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RECENT DEVELOPMENTS IN CHEMICAL DEPROTECTION OF ESTER FUNCTIONAL GROUPS

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1 INTRODUCTION

A crucial problem in planning a synthesis is the selection of protective groups to prevent or to modify reaction at a specific functional group during a synthetic sequence. Organic chemists are continually searching for milder, high yield and more selective methods to effect protection and deprotection. A very useful compilation of functional group protection and deprotection has been published recently.[1]

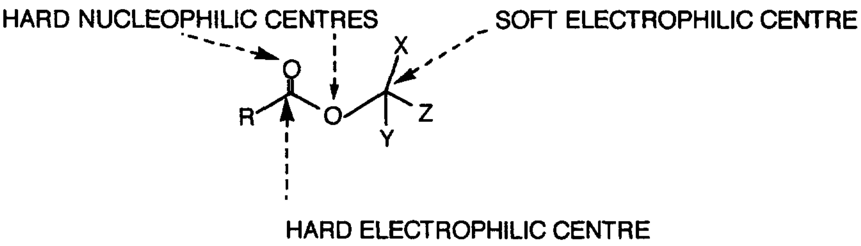
In particular there has been a continued search for mild and chemoselective reagents for conversion of carboxylic acids into esters and for cleavage of carboxylic ester protecting groups. A wide range of methods is available for the protection of carboxyl functions by means of methyl, ethyl, substituted methyl and ethyl, t-butyl, allyl, benzyl, substituted benzyl, diphenyl methyl and silyl esters among others.[1,2,3] However, in many synthetic processes it is necessary or desirable to avoid exposing a particular substrate to acidic, basic, or hydrogenolytic conditions. In these circumstances the alternative approach of cleaving ester groups under different (non-hydrolytic) conditions can be employed. For such polyfunctional molecules containing other sensitive groups, success has been achieved with reagents such as soft[4,5] nucleophilic anions; a hard Lewis acid and a soft nucleophile internal bifunctional system; a hard Lewis acid and soft nucleophile combination of two monofunctional reagents; a hard Lewis acid; a hard Lewis acid and hard nucleophile; internal bifunctional system; nucleophiles activated with Pd°; titanium (II) reagent derived from Mg/Hg-$TiCl_4$; potassium superoxide in the presence of 18-crown-6; nitrosonium tetrafluoroborate; 2,3-dichloro-5,6-dicyano-benzoquinone; electrochemical methods; a phenolic matrix; ozonolysis and β-elimination; photolytic cleavage; and with esterase enzymes.

In this review we provide an up date on methods for chemical deprotection of ester functional groups and also give representative applications from recent literature (1980 to middle of 1992). It is beyond the scope of this review to discuss photoremovable[6] and enzymatic[7,8] cleavage of protecting ester groups. Excellent reviews on those methodologies have been published recently.[6,8]

2 STRUCTURAL ASPECTS

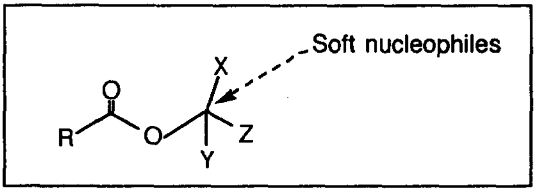
Since an ester has two sites that can be potentially attacked by a nucleophile, one should choose a nucleophile which either exhibits a preference for attack at the carbinol carbon or which attacks the carbonyl carbon. Using the principles of hard/soft acid/base theory,[4,5] soft nucleophiles are predicted to show a preference for attack on the carbinol carbon centre (soft-soft interaction) and hard nucleophiles prefer the carbonyl carbon center (hard-hard interaction) (Figure 1).

Figure 1



3 SOFT NUCLEOPHILES

Soft nucleophiles with unhindered alkyl esters exhibits a preference for attack at the soft carbinol carbon.

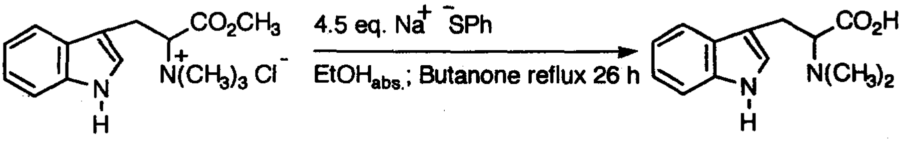


3.1 Thiophenoxide anion.

In 1964 Sheehan and Doyle[9] first reported successful use of sodium thiophenoxide in dipolar aprotic solvent (DMF) at or below room temperature to effect **alkyl-oxygen** cleavage of phenacyl esters to generate the sodium salts of the corresponding carboxylic acids in good to excellent yields.

An interesting application of the sodium thiophenoxide to effect simultaneous cleavage at the **alkyl-oxygen** bond of a carboxylic methyl ester and at the **alkyl-nitrogen** bond of an N-alkyl trimethylammonium group for the synthesis of N,N-dimethyltryptophan[10] is shown in Scheme 1.

Scheme 1



1

55% 2

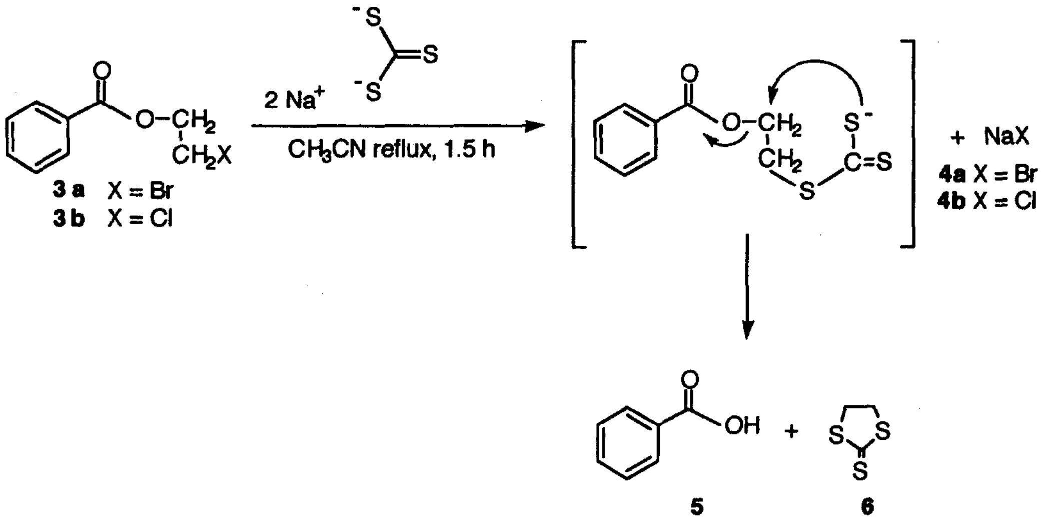
3.2 Alkanethiolate anions.[11]

Subsequent to the report of Sheehan and Doyle, various others thiolates were developed for cleavage of the **alkyl-oxygen** bond of methyl esters by nucleophilic displacement of the carboxylate anion from the methyl group. Of these, the most widely used are: lithium thiopropoxide,[12] sodium thioethoxide,[13] and lithium thiomethoxide.[14]

3.3 Trithiocarbonate anion.

In 1974 Ho reported the use of trithiocarbonate anion for the cleavage of 2-haloethyl esters. The rationale of the cleavage involves stepwise displacement of the halide and the carboxylate; the second step is an intramolecular substitution[15] (Scheme 2).

Scheme 2



3.4 Ethanedithiolate anion.

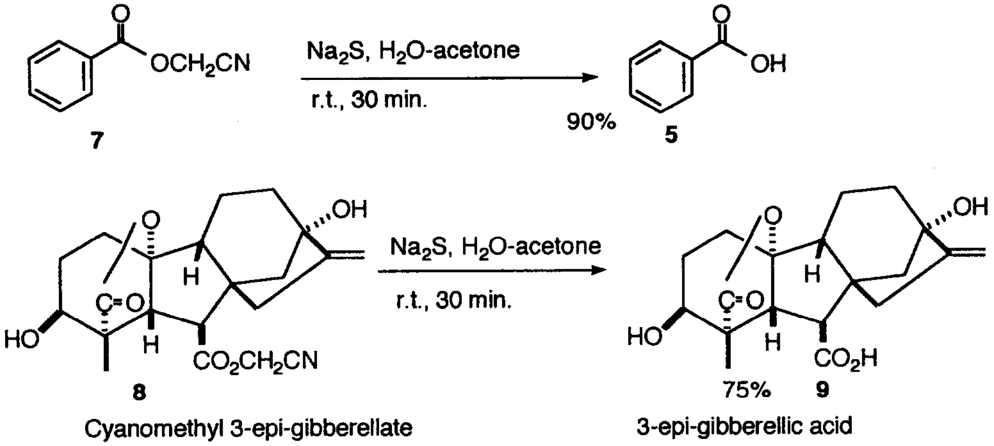
In 1975 Ho reported that sodium ethanedithiolate is also useful for the selective cleavage of 2-haloethyl esters by a similar double displacement mechanism.[16]

3.5 Sulfide anion.

Based on similar rationale of an intramolecular displacement in the second step, Ho in 1974 used sodium sulfide in aqueous acetonitrile to cleave 4-chlorobutyl and 5-chloropentyl esters.[17]

Very recently, Hugel and coworkers[18] reported that alkylation of carboxylate salts with chloroacetonitrile produces cyanomethyl esters. Deprotection of the carboxyl group was succesfully performed with an aqueous solution of sodium sulfide. Two examples of this methodology are shown in Scheme 3.

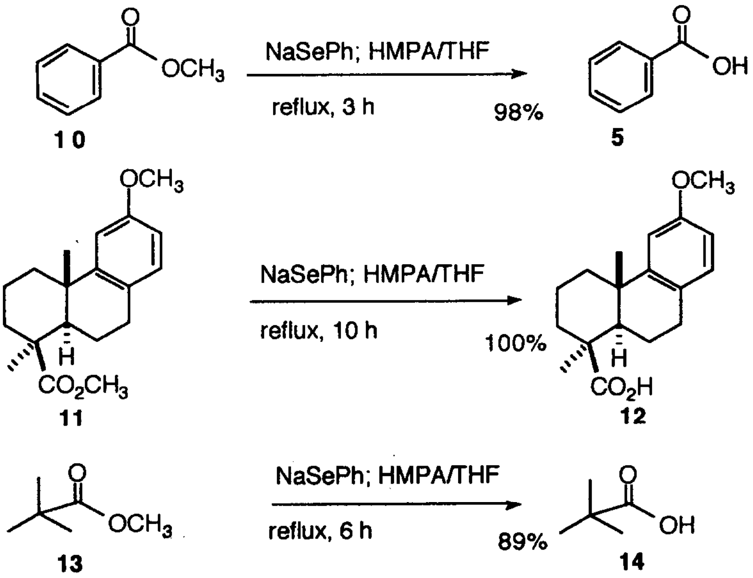
Scheme 3



3.6 Phenyl selenide anion.

In 1977 Liotta and coworkers reported preliminary details of their studies on the synthetic utility of phenyl selenide anion for the S_N2-type cleavage of esters[19] and lactones.[20] In a subsequent paper[21] in 1981 Liotta and coworkers reported details of the scope and limitations of S_N2-type cleavages of alkyl esters and lactones with phenyl selenide anion. These authors found that the phenyl selenide anion when generated uncomplexed, is an effective soft nucleophile for S_N2-type ester cleavages. However, its nucleophilicity can be greatly attenuated by change in the counterion and/or in the degree of solvation of the ion pair. Thus, the more ionic sodium is significantly more reactive than its lithium counterpart and therefore should be used in cases that require a power-

Scheme 4

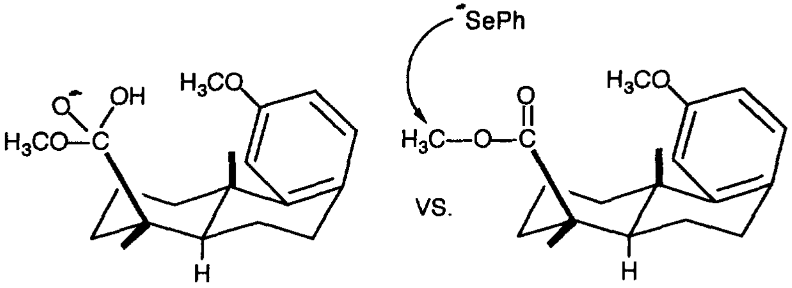


ful nucleophile. On the basis of their results, Liotta and coworkers,[21] proposed the following reactivity gradient for phenyl selenide anion: NaSePh/18-Crown-6/THF > NaSePh/HMPA/THF > LiSePh/HMPA/THF > LiSePh/THF = LiSePh/ether

Representative examples of the synthetic utility of phenyl selenide are presented in Schemes 4 and 5. Upon exposure to phenyl selenide anion, methyl esters undergo facile **alkyl-oxygen** cleavage, irrespective of how hindered the ester is With esters **10**, **11**, and **13** high yields of cleavage products were obtained, despite a large increase in the relative degree of steric hindrance around the ester (Scheme 4).

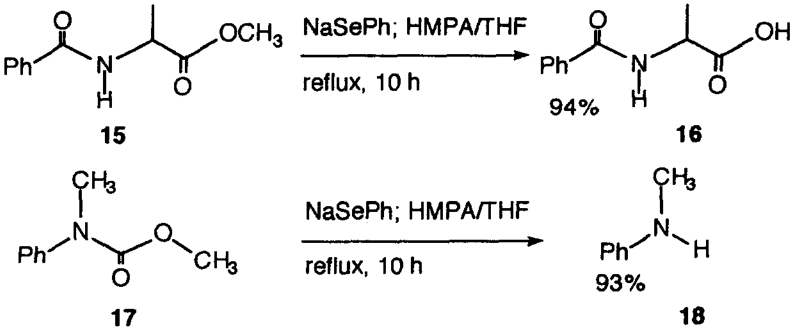
The authors pointed out that compound **10** under normal saponification conditions is relatively unreactive and that this sluggish reactivity toward aqueous base presumably results from severe steric interactions that develop between the angular methyl group and the tetrahedral intermediate generated upon attack by hydroxide anion. By contrast, in the S_N2 cleavage of **10** the carboxylate leaving group remains trigonal throughout the reaction. Therefore, since no "new" steric interactions develop during the S_N2 transition state, the reaction proceeds smoothly. Since in sterically hindered esters the carbinol carbon is virtually always less hindered than the carbonyl carbon, the phenyl selenide induced S_N2 cleavage of hindered methyl esters represents an attractive synthetic alternative to acid- or base-catalyzed hydrolyses (Figure 2).

Figure 2



Additional examples with benzyl, isoamyl, and isopropyl esters indicate that phenyl selenide anion reacts to give the corresponding acids in nearly quantitative yields.

Scheme 5



As the degree of substitution at or near the carbinol carbon increases, the rate of alkyl-oxygen cleavage decreases. In fact, this rate differential can, in certain cases, be exploited to allow for selective cleavage of a methyl ester in the presence of an ester of a higher alcohol.

Liotta and coworkers also demonstrated that amides (e.g. **15**) are completely inert to phenyl selenide anion. Urethane **17** also undergoes ester cleavage and subsequent decarboxylation to give N-methylaniline **18** in excellent yield (Scheme 5).

3.7 Hydrogen selenide anion.

In 1988, Zhou, Kong, and Chen reported[22] that sodium hydrogen selenide generated from selenium and sodium borohydride in dimethylformamide is effective for dealkylation of methyl, benzyl, and some n-alkyl esters, while *iso*-alkyl esters are unaffected under the same conditions. The authors assumed that the reaction of sodium hydrogen selenide with esters follows an S_N2 pathway. They claimed that this new methodology for cleaving ester functional groups is more convenient than the reported one with tellurides.

3.8 Telluride anions.

In 1987, Zhou and Chen reported[23] a new method for producing sodium telluride, sodium hydrogen telluride, and sodium ditelluride from tellurium and sodium borohydride in dimethylformamide. These authors found that these tellurium reagents dealkylate methyl, ethyl, and benzyl carboxylates selectively. The ester cleavage by the above named tellurium reagents followed a typical S_N2 pathway.

4 HARD NUCLEOPHILES

4.1 Tetrabutylammonium fluoride

Tetrabutylammonium fluoride has been widely used for deprotecting silyl ethers and esters. This reagent was also

Table I. Cleavage of *p*-nitrobenzyl, 2.2.2-trichloroethyl, phenacyl and cyclohexyl esters of protected amino acids by tetrabutylammonium fluoride in aprotic solvents.

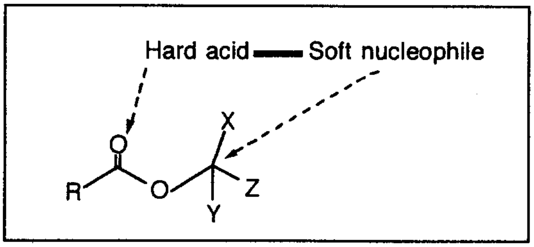
Ester	Product	Conditions[a]	Yield, %
Boc-Glu-(OBn)-ONbn **19**	Boc-Glu(OBn)-OH **20**	6 eq. Bu_4NF, THF	92
Boc-Glu(OAll)-ONbn **21**	Boc-Glu(OAll)-OH **22**	5 eq. Bu_4NF, DMF	96
Boc-Asp(O-*t*-Bu)-ONbn **23**	Boc-Asp(O-*t*-Bu)-OH **24**	5 eq. Bu_4NF, THF	93
Boc-Asp(OChx)-ONbn **25**	Boc-Asp(OChx)-OH **26**	3 eq. Bu_4NF, THF	94
Boc-Leu-Pro-OTce **27**	Boc-Leu-Pro-OH **28**	2 eq. Bu_4NF, THF	95
Cbz-Ala-OPac **29**	Cbz-Ala-OH **30**	4 eq. Bu_4NF, DMF	98

[a] All the reactions were complete in 10-30 min at r.t.

used for cleavage of benzyl as well as *p*-nitrobenzyl esters.[24,25] Recently, Rinehart and coworkers[26] also successfully used it to cleave *p*-nitrobenzyl (Nbn), 2,2,2-trichloroethyl (Tce), phenacyl (Pac), and cyclohexyl N-(Chx) esters of N-carbobenzoxy- (N-Cbz) or N-*tert*-butyloxycarbonyl- (N-Boc) protected amino acids and dipeptides using tetrahydrofuran, dimethylformamide or dimethylsulfoxide as a solvent. The authors indicated that no significant difference was observed between the three solvents employed, and the choice can be based on the solubility of the substrate. The carbobenzoxy- and *tert*-butyloxycarbonyl-protecting groups were preserved under the conditions used. Another advantage of this method is that no racemization occurred in all the model compounds studied. To our knowledge no mechanistic studies have been reported on the use of this hard nucleophile. Representative examples taken from the work of Rinehart and coworkers[26] are presented in Table I.

p-Nitrobenzyl esters of glutamic and aspartic acid were chemoselectively cleaved in the presence of benzyl (Bn), allyl (All), *tert*-butyl (*t*-Bu), and cyclohexyl (Chx) esters. The reaction was also succesfully applied to dipeptides such as the N-Boc-leucyl-proline 2,2,2-trichloroethyl ester **27** to give N-Boc-leucyl-proline, **28**, without racemization.

5 A HARD ACID AND A SOFT NUCLEOPHILE INTERNAL BIFUNCTIONAL SYSTEM



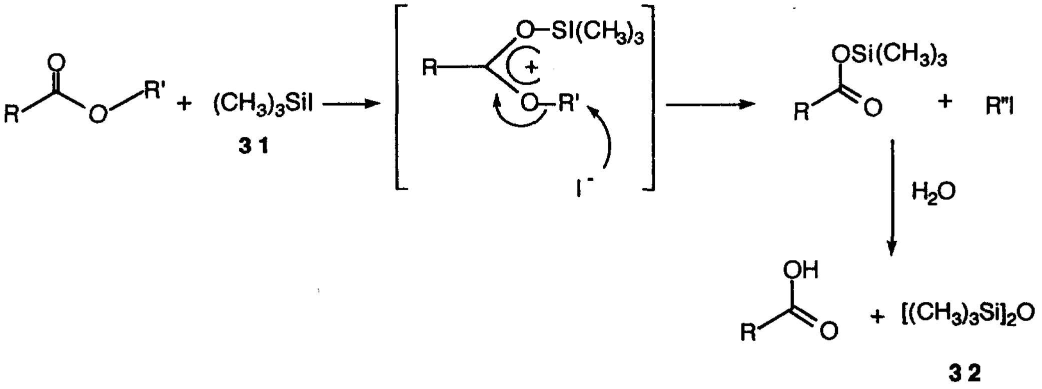
5.1 Trimethylsilyl iodide.

Trimethylsilyl iodide (iodotrimethylsilane) **31** was introduced by Jung[27] and by Olah[28] as an efficient and convenient reagent for the cleavage of esters and ethers under neutral conditions. A carboxylic ester is heated with iodotrimethylsilane either neat[28] or in an aprotic solvent, e.g., carbon tetrachloride or deuterochloroform, gave the corresponding acid on subsequent aqueous hydrolysis (Scheme 6). Iodotrimethylsilane contains silicon as a hard acid and iodide as a soft nucleophile. The silicon reacts very readily with organic compounds containing oxygen (a hard base) forming a strong silicon-oxygen bond. The iodide then acts as a soft nucleophile in a subsequent displacement that cleaves an oxygen-alkyl bond, with formation of alkyl iodide (Scheme 6).[29]

Methyl and ethyl esters are cleaved in almost quantitative yield. Even hindered esters (e.g. methyl pivalate) are cleaved by this reagent. Iodotrimethylsilane cleavage of esters allows selectivity because benzyl and tert-butyl esters react at a much faster rate than do the methyl, ethyl, and isopropyl esters. It is therefore possible selectively to cleave benzyl and tert -butyl esters in the presence of methyl, ethyl, and isopropyl esters at 25 °C.

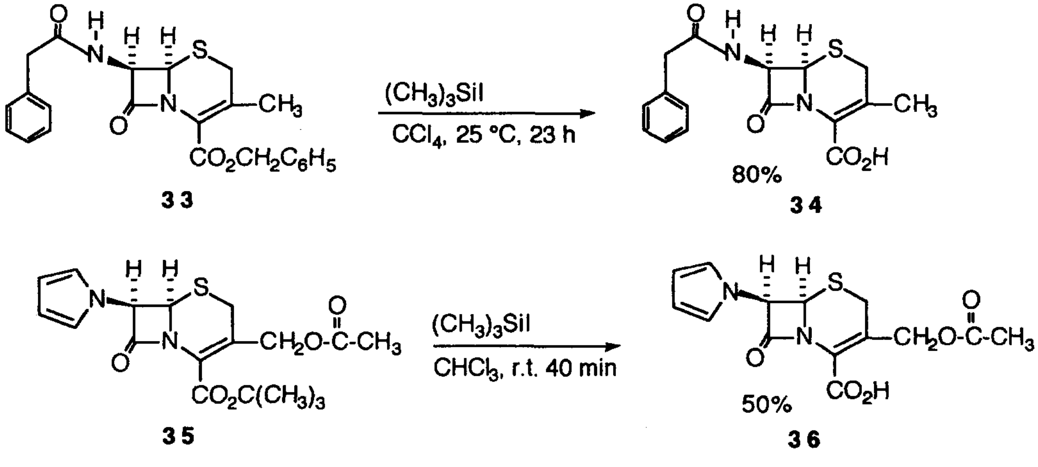
Ester cleavage with iodotrimethylsilane does not affect isolated double bonds, ketones, thioethers, amines, or amides.[30] A mixture of chlorotrimethylsilane/sodium iodide in acetonitrile was found to be a convenient alternative to iodotrimethylsilane for the cleavage of esters, lactones, carbamates and ethers.[31]

Scheme 6

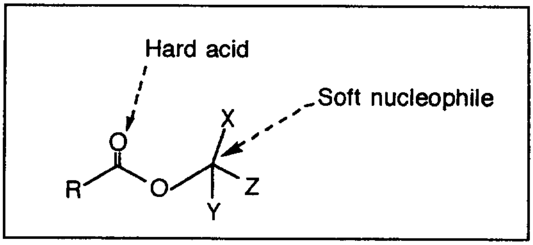


Representative examples are shown in Scheme 7. Cleavage of the protecting benzyl group of cephalosporin **33** was achieved with iodotrimethylsilane, while usual hydrogenolysis (Pd/C, H_2 at 3 atm.) was ineffective.[32] The great selectivity of iodotrimethylsilane was attested by the removal of the *tert*-butyl group of the cephalosporin **35**, leaving the acetate group intact. The instability of pyrroles to strongly acidic conditions led to decomposition of the compound when subjected to trifluoroacetic acid.[30]

Scheme 7



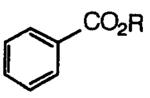
6 A HARD LEWIS ACID AND A SOFT NUCLEOPHILE. COMBINATION OF TWO MONOFUNCTIONAL REAGENTS.



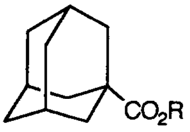
6.1 and 6.2 Aluminium Halide-Ethanethiol and Aluminium Halide-Dialkyl Sulfide.

Fujita and coworkers in a preliminary communication in 1978, reported that aluminium halide-ethanethiol system is effective for deesterification of methyl and benzyl esters.[33] The authors assayed various Lewis acids and found that aluminium halide was much more active than boron trifluoride etherate. In 1981, the same authors detailed the scope and applications of the aluminium halide-ethanethiol and aluminium halide-dialkyl sulfide systems.[34]

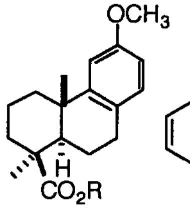
Chart 1



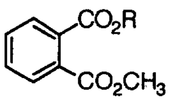
37 R=CH_2Ph
10 R=CH_3
38 R=CH_2CH_3
39 R=$CH_2CH_2CH_3$
40 R=$CH(CH_3)_2$
5 R=H



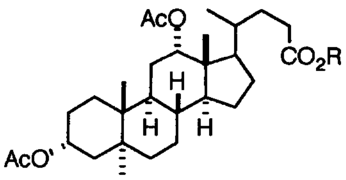
41 R=CH_3
42 R=H



11 R=CH_3
12 R=H



43 R=CH_2Ph
44 R=H



45 R=CH_3
46 R=H

Table II. Dealkylation of esters by AlX_3 (X=Cl or Br) and ethanethiol[a]

Compd.	Lewis acid	Time (h)	Product	Yield (%)
37	$AlCl_3$	1.7	**5**	91.1
10	$AlBr_3$	6.5	**5**	93.9
38	$AlBr_3$	36.0	**5**	16.1
39	$AlBr_3$	77.0	**5**	8.0
40	AlB_{r3}	77.0	**5**	6.1
41	$AlBr_3$	24.0	**42**	95.2
11	$AlBr_3$	7.5	**12**	95.7
43	$AlCl_3$	3.0	**44**	75.0
45	$AlBr_3$	48.0	**46**	80.5

[a] For full experimental details see ref. 34

Representative examples of dealkylation of esters with aluminium chloride and bromide-ethanethiol are summarized in Table II. (See Chart I for the structures).

The reactions with benzyl benzoate **37** proceeded rapidly and gave high yields of benzoic acid **5**; with methyl esters **10**, **41** and **45** reactions smoothly gave very high yields of the corresponding carboxylic acids **5**, **42** and **46**. In the case of ethyl benzoate **38**, n-propyl benzoate **39**, and *iso*-propyl benzoate **40** the yields decreased, even with prolonged reaction times, because of the steric hindrance of alkyl moieties.

Methyl O-methylpodocarpate **11** on treatment with aluminium bromide and ethanethiol gave podocarpic acid **12** in almost quantitative yield. Deesterifications of sterically hindered methyl esters, i.e., methyl 1-adamantanecarboxylate **41** and methyl O-methylpodocarpate **11** demonstrated the efficiency of this reagent system. In the reaction with compound **45** the acetoxy groups remained intact. The carbons atoms attached to the acetoxy groups are secondary and sterically hindered for the S_N2 attack by thiol; hence, the reaction at these centers is much slower than that at the methyl ester moiety.

In compound **43**, which possesses two different esters selective dealkylation of the benzyl ester in the presence of methyl ester was achieved.

Fujita and coworkers also reported in another publication[35] that when lactones were treated with aluminium halide and alkanethiol, they were converted to ω-carboxylic acids in high yields through ω-carbon-oxygen bond cleavage.

Another reagent system developed by Fujita and coworkers involves a combination of aluminium halide and dialkyl sulfide. They reported that this system is more powerful than the aluminium halide-ethanethiol. Some examples are summarized in Table III; for examples using different dialkyl sulfides see reference 34.

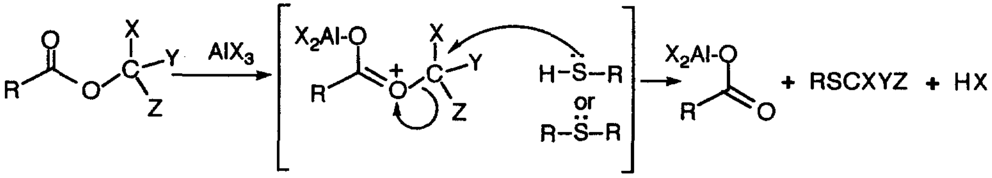
Table III Dealkylations of esters by $AlBr_3$-$(CH_3)_2S$

Compd.	time (h)	product	yield (%)
10	0.5	**5**	93.9
38	4.0	**5**	85.6
39	19.5	**5**	75.4
40	22.0	**5**	70.0

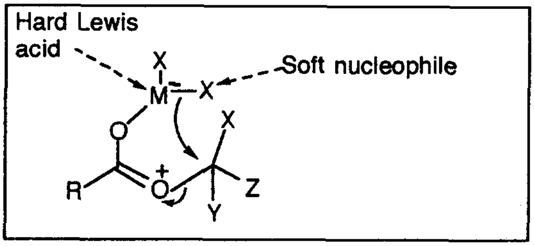
[a]For full experimental details see ref. 34

Demethylation of methyl benzoate **10** proceeded much more rapidly with this new reagents system than with aluminium halide-ethanethiol. Even dealkylation of the higher esters, which hardly took place with the aluminium halide-ethanethiol system, proceeded smoothly and in good yields. Examples include dealkylations of ethyl benzoate **38**, *n*-propyl benzoate **39** and *iso*-propyl benzoate **40** (see Table III; and compare with Table II). The authors rationalized both reactions by the hard and soft acids and bases principle.[34,36] Coordination of a hard acid with the oxygen, which is a hard base, activates the carbon-oxygen bond and is followed by attack of a soft nucleophile on the carbinol carbon, which is regarded as a soft acid, to accomplish a carbon-oxygen bond cleavage (see, Scheme 8). As both the so-called "pulling factor" (the coordination of a hard acid with the oxygen atom) and "pushing factor"[36] (the nucleophilic attack on the carbinol carbon by a soft nucleophile) are indispensable in this type of reactions, the transition state is likely situated somewhere between S_N1 and S_N2 at the carbon.

Scheme 8



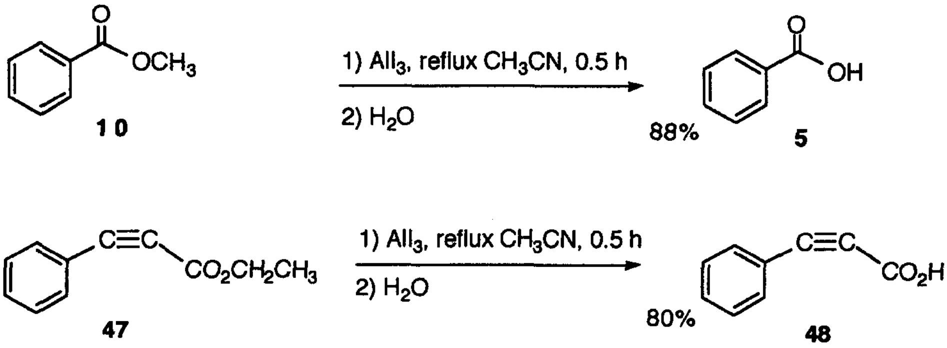
7 A HARD LEWIS ACID



7.1 Aluminium triiodide

Sandhu and coworkers[37] recently reported that aluminium triiodide efficiently cleaves carboxylic esters to carboxylic acids in dry acetonitrile under mild conditions with high yields. Representative examples are given in Scheme 9.

Scheme 9



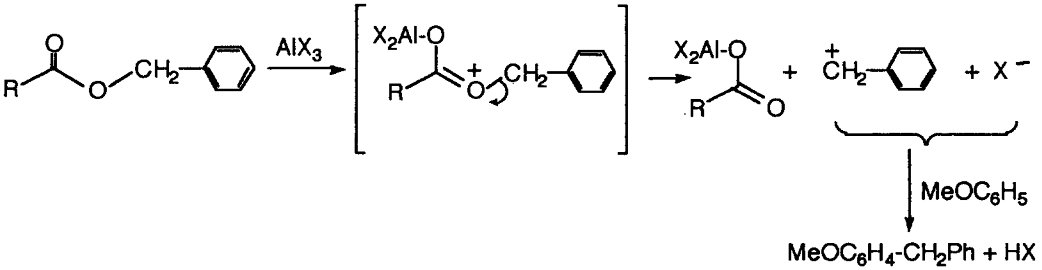
A possible mechanism may involve coordination of hard aluminium acid with the oxygen, which is a hard base, followed by a simultaneous or stepwise transfer of the soft iodide to the carbinol carbon The use of soft nucleophiles such as iodide,[38] cyanide, or thiolate ion in dipolar aprotic solvent for ester cleavage through an S_N2 process is well documented.[11]

7.2. and 7.3. Aluminum trichloride and a combination of aluminium trichloride and anisole

In 1979 Tsuji and coworkers[39] reported that a benzyl ester group in cephalosporin derivatives can be cleanly removed in high yields by treatment with aluminium trichloride under mild conditions, preferably in the presence of anisole.

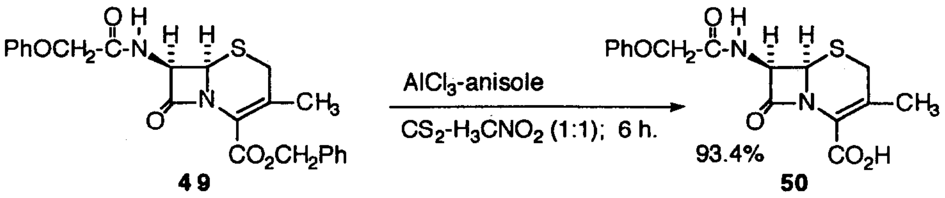
A mechanism was proposed based on aluminium trichloride coordination with the carbonyl oxygen to assist generation of the benzyl cation which is, in turn, trapped by anisole (Scheme 10).

Scheme 10



The utility of this methodology is illustrated (Scheme 11) by the deprotection of the benzyl ester of a cephalosporin derivative. The alternative deprotection by hydrogenolysis needs a large amount of a metal catalyst or a prolonged reaction time owing to poisoning by the sulfur of the cephem nucleus.

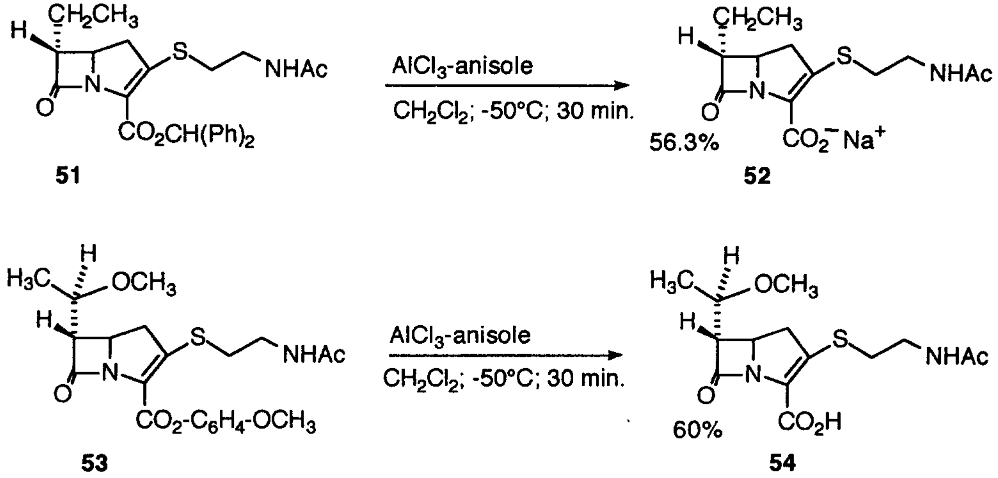
Scheme 11



Tsuji et al. also reported that under similar conditions in the absence of anisole cleavage of the benzyl cephalosporinate **49** gave the corresponding cephalosporanic acid **50** with similar yield, but in lower purity. Titanium tetrachloride was another Lewis acid which effected deprotection of benzyl ester **49**.

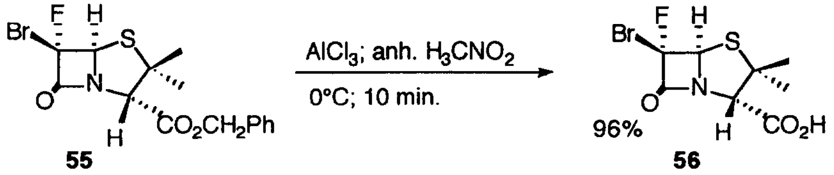
In 1984 Narisada and coworkers[40] described the mild deprotection of diphenylmethyl and *p*-methoxybenzyl esters of carbapenem derivatives by aluminium trichloride in combination with anisole. These authors pointed out that one crucial step in the synthesis of carbapenem antibiotics is final deprotection of the ester functionality, because the carbapenem nucleus is very unstable to acidic conditions. Representative examples are given in Scheme 12.

Scheme 12



In connection with the synthesis of 6β-bromo-6α-fluoropenicillanic acid **56** we chose the benzyl ester as a carboxyl protecting group. It was cleanly and quantitatively removed by treatment with aluminium trichloride under mild conditions.[41] Deprotection by hydrogenolysis would have likely removed the bromine.[42] (Scheme 13)

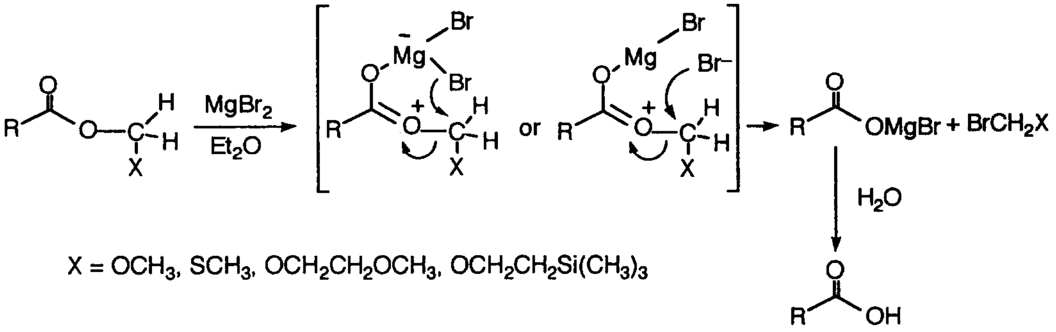
Scheme 13



7.4 Magnesium bromide

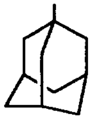
In 1991 Kim and coworkers[43] reported that methoxymethyl (MOM), methylthiomethyl (MTM), methoxyethoxymethyl (MEM) and β-(trimethylsilyl)ethoxymethyl (SEM) esters are deprotected by treatment with magnesium bromide in ether at room temperature. These esters can also be deprotected by simple acidic hydrolysis.[1] The MTM esters can also be deprotected with $HgCl_2/H_2S$,[44] by ammonium molybdate-catalyzed peroxide oxidation,[45] and by iodomethane.[45] As previously suggested for other hard Lewis acids, a possible mechanism for the cleavage reaction may involve coordination of the hard magnesium with the oxygen, followed by an intramolecular transfer or ionization of a bromide to give, after aqueous work-up, the corresponding carboxylic acids and the bromide products (Scheme 14).

Scheme 14



Some representative examples of this methodology are shown in Table IV.

Table IV Deprotection of MOM, MTM, MEM, and SEM esters with $MgBr_2$ in ether

R	$R\text{-}CO_2MOM$		RCO_2MTM		RCO_2MEM		RCO_2SEM	
	Time[a]	Yield[b]	Time	Yield	Time	Yield	Time	Yield
$Ph\text{-}CH_2-$	1	94	1.5	88	24	91	1	94
	4	90	12	74	48	92	6	93
$CH_3CH{=}CHCH_2-$	0.3	77	1.5	75	24	75	0.3	77

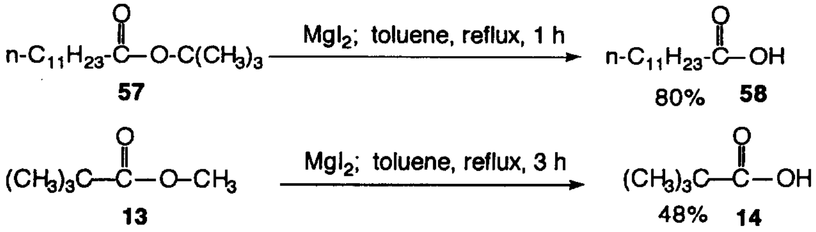
[a]Time in hours [b]Yield in (%)

As shown in Table IV, the deprotection of MEM esters is very slow, as compared with that of MOM, MTM, and SEM esters, and required more than 24 hours for completion.

7.5 Magnesium iodide

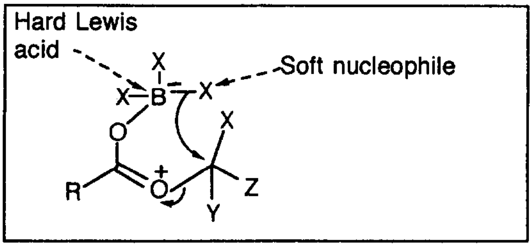
In 1991, García Martínez, Hanack, and coworkers[46] reported an efficacious procedure for cleavage of primary, secondary, and tertiary carboxylic esters with magnesium iodide in aprotic non-polar solvents. These authors indicated that their methodology allows cleavage of sterically hindered esters under mild conditions. Two representative examples are shown in Scheme 15.

Scheme 15



7.6 Boron halides and derivatives

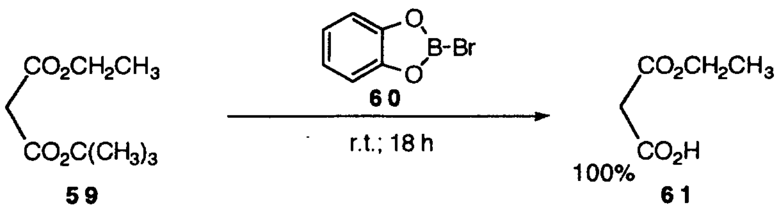
Although no mechanism has been postulated to explain the reactions with boron halides and derivatives, we believe based on studies with other hard Lewis acids, that the first step should be the coordination of the hard boron with the hard oxygen of the carbonyl group, followed by transfer of the bromide or chloride anions.



7.6.1 Catechol boron bromide (2-bromo-1,3,2-benzodioxaborole)

The use of catechol boron bromide and chloride as stable, non corrosive, mild and selective reagents for cleavage of certain ether, ester, and carbamate protecting groups was reported by Boeckman and Potenza in 1985.[47] These authors found that catechol boron bromide is useful for cleavage of a *tert*-butyl ester in the presence of an ethyl ester under mild conditions (Scheme 16).

Scheme 16



Beside its utility for cleaving *tert*-butyl esters, catechol boron bromide was found a very convenient reagent for selective cleavage of MOM and MEM ethers, as well as N-*tert*-butyloxycarbonyl and N-benzyloxycarbonyl protecting groups.

7.6.2 Boron tribromide (tribromoborane)

Boron tribromide is a moisture-sensitive liquid which is easily transferred under an inert atmosphere by standard cannula or syringe techniques. It is commercially available neat or as 1.0 M solutions in hexane or dichloromethane.

Felix[48] reported that boron tribromide in dichloromethane gave rapid conversion of methyl, ethyl, *tert*-butyl, benzyl, and *p*-nitrobenzyl esters to their corresponding acids. Many of the widely used amino acid side chain protecting groups Ser(Bn), Tyr(Bn), Thr(*t*-Bu), Glu(OMe), Glu(OEt), Glu(OBn), Asp(O-*t*-Bu) and Lys(Cbz) were also removed, whereas certain other groups as Arg(Tos), Cys(Bn) and His(im-Bn) were not affected.

Treatment of Cbz-ala-leu-OBn **62** or Cbz-ala-leu-OEt **63** with boron tribromide gave the free dipeptide, ala-leu **64**, exclusively. The amide bonds were not cleaved under these conditions (Scheme 17).

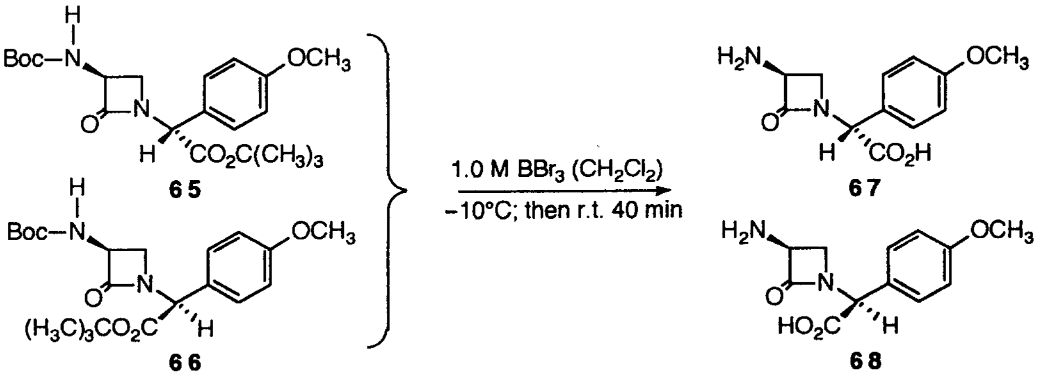
Scheme 17

$$\left.\begin{array}{c}\text{Cbz-Ala-Leu-CO}_2\text{CH}_2\text{Ph}\\ \mathbf{62}\\ \text{Cbz-Ala-Leu-CO}_2\text{CH}_2\text{CH}_3\\ \mathbf{63}\end{array}\right\} \xrightarrow[\substack{\text{-10°C, 1 h; then 25°C, 2 h}\\ \text{2) H}_2\text{O}}]{\text{1) 1.0 M BBr}_3\ (\text{CH}_2\text{Cl}_2)} \begin{array}{c}\text{Ala-Leu}\\ \mathbf{64}\end{array}$$

Yield: **62** → **64** 73.5%
63 → **64** 92.1%

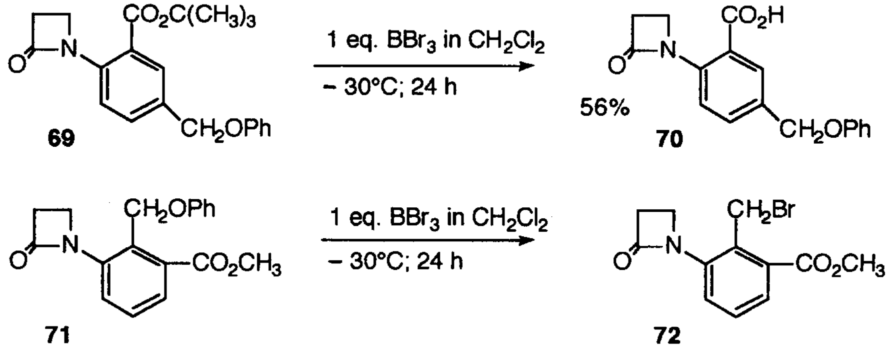
Mattingly and Miller[49] reported that boron tribromide and iodotrimethylsilane efficiently cleaved the N-Boc and *tert*-butyl ester groups of a 4:3 mixture of epimeric *tert*-butyl-3-amino-*tert*-butyloxycarbonylcardicinate **65**-**66**, but no yield was given (Scheme 18). However, these authors reported that conditions necessary to remove the benzyl or ethyl ester of 3-aminocardicinates destroyed the β-lactam ring.

Scheme 18



More recently Wakselman and Zrihen[50] reported that boron tribromide at -30 °C is a milder reagent than iodotrimethylsilane or the combination of chlorotrimethylsilane and sodium iodide for cleavage of a *tert*-butyl ester group in the presence of the phenoxybenzyl ether group of N-aryl azetidinones, like compound **69** without destroying the β-lactam ring (Scheme 19). However, use of more than one equivalent of boron tribromide led to a complex mixture of products. Under similar conditions the methyl ester of compound **71** was not removed, whereas the benzyl ether was cleaved. From these results, the authors concluded that the order of reactivity for the cleavage by BBr_3 is: $CO_2C(CH_3)_3 > CH_2OPh > CO_2CH_3$.

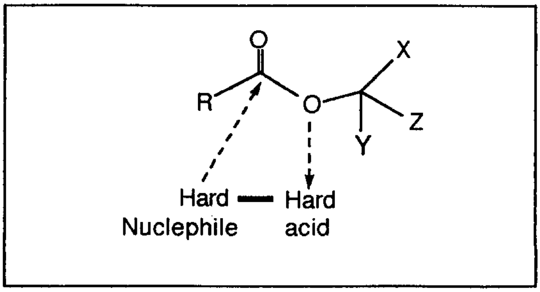
Scheme 19



7.6.3 Boron trichloride (trichloroborane)

In 1971 a preliminary report by Manchand[51] indicated that relatively simple, hindered esters can be cleaved efficiently by boron trichloride in methylene chloride. No experimental details and no full report have since appeared on the use of this reagent.

8 A HARD ACID AND A HARD NUCLEOPHILE. INTERNAL BIFUNCTIONAL SYSTEM

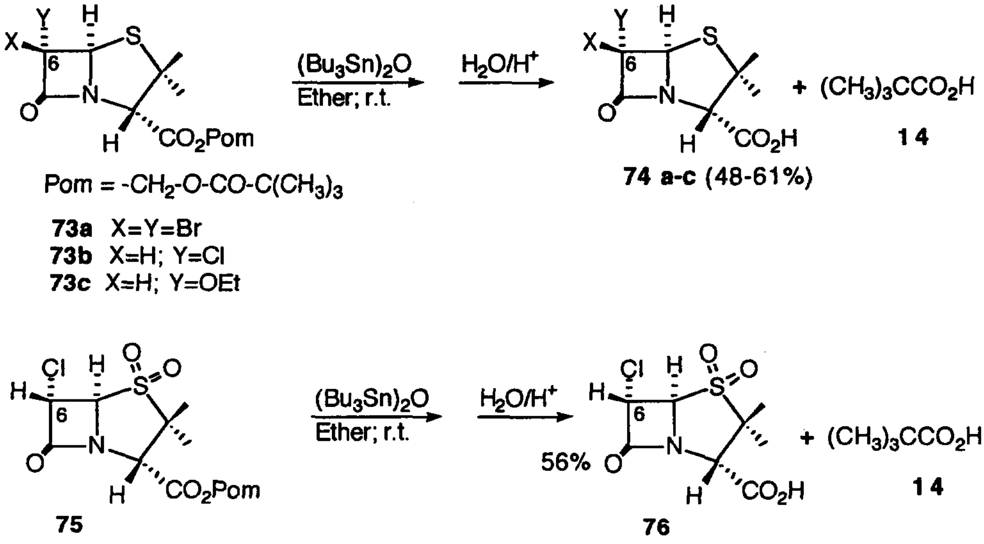


8.1 Bis(tributyltin) oxide.

In connection with development of an assay for β-lactamase activity, we required a method for deprotection of (pivaloyloxy)methyl (Pom) esters to liberate the carboxyl group. The classic saponification and the acidic hydrolytic methods were not applicable since they destroyed the β-lactam ring. Sodium thiophenoxide,[9] a soft nucleophile was unsuitable since this reagent in the 6,6-dihalo- and 6-halopenicillanate series might lead to substitution at carbon 6. We found that iodotrimethylsilane did not cleave Pom penicillanate derivatives; and with boron tribromide the results were not very reproducible.

Recently we first described the use of bis(tributyltin)oxide (henceforth abbreviated BBTO) for cleavage of simple esters, such as methyl, ethyl and phenyl esters as well as for the deprotection of double esters such as Pom esters (Scheme 20).[52] With the BBTO the mild conditions allow the selective cleavage of the (pivaloyloxy)methyl ester in the presence of the others functional groups of the azetidinone and thiazolidine rings and their substituents.

Scheme 20



We have explored the scope of this reaction with selected substrates.[52,53,54] Some examples of the usefulness of BBTO appear in Table V.

It is evident from these examples that cleavage of esters by BBTO is tolerant of a large range of functional groups, and also the chemoselectivity towards carboxylic diesters was found to be excellent.

Table V. Deprotection of esters by BBTO

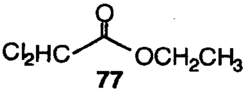
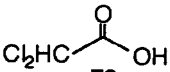
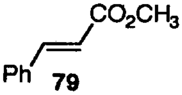
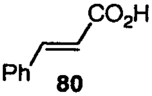
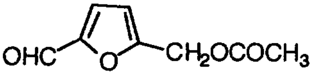
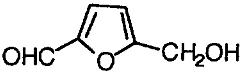
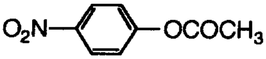
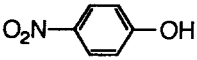
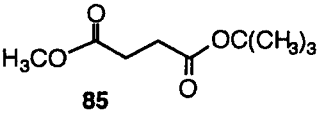
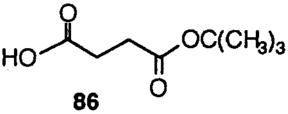
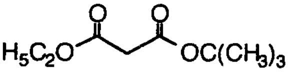
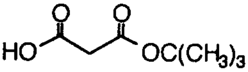
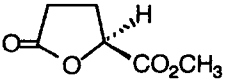
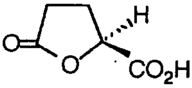
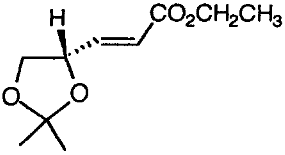
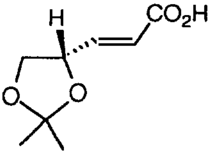
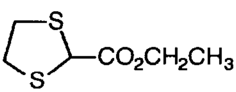
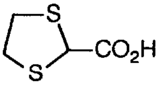
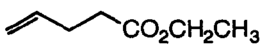
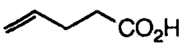
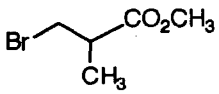
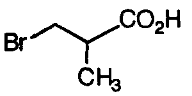
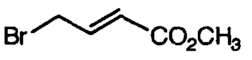
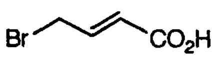
Ester	Product	Conditions	Yield (%)
 **77**	 **78**	benzene, 80 °C, 10 h	100
 **79**	 **80**	benzene, 80 °C, 24 h	90
 **81**	 **82**	benzene, 80 °C, 8 h	92
 **83**	 **84**	benzene, 25 °C, 10 h	96
 **85**	 **86**	toluene, 80 °C, 14 h	70
 **87**	 **88**	toluene, 104 °C, 3 h	50
 **89**	 **90**	acetonitrile, 60 °C, 24 h	55
 **91**	 **92**	toluene, 80 °C, 10 h	70
 **93**	 **94**	toluene, 80 °C, 10 h	35

Table V continued

Ester	Product	Conditions	Yield (%)
 **95**	 **96**	toluene, 90 °C, 48 h	42
 **97**	 **98**	toluene, 111 °C, 48 h	60
 **99**	 **100**	toluene, 80 °C, 10 h	70

There is always a constant need for new, easy to introduce, and selectively removable protecting group in peptide synthesis.[3] This is especially true in methodologies where the design of protection schemes requires two or three independent dimensions of orthogonality[55] for N-α- and N-ω- permanent protection and temporary protection of carboxylic acids.

We have studied the application of the BBTO reagent for deprotection of methyl and benzyl esters of amino acids and dipeptides in the presence of the most commonly used amino-protecting groups such as the benzyloxycarbonyl, the *tert*-butyloxycarbonyl and the 9-fluorenylmethyloxycarbonyl groups (Fmoc).[3] The examples compiled in the Table VI demonstrate the utility of BBTO with several selected N-α-N-ε-protected amino acids and dipeptides. As limitation of the new removal method using BBTO, instability of the Fmoc and Cbz groups in N-α-Fmoc-N-ε-Cbz-L-lysine methyl ester, **106**, toward this reagent has already been noted.

The absence of racemization during the deprotection of N-α-Boc-N-ε-Fmoc-L-lysine methyl ester **104**, and of the dipeptides N-Cbz-L-alanyl-L-alanine methyl ester **110** and N-Boc-L-phenylalanyl-L-proline methyl ester **112** was checked; the products were found to be enantiomerically and diastereoisomerically pure.[54]

The great selectivity of BBTO is evident from the selective deprotection of the benzyl ester in the presence of the benzyl carbamate group of N-α-Boc-N-ε-Cbz-L-lysine benzyl ester **103**.

Attempts to effect cleavage of (pivaloyloxy)methyl 6α-fluoro- and 6β-bromo-6α-fluoropenicillanates with BBTO resulted in destruction of the β-lactam moiety.[53] This may be due to a fluoro-destannylation reaction.[56] It is well known that the hard atom of tin has a great tendency to interact with the hard fluorine atom.[57]

Mechanism

We have also studied the mechanism of the BBTO reaction. Studies on esters of chiral alcohols showed that BBTO promotes regioselective cleavage at the **acyl-oxygen** bond of (1R,2S,5R)-(-)-menthyl acetate **114** and affords exclusively (1R,2S,5R)-(-)menthol[53] **115** (Scheme 21).

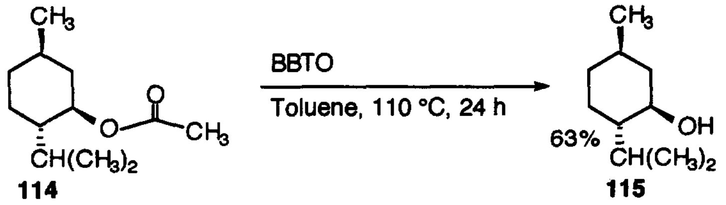
Table VI. Deprotection of esters in N-protected amino acids and dipeptides by BBTO

Ester	Product	Conditions	Yield (%)
Esters of N-protected amino acids			
N-α-Boc-N-ε-Cbz-L-lysine methyl ester **101**	N-α-Boc-N-ε-Cbz-L-lysine **102**	tol, 100 °C, 10 h	65
N-α-Boc-N-ε-Cbz-L-lysine benzyl ester **103**	N-α-Boc-N-ε-Cbz-L-lysine **102**	tol, 80 °C, 48 h	51
N-α-Boc-N-ε-Fmoc-L-lysine methyl ester **104**	N-α-Boc-N-ε-Fmoc-L-lysine **105**	tol, 100 °C, 24 h	67
N-α-Fmoc-N-ε-Cbz-L-lysine methyl ester **106**	N-α-Fmoc-N-ε-Cbz-L-lysine **107**	tol, 80 °C, 24 h	23^a
Esters of N-protected dipeptides			
N.N-dimethyl-L-aspartyl-L-phenylalanine methyl ester **108**	N.N-dimethyl-L-aspartyl-L-phenylalanine **109**	b, 80 °C, 14 h	60
N-Cbz-L-alanyl-L-alanine methyl ester **110**	N-Cbz-L-alanyl-L-alanine **111**	a, 80 °C, 48 h	52
N-Boc-L-phenylalanyl-L-proline methyl ester **112**	N-Boc-L-phenylalanyl-L-proline **113**	tol, 90 °C, 36 h	69

Abbreviations: b = benzene, tol = toluene, a = acetonitrile

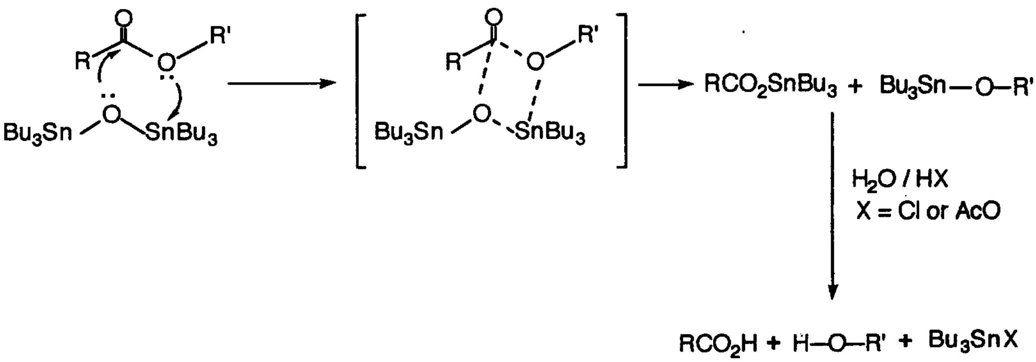
^{a}The low yield did result of partial loss of the Fmoc and Cbz groups.

Scheme 21



In conformity with the complete retention of configuration in (1R,2S,5R)-(-)-menthol, **115**, and with other experimental results (see below), this reaction can be explained by the principle of hard and soft acids and bases.[4,5] Cleavage of the **acyl-oxygen** bond with bis(tributyltin) oxide is based on nucleophilic attack of the hard oxygen on the hard carbonyl carbon centre, followed by or simultaneously with attack of the hard nucleophilic oxygen of the carbinol moiety on the hard electrophilic tin (hard Lewis acid), with formation of tributyltin carboxylate and tributyltin alkoxide (Scheme 22). It is well known that tin attached to oxygen enhances the nucleophilicity of the latter without increasing its basicity.[58,59]

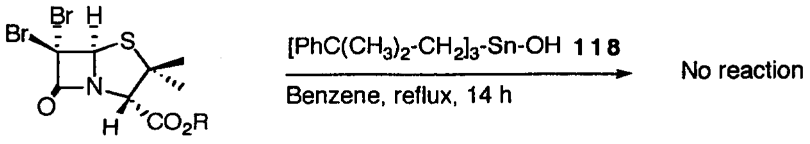
Scheme 22



It is also well known than the tin-oxygen bond is much more easily cleaved than the silicon-oxygen bond. As a consequence, the intermediate tributyltin carboxylate is readily hydrolyzed by aqueous acid or even during silica gel column purification. We also developed a simple procedure for recovering the alcohol from the intermediate tin alkoxide.[53] The formation of carboxylic esters, (the most common is the acetate) is a useful and widely employed method for protection of the alcohol functional group.[1]

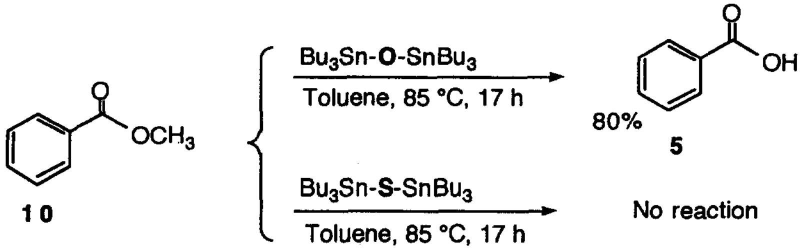
In the crystal, the tin in bis(tributyltin) oxide is tetrahedrally tetra-coordinated and the Sn-O-Sn bond angle is 137°.[60,61] The following results support the validity of our mechanistic assumptions 1) In support of the notion that a second atom of tin is neccesary to accomplish this reaction, through a stepwise or four center mechanism, we found that no ester cleavage occurred, when (pivaloyloxy)methyl, methyl or benzyl esters of 6.6-dibromopenicillanic acid, **73a**, **116**, **117** were treated with *tris*[2-methyl-2-phenylpropyl(neophyl)]tin hydroxide **118** instead of BBTO. With BBTO the 6,6-dibromopenicillanic acid was isolated in yields ranging from 47 to 60%. In the case of trineophyltin hydroxide the starting material was quantitatively recovered (Scheme 23). 2) The necessity for a hard oxygen atom in that tin reagent was verified experimentally by the fact the methyl benzoate, **10**, was not cleaved to benzoic acid, **5**, by bis(tributyltin) sulfide, but was recovered quantitatively. (Formally, the hard oxygen atom is replaced by a soft sulfur). Under identical experimental conditions using bis(tributyltin) oxide, benzoic acid was isolated in 80% yield (Scheme 24).

Scheme 23



73a R = Pom
116 R = CH_3
117 R = CH_2Ph

Scheme 24



The versatility of BBTO for the formation of tributyltin carboxylates is well documented.[52,61] Its utility for *the carboxylic acid-tributyltin ester-to alkyl ester* transformation was very recently demonstrated.[2e] Additional significance of the synthetic versatility of BBTO lies in the back transformation *alkyl ester-to tributyltin ester-carboxylic acid.* These findings, the unreactivity of BBTO toward functional groups other than carboxylic esters, and its selectivity between methyl, ethyl and *t*-butyl esters, clearly indicates that it is possible to mask carboxylic acids temporarily as methyl and ethyl esters in the course of a multistep synthesis of polyfunctional molecules.

The advantages of this method may be summarized as follows. 1) The methyl as well as other alkyl esters are readily formed and in high yield. [2e] 2) Apparently, no racemization occurs in the course of the ester cleavage. 3) BBTO is commercially available and inexpensive. 4) The cleavage conditions are mild and the process is fast. 5) The BBTO cleavage of diverse esters is compatible with a large range of functional groups.

One of the drawbacks in our experience is the difficulty of completely eliminating the excess of bis(tributyltin) oxide and the tin byproducts. These tin derivatives are highly soluble in nonpolar solvents. In some of the examples presented in Tables V and VI the low yield was due to loss of material during work-up. Most of these organotin compounds are very insoluble in water. Accordingly, we have used these properties extensively to purify carboxylic acids. Normally, carboxylate salts are cleanly extracted into an aqueous phase, while the tin derivatives remain in the organic phase. We have also made extensive use of the procedure developed by Berge and Roberts.[62] Their method is based on the very high solubility of organotin derivatives in hexane and the preferential partitioning of other organic molecules into acetonitrile in the acetonitrile-hexane two phase system. We have also found that filtration through a short pad of C-18 reverse-phase silica gel and elution with mixtures of acetonitrile-water is one of the most useful ways to clean-up the organotin derivatives.[54] More recently, Farina[63] reported a simple procedure for purification of organotin derivatives by column chromatography using reverse-phase silica gel, however, its application in preparative work is hampered by the high cost of the C-18 silica gel.

9 CATALYTIC TRANSFER HYDROGENATION

Catalytic transfer hydrogenation is a method for the simultaneous removal of all protecting groups that are normally removed by catalytic hydrogenation.

9.1 10% Pd/C and cyclohexene

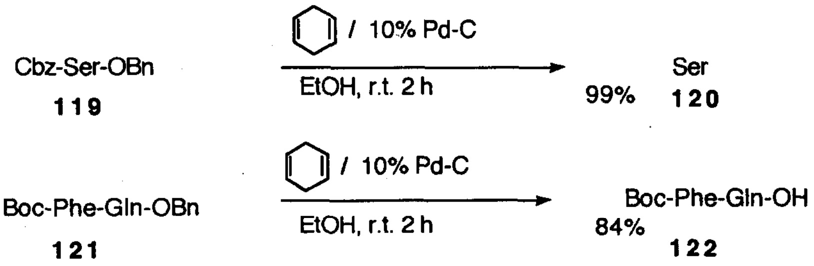
Two early reports[64,65] described the use of catalytic transfer hydrogenation for removal of N-benzyloxycarbonyl and benzyl ester protecting groups in peptide synthesis. Good yields of homogeneous and nonracemized products were obtained when cyclohexene was used as hydrogen donor at temperatures >65 °C in the presence of 10% palladium-carbon catalyst. If freshly prepared palladium black catalyst is used, others common protecting groups like N-π-benzyl (histidine), benzyl ether (tyrosine, serine), and nitro (arginine) could also be removed much more rapidly than by the usually employed catalytic hydrogenation.

9.2 10% Pd/C and 1,4-cyclohexadiene

In 1978 Felix and coworkers[66] first reported that 10% palladium on carbon as catalyst and 1,4-cyclohexadiene as hydrogen donor for catalytic transfer hydrogenation is a very mild and effective way to deprotect various kinds of benzyl protecting groups in peptides.

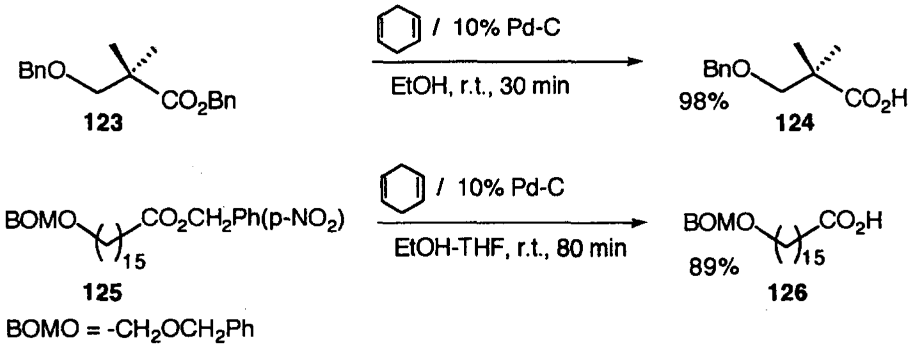
N-Benzyloxycarbonyl, benzyl ester and benzyl ether (tyrosine) protecting groups were rapidly removed at 25 °C, whereas *tert*-butyl protecting groups were completely stable under these conditions. Two examples of removal of benzyl-type protecting groups are shown in Scheme 25.

Scheme 25



Very recently Bajwa[67] reported the chemoselective deprotection of benzyl esters in the presence of benzyl ethers, benzyloxymethyl ethers, and N-benzyl groups by hydrogenolysis under catalytic transfer hydrogenation conditions using 10% palladium on carbon as catalyst and cyclohexadiene as the hydrogen donor. The author indicated that the rate of the transfer hydrogenation is highly dependent upon the quality of the catalyst.Two examples in which benzyl and *p*-nitrobenzyl esters were selectively debenzylated in the presence of benzyl and benzyloxymethyl ethers are shown in Scheme 26.

Scheme 26

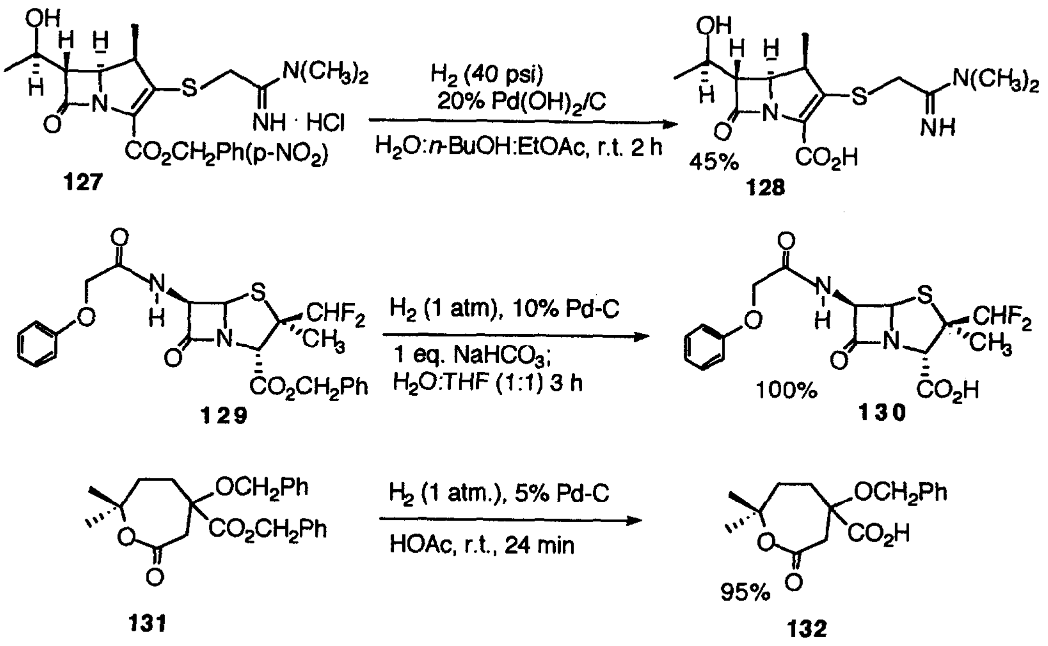


10 HYDROGENOLYSIS

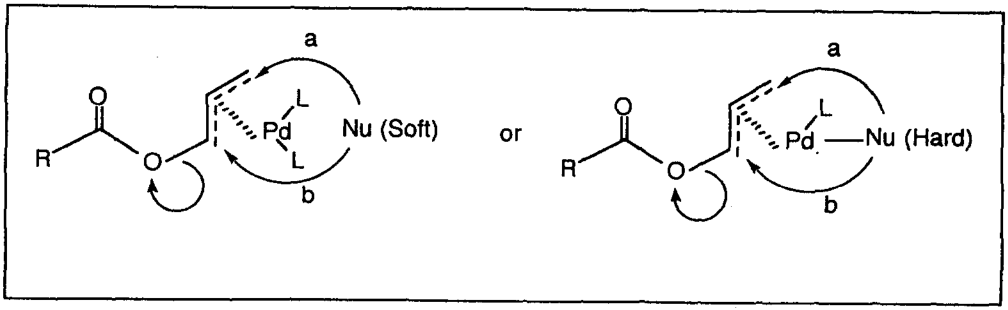
10.1 H_2 - Palladium on carbon

This method remains one of the most versatile approaches for cleaving benzyl esters. During the past few years, the hydrogenolytic method has been successfully applied to deprotect the *p*-nitrobenzyl ester of 1β-methylcarbapenem,[68] **127**, benzyl penicillanates,[69] benzyl cephalosporinates,[69] and benzyl 4-benzyloxy-7,7-dimethyl-2-oxo-1-oxacycloheptane-4-carboxylate,[70] **131**, (Scheme 27).

Scheme 27



11 NUCLEOPHILIC SUBSTITUTION OF ALLYLIC SYSTEM ACTIVATED WITH Pd°

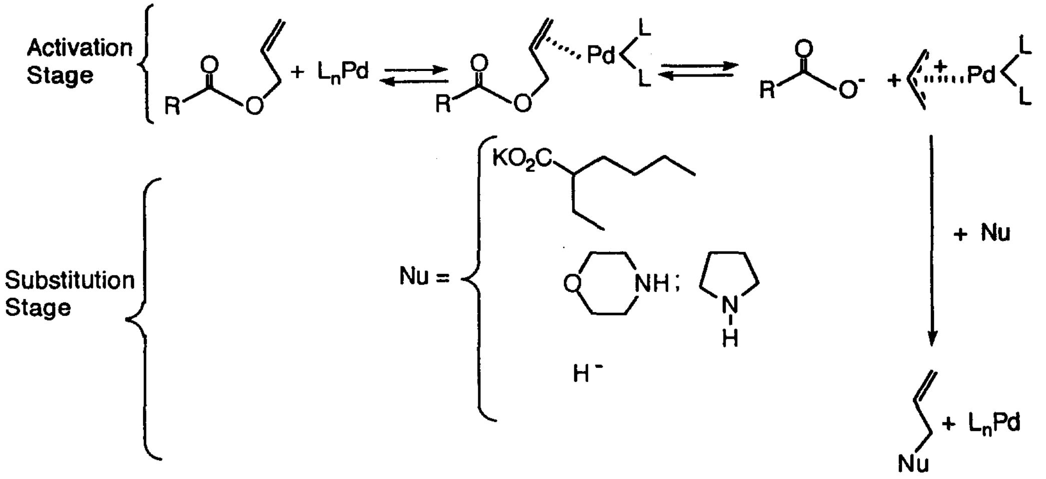


During the past 12 years several reagents have been introduced for the cleavage of allylic esters using tetrakis(triphenylphospine)palladium(0) as well as other soluble palladium complexes as catalysts and potassium 2-ethylhexanoate, morpholine, pyrrolidine, and the hydride donors, formate, tributyltin hydride, borohydride and cyanoborohydride, as a nucleophile to effect an allylic exchange reaction.

This reaction principle was originally introduced by Trost and others for the alkylation of π-allylpalladium complexes.[71] Trost reported that whereas organometallic reagents are normally thought of as nucleophiles, π-palladium complexes are, in fact, electrophilic conjunctive reagents; and phosphine ligands increase the electrophilic nature of the π-palladium complexes.

The reaction can be explained by the following mechanism. The activation stage consists of coordination of the palladium (0) species with the alkene to provide a π-allyl palladium complex,[71] followed by disengagement of the carboxylate group to generate the π-allylic cationic intermediate. Nucleophilic attack by the carboxylate of 2-ethylhexanoate, the amines, morpholine and pyrrolidine or the hydride ion gives allylic transesterification, amination, or formation of the alkene products and regenerates the palladium (0). Thus, palladium (0) serves initially as a nucleophile and having, done so, becomes a leaving group (see Scheme 28).

Scheme 28



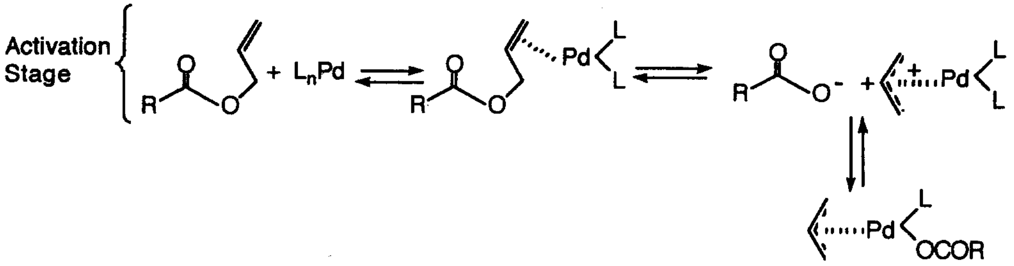
Cleavage of the (allyloxy)carbonyl function was first effectively carried out with nickel carbonyl,[72] mercuric acetate/potassium thiocyanate,[73] and organocuprates.[74]

11.1 Tetrakis(triphenylphosphine)palladium(0)-potassium 2-ethylhexanoate

Jefrey and McCombie[75] described the first use of the combination of tetrakis(triphenylphosphine)-palladium(0) and potassium 2-ethylhexanoate for cleavage of the (allyloxy)carbonyl function using catalytic π-allyl activation and transesterification. They also found that other phosphine-palladium complexes are effective exchange catalysts, e.g., $Pd(OAc)_2$-PPh_3; $Pd(OAc)_2$-$(EtO)_3P$. These combinations generate catalytically active species by *in situ* reduction of palladium acetate in the presence of phosphine ligands. Jefrey and McCombie reported that deprotection of allylic carbonates and carbamates by palladium(0)-catalyzed exchange was also effective.

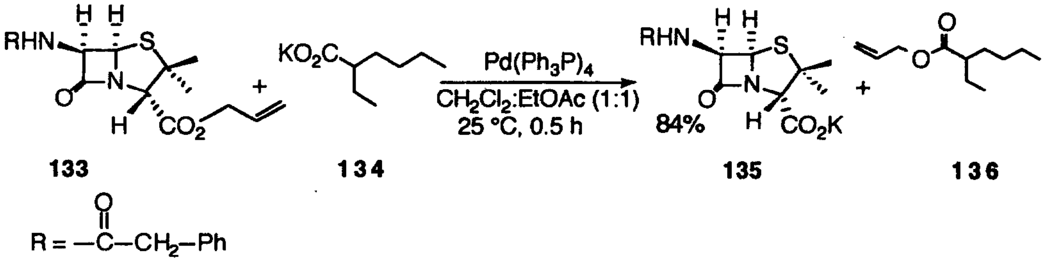
The authors proposed that equilibria of the activation step in the case of allylic carbon-carbon bond formation with *soft nucleophiles* such as stabilized carbanions, the cationic complex is involved, whereas with *hard nucleophiles,* like the oxygen of the carboxylates (and by extension the *hard* hydride) transfer via coordination to the metal is implicated[75] (Scheme 29).

Scheme 29



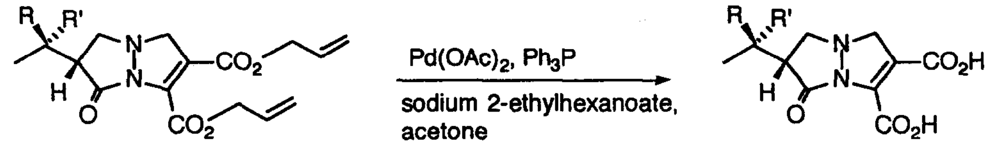
The homogeneous palladium(0) catalyzed carboxylate exchange makes allyl esters convenient protecting groups, selectively removable under such mild conditions that the sensitive functionalities of the penam, penem and cephem nuclei are completely preserved. The utility of this method in the β-lactam field is illustrated by the conversion of penicillin G allyl ester to penicillin G potassium salt (Scheme 30). Displacement of the exchange equilibrium toward the desired product is assured by use of the alkali metal salts of 2-ethylhexanoic acid, which are soluble in most common solvents, except hydrocarbons. The authors reported that precipitation of the salt **135** was essentially complete in 1 h at 25 °C, and simple filtration gave pure product in 84% yield.

Scheme 30



An interesting application[76] of this method is the removal of the allyl ester groups of the bicyclic pyrazolidinone **137-138** (Scheme 31).

Scheme 31



137 R = OH, R' = H
138 R = H, R' = OH

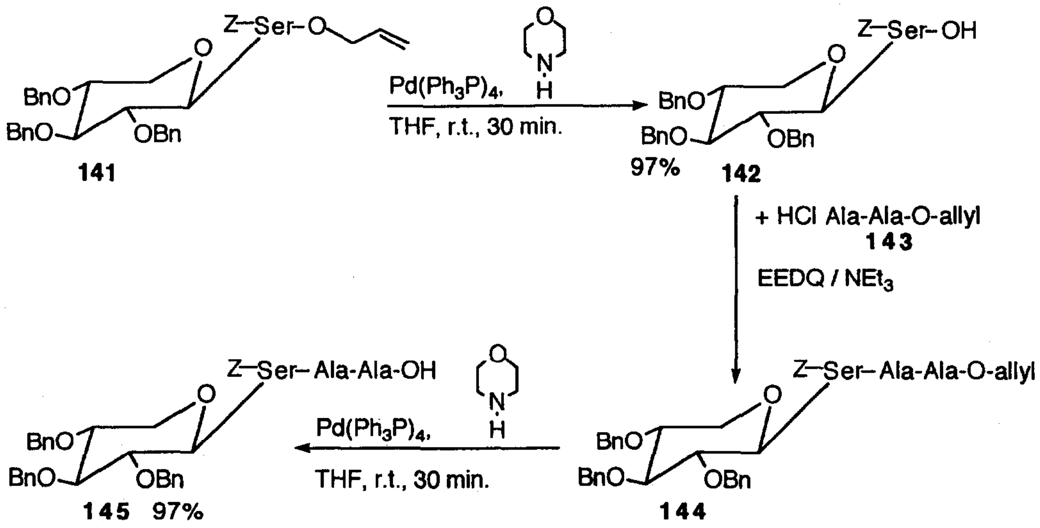
139 R = OH, R' = H
140 R = H, R' = OH

11.2 Tetrakis(triphenylphosphine)palladium(0)-morpholine

An extensive study by Kunz and coworkers[77] has demonstrated that an allyl esters is a valuable carboxy protecting group for glycopeptide synthesis. It is stable to acids and bases but can be removed selectively under mild conditions with tetrakis(triphenylphosphine)palladium(0) as a catalyst and morpholine (tenfold excess) as the accepting nucleophile. These authors remarked that this method is particularly useful for O-glycosyl-serine and -threonine bonds are present since both are acid and base-labile.[78]

Pd(0)-catalyzed selective cleavage of the O-glycosyl-Cbz-serine allyl ester derivative **141**, C-terminal elongation of the peptide chain; and selective removal of the allyl ester from the glycotripeptide **144** is illustrated in Scheme 32. In this example the allyl ester group is selectively removed in the presence of benzyloxycarbonyl groups, as well as, O-glycosidic and peptide bonds.

Scheme 32

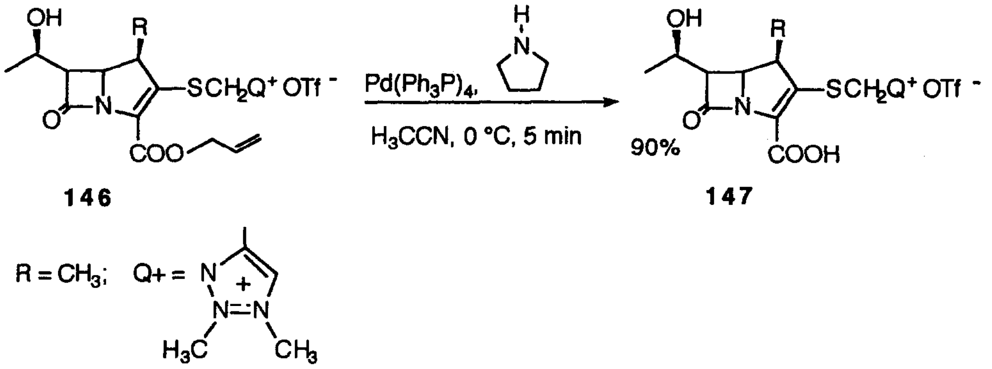


Waldmann and Kunz also reported the selective removal of allylic esters using tris(triphenylphosphine)rhodium(I) chloride in a mixture of ethanol-water (1:1) as solvent.[79]

11.3 Tetrakis(triphenylphosphine)palladium(0)-pyrrolidine

More recently, Deziel[80] reported that the amine, pyrrolidine, smoothly deprotected an allyl ester at 0 °C in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0). This method has been efficiently applied in the β-lactam field to deprotect carbapenem, penam, and cephem allyl esters. Deziel also successfully applied it to deprotect within a few minutes in a very good yield the carbapenem allyl ester **146** as well as other R and Q^+ derivatives. On the other hand, when compound **146** and also other carbapenem allyl esters were subjected to the procedure of Jefrey and McCombie,[75] decomposition occurred very rapidly, whereas the procedure of Kunz[77b] failed to give the zwitterion **147** (Scheme 33).

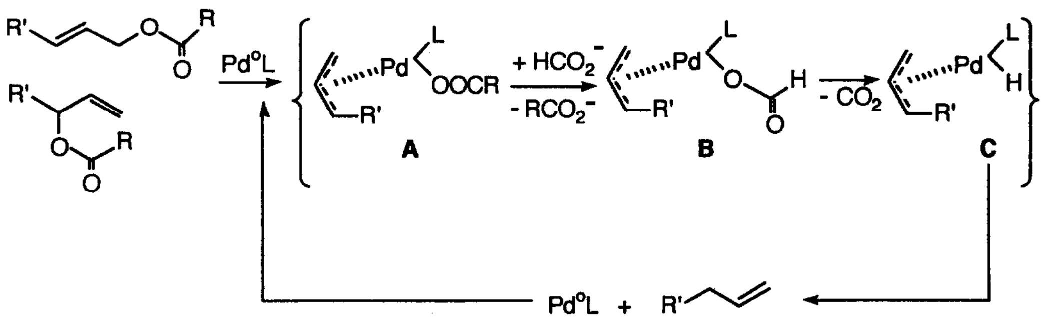
Scheme 33



11.4 Dichlorobis(triphenylphosphine)palladium(II)-ammonium formate

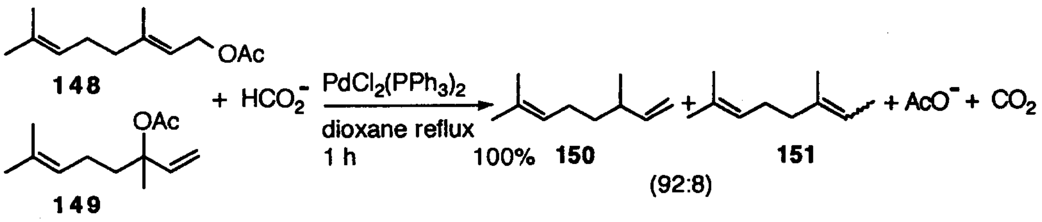
In 1979 Tsuji and Yamakawa[81] reported the formation of conjugated dienes and also the cleavage of several carboxylate allyl esters as well as allyl phenyl ethers using $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ with PPh_3 as catalyst and ammonium formate as a source of hydride ion. The authors indicated that ammonium, triethylammonium, and pyridinium salts of formic acid, gave better results than formic acid itself. Tsuji and Yamakawa explained that mechanistically an oxidative addition of the allylic compound to the Pd^0 species takes place to form the π-allylic complex (see general mechanism in Scheme 29). Displacement of the carboxylate group by formate affords the formate complex, which is then converted to the palladium-hydride with generation of carbon dioxide. Then the olefins is liberated by reductive elimination with regeneration of the Pd^0 species. In this step, the hydride attacks preferentially the more substituted side of the π-allylic system to afford 1-olefins predominantly (Scheme 34). The authors gave supporting evidence for the formation of the formate complex **B** by treating 2,7-octadienyl formate with the palladium catalyst in the absence of ammonium formate, and 1,7-octadiene was obtained as the major diene product.

Scheme 34



A typical example to illustrate this method is the cleavage of geranyl acetate, **148**, (or linalyl acetate, **149**, since it forms the same π-allylic complex) from which olefins **150** and **151** are formed in the same (92:8) ratio by reductive elimination (Scheme 35).

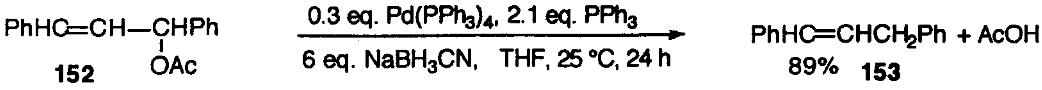
Scheme 35



11.5 Tetrakis(triphenylphosphine)palladium(0)-sodium borohydride or sodium cyanoborohydride

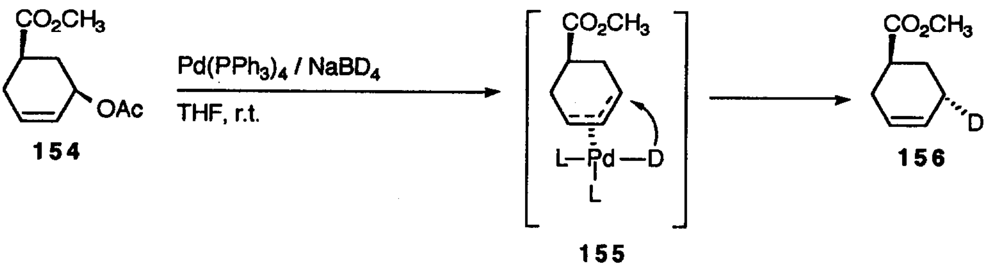
In 1980 Hutchins and coworkers[82] reported the chemoselective cleavage of allylic acetates by hydride transfer from donors such as $NaBH_4$ and $NaBH_3CN$ via catalytic activation by palladium(0) complexes. The reductive displacement of the allylic acetate in 1,3-diphenyl-2-propenyl acetate by hydride transfer with activation with $Pd(PPh_3)_4$ illustrates this methodology (Scheme 36).

Scheme 36



Keinan and Greenspoon[83] reported that the hydride is internally transferred from the π-allyl palladium complex to the allylic system with endo stereochemistry (Scheme 37).

Scheme 37



The major drawback of $NaBH_4$ and $NaBH_3CN$ as hydride donor is that these reagents are incompatible with a electrophilic functional groups, such as ketones and aldehydes.

11.6 Dichloro-bis-(triphenylphosphine)palladium(II)-tributyltin hydride

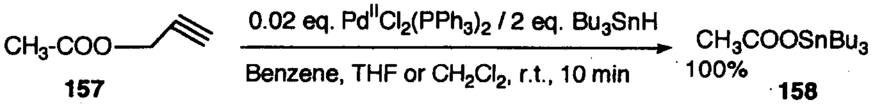
Keinan and Greenspoon[83] found that tributyltin hydride, as hydride donor, allows highly chemoselective palladium catalyzed reductions of allylic heterosubstituents even in the presence of aldehydes, benzyl acetate, and benzyl chloride.

Guibé and coworkers[84] also have showed that the allyl derivatives of carboxylic acids or phenols and the allyloxy carbonyl derivatives of alcohols and amines can be deprotected by palladium-catalyzed cleavage with tributyltin hydride.

Reactions with the propargylic electrophile, similar in chemical properties to its allylic counterpart, were first described by Keinan and Bosch.[85] They studied the relative reactivities of allylic and propargyllic acetates in palladium(0)-catalyzed substitutions by various nucleophiles using three types of model substrates: a) monofunctional allylic and propargylic acetates with similar structural properties; b) a bifunctional substrate containing both allyl and propargyl functionalities with no apparent interaction between them; c) conjugated bifunctional systems, in which the two functionalities may interact with each other.

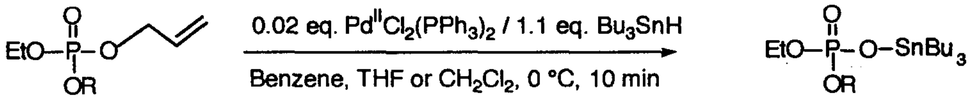
Guibé and coworkers[86] applied this procedure to the deprotection of propargyl *p*-methylbenzoate, diethyl propargyl phosphate, propargyl benzyl carbonate, and benzylamine propargyl carbamate. Scheme 38 shows that for example, propargyl acetate, **157**, after 10 minutes was totally converted into tributyltin acetate, **158**. The tin carboxylates were then converted into the sodium salts or into the carboxylic acids by treatment with aqueous sodium carbonate or with various protonating agents, such as, water, acetic acid, *p*-nitrophenol, etc.

Scheme 38



Guibé and coworkers[87] extended this procedure to the deprotection of allyl groups of phosphate esters, and they found that other phosphate protecting groups, such as p-chlorophenyl, β-trichloroethyl, and β-cyanoethyl, are stable under these conditions (Scheme 39). Tributyltin phosphates are readily converted into inorganic phospates by treatment with chloroboronates $ClB(OR)_2$ followed by hydrolysis of the mixed phosphoric-boronic anhydride. Tributyltin phosphates may also be converted to their trimethylsilyl analogs, which in turn are rapidly alcoholized in the presence of base. Allyl protection in phosphate chemistry using other palladium-catalyzed deprotection procedures has also been studied by others authors.[88]

Scheme 39



163-166

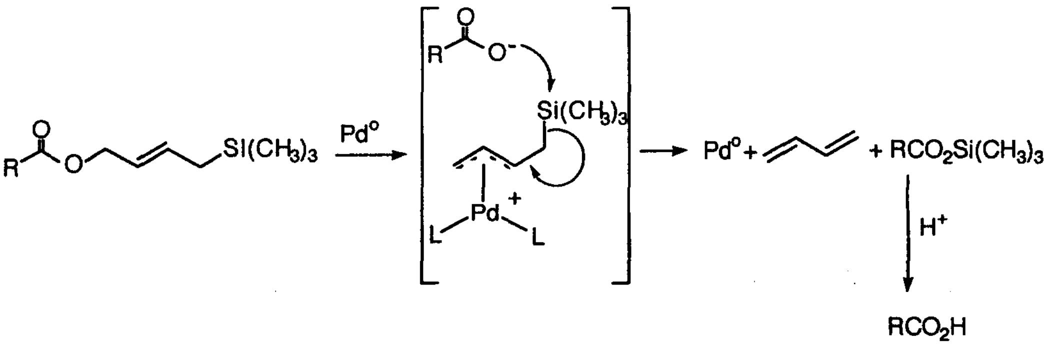
159-162; R = CH_3-CH_2-, *p*-Cl-Ph-, Cl_3-CH_2-, NC-CH_2-CH_2-, respectively

Guibé and coworkers[87] also found that with *n*-butylamine or dimedone[89] as the allyl acceptor, the very reactive allyl phosphate and allyl carbonates are readily and selectively cleaved, whereas the propargyl and propargyloxycarbonyl groups are perfectly stable under these conditions. They mention that based on these findings these groups can be used for semipermanent protection in conjunction with the temporary allyl and allyloxycarbonyl protecting groups when multiprotection is needed, as is especially the case in nucleotide chemistry. They also found that allyl carboxylates and carbamates can be selectively deprotected in the presence of propargylic esters by the use of dimedone or its benzylamine salt as the allyl acceptor.

11.7 Tris(triphenylphosphine)palladium(0)

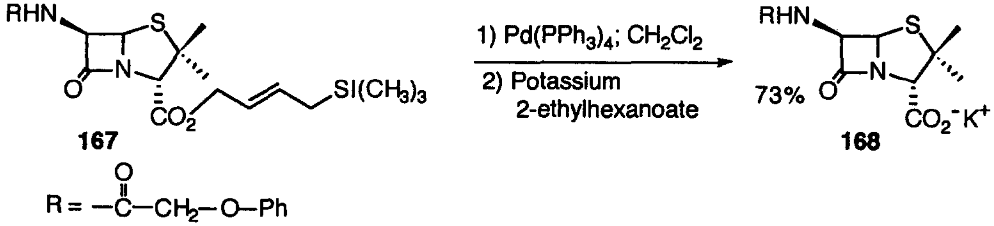
Trost and Chan[90] first demonstrated that a silyl group can also functions as an electrofuge if situated α to the π-allyl complex. Based on this property Mastalerz[91] reported the cleavage of 4-trimethylsilyl 2-butenyl esters by catalytic activation with Pd(0) to afford trimethylsilyl esters, which are readily hydrolyzed. In this method, there is no need for any nucleophilic species as the group to be liberated acts as its own deprotecting agent (Scheme 40).

Scheme 40



The cleavage of 4-trimethylsilyl 2-butenyl ester of penicillin V, **167**, illustrates the utility of this method (Scheme 41).

Scheme 41



12 CLEAVAGE OF CARBOXYLIC ESTERS VIA A RADICAL MECHANISM

12.1 Superoxide anion radical

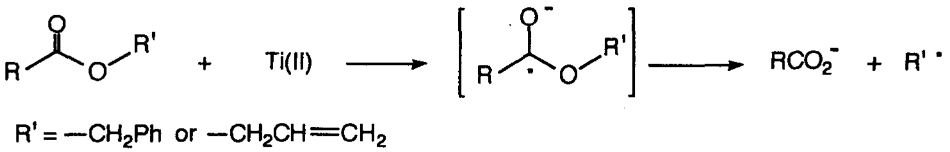
In 1976 San Filippo and coworkers[92] reported that several carboxylic acid and certain phosphate esters are cleaved by potassium superoxide in benzene in the presence of 18-crown-6 ether to produce the corresponding carboxylic acid and alcohol in good to excellent yields. Amides and nitriles were unaffected by superoxide. The authors consider several plausible mechanims including a nucleophilic radical substitution.[93]

12.2 Titanium(II) Reagent

In 1989 Chandrasekaran and coworkers[94] reported the reductive cleavage of a variety of allylic and benzylic esters with a titanium(II) reagent, generated by the reduction of $TiCl_4$ with amalgamated magnesium. In addition to the corresponding carboxylic acids, dimeric hydrocarbons are formed.

Mechanistically the reaction was postulated to proceed through an anion radical intermediate, which undergoes cleavage of the O-benzyl or O-allyl bond with formation of the carboxylate anion and a stable benzyl or allyl radical (Scheme 42).

Scheme 42



The presence of carbonyl and nitro groups is not compatible with this methodology. However, the major drawback of this methodology appears to be the possibility of further reduction of the carboxylic acid.

13 OXIDATIVE CLEAVAGE

13.1 Nitrosonium hexafluorophosphate

In 1977 Olah and Ho reported a selective oxidative method for cleavage of benzylic esters with nitrosonium hexafluorophosphate.[95] The method is based on hydride transfer from the benzylic hydrogens of benzyl esters to the nitrosonium cation (NO^+), with concomitant formation of a cationic center, which spontaneously fragments into an acylium ion and a carbonyl compound. Subsequent quenching of the acylium ion leads to the carboxylic acids.

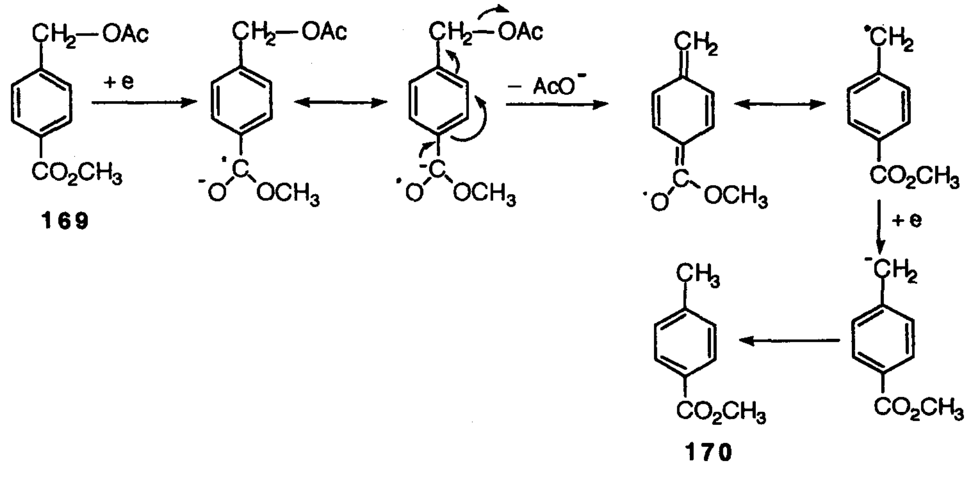
13.2 2,3-Dichloro-5,6-dicyano benzoquinone (DDQ) and ceric ammonium nitrate (CAN)

In 1985 Kim and Misco[96] reported the oxidative cleavage of 2,6-dimethoxybenzyl carboxylic esters by DDQ to the corresponding carboxylic acids. They also found that phenyl ester derivatives substituted with hydroxy, methoxy, and dimethylamino groups were cleaved oxidatively with ceric ammonium nitrate.

14 ELECTROCHEMICAL CLEAVAGE OF CARBON-OXYGEN BONDS IN CARBOXYLIC ESTERS

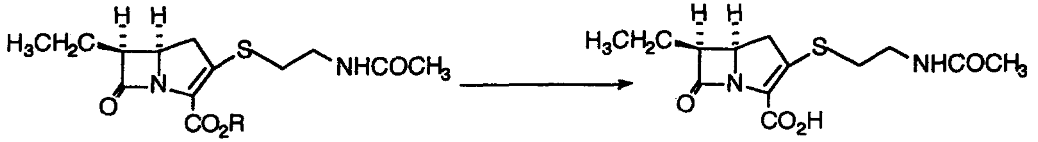
In 1970, Utley and coworkers[97] first described the cathodic reductive cleavage of *p*-carbomethoxybenzyl acetate **169** to produce methyl *p*- toluate **170** and acetic acid. They proposed a mechanism that involves electron transfer according to Scheme 43.

Scheme 43



Eglinton and Corbett[98] applied the method of electrochemical reductive cleavage to the *p*-carbomethoxybenzyl esters to carbapenem systems. The cleavage of olivanic acid derivative **171** was effected by reduction at a Hg cathode (-1.9 V *vs.* standard calomel electrode) in a divided cell (Pt anode; 0.1M Bu_4NBF_4; DMF). No yield was reported (Scheme 44).

Scheme 44



171 R = $-CH_2C_6H_4CO_2CH_3$-*p* **172**

15 DEPROTECTION OF 3-BUTENYL ESTERS VIA OZONOLYSIS AND β-ELIMINATION

Recently Barrett and coworkers[99] described the preparation and deprotection of 3-butenyl esters. Deprotection was carried out via ozonolysis and β-elimination of the resultant 3-acyloxypropanal with the bases triethylamine or DBU, to generate the carboxylic acid.

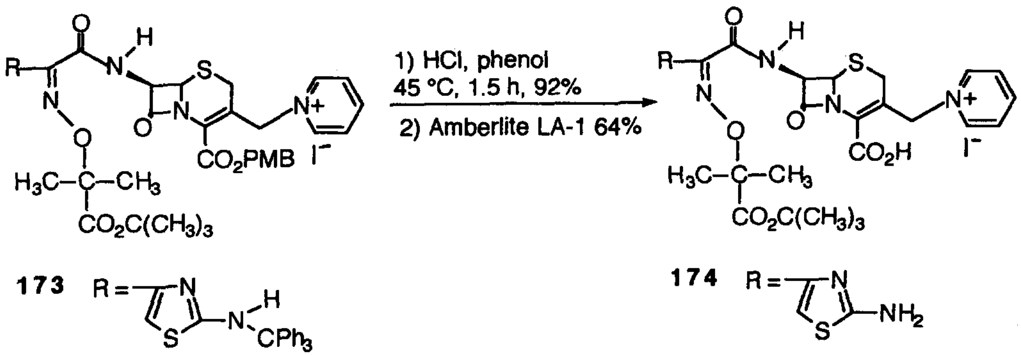
Those authors applied this deprotection sequence effectively for selective deprotection of 3-butenyl esters of sensitive functionalized molecules such as penicillins (among others) and of diesters like *p*-nitrophenyl 3-butenyl-2-methyl malonate.

16 BY A PHENOLIC MATRIX

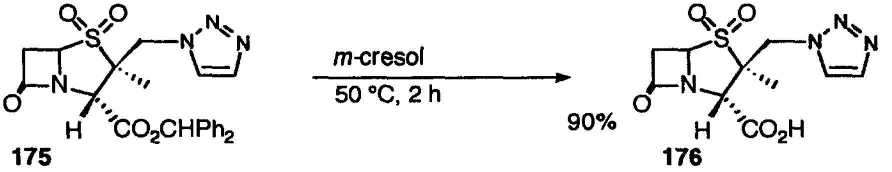
Recently Tori and coworkers[100] described a very useful modification of the classic protic acid method for the deprotection of *p*-methoxybenzyl, diphenylmethyl, and *tert*-butyl esters which involves an acid-catalyzed process that proceeds via a proton relay through a hydrogen-bonded phenolic matrix.

They demonstrated the versatility of the method by applying it to the deprotection of various PMB, BH, and *t*-Bu esters of β-lactam compounds. We illustrate the utility of this method by the deprotection of esters of ceftazidima,[101] **173**, (a commercial third generation cephalosporin antibiotic) (Scheme 45) and of tazobactam,[102] **175**, a new commercial β-lactamase inhibitor (Scheme 46).

Scheme 45

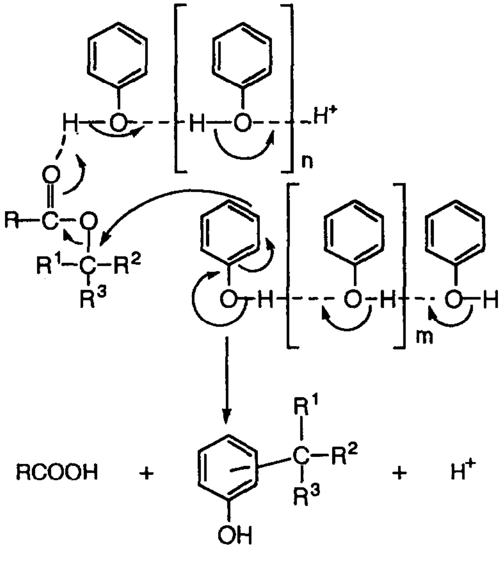


Scheme 46



To rationalize the experimental results the authors postulated the existence of a hydrogen bond network whitin a phenol matrix (Scheme 47). The proton required for the cleavage can be supplied initially by added acids and, thereafter, catalytically via an SNAr (Aromatic Nucleophilic Substitution) involving a nucleophile like anisol or phenol. Although the concentration of protons would be expected to be rather low under these conditions, protons could be efficiently relayed to the reaction center through the hydrogen bonding network of the phenolic matrix. This phenolysis of an ester can be viewed as the alkylation of a phenol by an alkyl ester, with the carboxylate acting as a leaving group.

Scheme 47



17 HYDROLYSIS

Hydrolysis of esters is one of the most widely used transformations in organic synthesis. Normally, an acidic or basic aqueous solution is used. Ester hydrolysis catalyzed by acid or base may involve **acyl-oxygen** or **alkyl-oxygen** cleavage, and in each case the rate determining step may be uni- or bimolecular. The various mechanisms are designated $A_{ac}1$, $A_{ac}2$, $B_{ac}2$, $A_{al}1$, $B_{al}1$ and $B_{al}2$. It is beyond the scope of this report to cover ester hydrolysis in depth; instead we describe only recent developments. Excellent reviews on esterification and ester hydrolysis have been published.[103,104]

17.1 Under acidic conditions

17.1.1 10M H_2SO_4 or 9 M HBr or 12 M HCl in two phase system

In 1982 Landini and Rolla[105] reported the acid hydrolysis of carboxylic *tert*-butyl esters to afford carboxylic acids using a two phase system in the presence of catalytic amounts of quaternary onium salts. The reaction was carried out in a two-phase system at room temperature with the ester neat or in chloroform and an aqueous mineral acid, i.e., 10 M H_2SO_4, 9 M HBr, or 12 M HCl, in the presence of hexadecyltributylphosphonium bromide (Q^+X^-). They used *tert*-butyl octanoate as a standard substrate for the screeening of reaction conditions (Scheme 48).

Scheme 48

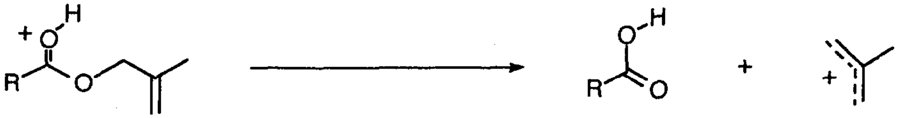
$$\underset{\textbf{177}}{H_3C—(CH_2)_6—CO_2C(CH_3)_3} \xrightarrow[\text{r.t., 45 min}]{\text{5 eq. HBr, 0.1 eq. } Q^+ X^-} \underset{96\% \quad \textbf{178}}{H_3C—(CH_2)_6—CO_2H}$$

17.1.2 90% Formic acid

Very recently, Schmid[106] reported that methallyl, crotyl, and cinnamyl esters are readily cleaved in refluxing 90% formic acid to afford the carboxylic acids, whereas simple allyl and benzyl esters were recovered unchanged under the same experimental conditions.

To rationalize these results, Schmid suggested a simple allylic ionization of the protonated esters (Scheme 49) and postulated that the increased propensity for reaction in substituted or extended allylic systems over that in simple allyl or benzyl cases might be explained by increased allyl cation stability provided by alkyl substitution or conjugation. This postulate suggests that other methallyl-based protecting groups (e.g. carbonates, carbamates and ethers) might display similar acid lability.

Scheme 49



17.2 Under basic conditions

17.2.1 Alkali metals carbonates and bicarbonates

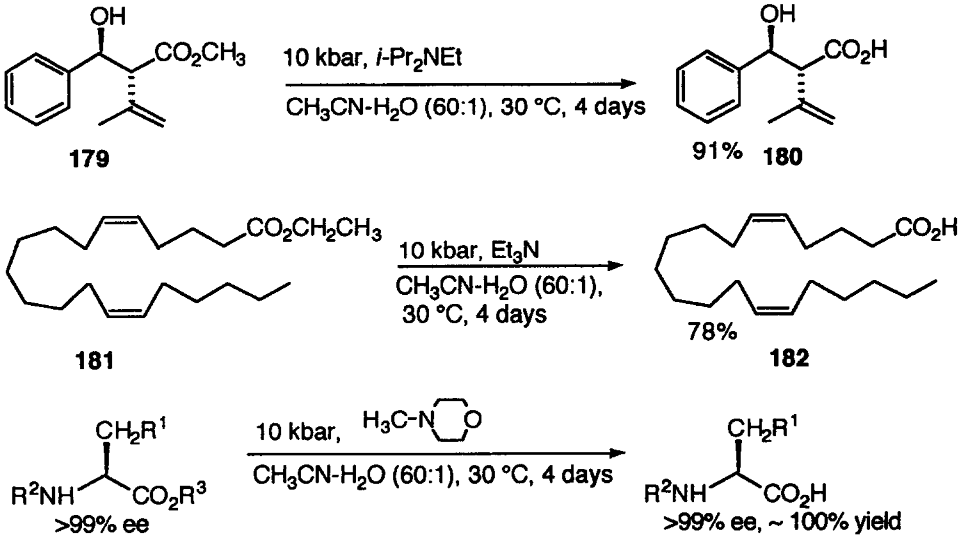
In 1991 Anwer and coworkers[107] reported the cleavage of methyl, ethyl, and benzyl esters using aqueous solution of carbonates and bicarbonates of alkali metals. An organic cosolvent, such as methanol or ethanol, was required to keep the esters in solution. Several peptide methyl, ethyl, and benzyl esters were hydrolyzed to demonstrate the utility of this method. The rate of hydrolysis and the level of racemization were found to depend on the water-alcohol ratio used. With less than 30% of water, no racemization was observed, whereas with anhydrous methanol considerable transesterification was reported.

17.2.2 Diisopropyl ethyl amine, triethylamine or N-methylmorpholine under high pressure

Very recently Yamamoto and coworkers[108] reported the hydrolysis of esters of amino acids, aliphatic, unsaturated acids, and β-hydroxy acids, at room temperature under >8 kbar of pressure in the presence of diisopropyl ethyl amine, triethylamine, or N-methylmorpholine using a mixture of acetonitrile-water (60:1) as the solvent. The authors noted no racemization, no isomerization, and no side reactions tooks place.

Representative examples of this new approach to ester hydrolysis are presented in Scheme 50. In the case of β-hydroxy ester **179** the corresponding β-hydroxy acid **180** was isolated in high yield; no side products from isomerization of the double bond and no retroaldol reaction were observed. Ethyl arachidonate **181** gave arachidonic acid **182** in high yield. Hydrolysis of N-protected amino acids (**183**-**186**) proceeded smothly without racemization to give the corresponding N-protected amino acids.

Scheme 50



183, R^1 = OH, R^2 = Cbz, R^3 = CH_2Ph
184, R^1 = H, R^2 = Boc, R^3 = CH_3
185, R^1 = CO_2CH_2Ph, R^2 = Cbz, R^3 = CH_2Ph
186, R^1 = H, R^2 = Cbz, R^3 = CH_2Ph

187, R^1 = OH. R^2 = Cbz
188, R^1 = H, R^2 = Boc
189, R^1 = CO_2CH_2Ph, R^2 = Cbz
190, R^1 = H, R^2 = Cbz

18 CONCLUDING REMARKS

During the last 12 years several new valuable reagents for the chemoselective deprotection of ester functional groups were developed, mainly because of the needed for protection of carboxyl groups as ester functions in the synthesis of complex and sensitive molecules.

In this regard, some of the most important strategic considerations for the introduction and removal of protecting groups for carboxylic acids in molecules with a high degree of functionalization are:

- for the protection step, the choice of ester depends critically on the simplicity, ease and high yield of its preparation.
- their insensitivity to other reagents throughout the course of the synthetic sequence
- for the deprotection step it is important to balance the yield versus the chemoselectivity.

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REFERENCES

1. Greene, T.W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis;* J. Wiley & Sons, Inc.; New York, **1991**.
2. a) For a recent review on esterification of the carboxyl group, see: Ogliaruso, M.A.; Wolfe J.F. *Synthesis of Carboxylic Acids, Esters and Their Derivatives;* J. Wiley and Sons, Inc.; New York **1991**; pp. 377-526. b) See, also: Haslam E. *Tetrahedron,* **1980**, 36, 2409. c) For recent methods of esterification using phase transfer conditions without solvents, see: Vinczer, P.; Novak, L.; Szantay, C.*Synth. Commun.* **1991**, 21, 1545. d) For recent methods of formation of allyl esters, see: Belshaw, P.J.; Mzengeza, S.; Lajoie, G.A. *Synth. Commun.* **1990**, 20, 3157 and references cited therein. e) For convenient synthesis of alkyl and phenacyl carboxylic esters using tributyltin carboxylates, see: Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1992**, 57, 2166 and Vijayaraghavan, S.T.; Balasubramanian T.R.*J. Organometallic Chem.* **1985**, 282, 17, respectively. f) For a recent method for the synthesis benzyl carboxylate, see: Dakka, J.; Sasson, Y.; Khawaled, K.; Bram, G.; Loupy, A. *J. Chem. Soc. Chem. Commun.* **1991**, 853.
3. For a more peptide oriented review of methods of esterification, see: Bodanszky, M., *Principles of Peptide Synthesis;* Springer-Verlag, **1984**, p. 69. Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag, **1984**, p. 33.
4. a) Pearson, R.G. *J. Am. Chem. Soc.* **1963**, 85, 3533. b)Hudson, R.F. *Coordination Chemistry Reviews* **1966**, 89. c) Saville, B *Angew. Chem. Internat Edit.* **1967**, 6, 928. d) Pearson, R.G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, 89, 1827. e) Pearson R.G.; Songstad, J. *J. Org. Chem.,* **1967**, 32, 2899. f) Parr, R.G; Pearson R.G. *J. Am. Chem. Soc.* **1983**, 105, 7512. g) Pearson R.G. *J. Am. Chem. Soc.* **1988**, 110, 7684. h) Pearson R.G. *J. Org. Chem.* **1989**, 54, 1423.
5. For a review, see: a) Pearson, R.G. *Hard and Soft Acids and Bases;* Dowden, Hutchinson, & Ross Inc.; Stroudsberg, **1973**. b) Ho, T.L. *Hard and Soft Acids and Bases Principle in Organic Chemistry;* Academic Press; New York, **1977**. c) Ho, T.L.; *Chem. Rev.* **1975**, 75, 1.
6. For a review, see: Pillai, V.N.R.; *Synthesis.* **1980**, 1.
7. a) Pedrocchi-Fantoni, G.; Servi, S. *J. Chem. Soc.Perkin Trans. 1,* **1992**, 1029. b) Schultz, M.; Hermann, P.; Kunz, H. *Synlett,* **1992**, 37. c) Braun, P.; Waldmann, H.; Kunz, H. *Synlett,* **1992**, 39. d) Hultin, P.G.; Mueseler, F.J,; Jones, J.B. *J. Org. Chem.,* **1991**, 56, 5375. e) Shin, C.; Seki, M. *Chem. Lett.* **1991**, 887. f) Naemura, K.; Takahashi, N.; Ida, H.; Tanaka, S. *Chem. Lett.* **1991**, 657. g) Kamal, A. *Synth. Commun.* **1991**, 21, 1293.

8. For recent reviews, see: a) Roberts, S.M.; Turner, N.J. *J. Biotechnol.* **1992**, 22, 274. b) Waldmann, H. *Kontakte (Merck)* **1991**, 33. c) Boland, W.; Frößl, C; Lorenz, M. *Synthesis* **1991**, 1049 d) Zhu, L.M.; Tedford, M.C. *Tetrahedron* **1990**, 46, 6587. e) Klibanov, A.M. *Acc. Chem. Res.* **1990**, 23, 114. f) Ohno, M.; Otsuka, M. *Org. React.* **1989**, 37, 1. g) Chen, C.S.; Sih, C.J. *Angew. Chem., Int. Ed. Eng.* **1989**, 28, 695. h) Davies, H.G.; Green, R.H.; Kelly, D.R.; Roberts, S.M. *Biotransformations in Preparative Organic Chemistry,* **1989**, Academic Press, London. i) Jones, J.B. *Tetrahedron* **1986**, 42, 3351. j) Whitesides, G.M.; Wong, C.H. *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 617.
9. Sheehan, J. C.; Doyle Daves, O. *J. Org. Chem.*, **1964**, 29, 2006.
10. Mascaretti, O.A.; Merkuza, V.M.; Ferraro, G.E.; Ruveda, E.A.; Chang, C.J.; Wenkert, E. *Phytochem.* **1972**, 11, 1133.
11. For an earlier review see Mc Murry J.E. *Org. React.* **1976**, 24, 187.
12. Bartlett, P.A.; Johnson, W.S. *Tetrahedron Lett.*, **1970**, 4459.
13. a) Feutrill, G. I.; Mirrington, R.N. *Aust. J. Chem.*, **1972**, 25, 1719 and 1731. b) Feutrill, G.I.; Mirrington, R.N. *Tetrahedron Lett.*, **1970**, 1327.
14. Ross Kelly, T.; Daki, H.M.; Tsang, W.G. *Tetrahedron Lett.*, **1977**, 3859.
15. Ho; T.L. *Synthesis* **1974**, 715.
16. Ho; T.L. *Synthesis* **1975**, 510.
17. Ho, T.L. *Synth. Commun.* **1974**, 4, 307.
18. Hugel, H.M.; Bhaskar, K.V.; Longmore, R.W. *Synth. Commun.* **1992**, 22, 693.
19. Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.*, **1977**, 4365.
20. Liotta, D.; Santiesteban, H. *Tetrahedron Lett.*, **1977**, 4369.
21. Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.*, **1981**, 46, 2605.
22. Kong, F.; Chen, J.; Zhou, X. J. *Synth. Commun.*, **1988**, 18, 801.
23. Chen, J.; Zhou, X. J. *Synthesis,* **1987**, 586.
24. Sieber, P. *Helv. Chim. Acta* **1977**, 60, 2711.
25. Uelti, M.; Kai, K.; Amemiya, M.; Horino, H.; Oyamada, H. *J. Chem. Soc. Chem. Commun.* **1988**, 414.
26. Namikoshi, M.; Kundu, B.; Rinehart, K.L. *J. Org. Chem.* **1991**, 56, 5464.
27. Jung, M.E.; Lyster, M.A. *J. Am. Chem. Soc.*, **1977**, 99, 968.
28. Ho, T: L.; Olah, G.A. *Angew. Chem. Int. Ed. Eng.* **1976**, 15, 774.
29. For a review, see: a) Olah, G.A.; Narang. S. C. *Tetrahedron*, **1982**, 38, 2225. b) Groutas, W.C.; Felker, D. *Synthesis* **1980**, 861.
30. Nudelman, A.; Braun, F.; Karoly, E. *J. Org. Chem.*, **1978**, 43, 3788.
31. Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R., *J. Org. Chem.*, **1979**, 44, 1247.
32. Mangia, A.; Scandroglio, A. *Tetrahedron Lett.*, **1978**, 5219.
33. Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett.*, **1978**, 5211.
34. Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.*, **1981**, 46, 1991.
35. Node, M.; Nishide, K.; Ochiai, M; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, 46, 5163.
36. a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, 28, 3662. b) Fuji, K.; Kawabata,T,; Node, M.; Fujita, E. *J. Org. Chem.*, **1984**, 49, 3214.
37. Mahajan, A.R.; Dutta, D.K.; Boruah, R,C,; Sandhu, J.S. *Tetrahedron Lett.* **1990**, 27, 3943.

38. Nagata, W.; Wakabayashi, T.; Narisada, M.; Hayase, Y.; Kumata, S. *J. Am. Chem. Soc.* **1971**, 93, 5740.
39. Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, K.; Nishitani, Y.; Hirai, S.; Maeda, T.; Nagata, W. *Tetrahedron Lett.* **1979**, 2793.
40. Ohtani, M.; Watanabe, F.; Narisada, *J. Org. Chem.* **1984**, 49, 5271.
41. Danelon, G.O.; Laborde, M.; Mascaretti, O.A.; Boggio, S.B.; Roveri, O.A. Submited for publication.
42. a) Setti, E.L.; Mascaretti, O.A. *J. Org. Chem.* **1989**, 54, 2233. b) Setti, E.L.; Belinzoni. D.U.; Mascaretti O.A. *J. Org. Chem.* **1989**, 54, 2235.
43. Kim, S.; Park, Y.H.; Kee, I.S. *Tetrahedron Lett.* **1991**, 32, 3099.
44. Wade, L.G.; Gerdes, J.M.; Wirth, R.P. *Tetrahedron Lett.* **1978**, 19, 731.
45. Gerdes, J.M.; Wade, L.G. *Tetrahedron Lett.* **1979**, 20, 689.
46. García Martínez, A.; Osío Barcina, J.; Hidalgo del Veccio, G.; Hannack, M.; Subramanian, L.R. *Tetrahedron Lett.* **1991**, 32, 5931.
47. Boeckman, R,K.; Potenza, J.C. *Tetrahedron Lett.* **1985**, 26, 1411.
48. Felix, A. M. *J. Org. Chem.* **1974**, 39, 1427.
49. Mattingly, P.G.; Miller, M.J. *J. Org. Chem.* **1981**, 46, 1557.
50. Wakselman, M.; Zrihen, M. *Chem. Lett.* **1982**, 333.
51. Manchand, P.S. *J. Chem. Soc. Chem. Commun.* **1971**, 667.
52. Mata, E.G.; Mascaretti, O. A. *Tetrahedron Lett.* **1988**, 29, 6893.
53. Salomon, C.J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1991**, 32, 4239.
54. Salomon, C.J.; Mascaretti, O.A. Unpublished results.
55. An orthogonal system is defined as "a set of completely independent classes of protecting groups, such that each class of groups can be removed in any order and in the presence of all other classes". See: Barany, G.; Albericio F.J. *J. Am. Chem Soc.* **1985**, 107, 4936.
56. Harp, D.N.; Gingras, M. *Tetrahedron Lett.* **1987**, 28, 4373.
57. Harp, D.N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, 110, 7737.
58. David, S.; Hanessian, S. *Tetrahedron,* **1985**, 41, 643.
59. Pereyre, M.; Quintard, J. P.; Rahm, A. "*Tin in Organic Synthesis*", Butterworths, London, **1987**, pp. 269-277.
60. Glidewell, C.; Liles, D.C. *Acta Crystallogr.* **1978**, B34, 1693.
61. For recent reviews in the field of organotin chemistry, see: a) Davies, A.G.; Smith, P.J. in "*Comprehensive Organometallic Chemistry*" Wilkinson, G. Stone, F.G.A.; Abel, E.W. Ed. Pergamon Press, Oxford, **1982**, Vol 2, p. 519. b) Pereyre, M.; Quintard, J.P.; Rahm, A. "*Tin in Organic Synthesis*" Butterworths, London, **1987**. c) Omae, I. "*Organotin Chemistry*" Elsevier, Amsterdam, **1989**.
62. Berge, J.M.; Roberts, S.M. *Synthesis,* **1979**, 471.
63. Farina, V. *J. Org. Chem.* **1991**, 56, 4985.
64. Jackson, A.E.; Johnstone R.A.W. *Synthesis,* **1977**, 685.
65. Anantharamaiah, G.M.; Sivanandaiah, K.M. *J. Chem. Soc. Perkin Trans. 1,* **1977**, 490.
66. Felix, A.M.; Heimer, E.P.; Lambros, T.J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.,* **1978**, 43, 4194.
67. Bajwa, J.S. *Tetrahedron Lett.* **1992**, 33, 2299.

68. Shih, D.H.; Baker, F.; Cama, L.; Christensen, B.G. *Heterocycles*, **1984**, 21, 29.
69. Baldwin, J.E.; Cobb, J.E.; Sheppard, L.N. *Tetrahedron Lett.* **1987**, 43, 1003.
70. Ross Kelly, T.; McNutt, R.W.; Montury, M.; Tosches, N.P. *J. Org. Chem.* **1979**, 44, 63.
71. For reviews of the use of palladium-catalyzed allylic reactions see, a) Trost. B.M.; *Acc. Chem. Res.* **1980**, 13, 385. b) Tsuji, J. *Organic Synthesis With Palladium Compounds*, p 125, Springer-Verlag, Berlin, Heidelberger, New York, **1980**. c) Trost, B.M.; Verhoven, T.R. In "*Comprehensive Organometallic Chemistry*"; Wilkinson, G. Ed.; Pergamon Press: Oxford, **1982**, Vol. 8, p. 836
72. Corey, E.J.; Suggs, J.W. *J. Org. Chem.*, **1973**, 38, 3223.
73. Corey, E.J.; Tius, M.A. *Tetrahedron Lett.* **1977**, 2081.
74. Ho, T.L. *Synth. Commun.* **1978**, 8, 15.
75. Jeffrey, P.D.; McCombie, S.W. *J. Org. Chem.* **1982**, 47, 587.
76. Jungheim, L.N. *Tetrahedron Lett.* **1989**, 30, 1889.
77. a) Bochnitschek, S.F.; Waldmann, H.; Kunz, H. *J. Org.Chem.* **1989**, 54, 751. b) For a preliminary report see: Kunz, H.; Waldmann, H. *Angew. Chem. Int. Ed. Eng.* **1984**, 23, 71.
78. For a review of other methods for selective deprotection of allylic esters in polyfunctional glycopeptides, and for the chemistry of glycopeptides see: Kunz, H. *Angew. Chem. Int. Ed. Eng.* **1987**, 26, 294.
79. Waldmann, H.; Kunz, H. *Justus Liebig Ann. Chem.* **1983**, 1561.
80. Deziel, R. *Tetrahedron Lett.* **1987**, 28, 4371.
81. Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613. Compare this work to an earlier report that used formic acid: Hey, H.; Arpe, H.J. *Angew. Chem. Int. Ed. Eng.* **1973**, 12, 928.
82. Hutchins, R.O.; Learn, K.; Fulton, R.P. *Tetrahedron Lett.* **1980**, 21, 27.
83. Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1982**, 23, 241.
84. Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, 52, 4984. For an earlier report on palladium-catalyzed hydrostannolysis of α-disubstituted allyl β-keto esters see: Guibé, F.; Xian, Y.T.; Zigna, A.M.; Balavoine, G. *Tetrahedron Lett.* **1985**, 26, 3559.
85. For a discussion of mechanistic aspects see: Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, 51, 4006.
86. Zhang, H.X.; Guibé, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, 29, 619.
87. Zhang, H.X.; Guibé, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, 29, 623.
88. a) Hayakawa, Y.; Uchiyama, M.; Kato, H.; Noyori, R. *Tetrahedron Lett.* **1985**, 26, 6505. b) Hayakawa, Y.; Uchimaya, M.; Kajimo, H.; Noyori, R. *J. Org. Chem.* **1986**, 51, 2402. c) Hayakawa, H.; Wakabayashi, S.; Nobori, T.; Noyori, R. *Tetrahedron Lett.* **1987**, 28, 2259. d) Hayakawa, H.; Nobori, T.; Noyori, R.; Himai, J. *Tetrahedron Lett.* **1987**, 28, 2623.
89. For other Pd(0)-catalyzed nucleophilic substitutions by 1,3-dicarbonyl compounds see: a) Kuntz, H.; Unvesagt, C. *Angew. Chem. Int.Ed. Eng.* **1984**, 23, 436. b) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu,I. *J. Am. Chem. Soc.* **1985**, 107, 2196.
90. Trost, B.M.; Chan, D.M. *J. Am. Chem. Soc.* **1983**, 105, 2315.
91. Mastalerz, H *J. Org. Chem.* **1984**, 49, 4092.
92. San Filippo, J.; Romano, L.J.; Chern, C.I.; Valentine, J.S. *J. Org. Chem.*, **1976**, 41, 536.
93. For a recent report on the use of superoxide anion radical, see: Singh, M.; Singh, K.; Misra, R. A. *Bull. Chem. Soc. Jpn.*, **1991**, 64, 2599.
94. Satyanarayana, K.; Chidambaram, N.; Chandrasekaran, S. *Synt. Commun.* **1989**, 19, 2159.

95. Ho, T,L.; Olah, G.A. *Synthesis,* **1977**, 418.
96. Kim, C,U.; Misco, P.F. *Tetrahedron Lett.* **1985**, 26, 2027.
97. Coleman, J.P.; Gilde, H.G.; Utley, J.H.P.; Weedon, B.C.L. *J. Chem. Soc. Chem. Commun.* **1970**, 738.
98. Corbett, D.F.; Eglington, A.J. *J. Chem. Soc. Chem. Commun.* **1980**, 1083.
99 Barrett, A.G.M.; Lebold, S.A.; Zhang, X. *Tetrahedron Lett.* **1989**, 30, 7317.
100. a) Torii, S.; Tanaka, H.; Taniguchi, M.; Kameyama, Y. *J. Org. Chem.* **1991**, 56, 3633. b) For a preliminary report, see: Tanaka, H.; Taniguchi, M.; Kameyama , Y.; Torii, S.; Sasaoka, M.; Shiroi, T,; Kikuchi, R.; Kawahara, I.; Shimabayashi, A.; Nagao, S. *Tetrahedron Lett.* **1990**, 31, 6661.
101. O'Callaghan, C.H.; Acred, P.; Harper, P.B.; Ryan, D.M.; Kirby, S.M.; Harding, S.M. *Antimicrob. Agents Chemother.* **1980**, 17, 876.
102. Micetich, R.G.; Maiti, S.N.; Spevak, P.; Tanaka, M.; Yamazaki, T.; Ogawa, K. *Synthesis,* **1986**, 292.
103. Euranto, E.K. "*Esterification and Ester Hydrolysis*" in "*The Chemistry of Carboxylic Acids and Esters*" Edited by Patai, S. John Wiley & Sons, New York, **1969**.
104. March, J. "*Advanced Organic Chemistry*" 4th Ed. John Wiley & Sons, New York, **1992.**
105. Landini, D.; Rolla, F. *J. Org. Chem.* **1982**, 47, 145.
106. Schmid, C.R. *Tetrahedron Lett.* **1992**, 33, 757.
107. Kaestle, K.L.; Anwer, M.K.; Audhya, T.K.; Goldstein, G. *Tetrahedron Lett.* **1991**, 32, 327.
108. Yamamoto, Y.; Furuta, T.; Matsuo, J.; Kurata, T. *J. Org. Chem.* **1991**, 56, 5737.