Tetrahedron Vol. 45, No. 5, pp. 1233 to 1261, 1989
Printed in Great Britain.

0040-4020/89 $5.00+.00
Pergamon Press plc

TETRAHEDRON REPORT NUMBER 248

COUNTERATTACK REAGENTS IN ORGANIC REACTIONS AND IN SYNTHESES†

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(*Received in USA* 10 *July* 1988)

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A. INTRODUCTION

Nucleophilic and electrophilic substitutions provide a powerful tool for functional group transformations. Reagents used in these reactions often contain a leaving group, which is selected solely for its leaving ability. The leaving group does not provide other functions. Deliberate selection of a reagent with an appropriately reactive leaving group can allow two consecutive transformations to occur in one flask: the leaving group resulting from the first transformation reacts with the substrate of the second transformation.

This Report illustrates an efficient way to use reagents. We define and show examples of "counterattack reagents"—certain compounds that serve dual or multiple roles in "one-flask" reactions.

†Respectfully dedicated to Professor Eugene E. van Tamelen
‡Research fellow of the Alfred P. Sloan Foundation (1986–1990)

B. DEFINITION

The term "reagent" used in organic synthesis can possess a more specific meaning than when used for individual reactions. In organic synthesis, "reagent" refers to a compound that converts the starting substrate to a synthetic intermediate, one intermediate to another intermediate, or an intermediate to the final product. In contrast, for *individual* reactions between two reactants, the "reagent" can be arbitrarily designated as one reactant and the substrate as the other.[1]

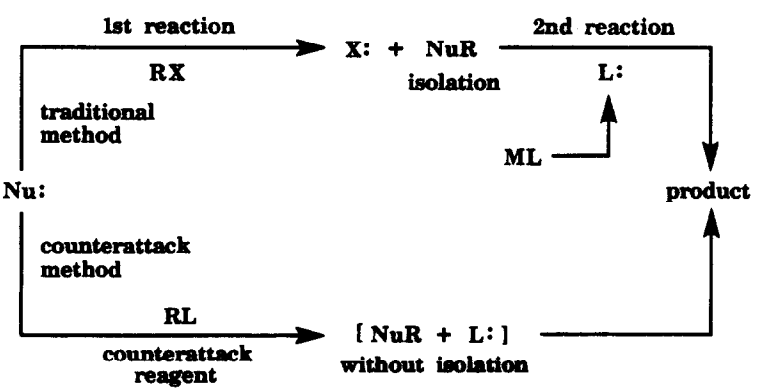
Arrows are commonly used in reaction mechanisms to depict the presumed direction of electron flow between reagents and substrates. However, arrows cannot specify which species attacks or is attacked. When a collision occurs between reagent and substrate, we may arbitrarily say that the reagent is attacked by the substrate whether that reagent is a nucleophile or electrophile. Based on this viewpoint, we define the term *counterattack reagent* as follows:[2]

> *A counterattack reagent is a compound that accomplishes, in one flask, two transformations designed to give a desired product. In the first transformation, this* ***reagent*** *is attacked by the other reactant to give a stable intermediate. In the second transformation, which affords the product, a moiety produced from this initially consumed* ***reagent*** *counterattacks that intermediate or some species derived from the first transformation.*

Counterattack reagents can be classified into two categories: electrophilic and nucleophilic. An electrophilic counterattack reagent acts as an electrophile and thus undergoes nucleophilic attack by another substance in the first transformation. A nucleophilic counterattack reagent is a nucleophile and is electrophilically attacked by another substance.

Use of counterattack reagents in reactions can minimize laboratory manipulation. Scheme 1 presents a comparison of the traditional and the counterattack procedures, exemplified by an electrophilic counterattack reagent. The traditional procedure normally requires two reactions to convert Nu: to the product; intermediate

Scheme 1



NuR is usually isolated; nucleophile L: has to come from another source. With the counterattack procedure, isolation of the intermediate NuR after the first step is not necessary. Also, generation of the counterattack moiety (L:) by a separate procedure is not needed.

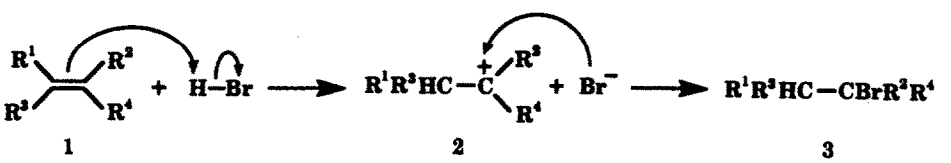
Counterattack reagents possess several characteristics:

(1) Reaction of an electrophilic counterattack reagent with an anionic species should give a stable, uncharged intermediate and a leaving group with an electron pair. The leaving group can act as a nucleophile for substitution, for addition or for elimination. Alternatively the leaving group can behave like a base to remove an acidic proton from the product of the first transformation.

(2) Reaction of an electrophilic counterattack reagent with a soft base, such as an amine or a sulfide, may afford a stable salt. The leaving group in the electrophilic counterattack reagent becomes a part of the salt. Then the leaving group with a negative charge attacks the corresponding cationic species to give the product.

(3) A counterattack reagent must be involved in a one-flask process that includes two or more transformations. A *stable* intermediate is generated in one or more of these transformations. For example, ionic addition of HBr to alkenes **1** gives carbocations **2** and Br^- (Scheme 2).[3,4] Although Br^- rapidly counterattacks **2** to give alkyl bromides **3**, carbocations **2** are unstable intermediates. Therefore HBr is *not* considered as a counterattack reagent in this reaction.

Scheme 2



1 **2** **3**

(4) Counterattack reagents can be employed in excess, but do not require common ions from other reagents or solvents to assist the chemical transformation. For example, Stork, Grieco, and Gregson reported that treatment of geraniol with MeLi followed by addition of 1.0 equivalent of *p*-toluenesulfonyl *chloride* and 2.8 equivalents of lithium *chloride* provided geranyl chloride in 80% yield.[5,6] Taylor et al. reported that oxidation of phenols with thallium(III) *trifluoroacetate* in *trifluoroacetic* acid as the solvent gave *p*-quinones in good to excellent yields.[7] Neither *p*-toluenesulfonyl chloride nor thallium(III) trifluoroacetate in these reactions is a counterattack reagent.

(5) Whether a compound is a counterattack reagent depends on its function in a specific reaction. The same compound could be a counterattack reagent in one circumstance, but not in another.

(6) A counterattack reagent can be small (e.g., diatomic), or it can be as large as an enzyme.

Counterattack reagents have been utilized in various types of reactions. Representative examples illustrated thereinafter include acetoxylation, alkylation,

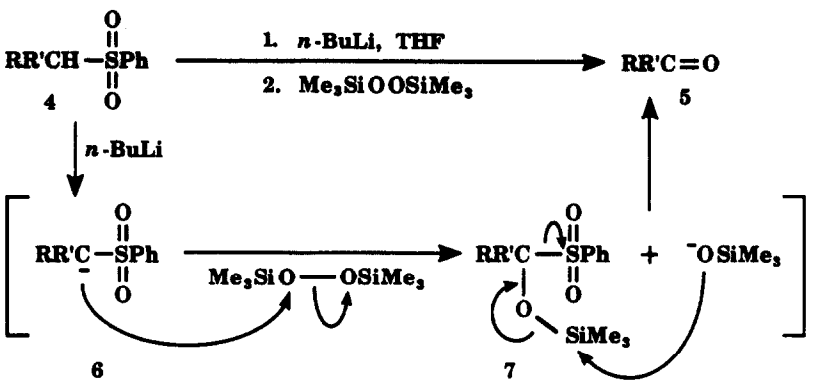
cyclization, dehydration, desilylation, desulfonylation, fragmentation, halogenation, oxidation, oxime formation, phosphonylation, saponification, silylation, substitution, etc.

C. ELECTROPHILIC COUNTERATTACK REAGENTS

C.1. *Bis(trimethylsilyl)peroxide: $Me_3SiOOSiMe_3$*

Scheme 3 shows a procedure for the oxidative desulfonylation of sulfones to aldehydes and ketones.[8] Removal of an α proton of phenylsulfones **4** with *n*-BuLi in THF gives the corresponding carbanions **6**. Then $Me_3SiOOSiMe_3$ is added and attacked by **6** to generate siloxysulfones **7** and Me_3SiO^-. Without isolation, **7** is counterattacked by Me_3SiO^- to give carbonyl product **5**. This one-flask method can readily convert alkyl, allylic, benzylic, and cycloalkyl sulfones to aldehydes or ketones in 66–91% yields.

Scheme 3



In the attacking step (**6** → **7**), the trimethylsiloxyl moiety in $Me_3SiOOSiMe_3$ behaves like a leaving group. In the counterattacking step (**7** → **5**), Me_3SiO^- acts as a nucleophile. Therefore $Me_3SiOOSiMe_3$ is an electrophilic counterattack reagent in this oxidative desulfonylation.

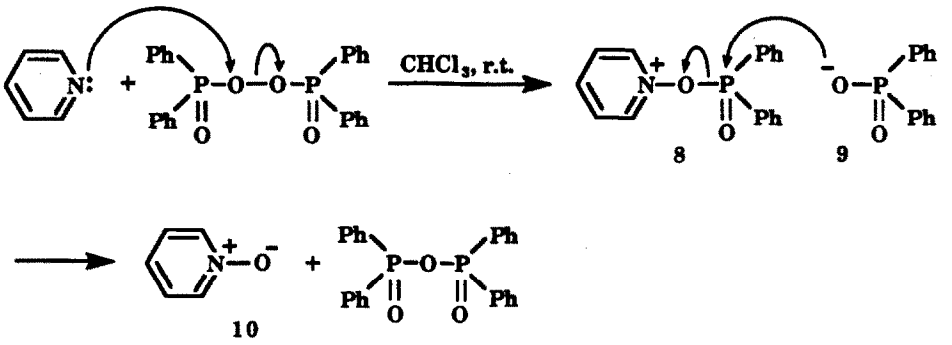
C.2. *Bis(diphenylphosphinyl)peroxide: $Ph_2P(O)OOP(O)Ph_2$*

Counterattack reagent $Ph_2P(O)OOP(O)Ph_2$ can oxidize pyridine to pyridine *N*-oxide (**10**) at room temperature (Scheme 4).[9,10] Yaouanc, Masse, and Sturtz observed phosphinylated species **8** and **9** by ^{31}P NMR; these species slowly changed to $Ph_2P(O)OP(O)Ph_2$ and **10**.[9]

C.3. *Benzeneseleninic Anhydride: $(PhSeO)_2O$*

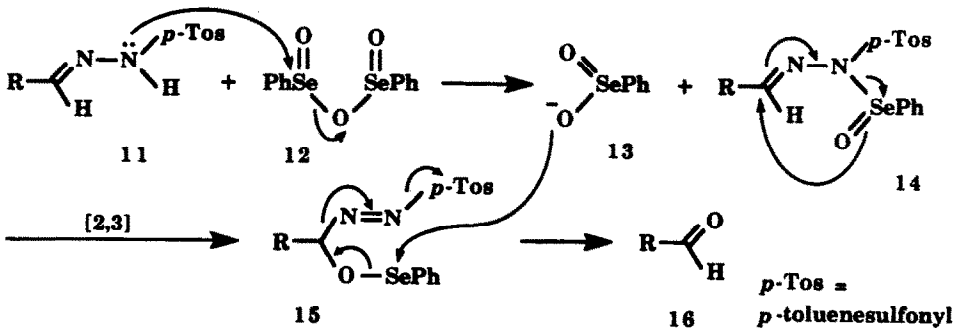
Barton, Lester, and Ley reported that $(PhSeO)_2O$ (**12**) can convert tosylhydrazones to the parent aldehydes in THF at 50 °C in 68–99% yield (Scheme 5).[11] First, benzeneseleninic anhydride (**12**) is attacked by hydrazone **11** to give $PhSe(O)O^-$ (**13**) and **14**, which subsequently undergoes [2,3]-sigmatropic rearrangement to **15**. Then leaving

Scheme 4



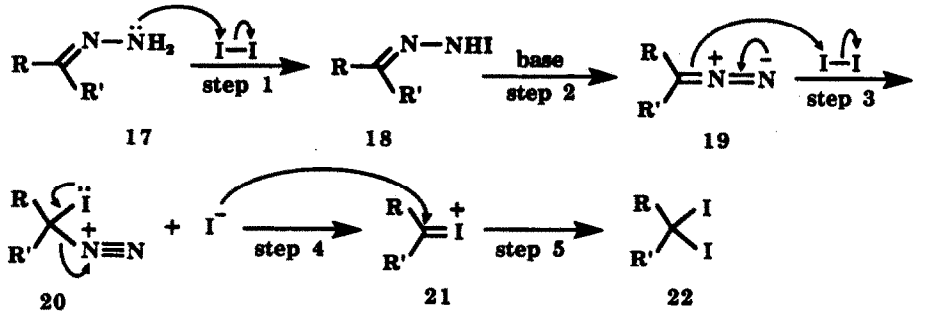
group **13** counterattacks compound **15** in situ to generate aldehyde **16**. Phenylhydrazones, *p*-nitrophenylhydrazones, tosylhydrazones, and oximes can also be transformed to the parent ketones under the same conditions.

Scheme 5



Barton and co-workers also reported a procedure for the conversion of hydrazones (**17**) to *gem*-diiodides (**22**).[12–14] Scheme 6 depicts the reaction mechanism, which was further studied by Pross and Sternhell.[15] This reaction requires two equivalents of I_2. The first equivalent of I_2 is attacked by **17** to give stable intermediates **18** and I^- (step 1). Leaving group I^- finally counterattacks **21** to yield diiodides **22** (step 5). Between the attack and the counterattack (i.e., steps 1 and 5), addition of another reagent (e.g., Et_3N or guanidines as a base) is necessary to decompose stable intermediates **18**.

Scheme 6



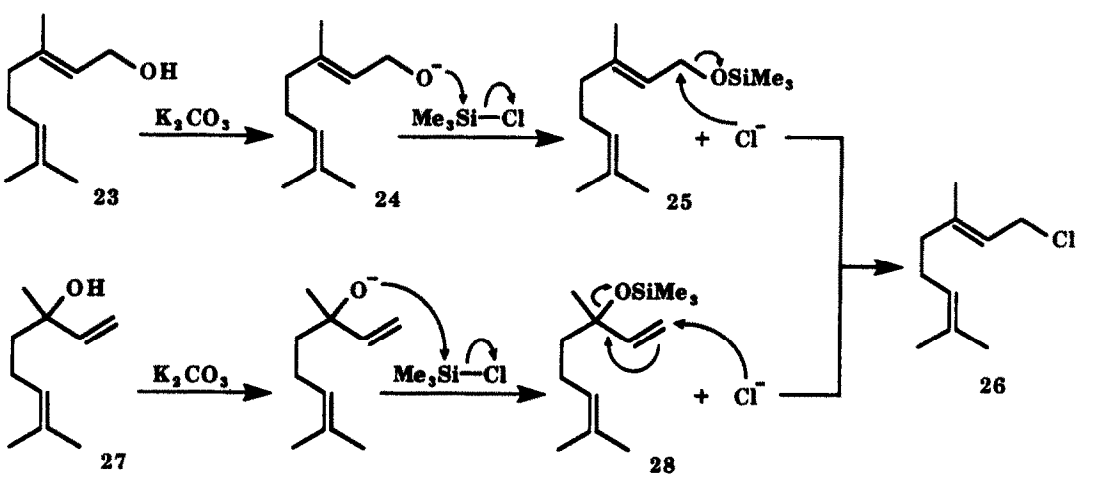
After an attack occurs, the leaving group from the counterattack reagent should finish a transformation without assistance from other reagents: otherwise use of counterattack reagents does not have advantages and is not distinct from traditional procedures. In Scheme 5, counterattack moiety **13** reacts with rearranged compound **15**, instead of **14**. The conversion of **14** to **15** does not need any reagent, therefore $(PhSeO)_2O$ is classified as a counterattack reagent. In contrast, step 2 in Scheme 6 needs a base. Thus the I_2 used in step 1 is not a counterattack reagent.

Conversion of **19** to **22** (Scheme 6) includes three steps: the second equivalent of I_2 is attacked by **19**; decomposition of **20** gives **21**; and leaving group I^- counterattacks **21**. However, intermediates **20** and **21** are not stable species. Consequently, neither is I_2 in step 3 a counterattack reagent.

C.4. *Chlorotrimethylsilane: Me_3SiCl*

Lissel and Drechsler prepared geranyl chloride (**26**) from geraniol (**23**) in 89–97% yield by using Me_3SiCl and a base, such as Na_2CO_3, K_2CO_3, or $CaCO_3$ (Scheme 7).[16] Oxide **24** reacts with Me_3SiCl to give a silyl ether (**25**) and Cl^- which attacks **25** in situ by an S_N2 process. When the starting material is linalool (**27**), Cl^- attacks the *tert*-allylic silyl ether (**28**) by an S_N2' pathway to give the same product (**26**) in 89% yield.

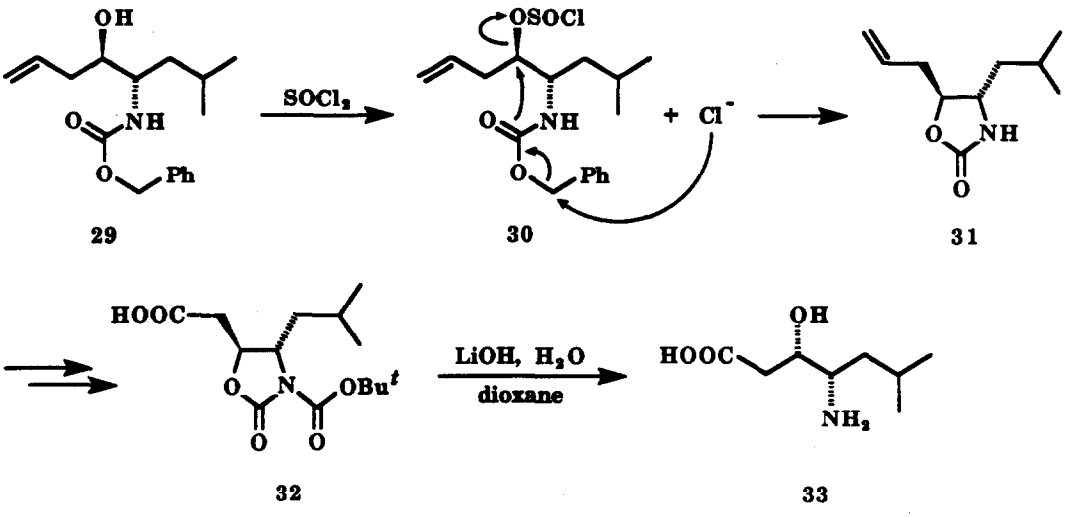
Scheme 7



C.5. *Thionyl Chloride: $SOCl_2$*

In order to epimerize the carbon bearing a hydroxyl group in 2-amino alcohols, Kano et al. developed a strategy that involved a cyclocarbamation and oxazolidinone ring opening.[17] Scheme 8 shows an application of this strategy to the synthesis of statine (**33**) from alcohol **29**. Treatment of **29** with an excess of $SOCl_2$ gives cyclocarbamate **31** in 67% yield. The authors proposed **30** as the intermediate, which is attacked in situ by Cl^-—the leaving group of $SOCl_2$. Thus $SOCl_2$ is a counterattack reagent in the conversion of **29** to **31**.

Scheme 8

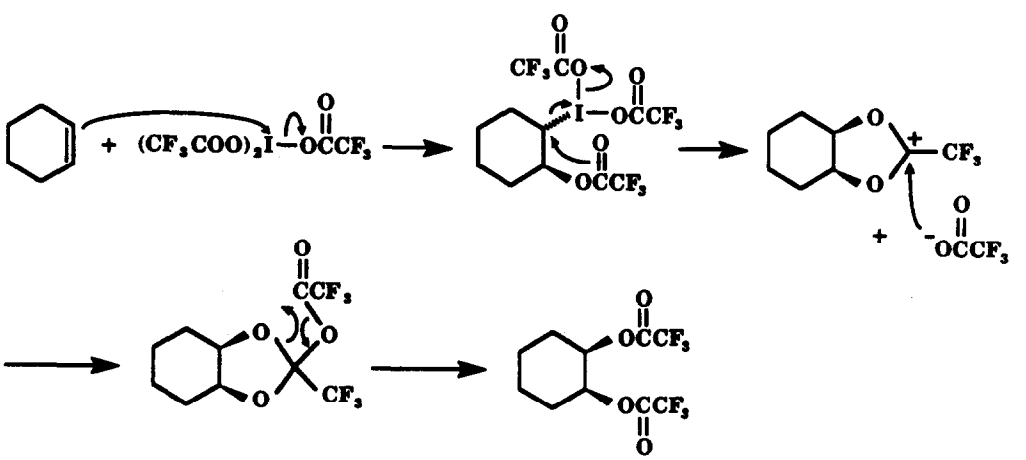


After protection of the nitrogen and oxidation of the C=C double in **31**, ring opening of oxazolidinone **32** with LiOH in aqueous dioxane gives statine (**33**). The stereoconfiguration of the carbon with a hydroxyl group changes from *R* in **29** to *S* in **33**.

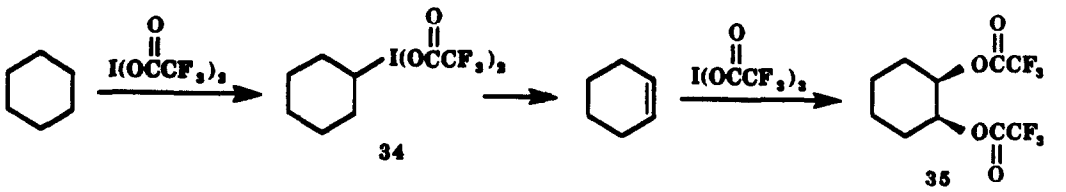
C.6. *Iodine Tris(trifluoroacetate): $I(OCOCF_3)_3$*

Buddrus used $I(OCOCF_3)_3$ to oxidize alkenes stereoselectively to 1,2-bis(trifluoroacetoxy)alkanes in 50–70% yield.[18] Based on the proposed mechanism shown in Scheme 9,[19,20] the trifluoroacetoxyl moiety functions as a leaving group and a counterattack species. The acetoxylation of the C=C double bond is also involved in part in the conversion of cyclohexane to bisacetates **35** (Scheme 10).[21] Electrophilic attack of a C–H bond in cyclohexane by $I(OCOCF_3)_3$ gives (diacetoxyiodo)alkane **34**. Compound **34** undergoes a 1,2-elimination to afford cyclohexene, which then reacts with another equivalent of $I(OCOCF_3)_3$ to give **35**.

Scheme 9



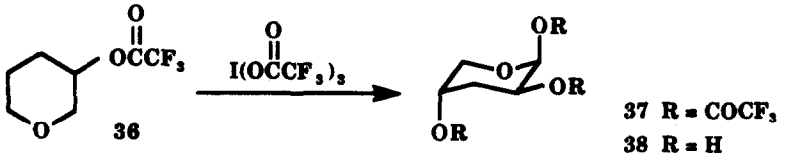
Scheme 10



34 35

Iodine tris(trifluoroacetate) was utilized in carbohydrate synthesis.[22,23] For example, this reagent acetoxylates 3-(trifluoroacetoxy)tetrahydro-2*H*-pyran (**36**) to give deoxypentopyranose **37** as the major product (Scheme 11).[22] Hydrolysis of **37** yields 3-deoxy-*threo*-pentose (**38**).

Scheme 11



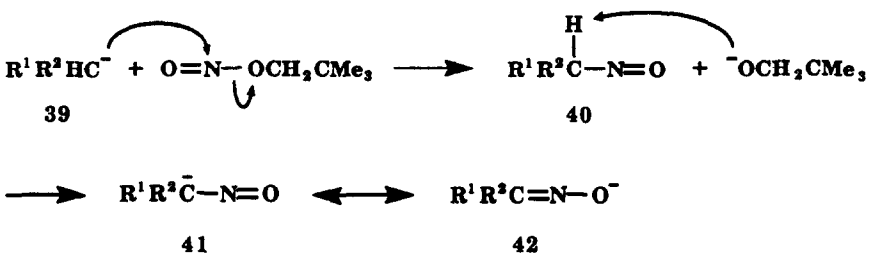
36

37 R = $COCF_3$
38 R = H

C.7. *2,2-Dimethylpropyl Nitrite: $(CH_3)_3CCH_2ONO$*

In a study of gas phase reactions, DePuy et al. treated carbanions **39** with $(CH_3)_3CCH_2ONO$ to give the resonance hybrid of nitroso anions **41** and oxime anions **42** (Scheme 12).[24] Carbanions **39** were generated in the gas phase by proton abstraction from alkenes, alkynes, dienes, ketones, and nitriles with NH_2^-.

Scheme 12



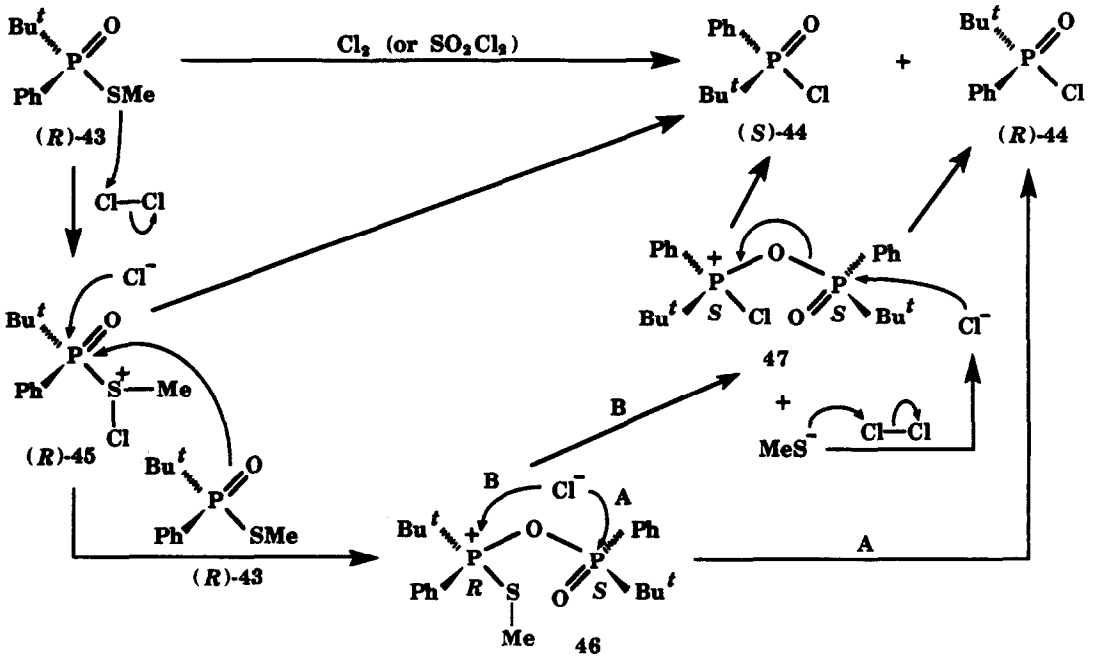
39 40 41 42

The initial step involves a nucleophilic attack by carbanions **39** on the nitrogen of $(CH_3)_3CCH_2ONO$ to give nitroso intermediates **40** and $(CH_3)_3CCH_2O^-$. Then the leaving group $(CH_3)_3CCH_2O^-$ counterattacks **40** and removes an acidic proton to give anions **41** and **42**. DePuy et al. concluded that the products from nitrosation (i.e., **40** and $(CH_3)_3CCH_2O^-$) are bound for periods long enough for another transformation to occur.[24] This example also demonstrates that counterattack reagents can be used in the gas phase.

C.8. *Chlorine and Sulfuryl Chloride: Cl_2 and SO_2Cl_2*

In the study of the stereochemistry of phosphinothiolate chlorinolysis, Michalski et al. treated (*R*)-**43** with Cl_2 to give a mixture of phosphinochloridates (*S*)-**44** and (*R*)-**44**.[25] Scheme 13 shows the proposed mechanism, in which (*R*)-**44** is the major product. Chlorine is attacked by the sulfur atom in **43** to liberate Cl^-. Then the sulfonium **45** reacts with Cl^- to give (*S*)-**44**, or with unreacted starting material (*R*)-**43** to give phosphonium **46**. Once **46** is generated, Cl^- can attack **46** either at the phosphorus center with *S* configuration (pathway A), or at the phosphonium center with *R* configuration (pathway B). Pathway A leads to (*R*)-**44**; pathway B affords ligand-exchanged species **47** and MeS^-.

Scheme 13



The resulting MeS^- reacts with Cl_2 to give Cl^- which then attacks **47**. Because nucleophilic substitutions at the phosphorus center in *tert*-BuPhP(O)X occur with inversion of configuration, transformation of **47** with Cl^- gives two molecules of **44** with opposite configuration: (*S*)-**44** and (*R*)-**44**.

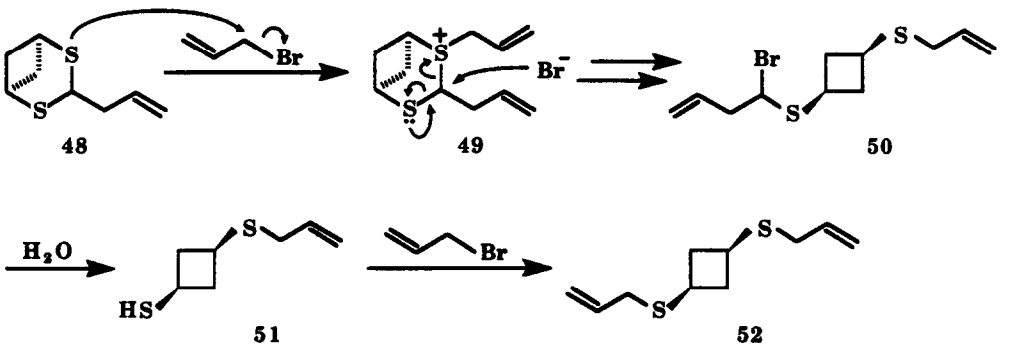
Michalski et al. proved the existence of **45**, **46**, and **47** by ^{31}P NMR spectroscopy.[25] They also replaced Cl_2 with another counterattack agent SO_2Cl_2 to perform the same chlorinolysis.

C.9. *Allyl Bromide: $CH_2=CHCH_2Br$*

In attempting to synthesize potentially water-soluble homologues of thromboxane A_2, Block, Laffitte, and Eswarakrishnan refluxed dithiabicycloheptane **48** in excess allyl bromide.[26] They isolated bis(allylthio)butane **52**, instead of the desired product **49**,

in 63% yield. Scheme 14 illustrates the mechanism for the formation of **52** from **48**. Leaving group Br^- from the initial allyl bromide attacks the carbon adjacent to both the sulfur and the sulfonium atoms in **49** to give dithiacyclobutane **50**. Upon hydrolysis of **50**, the resulting thiol **51** is further alkylated by excess allyl bromide to afford **52**. The first equivalent of allyl bromide in Scheme 14 acts as a counterattack reagent.

Scheme 14

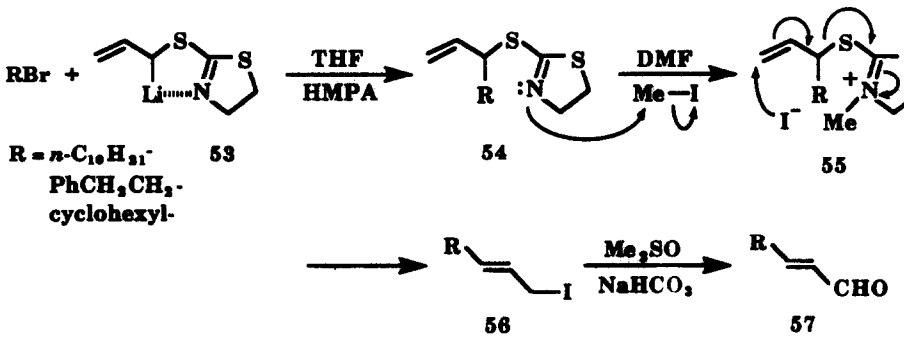


48 49 50 51 52

C.10. *Methyl Iodide: CH_3I*

Hirai and Kishida iodopropenylated primary and secondary alkyl bromides in good yields by using lithium (2-allylthio)thiazolide (**53**)[27] and excess of CH_3I (Scheme 15).[28] The nitrogen in intermediate **54** attacks CH_3I to give iminium salt **55**, in which I^- counterattacks the terminal ethylenic carbon. The product, allyl iodide **56**, is obtained with exclusively trans stereochemistry. By using the Kornblum oxidation procedure,[29] they readily converted **56** to *trans*-enal **57** with Me_2SO and $NaHCO_3$ at 130 °C.

Scheme 15

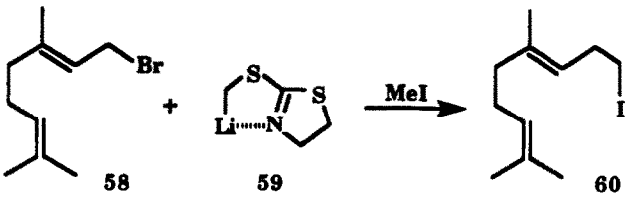


R = *n*-$C_{10}H_{21}$- PhCH$_2$CH$_2$- cyclohexyl-

53 54 55 56 57

Based on the same strategy, lithium (2-methylthio)thiazolide (**59**) and CH_3I can homologate alkyl halides.[28] Scheme 16 shows an example, in which geraniol bromide (**58**) is converted to the corresponding homoiodide **60**.[30]

Scheme 16

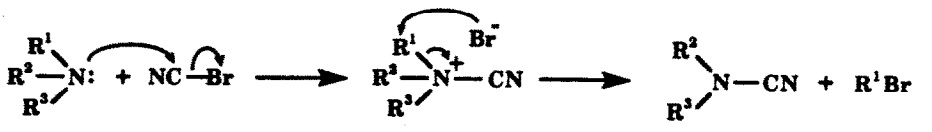


58 59 60

C.11. *Cyanogen Bromide: BrCN*

In von Braun degradation,[31,32] BrCN reacts with *tert*-amines to give *N,N*-disubstituted cyanamides (**62**) and alkyl bromides (Scheme 17). In the first transformation, the amine attacks the carbon in BrCN to give ionic adducts **61**. Intermediates **61** are stable at low temperatures. In the second transformation, Br^- nucleophilically attacks an alkyl group in **61**.

Scheme 17



61 62

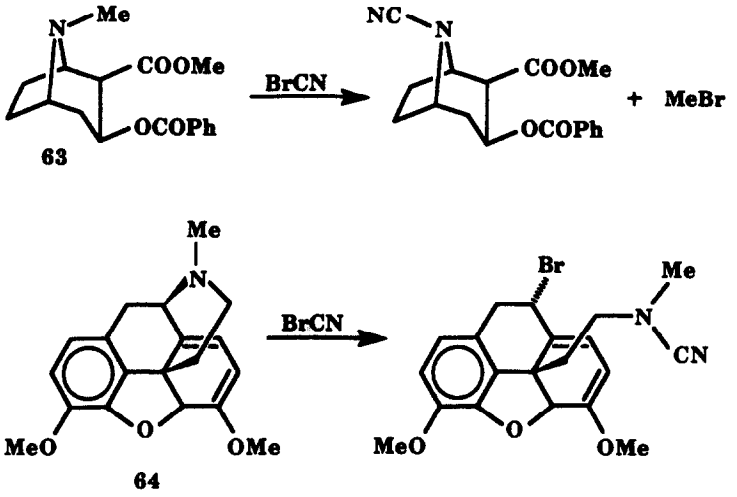
Cyanogen bromide also reacts with thio ethers, *tert*-phosphines, *tert*-arsines, and *tert*-stibines in much the same manner as with *tert*-amines.[32] A thio ether undergoes cleavage to form a thiocyanate and an alkyl bromide. A tertiary arsine or a stibine reacts with BrCN to give an adduct, which is considerably more stable than that from a *tert*-amine. For example, Ph_2AsEt yields an isolable addition complex, $Ph_2As(CN)EtBr$.[33]

Traditionally, von Braun degradation is applied in structural analysis of alkaloids. For example, demethylation occurs when cocaine (**63**) is treated with BrCN in chloroform solution;[34] bromocyanogenation takes place when thebaine (**64**) is the substrate (Scheme 18).[35]

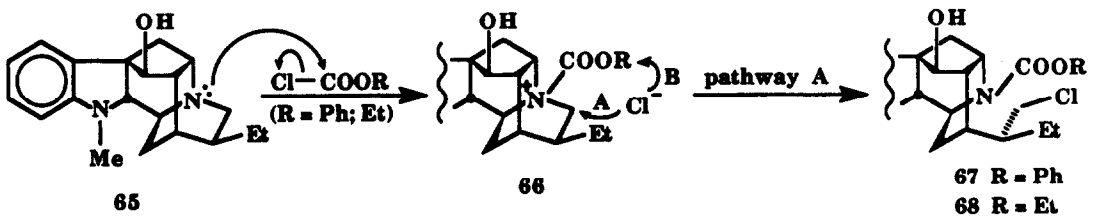
C.12. *Phenyl and Ethyl Chloroformates: ClCOOPh and ClCOOEt*

Chloroformates, such as ClCOOPh and ClCOOEt, are dealkylating agents for *tert*-amines.[36] The reaction mechanism is analogous to that of von Braun degradation. For example, Hobson and McCluskey treated 21-deoxyajmaline (**65**) with ClCOOPh in CH_2Cl_2 at 20 °C for 18 hours to give urethane **67** in 96% yield (Scheme 19).[37] Use of ClCOOEt under comparable conditions affords urethane **68** in 55% yield. Phenyl chloroformate is more effective than ethyl chloroformate probably owing to the suppression of the competing pathway B, as indicated in **66**.

Scheme 18



Scheme 19



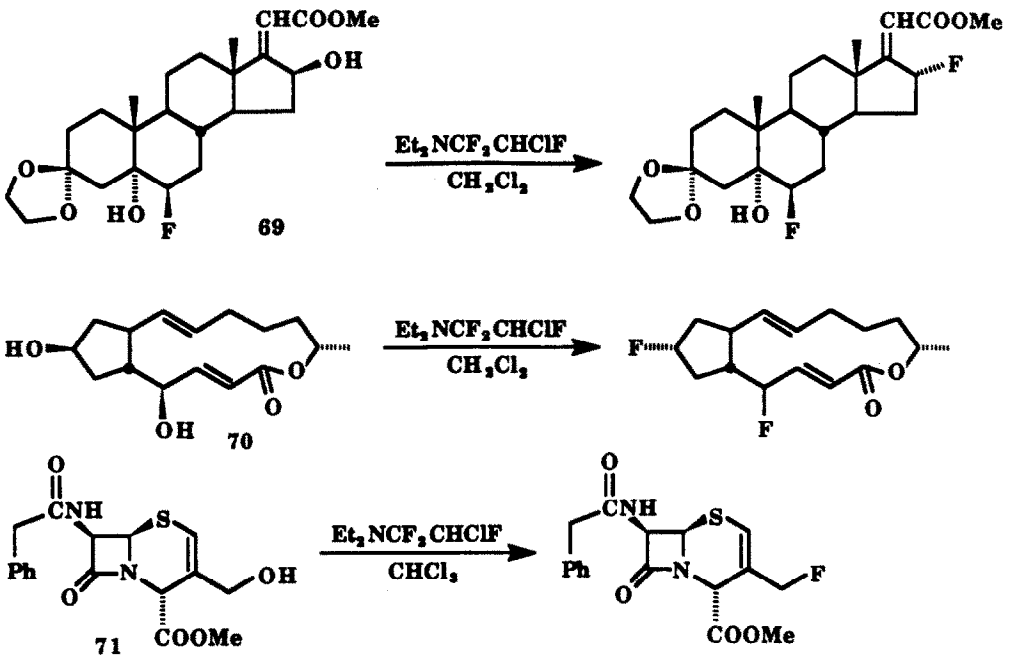
C.13. *2-Chloro-N,N-diethyl-1,1,2-trifluoroethanamine: Et_2NCF_2CHClF*

The Yarovenko reagent, Et_2NCF_2CHClF, reacts with primary and secondary alcohols to give the corresponding fluorides in a highly chemoselective manner.[38–40] This mild fluorinating reagent was widely applied to different classes of compounds; representatives shown in Scheme 20 comprise steroid **69**, brefeldin A (**70**), and β-lactam antibiotic **71**.[41–43] Scheme 21 illustrates an S_N2 mechanism for the fluorination of alcohols with Et_2NCF_2CHClF.[44] One of the *C*-1 fluorine atoms in Et_2NCF_2CHClF behaves as a leaving group in **72** and is the counterattack species for **73**.

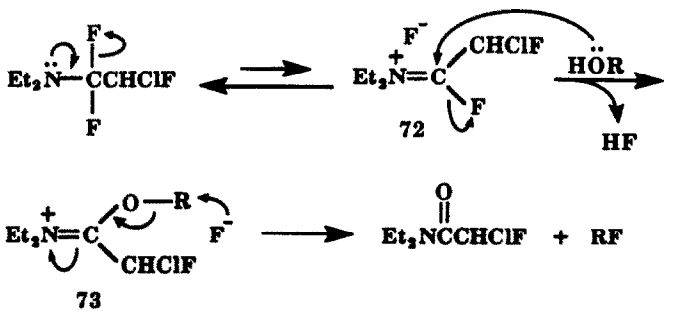
C.14. *Iminium Salts: $R^1R^2N^+{=}CHX^1X^-$ and $R^1R^2N^+{=}CCl_2X^-$*

Halogen-containing iminium salts the Vilsmeier–Haack reagent ($R^1R^2N^+{=}CHCl{\bullet}PO_2Cl_2^-$),[45,46] the Arnold reagent ($R^1R^2N^+{=}CHCl{\bullet}Cl^-$),[47,48] and the Viehe reagent ($R^1R^2N^+{=}CCl_2{\bullet}Cl^-$),[49,50] as well as some pyridazinium salts,[51] can be regarded as counterattack reagents when they react with alcohols, amides or carboxylic acids.[49–52] In order to prepare 2-dialkylamino-4-chloroquinazolines (**76**), Kokel et al. developed a novel "one-flask" heterocyclization of aminobenzonitriles **74** with the Viehe

Scheme 20

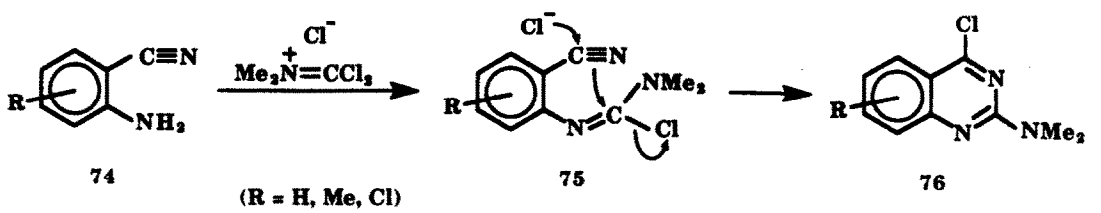


Scheme 21



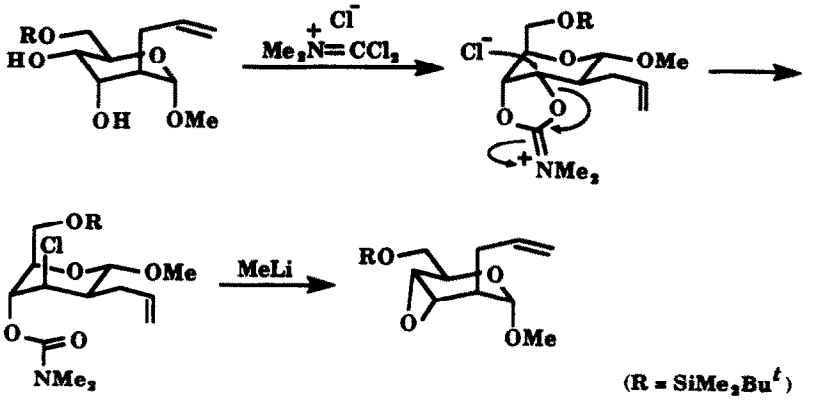
reagent as shown in Scheme 22.[53] The intermediates (75) can be isolated and spectroscopically characterized. Recently Fraser–Reid et al. have also used the Viehe

Scheme 22



reagent followed by MeLi to convert a vicinal *cis*-diol moiety in a carbohydrate to the corresponding epoxide, as shown in Scheme 23.[54]

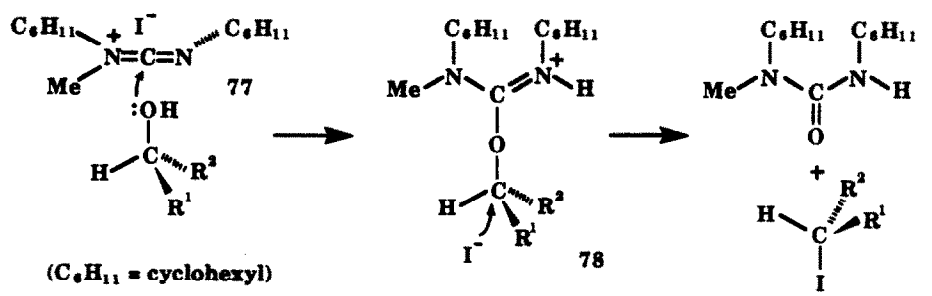
Scheme 23



C.15. *N-Methyl-N,N'-dicyclohexylcarbodiimidium Iodide and 1-Chloro-N,N,2-trimethylpropenylamine:* $MeC_6H_{11}N^+{=}C{=}NC_6H_{11}I^-$ *and* $Me_2C{=}CClNMe_2$

Aliphatic primary and secondary alcohols react with $MeC_6H_{11}N^+{=}C{=}NC_6H_{11}I^-$ (**77**)[55] in benzene, hexane, or THF at 35–50 °C to give the corresponding iodides in good yields (Scheme 24). The first step gives the stable protonated isourea (**78**); subsequent

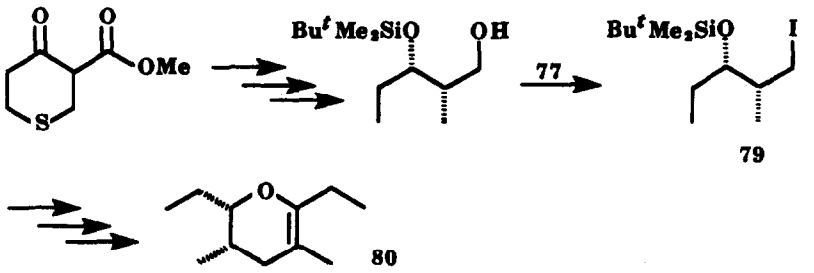
Scheme 24



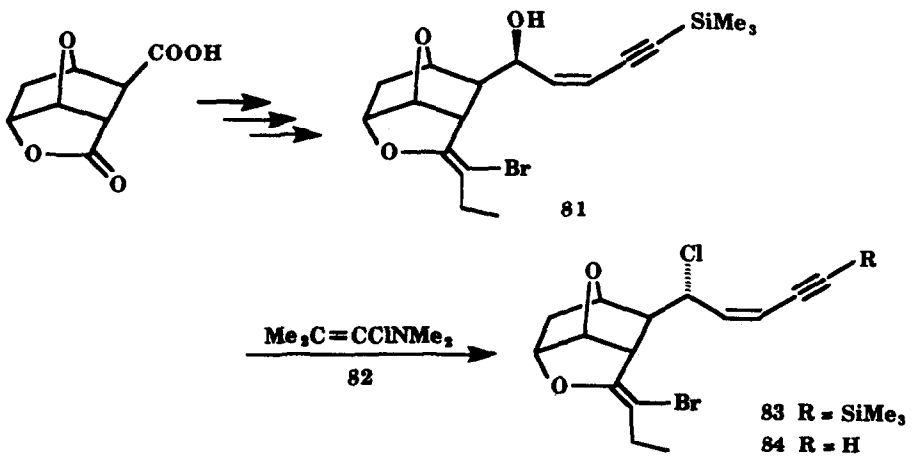
substitution by I^- occurs with inversion of configuration at the alkoxyl carbon atom. Hoffmann, Helbig, and Ladner utilized this iodination to prepare **79**, an intermediate in the synthesis of sex pheromone anhydroserricornine (**80**, Scheme 25).[56]

By analogy, Holmes, Jennings-White, and Kendric[57] efficiently converted allylic alcohol **81** to chloride **83** with $Me_2C{=}CClNMe_2$ (**82**,[58] Scheme 26). The chlorination, causing the inversion of configuration at the allylic carbon center, is a key step in the total synthesis of *cis*-maneonene-A (**84**).

Scheme 25



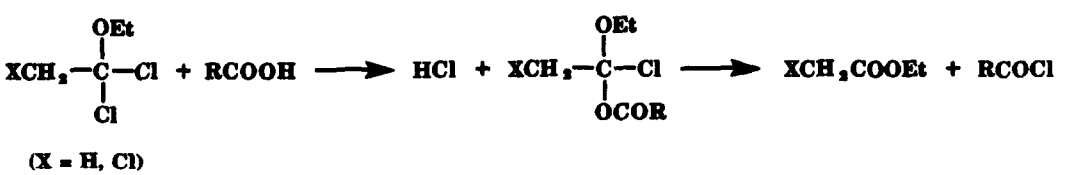
Scheme 26



C.16. *α,α-Dichlorodiethyl Ether and α,α,β-Trichlorodiethyl Ether: $MeCl_2COEt$ and ClH_2CCl_2COEt*

In the study of the reactivity of chlorinated ethers, Heslinga, Katerberg, and Arens converted carboxylic acids to the corresponding acyl chlorides by using $MeCl_2COEt$ (Scheme 27).[59] The substrates can be either aliphatic acids, such as acetic acid and octanoic acid, or unsaturated compounds, such as acrylic acid, benzoic acid, and cinnamic acid. When the substrate is succinic acid, they obtained succinic anhydride as the only product (96%). The intermediate of this reaction is the corresponding mono-acyl chloride.

Scheme 27

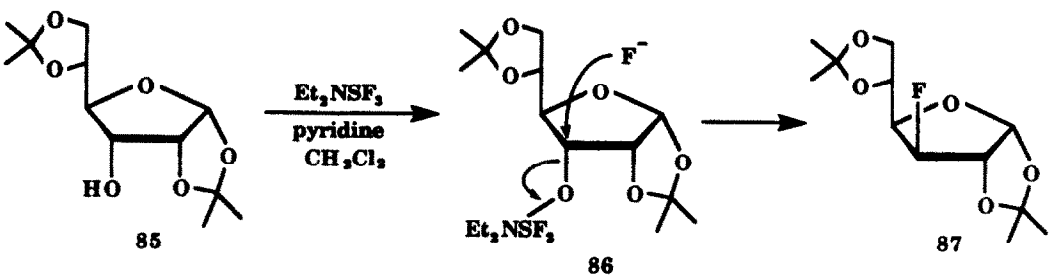


A related ether, ClH_2CCl_2COEt, can also convert acids to acyl chlorides by a similar pathway.[59] However, a higher temperature is required and the products are less pure.

C.17. *Diethylaminosulfurtrifluoride, Phenyltetrafluorophosphorane, and Diphenyltrifluorophosphorane: Et_2NSF_3, $PhPF_4$, and Ph_2PF_3*

Middleton first reported that Et_2NSF_3 can convert alcohols to fluorides.[60] The fluorination generally proceeds by an S_N2 mechanism,[61–63] and can be applied to a variety of substrates, including sugars,[63,64] prostanoids,[65] and sterols.[61] For example, treatment of glucofuranose **85** with Et_2NSF_3 gives the corresponding fluoride **87** in 90% yield (Scheme 28).[64] Using ^{19}F NMR spectroscopy, Tewson and Welch detected the

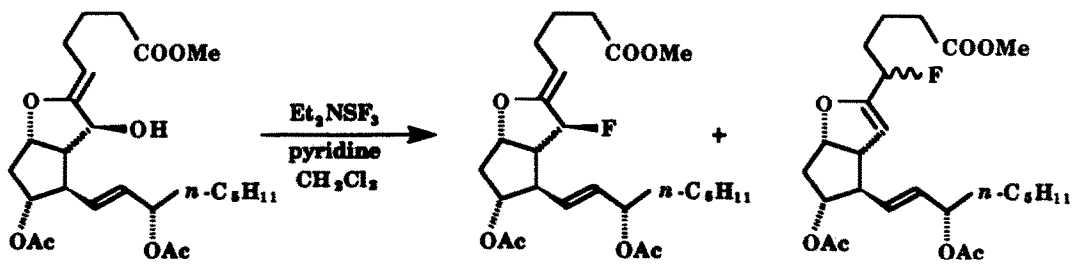
Scheme 28



85 86 87

intermediate (**86**). For preparing prostaglandin I_2 analogs (Scheme 29), Kurozumi et al. treated prostacyclin **88** with Et_2NSF_3 to give a mixture of allylic fluorides **89** (22%) and **90** (32%).[65] However, Et_2NSF_3 reacts with silylated prostacyclin **91** to afford tricyclic ether

Scheme 29

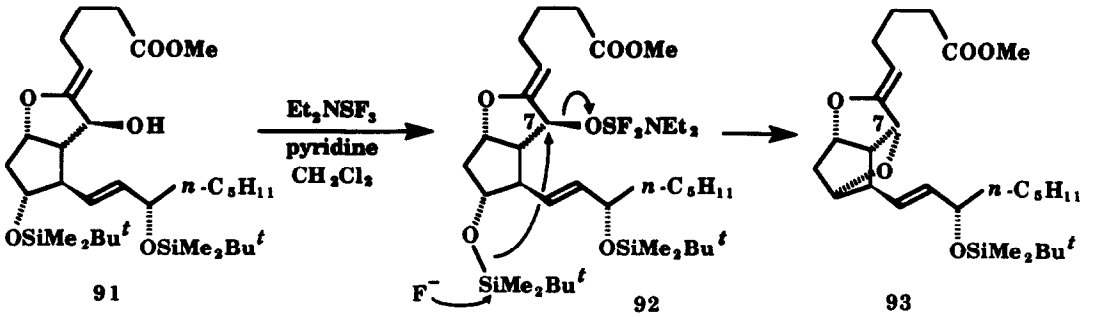


88 89 (22%) 90 (32%)

93 in 52% yield. The 7,11-epoxy moiety in **93** comes from the nucleophilic counterattack of leaving group F^- at the silicon in **92**, followed by intramolecular cyclization (Scheme 30).

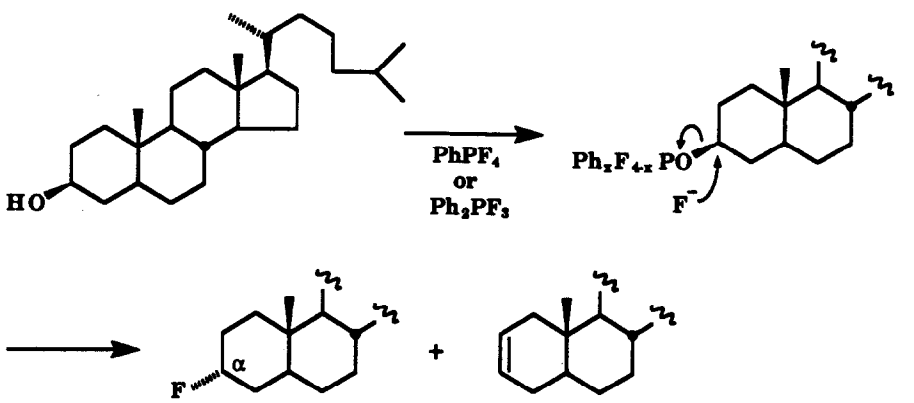
Fluorinating agents $PhPF_4$ and Ph_2PF_3 are also counterattack reagents in the conversion of alcohols to the corresponding fluorides. Kobayashi et al.[66] found that these

Scheme 30



two reagents, inferior to Et_2NSF_3, reacted with alcohols to give a significant amount of dehydration products, as exemplified in Scheme 31.

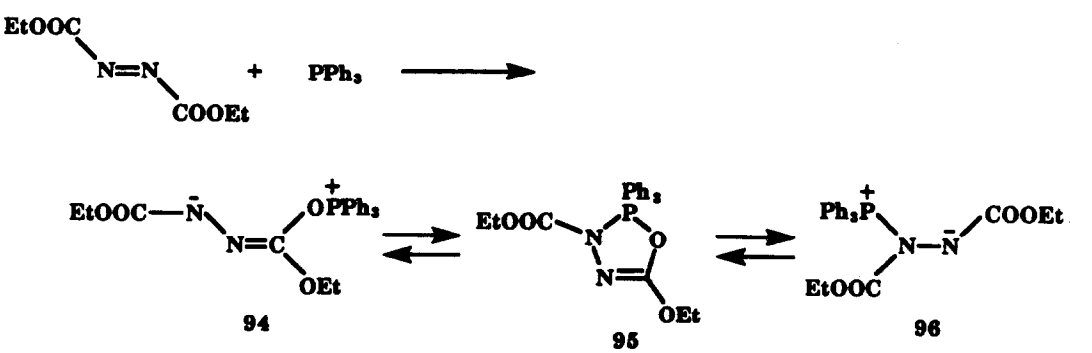
Scheme 31



C.18. *Diethyl Azodicarboxylate•Triphenylphosphine: EtOOCN=NCOOEt•PPh$_3$*

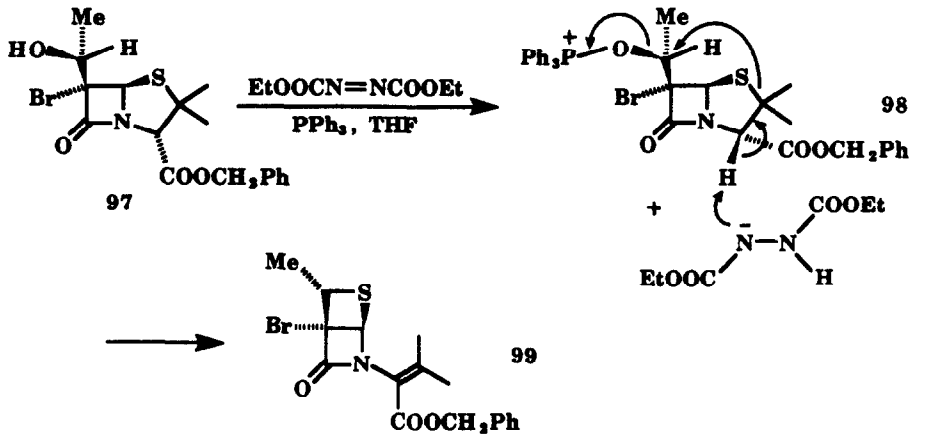
The adduct from EtOOCN=NCOOEt and PPh_3 exists in two forms **94** and **96**, which may dynamically equilibrate with **95** (see Scheme 32).[67] This adduct can facilitate an

Scheme 32



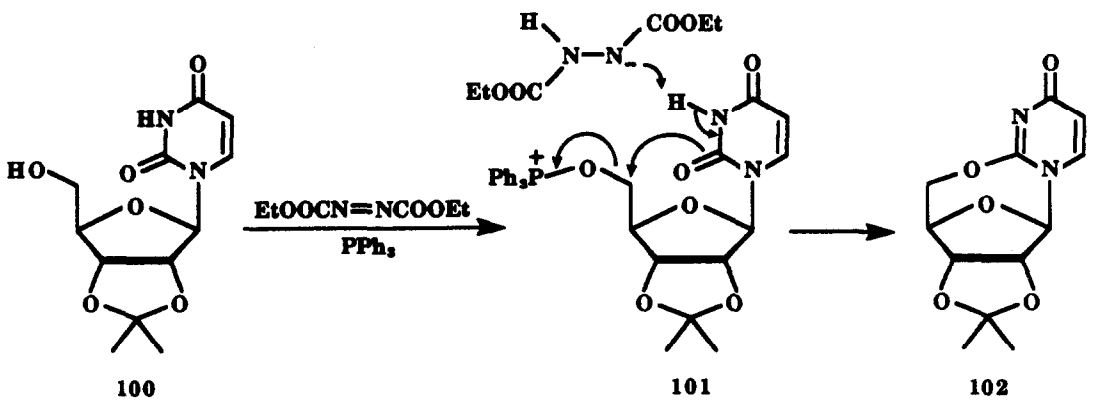
intramolecular cyclization to give a dehydration product. For example (Scheme 33), DiNinno treated penam **97** with 2.2 equivalents of EtOOCN=NCOOEt and 2.5 equivalents of PPh_3 in THF at 25 °C to give intermediate **98**, which is nucleophilically attacked by the anion of diethyl hydrazodicarboxylate. Subsequent ring opening followed by intramolecular ring closure gives β-lactam **99** in 20–30% yield.[68]

Scheme 33



Wada and Mitsunobu also observed an intramolecular dehydrative cyclization in the conversion of 2',3'-*O*-isopropylideneuridine (**100**) to cyclic uridine **102** with EtOOCN=NCOOEt and PPh_3 (Scheme 34).[69] The intermediate **101** undergoes a proton abstraction and ring closure to give **102** in 80% yield.

Scheme 34

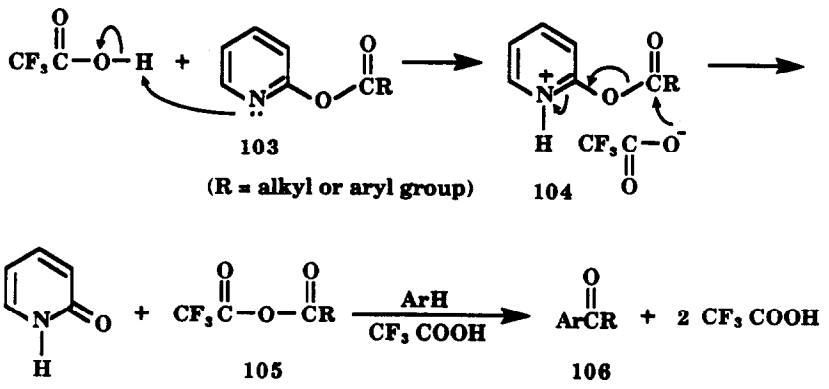


C.19. *Trifluoroacetic Acid: CF_3COOH*

2-Acyloxypyridines (**103**, R = alkyl or aryl group) react with CF_3COOH to give anhydrides **105**, which are powerful acylating agents for arenes, such as anisole, 1,4-

dimethoxybenzene, durene, fluorene, mesitylene, and thiophene.[70] Keumi, Taniguchi, and Kitajima suggested that CF_3COOH was initially attacked by **103** to give pyridinium salts **104**, in which the trifluoroacetate moiety counterattacked the carbonyl carbon to afford 2(1*H*)-pyridone and anhydrides **105** (Scheme 35). Mixed anhydrides **105** then react with arenes in the presence of CF_3COOH to give aromatic ketones **106** in 77–98% yield.

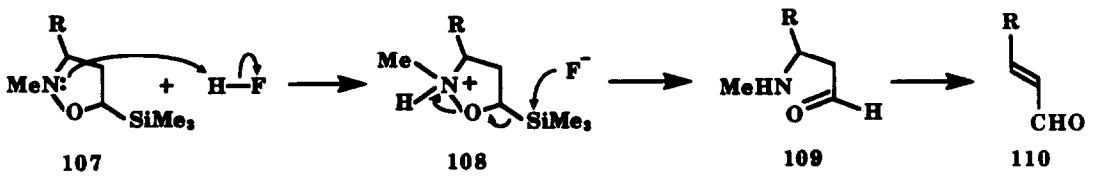
Scheme 35



C.20. *Hydrogen Fluoride: HF*

DeShong and Leginus reported that (trimethylsilyl)isoxazolidines **107** reacted with HF in MeCN to give *trans*-enals **110** in 59–95% yield (Scheme 36).[71] The reaction includes three steps: attack of HF by **107** to give ammonium salts **108**, F^- induced fragmentation of **108** to generate β-amino aldehydes **109**, and deamination of **109** to afford enals **110**. Hydrogen fluoride serves as a counterattack reagent in the conversion of **107** to **109**.

Scheme 36



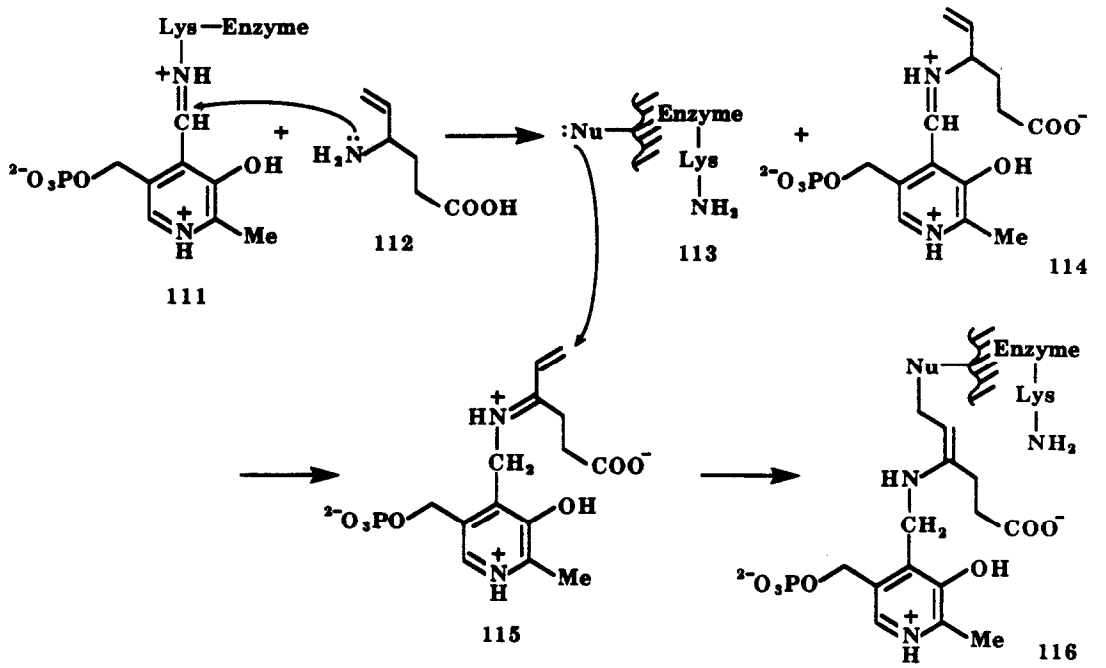
C.21. *Aminobutyrate Transaminase-Pyridoxal Phosphate Aldimines*

4-Aminohex-5-en-1-oic acid (**112**) can irreversibly inactivate mammalian brain aminobutyrate transaminase. Lippert et al. proposed a mechanism (Scheme 37) for the inhibition process which included a resting enzyme–coenzyme aldimine; that is, aminobutyrate transaminase–pyridoxal phosphate aldimine (**111**).[72]

In the first step, amino acid **112** attacks the iminium moiety in **111** to give aldimine **114** and enzyme **113**; the enzyme moiety in **111** acts as a leaving species. Aldimine **114** then tautomerizes to α,β-unsaturated ketimine **115**. This ketimine undergoes a Michael addition with a nucleophilic residue from the active site of the liberated enzyme (**113**) to give enamine **116**. Thus aminobutyrate transaminase–pyridoxal phosphate aldimine

(111) is a counterattack reagent in the transformation of **112** to **116**. Similar counterattacks also occur when asparate transaminase is irreversibly inhibited by L-cycloserine[73] or vinylglycine.[74,75]

Scheme 37

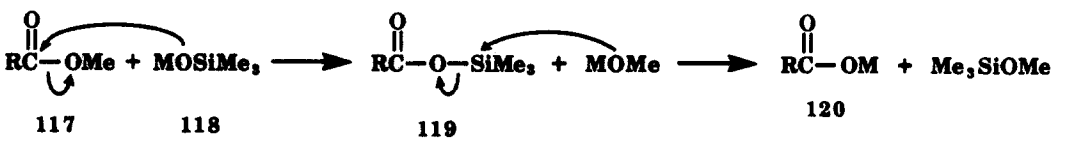


D. NUCLEOPHILIC COUNTERATTACK REAGENTS

D.1. *Lithium, Sodium and Potassium Trimethylsilanolates: $LiOSiMe_3$, $NaOSiMe_3$, and $KOSiMe_3$*

Laganis and Chenard converted esters to the corresponding acid salts by using one equivalent of $LiOSiMe_3$, $NaOSiMe_3$, or $KOSiMe_3$ in ether, THF, toluene, or CH_2Cl_2 at ambient temperatures (Scheme 38).[76] This saponification can directly provide organic acid salts in anhydrous form. In the first step, trimethylsilanolates **118** behave as a nucleophile; **118** undergoes an electrophilic attack by esters **117** to give isolable silyl

Scheme 38



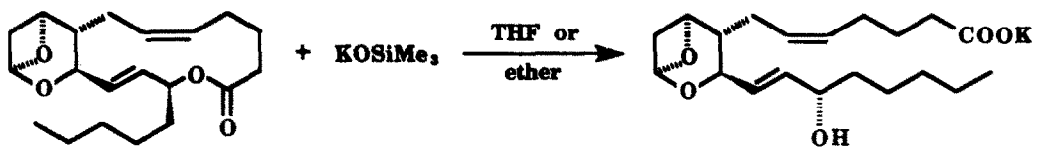
R = *n*-C_6H_{13}, ClPh, CF_3CF_2-

M = Li, Na, K

esters **119** and MOMe (M = Li, Na or K). Then the trimethylsilyl group in **119**, stemming from counterattack reagent $MOSiMe_3$, electrophilically counterattacks MOMe to give acid salts **120** in situ.[77]

Still et al. utilized this type of saponification to synthesize the potassium salt of thromboxane A_2 (**122**, Scheme 39).[78] Macrolide ring opening of **121** with $KOSiMe_3$ in THF or ether gives an amorphous solid after the solvent is removed. Various biological assays show that the solid is indistinguishable from the natural platelet-derivated thromboxane A_2.[79]

Scheme 39

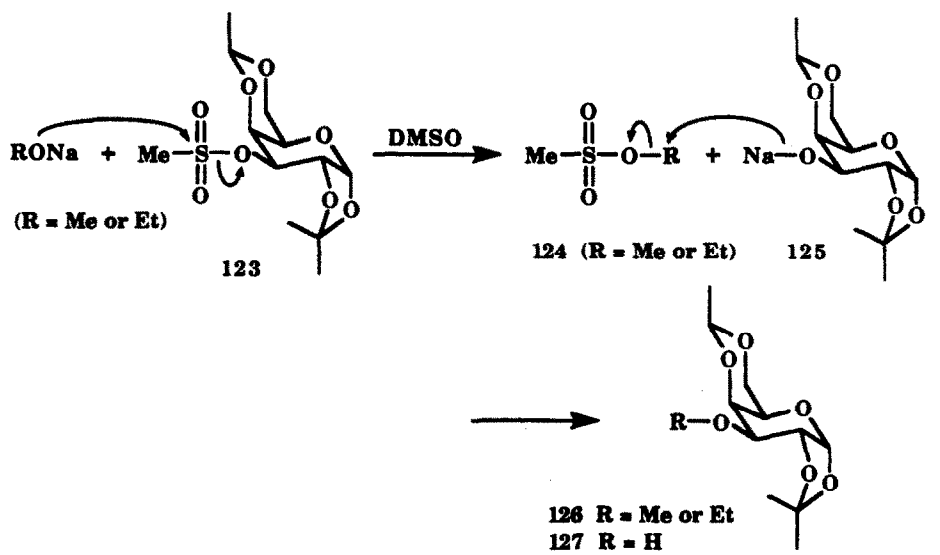


121 **122**

D.2. *Sodium Methoxide and Sodium Ethoxide: NaOMe and NaOEt*

Methanesulfonyl galactoside **123** reacts with a large excess of NaOMe or NaOEt in Me_2SO at 70 °C to give a mixture of alkyl ether **126** and alcohol **127**.[80,81] Scheme 40 shows the mechanism proposed by Eades, Ball, and Long. In the conversion of **123** to **126**, NaOMe and NaOEt act as nucleophilic counterattack reagents. The sulfur in methanesulfonate **123** electrophilically attacks NaOMe or NaOEt to give alkyl sulfonate **124** and alkoxide **125**. Then the methyl or ethyl group in **124**, originating from reagent NaOMe or NaOEt, counterattacks **125** to give product **126** in situ.

Scheme 40

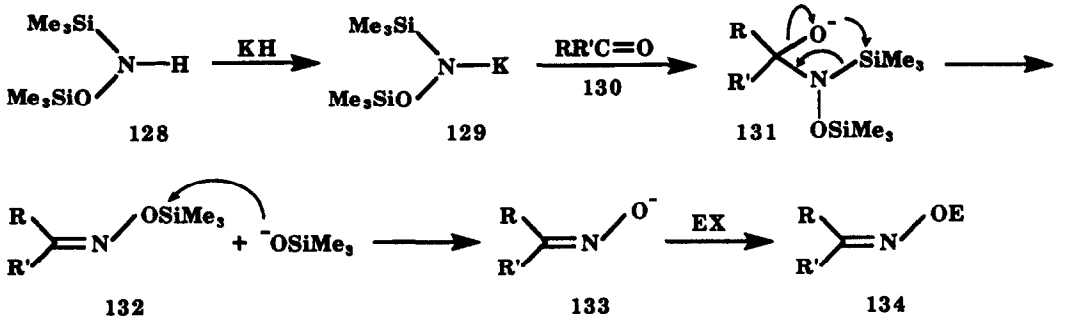


123 **124 (R = Me or Et)** **125**

D.3. *Potassium N,O-Bis(trimethylsilyl)hydroxylamide: $KN(SiMe_3)OSiMe_3$*

Recently Hoffman and Buntain have reported a method for the preparation of oxime derivatives from carbonyl compounds by use of $HN(SiMe_3)OSiMe_3$ (**128**) and KH (Scheme 41).[82] The amide, $KN(SiMe_3)OSiMe_3$ (**129**), undergoes an electrophilic attack by aldehydes or ketones **130** to give silyl oximes **132** and Me_3SiO^- via intermediates **131**. In **132**, the trimethylsilyl group that arose from amide **129**, counterattacks the nucleophile Me_3SiO^- to afford $Me_3SiOSiMe_3$ and oxime anions **133**. The anions **133** can be trapped in situ by subsequent addition of an electrophile to the reaction mixture to give oxime derivatives **134** in 41–88% yield.

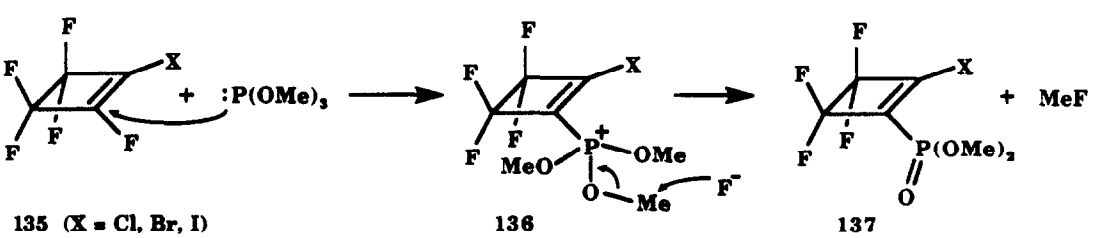
Scheme 41



D.4. *Trimethyl Phosphite and Tris(2,2-dimethylpropyl) Phosphite: $(MeO)_3P$ and $(Me_3CCH_2O)_3P$*

Treatment of trialkyl phosphites ($(RO)_3P$) with alkyl halides (R'X) to give phosphonates $(RO)_2R'P{=}O$ and halides RX is known as the Michaelis–Arbuzov reaction.[83,84] The intermediates, $(RO)_3R'P^+X^-$, in this reaction are generally unstable.[85] However, Bauer, and Hägele reported that $(MeO)_3P$ underwent an electrophilic attack by 1-halo(pentafluoro)cyclobutenes (**135**) to generate stable species **136** in almost quantitative yield (Scheme 42).[86] Under thermolysis conditions, a methyl group in **136** electrophilically counterattacks F^- to afford the desired dimethyl phosphonates **137**. Therefore, $(MeO)_3P$ is a nucleophilic counterattack reagent in the conversion of **135** to **137**.

Scheme 42



Hudson, Rees, and Weekes also reported that $(Me_3CCH_2O)_3P$ reacted with one equivalent of MeI at room temperature to give $(Me_3CCH_2O)_3MeP^+I^-$ as a stable, crystalline Michaelis–Arbuzov intermediate.[87] This intermediate decomposes in chloroform in a first-order reaction to give $(Me_3CCH_2O)_2MeP{=}O$ and Me_3CCH_2I. Consequently, $(Me_3CCH_2O)_3P$ can be regarded as a counterattack reagent.

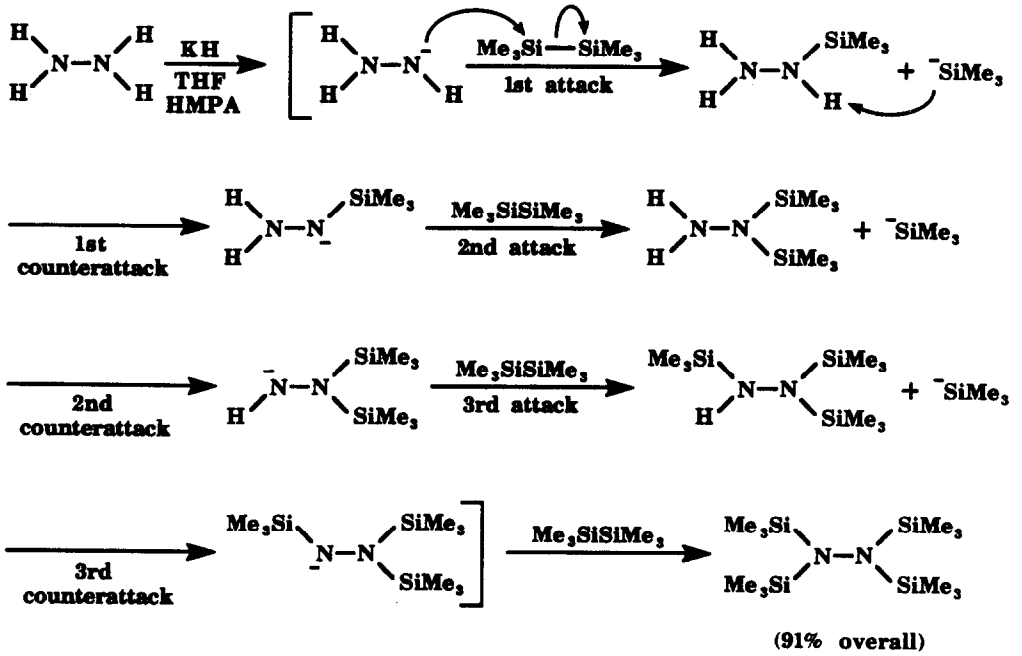
E. DOUBLE- AND MULTIPLE-COUNTERATTACK PROCESSES

For some reactions, two or more equivalents of a counterattack reagent are used, and each equivalent of the reagent is involved in a sequence with both attacking and counterattacking steps. We refer to these reactions as "consecutive double- or multiple-counterattack processes." Alternatively, some reactions consume only one equivalent of counterattack reagent, but a moiety of the reagent repeatedly attacks (or is attacked by) intermediates. We classify these reactions as "tandem double- or multiple-counterattack processes."

E.1. *Hexamethyldisilane and 1,2-Dimethyl-1,1,2,2-tetraphenyldisilane: $Me_3SiSiMe_3$ and $Ph_2MeSiSiMePh_2$*

Very recently, our laboratory found that reaction of H_2NNH_2 with 4.2 equivalents of $Me_3SiSiMe_3$ and 0.3 equivalent of KH in a mixture of THF and HMPA gives $(Me_3Si)_2NN(SiMe_3)_2$ in 91% yield (Scheme 43).[88] Disilane $Me_3SiSiMe_3$ plays a dual role in this reaction. It is a silylating agent for hydrazine; it is also the source of base

Scheme 43



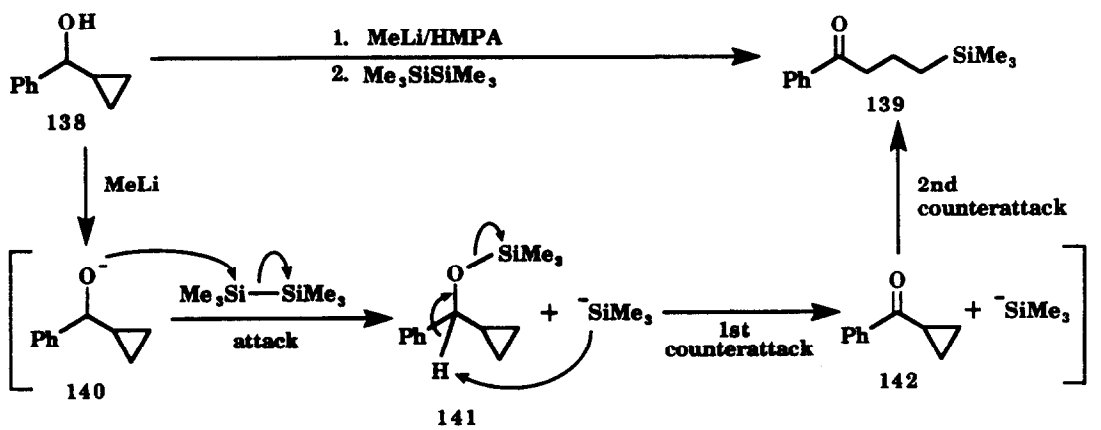
Me_3Si^-, which counterattacks a silylated hydrazine to remove an acidic proton. Scheme 43 illustrates the mechanism of this one-flask reaction and gives an example of a "consecutive triple-counterattack process."

A traditional way to prepare $(Me_3Si)_2NN(SiMe_3)_2$ from H_2NNH_2 includes three separate silylations, utilizes two different bases (i.e., pyridine and *n*-BuLi), requires strong silylating agent Me_3SiBr, and gives only ~8% overall yield.[88] The method by use of counterattack reagent $Me_3SiSiMe_3$ is much more efficient, and many poly-trimethylsilylated hydrazines were prepared in high yields accordingly. Furthermore, methyldiphenylsilylated hydrazines can be synthesized in the same manner by use of $Ph_2MeSiSiMePh_2$.

E.2. *Hexamethyldisilane: $Me_3SiSiMe_3$*

By use of $Me_3SiSiMe_3$ as a counterattack reagent, α-cyclopropylbenzyl alcohol (**138**) can be converted to γ-trimethylsilylbutyrophenone (**139**) under alkaline conditions (Scheme 44).[2] Disilane $Me_3SiSiMe_3$ is attacked by alkoxide **140** to produce a silyl ether (**141**) and Me_3Si^-. Subsequently Me_3Si^- counterattacks the benzylic proton in **141** to give cyclopropyl phenyl ketone (**142**) and regenerates Me_3Si^-. Then Me_3Si^- performs the second counterattack to convert intermediate **142** to **139** as the major product.[89]

Scheme 44



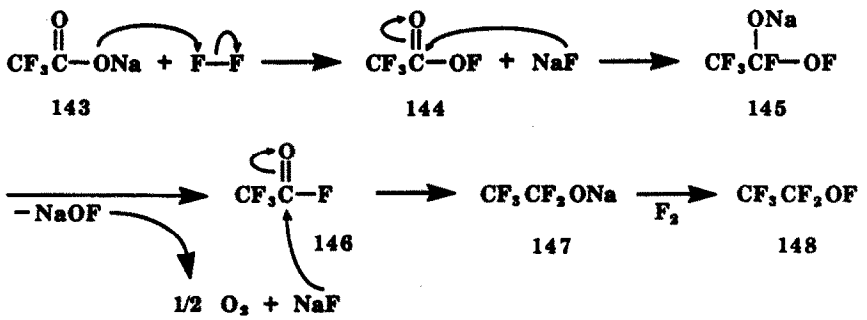
The mechanism shown in Scheme 44 includes two counterattack processes. The first is to convert **140** to **142** by $Me_3SiSiMe_3$; the trimethylsilyl moiety serves as a leaving group in $Me_3SiSiMe_3$ and as a counterattack species for intermediate **141**. The second is to transform **141** to **139** by Me_3Si^-; the trimethylsilyl moiety behaves as a leaving group in **141** and as a counterattack species for intermediate **142**. This sequence provides an example of a "tandem double-counterattack process."

E.3. *Fluorine: F_2*

Perfluoro ether CF_3CF_2OF (**148**) is a good source of electrophilic fluorine;[90,91] Rozen and Lerman reported a simple procedure for its preparation (Scheme 45): reaction

of a suspension of CF_3COONa (**143**) in Freon with nitrogen-diluted F_2 at –75 °C gave a solution with CF_3CF_2OF as a major component. Fluorine is initially attacked by **143** to give CF_3COOF (**144**) and NaF which counterattacks **144** in situ to provide **145**. Intermediate **145** "splits off" NaOF to produce CF_3COF (**146**); NaOF subsequently decomposes to O_2 and NaF. Then NaF "doubly" counterattacks acyl fluoride **146** to give **147**. Reaction of **147** with a second equivalent of F_2 provides the desired product **148**.

Scheme 45

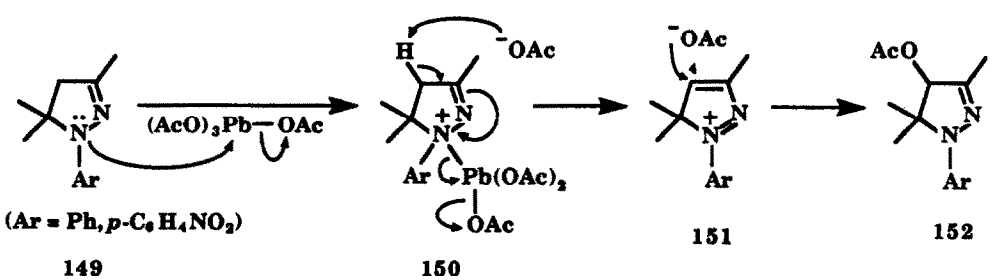


Fluorine serves as a counterattack reagent in the conversion of **143** to **147**. This process includes a "tandem double counterattack."

E.4. *Lead Tetraacetate: $Pb(OAc)_4$*

In the acetoxylation of non-aromatizable pyrazolines, Gladstone and Norman treated **149** with $Pb(OAc)_4$ in CH_2Cl_2 to give **152**.[92] Scheme 46 shows the proposed mechanism, which involves a "tandem double-counterattack process." Lead tetraacetate is attacked by pyrazoline **149** to liberate AcO^-, which counterattacks intermediate **150** to give **151**. From **150** to **151**, AcO^- is regenerated and subsequently counterattacks *C*-4 of **151** to give acetoxylated pyrazoline **152**. In the one-flask process from **149** to **152**, an acetate moiety serves as a leaving group in both $Pb(OAc)_4$ and **150**; an acetate moiety also acts twice as a nucleophile to attack **150** and **151**, respectively.

Scheme 46



F. RECOGNITION OF ELECTROPHILIC AND NUCLEOPHILIC COUNTERATTACK REAGENTS

When a nucleophilic counterattack reagent is used in an individual reaction—not a step in a synthetic sequence—the substrate is an electrophile. Alternatively, the substrate in the same reaction can be regarded as a reagent and the reagent as a substrate. Therefore, looked upon in this latter way, this reaction has an electrophilic counterattack reagent and a nucleophilic substrate.

For example, the saponification shown in Scheme 38 involves $KOSiMe_3$ as a nucleophilic counterattack reagent and RCOOMe (**117**) as the substrate. Because the designation of reagent and substrate in an *individual* reaction is arbitrary, it is also adequate to regard RCOOMe as the reagent and $KOSiMe_3$ as the substrate. Then RCOOMe is an electrophilic counterattack reagent in the reaction shown in Scheme 38.

In contrast, the terms "reagent" and "substrate" are used in a more specific manner in organic synthesis, which involves a sequence of reactions leading to a final product. In the sequence, the product of each reaction, except the last, is the starting material for the next reaction. These products (i.e., synthetic intermediates) are regarded as "substrates" when used in the next reaction. Accordingly the term "reagents" refers to compounds that react with the substrates; "counterattack reagents" employed in organic syntheses must serve as "reagents" rather than as substrates. When the saponification procedure shown in Scheme 38 is utilized in organic synthesis as illustrated in Scheme 39, the intermediate thromboxane derivative (**121**) is recognized as the substrate. Then only $KOSiMe_3$ should be considered as the reagent: a nucleophilic counterattack reagent.

G. CONCLUSIONS

All counterattack reagents possess both electrophilic and nucleophilic centers. In a one-flask reaction, both of the centers of a counterattack reagent are involved. An *electrophilic counterattack reagent* first uses its electrophilic center to accept an attack from the substrate; then the moiety containing the nucleophilic center counterattacks the stable intermediate generated in the first transformation. A *nucleophilic counterattack reagent* first uses its nucleophilic center to accept an attack from the substrate, then the moiety containing the electrophilic center counterattacks.

Use of counterattack reagents can simplify multistep chemical transformations and minimizes laboratory manipulations. A counterattack reagent is used in a one-flask reaction that often involves a complicated reaction mechanism. Therefore, deliberate design is necessary in order to create new counterattack reagents. We hope that this Report will serve as an encouragement for chemists to develop novel counterattack reagents for organic reactions and syntheses.

Acknowledgment—We are grateful to Professors Alex Nickon, Kenneth S. Feldman, and Paul A. Wender for their suggestions in preparation of this Report. We also thank Mr. Naelong Wang for his assistance in defining the scope of counterattack chemistry. B.A.G. acknowledges Dr. Henry Sonneborn III for a fellowship.

For financial support, we are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society; to the American Heart Association, the Maryland Affiliate, Inc.; to the American Cancer Society for an Institutional Research Grant IN-11Z; to the National Institutes of Health for a Biomedical Research Support Grant S07 RR7041; and to Stuart Pharmaceuticals, Division of ICI Americas Inc.

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