Organic synthesis

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

P. J. Kocienski *Protecting Groups*

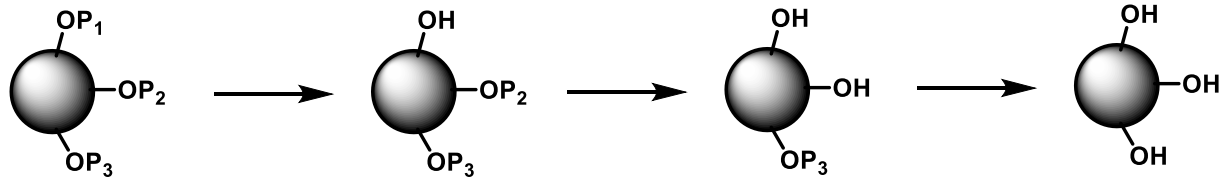
• the substrate contains reactive functional groups (typically OH, NH, CO, COOH …)

that are not compatible with reaction conditions

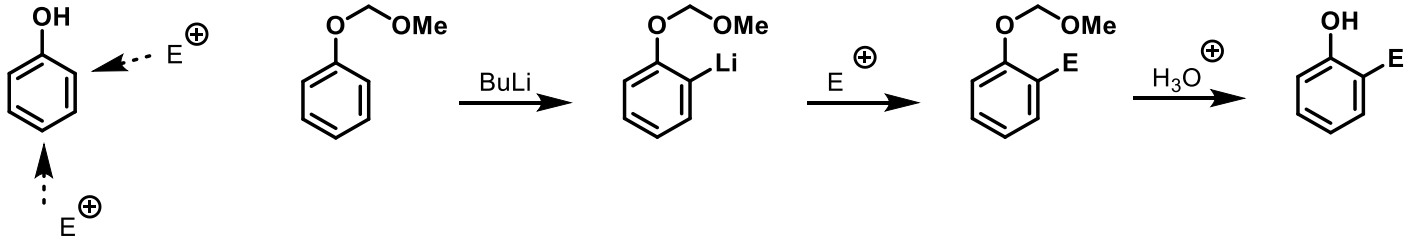
two additional steps in the synthetic sequence (installation & removal)

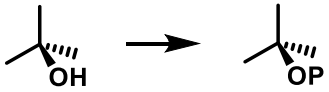
Young, I. S.; Baran, P. S. *Nature Chemistry* **2009**, *1*, 193.
„Protecting-group-free-synthesis as an opportunity for invention“

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

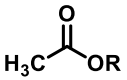


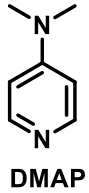
• some Ps can be used to direct (regio)selectivity of particular transformations





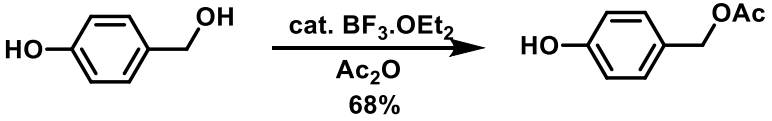
esters:

acetates **Ac-OR** 



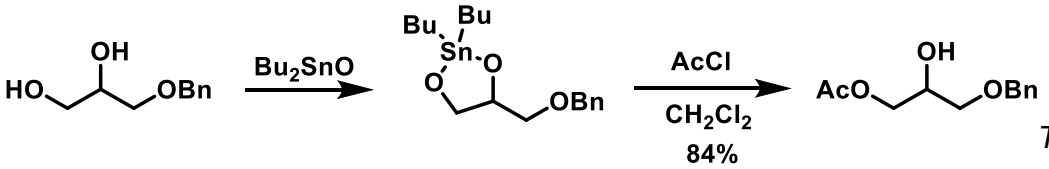
formation: typically: acetylating agent (Ac_2O, AcCl) + base (pyridine, TEA, DMAP)

also:



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

• acetylation of more nucleophilic OH



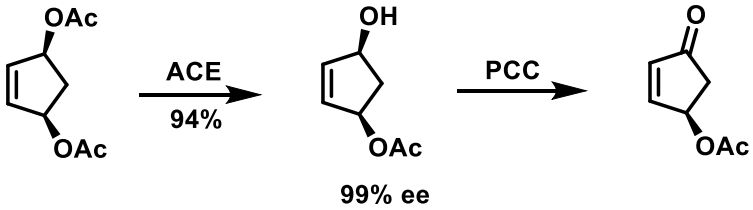
Synthesis **1989**, 225.

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

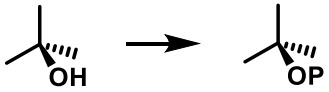
cleavage: basic hydrolysis (K_2CO_3 in MeOH; NH_3 in MeOH)

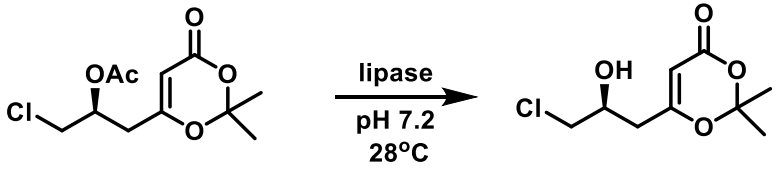
several OH groups in the molecule: acetate can migrate

some lipases can cleave acetates enantioselectively (under mild conditions)



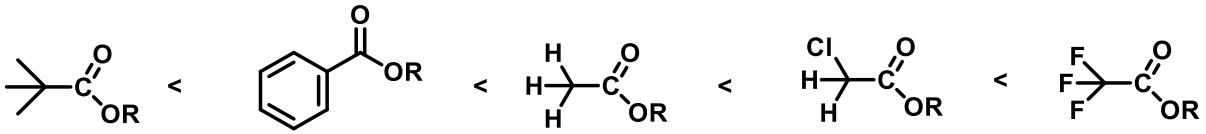
Tetrahedron Lett. **1986**, *27*, 1255.



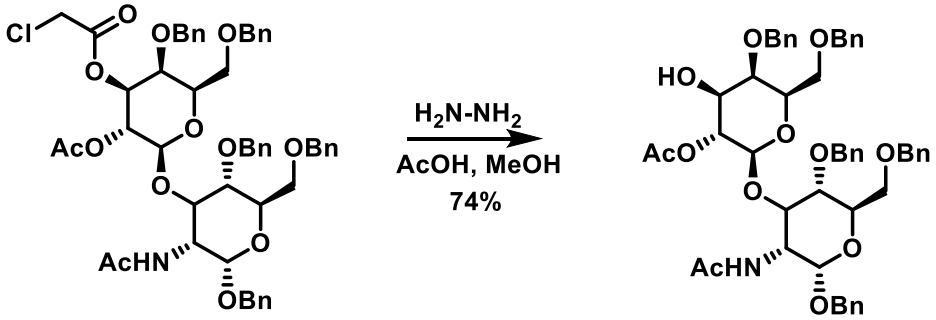


Tetrahedron: Asymmetry **1991**, *2*, 343.

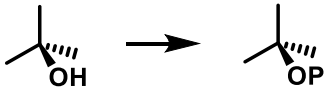
ease of basic hydrolysis:



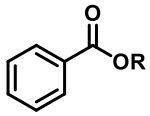
strong base (KOH/MeOH) pH 7



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

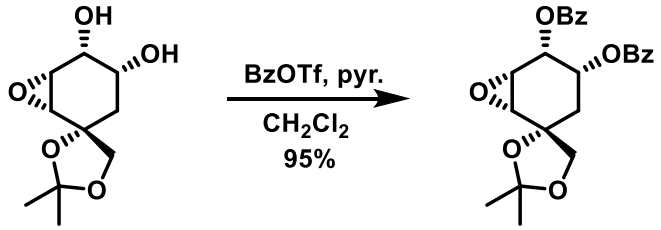


benzoates **Bz-OR**

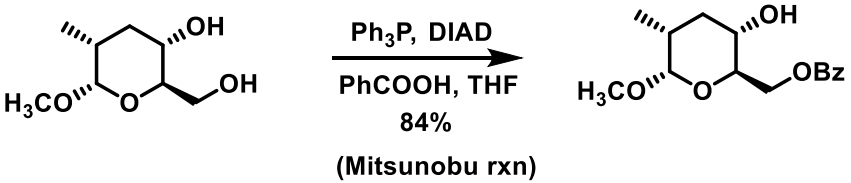


formation: Bz_2O, BzCl + base (pyridine, TEA)

• in polyhydroxylated systems typically much more selective than acetylaction

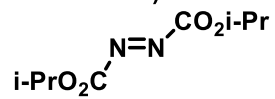


J. Org. Chem. **1984**, *49*, 3875.



(Mitsunobu rxn)

DIAD:

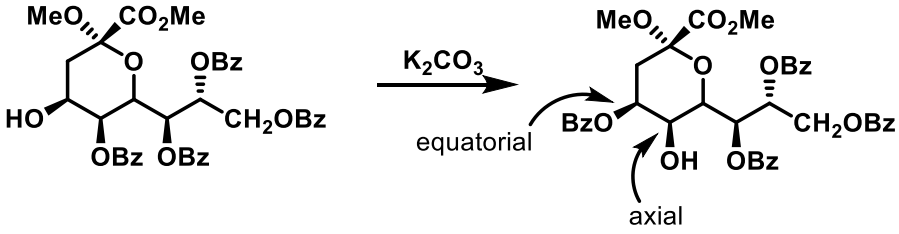


Tetrahedron Lett. **1989**, *30*, 1037.

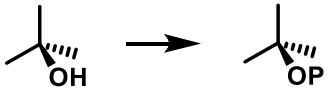
cleavage: basic hydrolysis (NaOH in MeOH; TEA in MeOH)

migration: typically to much lesser extent than with acetates

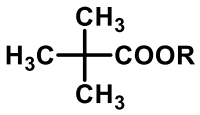
(but can be forced, if thermodynamically more stable isomer is formed)



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

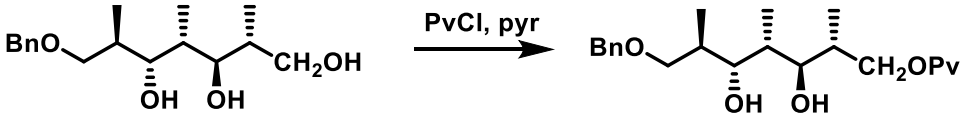


pivaloates **Pv-OR**

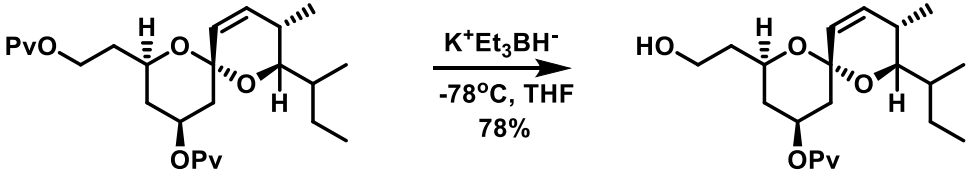


formation: PvCl + base (pyridine, TEA)

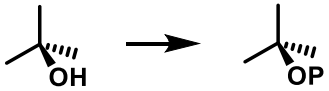
- primary OHs can be selectively acylated

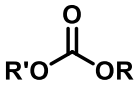


cleavage: strong base (KOH in MeOH, hydrides)



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



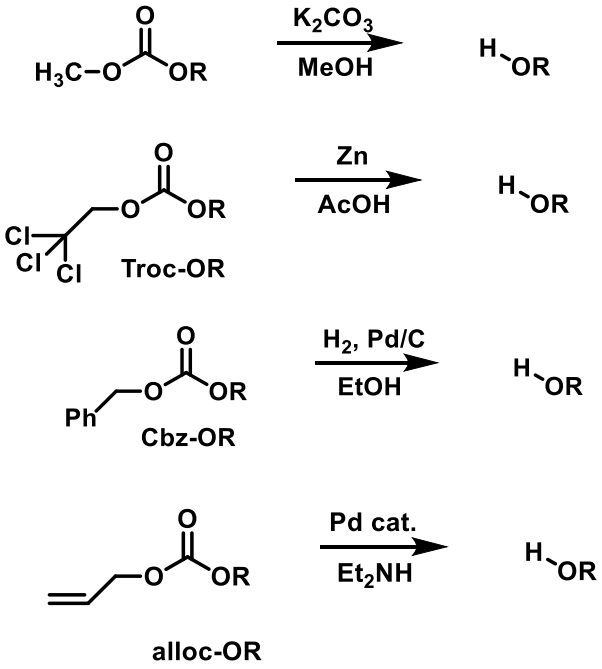
carbonates: 

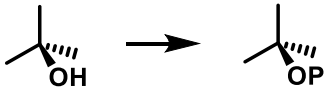
- more stable than esters towards basic hydrolysis

formation: R'OCOCl+ base (pyridine, TEA)

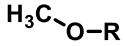
cleavage: in general, basic hydrolysis

but: conditions can be specific for different carbonates

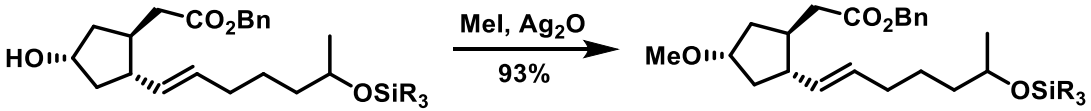




ethers:

methyl ether Me-OR 

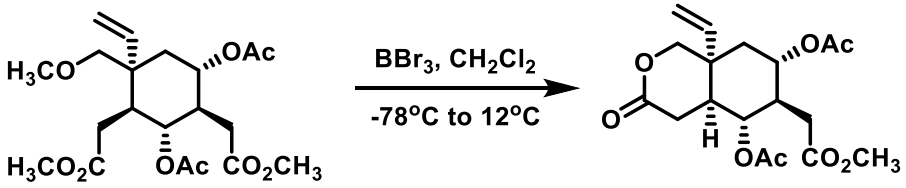
formation: MeI, Me_2SO_4 + base (NaOH, NaH, Ag_2O); CH_2N_2



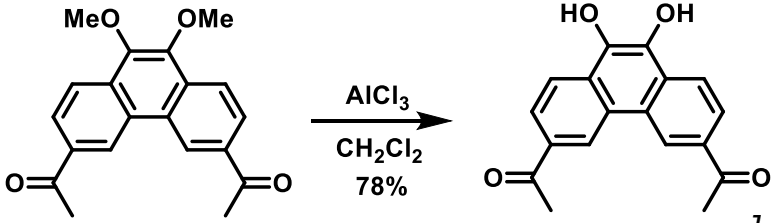
J. Am. Chem. Soc. **1980**, *102*, 7583.

cleavage:

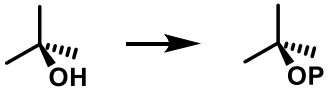
1. Lewis acids (BBr_3, TMSI, $AlCl_3$)



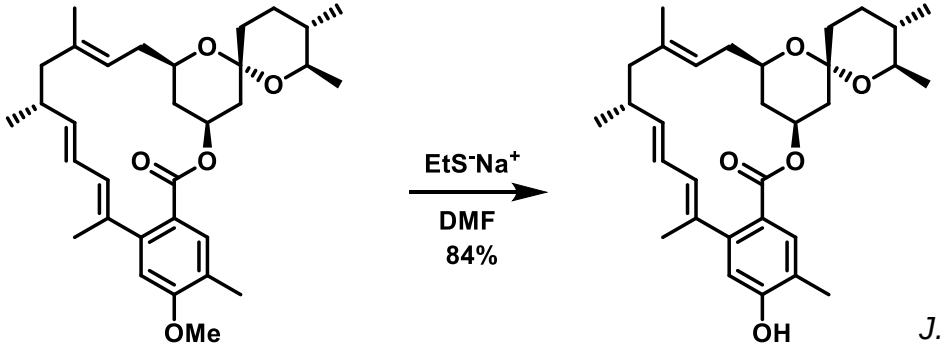
J. Am. Chem. Soc. **1977**, *99*, 5773.



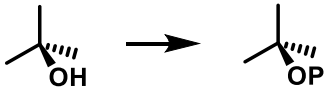
J. Org. Chem. **2000**, *65*, 7602.

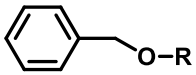


2. strong nucleophiles (phenolic methyl ethers)



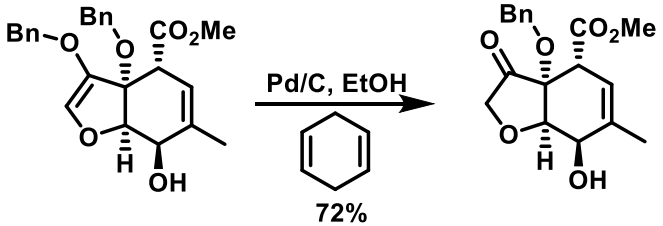
J. Am. Chem. Soc. **1986**, *108*, 2662.



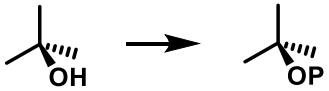
benzyl ether **Bn-OR** 

formation: BnBr + base (NaH)

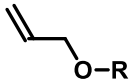
cleavage: hydrogenolysis (H_2, Pd/C, EtOH)



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

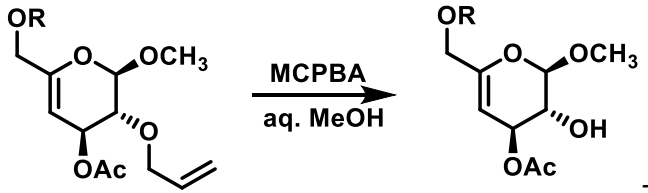


allyl ether



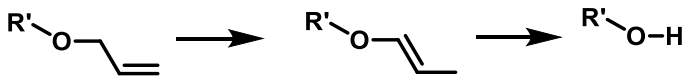
formation: CH_2=CH-CH_2Br + base (NaH)

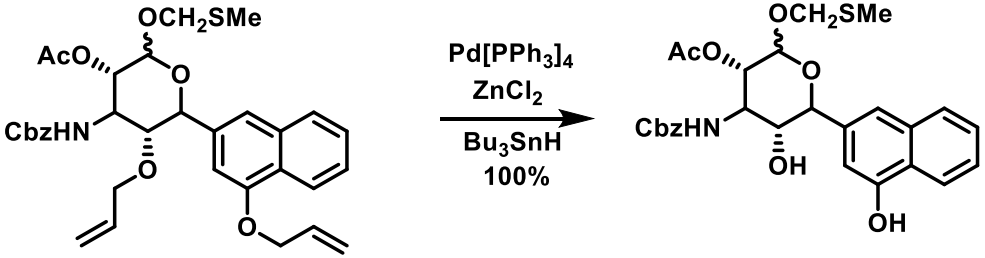
cleavage: 1. oxidative (SeO_2, H_2O_2, MCPBA)



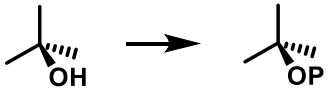
Tetrahedron **1990**, *46*, 5365.

2. Pd-catalyzed

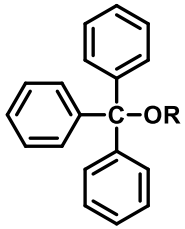




J. Org. Chem. **1992**, *57*, 644.

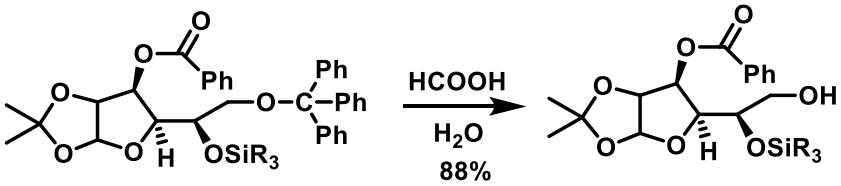


triphenylmethyl ether **trityl-OR, Tr-OR**



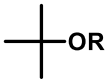
formation: Ph_3CCl + base (DMAP, NaH)

cleavage: acidic conditios



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

_t_-butyl ether **_t_-Bu-OR**

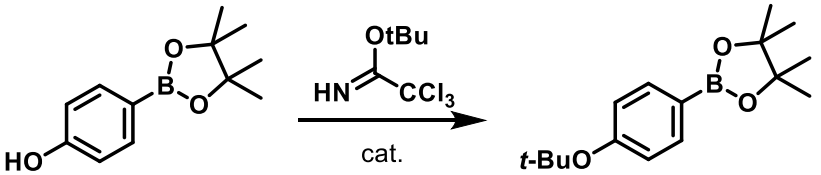


- protection of phenols

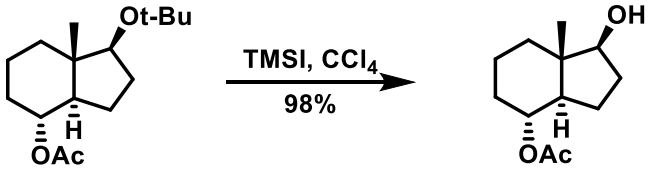
formation: t-BuBr + pyr. or H^+ +

cleavage: H^+, Lewis acids

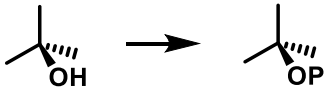
recent protocol:



J. Org. Chem. **2021**, 86, 4877.

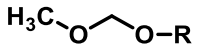


J. Am. Chem. Soc. **1982**, *104*, 2945.

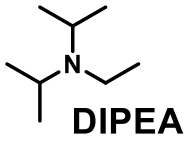


acetals

methoxymethyl ether MOM-OR

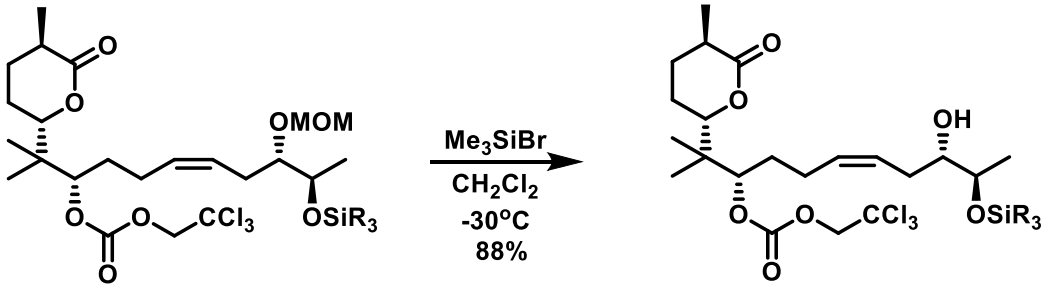


formation: $MeOCH_2Cl$ + base (DIPEA, NaH)

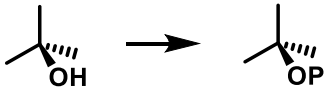


DIPEA

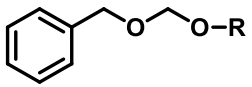
cleavage: acidic conditions (HCl/MeOH, TMSBr, $BF_3.OEt_2$)



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

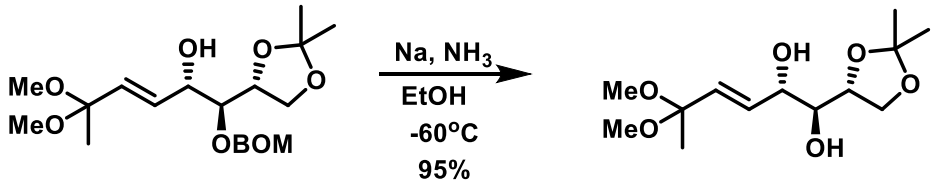


benzyloxymethyl ether BOM-OR

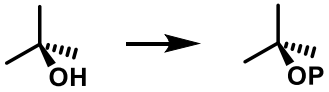


formation: $BnOCH_2Cl$ + base (DIPEA)

cleavage: hydrogenolysis (H_2/Pd/C); Na/NH_3

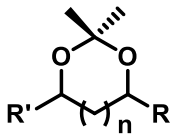


J. Am. Chem. Soc. **1987**, *109*, 3981.

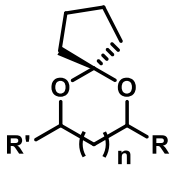


1,2- a 1,3 diols

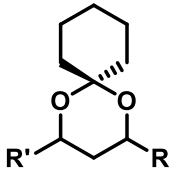
acetals



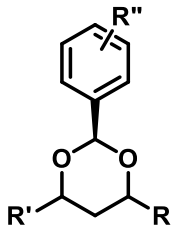
acetonides



cyclopentylidene ketals

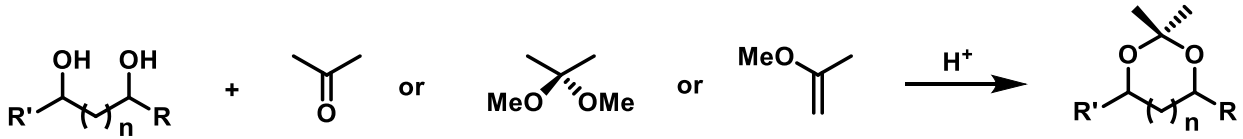


cyclohexylidene ketals



benzylidene acetals

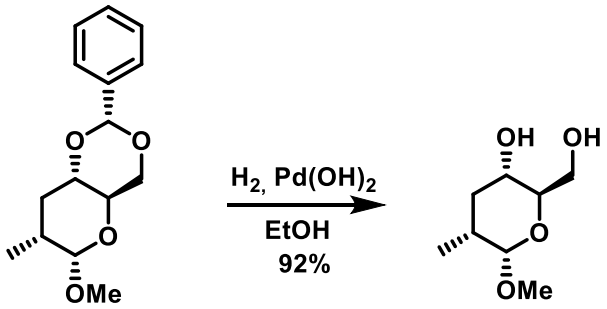
formation: H^+



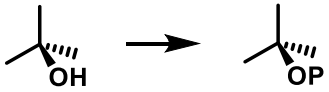
polyols: acetonides: typically 1,2-
benzylidene acetals: typically 1,3-

cleavage: H^+, H_2O
Lewis acids + hydride donor (Et_3SiH)

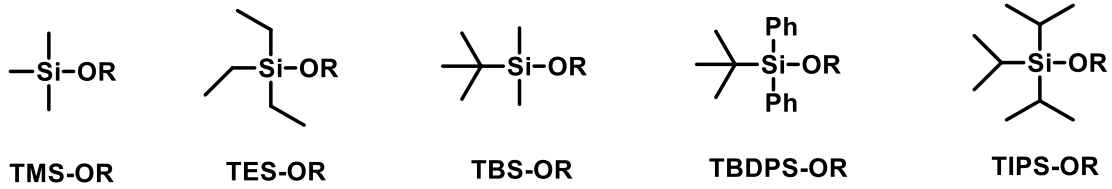
reduction (H_2, Pd/C) of benzylidene acetals



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



silyl ethers



formation: R_3SiCl or R_3SiOTf + base (imidazole; DIPEA; 2,6-dimethylpyridine)

cleavage: H^+

K_2CO_3/MeOH (TMSOR)

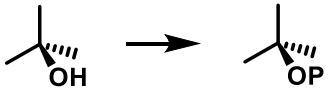
source of F^- (BuN^+F^-, HF.pyr, $HF.Et_3N$)

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

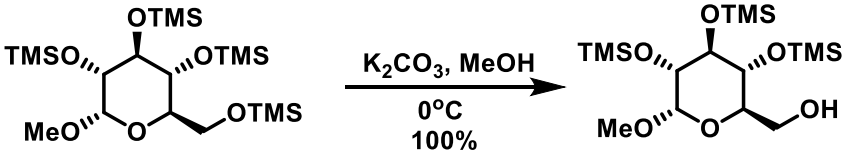
Si-F : 582 kJ/mol (Si-O : 452 kJ/mol C-H : 411 kJ/mol C-C : 346 kJ/mol)

silyl ether	half life NaOH/MeOH	half life HCl/MeOH
$C_6H_{13}OTMS$	< 1 min	< 1 min
$C_6H_{13}OTBS$	> 24 h	< 1 min
$C_6H_{13}OTIPS$	> 24 h	55 min
$C_6H_{13}OTBDPS$	> 24 h	225 min

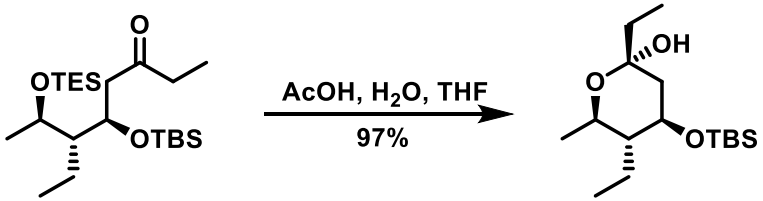
J. Chem. Soc. Perkin Trans. 1 **1992**, 3043.



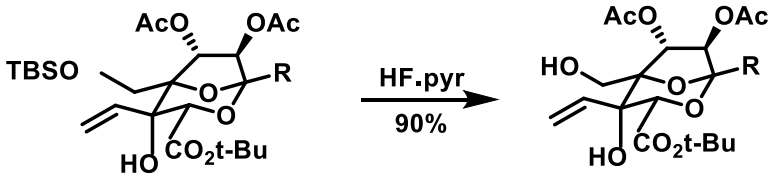
selective cleavage of silyl ethers



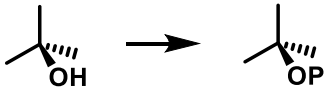
Can. J. Chem. **1965**, *43*, 2004.



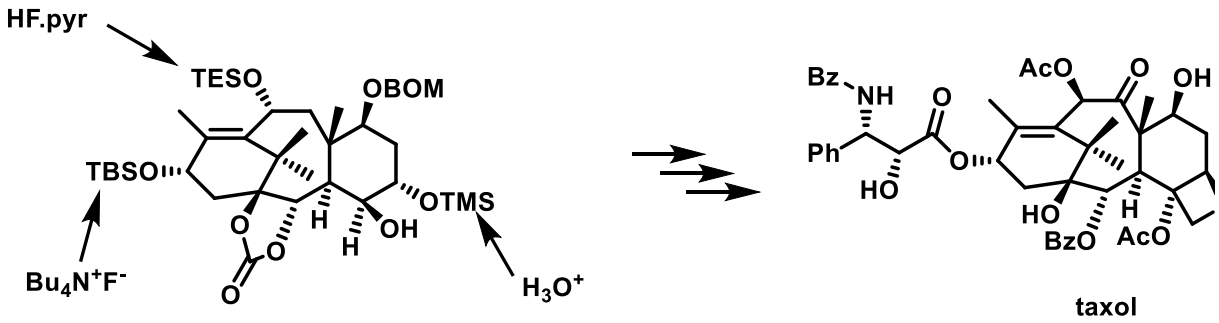
Liebigs Ann. Chem. **1986**, 1281.



J. Am. Chem. Soc. **1976**, *32*, 2157.



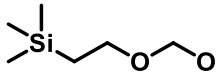
sequential removal of silyl ethers



taxol

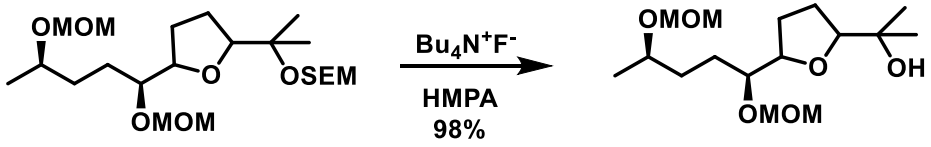
J. Am. Chem. Soc. **1994**, *116*, 1599.

2-(trimethylsilyl)ethoxymethyl ether SEM-OR

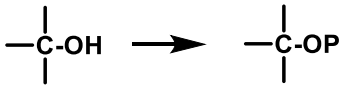


formation: $TMSCH_2CH_2OCH_2Cl$ + base (DIPEA)

cleavage: 1. acidic conditions
2. fluoride



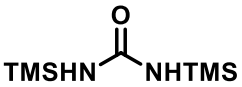
Tetrahedron Lett. **1988**, *29*, 5417.

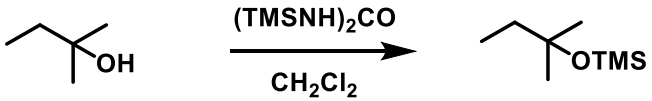


Si-F : 582 kJ/mol (Si-O : 452 kJ/mol C-H : 411 kJ/mol C-C : 346 kJ/mol)

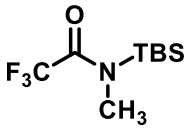
Si-N : 355 kJ/mol

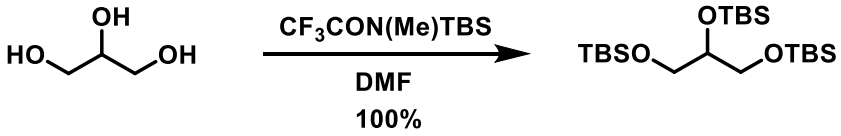
- silylated amines are significantly less stable than silylated alcohols
- N-silylated compounds can be used for transfer of the silyl group





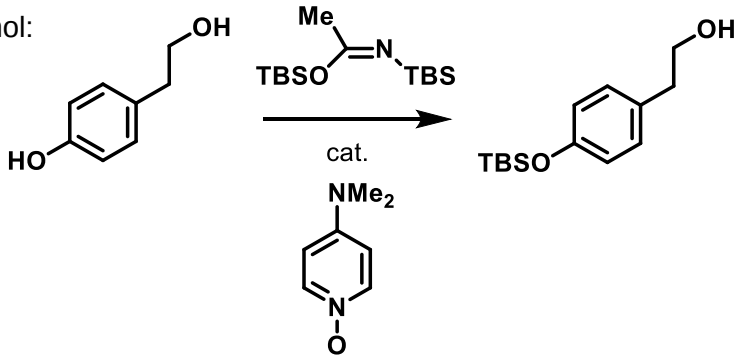
Synthesis **1981**, 807.



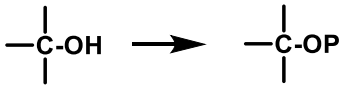


J. Org. Chem. **1982**, *57*, 3336.

selective protection of phenol:

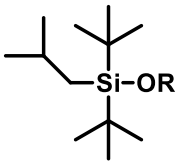


Chem. Lett. **2022**, *51*, 953.



- **silyl *esters*:** significantly more labile compared to silyl *ethers*

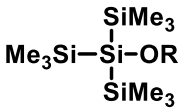
modern and non-traditional Si-based protecting groups



BIBSOR

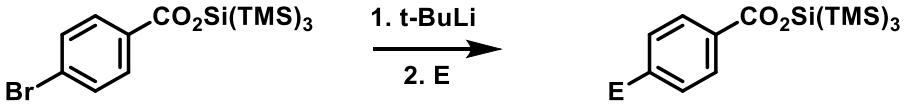
- very resistant to bases/nucleophiles
- BIBS *esters* are quite stable

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

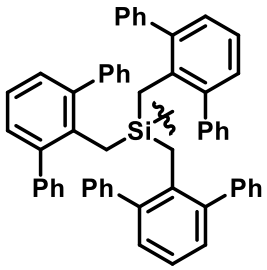


$(TMS)_3SiOR$

- „supersilyl“
- *esters* are quite stable



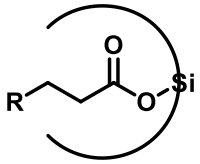
Angew. Chem. Int. Ed. **2013**, *52*, 8165.

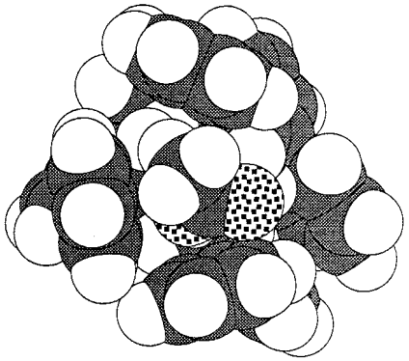


TDS

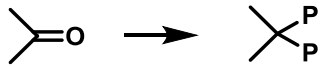
tris(2,6-diphenylbenzyl)silyl

- *esters* resistant to $LiAlH_4$, RLi etc.

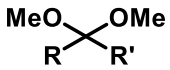




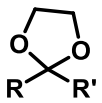
J. Am. Chem. Soc. **2000**, *122*, 10238.



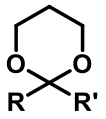
acetals/ketals



dimethyl acetal



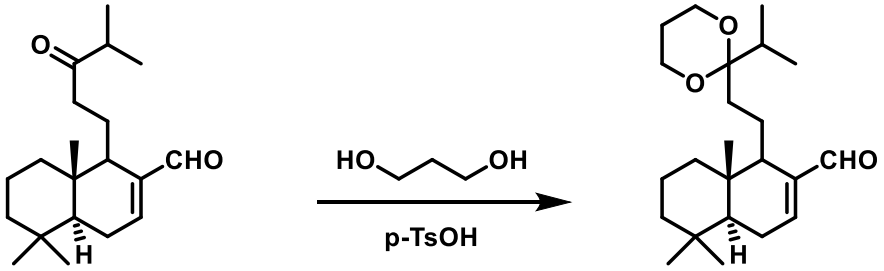
1,3-dioxolane



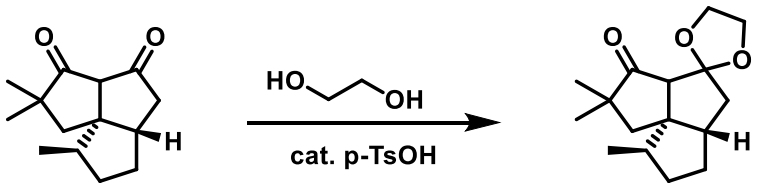
1,3-dioxane

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

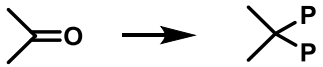
- aldehydes typically more reactive than ketones



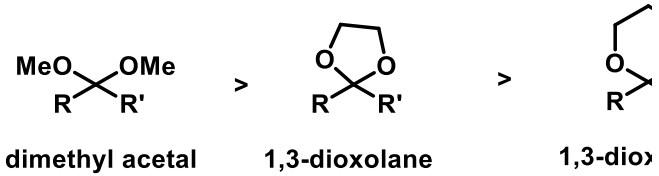
Tetrahedron Lett. **1982**, *23*, 1087.



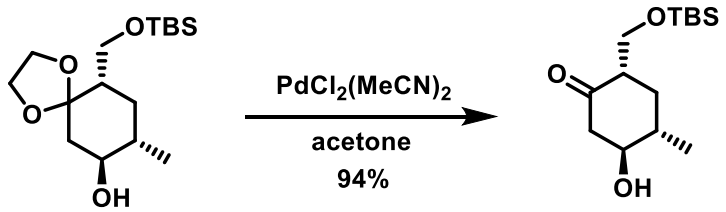
J. Am. Chem. Soc. **1986**, *108*, 800.



cleavage: H^+, H_2O

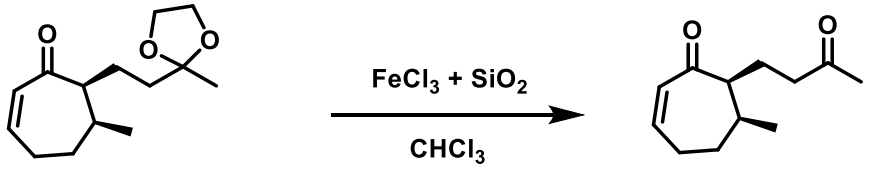


cat. $PdCl_2(MeCN)_2$ + acetone

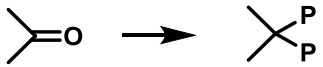


Tetrahedron Lett. **1987**, *28*, 5755.

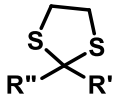
$FeCl_3 + SiO_2$



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

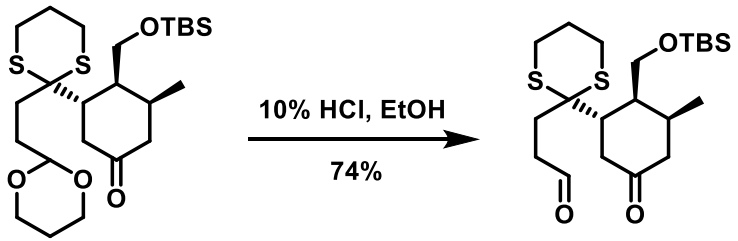


cyclic dithioacetals/ketals



formation: $HS(CH_2)_nSH$ + (Lewis) acid

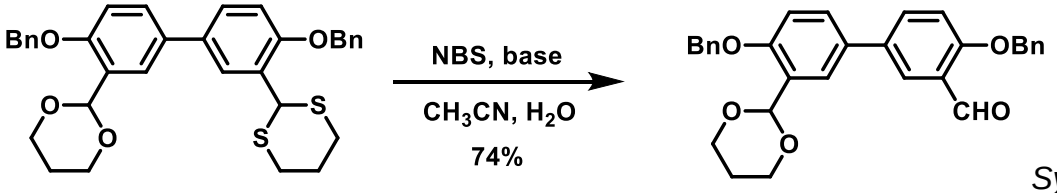
- dithioacetals are significantly less sensitive to acids than acetals



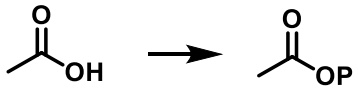
J. Org. Chem. **1985**, *50*, 1190.

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

- coordination of S with metals: $Hg(ClO_4)_2$, $CuCl_2$, CuO
- oxidation: MCPBA, Ac_2O, TEA
- alkylation: MeI

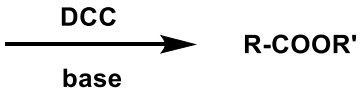


Synthesis **1992**, 1025.

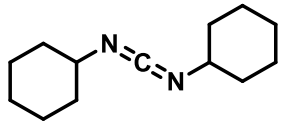


esters

formation: esterification



DCC:



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

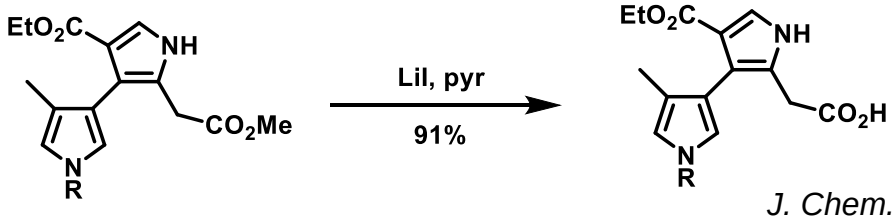
t-butyl esters: acidic hydrolysis (CF_3COOH)

allyl esters: Pd-catalyzed cleavage ($Pd(PPh_3)_4$)

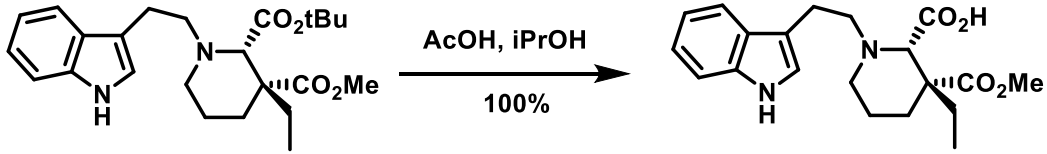
benzyl esters: hydrogenolysis (H_2, Pd/C)

silyl esters: fluoride, acidic & basic hydrolysis

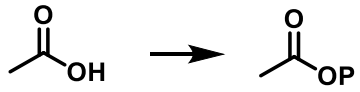
(less stable than silyl ethers)

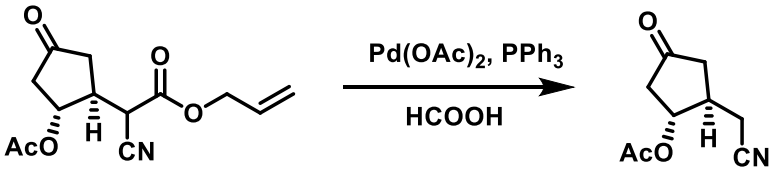


J. Chem. Soc., Chem. Commun. **1984**, 389.

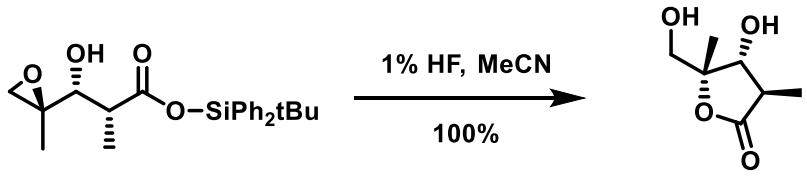


J. Org. Chem. **1990**, *55*, 3068.

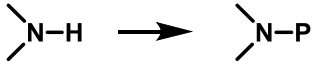




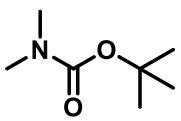
Tetrahedron Lett. **1991**, *32*, 2409.



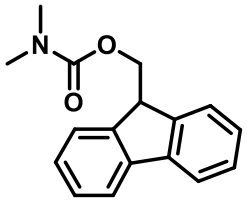
Tetrahedron Lett. **1982**, *23*, 4199.



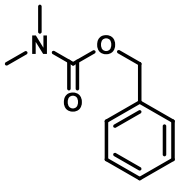
carbamates



Boc



Fmoc



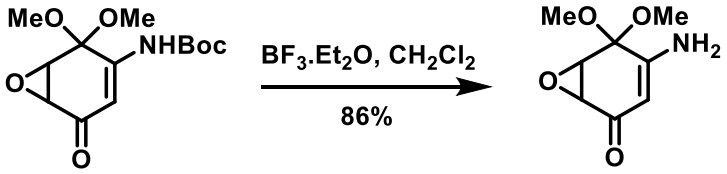
Cbz

formation: ROCOCl or $(ROCO)_2O$ + base

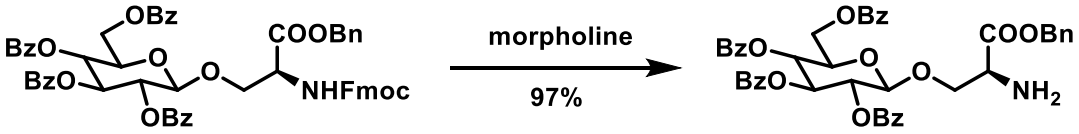
cleavage: Boc: CF_3COOH (+ PhOMe); Lewis acids

Fmoc: amine (piperidine, morpholine)

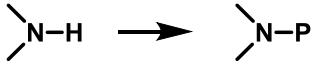
Cbz: H_2, Pd/C

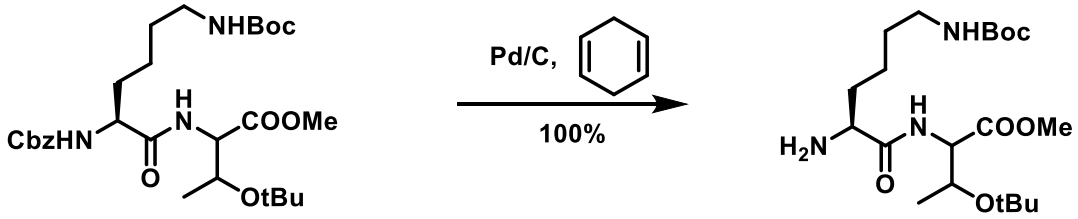


Synth. Commun. **1997**, *27*, 1819.



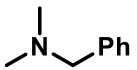
Angew. Chem. Int. Ed. **1983**, *22*, 62.



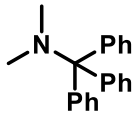


The Practice of Peptide Synthesis **1984**, 158.

alkylated amines



Bn

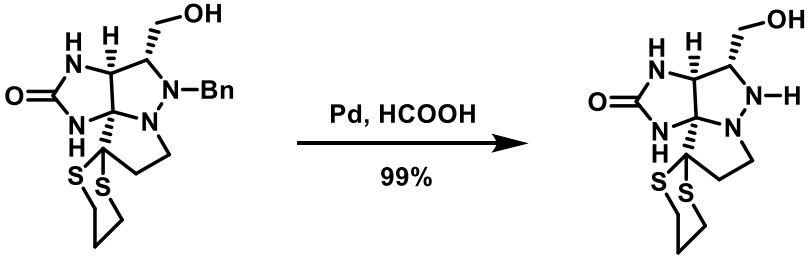


Tr

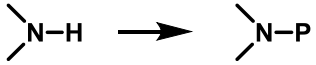
formation: BnBr or TrCl + base (NaH)

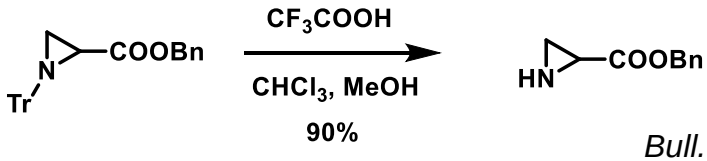
cleavage: Bn: hydrogenolysis

Tr: hydrogenolysis, CF_3COOH



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





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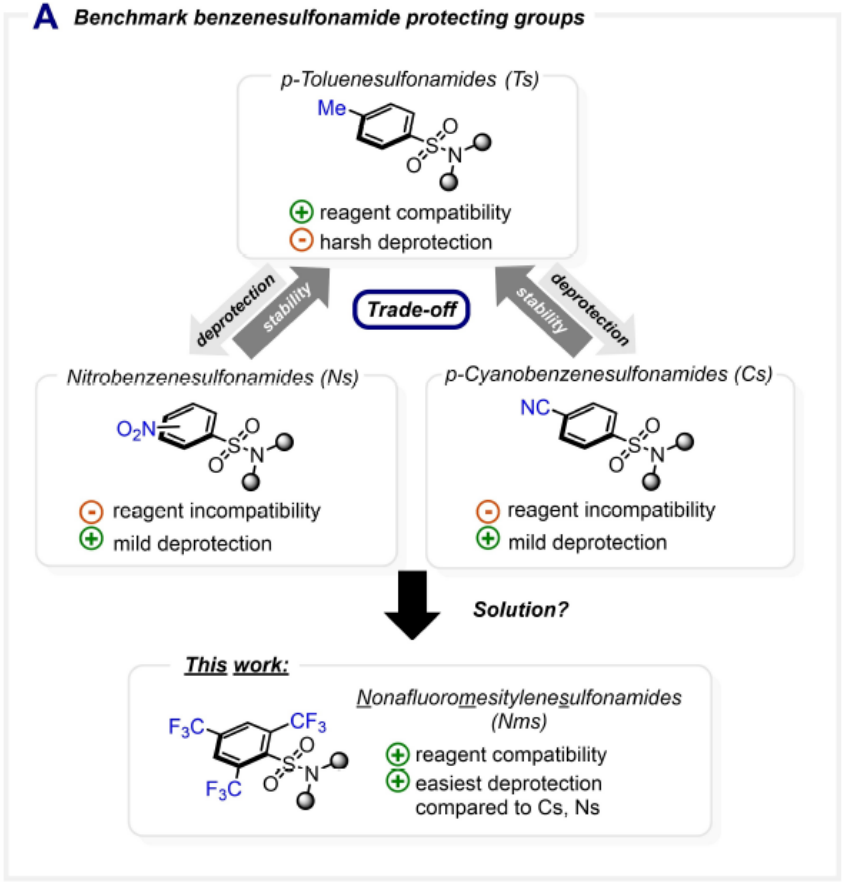
Nms-Amides: An Amine Protecting Group with Unique Stability and Selectivity

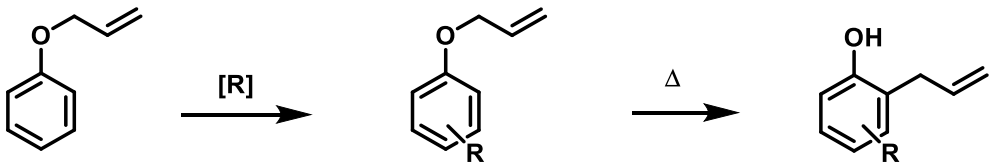


Chem. Eur. J. **2023**, e202301312.

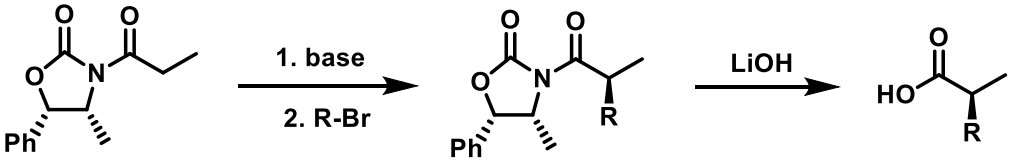
„combined“ use of protecting groups

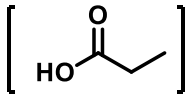
protection of reactive centers *plus*:

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



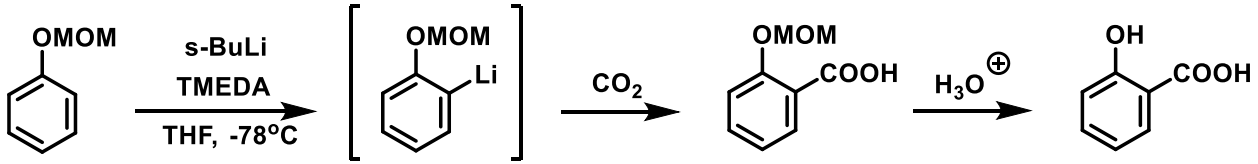
• diastereoselectivity (chiral Ps; „chiral auxiliary“ – e.g. Evans oxazolidinones)





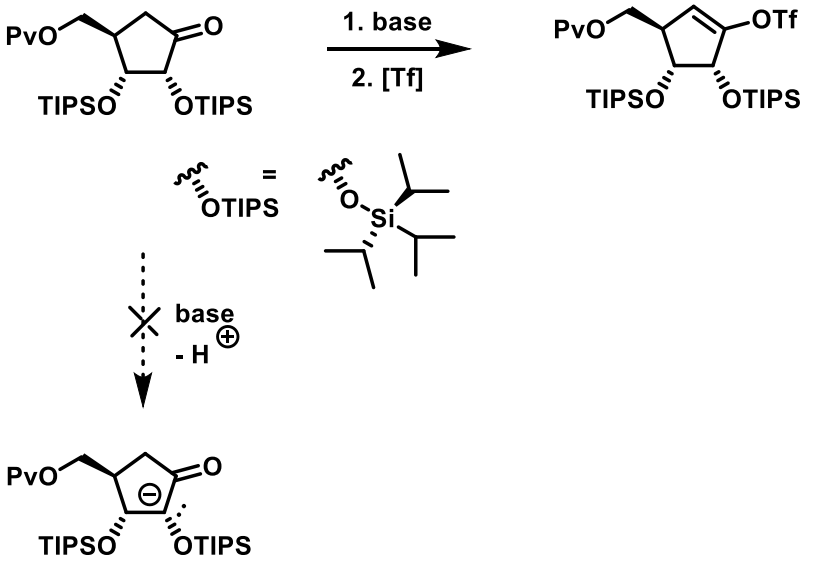
J. Am. Chem. Soc. **1982**, *104*, 1737.

• 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