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FEATURE ARTICLE

Counterattack reagents in organic synthesis: versatility and efficiency

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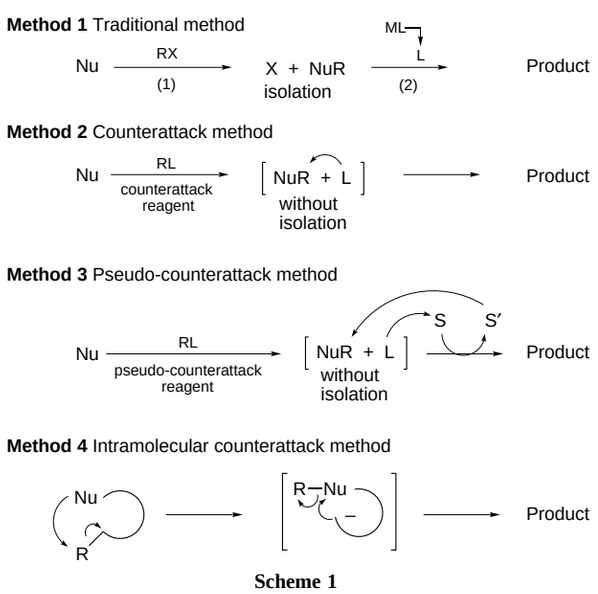
The concept of 'counterattack reagents' has been applied in the development of various chemical transformations. The use of counterattack reagents allows complicated reactions to be accomplished in a single flask without the isolation of intermediates. Thus multistep transformations can be simplified to 'one-step' operations. Representative examples of applications illustrated herein include oxidation, reduction, C–C single and double bond formation, cyclization, C–Si bond formation, *O*- and *N*-silylations and allylsilylation, as well as dealkylation. Comparisons are made between the results from traditional and 'counterattack' methods. Examples also include the utilization of 'pseudo-counterattack' and 'intramolecular counterattack' strategies in organic synthesis. The 'counterattack reagents' involved in those reactions are often, but not limited to, silicon-containing compounds.

Synthetic chemists are always seeking processes that lead from starting materials to target molecules with efficiency and a minimum number of operations. Here we describe the application of the concept of 'counterattack reagents' which provides a method to improve the efficiency of organic syntheses.

A synthetic sequence involving two steps often requires two individual reactions by traditional approaches. Method 1 in Scheme 1 shows an example in which a nucleophile Nu is treated with the reagent RX to give X and NuR in the first reaction. After isolation, the intermediate NuR is allowed to react with nucleophile L (from another source ML) to give the desired product in the second reaction. For certain synthetic sequences, one may combine these two reactions into one by using the 'counterattack strategy', as shown in Method 2.[1] The reagent RL is chosen with care; it is first attacked by Nu to give NuR and L. The leaving group L then counterattacks the intermediate NuR *in situ* to afford the final product. The reagent RL is thus referred to as a 'counterattack reagent'.[1]



Scheme 1

Method 3 in Scheme 1 shows another efficient way that sequential reactions can be combined into a 'one-flask' process.[2] The first step, analogous to that in Method 2, involves the reaction between Nu and RL to give NuR and the leaving group L. This leaving group then reacts with compound S to generate an active species S′, which subsequently attacks the intermediate NuR *in situ*. Because L does not counterattack NuR directly as in Method 2, we refer to the compound RL as a 'pseudo-counterattack reagent'.[2] Furthermore, Method 4 in Scheme 1 represents an 'intramolecular counterattack process'.[3] It involves attacking and subsequent counterattacking processes occurring in one molecule.

In the past fifteen years, our research group has applied the concept of 'counterattack reagents' to organic reactions of various types. Here, twelve novel and efficient chemical transformations will be illustrated which involve the use of various organic compounds in a counterattack, pseudo-counterattack or intramolecular counterattack process.[2–15]

Counterattack *versus* traditional methods

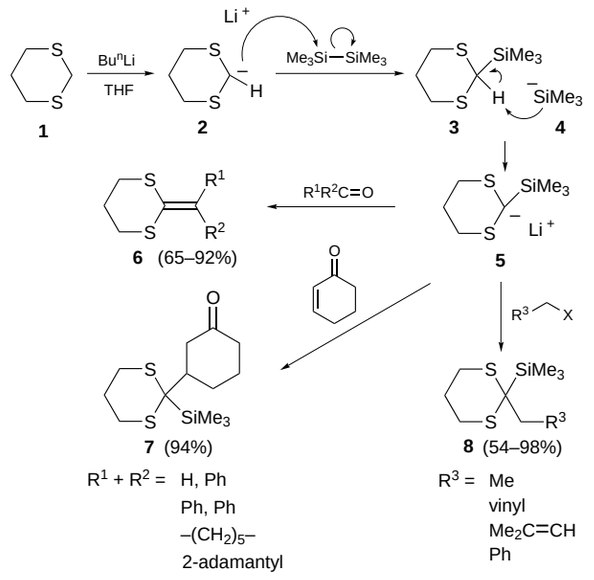
Given the potential advantages associated with counterattack reagents, we will first make a direct comparison of their results with those from traditional methods.

Direct synthesis of ketene dithioacetals and 2-trimethylsilyl-1,3-dithiane derivatives from 1,3-dithiane[4]

Ketene dithioacetals **6** are useful synthetic intermediates.[16] Traditionally, the preparation of ketene dithioacetals involves two steps. The first step involves generation and isolation of 2-trimethylsilyl-1,3-dithiane **3** (71% yield) from 1,3-dithiane **1**.[17] The second step involves reaction of its corresponding lithium salt **5** with various carbonyl compounds to give the desired ketene dithioacetals **6** in 62–80% yield.[18–20] The overall yields are in the range 40–57%. In comparison, use of the 'counterattack strategy', as shown in Scheme 2, allows a 'one-flask' synthesis of **6** in 65–92% yield from 1,3-dithiane **1**.

Scheme 2 depicts the mechanism, which includes an intriguing role for $Me_3SiSiMe_3$. Bu^nLi is used to remove a C-2 proton from 1,3-dithiane **1** to give anion **2**, which attacks $Me_3SiSiMe_3$ to produce 2-trimethylsilyl-1,3-dithiane **3** and Me_3Si^- **4**. This anionic silyl leaving group then counterattacks compound **3** to generate the Me_3Si-stabilized anion **5**. Thus $Me_3SiSiMe_3$ can be regarded as a 'counterattack reagent'.

Using this 'one-flask' synthetic strategy, α,β-unsaturated ketones can act as Michael acceptors for **5** to give ketones **7** in 94% yield. Furthermore, alkyl, allyl and benzyl bromides undergo substitution to produce Me_3Si-containing 1,3-dithianes **8** in 54–98% yields.

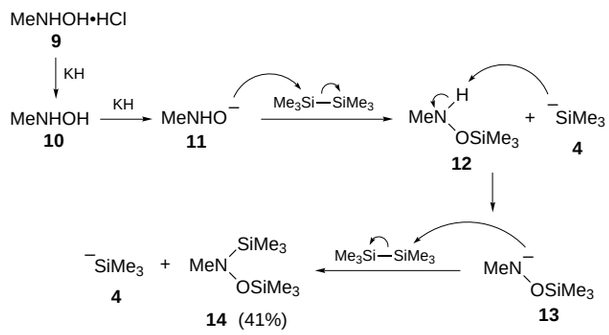


Scheme 2

Preparation of N-*methyl*-N,O-*bis(trimethylsilyl)-hydroxylamine from hydroxylamine*[5]

N-Methyl-*N*,*O*-bis(trimethylsilyl)hydroxylamine **14**, which is widely used in organic synthesis,[21] is the trimethylsilylated equivalent of *N*-methylhydroxylamine **10**. Silylated hydroxylamine **14** can be prepared from anhydrous *N*-methylhydroxylamine **10**.[22] Nevertheless, the route used to obtain **10** is tedious. Alternatively, hydroxylamine **14** can also be synthesized *via* use of hexamethyldisilazane; however, the yield is only 18%.[23,24] A way to solve these problems is to apply the concept of 'counterattack reagents'.

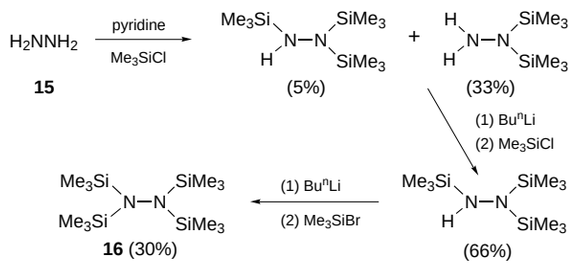
Thus, MeNHOH·HCl **9** is treated with KH and then $Me_3SiSiMe_3$ in a mixture of Et_2O and HMPA to give the desired hydroxylamine **14** in 41% yield. The mechanism is depicted in Scheme 3. After removal of the acid (*i.e.* HCl) in salt **9** and the OH proton in **10** using KH, the resultant oxide **11** attacks $Me_3SiSiMe_3$ to generate monosilylated hydroxylamine **12** and $^-SiMe_3$ **4**. This silyl anion **4**, acting as a base, counterattacks compound **12** to give amide **13**. Reaction of **13** with a second equivalent of $Me_3SiSiMe_3$ affords the desired product **14** and $^-SiMe_3$ **4**, which could substitute for KH to convert **10** to **11** by proton abstraction. Therefore **14** can be obtained from a mixture of **10** and $Me_3SiSiMe_3$ by use of a catalytic amount of KH.



Scheme 3

Direct preparation of polysilylated hydrazines from hydrazines:[6] *a consecutive triple-counterattack process*

Polysilylated hydrazines are ideal starting materials for the generation of various organic species.[25,26] Nevertheless, it is tedious to prepare these compounds by classic means.[27] A typical way to prepare $(Me_3Si)_2NN(SiMe_3)_2$ **16** from H_2NNH_2 **15** includes three separate silylations, utilizes two different bases (pyridine and Bu^{n}Li), requires strong silylating agents (Me_3SiCl and Me_3SiBr) and gives only a *ca.* 8% overall yield (see Scheme 4). Use of hexamethyldisilane as a 'counterattack reagent', however, allows the hydrazines to be polysilylated in one reaction without isolation of any of the intermediates, and provides the target **16** in an excellent yield (91%).



Scheme 4

Scheme 5 illustrates this 'one-flask' preparation of tetrakis(trimethylsilyl)hydrazine **16** from hydrazine **15** and Me_3Si-$SiMe_3$ under alkaline conditions. The disilane, $Me_3SiSiMe_3$, plays a dual role in this reaction: silylating agent and source of base. In the overall process, proton abstraction alternates with silylation. This alternation is repeated four times and thus allows H_2NNH_2 **15** to be converted to $(Me_3Si)_2NN(SiMe_3)_2$ **16** in an efficient way.

With regard to both the manipulation and the yield (91 *versus* 8%), the counterattack method shown in Scheme 5 is much more efficient than the classic procedure shown in Scheme 4. It also represents an example of a 'consecutive triple-counterattack process.'

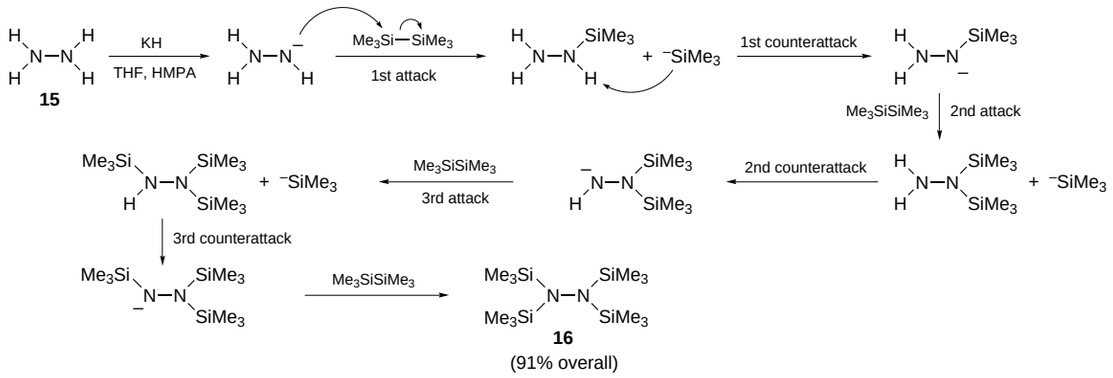
New counterattack methods

The concept of 'counterattack reagents' has also been applied to new methods for the generation of molecules with synthetically valuable functionalities or biological significance. Scheme 6 shows an example in which various starting materials are converted to an important class of products. Scheme 8 shows examples of how a simple starting materials can be transformed into products of various kinds.

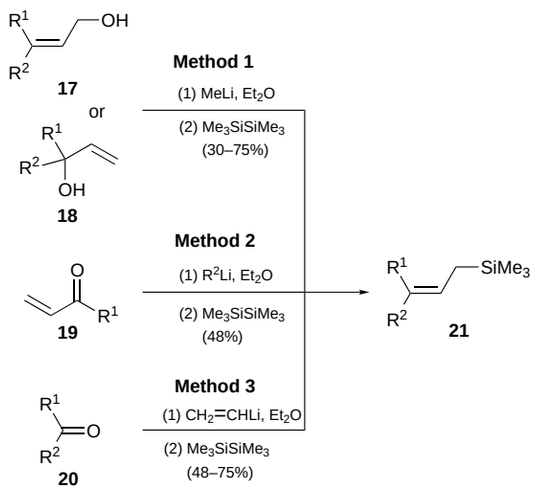
Direct conversion of aldehydes, ketones and allyl alcohols to allyltrimethylsilanes[7]

The allyltrimethylsilane moiety possesses umpolung character and is regarded as a synthon for allyl cations and anions.[28,29] Use of the counterattack method facilitates the preparation of allyltrimethylsilanes from allyl alcohols, enals, enones, aldehydes or ketones, as shown in Scheme 6. Treatment of allyl alcohols (*i.e.* **17** and **18**) with MeLi and $Me_3SiSiMe_3$ in a mixture of HMPA and Et_2O gives the desired allylsilanes **21** (Method 1). The substrates include primary allyl alcohols **17** [*e.g.* geraniol, (−)-myrtenol], secondary allyl alcohols **18** (*e.g.* linalool), benzyl alcohol and homobenzylic alcohol (*e.g.* phenylethyl alcohol). Method 2 in Scheme 6 shows a new method for the preparation of allylsilanes **21** from enals and enones (*i.e.* **19**) by use of alkyllithium and $Me_3SiSiMe_3$. Acrolein and methyl vinyl ketone are converted to allylsilanes by use of Bu^{n}Li and $Me_3SiSiMe_3$. Moreover, reactions of saturated aldehydes and ketones (*i.e.* **20**) with vinyllithium and $Me_3SiSiMe_3$ generate allylsilanes **21** as indicated in Method 3. The starting materials include hexanal, heptan-2-one, and cyclohexanone.

For the preparation of allyltrimethylsilanes by Methods 1–3, the first step is to generate an allyl alkoxide: removal of a proton from an allyl alcohol with MeLi in Method 1; 1,2-addition of RLi to an α,β-unsaturated aldehyde or ketone in Method 2; or addition of vinyllithium to a saturated carbonyl compound in

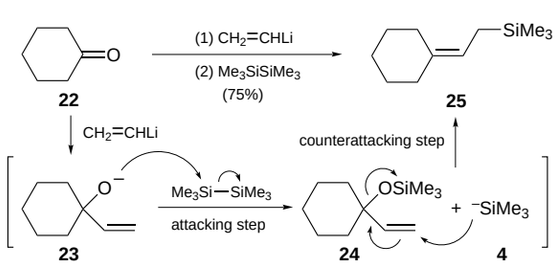


Scheme 5



Scheme 6

Method 3. The allyl alkoxides then react with $Me_3SiSiMe_3$ by a novel pathway to give allyltrimethylsilanes *in situ*, as represented in Scheme 7. Hexamethyldisilane is attacked by allyl alkoxides **23**, generated by addition of vinyllithium to ketone **22**, to give allyl trimethylsilyl ether **24** and Me_3Si^- **4**. An *in situ* substitution reaction subsequently occurs between **24** and **4** to produce allyltrimethylsilanes **25** in 75% yield. Hexamethyldisilane acts as an 'electrophilic counterattack reagent' in these one-flask reactions.

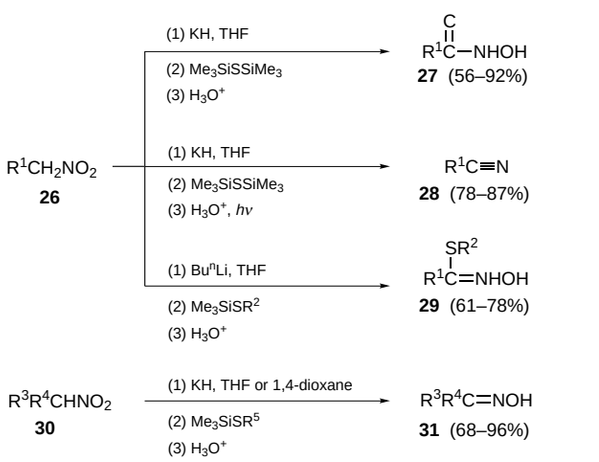


Scheme 7

Formation of thiohydroxamic acids, thiohydroximates, nitriles and oximes from nitro compounds[8,9]

Thiohydroxamic acids [RC(=S)NHOH] and thiohydroximates [RC(SR′)=NOH] contain a moiety with three adjacent nucleophilic atoms (*i.e.* N, O and S). Thiohydroxamic acids play various roles in analytical and biological chemistry. Phenylacetothiohydroximate exists in *Tropaeolum majus*;[33,34] it is also an intermediate in the biosynthesis of benzyl glucosinolate, a mustard oil glucoside.[33] Thiohydroximates are also used as starting materials for the synthesis of the carbamate derivatives $R^1C(SR^2)=NOC(=O)NR^3R^4$.[35] Some carbamates are utilized as pesticides.

The counterattack strategy has been applied in the syntheses of thiohydroxamic acids from readily available nitro compounds (Scheme 8). Thus reaction of various primary nitro compounds **26** with KH and hexamethyldisilathiane in THF gives thiohydroxamic acids **27** in 56–92% yield. The substrates, including esters, acetals, arenes and thiols, are all stable to the reaction conditions. By the same strategy, a thiohydroxamic acid is obtained in 50% yield after treatment of *trans*-β-nitrostyrene with Pr^iSLi and $Me_3SiSSiMe_3$ in THF.



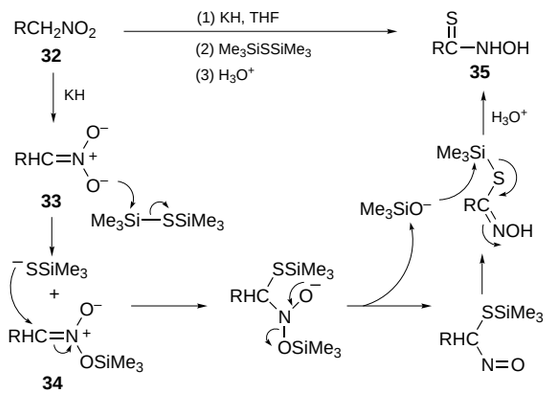
R^1 = Me, C_5H_{11}, $MeO_2C(CH_2)_2$, $THPOCH_2$, Bn, PhMeCH, $Ph(Pr^iS)CH$
R^2 = Me, Ph
$R^3 + R^4$ = Me + Me, Me + C_5H_{11}, Me + Ph, Me + $Ph(CH_2)_2$, $-(CH_2)_5-$, $-(CH_2)_4CHMe-$, 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl
R^5 = $SiMe_3$, Me

THP =

Scheme 8

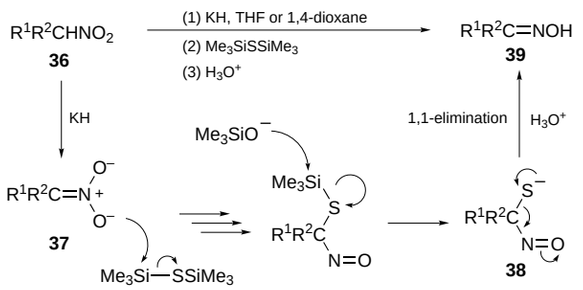
Moreover, primary nitro compounds **26** can be converted to nitriles **28** under UV irradiation. The first step is to generate potassium thiohydroxamates in the dark as previously described. These salts are then neutralized with an acid and desulfurized by light to afford nitriles **28** in 78–87% yield (Scheme 8).[9] On the other hand, treatment of primary nitro compounds **26** with Bu^nLi and thiosilanes (*i.e.* $MeSSiMe_3$ or $PhSSiMe_3$) in THF generates the corresponding thiohydroximates **29** in 61–78% yield. Secondary nitro compounds **30** are converted to oximes **31** in 68–96% yields by reaction with KH and $Me_3SiSSiMe_3$ or $MeSSiMe_3$ in THF or 1,4-dioxane.

The role of $Me_3SiSSiMe_3$ is depicted in Scheme 9 for the 'one-flask' conversion of primary nitro compounds **32** into thiohydroxamic acids **35**. The entire transformation involves multiple steps and the formation of several intermediates, of which isolation is unnecessary. Scheme 10 illustrates a mechanism for the conversion of secondary nitro compounds **36** into oximes **39** *via* reaction with $Me_3SiSSiMe_3$. In this transformation, a 1,1-elimination occurs in the intermediate $R^1R^2C(N{=}O)S^-$ **38** to give sulfur and an oxime.



Scheme 9

A common feature of the reactions shown in Scheme 8 is the generation of a nitronate intermediate (*cf.* **33** in Scheme 9 and **37** in Scheme 10). Reagents $Me_3SiSSiMe_3$, $MeSSiMe_3$ and $PhSSiMe_3$ are first attacked by nitronates (*i.e.* **33** and **37**) at a silicon centre. The leaving group, Me_3SiS^-, MeS^- or PhS^-, then counterattacks the silylated nitronate intermediates (*e.g.* **34**). Thus $Me_3SiSSiMe_3$, $MeSSiMe_3$ and $PhSSiMe_3$ can be regarded as 'counterattack reagents'.



Scheme 10

Protection and deprotection of hydroxy groups

The protection and deprotection of hydroxy groups are common synthetic processes. Traditional methods for the disilylative protection of diols and bis-*O*-demethylation of protected aromatic diols are performed stepwise. The disadvantages include low yields and tedious transformations. The concept of counterattack reagents can be applied to perform the protection and deprotection in an efficient manner.

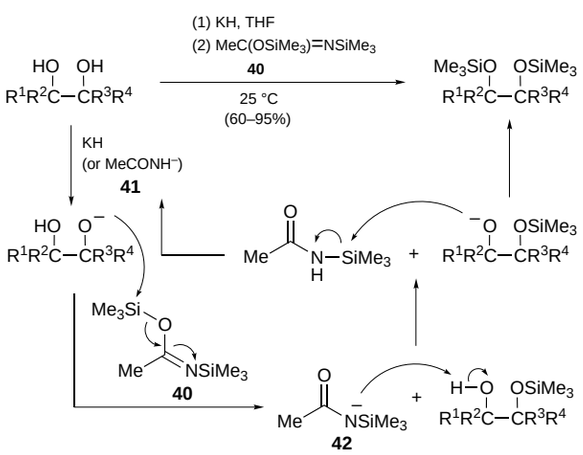
Disilylation of diols by use of MeC(OSiMe₃)=NSiMe₃:[10] *a tandem double-counterattack process*

Trimethylsilylation is useful in the protection of functional groups bearing labile protons. Silylation of alcohols, especially diols, polyols and carbohydrates, can increase their volatility and thermal stability. Consequently, the silylated species are more suitable than the parent alcohols for analysis by GC and mass spectrometry.[36]

Reaction of various diols with bis(trimethylsilyl)acetamide **40** in THF under alkaline conditions gives the corresponding bis(trimethylsilyl) ethers in good to excellent yields (60–95%). The diols may contain other functionalities, such as amides, amines, ethers and thioethers.[10]

Stepwise silylations of resorcinol with hexamethyldisilathiane give the corresponding disiloxylbenzene in 55% overall yield;[37] however, the counterattack method leads to an 80% yield. Use of chlorotrimethylsilane and pyridine to silylate the diols in a carbohydrate gives the corresponding bis(trimethylsilyl) ether in 41% yield;[38] the counterattack method results in a 65% yield. These results clearly indicate the efficiency of the counterattack method.

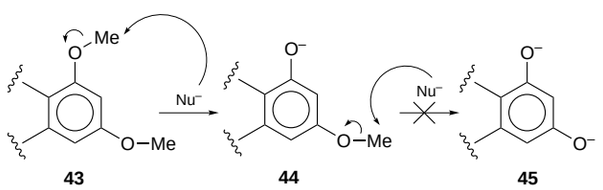
In the disilylation, $MeC(OSiMe_3){=}NSiMe_3$ **40** acts as a counterattack reagent and exhibits multiple functions (see Scheme 11). In addition to transferring both Me_3Si groups onto the diol, reagent **40** provides amide anions **41** and **42**. These anions deprotonate the intermediates and the starting diols. Therefore, only a catalytic amount of base (*i.e.* KH) is needed for initiation of the disilylation. This 'one-flask' disilylation involves sequential deprotonation–silylation–deprotonation–silylation. This double trimethylsilylation also represents an example of a 'tandem double-counterattack process', in which bis(trimethylsilyl)acetamide offers three reacting centres (*i.e.* two electrophilic silicon atoms and one nucleophilic nitrogen atom).



Scheme 11

Deprotection of aryl methyl ethers by sodium trimethylsilanethiolate and hexamethyldisilathiane[11]

Commonly used reagents for demethylation of aryl methyl ethers give mono-*O*-demethylated products; a few of them can bis-*O*-demethylate substrates.[39] Sequential demethylation of dimethoxybenzenes in one flask is difficult using nucleophilic reagents, as shown in Scheme 12. The first demethylation involves attack of a nucleophilic reagent on a methyl group of dimethoxybenzenes **43** to give methoxyphenolates **44**. It is unlikely that nucleofuge **44** could be demethylated by another nucleophile in an efficient manner (*i.e.* **44** → **45**) because the resultant species **45** would bear two negative charges.



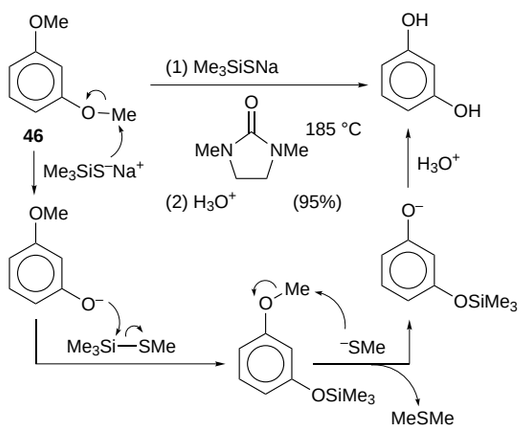
Scheme 12

This problem can be circumvented by utilization of the 'counterattack reagent' concept. Use of Me_3SiSNa and Me_3-

$SiSSiMe_3$ as counterattack reagents causes aryl methyl ethers to bis-*O*-demethylate efficiently under alkaline conditions. Treatment of an aryl methyl ether containing two methoxy units with *ca*. 2.5 equiv. of Me_3SiSNa in 1,3-dimethyl-2-imidazolidinone at 185 °C in a sealed tube gives the corresponding aryl diols in 78–96% yield after aqueous workup. The starting materials also include an aryl alcohol containing a biphenyl or naphthalene unit.

Moreover, $Me_3SiSSiMe_3$ is used to bis-*O*-demethylate aromatic compounds containing one free hydroxy group and two methoxy units, which react with 1.5 equiv. of NaH and then with 1.5 equiv. of $Me_3SiSSiMe_3$ at 185 °C in a sealed tube to afford the corresponding triols in 78–83% yield. Sodium trimethylsilanethiolate and hexamethyldisilathiane can be used to remove two methyl groups *in situ* from an aryl methyl ether. In these bis-*O*-demethylations, Me_3SiSNa and $Me_3SiSSiMe_3$ act as 'counterattack reagents'.

Scheme 13 shows the mechanism for the bis-*O*-demethylation of 1,3-dimethoxybenzene **46**, in which Me_3SiSNa acts as a 'nucleophilic counterattack reagent'. This reagent contains both a nucleophilic centre (*i.e.* S) and an electrophilic centre (*i.e.* Si), which react with the intermediates at different points in the reaction. Furthermore, Scheme 14 depicts an example involving $Me_3SiSSiMe_3$ as an 'electrophilic counterattack reagent', which is used for the bis-*O*-demethylation of dimethoxyphenol **47**. The reactions shown in Schemes 13 and 14 share common features—the design is complicated and the manipulation is simple.



Scheme 13

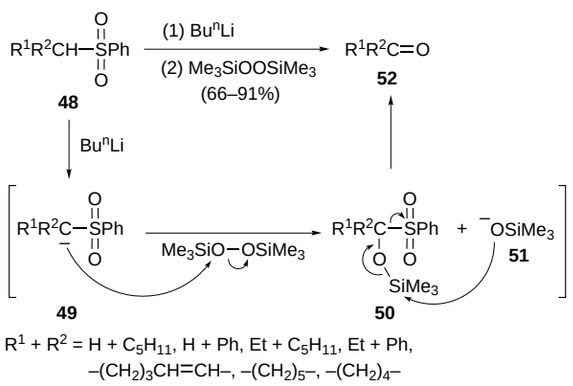
Similarly, this demethylation procedure is also applicable to pyridines with two methoxy groups, using Me_3SiSNa.[40] Furthermore, chlorotrimethylsilane, in combination with sodium sulfide, can be used as the equivalent of sodium trimethylsilanethiolate in the demethylation of dimethoxybenzenes.[41]

Oxidation reactions involving counterattack strategy

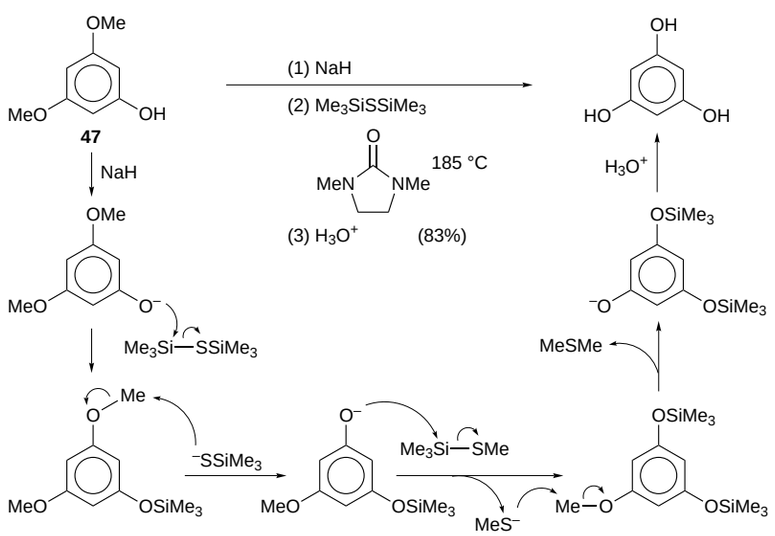
Counterattack strategy can also be applied to oxidation reactions. Examples include the oxidative desulfonylation of sulfones to aldehydes or ketones, oxidation of hydrazines to 2-tetrazenes, and conversion of benzyl alcohols to phenones or benzaldehydes. In these transformations, silicon reagents are utilized both as an oxidant and as a 'counterattack reagent'.

Oxidative desulfonylation of sulfones to aldehydes or ketones by use of $Me_3SiOOSiMe_3$[12]

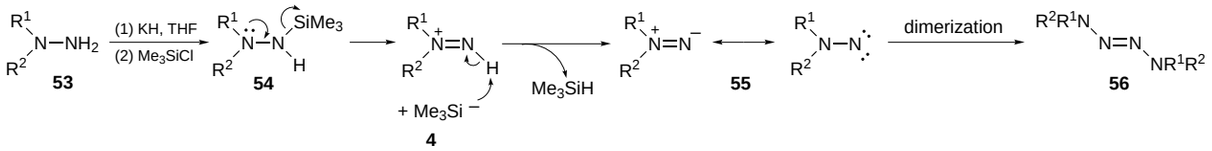
The sulfone group is commonly used in organic synthesis. This group generally has to be removed after the desired transformations have been accomplished. An efficient method for the oxidative desulfonylation of sulfones to aldehydes or ketones is reported, which uses $Me_3SiOOSiMe_3$ under alkaline conditions. As shown in Scheme 15, removal of a proton in sulfone **48** with Bu^nLi in THF at −78 °C generates the corresponding carbanion **49**. $Me_3SiOOSiMe_3$ is then attacked by the sulfonyl carbanion **49** to generate siloxy sulfone **50** and Me_3SiO^- **51**. Without isolation, the siloxy sulfone **50** is counterattacked by Me_3SiO^- to give the desired carbonyl product **52**.



Scheme 15

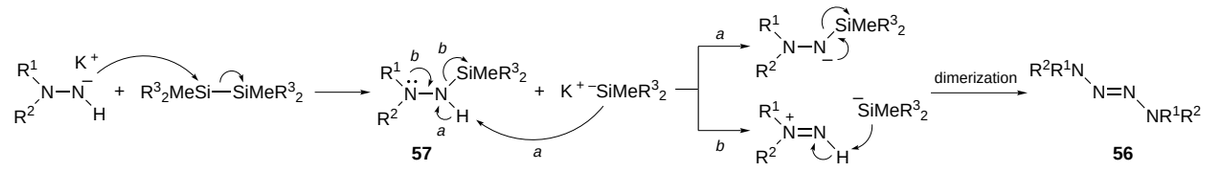


Scheme 14



$R^1 + R^2$ = Ph + Me, $–(CH_2)_5–$, $–CHMe(CH_2)_3CHMe–$, $–CH_2CH_2OCH_2CH_2–$, $–(CH_2)_6–$

Scheme 16



$R^1 + R^2$ = Ph + Me, $–(CH_2)_5–$, $–CHMe(CH_2)_3CHMe–$, $–CH_2CH_2OCH_2CH_2–$, $–(CH_2)_6–$

R^3 = Me, Ph

Scheme 17

This 'one-flask' method can be used to convert alkyl, allylic, benzylic and cycloalkyl sulfones to aldehydes or ketones in 66–91% yield. In the attacking step (**49** → **50**) as shown in Scheme 15, the trimethylsiloxy moiety in $Me_3SiOOSiMe_3$ behaves like a leaving group. In the counterattacking step (**50** → **52**), Me_3SiO^- **51** acts as a nucleophile. Therefore $Me_3SiOOSiMe_3$ is an 'electrophilic counterattack reagent' in this oxidative desulfonylation.

Conversion of hydrazines to 2-tetrazenes by use of Me_3SiCl, $Me_3SiSiMe_3$ and $Ph_2MeSiSiMePh_2$ as oxidizing agents[13]

Silicon compounds Me_3SiCl, $Me_3SiSiMe_3$ and $Ph_2MeSiSiMePh_2$ are commonly used as silylating or reducing agents. By use of a 'counterattack procedure', these silicon reagents can be utilized as oxidants. Reaction of 1,1-disubstituted hydrazines **53** with Me_3SiCl, $Me_3SiSiMe_3$ or $Ph_2MeSiSiMePh_2$ in the presence of KH gives the corresponding 2-tetrazenes **56** in fair to good yields (Schemes 16 and 17). In these reactions, Me_3SiCl, $Me_3SiSiMe_3$ and $Ph_2MeSiSiMePh_2$ behave as oxidizing agents.

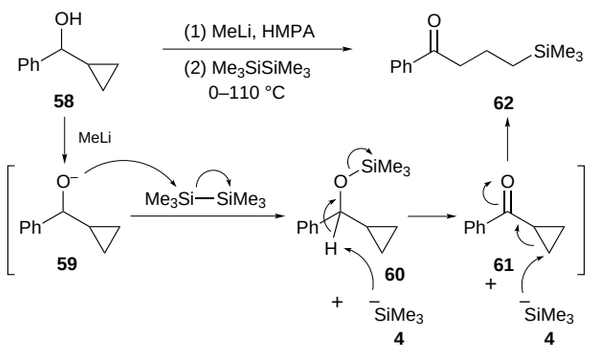
These new methods for the formation of 2-tetrazenes **56** involve several transformations: silylation of hydrazines **53** to give monosilylhydrazines **54**, decomposition of monosilylhydrazines **54** to generate amino nitrenes **55**, and dimerization of amino nitrenes **55** to afford 2-tetrazenes **56**. The characteristic feature of these reactions is that the R_3Si^- species can depart from the $NSiR_3$ moiety in **54** and **57**. Schemes 16 and 17 depict the 'counterattack processes' for the oxidation of hydrazines to 2-tetrazenes by Me_3SiCl and disilanes, respectively.

Oxidation of benzyl alcohols to phenones[14] *or benzaldehydes*[15] *by use of $Me_3SiSiMe_3$: a tandem double-counterattack process*

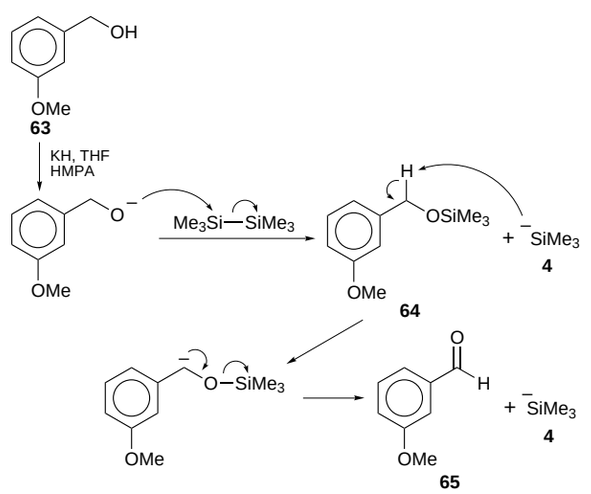
Hexamethyldisilane can also act as an oxidant in the conversion of benzyl alcohols to carbonyl compounds. Under basic conditions, reaction of α-cyclopropylbenzyl alcohol **58** or 3-methoxybenzyl alcohol **63** with $Me_3SiSiMe_3$ generates γ-trimethylsilylbutyrophenone **62** or 3-methoxybenzaldehyde **65**, respectively.

The mechanism for the one-flask oxidation and cyclopropyl ring opening procedure is depicted in Scheme 18.[14] Disilane $Me_3SiSiMe_3$ is attacked by alkoxide **59** to produce silyl ether **60** and Me_3Si^- **4**. Subsequently, Me_3Si^- counterattacks the benzylic proton in **60** to give cyclopropyl phenyl ketone **61** and regenerates Me_3Si^-. Me_3Si^- then re-counterattacks intermediate **61** to give γ-silylphenone **62** as the major product. The entire mechanism includes two counterattack processes. The first is to convert **59** to **61** using $Me_3SiSiMe_3$; the trimethylsilyl moiety serves as a leaving group in $Me_3SiSiMe_3$ and as a counterattack species for intermediate **60**. The second is to transform **60** to **62** using Me_3Si^- **4**; the trimethylsilyl moiety behaves as a leaving group in **60** and as a counterattack species for intermediate **61**. This sequence provides an example of a 'tandem double-counterattack process'.

Similarly, the oxidation of 3-methoxybenzyl alcohol **63** to 3-methoxybenzaldehyde **65** by use of $Me_3SiSiMe_3$ under basic conditions occurs *via* the mechanism shown in Scheme 19.[15] In these transformations, the Me_3Si^- species is utilized as a catalyst, which can also oxidize trimethylsilyl ethers (*i.e.* **60** in Scheme 18 and **64** in Scheme 19) possessing acidic protons at the position α to the corresponding carbonyl compounds (*i.e.* **62**

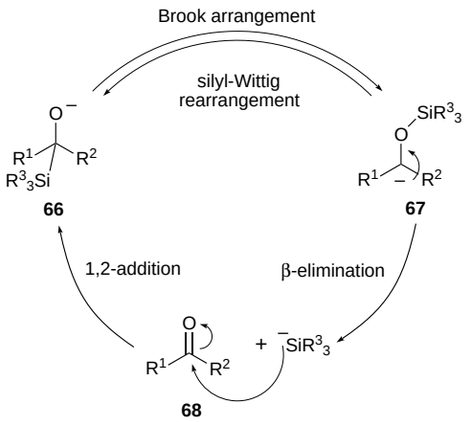


Scheme 18



Scheme 19

and **65**). Thus the interconversions can constitute a novel cycle among α-silylalkoxides **66**, α-siloxy carbanions **67** and carbonyl compounds **68** accompanied by R_3Si^-, as shown in Scheme 20.[15] This newly established cycle involves Brook rearrangement, the silyl-Wittig rearrangement, a β-elimination and a 1,2-addition.

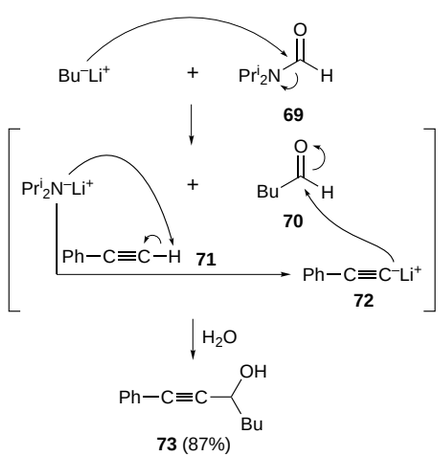


Scheme 20

Preparation of prop-2-ynylic alcohols by use of organic amides as pseudo-counterattack reagents[2]

Prop-2-ynylic alcohols can be used in the synthesis of pheromone components[42] and the ω-chain in prostaglandins.[43] For the preparation of prop-2-ynylic alcohols, a one-flask method has been established by use of a 'pseudo-counterattack process'. Reaction of an organolithium reagent, an organic amide and phenylacetylene generates prop-2-ynylic alcohols in 71–93% yield. The amides, including *N*,*N*-dimethyl-, *N*,*N*-diethyl- and *N*,*N*-diisopropyl-formamide, 1-formylpyrrolidine, 1-formylpiperidine, *N*,*N*-dimethylacetamide and *N*,*N*-diethyldodecanamide, behave as pseudo-counterattack reagents in this transformation.

The mechanism is illustrated in Scheme 21 for the reaction involving Bu^nLi, *N*,*N*-diisopropylformamide **69** and phenylacetylene **71**. In the first step, *N*,*N*-diisopropylformamide **69** is attacked by Bu^nLi to give the stable intermediate valeraldehyde **70**. The $Pr^i_2N^-$ anion formed from the amide reacts with phenylacetylene **71** to generate lithium phenylacetylide **72**. This nucleophilic species attacks the intermediate valeraldehyde **70** *in situ* to afford the desired prop-2-ynylic alcohol **73** in 87% yield. Thus, *N*,*N*-diisopropylformamide serves both as a substrate for the organolithium reagent and as the solvent. In the entire transformation, the organic amide can be considered as a 'pseudo-counterattack reagent'.

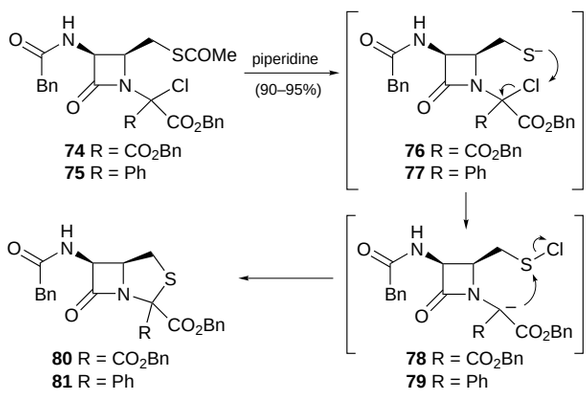


Scheme 21

Intramolecular counterattack strategy in the synthesis of biologically active isopenams[3]

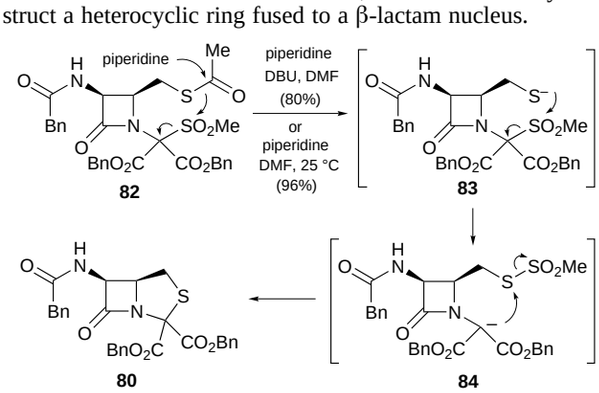
The concept of counterattack reagents can be extended to the performance of chemical transformations in one molecule. Use of this method allows the synthesis of isopenams having important biological activities in high yields.

The synthesis of isopenams, involving an 'intramolecular counterattack process', is illustrated in Scheme 22. Formation of the thiazolidine ring in isopenams **80** and **81** from the corresponding thioesters **74** and **75**, respectively, is accomplished under basic conditions. Accordingly, the sulfides **76** and **77** are generated by deacetylation of thioesters **74** and **75**, respectively, with piperidine. The α-chloro ester moiety in **76** and **77** is first attacked intramolecularly by the sulfide moiety. The resultant carbanions **78** and **79** then counterattack the S–Cl unit to form the thiazolidine ring in **80** and **81**. Thus the thioesters **74** and **75** act as 'intramolecular counterattack reagents'.



Scheme 22

A similar mechanism, shown in Scheme 23, is responsible for the transformation of sulfone malonate **82** to isopenam **80** *via* sulfide **83** and malonate anion **84**. The key steps involve the sulfone moiety in **83** being attacked by the sulfide unit, and the resultant carbanion **84** counterattacking the S–SO_2Me unit to form the thiazolidine ring in **80**. Thus sulfone **82** also functions as an 'intramolecular counterattack reagent'. Using this intramolecular counterattack mechanism, we can efficiently construct a heterocyclic ring fused to a β-lactam nucleus.



Scheme 23

Conclusions

Twelve examples have been given which demonstrate the efficient ways counterattack reagents can be used in organic synthesis. These reagents function either as electrophilic or nucleophilic 'counterattack reagents'. Their structures can be symmetric or non-symmetric. In addition to being attacked by substrates and then counterattacking the intermediates *in situ*, some counterattack reagents can follow very complicated

reaction pathways, such as the 'tandem double-counterattack process' and the 'consecutive triple-counterattack process'. This new concept has also been extended to the 'intramolecular counterattack strategy' and the 'pseudo-counterattack process' in the synthesis of valuable organic targets.

A multistep chemical transformation can be simplified into a 'one-flask' reaction using a counterattack reagent. In comparison with established classic methods, this new approach often gives higher yields with less manipulation. There is a bright future for the application of counterattack reagents to transformations of various types. An extreme example might involve hundreds or thousands of consecutive attacking and counter-attacking processes in polymer syntheses. The deliberate design of the reagent applied in each transformation is the key to the creation of new 'counterattack reagents'.

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