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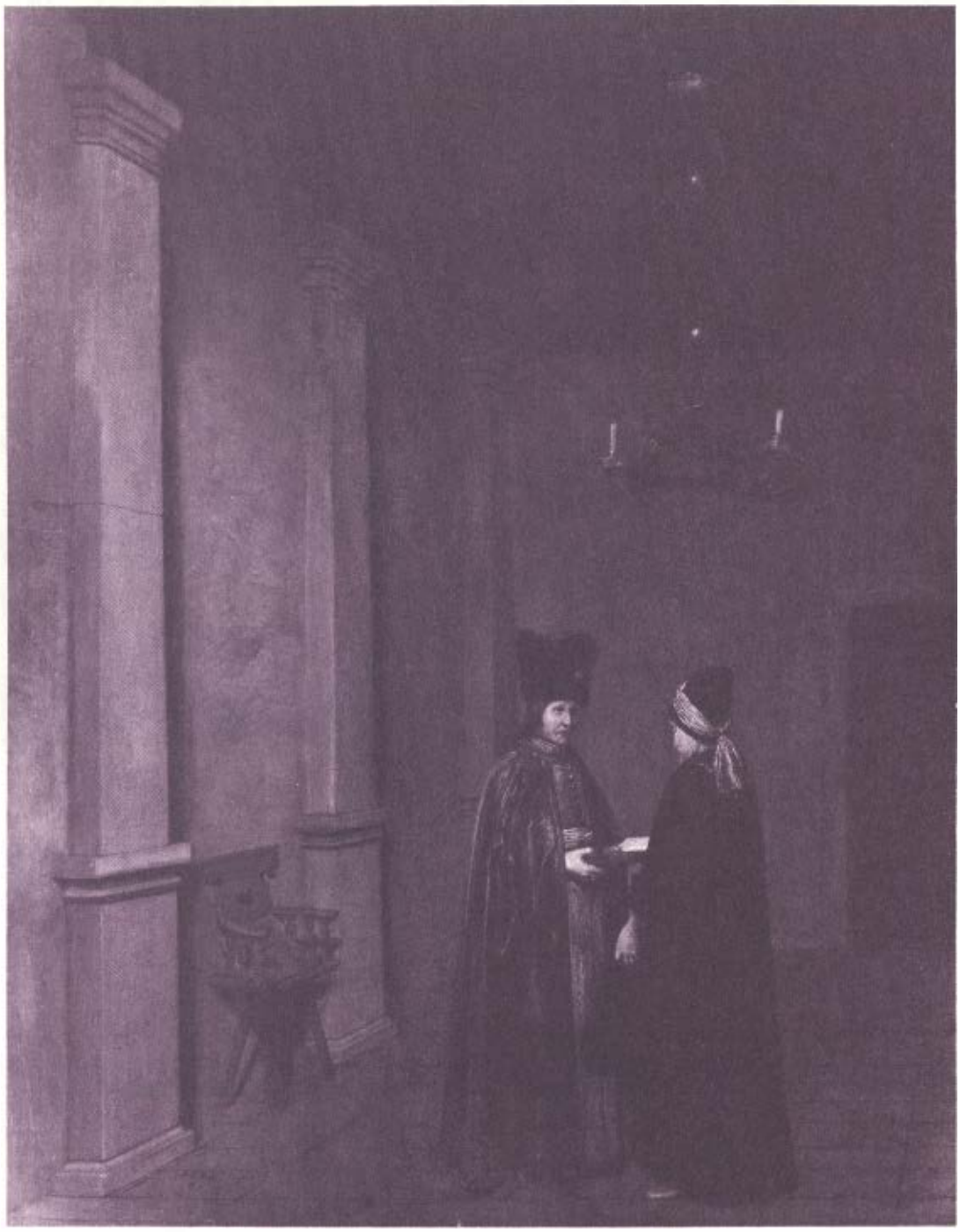

The Preparation and Reactions of Diazomethane. Triflic Acid and its Derivatives.

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Aldrichimica Acta

Volume 16, Number 1, 1983
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About Our Cover:

There are all sorts of interesting art-historical problems; the most common is the identification of the artist. In the case of the painting on our cover, the quest is rather unusual: we know some ten small paintings by the same hand, all monogrammed IS (intertwined) and usually dated in the 1640's and 50's. The best known of these, dated 1651, is a beautiful study of an old woman (Fig. 1) in the museum in Vienna. Our panel (17 x 13 inches) is monogrammed and dated 1649.

Fig. 1

Who was this Master, IS? Probably a student of Rembrandt, perhaps from Scandinavia or Poland — the costumes of the two men in earnest discussion look Polish. What is the subject of their discussion? A puzzle within a puzzle, heightened by the mysteriousness of that large room, and the subtle color accents, the cinnabar of the chair, the purple and gold of the cloak of the man with the fur hat.

When our chemist started collecting, he knew of three distinct unidentified personalities among 17th-century Netherlandish painters. They were the Master of the Winter Landscapes, now identified as Gysbrecht Leytens, the Pseudo van der Venne (see the *Aldrichimica Acta*, *7*, 1974) now identified as Jan van de Venne, an Antwerp artist of the early 1600's, and the Monogrammist IS, one of the most subtle and mysterious of the many artists influenced by Rembrandt. I.S. — a monogram in search of a name.

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 Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our *Acta* covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

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 often find it necessary to identify parts and fittings made from Viton®, since after use, Viton may be confused with Buna-N, rubber or other elastomers. When Viton is needed, it can be dangerous or disastrous to use a substitute.

A simple identification test can be made with perchloroethylene. If the part sinks it is made of Viton, if it floats it is made of something else.

Bob McCreary
Decatur Pump Co.
2750 Nelson Park Rd.
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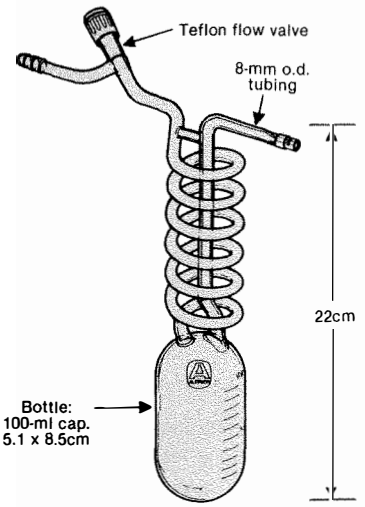
When a gas (*e.g.*, Cl_2, SO_2, CH_3Br or CH_3SH) is required for synthetic work, it is sometimes necessary to measure the amount to be added to the reaction mixture. This can be accomplished by condensing the gas in the apparatus shown below (cooled in dry-ice/acetone), and then determining its weight or volume.



The rate of gas addition to the reaction mixture can be controlled by warming/cooling the bottle. A constant flow is achieved by insulating the bottle with a cloth towel.

Of course, the material can also be dispensed as a liquid.

Kanu Parikh
Aldrich Chemical Co.

Editor's note: For our customers' convenience, we now offer the apparatus described above and the appropriate Dewar flask.

As the importance of environmental protection and the awareness of chemical carcinogenicity increase, we wish to share our idea for the more efficient recovery of solvents from the rotary evaporator. We have connected a dry-ice trap between the water aspirator and the water-cooled rotary evaporator. This set-up allows for the efficient trapping of low-boiling solvents at the dry-ice stage, while collecting the higher-boiling solvents at the water-cooled stage. The common problem of getting solidified aromatic solvents at the dry-ice trap is thus avoided, and low-boiling chlorinated solvents no longer escape the system through the aspirator.

The Nitrone Group
277 Chemistry
Wayne State University
Detroit, MI 48202

Editor's note: Another efficient method of solvent recovery is by use of a dry-ice condenser. See page 23 for illustration.

The loss of intensity of both mounted and hand-held shortwave ultraviolet lamps used to visualize TLC plates can be traced to problems with the filter. In our experience, the lamp has a long lifetime, but the filter, through a process termed solarization, becomes less transparent over a period of a few months. A typical shortwave UV filter has a transmittance of 35-40%; a UVS-54 lamp (Ultraviolet Products) in heavy use for *ca.* 2.5 years was found to have a 254-nm transmittance of 0.8% as measured in a Cary-14 UV-Vis spectrophotometer.

Replacement filters cost between $40.00 and $60.00, but an inexpensive solution to the problem is to rejuvenate the filters by a simple annealing process as follows: The filters are dislodged from their plastic mounting with the aid of a knife and are scraped clean of adhering glue, washed with acetone, and dried. Rough side down, they are laid on smooth blocks of graphite/-ceramic cloth in an ordinary glass working oven and subjected to a typical annealing cycle of 575° C for 1-2 hours, with slow (*ca.* 1-2 hr.) cooling (a cycle used here for pyrex glass). Some flowing of the glass is normal, and some trimming may be required to fit the filters to the frame holder. A typical UV scan shows a U-shaped curve with the following % T values: 36 (254 nm), 13.2 (310) and 46 (390). For stubborn cases, two or three annealing cycles are required.

We recommend that rejuvenation of the filters be a yearly maintenance task, as the loss of intensity is gradual and is recognized only after much frustration with weak light output.

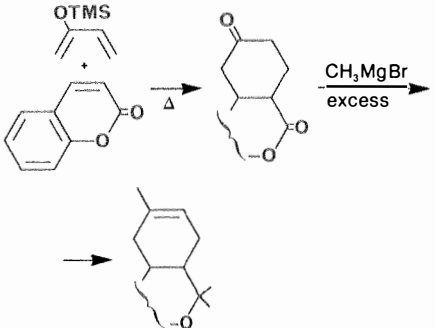
Professor David C. Baker
Merrill B. Watson, Glassblower
Department of Chemistry
The University of Alabama
University, AL 35486

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **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 Ayfred Bader.

Recently Professor K. Jankowski at the University of Moncton suggested that we offer 2-trimethylsilyloxy-1,3-butadiene, a reactive diene useful in Diels-Alder reactions leading, in three steps, to Δ^1-THC from



coumarin,[1] and to substituted cyclohexanones.[2,3] Naturally, we made it.

1) Jankowski, K. Unpublished results.
2) Jung, M.E.; McCombs, C.A. *Tetrahedron Lett.* **1976**, 2935.
3) Liu, H.-J.; Ngooi, T.K. *Synth. Commun.* **1982**, 715.

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

The Preparation and Reactions of Diazomethane

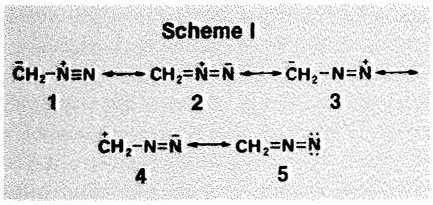
T. Howard Black
Aldrich Chemical Company, Inc.

In 1894, von Pechman established the structure CH_2N_2 for the yellow gas liberated from nitrosomethylurethane upon treatment with alkali.[1] During the subsequent 90 years, diazomethane (less commonly referred to as azimethylene or diazirane) has proven to be one of the most valuable and versatile reagents available to the synthetic chemist. It is easily the most common methylating reagent for carboxylic acids, and has found wide application in the methylation of phenols, alcohols, enols, and heteroatoms such as nitrogen and sulfur. Diazomethane effects the ring expansion (or chain homologation) of ketones or, under suitable conditions, forms epoxides from the same ketones in the manner of sulfur ylids. Acid chlorides are converted to α-diazoketones which are valuable synthetic intermediates in their own right. In addition, CH_2N_2 acts as a powerful dipole in many cycloaddition reactions with unsaturated systems, and often the resulting nitrogen-containing heterocyclic ring can be decomposed (either thermally or photochemically) to afford cyclopropane (or other) derivatives. Each of the above reaction categories will be treated separately in the **REACTIONS** section.

STRUCTURE

The structure of diazomethane can be represented by the valence tautomers **1** through **5** (Scheme I). Although the true electronic distribution over the the molecule can be represented as a weighted sum of the five structures shown, the majority of diazomethane reactions are best conceptualized and explained by structure **1**. Recently the total electronic energies and energies of isomerization for the optimized geometries of the isomers of diazomethane were calculated.[2]

Scheme I



A gas at room temperature, diazomethane liquifies at -23 °C (density 1.45) and freezes at -145 °C. It can be protonated in fluorosulfonic acid at very low temperatures[3] and possesses an ionization potential of 9.03eV.[4]

The most recent comprehensive review of diazomethane chemistry appeared nine years ago;[5] the reader is directed to this work for references to earlier reviews. Recently, two reviews concerning diazoalkanes have appeared; one involves organometallic synthesis[6] and the other the synthesis of "unusual organic molecules".[7]

SAFETY CONSIDERATIONS

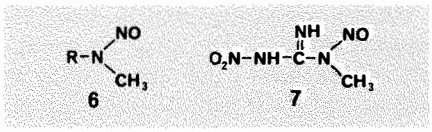
Although quite safe when handled as a dilute solution in an inert solvent, diazomethane presents several safety hazards of which all users of the reagent should be aware. It is both extremely toxic[8] and highly irritating,[9] causing pulmonary edema when inhaled in high concentrations. Long-term, low-level exposure may lead to sensitization, resulting in asthma-like symptoms.[10] Also, diazomethane and several of its chemical precursors have been cited as carcinogens.[11]

Diazomethane has been known to explode quite unaccountably, both as a gas and a liquid, although rough surfaces are proven initiators of detonations.[12] Thus, ground-glass joints and any glassware which have not been carefully firepolished must **never** be allowed to come in contact with diazomethane or its solutions. In addition, contact with alkali metals or drying agents such as calcium sulfate can result in an explosion. If moisture must be removed from a solution containing diazomethane, the recommended drying agent is potassium hydroxide pellets. Finally, solutions should not be exposed to strong light, which has been reported[12] to initiate detonations.

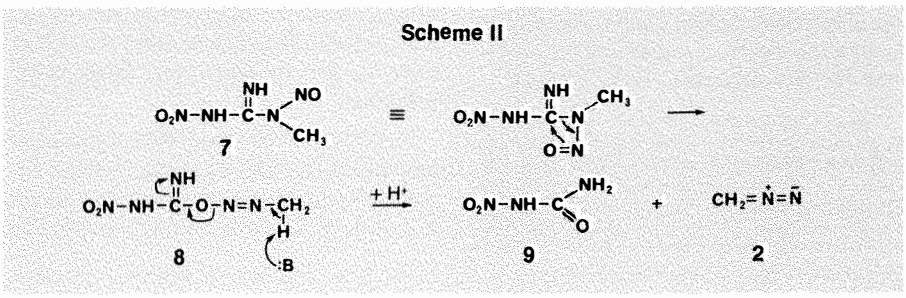
Fortunately, if the reagent is generated using the proper equipment and is handled only as a dilute solution at low temperature (*ca.* 0 °C), the risks cited above are minimized. Of course, **all reactions** involving diazomethane should be carried out in an **efficient fume hood** and behind a **sturdy safety shield**. Finally, it is recommended that solutions of diazomethane be used immediately and not stored, even at low temperature.

PREPARATION

By far, the most common and convenient method for generating diazomethane is by the base-catalyzed decomposition of N-methyl-N-nitroso amines of the general structure **6**, where R represents a sulfonyl, carbonyl, or similar electron-withdrawing group. The mechanism of diazomethane generation is outlined in Scheme II. For clarity, a specific chemical presursor is employed: *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG, 7). In the first step, an elec-

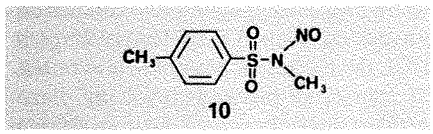


Scheme II



tronic rearrangement occurs to afford the unstable intermediate **8**. Abstraction of a methyl proton initiates cleavage of the nitrogen-oxygen bond (as shown) to liberate a molecule of diazomethane and the carbonyl-containing remnant of the precursor compound (in this case *N*-nitrourea, **9**). The replacement of water by 2-(2-ethoxyethoxy)-ethan(ol)-*d* and the use of NaOD as base allows the preparation of deuterated diazomethane (CD_2N_2) in high isotopic purity (see Aldrich Technical Bulletin AL-124).

As might be anticipated from the generality of structure **6**, a large number of compounds have served as precursors to diazomethane, including *N*-methyl-*N*-nitrosourea and *N*-[*N'*-methyl-*N'*-nitroso(aminomethyl)]benzamide. However, the great majority of workers in the field currently employ only two compounds which have proven to be superior in terms of shelf life, facility of diazomethane generation, and safety of handling; *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG, **7**) and *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®, **10**). The choice of one over the other is primarily determined by reaction scale,



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and since the techniques and equipment are substantially different for each precursor, they are discussed separately.

MNNG

Since its introduction as Aldrich's first product listing in 1951, MNNG has emerged as the precursor of choice when **less than one millimole** of diazomethane is required. The compound is highly crystalline [mp 118 °C (d)], possesses a long shelf life (years), and liberates diazomethane upon treatment with aqueous base at room temperature or below. It is, however, a powerful mutagen[13] and some individuals develop a skin sensitivity. Thus, extreme care should be taken to avoid all skin contact.

Aldrich offers a diazomethane kit which employs MNNG, shown in Fig. 1; it is available with either a butyl rubber O-ring or with a Clear-Seal®* joint. The major advantage to the unit is that diazomethane is produced in a closed system, preventing escape to the atmosphere. A representative procedure for this millimole-size kit follows.

"Thus, 1mmole (133mg) or less of the reagent is placed in the inside tube through its screw cap opening along with ½ml of water to dissipate any heat generated. Ether (~3ml) is placed in the outside tube and the two parts are assembled with a butyl O-ring and held with a pinch-type clamp. The lower part is immersed in an

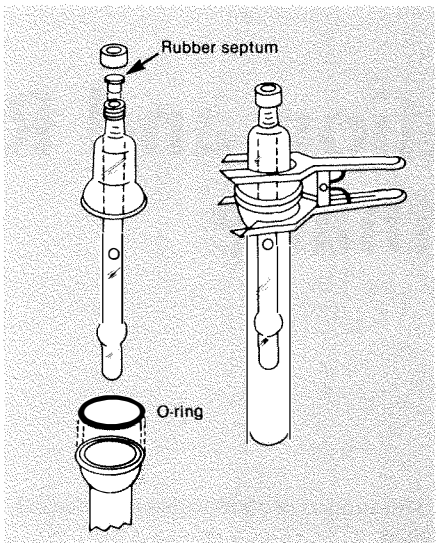


Fig. 1. Apparatus for preparing diazomethane from MNNG.

ice bath and about 0.6ml of 5*N* sodium hydroxide is injected through the silicone rubber septum *via* a syringe with a *narrow-gauge* (No. 22) needle to prevent leakage around the shank."* ***[The addition of the alkali to MNNG must be done very slowly (dropwise) to prevent the mixture from getting too hot and to control the volume of gas produced.]*** The diazomethane collects in the ether ready for use.

Some important points concerning the MNNG kits include:

1) A small needle (22ga or smaller) is imperative to prevent diazomethane escape.
2) The septum must be changed frequently, preferably each time.
3) The base solution must be added **no faster** than one drop/five seconds to avoid excessive pressure buildup.
4) At least 45 minutes must elapse following base injection to assure an acceptable yield (over 50%) of diazomethane.
5) It is best to dissolve the substrate in the ether contained in the outer tube prior to diazomethane generation so that the reagent is consumed as it is formed.

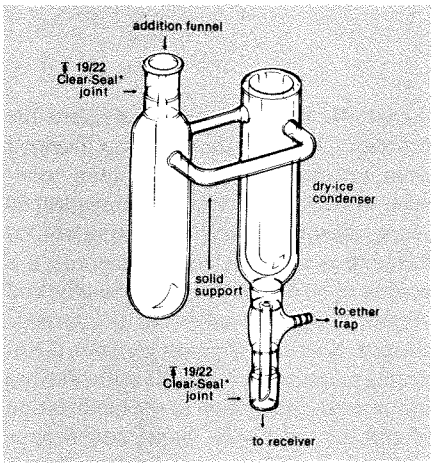
DIAZALD®

When greater than one millimole of diazomethane is required, Diazald (*Diazo*methane/*Ald*rich) is the most common precursor. Although its shelf life (1-2 years) is somewhat shorter than that of MNNG, its reaction with base is somewhat smoother; thus, it is preferred for larger-scale reactions.

Three kits for diazomethane preparation employing Diazald are available from Aldrich. For safety reasons, closed systems are not used, the diazomethane being collected as a codistillate with ether. All three units feature Clear-Seal joints and (when applicable) Teflon stopcocks.

Mini-Diazald Apparatus

Designed for the preparation of between 1-50mmoles of diazomethane, this unit consists of a reaction vessel and condenser in one compact piece. The only additional equipment needed are an addition funnel and receiver flask (of course, both must have Clear-Seal joints). The major feature of this apparatus is the "cold-finger" in place of a water-jacketed condenser. When



filled with dry-ice/acetone slush, the condenser very efficiently prevents diazomethane/ether vapor from escaping into the atmosphere. A typical experimental procedure employing this apparatus follows.

Fill the condenser with dry ice, then add acetone **slowly** until the cold-finger is about one-third full. Add ethanol (95%, 10ml) to a solution of potassium hydroxide (5g) in water (8ml) in the reaction vessel. Attach a 100-ml receiving flask (with Clear-Seal joint) to the condenser and cool the receiver in an ice bath. Provide an ice-cooled ether (*ca.* 2ml) trap at the sidearm (the glass tube must have *firepolished* ends).

Place a separatory funnel (with Clear-Seal joint) over the reaction vessel and charge funnel with a solution of Diazald (5.0g, 23mmol) in ether (45ml). Warm the reaction vessel to 65° with a water bath and add the Diazald solution over a period of 20 minutes. The rate of distillation should approximate the rate of addition. Replenish cold finger with dry ice as necessary. When all the Diazald has been used up, slowly add 10ml of ether and continue the distillation until the distillate is colorless. The ethereal distillate will contain about 700mg (16.6mmol) of diazomethane.

Diazald Kit

This kit is a set of distillation glassware for the preparation of up to 100 mmoles of diazomethane. Consisting of various-sized round-bottom flasks, condensers, and other pieces (all with Clear-Seal joints), its primary advantage is its versatility, in that many different reaction setups are possible. The method of diazomethane generation is essentially a scale-up of the procedure outlined for the Mini-Diazald apparatus.

Macro-Diazald Set

Designed by Professor Milos Hudlicky,[14] this set enables the safe preparation of

®Trademark of Aldrich Chemical Co., Inc.
®*Clear-Seal, License Ronor S.A., Berne, Switzerland

*Fales, H.M.; Jaouni, T.M.; Babashak, J.F. *Anal. Chem.* **1973**, *45*, 2302.

200-300 mmoles of diazomethane. Like the Mini-Diazald generator, it features a dry-ice cold-finger condenser, but also includes a U-tube vapor trap and Teflon stopcock to ensure trapping of all vapors. Recently, Professor Hudlicky has proposed a modification employing a cold trap (such as the type used in vacuum systems) as the receiver vessel.[15]

Table 1

Amount	Name	Catalog Number	Tech. Bull. No./-Reference
1 mmole	MNNG-Diazomethane kits	Z10,100-1, Z10,159-1	AL-132
1-50 mmoles	Mini-Diazald Apparatus	Z10,889-8	AL-121
1-100 mmoles	Diazald Kit	Z10,025-0	AL-131
200-300 mmoles	Macro-Diazald Set	Z10,851-0	see *J. Org. Chem.* **1980**, *45*, 5377.

SUMMARY

For ready reference, Table 1 summarizes the glassware available from Aldrich for the preparation of diazomethane.

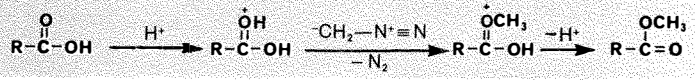
REACTIONS

METHYLATION

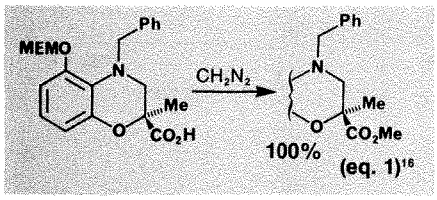
O-Methylation

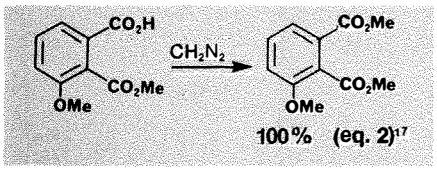
The methylation of oxygen atoms, in particular carboxylic acids, is by far the most widely employed and popular diazomethane reaction. Discovered by von Pechman,[1] it is believed to proceed *via* a positively charged intermediate as depicted in Scheme III, which explains the observation that alcohols are inert toward diazomethane in the absence of a Lewis acid catalyst.

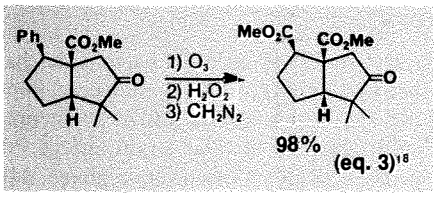
Scheme III

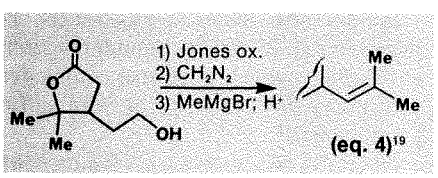


The major advantages of employing diazomethane for methylation reactions are: speed of reaction, mildness of reaction conditions, absence of non-volatile byproducts, ease of workup, and selectivity in the presence of functional groups. Eqs. 1 through 4 represent some routine applications of the carboxylic acid esterification reaction. Note the quantitative yields obtained in nearly all cases.



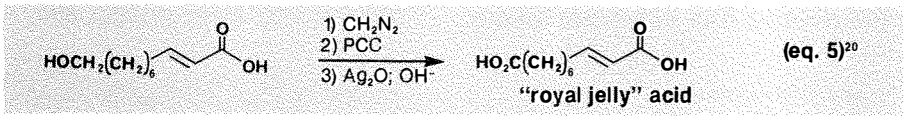


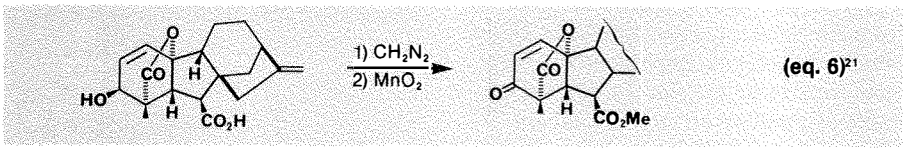


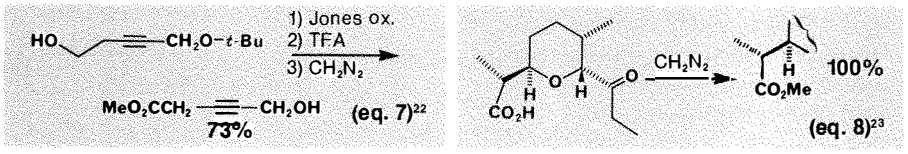


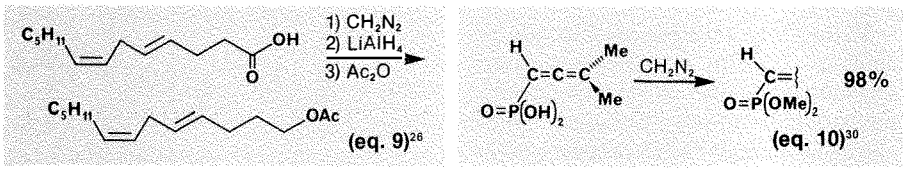
As mentioned above, the more electron-rich oxygen atoms lack the electrophilicity necessary for reaction with diazomethane. Thus, their presence is not a hindrance to the esterification of a carboxylic acid function elsewhere in the molecule. Accordingly, alcohols, whether isolated (eq. 5), allylic (eq. 6), or propargylic (eq. 7), do not interfere. Although many ketones react with diazomethane, selective esterification in their presence poses no problem (eq. 8). This is also true for lactones[24] and nitriles.[25] Similarly, isolated alkenes are not attacked (eq. 9), nor are silanes, whether vinylic[27] or allylic.[28] Nitro groups can be O-methylated (eq. 18), but not those on an aromatic ring.[29] Allenes commonly undergo cycloaddition with diazomethane,[7] but are not attacked during a competing esterification reaction (eq. 10, note that this case involves a **phosphoric** acid).

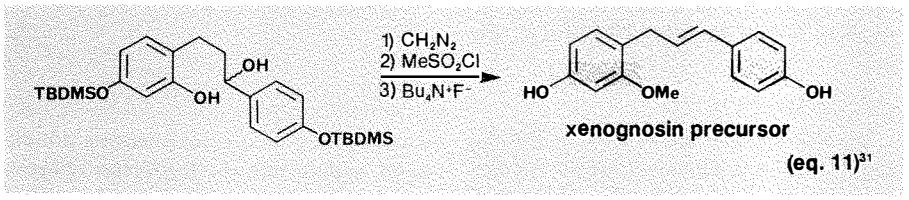
Phenols also possess sufficient acidity for uncatalyzed reaction with diazomethane. Of course, alcohols can be present in the same molecule, as indicated in eqs. 11 and 12. Eq. 12 involves a tropolone methylation *en route*

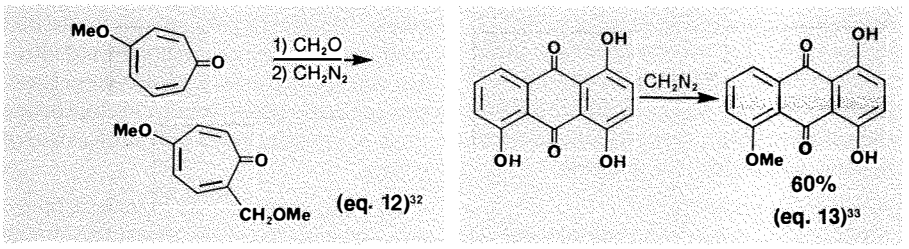












to a tropoquinonophane precursor. Selective methylations of phenolic hydroxyl groups also have been attained, based on the greater relative acidity of the reacting functionality (eq. 13).

Enols undergo similar reactions. In the case of β-dicarbonyl compounds, no acid catalyst is required (eq. 14). A recent application effected the bis-methylation of a cyclic keto anhydride (eq. 15). Amide and lactam enols can be methylated, provided silica gel is present as an acid catalyst (eq. 16).

Alcohols require acid catalysis for methylation. Since mineral acids react with diazomethane, Lewis acids are employed. Boron trifluoride etherate (eq. 17) is the favorite, although silica gel is also effective.[38] An exception is N-hydroxy compounds, wherein the electronegativity of the adjacent nitrogen atom makes catalysis unnecessary.[39]

Recently, phenylsulfonylnitromethane was O-methylated using diazomethane, the product of which was treated with base to afford the dimer of benzenesulfonylcarbonitrile oxide, a useful reagent in cycloaddition reactions with unactivated alkenes (eq.18).

N- and S-Methylation

Not surprisingly, nitrogen and sulfur can be methylated using diazomethane. In the absence of other nucleophilic atoms, the reaction can be quite clean (eq. 19), but mixtures of products are not uncommon.[42,43] This is especially true in purine chemistry.[44–46] Oxygen-sulfur exchange occurred during an S-methylation reaction reported recently, probably *via* a cationic four-membered transition state. (eq. 20).

C-Methylation

Methylations at carbon are relatively uncommon. Usually, a molecule of diazomethane reacts with an electron-deficient double bond to form a cycloadduct[48] which eliminates nitrogen.[49,50] Occasionally the reaction is quite useful, yielding products difficult to obtain *via* other routes (*e.g.*, eq. 21).

CYCLOADDITIONS

Diazomethane is a powerful 1,3 dipole, and its reactions with unsaturated systems are quite well understood.[52] Generally, such interactions are accepted as being controlled by the HOMO of the diazomethane molecule and the LUMO of the dipolarophile.[53] Recent evidence,[54] however, argues for a diradical mechanism, the possibility of which remains an unanswered question.[55]

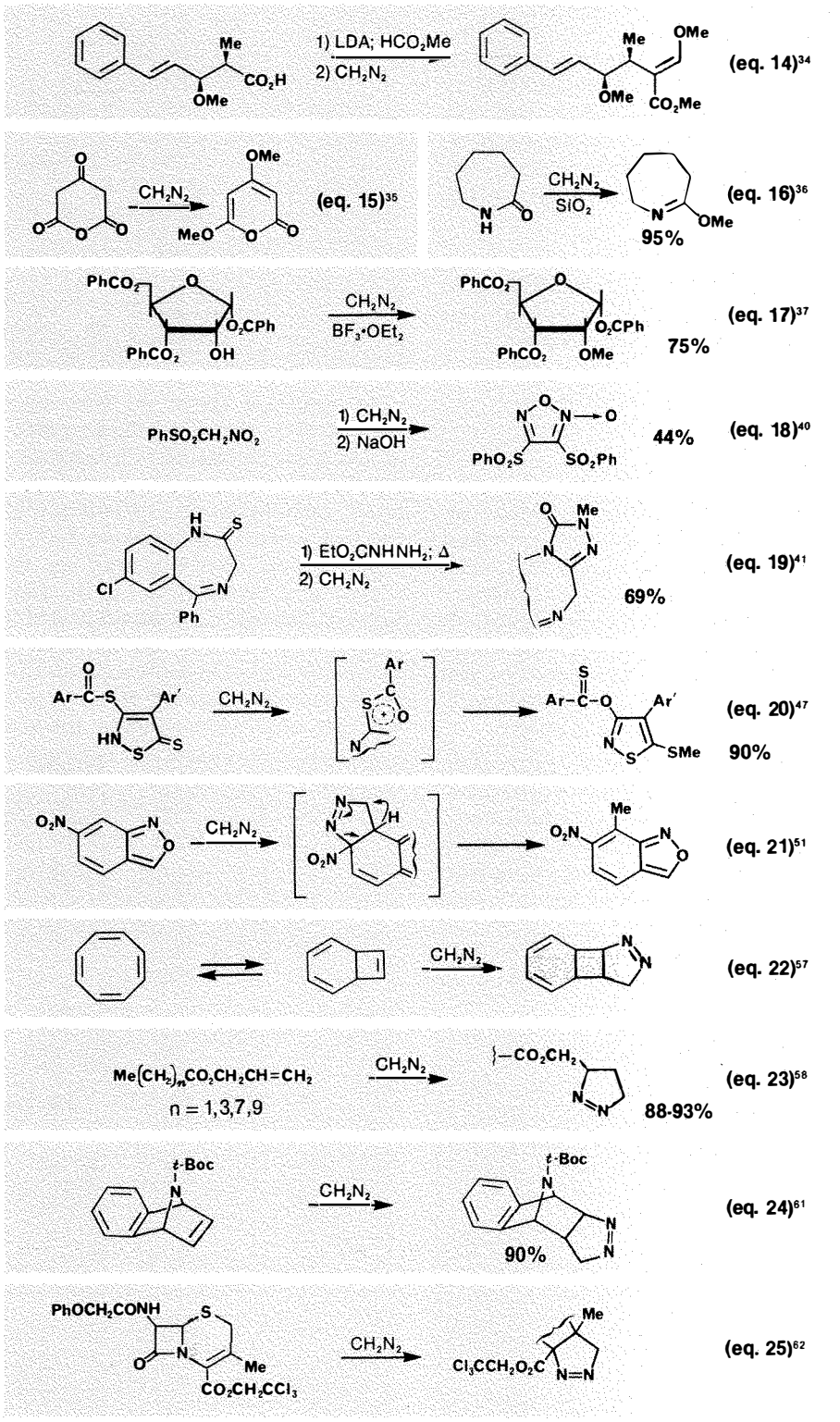
Pyrazoline Formation

Pyrazolines result from the addition of diazomethane to a carbon-carbon double bond, and the rate of reaction is often governed by the strain energy of the involved alkene.[56] Often the pyrazoline is the desired product; however, instability toward nitrogen elimination makes pyrazolines attractive synthetic precursors to cyclopropane rings or (as mentioned previously) methyl groups.

Cyclooctatetraene, *via* its valence tautomer, affords a tricyclic pyrazoline in one step (eq. 22). A series of bactericides has been prepared from allyl ester precursors (eq. 23). Norbornene derivatives are favorite substrates due to their strain energy;[59,60] product yields are often very high (eq. 24).

Enones also afford cycloadducts, as shown in eqs. 25 and 26. Similar reactions have been observed for alkenes conjugated with phosphoryl groups[64] or with sulfur 1,1-dioxides.[65]

Of course, enediones react readily with



diazomethane.[66] In these cases, the initial cycloadduct usually undergoes a 1,3 proton migration to afford the more stable Δ^2-pyrazoline (eq. 27).

Cyclopropane Formation

As pointed out previously, pyrazolines are ideal precursors to cyclopropanes through heat- or light-initiated decomposition with concomitant extrusion of nitrogen. Sometimes the pyrazoline is sufficiently unstable that its decomposition occurs spontaneously.

A wide variety of alkenes participate in this reaction. Eq. 28 shows the construction of a novel tetracyclic hydrocarbon employing this chemistry. Conjugated alkenes also react smoothly,[69] since their affinity for dipoles is increased (eq. 29). Allenes afford methylenecyclopropane derivatives.[71]

Spontaneous pyrazoline decomposition is observed with the more electron-deficient alkenes. Thus, a vinyl oxazolone[72] and quaternized imine[73] gave cyclopropanes immediately. Not surprisingly, the cyclopenta[*b*]-pyran-2,5-dione in eq. 30 afforded the tricyclic product shown with no pyrazoline intermediate being isolated.

The cyclopropanation of carbonyl groups is usually not synthetically useful; an example appears in the section on miscellaneous reactions.

Pyrazole Formation

Pyrazoles are formed by either the dehydrogenation of a pyrazoline or by the reaction of diazomethane with an acetylenic precursor. The former is often initiated by conjugation with a carbonyl (eq. 31) or phosphoryl[75] functionality.

More common is the reaction with acetylenes (eq. 32). A germanyl pyrazole was constructed in this way.[78] An interesting case is shown in eq. 33; excess diazomethane effected N-methylation of the resulting pyrazole along with esterification of the carboxylic acid.

Triazoline/Triazole Formation

Analogous to the formation of pyrazolines and pyrazoles is the preparation of their three-nitrogen analogs from imine and nitrile precursors. Although occasionally triazolines are themselves synthetic targets,[80] more often they are decomposed to afford various products (*e.g.*, eq. 34). Triazoles have resulted from the spontaneous dehydrochlorination of triazolines (eq. 35) or from reaction with a carbodiimide.[83]

Thiadiazole Formation

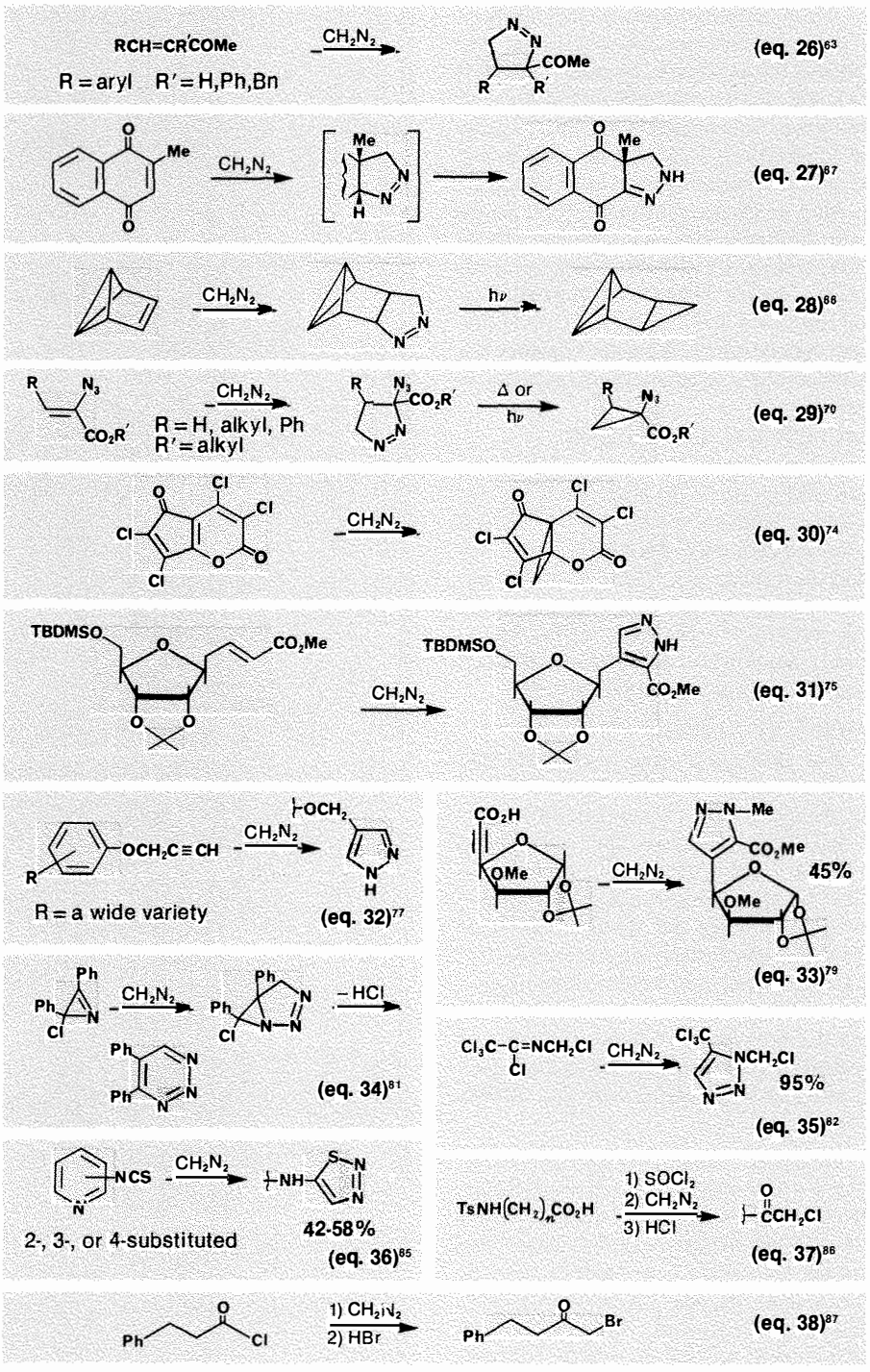
A little-used but potentially valuable construction of thiadiazoles involves the reaction of diazomethane with isothiocyanates.[84] As indicated in eq. 36, the result is an N-substituted amino thiadiazole ring.

α-DIAZOKETONE CHEMISTRY

α-Diazoketones are formed by the reaction of acid halides with diazomethane. They are important synthetic intermediates with three primary uses — the preparation of α-halo ketones, Wolff rearrangements, and intramolecular cyclopropanations *via* carbene intermediates. The first category is best illustrated by examples (eqs. 37 and 38).

The Wolff rearrangement is a classic synthetic maneuver of proven value. The α-diazoketone is decomposed by a silver salt in the presence of a hydroxylic compound which adds to the nitrene intermediate. Often an ester is the desired product (eq. 39), although acid homologation is also possible (eq. 40).

In the presence of copper or Brönsted acids, α-diazoketones decompose to carbenoid species which are capable of intramolecular attack on a nearby olefinic bond. This reaction has been exploited in numerous natural product syntheses (*e.g.*, eq. 41). In addition, the voracious electrophilicity of the carbene has enabled the construction of four- (eq. 42), five- (eq. 43), and six-membered (eq. 44) rings, as well as a five/six-fused spiro dienone (eq. 45).



RING EXPANSIONS

The reaction of diazomethane with ketones has been known and studied for some time. The possible products of such interaction are shown in Scheme IV. Epoxide formation is usually inconsequential (although at times it is the major reaction), and homologation (or ring expansion in the case of cyclic ketones) is the dominant reaction pathway.[75] The two major complications of the ring expansion reaction are 1) conflicting migratory aptitude of the involved carbon atoms (eq. 46) and 2) reaction of the product with excess diazomethane to produce undesired higher homologs (eq. 47).

The most useful ring expansion reactions involve substrates in which either symmetry negates the question of migratory aptitude (eq. 48) or where the aptitude of one carbon atom is so much greater than the other as to effectively yield only one product. A very useful cyclopentanone annulation sequence involves the reaction of an alkene with dichloroketene, ring expansion with diazomethane, and reductive cleavage of the chlorine atoms. The example outlined in eq. 49 featured a 62% overall yield in 95% regioisomeric purity. A similar sequence was employed in a recent synthesis of (±)-pentalenene.[100]

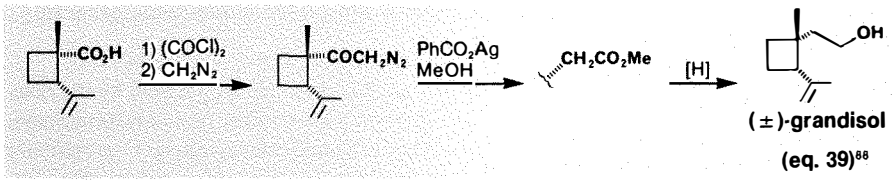
METHYLENE INSERTIONS

In some instances, reaction with diazomethane results in the insertion of a methylene unit into a single bond. This has been observed in the case of bonds between sulfur and phosphorus (eq. 50), sulfur and selenium,[102] sulfur and chlorine,[103] platinum and phosphorus,[104] and others.[105] The mechanism is not clearly understood but a free radical process has been implicated.[105]

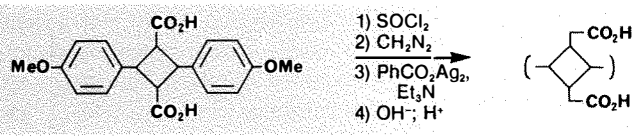
MISCELLANEOUS REACTIONS

The variety of unique reactions effected by diazomethane is testament that this field of chemistry is far from being fully understood. They range from the formation of a 1,3-methylenedioxy unit from a 1,2 quinone (eq. 51) to the interesting dimerization of tropothione (eq. 52). A series of aldehydo esters is available from lactol precursors (eq. 53). The reaction of a thioketone with diazomethane afforded the expected thiirane which thermally decomposed to an exocyclic methylene group (eq. 54). This cyclopropanation reaction can also occur with carbonyls.[8]

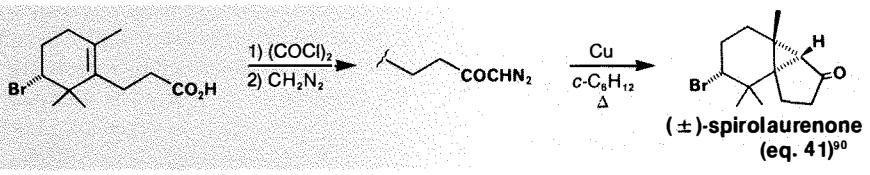
Hopefully, this short review has provided the reader with an appreciation of the tremendous usefulness and versatility of one of synthetic chemistry's truly indispensable reagents. Consider the transformation depicted in eq. 55, wherein diazomethane effected simultaneous expansion of the oxazolidone ring, cycloaddition to the benzylid-



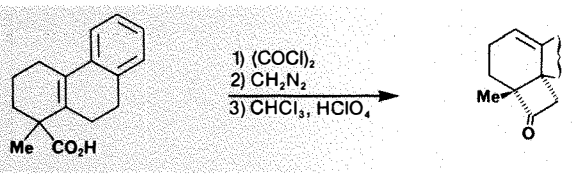
(eq. 39)[88]



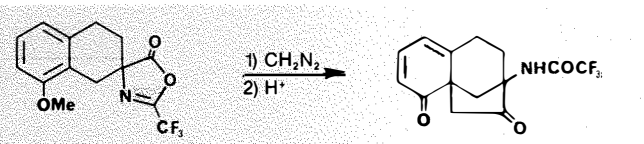
(eq. 40)[89]



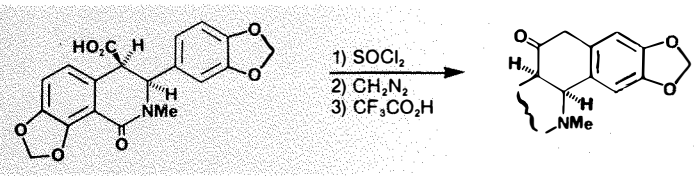
(eq. 41)[90]



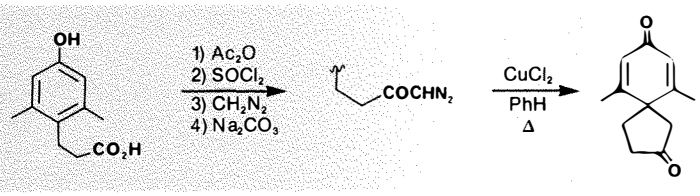
(eq. 42)[91]



(eq. 43)[92]

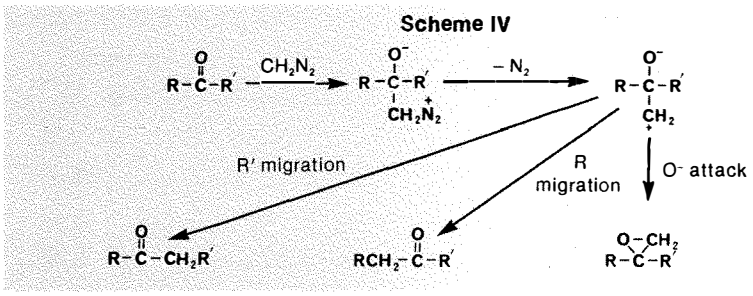


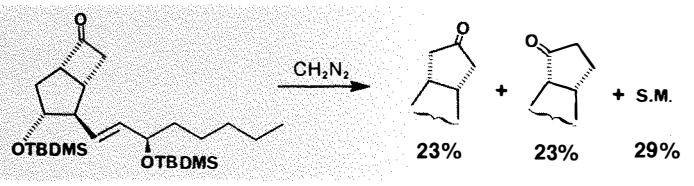
(eq. 44)[93]



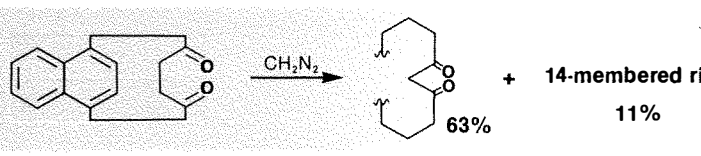
(eq. 45)[94]

Scheme IV

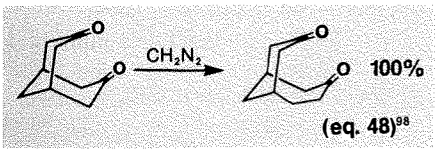


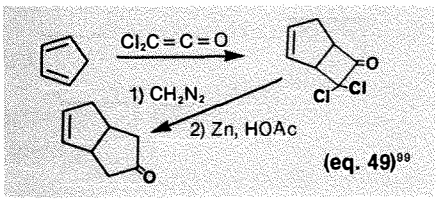


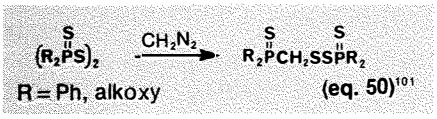
(eq. 46)[96]

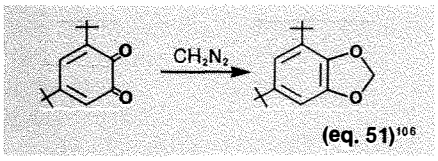


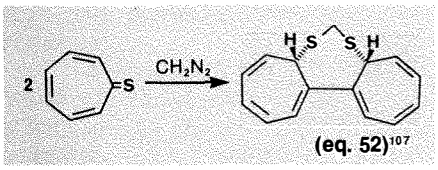
(eq. 47)[97]

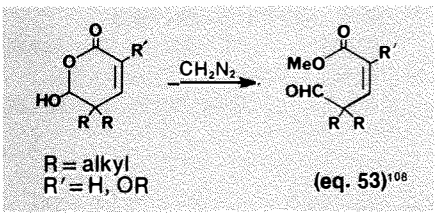


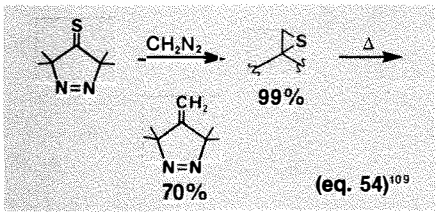


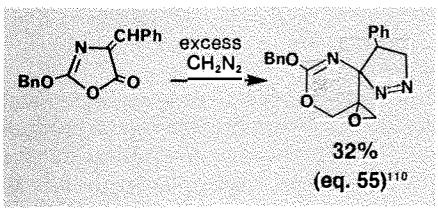












ene double bond, and cyclopropanation of the carbonyl group! Certainly, consideration of diazomethane chemistry is an important part of any synthetic plan.

References:

1) von Pechman, H. *Chem. Ber.* **1894**, *27*, 1888; **1895**, *28*, 855.
2) Moffat, J.B. *J. Mol. Struct.* **1979**, *52*, 275.
3) Berner, D.; McGarrity, J.F. *J. Am. Chem. Soc.* **1979**, *101*, 3135.
4) Paulett, G.S.; Ettinger, P. *J. Chem. Phys.* **1963**, *39*, 825.
5) Pizey, J.S. In "Synthetic Reagents"; Halsted: New York, 1974; Vol. II, Chapter 4.
6) Herrmann, W.A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 800.
7) Adam, W.; DeLucchi, O. *ibid.* **1980**, *19*, 762.
8) Gutsche, C.D. In "Organic Reactions"; Adams, R., Ed.; John Wiley & Sons: New York, 1954; Vol. VIII, p 392.
9) Lewis, Sr., R.J.; Tatken, R.L., Eds. "Registry of Toxic Effects of Chemical Substances", 1982 ed.; NIOSH: Cincinnati, OH, 1982; PA7000000.
10) Lewis, C.E. *J. Occup. Med.* **1964**, *6*, 91.
11) Schoental, R. *Nature* **1960**, *188*, 420.
12) de Boer, T.J.; Backer, H.J. In "Organic Syntheses, Collective Volume IV", Rabjohn, N., Ed.; John Wiley & Sons: New York, 1963; p 250.
13) Mandell, J.D.; Greenberg, J. *Biochem. Biophys. Res. Commun.* **1960**, *3*, 575; Adelberg, E.A.; Mandel, M.; Chen, G.C.C. *ibid.* **1965**, *18*, 788.
14) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.
15) *Idem Org. Prep. Proc. Int.* **1982**, *14*, 354.
16) Kozikowski, A.P.; Sugiyama, K.; Springer, J.P. *J. Org. Chem.* **1981**, *46*, 2428.
17) Alexander, J.; Bhatia, A.V.; Mitscher, L.A. *Org. Prep. Proc. Int.* **1981**, *13*, 185.
18) Yates, P.; Stevens, K.E. *Can. J. Chem.* **1982**, *60*, 825.
19) Guzman, A.; Mendoza, S. *Synthesis* **1981**, 989.
20) Fujisawa, T.; Sato, T.; Itoh, T. *Chem. Lett.* **1982**, 219.
21) Kirkwood, P.S.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 689.
22) Jung, M.E. *et al. J. Org. Chem.* **1982**, *47*, 1150.
23) Nicolaou, K.C. *et al. J. Am. Chem. Soc.* **1981**, *103*, 6967.
24) Greenlee, W.J.; Woodward, R.B. *Tetrahedron* **1980**, *36*, 3367.
25) Gilman, N.W. *Synth. Commun.* **1982**, *12*, 373.
26) Fujisawa, T. *et al. Tetrahedron Lett.* **1982**, *23*, 3583.
27) Padwa, A.; MacDonald, J.G. *ibid.* **1982**, *23*, 3219.
28) Naruta, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 961.
29) Fusco, R.; Sannicolo, F. *J. Org. Chem.* **1982**, *47*, 1691.
30) Macomber, R.S. *Synth. Commun.* **1977**, *7*, 405.
31) Kamat, V.S. *et al. Tetrahedron Lett.* **1982**, *23*, 1541.
32) Kawamata, A. *et al. ibid.* **1982**, *23*, 1083.
33) Blade, R.J.; Hodge, P. *Chem. Commun.* **1979**, 85.
34) Nakata, T. *et al. Tetrahedron Lett.* **1982**, *23*, 1015.
35) Ray, J.A.; Harris, T.M. *ibid.* **1982**, *23*, 1971.
36) Nishiyama, H.; Nagase, H.; Ohno, K. *ibid.* **1979**, 4671.
37) Chavis, C. *et al. J. Org. Chem.* **1982**, *47*, 202.
38) Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, 4405.
39) Zinner, G.; Schmidt, J.; Kilwing, W. *Arch. Pharm.* **1980**, *313*, 35.
40) Wade, P.A.; Pillay, M.K. *J. Org. Chem.* **1981**, *46*, 5425.
41) Hester, Jr., J.B.; Rudzik, A.D.; Von Voigtlander, P. *J. Med. Chem.* **1980**, *23*, 402.
42) Engelfried, C. *et al. Annalen* **1979**, 973.
43) Potts, K.T.; Ehlinger, R.; Kanemasa, S. *J. Org. Chem.* **1980**, *45*, 2474.
44) Barlin, G.B. *Aust. J. Chem.* **1981**, *34*, 1361.
45) Bergmann, F.; Brown, D.J. *ibid.* **1979**, *32*, 859.
46) Lister, J.H. *ibid.* **1979**, *32*, 2771.
47) Nishiwacki, T.; Kawamura, E.; Abe, N.; Iori, M. *Chem. Lett.* **1980**, 401.
48) For a mechanistic study, see Clinging, R.; Dean, F.M.; Houghton, L.E. *J. Chem. Soc. (C)* **1970**, 897; *Idem J. Chem. Soc., Perkin Trans. 1* 1974, 66.
49) Burger, K.; Eggersdorfer, M. *Annalen* **1979**, 1547.
50) Dean, F.M.; Johnson, R.S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 224.
51) Boruah, R.C.; Devi, P.; Sandhu, J.S. *J. Heterocycl. Chem.* **1979**, *16*, 155.
52) Cowell, G.W.; Ledwith, A. *Quart. Rev., Chem. Soc.* **1970**, *24*, 119.
53) a) Houk, K.N. *et al. J. Am. Chem. Soc.* **1973**, *95*, 7287; b) *Idem ibid.* **1973**, *95*, 7301; c) Geittner, J.; Huisgen, R. *Tetrahedron Lett.* **1977**, 881.
54) Firestone, R.A. *Tetrahedron Lett.* **1980**, 2209.
55) For a detailed discussion, see Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.
56) Huisgen, R. *et al. J. Am. Chem. Soc.* **1980**, *102*, 3951.
57) Calatroni, A.; Gandolfi, R. *Heterocycles* **1980**, *14*, 1115.
58) Makhsumov, A.G. *et al. Dokl. Akad. Nauk. Uzb. SSR* **1978**, 51; *Chem. Abstr.* **1980**, *92*, 58675q.
59) Rieber, N.; Bohm, H. *J. Heterocycl. Chem.* **1981**, *18*, 1.
60) Sasaki, T. *et al. J. Am. Chem. Soc.* **1981**, *103*, 565.
61) Sasaki, T.; Manabe, T.; Nishida, S. *J. Org. Chem.* **1980**, *45*, 479.
62) Farkas, E.R.; Gunda, E.T.; Jaszberenyi, J.C. *Tetrahedron Lett.* **1973**, 5127.
63) Saito, G. *et al. Akita Daigaku Kyoikugakubu Kenkyu Kiyo, Shizeu Kagaku* **1979**, 46; *Chem. Abstr.* **1980**, *92*, 128803f.
64) Gareev, R.D. *et al. Zh. Obshch. Khim.* **1979**, *49*, 493; *Chem. Abstr.* **1979**, *91*, 4894w.
65) a) DeBenedetti, P.G. *et al. J. Org. Chem.* **1980**, *45*, 3646; b) Fischer, U.; Schneider, F. *Helv. Chim. Acta* **1980**, *63*, 1719.
66) Awad, W.I.; Ismail, M.F.; Ghobrial, N.M. *Egypt. J. Chem.* **1976**, *19*, 1.
67) Dean, F.M. *et al. J. Chem. Soc., Perkin Trans. 1* **1980**, 1994.
68) Christl, M.; Brunn, E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 850.
69) Greenlee, W.J.; Woodward, R.B. *Tetrahedron* **1980**, *36*, 3361.
70) Hiyama, T.; Kai, M. *Tetrahedron Lett.* **1982**, *23*, 2103.
71) Crawford, R.J.; Chang, M.H. *Tetrahedron* **1982**, *38*, 837.
72) King, S.W. *et al. J. Org. Chem.* **1982**, *47*, 3270.
73) Evans, D.A. *et al. J. Am. Chem. Soc.* **1980**, *102*, 5955.
74) Kusuda, K.; Roedig, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 811.
75) Sato, T.; Noyori, R. *ibid.* **1980**, *53*, 1195.
76) Macomber, R.S. *Synth. Commun.* **1977**, *7*, 405.
77) Makhsumov, A.G. *et al. Fiziol. Akt. Veshchestva* **1979**, *11*, 101; *Chem. Abstr.* **1980**, *92*, 94292w.
78) Demina, M.M. *et al. Zh. Obshch. Khim.* **1979**, *49*, 1331; *Chem. Abstr.* **1979**, *91*, 123823g.
79) Tronchet, J.M.J. *et al. Helv. Chim. Acta* **1980**, *63*, 1181.
80) Aleksandrova, I.A. *et al. Khim. Geterotsikl. Soedin.* **1979**, 604; *Chem. Abstr.* **1979**, *91*, 91444r.
81) Gallagher, T.C.; Storr, R.C. *Tetrahedron Lett.* **1981**, *22*, 2909.
82) Boehme, H.; Drechsler, H.J. *Chem. Ztg.* **1979**, *103*, 188.
83) Svetlik, J.; Lesko, J.; Martvon, A. *Monatsh. Chem.* **1980**, *111*, 635.
84) Ogura, H.; Takahashi, H.; Sato, O. *Chem. Pharm. Bull.* **1981**, *29*, 1843.
85) Marchalin, M.; Martvon, A. *Collect. Czech. Chem. Commun.* **1980**, *45*, 2329.
86) Sajadi, Z. *et al. J. Med. Chem.* **1980**, *23*, 275.
87) Ackrell, J. *J. Heterocycl. Chem.* **1980**, *17*, 1081.
88) Clark, R.D. *Synth. Commun.* **1979**, *9*, 325.
89) Ruehle, R.H. *et al. J. Med. Chem.* **1980**, *23*, 1410.
90) Murai, A.; Kato, K.; Masamune, T. *Tetrahedron Lett.* **1982**, *23*, 2887.
91) Ghatak, U.R. *et al. J. Chem. Soc., Perkin Trans. 1* **1981**, 1203.
92) Blair, I.A.; Mander, L.N. *Aust. J. Chem.* **1979**, *32*, 1055.
93) Cushman, M. *et al. Tetrahedron Lett.* **1980**, 3845.
94) Iwata, C. *et al. Chem. Commun.* **1981**, 463.
95) For a good mechanistic study, see Hagan, S.; Anthonsen, T.; Kilaas, L. *Tetrahedron* **1979**, *35*, 2583.
96) Newton, R.F.; Wadsworth, A.H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 823.
97) Wiberg, K.B.; O'Donnell, M.J. *J. Am. Chem. Soc.* **1979**, *101*, 6660.
98) Momose, T.; Muraoka, O.; Atarashi, S. *Heterocycles* **1979**, *12*, 37.
99) Greene, A.E.; Dupres, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003.
100) Annis, G.D.; Paquette, L.A. *ibid.* **1982**, *104*, 4504.
101) Khaskiv, B.A. *et al. Zh. Obshch. Khim.* **1980**, *50*, 1990; *Chem. Abstr.* **1981**, *94*, 103477f.
102) Back, T.G. *J. Org. Chem.* **1981**, *46*, 5443.
103) Venier, C.G.; Hsieh, H.-H.; Barager, H.J. *ibid.* **1973**, *38*, 17.
104) Azam, K.A. *et al. Chem. Commun.* **1982**, 614.
105) a) Silicon-carbon, see Cunico, R.F.; Lee, H.M.; Herbach, J. *J. Organometal. Chem.* **1973**, *52*, C7; b) Mercury-chlorine, see Barluenga, J. *et al. Synthesis* **1979**, 893.
106) Rundell, W.; Kastner, P. *Annalen* **1970**, *737*, 87.

107) Machiguchi, T. *et al. Tetrahedron Lett.* **1973**, 2627.
108) Frimer, A.A. *et al. ibid.* **1982**, *23*, 1301.
109) Bushby, R.J.; Pollard, M.D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2401.
110) Jones, J.H.; Witty, M.J. *ibid.* **1980**, 858.

About the Author

After undergraduate work at Ohio Wesleyan University, Dr. Howard Black received the M.S. degree in 1977 from Central Michigan University, where he worked in the area of organic photochemistry. He obtained the Ph.D. degree in 1980 from Northwestern University , where he prepared and studied strained bicyclic alkenes under the direction of Professor James A. Marshall. Dr. Black is currently the manager of Aldrich's Pilot Plant.

Triflic Acid and Its Derivatives

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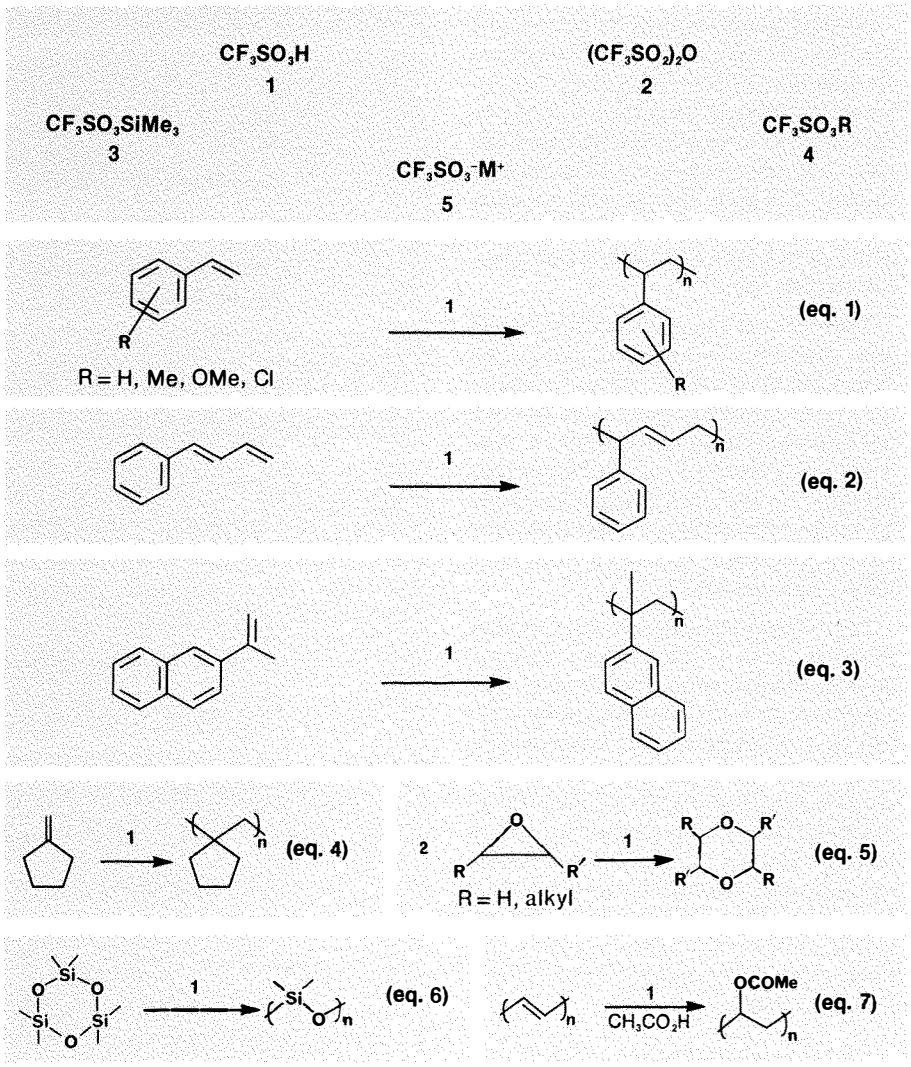
Trifluoromethanesulfonic acid (**1**), commonly known as triflic acid, was first reported in 1954 by Haszeldine and Kidd.[1,2] Since then there has been a rapid growth in the chemistry of **1** and its derivatives: triflic anhydride (**2**), trimethylsilyl triflate (**3**), alkyl and vinyl triflates (**4**), and triflate salts (**5**). The purpose of this review is to call attention to recent developments in the uses of triflic acid and its derivatives **2-5**. Several reviews already exist,[3-9] however, some are dated or limited to one topic. Where a subject has been very recently reviewed,[8,9] this article restricts itself to a few examples and refers the interested reader to the appropriate review for details.

Triflic acid was first made by acid oxidation of bis(trifluoromethylthio)mercury,[1] although a simpler process, electrochemical fluorination of methanesulfonyl fluoride (or chloride), was devised almost immediately.[10] Triflic acid has several advantages over other acid systems. It is one of the strongest acids known, yet it is nonoxidizing. It does not provide fluoride ions, even in the presence of strong nucleophiles, and it possesses superior thermal stability and resistance to both oxidation and reduction.

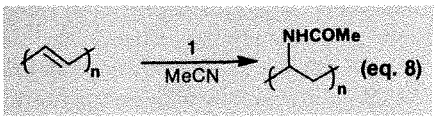
The last few years have seen a tremendous growth in the use of **1** as an oligomerization/polymerization catalyst. A variety of aromatic olefins have been oligomerized, including styrene,[11-15,17] methylstyrenes,[14-16] chloro- and methoxystyrenes,[17] 1-phenylbutadiene,[18] and 2-isopropenylnaphthalene (eqs. 1-3).[19] Stopped-flow kinetic measurements have been done on systems using **1** as a catalyst.[20-23] Conducting heteropolyphenylenes have recently been made using **1**,[24,25] while Hasegawa and Higashimura have reported the synthesis of isobutylene tetramer.[26] Higashimura has polymerized methylenecyclopentane (eq. 4)[27] and polyacetylene has been made using **1** as catalyst.[28] CF_3SO_3H is important in many of these cases as other acids may not work.[21]

Tetrahydrofuran (THF) is readily polymerized by catalytic amounts of **1**. Under appropriate conditions, either cyclic[29] or straight-chain polyethers[30,31] can be formed. CF_3SO_3H is a catalyst in the polymerization



of triethylene glycol cyclic formal.[32] Epoxides, in the presence of **1**, give 1,4-dioxanes (eq. 5);[33,34] epichlorohydrin, however, gives a polymer.[35] Systems which have used **1** as catalyst include polydimethylsiloxane (eq. 6),[36] polymethylenepolyphenyl carbamates[37,38] and polymers from 2-alkyl-2-oxazolines.[39]

A related area where triflic acid has proven useful is the modification of unsaturated polymers to give specifically functionalized polymers. For example, acetic acid gives polymers with acetate groups (eq. 7),[40,41] acrylic acid adds to polybutadiene to give acrylic ester rubbers,[42] and (with aqueous catalytic **1**) acetonitrile adds to polybutadiene to give 5% amide groups on the rubber (eq. 8).[43] Polyacetylene has been doped with **1** to give a p-type semiconductor[44] and Muench and co-workers have recently patented several conducting polymers using **1**.[45,46] CF_3SO_3H also effects the crosslinking of epoxy resins.[47]



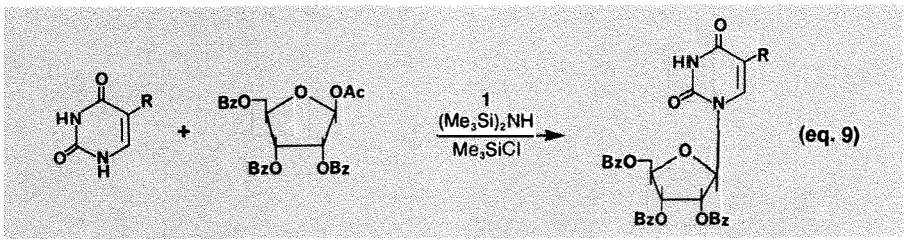
An interesting new area for the use of **1** is in fuel cell technology.[48-52] The systems are usually hydrogen/air or alkane/air, using either platinum or nickel electrodes. In the reduction of oxygen at a platinum surface, **1** is 100 times more efficient as a catalyst than 85% H_3PO_4, with a barrier that is 10.3 kcal/mol lower. This may lead to the use of **1** as an electrolyte in low-temperature fuel cells.[50]

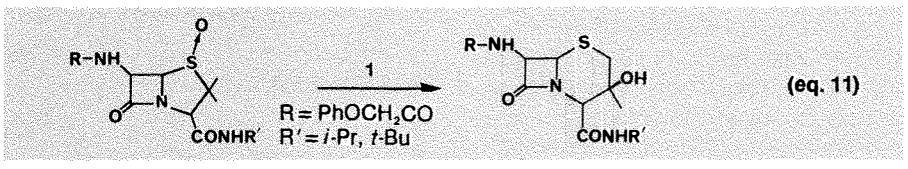
The ability of **1** to protonate olefins and even alkanes has been put to good use in the fuel production industry. Alkanes containing four to six carbons react with light olefins (3-5 carbons) in the presence of catalytic **1** and sulfuric acid to give high-octane gasoline,[53] while small linear alkanes are isomerized directly by **1**.[54-56] Hydrocarbon oils have also been produced from coal, phenol and catalytic **1**.[57]

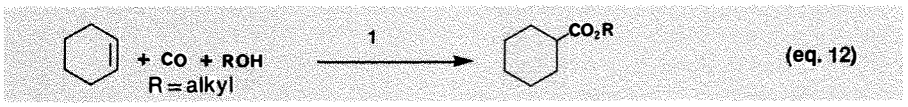
Several biomolecules have been made or modified using **1**. For example, uridines have been made using a system which silylates the uracil *in situ*, then attaches the sugar moiety in a Friedel-Crafts-catalyzed silyl-Hilbert-Johnson reaction (eq. 9).[58,59] This reaction is in fact a reaction of trimethylsilyl triflate (**3**), which is preformed from **1** and trimethylsilyl chloride (eq. 10). Another interesting reaction using **1** is a ring-expansion of penicillin S-oxides to give cephalosporins (eq. 11).[60] Also, a cephem acid tetrazole has been prepared using **1**,[61] and β-lactams have been made.[62]

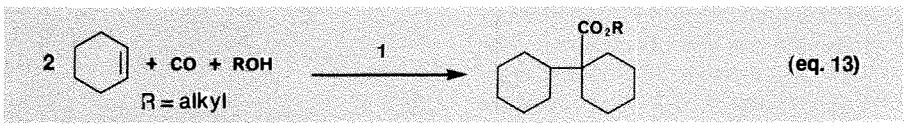
CF_3SO_3H is useful in the removal of protecting groups from oxygen and nitrogen functionalities (deblocking) of synthetic proteins. Typical reaction systems use **1** as cation generator, and either anisole[63,64] or thioanisole[65-69] as cation acceptor. Groups that can be removed by these systems include methyl,[65-67] benzyl,[64,67,69] carboxybenzyl,[63] and tosyl.[64,67,68] This deblocking methodology has been used in the synthesis of tuftsin,[64] enkephelin,[65,66] bovine pancreatic RNase,[69] and chicken neurotensin.[70]

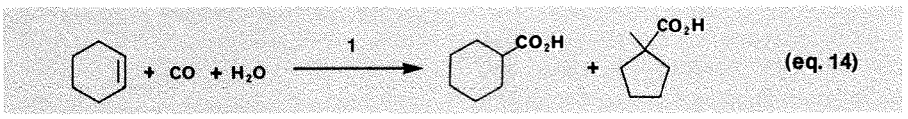
Friedel-Crafts chemistry has seen an increased use of triflic acid. For instance, the Koch synthesis of carboxylic acids has been carried out using carbon monoxide and cyclohexene.[71,72] If an alcohol is present, the product is an ester (eq. 12). If excess cyclohexene is used, a dimer is formed initially which is then carboxylated (eq. 13).[71] If water is present, a mixture of acids is formed (eq. 14).[72] Under anhydrous conditions, toluene is carbonylated to *o*- and *p*-tolualdehyde using **1** as catalyst (eq. 15).[73] Various substituted benz-4-pyrones have been made from the **1**-catalyzed Friedel-Crafts acylation (followed by ring closure and dehydration) of hydroquinone with β-ketoesters (eq. 16).[74] Butter and Morley have shown that **1** is a better catalyst than aluminum chloride for the Friedel-Crafts acylation of *p*-xylene.[75] They also studied this reaction for a variety of substrates and acid halides. In a related system, substituted aromatics were

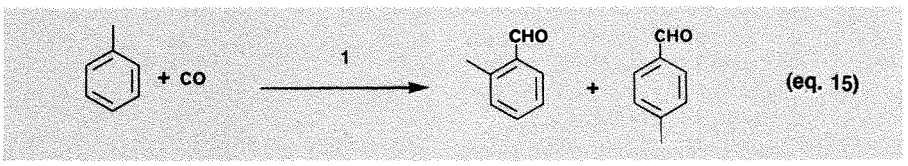


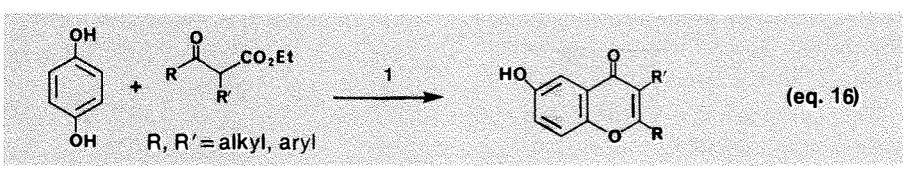


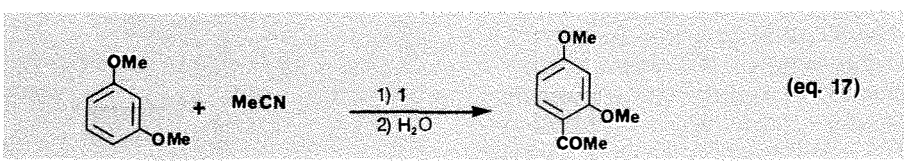












acylated in a two-step process using aliphatic nitriles (eq. 17).[76]

Friedel-Crafts alkylations have also been mediated by CF_3SO_3H. Thus, α,α,α-trifluoroacetophenone, treated with two equivalents of toluene, gives 1,1,1-trifluoro-2,2-bis(4-methylphenyl)-2-phenylethane (eq. 18).[77] Benzene was alkylated using a mixture of light alkanes and the superacid CF_3SO_3H/SbF_5 as catalyst.[78] Xylene and 2,2,4-trimethylpentane with **1** as catalyst gave *tert*-butylated aromatics.[79] A new substituted pyridine synthesis makes use of **1** to generate isobutylene *in situ* which is then acylated with pivaloyl chloride to give an intermediate pyrylium triflate (eq. 19).[80] Other amines have been made by Takayama and Suzuki and their co-workers.[81,82]

A related field is the rearrangement of species protonated by triflic acid, such as homoadamantane (eq. 20) by Schleyer and co-workers,[83] and 2-homoprotoadamantane.[84] Paquette also used **1** extensively in the synthesis of 1,16-dimethyldodecahedrane.[85] Non-hydrocarbon species such as *o*-bromophenol are also isomerized by **1**.[86-88]

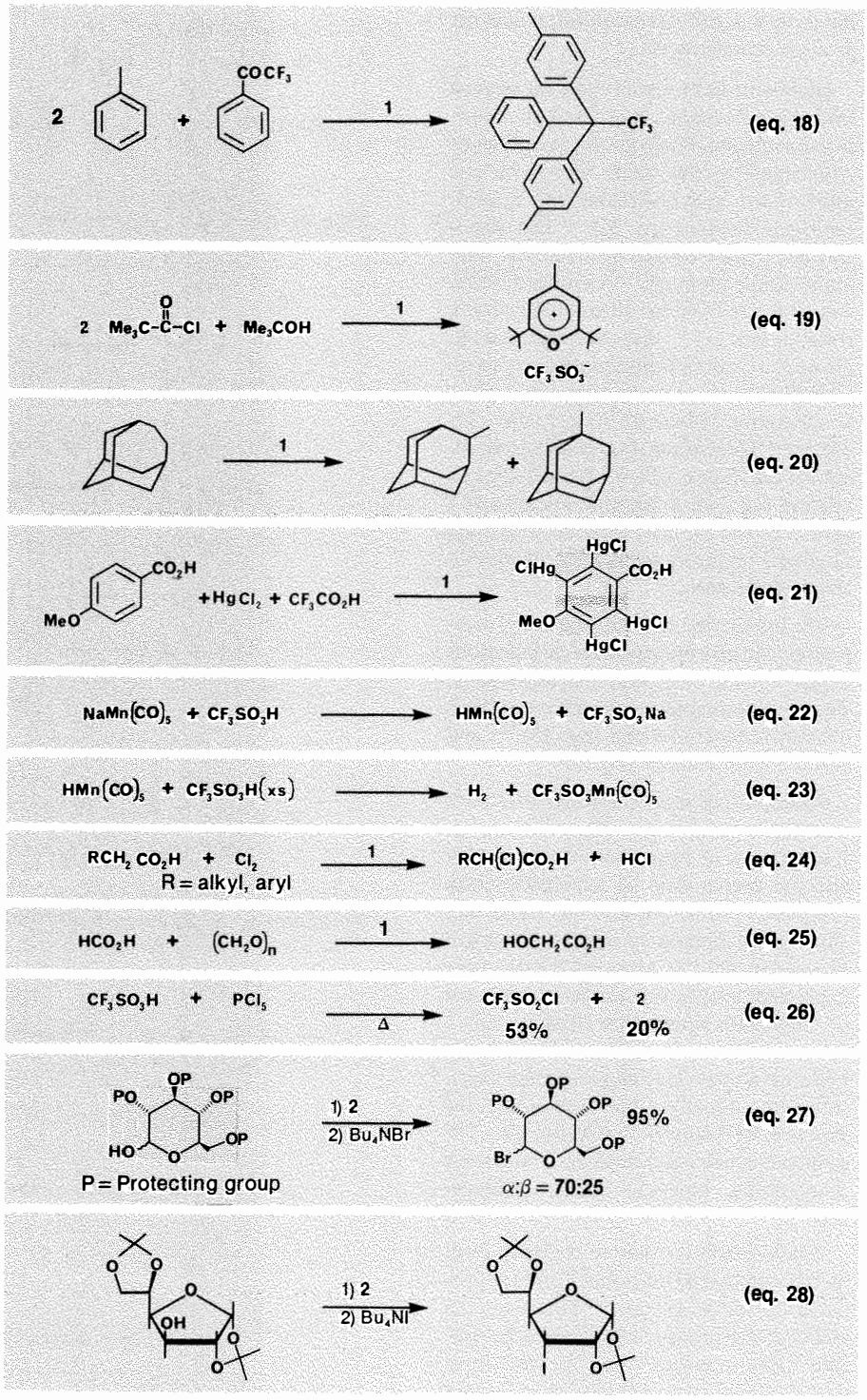
CF_3SO_3H has been well utilized in organometallic chemistry. It has catalyzed the mercuration of *p*-methoxybenzoic acid (eq. 21)[89] and perfluoroaromatics.[90] Mixed alkylgold-phosphine complexes are selectively dealkylated *cis* to the phosphine when treated with **1**.[91] Unstable copper carbonyl and silver carbonyl cation complexes have been generated in triflic acid.[92] The sulfide ligands of iron sulfide-protein analog complexes can be protonated and removed by **1**.[93] Iron carbonyl clusters can give iron carbonyl-carbide complexes on treatment with **1**,[94] a deoxygenation of a carbonyl! CF_3SO_3H can be used to protonate the manganese carbonyl anion (eq. 22),[95] but an excess can cause the formed hydride to act as a hydride source (producing H_2),[96] in spite of the high acidity of the complex (eq. 23). The metal-metal bond in a binuclear Re_2 complex can be protonated by **1**;[97] a Ru_3 cluster has also been protonated at its core.[98] Platinum(0) complexes can produce ethane from ethylene, and hydrogen from **1** alone.[99]

There are, of course, a large number of other applications of **1** in synthesis. Examples are the selective R–O or P–N cleavage in phosphoramidates and related compounds,[100,101] α-chlorination of carboxylic acids (eq. 24),[102] production of N-containing macrocycles,[103] and the industrial preparation of glycolic acid from formic acid (eq. 25).[104,105]

The first preparation of triflic anhydride (**2**) was reported by Brice and Trott in 1956, as a byproduct in the synthesis of triflyl chloride (eq. 26).[106] A better procedure involves treating triflic acid with P_2O_5.[10,107] Redistillation of the crude **2** from P_2O_5 gives a non-fuming, clear, water-white liquid.

The largest use of **2** is in the synthesis of alkyl and vinyl triflates **4**, a later topic in this review. However, **2** has had widespread application in carbohydrate research. Partially protected monosaccharides can be treated with **2** to give very reactive triflates which can be used to give anomeric halides (eq. 27),[108,109] deoxyhalo sugars,[110,111] pyranosylamines,[112] O-glycosylamino acids,[113] and glycosylglycosides.[114] The first synthesis of 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose was accomplished using **2** and tetrabutylammonium iodide (eq. 28).[110]

Various kinds of sulfonamides can be easily prepared with triflic anhydride and amines (eq. 29). These sulfonamides can be used as herbicides,[115-119] antimicrobials,[120] antiobesity drugs,[121] and other drugs.[122] One bissulfonamide is chemiluminescent.[123] The triflyl group on nitrogen activates the C–N



bond; thus, some of these sulfonamides act as alkyl-transfer agents.[124]

Dicationic salts which have an oxygen bridge can be made using **2** and an appropriate substrate. For instance, two moles of triphenylphosphine oxide react with one mole of **2** to give bis(triphenylphosphenium)oxide ditriflate (eq. 30).[125] The monocationic triflate cannot be made this way, as previously reported.[126] A similar dication can be made from hexamethylphosphoric triamide (eq. 31).[125] If the substrate is a nucleophilic carbonyl compound (such as tetramethylurea), then reaction with **2** gives a dicationic ether ditriflate (eqs. 32, 33).[127,128] Thiocarbonyls give dicationic disulfide ditriflates, where **2** has acted as an oxidant (eq. 34).[129] Another instance of **2** acting as oxidant is its reaction with alkyl Grignard reagents, giving alkyl halides instead of sulfones.[130]

The interaction of **2** with carbonyl compounds can give intermediate carbocations which undergo structural rearrangements. Two recent examples are the rearrangements of spiro[2.5]octan-4-one (eq. 35),[131] and pericyclocamphanone (eq. 36).[132]

Several other interesting uses of **2** have emerged in recent years. These include destannylation of stannylamines (eq. 37)[133] and the preparation of a vinylideneiron complex,[134] some geminal ditriflates (eq. 38),[135] and trifluoromethyl aryl sulfones (triflones) (eq. 39).[136,137] Moss and Sanders have made some specific surfactants by treatment of long-chain ammonium ethanols with **2** followed by a nucleophile.[138] In this case, triflate is a better leaving group than a neutral amine. Finally, **2** has been used in the synthesis of 3-fluoro-3-nitrooxetane,[139,140] semiconducting polyacetylene,[141] and some β-adrenergic blocking agents (β-blockers).[142]

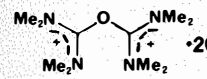
Trialkylsilylation has historically been used for analytical purposes[143] and for protection of polar groups.[144] However, the ability of silyl groups to stabilize both β-cations[145] and α-anions[146] and the ease of removal of silyl groups[147] has led to a rapid expansion in the use of silylated compounds. Trimethylsilyl triflate (**3**) is one of the most widely used silylating reagents, with a silylating potential that is nearly 10^9 compared to chlorotrimethylsilane.[148] Trialkylsilyl perfluoroalkanesulfonates in general have been reviewed.[8] Trimethylsilyl triflate, **3**, can be made by heating **1** with chlorotrimethylsilane,[149-151] or by protodesilylation of phenyltrimethylsilane by **1**.[152]

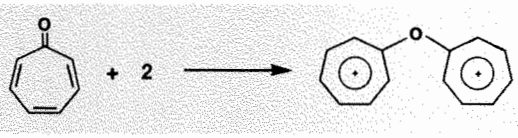
Carbonyl compounds can be readily silylated at oxygen with **3**; thus, aldehydes and ketones with α-hydrogens give silyl enol ethers (eq. 40).[153-157] While bulky groups in the substrate lower the silylation rate, electron-withdrawing substituents have little effect. Cyclic ketones work well, and cyclic enones give the silyl enol ethers very readily. Some 1,3-diketones undergo bissilylation to give 1,3-bis(trimethylsilyloxy)-1,3-dienes (eq. 41).[158-162]

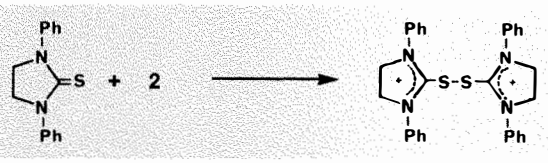
$RR'NH + 2 \rightarrow RR'NSO_2CF_3$ R, R′ = H, alkyl, aryl (eq. 29)

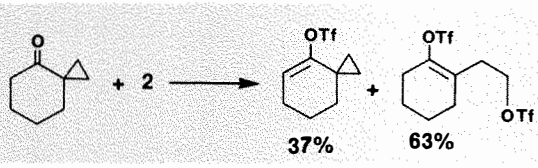
$2Ph_3PO + 2 \rightarrow Ph_3P^+-O-P^+Ph_3 \cdot 2CF_3SO_3^-$ (eq. 30)

$2(Me_2N)_3PO + 2 \rightarrow (Me_2N)_3P^+-O-P^+(NMe_2)_3 \cdot 2CF_3SO_3^-$ (eq. 31)

$2(Me_2N)_2CO + 2 \rightarrow$  (eq. 32)

 (eq. 33)

 (eq. 34)

 (eq. 35)

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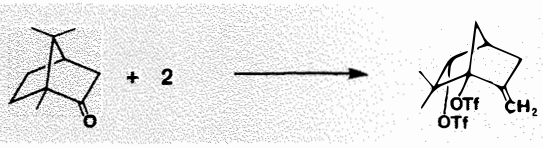
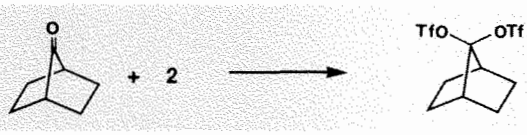
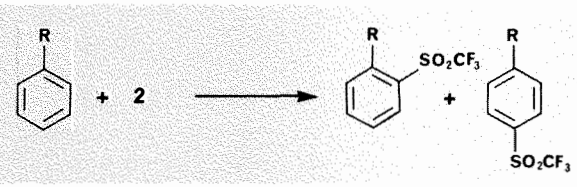
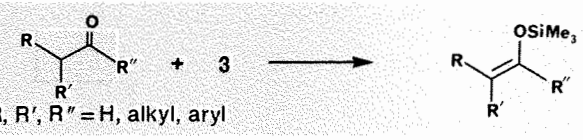
 (eq. 36)

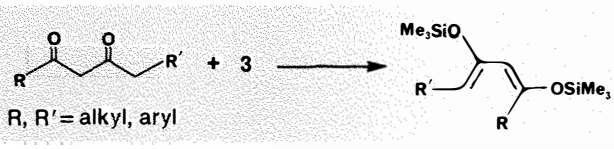
$PhN(SnMe_3)_2 + 2 \rightarrow PhN(SO_2CF_3)SnMe_3 + PhN(SO_2CF_3)_2$ (eq. 37)

 (eq. 38)

 (eq. 39)

 (eq. 40)

R, R′, R″ = H, alkyl, aryl

 (eq. 41)

R, R′ = alkyl, aryl

Esters can give more than one product on treatment with TMS triflate. One equivalent of **3** gives ketene O-alkyl-O-(trimethylsilyl)acetals (eq. 42);[163-169] excess **3** leads to mixtures of the ketene acetal and 2-trimethylsilylalkanoates. These mixtures are thermodynamically controlled.[166,170] However, since the ketene acetals are more sus-

ceptible to hydrolysis, the alkanoates can be isolated from these mixtures. Lactones are more reactive than the esters, and give cyclic bissilylated products (eq. 43).[165,166] Oxetan-2-one undergoes ring opening.[166]

N,N-Dialkyl amides react readily with **3**, giving an intermediate iminium salt (eq. 44),[165,166,171,172] which can be deprotonated by triethylamine to give ketene N,O-acetals if the amide contains an electron-withdrawing group.[172]

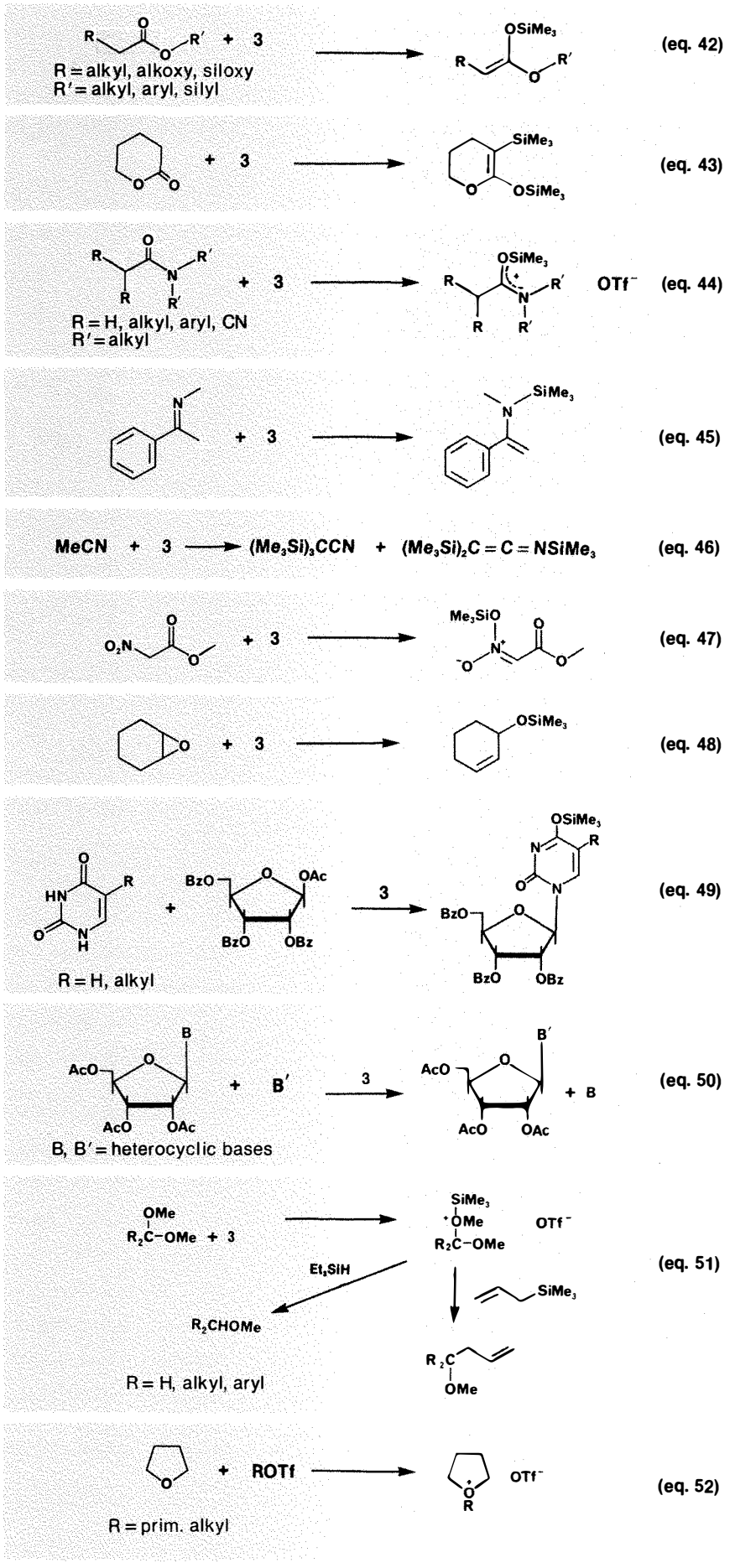
There are a variety of other nitrogen-containing organics which react readily with **3**. Tertiary amines which are used for deprotonation in the silylation reactions of **3** will also form adducts with **3**.[173] These adducts are very water-sensitive. Imines that have α-hydrogens can be silylated by **3** at nitrogen to give N-trimethylsilylenamines (eq. 45).[174] Nitriles are silylated in the α-position using **3**/amine base.[175] Excess **3** can lead to multisilylation, and usually a mixture (eq. 46). Nitroalkanes react with **3** to give silyl nitronates (eq. 47).[176–178]

Unlike trimethylsilyl iodide, TMS triflate does not give cleavage products when reacted with ethers except tetrahydrofuran.[179] Epoxides, however, react readily with **3** in the presence of DBU,[180] usually yielding trimethylsilyl ethers of the allylic alcohols (eq. 48).

Trimethylsilyl triflate, like triflic acid or triflic anhydride, can also be used to generate cations, but without the Brönsted acidity of **1**. This means that reactions such as eq. 49 proceed without protonation of the heterocyclic base, giving improved yields of the desired nucleosides.[181–184] Transglycosylation of sugars on nucleosides (eq. 50) has also been effected using **3**, with yield improvements over the tin(IV) chloride method.[185]

TMS triflate converts acetals to ethers *via* treatment of the cationic intermediate with alkylsilanes (eq. 51).[186] With allyltrimethylsilane, the ether of a homoallylic alcohol is obtained.[187]

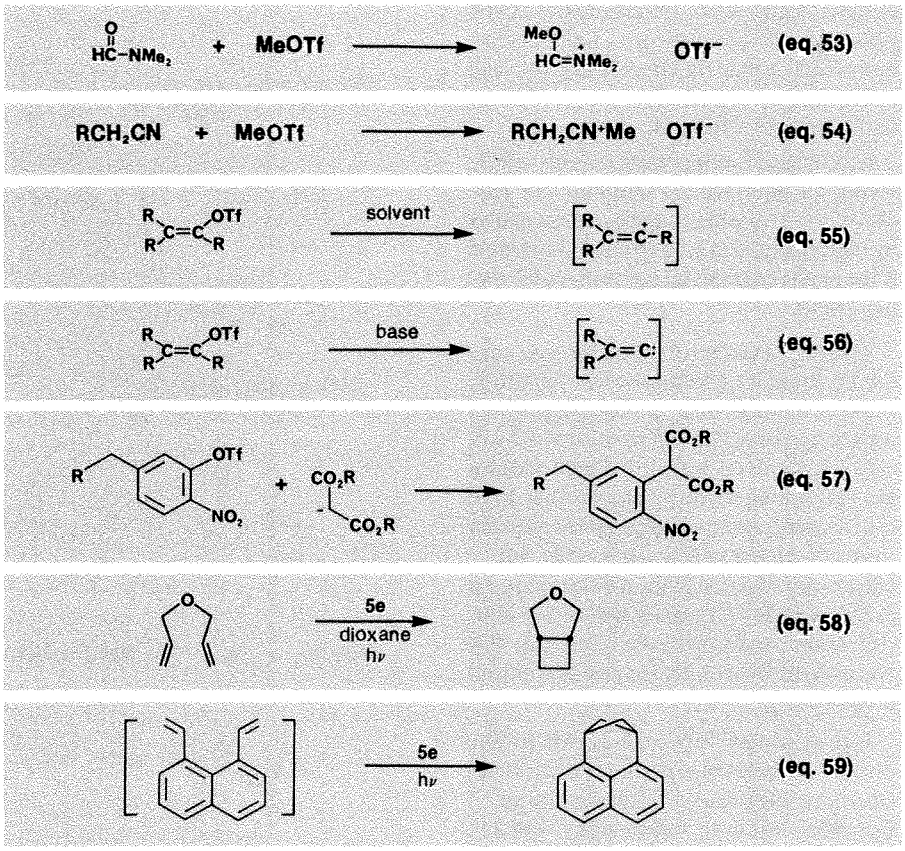
The alkyl, vinyl, and aryl esters of CF_3SO_3H have been included in a very recent review.[9] Please refer to this review for a complete description of the methods of preparation of these esters. Some applications of these triflates deserve mention here. Alkyl triflates can be used for alkylation at oxygen (eq. 52, 53)[188–192] and nitrogen (eq. 54),[193–197] and for the generation of carbocations.[198–203] Vinyl triflates generate reactive intermediates such as vinyl cations[204] and unsaturated carbenes (eq. 55,56).[205–209] Although aryl triflates do not generate phenyl cations,[210] they can be used to arylate carbanions (eq. 57).[211,212]



Many metal triflate salts (**5**) are now known, including those of sodium (**5a**), potassium (**5b**), barium (**5c**), cesium (**5d**), copper(I) (**5e**), and silver(I) (**5f**).[4] Pure **1** can be recovered on a large scale from **5a** or **5b** (or trialkylammonium triflates) by suspending the metal salt in 100% sulfuric acid and then distilling.[8,106,179] Pure **5f** as well as **1**-d_1 can be made from **5c**.[1,10]

Two of the most used salts are copper(I) triflate (**5e**) and silver(I) triflate (**5f**). The historic uses of **5e** have been olefin complexation and cyclodimerization.[4] Recently, Evers and Mackor[213,214] and Salomon and co-workers[215] cited numerous examples of photocyclodimerization of olefins using **5e** as catalyst (eq. 58). Wilcox and co-workers studied the photolysis of 1,8-divinylnaphthalene in the presence of **5e** (eq. 59).[216] Copper(I) triflate also catalyzes the addition of carbenes to olefins.[217] The complex, *trans*-cyclohexene/**5e**, has been the subject of a pseudorotational conformation study.[218] The chemistry of **5f** is quite varied, and includes the formation of olefin, alkyne,[219] and arene "crypt" complexes,[220] trifluoromethyl triflate,[221] oxapenam derivatives,[222] and aryl halides.[223] Complexes of gold,[224,225] platinum,[226] and ruthenium[227] have been selectively modified by using **5f**. Its use in carbohydrate chemistry is well known,[228,229] and has been reviewed.[230] THF polymers can also be made using **5f** as catalyst.[231,232]

In summary, it is evident from the foregoing that triflic acid and its derivatives are useful in a broad spectrum of organic chemistry, ranging from mechanistic and organometallic to carbohydrate, polymer, and synthetic chemistry. Inorganic chemistry has also made good use of **1**. Triflic acid and its derivatives can be used both catalytically and as stoichiometric reagents. This widespread use of **1** is attributable to a unique combination of three major properties of the acid, namely its very high acidity, its great thermal stability, and its non-oxidizing nature. Its continued use in the future, including expanded use in industrial processes, is clearly indicated by the exponential growth of literature references in this area since the first appearance of **1** in the mid-1950's.



Acknowledgments

Our own efforts during the last decade in this area, involving various compounds derived from triflic acid, have been generously supported by the National Science Foundation and the National Cancer Institute of the National Institutes of Health.

References:

1) Haszeldine, R.N.; Kidd, J.M. *J. Chem. Soc.* **1954**, 4228.
2) *Idem ibid.* **1955**, 2901.
3) Senning, A. *Chem. Rev.* **1965**, *65*, 385.
4) Howells, R.D.; McCown, J.D. *ibid.* **1977**, *77*, 69.
5) Fujinaga, T.; Sakamoto, I. *Kagaku (Kyoto)* **1976**, *31*, 718; *Chem. Abstr.* **1977**, *86*, 195790p.
6) IUPAC Analytical Chem. Div. *Pure Appl. Chem.* **1980**, *52*, 1387.
7) Zong, R.-S. *Hsueh Tung Pao* **1981**, 168; *Chem. Abstr.* **1981**, *95*, 41571s.
8) Emde, H.; Dietmar, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H.H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.
9) Stang, P.J.; Hanack, M.; Subramanian, L.R. *ibid.* **1982**, 85.
10) Gramstad, T.; Haszeldine, R.N. *J. Chem. Soc.* **1956**, 173.
11) Masuda, T.; Sawamoto, M.; Higashimura, T. *Makromol. Chem.* **1976**, *177*, 2981.
12) Shimizu, I.; Tsuji, O.; Matsuzuka, E.; Sato, A. Ger. Offen. 2 943 147, 1980.
13) Hamaya, T.; Yamada, S. *Makromol. Chem., Rapid Commun.* **1980**, *1*, 379.
14) Nippon Petrochemicals Co., Ltd. Jpn. Kokai Tokkyo Koho 80 57 524, 1980; *Chem. Abstr.* **1981**, *94*, 3846g.
15) Sawamoto, M.; Higashimura, T. *Macromolecules* **1981**, *14*, 467.
16) Nishi, H.; Higashimura, T. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, *15*, 1179.
17) Hiza, M.; Hasegawa, H.; Higashimura, T. *Polym. J.* **1980**, *12*, 379
18) Higashimura, T.; Hasegawa, H. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 59.
19) Engle, D.; Schulz, R.C. *Makromol. Chem.* **1979**, *180*, 2991.
20) Kunitake, T.; Takarabe, K. *Polym. J.* **1978**, *10*, 105.
21) Sawamoto, M.; Higashimura, T. *Macromolecules* **1979**, *12*, 581.
22) Sawamoto, M.; Higashimura, T. *Polym. Prepr., Am. Chem. Soc., Div. Polym. Chem.* **1979**, *20*, 727; *Chem. Abstr.* **1979**, *91*, 108274k.
23) Takarabe, K.; Kunitake, T. *Makromol. Chem.* **1981**, *182*, 1587.
24) Feichtmayr, F.; Naarmann, H.; Naegele, D.; Penzien, K. Ger. Offen. 3 018 459, 1981; *Chem. Abstr.* **1982**, *96*, 86656k.
25) Naarmann, H.; Naegele, D.; Penzien, K.; Schlag, J. Ger Offen. 3 025 771, 1982; *Chem. Abstr.* **1982**, *96*, 200588s.
26) Hasegawa, H.; Higashimura, T. *J. Appl. Polym. Sci.* **1982**, *27*, 171.
27) Higashimura, T. Jpn. Kokai Tokkyo Koho 81 34 636, 1981; *Chem. Abstr.* **1981**, *95*, 97180f.
28) Aldrissi, M.; Linaya, C.; Sledz, J.; Schue, F.; Giral, L.; Fabre, J.M.; Rolland, M. *Polymer* **1982**, *23*, 243.
29) Pruckmayr, G.; Wu, T.K. *Macromolecules* **1978**, *11*, 265.
30) Maeda, S.; Kondo, A.; Okabe, K.; Nakanishi, Y. Jpn. Kokai 77 22 098, 1977; *Chem. Abstr.* **1977**, *86*, 156244u.
31) Pruckmayr, G.; Wu, T.K. *Macromolecules* **1978**, *11*, 662.
32) Schulz, R.C.; Albrecht, K.; Quynh Van Tran Thi; Nienburg, J.; Engel, D. *Polym. J.* **1980**, *12*, 639.
33) Kobayashi, S.; Morikawa, K.; Saegusa, T. *ibid.* **1979**, *11*, 405.
34) Kawakami, Y.; Ogawa, A.; Yamashita, Y. *Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 3785.
35) Ito, K.; Usami, N.; Yamashita, Y. *Polym. J.* **1979**, *11*, 171.
36) Chojnowski, J.; Wilczek, L. *Makromol. Chem.* **1979**, *180*, 117.
37) Shawl, E.T. U.S. Patent 4 162 362, 1979; *Chem. Abstr.* **1979**, *91*, 140597d.
38) Miyata, K.; Hasegawa, S.; Aoki, S.; Hara, I. Ger. Offen. 2 950 260, 1980; *Chem. Abstr.* **1980**, *93*, 204310f.
39) Saegusa, T.; Ikeda, H.; Aotani, S.; Sakabe, N.; Suminoe, T. Jpn. Kokai 76 121 100, 1976; *Chem. Abstr.* **1977**, *86*, 55959a.
40) Roberts, R.M.G. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1183. Not done on polymers, but gives the basic reaction of acetic acid with olefins.
41) Ikeda, H. Jpn. Kokai Tokkyo Koho 79 139 695, 1979; *Chem. Abstr.* **1980**, *92*, 77815b.
42) Ikeda, H. Jpn. Kokai Tokkyo Koho 79 118 489, 1979; *Chem. Abstr.* **1980**, *92*, 59468m.
43) Ikeda, H. Jpn. Kokai Tokkyo Koho 80 36 234, 1980; *Chem. Abstr.* **1980**, *93*, 27114x.
44) Showa Denko, K.K. Jpn. Kokai Tokkyo Koho 80 129 425, 1980; *Chem. Abstr.* **1981**, *94*, 66666u.
45) Muench, V.; Naarmann, H.; Penzien, K. Ger. Offen. 3 018 389, 1981; *Chem. Abstr.* **1982**, *96*, 35908m.

46) *Idem* European Pat. Appl. 44 935, 1982; *Chem. Abstr.* **1982**, *96*, 182275f.
47) Alm, R.R. *Paint. Coat.* **1980**, *70*, 88.
48) Baker, B. *Spec. Rep. - Electr. Power Res. Inst.* **1975**, 5R-13; *Chem. Abstr.* **1975**, *83*, 134925c.
49) Adams, A.A.; Foley, R.T. *Gov. Rep. Announce. Index (US)* **1977**, *77*, 98; *Chem. Abstr.* **1977**, *87*, 25991h.
50) Appleby, A.J.; Baker, B.S. *J. Electrochem. Soc.* **1978**, *125*, 404.
51) Hughes, V.B.; McNichol, B.D. *ibid.* **1980**, *127*, 2646.
52) Adams, A.A.; Foley, R.T. *ibid.* **1980**, *127*, 2647.
53) Brockington, J.W.; Bennett, R.H. U.S. Patent 4 038 212, 1977; *Chem. Abstr.* **1977**, *87*, 104338d.
54) McCaulay, D.A.; Nevitt, T.D. U.S. Patent 4 035 286, 1977; *Chem. Abstr.* **1977**, *87*, 104332x.
55) Innes, R.A. *A.C.S. Symp. Ser.* **1977**, *55*, 57; *Chem. Abstr.* **1978**, *88*, 76210f.
56) Brunel, D.; Itier, J.; Commeyras, A.; Phan Tan Luu, R.; Mathieu, D. *Bull. Soc. Chim. Fr.* **1979**, 249 and 257.
57) Moore, R.H.; Cox, J.L. U.S. Patent 4 090 944, 1978; *Chem. Abstr.* **1978**, *89*, 92216p.
58) Vorbrüggen, H.; Bennua, B. *Tetrahedron Lett.* **1978**, 1339.
59) *Idem Chem. Ber.* **1981**, *114*, 1279.
60) Ichikawa, Y.; Nakagawa, K. Jpn. Kokai 77 83 584, 1977; *Chem. Abstr.* **1978**, *88*, 105364s.
61) Yamanouchi Pharm. Co., Ltd. Jpn. Kokai Tokkyo Koho 80 153 790, 1980; *Chem. Abstr.* **1981**, *94*, 208887t.
62) Appleby, I.C.; Woodward, F.E. Brit. U.K. Pat. Appl. 2 077 728, 1982; *Chem. Abstr.* **1982**, *96*, 199411v.
63) Fujii, N.; Funakoshi, S.; Sasaki, T.; Yajima, H. *Chem. Pharm. Bull.* **1977**, *25*, 3096.
64) Chaudhuri, M.K.; Najjar, U.A. *Anal. Biochem.* **1979**, *95*, 305.
65) Kiso, Y.; Ito, K.; Nakamura, S.; Kitagawa, K.; Akita, T.; Moritoki, H. *Chem. Pharm. Bull.* **1979**, *27*, 1472.
66) Kiso, Y.; Nakamura, S.; Ito, K.; Ukawa, K.; Kitagawa, K.; Akita, T.; Moritoki, H. *Chem. Commun.* **1979**, 971.
67 Kiso, Y.; Ukawa, K.; Satomi, M.; Nakamura, S.; Kitagawa, K.; Akita, T. *Pept. Chem.* **1979**, 193.
68) Kiso, Y.; Satomi, M.; Ukawa, K.; Akita, T. *Chem. Commun.* **1980**, 1063.
69) Yajima, H.; Fujii, N. *Biopolymers* **1981**, *20*, 1859.
70) Yajima, H.; Minamitake, Y.; Funakoshi, S.; Akaji, K.; Oishi, M.; Akazuwa, Y.; Segawa, T.; Nakata, Y.; Inoue, A. *Chem. Pharm. Bull.* **1981**, *29*, 2587.
71) Norell, J.R. U.S. Patent 3 965 132, 1976.
72) Booth, B.L.; El-Fekky, T.A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2441.
73) Suzuki, Y.; Murao, Y.; Yamamura, T. Jpn. Kokai 76 146 430, 1976; *Chem. Abstr.* **1977**, *87*, 5590y.
74) Woods, L.L. *Trans. Can. Acad. Sci.* **1972**, *75*, 279.
75) Butter, I.R.; Morley, J.O. *J. Chem. Res., Synop.* **1980**, 358.
76) Booth, B.L.; Noori, G.F.M. *J. Chem. Soc., Perkin. Trans. 1* **1980**, 2894.
77) Kray, W.D.; Rosser, R.W. *J. Org. Chem.* **1977**, *42*, 1186.
78) Miethchen, R.; Gaertner, A.; Roth, U.; Wiechert, K.; Kroeger, C.F. *J. Prakt. Chem.* **1977**, *319*, 383.
79) Kroeger, C.F.; Miethchen, R.; Mann, H.; Hoffmann, K.; Wiechert, K. *ibid.* **1978**, *320*, 881.
80) Anderson, A.G.; Stang, P.J. *J. Org. Chem.* **1976**, *41*, 3034.
81) Takayama, H.; Suzuki, T.; Nomoto, T. *Chem. Lett.* **1978**, 865.
82) Takayama, H.; Suzuki, T.; Takamoto, M.; Okamoto, T. *Heterocycles* **1978**, *9*, 1429.
83) Takaishi, N.; Inamoto, Y.; Fujikura, Y.; Aigami, K.; Golicmik, B.; Mlinaric-Majerski, K.; Majerski, Z.; Osawa, E.; Schleyer, P.v.R. *Chem. Lett.* **1976**, 763.
84) Takaishi, N.; Inamoto, Y.; Aigami, K.; Fujikura, Y.; Osawa, E.; Kawanishi, M.; Katsushima, T. *J. Org. Chem.* **1977**, *42*, 2041.
85) Paquette, L.A.; Balogh, D.W. *J. Am. Chem. Soc,* **1982**, *104*, 774.
86) Rebek, Jr., J.; Trend, J.E. *ibid.* **1978**, *100*, 4315.
87) Jonkheer, P.C.T.M.; Moen, J.; Wolters, J.; Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 223.
88) Campbell, J.R. U.S. Patent 4 156 790, 1979; *Chem. Abstr.* **1979**, *91*, 91350g.
89) Deacon, G.B.; O'Donoghue, M.F. *J. Organometal. Chem.* **1980**, *194*, C60.
90) Deacon, G.B.; Tunaley, D. *ibid.* **1978**, *156*, 403.
91) Komiya, S.; Kochi, J.K. *J. Am. Chem. Soc.* **1976**, *98*, 7599.
92) Souma, Y.; Iyoda, J.; Sano, H. *Osaka Kogyo Gijutsu Shikensho Kiho* **1976**, *27*, 277; *Chem. Abstr.* **1976**, *84*, 129811d.
93) Johnson, R.W.; Holm, R.H. *J. Am. Chem. Soc.* **1978**, *100*, 5338.
94) Holt, E.M.; Whitmore, K.H.; Shriver, D.F. *J. Organometal. Chem.* **1981**, *213*, 125.
95) Gladysz, J.A.; Tam, W.; Williams, G.M.; Johnson, D.L.; Parker, D.W. *Inorg. Chem.* **1979**, *18*, 1163.
96) Trogler, W.C. *J. Am. Chem. Soc.* **1979**, *101*, 6459.
97) Lewis, L.N.; Caulton, K.G. *Inorg. Chem.* **1981**, *20*, 1139.
98) Barner-Thorsen, C.; Rosenberg, E.; Saatjian, G.; Aime, S.; Milone, L.; Osella, D. *ibid.* **1981**, *20*, 1592.
99) Foley, P.; Whitesides, G.M. *ibid.* **1980**, *19*, 1402.
100) Modro, T. *Chem. Commun.* **1980**, 201.
101) Modro, T.; Graham, D.H. *J. Org. Chem.* **1981**, *46*, 1923.
102) Proctor and Gamble Co. Jpn. Kokai Tokkyo Koho 79 39 013, 1979; *Chem. Abstr.* **1979**, *91*, 19907b.
103) Tait, A.M.; Busch, D.H. *Inorg. Synth.* **1978**, *18*, 2.
104) Leupold, E.I.; Arpe, H.J. Ger. Offen. 2 652 003, 1978; *Chem. Abstr.* **1978**, *89*, 42452s.
105) *Idem* Ger. Offen. 2 652 072, 1978; *Chem. Abstr.* **1978**, *89*, 108182n.
106) Brice, T.J.; Trott, P.W. U.S. Patent 2 732 398, 1956.
107) Stang, P.J.; Dueber, T.E. *Org. Synth.* **1974**, *54*, 79.
108) Leroux, J.; Perkin, A.S. *Carbohydr. Res.* **1976**, *47*, C8.
109) *Idem ibid.* **1978**, *67*, 163.
110) Binkley, R.W.; Hehemann, D.G. *J. Org. Chem.* **1978**, *43*, 3244.
111) Binkley, R.W.; Ambrose, M.G.; Hehemann, D.G. *ibid.* **1980**, *45*, 4387.
112) Pavia, A.A.; Ung-Chhun, S.N.; Durand, J.L. *ibid.* **1981**, *46*, 3158.
113) Lacombe, J.M.; Pavia, A.A.; Rocheville, J.M. *Can. J. Chem.* **1981**, *59*, 473.
114) Pavia, A.A.; Ung-Chhun, S.N. *ibid.* **1981**, *59*, 482.
115) Moore, G.G.I.; Harrington, J.K. U.S. Patent 4 005 141, 1977; *Chem. Abstr.* **1977**, *86*, 189509n.
116) Tobler, H.; Foery, W.; Schurter, R. Ger Offen. 2 815 820, 1978; *Chem. Abstr.* **1979**, *90*, 121396a.
117) Shen, K.K.; Belles, W.S. U.S. Patent 4 123 251, 1978; *Chem. Abstr.* **1979**, *90*, 121614v.
118) Nishiyama, R.; Fujikawa, K.; Kimura, F.; Nasu, P.; Sakashita, N.; Nishimura, S. Ger. Offen. 2 850 821, 1979; *Chem. Abstr.* **1979**, *91*, 107897d.
119) Wareing, J.R. Ger. Offen. 2 916 714, 1979; *Chem. Abstr.* **1980**, *92*, 94063x.
120) Moore, G.G.I.; Harrington, J.K. U.S. Patent 3 972 926, 1976; *Chem. Abstr.* **1977**, *86*, 29487a.
121) Foye, W.O.; Sane, J.N. *J. Pharm. Sci.* **1977**, *66*, 923.
122) Robertson, J.E.; Harrington, J.K.; Kvam, D.C. U.S. Patent Reissue 29 032, 1976; *Chem. Abstr.* **1977**, *86*, 139625b.
123) Tseng, S.S.; Rauhut, M.M. U.S. Patent 4 282 357, 1981; *Chem. Abstr.* **1981**, *95*, 169220u.
124) Townsend, C.A.; Theis, A.B. *J. Org. Chem.* **1980**, *45*, 1697.
125) Aaberg, A.; Gramstad, T.; Husebye, S. *Tetrahedron Lett.* **1979**, 2263.
126) Hendrickson, J.B.; Schwartzmann, S.M. *ibid.* **1975**, 277.
127) Stang, P.J.; Maas, G.; Fisk, T.E. *J. Am. Chem. Soc.* **1980**, *102*, 6361.
128) Stang, P.J.; Maas, G. *ibid.* **1981**, *103*, 4837.
129) *Idem J. Org. Chem.* **1981**, *46*, 1606.
130) Creary, X. *ibid.* **1980**, *45*, 2727.
131) Garcia, F.A.; Garcia Martinez, A.; Herrera, F.A.; Sanchez Garcia, J.M. *An. Quim.* **1979**, *75*, 723.
132) Garcia Martinez, A.; Garcia, F.A. *ibid., Ser. C* **1980**, *76*, 127.
133) Roesky, H.W.; Ambrosius, K. *Isr. J. Chem.* **1978**, *17*, 132; *Chem. Abstr.* **1979**, *90*, 23191k.
134) Boland, B.E.; Fam, S.A.; Hughes, R.P. *J. Organometal. Chem.* **1979**, *172*, C29.
135) Garcia Martinez, A.; Espada Rios, I.; Teso Vilar, E. *Synthesis* **1979**, 382.
136) Hendrickson, J.B.; Bair, K.W. *J. Org. Chem.* **1977**, *42*, 3875.
137) Bair, K.W. *Diss. Abstr. Int. B.* **1977**, *37*, 6122.
138) Moss, R.A.; Sanders, W.J. *J. Am. Chem. Soc.* **1978**, *100*, 5247.
139) Baum, K.; Berkowitz, P.T. U.S. Patent Appl. 933 364, 1979; *Chem. Abstr.* **1979**, *90*, 186768t.
140) Berkowitz, P.T.; Baum, K. *J. Org. Chem.* **1980**, *45*, 4853.
141) Japan Synthetic Rubber Co., Ltd. Jpn. Kokai Tokkyo Koho 80 144 005, 1980; *Chem. Abstr.* **1981**, *94*, 15801le.
142) Lumma, Jr., W.C. *J. Org. Chem.* **1981**, *46*, 3668.
143) Pierce, A.E. *Silylation of Organic Compounds*, Pierce Chemical Co., Rockford, Illinois, 1968; Giesselmann, G. *Methodicum Chimicum, Vol. 1*, Georg Thieme Verlag, Stuttgart, 1973, p. 254ff.
144) Colvin, E.W. *Chem. Soc. Rev.* **1978**, *7*, 15.
145) Eaborn, C. *Chem. Commun.* **1972**, 1255.
146) Kwart, H.; Kling, K.G. "d-Orbitals in the Chemistry of Silicon, Phosphorus, and Sulfur"; Springer-Verlag: Berlin, Heidelberg, New York, 1977.
147) Stang, P.J.; Fisk, T.E. *Synthesis* **1979**, 438.
148) Hergott, H.H.; Simchen, G. *Justus Liebigs Ann. Chem.* **1980**, 1781.
149) Schmeisser, M.; Sartori, P.; Kippsmeir, B. *Chem. Ber.* **1970**, *103*, 868.
150) Roesky, H.W.; Giere, H.H. *Z. Naturforsch.* **1970**, *25*, 773.
151) Marsmann, H.C.; Horn, H.G. *ibid.* **1972**, *27*, 1448.
152) Häbich, D.; Effenberger, F. *Synthesis* **1978**, 755.
153) Emde, H.; Götz, A.; Hofmann, K.; Simchen, G. *Justus Liebigs Ann. Chem.* **1981**, 1643.
154) Simchen, G.; Kober, W. *Synthesis* **1976**, 259.
155) Kraus, W.; Patzelt, H.; Sawitzki, G. *Tetrahedron Lett.* **1978**, 445.
156) Reetz, M.T.; Neumeier, G. *Chem. Ber.* **1979**, *112*, 2209.
157) Gerber, U.; Widmer, U.; Schmidt, R.; Schmidt, H. *Helv. Chim. Acta* **1978**, *61*, 83.
158) Ibuka, T.; Mori, Y.; Inubishi, Y. *Tetrahedron Lett.* **1976**, 3169.
159) Ibuka, T.; Mori, Y.; Aoyama, T.; Inubishi, Y. *Chem. Pharm. Bull.* **1976**, *26*, 456.
160) Torkelson, S.; Ainsworth, C. *Synthesis* **1977**, 431.
161) Ibuka, T.; Ito, Y.; Mori, Y.; Aoyama, T.; Inubishi, Y. *Synth. Commun.* **1977**, *7*, 131.
162) Ibuka, T.; Hayashi, K.; Minikata, H.; Inubishi, Y. *Tetrahedron Lett.* **1979**, 159.
163) Schmidt, U.; Schwochau, M. *Monatsh. Chem.* **1967**, *98*, 1492; *Chem. Abstr.* **1968**, *68*, 2559s.
164) Rühlmann, K.; Seefluth, H.; Kiriakidis, T.; Michael, G. *J. Organometal. Chem.* **1971**, *27*, 327.
165) Emde, H.; Simchen, G. *Synthesis* **1977**, 867.
166) Emde, H. *Dissertation*, Stuttgart, 1979.
167) Wissner, A. *J. Org. Chem.* **1979**, *44*, 4617.
168) Hofmann, K. *Dissertation*, Stuttgart, 1979.
169) Steppan, W. *Zulassungsarbeit*, Stuttgart, 1980.
170) Oesterle, Th. *Diplomarbeit*, Stuttgart, 1981.
171) West, W. *Zulassungsarbeit*, Stuttgart, 1976.
172) Frick, U. *Diplomarbeit*, Stuttgart, 1979.
173) Domsch, D. *Diplomarbeit*, Stuttgart, 1978.
174) Albrecht, H.; Düber, E.O. *Synthesis* **1980**, 630.
175) Emde, H.; Simchen, G. *ibid.* **1977**, 636.
176) Colvin, E.W.; Robertson, A.D.; Seebach, D.; Beck, A.K. *Chem. Commun.* **1981**, 952.
177) Olah, G.A.; Balaram Gupta, B.G. *Synthesis* **1980**, 44.
178) Feger, H.; Simchen, G. *ibid.* **1981**, 378.
179) Simchen, G. Unpublished results.
180) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.
181) Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 421.
182) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234
183) Vorbrüggen, H.; Höfle, G. *ibid.* **1981**, *114*, 1234.
184) Long Su, T.; Bennua, B.; Vorbrüggen, H.; Lindner, H.J. *ibid.* **1981**, *114*, 1269.
185) Azuma, T.; Isono, K. *Chem. Pharm. Bull.* **1977**, *25*, 3347.
186) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, 4679.
187) *Idem ibid.* **1980**, 71.
188) Alder, R.W. *Chem. Ind. (London)* **1973**, 983.

189) Arnap, J.; Kenne, L.; Lindberg, B.; Lönngren, J. *Carbohydr. Res.* **1975**, *44*, C5.
190) Berry, J.M.; Hall, L.D. *ibid.* **1976**, *47*, 307.
191) Arnap, J.; Lönngren, J. *Acta Chem. Scand. B* **1978**, *32*, 465.
192) Salomon, M.F.; Salomon, R.G.; Gleim, R.D. *J. Org. Chem.* **1976**, *41*, 3983.
193) Borch, R.F. *Chem. Commun.* **1968**, 442.
194) Ferguson, A.N. *Tetrahedron Lett.* **1973**, 2889.
195) Hall, Jr., H.K.; Ykman, P. *Chem. Commun.* **1974**, 587.
196) Minato, H.; Okuma, K.; Kobayashi, M. *J. Org. Chem.* **1978**, *43*, 652.
197) Booth, B.L.; Jibodu, K.O.; Proenca, M.F. *Chem. Commun.* **1980**, 1151.
198) Peterson, P.E.; Boron, W.F. *J. Am. Chem. Soc.* **1971**, *93*, 4076.
199) Hummel, K.; Hanack, M. *Justus Liebigs Ann. Chem.* **1971**, *746*, 211.
200) Wiering, P.G.; Steinberg, H.; Boer, T.J. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 119.
201) Groves, J.T.; Ma, K.W. *J. Am. Chem. Soc.* **1977**, *99*, 4016.
202) Cristol, S.J.; Mayo, G.O.; Kochansky, J.P. *J. Org. Chem.* **1977**, *42*, 1131.
203) Hanack, M.; Collins, C.J.; Stutz, H.; Benjamin, B.N. *J. Am. Chem. Soc.* **1981**, *103*, 2356.
204) Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. "Vinyl Cations"; Academic Press: New York, 1979.
205) Stang, P.J.; Mangum, M.G.; Fox, D.P.; Haak, P. *J. Am. Chem. Soc.* **1974**, *96*, 4562.
206) Stang, P.J. *Accts. Chem. Res.* **1982**, *15*, 348.
207) Stang, P.J.; Anderson, G.H. *J. Org. Chem.* **1981**, *46*, 4585.
208) Stang, P.J.; Fisk, T.E. *J. Am. Chem. Soc.* **1980**, *102*, 6813.
209) Stang, P.J.; Ladika, M. *ibid.* **1981**, *103*, 6437.
210) Streitwieser, Jr., A.; Daffron, A. *Tetrahedron Lett.* **1976**, 1435.
211) Atkinson, J.G.; Wasson, B.K.; Fuentes, J.J.; Girard, Y.; Rooney, C.S. *ibid.* **1979**, 2857.
212) Williams, H.W.R.; Rooney, C.S. *J. Org. Chem.* **1979**, *44*, 4060.
213) Evers, J.T.M. *Dissertation*, Utrecht, 1979, and references cited therein. This reference constitutes a review of the chemistry of 5e up to early 1979.
214) Evers, J.T.M.; Mackor, A. *Tetrahedron Lett.* **1980**, 415.
215) Salomon, R.G.; Coughlin, D.J.; Easler, E.M. *J. Am. Chem. Soc.* **1979**, *101*, 3961.
216) Wilcox, R.D.; Pagni, R.M.; Hasseneen, H.M.; Kabalka, G.W. *J. Org. Chem.* **1981**, *46*, 1931.
217) Petiniot, N.; Noels, A.F.; Anciaux, A.J.; Hubert, A.J.; Teyssie, P. *Fundam. Res. Homogeneous Catal.* **1979**, *3*, 421.
218) Michl, J.; Wallraff, G. Unpublished results.
219) Lewandos, G.S.; Gregston, D.K.; Nelson, F.R. *J. Organometal. Chem.* **1976**, *118*, 363.
220) Pierre, J.L.; Baret, P.; Chautemps, P.; Armond, M. *J. Am. Chem. Soc.* **1981**, *103*, 2986.
221) Kobayashi, Y.; Yoshida, T.; Kumadaki, I. *Tetrahedron Lett.* **1979**, 3865.
222) Kobayashi, T.; Iwano, Y.; Hirai, K. *Chem. Pharm. Bull.* **1978**, *26*, 1761.
223) Kobayashi, Y.; Kumadaki, I.; Yoshida, T. *J. Chem. Res., Synop.* **1977**, 215.
224) Van Koten, G.; Jastrzebski, J.T.B.H.; Noltes, J.G. *Inorg. Chem.* **1977**, *16*, 1782.
225) Komiya, S.; Huffman, J.C.; Kochi, J.K. *ibid.* **1977**, *16*, 2138.
226) Anderson, G.K.; Cross, R.J. *J. Chem. Soc., Dalton Trans.* **1979**, 690.
227) Itoh, K.; Oshima, N.; Jameson, G.B.; Lewis, H.C.; Ibers, J.A. *J. Am. Chem. Soc.* **1981**, *103*, 3014.
228) Koto, S.; Sato, T.; Morishima, N.; Zen, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1761.
229) Takeo, K. *Carbohydr. Res.* **1980**, *87*, 147.
230) Norberg, T. *Chem. Commun., Univ. Stockholm 1979, 1; Chem. Abstr.* **1980**, *93*, 150502z.
231) Woodhouse, M.E.; Lewis, F.D.; Marks, T.J. *J. Am. Chem. Soc.* **1978**, *100*, 996.
232) Dreyfus, P.; Kennedy, J.P. U.S. Patent 4 136 136, 1979; *Chem. Abstr.* **1979**, *90*, 138582f.

About the Authors

Professor Peter J. Stang was born in Germany (Nurnberg, 1941), raised in Hungary (until 1956), and educated in the USA. He received a B.S. degree from DePaul University in Chicago in 1963 and the Ph.D. degree (under A. Streitwieser, Jr.) from the University of California at Berkeley in 1966. After two years of postdoctoral work with P. von R. Schleyer at Princeton, he was appointed assistant professor of chemistry at Utah in 1969 and promoted to associate professor and professor in 1975 and 1979, respectively.

Dr. Stang's major research interests are in mechanistic organic chemistry with emphasis on unsaturated reactive intermediates. Early work involved new methods of generation and the chemistry of vinyl cations and resulted in a co-authored monograph on the subject (with Z. Rappoport, M. Hanack and L.R. Subramanian) published by Academic Press in 1979. Since the mid-70's he has been involved in the generation, nature, and chemistry of unsaturated carbenes; $R_2C=C_n=C$: (n = 0,2,4). Most recently he has become interested and active in organometallic chemistry (transition-metal complexes of cumulenes) and medicinal chemistry, specifically novel, irreversible, antitumor alkylating agents. Most of this work involved triflic acid or one of its derivatives in one form or another.

Professor Stang is a member of the American Chemical Society, the Chemical Society (London) and the AAAS. In 1977 he received the Alexander von Humboldt "Senior US Scientists" Award, and he is presently an Associate Editor of the Journal of the American Chemical Society and an Editorial Advisor for Academic Press.

Mitchell R. White is currently a graduate student at the University of Utah under the direction of Dr. Stang, about to receive the Ph.D. He received the B.S. degree in Mathematics and Chemistry from Texas Lutheran College in 1976, and then studied the theory of Rydberg spectra for a short period at the University of Texas in San Antonio under Dr. Petr Hochmann. He moved to Utah in 1978.

White has won several scholarships and awards, including a Robert A. Welch Fellowship and a departmental Research Fellowship. His current work is in the chemistry of metallated cumulenes and complexes of novel unsaturated species.

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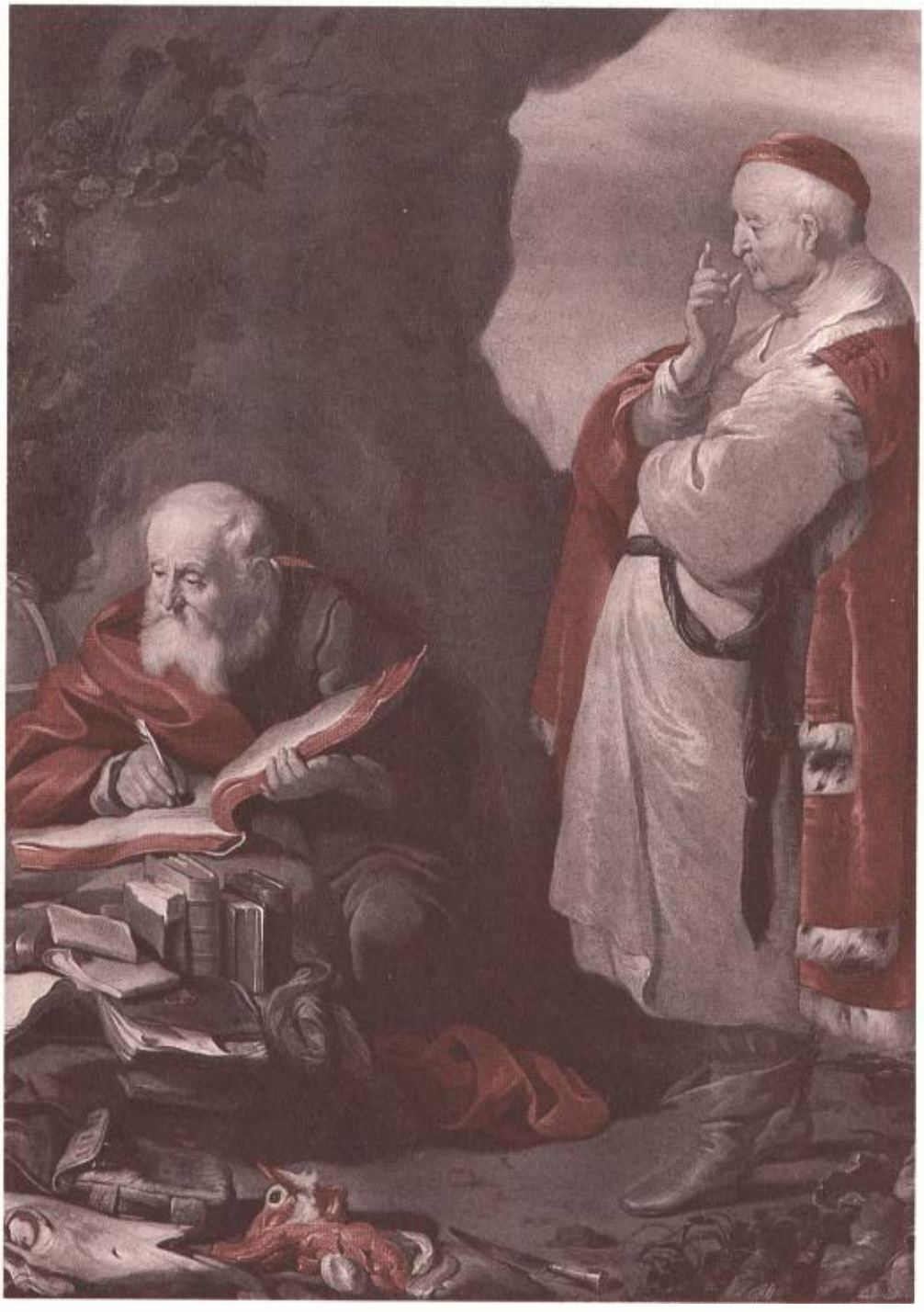

Enzymes as Catalysts in Organic Synthesis

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Enzymes as Catalysts in Organic Synthesis

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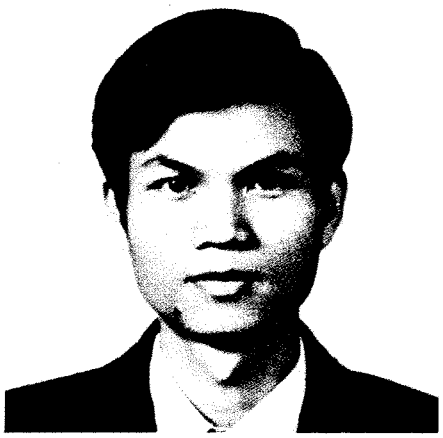


Enzymes are proteins having catalytic activity. They are involved in virtually every transformation which occurs *in vivo*, and thus catalyze large numbers of transformations of biologically important molecules. They also catalyze reactions of many substances which do not occur *in vivo*. Given this wide range of catalytic activity, one might expect enzymes to be widely used in organic synthesis *in vitro*. In fact, their use has been small compared with other classes of catalysts (acids and bases, metals, organometallic compounds).

Why are enzymes *not* more widely used as catalysts in organic synthesis? A number of factors contribute to a long-standing preference of organic chemists for non-enzymatic catalysis:

First, tradition, coupled with a certain lack of motivation. Organic synthesis, in recent years, has focused on terpenes, steroids, alkaloids, prostanoids, and other classes of water-insoluble substances. Its principal concerns have been the formation of carbon-carbon bonds and the regioselective functionalization of hydrocarbon skeletons. Enzymes which form carbon-carbon bonds are, in fact, neither the easiest to obtain nor the most straightforward to use. For the reactions involved in synthesis of complex carbon skeletons, conventional chemical methods are generally more efficient than biological methods.

Second, perceived technical difficulties. Organic chemists believe that enzymes are expensive and delicate. In fact some are and some are not, and even those which *are* expensive and delicate may still be very effective and inexpensive *as catalysts* by virtue of their high catalytic rate constants or their ability to simplify complex synthetic schemes. Many of the problems of instability and cost can be ameliorated by appropriate experimental technique.

Third, specificity. One of the strengths of conventional organic synthesis is that it produces methods which often have wide generality. Organic chemists suspect enzymes of being highly specific in their action. Again, some are and some are not. High specificity may be a disadvantage if one is trying to produce general synthetic methods; it can be a great advantage if one is interested in that particular transformation which the enzyme catalyzes.

Fourth, unfamiliarity. The techniques for isolating, manipulating, and assaying enzymes are unfamiliar to most organic chemists.[1,2] Many enzymes useful in synthesis are, of course, now commercially available, and others of use in new applications could be made available commercially if demand for them existed. The techniques for manipulating enzymes are, in general, relatively straightforward experimentally. Enzymatic *assays* represent a point of considerable and lingering dissatisfaction to many people trained in the relatively precise and easily understood analytical methods of organic chemistry. Enzyme assays seem intrinsically sloppy and ill-defined, relative to methods based on GLC or HPLC. It is nonetheless possible, by an excercise of will, to overcome one's sense of distrust and unease in using these methods, and to obtain reproducible and reliable results.

Enzymatic catalysis is, of course, no panacea. While enzymes have deficiencies as catalysts relative to metallic platinum, for example, the reverse is also true. The real strength of catalysis by enzymes lies in its selectivity. The real strength of catalysis by platinum lies in its generality. Which type of catalyst is best suited for a particular application? The answer depends upon the application. As chemistry turns more to the synthesis of complex substances which are derived from biology or related to biologically important materials (or, more accurately, as chemistry is *forced* to turn to these classes of materials by advances in other areas of science and by exhaustion of current problems in conventional chemistry), a number of new methods — enzymology, recombinant DNA technology, fermentation, tissue culture — will become an increasingly important part of the synthetic chemist's armamentarium.[3] Enzymology is the most fundamental of these biological techniques (the others simply represent methods of using enzymatic catalysts in preformed, packaged, cellular systems) and is certainly the most "chemical" of these techniques.

Nomenclature. One significant obstacle (not mentioned above) to the use of enzymes by organic chemists has been nomenclature. Certain enzymes are named accord-

ing to tradition ("old yellow enzyme") or according to their source (papain from papaya). These names give no hint of their catalytic activity, and make browsing for useful activities difficult for synthetic chemists not trained in biological chemistry. The systematic IUB (International Union of Biochemistry) nomenclature divides enzymes into six groups, and assigns a name and number to each based on its assumed function *in vivo* (Table 1). The numbers in this system are of archival use only. The names are often misleading: occasionally they do not correspond even to the principal function of the enzyme *in vivo*, and frequently do not indicate usefully the type of catalytic activity nor the specificity of the enzyme. For example, the enzyme glycerol kinase (EC 2.7.1.30) catalyzes the phosphorylation of glycerol to *sn*-glycerol-3-phosphate. The name of the enzyme does not imply that the phosphorylation is enantiospecific. More importantly, it does not indicate that this enzyme phosphorylates several other useful substrates (for example, it smoothly converts dihydroxyacetone to dihydroxyacetone phosphate — a substrate of great utility in aldol reactions catalyzed by aldolase). Unfortunately, from the vantage of a synthetic chemist searching for useful catalytic activity, there is presently no solution to the problem of recognizing the synthetically important features of the catalytic activity of a particular enzyme aside from simply knowing the appropriate literature (and often, even here, experimental research is required because the substrates of interest to biologists are not always those of interest to organic chemists).

We caution organic chemists that a uniform system of units for expressing catalytic activity is not used throughout biochemistry and enzymology. The standard unit of enzymatic activity is the International Unit (1 I.U. = 1 μmole of substrate transformed or product formed per min), but units such as nmol/min or hour and those based on optical absorbance are also common. Another system of units based on the katal (1 kat ≡ 1 mol s^{-1} substrate transformed or product formed) has also been recommended, but has not been widely used. In searching the literature for characteristics of a new enzyme, it is essential to check explicitly the units in which catalytic activity is expressed. For reference, approximately 700 I.U. of enzymatic activity will catalyze the formation of one mole of product per day.

Rather than follow the IUB system of enzyme nomenclature, we have found it more useful to divide enzymes into five groups,

Table 1. International classification of enzymes (class names, code numbers, and types of reactions catalyzed) (partial listing)

1. Oxido-reductases (oxidation-reduction reactions)
   - 1.1 Acting on >CH—OH
   - 1.2 Acting on >C=O
   - 1.3 Acting on >C=CH—
   - 1.4 Acting on >CH—NH_2
   - 1.5 Acting on >CH—NH—
   - 1.6 Acting on NADH; NADPH
2. Transferases (transfer of functional groups)
   - 2.1 One-carbon groups
   - 2.2 Aldehydic or ketonic groups
   - 2.3 Acyl groups
   - 2.4 Glycosyl groups
   - 2.7 Phosphate groups
   - 2.8 S-containing groups
3. Hydrolases (hydrolysis reactions)
   - 3.1 Esters
   - 3.2 Glycosidic bonds
   - 3.4 Peptide bonds
   - 3.5 Other C—N bonds
   - 3.6 Acid anhydrides
4. Lyases (addition to double bonds)
   - 4.1 >C=C<
   - 4.2 >C=O
   - 4.3 >C=N—
5. Isomerases (isomerization reactions)
   - 5.1 Racemases
6. Ligases (formation of bonds with ATP cleavage)
   - 6.1 C—O
   - 6.2 C—S
   - 6.3 C—N
   - 6.4 C—C

in order of their increasing complexity of use in organic synthesis:

1) *Simple hydrolases and isomerases.*

2) *Enzymes requiring no added cofactors* (especially those using flavins and pyridoxal phosphate as cofactors).

3) *Enzymes requiring cofactor regeneration* [that is, those using ATP or other nucleoside triphosphates and NAD(P)(H)].

4) *Enzymes having particular problems of availability or stability*, or those requiring uncommon cofactors (S-adenosylmethionine or adenosine 3′-phosphate 5′-phosphosulfate).

5) *Complex multi-enzyme systems.*

This review will concentrate on the first three classes of enzymes. Its principal objective is to illustrate the types of synthetic reactions for which enzymes might be considered as catalysts.

GENERAL CONSIDERATIONS

Enzymes have three characteristics as catalysts:

i) they accelerate rates of reactions;

ii) they are often highly selective in their activity;

iii) their catalytic activity may be regulated, that is, strongly influenced by the concentration of reactants, products, cofactors or other species present in solution.

The first and second are the bases for the utility of enzymes as catalysts; the third is most often the cause of problems since it is the basis for product inhibition, that is, the (not infrequent) decrease in catalytic activity of the enzyme as relatively low concentrations of products accumulate.

Enzymes are normally most soluble and stable in water or in water containing relatively small quantities of polar co-solvents (especially polyhydric alcohols, dimethyl sulfoxide, and related species). They normally function best with substrates which are soluble in these media, although it is often possible to carry out reactions using substrates which are only partially soluble in water. Two-phase systems comprising water and an insoluble organic phase as well as miscible aqueous/organic solvent systems are being explored extensively as media in which to reverse hydrolytic reactions, *i.e.*, dehydrations.[4-6] Presently, these types of reactions are primarily of use in protein chemistry,[7-8] but their applications will probably be extended to other areas.

Enzymes are most often immobilized on insoluble supports.[9,10] There are two reasons for immobilizing enzymes: to make it possible to recover and reuse them at the conclusion of a reaction, and to enhance their stability under the conditions of the reaction. The second is usually the more important. In practice, we almost always use enzymes in immobilized form, because the stability enhancement more than compensates for the activity lost during immo-

bilization. We have developed a method (based on a water-soluble polyacrylamide derivative containing active ester functionalities — polyacrylamide-co-*N*-acryloxysuccinamide, PAN) which has very wide applicability to the relatively delicate enzymes useful in complex organic synthesis (Scheme I).[11] Many other methods are available,[12] but in our experience, procedures based on PAN have shown the widest generality and have given the highest retention of enzymatic activity on immobilization. This procedure is particularly useful in enzyme-catalyzed synthesis of complex organic compounds on scales of 1g to several kilos.

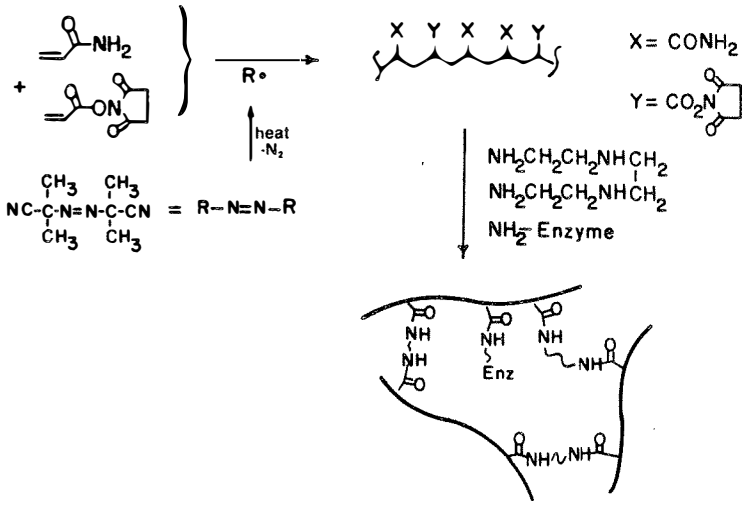
Enzymes used as catalysts in organic synthesis (as opposed to enzymes for mechanistic enzymology studies) need not be particularly pure. The major considerations are that the cost of a unit of activity (in this context "cost" means either the purchase price or the expenditure of effort in a biochemical preparation) and the specific activity — the number of units of activity per milligram of protein — be acceptable. The second parameter is of practical importance in immobilization: an enzyme having a low specific activity may require a very large volume of polymer gel for immobilization, and may therefore be difficult or impractical to handle in immobilized form.

The stability of an enzyme determines its lifetime under operating conditions, and can be quite high. The major factors leading to stability are immobilization, exclusion of dioxygen and other oxidizing agents (when working with enzymes having oxidation-sensitive groups — especially cysteine SH groups[13] — close to the active site), and exclusion of proteases (which might degrade the enzyme) from the reaction medium. The stability of many enzymes is improved by the addition of substrates or products to their solutions so that their active sites are always occupied; this strategy is usually absolutely necessary for obtaining high yields during immobilization.[11]

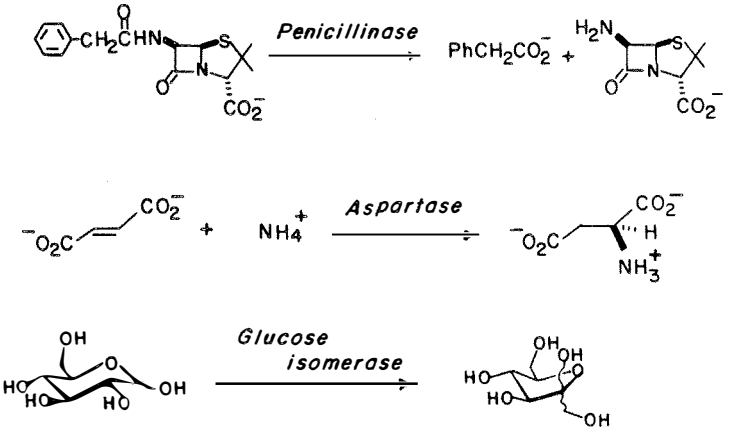
SPECIFIC CHARACTERISTICS

Simple hydrolases and isomerases. The first group of enzymes is that most widely used in industrial enzymology: the production of 6-aminopenicillanic acid[16] and aspartic acid,[17] the isomerization of glucose to fructose,[18] and the various applications of proteases and glycosidases in detergents and food processing all depend upon this type of enzyme (Scheme II).[9,10,12] Most of these processes have been developed for specific large-volume applications, *e.g.*, the interconversion of glucose and fructose is carried out on a scale of more than 10^9 lbs

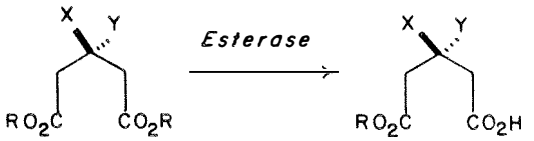
Scheme I



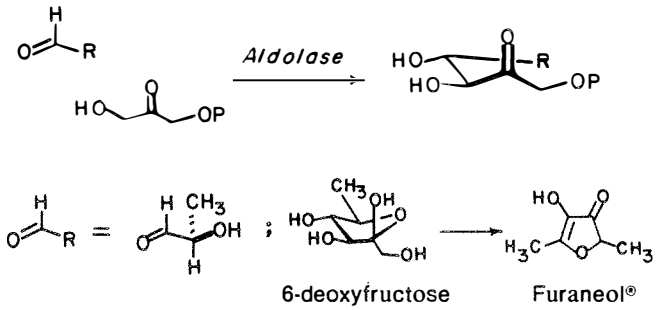
Scheme II



Scheme III



Scheme IV



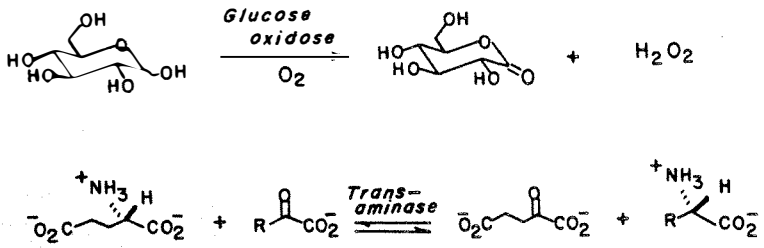
per year in the United States. These industrial processes are interesting in that they establish the practicality of enzymatic processes for large-scale synthesis, but they are not of wide generality. They also establish the fact that these enzymes can be manipulated by chemical engineers.

Applications of these enzymes to research should be more widespread than they are, because, as a class, they are readily available and easily handled. One important example is provided by the asymmetric synthesis based on the hydrolysis of diesters by esterase (Scheme III).[19] A second is the generation of unusual sugars by the regiospecific aldol condensation catalyzed by aldolase (Scheme IV).[20] The preparation of 6-deoxyfructose (used as a starting material for the flavor principle Furaneol®) provides an illustration of the application of this type of reaction.

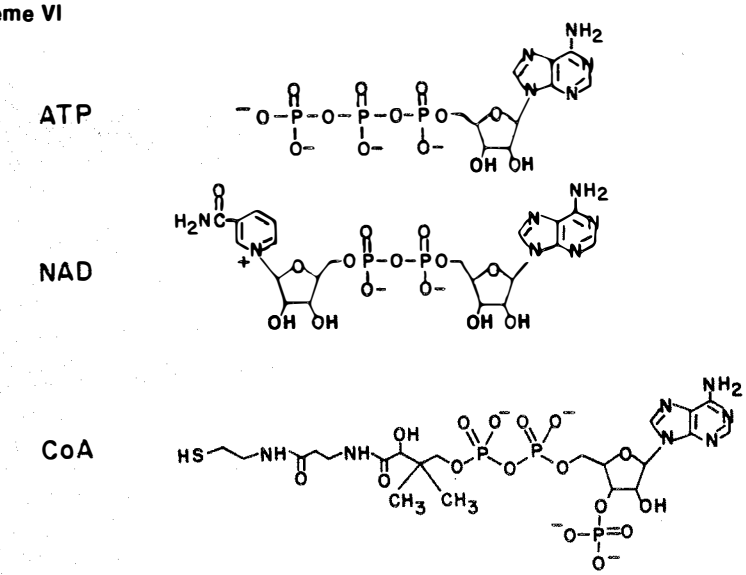
More complex enzymes requiring no added cofactors. The second group involves enzymes which require cofactors which do not themselves require an added regeneration system. Flavins, pyridoxal phosphate, lipoic acid, biotin, metal porphyrin complexes, and related species bind tightly to their respective enzymes, and in general, regenerate automatically during the course of the enzyme-catalyzed reactions. This group includes oxygenases and hydroxylases (flavoenzymes), transaminases (pyridoxal-phosphate-containing enzymes), carboxylases and decarboxylases (lipoic-acid- and biotin-containing enzymes), monooxygenases, peroxidases and mutases (metal-porphyrin-containing enzymes).[21] With the exception of glucose oxidase (primarily to remove dioxygen from foods)[22] and transaminases (occasionally for analysis),[23] this group has had relatively few applications in organic synthesis (Scheme V). Potential uses of these enzymes are amino acid synthesis (transaminases), selective hydroxylation and peroxidation (peroxidases,[24] hydroxylases, prostaglandin cyclooxygenases, lipoxygenase[25]), Baeyer-Villiger oxidation and asymmetric epoxidation (ketone monooxygenases), selective elimination and addition of water (dehydrases), epimerization (epimerases), and carbon-skeleton rearrangement (B_{12}-containing mutases).[21]

Enzymes requiring nucleoside triphosphate or nicotinamide cofactors. The third group of enzymes — those requiring nucleoside triphosphates (especially ATP) or nicotinamide cofactors [NAD(P)(H)] — is probably the group of greatest interest to academic synthetic organic chemists and to others concerned with syntheses of fine chemicals.[26] Most enzymatic synthetic reactions — the transformation of smaller molecules to larger, more complex ones — involve the nucleoside triphosphates; the nicotinamide cofactors are utilized in most enzymatic redox reactions (Scheme VI). It has been estimated that approximately 70% of all enzymes use XTP, NAD(P)(H) or CoA as a cofactor. In general, these are the enzymes which seem to hold the key to the enzyme-catalyzed synthesis of complex substances.

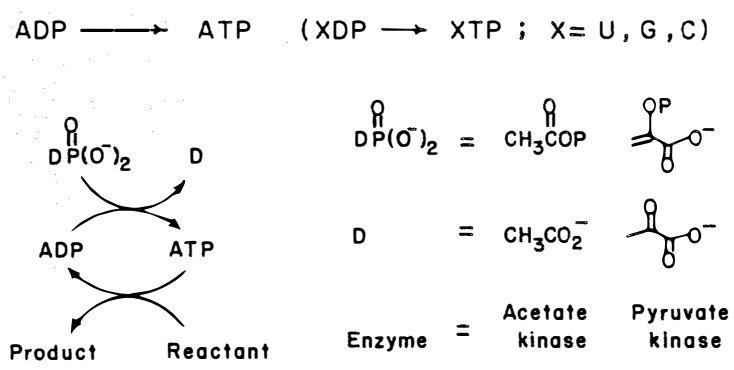
Scheme V



Scheme VI



Scheme VII



The principal barrier to the use of these enzymes has been the cost of the cofactors. These costs range from approximately $1,000/mol for NAD^+ to several hundred thousand dollars/mol for the more expensive cofactors; these prices are sufficiently high that they exclude stoichiometric use of the cofactors. Instead, it has been necessary to develop schemes for the *in situ* regeneration of the cofactors. The problems of cofactor regeneration have been essen-

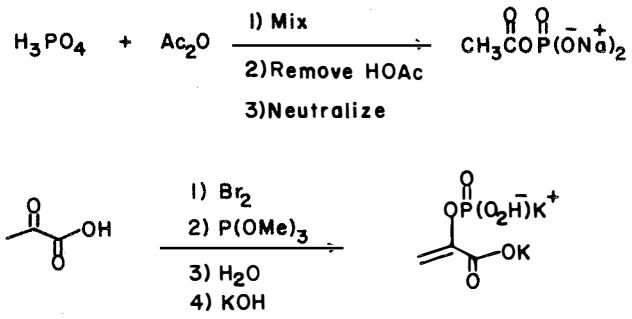
tially solved (at least at the level required for synthesis of fine chemicals) for ATP[27-30] and NAD(P)(H);[31-39] the regeneration of XTP (X = G,C, and U) from XDP[40] is also straightforward. Scheme VII shows the two methods preferred for the *in situ* regeneration of ATP from ADP. Both of these schemes are well known, and have been used on small scales in analytical and mechanistic enzymology for many years. The trick in developing procedures valuable in large-scale synthesis was to find convenient routes to the phosphate donors, acetyl phosphate and phosphoenol pyruvate. Acetyl phosphate can now be made by a very simple procedure involving acylation of phosphoric acid with acetic anhydride, removal of the excess acetic acid by extraction, and neutralization (Scheme VIII).[41] Phosphoenol pyruvate (PEP) requires a slightly more complex synthesis,[29] but can also be made easily on a mole scale. Both of these regeneration procedures have their specific applications. The preparation of acetyl phosphate is experimentally the simpler of the two, and the corresponding regeneration procedure is the more commonly used. PEP is, however, much more stable in solution, and a stronger phosphorylating agent than AcP. It is used when either of these characteristics is a convenience or a requirement.

A number of reactions which consume ATP generate AMP as a product. A simple modification of the scheme illustrated above makes possible the regeneration of ATP from AMP (Scheme IX).[42,43] The same enzymes and cofactors are required, and only one other component is added — the enzyme adenylate kinase, which catalyzes the phosphorylation of AMP to ADP by ATP.

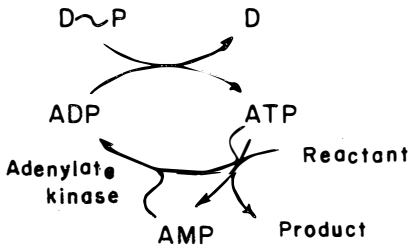
Acetate kinase and pyruvate kinase will accept all of the nucleoside diphosphates as substrates, and catalyze their conversion to nucleoside triphosphates.[2,44] This fact provides the basis for regeneration of all of the nucleoside triphosphates from nucleoside diphosphates. Relatively few reactions generate XMP (X = U, G, C); for these few, at present, no truly practical regeneration scheme exists since adenylate kinase is specific for AMP.

Scheme X provides examples of applications of the ATP regeneration systems. The selective phosphorylation of glucose at C_6 illustrates the selective derivatization of an unprotected carbohydrate;[27] the conversion of glycerol to *sn*-glycerol-3-phosphate is enantiospecific and is the best route presently available to the chiral synthon required for enantiomerically pure phospholipids.[43] Phosphoribosyl pyrophosphate (PRPP) is an important intermediate in nucleoside and nucleotide biosynthesis, and should be valuable in a number of synthetic applications.[45]

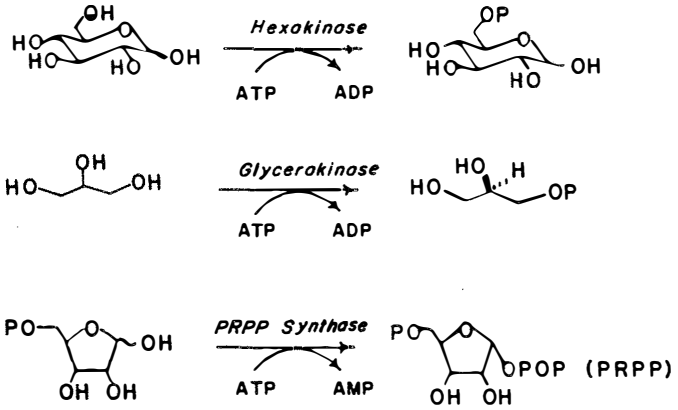
Scheme VIII



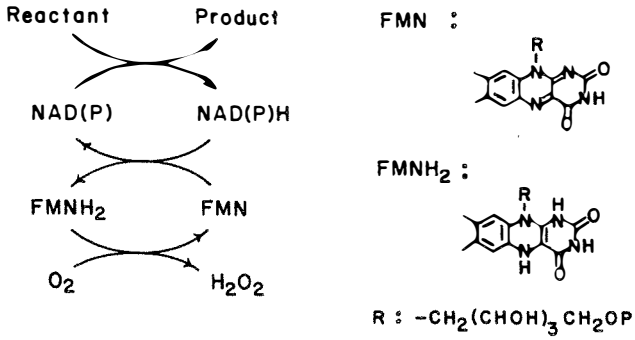
Scheme IX



Scheme X



Scheme XI



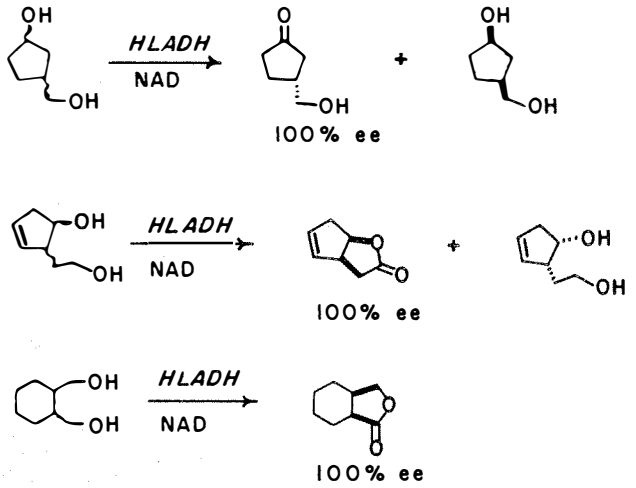
The ATP used in these syntheses is typically cycled *in situ* approximately 100 times; this value is limited only by achievement of a convenient rate in the reaction — the

nucleoside triphosphate cofactors are themselves intrinsically stable in solution. The total turnover numbers obtained for the enzymes (total turnover number = TTN = mol of product/mol of enzyme) is usually in the range of 10^6 to 10^8. The enzymes can usually be recovered in good yield and reused if immobilized.

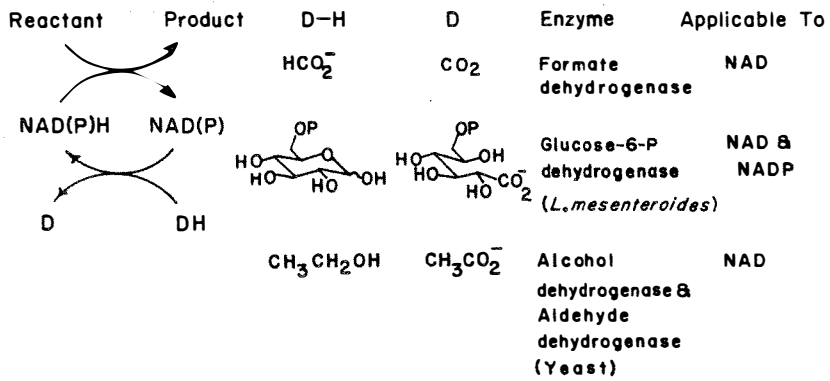
Regeneration of the nicotinamide cofactors presents an intrinsically more complex problem than that for the nucleoside triphosphates, both because many of these materials are more expensive than the nucleoside triphosphates and because their stability in solution is only modest. Nonetheless, satisfactory routes for regeneration of all of these species are now available. For oxidative regeneration from reduced cofactors, the best procedure is that developed by Jones and co-workers, utilizing an intermediate flavin with dioxygen as the ultimate oxidizing agent (Scheme XI).[46] When oxygen cannot be used in the system due to the sensitivity of one of the constituent enzymes, an alternative system based on conversion of α-ketoglutarate to glutamic acid can be used.[28] Scheme XII gives examples of synthetic applications which require regeneration of oxidized nicotinamide cofactors. The most widely explored system is that based on the ability of horse liver alcohol dehydrogenase (HLAD) to oxidize alcohols selectively to ketones or aldehydes.[47-49]

The regeneration of reduced from oxidized nicotinamide cofactors is a more difficult problem, for several technical reasons. A number of routes have been explored to accomplish this regeneration. The most practical for use in organic synthesis involve glucose-6-phosphate,[31] formate,[32] or ethanol[39] as the ultimate reducing agents (Scheme XIII). The advantages of the route based on formate dehydrogenase are that no byproduct is formed in the reaction and workup is very simple. Its disadvantages are that it is applicable only to the reduction of NAD and the enzyme is relatively expensive. The scheme utilizing glucose-6-phosphate dehydrogenase from *L. mesenteroides* is applicable to both NAD and NADP, and the enzyme is readily available, sturdy, and inexpensive. The substrate for the reaction (glucose-6-phosphate) is, however, less readily available than formate or ethanol and the product — 6-phosphogluconate — may complicate the workup in some circumstances. The procedure using ethanol as a starting material has the advantages of a readily available reducing agent and an innocuous product. However, two relatively expensive enzymes are required, and it is applicable only to NAD.

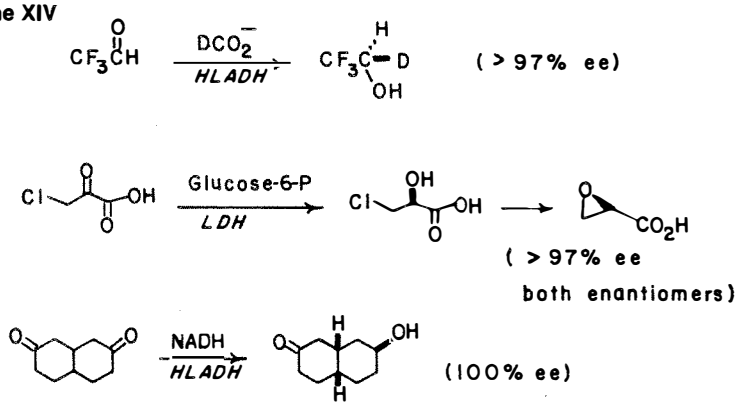
Scheme XII



Scheme XIII



Scheme XIV



In our laboratory, all of these three systems are commonly used. Scheme XIV gives examples of applications of the reducing regeneration systems to typical problems in organic synthesis.[48,50,51]

Multistep syntheses involving cofactors. The examples given so far have been primarily those involving one-step transformations of simple molecules. An important use of synthetic enzymology is the construction of schemes involving multiple, coupled enzymatic steps and which carry out complex syntheses. Scheme XV outlines the conversion of glucose to ribulose-1,5-diphosphate;[28] Scheme XVI illustrates the synthesis of lactosamine.[52] These represent the most complex syntheses which are practical at this time. The synthesis of ribulose-1,5-diphosphate is a particularly interesting example. This substance is important as a substrate in studies of the enzymology of

ribulose diphosphate carboxylase, the critical enzyme in carbon dioxide fixation in plants. The characteristics of the molecule are such that development of a practical synthesis based on conventional chemical transformations seems improbable. The enzymatic route, despite its apparent complexity, has been carried out on a scale yielding several-hundred-gram quantities of ribulose diphosphate. The synthesis of lactosamine, however, represents the first successful step in a program utilizing the Leloir pathway enzymes for carbohydrate synthesis.

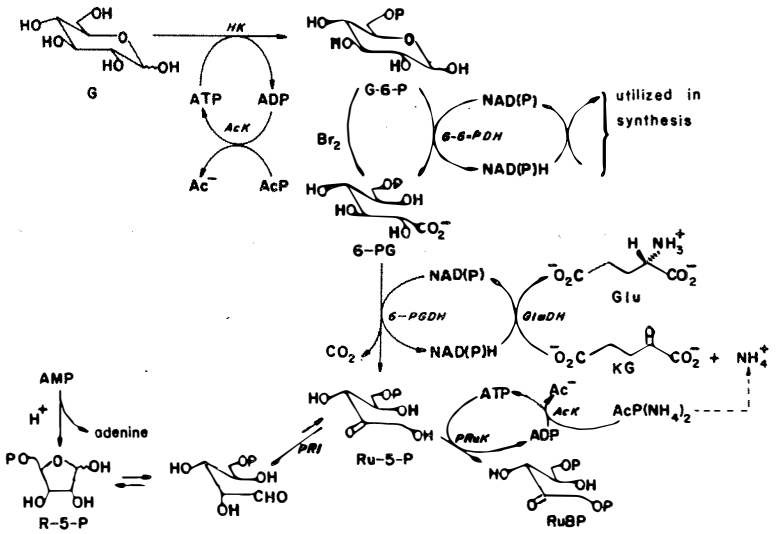
Summary. For what types of reactions should organic chemists consider enzymes as catalysts? The range of applications in the preceding treatise suggests that syntheses involving (or producing) sugars, chiral substances, polysaccharides, amino acids,[53] proteins, nucleic acids, and intermediates in major metabolic pathways are all plausible candidates for enzymatic reactions. Enantioselective or regioselective hydrolyses of esters and amides,[54] and selective oxidation of alcohols to ketones or reduction of ketones to alcohols are also plausible candidates for current enzymology. Reactions for which enzymology is not applicable are those which produce water-insoluble hydrocarbons and related species and those in which the principal technical problem centers on the construction of carbon-carbon bonds.

THE FUTURE: MORE COMPLEX SYNTHESES

A very large number of enzymes are known. The majority of the enzymes which so far have been exploited in synthesis are those which are commercially available and inexpensive. This group of enzymes is now accessible to all synthetic organic chemists at the modest cost of learning the experimental techniques required to assay, manipulate, and immobilize them. An enormously larger number of catalytic activities are available to those willing to carry out simple isolations (often from commercially available cell sources such as yeast, animal and plant tissue, or *E. coli*) and small-scale fermentations. Quantities of enzymes are often now limiting, but it is important to remember that, in principle, virtually any enzyme can be made in quantity using recombinant DNA techniques if the demand for that enzyme justifies the effort.

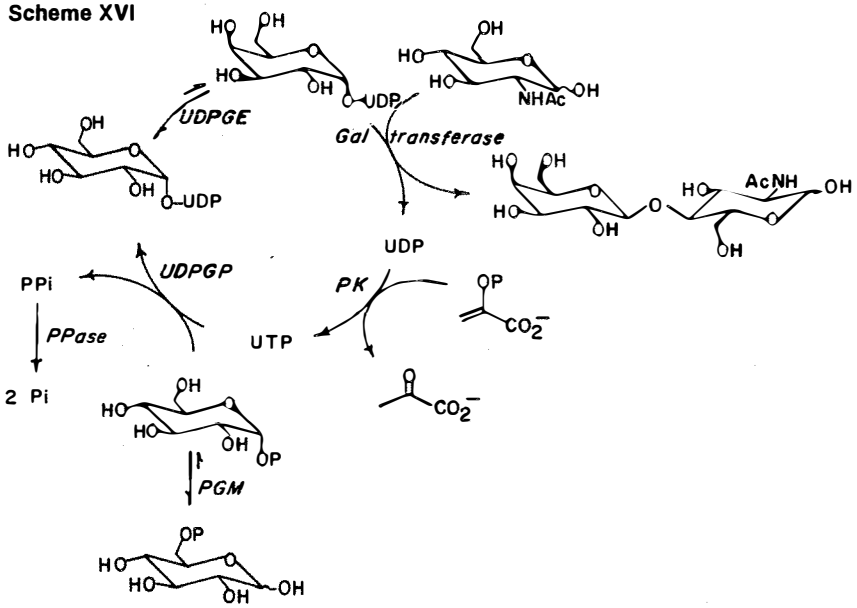
Many of the most exciting areas of biology and pharmacology — immunology, neurobiology, endocrinology, molecular genetics, membrane biology — are becoming more molecular. Plant and insect biology are also being explored actively at the molecular level. An increasing number of applications which will depend upon the availability of biological substrates will arise in these areas. Synthetic enzymology will play an important role in the synthesis of these substances. The compounds to which it is best applied — water-soluble biological molecules or molecules analogous to biological molecules, especially carbohydrates, nucleic acids, lipids, and proteins — are those for which conventional "abiological" chemistry has not (yet) developed satisfactory synthetic methods. Applied enzymology will thus complement conventional chemistry on the one hand, and more biological synthetic techniques (fermentation, recombinant DNA technology, and tissue culture) on the other. This entire group of biologically derived synthetic techniques will represent an important part of organic synthesis in the future, and an essential set of techniques for those who wish to work at the boundary between molecular biology and biochemistry or medicinal chemistry.

Scheme XV



Abbreviations: HK, hexokinase; AcK, acetate kinase; G-6-PDH, glucose-6-phosphate dehydrogenase; 6-PGDH, 6-phosphogluconate dehydrogenase; GluDH, glutamic dehydrogenase; PRuK, phosphoribulokinase; PRI, phosphoriboisomerase.

Scheme XVI



Abbreviations: Gal transferase, galactosyltransferase; PK, pyruvate kinase; PGM, phosphoglucomutase; UDPGP, UDP-glucose pyrophosphorylase; UDPGE, UDP-glucose epimerase; PPase, inorganic pyrophosphatase.

Lectins

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Recent years have witnessed a remarkable increase in the clinical and research applications of a group of biochemical reagents collectively known as lectins. These receptor-specific proteins[1] have been isolated from a wide variety of natural sources: seeds, plant roots and bark, fungi, bacteria, seaweed and sponges, mollusks, fish eggs and from the body fluids or sera of both invertebrates and lower vertebrates. They have also been found in mammalian cell membranes.[2] The precise physiological role of lectins in nature is still unknown: sugar transport or storage, attachment of nitrogen-fixing bacteria to plant root nodules and effectors or modifying agents of cell division (mitosis) are among the many suggestions which have been advanced. Despite this lack of knowledge concerning their role *in vivo*, lectins have proved to be very valuable in a wide variety of applications *in vitro*.[1,3,4]

Lectins, originally termed phytohaemagglutinins, were discovered just before the turn of the century. Stillmark,[5] employed with Kobert in 1888 to investigate an outbreak of cattle food poisoning, found that extracts of the castor oil plant *Ricinus communis* would cause haemagglutination (the specific aggregation of a suspension of red blood cells in isotonic salt solution). It was soon found that ricin, as the extract was called, was not only toxic and haemagglutinating but also antigenic; so it was used together with anti-ricin by Ehrlich in 1891 as a model for bacterial toxins in his fundamental work on antitoxic immunity.[6] Ricin occurs in two forms with different specificities: RCA 120 and RCA 60, with molecular weights of 120,000 and 60,000, respectively.

Following the discovery of ricin, extracts of plants were examined for haemagglutinating activity and a number of interesting lectins were discovered. These included abrin, the toxic lectin from the seeds of *Abrus precatorius*,[7] lentil lectin from *Lens culinaris*,[8] phytohaemagglutinin (PHA) from *Phaseolus vulgaris*,[9] and concanavalin A (now referred to as Con A) which was found in extracts of jack bean meal, *Canavalia ensiformis*. Con A was the first lectin to be purified.[10] Among the first lectins to be isolated from plant tissues rather than from seeds were those from the potato, *Solanum tuberosum*, and tomato, *Lycopersicon esculentum*.[11] However, they appeared to have no important scientific or commercial application. Then in 1948 the first blood-group-specific lectins were discovered.[12,13] Extracts of Lima beans (*Phaseolus limensis*) and of *Vicia cracca* seeds were found specifically to agglutinate the red cells of individuals of blood group A. Red cells from individuals of blood group B or O were not agglutinated. In addition, extracts of *Cytisus sessilifolious*, *Laburnum alpinum* and *Lotus tetragonolobus* (syn. *Tetragonolobus purpureus*) were shown preferentially to agglutinate red cells of blood group O, rather than those of blood group A or B. This discovery resulted in a renewed interest in the reagents, for which the term lectin was coined (from the Latin for "to pick out" or "to choose").[14] In the intervening years many other lectins have been discovered with and without blood-group specificity, and from research into their structure and specificity, the following "definition" of a lectin has emerged.[1,15] Lectins are proteins or glycoproteins of non-immune origin that agglutinate cells and/or precipitate complex carbohydrates. With one possible exception, all lectins so far described are highly specific carbohydrate-binding molecules; this binding activity is usually inhibited by a simple monosaccharide solution, although for some lectins solutions of di-, tri- and even polysaccharides are required. The exception, a glycoprotein isolated from a strain of the bacterium *E. coli*, agglutinates erythrocytes; the agglutination is not inhibited by carbohydrates, but by the amino acid L-histidine.[16] It is thought that this reagent may fall into a completely separate group of receptor-specific proteins.

Although it was originally hoped that lectins might totally replace antisera for blood grouping, the range of blood-group specificities has proved to be limited. However, the blood-group-specific lectins are extremely valuable in automated procedures where large volumes are required. Prime examples are the anti-A-specific lectin[17] from the snail *Helix pomatia*, and the anti-A_1-specific lectin[18] from the seeds of *Dolichos biflorus*. One long-standing problem has been the lack of a suitable anti-B-specific lectin; this deficiency may at last have been overcome[19] with the isolation of the anti-B lectin from the seaweed *Ptilota plumosa*.

Other applications in the biological sciences (see refs. 1, 3, 4), with examples of the relevant lectins in parentheses, include the mitogenic stimulation of lymphocytes resulting in cell division (PHA, Con A and PWM from *Phytolacca americana*), the isolation, purification and structural studies of carbohydrate-containing molecules (Con A, *Lens culinaris*), and the fractionation of cells and other particles (*i.e.*, viruses) (*Helix pomatia*, *Glycine max*, *Arachis hypogaea*, Con A). Lectins also act as probes for studying the structure of cell surfaces (*Helix pomatia*, *Dolichos biflorus*, *Triticum vulgare*, *Arachis hypogaea*). This last area is perhaps the most exciting recent development. To the pathologist, lectins are available as specific tissue markers for easy identification of lectin-binding sites in thin sections of human tissues, both frozen and formalin-fixed/paraffin-embedded, or membranes of isolated cells in suspension. To facilitate such studies lectins are conjugated with readily identifiable markers such as the fluorescent dyes fluorescein isothiocyanate (FITC), dichlorotriazinylaminofluorescein (DTAF) and tetramethylrhodamine isothiocyanate (TRITC), radioopaque substances (radioactive isotopes, ferritin), enzymes (peroxidase, alkaline phosphatase) or biotin. The binding specificity of labelled lectin can be demonstrated by binding inhibition with the addition of the competitive sugar, or by prevention of binding by prior treatment with specific purified glycosidases. Using these techniques, lectins have been found to represent a valuable histochemical tool for studying tissues and cells under normal and pathological conditions. Results so far achieved seem to be particularly relevant in the field of gastrointestinal pathology, malignant lymphomas, skin tumors and breast pathology.

References:

1) Gold, E.R.; Balding, P. "Receptor-specific Proteins: Plant and Animal Lectins"; Excerpta Medica: Amsterdam, 1975.
2) Simpson, D.L.; Thorne, D.R.; Loh, H.H. *Life Sci.* **1978**, *22*, 727.
3) Roth, J. "The Lectins, Molecular Probes in Cell Biology and Membrane Research"; Gustav Fischer Verlag: Jena, 1978.
4) Bøg-Hansen, T.C., Ed. "Lectins: Biology, Biochemistry, Clinical Biochemistry"; W. de Gruyter: Berlin, 1980, 1981, 1982; Vols. I, II, III.
5) Stillmark, H. In "Arbeiten des Pharmakologischen Institutes zu Dorpat"; R. Kobert, Ed.; Enke: Stuttgart, 1889; Vol. 3, p 57.
6) Ehrlich, P. *Deutsch. Med. Wschr.* **1891**, *17*, 976.

7) Kobert, R. *Landwirtsch. Versuchstat* **1913**, *79/80*, 97.
8) Mendel, L.B. *Abstr. Arch. Fisiol.* **1909**, *7*, 162.
9) Münk, G. Thesis, "Beiträge zur Kenntnis der Bestandteile und Wirkungen der Lupinen Samen," University of Rostock, Germany.
10) Sumner, J.B.; Gralen, V.; Erickson-Quensel, I.B. *J. Biol. Chem.* **1938**, *125*, 45.
11) Marcusson-Begun, H. *Z. Immun.- Forsch.* **1925**, *45*, 43.
12) Renkonen, H.D. *Ann. Med. Exp. Fenn.* **1948**, *26*, 66.
13) Boyd, W.C.; Reguera, R.M. *J. Immunol.* **1949**, *62*, 333.
14) Boyd, W.C. In "The Proteins: Chemistry, Biological Activity and Methods"; Murath, H.; Bailey, K., Eds.; Academic Press: New York and London, 1954; Vol. 2, p 788.
15) Goldstein, I.J.; Hughes, R.C.; Monsigny, M.; Osawa, T.; Sharon, N. *Nature* **1980**, *285*, 66.
16) Balding, P. In "Protides of the Biological Fluids"; Peeters, H., Ed.; Pergamon Press: Oxford, 1979; Vol. 27, p 405.
17) Prokop, O.; Schlesinger, D.; Rackwitz. A. *Z. Immun.- Forsch.* **1965**, *129*, 402.
18) Bird, G.W.G. *Curr. Sci.* **1951**, *20*, 298.
19) Rogers, D.J.; Blunden, G.; Evans, P.R. *Med. Lab. Sci.* **1977**, *34*, 193.

Lectins cited in the text are listed below; with a range of conjugates, they are available from Sigma.

L9758 Abrus precatorius (abrin)
L0881 Arachis hypogaea (peanut)
L2380 Bandeiraea simplicifolia
C7275 Canavalia ensiformis (Con A)
L1135 Dolichos biflorus
L8004 Glycine max
L3382 Helix pomatia
L5880 Lens culinaris
L2886 Lycopersicon esculentum (tomato)
L8754 Phaseolus vulgaris (phytohaemagglutinin)
L9379 Phytolacca americana (pokeweed mitogen)
L9260 Ptilota plumosa
L8508 Ricinus communis (Ricin-RCA 60)
L8259 Ricinus communis (Ricin-RCA 120)
L5010 Solanum tuberosum (potato)
L9254 Tetragonolobus purpureus
L1005 Triticum vulgare (WGA)
L6005 Phaseolus limensis (lima bean)
L6760 Laburnum alpinum
R1254 Anti-Ricinus communis lectin (rabbit serum)

5-Thio-D-Glucose: How Do Enzymes Work?

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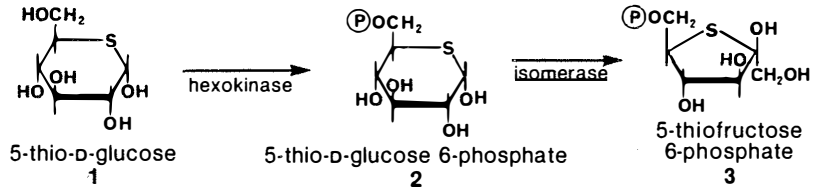
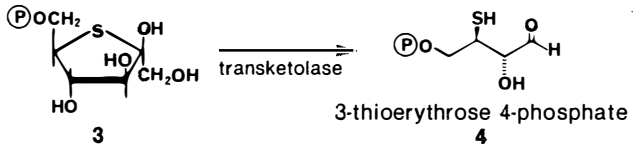
5-Thio-D-glucose (**1**) can be a key to the enzymatic synthesis of a myriad of products, each of which would constitute a unique enzymic mechanistic probe.

Monomeric carbohydrates in aqueous solution can exist as pyranoses, furanoses, acyclic carbonyls, or acyclic hydrates. Generally enzymes will bind only one of the forms available to a substrate although this may not be the form subsequently processed by the enzyme. Since the rate of ring opening for sugars with sulfur substituted for the ring oxygen is particularly slow,[1,2] these molecules can place dramatic limits on enzyme catalysis. In the glycolytic pathway (Scheme I) successful conversion of **1** to 5-thio-D-fructose 6-phosphate (**3**) *via* hexokinase (Sigma) and isomerase (Sigma) would explain the nature of the substrate bound and reactive intermediates exploited by these enzymes.

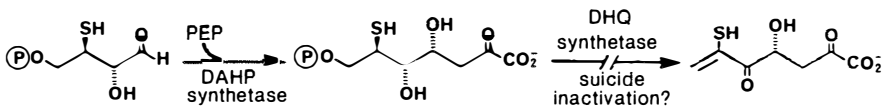
Scheme I - Glycolysis



Scheme II - Pentose Phosphate Shunt



Scheme III - Shikimic Acid Pathway



Conversion (Scheme II) of **3** to 3-thioerythrose 4-phosphate (**4**) with transketolase (Sigma) would provide a key biosynthetic intermediate for the shikimic acid pathway. In microorganisms erythrose 4-phosphate is the starting point for biosynthesis of aromatic amino acids while in plants it is ultimately converted to lignins and tannins. The most important new herbicide on the market is glyphosate (*N*-phosphonomethylglycine). It is known that glyphosate functions on the plant enzymic level as a competitive inhibitor of the binding of erythrose 4-phosphate.[3] Successful conversion of **1** to **4** would pose fascinating questions:

a) Is **4** a competitive inhibitor of erythrose 4-phosphate or is it a substrate for DAHP synthetase (Scheme III)?
b) If 6-thio-DAHP (**5**) is formed would it be a suicide substrate for dehydroquinate (DHQ) synthetase, the next enzyme on the shikimic acid pathway?

As can be seen, 5-thio-D-glucose could be an interesting starting point for glycolysis, the pentose phosphate shunt, and the shikimic acid pathway. Aside from mechanistic conclusions drawn from its action with enzymes, 5-thio-D-glucose may even yield a safe, mechanism-based herbicide.

References:
1) Grimshaw, C.E.; Whistler, R.L.; Cleland, W.W. *J. Am. Chem. Soc.* **1979**, *101*, 1521.
2) Grimshaw, C.E.; Cleland, W.W.; Whistler, R.L. *Carbohydr. Res.* **1980**, *82*, 353.
3) Rubin, J.L.; Gaines, C.G.; Jensen, R.A. *Plant Physiol.* **1982**, *70*, 833.

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About Our Cover:

Our chemist-collector bought the painting on our cover for the best reason we know: the sheer joy of looking at it.

Fig. 1

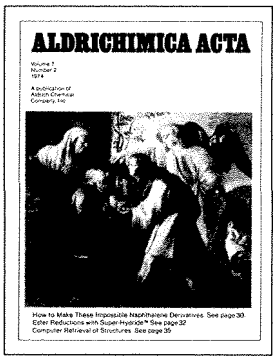


Fig. 2

He had never heard of Guidobono, a little known Italian artist of the 17th century, who painted this moving *Parting of Tobias from his Blind Father*. Baroque artists loved this apocryphal story, perhaps because of their concern with blindness, and this is the third Tobias to appear on an *Acta* cover.

This depiction is very different from our two previous *Acta* covers (Figs. 1 and 2), and a comparison of them shows clearly the differences between Italian, Flemish and Dutch baroque art. The Dutch painting (Fig. 1) by a Rembrandt student, Paulus de Lesire, is of subdued color, and father, mother and son — and even the angel — look like contemporary placid Dutchmen. The father in the Flemish painting by Jan van de Venne (Fig. 2) looks like an Eastern European Jew who found his way to Antwerp into a much more colorful, theatrical setting. The Italian painting, vibrant with vivid blues and reds, concentrates on the blind father's emotion-filled face and gnarled hand as he clutches his son in a last embrace. And how differently the painters saw the son! The Dutch Tobias is an experienced doctor who knows exactly how to treat his father's eyes. The Flemish son is a youth, while the Italian is merely a child about to leave home for the first time. Here are one beginning and two conclusions to the story. Baroque artists painted many different episodes in the story, and our chemist-collector hopes to find others.

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 Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our *Acta* covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

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

Lab Notes

Recently we encountered difficulty during small-scale ester rectification. Several esters, dried over anhydrous $MgSO_4$, foamed vigorously on vacuum rectification, sometimes with foam reaching the top of the column. We tried anti-foaming agents and filling the glass with glass wool but have now found two techniques satisfactory.

a. A blowing-over capillary — a capillary tube from which air or N_2 is blown horizontally above the liquid to destroy the foam. This method is less satisfactory because air or N_2 passing the column affects the rectification.

b. A gas-phase turbine-type stirrer — a stirrer placed directly above the liquid phase, thereby immediately destroying the foam produced. This method is preferred because the distillation is not affected at all. We had no difficulty maintaining the vacuum, using an all-glass stirrer with KPG collar, even without special devices like a nitrogen inlet. The esters probably do not dissolve the collar grease, which sometimes happens with other organic solvents.

J. Housmans
Central Laboratory DSM
Department POCP
P.O. Box 18
6160 MD Geleen, Netherlands

We had occasion to use 200-ml amounts of anhydrous liquid HF in an organic preparation. The reaction was carried out in a plastic bottle in a well ventilated hood. At the conclusion of the reaction and before work-up, the excess HF was slowly blown off under a stream of nitrogen. This caused etching and translucency of the safety glass panels of the hood door, side panel and the light fixtures. These had to be replaced at a significant cost and lost operation time in the hood. Thereafter, all inside glass panels were covered with a 4-mil polyethylene plastic sheet cut to size and fastened to the metal frames with a cloth adhesive tape. After a number of reruns of this preparation, the glass panels have remained transparent.

O.P. Goel, Ph.D.
Warner-Lambert Company
Pharmaceutical Research Division
Ann Arbor, MI 48105

In our laboratory, we have found that an efficient, low-dead-volume flow restrictor for HPLC fraction collection can be quickly fabricated from a discarded section of a fused silica capillary GC column. Simply swage several feet of column to the detector outlet using a graphite-vespel ferrule and a zero-dead-volume double female connector. This has proven absolutely trouble-free in hundreds of LC runs. It completely prevents bubble formation in the detector cell and preserves excellent resolution in the collected fractions, with minimum holdup.

Michael Alexander
Department of Pharmacology
The Ohio State University
Columbus, Ohio 43210

I wish to point out a method of cleaning nonpolar materials from glassware. Organic chemists tend to use relatively polar solvents such as acetone or alcohol for removing tars and residues from flasks. Although such solvents are quite effective for moderately polar materials, hydrocarbons and chlorinated solvents are more effective with nonpolar materials such as silicone oil. With crude oil (petroleum), acetone is indeed not the solvent of choice, so I tried one of the degreasers sold for cleaning automobile engines, machinery, garage floors, etc. The material, essentially a solution of a dispersing agent in a kerosene-type solvent, works quite well. After the organic material has dissolved (with warming if necessary), the solution can be disposed of with waste solvents. Water disperses most of the degreaser and dissolved material and washing with soap and water removes most of the rest. An advantage over the usual solvent-cleaning approach is that, unless the amount of residue in the glassware is considerable, one portion of degreaser can remove the material. At least one brand of degreaser is sold as a concentrated solution to be diluted with kerosene; presumably a somewhat more polar diluent, or one with a different boiling point, could be used.

Joseph H. Ross
Associate Professor of Chemistry
Indiana University at South Bend
South Bend, IN 46634

We have used the AtmosBag™ to sample water-sensitive and toxic reagents in the warehouse.

The AtmosBag is placed over the 55-gal. drum of raw material and a positive nitrogen pressure is created by passing nitrogen through one of the inlets. The drum is opened, the cover placed to one side and the sample withdrawn. When sampling is completed the drum is covered and the bag withdrawn.

We have thus sampled thionyl chloride and sodium methoxide, both of which are toxic and moisture-sensitive.

We have also sampled smaller drums, but in this case the bag is placed over the whole drum.

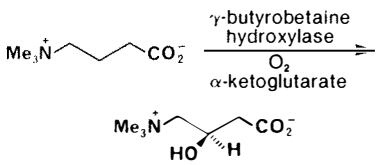
Luis N. Guedes
Q.A. Manager
Janssen Inc.
Gurabo, Puerto Rico 00658

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

"Please Bother Us."

by Alfred Bader.

γ-Butyrobetaine hydroxylase catalyzes the final reaction in the biosynthesis of *R*-carnitine.[1] This interesting enzyme is overproduced by *Pseudomonas sp. AKI* grown with γ-butyrobetaine as its sole source of carbon. Dr. Robert Pascal of Princeton University needed an inexpensive source of γ-butyrobetaine for the large-scale preparation of this hydroxylase for mechanistic studies.



Naturally, we made it.

1) Lindstedt, G.; Lindstedt, S.; Nordin, I. *Biochemistry* **1977**, *16*, 2181.

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

The Chemical Synthesis of DNA

Geoffrey C. Crockett
Aldrich Chemical Company, Inc.

1. Introduction

The chemical synthesis of oligodeoxyribonucleotides (DNA) has been under investigation for many years, as evidenced by various reviews.[1-11] However, it is only in the last few years that significant advances have been made in synthetic techniques which afford improved yields of relatively easily purified products within a reasonable period of time. Many of these advances have been spurred by the current intense interest in recombinant DNA research, in both the academic and industrial fields.

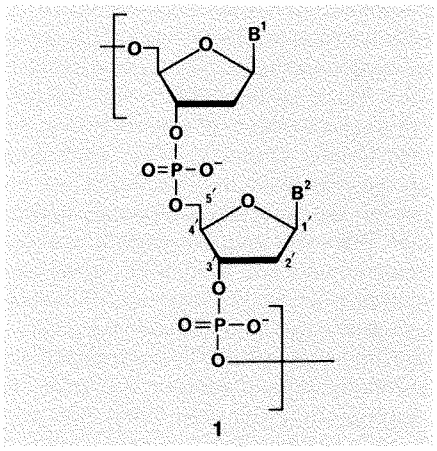
Despite the importance of oligonucleotide synthesis to recombinant DNA work, the field is well known only to people working in the area. It is viewed as one dominated by biochemists, microbiologists, and geneticists when, in fact, much of the work is done by synthetic organic chemists. Recent publications by Büchi[12] and Rapoport[13] indicate that oligodeoxynucleotide synthesis is attracting natural-product chemists as well.

The total synthesis of an oligonucleotide poses a bewildering array of problems and it is the methodology developed to solve these problems that makes this field interesting. In large part, synthesis is similar to that of many other natural products — selective protection and deprotection of functional groups. It is not the intent of this article to review the extensive literature devoted to the development and use of the various protecting strategies as that is covered amply by review articles.[1-11] Rather, this review will describe the approaches to DNA synthesis which are most widely used.

Why synthesize such a molecule? Such a synthesis may be motivated by the same driving force as for many natural-product syntheses — the challenge. In addition, synthetic oligodeoxynucleotides have important uses in the study of DNA. Aside from the obvious — the chemical synthesis of a gene ("...conceptually simple, but chemically sophisticated..."[14]) — these macromolecules are used in studies of DNA structure and function, gene regulation, and for providing "short" sequences for recombination of DNA fragments from natural sources. These topics are beyond the scope of this review; the reader is referred to the excellent summary by Wu, Bahl, and Narang[15] and the informative and entertaining monograph cited in reference 14.

2. The Structure of DNA

Single-stranded DNA is a polymeric molecule comprised of a backbone of a sugar (deoxyribose)-phosphate oligomer to which is appended, at each sugar residue, a heterocyclic base (B^x in **1**). The four most



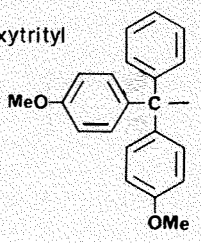
1

Common Symbols and Abbreviations

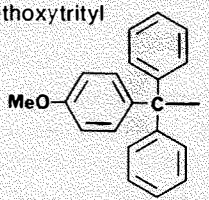
Nucleosides
dA: 2′-deoxyadenosine
dC: 2′-deoxycytidine
dG: 2′-deoxyguanosine
T: thymidine (sometimes seen as dT)

Nucleotides
dpA: 2′-deoxyadenosine-5′-O-phosphate
dpC: 2′-deoxycytidine-5′-O-phosphate
dpG: 2′-deoxyguanosine-5′-O-phosphate
pT: thymidine-5′-O-phosphate

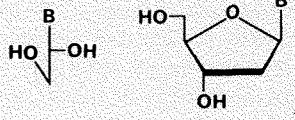
DMT: dimethoxytrityl



MMT: monomethoxytrityl



Bz: benzoyl
An: anisoyl
iBu: isobutyryl
Ac: acetyl
B = general nucleoside base
B′ = general N-protected nucleoside base

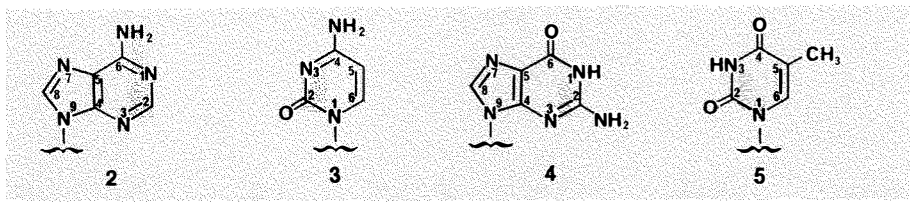


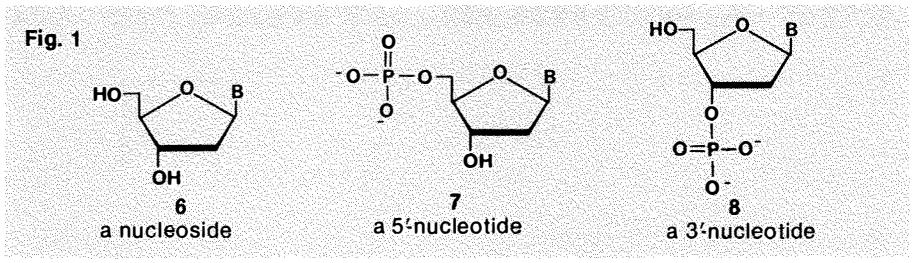
common bases B^x are adenine (A, **2**), cytosine (C, **3**), guanine (G, **4**) and thymine (T, **5**). The combination of sugar and base is called a nucleoside, while the nucleic acid monomer, *i.e.*, the combination of the sugar, base, and phosphate residues, is termed a nucleotide (Fig. 1).

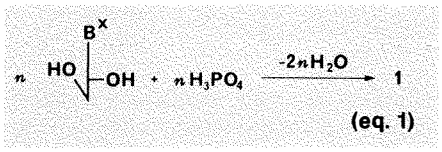
The four common 2′-deoxynucleosides are 2′-deoxyadenosine (dA; **6**, B = A); 2′-deoxycytidine (dC; **6**, B = C); 2′-deoxyguanosine (dG; **6**, B = G); and thymidine (T; **6**, B = T). A common abbreviated structure of a deoxynucleoside is shown in Fig. 2 and will be used in this article.

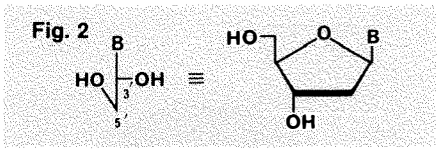
A simplistic assembly of a synthetic DNA from readily available starting nucleosides, is shown in eq. 1. Such a reaction is impractical — there are too many sites in the molecule (**6**) which can react with phosphoric acid. Also, the molecule is sensitive and therefore harsh reaction conditions must be avoided. Deoxyguanosine dramatically illustrates the extent of these problems (Fig. 3). The sites of possible side reactions in the other nucleoside bases are readily identifiable.

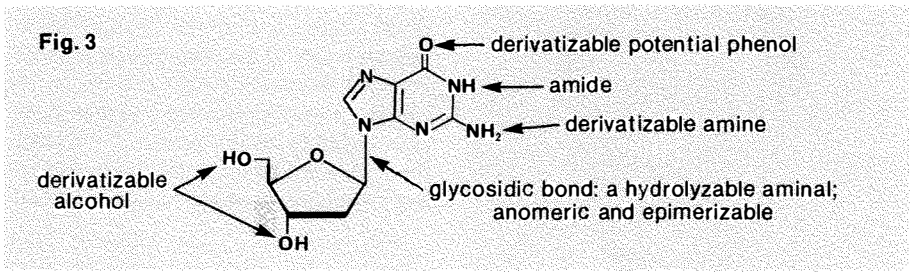
The problem of DNA synthesis entails the formation of a linear polymeric sugar phosphate ester by the stepwise addition of ester bonds at exactly the correct phosphorus atoms and hydroxyls of the sugar residues. This is accomplished by selective protection/deprotection of reactive sites in the appropriate sequence. The protecting groups must be easily introduced and removed, the latter being especially important. Due to the sensitive nature of the monomeric units and DNA itself, great care must be taken to circumvent two of the biggest problems: internucleotide bond cleavage (breaking of the DNA strand) and depurination (loss of adenine or guanine *via* cleavage of the glycosidic bond). Not only do side reactions lower the yield of final product, they can create serious purification problems. The difference between an octadecanucleotide which lacks one adenine somewhere in the chain, and one that does not, may be physically minimal but biochemically disastrous.











3. Protection I — The Base Residues

Of the four common deoxynucleoside bases, only thymine does not contain a primary amino group capable of being acylated, phosphorylated, or sulfonated. (Sulfonation is a potential side reaction in the condensation reaction in which the sugar-phosphate ester bond is formed; see Section 6.2.) The amino groups of the other bases are usually protected as amides, the most common derivatives being the following: for dA, benzoyl (Bz); for dC, benzoyl or, less frequently, anisoyl (An); and for dG, isobutyryl (iBu). These specific groups were developed some twenty years ago through arduous research by Khorana and co-workers,[16] and are still applied to the bases of deoxyribonucleosides and -tides (as well as the ribonucleosides and -tides from which synthetic RNA is prepared). In addition to affording chemical protection, derivatization serves another useful purpose — monomers and oligomers are rendered more soluble in common organic solvents, making chemical and purification operations (especially chromatography) easier to perform. A comprehensive study of acyl protecting groups for the three nucleosides has been made;[17] the conclusions suggest that the above derivatives are the best.

3.1. The Choice of Acyl Groups

One might wonder why the three bases require different acyl groups. The reasons for, and the development of each group are outlined briefly.

3.1.1. Deoxyadenosine

Initial work on the protection of N^6 of dA focused on the anisoyl group, presumably because of its success with dC-N^4 protection (see Section 3.1.2). However, in the attempted preparation of dA^{An}, extensive loss of the anisoyl group was observed.[18] Benzoylation was then investigated, and found suitable.[18] A discussion on N^6-protection of dpA can be found in ref. 16a.

The N^6 benzoylation of dA has one shortcoming. Reese has reported[7] that the glycosidic bond (1′-sugar to base) of N^6-Bz-dA (dA^{Bz}) is considerably more labile in acidic media than that of dA. Thus, a side reaction that occurs with dA^{Bz} is depurination. This fact has obvious implications in the preparation of multiprotected mononucleosides and oligonucleotides. Presumably dA^{Bz} residues within an oligomer possess the same acid lability. Depurination of dA^{Bz} also occurs in basic media.[18] A solution is still being sought for this problem, which is of particular concern during acid removal of the 5′-*O*-dimethoxytrityl group, as discussed in Section 5.

3.1.2. Deoxycytidine

The benzoyl group was evidently selected for N^4 protection of dC after the development of its use on dpC.[16b] With dpC, the acetyl group was initially investigated, but was found to be too acid-labile in later steps. In addition, dpC^{Ac} was too insoluble in pyridine for subsequent reactions. The benzoyl group proved more satisfactory in both these regards.

In the same work,[16b] anisoyl was preferred to benzoyl, the N^4-An group being less sensitive to base. The same preference has been cited by Catlin and Cramer.[19] However, benzoyl is the group most frequently cited in the literature of the past

two years, and dC^{Bz} is the predominant derivative available commercially. This may reflect the difficulties encountered in the preparation of dC^{An}.[20]

3.1.3. Deoxyguanosine

The task of finding an acceptable protecting group for the exocyclic nitrogen (N^2) of dG was more difficult than for dA and dC. Attempted preparation of 3′,5′,N^2-triacetyl-dG gave only 3′,5′-diacetyl-dG[18] — the N^2-acetyl group was not stable enough to survive the workup of the reaction. The use of benzoyl showed some success.[21,22] However, dG^{Bz} oligonucleotides eluted very slowly on ion-exchange chromatography, a phenomenon ascribed to the low pK_a (*ca.* 8.5) of the amide proton;[21] deprotonation resulted in increased retention. Finally, the isobutyryl group was considerably more stable than acetyl, and without the drawback of the benzoyl group.[21,22]

3.2. Introduction of the Acyl Groups

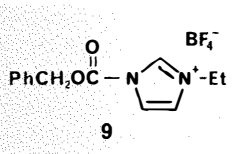
The preparation of base-protected nucleosides is generally still accomplished by the classic method of Khorana,[23,24] a rather tedious process (eq. 2). The nucleoside is first peracylated. Then, the O-acyl groups are removed by treatment with NaOH/alcohol/pyridine. The reaction workup consists of neutralization of NaOH with an excess of the pyridinium form of Dowex 50 ion-exchange resin. This is followed by filtration and extensive washing of the resin and concentration of the combined filtrate and washings. The product is crystallized from the solution and further purified as necessary. This general procedure is quite effective, but rather cumbersome on a large scale as relatively large volumes of solution are obtained. For example,[23] in a preparation of dG^{iBu} starting from 2.85g (10 mmol) of dG, the procedure involved washing the resin with *two liters* of ethanol. The yield of product was not specified, but may be assumed to be about 80% based on a scale-up by another author.[24]

In the preparation of N^6-benzoyldeoxyadenosine (dA^{Bz}), the peracylation procedure results in a unique intermediate. The product contains two N-benzoyl groups (see ref. 25); the relatively unstable second benzoyl group is removed during deesterification.[16c,27]

Until very recently, no significant advances had been made toward a simplified general preparation of base-protected mononucleosides, with the possible exception of dC.[28] Jones *et al.*[27] have published a procedure for all three N-acylated nucleosides which obviates the need for two separate steps. The approach, termed "transient protection," is based on persilylation of the nucleoside, followed by *in situ* N-acylation and silyl ether hydrolysis yielding dA^{Bz}, dC^{Bz} and dG^{iBu} in a one-pot reaction sequence (eq. 3). In the case of dA, quenching with aqueous bicarbonate rather than with aqueous ammonia in the last step gives dA^{Bz} (*vide supra*).

"Transient protection" has been applied by Hata *et al.* to N^6 of dA with the phthaloyl group.[29]

Very recently, Rapoport and co-workers[13] investigated a new general approach based on the benzyloxycarbonyl (Cbz) group.[30] A new method of introduction using 1-(benzyloxycarbonyl)-3-ethylimidazolium tetrafluoroborate (**9**) was developed to circumvent the weak nucleophilicity of the nucleoside amino groups. The strategy is outlined in eqs. 4, 5 and 6. Note that the procedure for dA is different from that for dC, resulting in a higher yield of dA^{Cbz}. Further, in the protection of dG (eq. 6), the 6-oxo function is **also** blocked, an important solution to a problem which has plagued oligonucleotide chemists for years, *viz.*, side reactions involving the O^6 of dG



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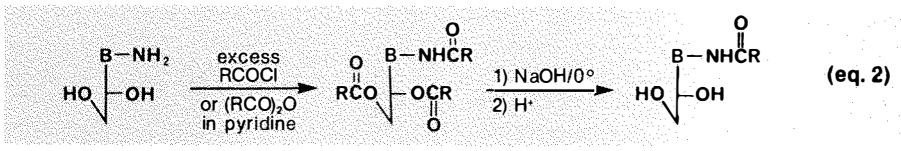
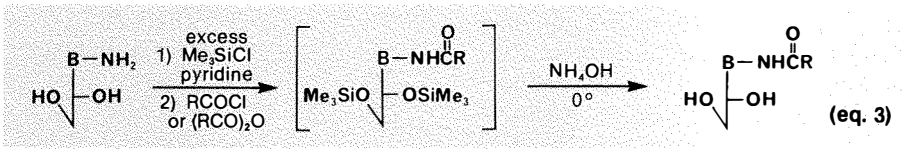
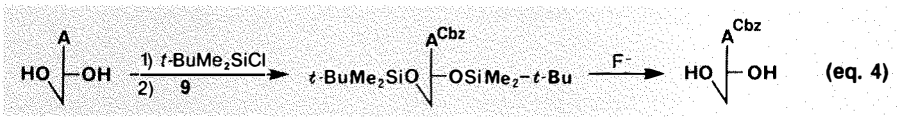


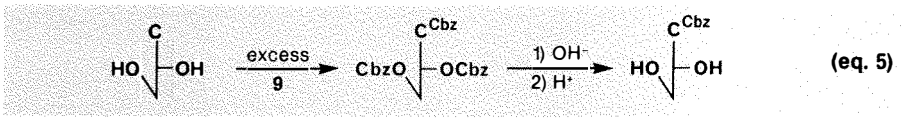
(eq. 2)



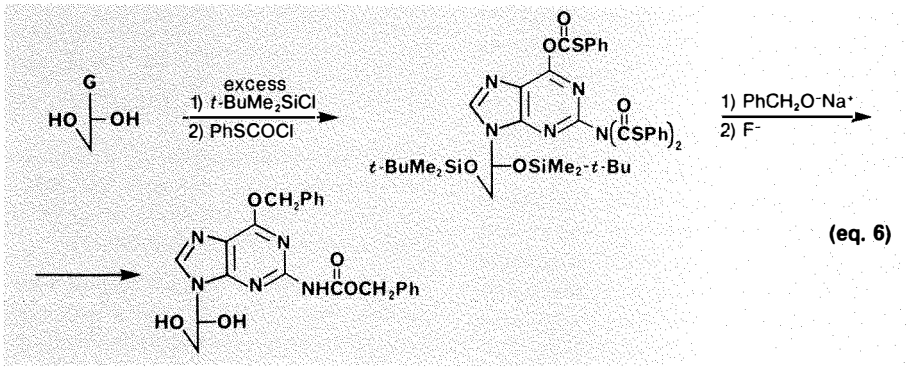
(eq. 3)



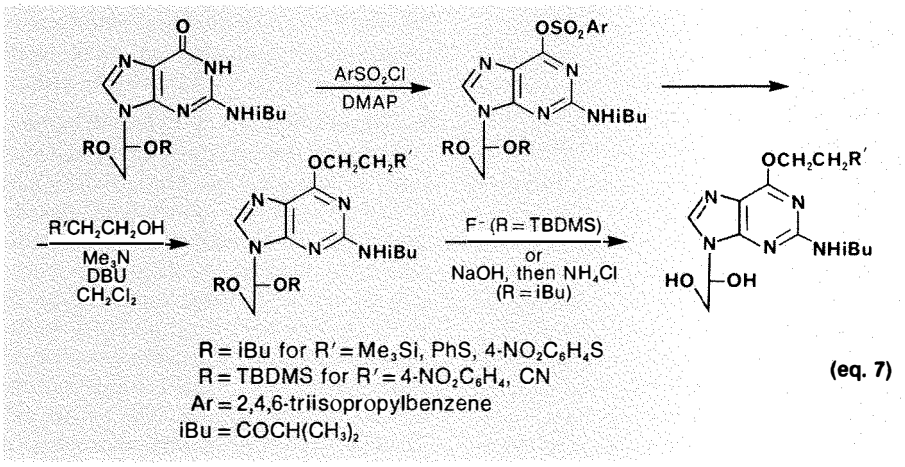
(eq. 4)



(eq. 5)



(eq. 6)

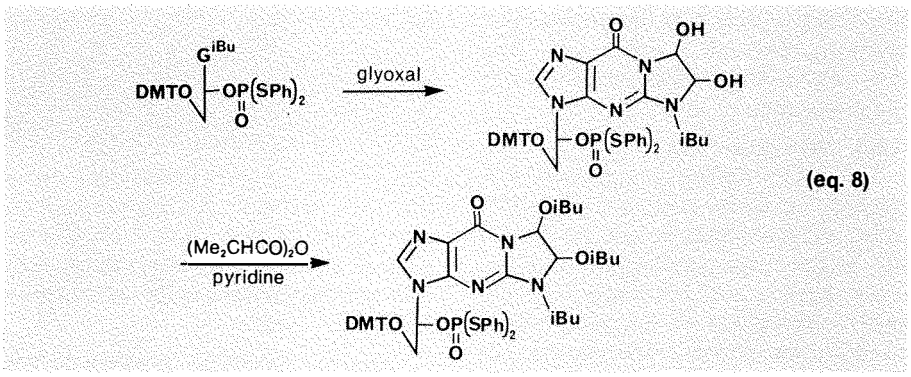


R = iBu for R′ = Me_3Si, PhS, 4-$NO_2C_6H_4S$
R = TBDMS for R′ = 4-$NO_2C_6H_4$, CN
Ar = 2,4,6-triisopropylbenzene
iBu = $COCH(CH_3)_2$

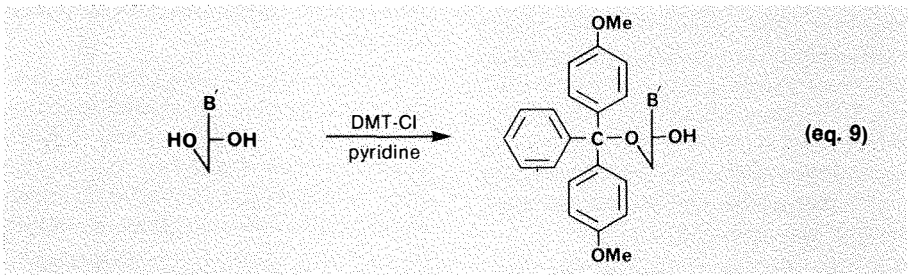
(eq. 7)

leading to undesirable byproducts. This problem is discussed at length by Gaffney and Jones in a paper describing another solution.[31] Their strategy for O^6-protection of dG is outlined in eq. 7. The groups shown in eq. 7 protected the guanine ring during phosphorylation, avoiding extensive byproduct formation. The limitations of these various groups and conditions for their removal are also discussed.[31]

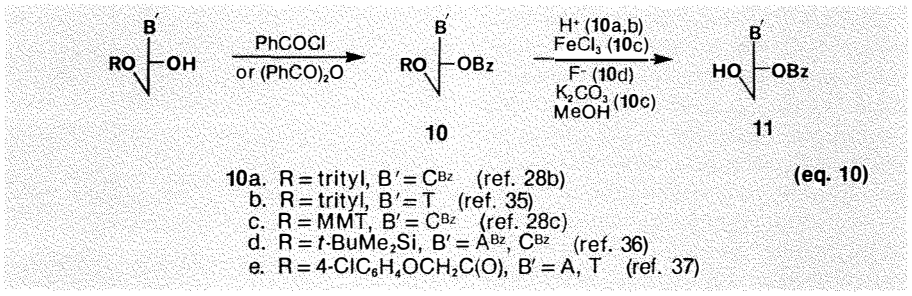
Hata[32] recently reported another protection strategy for dG (outlined in eq. 8) and showed that the protected guanine ring survives typical oligomer synthesis reactions.



(eq. 8)

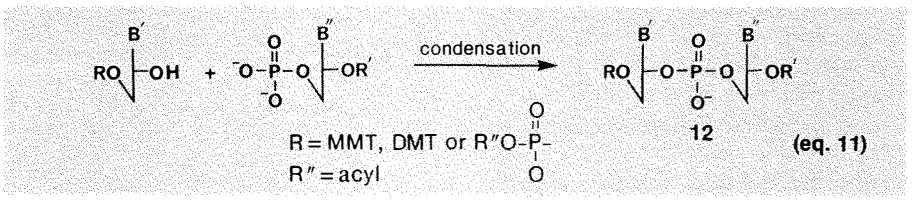


(eq. 9)



10a. R = trityl, B′ = C^{Bz} (ref. 28b)
b. R = trityl, B′ = T (ref. 35)
c. R = MMT, B′ = C^{Bz} (ref. 28c)
d. R = *t*-BuMe$_2$Si, B′ = A^{Bz}, C^{Bz} (ref. 36)
e. R = 4-Cl$C_6H_4OCH_2C(O)$, B′ = A, T (ref. 37)

(eq. 10)



(eq. 11)

4. Protection II — The Sugar Hydroxyls

Oligodeoxynucleotide synthesis is generally designed such that only the 5′-hydroxyl group of the sugar moiety requires protection. The monomethoxytrityl (*p*-anisyldiphenylmethyl; MMT) and dimethoxytrityl (di-*p*-anisylphenylmethyl; DMT) groups are most frequently used, with the latter predominating in the recent literature. Khorana pioneered the use of these groups which were initially investigated as alternatives to the unmethoxylated trityl (Tr) group for the 5′-O-protection of uridine, a ribonucleoside.[33] In these studies, it was found (as predicted) that the rates of acid hydrolysis increased ten-fold with each methoxy group. Trimethoxytrityl (tri-*p*-anisylmethyl) was briefly investigated, but was too labile. The ease of removal of the 5′-O-protecting group is very important in oligodeoxynucleotide synthesis. For every monomer added to the chain, a DMT (or MMT) group must first be removed. As noted earlier (Section 3.1.1), significant depurination of dA^{Bz} residues (to a lesser extent, dG^{iBu}) can occur under acidic conditions (see also the next section).

Introduction of the DMT (or MMT) group is easily accomplished (eq. 9). The base-protected deoxynucleoside in pyridine is treated with a slight excess of dimethoxytrityl chloride. After reaction and aqueous work-up, the product is purified by chromatography to remove DMT alcohol and any unreacted or 3′,5′-*bis*-tritylated nucleoside. Experimental procedures for the introduction of MMT and DMT to the four nucleosides (dA^{Bz}, dC^{Bz}, dG^{iBu} and T) can be found in references 23 and 24, respectively.

DMT (or MMT) groups confer a number of useful properties on the nucleoside, nucleotide, and oligonucleotide intermediates. They are more soluble in organic solvents because of the lipophilic DMT (or MMT) groups and are thus easier to work with, and they are more amenable to purification by conventional silica gel chromatography. The methoxytrityl groups contain a powerful chromophore which enables quantitative evaluation of reactions and products by UV spectroscopy.[34] Lastly, the MMT and DMT groups are easily removed in dilute acid solution (see Section 5).

Some synthetic strategies require a nucleoside with a free 5′- and a protected 3′-hydroxyl group (**11**). Usually this is obtained by 3′-O-benzoylation of a 5′-O-tritylated,[28b,c,35] silylated,[36] or *p*-chlorophenoxyacetylated[37] nucleoside (eq. 10) followed by removal of the 5′-O-protecting group.

5. Deprotection I — 5′-O-Detritylation

Although deprotection[33] (80% aqueous acetic acid) resulted in substantial depurination of dA residues,[38] only recently has the search for less harsh but effective conditions been undertaken. Since the publication of the first major modification in 1977,[38] an overwhelming number of methods has developed. The depth of the problem is evident from Table 1, which is probably not comprehensive. The entries are listed in chronological order to emphasize the intense activity.

It is difficult to predict which method will prove best and/or most generally accepted. Each new method is considered for speed, efficacy and extent of depurination. In a few instances[13,39b,46] a comprehensive comparison of methods is given.

Interestingly, removal of DMT groups using 80% acetic acid *at the end* of the oligomer synthesis is easily accomplished with *no* depurination, provided the base N-acyl groups have been removed.[39b]

6. Assembly of the Oligonucleotide — Phosphorylation

6.1. The Phosphodiester Approach

The phosphodiester synthesis was developed by Khorana for oligonucleotide preparation. The name implies the phosphorylation product (**12**, eq. 11), a diester of phosphoric acid. For many years it was the mainstay of oligonucleotide synthesis; most of the essential techniques of protection, phosphorylation (condensation), and de-

Table I
Reagents for Detritylation

Reagents	Year Introduced	Ref.
80% acetic acid/20% water	1962	33
2% $PhSO_3H$/7:3 chloroform-methanol	1977	38
10% Cl_3CCO_2H/7:3 chloroform-methanol	1980	34a, 39b
$ZnBr_2$ in CH_3NO_2 (sat'd. solution)	1980	39a
$ZnBr_2$ in CH_2Cl_2 (sat'd. solution)[a]	1980	40
$FeCl_3$ in CH_2Cl_2	1980	28c
0.1*N* TsOH/CH_3CN	1981	39b
2.5% $AlCl_3$, 1% 2,6-di-*tert*-butylpyridine in CH_3CN	1981	39b
2.5% BF_3, 1% 2,6-di-*tert*-butylpyridine in CH_3CN	1981	39b
$ZnBr_2$ in 85:15 CH_2Cl_2-isopropanol	1981	41
$ZnBr_2$ in 1% H_2O-CH_3NO_2 (sat'd. solution)	1981	42
1*M* $ZnBr_2$ in 85:15 CH_2Cl_2-MeOH	1982	43
Et_2AlCl in hexane; *i*-Bu_2AlCl in toluene; rxn. run in CH_2Cl_2[a]	1982	44
1% or 2% F_3CCO_2H in chloroform	1982	29, 32
10% Cl_3CCO_2H in chloroform	1982	45
3% Cl_3CCO_2H in CH_3NO_2	1982	46
1% or 2% F_3CCO_2H in CH_2Cl_2-CH_3CN	1982	47
3% $PhSO_3H$ in 9:1 CH_2Cl_2-DMF	1982	48
2% $PhSO_3H$ in 7:3 CH_2Cl_2-MeOH	1982	34c

[a]Only trityl groups studied

protection, as well as purification and characterization, were developed in the application of this chemistry. Although not widely utilized today, the diester method has been used to synthesize large oligomers successfully. A recent example is the total synthesis of a gene.[23]

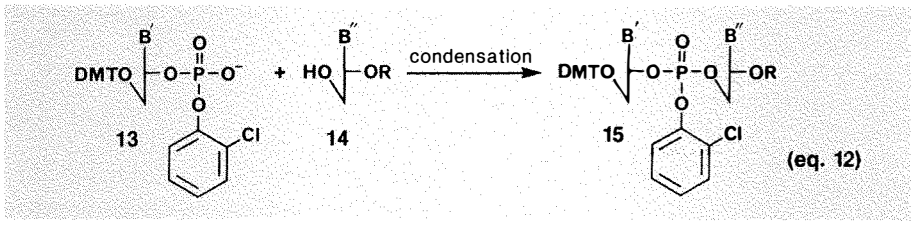
6.2. The Phosphotriester Approach (Protection III)

The triester approach was developed[4,7,19] to overcome the drawbacks of the diester approach, including low yield and limited solubility of reactants and products in organic solvents (most reactions are run in pyridine because of this) due to a charged phosphodiester at each internucleotide linkage (**12** in eq. 11). Obviously, these difficulties increase with increasing chain length. The limitations of the diester approach have been adequately discussed.[7,10]

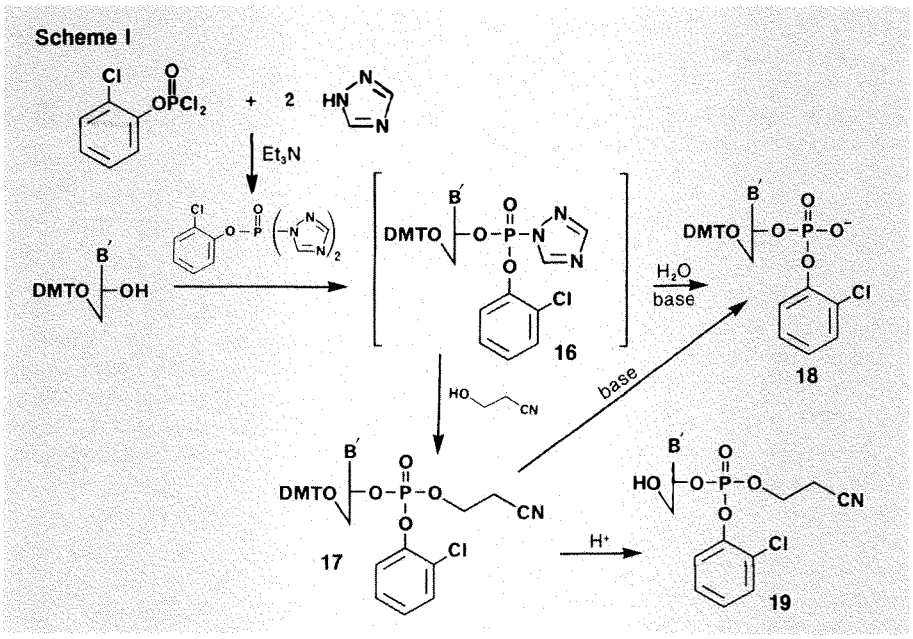
The important difference between the di- and triester approaches is that in the latter, a *fully protected* nucleotide, a *tri*ester of phosphoric acid, is formed with the establishment of each internucleotide linkage (eq. 12). This has several advantages for both reactants and products,[7] not the least of which is increased solubility in common organic solvents. The protecting group on phosphorus (*e.g.*, the 2-chlorophenyl group of **13** and **15**) remains until the end of the oligomer synthesis. (See Section 8.1 for a discussion on the selection and removal of this group.)

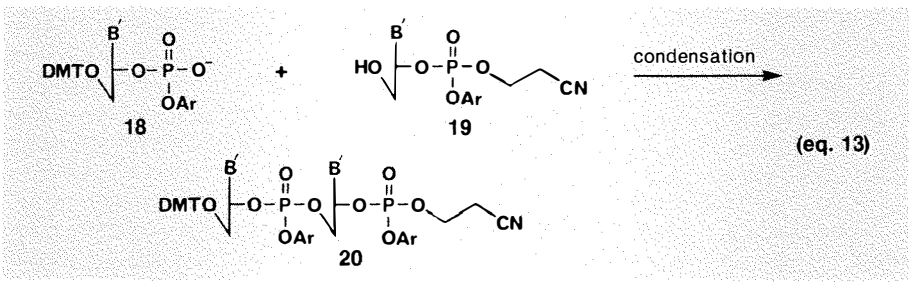
The triester approach has been so refined as to be regarded as "standard" for oligonucleotide synthesis in solution. It has been adopted successfully by the more traditional organic chemists who have entered the field recently.[12,13] Several fairly comprehensive outlines of the "improved triester approach" exist in the literature,[24,49,50] in addition to the review articles already cited. In this strategy, fully blocked nucleoside 3′-phosphates (**17**) are prepared (Scheme I) from each of the four nucleosides. These derivatives are relatively easily purified by conventional chromatographic techniques, and may be stored for later use. The purified materials can then be decyanoethylated *via* β-elimination with triethylamine (**17** → **18**) or detritylated with acid (**17** → **19**). The products **18** can be stored as triethylammonium[24] or hemi-barium salts.[51]

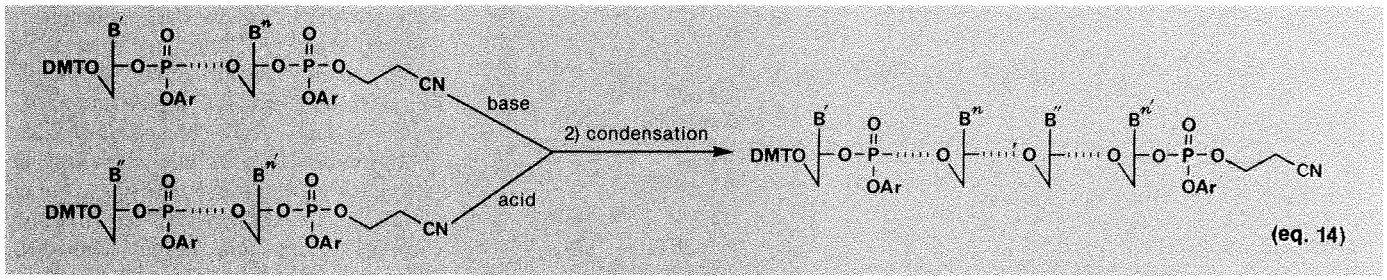
With the building blocks **18** and **19** of all four nucleosides, the process of chain assembly can be initiated with the condensation of a 5′-OH component and a 3′-O-phosphate component (eq. 13). Chain extension can then proceed *via* detritylation or decyanoethylation of **20**, followed by condensation with the appropriate **18** or **19**, respectively.



Scheme I

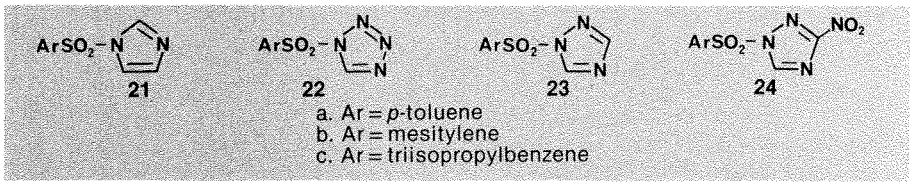


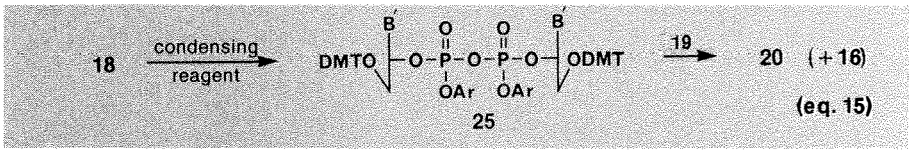


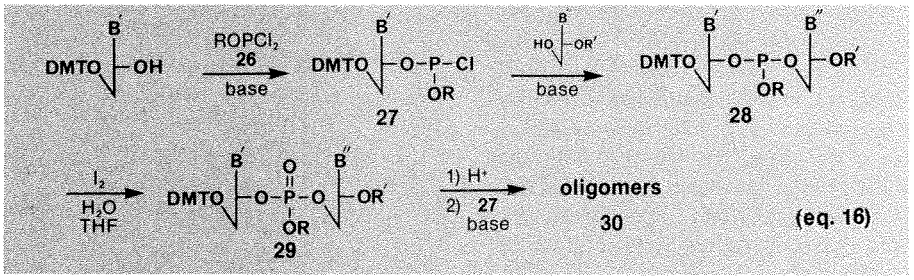


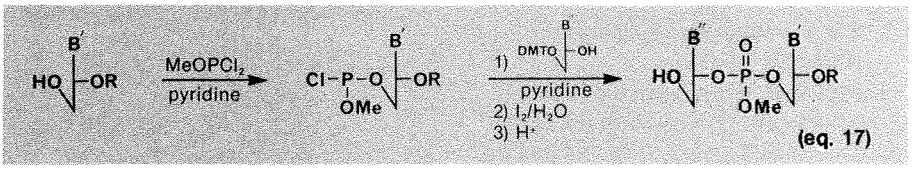
In solution syntheses it is easier and more economical to use a block synthesis than to add mononucleotides *ad infinitum* to a growing chain.[24,49-51] Fully protected oligonucleotide blocks, usually containing five to eight nucleoside residues, are prepared and after appropriate deprotection two blocks are condensed to form a longer chain (eq. 14).

Much effort has gone into the search for condensing reagents for a rapid and clean second phosphorylation reaction (eqs. 13, 14). Dicyclohexylcarbodiimide (DCC) and arylsulfonyl chlorides, first used by Khorana,[1] have been replaced for the most part by arylsulfonolides of heterocyclic bases, *e.g.*, **21**-**24**, which give much cleaner reactions. Chemical modification of guanosine bases by **24** is usually observed, but is reversed during final deprotection of the phosphates.[52,53]









Recently the combination of triisopropylbenzenesulfonyl chloride (TPSCl)[31] and *N*-methylimidazole was reported superior to the sulfonolides in both speed and absence of side reactions.[47,54] The authors also cite many references to condensation reagents.

The mechanism of the condensation reaction has finally been clarified. Russian chemists have reported evidence from ^{31}P NMR experiments that an intermediate pyrophosphate, **25**, is formed from the 3′-O-phosphate intermediate **18** (eq. 15).[55] This pyrophosphate then reacts with the 5′-OH component to give the triester product **20**.

Worth noting in this section is the recent publication of a method for the 5′-O-phosphorylation of deoxynucleotides and oligomers.[56] The synthetic strategy is a triester approach. However, as the protecting groups used are radically different than those used in the above examples, a discussion of this new technique is beyond the scope of this article.

6.3. The Phosphite Approach

This strategy, developed after the triester approach, incorporates a totally different phosphorylation protocol. Conceived by Letsinger,[57] it was shown to be very effective in the synthesis of oligothymidylic acids **30** (B^x = T, R = trichloroethyl; eq. 16).

This strategy uses the fact that dichlorophosphites **26** react faster than dichlorophosphates, even at low temperatures. In addition, the phosphite triester intermediates **28** are easily and mildly oxidized to phosphates **29** with iodine and water. Thus, it overcame a major disadvantage of the triester method — that it was not easily modified to give good yields of products in solid-phase (polymer-supported) synthesis.[57] It is also noteworthy that the second phosphitylation step (**27** → **28**) requires only an organic base like collidine.

A milestone in phosphite technology was reached in 1980-1981. In the course of adapting the Letsinger procedures to the synthesis of mixed oligonucleotides on a solid support, Caruthers[39] used methyl dichlorophosphite, a reagent originally used by van Tamelen[58] in oligoribonucleotide (RNA) synthesis. The principal advantage of this reagent is that the methyl protecting group is removed under milder conditions (S_N2 displacement with thiophenoxide anion under non-hydrolytic conditions; see Section 8.2) than a trichloroethyl group, which Letsinger removed with sodium naphthalenide in HMPA.[57] Caruthers used the basic Letsinger approach shown in eq. 16. The chlorophosphites **27**, although highly reactive, are stable enough for storage at -78° for up to a week.[39]

This technology was rapidly accepted by other investigators for solid-phase oligonucleotide synthesis,[10,42,46,59,60] with little variation in synthetic strategy other than the modifications in the 5′-O-detritylation already presented in Section 5. A major departure from the general Letsinger-Caruthers scheme (eq. 16) is that shown in eq. 17, in which the 5′-OH of the nucleoside bound to the support is phosphitylated with $MeOPCl_2$. The resulting 5′-O-monochlorophosphite is then treated with a 5′-O-DMT base-protected nucleoside. After oxidation and detritylation, chain extension continues.[34c]

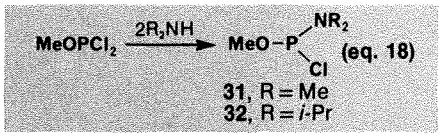
In an extension of this phosphite work, Caruthers[61,62,63a] and others[63b] have developed new phosphite reagents of increased stability to both hydrolysis and air oxidation. These reagents (**34**) are synthesized

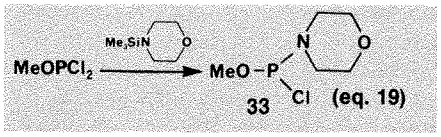
(eq. 20) from protected nucleosides and phosphoramidites **31-33** prepared from $MeOPCl_2$ (eqs. 18 and 19).[63a] The hydrolytic stability of the nucleoside phosphoramidites **34** is dramatically demonstrated by their high-yield preparation in a reaction sequence which includes an *aqueous* workup.[63a]

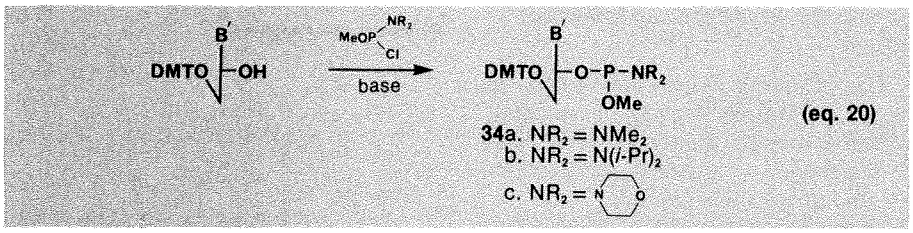
A further advantage of phosphoramidite chemistry is that little or no 3′-3′ dimer **(35)** is formed. This dimer is a significant by-product in the reaction with $MeOPCl_2$,[62] a procedure that is thus rather wasteful of the expensive nucleoside starting material.

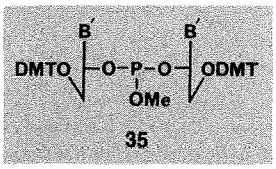
The amidite **34** must first be activated for subsequent reaction with a 5′-OH residue. This is done with a weak acid (eq. 21); the resulting reagent **(36)** is then reacted *in situ* with a 5′-OH nucleotide of the growing chain. The use of tetrazole is advantageous in that additional base need not be used.[62,63]

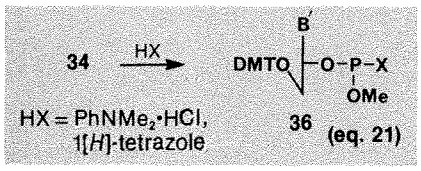
In another recent development, Letsinger reported a new reagent **(37)** which is more selective in 3′-O-phosphitylation than either methyl dichlorophosphite or 2,2,2-trichloroethyl dichlorophosphite.[64] The phosphate protecting groups derived from **37** are removed from the oligomer with tri-*n*-butylphosphine in DMF/triethylamine.











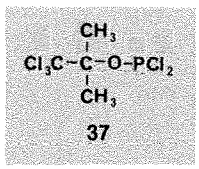
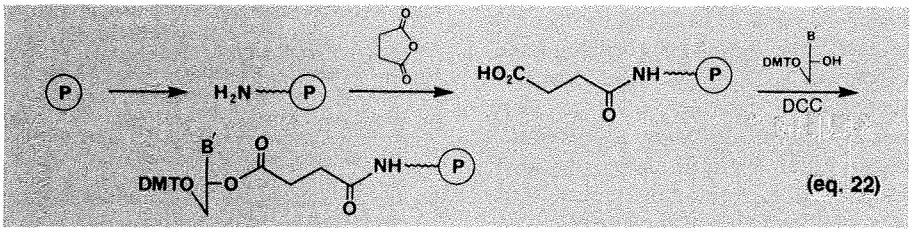


Table II
Synthetic Technology

Resin Type	Phosphotriester	Phosphite
Organic Polymer	34a, 34d, 43, 45, 48, 65	
Silica Gel	34c, 66	10, 34b, 39, 42, 46, 57, 60, 61, 62, 63, 64



7. Polymer-supported Synthesis of Oligodeoxynucleotides

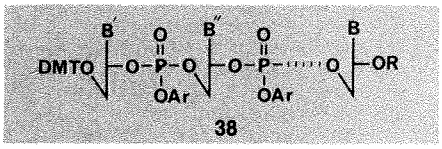
The aim of much research on oligonucleotide synthesis is the development of an automated system. The commercial advantages are obvious. As with polypeptide synthesis, the easiest way to automate is to immobilize the growing chain on a solid polymer support so that reagent and wash solutions can be mixed in or pumped through. Polymer-supported synthesis in this area is still in its infancy; no one synthetic technique (phosphotriester or phosphite) has won overwhelming acceptance, although the use of a derivatized silica gel and the phosphite technology seems favorable. Early work in this area is covered in several review articles.[8-11] Table II cross-references recent articles by technology and solid supports used.

A polymer-supported synthesis begins with the selection of a support. Selection is based on a number of factors, most of which are beyond the scope of this review (refer to articles cited in Table II). The choice of a support is limited to one which can be derivatized to bind a nucleoside. This usually requires appending to the resin some group with a free primary amine. The amine is treated with succinic anhydride, and the resulting polymer-bound half-acid is esterified with the free 3′-OH of the desired nucleoside (eq. 22). Chain extension then proceeds stepwise, nucleotide residues being added using phosphotriester or phosphite technology. Removal of the protecting groups from the oligomer, and removal of the final product from the solid support, are discussed in the following section.

8. Deprotection II — Unblocking Synthetic DNA

8.1. Phosphotriester-synthesized Oligomers

At the end of a phosphotriester synthesis (Section 6.2), one is left with an oligonucleotide of the general structure **38**, in



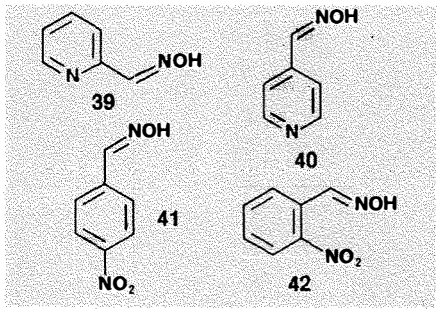
which Ar is 2-chlorophenyl and R is either a protected phosphate (-P(O)(OAr)OCH_2CH_2CN) or a benzoyl group. Typically, the protecting groups are removed by the following sequence:

1) triethylamine-pyridine for the P-O-cyanoethyl groups;
2) tetramethylguanidine-aromatic aldoxime in aqueous dioxane for the P-O-2-chlorophenyl groups;
3) concentrated ammonium hydroxide for the acyl groups from the base residues (this will also remove a benzoyl group from the 3′-O position); and
4) 80% acetic acid (aq.) for the dimethoxytrityl group.

Particular attention has been devoted to step 2. An enormous amount of effort has gone into the development of a protection-deprotection system for the phosphoric acid residues, culminating in the development, in Reese's laboratories, of the widely accepted system using 2-chlorophenyl as the blocking group (4-chlorophenyl is also used, but 2-chlorophenyl appears to be preferred because it is removed 2.5 times as quickly in the deblocking step[67,68]) and aldoximate anion as the deblocking agent. This anion is generated *in situ* from the aldoxime and the strong organic base tetramethylguanidine. This combination was established through consideration of the pK_a of the phenol from which the blocking group is derived and the pK_a of the aldoxime (for details, see ref. 67). These studies were aimed at developing a blocking-de-

blocking protocol in which the blocking group would be sufficiently stable to the reaction conditions in various steps of oligonucleotide synthesis, but would be removed with minimal cleavage of internucleotide phosphate bonds and other side reactions.

This deblocking step apparently involves nucleophilic displacement of phenoxide at phosphorus by aldoximate anion, followed by elimination of aromatic nitrile to give the phosphate anion (eq. 23).[67]



Four aldoximes (**39**-**42**) were investigated by Reese; the last is suggested as the best.[67] The use of all four is described in the literature.

8.2. Phosphite Triester-synthesized

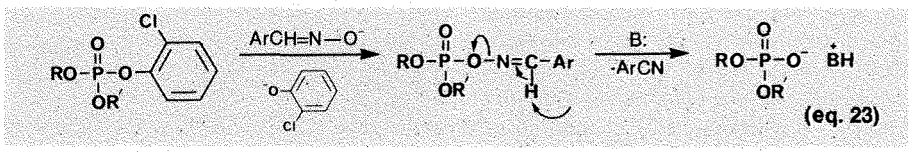
The major difference in deprotection of oligomers prepared by phosphite technology is that the phosphate protecting group to be removed is methyl rather than aryl. Methyl-group cleavage is accomplished with thiophenoxide anion, as mentioned above. Although ammonia may be used, thiophenoxide deprotection is much cleaner.[46] All other deprotection operations are accomplished in the same manner as in Section 8.1. Descriptions can be found in the articles already cited.

8.3. Polymer-supported Syntheses

The operations are the same as those in the preceding sections. Cleavage of the oligomer from the support is accomplished at the time the acyl groups are removed from the base residues with ammonia.

9. Summary

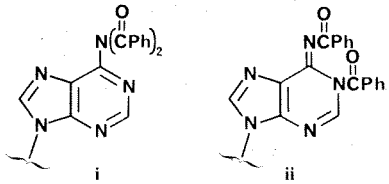
There is much demand for sequence-specific DNA fragments, which have a variety of uses in molecular biology and genetic engineering. The most reliable method of producing these fragments is by chemical synthesis for which several synthetic protocols are in use today. This article has briefly summarized the most common methodologies to introduce organic chemists to this rapidly expanding field. Detailed discussions of the various strategies may be found in the review articles cited.[**] A compilation of references is also available in the brochure "Reagents for Oligonucleotide Synthesis" published by the Aldrich Chemical Company (1982).



(eq. 23)

References and Footnotes

1) Agarwal, K.L.; Yamazaki, A.; Cashion, P.J.; Khorana, H.G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 451.
2) Narang, S.A.; Wightman, R.H. In "Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1973; Vol. I, pp 279-330.
3) Zhandov, R.I.; Zhenodarova, S.M. *Synthesis* **1975**, 222.
4) Reese, C.B. *Phosphorus and Sulfur* **1976**, *1*, 245.
5) Amarnath, V.; Broom, A.D. *Chem. Rev.* **1977**, *77*, 183.
6) Slotin, L.A. *Synthesis* **1977**, 737.
7) Reese, C.B. *Tetrahedron* **1978**, *34*, 3143.
8) Ikehara, M.; Ohtsuka, E.; Markham, A. *Adv. Carbohydr. Chem. Biochem.* **1979**, *36*, 135.
9) Gait, M.J. In "Polymer-supported Reactions in Organic Synthesis"; Hodge, P.D.; Sherrington, D.C., Eds.; Wiley: London, 1980, pp 435-456.
10) Ogilvie, K.K. *et al. Science* **1981**, *214*, 270.
11) Ohtsuka, E.; Ikehara, M.; Söll, D. *Nucl. Acids Res.* **1982**, *10*, 6553. During the preparation of this paper, the following review articles appeared: (a) Narang, S.A. *Tetrahedron* **1983**, *39*, 3. (b) Atkinson, T.C. *BioTechniques* **1983**, *1*, 6. (c) Davies, J.E.; Gassen, H.G. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 13. (d) Sheppard, R.C. *Chem. Br.* **1983**, *19*, 402.
12) Fowler, K.W.; Büchi, G.; Essigmann, J.M. *J. Am. Chem. Soc.* **1982**, *104*, 1050.
13) (a) Watkins, B.E. ; Kiely, J.S.; Rapoport, H. *ibid.* **1982**, *104*, 5702. (b) Watkins, B.E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471.
14) Cherfas, J. "Man Made Life"; Basil Blackwell: Oxford, U.K., 1982, p 146 (available in the U.S. through Pantheon Books, Inc., New York).
15) Wu, R.; Bahl, C.P.; Narang, S.A. *Prog. Nucl. Acid Res. Mol. Biol.* **1978**, *21*, 101.
16) In most instances, protecting groups for the base residues of both deoxynucleosides and deoxynucleotides (nucleoside-5'-phosphates) were developed concurrently. The reasons for the choice of a specific group may be somewhat different for the two: (a) dpA: Ralph, R.K.; Khorana, H.G. *J. Am. Chem. Soc.* **1961**, *83*, 2926; (b) dpC: Khorana, H.G.; Turner, A.F.; Vizsolyi, J.P. *ibid.* **1961**, *83*, 687; (c) dpG: Ralph, R.K.; Connors, W.J.; Schaller, H.; Khorana, H.G. *ibid.* **1963**, *85*, 1983.
17) Köster, H.; Kalikowski, K.; Liese, T.; Heikens, W.; Kohli, V. *Tetrahedron* **1981**, *37*, 363.
18) Schaller, H.; Weimann, G.; Lerch, B.; Khorana, H.G. *J. Am. Chem. Soc.* **1963**, *85*, 3821.
19) Catlin, J.C.; Cramer, F. *J. Org. Chem.* **1973**, *38*, 245.
20) Cashion, P.; Notman, H.; Sathe, G.; Cadger, T.; Tranquilla, T. *J. Chromatogr.* **1977**, *136*, 159.
21) Weber, H.; Khorana, H.G. *J. Mol. Biol.* **1972**, *72*, 219.
22) Büchi, H.; Khorana, H.G. *ibid.* **1972**, *72*, 251.
23) Brown, E.L.; Belagaje, R.; Ryan, M.J.; Khorana, H.G. *Methods Enzymol.* **1979**, *68*, 109.
24) Narang, S.A.; Brousseau, R.; Hsiung, H.M.; Michniewicz, J.J. *ibid.* **1980**, *65*, 610.
25) This is also the case in the peracylation of adenosine. Reese[26] has shown that the second benzoyl group is attached to the same nitrogen atom as the first (**i** as opposed to **ii**).



i ii

This is assumed to be the case for dA as well.[27] The second benzoyl group is removed during the base treatment.[18,27]
26) Lyon, P.A.; Reese, C.B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2645.
27) Ti, G.S.; Gaffney, B.L.; Jones, R.A. *J. Am. Chem. Soc.* **1982**, *104*, 1316.
28) Alternative procedures exist for the direct selective N^4-acylation of dC only. (a) With benzoic anhydride in refluxing ethanol: Otter, B.A.; Fox, J.J. In "Synthetic Procedures in Nucleic Acid Chemistry"; Zorbach, W.W.; Tipson, R.S., Eds.; Interscience: New York, 1968, Vol. I, p 285. (b) With benzoic anhydride in pyridine: Benz, E.; Elmore, N.F.; Goldman, L. *J. Org. Chem.* **1965**, *30*, 3067. (c) With pentafluorophenyl benzoate: Igolen, J.; Morin, C. *ibid.* **1980**, *45*, 4802. This last article also gives references to other methods.
29) Kume, A.; Sekine, M.; Hata, T. *Tetrahedron Lett.* **1982**, *23*, 4365.
30) The selection of this group was based on its successful applications in polypeptide chemistry.[13] The adaptation of peptide reagents to nucleotides is, not surprisingly, a recurrent theme in oligonucleotide chemistry.
31) Gaffney, B.L.; Jones, R.A. *Tetrahedron Lett.* **1982**, *23*, 2257; see also *idem ibid.* **1982**, *23*, 2253.
32) Sekine, M.; Matsuzaki, J.; Hata, T. *ibid.* **1982**, *23*, 5287.
33) Smith, M.; Rammler, D.H.; Goldberg, I.H.; Khorana, H.G. *J. Am. Chem. Soc.* **1962**, *84*, 430.
34) For example, the amount of dimethoxytritylated nucleoside bound to a support for solid-phase synthesis has been determined in this manner: (a) Gait, M.J.; Popov, S.G.; Singh, M.; Titmas, R.C. *Nucl. Acids Res.* **1980**, *Symposium Series No. 7*, 242. (b) Jayaraman, K.; McClaugherty, H. *Tetrahedron Lett.* **1982**, *23*, 5377. (c) Ohtsuka, E.; Takashima, H.; Ikehara, M. *ibid.* **1982**, *23*, 3081. (d) Miyoshi, K.; Miyake, T.; Hosumi, T.; Itakura, K. *Nucl. Acids Res.* **1980**, *8*, 5473.
35) Eckstein, F. *Chem. Ber.* **1967**, *100*, 2228.
36) Ogilvie, K.K. *Can. J. Chem.* **1973**, *51*, 3799.
37) deRooji, J.F.M.; Wille-Hazeleyer, G.; van Deursen, P.H.; Serdijn, J.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 537.
38) Stawinski, J.; Hozumi, T.; Narang, S.A.; Bahl, C.P.; Wu, R. *Nucl. Acids Res.* **1977**, *4*, 353.
39) (a) Matteucci, M.D.; Caruthers, M.H. *Tetrahedron Lett.* **1980**, *21*, 3243. (b) *Idem J. Am. Chem. Soc.* **1981**, *103*, 3185.
40) Kohli, V.; Blöcker, H.; Köster, H. *Tetrahedron Lett.* **1980**, *21*, 2683.
41) Kierzek, R.; Ito, H.; Bhatt, R.; Itakura, K. *ibid.* **1981**, *22*, 3761.
42) Chow, F.; Kempe, T.; Palm, G. *Nucl. Acids Res.* **1981**, *9*, 2807.
43) Ito, H.; Ike, Y.; Ikuta, S.; Itakura, K. *ibid.* **1982**, *10*, 1755.
44) Köster, H.; Sinha, N.D. *Tetrahedron Lett.* **1982**, *23*, 2641.
45) Gait, M.J.; Matthes, H.W.D.; Singh, M.; Titmas, R.C. *Chem. Commun.* **1982**, 37.
46) Tanaka, T.; Letsinger, R.L. *Nucl. Acids Res.* **1982**, *10*, 3249.
47) Efimov, V.A.; Reverdatto, S.V.; Chakhmakhcheva, O.G. *ibid.* **1982**, *10*, 6675.
48) Patel, T.P.; Millican, T.A.; Bose, C.C.; Titmas, R.C.; Mock, G.A.; Eaton, M.A.W. *ibid.* **1982**, *10*, 5605.
49) Broka, C.; Hozumi, T.; Arentzen, R.; Itakura, K. *ibid.* **1980**, *8*, 5461.
50) (a) Narang, S.A.; Hsiung, H.M.; Brousseau, R. *Methods Enzymol.* **1979**, *68*, 90. (b) Hsiung, H.M. *Tetrahedron Lett.* **1982**, *23*, 5119.
51) See Gough, G.R.; Brunden, M.J.; Nadeau, J.G.; Gilham, P.T. *Tetrahedron Lett.* **1982**, *23*, 3439 and previous papers in this series.
52) Reese, C.B.; Ubasawa, A. *ibid.* **1980**, *21*, 2265.
53) *Idem Nucl. Acids Res.* **1980**, *Symposium Series No. 7*, 5.
54) Efimov, V.A.; Reverdatto, S.V.; Chakhmakhcheva, O.G. *Tetrahedron Lett.* **1982**, *23*, 961.
55) Ivanova, E.M.; Khalimskaya, L.M.; Romanenko, V.P.; Zarytova, V.F. *ibid.* **1982**, *23*, 5447.
56) van de Marel, G.A.; van Boeckel, C.A.A.; Wille,

G.; van Boom, J.H. *Nucl. Acids Res.* **1982**, *10*, 2337.
57) (a) Letsinger, R.L.; Lunsford, W.B. *J. Am. Chem. Soc.* **1976**, *98*, 3655. (b) Melnick, B.P.; Finnan, J.L.; Letsinger, R.L. *J. Org. Chem.* **1980**, *45*, 2715.
58) Daub, G.W.; van Tamelen, E.E. *J. Am. Chem. Soc.* **1977**, *99*, 3526.
59) Smith, D.J.H.; Ogilvie, K.K.; Gillen, M.F. *Tetrahedron Lett.* **1980**, *21*, 861.
60) Elmblad, A.; Josephson, S.; Palm, G. *Nucl. Acid Res.* **1982**, *10*, 3291.
61) Caruthers, M.H.; Beaucage, S.L.; Efcavitch, J.W.; Fischer, E.F.; Matteucci, M.D.; Stabinsky, Y. *Nucl. Acids Res.* **1980**, *Symposium Series No. 7*, 215.
62) Beaucage, S.L.; Caruthers, M.H. *Tetrahedron Lett.* **1981**, *22*, 1859.
63) (a) McBride, L.J.; Caruthers, M.H. *ibid.* **1983**, *24*, 245. (b) Adams, S.P.; Kavka, K.S.; Wyckes, E.J.; Holder, S.B.; Galluppi, G.R. *J. Am. Chem. Soc.* **1983**, *105*, 661.
64) Letsinger, R.L.; Groody, E.P.; Tanaka, T. *J. Am. Chem. Soc.* **1982**, *104*, 6805.
65) Köster, H.; Hoppe, N.; Kohli, V.; Kröepelin, M.; Kaut, H.; Kulikowski, K. *Nucl. Acids Res.* **1980**, *Symposium Series No. 7*, 39.
66) Kohli, V.; Balland, A.; Wintzerith, M.; Sauerwald, R.; Staub, A.; Lecoq, J.P. *ibid.* **1981**, *10*, 7439.
67) Reese, C.B.; Zard, L. *ibid.* **1981**, *9*, 4611.
68) Ohtsuka, E.; Taniyama, Y.; Marumoto, R.; Sato, H.; Hirosaki, H.; Ikehara, M. *ibid.* **1982**, *10*, 2597.
69) Readers interested in learning more about the technical aspects of purification and use of oligonucleotides in molecular biology are referred to *Methods Enzymol.*, Vol. 65 (Nucleic Acids, Part 1) and Vol. 68 (Recombinant DNA), ref. 14, and Old, R.W.; Primrose, S.B. "Principles of Gene Manipulation", 2nd ed.; Blackwell Scientific Publications: Oxford, U.K., 1981 (available in the U.S. through the University of California Press, Berkeley, CA). A recent issue of *Science* (**1982**, *219*, No. 4585) is devoted exclusively to biotechnology.

About the Author

Dr. Geoffrey C. Crockett received the B.A. degree in Chemistry from the University of Minnesota. After several years in the Synthetic Chemicals Division of Eastman Kodak he returned to school, receiving the M.S. degree from the Rochester Institute of Technology and the Ph.D. from the University of Colorado. Dr. Crockett has been with Aldrich since leaving graduate school, and is currently Supervisor of the Development Department.

New Developments in Chemiluminescence Research

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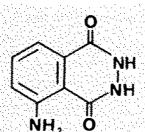
One can scarcely open the current abstracts without seeing new patents or articles pertaining to the applications of bio- and chemiluminescence.[1] A laboratory curiosity a few decades ago, the branch of photochemistry dealing with these phenomena has evolved into a specialty in itself.

My interest in chemiluminescence (CL) began at an early age, when I observed the action of base and peroxide on 3-aminophthalhydrazide (luminol, **1**), one of the



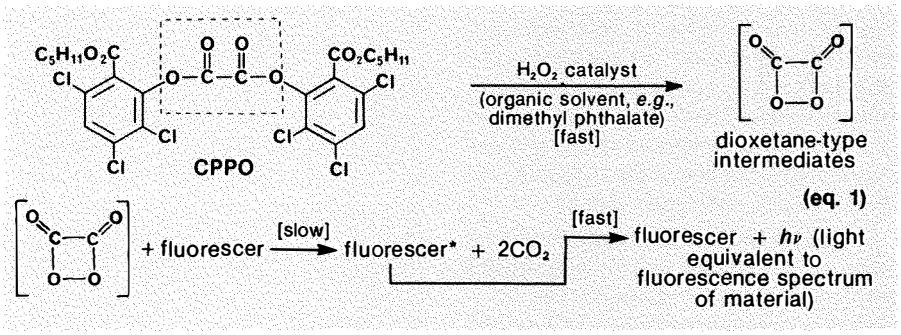
1 (luminol)

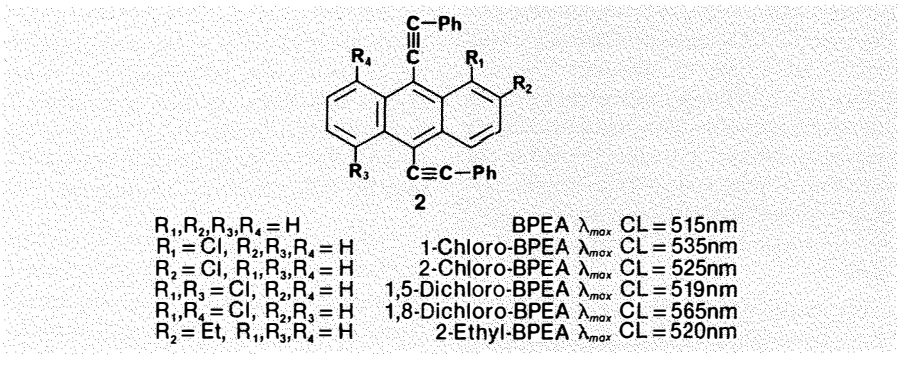
first compounds with this property to have been discovered.[2] My interest grew as the oxalate system ("CYALUME®" light sticks) began to appear in the literature.[3] As a result, I did a great deal of research in this area while in school, work that continues today.

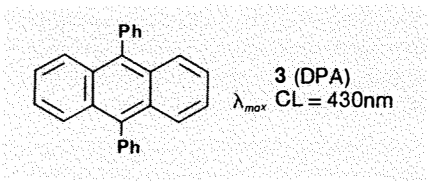
Much of my energy has been focused on the oxalate system (CYALUME®-type compounds). Besides being the most efficient man-made system (with quantum yields approaching 32%),[4] its mechanism allows one to choose a fluorescer of any desired spectral output.[5] This is because the oxalate ester merely generates the energy from which light is produced by singlet to ground-state relaxation of the fluorescer (eq. 1).[6]

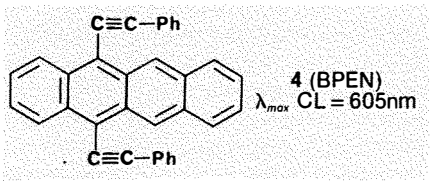
Ideally, the fluorescer should be soluble in organic solvents, stable to peroxides, and efficient (having a high $\Phi_{fluorescence}$). Of the compounds known to the art, the bis(phenylethynyl)anthracenes (BPEA, **2**) are especially good.[7] They are readily synthesized[8] and many have fluorescence quantum yields approaching unity,[9] suggesting their use as scintillation agents, laser dyes, and electrochemiluminescence fluorescers. Indeed, initial results in our laboratories with 1-chloro-BPEA have been very encouraging, satisfying all three criteria.

Other commonly used fluorescers are 9,10-diphenylanthracene (DPA, **3**), bis(phenylethynyl)naphthacene (BPEN, **4**), and rubrene (5,6,11,12-tetraphenylnaphthacene, **5**). Rubrene gives the highest

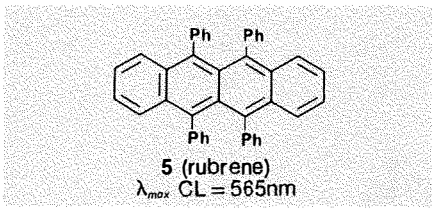








known quantum yield in this system.



5 (rubrene)
λ_{max} CL = 565nm

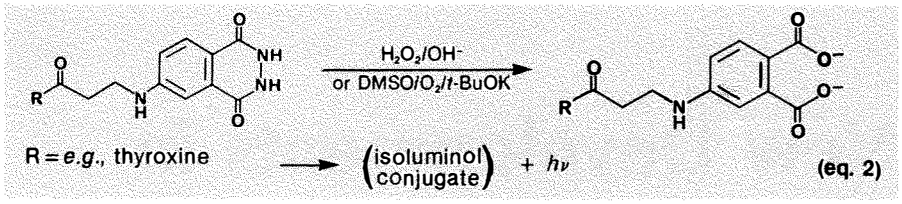
Besides the well known uses of the oxalate system for emergency lighting, sportfishing lures, life jacket markers, etc., it is beginning to be recognized as an excellent analytical tool.

The use of chemiluminescence in analysis is not new; many articles have been published on the use of luminol for the determination of numerous inorganic cations,[10] hydrogen peroxide,[11] and even blood, depending on the catalytic effect of hemoglobin.[12] Siloxene, a silicone hydroxyhydride pseudomorphic after calcium silicide, is a little known but highly effective chemiluminescence redox indicator,[13] indicating excess oxidizer by its yellow-orange light emission.[14] Tetrakis(dimethylamino)ethylene (TKDE) is a sensitive indicator of the presence of oxygen,[15] showing the concentration of O_2 by its blue-green "oxyluminescence".[16] Even pyrogallol,[17] lucigenin,[18] and lophine[18] have been used as CL indicators for various analytical pathways.

Recently, a number of patents[19] have covered the derivation of isoluminol and naphthoic hydrazides to produce compounds that are, in effect, chemiluminescence-labelled. This is an area of current research and development, and we may expect a number of new assay systems based on isoluminol conjugates (eq. 2).

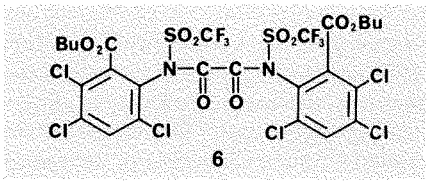
It is my belief that eventually modifications of the oxalate system will replace many of these other techniques. The versatility of a fluorescer structure, the ease with which oxalate esters are synthesized, and the superior CL quantum efficiency of the system leads one to speculate that the future will bring many extremely sensitive CL analytical techniques based on oxalate chemistry. Indeed, it is already used in the detection of polycyclic aromatic hydrocarbons,[20] dansyl derivatives of amino acids[21] and picomole quantities of hydrogen peroxide.[22]

Our research has centered mostly around the optimization of the various CL systems, as well as applying them to everything from educational displays to the performing arts. Actually, the possible artistic applications of chemiluminescence have been recognized by a few individuals — CL in the form of necklaces (repackaged CYALUME® for the most part) can be seen at any rock concert these days.



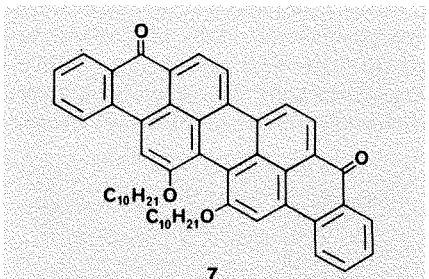
It is interesting to note the slow commercial response to this potentially lucrative market.

Part of our research has been in this area, though technical application remains our primary focus. We look forward to the development of new oxalates with higher quantum efficiency, *e.g.*, compound **6**, as well as new fluorescers to broaden the spec-

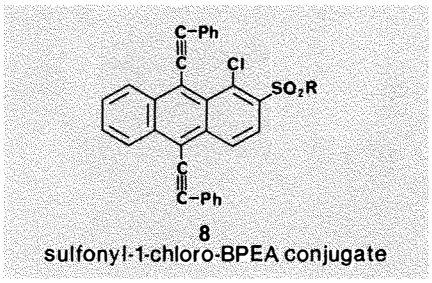


6

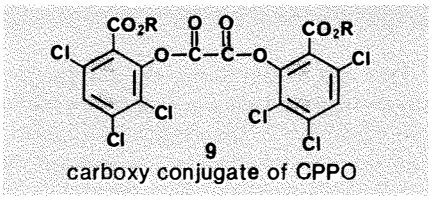
tral range. Already, infrared emitters such as **7** are known,[23] and with the oxalate ester system having an energy output of about



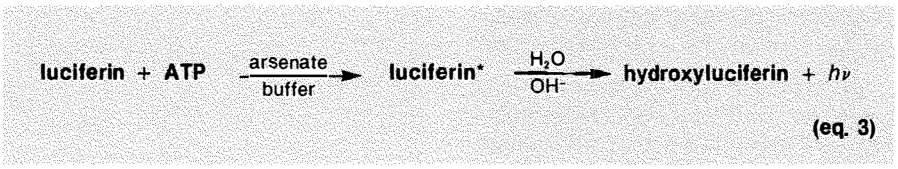
7
16,17-didecyloxyviolanthrone (DDV)
λ_{max} = 750nm



8
sulfonyl-1-chloro-BPEA conjugate



9
carboxy conjugate of CPPO



110 kcal/mole, the near ultraviolet should not be inaccessible. (An amazingly efficient system that peaks at 325 nanometers is known!)[24] It is hoped that a CL laser can be developed along these lines, though this remains "blue sky" at the moment.

The possiblities inherent in the oxalate system are demonstrated by recent patents detailing its conversion into a water-soluble reaction.[25] Thus, by appropriate substitution of fluorescers (*e.g.*, **8**), or the oxalate ester itself (*e.g.*, **9**), it should be no problem to prepare extremely sensitive, specific CL immunoassay standards in a manner analogous to isoluminol derivatives.

As a closing comment, I should mention the comparative efficiency of bioluminescence (BL). Much of the mechanism of BL reactions has been elucidated with the advent of new CL systems and, of course, firefly luciferin has been the standard for ATP assay for many years.[26] With quantum efficiencies of 75 to 90%, much remains to be learned from these systems. This sister field is also yielding many new tools for analytical and diagnostic uses, and will be more useful with time. (For a good overview of the subject, see Deluca, M.; McElroy, W.D., Eds. "Bioluminescence and Chemiluminescence — Basic Chemistry and Analytical Applications"; Academic Press: New York, 1981.)

A world of possibilities awaits the researcher. Whether its applications be in special effects or costumes for the performing arts, or in new analytical techniques, CL research is expanding rapidly, and we may expect great advances during the next few years.

References:

1) Gunderman, K.D. "Chemiluminescenz der Organische Verbindungen"; Springer Verlag: Berlin, 1968. Gunderman, K.D. *Top. Curr. Chem.* **1974**, *46*, 61. Haas, Jr., J.W. *J. Chem. Ed.* **1967**, *44*, 396. Schuster, G.B.; Schmidt, S.P. *Adv. Phys. Org. Chem.* **1982**, *18*, 187.

2) Luminol was discovered around 1853. See Cottman, E.W. *J. Chem. Ed.* **1939**, *16*, 292 and White, E.H.; Roswell, D.F. *Accts. Chem. Res.* **1970**, 54.

3) (a) Rauhut, M.M.; Bollyky, L.J.; Roberts, B.G.; Loy, M.; Whitman, R.H.; Iannotta, A.V.; Semsel, A.M.; Clarke, R.A. *J. Am. Chem. Soc.* **1967**, *89*, 6515. (b) Bollyky, L.J.; Whitman, R.H.; Roberts, B.G.; Rauhut, M.M. *ibid.* **1967**, *89*, 6523. CYA-

LUME® is a trademark of American Cyanamid Company.
4) Tseng, S.-S.; Mohan, A.G.; Haines, L.G.; Vizcarra, L.S.; Rauhut, M.M. *J. Org. Chem.* **1979**, *44*, 4113.
5) Maulding, D.R.; Zweig, A. U.S. Patent 3 729426, 1973. Bollyky, L.J.; Rauhut, M.M. U.S. Patent 3 597 362, 1971.
6) Rauhut, M.M. *Accts. Chem. Res.* **1969**, 80. See ref. 3a also.
7) Maulding, D.R.; Roberts, B.G. *J. Org. Chem.* **1969**, *34*, 1734. Ried, W.; Donner, W.; Schlegelmilch, W. *Chem. Ber.* **1961**, *94*, 1051.
8) Maulding, D.R. U.S. Patent 3 911 038, 1975. See ref. 7 also.
9) Lechtken, P.; Turro, N.J. *Mol. Photochem.* **1974**, *6*, 95. Heller, C.; Henry, R.A.; McLaughlin, B.A.; Bliss, D.E. *J. Chem. Eng. Data* **1974**, *19*, 214.
10) Chang, C.A.; Patterson, H.H. *Anal. Chem.* **1980**, *52*, 653. Marino, D.F.; Ingle, Jr., J.D. *ibid.* **1981**, *53*, 455.
11) Schroeder, H.R.; Volgelhut, P.O. *Anal. Chem.* **1979**, *51*, 1583.
12) Schroeder, H.R.; Boguslaski, R.C.; Carrico, R.J.; Buckler, R.T. In "Bioluminescence and Chemiluminescence. Methods of Enzymology, Vol. 57"; Deluca, M.A., Ed.; Academic Press: New York, 1978; p 428.
13) Dryer, J.; Lusk, W. U.S. Patent 3 509 062, 1970. Hengge, E.; Pretzer, K. *Chem. Ber.* **1963**, *96*, 470. Hengge, E. *ibid.* **1962**, *95*, 648.
14) Kenny, F.; Kurtz, R.B. *Anal. Chem.* **1950**, *22*, 693.
15) Winberg, H.E.; Downing, J.R.; Coffman, D.D. *J. Am. Chem. Soc.* **1965**, *87*, 2054. Westerdahl, R.P. NTIS Publication No. AD 766704/1, 1973.
16) Freeman, T.M.; Seitz, W.R. *Anal. Chem.* **1981**, *53*, 98.
17) Slawinska, D.; Slawinski, S. *Zesz. Nauk. Wyzsz. Szk. Roln. Szczecinie* **1963**, *10*, 163.
18) Erdey, L.; Buzas, I. *Anal. Chim. Acta* **1956**, *15*, 322.
19) Maier, Jr., C.L. U.S. Patent 4 104 029, 1978. *Idem* U.S. Patent 4 181 650, 1978. Buckler, R.T.; Schroeder, H.R. U.S. Patent 4 331 808, 1982. *Idem* U.S. Patent 4 334 069, 1982. Burd, J.F.; Li, T.M. U.S. Patent 4 318 981, 1982. Boguslaski, R.C.; Carrico, R.J. U.S. Patent 4 238 195, 1980. Plakas, C.J. U.S. Patent 4 013 418, 1977.
20) Sigvardson, K.W.; Birks, J.W. *Anal. Chem.* **1983**, *55*, 432.
21) Kobayashi, S.; Imal, K. *ibid.* **1980**, *52*, 424.
22) Scott, G.A.; Seitz, W.R.; Ambrose, J. *Anal. Chim. Acta* **1980**, *115*, 221. Honda, K.; Sekino, J.; Imal, K. *Anal. Chem.* **1983**, *55*, 940.
23) Rauhut, M.M.; Roberts, B.G.; Maulding, D.R.; Bergmark, W.; Coleman, R. *J. Org. Chem.* **1975**, *40*, 330. Mohan, A.G.; Klingsberg, E.; Arthen, F.J.; Dulina, R.G.; Vizcarra, L.S. NTIS Publication No. AD 073331, 1979.
24) Goto, T.; Nakamura, H. *Chem. Commun.* **1978**, 781.
25) Mohan, A.G.; Dulina, R.G.; Doering, A.A. NTIS Publication No. PB272034, 1976. Rauhut, M.M.; Mohan, A.G. Eur. Patent 76 664E, 1982. Rauhut, M.M.; Tseng, S.-S. U.S. Patent 4 338 213, 1982. Rauhut, M.M.; Mohan, A.G.; Tseng, S.-S. U.S. Patent 4 282 357, 1980. Mohan, A.G. U.S. Patent 4 053 430, 1977.
26) Kricka, T.; Carter, L., Eds. "Clinical and Biochemical Applications of Luminescence"; Marcel Dekker, Inc.: New York, 1982.

About the Author

Steven K. Gill was born in Hayward, California and grew up in Marin County where he attended the College of Marin for several years. He did two years of graduate-level work in organic chemistry at San Francisco State University and five years of part-time work in industry as well as research on his own. After forming Liquid Light Laboratories, he focused on the area of photochemistry and the chemistry of physicochemical oscillations. His interests include high-technology art, desert camping, and music.

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Aldrichimica Acta

Volume 16, Number 4, 1983

New Transformations of 2,3-Epoxy Alcohols and Related Derivatives. Easy Routes to Homochiral Substances.

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Aldrichimica Acta

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About Our Cover:

While the subject of this beautiful landscape is clear, its author is still unknown. The Dutch dealer who sold it assured our chemist collector that it was by a little known Cologne artist, Johann Hulsmann. It reminded our chemist of the work of Rembrandt's teacher, Jacob Pynas. Both were mistaken, for the painting is monogrammed MCG and dated 1670, by which time Hulsmann and Pynas had long passed away. Who was the artist of this beautiful long view? French, Flemish, Dutch, German? He tried to write God's Hebrew name, the tetragrammaton, in the sky but certainly did not know Hebrew. Our chemist would be most grateful to hear from any reader who can identify this monogrammist MCG.

The story of Noah has a special appeal. All mankind descended from this one man, who was not a member of an identified people, just a man who listened to God. Here Noah and his family bring an offering after the flood, and the first rainbow appears as a token of God's promise never again to destroy all of mankind.

There is a particular poignancy to this story today. God promised that He would not destroy the world, but have we any assurance that we will not destroy it ourselves?

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 Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our *Acta* covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

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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

Since the introduction of flash chromatography by Still *et al.*[1] in 1978, the technique has become a "standard" method of purification in many laboratories. Often, we find that the initial packing of the column is the most troublesome aspect of the technique. It takes several column volumes of solvent to degas completely the silica gel, and if excess pressure is applied to the column to force out the last air bubbles, the column is liable to crack when the pressure is released. This problem is particularly prominent with small-diameter (~2cm) columns. An easy and efficient modification of the packing procedure is as follows: The solvent is poured onto the silica gel and allowed to percolate through the column *without* external pressure until it drips from the column. (This takes 5-10 minutes.) Application of pressure then usually packs the column within 30 seconds. Columns thus packed are also less likely to crack.

J. Michael Chong & Ian D. Suckling
Department of Chemistry
University of British Columbia
Vancouver, B.C. V6T 1Y6, Canada

[1]Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Editor's note: Flash chromatography columns of various capacities are available from Aldrich. In addition to those listed on page 1352 of the 1982-1983 Catalog/Handbook, Aldrich now offers the two-liter apparatus and solvent reservoirs for all the columns. See page 80.

We have increased the usefulness of your Kugelrohr distillation apparatus by using the frame of a horizontal rotary evaporator for support. The collection bulbs replace the evaporator and condenser flasks and rest on the rollers provided. The bulbs can be cooled with water, ice, etc. The existing connections for vacuum are used. The air-driven rocker motor is connected to the evaporator-drive pulley with a belt. The modified apparatus is convenient to use and easy to operate.

Robert G. Jensen, Professor
Mark B. Fey, Graduate Assistant
Department of Nutritional Sciences
University of Connecticut
Storrs, CT 06268

I wish to point out a method of cleaning nonpolar materials from glassware. Organic chemists tend to use relatively polar solvents such as acetone or alcohol for removing tars and residues from flasks. Although such solvents are quite effective for moderately polar materials, hydrocarbons and chlorinated solvents are more effective with nonpolar materials such as silicone oil. With crude oil (petroleum), acetone is indeed not the solvent of choice, so I tried one of the degreasers sold for cleaning automobile engines, machinery, garage floors, etc. The material, essentially a solution of a dispersing agent in a kerosene-type solvent, works quite well. After the organic material has dissolved (with warming if necessary), the solution can be disposed of with waste solvents. Water disperses most of the degreaser and dissolved material and washing with soap and water removes most of the rest. An advantage over the usual solvent-cleaning approach is that, unless the amount of residue in the glassware is considerable, one portion of degreaser can remove the material. At least one brand of degreaser is sold as a concentrated solution to be diluted with kerosene; presumably a somewhat more polar diluent, or one with a different boiling point, could be used.

Joseph H. Ross
Associate Professor of Chemistry
Indiana University at South Bend
South Bend, IN 46634

We find the Aldrich AtmosBag™ Floor Base (Z10,691-7) ideal as a TLC reagent spray chamber base. Our home-made Plexiglas chamber (14" x 14" x 14") is placed on the polyethylene base (32" x 22") which is located in a fume hood. The base is very durable to the corrosive sprays and is easily cleaned.

D. DeClercq
Grain Research Laboratory Division
1404-303 Main Street
Winnipeg, Manitoba
R3C 3G8 Canada

TLC analysis of reaction mixtures in high-boiling solvents such as dimethyl sulfoxide, dimethylformamide, pyridine, etc., is beset with problems of low resolution, excessive spreading, and gross changes in mobility of appropriate spots. Overlap of a solvent spot with those of reaction products can further complicate the separation. Drying of TLC plates with hot air or infrared lamp could lead, in many instances, to decomposition of sensitive materials. These difficulties are circumvented by drying the TLC plate *in vacuo* below 0.1mm prior to development. In our laboratory, we conveniently use lyophilization flasks attached to a lyophilizer, but a vacuum desiccator connected to an ordinary oil pump may also be employed. The whole procedure can easily be monitored visually. The original "wet" spot usually becomes dry in 2-3 min.

Jiri Zemlicka, Ph.D.
Michigan Cancer Foundation
Detroit, Michigan 48201

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

"Please Bother Us."

by Ronald Bader.

Recently Dr. Arnold Brossi at the NIH suggested that we offer bis(tricyclohexyltin) sulfide which has been described as an elegant reagent for the conversion of carbonyls to thiocarbonyls. The authors describe our other sulfurating reagent, Lawesson's Reagent, as the "most effective sulfurating reagent to be reported to date..." but "extremely sensitive to moisture and very difficult to prepare and handle in pure form." We have sold many hundreds of bottles of Lawesson's Reagent, albeit of only 97% purity. Clearly this new tin reagent will have advantages for some reactions where Lawesson's Reagent is cumbersome to use.

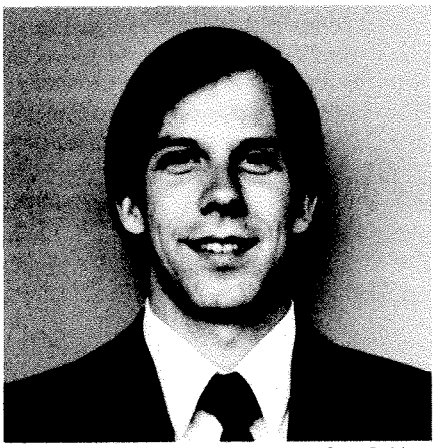
Naturally we now offer both.

Steliou, K.; Mrani, M. *J. Am. Chem. Soc.* **1982**, *104*, 3104.

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

New Transformations of 2,3-Epoxy Alcohols and Related Derivatives. Easy Routes to Homochiral Substances

Carl H. Behrens
K. Barry Sharpless
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139



C.H. Behrens

1. INTRODUCTION

Epoxides are highly regarded as intermediates in organic synthesis, a reputation resulting from the special reactivity exhibited by this functional group.[1] The introduction of an epoxide moiety into a polyfunctional compound is normally straightforward since epoxides are easily accessible from carbonyl or olefin precursors.[2] The Darzens condensation and the reaction of sulfur ylides with aldehydes or ketones represent familiar epoxide syntheses from carbon-oxygen double bonds. However, selective oxidation of an olefinic system is decidedly the most common and reliable route. Functionalized epoxides are generally accessible from substituted olefins because alkenes are oxidized more readily than most functional groups.

The opening of epoxides with nucleophiles occurs under an extremely wide range of reaction conditions. Good nucleophiles (*e.g.*, RS^-, RSe^-) react with epoxides under neutral or alkaline conditions. In an acidic medium even weak nucleophiles (*e.g.*, ROH, H_2O) react rapidly with epoxides. The epoxide-opening reaction is one of the best methods for the synthesis of two contiguous stereochemically defined sp^3 carbon centers. The mechanism, and hence the stereoselectivity, of this reaction is dependent on the conditions employed. Under neutral or alkaline conditions the ring opening can proceed by either an S_N2 mechanism or a borderline S_N2 mechanism in which the S_N2 transition state possesses substantial S_N1 character.[1k] In either case the epoxide is opened stereospecifically with inversion. Ring opening in an acidic medium can occur by either a borderline S_N2 or an S_N1 mechanism. An S_N1 mechanism is implicated by a loss of stereochemical integrity at the carbon atom being substituted. With scant exception, the S_N1 mechanism does not intrude unless the epoxide bears at least one functional group (*e.g.*, phenyl, vinyl, methoxyl) which has the capacity to stabilize an adjacent carbonium ion through resonance.

The regioselectivity of an epoxide-opening reaction is related to the mechanism of the reaction, and is therefore dependent on the reaction conditions. Experience predicts that an epoxide-cleavage reaction that is conducted in acid (*i.e., via* a borderline S_N2 mechanism) will result in ring opening at the more substituted epoxide terminus, whereas the opposite regioselectivity is anticipated when the epoxide cleavage is conducted under basic conditions where an S_N2 mechanism will be operative. Although the regioselectivity is strongly dependent on the mechanism of the reaction, it is also influenced by the particular steric, conformational and electronic effects in a given substrate. The complex interrelationship that exists among these factors makes the study of regioselective epoxide opening reactions a fascinating topic worthy of the continued attention it has received.

The diastereoselective synthesis of epoxy alcohols has advanced considerably in the past several years. The peracid-[3] and transition-metal-catalyzed[1d,4] epoxidations now used to prepare this important class of compounds are highly effective and reliable. The recently developed asymmetric epoxidation reaction is unique in that it allows the enantioselective synthesis of 2,3-epoxy

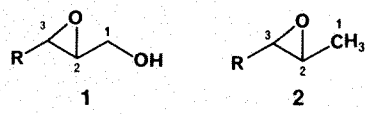
Professor K. Barry Sharpless (right) receiving the A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

alcohols.[5] Since the catalyst system for asymmetric epoxidation tolerates many substitution patterns, a large variety of homochiral (enantiomerically pure) 2,3-epoxy alcohols are now conveniently accessible. Clearly, the asymmetric epoxidation of prochiral allylic alcohols in conjunction with selective epoxide-cleavage reactions shows great potential as a versatile route to homochiral substances. That potential is already being demonstrated in the rapid adoption of the method for a variety of synthetic applications.[1c] Nevertheless, we have known since the birth of asymmetric epoxidation in 1980 that the rate-limiting step in finding applications for it is finding new uses for 2,3-epoxy alcohols (*e.g.*, **1**). Chemists know well what to expect of simple epoxides but the presence of an adjacent hydroxyl constitutes a less precedented situation. *A priori* one imagines that it would be much better if the asymmetric epoxidation process worked with simple olefins so that one could make epoxide **2** rather than the hydroxy substituted analog **1**. However, further consideration and especially our research experiences of the past two years lead us to believe that chiral epoxy alcohols (*e.g.*, **1**) are actually more useful intermediates than their deshydroxyl analogs (*e.g.*, **2**). The reasons for this conclusion will become evident as the present account unfolds. This article focuses on our recent investigations of 2,3-epoxy alcohols and closely related derivatives. It is not a typical review article in that most of the results discussed here have not been previously published.[6]

2. TERMINAL EPOXIDES (1,2-Epoxy-3-ols)

Although barely studied until a few years ago, the 2,3-epoxy alcohol moiety has proven to be quite an interesting substrate for nucleophilic ring-opening reactions. In principle, there are three reactive sites for nucleophilic substitution in a 2,3-epoxy alcohol (**1**, Scheme I) corresponding to the carbon backbone of the epoxy alcohol. The reactivity of the C-2 and C-3 positions is immediately apparent, but a discussion of this topic is deferred until Section 3.2. A subtle latent reactivity at the C-1 position can be revealed in one step by means of the Payne rearrangement.[7] Payne was the first to publish detailed observations on epoxide migration in simple acyclic 2,3-epoxy alcohols. However, these epoxide migrations were already well known in carbohydrate chemistry.[1e,1h] The Payne rearrangement is carried out in aqueous sodium hydroxide, usually in the presence of a co-solvent, and involves the equilibration of a 2,3-epoxy alcohol with the isomeric 1,2-

Scheme I



1 **2**

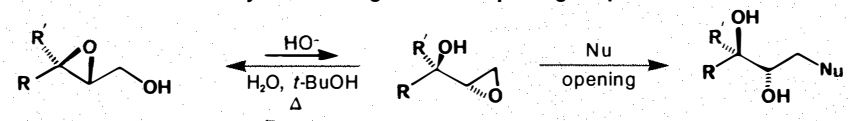
epoxy-3-ol. Although aqueous NaOH is the usual catalyst for the Payne rearrangement, weaker bases such as K_2CO_3 or DBN have also been observed to catalyze the rearrangement.[8] The relative proportions of 1,2- and 2,3-epoxy alcohols at equilibrium are remarkably substrate-dependent, but the germane observations are that primary epoxy alcohols are more stable than secondary epoxy alcohols, and that the *trans* configuration is more favorable than the *cis*.[7,9] Since the Payne rearrangement usually produces a mixture of epoxy alcohols, it has limited preparative value *per se*.

The Payne rearrangement occurs fairly rapidly, and a considerable difference in reaction rates of the isomeric terminal and internal epoxides was anticipated. Therefore, it appears plausible that **4**, which is continuously regenerated *in situ via* the Payne rearrangement of **3**, could be selectively and irreversibly captured by a nucleophile (Nu) as shown in Scheme II.[10] This Payne rearrangement-opening strategy was independently conceived and developed by the Ganem group at Cornell.[11]

The first choice of nucleophile in the Masamune-Sharpless exploration[10] of this concept was PhSNa, but *t*-BuSNa was later found to be even more selective in this application. The 2,3-epoxy alcohol is heated to reflux in aqueous *t*-BuOH in the presence of NaOH, and the mercaptan is slowly introduced over a period of 1-2 hours. A faster rate of addition depletes **4** resulting in increased formation of C-2- and/or C-3-opened products, while a slower rate leads to lower yields attributable to the formation of triol (*via* C-1 opening of **4** by hydroxide). The optimized yields of **5**a and **5b** are 85% and 81%, respectively. This reaction has been applied to many other 2,3-epoxy alcohols, with the yield of 2,3-dihydroxy sulfides ranging from 47-88%.[1c,12,24b] Very recently it was found that simple amines may be superior to thiolates as nucleophiles in the Payne rearrangement-opening sequence.[13] As shown in eqs. 1-3, diethylamine is introduced selectively at the C-1 position of the 2,3-epoxy alcohols in what is clearly a rearrangement-opening process. Probably because alkyl amines are less reactive nucleophiles than alkyl thiolates (RS^-), the undesired ring opening of

Scheme II

Payne Rearrangement — Opening Sequence



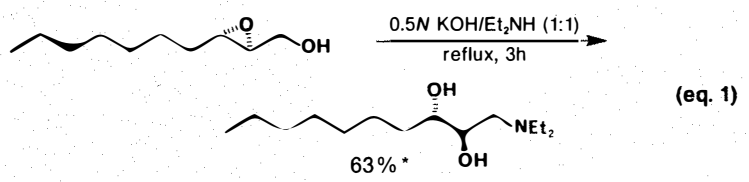
3a R = $BnOCH_2$, R′ = H
3b R = H, R′ = $BnOCH_2$
Bn = $PhCH_2$

Payne rearrangement: HO^-, H_2O, *t*-BuOH, Δ

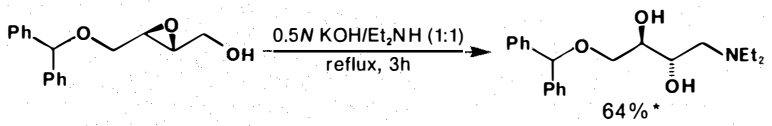
4a R = $BnOCH_2$, R′ = H
4b R = H, R′ = $BnOCH_2$

Nu opening

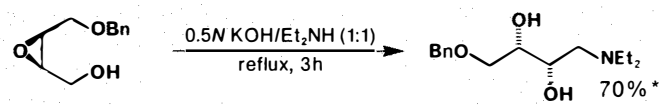
5a R = $BnOCH_2$, R′ = H, Nu = *t*-BuS, 85% yield
5b R = H, R′ = $BnOCH_2$, Nu = *t*-BuS, 81% yield



(eq. 1)



(eq. 2)



(eq. 3)

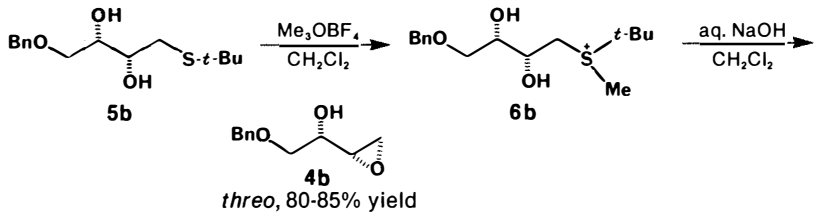
*These yields are not optimized.

the 2,3-epoxy alcohols at the C-3 or C-2 position appears to be less of a problem with amines than with RS^- as the nucleophile. Another noteworthy feature of this discovery is that the uncharged amine, albeit present in great excess, is the successful nucleophile in spite of the presence of the hydroxide ion.

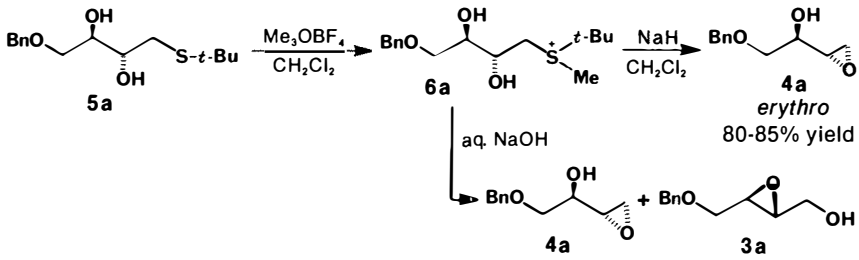
The Payne rearrangement-opening sequence is limited in that many nucleophiles are incompatible with the reaction conditions; almost all organometallic reagents, including cuprates, organolithiums, metal hydrides, etc., are too basic to survive the protic conditions. Furthermore, some reagents (*e.g.*, $NaBH_4$) that can tolerate the reaction conditions only work well with the most favorable epoxy alcohol substrates.[1c] In order to increase the scope of the Payne rearrangement-opening reaction, it is necessary to isolate the terminal epoxy alcohols **4**. The 2,3-dihydroxy sulfides **5** were identified as viable starting materials because their availability from **3** had been demonstrated. The conversion of a 2,3-dihydroxy sulfide to a 1,2-epoxy alcohol is conceptually accomplished by selective *S*-alkylation followed by base-mediated intramolecular elimination as shown in Scheme III.[14] In practice, the reaction of **5b** with Me_3OBF_4 (Meerwein's reagent)[15] afforded the methyl sulfonium salt **6b** as expected. The CH_2Cl_2 solution of the crude reaction mixture was then treated with aqueous NaOH to effect closure to the epoxide **4b** by elimination of *t*-butyl methyl sulfide. As expected, there was no evidence of oxetane formation, and *threo* **4b** was isolated in high yield as a relatively pure oil. In the case of **5a**, the *S*-alkylation with Meerwein's reagent was also efficient (Scheme IV), but attempted sulfonium-salt elimination using aqueous NaOH afforded *erythro* **4a** contaminated with substantial amounts of **3a**.[16] That the *erythro*-1,2-epoxy alcohol is much more sensitive to base-catalyzed rearrangement than the *threo*-1,2-epoxy alcohol is a reflection of the relative stability of the parent *trans*- and *cis*-2,3-epoxy alcohols.[9,17] In order to obtain pure *erythro* **4a** it was necessary to conduct the elimination reaction under non-isomerizing conditions.[7] Thus, treatment of **6a** with NaH in CH_2Cl_2 afforded pure **4a** as a colorless oil in high yield; similar results were obtained with methanolic **Me_4NOH**.[18]

The advantages of this three-step sequence for the rearrangement of a 2,3-epoxy alcohol to the 1,2-epoxy alcohol *via* a 2,3-dihydroxy-1-sulfide (diol sulfide route) are illustrated in Scheme V, in which a series of high-yield ring-opening reactions of both *erythro*- and *threo*-1,2-epoxy alcohols **4** is presented. Consider eq. 4, in which NaN_3 is introduced at C-1. Earlier we reported that NaNHTs reacts with **3b** in refluxing aq. *t*-BuOH in the presence of NaOH to give a 61% yield of the corresponding *threo*-2,3-dihydroxy-1-toluenesulfonamide.[1c] Sodium azide is not an effective substitute for NaNHTs in the Payne rearrangement-opening sequence. However, under non-isomerizing conditions azide is an excellent nucleophile for the ring opening of 1,2-epoxy-3-ols. This indirect route for substituting nitrogen at C-1 also has the advantages of substrate generality[19] and the fact that azides may be reduced to primary amines under a variety of mild conditions in near-quantitative yield, while the deprotection of a toluenesulfonamide is much more difficult. The $NaBH_4$ reduction of 2,3-epoxy alcohols under Payne rearrangement-opening conditions is only reliable for certain *cis*-epoxy alcohols.[1c] With

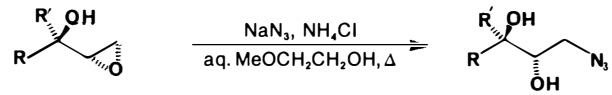
Scheme III



Scheme IV

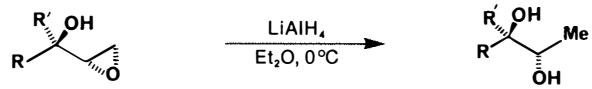


Scheme V



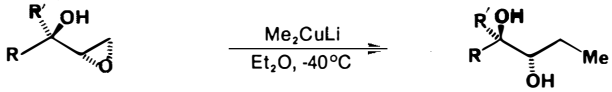
(eq. 4)

4a R = $BnOCH_2$, R′ = H (*erythro*) — **7a** 91% yield
4b R = H, R′ = $BnOCH_2$ (*threo*) — **7b** 83% yield



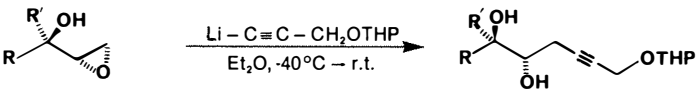
(eq. 5)

4a R = $BnOCH_2$, R′ = H (*erythro*) — **8a** 83% yield
4b R = H, R′ = $BnOCH_2$ (*threo*) — **8b** 84% yield



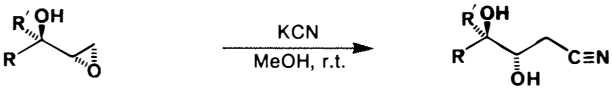
(eq. 6)

4a R = $BnOCH_2$, R′ = H (*erythro*) — **9a** 74% yield
4b R = H, R′ = $BnOCH_2$ (*threo*) — **9b** 75% yield



(eq. 7)

4a R = $BnOCH_2$, R′ = H (*erythro*) — **10a** 63% yield
4b R = H, R′ = $BnOCH_2$ (*threo*) — **10b** 55% yield



(eq. 8)

4a R = $BnOCH_2$, R′ = H (*erythro*) — **11a** 50% yield
4b R = H, R′ = $BnOCH_2$ (*threo*) — **11b** 89% yield

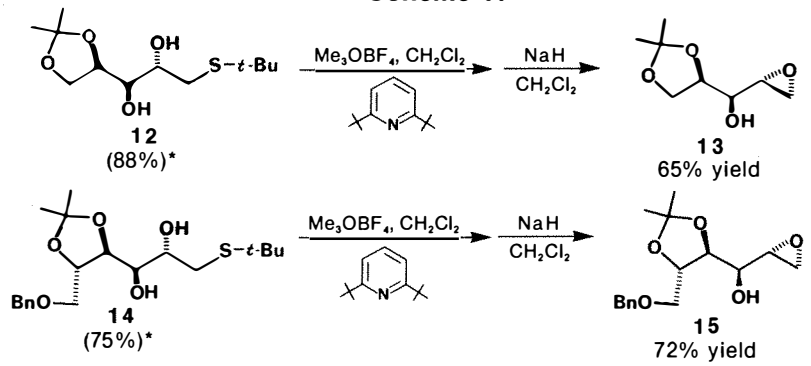
most 2,3-epoxy alcohols, reduction with $NaBH_4$ under isomerizing conditions leads to a mixture of 1,2-, 1,3-, and 2,3-diols. In contrast, Red-Al® has been recognized as an extremely selective reagent for the reduction of 2,3-epoxy alcohols at C-2 to yield 1,3-diols exclusively.[20] In this reaction a mechanism involving intramolecular delivery of the hydride has been proposed to account for the very high selectivities observed. The LAH reduction of 1,2-epoxy alcohols at C-1 affords 2,3-diols (eq. 5), nicely complementing the Red-Al reaction. The remaining examples (eqs. 6-8) illustrate some of the types of carbon-carbon bond-forming reactions that may be useful in the synthesis of complex natural products; especially interesting is eq. 7.[21] Convenient entry to the higher internal deoxy sugars from **10** is anticipated by deprotection and reduction to the *E* or *Z* allylic alcohol followed by an asymmetric epoxidation as previously described.[12]

When applying this new epoxide-isomerization sequence to acid-sensitive substrates such as **12** and **14** (Scheme VI), it proved essential to buffer (using 2,6-di-*tert*-butylpyridine) the *S*-alkylation step or adventitious acid, produced by or introduced with the Meerwein's reagent, wreaked havoc upon the acetonide protecting groups. Using this modification, the *S*-alkylation of **12** and **14** was straightforward. Subsequent elimination using NaH in CH_2Cl_2 proceeded uneventfully to afford epoxy alcohols **13** and **15** in good yield. This buffered procedure is important since the reiterative method for the construction of homochiral polyhydroxylated compounds depends critically upon the properties of the acetonide protecting group.[12,22]

As just described, the diol sulfide route is ideal for the rearrangement of certain 2,3-epoxy alcohols to the 1,2-epoxy alcohols. For the diol sulfide route to work well, two requirements must be met. First, the substituents on the 2,3-epoxy alcohol moiety must be inert to both NaOH and *t*-BuSNa at 75°C. Second, the 2,3-epoxy alcohol must bear an alkoxy substituent at C-4. The latter arises from a consideration of the first step of the diol sulfide route. The isolated yield of 2,3-dihydroxy sulfide obtained in the Payne rearrangement-opening sequence with simple hydrocarbon 2,3-epoxy alcohols (*i.e.*, those not bearing an alkoxy substituent at C-4) can fall to 47% due to the formation of substantial amounts of C-3 and C-2 ring-opened isomers. A C-4 alkoxy substituent suppresses these side reactions and affords a greater yield of the C-1 ring-opened isomer.[24b]

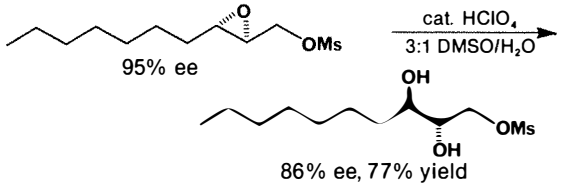
•Registered trademark of Aldrich Chemical Co., Inc.

Scheme VI

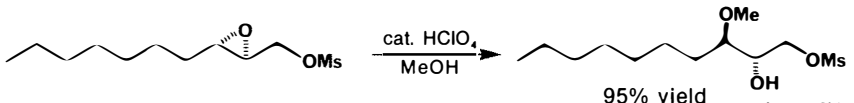


*Signifies yield from the 2,3-epoxy alcohol in the rearrangement-opening step.

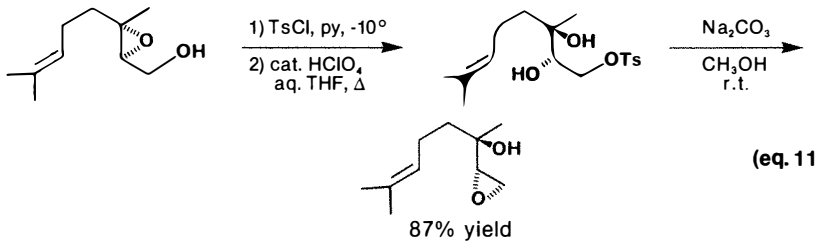
In an alternate route for the rearrangement of 2,3-epoxy alcohols, latent reactivity at the C-1 position is unveiled by conversion of the C-1 hydroxyl into a leaving group such as mesylate or tosylate. Under basic conditions, the reaction of 2,3-epoxy-1-sulfonate esters with nucleophiles generally results in the selective displacement of the sulfonate ester, leaving the epoxide unit intact.[1c,23] However, under acidic conditions the 2,3-epoxy-1-sulfonates may be regioselectively (C-3 opening) and stereospecifically (inversion at C-3) solvolyzed as shown in eqs. 9-11. These compounds may then be treated with mild base to eliminate the sulfonate ester group (eqs. 11-13), giving the desired 1,2-epoxy-3-ol. It should be apparent that the success of this diol sulfonate route for the synthesis of homochiral 1,2-epoxy alcohols depends critically upon the regioselectivity in the epoxide-opening step, since ring opening at C-3 leads to one 2,3-diol whereas ring opening at C-2 leads to its antipode. Thus, the high enantiomeric excess obtained in the asymmetric epoxidation step will be diminished



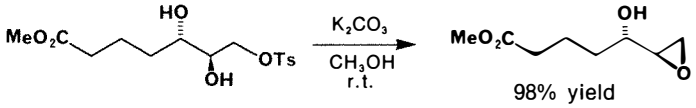
(eq. 9)[24a]



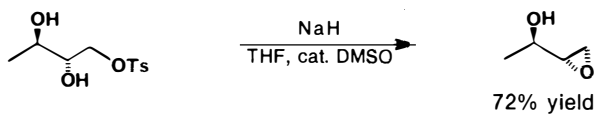
(eq. 10)[24a]



(eq. 11)[25a]



(eq. 12)[25b]



(eq. 13)[25c]

unless the epoxide hydrolysis is highly regioselective. Fortunately, in one carefully examined case, the C-3 : C-2 regioselectivity was at least 15 to 1. This was determined by the application of both the diol sulfonate and the diol sulfide routes to a sample of optically active (95% ee) (2*S*,3*S*)-2,3-epoxy-1-decanol as shown in Scheme VII. The diol sulfonate route (using **MsCl**) gave a 77% overall yield of 2,3-dihydroxy-1-mesylate. This compound was estimated to have an ee of *ca.* 86% by shift reagent NMR studies on the corresponding diacetate. This enantiomeric purity requires that the regioselectivity of the epoxide hydrolysis be at least 15 : 1. That the epoxide hydrolysis in this case occurs at C-3 (with inversion) was demonstrated by the conversion of the 2,3-dihydroxy mesylate to the 1,2-epoxy alcohol. This compound has an almost equal but opposite rotation to the 1,2-epoxy alcohol that is obtained stereospecifically from the same (95% ee) (2*S*,3*S*)-2,3-epoxy-1-decanol by a Payne rearrangement-opening sequence with ***t*-BuSH**.

The diol sulfonate route for the rearrangement of 2,3-epoxy alcohols to 1,2-epoxy alcohols requires reaction conditions and substrates which nicely complement those of the diol sulfide route. Thus, substituents on the 2,3-epoxy alcohol moiety must be resistant to fairly acidic conditions. In addition, the 2,3-epoxy alcohol must be free of any steric and/or electronic influences which disfavor ring opening at C-3. For this reason, a C-4 alkoxy substituent on the 2,3-epoxy alcohol would be detrimental to the enantioselectivity of the diol sulfonate route. It is interesting to note that in contrast to the diol sulfonate route, the diol sulfide route is not subject to a loss of enantiomeric purity due to a nonregioselective epoxide opening. A regioselectivity problem in the diol sulfide route leads to different substances (regioisomers instead of enantiomers) which are usually separable by flash chromatography. Another difference between the two routes is that they give opposite enantiomers of the 1,2-epoxy-3-ol from the same homochiral 2,3-epoxy alcohol (Scheme VII).

In summary, the stereospecific rearrangement of a 2,3-epoxy alcohol to the 1,2-epoxy-3-ol is a very important transformation because it makes a broad range of compounds accessible from a single 2,3-epoxy alcohol precursor. The two complementary methods presented above should allow this desirable conversion with a considerable variety of substrates.

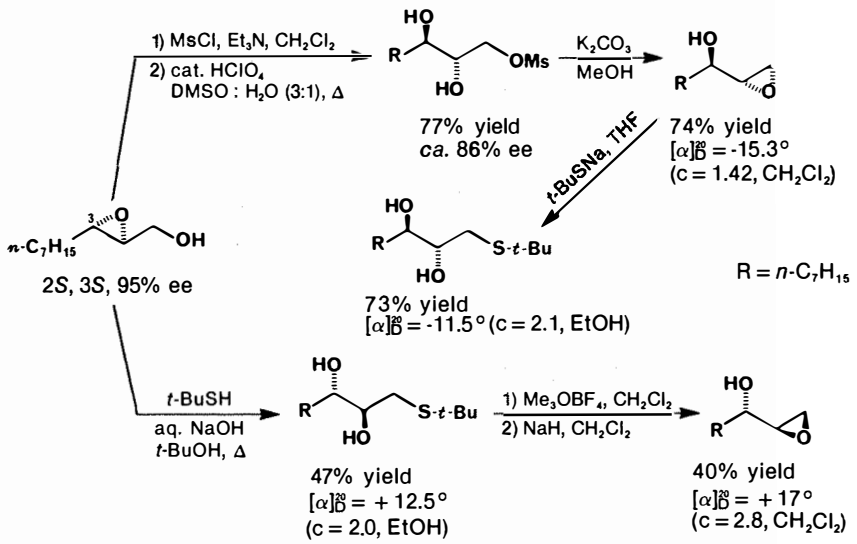
3. INTERNAL EPOXIDES

3.1 General Considerations on Steric and Electronic Effects in Epoxide-Opening Reactions

There is a general consensus that for internal epoxides the site of nucleophilic attack depends collectively on steric, electronic, and conformational effects. Conformational analysis in epoxide-opening reactions is usually restricted to the cyclohexane oxides and the epoxy sugars in which the epoxide is fused to the pyranose ring. With rare exception these epoxides are subject to highly selective *trans*-diaxial nucleophilic ring opening, dissonant steric and/or electronic effects notwithstanding. On the other hand, the conformational factors that affect the regioselectivity of the ring-opening reactions of acyclic epoxides are poorly understood and are generally weak. In these epoxides, substituent steric effects seem to dominate the regioselectivity exhibited by external nucleophiles. However, in some cases (*e.g.*, certain 2,3-epoxy alcohols), we are finding that the substituent steric effects often nearly cancel each other, and that the substituent electronic effects emerge as important factors influencing the regioselectivity exhibited by external nucleophiles.

Most S_N2 reactions are retarded by the presence of inductive electron-withdrawing substituents.[26] This is illustrated by several well known relative-rate studies (Schemes VIII-IX) in which substrates bearing such groups react with nucleophiles slower than comparably hindered model compounds.[27–29] This effect of electron-withdrawing substituents implies that the central carbon atom is more electron-deficient in the S_N2 transition state than in the ground state. It is interesting to note that the rate of pyramidal inversion of amines is also lowered by the presence of inductive electron-withdrawing groups.[30] On the basis of inductive electronic effects alone, functionalized epoxides should be opened by external nucleophiles regioselectively at the distal carbon atom if the functional group is electron-withdrawing. For example, the epoxy crotyl ether **16** is selectively opened at C-3 (eq. 14) by isopropylamine.[31] Another example is found in the highly selective solvolysis of 1,1,1-trifluoro-2,3-epoxybutane (**18**) in ethanol (eq. 15) to give 1,1,1-trifluoro-2-hydroxy-3-ethoxybutane (**19**) as the exclusive ($\geq$250 : 1) product.[32]

Scheme VII



Scheme VIII

		Relative rate[27]
Me–Br	PhSNa, MeOH, 0°C	1.0
Cl–Br	PhSNa, MeOH, 0°C	0.19
F–Br	PhSNa, MeOH, 0°C	0.16

Scheme IX

		Relative rate[28]
Me–Cl	KI, acetone, 75°C	1.0
CF_3–Br	KI, acetone, 75°C	0.00016
CF_3–OTs	KI, acetone, 75°C	0.00007

The simplest explanation for the observed regioselectivity in these reactions is that the electron-withdrawing inductive effect of the heteroatom(s) deactivates the proximate carbon atom of the epoxide for nucleophilic attack. In this connection, we interject the somewhat amusing observa-

tion that the epoxide group itself probably owes its very existence to this electron-withdrawing heteroatom inductive effect. That is, if it were not for the mutually deactivating (*i.e.*, stabilizing) effect of the adjacent C-O bonds inherent in the epoxide structure, the strain energy might well render the ring unstable to spontaneous, heterolytic opening at or below room temperature.

In contrast, resonance-donating substituents tend to promote S_N2 reactions because they are capable of effectively stabilizing the incipient partial positive charge on the carbon undergoing nucleophilic attack. Epoxides bearing resonance-donating substituents are often (but not always) opened at the proximate carbon atom, especially under acidic reaction conditions. But even under basic conditions, resonance stabilization of an adjacent incipient partial positive charge can outweigh steric and/or electron-withdrawing inductive effects in direct external nucleophilic ring-opening reactions. For example, each of the ring openings depicted in eqs. 16-18 cannot be explained by steric or electron-withdrawing inductive effects. In each case, resonance effects appear to be the dominant factor.

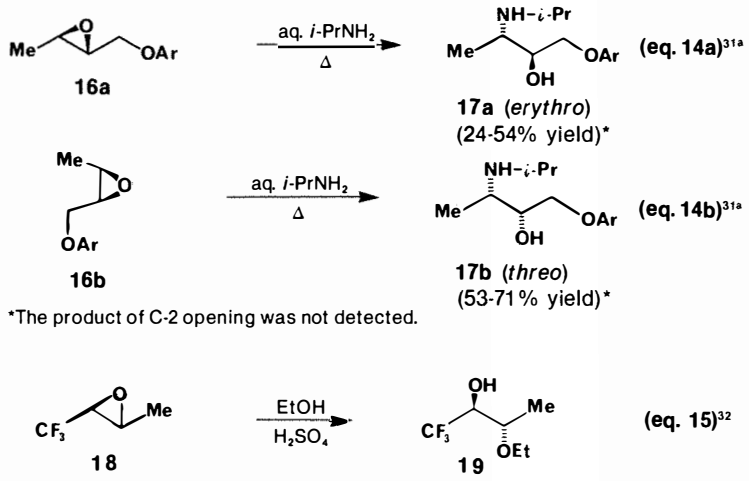
The effect of a carbonyl-containing functional group on nucleophilic substitution reactions at the adjacent carbon atom is quite dramatic. For example, it is well known that displacement reactions proceed faster (*ca.* 10^4 times) with acyl and phenacyl chloride than with *n*-butyl chloride. Ethyl chloroacetate is not as reactive as phenacyl chloride, but still reacts *ca.* 1700 times faster than *n*-butyl chloride.[28,35,36] Interestingly, we have noted (*vide infra*) that 2,3-epoxy amides show a high selectivity for C-2 ring opening with soft thiolate (RS^-) nucleophiles. This may be an example of the acyl type of activation influencing an epoxide ring-opening reaction. However, harder nucleophiles (especially amines) have been demonstrated to open 2,3-epoxy amides selectively at C-3. In these cases the acyl type activation does not appear to be operative.

Clearly a great deal of work is needed before these nucleophilic epoxide-opening reactions are well understood. However, in the remainder of this article we wish to convey our present level of understanding of the factors affecting the regioselectivity of these processes.

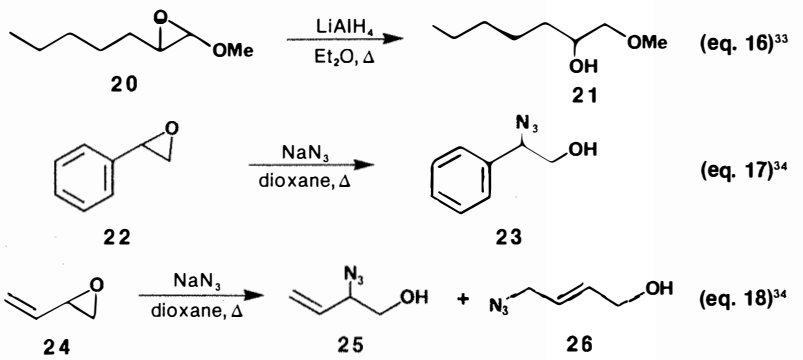
3.2 2,3-Epoxy Alcohols

Regiocontrol in the ring-opening reactions of 3-monosubstituted-2,3-epoxy alcohols is of considerable interest. As reliable, regioselective nucleophilic ring-opening procedures for these compounds become available, their utility as building blocks in organic synthesis will be greatly enhanced. One reliable means of regioselective ring opening utilizes the C-1 hydroxyl group as a point of attachment for internal nucleophiles. This strategy has been explored with great success by several research groups.[20,37] These intramolecular methods (Scheme XII) enable extremely selective nucleophilic substitution at the C-2 position. Derivatization of a 2,3-epoxy alcohol with a chloroformate or an isocyanate (eq. 19), followed by acid-catalyzed ring opening of the epoxide at C-2 by the carbonyl oxygen atom yields a 5-membered cyclic carbonate. Similarly, treatment of an epoxy alcohol with an isocyanate (eq. 20), followed by intramolecular base-catalyzed epoxide opening at C-2, affords a 5-membered cyclic urethane. In fact, this process can be performed as a one-pot operation by treatment of the epoxy alcohol with an isocyanate and NaH in THF.[37e] Although $LiAlH_4$ and DIBAL-H do not appear to be influenced

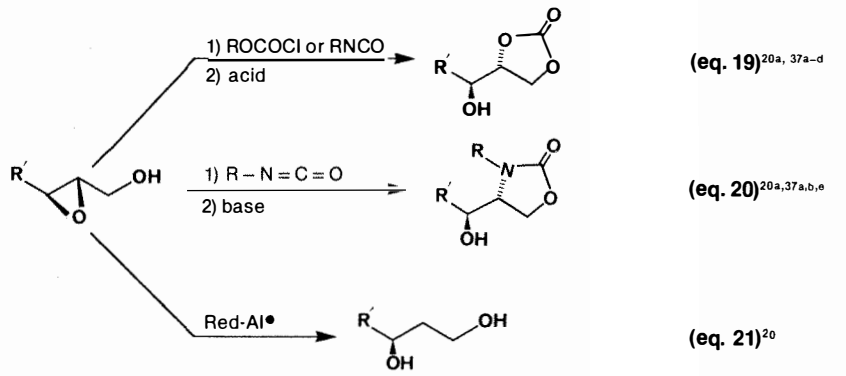
Scheme X



Scheme XI



Scheme XII



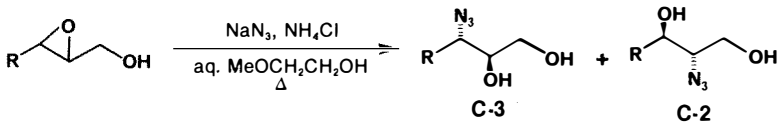
by hydroxyl-directing effects,[20c,d,38] the aforementioned (Section 2) Red-Al reduction of 2,3-epoxy alcohols to 1,3-diols (eq. 21) is thought to be another example of an intramolecular opening of 2,3-epoxy alcohols at C-2. Hydroxyl-directing effects have been implicated in the ring-opening reaction of 2,3-epoxy alcohols with other nucleophiles as well.[39,40]

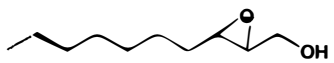
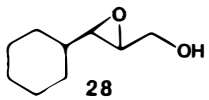
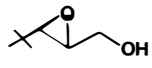
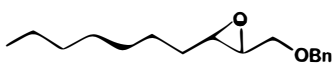
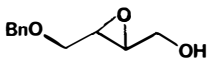
Although the intramolecular epoxide-opening reactions of 2,3-epoxy alcohols are quite selective, the range of nucleophiles that may be employed is restricted by the requirement that there be a means of attachment available. Intermolecular nucleophilic ring opening of 2,3-epoxy alcohols promises to be more versatile than the intramolecular method. For example, ring opening with dialkyl cuprates is an extremely useful reaction that has been the subject of considerable research. For the most part, dialkyl cuprates appear to open 2,3-epoxy alcohols at the least hindered position or non-selectively in the case where C-2 and C-3 are comparably hindered. These results, as well as results from the reactions of cuprates with 2,3-epoxy ethers and other miscellaneous epoxides, suggest that steric factors are decisive in determining the regioselectivity of the cuprate-addition reaction.[1c,3c,41] However, in some instances regioselective cuprate opening reactions are observed even in the absence of a significant steric bias for ring opening at either C-2 or C-3.[42] In contrast to dialkyl cuprates, organoaluminum reagents[21c,42a,43] and amines[31] appear to open 2,3-epoxy alcohols and ethers reliably at C-3 in substrates where there is presumably very little difference between the steric hindrance at C-2 and C-3.

We have been especially interested in the ring-opening reactions of *trans*-3-monosubstituted-2,3-epoxy alcohols that are available by asymmetric epoxidation of *trans*-3-monosubstituted-2-propenols. These 2,3-epoxy alcohols are internal epoxides and, as discussed in Section 3.1, the regioselectivity exhibited in the intermolecular nucleophilic ring opening of internal epoxides reflects the combination of the steric and electronic effects of all of the epoxide substituents. For all 2,3-epoxy alcohols, a common feature in the collective substituent-directing effects is the electronic deactivation of the C-2 carbon atom by the electron-withdrawing inductive effect of the C-1 hydroxyl group. This C-2 deactivation is responsible for the modest tendency toward regioselective nucleophilic ring opening at C-3 in simple 3-monosubstituted-2,3-epoxy alcohols. We have already seen (eq. 9) how conversion of the C-1 hydroxyl to the more strongly electron-withdrawing sulfonate ester can enhance regioselective opening at C-3. In order to examine this C-3 directing effect more closely, the ring-opening reaction of a series of 3-monosubstituted-2,3-epoxy alcohols with NH_4N_3 was performed, and the results are presented in Scheme XIII. From a comparison of the regioselectivities observed it is possible to qualitatively assess the relative importance of steric and electronic effects on regioselectivity. In the progression from compound **27** to **29** the steric hindrance at C-3 increases. The C-2 and C-3 positions of **27** are comparably hindered, but the ratio of C-3 to C-2 ring opening is 3.5 to 1.[44] The C-3 position in **28** is more hindered than that in **27**, but preferential C-3 opening is still obtained, although the C-3 : C-2 ratio has decreased to 1.7 to 1. These results are consistent with an electronic deactivation of the C-2 position by the C-1 hydroxyl group. This electronic deactivation effect is admittedly not very potent (at least when N_3^- is the nucleophile) and fails to cause any neopentyl substitution, as the ring-opening reaction of **29** occurs exclusively at C-2. This is not surprising, since neopentyl substitution is difficult to achieve under any circumstance.[45] It is unlikely that intramolecular hydroxyl-directing effects have much influence on the selectivities observed in the ring opening of 2,3-epoxy alcohols with NH_4N_3. The C-3 : C-2 ratio for opening of **30** parallels that of the parent epoxy alcohol **27**. In another control experiment, 2,3-epoxy alcohol **31**, with comparable steric *and* electronic environments at C-2 and C-3, is opened nonselectively (1 : 1) by NH_4N_3.

Clearly the C-3 selectivity exhibited in the ring-opening reactions of 2,3-epoxy alcohols will vanish if C-3 bears a substituent that is not only sterically demanding but capable of exerting an electron-withdrawing inductive effect as well. Although the C-2 : C-3 ratio for ring opening of **32** (see Scheme XIV) with NH_4N_3 is low (2 : 1), 32 is one of the least hindered representatives of the family of 4-alkoxy-2,3-epoxy alcohols. The epoxy alcohols **34a-d**, available from D-glyceraldehyde as previously described,[12] are better model compounds for the highly oxygenated 2,3-epoxy alcohols that are normally encountered in the synthesis of polyhydroxylated natural products *via* the asymmetric epoxidation method. The selectivity for ring opening at C-2 in **34a-e** is greater than that in **32**. Treatment of **34a-e** with NH_4N_3 affords *ca.* 85-90% yields of the corresponding ring-opened products **35a-e**. The C-2 : C-3 ratios are found to be between 7 and 15 to 1 as determined by NMR analysis of the crude reaction mixtures both before and after peracetylation. The origin of the increased C-2 selectivity observed in compounds **34a-e** as compared to **32** is not entirely clear. Certainly an acetonide is a more sterically demanding protecting group than a methyl ether. In addition, the synergistic

Scheme XIII



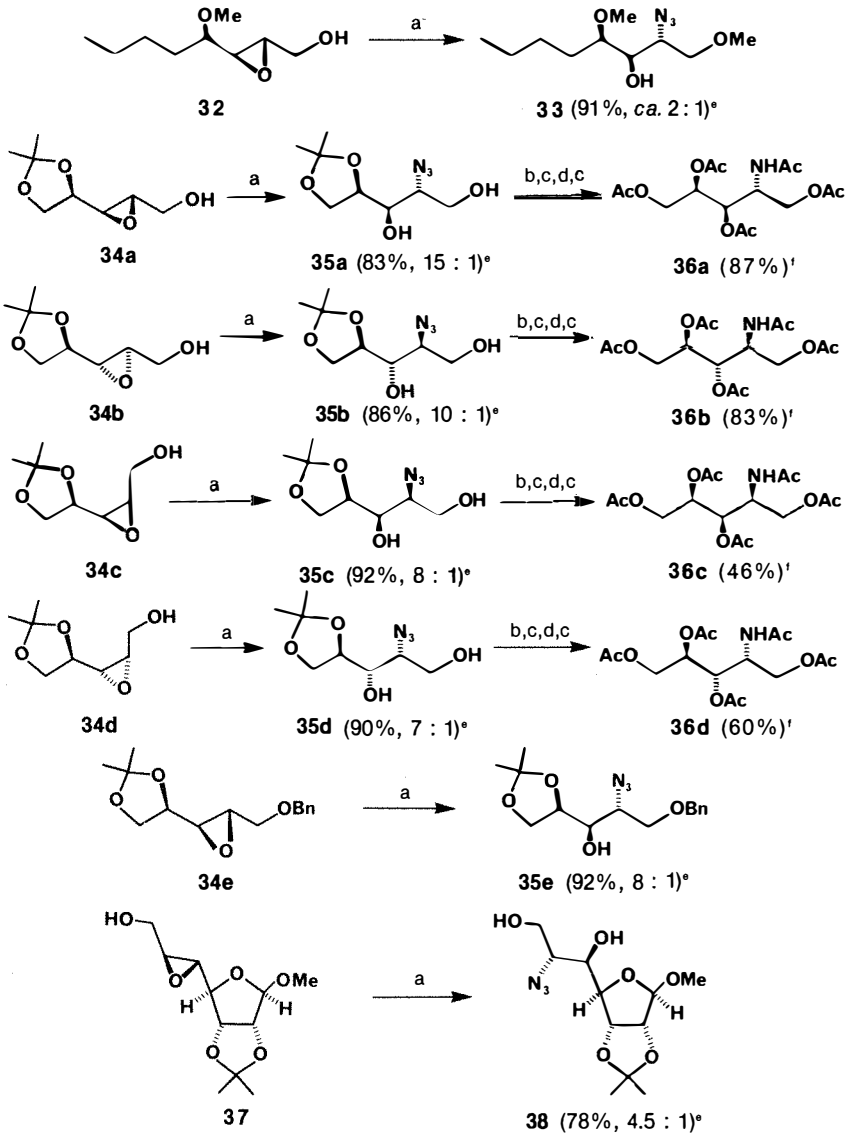
Substrate	% Yield, C-3 : C-2
 **27**	88%, 3.5 : 1
 **28**	93%, 1.7 : 1
 **29**	47%, C-2 only
 **30**	98%, 4.5 : 1
 **31**	95%, 1 : 1

electron-withdrawing inductive effect of the two oxygen atoms (on C-4 and C-5) of **34a-e** may be a more effective deterrent to nucleophilic ring opening at C-3 than the lone oxygen atom (on C-4) of **32**. However, we have found that the C-2 : C-3 ratio for ring opening of **37** with NH_4N_3 under identical conditions proceeds with an unusually low (4.5 : 1) selectivity for such a highly oxygenated 2,3-epoxy alcohol.

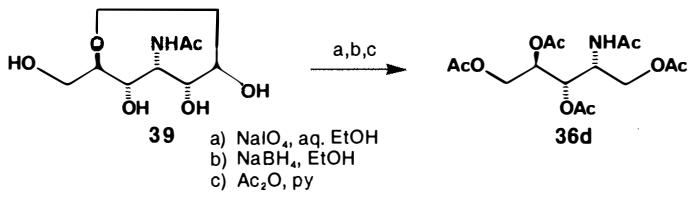
Ring opening of 2,3-epoxy alcohols with NH_4N_3, like base-catalyzed intramolecular opening of epoxides,[20a,37a-c] is expected to find applications in the synthesis of certain amino sugars. For example, compounds **35a-d** (Scheme XIV) are precursors to the four diastereomeric 2-amino-2-deoxy-D-pentitols. Reduction of the azide group with H_2 (catalyzed by Pd/C in methanol) followed by peracetylation with acetic anhydride/pyridine leads to the corresponding acetonide triacetates.[46] The acetonide protecting group is readily cleaved in aqueous methanol in the presence of 50X8-200 Dowex acidic resin. A second peracetylation affords the pentaacetates of the 2-amino-2-deoxy-D-pentitols (*i.e.*, **36a-d**) in good overall yield. An independent synthesis (Scheme XV) of **36d** starting from the commercially available 3-acetamido-3-deoxy-D-glucose (**39**) by sequential periodate oxidation,[47] borohydride reduction, and peracetylation establishes that the azide opening reaction of **34d** proceeds with the expected inversion of configuration at C-2.

The efficacy of steric and electronic influences on the regioselectivity of nucleophilic ring opening of 2,3-epoxy alcohols depends upon the nucleophile that is employed. For purposes of comparison, the selectivities for the ring-opening reactions of a series of 2,3-epoxy alcohols with PhSNa are presented in Scheme XVI. The regioselectivity observed in **27** through **29** with PhSNa parallels the regioselectivity established for the same epoxy alcohols with NH_4N_3. The 2,3-epoxy alcohols **34a,c,d** and epoxy ether **34e** are selectively opened with PhSNa at C-2 in a greater than 10 : 1 ratio. Similarly, **34a** is opened with PhSeNa ($NaHCO_3$ as a buffer) with a regioselectivity of about 10 : 1. The C-3 selectivity in the ring opening of **27** and **28** with PhSNa is somewhat lower than that obtained with azide. At the same time, the C-2 selectivity in **34a,c-e** with PhSNa (and PhSeNa) is at least as great as that with NH_4N_3. What appears to be a greater sensitivity (of thiolate nucleophiles) to steric than to electronic effects has been observed in other epoxide-opening reactions as well.[48]

Scheme XIV

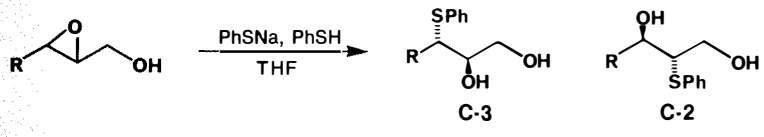


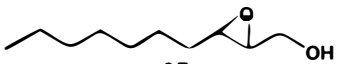
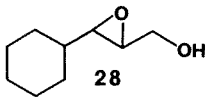
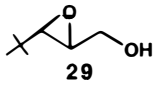
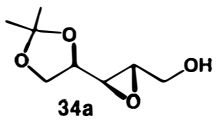
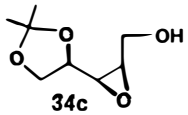
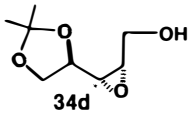
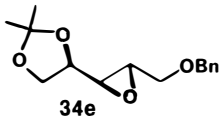
Scheme XV



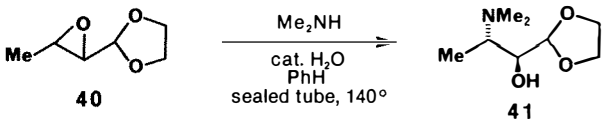
Regioselective ring opening of 2,3-epoxy alcohols described in Section 3.2 is a delicate balance of steric and electronic effects. Although modest to good C-3 selectivity (with external nucleophiles) is observed for some 3-monosubstituted-2,3-epoxy alcohols in which the C-3 substituent is a simple alkyl group, C-2 selectivity is obtained for epoxy alcohols such as **34a-d** in which the C-3 substituent is both sterically demanding and electron-withdrawing. Since the intramolecular nucleophilic ring opening of various derivatives of 2,3-epoxy

Scheme XVI



Substrate	% Yield, C-3 : C-2
 **27**	~80%, 2.5 : 1
 **28**	69%, 1 : 1
 **29**	76%, C-2 only
 **34a**	76%, C-2 only
 **34c**	67%, *ca.* 1 : 10
 **34d**	64%, *ca.* 1 : 10
 **34e**	~80%, *ca.* 1 : 10*

*Reaction conducted in DMF

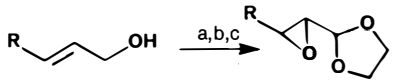


40 → **41** (eq. 22)[49]

alcohols also occur regioselectively at C-2, it has not been possible to introduce nucleophiles directly into the C-3 position of many 2,3-epoxy alcohols. However, derivatives of 2,3-epoxy alcohols, in which the hydroxymethyl group is replaced by a more sterically demanding and/or more electron-withdrawing functional group, are expected to exhibit a greater selectivity for ring opening at C-3 than the parent 2,3-epoxy alcohols. One obvious replacement for the hydroxymethyl group that might serve to increase the C-3 selectivity is one having a higher oxidation level than an alcohol. This section is concerned with the ring opening of 2,3-epoxides in which C-1 is at the aldehyde oxidation level (*i.e.*, 2,3-epoxy aldehydes). Section 3.4 is concerned with the ring opening of 2,3-epoxides in which C-1 is at the carboxylic acid oxidation level (*i.e.*, 2,3-epoxy acids).

2,3-Epoxy aldehydes are readily prepared by oxidation of the parent 2,3-epoxy alcohol. They are often difficult to purify, so it is not uncommon to use them immediately with little or no purification, in the subsequent synthetic step. We did not examine the nucleophilic ring opening of these 2,3-epoxy aldehydes, partly because they are difficult to work with and partly because the acetal derivative of the C-1 aldehyde was expected to be a more effective C-3 directing group than the parent aldehyde. There is extensive literature concerning nucleophilic ring opening of carbohydrate epoxy acetals, especially 2,3-anhydropyranosides.[lh] Unfortunately, the steric and electronic effects of the acetal functional group in these compounds are obscured by the strong preference for *trans*-diaxial opening of these epoxides. However, the potential utility of the acetal functional group as a regiochemical control element for nucleophilic opening reactions of acyclic epoxides is suggested by the forty-year-old example of selective ring opening of **40** (eq. 22) at C-3 with dimethylamine.[49]

Scheme XVII

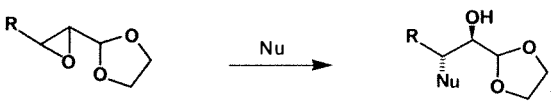


42 R = *n*-C_7H_{15} **43** R = *n*-C_7H_{15}
44 R = $BnOCH_2$ **45** R = $BnOCH_2$

a) PCC, 3Å Molecular sieves (powder), CH_2Cl_2, r.t.
b) $HOCH_2CH_2OH$, TsOH, PhH, azeotropic distillation
c) MCPBA, CH_2Cl_2, r.t.

Initially, the 2,3-epoxy acetals **43** and **45** were obtained in racemic form from the corresponding allylic alcohol by PCC oxidation to the α,β-unsaturated aldehyde, acid-catalyzed acetalization of the aldehyde with ethylene glycol, and finally MCPBA oxidation to the desired product (Scheme XVII). As shown in Scheme XVIII, these 2,3-epoxy acetals were opened highly regioselectively at C-3 with a variety of nucleophiles. Thus $LiAlH_4$, NH_4N_3, PhSNa and Me_2CuLi all react with **43**, to our limits of detection, only at C-3. The C-3 selectivity in epoxy acetal **43** is therefore much greater than in the corresponding epoxy alcohol **27**

Scheme XVIII



43 R = *n*-C_7H_{15}
45 R = $BnOCH_2$

C-3

Substrate	Reaction conditions	C-3-Opened product (Nu, % yield)*
43	$LiAlH_4$, Et_2O, 0°C	(H, 83%)
43	NaN_3, NH_4Cl, aq. THF : $MeOCH_2CH_2OH$	(N_3, 72%)
43	PhSNa, PhSH, THF, Δ	(PhS, 76%)
43	Me_2CuLi, Et_2O, -40°C	(Me, 81%)
45	Me_2CuLi, Et_2O, -40°C	(Me, 71%)

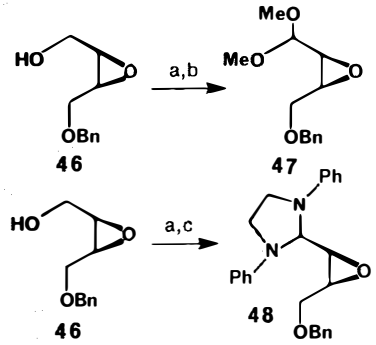
*No C-2 products were detected.

or the epoxy ether **30**. Ring opening of **45** with Me_2CuLi also occurs at the C-3 position. This contrasts to the selective cuprate ring opening of epoxy alcohol **31** at C-2 under similar reaction conditions.[42a,b]

Although the selective ring opening of 2,3-epoxy acetals at C-3 is a potentially useful transformation, it would be of much greater utility if the acetals were derived from homochiral 2,3-epoxy alcohols rather than the racemic substances shown in Scheme XVII. Oxidation of the 2,3-epoxy alcohol **46** (Scheme XIX) to the corresponding 2,3-epoxy aldehyde is readily accomplished.[50] However, acetalization proved to be very difficult. Several methods were tried without success, including the standard acid-catalyzed acetalization with azeotropic removal of water and two silicon-based methods.[51] In all cases concomitant acid-catalyzed epoxide opening was found to be a serious problem. At present the most successful method is to dissolve the 2,3-epoxy aldehyde in anhydrous methanol in the presence of anhydrous $CuSO_4$ and acetic acid, which function as desiccant and catalyst, respectively.[52] This procedure affords a mixture of products from which a **40%** yield of the 2,3-epoxy acetal **47** and a **14%** yield of the corresponding C-3-opened epoxide-methanolysis product can be obtained. The inefficiency of this reaction prompted us to consider an imidazoline protecting group for the C-1 aldehyde.

Reaction of *N,N'*-diphenylethylenediamine (Wanzlick's reagent) with 2,3-epoxy aldehyde **46** in methanol under acid catalysis affords the 2,3-epoxy imidazoline **48** in **60%** yield following chromatography. However, in preliminary experiments the C-3 selectivity in the ring opening of **48** with either $LiAlH_4$ or Me_2CuLi is not as high as the C-3 selectivity in the corresponding ring opening of **45** and **47**.

Scheme XIX

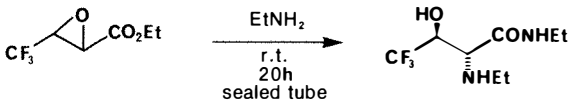


a) PCC, 3 Å Molecular sieves (powder), CH_2Cl_2, r.t.
b) anhydrous $CuSO_4$, HOAc, MeOH
c) $PhNHCH_2CH_2NHPh$, HOAc, MeOH

3.4 2,3-Epoxy Esters and Amides

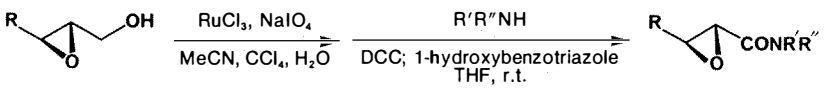
In the search for derivatives of 2,3-epoxy alcohols that are selectively opened at C-3 by external nucleophiles, the tactic of oxidation of the C-1 carbon to the aldehyde oxidation level (Section 3.3) has a logical extension in further oxidation to the carboxylic acid oxidation level. There have been numerous literature reports of ring-opening reactions of 2,3-epoxy acids (*i.e.*, glycidic acids), esters, and amides. These reports demonstrate that the regioselectivity of the ring opening is dependent on both the nature of the glycidic acid derivative and on the type of nucleophile employed. Thus, 2,3-epoxy esters are opened selectively at C-3 by trialkylaluminum and alkyl aluminate reagents,[48b,53] pyridinium fluoride,[54] and aniline.[55] The reaction of Me_2CuLi with ethyl 2,3-epoxycrotonate is unusual in that the major product is the result of epoxide opening at the C-2 position.[56] Ring opening of 2,3-epoxy amides occurs with high selectivity for C-3 with amine nucleophiles.[55,57] There are many examples of the very selective reaction of amines with 2,3-epoxy esters to give 3-amino-2-hydroxy carboxamides.[57a,b,c,e] However, most of these must actually be considered as selective C-3 ring-opening reactions of 2,3-epoxy amides because ester aminolysis occurs prior to epoxide cleavage in almost all cases. The only example in which a 2,3-epoxy amide is selectively opened at C-2 by an amine is shown in eq. 23.[58] Since ring opening of 2,3-epoxy amides with amines is known to occur selectively at C-3, even when C-3 is substantially more hindered than C-2,[59] the ability of a trifluoromethyl group to influence the regioselectivity of nucleophilic epoxide-opening reactions is quite impressive. Unfortunately, the trifluoromethyl group (which is also at the carboxylic acid oxidation level) is not easy to introduce to or remove from organic compounds in a selective fashion.

2,3-Epoxy amides may be conveniently prepared from the corresponding epoxy alcohols using the two-step procedure depicted in Scheme XX. The 2,3-epoxy alcohols are readily oxidized to 2,3-epoxy acids with RuO_4 in the improved $CH_3CN : CCl_4 : H_2O$ solvent system.[60] In one case, this is the only method among many tried which effected the desired transformation.[61] The 2,3-epoxy acid is then coupled with an amine using DCC and 1-hydroxybenzotriazole as catalyst.[62,57f] The results of ring opening of some 2,3-epoxy amides with NaN_3 in the presence of $MgSO_4$ [subsequently indicated as $Mg(N_3)_2$] are presented in Scheme XXI. Compounds **49a** and **49b** afford the C-3 and C-2 ring-opened products in a ratio of *ca.* 10 to 1. As expected, the C-3 : C-2 ratio is smaller (*ca.* 6 : 1) in the ring opening of the more hindered epoxy amide **49c**. Selective opening of a 2,3-epoxy amide at C-3 with $Mg(N_3)_2$ was a key step in a synthesis of bestatin.[1c] In contrast to 2,3-epoxy amides, ring opening of 2,3-epoxy esters with $Mg(N_3)_2$ occurs with little selectivity, as seen in Scheme XXII. Since an ester is a stronger electron-withdrawing group than an amide, the weaker C-3 selectivity observed with 2,3-epoxy esters with $Mg(N_3)_2$ is surprising. It is interesting to note that the reaction of NH_4N_3 with epoxy amide **49a** affords a nearly equimolar mixture of C-3 and C-2 ring-opened products. This result strongly

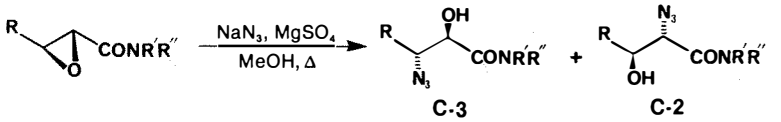


(eq. 23)[58]

Scheme XX



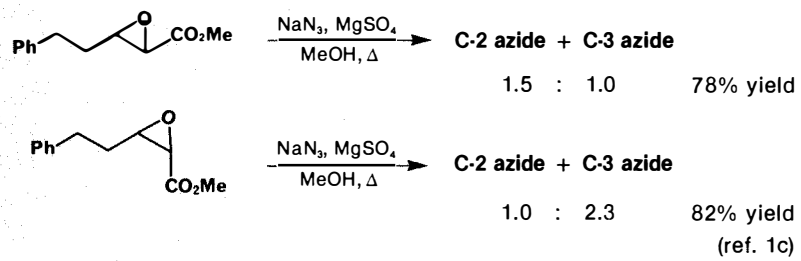
Scheme XXI



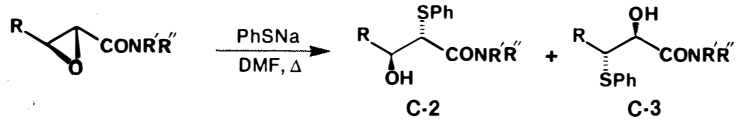
Substrate	% Yield, C-3 : C-2
49a R = *n*-C_7H_{15}, R' = Bn, R" = H	95%, 10 : 1
49b R = *n*-C_7H_{15}, R' = Bn, R" = Bn	76%, 10 : 1
49c R = c-Hex, R' = Bn, R" = H	41%*, 6 : 1

*72% yield based on recovered starting material

Scheme XXII



Scheme XXIII



Substrate	% Yield, C-3 : C-2
49a R = *n*-C_7H_{15}, R′ = Bn, R″ = H	70%, 5 : 1
49b R = *n*-C_7H_{15}, R′ = Bn, R″ = Bn	81%, C-2 only
49c R = c-Hex, R′ = Bn, R″ = H	60%, C-2 only

suggests that the magnesium cation is in some way assisting the C-3 selection in the opening of 2,3-epoxy amides with azide. The magnesium ion is expected to interact more strongly with an amide than an ester because of the former's greater basicity.[63] However, it is not clear just how the magnesium ion exerts its effect in the ring opening of 2,3-epoxy amides.

The ring-opening reactions of some 2,3-epoxy amides with PhSNa are presented in Scheme XXIII. In sharp contrast to the selective ring opening of these epoxy amides at C-3 with both amines and $Mg(N_3)_2$, selective ring opening at C-2 is observed with PhSNa. The C-2 : C-3 product ratio for the ring opening of **49a** with PhSNa is 5 : 1. The ring opening of **49b** and **49c** with PhSNa occurs exclusively at C-2. The C-2 selectivity of 2,3-epoxy amides with PhSNa may be mechanistically related to the unusually facile nucleophilic substitution reactions of phenacyl and acyl chlorides.

4. SUMMARY

This account has highlighted the regioselective ring-opening reactions of 2,3-epoxy alcohols and their derivatives. An effort was made to explain the observed regioselectivities in terms of a delicate balance between steric and electronic substituent effects. Emphasis was placed on developing a sufficient understanding of these effects so that one can reliably control the opening of a particular substrate to give the desired product. Scheme XXIV summarizes the major trends observed for ring-opening reactions of 2,3-epoxy alcohols and their close relatives.

Each of the carbon atoms of a 2,3-epoxy alcohol moiety is a potential reactive site for nucleophilic substitution. The latent reactivity of the C-1 position can be unmasked by three different procedures which transform 2,3-epoxy alcohols to their 1,2-epoxy alcohol isomers. Intramolecular ring-opening reactions of certain 2,3-epoxy alcohol derivatives at C-2 are highly selective. The ring-opening reactions of 2,3-epoxy alcohols with external nucleophiles may lead to selective attack at either C-2 or C-3. When R (the substituent on C-3) is not sterically demanding and does not exert an electron-withdrawing inductive effect, there is a preference for ring opening at C-3. However, when R is sterically demanding and/or inductively electron-withdrawing, the favored approach is to C-2. The C-1-oxidized derivatives of 2,3-epoxy alcohols are useful because the regioselectivity exhibited in their ring-opening reactions with external nucleophiles may be quite different from that observed for the original epoxy alcohol. The 2,3-epoxy acetals appear to be opened at C-3 by a variety of nucleophiles. At the carboxylic acid oxidation level it is interesting to note the switch from selective ring opening at C-2 in epoxy acids[64] to C-3 in epoxy amides (especially with amine nucleophiles).[1c]

2,3-Epoxy alcohols and their derivatives have already proven to be extremely versatile intermediates for the enantio- and stereoselective syntheses of polyfunctional organic molecules. However, our brief experience in this area convinces us that the majority of useful transformations of this important family of substances are yet to be discovered.

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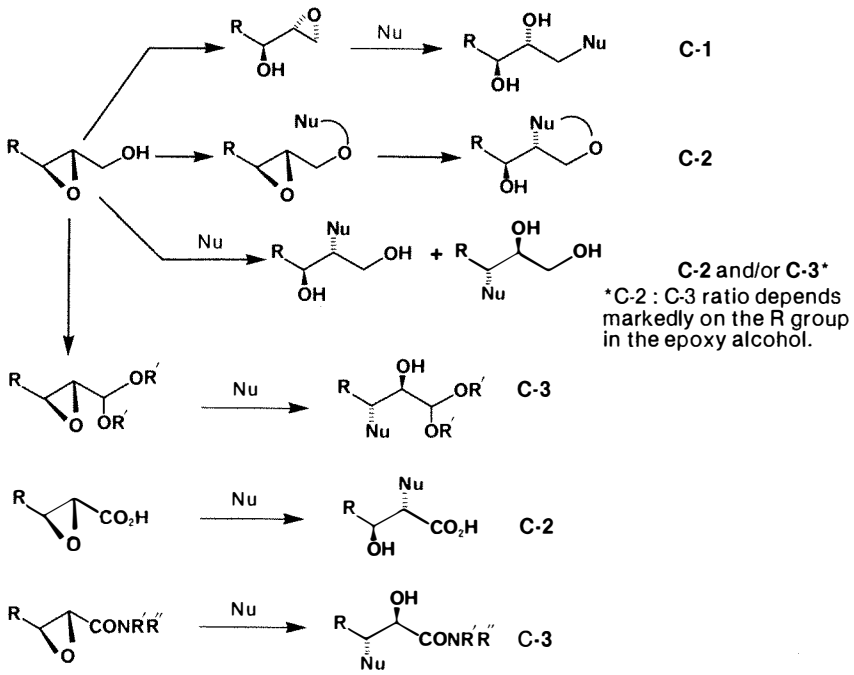
Scheme XXIV

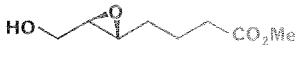


the very enjoyable and fruitful collaboration with Professor Masamune and his group which led to some of the most important discoveries cited in this article. We are greatly indebted to Mr. S.M. Viti and Drs. F.J. Walker, M. Takatani and A.W.M. Lee of our group for their contributions, both cited and uncited. We also thank Professors R.L. Danheiser, D.S. Kemp, and W.R. Roush for helpful discussions.

References:

1) The following are reviews concerned with the synthesis and selective transformations of epoxides:
   a) Seebach, D.; Weidmann, B.; Wilder, L. In "Modern Synthetic Methods 1983"; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, 1983; p 323.
   b) Rao, A.S.; Paknikar, S.K.; Kirtane, J.G. *Tetrahedron* **1983**, *39*, 2323.
   c) Sharpless, K.B.; Behrens, C.H.; Katsuki, T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodard, S.S. *Pure Appl. Chem.* **1983**, *55*, 589. This article is at present the best single source of information on the titanium-catalyzed asymmetric epoxidation reaction and its applications.
   d) Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* **1979**, *12*, 63.
   e) Berti, G. In "Topics in Stereochemistry"; Allinger, N.L.; Eliel, E.L., Eds.; Interscience Publishers: New York, 1973; Vol. 7, p 93.
   f) Buchanan, J.G.; Sable, H.Z. In "Selective Organic Transformations"; Thyagarajan, B.S., Ed.; Wiley: New York, 1972: Vol. 2, p 1.
   g) Yandovskii, V.N.; Ershov, B.A. *Russ. Chem. Rev.* **1972**, *41*, 403.
   h) Swern, D. In "Organic Peroxides"; Swern, D., Ed.; Wiley-Interscience: New York, 1971; Vol. 2, Chapter 5.
   i) Williams, N.R. In "Advances in Carbohydrate Chemistry and Biochemistry"; Tipson, R.S.; Horton, D., Eds.; Academic Press: New York, 1970; Vol. 25, p 109.
   j) Rosowsky, A. In "The Chemistry of Heterocyclic Compounds"; Weissberger, A., Ed.; Interscience: New York, 1964: Vol. 19, Part 1, Chapter 1.
   k) Parker, R.E.; Isaacs, N.S. *Chem. Rev.* **1959**, *59*, 737.
   l) Winstein, S.; Henderson, R.B. In "Heterocyclic Compounds"; Elderfield, R.C., Ed.; Wiley: New York, 1950; Vol. 1, Chapter 1.
2) Epoxides are also available from diols, halohydrins, acetylated halohydrins (*e.g.*, bromolactones) and other compounds.
3) a) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221.
   b) Narula, A.S. *ibid.* **1981**, *22*, 2017.
   c) Kishi, Y. *Aldrichimica Acta* **1980**, *13*, 23.
   d) Johnson, M.R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347.
   e) Johnson, M.R.; Nakata, T.; Kishi, Y. *ibid.* **1979**, 4343.
   f) Hasan, I.; Kishi, Y. *ibid.* **1980**, *21*, 4229.
   g) Chamberlain, P.; Roberts, M.L.; Whitham, G.H. *J. Chem. Soc. (B)* **1970**, 1374.
4) a) Narula, A. *Tetrahedron Lett.* **1982**, *23*, 5579.
   b) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *ibid.* **1982**, *23*, 3387.
   c) Mihelich, E.D.; Daniels, K.; Eickhoff, D. *J. Am. Chem. Soc.* **1981**, *103*, 7690.
   d) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, *22*, 4723.
   e) Sheldon, R.A.; Kochi, J.K. "Metal-Catalyzed Oxidations of Organic Compounds"; Academic Press: New York, 1981; Chapter 9, p 271.
   f) Sheldon, R.A. *J. Mol. Catal.* **1980**, *7*, 107.
   g) Mimoun, H. *ibid.* **1980**, *7*, 1.
   h) Dehnel, R.B.; Whitham, G.H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 953.
   i) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
   j) Rossiter, B.E.; Verhoeven, T.R.; Sharpless, K.B. *Tetrahedron Lett.* **1979**, 4733.
   k) Mihelich, E.D. *ibid.* **1979**, 4729.
   l) Michaelson, R.C.; Palermo, R.E.; Sharpless, K.B. *J. Am. Chem. Soc.* **1977**, *99*, 1990.
   m) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K.B.; Michaelson, R.C.; Cutting, J.D. *ibid.* **1974**, *96*, 5254.
   n) Sharpless, K.B.; Michaelson, R.C. *ibid.* **1973**, *95*, 6136.
5) a) Katsuki, T.; Sharpless, K.B. *ibid.* **1980**, *102*, 5974.
   b) Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *ibid.* **1981**, *103*, 6237.
6) A more detailed account of these new results is found in Behrens, C.H. Ph. D. Dissertation, Massachusetts Institute of Technology, Cambridge, MA., 1983.
7) Payne, G.B. *J. Org. Chem.* **1962**, *27*, 3819.
8) a) Koizumi, N.; Ishiguro, M.; Yasuda, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1401.
   b) Rokach, J.; Lau, C.-K.; Zamboni, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2763.
9) Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687.
10) This new concept was conceived, discovered, and developed in full collaboration with Prof. S. Masamune and his group as part of a joint program directed toward the synthesis of polyhydroxylated natural products. See ref. 12.
11) Wrobel, J.E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761. We thank Prof. Ganem for making their results available to us prior to publication.
12) a) Katsuki, T.; Lee, A.W.M.; Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Tuddenham, D.; Walker, F.J. *ibid.* **1982**, *47*, 1373.
   b) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47.
13) Ko, S.Y.; Behrens, C.H.; Sharpless, K.B.; unpublished results. This is an exciting lead with broad implications which we plan to explore. There is a precedent for this transformation in an abstract of a paper on the reaction of ammonia with 2,3-epoxy-2-methyl-3-phenylbutanol. See Macchia, B. *Farmaco, Ed. Sci.* **1972**, *27*, 559; *Chem. Abstr.* **1973**, *78*, 42759v.
14) The analogous conversion of 2-hydroxy sulfides and selenides to terminal epoxides by this sequence is well known. See, for example:
   a) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Tetrahedron Lett.* **1981**, *22*, 4823.
   b) Pirkle, W.H.; Rinaldi, P.L. *J. Org. Chem.* **1978**, *43*, 3803.
   c) Shanklin, J.R.; Johnson, C.R.; Ollinger, J.; Coates, R.M. *J. Am. Chem. Soc.* **1973**, *95*, 3429.
   d) Kano, S.; Yokomatsu, T.; Shibuya, S. *Chem. Commun.* **1978**, 785.
   e) Ikeda, Y.; Furuta, K.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7663.
   f) Townsend, J.M.; Sharpless, K.B. *Tetrahedron Lett.* **1972**, 3313.
   g) Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* **1973**, *95*, 7424.
   h) Schauder, J.R.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 4389.
   i) Van Ende, D.; Krief, A. *ibid.* **1976**, 457.
15) Curphey, T.J. *Org. Syn.* **1971**, *51*, 142.
16) Rokach and co-workers have also noted that in a similar 1,2-epoxy alcohol the *threo* isomer was much more resistant to base-catalyzed isomerization than the *erythro* isomer. See ref. 8b.
17) Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 958.
18) Corey, E.J.; Pan, B.-C.; Hua, D.H.; Deardorff, D.R. *J. Am. Chem. Soc.* **1982**, *104*, 6816.
19) An attempted ring opening of 3a with NaNHTs under similar conditions gave a poor result.
20) a) Minami, N.; Ko, S.S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.
   b) Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Viti, S.M. *J. Org. Chem.* **1982**, *47*, 1378.
   c) Finan, J.M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.
   d) Viti, S.M. *ibid.* **1982**, *23*, 4541.
   e) Nicolaou, K.C.; Venishi, J. *Chem. Commun.* **1982**, 1292.
   f) Mubarak, A.M.; Brown, D.M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 809.
   g) Takano, S.; Kasahara, C.; Ogasawara, K. *Chem. Lett.* **1983**, 175.
21) We first learned of the use of this particular acetylide nucleophile for opening an unprotected 1,2-epoxy-3-ol from Prof. J.D. White (M.I.T. Organic Seminar, Spring, 1983. See ref. 25c). For examples of related reactions, see:
   a) Mori, K.; Oda, M.; Matsui, M. *Tetrahedron Lett.* **1976**, 3173.
   b) Just, G.; Luthe, C. *ibid.* **1982**, *23*, 1331.
   c) Suzuki. T.; Saimoto, H.; Tomioka, H.; Oshima, K. *ibid.* **1982**, *23*, 3597.
22) Lee, A.W.M.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Walker, F.J. *J. Am. Chem. Soc.* **1982**, *104*, 3515.
23) a) Mori, K.; Ebata, T. *Tetrahedron Lett.* **1981**, *22*, 4281.
   b) Kigoshi, H.; Ojika, M.; Shizuri, Y.; Niwa, H.; Yamada, K. *ibid.* **1982**, *23*, 5413.
   c) Chen, R.; Rowand, D.A. *J. Am. Chem. Soc.* **1980**, *102*, 6609.
24) a) Viti, S.M.; Sharpless, K.B., unpublished results.
   b) Walker, F.J.; Behrens, C.H.; Sharpless, K.B., unpublished results.
25) a) Morgans, Jr., D.J.; Sharpless, K.B.; Traynor, S.G. *J. Am. Chem. Soc.* **1981**, *103*, 462.
   b) Corey, E.J.; Marfat, A.; Goto, G.; Brion, F. *ibid.* **1980**, *102*, 7984.
   c) White, J.D.; Kang, M.; Sheldon, B.G. *Tetrahedron Lett.* **1983**, *24*, 4539.
   d) See also: Salomon, I.; Reichstein, T. *Helv. Chim. Acta* **1947**, *30*, 1929.
26) There are examples in which electron-withdrawing functional groups increase the rate of nucleophilic substitution. See:
   a) Fuchs, R.; Carlton, D.M. *J. Am. Chem. Soc.* **1963**, *85*, 104.
   b) Holtz, H.D.; Stock, L.M. *ibid.* **1965**, *87*, 2404.
27) Hine, J.; Brader, Jr., W.H. *ibid.* **1953**, *75*, 3964.
28) Bordwell, F.G.; Brannen, Jr., W.T. *ibid.* **1964**, *86*, 4645.
29) Winstein, S.; Allred, E.; Heck, R.; Glick, R. *Tetrahedron* **1958**, *3*, 1.
30) a) Baechler, R.D.; Andose, J.D.; Stackhouse, J.; Mislow, K. *J. Am. Chem. Soc.* **1972**, *94*, 8060.
   b) Levin, C.C. *ibid.* **1975**, *97*, 5649.
31) a) Tucker, H. *J. Org. Chem.* **1979**, *44*, 2943.
   b) Shtacher, G.; Rubinstein, R.; Somani, P. *J. Med. Chem.* **1978**, *21*, 678.
32) McBee, E.T.; Hathaway, C.E.; Roberts, C.W. *J. Am. Chem. Soc.* **1956**, *78*, 4053.
33) Stevens, C.L.; Coffield, T.H. *ibid.* **1958**, *80*, 1919.
34) VanderWerf, C.A.; Heisler, R.Y.; McEwen, W.E. *ibid.* **1954**, *76*, 1231.
35) Conant, J.B.; Kirner, W.R.; Hussey, R.E. *ibid.* **1925**, *47*, 488.
36) There have been some experiments that suggest that α-keto carbonium ions may be resonance-stabilized.
   a) Creary, X.; Geiger, C.C. *J. Am. Chem. Soc.* **1982**, *104*, 4151.
   b) Creary, X. *ibid.* **1981**, *103*, 2463.
   c) *Idem J. Org. Chem.* **1979**, *44*, 3938.
   d) Béugé, J.-P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207.
37) a) Corey, E.J.; Hopkins, P.B.; Munroe, J.E.; Marfat, A.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 7986.
   b) Roush, W.R.; Brown, R.J. *J. Org. Chem.* **1982**, *47*, 1371.
   c) Roush, W.R.; Brown, R.J.; DiMare, M. *ibid.*, in press.
   d) Roush, W.R.; Brown, R.J. *ibid.*, in press.
   e) Roush, W.R.; Adam, M.A.; Hagadorn, S.M., unpublished results.
   f) Sorokin, M.F.; Shode, L.G.; Nogteva, S.I. *Tr.-Mosk. Khim.-Tekhnol. Inst. im. D.I. Mendeleeva* **1980**, *110*, 132; *Chem. Abstr.* **1982**, *96*, 121959k.
38) a) Hartman, B.C.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 4246.

b) Harris, III, R.N.; Sundararaman, P.; Djerassi, C. *J. Am. Chem. Soc.* **1983**, *105*, 2408.
39) Weissenberg, M.; Krinsky, P.; Glotter, E. *J. Chem. Soc., Perkin Trans. 1* **1978**, 565.
40) Danishefsky, S.; Tsai, M.-Y.; Kitahara, T. *J. Org. Chem.* **1977**, *42*, 394 and references cited therein.
41) a) Hartman, B.C.; Livinghouse, T.; Rickborn, B. *ibid.* 1973, *38*, 4346.
b) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M.R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962.
c) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
d) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491.
e) Lipshutz, B.H.; Kozlowski, J.; Wilhelm, R.S. *ibid.* **1982**, *104*, 2305.
42) a) Roush, W.R.; Adam, M.A.; Peseckis, S.M. *Tetrahedron Lett.* **1983**, *24*, 1377.
b) McWhorter, Jr., W.W.; Kang, S.H.; Kishi, Y. *ibid.* **1983**, *24*, 2243.
c) Fuganti, C.; Grasselli, P.; Servi, S.; Zirotti, C. *ibid.* **1982**, *23*, 4269.
43) Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 71.
44) In a related example, the 2,3-epoxy alcohol *i*



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affords a 7 : 1 mixture of isomers upon treatment with NaN_3 and NH_4Cl in ethanol. Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 331.
45) For an example in which the *trans*-diaxial opening rule is violated to avoid neopentyl substitution, see Sirat, H.M.; Thomas, E.J.; Wallis, J.D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2885.
46) These compounds were recently prepared and characterized by Kishi and co-workers. See ref. 20a.
47) a) Baer, H.H. *J. Am. Chem. Soc.* **1961**, *83*, 1882.
b) Baer, H.H.; Fischer, H.O.L. *ibid.* **1960**, *82*, 3709.
48) a) Berge, J.M.; Roberts, S.M.; Suschitzky, H.; Kemp, J.E.G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 690.
b) Trost, B.M.; McDougal, P.G. *Tetrahedron Lett.* **1982**, *23*, 5497.
49) Fourneau, J.P.; Chantalou, S. *Bull. Soc. Chim. Fr.* **1945**, *12*, 845.
50) a) Corey, E.J.; Marfat, A.; Goto, G. *J. Am. Chem. Soc.* **1980**, *102*, 6607.
b) Corey, E.J.; Marfat, A.; Monroe, J.; Kim, K.S.; Kaplin, P.B.; Brion, F. *Tetrahedron Lett.* **1981**, *22*, 1077.
c) Rossiter, B.E.; Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, *103*, 464.
d) Mills, L.S.; North, P.C. *Tetrahedron Lett.* **1983**, *24*, 409.
51) a) Tsunoda, T.; Suzuki, M.; Noyori, R. *ibid.* **1980**, *21*, 1357.
b) Chan, T.H.; Brook, M.A.; Chaley, T. *Synthesis* **1983**, 203.
52) Foster, A.B. In "The Carbohydrates"; Pigman, W.; Horton, D., Eds.; Academic Press: New York, 1972; Vol. IA, p 391.
53) a) Boireau, G.; Abenhaim, D.; Bernardon, C.; Henry-Basch, E.; Sabourault, B. *Tetrahedron Lett.* **1975**, 2521.
b) Abenhaim, D.; Namy, J.-L. *ibid.* 1972, 1001.
c) Roush, W.R.; Blizzard, T.A.; Basha, F.Z. *ibid.* **1982**, *23*, 2331.
d) Bartlett, P.A.; Tanzella, D.J.; Barstow, J.F. *J. Org. Chem.* **1982**, *47*, 3941.
54) Ourari, A.; Condom, R.; Guedj, R. *Can. J. Chem.* **1982**, *60*, 2707.
55) Elker, A.; Lehmann, J.; Zymalkowski, F. *Arch. Pharmaz.* **1979**, *312*, 26.
56) Herr, R.W.; Wieland, D.M.; Johnson, C.R. *J. Am. Chem. Soc.* **1970**, *92*, 3813.
57) a) Kamandi, E.; Frahm, A.W.; Zymalkowski, F. *Arch. Pharmaz.* **1974**, *307*, 871.
b) Kamandi, E.; Frahm, A.W.; Zymalkowski, F. *ibid.* **1975**, *308*, 135.
c) Tack, J.W.; Lehmann, J.; Zymalkowski, F. *ibid.* **1979**, *312*, 138.
d) Schönen, B.; Zymalkowski, F. *ibid.* **1981**, *314*, 464.
e) Kato, K.; Saino, T.; Nishizawa, R.; Takita, T.; Umezawa, H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1618.
f) Takeuchi, S.; Ohgo, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2136.
58) Walborsky, H.M.; Baum, M.E. *J. Am. Chem. Soc.* **1958**, *80*, 187.
59) See numerous references to Martynov's work in ref. 1k.
60) Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, *46*, 3936.
61) Still, W.C.; Ohmizu, H. *ibid.* **1981**, *46*, 5242.
62) a) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
b) *Idem ibid.* **1970**, *103*, 2024.
c) Windridge, G.C.; Jorgensen, E.C. *J. Am. Chem. Soc.* **1971**, *93*, 6318.
63) a) Arnett, E.M. In "Progress in Physical and Organic Chemistry"; Cohen, S.G.; Streitweiser, Jr., A.; Taft, R.W., Eds.; Interscience: New York, 1963; Vol. 1, p 223.
b) Drago, R.S.; Wayland, B.B. *J. Am. Chem. Soc.* **1965**, *87*, 3571.
64) Liwschitz, Y.; Rabinsohn, Y.; Perera, D. *J. Chem. Soc.* **1962**, 1116.

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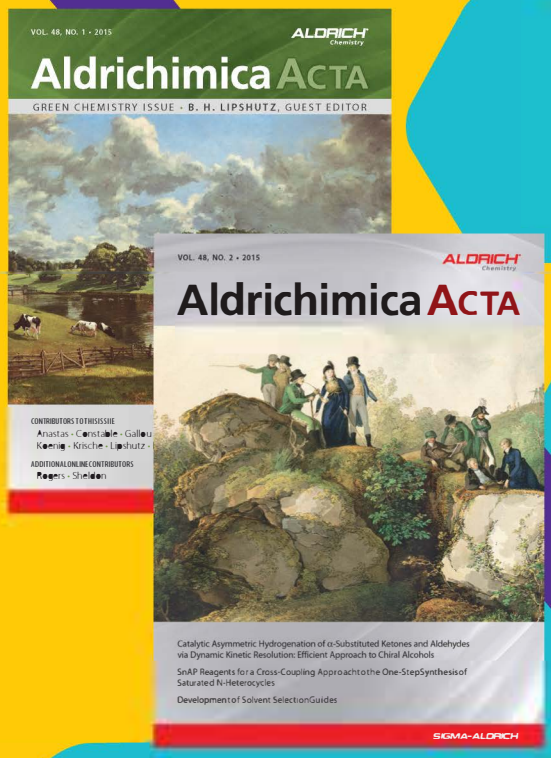

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