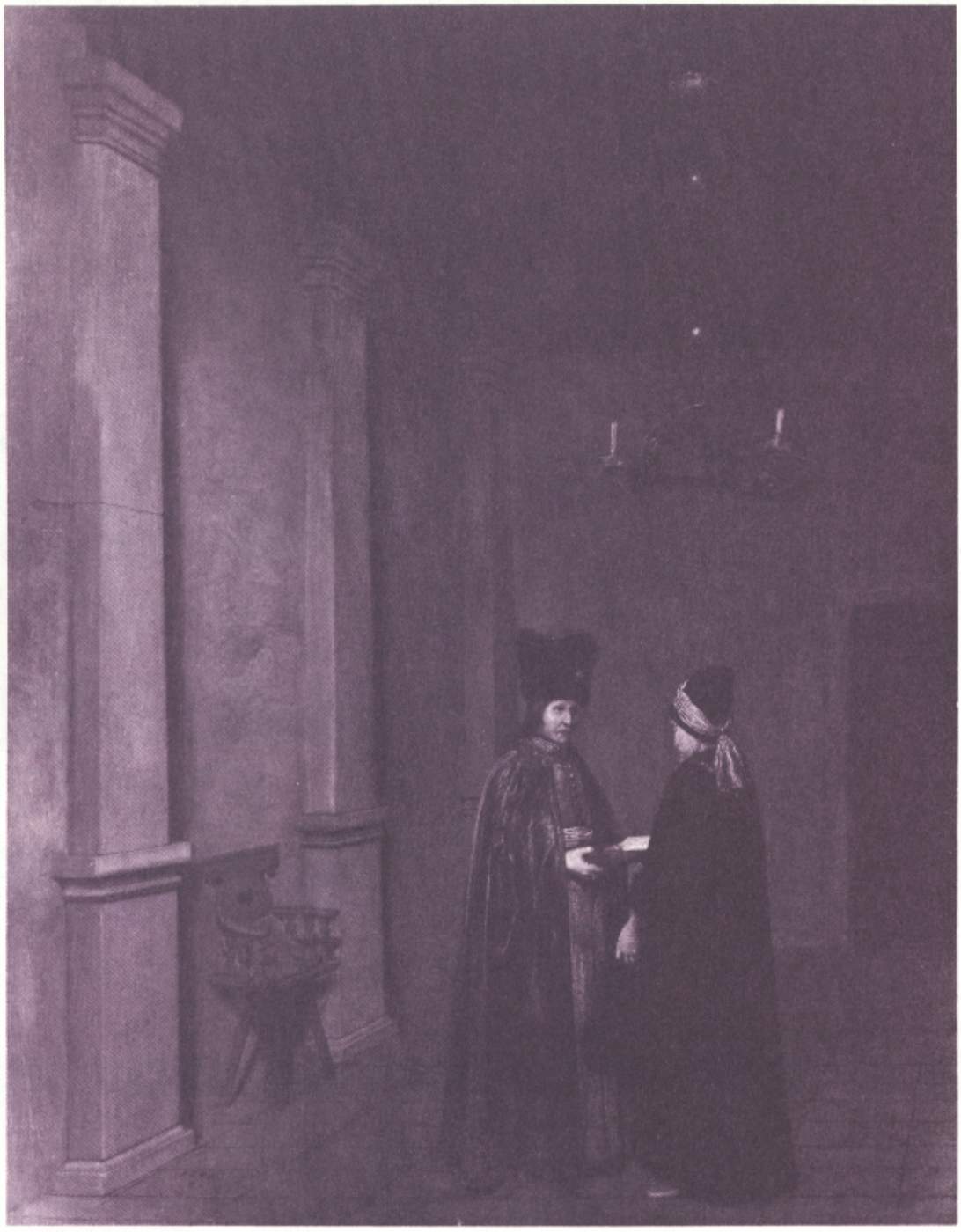
Aldrichimica Acta

Volume 16, Number 1, 1983



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

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Aldrichimica Acta

Volume 16, Number 1, 1983
A publication of the ALDRICH CHEMICAL COMPANY

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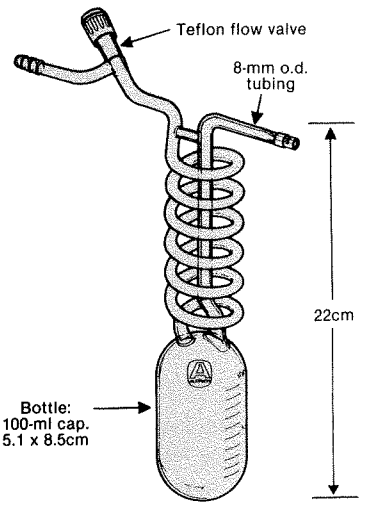
When a gas (*e.g.*, Cl_2, SO_2, CH_3Br or CH_3SH) is required for synthetic work, it is sometimes necessary to measure the amount to be added to the reaction mixture. This can be accomplished by condensing the gas in the apparatus shown below (cooled in dry-ice/acetone), and then determining its weight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

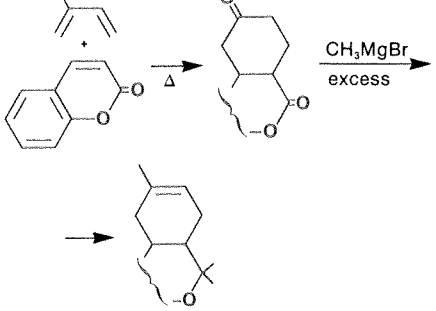
Professor David C. Baker
Merrill B. Watson, Glassblower
Department of Chemistry
The University of Alabama
University, AL 35486

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 Ayşa 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

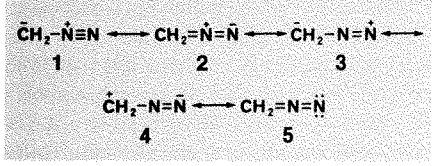
T. Howard Black
Aldrich Chemical Company, Inc.

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

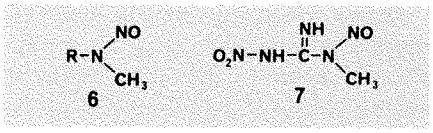
Although quite safe when handled as a dilute solution in an inert solvent, diazomethane presents several safety hazards of which all users of the reagent should be aware. It is both extremely toxic[8] and highly irritating,[9] causing pulmonary edema when inhaled in high concentrations. Long-term, low-level 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.

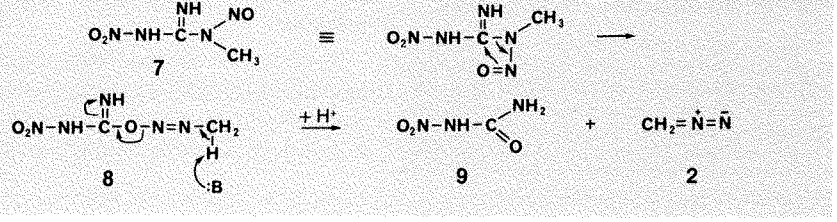
Fortunately, if the reagent is generated using the proper equipment and is handled only as a dilute solution at low temperature (*ca.* 0 °C), the risks cited above are minimized. Of course, **all reactions** involving diazomethane should be carried out in an **efficient fume hood** and behind a **sturdy 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-

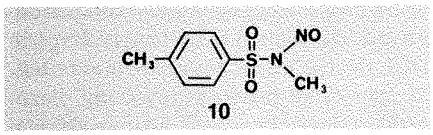


Scheme II



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

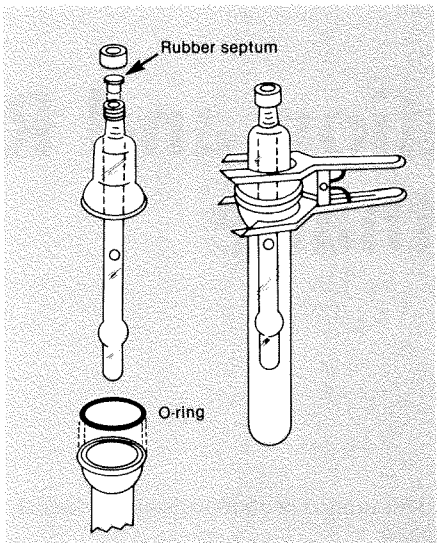


Fig. 1. Apparatus for preparing diazomethane from MNNG.

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.

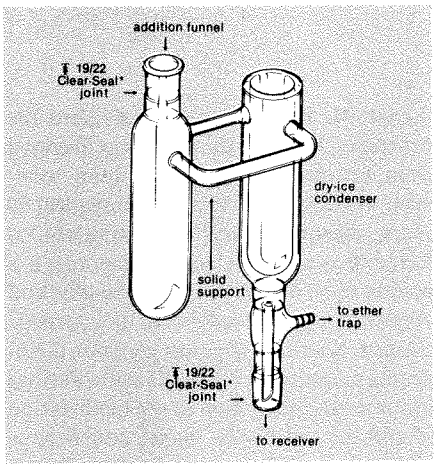
DIAZALD®

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 1-50 mmoles 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

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®*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.

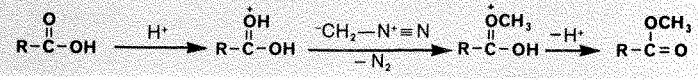
REACTIONS

METHYLATION

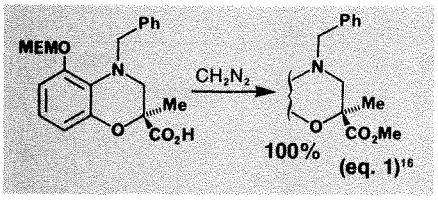
O-Methylation

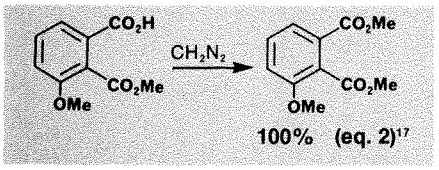
The methylation of oxygen atoms, in particular carboxylic acids, is by far the most widely employed and popular diazomethane reaction. Discovered by von Pechman,[1] it is believed to proceed *via* a positively charged intermediate as depicted in Scheme III, which explains the observation that alcohols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

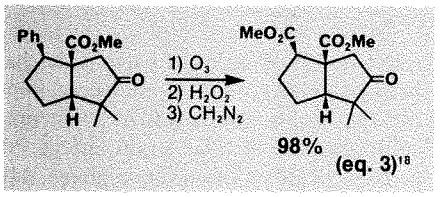
Scheme III

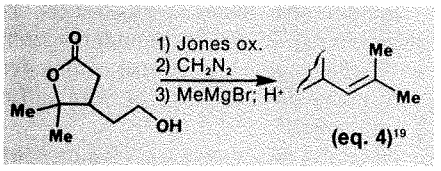


The major advantages of employing diazomethane for methylation reactions are: speed of reaction, mildness of reaction conditions, absence of non-volatile byproducts, ease of workup, and selectivity in the presence of functional groups. Eqs. 1 through 4 represent some routine applications of the carboxylic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



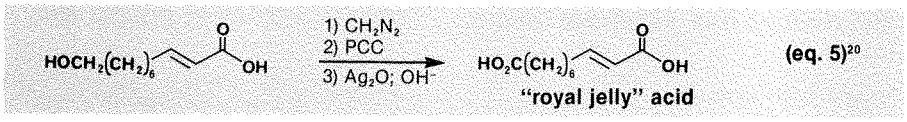


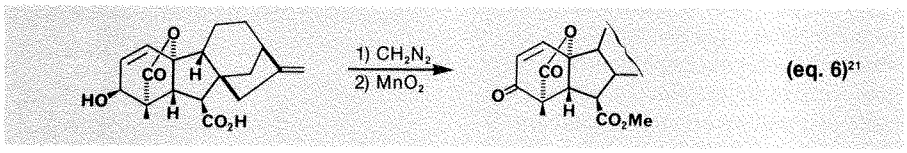


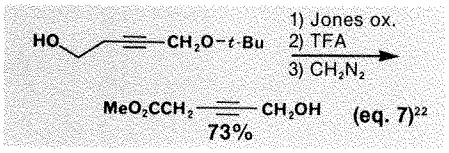


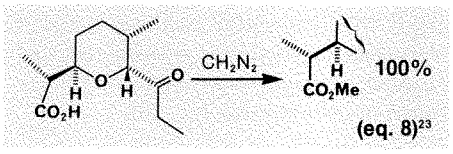
As mentioned above, the more electron-rich oxygen atoms lack the electrophilicity necessary for reaction with diazomethane. Thus, their presence is not a hindrance to the esterification of a carboxylic acid function elsewhere in the molecule. Accordingly, alcohols, whether isolated (eq. 5), allylic (eq. 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).

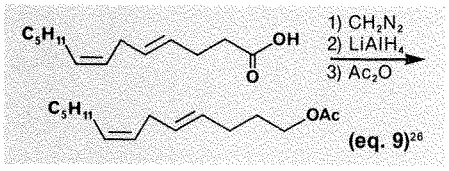
Phenols also possess sufficient acidity for uncatalyzed reaction with diazomethane. Of course, alcohols can be present in the same molecule, as indicated in eqs. 11 and 12. Eq. 12 involves a tropolone methylation *en route*

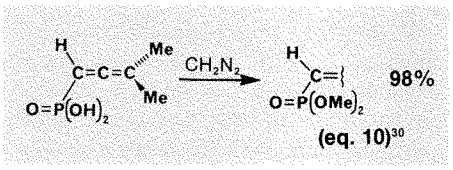


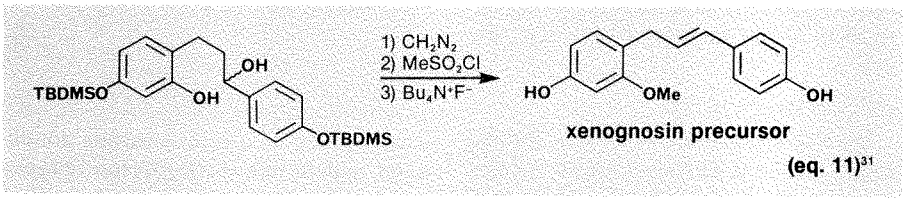


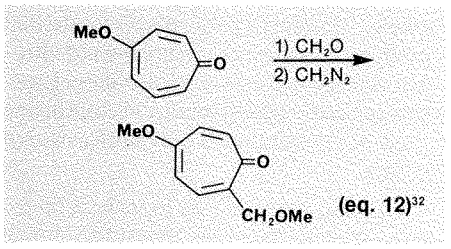


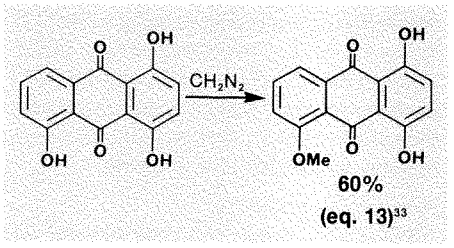












to a tropoquinonophane precursor. Selective methylations of phenolic hydroxyl groups also have been attained, based on the greater relative acidity of the reacting functionality (eq. 13).

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]

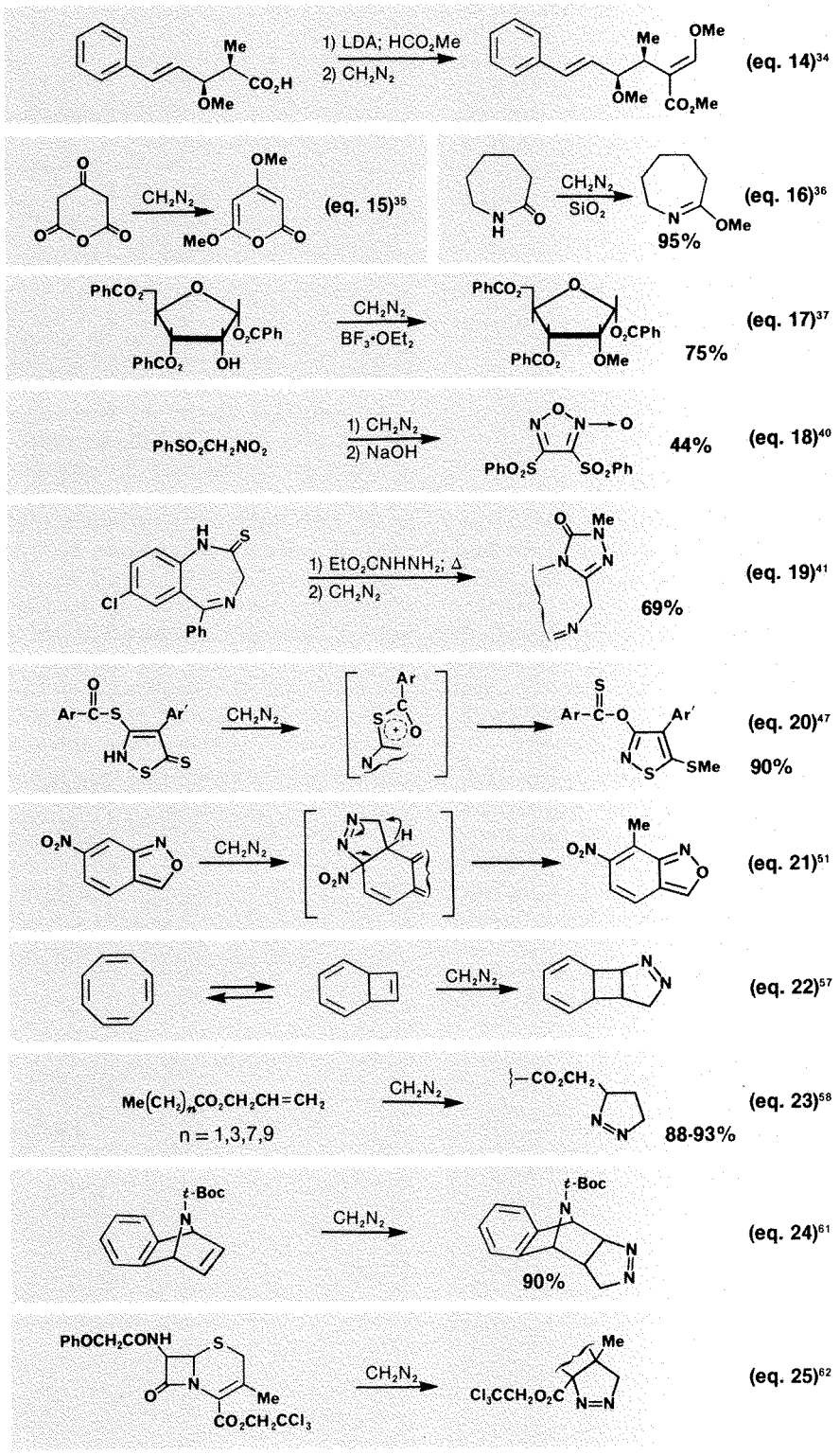
Pyrazoline Formation

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

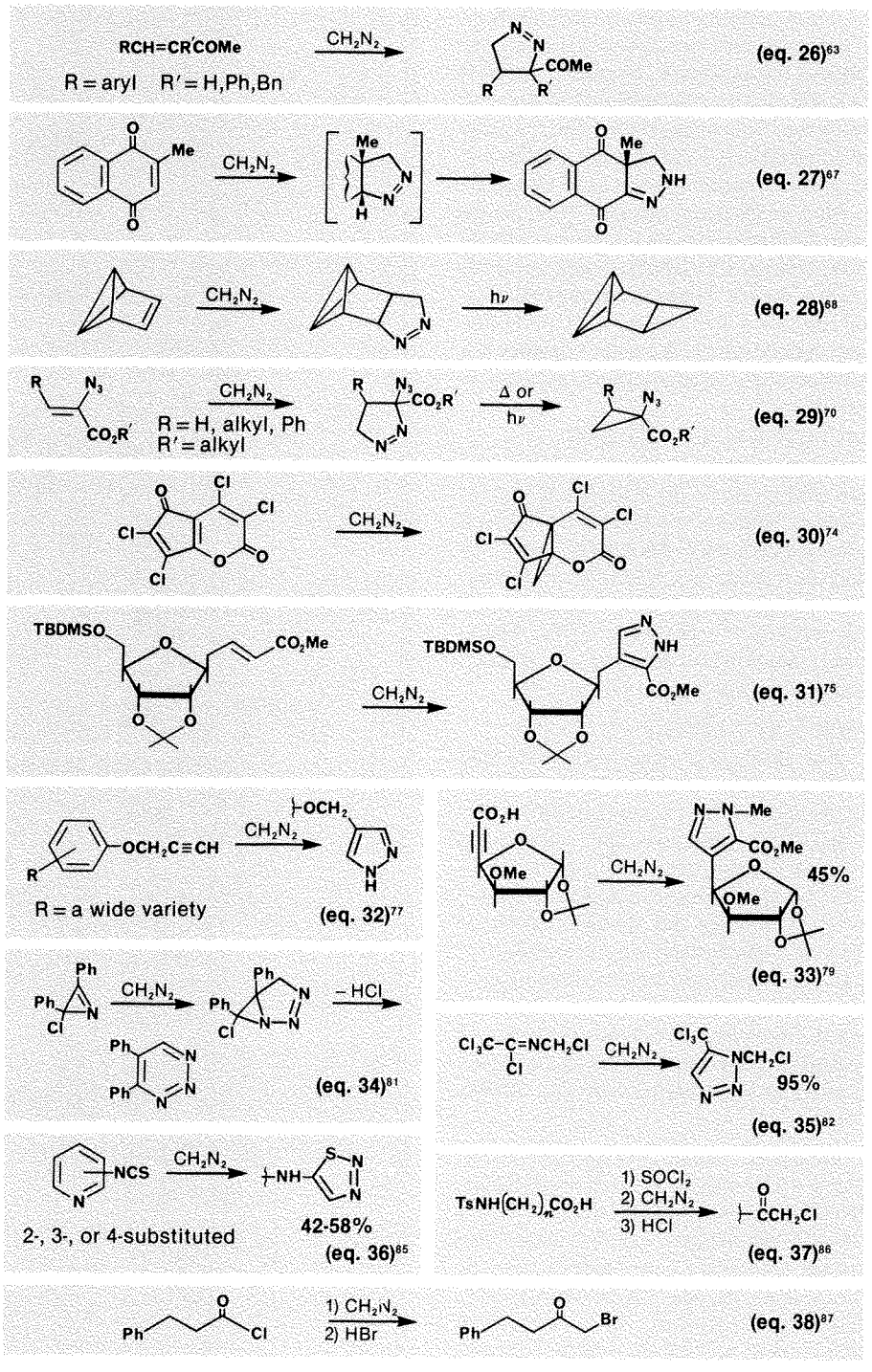
A little-used but potentially valuable construction of thiadiazoles involves the reaction of diazomethane with isothiocyanates.[84] As indicated in eq. 36, the result is an N-substituted amino thiadiazole ring.

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]

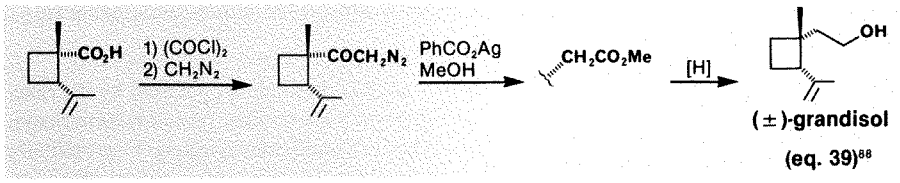
METHYLENE INSERTIONS

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]

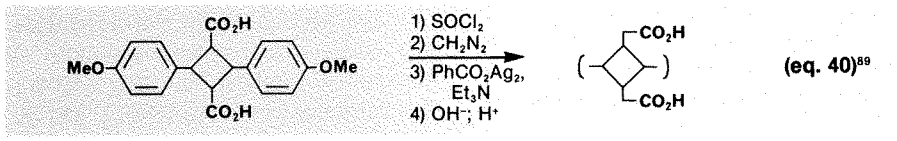
MISCELLANEOUS REACTIONS

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]

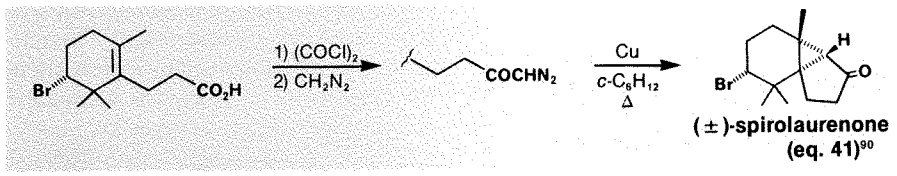
Hopefully, this short review has provided the reader with an appreciation of the tremendous usefulness and versatility of one of synthetic chemistry's truly indispensable reagents. Consider the transformation depicted in eq. 55, wherein diazomethane effected simultaneous expansion of the oxazolidone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



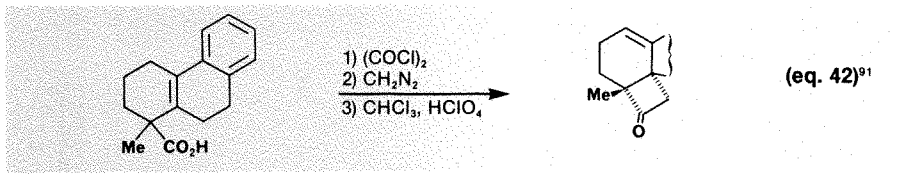
(eq. 39)[88]



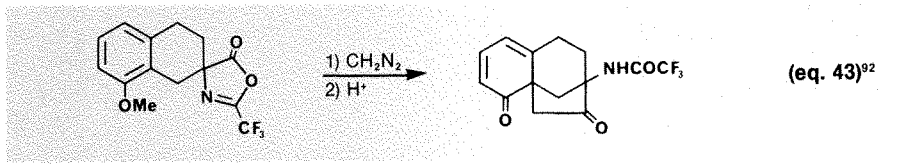
(eq. 40)[89]



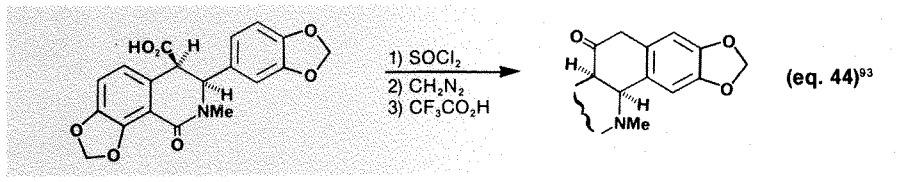
(eq. 41)[90]



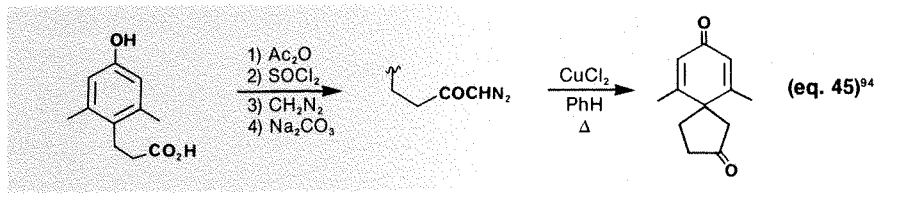
(eq. 42)[91]



(eq. 43)[92]

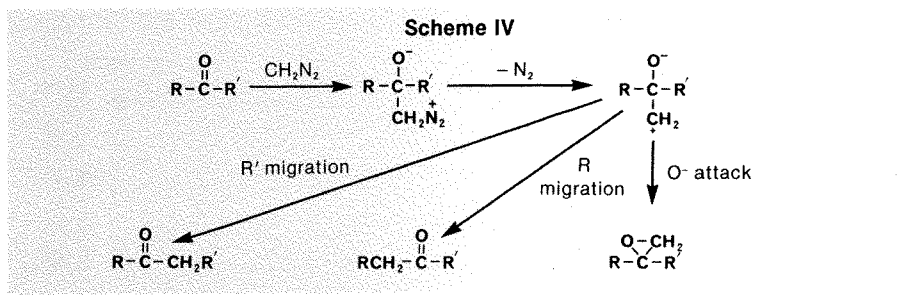


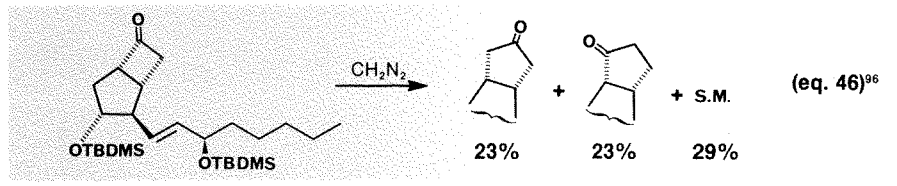
(eq. 44)[93]



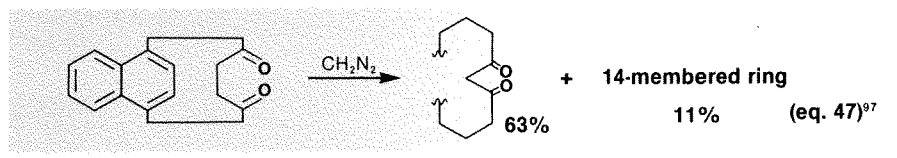
(eq. 45)[94]

Scheme IV

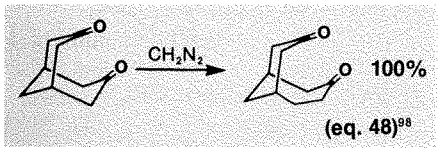


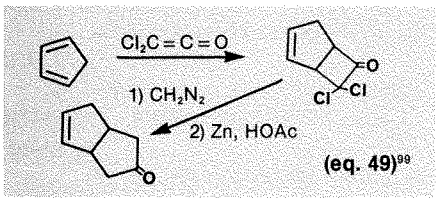


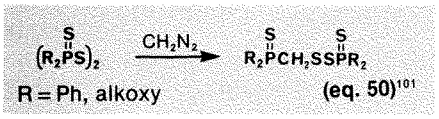
(eq. 46)[96]

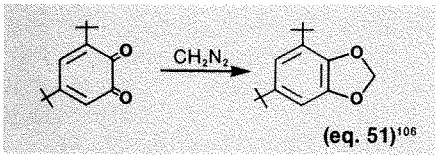


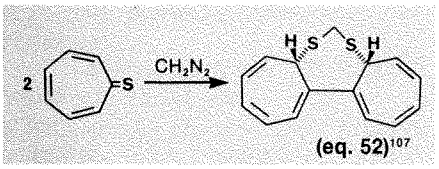
(eq. 47)[97]

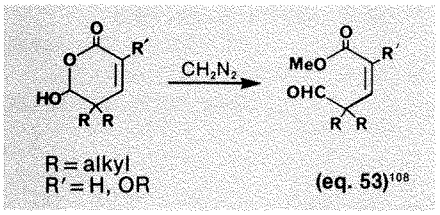


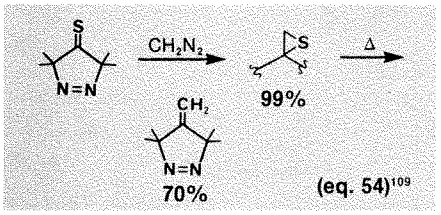


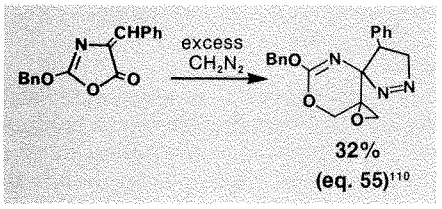












ene double bond, and cyclopropanation of the carbonyl group! Certainly, consideration of diazomethane chemistry is an important part of any synthetic plan.

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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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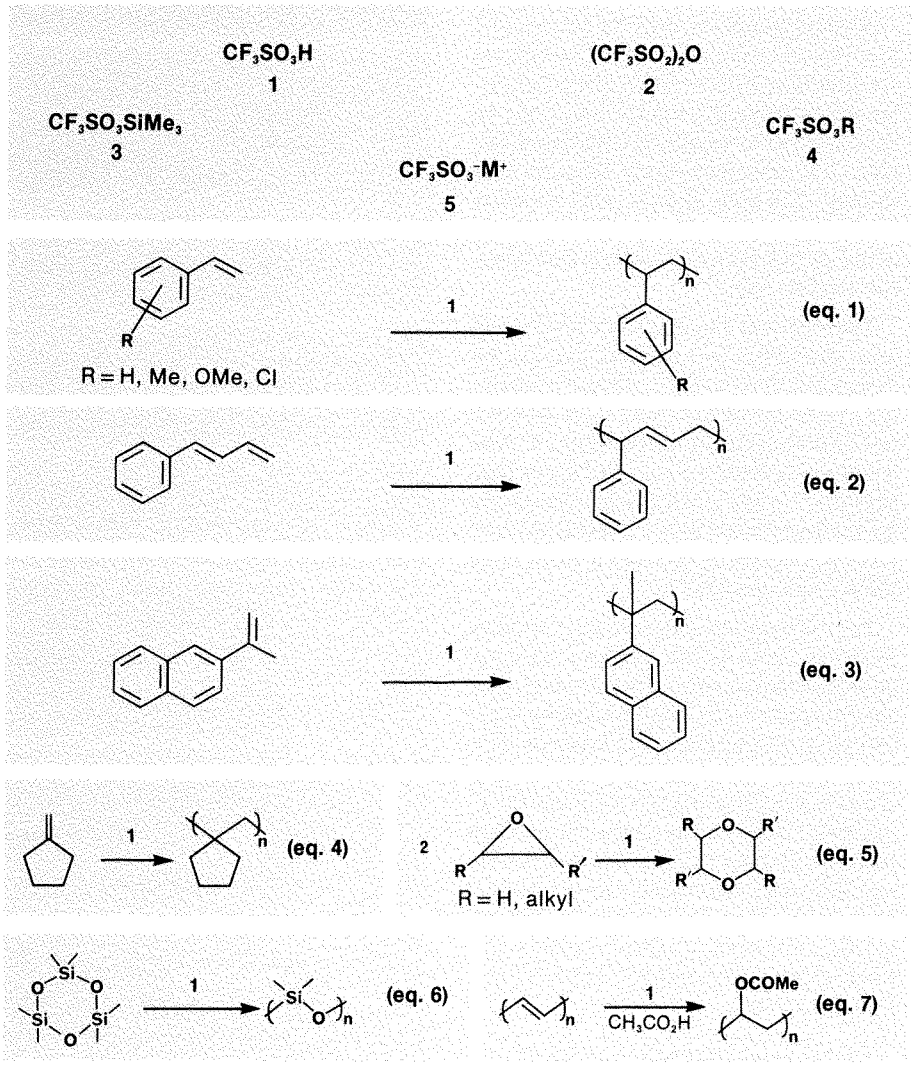
Trifluoromethanesulfonic acid (**1**), commonly known as triflic acid, was first reported in 1954 by Haszeldine and Kidd.[1,2] Since then there has been a rapid growth in the chemistry of **1** and its derivatives: triflic anhydride (**2**), trimethylsilyl triflate (**3**), alkyl and vinyl triflates (**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.

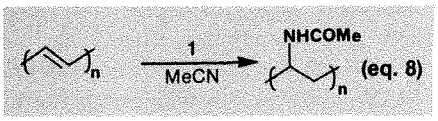
The last few years have seen a tremendous growth in the use of **1** as an oligomerization/polymerization catalyst. A variety of aromatic olefins have been oligomerized, including styrene,[11-15,17] methylstyrenes,[14-16] chloro- and methoxystyrenes,[17] 1-phenylbutadiene,[18] and 2-isopropenylnaphthalene (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]



(eq. 8)

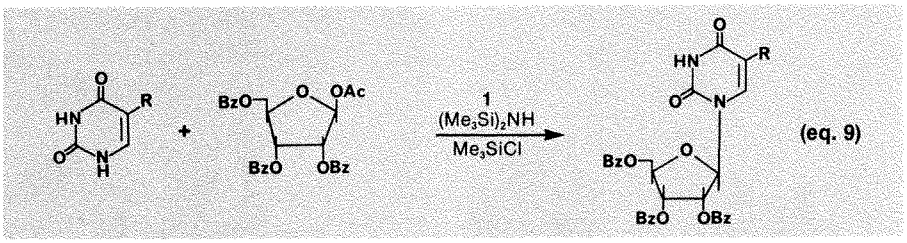
An interesting new area for the use of **1** is in fuel cell technology.[48-52] The systems are usually hydrogen/air or alkane/air, using either platinum or nickel electrodes. In the reduction of oxygen at a platinum surface, **1** is 100 times more efficient as a catalyst than 85% H_3PO_4, with a barrier 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]

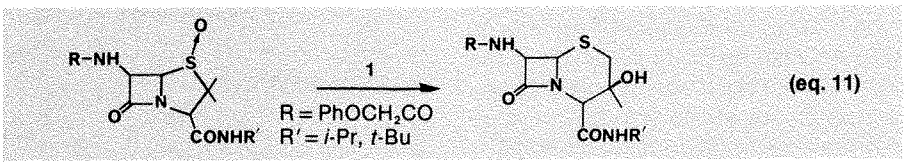
CF_3SO_3H is useful in the removal of protecting groups from oxygen and nitrogen functionalities (deblocking) of synthetic proteins. Typical reaction systems use **1** as cation generator, and either anisole[63,64] or thioanisole[65-69] as cation acceptor. Groups that can be removed by these systems 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



(eq. 9)

(eq. 10)



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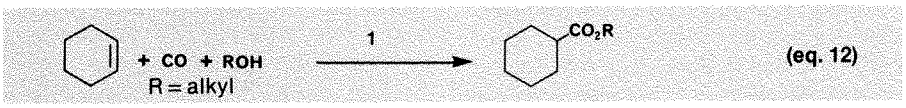

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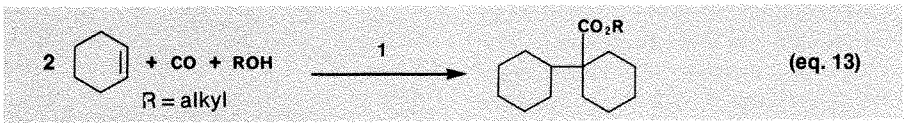

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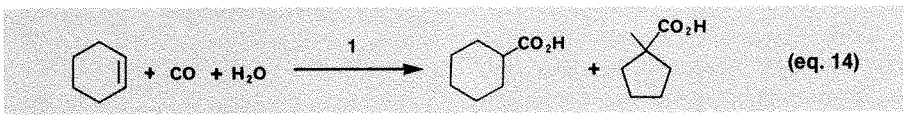

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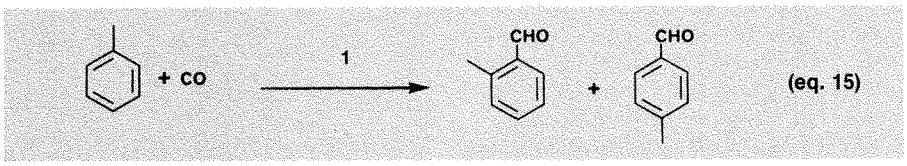

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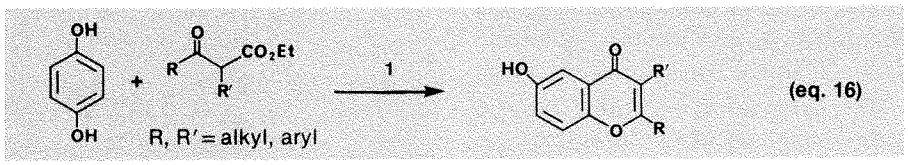
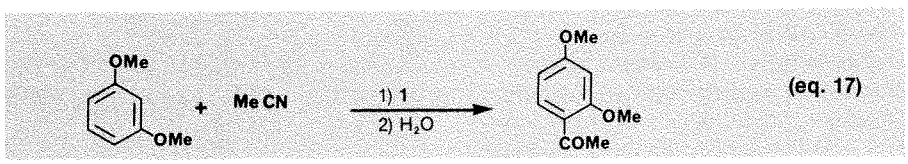


(eq. 16)



(eq. 17)

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

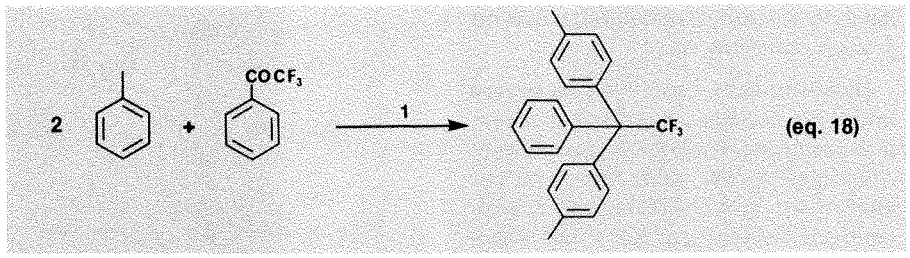
Friedel-Crafts alkylations have also been mediated by CF_3SO_3H. Thus, α,α,α-trifluoroacetophenone, treated with two equivalents of toluene, gives 1,1,1-trifluoro-2,2-bis(4-methylphenyl)-2-phenylethane (eq. 18).[77] Benzene was alkylated using a mixture of light alkanes and the superacid CF_3SO_3H/SbF_5 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]

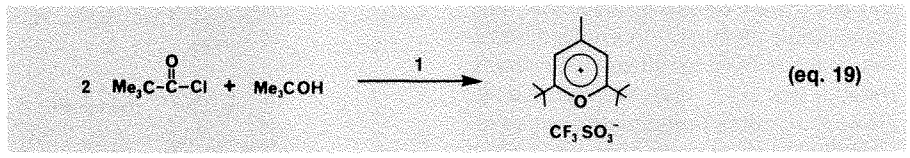
A related field is the rearrangement of species protonated by triflic acid, such as homoadamantane (eq. 20) by Schleyer and co-workers,[83] and 2-homoprotoadamantane.[84] Paquette also used **1** extensively in the synthesis of 1,16-dimethyldodecahedrane.[85] Non-hydrocarbon species such as *o*-bromophenol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

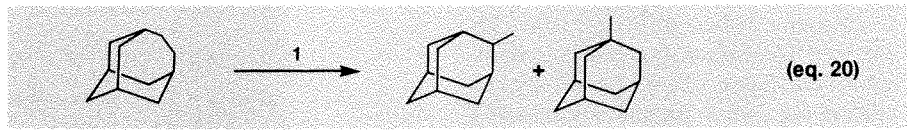
CF_3SO_3H has been well utilized in organometallic chemistry. It has catalyzed the mercuration of *p*-methoxybenzoic acid (eq. 21)[89] and perfluoroaromatics.[90] Mixed alkylgold-phosphine complexes are selectively dealkylated *cis* to the phosphine when treated with **1**.[91] Unstable copper carbonyl 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]

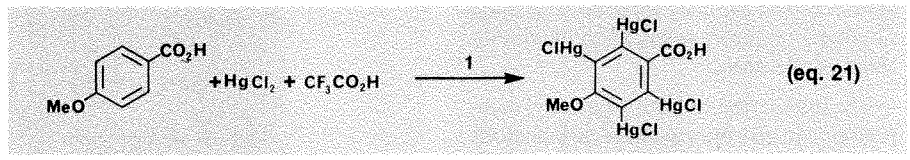
There are, of course, a large number of other applications of **1** in synthesis. Examples are the selective R–O or P–N cleavage in phosphoramidates and related compounds,[100,101] α-chlorination of carboxylic acids (eq. 24),[102] production of N-containing macrocycles,[103] and the industrial preparation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

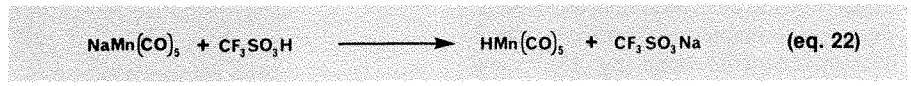
The first preparation of triflic anhydride (**2**) was reported by Brice and Trott in 1956,

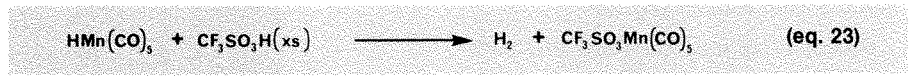


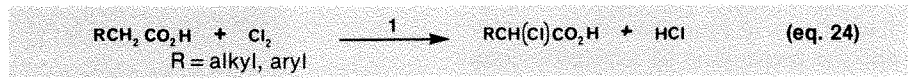


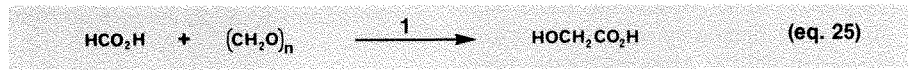


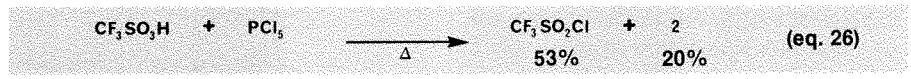


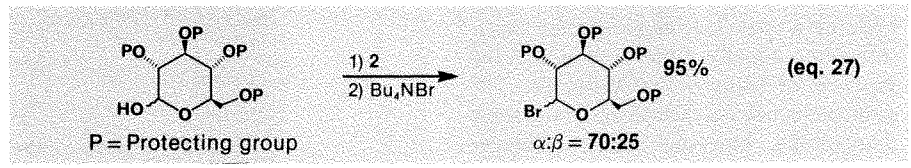


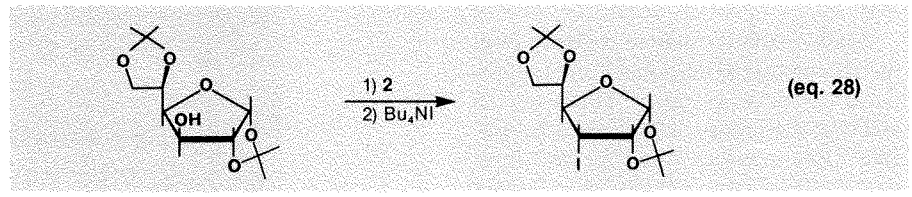












as a byproduct in the synthesis of triflyl chloride (eq. 26).[106] A better procedure involves treating triflic acid with P_2O_5.[10,107] Redistillation of the crude **2** from P_2O_5 gives a non-fuming, clear, water-white liquid.

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]

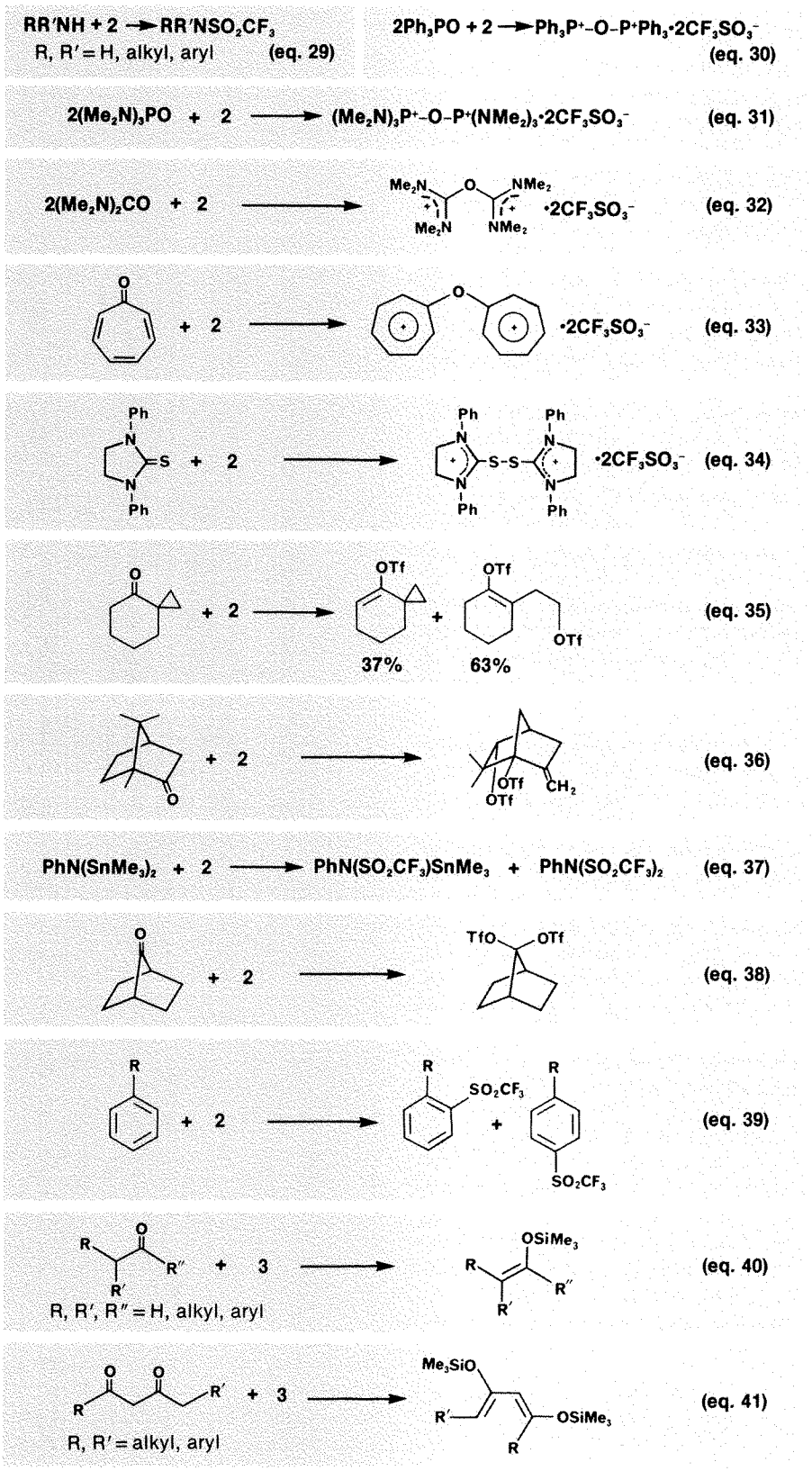
Dicationic salts which have an oxygen bridge can be made using **2** and an appropriate substrate. For instance, two moles of triphenylphosphine oxide react with one mole of **2** to give bis(triphenylphosphenium)oxide ditriflate (eq. 30).[125] The monocationic triflate cannot be made this way, as previously 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]



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]

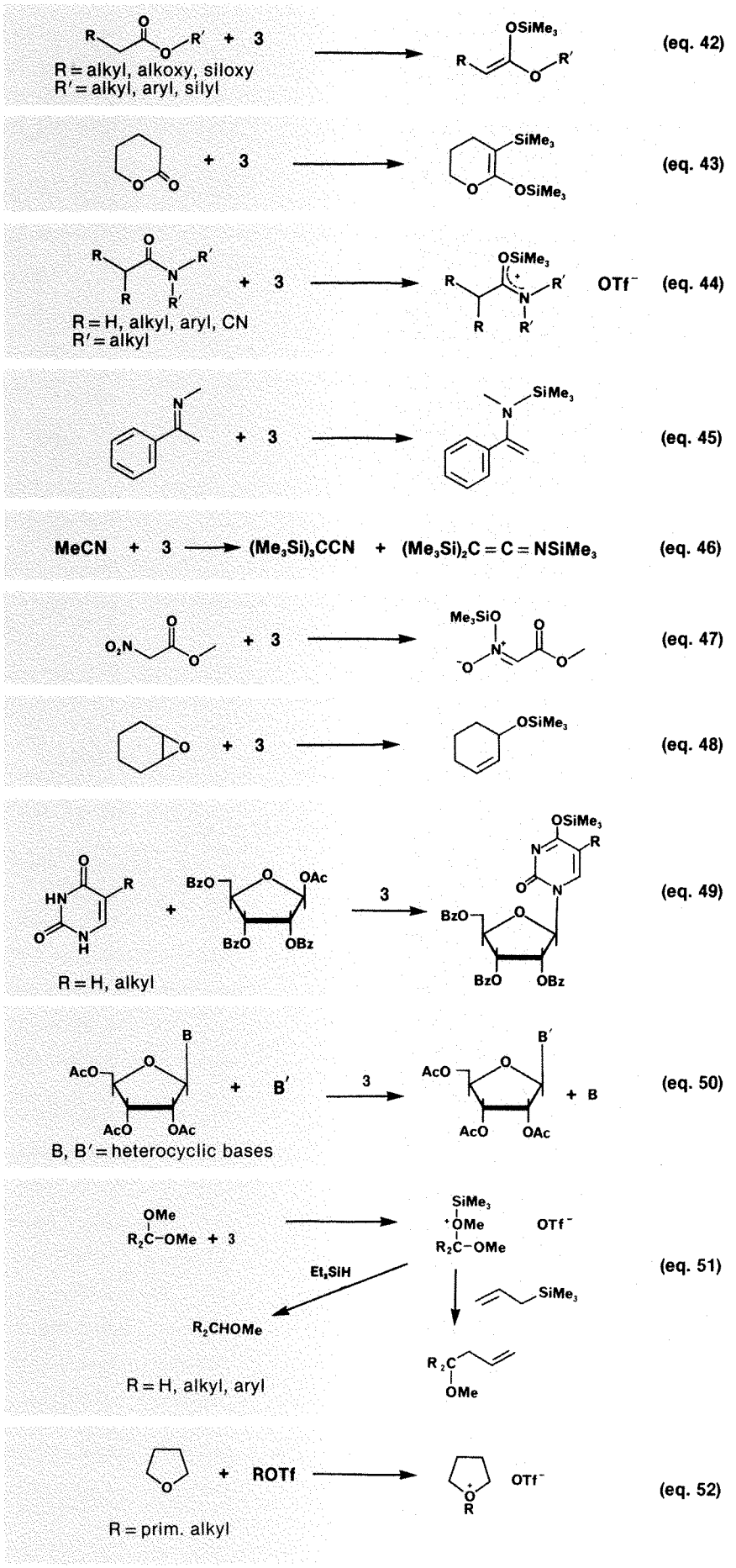
There are a variety of other nitrogen-containing organics which react readily with **3**. Tertiary amines which are used for deprotonation in the silylation reactions of **3** will also form adducts with **3**.[173] These adducts are very water-sensitive. Imines that have α-hydrogens can be silylated 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]

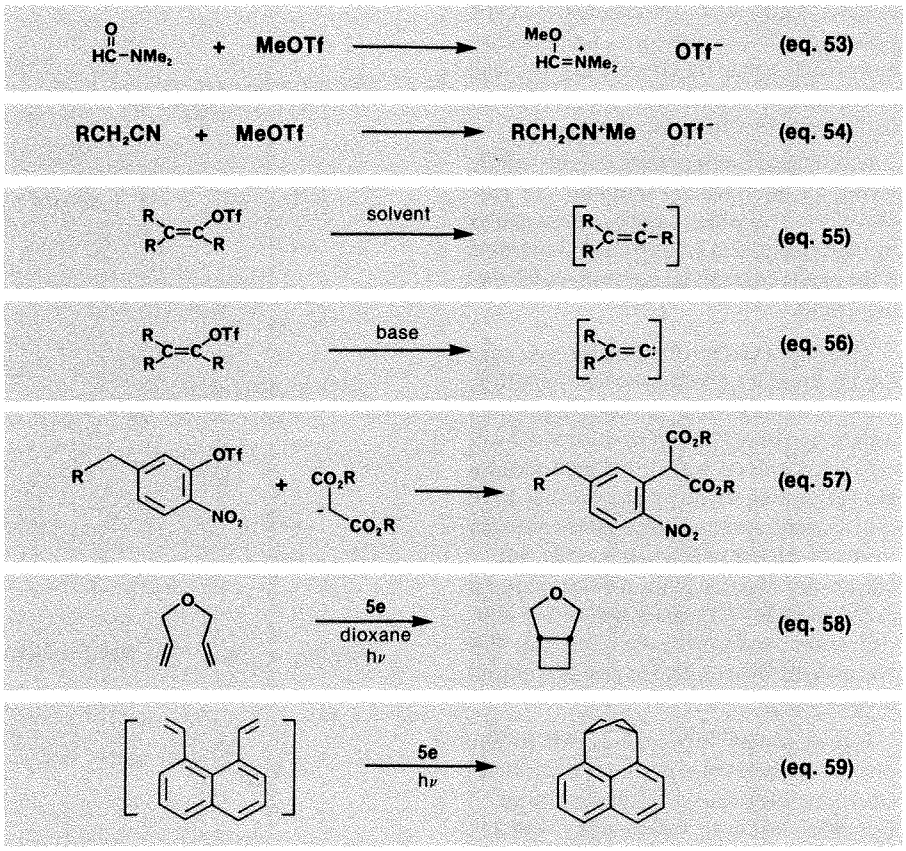
The alkyl, vinyl, and aryl esters of CF_3SO_3H have been included in a very recent review.[9] Please refer to this review for a complete description of the methods of preparation of these esters. Some applications of these triflates deserve mention here. Alkyl triflates can be used for alkylation at 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.

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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.

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