Aldrichimica Acta

Volume 10, Number 1, 1977

Dedicated to Professor Robert Burns Woodward on his sixtieth birthday.

Aldrichimica Acta

Volume 10, Number 1, 1977
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We at Aldrich are happy to dedicate this issue of the Aldrichimica Acta to Professor Robert Burns Woodward on the occasion of his sixtieth birthday.

Professor Woodward is one of the greatest living chemists. His name conjures visions of synthetic jewels and symmetry rules, of noble prose and Nobel Prize. Before his time, the world's greatest chemists were German, English and Swiss. Through his accomplishments, example and teaching, we now have great schools of chemistry in America.

May we say what the Bible says of the greatest lawgiver: Let his eyes not be dim nor his natural strength abated — from 60 to 120.

About Our Cover:

Our chemist-collector, who has known and admired Professor Woodward since 1947, had the pleasant problem of choosing that painting in his collection most fitting for the cover of the Acta dedicated to Professor Woodward. We were not surprised that he picked this *trompe l'oeil,* once in the collection of the King of Saxony and painted by a late seventeenth century Bolognese artist, for the analogy is clear. The painting depicts the marriage of King Alexander the Great and Princess Roxana, and thus the meeting of the greatest cultures — Greek and Persian — of their time. So we find in Professor Woodward the junction of the greatest sciences of our time — chemistry and the life sciences.

Are you interested in our Acta covers? *Selections from the Bader Collection,* with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

Few reactions in organic synthesis are as useful as the Wittig condensation. Often, however, high-purity intermediate alkyl triphenylphosphonium halides are essential for high and reproducible yields. We have developed a very general method for recrystallizing these compounds. In all cases we have experienced, the yield of the subsequent Wittig reaction has been improved by this purification.

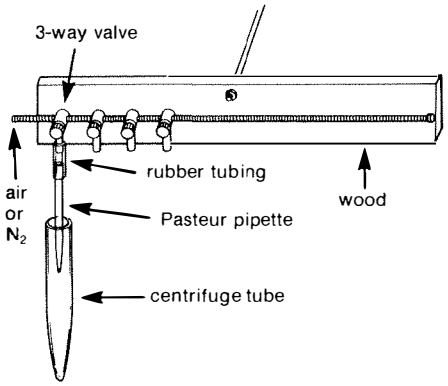
The impure phosphonium salt is dissolved in the minimum of methylene chloride (*n* ml). This solution is diluted with methylene chloride (*n* ml), then tetrahydrofuran (*n* ml). The resulting mixture is then concentrated to a volume of *n* to 2*n* ml, then cooled. The resulting crystalline material is pure phosphonium salt. Weight recovery is excellent.

This method has been applied to the purification of a wide range of both mono- and bis-phosphonium salts, and is suitable, with appropriate precautions, to the preparation of analytical samples.

Nicholas Darby, Ph.D.
Edmonton, Alberta
Canada T6C 4A9

We find the following evaporator effective and inexpensive for reducing solvent volume of sample extracts, such as urine and drug extracts, for thin layer chromatography and gas liquid chromatography.

The unit consists of one or more 3-way fish-aquarium valves connected in series and mounted on a "T" fashioned from a strip of wood and a length of threaded rod,



which can then be mounted on a ringstand. A disposable Pasteur pipette is attached to the appropriate prong of the valve to direct the flow of air or nitrogen for evaporation of solvent in a 15-ml conical bottom centrifuge tube. The rack of tubes can be placed in a water bath to promote evaporation.

Glenn Murphy, Chief Chemist
Toxicology Laboratory
Bureau for Health Services
Frankfort, Kentucky 40601

A very nice and inexpensive introduction chamber for a glove bag can be made from an empty coffee can and two pieces of copper tubing. This chamber obviates the need for evacuating and refilling the bag each time a sample is to be introduced into or removed from the bag.

The apparatus consists of a coffee can with both the metal ends cut off and replaced with the plastic caps which are provided for resealing the opened cans. Two holes are then drilled in the seam along the side of the can where it is soldered together. The two copper tubes are then soldered into these holes. To these tubes are attached a vacuum line and an inert gas line. The completed chamber can then be inserted into the opening of the glove bag, which is sealed to it by means of rubber bands.

There are two methods for flushing air from the antechamber: gas can be bled in and out simultaneously, or the can can be repeatedly pumped down and refilled. Most cans (and especially the smaller ones with low cap area) will take a respectable vacuum, and this can be improved by cementing hard plastic discs onto the outside of the plastic caps, which will help keep them from bowing inward too much.

Edward C. Greer
11 Old West, U.N.C.
Chapel Hill, N.C. 27514

When separating an organic phase from an aqueous phase, it is often difficult to distinguish one from the other on cursory examination. It often becomes necessary to consult tables of specific gravity or to carry out some other simple, but time-consuming investigation which interrupts the flow of the experiment.

I find that the following quick test produces the correct answer in most cases. A drop of each phase is placed on the edge of a piece of filter paper. Upon attempting to tear the filter paper, you will find that the aqueous spot tears without effort and the organic spot resists tearing.

Paul R. Horinka
Research Chemist
American Color and Chemical Corp.
Reading, Pa. 19603

In solution preparation in test tubes or flasks, one is faced occasionally with the problem of entrapped air, microbubbles or foam making it difficult to ascertain whether dissolution is complete. Since most labs now have ultrasonic cleaning baths, immersion of the tube or flask in the bath for one second, causes an instantaneous clearing of the solution for complete visibility.

A.C. Megalos
Senior Scientist
Technicon Instruments Corporation
Tarrytown, New York 10591

A large test tube mounted vertically with its mouth up and slightly below the surface of a stirred water bath will do an amazing job of collecting the dirt and debris that otherwise soon make such a bath murky.

R. Keith Osterheld
Professor
University of Montana
Missoula, Montana 59801

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 red and white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us!"

by Ofra Bader.

By a happy coincidence, the very first telephone call I received after our advertisement "Please Bother Us" appeared in *C & E News*, was from Professor R.B. Woodward at Harvard, who was looking for an out-of-the-way quinone, 2,5-dihydroxybenzoquinone. We have over three hundred quinones in our Library of Rare Chemicals; this one was among them, so we mailed 5g to Professor Woodward that day. Also, we decided to list it in our catalog-handbook, and now have several kilos in stock for immediate shipment.

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

Robert Burns Woodward: Three Score Years and Then?

David Dolphin
Department of Chemistry
University of British Columbia
Vancouver, British Columbia
Canada V6T 1W5

Synthetic organic chemistry began 150 years ago when, in 1828, Wöhler[1] prepared urea from ammonium cyanate. "The unexpected result," reported Wöhler, "is also a remarkable fact inasmuch as it presents an example of the artificial production of an organic, and so-called animal, substance from an inorganic substance." Liebig, who at this time was working in similar areas, initially doubted Wöhler's work but was soon convinced, however, of its correctness, and the two young chemists became close and lifelong friends. Only a decade after Wöhler's original discovery, he and Liebig, writing jointly on uric acid, asserted that, "The philosophy of chemistry will draw the conclusion that the synthesis of all organic compounds, as long as they are not a part of an organism, must be seen as not merely probable but certain."[2] No one has more completely fulfilled this prophecy than R.B. Woodward, who in 1965 was awarded the Nobel Prize for art in organic synthesis. Some of his most notable achievements are the synthesis of vitamin B_{12}, the most complex non-polymeric naturally occurring substance, as well as a series of other synthetic triumphs which have each in their turn established standards of elegance and creativity for which most other organic chemists can only hope to strive.

How does one tell the chemical community anything about Woodward which either they do not already know, or which they cannot readily learn by consulting any of the numerous collections of biographical data? I could list here the more than 30 honorary degrees which have been bestowed on him, and which are recorded in a closet in Cambridge as an array of multi-

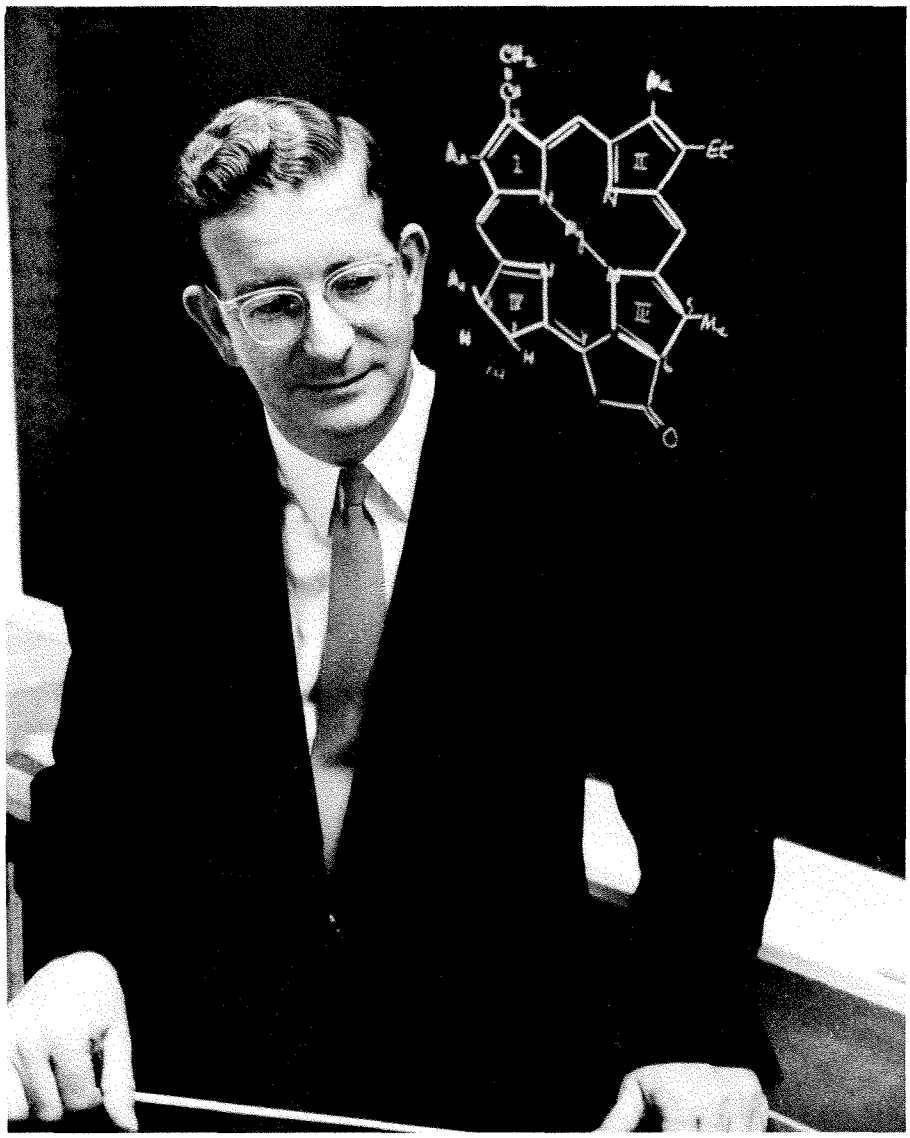


Fig. 1. Plan in detail, then carry it out (printed with permission of the American Chemical Society, from Chemical and Engineering News, Nov. 1965, p. 38).

hued academic robes (with the exception of one from a Scottish University, which shall remain unnamed, which insisted that if Woodward wanted the gown, he would have to buy it!). And I could follow this by a list of awards which would include the Theodore William Richards Medal, the Roger Adams Award, the Willard Gibbs Medal, the Pius XI Gold Medal, the National Medal of Science, the Nobel Prize in Chemistry, the Lavoisier Medal, the Decorated Order of the Rising Sun (Japan), and on into a list which would require more space for its completion than the *Aldrichimica Acta* has available. Rather than pursue this typical approach, I have decided to take a light-hearted look at the man as well as his chemistry.[3]

Neither teacher nor student of chemistry can have failed to have come across many of the contributions that R.B. Woodward has made to science in the past four decades. This was certainly true for me as an undergraduate, as well as a graduate of chemistry at the University of Nottingham where I worked with Alan Johnson in the early 60's. When it became clear that I would probably obtain my Ph.D., I asked my mentor what he would suggest I do after I was through at Nottingham, and he advised me that it might be good for my soul to go somewhere where I would be expected to work a little harder than I had been used to, and that I might think about trying to work with Woodward at Harvard. After some considerable agonizing I came to the conclusion that surely all of the rumors I had heard about this man, his work habits and those of his collaborators, could not possibly be true, and that I should indeed see if Woodward would give me a postdoctoral appointment in his laboratories. Having prepared a carefully worded letter I took it along to Alan Johnson to see if it met with his approval, and I was told I would be wasting my time if I sent it since Woodward never replied to letters. I have since learned that this was a slight exaggeration; nonetheless, the letter was never sent. Instead, however, when a few days later I was present at a half-day symposium on Vitamin B_{12} in London at the Royal Society, during one of the traditional tea breaks I was approached by an individual whom I knew, by the tell-tale cigarette and blue tie, could be none other than Woodward. Within ten seconds he ascertained that I did indeed wish to work with him, and suggested that I should write to his secretary and say that I would be arriving the following September.

Having made plans to cross the Atlantic in search of fame and fortune, I thought it advisable to familiarize myself in a general way with some of Woodward's work, and

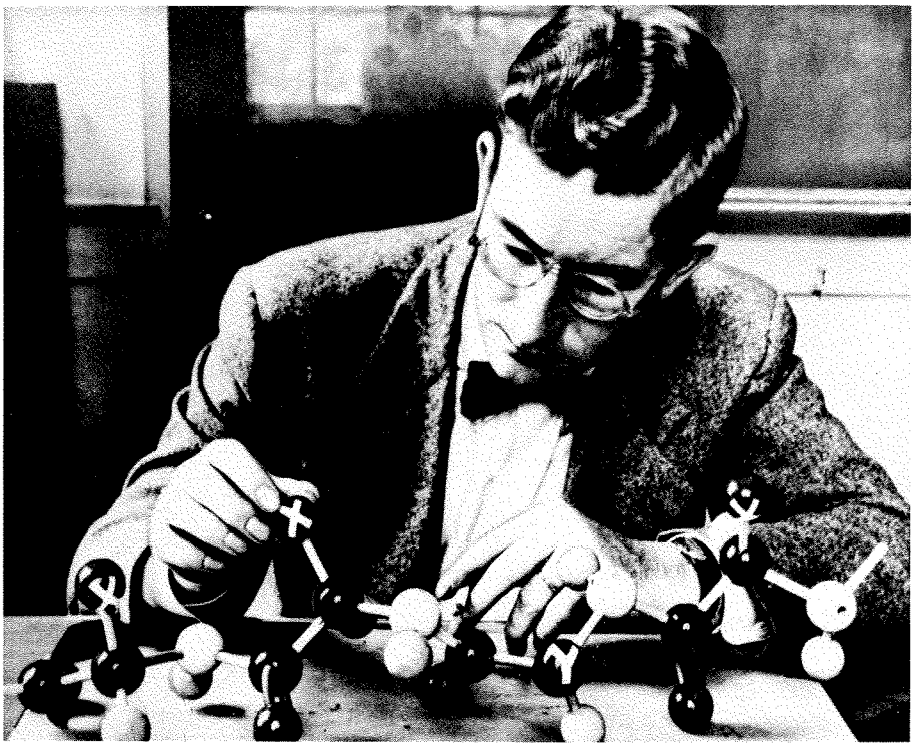


Fig. 2. RBW working with fibrous proteins (from the Boston Herald, Wednesday, June 18, 1947).

am sure that you will be as interested as I was to note that his first two papers were:

> Precipitation of barium in the coppertin group of qualitative analysis, W.J. Hall and R.B. Woodward, *Ind. Eng. Chem., Anal. Ed.,* **6,** 478 (1934).
>
> The staling of coffee II, S.C. Prescott, R.L. Emerson, R.B. Woodward, and R. Heggie, *Food Research,* **2,** 165 (1937).

But a glimpse of the greatness to come was evident in his third contribution to science:

> A pressure regulator for vacuum distillation, R.L. Emerson and R.B. Woodward, *Ind. Eng. Chem., Anal. Ed.,* **9,** 347 (1937).

Arriving in Boston in the fall of 1965, I was met by his secretary, Dodie Dyer, and told if I would like to wait in the library Dr. Woodward would soon see me. And indeed, two weeks later, I was shown into his office, where we discussed what I might do during my stay at Harvard and agreed that I would participate in the synthesis of B_{12}. Having established my scientific program for the period of my stay I turned my attention to more important matters such as the length of any holidays that I could expect. After a brief pause Woodward shrugged his shoulders and said, "Well, I take Christmas Day off."

During this first discussion I had been seated at the side of his desk. Convinced, as I am now, that Bob Woodward does nothing which he has not carefully thought out I have realized since that the small quotation I saw then in front of him was as much for the benefit of his colleagues as for him, and after slowly moving my position so that I was able to read it, at the conclusion of the interview I saw the words that were to encourage me in my work for the next year: "Let sleeping dogs lie."

That year I spent in Woodward's laboratories was an especially exciting one and was highlighted early one morning when, as I walked into the laboratories, I heard the clinking of champagne glasses, and realized that although I had missed the news, the inevitable had obviously happened. The speed at which the champagne appeared in Bob's office surprised me, but I soon found out that, in fact, the champagne had been laid down by the department some time earlier in anticipation of the Nobel Prize. As the party progressed it was generally felt that signed champagne bottles would make a suitable memento of the occasion; however, it transpired that there were more drinkers than bottles. Woodward soon remedied this problem by holding sufficient parties until enough bottles had been accumulated. A few days later the Swedish television company came into Bob's laboratories and said how disappointed they were that they had missed the party, since they felt that scenes of a less formal nature might be suitable for a program they were preparing on that year's Nobel Laureate. Not wishing to disappoint his visitors from Sweden, Bob threw another round of parties which were received by his group with no less enthusiasm

than the initial ones.

Since he obtained the highest accolade in his field it might be of interest to see how Woodward's career had developed up to the time of the Nobel Prize. Born on April 10, 1917 in Boston, Woodward spent his childhood in a suburb of that city, Quincy. To give you a brief glimpse of his childhood I quote from an article in the Boston Daily Globe of June 8, 1937. "As a boy in short pants in Quincy Grammar School, he consistently brought home report cards dimmed with a pair of D's for conduct and effort. The Woodward youngster, who was always playing in the cellar with a chemistry set, received three double promotions hurdling the fourth, seventh and tenth grades, all the while whispering in classes, chewing bubble gum, being the last one in after recess and pulling little girls' long curls." I can assure you, after ten years of close association with Bob Woodward, that things have certainly changed since his earlier days — I don't think I have seen him blowing bubble gum in a long while.

In addition, it would appear that the passing years have also instilled a little caution. Recently, at an MIT fraternity house Pat[4] introduced RBW to a striking young redhead who was interested in meeting him. Amid the din and accompanying revelry the two remained locked in an animated conversation. After some time RB, looking a little disillusioned, came over and said: "I find this young lady quite interesting. However, she has just made a strategic mistake." "What could she have done?" Pat queried. "Well," said RB, "she just told me that she had been engaged to a professional wrestler. And, Pat, that is a very hard act to follow."

Robert B. Woodward and William E. Doering, first to synthesize quinine

Fig. 3. Printed with permission of the American Chemical Society, from Chemical and Engineering News, 1944, p. 730.

Returning to the report from the Boston Globe we find that "in 1933, a sixteen year-old lad from Quincy with a very distinguished scholastic record appeared at MIT where professors, being only human, formed a quick but wrong impression of him. The savants at this institute solemnly soliloquized, 'Woodward as a freshman had much to learn. He was in no position to think the world his oyster in or out of season, so happy-go-lucky, not at all the grim and studious type.' " One professsor had remarked, "Well, the Institute, young man, is a different place than a public school." It would appear then, as now, that MIT professors can be mistaken, for in four years Woodward had obtained his Ph.D. from MIT — not, however, without some difficulties. His transcript which shows a 4.9 out of a possible 5 was highlighted by a double F in gym.

Clearly Woodward's career at MIT was atypical in that he obtained both his Bachelor's and Doctorate degrees by the age of 20. Again quoting from the Boston Globe, "The achievement was the more remarkable in that Woodward obtained his goal after only four years of study against the seven usually required; when during this period much of his time had been devoted to outside work to finance his collegiate career."

"I never heard of it being done by any young man before, either at Tech or anywhere in the world," was the commendation of James Flack Norris, Professor of Organic Chemistry and Director of the Tech Research Laboratory in the field in which young Woodward took his degree.

While taking the regular freshman courses, during the first semester at the Institute, Woodward applied for a seat in the laboratory. The Organic Department told him that only graduate students, men who possess degrees, are allowed that privilege; but his appeal interested the Department and he was told that if he could supply a list of the experiments he was planning, he might be given some consideration. A few days later he produced a list of experiments that showed such outstanding originality and scope that he was granted a seat.

Toward the end of the second semester of his freshman year Woodward walked into the examination room where third-year students were being tested in organic chemistry. He inserted a note in his examination book, asking the professor to correct it, and if possible, to give him credit.

At the beginning of his second year he was given his own laboratory in which to experiment. In that year he happened to attend an organic chemistry lecture in which the professor told about the difficulty of synthesizing the female sex hormone from carbon. At the end of the lecture Woodward came to the professsor and showed him a way which might lead to such a synthesis.

The professor was amazed; the entire organic chemistry department became excited. For Woodward had hit on something that might prove to be revolutionary in the field of organic chemistry.

During his third year Woodward took as many as 15 courses in one semester so that he might receive his Ph.D. sooner. The faculty permitted him to spend as little time as he wished in classes. Instead he studied the required subject matter independently and simply presented himself at the examinations. Again and again he walked off with honors in organic chemistry courses. At the end of his third year Woodward was notified that he was to be granted a bachelor's degree.

His last and fourth year at Tech, Woodward describes as his happiest, for he was able to spend his time in the research laboratory where he could resume his experiments, which he had begun in his second year at the Institute, on the female hormone. He did this work independently and wrote his thesis on it.

In explaining Tech's attitude toward Woodward, during that period of time, Professor Norris says, "We saw that we had in our midst a person who possessed a very unusual mind. We wanted to let it function at its best. If red tape, which was necessary for other less brilliant students, had to go, we cut it. We did for Woodward what we have done for no other student in our department, for we have had no student like him in our department. And we think he will make a name for himself in the scientific world." Norris further said, "But unlike some scholars, he will not burn out suddenly." It was not to be long before these prophesies were to be fulfilled.

Upon graduating from MIT Woodward spent the summer of 1937 at the University of Illinois but, with the approach of winter, migrated to warmer climes and moved back to Cambridge, where he became an assistant to Professor Elmer Peter Kohler at Harvard. The following year he was elected to the Harvard Society of Fellows, and by 1941 had published a series of papers on ultraviolet spectral structure correlations which are still used to this day. In 1944 Woodward (as a consultant for the Polaroid Corp.) and Bill Doering achieved

the total synthesis of quinine in only 14 months (Fig. 3). In 1947 he was to elucidate the structure of strychnine, to be followed in 1954 by total synthesis of strychnine and lysergic acid. The synthesis of strychnine was not without its difficulties, however, and after several months of trying to close the 6th ring, and after the most recent experiments had failed, Bob is recorded as saying, "If we can't make strychnine, we'll take strychnine!"

Prior to the total synthesis of strychnine both cholesterol and cortisone were synthesized, and in 1952 Woodward proposed the sandwich structure for ferrocene.

Few personal accounts of the major discoveries in chemistry are documented. An exception to this is the dream of August Kekulé[5] which led to the suggestion that benzene contained a cyclic structure. "There I sat and wrote my Lehrbuch," reported Kekulé, "but it did not proceed well, my mind was elsewhere. I turned my chair to the fireplace and fell half asleep. Again the atoms gamboled before my eyes. Smaller groups this time kept modestly to the background. My mind's eye, trained by repeated visions of a similar kind, now distinguished larger formations of various shapes. Long rows, in many ways more densely joined; everything in movement, winding and turning like snakes. And look, what was that? One snake grabbed its own tail, and mockingly the shape whirled before my eyes. As if struck by lightning I woke; this time I again spent the rest of the night to work out the consequences."

This dream of 1865, occurred 35 years before Sigmund Freud's theories were published in 1900,[6] and one can but wonder about Freud's reaction to snakes' biting their own tails! If, however, this led to the elucidation of the structure of benzene, what thoughts led Woodward to the sandwich structure of ferrocene would, I am certain, prove fascinating.

While the suggested structure for ferrocene initiated an era of organometallic chemistry, it also aided in the demise of Woodward's continuing practice at the bench. About 3 a.m. one day the group was gathered in the laboratory suggesting ways to try and oxidize or reduce the then-new ferrocene. RB put a lump of $FeSO_4$ into a separatory funnel and shook it with a solution of ferrocinium ion to reduce it. On being shaken, the funnel was broken by the lump, and the solution poured out onto RB's trousers (where it had the audacity to remain oxidized).

In 1960 Woodward announced the total synthesis of chlorophyll (Fig. 1), having already synthesized lanosterol and reserpine, and followed these successively with

Fig. 4. A telegram from Sweden!

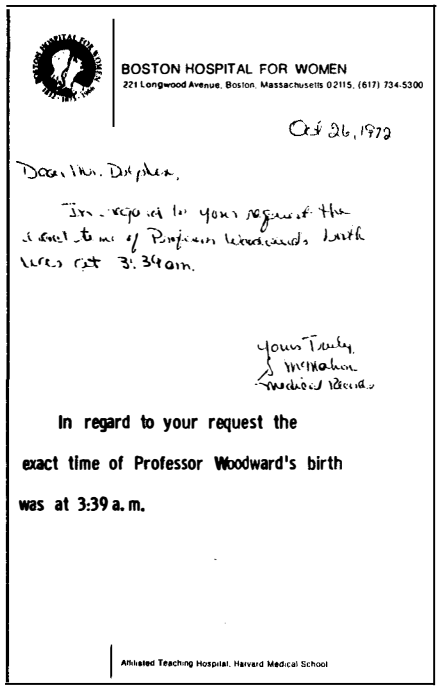
syntheses of tetracycline, cortisone and cephalosporin during the period in which he was awarded the Nobel Prize (Fig. 4).

While I have chosen only a few of the highlights in the above list of achievements in synthesis, it must be remembered that the theoretical aspects of organic chemistry are areas to which Woodward has also turned his talents. The latest of these is the conservation of orbital symmetry developed by Woodward and Hoffmann in the late 60's, and so elegantly summed up by them in their *Angewandte Chemie* article in 1968 where, in considering violations to the rules, they concluded "there are none!" Oosterhoff had suggested that orbital symmetry might play a role in electrocyclic reactions, and, while introducing Roald Hoffmann to an audience, made the observation that throughout the history of organic chemistry a number of significant contributions had been made by various distinguished Hoffmanns, among them being August Wilhelm von Hoffmann, and Friedrich Hoffmann. However, Oosterhoff noted, "of all the Hoffmanns the most famous is undoubtedly the Hoffmann whose first name is Woodward."

The greatest of all of Woodward's synthetic achievements is that of Vitamin B_{12}, which, in collaboration with Albert Eschenmoser, was completed in the early 70's. As colloquia chairman at Harvard I persuaded Woodward to present a talk on the synthesis of B_{12}. Our colloquia at Harvard were normally of an hour duration, and at first Bob was reluctant to lecture, since he assured me that there would be no way he could say his piece in an hour. If we were to schedule the talk at 5 p.m. as normal, we might break into the dinner hour and upset the audience. We easily overcame these objections by starting the talk at 8 p.m. which of course left us the rest of the evening, and if necessary the following morning, for the remainder of the presentation. It had not gone unnoticed, on earlier occasions, that Woodward's talks had occupied several hours, and since I had no reason to expect that this occasion would be any different I felt it might be appropriate to give a more detailed than usual introduction of our speaker.

A few weeks earlier Duilio Arigoni had presented the Tishler lectureship to the department, and had been introduced by Woodward who took some delight in giving a detailed discussion of a horoscope that had been prepared for Arigoni. I remembered, too, that Woodward had told me several years earlier that one should use all available avenues to gain information about a subject. In particular I remember that Woodward was trying to repeat some of Thorpe's earlier work in which he had claimed to have synthesized some derivatives of tetrahedrane. By the time Woodward was attempting to repeat this work Thorpe had died and parts of the experimental details were no longer available. Woodward knew, however, that Lady Thorpe was a clairvoyant who claimed to be in touch quite regularly with her husband, so Bob thought that this might indeed be a unique way of obtaining information and would certainly constitute a novel footnote. It thus seemed appropriate to me that, in the absence of a clairvoyant, possibly a detailed analysis of a horoscope prepared for Woodward might be included in my own introduction. At the time of the

preparation of Arigoni's horoscope, it had been suggested by the young lady preparing the horoscope, that perhaps Bob himself might like to have a horoscope prepared, but that in order to do this she would need the exact time, to the minute, of Woodward's birth. Woodward suggested that rather than use that time, which he didn't know anyway, and doubted that it could now be found, the young lady should prepare a horoscope for every minute of the day of his birth, and then by looking at the various comments decide what time he was born. Since I had neither the time nor the resources to undertake this obvious scientific but rather lengthy procedure, I determined to try and establish the exact time of Woodward's birth. A trip to the Massachusetts State House told me that Woodward was born on April 10, 1917 in the Boston Lying In Hospital for Women, but unfortunately no time had been recorded. However, the Boston Lying In Hospital for Women is an old established hospital and they informed me that for a small research fee they would check their records and find the information I needed, and behold a few days later a letter (Fig. 5) appeared recording Woodward's time of birth as 3:39 a.m. This is an especially significant time I feel, for I remember, one morning toward the end of a party in Bob's apartment, we saw the sun rise over the river Charles at about four in the morning. Woodward commented that yes, indeed he observed this every morning. Somewhat to our amazement he told us that he slept only three hours a day and had done so for as long as he could remember, and that he usually went to bed about 1 a.m. and got up



BOSTON HOSPITAL FOR WOMEN
221 Longwood Avenue, Boston, Massachusetts 02115, (617) 734-5300

Oct 26, 1972

Dear Mr. Dykes,

In response to your request the exact time of Professor Woodward's birth was at 3:39 a.m.

Yours Truly,
J. McMahon
Medical Records

In regard to your request the exact time of Professor Woodward's birth was at 3:39 a.m.

Affiliated Teaching Hospital, Harvard Medical School

Fig. 5.

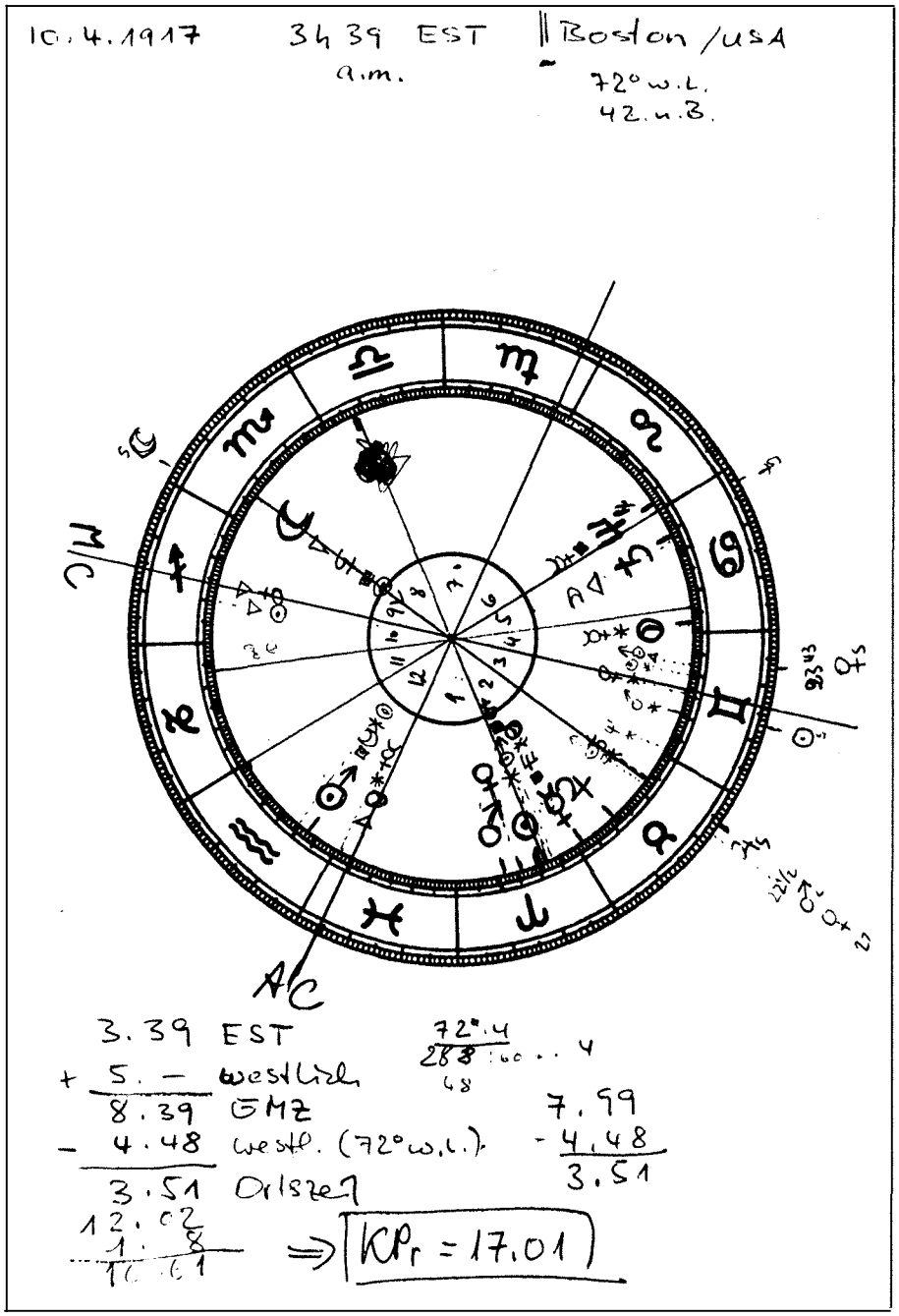


Fig. 6. Horoscope prepared for Woodward.

around 4 a.m. It would appear that he acquired this habit at a very young age then, and hasn't changed it since.

Having determined the exact time of Woodward's birth, I transmitted this information to Zürich and on the day of Woodward's lecture at Harvard, Arigoni flew in with the appropriate document and a somewhat detailed analysis of the horoscope. You will appreciate that it would be ignoble of me to outline here details of many of the comments that were made, but I reproduce in Fig. 6 the horoscope, so that those of you who are trained in the art of interpreting such documents can come to your own conclusions. I must make it clear right from the beginning that up until that time I had little faith in horoscopes, but many of the interpretations were indeed accurate in many respects; we knew we were on to a good thing with the first comment — Woodward's favorite color was red! It was noted, however, that his career had begun at 22, an accurate deduction, and that the man for whom this horoscope had been prepared should be a scientist. And not only that, that he should be a chemist, too. I must admit that to this day I do not know how much of this information came from the horoscope and how much came via Arigoni. The analysis went on to point out the subject was a user of nicotine and liquor, but was such a strong individual that

these had no effect on his health. Woodward ran true to form to show us, that night, how accurate the statement was by consuming his usual number of packages of Benson & Hedges and by finishing the two pints of Daiquiri that had been prepared for him as part of my introduction. Despite what non-smokers believe, among them such crusaders as James the First, who had this to say —

> Smoking is a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fumes thereof nearest resembling the Stygian smoke of the pit that is bottomless.

— the habit has been a tradition amongst synthetic chemists since the time of Wöhler and Liebig, both of whom were heavy smokers, especially Wöhler, who once made this comforting comment to a non-smoking colleague: "there are examples of non-smokers who became bearable chemists; however, this occurs only rarely."[7]

The horoscope indicated that the individual was forceful, energetic, had a good practical sense but was by no means diplomatic, and that he impressed others with his own personal viewpoint. And the individual was possessed with a phenomenal memory. To this I can personally attest. In late 1973 just before I left Harvard to move to the University of British Columbia, I was discussing the oxidizing power of oxaziridines with Woodward, who said that he recalled a paper from the Redstone Arsenal which he had read a while ago, where oxaziridines were titrated with iodide and hence oxidants. As a measure of Woodward's memory it transpires that the paper he referred to had been written about twenty years earlier, and that the iodide titrations were described in a footnote to the experimental section.

But let me return to Woodward's latest accomplishment. Although the total synthesis of B_{12}, in the form of cobyrinic acid, formally represented a total synthesis of the vitamin itself, it was only a year ago that the complete synthesis was achieved, when the nucleotide loop was attached to the cobyrinic acid. (Fig. 7)

My latest count of the people involved in this undertaking, in both Cambridge and Zürich, totalled about 100 postdoctoral fellows. It is, of course, apparent that during the past 40 years Woodward's achievements must also be gauged in reference to Woodward as a teacher. During these past four decades nearly 400 students have been associated with him. It is said that a man can be judged by the company he keeps, and it is certainly true that a chemist can be measured by the men he has trained. It would be inappropriate to list here all 400 colleagues; other ventures being planned to celebrate Woodward's 60th birthday will better measure the magnitude of this group.[8] I have however gone through the list of Woodward's collaborators and randomly selected about ten percent of the names:

> Bill Ayer, Jerry Berson, Ray Bonnett, Rich Borch, Axsel Bothner-By, Ron Breslow, Bill Chan, Malcolm Clark, Gerhard Closs, Pat Confalone, Pierre Deslongchamps, Bill Doering, Paul Dowd, Ian Fleming, Chris Foote, David Ginsburg, Jacques Gosteli, Hans Gschwend, James Hendrickson, Kenichi Hiroi, Ken Houk, Shô Itô, Bill Jencks, Tom Katz, Andy Kende, Yoshi Kishi, Hoshiro Kobayashi, Jean-Marie Lehn, Willy Leimgruber, David Lemal, Paul de Mayo, Jerry Meinwald, David Ollis, Roy Olofson, Avram Patchornik, Subramania Ranganathan, Myron Rosenblum, Dick Schlessinger, Franz Sondheimer, Bal Dattaraya Tilak, Denny Valenta, Harry Wasserman, Larry Weiler, Ernie Wenkert, Emil White, Mark Whiting, Alex Wick, Charles Wiesner, Reuven Wolovsky, Peter Yates, Alexander Gregoryevitch Yurlchenko, Howie Zimmerman.

It is inevitable, in preparing a list of this type, that some of the more famous colleagues should have been left out. These names I have added below.[9]

In May of 1944 *The Tech* (The MIT newspaper) made the following comment. "Professors who have known him well have stated that Woodward was excellent not only in *chemical* subjects but in *academic* studies as well." Those same professors would now have to admit that through the efforts of Robert Burns Woodward chemistry can at last be acclaimed a scholarly and academic pursuit.

And what of the future? You might imagine that the best answer to this question would come from the oracle himself. However, such pilgrimages are usually destined to failure. For example, I remember a press conference that was held on the morning that Bob won the Nobel Prize. A reporter from one of the local newspapers asked if he thought that he now would begin to synthesize life in the test tube. After a moment's reflection he looked up and said, "No, I am quite happy with the way it is done now."

After all of Woodward's scientific achievements one might imagine that there is nothing that he can do to exceed, for instance, the elegance or complexity of the B_{12} synthesis. I am certain that this is not so, and that we shall see even greater triumphs in the future. If you doubt this statement I leave you with the words of Lewis Carroll:

> "There is no use trying," she said; "one can't believe impossible things." "I dare say you haven't had much practice," said the Queen. "When I was your age, I always did it for half an hour a day. Why, sometimes I believed as many as six impossible things before breakfast."

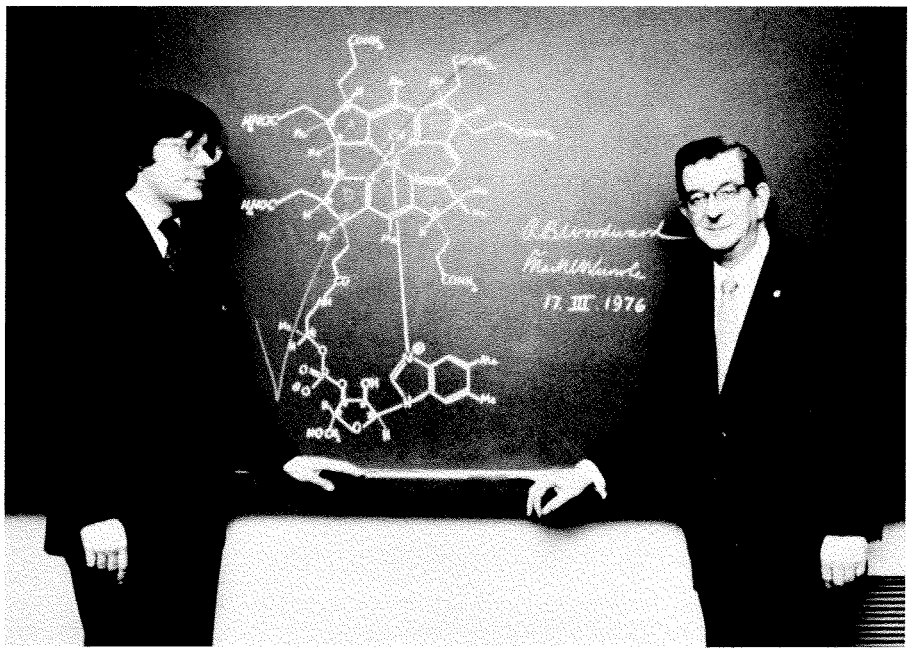
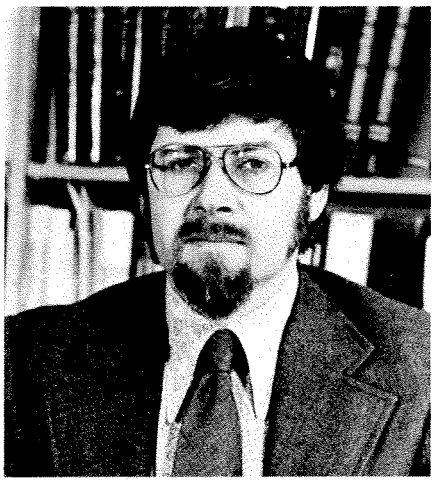


Fig. 7. Mark Wuonola and RBW announce the completed synthesis of vitamin B_{12}.

Footnotes:

1) F. Wöhler, *Ann. d Physik,* **12,** 253 (1828).
2) F. Wöhler and J.v. Liebig, *Justus Liebigs Ann. Chem.,* **26,** 254 (1838).
3) This article is written as an appreciation of all that Woodward has done for chemistry in general and for me in particular, and is dedicated to him on the anniversary of his sixtieth birthday. If at any stage the reader should feel that my personal account transgresses the bounds of gentlemanly behavior, then I would refer them to the first piece of advice that Woodward ever gave me: "David, there is not time enough to worry over what others think about you."
4) I thought of changing your name, Pat, but I know, and you know, and he knows where the story comes from, so what's the point?
5) R. Anschütz, "August Kekulé 1829-1896" in *Great Chemists,* ed. E. Farber, *Interscience,* New York, 1961, p. 697.
6) Sigmund Freud, *The Interpretation of Dreams,* trans. A.A. Brill, completely revised edition (London: George Allen and Unwin, Ltd., 1937).
7) F. Haber, "Justus von Liebig 1803-1873" in *Great Chemists,* ed. E. Farber, *Interscience,* New York, 1961, p. 535.
8) In addition to papers, dedicated to Woodward on the occasion of his sixtieth birthday, which will be published throughout the scientific literature, *Heterocycles,* under the editorship of Tetsuji Kametani, will publish an issue containing papers dedicated to Woodward.
   This year's Leermakers Symposium, to be held at Wesleyan University three weeks after Woodward's birthday, is to be built around the impact Woodward has made on total synthesis. Additional information on the symposium, of which Woodward is the Honorary Chairman, can be obtained from Professor Max Tishler, Department of Chemistry, Wesleyan Univesity, Middletown, CT 06457.
9) David Dolphin.



David Dolphin

About the Author

After obtaining his Ph.D. with Alan Johnson in 1965 David Dolphin spent a year's postdoctoral fellowship with Woodward, and he then joined the faculty of the chemistry department at Harvard where he stayed for eight years, moving in 1974 to his present location at the University of British Columbia.

Handling Air-Sensitive Reagents

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A large variety of air-sensitive reagents is available from Aldrich. Specific examples include solutions of borane complexes, organoboranes, borohydrides, Grignard reagents, organoaluminums, organolithiums, and organozincs. Since all of these reagents react with water or oxygen or both, they must never be exposed to the atmosphere.

Most modern synthetic chemists are familiar with the utility of these versatile organometallic reagents. However, because the compounds are air-sensitive or pyrophoric, some workers hesitate to make use of the remarkable chemistry of these reagents. Some chemists still believe that very specialized equipment and complicated techniques are required for handling air-sensitive reagents. This is often not the case.

Air-sensitive materials can be separated into two categories: those which react catalytically with air and/or water and those which react stoichiometrically. In the latter case, which fortunately includes most of the synthetically useful reagents, the reagents can be handled easily on a laboratory scale using syringe and syringe-related techniques. The catalytically sensitive materials often require the use of more sophisticated apparatus such as vacuum lines, Schlenk-apparatus, or inert-atmosphere glove boxes.

Brown and coworkers have recently described simple, convenient bench-top methods for handling stoichiometrically sensitive compounds on a laboratory scale.[1] Shriver has presented an excellent description of the more sophisticated techniques used to manipulate catalytically sensitive materials.[2]

The present discussion is limited to those techniques necessary for handling air-sensitive reagents on a preparative scale. In addition, several pieces of specialized equipment which greatly facilitate the safe and effective handling of these reagents will be described. The book by Brown and coworkers should be consulted for more detailed descriptions of simple techniques for working with air-sensitive materials.

Air-sensitive reagents available from Aldrich are packaged in special bottles. The Aldrich Sure/Seal packaging system (Fig. 1) provides a convenient new method for storing and dispensing research quantities of air-sensitive reagents. With this

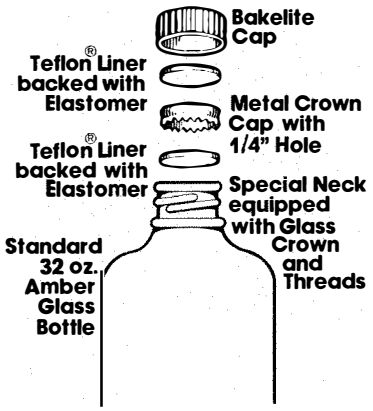


Fig. 1. The Aldrich Sure/Seal packaging system.

new bottle, reactive materials can be handled and stored without exposure to atmospheric moisture or oxygen. The reagent comes in contact only with glass and Teflon®, yet it can be readily transferred using standard syringe techniques.

Syringe transfer techniques will be described in more detail later, but a short discussion at this point will illustrate the convenience of the new Sure/Seal packaging system.

The Bakelite cap on a Sure/Seal bottle can be safely removed because the crown cap, with its Teflon/elastomer liner, is already crimped in place. The reagent can then be dispensed using a syringe or double-tipped needle inserted through the hole in the metal crown cap. After the needle has been withdrawn from the bottle, a small hole will remain in the Teflon/-elastomer liner. Under normal circumstances, the hole in the liner will self-seal and the reagent will not deteriorate. However, the possibility exists that once an elastomer liner is punctured, it may leak on long-term storage. This possibility is virtually eliminated with the Sure/Seal system because when the Bakelite cap is replaced, the Teflon/elastomer liner in the cap forms a seal against the top of the metal crown. Thus, the contents are effectively protected from moisture and oxygen in the atmosphere.

Reactions involving our air-sensitive reagents may be carried out in common ground-glass apparatus. The only additional equipment required is a source of inert gas, a septum inlet, a bubbler, and syringes fitted with suitable needles. Aldrich offers a variety of septums, syringes and syringe-related hardware, several pieces of septum-inlet-equipped glassware, and a bubbler.

Laboratory glassware contains a thin film of adsorbed moisture which can be easily removed by heating in an oven (125°/overnight or 140°/4 hrs). The hot glassware should be cooled in an inert atmosphere by assembling the glassware

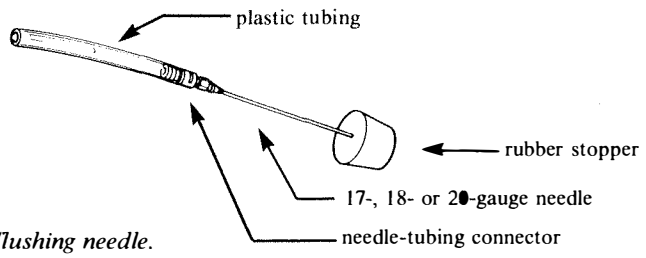


Fig.2. Nitrogen-flushing needle.

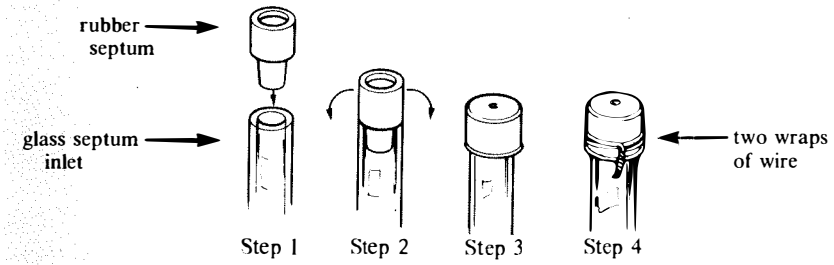


Fig. 3. Procedure for utilization of rubber septum.

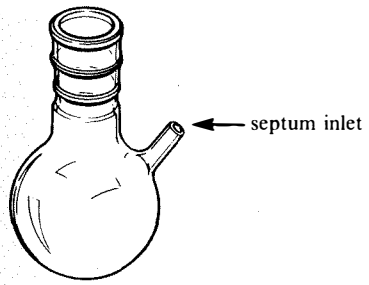


Fig. 4. Flask equipped with septum inlet.

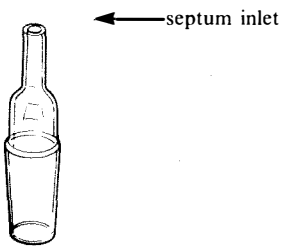


Fig. 5. Septum inlet adapter.

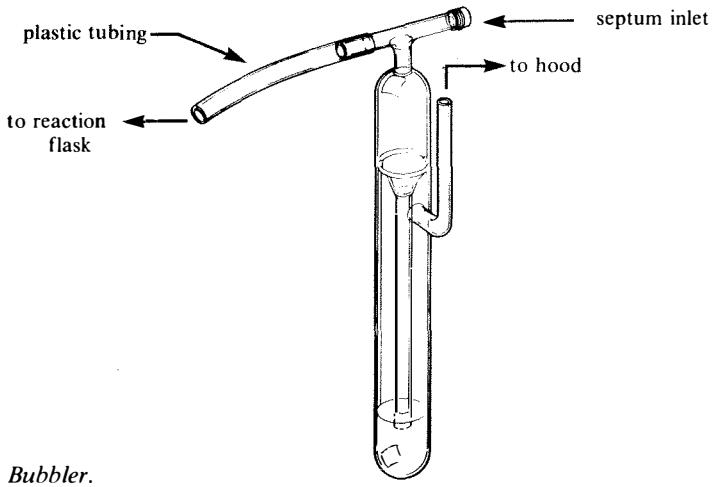


Fig. 6. Bubbler.

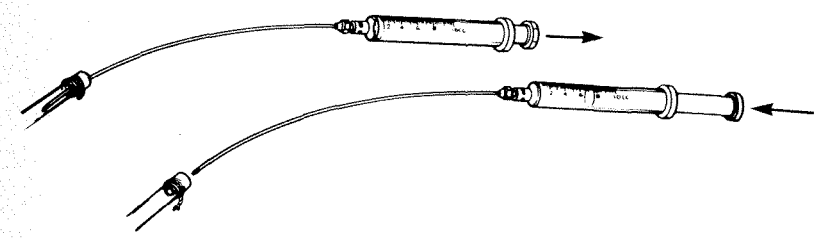


Fig. 7. Flushing a syringe with nitrogen.

while hot and flushing with a stream of dry nitrogen or argon. A thin film of silicone or hydrocarbon grease must be used on all standard taper joints to prevent seizure upon cooling. Alternatively, the apparatus may be assembled cold and then flamed with a Bunsen burner while flushing with dry nitrogen.

The oven drying procedure is more efficient than flaming with a burner because it removes moisture from inner surfaces of condensers and from other intricate parts. Spring clips or rubber bands are required to secure joints during the flushing since the nitrogen pressure may open the seals of unsecured standard taper joints, especially when the joints are hot.

Only high-purity, dry nitrogen from a cylinder with a pressure regulator (adjusted to 3-5 psi) should be used for flushing. Plastic tubing (Aldrich Catalog No. Z10,119-2) can be used to connect the nitrogen line to a tube connector adapter (equipped with a stopcock) on the reaction apparatus. Nitrogen may also be introduced through a rubber septum *via* a hypodermic needle connected to the end of the flexible tubing on the nitrogen line. The needle-tubing connector (Aldrich Catalog No. Z10,116-8) provides a simple method for attaching the needle to the tubing. When not in use, this nitrogen-flushing needle (Fig. 2) should be closed by inserting the needle into a solid rubber stopper to prevent diffusion of air into the needle when the nitrogen supply is turned off.

Large rubber septums may be used to cap female joints. However, the use of 6-mm septums and 8-mm o.d. standard wall or 9-mm o.d. medium wall (6-mm i.d.) glass septum inlets is preferred. The small rubber septum (Aldrich Catalog No. Z10,072-2) provides a more positive reseal after puncture and allows less rubber to be in contact with organic vapors in the reaction vessel. The use of 9-mm o.d. medium wall tubing, instead of the more common 8-mm o.d. standard wall, with 6-mm septums is preferred. With the medium wall tubing, the 6-mm septum not only fits the inside diameter of the glass tube but also fits snugly over the outside when the top is folded over (Fig. 3). The glass septum inlet can be built into the reaction flask (Fig. 4) or placed on an adapter (Fig. 5) for use with unmodified glassware.

The rubber septum may be wired in place as shown in Figure 3. However, if the 6-mm septum is properly fitted to 9-mm medium wall tubing, the wiring step may be omitted unless high pressures (>10 psi) are expected.

To maintain an air-tight system the reaction vessel must be vented through a mer-

cury or mineral oil bubbler. Obviously, simple drying tubes will *not* prevent oxygen from entering the system. At all times during the reaction, the system should be under a slight positive pressure of nitrogen as visually indicated by the bubbler. Figure 6 illustrates a suitable bubbler (Aldrich Catalog No. Z10,121-4).

A pressure reversal in the reaction vessel may cause the liquid in the bubbler to be sucked back. The enlarged head space in the bubbler will minimize the danger of the bubbler liquid being sucked back *into the reaction vessel.* However, if a large pressure reversal occurs, *air will be admitted* into the reaction vessel. The T-tube bubbler shown can be used to prevent this problem because nitrogen pressure can be introduced intermittently through the septum inlet. The problem can be completely eliminated by a slow and continuous nitrogen flow.

When the assembled (nitrogen-flushed) glassware has cooled, air-stable solids may be introduced through an entry port under a blanket of nitrogen. The entry port is closed and the system is flushed with nitrogen.

Small quantities (up to 50ml) of air-sensitive reagents and dry solvents may be transferred with a syringe equipped with a needle (length 1-2ft). The long needles are used to avoid having to tip reagent bottles and storage flasks. Tipping often causes the liquid to come in contact with the septum. Contact of rubber septums with many organic liquids causes swelling and deterioration of the septums, and should therefore be avoided.

A rubber septum in contact with organic vapors provides a positive seal for only a limited number of punctures, depending upon the needle size. The lifetime of the septum may be extended by always reinserting the needle through an existing hole. It is also advantageous to put a layer of silicone or hydrocarbon grease on a rubber septum to facilitate passage of the needle through the rubber and to minimize the size of the hole in the septum. Ideally, the syringe and needle should be dried in an oven prior to use. Naturally, the syringe body and plunger should *not* be assembled before being placed in the oven. The syringe should be flushed with nitrogen during the cooling. A syringe may also be flushed 10 or more times with dry nitrogen as illustrated in Figure 7 to remove the air and most of the water adsorbed on the glass. A dry syringe may be closed to the atmosphere by inserting the tip of the needle into a rubber stopper.

The syringe-needle assembly should be tested for leaks prior to use. The syringe is half filled with nitrogen and the needle tip is inserted in a rubber stopper. It should be possible to compress the gas to half its original volume without any evidence of a leak. A *small* amount of stopcock grease or a drop of silicone oil placed on the Luer lock tip will help insure tightness.

The syringe transfer of liquid reagents is readily accomplished by first pressurizing the Sure/Seal reagent bottle with dry, high-purity nitrogen followed by filling the syringe as illustrated in Figure 8. The nitrogen pressure is used to slowly fill the syringe with the desired volume plus a slight excess (to compensate for gas bubbles) of the reagent. Note that the nitrogen pressure pushes the plunger back as the reagent enters the syringe. The plunger should not be pulled back since this tends to cause leaks and creates gas bubbles. The excess reagent along with any gas bubbles is forced back into the reagent bottle as illustrated in Figure 9. The accurately measured volume of reagent in the syringe is quickly transferred to the reaction apparatus by puncturing a rubber septum on the reaction flask or addition funnel, as shown in Figure 10. Syringes with capacities up to 100ml are available. However, the large syringes become

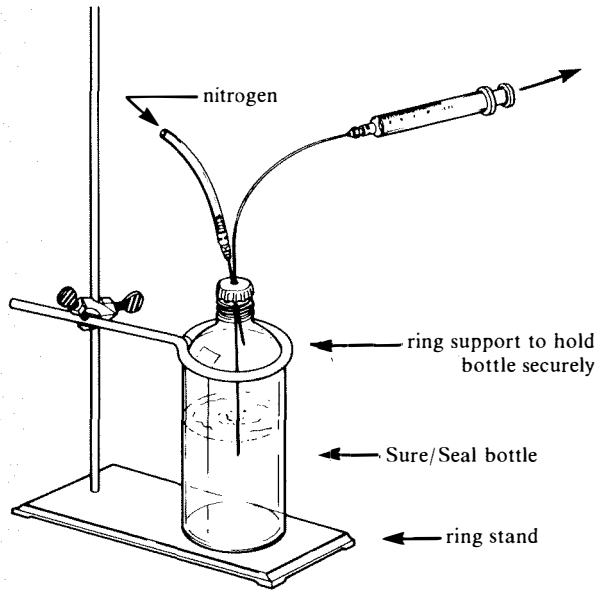


Fig. 8. Filling syringe using nitrogen pressure.

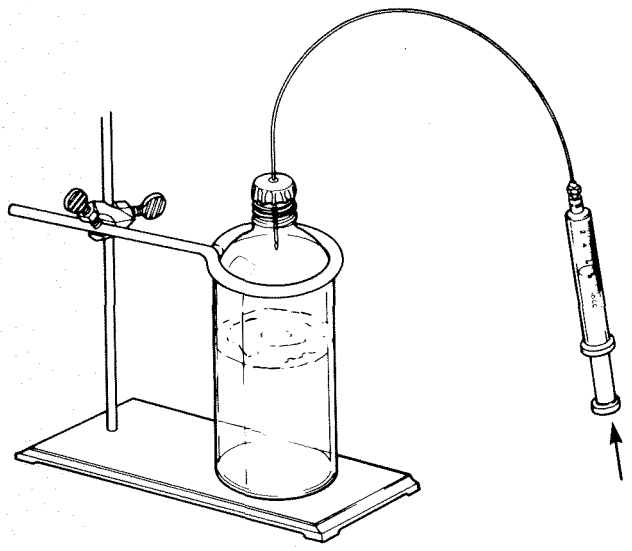


Fig. 9. Removing gas bubbles and returning excess reagent to the Sure/Seal bottle.

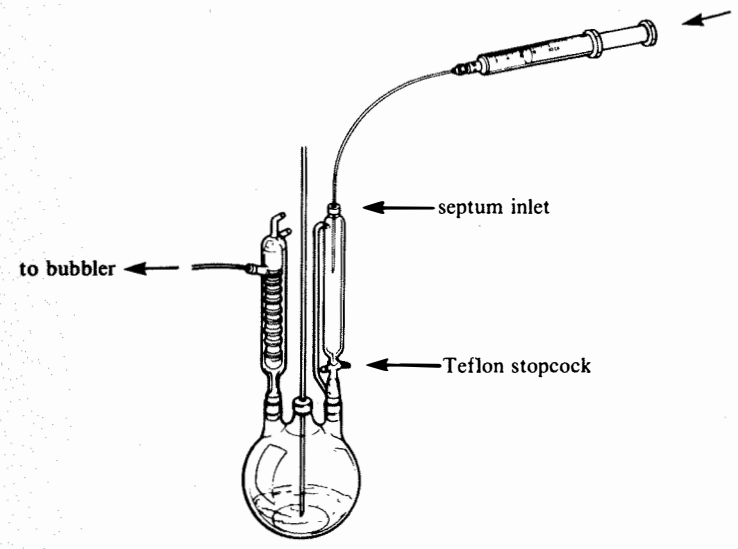
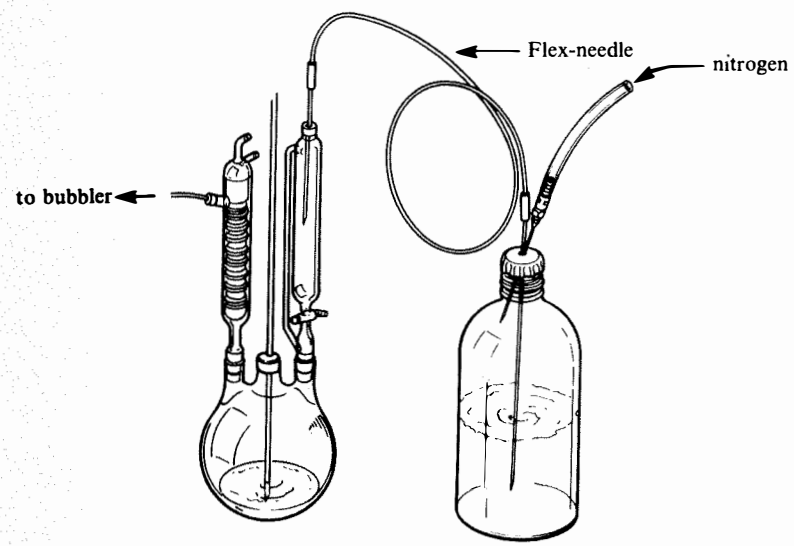


Fig. 10. Syringe transfer of reagent to reaction vessel.



awkward to handle when completely full.

When the transfer of more than 50ml of solvent or liquid reagent is required, it is generally much more convenient to use the double-tipped needle technique. Figure 11 illustrates liquid–reagent transfer under nitrogen pressure using this technique.

To accomplish the double-tipped needle transfer, the needle is first flushed with nitrogen. The Sure/Seal bottle is pressurized with nitrogen using the nitrogen flushing needle. The double-tipped needle is then inserted through the septum on the reagent bottle into the head space above the reagent. Nitrogen immediately passes through the needle. Finally, the other end of the double-tipped needle is inserted through the septum on the reaction apparatus, and the end of the needle in the reagent bottle is pushed down into the liquid. The volume of liquid reagent transferred is measured by using a calibrated flask or addition funnel. When the desired volume has been transferred, the needle is immediately withdrawn to the head space above the liquid, flushed slightly with nitrogen, and removed. The needle is first removed from the reaction apparatus and then from the reagent bottle.

An alternative method for transferring measured amounts of reagents is shown in Figure 12. The reagent is first transferred *via* a double-ended needle from the Sure/-Seal bottle to a dry, nitrogen-flushed graduated cylinder equipped with a female ₹ joint and a double inlet adapter (glassware G as illustrated in equipment section). Only the desired amount of reagent is transferred to the cylinder. The needle is then removed from the Sure/Seal bottle and inserted through the septum on the reaction apparatus. By applying nitrogen presssure as before, the reagent is added to the reaction apparatus. If it is necessary to add the reagent slowly, a modified double-tipped needle can be used. This useful transfer needle is constructed from two long standard needles and a male Luer lock to male Luer lock syringe valve (accessory O as illustrated in equipment section). The valve may be opened slightly allowing only a very slow flow of reagent. Thus, the addition funnel is not needed and many reactions can be carried out in single-necked flasks as shown in Figure 13.

The 12-gauge stainless steel needles on the Flex-needle provide a rapid means of transferring air-sensitive reagents under nitrogen pressure. However, the needles are so large that once the crown cap liner on the Sure/Seal bottle is punctured, the liner will not self-seal. If only a portion of the contents is to be used up, a needle no larger than 16-gauge should be utilized. By using small needles and by always tightly replacing the Bakelite cap, the reagent in a Sure/Seal bottle will not deteriorate even after numerous septum punctures. However, if the reagent is to be used repeatedly for small-scale reactions or if an unused portion is to be stored for an extended length of time, the material should be transferred from the Sure/Seal bottle to a suitable storage bottle. One type of container (Aldrich Catalog No. Z10,248-2) for air-sensitive reagents is shown in Figure 14. Alternatively, an appropriate adapter (Fig. 15) can be used to convert a round-bottomed flask into a storage vessel.

The Teflon stopcock on the storage bottle keeps solvent vapors away from the septum, thereby minimizing swelling and deterioration of the septum. Furthermore, the stopcock allows for replacement of the septums. A change of septums is sometimes necessary because they tend to deteriorate on prolonged standing in a laboratory atmosphere.

Naturally, this storage bottle must be oven-dried and flushed with nitrogen before use. A clean and dry Flex-needle should be used to transfer the contents of the Sure/Seal bottle to the storage bottle, using the standard double-tipped needle technique.

Clean-up of equipment that has been used to transfer air-sensitive reagents must not be taken lightly. Since many of these reagents react violently with water, fires are a potential hazard. The crown cap and liner of an "empty" Sure/Seal bottle should be removed and the open bottle placed in a hood to allow the last *traces* of reactive

reagent to slowly air-hydrolyze and oxidize. After at least a day, the inorganic residue can be rinsed out with water. Empty storage bottles and storage flasks should be treated similarly. Air-hydrolysis in a hood is appropriate only for the last *traces* of material that remain after a Sure/Seal bottle has been emptied as completely as possible *via* syringe or double-ended needle transfer. The Aldrich Catalog/Handbook should be consulted for the recommended disposal procedures for larger amounts of reactive chemicals.

All syringes and needles that have been used to transfer air-sensitive materials must be cleaned *immediately* following use. Also, in general, a syringe should only be used for a single transfer. Failure to follow this practice will invariably result in plugged needles and "frozen" syringes due to hydrolysis or oxidation of the reagents. The double-tipped needles are flushed free of reagent with nitrogen in the transfer system, and then immediately removed and placed in a clean sink. With water running in the sink and in the complete absence of flammable solvents and vapors, the double-tipped needles or Flex-needle can be rinsed with water. When activity in the rinse water is no longer observed, acetone from a squeeze bottle can be flushed through the needle. Depending on the reagent transferred, it may be necessary to use dilute aqueous acid or base from a squeeze bottle to remove inorganic residue that is not water-soluble.

Following its use, a syringe contains a larger residual amount of reagent. It is advisable to rinse out the reactive reagent by first placing a few milliliters of the *same* solvent that was used for the reagent in a small Erlenmeyer flask in the hood. Keeping the needle tip under the solvent at all times, no more than half the solvent is then sucked into the syringe until the syringe is at least half-full. The solvent plus dissolved residual reagent is ejected from the syringe back into the same Erlenmeyer flask. This rinsing treatment is repeated at least three times. The wash solution can be safely combined with other waste solvents for eventual burning, and the syringe may be further cleaned with water and acetone in the sink. Again, treatment with dilute aqueous acid or base may be necessary.

Once the syringe needles and double-tipped needles have been rinsed in a sink, they can be further cleaned and dried using a device similar to that shown in Figure 16. Needles are cleaned by inserting them through the septum. Vacuum from a water aspirator is used to pull solvents from squeeze bottles through the needles. After pulling air through the system for a few minutes, the syringe plus needle or the

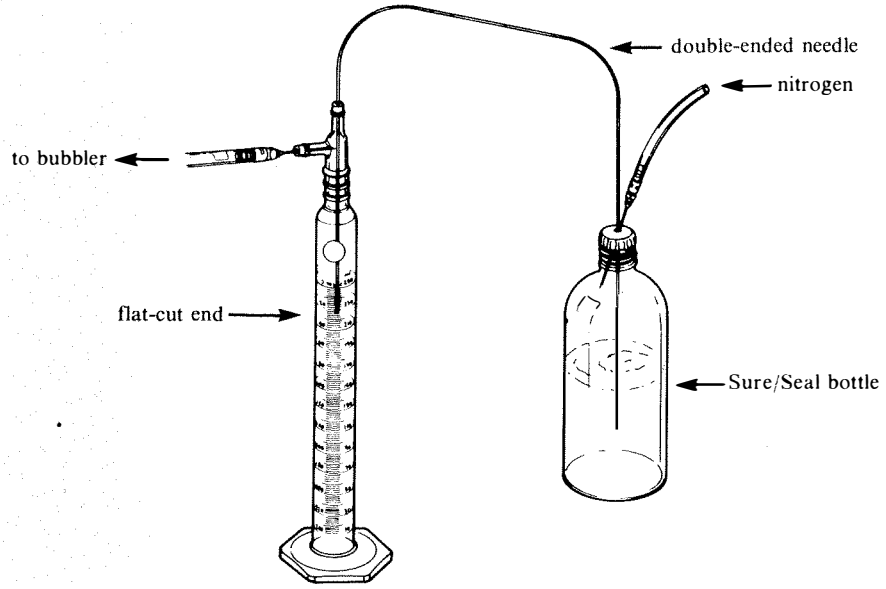


Fig. 12. Double-ended needle transfer to graduated cylinder.

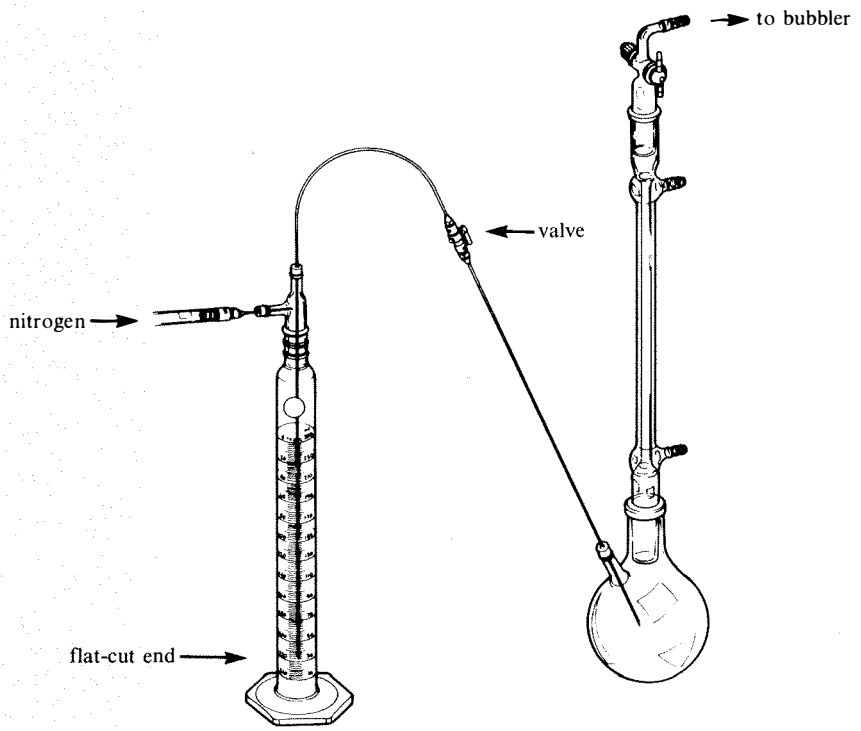


Fig. 13. Double-ended needle transfer with syringe valve.

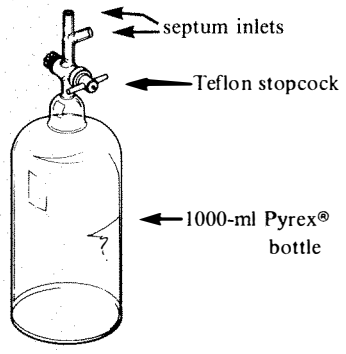


Fig. 14. Storage bottle equipped with Teflon stopcock.

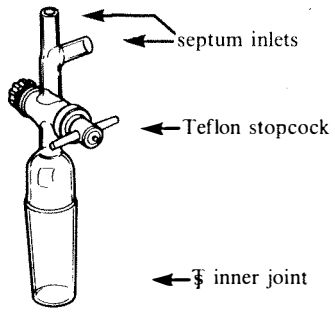


Fig. 15. Septum inlet adapter for storage flask.

double-tipped needle will be dry. The syringe plunger should be replaced in the barrel for storage. If a syringe plunger and barrel are not assembled for storage, dust can settle on the plunger and in the barrel. Upon reassembly, these fine particles will occasionally scratch the barrel or cause seizure of the plunger in the barrel. However, the plunger and barrel must be disassembled before oven drying.

Most of the above techniques were developed for handling various organoborane reagents. However, these methods are applicable to other air-sensitive materials.

When handling air-sensitive materials, it is important that the user be thoroughly familiar with the basic chemistry of the reagent. Also, the user should be prepared for unexpected problems. For example, at least one extra set of clean, dry syringes and needles or double-tipped needles should always be available in case the first set of equipment becomes plugged.

As in all laboratory practices, simple "common sense" is required. It is impossible to describe in detail the techniques required for all possible situations. As a rule-of-thumb, the chemist working with these air-sensitive reagents should always keep in mind that, if at all possible, these solutions should never be allowed to come in contact with the atmosphere.

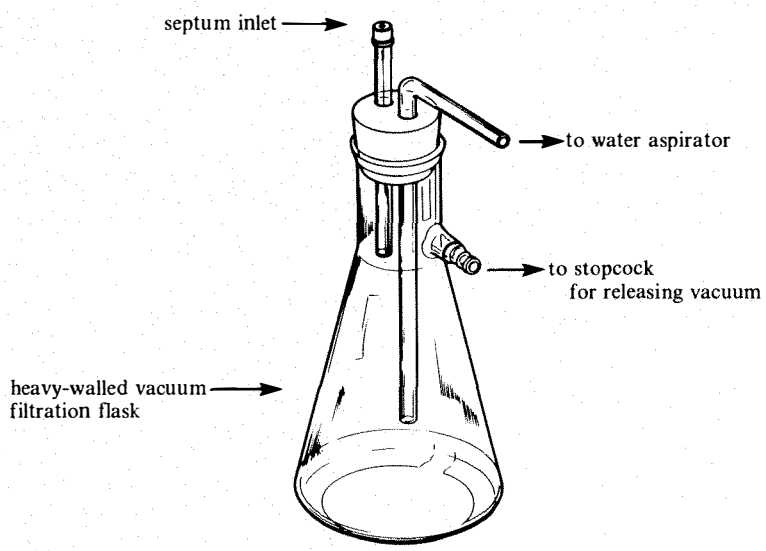


Fig. 16. Needle cleaning and drying apparatus.

Finally, it is our sincere hope that with the convenience of our new Sure/Seal packaging system, coupled with simple, convenient syringe techniques, no technically qualified chemist will ever again hesitate to use air-sensitive reagents.

References:

1) G.W. Kramer, A.B. Levy, and M.M. Midland in H.C. Brown, "Organic Syntheses *via* Boranes," John Wiley and Sons, Inc., New York, N.Y., 1975 (Aldrich Catalog No. Z10,144-3, $17.50).

2) D.F. Shriver, "The Manipulation of Air-sensitive Compounds," McGraw-Hill Book Company, New York, N.Y., 1969.

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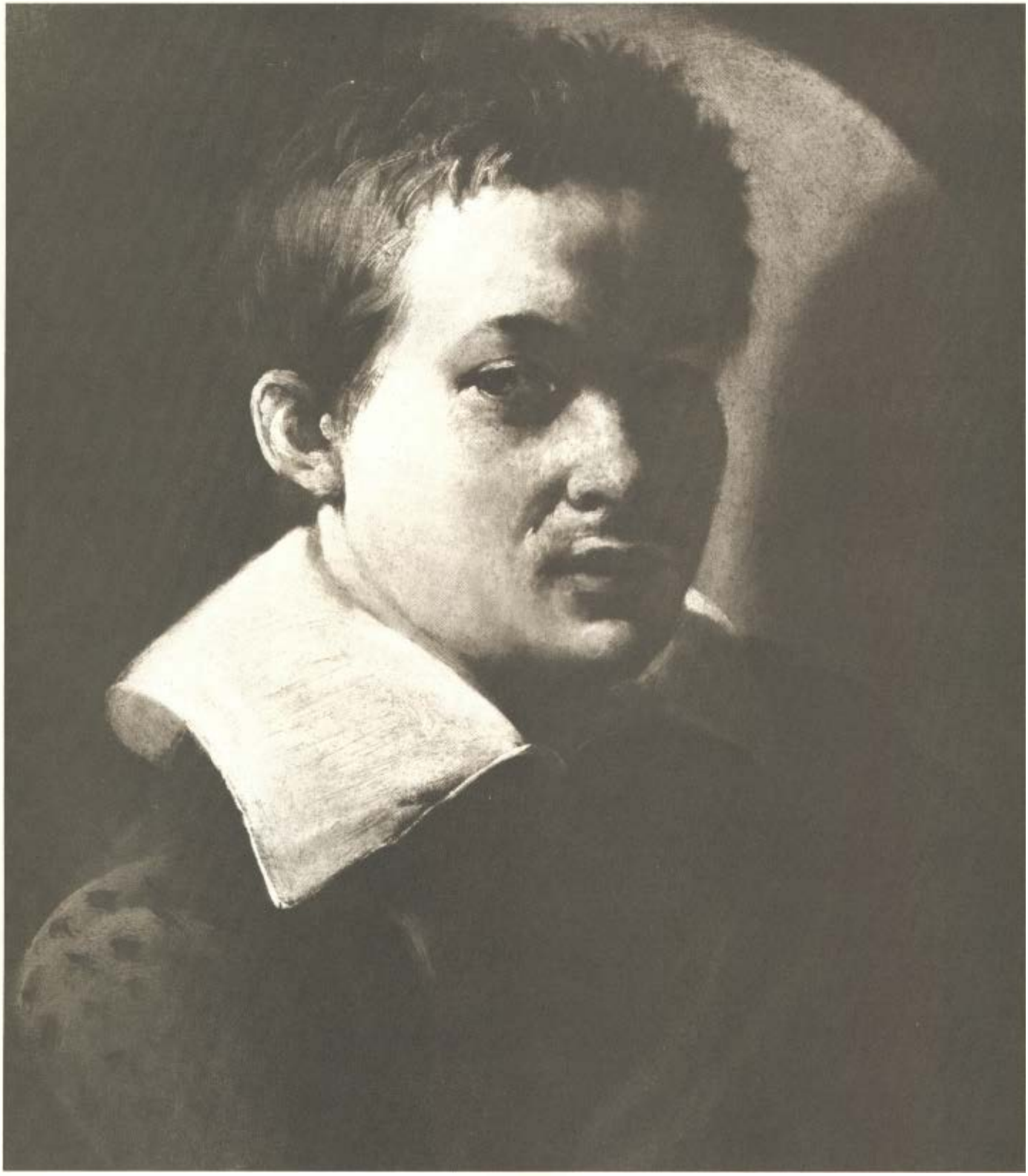
Aldrichimica Acta

Volume 10, Number 2, 1977



Chlorosulfonyl Isocyanate, a review. **See page 23.**

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Aldrichimica Acta

Volume 10, Number 2, 1977

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About Our Cover:

Our chemist-collector purchased this sensitive portrait of a young man (oil on canvas 23 x 19 inches) at a Milwaukee gallery recently. A previous owner had bought it in an antique store in Vienna in 1926, and had then been told that it was mid-seventeenth century Dutch. Subsequently, it was exhibited at the Milwaukee Art Center as a newly discovered Frans Hals! Our chemist believes it is Italian — perhaps Bolognese — rather than Dutch, and earlier, *ca.* 1580-1590.

Latest Addition to Local Galleries Is Believed to Have Been Painted by Franz Hals and Was Purchased for $500 in an Antique Shop in Vienna

Reprinted with permission from The Milwaukee Journal, October 14, 1928, page 7.

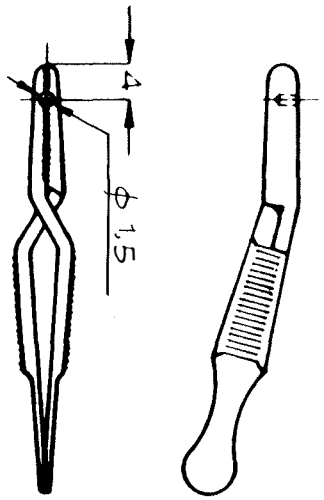
Are you interested in our Acta covers? *Selections from the Bader Collection,* with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

Crucibles used in mass spectrometer direct-introduction probes should be handled with special tweezers that are usually pinched closed. This is important since it eliminates the need to press in order to ensure that the crucible does not drop (which is all too often the case with standard lab pincers) during manipulation, before being placed in its receptacle.

We found that surgical hemostats, which are a mass-produced item, may be converted to fit this need by drilling a small hole into them as shown in the accompanying drawing.



The diameter of the hole should be about $^1/_2$mm less then the crucible's outside diameter and have a depth of $^1/_3$ to $^1/_2$ of its length.

The crucible is held firmly by such a device and is released by squeezing.

We believe that the community of mass-spectrometrists would benefit from this idea.

Meir Peled and Adam Vincze
Israel Institute for Biological Research
Ness-Ziona, P.O.B. 19, Israel

We have found the following apparatus ideally suited for the preparation of totally dry samples for Fourier transform nmr experiments where the slightest trace of water can obscure important peaks or cause unwanted line broadening.

The unit is constructed from the barrel of a 0.5-ml Luer lock syringe (preferably one whose plunger has been broken) and a 15-ml volumetric pipette. The end of the syringe barrel is cut off as is all but 1 in. of the narrow tubing of the volumetric pipette. The two pieces are then joined. One end is filled with glass wool, and then fine (5Å) molecular sieves are poured into the "column" until they just start to fill the narrow tubing. A 6-in. stainless steel syringe needle is attached to the Luer lock and the entire apparatus is baked at 300°C for at least 12 hours to activate the sieves. The apparatus is then cooled in a dessicator or, preferably, by passing a slow, steady stream of purified dry nitrogen through the column.

After the column has cooled to slightly above room temperature, the solvent to be dried is injected through the glass wool into the sieves. The solvent is then dispensed through the needle into a septum-equipped nmr tube which has been attached to a vacuum pump for at least 4 hours. A small-gauge needle is used as a vent on the nmr tube. The solvent-transfer is accomplished by attaching a nitrogen line to the column, and to increase the flow rate, the column can be warmed with a heat gun.

The column can be reused immediately after transfer. We have obtained four dry samples before having to reactivate the column.

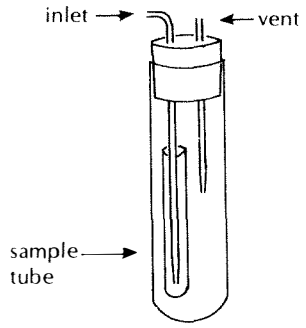
Joseph Alper
University of Wisconsin
Department of Biochemistry
420 Henry Mall
Madison, WI 53705

A common problem encountered in the use of silver chloride infrared cells is their darkening upon exposure to light. A simple and effective method of clearing up these darkened cells consists of simply soaking them in pyridine, wiping with a soft towel, and then rinsing with carbon tetrachloride. Clarity very close to that of brand new cells is achieved.

Thomas E. Nemo
Chemistry Department
University of Michigan
Ann Arbor, Michigan 48109

I have found the following trap very convenient for manually collecting nmr samples quickly and efficiently from a gas chromatograph. The trap consists of a 200 x 25mm test tube with a #4 2-hole stopper which is fitted with an inlet and a vent, both of which are easily fashioned from disposable pipets or 7-mm glass tubing. An nmr tube is simply placed in the test tube and the inlet tube inserted into it for collection.

After collection of a sample, the nmr solvent of choice can be measured out by syringe and flushed through the inlet tube.



Lee Flippin
Graduate Student
Department of Chemistry
University of Colorado
Boulder, Colorado 80309

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 red and white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Ywa Bader.

During a recent visit to the University of Michigan, Professor Richard G. Lawton told me of a very interesting new biochemical reagent, Cyssor I (an acronym for cysteine-specific scission by an organic reagent), which he thought would be of great interest as a reagent for cysteine modification and cleavage of proteins [T.J. Holmes and R.G. Lawton, *J. Am. Chem. Soc.*, **99**, 1984 (1977)]. Professor Lawton thought that the availability of this reagent would help many biochemists, and he asked whether we would try to make it. Naturally, we tried and are happy to offer it.

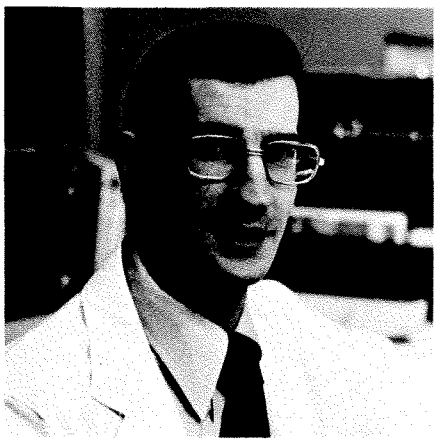
It was no bother at all, just a pleasure to be able to help.

19,584-7 Cyssor I [2-methyl-N^1-benzenesulfonyl-N^4-(bromoacetyl)quinonediimide]

Chlorosulfonyl Isocyanate

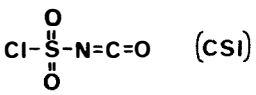
Silver Anniversary of a Lively Heterocumulene

William A. Szabo
Aldrich Chemical Company, Inc.
Milwaukee, Wisconsin 53233



Introduction

Chlorosulfonyl isocyanate (CSI) is probably the most chemically reactive isocyanate known. It was discovered by Graf[1] 25 years ago and has been the subject



of several reviews.[2] The present survey will emphasize the synthetic applications of this extremely versatile reagent.

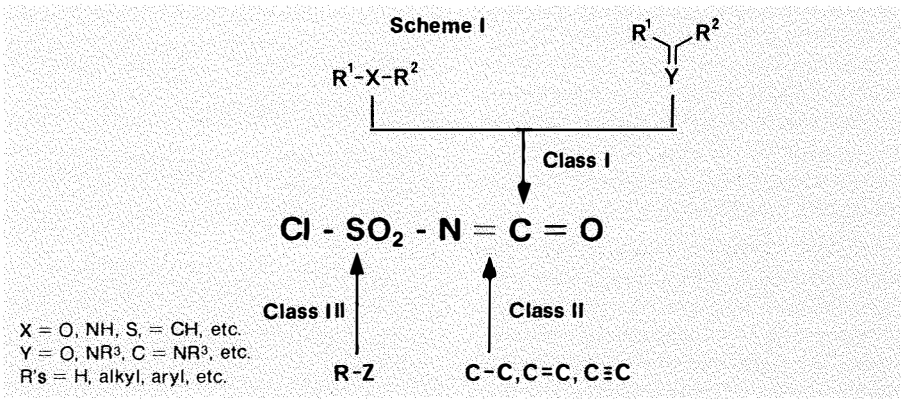
Chlorosulfonyl isocyanate is a clear, colorless, mobile liquid which freezes at -43°C and boils at 107-108°/760mm (38°/50mm).[2b] It shows no sign of thermal decomposition up to 300°. CSI fumes slightly on exposure to humid air, but reacts *violently* with water. Solvents which are generally inert to CSI include aliphatic, aromatic, and chlorinated hydrocarbons, diethyl ether (but not tetrahydrofuran), and acetonitrile. The high reactivity of CSI precludes the use of protic solvents.

Chlorosulfonyl isocyanate has enabled a wide variety of useful and often novel synthetic transformations. For clarity, reactions will be classified according to the probable site of initial attack on the CSI molecule by a given nucleophile, as depicted in Scheme I. Accordingly, Class I reactions will involve initial attack on the isocyanate carbon atom; Class II reactions will include formal [2+2] cycloadditions of carbon-carbon bonds across the isocyanate C=N bond; and Class III reactions of CSI will include the relatively few reported examples of nucleophilic additions to the sulfur atom. These are, of course, somewhat arbitrary classifications intended to facilitate an organized presentation of chlorosulfonyl isocyanate chemistry.

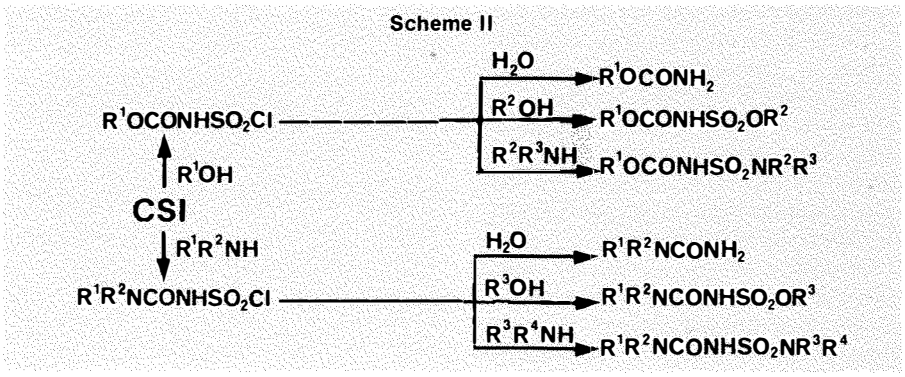
Class I: Nucleophilic Addition to the Isocyanate Carbonyl

CSI undergoes the expected nucleophilic additions by **alcohols, phenols,** and **amines.**[2] The resulting *N*-chlorosulfonyl derivatives may be subsequently functionalized, as shown in Scheme II. The use of CSI thus enables the formal insertion of the $-CONHSO_2-$ linkage between alcohol and/or amine functional groups. The reac-

Scheme I



Scheme II



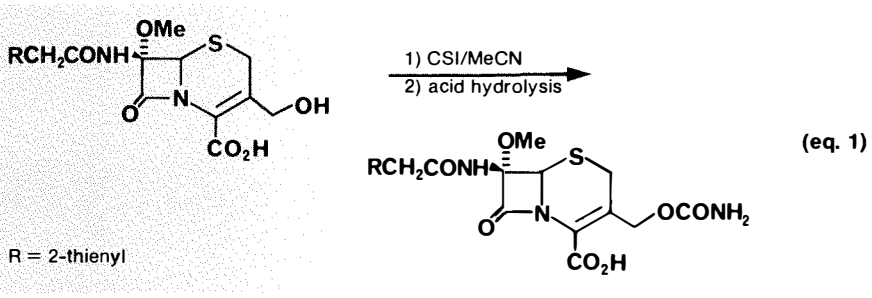
tivity of CSI with **alcohols** is so great that primary alcohols can be derivatized in the presence of other functionalities. In addition, reaction with CSI generally does not alter the stereochemistry at other centers, even of complex molecules. The examples shown in equations 1[3] and 2[4] illustrate this selectivity. A synthesis of the oxazolones **2** depends on the facile reaction of CSI with the alcoholic function of **α-hydroxy ketones** (equation 3).[5] Ring closure of the resulting carbamates (**1**) was accomplished by heating at 175-250°.

The novel reagent **4**[6] (Scheme III), prepared by the reaction of CSI with methanol followed by treatment of the resulting (in 92% yield) carbamate **3** with triethylamine, has been used by Burgess[6] to synthesize carbamates from primary alcohols and to dehydrate secondary alcohols. Intermediate **3**, itself a useful reagent,[7] has been used for the preparation of heterocycles **5**,[7a] **6**, and **7**. The ratio of **6** to **7** is both temperature and solvent dependent.[7b] Compounds such as **3** which are derived from certain **phenols** (*e.g.*, 2,4,6-trichlorophenol) are claimed to be useful bactericides and fungicides.[8] They may be further functionalized by treatment with alcohols, as shown in equation 4. Heating the resulting carbamates **8** above 100° produces alkoxysulfonyl isocyanates **9** in 47-77% overall yields.[9]

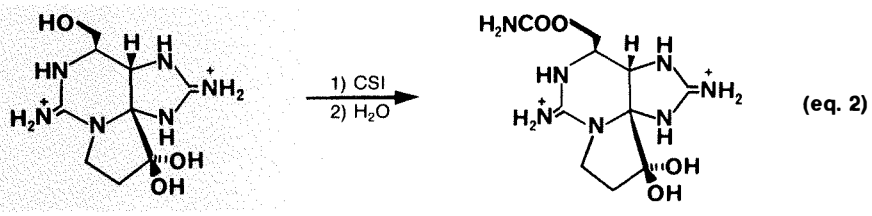
The reaction of CSI with **mercaptans** affords *thio*carbamates **10**, intermediates for the synthesis of potential herbicides (*e.g.*, **11**, equation 5[10]).

The reaction of CSI with **ketals** results in the insertion of the -*CON*(SO_2Cl)- linkage between oxygen and carbon atoms of the ketal functional group.[11] This transformation has been used by Hall *et al.*[11b] for the net conversion of the isopropylidene-protected sugar **12** (equation 6) to its corresponding 1,2-carbonate (**13**).

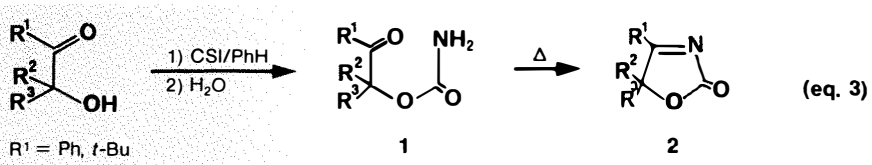
Aromatic compounds that readily undergo electrophilic substitution react with chlorosulfonyl isocyanate to produce the corresponding *N*-chlorosulfonyl carboxamides **14** (equation 7). Lohaus[12] has demonstrated that these intermediates can be converted *in situ* to nitriles in good overall yields by treatment with dimethylformamide. The method is characterized by mild reaction conditions (15-20°) and facile workup (quenching with ice and extraction). A related sequence converts enolizable **ketones** (equation 8[13]), certain cyclic **enamides** (*e.g.*, **15** in equation 9[14]), and **carboxylic acids** (equation 10[15]) to the corresponding nitriles. In the case of the latter the intermediate **16** is often stable enough to be isolated, depending on the nature of the starting acid.[15] Faubl[16] has



(eq. 1)

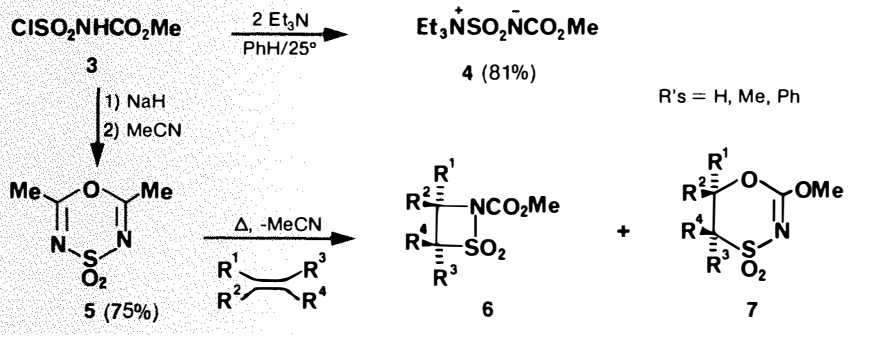


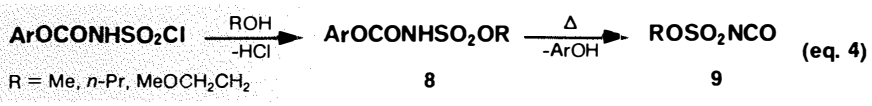
(eq. 2)



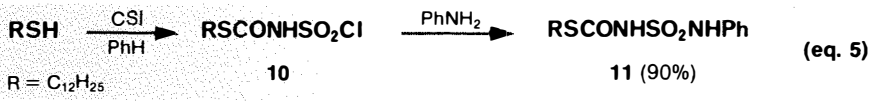
(eq. 3)

Scheme III

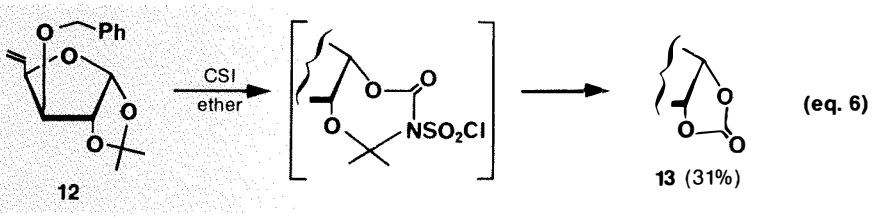




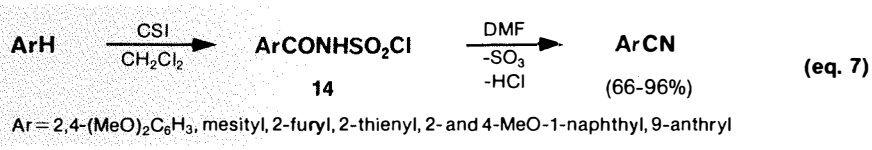
(eq. 4)



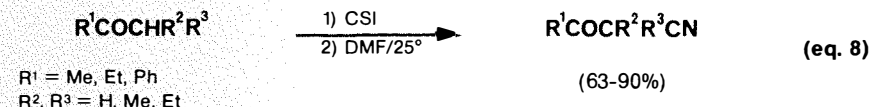
(eq. 5)



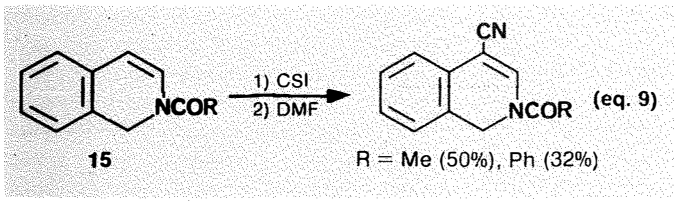
(eq. 6)

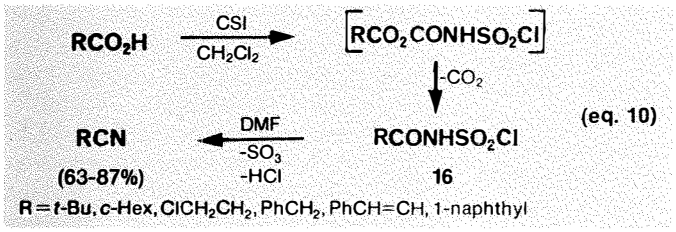


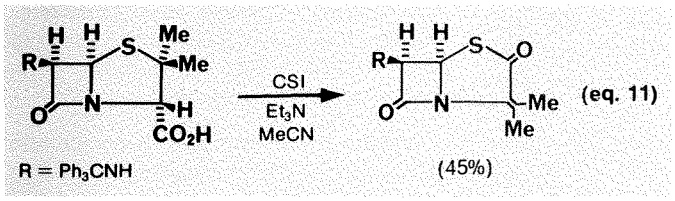
(eq. 7)

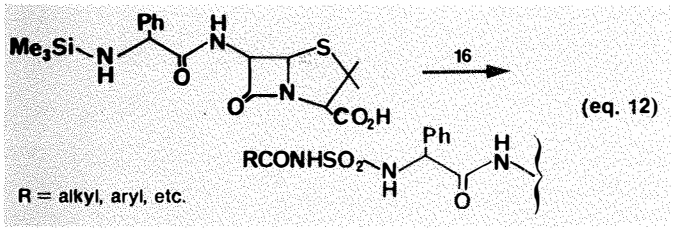


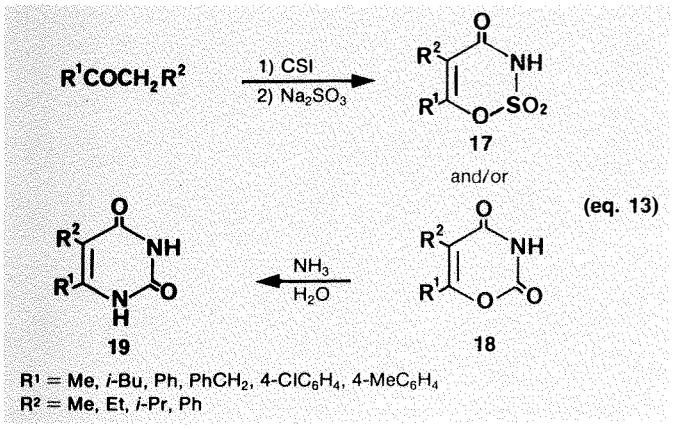
(eq. 8)

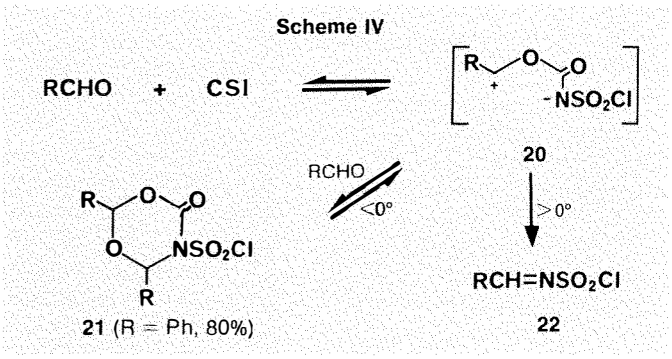


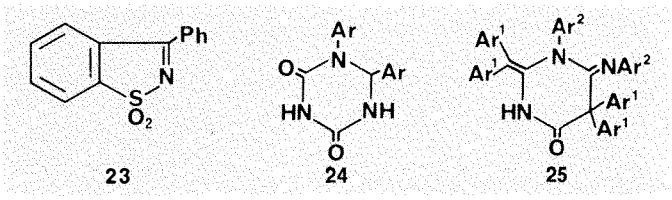


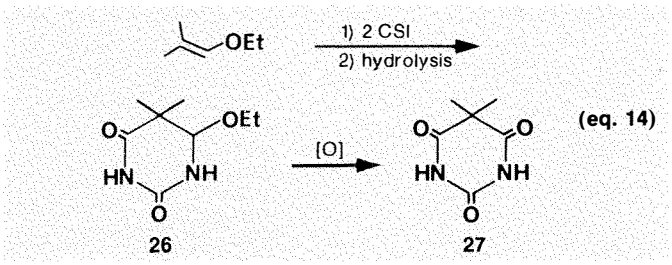


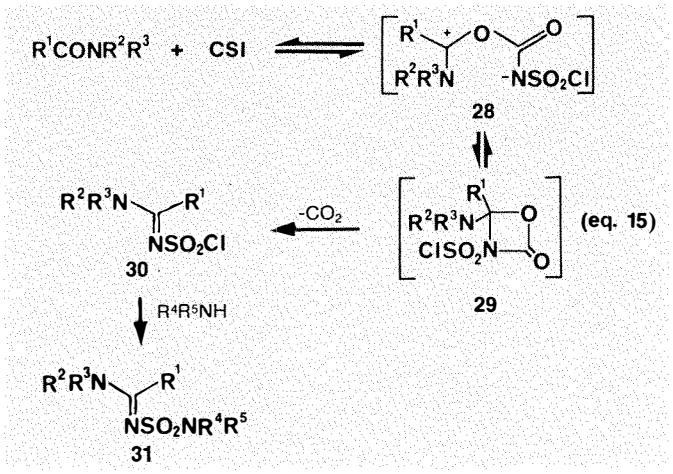












recently reported an anhydropenicillin rearrangement (equation 11) induced by chlorosulfonyl isocyanate, which is thought to proceed *via* an intermediate of type **16**. As an interesting aside, intermediates such as **16** can also displace *N*-trimethylsilyl groups under mild conditions. An example is given in equation 12.[17]

A variation of equation 8 provides either the potential "third-generation" sweeteners[18] **17** or substituted uracils **19** (derived from products **18**), as outlined in equation 13.[19] The ratio of **17** to **18** is dependent on the nature of the substituents on the starting ketone and on the solvent. This work by Hassner and Rasmussen is a particularly striking example of the versatility of chlorosulfonyl isocyanate for the synthesis of useful intermediates from readily accessible starting materials.

The reaction of CSI with certain **aldehydes**[20] can also be included in Class I, since evidence recently published by Clauss *et al.*[11a] suggests that products **21** and **22** (Scheme IV) are derived from 1,4-dipolar intermediates **20**, the apparent result of nucleophilic attack by the aldehydic carbonyl on the isocyanate carbon atom. The reaction of benzophenone with CSI in nitrobenzene at 130° produces benzoisothiazole **23**,[11] probably *via* cyclization of the diphenyl *ketimine* corresponding to **22**. Such species can be isolated from the reaction of CSI (and other activated isocyanates) with **γ-pyrones**.[21] *N*-Aryl **imines** and **ketenimines** afford (after removal of the *N*-chlorosulfonyl group) heterocycles of types **24**[22] and **25**,[23] respectively. A similar cyclization takes place with ethyl isobutenyl ether to produce, after oxidation of intermediate **26** (equation 14), dimethylbarbituric acid (**27**).[2b] This is an interesting, but atypical (*vide infra*), mode of addition of an olefin to CSI. Products which are analogous to **26** have also been obtained from certain *sulfur*-substituted olefins.[24]

Dipolar intermediates have been postulated for the reaction of CSI with *N,N*-**dialkylamides**.[25] As shown in equation 15, collapse of dipole **28** to form the unstable **29**, followed by loss of carbon dioxide, produces the observed amidines, **30**. The amidines can be further functionalized to prepare derivatives of type **31**, which have been claimed to exhibit insecticidal and acaricidal activity.[26]

Class II: Net [2+2] Cycloaddition of Carbon-Carbon Bonds to the Isocyanate C=N

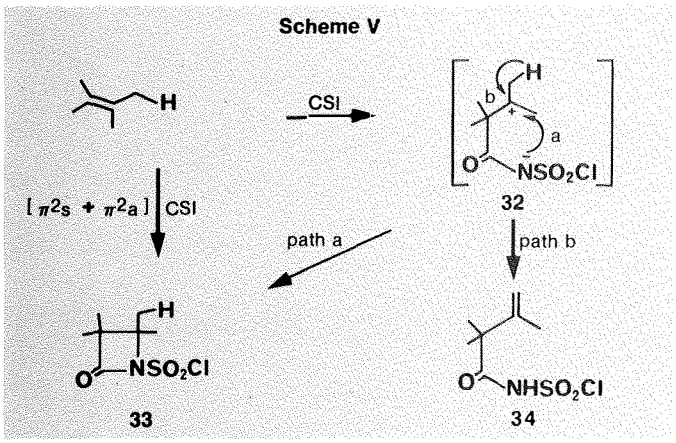
The ability of chlorosulfonyl isocyanate to undergo cycloaddition to carbon-carbon bonds adds another dimension to its usefulness. The most studied case to date is the net [2+2] cycloaddition of CSI to a wide variety of olefins to produce β-lactams (**33**, Scheme V).[27] Adducts of type **34** are common by-products. Their proportion in the product mixture appears to be a function of the pattern and type of substitution on the olefin. For example, the ratio of **33** to **34** has been determined by Graf[28] for the following olefins: **35**, 50:50; **36**, 65:35; **37**, 70:30; **38**, 80:20; and **39**, *ca.* 100% β-lactam.

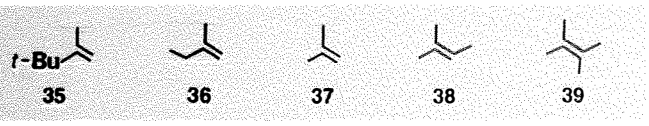
Both concerted[28] (involving orthogonal approach of the CSI and olefin π orbitals[29]) and nonconcerted, 1,4-dipolar[20,30] (*via* **32**) mechanisms have been proposed for these reactions. It seems likely that either or both mechanisms may be operative, depending on the substitution (and, hence, charge stabilization) of the olefin.[31] The cycloadditions are highly stereo- and regiospecific: the *cis* adduct is always formed, and addition takes place in such a way that the most stable carbonium ion would be generated.[2] The examples cited in equations 16 through 25[32-37] illustrate the utility and high specificity of Class II reactions of chlorosulfonyl isocyanate. Note that reductive hydrolysis of the initial cycloadduct to the corresponding N-unsubstituted β-lactam can be accomplished by employing a two-phase system consisting of organic solvent and aqueous sodium sulfite, the latter being kept slightly basic by the addition of KOH.[38] Note, too, that the low temperatures indicated in several of the examples are necessary to preclude Wagner-Meerwein rearrangement of the intermediate *N*-chlorosulfonyl β-lactams. Vinylcyclopropanes (including **40**) are particularly prone to rearrangement, especially when the reaction with CSI is conducted at or above room temperature (see, for example, equations 26 and 27[39]).

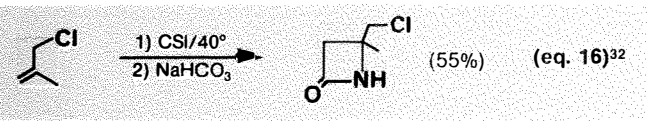
Heterosubstituted β-lactams, which comprise the fundamental nucleus of the penicillin and cephalosporin antibiotics, may be prepared by the reaction of CSI with a variety of vinyl esters (**41**, equation 28).[40] The acyloxy substituent of the resulting β-lactams (**42**) may be selectively replaced by a variety of nucleophiles (*e.g.*, RCO_2^-, RSO_2^-, N_3^-, RO^-, and RS^-) in good to excellent yields, leaving the four-membered ring intact.

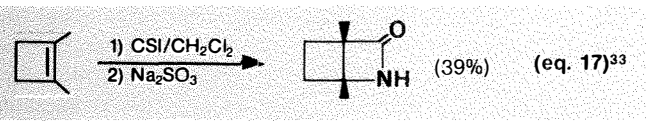
In view of the stereospecific cis addition of chlorosulfonyl isocyanate to olefins and

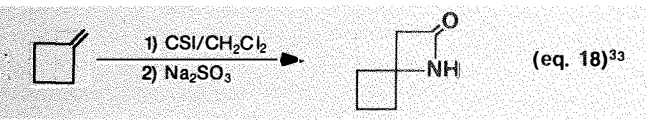
Scheme V

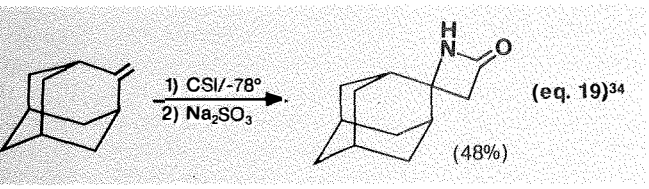


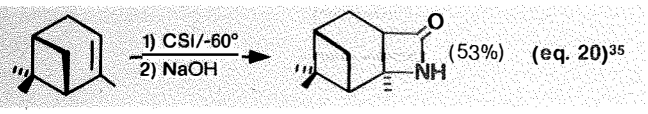


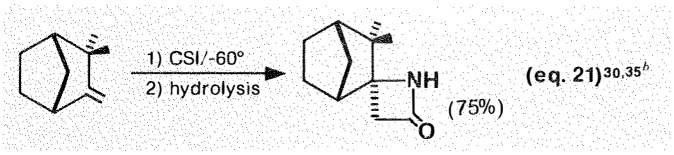


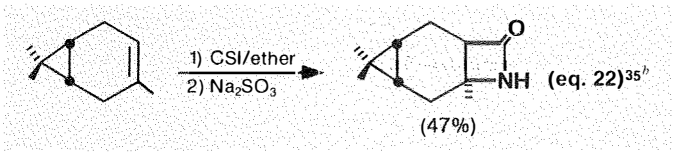


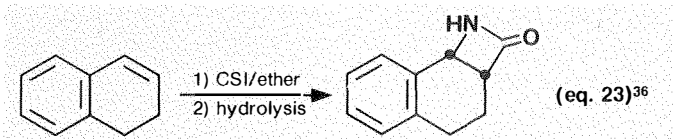


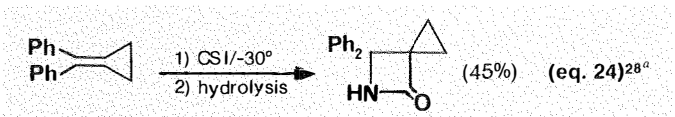


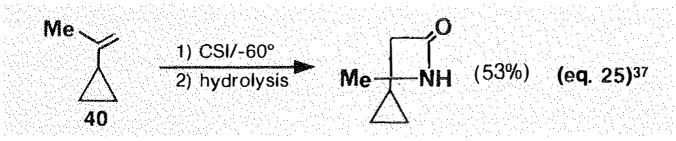


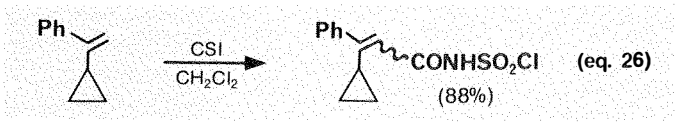


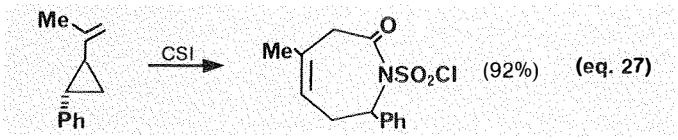


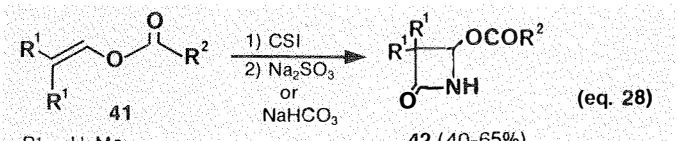












R1 = H, Me
R2 = Me, Et, *i*-Pr, *t*-Bu, Ph

the facile cleavage of the resulting β-lactams, this versatile reagent provides a convenient route to *erythro*- and *threo*-β-amino acids (**43**, equation 29).[41]

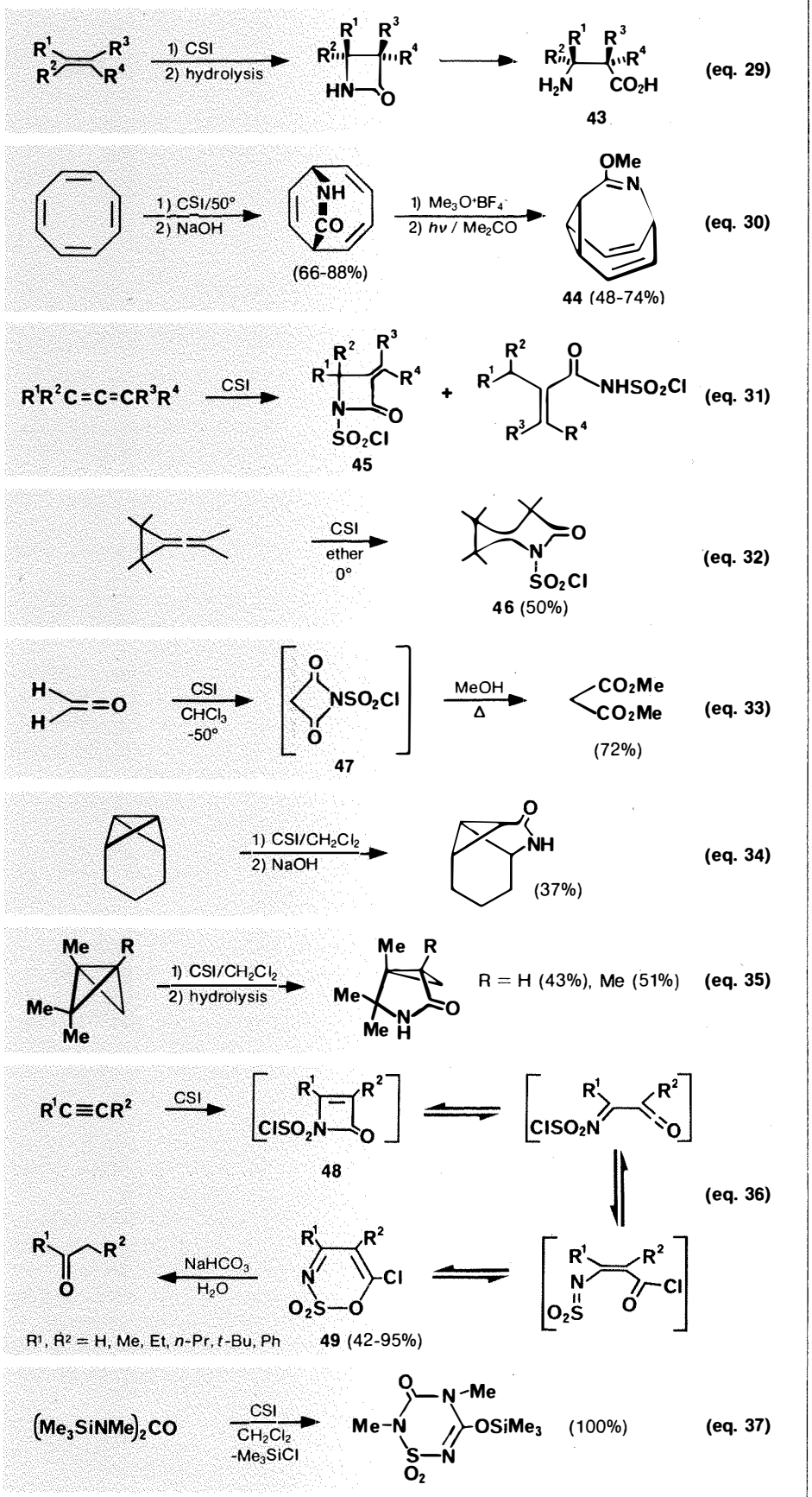
The uniparticulate electrophile CSI can be an extremely useful reagent for the generation and intramolecular trapping of carbonium ions in **polyenes**. Paquette[42] has amply demonstrated this use of CSI as a *mechanistic probe* in his studies of molecules such as bullvalene,[42a] barrelene,[42b] and homobarrelene.[42c] A practical synthesis of methoxyazabullvalene **44** (equation 30) has emerged from this research on fluxional systems.[43]

Reaction of CSI with residual olefinic bonds in certain **polymers**, followed by cleavage of the chlorosulfonyl groups from the resulting β-lactam units, has been claimed to enhance the resistance of some natural and synthetic rubbers to thermal and physical stress.[44] In addition, chlorosulfonyl isocyanate has been used as a probe for the study of polymer microstructure in certain rubbers.[45] Recently, CSI has figured in the preparation of desalination membranes from a variety of polyisoprenes.[46]

CSI reacts with *cumulated* double bonds to produce a multitude of interesting compounds. For example, simple **allenes** react quickly at room temperature to afford mixtures of β-lactams (**45**) and α,β-unsaturated amides, as shown in equation 31.[47] The lactams generally predominate. Cyclopropylidene derivatives are exceptions[48] in that they react with CSI to produce "reversed" regioisomers such as **46** (equation 32[48b]), the apparent result of electrophilic attack by CSI at a *terminal* allenic carbon atom. Mundlos and Graf[49] have suggested that the reaction of **ketene** with CSI at low temperature produces the unstable imide **47**,[50] which is readily transformed into malonic acid derivatives, as shown in equation 33.

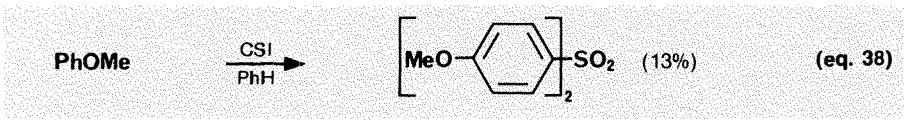
Strained, carbon-carbon single bonds of certain **bicyclic hydrocarbons** undergo formal cycloaddition reactions with chlorosulfonyl isocyanate as a consequence of their high degree of p character.[51] The products obtained are often novel heterocycles which might be difficult to prepare by other methods. Examples taken from Paquette's work[51b] are given in equations 34 and 35 (the major products are indicated).

CSI reacts with most **acetylenes** to produce good yields of 1:1 adducts **49**, probably *via* the intermediates shown in equation 36.[52] Although it was claimed[53] that intermediates of type **48** could be isolated from the reaction mixture, the species isolated were shown by Moriconi and Shimakawa[52] to be products **49**. The hydrolysis of such products affords ketones, as indicated in equation 36. Interestingly, CSI reacts only with the *acetylenic* function of 1-octen-4-yne: an equimolar mixture of these two materials in CH_2Cl_2 produced only **49**, R^1 = *n*-Pr, R^2 = $CH_2CH{=}CH_2$.[52]

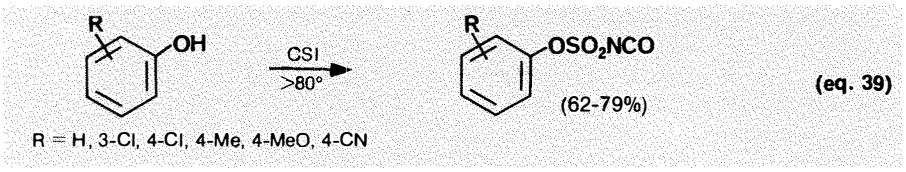


Class III: Nucleophilic Addition to Sulfur

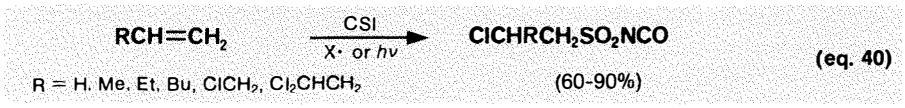
Compounds that are unreactive toward the isocyanate moiety of CSI may react with the chlorosulfonyl group. Equations 37[54] and 38[55] depict reactions whose products are probably derived from this mode of addition. Certain experimental conditions also promote Class III reactions. Equations 39[56] and 40[57] illustrate such additions to CSI under the influence of high temperature and free-radical conditions, respectively.



(eq. 38)



(eq. 39)



(eq. 40)

Conclusion

Considering the rich chemistry of chlorosulfonyl isocyanate, and now its inexpensive and ready commercial availability from Aldrich, it is safe to predict that CSI will enjoy many more "anniversaries" as one of the most useful reagents in synthetic organic chemistry.

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About the Author

William A. Szabo received his Ph.D. degree in organic chemistry from the University of Florida in 1974. He did postdoctoral work at Wesleyan University with Professor Max Tishler before joining Aldrich. Dr. Szabo's interests span synthetic and medicinal organic chemistry, in particular, new reagents, synthetic strategy, and drug design.

It is easy to exaggerate the dangers of new inventions and to forget that we have learned to live with the hazards of familiar materials. In Newsletter 70 I reprinted an article which assumed that coal had just been discovered but that nuclear energy had been in use for a long time. In the following, we assume that water, in the pure form, has been unknown — there are no seas, no rivers, no lakes — and has just been discovered.

NEW FIRE-FIGHTING AGENT MEETS OPPOSITION
"COULD KILL MEN AS WELL AS FIRES"

T. A. Kletz
Division Safety Adviser
Imperial Chemical Industries Limited

ICI has announced the discovery of a new fire-fighting agent to add to their existing range. Known as WATER (Wonderful And Total Extinguishing Resource), it augments, rather than replaces, existing agents such as dry powder and BCF which have been in use from time immemorial. It is particularly suitable for dealing with fires in buildings, timber yards and warehouses. Though required in large quantities, it is fairly cheap to produce and it is intended that quantities of about a million gallons should be stored in urban areas and near other installations of high risk ready for immediate use. BCF and powder are usually stored under pressure, but WATER will be stored in open ponds or reservoirs and conveyed to the scene of the fire by hoses and portable pumps.

ICI's new proposals are already encountering strong opposition from safety and environmental groups. Professor Connie Barrinner has pointed out that, if anyone immersed their head in a bucket of WATER, it would prove fatal in as little as 3 minutes. Each of ICI's proposed reservoirs will contain enough WATER to fill half a million two-gallon buckets. Each bucket-full could be used a hundred times so there is enough WATER in *one* reservoir to kill the entire population of the UK. Risks of this size, said Professor Barrinner, should not be allowed, whatever the gain. If the WATER were to get out of control the results of Flixborough or Seveso would pale into insignificance by comparison. What use was a fire-fighting agent that could kill men as well as fires?

A Local Authority spokesman said that he would strongly oppose planning permission for construction of a WATER reservoir in this area unless the most stringent precautions were followed. Open ponds were certainly not acceptable. What would prevent people falling in them? What would prevent the contents from leaking out? At the very least the WATER would need to be contained in a steel pressure vessel surrounded by a leak-proof concrete wall.

A spokesman from the Fire Brigades said he did not see the need for the new agent. Dry powder and BCF could cope with most fires. The new agent would bring with it risks, particularly to firemen, greater than any possible gain. Did we know what would happen to this new medium when it was exposed to intense heat? It had been reported that WATER was a constituent of beer. Did this mean that firemen would be intoxicated by the fumes?

The Friends of the World said that they had obtained a sample of WATER and found it caused clothes to shrink. If it did this to cotton, what would it do to men?

In the House of Commons yesterday, the Home Secretary was asked if he would prohibit the manufacture and storage of this lethal new material. The Home Secretary replied that, as it was clearly a major hazard, Local Authorities would have to take advice from the Health and Safety Executive before giving planning permission. A full investigation was needed and the Major Hazards Group would be asked to report.

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On crown ether nomenclature. . . .

June 8, 1977

Aldrich Chemical Company, Inc.
940 West Saint Paul Avenue
Milwaukee, Wisconsin 53233

Dear Sirs:

I am writing with respect to your advertisements and "Aldrichimica Acta," which so many organic chemists read with both enjoyment and profit. Because of their general high quality, they exert a noticeable influence. I hope, therefore, that you will allow me to call your attention to a particular flaw by which, unwittingly, you are the source of some harm to the orderly development of organic chemistry.

I refer to crown ethers and the name given to one of them. The name "dicyclohe*xyl*-18-crown-6" is consistently used in your articles and advertisements for the hydrogenated derivative of dibenzo-18-crown-6. The latter name, although not of official status, violates no general principle of nomenclature, but the former is simply a misnomer, perpetrated unthinkingly by Pedersen in his original publication. In this name, "cyclohexyl" is used for a compound that contains no cyclohexyl group. It is as unacceptable and deceptive as to use "cyclohexylbenzene" for tetralin. If someone should ever make, perhaps even market, an 18-crown-6 ether with two cyclohexyl substituents, which should properly bear the name dicyclohexyl-18-crown-6, there would be intolerable confusion. The name that Pedersen should have used is, of course, "dicyclohe*xano*-18-crown-6," and it was an unfortunate oversight on the part of the referees and editor not to have caught this lapse. The consequence has been the mindless perpetuation of this nomenclatural barbarism by large numbers of chemists who should know better. This situation is particularly discouraging to those of us who teach chemistry, and try to instill in young chemists an appreciation for the elementary rules of unambiguous nomenclature.

I hope I can enlist your sympathetic aid in this matter. I hope it is clear that I am not at all concerned with the general system of "crown" nomenclature, which is widely useful, and must eventually stand or fall on its own merits. It is only the improper use of "cyclohexyl," in a way that violates the most elementary principles of any nomenclature system, that I wish to blow the whistle on. If you would just change the name of your compound 15,840-2 to "dicyclohexano-18-crown-6," the teachers of organic chemistry will bless you!

Sincerely yours,

Peter A.S. Smith
Professor of Chemistry
The University of Michigan
Member, ACS Nomenclature Committee

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Aldrichimica Acta

Volume 10, Number 3, 1977

Deuterium NMR. **See page 35.**
Selective Reductions Using Borane Complexes. **See page 41.**

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About Our Cover:

One of the great differences between the Bible and the histories of most peoples is the forthrightness with which the Bible describes its heroes. The Biblical heroes are described as very human, with frailties and sins often surpassing those of ordinary people. King David, the great psalmist, is considered one of the greatest of Biblical kings. His greatest weakness involved sex, and it is interesting to compare the two best known of his eighteen wives, Bathsheba and Abigail. Each was married when she met David. Bathsheba, David's most famous wife, was willing to commit adultery (and may have enticed David to do so) and stood by idly in her husband's murder. Abigail, by contrast, saved her churlish husband Nabal, though she could not save him from his own greed: he suffered a stroke when he heard of all the provisions Abigail had given to David and his band of outlaws. Jewish tradition says that the four women of surpassing beauty were Sarah, Rahab, Abigail and Esther, and one cannot but wonder what David's life would have been like if he had loved only that beautiful, sensitive and intelligent woman.

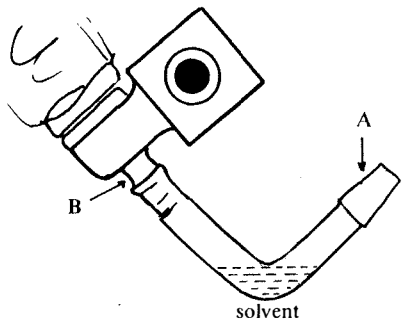
This painting (oil on copper, 19-3/4 x 31-1/4 inches) by Frans Francken the Younger, signed and dated 1630, depicts the first encounter of Abigail with David, when she and her maidens bring provisions to appease him. Particularly amusing is David depicted as a medieval knight complete with a banner bearing a harp.

Are you interested in our Acta covers? *Selections from the Bader Collection,* with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

We wish to report a quick and easy method for cleaning a rotary evaporator. A bent connecting tube (distilling apparatus adapter A) is attached to the spindle B. Vacuum is applied on the rotary evaporator. Solvent is introduced through A with a wash bottle. The opening at A is



blocked with the thumb until vacuum develops. Controlled release of thumb pressure causes the wash liquid to be aspirated into the condenser. This method consumes little solvent and cleans even the upper parts of the condenser.

Thierry M. de Theux and
Jacques H. Poupaert
Department of Medicinal Chemistry
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A disturbing problem in overnight chromatographic column operation is the difficulty in adjustment of the stopcock to give a consistent flow rate over long periods of time. A dependable and inexpensive solution to this problem involves the attachment of a length of small-diameter tubing such as polyethylene catheter tubing (.07″ i.d.) to the bottom of the column.

The tubing should be at least as long as the column and the free end of the tubing raised to a level slightly below the solvent level on the column. The tubing can be attached to the bottom of the column with a short length of rubber tubing or a suitable plastic adapter. By opening the stopcock completely and raising or lowering the end of the small-diameter tubing, the flow rate can be accurately adjusted from no flow to the maximum flow rate of the column. Since there is no constriction in the tubing, small particles in the effluent cannot stop the flow as frequently occurs in a partially closed stopcock. A uv monitor can be easily spliced in series with the tubing leading from the column to the fraction collector. A constant-level, "chicken feeder" type solvent supply system such as an inverted volumetric flask should be used to add solvent to the column.

Robert D. Elliott
Southern Research Institute
Birmingham, Alabama 35205

The difficulty and inconvenience associated with accurate control of slow addition using standard addition funnels lead many to use the more expensive Hershberg funnel or a syringe pump. A simpler solution providing excellent results is the following: the plug of an ordinary addition funnel is scored with a file to about 90° around from one hole; this procedure is repeated on the other side. The flow rate is now much more finely metered. A uniform scratch gives a flow proportional to plug rotation; a tapered one provides a larger range of flow rates. In either case, the exact dimensions and alignment are not critical. The same technique works equally well for Teflon® plugs; here a razor blade may prove more effective than a file.

Alaric Naiman
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Berkeley, CA 94720

Many laboratory-scale reactions are carried out at Dry-Ice/acetone temperatures over periods of several hours. The scale of these reactions is frequently such that the reaction flask will not fit into normal-size Dewar vessels, and large Dewar vessels are expensive. We have found that a large crystallizing dish placed in a cardboard, or preferably wooden, box and surrounded by vermiculite (often obtainable as the packing around chemicals) is ideal for such cold baths. A cardboard top taped or nailed to the box and with a hole cut for the crystallizing dish ensures that the vermiculite remains in place. Vermiculite has the advantage over polystyrene in that it does not "dissolve" during solvent spill-over. This apparatus can also be used with a magnetic stirrer whereas, with Dewar vessels, this is often difficult.

P. Horsewood
Department of Chemistry
McMaster University
Hamilton, Ontario L8S 4M1

When extracting with chloroform from an aqueous phase of a very darkly colored reaction mixture, the problem of determining the point of division between the two phases in the separatory funnel often arises.

Given that a reasonably good phase separation has taken place, a small quantity of Celite filter-aid added through the top of the separatory funnel will settle down between the two phases, thus clearly delineating the point of separation. The Celite can later be filtered off.

James P. Hasak
270 Baldwin Road
Parsippany, NJ 07054

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 red and white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Defra Bader.

A number of biochemists had talked to me about the great usefulness of methotrexate (MTX, amethopterin) in the isolation of enzymes by affinity chromatography [B.T. Kaufman and J.V. Pierce, *Biochem. Biophys. Res. Commun.*, **44**, 608 (1971); B.T. Kaufman and V.K. Kemerer, *Arch. Biochem. Biophys.*, **172**, 289 (1976); B.T. Kaufman, *Methods Enzymol.*, **34**, 272 (1974)].

The only difficulty was that methotrexate was selling at hundreds of dollars per gram! The synthesis is quite involved and of many steps, but we are happy to be able to help. We now offer methotrexate at $62/g and we'll be able to reduce the price substantially for larger quantities.

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

Deuterium NMR - A Useful Technique in Chemistry, Physics, and Biology

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INTRODUCTION

Deuterium nmr has been much neglected as a means to study chemical structures and processes. Its enormous potential was demonstrated in a thorough report by Diehl and Leipert in 1964,[1] but due to the unavailability of spectrometers and to an ingrained prejudice in nmr textbooks it has only come to the fore in the last five years. A recent comprehensive review cites 350 references.[2]

The nuclear moment of ^2H is considerably lower than that of ^1H; it resonates at 15 M Hz in a magnetic field of 23 kG. Its detection sensitivity relative to ^1H is 0.00965. This, combined with a natural abundance of 0.015%, makes detection in unenriched compounds relatively difficult.[3] Nonetheless, ordinary tap water yields a signal-to-noise ratio of 2/1 for a single scan of ^2H at natural abundance;[2] as we shall see later this can cause difficulties in some experiments where H_2O is used as a solvent. With the availability of sensitive FT spectrometers detection of deuterium has become routine. Enrichment in ^2H is reasonably inexpensive, and becomes more so as the use of deuterated compounds increases.

Deuterium has a quadrupole moment, albeit relatively small; the quadrupole coupling constant varies from 130 to 210 kHz depending upon the chemical nature of the compound.[2] The quadrupole moment was presumed to be a source of prohibitively broad resonances as it will dominate the relaxation behavior of ^2H. However, for small molecules line widths of 0.5-2 Hz are common. Some of the broad resonances observed previously were due to the presence of unresolved ^1H-^2H couplings which are easily removed by ^1H- decoupling.

The low magnetogyric ratio of ^2H leads to spin-spin couplings much lower than those observed for ^1H; ^2H-^1H and ^2H-^2H couplings will be only 15% and 2.3%, respectively, of their ^1H-^1H analogs. This greatly simplifies ^2H spectra. Although ^2H chemical shifts are essentially identical in ppm to those of the corresponding ^1H, the scale in Hz is only 15% of that of ^1H. The greatly reduced or unobservable spin-spin couplings compensate partly for this apparent disadvantage. In the analysis of complex ^1H spectra the chemical shifts of ^2H, which are easily determined, yield a valuable starting point.[3,4]

Deuterium chemical shifts are as sensitive as those of ^1H to conformation or configuration, although small differences may be masked by the greater line widths of large molecules.[2] ^2H nmr has been used to follow the paths of chemical reactions[5-7] and is particularly valuable when exchange of hydrogen is incomplete.It is an excellent method to distinguish simply the degree of exchange of two very similar hydrogens.[6,7] As an isotopic tracer in metabolic or biosynthetic studies ^2H is an inexpensive substitute for ^{13}C.[8]

The spin-spin and spin-lattice relaxation times (T_1 and T_2, respectively) of ^2H are useful in studies of molecular dynamics as they are completely dominated by a quadrupolar exchange mechanism.[9] They are insensitive to the presence of oxygen and less sensitive than those of ^1H and ^{13}C to the presence of paramagnetic metal ions.[1,2] The relatively short T_1 values of ^2H[9,10] allow rapid data accumulation in the pulsed Fourier transform mode of acquisition.

In highly ordered systems such as lyotropic liquid crystals[11] or biological membranes[12] the partially averaged quadrupole splittings of ^2H yield valuable estimates of the degree of molecular order. For highly symmetric ions (such as ND_4^+) interacting with colloids or ionic surfaces, similar quadrupolar splittings are indicative of distortions from tetrahedral or cubic symmetry.[13]

SOME CHEMICAL APPLICATIONS

A classic example of the usefulness of ^2H nmr was reported in pre-Fourier transform days by Montgomery *et al.*[14] They explored the mechanism of substitution of cyclic olefinic halides with strongly basic nucleophiles. Three mechanisms are possible: (1) direct substitution, (2) formation of a cycloalkyne intermediate or (3) formation of a cycloallene intermediate. Direct substitution of Cl in 1-chlorocycloheptene-

*Issued as NRCC Publication Number 16204.

2,7,7-d_3 (**A**) (See Scheme I) by the phenyl moiety of phenyllithium would yield **B** whose ^2H nmr spectrum would comprise two groups of resonances of relative intensity 2:1, the former in the allylic and the latter in the olefinic region. Allenic elimination of chlorine and subsequent addition to the center of the allenic system would lead to **C** with resonances in similar positions but of relative intensities 1:1. Cycloalkyne formation at carbon-1 would lead to two possible products **D** and **E** depending upon how phenyllithium added to the triple bond. The ^2H nmr spectrum of the product revealed two resonances of equal intensity at δ= 2.50 and 2.80 ppm in agreement with the cycloalkyne pathway.

More recently Stothers and coworkers have investigated the mechanism of homoenolization in bicyclic ketones.[6,7] In both studies the shift reagent $Pr(fod)_3$ was used to obtain better dispersion of the ^2H resonances. A ^2H nmr spectrum of fenchone-$d_{1.94}$ is shown in Figure 1. Even with the aid of the shift reagent some overlap of resonances is evident. The spectra were computer-simulated using the input resonances shown below the experimental and calculated composite spectra. The degree of substitution as a function of time was thus measured, and the results are summarized in Table 1. Note that for shorter reaction times substitution of the *endo* and *exo* protons at position 6 showed a preference for the *exo* proton, whereas after three hundred hours the two were equally exchanged. A strong preference for the *exo* methyl group was maintained. The authors claimed an accuracy of 1-2% for this method.

Scheme I

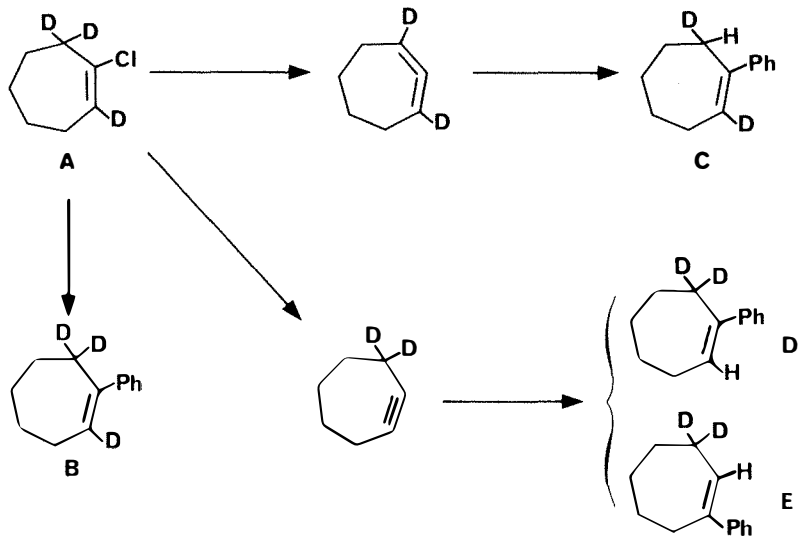


TABLE 1
Quantitation by ^2H-NMR of ^2H Incorporation in Fenchone as a Function of Reaction Time.[7]

	C-6		CH_3			
Time (h)	*Exo*	*Endo*	Total	*Exo*	*Endo*	Bridge
10	0.26	0.08	0.01_8			
20	0.34	0.12	0.02_5			
40	0.70	0.38	0.10	0.09		0.01
100	0.75	0.58	0.33	0.26	0.05	0.01_8
200	0.68	0.68	0.39			
300	0.65	0.64	0.65	0.42	0.16	0.06

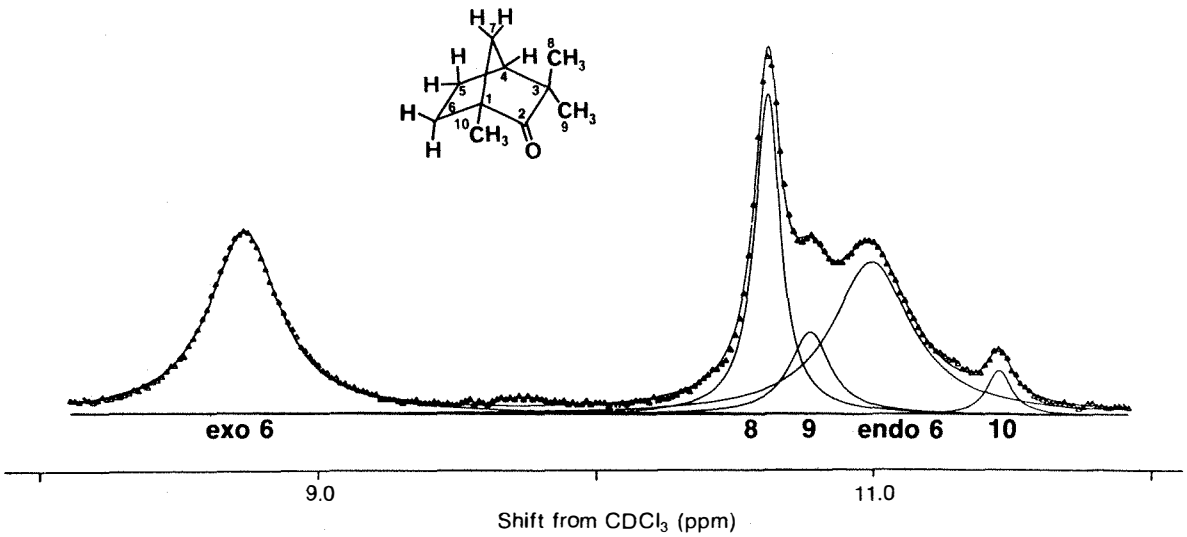


Figure 1 Experimental (Δ) and computer-fitted (—) ^2H nmr spectra (15.4 MHz) of fenchone-$d_{1.94}$ containing 0.26 equivalent of $Pr(fod)_3$. The spectrum was obtained with noise-modulated ^1H-decoupling in a solvent system of $CHCl_3$:C_6F_6 (1:4 v/v). Individual Lorentzian curves for each absorption are shown beneath the composite envelope.[7]

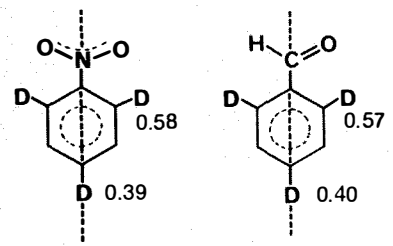
The mechanism of formation of nortricyclanone during deamination of 2-*exo*-aminonorbornan-3-one was elucidated by Edwards *et al.*[15] Figure 2 shows the ^2H nmr spectra of the product with and without ^1H-decoupling. The resonance at 1.3 ppm is clearly coupled to a geminal proton (^2J = 1.5 Hz) whereas the resonance at 1.5 ppm is broadened due to three unequal and small vicinal couplings. This demonstrates that the product has the structure shown in Figure 2. The positions of deuteration were confirmed by ^{13}C nmr which, however, could not distinguish whether the *endo* or *exo* proton at position 6 had been substituted.

Using ^2H nmr DePuy and coworkers[16] presented evidence for an asymmetrical, nonrotating, corner-protonated cyclopropane intermediate in the electrophilic ring opening of substituted cyclopropanes by $^2H^+$.

MOLECULAR DYNAMICS

The relaxation behavior of ^2H is totally dominated by a quadrupolar mechanism and therefore is indicative of molecular dynamics (internal and/or overall motion) at the position of substitution. This makes interpretation of relaxation data much simpler for ^2H than for ^1H or ^{13}C. For the simplest case of rapid isotropic motion, $1/T_1(^2H) = (3e^2qQ/8h)^2\tau_c$, where e^2qQ/h is the quadrupole coupling constant in radian sec^{-1} and τ_c is the correlation time for rotation of the C-^2H bond. As a rule of thumb one can say the longer is T_1, the more mobile is the C-^2H bond. For more complex or slower motions the relationships become more complicated.[2]

Mantsch *et al.* measured the T_1 values for a wide range of deuterated compounds.[9,10] The data for benzaldehyde and nitrobenzene are shown below. The inequality of the T_1 values for the *ortho* and *para* deuterons is in each case due to



^2H T_1's (sec)

anisotropic motion of the molecules, with the rate about an axis through the *para* and substituted carbons being considerably more rapid than those about the two other orthogonal axes. Note that rotation about this particular axis does not change the angle between the para C-^2H bond and the external magnetic field. The T_1 value at this position is therefore determined only by the slower motions and is shorter than that for the *ortho* deuterons which are affected by the rapid motion.

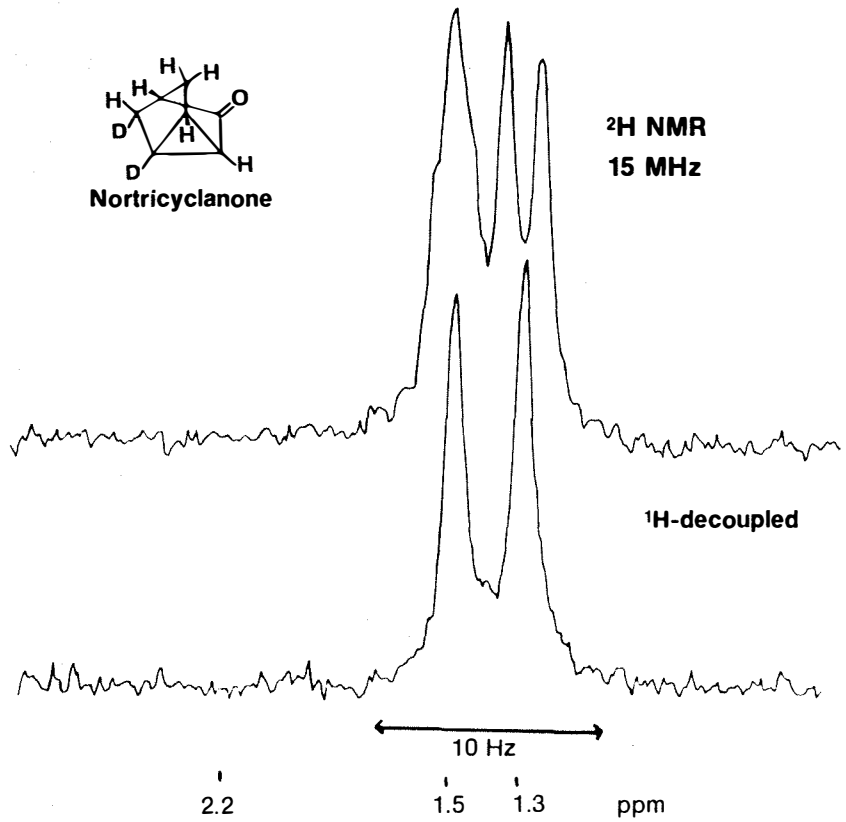
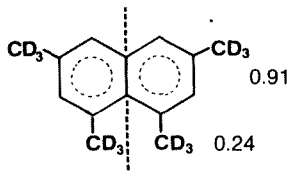


Figure 2 ^2H nmr spectra (15.4 MHz) of nortricyclanone with and without broad band ^1H-decoupling.[15]

The relative T_1 values of the α- and β-deuteromethyl groups of naphthalene-$\alpha,\alpha',\beta,\beta'$-$(C^2H_3)_4$ are a dramatic example of the influence of steric hindrance on the rate of methyl-group rotation. In contrast to ^{13}C, where the relative importance of dipole-dipole and spin-rotation mechanisms must be determined, the ^2H data may be simply interpreted in terms of the modulation of the quadrupole interaction by rotation of the methyl groups relative to the naphthalene framework. Clearly the proximal methyl groups (α,α') interfere with each other's motion, whereas the β-methyl groups approximate free rotors.



^2H T_1's (sec)

The conclusion[17] from ^{13}C nmr that a high degree of rapid intracyclic motion (pseudorotation) occurs in the amino acid proline was confirmed by ^2H nmr T_1 measurements on a series of deuterated prolines.[18] The ^2H T_1 value of the α-carbon (0.27 sec) was considerably less than those of the β, γ, and δ-deuterons (0.42, 0.44, 0.40 sec, respectively) which had been thought to take part in rapid ring-puckering.

BIOSYNTHETIC MECHANISMS

Just as with organic reactions, ^2H nmr can be very valuable in establishing the pathways by which large molecules are synthesized biologically.[8] An example of the resolution of the technique is the spectrum of griseofulvin shown in Figure 3.[19] The compound was produced by growth of *Penicillium urticae* on a medium containing sodium acetate-2-d_3. Synthesis of a series of derivatives with different positions of deuteration confirmed the assignments shown in Figure 3.

The metabolic product of the urinary antibiotic nalidixic acid administered orally to a monkey was elucidated using ^2H nmr.[20] Freeze-dried urine was dissolved in trifluoroacetic acid and the spectra run without further purification. In separate experiments with nalidixic acid deuterated at either the methyl or ethyl group it was shown that the principal metabolic product involves hydroxylation of the methyl group. The advantages of the ^2H nmr method are that only resonances derived

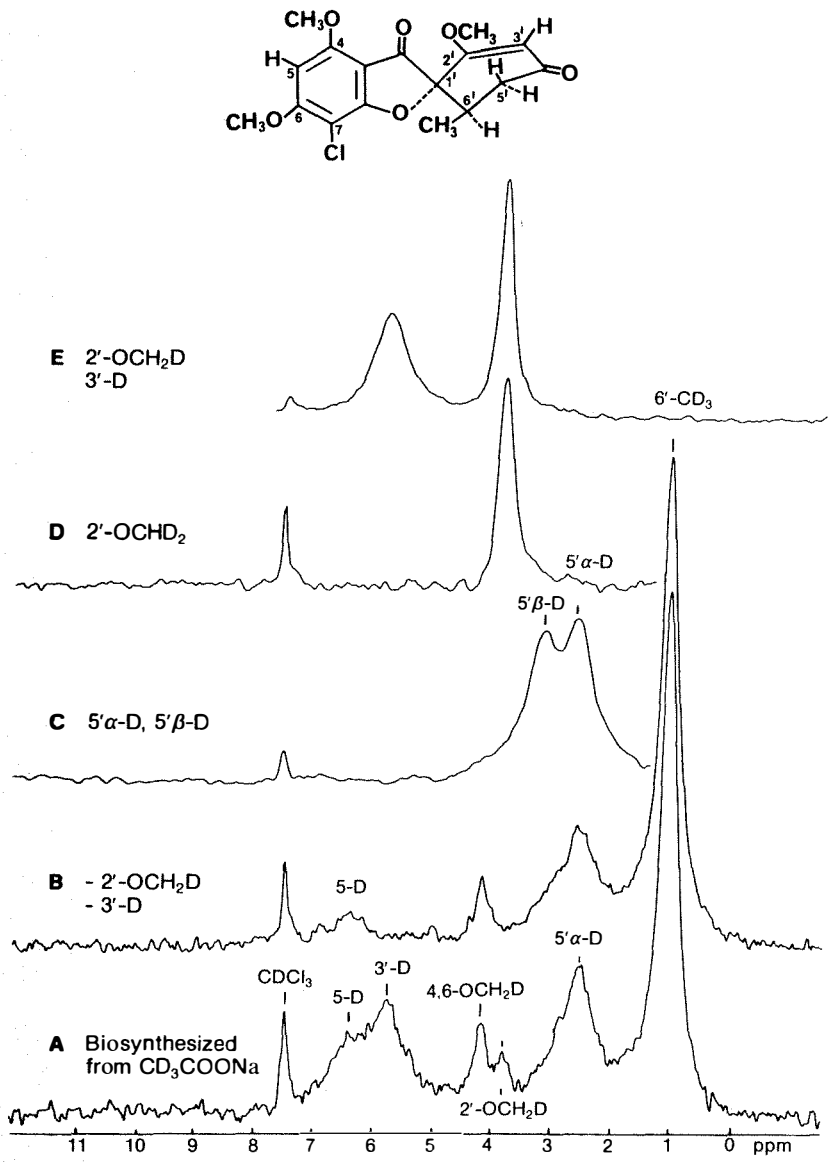


Figure 3 ^2H nmr spectra (15.3 MHz, ^1H-decoupled) of $CHCl_3$ solutions of griseofulvin (A) deuterated by growth of *P. urticae* on sodium acetate-2-d_3 and of a series of specifically deuterated derivatives: B, without ^2H at 2' and 3'; C, 5'α,5'β-D_2; D, 2'-$OCHD_2$; E, 2'-OCH_2D, 3'-D. Comparison of ^1H-coupled and ^1H-decoupled spectra demonstrated that the two peaks centered around 4 ppm in A were coupled to ^1H.[19]

from the original compound are observed, the measured chemical shift is indicative of the chemical nature of the compound, and no separation of the product must be made to avoid interference with other compounds present in the physiological fluid.

It is expected that ^2H nmr will be applied to a wide variety of biosynthetic problems in the near future.

BIOLOGICAL MEMBRANES

By far the most fruitful biological application of ^2H nmr has been to the problem of the degree of molecular organization in membranes. The fatty acyl chains of the phospholipids in membranes are known to exist at physiological temperatures in a state resembling liquid crystals, *i.e.*, the chains are fixed at the carboxyl end due to attachment to a pseudo-ionic lattice, but are relatively free at the terminal methyl groups. Rapid motion occurs about the C-C bonds of the fatty acyl chain; its rate and amplitude are expected to vary considerably from one end of the chain to the other. Incomplete averaging of the ^2H quadrupole interaction takes place in the case of such anisotropic motion, and partially averaged quadrupole splittings are observed. These splittings are directly related to the degree of molecular order (packing, relative numbers of *gauche* and *trans* C-C bonds) at the position of deuteration. A variety of model systems has been studied [21,22] and the method has been applied successfully to the plasma membrane of the microorganism *Acholeplasma laidlawii*.[23,24] A review of this technique has appeared recently.[12]

The type of spectrum obtained from a biological membrane is shown in Figure 4. The membrane phospholipids were enriched in palmitic acid-16,16,16-d_3 by growth on a medium supplemented with this compound. The relatively small quadrupole doublet observed is due to a low degree of molecular packing at this position. Using lipids specifically deuterated at different positions along the chain it was found that the degree of order for the first ten carbon positions of the sixteen-carbon chain was relatively high and constant, and that it decreased rapidly with position thereafter to a minimum value at the terminal methyl group. This is similar to the behavior seen in the model systems of dipalmitoyl[21] and egg lecithin[22] and serves to justify the use of these model systems as well as providing the first detailed insight into the structure of biological membranes at the molecular level.[24]

A technical problem encountered with ^2H nmr of membrane systems is the strong resonance observed in the center of the spectrum. This is due to ^2H at natural abundance in water (0.015%). As the quadrupole splittings become larger, difficulties are encountered with this peak due to dynamic range limitations of the spectrometer. By the use of ^2H-depleted water (*ca.* 0.00015%) this problem is minimized. The ^2H-depleted water is also useful in ^2H nmr studies of small molecules in H_2● where the chemical shifts of the positions of interest lie close to that of water.

PROGNOSIS

^2H nmr has finally come of age. Its usefulness in chemistry, physics, and biology has been well documented.[2] With the greater availability of multinuclear spectrometers we are now in a position to take advantage of its versatility and advantages, and I expect that we shall witness a literature explosion in this subject in the near future.

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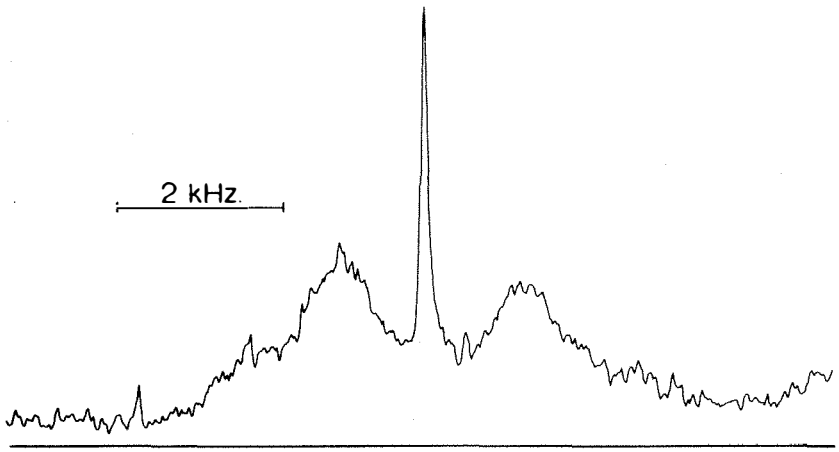

Figure 4 ^2H nmr spectrum (15.4 MHz) of the cytoplasmic membranes of *A. laidlawii* enriched in the phospholipids with palmitic acid-16,16,16-d_3. The spectrum was taken in H_2O at 43° and required the accumulation of 2 x 10^5 free-induction decays before Fourier transformation.[12,23,24]

Chem. Soc., in press.

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ABOUT THE AUTHOR

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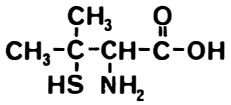
Currently he is a Senior Research Officer at the National Research Council of Canada, Division of Biological Sciences, Ottawa, Canada as well as an Adjunct Professor of Chemistry at Carleton and Ottawa Universities, Ottawa, and Adjunct Professor of Physiology and Biophysics at the University of Illinois, Chicago, U.S.A.

L-(+)-Penicillamine



L-(+)-Penicillamine is a metal chelating agent[1,2] and a useful agent for the induction of experimental convulsions in the rat.[3]

1) R.P. Martin and J. Riaute, *16th. Proc. Int. Conf. Coord. Chem.*, 1.7b (1974); *Chem. Abstr.*, **85**, 63322g (1976).
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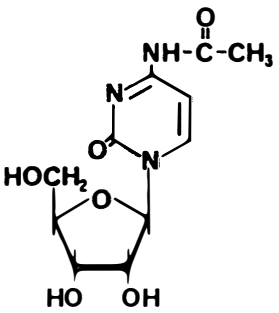
3) T. Kirikae, *Iwate Igaku Zasshi*, **27**, 355 (1975); *Chem. Abstr.*, **84**, R159420t (1976).

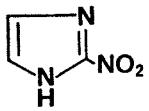
Interesting Nucleoside



N^4-Acetylcytidine is a minor component of *E. coli* methionine *t*RNA.

1) Z. Ohashi, K. Murao, T. Yahagi, D.L. von Minden, J.A. Mc Closkey and S. Nishimura, *Biochim. Biophys. Acta*, **262**, 209 (1972).

Antimicrobial Agent



2-Nitroimidazole (azomycin) possesses antimicrobial activity and is an important intermediate in the preparation of 2-nitroimidazolyl carbamates,[1,2] potential protozoacides.

1) F. Hoffmann-La-Roche and Co., A.-G., Fr. Patent 2,260,996 (1975); *Chem. Abstr.*, **84**, 150631e (1976).
2) A.G. Beaman and W.P. Tautz, U.S. Patent 3,865,823 (1975); *Chem. Abstr.*, **82**, 170944w (1975).

Selective Reductions Using Borane Complexes*

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Aldrich - Boranes, Inc.
Milwaukee, Wisconsin 53233

Boron hydride reducing agents are becoming increasingly important in synthetic organic chemistry. Sodium borohydride, sodium cyanoborohydride,[1] the Selectride® reagents,[2] and Super-Hydride®[2,3] are all widely utilized for selective reductions. These borohydride reagents react principally by nucleophilic attack on an electron-deficient center. Conversely, borane, which is electron-deficient, is believed to function through attack on an electron-rich center.[4] Thus, borane complexes are acidic-type reducing agents which exhibit markedly different selectivity from the basic-type reducing agent, sodium borohydride.[5] This interesting difference in the reducing activity of diborane and sodium borohydride prompted an extensive study of the reduction of organic compounds with borane-ether complexes.[6,7]

In addition to the Lewis acid character of borane, other important chemical properties have enhanced the utility of borane complexes as reducing agents. Many reactions involving borane complexes have unusually low activation energies. Consequently, most reactions occur readily at or below room temperature. These low temperatures favor clean reaction mixtures. Because of the solubility of borane complexes, the reactions are usually homogeneous, proceed without induction periods, and are easily controlled. Finally, the inorganic by-product of a borane reduction is usually an inert, water-soluble borate salt, which can be washed away over a broad **pH** range. All of these chemical and physical properties combine to make borane one of the most chemically versatile compounds known.

*For a more comprehensive treatment of this topic, see C.F. Lane, *Chem. Rev.*, **76**, 773 (1976).

THE REAGENTS

The high reactivity of diborane is presumably due to its ready dissociation into borane (BH_3).[8] The borane molecule behaves as a strong electron-pair acceptor (Lewis acid) forming coordination complexes with suitable electron donors (Lewis bases). Of the various known complexes, the borane-amine, borane-ether, and borane-alkyl sulfide complexes are all particularly interesting because of their wide range of physical and chemical properties. More importantly, these borane-Lewis base complexes provide a convenient source of borane for use as a reducing agent.

1) BH_3·Amine Complexes

The borane-amine complexes are very useful reagents which have many important laboratory and industrial applications.[9]

The first borane-amine complex was reported in 1937 and was prepared by the direct reaction of diborane with trimethylamine (eq. I).[10] Since then almost all structural types of amines have been used to

$$2\ (CH_3)_3N + B_2H_6 \longrightarrow 2\ (CH_3)_3N{:}BH_3 \qquad \text{(eq. 1)}$$

prepare borane-amine complexes. A wide variety of these complexes is now available from Aldrich.

An important feature of the borane-amine complexes is their broad range of physical properties. Liquid, low-melting solid, and high-melting solid borane-amines are known. The borane-amines also have low vapor pressures and can be purified by distillation and/or recrystallization. They are also soluble in a wide variety of solvents.[9,11]

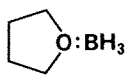
Most borane-amines are stable indefinitely at room temperature and are unaffected by dry air. The borane-amines prepared from primary and secondary amines are surprisingly resistant to loss of hydrogen.

Only the borane complexes with *N*-aryl-amines (*N*-phenylmorpholine and *N*,*N*-diethylaniline) are hydrolyzed by water (atmospheric moisture) and alcohols.[11] However, by careful and rapid handling, they may be transferred in air with only minimal loss of hydride activity. All of the other borane-amines are stable in hydrolytic solvents at neutral pH for a minimum of 12hr at 25°.[11]

The most important chemical property of the borane-amine complexes is their ability to act as reducing agents.[9] The use of borane-amines for the reduction of organic functional groups will be discussed in later sections of this review.

2) BH_3·THF

A Raman spectroscopic investigation of the liquid systems diborane-THF, diborane-dimethyl ether, and diborane-diethyl ether, provides evidence for the formation of a $R_2O{:}BH_3$ addition complex in each system.[12] Also, a study of the solid-liquid equilibrium for diborane-THF clearly indicates the formation of the compound tetrahydrofuran-borane (**1**).[13] On



1

the basis of these two studies, the stability of borane-ether complexes is believed to decrease in the order: **1** $>Me_2O{:}BH_3 >> Et_2O{:}BH_3$. Additional evidence is available for the existence of **1** in a THF solution of diborane. In THF the solubility of

diborane is much greater than perfect-solution predictions, *i.e.*, the solubility increases as the square root of diborane pressure increases.[14] Also, a phase diagram study[15] and two ^{11}B plus ^{1}H nmr studies[16] provide convincing evidence for the existence of **1** in excess THF. It is apparent that diborane must be present in THF solution as the complex **1**. The stability of **1** is quite unique and is mainly responsible for the interest in and utility of BH_3-THF as a convenient reducing agent.

3) $BH_3 \cdot Me_2S$

The first reported preparation of a borane-alkyl sulfide complex was by Burg and Wagner.[17] Condensation of dimethyl sulfide and diborane on a vacuum line produced a stable, liquid adduct of borane-methyl sulfide (BMS) (eq. 2).

$$2\ (CH_3)_2S + B_2H_6 \longrightarrow 2\ (CH_3)_2S{:}BH_3 \quad \text{(eq. 2)}$$

BMS

The surprising stability of BMS at room temperature prompted a more detailed study of borane-alkyl sulfide complexes by Stone and coworkers.[18]

The physical and chemical properties of BMS make this reagent an attractive source of BH_3, and its numerous advantages over BH_3-THF as a storable reagent were first discussed by Adams and coworkers.[19] The BH_3-THF reagent possesses certain characteristics which limit its preparation, storage, and use as a commercial source of BH_3, namely: (1) BH_3-THF can only be sold as a dilute solution (1*M*) in THF (1.5 wt % BH_3), (2) THF is slowly cleaved by BH_3 at room temperature, and (3) sodium borohydride (<5 mole %) must be added to BH_3-THF to inhibit the cleavage of THF.

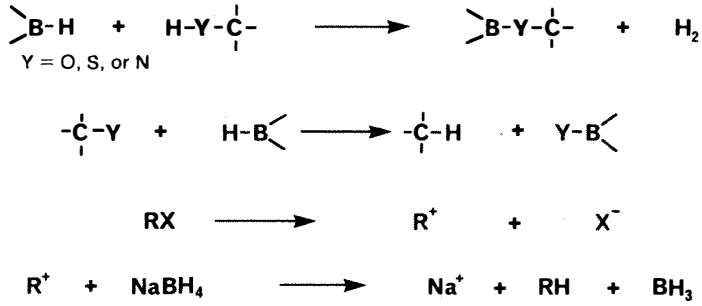
Fortunately, BMS has been found to overcome all of these disadvantages. BMS has a molar concentration of BH_3 *ten times* that of the BH_3-THF reagent. It can be stored for months at room temperature without loss of hydride activity and is apparently stable indefinitely when refrigerated. Also, BMS is soluble in, and unreactive toward, a wide variety of aprotic solvents including ethyl ether, THF, hexane, heptane, toluene, xylene, methylene chloride, glyme, and diglyme. BMS dissolves readily in alcohols with the quantitative evolution of hydrogen. However, it is insoluble in water and only very slow hydrolysis occurs. The addition of water to ether solutions of BMS results in rapid hydrolysis.

Quantitative hydroborations with BMS are possible under mild conditions in a variety of aprotic solvents such as ethyl ether, THF, hexane, toluene, and methylene chloride.[20] The air-stability and ease of handling of this reagent have permitted its use in an undergraduate laboratory.[21] The successful hydroboration of alkenes with BMS prompted similar studies with BMS as a reducing agent.[22] The results of these investigations make it apparent that BMS is a very useful reagent for the reduction of organic functional groups.

REACTION WITH ACIDIC HYDROGENS

BMS and BH_3-THF react rapidly and quantitatively with various acidic hydrogens (H-Y), liberating one mole of hydrogen per equivalent of boron hydride (eq. 3). The acidity of the hydrogen and the ability of the donor atom Y to share a pair of electrons influence the rate of these reactions.[7]

The direct measurement of the volume of hydrogen gas produced upon hydrolysis of a boron hydride provides a convenient and accurate method for the determination of either the purity of a boron hydride or the concentration of a boron hydride solution.[23]



In reactions of borane complexes with compounds containing acidic hydrogens, hydrogenolysis of the C-Y bond is usually not observed. Upon hydrolysis the alcohol, amine, thiol, or related functional group is regenerated. However, in a few specialized cases, those alcohols which can readily form carbonium ions are transformed by diborane into the corresponding hydrocarbons (*vide infra*). Even though the alcohol, thiol, and amine groups are normally recovered, their presence and reactivity must by considered when carrying out a borane reaction, *i.e.*, sufficient borane reagent must be added to compensate for loss of hydride activity upon reaction with acidic hydrogens.

Other functional groups which contain acidic hydrogens such as carboxylic acids and primary and secondary amides, react with borane with evolution of hydrogen. However, since these groups react further with borane, they will be discussed in later sections dealing with the reduction of such functional groups.

REDUCTIVE CLEAVAGE

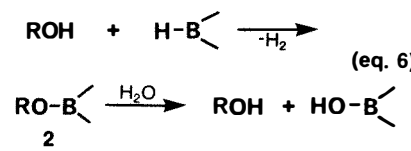
In general, this section deals with those reactions which involve the reductive cleavage of a C-Y single bond (eq. 4). The reduction of organic functional groups containing carbon-sulfur, carbon-nitrogen, or carbon-oxygen multiple bonds will be discussed in later sections. Naturally, some overlap is inevitable; but by subdividing the sections into discussions of specific functional groups, the retrieval of information about the reducing characteristics of borane complexes should be simplified.

1) Organic Halides

Primary, secondary, and tertiary alkyl and aryl fluorides, chlorides, bromides, and iodides are all inert toward the various borane-Lewis base complexes.[7] Even under vigorous conditions (1hr at reflux), the more reactive primary alkyl bromides and iodides are stable to BH_3-THF.[24] Under similar conditions, lithium aluminum hydride (LAH) is extremely reactive.[25] Under solvolytic conditions, sodium borohydride reacts with readily ionizable secondary and tertiary organic halides to give good yields of the corresponding hydrocarbons (eq. 5).[26] Obviously, the presence of sodium borohydride as a stabilizer in commercial BH_3-THF must be considered when using this reagent for the reduction of an organic compound containing a readily ionizable halide since a small amount of a side reaction involving the $NaBH_4$ can occur as shown above.

2) Alcohols

Alcohols normally react rapidly with diborane to give alkoxyboranes (**2**). Hydrogenolysis of the carbon-oxygen bond usually does not occur. Thus, the alcohol is regenerated upon hydrolytic work-up (eq. 6). However, this does not

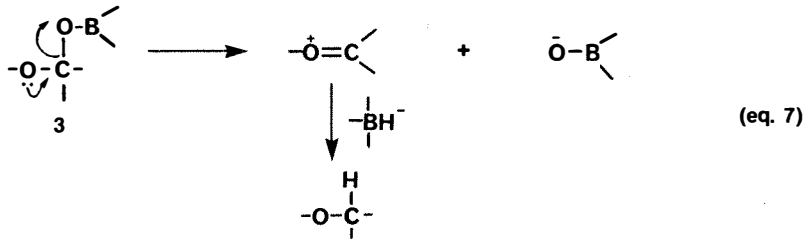


mean that reductive cleavage of the carbon-oxygen σ bond is unimportant in borane reductions. When the intermediate alkoxyboron compound is of the correct structural type, cleavage of the carbon-

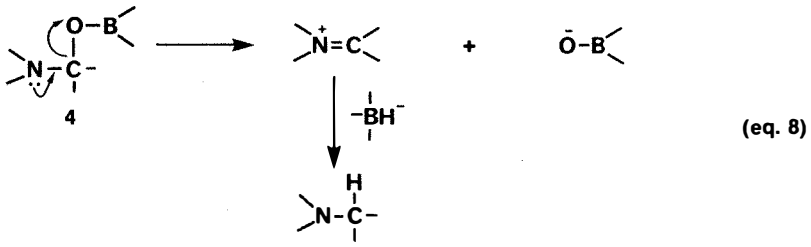
oxygen bond becomes the major reaction pathway. Equations 7-10 illustrate a variety of known carbon-oxygen bond cleavage reactions.

Although the mechanism may be more complex, the presence of an *electron-donating* atom is required before cleavage of the C-O bond is observed in a C-O-B type of intermediate. Other examples are known and will appear later, but intermediates **3-6** illustrate the generality of this *electron-donation-induced cleavage*.

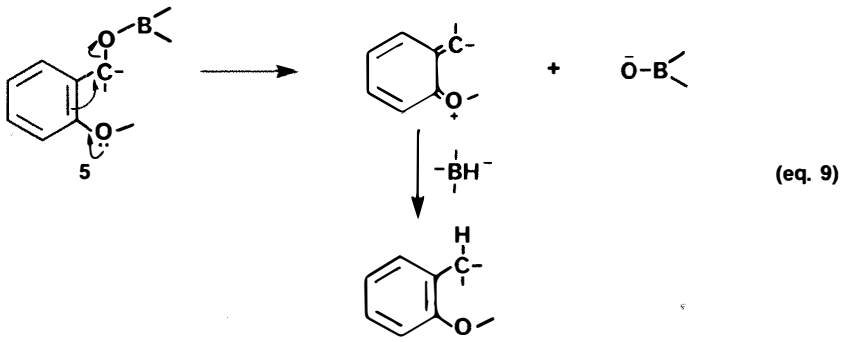
Obviously, intermediate 3 is formed during the reaction of esters and lactones with borane and the importance of this reductive cleavage will be discussed in a later section. Also, the fragmentation of intermediate **4** constitutes the reaction pathway observed in the facile reduction of amides with borane reagents. Intermediates of the type illustrated by **6** can be formed by reduction of the corresponding aldehyde or ketone. Finally, intermediates similar to **5** are formed not only during the reduction of certain aldehydes and ketones but can also arise directly from an appropriate alcohol. Reductive cleavage of the alcohol then results. A specific example is illustrated by equation 11.[27]



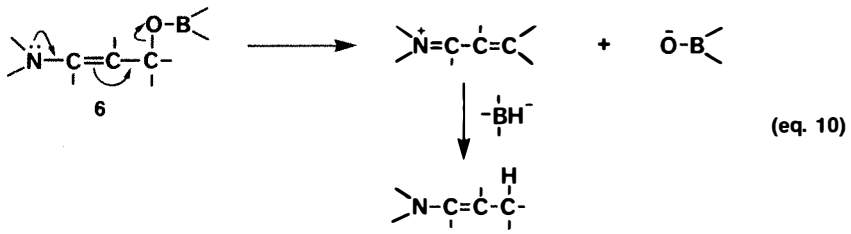
(eq. 7)



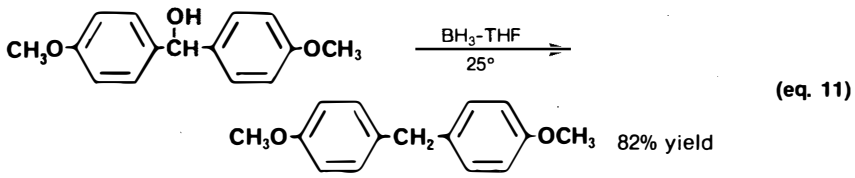
(eq. 8)



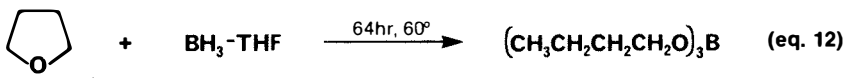
(eq. 9)



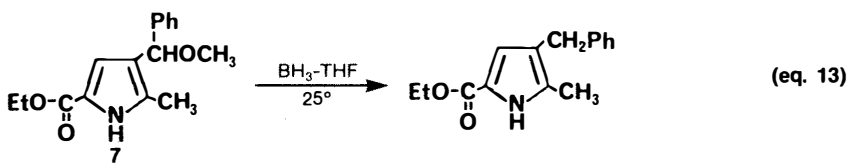
(eq. 10)



(eq. 11)



(eq. 12)



(eq. 13)

3) Ethers

The formation of borane-ether complexes is known to occur, but more crucial is the fact that reductive cleavage of ether linkages by borane is also known. Fortunately, reductive cleavage is a relatively slow reaction under normal conditions.[28,29] With BH_3-THF, heating for an extended period of time in a sealed tube is necessary to obtain a reasonable yield of tri-*n*-butyl borate (eq. 12).[28,30]

The reductive cleavage of THF by BH_3-THF is negligible for the laboratory use of this reagent. The BH_3-THF reagent is stable for several months when prepared and stored at 0° under nitrogen.[31] The reagent loses 1-3% of the available BH_3 per day when stored at ordinary temperatures (25-30°).[29] This becomes a major problem during the manufacture, storage, and shipment of the commercial material. Fortunately, Brown discovered that a small amount of dissolved sodium borohydride stabilizes the BH_3-THF reagent and effectively eliminates the loss of hydride due to reductive cleavage.[29] The commercial availability of the reagent is a result of this observation. The stabilized BH_3-THF reagent shows no loss in active hydride after 2 weeks at 25°.[29] Even so, whenever possible, the reagent should be stored at 0° to maintain maximum hydride activity.

Brown also disclosed that solutions of diborane in THF are stabilized against decomposition for at least 8 weeks by the presence of an organic sulfide.[32]

As was observed for the hydrogenolysis of alcohols, the presence of electron-donating groups greatly enhances the ease of reductive cleavage. The reductive cleavage of the benzylic ether **7** is a specific example (eq. 13).[33] This reaction presumably involves an intermediate analogous to **6**.

Acetals and ketals are reductively cleaved with borane reagents under milder conditions (2-3hr at 25-30°) than are required for simple ethers.[34,35] A probable reaction pathway is illustrated in equation 14. This mechanism is a straightforward extension of the idea of electron-donation-induced cleavage. Two specific examples are illustrated in equations 15 and 16.[35] Although it

has not been shown in these equations and will generally be omitted in later equations, a hydrolysis step is usually necessary in the borane reductions.

4) Epoxides

Brown and Yoon have demonstrated the pronounced catalytic action of both $NaBH_4$ and BF_3 on the reduction of epoxides with BH_3-THF.[36,37] For example, in the presence of a catalytic quantity of boron trifluoride, styrene oxide undergoes a quantitative, regioselective, reductive, ring-opening reaction (eq. 17).[36]

REDUCTION OF ORGANIC SULFUR COMPOUNDS

Dimethyl sulfoxide is reduced to dimethyl sulfide with BH_3-THF at a moderate rate at 0°.[7] Such a deoxygenation reaction was recently used as the final step in the first reported preparation of 1,3-dithietane (eq. 18).[38]

All other compounds containing sulfur-oxygen double bonds, including aromatic and aliphatic sulfones and cyclohexyl tosylate, are inert to BH_3-THF under standard conditions.[7]

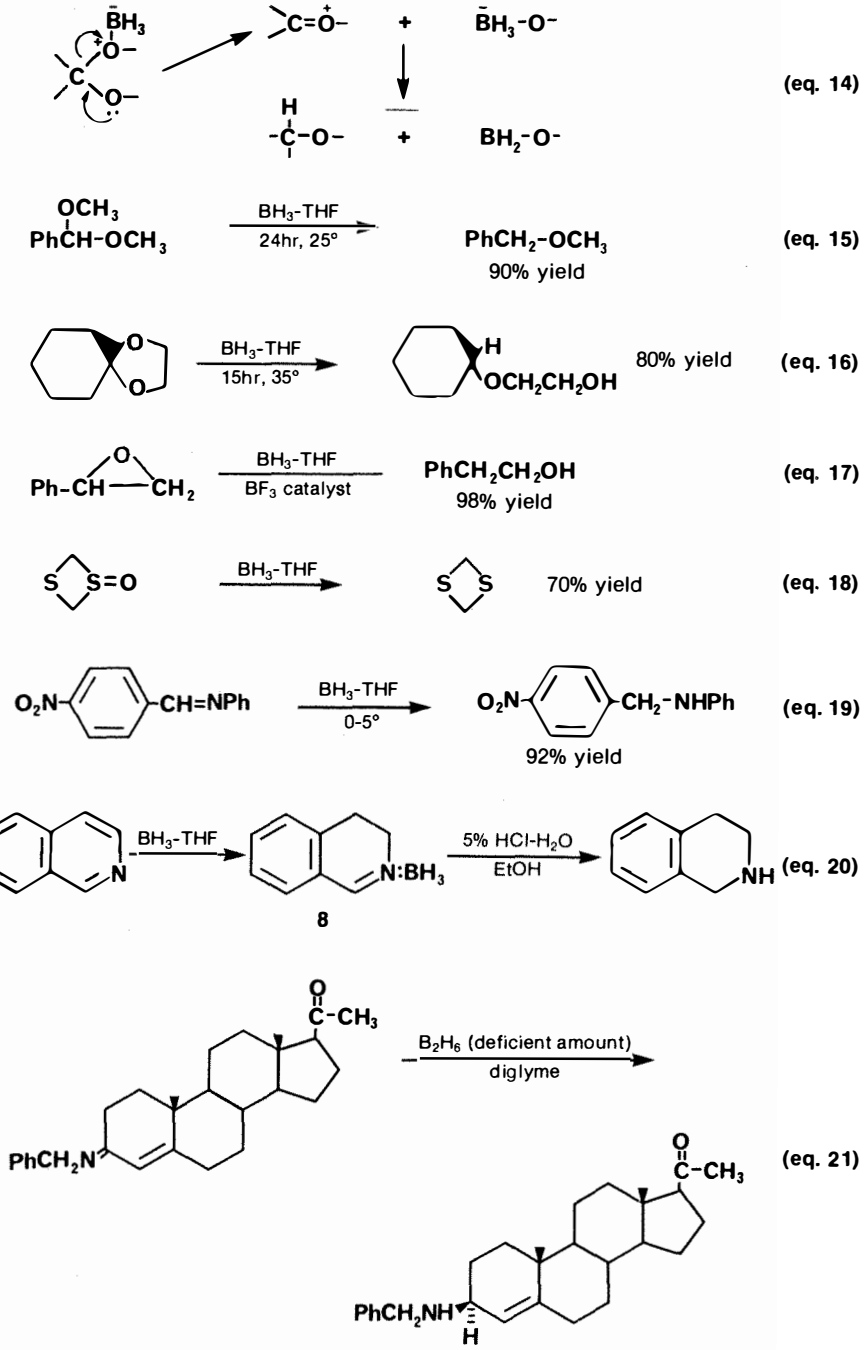
REDUCTION OF ORGANIC NITROGEN COMPOUNDS

A variety of organic functional groups containing a multiple-bonded nitrogen is reduced with borane reagents. Most of the effort has been directed towards the reduction of imines, oximes, nitro derivatives, and nitriles. The reaction of borane reagents with these functional groups will be discussed in detail in individual sections. However, a number of other nitrogen-containing groups undergo reaction with borane.

Diazomethane reacts readily with BH_3-THF giving an almost quantitative yield of a highly crystalline, boron-containing polymethylene.[39] Diborane reacts with organic isocyanates and isothiocyanates to give thermally unstable diadducts at low temperatures.[40] At higher temperatures decomposition leads to complex mixtures which include aminoboranes and boron-nitrogen cyclic trimers. Finally, pyridine *N*-oxide is reduced at a moderate rate, but hydride uptake and examination of the ir spectrum of the product indicate attack on the aromatic ring.[7]

1) Imines

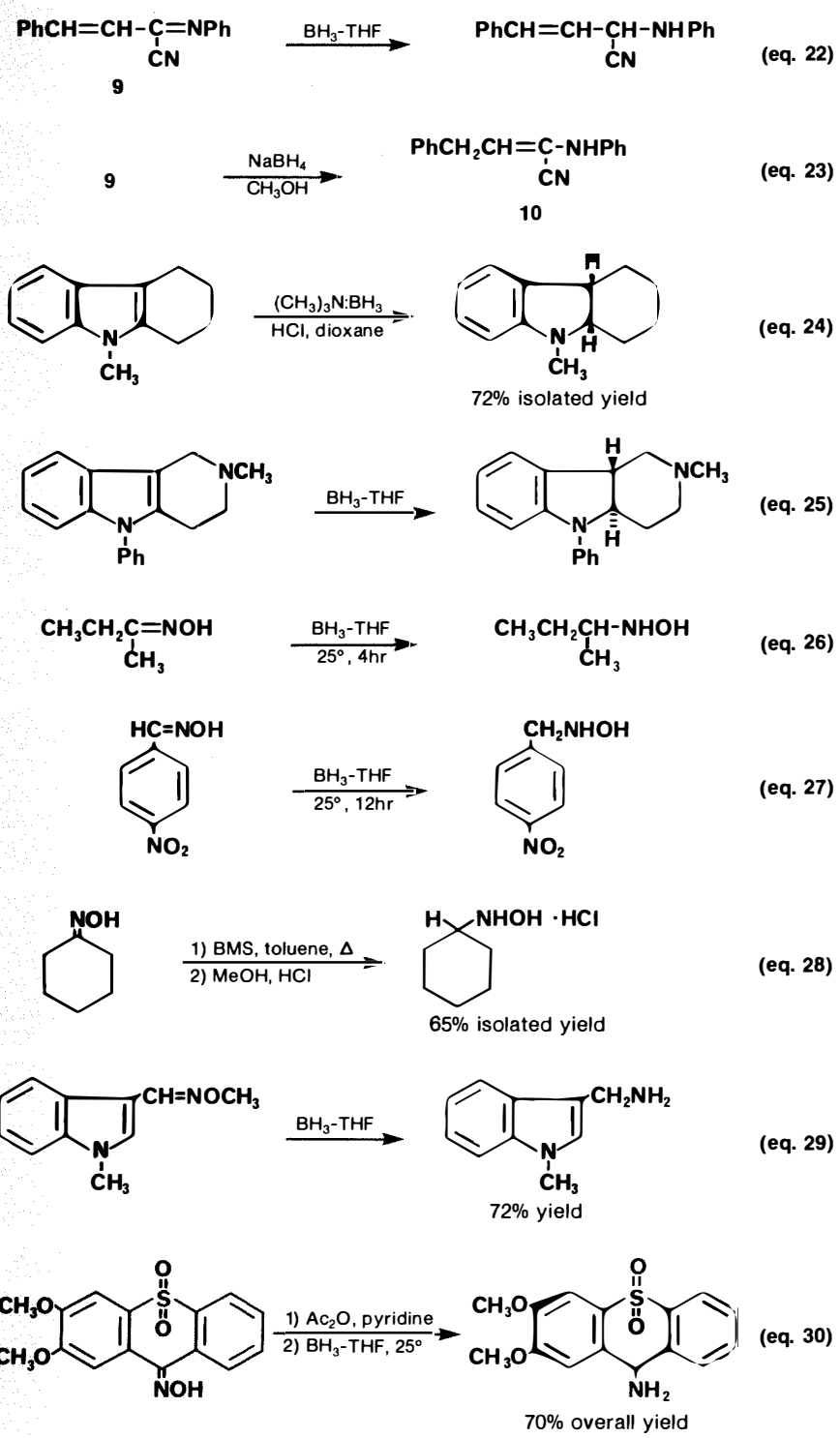
The reduction of Schiff bases with BH_3-THF proceeds under very mild conditions giving excellent yields of the corresponding amines.[41] A specific example is shown in equation 19, but this reduction and similar reductions of Schiff bases can also be carried out with the milder reducing agent, sodium borohydride. Consequently, the borane reagents would appear to be of limited utility for imine reductions.



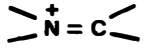
With a number of specific systems, borane either exhibits superior selectivity or gives a product that is not possible using sodium borohydride as the reducing agent. For example, isoquinoline reacts with BH_3-THF giving an intermediate dihydroisoquinoline-borane adduct **8** which is reduced further to tetrahydroisoquinoline upon treatment with dilute, aqueous hydrochloric acid in ethanol (eq. 20).[42] The selectivity of borane is illustrated by the reported reduction of an imine group in the presence of a ketone (eq. 21).[43] When sodium borohydride in methanol was used as the reducing agent, both the imine and ketone were readily reduced.

The selective reduction of the cyano-substituted imine **9** is possible using BH_3-THF (eq. 22).[44] When sodium borohydride in methanol at room temperature is used, a rearranged nitrile (**10**) is obtained (eq. 23).[44]

For alkyl-substituted imines, an equilibrium may exist between the imine and the corresponding enamine. Evidence for this equilibrium was provided by the observation that hydroboration-oxidation of some cyclohexanone imines gave both the corresponding amine and the 2-hydroxycyclohexylamine.[45]



The reaction of N-unsubstituted indoles with excess BH_3-THF results in an initial, rapid evolution of hydrogen gas.[46] Addition of excess acetone or slow inverse addition to a large excess of methanol gives the starting indole. However, if the reaction mixture is treated with methanol under neutral, acidic, or basic conditions, reduction to an indoline is observed.[46] The mechanism probably involves an intermediate iminium ion (**11**).



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Recently, Berger found that various indoles can be reduced *via* their indolinium salts by borane-trimethylamine in generally good yields.[47] The success of Berger's method is a result of the fact that borane-trimethylamine is a hydridic species which is remarkably stable under the highly acidic conditions required to generate indolinium ions. The reduction of a tetrahydrocarbazole provides a specific example (eq. 24).[47] Surprisingly, in certain specific cases, a related reduction with BH_3-THF gives the *trans*-fused ring system (eq.25).[48,49]

An intermediate iminium ion must also be involved when borane-amines are used for the reductive amination of ketones. Reduction of ketones with a borane-amine in the presence of an excess of ammonia, methylamine, or dimethylamine (pH ~9-10) at room temperature gives reasonable yields of the corresponding amines.[50] An interesting modification of this reaction was used to prepare α-amino acids. Thus, several substituted pyruvic acids were reduced at room temperature with a borane-amine complex in the presence of a 5-fold excess of ammonia to give the corresponding α-amino acid in 66-72% yield.[50]

Borane-amines can also be used for the reduction of imines. Borane-dimethylamine selectively reduces the imino linkage in the presence of the chloro, nitro, alkoxy, hydroxy, carboxy, carbethoxy, and sulfonamido groups.[51] This reduction proceeds rapidly and smoothly in glacial acetic acid to give excellent yields of secondary amines.

When the reduction of imines is carried out under more vigorous conditions using an excess of borane-trimethylamine, reductive acylation is observed.[52]

2) Oximes

The reduction of readily available aldoximes and ketoximes with BH_3-THF provides a facile and convenient synthesis of N-monosubstituted hydroxylamines (eqs. 26,27).[53] BMS can also be used as the reducing agent and offers the advantage of a much simpler isolation procedure (eq. 28).[22]

Heating the intermediate from the BH_3-THF reduction of an aliphatic oxime to 105-110° in a diglyme-THF solvent system gives complete reduction to the corresponding amine.[54] On the other hand, oxime ethers and oxime esters are reduced readily at 25°.[54,55] Hydrolysis then gives excellent yields of the corresponding amines (eqs. 29, 30).

3) Nitro Compounds and Related Derivatives

Nitrobenzene and 1-nitropropane fail to react with BH_3-THF in any reasonable time under normal conditions.[7] Also, the aryl nitro group fails to react with BMS even under somewhat more vigorous conditions.[22] Azoxybenzene is unreactive, but azobenzene is reduced at a moderate rate, utilizing two hydrides with hydrogen evolution and giving aniline upon hydrolysis.[7]

Even though the nitro group is inert, salts of nitroalkanes are readily reduced to hydroxylamines with BH_3-THF.[56] Presumably, the anion provides a point of attack for the electrophilic borane species.

The reduction of aromatic nitroso compounds with BH_3-THF at 25° affords the corresponding amines in good yields.[57]

4) Nitriles

The BH_3-THF reagent reacts slowly at 0° with both aliphatic and aromatic nitriles.[7] However, by using an excess of borane reagent and a higher temperature, reasonable isolated yields of amines are possible upon acid hydrolysis of the intermediate borazines (eqs. 31-33).

BMS is also a useful reagent for the preparation of amines *via* reduction of nitriles (eq. 34).[22]

An interesting nitrile reduction step has been used for the preparation of ^{11}C-labeled norepinephrine hydrochloride (eq. 35).[59] It should be possible to use the same procedure to reduce other cyanohydrins. Indeed, recently, various substituted benzaldehyde cyanohydrins were reduced with BH_3-THF to give 70-80% isolated yields of the corresponding β-amino alcohols.[60]

REDUCTION OF ORGANIC OXYGEN COMPOUNDS

1) Aldehydes and Ketones

Excess diborane reacts readily at room temperature with aldehydes and ketones to yield the corresponding dialkoxyboranes (eq. 36).[4] All attempts to isolate the monoalkoxy derivative have been unsuccessful.[4,61] When an excess of aldehyde or ketone is used, the trialkyl borate is formed (eq. 37).[4]

BH_3-THF reacts similarly. For example, the reaction of two equivalents of acetone with one equivalent of BH_3-THF gives a 95% yield of diisopropoxyborane.[62] Aliphatic and aromatic aldehydes and dialiphatic, monoaromatic, and alicyclic ketones all react rapidly with BH_3-THF at 0°.[7] Only with benzophenone is the rate considerably slower, probably a consequence of the combined steric and electronic effects of the phenyl groups.[7]

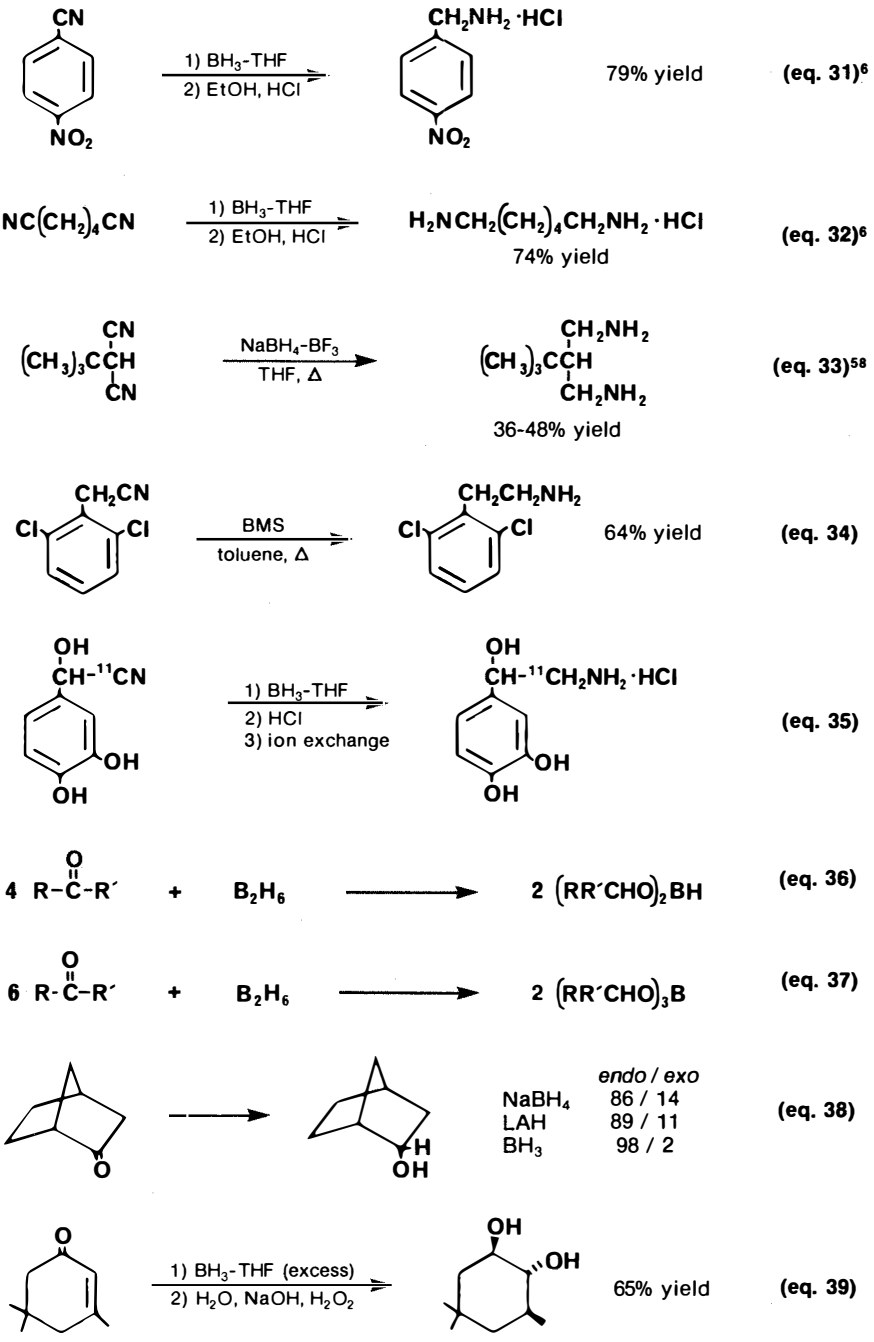
Borane-*N*-arylamine complexes reduce cyclohexanone in less than 3hr at 25° in THF.[11] However, again only two of three hydrides on boron are available for reaction, *i.e.*, the intermediate $(RO)_2BH$ must fail to react with ketones as observed for BH_3-THF reductions. Borane-pyridine and borane-trimethylamine in THF give no detectable reduction of a carbonyl compound after 38hr at 25°.[11] Under more vigorous conditions (benzene or toluene at reflux), borane-pyridine reduces aldehydes and ketones to the corresponding alcohols.[63,64]

Interestingly, the borane-amines are much more effective reducing agents in strong aqueous acid. The rate of reaction with carbonyl compounds actually increases with increasing acidity of the medium.[65] A tremendous increase in rate occurs upon addition of either a mineral acid[11] or a Lewis acid.[66] The effect of added boron trifluoride etherate is very striking.[66] It has been used for the reduction of ketones with borane-d_3-trimethylamine to give α-deuterio alcohols.[67]

Sodium borohydride is a much milder reducing agent than BH_3-THF and is normally the reagent of choice for the preparation of alcohols *via* reduction of aldehydes and ketones. However, with a number of systems, reduction with a borane reagent gives a selectivity or a product that is not possible using sodium borohydride. For example, the reduction of norcamphor with BH_3-THF is unusually stereoselective (eq. 38).[7]

The borane reduction of α,β-unsaturated carbonyl systems does not provide a general synthetic procedure for the preparation of allylic alcohols.[68] Hydroboration of the carbon-carbon double bond competes as a side reaction and proceeds to completion when sufficient borane reagent is used.

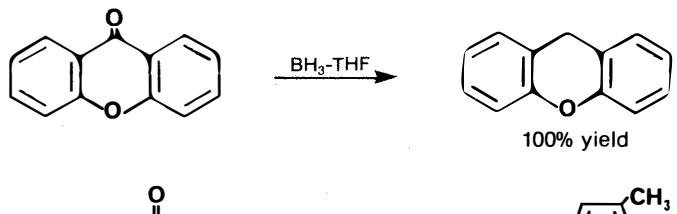
The double bond may undergo hydroboration directly, or a 1,4-addition of boron hydride may occur. Reduction of isophorone with excess BH_3-THF probably involves a direct hydroboration



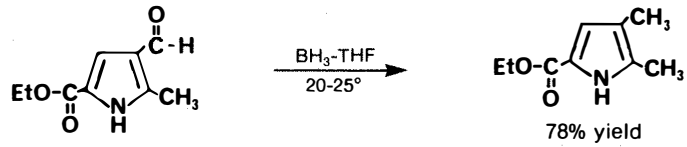
of the carbon-carbon double bond. The 1,2-diol is obtained upon alkaline peroxide oxidation (eq. 39).[69]

The electron-donation-induced reductive cleavage of carbon-oxygen bonds is of fundamental importance in the reduction of aldehydes and ketones with borane reagents. Intermediates corresponding to **5** and **6** are formed during the reduction of many functionally substituted carbonyl compounds. The reductive cleavage is known to be catalyzed by trace amounts of both BF_3[70] and $NaBH_4$.[27] The exact mechanism is unknown, but in all cases an intermediate closely related to **5** or **6** is probably involved. For the reduction of certain systems, this process is an unfortunate and undesirable side reaction. However, if the product of choice is the alcohol, then sodium borohydride should be used for the reduction.

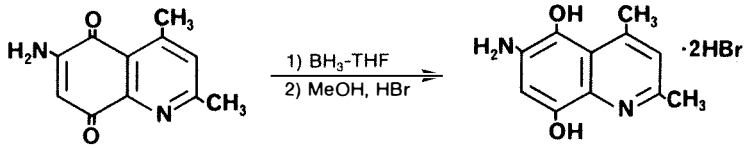
In many cases the methylene derivative is the product of choice. Consequently, the reduction of these appropriately substituted carbonyl compounds with a borane reagent provides a mild, synthetically useful deoxygenation procedure. The borane deoxygenation of xanthone and pyrrole derivatives is particularly important and has been widely utilized (eqs. 40, 41).



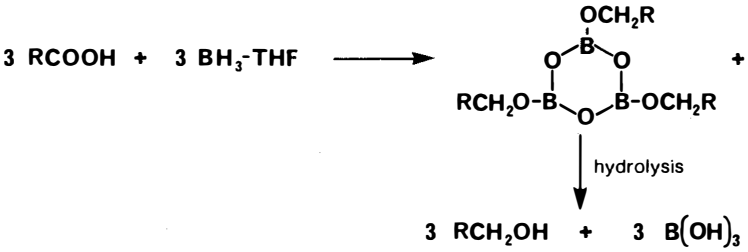
(eq. 40)[71]



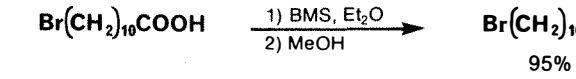
(eq. 41)[33]



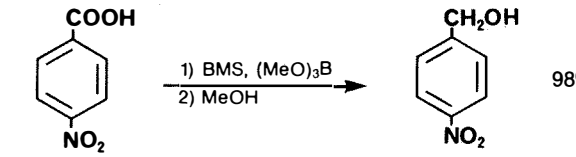
(eq. 42)



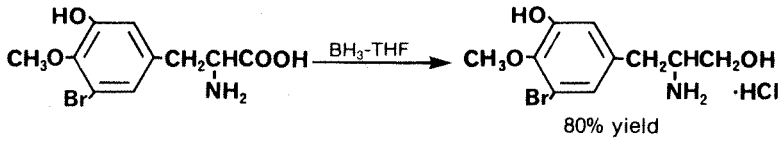
(eq. 43)



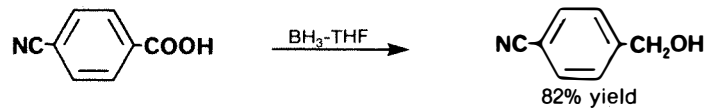
(eq. 44)



(eq. 45)



(eq. 46)[75]



(eq. 47)[73]

2) Quinones

p-Benzoquinone reacts slowly with BH_3-THF utilizing two hydrides, one for reduction and one for hydrogen evolution.[7] This stoichiometry corresponds to reduction to hydroquinone. In fact, Brown and coworkers obtained a quantitative yield of hydroquinone following methanolysis.[7]

An interesting application of this reduction involves the conversion of a 5,8-quinolinedione to a 5,8-dihydroxyquinoline in an 86% isolated yield (eq. 42).[72]

3) Carboxylic acids

Both aliphatic and aromatic carboxylic acids are reduced by BH_3-THF to the corresponding primary alcohols rapidly and quantitatively under remarkably mild conditions (eq. 43).[7] The obvious potential of this reaction for selective reductions in multifunctional molecules prompted a detailed study of the scope of this reduction.[73] This investigation by Brown and coworkers summarizes the reactivity and selectivity observed for the reaction of BH_3-THF with carboxylic acids. Also, some mechanistic possibilities are given.[73]

Aliphatic carboxylic acids react readily at 25° with BMS in a variety of solvents.[22] This reaction has been developed into a useful synthetic procedure for the preparation of 11-bromo-1-undecanol (eq. 44).[22] Aromatic carboxylic acids react very slowly with BMS, but reduction occurs rapidly in the presence of trimethyl borate.[74] The reduction of *p*-nitrobenzoic acid provides an example of the synthetic utility (eq. 45).[74]

The use of borane reagents provides a highly convenient synthetic procedure for the selective reduction of the carboxylic acid group in the presence of other potentially reactive functional groups. Numerous examples could be cited, but equations 46-51 should be sufficient to indicate the selectivity that is possible. For simplicity the hydrolysis step has been omitted, and the yield given is for isolated, purified product.

As illustrated by the examples, the reduction of carboxylic acid groups is possible in the presence of nitro, amino, nitrile, keto, ester, lactone, and amide groups. Even in cases where a selective reduction is not required, the BH_3-THF reagent is often used to reduce carboxylic acid groups because of the mild reaction conditions and ease of product isolation.

The mild conditions and selectivity indicate the potential for carrying out carboxylic acid reductions on complex biological systems. For example, a series of dipeptides (as *N*-trifluoroacyls) was treated with BH_3-THF to give 62-100% reduction of the C-terminal amino acid.[80] This pro-

cedure was later applied to a series of polypeptides and naturally occurring proteins and specific reduction of the free carboxyl groups was achieved in these complex systems.[81] Interestingly, if *N*-acylamino acids are used instead of *N*-trifluoroacyl, a substantial amount of amide reduction is also observed.[82]

Obviously, in most, if not all, of the above examples, the BH_3-THF reagent is superior to LAH. In a specific case, the LAH reduction of polysiloxanes containing terminal carboxyl groups results in extensive reductive cleavage of silicon-oxygen bonds whereas with BH_3-THF, the terminal carboxyl groups are reduced cleanly.[83]

When appropriate electron-donating groups are present, complete reduction to a methyl group is possible (eqs. 52, 53).

4) Carboxylic Anhydrides

n-Hexanoic anhydride and benzoic anhydride are satisfactorily reduced with BH_3-THF giving a 94% isolated yield of 1-hexanol and an 82% isolated yield of benzyl alcohol.[86]

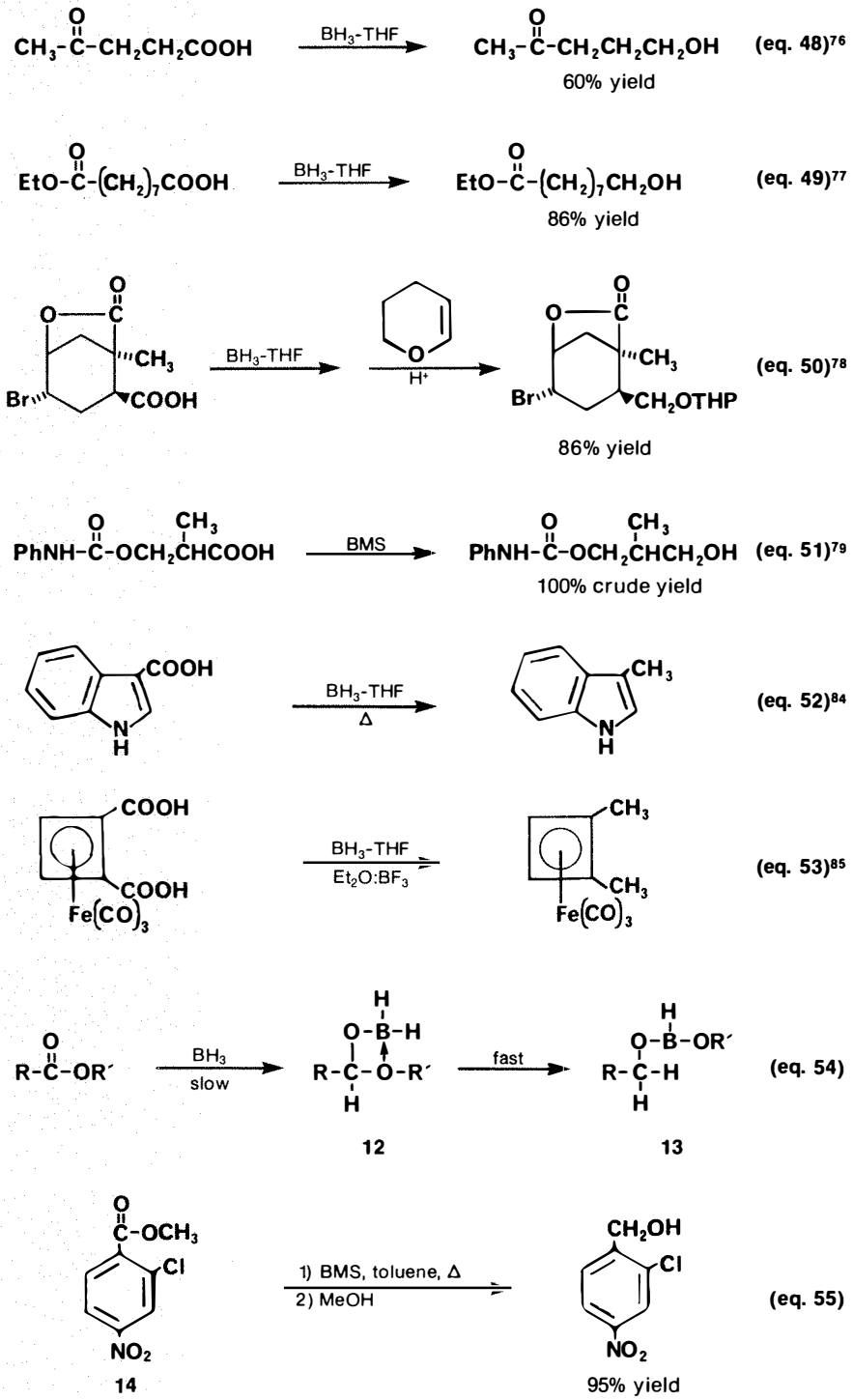
5) Esters and Lactones

Aliphatic esters and lactones are reduced relatively slowly with BH_3-THF at 0°.[7] A 12-24hr period is required for complete conversion to the corresponding alcohol. Phenyl acetate is reduced somewhat more slowly, but the aromatic esters and lactones are almost completely unreactive at 0°, exhibiting only 4-6% uptake of hydride after 24hr.[7] Apparently, resonance of the aromatic ring with the carbonyl group renders the group less susceptible to electrophilic attack by the borane species.

In general, the lower reactivity of the ester group is probably a result of the electron-withdrawing inductive effect of oxygen on the carbonyl group. For example, carbonate esters[24] and polycarbonates[87] are stable to BH_3-THF at room temperature.[88] Steric hindrance can also lower the reactivity of esters. Thus, pivalate esters are stable toward BH_3-THF at room temperature.[24] During reduction of esters to alcohols, there is no detectable aldehyde formation, indicating that no stable intermediate is formed.[7] A probable mechanism which explains all of the above results is shown in equation 54.

Intermediate **12** is probably very unstable, and a rapid intra- or intermolecular hydride transfer occurs to give the stable intermediate **13**. This hydride transfer could be promoted by an intramolecular coordination of boron and oxygen in **12**.

BMS can be used to reduce a variety of functional groups and is particularly useful for the high-temperature reduction of normally unreactive esters. The reduction of **14** illustrates a specific example in which



the relatively high temperature found necessary to reduce the ester function still did not result in reduction of the nitro group (eq. 55).[22]

During the selective reduction of a more reactive group with BH_3-THF, the slow reduction of an ester group is sometimes a problem. However, Jackson and coworkers found that the reduction of an aliphatic ester group is inhibited by the presence of ethyl acetate.[89]

Electron-donation-induced reductive cleavage *via* an intermediate analogous to **6** can also occur during borane reduction of an ester group resulting in complete reduction to a methyl group. Again many examples are found in derivatives of pyrrole, equation 56 being representative.[90]

Reduction of an appropriately substituted lactone with a borane reagent can result in complete deoxygenation of the carbonyl group to give an ether. Steroidal δ-lactones were examined in the most detail and experimental conditions were developed for the conversion of these lactones to cyclic ethers. This is another exam-

ple of an electron-donation-induced reductive cleavage which probably involves an intermediate similar to 3.[91] The original procedure used by Pettit consisted of treating the lactone with diborane in the presence of a large excess of boron trifluoride.[92] He later found that the ester to ether conversion was favored if the ester or lactone was derived from a tertiary, hindered alcohol,[93] but branching next to the carbonyl had little influence on the yield of ether and only decreased the rate of reduction.[94]

Recently, Pettit found that the large excess of BF_3 is not necessary in many cases, *i.e.*, a large excess of BH_3-THF gives essentially analogous results.[91] A large number of cyclic ethers has been prepared using these procedures. Equations 57 and 58 provide specific examples.

6) Amides

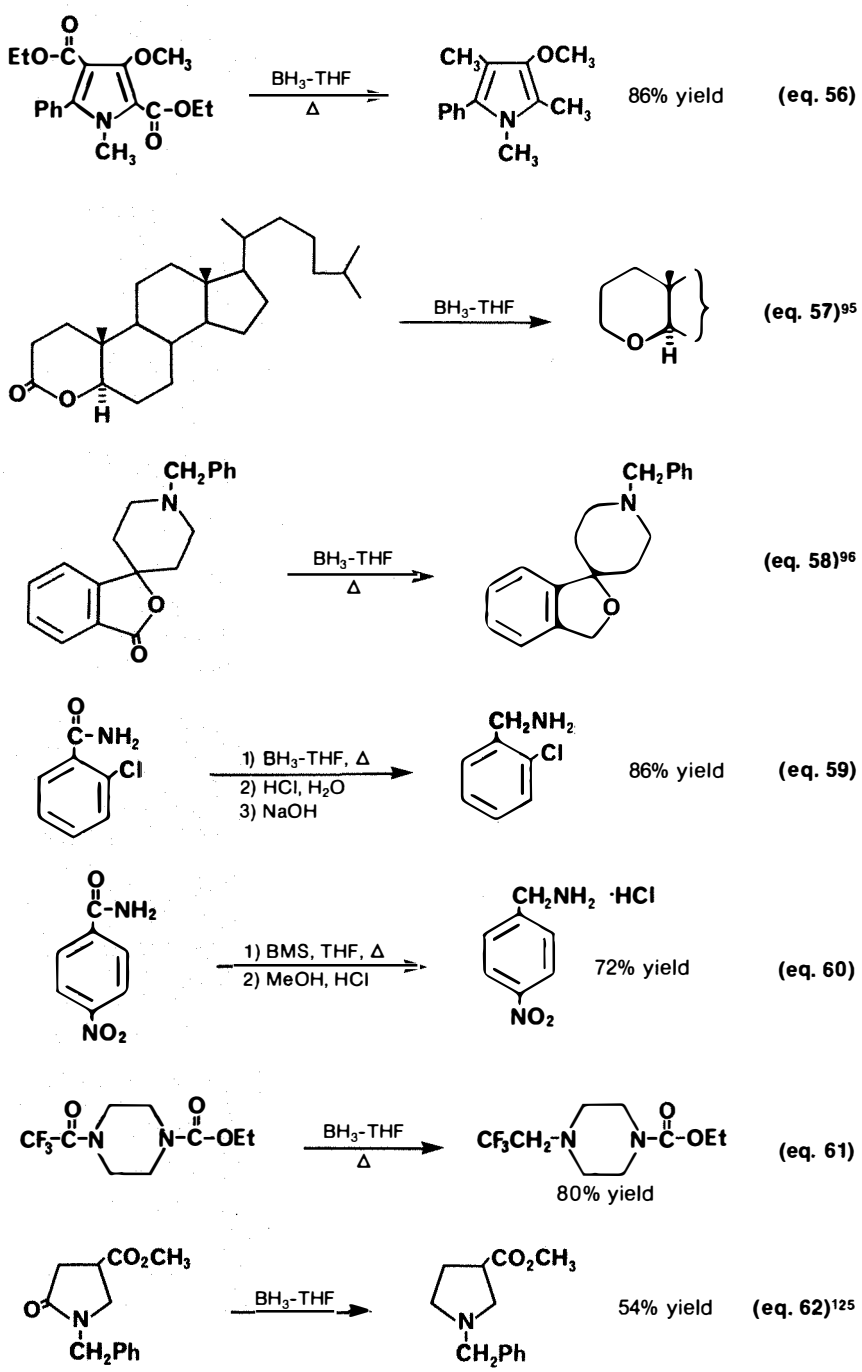
Primary, secondary and tertiary amides derived from both aliphatic and aromatic carboxylic acids are reduced rapidly with BH_3-THF in THF at reflux. Acidic or basic hydrolysis then provides the corresponding amine in excellent yield. The reduction of amides with diborane was originally investigated by Brown and Heim[97] and a full report of their detailed study has been published.[98]

Commercial BH_3-THF (eq. 59)[99] and BMS (eq. 60)[22] have both been used for selective amide reductions. In general, this reaction provides a convenient synthetic procedure and has been used extensively over the past 12 years, since the appearance of Brown's original communication.[97]

The syntheses of natural products and new pharmaceuticals are two important areas where many applications and advances have been made using this reduction. For example, the reduction of an amide functional group with BH_3-THF provided one of the key steps in the synthesis of the naturally occurring polyamine, *sym*-homospermidine.[100] An amide reduction was involved in an interesting synthesis of the eburnamine alkaloid ring system.[101] Also, amide reductions with borane reagents have been used for the preparation of catecholamines,[102] dehydrobufotenine,[103] tetrahydrocarbolines,[104] desoxypithecolobines,[105] and derivatives of ephedrine.[106]

Numerous chemicals of interest and importance in medicinal chemistry have been prepared through an amide reduction with a borane reagent. A few specific examples include derivatives of 2-fluoroethylamine[107] (potential carcinolytic agents), derivatives of *N*-(2-haloethyl)benzylamine[108] (antineoplastic agents), 1-deaza-1-thiareserpine[109] (antihypertensive), 6-(*N*-alkyl-*N*-arylamino)pyrimidines[110] (potential antimetabolites), various derivatives of 1,4-benzodiazepine[111] (antianxiety drugs), derivatives of 2-oxa-5-azabicyclo[2.2.1]heptane[112] (anticholinergic agents), 1,2-dihydro-3*H*-imidazo[1,5-*a*]-indol-3-ones[113] (CNS-active agents), and 4,4′-diaminodiphenyl sulfone derivatives[114] (antileprotic agents).

Various other metal hydride reagents are known to reduce amides to amines, but LAH is probably the most widely used alternative to the borane reagents. However, LAH is an extremely powerful reducing agent which will attack a large variety of sensitive functional groups. Thus, the utility of LAH as a selective reducing agent is rather limited. Examples of groups attacked by LAH during attempted amide reduction include α-fluoro,[110,115] α-bromo,[116] *N*-cyclopropyl,[117] (trifluoromethyl)aryl,[84,117,118] and sulfonyl.[119] Also, LAH reductions of trifluoroacetamides are extremely violent[120] and other trifluoromethyl groups are known to undergo complete hydrogenolysis with LAH.[121] Finally, reductive cleavage of the *N*-benzyl group is usually a serious problem during LAH reduction of benzamide derivatives.[112,122] Fortunately, amides which contain the above substituents or structural features are readily and cleanly reduced to amines using one of the borane reagents.[123]



In addition to the selective reductions mentioned above, the BH_3-THF reagent also reduces an amide substituent in the presence of either a carbamate (eq. 61)[124] or an ester (eq. 62).[125,126]

The preceding discussion and examples should indicate that BH_3-THF is usually the reducing agent of choice for the conversion of amides to the corresponding amines.

CONCLUSION

Brown and Korytnyk established the relative rates of reduction by BH_3-THF for a number of representative classes of organic compounds.[127] The results of these experiments indicate that the rate of reaction decreases in the order: carboxylic acids > alkenes > ketones > nitriles > epoxides > esters > acid chlorides. However, the reactivity of a given functional group can be greatly modified by the structure of the molecule. It is important to recognize that these relative reactivities must be considered approximate values for simple, representative groups, and may be altered or even inverted by modifications in the molecular structure. Hopefully, this review will help to further define the reactivity of the borane reducing agents and will assist organic chemists in deciding when it would be advantageous to utilize a borane reduction to solve a synthetic problem.

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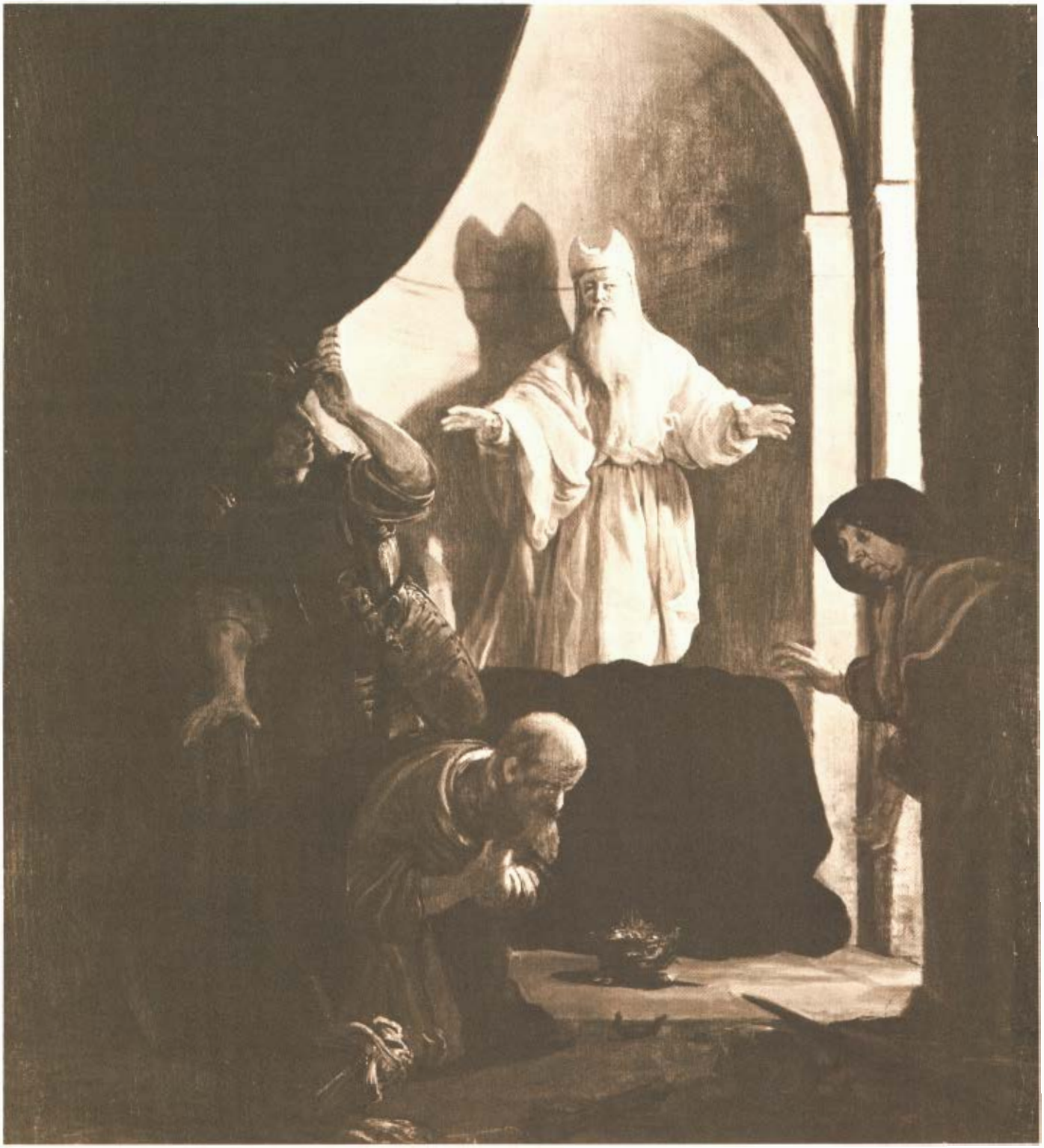

Lanthanide NMR Shift Reagents. See page 54.
Synthesis of Conjugated Lactones. See page 64.

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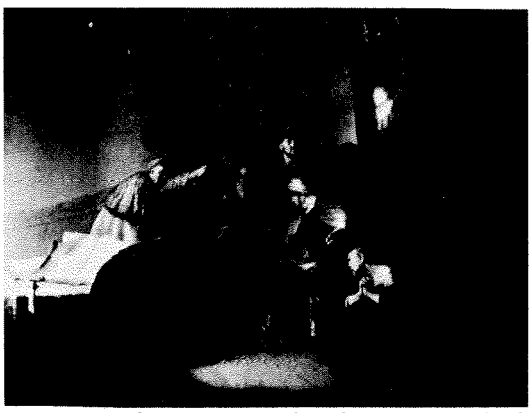
About Our Cover:

One of our chemist-collector's most interesting paintings is this curious depiction of King Saul and the witch of Endor, by Ferdinand Bol, one of Rembrandt's students, painted around 1650.

Here Saul is shown on his knees in a 'magic circle' complete with skull and crossbones, used in necromancy in the seventeenth century. The despondent figure of Saul is reminiscent of the figure of Judas in Rembrandt's painting of 1629 shown below. Judas and Saul both died the next day, and Bol showed deep insight by depicting Saul in his despair as Rembrandt had painted Judas.

There has been a great deal of discussion among Jewish scholars whether the apparition of Samuel was genuine, hallucination, or an imposture. The Rabbis of the Talmud, while condemning necromancy, also believed in it. Most later scholars either believed that the witch had no powers, but that God wanted the ghost of Samuel to appear to Saul (so Saadya and Nachmanides) or considered it a total fraud (so Maimonides and Ibn Ezra).

Believers in ghosts know that ghosts throw no shadows and one wonders why Ferdinand Bol made the shadow of the ghost of Samuel so prominent.



Rembrandt, *Judas Returning the Thirty Pieces of Silver*

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A Practical Guide To Uses of Lanthanide NMR Shift Reagents

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Lanthanide nmr shift reagents have become extremely valuable tools in a relatively short period of time. The potential user of nmr shift reagents needs to know what types of information can be obtained from their use, and how this information can be used in solving problems of chemical importance. This article is concerned with these questions, and topics such as stereochemical studies, polymer studies, chiral shift reagents, and the factors important in choosing a shift reagent for a particular application will also be discussed. Several general works on shift reagents have been published.[1-6] The present paper is intended primarily as a practical user's guide, in contrast with several previous reviews which were directed principally at people doing research on shift reagents.

In 1969, Hinckley[7] found that the dipyridine adduct of $Eu(thd)_3$ [$Eu(thd)_3$ = tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III), also called $Eu(dpm)_3$, where $Eu(dpm)_3$ = tris(dipivaloylmethanato)europium(III)] induced shifts in the nmr spectrum of cholesterol monohydrate. Sanders and Williams[8] then found that unsolvated $Eu(thd)_3$ was even more effective as a shift reagent than the dipyridine adduct, inducing shifts up to four times as great in magnitude. Since this early work, over 600 publications concerning shift reagents have appeared. Approximately 400 of the earlier articles are referenced in the bibliography of the book, "Nuclear Magnetic Resonance Shift Reagents,"[2] so they are not repeated here.

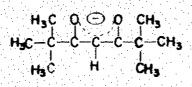
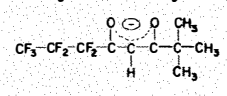
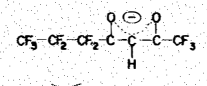
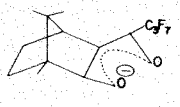
The most commonly used shift reagents are lanthanide β-diketonates. They function by acting as Lewis acids, forming a complex with the substance under analysis, which acts as a nucleophile. Induced shifts are attributed to a pseudo-contact, or dipolar, interaction between the shift reagent and the nucleophile.[2] What one normally sees in the "shifted spectrum" are averaged environments of the nuclei in the complexed and uncomplexed nucleophiles. The position of a given peak is consequently related to the stability of the complex formed, the amount of shift reagent added, and the McConnell-Robertson equation, which will be discussed later.

A reasonably large number of different combinations of β-diketonates and lanthanide metals can serve as shift reagents. The most commonly used metal chelates are those of Eu(III) and Yb(III), which normally induce downfield shifts, and Pr(III), which induces upfield shifts. In the earliest studies, complexes of the thd ligands were usually employed. In 1971, Rondeau and Sievers[9] reported that shift reagents which contained the fluorinated ligand, 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione, $Eu(fod)_3$ and $Pr(fod)_3$, were superior to $Eu(thd)_3$ in clarifying spectra. Figure 1 shows the effectiveness of the fod chelate in altering the spectra of di-*n*-butyl ether. The success of the fluorinated shift reagents was attributed to their improved solubility and increased Lewis acidity due to the electron-withdrawing effect of the fluorine atoms. Table I lists β-diketonates which are commonly employed as ligands.

APPLICATIONS

The simplification and clarification of spectra often yield a great deal of useful information. An elegant example of the use of shift reagents is shown in Figure 2.[10] The completely unintelligible spectrum of friedelan-3β-ol is greatly spread out and simplified, leading to assignment of almost all proton resonances. Demarco *et al.*[11] obtained a first order spectrum of *cis*-4-*tert*-butylcyclohexanol in $CDCl_3$ with addition of increasing amounts of $Eu(thd)_3$. They were then able to determine approximate

Table I. β-Diketonates Commonly Employed as Shift Reagent Ligands[a]

Ligand	Abbreviation	Structure of Anion
2,2,6,6-tetramethyl-3,5-heptanedione (dipivaloylmethane)	thd (tmhd) (dpm)	
6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione (1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)	fod	
1,1,1,5,5,6,6,7,7,7-decafluoro-2,4-heptanedione (1,1,1,2,2,3,3,7,7,7-decafluoro-4,6-heptanedione)	dfhd	
3-trifluoroacetyl-*d*-camphor [3-(trifluoromethylhydroxymethylene)-*d*-camphor]	facam	
3-heptafluorobutyryl-*d*-camphor [3-(heptafluoropropylhydroxymethylene)-*d*-camphor]	hfbc	

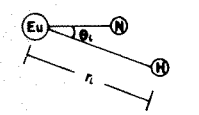
[a]Less preferred names and abbreviations are given in parentheses.

initial resonance positions of protons by plotting chemical shift *vs.* moles of shift reagent added, and extrapolating the least squares line thus obtained to zero concentration of shift reagent (see Figure 3). Similar methods of obtaining initial shifts have been used by other workers with good results.[12,13] Figure 3 also illustrates the effect of concentration of shift reagent on the magnitude of the induced shifts. This is a point which must be taken into account, especially when comparing results of different studies.

Frequently, coupling constants which were initially impossible to measure because of peak overlap can be estimated from a "shifted spectrum." In general, values thus obtained may be assumed to be valid for the unaltered spectra,[14] although some caution should be exercised.[4] It must be kept in mind that one is actually observing the spectrum of the complexed nucleophile, and the coupling constants may not always be the same for the uncomplexed species. Decoupling or double irradiation experiments which were not normally practical[15] may become feasible with addition of a shift reagent. Servé *et al.*[14] treated two 2-oxabicyclo[4.2.0]octane derivatives with Eu(fod)$_3$. For 7,8-*cis*-*endo*-diphenyl-2-oxabicyclo[4.2.0]octane, several multiplets were separated from an initially complex group of peaks (Figure 4), allowing determination of coupling constants and double irradiation experiments to be carried out. Addition of Eu(fod)$_3$ clarified the spectrum of the other derivative in a similar fashion. Among the many other good discussions of the application of coupling constant and decoupling experiment information obtained from simplified spectra are the analysis of di- and trimethoxybenzaldehydes by Neville,[16] the assignment of stereochemistry in isomeric perhydrophenalenols by Carey,[17] and the study of configurations of acetylated aryl glycopyranosides by Matsui and Okada.[18]

More detailed structural and stereochemical information may be obtained by the application of the McConnell-Robertson equation,[19]

$$\frac{\Delta\nu_i}{\nu_i} = \frac{K(3\cos^2\theta_i - 1)}{r_i^3} \qquad \text{(eq. 1)}$$



which shows the relationship between the induced chemical shift of the ith nucleus, $\Delta\nu_i$, and the location of the nucleus. Here K is a constant, r_i is the distance from the ith nucleus to the lanthanide ion, and θ_i is the angle between the principal magnetic axis

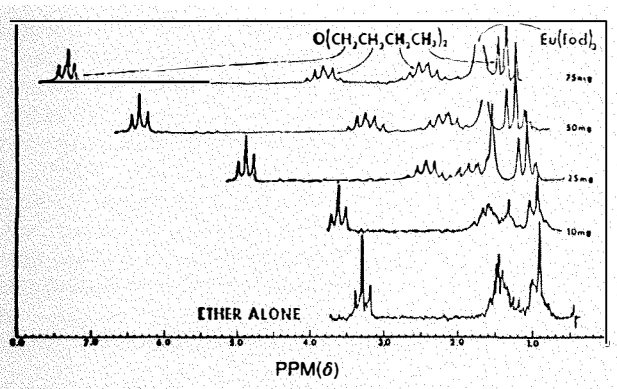


Figure 1. Clarification of the spectrum of di-*n*-butyl ether by addition of Eu(fod)$_3$.[9]

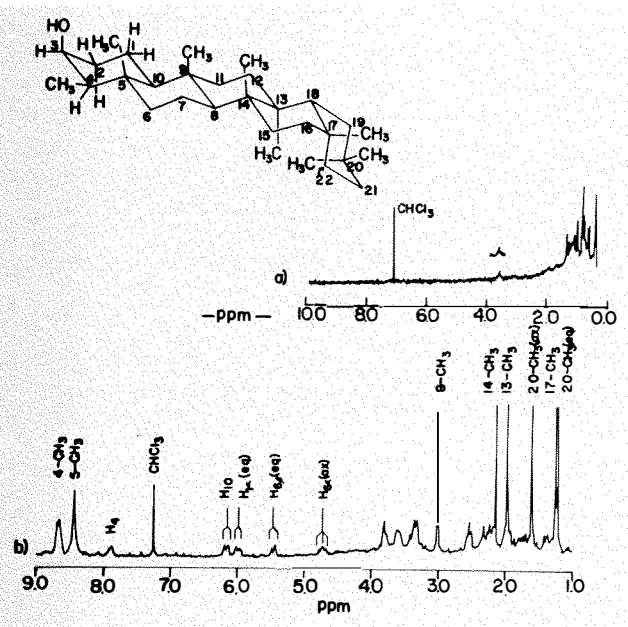


Figure 2. NMR spectrum of friedelan-3β-ol (10mg, 0.24 × 10^{-4} mol in 0.4 ml of $CDCl_3$): a) normal spectrum at 100 MHz, b) partial 220-MHz spectrum of solution of friedelan-3β-ol containing one mol equivalent of Eu(thd)$_3$ (17mg).[10]

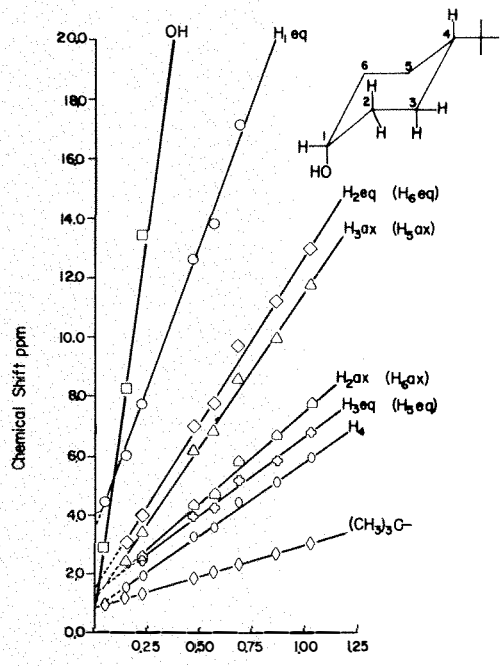


Figure 3. Variations in the chemical shift for the different protons of *cis*-4-*tert*-butylcyclohexanol with increasing concentration of Eu(thd)$_3$.[11]

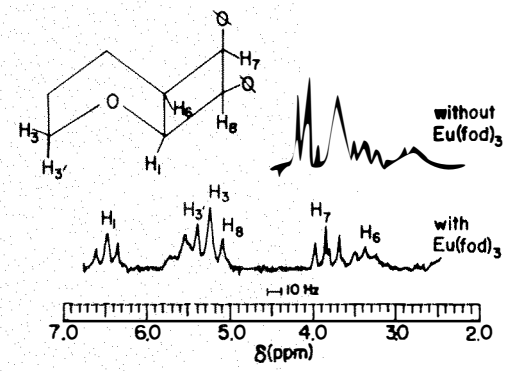


Figure 4. Effect of Eu(fod)$_3$ on 7,8-*cis*-*endo*-diphenyl-2-oxabicyclo[4.2.0]octane.[14]

of the complex, usually assumed to be essentially colinear with the lanthanide-nucleophile bond axis, and a line drawn from the nucleus of interest to the lanthanide ion. The use of the McConnell-Robertson equation entails several assumptions, usually taken to be:[20]

i) The observed shifts used in the analysis are entirely pseudo-contact in origin.
ii) Only one stoichiometric species exists in solution in equilibrium with the uncomplexed substrate.
iii) Only one geometric isomer of this species is present.
iv) This isomer is magnetically axially symmetric, so that the shifts are proportional to the geometric factor: $K(3\cos^2\theta_i - 1)r_i^{-3}$.
v) The principal magnetic axis has a particular, known orientation with respect to the substrate ligand or ligands.
vi) The substrate ligand exists in a single conformation, or an appropriate averaging over internal motions is performed.

Horrocks[21] has suggested that even if axial symmetry of the complex does not exist in the crystal, the averaged effect of rapidly interconverting geometrical isomers in solution leads to shifts approximating those which would be obtained from an axial model. Briggs *et al.*[22] have shown that an equation similar in form to the McConnell-Robertson equation can be derived and should be valid for the case in which the substrate ligand undergoes free rotation about an axis passing through the lanthanide ion, and for the case where the substrate-chelate complex forms three or more interconverting rotamers that are equally populated. Significantly, in this derivation there are no *a priori* assumptions made concerning the symmetry of the complex.

The angle term in Equation 1 gives positive values, except when θ is greater than 55°, but less than 125°. At these angles induced shifts will be in the opposite direction to the normal shifts, *e.g.*, upfield for Eu and downfield for Pr. This reversal in the direction of the shift corresponds to the term $3\cos^2\theta$-1 becoming negative for this range of angles. This accounts for the occasional observation that as one adds a shift reagent such as Eu(fod)$_3$, most peaks are shifted downfield, but some are shifted upfield or remain unchanged.[23] Initial reports frequently neglected the angle term, considering distance only, but the importance of including the term has been documented by many workers.[24,25]

An example of the effects of the angle dependence on shifts has been given by Rondeau and Berwick,[15] who used Eu(fod)$_3$ to determine the isomeric composition of the mixture of *p,p'*-disubstituted azoxybenzenes. The two geometrical isomers of *p*-methoxy-*p'*-methylazoxybenzene are shown in Figure 5. A scale model was used to estimate the H-Eu-O angles for the methoxy and methyl protons of one isomer (see Figure 6). If one assumes that the Eu-O bond length is approximately 2Å, the angle made with the methoxy protons is 84° and the angle with the methyl protons is 40°, for this isomer. Consequently, as predicted from the McConnell-Robertson equation, the methyl peak is shifted downfield ($\theta < 55°$) while the methoxy peak is shifted upfield ($\theta > 55°$). In the second isomer, the position of the oxygen, and consequently the europium, causes the reverse for the methoxy and methyl protons because of changes in θ.

The spectra shown in Figure 5 illustrate this phenomenon for the mixture of the two geometrical isomers. Before addition of Eu(fod)$_3$, the resonances of the methyl and methoxy peaks for both isomers were each accidentally degenerate; adding Eu(fod)$_3$ causes each of the nuclei to experience a different local magnetic field. The methyl peak of the least abundant isomer moves upfield and its methoxy peak moves downfield, while the more abundant isomer exhibits the opposite behavior. The relative amounts of the isomers can be obtained by integration of peaks.

The use of shift reagents for distinguishing isomers, as above, is widespread. Glover and Pointer[26] were able to estimate proportions of two isomeric methylated imidazoles by making use of the fact that for one isomer, steric hindrance prevented strong complexation with the shift reagent. Addition of Eu(thd)$_3$ or Eu(fod)$_3$ led to separation of resonances, as one isomer experienced shifts and the other did not. Corfield and Trippett[27] measured lanthanide-induced shifts in *cis* and *trans* isomers of 2,2,3,4,4-pentamethylphosphetan oxides (see Figure 7). The set of isomers which was known or assumed to be *cis* showed one range of shifts for the 3-proton, while the set known or assumed to be *trans* gave another range of shifts for the same proton resonance. Shifts for other protons were less definitive but a consistent difference between the two sets was observed. Thus the shifts of an unknown isomer could be compared with these results and its configuration assigned.

From the above examples it is clear that much stereochemical information can be obtained with a minimum of time and effort by adding shift reagents. In order to obtain detailed stereochemical information of the type provided by calculations based on the McConnell-Robertson equation, more effort and access to computing

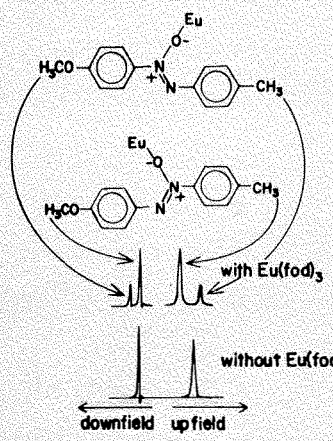


Figure 5. Isomers of *p*-methoxy-*p'*-methylazoxybenzene and partial nmr spectra of the isomeric mixture showing upfield and downfield shifts induced by the addition of Eu(fod)$_3$.[15]

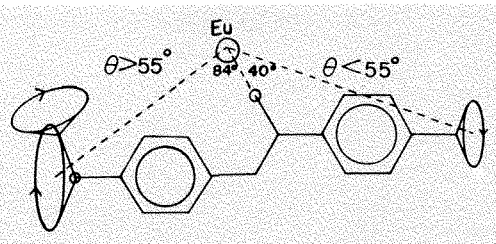


Figure 6. Scale model of Eu-azoxybenzene adduct.[15]

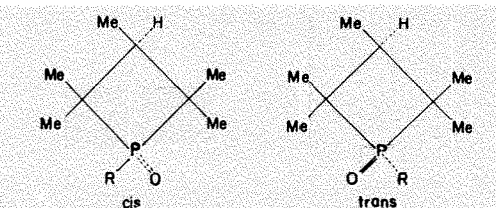


Figure 7. *Cis* and *trans* isomers of 2,2,3,4,4-pentamethylphosphetan oxides.[27]

facilities are required. Such studies may be well worth the effort because they can provide information about preferred structures of molecules *in solution*. One of the great uncertainties with which chemists have long had to contend is the question of whether structures of molecules determined by x-ray crystallography in a crystal lattice are really the same when that compound is in solution. Since behavior in solution is usually of more importance than in the solid state, any technique which can give information about structures in solution should be explored and perfected. Much remains to be learned about the capabilities and the limitations of using shift reagents for solution structural studies, but the stakes are so high, and the alternatives so few, that this area is likely to continue to be explored with vigor.

In general, it is assumed that marked changes in conformation of the nucleophile are not introduced by complexation with the shift reagent, but exceptions may occur. If the site of complexation is on a flexible part of the molecule, more caution must be exercised than if the complexation occurs on a rigid part.[28] Different types of conformational problems have been approached; a few examples follow. A comprehensive discussion of conformational studies with shift reagents has been given by Hofer.[28]

Both planar and boat conformations for 1,4-cyclohexadiene and its derivatives have been proposed by different workers. Paschal and Rabideau[29] found that Eu(fod)$_3$ allowed determination of the conformation of 1,4-dihydrobenzyl alcohol (see Figure 8). Addition of Eu(fod)$_3$ and double

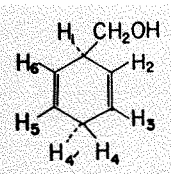


Figure 8. 1,4-Dihydrobenzyl alcohol.[29]

and triple irradiation experiments made measurement of all coupling constants possible. The fact that the vicinal coupling constants, $J_{3,4}$ and $J_{3,4'}$, were equal indicated a planar conformation for the ring; other coupling constant data were in accord with this conclusion. A possible rapid boat-to-boat inversion was ruled out by measurement of coupling constants of 3-fluoro-1,4-dihydrobenzyl alcohol-d_2 obtained from unaltered spectra and spectra of the compound treated with Eu(fod)$_3$.

A study of the preferred conformation of the P=O bond in *trans*-2-methyl-5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane (see Figure 9) was done by Yee and Ben-

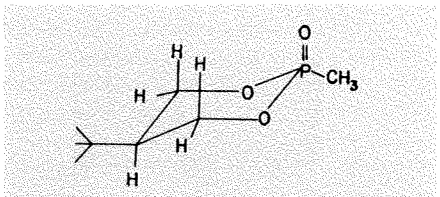


Figure 9. *trans*-2-Methyl-5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane.[30]

trude.[30] Here, magnitudes of induced proton shifts and use of models led to a choice between axial or equatorial orientations. A later report[31] dealt with the effect of substituents at the phosphorus atom on the P=O conformation in 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanes. Magnitudes of shifts induced by Eu(fod)$_3$ indicated that for certain R groups the P=O bond was mainly axial and for others mainly equatorial. Further confirmation of axial orientation of P=O for specified derivatives was given by the fact that their induced shift behavior was similar to that of 5,5-dimethylmethylene sulfite, in which there is strong indication of an axial S=O bond.

Quantitative approaches to analysis of lanthanide-induced shift data are often important. Computational methods using computer calculations have been used by numerous authors to determine preferred conformations and to identify isomers. In general, a set of lanthanide-induced relative shifts expected from the McConnell-Robertson equation is calculated for a particular structure and then compared with observed shifts.

Studies by Davis, Willcott and coworkers[32-36] have shown the power of quantitative calculations. From calculations similar to those used in x-ray spectroscopy, they have been able to distinguish between possible isomers with greater confidence than would otherwise be possible.

Calculated and observed lanthanide-induced shifts were compared[34] for isomers of methacrylonitrile. Poor agreement was obtained when the incorrect isomer was assigned to a particular set of values; good agreement was obtained for the correct isomer. Both computer methods and qualitative arguments were used in identification of isomers of methylbicyclooctenols.[36]

These workers and others[37] have performed a systematic study of the application of the McConnell-Robertson model to the interpretation of shifts in rigid oxygenated bicyclic molecules. One method[32] involves locating the molecule under analysis in a Cartesian coordinate system with the functional group at the origin. Then different positions of the lanthanide ion are examined by moving the ion over the surface of a sphere of radius d, the assumed Eu-heteroatom distance, through all angular values. At each lanthanide position, shifts for all the protons are calculated from the McConnell-Robertson equation. These are then compared with observed shift values and a best fit is determined. Calculations for a number of oxygenated hydrocarbons gave a reasonable position for the lanthanide in every case, and a range of lanthanide-oxygen distances, d, of 2.5 to 3.5Å gave good fits. It is somewhat reassuring that x-ray structural studies on lanthanide complexes show Eu-O bond distances of approximately 2.5Å.

In another quantitative study, Demarco *et al.*[38] found that while the europium-heteroatom distance was not sensitive to the basicity or nature of the functionality at which complexation occurred, steric effects did have an influence. Other structural studies[39-41] also have been carried out.

Young[42] *et al.* used fod shift reagents to investigate rotamers of cyclic dipeptides. Proton coordinates from the rigid peptide backbone and induced shifts for these protons were used to locate the best positions of the lanthanide with a computer program. Then shifts for protons on the rotating side chain could be predicted and compared with observed shifts, to determine the preferred rotamer. For seven out of eight cyclic dipeptides, use of shift reagents allowed identification of preferred rotamers. Ammon *et al.*[43] used a similar method to study conformations of methyl and ethyl groups on products from the ring expansion of a β-lactam. A good discussion of the use of a computer method for conformational investigations, including estimations of conformer populations at equilibrium, has been given by Montaudo *et al.*[44]

An alternative computational method has been proposed by Wing *et al.*[45] It involves placing the structure of a molecule on a map of the dipolar field and reading off predicted shifts, which are scaled with observed shifts. Good agreements were obtained for pyridine, *cis*-4-*tert*-butylcyclohexanol, and 1-adamantanol.

Shift reagents are effective with many organic compounds. Examples of shift reagent studies with alcohols, including polycyclic alcohols[46] and mixtures of alcohols,[47] are numerous.[48-50] Ketones,[51-55] aldehydes,[56] esters,[57,58] ethers,[9,14] and flavones[59,60] have also been examined. Sanders and Williams[8] reported that Eu(thd)$_3$ decomposed in the presence of phenols and carboxylic acids. However, several workers have found that Eu(fod)$_3$ can be used successfully with these sub-

strates. Dyer *et al.*[61] reported that shifts in the spectrum of *n*-butyric acid in the presence of $Eu(fod)_3$ remained constant over a seven-day period, and that the $Eu(fod)_3$-treated spectrum of *N*-trifluoroacetyl-*d*-alanine did not change for several hours, suggesting use of fod shift reagents for examining peptides and their derivatives. *n*-Hexanoic acid exhibited induced shifts in the presence of $Eu(fod)_3$ which did not change over a period of several days.[62] Induced shifts for phenols, xylenols, and cresols, as well as successful analysis of a mixture of cresols, have been reported by Shoffner.[63] Other workers have done similar studies,[13,64] confirming the usefulness of $Eu(fod)_3$ for studies of phenol and substituted phenols.

Among the nitrogen-containing compounds that have been studied are amines,[65,66] amides,[67] nitriles,[12] oximes,[68,69] and others.[70-73] Sulfoxides,[74] sulfones,[75] diphenylsulfines,[76] and other sulfur-containing compounds[77,78] have been examined; phosphoryl-containing compounds,[79] dioxaphosphorinanes,[30,31,80] and various organophosphorus compounds[81] are also subjects of reports. The reader is referred to Cockerill *et al.*[4] for a comprehensive discussion of other types of organic substrates.

While one would anticipate that lanthanide shift reagents, which are hard Lewis acids, would be likely to interact with functionalities containing oxygen and nitrogen, their effectiveness with alkenes would not normally be expected. Normally there are no appreciable shifts in the spectra of olefins; however, there are ways that one might be able to alter the spectra by forming a binuclear metal complex. Evans *et al.*[82] used a mixture of a fod chelate and silver heptafluorobutyrate to alter the spectra of alkenes. As a soft Lewis base, silver (I) interacts with the alkene, and apparently holds it in the vicinity of the paramagnetic europium(III). One possible mode of interaction of the lanthanide with the alkene is shown in Figure 10. The shifts (shown in the figure in ppm) are relatively

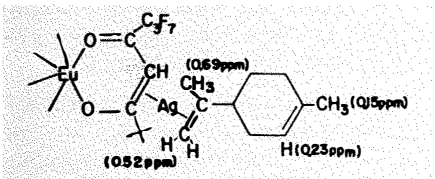


Figure 10. Possible mode of interaction of lanthanide with alkene [0.1*M* $Eu(fod\text{-}d_9)_3$, 0.1*M* $C_3F_7CO_2Ag$, 0.2*M* limonene in CCl_4].[82]

small; consequently, there is much room for improvement. Studies are presently underway at the University of Colorado to synthesize binuclear complexes which will be more effective for the alkenes.

The two major factors which determine the probability of lanthanide interaction with a functional group are basicity and steric effects. A nearly linear correlation between basicity and induced shifts was found for the *ortho* and *meta* protons of *para*-substituted anilines.[83] For a group of substituted phenols, the smallest shift was observed for the most acidic phenol, *p*-nitrophenol.[13] Morrill *et al.*[84] have proposed the hard-soft acid-base (HSAB) theory as an indicator of expected interaction of shift reagent with substrates. They found that the degree of interaction of organosulfur compounds was proportional to the polarizability (HSAB character) of the nucleophile functionality. A study of seven amines indicated that, in general, those with the most steric hindrance exhibited smaller magnitudes of induced shifts in comparison with less hindered amines.[85] The effects of steric hindrance are also apparent in the case of *N*-methylaniline and *N,N*-dimethylaniline,[83] which show greatly reduced induced shifts even though they are more basic than aniline.

Sanders and Williams[86] reported that functional groups gave magnitudes of induced shifts which decreased as $-NH_2 > -OH > \rangle C{=}O > -O- > -CO_2R > -CN$. Thiols, thioethers, and acyl phosphines generally have less interaction with the lanthanide than oxygen and nitrogen analogs.[87] A series of inter- and intramolecular competition experiments in the presence of shift reagent has been done by Hart and Love.[88]

A preferred site of complexation usually exists within a functional group with more than one potential site of complexation. In amides, complexation at the carbonyl oxygen rather than the nitrogen atom has been noted.[72,89] A study of the lactam, lupanine, also indicates that the carbonyl oxygen is the preferred coordination site.[90] In *N*-methyl-*N*-isopropylthioformamide, the lanthanide is apparently complexed to the sulfur atom.[91]

In polyfunctional substrates, one group is often the preferred complexation site. Relative basicity and steric effects, as discussed above, can be used in determining this preferred site. A few examples of shift reagent studies on polyfunctional molecules include a study of anhydrides, with both ether and carbonyl sites,[92] of N- and O-acetylated carbohydrates and nucleosides which have acetate and amide functionalities,[93] and of azetidine derivatives with hydroxyl oxygen and a ring nitrogen.[94] Gore and Armitage[95] used a computer simulation to determine the preferred binding site of europium in diastereomers of multistriatin. When sufficient concentrations of shift reagent lead to saturation at the preferred site of complexation, coordination may begin at a less favored functional group.[96,97] Cockerill *et al.*[4] have given an in-depth discussion of competition between functional groups, including hydroxyl groups, esters and lactones, ethers and epoxides, ketones, quinones and anhydrides, amides and lactams, amines, and others.

Carbohydrates[98-101] and steroids[102,103] have been subjects of reports. In general, lanthanide salts, *e.g.*, nitrates and chlorides, are used for studies of biological molecules that are soluble in water.[104-106]

POLYMER STUDIES

Shift reagents are also useful in polymer studies. For atactic poly(methyl methacrylate), addition of shift reagent resolved the three peaks of the C-methyls in isotactic, heterotactic, and syndiotactic triads.[107] The resolution of resonances of polypropylene oxide with $Eu(fod)_3$ is shown in Figure 11.[108] In the untreated spectrum, the triads of the methyl groups

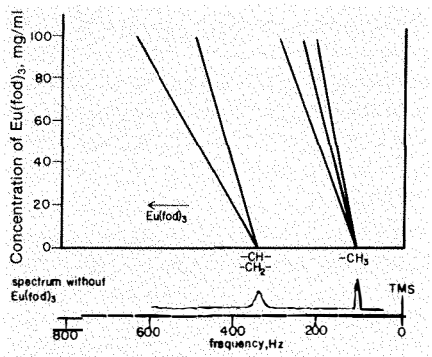


Figure 11. Effect of progressive addition of $Eu(fod)_3$ on the spectrum of polypropylene oxide.[108]

appear as three overlapping doublets. The graph illustrates how progressive addition of $Eu(fod)_3$ separated these as well as the $-CH=$ and $-CH_2-$ resonances. Ho[109] found that molecular-weight determination by end-group analysis was facilitated by the separation of resonances brought about by addition of $Eu(thd)_3$.

ISOTOPE EFFECTS

Smith *et al.*[110] have reported an interesting deuterium isotope effect in alcohols upon addition of $Eu(fod)_3$. Substitution of deuterium for the hydrogen vicinal to the OH group led to an increase in shift magnitudes for other protons in the substituted alcohol. This is attributed to one or both of two factors. The deuterium may undergo greater hydrogen bonding with the oxygen of the shift reagent than hydrogen does, thus increasing complex stability. Alternatively, the presence of the deuterium may increase the basicity of the oxygen in the alcohol. A long-range deuterium isotope effect has been observed

by DePuy *et al.*[111] Two pairs of diastereomers of deuterium-substituted methyl ethers, obtained from the ring opening of trimethylcyclopropane, were distinguished by adding $Eu(fod)_3$. This finding is remarkable because the only difference in a pair is the position of deuterium substitution five bonds away from the $Eu(fod)_3$, assuming coordination of the methoxyl group. It was suggested that this may be a result of reduced steric hindrance at the complexation site, due to the smaller vibrational amplitude and space occupied by a C-D bond.[111]

KINETIC MEASUREMENTS

The applicability of dynamic nuclear magnetic resonance spectroscopy, a technique used in studying relatively rapid molecular motions and reactions, has been limited by problems involving $\Delta\nu_{\infty}$, the magnitude of the difference of the resonance frequencies of exchanging nuclei in the absence of exchange.[112] Small values of $\Delta\nu_{\infty}$ often cause limited or inaccessible temperature ranges which are amenable to kinetic measurements. Furthermore, accidental degeneracy also sometimes limits one's ability to perform kinetic measurements by peak coalescence techniques. The ability of lanthanide shift reagents to alter $\Delta\nu_{\infty}$, thereby changing the nmr time scale, to facilitate kinetic measurements has been reported by Tanny *et al.*[112]

Addition of a lanthanide chelate such as $Eu(fod)_3$ can help in two distinct ways. It can change the time scale by increasing $\Delta\nu_{\infty}$, and it may, in some cases, slow down the rearrangement by complexation. This interesting and unusual use of shift reagents is an example of many possible new applications of these already important compounds.

CHIRAL SHIFT REAGENTS

The use of chiral shift reagents offers a new approach for determination of enantiomeric purity by nmr. For a review of the early chiral shift reagent literature, the reader is referred to Kutal.[113] Resonances of enantiomers undergo different chemical shifts in a chiral environment, leading to determination of enantiomeric relative abundances.[114] Consequently, one can use chiral shift reagents to determine whether reactions have occurred with retention of configuration, inversion, racemization or some combination. Protons and groups which are enantiotopic by internal comparison[115] also show separation of resonances in the presence of a chiral shift reagent, and this fact can be used to differentiate *meso* from *dl* diastereomers.

Whitesides and Lewis introduced chiral shift reagents in 1970.[116] They found that addition of tris[3-(*tert*-butylhydroxymethylene)-*d*-camphorato]europium(III) separated resonances of *R* and *S* enantiomeric amines. Soon after, Goering *et al.*[117] reported that the fluorinated shift reagent, tris[3-trifluoroacetyl-*d*-camphorato]europium(III), $Eu(facam)_3$, separated peaks for enantiomers of 2-phenyl-2-butanol and other compounds. Since that time the most frequently used chiral shift reagents have been $Eu(facam)_3$ and $Eu(hfbc)_3$. Figure 12 compares the results of addition of $Eu(thd)_3$ and $Eu(facam)_3$ to *dl*-2-phenyl-2-butanol. As expected $Eu(thd)_3$ did not cause different shifts for one enantiomer relative to its mirror image, but $Eu(facam)_3$ caused separation of the α-methyl resonance into two peaks, and resolved the β-methyl triplets into a quintuplet, thus distinguishing the two enantiomers. $Eu(facam)_3$ also was used[117] to determine the enantiomeric composition of a sample of *dl*-3-methyl-3-phenyl-2-pentanone. The chiral shift reagent caused separation of some of the peaks arising from the two enantiomers. In Figure 13, at the far left, the acyl methyl proton resonances are well separated and their relative areas can be integrated. The optical purity was determined by nmr to be 27.3%, in satisfactory agreement with that determined by polarimetry (25.4%). Because workers in almost every laboratory have access to nmr spectrometers while relatively few groups have polarimeters, this is a particularly attractive method for determining enantiomeric composition when differential shifts can be induced for the two optical isomers. Other workers[118,119] have also used chiral shift reagents to determine enantiomeric composition successfully. Fraser *et al.*[120] found that tris[3-heptafluorobutyryl-*d*-camphorato]-europium(III), $Eu(hfbc)_3$ separated proton resonances of enantiomers of alcohols and other compounds.

To determine enantiomeric compositions by use of chiral shift reagents, one must choose one or more signals to monitor for enantiomeric shift differences, or differential shifts, $\Delta\Delta\delta$.[117] A general guideline for choosing such signals is that they show sufficient response to the shift reagent and be adequately separated from other signals.[119] A good discussion of practical aspects of use of these reagents, such as the selection of solvents and sample preparation, has been given by McCreary *et al.*[121]

The ability of chiral shift reagents to cause differential shifts in protons or groups which are enantiotopic by internal comparison,[115] *i.e.*, enantiotopic protons or groups on the same molecule, has been reported by Fraser *et al.*[122] They found that $Pr(hfbc)_3$ induced a chemical shift difference for the CH_2 protons of benzyl alcohol, allowing determination of the geminal coupling constant. No significant change in the value of the coupling constant occurred until 0.3 equivalent of shift reagent had been added. Addition of

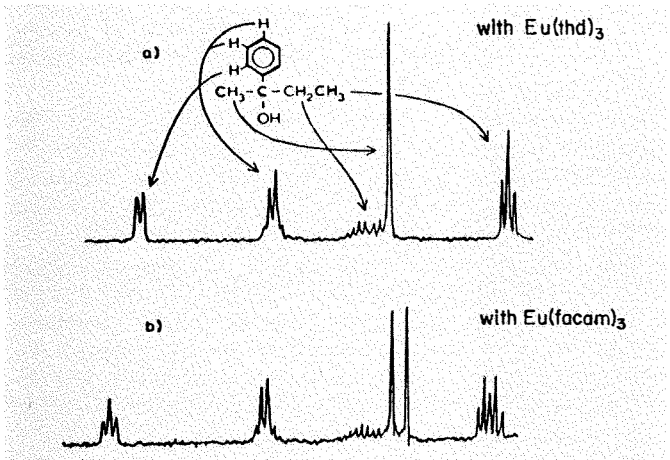


Figure 12. Differences in shifts of enantiomers induced by adding a chiral shift reagent. Spectra of 0.54*M* 2-phenyl-2-butanol in CCl_4 in the presence of (a) 0.13*M* $Eu(thd)_3$, and (b) 0.42*M* $Eu(facam)_3$.[117]

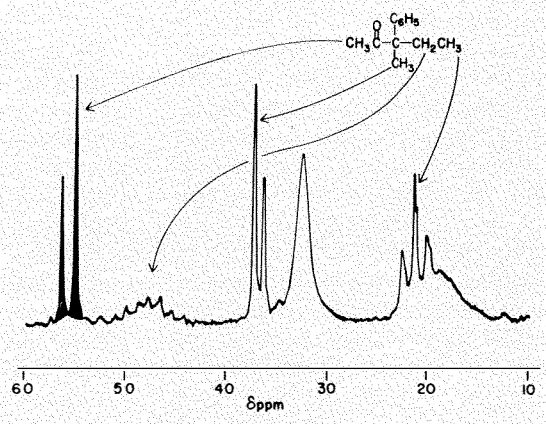


Figure 13. Spectrum of a CCl_4 solution of *dl*-3-methyl-3-phenyl-2-pentanone in 0.5*M* $Eu(facam)_3$.[117]

Pr(hfbc)$_3$ also distinguished methyl groups of dimethyl sulfoxide and 2-propanol which are enantiotopic by internal comparison. Goering *et al.*[123] reported that Eu(hfbc)$_3$ induced differential shifts in enantiotopic protons of six substrates, while Eu(facam)$_3$ induced such an effect in one case.

Kainosho and coworkers[124] distinguished *meso* from *dl* diastereomers with Eu(facam)$_3$. A mixture of *cis*- and *trans*-2,3-butylene oxide treated with Eu(facam)$_3$ exhibits four pairs of methine and methyl multiplet signals, one set each for the *d* and *l* isomers, and two sets from the meso isomer. The existence of coupling between protons enantiotopic by internal comparison in the presence of chiral shift reagents also allowed determination of *meso*-dimethyl 2,3-diaminosuccinate and the *meso* stereochemistry of the pesticide, dieldrin.[124] Goe[125] differentiated the dimethyl esters of *cis*- and *trans*-3,3,4,4-tetramethylcyclobutane-1,2-dicarboxylic acid on the basis of coupling observed for the *meso*, *cis* isomer; and Cameron *et al.*[126] performed similar studies on bianthrones.

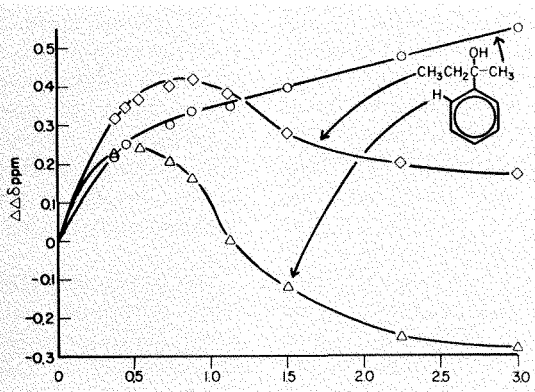


Figure 14. Plots of $\Delta\Delta\delta$ *vs.* reagent-substrate molar ratio for three sets of protons of 2-phenyl-2-butanol; in 0.3*M* Eu(hfbc)$_3$.[123]

There is great interest in attempting to determine absolute configurations of molecules from nmr spectra in the presence of chiral shift reagents. It has been possible to do this for closely related compounds,[127,128] but much more must be learned before this can be done with confidence for compounds with greater structural differences. Several workers have described the difficulties and uncertainties[127-130] associated with this. An illustration of one of the difficulties that may be encountered is seen in Figure 14. The sense of non-equivalence, *i.e.*, the relative field position of the resonance of one isomer relative to the corresponding resonance of its enantiomer[114] and the magnitude of the induced differential shift, $\Delta\Delta\delta$, of resonances of enantiomers have a complicated dependence on the reagent-substrate molar ratio. Different sets of protons may simultaneously exhibit different magnitudes of $\Delta\Delta\delta$ and senses of non-equivalence. These phenomena are illustrated by 3 sets of protons of 2-phenyl-2-butanol.[123] Figure 14 shows that as the molar ratio is increased, $\Delta\Delta\delta$ for the α-methyl resonances increases steadily, while the differential shift for the β-methyl protons reaches a maximum, then declines and levels off. For the *ortho* protons, a reversal in the sense of non-equivalence occurs at a molar ratio approximately equal to unity. McCreary *et al.*[121] noticed similar behavior of the *ortho* proton of 1-phenylethylamine.

Different shift reagents may also affect the sense of non-equivalence. This is not surprising because the shape of the chiral pocket, which accommodates the nucleophile, is different for different shift reagents. In the presence of tris[3-(*tert*-butylhydroxymethylene)-*d*-camphorato]-europium(III), all *R* enantiomer proton resonances of 1-phenylethylamine are at lower field than *S* enantiomer resonances. With two other chiral shift reagents, the CH protons of the *R* enantiomer are at lower field than those of the *S* enantiomer, while the opposite is true of the methyl protons.[131]

The implications of this behavior of magnitudes and senses of non-equivalence are both theoretical and practical. If $\Delta\Delta\delta$ was caused solely by preferential complexation of one enantiomer to the shift reagent, *i.e.*, different binding constants for enantiomers, then the sense of non-equivalence should be the same for all proton resonances, and $\Delta\Delta\delta$ should increase to a maximum and then level off.[123] The fact that this is not the case suggests that different magnetic environments[117] or stoichiometries[123] of shift reagent-substrate adducts are responsible for $\Delta\Delta\delta$. On the practical side, one must be aware of these phenomena whenever measurements of $\Delta\Delta\delta$ are made.

PRACTICAL TECHNIQUES AND THE CHOICE OF SHIFT REAGENTS

The fastest and easiest technique for obtaining induced shifts is to add a few milligrams of shift reagent directly to the nucleophile dissolved in solvent. Increments of shift reagent can be added until sufficient resolution is attained; this procedure also allows one to observe peak changes gradually, and to monitor any crossover of peaks. Shapiro and Johnston[132] have outlined an "incremental dilution method" which has some advantages over simple addition of the solid shift reagent, including improved accuracy of results at low shift reagent-substrate concentrations.

The most frequently used solvents are chloroform and carbon tetrachloride, although some workers have recommended the use of carbon disulfide.[133] A study of solvent effects on induced shifts has been performed by Bouquant and Chuche.[143] Temperature dependence of shifts is another variable that can be taken advantage of in some instances.[135-139]

Eu(fod)$_3$ is generally obtained as a hydrate. While the chelate rigorously dried *in vacuo* over P_4O_{10} has been found to be more effective than the hydrate, *e.g.*, about twice as effective for pinacolone,[61] the hydrate generally gives sufficient shifts and is easier to store and handle. Bruder *et al.*[140] have shown that the truly anhydrous species is very difficult to obtain and to keep anhydrous, but for practical purposes samples stored in a desiccator over P_4O_{10} function quite effectively for shift reagent applications.

Once the applicability of shift reagents to a particular problem has been ascertained, the question of which shift reagent to use still remains. There are no set rules to be followed in choosing a shift reagent, and often trials with several different ones may be necessary to obtain good results. However, a few general principles can be outlined.

The general superiority of the fluorinated shift reagents due to their increased Lewis acidity and improved solubility has been mentioned earlier. Gas chromatographic studies by Feibush *et al.*[141] and Brooks and Sievers[142] have demonstrated the improved ability of the fluorinated reagents to form complexes with nucleophiles. Both fluorinated and unfluorinated lanthanide chelates were incorporated into the liquid stationary phase of gas chromatography columns.[141] For numerous organic substrates, including ethers, ketones, esters, and alcohols, longer retention times were found for the columns with the fluorinated reagents. Increased

solubility of the fluorinated reagents often allows studies which could not otherwise be carried out.[9]

$Eu(fod)_3$ is now the most widely used shift reagent and has the best general applicability. It should be the first shift reagent tried unless circumstances indicate otherwise. If the *tert*-butyl resonances of $Eu(fod)_3$ interfere with the resonances of the nucleophile, one can employ the deuterated reagent or the more extensively fluorinated complex, $Eu(dfhd)_3$.

For some cases, chelates of other lanthanides may give better results than the europium(III) chelates. The downfield shifts induced by europium reagents may lead to complication rather than simplification of spectra, due to increased overlap of peaks. In this situation an upfield-shifting reagent may give better results; of these, $Pr(fod)_3$ is usually the best. $Ho(fod)_3$ usually induces the largest magnitude of shifts,[23] but increased line-broadening may also result, obliterating fine structure. If increased magnitudes of shifts are desired and line-broadening can be tolerated, $Ho(fod)_3$ may be the reagent of choice. In an early study Tomic *et al.*[143] found $Ho(thd)_3$ more effective than $Pr(thd)_3$ for analysis of two alcohols, as it separated resonances more distant from the complexation site, which could not be sufficiently resolved by addition of $Pr(thd)_3$. Gas chromatographic studies have shown that decreasing the ionic radius of the metal ion increases the stability of the shift reagent-nucleophile adduct.[23] Thus, for extremely weak nucleophiles, $Yb(fod)_3$ may give better results, or complexes of 1,1,1,5,5,6,6,7,7,7-decafluoro-2,4-heptanedione, dfhd, may be even better.

Chelates of dfhd have been synthesized, characterized,[144] and evaluated as shift reagents.[145] This new class of shift reagents has been found to be superior in certain applications. Increasing the fluorine substitution over that of the already useful fod chelates has led to even better solubility in certain solvents and greater Lewis acidity.[145] While $Ln(fod)_3$ complexes have better solubility in chloroform, $Ln(dfhd)_3$ complexes are more soluble in acetonitrile and dioxane, solvents in which many biologically important compounds are soluble. $Ln(dfhd)_3$ complexes show superior shifting ability with such weak bases as nitromethane and acetonitrile[145] (see Table II). Less line broadening was exhibited by $Eu(dfhd)_3$ than by the Yb and Pr chelates. Lanthanide-dfhd shift reagents are also able to induce shifts in the weak Lewis bases, *p*-chloronitrobenzene and *p*-nitrotoluene;[145] nitro-containing compounds have not exhibited appreciable interaction with other shift reagents. A further advantage of the dfhd shift reagents is that the *tert*-butyl groups of fod chelates, which sometimes overlap nucleophile resonances, are replaced by $-CF_3$ groups in dfhd, which do not interfere.

Table II [145]

Comparison of Shifts Induced by dfhd and Other Shift Reagents in the Spectra of Weak Lewis Bases [a]

Shift Reagent	Acetonitrile	Nitromethane
$Pr(dfhd)_3$	-3.45	-2.27
$Yb(dfhd)_3$	5.67	3.00
$Eu(dfhd)_3$	1.92	0.88
$Eu(fod)_3$	0.85	0.23
$Eu(thd)_3$	0.75	0.23

[a] Shifts are given in ppm. Data obtained at 60 MHz with 10^{-4} mole shift reagent dissolved in 0.5g $CDCl_3$. The mole ratio of shift reagent to substrate was 0.3.

Another striking example of the ability of $Eu(dfhd)_3$ to interact with weak nucleophiles is the alteration of the spectrum of *n*-octyl fluoride.[146] Upon addition of $Eu(dfhd)_3$ large shifts were observed, *e.g.*, ~4ppm. It is clear that increasing the extent of fluorine substitution in the chelate has resulted in a "super Lewis acid". It should be mentioned that $Eu(dfhd)_3$ is usually isolated as a dihydrate. Because it is such a strong acid the two water molecules are tightly bound and cannot be removed readily.[144] Nonetheless, the dihydrate functions as a very effective shift reagent and the nucleophile either adds to the hydrated chelate or displaces the water molecule(s). Because it is difficult to know the water content of the shift reagents with certainty, most authors indicate the method of drying and conditions of storage, but do not specify the state of hydration. The notations, "$Eu(fod)_3$" and "$Eu(dfhd)_3$" are in actuality usually designating $Eu(fod)_3(H_2O)_{0.5}$ and $Eu(dfhd)_3(H_2O)_2$, respectively. Furthermore, the solvents often contain some water, so perhaps this imprecision is not of great significance.

In summary, no single shift reagent will be the best for all applications. Bender *et al.*[147] have reported that $Eu(thd)_3$ led to isomeric differentiation where $Eu(fod)_3$ could not. In some cases, larger magnitudes of shifts may be induced by $Eu(thd)_3$.[148] Bose *et al.*[149] observed that for some compounds $Eu(fod)_3$ actually reduced the separation of proton resonances of diastereotopic protons, while $Pr(fod)_3$ brought about resolution of these resonances. Thus, while $Eu(fod)_3$ is of best general applicability, utilization of alternatives is sometimes essential in order to learn as much as possible about a given system. The dfhd chelates are an exciting new possibility with many potential applications.

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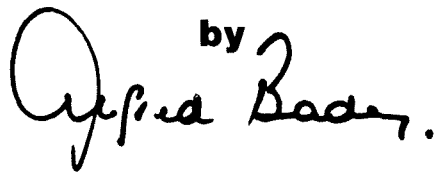

Last winter the New Orleans Section of the ACS invited me to speak on chemistry and art. I had never been to New Orleans before, really enjoyed the visit and even found three old master paintings. Naturally, I took the opportunity to visit many chemists in the area. At Tulane School of Medicine, Professor Krishna C. Agrawal told me that there was a lot of interest in azomycin (2-nitroimidazole), an antimicrobial agent. We found the scale-up from gram quantities fairly difficult, but have now made the first 100-gram batch.

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

Recent Methods for the Synthesis of Conjugated Lactones

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Recently, a number of naturally occuring sesquiterpenes with potential cytotoxic activity were found to contain the α-methylene-γ-butyrolactone moiety.[1] To a lesser extent, the 6-membered ring analog, α-methylene-δ-valerolactone unit, was found in several biologically active natural products. The presence of the $\Delta^{\alpha,\beta}$-butyrolactone unit in cardenolides and isocardenolides[2] and the α-pyrone unit in biologically active bufadienolides[3] and marinobufatoxins[4] has aroused considerable interest. The structural diversity and stereochemical complexity combined with the necessity to synthesize these natural products and their analogs prompted intense synthetic interest in these lactones.

α-Methylene lactones have been the focal point of this synthetic upsurge and the subject of several excellent reviews.[5,6] The chemistry of unsaturated lactones has been reviewed by Rao.[7] This brief survey covers the highlights of the synthetic aspects of (A) the α-methylene and (B) the endocyclic conjugated 5- or 6-membered lactones of biological interest reported in the last two to three years.

A. 5- AND 6-MEMBERED α-METHYLENE LACTONES

α-Methylene-γ-butyrolactone and α-methylene-δ-valerolactone units are found in various cytotoxic sesquiterpenes. Generally, these moieties are either *cis*- or *trans*-fused to 6-, 7- or 10-membered ring systems. The following examples demonstrate their structural diversities. Pseudoguaianolides like helenalin (**1**), mexicanin I (**2**)[8] or damsin (**3**)[9] are examples of γ-lactones *cis*- or *trans*-fused to a 7-membered ring.

The highly functionalized cytotoxic elemanolide dilactones, vernolepin (**4**)[10] and vernomenin (**5**),[10] have both a *trans*-γ-lactone and a *cis*-δ-lactone unit fused to a cyclohexane ring. The germacrane sesquiterpene, costunolide (**6**),[11] has an α-methylene-γ-butyrolactone moiety *trans*-fused to a 10-membered ring. Synthesis of these lactones or their analogs offers a challenge to the present-day synthetic methodology.

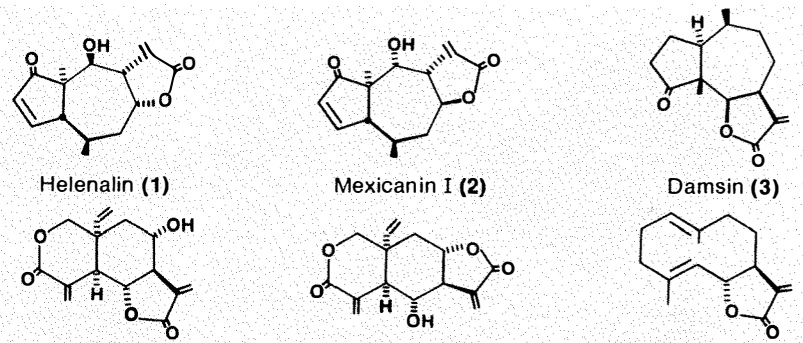
These lactones may be synthesized either through: 1) α-methylenation of a lactone or 2) lactonization of a precursor having a preformed α-methylene unit. These along with 3) rearrangement pathways and 4) some miscellaneous routes, are discussed here. Choice of the route is dictated chiefly by stereochemical requirements as well as the ease of introduction of proper functionalities.

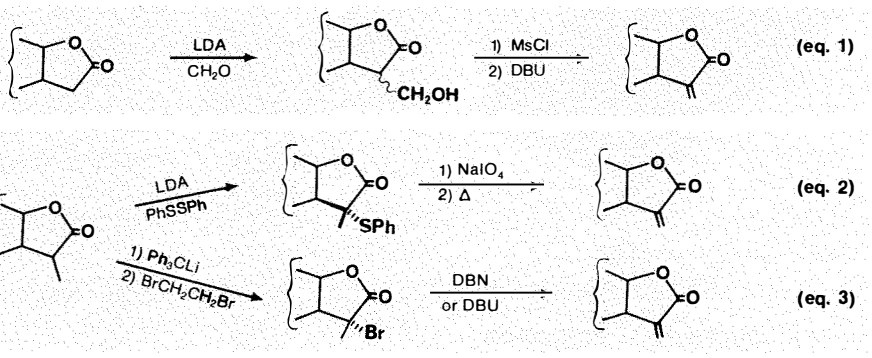
1) α-METHYLENATION OF LACTONES

α-Methylenation of lactones is often achieved by the reaction of lactone enolates with formaldehyde to yield α-hydroxymethylene lactones which undergo mesylation and base-induced β-elimination (eq. 1).[5]

Reactions of the enolates of α-methyl lactones with diphenyl disulfide followed by oxidative elimination (eq. 2) or a bromination-dehydrobromination sequence (eq. 3) to introduce the *exocyclic* double bond have been well reviewed.[5,6]

In recent years, the use of organoselenium reagents added a new dimension





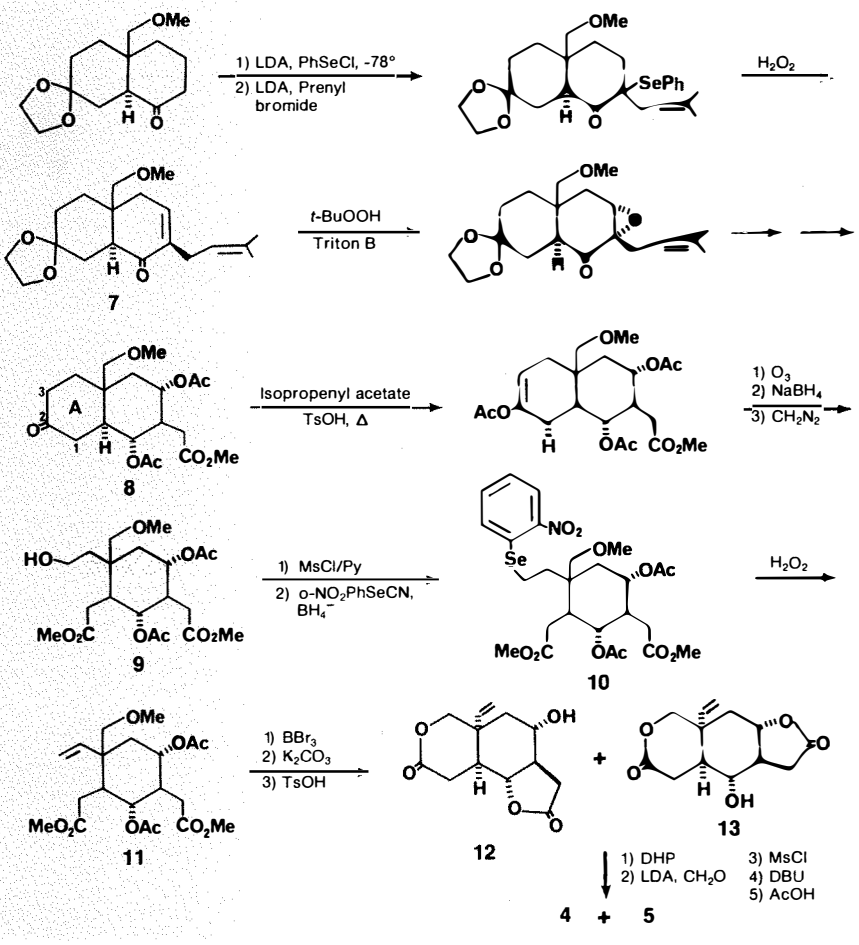
to stereospecific olefin synthesis.[12] Lithium enolates of ketones, aldehydes and esters undergo α-phenylselenenylation followed by mild oxidation with concomitant *syn*-elimination of benzeneseleninic acid to form the corresponding enones.[12] Such a mild olefination sequence has been used very successfully by Grieco in the total synthesis of various biologically active α-methylene lactones.

In the first reported total synthesis of the dilactones, vernolepin (**4**) and vernomenin (**5**), Grieco and co-workers[13] utilized this *syn*-β-elimination of phenyl selenoxide technique to introduce the *endocyclic* double bond in **7** (Scheme I). Epoxidation of **7** with *tert*-butyl hydroperoxide in the presence of Triton B gave exclusively the α-epoxide, which could be elaborated to the strategically important intermediate **8**, having all the asymmetric centers as in the target compounds **4** and **5**. In the next stage of the synthesis, Grieco utilized enolacetylation of **8** followed by ozonolysis to cleave the C-2, C-3 bond of ring A (Scheme I). Mesylation of **9** and subsequent treatment with *o*-nitrophenyl selenium anion[14] and ready oxidative elimination of the aryl selenoxide resulted in the introduction of the angular vinyl group in **11**. Sequential lactonization then formed bisnorvernolepin (**12**) and bisnorvernomenin (**13**). Finally, bis-α-hydroxymethylenation of THP-protected **12** and **13** followed by DBU-induced β-elimination, completed the synthesis of **4** and **5** (Scheme I).

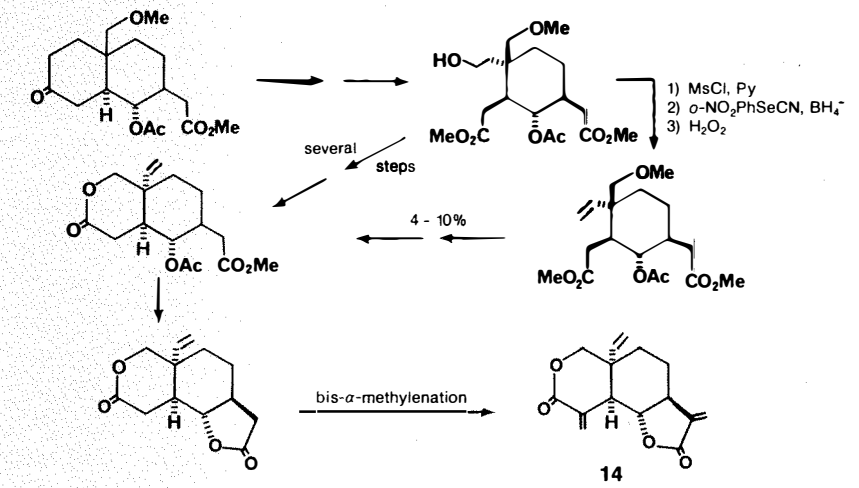
Later, Grieco[15] observed that, in the course of the conversion of **9** to **10** (see Scheme I), mesylation could be avoided. Thus, reaction of alcohol **9** with *o*-nitrophenyl selenocyanate in the presence of tri-*n*-butylphosphine resulted in direct formation of **10**. Use of the same reagent, *o*-nitrophenyl selenocyanate, enabled Grieco and co-workers[16] to introduce the angular olefinic function in deoxyvernolepin (**14**) as well.

The total synthesis of deoxyvernolepin[16] (which was found more potent than vernolepin itself[16b]) was accomplished with essentially the same methodology (Scheme II) as in vernolepin, *viz.*, a) construction of a suitably substituted decalone ring system having proper stereochemistry for all 5 (4 for deoxyvernolepin) chiral centers, b) cleavage of the C-2, C-3 bond in ring A, c) introduction of an angular vinyl group through oxidative elimination of *o*-nitrophenyl selenoxide, d) sequential formation of δ- and γ-lactone rings, and finally, e) simultaneous α-methylenation of both the lactone rings. The success of the bis-α-hydroxymethylenation step[16a] in the

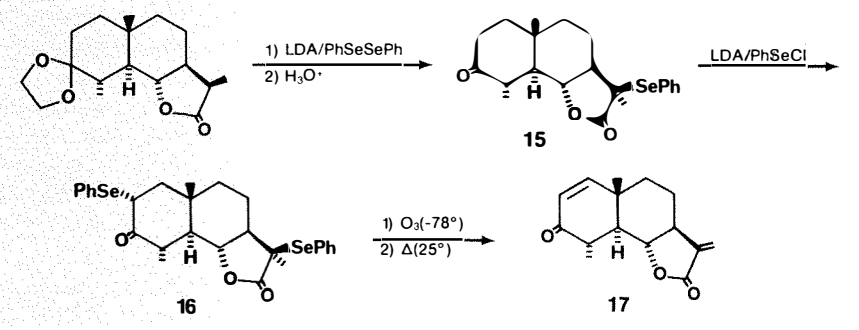
Scheme I



Scheme II



Scheme III



ultimate stage of the synthesis played a major role in the total synthesis of **4** and **5**.[13]

Grieco[17] demonstrated the utility of organoselenium reagents in the total synthesis of (±)-tuberiferine (**17**). α-Methyl-α-phenylseleno lactone **15** served as a protected α-methylene lactone which, after further α-phenylselenenylation, afforded the bis-selenide **16** (Scheme III). In the key final step, oxidative elimination introduced simultaneously the α-methylene unit and the $\Delta^{1,2}$-double bond in **17**.

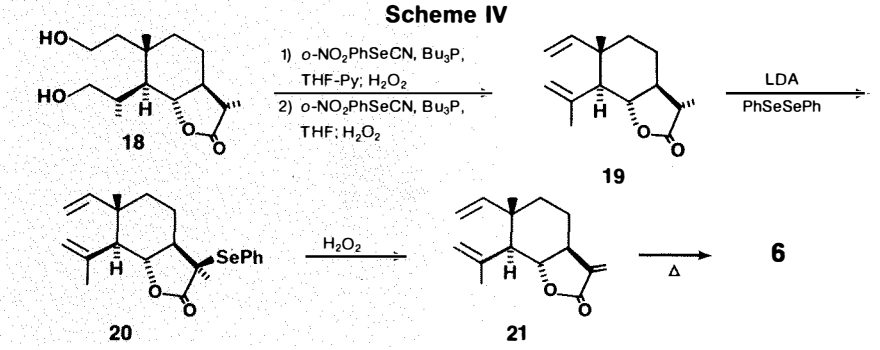
Recently, Grieco and Nishizawa[18] reported the first total synthesis of (+)-costunolide (**6**), demonstrating another useful application of selenium in organic synthesis. From the diol **18**, saussurea lactone (**19**) was obtained through sequential reaction with *o*-nitrophenyl selenocyanate followed by oxidative elimination (Scheme IV). α-Phenylseleno lactone **20** was prepared from **19** and, in turn, the α-methylene lactone dehydrosaussurea lactone (**21**) was obtained. Cope rearrangement of **21** yielded costunolide (**6**).

In effect, Grieco has successfully demonstrated the utility of this method as a mild, general procedure for α-methylenation of fused lactones,[5,19] *via* the α-phenylseleno lactones. Since the phenyl selenoxides undergo stereospecific *syn*-elimination, success of this procedure depends on the proper stereochemical relationship between the α-phenylseleno substituent and the proton β to the lactone carbonyl. The order of introducing these α-substituents, *e.g.*, a methyl and a phenylseleno group, may be altered in order to attain the desired stereochemistry.

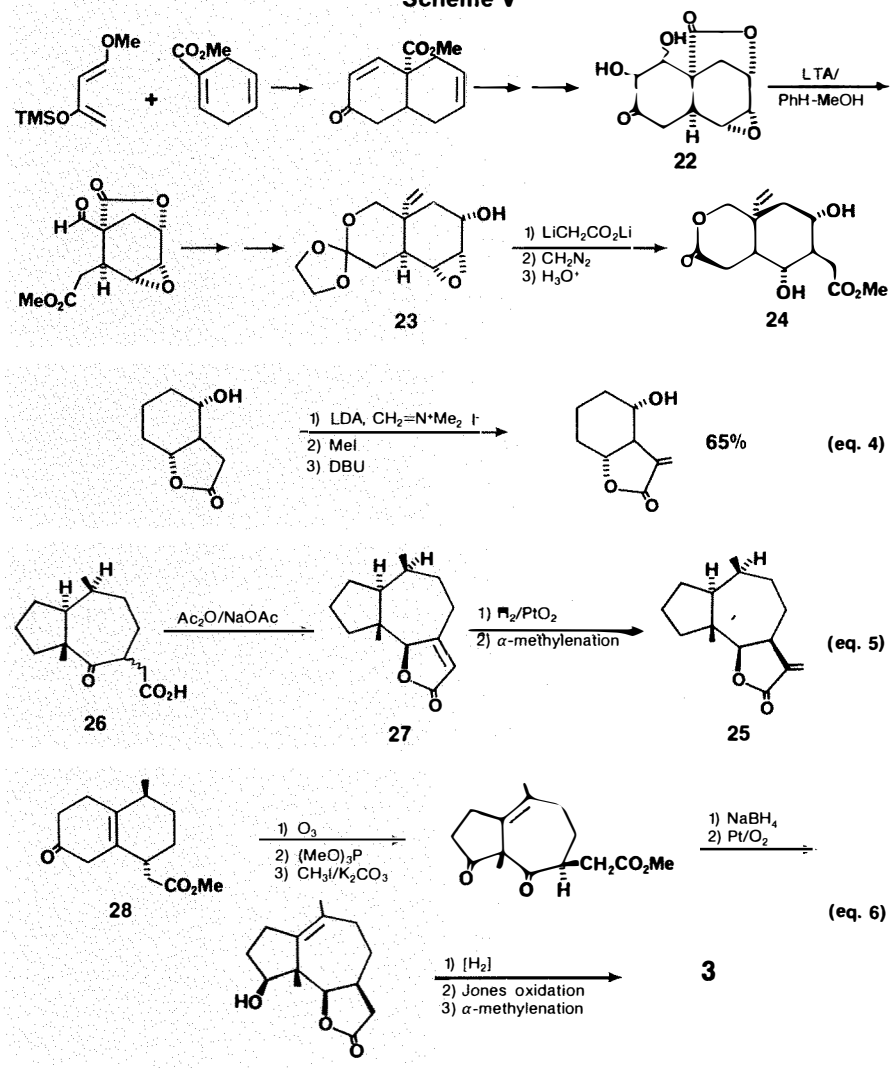
Since bis-α-methylenation of "prevernolepin" **12** and "prevernomenin" **13** was achieved,[13] the synthesis of these compounds by Danishefsky,[20] in effect, constitutes another formal synthesis of **4** and **5**. Starting with a Diels-Alder reaction, followed by an iodolactonization process, and further elaboration, synthesis of the epoxydiol **22** has been attained (Scheme V). Lead tetraacetate decomposition of the epoxydiol **22** led to the strategically important intermediate, the β-epoxy orthoester **23**.

The highlight of Danishefsky's synthesis[20] is a remarkable epoxide ring opening with dilithioacetate. Due to steric crowding by the orthoester in **23**, a generally favored "*trans-diaxial*" opening of the epoxide from the low-energy conformer did not occur; rather, the ring opening proceeded exclusively through an energetically disfavored conformer yielding **24** (Scheme V). Lactonization of **24** gave both **12** and **13**. Recently, Danishefsky[21] reported a detailed study of the directing effects in the opening of vicinal hydroxy epoxides.

Scheme IV



Scheme V

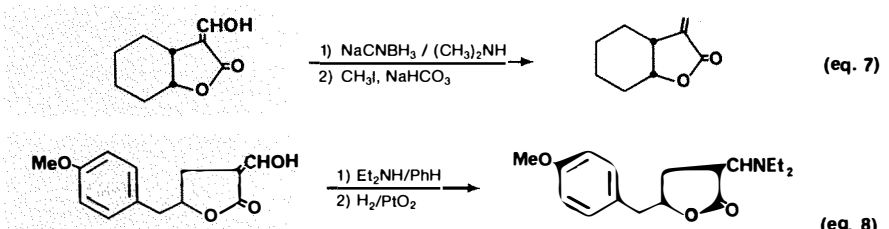


Dimethylaminomethylation of lactones *via* their enolates can be achieved by the Mannich reagent, dimethyl(methylene)-ammonium iodide.[22] Subsequent methiodide formation and treatment with DBU introduces an α-methylene function without protection of the hydroxy group in the molecule (eq. 4).[23] Danishefsky thus converted **12** and **13** to vernolepin (**4**) and vernomenin (**5**) respectively.[23]

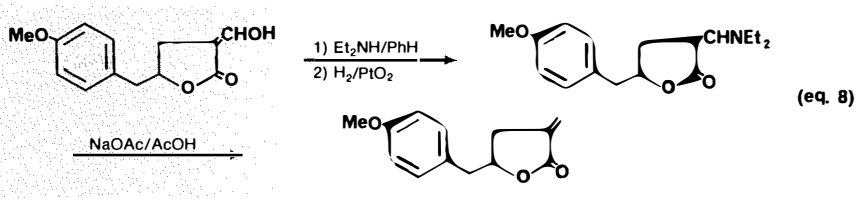
Due to their complex stereochemistry, pseudoguaianolides present a challenging synthetic problem to organic chemists. Marshall and Snyder[24] synthesized a relatively simple pseudoguaianolide derivative, (±)-4-deoxydamsin (**25**). The *trans*-fused bicyclic keto acid **26** lactonized in an unprecedented way to yield the $\Delta^{\alpha,\beta}$-lactone **27**. It is conceivable that the enol-lactone undergoes a double-bond isomerization. Hydrogenation of **27** in the presence of PtO_2 yielded the *cis*-lactone, which could be α-methylenated to **25** (eq. 5).

Damsin (**3**) itself was synthesized by Kretchmer and Thompson[25] from the octalone derivative **28** (eq. 6).

The reductive amination of α-formyl lactones to introduce the α-methylene group has been well reviewed.[5] Usually, α-hydroxymethylene lactones are treated with sodium cyanoborohydride in the presence of dimethylamine, followed by an elimination to afford the α-methylene function (eq. 7).[26] Earlier, Yamada and co-workers[27] developed a method which does not require the use of sodium cyanoborohydride (eq. 8).



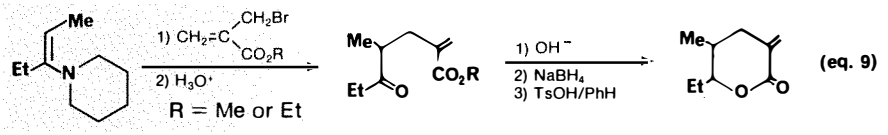
(eq. 7)



(eq. 8)

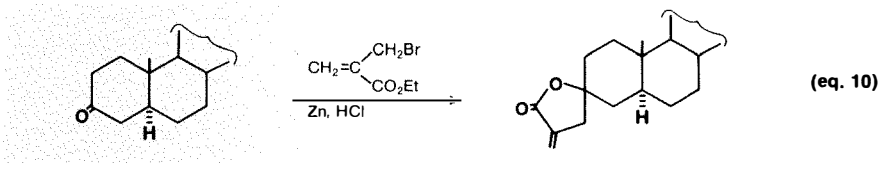
2) LACTONIZATION OF A PRECURSOR HAVING A PREFORMED α-METHYLENE GROUP

This method is another important general route to the synthesis of α-methylene lactones.[6] Reaction of enamines of cyclic or alicyclic ketones with methyl or ethyl α-(bromomethyl)acrylate leads to α,β-unsaturated esters.[28] Saponification, reduction and dehydration afford α-methylene-δ-lactones (eq. 9).

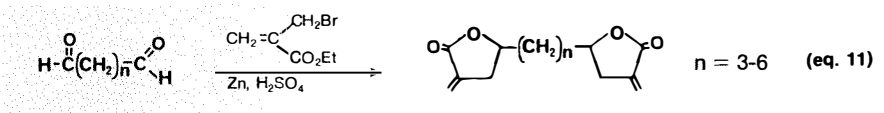


(eq. 9)

Similar use of ethyl α-(bromomethyl)-acrylate in a convenient Reformatsky-type reaction by Lee[29] afforded several significantly cytotoxic steroidal α-methylene-γ-lactones (eq. 10). Ramalingam and Berlin[30] recently synthesized several other spiro α-methylene-δ-butyrolactones through similar Reformatsky-type reactions using ethyl α-(bromomethyl)acrylate. In the same manner, Cassady and co-workers[31] prepared a series of bis-(α-methylene-γ-butyrolactones) by the reaction of dialdehydes with ethyl α-(bromomethyl)-acrylate (eq. 11).

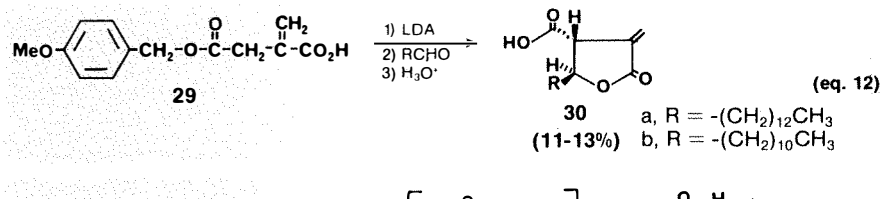


(eq. 10)

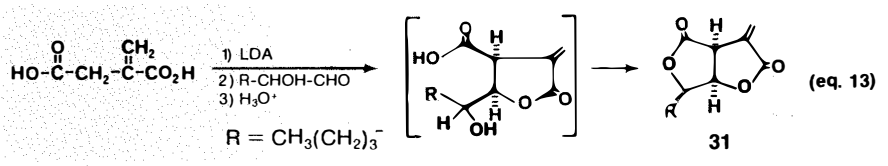


(eq. 11)

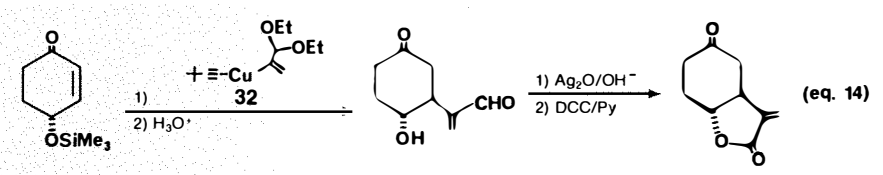
Condensation of dianions derived from the itaconic acid derivative **29** with the proper ketone or aldehyde enabled Carlson and Oyler[32,33a] to synthesize directly a number of α-methylene-γ-lactones including protolichesterinic acid (**30a**) and nephrosterinic acid (**30b**) albeit in low yield (eq. 12). The same authors[33a] employed the trianion of itaconic acid itself for condensation with a protected α-hydroxyaldehyde to prepare the bis-lactone canadensolides **31** (eq. 13).[33b]



(eq. 12)

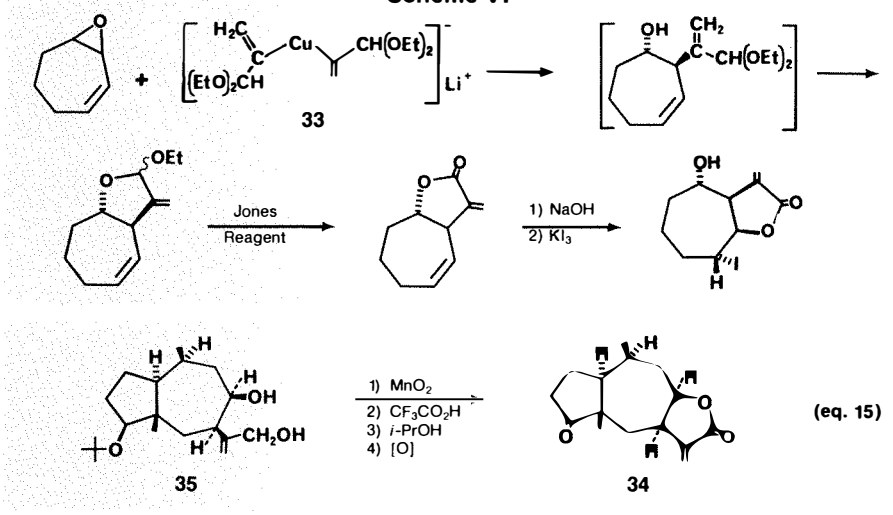


(eq. 13)



(eq. 14)

Scheme VI



(eq. 15)

For the synthesis of a *trans*-fused α-methylene-γ-lactone, Boeckman and Ramaiah[34] used conjugate addition of the cuprate **32** to introduce an appropriate methylene function (eq. 14).

Marino and Farina[35] studied the reactions of several organocopper acrylate synthons for the stereospecific synthesis of α-methylene-γ-butyrolactones. The reaction of such organometallic reagents with cyclic allylic epoxides to yield the *trans*-hydroxy-*cis*-α-methylene-γ-lactone moiety as found in helenalin (**1**) is of particular interest. The 1,2-adduct of 3,4-epoxycycloheptene with the organolithium cuprate **33** was

elaborated to the *cis*-fused lactone system found in **1** (Scheme VI).

Marshall and Ellison[36] reported a stereoselective synthesis of a pseudoguaianolide sesquiterpene, confertin (**34**) (eq. 15). The diol **35**, with an α-methylene group, was lactonized leading to **34**.

3) REARRANGEMENTS

Of the few rearrangement pathways used to synthesize α-methylene lactones, acid- or metal-catalyzed cyclopropane ring rearrangement[5,6] is most important. Recently, Hudrlik[37] reported an extension of his method to the synthesis of a *cis*-fused-α-methylene-γ-butyrolactone having a double bond, as in **36** (eq. 16).

Marshall and Ellison[38] found that the cyclopropyl-carbinol solvolysis route to fused-ring γ-butyrolactones is highly efficient and stereoselective. Using this method, they synthesized both *cis*- and *trans*-fused γ-butyrolactones (eq. 17).

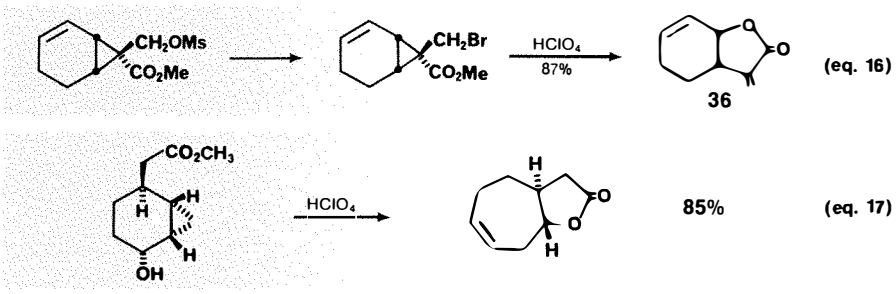
A modified Claisen rearrangement[39a] was successfully employed by Still and Schneider in the total synthesis of (±)-frullanolide (**37**) (Scheme VII).[39b] The hindered allylic alcohol **38** was transformed to its β-pyrrolidinopropionate derivative **39** through the reaction of its lithium salt with acryloyl chloride and pyrrolidine. This allylic ester was converted to the corresponding silylketene and subjected to Claisen rearrangement followed by conversion to the olefinic acrylate **40**. All these latter steps were carried out in a "one-pot" procedure. Iodolactonization of **40** followed by dehydrohalogenation afforded **37**.

4) MISCELLANEOUS

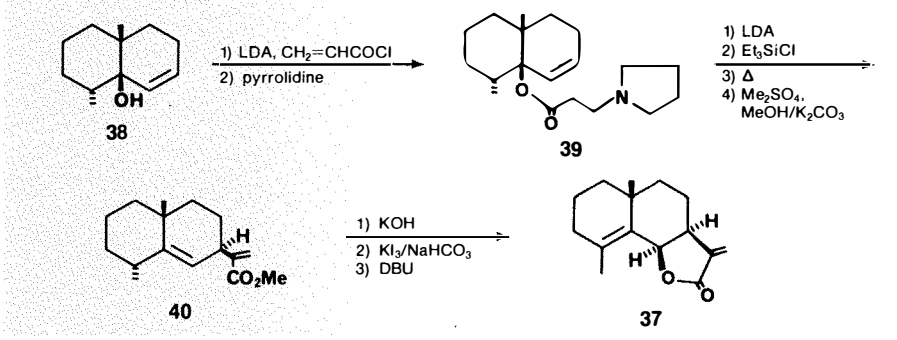
The nickel-catalyzed carbonylation of alkynyl alcohols has been reviewed.[5] In an extension of this cyclocarbonylation method, Norton[40] avoided the use of toxic $Ni(CO)_4$ and used a $PdCl_2$-thiourea mixture to synthesize *trans*-fused bicyclic α-methylene-γ-lactones (eq. 18). The mechanism of this reaction remains unclear. However, the use of thiourea seems to be essential. *cis*-Acetylenic alcohols can be obtained from the *trans* isomers and hence, *cis*-fused lactones can be synthesized (eq. 19).[41]

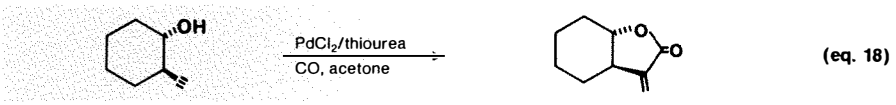
Due to the intense synthetic interest in vernolepin (**4**) and its congener vernomenin (**5**), several research groups have presented different approaches for the synthesis of their precursors or prototypes. Heathcock[42] utilized conjugate addition of lithium divinylcuprate to introduce the angular vinylic group (eq. 20) and an ozonolytic bond cleavage sequence[43] to form a *cis*-fused δ-lactone unit as in **4** and **5**.

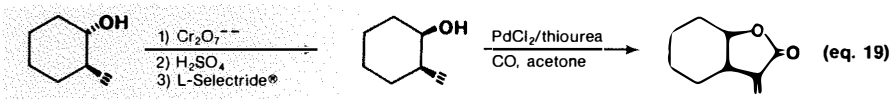
In a multistep synthesis, Heathcock and co-workers[44] prepared the bicyclic keto lac-

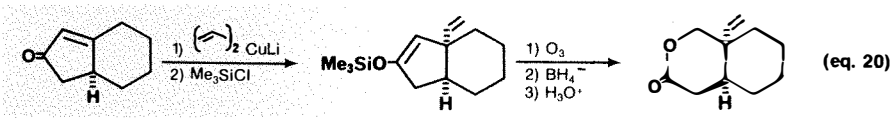


Scheme VII

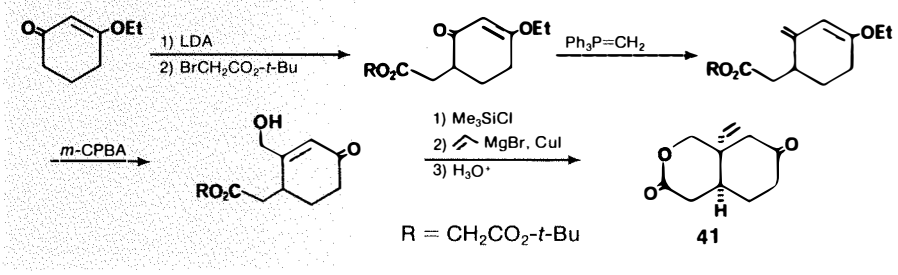


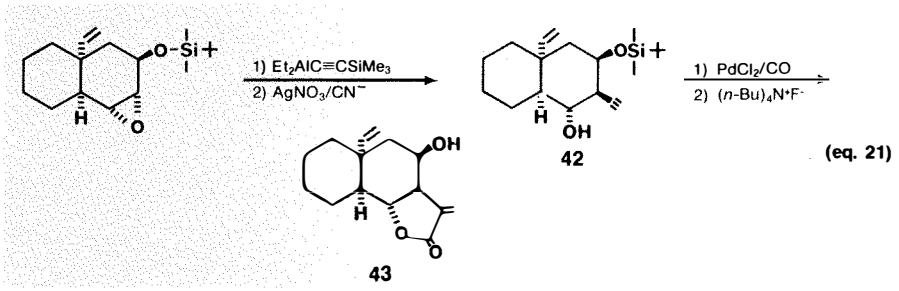


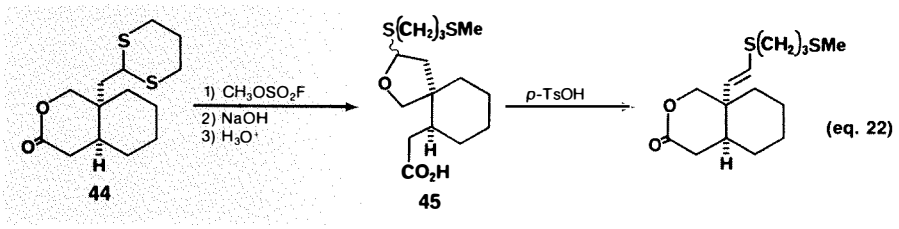




Scheme VIII







tone **41** (Scheme VIII), a possible precursor to vernolepin (**4**). In his research efforts to synthesize "prevernolepin" regioselectively, as opposed to indiscriminate formation of both the vernolepin and vernomenin precursors formed in Grieco's[13] and Danishefsky's[20] syntheses, Heathcock[45] utilized ring opening of a protected *trans*-2,3-epoxy alcohol[46] to yield the *vic*-alkynyl alcohol **42** and subsequent cyclocarbonylation[40] steps (eq. 21) to form the *cis*-hydroxy lactone **43**.

Marshall and Seitz[47] developed a two-step method to prepare the hemithioacetal **45** by cleavage of the thioacetal **44** (eq. 22). Subsequent treatment of **45** with *p*-TsOH induced elimination and concomitant lactonization. Desulfurization with Raney nickel gave the vernolepin prototype.

For the formation of the 2-oxa-3,6-dioxo-9-vinyl-*cis*-decalin skeleton found in vernolepin (**4**) and vernomenin (**5**), Torii and co-workers[48] recently reported a sodium or potassium fluoride-catalyzed intramolecular Michael reaction (eq. 23).

Trost and Miller[49] demonstrated the utility of a ring-enlargement procedure for the synthesis of several α-methylene-δ-lactones starting with the γ lactones (Scheme IX).

In a recent report regarding α-diazo-β-dicarbonyl compounds, Wenkert and co-workers[50] reported the synthesis of the diol **46** (eq. 24) from an enol ether. Conversion of **46** to the corresponding α-methylene-δ-lactone has been reported by Marshall and Cohen.[51] Sucrow and Klein[52] reported the formation of γ-butyrolactones from 3-hydroxy-*N,N*-dimethyl-1-carboxamides. Thus, the ring opening of a spiro-oxirane can lead to the corresponding spiro γ-lactone (eq. 25).

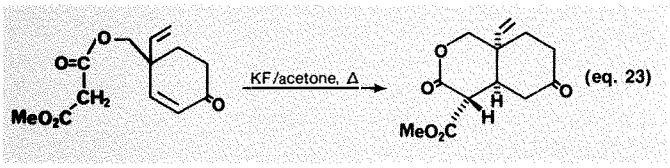
Cyclopropyl-fused lactones like **47**, obtained from diazomalonate (eq. 26), can isomerize to lactones. Thermolytic cleavage of **47** enabled the preparation of the spiro lactone **48**.[53]

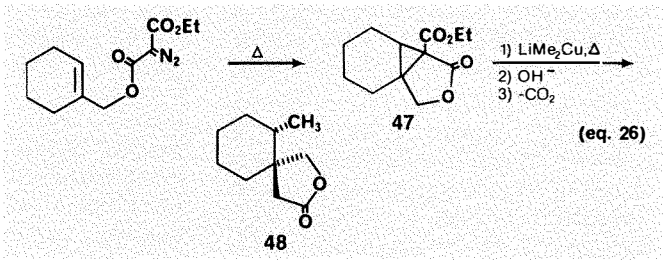
B. ENDOCYCLIC CONJUGATED LACTONES

An excellent review surveying the chemistry of unsaturated lactones has appeared.[7] It is not within the limits of this short review to include that chemistry in detail. However, since the steroidal cardenolides like digitoxigenin (**49**)[7] contain an *endocyclic* conjugated γ-lactone moiety, while bufalin (**50**)[3] has an α-pyrone ring, a few interesting synthetic pathways pertaining to these lactone systems will be discussed in this section.

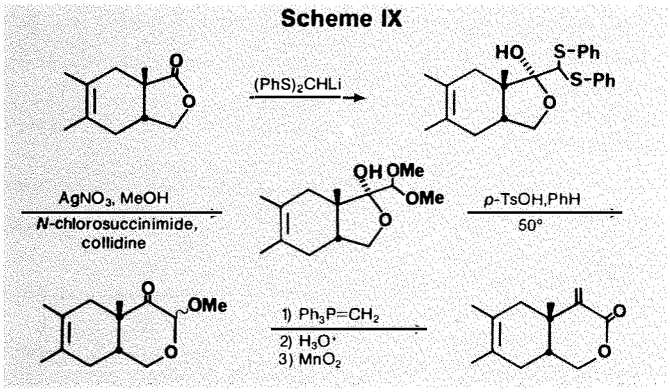
An *endocyclic* double bond conjugated to a lactone carbonyl can be introduced through a general sequence of β-elimination[6] of suitable groups (eq. 27). Annelation of 1,3-dicarbonyl compounds[54] with β-vinyl butenolides led to the formation of fused lactones, *e.g.*, **51** (eq. 27).

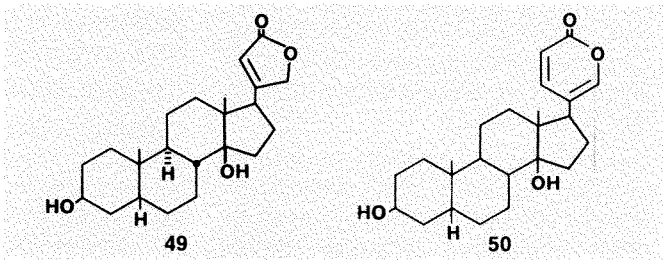
Martin and Moore[55] recently reported a new procedure for the synthesis of $\Delta^{\alpha,\beta}$-butenolides. In this sequence (Scheme X), freshly prepared α-hydroxymethylene lactones **52a** or the vinylogous urethanes **52b** were treated with *n*-butanethiol to form the α-*n*-butylthiomethylene lactones **53**. The γ-lactone **53** reacted smoothly with lithium dimethylcuprate or lithium di-*n*-butylcuprate to give the corresponding α-alkylidene-γ-lactones. Isomerization of

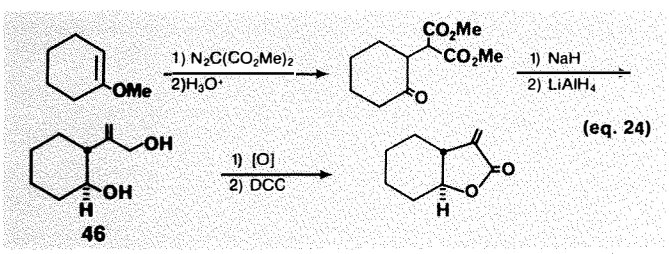


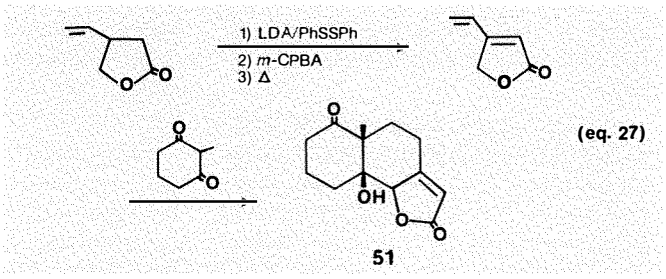


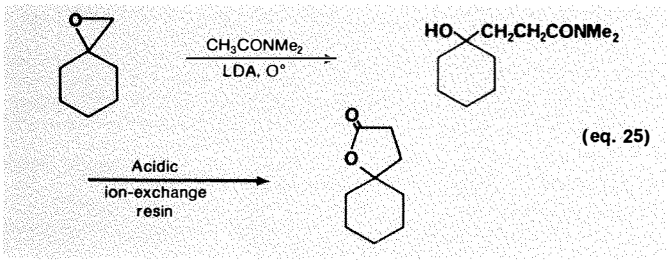
Scheme IX



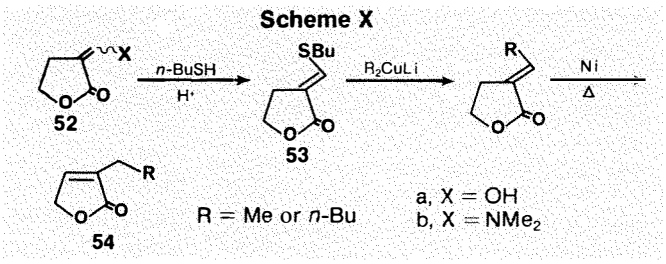


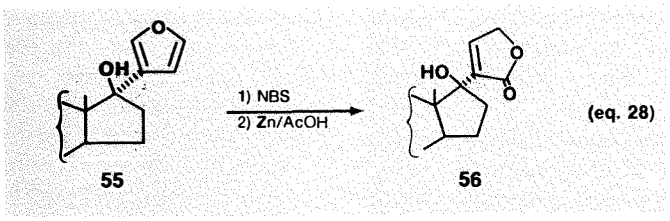


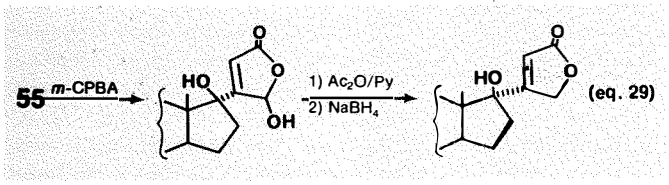


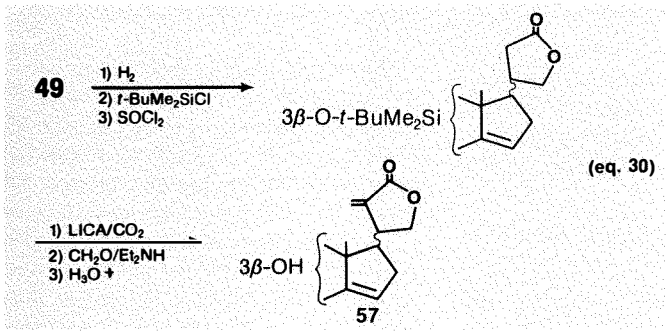


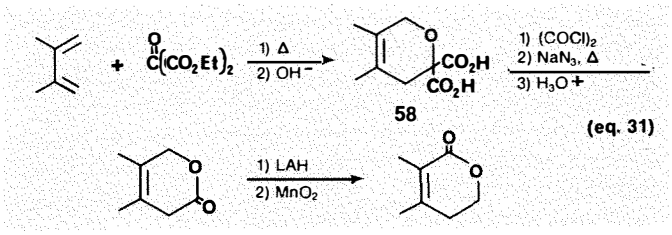
Scheme X

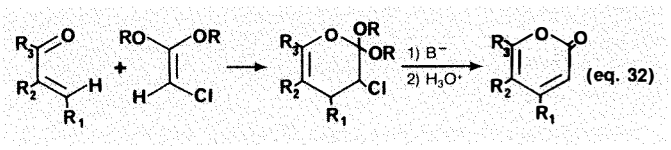




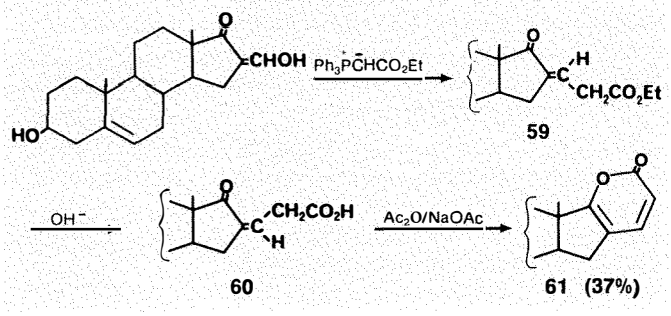








Scheme XI



the *exocyclic* double bond to the more stable *endocyclic* position was effected by heating with deactivated Raney nickel to give the $\Delta^{\alpha,\beta}$-butenolides **54** in good yield.

Oxidation of steroidal furans to the corresponding γ-lactones is exemplified in equations **28** and **29**.[56] The hydroxyfuran **55**, when treated with excess *N*-bromosuccinimide followed by zinc and acetic acid, yielded the $\Delta^{1,2}$-lactone **56** (eq. 28). Alternatively, **55** could be oxidized with *m*-chloroperoxybenzoic acid to give isomeric hydroxy lactones, the acetate derivatives of which could be reduced to the corresponding lactones (eq. 29).

In the pursuit of preparing cardenolide analogs, Fullerton and co-workers[57] recently reported the synthesis of the α-methylene lactone **57** from digitoxigenin, **49** (eq. 30). Even without the 14β-hydroxy group the 20(*R*)-isomer of **57** showed remarkable Na^+, K^+-ATPase inhibitory activity.

For the synthesis of $\Delta^{1,2}$-δ-lactones, Ruden and Bonjouklian[58] reported the use of diethyl ketomalonate in a Diels-Alder reaction (eq. 31). The adduct **58** was subjected to the Curtius rearrangement followed by reduction and oxidation of the resulting diol, to yield the desired lactone.

The cycloadducts of chloroketene acetals and α,β-unsaturated aldehydes and ketones can be treated with alkoxides to furnish α-pyrones directly (eq. 32).[59] Belanger and Brassard[59h] have extended this method for the preparation of β-functionalized α,β-enones and 4-methoxy-α-pyrones.

In the course of preparing α-pyrones fused to the steroidal D-ring, Green and Newaz[60] successfully utilized the Wittig reaction of an α-hydroxymethylene ketone for substitution at the methylene carbon (Scheme XI). This particular Wittig product **59** was obtained exclusively with the *E*-stereochemistry at the 16*a*-double bond. Base hydrolysis of the ester **59**, however, proceeded with concomitant isomerization to yield the desired *Z*-acid **60**, which was easily lactonized to give the fused α-pyrone **61** in moderate yield.

CONCLUSION

Kupchan and co-workers[61,62] studied the role of the α-methylene-γ-lactone moiety for the cytotoxic activity of the corresponding sesquiterpenes. They concluded that the "Michael-type" reaction of such lactones with the sulfhydryl groups of cysteine may be responsible for the biological activity of these lactones. A similar role for "*other conjugated systems*" was contemplated as well.

In a systematic study of the structure activity relationship for helenalin (**1**), Lee[63] has demonstrated conclusively that for its cytotoxic activity, the role of the α-methylene lactone unit is *less* important than the cyclopentenone moiety. In recent nmr studies, Lee and co-workers[64] found that both an α-methylene lactone or an α,β-unsaturated ketone unit can alkylate the sulfhydryl groups of L-cysteine and reduced glutathione. Among others, simple ketones like cyclopentenone were found to exhibit significant antitumor activity.

Apparently, the mechanism of action for these biologically active lactones needs to be further investigated. Hence, in all probabilities, the synthetic interest toward these lactones will remain unabated for some time to come.

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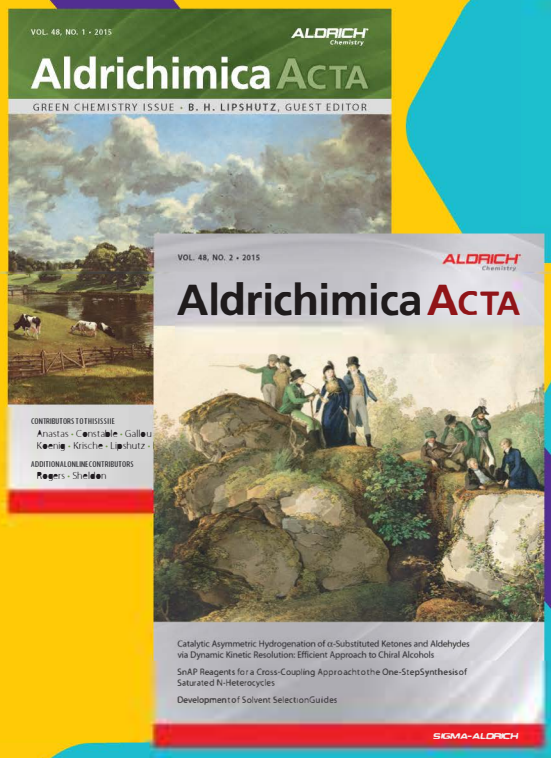

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