Elemental Fluorine and HOF·CH_3CN in Service of General Organic Chemistry

Shlomo Rozen*[a]

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At present, HOF·CH_3CN complex is the best oxygen transfer agent that chemistry has to offer. It is readily made by passing dilute fluorine through aqueous acetonitrile and does not require any isolation or purification. It is stable in aqueous acetonitrile solution for a few hours at room temperature, providing ample opportunities for various reactions. Epoxidation of regular olefins as well as of very electron-depleted ones proceeds smoothly. HOF·CH_3CN transfer oxygen also to heteroatoms, especially sulfur and nitrogen. Even very electron-depleted sulfides such as R_fSAr that are very difficult to oxidize, are converted into the respective sulfones in a matter of minutes. On the other hand, since the reaction conditions are very mild, the reagent can oxidize various thiophenes and amino acids to the corresponding *S*,*S*-dioxides and α-nitro acid derivatives. HOF·CH_3CN was also instrumental in ending the 50 years quest for making the elusive 1,10-phenanthroline *N*,*N*-dioxide and for the novel transformation of azides to nitro derivatives. The use of BrF_3 for making symmetric esters and of *t*BuOF as an electrophilic *tert*-butoxylation agent is also mentioned.

Introduction

Elemental fluorine was isolated in 1886 by Moissan who was awarded a Noble prize for this achievement.[1] Moissan himself employed this element in his work with organic substrates, but the results were such that a whole generation had to pass before a second set of experiments took place.[2] High dilution and low temperature were the key for better control, and some interesting nonviolent reactions were recorded.[3] Still the interest in this reagent remained very limited and many legends and prejudice were steadily fabricated to a point that practically no organic chemist was ready to experiment with this "dangerous" element. The Second World War generated a lot of interest in fluorine containing compounds, but F_2 was again used mainly in the inorganic branch of chemistry. In the mid 1950s, the real boom in fluoroorganic chemistry started with Fried's discovery that fluorocortisone is much more active than cortisone itself.[4] The following decades were witnesses to many thousands of publications describing all aspects of fluoroorganic chemistry such as polymers, solvents, surfactants, drugs, compounds essential for diagnostics such as PET, artificial blood, agriculture fluoroorganics and anesthetics to mention just a few. Still, almost all of these numerous works relied on sources such as HF and metal fluorides offering nucleophilic fluorine species. Very rarely elemental fluorine was seen as a tool for introducing this atom into organic molecules.[5]

[a] School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University,
Tel-Aviv 69978, Israel
Fax: +972-3-6409293
E-mail: rozens@post.tau.ac.il

Shlomo Rozen was born in 1942 in Bulgaria and arrived to Israel as a small child. He received his B.Sc., M.Sc. and Ph.D. from the Hebrew University of Jerusalem, under the supervision of the late Ernst D. Bergmann, the pioneer of fluorine chemistry in Israel, and I. Shahak. He spent 3 years in the Research Institute for Medicine and Chemistry, Cambridge, MA. with D. H. R. Barton, R. H. Hesse and M. M. Pechet, where he started working with elemental fluorine. In 1976 he joined the School of Chemistry at the Tel Aviv University were he assumed the position of Professor in 1989. In 1999, he became a Josef Kryss professor in Organic Chemistry and held the position of the Head of the School of Chemistry from 1997 until 2001. He is the recipient of "Teva Founders" award, of the 2005 ACS Award for Creative Work in Fluorine Chemistry and of the Israel Chemical Society 2004 Award. For many years, he was a visiting scientist at the Central Research Department of the DuPont Company in DE, USA. His main goal in chemistry is to demonstrate that elemental fluorine can be a very useful reagent in general organic chemistry, as well as in fluorine chemistry, and chemists should discard their unjustified fear and prejudice against this long known but somewhat neglected element.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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About 25 years ago, with the encouragement of Prof. D. H. R. Barton, we started to explore the synthetic potential of this element.[6] Soon after, it was clear that F_2 (1–20% diluted with nitrogen) and reagents generated in situ from it have enormous synthetic potential.[7] Still, the process of convincing chemists, as well as some reviewers of scientific papers, that it is possible to routinely use F_2 for reactions with high specificity, was quite slow and tedious. With time, however, progress has been made and our group took active role in bringing this element to the consciousness of many chemists. In 1988, we published our first "account"[8] dealing with this subject, followed by several other reviews summarizing the progress in several fields of fluoroorganic chemistry whose starting point was elemental fluorine.[9–11]

While it was not easy to convince people to use F_2 for selective fluorinations, trying to convince them to use this element for general organic synthesis leading to fluorine-free products, could categorize the promoter of such an idea as a member of a group suggesting to turn sand into gold. Yet, with time, this field gained a respectable status as well, and in 1996, we published another "account" dealing with exactly this subject – using F_2 for constructing fluorine-free organic compounds that are either very difficult or even impossible to otherwise make.[12]

Today, although F_2 is not yet a common reagent found in each and every lab, people are much more receptive to the idea that the most reactive element of the periodic Table can be used for selective reactions. It is estimated that about 200 labs around the world are using this element at one time or another.

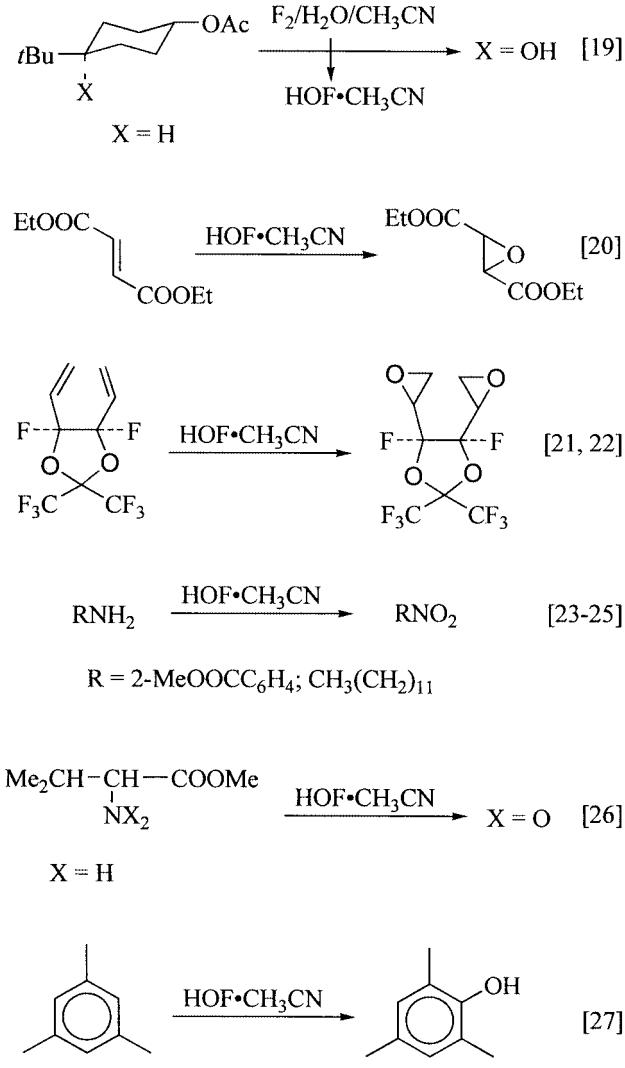
This review covers mostly our work aimed at the synthesis of fluorine-free compounds that are difficult to make or even unobtainable without the use of F_2. Most of the material presented here is not covered by the previous reviews mentioned above.

A. HOF·CH_3CN Complex, the Best Oxygen Transfer Agent Chemistry Has to Offer

1. General Background

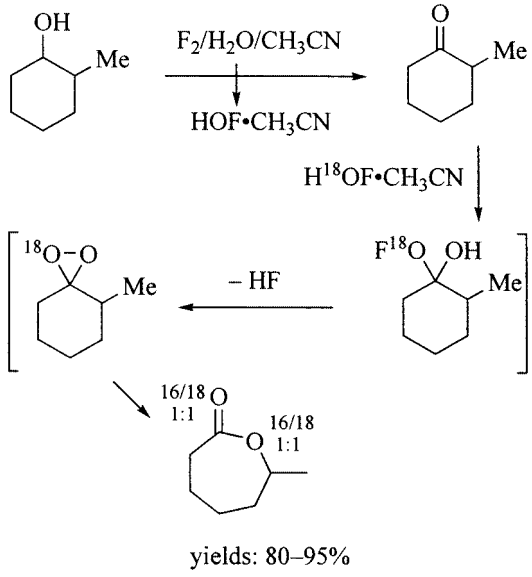
As with many discoveries, the first formation of HOF·CH_3CN complex was incidental. At the time we were examining various solvents suitable for work with F_2, and had even some hopes that there would be some media which could dissolve F_2 somewhat better then $CFCl_3$.[13,14] We did not have any luck with rigorously dried acetonitrile, but to our surprise wet CH_3CN produced an oxidizing solution which was stable for few hours at room temperature.[15] Soon after, however, we realized that the origin of this oxidizing power is not the dissolved F_2 nor this solution is a source of electrophilic fluorine, but rather a source of an electrophilic oxygen atom! After some additional research, we reached the conclusion that the oxidant is a complex between the known, but extremely unstable (and therefore not very useful) HOF,[16] and acetonitrile. This conclusion was supported by spectroscopic data and by preparation of neat HOF and complexing it with one mol equivalent of CH_3CN, recording all complexation constants.[17] An X-ray analysis of the complex was also taken at low temperature, revealing a hydrogen bond between the nitrogen atom of the acetonitrile and the hydrogen of the hypofluorous acid.[18]

Taking advantage of being the first laboratory to synthesize the relatively stable HOF·CH_3CN, we have started to investigate the scope of its usefulness in organic chemistry. We found that this reagent is able to hydroxylate tertiary sp^3 C–H centers,[19] epoxidize olefins,[20] including fluorinated ones,[21,22] oxidize aromatic[23,24] and aliphatic[25] amines, including amino acids[26] to the corresponding nitro derivatives and functionalize aromatic rings.[27] Most of these reactions require very short reaction times and proceed with excellent yields (Scheme 1).



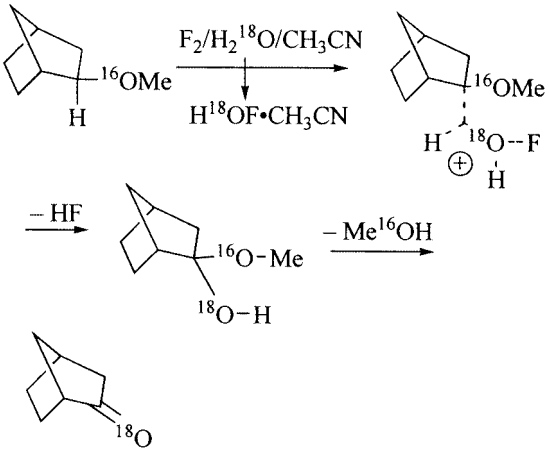
Scheme 1. One example of each reaction described in ref.[19–27].

HOF·CH_3CN is also an excellent reagent for oxidizing alcohols to ketones and the latter to esters by Baeyer–Villiger reaction through the original dioxirane mechanism proposed by Baeyer (Scheme 2).[28]



Scheme 2. Oxidizing alcohols and ketones.

We have also demonstrated that this reagent is able to perform the very rare transformation of oxidizing methyl ethers to ketones by the nonclassical 3-center-2-electrons carbonium ion mechanism placing the ^{18}O isotope in the resulting carbonyl (Scheme 3).[29]

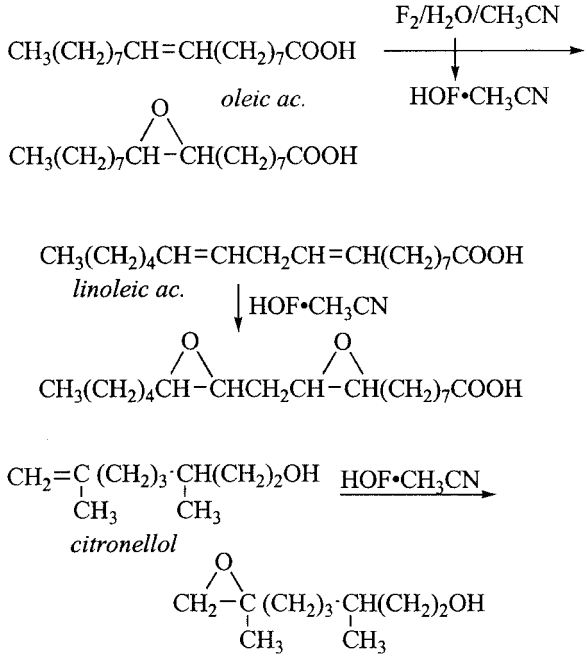


Scheme 3. Methyl ether oxidation.

2. HOF·CH_3CN – The Last Eight Years

2.1 Unique Epoxidations

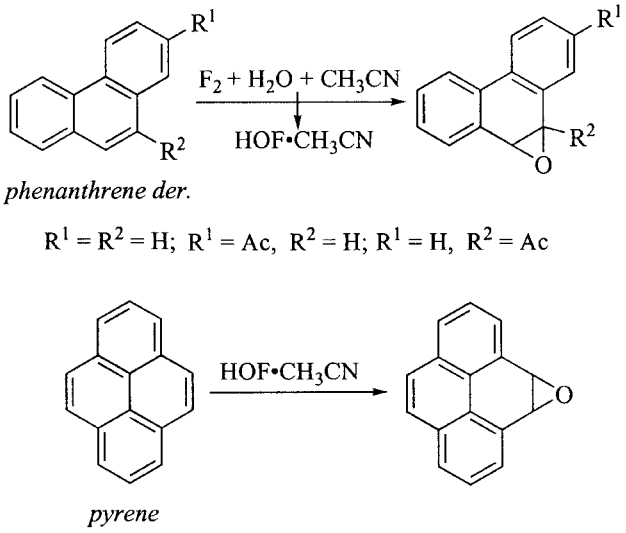
As mentioned above, the acetonitrile complex of the hypofluorous acid can successfully complete reactions even where other oxygen transfer agents encounter difficulties. One such reaction is the epoxidation of double bonds found in unprotected acids and alcohols.[30] The epoxidation of oleic acid, for example, has been studied in detail in connection with its use as a plasticizer and stabilizer for PVC and other plastics. At the time this epoxidation had barely reached 65% yield after many hours at elevated temperatures. Applying HOF·CH_3CN at room temperature resulted in the formation of the desired epoxide in 90% yield in about 10 minutes. Similarly, the bis-epoxide of linoleic acid had been made in the past by a variety of peracids, achieving yields of maximum 35% after many hours. Applying twofold excess of HOF·CH_3CN formed the diepoxide in a clean reaction (90% yield) in 3 minutes. Unsaturated alcohols such as citronellol, proved that a free hydroxy group is not an obstacle either, and the only product formed in 90% yield proved to be the citronellol epoxide. Apparently, this reagent has the advantage over alternative methods by not reacting with the free carboxy or hydroxy groups to produce peroxides, which can decompose via a radical pathway resulting in low yields (Scheme 4).



Scheme 4. Epoxidation of free acids and alcohols.

Arene oxides have been identified as the primary metabolites of polycyclic aromatic compounds produced by mammalian cells. Their biological importance has stimulated deep interest in their syntheses and chemistry.[31] Several preparation routes have been studied for these epoxidations most with unsatisfactory yields. It was of interest to examine the utilization of HOF·CH_3CN on some phenanthrene and pyrene derivatives.[32] Indeed, phenanthrene and some of its derivatives were converted into the desired corresponding oxides in high yields. It took pyrene only 5 seconds to be converted into the pyrene 4,5-oxide in 80% yield considerably higher than most other published methods (Scheme 5).

Among the tens of thousands of epoxides described, relatively few are tetrasubstituted ones and even fewer derived from electron-deficient tetrasubstituted double bonds. The HOF·CH_3CN complex, proved itself valuable in this area as well, and it was the key factor in developing the first method for making crowded tetrasubstituted epoxides directly from the corresponding olefins.[33]

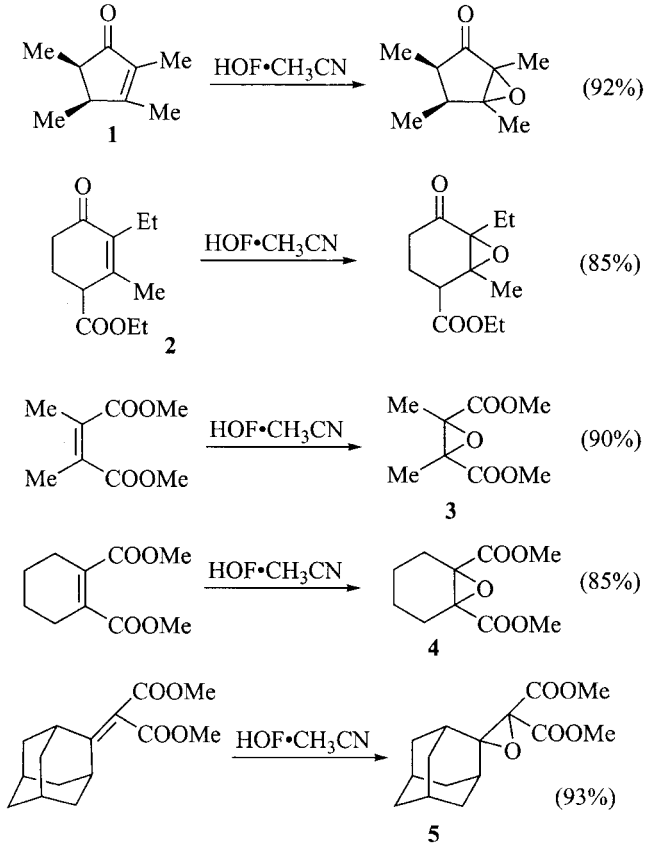


Scheme 5. Epoxidation of polyaromatics.

The epoxidation of *cis*-2,3,4,5-tetramethyl-2-cyclopentenone (**1**, Scheme 6), for example, is not known in the literature. When we treated it with basic H_2O_2, *m*CPBA or dimethyldioxirane (DMDO) for 24 hours, we got very poor yields of the epoxide. When, however, this sterically hindered, electron-deficient olefin was treated with HOF·CH_3CN it took only a minute to convert it to the desired epoxide with yields exceeding 90%. The sterically hindered double bond of ethyl 3-ethyl-2-methyl-4-oxo-2-cyclohexene-1-carboxylate (**2**) has never been epoxidized as well. In addition to the extensive steric hindrance, this olefin is much deactivated toward electrophilic attacks by the two electron-withdrawing groups in both α positions. Employing an excess of HOF·CH_3CN produced the target epoxide in high yield. Dimethyl 2,3-dimethyl-2,3-epoxymaleate (**3**), dimethyl 1,2-epoxycyclohexane-1,2-dicarboxylate (**4**), and the epoxy derivative of dimethyl adamantalidenemalonate (**5**) were all obtained in fast high yield reactions (Scheme 6).

To conclude this subject, it would be illuminating to compare a few epoxidation methods of some unique olefins with respect to reaction yields, conditions and times.[34] Tropone (**6**) has never been directly epoxidized. The only method reported for the preparation of its triepoxide involved five steps, which took 4 days and consecutive use of a number of oxidizing agents.[35] In contrast, treating **6** with the HOF·CH_3CN complex, accomplished the epoxidation of all three double bonds of this stable aromatic compound in only 15 minutes in a high yield (Scheme 7). Cyclooctatetraene (**7**) was completely epoxidized with excess of dimethyldioxirane (DMDO) but the procedure required 17 days.[36] With HOF·CH_3CN, the yield was quantitative as well, but the two and a half weeks reaction time was reduced to less than 30 seconds.

The two double bonds of 2,6-dimethylbenzoquinone (**8**) are much deactivated towards electrophilic attack by the two electron-withdrawing groups in both α-positions. Indeed, there is only one method, rather complicated, known

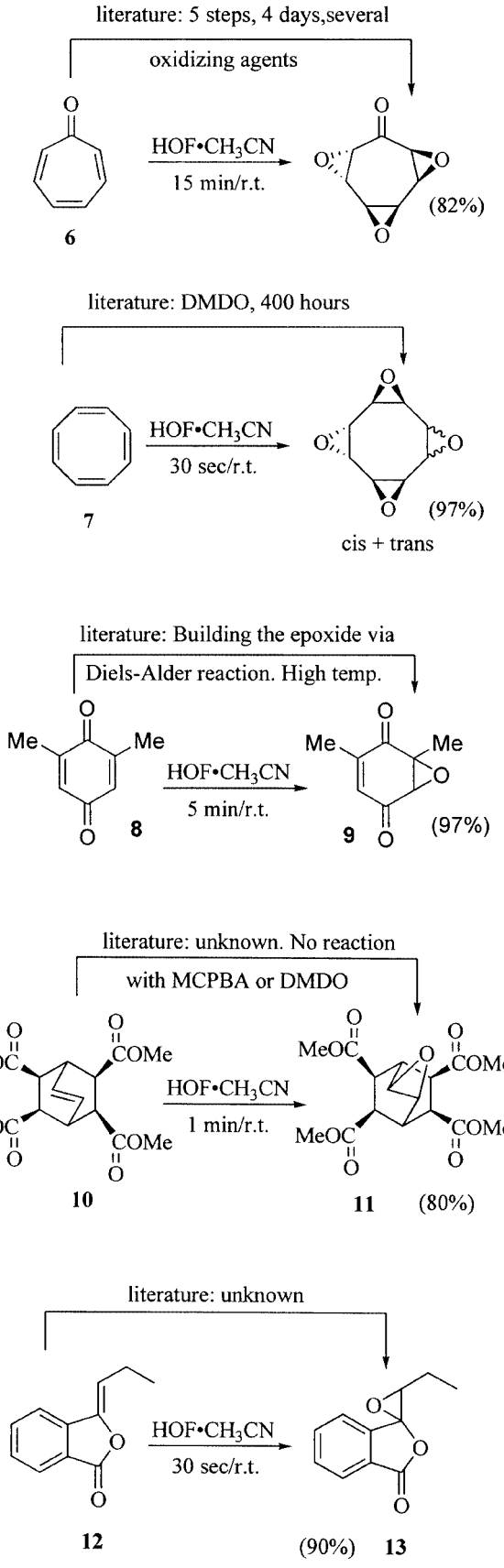


Scheme 6. Epoxidation of tetrasubstituted olefins.

in the literature for the synthesis of 2,6-dimethyl-2,3-epoxybenzoquinone (**9**) involving the epoxidation of the Diels–Alder adduct – cyclopentadienequinone followed by a high-temperature cleavage.[37] HOF·CH_3CN forms the same epoxide **9** in a single step, at room temperature, within 5 minutes and in almost quantitative yield.

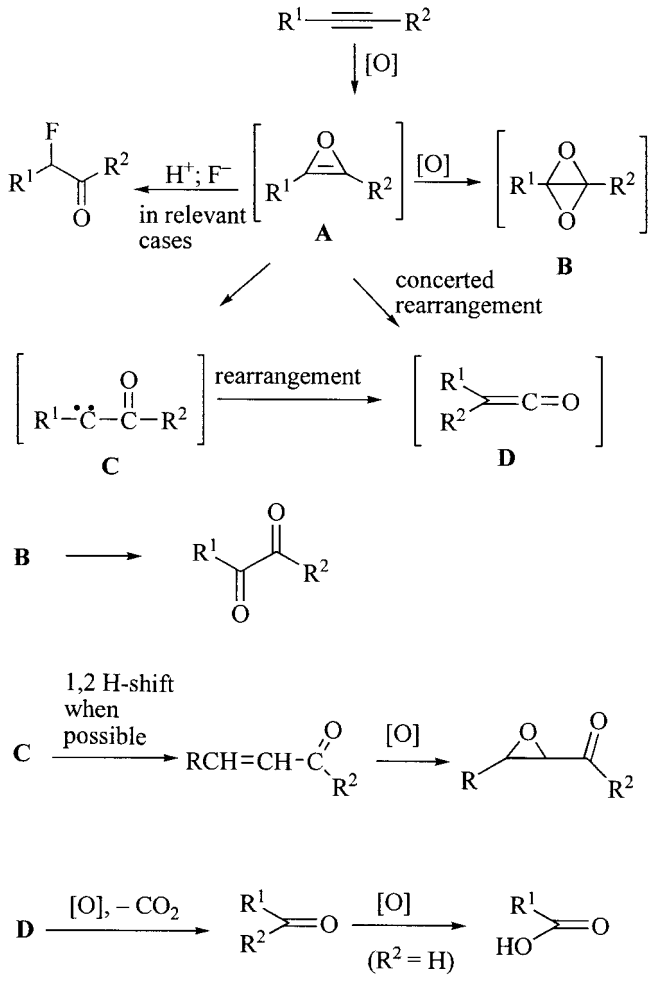
The weakly nucleophilic double bond in the oxygen-rich tetramethyl bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylate (**10**) had never been epoxidized. We have tried to epoxidize it with both *m*CPBA and DMDO, but were able to isolate only the starting material. HOF·CH_3CN converted it readily into the corresponding epoxide **11** in 80% yield. Enol ethers with low nucleophilic double bonds were also converted into epoxides. For Example, 3-propylidene-3*H*-isobenzofuran-1-one (**12**), was converted into the corresponding unknown epoxide **13** in 90% yield in less than a minute.

The action of HOF·CH_3CN on the π-centers of acetylenes was also studied.[38] Several methods for the oxidation of alkynes are described in the literature involving different types of reagents such as metal-containing oxidants,[39] hydrogen peroxide catalyzed by metal complexes,[40,41] [fluoro-(trifluoromethylsulfonyloxy)iodo]benzene[42] and dimethyldioxirane,[43] each used for a specific substrate. All these procedures have apparently a common mechanism that involves a formation of oxirene **A** which, although never isolated, was assumed to be the first step.[44] It has also been assumed that **A** can either undergo an additional oxidation to give a double epoxide **B** or lead, via concerted rearrange-



Scheme 7. Comparing epoxidation methods.

ment to an intermediate **C** and a ketene of type **D** resulting eventually into several products. The reaction with HOF·CH_3CN followed in general the same pattern, although in considerably better yields, much shorter reaction times and always under much milder conditions (Scheme 8).



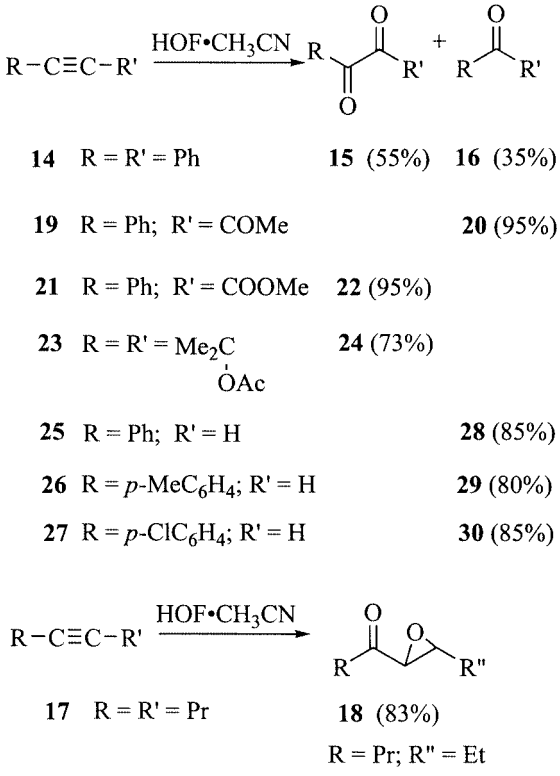
Scheme 8. Mechanism pathway for oxygen transfer to acetylenes.

The reaction of diphenylacetylene (**14**) with HOF·CH_3CN gave both benzil (**15**) as the main product (55% yield) and benzophenone (**16**) (35% yield), as a result from a loss of a carbon atom. Aliphatic acetylenes such as 4-octyne (**17**) on the other hand formed the α,β-epoxy-4-octanone (**18**) as the major product (83% yield) originating from the epoxidation of 3-octen-4-one (intermediate **C**, Scheme 8).

Using substrates bearing electron-withdrawing substituents on the triple bond, such as 4-phenyl-3-butyne-2-one (**19**) gave, via the respective intermediate **D**, 1-phenyl-1,2-propanedione (**20**), in nearly quantitative yield. In the case of methyl phenylpropyolate (**21**) where such a rearrangement is less favorable, the diketo ester **22** was obtained as the only product in very high yield.

Symmetrical acetylenes with electron-withdrawing groups also react fast and well. 2,5-Dimethyl-2,5-diacetoxy-3-hexyne (**23**), gave a single product identified as 2,5-dimethyl-2,5-diacetoxy-3,4-hexanedione (**24**) a product

formed via the bis epoxide intermediate **B**. Similar results were observed with terminal arylacetylenes, which formed benzaldehydes. Thus, the reaction of phenylacetylene (**25**), 4-(methylphenyl)acetylene (**26**) and 4-(chlorophenyl)acetylene (**27**) produced the respective aldehydes **28**–**30** in 80–85% yield (Scheme 9).



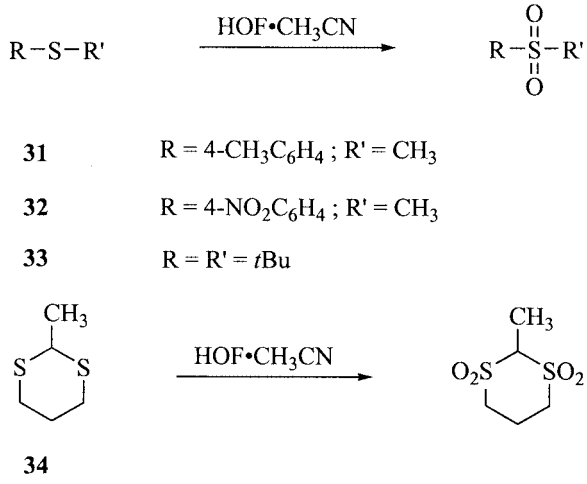
Scheme 9. Transferring oxygen atoms to acetylenes.

2.2 Reactions Around Sulfur Atoms

2.2.1 Reactions on Dialkyl Sulfides

Oxidizing sulfides to sulfones can be achieved through several well-established procedures. The transformation, however, requires either lengthy treatment with oxidants, which contain polluting heavy metals such as $KMnO_4$, or the use of various peroxides including dimethyldioxirane.[45] In addition, the reactions may require many hours and high temperatures. The HOF·CH_3CN complex is an excellent oxidant for sulfur atoms and it rapidly oxidizes most sulfides to the corresponding sulfone in very high yields at room temperature or below.[46]

Sulfides with electron-donating aromatic rings such as methyl *p*-tolyl sulfide (**31**), electron-withdrawing ones, e.g. methyl 4-nitrophenyl sulfide (**32**), aliphatic sulfides – even the sterically hindered ones like di-*tert*-butyl sulfide (**33**), were all oxidized to the corresponding sulfones in quantitative yield in 4–6 minutes. The reaction proceeds well also when two sulfur atoms were present in the same molecule as in 2-methyl-1,3-dithiane (**34**). The corresponding disulfones were obtained at room temperature in a few minutes and in higher than 90% yield (Scheme 10).

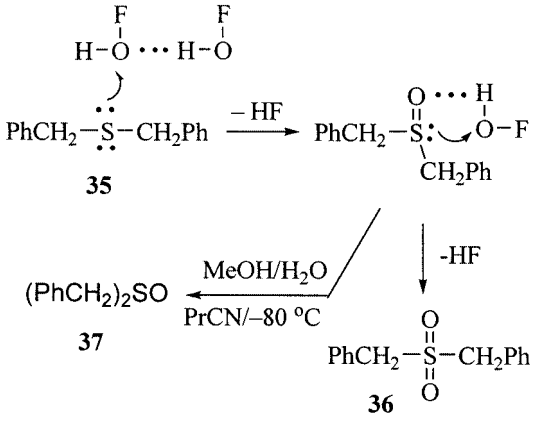


Scheme 10. Transferring oxygen atoms to sulfides forming sulfones.

A major question with this procedure is whether it is possible to stop at the sulfoxide step. When 2 mol/equiv. of the HOF·CH_3CN are used, no sulfoxide is formed. Using one mol equivalent of HOF·CH_3CN with dibenzyl sulfide (**35**) produced 45% of the sulfone **36** while another 45% was identified as the starting material. Only 10% of the dibenzyl sulfoxide (**37**) was isolated. HOF·CH_3CN possesses an acidic hydrogen that encourages the formation of clusters of the reagent's molecules through hydrogen bonding. The cluster formation is enhanced even more by the electrophilic oxygen, which also interacts with the sulfur non-bonding electrons of the newly formed sulfoxide. This close proximity allows the continuation of the oxidation to the respective sulfone before the reagent has a chance to depart from the sulfoxide vicinity and react with another sulfide molecule. Should this reasoning be valid, the use of methanol and water should increase the sulfoxide production by weakening the above interactions between the sulfoxide and the reagent. It does so, and the formation of the sulfoxide was found to be equal to the sulfone.

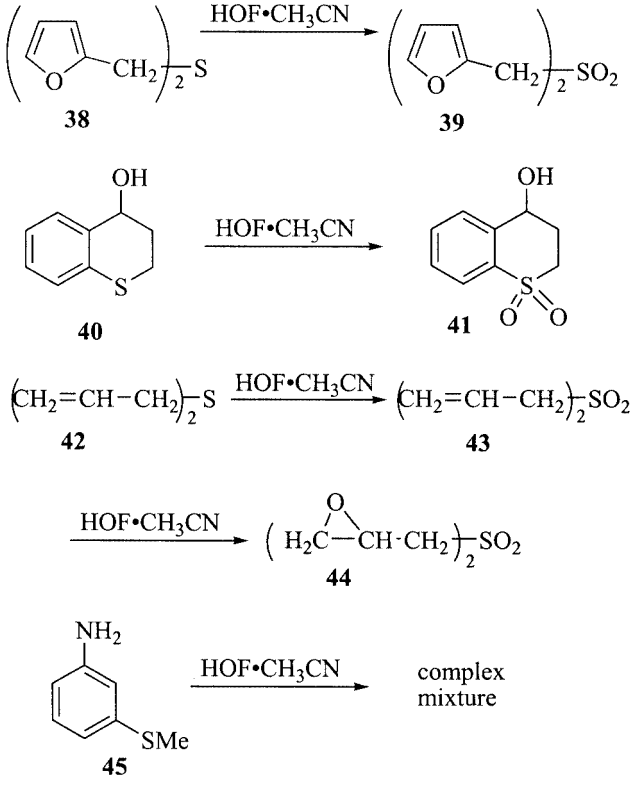
The amount of the sulfoxide **37** could be further increased by lowering the reaction temperature to –78 °C by replacing acetonitrile with propionitrile. At this temperature and conditions the oxidation of the resulting sulfoxide **37** to sulfone slows down to such an extent that after 10 minutes the dibenzyl sulfide (**35**) was converted into the sulfoxide **37** in higher than 90% yield along with only traces (less than 2%) of the sulfone **36** (Scheme 11).

In order to examine the compatibility of other functional groups with the sulfide we reacted sulfur-containing heterocyclics such as furfuryl sulfide **38** with HOF·CH_3CN. It was transformed to the corresponding sulfone **39** in 85% yield indicating that the sulfur atom reacts preferably to the π centers in the weakly aromatic **37**. Thiochroman-4-ol (**40**) was converted to, thiochroman-4-ol *S*,*S*-dioxide (**41**), in higher than 90% yield pointing to the fact that the sulfur reacts faster than the hydroxy moiety as well. For the sake of comparison, **41** had to be previously made through the reduction of the 4-keto derivatives, since oxidation of the sulfur atom affected the alcohol group too.[47] We also ex-



Scheme 11. Sulfones vs. sulfoxide formation.

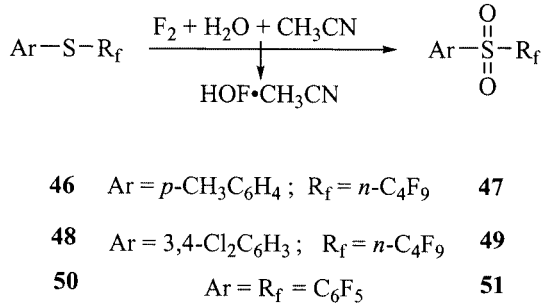
amined diallyl sulfide (**42**), which gave diallyl sulfone (**43**) leaving the double bond untouched. Only when an excess of the oxidizing complex was employed for 10 minutes, both the sulfur atom and the double bonds reacted to form bis(2,3-epoxypropyl)sulfone (**44**) in 70% yield. It seems that only amino groups could have complicated the sulfide–sulfone transformation and 3-aminophenyl methyl sulfide (**45**) gave an inseparable mixture of products arising from indiscriminating attacks on both heteroatoms (Scheme 12).



Scheme 12. Compatibility with other functional groups.

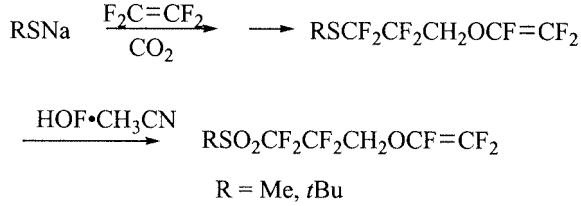
2.2.2 Reactions with Electron-Depleted Sulfides

While there are quite a few alternatives for oxidizing sulfides to sulfones, practically none existed for clean oxidation of very electron-deficient ones. There have been reports on attempts to oxidize perfluoroalkyl sulfides to sulfones with oxidants such as chromic anhydride or concentrated H_2O_2 in trifluoroacetic acid/trifluoroacetic anhydride, but even these potent oxidants were not very efficient.[48–50] The HOF·CH_3CN complex did succeed where all other oxidants failed, although relatively large excess of it was required and the reaction times could reach 10 to 30 minutes.[51] Thus, perfluorobutyl *p*-tolyl sulfide (**46**) was treated at room temperature with 4.5 mol equivalents of HOF·CH_3CN for 20 minutes to furnish the sulfone **47**. Replacing the electron-donating methyl group with electron-withdrawing ones such as chlorines did not affect the outcome and 3,4-dichlorophenyl perfluorobutyl sulfide (**48**) was converted into the sulfone **49.** Even more electron-depleted molecules, such as dipentafluorophenyl sulfide (**50**) could be converted into the desired sulfone **51**. All these reactions proceeded in nearly quantitative yields (Scheme 13).



Scheme 13. Oxidation of electron-depleted sulfides.

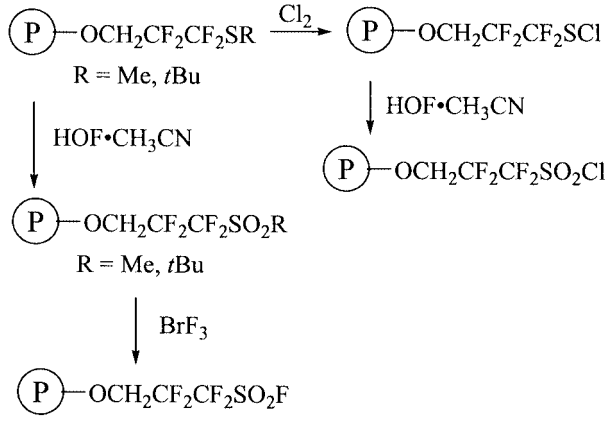
Perfluorinated ion-exchange resins (Nafions®) are used as very stable membranes and strong acid catalysts. The polymers are of general structure possessing a perfluorinated backbone for high chemical and thermal stability and side chains with sulfonate or carboxylate groups providing for cation transport. These resins are usually prepared by copolymerization of tetrafluoroethylene (TFE) with functionalized perfluorovinyl ethers. In order to prepare some more flexible polymers and make the polymerization process more efficient we made some trifluorovinyl ethers with hydrogens in the alkyl group adjacent to an oxygen atom (CF_2 = $CFOCH_2R$). The first step was to prepare such sulfur containing ether monomers, followed by homopolymerizations and copolymerizations with TFE. The role of HOF·CH_3CN was to convert the sulfide groups to the needed sulfones (Scheme 14).[52]



Scheme 14. Polyfluoroethers – monomer synthesis.

The monomers in Scheme 14 could be polymerized and copolymerized with TFE. Treating these polymers with chlorine produced the corresponding sulfenyl chloride.

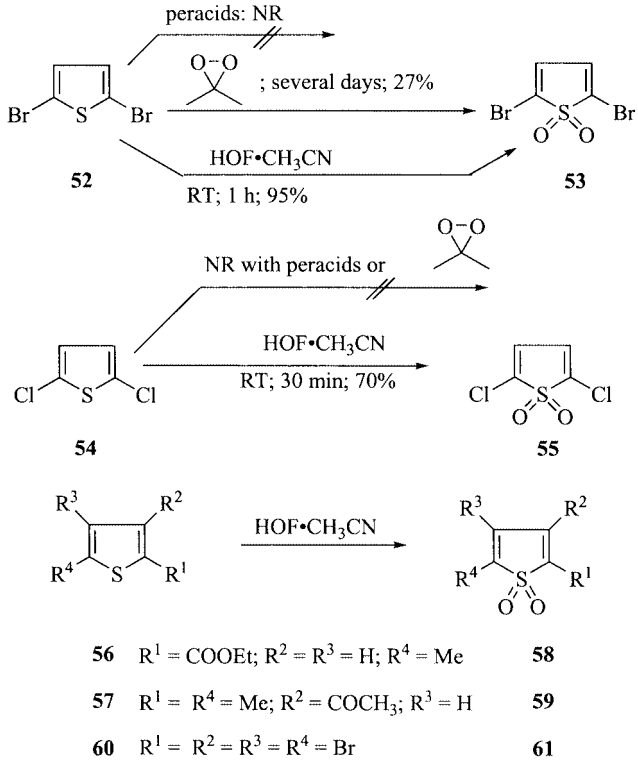
HOF·CH_3CN proved itself as effective with the polymers as with the monomers and the conversion to the desired sulfonyl chlorides proceeded with good yields. Alternatively, the alkyl sulfenyl could be oxidized first and then treated with BrF_3 producing the respective sulfonyl fluorides, again in good yields (Scheme 15).



Scheme 15. Oxidation of polymeric sulfenyls to sulfonyl halides.

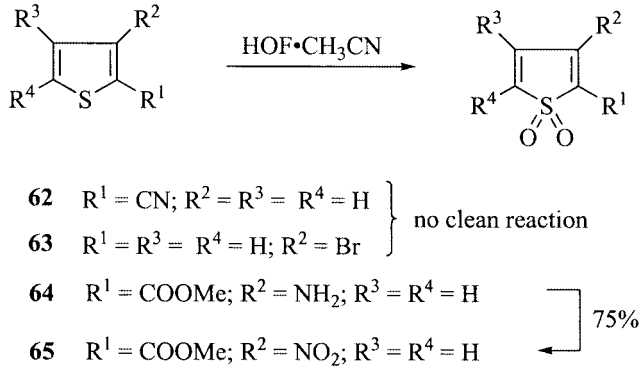
2.2.3 Reactions with Thiophenes

Sulfur-containing compounds of a different type are the thiophenes. Oxidizing the heteroatom of this system is challenging since there are two opposing factors involved. On one hand, the reaction has to overcome a substantial aromatic stabilization, requiring relatively harsh conditions. On the other hand the nonaromatic *S*,*S*-dioxide products do not enjoy such stabilization and are therefore, sensitive to Diels–Alder and other ene and diene reactions. These processes are strongly facilitated by high temperatures and prolonged reaction times. Indeed, the lack of easy availability of such dioxide compounds is the main reason for their under-developed chemistry despite the high interest they inspire.[53,54] One of the advantages of HOF·CH_3CN as an oxidant is that it is strong enough to act quickly under the mildest possible conditions.[55] Oxidation of the somewhat electron-depleted rings such as 2,5-dibromothiophene (**52**) could not be achieved with peracids and it took days for dimethyldioxirane to form the dioxide **53** in 27% yield. HOF·CH_3CN achieved this transformation in 95% yield in 20 minutes. The 2,5-dichlorothiophene (**54**), whose sulfur atom is more electron-depleted, is beyond the oxidizing power of all traditional oxidizers, but HOF·CH_3CN oxidized it at room temperature to 2,5-dichlorothiophene *S*,*S*-dioxide (**55**) in 70% yield in about 30 minutes. Similarly, this reagent was able to oxidize, for the first time, both ethyl 2-methyl-5-thiophenecarboxylate (**56**) and 3-acetyl-2,5-dimethylthiophene (**57**) to the corresponding *S*,*S*-dioxides **58** and **59** in 20 minutes and in excellent yields. Even tetrabromothiophene (**60**) was successfully converted into the tetrabromothiophene *S*,*S*-dioxide (**61**) in 20 minutes and 70% yield (Scheme 16).



Scheme 16. Transferring oxygen atoms to thiophenes.

It seems however, that in some cases, efficient and clean oxidation requires substituents on both sides of the thiophene ring, otherwise the unsubstituted double bond will either take part in Diels–Alder reaction or be epoxidized. Thus, 2-cyano- (**62**) and 3-bromothiophene (**63**) gave mainly unidentified dimeric products. Other 2,3-disubstituted thiophenes tended to produce a mixture of the desired *S*,*S*-dioxide with the epoxythiophene *S*,*S*-dioxide. It should be noted that unprotected amino groups are also not compatible with this oxidation since the amino group is quickly oxidized to the corresponding nitro derivatives (e.g. **64** to **65**) as shown in Scheme 17.



Scheme 17. Transferring oxygen atoms to thiophenes II.

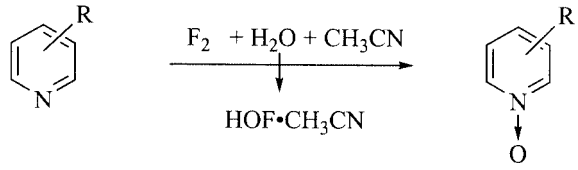
2.3 Reactions around Nitrogen Atoms

2.3.1 Reactions around Tertiary Nitrogen Atoms

Tertiary amine *N*-oxides constitute a class of compounds that assume increasing importance. They are used in a vari-

ety of processes as well as in final products such as fiber preparation,[56] hair tonics,[57,58] topical pharmaceuticals,[59] and cellulose solvents.[60] The increased attention these compounds command encouraged us to examine the preparation of aromatic as well as aliphatic *N*-oxides by the HOF·CH_3CN complex.[61]

Pyridines react quickly to produce the *N*-oxide derivatives in good yields. Pyridine (**66**) itself was transformed into its *N*-oxide in 85% yield within less than five minutes. Rings substituted with either strong electron-donating groups such as 2-methoxypyridine (**67**) or electron-withdrawing ones such as 2-cyano- (**68**), also proved to be excellent substrates producing the respective *N*-oxides. It should be noted that when there is a competition between a double bond and a nitrogen atom the latter is activated first. Thus, 4-vinylpyridine (**69**) was converted in 70% yield to the corresponding *N*-oxide without affecting the olefin. Another interesting example is 4-(dimethylamino)pyridine (**70**) with its two tertiary nitrogen atoms. Under the mild reaction conditions applied, only the ring-nitrogen atom was oxidized to give the 4-(dimethylamino)pyridine *N*-oxide in 70% yield (Scheme 18).

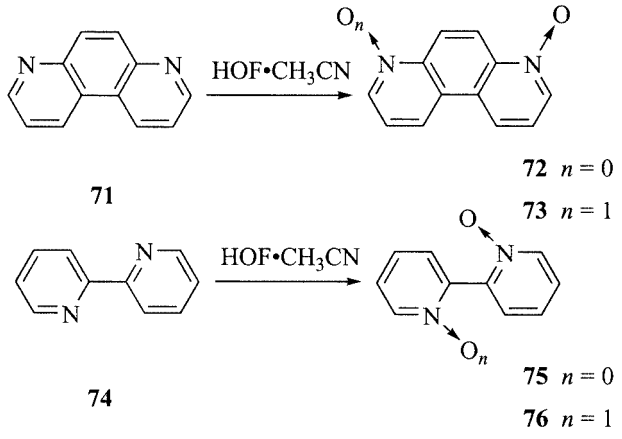


66	R = H	(95%)
67	R = 2 - OMe	(70%)
68	R = 2 - CN	(98%)
69	R = 4 - $CH=CH_2$	(70%)
70	R = 4 - NMe_2	(70%)

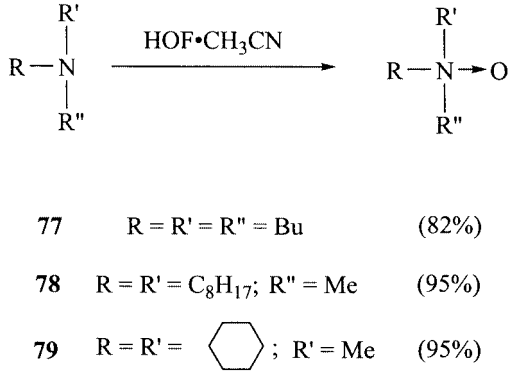
Scheme 18. Synthesis of pyridine *N*-oxides.

More complex polycyclic heteroaromatic derivatives were also readily converted into their *N*-oxides. Reacting 4,7-phenanthroline (**71**), for 10 min, gave the mono *N*-oxide **72** in 80% yield. However, increasing the excess of HOF·CH_3CN complex resulted in the formation of di-*N*-oxide **73** in 70% yield. Similarly, 2,2-bipyridine (**74**) was oxidized to the mono-*N*-oxide **75** and the di-*N*-oxide **76** in 80%, depending on the concentration of the reagent (Scheme 19).

The reaction is by no means restricted to pyridine derivatives. Tertiary aliphatic and alicyclic amines have proved to be excellent substrates as well. Tributylamine (**77**) gave the corresponding *N*-oxide in 82% yield. Similarly dioctyl methylamine (**78**) was converted in 95% yield to its *N*-oxide, an important industrial chemical, which was a subject of several patents.[62,63] Among other successfully reacted tertiary amines we will also mention (dicyclohexyl)methylamine (**79**) whose *N*-oxide is used to dissolve cellulose (Scheme 20).[64]



Scheme 19. Synthesis of aromatic *N,N′*-dioxides.

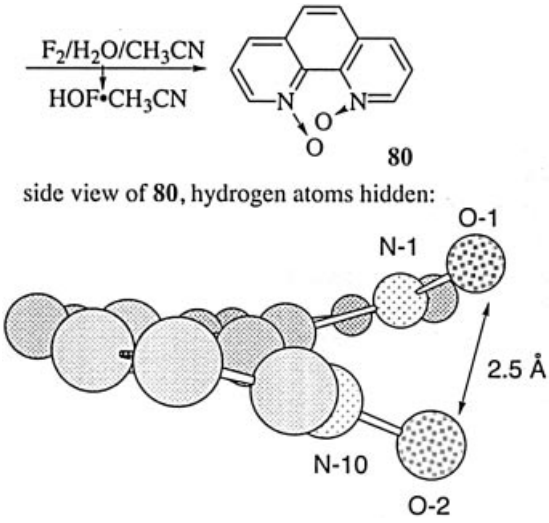


77	R = R' = R" = Bu	(82%)
78	R = R' = C_8H_{17}; R" = Me	(95%)
79	R = R' = ⬡; R' = Me	(95%)

Scheme 20. Synthesis of aliphatic *N*-oxides.

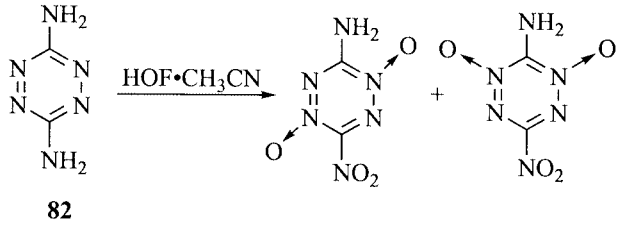
The successful preparation of *N,N*-dioxides such as **73** and **76** introduced us to the fascinating story of 1,10-phenanthroline *N,N*-dioxide (**80**)[65] which starts more than 50 years ago. Many chemists tried to make **80** including Corey[66] and Woodward[67] but got only the mono *N*-oxide. The reason for the failure of these attempts is, of course, the limited space in the bay area of the flat 1,10-phenanthroline molecule, which cannot accommodate two oxygen atoms. The arsenal of chemical reagents lacked the agent that could force the aromatic 1,10-phenanthroline out of planarity, a precondition for a successful synthesis of **80**. HOF·CH_3CN proved to be the reagent capable to accomplish this difficult task.

Reacting 1,10-phenanthroline with 1.1 mol/equiv. of HOF·CH_3CN at 0 °C for 5 minutes resulted in a good yield of the mono *N*-oxide (**81**). Increasing the amount of the reagent to 2.2 mol/equiv. produced after another 5 minutes the desired 1,10-phenanthroline *N,N*-dioxide (**80**) in higher than 60% yield (Scheme 21). It should be mentioned that the crystal structure shows that indeed, the two oxygen atoms force the whole phenanthroline skeleton out of planarity but they still interact with each other through space (2.5 Å).



Scheme 21. The synthesis of 1,10-phenanthroline *N*,*N*′-dioxides.

There is an interest in *N*-oxide derivatives also from institutions dealing with highly energetic materials. Some of these *N*-oxides could be prepared by HOF·CH_3CN. Hiskey,[68] from the U.S. Los Alamos National Laboratories, points that 1,2,4,5-tetrazines are such materials. 3,6-Diamino-1,2,4,5-tetrazine (**82**) was thus treated with HOF·CH_3CN to produce the corresponding energetic nitro *N*,*N*-dioxide derivatives (Scheme 22).

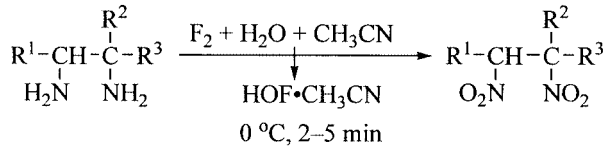


Scheme 22. Synthesis of the energetic tetrazine *N*,*N*′-dioxides.

2.3.2 Direct Synthesis of Vicinal Dinitro Derivatives

Vicinal dinitro compounds can serve as precursors for tetra-substituted olefins and electronic switching devices. However, the difficulties associated with their preparation (very low yields, use of highly toxic N_2O_4, and aromatic nitration which tend to give *meta* isomers) are serious limiting factors. Conventional oxidation of the vicinal diamino group does not work due to the "push-pull" effect generated during the oxidation process, which tends to break the central C–C bond. This fragmentation is encouraged by high temperatures and prolonged reaction times needed for such oxidations.[69] These limitations are easily overcome by the HOF·CH_3CN complex.[70]

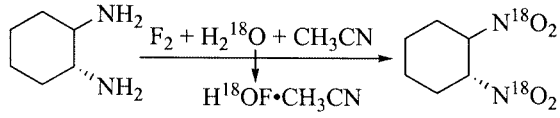
It took 3 minutes to convert 1,2-diaminopropane (**83**) to 1,2-dinitropropane (**84**) in 82% yield. For comparison, this product was previously prepared from propene and N_2O_4 in 20% yield only.[71] The reaction proceeded with tertiary amines as well, and it took only a minute to transform 1,2-diamino-2-methylpropane (**85**) to 1,2-dinitro-2-methylpropane (**86**) in 90% yield. The stereochemistry around the nitrogen-bonded carbon atoms is retained as evident from the reaction of (1*S*,2*S*)-(–)-1,2-diphenylethylenediamine (**87**), $[\alpha]_D$ = –102 converted in 95% yield to (1*S*,2*S*)-(–)-1,2-dinitro-1,2-diphenylethane (**88**), $[\alpha]_D$ = –414 (Scheme 23).



83	$R^1 = CH_3$; $R^2 = R^3 = H$	**84**	82%
85	$R^1 = H$; $R^2 = R^3 = CH_3$	**86**	90%
87	$R^1 = R^3 = Ph$; $R^2 = H$ (1*S*, 2*S*)	**88**	95%

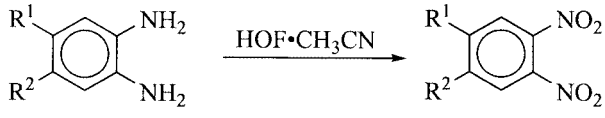
Scheme 23. Synthesis of vicinal dinitro compounds.

One of the advantages of HOF·CH_3CN is that its electrophilic oxygen originates in water, which is the most convenient source for all oxygen isotopes. We have passed fluorine through a solution of acetonitrile and $H_2{}^{18}O$ and obtained $H^{18}OF{\cdot}CH_3CN$ that was reacted with *trans*-1,2-diaminocyclohexane (**89**). The mass spectrum (cluster CI with MeOH, *m*/*z* = 183 $[M + 1]^+$)[72,73] clearly confirms that all four oxygen atoms of [all ^{18}O]-*trans*-1,2-dinitrocyclohexane (**90**) (94% yield) are the expected ^{18}O isotope. This was the first time that a compound containing four ^{18}O atoms was described (Scheme 24).



Scheme 24. Synthesis of vicinal all ^{18}O-dinitro compounds.

The oxidation proceeds well also with aromatic diamines. 4,5-Dimethyl-1,2-phenylenediamine (**91**) was brought in contact with HOF·CH_3CN for 4 min at –15 °C resulting in 4,5-dimethyl-1,2-dinitrobenzene (**92**) in 87% yield. The presence of an electron-withdrawing group on the aromatic ring reduces the nucleophilicity of the amino nitrogen atoms and the reaction of 3,4-diaminobenzophenone (**93**) proceeded with 55% yield only to give 3,4-dinitrobenzophenone (**94**) (Scheme 25).

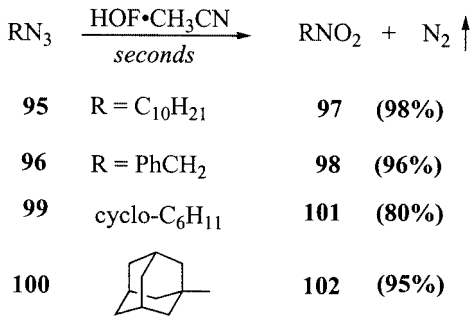


91	$R^1 = R^2 = CH_3$	**92**	87%
93	$R^1 = PhCO$; $R^2 = H$	**94**	55%

Scheme 25. Synthesis of aromatic vicinal dinitro compounds.

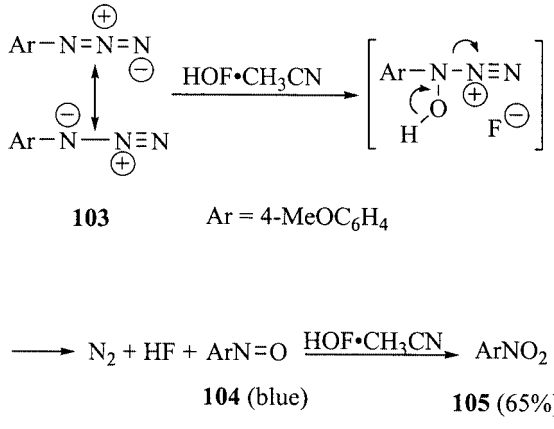
2.3.3 From Azides to Nitro Derivatives in One Step

The chemistry of azides is quite underdeveloped and mainly associated with reduction to amines. The oxidation of azides to nitro compounds was practically unknown. Since HOF·CH_3CN is indeed, a very strong electrophile it was reasonable to assume that the carbon-bonded nitrogen atom of azides would be nucleophilic enough to interact with the oxygen atom of the reagent.[74] This turned to be so, and reacting 1-azidodecane (**95**) or benzyl azide (**96**) with HOF·CH_3CN resulted in immediate N_2 release and formation of 1-nitrodecane (**97**) and α-nitrotoluene (**98**) in higher than 95% yield. Secondary and tertiary azides were no exception. Cyclohexyl (**99**) and 1-azidoadamantane (**100**) where converted to nitrocyclohexane (**101**) and 1-nitroadamantane (**102**) in 95% yield in seconds (Scheme 26). This work was considered to be of special interest and was highlighted in ref.[75]



Scheme 26. From aliphatic azides to nitro derivatives.

This oxygen transfer process works also with aromatic azides although it is not as practical as with the aliphatic ones mainly because these azides are usually made from the corresponding amines, which by themselves can be directly oxidized by HOF·CH_3CN to the nitro derivatives. In general, aromatic azides react much slower than their aliphatic counter-parts but the reaction with 4-methoxyazidobenzene (**103**) was of special interest since it could shed some light on the mechanism of this oxidation. Its reaction was considerably faster than that of azidobenzene (10 min vs. 1 h), but the important point was the development of an intensive blue color of the nitroso derivative (**104**), which disappeared in a few seconds forming eventually 4-nitroanisole (**105**) in 65% yield. These and other observations support a two-step reaction mechanism. The first and the slower step is an attack on the relatively electron-rich nitrogen by the reagent's electrophilic oxygen atom forming a nitroso derivative accompanied by a release of N_2 and HF. Consequently, the respective nitroso reacts fast with an additional molecule of HOF·CH_3CN to form the desired nitro compound (Scheme 27).



Scheme 27. On the mechanism of turning azides to nitro derivatives.

2.4 Hydroxylations α to Carbonyls

2.4.1 Hydroxylations α to Ketones

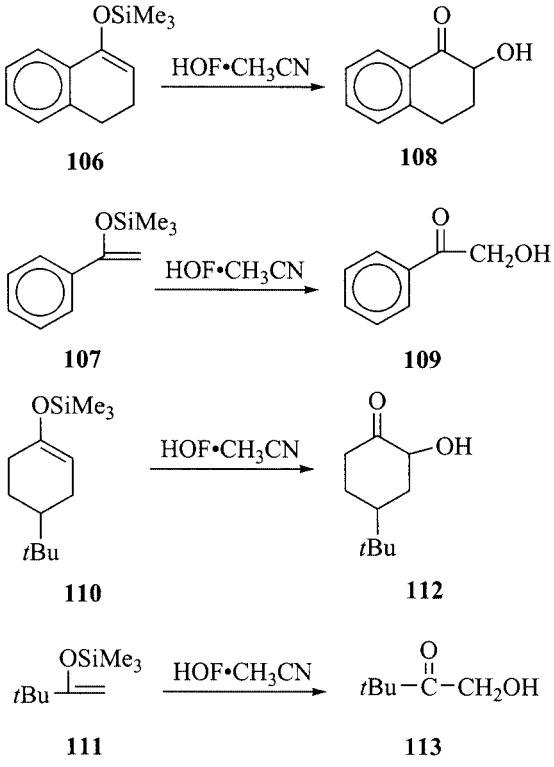
The synthesis of α-hydroxy carbonyl derivatives has been of continuous interest to organic chemists for a long time. Some of the more recently developed methods make extensive use of heavy metal containing oxidants such as CrO_2Cl_2,[76] but of course, the goal is to minimize the use of these potentially contaminating agents. HOF·CH_3CN was found to be very effective in transferring its electrophilic oxygen to enol derivatives of various ketones.[77]

Both tetralone and acetophenone trimethylsilyl enol ethers (**106**, **107**) were reacted at room temperature with a twofold excess of HOF·CH_3CN forming α-hydroxytetralone (**108**) and α-hydroxyacetophenone (**109**) in higher than 90% yield, each in a matter of 5 to 10 minutes. The aliphatic silyl enol ethers of the 4-*tert*-butylcyclohexanone and of the pinacolone (**110** and **111**) also reacted successfully to produce *trans*-2-hydroxy-4-*tert*-butylcyclohexanone (**112**) and α-hydroxypinacolone (**113**) in almost quantitative yield, at room temperature in 10 minutes (Scheme 28).

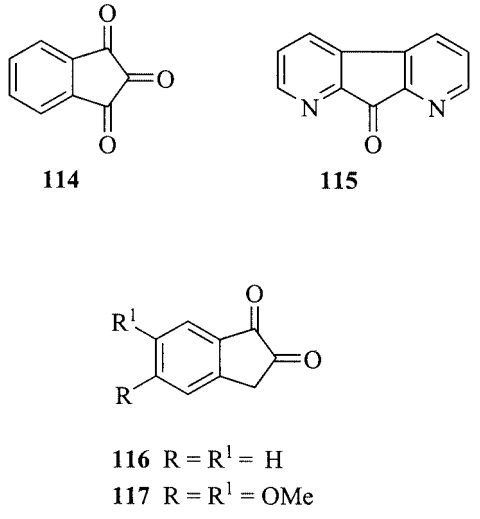
Indanediones present a special case in the category of hydroxylations α to ketones.[78] Most police departments use ninhydrin (**114**) and 1,8-diazafluorene-9-one (**115**) for the visualization of latent fingerprints on paper items. These reagents suffer from some deficiencies, such as high cost and low solubility in nonpolar solvents, so the search for better ones continues. Recently, it was discovered that 1,2-indanedione (**116**), and some of its derivatives, particularly 5,6-dimethoxy-1,2-indanedione (**117**), can visualize latent fingerprints by direct fluorogenic reaction at least as efficiently as **114** and **115** and in some cases considerably better (Scheme 29).[79]

Until not long ago the best method for preparing 1,2-indanediones was the hydrolysis of 2-oximino-1-indanones prepared from 1-indanone derivatives.[80] Although successfully employed for the preparation of **116** and **117**, it failed when attempting to prepare other potentially interesting derivatives such as the unknown 3-methyl-1,2-indanedione (**118**) and benzo[*f*]indane-1,2-dione (**119**). We hoped that the combination of the exceptional oxygen transfer ability of HOF·CH_3CN along with the very mild reaction conditions associated with it would help us overcome most difficulties encountered by all previously described methods.

The trimethylsilyl enol ethers of 1-indanone, 3-methyl-1-indanone and benzo[*f*]indan-1-one (**120**–**122**) were readily

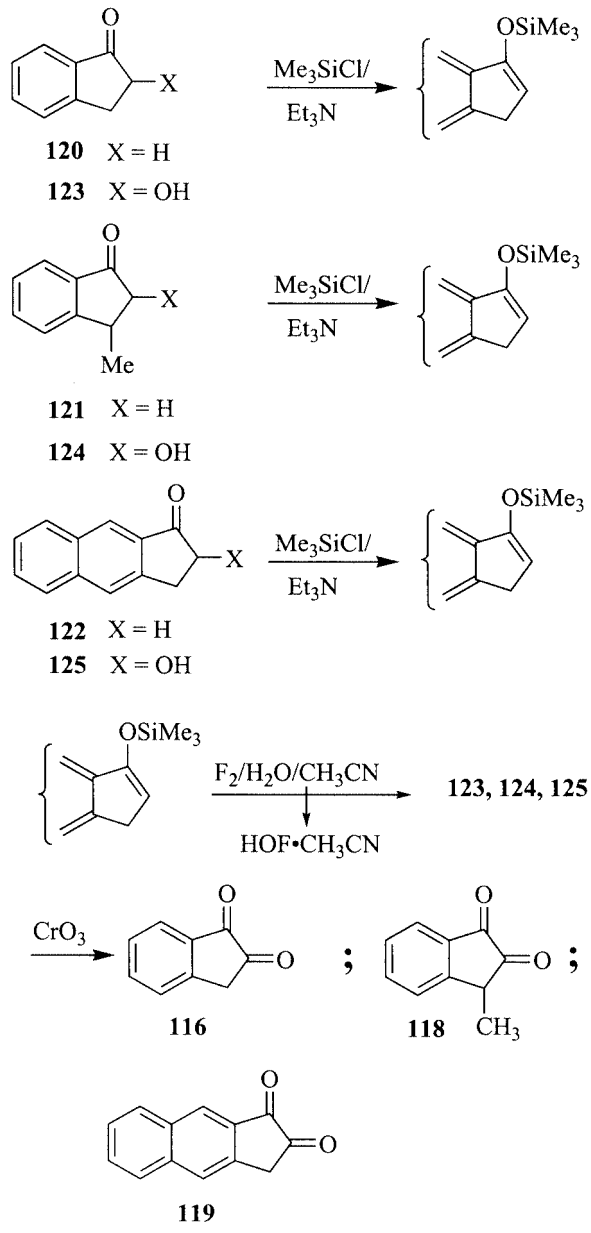


Scheme 28. α-Hydroxylation of ketones.



Scheme 29. Reagents for fingerprints visualization.

prepared and then reacted with HOF·CH_3CN to form the respective 2-hydroxy-1-indanone derivatives **123**–**125** in very good yield. The reagent was not able, though, to further oxidize the hydroxy group since alcohol oxidation with HOF·CH_3CN proceeds through an abstraction of the geminal hydrogen that in these cases form relatively electron-deficient C–H bonds.[28,29] The hydroxy group, however, could be easily oxidized with chromic acid (Jones reagent) forming the desired **116, 118** and **119** in 65% overall yield (Scheme 30).



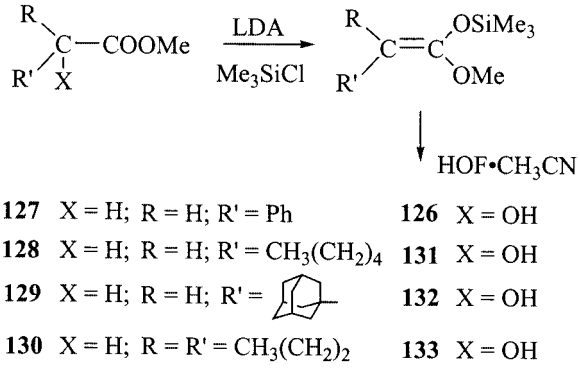
Scheme 30. Synthesis of 1,2-indanediones.

The above and additional indanediones, have been tested for fingerprint visualization with very promising results.[81] The chemistry, as well as the detection techniques were also a base for a reportage in TIME magazine.[82]

2.4.2 Hydroxylations α to Carboxylic Esters and Acids

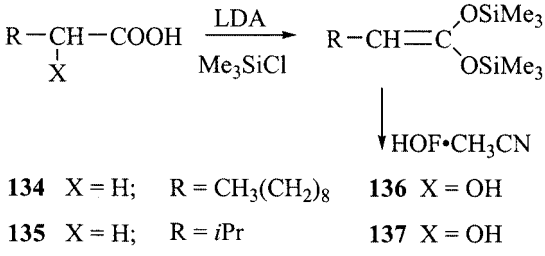
Following the α-hydroxylation of ketones, it was only natural to examine the behavior of esters and acids via their alkyl trimethylsilyl ketene acetals using trimethylsilyl chloride and a strong base such as LDA. Reacting such ketene acetals with HOF·CH_3CN gave indeed the α-hydroxy esters in excellent yields.[83] Methyl mandelate (**126**) was obtained within 5 min from the trimethylsilyl ketene acetal of methyl phenylacetate (**127**) in 95% yield. Similarly, methyl heptanoate (**128**) and methyl 3-adamantylpropanoate (**129**) as well as the secondary methyl 2-propylpentanoate (**130**) were

converted into their α-hydroxy derivatives **131**–**133** in excellent yields (Scheme 31).



Scheme 31. Synthesis of α-hydroxy esters.

It is also possible to use acids as substrates, although the yields are somewhat lower. It is necessary to prepare the carboxylic corresponding ketene bis(trimethylsilyl acetals) which are quite sensitive to hydrolysis by the acidic aqueous media in which the HOF·CH_3CN is present. Thus in all cases examined the only by-product obtained was the starting acid. Still, undecanoic and isovaleric acids (**134**) and (**135**), for example, were converted into the 2-hydroxyundecanoic acid (**136**) and 2-hydroxyisovaleric acid (**137**) in 60 and 75% yield, respectively, in a short reaction times (Scheme 32).



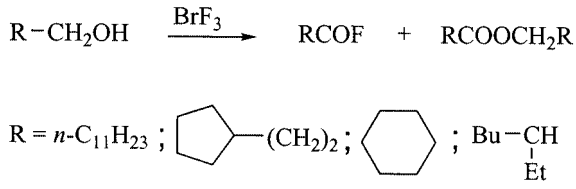
Scheme 32. Synthesis of α-hydroxy acids.

B. Miscellaneous

1. Synthesis of Symmetric Esters Using BrF_3

Unlike HOF·CH_3CN, which has to be prepared prior to its use, BrF_3, is a commercial reagent used quite frequently in inorganic chemistry. Although we have started recently to use it quite extensively and demonstrate that despite the fact that it generates unjustified fears, as did elemental fluorine two decades ago, organic chemists do not have to shy away from it. Most of the chemistry of this reagent, which we developed, is beyond the scope of this review, but still we would like to mention one reaction that leads to fluorine-free esters that are sometimes difficult to make by alternative ways.[84]

When an excess of BrF_3 was allowed to react with a primary alcohol, an immediate reaction took place and mainly the corresponding oxidized acyl fluoride was formed. When, however, the alcohol was found in excess, the symmetrical ester, resulted from a secondary reaction of the acyl fluoride with the starting alcohol, was formed in good yields. Some of the esters made by this way are presented in Scheme 33.

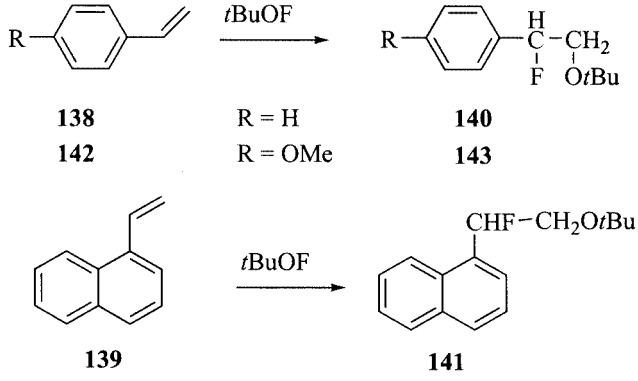


Scheme 33. Esters from alcohols using BrF_3.

2. *t*BuOF, the Second Alkyl Hypofluorite

MeOF,[85,86] the first alkyl hypofluorite described, which incidentally was also the smallest organic molecule that had not been prepared at the time, was mentioned in our previous review.[10] The second, out of total of three,[87] alkyl hypofluorite which was possible to make was *t*BuOF.[88] It was a good source for the electrophilic *tert*-butoxylium, a species that was practically nonexistent.

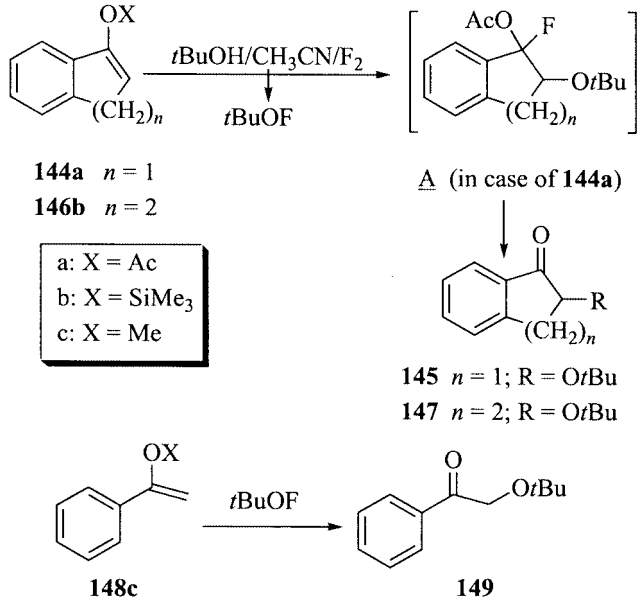
tert-Butyl hypofluorite can be readily prepared in situ by the reaction of fluorine with *tert*-butyl alcohol using acetonitrile as a solvent. It adds smoothly across unhindered benzylic double bonds such as styrene (**138**) or 1-vinylnaphthalene (**139**) forming 1-fluoro-1-phenyl- (or, 1-naphthyl-) 2-*tert*-butoxyethane (**140** or **141**) in 60% yield. The regiochemistry of the reaction indicates an initial electrophilic attack by the *tert*-butoxylium moiety. Better yields were obtained with the more electron-rich double bond of 4-methoxystyrene (**142**) which gave the corresponding adduct 1-fluoro-1-(4-methoxyphenyl)-2-*tert*-butoxyethane (**143**) in 70% yield (Scheme 34).



Scheme 34. Adding *t*BuOF across double bonds.

The last result prompted us to investigate the reaction with electron-rich enol derivatives, which produced eventually α-*tert*-butoxy carbonyl compounds. When the enol acetate of 1-indanone (**144a**) was treated with *t*BuOF, 2-*tert*-butoxy-1-indanone (**145**) was isolated in 45% yield. Similarly, tetralone trimethylsilyl enol ether (**146b**) afforded the expected 2-*tert*-butoxy-1-tetralone (**147**) in good yields. Enol derivatives of open-chain benzylic ketones also proved

to be suitable substrates and for example, the methyl enol ether **148c** was converted to **149** in 65% yield. The reaction seems to proceed through an addition elimination pathway, associated with most electrophilic reagents possessing the OF moiety.[89,90] Support for this assumption could be found in the reaction of *tert*-butyl hypofluorite with **144a**, in which an intermediate **A**, was isolated and characterized. This adduct, however, was unstable and eventually decomposed to the expected **145** (Scheme 35).



Scheme 35. Adding *t*BuOF across enolic double bonds.

Despite the novelty of this reagent, it seems to be of limited use with aliphatic and non-benzylic ketones. The methyl enol ethers of 4-*tert*-butyl cyclohexanone, adamantyl methyl ketone, as well as the trimethylsilyl enol ethers of pinacolone and cyclooctanone did not react satisfactorily and produced either tars or low yields of the desired α-*tert*-butoxy ketones. This probably reflects the relatively low electron density of the enolic double bond of aliphatic ketones, resulting in insufficient nucleophilicity towards the *t*BuOF. Needless to point out that this reagent is also strongly affected by even moderate steric factors.

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