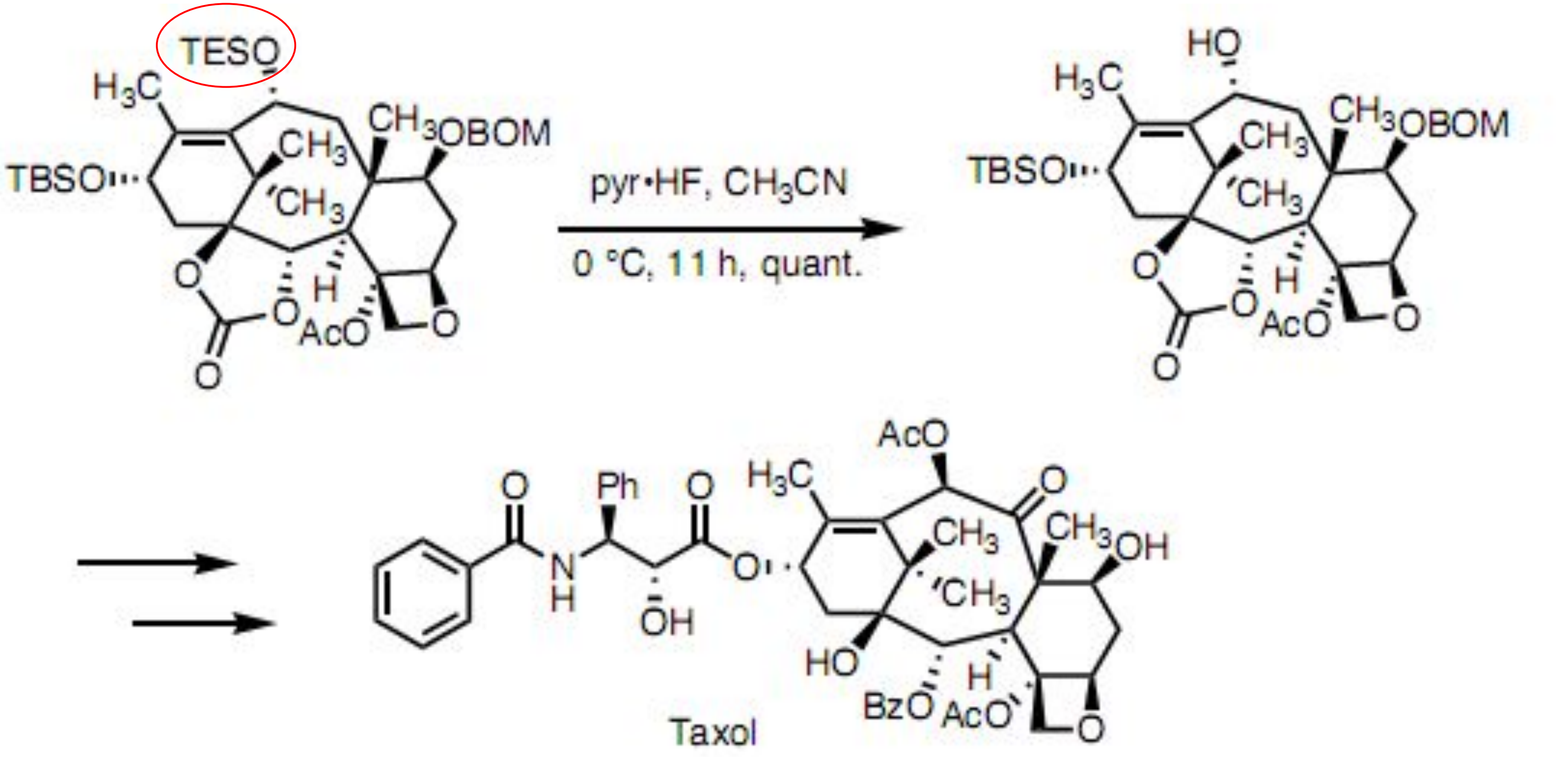
Селективная защита в сложных молекулах



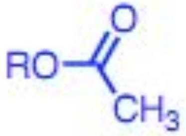
- TESCl/imidazole and TESOTf, 2,6-lutidine both gave the bis-silylated product.

Phorboxazole B

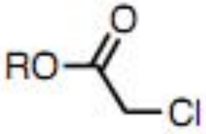
Селективное снятие защиты – тоже очень важный момент синтеза. Условия подбираются в эксперименте



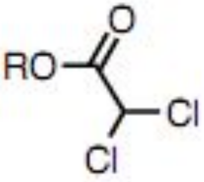
Защита спиртовых групп через сложные эфиры



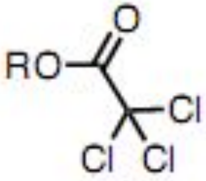
Acetate (Ac)



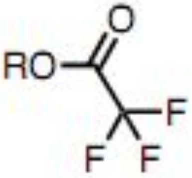
Chloroacetate



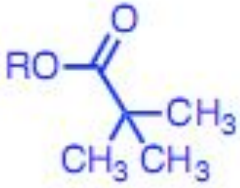
Dichloroacetate



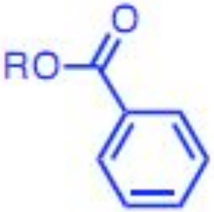
Trichloroacetate



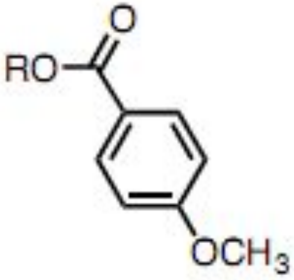
Trifluoroacetate (TFA)



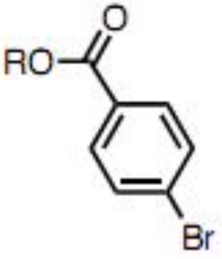
Pivaloate (Pv)



Benzoate (Bz)

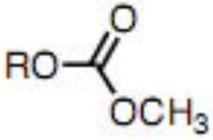


p-Methoxybenzoate

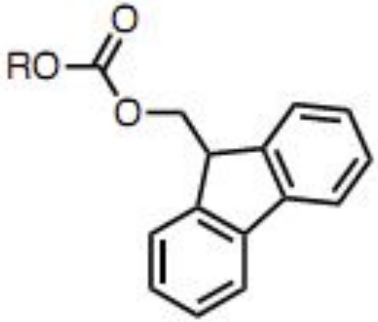


p-Bromobenzoate

карбонаты

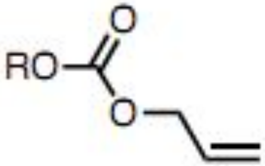


Methyl Carbonate



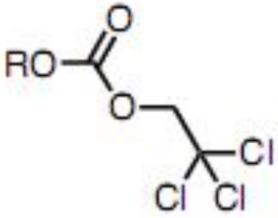
9-(Fluorenylmethyl) Carbonate

(Fmoc)



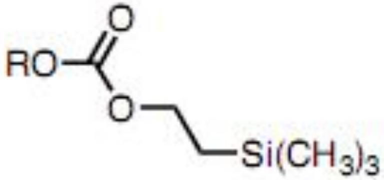
Allyl Carbonate

(Alloc)



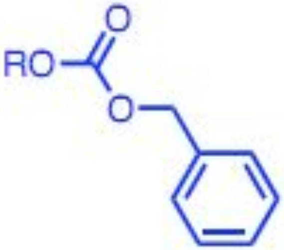
2,2,2-Trichloroethyl Carbonate

(Troc)



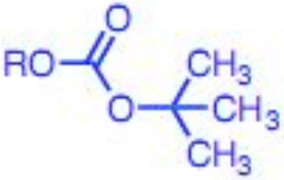
2-(Trimethylsilyl)ethyl Carbonate

(Teoc)



Benzyl Carbonate

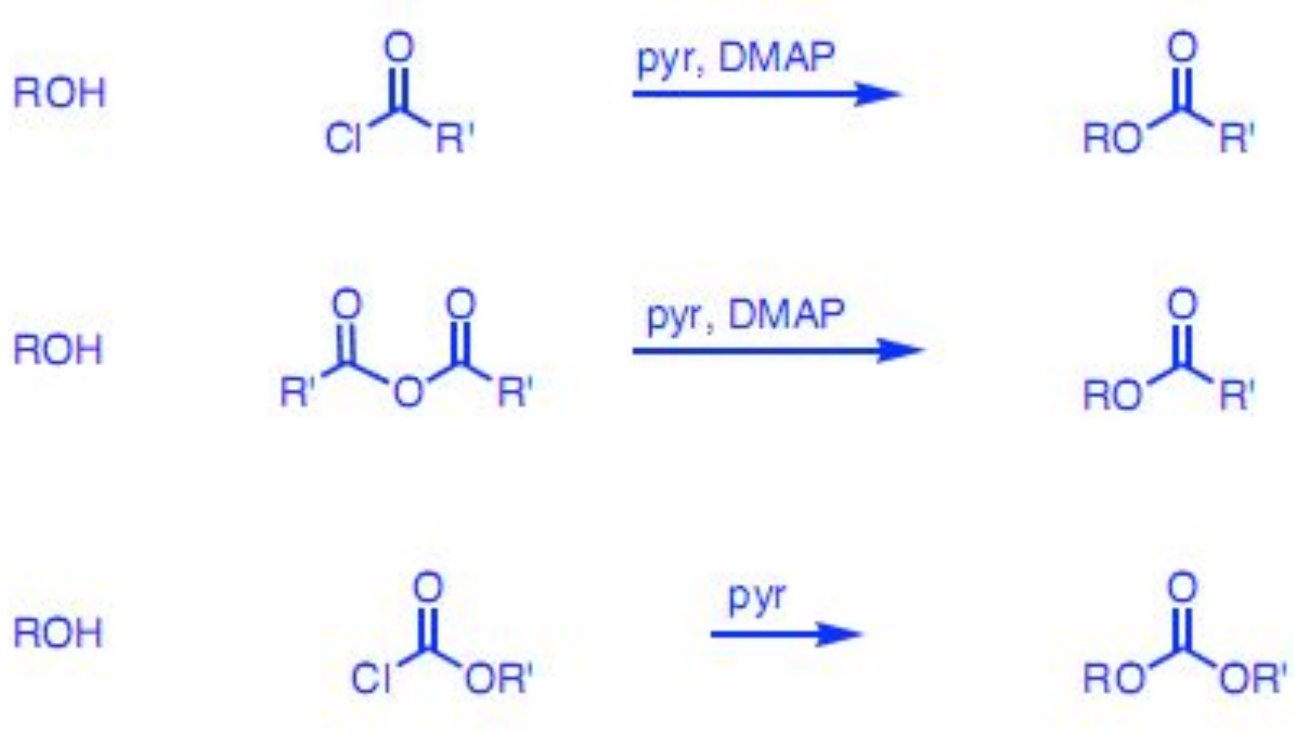
(Cbz)



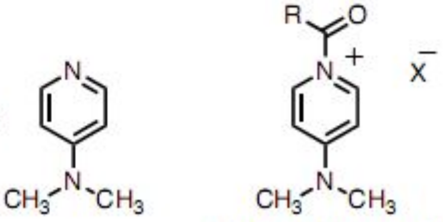
t-Butyl Carbonate

(Boc)

Основная методика

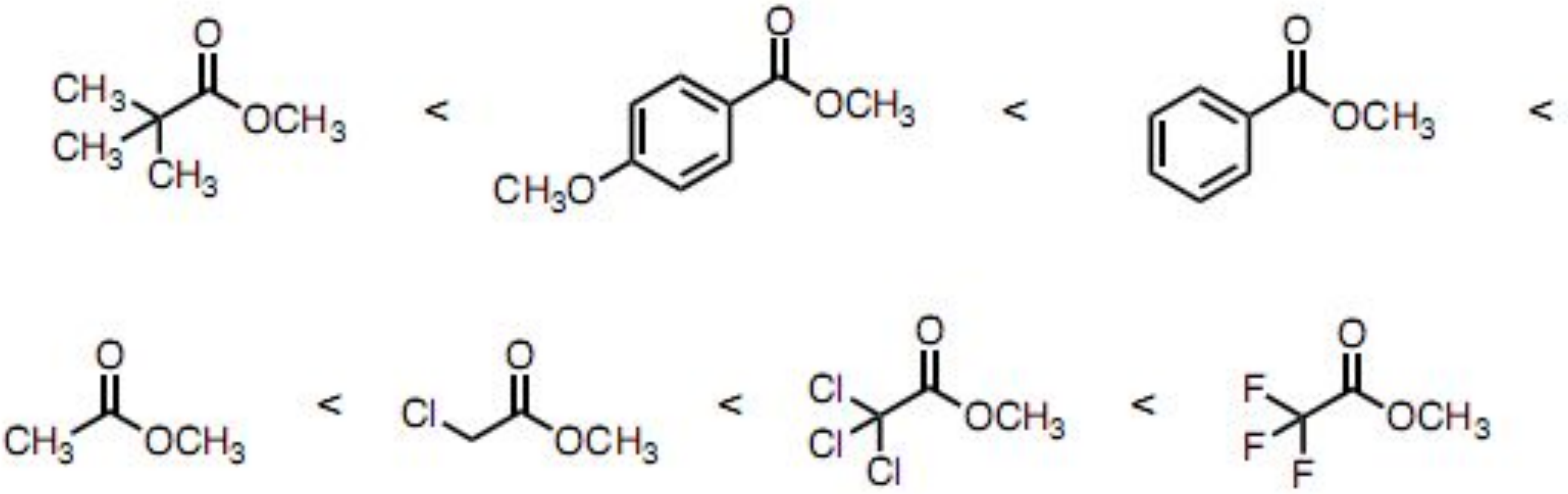


DMAP = 4-Dimethylaminopyridine:

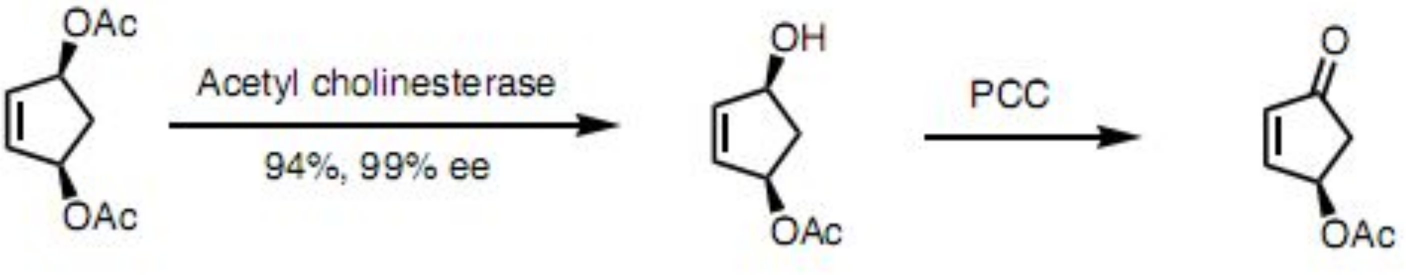


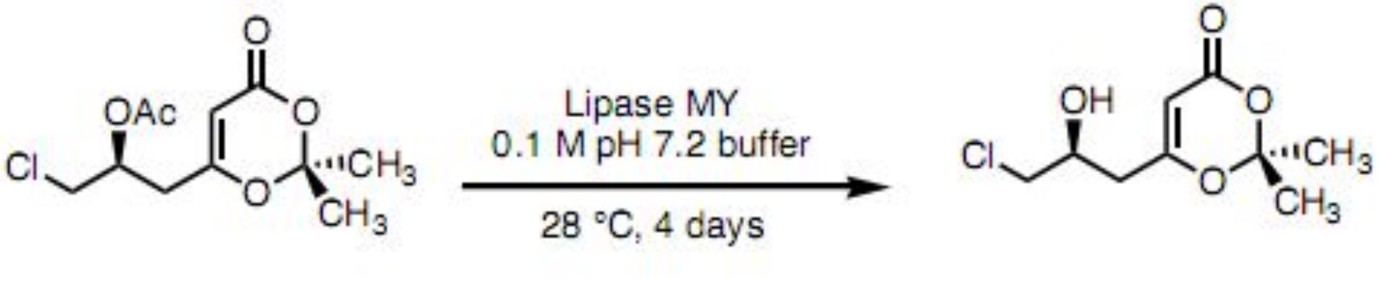
- Proposed intermediate

Чем выше кислотность кислоты, тем легче идет реакция щелочного гидролиза



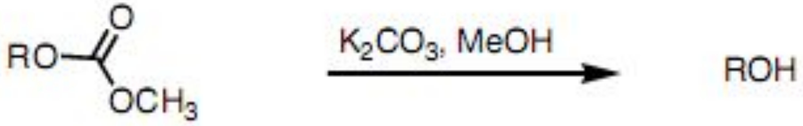
Ацетаты хорошо гидролизуются ферментами



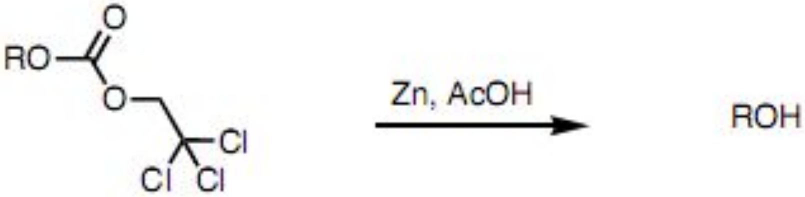


Снятие карбонатной защиты

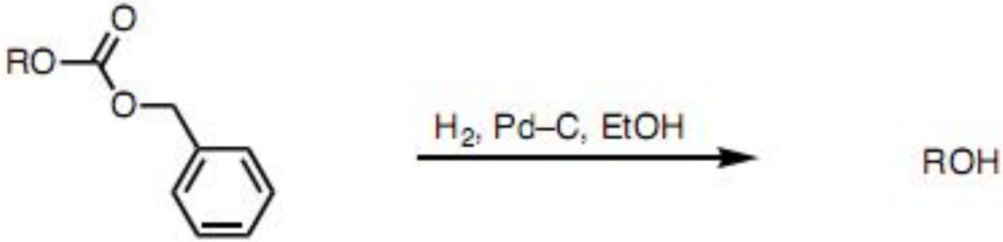
Methyl Carbonate:



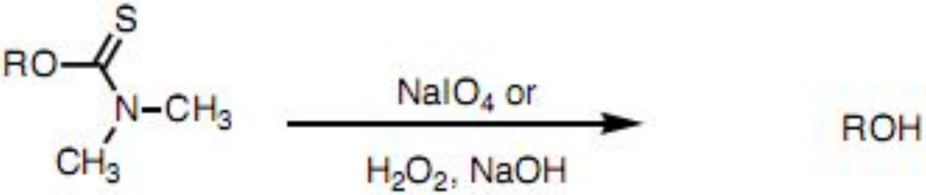
Trichloroethyl Carbonate:



Benzyl Carbonate:



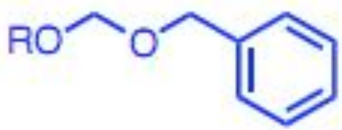
Dimethylthiocarbamate (DMTC) Carbamate:



Ацетальная защита

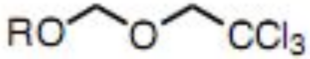
Methoxymethyl Ether

(MOM)



Benzyloxymethyl Ether

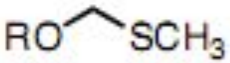
(BOM)



2,2,2-Trichloroethoxymethyl Ether

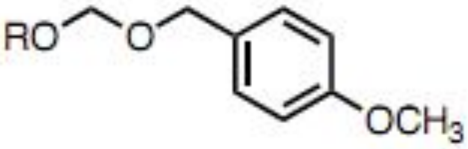
2-Methoxyethoxymethyl Ether

(MEM)



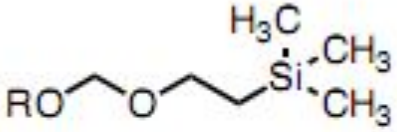
Methylthiomethyl Ether

(MTM)



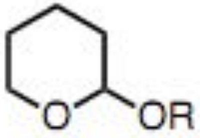
p-Methoxybenzyl Ether

(PMBM)



2-(Trimethylsilyl)ethoxymethyl Ether

(SEM)

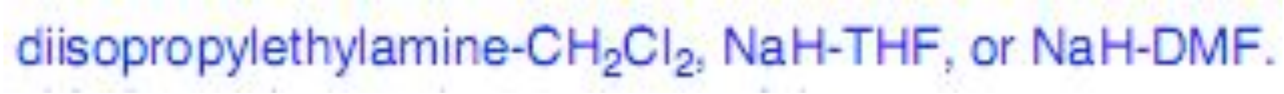


Tetrahydropyranyl Ether

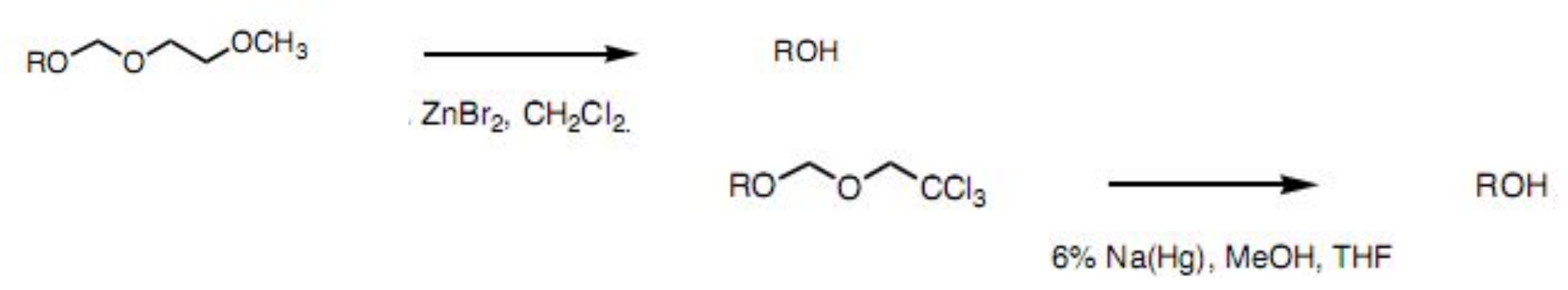
(THP)

Основная методика

Комбинация основание –
растворитель обычно следующая

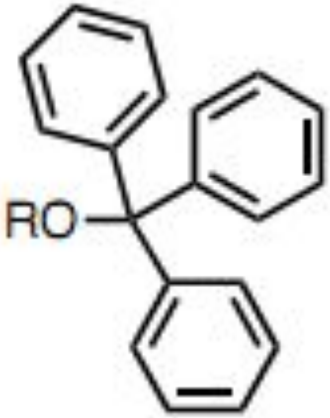

diisopropylethylamine-CH_2Cl_2, NaH-THF, or NaH-DMF.

Условия снятия защиты разные

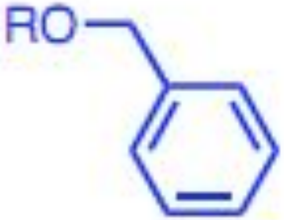


Эфирная защита спиртов

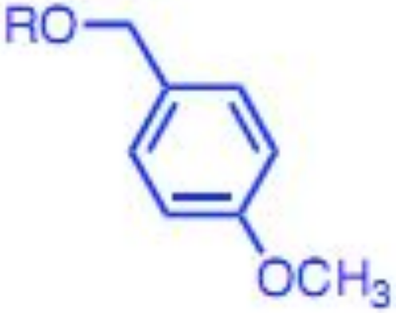
Allyl Ether



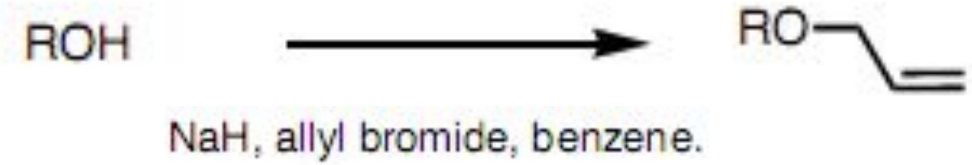
Trityl Ether

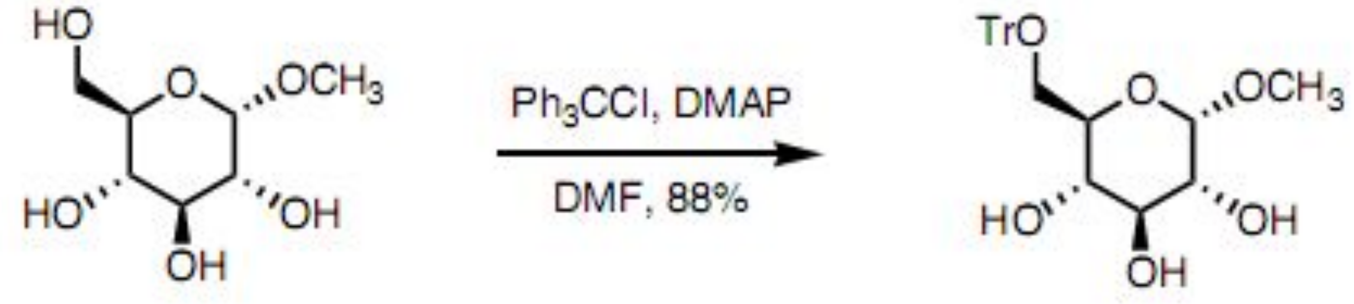


Benzyl Ether



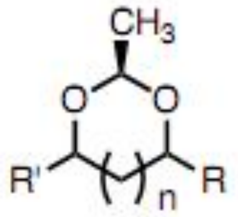
p-Methoxybenzyl Ether



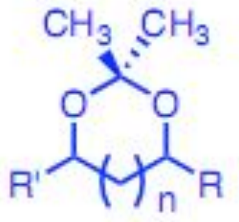


Снимают по-разному. В том числе в условиях реакции восстановления

Защита
1,2- и 1,3-диолов

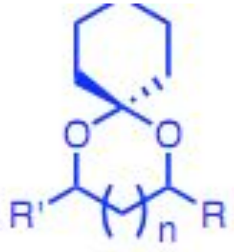


Ethylidene Acetal

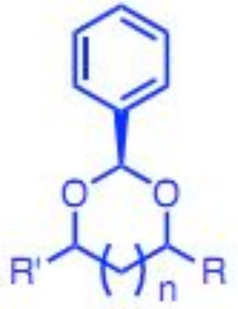


Acetonide

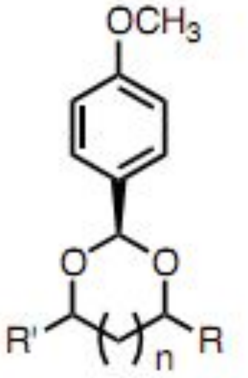
Cyclopentylidene Ketal



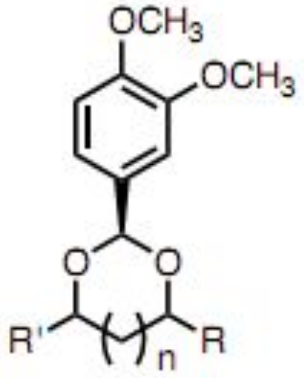
Cyclohexylidene Ketal



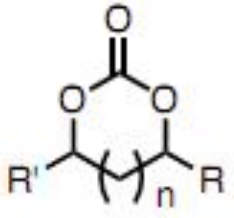
Benzylidene Acetal



4-Methoxybenzylidene Acetal



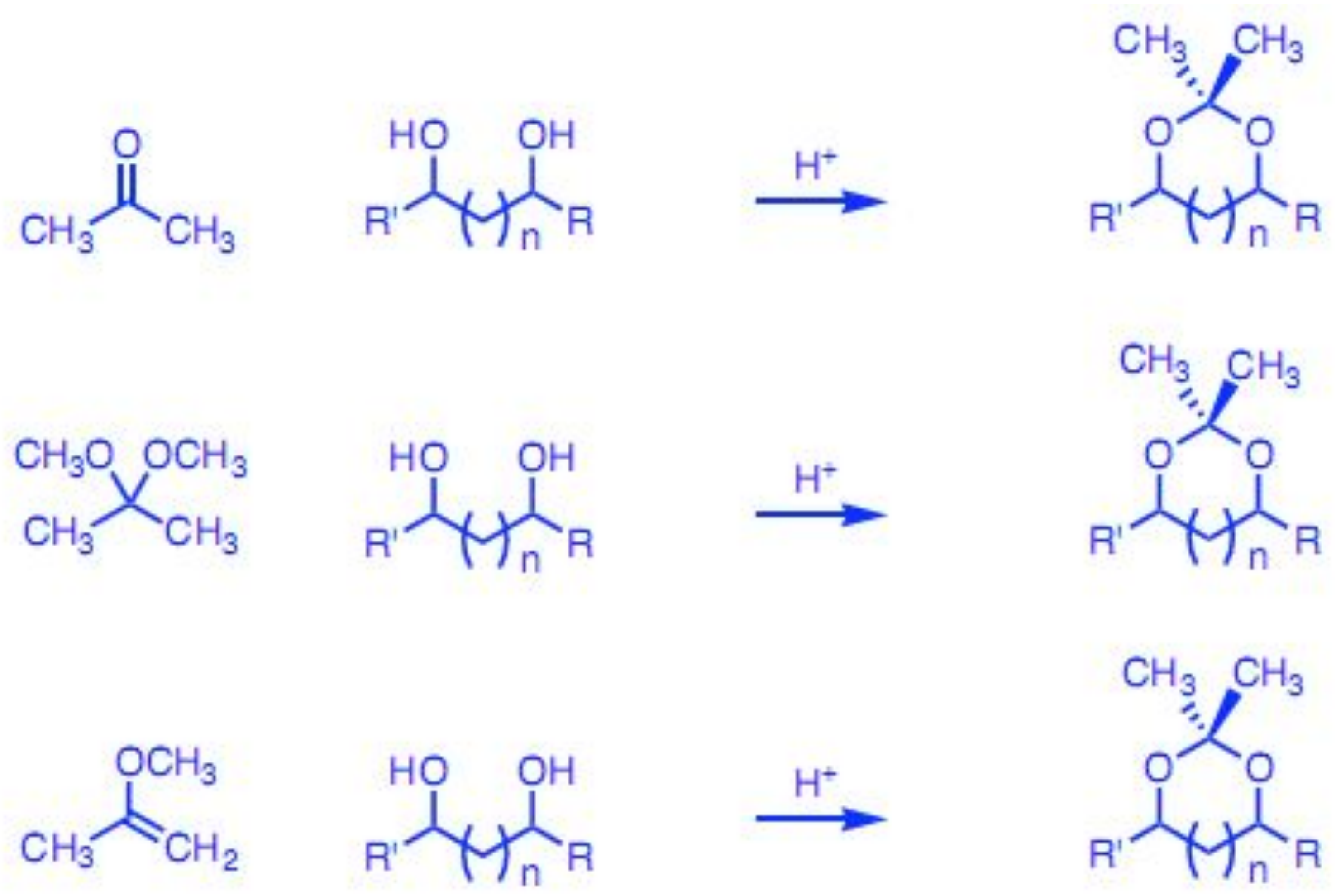
3,4-Dimethoxybenzylidene Acetal



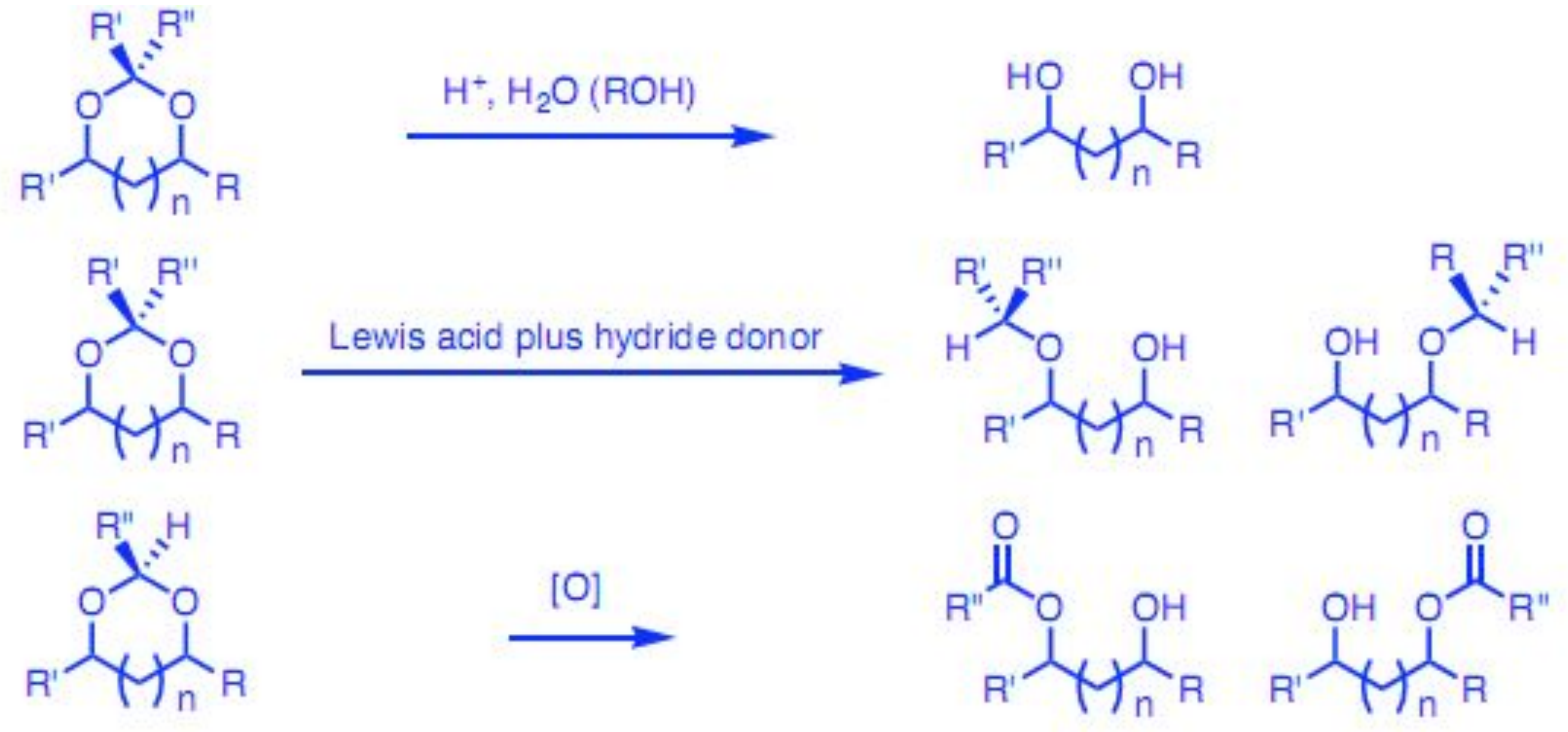
Cyclic Carbonate

- Generally, n = 0 or 1.

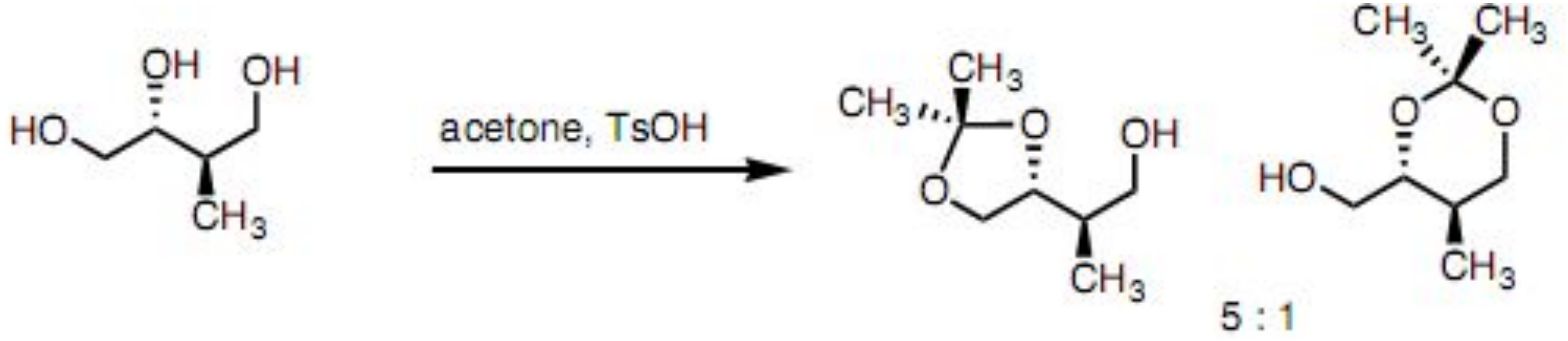
Основная методика

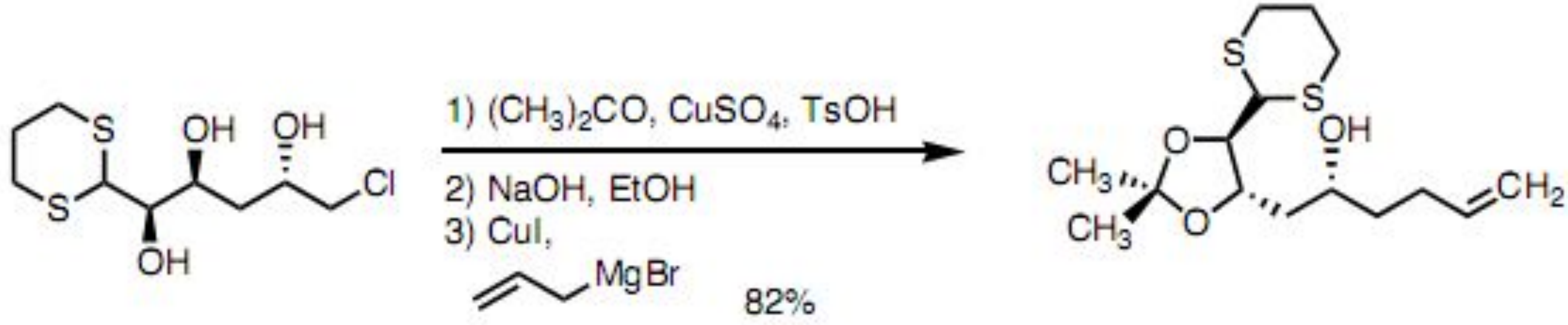


Основные методы снятия защиты

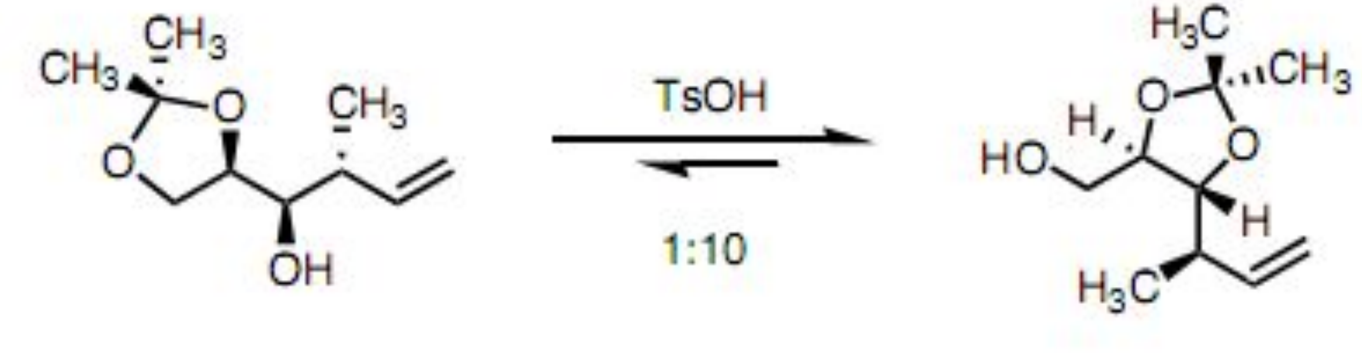


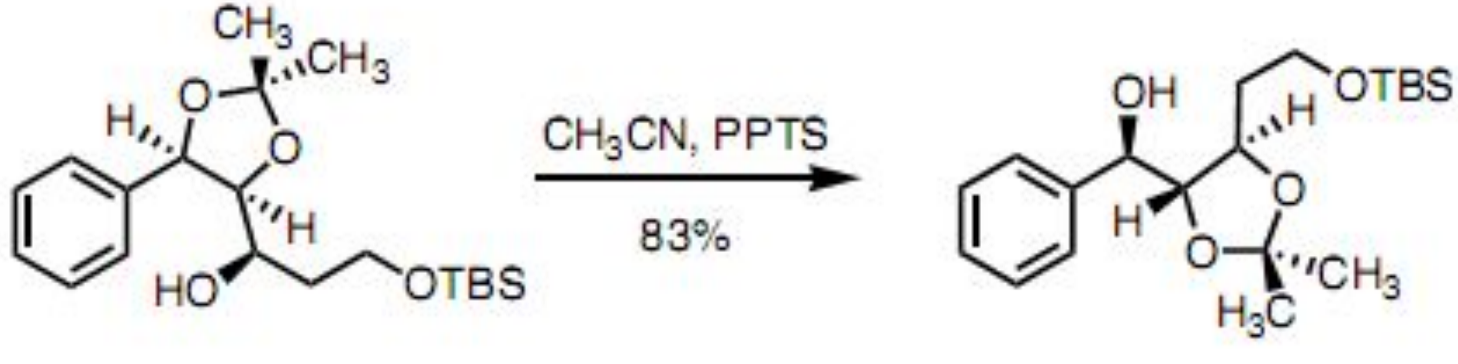
Примеры селективной защиты на полиолах

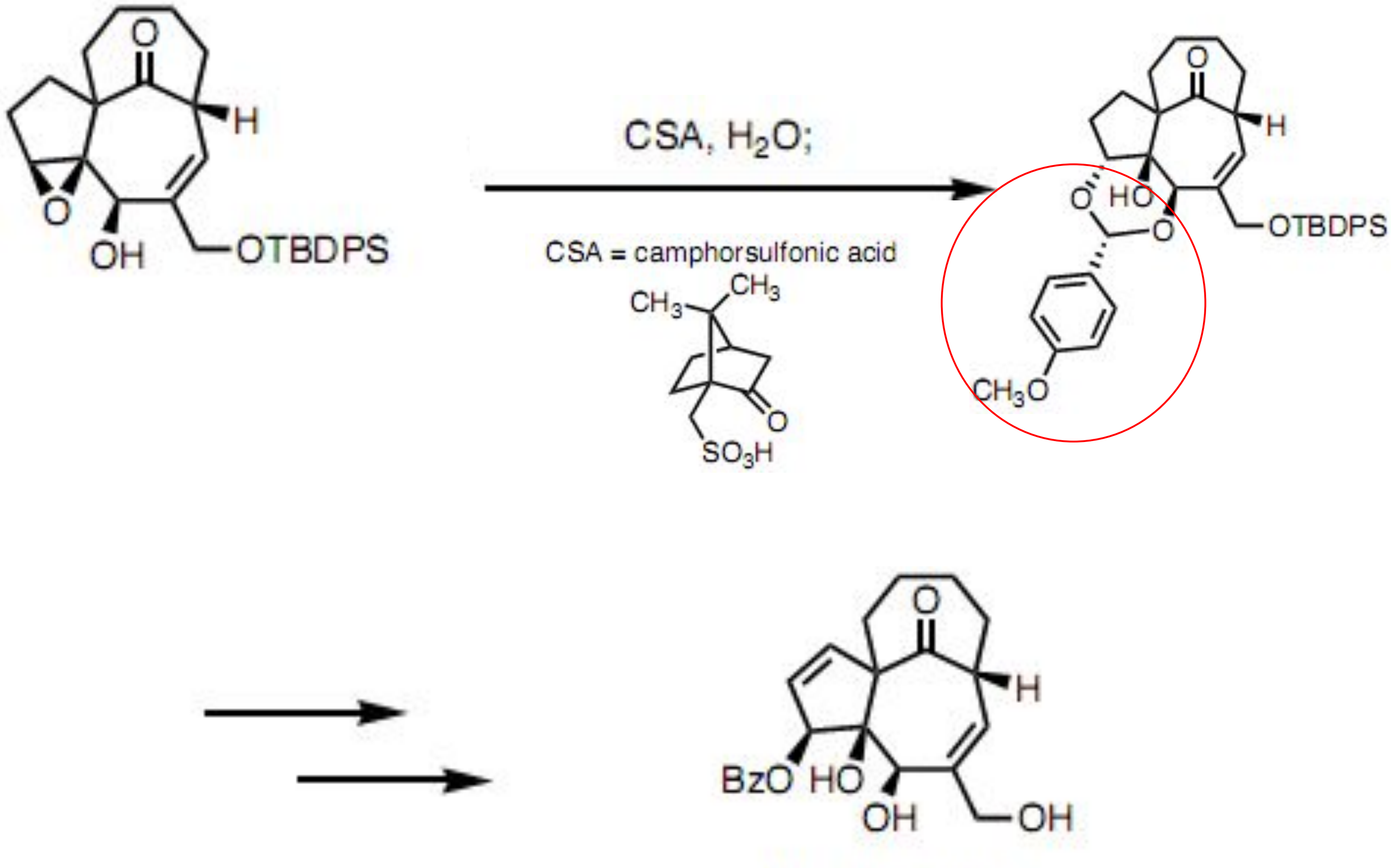




При подборе условий можно получить преимущественно цикл с участием транс OH-групп



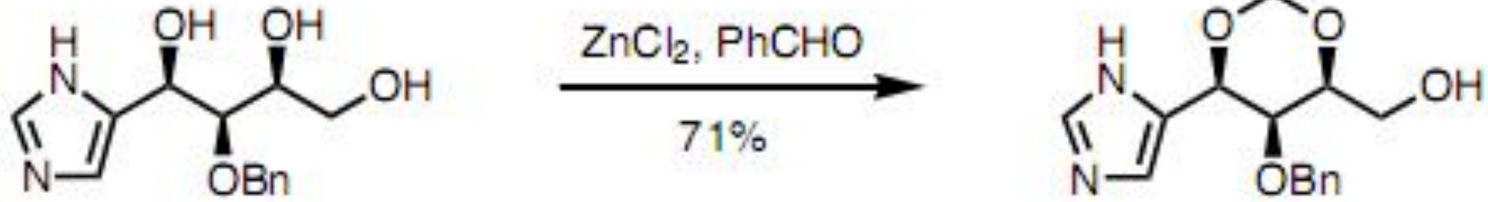


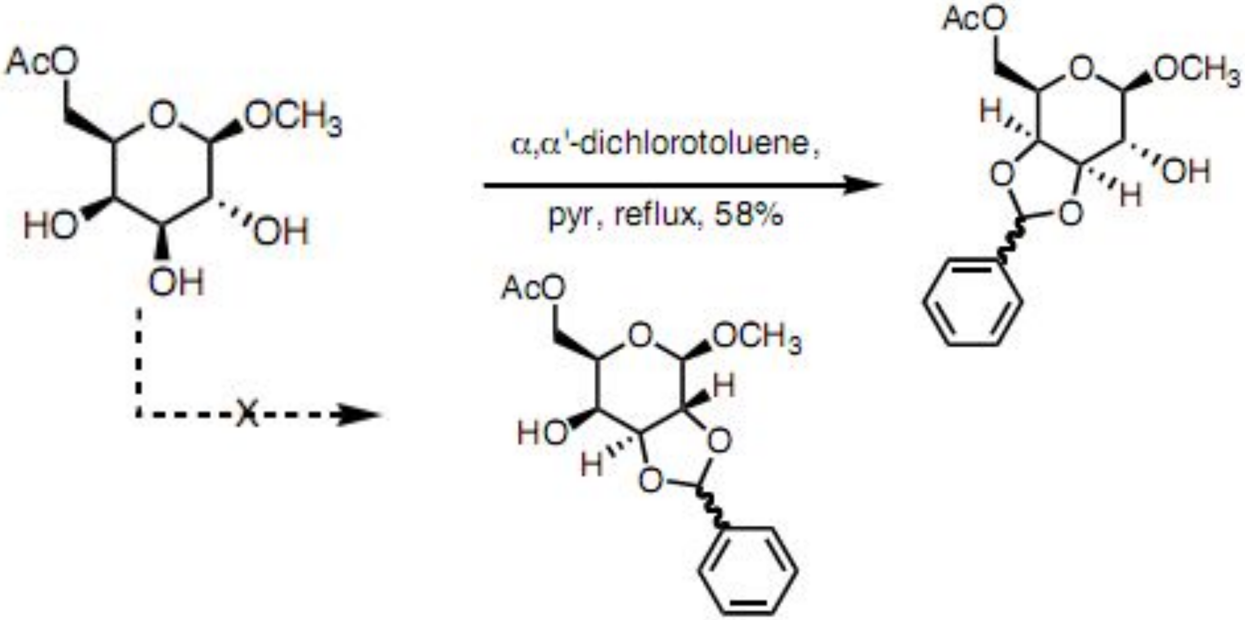


CSA, H_2O;

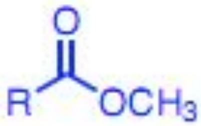
CSA = camphorsulfonic acid

Ingenol analog

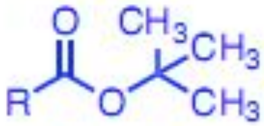

H
N
N
OH
OH
OH
OBn
ZnCl2, PhCHO
71%
H
N
N
O
O
OH
OBn


AcO
O
OCH3
HO
OH
OH
α,α'-dichlorotoluene,
pyr, reflux, 58%
AcO
O
OCH3
H
O
O
H
OH
X
AcO
O
OCH3
H
HO
H
O
O

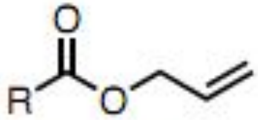
Защита
карбоксильной группы



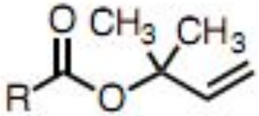
Methyl Ester



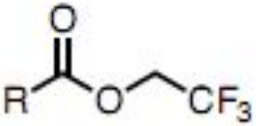
t-Butyl Ester



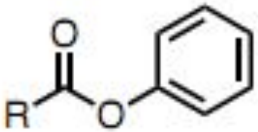
Allyl Ester



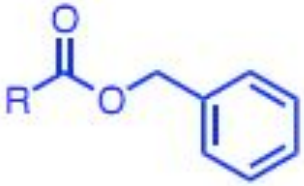
1,1-Dimethylallyl Ester



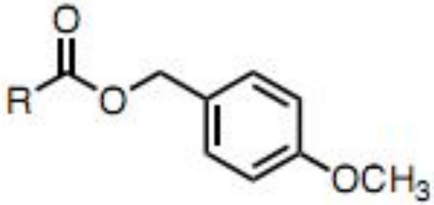
2,2,2-Trifluoroethyl Ester



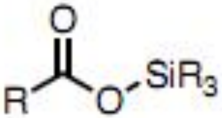
Phenyl Ester



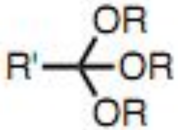
Benzyl Ester



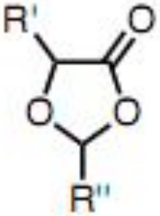
4-Methoxybenzyl Ester



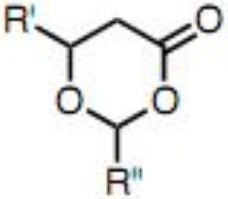
Silyl Ester



Ortho Ester



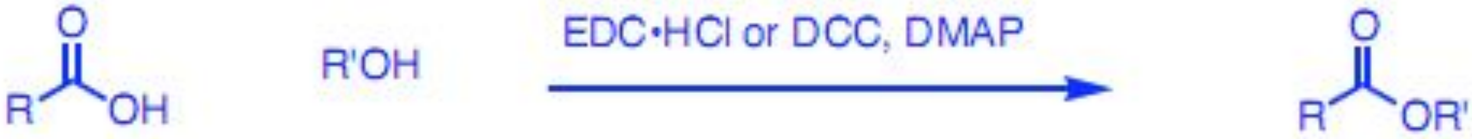
1,3-Dioxalone



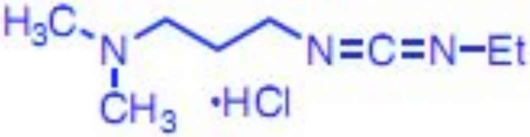
1,3-Dioxanone

Specific to a- and ß-hydroxy acids

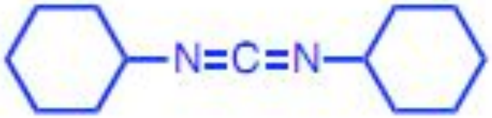
Основная процедура



EDC = 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride

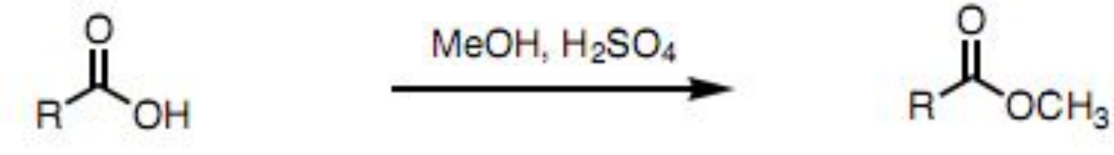


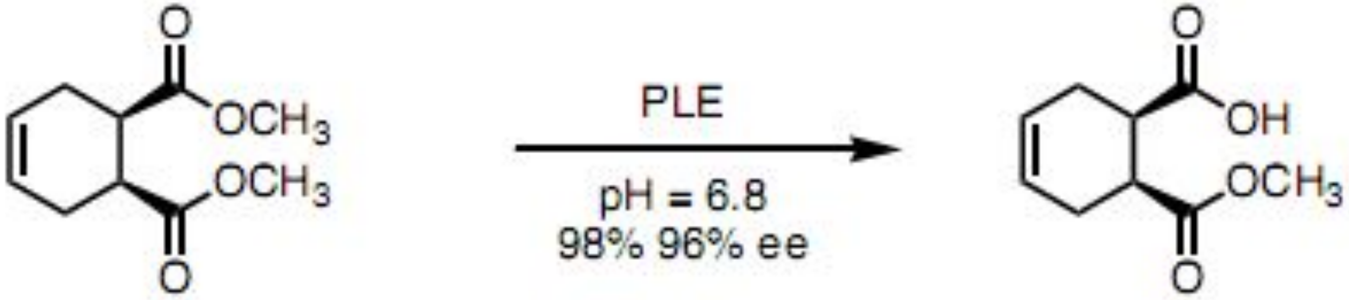
DCC = dicyclohexyldiimide



EDC •HCl is more expensive, but the urea by-product is water soluble and simplifies the purification of products.

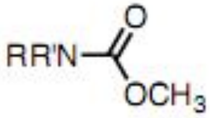
Расщепление сложных эфиров

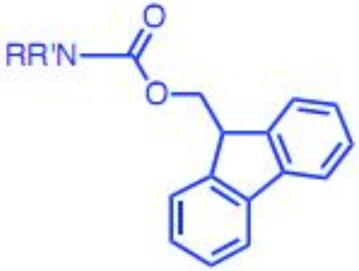




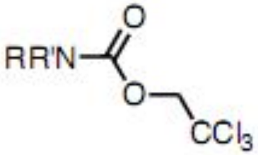
Эстераза печени свиньи

Защита аминогруппы

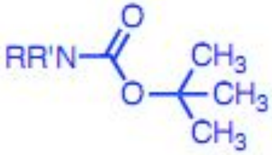

Methyl Carbamate


9-Fluorenylmethyl Carbamate

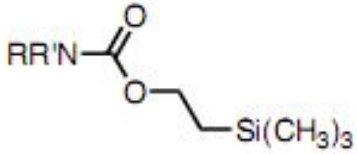
(Fmoc)


2,2,2-Trichloroethyl Carbamate

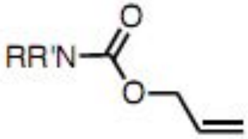
(Troc)


t-Butyl Carbamate

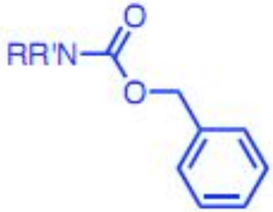
(Boc)


2-(Trimethylsilyl)ethyl Carbamate

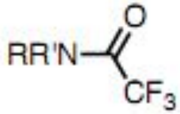
(Teoc)

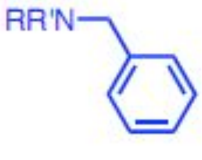

Allyl Carbamate

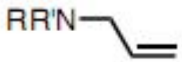
(Alloc)

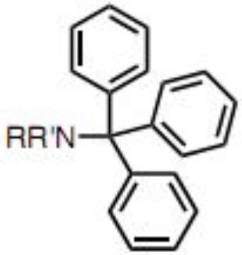

Benzyl carbamate

(Cbz)

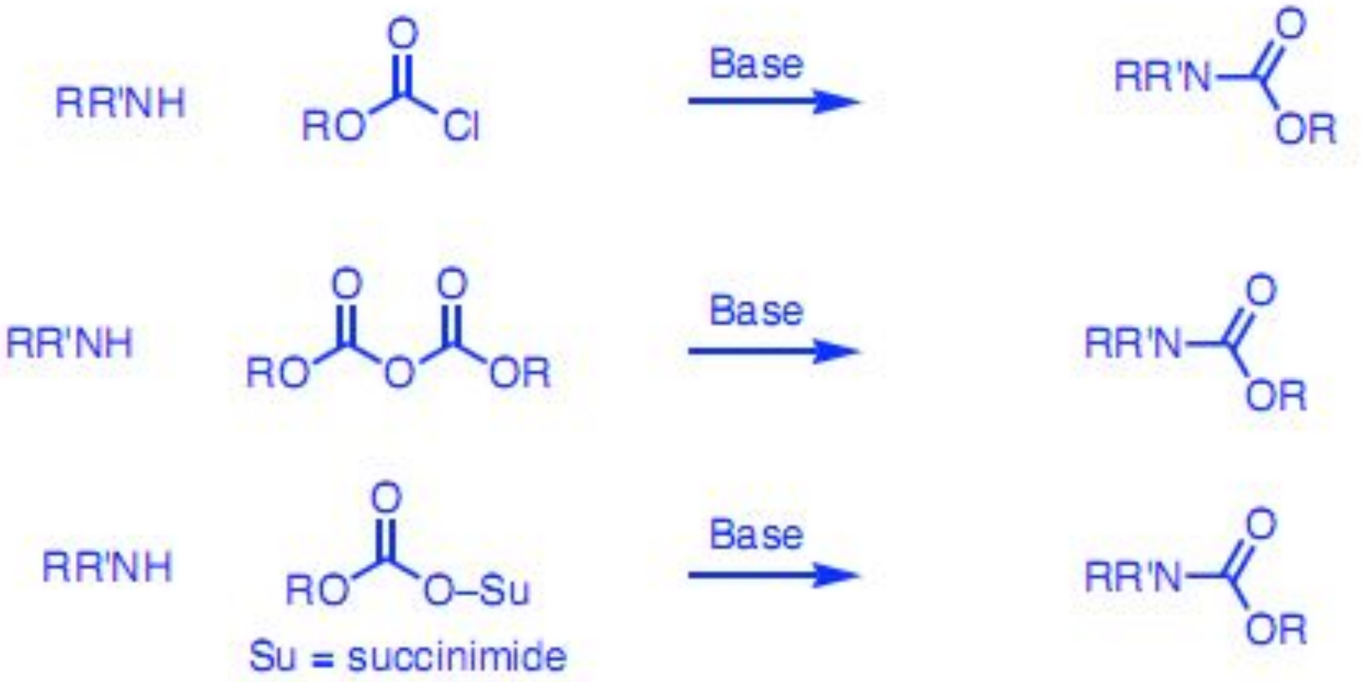

Trifluoroacetamide


Benzylamine


Allylamine


Tritylamine

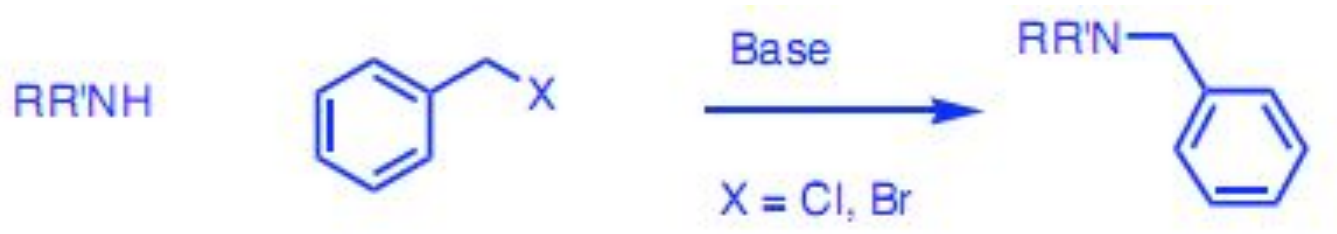
Основная процедура постановки защиты



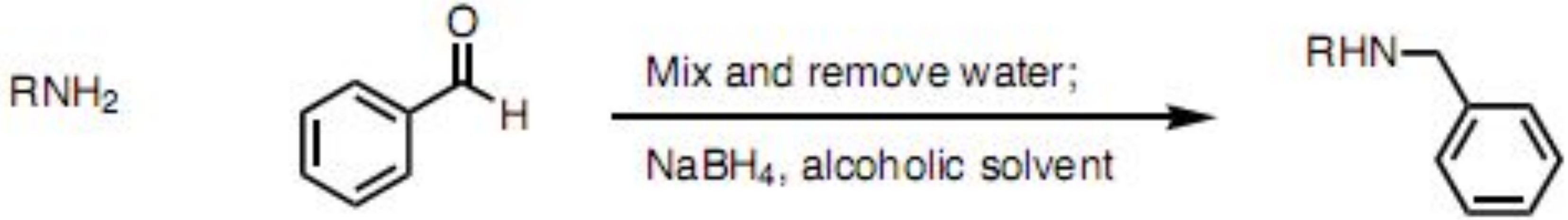
Su = succinimide

Bases that are typically employed are tertiary amines or aqueous hydroxide.

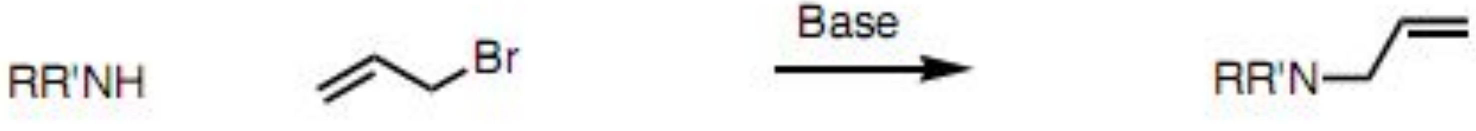
Получение бензиламинов



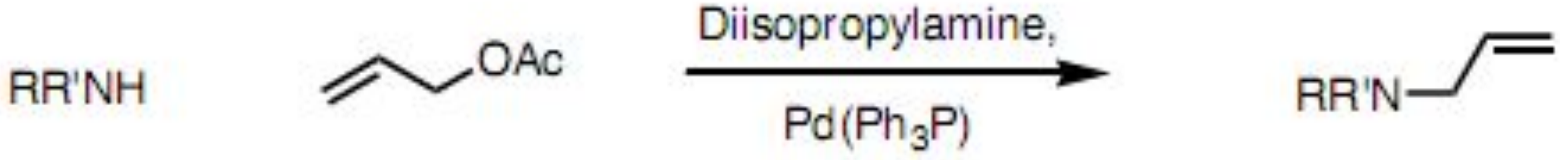
If primary amines are the starting materials, dibenzylamines are the products.



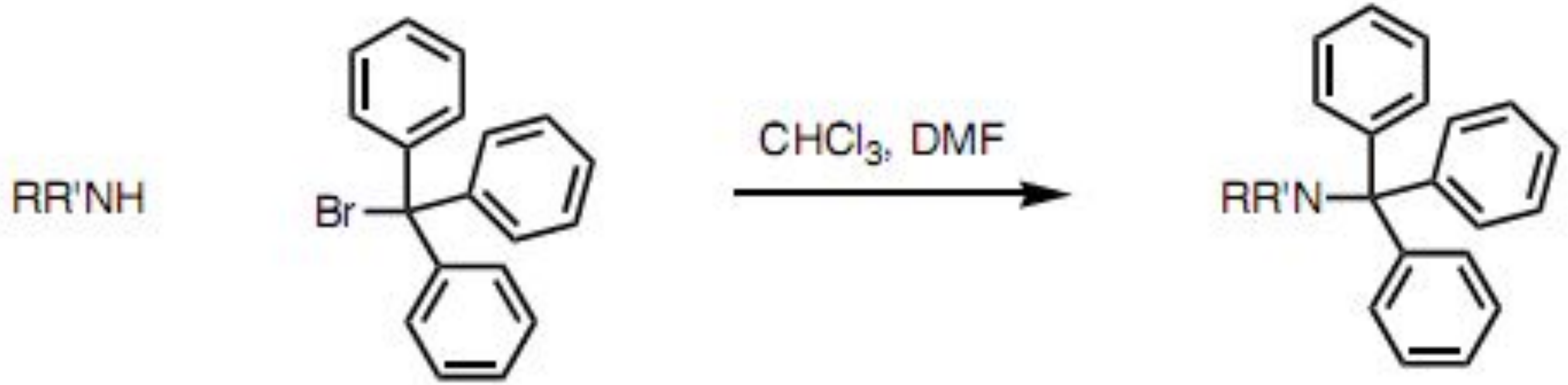
Получение аллиламинов



If primary amines are the starting materials, diallylamines are the products.



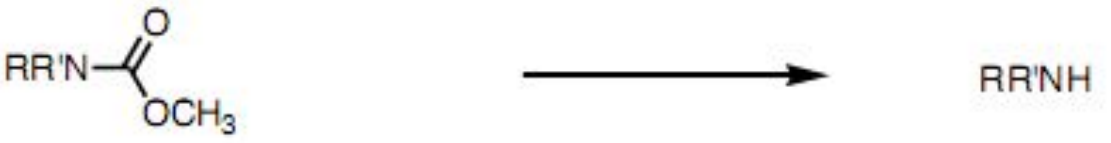
Получение тритиламинов



Mutter, M.; Hersperger, R. *Synthesis* **1989**, 198.

Расщепление карбаматов:

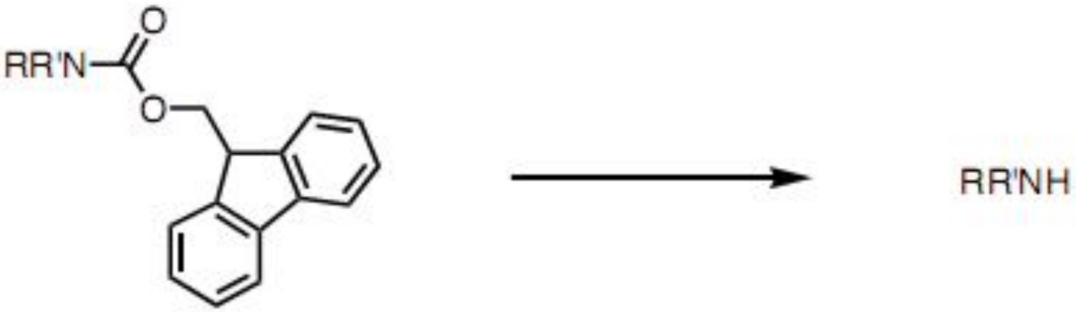
Methyl Carbamate:



1. TMSI, CH_2Cl_2. Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442.

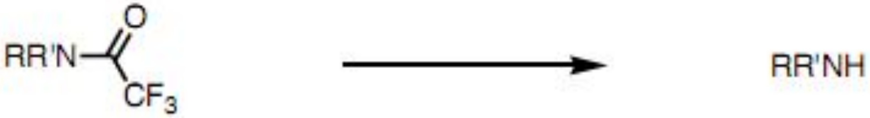
2. MeLi, THF. Tius, M.; Keer, M. A. *J. Am. Chem. Soc.* **1992**, *114* , 5959.

9-Fluorenylmethyl Carbamate:



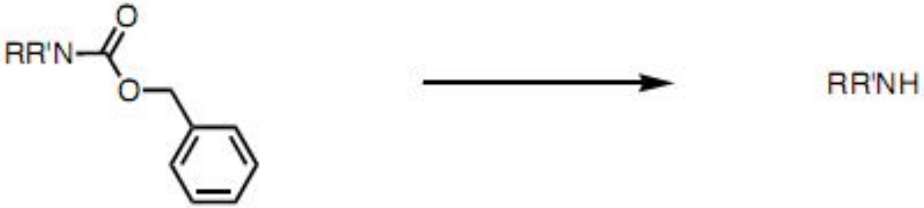
1. Amine base. The half-lives for the deprotection of Fmoc-ValOH have been studied Atherton, E.; Sheppard R. C. in *The Peptides*, Udenfriend, S. and Meienhefer Eds., Academic Press: New York, **1987**, Vol. 9, p. 1.

Trifluoroacetamide:



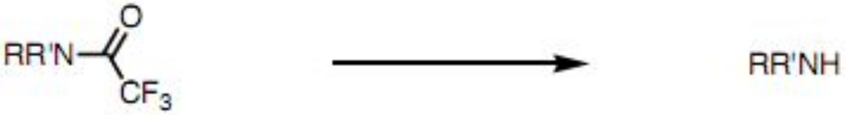
1. K_2CO_3, MeOH. Bergeron, R. J.; McManis, J. J. *J. Org. Chem.* **1988**, *53*, 3108.

Benzyl Carbamate:



1. H_2/Pd–C. Bergmann, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1192.
2. H_2/Pd–C, NH_3. These conditions cleave the benzyl carbamate in the presence of a benzyl ether. Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465.
3. BBr_3, CH_2Cl_2 Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427.

Trifluoroacetamide:



1. K_2CO_3, MeOH. Bergeron, R. J.; McManis, J. J. *J. Org. Chem.* **1988**, *53*, 3108.