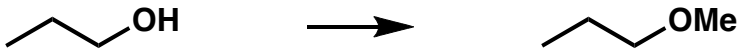
Chem 6352

Protecting Groups

Hydroxyl Protection

Methyl Ethers

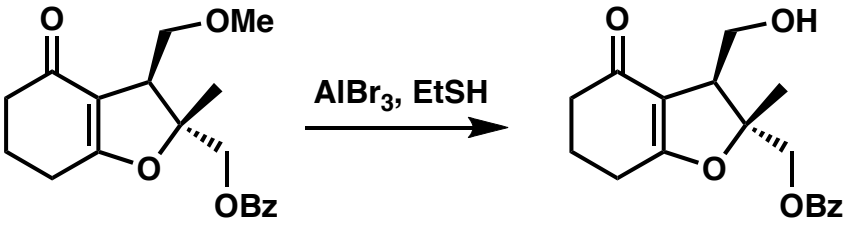


Formation: CH_2N_2, SiO_2 or HBF_4
NaH, MeI, THF

Stability: Stable to Acid and Base

Cleavage: $AlBr_3$, EtSH
$PhSe^-$
Ph_2P^-
Me_3SiI

Adv./Disadv.: Methyl ethers, with the exception of aryl methyl ethers, are often difficult to remove. However, there are exceptions.



TL **1987**, *28*, 3659

Methylthiomethyl Ethers (MTM)

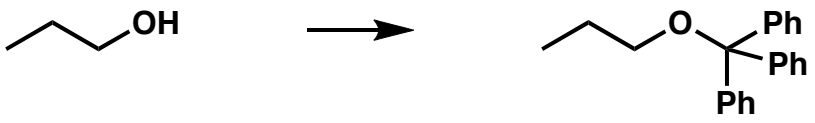
Formation: $MeSCH_2Cl$, NaH, THF

Stability: Stable to base and mild acid

Cleavage: $HgCl_2$, CH_3CN, H_2O
$AgNO_3$, THF, H_2O, base

Adv./Disadv.: The MTM group is a nice substituted methyl ether protecting group that can be removed under neutral conditions employing the indicated thiophiles.

Trityl Ethers



Formation: Ph_3CCl, pyridine, DMAP
$Ph_3C^+BF_4^-$

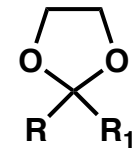
Stability: Stable to Base

Cleavage: Mild Acid (formic or acetic)

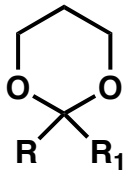
Adv./Disadv.: The trityl group usually goes on and comes off easily. In addition, its steric bulk allows for good selectivity in protecting primary over secondary alcohols.

Protection of 1,2- and 1,3-diols

The protecting groups that mask 1,2- and 1,3-diols (forming either the dioxolane or dioxane, respectively) are often referred to (PREFIX)ylidenes, where the prefix depends on the nature of R and R_1.

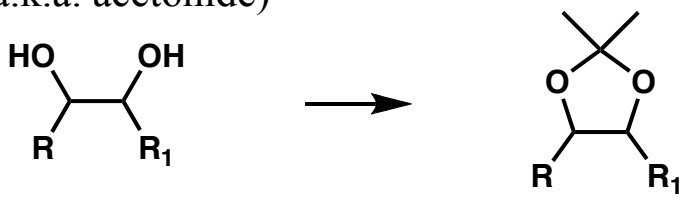


dioxolane



dioxane

Isopropylidene (a.k.a. acetonide)



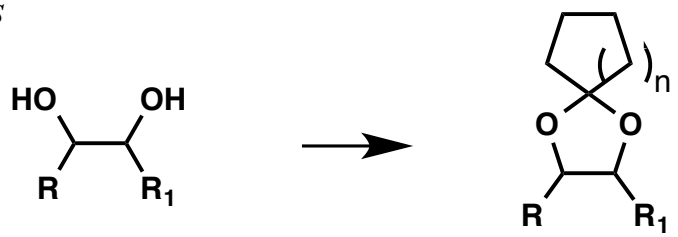
Formation: 2,2-dimethoxy propane or 2-methoxy propene and cat. acid

Stability: Stable to base

Cleavage: cat. Camphor Sulfonic Acid (CSA) and MeOH

Adv./Disadv.: The acetonide is commonly used to protect 1,2- and 1,3-diols. It forms readily and is easily removed. Generally, the acetonide will form a dioxolane selectively over a dioxane.

Cycloalkylidenes



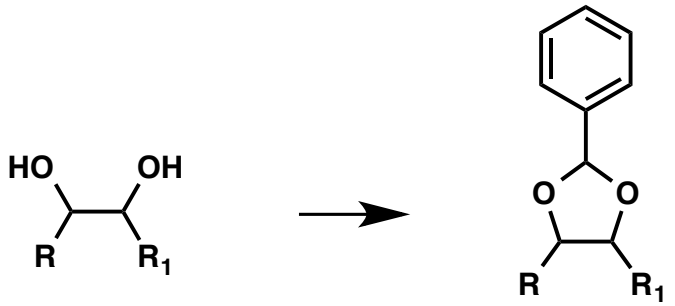
Formation: Corresponding ketone or dimethyl acetal and acid catalyst

Stability: Stable to Base

Cleavage: cat. Camphor Sulfonic Acid (CSA) and MeOH

Adv./Disadv.: Similar to acetonides

Benzylidene



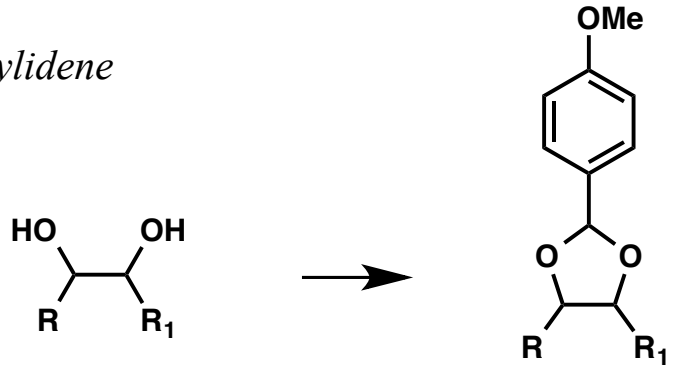
Formation: PhCHO, H^+, H_2O removal
$PhCH(OMe)_2$, H^+

Stability: Stable to base

Cleavage: cat. Camphor Sulfonic Acid (CSA) and MeOH
H_2, catalyst

Adv./Disadv.: The benzylidenes are readily formed; in competition between 1,2- and 1,3-diols they will generally form the dioxane. Hydrogenolysis provides a nice orthogonal mode of deprotection. However, benzylidenes are usually hydrogenolyzed more slowly than benzyl ethers or olefins.

p-Methoxy Benzylidene



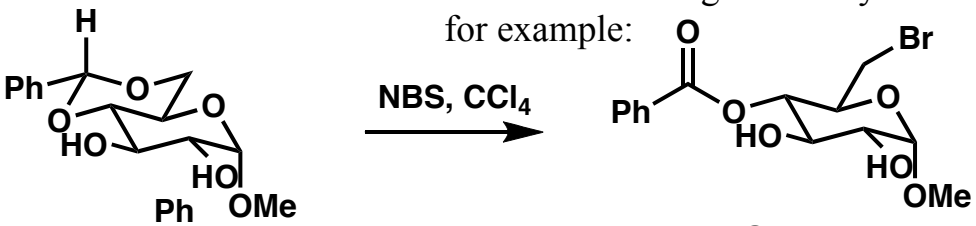
Formation: See benzylidenes

BENZYLIDENE CONTINUED ON NEXT PAGE

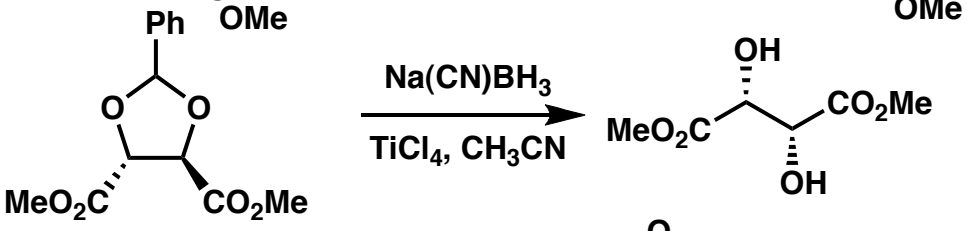
Stability: Stable to Base

Cleavage: AcOH, H_2O
CAN

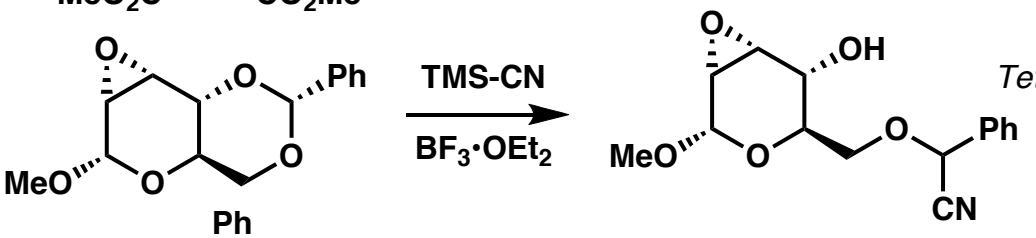
Adv./Disadv.: The PMB and Bn acetals have many advantages and are usually easy to prepare and cleave. The PMB and Bn acetals can undergo a variety of interesting transformations, for example:



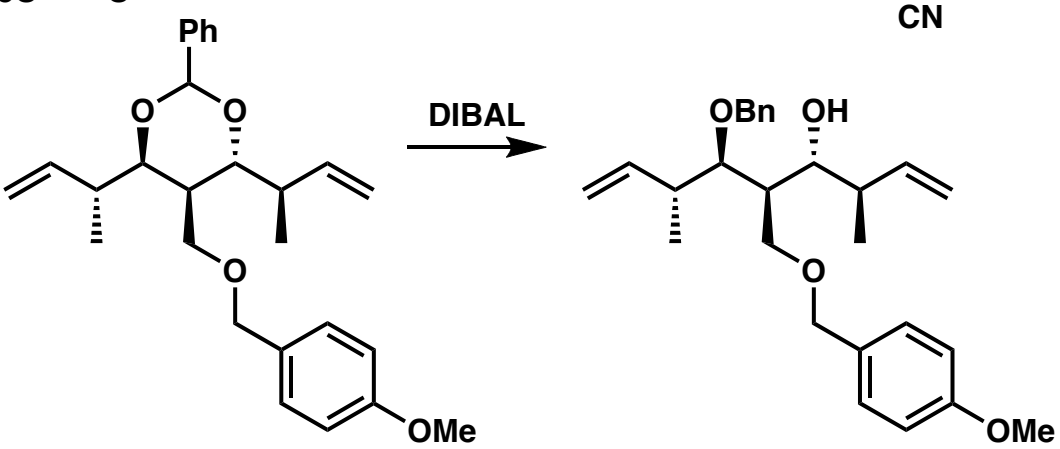
Org. Syn. **1987**, *65*, 243



Synthesis **1988**, 373

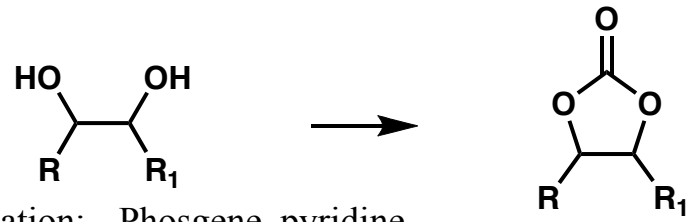


Tetrahedron **1985**, *41*, 3867



TL **1988**, *29*, 4085

Carbonates



Formation: Phosgene, pyridine
Triphosgene, pyridine
Carbonyl diimidazole

Stability: Stable to Base

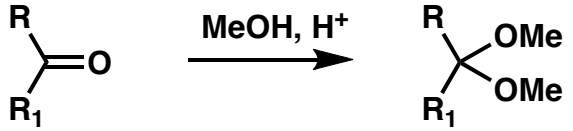
Cleavage: Easily removed with ^{-}OH or ^{-}H

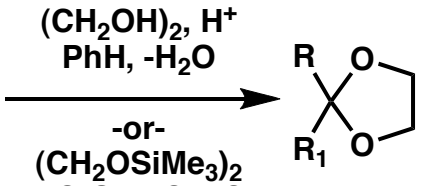
Adv./Disadv.: Carbonates are generally easy to put on and take off and provide nice orthogonality to the numerous acid labile protecting groups for 1,2- and 1,3-diols.

Protecting Groups for Ketones and Aldehydes

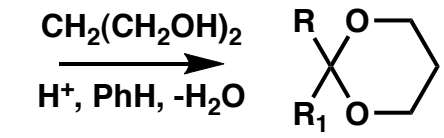
Aldehydes and ketones are most often protected as cyclic and acyclic actals.

Formation:



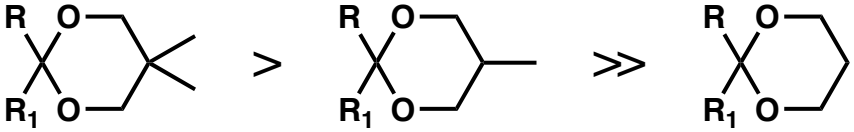


TL **1988**, *29*, 4085

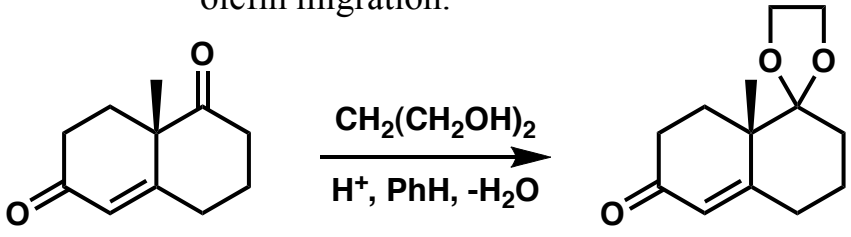


Stability: Stable to base

Cleavage: Acetals are generally removed with H_3O^+. Cleavage rates of 1,3-dioxanes have been studied (*Chem Rev* **1967**, *67*, 427) and are:

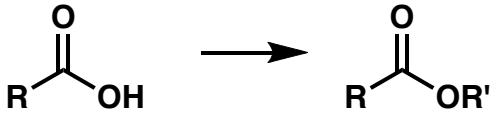


Adv./Disadv.: Acetals are generally easily prepared and removed. It is of note that α,ß-unsaturated carbonyls form acetals much slower than their saturated counter parts, and often result in olefin migration.



Carboxylic Acid Protection

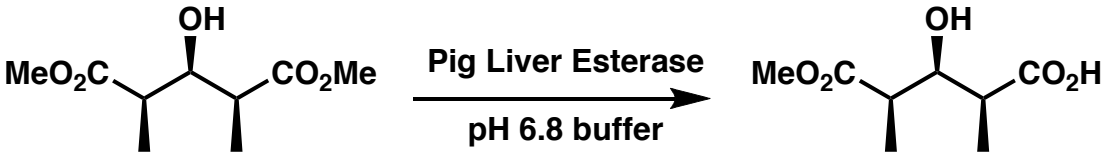
Alkyl Esters



Formation: Fisher esterification (RCOOH + R'OH + H^+)
Acid chloride + ROH, pyridine
t-Butyl esters: isobutylene, H^+
Methyl esters: diazomethane

Stability: *t*-Butyl: stable to mild base and ammonia
Others: stable to acid

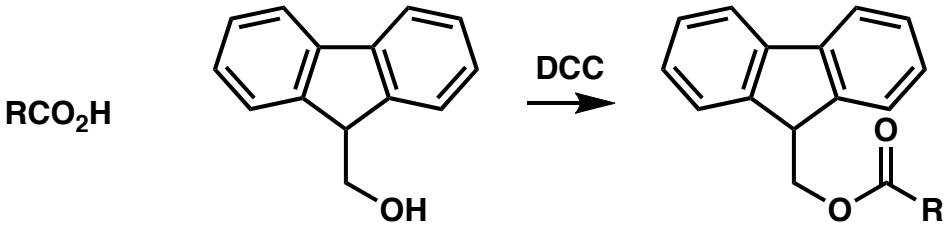
Cleavage: *t*-Butyl: cleaved by moderately acidic hydrolysis
Others: LiOH, THF, H_2O
enzymatic hydrolysis



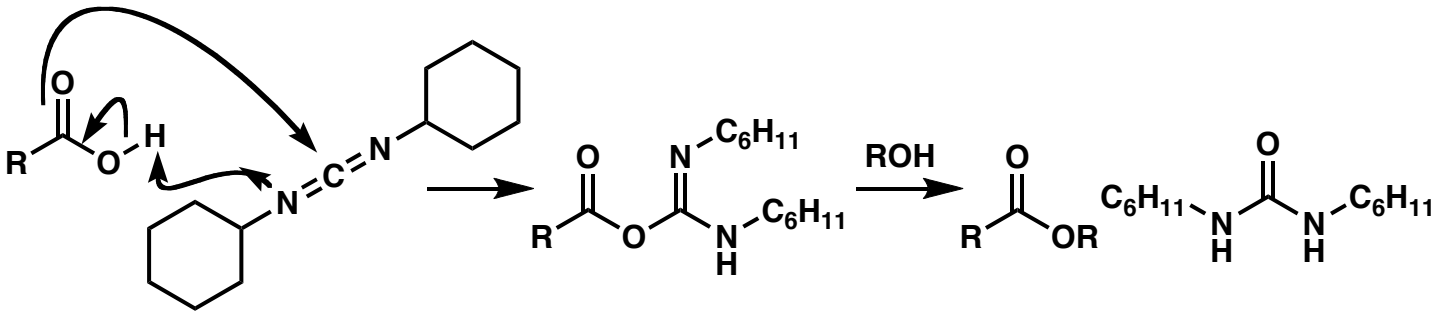
Review: *Org Reactions* **1989**, *37*, 1

9-Fluorenylmethyl Esters (Fm)

TL **1983**, *24*, 281



Note that DCC coupling proceeds as follows:

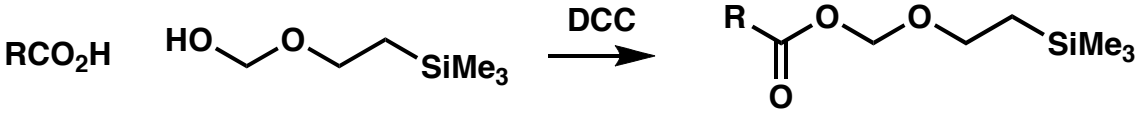


Stability: Fm is stable to acid

Cleavage: Fm is cleaved by mild base (Et_2NH)

2-(Trimethylsilyl)ethoxymethyl Esters (SEM)

Helv Chim Acta **1977**, *60*, 2711

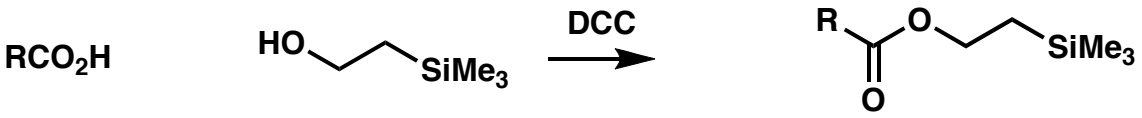


Stability: Stable to Acid

Cleavage: SEM is removed with fluoride (e.g. TBAF in DMF)

2-(Trimethylsilyl)ethyl Esters

JACS **1984**,*106*, 3030

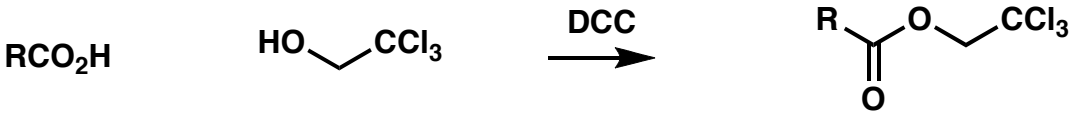


Stability: Stable to Acid

Cleavage: SEM is removed with fluoride (e.g. TBAF in DMF)

2,2,2-Trichloroethyl Ester

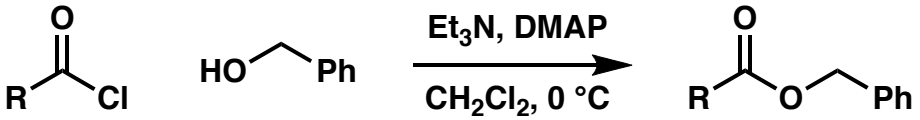
JACS **1966**, *88*, 852



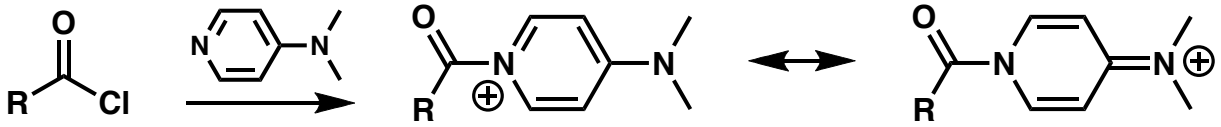
Stability: Stable to Acid

Cleavage: Zn, AcOH

Benzyl Esters



Note: DMAP = 4-dimethylamino pyridine



For a review of 4-dialkylaminopyridines see **ACIEE** *1978*, *17*, 569

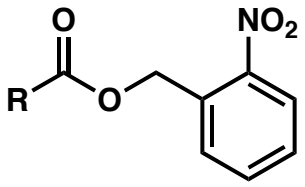
Formation: Acid Chloride and benzyl alcohol (see above)

Stability: Stable to Acid

Cleavage: Hydrogenolysis
Na, NH_3

o-Nitrobenzyl esters

Synth **1980**, 1



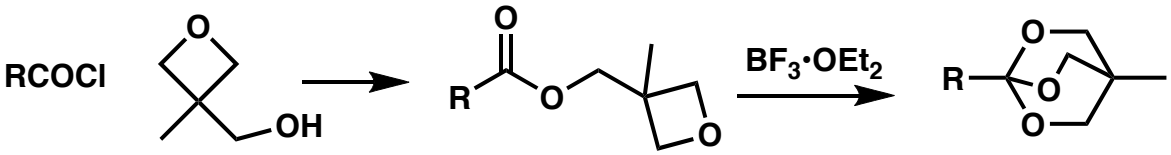
Formation: see Benzyl

Stability: see Benzyl

Cleavage: can be cleaved by photolysis

Orthoesters

TL **1983**, *24*, 5571



Formation: See above reaction

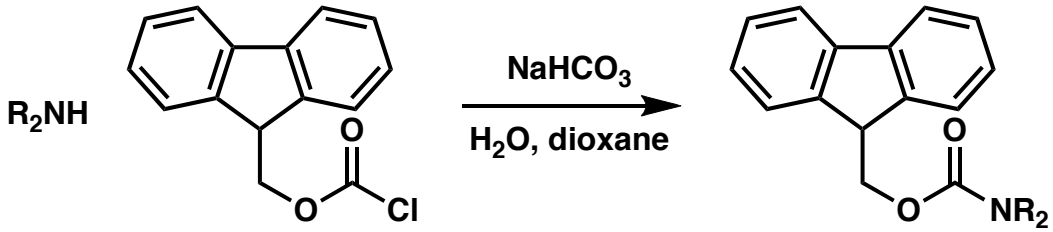
Stability: Stable to Base!

Cleavage: Removed with mild acid

Protection of Amines

9-Fluorenylmethyl carbamate (FMOC)

Acc Chem Res **1987**, *20*, 401

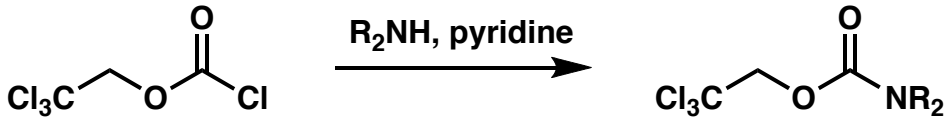


Formation: As above

Stability: Stable to acid

Cleavage: Removed with amine base: Et_2N, piperidine, etc.

2,2,2-Trichloroethyl Carbamate (TROC)

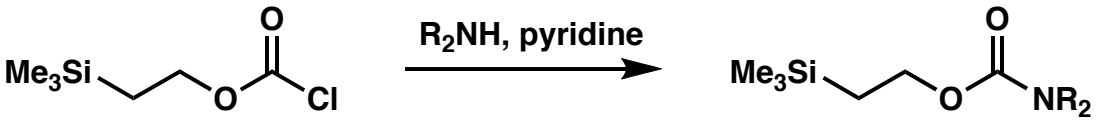


Formation: As above

Stability: Stable to mild base and acid

Cleavage: Zn dust

2-(Trimethylsilyl)ethyl Carbamate (TEOC)

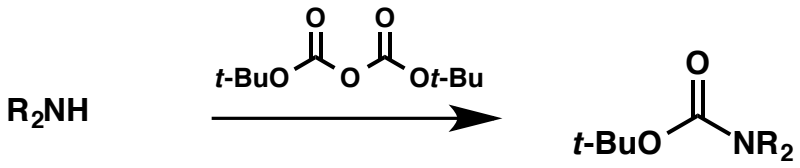


Formation: As above

Stability: Stable to mild base and acid

Cleavage: TBAF or TFA

t-Butyl Carbamate (BOC)



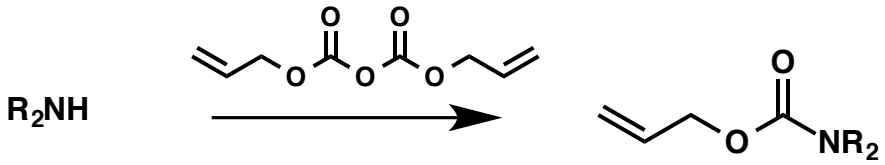
Formation: As above (and many others)

Stability: Stable to base

Cleavage: Strong protic acid (TFA or 3M HCl)
TMSI

Allyl Carbamate (ALLOC)

TL **1986**, *27*, 3753

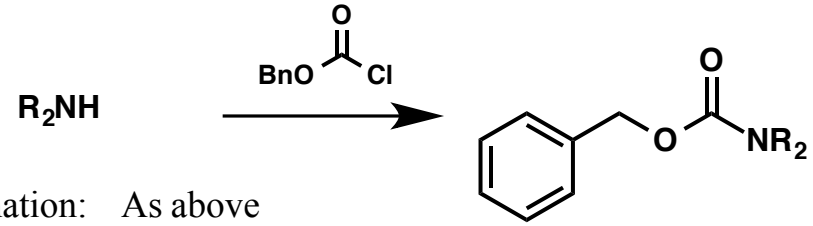


Formation: As above or with Alloc-Cl

Stability: Stable to mild base and acid

Cleavage: Removed with Pd(0) and reducing agent

Benzyl Carbamate (CBZ)

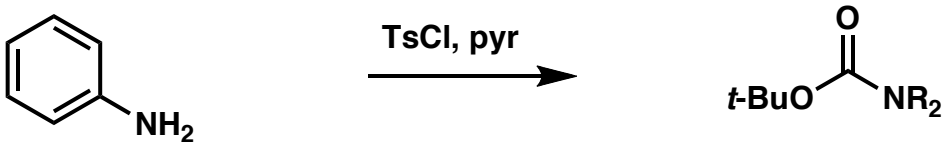


Formation: As above

Stability: Stable to mild base and acid

Cleavage: Hydrogenolysis
$PdCl_2$, Et_2SiH
TMSI
BBr_3
hν (254 nm)
Na/NH_3

Sulfonamides (Ts, Ms)



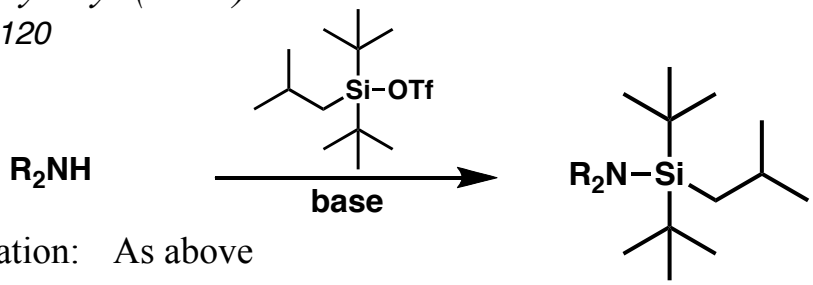
Formation: As above

Stability: Usually stable to acid and base

Cleavage: Reduction (Mg, NH_4Cl, MeOH)
For 3-substituted indoles basic hydrolysis

isobutyldi-tert-butylsilyl (BIBS)

OL 2011, 13, 4120



Formation: As above

Stability: Stable to mild base and acid

Cleavage: Removed fluoride