

# **Organic synthesis**

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T. W. Greene, P. G. M. Wuts *Protective Groups in Organic Synthesis*

P. J. Kocienski *Protecting Groups*

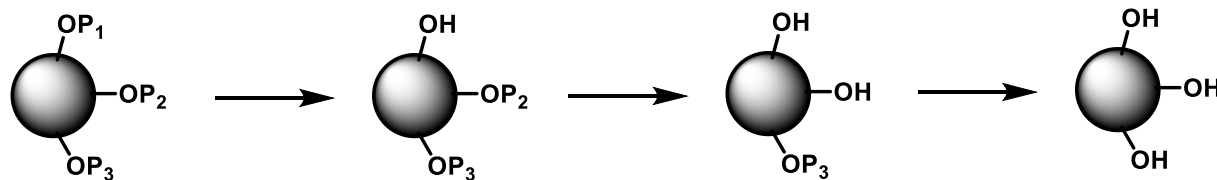
- the substrate contains reactive functional groups (typically OH, NH, CO, COOH ...)  
that are not compatible with reaction conditions

two additional steps in the synthetic sequence (installation & removal)

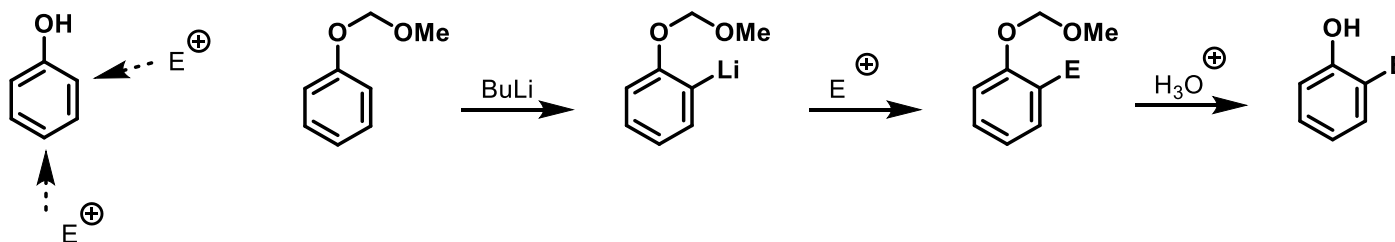


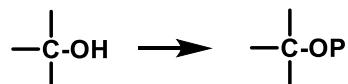
Young, I. S.; Baran, P. S. *Nature Chemistry* **2009**, 1, 193.  
„Protecting-group-free-synthesis as an opportunity for invention“

orthogonally protected substrates: several different Ps that can be selectively introduced and *removed*



- some Ps can be used to direct (regio)selectivity of particular transformations

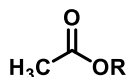




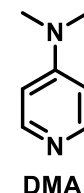
**esters:**

acetates

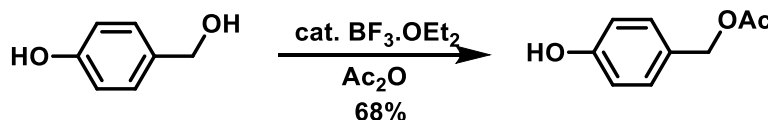
Ac-OR



formation: typically: acetylating agent ( $\text{Ac}_2\text{O}$ ,  $\text{AcCl}$ ) + base (pyridine, TEA, DMAP)

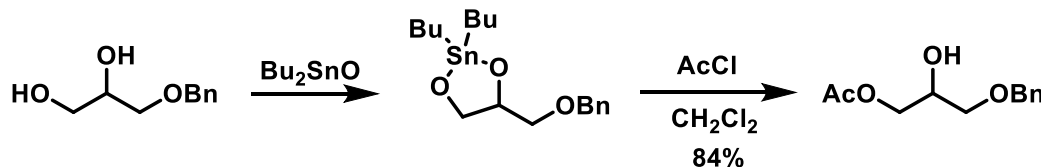


also:



*Chem. Pharm. Bull.* **1981**, 29, 3202.

• acetylation of more nucleophilic OH



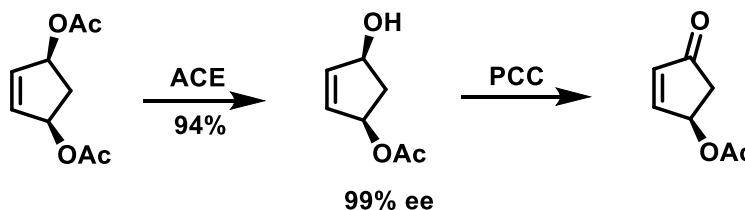
*Synthesis* **1989**, 225.

*Tetrahedron* **1985**, 41, 643.

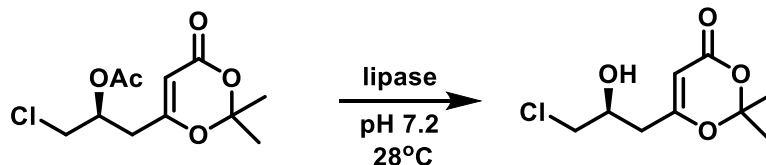
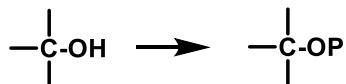
cleavage: basic hydrolysis ( $\text{K}_2\text{CO}_3$  in MeOH;  $\text{NH}_3$  in MeOH)

several OH groups in the molecule: acetate can migrate

some lipases can cleave acetates enantioselectively (under mild conditions)

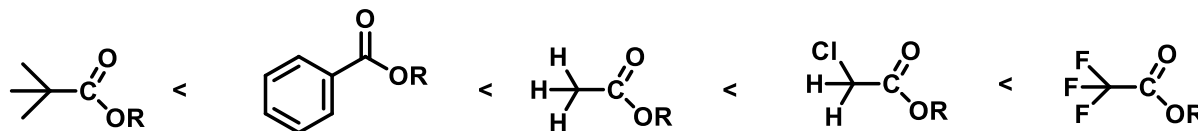


*Tetrahedron Lett.* **1986**, 27, 1255.



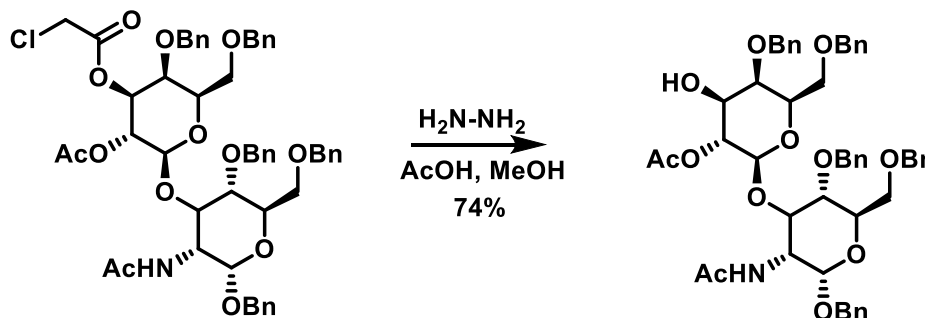
*Tetrahedron: Asymmetry* **1991**, 2, 343.

ease of basic hydrolysis:

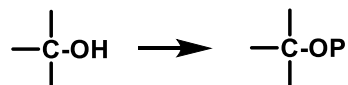


strong base (KOH/MeOH)

pH 7

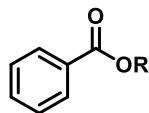


*Tetrahedron* **1992**, 48, 4713.



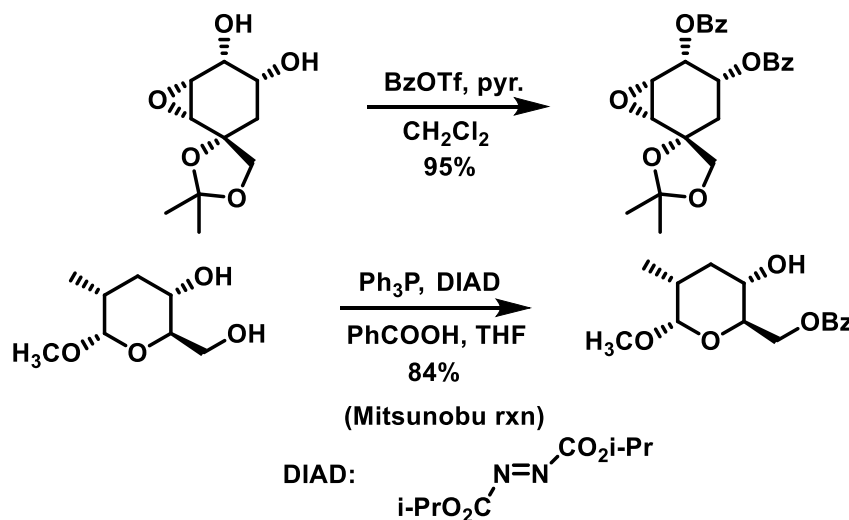
benzoates

Bz-OR



formation: Bz<sub>2</sub>O, BzCl + base ( pyridine, TEA)

- in polyhydroxylated systems typically much more selective than acetylation



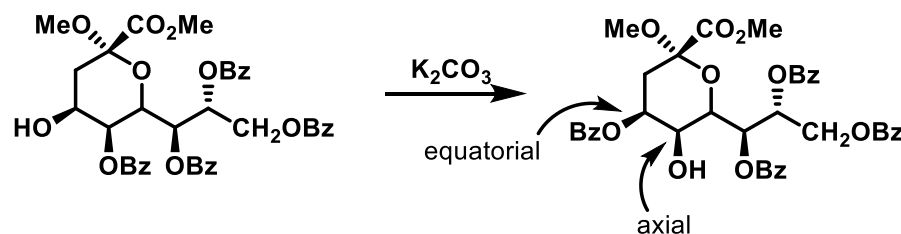
*J. Org. Chem.* **1984**, 49, 3875.

*Tetrahedron Lett.* **1989**, 30, 1037.

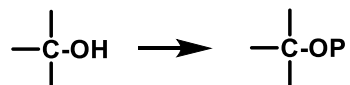
cleavage: basic hydrolysis (NaOH in MeOH; TEA in MeOH)

migration: typically to much lesser extent than with acetates

(but can be forced, if thermodynamically more stable isomer is formed)

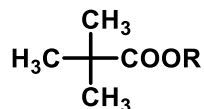


*J. Am. Chem. Soc.* **1988**, 110, 3929.



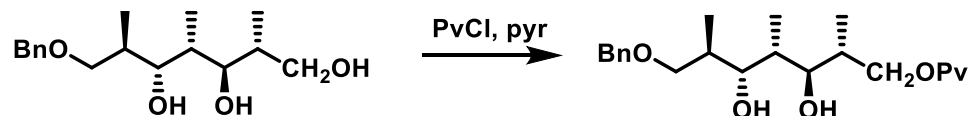
pivaloates

Pv-OR

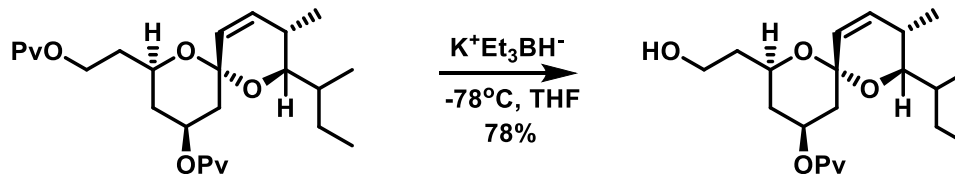


formation: PvCl + base (pyridine, TEA)

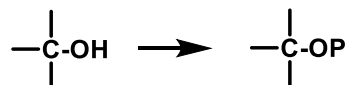
- primary OHs can be selectively acylated



cleavage: strong base (KOH in MeOH, hydrides)



*J. Am. Chem. Soc.* **1989**, 111, 2967.

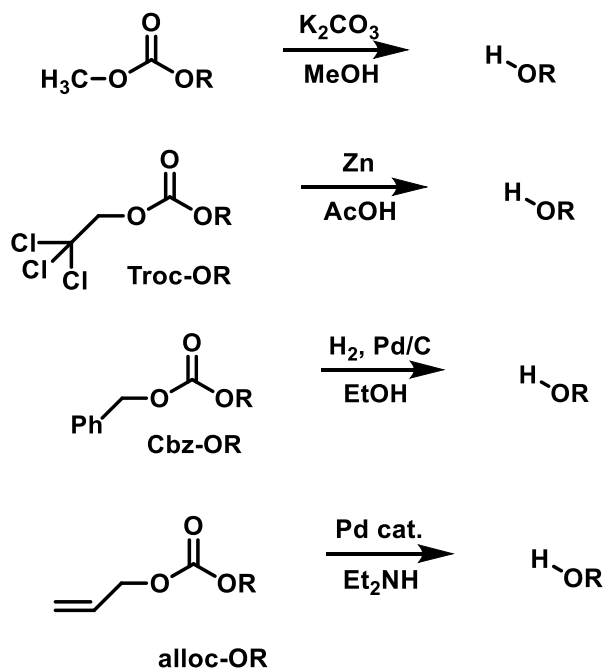


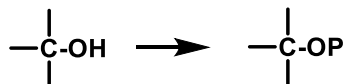
- more stable than esters towards basic hydrolysis

*formation:*  $\text{R}'\text{OCOCI} + \text{base}$  (pyridine, TEA)

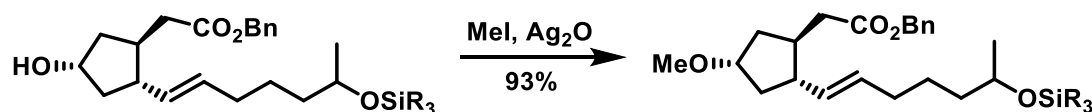
*cleavage:* in general, basic hydrolysis

but: conditions can be specific for different carbonates

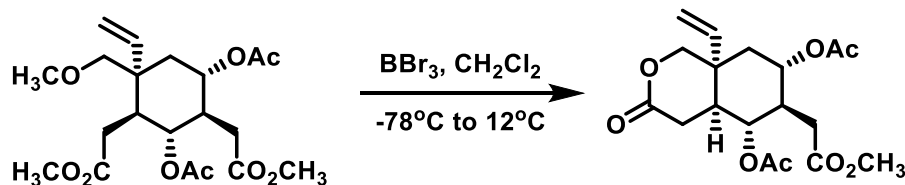
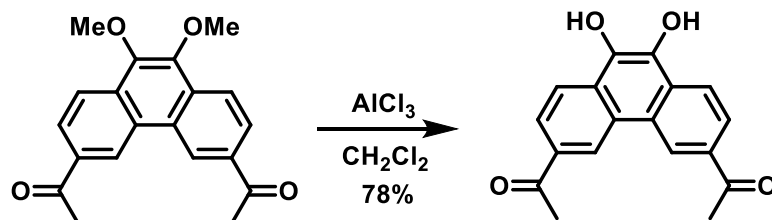




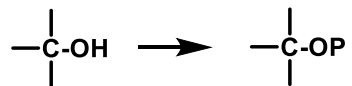
ethers:

methyl ether **Me-OR**  $\text{H}_3\text{C}-\text{O}-\text{R}$ formation: MeI,  $\text{Me}_2\text{SO}_4$  + base ( NaOH, NaH,  $\text{Ag}_2\text{O}$ );  $\text{CH}_2\text{N}_2$ *J. Am. Chem. Soc.* **1980**, 102, 7583.

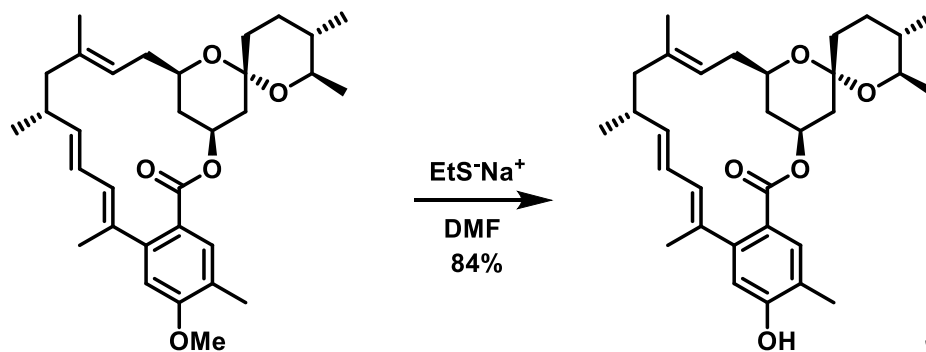
cleavage:

1. Lewis acids ( $\text{BBr}_3$ , TMSI,  $\text{AlCl}_3$ )*J. Am. Chem. Soc.* **1977**, 99, 5773.*J. Org. Chem.* **2000**, 65, 7602.

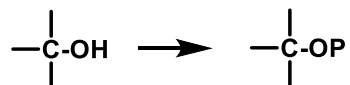




2. strong nucleophiles (phenolic methyl ethers)

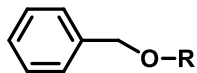


*J. Am. Chem. Soc.* **1986**, *108*, 2662.



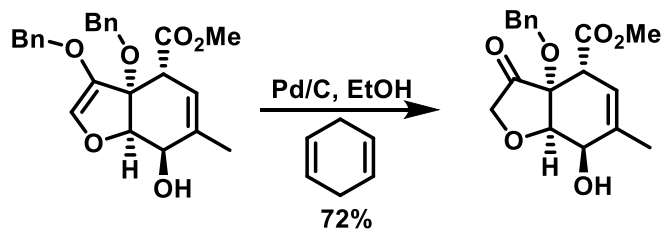
benzyl ether

Bn-OR

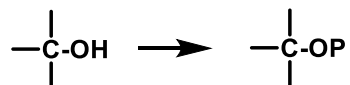


formation: BnBr + base ( NaH)

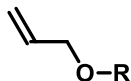
cleavage: hydrogenolysis (H<sub>2</sub>, Pd/C, EtOH)



*J. Am. Chem. Soc.* **1984**, *106*, 8327.

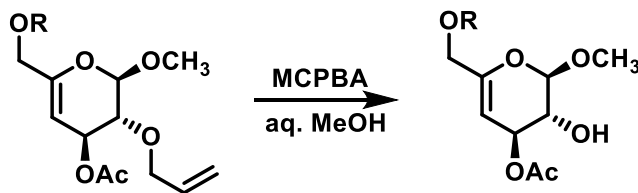


allyl ether



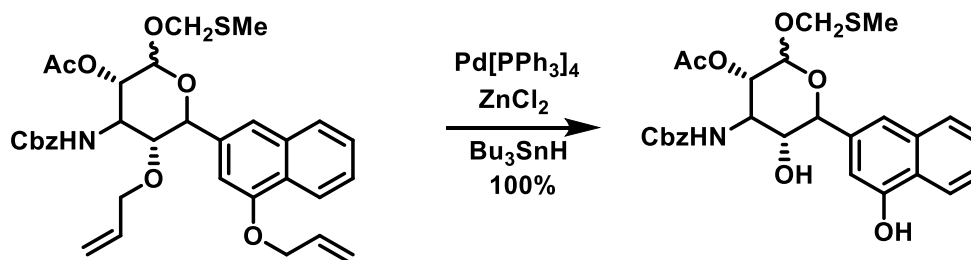
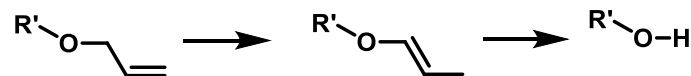
formation:  $\text{CH}_2=\text{CH}-\text{CH}_2\text{Br} + \text{base (NaH)}$

cleavage: 1. oxidative ( $\text{SeO}_2$ ,  $\text{H}_2\text{O}_2$ , MCPBA)

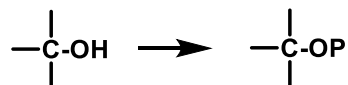


*Tetrahedron* **1990**, 46, 5365.

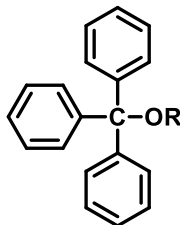
2. Pd-catalyzed



*J. Org. Chem.* **1992**, 57, 644.

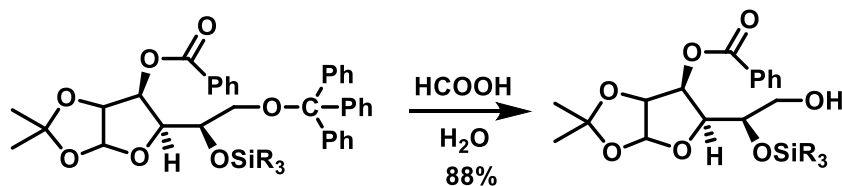


triphenylmethyl ether    trityl-OR, Tr-OR



formation:  $\text{Ph}_3\text{CCl} + \text{base}$  (DMAP, NaH)

cleavage: acidic conditions



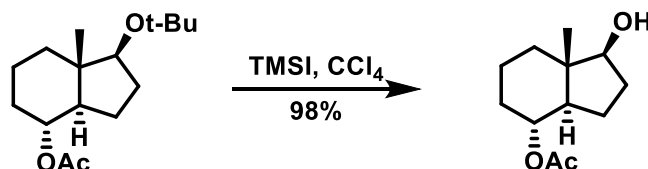
*Tetrahedron Lett.* **1986**, 27, 579.

*t*-butyl ether    *t*-Bu-OR   

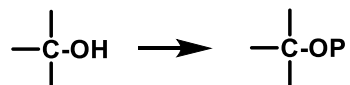
• protection of phenols

formation:  $t\text{-BuBr} + \text{pyr. or H}^+ +$

cleavage:  $\text{H}^+$ , Lewis acids



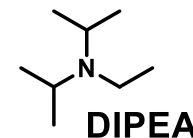
*J. Am. Chem. Soc.* **1982**, 104, 2945.



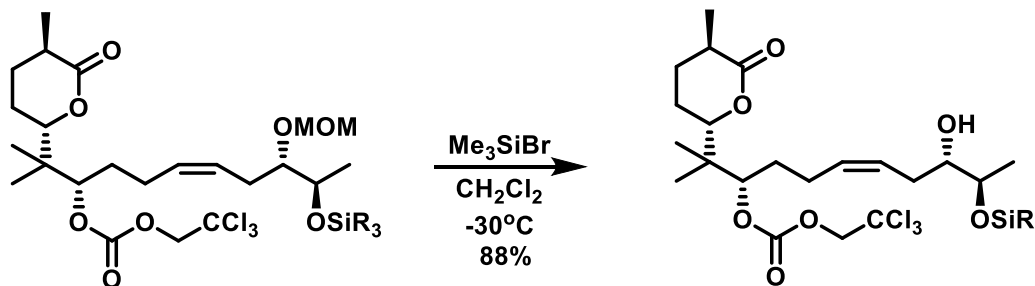
## acetals

methoxymethyl ether **MOM-OR**  $\text{H}_3\text{C}-\text{O}-\text{CH}_2-\text{O}-\text{R}$

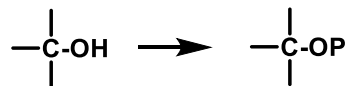
formation:  $\text{MeOCH}_2\text{Cl} + \text{base (DIPEA, NaH)}$



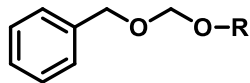
cleavage: acidic conditions ( $\text{HCl/MeOH}$ ,  $\text{TMSBr}$ ,  $\text{BF}_3 \cdot \text{OEt}_2$ )



*Tetrahedron Lett.* **1984**, 25, 2515.

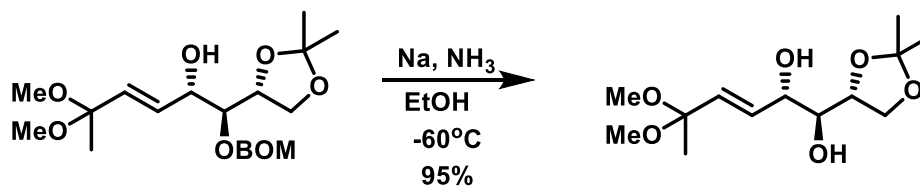


benzyloxymethyl ether BOM-OR

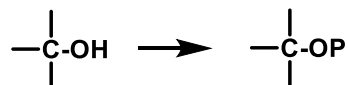


formation:  $\text{BnOCH}_2\text{Cl}$  + base (DIPEA)

cleavage: hydrogenolysis ( $\text{H}_2/\text{Pd/C}$ );  $\text{Na}/\text{NH}_3$

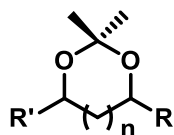


*J. Am. Chem. Soc.* **1987**, 109, 3981.

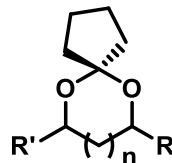
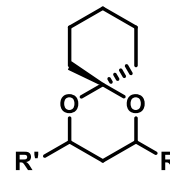
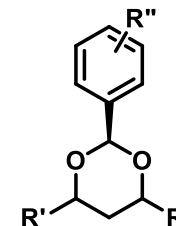
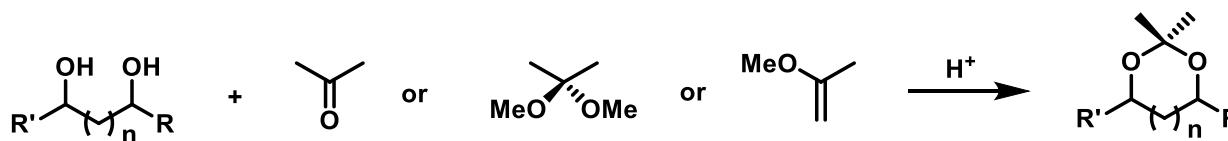


1,2- a 1,3 diols

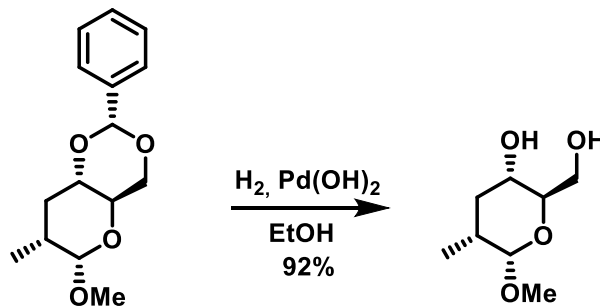
acetals



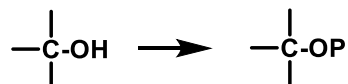
acetonides

cyclopentylidene  
ketalscyclohexylidene  
ketalsbenzylidene  
acetalsformation:  $\text{H}^+$ 

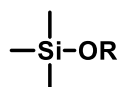
polyols: acetonides: typically 1,2-  
benzylidene acetals: typically 1,3-

cleavage:  $\text{H}^+$ ,  $\text{H}_2\text{O}$ Lewis acids + hydride donor ( $\text{Et}_3\text{SiH}$ )reduction ( $\text{H}_2$ , Pd/C) of benzylidene acetals

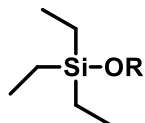
Tetrahedron Lett. 1989, 30, 1037.



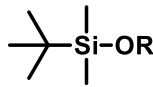
## silyl ethers



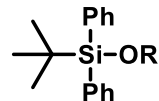
TMS-OR



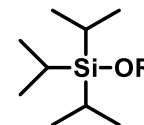
TES-OR



TBS-OR



TBDPS-OR



TIPS-OR

formation:  $\text{R}_3\text{SiCl}$  or  $\text{R}_3\text{SiOTf}$  + base (imidazole; DIPEA; 2,6-dimethylpyridine)

cleavage:  $\text{H}^+$

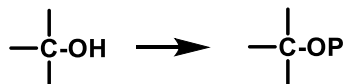
$\text{K}_2\text{CO}_3/\text{MeOH}$  (TMSOR)

source of  $\text{F}^-$  ( $\text{BuN}^+\text{F}^-$ ,  $\text{HF.pyr}$ ,  $\text{HF.Et}_3\text{N}$ )

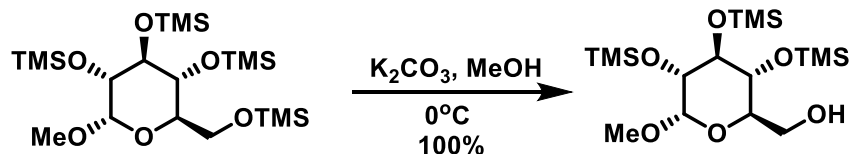
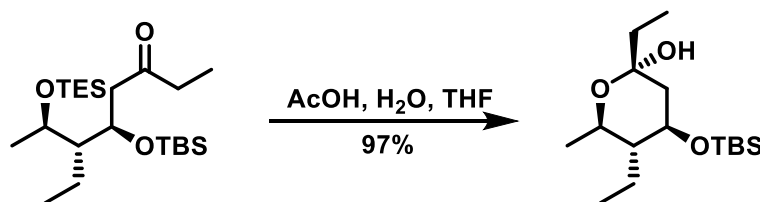
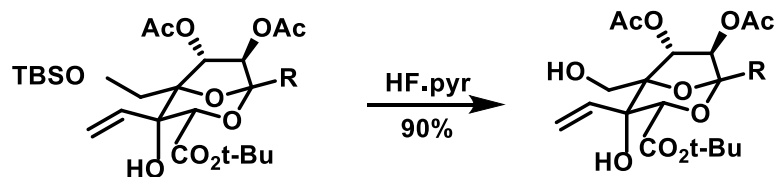
• **selective cleavage under mild (neutral) conditions**

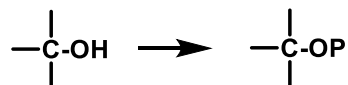
silyl ether	half life NaOH/MeOH	half life HCl/MeOH
$\text{C}_6\text{H}_{13}\text{OTMS}$	< 1 min	< 1 min
$\text{C}_6\text{H}_{13}\text{OTBS}$	> 24 h	< 1 min
$\text{C}_6\text{H}_{13}\text{OTIPS}$	> 24 h	55 min
$\text{C}_6\text{H}_{13}\text{OTBDPS}$	> 24 h	225 min



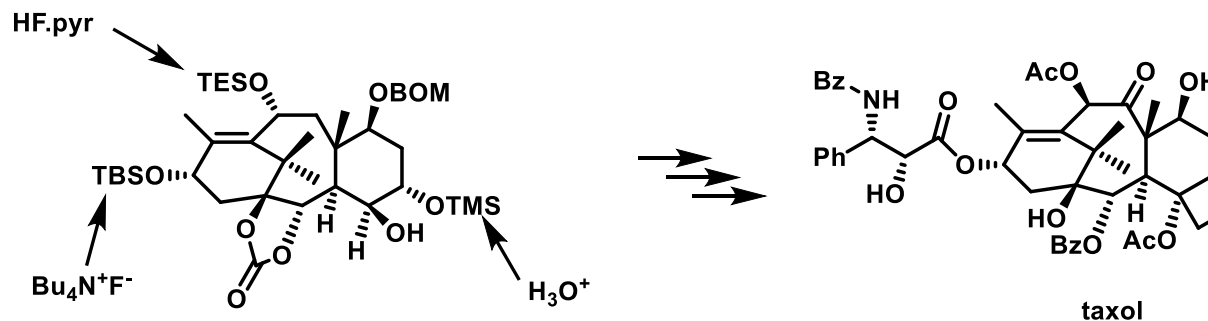


selective cleavage of silyl ethers

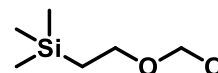
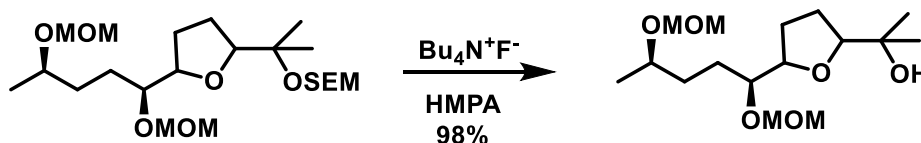
*Can. J. Chem.* **1965**, 43, 2004.*Liebigs Ann. Chem.* **1986**, 1281.*J. Am. Chem. Soc.* **1976**, 32, 2157.

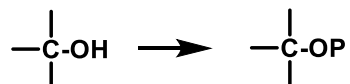


sequential removal of silyl ethers

*J. Am. Chem. Soc.* **1994**, 116, 1599.

2-(trimethylsilyl)ethoxymethyl ether SEM-OR

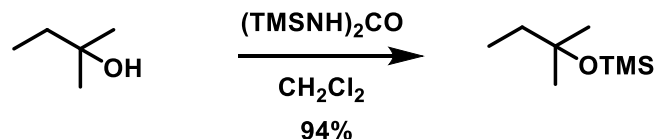
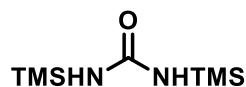
formation:  $\text{TMSCH}_2\text{CH}_2\text{OCH}_2\text{Cl}$  + base (DIPEA)cleavage: 1. acidic conditions  
2. fluoride*Tetrahedron Lett.* **1988**, 29, 5417.



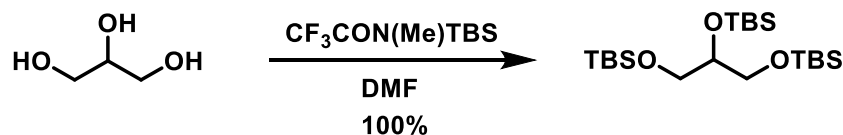
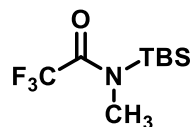
Si-F : 582 kJ/mol (Si-O : 452 kJ/mol C-H : 411 kJ/mol C-C : 346 kJ/mol)

Si-N : 355 kJ/mol

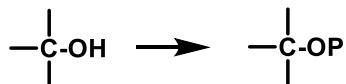
- silylated amines are significantly less stable than silylated alcohols
- N-silylated compounds can be used for transfer of the silyl group



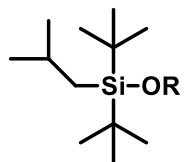
*Synthesis* **1981**, 807.



*J. Org. Chem.* **1982**, 57, 3336.



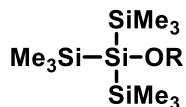
- **silyl esters:** significantly more labile compared to silyl *ethers*
- modern and non-traditional Si-based protecting groups**



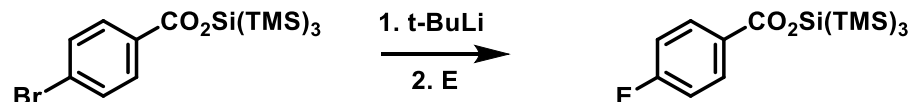
BIBSOR

- very resistant to bases/nucleophiles
- BIBS esters are quite stable

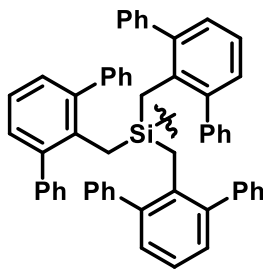
*Org. Lett.* **2011**, 13, 4120.

(TMS)<sub>3</sub>SiOR

- „supersilyl“
- esters are quite stable



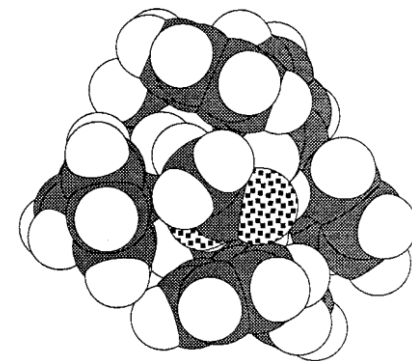
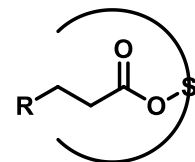
*Angew. Chem. Int. Ed.* **2013**, 52, 8165.



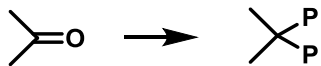
TDS

tris(2,6-diphenylbenzyl)silyl

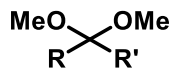
- esters resistant to LiAlH<sub>4</sub>, RLi etc.



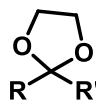
*J. Am. Chem. Soc.* **2000**, 122, 10238.



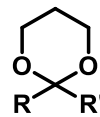
## acetals/ketals



dimethyl acetal



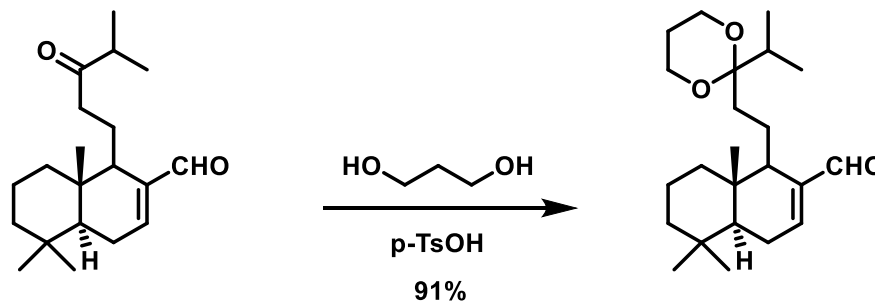
1,3-dioxolane



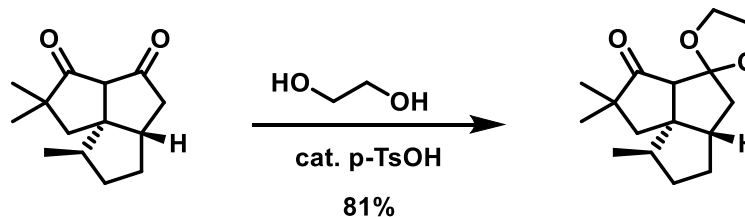
1,3-dioxane

formation:  $H^+$  + alcohol  
 $HC(OMe)_3$  + (Lewis) acid

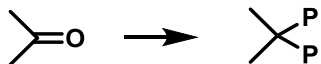
- aldehydes typically more reactive than ketones



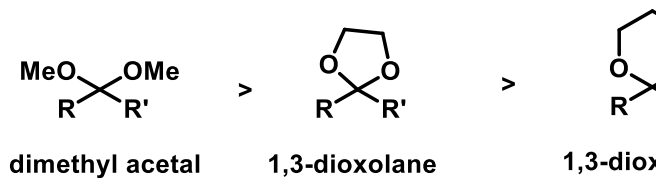
*Tetrahedron Lett.* **1982**, 23, 1087.



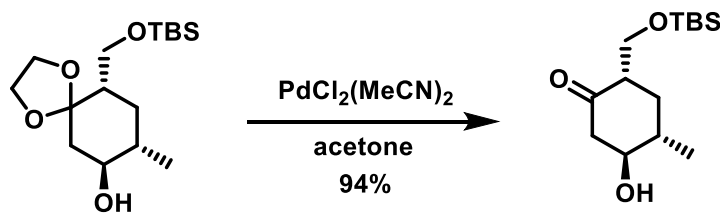
*J. Am. Chem. Soc.* **1986**, 108, 800.



cleavage:  $\text{H}^+$ ,  $\text{H}_2\text{O}$

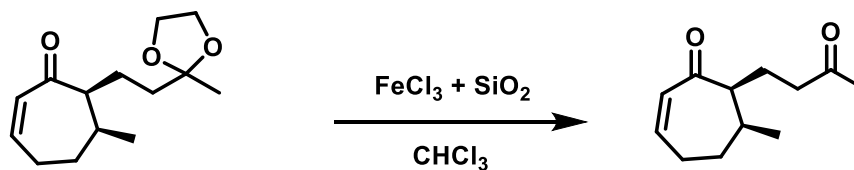


cat.  $\text{PdCl}_2(\text{MeCN})_2$  + acetone

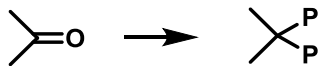


*Tetrahedron Lett.* **1987**, 28, 5755.

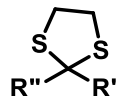
$\text{FeCl}_3 + \text{SiO}_2$



*Tetrahedron Lett.* **1987**, 28, 2489.

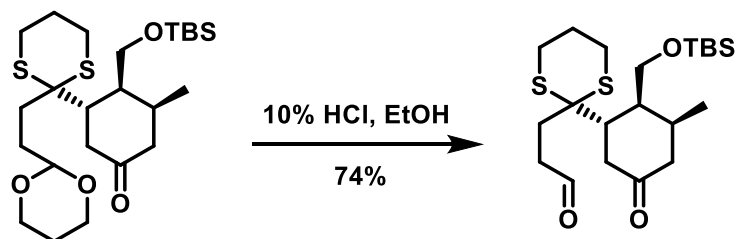


## cyclic dithioacetals/ketals



formation:  $\text{HS}(\text{CH}_2)_n\text{SH} + (\text{Lewis}) \text{ acid}$

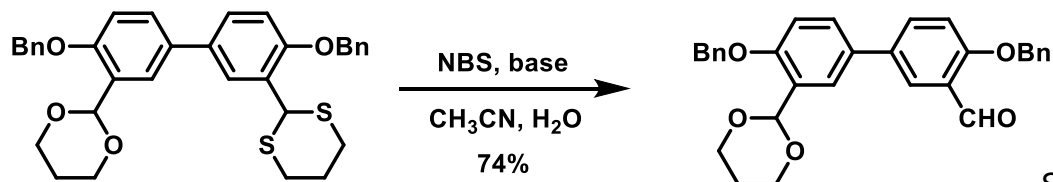
- dithioacetals are significantly less sensitive to acids than acetals



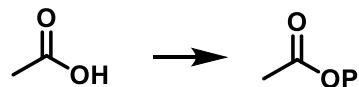
*J. Org. Chem.* **1985**, 50, 1190.

cleavage: conversion to a better leaving group (and then hydrolysis)

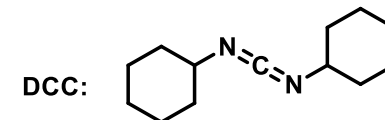
- coordination of S with metals:  $\text{Hg}(\text{ClO}_4)_2$ ,  $\text{CuCl}_2$ ,  $\text{CuO}$
- oxidation: MCPBA,  $\text{Ac}_2\text{O}$ , TEA
- alkylation: MeI



*Synthesis* **1992**, 1025.



## esters



cleavage: methyl esters: basic hydrolysis (LiOH, MeOH), nucleophilic cleavage (LiI, NaCl)

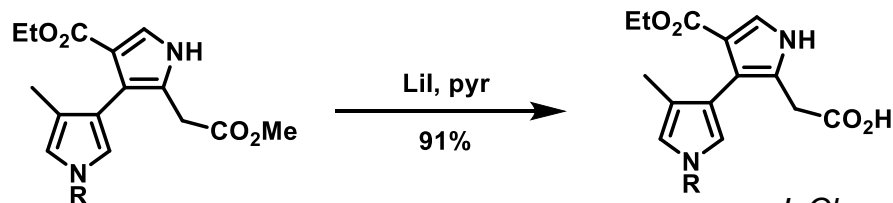
t-butyl esters: acidic hydrolysis (CF<sub>3</sub>COOH)

allyl esters: Pd-catalyzed cleavage (Pd(PPh<sub>3</sub>)<sub>4</sub>)

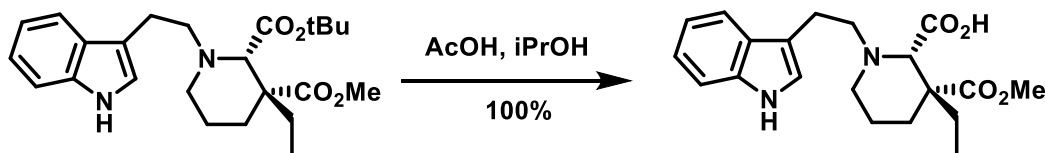
benzyl esters: hydrogenolysis (H<sub>2</sub>, Pd/C)

silyl esters: fluoride, acidic & basic hydrolysis

(less stable than silyl ethers)

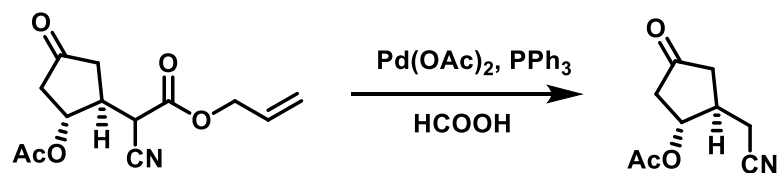
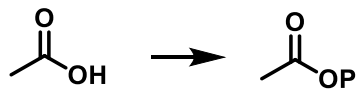


*J. Chem. Soc., Chem. Commun.* **1984**, 389.

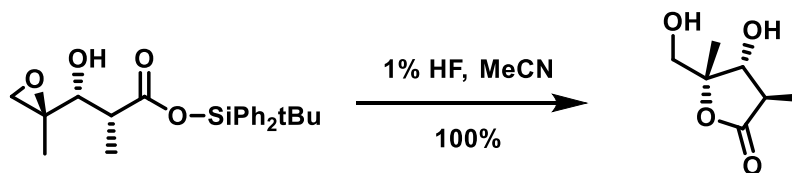


*J. Org. Chem.* **1990**, 55, 3068.

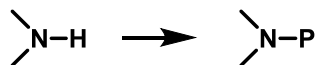




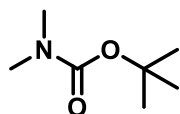
*Tetrahedron Lett.* **1991**, 32, 2409.



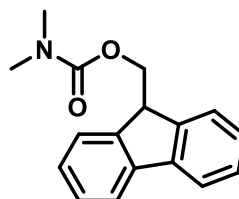
*Tetrahedron Lett.* **1982**, 23, 4199.



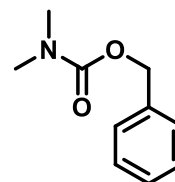
## carbamates



**Boc**



**Fmoc**



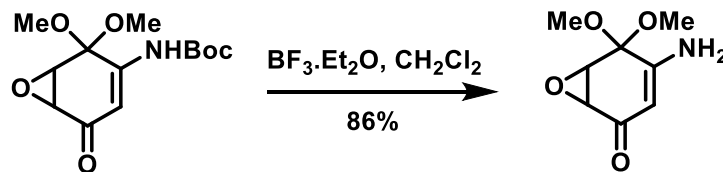
**Cbz**

*formation:*  $\text{ROCOCl}$  or  $(\text{ROCO})_2\text{O}$  + base

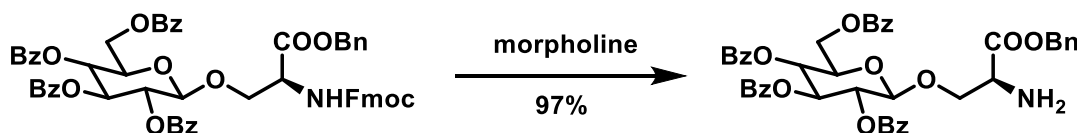
*cleavage:* Boc:  $\text{CF}_3\text{COOH}$  (+ PhOMe); Lewis acids

Fmoc: amine (piperidine, morpholine)

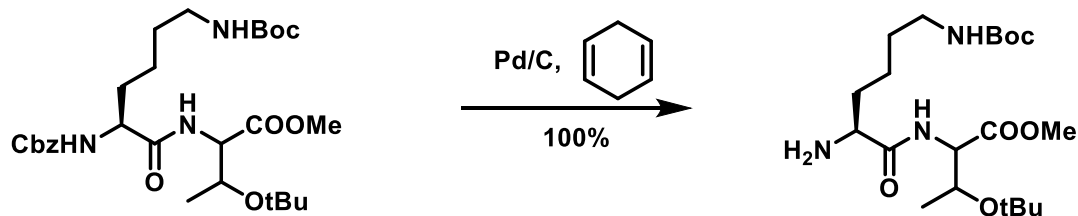
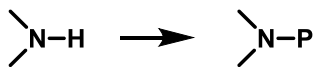
Cbz:  $\text{H}_2$ , Pd/C



*Synth. Commun.* **1997**, 27, 1819.

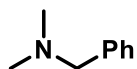


*Angew. Chem. Int. Ed.* **1983**, 22, 62.

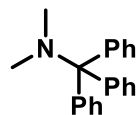


*The Practice of Peptide Synthesis* **1984**, 158.

## alkylated amines



**Bn**

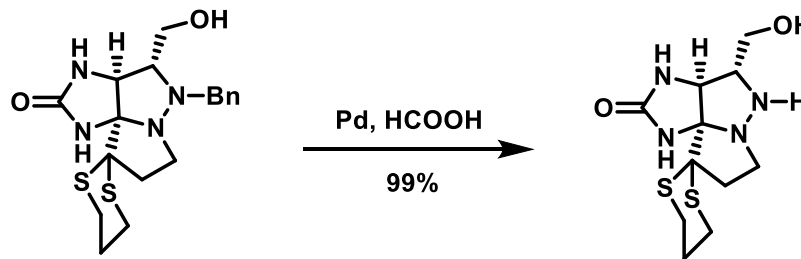


**Tr**

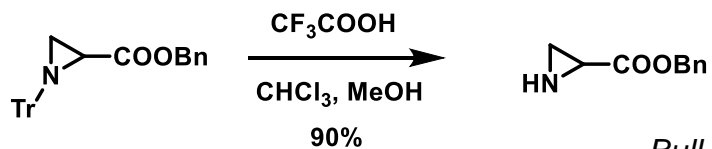
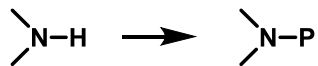
*formation:* BnBr or TrCl + base (NaH)

*cleavage:* Bn: hydrogenolysis

Tr: hydrogenolysis, CF<sub>3</sub>COOH



*J. Am. Chem. Soc.* **1984**, 106, 5594.

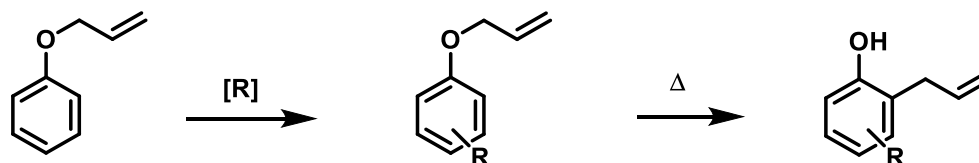


*Bull. Chem. Soc. Jpn.* **1978**, 51, 1577.

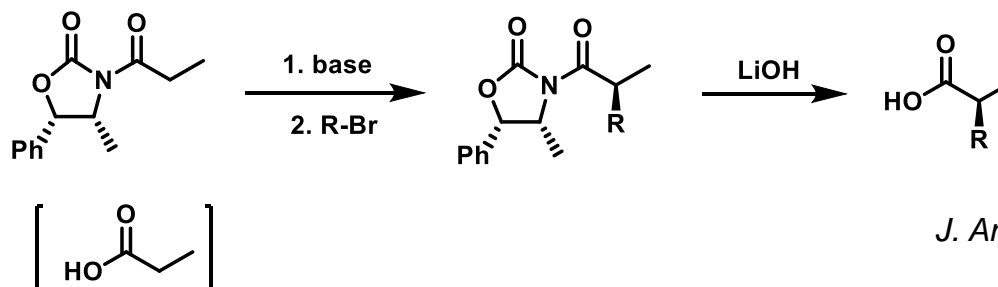
## „combined“ use of protecting groups

protection of reactive centers *plus*:

- incorporation of the P atoms into the target molecule (e.g. Claisen rearrangement of allyl ethers)

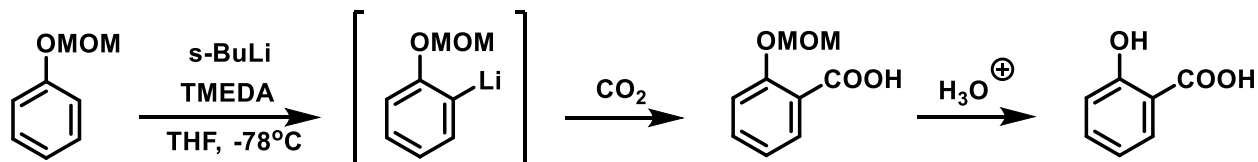


- diastereoselectivity (chiral Ps; „chiral auxiliary“ – e.g. Evans oxazolidinones)



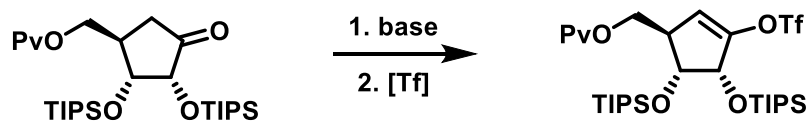
*J. Am. Chem. Soc.* **1982**, 104, 1737.

- regioselectivity (e.g. directed ortho-metalation using MOM, CONRR' etc.)

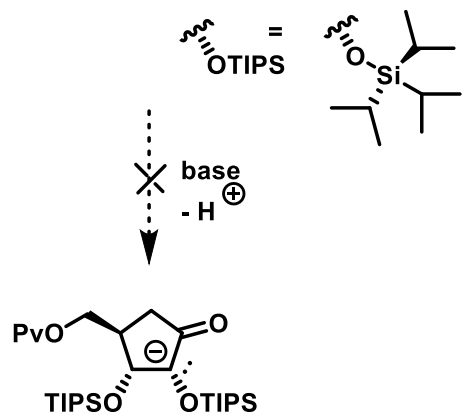


## „combined“ use of protecting groups

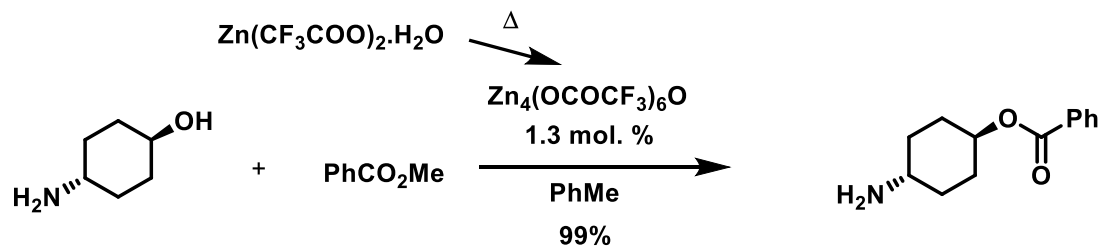
- protections of more reactive centers (one primary, one adjacent)



*J. Org. Chem.* **2017**, *82*, 3382.



modern methods: alternatives to (traditional) protecting groups-based approaches



*J. Am. Chem. Soc.* **2008**, 130, 2944.