Aldrichimica Acta

Volume 21, Number 1, 1988

Fluoroaromatic Compounds: Synthesis, Reactions and Commercial Applications

chemists helping chemists in research & industry

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Aldrichimica Acta

Volume 21, Number 1, 1988
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About Our Cover:

Our readers may well guess that our chemist-collector bought this painting (oil on canvas, 104 x 118cm) for its subject, rather than its attribution. He loves the story of Tobias, and perhaps some day he will be able to arrange for an exhibition of paintings which will illustrate this story of man's faith. There are hundreds of paintings of its many scenes, but this depiction of Tobias and the angel baking the fish is very unusual.

When our chemist-collector purchased this painting, he was told it was a work by Philips Koninck, for it was recorded as No. 119 in Horst Gerson's monograph of the artist. Koninck, a student of Rembrandt, was one of the greatest masters of landscape, but he occasionally also tried his hand at genre and historical paintings. For a beautiful landscape by Philips Koninck, see the cover of the *Aldrichimica Acta*, Volume 18, No. 1, 1985.

Fig. 1

But collecting has its pitfalls. Imagine the surprise when cleaning revealed the signature and date (Fig. 1) — certainly not the signature of Philips Koninck! Martin van der Fuick is almost unknown, and yet an artist who painted with such imagination must have produced other works. His only other known work is a painting of militiamen of the town of Den Briel, done in 1660. Perhaps Fuick was an artist who died young, and probably other paintings remain to be discovered.

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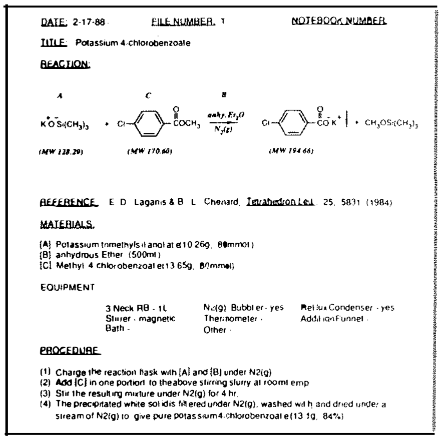
The combination of WIMP™ and Pagemaker® programs allows the chemist to keep an electronic notebook, complete with computer-generated structures. The electronically stored notebook can then be printed out and pasted into a legally acceptable notebook. This system offers the advantage that a template of an earlier experimental record can be used to generate new experimental procedures quickly and efficiently, saving the chemist a great deal of time in the long run.



DATE: 2-17-88 FILE NUMBER: 1 NOTEBOOK NUMBER:

TITLE: Potassium 4-chlorobenzoate

REACTION:

REFERENCE: E. D. Laganis & B. L. Chenard, Tetrahedron Lett. 25, 5831 (1984)

MATERIALS:

(A) Potassium trimethylsilanolate (10.26g, 80mmol)
(B) anhydrous Ether (500ml)
(C) Methyl 4-chlorobenzoate (13.65g, 80mmol)

EQUIPMENT

3 Neck RB - 1L	N2(g) Bubbler - yes	Reflux Condenser - yes
Stirrer - magnetic	Thermometer -	Addition Funnel -
Bath -	Other -	

PROCEDURE:

(1) Charge the reaction flask with (A) and (B) under N2(g)
(2) Add (C) in one portion to the above stirring slurry at room temp
(3) Stir the resulting mixture under N2(g) for 4 hr.
(4) The precipitated white solid is filtered under N2(g), washed with and dried under a stream of N2(g) to give pure potassium 4-chlorobenzoate (13.1g, 84%)

Evan D. Laganis
E.I. du Pont de Nemours & Co., Inc.
Research & Development Division
Wilmington, Delaware 19898

Editor's note: For additional information on WIMP™ publishing software for chemists see page F26 of the 1988-1989 Aldrich Catalog/Handbook. Call or write for Technical Information Bulletin AL-162 describing the WIMP molecule-drawing software.

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Sampling a reaction mixture for GC or TLC analysis while maintaining an inert atmosphere can be inconvenient, especially when one is using a deep reaction vessel or wishes to remove only a few microliters of solution. This operation can be easily done using a short (12-24-inch) piece of fused silica capillary (0.2-0.33mm i.d.) such as is often discarded during maintenance of capillary gas chromatographs. With the reaction mixture under slightly greater than atmospheric pressure, the capillary is inserted through a slit in the septum and very briefly (1-2sec) dipped below the surface of the liquid. A few seconds later (depending on the pressure applied and viscosity of the liquid) a tiny droplet emerges from the other end of the capillary and it can be derivatized or diluted as necessary for analysis. The capillary is readily cleaned by forcing a small amount of solvent through it using the same technique. In this manner, very small samples ($\leqslant$10 microliters) can be taken conveniently without disturbing the reaction mixture. I have found that these fused-silica capillaries are quite durable and can be used indefinitely.

Charles M. Garner
Department of Chemistry
University of Utah
Salt Lake City, UT 84112

Hot oil baths present a serious fire hazard in the laboratory, particularly when they are used for unattended experiments overnight. Wood's metal (m.p. 70 °C) is safer in that respect, but it is expensive and toxic.

Flaked graphite has advantages over both oil and Wood's metal. It is clean and inexpensive. It is a good conductor of heat and permits magnetic stirring. In addition, it is thermally stable and not flammable under normal laboratory conditions.

Professor A.G. Davies
Department of Chemistry
University College London
20 Gordon Street
London WC1H OAJ
England

Anyone who uses silicone oil baths to heat chemical reactions can attest to the fact that, over time, the oil becomes discolored due to soluble and insoluble contaminants. Simple filtration of the bath oil will not remove the discoloration but we have found that the addition of a small amount of decolorizing carbon to the bath, followed by filtration of the mixture, yields oil that is as good as new. Water can be removed by the addition of anhydrous magnesium sulfate before stirring with decolorizing carbon. The filtration may be accomplished by using water aspirator vacuum (be sure to use filter cel to protect the glass frit) or more conveniently, by gravity filtration overnight.

Deborah A. Davis
Department of Chemistry
Dartmouth College
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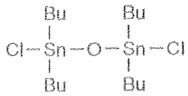
Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Alfred Bader.



$$\begin{matrix} & \text{Bu} & & \text{Bu} & \\ & | & & | & \\ \text{Cl}- & \text{Sn} & -\text{O}- & \text{Sn} & -\text{Cl} \\ & | & & | & \\ & \text{Bu} & & \text{Bu} & \end{matrix}$$

Professor Hitosi Nozaki at Okayama University of Science in Japan suggested that we offer bis(chlorodibutyltin) oxide as a catalyst to convert ω-hydroxycarboxylic acids to macrolides. The transformation occurs under neutral and mild conditions in a variety of organic solvents including decane.

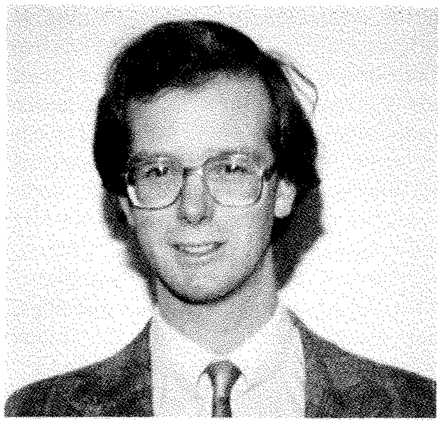
Naturally we made the compound.

Otera, J.; Yano, T.; Himeno, Y.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 4501.

It was no bother at all, just a pleasure to be able to help.

Fluoroaromatic Compounds: Synthesis, Reactions and Commercial Applications

Christopher D. Hewitt
Michael J. Silvester
Bristol Organics Division
Sharpness Docks
Berkeley
Glos. GL13 9UG
England



I. INTRODUCTION

In 1986 a major international conference was held to celebrate the centenary of the discovery of fluorine by Moissan[1] and the wide range of topics discussed illustrated the exciting developments which have occurred since 1886.[2] The requirements of the 'Manhattan Project' provided a major stimulus to the investigation of organofluorine chemistry, with the interest stemming from the special properties conferred upon a molecule by the presence of fluorine. These properties range from the high stability of fluorinated polymers to the enhanced behavior of agrochemicals and pharmaceuticals. The influence of fluorine on a molecule can be summarized as follows:

a. Fluorine is comparable in size to hydrogen and can, for example, mimic hydrogen at enzyme-receptor sites.
b. The strength of the carbon-fluorine bond leads to enhanced thermal stability.
c. The high electronegativity of fluorine frequently alters chemical reactivity.
d. Lipid solubility is usually increased when hydrogen is replaced by fluorine.

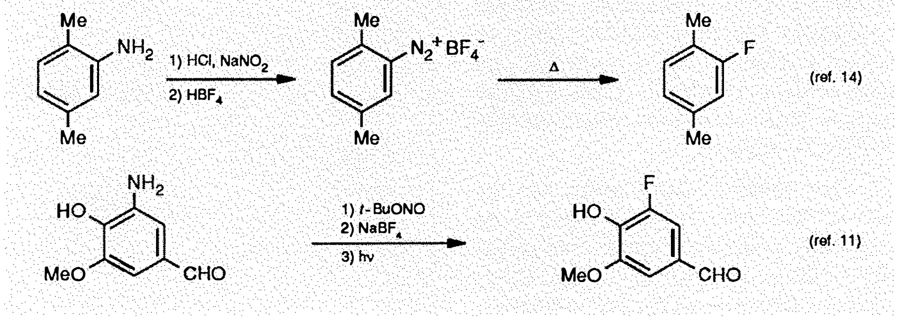
In conjunction with an increased understanding of the properties of organofluorine compounds, there has been ample opportunity for the organic chemist to develop new synthetic methods.[3,4] These range from the taming of the once infamous elemental fluorine to highly developed methods for the selective introduction of fluorine and polyfluoroalkyl groups into biologically significant molecules. The chemistry of organofluorine compounds is as diverse as it is interesting and, therefore, this article will concentrate on aromatic compounds containing either fluorine or polyfluoroalkyl groups, with the aim of giving a general introduction to the area. For the interested reader there are many texts available covering further aspects of the field of organofluorine chemistry.[5]

II. SYNTHESIS

A. Introduction of Fluorine into the Ring

The classical method of introducing fluorine into an aromatic ring is the Balz-Schiemann reaction in which an aromatic NH_2 is replaced by fluorine.[6] Diazotization of the aromatic amine in the presence of tetrafluoroboric acid enables fluorine to be introduced into a wide range of aromatic compounds (Scheme 1). More recent developments include the formation of hexafluorophosphate salts,[7] the addition of solvents or salts to moderate the decomposition,[8,9] and the use of ultrasound.[10] Photochemical decomposition of tetrafluoroborate salts has found limited use in the preparation of thermally sensitive products, for example, in the preparation of fluorovanillins (Scheme 1).[11] Diazotization and decomposition in hydrogen fluoride has developed into an industrial process.[12] Interest is also being shown in the use of anhydrous hydrogen fluoride-pyridine mixtures as solvents for the diazotization reaction. Conversion to the fluoroaromatic occurs on warming and the method offers the advantage of not requiring isolation of the salt intermediate.[13]

Scheme 1



The Balz-Schiemann reaction can be used to replace, sequentially, up to four hydrogens in benzene, beyond which side reactions take place. To obtain highly fluorinated aromatics two possible routes are available, as illustrated in Scheme 2. Aromatics can be fluorinated with cobalt trifluoride and, depending on the extent of fluorination, subsequent defluorination or dehydrofluorination yields the fluoroaromatic.[15] Defluorination can be carried out either over hot metals[15a] or by electrochemical means.[15a] The former process was developed on an industrial scale during the 1950's and gave a major boost to the field.

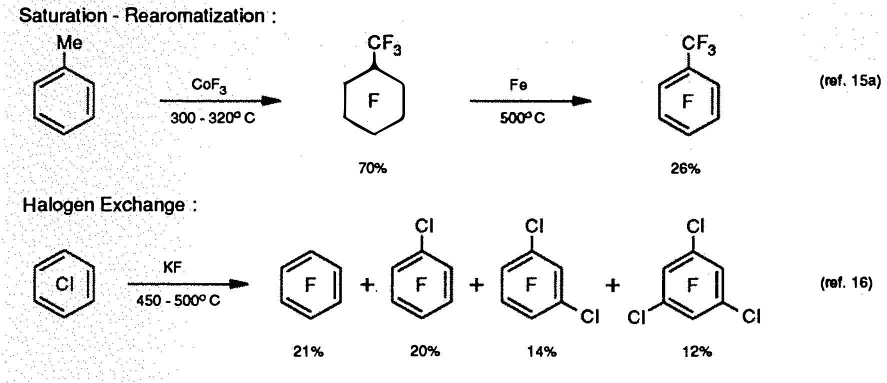
The halogen-exchange method offers the advantage that functional groups, such as nitrile, are unaffected.[17] Potassium fluoride offers a readily available source of reactive fluoride ion, and one of the driving forces for the reaction is the difference in lattice energies between the ionic halides. The use of crown ethers, solvents and other sources of fluoride ion enable the reaction conditions to be varied according to the starting material and required product.[19] Indeed, the desire to obtain compounds in higher yield and selectivity, under mild conditions, has proved the focal point for much research into, for example spray-dried KF[20] and new reagents such as quaternary phosphonium fluorides.[21] Phase-transfer catalysts[22] and KF in poly(ethylene glycol)-acetonitrile[23] have also been used with the aim of obtaining highly reactive 'naked' fluoride ion to facilitate halogen exchange (Scheme 3).

An alternative to the displacement of chlorine is fluorodenitration. For example, reaction of 3-chloro-2-fluoronitrobenzene with potassium fluoride in the presence of phthaloyl chloride and tetraalkylammonium chloride gave 1-chloro-2,3-difluorobenzene.[24] The use of *anhydrous tetrabutylammonium fluoride* (TBAF) promotes fluorodenitration under very mild conditions[25] (Scheme 3).

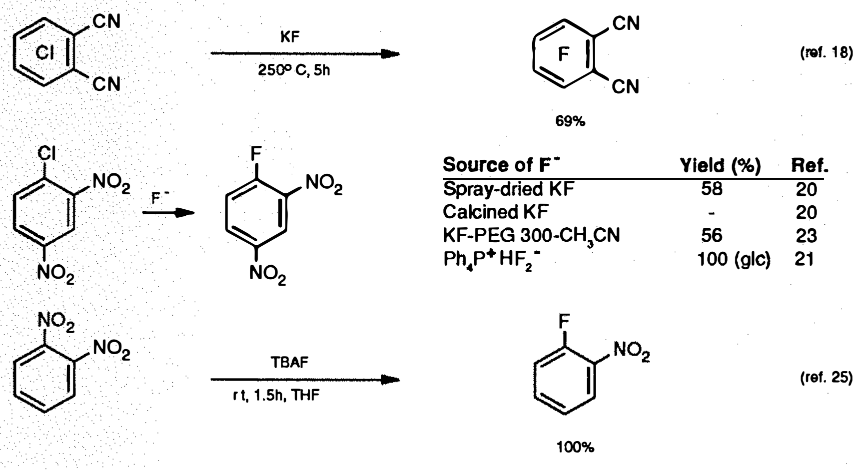
A great deal of effort has been directed towards the selective introduction of fluorine into biologically active molecules, and the requirement of ^{18}F-labeled compounds for positron emission transaxial tomography has given added impetus to this work. This has led, over the last few years, to the development of new exciting reagents which are sources of *electrophilic fluorine* (Scheme 4).

Trifluoromethyl hypofluorite can be used to fluorinate aromatic compounds selectively, if the aromatic is substituted with an electron-donating group.[26] Complications can arise with other aromatics,

Scheme 2



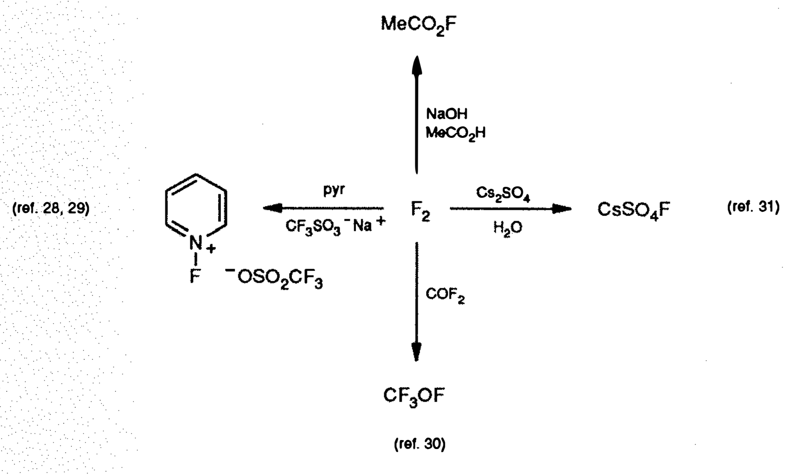
Scheme 3



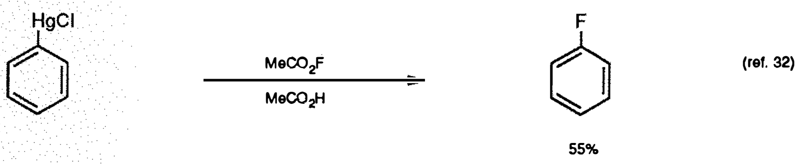
Source of F⁻	Yield (%)	Ref.
Spray-dried KF	58	20
Calcined KF	-	20
KF-PEG 300-CH_3CN	56	23
$Ph_4P^+HF_2^-$	100 (glc)	21

Scheme 4

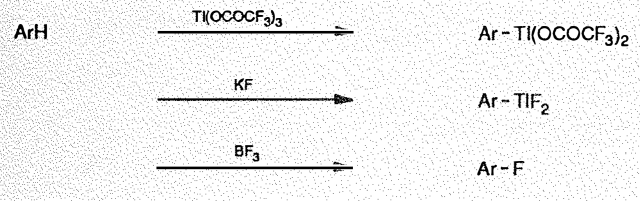
(ref. 27)



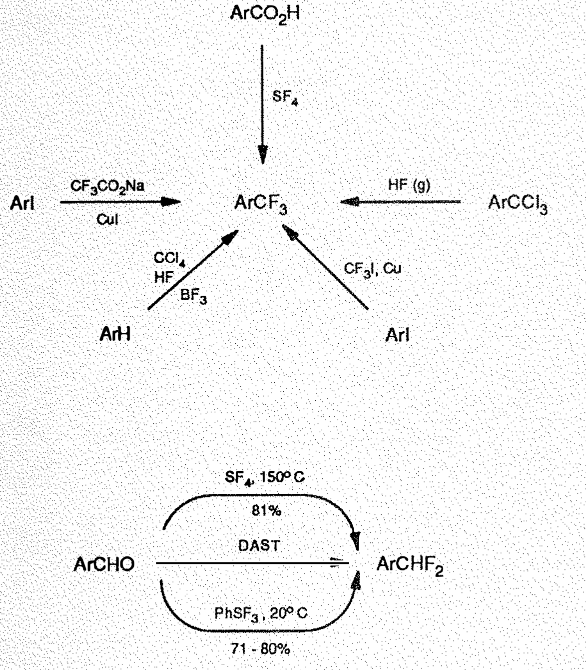
Electrophilic Fluorinating Agents



Scheme 5



Scheme 6



but the interest generated by the use of this reagent has led to many other new and important reagents. For example, acetyl hypofluorite can be used to prepare fluoroaromatics in good yield from aryl mercury compounds; the product shown in Scheme 4 is obtained at room temperature in under 5 minutes.[32] Fluorination of aryl tin compounds can be carried out using either fluorine[33] or CF_3OF[34] and with reaction occurring at the metallated site there is a high degree of selectivity. Cesium fluoroxysulfate can be used similarly[35] and offers the advantage that it can be isolated and stored in contrast to acetyl hypofluorite which is generated *in situ.*

N-Fluoropyridinium triflates have been developed as versatile fluorinating reagents whose strength can be varied by altering substitution in the pyridine ring.[28,29]

Although the reagents shown in Scheme 4 are commonly referred to as sources of *electrophilic fluorine*, the actual mechanism is a source of much discussion.[36] Acetyl hypofluorite is now believed to react *via* an electron-transfer mechanism to give a radical cation followed by fluoride-ion transfer.[37]

Xenon difluoride can be used to mono- and difluorinate aromatics and a catalyst such as hydrogen fluoride is usually required.[38,39] An interesting means of introducing fluorine into an aromatic ring is by the use of thallium tris(trifluoroacetate)-potassium fluoride (Scheme 5).[40]

B. Introduction of Polyfluoroalkyl Substituents

The synthesis of polyfluoroalkyl-substituted aromatics falls into two classes:

a . Fluorination of a group already present.
b . Introduction of a polyfluoroalkyl group.

By far the most important substituent is the trifluoromethyl group and the synthesis of benzotrifluoride readily illustrates both of these classes (Scheme 6). Although SF_4 presents certain handling difficulties, it is a popular reagent and has the advantage that it can also be used to convert CHO to CHF_2 and CH_2OH to CH_2F.[41] New reagents which offer the benefits of SF_4 without the practical disadvantages are continually being sought. Diethylaminosulfur trifluoride (DAST) can be used to convert CHO to CHF_2 and is finding increasing use.[42] Phenylsulfur trifluoride (liquid)[43] and diphenylsulfur difluoride (solid)[44] also convert CHO to CHF_2 and these reagents offer practical advantages over SF_4.

Halogen exchange involving the side chain can be brought about readily by the use of Swarts-type catalysts based on antimony fluorides and chlorides.[45] Reactive halides, such as benzylic, can be converted using anhydrous HF[46] or by using sources of activated fluoride ion such as 18-crown-6-ether-potassium fluoride.[47] Other reagents include potassium fluoride supported on calcium fluoride[48] or alumina,[49] where the improved reactivity is believed to come from an increase in surface area.

Simultaneous introduction of CCl_3 and fluorination enables the CF_3 group to be formed directly.[50]

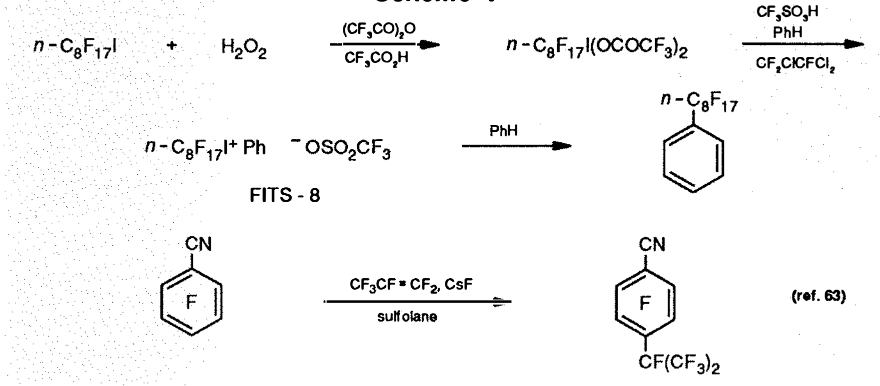
Coupling of an aromatic iodide, in the presence of copper, with a perfluoroalkyl iodide is a general route to perfluoroalkyl-substituted aromatics.[51] Although it can be applied to the synthesis of benzotrifluorides, a more convenient and cheaper source of the CF_3 group is sodium trifluoroacetate with copper iodide.[52] The mechanism of these copper-mediated reactions is a source of continuing investigation, with the intermediacy of an organofluorine copper being proposed in some cases.[53] Trifluoromethylcopper can be obtained from dibromodifluoromethane.[54] A less selective method of trifluoromethylation is the generation of CF_3 radicals either photochemically,[55] or thermally by the use of peroxides.[56] Various thermolytic methods for the introduction of the CF_3 group are available including reaction of perfluoroaromatics with difluorocarbene[57] and flash thermolysis of aryl trifluoroacetates.[58]

The importance of the CF_3 group has led to continued investigation into new reagents. Recently, *N*-trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide has been developed and can be used to trifluoromethylate activated aromatics directly or *via* trifluoromethylcopper generated *in situ.*[59,60]

Electrophilic perfluoroalkylation of aromatics is possible through the availability of perfluoroalkyl(aryl)iodonium trifluoromethanesulfonate (FITS) reagents.[61] These are quite versatile reagents (Scheme 7) and their synthetic utility has been extended by the availability of polymer-supported FITS reagents.[62]

Nucleophilic perfluoroalkylation of suitably activated fluoroaromatics is a particular instance of a reaction which has very wide applicability in perfluoroheterocyclic chemistry (Scheme 7).[5a]

Scheme 7

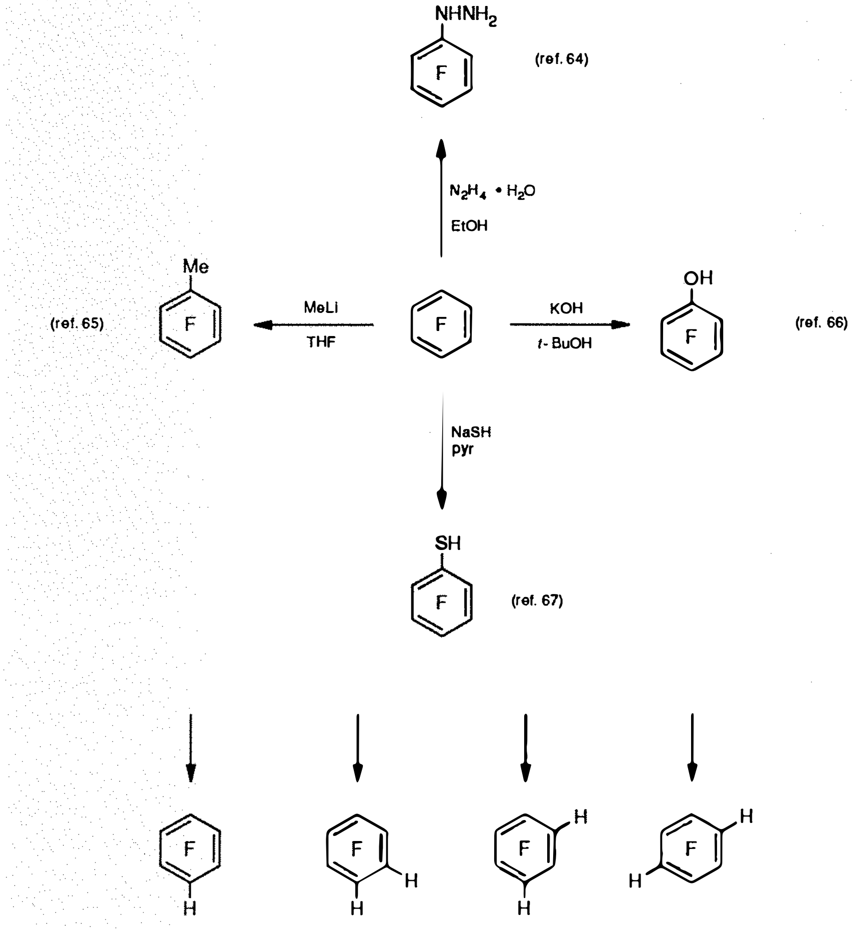


C. Reactions of Fluorinated Aromatics

The chemistry of polyfluoroaromatics is dominated by nucleophilic aromatic substitution and a wealth of research has been concerned with the elucidation of factors governing orientation and activation.[5a]

Hexafluorobenzene reacts with a wide range of nucleophiles and illustrative examples are given in Scheme 8. Similar reactions are shown by penta- and tetrafluorobenzenes, with the added interest that the orientation of substitution and activating influences of fluorine become important. Considerable research has been involved in determining the influence of fluorine on reaction centers. In the instance of nucleophilic aromatic substitution, it is believed that the activating influence of fluorine *ortho* and *meta* to the point of substitution is dominant in determining the orientation of attack.[5a] Thus, for pentafluorobenzene, *para* substitution is observed, while for the tetrafluorobenzenes the orientation is as shown in Scheme 8. Similar nucleophilic substitution reactions are shown by, for example, octafluoronaphthalene and decafluoroanthracene.

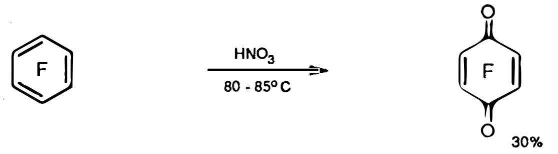
Scheme 8



It is clear that an extensive range of compounds can be prepared by the use of simple nucleophiles and interest is further developed by cyclization reactions (Scheme 9) involving bifunctional nucleophiles on suitable substrates. Indoles, benzothiophenes and benzofurans can also be readily obtained. Thermal reaction of $C_6F_5CH=NC_6H_4OH$-*o* gives a benzoxazepine.

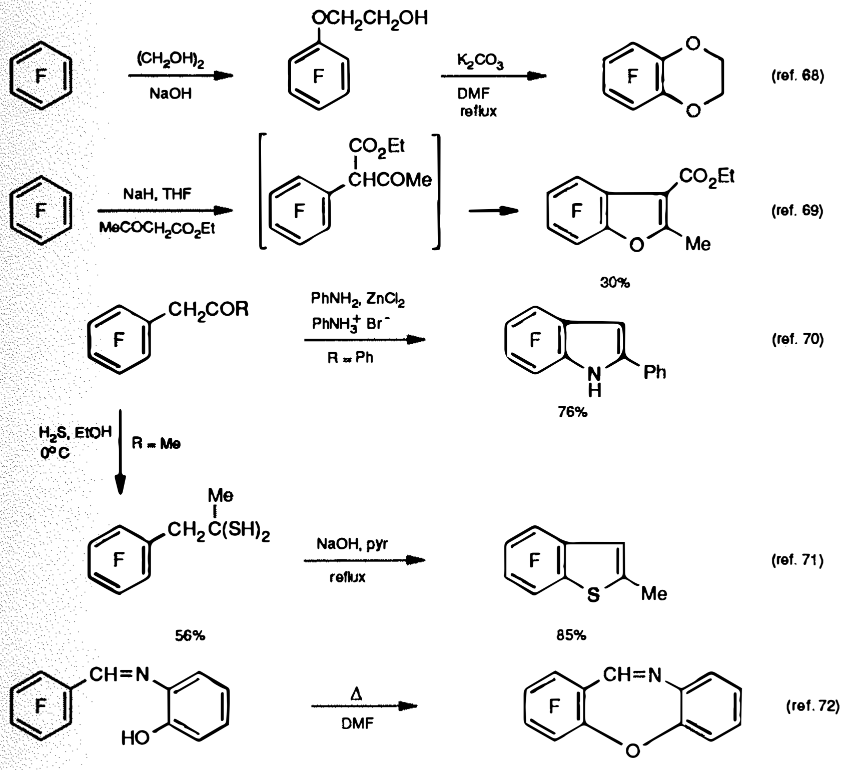
Although nucleophilic aromatic substitution dominates the chemistry of polyfluoroaromatics, it should not be forgotten that reaction with electrophilic reagents can occur. For example, hexafluorobenzene reacts with nitric acid to yield tetrafluoro-*p*-benzoquinone (Scheme 10).[73]

Scheme 10

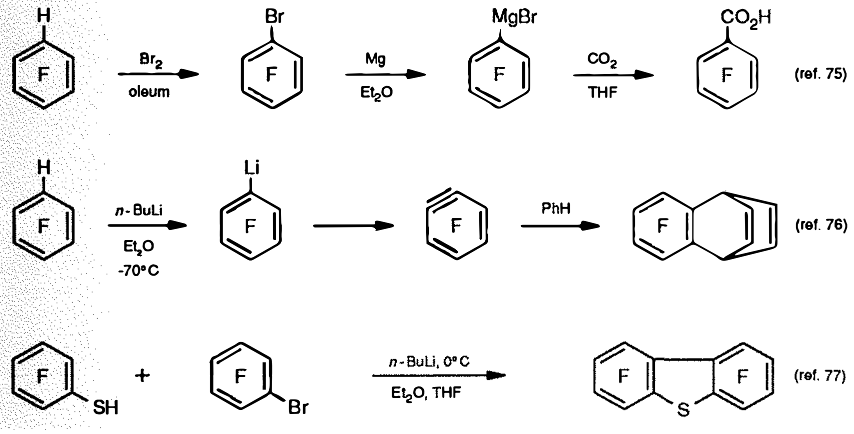


Pentafluorobenzene and less highly fluorinated aromatics undergo electrophilic aromatic substitution; for example, bromination of pentafluorobenzene gives bromopentafluorobenzene in high yield.[74] The availability of bromofluoroaromatics enables Grignard reagents to be readily obtained which can then be used in standard syntheses (Scheme 11). Indeed, an extensive chemistry is based on polyfluoroaromatic organometallics[78] and lithium, magnesium, and copper reagents are especially useful. The lithium compounds are versatile reagents and can be obtained

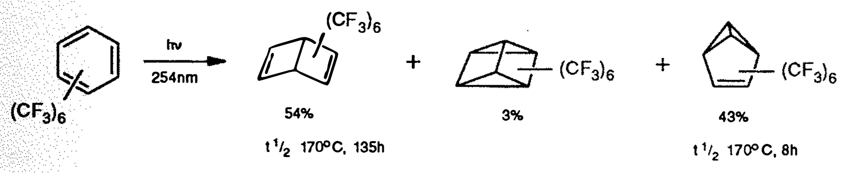
Scheme 9



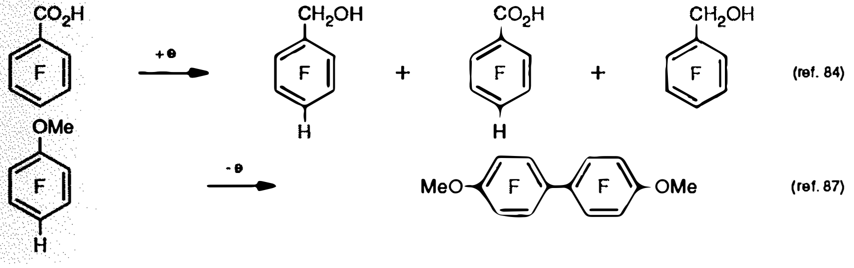
Scheme 11



Scheme 12



Scheme 13



either by metal-halogen exchange[79] or by metallation of the hydro compound.[80] β-Elimination of lithium fluoride from pentafluorophenyllithium gives the highly electrophilic tetrafluorobenzyne which can undergo reactions not readily shown by benzene (Scheme 11).[76] Tetrafluorobenzyne is believed to be an intermediate in an interesting reaction which yields dibenzothiophene.[77] The copper reagents can be considered as complementary to the lithium analogs and in the case of pentafluorophenylcopper show marked stability.[81]

A major contribution to organic chemistry has come from the photochemistry of fluoroaromatics and, in particular, those substituted with perfluoroalkyl groups, with the formation of surprisingly stable valence isomers.[82] The beneficial effect of fluorine substitution arises from the strength of the C-F bond leading to fewer side products, the stabilizing influence of a perfluoroalkyl group on a small ring, and the steric demand of the perfluoroalkyl group. Irradiation of hexatris(trifluoromethyl)benzene gives valence isomers of quite remarkable stability illustrating the benefits of perfluoroalkyl substitution (Scheme 12);[83] this enhanced stability enables further chemistry to be carried out.

Fluoroaromatic compounds can also be used in the expanding field of electroorganic chemistry (Scheme 13). For example, electrochemical reduction of pentafluorobenzoic acid gives either 2,3,5,6-tetrafluorobenzyl alcohol and pentafluorobenzyl alcohol or 2,3,5,6-tetrafluorobenzoic acid as major products, depending on electrode potential and proton availability.[84] As expected, electrochemical oxidation is more difficult to achieve; however, oxidation of fluoroaromatics in fluorosulfonic acid-acetic acid enabled their radical cations to be observed by ESR.[85] Introduction of electron-donating substituents such as NH_2[86] and OCH_3[87] lowers the oxidation potential and coupling reactions are observed.

III. COMMERCIAL APPLICATIONS

In the introduction to this article the effects of fluorine on a molecule were briefly summarized and it would be useful to end this discussion of fluoroaromatics with some examples of their applications.[88] These compounds fall broadly into two groups based on synthetic utility or its usefulness as a substituent in the final product.

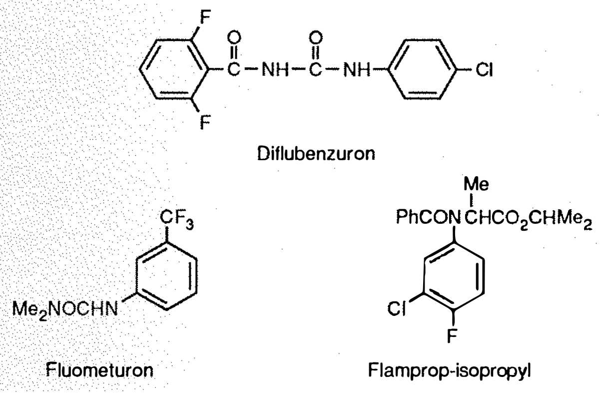
Fluoroaromatics find wide use in biomedical applications; for example, 1-fluoro-2,4-dinitrobenzene (Sanger's Reagent) is used as a reagent for labeling peptides and terminal amino acid groups in proteins.[89] Similarly, 1,5-difluoro-2,4-dinitrobenzene can be used in the determination of D-amino acids by HPLC.[90] In both these instances the availability of fluorine as an anionic leaving group in an activated compound facilitates the reaction. Likewise, octafluorotoluene can be used to protect phenolic and alcoholic functions in steroids.[91] Fluorinated aromatics can be used to aid analysis; for example, 3,5-bis-(trifluoromethyl)aniline can be used in the derivatization of carboxylic acid herbicides for gas chromatography.[92]

The efficacy of agrochemicals[93] (Table 1) and pharmaceuticals[94] (Table 2) can be improved by the presence of fluorine. Desirable attributes can include lower dosage, lower toxicity, increased selectivity and, conversely, broad-spectrum activity.

Trifluralin has proved to be a highly successful herbicide and its synthesis is shown in Scheme 14; variations in R can lead to changes in activity and selectivity. Diflubenzuron is used as an insecticide and it is interesting to note that the 2,6-difluorobenzoyl group is more effective than either the 2-chloro- or 2,6-dichlorobenzoyl group. Fluometuron and Flamprop-isopropyl are further examples of useful agrochemicals.

Fluorine-containing compounds have contributed to major developments in nonsteroidal antiinflammatory drugs. For example, Diflunisal is a very effective antiinflammatory agent with superior activity compared to aspirin while being better tolerated. Flurbiprofen is a very effective analgesic with few side effects. The increased lipid solubility of fluorinated molecules has played a major role in development of new and important central nervous system agents;[95] Haloperidol, Fenfluramine, and Perfluridol are three examples. Increased resistance of malaria to many drugs has resulted in much interest in potential replacements and the development of Mefloquine (Scheme 15) has proved a major advancement. It is prepared from 2-aminobenzotrifluoride.[96] This reaction indicates the usefulness of fluoroaromatics as building blocks in the formation of complex and useful molecules and a further example is shown using 1-bromo-2,4,5-trifluorobenzene. (Scheme 15).[97]

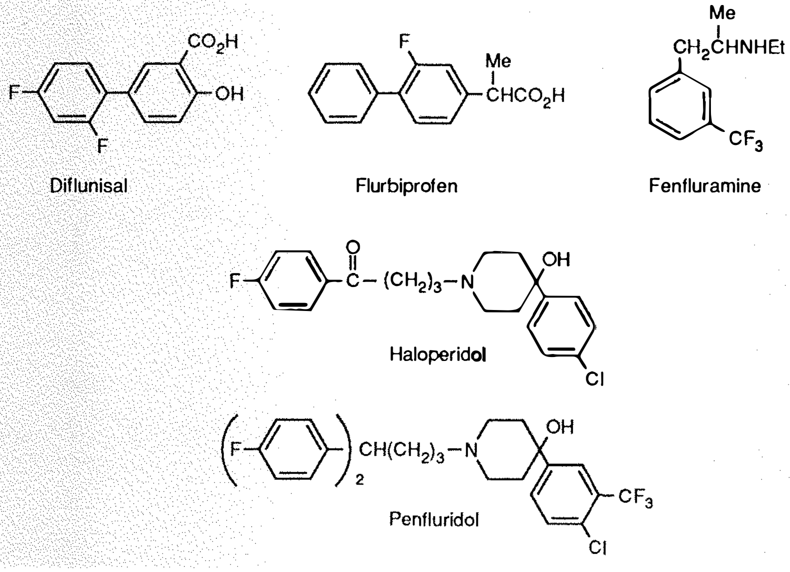
Table 1


Diflubenzuron

Fluometuron

Flamprop-isopropyl

Table 2


Diflunisal

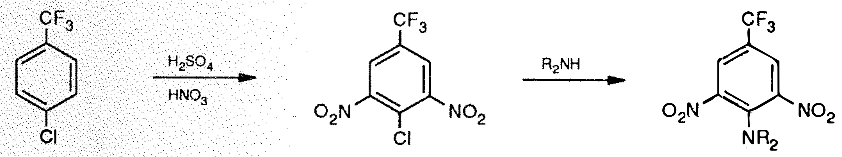
Flurbiprofen

Fenfluramine

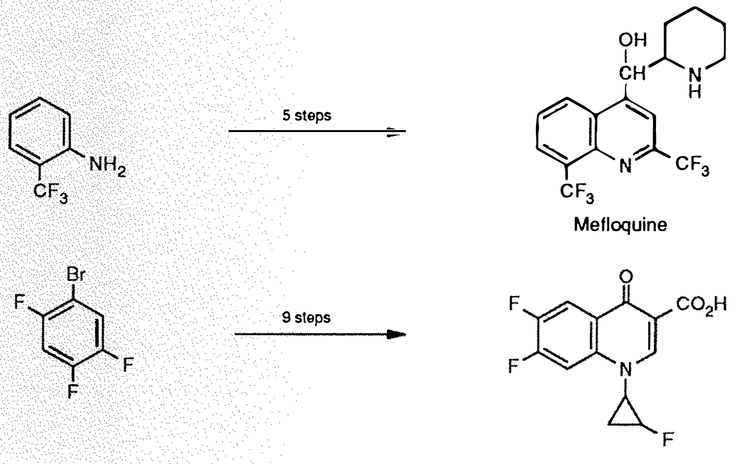
Haloperidol

Penfluridol

Scheme 14


R = n-Pr, Trifluralin

Scheme 15


Mefloquine

(ref. 96)

(ref. 97)

More recently, the availability of positron emitter ^{18}F ($t_{1/2}$ 110 min.) has proved invaluable to the development of positron emission transaxial tomography (PETT) as a noninvasive diagnostic tool.[98] Positron emitters have the advantage that when included in bioactive molecules, their defined pathways *in vivo* are not altered. The requirements of this technique have led to much synthetic work using both 'old' and 'new' fluorinating agents. For example, $^{18}F^-$ with activated aromatics[99] and $CH_3COO^{18}F$ in the synthesis of 6-fluoro-[^{18}*F*]-L-DOPA (Scheme 16)[100] to allow the study of brain chemistry.

Fluoroaromatic compounds have found use in polymer chemistry. The use of fluorine as a leaving group is well demonstrated in the preparation of the high-performance thermoplastic, PEEK, by reaction of 4,4′-difluorobenzophenone with hydroquinone.[101] Examples where fluorine is retained include pentafluorostyrene as a monomer for optical fibers[102] and 3,4-difluorobenzoyl chloride in liquid crystal compositions.[103]

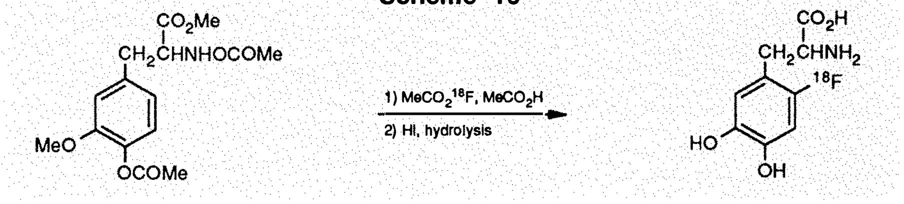
IV. CONCLUSION

The presence of fluorine in an organic molecule confers a great many advantages of both synthetic and industrial value. With the development in synthetic techniques gathering momentum, it is clear that the availability and range of fluorinated compounds will increase. In this article we have given an introduction to the synthesis and reaction of fluoroaromatic compounds which we hope will stimulate further interest in their use.

Acknowledgements

We would like to express our thanks to Professor R.D. Chambers for introducing us to the world of organofluorine chemistry.

Scheme 16



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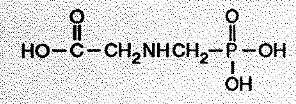
Dr. Christopher D. Hewitt received his B.Sc. degree from the University of York in 1982 and studied for the Ph.D. degree at the University of Durham, in the area of fluorinated imines, under the guidance of Professor Richard D. Chambers. Since October 1986 he has been employed by Aldrich Chemical Co., Ltd., Bristol Organics Division where he is a member of the new products development team.

Dr. Michael J. Silvester received his B.Sc. and Ph.D. degrees from the University of Durham in 1977 and 1981, respectively. The latter involved a study into the application of electro-organic chemistry to organofluorocarbons under the supervision of Professor Richard D. Chambers. He continued to pursue his interest in organofluorine chemistry as Senior Research Assistant working with Professor Chambers. After contract research and development work, he joined Aldrich Chemical Co., Ltd., Bristol Organics Division, as a Senior Production Chemist in 1986.

How To Find A Great Herbicide

Alfred Bader

In the spring of 1984, we at Aldrich were surprised by the visit of two teams of lawyers and chemical experts who came to question us about the best-selling herbicide ever. Round-up® herbicide which contains *N*-(phosphonomethyl)glycine (**1**) as its active ingredient was patented by Monsanto in 1974 and 1983 (U.S. Patents 3,799,758 and 4,405,531), but the Stauffer Chemical Company had developed a related herbicide having the trademark Touchdown® and questioned the validity of Monsanto's patents.



$$HO-\overset{\overset{\large O}{\|}}{C}-CH_2NHCH_2-\underset{\underset{\large OH}{|}}{\overset{\overset{\large O}{\|}}{P}}-OH$$

1

We had offered the compound at Aldrich through our *Library of Rare Chemicals*, and had listed it in both the 1967 library catalog and the 1972 Catalog/Handbook — hence, the day-long interrogation by the two teams of lawyers and their experts. How had we obtained the compound, when and why, and what had we done with it?

The compound we had was made in 1950 by Dr. Henri Martin, a very able Swiss chemist at Cilag in Schaffhausen. Dr. Martin had started with Geigy in 1934, worked with Paul Mueller on DDT, and then with Cilag until 1958, when he joined Ciba. There he developed a number of important herbicides, for example, Cotoran (*Merck Index*, 10th ed., 1983, No. 4054). Since his retirement in 1973, he has continued work at the University of Basel. He and Prof. Schwarzenbach in Zurich were collaborating on the development of complexing agents, and Dr. Martin thought that compound **1** might be a good complexing agent.

Cilag was an independent manufacturer of pharmaceuticals and fine chemicals in Schaffhausen at the Swiss-German border, until 1959 when it was purchased by Johnson & Johnson. Aldrich was Cilag's United States agent, and I had become the good friend of their director of research, Dr. Carl Richter. In Belgium, I had also become a good friend of Dr. Paul Janssen, the head of Janssen Pharmaceutica, which was also purchased by J & J. Paul Janssen is one of the world's ablest medicinal chemists, and he and his team had come up with an incredible number of medicinal products, far more than the rather sleepy team at Cilag. So I was not surprised when J & J decided that Cilag should stop all medicinal research and that it be concentrated at Janssen.

When I learned this, I asked Dr. Richter what Cilag was going to do with the thousands of research samples that had been made during the previous twenty years. It had long been my hobby to purchase such samples for our *Library of Rare Chemicals* — usually from professors, but why not from Cilag? And so I arranged for the purchase of those research samples and their inclusion in our Library.

Dr. Martin had made compound **1** very straightforwardly from chloromethylphosphonic acid, glycine and sodium hydroxide in boiling water (Fig. 1), but unfortunately for Cilag, he never had it tested as a herbicide. Nor did he think of it when he joined Ciba's herbicide research.

It became No. S39,860-8 in our *Library of Rare Chemicals*, and beginning in 1966, several companies bought small quantities, probably for screening purposes, without realizing its potential.

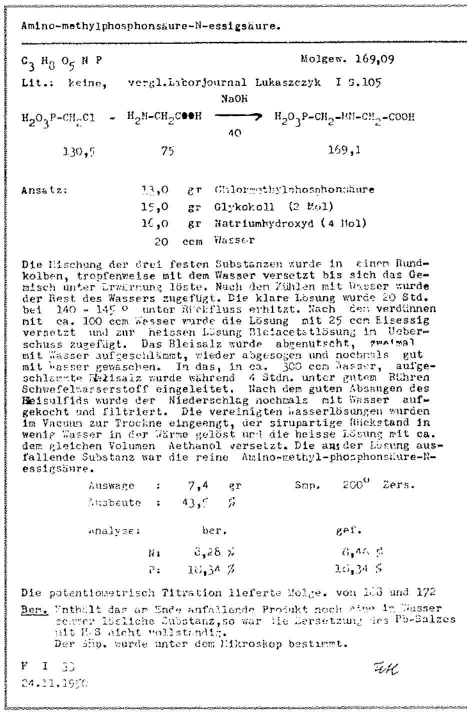
In 1970, Dr. J. E. Franz at Monsanto discovered the great herbicidal activity of this product, Monsanto's CP67573, and obtained patents in most countries of the world. Monsanto could not obtain a patent on the compound itself because of the earlier disclosures in our catalogs, and because of an earlier Stauffer patent, 3,160,632 which, however, had not made any herbicidal claims for it.

Since then compound **1** has become the active ingredient in the world's best-selling herbicide. Monsanto sells over $500 million worth of Round-up® herbicide annually.

At Aldrich we now have over 40,000 research samples in our Library. How many of these might give valuable leads, agriculturally and medicinally? Clearly, to have the compounds is not enough — you must also have the screens, and these are improving. Would it not make sense for every company interested in wide screening to have its own library — to be used and re-used as new screens are developed and old ones improved?

Over the years I have acquired many, many thousands of research samples from all over the world. But as time goes on, the size of the samples made gets smaller and smaller. Dr. Martin made 7.4 grams of *N*-(phosphonomethyl)glycine in 1950; today, many chemists make just milligram quantities of their new products. When I acquire a collection made over a long period of time, I can tell pretty accurately in which decade the compounds were made.

Time is running out, and that is why we have been working so hard to acquire our Library, and to offer these often unique samples to chemists around the world.



Amino-methylphosphonsäure-N-essigsäure.

$C_3 H_8 O_5 N P$ Molgew. 169,09

Lit.: keine, vergl. Laborjournal Lukaszczyk I S.105

$$H_2O_3P-CH_2Cl \; + \; H_2N-CH_2COOH \xrightarrow[40]{NaOH} H_2O_3P-CH_2-HN-CH_2-COOH$$

130,5 75 169,1

Ansatz:
13,0 gr Chlormethylphosphonsäure
15,0 gr Glykokoll (2 Mol)
16,0 gr Natriumhydroxyd (4 Mol)
20 ccm Wasser

Die Mischung der drei festen Substanzen wurde in einen Rundkolben, tropfenweise mit dem Wasser versetzt bis sich das Gemisch unter Erwärmung löste. Nach dem Kühlen mit Wasser wurde der Rest des Wassers zugefügt. Die klare Lösung wurde 20 Std. bei 140 - 145 ° unter Rückfluss erhitzt. Nach dem verdünnen mit ca. 100 ccm Wasser wurde die Lösung mit 25 ccm Eisessig versetzt und zur heissen Lösung Bleiacetatlösung im Ueberschuss zugefügt. Das Bleisalz wurde abgenutscht, zweimal mit Wasser aufgeschlämmt, wieder abgesogen und nochmals gut mit Wasser gewaschen. In das, in ca. 300 ccm Wasser, aufgeschlämmte Bleisalz wurde während 4 Stdn. unter gutem Rühren Schwefelwasserstoff eingeleitet. Nach dem guten Absaugen des Bleisulfids wurde der Niederschlag nochmals mit Wasser aufgekocht und filtriert. Die vereinigten Wasserlösungen wurden im Vacuum zur Trockne eingeengt, der sirupartige Rückstand in wenig Wasser in der Wärme gelöst und die heisse Lösung mit ca. dem gleichen Volumen Aethanol versetzt. Die aus der Lösung ausfallende Substanz war die reine Amino-methyl-phosphonsäure-N-essigsäure.

Auswage : 7,4 gr Smp. 200° Zers.
Ausbeute : 43,5 %

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Fig. 1

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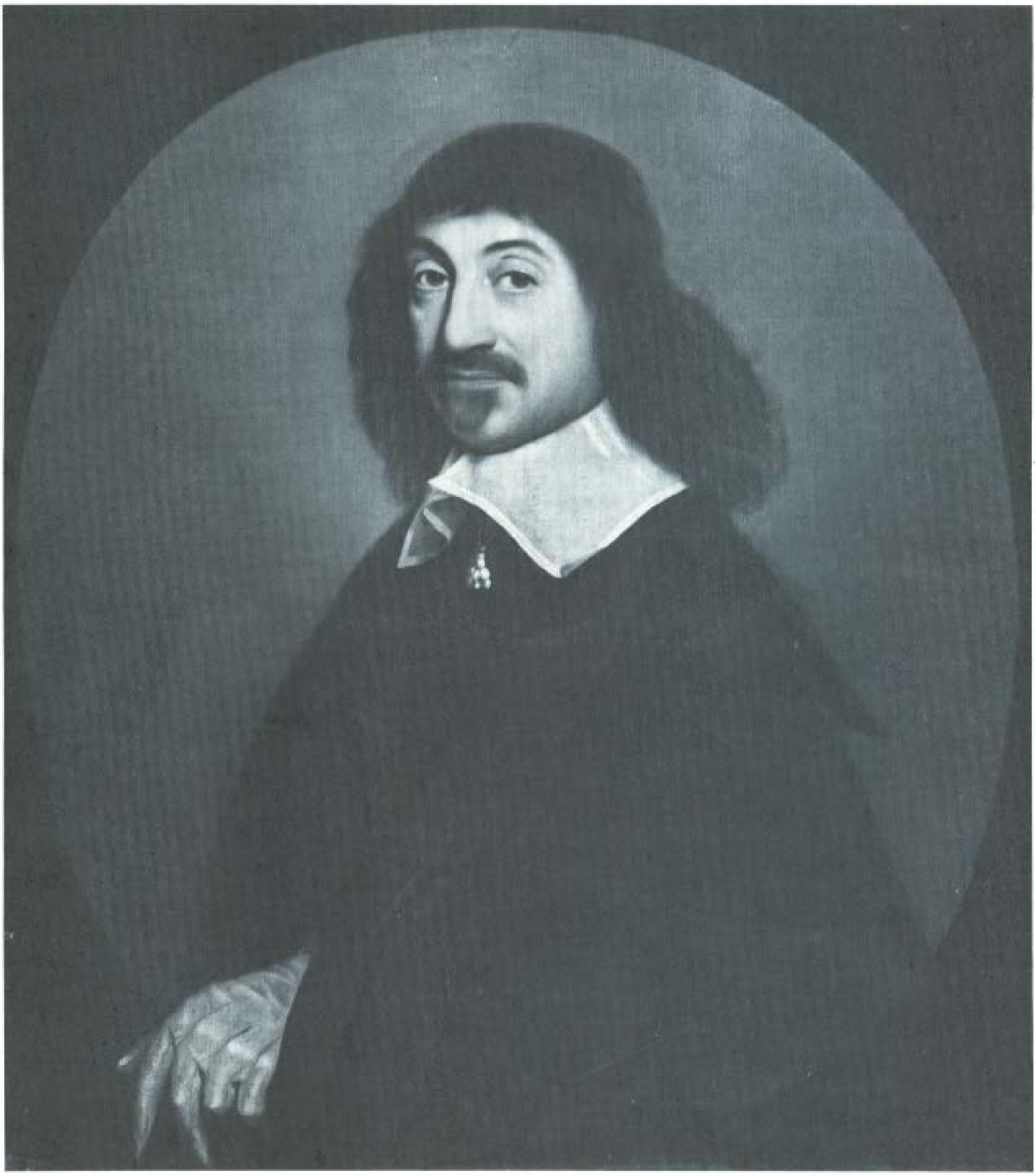
Aldrichimica Acta
Volume 21, Number 2, 1988



Ultrasound in Organic Synthesis

chemists helping chemists in research & industry
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Aldrichimica Acta

Volume 21, Number 2, 1988
A publication of the ALDRICH CHEMICAL COMPANY

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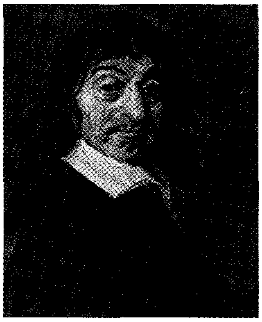

Fig. 1

Professor Seymour Slive at Harvard voiced an interesting question in aesthetics when he saw this arresting portrait of Descartes: "Why is a portrait vastly enhanced when we know that the sitter is one of the great Western philosophers?" Perhaps because we can grasp the man's character and so understand him better — some of the toughness and "blackness" to which Descartes' contemporaries referred, in admiration bordering on fear.

René Descartes (1596-1650) was a Frenchman of many parts — soldier, philosopher, mathematician, physicist, teacher, the founder of modern rationalism. Few great thinkers have been so versatile. Cartesian philosophy complemented that of Spinoza, his mathematics that of Huygens, his physics foreshadowed that of Newton.

As Descartes lived in Holland from 1629 to 1649, and was there recognized as one of the greatest philosophers of his time, many Dutch artists — Rembrandt, Jan Lievens and Frans Hals among them — depicted Descartes, and there has been a good deal of speculation which of these is the best likeness.[1] Rembrandt's brush drawing had been in a famous collection of Rembrandt's work, that of Valerius Röver in Delft early in the 18th century, and is now lost. If only we could see it!

Our portrait (oil on canvas, 30 x 25 inches) was done in 1647 by Peter Nason, an able portraitist from The Hague. He shows Descartes with such spirit that it is likely he painted it from life.

Frans Hals' little portrait (Fig. 1), now in Copenhagen, shows Descartes with similarly fierce intensity, and was probably done a year or two later. Most of the many portraits and prints of Descartes known to us were done posthumously and were based on Hals' portrait. Nason's portrait, signed and dated 1647, corroborates Descartes' almost frightening intensity.

(1) For a detailed discussion of some of the portraits of Descartes, see S. Slive, *Frans Hals,* Phaidon 1970-74; Vol. 1, pp 164-168; Vol. 3, No. 175, pp 89-91.

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

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Eight beautiful 14 x 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

Lab Notes

Some of the components of the analytical instrumentation in our laboratory require frequent cleaning for satisfactory instrument performance. The nebulizer assembly on our atomic absorption spectrometer is such a component.

A quick way to clean these components is to use a freezer-weight "ziploc" or a Whirl-pak™ bag and an ultrasonic bath.

By placing the items to be cleaned in a "ziploc" bag, you not only prevent the loss of small pieces, but you can also regulate the cleaning environment within each bag and separate delicate (and usually expensive) glassware from the nuts and bolts. We have found the use of a small amount of a nonionic detergent, such as Triton® X-100, and type II water to be an excellent cleaning medium.

Moreover, since the items to be cleaned are not placed directly in the water of the ultrasonic bath, you can keep the bath filled with tap water and you need not be too worried about the condition of the bath's water. This is truly convenient if you are "borrowing" the ultrasonic bath from the lab next door.

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Jim Genes
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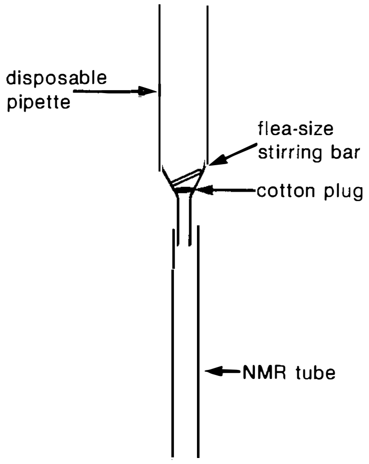
Editor's note: We list ultrasonic cleaners and zipper-top bags. Consult the equipment section of our Catalog/Handbook.

I have found that hexanes may be substituted for benzene in preparing acetals by azeotropic removal of water, thereby eliminating exposure to benzene. However, because of the similarities in refractive index between water and hexanes, the interface between layers in the Dean-Stark trap is difficult to see. This problem may be solved by adding a drop of food color to the bottom of the Dean-Stark trap before starting the reaction. The accumulating water is colored and the interface easily seen. The enjoyment of monitoring the reaction's progress is also enhanced.

Timothy J. Wilkinson
Chemistry Department
Wheaton College
Wheaton, IL 60187-5593

One possible explanation for the general broadening of signals occasionally seen in NMR spectra is the presence of microscopic paramagnetic particles in the sample solution. This problem can be solved by filtering the sample through a plug of cotton with a flea-size magnetic stirring bar placed at the neck of a disposable Pasteur pipette. The stirring bar is very effective for removing the interfering paramagnetic particles.



Dr. Hing Sham
Abbott Laboratories
D-74B; AP10
Abbott Park, IL 60064

Editors note: Aldrich offers stirring bars in the size suggested by the author.

The continuous use of high-capacity drying agents such as silica gel and Drierite® in desiccators and drying columns is hampered by the long reactivation times required for these agents. Our work in the field of air-quality monitoring often requires that large amounts of these desiccants be dried for several hours. The process of reactivation can be greatly speeded up by the use of conventional microwave ovens. Silica gel or Drierite is placed in a large porcelain evaporating dish and treated at full power (500 to 1000 watts) for a period of 10 to 20 minutes. Drying agents activated in this manner are indistinguishable from material dried in a conventional oven.

We have tested the process on silica gel (both indicating and chromatographic grades) and granular Drierite and have found the method satisfactory. Furthermore, we believe the method shows potential for drying other desiccants such as calcium chloride and molecular sieves.

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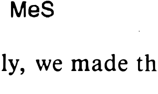
Adam P. Latawiec
Stan E. Macbeth
Ontario Ministry of the Environment
Air Quality Section, South-East Region
Kingston, Ontario K7K 6C2, Canada

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Alfred Bader.

Professor G. Capozzi at the University of Florence suggested that we make methylbis(methylthio)sulfonium hexachloroantimonate, a useful reagent[1] which forms stable episulfonium[2] and thiiranium[3] salts on reaction with alkenes and alkynes. The compound is also useful for the preparation of substituted oxazolines[4] and benzofurans.[5]



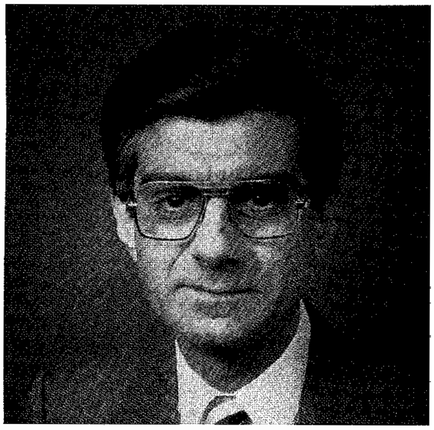
Naturally, we made the compound.

(1) Weiss, R.; Schlierf, C. *Synthesis* **1976**, 323. Capozzi, G. *Pure Appl. Chem.* **1987**, *59*, 989.
(2) Capozzi, G. *et al. Tetrahedron Lett.* **1975**, 2603.
(3) *Idem Chem. Commun.* **1975**, 248.
(4) Capozzi, G. *et al. Tetrahedron Lett.* **1981**, *22*, 3325.
(5) Capozzi, G. *et al. J. Chem. Soc., Perkin Trans. 1* **1981**, *12*, 3106.

It was no bother at all, just a pleasure to be able to help.

Ultrasound in Organic Synthesis

Riaz F. Abdulla
Lilly Research Laboratories
Division of Eli Lilly and Company
Indianapolis, IN 46285



The connection between the rate of a chemical reaction and electromagnetic radiation is a well established axiom in synthetic organic chemistry. Traditional sources of radiation include heat, light and electric discharge. The application of heat limits the temperature of the reaction to either the bulk decomposition temperature of the starting materials or products, or the boiling point of the solvent if one is used. While visible and UV light have found commonplace use, lasers require sophisticated equipment beyond the reach of many budgets, and invoke safety concerns. Electric discharges, while readily achieved, occur in sealed tubes and these produce chemical changes in only very small amounts of material.

During the past twelve years, a body of literature has been generated in laboratories around the world dealing with the acceleration and execution of chemical reactions *via* the use of nonelectromagnetic radiation, *viz.*, ultrasound; this technique has generated a field which has been labeled *sonochemistry*. Ultrasound can be delivered safely and more conveniently, and can generate power densities comparable to those obtained from lasers delivering around 1,000,000 watts/cm^2. This review aims at documenting the literature as it pertains to the execution of organic reactions that are either facilitated by ultrasound, or are otherwise unattainable in the synthesis laboratory.

I. ULTRASOUND CHRONOLOGY

In 1926, experiments were published on the production of sound waves *via* a reversal of the Curie piezoelectric effect, for purposes of submarine signalling.[1]

Subsequently, in 1927, Loomis *et al.* produced sonic waves of great intensity in high-frequency fields of 100,000-500,000 oscillations per second, from a 2-kW oscillator using 12-mm-thick quartz crystals immersed in oil between electrodes with a potential difference of 50,000 volts.[2]

The initial result of these early investigations, *e.g.*, of Langevin in France was a "death ray" for small fish.[3] Richards and Loomis[2] listed the following sonochemical effects:

1. Sensitive or metastable systems are discharged by ultrasound, *e.g.*, NI_3 explodes, yellow HgI_2 is converted to red HgI_2 at temperatures below 120°C.
2. CCl_4 superheated by only 5°C undergoes explosive evaporation.
3. Emulsions of metallic Hg in water can be prepared, which decolorize potassium permanganate. The emulsion remains in suspension for several days.
4. A test tube of distilled water clear to the Tyndall beam before raying shows a cone after raying owing to small glass fragments "atomized" from the walls.
5. Hydrolysis of dimethyl sulfate in basic solution is accelerated by ultrasound.
6. Reduction of potassium iodate by sulfurous acid — the so-called iodine clock reaction — is accelerated.

In spite of these initial reports, the use of ultrasound to accelerate or produce chemical reactions remained dormant until the 1950's when equipment became accessible for general use.[3] After a second period of neglect in the 1960's,[4] papers on sonochemistry started to appear sporadically in the 1970's. Within the past six years, however, sufficient proliferation of the literature has occurred, prompting this review.

II. SONOCHEMICAL EFFECTS — ORIGIN, NATURE AND DESCRIPTION

Ultrasound affects chemical reactions in solution when the sound wave induces "cavitation," the rapid growth and sudden collapse of bubbles within the liquid. In the rarefaction phase of sound waves, a cavitation nucleus undergoes isothermal expansion, during which time gases diffuse into the cavity from the liquid. In the compression half-phase, the bubble is swiftly and adiabatically compressed, leading to intense, localized pressure and temperature differentials, as well as electric discharges, owing to the development of nonuniformly distributed and uncompensated charges on the surface of the bubble. Margulis[5] has shown that in such a process, remarkably high differentials of pressure, temperature, and electrostatic potential are possible.

Before sonochemical effects can be shown, both efficient bubble collapse and a high concentration of collapsing bubbles must be achieved. Eight factors have been documented as affecting the efficiency of bubble collapse:[6]

1. Vapor pressure

For reversible adiabatic collapse, the final temperature reached in a collapsing cavity is given by the equation:

$$T_{\text{final}} = T_{\text{initial}}\ (P_f/P_i)^{(\gamma-1/\gamma)} \qquad \text{(eq. 1)}$$

P = pressure inside cavity
γ = C_p/C_v for the gaseous interior

At high solvent or solute vapor pressure, P_{initial} is high, so that P_f/P_i is small. This will cause T_{final} to be low and thermal effects to be at a minimum.

2. C_p/C_v of the gas in the cavity

According to eq. 1, a large value of C_p/C_v makes the factor $(P_f/P_i)^{(\gamma-1/\gamma)}$ large and T_f high. Thus T_f will be higher if argon, with $\gamma = 1.66$, is dissolved in the liquid than it will be if Freon® 114, with $\gamma = 1.09$, is dissolved.

3. Temperature

Since the composition of the interior of the cavity and solvent vapor pressure depend on the temperature of the solution, so also do γ and π. For each solvent/solute pair, there exists a temperature at which cavitation is the most intense. Thus, water which is saturated with air undergoes cavitation most efficiently at 35°C, while tetralin saturated with air undergoes cavitation most efficiently at 55 °C.

4. *Thermal conductivity*

The highest temperatures and pressures are achieved in adiabatic collapse. Those liquids and dissolved gases of lowest thermal conductivity will therefore produce the most efficient cavitation.

5. *Surface tension and viscosity*

Surface tension and viscosity contribute to the rate of coalescence of bubbles, the size to which they grow, and the nature of their growth and collapse. Thus, bubbles that grow larger than some critical radius will rise to the surface and escape, and may fragment into ineffective bubbles or simply oscillate in size without producing any sonochemical effect. In contrast, bubbles that do not grow large enough during rarefaction, will undergo less favorable adiabatic collapse during compression and will result in lower differentials of pressure, temperature and electrostatic potential.

6. *Frequency of ultrasound*

The minimum time necessary for a bubble of radius R_{max} to collapse is given by eq. 2:

$$T_{min} = 0.915 R_{max} (\rho_l / P)^{1/2} \qquad \text{(eq. 2)}$$

ρ_l = density of liquid
P = pressure of sound

If T_{min} is large compared to the length of the compression phase, the bubble cannot collapse completely, and the temperature and pressure differentials that are ideally possible will not be approached in practice. Therefore, a limit is placed on the frequency of ultrasound that can result in chemical effects.

7. *Acoustic intensity*

Most systems show a direct, linear relationship between sonochemical effects and acoustic intensity.

8. *Shape of reaction vessel and volume of liquid*

Since standing waves can be set up in fluids where the height of the fluid is a function of the half-wavelength of the longitudinal wave, cylindrical reaction vessels with liquid height adjusted to a multiple of the half-wavelength of the ultrasound radiation will produce the maximum cavitation intensity.

III. SONOCHEMISTRY

The general advantage of ultrasound is to accelerate reactions and produce higher yields under more convenient reaction conditions. In homogeneous reactions, *viz.*, those in which all substances are present in one phase, there is experimental evidence that the primary effects of cavitation are responsible for the sonochemical effects observed. In heterogeneous reactions, cavitation is responsible for the production of secondary effects on the phases present, such as efficient mixing, emulsification or the ultrasonic cleaning of metal surfaces. Most sonochemical reactions carried out in water are actually secondary reactions induced by the thermolytic or electronic breakdown of H_2O to give H_2O_2, the major chemical oxidant found in sonicated water.[7]

The synthesis of amino acids has been reported by Sokol'skaya[8] in which a nitrogen-saturated solution of formaldehyde (2.5% aqueous solution of HCHO) was irradiated with ultrasound (850kHz, 10 watts/cm^2, 12h). Glycine was the major product, accompanied by smaller amounts of alanine, lysine and glutamic acid. It is speculated that the synthesis occurs *via* the *in-situ* formation of hydroxylamine and ammonia.

The effects of ultrasonic radiation on nucleic acid bases and on amino acid solutions have been reported and have potentially serious implications for living systems. Thus, McKee *et al.*[9] report that cytosine, uracil, guanine, thymine and adenine all degrade into unknown products in aqueous solution under the effect of 1-MHz (5 watts/cm^2) ultrasound with the rate-limiting step suggested as attack of OH$^\bullet$ on the bases. Staas *et al.*[10] report that 0.8-MHz ultrasound decomposes a variety of amino acids (*e.g.*, glycine, alanine, glutamic acid, glutamine, phenylalanine, histidine, methionine, cystine and cysteine) over a 6-hour period. Cysteine is oxidized to the dimer cystine. The other amino acids are deaminated and decarboxylated by the action of free radicals on the alpha-carbon atom.

The main discussion in this review will address the area of organic sonochemistry, *viz.*, the influence of ultrasound irradiation in laboratory organic reactions. These reactions are subdivided into those that are carried out in homogeneous phases/emulsions and those that are affected or accelerated when multiple phases are present.

IV. HOMOGENEOUS ULTRASOUND REACTIONS

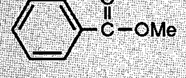
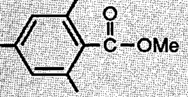
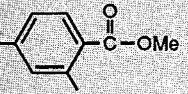
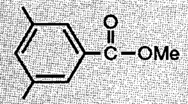
In 1970, Reifsneider and Spurlock reported on the 800-kHz irradiation of di-*n*-butyl sulfide and showed that under argon atmosphere in water there was decomposition to di-*n*-butyl sulfoxide, *n*-butylsulfonic acid, butanoic acid, carbon monoxide, methane, ethylene and acetylene.[11]

It was subsequently concluded that butanal was the intermediate responsible for the production of the hydrocarbon fragments and that a variety of organic aldehydes and acids was fragmented and decomposed by ultrasound.[12]

Homogeneous sonochemical solvolysis of aromatic and aliphatic esters and of alkyl halides is another kind of reaction that has received mention. Moon *et al.*[13] applied 20-kHz ultrasound to a mixture of a series of methyl benzoates and attributed the acceleration of the hydrolysis relative to control experiments as being due to the

Table 1

Isolated % Yields of Acids

Compound hydrolyzed	Reflux (90 min)	Ultrasound (10 min)	Ultrasound (60 min)	100° C, oil (90 min)	120° C, oil (10 min)
	97	98	NT	13	77
	0	0	0	NT	NT
	15	15	94	4	NT
	71	62	96	10	NT

Note: "NT" corresponds to "Not Tested".

secondary effects of cavitation, such as emulsification. Their results are summarized in Table 1.

Kristol *et al.*[14] reported a yield enhancement of about 14% in the hydrolysis of a series of p-nitrophenyl esters and were able to demonstrate that the acceleration was not due to macroscopic heating effects but to the applied ultrasound.

Similarly, Mason *et al.*[15] investigated the homogeneous solvolysis of 2-chloro-2-methylpropane in aqueous ethanol mixtures using 20-kHz/120-watt ultrasound irradiation. Their conclusion was that the energy input *via* ultrasonic irradiation is sufficient to lower the energy of activation for the reaction and that the amount by which this lowering occurs was dependent also on the solvent composition. Mason *et al.* speculate that the dependence of the energy of activation on solvent composition could be due to the disruption of solvent H-bonded structures and increases in the transition-state H-bonded structures under sonication.

A series of primary allylic azides, propargyl azide and azidoacetonitrile have been prepared from the corresponding activated primary halides and aqueous sodium azide under ultrasonic irradiation using a commercial ultrasonic cleaner. Reactions were done in an Erlenmeyer flask and were not reported to explode, though all of the compounds prepared are known to be potentially explosive.[16] These reactions are shown in Scheme 1.

Scheme 1

$$RX \xrightarrow[))))]{NaN_3/H_2O} RN_3 + NaX$$

R

1. $HC{\equiv}CCH_2–$
2. $N{\equiv}CCH_2–$
3. $H_2C{=}CHCH_2–$
4. $H_2C{=}CClCH_2–$
5. $H_2C{=}CBrCH_2–$

X = Cl for 1 - 4, Br for 5

Söllhuber and co-workers have reported facilitation of the Strecker synthesis of amino nitriles from benzo[*a*]quinolizin-2-ones in a homogeneous acetic acid solution using ultrasound at 50-55kHz (150 watts).[17] Equation 3 shows the conversion and Table 2 shows the results obtained.

V. HETEROGENEOUS ULTRASOUND REACTIONS

In contrast to the homogeneous-phase ultrasound-catalyzed reactions, a substantial body of literature has been generated for heterogeneous reactions. This review will attempt to segment these reactions into the following categories:

1. Sonochemistry of organometallic reactions.
2. Miscellaneous applications of ultrasound to heterogeneous organic reactions.

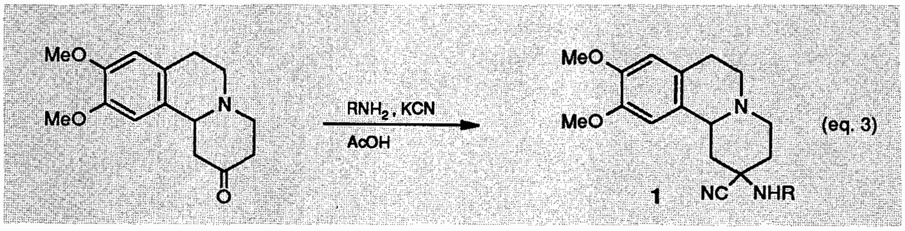
1. Sonochemistry of organometallic reactions

A. Dispersed mercury

Fry *et al.* reported[18,19] that α,α'-dibromocycloalkanones[20] of ring-size 5-12 could be reduced by ultrasonically dispersed mercury in acetic acid to afford cycloalkanones[21] and accompanying α-acetoxycycloalkanones[22] (Scheme 2).

B. Organocopper reagents

Luche *et al.*[20] showed that, as with organolithium reagents, organocopper compounds could be generated *in situ* using a series of alkyl bromides and cuprous iodide in dry THF. Ultrasound irradiation of 80kHz at 30 watts was provided. Thus, α,β-unsaturated ketones were converted efficiently to the conjugate adduct in 76-91%



(eq. 3)

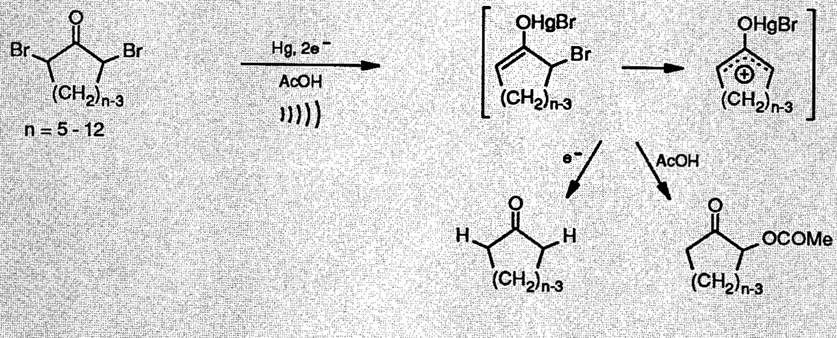
Table 2

Synthesis of Amino Nitriles (1)

R	Yield (%) A*	Yield (%) B	Reaction time A*/(hours)	Reaction time B/(days)
H	100.0	62.1	25	12
n-Bu	87.5	60.3	25	12
C_6H_5	99.7	73.2	35	13
$4\text{-}MeC_6H_4$	97.1	69.3	35	13
CH_2Ph	99.4	78.9	20	12
CH_2CH_2Ph	99.8	68.5	20	12

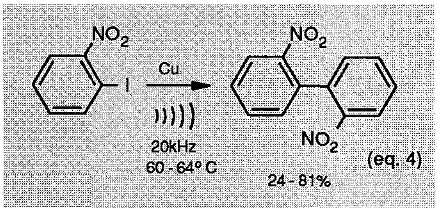
* Sonication

Scheme 2



yields with some examples providing poorer yields, as shown in Table 3.

Recently, Mason *et al.*[21] (eq. 4) reported the enhancement of the Ullmann coupling reaction by ultrasound. They discovered that sonication during the Ullmann diaryl synthesis with 2-iodonitrobenzene in the presence of a 4-fold excess of copper powder leads to a 50-fold increase in reactivity. It is speculated that the rate enhancement is due not only to reduced particle size, but more importantly, to the sweeping away of reacted species from the metal surface, exposing a fresh surface upon which reaction may occur. The authors are currently conducting electron-microscopy studies of the copper surfaces and using different solvents to observe the effects of more powerful cavitation on reaction rate.



The ultrasound-promoted hydroperfluoroalkylation of alkynes with perfluoroalkylzinc iodide and cuprous iodide was reported by Ishikawa and Kitazume.[22] In this manner, a series of terminal alkynes was converted into perfluoromethyl and higher perfluorinated alkenes (Scheme 3).

C. Organolithium reagents

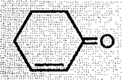
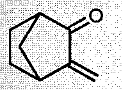
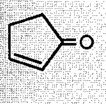
In 1980, Luche and Damiano reported the effects of sonication in the generation and reactions of organolithium reagents with aromatic and aliphatic aldehydes (Barbier Reaction).[23] It was reported that using a 50-kHz, 60-watt source of ultrasound (common laboratory cleaner), the Barbier Reaction could be carried out in wet, technical-grade THF within 1 hour (usually 10-15 minutes) and was a procedure that generated the lithium reagent in good yields, suitable for industrial processes. Equation 5 summarizes some of Luche's results.

More recently, Luche has shown that the Bouveault Reaction is enhanced by ultrasound.[24,25] This treatment of the amides **2** and **3** with aryllithium reagents generated *via* ultrasound, affords the aromatic aldehydes 4 in a *one-step* sonochemical reaction in 60-80% yield depending on the solvent (Scheme 4).

Boudjouk and Han reported the ultrasound-promoted coupling of chlorosilanes and stannanes in the presence of lithium wire.[26] Equation 6 shows the results of

Table 3

Reactions of α,β-Unsaturated Ketones

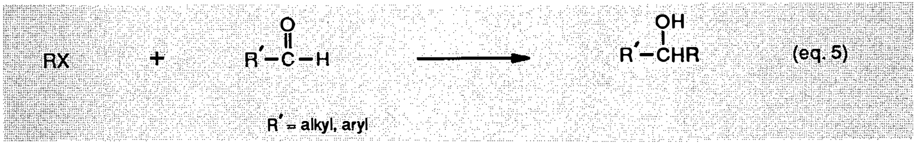
Compound hydrolyzed	Halide	Isolated yield (%) * (sonication)	Literature yield (%)
	n-BuBr	89 - 91	82
	PhBr	64 - 67	—
	n-C_7H_{15}Br	19 - 88	—

* The higher yields are obtained by prior preparation of cuprate followed by addition of ketone.

Scheme 3

$$R_fI + Zn \xrightarrow[\text{THF}]{\text{35kHz, 35W}\ )))))} [R_fZnI] \xrightarrow[\text{THF}\ )))))]{\text{CuI}} [(R_f)_2CuZnI] \xrightarrow[2.\ H_3O^+]{1.\ HC\equiv CR} R_fCH{=}CHR$$

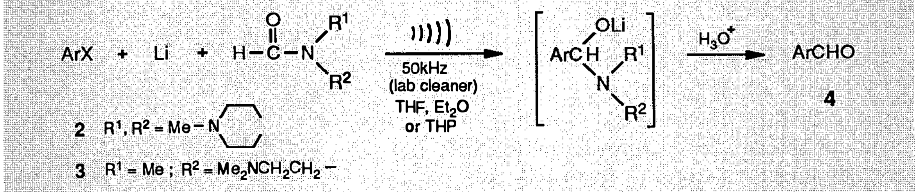
$R_f = CF_3$, i-Pr, n-C_6H_{13}



$$RX + R'-\overset{O}{\overset{\|}{C}}-H \longrightarrow R'-\overset{OH}{\overset{|}{C}}HR \quad \text{(eq. 5)}$$

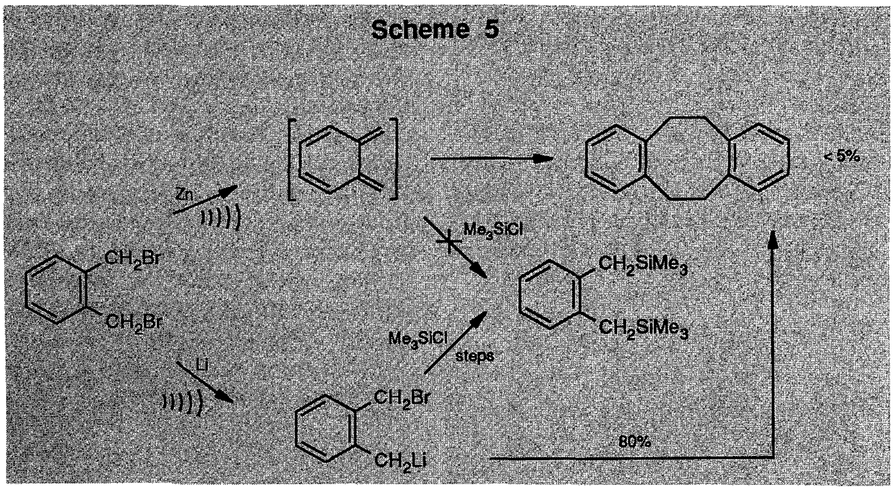
R′ = alkyl, aryl

Scheme 4



$$R_3SiCl \xrightarrow{)))))} R_3Si-SiR_3 \quad \text{(eq. 6)}$$

Scheme 5



Scheme 6

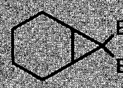
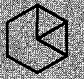
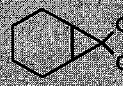
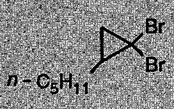
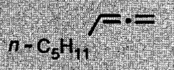
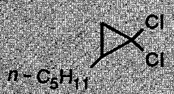
$$R^1R^2PPh \xrightarrow[7\text{-}25\text{ min}]{\text{Li/THF},\ )))} R^1R^2P^-\ Li^+ \xrightarrow{E^+} R^1R^2P\text{-}E$$

$R^1 = R^2 = Ph$

$R^1 = R^2 = Ph$
$R^1 = Me, R^2 = Ph$
E = electrophile (MeI, CH_2Br_2, $ClCH_2CH_2Cl$, $BrCH_2CH_2CH_2Br$)

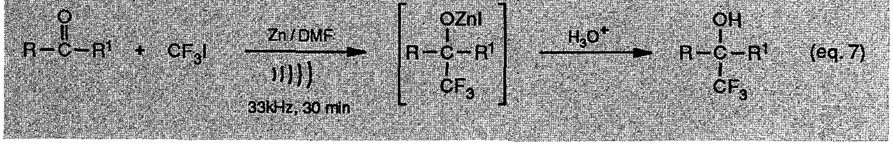
Table 4

Results of the Reaction of gem-Dihalocyclopropanes and Metals under Ultrasonic Irradiation[a]

gem - Dihalocyclopropane	Metal	Main product[b]	Irradiation time (min.)	Isolated yield (%)
	Li		15	46
	Mg		15	44
	Na		5	30
	Li		10	81
	Mg		10	87
	Na		5	68

[a] Room temperature

[b] Identified by ^1H - NMR, IR and GC - MS. The spectra obtained were the same as those in the literature.



$$R-\overset{O}{\overset{\|}{C}}-R^1 + CF_3I \xrightarrow[33kHz,\ 30\text{ min}]{Zn/DMF,\ )))} \left[R-\underset{CF_3}{\overset{OZnI}{C}}-R^1\right] \xrightarrow{H_3O^+} R-\underset{CF_3}{\overset{OH}{C}}-R^1 \quad (eq. 7)$$

their experiments. They noted that in the absence of sonication no reaction was observed. Optimal conditions were the use of 0.01 mole of silane in THF using 0.02 mole equivalent of lithium wire in THF. A common ultrasonic cleaning bath was used. Highly effective Würtz coupling in the presence of ultrasound using lithium wire is also reported.

More recently,[27] Boudjouk *et al.* reported the ultrasonically accelerated reactions summarized in Scheme 5 using lithium or zinc metal powder or wire.

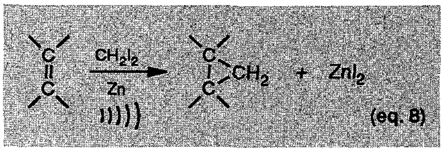
Metallic lithium under sonication was reported by Chou *et al.*[28] to effect reductive cleavage of phosphorus-carbon bonds, affording a simple preparation of tertiary phosphines. The reaction is shown in Scheme 6.

Xu *et al.*[29] discovered that cyclopropylidenes can be generated in a facile manner by reacting geminal-dihalocyclopropanes with lithium, sodium or magnesium under sonication. The reactions generally are completed in 5-15 minutes at ambient temperature. No induction period was observed using THF as a solvent with the ultrasound source being a common laboratory cleaner. Table 4 summarizes the results.

D. Organozinc reagents

A variety of bond-forming reactions using organozinc reagents has been promoted or moderated by ultrasound. In 1981, Kitazume and Ishikawa reported the trifluoromethylation of carbonyl compounds with trifluoromethylzinc iodide, which was prepared by sonicating dispersed zinc in the presence of trifluoromethyl iodide.[30] The α-trifluoromethylcarbinols were obtained in good yields (eq. 7).

Repic and Vogt[31] at Sandoz observed that sonication favorably moderated the course of the Simmons-Smith cyclopropanation reaction using zinc/diiodomethane in the presence of alkenes. Without ultrasound, the cyclopropanation did not proceed unless the zinc was activated either by the formation of zinc-copper or zinc-silver couples. Alternatively, iodine or lithium were used as activators. With sonication (150 watts, 55kHz, common ultrasonic laboratory cleaner), the zinc was activated to such an extent that its reaction with diiodomethane proceeded rapidly but smoothly, without delayed exotherms giving, in the presence of olefins, high yields of cyclopropanated products (eq. 8).

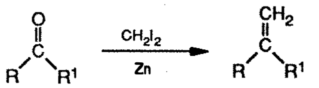


(eq. 8)

Luche *et al.*, continuing their studies on ultrasound-promoted reactions, reported a simplified preparation of diarylzinc reagents and their conjugate addition to α-enones.[32] Subsequently, they expanded this reaction to dialkylzinc conjugate additions to α-enones in the presence of nickel acetoacetonate.[33] Sonication (40kHz, 96 watts) of aryl bromides in the presence of lithium wire and zinc bromide in dry ether or THF at 0°C for 30-35 minutes gave complete formation of the diarylzinc reagents with little or no Ullmann or Würtz coupling (eq. 9). Sonication was essential and lowering the energy output of the sonicator or replacing it by stirring produced less efficient and slower reactions.

$$ArBr \xrightarrow{Li,\ ZnBr_2} (Ar)_2Zn \qquad \text{(eq. 9)}$$

In related experiments, Yamashita *et al.* extended the Simmons-Smith reaction to aromatic and saturated and unsaturated carbonyl compounds obtaining a convenient methylenation with zinc/diiodomethane by sonication in the presence of aldehydes or ketones. Reactions were carried out at room temperature in THF using 53-watts, 41-kHz ultrasound from a common laboratory cleaner (eq. 10).[34]



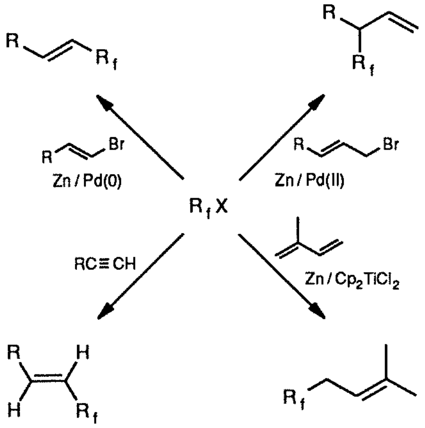
$$R\overset{O}{\overset{\|}{C}}R^1 \xrightarrow[Zn]{CH_2I_2} R\overset{CH_2}{\overset{\|}{C}}R^1$$

(eq. 10)

Bose, Manhas *et al.* used ultrasound to promote the Gilman-Speeter Reaction between ethyl bromoacetate, zinc and a Schiff base to obtain excellent yields of β-lactams in a few hours at room temperature. They rigorously compared traditional Gilman-Speeter Reactions with those run *via* sonication and achieved significant yield increases in the cases studied,[35] even at room temperature (Scheme 7). Yamashita *et al.* have studied the dehalogenation of a series of aryl halides using $NiCl_2/Zn$ in $HMPA/H_2O$ at 60°C with sonication (53 watts, 41kHz). Reaction times varied from 1 to 8 hours and yields of greater than 80% were obtained in several dehalogenations.[36] The authors note that the sonication method proceeds, in the absence of triphenylphosphine, at a 20-50% accelerated rate when compared to the reaction without sonication.

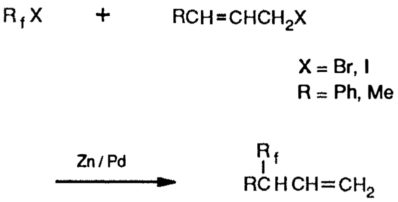
Recently, Kitazume and Ishikawa[37] extended their earlier work[30] and achieved ultrasound-promoted perfluoroalkylation of a large number of substrates by zinc/perfluoroalkyl halides. Accompanying asymmetric induction was obtained when optically active enamines functioned as nucleophiles. The authors first extended their earlier reported carbinol synthesis[30] and provided numerous new examples of attack by perfluoroalkylzinc reagents on carbonyl compounds. In addition, the perfluoroalkylation of vinyl halides, reductive perfluoroalkylation of acetylenes, butadienes and enamines were reported (Scheme 8).

Scheme 8



The perfluoroalkylation of vinyl and allylic halides was achieved by using tetrakis(triphenylphosphine)palladium as catalyst with zinc in THF (Table 5).

In a similar manner, palladium-catalyzed perfluoroalkylation of allylic halides with perfluoroalkylzinc halides, generated *in situ* from perfluoroalkyl bromides or iodides and zinc powder under sonication (32kHz, 35 watts or 45kHz, 100 watts; quartz vessel), proceeded smoothly. Perfluoroalkyl groups were regioselectively introduced (>95%) at the γ-position of the allylic derivatives as shown (eq. 11).

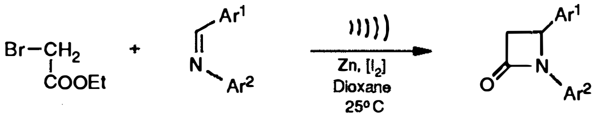


$$R_fX + RCH{=}CHCH_2X \xrightarrow{Zn/Pd} RC\overset{R_f}{\overset{|}{H}}CH{=}CH_2$$

X = Br, I
R = Ph, Me

(eq. 11)

Scheme 7



Ar¹	Ar²	Reaction time (h)	Yield (%)
4 - Me - C_6H_4	4 - MeO - C_6H_4	4	95
Ph	4 - MeO - C_6H_4	5	82
Ph	Ph	5	70
4 - Cl - C_6H_4	4 - MeO - C_6H_4	6	77

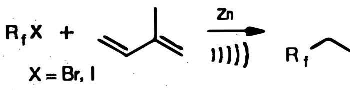
Table 5
Perfluoroalkylation of the Vinylic Position

Hydrolyzed	R_fX	Product	Reaction time (h)	Yield (%)
(*E*) - PhCH=CHBr	CF_3I	(*E*) - PhCH=$CHCF_3$	1	65
	CF_3Br		3	53
	C_2F_5I	(*E*) - PhCH=CHC_2F_5	1	47
	n - C_3F_7I	(*E*) - PhCH=CHC_3F_7	1	66
	i - C_3F_7I		1	72
	n - C_4F_9I	(*E*) - PhCH=CHC_4F_9	1	62
	n - C_4F_9Br		3	32
(*E*) - 4 - MeC_6H_4CH=CHBr	CF_3I	(*E*) - 4 - MeC_6H_4CH=$CHCF_3$	1	67
	CF_3Br		3	41
	n - C_3F_7I	(*E*) - 4 - MeC_6H_4CH=CHC_3F_7	1	68

The hydroperfluoroalkylation of acetylenes and dienes was accomplished by generating perfluoroalkyl cuprates, which were formed *in situ* from perfluoroalkyl iodides or bromides and zinc in the presence of cuprous iodide in THF under sonication followed by addition of the alkyne. The perfluoroalkylation was regioselective but not stereoselective (eq. 12).

$$\underset{X\,=\,Br,\,I}{R_fX} + RC{\equiv}CH \xrightarrow[THF]{Zn/CuI} RCH{=}CHR_f \qquad \text{(eq. 12)}$$

In a similar manner, it was found that reaction of bis(π-cyclopentadienyl)titanium(II) (generated *in situ* from titanocene dichloride *via* reduction) with zinc under sonication accelerated the hydroperfluoroalkylation of isoprene (eq. 13).



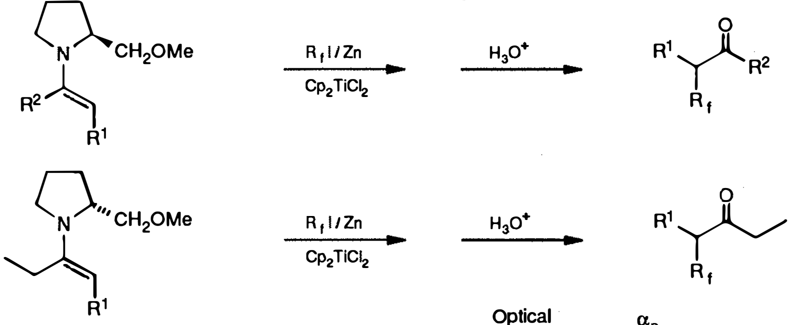
(eq. 13)

Finally, Kitazume and Ishikawa contributed the first reported instance of asymmetric induction with the introduction of perfluoroalkyl groups under sonication. Thus, chiral enamines derived from (*S*)-proline or (*S*)-glutamic acid were perfluoroalkylated and the results are summarized in Scheme 9. No mechanism was proposed nor was the role of the catalyst speculated upon by the authors.

From the many examples and experimental verifications, Kitazume and Ishikawa conclude that ultrasound-induced perfluoroalkylation is the method of choice for such reactions. Mehta and Rao[38] have discovered that ultrasound promotes the olefin-dichloroketene [2 + 2] cycloaddition reaction mediated by zinc. Short reaction times, ambient temperature and use of "bench-top" zinc were the significant advantages (Table 6).

Another example of zinc/copper-promoted cycloaddition under sonication was provided by Joshi and Hoffmann.[39]

Scheme 9



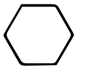
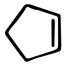
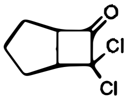
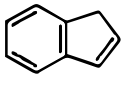
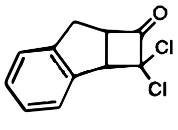
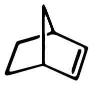
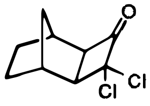
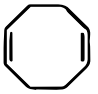
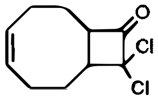
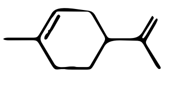
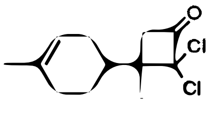
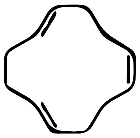
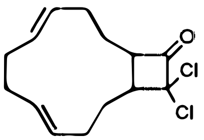
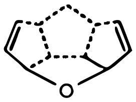
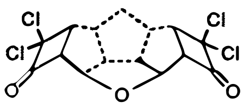
R_fX	R^1	R^2	Yield (%)	Optical purity (%)	α_D (neat: l = 1)
CF_3I	Et	Me	38	62	- 11.3
CF_3Br	Et	Me	46	76	- 13.9
C_2F_5I	Et	Me	51	54	- 16.5
n-C_3F_7I	Et	Me	48	59	- 13.1
n-C_4F_9Br	Et	Me	58	64	- 14.6
n-$C_6F_{13}I$			57	68	+ 9.8
n-$C_8F_{17}I$	Et	Me	56	72	- 8.6
CF_3I	Et	Me	31	67	+ 12.2
C_2F_5I	Et	Me	42	59	+ 18.0

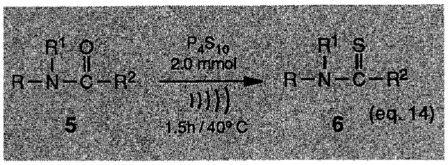
Table 6
Dichloroketene-Olefin Cycloadditions

Olefin	Product	Yield (%)	Reaction time (min.)
		70	20
		80	60
		75	45
		70	45
		80	20
		90	20
		45	30

Thus, for the first time, highly hindered bicyclo[3.2.1]oct-6-en-3-ones became accessible from α,α′-dibromoketones and 1,3-dienes (Scheme 10).

2. Miscellaneous applications of ultrasound to organic synthesis

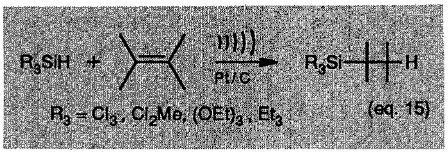
An improved procedure for the synthesis of thioamides **6** from amides **5** using a common ultrasonic laboratory cleaner was reported by Raucher and Klein.[40] The advantages of this procedure over previous methods are shorter reaction times, lower reaction temperatures, and elimination of the need for a large excess of P_4S_{10} (eq. 14).



(eq. 14)

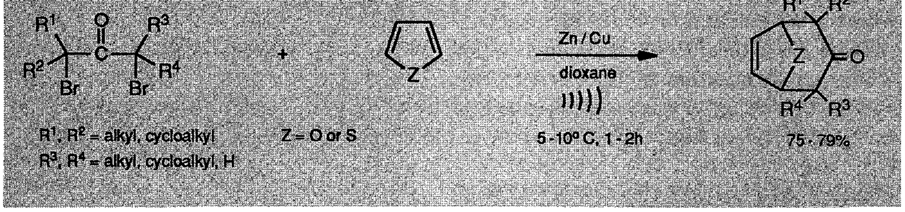
The deleterious effect of ultrasound on ion-exchange kinetics, the sole example of retardation of a process by ultrasound, was discovered by Cheng and Wang in 1982.[41] The authors explained the superiority of simple mechanical stirring over ultrasound by postulating that the shockwave associated with cavitation is responsible for the interruption of the film-diffusion process of ion exchange, resulting in the lower rate. USDA researchers noted in 1983 that a combination of copper chromite catalysis and ultrasound increased the rate of hydrogenation of soybean oil by 100-fold.[42] They reported that the process has three advantages. First, the cost is reduced because the process eliminates nickel as a catalyst. Secondly, it reduces the unstable linolenate fraction to zero while retaining a high level of the desirable linoleate fraction where copper chromite is used. Finally, it eliminates the need to winterize. In a typical procedure, 87% hydrogenation of linolenate in soybean oil was obtained in **9 seconds** at 115 psig hydrogen gas with 1% copper chromite at 181 °C.

Boudjouk and Han reported the ultrasonic acceleration of the hydrosilylation reaction catalyzed by platinum across C = C and C≡C bonds at 30 °C.[43] Previously,[44] hydrosilylations were performed at 45-115 psi at 100-300 °C using trichlorosilane, triethoxysilane and other silanes with terminal alkenes. Boudjouk and Han's results are summarized in Equation 15.



$R_3 = Cl_3$, Cl_2Me, $(OEt)_3$, Et_3 (eq. 15)

Scheme 10



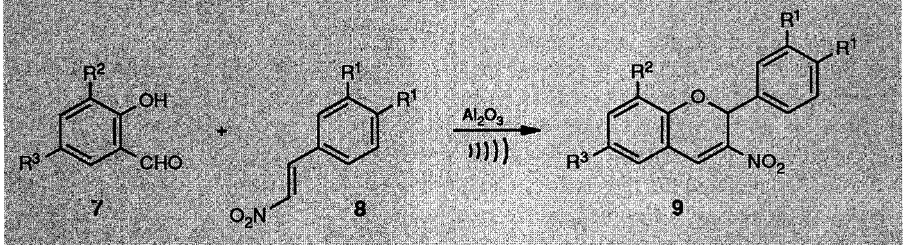
R^1, R^2 = alkyl, cycloalkyl
R^3, R^4 = alkyl, cycloalkyl, H
Z = O or S

Table 7

Oxidation by Solid Potassium Permanganate under Ultrasonic Irradiation

Substrate	Product	Solvent	Reaction time (h)	Yield (%) Ultrasound	Yield (%) Mech. agit.
2-octanol	2-octanone	hexane	5	92.8	2.6
cyclohexanol	cyclohexanone	hexane	5	53.2	4.2
cyclododecanol	cyclododecanone	benzene	24	85.7	15.7
Ph $CH{=}CHCH_2OH$	Ph $CH{=}CHCHO$	benzene	3	82.8	4.5
1-octen-3-ol	1-octen-3-one	benzene	24	43.6	0.8

Scheme 11



7 8 9

R^1 = H, OEt
R^2 = H, OMe
R^3 = H, Cl

Ando *et al.* studied the ultrasound-accelerated oxidation of secondary alcohols by solid potassium permanganate suspended in nonpolar organic solvents.[45] The results are summarized in Table 7. Ando *et al.* note that when alumina is included as a heterogeneous support, there is no advantage from additional sonication.

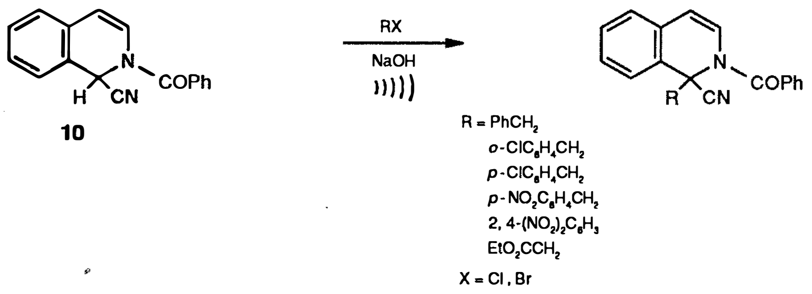
Kabalka and Varma reported[46] that ultrasound had an accelerating effect on the condensation of o-hydroxybenzaldehydes **7** with β-nitrostyrenes **8** using basic alumina as a heterogeneous support in the absence of a solvent. After reaction, the product, 3-nitro-2*H*-chromenes **9**, were extracted with acetone (Scheme 11).

Ultrasound acceleration of phase-transfer catalysis (PTC) has received some attention. Davidson *et al.*[47] N-alkylated a variety of amines with alkyl halides under phase-transfer conditions using both poly(ethylene glycol methyl ether) and quaternary ammonium compounds as catalysts. They observed a decrease in the time required to effect reactions. Indole, carbazole and diphenylamine were the amines used. Table 8 summarizes their results.

Table 8
Yield of N-Alkylation of Amines with Alkyl Halides in Toluene/KOH Using Ultrasound

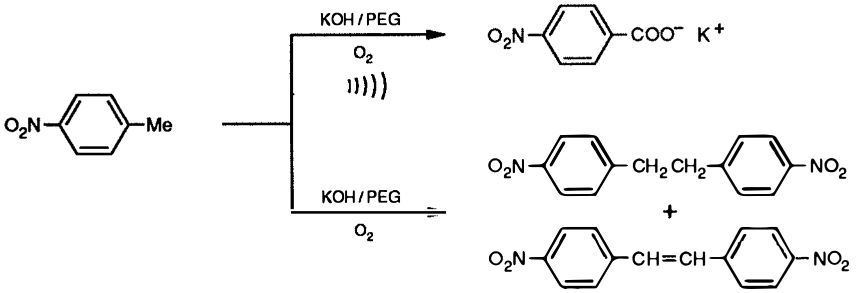
Compound	Alkylating agent	Catalyst	Conditions	Yield (%)
Indole	Iodomethane	PEG methyl ether	Stirred, 20° C, 5h	60
			Ultrasound, 0.5h	65
Indole	Benzyl bromide	PEG methyl ether	Stirred, 20° C, 8h	80
			Ultrasound, 2h	95
Indole	1-Bromododecane	PEG methyl ether	Stirred, 25° C, 72h	48
			Ultrasound, 1.3h	60
Carbazole	1-Bromododecane	Tetrabutyl-ammonium iodide	Ultrasound, 3h	84
Diphenylamine	Benzyl bromide	PEG methyl ether	Ultrasound, 1h	98

Scheme 12

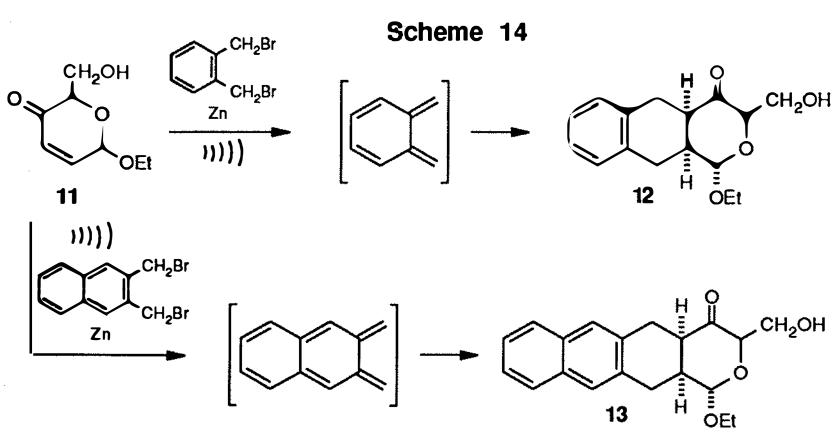


10

Scheme 13



Scheme 14



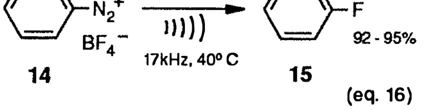
11 **12** **13**

Ezquerra and Alvarez-Builla[48] performed comparative experiments which demonstrated that ultrasonic irradiation improved the yields and reduced the reaction times times in the phase-transfer-catalyzed alkylation of 2-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile, **10** (Reissert compound) (Scheme 12).

The base-catalyzed autooxidation of alkylnitrobenzenes, such as 4-nitrotoluene, to give the corresponding nitrobenzoic acids using ultrasound in the presence of poly(ethylene glycol) (PEG) has been reported by Sasson and Newmann.[49] These conditions reportedly altered the reaction coordinate and, instead of affording the usual dimeric species, gave the carboxylic acid (Scheme 13).

Ferrier and Chew[50] have applied ultrasound in carbohydrate chemistry to obtain as final products optically pure functionalized hexahydroanthracenes and naphthacenes. Reactions of the carbohydrate enone **11** with o-xylylenes derived from 1,2-bis-(bromomethyl)benzene and 2,3-bis(bromomethyl)naphthalene by treatment with zinc powder under sonication afforded tri- and tetracyclic products **12** and **13** which were subsequently converted to anthracene and naphthacene derivatives (Scheme 14). These experiments provided routes to anthracyclinone analogs.

The action of ultrasound on aromatic diazonium salts **13** has been studied by two groups. Müller *et al.* have studied the effects of ultrasound on the course of the Balz-Schiemann Reaction of aryldiazonium tetrafluoroborates and found that in the presence of triethylamine trishydrofluoride in Freon® 113, 17-kHz ultrasound at 40 °C gave 92-95% yields of fluorobenzene (**14**) in 8 hours.[51] Without ultrasound, only 85% yield was obtained after 16 hours of reaction (eq. 16).



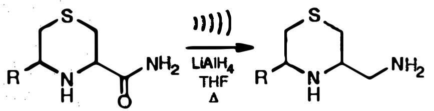
14 **15**

(eq. 16)

The spin trapping of radicals by the destruction of aromatic diazonium salts with ultrasound was performed by Rehorek and Janzen. The spin-trapping technique has been shown to be a suitable technique for detection of free-radical intermediates.[52]

In an effort to address the problem of the degradation of PCB's (polychlorinated biphenyls), whose disposal presents serious environmental problems, Rushing and Connors have discovered a facile procedure using ultrasound.[53] Thus "commercial mixtures" of PCB's were successfully dechlorinated to biphenyl by ultrasonically-assisted electroreduction with and without soluble catalysts. Sonication was found to increase the rate of electrolysis at stirred-mercury-pool electrodes by 2- to 3-fold (eq. 17).

A number of examples are found in the recent literature of sonic acceleration of metal- and/or mixed-hydride reactions with various substrates. Eremeev *et al.*[54] found that ultrasound promoted the $LiAlH_4$ reduction of thiomorpholine carboxamides **16** to amines **17** in THF (55kHz, 125 watts) at 50°C/6h in 80% yield (eq. 18).



16 **17** (eq. 18)

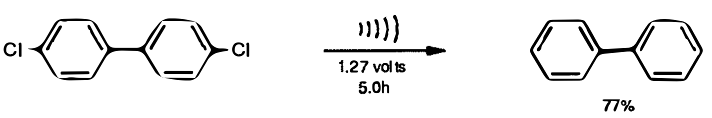
A novel and powerful method for rapid hydroboration was described by Brown and Racherla who observed that, with ultrasound, there was a remarkable enhancement of the rate of hydroboration of certain alkenes with a number of boranes. Without ultrasound, slow reaction was encountered.[55] This enhancement was particularly noteworthy for certain heterogeneous hydroborations. Consequently, some important organoboranes can now be prepared without resorting to long reaction periods or to prolonged heating. Brown and Racherla's results are shown in Table 9.

Brown and Racherla[56] subsequently reported a rapid synthesis of organoboranes using sonication *via* a modified organometallic route. Thus, a variety of organoboranes was prepared directly from organic halides *via* the *in-situ* generation of Grignard reagents in the presence of boron trifluoride etherate for the first time (eq. 19). The authors compared the ultrasound-accelerated reactions to those done traditionally in two steps without sonication (Table 10).

$$3\,RX \xrightarrow[\text{Et}_2\text{O, 15-30 min}]{\text{Mg, BF}_3\bullet\text{OEt}_2\quad)))))} R_3B \quad \text{(eq. 19)}$$

90-100%
99% purity

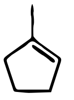
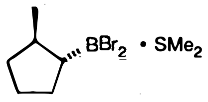
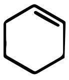
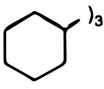
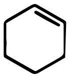
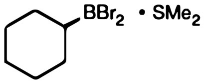
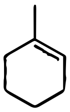
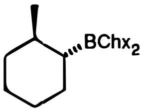
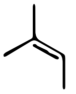
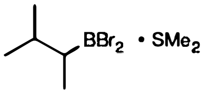
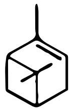
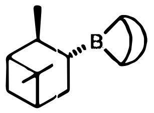
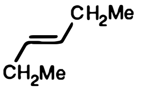
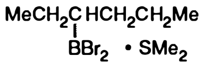
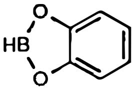
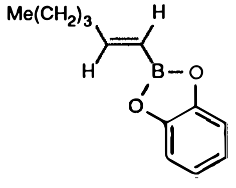
In a similar manner, Liou *et al.* prepared triethylborane by irradiating ethyl bromide and aluminum powder with 43kHz, 180 watts ultrasound to form ethylaluminum sesquibromide. This product was then treated with triethyl borate to give triethylborane in up to 90% yield (Scheme 15). The overall reaction was dependent on the ratio of reagents and the amount of iodine used to activate the aluminum.[57]



(eq. 17)

Table 9

Ultrasound-Assisted Hydroboration

Olefin	Hydroborating agent	Product	Reaction conditions 25° C, Ultrasound	Yield (%)
	$HBBr_2 \bullet SMe_2$		CH_2Cl_2, 1h	99
	$H_3B \bullet SMe_2$		THF, 1h[a]	98
	$HBBr_2 \bullet SMe_2$		CH_2Cl_2, 1h	99
	$HBChx_2$		THF, 1h[a]	99
	$HBBr_2 \bullet SMe_2$		CH_2Cl_2, 1h	98
			THF, 3h neat, 1h[a]	99
	$HBBr_2 \bullet SMe_2$	 $\underset{BBr_2\ \bullet\ SMe_2}{MeCH_2CHCH_2CH_2Me}$	CH_2Cl_2, 2h	97
$Me(CH_2)_3C{\equiv}CH$			neat, 6h	96

[a] Heterogeneous reaction

Scheme 15

$$3\,MeCH_2Br \;+\; 2\,Al \xrightarrow{)))))} Et_3Al_2Br_3 \xrightarrow{B(OEt)_3} Et_3B$$

It has been reported that the reduction of aromatic nitro compounds with hydrazine and iron in the presence of activated carbon in ethanol afforded 88-95% yields of the corresponding anilines. However, the reduction failed with aliphatic nitro compounds such as nitromethane.[58]

Scheme 16

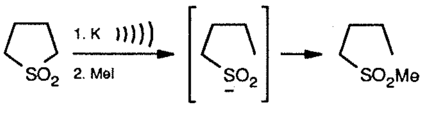
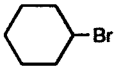
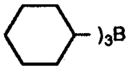
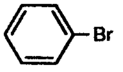
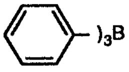
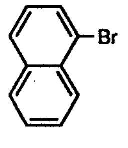
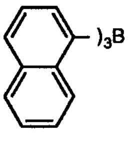
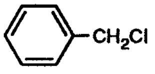
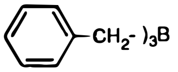
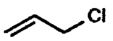
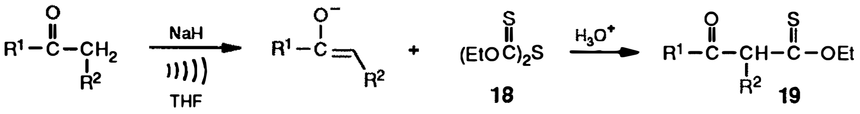


Table 10
Trialkylboranes via Ultrasound

Alkyl halide	Product	Reaction time (h) No ultrasound (Et_2O, Δ)	)))) (Et_2O, Δ)	Yield (%) No ultrasound (Et_2O, Δ)	)))) (Et_2O, Δ)
n-PrBr	$(n\text{-}Pr)_3B$	2	0.25	98	100
		24	0.50	90	99
		3	0.25	94	97
		24	0.50	91	93
		24	0.50	96	99
		3	0.25	94	94

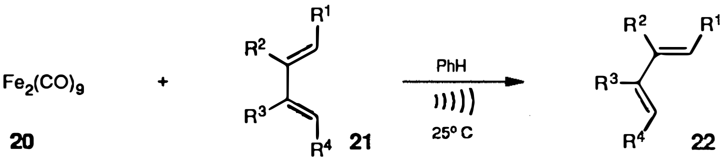
Scheme 17



18

19

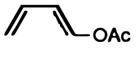
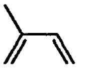
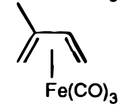
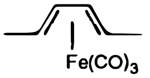
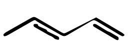
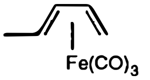
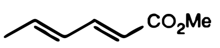
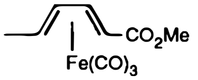
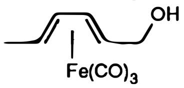
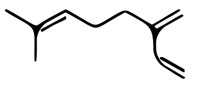
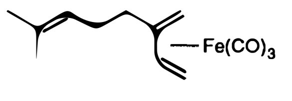
Scheme 18



20

21

22

Diene	Complex	Yield (%)
		100
		70
		50
		62
		100
		51
		95

Chou and You[59] reported a novel ring-opening reaction of cyclic sulfones with ultrasonically dispersed potassium in anhydrous toluene at 0°C under nitrogen. Scheme 16 provides some examples of this method. The authors report generation of a blue color and rapid disappearance of potassium under sonication.

In another reported use of ultrasound, Chou *et al.* observed the formation of bis(alkylphenylphosphino)alkanes from corresponding bis(diphenylphosphino)-alkanes *via* alkali metal cleavage followed by alkylation.[60]

Miethchen *et al.* have reported an "unconventional" Friedel-Crafts alkylation with 2,2,4-trimethylpentane in the presence of a variety of Friedel-Crafts catalysts.[61] Mixtures of mono- and di-*tert*-butylated benzenes are obtained, but the preparative value of this procedure is not apparent.

Vega *et al.* have described the generation and C-ethoxythiocarbonylation of enolates using ultrasound.[62] Thus, when enolates were treated with *O,O*-diethyl trithiodicarbonate (**18**), only the O-ethyl 3-oxothiono esters **19** were obtained in 75% yield. Without ultrasound during enolate generation, yields diminished to 18% (Scheme 17).

Ultrasound has also been applied by Ley *et al.*[63] to the preparation of tricarbonyliron diene complexes. Thus, the reaction of nonacarbonyldiiron (**20**) with 1,3-dienes **21** was promoted by ultrasound, affording high yields of the corresponding η^4-(diene)tricarbonyliron complexes **22**. These products are potentially synthetically useful reagents[64] (Scheme 18).

VI. CONCLUSION

Numerous organic reactions are accelerated by ultrasound under both homogeneous and heterogeneous reaction conditions. The savings in time effected by sonicating these reactions is now well documented. Most ultrasound reactions may be effected by means of simple, readily available "common laboratory cleaners." For the cognoscente, an array of transducers and probes is available. All should enjoy the savings in time and increases in yields that the numerous documented examples of sonication offer.

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About the Author

Dr. Riaz F. Abdulla was born in Calcutta, India, in 1943. He received the B.Sc. degree from St. Xavier's College, University of Calcutta, in 1964. He obtained the Ph.D. degree from the Indian Institute of Technology, Kharagpur, India, in 1970, working on the synthesis of β-lactams.

Dr. Abdulla was Sir P.C. Ray Gold Medallist at St. Xavier's College in 1965, and Damon Runyon Memorial Cancer Research Fellow at Princeton University from 1971-1973, under Professor E.C. Taylor. He joined Lilly Research Laboratories, Greenfield, in 1973. He was Group Leader, Computer-Assisted Molecular Design, Division of Agricultural Chemistry, in 1987, and is presently Manager, Supercomputing Applications, Eli Lilly & Co., Lilly Corporate Center, Indianapolis.

The following are some of the reagents mentioned by Dr. Abdulla and listed by Aldrich. For a listing of ultrasonic cleaners see page 43.

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Aldrichimica Acta
Volume 21, Number 3, 1988

Synthetic Methodology in the Context of Natural Product Total Synthesis

John D. Roberts

Dedicated to Professor John D. Roberts on his seventieth birthday

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Aldrichimica Acta

Volume 21, Number 3, 1988
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About Our Cover:

As readers of "About our Cover" know, our chemist-collector loves puzzles, particularly those involving Biblical paintings of the 17th century.

The painting reproduced here (oil on canvas, 41½ x 52¼ inches) was in the collection of the Earls Spencer at Althorp for more than three hundred years, attributed to the great Italian painter Domenico Fetti, whose work it is not. Our collector is not even certain that it is Italian; the landscape looks so Dutch, *ca.* 1620 — but who painted this masterpiece? Is it, per chance, by two hands — the landscape by a Dutchman in Italy and the great figures by an Italian? What luck that we do not know — were the artist(s) known, it might not have been sold.

The subject is clear: the angel appearing to Hagar (*Gen. 16,* 7-14). There were two such meetings. In the first, shown here, the angel tells Hagar to return to Abraham and Sarah. In the second, the angel helps Hagar and Ishmael after their expulsion from the patriarch's home.

The first appearance of an angel was not to a king or a general, nor even to Noah or Abraham, but to a runaway Egyptian slave. There is a lesson here, as there is in the angel's questions, which each of us should ask ourselves:

"Whence camest thou, and whither wilt thou go?"

Coloristically, this painting is a marvel, with the wonderful contrast between the rich red of Hagar's mantle and the shot silk of her gown juxtaposed with the coolness of the angel's shimmering white robe and wings. And what an angel, beautifully naive, the same angel that art lovers have met so often in annunciations to Mary. Hagar listens so attentively, her face framed by that multicolored gypsy bern — appropriate for Hagar the Egyptian, for in the 17th century, gypsies were believed — as the name implies — to be descendants of the Egyptians. Now Hagar is contrite, but the mocking face on the fountain reminds us of her previous haughtiness.

If someone had told our chemist-collector before he acquired this painting that he could not tell the difference between paintings done *ca.* 1620 in Rome and in Amsterdam, he would just have laughed. He doesn't laugh anymore, and would greatly appreciate help from readers.

This is one of our chemist-collector's finest paintings, and hence a fitting cover for the *Acta* dedicated to Professor Jack Roberts.

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among the thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historian information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

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Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta,* we now offer a collection of articles from volumes 1-15: 354 pages of great review articles, in one beautiful hardbound volume. All articles are included except those whose subject matter has been updated in later issues.

Lab Notes

A good example of the utility of the Flash Vacuum Thermolysis (FVT) method[1] is the preparation of ^{13}C-labeled acrylonitrile *via* elimination of acetic acid from 2-cyanoethyl acetate.[2] Pyrolysis of acetates to olefins.is a classic thermal reaction[3] that proceeds essentially quantitatively under FVT conditions.[2] However, the separation of volatile olefins like acrylonitrile from acetic acid requires laborious workup techniques, such as preparative GC or flash distillation. This purification step can be omitted when a benzoate (in our case 2-cyanoethyl benzoate instead of 2-cyanoethyl acetate) is used instead of an acetate. Elimination occurs under the same experimental conditions, but the eliminated benzoic acid crystallizes directly behind the hot zone in the bend of the quartz tube at room temperature and acrylonitrile is collected in the trap in essentially pure state (see Fig. 1).

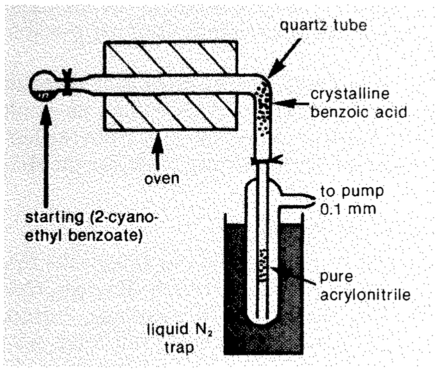

Fig. 1

We feel that the use of benzoates instead of acetates makes the preparation of simple, pure (volatile) olefins by FVT a very convenient procedure, requiring only that the benzoate be sublimed into the quartz tube.

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Leo W. Jenneskens
Ulfert E. Wiersum
Akzo Corporate Research
P.O. Box 9300, 6800 9B
Arnhem
The Netherlands

I wish to report that 2.8 denier white poly(propylene) staple is an outstanding replacement for glass wool in many applications. As a porous plug for packing columns, it has the following advantages: it packs densely and will hold back 30-micron particles without breakthrough of the particles. It does not produce fragments which can clog lines downstream, thus it can be applied in systems using microbore tubing. It is hydrophobic and ideal for systems where moisture must be excluded. Its flexibility allows it to be packed in very-small-diameter bores, allowing reliable plugs or filters to be made simply in 0.0625-in. i.d. columns. While poly(propylene) is relatively chemically inert, it dissolves in hot nonpolar solvents; so this is a possible limitation. Since poly(propylene) fibers are manufactured on a large scale for yarns and fabrics, the cost is potentially on the order of a few dollars per pound for large-scale chemical applications.

Douglas Jewett
The University of Michigan Medical School
Cyclotron/P.E.T. Facility
Division of Nuclear Medicine
3480 Kresge III
Ann Arbor, Michigan 48109-0552

Editor's note: We now offer the poly(propylene) wool recommended by Professor Jewett.

The Editor
Aldrichimica Acta

Dear Editor:

When I prepared my paper, *Ultrasound in Organic Synthesis,* for the *Aldrichimica Acta,* Vol. 21, No. 2, 1988, I relied heavily on notes I had made for a presentation on sonochemistry at Eli Lilly in 1982. In that presentation, I had used a review on sonochemistry prepared by Dr. Charles B. Little, then at the Department of Chemistry of the University of Illinois in Urbana. That review had been presented by Dr. Little at a Chemistry Department seminar in December, 1981, and I cited the review in my presentation at Lilly. Unfortunately, my own notes of my talk at Lilly did not include the reference to Dr. Little's work, and in the years between my presentation at Lilly and my preparation of the paper for you, I had forgotten this important source and so did not cite it.

It has also been brought to my attention that my paper failed to cite some seminal work on sonochemistry, for instance:

Suslick, K.S.; Goodale, J.W.; Schubert, P.F.; Wang, H.H. *J. Am. Chem. Soc.* **1983,** *105,* 5781.

Suslick, K.S.; Johnson, R.E. *ibid.* **1984,** *106,* 6856.

Suslick, K.S. *Mod. Synth. Methods* **1986,** *4,* 1.

Suslick, K.S.; Hammerton, D.A.; Cline, R.E., Jr. *J. Am. Chem. Soc.* **1986,** *108,* 5641.

Suslick, K.S.; Casadonte, D.J. *ibid.* **1987,** *109,* 3459.

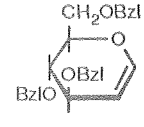
Suslick, K.S.; Flint, E.B. *Nature* **1987,** *330,* 553.

Riaz F. Abdulla, Ph.D.
Lilly Research Laboratories

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Alfred Bader.



Dr. David Crich at University College, London, suggested that we offer tri-*O*-benzyl-D-glucal, an important glycoside building block.[1-3]

Naturally we made it.

1) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987,** *28,* 2723.
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3) Kinzy, W.; Schmidt, R.R. *Ann.* **1985,** 1537.

It was no bother at all, just a pleasure to be able to help.

Synthetic Methodology in the Context of Natural Product Total Synthesis*

Dedicated to John D. Roberts on his seventieth birthday

Robert E. Ireland
Thomas Jefferson Professor of Chemistry
Chemistry Department
University of Virginia
McCormick Road
Charlottesville, VA 22901

I. INTRODUCTION

The plethora of structurally fascinating natural products has for many years driven the art and science of synthetic organic chemistry. In many instances, these naturally occurring molecules are of important therapeutic value to mankind and have, therefore, stimulated much synthetic work. Nevertheless, other systems lacking this intrinsic incentive have been important substrates for the exploration of valuable synthetic methodology. The purpose of this article is to demonstrate how synthetic strategy has been the force that has led to the development of such useful methodology as well as the construction of complex natural products.

II. TERPENOID SYSTEM

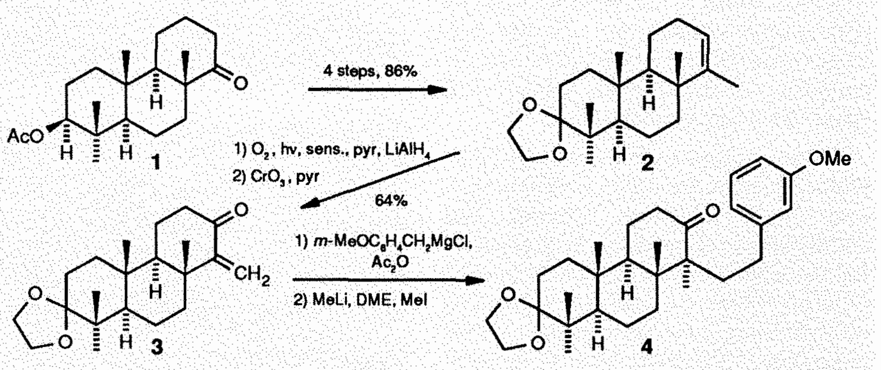
1. Germanicol synthesis

One such case is the investigation of a route for the synthesis of some terpenoid systems. In the course of the investigation of the total synthesis of the unsymmetrical triterpene germanicol,[1] the utility of the α-methylene ketone **3** became apparent. Through organometallic conjugate addition, followed by enolate trapping and then methylation, **3** led to the regioselectively and stereoselectively alkylated ketone **4** in good yield (Scheme 1). This latter ketone **4** was converted to the target molecule. The crucial structural and stereodemanding steps were accomplished through the α-methylene ketone **3** and they proved that such systems are of great synthetic value.

In this case, the preparation of the α-methylene ketone **3** was readily accomplished through photooxygenation of olefin **2** which itself was available by classical methods from ketone **1**. In order to generalize this synthetically valuable strategy, it was necessary to devise means for the construction of other less readily accessible olefins such as **5** to serve as photooxygenation substrates. Such systems could *not* be obtained by the classical methodology used for the transformation of ketone **1** to olefin **2**; a new method was necessary. The methodology devised for this process has been found to have synthetic value beyond the problem at hand.

A means for the deoxygenation of an enol was sought as a possible synthetic route. Enolization of a keto group provides for the regioselective introduction of a double bond *if* the carbon-oxygen bond can be reductively cleaved. Such a process was available through metal-amine reduction of an enol phosphate derivative.[2] For olefin **5**, this translated into reducing enone **6** with lithium/ammonia, and trapping the resulting enolate with diethyl phosphorochloridate in order to fix the location of the double bond. Subsequent reduction of the derived enol phosphate **7** gave olefin **5** in excellent yield (Scheme 2). The availability of **5** then led to further explorations into

Scheme 1

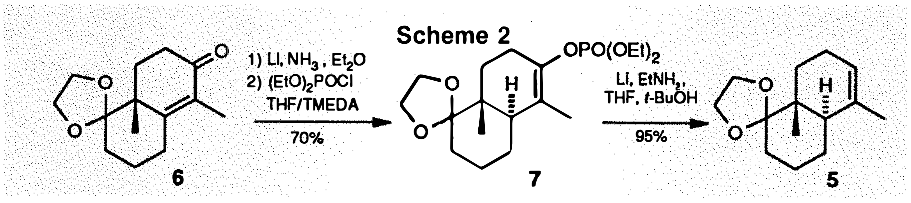


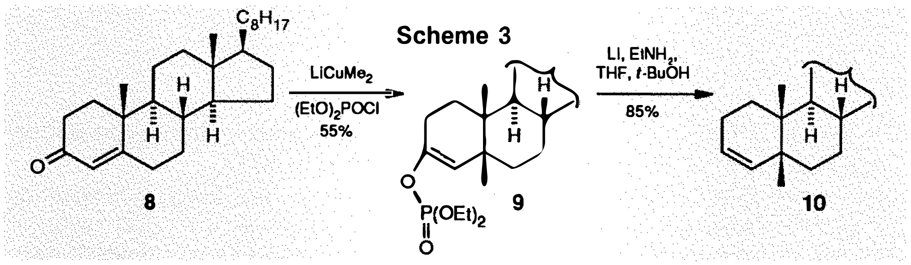
Professor Robert E. Ireland (left) receiving the A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Alfred Bader, Chairman of the Board, Sigma-Aldrich Corporation.

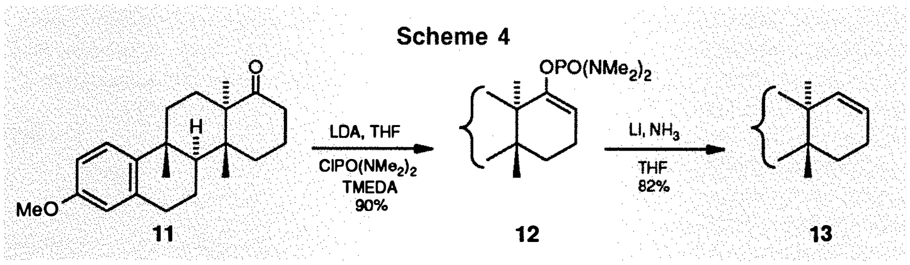
terpene and steroid syntheses through conjugate additions to derived α-methylene ketones.

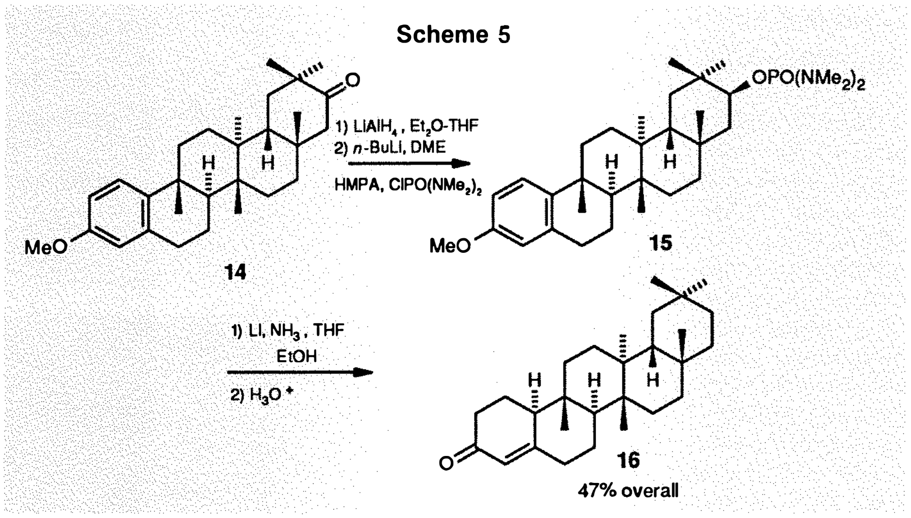
The efficiency and uniqueness of the phosphate reduction process suggested further examination of this method, and some very useful transformations have resulted. The conjugate addition/enolate-trapping process proved effective for the conversion of enone **8** to olefin **10** in good yield[3] (Scheme 3). Direct enolization and then trapping with *N,N,N',N'*-tetramethyldiamidophosphorochloridate provided access to the phosphorodiamidate derivative **12** from the tetracyclic ketone **11**[4] (Scheme 4). The phosphorodiamidate group makes the reduction process even more facile and opens the way to effect general carbon-oxygen bond cleavage. In the case at hand, reductive deoxygenation[5] of the enol phosphorodiamidate **12** was *more facile* than anisole-ring reduction in lithium/ammonia solution with no alcohol present. When alcohol was added to the reducing medium, both phosphorodiamidate cleavage *and* anisole-ring reduction took place, *i.e.*, the conversion of the aromatic ketone **14** to enone **16**[6] occurred (Scheme 5).

The latter process showed that the phosphorodiamidate derivative of simple alcohols can be reductively removed. This useful reduction process can be generalized for the removal of other alcohol-bearing systems. Three structurally demanding cases (Scheme 6) are the neopentyl system in alcohol **17** that gives ketal **19** in excellent yield, the tertiary axial alcohol **20** that cleanly provides hydrocarbon **22** and the hindered secondary alcohol **23** that is very effectively removed by this procedure.[5] An added feature of the phosphorodiamidate grouping is its stability under a wide range of common reaction conditions. This group is most effectively removed by metal/ammonia reduction but it can also be removed with excess *n*-butyllithium to regenerate the original alcohol.


Scheme 2

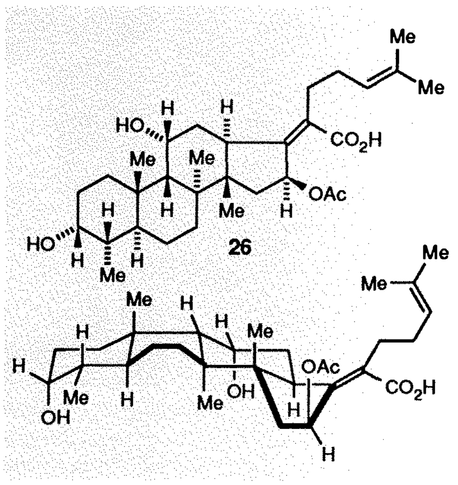

Scheme 3


Scheme 4


Scheme 5

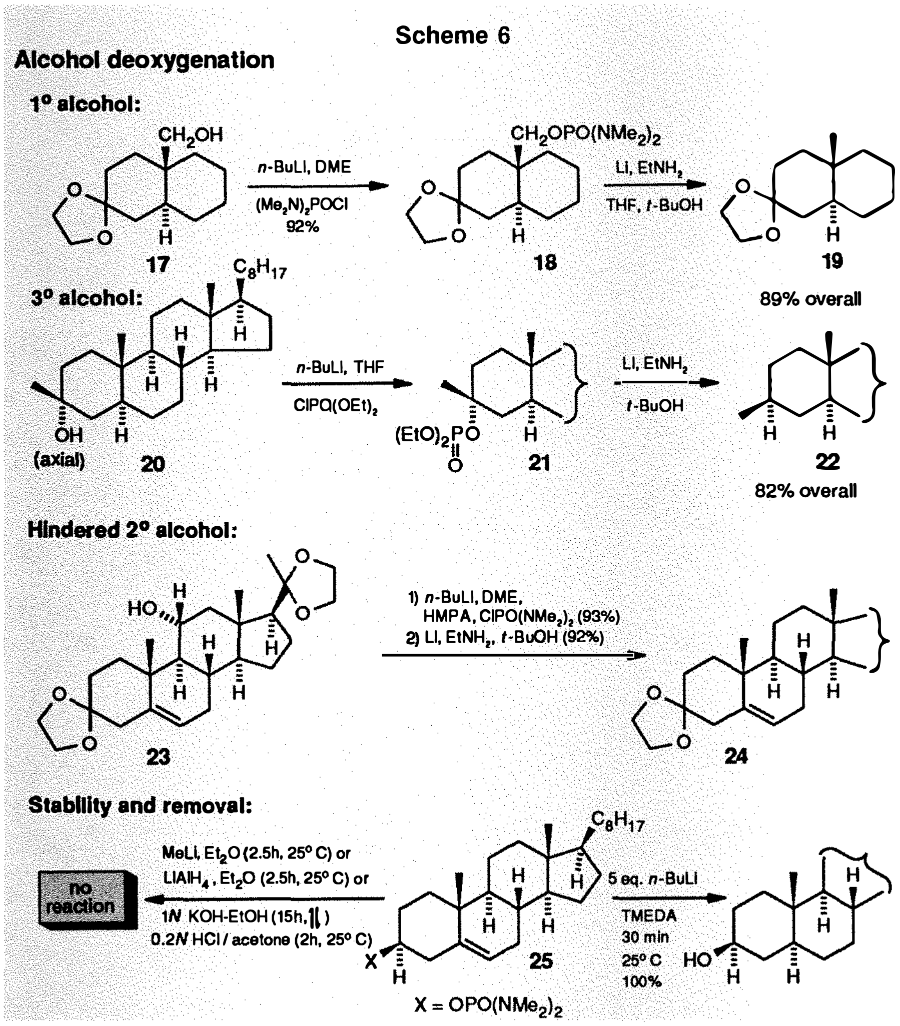
2. Fusidic acid synthesis

During the formulation of a plan for the synthesis of the terpenoid antibiotic fusidic acid (**26**),[7] the deoxygenation process played a central role. Aside from the general logistics problems that a molecule such as **26** presents, the presence of a boat B-ring posed a severe challenge. Standard steroid and terpenoid synthetic methodology that relies on metal/ammonia reduction of enones will not produce the strained fusidic acid nucleus. This was shown[8] in a model tricyclic series when the monoketal of diketone **27** gave the *cis-syn-trans* ketone ketal **30** exclusively on metal/ammonia reduction or catalytic hydrogenation (Scheme 7). Catalytic hydrogenation or hydroboration of the C-5 - C-6 double bond of bisketal **28** also led exclusively to the same *cis-syn-trans* skeleton. The *inter*-molecular reactions on these substrates take place reasonably from the less hindered β-face of the molecule and lead to the undesired *cis-syn-trans* structures.



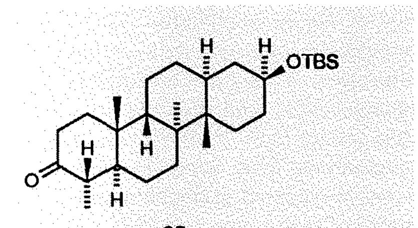
In order to overcome this structural feature of the tricyclic model system, advantage was taken of the C-5 - C-6 double bond of **28**. This led to β-epoxide **29** wherein the C-6 hydrogen is of necessity α-oriented and intramolecular rearrangement then gave the desired *trans-syn-trans*

Scheme 6



ketone **32**. That this B-ring boat structure **32** was thermodynamically the less stable arrangement was shown by base-catalyzed isomerization to the then known *cis-syn-trans* structure **31** (Scheme 7).[8]

While the foregoing procedure led to the desired *trans-syn-trans* ring system, a new problem was presented: how to remove the C-6 ketone *without* isomerization to the *cis-syn-trans* structure. Again, the phosphorodiamidate reductive deoxygenation played a central role. Thus, hydride reduction of **32** and then acylation with the phosphorochloridate reagent led cleanly to phosphorodiamidate **33** without isomerization. Lithium/ethylamine reduction then secured the *trans-syn-trans* structure, and hydrolysis provided diketone **34** (Scheme 8). Similar transformations gave the tetracyclic system **35** which formed the basis for further explorations of a fusidic acid synthesis.[9]



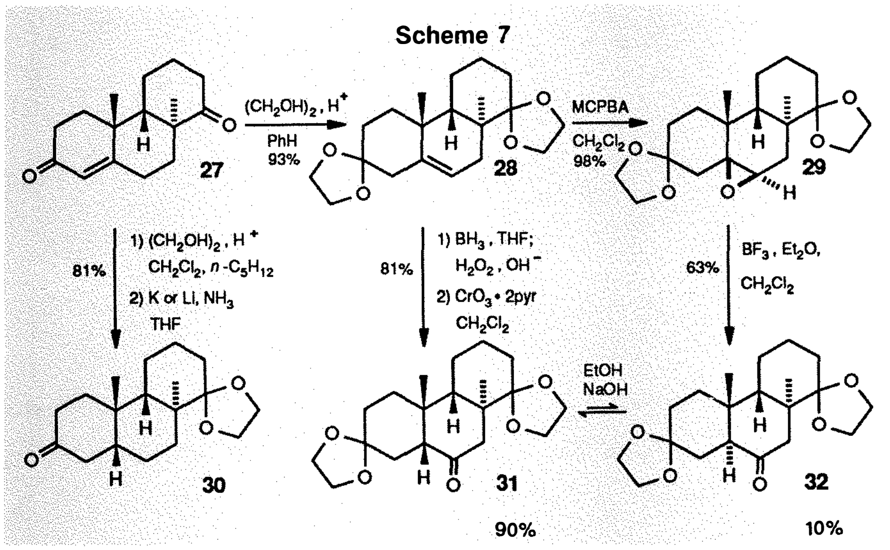
35

3. Aphidicolin synthesis

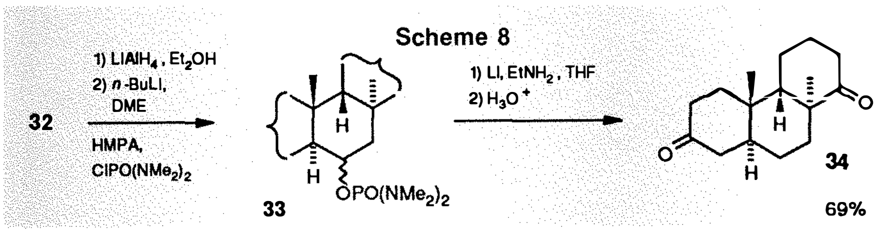
Another useful method was developed during a synthesis of aphidicolin (**37**).[10] The tetracyclic enone **38** became available[11] as a result of a synthetic scheme *via* the saturated A/B *cis* ketone **36**. The problem posed by the aphidicolin structure at this point was the addition of two *different* substituents at C-4 in place of the double bond present in enone **38**. Metal/ammonia reduction of **38** gave A/B *trans* **39** without blocking enolization at C-2. Alkylation of C-4 was not possible (Scheme 9). Direct alkylations of the enolate of **38** gave unacceptable yields of monoalkylation products and while metal/ammonia reduction and then alkylation led to monoalkylation of C-4, further C-4 alkylation of the resulting A/B *trans* fused saturated ketone again would require blocking at the C-2 position.

The methodological solution to this problem should have general utility for the formation of α,α-(dissimilarly)-disubstituted ketones of many types. Thus, again the value of the α-methylene ketone, here prepared *in situ*, was shown. Utilization of the Petrov reaction[12] efficiently allowed for the conversion of **38** to phenylthiomethyl

Scheme 7

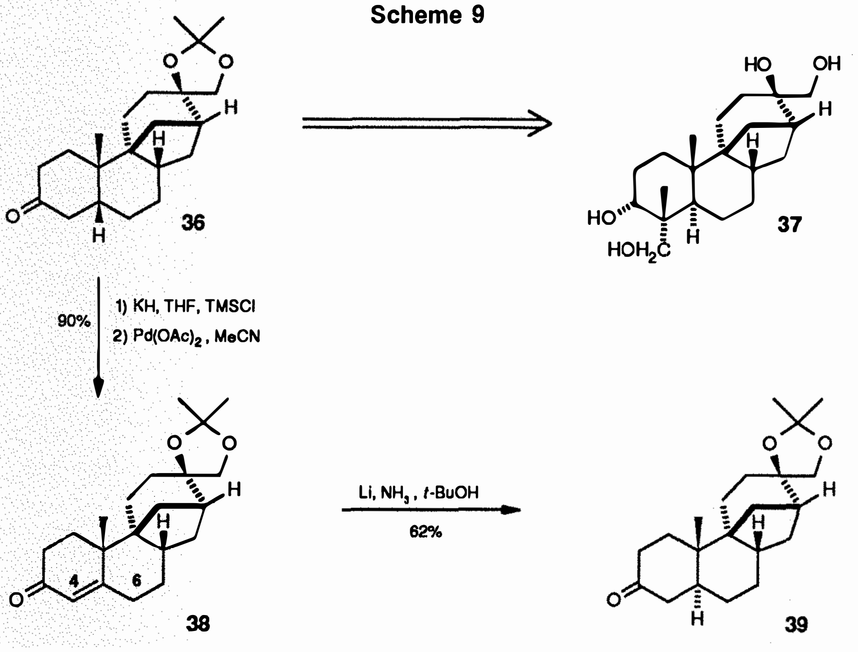


Scheme 8

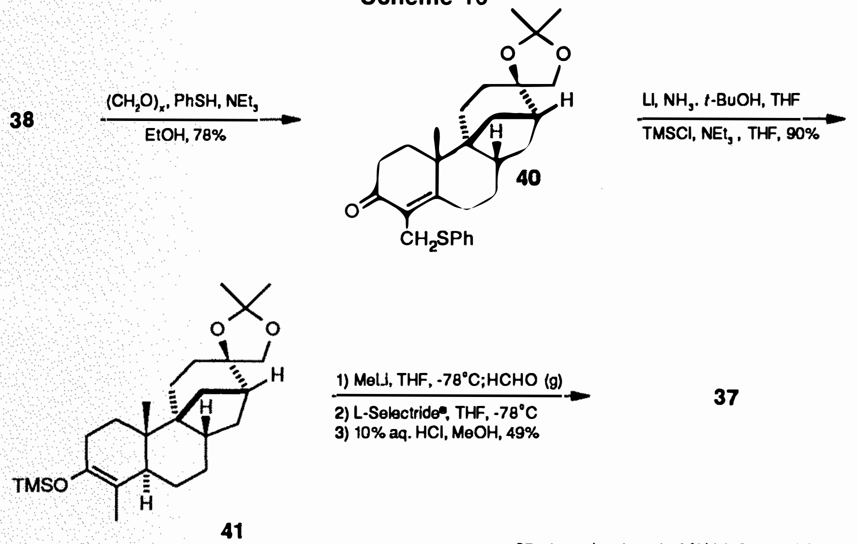


enone **40** (direct Mannich condensation occurred exclusively at C-6[12]). Subsequent lithium/ammonia reduction provided, *via* the α-methylene ketone formed by thiophenoxide elimination, the C-3(4) ketone enolate formed by reduction of this reactive intermediate. After the enolate was trapped with TMSCl, the silyl enol ether **41** was formed in excellent yield (Scheme 10). This process thus accomplished the formation of the A/B *trans* ring fusion and the introduction of the C-4 methyl group and preserved the reactivity of the C-3(4) ketone enolate for further reaction. Subsequent formylation,[13] reduction and hydrolysis completed the synthesis[14] in an expeditious manner. The utility of the bisalkylation procedure remains to be explored.

Scheme 9



Scheme 10



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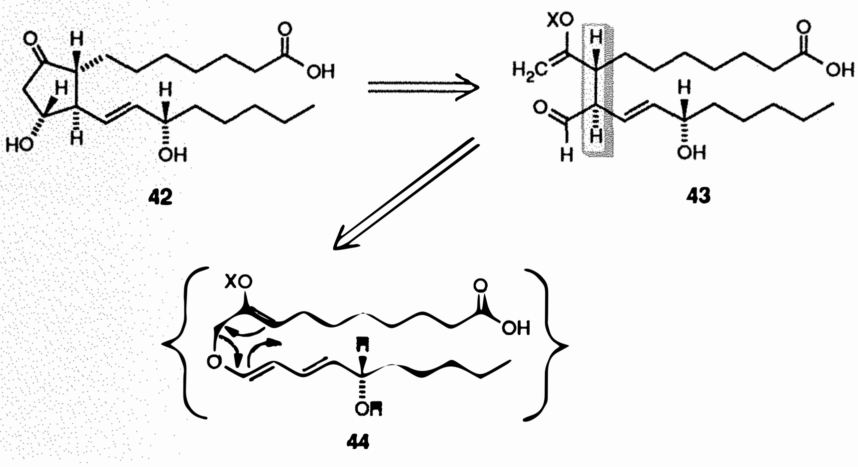
III. PROSTAGLANDIN SYSTEM

Another structure that has elicited much synthetic work and has thus been responsible for some valuable synthetic methodology is the prostaglandin system. These biologically important structures are generally based on a 1,2-disubstituted cyclopentane skeleton, and the oxidation pattern that results from lipoxygenase action on arachidonic acid generally produces a 1,3-dioxygenated cyclopentanoid. An example of such a system is PGE_1 (**42**). From a purely synthetic point of view, these structural features suggested the retrosynthetic approach. Thus, the reverse aldol process converts the PGE_1 molecule to the stylized aldehyde enol derivative **43** in which only *one* carbon-carbon bond (highlighted) serves to unite top and bottom halves of the system (Scheme 11). This stylized intermediate (**43**) presents the intriguing question of whether synthetic means could be found that would serve to join preformed top and bottom halves with the formation of this crucial carbon-carbon bond. This process seemed possible through the application of the Claisen rearrangement and suggested that a hypothetical intermediate such as **44** would accomplish the transformation. Obviously, in order to realize these operations, the hypothetical intermediates **43** and **44** would require modification to protect and/or alter functionality carried through the process; but the first order of business was the exploration of the feasibility of the Claisen rearrangement for the scheme proposed.

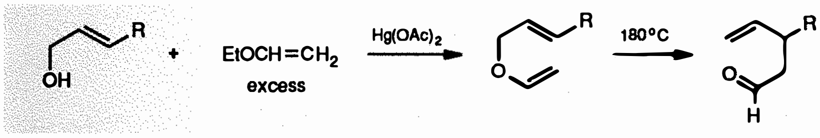
Scheme 11



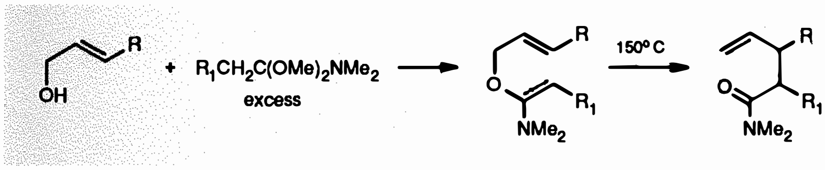
1. Claisen methodology

a. Ester enolate Claisen rearrangement

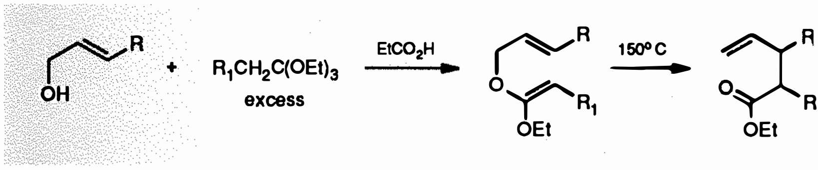
The Claisen rearrangement procedures available at the time were the vinyl ether



(eq. 1)

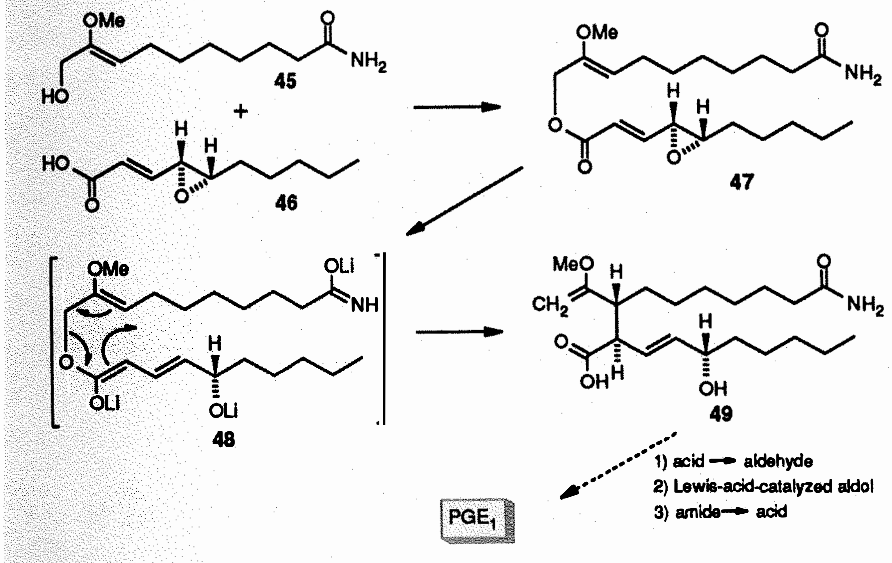


(eq. 2)

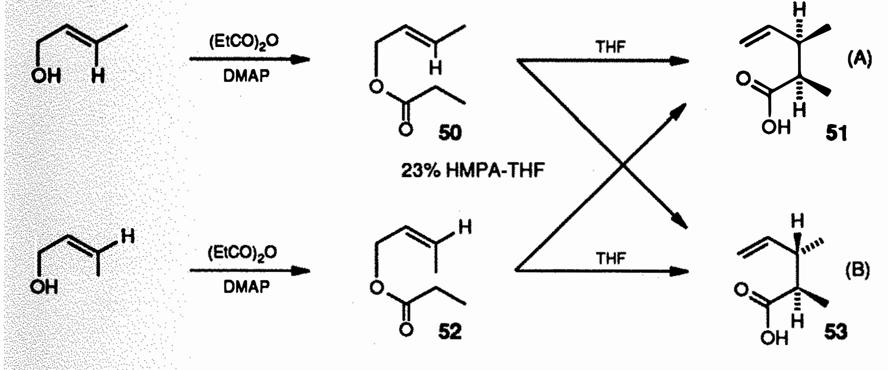


(eq. 3)

Scheme 12

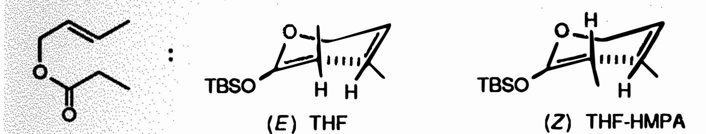


Scheme 13



Conditions: LDA, sol., -78°C, then TBSCl, THF, HMPA; warm to 67° C; 10% HCl, THF.
Product ratios are 4-5:1 in favor of structure shown.

For chair-like transition state:



(*E*) THF
erythro (A)

(*Z*) THF-HMPA
threo (B)

(Burgstahler, eq. 1),[15] the amide acetal (Eschenmoser, eq. 2)[16] and the ortho ester (Johnson, eq. 3)[17] processes. As valuable and elegant as these procedures are, they did not satisfy the requirements set forth for the proposed prostaglandin synthesis. In each case, the carbonyl-generating component must be used *in excess* and the logistic value of the bottom-half component in the proposed synthesis precluded its utilization in such excess. Means were required that would unite the top and bottom halves of a Claisen rearrangement precursor in stoichiometric fashion. A solution was proposed (Scheme 12) whereby top-half allylic alcohol **45** would be joined to bottom-half acid **46** through esterification. The required 1,5-diene system **48** was then generated by enolization of the resulting ester **47**. Subsequent Claisen rearrangement of this ester enolate **48** was proposed to result in the union of the two halves by formation of the crucial carbon-carbon bond to generate the acid **49**. Functional-group modification and intramolecular aldol condensation would then lead to PGE$_1$ (**42**).

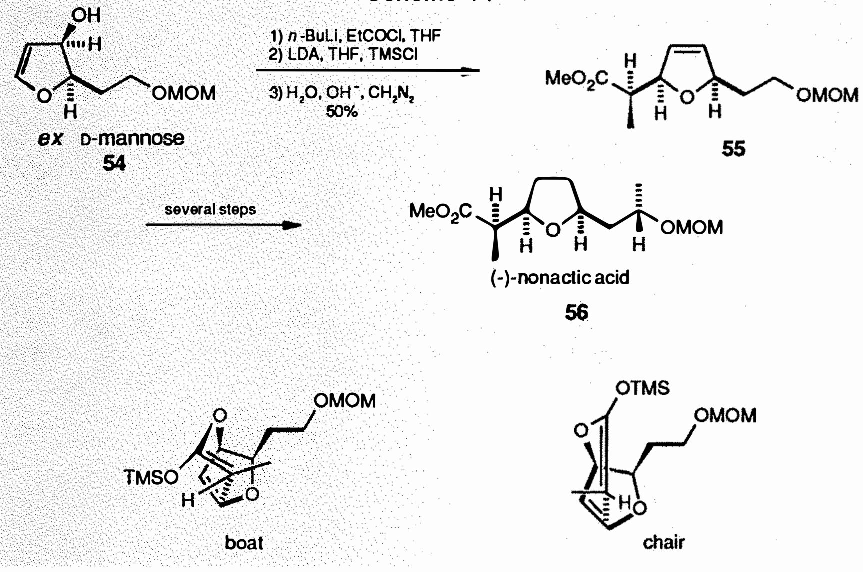
While this scheme has yet to lead to PGE$_1$ (**42**), the A series was prepared. The investigation of the ester enolate Claisen rearrangement that this prostaglandin synthesis spawned has resulted in the development of valuable methodology.

Utilizing the crotyl propionates **50** and **52**, it was shown early that both the ester enolates themselves and, better, the derived silyl ketene acetals underwent the Claisen rearrangement efficiently and at surprisingly low reaction temperatures (37-67 °C) (Scheme 13).[18] Particularly valuable was the definition of the role of the solvent in the stereochemical outcome of the ester enolization process.[19] Through definition of the geometry of the two participating double bonds, the stereochemistry of the newly formed single bond is proscribed when the character of the Claisen transition state is selectively either chair- or boat-like.[20] For the acyclic systems **50** and **52**, the chair-like transition state can be assumed to be the lower energy arrangement and then definition of the product stereochemistry results in the assignment of the geometry of the ester enolate. With this caveat about the transition state, the enolization in pure THF gave the *Z*-enolate, and in 23% HMPA/THF the *E*-enolate was formed. From the former enolate, the *E*-ketene acetal was generated and led to the *erythro*-acid (A). Correspondingly, the *E*-ester enolate produced the *Z*-ketene acetal and thence the *threo*-acid (B).

b. Nonactic acid synthesis

The chair-like Claisen transition state may not always be assumed to be the lower energy pathway and in rigid cyclic systems, the boat-like arrangement is preferred.[21] In the nonactic acid (**56**) synthesis (Scheme 14), if the reasonable assumption is made that ester enolization takes the same stereochemical course as above, analysis of product stereochemistry suggests that rearrangement prefers the boat-like process. Thus, conversion of the furanoid glycal **54** to its propionate ester *in situ* and then enolization, trapping and rearrangement provided ester **55** through the boat transition-state pathway. Definition of the stereochemistry of this process resulted from the conversion of **55** to (-)-nonactic acid (**56**).[22]

Scheme 14

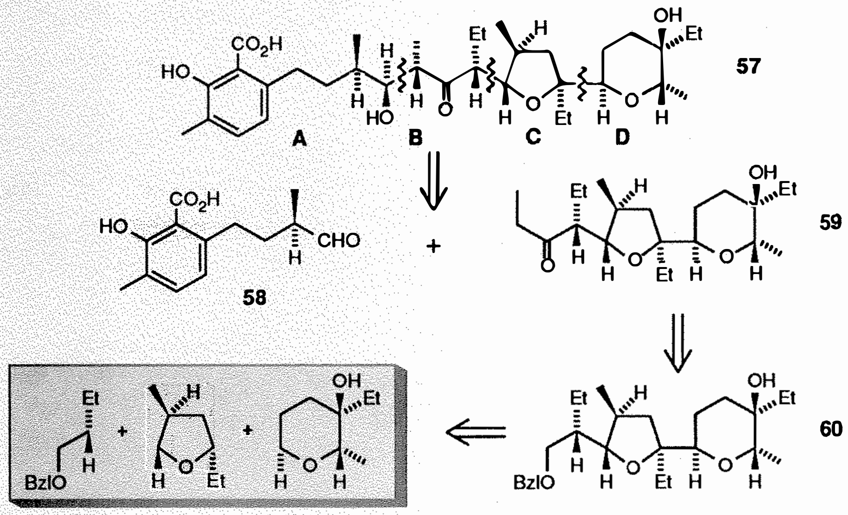


c. Polyether systems

(i) Lasalocid A synthesis

Based on these parameters, the scope of the ester enolate Claisen rearrangement was explored through the synthetic challenges presented by several other complex natural products. A class of such systems is the polyether antibiotic group. The first proving ground was lasalocid A (X537A) (**57**). This system can be schematically envisaged as shown (Scheme 15). Thus, the retroaldol process converts lasalocid A (**57**) into aldehyde **58** and ketone **59**, which can be obtained from the ether **60**.[23]

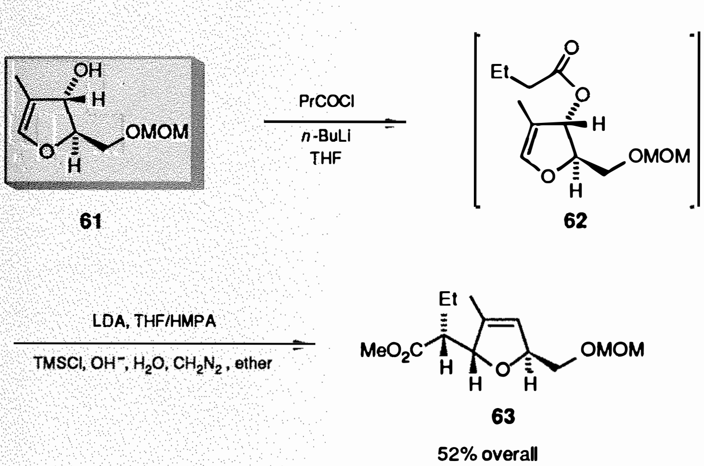
Scheme 15



Ether **60** represents the core challenge for this synthesis as well as for other polyether antibiotics and their analogs. If efficient general means can be developed for the construction of ether **60**, these same procedures hold the potential for use in the construction of a wide range of polyethers. Central to the current approach was the development of a potentially iterative building block approach which suggests that ether **60** be made from the subunits highlighted by the box. It was necessary to develop means for the stereoselective addition of the 4-carbon side chain to the tetrahydropyran ring *and* the union of the tetrahydrofuran and tetrahydropyran rings through the stereoselective formation of the 1,2-glycol ether single bond. This is akin to the preparation of the dimethyl ether of ethylene glycol (diglyme) by formation of the carbon-carbon bond (not an easy task). Here was a case where structure suggested the development of methodology, and the ester enolate Claisen rearrangement was up to the challenge.

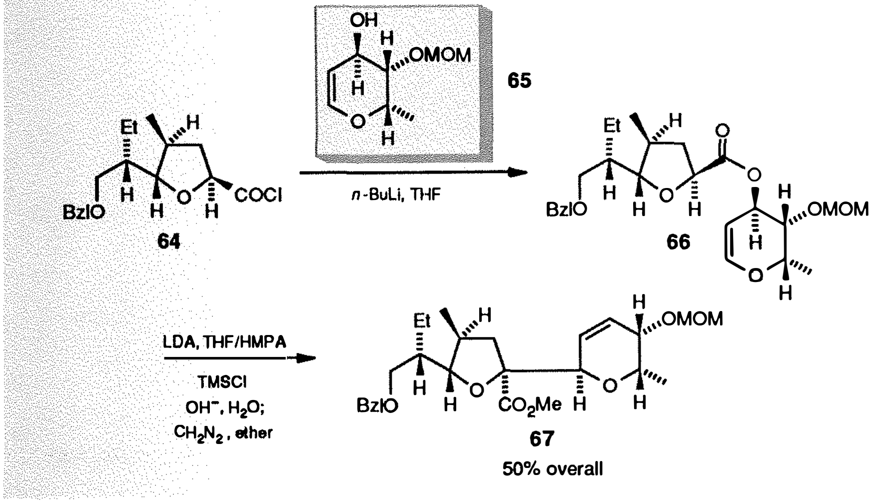
Rearrangement of the *n*-butyrate **62** of furanoid glycal **61** proceeded smoothly and gave the desired isomer **63** in 52% overall yield (Scheme 16). The unstable butyrate

Scheme 16

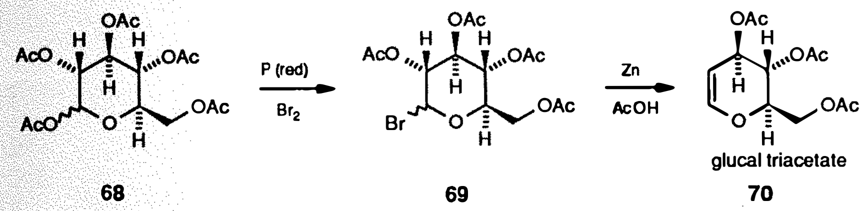


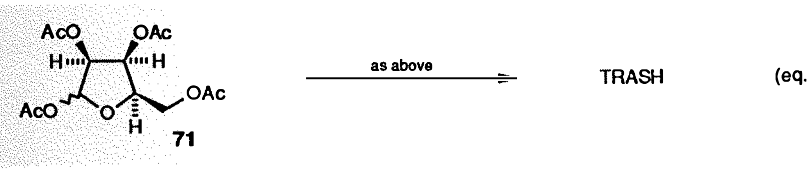
52% overall

Scheme 17



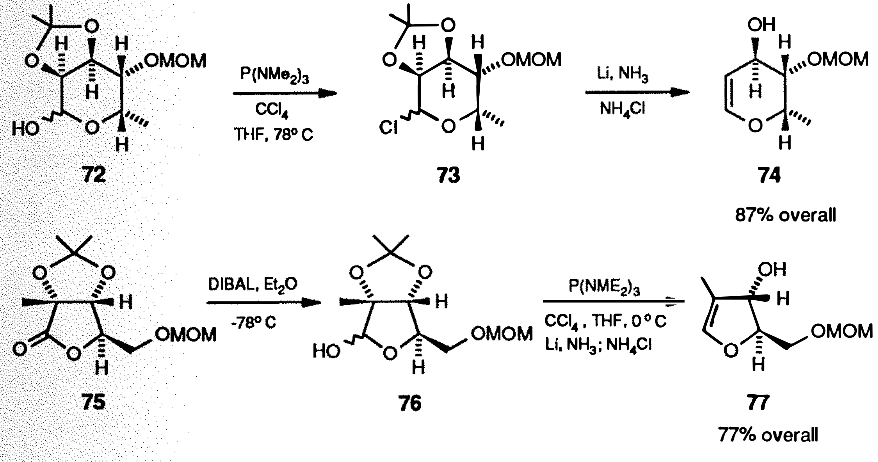
Scheme 18





(eq. 4)

Scheme 19



62 was not isolated during this process, as elimination readily gave the undesirable furan derivative. Correspondingly, esterification of the pyranoid glycal **65** with the furanoid acid chloride **64** and then rearrangement readily produced the dicyclic diether **67** in 50% overall yield (Scheme 17). The convergency of this building block approach led to an efficiency that overshadowed these basic yields and made the crucial dicyclic diether readily available. In addition, the simplicity of the methodology (esterification and then rearrangement) lent itself easily to expansion and modification of the synthetic scheme.

(ii) Glycal formation

As useful as this approach to polyether synthesis proved to be, it was necessary to first develop general means for the synthesis of *glycals.* The standard procedure still used for pyranoid glycals is that due to Fischer and Zach[24] which worked well for the conversion of glucose pentaacetate (**68**) to glucal triacetate (**70**) through reductive elimination of the glycosyl bromide **69** (Scheme 18). Acid treatment of a furanoid analog, such as **71**, leads to furanoid glycal acetate destruction (eq. 4). A more general, high-yield process was necessary and was developed by reductive elimination under *basic* conditions. Thus, utilization of the fragmentation of a 2,3-acetonide under basic metal/ammonia reduction of a glycosyl halide gave *both* the pyranoid *and* furanoid glycals in high yields (Scheme 19).[25] This method has been applied to many monosaccharides with uniformly good results.

(iii) Monensin problem

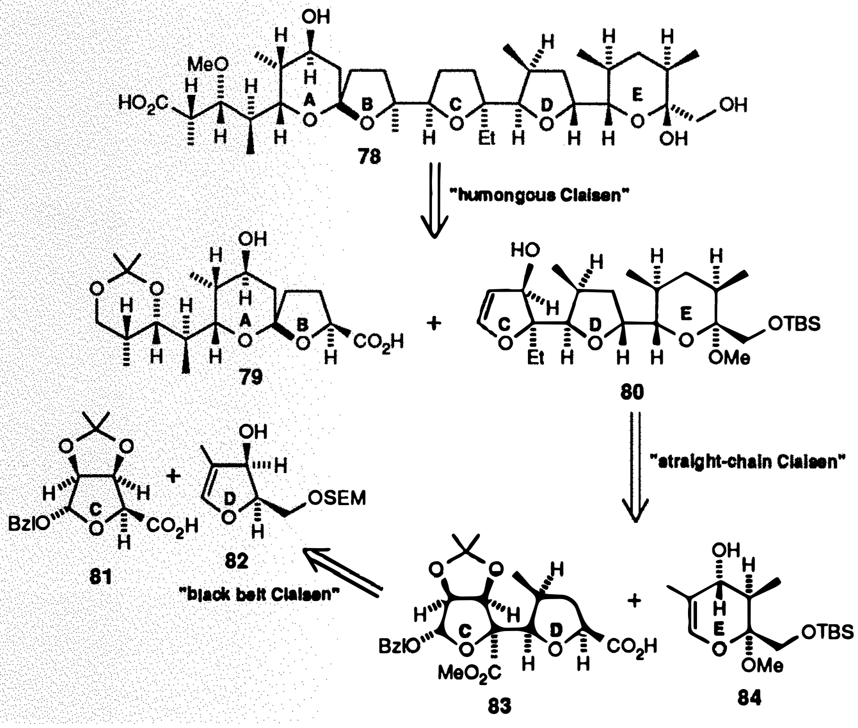
The building-block approach to the polyether portion of lasalocid having been proved successful, attention was turned to the more complex polyether system, monensin (**78**). The synthetic plan for this molecule required the addition of several more dimensions to the scope of the ester enolate Claisen rearrangement. A plan is shown that highlights the demanding stages of the synthesis (Scheme 20).

In order to preserve the convergence of the approach, the first retrosynthetic conversion was to acid **79** and alcohol **80**. Should this Claisen rearrangement step be synthetically possible, it would become one of the largest and most complex rearrangements attempted and, as a result, this step was fondly named the ***Humongous Claisen.***

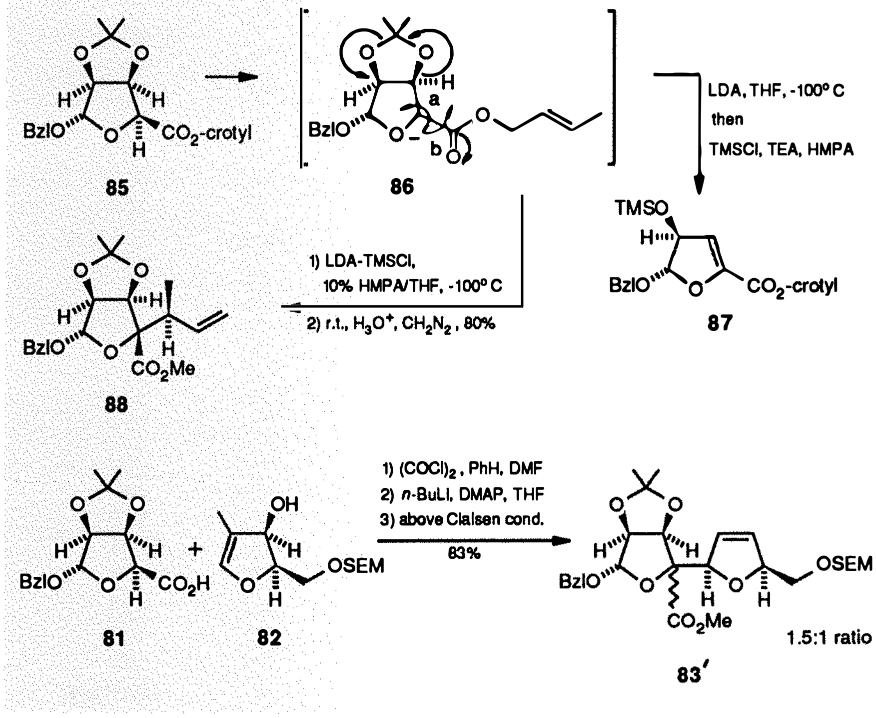
The next retrosynthetic step entailed the addition of the *E* ring **84** to the preformed C/D ring system **83**, again through a Claisen rearrangement. In contrast to previous unions of this sort, it was necessary to *decarboxylate* the initial Claisen product rather than merely convert the carboxyl group to the methyl or ethyl group. The Claisen rearrangement by its nature generates *branched*-chain acids and the requirement was that the carboxyl group be removed so as to form a *straight* carbon chain. This process was euphemistically labeled the ***Straight Chain Claisen.***

The formation of the C/D ring system **83** *via* the Claisen rearrangement sequence from the two furanoid systems **81** and **82** was also fraught with potential difficulty. Enolization of the ester formed between acid **81** and alcohol **82** could easily lead to reductive fragmentation prior to being trapped by a silylating agent. In order to make such a Claisen sequence viable, excellent experimental technique was required and again the sequence acquired a pet name, ***Black Belt Claisen.*** Under the now established ester enolate trapping conditions (enolization and then addition of the silylating agent) the crotyl ester **85** did, indeed, lead exclusively to the product **87** by reductive fragmentation *via* **86a** (Scheme 21). However, when ester enolization was carried out in a solution of *premixed* LDA and TMSCl and then the reaction mixture warmed to ambient temperature, the ester enolate Claisen rearrangement took place in an excellent 80% yield.[26] Preliminary experiments had shown that LDA and TMSCl were compatible in a reaction mixture. Application of this procedure to the combination of the furanoid acid **81** and the alcohol **82** led in excellent yield to the desired dicyclic ether **83**.[27] From this experiment, it appeared that the *in situ* trapping of an enolate in such a mixture of reagents was a useful means to avoid potentially deleterious side reactions.

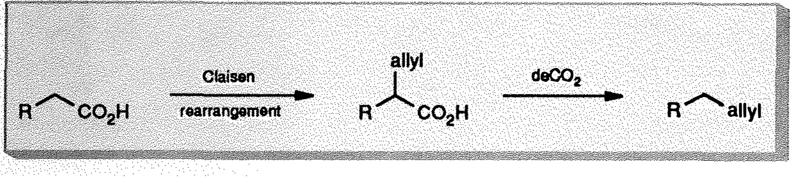
Scheme 20



Scheme 21



Scheme 22



The next question was the ***Straight Chain Claisen*** (Scheme 22) whereby an acid could be α-allylated and then lead to a straight, allyl-containing chain system *via* decarboxylation. This case was particularly demanding, since the product (**91**) of the esterification and Claisen rearrangement of the dicyclic ether acid **89** and the pyranoid glycal **90** is very hindered (Scheme 23). The planned procedure was the conversion of the tricyclic acid **91** to a selenyl ester that could then be decarboxylated by a radical reaction. Standard methods for the formation of such an ester (Scheme 24) were completely ineffective, as any intermolecular attack on the carbonyl carbon of the acid **91**, was precluded by steric hindrance. An *intramolecular* esterification method was necessary. The interaction between the mixed anhydride formed from the acid **91**, phenyl dichlorophosphate[27] and a phenyl selenide (PhSeH, NEt_3) would give the acid **91** through the mechanism shown *via* intramolecular transfer of the selenyl group. This sequence was not only performed successfully in model studies, but also led to the phenylselenyl ester **92** in excellent yield (Scheme 25). The transformation clearly demonstrated the utility of this esterification procedure in a demanding steric and multifunctional case.[28] Decarboxylation of the phenylselenyl ester **92** with tri-*n*-butyltin hydride is expectedly efficient but unfortunately, radical abstraction proved to generate the incorrect isomer **93** for the monensin synthesis.[28] Modification of the current substrates is aimed at a change in these results.

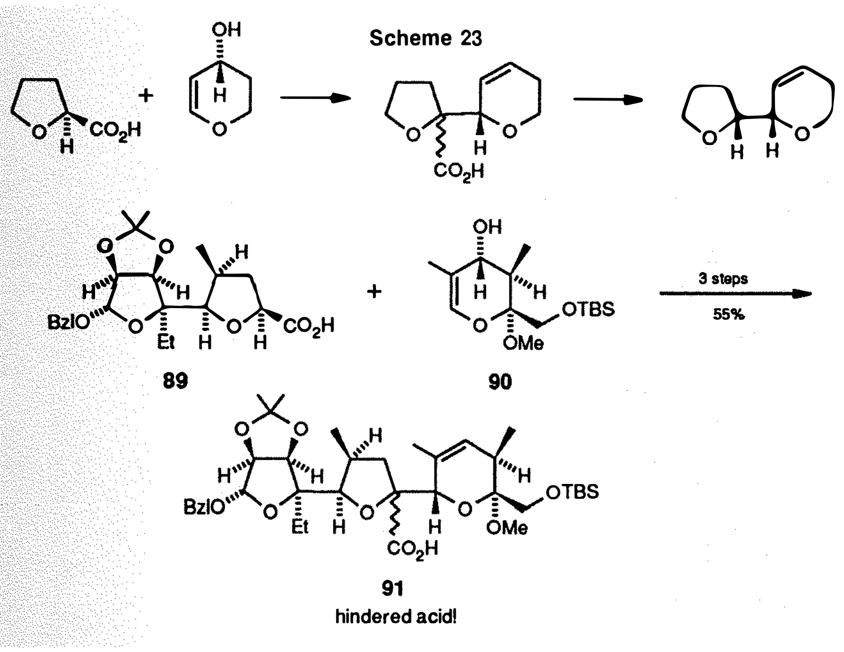
In spite of this stereochemical adversity, the value of this sequence should not be overlooked. A useful esterification procedure has been demonstrated which, when combined with the formation of a selenyl ester and radical-initiated decarboxylation, becomes a solution to the problem of the ***Straight Chain Claisen.***

d. Chlorothricolide problem

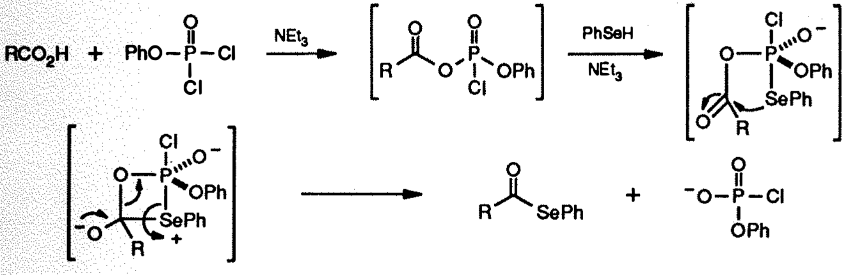
This esterification-decarboxylation sequence became valuable in the construction of the macrolide antibiotic chlorothricolide (**94**) (Scheme 26). The synthetic plan was the union of a top-half **95** and a bottom-half **96** through an ester enolate Claisen rearrangement followed by decarboxylation. The initial approach involved ester formation between the halves to form **97** (Scheme 27). Rearrangement then led to the acid **98** in good yield. Interestingly, decarboxylation of **98** led to two undesired products. First, decarbonylation of the derived aldehyde with Wilkinson's catalyst led predominantly to the cyclopropane derivative **99** together with *cis/trans* double-bond isomers.[29] Secondly, radical decarboxylation through the phenylselenyl ester led, not unexpectedly, to olefin addition and the formation of the bizarre structure **100**.

Ultimately, a useful expansion of the scope of the ester enolate Claisen rearrangement followed by the phenylselenyl ester decarboxylation process led to the desired product.[30] Initial formation of the dilactone **101** provided the substrate for the rearrangement process which, in turn, led to the macrocyclic acid **102** (Scheme 28). Due to the constraints of the macrocyclic ring system, decarboxylation of the derived phenylselenyl ester led to the required macrocyclic product **103** in excellent yield. Thus, an appropriate procedure seems available for the preparation of straight-carbon-chain systems with the degree of

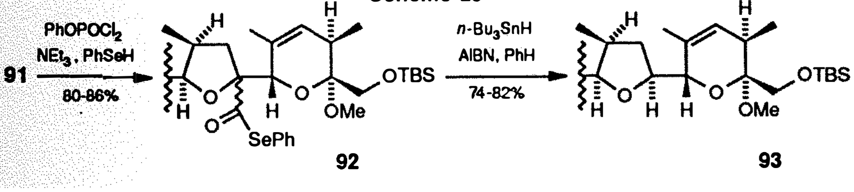
Scheme 23



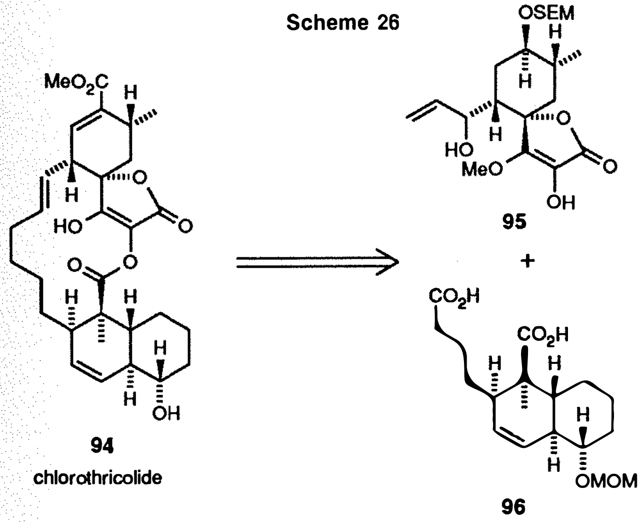
Scheme 24



Scheme 25



Scheme 26



stereochemical control that is inherent in the ester enolate Claisen rearrangement.

Acknowledgement: *I want to express my sincere and heartfelt thanks for this recognition by my colleagues in the American Chemical Society and to Dr. Alfred Bader and the Aldrich Chemical Company who made it possible. The respect of and acceptance by my peers represent the highest accolade that I can receive and I am most genuinely grateful.*

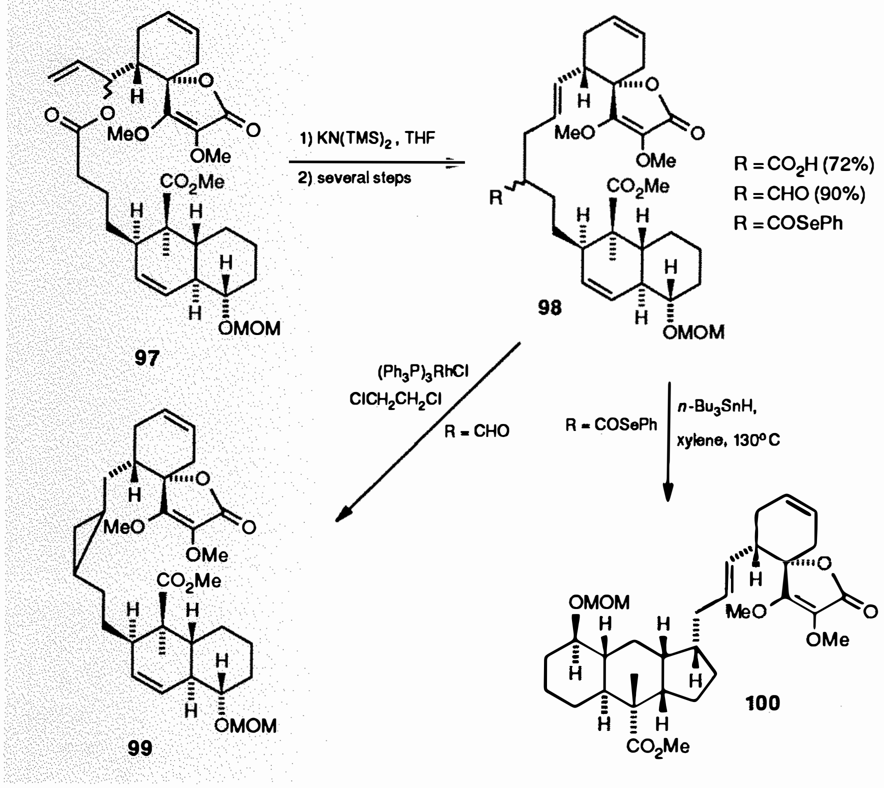
This brief and necessarily uncomprehensive review is presented on behalf of a **very talented** *collection of congenial, hard-working and spirited co-workers who made things happen. Those mentioned in the references are a few of the contributors and the opportunity to make this report is due to* **all** *of them. I have been blessed to know and work with these fine scientists.*

Every person knows a few special people from whom he receives more than he gives and for whom there is deep respect and admiration. In this public forum, I want to acknowledge the contribution to my life and science by a few such people. Two former students, James A. Marshall and David A. Evans, have provided constant support, warm friendship and standards of excellence that have led my science as well as that of others. The counsel, friendship and scientific stimulation of Peter B. Dervan have provided solace in time of need and stimulation throughout.

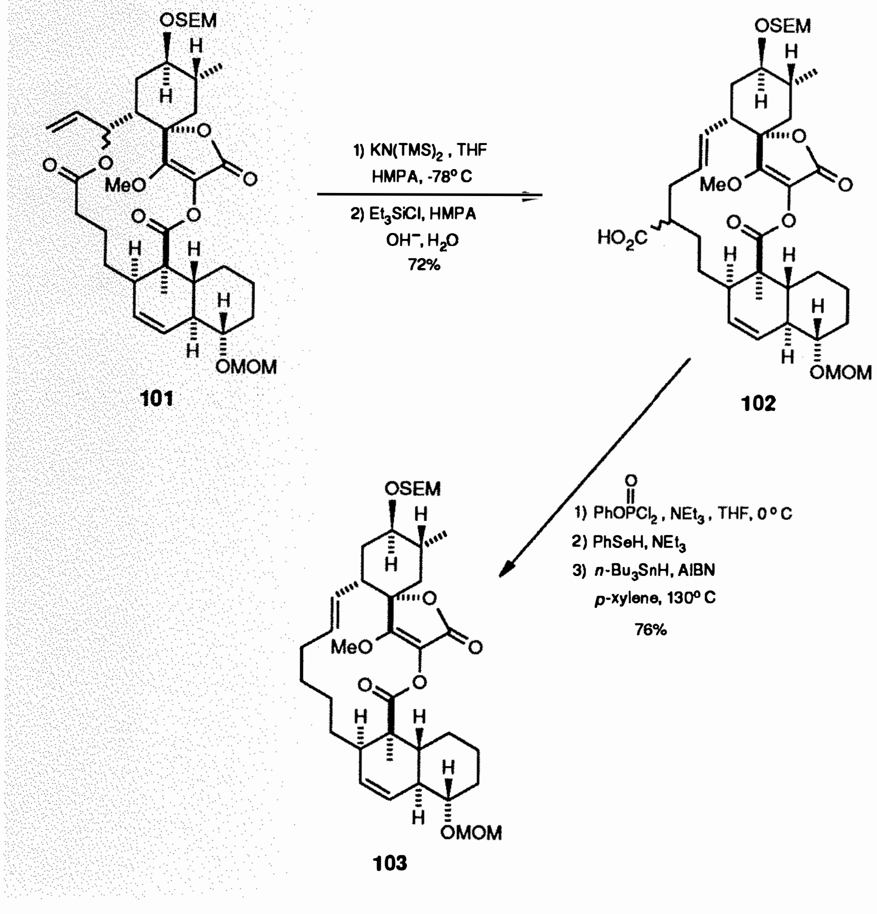
I have been exceedingly fortunate in my career to have been associated with three renowned scientists whose standards and love of science I have tried mightily to approach. Professor Albert Eschenmoser has provided me with a surrealistic love of synthetic organic chemistry. Professor William S. Johnson has been the very best teacher of science and creativity in synthesis. I learned from him that if it was worth doing, it was worth doing well, and I learned the love of science. In my heart, he will always be respectfully "Professor Johnson" to me.

Last, but by no means least, is the man to whom this issue of Aldrichimica Acta is dedicated. Professor John D. Roberts is a legend in organic chemistry and I count myself to be one of the very fortunate people to know Jack well. Jack's counsel, advice and collegial knuckle-rapping have been constant mileposts on a road to excellence and understanding. His insight and statesmanship find few, if any, matches and Jack fulfills to the fullest his role as my idol. Happy Birthday, Jack, and thanks.

Scheme 27



Scheme 28



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*These studies were funded in part by the NIH and NSF.

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About the Author

Dr. Robert E. Ireland was born in Cincinnati, Ohio, in 1929. He received the B.A. degree from Amherst College in 1951 and the Ph.D. degree in 1954 from the University of Wisconsin, under the direction of Professor William S. Johnson. He spent two years as an NSF postdoctoral fellow with Professor William G. Young at UCLA.

He joined the University of Michigan in 1956, and became Associate Professor in 1962. His research was centered on the total synthesis of dehydroabietic acid and pimaradiene. In 1965, he was appointed Professor of Organic Chemistry at Caltech. His research efforts resulted in the total synthesis of several pentacyclic triterpenes, for which he was recognized by the American Chemical Society with the 1977 Ernest Guenther Award in the Chemistry of Essential Oils and Related Products.

In 1985, Dr. Ireland assumed the position of Vice President of the Merrell Dow Research Institute and Director of the Strasbourg (France) Research Center. He joined the University of Virginia, in 1987 as Commonwealth Professor of Chemistry and was named Chairman of the Chemistry Department in mid-1987, and Thomas Jefferson Professor of Chemistry in mid-1988. The American Chemical Society recognized Dr. Ireland's work with the 1988 Award for Creative Work in Synthetic Organic Chemistry. His current research effort is concerned with the total synthesis of macrolide and ionophore antibiotics.

Dr. Ireland has held distinguished lectureships including the Bachman Memorial Lectureship at the University of Michigan, The Karl Pfister Visiting Professorship at MIT, Lutz Lectureship at the University of Virginia, Phillips Lectureship at the University of Pittsburgh and Main Speaker at the Third and Ninth International Symposia on Synthesis in Organic Chemistry (Oxford). He has served on NIH Study Section (1965-1972) and the Joint Chemistry Study Panel, NAS-CNPq (Brazil). He was a member of the Editorial Advisory Board of the *Journal of the American Chemical Society* and the *Journal of Organic Chemistry* and is on the Advisory Board of *Organic Syntheses,* after having edited a volume of this series. In 1980, he was Chairman of the Organic Division of the American Chemical Society. Dr. Ireland was a Robert A. Welch Foundation Lecturer and the Chairman of the Leimgruber Symposium in 1982. He is the author of over 100 research papers and a book entitled *Organic Synthesis.*

JOHN D. ROBERTS

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I met the *great* John D. Roberts at Caltech for the first time in 1972. He seemed larger than life: a tall, handsome, rugged man with a shock of curly grey hair, broad warm grin, huge embracing handshake, and twinkle in his eye. This was the man who has inspired a generation of organic chemists by his intellectual leadership, his innovation in developing new techniques to explore mechanistic organic chemistry, his contributions to undergraduate and graduate education and the advancement of scientific societies.

George Hammond, a brilliant pioneer in the field of molecular photochemistry and Roberts' colleague at Caltech, wrote in October, 1969:[1]

> *"For as long as my mind thinks, John Roberts will remain as a unique image therein. He is a rare man and a rarer scientist. As an academic colleague and a scientific peer, he has probably made me as angry, and yet inspired in me as much respect and admiration, as any man I have known. I first met Jack Roberts in 1945 when he arrived at Harvard as an NRC Research Fellow. Later I shared a laboratory with him for the better part of a year. Memories of that year are highlighted by three peaks: our sharing of the broadcasts of Red Sox games at a volume that had Paul Bartlett jumping out of his skin in his office across the hall; Jack's brutal evaluation of my laboratory housekeeping; and the feeling of exhilaration when Roberts engaged me in scientific argument. To debate science with Roberts is a unique experience. He combines the style of a dyspeptic porcupine and the wily cunning of a Las Vegas dealer with fundamental integrity to produce a style that is both frightening and stimulating.*
>
> *"If John Roberts were only a scientific disputant, he would still have earned a place in scientific history. However, the things that he has done far outrank the things that he has said. Roberts fastened onto carbon-14 when most chemists still feared that radioactivity would sterilize them; he learned molecular orbital theory when most organic chemists regarded an operator as a bogeyman; he set a style now copied by hundreds of young men for the study of small carbocyclic compounds; he applied nuclear magnetic resonance to organic compounds when most of us were still pondering spin flipping in ice; and he emerged from a violent romance with computer science as a truly triumphant lover.*
>
> *"When you read the papers by Roberts and his coworkers published in the early 1950's, you see the concatenation of a shrewd analytical intellect, the appreciation of the power of a new experimental method, and a deep perception in the choice of problems. The use of carbon-14 to probe the timing of skeletal rearrangements and protonic peregrinations in carbonium ions set a new standard for a dominant field of chemistry.*
>
> *"Perhaps the most shocking single mechanistic pronouncement of our times was the elucidation of the benzyne mechanism for cata substitution in the reactions of unreactive aryl halides with powerful nucleophilic reagents. I recall one prominent American chemist who made an impassioned plea in a symposium that the benzyne mechanism be abandoned because it was an affront to both common sense and established theory of chemical bonding. Fortunately, the mechanistic model survived such attacks and has now become a potent tool in the hands of synthetic chemists.*
>
> *"Roberts' work in the field of molecular orbital calculations and nuclear magnetic resonance is of paramount importance in modern organic chemistry.*

Fig. 1 - John D. Roberts.

Today, nearly every student of organic chemistry casually feeds secular determinants to high-speed computers and admires the parameters generated by the electronic brain. Roberts was doing the job when one had to diagonalize matrices by direct use of group theory and drudgery.

"If Roberts had not entered the field of NMR at an early stage, I believe that the field would have developed differently and far less effectively. His dogged determination to do things right led him to treat the problems of spin-spin coupling and chemically induced spin relaxation in a way that was alien to the style of organic chemists. To be sure, such work would have been done, but if Roberts had not been a creative participant, organic chemists would probably have regarded complex spin-coupling problems as esoteric exercises lying within the province reserved for the physical chemical elite. To see the reality of this pace-setting activity, compare the sophisticated way organic chemists handle NMR problems with their dedicated adherence to totally empirical analysis in the fields of ultraviolet and infrared spectroscopy.

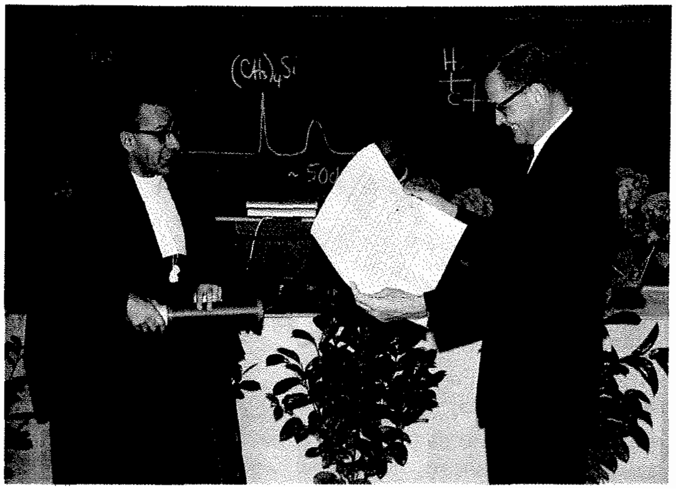
Fig. 2 - Roberts received an honorary degree at the Universität München (1962).

"Roberts' respect for integrity is exemplified by his professional self-consistency. Despite his wide-ranging interests, he stands like the Rock of Gibraltar as an organic chemist. Some of us wonder about the labels placed on chemists and want to redescribe our intellectual and experimental pursuits. However, we recognize that the field of organic chemistry must last at least as long as John Roberts, since he will continue to define some of the boundaries of the field by his own activities."

John D. Roberts was born in Los Angeles on June 8, 1918. From his father, Allen, he inherited a mechanical bent and great curiosity; from his mother, Flora, a love of music and literature. At the age of 10 he suffered a hearing loss. As a young boy he was an avid book reader, especially of the lives of scientists. To this day, Roberts writes with a beautiful story-telling style. Jack went to college at UCLA shortly after the Great Depression and all expenses for college were earned by working nights and Saturdays at a bakery store.[2] In 1942 he married the beautiful Edith Mary Johnson and they would raise four wonderful children: Anne, Donald, John Paul and Allen.

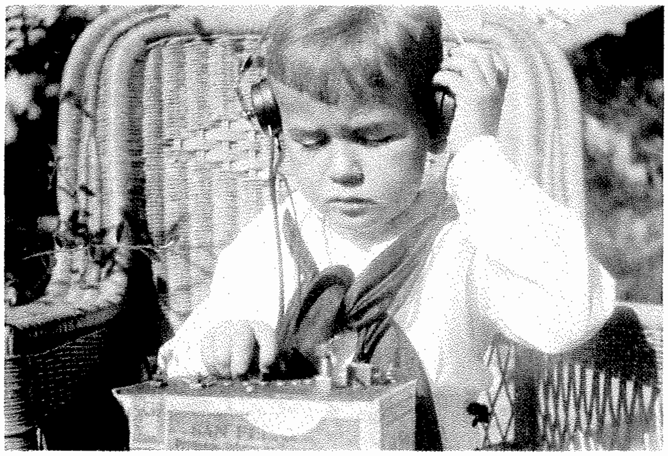
Fig. 3 - As a young lad, Roberts showed a keen interest in electronics.

Roberts had the benefit of many inspirational scientific mentors at UCLA and Caltech that undoubtedly shaped his early career toward organic chemistry. In the 1930's, W.R. Cromwell at UCLA gave undergraduate Roberts his first shot at research as a sophomore. Roberts went on to publish his first paper jointly with Cromwell and Caltech's D.M. Yost.[3] Organic chemistry at the time was greatly influenced by Caltech's Howard Lucas, the Ph.D. mentor of UCLA Professor William Young who would become Roberts' Ph.D. advisor, and UCLA Professor Saul Winstein, one of the great intellects of that era. Roberts' first mentor was Professor Frank Whitmore, a talented physical organic chemist at Penn State. Whitmore was extraordinarily well-organized and required monthly research reports from all his students.[2] Although Roberts only stayed at Penn State 4 months, due to the attack on Pearl Harbor, the "*monthly research report*" later became a Roberts tradition in training his own research students at MIT and Caltech.

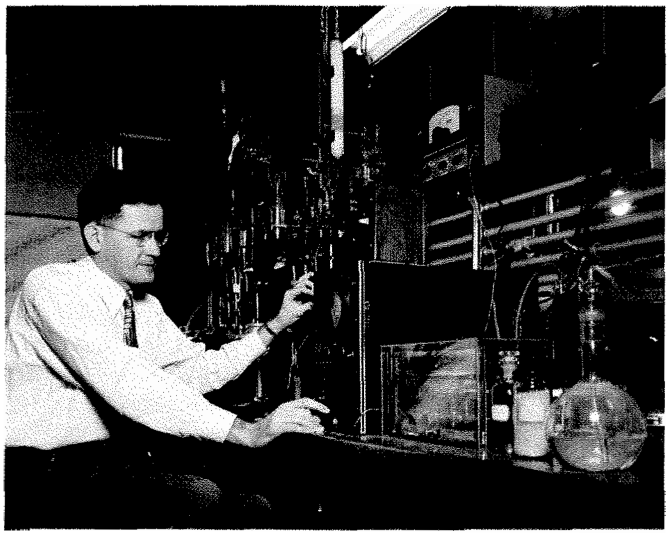
Fig. 4 - Roberts' early research experience at UCLA shaped his career toward organic chemistry.

Upon returning to UCLA to work on the war effort, Roberts wrote his thesis in 11 months and took no formal courses! He must have decided that this was not so bad. At Caltech, Roberts had been a strong proponent of getting graduate students (and undergraduates) out of the classroom and into the research laboratory as early as possible.

During his Priestley Medal address in April, 1987, Roberts tells us with characteristic modesty how lucky he was, as he puts it, *"to be in the right place at the right time."*[4]

> *"Never being much good at physics or mathematics, I feel I was very fortunate to get started in chemistry during a period when it was a much more descriptive science than it is today — when a knowledge of glassblowing was more important than a knowledge of electronics or quantum mechanics; when slide rules and log tables were our computers; and when the fanciest instrument in the organic laboratory was a refractometer or possibly a polarimeter. Those things I could understand.*
>
> *"Of course, a lot of other people were also fortunate in starting in chemistry in 'the good old days', but I was additionally fortunate in starting my undergraduate work at UCLA in 1936. At that time, UCLA had no Ph.D. program, but it was on the verge of getting one. As a result, UCLA was able to hire bright, young chemistry faculty, eager to do research. And those faculty encouraged me to get into research early — in fact, at the end of my sophomore year. This was very important to me, because, although I was no great shakes at course work, it turned out that I was pretty good at research and I loved it. Almost for the first time in my life, I did something really well.*
>
> *"With only a few M.S. candidates and a growing undergraduate enrollment, UCLA was also short on teaching assistants. And again I was fortunate, because I was allowed to be the equivalent of a graduate teaching assistant — all told, in six different undergraduate courses. I was not the only one to profit from this particular golden period at UCLA. During that time, the school produced seven future members of the National Academy of Sciences and of those, two became Nobel Prize winners in chemistry, and two became presidents of the ACS. Not bad.*

Fig. 5 - Compelling evidence supporting the intermediacy of free benzyne came from Roberts' ^{14}C isotope-labeling experiments.

> *"Although I finished UCLA with four rather decent undergraduate research publications, these were not enough to overcome a spotty scholastic record and get me admitted to Wisconsin for graduate study. However, Penn State was willing to take a chance and I was again fortunate, even if for only a brief period because of the start of World War II, to work with Frank C. Whitmore — a remarkable organic chemist, who became a lifelong inspiration.*
>
> *"At the end of my war research, UCLA had gotten their Ph.D. program going and I was fortunate again to have a really bangup Ph.D. project with William G. Young, who himself later became a Priestley Medalist. The frosting on the cake of my graduate period was to be able to interact in a very close way with Saul Winstein, a physical organic chemist of remarkable scholarship, imagination and intellectual tenacity.*
>
> *"Then I was indeed lucky,* **not** *to be offered a job at du Pont, but to instead go off to Harvard as a postdoctoral fellow, just at the time R.B. Woodward was getting started there and when Paul Bartlett and Louis Fieser were in their prime. It was a confidence builder to find out that a country boy from the far West could more or less hold his own among the Harvard graduate students and postdoctoral fellows. Bartlett and Woodward helped greatly to shape my perception of what one's objectives should be in research, and the Harvard year was a great experience. It was easy to appreciate how lucky I was to be there.*
>
> *"And yet, I certainly can't claim to have always recognized good fortune immediately when it came my way. Thus, I had hoped, after my Harvard year, to get a teaching position at Berkeley and was disappointed, even a bit dismayed, when the only opening turned out to be at MIT, where Arthur C. Cope and colleagues like John Sheehan and Gardner Swain turned out to be good fortune beyond belief. And I was, and I am still, very grateful to MIT for the opportunity I was given there to get a research program underway. Admittedly, it was a bit ungracious to leave in 1953, but I felt I repaid MIT in spades by persuading Art Cope to sign up George Whitesides for a faculty position almost a year before he got his Ph.D. at Caltech. Still, it was painful to leave Cambridge just as another of my heroes, Frank Westheimer, was moving from Chicago to Harvard. But the culmination of my academic good fortune was to be offered a professorship at Caltech — a small institution, but one with a lot of clout. When I travel and meet people, they often ask how large is the Caltech student body. I always ask back — 'How large do you think it is?' The answer usually ranges from 10,000 to 40,000 and the*

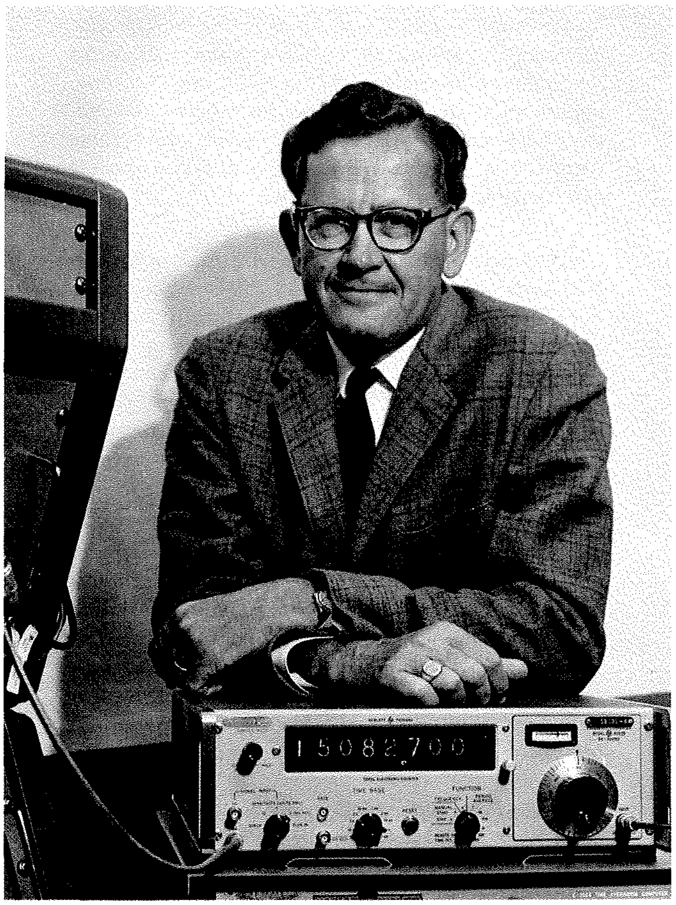

Fig. 6 - An underpinning to Roberts' success in proton, ^{13}C and ^{15}N NMR spectroscopy was the outstanding research spectrometers built by Varian and Bruker.

truth of about 1500 comes as a shock. Caltech turned out to be the ideal place for me to do science.

"Of course, I have had my share of missed opportunities. Somewhere around 1951, Richard Ogg of Stanford tried to convince me that nuclear magnetic resonance (NMR) spectroscopy was going to revolutionize chemistry. Being nearly illiterate in electricity and magnetism, I did not even understand what he was talking about. Four years later, I was fortunate, in the course of my du Pont consulting, to have William D. Phillips show me what NMR could do when applied to specific organic structural and rate problems. Only then did I realize how right Richard Ogg was. At that point, I didn't care whether I would ever know how NMR worked, I just knew it would solve problems that I was interested in, and, with the help of Linus Pauling, the Caltech administration, bless them, came up with the funds to buy the first commercial NMR installation in a university. And so I was able to ride the early crest of the NMR wave which has swept along through chemistry and biochemistry, as well as into medicine, with growing intensity and importance for almost forty years.

"I was also fortunate to be able to ride the early wave of the application of molecular orbital theory to organic chemistry. The later molecular-orbital waves have gotten so big, so steep and so hard to ride that I've been happy to stay on shore. Still around 1950, Hückel molecular-orbital theory (the simplest kind) had been cleverly, and carefully, kept secret by the theorists from organic chemists. 'Too tough mathematically for you guys' was the watchword. But, one day, I was lucky to look over the shoulder of my friend, William G. McMillan, one of the high priests of theory, and find to my surprise that he was using **simple algebra** *to solve a molecular-orbital problem I was interested in. I said, 'Hey, what's going on here! I can do that too!' Talk about being at the right place at the right time! So wisdom not only comes with good fortune. Sometimes you need good fortune to hit you over the head!"*

A central issue in the field of organic chemistry in the 1940's (as it is today) was understanding reactivity in organic molecules. What do we mean when we write chemical structures on paper? The scholars of the day in the growing field of physical organic chemistry were trying to come to grips with this problem. Part of the complex story unfolded in the area of carbocation rearrangements. At MIT, Roberts discovered that the rate of solvolysis of cyclopropylmethyl chloride is *exceptionally* large for a primary halide.[5] Moreover, cyclobutyl chloride is more reactive than expected. What is so special about the $C_4H_7^+$ cation! Roberts recognized early on that science is technique driven. He brilliantly invented a ^{14}C "*isotope-position rearrangement*" experiment which allowed him to conclude that the *bicyclobutonium* cation is insufficient to explain the data.[6] After late-night discussions with Woodward,[2] Roberts postulated the more symmetrical *tricyclobutonium* cation and dubbed this a "*nonclassical*" cation[6] — a term that would be much used, abused, and debated over the next few decades. Much of the work Roberts did on the $C_4H_7^+$ cation placed him as a central figure (referee?) in the public debate over nonclassical carbocations between Saul Winstein and Herb Brown. Later, George Olah (now at USC) would stun the world with proton- and ^{13}C-NMR spectra of concentrated solutions of carbocations. Olah's spectacular work ruled out the symmetrical pyramidal structure of the $C_4H_7^+$ cation (tricyclobutonium) and pointed more likely to a set of rapidly equilibrating bicyclobutonium cations. The ^{14}C isotope-position rearrangement method would again be brilliantly

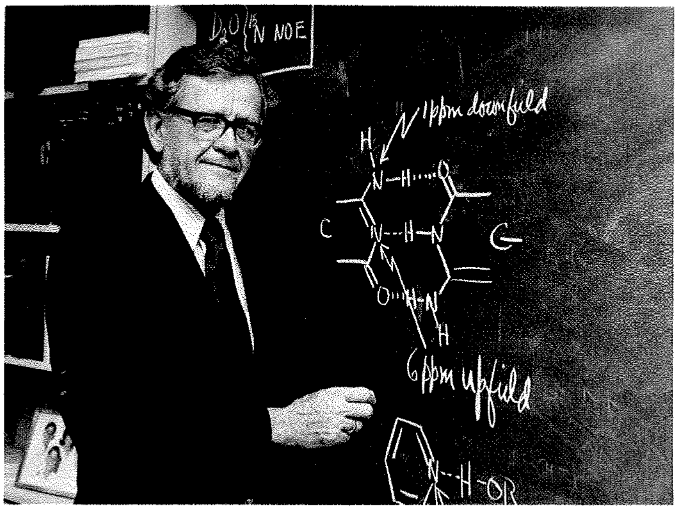

Fig. 7 - The extraordinary range of ^{15}N chemical shifts and their sensitivity to the state of protonation provides a powerful method for mechanistic studies on biologically interesting high-molecular-weight molecules such as proteins and nucleic acids.

applied by Roberts to reveal the intermediacy of benzyne as a free species in solution.[7]

Although to some Roberts seems like an intimidating figure (he is really a teddy bear), he is a man who rejects obfuscation as a matter of integrity. It does not surprise me that the same man who professes a weak background in physics and mathematics had great success in helping to popularize for organic chemists, molecular orbital theory and nuclear magnetic resonance spectroscopy, which were the province of the physical chemistry community in the 1950's. Roberts' books on both molecular orbital theory[8] and NMR[9,10] were outstanding pedagogical examples of demystification that opened the doors for organic chemists.

I have watched Roberts in faculty meetings. Nothing gets by him with regard to following the rules of the faculty handbook. A superficial analysis might lead one to consider that Roberts is conservative. Although this may be true, he is an adventuresome, forward-looking person as evidenced by his forays into ^{14}C labeling, NMR spectroscopy and molecular orbital theory in the 1950's. Roberts brought the first woman Ph.D. student, Dorothy Semenow, to Caltech, a move which was overdue.

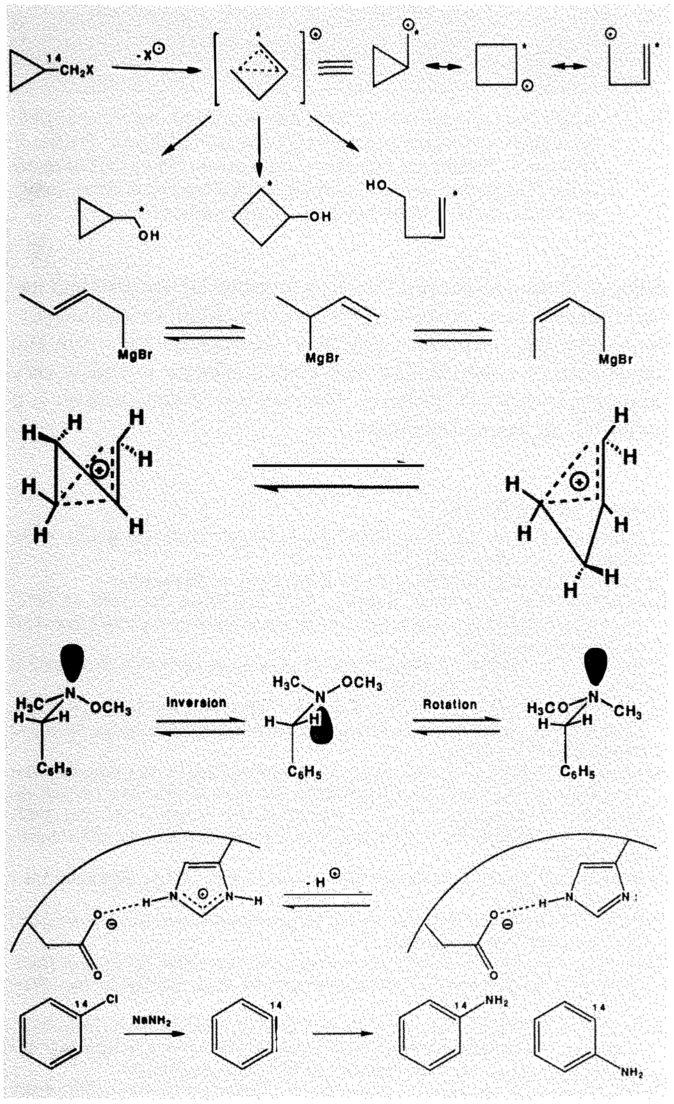

Fig. 8 - Roberts' pioneering research (isotope-position rearrangements, non-classical cations, conformational analysis by NMR, mechanism of serine proteases, and benzyne) has merged with the body of knowledge in organic chemistry.

When Linus Pauling brought Roberts to Caltech in 1955, he convinced the Board of Trustees to buy Jack one of the first Varian NMR spectrometers. Exciting discoveries were made in those days, such as the magnetic nonequivalence arising from internal molecular asymmetry, and it became apparent that this new spectroscopic tool would allow *direct measurement of rates of rotation* about *single* bonds in ethane derivatives.[11,12] Roberts was a big hit at the 1958 Reaction Mechanisms Conference when he lectured to the physical organic community about the potential that lay ahead in this field. After intense productive research using proton NMR to study the equilibrium distribution of rapidly interconverting butenyl Grignard reagents,[13] and a conformational analysis of the structure of simple cyclic hydrocarbons,[14] Roberts convinced Varian to build a spectrometer for natural abundance ^{13}C. The potential of this became evident with the important publication from the Caltech group reporting 25 distinct resonances of 27 carbons of cholesterol.[15] Despite the fact that natural abundance ^{15}N is about a millionth of the signal strength of protons, Roberts recognized the extraordinary range of ^{15}N chemical shifts (900 ppm) 100 times that of the ordinary shift range of protons.[16] During the 1970's, Roberts demonstrated with his Bruker WH-180 the powerful role that ^{15}N spectra could have with biologically interesting high-molecular-weight molecules such as proteins and nucleic acids. This culminated in an incisive mechanistic inquiry in the "charge relay" mechanism postulated for the hydrolysis of peptide bonds by serine protease.[17]

After service to Caltech as Vice President, Provost, and Dean of the Faculty in 1980-83, Roberts has been studying the applications of NMR to medicine (magnetic resonance imaging) with a world-class team in Pasadena's Huntington Medical Research Institute.

Despite Roberts' extraordinary committment to science, he has always maintained a great interest in people and the world around him, especially the great outdoors. At Caltech he is a dynamic figure on the tennis courts, frequently seen smashing a vigorous forehand at Harry Gray or Rudy Marcus in the cool midsummer mornings. For many years he was part owner of a boat (yacht?) with Don Cram and sailing to Catalina Island was grand fun. Summers have been occupied with treacherous white-water rafting in Colorado and Chile with Edith and his sons. Winter holidays are downhill

Fig. 9 - Jack and Edith.

Fig. 10 - Roberts' family sailing off Catalina Island.

skiing and science discussions at Nelson Leonard's hideaway in Snowmass Village, Colorado. On a typical day at Caltech's Athenaeum, Roberts can be seen at a round lunch table for eight embroiled with engineers, physicists, geologists and biologists, in intense discussion about the design of future sailing vessels for defense of the America's Cup or his most recent lecture trips to China or safari in Kenya, Africa with the Leakey Foundation.

Epilogue

During the past four and one-half decades Roberts has been part of the explosive growth of physical organic chemistry. The important conceptual influences that shaped this field created one of the great advances in the history of science. The study of reactive intermediates as a method of generalizing organic reactions and the importance of characterizing their kinetic behavior was developed by pioneers such as Roberts, his students and his contemporary colleagues — in both industry and academia — researchers of extraordinary intellect, individualism, discipline and commitment. The mechanistic framework that developed during those decades has profoundly influenced the way we currently *think and teach* organic chemistry. This lasting legacy has changed the intellectual framework of the field.

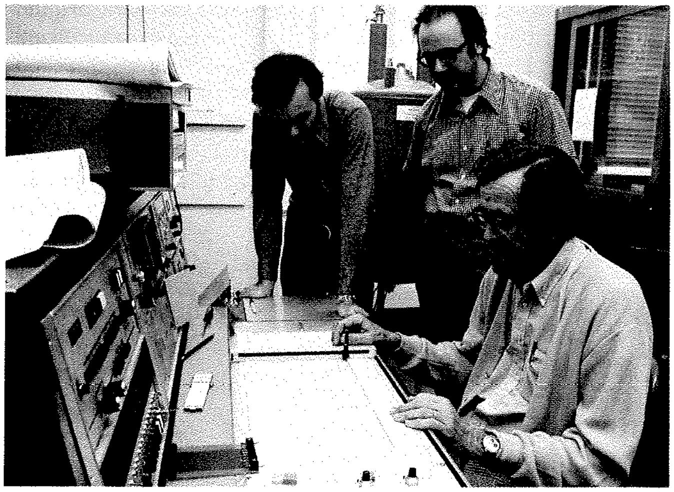

Fig. 11 - The Bruker WH-180 was a fantastic machine. Roberts' group enjoyed the luxury of a dedicated ^{15}N spectrometer which allowed them to run spectra as long as 72 hours.

Roberts' direct scientific contributions are significant and for these he has been greatly honored by his profession.[18] Likely, this pioneering research (isotope-position rearrangements, benzyne, nonclassical cations, conformational analysis by NMR) will lose its identity and merge with the great body of knowledge in organic chemistry. My own feeling is that Roberts' contribution to science is much larger than that. He has shown by example that, in addition to research output (460 scientific papers published), teaching students, writing textbooks,[19] serving on editorial boards[20] and national committees,[21] consulting for industry, administering departments and universities are not only important, they form the mainstream of scientific life. The human element is clearly very important to John D. Roberts. This balance of achievement is a model for all young scientists.

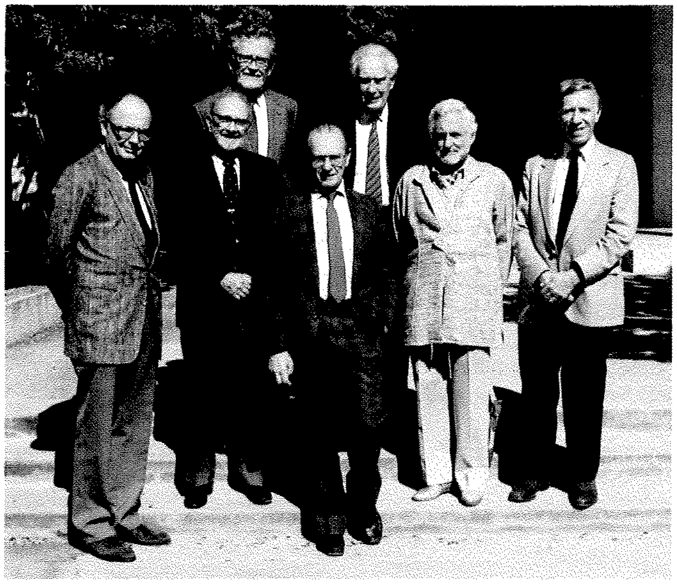

Fig. 12 - Great men of science who have contributed so much to the field of organic chemistry pose at a symposium to honor Professor William S. Johnson at Stanford University in 1986. (Left to right) Albert Eschenmoser, Bill Johnson, Jack Roberts, Gilbert Stork, Sir Derek Barton, Carl Djerassi, Conrad Block.

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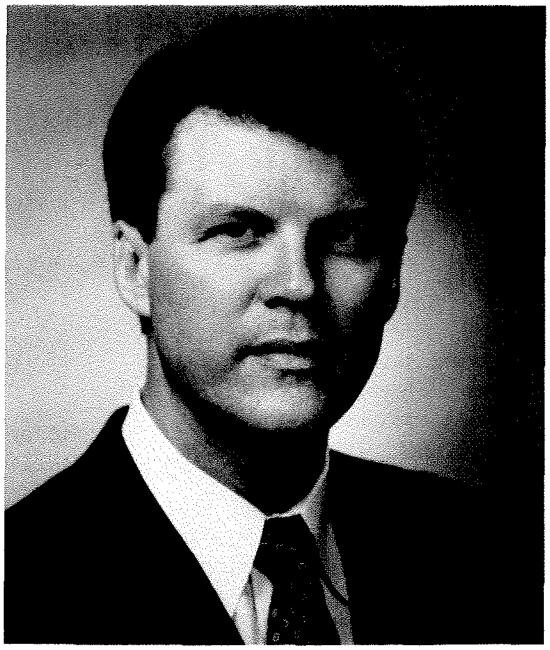
18) Professor Roberts has been awarded honorary degrees from the University of Munich and Temple University. He is a member of the American Chemical Society, the American Academy of Arts and Sciences, the American Philosophical Society, and the National Academy of Sciences. He received the ACS Award in Pure Chemistry (1954), the Harrison Howe Award (1957), the 1957 UCLA Alumni Professional Achievement Award in the Field of Science, the Roger Adams Medal and Award in Organic Chemistry (1967), the Nichols Award (1972), the Richard C. Tolman Medal (1975), the Michelson-Morely Award (1972), the James Flack Norris Award (1979), the Linus Pauling Award (1980), the Theodore William Richards Medal (1982), the Willard Gibbs Gold Medal (1983), the American Academy of Achievement Golden Plate Award (1984), and the Priestley Medal (1987).

19) Roberts, J.D.; Caserio, M.C. *Basic Principles of Organic Chemistry;* W.A. Benjamin, Inc.: New York; 2nd. ed.; 1977.

20) Professor Roberts has been a member of the editorial board of the American Chemical Society. He has been Editorial Consultant of W.A. Benjamin, Inc., of which he also served as Director, from the founding of the company until the spring of 1967. He has been a Director of Organic Synthesis, Inc. since 1977, and presently serves on the editorial boards of *Tetrahedron, Nouveau Journal de Chimie, Magnetic Resonance in Chemistry* and *Spectroscopy.* Since 1984, Professor Roberts has been a member of the Council of the International Society of Magnetic Resonance, the Board of Directors of the Huntington Medical Research Institute, the Board of Directors of the Caltech Y, the Board of Trustees of the L.B.S. Leakey Foundation, and the Executive Committee of the American Academy of Arts and Sciences Western Section.

21) He was a member and chairman of both the Advisory Panel for Chemistry of the National Science Foundation (1957-1960) and the Advisory Committee of Mathematical and Physical Sciences of the NSF (1962-1966); he was Chairman of the National Academy of Sciences Section of Chemistry (1968-1971), Chairman of Class I (Mathematical and Physical Sciences) (1976-1980), and Member of the Council (1980-1983). He also served on the National Academy of Sciences Committee for the Survey of Chemistry, which produced the report "Chemistry: Opportunity and Needs", on the Panel on Scientific Communication and National Security, and on the Committee on Science, Engineering, and Public Policy. He was elected Councillor, Class I, of the American Philosophical Society in 1983.

About the Author



Professor Peter B. Dervan was trained as a physical organic chemist working with Jerome A. Berson at Yale University (1972). After postdoctoral research at Stanford, he joined the chemistry faculty at the California Institute of Technology in 1973 where he is now Bren Professor of Chemistry. Professor Dervan's research interests span physical organic and bioorganic chemistry. He is a member of the National Academy of Sciences and a Fellow of the American Academy of Arts and Sciences.

Award-Winning Chemistry

1988 - Professor Robert E. Ireland

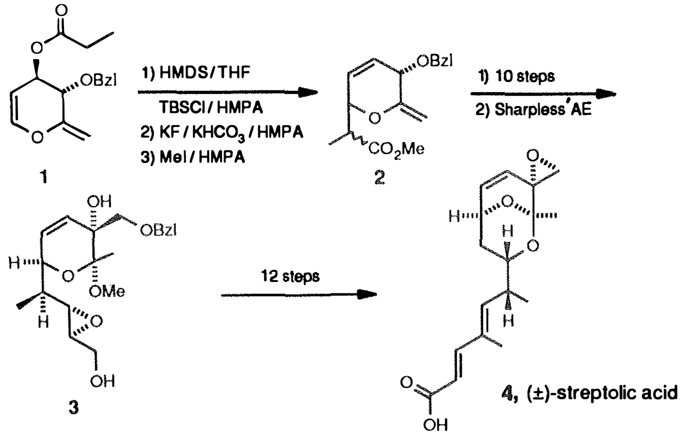
Professor Robert E. Ireland of the University of Virginia is the recipient of the 1988 A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich.

Professor Ireland is one of the chemists who have truly mastered the art of organic synthesis. The practiced ease and elegance with which he has developed new synthetic methods and applied them to Natural Product Total Synthesis are evident throughout his work. Of particular note is the ester enolate Claisen rearrangement[1,2] and its application to the synthesis of prostaglandins,[2] polyether ionophore antibiotics[3] and macrolide antibiotics.[4] He has also pioneered the use of metal-ammonia-mediated deoxygenation of enol and alcohol phosphoramidites[5] and has exploited this method in the synthesis of terpenoid[6] and steroidal[7] natural products.

We extend our congratulations to Professor Ireland for this well-deserved honor and herein acknowledge some of his already well-known contributions.*

Synthesis of (±)-Streptolic Acid:[8]

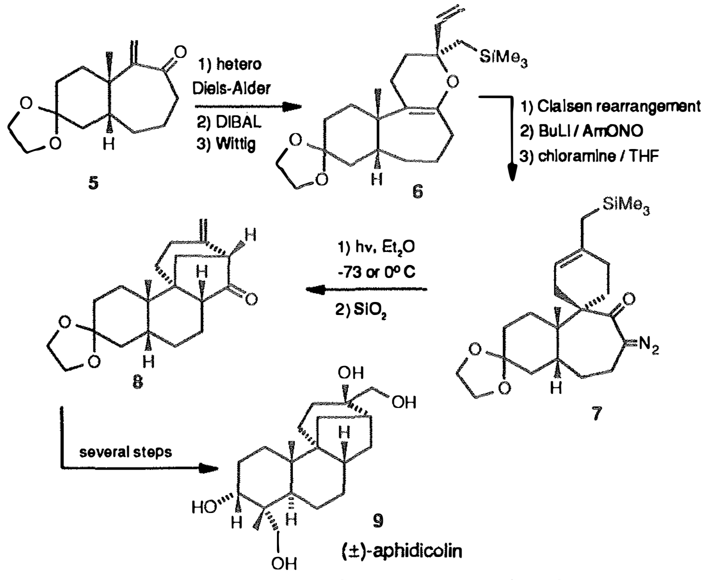
An interesting application of the ester enolate Claisen rearrangement involves the recently reported synthesis of (±)-streptolic acid, the most potent member of the 3-acyltetramic acid antibiotics.



D-(+)-Glucose-derived starting material **1** was converted to the Claisen rearranged product **2** which in turn was converted to the epoxide **3** *via* Sharpless' AE[9] of the appropriate allylic alcohol. This intermediate was then elaborated to furnish the target compound (**4**).

Total Synthesis of (±)-Aphidicolin:[10]

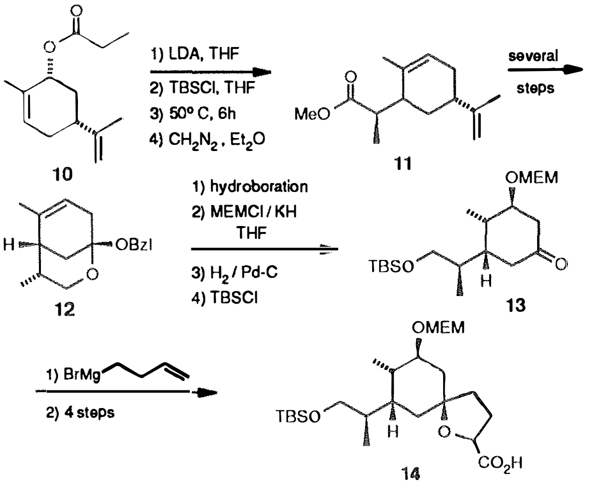
Four key synthetic transformations form the basis of the total synthesis of this tetracyclic diterpene.



The methylene ketone precursor **5** was prepared utilizing a photosensitized oxygenation procedure developed earlier by Ireland and co-workers.[11] A hetero Diels-Alder reaction followed by Claisen rearrangement and subsequent reactions led to diazo ketone **7**, which upon photolysis and silica gel treatment, underwent a cyclobutanone rearrangement (rather than ring contraction) to give **8**. The problem of stereoselective alkylation of C-4 with two different substituents was then solved through the α-methylene ketone methodology to prepare (±)-aphidicolin.

Synthesis of a Polyether Ionophore Antibiotic:[3a]

The ester enolate Claisen rearrangement was applied by Ireland and co-workers in the synthesis of a versatile A-ring carbomonensin intermediate.



Thus, the (*R*)-(-)-carvone-derived precursor **10** was converted to **11** *via* an ester enolate Claisen rearrangement. The bicyclic intermediate **12** derived from **11** underwent a regio- and stereoselective hydroboration ultimately yielding **13**. This ketone, which possesses a β-alkoxy leaving group, underwent smooth Grignard reaction and was eventually transformed into carbomonensin intermediate **14**.

References:

*See page 59 for a review by Professor Ireland.

(1) Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (2) Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Org. Chem.* **1976**, *41*, 986. (3) a) Ireland, R.E.; Maienfisch, P. *ibid.* **1988**, *53*, 640. b) Ireland, R.E.; Haebich, D.; Norbeck, D.W. *J. Am. Chem. Soc.* **1985**, *107*, 3271. c) Ireland, R.E.; Norbeck, D.W. *ibid.* **1985**, *107*, 3279. d) Ireland, R.E.; Courtney, L.E.; Fitzsimmons, B.J. *J. Org. Chem.* **1983**, *48*, 5186. (4) Ireland, R.E.; Daub, J.P. *ibid.* **1983**, *48*, 1303. (5) a) Ireland, R.E.; Muchmore, D.C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. b) Ireland, R.E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145. (6) Ireland, R.E.; Kowalski, C.J.; Tilley, J.W.; Walba, D.M. *J. Org. Chem.* **1975**, *40*, 990. (7) Ireland, R.E.; O'Neil, T.H.; Tolman, G.L. *Org. Synth.* **1983**, *61*, 116. (8) Ireland, R.E.; Smith, M.G. *J. Am. Chem. Soc.* **1988**, *110*, 854. (9) Sharpless, K.B. *et al. ibid.* **1987**, *109*, 5765. (10) Ireland, R.E.; Dow, W.C.; Godfrey, J.D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001. (11) Ireland, R.E.; Aristoff, P.A.; Hoyng, C.F. *ibid.* **1979**, *44*, 4318.

For a list of Aldrich reagents utilized in this chemistry, see page 69 of this issue of Aldrichimica Acta.

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Aldrichimica Acta
Volume 21, Number 4, 1988

The Mechanisms of Oxygen Transfer from Acyl and Alkyl Hydroperoxides to Metal(III) Porphyrins and the Epoxidation of Alkenes by the Resultant Hypervalent Metal-Oxo Porphyrin Products

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About Our Cover:

You may be surprised to find a still life (oil on panel 17½ x 13½ inches) on our cover, the first in over twenty years of *Acta* covers. But it is so beautiful, apparently simple, yet subtle, a fitting work to grace the *Acta* with two very different papers, both brilliant in their innovation.

This is a "vanitas" still life, the broken brazier suggesting the vanity of material things and the transience of human life. It was painted in Amsterdam in 1664 by Evert Collier — we know this because it is signed and dated, and the seal on the jug is that of the city of Amsterdam.

This vanitas was painted on top of a portrait of a man with a white ruff; the outline is clearly visible through the thinly painted still life and more can be seen on an X-ray. You can read all about the painting in the catalog, "The Detective's Eye: Investigating the Old Masters", described below.

NEW

The Detective's Eye: Investigating the Old Masters

Twenty paintings (including the still life on this cover) that have been reproduced on our *Acta* covers and five that have been on our catalog covers are among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 - March 19, 1989) for which Isabel and Alfred Bader are guest curators.

If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this fully illustrated catalog, and you will learn something about our chemist-collector's interest in art and connoisseurship as well.

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among the thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

Reprints of Aldrich Catalog Covers

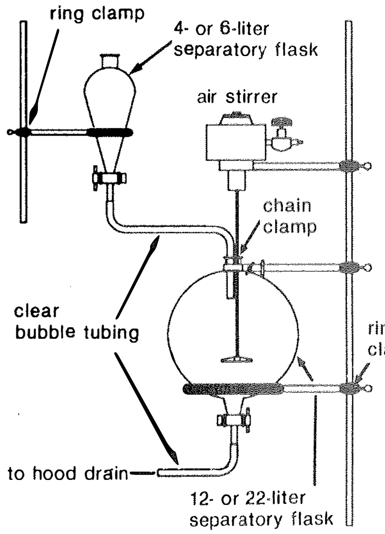
Eight beautiful 14 x 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta,* we now offer a collection of articles from volumes 1-15: 354 pages of great review articles, in one beautiful hardbound volume. All articles are included except those whose subject matter has been updated in later issues.

Lab Notes

I wish to report a safe and efficient method for quenching large volumes of acids, $SOCl_2$, PCl_3 and related compounds.



For example, place a 50% NaOH/ice mixture in the lower flask. Place the material to be quenched in the upper flask. Slowly add material to the lower flask, replacing ice as necessary. When the material is quenched or the NaOH solution has been neutralized, open the bottom stopcock and run the contents down the hood drain. This method reduces close contact with the acid/base solutions, avoids the use of clumsy 5-gallon buckets and solutions can all be vacuum-transferred.

Mary Doyle
Production Department
Aldrich Chemical Co., Inc.

2-Nitro-5-thiocyanatobenzoic acid is a good cyanylating agent for protein sulfhydryl groups and for the cleavage of proteins at cysteine [*Aldrichimica Acta* **1987,** *20*(3), 87].

For these purposes, 1-cyano-4-(dimethylamino)pyridinium tetrafluoroborate compares favorably with this reagent (Banks, G.R. *Biochemistry* **1986,** *25,* 5882; *Chem. Commun.* **1976,** 21). Moreover, the latter reagent may be used for the covalent attachment of ligands to polysaccharide resins (Wilchek, M. *Appl. Biochem. Biotechnol.* **1984,** *9,* 285) and for the C-cyanation of imidazoles (Witten, J.P. *Synthesis* **1988,** 470).

M. Wakselman
Centre National de la Recherche Scientifique
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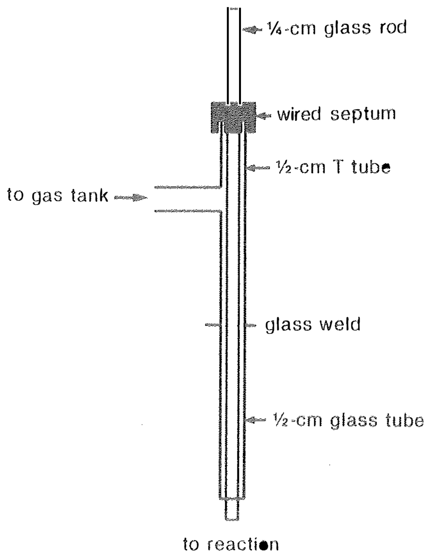
2 à 8 rue Henri - Dunant
B.P. 28 - 94320 Thiais, France

Editor's note: Aldrich carries the reagents mentioned by the author.

We do many salt exchanges in our lab, replacing the HBr salt with the HCl salt. This is accomplished by dissolving the HBr salt in hot methanol and then adding HCl gas to the refluxing mixture. The HCl salt then precipitates out of solution and is collected. However, a problem arises in this procedure because the gas-inlet tube often becomes plugged with precipitate before the exchange is complete. The gas must then be shut off, the tube removed and cleaned, and the tube replaced before gas addition can continue. I have found a simple solution to this problem which could be applied to any system where gas-inlet tubes become plugged.



Have a glassblower attach a ½cm-diameter T-tube to a similar glass rod as shown. Stopper the top of the T-tube with a rubber septum and insert a ¼cm-diameter glass rod through the septum. The rod must be longer than the combined length of the T-tube and tube. The other opening of the T-tube goes to the gas tank and the ½-cm glass tube is inserted through a septum into the reaction. As the inlet tube becomes plugged, working the rod up and down will free the precipitate.

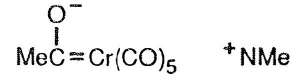
Jay B. Fell
Research Biochemicals Inc.
9 Erie Drive
Natick, MA 01760-1390

Any interesting shortcut or laboratory hint you'd like to share with the Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Alfred Bader.

Dr. Stéphane De Lombaert at Colorado State University suggested that we offer the tetramethylammonium salt of (1-hydroxyethylidene)pentacarbonylchromium.[1]



$$\overset{O^-}{\overset{|}{MeC}}{=}Cr(CO)_5 \quad {}^{+}NMe_4$$

This particularly stable organometallic reagent is readily converted into a variety of synthetically useful heterosubstituted chromium carbene complexes[2] after activation with an acylating agent.[3]

Naturally, we made it.

1) Fischer, E.O.; Maasböl, A. *Chem. Ber.* **1967,** *100,* 2445.
2) a) Dötz, K.H. *Angew. Chem., Int. Ed. Engl.* **1984,** *23,* 587.
   b) Hegedus, L.S.; de Weck, G.; D' Andrea, S. *J. Am. Chem. Soc.* **1988,** *110,* 2122.
3) a) Fischer, E.O.; Selmayr, T.; Kreissl, F.R. *Chem. Ber.* **1977,** *110,* 2947.
   b) Connor, J.A.; Jones, E.M. *J. Chem. Soc. (A)* **1971,** 3368.

It was no bother at all, just a pleasure to be able to help.

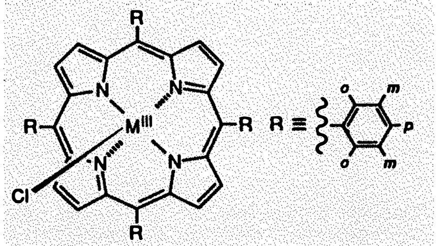
The Mechanisms of Oxygen Transfer from Acyl and Alkyl Hydroperoxides to Metal(III) Porphyrins and the Epoxidation of Alkenes by the Resultant Hypervalent Metal-Oxo Porphyrin Products

Thomas C. Bruice
Department of Chemistry
University of California at Santa Barbara
Santa Barbara, CA 93106

"Oxene equivalent" transfer to metalloporphyrins to provide hypervalent metal-oxo porphyrins and the reactions of the latter in epoxidation and oxygen insertion have received considerable attention. The following report summarizes our recent investigations. Consideration is given to two problems: (1) the mechanisms of oxidation of various porphyrin metal complexes by oxygen transfer from acyl hydroperoxides, hydrogen peroxide and alkyl hydroperoxides; and (2) the mechanism of epoxidation of metal-oxo porphyrin species two-electron-oxidized above the metal(III) porphyrin state.

Metal(III) porphyrins are easily oxidized at the four *meso*-positions of the porphyrin ring. Susceptibility to oxidation can be greatly impeded by protecting these *meso*-positions with phenyl substituents. The *meso*-tetrakis(phenyl)porphinato metal(III) salts [(TPP)M^{III}(X)$_n$] (TPP = tetraphenylporphyrin, M = metal cation and X = axial ligand or counter anion), and analogues bearing substituents on the phenyl rings (Table I), have been used in modeling protoporphyrin-IX mixed-function oxidases (peroxidases, catalases and cytochrome P-450 enzymes).

Table I



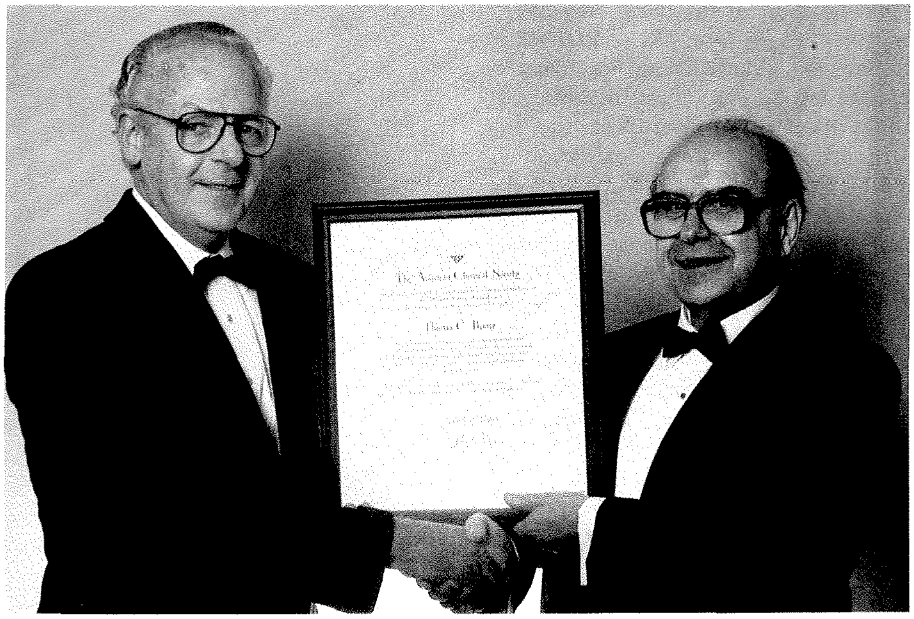
Abbreviation	M^{III}	o	m	p
(TPP)Fe^{III}(Cl)	Fe	H	H	H
(TPP)Cr^{III}(Cl)	Cr	H	H	H
(TPP)Mn^{III}(Cl)	Mn	H	H	H
(TPP)Co^{III}(Cl)	Co	H	H	H
(F$_{20}$TPP)Fe^{III}(Cl)	Fe	F	F	F
(Cl$_8$TPP)Fe^{III}(Cl)	Fe	Cl	H	H
(Cl$_8$TPP)Mn^{III}(Cl)	Mn	Cl	H	H
(Br$_8$TPP)Fe^{III}(Cl)	Fe	Br	H	H

Oxidation by Oxygen-Transfer Step

The first step in the mixed-function oxidation is transfer of an "oxene equivalent" to the metal(III) porphyrin such that the oxygen becomes an axial ligand of the metal and the metal(III) porphyrin undergoes two-electron oxidation (eq. 1). It is conventional to refer to the product of the two-electron oxidation of a metal(III)-oxo porphyrin as "compound I" and the product of one-electron reduction of compound I as "compound II". This nomenclature does not specify the structure of the products of two-electron and one-electron oxidation of the metal(III)-oxo porphyrin. The structure of compound I is dependent upon the nature of the metal(III) species and the presence or absence of a strongly basic axial oxo ligand. When an oxo ligand is present, compound I may have the structure of a metal(V)-oxo porphyrin, a metal(IV)-oxo porphyrin π-cation radical or a metal(III)-oxo porphyrin dication (Fig. 1).

$$[(\text{porphyrin})\text{Fe}]^+\,[\text{X}]^- \xrightarrow{[\text{O}]} [(\text{porphyrin})\text{Fe(O)}]^+\,[\text{X}]^- \qquad \text{(eq. 1)}$$

Our initial studies of the dynamics of oxidation by oxygen transfer using acyl hydroperoxides, hydrogen peroxide and alkyl hydroperoxides (ROOH species) were carried out in various organic solvents. The following metal(III) complexes were investigated in the solvents indicated: (EDTA)Fe^{III} (in MeOH)[1]; (TPP)Cr^{III}(Cl) (in CH_2Cl_2)[2,3]; (TPP)Mn^{III}(Cl) (in PhCN)[4]; (TPP)Fe^{III}(Cl) (in MeOH)[3,5]; and



Professor Thomas C. Bruice (left) receiving the Alfred Bader Award in Bioinorganic and Bioorganic Chemistry from Dr. Alfred Bader, Chairman of the Board, Sigma-Aldrich Corporation.

(TPP)Co^{III}(Cl) (in CHCl$_3$)[6]. Second-order rate constants (k_{ROOH}) for reaction of each metal(III) complex with a series of ROOH compounds were generally determined by trapping of the compound I or compound II species. Trapping was carried out by the use of one or another agent that upon one-electron oxidation provides a monitorable colored radical (eqs. 2 and 3) or by monitoring the formation of compound II species which arise by the comproportionation of compound I with remaining metal(III) porphyrin (eq. 4). Plots of log k_{ROOH} *vs.* the pK_a (in water) of the leaving ROH group establish linear relationships between the free energy of activation (ΔG^*) and the standard free energies (ΔG°) of acid dissociation of ROH. The pK_a values of the leaving ROH group are an index of the polarity of the RO-OH bond. Plots of log k_{ROOH} *vs.* pK_a of ROH are shown in Figure 2.

Traylor and associates[7] used PhCH$_2$CO$_3$H as oxygen donor in order to differentiate between oxygen-transfer reactions which involve heterolytic and homolytic O-O bond cleavage. A heterolytic mechanism provides PhCO$_2$H while homolytic O-O bond cleavage gives PhCH$_2$CO$_2$• which immediately decomposes into PhCH$_2$• and CO$_2$. By finding PhCH$_2$CO$_2$H as the product of reaction of PhCH$_2$CO$_3$H, we showed that oxygen transfers by percarboxylic acids to (EDTA)Fe^{III}, (TPP)Cr^{III}(Cl), (TPP)Mn^{III}(Cl), and (TPP)Co^{III}(Cl) occur by heterolytic O-O bond scission. Thus, metal(III) porphyrins are oxidized by acyl hydroperoxides to the compound I oxidation state (eq. 5).

Examination of the linear free-energy plots of log k_{ROOH} *vs.* pK_a of ROH (Fig. 2) shows that a single line suffices to correlate the log k_{ROOH} values for both acyl and alkyl hydroperoxides when the species undergoing oxidation is (EDTA)Fe^{III} or (TPP)Cr^{III}(Cl). With the exception of the least acidic alkyl hydroperoxides, this is also true of the imidazole (ImH)-ligated manganese(III) complex (TPP)Mn^{III}(Cl)(ImH) (CH$_2$Cl$_2$ solvent).[8] It is reasonable to assume that in these cases, both acyl hydroperoxide and alkyl hydroperoxide reactions involve heterolytic O-O bond scission. The linear free energy plots for (TPP)Fe^{III}(Cl) and (TPP)Co^{III}(Cl) exhibit a break at a pK_a of ROH of between 9 and 11. We have proposed that this is due to a change from heterolytic O-O bond scission to rate-determining homolytic O-O bond scission for the alkyl hydroperoxides. The slopes ($-\beta_{1g}$) of the linear free-energy plots for the heterolytic mechanism with (EDTA)Fe^{III},

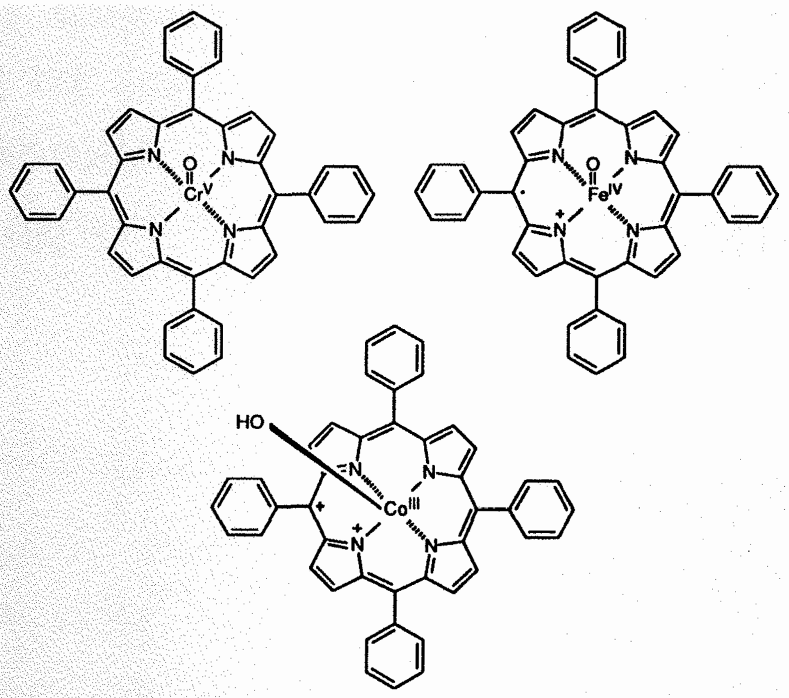


Fig. 1 - Structures formed by 2e$^-$ oxidation of 5,10,15,20-tetraphenylporphinato metal(III)-oxo species are dependent upon the metal. Shown are the Cr^V-oxo species, the Fe^{IV}-oxo porphyrin π-cation radical and the Co^{III}-OH porphyrin dication.

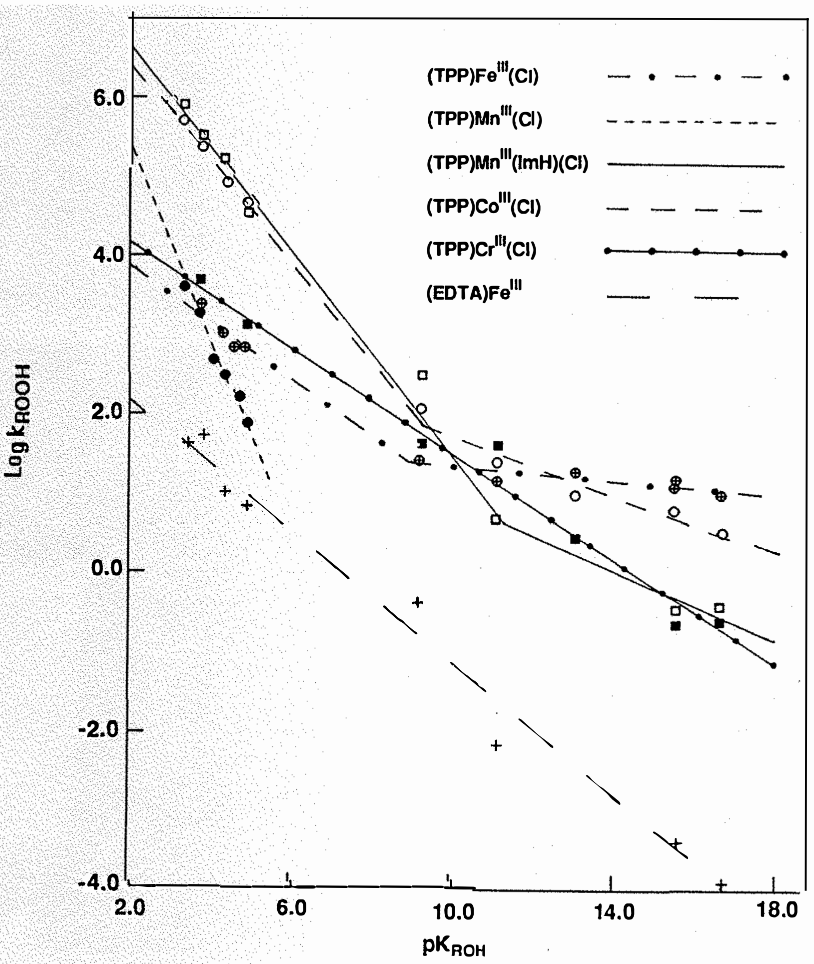


Fig. 2 - Linear free-energy plots of the log of the second-order rate constant (k_{ROOH}) for reaction of acyl and alkyl hydroperoxides with a series of metal complexes vs. the pK_a of the corresponding carboxylic acids and alcohols.

$$\text{compound I} + \text{trap} \longrightarrow \text{compound II} + \text{trap}\bullet \qquad \text{eq. 2}$$

$$\text{compound II} + \text{trap} \longrightarrow (\text{TPP})\text{M}^{\text{III}}(\text{X}) + \text{trap}\bullet \qquad \text{eq. 3}$$

$$\text{compound I} + (\text{TPP})\text{M}^{\text{III}}(\text{X}) \longrightarrow 2\,\text{compound II} \qquad \text{eq. 4}$$

$$(\text{TPP})\text{M}^{\text{III}}(\text{X}) + \text{RCO}_3\text{H} \longrightarrow \text{compound I} + \text{RCO}_2\text{H} \qquad \text{eq. 5}$$

$$2\,(\text{porph})\text{M}^{\text{III}}(\text{OH}_2) \longrightarrow (\text{porph})\text{M}^{\text{III}}\text{-O-M}^{\text{III}}(\text{porph}) + \text{H}_2\text{O} + 2\,\text{H}^+ \qquad \text{eq. 6}$$

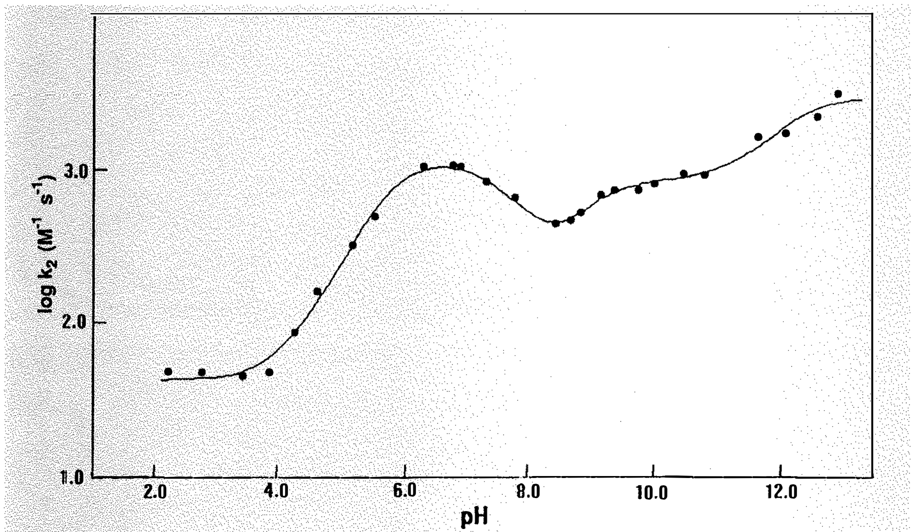
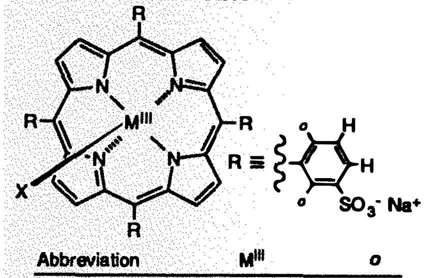


Fig. 3 - The log of the apparent second-order rate constant vs. pH profile for reaction of t-BuOOH with water-soluble and non-μ-oxo dimer forming 5,10,15,20-(2,6-dimethyl-3-sulfonatophenyl)-porphinato iron(III) hydrate [(1)Fe^{III}(X), where $X = H_2O$ or HO^-].

$$k_{1y} = \underbrace{\frac{(k_2k_1)}{(k_{-1}+k_2)}}_{(A)} + \underbrace{\frac{\dfrac{(k_3K_{a2})k_1[H^+]}{(k_{-1})}}{\dfrac{(k_3K_{a2}+H^+)(K_{a1}+H^+)}{k_{-1}}}}_{(B)} + \underbrace{\frac{\dfrac{(k_5K_{a3})k_4}{(k_{-4})}}{\dfrac{(k_5K_{a3}+H^+)}{k_{-4}}}}_{(C)} + \underbrace{\frac{k_6K_{a4}}{(K_{a4}+H^+)}}_{(D)} \qquad \text{eq. 7}$$

Table II



Abbreviation	M^{III}	o
(1)H$_2$	2H$^+$	Me
(2)H$_2$	2H$^+$	Cl
(1)Fe^{III}(X)	Fe^{III}	Me
(1)Mn^{III}(X)	Mn^{III}	Me
(2)Fe^{III}(X)	Fe^{III}	Cl
(2)Mn^{III}(X)	Mn^{III}	Cl

X = H_2O or HO^-, depending on the pH.

(TPP)Cr^{III}(Cl), (TPP)Fe^{III}(Cl), and (TPP)Co^{III}(Cl) are between ~0.4 to 0.6. The -β_{lg} of 1.27 for (TPP)Mn^{III}(Cl) complex is an exception. In this instance, the great sensitivity of log k_{ROOH} to pK_a of ROH precludes a measurable reaction of (TPP)Mn^{III}(Cl) with alkyl hydroperoxides. Ligation of (TPP)Mn^{III}(Cl) with imidazole to provide (TPP)Mn^{III}(Cl) (ImH) decreases -β_{lg} to 0.6 and in general greatly increases the values of log k_{ROOH} so that the second-order rate constants for reactions of (TPP)Mn^{III}(Cl)(ImH) with alkyl hydroperoxides are easily determined. The much smaller values of -β_{lg} for the reaction of alkyl hydroperoxides with (TPP)Fe^{III}(Cl) and (TPP)Co^{III}(Cl) (0.04 and 0.19, respectively) reflect the low polarity of the transition state in the homolytic O-O bond-breaking process.

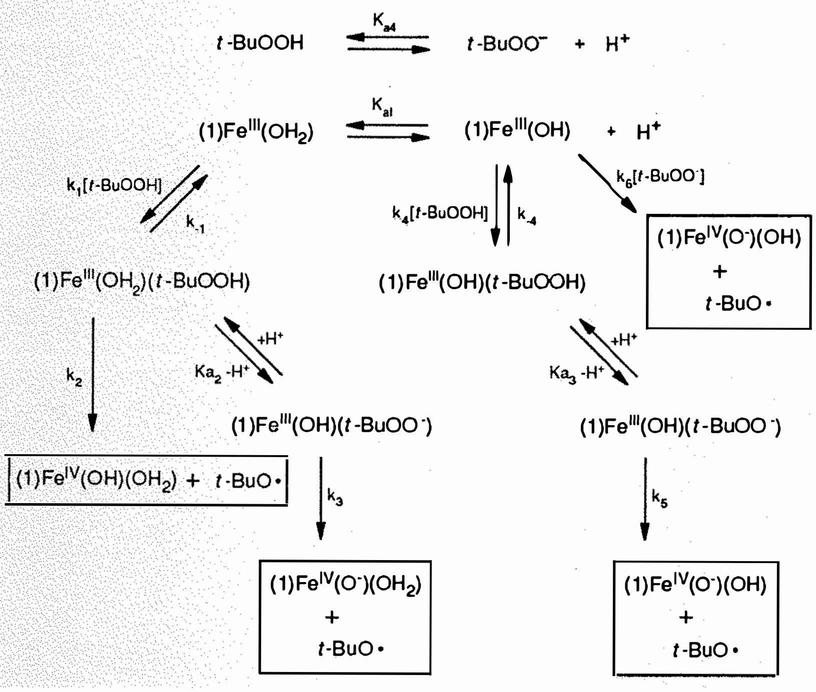
The foregoing discussion pertains to reactions studied in organic solvents. Though such studies have been shown to be valuable, use of organic solvents does not allow one to obtain a detailed description of the reaction mechanisms. This is so because the hydrogen-ion activity in organic solvents is not easily determined. Related to this is the difficulty, in organic solvents, of determining the acid-dissociation constants of reactants and the role of general-acid and general-base catalysis in the rate-limiting oxygen-transfer reaction. Both acyl-OOH and alkyl-OOH compounds (ROOH) possess dissociable protons. Oxygen transfer from ROOH species to a metal(III) porphyrin is preceded by metal(III) porphyrin ligation of ROOH. Once ligated, the acid-dissociation constant of ROOH is decreased by *ca.* 10^6. Also, the ligand X may be exchanged for ROH in the course of reaction of metal(III) porphyrin with ROOH and ligated ROH would have an acid-dissociation constant. To determine the details of the oxygen-transfer reaction, we have used *meso*-tetrakis(2,6-dimethyl-3-sulfonatophenyl)porphyrin [(1)H$_2$] and *meso*-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphyrin [(2)H$_2$] and have metallated these species with iron(III) and manganese(III) to provide the hydrates (1)Fe^{III}(X)(H_2O), (1)Mn^{III}(X)(H_2O), and (2)Fe^{III}(X)(H_2O) (where X = H_2O or HO^-) (Table II). The *ortho*-methyl and *ortho*-chloro substituents of 1 and 2 sterically prevent μ-oxo dimer formation (eq. 6) and stacking of the porphyrin rings — the (1)M^{III}(X) and (2)M^{III}(X) species remain monomeric at all pH values in H_2O.

The reactions of ROOH species with (1)Fe^{III}(X), (2)Fe^{III}(X) and (1)Mn^{III}(X) are first-order in metal(III) porphyrin and

ROOH.[9-14] The pH dependency of the determined second-order rate constants (k_{ly}) for reaction of both (1)Fe^{III}(X) and (2)Fe^{III}(X) with various alkyl hydroperoxides, are much alike. The pH profile for k_{ly} is shown for reaction of *t*-BuOOH with (1)Fe^{III}(X) in Figure 3. Points in Figure 3 are experimental and the line is generated from equation 7. In turn, equation 7 has been derived by steady-state assumption of the intermediates of Scheme 1. Our conclusion is that oxygen-transfer reactions with alkyl hydroperoxides occur from the complexes (Porph)$M^{III}(OH_2)$(ROOH), (Porph)$M^{III}(OH_2)(ROO^-)$, and (Porph)$M^{III}(HO^-)$ (ROO^-) and that the rate of the oxygen-transfer reaction increases upon stepwise proton dissociation. By the choice of the appropriate pH, one can examine the dependence of ROOH and metal(III) porphyrin structures on the second-order rate constant for oxygen transfer by way of one or another of these complexes. The dependence of the second-order rate constant for oxygen transfer at pH ~2 and ~7 is shown in Figures 4 and 5 when using (1)Fe^{III}(X) and (2)Fe^{III}(X). Comparison of the plots of Figures 4 and 5 to those of Figure 2 for (TPP)Fe^{III}(Cl) shows their near identity. Again, the logs of the second-order rate constants for the weakly acidic alkyl hydroperoxides reside on a line of small $-\beta_{lg}$ while the logs of the second-order rate constants for the acyl hydroperoxides reside on a line of appreciable $-\beta_{lg}$. Also, with alkyl hydroperoxides and hydrogen peroxide, oxygen-transfer reactions are not subject to either general-acid or general-base catalysis by oxy-acids or bases [like results have been obtained with (1)Mn^{III}(X)].

That oxygen transfer from alkyl hydroperoxides (but not acyl hydroperoxides) involves a rate-limiting O-O bond homolysis is shown by the following evidence. Decomposition products of the alkyl hydroperoxides can always be accounted for by a radical fragmentation of alkyl O• followed by a rebound hydroxylation of an alkyl radical moiety (Scheme 2). In the reaction of (1)Fe^{III}(X) or (2)Fe^{III}(X) with either acyl or alkyl hydroperoxides, there is observed the formation of intermediate iron(IV)-oxo porphyrin species. In order to observe the iron(IV)-oxo porphyrin intermediate with alkyl hydroperoxides, oxygen must be present. Oxygen need not be present to see such intermediates when using acyl hydroperoxides. These observations may be explained as follows. An iron(II) porphyrin intermediate is formed with alkyl hydroperoxides (Scheme 2). The reaction of the iron(II) porphyrin with oxy-

Scheme 1



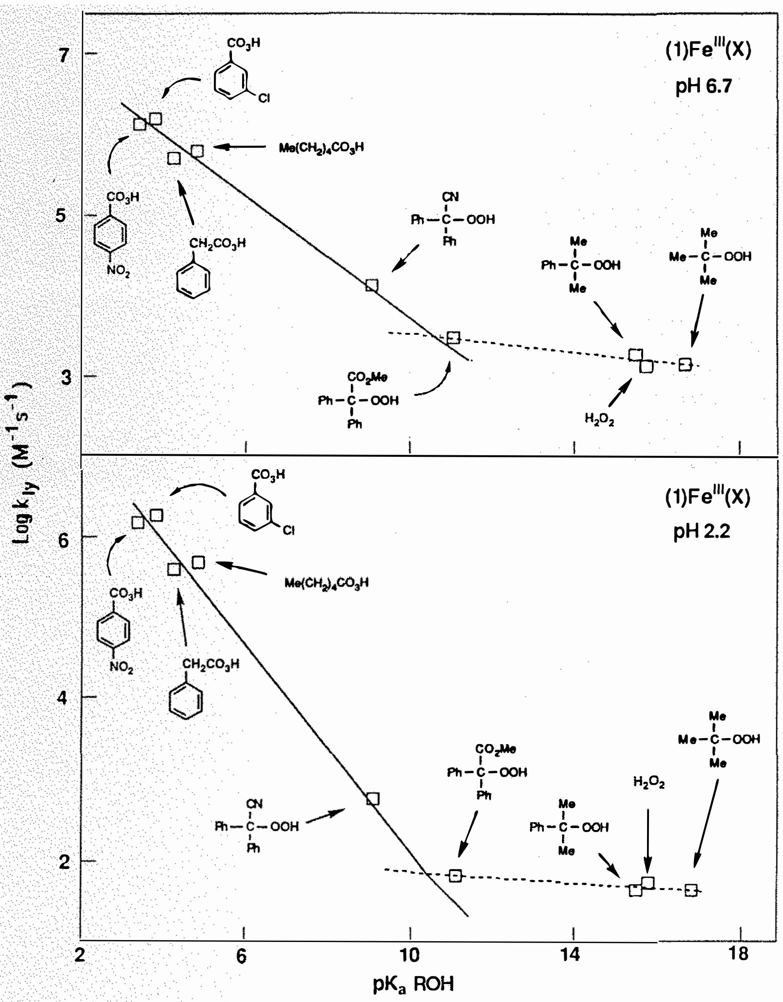


Fig. 4 - Plots of the log of the apparent second-order rate constants, determined at pH 6.7 and 2.2, for reaction of acyl and alkyl hydroperoxides with (1)Fe^{III}(X) vs. the pK_a of the corresponding carboxylic acids and alcohols.

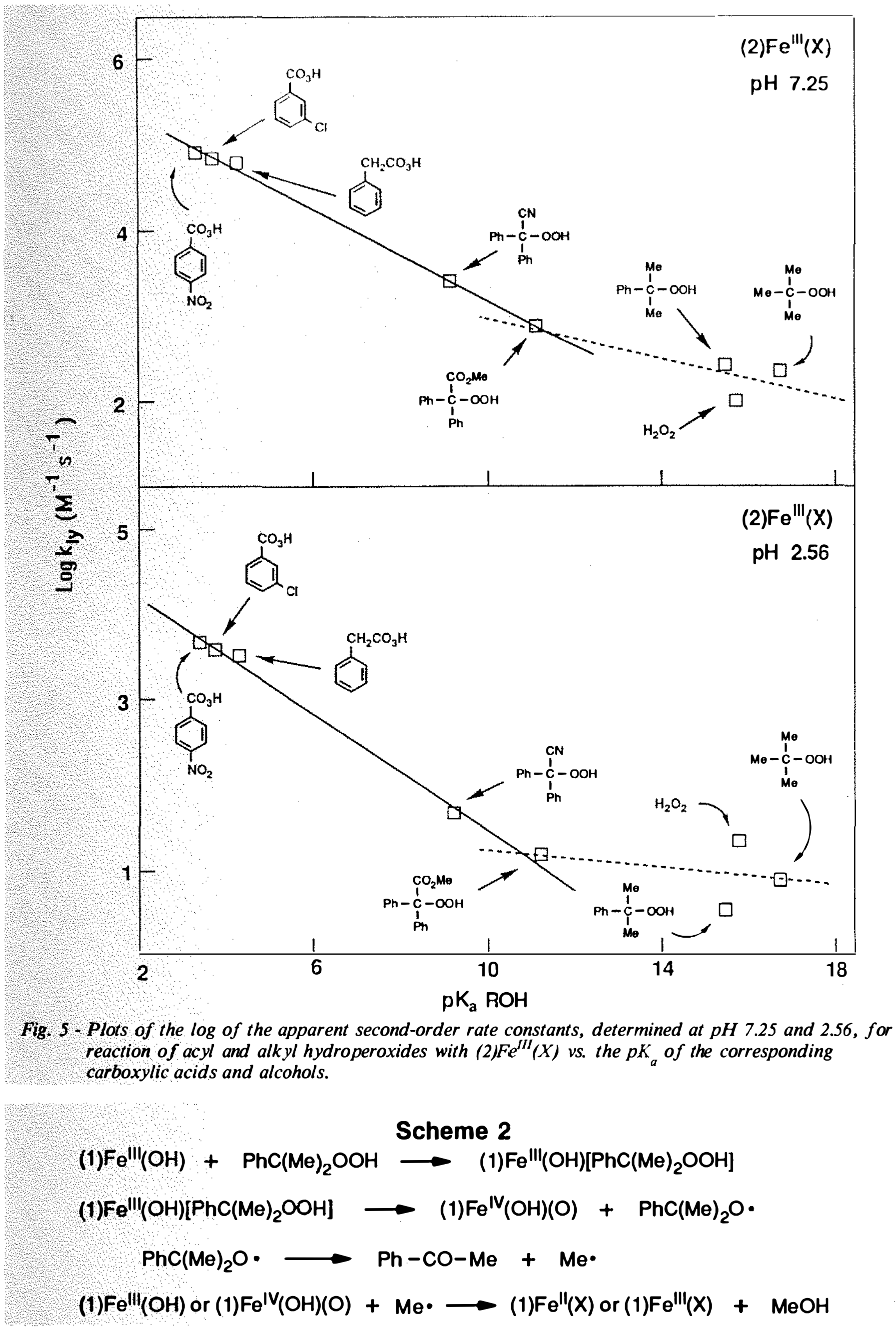


Fig. 5 - Plots of the log of the apparent second-order rate constants, determined at pH 7.25 and 2.56, for reaction of acyl and alkyl hydroperoxides with (2)Fe^{III}(X) vs. the pK$_a$ of the corresponding carboxylic acids and alcohols.

Scheme 2

$$(1)Fe^{III}(OH) + PhC(Me)_2OOH \longrightarrow (1)Fe^{III}(OH)[PhC(Me)_2OOH]$$

$$(1)Fe^{III}(OH)[PhC(Me)_2OOH] \longrightarrow (1)Fe^{IV}(OH)(O) + PhC(Me)_2O\bullet$$

$$PhC(Me)_2O\bullet \longrightarrow Ph{-}CO{-}Me + Me\bullet$$

$$(1)Fe^{III}(OH) \text{ or } (1)Fe^{IV}(OH)(O) + Me\bullet \longrightarrow (1)Fe^{II}(X) \text{ or } (1)Fe^{III}(X) + MeOH$$

$$2\ (1)Fe^{II}(X) + O_2 \longrightarrow (1)Fe^{III}(X){-}O{-}O{-}Fe^{III}(X)(1) \longrightarrow 2\ (1)Fe^{IV}(X)(O) \qquad \text{eq. 8}$$

$$(1)Fe^{III}(X) + (^{+\bullet}1)Fe^{IV}(O)(X) \longrightarrow 2\ (1)Fe^{IV}(X)(O) \qquad \text{eq. 9}$$

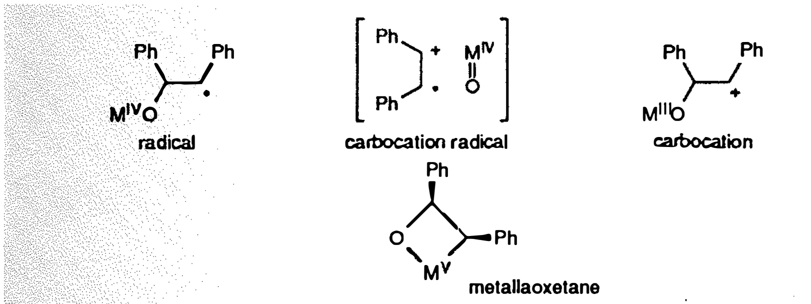


Fig. 6 - Proposed intermediates in the epoxidation of alkenes by hypervalent metal-oxo porphyrins.

gen gives rise to the observed iron(IV)-oxo-porphyrin species (eq. 8). In the case of the acyl hydroperoxides, the iron(IV)-oxo porphyrin would be formed by a comproportionation reaction (eq. 9). That these are reasonable assumptions has been shown by the trapping of both (1)Fe^{II}(X) and (2)Fe^{II}(X) species by CO in reactions involving alkyl hydroperoxides.

In organic solvents, rate-determining homolytic O-O bond breaking may be followed by a second electron transfer such that the products would be that of heterolytic O-O bond breaking $\{[(P)Fe^{IV}(O)(X)\ \bullet OR] \dashrightarrow (+\bullet P)Fe^{IV}(O)(X) + {}^{-}OR\}$.

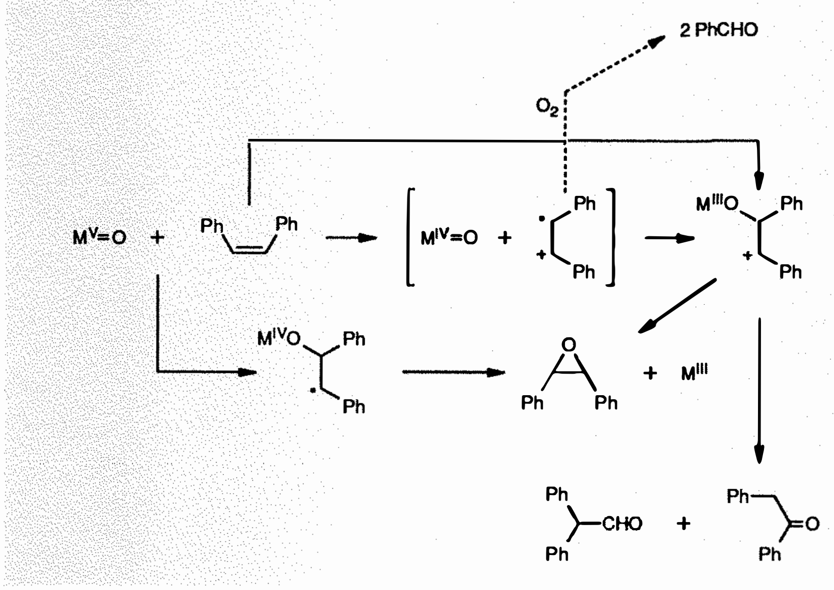
The Mechanism of Epoxidation of Alkenes

The intermediates of Figure 6 have been proposed to arise in the epoxidation of alkenes by compound I species of metalloporphyrins. The basis for the implication of these intermediates is the extent of stereoelectronic control in the epoxidation and the nature of products, other than epoxide. The stereochemistry of the epoxide must relate directly to the mechanism of its formation. However, the structures of products, other than epoxide, may or may not contain information concerning the mechanism of epoxidation. At one extreme, all products arise from intermediates in a step-wise mechanism of epoxidation, while at the other extreme, epoxidation would be concerted and all other products would arise *via* competing parallel pathways. The epoxidation of *cis*-stilbene by the compound I series formed from *meso*-tetrakis(pentafluorophenyl)-porphinato iron(III) chloride [(F$_{20}$TPP)Fe^{III}(Cl)], *meso*-tetrakis(2,6-dichlorophenyl)porphinato iron(III) chloride [(Cl$_8$TPP)Fe^{III}(Cl)] and *meso*-tetrakis-(2,6-dichlorophenyl)porphinato manganese(III) chloride [(Cl$_8$TPP)Mn^{III}(Cl)] has been carefully examined.[15] Assuming that epoxidation involves a stepwise mechanism, the formation of all products may be rationalized by use of Scheme 3. In the Scheme, M^{V}=O represents the compound I species while M^{IV}=O represents the compound II species formed on one-electron reduction of the M^{V}=O species. The reversible formation of M^{IV}=O and carbocation radical by one-electron transfer from alkene to M^{V}=O could explain the observed conversion of *cis*-stilbene to *trans*-stilbene as well as the formation of PhCHO by oxygen trapping of stilbene carbocation radical and decomposition of the resultant dioxetane. Evidence for a carbocation intermediate would be based on the observed formation of

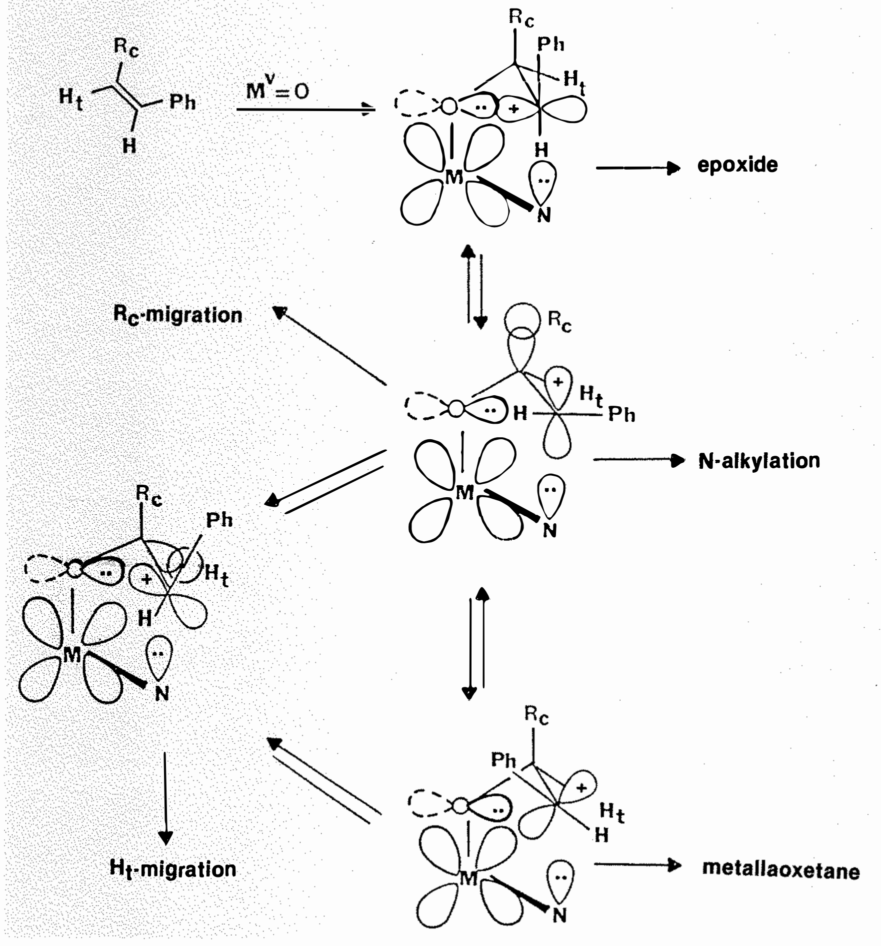
Ph_2CHCHO (phenonium migration) and $PhCH_2COPh$ (proton migration). The stereo-orbital diagram of Scheme 4 depicts acyclic structures as possible intermediates in epoxidation, preferential substituent rearrangements, porphyrin N-alkylation, and metallaoxetane formation. Though experimental observations may be rationalized on the basis of a stepwise mechanism, they may also be rationalized by a concerted one-step epoxidation in competition with processes which generate carbocation radical and carbocation. We have set out to differentiate these possibilities.

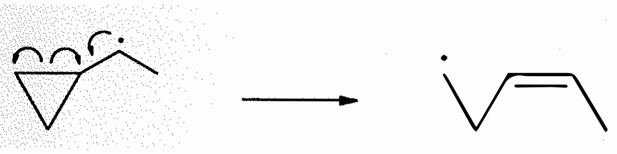
Radical intermediates in chemical and enzymatic reactions have been trapped by use of cyclopropyl substituents by way of the cyclopropylcarbinyl to homoallylcarbinyl radical rearrangement (CPCRR). The rate constant ($\sim 2 \times 10^7$ s^{-1}) for the CPCRR on conversion of a 2° radical to a 1° radical (eq. 10) is not sufficiently large to assure trapping of unstable radical intermediates. We have introduced the use of the *trans*-2,*trans*-3-diphenylcyclopropyl substitutent[16,17] because the standard free-energy change in the CPCRR conversion of a 2° radical to a 2° benzyl radical (eq. 11) should be favored by minimally 15 Kcal/mol over CPCRR for conversion of a 2° radical to a 1° radical. The "clock time" for the CPCRR with the *trans*-2,-*trans*-3-diphenylcyclopropyl substituent has been determined from the intramolecular competitive reactions of Equation 12 as $\geqslant 2 \times 10^{10}$ s^{-1}. Epoxidation of *Z*-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene by the compound I species formed from $(F_{20}TPP)Fe^{III}(Cl)$ provides *cis*-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)oxirane in 95% yield (eq. 13). No *trans*-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)oxirane could be detected (to 0.1%) so that the stereochemistry of the alkene is preserved upon epoxidation. This observation speaks against the accumulation of a carbocation radical. Of the 5% side product, none could be ascribed to CPCRR involving the neutral radical species. Thus, formation of the neutral radical intermediate would require this species to convert to epoxide with a rate constant of $\geqslant 2 \times 10^{12}$ s^{-1} (Scheme 5). The neutral radical, therefore, cannot be a detectable intermediate in epoxidation. When similar considerations are applied to the carbocation radical, it is found that this species as an intermediate would be required to pass on to epoxide with a rate constant of $\geqslant 2 \times 10^{11}$ s^{-1} (Scheme 6). If the radical cation is an intermediate, its free-energy content must approach that of the transition state for its conversion to epoxide.

Scheme 3

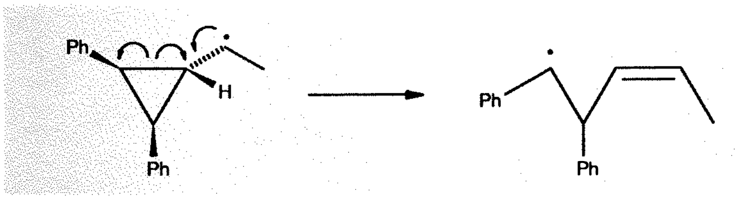


Scheme 4

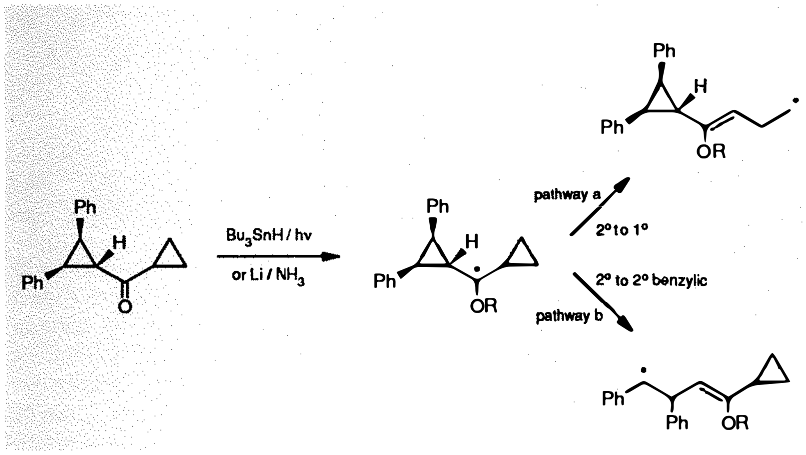




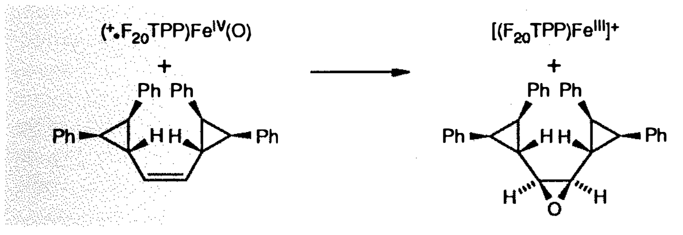
eq. 10



eq. 11

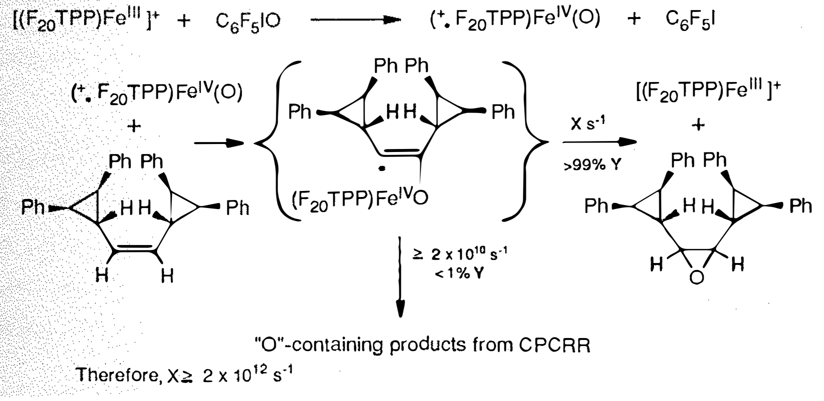


eq. 12

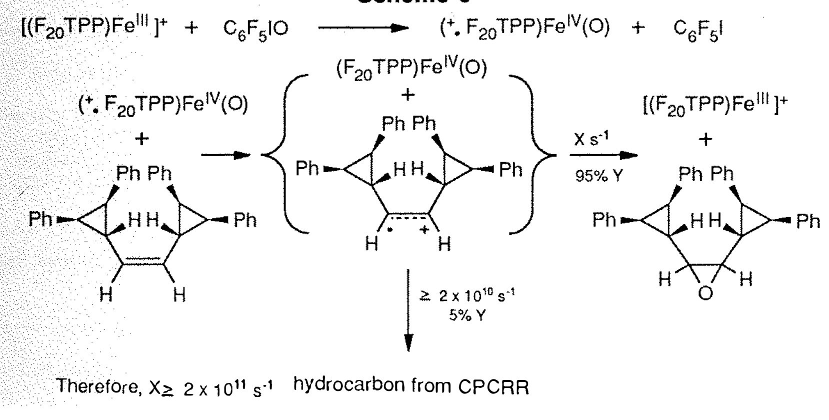


eq. 13

Scheme 5



Scheme 6



Another approach to the assessment of the intermediacy of the carbocation radical intermediate has employed a number of chromium(V)-oxo tetraphenyl porphyrins as epoxidation agents.[18] The results with *meso*-tetrakis(2,6-dibromophenyl)porphinato chromium(V)-oxo [(Br$_8$TPP)Cr^V(O)(X)] will be discussed.[19] The logs of the second-order rate constants (log k$_f$) for the epoxidation of a number of alkenes by (Br$_8$TPP)Cr^V(O)(X) are plotted *vs.* the E$_{1/2}$ for one-electron oxidation of the alkenes in Figure 7. The apparent linear free-energy relationship might be employed to implicate a one-electron transfer step (to yield carbocation radical) as rate limiting in the epoxidations. This, however, cannot be the case.

With the assumption of a carbocation radical intermediate, the reaction coordinate cartoon of Figure 8 may be constructed. Values of ΔG_f^* are calculated from the second-order rate constant (k$_f$) for epoxidation, and the values of the standard free energies (ΔG°) of formation of the putative intermediate [(Br$_8$TPP)Cr^{IV}(O) + carbocation radical] state can be calculated from emf values available from a knowledge of the E$_{1/2}$ for alkene one-electron oxidation and the E$_{1/2}$ for one-electron reduction of (Br$_8$TPP)Cr^V(O)(X) to (Br$_8$TPP)Cr^{IV}(O) (Scheme 7). From ΔG_f^* and ΔG° one obtains a calculated free energy of activation (ΔG_r^*) for reaction of carbocation radical with (Br$_8$TPP)Cr^{IV}(O) to provide alkene plus (Br$_8$TPP)Cr^V(O)(X) and from ΔG_r^* there are obtained values of the retrograde constant k$_r$ (Figure 8). Calculated values of k$_r$ range, for most alkenes, from 10^{15} to 10^{26} M^{-1} s^{-1}. Clearly, the carbocation radical is not an intermediate in the epoxidation reaction. The apparent linear free-energy relationship between alkene oxidation potentials and log k$_f$ reflect the dependence of both on the electron density of the carbon-carbon double bond.

The use of the compound I species generated from (Br$_8$TPP)Fe^{III}(Cl) has allowed a definition of the geometry of the critical complex of alkene and compound I in epoxidation.[20] When (Br$_8$TPP)Fe^{III}(Cl) is used as a catalyst in the epoxidation of alkenes by C$_6$F$_5$IO, epoxides are obtained in very high yield. With 2,3-dimethyl-2-butene epoxidation yields of 100% (based upon [C$_6$F$_5$IO]$_i$) are obtained. In Figure 9, 2,3-dimethyl-2-butene is docked at the oxygen moiety of (• + Br$_8$TPP)Fe^{IV}(O)(Cl). Inspection of Figure 9 shows that the alkene can only approach from the top and that overlap with iron d-orbitals is not possible. This tends to rule

Scheme 7

$$\begin{array}{lcr}
(\mathrm{Br_8TPP})\mathrm{Cr^{V}(O)(X)} + e^- \longrightarrow (\mathrm{Br_8TPP})\mathrm{Cr^{IV}(O)} + X^- & & E_1 \\
\text{carbocation radical} + e^- \longrightarrow \text{alkene} & & E_2 \\
\hline
(\mathrm{Br_8TPP})\mathrm{Cr^{V}(O)(X)} + \text{alkene} \longrightarrow \text{carbocation radical} + (\mathrm{Br_8TPP})\mathrm{Cr^{IV}(O)} & & \text{emf}
\end{array}$$

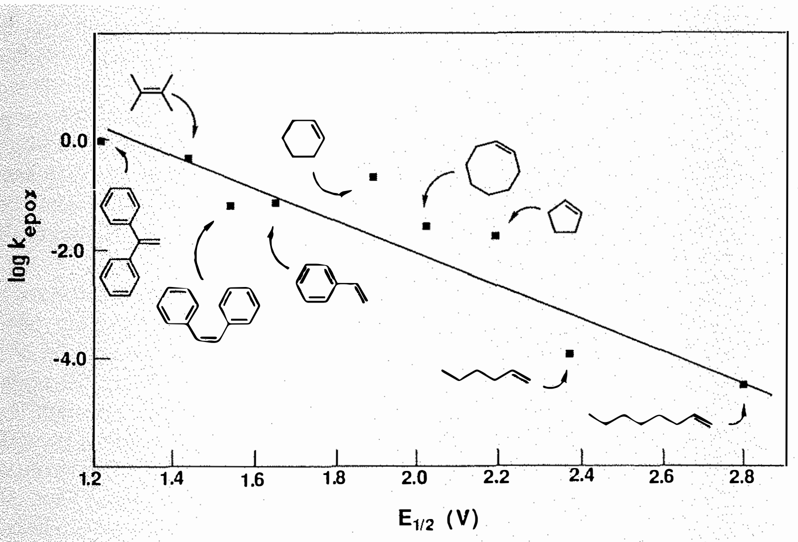


Fig. 7 - A plot of the log of the second-order rate constant for the epoxidation of alkenes by $(Br_8TPP)Cr^{V}(O)(X)$ vs. the potential for alkene $1e^-$ oxidation.

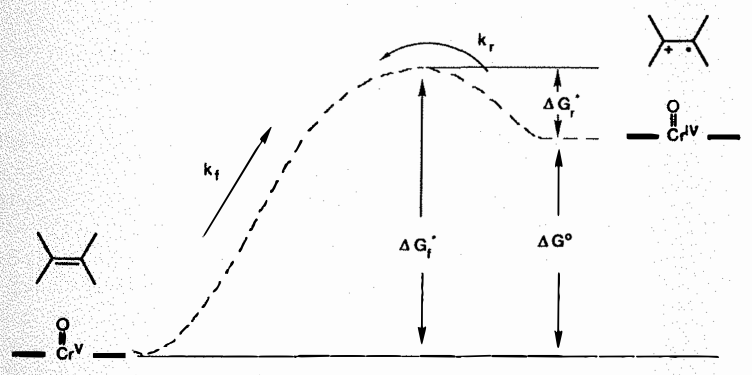


Fig. 8 - Reaction coordinate for the $1e^-$ oxidation of alkene by $(Br_8TPP)Cr^{V}(O)(X)$.

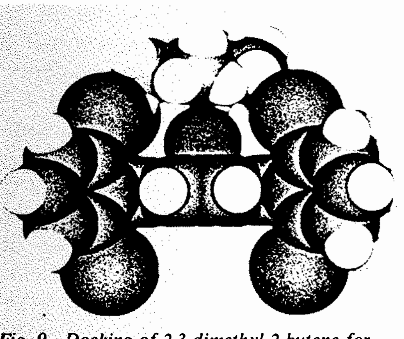


Fig. 9 - Docking of 2,3-dimethyl-2-butene for epoxidation by $(^{+}\bullet Br_8TPP)Fe^{IV}(O)$ shows that the alkene can only approach the oxygen moiety.

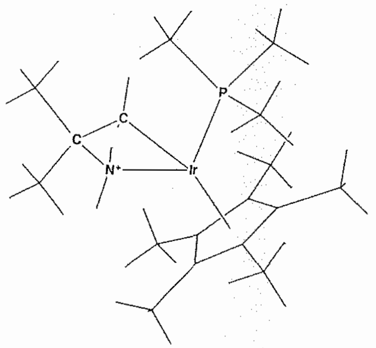


Fig. 10 - X-ray-derived structure of an iridium metallaazetane (ref. 21).

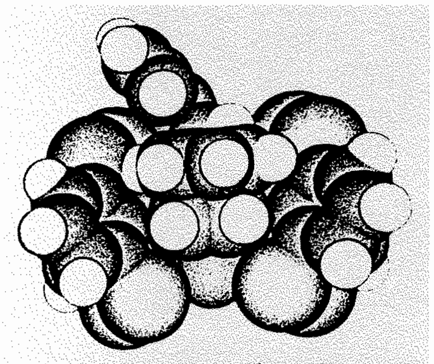


Fig. 11 - meso-Tetrakis(2,6-dibromophenyl)porphinato iron(III) cis-stilbene structure.

out a metallaoxetane as an intermediate in epoxidation. In Figure 10, there is shown a recent X-ray structure of an iridium metallaazetane determined in Bergman's laboratory.[21] Assuming that a metallaoxetane possesses the same structure, it can be shown by computer graphics that a metallaoxetane structure formed with *cis*-stilbene and *meso*-tetrakis(2,6-dibromophenyl)porphinato iron moiety could not exist due to overlap of both porphyrin ring and bromo substituents with a phenyl substituent of the metallaoxetane structure (Figure 11). In order to relieve these interactions, it would be required that the Fe-O and Fe-C bond lengths be ~3Å.

Acknowledgement

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About the Author

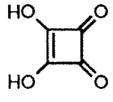
Thomas C. Bruice is the first (1988) recipient of the Alfred Bader Award in Bioorganic and Bioinorganic Chemistry. Dr. Bruice received his Ph.D. from the University of Southern California and was a National Research Council Fellow at UCLA before joining the faculty of the Department of Biochemistry at Yale University. Following Yale, he served as a faculty member in the Department of Physiological Chemistry at the Johns Hopkins School of Medicine and the Department of Chemistry at Cornell. He is presently Professor of Chemistry at the University of California at Santa Barbara.

Professor Bruice has been honored as a National Institutes of Health Career Development awardee, as a recipient of a National Institutes of Health Career Investigatorship, and as a Guggenheim Fellow. He was the 1970 recipient of the University of California at Santa Barbara Faculty Research Award. In 1974, he was elected a member of the National Academy of Sciences and in 1976 a member of the American Academy of Arts and Science. Dr. Bruice has been a Phillips Lecturer, a Robert A. Welch Foundation Lecturer, an E.C. Franklin Memorial Lecturer, and a Birgenstok Lecturer. In 1978, Dr. Bruice was awarded the Richard C. Tolman Medal of the Southern California Section of the American Chemical Society, and in 1988 the Distinguished Renaud Lecturer Award of the Michigan State Section of the American Chemical Society. In 1987, he was chosen by the Organic Division of the American Chemical Society as an Arthur C. Cope Scholar awardee and by the Biochemistry Division of the American Chemical Society as the second recipient of the Repligen Medal.

Professor Bruice has served as a consultant to the National Institutes of Health, the National Science Foundation and has been a member of the Advisory Board of the Petroleum Research Foundation and the visitation committee to the Chemistry Department at Brookhaven National Laboratories. He has been Vice Chairman and Chairman of the Biochemistry Division of the American Chemical Society and has served as a member of the Editorial Board for the journals *Biochemistry* and *Bioorganic Chemistry.*

Professor Bruice was a pioneer in the creation of the field of bioorganic chemistry. He has contributed importantly to research in such diverse areas as the mechanisms of acyl-transfer reactions, general catalysis mechanisms, and the mechanisms of reactions of iron-sulfur clusters, pyridoxal, biotin, flavins and methoxatin. Most recently, Dr. Bruice's work has focused on elucidating the mechanism of oxygen transfer to metalloporphyrins and the oxidations of organic substrates by the resultant hypervalent metal-oxo porphyrin species. In 1985, Merck, Sharp and Dohme Research Laboratories sponsored the two-day symposium "Reaction Mechanisms in Chemistry and Enzymology" to honor the fundamental contributions of Professors Thomas Bruice and William Jencks.

Squaric Acid Derivatives – Benzoquinone Synthons



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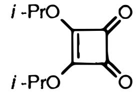

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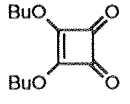
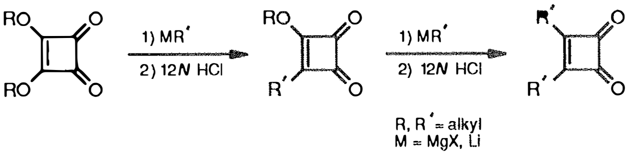
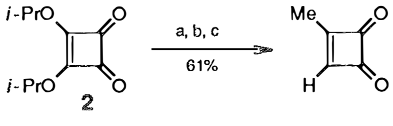


3

Research efforts by Professors L. Liebeskind (Florida State and Emory Universities) and H. Moore (University of California at Irvine) have focused on the use of **3,4-dihydroxy-3-cyclobutene-1,2-dione (squaric acid, 1)** and its derived esters as important starting materials for the synthesis of a variety of benzoquinones with interesting bioactivity. Generally, syntheses start with the formation of a dialkyl ester. The isopropyl ester (**2**) has received recent emphasis due to enhanced regioselectivity, yield and ease of handling.[1]

Defining functionality in the benzoquinone portion of the target molecule begins by nucleophilic addition of lithium or Grignard reagents in a stepwise or "one-pot" manner to yield several types of cyclobut-3-ene-1,2-diones.[1-3] The stepwise method allows for the introduction of two different substituents *via* protection of an intermediate alcohol as the *tert*-butyldimethylsilyl derivative and subsequent nucleophilic addition.[1]

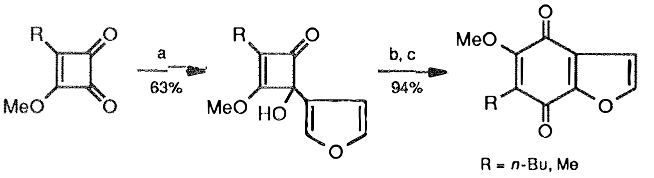




(a) LiAl(O-*t*-Bu)$_3$H; aq. work-up; 89%. (b) TBDMSCl, DMF, DMAP; 96%. (c) MeLi, -78°C, 12*N* HCl; 71%.

Transformation of these substituted cyclobut-3-ene-1,2-diones into benzoquinones follows two general routes: 1) nucleophilic addition and subsequent thermal rearrangement or 2) formation of a maleoylcobalt complex and reaction with an alkyne in the presence of Lewis acids. Examples of these methods follow.

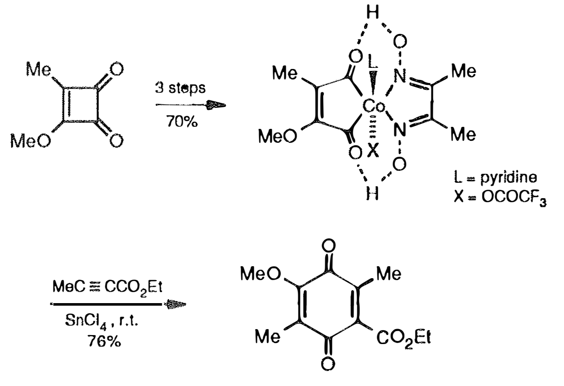
Type 1[4,5]



R = *n*-Bu, Me

(a) 3-Lithiofuran; work-up, -78°C, NH$_4$Cl. (b) Xylene/reflux. (c) Ag$_2$O, K$_2$CO$_3$.

Type 2[6]



regioselectivity 18:1

Several other applications are reported in the literature.[7-10]

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(3) Kraus, J.L. *Tetrahedron Lett.* **1985,** *26,* 1867.
(4) Liebeskind, L.S. *et al. J. Org. Chem.* **1986,** *51,* 3065.
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(6) Iyer, S.; Liebeskind, L.S. *J. Am. Chem. Soc.* **1987,** *109,* 2759.
(7) Perri, S.T.; Moore, H.W. *Tetrahedron Lett.* **1987,** *28,* 4507.
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"CLAYCOP," A User-Friendly Oxidizing and Nitrating Reagent

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CLAYCOP (short for clay-supported cupric nitrate) is a new oxidizing and nitrating reagent and catalyst. *Claycop* was designed to have a reactivity comparable to that of its congener, *clayfen* (clay-supported ferric nitrate), and be stable, without suffering from the problem of slow decomposition that *clayfen* does.[1]

I. PREVIEW

A comparison between representative properties of iron and copper cations is made in Tables I[2], II[3] and III.[4] The greater stability of *claycop*, as compared to *clayfen*, can be attributed to a better match between the metal and the nitrato ligands. The NO_3^- anion is a soft base, the Cu^{+2} cation is a soft Lewis acid. Thus, their union is a stable one.

Table I
Comparison of Standard Reduction Potentials of Iron and Copper Cations

Cu^+	+	$\bar{e}$	$\rightleftharpoons$	Cu	0.522V
Cu^{2+}	+	$\bar{e}$	$\rightleftharpoons$	Cu^+	0.158V
Cu^{2+}	+	$2\bar{e}$	$\rightleftharpoons$	Cu	0.340V
Fe^{2+}	+	$2\bar{e}$	$\rightleftharpoons$	Fe	-0.409V
Fe^{3+}	+	$\bar{e}$	$\rightleftharpoons$	Fe^{2+}	0.770V
Fe^{3+}	+	$3\bar{e}$	$\rightleftharpoons$	Fe	-0.036V

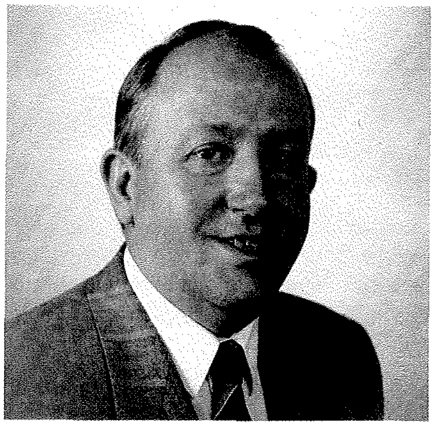
Table II
Comparison of Ionization Potentials (eV) of Copper and Iron

	1st	2nd	3rd	4th
Fe	7.90	16.18	30.64	57.1
Cu	7.72	20.29	36.83	58.9

Table III
The Parr-Pearson Hardness (eV) of Iron and Copper Cations

Cu^+	:	6.3	Fe^{2+}	:	7.3
Cu^{2+}	:	8.3	Fe^{3+}	:	13.1

Photograph by P. Troyanowsky



Photograph by J. Simon

Such reasoning, based upon the hard-soft acid-base (HSAB) principle, can be extended predictably. Both the nitronium (NO_2^+) and the nitrosonium (NO^+) ions are relatively soft. Generating them from *claycop* implies greater softness stemming from the softness of Cu(II) as compared to Fe(III), since the softness of a metallic center provides, synergistically, the hard-soft character of its ligands.[4,5]

Accordingly, one can make a large number of predictions regarding the reactivity of *claycop*. Two will suffice, and can be stated thus:

1. The soft sulfur atoms should bind readily to the soft nitrosonium ions given off by *claycop*; applications of this concept to the formation of thionitrites from thiols and to the cleavage of thioketals for regeneration of hitherto protected carbonyls will be discussed later.

2. Soft nitronium ions emanating from *claycop* should interact with aromatic π electrons (soft Lewis bases) under orbital control, as originally pointed out by Klopman.[6]

This second feature is the key to regioselective aromatic nitrations: if they are initiated by the monoelectronic transfer $ArH + NO_2^+ \rightarrow ArH^{\bullet+}\ NO_2^{\bullet}$, then the nitro radicals will seek the single position of maximum unpaired electronic density. Conversely, if the substituent enters as the nitronium electrophile, it will look for the nearest polarizable electronic distribution with which to stabilize itself.

Claycop is inexpensive, readily prepared, and very easy to handle: product isolation only requires filtering the solid reagent and evaporating the solvent. Many reactions are thus carried out in a mild and efficient manner.

II. WHY A METALLIC NITRATE?

Nitrates of most metallic elements are known. They are normally available as hydrates and, therefore, ionic crystals. These salts are usually water soluble. The nitrate ion has a D_{3h} planar structure, with an NO bond length of *ca.* 1.22Å. As a ligand, it can be considered as a disk with a diameter of 4.62Å and a thickness of 2.2Å.[7]

With rather few exceptions (*e.g.*, the Menke nitrating procedure)[8] the chemistry of metal nitrates has long concerned itself almost exclusively with ionic nitrates in aqueous environments. The breakthrough came at the end of the 1950's, from Addison's group in Nottingham, England. They prepared covalent metallic nitrates under anhydrous conditions and showed that vibrational spectroscopy could differentiate readily between various modes of attachment of the nitrato group to the metal (Table IV).[9]

Many covalent nitrato complexes are thus known. Nitrato ligands interact with the metal according to three basic bonding schemes: unidentate, bidentate (symmetrical or unsymmetrical) and bridging (Fig. 1). The bidentate structure is that most often found yet, a metal in a given oxidation state may coordinate nitrato groups in more than one mode, depending on the physical state (Figs. 2[10] and 3[11]) and nature of other ligands.

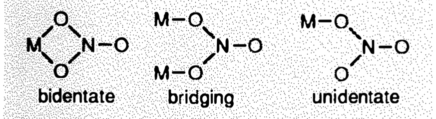


Fig. 1 - Covalent nitrato bonding scheme.

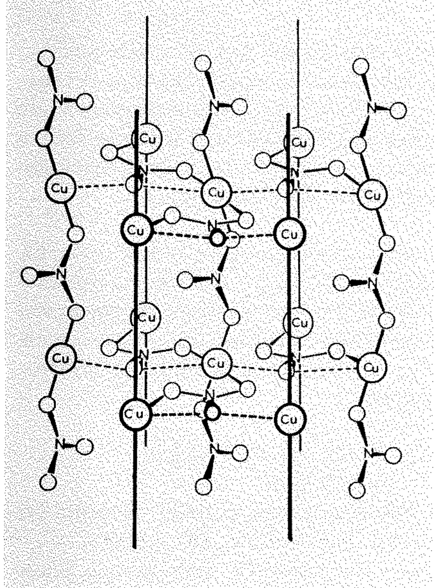


Fig. 2 - Crystal structure of anhydrous cupric nitrate (α-form).

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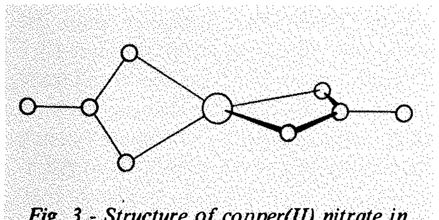

Fig. 3 - Structure of copper(II) nitrate in the vapor phase.

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Table IV

N-O Stretching Frequencies in Some Nitrates of Established Structure

Compound	N-O Stretching Frequencies (cm^{-1})			Mode of Bonding
$Sn(NO_3)_4$	1629	1250	973	symmetrically bidentate
$Ti(NO_3)_4$	1635	1225	993	symmetrically bidentate
$(Ph_4As)_2[Co(NO_3)_4]$	1525 1486	1335 1287	1042 1025	unsymmetrically bidentate
$K[Au(NO_3)_4]$	1570	1286	920	unidentate
HNO_3	1710	1320	886	unidentate
$Cu(NO_3)_2MeNO_2$	1519	1291	1008	bridging
$Cu(NO_3)_2$ (α form)	1510 1502 1478 1435	1300	1049 1015	bridging

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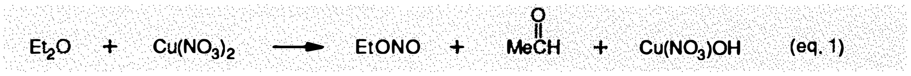
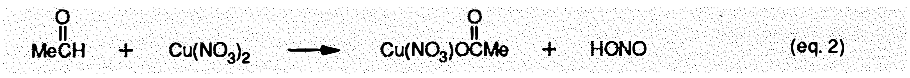
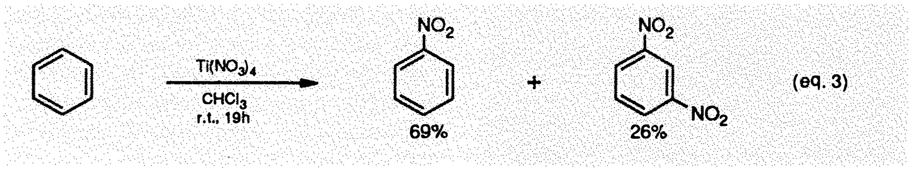


$$Et_2O + Cu(NO_3)_2 \longrightarrow EtONO + \overset{O}{\overset{\|}{MeCH}} + Cu(NO_3)OH \qquad \text{(eq. 1)}$$



$$\overset{O}{\overset{\|}{MeCH}} + Cu(NO_3)_2 \longrightarrow Cu(NO_3)O\overset{O}{\overset{\|}{C}}Me + HONO \qquad \text{(eq. 2)}$$



Some of these anhydrous metal nitrates possess exceptional oxidizing properties to the extent that they are potential rocket fuel components! They react, often violently, with organic material, oxidizing aliphatic residues (eqs. 1 and 2)[12] or nitrating aromatic rings (eq. 3).[13]

Addison gave these requirements for metallic nitrates to be strong oxidants: covalent bonding; bidentate coordination of the nitrato groups; availability of stable lower oxidation states of the metal.[14]

Despite their reactivity as powerful oxidants, metallic nitrates remained unexploited in organic synthesis. The standard organic laboratory is not equipped for preparation and handling of covalent metallic nitrates. Harnessing their untamed reactivity would be extremely hazardous.

We made the initial choice of ferric nitrate because iron is abundant, cheap, and of low toxicity. Complexes containing the tetranitratoferrate anion with covalent iron-nitrato coordination had been described in the literature.[15] In these complexes, the nitrato group is the symmetrical bidentate ligand required for high reactivity as an oxidant.[14] Furthermore, we could devise a preparation of anhydrous ferric nitrate suitable for routine use in an organic chemistry laboratory. Simple evaporation of an acetone solution of the commercial ferric nitrate provides a very reactive acetone solvate whose spectroscopic and chemical characteristics show it to be ferric nitrate with bidentate nitrato groups on iron. The instability of this solvate (by thermochemical calculations, it has one-third of the explosive power of TNT!) precluded its use without some stabilization. This was achieved in the same manner that Alfred Nobel stabilized nitroglycerine on kieselguhr to make dynamite — by deposition on a lamellar solid, the K 10 clay, an acidic montmorillonite-based industrial catalyst. Parallel methods were used for preparation of other clay-supported nitrates.

III. COPPER(II) NITRATE

In 1648, J.R. Glauber first described copper nitrate prepared by evaporation of a solution of copper in nitric acid. R. Boyle, in 1664, reported crystalline material obtained similarly.[16] At the present time, aqueous solutions of the salt are prepared by the action of nitric acid (40-44° Bé) on the metal, or by dissolving the oxide, hydroxide or carbonate in dilute nitric acid.[17] Various hydrates, with nine, six, three, or two-and-a-half water molecules, can be crystallized from these mother liquors.[18] The trihydrate and the hemipentahydrate are the most common and commercially available forms. Their industrial uses are multiple, for example, in manufacture of light-sensitive reproducing paper, in textile dyeing, as pigments for ceramics, as catalytic components in solid rocket fuels, in aluminum brightening and in electroplating baths. Basic cupric trihydroxynitrate, named gerhardite, is found in Jerome, Arizona, as a natural mineral.

The anhydrous salt was first prepared by Ditti in 1879. He dissolved the trihydrate in fuming nitric acid, from which he obtained the anhydrous solid salt by lowering the temperature. The modern procedure involves reacting the metal with dinitrogen tetroxide in ethyl acetate, yielding a compound $Cu(NO_3)_2{\bullet}2N_2O_4$. When heated at 85°C, it loses dinitrogen tetroxide and forms the solid anhydrous nitrate (α form).[19] These crystals consist of an assembly of parallel infinite chains, alternating copper and bridging nitrato groups (Fig. 2).[10] This salt sublimes easily and exists as monomeric units in which the metal coordinates with two bidentate nitrato units (Fig. 3).[11] Copper(II) coordinates covalently with nitrato ligands in a wide variety of modes; some representative structures are listed in Table V.[9]

Table V
Coordination of a Few Nitrato Compounds of Copper(II)

Symmetrically bidentate nitrato groups
$Cu(NO_3)_2$ (gas phase)
$Cu(NO_3)_2(Ph_3P)_2$
Unidentate nitrato groups
$Cu(NO_3)_2\ (C_5H_5NO)_2$
Bridging nitrato groups
α-$Cu(NO_3)_2$
$Cu(NO_3)_2 \bullet MeNO_2$

IV. WHY A MONTMORILLONITE FOR A SUPPORT?

Montmorillonites are phyllosilicates, *i.e.*, they are clay minerals (aluminosilicates) with a layered structure.[20,21] Each layer consists of a two-dimensional array of aluminum-oxygen octahedra sandwiched between silicon-oxygen tetrahedra. This arrangement of the 2:1 clay minerals is represented in Fig. 4.[20]

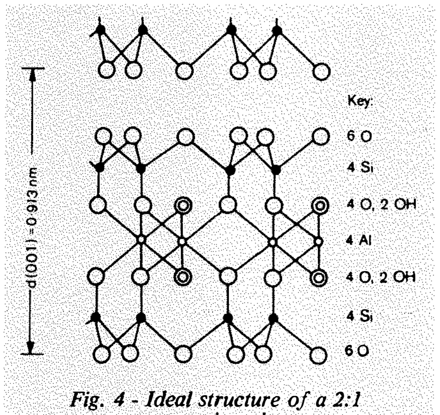


Fig. 4 - Ideal structure of a 2:1 type mineral.

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The actual structure of a montmorillonite differs somewhat from this ideal description. Some of the tetrahedral Si(IV) and octahedral Al(III) atoms are replaced isomorphously by lower-valency elements. This results in a net negative charge on the aluminosilicate sheet. The charge is counter-balanced by exchangeable cations. A montmorillonite crystallite is made up of stacks of such aluminosilicate layers with the counter-cations in the interlamellar space (Fig. 5).

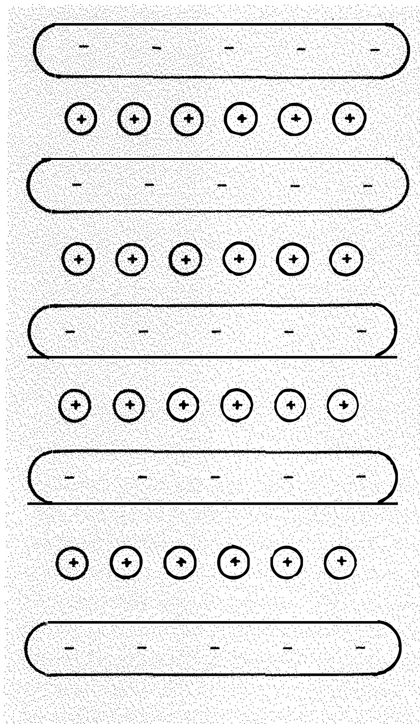


Fig. 5 - Stacking of aluminosilicate sheets of (- - -) montmorillonite, with interstitial hydrated cations (⊙).

Montmorillonite belongs to the class of smectites, *i.e.*, swelling clays. The interlayer spacing can be varied from a minimum of *ca.* 10Å to 50-100Å, which allows for intercalation of even large cations or neutral molecules. The nitrogen BET specific area of montmorillonites ranges between 500 and 750 m²/g.

Montmorillonite clays can be very acidic. The measured Brønsted surface acidity of natural montmorillonites ranges from +1.5 to -3 in Hammett's H_0 scale. Exchanging the interstitial metallic cations (Na^+, K^+, etc.) for H^+ brings these values down to -6 to -8, *i.e.*, between concentrated nitric acid ($H_0 = -5$) and concentrated sulfuric acid ($H_0 = -12$). This high protic acidity stems from congregation of exchangeable cations near the charged silicate sheet. These cations strongly polarize coordinated water molecules and enhance their dissociation. The acidity increases at low water content, and is further enhanced by the presence of hard, high-charge cations such as Al(III), Fe(III) or Cr(III). Clays are excellent Brønsted acidic catalysts for quite a number of applications.[22,23]

Potential Lewis acid centers also exist in smectite clays. Al(III) cations, while normally associated with the octahedral sheets, remain exposed at the crystal edges, where they coordinate water molecules. If these are removed, Lewis acid sites become available. Dehydration may also affect the exchangeable interlamellar cations, some of which may become coordinatively unsaturated. These clays, when further doped with Lewis acids, are effective catalysts for Friedel-Crafts alkylations or acylations. Only genuinely catalytic amounts are needed for applications such as the alkylation of aromatics by alcohols, in contrast with the stoichiometric amounts of Lewis acids that the standard procedure requires (in fact, in spite of this, we keep telling our students that "the Friedel-Crafts reaction is *catalyzed* by Lewis acids").[24]

Layered minerals have smooth surfaces. This reduces the dimensionality of the reaction space for adsorbates from three to nearly two. Accordingly, encounter rates of reactants are increased by several orders of magnitude.[25] Redox reactions also readily occur at clay surfaces. Aromatic molecules are oxidized to radical cations by smectites exchanged with Cu(II) or Fe(III).[26] One can effect water photocleavage on methyl viologen-exchanged montmorillonite.[27]

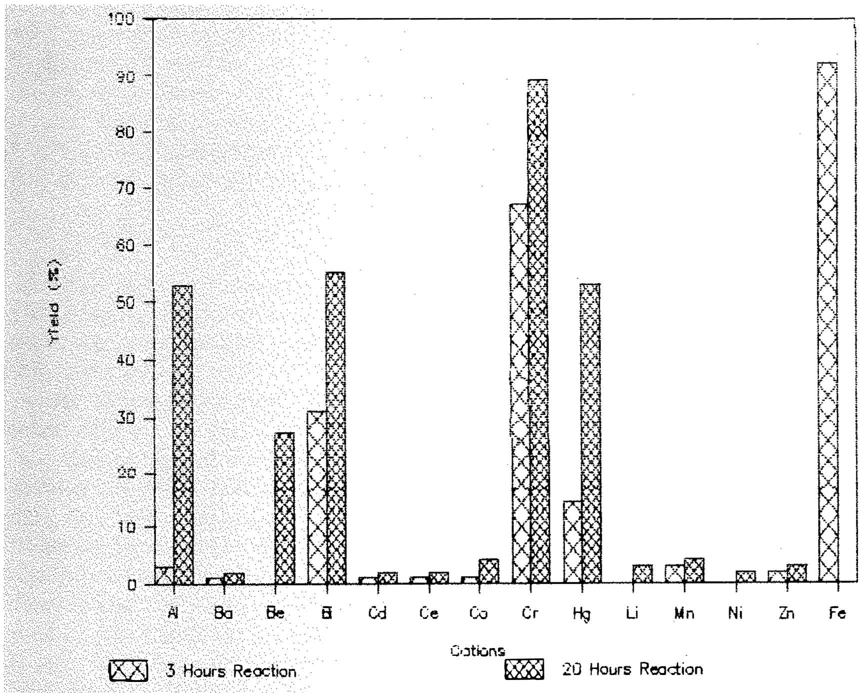


Fig. 6 - Nitration of p-tert-butylphenol by clay-supported metal nitrates.

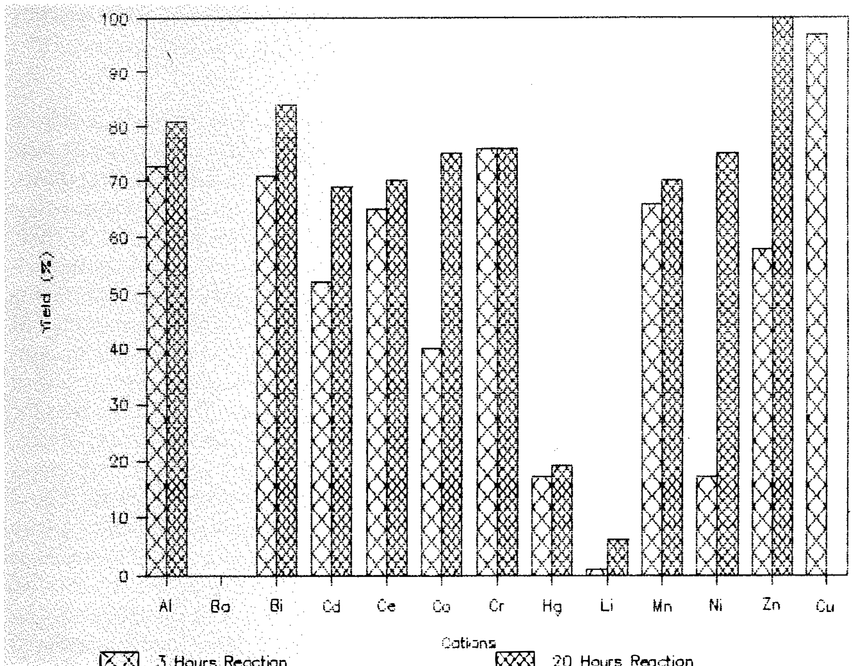


Fig. 7 - Nitration of toluene by clay-supported metal nitrates in the presence of small amounts of acetic anhydride (Menke conditions).

V. CLAY-SUPPORTED METALLIC NITRATES

Reagents supported by inorganic solids display modified reactivity and selectivity.[28] An added bonus is easy workup and isolation.[29] For instance, reactions with *claycop* are carried out simply by stirring the suspended reagent in a solution of the substrate. When the reaction is over, filtration is sufficient for removal of the reagents.

Clayfen was our first try. The fact that it was impossible to store it in closed containers for more than a few hours because of the evolution of nitrogen oxides was a nuisance. We looked at the reactivity of other supported metallic nitrates and found *claycop* to be promising. Results with two test reactions, nitration of *p-tert*-butylphenol in tetrahydrofuran, and nitration of toluene in the presence of acetic anhydride (Menke conditions) are shown in Figs. 6 and 7.[30]

Let us note that *claycop* is far from being totally anhydrous. *Claycop* 11/10 (see below) retains about 10% H_2O. Further dehydration may be necessary for certain applications.

VI. EXPERIMENTAL PROCEDURES

1. Preparation of *claycop*

In a 1-liter pear-shaped evaporating flask, copper(II) nitrate trihydrate (20g) is dissolved in acetone (375ml). K 10 clay (30g) is then dispersed in the solution with vigorous stirring. The solvent is evaporated under reduced pressure (rotary evaporator, water aspirator) on a water bath at 50°C. After 30min., the dry solid crust adhering to the flask is flaked off and roughly crushed with a spatula; drying is resumed under the same conditions for another 30min. This procedure yields 50g of clay-supported copper(II) nitrate (*claycop* 10/15, *i.e.,* loaded with 10g of nitrate for 15g of clay) as a dry blue powder. This powder is shelf-stable for months without any particular care.

Notes:

1. With *claycop* (this is not so for *clayfen*), the nitrate-to-clay ratio can be substantially increased. This may require modification of the drying conditions. For example, the making of *claycop* 11/10 (11g of copper nitrate trihydrate deposited on 10g of K 10 clay) requires use of a water bath at 70°C for solvent evaporation and drying.

2. The physical state of the crust at the stage of the flaking-off is crucial; if it is still muddy, it will aggregate in spherules remaining wet inside, and the reagent will display poor reactivity, if any.

3. A simple and inexpensive reactivity test[1] is the oxidative coupling of thiophenol to diphenyl disulfide (Scheme 1):[31] Thiophenol (2.2g, 20 mmol) is added to a stirred suspension of *claycop* (10g) in *n*-hexane (100ml). After a few seconds, an intense color develops, followed by evolution of reddish nitrous fumes and fading off of the color. The whole process, with normally active reagent, is over in less than five minutes. Formation of diphenyl disulfide is quantitative.

Scheme 1

$$\mathrm{RSH} + \mathrm{NO}^+ \longrightarrow \mathrm{RSNO} + \mathrm{H}^+$$

$$\mathrm{RSNO} \longrightarrow \mathrm{RS}\bullet + \mathrm{NO}$$

$$2\ \mathrm{RS}\bullet \longrightarrow \mathrm{RSSR}$$

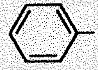
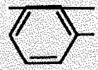
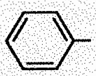
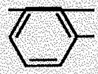
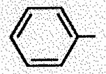
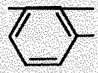
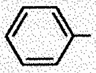
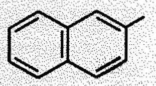
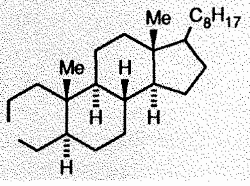
2. Oxidative coupling of thiols

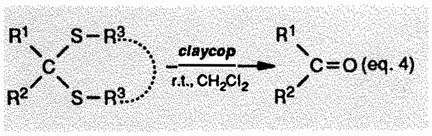
Claycop, like *clayfen*, is a convenient source of nitrosonium ion (NO$^+$), a soft, highly reactive Lewis acid species. This is the basis of the above-described reactivity test. By analogy to the well established mechanism observed with *clayfen*,[31] we postulate the intermediacy of a thionitrite, responsible for the intense color seen upon mixing of the reagents. This intermediate then decomposes homolytically into thiyl radicals which couple into disulfides (Scheme 1).

3. Carbonyl group regeneration from thioacetals

Success of the Corey and Seebach *umpolung* hinges upon the availability of a mild and efficient procedure for unmasking the carbonyl group protected as the thioacetal.[32] This is often a rather tricky step for which the use of soft cations, such as the NO$^+$, has been recommended.[33] NO$^+$ ions are conveniently generated from *claycop*. The reagent, innocuous toward carbonyl groups (even in benzaldehyde), is our best choice for removal of thioacetal protecting groups (eq. 4 and Table VI).[34] This is particularly true with cyclic thioacetals, such as the very popular dithianes or dithiolanes. The removed disulfur moiety polymerizes and is adsorbed on the spent support, which is then eliminated by simple filtration. Quantitative regeneration of the carbonyl group is thus achieved.[34]

Table VI
Dithioacetalization Using ***Claycop***

R^1	R^2	$R^3 \ldots R^3$	Time (h)	Yield (%)
	H	$-(CH_2)_3-$	5	100
		Et Et	4	99
		$-(CH_2)_2-$	6	100
		$-(CH_2)_3-$	5	97
	H	$-(CH_2)_2-$	6	99
n-C_9H_{19}	H	Et Et	3	88
n-C_9H_{19}	H	$-(CH_2)_3-$	4	91
n-C_9H_{19}	Me	$-(CH_2)_3-$	4	98
n-Bu	n-Bu	$-(CH_2)_3-$	6	98
		Et Et	5	61
		$-CH_2-$	4	97



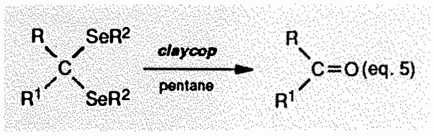
$$R^1R^2C(S{-}R^3)_2 \xrightarrow[\text{r.t., CH}_2\text{Cl}_2]{\textit{claycop}} R^1R^2C{=}O \quad \text{(eq. 4)}$$

General procedure:

Stirring of 0.01 mole of thioacetal for a few hours at room temperature with 12.1g of *claycop* (10/15 w/w nitrate to clay ratio) in dichloromethane rapidly results in an intense color development, followed by evolution of nitrogen oxides. The clay is then filtered off and washed twice with 50-ml portions of solvent. The resulting pale-yellow or slightly green solution is filtered through a small bed of neutral alumina. Solvent evaporation affords the pure carbonyl compound in the case of cyclic thioacetals (dithiane and dithiolane derivatives). In the case of monofunctional thiol derivatives, a further purification step is required to get rid of the by-products originating from the oxidation of the thiol moiety.

4. Carbonyl group deprotection from selenoacetals

Selenoacetals have also shown their worth for protection or for *umpolung* of carbonyls.[35] Bis(methylseleno)- and bis(phenylseleno)acetals are mildly cleaved into aldehydes or ketones by *claycop*, in *n*-pentane solution, at room temperature (eq. 5 and Table VII).[36]



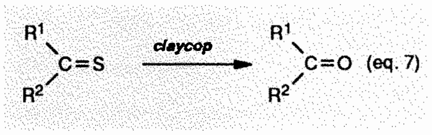
$$R^1RC(SeR^2)_2 \xrightarrow[\text{pentane}]{\textit{claycop}} R^1RC{=}O \quad \text{(eq. 5)}$$

5. Aromatization of 1,4-dihydropyridines

Claycop, here also through the release of nitrosonium ions, promotes the aromatization of 1,4-dihydropyridines (eq. 6). The procedure has been applied to the synthesis of pharmacologically active derivatives[37] (Table VIII).

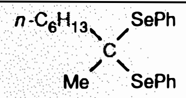
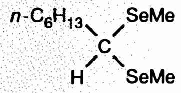
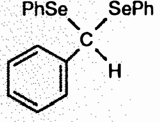
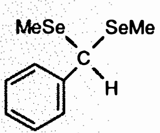
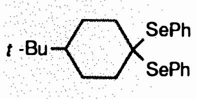
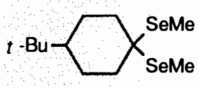
6. Thiocarbonyl-to-carbonyl transformation

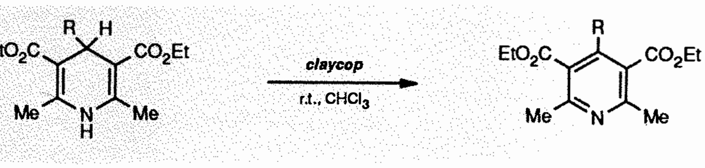
Nitrosonium ions convert thiocarbonyl groups into their oxo analogs (eq. 7). In this



$$R^1R^2C{=}S \xrightarrow{\textit{claycop}} R^1R^2C{=}O \quad \text{(eq. 7)}$$

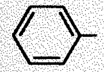
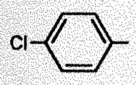
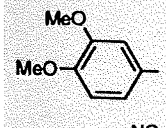
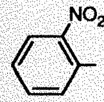
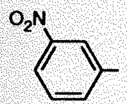
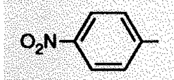
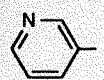
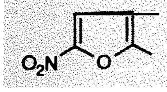
Table VII
Cleavage of Selenoacetals by ***Claycop***

Selenoacetals	Reaction time (min)	Isolated yield (%)
	(very slow)	–
	90	65
	10	78
	10	62
	30	86
	120	60



(eq. 6)

Table VIII
Aromatization of Dihydropyridines by *Claycop*

R	Time (h)	Yield (%)
H	11.0	40
	1.5	92
	1.5	86
	1.5	89
	1.5	93
	6.0	93
	7.0	78
	12.5	92
	8.0	80

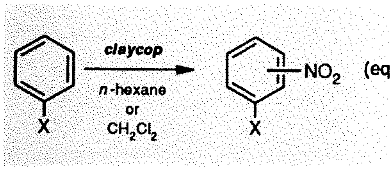
application, where *clayfen* gives excellent results with aromatic substrates, *claycop* is not as reactive and is limited in use to aliphatics (Table IX).[38]

Table IX
Ketones from Their Thioketone Analogs with *Claycop*

Ketone	Yield (%)
fenchone	17
dicyclopropyl ketone	39
camphor	30
2-adamantanone	68

7. Nitration by *claycop* under Menke conditions

To close, let us present an entirely different facet of *claycop* reactivity. In the presence of acetic anhydride, *claycop* is a powerful nitrating agent, active even toward deactivated halobenzenes (eq. 8). The regioselectivities become remarkable (Table X).[39]



(eq. 8)

Table X
Para / Ortho Ratios in the Nitration of Halobenzenes

Methods	PhF	PhCl	PhBr	PhI
claycop	25.0	7.5	5.0	2.3
HNO_3 / H_2SO_4	6.6	1.8	1.3	1.2
$AgNO_3$ / BF_3	2.7	1.3	3.0	4.7
NO_2BF_4 / sulfolane	10.8	3.5	2.8	1.8
Ac_2ONO_2 / $MeNO_2$	–	2.3	1.7	1.6
HNO_3 / Ac_2O	–	9.0	3.0	–
HNO_3/ Nafion-H	–	1.6	1.2	–

This *para* preference (desirable for some industrial applications) can be further improved: lowering the temperature (working at 0°C instead of 25°C) increases the para/ortho ratio from 25 to 35 for fluorobenzene.

General procedure:

Acetic anhydride (100 mmol) and 5g *claycop* (26/30 nitrate/clay) are added to a solution of the halobenzene (10 mmol) in *n*-hexane (50 ml) (or dichloromethane in the case of iodobenzene). The mixture is stirred at room temperature for the required reaction time (Table XI), filtered under reduced pressure, and the spent reagent is thoroughly washed with fresh solvent. After concentration (rotary evaporator), the nitro derivatives are separated by column chromatography [silica gel, cyclohexane/ethyl acetate (9/1 v/v)].

Warning

The procedures described in this paper were safe in the hands of the authors. However, nitrates are potentially dangerous compounds, and appropriate precautions must be taken in each step. Moreover, scaling-up should be attempted only after appropriate safety tests.

VII. CONCLUDING REMARKS

Forgoing old inhibitions, the chemical community is now becoming aware of the usefulness of heterogeneous reaction conditions. Biochemistry has been leading the way, making imaginative use of solid supports, for example, Merrifield's automated peptide synthesis. Ample new chemical knowledge is to be gleaned from the study of reactions run on solid surfaces. We hope that the examples of their planned use provided in this paper will stimulate research work in this area.

Acknowledgements

This research was generously supported by Programmation de la Politique Scientifique, Brussels ("Action Concertée 82/87-34"). Support by Fonds National de la Recherche Scientifique, Brussels, in the purchase of major HPLC and NMR instrumentation, is gratefully acknowledged. We thank all of our co-workers listed in the references for their innovative spirit and enthusiastic hard work.

Table XI
Yields and Reaction Conditions for Nitration of Halobenzenes by Clay-Supported Cupric Nitrate

Substrate	Solvent	Reaction time	Isolated yields in nitro products (%)
fluorobenzene	*n*-hexane	48h	53
chlorobenzene	*n*-hexane	48h	73
bromobenzene	*n*-hexane	30h	74
iodobenzene	dichloromethane	7 days	38

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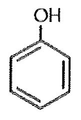
About the Authors

Professor Pierre Laszlo was born in Algiers in 1938. He graduated from the Sorbonne in 1960 and began his doctorate work with E. Lederer on the structural elucidation of diterpenes. He obtained his D. Sc. in 1965, also from the Sorbonne. In the meanwhile, he was a research associate with Professor Paul von Ragué Schleyer at Princeton University in 1962-1963, where he worked on the NMR of bicyclic systems. He was an instructor at the University of Paris-Orsay from 1963 to 1966. He returned to Princeton University as an assistant professor (1966-1970). He was called to the University of Liège, Belgium, as a full professor in 1970. He remained there until 1986, when he was appointed at the Ecole Polytechnique, near Paris. He retains an appointment in Liège, as an *extraordinarius.*

Professor Laszlo has held numerous visiting professorships: at the Universities of Lausanne, Colorado, Hamburg, Crakow, Kansas, Johns Hopkins, Connecticut, Cornell, Chicago, and at the Institute of Molecular Science in Okazaki, Japan. He has received the "Prix Triennal" of the Belgian Chemical Society (1977-1980), the Prize of the French Academy of Sciences in Homage to the French Scholars Murdered by the Germans in 1940-1945 (1981), and the Randolph T. Major medal of the University of Connecticut (1985). He is European editor of the *Journal of Physical Organic Chemistry,* and also edits the "Chemical Past Times" section of the *Nouveau Journal de Chimie.* Professor Laszlo has authored several books; the latest, related to this article, is *Preparative Chemistry Using Supported Reagents,* Academic Press, San Diego, 1987. He is also the author of over 200 publications.

Dr. André Cornélis was born in Belgium in 1945. He received the B.Sc. in 1967, and his doctorate in chemistry in 1974, both from the University of Liège, where he is presently an instructor. He has been a coworker of Dr. Pierre Laszlo since 1970. Together they started the clay-supported reagents project in 1980.



Filtering-Column Chromatography –
a fast, convenient chromatographic method

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The most commonly used chromatographic method in preparative organic synthesis is flash-column chromatography.[1] Indeed, this method provides chemists with a powerful tool in the rapid purification of crude products. However, based on our experience, flash-column chromatography still suffers some minor drawbacks such as: 1) operation under pressure; 2) use of a considerable amount of solvent; 3) an apparatus (including the solvent reservoir) which is too high to manipulate with ease inside the hood; and 4) the need for various sizes of columns to accommodate milligram- to multigram-scale separations. We report here a fast and convenient chromatographic method, *i.e.* filtering-column chromatography, as an alternative to flash-column chromatography. In the past several years, we have successfully purified a variety of compounds in amounts ranging from 30mg to 10g by using filtering-column chromatography. This method uses a smaller volume of solvent, does not operate under pressure, is more convenient to use in the hood, and yet it can provide resolving power similar to that obtained by flash-column chromatography.

Figure 1 is a picture of the apparatus which was used for filtering-column chromatography. Only two column sizes are used, depending on the amount of sample to be loaded, and their specifications are listed in Table 1. Figures 2 and 3 are examples of the tlc analysis of column effluents which demonstrate the usefulness of the method.

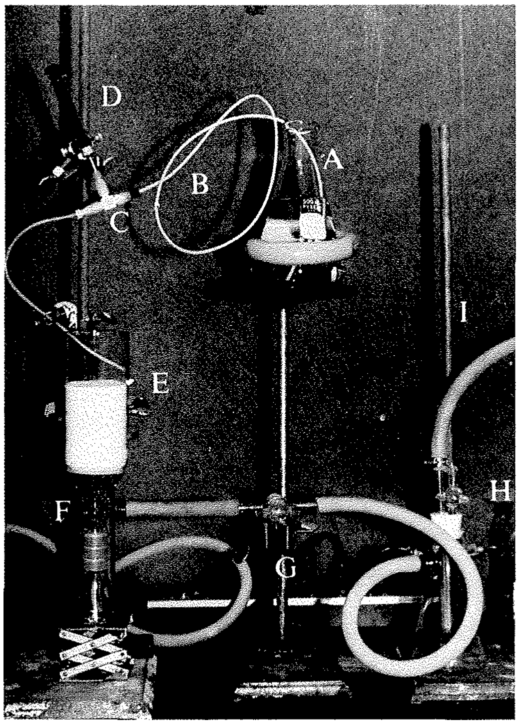

Fig 1. Apparatus for filtering column chromatography

A - Solvent reservoir (250- or 500-ml Erlenmeyer flask). **B** - Teflon® tube (3mm o.d. x 1.5mm i.d.). **C** - Three-way purge valve. **D** - Syringe. **E** - Medium pore-size fritted disc filtering column with ground-glass joint outlet. **F** - Erlenmeyer flask with inlet ground-glass joint. **G** - Three-way stopcock. **H** - Two-way stopcock and trap. **I** - To aspirator.

Table 1 - Column Specifications

Column	i.d. (mm)	Height (from disc to top) (in.)	Amount of silica gel (g)	Ground-glass joint	Sample-loading capacity (g)
I	44	4½	40-50	14/20	0.03-1.20
II	66	5¾	100-160	24/40	0.80-10.0

General Procedure

To a firmly clamped filtering-column which contains a proper amount of dry silica gel (60Å, 230-400 mesh) is added an adequate amount of eluant (usually 1-2 inches higher than the top of the silica gel bed). Full suction[2] is applied and the addition of eluant is continued until the whole silica gel bed is wet. With the suction off and eluant 1-2 inches higher than the top of silica gel bed, a spatula with a smooth and flat end is used to stir the bed until a homogeneous slurry is formed.[3] Air bubbles are removed by tapping the outside wall of the column with finger tips and the excess amount of solvent is removed by applying full suction. If there are any air bubbles still remaining in the bed, the filtered eluant can be poured back into the column and the above procedure repeated. Usually all the air bubbles can be removed after the second cycle of stirring, tapping, and washing of the column.

The silica gel is then packed as tightly as possible by tapping the wall of the column and draining (by gravity or by partial suction) the excess eluant several times (usually 5-7 times) until there is no more excess eluant to be drained (*i.e.,* no eluant above the top of the bed surface). This tap-packing process will leave some silica gel stuck to the wall of the column above the bed surface. This silica gel is washed down gently with eluant. It is critical at this point that a flat and horizontal surface is still maintained. The silica gel should be kept wet during the whole process.[4]

The sample in a minimum amount of solvent, generally 1-2ml for column I and 2-4ml for column II, is introduced directly on the top of the silica gel bed[5] evenly and smoothly by a pasteur pipet. Small amounts of eluant are introduced by a pasteur pipet along the wall very gently to bring the sample down underneath the bed surface (usually 3 x 1ml for column I and 3 x 2ml for column II). More eluant is introduced by pipet to about ¼ inch high and then by the already purged Teflon® tube **B** from the solvent reservoir **A**. The silica gel bed should not be disturbed under any circumstance. Aluminum foil can be used here to cover the top of the column if the eluant is very volatile. Eluant introduction rate can be controlled simply by the adjustment of the three-way purge valve **C** while the solvent reservoir **A** is kept in a proper fixed position. Fractions of the filtering-column chromatography are collected by using the Erlenmeyer flasks **F**[6] and the flow rates are adjusted to 5-12 ml/min for column I and 10-24 ml/min for column II by proper adjustment of the two-way stopcock **H**. The three-way stopcock **G** is used when switching of flasks between fractions is needed. The temporary interruption of the flow rate due to flask switching does not affect the resolution of the chromatography. Generally speaking, for a sample of $R_f = 0.5$, the whole chromatographic process can be done within 1 hour. After finishing the separation, full suction is applied for about 10min to remove eluant and to dry the silica gel bed. The dried silica gel is easily poured out and the empty column is rinsed clean with methanol and chloroform.

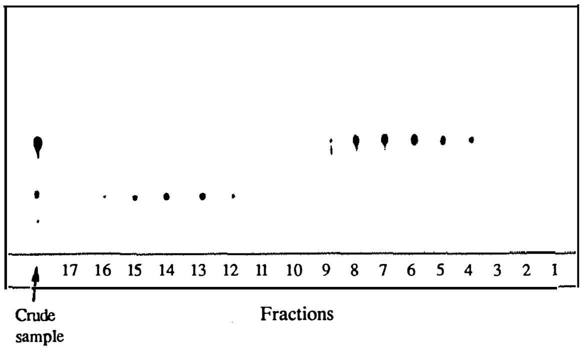

Fig 2. A typical separation performed on column I.
Sample loading: 243mg. Eluant: 500ml $CHCl_3$/acetone (9/1). Flow rate: ~9 ml/min. Silica gel: 44g (60Å, ~230-400 mesh).

Reference and Notes:

1) Still, W.C.; Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923, and references cited therein.
2) The term 'full suction' means operation with water aspirator on and the two-way stopcock **H** closed. The term 'partial suction' means operation with water aspirator on and the two-way stopcock **H** opened or partially opened.
3) Caution should be taken here to avoid possible damage of the fritted disc by using any sharp-end spatula.
4) Without adding eluant, the wet silica gel bed can last for more than three minutes. This allows the next sample introduction to be performed without any difficulties.
5) Introduction of the sample along the column wall is not recommended here because that will increase the sample band width and therefore reduce the resolution which the column could provide.

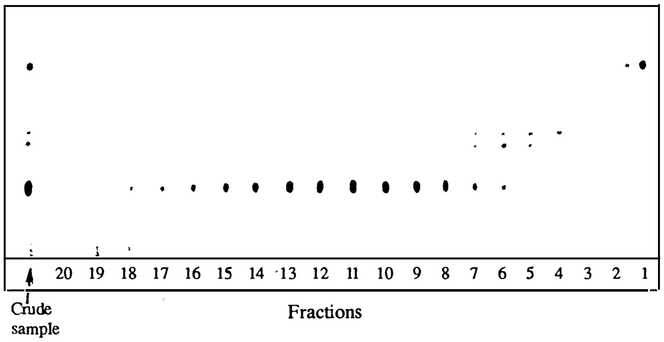

Fig 3. A typical separation performed on column II.
Sample loading: 9.43g. Eluant: 2L of CH_2Cl_2/EtOAc/Et_3N (60/40/1). Flow rate: ~18 ml/min. Silica gel: 158g (60Å, ~230-400 mesh).

6) The quantities and sizes of flasks needed are five 50-ml and fifteen 25-ml flasks for Column I, and one 250-ml, two 125-ml and twenty 50-ml flasks for column II.

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Aldrich offers the silica gel for use in this procedure.

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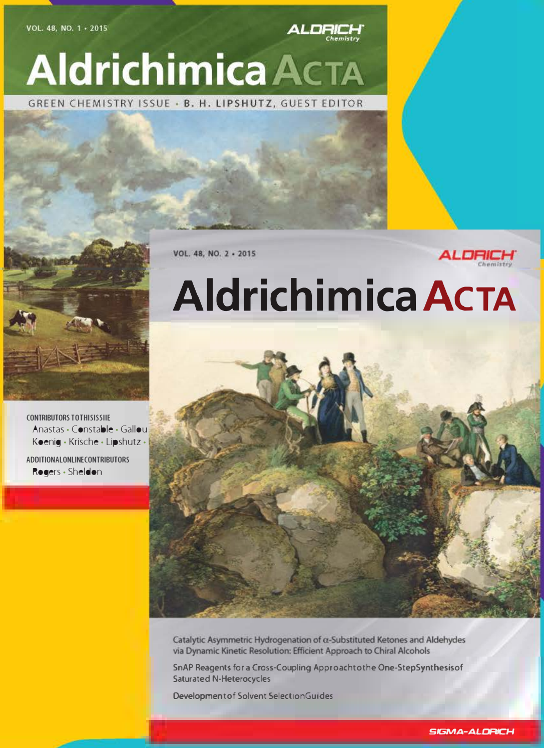

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