Protecting groups are a sad fact of synthetic chemistry

They are usually needed, but rarely desired

Many syntheses have stalled because of trouble putting on or removing protecting groups

4 basic questions to address when choosing a P.G.:

1. **Can I put it on where and only where I want?**
2. **Can I take it and only it off?**
3. **Will it survive all future reaction conditions?**
4. **Will it affect the reactivity of my substrate?**

Your guide to these questions should be: Protective Groups in Organic Synthesis by Theodora Greene and Peter Wuts

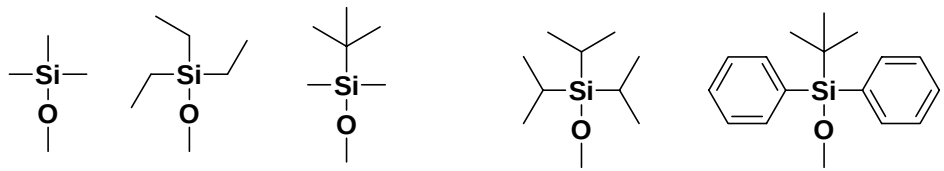
An even better strategy is to plan your syntheses to avoid protecting groups

We will discuss general features of protecting groups, for specific examples and exotic methods for attachment or removal, see Greene

Protecting Groups for Alcohols

4 major classes: silyl ethers, ethers, esters, acetals

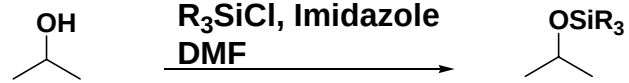
Silyl Ethers



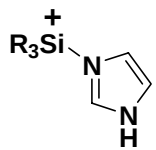
TMS **TES** **TBS or TBDMS** **TIPS** **TBDPS**

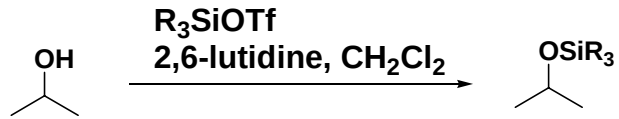
TBS: Corey, JACS, 1972, 6190 (23rd most cited JACS paper)

ON:



via

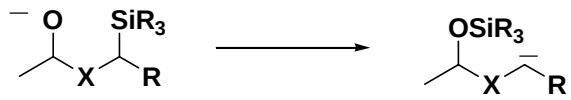




These transformations are very water sensitive.

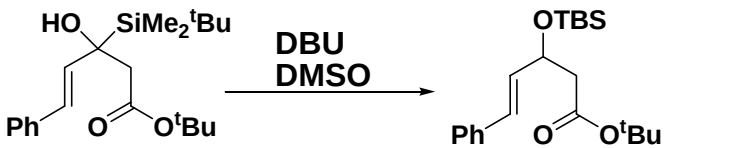
Less Common methods for Silyl introduction:

Brook Rearrangement

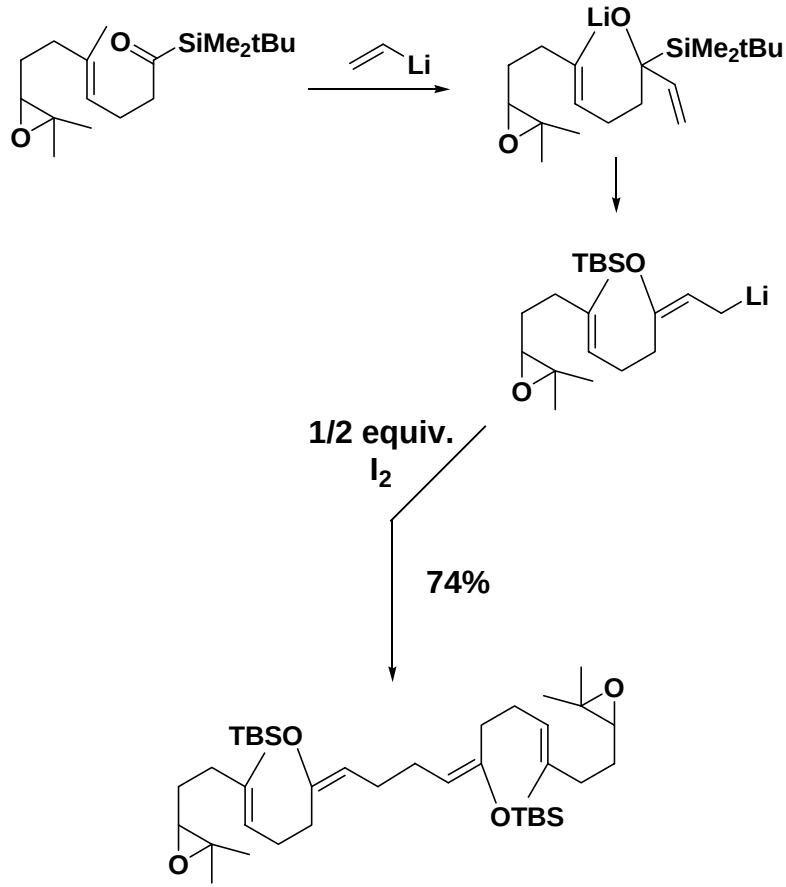


bond	BDE (kcal/mol)
C–Si	69
O–Si	103
F–Si	141

question: using approx. pKa values and the BDE above, estimate Keq for different R's in the equation 1.



TL, 1998, 5243

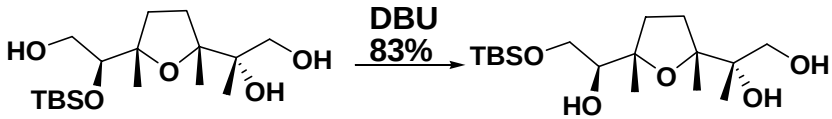


Corey, JACS, 2002, 11290

Other potential methods:

Hydrosilylation of ketones: always some stupid silyl group
Tamao oxidation of alkyl silanes: Silyl group rarely survives

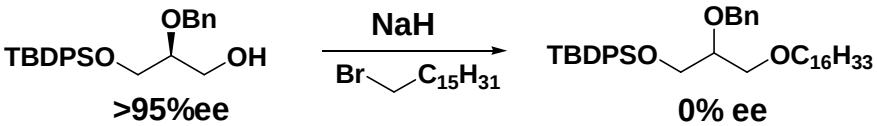
silyl migrations
- **-smaller is faster**
- **-1,2 and 1,3 most common**
- **-good if planned; usually not planned**



Note: 2 primary alcohols would make selective protection difficult

Molander, JOC 1994, 7148

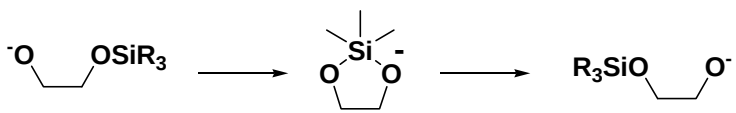
how does this happen?



>95%ee **0% ee**

Welzel, Tet, 1987, 3803

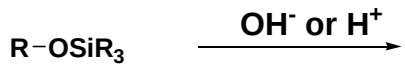
Migrations likely via associative displacement:



pentavalent intermediate

Removal

Usually F^- or H^+
Usually, bigger is more stable

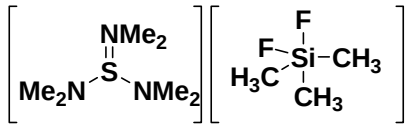


Silyl group	k_{rel} H^+	k_{rel} ^-OH
TMS	5,000,000	500,000
TES	100,000	50,000-5,000
TBDMS	250	5
TIPS	10	5
TBDPS	1	1

Recall BDE: O-Si (~100 kcal/mol) vs F-Si (~140 kcal/mol)

Common F^- sources:

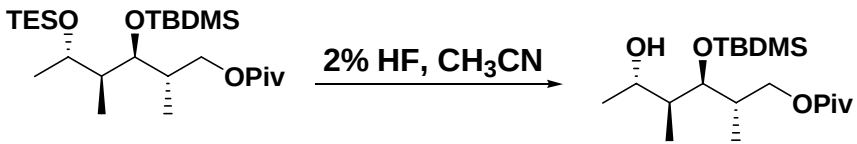
TBAF (nBu_4NF)
HF-Pyridine
3HF-Et_9N
HF
TASF [tris(dimethylamino)sulfonium difluorotrimethylsilicate]



relative rates of Fluoride-induced cleavage:

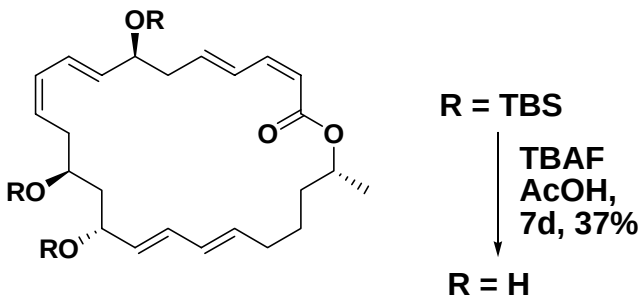
Silyl group	1/2 life
TBS	20 min
TIPS	15 min
tHexDMS	15 min
TBDPS	50 min
TPS	2.5h

Selective cleavage (review: Synthesis, 1996, 1065)

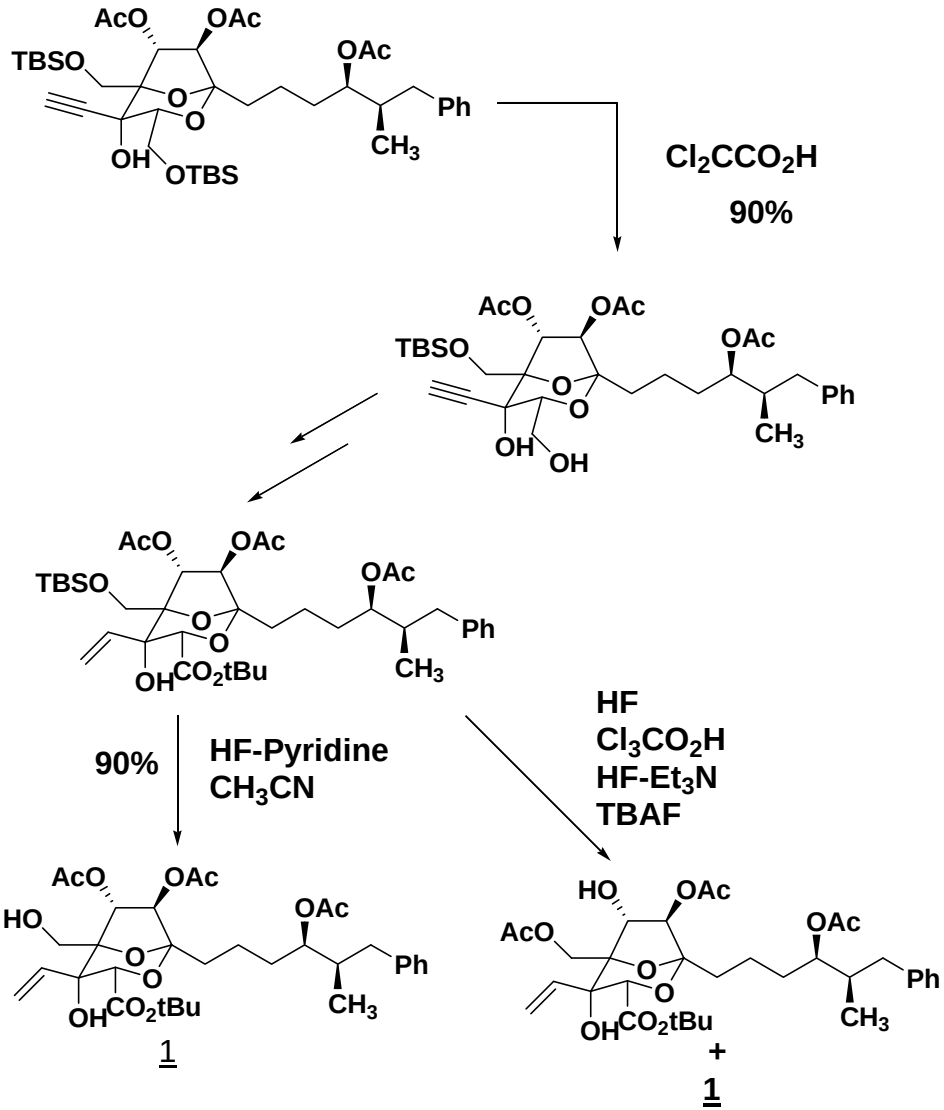


Masamune, TL, 1985, 5239

Commercial TBAF is wet (to varying degrees).
Dry TBAF is very basic; may need buffer:



Conditions often need to be determined empirically

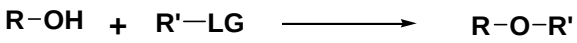


Carreira, Du Bois JACS, 1995, 8106

Ethers

usually very robust, with orthogonal modes of removal

usually:



common ethers:

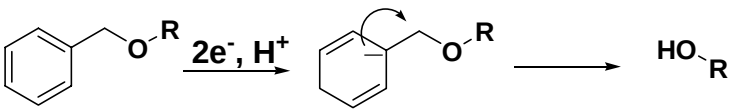
Methyl ether: easy on, hard off. Usually only good for phenols

On: MeI, Me_2SO_4, $Me_3O\ BF_4$
Off: BBr_3, TMSI,

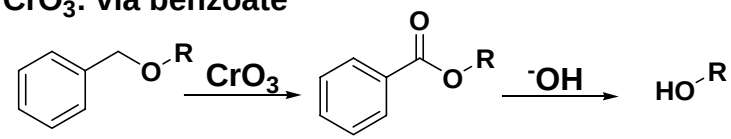
Benzyl ether (Bn)

On: usually BnCl + base; somtimes with cat. I^- (do you know what I^- does?)
Off: H_2, Pd/C - competitive (usually slower) than olefin reduction
Lewis Acid: S_N1 mechanism

Na/NH_3

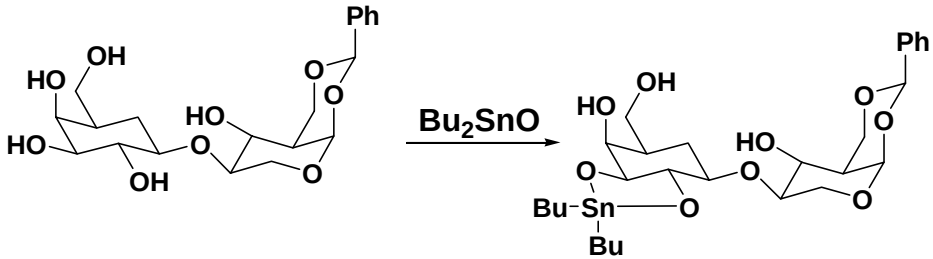


CrO_3: via benzoate



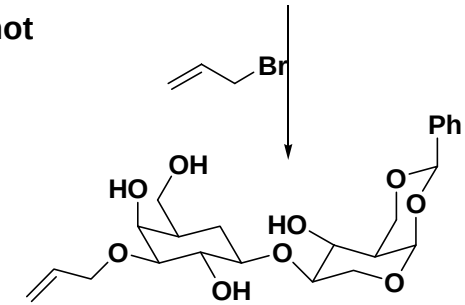
allyl ether

on: usually allyl Br/Cl + base. Usually easy



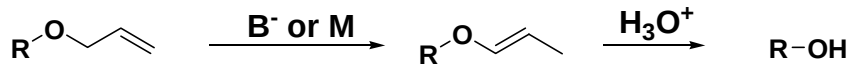
"stanylene acetal"

This is a general method for monprotection of a 1,2 diol (not limited to allyl). In this case, note selective formation with equitorial OH's.

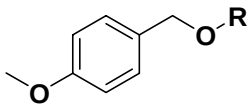


95%
Ogawa, TL, 1988, 4097

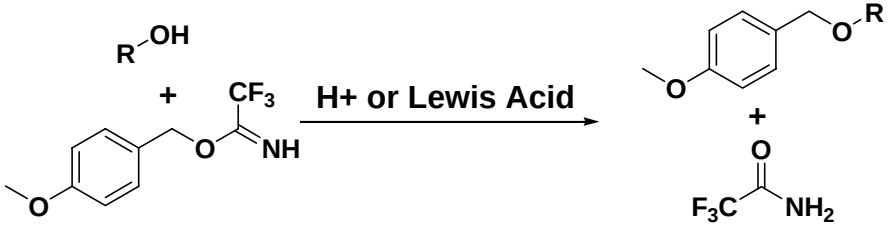
Off: Isomerization with base or transition metal, then hydrolysis:



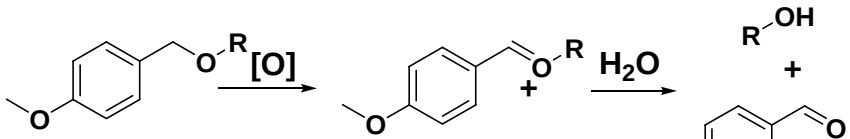
p-methoxybenzyl (PMB or MPM)



On: PMB-Cl, base

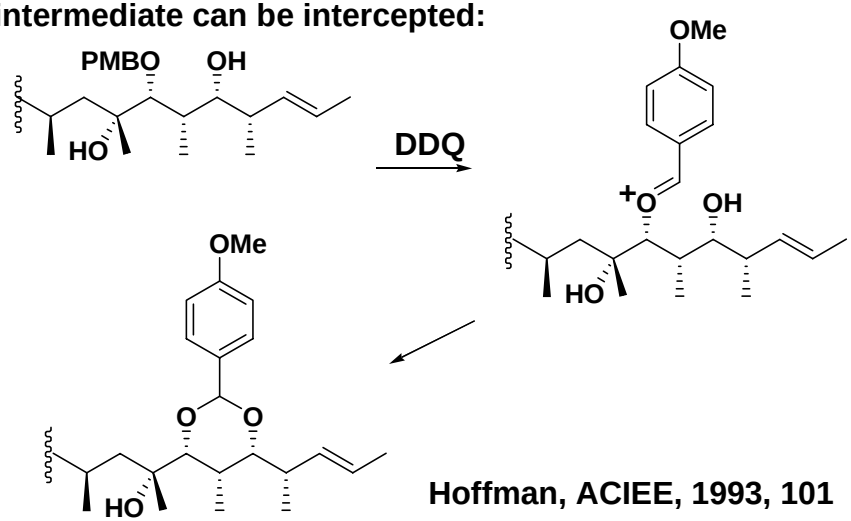


Off: Oxidation



[O] = DDQ, CAN, $Ph_3C\ BF_4$, Br_2, NBS

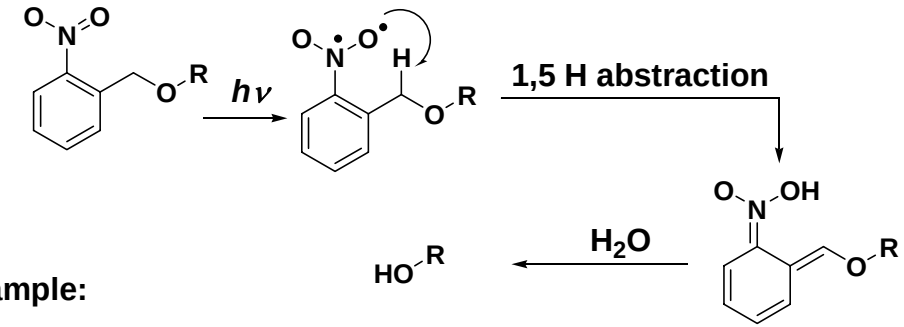
intermediate can be intercepted:



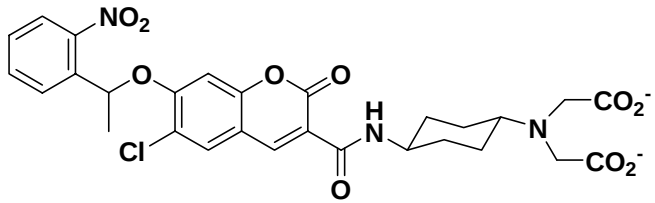
Hoffman, ACIEE, 1993, 101

o-nitrobenzyl

Off: *hν*



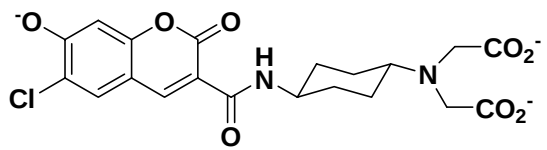
example:



non-fluorescent

365 nm hν

pKa ArOH = 5.1



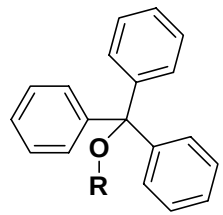
fluorescent

Wen-Hong Li, JACS, 2004, 4653

Triphenyl Methyl (trityl)

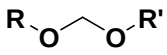
On: Ph_3CCl, via S_N1

Off: Acid

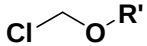


acetals

acetals of mono-ols:

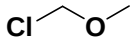
many eg's of the form 

advantages:

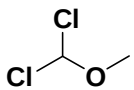
 **very active electrophile**

likely forms 

Methoxy Methyl (MOM)

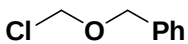
On: 

'MOM-Cl' thought to be very toxic

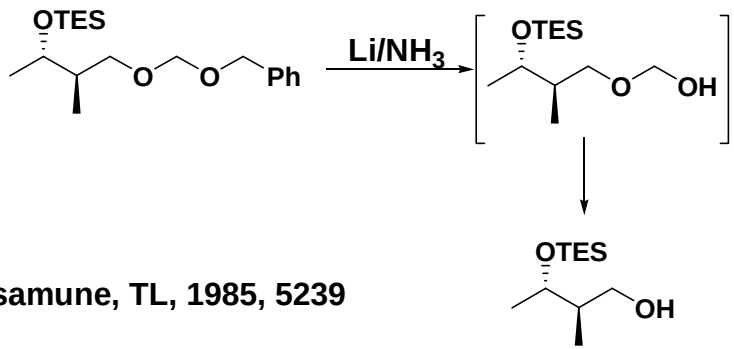
 **even more toxic**

Off: Acid

Benzyloxy methyl (BOM)

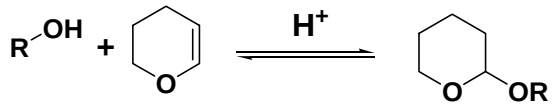
On: 

Off: all the methods for removing Bn groups:

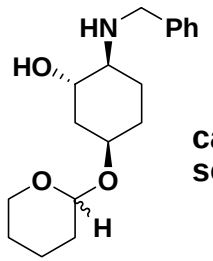


Masamune, TL, 1985, 5239

Tetrahydropyranyl (THP)



Easy on, easy off, cheap.
But get diastereomers with chiral molecues:

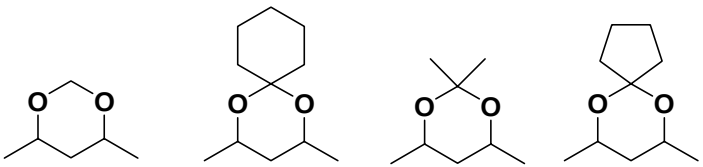


can complicate NMR spectra (and sometimes chromatography)

acetal protection of diols

Cyclic acetal are wonderful protecting groups for 1,2 and 1,3 diols.

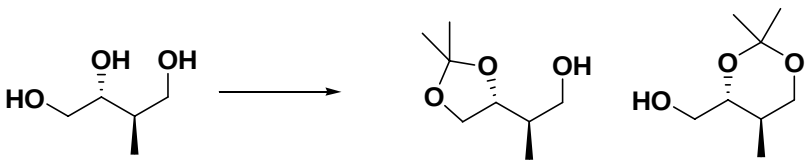
Some of the most common:



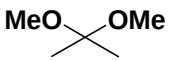
'acetonide'

most stable ⟶ least stable

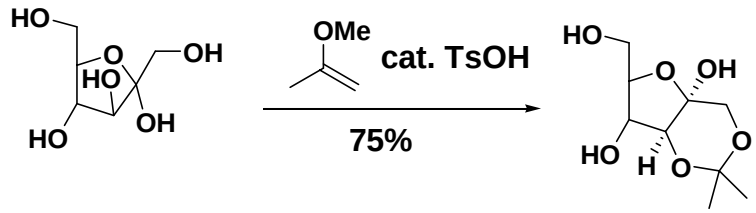
Usually, 1,2 >1,3>1,4



5 : 1

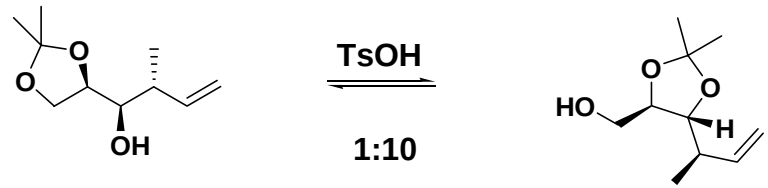
On:  Cat. H^+ or  cat. H^+

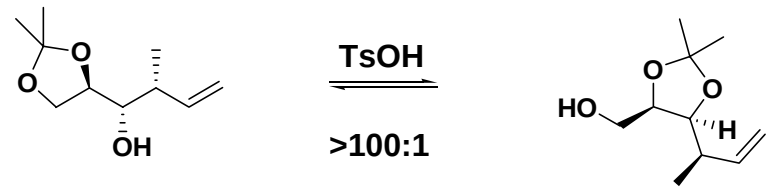
why not acetone + H+?
Hint: Consider pKa's of protonated ketones vs ethers



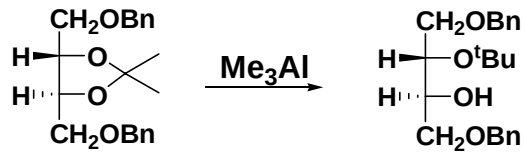
Corey...Falck...JACS, 1978, 4620

reactions often under thermodynamic control:



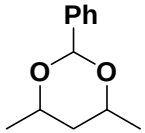


oxonium intermediates can be intercepted



TL 1988, 1823

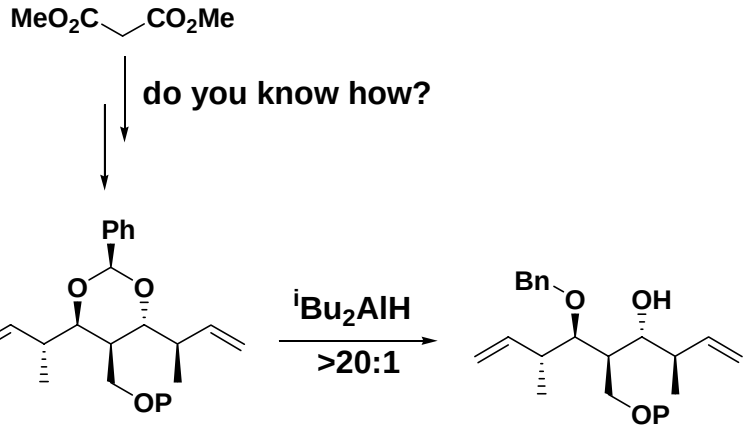
benzylidene acetals

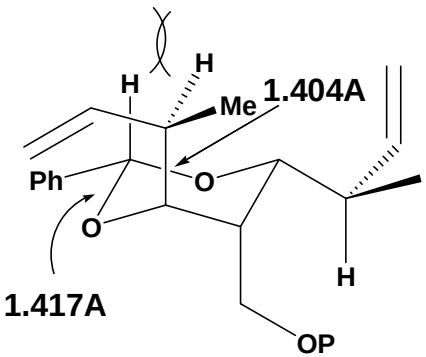


On: $PhCHO/H^+$ or Lewis acid

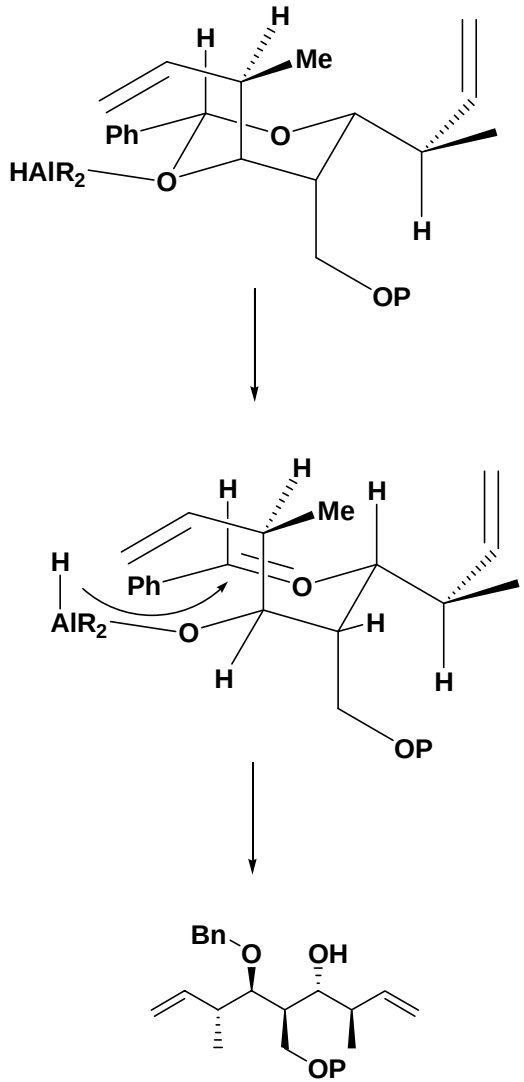
Off: H_3O^+ or H_2 Pd/C

Can be converted to benzyl:





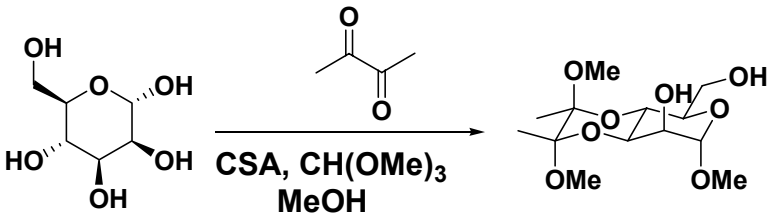
from X-ray



Schreiber, TL, 1988, 4085.
Usually see protection of less hindered OH

For protection of more hindered OH by a similar reaction, see Yamamoto, TL, 1988, 1947-1950

diols can be protected as diacetals:

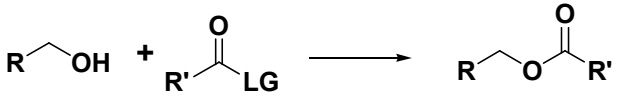


Ley, Perkin 1, 1997, 2023

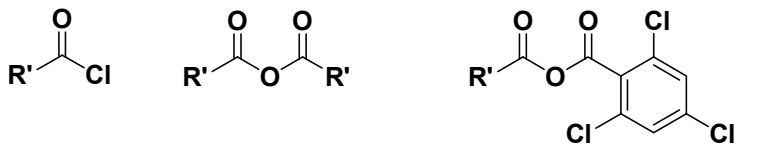
Esters as protecting groups

In general, ease of introduction and removal is function of sterics and electronics

usually:



egs

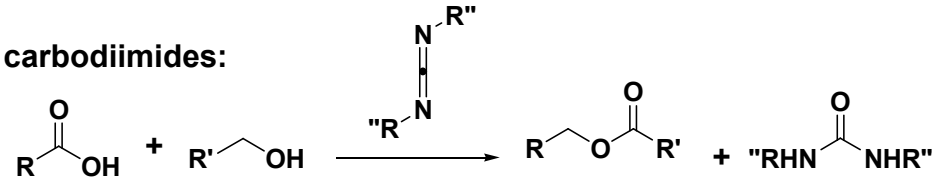


'Yamaguchi conditions' more often for macrolactonizations

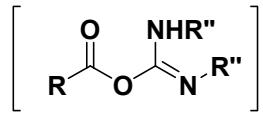
Include CH2N2

in situ generated active ester

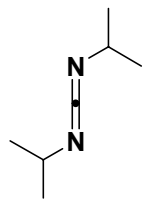
carbodiimides:



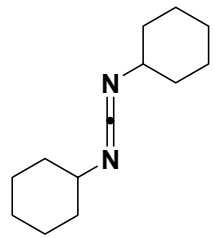
via



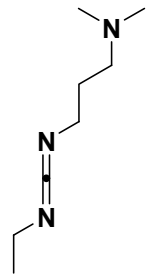
rxn is 'self-drying'
removal of urea can be trouble
most common egs:



DIC - liquid at rt, easy to use on small scale

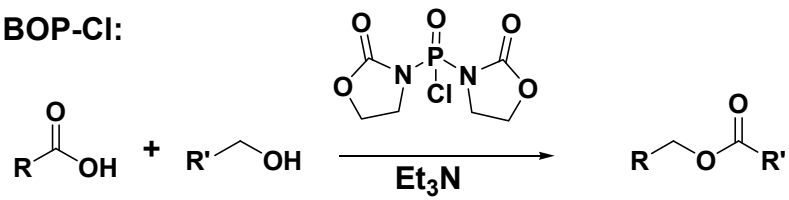


DCC - mp=34°C
reported sensitizer
increased solubility



EDCI - can extract urea with acid

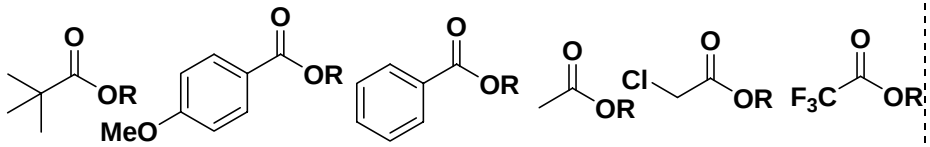
BOP-Cl:



synthesis, 1980, 547

Cleavage: base hydrolysis rates depend on sterics and electronics

stability to base

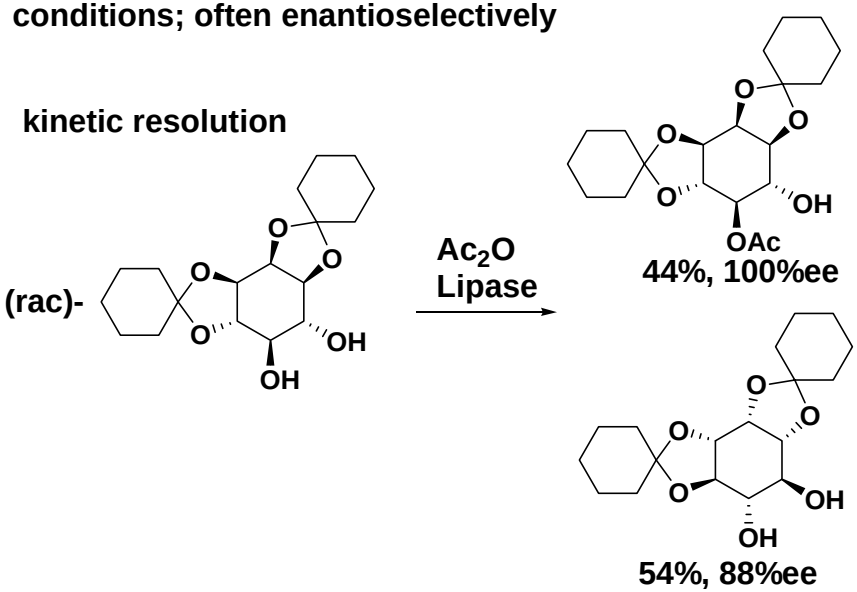


Piv **Bz** **Ac** **TFA**

more stable → **less stable**

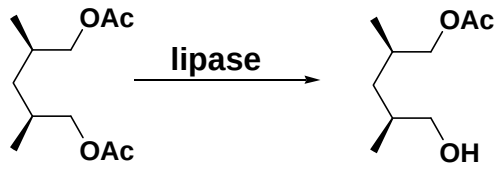
Lipases: ester (usually Ac) on or off under mild conditions; often enantioselectively

kinetic resolution



TL, 1992, 1911

desymmetrization



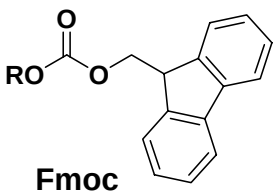
96%ee

for references, see Greene, 3rd ed.p156

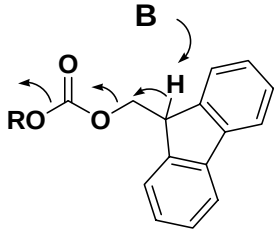
Carbonates

similar deal as with esters, but more stable to base. Also, some alternative cleavage methods possible.

group cleavage

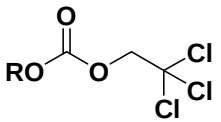


Fmoc



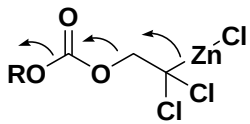
pKa ~ 10

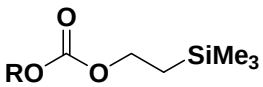
B= Et_3N, $T_{1/2}$=20min



Troc

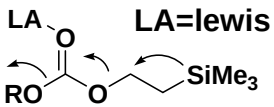
Zn(0)



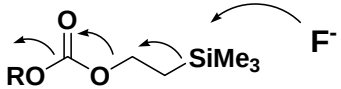


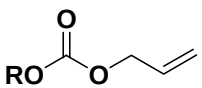
Teoc

LA=lewis acid



or

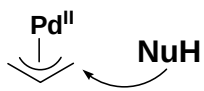


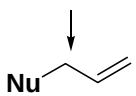


Alloc

cat Pd(0)

NuH

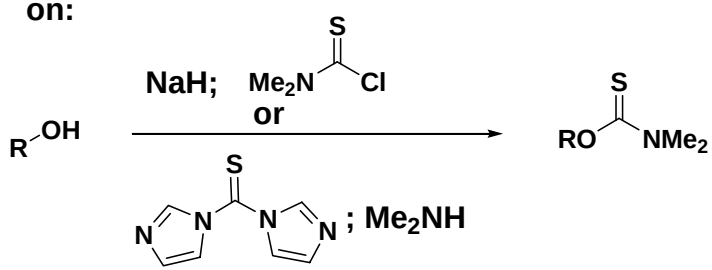


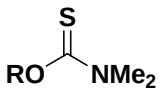


+ ROH + CO_2

Dimethyl Thiocarbamate

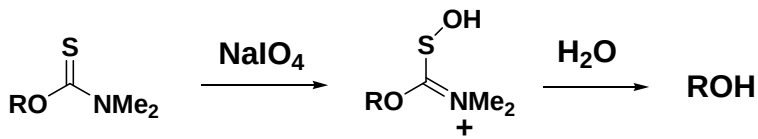
on:





stable to: Cr(VI); EtMgBr; DIBAL; $LiAlH_4$; BH_3; nBuLi; Wittig; TBAF; DDQ; $TiCl_4$

OFF:



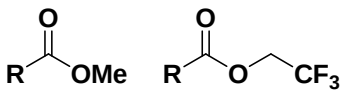
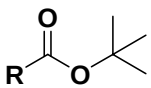
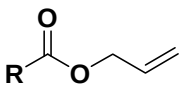
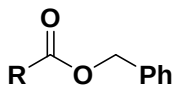
or $NaOH/H_2O_2$

Falck, Org. Lett., 2003,4755

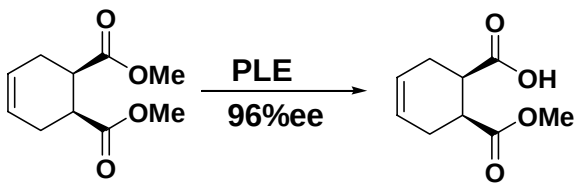
Protection for carboxylate

Mostly, same deal as ester and carbonate

common Eg's

protected substrate	deprotection
	K_2CO_3/MeOH
	H^+ (TFA, HCl, TsOH)
	Pd(0), NuH
	H_2 Pd/C or Li/NH_3

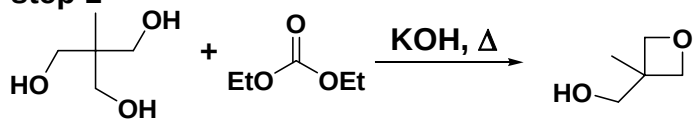
as before, enzymes can work



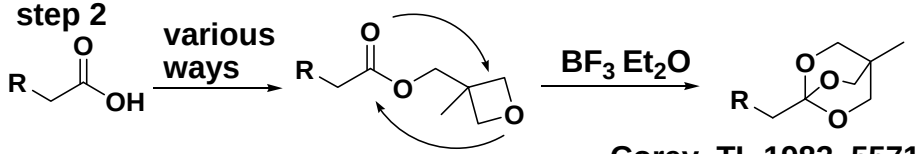
PLE = pig liver esterase
When enzymes work, they're nearly perfect.
Hard to get ent-PLE

ortho esters: not electophilic, no acidic protons

step 1

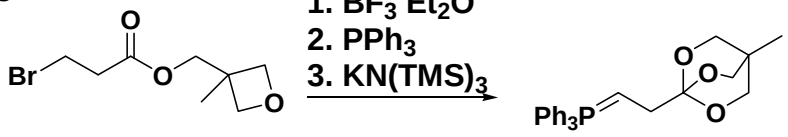


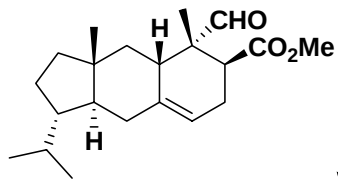
step 2

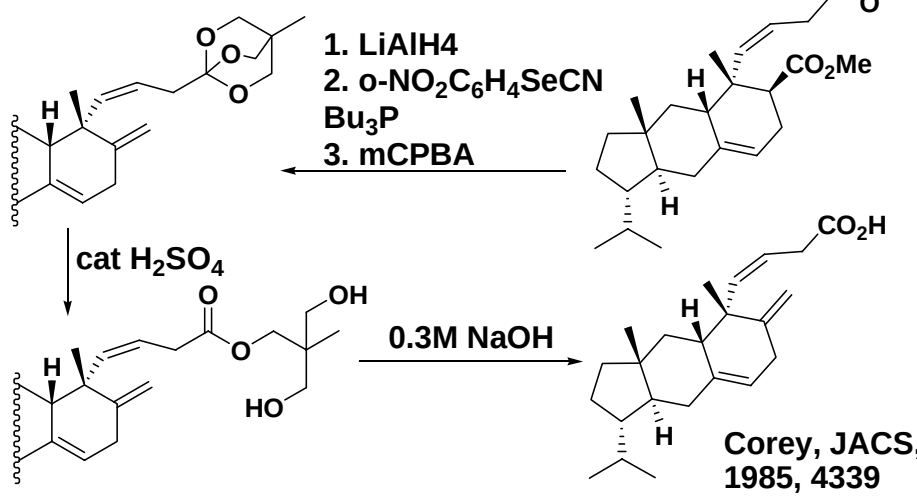


Corey, TL 1983, 5571

eg





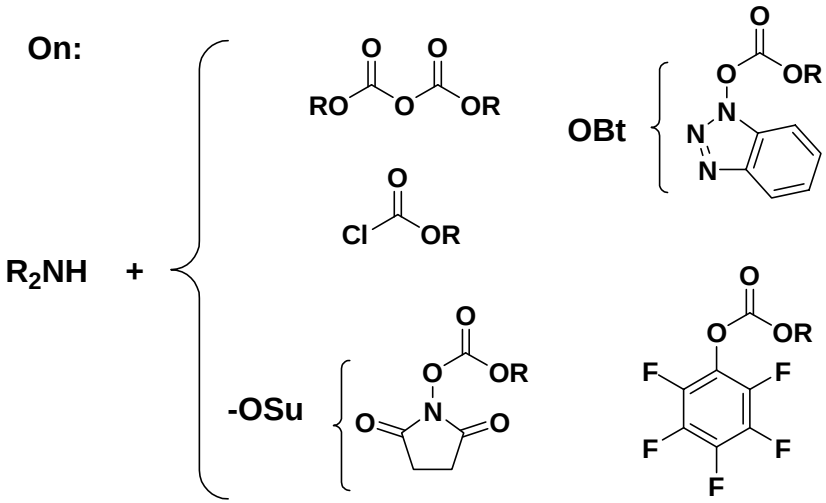


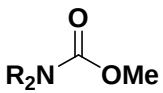
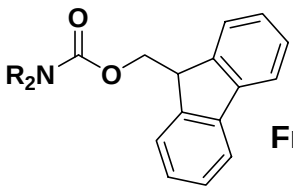
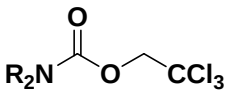
Corey, JACS, 1985, 4339

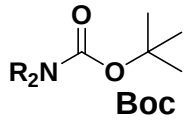
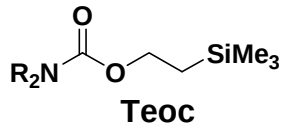
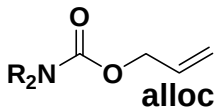
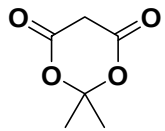
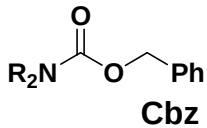
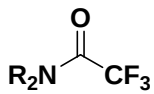
Protection for amines

Mostly carbamates; same deal as ester and carbonate

On:



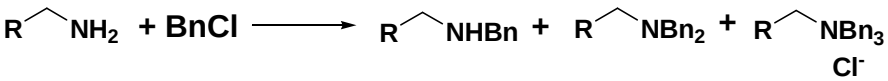
Group	Removal
	NaOH; PrSLi
 Fmoc	amine base (piperidine most common)
 Troc	Zn(0)

Group	Removal
 Boc	acid (TFA most common)
 Teoc	F^- (TBAF most common)
 alloc	Pd(0), NuH
	Meldrum's acid; common NuH
 Cbz	H_2, Pd/C; Na/NH_3
 TFA	NaOH

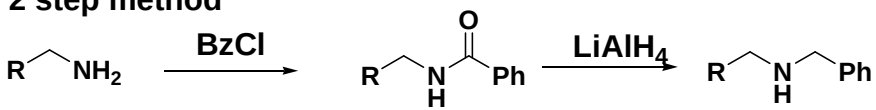
Benzyl groups for amine protection

On:

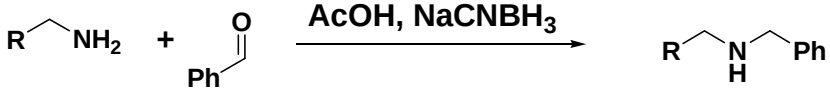
simple alkylation can be difficult



2 step method

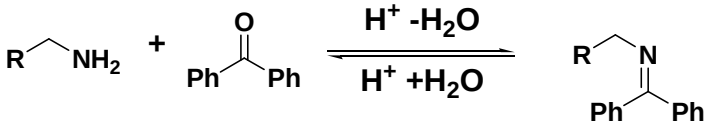


reductive amination



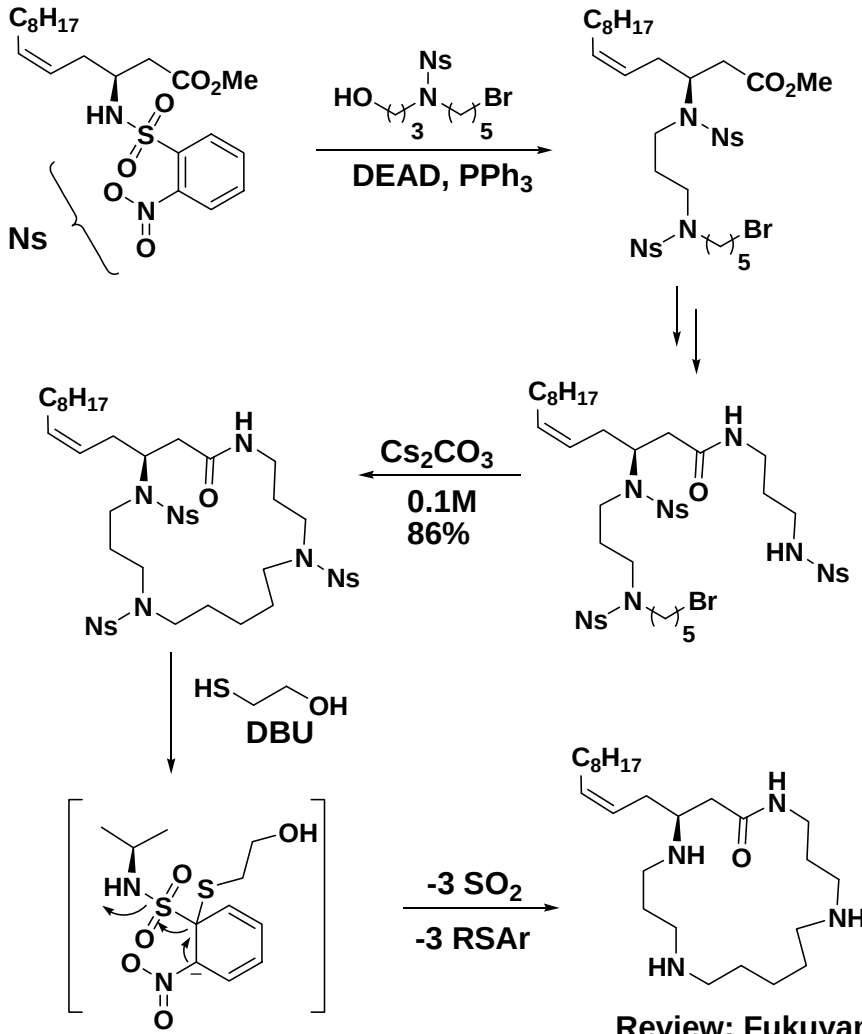
Schiff's bases:

Many examples, benzhydryl one of most common



Sulfonates

Tosyl: Easy on (TsCl); can be difficult to remove
Nosyl (Ns) nice alternative:



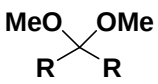
Nucleophilic aromatic substitution

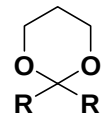
Review: Fukuyama
Chem Comm. 2004, 353

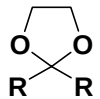
Protection of carbonyl group

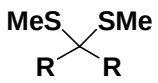
mostly of the form:  X and Y = OR, SR, NR, CN

Most common:


dimethyl acetal


1,3 dioxane


1,3 dioxolane


dimethyl thioacetal

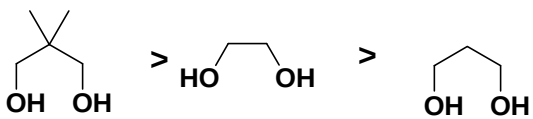

1,3 dithiane


1,3 dithiolane

acetals:

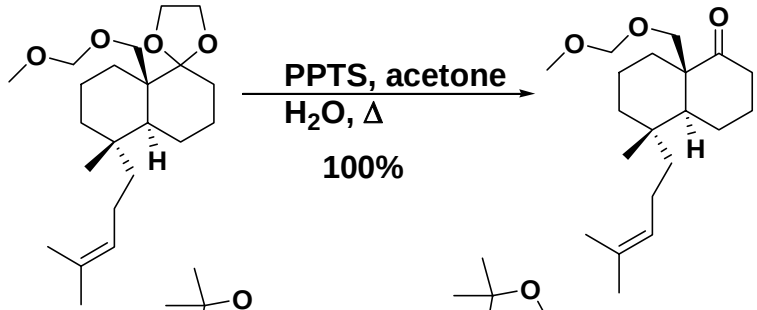
Formation:

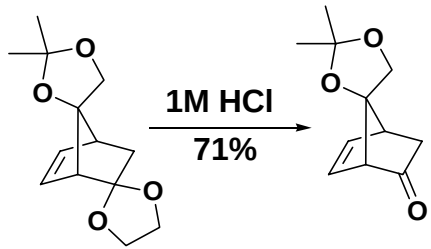
relative rates: for the ketone, relative rates same as normal addition to carbonyls: aldehyde>acylic ketone~cyclohexanone>cyclpentanone>enone>>aromatic ketone



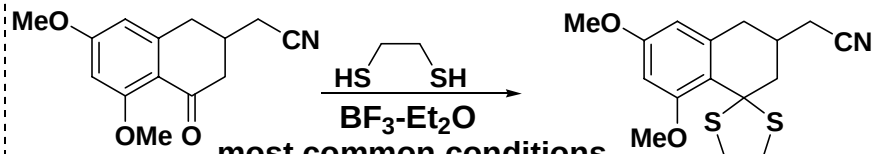
Many variations on this theme; in practice, consult Greene

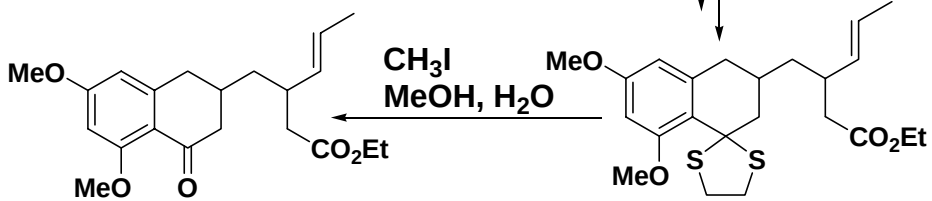
Cleavage: usually hydrolysis or transketalization.
Relative rate usually follows cation (oxonium) stability





Dithioacetals





Weinreb, JOC, 1978, 4172

Other Offs: Sulfur-loving metals (Hg^{II}), [O] (IBX, NBS, I_2)