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PROTECTING GROUPS FOR ORGANIC SYNTHESIS

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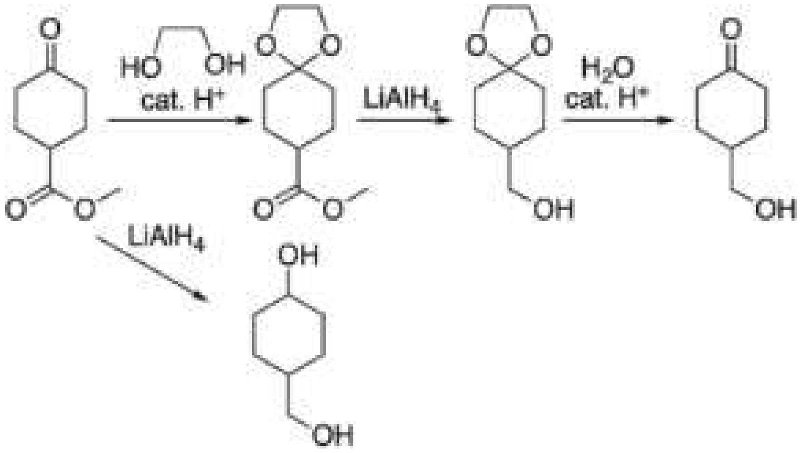
Abstract: A protecting group (English protecting group - therefore often referred to as common abbreviation in formula schemes PG) is in chemistry a substituent which, during a more complicated, multi-step chemical synthesis in a molecule is introduced to a specific functional group to protect temporarily and so an undesirable reaction to prevent this group. After the desired reaction has been carried out elsewhere on the molecule, the protective group is split off again. For many functional groups several possible protective groups are known which differ in their stability and the conditions for their cleavage. In the synthesis of special classes of compounds with repeating functional groups - usually biomolecules such as peptides, oligosaccharides or nucleotides - standard sets of protective groups have become established. Protecting groups have become an important tool in the synthesis of complex compounds today. The requirements for a protection group are quite high. This includes that it can be introduced specifically to a functional group with very good vield and that it must also be able to be split off yield and that it must also be able to be split off again under mild conditions. It should be possible to standardize the reaction conditions for both steps. In addition, the protective group must be stable under as many reaction conditions as possible. If possible, the resulting reaction products should be easily separable, and optimally the protective group reagent is also inexpensive. The broader the experience with a protective group, the better the predictability of the reactivity of the protective group.

Keywords: -

Annotation

What is the protecting group

A protecting group or protective group is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a subsequent chemical reaction. It plays an important role in multistep organic synthesis.

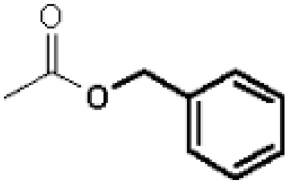


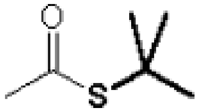
Acetal protection of a ketone with ethylene glycol during reduction of an ester, vs. reduction to a diol when unprotected.

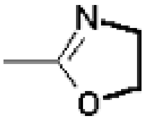
In many preparations of delicate organic compounds, some specific parts of their molecules cannot survive the required reagents or chemical environments. Then, these parts, or groups, must be protected. For example, lithium aluminium hydride is a highly reactive but useful reagent capable of reducing esters to alcohols. It will always react with carbonyl groups, and this cannot be discouraged by any means. When a reduction of an ester is required in the presence of a carbonyl, the attack of the hydride on the carbonyl has to be prevented. For example, the carbonyl is converted into an acetal, which does not react with hydrides. The acetal is then called a protecting group for the carbonyl. After the step involving the hydride is complete, the acetal is removed (by reacting it with an aqueous acid), giving back the original carbonyl. This step is called deprotection

Use of the Protecting groups in the industrial scales

Protecting groups are more commonly used in small-scale laboratory work and initial development than in industrial production processes because their use adds additional steps and material costs to the process. However, the availability of a cheap chiral building block can overcome these additional costs (e.g. shikimic acid for oseltamivir).





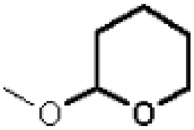


Hydroxyl

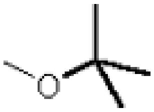
>> Stability

Methoxymethyl ether (MOM-OR)

Tetrahydropyranyl ether (THP-OR)

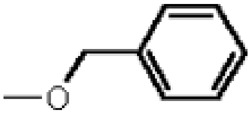


t-Butyl ether

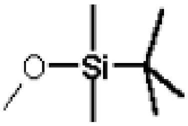


Allyl ether

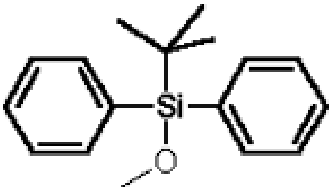
Benzyl ether (Bn-OR)



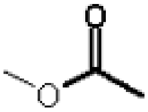
t-Butyldimethylsilyl ether (TBDMS-OR)



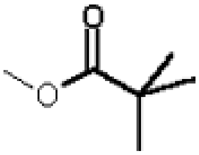
t-Butyldiphenylsilyl ether (TBDPS-OR)



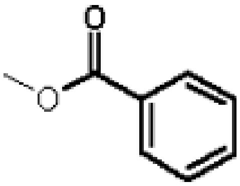
Acetic acid ester



Pivalic acid ester



Benzoic acid ester

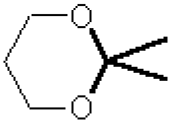


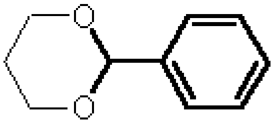
1,2-; 1,3-Diols

Acetonide

Benzylidene acetal

>> Stability





protecting by decree sing raqfinty

A protective group (also referred to as "protecting group") is a reversably formed derivative of an existing functional group in a molecule. The protective group is temporarily attached to decrease reactivity so that the protected functional group does not react under synthetic conditions to which the molecule is subjected in one or more subsequent steps. As an example, whereas amines are nucleophiles and react with electrophiles, the amino group is no longer nucleophilic after being converted to a carbamate. Protecting an amine as a carbamate therefore enables other functional groups to undergo selective reactions with electrophiles whereby the carbamate (protected amino group) is left intact. However, two additional synthetic steps are needed to achieve this protection: the step to form the protected intermediate and a deprotection once the additional selective synthetic steps have been completed. In addition, the nature of the protective group must be chosen carefully to ensure adequate stability throughout all the intermediary synthesis steps. Moreover, the conditions for the protection and deprotection steps and the nature of the protective group itself mustn't interfere with other functional groups present in the molecule.

If more than one functional group of the same type is present in a molecule, subtle differences in reactivity - for example caused by steric effects - can help to achieve the selective protection of just one functional group while another such functional group remains unprotected. Alternatively, a second such functional group could be

protected with a different protecting group that has a different reactivity profile. Another opportunity is to build a larger molecule from subunits in which similar or identical functional groups have been differently protected beforehand. For example, a Boc- protected amino group can be deprotected in acidic media, whereas a Fmoc-protected amino group can be deprotected under basic conditions. The presence of both protective groups in the same molecule therefore enables selective deprotection of one protected amino group for a further reaction while the second protected amino group remains untouched. This is referred to as an orthogonal protecting group strategy.

Not only is selectivity important, but the yields for the protection and deprotection steps must be high to avoid making the reaction sequence inefficient. As a result, chemists in recent years prefer to design synthesis pathways that employ steps conducted under more selective reaction conditions, engineered to affect and convert only the specific desired functional group rather than harsher, less selective conditions that require protection for differentiation. Another tactic is to employ reaction conditions under which the functional group "protects itself" temporarily, for example as an anion under basic conditions or a cation under acidic conditions. These minimalist approaches can be summarized in the statements that, "the best protective group is no protective group", and "the best protective group is the one that isn't required". The demands of designing environmentally friendly ("green") synthesis pathways, or simply more efficient synthesis pathways with fewer steps and higher overall yields, have resulted in a number of reports of synthetic sequences to produce natural compounds or other synthesis targets that are fully protective group-free.

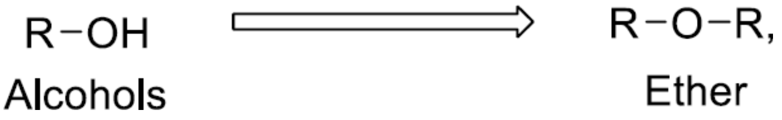
Protection of protecting groups for organic synthesis in which to produced

1. Hydroxyl groups
2. Ketones and aldehydes
3. Amines

4. Carboxylic Acids
5. Alkynes

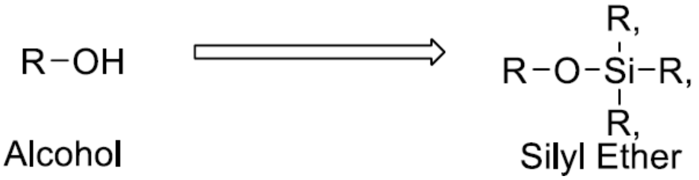
1. Protecting Groups for Alcohols

The common protecting groups for alcohols are ether-protecting groups. Ethers are among the least reactive of the organic functional groups

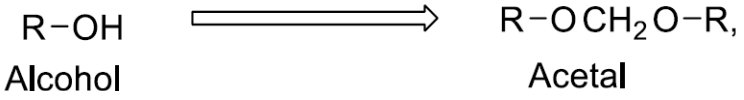


The ether protecting groups of alcohols can be grouped in the following categories:

1. Silyl ether protecting groups

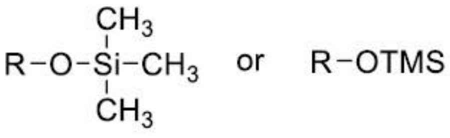


2. Acetal protecting groups

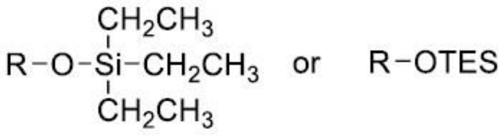


These protections replace the acidic proton on an alcohol with an unreactive ether moiety.

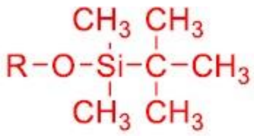
Common Silicon-Based Protecting Groups for Alcohols



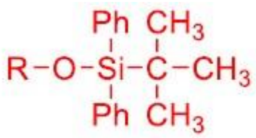
Trimethylsilyl



Triethylsilyl



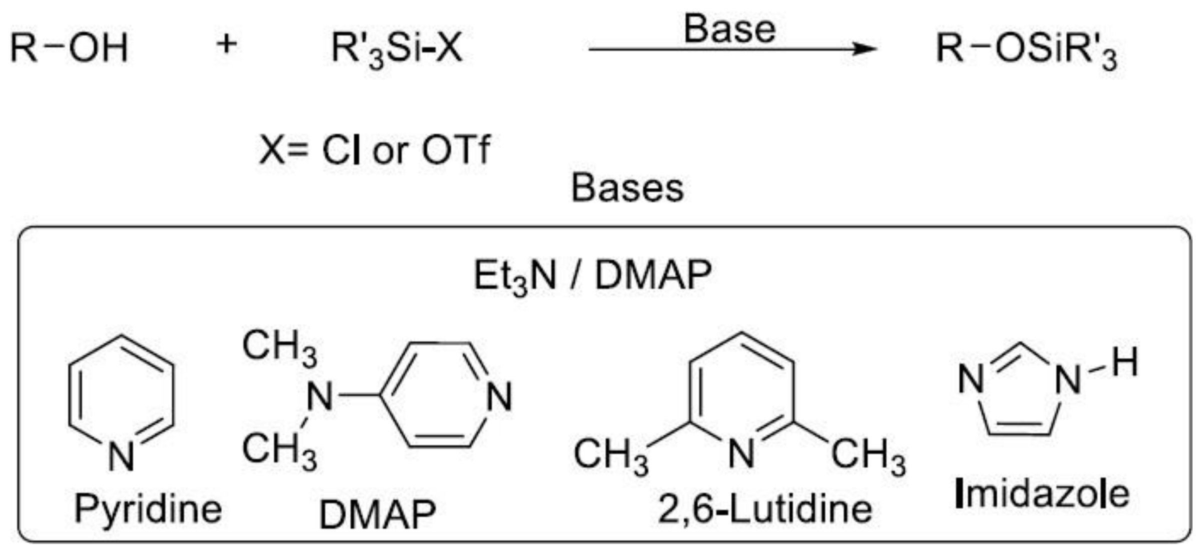
Tert-Butyldimethylsilyl (TBDMS)



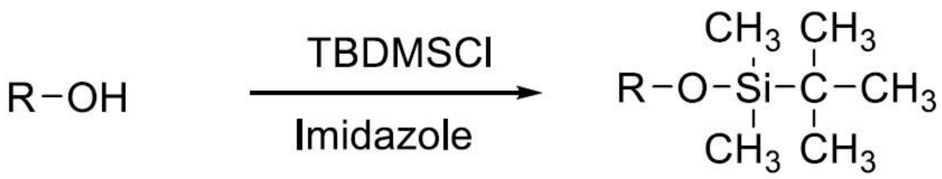
Tert-Butyldiphenylsilyl (TBDPS)

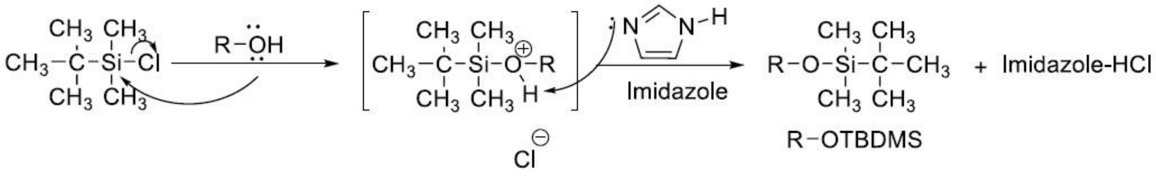
Formation

Silicon-Based Protecting Groups for Alcohols

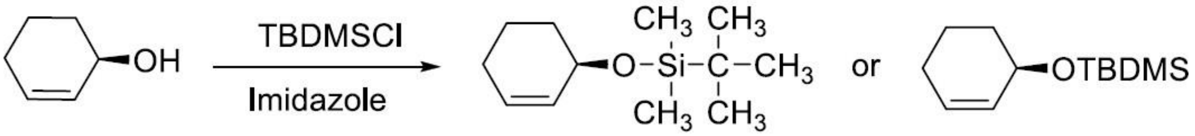


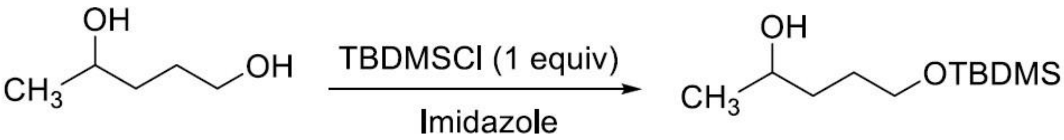
Tert-Butyldimethylsilyl ethers (TBDMS)





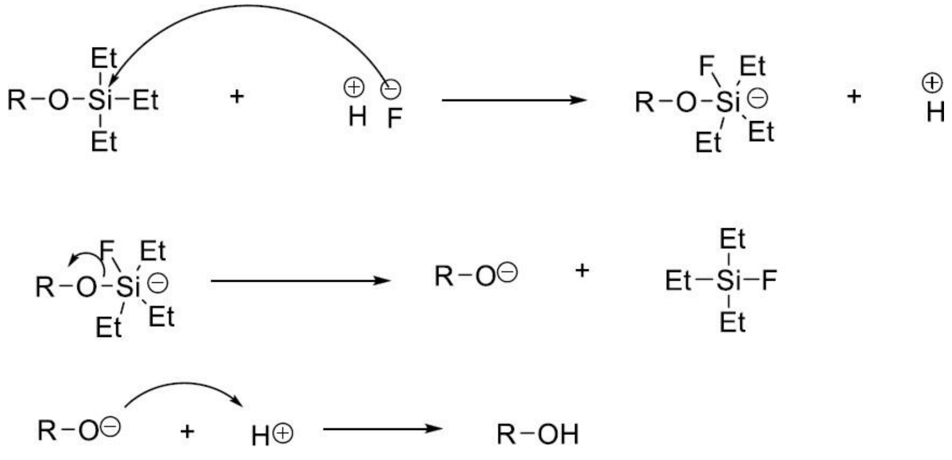
Example





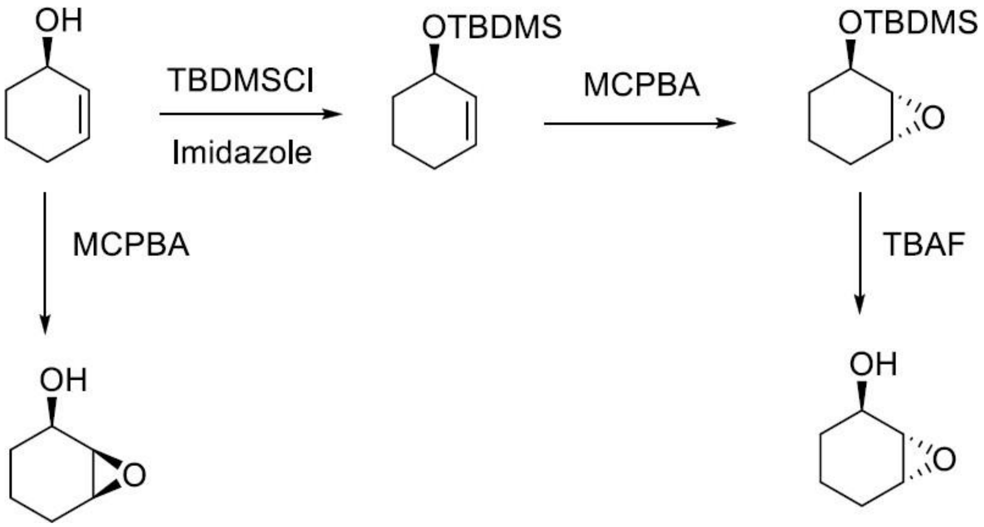
(Silyl Protecting Groups) Cleavage

Deprotection of Silicon-Based Protecting Groups



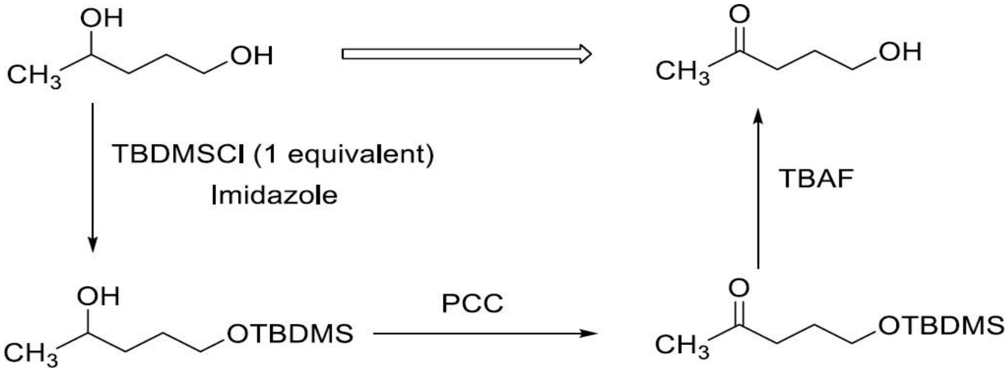
Synthetic Applications of Silyl Protecting Groups

The bulkiness of TBDMS and TBDPS ether protecting groups can be used to advantage to suppress hydrogen-bonding to the oxygen restricting any incoming reagents to approach from the least hindered side of the molecule.

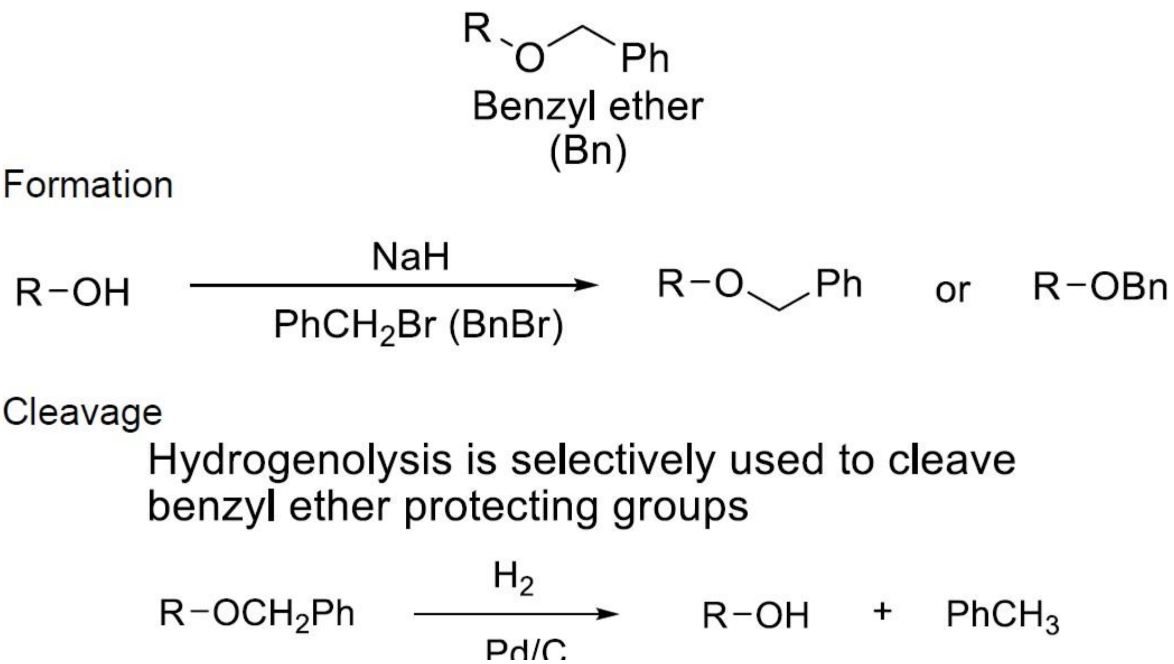


Synthetic Applications of Silyl Protecting Groups

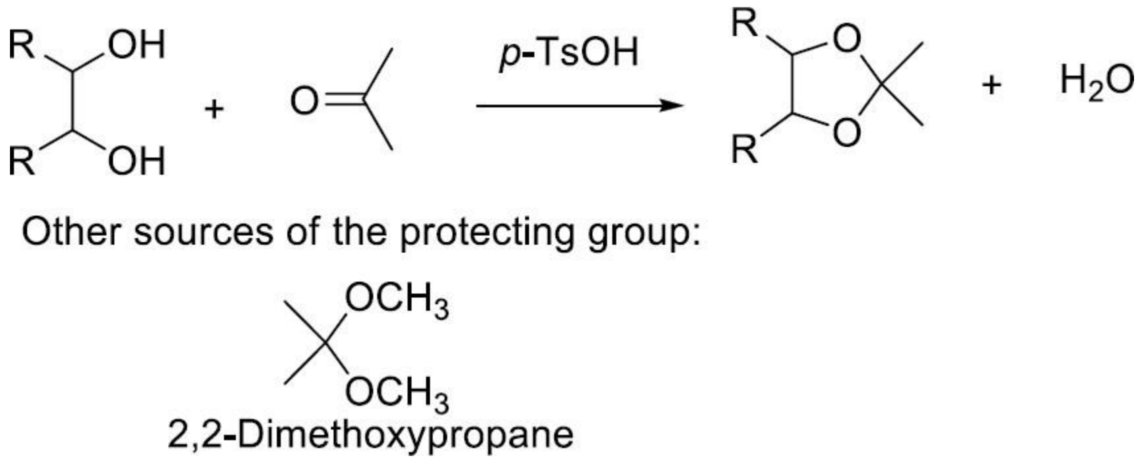
The bulkiness of TBDMS and TBDPS ether protecting groups can also be exploited in incorporating the protecting group on less sterically encumbered primary hydroxyl groups selectively using submolar amounts of the silyl chloride.



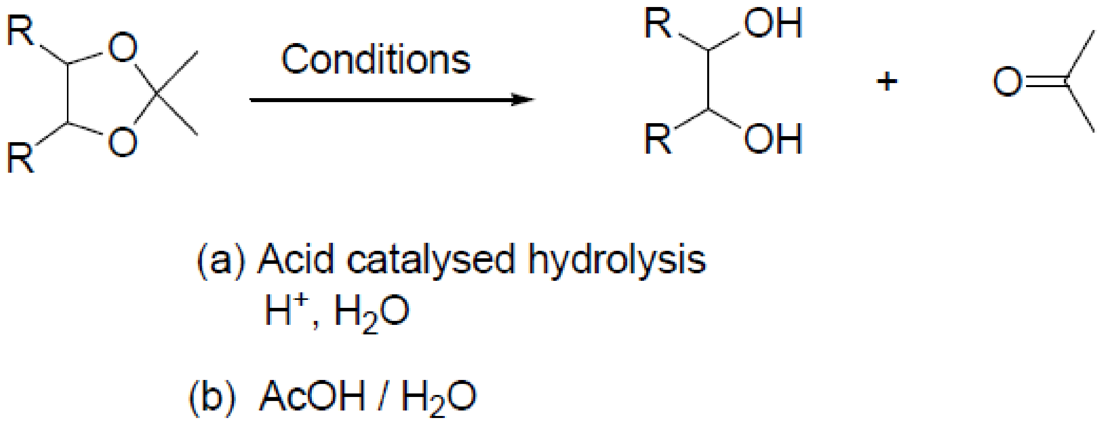
Rarely are alkyl ethers used as protecting groups for alcohols, but benzyl ethers are special.



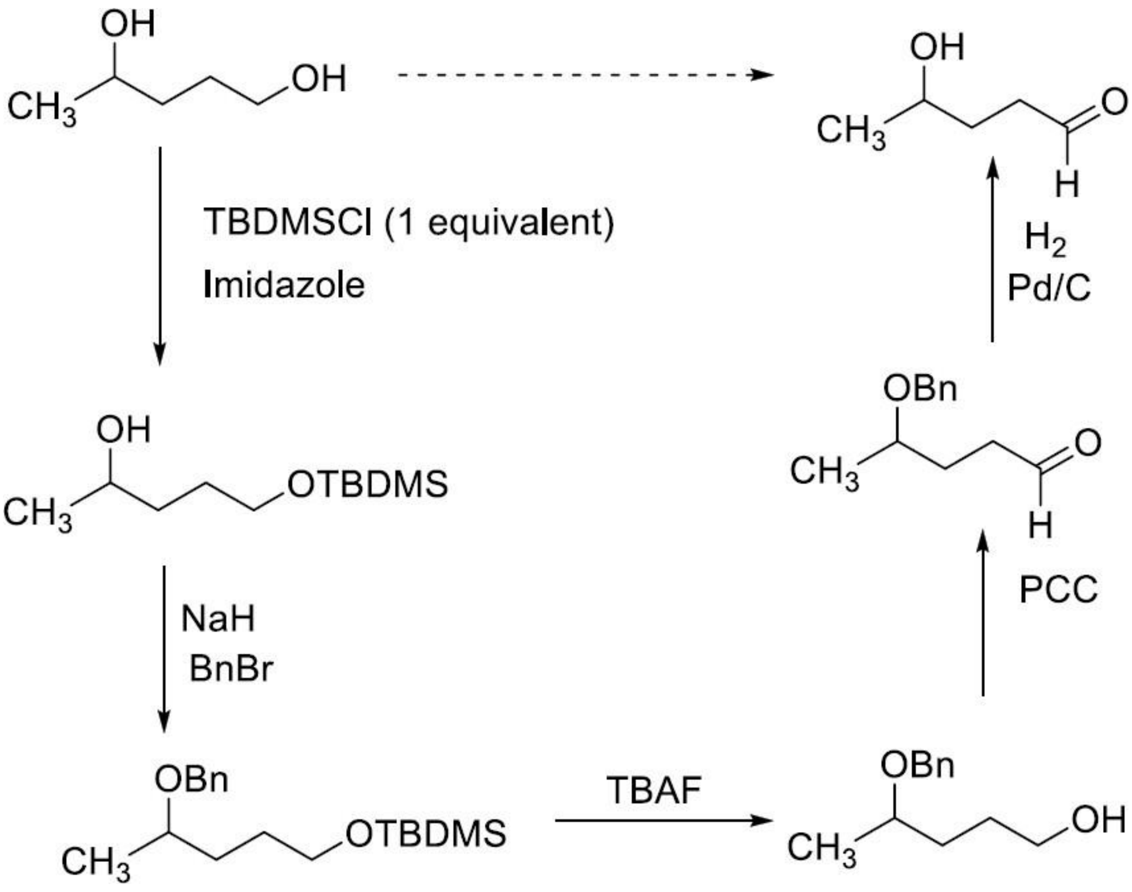
Acetonide Protecting Groups for 1,2-Diols Formation

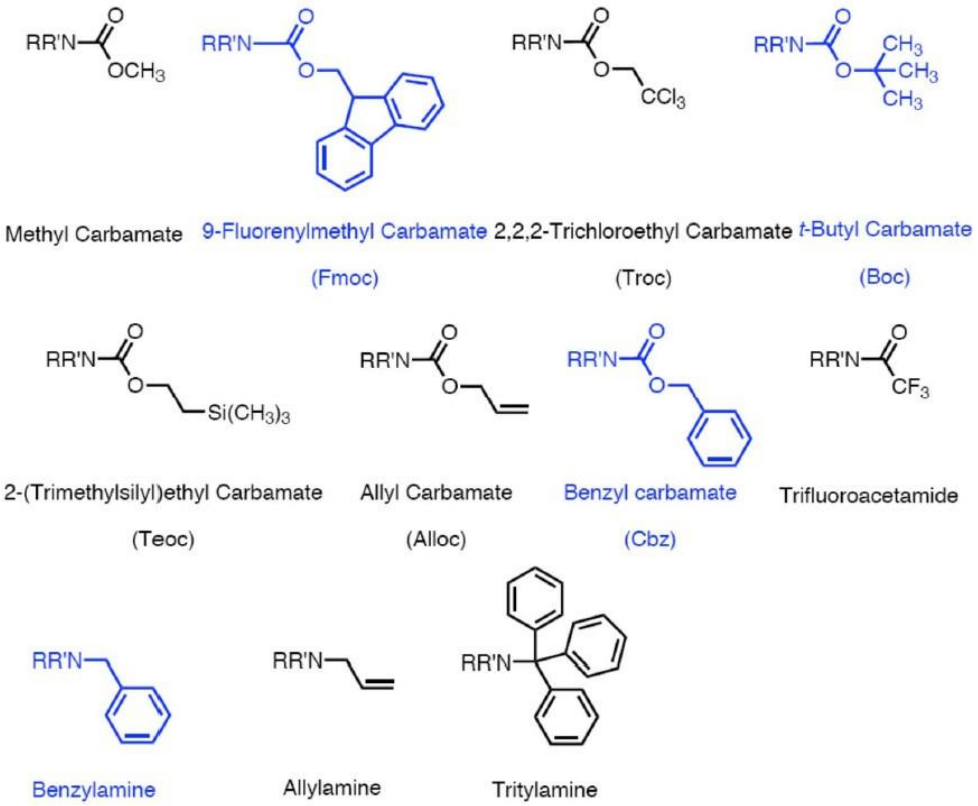


Cleavage



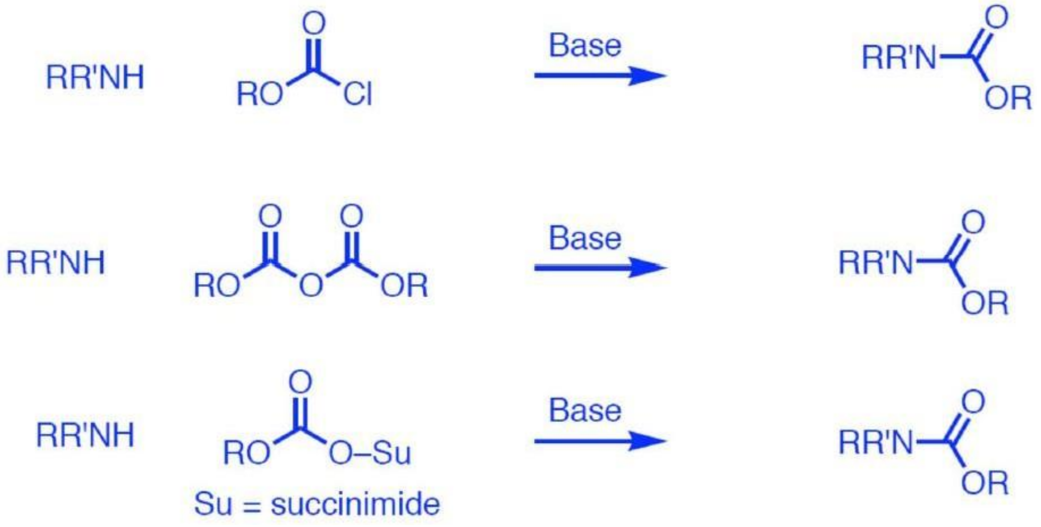
Synthetic Applications of Ether Protecting Groups





2. Amine Protecting Groups

General preparation

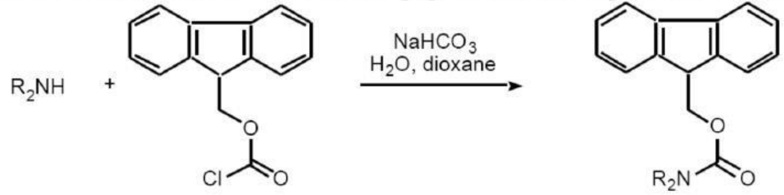


Carbamates

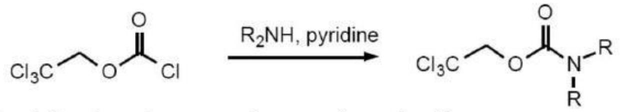
9-Fluorenylmethyl Carbamate (Fmoc)

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

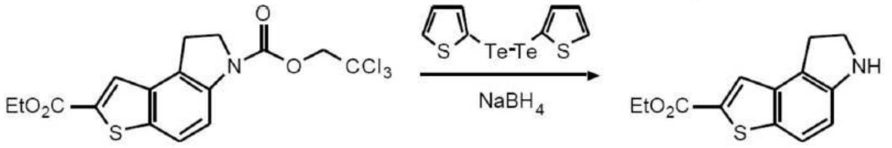
- Cleaved with mild base such as piperidine, morpholine or dicyclohexylamine



2,2,2-Trichloroethyl Carbamate



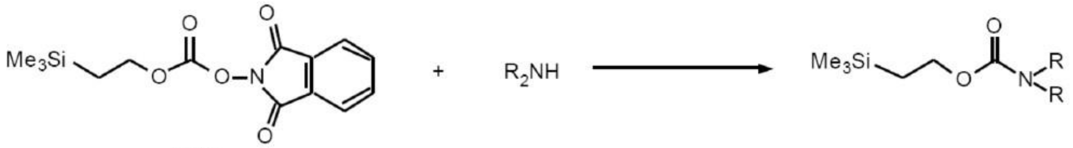
- Cleaved with zinc dust or electrochemically.

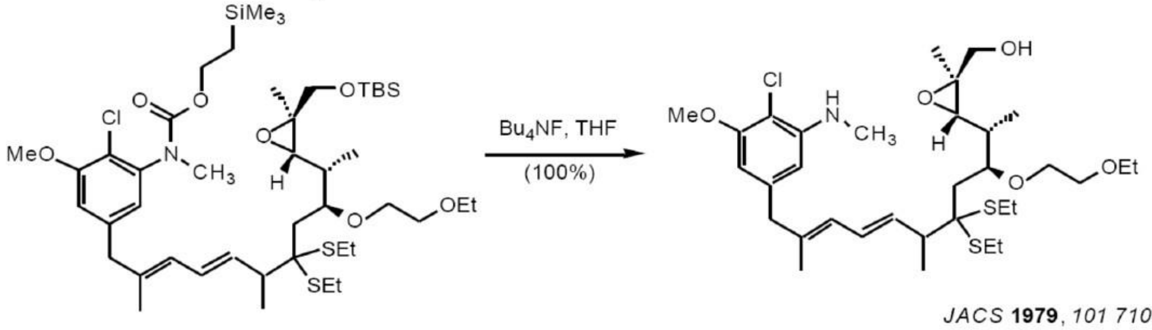


TL **1986**, *27* , 4687

2-Trimethylsilylethyl Carbamate (Teoc)

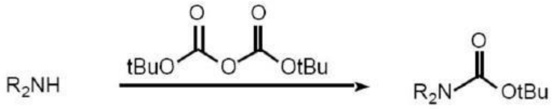
- cleaved with fluoride ion.



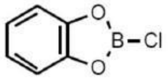


JACS **1979**, *101 7104*

t-Butyl Carbamate (BOC)

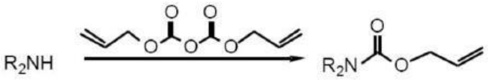


Cleavage:
- with strong protic acid (3M HCl, CF$_3$COOH)
- TMS-I
-

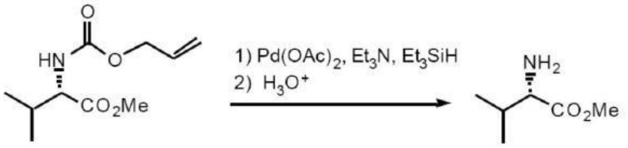


TL **1985**, *26* , 1411

Allyl Carbamate (Alloc)

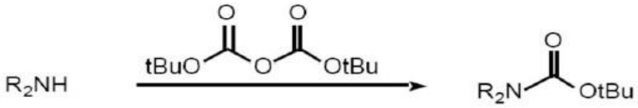


- removed with Pd(0) and a reducing agent (Bu$_3$SnH, Et$_3$SiH, HCO$_2$H)

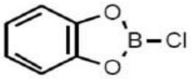


TL **1986**, *27* , 3753

t-Butyl Carbamate (BOC)

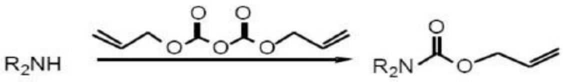


Cleavage:
- with strong protic acid (3M HCl, CF$_3$COOH)
- TMS-I
-

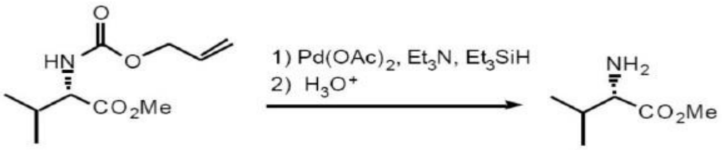


TL **1985**, *26* , 1411

Allyl Carbamate (Alloc)

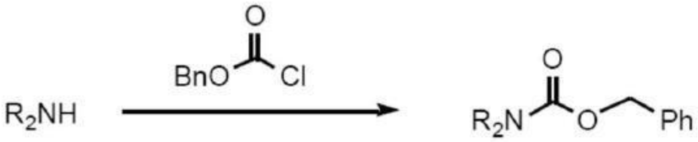


- removed with Pd(0) and a reducing agent (Bu$_3$SnH, Et$_3$SiH, HCO$_2$H)



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

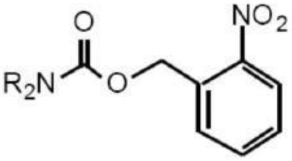
Benzyl Carbanate (Cbz)



Cleavage:
- Hydrogenolysis
- $PdCl_2$, Et_3SiH
- TMS-I
- BBr_3
- hν (254 nm)
- Na/ NH_3

m-Nitrophenyl Carbamate

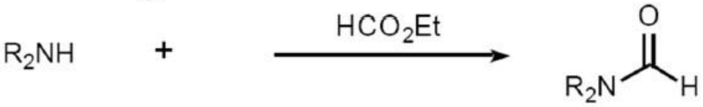
JOC **1974**, *39* , 192



- removed by photolysis

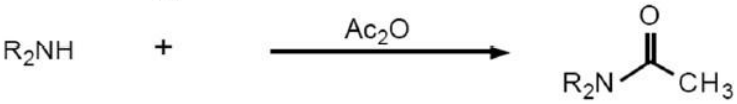
Formamides

- removed with strong acid



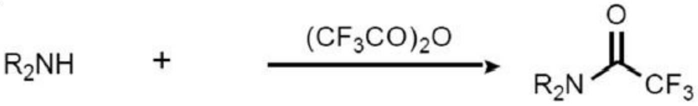
Acetamides

- removed with strong acid

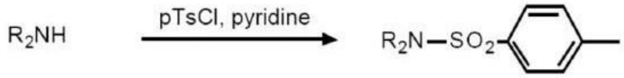


Trifluoroacetamides

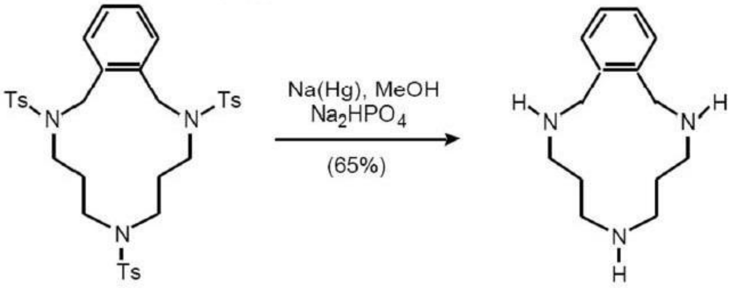
Cleavage:
- base (K_2CO_3, MeOH, reflux)
- NH_3, MeOH



p-Toluenesulfonyl (Ts)

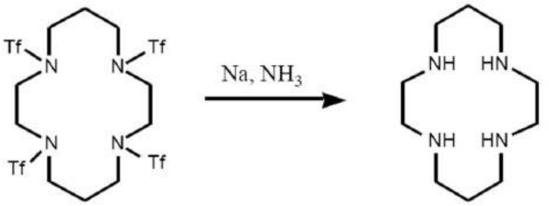


Cleavage:
- Strong acid
- sodium Naphthalide
- Na(Hg)



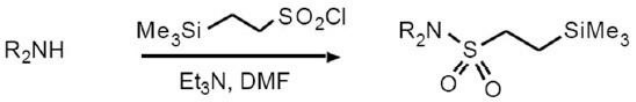
JOC **1989**, *54* , 2992

Trifluoromethanesulfonyl

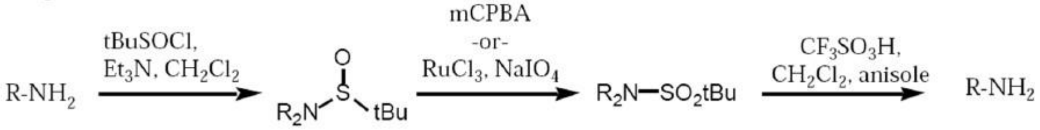


JOC **1992**, *33*, 5505

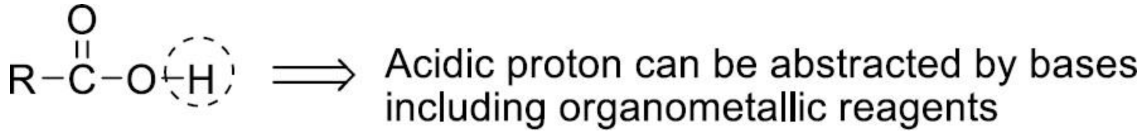
Trimethylsilylethanesulfonamide (SES)
TL **1986**, *54* , 2990; *JOC* **1988**, *53*, 4143
- removed with CsF, DMF, 95°C



tert-Butylsulfonyl (Bus) *JOC* **1997**, *62*, 8604



3. Protecting Groups for Carboxylic Acids

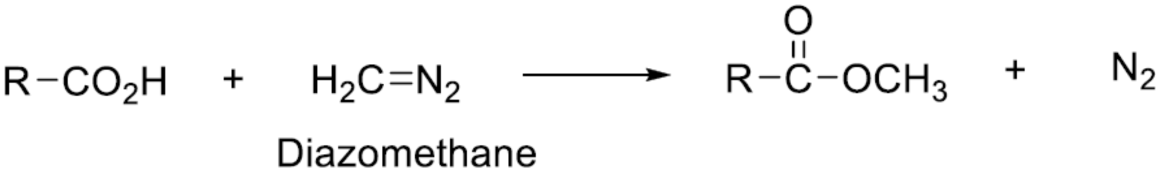


$$R-\overset{O}{\overset{\|}{C}}-O-H \Longrightarrow$$

Acidic proton can be abstracted by bases including organometallic reagents

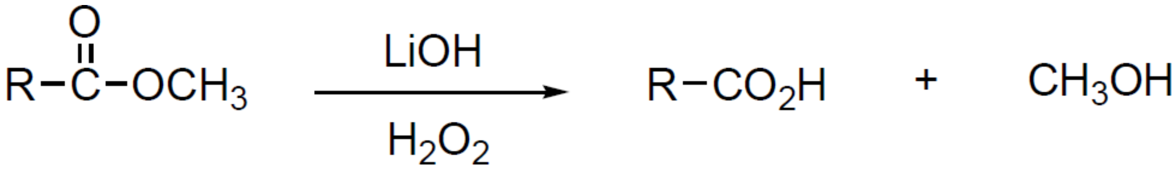
The common ester protecting groups for carboxylic acids are methyl, ethyl and benzyl esters.

Methyl Esters Formation



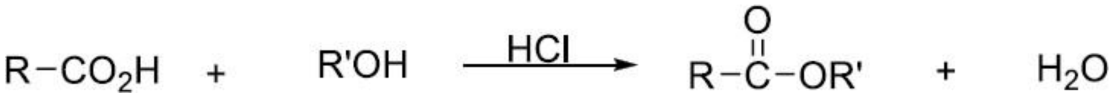
$$R-CO_2H + \underset{\text{Diazomethane}}{H_2C=N_2} \longrightarrow R-\overset{O}{\overset{\|}{C}}-OCH_3 + N_2$$

Cleavage



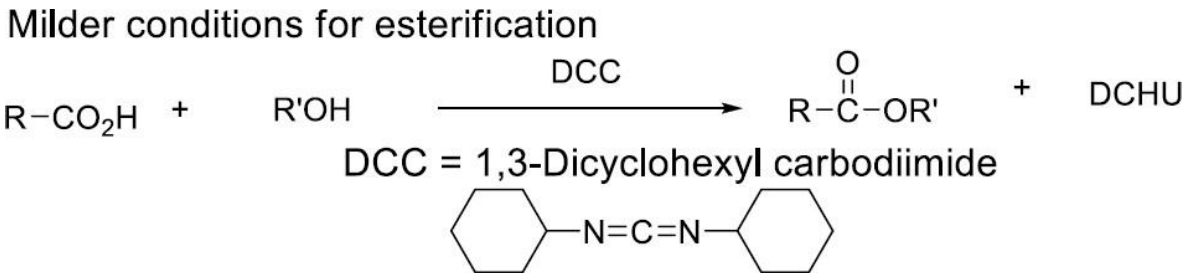
$$R-\overset{O}{\overset{\|}{C}}-OCH_3 \xrightarrow[H_2O_2]{LiOH} R-CO_2H + CH_3OH$$

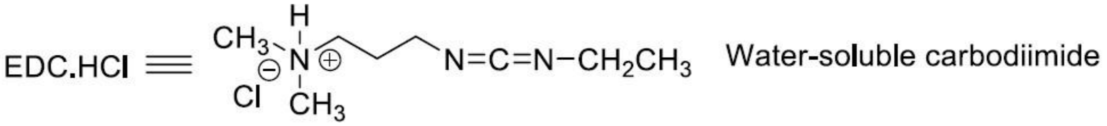
Ethyl and benzyl esters are prepared based on the following rationale:



$$R-CO_2H + R'OH \xrightarrow{HCl} R-\overset{O}{\overset{\|}{C}}-OR' + H_2O$$

Best approach:



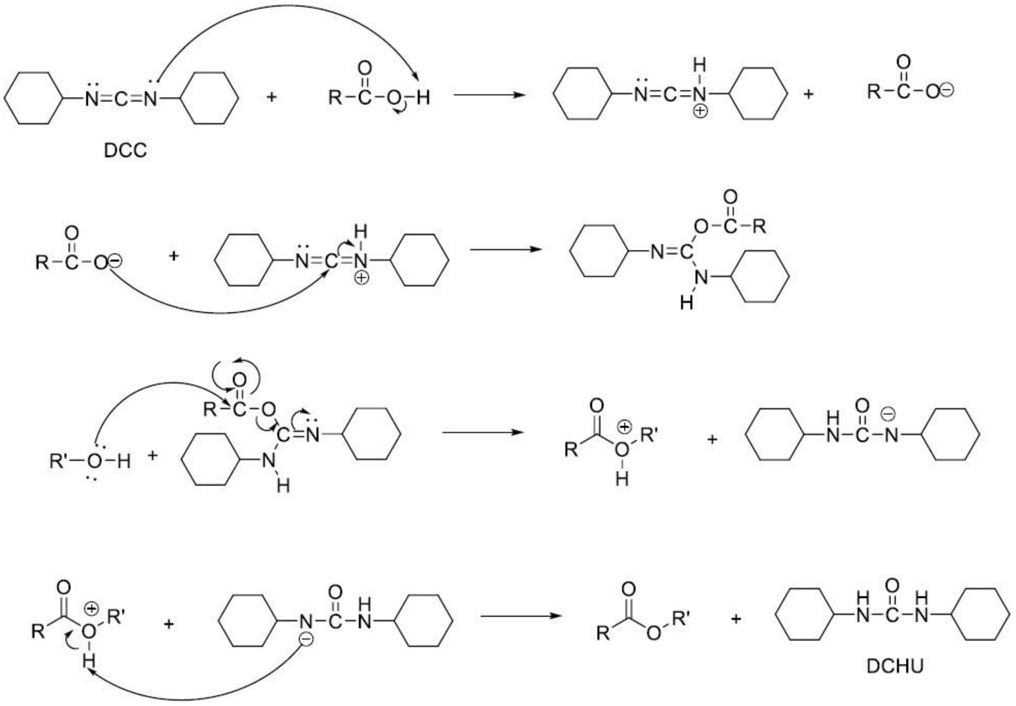


Water-soluble carbodiimide

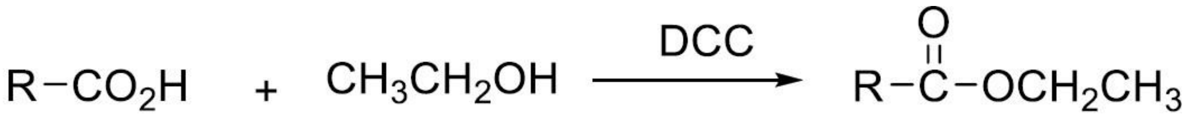
EDC = 1-[3-(Dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride

EDC.HCl is more expensive, but the urea by-product derived from it is water soluble and simplifies the purification process

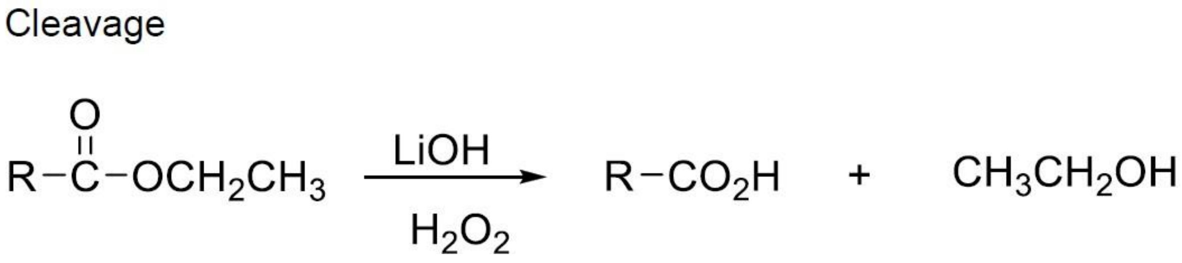
Mechanism of DCC coupling



Ethyl Esters Formation

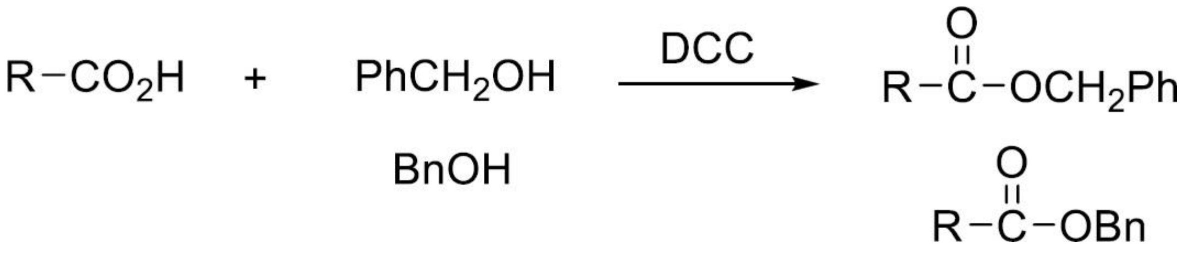


$$R-CO_2H + CH_3CH_2OH \xrightarrow{\text{DCC}} R-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$$



$$R-\overset{O}{\overset{\|}{C}}-OCH_2CH_3 \xrightarrow[H_2O_2]{\text{LiOH}} R-CO_2H + CH_3CH_2OH$$

Benzyl Esters Formation

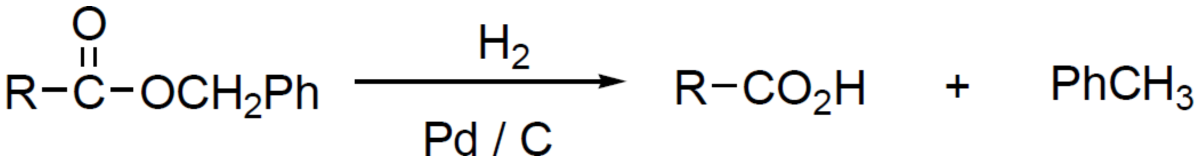


$$R-CO_2H + \underset{\text{BnOH}}{PhCH_2OH} \xrightarrow{\text{DCC}} R-\overset{O}{\overset{\|}{C}}-OCH_2Ph$$

$$R-\overset{O}{\overset{\|}{C}}-OBn$$

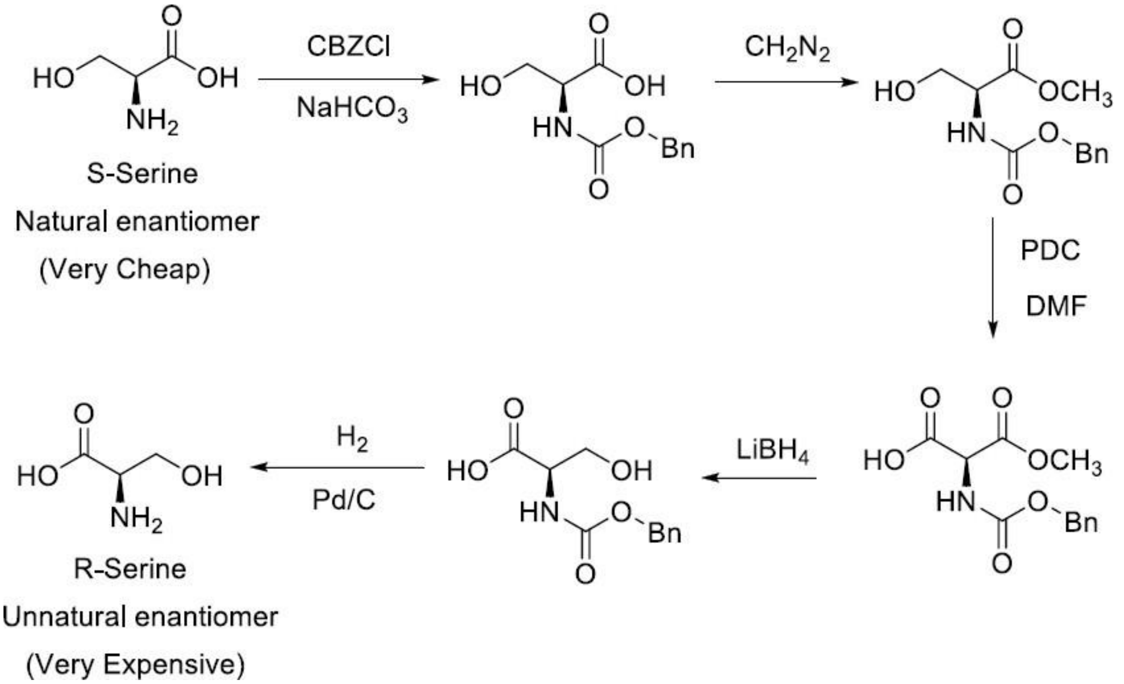
Cleavage

By hydrogenolysis: A very mild method for most functional groups except with alkenes, alkynes and nitriles.



$$R-\overset{O}{\overset{\|}{C}}-OCH_2Ph \xrightarrow[\text{Pd / C}]{H_2} R-CO_2H + PhCH_3$$

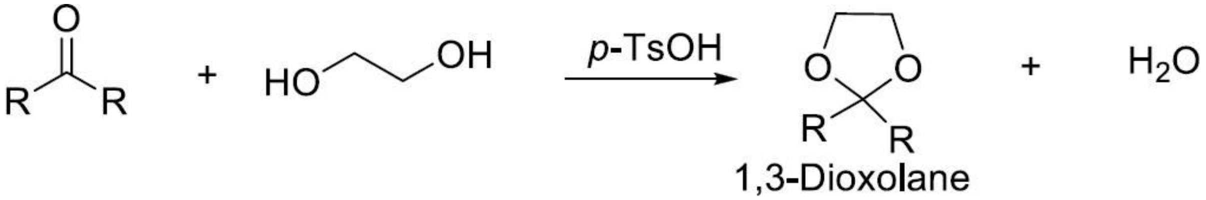
Perspectives in the Synthetic Applications of the Ester Protecting Groups



NotethatLiBH4canreducethemorereactiveesterfunctionalgroupleavingthe lessreactivecarboxylicacidandcarbamategroupsunaffected.

Protecting Groups for Aldehydes & Ketones

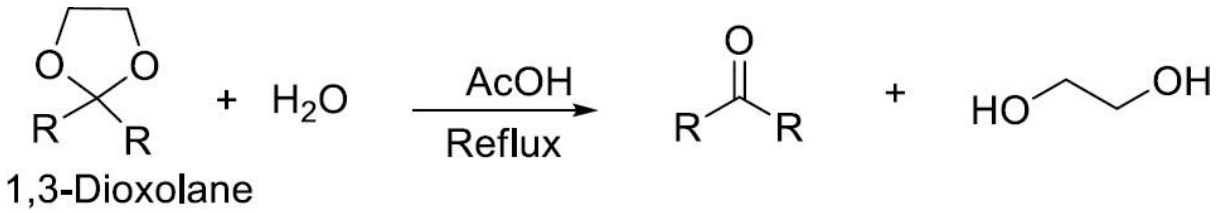
Acetal Protecting Group Formation



Cleavage

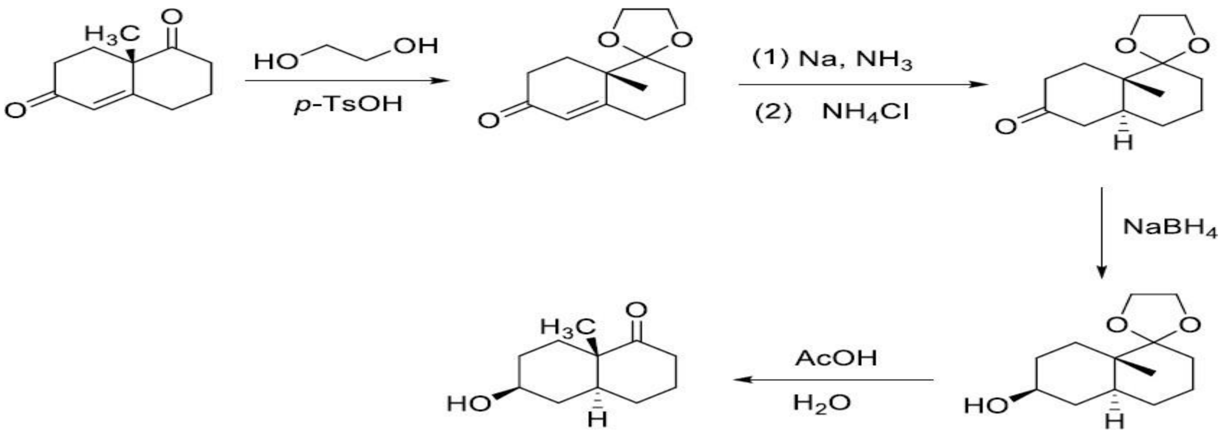
Acid catalysed hydrolysis (dilute HCl or AcOH / H2O or TFA/ H2O or

p- TsOH in acetone) can be used.



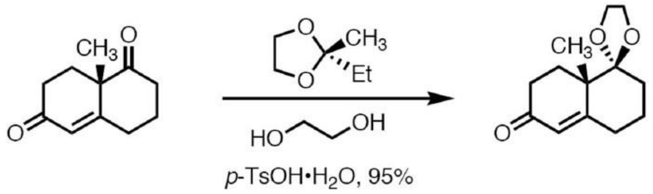
Synthetic Applications of the Acetal Protecting Group

The Wieland-Miescher ketone is a common intermediate in the synthesis of both natural and synthetic steroids.



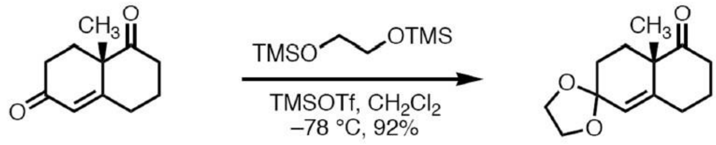
Because of resonance stabilization, the carbonyl of the a,bunsaturated ketone is less electrophilic and therefore less reactive to nucleophiles compared to an isolated ketone.

- In general, saturated ketones can be selectively protected in the presence of α,β-unsaturated ketone



Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, T.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773.

- Conditions have been developed to protect α,β-unsaturated ketones selectively.



Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

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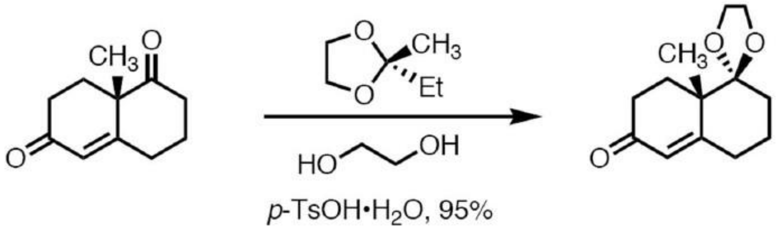
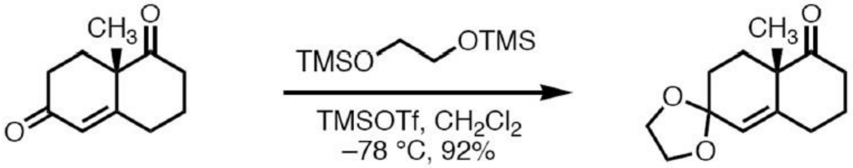


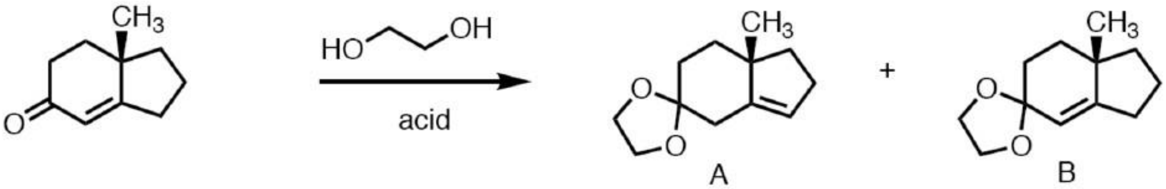
Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, T.; Tatsuoka, T.; Meinwald, J.
J. Org. Chem. **1986**, *51*, 773.

- Conditions have been developed to protect α,β-unsaturated ketones selectively.



Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

- When protecting α,β-unsaturated ketones, olefin isomerization is common.



Strong acids ($pK_a \approx 1$) tend to favor isomerization, while weaker acids ($pK_a \geq 3$) favor isomerization much less so, or not at all.

acid	pK_a	%A	%B	% conversion
fumaric acid	3.03	100	0	90
phthalic acid	2.89	70	30	90
oxalic acid	1.23	80	20	93
TsOH	< 1.0	0	100	100

Cleavage of 1,3-dioxanes and 1,3-dioxolanes:

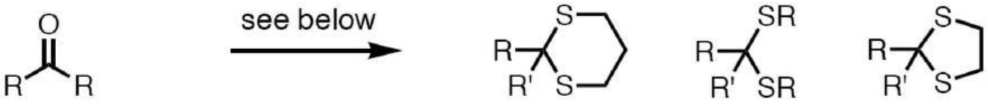
1. PPTS, acetone, H_2O, heat. Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1351.

2. 1M HCl, THF. Grieco, P. A.; Nishizawa, M.; Oguri, T. Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *43*, 4178.

3. Me_2BBr, CH_2Cl_2, –78 °C. This reagent also cleaves MEM and MOM ethers. Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969.

4. NaI, $CeCl_3{\cdot}7H_2O$, CH_3CN. Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183. This method is selective for cleavage of ketals in the presence of acetals. It is also selective for ketals of α,β-unsaturated ketones over ketals of saturated ketones.

General methods of formation of *S*,*S*'-dialkyl acetals:

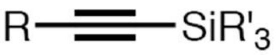


1. RSH, HCl, 20 °C. Zinner, H. *Chem. Ber.* **1950**, *83*, 275.

2. $RSSi(CH_3)_3$, ZnI_2, Et_2O. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

3. RSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2. Marshall, J. A.; Belletire, J. L. *Tetrahedron Lett.* **1971**, 871. See also Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. α,β-Unsaturated ketones are reported not to isomerize under these conditions. However, with any of the above mentioned conditions conjugate addition is a concern.

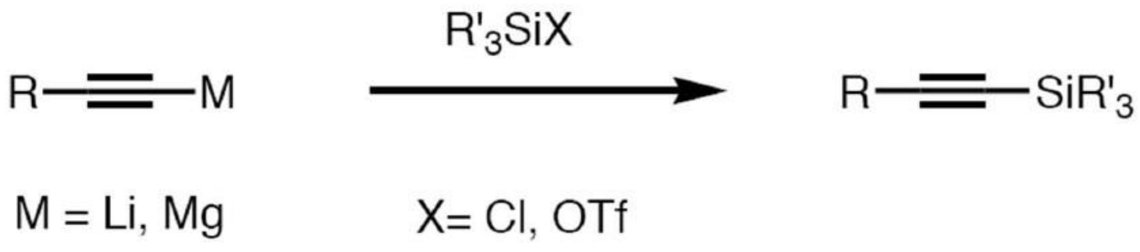
5.Alkyne Protecting Groups


$R-C\equiv C-SiR'_3$

trialkylsilylalkyne

- Typical silyl groups include TMS, TES, TBS, TIPS, and TBDMS.
- Many silyl acetylenes are commercially available, and are useful acetylene equivalents.

General preparation of silyl acetylenes:

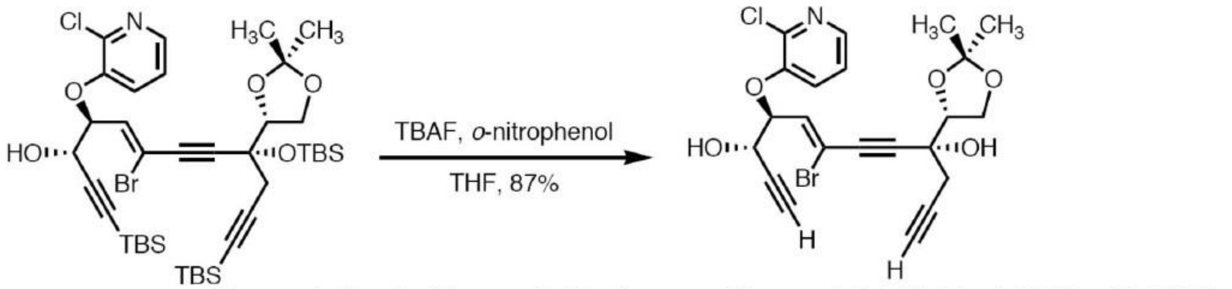


Silyl chorides are suitable for smaller silyl groups, but the preparation of more hindered silyl acetylenes may require the use of the more reactive silyl triflate.

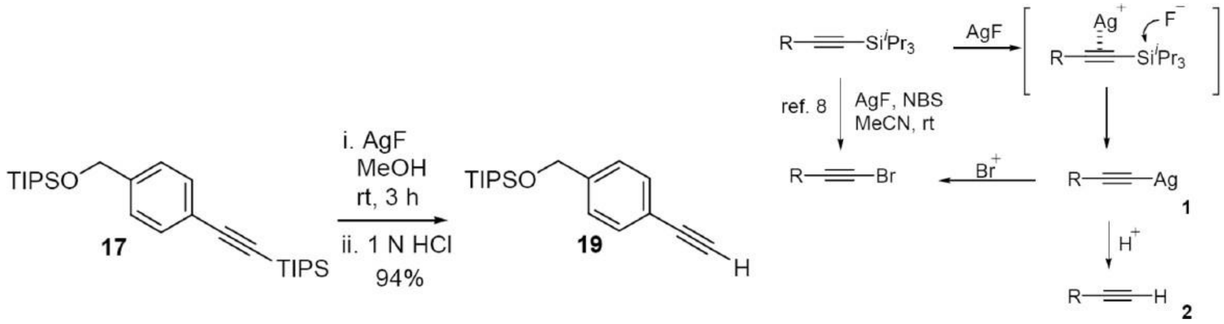
Cleavage of trimethysilylalkynes:

1. KF, MeOH, 50 °C. Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694.
2. $AgNO_3$ 2,6-lutidine. Carreira, E. M.; Du Bois, J. *J. Am. Chem Soc.* **1995**, *117*, 8106.
3. K_2CO_3, MeOH. Cai, C.; Vasella, A. *Helv. Chim. Acta.* **1995**, *78*, 732.

- Buffered TBAF was used to deprotect the silyalkynes in the example shown below to prevent elimination of the sensitive vinyl bromide.



Myers, A.G.; Goldberg, S. D. *Angew. Chem., Int. Ed. Engl.* **2000**, *15*, 2732.



References

[1]. Kehler, J. and Breuer, E. (1998) Synthesis, 1419–1420.
[2]. Hanessian, S. and Wang, X. (2009) Synlett, 2803–2808.
[3]. Mutter, M. and Hersperger, R. (1989) Synthesis, 198–200.
[4]. Barlos, K., Papaioannou, D., and Theodoropoulos, D. (1982) TheJournal of Organic Chemistry, 47, 1324–1326.
[5]. Albericio, F. (2000) Peptide Science, 55, 123–139.
[6]. Alsina, J., Giralt, E., and Albericio, F. (1996) TetrahedronLetters, 37, 4195–4198.
[7]. Sieber, P., Kamber, B., Hartmann, A., J€ohl, A., Riniker, B., andRittel,W. (1977) Helvetica Chimica Acta, 60, 27–37.
[8]. Pless, J. (1976)Helvetica ChimicaActa, 59, 499–512. 9.
[9]. Reetz, M.T. (1999) Chemical Reviews, 99, 1121–1162.
[10]. Gorbunova, M.G., Gerus, I.I., Galushko, S.V., and Kukhar, V.P.(1991) Synthesis, 207–209.
[11]. Kates, S.A., Sole, N.A., Beyermann, M., Barany, G., andAlbericio, F. (1996) Peptide Research, 9, 106–113.
[12]. Carpino, L.A., Sadat-Aalaee, D., and Beyermann, M. (1990) TheJournal of Organic Chemistry, 55, 1673–1675.
[13]. Sheppeckll, J.E., Kar, H., and Hong, H. (2000) TetrahedronLetters, 41, 5329–5333.
[14]. Ueki, M. and Amemiya, M. (1987) Tetrahedron Letters, 28,6617–6620.
[15]. Jiang, J., Li, W.-R., and Joullie,M.M. (1994) SyntheticCommunications, 24, 187–195.
[16]. Li, W.-R. and Chou, H.-H. (2000) Synthesis, 84–90.

[17]. Tantry, S.J., Venkataramanarao, R., Chennakrishnareddy, G.,and Sureshbabu, V.V. (2007) The Journal of Organic Chemistry,72, 9360–9363.

[18]. Rajh, H.M., Mariman, E.C.M., Tesser, G.I., and Nivard, R.J.F. (1980) International Journal of Peptide and Protein Research, 15,200–210.

[19]. Samukov, V.V., Sabirov, A.N., and Pozdnyakov, P.I. (1994) Tetrahedron Letters, 35, 7821–7824.

[20]. (a) Carpino, L.A., Philbin, M., Ismail, M., Truran, G.A., Mansour, E.M.E., Iguchi, S., Ionescu, D., El-Faham, A., Riemer,C., Warrass, R., and Weiss, M.S. (1997) Journal of the American Chemical Society, 119, 9915–9916; (b)Carpino, L.A., Ismail, M., Truran, G.A., Mansour, E.M.E., Iguchi, S., Ionescu, D., El-Faham, A., Riemer, C., and Warrass, R. (1999) The Journal of Organic Chemistry, 64, 4324–4338.

[21]. Kunz, H. and Unverzagt, C. (1984) Angewandte Chemie, 96, 426–427.

[22]. Dangles, O., Guibe, F., Balavoine, G., Lavielle, S., and Marquet, A. (1987) The Journal of Organic Chemistry, 52, 4984–4993.