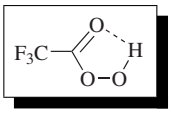
Trifluoroperacetic Acid[1]



[359-48-8] $C_2HF_3O_3$ (MW 130.03)
InChI = 1S/C2HF3O3/c3-2(4,5)1(6)8-7/h7H
InChIKey = XYPISWUKQGWYGX-UHFFFAOYSA-N

(electrophilic reagent capable of reacting with many functional groups; delivers oxygen to alkenes, arenes, and amines;[1] useful reagent for Baeyer–Villiger oxidation of ketones[27,44])

Alternative Names: TFPAA; peroxytrifluoroacetic acid.

Solubility: sol CH_2Cl_2, dichloroethane, ether, sulfolane, acetonitrile.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: assay using iodometry.[2]

Preparative Methods: the preparation and handling of TFPAA should be carried out behind a safety shield. A mixture of ***Trifluoroacetic Anhydride*** (46.2 g; 0.22 mole) and CH_2Cl_2 (50 mL) is cooled with stirring in an ice bath. 90% H_2O_2 (caution: for hazards see ***Hydrogen Peroxide***) (5.40 mL, 0.20 mol) is added in 1 mL portions over a period of 10 min. When the mixture has become homogeneous, it is allowed to warm to rt and then again cooled to 0 °C.[3] TFPAA prepared from 30% aqueous H_2O_2 and ***Trifluoroacetic Acid*** has been used for some reactions.[4–6] Hydrogen peroxide of high concentration (70%) is not widely available due to hazards involved in handling, storage, and transportation. The commercially available ***Hydrogen Peroxide–Urea*** (UHP) system, which is safe to handle, has been introduced recently as a substitute for anhydrous H_2O_2 in the preparation of TFPAA.[2,7,8]

Purification: in the preparation of TFPAA, a slight excess of trifluoroacetic anhydride is used to ensure that no water is present in the reagent. The reaction between H_2O_2 and trifluoroacetic anhydride is very fast; the reagent is ready for use after the reactants have been mixed and the solution has become homogeneous. No special purification steps are employed. Suitable buffers (Na_2CO_3, Na_2HPO_4) are used to neutralize the highly reactive and strongly acidic trifluoroacetic acid which is present along with TFPAA in the reagent.

Handling, Storage, and Precautions: the reagent can be stored at −20 °C for several weeks[9] and exhibits no loss in active oxygen content after 24 h in refluxing CH_2Cl_2.[40] However, since it can be prepared in a short time, the usual practice is to prepare the reagent when needed. Note that solutions of TFPAA in CH_2Cl_2 can lose activity by evaporation of the volatile peracid.[41] Since peroxy acids are potentially explosive, care is required while carrying out the reactions and also during workup of the reaction mixture. Solvent removal from excess H_2O_2–CF_3CO_2H experiments can result in explosions; the peroxide must be destroyed by addition of MnO_2 (until a potassium iodide test is negative) before solvent removal.[10a] For a further discussion of safety, see Luxon.[10b] This reagent should only be handled in a fume hood.

Original Commentary

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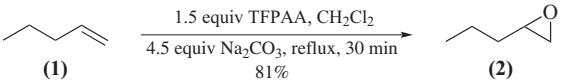
General Considerations. Trifluoroperacetic acid oxidizes simple alkenes, alkenes carrying a variety of functional groups (such as ethers, alcohols, esters, ketones, and amides), aromatic compounds, alkanes,[11] amines and N-heterocycles. Ketones undergo oxygen insertion reactions (Baeyer–Villiger oxidation).

Epoxidations of Alkenes. Due to the presence of the strongly electron withdrawing CF_3 group, TFPAA is the most powerful organic peroxy acid and as such is more reactive than performic[21] or 3,5-dinitroperbenzoic acids.[41] It reacts readily even with electron-poor alkenes to furnish the corresponding epoxides (see ***m-Chloroperbenzoic Acid***).

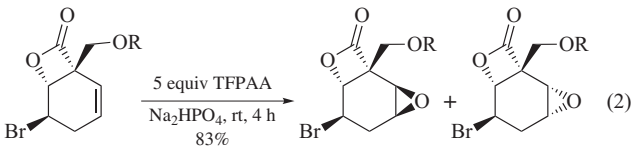
Trifluoroacetic acid is a strong acid which opens epoxides readily.[12,44] Since TFPAA is a much weaker acid than trifluoroacetic acid (pK_a 3.7 vs. 0.3), the latter reagent can be selectively neutralized with Na_2CO_3 or Na_2HPO_4, leading to the isolation of epoxides in high yields. When the substrate is highly reactive, Na_2CO_3 is used as buffer; when the substrate reacts sluggishly, Na_2HPO_4 is used as buffer.[12] The TFPAA reagent is rapidly decomposed by Na_2CO_3.

Since monosubstituted alkenes are not electron rich, they react sluggishly with the standard organic peroxy acids. By contrast, the monosubstituted alkene 1-pentene (**1**) is epoxidized efficiently by TFPAA (eq 1).[12] TFPAA prepared from 0.3 mol of 90% H_2O_2 and 0.36 mol of trifluoroacetic anhydride in CH_2Cl_2 is added during 30 min to a stirred mixture of (**1**) (0.2 mol), Na_2CO_3 (0.9 mol), and CH_2Cl_2 (200 mL). Since the alkene is volatile the reaction flask is fitted with an efficient ice water-cooled condenser. The reaction mixture boils during the addition of the peracid. After all the reagent has been added, the reaction mixture is heated under reflux for 30 min, cooled, and the insoluble salts are removed by centrifugation. The salt is thoroughly washed with CH_2Cl_2. Fractional distillation of the combined CH_2Cl_2 extracts furnishes the epoxide **2** in 81% yield.



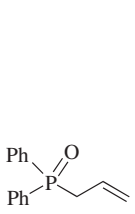
(1)

The alkene (**3**), which is resistant to epoxidation by *m*-CPBA or ***Peracetic Acid***, has been epoxidized with TFPAA to furnish in 83% yield a mixture of esters (**4**) and (**5**) (eq 2).[13] Esters (**4**) and (**5**) undergo facile deacylation when chromatographed on silica gel to furnish alcohols (**6**) and (**7**).

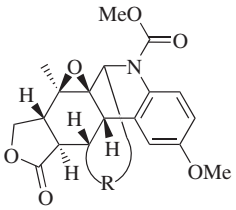


(2)

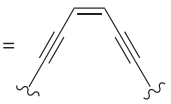
Epoxidation of allyldiphenylphosphine oxide (**8**) with TFPAA furnishes in quantitative yield the corresponding epoxide, 2-(diphenylphosphinoylmethyl)oxirane; *m*-CPBA epoxidation of (**8**) furnishes the epoxide in only 56% yield.[14] Epoxide (**9**) is obtained in 80% yield through regio- and stereoselective epoxidation of the corresponding alkene with TFPAA in CH_2Cl_2 in the presence of Na_2HPO_4 buffer.[15]



(**8**)

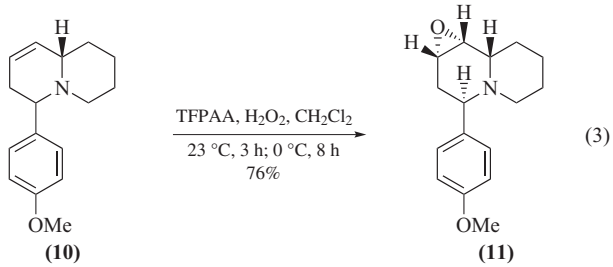


(**9**) R =



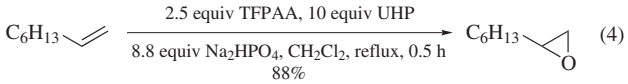
(*Z*)

The tertiary amine of (**10**) is expected to react more readily than the disubstituted double bond on treatment with an organic peracid. Selective epoxidation of the double bond in (**10**) was achieved by initially treating it with CF_3CO_2H. This led to salt formation due to protonation of the amine. Epoxidation of the salt with TFPAA and subsequent workup furnished the epoxide (**11**) (eq 3).[16]



(**10**) (**11**) (3)

Alkenes have been epoxidized efficiently employing TFPAA prepared by the UHP method (eq 4).[2]

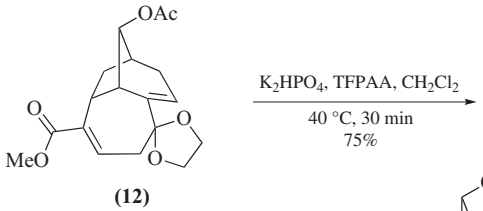


(4)

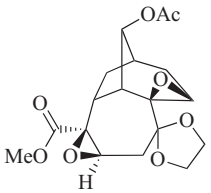
α,β-Unsaturated esters and α,β-unsaturated ketones are resistant to epoxidation by organic peracids since the double bonds are not electron rich; however, these compounds can be epoxidized by TFPAA. 1-Acetylcyclohexene[17] and methyl methacrylate[12] furnish the corresponding epoxides in 50% and 84% yields, respectively, when treated with TFPAA/Na_2HPO_4 in CH_2Cl_2 (reflux for about 0.5 h). The α,β-unsaturated ester (**12**) has been epoxidized stereoselectively by TFPAA (eq 5).[18] With *m*-CPBA, this epoxidation requires a higher reaction temperature which results in the formation of a complex mixture.

With organic peracids, allyl alcohols form hydrogen bonds involving the hydrogen of the alcohol, as in (**13**).[19] Ganem has suggested that, with TFPAA, allylic ethers form hydrogen bonds involving the hydrogen of the peracid (**14**).

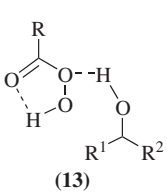
Epoxidation of (**15**) having an allylic ether substituent axially oriented is *syn* selective (*syn:anti* epoxidation = 12.4:1) (eq 6);.[19] this selectivity is due to the formation of the hydrogen bond of the type shown in (**14**). The stereoselectivity in the epoxidation of (**15**) is solvent dependent. When (**15**) is epoxidized in THF (which disrupts hydrogen bonding) the ratio of *syn*:*anti* epoxides obtained is 1:12. The epoxidation of the allyl alcohol (**16**) with TFPAA is highly *syn* selective (*syn*:*anti* epoxidation = 100:1); the *syn* selectivity in the epoxidation of (**16**) with *m*-CPBA is much less (*syn*:*anti* epoxidation = 5.2:1).



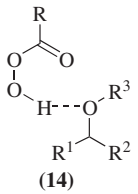
(**12**)



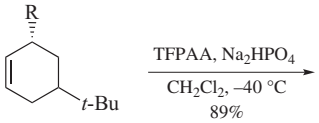
(5)



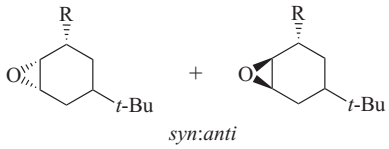
(**13**)



(**14**)

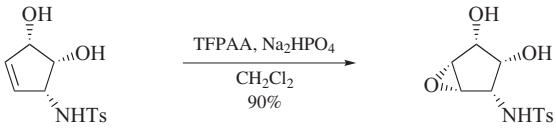


(**15**) R = OTBDMS
(**16**) R = OH



syn:*anti* (6)

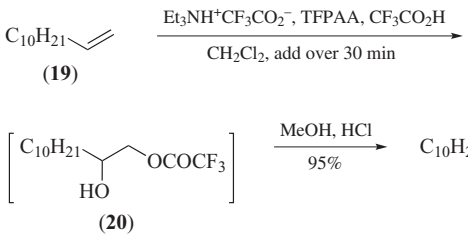
The diol (**17**) is epoxidized stereoselectively to furnish (**18**) (eq 7).[20]



(**17**) (**18**) (7)

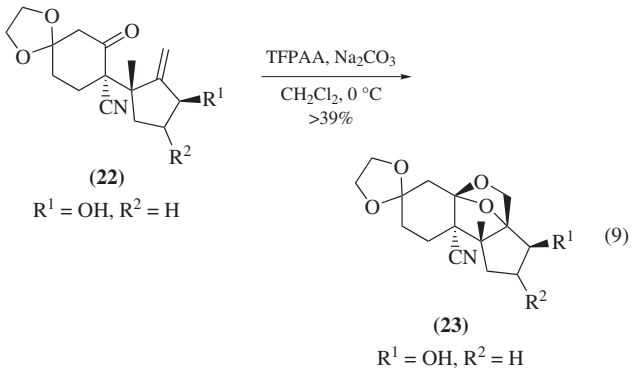
Oxidation of Alkenes to Diols and Ketones. Alkenes react readily with a CF_3CO_3H/CF_3CO_2H mixture to furnish hydroxy trifluoroacetates, e.g. (**19**) → (**20**) (eq 8).[21] In this reaction, high molecular weight byproducts are formed due to the condensation of hydroxy trifluoroacetates with the epoxides formed from alkenes. The formation of the byproduct can be avoided by adding triethylammonium trifluoroacetate. After the formation of the glycol ester is complete, the solvent is evaporated under reduced pressure and the crude ester is subjected to methanolysis to furnish the

vicinal diol (**21**). α,β-Unsaturated esters are also hydroxylated by this procedure.



(**19**) (**20**) (**21**) (8)

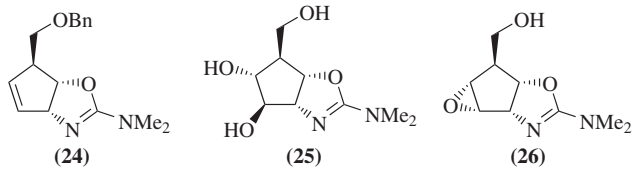
The allyl alcohol (**22**) reacted readily with TFPAA to furnish the 1,3-dioxolane (**23**) (eq 9).[8] This reaction could not be carried out with *m*-CPBA even in refluxing ethylene dichloride. The homoallyl alcohol (**22**) (R^1 = H, R^2 = OH) was reacted with TFPAA prepared from commercially available urea–hydrogen peroxide; the major product formed was the dioxolane (**23**) (R^1 = H, R^2 = OH).



(**22**)
R^1 = OH, R^2 = H

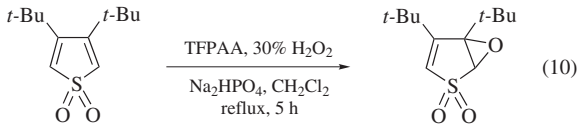
(**23**)
R^1 = OH, R^2 = H (9)

(±)-Allosamizoline (**25**) has been synthesized from the (dimethylamino)oxazoline **24**.[22] 5.4 M TFPAA in CF_3CO_2H is added carefully to (**24**) at 0 °C. The reaction mixture is evaporated in vacuum and the resulting mixture of epoxides is solvolyzed by heating with 10% aqueous CF_3CO_2H at 40 °C. Hydrogenolysis (Pd/C, H_2, MeOH) of the solvolysis product furnishes pure (±)-(**25**) (overall yield 67%) and the epoxide (**26**) (yield 16%).



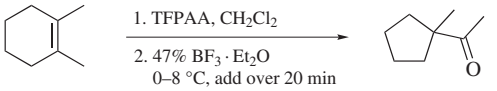
(**24**) (**25**) (**26**)

Epoxidation of sterically congested alkenes occurs with TFPAA under basic conditions (eq 10).[45]



(10)

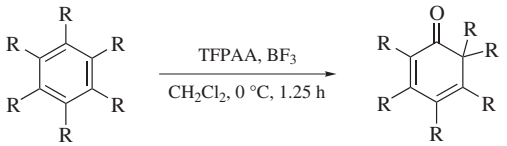
Treatment of tetrasubstituted alkenes with TFPAA/BF_3 furnishes ketones via rearrangement. 1,2-Dimethylcyclohexene has been transformed to the ketone (**27**) (eq 11);[23] the reagents TFPAA and 47% ***Boron Trifluoride Etherate*** are added simultaneously.



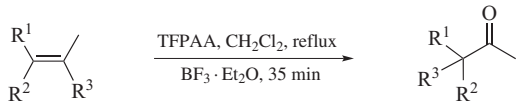
(**27**) (11)

Arene Oxidation. Arenes are exhaustively oxidized to aliphatic carboxylic acids. Heteroaromatic systems, such as pyridine, quinoline, and dibenzothiophene, are quantitatively oxidized to their *N*-oxides and sulfone rather than undergo ring oxidation. The heteroatom oxidation deactivates the ring towards electrophilic attack by TFPAA.[6] Benzene undergoes direct catalytic oxidation to phenyl trifluoroacetate using a TFPAA/Co^{III} reagent.[24]

With BF_3. The combination TFPAA/***Boron Trifluoride*** is a potent electrophilic oxidant for π-systems.[46] As a source of positive hydroxyl, it is used to convert aromatics into cyclohexadienones (eq 12)[26a] and phenols,[25] and alkenes into ketones (eq 13).[26b] See also eq 11 above.



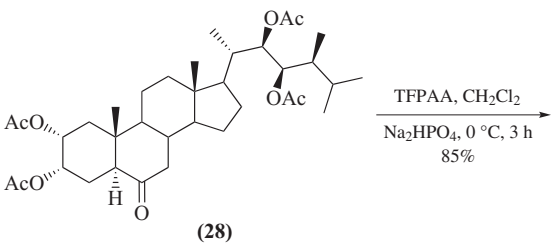
(12)
R = Me, 93%
R = Et, 82%



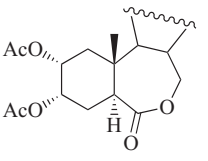
(13)

R^1	R^2	R^3	Yield
Me	Me	Me	75%
Me	Me	H	53%
Et	Me	H	70%
Me	Cl	Me	77%

Baeyer–Villiger Oxidation. On treatment with organic peroxy acids, ketones undergo oxygen insertion reactions to furnish esters (see ***m-Chloroperbenzoic Acid***).[44] This reaction, known as the Baeyer–Villiger rearrangement, has several applications and has been reviewed recently.[27] When carrying out this oxidation with TFPAA, Na_2HPO_4 buffer is added to prevent the reaction between trifluoroacetic acid and the Baeyer–Villiger product. The ketone (**28**) reacts with TFPAA to furnish brassinolide tetracetate (**29**) (eq 14).[28] The migration of C-7 rather than C-5 carbon in



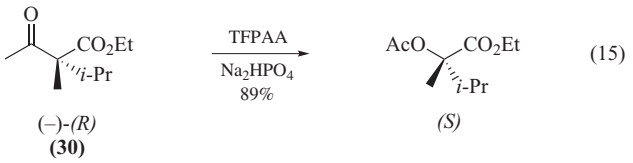
(**28**)



(**29**) (14)

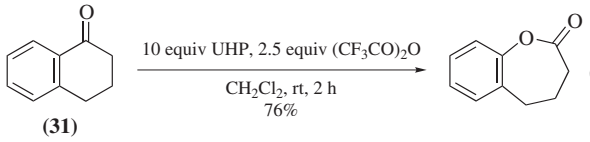
this oxidation is due to the effect of the acetate groups at C-2 and C-3. A systematic study of the Baeyer–Villiger reaction of 5α-cholestan-6-ones having substituents at C-1, C-2, and C-3 has been carried out.[29]

The oxidations of the ketone (**30**) and α-tetralone (**31**) have been reported (eqs 15 and 16).[30,2] Epimerization of α-substituents is generally not observed when ketones are oxidized with buffered TFPAA.[42]



(15)

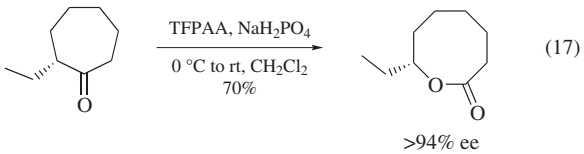
(–)-*(R)* **(30)** *(S)*



(16)

(31)

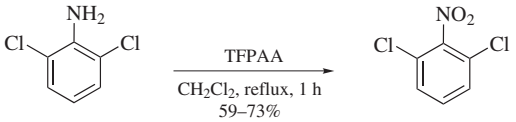
Complete stereospecificity and high regioselectivity (25:1) is observed in the oxidation of an *erythro* ketone (eq 17). Oxidation of the *threo* ketone is also stereospecific but gives a 5:3 mixture of ester regioisomers.[47]



(17)

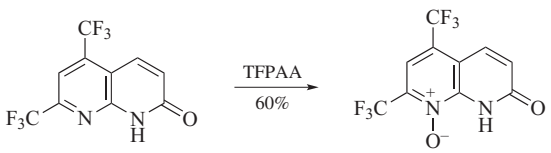
>94% ee

Heteroatom Oxidations. Aromatic primary amines carrying electron-withdrawing groups are oxidized efficiently by TFPAA to the corresponding nitro compounds (eq 18).[21,31] The amine dissolved in CH_2Cl_2 is added to the peracid. The above oxidation cannot be carried out with aromatic amines such as *p*-anisidine, which are unusually sensitive to electrophilic attack; for these sensitive amines, peracetic acid is the preferred oxidant.



(18)

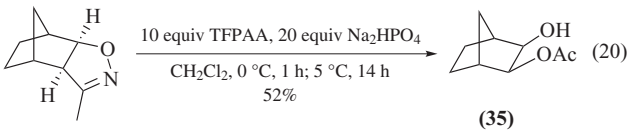
Oxidation of 2,3,4,5,6-pentachloroaniline with TFPAA in $CHCl_3$–water at rt furnishes, in 78% yield, 2,3,4,5,6-pentachloronitrosobenzene.[32] The electron-deficient heterocycle (**32**) furnishes the *N*-oxide (**33**) on oxidation with TFPAA prepared from urea–hydrogen peroxide (eq 19).[7] Electron-deficient pyridines are oxidized to the corresponding *N*-oxides with TFPAA; perbenzoic and peracetic acid are not effective for this transformation.[43]



(19)

(32) **(33)**

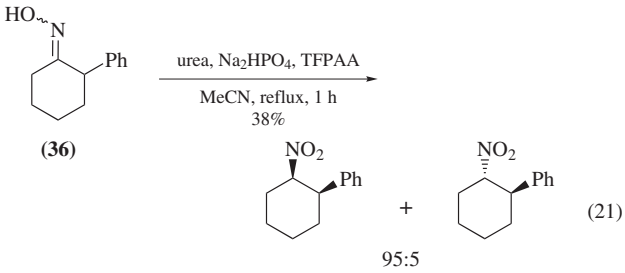
Oxidation of the isoxazoline (**34**) furnishes the hydroxy ester (**35**) (eq 20) via an initial oxaziridine intermediate.[33]



(20)

(34) **(35)**

Nitro compounds have many applications in organic chemistry.[34] Strained polynitro polycyclic compounds are of interest as a new class of energetic materials.[35] Since oximes are readily available, their oxidation to nitro compounds has been studied. Oxidation of the oxime (**36**) furnishes a mixture of nitro compounds; the major component is the *cis* isomer (eq 21).[36] During the oxidation of oximes, ketones are obtained as byproducts. Hindered oximes such as camphor oxime are not oxidized by TFPAA.

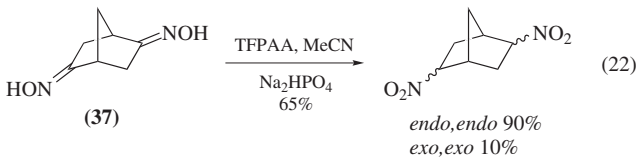


(21)

(36) 95:5

Oximes yield primary, secondary, and alicyclic nitroalkanes (72%),[48] and α-chloro ketoximes give α-nitroalkenes (31–66%).[49]

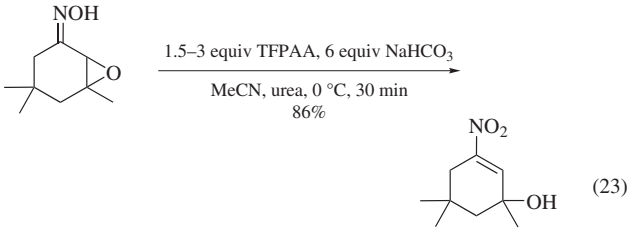
Oxidation of the oxime (**37**) furnishes a mixture of *endo,endo* and *exo,exo* isomers (eq 22).[35b] Oximes have been converted to nitro compounds using a multistep method.[35a] ***Sodium Perborate*** in glacial acetic acid oxidizes oximes to nitro compounds.[37]



(22)

(37) *endo,endo* 90%
exo,exo 10%

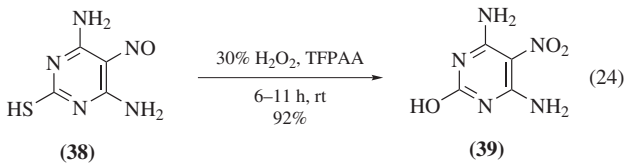
α-Unsubstituted α,β-epoxy ketoximes are oxidized to γ-hydroxy-α-nitroalkenes (eq 23).[38] Aldoximes are oxidized to nitroalkanes (60–80%) with the reagent prepared from urea–H_2O_2 and trifluoroacetic anhydride. Ketoximes fail to react with this reagent system.[50]



(23)

Nitroso compounds are oxidized to the corresponding nitro compounds (eq 24)[39] or to nitramines.[40,51] 30% H_2O_2 is added to a solution of the nitrosopyrimidine (**38**) in CF_3CO_3H during

1.5 h. After workup the nitro compound (**39**) is obtained in high yield; in this reaction, oxidative hydrolytic desulfurization is observed.



(**38**) (**39**) (24)

Miscellaneous Reactions. Aromatic azines are oxidized to their azine monoxides with TFPAA.[52] Organosulfides can be oxidized by TFPAA to either sulfoxides or sulfones under mild conditions in high yield.[5,53]

First Update

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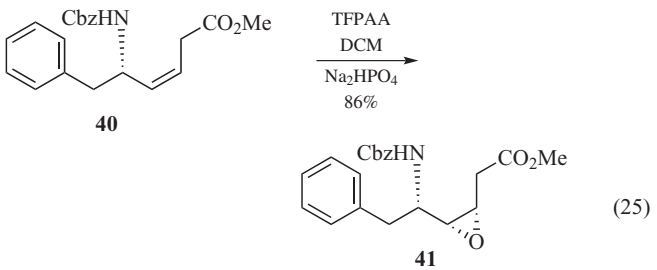
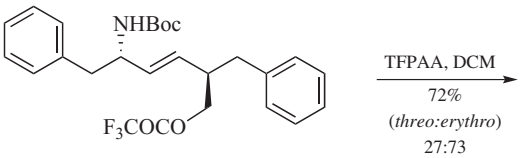
Epoxidation of Alkenes. During the epoxidation of olefins with peracids, it has been known for some time that the π-electrons of the alkene react with the σ^* orbital of the peracid. Quantum chemical calculations have probed the mechanism in great detail to explain the exceptional reactivity displayed by TFPAA. In particular, the acid catalysis and solvent effects that are experimentally observed have been explained.[54–56]

The electronic structure of TFPAA compared to other peroxy acids confers upon it a unique reactivity profile that can be exploited to attain stereoselective epoxidation reactions in the presence of coordinating directing groups. This stereoselectivity is most often attributed to the strong hydrogen bond complex formed between the highly electron-deficient TFPAA and a pendant oxygen or nitrogen lone pair. An example of this selectivity comes in the epoxidation of allylic amine (**40**) that results in complete *syn*-selectivity when treated with TFPAA to give **41**.[57] When **40** was treated with the more electron-rich and weaker coordinating *m*-CPBA, the *syn-anti* selectivity was a mere 3:1 (eq 25).



40 **41** (25)

In a related study, the directing group preference for TFPAA was investigated by installing groups that could compete for coordination of the peroxyacid and analyzing the resulting product mixtures.[58] From these experiments, it was concluded that compared to the NHBoc group, TFPAA coordinates more strongly to trifluoroacetate (**42**) and weakly to TBS ethers (**45**). The free homoallylic alcohol was shown to have essentially the same coordination capacity as the carbamate resulting in an equal mixture of *threo*- and *erythro*-epoxides. A strong *threo*-selectivity was observed in all cases when *m*-CPBA was used indicating a strong coordination preference for the carbamate functionality (eqs 26 and 27).



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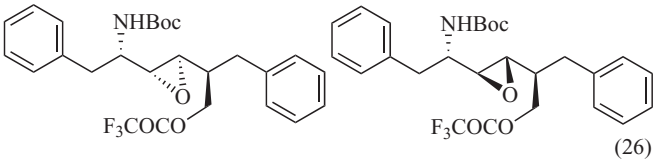
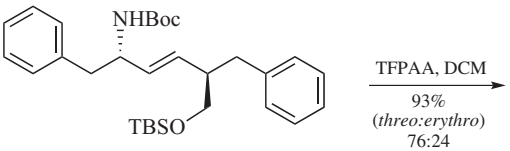


43 (*threo*) **44** (*erythro*) (26)



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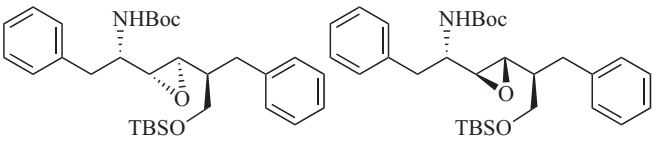
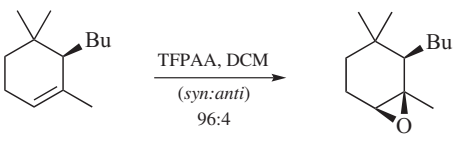
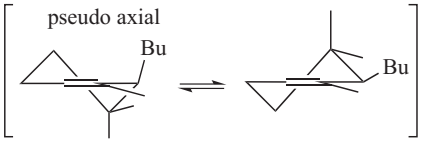


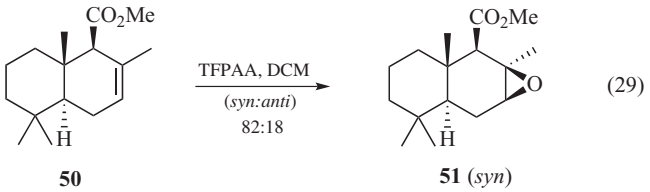
46 (*threo*) **47** (*erythro*) (27)

Conformational effects can also be exploited to give stereoselective epoxidation reactions. In a study of such conformational influences, TFPAA was strongly selective for *syn*-epoxidation of **48**, even in the absence of directing groups and despite the fact the reaction proceeds via epoxidation at the sterically congested face of the alkene to give **49**.[59] This reactivity preference is due to the pseudoaxial orientation of the butyl group in the transition state for the reaction. To test the *syn*-selectivity further, *trans*-decalin **50** in which the ester is locked in the pseudoequatorial position was treated with TFPAA and again the reaction occurred preferentially from the more hindered face to give *syn*-epoxide **51**. The stereoselectivity obtained was opposite to that of *m*-CPBA under the same conditions and was rationalized by the increased importance of electrostatic interactions in the case of TFPAA (eqs 28 and 29).

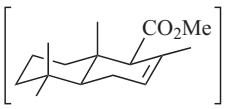


48 **49** (*syn*) (28)

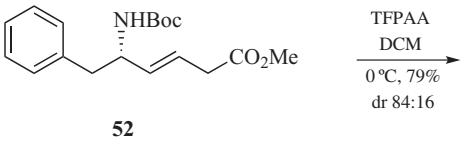




50 **51** (*syn*) (29)



The stereoselective nature of epoxidation reactions with TFPAA can be due to strongly coordinating directing groups, conformational preferences of the substrates, or a combination of the two.[60] In case of **52**, the carbamate and ester functionalities work in tandem to give the product of *syn*-epoxidation. In case of **54**, the preferred conformation in which the benzyl group resides in a staggered position causes the two directing groups to oppose one another and when in competition, the ester having the stronger coordination to TFPAA controls the facial selectivity (eqs 30 and 31).



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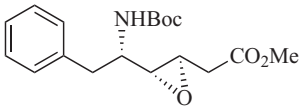
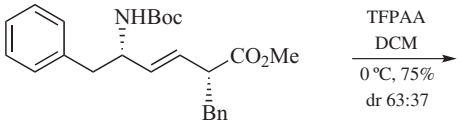


53 (30)



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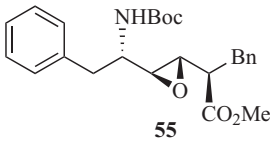
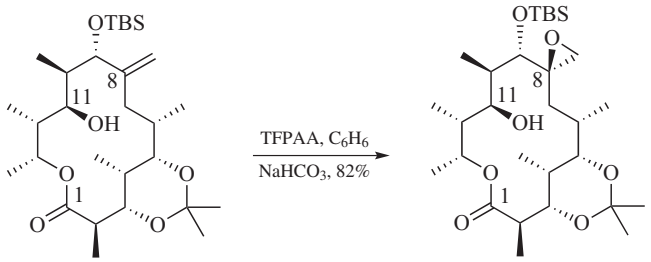
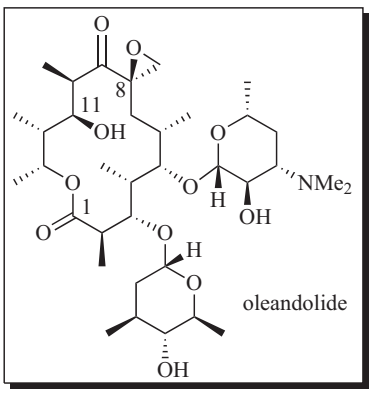


55 (31)

In addition to reversing the stereochemical outcome of olefin epoxidation reactions, TFPAA has been shown to be generally more reactive than the more commonly employed *m*-CPBA. This increased reactivity has been exploited in many synthetic approaches to complex natural products such as oleandolide,[61] deoxynojirimycin,[62] and neocarzinostatin chromophore.[63] In many cases, all other epoxidation attempts failed, while TFPAA provided the desired epoxide in high yield. During the total synthesis of oleandolide, the exocyclic olefin in **56** was stereoselectively epoxidized by treatment with TFPAA. It was also found that if the C11 hydroxyl was protected as the benzyl ether, no epoxidation could be realized, regardless of conditions. A study on the synthesis of the amino sugar analog deoxynojirimycin required the epoxidation of **58** that was only possible with TFPAA as treatment with *m*-CPBA returned only the starting olefin. Likewise, the hindered trisubstituted olefin in **60** was resistant to a number of epoxidation conditions, but succumbed when treated with TFPAA during the total synthesis of neocarzinostatin chromophore (eqs 32–34).



56 **57**



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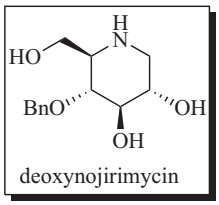
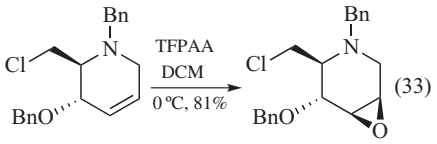
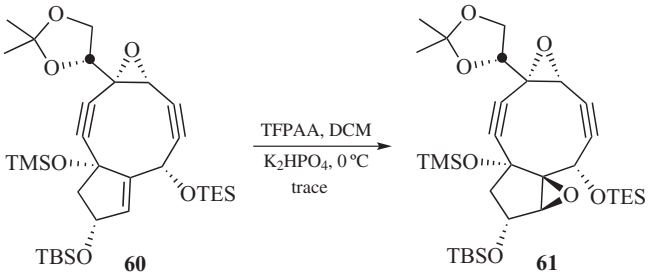


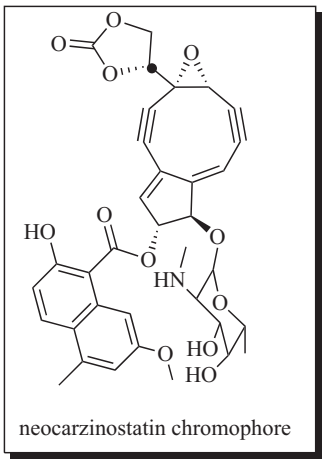


58 **59** (33)

Oxidation of Alkenes to Diols and Ketones. Recently, polyhydroxylated piperidine derivatives or azasugars have received a great deal of attention because of a wide spectrum of biological activity.[64] Insight into the biosynthetic pathways involved in their synthesis has been gained by probing various fungal strains known to produce them and then making stereochemical assignments based on direct comparison with synthetically produced samples. The *trans*-diol **63** was synthesized for this purpose by treating **62** with TFPAA in the presence of boron trifluoride etherate and was shown to be identical to the biologically derived sample (eq 35).

Arene Oxidation. A Baeyer–Villiger oxidation of 7-oxodeacetamidocolchicine (**64**) was attempted by Berg et al.[65] Unfortunately, the desired lactone was not observed when **64** was treated with TFPAA at 0 °C. Instead, phenol **65** was formed resulting from oxidation of the highly electron-rich aromatic ring. The less reactive *m*-CPBA also did not produce any of the desired lactone, only returning unreacted starting material (eq 36).





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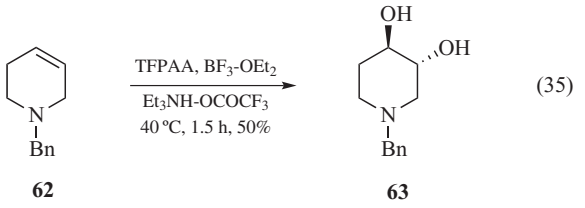

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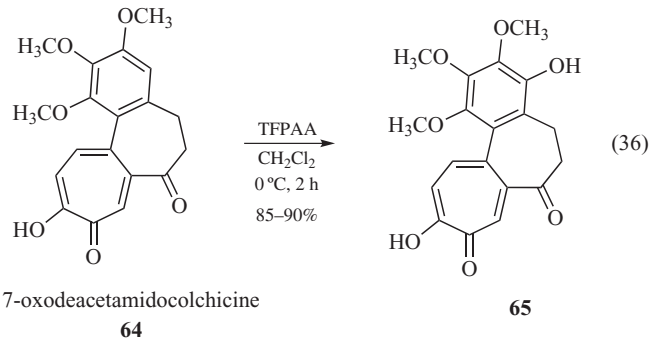
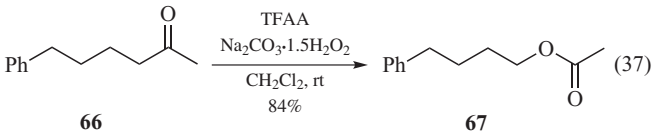


(36)

Baeyer–Villager Oxidation. The use of trifluoroperacetic acid in the Baeyer–Villiger oxidation of ketones and aldehydes has increased because of the higher reactivity compared to other peracids. Due to its increased popularity in this context, an additional method for preparing TFPAA was reported using sodium percarbonate and trifluoroacetic anhydride in which the need for an additional buffering agent is obviated by the presence of the sodium carbonate produced.[66] The TFPAA generated in situ was shown to be quite effective for the Baeyer–Villiger oxidation of a number of complex ketone substrates, including methyl ketone **66** to afford the expected ester **67** (eq 37). In order to better understand the reaction mechanism and catalytic effects, quantum chemical calculations have been performed by several groups. The first step of the generally accepted mechanism involves the addition of the peracid to the carbonyl to form the Criegee intermediate. This step has been demonstrated to be acid catalyzed and concerted in nonpolar media.[67,68] The Criegee intermediate rearranges in a concerted fashion with migration of one of the adjacent substituents. This process may also be acid catalyzed.[69] Experimentally, the second migration step was believed to be rate limiting, but calculations have found the rate-determining step to depend on the substrate, solvent, and oxidant used (eq 38).[70,71]



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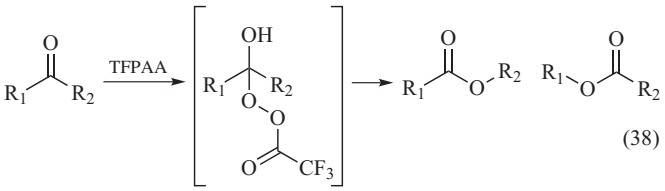
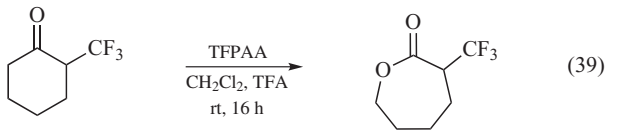


(38)

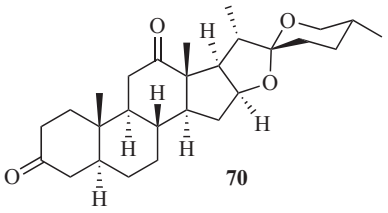
Criegee intermediate

The migrating aptitude of a substituent in the Baeyer–Villiger rearrangement is primarily related to the ability of the substituent to stabilize the positive charge formed in the transition state. However, stereoelectronic effects have been demonstrated to be important as well. Mikami and coworkers were interested in elucidating the stereoelectronic effect further with the study of α-CF_3-cyclohexanone (**68**).[72] The sole product (**69**) obtained in 89% yield corresponds to the migration of the methylene distal to the CF_3 group with TFPAA in CH_2Cl_2. This result is contrary to product obtained with α-F-cyclohexanone. The authors conclude that reaction via the less favored axially located CF_3 occurs to avoid unfavorable dipole–dipole interactions between the two CF_3 groups (eq 39).



(39)

Another study of the migrating ability of methylenes was undertaken in steroidal systems by Rivera et al.[73] The Baeyer–Villiger oxidation of 3-keto-5 α-steroid (**70**) is highly regioselective due to the increased conformational flexibility at C2. The product (**71**) is observed in high yield with both TFPAA (67%) and *m*-CPBA (77%). However, when the 3-keto-5 β-steroid (**72**) is treated under identical conditions, good regioselectivity is still observed with TFPAA (4:1), while no selectivity is observed with *m*-CPBA (1:1). The authors propose that a mixture of axial and equatorial attack by *m*-CPBA on the carbonyl group negates the selectivity imparted by the rigid steroid (eqs 40 and 41).



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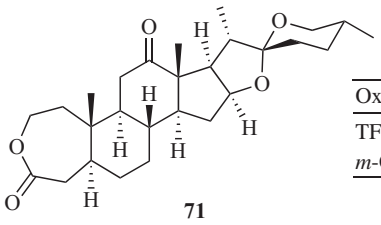
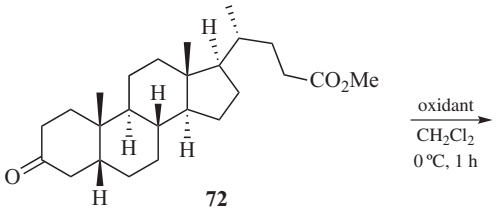


71

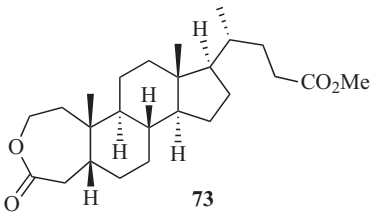
Oxidant	Yield (%)
TFPAA	67
m-CPBA	77

(40)



72

Oxidant	**73** (%)	**74** (%)
TFPAA	60	15
m-CPBA	42	42



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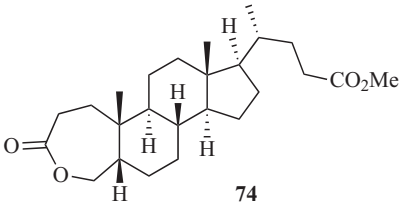
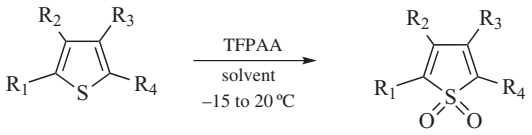


74

(41)

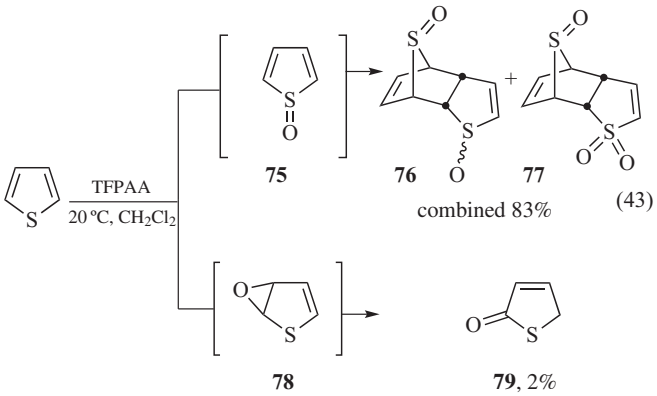
Heteroatom Oxidations. The oxidation of thiophenes to thiophene dioxides using TFPAA was first described by Liotta and Hoff,[6] but the utility and mechanism of this transformation was not fully investigated. The substrate scope of this transformation was found to be quite broad and high yielding.[74] For the electron-rich thiophenes, the oxidation was conducted in a dichloromethane/acetonitrile mixture in less than 1 h (eq 42, entry 1). For thiophenes containing a single electron-withdrawing group, the oxidation was performed in acetonitrile or trifluoroacetic acid, and still produced the dioxide in high yield (entry 2). When the oxidation was done on thiophenes containing two electron-withdrawing groups, the oxidation needed to be performed in trifluoroacetic acid for several days, but still produced the dioxide in a synthetically useful yield (entry 3).



(42)

Solvent	R_1	R_2	R_3	R_4	Yield (%)
CH_2Cl_2/CH_3CN	Ph	H	Ph	H	98
CH_3CN	Cl	H	CO_2H	Cl	80
CF_3CO_2H	H	CN	H	CN	45

The mechanism of the oxidation of thiophene by peracids, such as TFPAA, was investigated by Treiber et al.[75] They found that treatment of thiophene with substoichiometric amounts of TFPAA formed the thiophene-*S*-oxide. This intermediate could not be isolated and instead underwent a Diels-Alder dimerization to form **76** and a more oxidized adduct **77** in a combined yield of up to 83% based on NMR. Competing with the heteroatom oxidation was formation of thiophene-2-one (**79**). This by-product is believed to be formed by arene oxidation and the intermediacy of thiophene-2,3-epoxide (**78**) (eq 43).



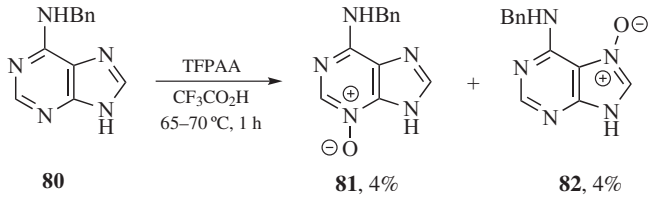
75 **76** **77**

combined 83%

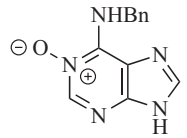
(43)

78 **79**, 2%

As previously mentioned, simple heteroaromatic systems can be selectively mono-oxidized with TFPAA. The oxidation of a purine, which contains multiple sites of reactivity, was found to be more challenging than simple heteroarenes. Specifically, treatment of N^6-benzyladenine **80** with TFPAA in trifluoroacetic acid as a solvent produced both the N(3)-oxide (**81**) and the N(7)-oxide (**82**).[76] Upon extensive purification, both products were obtained in 4% yield. The regioselectivity for this transformation is not well understood, but gives a contrasting result to the 35% yield of the N(1)-oxide **83** produced with *m*-CPBA (eq 44).



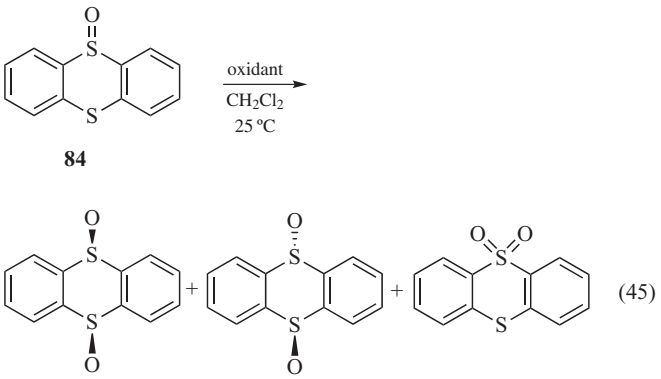
80 **81**, 4% **82**, 4%



(44)

83, 0%

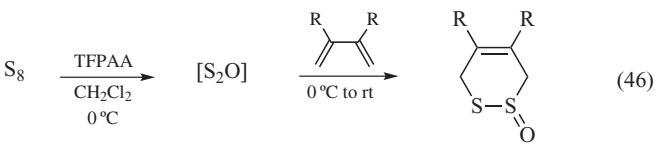
Thianthrene 5-oxide (SSO, **84**) is an established mechanistic probe for determining the electrophilic/nucleophilic character of an oxidant. The more electron-rich sulfide undergoes oxidation with electrophilic oxidants to give two isomeric bis(sulfoxides) (*cis*-**85** and *trans*-**86**). Alternatively, the sulfoxide can also undergo oxidation with electrophilic or nucleophilic oxidants to give the sulfone (**87**). TFPAA causes rapid oxidation at the sulfide site to give the more theromodynamically stable *cis*-product (**85**).[77] Notably, formation of TFPAA in situ using trifluoroacetic acid (TFA) and urea hydrogen peroxide (UHP) forms a similar product distribution. Other commonly used electrophilic oxidants such as dimethyldioxirane (DMDO) and *m*-CPBA favor the *trans*-sulfoxide (**86**) along with small but significant amounts of the sulfone. Finally, using *m*-CPBA under basic conditions gives the sulfone product **87** with high selectivity (eq 45).



84 → **85** + **86** + **87** (45)

	Product ratio		
Oxidant	**85**	**86**	**87**
TFPAA	75	23	1
TFA/UHP	67	32	1
DMDO	3	90	7
m-CPBA	20	67	12
m-CPBA/NaOH	0	0	100

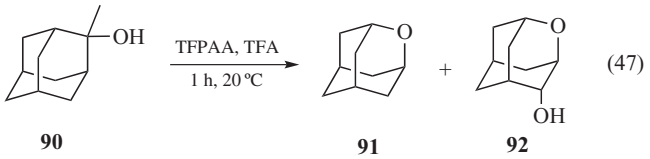
The synthetic use of disulfur monoxide has been limited because a simple synthesis from inexpensive materials was lacking. Ishii et al. have overcome this limitation by discovering that S_2O can be synthesized by directly oxidizing elemental sulfur (S_8) with TFPAA.[78] The resultant disulfur monoxide can be trapped by dienes to produce the expected Diels–Alder adducts **88** and **89** in 40%–37% yield, respectively (eq 46).



(46)

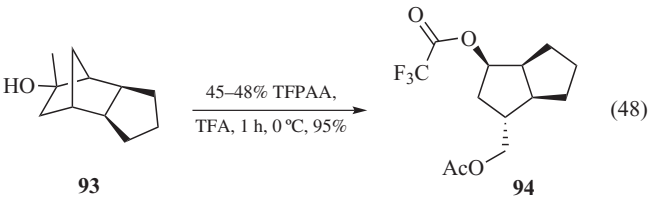
R = Me (**88**), 40%
R = Ph (**89**), 37%

Miscellaneous Reactions. The compact and structurally complex architecture of adamantane-based tertiary alcohol (**90**) displays unique reactivity when treated with TFPAA to generate oxaadamantanes.[79] The process involves a Criegee rearrangement followed by Baeyer–Villiger oxidation and subsequent ring closure via carbocation attack or epoxide opening to give **91** and **92** (eq 47).



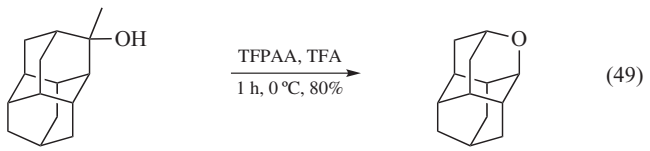
90 → **91** + **92** (47)

In order to gain a better understanding of the scope and limitations of this process, other highly compact cage-like systems were probed. For example, the bridged bicyclic alcohol **93** was treated with TFPAA in the presence of TFA. In this case, a similar rearrangement took place involving iterative oxygen insertion reactions made possible by the formation of highly stabilized oxonium ion intermediates.[80] In this instance, the only product formed results from the strain release opening of the bridged bicyclic system to give the fused and highly oxygenated **94** (eq 48).



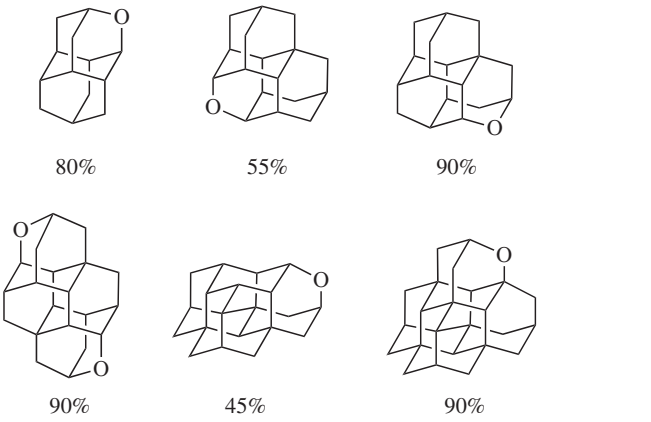
93 → **94** (48)

Various other diamond-like lattices have subsequently been shown to undergo the same reaction to produce oxygen-doped nanodiamonds.[81] Due to the additional steric bias in these systems, no products were observed resulting from epoxide opening as was previously reported in the simpler adamantane system. The reaction was shown to be quite general and high yielding regardless of the complexity of the system (eq 49).



(49)

Oxygen-doped nanodiamonds formed

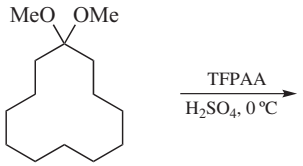


80% 55% 90%

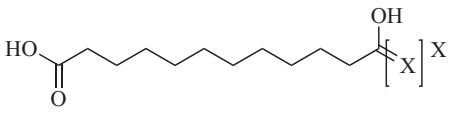
90% 45% 90%

A final application of TFPAA is its ability to oxidize cycloalkanone acetal (**95**) to the corresponding acyclic dicarboxylic acid

(**96**) or the more reduced alcohol carboxylic acid (**97**).[82] The process was shown to be rather general in that it could also be achieved with performic and peracetic acids in comparable yields (eq 50).



95



(50)

Related Reagents. *m*-Chloroperbenzoic Acid; Hydrogen Peroxide–Urea; Peracetic Acid; Perbenzoic Acid.

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