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Calixarenes

Mismatches and Mutagenic Lesions in Nucleic Acids

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A key work in the development of Neoclassical portraiture and one of the milestones of Jacques Louis David's artistic career, this lifesize double portrait (oil on canvas, 259.7 x 194.6 cm) of 1788 depicts the celebrated statesman and chemist Antoine Laurent Lavoisier and his wife, Marie Anne Pierrette Paulze. Lavoisier, who is perhaps best known for his pioneering studies of oxygen, gunpowder, and the chemical composition of water, also developed and codified a reformed system of chemical nomenclature. In 1789 his theories were published in the *Traité élémentaire de chimie*, a volume for which Madame Lavoisier, who often assisted her husband and is said to have studied under David, prepared the illustrations. While the talents of Madame Lavoisier, here represented as a kind of muse inspiring her husband, are evoked by the portfolio of drawings that rests on an armchair behind her, Lavoisier's chemical experiments, including two relating to gunpowder and oxygen, are amply represented by the various scientific instruments on the table and floor. The manuscript from which he is distracted may be that of the *Traité*, on which he is known to have been working in 1788.

The Metropolitan Museum of Art, Purchase, Mr. and Mrs. Charles Wrightsman Gift, in honor of Everett Fahy, 1977.

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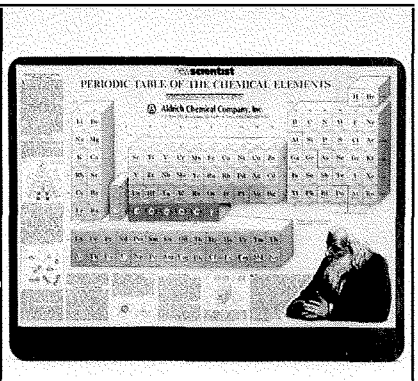

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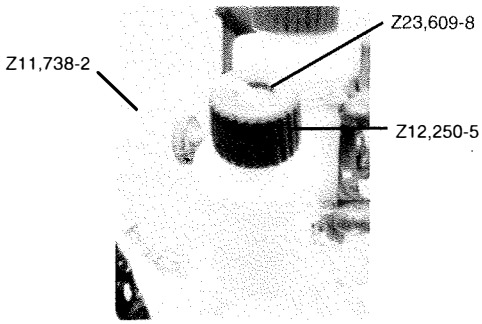

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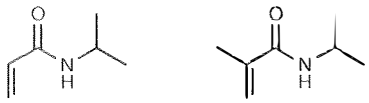
by Jai Nagarkatti

Jai Nagarkatti, President

"Molecular Accordion" Synthesis



1 2

Poly-*N*-isopropylacrylamide and its derivatives have unique solution properties. For example, when this polymer is adsorbed on a liposome surface, it exhibits a reversible folding or a "molecular accordion" effect. The above two acrylamides, suggested by Dr. Francoise Winnik are the needed monomers and both are now available.

Rignsdorf, H.; Vezemer, J.; Winnik, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 315.

Calixarenes

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A. Introduction

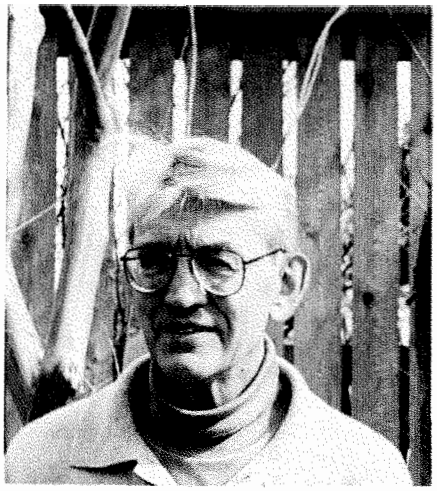
Calixarenes are rather recent arrivals on the scene of host/guest chemistry.[1] Although rooted in the nineteenth century phenol/formaldehyde chemistry of Adolf von Baeyer,[2] they did not become identified entities until approximately 50 years ago when Alois Zinke[3] treated *p*-alkylphenols with formaldehyde in the presence of base at high temperatures and obtained high melting substances to which he assigned cyclic tetrameric structures. However, the Zinke products proved to be mixtures[4] whose preparation was capricious.

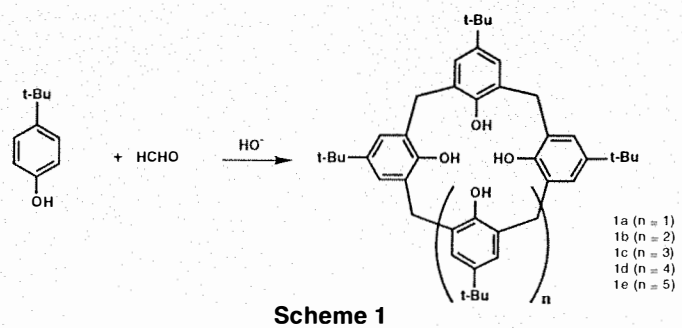
These problems were not overcome until the late 1970's when Gutsche showed that careful control of reaction conditions can provide good yields of pure compounds of various ring sizes.[5] Concomitantly, he named these compounds "calixarenes" because of their resemblance in shape to a type of Greek vase called a "calix crater".[3] Today, the easy one-step preparations of the cyclic tetramer[6a] (**1a**), cyclic hexamer[6b] (**1c**), and cyclic octamer[6c] (**1e**) from *p-tert*-butylphenol and formaldehyde make these materials extremely attractive for a variety of types of structural, conformational, and host/guest studies, as set forth in detail in two books[7] and several review articles.[8]

B. Synthesis and structural proof

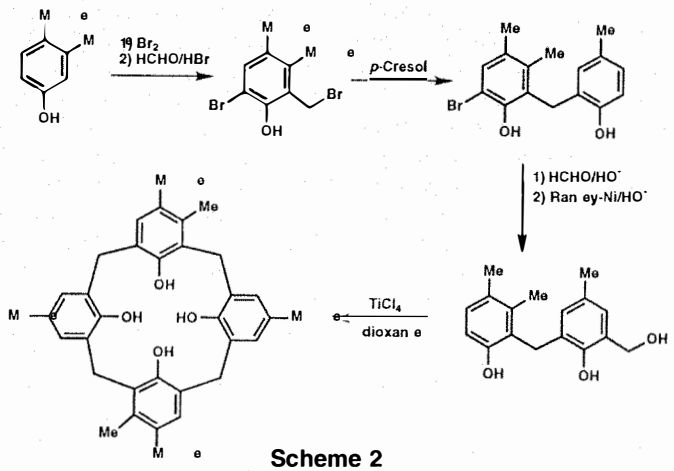
The quintessential one-step calixarene synthesis is the base-induced condensation of *p-tert*-butylphenol which, depending on reaction conditions, produces **1a** in 50% yield, **1c** in 85% yield, or **1e** in 65% yield (**Scheme 1**). The odd-numbered *p-tert*-butylcalixarenes **1b**[6d] and **1d**[6c] can also be obtained but in yields of only 10-15%, while *p-tert*-butylcalixarenes containing 9-14 aryl rings can be isolated in yields of 1% or less.[9] Although the one-step procedure is generally less successful with other *p*-alkylphenols, a number of such syntheses have been reported including the preparation of *p*-benzylcalix[5]arene in 33% yield,[10a] *p*-methylcalix[6]arene in 74% yield,[10b] and *p*-adamantylcalix[8]arene in 72% yield.[10c]

Concomitant with the work in Gutsche's laboratory that led to useful one-step





Scheme 1



Scheme 2

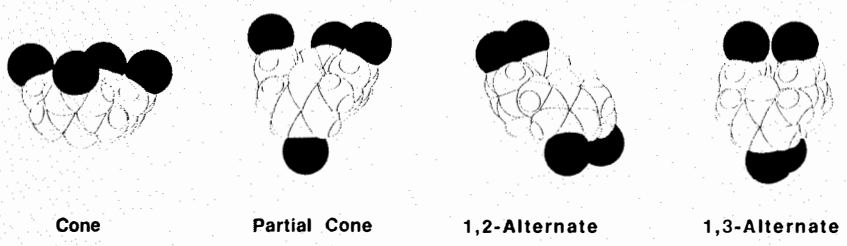
syntheses, investigations were being conducted in Kämmerer's laboratory[11] exploiting the multi-step synthesis reported earlier by Hayes and Hunter.[12] This approach, which has been greatly improved and expanded by Böhmer[13] through the use of convergent procedures, permits the synthesis of unsymmetrically-substituted calixarenes, as illustrated in **Scheme 2**.

The gross structures of the calixarenes obtained by the one-step procedure were correctly inferred from chemical and spectral evidence.[5] However, conclusive confirmation of the structure was provided by Andreetti, Ungaro, and Pochini's X-ray crystallographic determinations, first on **1a**[14] and subsequently on a number of other calixarenes. Today, almost 200 calixarene structures have been established by this technique.

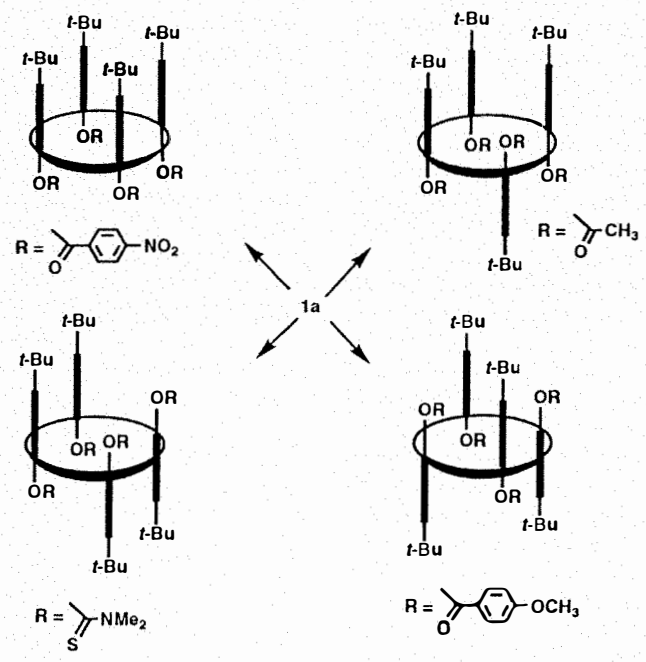
C. Physical Properties

The parent calixarenes are high-melting compounds. Absolutely pure **1e**, for example, melts at 418-420°C, and *p*-adamantylcalix[4]arene melts above 450°C. Although they are almost completely insoluble in water and only sparingly soluble in organic solvents, appropriate derivatization can render them soluble in both environments.

Calixarenes are surprisingly acidic. The pK_1 for *p*-nitrocalix[4]arene,[15] for example, is 2.9, while pK_2, pK_3, and pK_4 values are more normal and fall in the range 10.9 to >14. This hyperacidity is ascribed to the exceptionally strong intramolecular hydrogen bonding in the calix[4]arenes as indicated by the OH stretching at 3160cm^{-1} in the IR spectrum of **1a,** a value that is approximately 400cm^{-1} lower than for simple phenols.



Scheme 3



Scheme 4

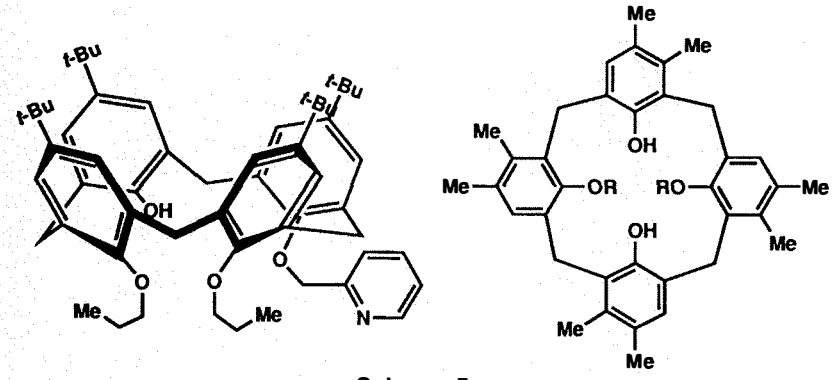
D. Stereochemical Properties

The most intensively studied stereochemical property of the calixarenes is their conformational behavior which results from the interconversion of the aryl units between "up" and "down" orientations. For calix[4]arenes, this occurs only by a "lower rim (i.e., OH groups) through the annulus" pathway regardless of the *p*-substituent, but for larger calixarenes an "upper rim through the annulus" pathway is also available if the *p*-substituents are sufficiently small.

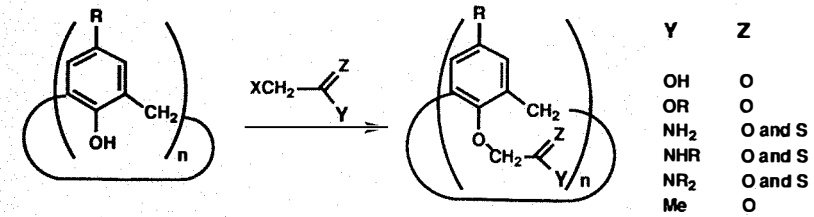
As first perceived by Cornforth,[4a] calix[4]arenes can exist in four "up/down" conformations which sometime later were named[7a] "cone", "partial cone", "1,2-alternate", and "1,3-alternate" (**Scheme 3**). Because of strong intramolecular hydrogen bonding **1a** exists almost entirely as the cone conformer. With increasing numbers of aryl groups, however, the flexibility and variety of available conformations rapidly escalate, and the predominance of the cone conformer diminishes. The cyclic octamer **1e**, for example, assumes an almost planar, pleated loop conformation in the solid state.[16]

Conformational interconversion can be curtailed if the *p*-carbons and the phenolic oxygens both carry sufficiently large groups. In the calix[4]arenes, a hydrogen atom suffices for the *p*-substituent and an *n*-propyl group for the *O*-substituent.[17] In the calix[5]arenes, *p*-substituents larger than a hydrogen atom and *O*-substituents larger than a butyl group are required.[18] In the calix[6]arenes even a *tert*-butyl group is not quite large enough as the *p*-substituent,[19a] and a benzyl group is not quite large enough as the *O*-substituent.[19b] When the mobility of a calixarene is curtailed by appropriate derivatization the system freezes into one or more of the available conformations, depending on a variety of factors not yet completely understood. For example, **1a** reacts with *p*-nitrobenzoyl chloride to yield the cone conformer,[20a] with acetyl chloride to give the partial cone conformer,[20b] with *p*-methoxybenzoyl chloride to give the 1,3-alternate conformer,[20a] and with *N,N*-dimethylthiocarbamoyl chloride to give, *inter alia*, the 1,2-conformer[20c] (**Scheme 4**).

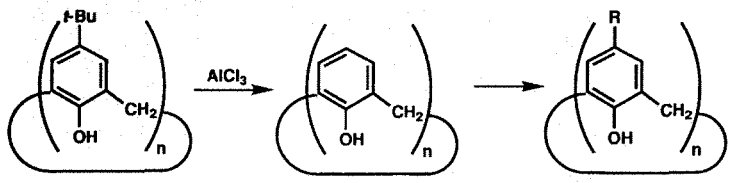
NMR spectral studies have proven to be invaluable for examining the conformational behavior of the calixarenes. They provide a means for measuring the rate of conformational interconversion of the mobile calixarenes, and a means for establishing



Scheme 5

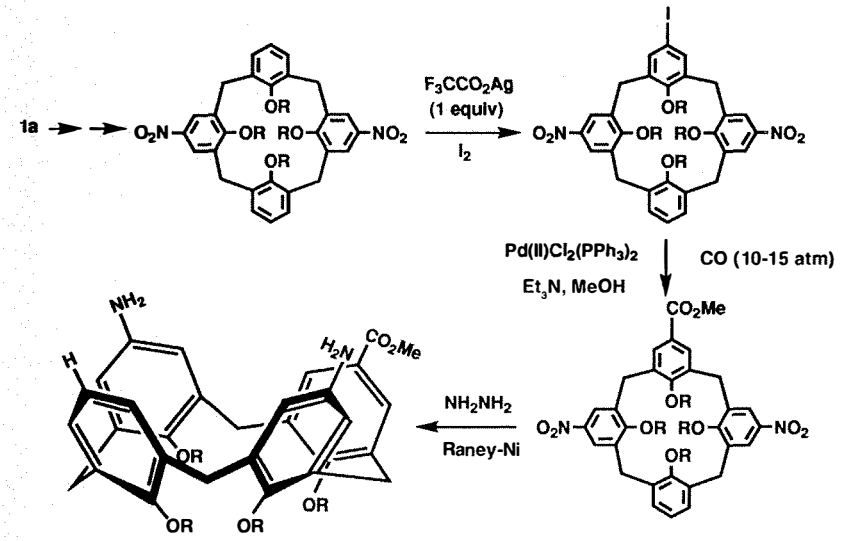


Scheme 6



R = Br, I, NO_2, NH_2, CH_2NR_2, CH_2NH_2, N_2Ar, CN, $CH_2CH_2NH_2$, CO_2H, CH_2CO_2H, $CH_2CH_2CO_2H$, CH_2OH, CH_2SH, SO_3H, SO_2Cl, CHO, $COCH_3$, COC_6H_5

Scheme 7



Scheme 8

the identity of the conformations of the immobile calixarenes. In both applications attention is focused on the $ArCH_2Ar$ methylene groups, taking advantage of the pattern of the resonance in the ^1H-NMR spectrum[21] and the position of the resonance in the ^{13}C- NMR spectrum.[22]

Calixarenes can be rendered chiral by the attachment of chiral moieties[23] or through the creation of an unsymmetrical substitution pattern via upper rim and/or lower rim substitution combined with conformational control. A number of inherently chiral calixarenes have been synthesized,[24] the earliest example being reported by Gutsche.[24a] Only recently, however, have optical resolutions of calixarenes such as those shown in **Scheme 5** been achieved.[25]

E. Reactions

Lower Rim Functionalization. The OH groups of the lower rim provide obvious sites for the attachment of other functional groups via ether and ester formation. A particularly useful group of syntheses involves the reaction with α-halocarbonyl compounds to give the esters, acids, amides, thioamides, and ketones shown in **Scheme 6**.[26]

Upper Rim Functionalization. It is a fortunate circumstance that *tert*-butyl groups attached to phenyl rings are easily removed by Lewis acid-catalysis.[27] Thus treatment of **1a-1e** with $AlCl_3$ yields the corresponding calixarenes with a hydrogen atom instead of a *tert*-butyl group in the *p*-position.

A variety of procedures have been employed for subsequently introducing groups into the *p*-positions, including electrophilic substitution (i.e., bromination,[28] iodination,[29] nitration,[30] sulfonation,[31] chlorosulfonation,[32] acylation,[33] diazo coupling,[34] formylation[35]), Claisen rearrangement of *O*-allyl to *p*-allylcalixarenes followed by transformations of the allyl group,[36] Mannich reaction with dialkylamines followed by quaternization and treatment with nucleophiles,[37] chloromethylation followed by treatment with nucleophiles,[38] mercuration,[39] and tricarbonylchromylation.[40] By means of these procedures calixarenes are now available containing, *inter alia*, the functional groups shown in **Scheme 7**. Also, the depth of the cavity has been extended by the introduction of aryl groups onto the *p*-positions.[41]

Selective Functionalization. Selective lower rim functionalization can be effected by the appropriate choice of reagents and conditions. Calix[4]arenes, for example, can be converted to mono-, 1,2-di-, 1,3-di-, tri-, or tetra-ethers and -esters, although comparable reactions for the larger calixarenes remain incompletely worked out. The earliest example of an upper rim

selective functionalization is the synthesis of calix[4]arene carrying a single *p*-allyl group, accomplished by subjecting the mono-*O*-allyl tribenzoate to Claisen rearrangement.[42] One of the several recent examples[43] is the synthesis of the *p*-diaminocarbomethoxycalix[4]arene shown in **Scheme 8**.[43d]

Bridging and Coupling Reactions. Numerous examples exist of calixarenes bridged across the lower rim and/or upper rim, or coupled between two or even three calixarenes. Typical of lower rim bridging (**Scheme 9**) are ferrocene-bridged calix[4]-arenes,[44] hemispherand-bridged calix[4]-arenes,[45] double cavity calix[4]arenes,[46] polyoxyethylene-bridged calix[4]arenes and calix[5]-arenes,[47] diamide-bridged calix[4]-arenes[48] aryl-bridged calix[4]arenes[49a] and calix[6]arenes,[49b] and phosphorus-bridged calix[4]arenes.[50] Examples of upper rim bridging include polymethylene-bridged calix[4]arenes[51] and polyoxyethylene-bridged calix[4]arenes.[52] Bis-calixarenes have been made by lower rim-lower rim juncture,[53] upper rim-upper rim juncture,[54] and lower rim-upper rim juncture (**Scheme 9**).[55] Calixarenes coupled to calix-resorcarenes[56] and to cyclodextrins[56,57] have also been prepared.

Polymerization Reactions. Calixarenes have been incorporated into polymers in various ways, such as the radical-induced polymerization of a calix[4]arene carrying a methacrylate moiety.[58]

Replacement of OH. Calix[4]arenes have been prepared in which one, two, three, or all four of the OH groups have been replaced by H[59] or SH,[60] or one and two OH groups by NH_2.[61] A calix[5]arene has been prepared in which one OH group has been replaced by H.[62]

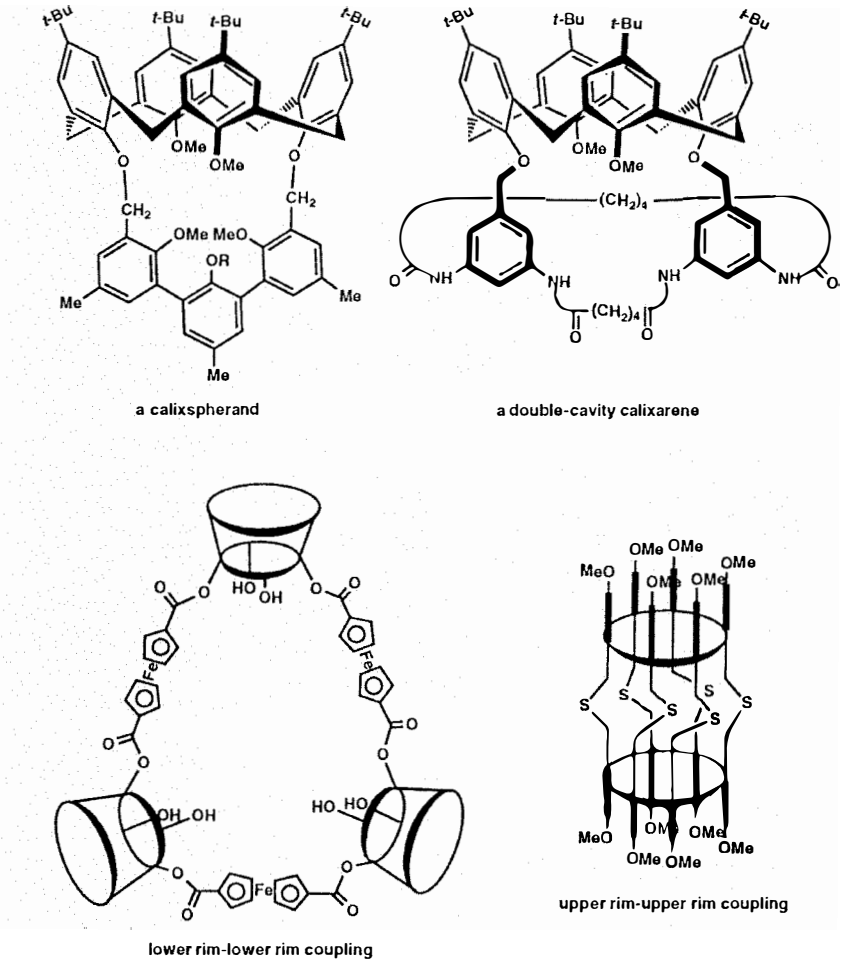
Oxidation. Chromium reagents have been used to convert the $ArCH_2Ar$ methylenes to carbonyl groups.[63] Ring oxidation to produce calix[4]tetraquinone has been effected in a multi-step process[64a] and in a single step process by the action of ClO_2 on calix[4]arene or $Tl(OCOCF_3)_3$ on *p-tert*-butylcalix[4]-arene.[64b] Calix[5]pentaquinone and calix[6]hexaquinone have also been obtained by the ClO_2 procedure.[64b] Calix[4]arenes containing fewer than 4 quinone rings have been prepared.[64b,c] Oxidation of **1a** with tetrabutylammonium tribromide yields bis(spirodienone) derivatives.[65]

F. Complexation Studies[66]

Solid State Complexation. The formation of stable solid state complexes was observed even before the structures of the calixarenes had been established, and this feature continues to be a topic for study by X-ray crystallographers. It is also the nemesis of experimenters striving to prepare pure, solvent-free calixarenes for elemental analysis. Complex formation with molecules is exemplified by **1a** which tightly binds $CHCl_3$, benzene, toluene, xylene, and anisole,[67a] and **1b** which binds tetralin.[67b] Numerous cases of solid state cation binding have been reported. Typical examples include the titanium[68a] and nickel[68b] complexes of **1a**, a titanium complex[68c] of **1c**, a thorium[69d] complex of **1e**, europium complexes[68e] of **1a** and **1e** (including third-sphere coordination),[68f] a mercury complex of calix[4]arene-tetrathiol,[68g] and the tetraalkylammonium complexes of calixarene anions.[68h]

Solution State Complexation of Ions. Much of the current study of complex formation with calixarenes focuses on the solution state binding of metal cations as first observed by Izatt[69] with the parent calixarenes **1a**, **1c**, and **1e**. McKervey[70] and others have carried out extensive measurements of the interaction of Group I and II cations with calixarenes of the type shown in **Scheme 6.** They have demonstrated that calix[4]arenes show a preference for Na^+ while calix[6]arenes show a preference for K^+, Rb^+, and Cs^+ with the tetraketones (Y = Me, Z = O) being better extractants for Li^+, Rb^+, and Cs^+ than the tetraesters (Y = OR, Z = O). Calix[4]arene with two carboxylic acid groups on the lower rim[71a,b] shows high selectivity for Ca^{2+} in the presence of cationic mixtures of Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}, and a calix[4]arene carrying indoaniline moieties on the upper rim provides a chromogenic ionophore for this cation.[71c] Various other moieties, including pyrene,[72a] benzothiazene,[72b] anthracene,[72c] nitrophenol,[72d] and pteridine,[72e] have also been incorporated into various calixarenes as chromogenic ionophores for selected cations.

Lanthanides form complexes with calix[4]arenes carrying ethylphosphonate groups on the lower rim.[73] Calix[4]-arenetetraamides form complexes with europium, gadolinium, and terbium,[74] providing potentially useful fluoroimmuno assay agents. Calixspherands (**Scheme 9**) are



Scheme 9

particularlyeffective complexing agents for Rb^+ and are useful for monitoring blood flow.[75]

Calix[4]arenes substituted on the upper rim with aminoethyl groups[37a] or the lower rim with oximino groups[76] form complexes with Cu^{2+}, Ni^{2+}, Co^{2+}, Pt^{2+}, and Fe^{3+}. The complexation of UO_2^{2+} has received special attention, particularly from Shinkai and coworkers, because of its pertinence to nuclear fission processes. Especially effective and highly selective with respect to other cations such as Ni^{2+}, Mg^{2+}, and Zn^{2+} is a calix[6]arene carrying three methyl ether groups and three carboxymethyl ether groups on the lower rim.[77] A chromogenic UO_2^{2+} sensor incorporates a *p*-dimethylaminophenylazo moiety on the upper rim of a calix[6]arene.[78]

A few studies of anion complexation by calixarenes have been reported, as for example the binding of halides, $H_2PO_4^-$, and HSO_4^- has been demonstrated by a calix[4]arene carrying bipyridyl residues complexed to Ru^{2+} on the lower rim.[79]

Solution State Complexation of Molecules. Among the numerous molecules (e.g., various aromatic hydrocarbons)[80] that form complexes with calixarenes, fullerene has captured particular attention.[81]

G. Catalysis Studies[82]

Although calixarenes of several ring sizes carrying a variety of functional groups are now available, relatively few examples of calixarene-catalyzed reactions have been reported. One of the earliest is Shinkai's demonstration that *p*-sulfonatocalix[6]-arene catalyzes the hydration of *N*-benzyl-1,4-dihydronicotinamide,[83a] subsequently shown to also be catalyzed by *p*-carboxyethylcalixarenes.[37b] A more recent example is a calixarene-crown-5 prepared by Ungaro and coworkers[84] in which an ester moiety on the lower rim undergoes methanolysis 10^6 times faster in the presence of Ba^{2+} than in its absence, attributed to electrophilic catalysis by the complexed Ba^{2+}.

H. Practical Applications[85]

From the outset, calixarenes have had close ties with industrial operations. Zinke's investigations were undertaken to study the curing process in Bakelite formation, Kämmerer's work grew out of polymer studies, and Gutsche's involvement stemmed from knowledge of the phenol/formaldehyde processes employed by the Petrolite Corporation in the manufacture of surfactants.

Today, almost 100 patents have been issued for uses and processes involving calixarenes, including removal of Cs from nuclear wastes,[86a] removal of UO_2^{2+} from sea water,[86b] acceleration of polymerization of Loctite adhesive,[86c] stabilizers for organic materials,[86d] toners for developing electrostatic images,[86e] hair dyes,[86f] recovery of lactic acid from solutions,[86g] ion-sensitive field-effect transistors (ISFET),[86h] and liquid crystal applications[86i] to mention only some. Clearly, the calixarenes have established themselves not only as interesting items for study in the laboratory, but as potentially useful commodities as well.

I. References and notes

(1) The term "calixarene" was originally intended to describe the meta[1$_n$] cyclophanes carrying intra-annular OH groups. A closely related type of cyclic tetramer carrying eight extra-annular OH groups is obtained from the acid-catalyzed reaction of aldehydes (except HCHO) with resorcinol. These compounds, named "calix[4]resorcinarenes" or "calix[4]resorcarenes", are not included in the present review. Also omitted are the oxacalixarenes in which one or more of the bridging units is a CH_2OCH_2 moiety.

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About the author

David Gutsche received a B.A. degree from Oberlin College in 1943, worked 18 months on the U.S. Department of Agriculture's penicillin project in the Department of Biochemistry at the University of Wisconsin, and then began graduate work in the Department of Chemistry.

Upon receiving the Ph.D. degree in 1947 under the direction of Wm. S. Johnson, he joined the faculty of Washington University in St. Louis where he remained for the next 42 years, rising to the rank of Professor and serving as Chairman of the department 1970-1976. Leaving Washington University as Professor Emeritus in 1989 he became the Robert A. Welch Professor at Texas Christian University where he continues to conduct research.

His research interests have included organic synthesis, diazoalkane ring enlargements, carbene reactions, photochemistry, micelle chemistry, polyfunctional catalysis, and, most recently, calixarene chemistry.

He has served on numerous boards, and among his honors are the St. Louis Award of the ACS, the Midwest Award of the ACS, Alumni Foundation Teaching Award from Washington University, election to AAAS Fellow, and a Guggenheim Fellowship.

Mismatches and Mutagenic Lesions in Nucleic Acids

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Introduction

Deoxyribonucleic acid (DNA) is the molecular store of genetic information. It normally exists as a right-handed double helix which is stabilised by hydrogen bonding between purine and pyrimidine (Watson-Crick) bases in complementary antiparallel strands and by base stacking interactions. The information stored in DNA is used to control the synthesis of proteins and this information must be copied or transcribed into a single strand of messenger ribonucleic acid (*m*-RNA) which directs protein synthesis. The messenger RNA interacts with the ribosomes and its genetic code is translated into a protein consisting of a specific sequence of amino acids.

One package of information or "gene" codes for one protein and the process whereby "DNA makes RNA makes PROTEINS" is known as the central dogma of molecular biology. The DNA code has only four letters — A, G, C, and T — and the genetic information within DNA is stored in the form of three letter words or triplets. There are 43 or 64 triplets, and each triplet codes for a specific amino acid. No two amino acids have the same code, but some amino acids have more than one triplet code and the codes for such amino acids are therefore degenerate. The elucidation of the genetic code between 1952 and 1966 heralded one of the most important scientific advances of modern times.

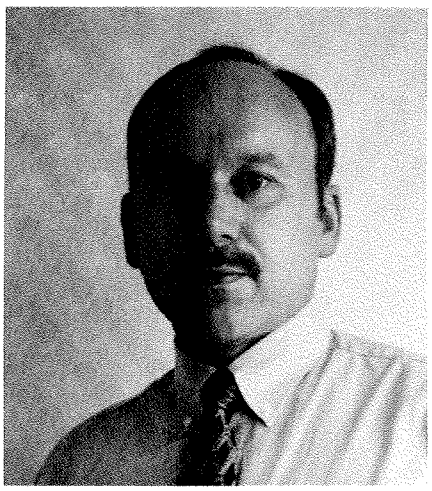
The origin of point mutations

Each time a cell divides, the two single strands of DNA act as templates from which new complementary strands are copied. This process is known as replication and it is not perfect. Perfection is expensive in terms of time and energy, and if DNA replication did not occasionally produce mistakes there would be no evolution.

The human genome has approximately 3×10^9 base pairs. The copying of such a huge amount of chemical information is a mammoth task and inevitably a few mistakes will be made. Genetic mistakes during replication occur at a very low level and point mutations are usually deleterious to the survival of the cell. A single mutation which alters one triplet of information will lead to a protein containing one incorrect amino acid. Some amino acid changes do not affect protein function. On occasion, a mutant protein may have reduced activity, leading to cell death, genetic disease, or carcinogenesis.

Occasionally, however, the mistake will produce a protein that works even better than the original, or even performs a new function. The mutant organism will therefore have an advantage over its wild-type counterparts and it will spread along with its altered gene through the population.

The molecular mechanism of replication, by which a DNA strand acts as a template to direct the synthesis of a new strand, was determined in 1953 by Francis Crick and James Watson.[1,2] The hydrogen bonding characteristics of the purine base guanine (G) are complementary to those of the pyrimidine cytosine (C), and likewise the purine adenine (A) is complementary to the pyrimidine thymine (T) (**Figure 1**). Consequently, the almost exclusive formation of Watson-Crick G.C and A.T base pairs during replication ensures that information contained in a parent DNA strand is copied accurately to the daughter strand.



However, the degree of fidelity achieved by the association of Watson-Crick base pairs is nowhere near sufficient to maintain genetic integrity. In addition to the correct G.C and A.T base pairs there are eight possible mispairs of varying thermodynamic

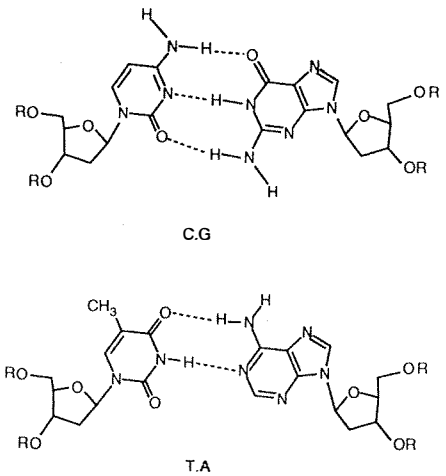


Figure 1. *Watson-Crick cytosine.guanine (C.G) and thymine.adenine (T.A) base pairs.*

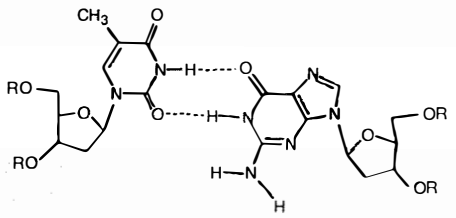


Figure 2. *The T.G wobble mismatched base pair found in X-ray structure analyses of DNA duplexes.*

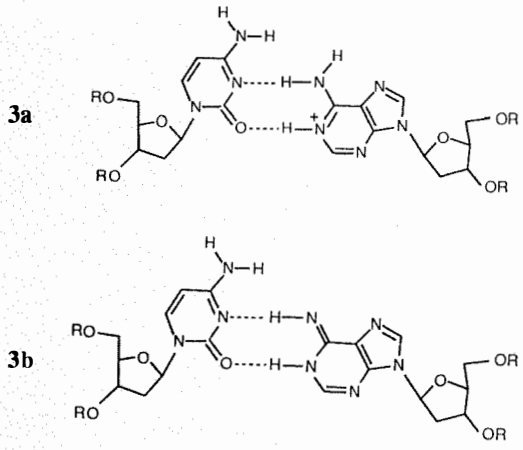


Figure 3. *The C.A wobble mismatched base pair found in X-ray structure analyses of DNA duplexes. Two possible arrangements of exchangeable protons are consistent with the structure of the C.A mismatch: the C.A⁺ form (**3a**) and the C.A(imino) form (**3b**). Ultraviolet melting and NMR experiments have subsequently shown that the C.A⁺ mispair is the most likely.*

stability, namely A.A, G.G, A.G, C.C, T.T, C.T, A.C, and G.T mismatches. DNA polymerase enzymes discriminate against mismatches during replication, but despite this, an occasional mispair is incorporated into the growing DNA strand. Proofreading and repair enzymes excise and replace mismatches with Watson-Crick base pairs, and these and related enzymes also repair chemical damage caused by cellular and environmental mutagens, ultraviolet light, and ionising radiation. Repair enzymes are remarkably efficient, reducing error rates during replication to levels as low as 1 in 10^9! In certain special contexts, non-Watson-Crick base pairs occur spontaneously and play important roles within the cell. Most notably such structures occur in *t*-RNA,[3] DNA triplexes,[4,5] and at telomeres at the ends of chromosomes.[6]

How can repair enzymes determine which strand of the DNA duplex should be repaired? A very neat and simple method has evolved to solve this problem. There is a small chemical difference between the parent strand and the daughter strand. In the parent strand some of the cytosine bases are methylated at the 5-position. Repair enzymes recognise this methyl group and make changes only to the daughter strand. When the proofreading and repair enzymes have determined that the daughter strand is a faithful complementary copy to the parent, an enzyme methylates specific cytosine bases. This signifies that the new DNA strand has been fully checked and found to be acceptable.

In order to gain insight into the fascinating problem of how repair enzymes recognise incorrect base pairs, we are investigating the structure and thermodynamic stability of DNA duplexes containing non-Watson-Crick base pairs. Our approach is to use a variety of physical techniques, principally X-ray crystallography, ultraviolet melting, and nuclear magnetic resonance spectroscopy.

Mispairing between the unmodified nucleic acid bases

G.T and A.C base pairs

The first mispair to be characterised in DNA by X-ray cystallographic methods was the purine-pyrimidine G.T mismatch (**Figure 2**).[7] This base pair adopts a "wobble" conformation of the type first proposed by Crick to explain G.U mispairing at the third codon position during codon:anticodon (*m*-RNA:*t*-RNA) interactions (U = uridine, the RNA equivalent of thymine). Such base pairing at the ribosome is partly responsible for the degeneracy in the genetic code.[8] The A.C mismatch in DNA[9] has a similar overall shape

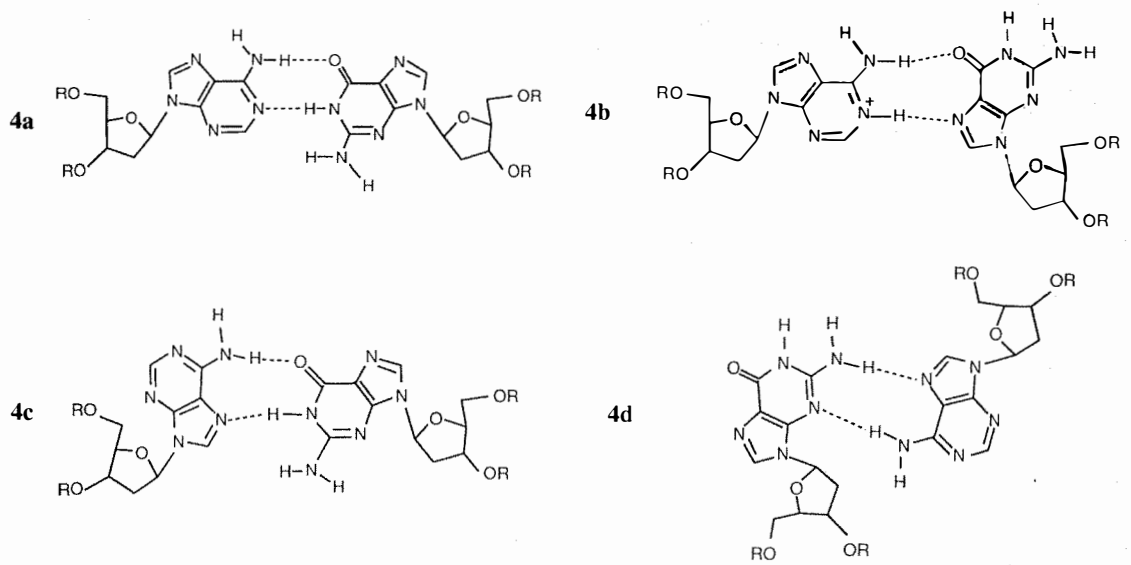


Figure 4. *Various forms of the G.A mismatch, all of which have been characterised in different duplexes: **4**a. A(anti).G(anti); **4b**. A⁺(anti).G(syn); **4c**. A(syn).G(anti); and **4d**. the stable G(anti).A(anti) base pair occurring in tandem G.A mismatches.*

to the G.T mispair, but it is not clear from the X-ray analysis how such an association can produce two inter-base hydrogen bonds.

It is rarely possible to determine the X-ray structure of a DNA duplex to a sufficiently high resolution to reveal hydrogen atoms, so other techniques must be employed if there is an ambiguity over the precise details of hydrogen bonding. In the case of the A.C mismatch there are two possible arrangements, either the adenine base is protonated (**Figure 3a**) or it exists in a rare tautomeric form (**Figure 3b**). Thermal denaturation studies on DNA duplexes can be carried out using the technique of ultraviolet melting. In this experiment the DNA is dissolved in an aqueous buffer and slowly heated until the duplex dissociates (or melts) to give two single strands. This leads to a significant increase in the ultraviolet absorption of the heterocyclic bases due to unstacking. The transition is monitored by ultraviolet spectroscopy. The melting temperature of the duplex is defined as the midpoint of the transition, corresponding to the maximum point in the first derivative of the melting curve.

Ultraviolet melting experiments and NMR spectroscopy over a wide pH range have shown that DNA duplexes containing A.C base pairs are unusually stable at low pH, strongly suggesting that the *N*(1)-atom of the adenine base is protonated.[10] In general, it is possible to postulate many mismatch base pairs with one base present as a minor tautomer. However, there is no direct experimental evidence for the existence of such base pairs. This idea, known as the tautomer hypothesis of base mispairing, has been discussed in detail by other workers.[11,12]

G.A base pairs

There is an intense interest in G.A base pairs as biochemical studies have shown that they are repaired less efficiently than other mismatches. There is no unique G.A mismatch structure and no fewer than four different forms have been characterised by X-ray crystallography and NMR techniques (**Figure 4**).[13-18] The precise form of the G.A mismatch is determined by the base-stacking environment, salt concentration, and pH. Thus, the enzymic repair of G.A mismatches raises a particular problem as the various forms of the G.A base pair represent very diverse targets for enzymic recognition.

We have recently found that in certain base stacking environments tandem G.A mismatches are as stable as Watson-Crick base pairs.[19,20] This is a significant discovery as it was previously thought that mismatches always destabilise DNA duplexes. However, in the special case of pyrimidine-G.A-purine tetramers this is certainly not true. The duplex formed by the deoxydecamer d(GAGTGAACGA)$_2$ contains six G.A base pairs and four Watson-Crick base pairs and is as stable as the equivalent Watson-Crick d(TAGTTAACTA)$_2$ duplex! This special stability of tandem G.A mismatches may have biological significance as single strands of DNA containing multiple G.A base pairs are known to be involved in triplex formation with two strands of C.T rich DNA. Self-association of the "spare" G.A rich DNA strand to form stem-loop structures containing stable tandem G.A base pairs may promote the formation of such triplexes.

Tandem G.A mismatches of this very stable kind have an unusual conformation (**Figure 4d**). The distortion of the sugar-phosphate backbone and the abnormal interaction of the two purine bases allow several functional groups to protrude into the major and minor grooves of the DNA duplex, thus offering potential targets for protein recognition.

The study of mismatches in RNA is particularly interesting as single strands of RNA, as in messenger RNA, are free to fold into complex tertiary structures which interact with the proteins that control translation. These structures are not yet well understood, but it is clear that tertiary structures within RNA are stabilised by both Watson-Crick and non Watson-Crick base pairs. Very recently, we have solved the structure of an RNA duplex containing two G.A mismatches and found the mispairs to be of the type G(*anti*).A(*anti*) (**Figure 4a**).[21] We are continuing our attempts to crystallise RNA stem-loops.

Mismatch structure and mutation frequency

Watson-Crick base pairs are pseudo symmetric about the glycosidic bonds joining the deoxyribose sugars to the bases. Thus, G.C, C.G, A.T, and T.A base pairs are all similar in overall shape. This is not generally the case for mismatches, and in general asymmetric mismatch base pairs are more easily detected by repair enzymes than symmetric mismatches. Thus, the asymmetric G.T and C.A pairs are more easily recognised than the less asymmetric G.A pairs (**Figure 5**). In addition to the asymmetry of certain mismatches, the distance between the C-1' atoms of the nucleotides is a potential

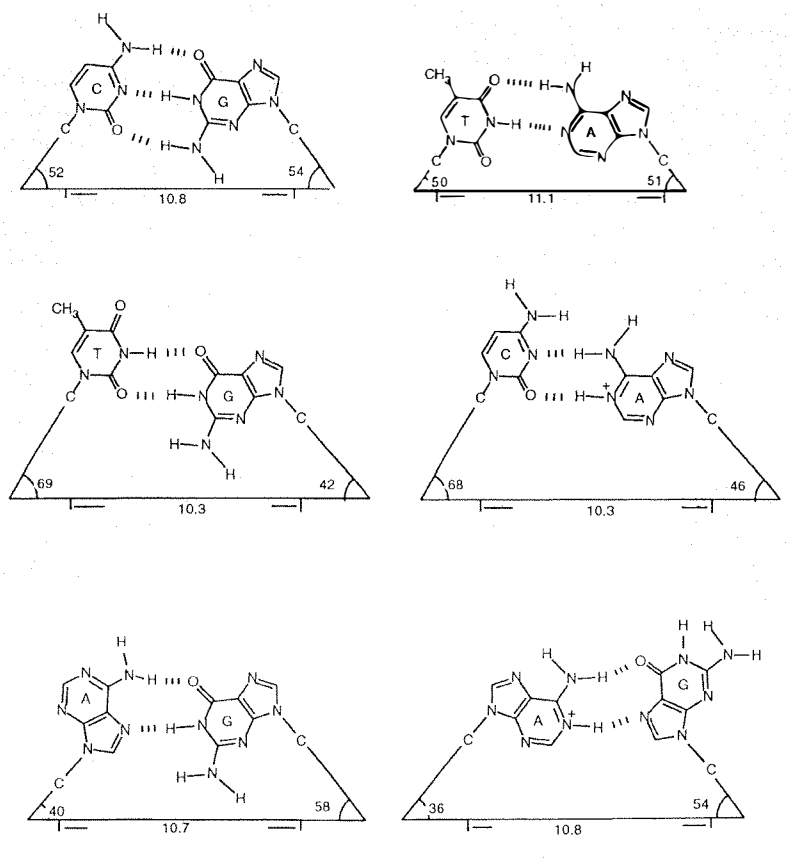


Figure 5. *Relative symmetry and width of a variety of Watson-Crick and mismatch base pairs. Internucleoside distances are measured in Angstrom units.*

source of discrimination as it has a direct effect on the width of the minor groove. For all purine(*anti*).purine(*anti*) base pairs this distance is longer than for Watson-Crick base pairs, and for all pyrimidine.pyrimidine mismatches the distance is shorter. We have carried out pH-dependent ultraviolet melting studies on pyrimidine.pyrimidine mismatches and our research suggests that the C.C base pair is protonated, whereas the T.C base pair is not (**Figure 6**).

Deoxyinosine

Inosine (I) is the analogue of guanosine which lacks an amino group at the 2-position of the purine ring (**Figure 7**). In RNA codon-anticodon interactions it participates in base pairing with A, C, and U, thus contributing to the degeneracy of the genetic code. Deoxyinosine occurs only rarely in DNA where it arises by deamination of deoxyguanosine. It is potentially mutagenic and a specific enzyme, hypoxanthine DNA glycosylase, has evolved to remove it.

A number of DNA duplexes containing deoxyinosine have been analysed by X-ray crystallographic methods in an attempt to explain the mutagenicity of this nucleoside. The I.T mismatch was found to adopt the same wobble configuration as the G.T mismatch,[22] whereas the I.A base pair displays similar diversity to the G.A base mispair.[23,24] Therefore, it seems unlikely that the mutagenicity of inosine can be explained on structural grounds.

We have used the technique of ultraviolet melting to show that some deoxyinosine-containing mismatches have surprisingly high thermodynamic stability. Mismatches generally destabilise the DNA duplex and give rise to local "melting", or opening up of the double strand. Repair enzymes almost certainly make use of this phenomenon to recognise incorrect base pairs. There is a correlation between mismatch instability and ease of repair. Therefore, in this respect deoxyinosine-containing mismatches would be particularly difficult to recognise. Interestingly, molecular biologists have made use of the special properties of inosine-containing mismatches when designing hybridisation probes from known protein sequences. Deoxyinosine is inserted into oligonucleotides in positions where there is a sequence ambiguity due to the degeneracy of the genetic code. The high thermal stability of inosine-containing mismatches ensures that the oligonucleotide hybridises efficiently to the target nucleic acid.

Mutagenic lesions in DNA-base pairs involving modified bases

The phosphates, sugars, and heterocyclic bases of DNA are susceptible to modification by a variety of reagents, including chemical carcinogens, ionising radiation, and ultraviolet light. Important examples of the changes that can occur to the DNA bases are methylation of guanine by alkylnitroso ureas, and oxidation of the 8-position of adenine or guanine by hydroxyl radicals generated by oxidation or γ-rays.

O(6)-methyl deoxyguanosine

In DNA, methylation of guanine at the O(6)-position changes the hydrogen bonding characteristics of the base and induces G to A transition mutations.[25] This indicates that the O(6)-MeG.T mispair is selected during replication in preference to the O(6)-MeG.C pair, (i.e., the mismatch is preferred to the putative Watson-Crick base pair). As both base pairs have very similar thermodynamic stability, discrimination by DNA polymerases must have a structural basis. Indeed, investigations have shown that at physiological pH, the O(6)-MeG.T mispair resembles a Watson-Crick base pair (**Figure 8a**), whereas the O(6)-MeG.C pair adopts a wobble conformation (**Figure 8b**).[26] Thus, the proofreading domain of DNA polymerase will "force" the modified guanine base to accept thymine as a partner instead of cytosine and the enzyme is tricked into allowing a mistake to pass by uncorrected.

Ultraviolet melting studies in our laboratory suggest that at low pH (below pH 6), the O(6)-MeG.C base pair resembles a Watson-Crick base pair (**Figure 8c**). Thus under these conditions, the O(6)-MeG base will behave like guanine and code correctly. We therefore predict that the mutagenic effect of O(6)-MeG will be pH-sensitive. Due to the highly mutagenic nature of O(6)-methyl guanine, a "suicide" enzyme has evolved which specifically repairs this base modification by excising the methyl group. The existence of this enzyme, O(6)-methyl guanine transferase, indicates that the DNA of all living organisms has been continually exposed to naturally occurring alkylating agents over an evolutionary time scale.

8-oxo purine bases

The reaction of the purine bases of DNA with hydroxyl radicals can result in the formation of 8-oxoadenine (O8A) and 8-oxoguanine (O8G). These bases exist predominantly in the 8-keto form (**Figure 9**) and their contribution to mutagenesis is currently the subject of a great deal of interest. Modification at the 8-position does not directly affect the ability of A and G to form Watson-Crick base pairs, but the presence of the bulky oxygen atom increases their

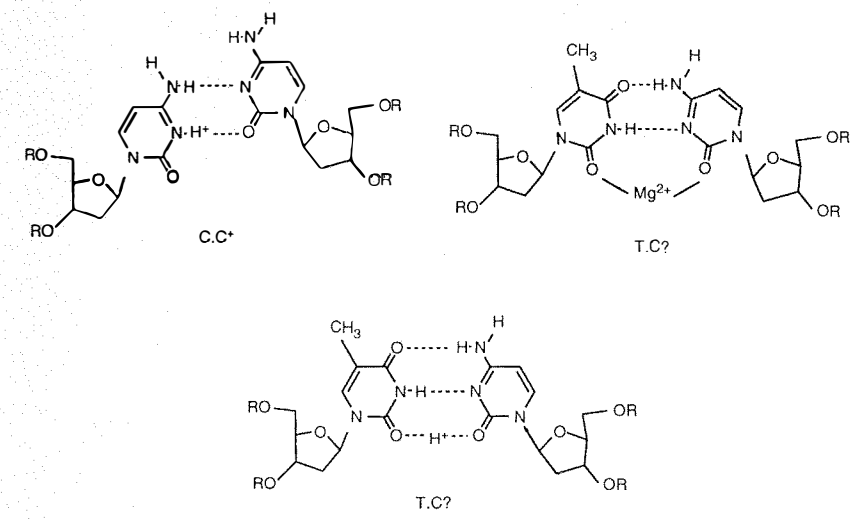


Figure 6. *Proposed structures of pyrimidine.pyrimidine mismatches.*

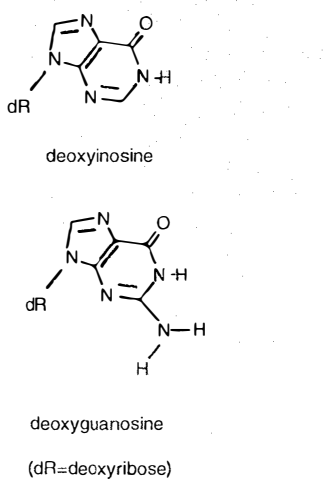


Figure 7. *A comparison of deoxyinosine and deoxyguanosine.*

tendency to adopt the *syn* conformation, thereby providing new possibilities for base mispairing. The presence of an O8G base in genomic DNA can lead to a G to T transversion mutation via an intermediate O8G.A base pair.

Investigations on oligonucleotide duplexes by NMR spectroscopy and recent X-ray crystallographic studies in our laboratory have shown that the base pair adopts an O8G(*syn*).A(*anti*) conformation (**Figure 9**) which is stabilised by two inter-base hydrogen bonds.[27,28] In addition to possessing reasonable thermodynamic stability, the O8G.A base pair is pseudo symmetric about the glycosidic bonds (the bonds joining the sugars to the bases) and therefore bears some structural resemblance to Watson-Crick base pairs. The similarity is particularly striking in the minor groove where the 8-oxygen atom of O8G lies in the position that would be occupied by the 2-oxygen atom of the thymine base in an A.T base pair. Thus, the O8G.A base pair is not readily recognised by proofreading enzymes.

In contrast to O8G, O8A (8-hydroxyadenine) is not particularly mutagenic. This is because the modified adenine base maintains a strong preference for thymine as a partner. An X-ray crystallographic study of a dodecanucleotide duplex has shown that the most likely alternative base pair, G.O8A, is asymmetric and bears some resemblance to a purine.pyrimidine mismatch.[29] It is therefore likely to be an easy target for repair enzymes. The G(syn).O8A(anti) base pair (**Figure 10**) is structurally very interesting, as it appears to be held together by four bifurcated hydrogen bonds. This arrangement allows the 2-amino group of guanine to fulfill its hydrogen bonding capacity by interacting with the oxygen atom of O8A as well as a neighbouring water molecule (not shown). Any form of base pairing that prevents the guanine 2-amino group from fulfilling its hydrogen bonding potential, either with the opposing base or with neighbouring water molecules, will tend to be unstable relative to the individual unpaired bases which are free to hydrogen bond to water molecules. This explains the thermodynamic instability of some forms of the G.A mismatch, in which the 2-amino group is sterically hindered, and the relatively high stability of certain inosine-containing base pairs, which lack the 2-amino group.

Other mutagenic lesions

1-*N*(6)-ethenoadenine (εA) is produced when DNA comes into contact with the chemical carcinogen chloroacetaldehyde. The modified base can no longer act as a hydrogen bond donor and, as a consequence, it forms unstable base pairs with all possible Watson-Crick bases. The least unstable of these is the εA.G base pair. We have recently determined the X-ray structure of this mispair in a DNA duplex. The εA base adopts the *syn* conformation and the base pair is neatly accommodated in the double helix (**Figure 11**).[30] We are currently studying the chemically modified base 3-*N*(4)-ethenocytosine which is also produced by the chemical reaction of chloroacetaldehyde on DNA. This base is known to be mutagenic, although the molecular basis of its mutagenicity is not yet understood.

Summary

Structural and thermodynamic studies on nucleic acids have revealed striking differences between Watson-Crick base pairs and mismatched base pairs. Unusually stable G.A mismatches have been characterised and these are the subject of continuing research. Very recent work has enabled us to explain the mutagenic nature of chemically induced lesions in DNA at the molecular level. Our current research is directed at developing immunochemical methods of quantifying DNA damage arising from the reaction of DNA with chemical carcinogens. Eventually, we hope to relate chemical damage and its effect on DNA structure to mutational frequency in a much more precise manner than is currently possible.

Acknowledgments

This work was sponsored by the U.K. SERC Molecular Recognition Initiative and by the Wellcome Trust. The author would also like to thank the Royal Society of Edinburgh for a Caledonian Research Fellowship.

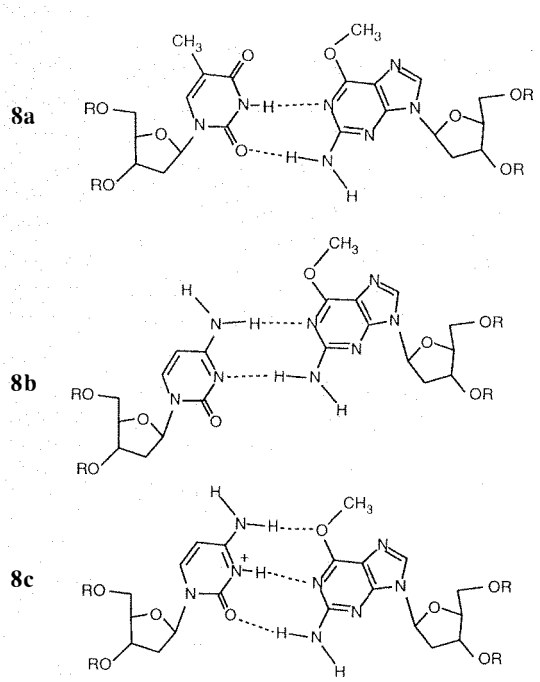


Figure 8. *The O(6)-MeG.T base pair (**8a**) which resembles a Watson-Crick base pair, the O(6)-MeG.C wobble base pair (**8b**), and the O(6)-MeG.C⁺ base pair (**8c**) which we predict will occur at low pH.*

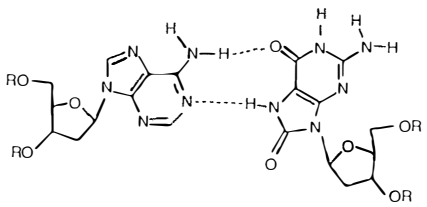


Figure 9. *The A(anti).O8G.(syn) base pair.*

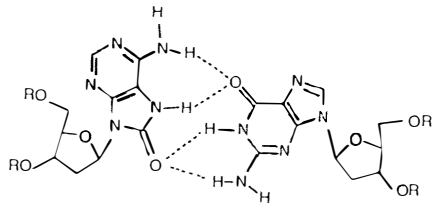


Figure 10. *The O8A(syn).G(anti) base pair.*

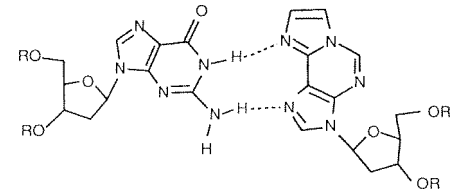


Figure 11. *The G(anti).εA(syn) base pair.*

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About the author

Professor Tom Brown was recently awarded the first Josef Loschmidt award, sponsored by Dr. Alfred Bader, for research into structure and mechanism in organic chemistry.

Professor Brown was educated at Broadway Grammar School Barnsley and Bradford University where he obtained a First Class Honours Degree in Chemistry (1975) and a Ph.D. in Organic Chemistry (1979) under the supervision of Professor Gordon Shaw. He then carried out postdoctoral research at Nottingham University, Oxford University, and Cambridge University. In 1985 he became lecturer in Organic Chemistry at Edinburgh University under the "New Blood" initiative. After five years he was promoted to reader, and in 1993 he was appointed Professor of Nucleic Acid Chemistry. Professor Brown's research interests are in two main areas: structural and thermodynamic properties of nucleic acids; and the application of novel chemically modified oligonucleotides to problems in molecular biology and medicine. He was recently awarded the MakDougall-Brisbane prize of the Royal Society of Edinburgh for scientific research achievement and he is currently a Royal Society of Edinburgh Caledonian Research Fellow.

In addition to his teaching and research responsibilities, Professor Brown is director of the ●SWEL DNA Unit which supplies standard and chemically modified oligonucleotides worldwide to over 2000 research groups in biology and medicine.

Professor Brown has recently moved to Southampton University to become the first Professor of Bio-organic Chemistry.

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About our Cover:

The painting that graces our cover is *Flowers in a Chantilly Vase* by Louis Tessier (ca. 1760, oil on canvas, 65.1 x 54.7 cm). Tessier was a member of a family of craftsmen and artists working for the Goeblins, and his chief fame rests on the flower designs he produced for tapestries and furniture upholstery. Best known are Tessier's designs for the sixth set of enframements for Charles-Antoine Coypel's *Don Quixote* series of tapestries. He also fashioned the ornament for Boucher's *Loves of the Gods* series. In addition, he produced paintings and drawings of flowers and still lifes.

Flowers in a Chantilly Vase displays a porcelain container from the royal Chantilly porcelain factory. The vase has a delightful design, apparently influenced by Japanese prototypes, and is filled with a flower arrangement that unrealistically, but delightfully, spreads to fill the rectangular space with a riot of color and form. It bears witness to the high competence of the professional specialists in flower and still-life painting in the age of Louis XV.

The painting is in the collection of The Saint Louis Art Museum.

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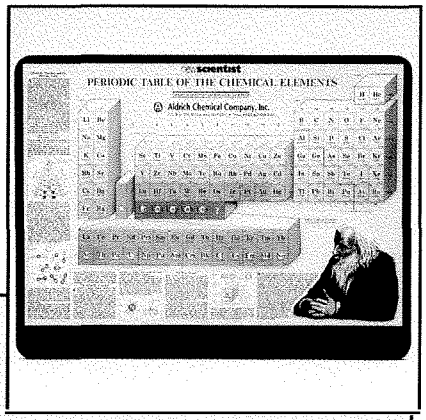

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"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President

$CF_3SO_3{}^{13}CH_3$

Dr. Shafiq of the University of Rochester (currently at the University of Florida) suggested that we make methyl-^{13}C triflate, the ^{13}C-analog of methyl triflate (Cat. No. **16,428-3**). Methyl triflate is known to be one of the most powerful methylating agents, readily methylating carbon, oxygen, nitrogen, and sulfur centers.[1-4]

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$CF_3SO_3CD_3$

We have also added the corresponding deuterium analog.

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

Triethylamine Tris(hydrogen fluoride): Applications in Synthesis

Martin A. McClinton
FAR Research Inc.
2210 Wilhelmina Ct.
Palm Bay, FL 32907
USA

Introduction

Although hydrogen fluoride is probably the most widely used industrial fluorinating reagent, its low boiling point and high corrosivity make it a difficult material to handle. Furthermore, in using hydrogen fluoride to synthesize organic molecules, its high reactivity often causes undesired side reactions, leading to lower yields, decreased purities, and a number of trace impurities.

In order to overcome the hazards involved in handling anhydrous hydrogen fluoride, a number of so called "onium poly(hydrogen fluorides)" have been developed.[1] Although Olah's Reagent [pyridinium poly(hydrogen fluoride)] is the most widely known of these complexes, triethylamine tris(hydrogen fluoride), **TREAT HF** (**1**), has a distinct advantage over this reagent in that it can be used in borosilicate glassware without corrosion.[2,3]

Properties

TREAT HF is a colorless liquid that boils at 78 °C at 1.5 mbar,[4] has a density of 0.996 g/L at 25 °C, and has a pH close to neutral.[5] The complex has a shelf life of at least one year and, as previously mentioned, is widely reported not to corrode borosilicate glassware (though on occasion, in elevated temperature applications, limited etching does occur in the vapor space above the liquid's surface). Although **1** is much less corrosive than anhydrous HF or Olah's Reagent, care must still be taken in handling the liquid.

Chemical reactions

TREAT HF is a mild and selective reagent that has been used in the fluorination of a wide variety of compounds. This review will discuss its chemistry in terms of different reaction types.

Addition

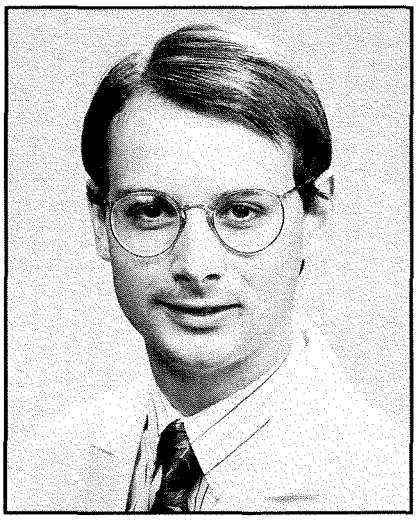
The Markovnikov addition of XF (X = halogen, SMe, SePh) to alkenes can be readily achieved using **1** and a suitable electrophilic reagent. For example, *N*-halosuccinimides in combination with the complex yield 1-fluoro-2-haloalkanes from alkenes (eq 1).[6,7] Note, however, that neighboring group participation often competes with the 1,2-addition. Such participation was effectively used in the synthesis of potential insecticides (eq 2).[8]

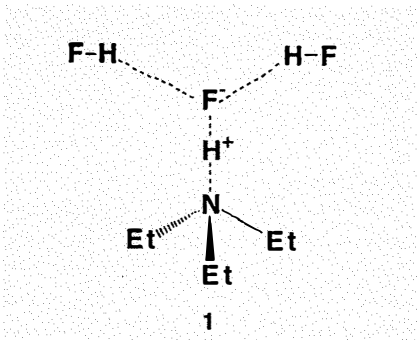
The addition of 'FSMe' has been achieved using a combination of dimethyl(methylthio)sulfonium tetrafluoroborate and **1** (eq 3).[9-11] As expected, the products of such reactions are specifically *anti*. In a similar fashion, 'FSePh' has been added to alkenes by employing *N*-phenylselenophthalimide (NPSP) and **1** (eq 4). It is worth noting that in this last example the acid-sensitive functionality remains intact during the reaction.[12]

Non-terminal alkynes also react with **1** and NPSP to give good yields of the corresponding *trans*-1-fluoro-2-benzeneselenylalkene (eq 5). Terminal alkynes, however, do not react specifically, yielding instead a wide variety of fluorinated products.[13] The benzeneselenyl functionality can be removed either by using MCPBA to give fluoroalkenes or by radical reduction to give the fluoroalkane.[12,13]

Substitution

Although the nucleophilicity of the fluoride ion in **1** is relatively low when compared to other fluoride ion sources (e.g., KF, Bu_4NF, etc.), it is substantial enough to permit substitution of labile leaving groups. The nucleophilicity can be further altered by varying the ratio of hydrogen fluoride to triethylamine (e.g., eq 6).[14] This shows that the relative fluorinating





1

Triethylamine tris(hydrogenfluoride)
= **TREAT HF**

ability varies in the order $Et_3N{\bullet}2HF > Et_3N{\bullet}3HF > Et_3N{\bullet}HF$. The variation in fluorinating ability appears to be linked to the stability of the complexes: upon heating under vacuum, triethylamine bis(hydrogen fluoride) loses triethylamine rather than hydrogen fluoride to form triethylamine tris(hydrogen fluoride).

Triethylamine bis(hydrogen fluoride) (**2**) can be easily prepared by the addition of triethylamine to **1** either prior to the reaction or slowly during its course (e.g., see reference 2). The difference in the

fluorinating abilities of the blends has been exploited in the preparation of fluorinated sugar molecules: **1** yielded the monofluorinated product whereas **2** gave the difluorinated sugar (eq 7). Interestingly, attempts to fluorinate the same sugar using $Et_4N^+HF_2^-$ resulted in tars.[14,15] A variety of other sugar derivatives have been fluorinated using **1** (eq 8).[16-18] It is worth noting, however, that substituents can 'walk' around the sugar ring (e.g., eq 7).

The fluorinating ability of **1** is not limited to sugar derivatives, as a number of active alkyl halides (eqs 9-11)[2,19,20] and even aromatic compounds (eqs 12-13)[2,20-23] are also reactive. In the example illustrated in equation 13, the use of ultrasound and **1** provided mild conditions for the decomposition of the diazonium salt.[23]

Oxiranes have been ring opened using **1** (eq 14).[24-26] In this example, **1** was found to be more selective than Olah's Reagent, pyridine tris(hydrogen fluoride), and collidine tris(hydrogen fluoride).[26] These latter reagents caused either destruction of the substrate or formation of mixtures.

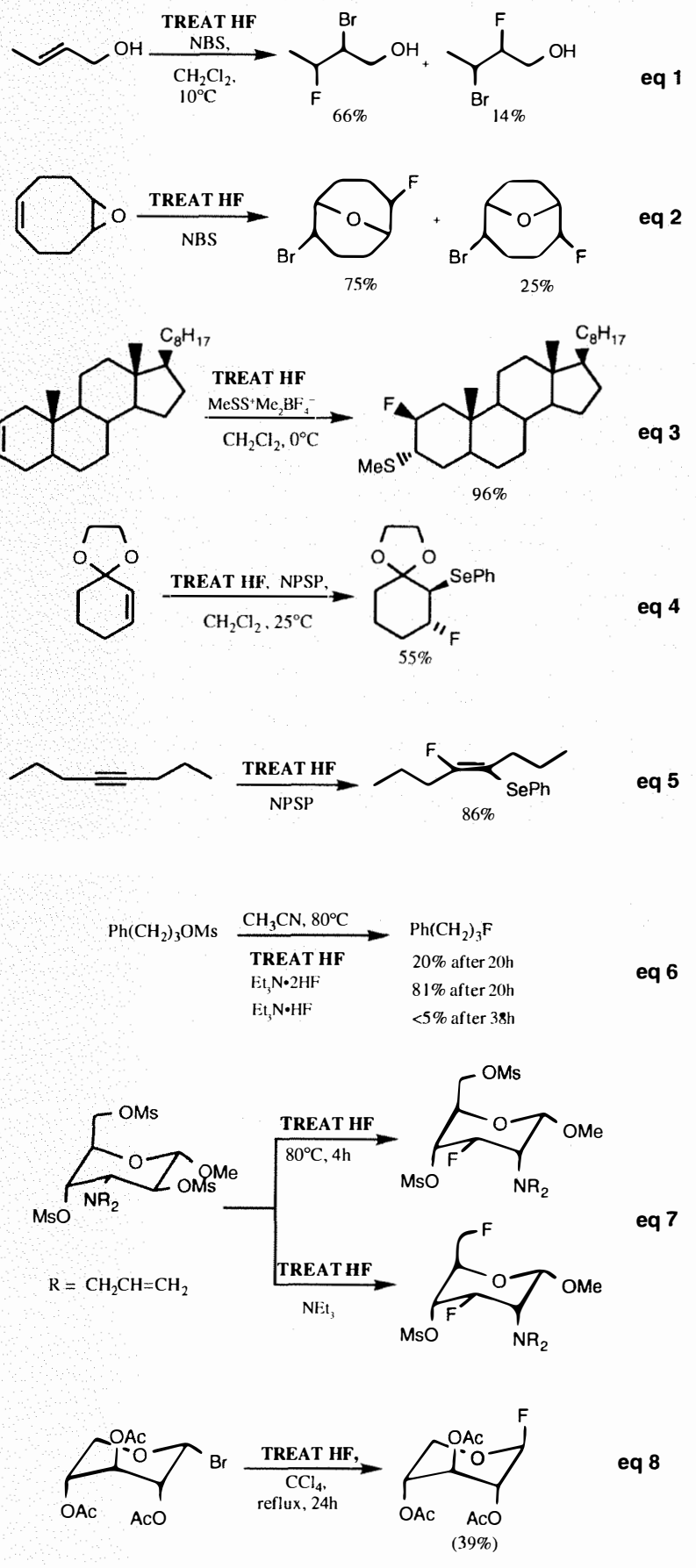
It should be noted that the ring opening of oxiranes using **1** is sensitive to temperature. Addition/substitution reactions have been successfully carried out on substituted oxiranes without any ring opened side products by employing lower reaction temperatures (eq 15).

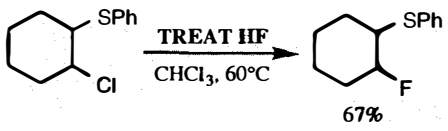
Finally, **1** was employed to open a strained cyclopropane ring as part of the synthetic strategy to prepare carbocyclic nucleosides as possible antiviral agents (eq 16).[27]

Desilylation

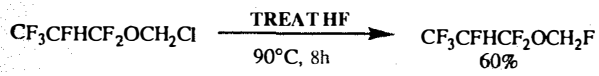
TREAT HF is rapidly becoming the reagent of choice for the desilylation of protected nucleotides, nucleosides, and oligonucleotides (eq 17).[28-30] It has proved more efficient than traditional reagents, especially for long RNA strands. Furthermore, **1** is less sensitive to moisture and provides a more facile workup than alternative reagents. Also, it has been found that **1** does not catalyze phosphodiester linkage migration.

TREAT HF has been used to deprotect silylated cyanohydrins and alcohols. In the former case, the reaction is reported to stop at the cyanohydrin stage. Conversion to the free ketone is readily achieved using aqueous sodium hydroxide in the reaction workup (eq 18).[31] Desilylation appears to be faster than substitution since diols protected with one silyl and one mesylate group can be selectively desilylated without fluorination occurring at the latter site (eq 19).[15]

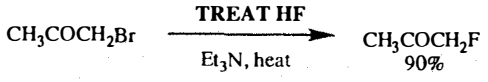




eq 9

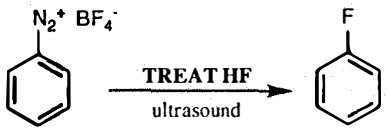


eq 10

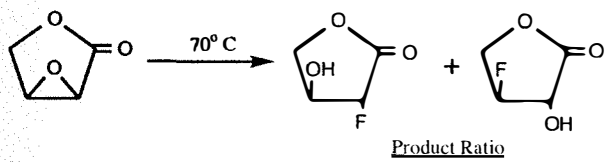


eq 11

eq 12

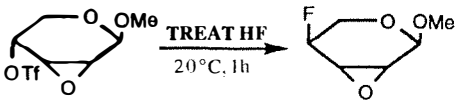


eq 13

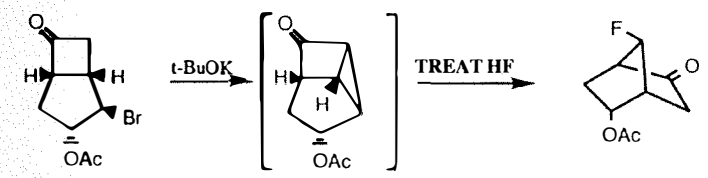


eq 14

	Product Ratio
TREAT HF, 3 days	1:0
Olah's Reagent, 1 day	destruction
Pyridine•3HF, 3 days	complex mixture
Collidine•3HF, 6 days	3:0



eq 15



eq 16

Inorganic compounds

TREAT HF has also been used to prepare fluorinated sulfur and phosphorus compounds.[2,32,33] Generally, the chlorinated analog is employed (e.g., eq 20), though the more elaborate leaving group $^{-}ON{=}CCl_2$ has been used to good effect.[34] In addition, the pentafluorotellurate ion has been generated from tellurium(IV) oxide and **1** (eq 21).[35]

Electrochemical reactions

The variety of substrates that have been electrochemically fluorinated using **1** include organosulfur, organoselenium, benzylic, olefinic, and aromatic compounds, in addition to aldehydes and hydrazones. In the case of organosulfur, organoselenium, and benzylic compounds, fluorination generally occurs α to the heteroatom or aromatic ring (eq 22).[36-38] This method has also been applied in the preparation of fluorinated β-lactams, which were not available using the previously reported methods (eq 23).[39] Longer reaction times and the passage of more current through the cell results in α,α-difluorination (eq 24).[36,40] The presence of a chiral auxiliary in the substrate can lead to enantioselectivity under monofluorinating conditions (eq 25).[41]

The electrochemical reaction of hydrazones with **1** yields monofluorinated products.[42] This is in contrast to other chemical methods that yield difluorinated compounds. Thus, benzophenone produced diphenylfluoromethane in 95% yield when electrolyzed with **1** in dichloromethane.

Aldehydes react with a variety of hydrogen fluoride-based solutions under electrochemical conditions to give acid fluorides.[43] The most effective solution reported was triethylamine penta(hydrogen fluoride) which gave 90% conversion to octanoyl fluoride from octanal by electrolysis. **TREAT HF** yielded 50% octanoyl fluoride under similar conditions.

When olefinic molecules are electrolyzed in the presence of **1**, addition occurs to yield the 1,2-difluoroadduct (eq 26), though 1,4-addition results with butadienes.[44] However, when acetonitrile is added to the solution, 1-fluoro-2-acetamides are also observed.[45] The electrolysis of solutions containing both aromatic compounds and **1** is usually nonspecific yielding a wide variety of products.[44,46,47] Finally, **1** has been used as the supporting electrolyte for the anodic methoxylation of organoselenium compounds.[48]

Conclusions

TREAT HF has proven itself to be an extremely useful source of fluoride ion for the synthesis of a wide range of organic compounds. Its almost neutral pH and non-corrosivity in borosilicate glassware make it an ideal reagent for both laboratory and industrial use.

Acknowledgment

I would like to thank Dr. T.S. Chou for his contribution to the development of this product at FAR Research, Inc.

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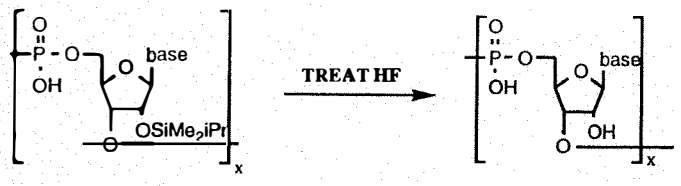
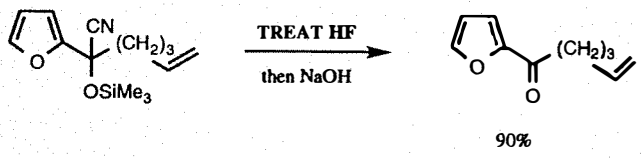


x > 50 **eq 17**

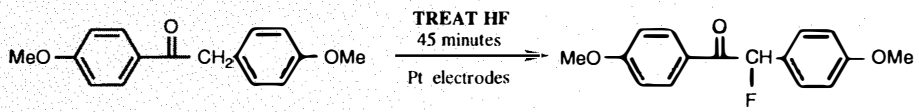


90% **eq 18**

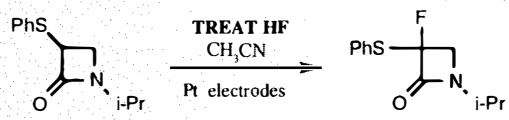
$CH_3CHOMsCH_2CH_2OSiPh_2Me \xrightarrow{\text{TREAT HF}} CH_3CHOMsCH_2CH_2OH$ **eq 19**

$4\,Et_3N{\cdot}3HF + 3\,SCl_2 \longrightarrow SF_4 + S_2Cl_2 + 4\,Et_3N{\cdot}HCl + 8HF$ (74%) **eq 20**

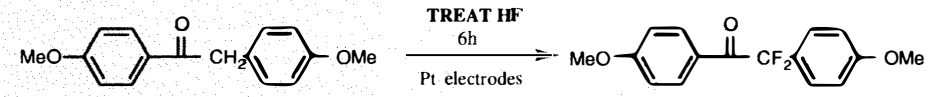
$TeO_4 \xrightarrow[\text{aq. HF}]{\text{TREAT HF,}} Et_3NH^+\,TeF_5^-$ **eq 21**



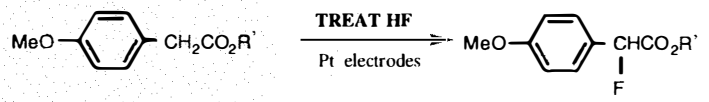
72% **eq 22**



69% **eq 23**



50% **eq 24**



R' = S-proline derivative

60% : diastereomeric ratio = 56/44 **eq 25**

$PhCH{=}CH_2 \xrightarrow[\text{Pt electrodes}]{\text{TREAT HF}} PhCHFCH_2F$ (51%) **eq 26**

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About the author

Dr. Martin A. McClinton received his B.Sc. from the University of York, U.K. in 1986. In 1990 he was awarded a PhD for investigation into new methodologies in organofluorine chemistry under the supervision of Professor James H. Clark. As a Fulbright Scholar, he worked with Professor John T. Welch at SUNY at Albany, NY. He continued his academic career both as the Demonstrator of Organic Chemistry at Exeter University, U.K. and as a postdoctoral fellow at the University of Florida working with Professor William Dolbier, Jr. In 1993 he joined FAR Research where he assists in the development of new chemical processes and products.

Spontaneous Polymerizations Can Occur During Cycloaddition Reactions of Olefins and Dienes

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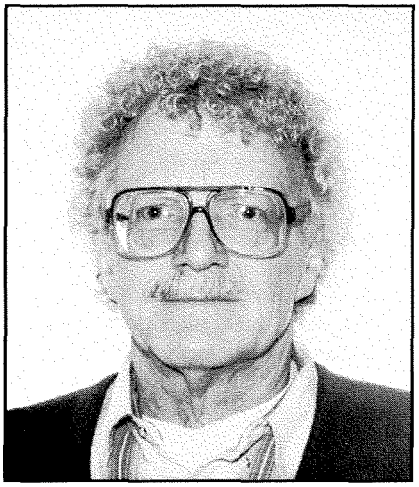
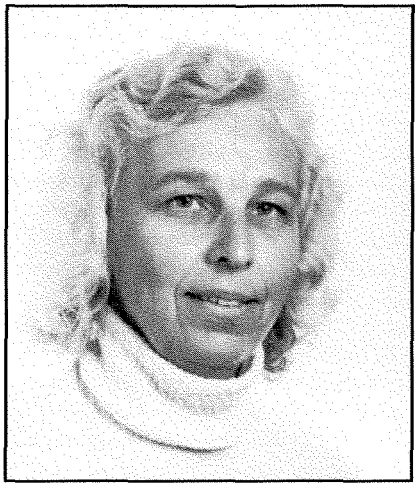
Introduction

Although the fields of organic chemistry and polymer chemistry are often considered to be separate disciplines, they are really different sides of the same coin. The organic molecules used in both disciplines behave by a single set of rules and the same mechanistic laws apply independent of the intent of the individual researcher. The results observed in each discipline, however, do depend greatly on the reaction conditions and on the observations of the scientist. This perceived discontinuity between the two disciplines, based solely on the different size of the molecules, can result in an incomplete view of the chemistry on hand. In this paper we will report on the reactions of electron-rich olefins with electron-poor olefins to illustrate that the complementary methods and points of view of both disciplines can lead to a greater understanding of the underlying chemistry.

Upon mixing an electron-rich olefin with an electron-poor olefin, several reactions are known to occur, depending on the nature of the substituents on the C=C bond, as shown in **Scheme 1**. Cycloadditions include formation of a cyclobutane or other small molecule adducts. Diels-Alder cycloadditions, either normal or inverse electron-demand, are likely when one substituent is an aromatic ring or a carboxylic ester. Other possible reaction products are polymers, either the homopolymer of one olefin or the copolymer of the two olefins. It is noteworthy that these polymers are formed without any added initiator.

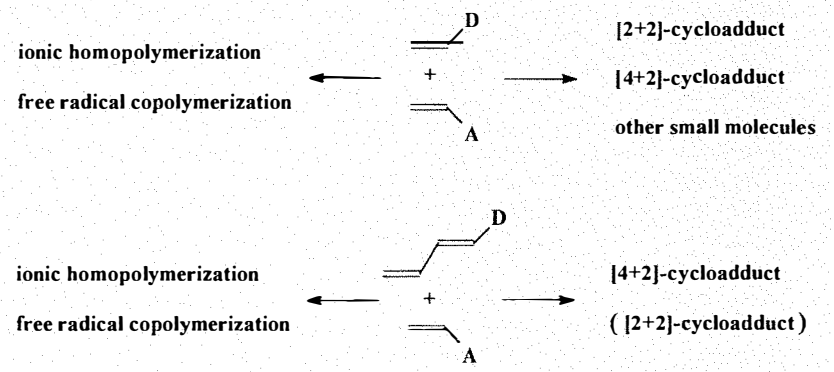
A similar competition between small molecule and polymer formation can be observed when mixing an electron-rich diene with an electron-poor olefin. The Diels-Alder cycloadduct is the expected reaction product, but cyclobutanes and other small molecule adducts may also form. Again spontaneous polymerizations can occur in these diene/olefin systems in the absence of any polymerization initiator.





Even the fathers of the reaction, Diels and Alder, added a free radical inhibitor to the reaction of isoprene with acrylonitrile, presumably to exclude adventitious polymerization.[1] Considering the purity of chemicals at that time they might have been preventing competing polymerizations initiated by impurities, but we have recently found that copolymerization competes with the Diels-Alder cycloaddition even when using extremely pure reagents.[2]

As both organic and polymer chemists, we have studied these systems in which cycloaddition and polymerization compete. We are seeking an overall mechanistic picture for these two processes that result in products differing greatly in physical properties, but which are all organic



D = 1 or more donor substituents such as *N*-carbazolyl, -OR, -PhOMe
A = 1-4 acceptor substituents such as -CN, -COOMe, -NO_2

Scheme 1

molecules differing only in size: small molecules and high molecular weight polymers.

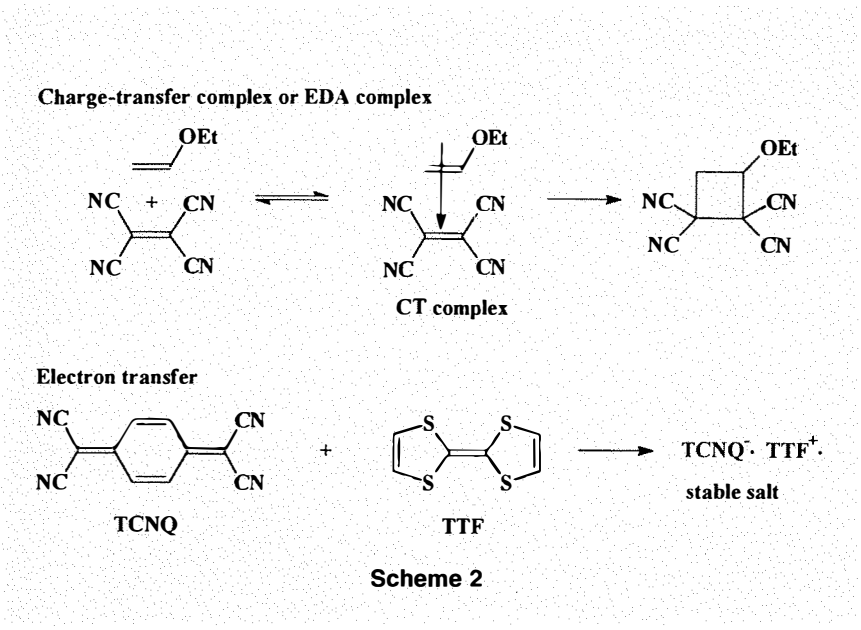
Background

Donor olefins are electron-rich olefins with substituents able to donate electron density into the π-system, such as alkoxy, phenyl, *p*-methoxyphenyl, and *N*-carbazolyl. In contrast, acceptor olefins are electron-poor owing to electron-withdrawing substituents, most often methoxycarbonyl (an ester group) or cyano groups.

The first requirement for polymerization to compete with cycloaddition is, of course, that the polymerization has to be possible if an initiator is deliberately present or absent. Which olefins can polymerize? As is generally true for any organic reaction, propagation to high molecular weight chains must be thermodynamically favorable, and kinetically and mechanistically possible.[3] The substitution pattern on the C=C bond has to fulfill two requirements: the propagating species, be it free radical or ionic, has to be stabilized by the substituents on C_1, while the steric hindrance at C_2 has to be kept to a minimum to allow attack by the propagating center. Therefore, most vinyl monomers that can homopolymerize are monosubstituted or 1,1-disubstituted. The former can be homopolymerized at almost any temperature. The latter ones are preferably homopolymerized at low or moderate temperatures because as steric repulsions increase in the polymer chain, depolymerization becomes thermodynamically more favorable. As a result, these sterically hindered polymers will revert back to monomers at higher temperatures.

Further substitution of the olefins (except for fluorine) makes the olefins non-homopolymerizable. In copolymerization much the same situation holds. However, a noteworthy aspect of free radical copolymerization is the increased reactivity observed between monomers of opposite polarity and their tendency to form alternating copolymers. This cross-propagation has been ascribed to the preference of an electrophilic radical, a radical stabilized by electron-withdrawing substituent(s), to react with a nucleophilic monomer and vice versa. This makes possible copolymerization between monosubstituted donor olefins with trisubstituted — and even tetrasubstituted — electron-poor olefins via a free radical mechanism.

Turning to mechanisms of chain propagation, four are currently recognized: free radical, cationic, anionic, and coordination (the last will not be dealt with in this review). The nature of the substituent dictates the feasibility of a given mechanism. Electron-donor substituents stabilize a propagating carbocation, while acceptor substituents do the same for propagating carbanions. Many of these same substituents can also stabilize free radicals, so that this mode is practiced most widely.



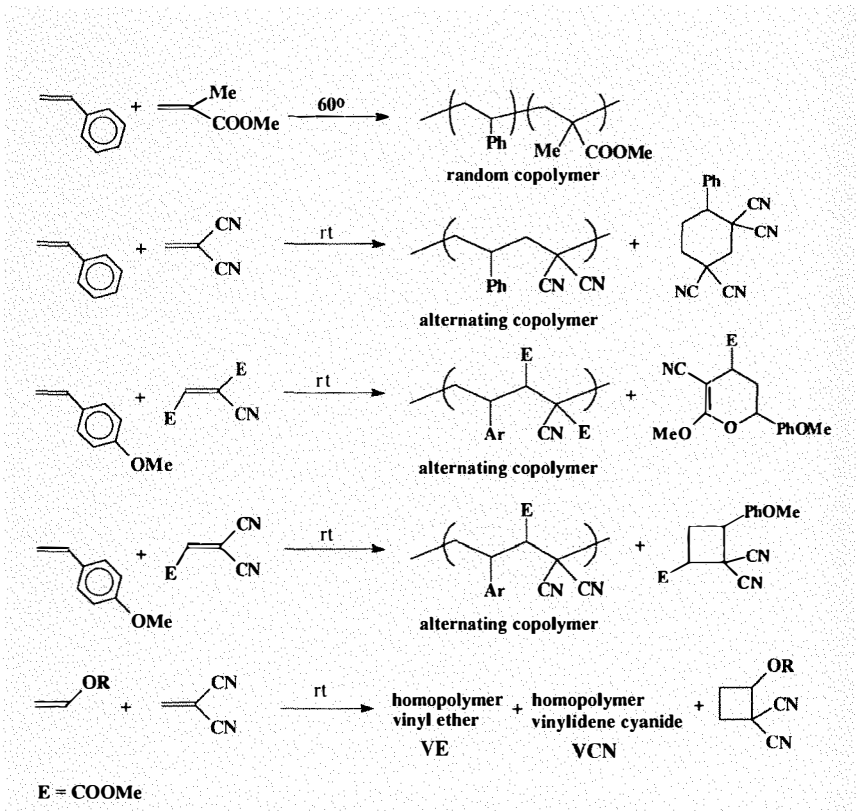
Scheme 2

Charge-transfer complexes

In polymer chemistry as in organic chemistry, many reactions are governed by the polarity difference between the reacting molecules. The best known example is the Diels-Alder reaction between a nucleophilic diene and an electrophilic dienophile. In most cases these reaction mixtures are colorless. However, when the polarity difference between the reaction partners is rather large, colored solutions will be observed. The color is due to a charge-transfer (CT) complex, which is also called an electron-donor-acceptor (EDA) complex (**Scheme 2**). *Partial* electron-transfer takes place between the two olefins resulting in a complex, as described by Mulliken.[4] A CT complex is in equilibrium with the parent olefins. A true electron transfer is a much higher energy process than the formation of a CT complex and only occurs at ambient conditions when extremely electron-rich olefins are mixed with extremely electron-poor olefins to form a cation-radical anion-radical pair. Such ion-radical salts can be isolated in certain cases, as for example the formation of the conducting salt between tetracyanoquinodimethane (TCNQ) and tetrathiafulvalene (TTF) (**Scheme 2**).

CT complexes are frequently mentioned in the polymer chemistry literature, but are generally ignored in the organic chemistry literature.[5] Organic chemists have mostly relied on the Frontier Molecular Orbital Model to explain the cycloaddition reactions between electron-rich and electron-poor partners, at least for the [4+2]-cases.[6] In contrast, theories proposed by polymer chemists to account for the observed alternating character of the copolymer, and also for the spontaneous initiations, seem to have been governed rather by the involvement of CT complexes. The early mechanisms proposed for the initiation of the so-called "charge-transfer" polymerizations all involved electron-transfer.[7] In these mechanisms the CT complex formation (partial electron transfer) is followed by electron transfer from the donor olefin to the acceptor olefin, resulting in a cation-radical/anion-radical pair. Separation of the ion-radical pair is then proposed to lead to the initiating species, be they radical or ionic (cationic or anionic). In our opinion these postulated processes all require too much energy to generate the initiating species in systems possessing rather small electron disparity between the two monomers.

As will be shown, based on solid precedents from physical organic chemistry, the spontaneous initiation can be explained without invoking complete electron transfer between the reacting olefins. In our view, the CT complexes are merely indicators of the electron disparity between the two monomers.



Scheme 3. *Systematic structure variation.*

Difference between a polymer chemist's approach and an organic chemist's approach

"Usually one finds what one is looking for."
R. Huisgen, 1984 [8]

Polymer chemists set up their experiments differently from organic chemists, and they work them up differently as well. To a substantial extent these artifacts dictate the outcome of the experiments.

Polymer chemists prefer concentrated solutions, even bulk monomers, to optimize the yield of polymer. Extraneous initiator is routinely added, even before the presence or absence of a spontaneous thermal polymerization has been established. The ratio of reactants (i.e., monomers/initator) is kept very high (>100:1) to obtain high molecular weights. The product is isolated by pouring into a large volume of nonsolvent, filtering, and drying. In this way cycloadducts and other small molecules, if present, are lost in the filtrates.

Organic chemists, on the other hand, prefer more dilute solutions and equivalent quantities of reactants. The product is often isolated by filtering and discarding any polymeric materials and evaporating the filtrate. *Each group throws away the others' product!*

Either process can be enhanced at the discretion of the researcher. Polymerization can be favored by deliberately adding extraneous initiator. Small molecules, in contrast, are favored when inhibitors are deliberately added. Still other complications arise if adventitious trace impurities are present which may initiate or inhibit chain polymerization reactions.

The end result of all these factors is that, at least for the reactions under discussion here, much of the literature is less definitive than is desirable. Valuable information is available from both the small molecules and the polymers. A cyclobutane, for example, is the signature of a tetramethylene intermediate. The type of polymer gives clues as to the nature of the spontaneously formed initiating intermediate, whether zwitterionic or diradical. *A particularly significant aspect of the trapping of an intermediate by initiating a polymerization is the enormous amplification that is involved.* An initiating species formed in a vanishingly small amount can still lead to a substantial quantity of polymer that is easily isolated and identified.

The effect of systematic structure variation

"Chemical reactions are electrical transactions"
C.K. Ingold, 1969[9]

Although similar olefins usually do not react when mixed, moderate disparity in electron-density between two olefins can cause spontaneous free radical copolymerizations at slow but reproducible rates. A mixture of styrene (St) and methyl methacrylate heated to 60 °C will form a random copolymer without added initiator, as described by Walling in 1949 (**Scheme 3**).[10] The copolymerization is faster than either spontaneous homopolymerization. Similarly a mixture of St and acrylonitrile (AN) forms a random copolymer at 100 °C.[11] This process is used on an industrial scale. We have very recently reexamined this system and shown that this initiation is not due to self-initiation by styrene, but to combination of St and AN.[12]

Styrene reacts differently with a more electrophilic olefin, such as vinylidene cyanide (VCN). The spontaneous polymerization now takes place at room temperature and a strictly alternating copolymer, within NMR detection limits, is formed (**Scheme 3**).[13] Following the early work of Trumbull, Stille and his co-workers found that 20% of a 2:1 VCN:St adduct was formed, along with the alternating copolymer. Another monomer pair in this category is the combination of *p*-methoxystyrene (MeOSt) and dimethyl cyanofumarate (CNF). Here again an alternating copolymer forms spontaneously at room temperature along with a cycloadduct (**Scheme 3**).[14] A detailed description of this system is given on page 41.

Greater electron disparity exists between *p*-methoxystyrene and methyl ß,ß-dicyanoacrylate. Mixing these two olefins results in formation of their cyclobutane adduct or alternating copolymer depending on the reaction conditions (**Scheme 3**).[15]

When olefins with still greater electron disparity are used, ionic homopolymerizations dominate the outcome of the reactions and cycloadditions compete more effectively. Mixing VCN with an alkyl vinyl ether (VE) at room temperature results in the homopolymerization of both the VE and VCN, cationic and anionic respectively.[16] Moreover, Stille was able to isolate the cyclobutane adduct of the two olefins from the reaction mixture.[17]

In the presence of a radical initiator, a mixture of the alternating copolymer and the two homopolymers was formed along with the cyclobutane adduct, showing that the free radical mechanism is viable with this monomer pair and leads to a different polymer than the one obtained in the spontaneous system. In this laboratory we investigated the reactions taking place in a mixture of *N*-vinylcarbazole (NVCz) and tetrasubstituted electrophilic olefins. Here again cationic homopolymerization of NVCz takes place along with cyclobutane formation.[18] This system will be described in detail on page 41.

This limited list of examples shows the general trends as we progress from weak donor/acceptor olefin pairs to the strong donor/acceptor olefin pairs:

1. The intensity and color of the charge transfer complex deepens and moves from yellow through red to blue.

2. The rates of the spontaneous reactions increase.

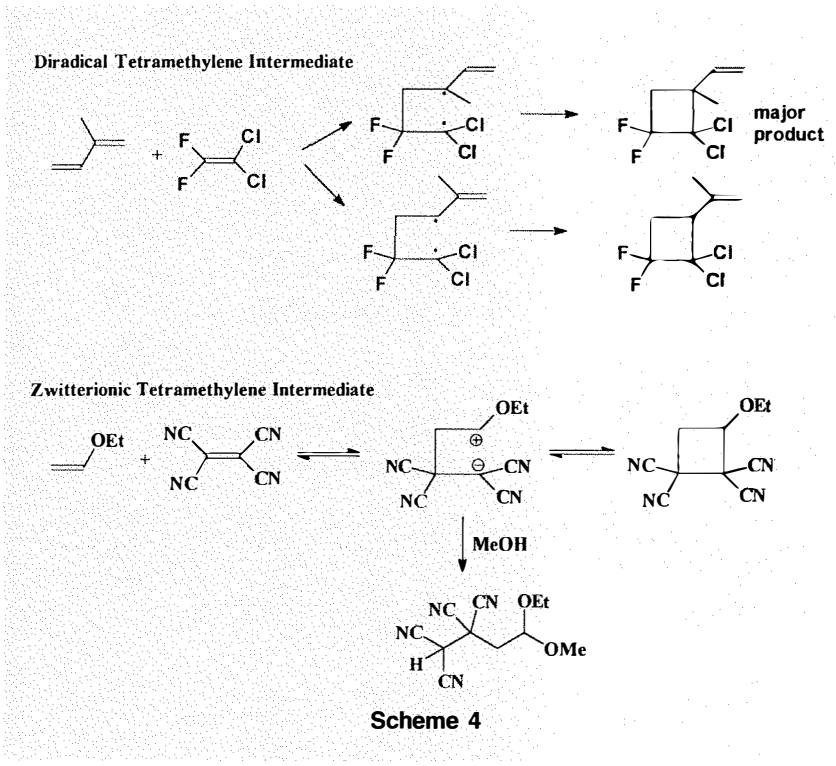
3. Progressively larger amounts of cycloadducts form. The cycloaddition pattern changes from Diels-Alder cycloaddition to [2+2] cycloaddition as the electron disparity between the olefins increases.

4. Spontaneous random (with little or no tendency to alternate) free radical copolymerizations at elevated temperatures (>50°) give way to spontaneous alternating copolymerizations at room temperature and, eventually, ionic homopolymerizations predominate with the strongest pairs. These general polymerization tendencies had been described by Iwatsuki and Yamashita in their seminal paper in 1971.[19]

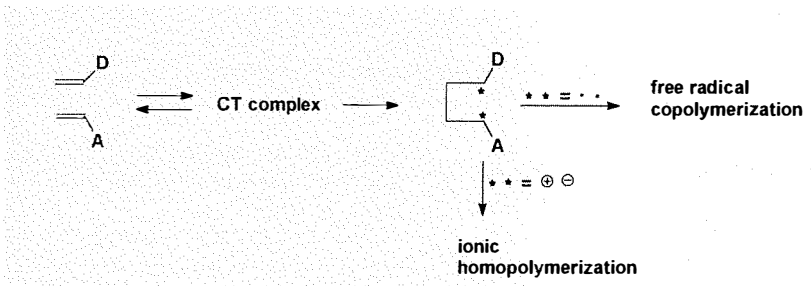
Proposed unifying mechanism for stepwise 2+2 cycloaddition and initiation of polymerization

Concerted $2_s + 2_s$ cycloadditions are forbidden by the Principle of Conservation of Orbital Symmetry as proposed by Woodward and Hoffmann in their famous short communications in 1965.[20] Accordingly, the necessary intermediates in these cyclobutane formations are tetramethylenes, which can be either diradical or zwitterionic in nature depending on the substituents. Bartlett investigated the cycloaddition of dienes and 1,1-dichloro-2,2-difluoroethylene and concluded, based on product distribution and stereochemical arguments, that these reactions proceed through a diradical tetramethylene intermediate, as shown in **Scheme 4**.[21] Huisgen and his co-workers extensively studied the cycloaddition of vinyl ethers and TCNE (**Scheme 4**).[22] These additions proceed quantitatively at room temperature and their rate is greatly influenced by the polarity of the solvent. Huisgen hypothesized that tetramethylenes are either predominantly zwitterionic or predominantly diradical in nature, depending on the substituents on the terminal centers, and may be regarded as resonance hybrids of the two extremes.

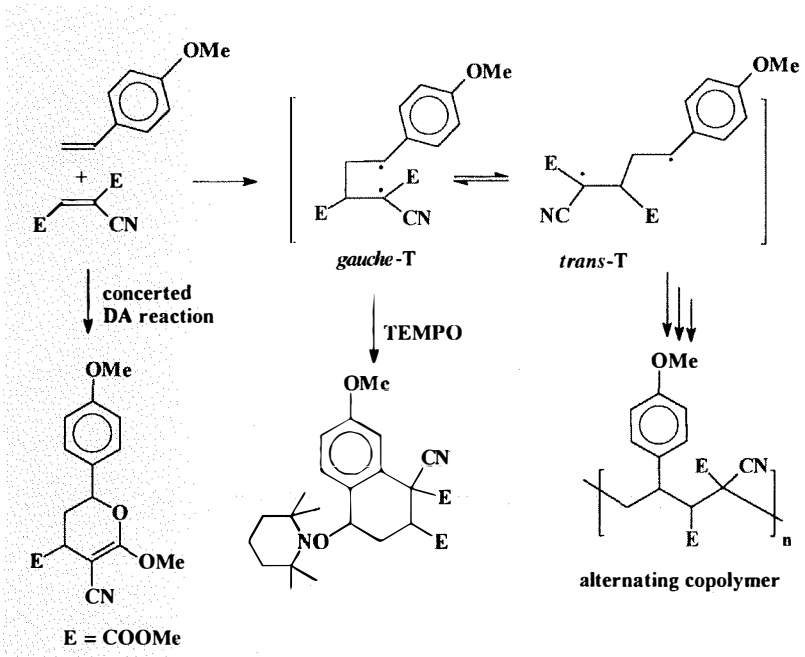
The Bond-Forming Initiation Theory, originally described in 1983,[23] proposes that these same tetramethylene intermediates are the true initiators of the observed spontaneous polymerizations (**Scheme 5**). The weaker donor and acceptor olefins form a predominantly diradical tetramethylene intermediate that can initiate free radical copolymerization, while the more nucleophilic and more electrophilic olefins form a predominantly zwitterionic intermediate that can initiate ionic homopolymerization. We will show that this concept is in agreement with both a selected spontaneous free radical copolymerization and a selected spontaneous cationic homopolymerization. In turn, polymer products offer a powerful diagnostic tool to characterize tetramethylenes, in contrast to small molecules. *It may not be too fantastic to regard stepwise cycloaddition as a polymerization that has no propagation step!*



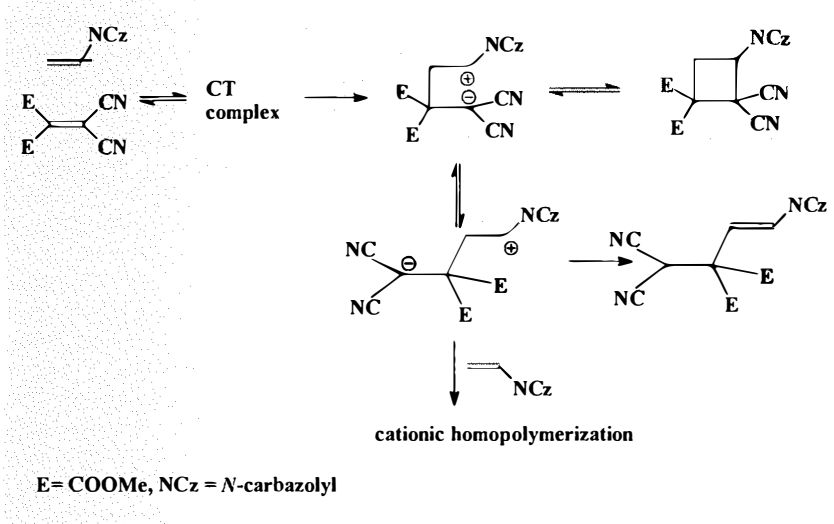
Scheme 4



Scheme 5. *Proposed initiation mechanism.*



Scheme 6. *Initiation for a spontaneous free radical copolymerization.*



Scheme 7. *Initiation mechanism for a spontaneous cationic homopolymerization.*

Detailed description of a spontaneous copolymerization

It is well known that proving a mechanism involving a radical species is more difficult than one involving ionic species. Combination of a moderately electron-rich olefin with an electron-poor olefin often leads to free radical copolymerizations. We postulate that a diradical tetramethylene is the initiator of these copolymerizations. These olefins are not very reactive and, therefore, will react rather slowly. As a consequence, the concentration of the initiating species will be low.

The system chosen for this study was the combination of *p*-methoxystyrene (MeOSt) and dimethyl cyanofumarate (CNF) (**Scheme 6**).[14] The polymerization proceeds at room temperature and takes about 8 hours. The copolymer is perfectly alternating within spectroscopic detection limits. The only byproduct in this reaction is the inverse-electron-demand Diels-Alder reaction forming the dihydropyran derivative at very low concentrations. The observed kinetics of the polymerization are in agreement with two assumptions; namely, that the diradical tetramethylene is the initiating species, and that the propagation proceeds in the same fashion as if the polymerization were initiated by a classical free radical initiator. No solvent polarity effect was found. The molecular weight of the polymer increases with time, which is contrary to the behavior observed for classical free radical chain polymerization (constant molecular weight throughout the run). If, as we propose, the initiating species is a diradical, then each polymer chain will always have two radical ends. This is in contrast to initiated polymerization which proceeds with only one radical end. Termination by recombination of two diradical polymer chains will result in a larger polymer chain, still with two radical ends. Therefore, the molecular weight continues to increase.

Most importantly, we were able to trap the diradical intermediate using TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) and the 1:1:1 adduct could be isolated (**Scheme 6**). The structure of this adduct supports our proposed structure for the tetramethylene intermediate. It might be argued that this 1:1:1 adduct could be formed from reaction of TEMPO with the hypothetical Diels-Alder adduct with CNF as the dienophile and the MeOSt as the diene. However, there can only be one possible Diels-Alder adduct from two reagents, and in this case we have shown that the inverse-electron-demand DA reaction occurs leading to the dihydropyran derivative. The trapping, in conjunction with the kinetics and the observed increase in molecular weight of the polymer, provide powerful evidence for the proposed diradical tetramethylene initiator.

Detailed description of a spontaneous homopolymerization

The reaction of the electron-rich olefin NVCz and the electron-poor olefin TCNE had already been investigated by several researchers in the polymer field.[24] We conducted a structure-reactivity study for this system by steadily decreasing the electrophilicity of the acceptor olefin through gradual replacement of the cyano groups by the weaker ester groups.[18] These reactions are a prime example of how the reaction conditions can determine the outcome of a reaction. When equimolar dilute solutions of NVCz and the electrophilic olefin are used, cyclobutane adducts are the main reaction product, with

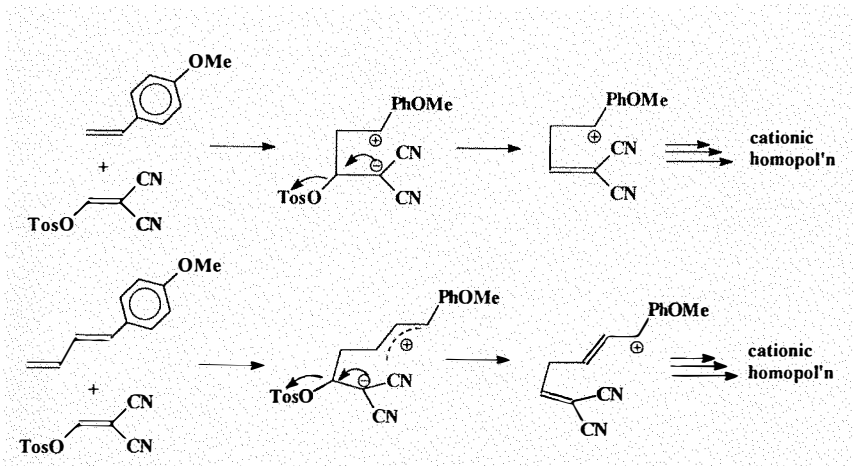
the amount of the open chain unsaturated isomeric side product dependent on the reaction time. However, when excess NVCz is used, the main product is the homopolymer of NVCz. The same behavior is found in the *N*-ethyl-3-vinylcarbazole /TCNE system.[25]

The reaction of NVCz and dimethyl 2,2-dicyanoethylene-1,1-dicarboxylate (DDED) was studied in great detail.[18] The color of the CT complex is visible as soon as the reagents are mixed, but disappears rather fast. The cyclobutane adduct is formed first in 100% yield and no more CT complex color is observed. If the reactant solution is left at room temperature, the homopolymer starts forming along with the open chain isomer. A powerful solvent effect is observed. The polymerization can be initiated with exactly the same efficiency using the isolated cyclobutane adduct as initiator. The polymerization is completely inhibited by the addition of methanol. The polymer formation and isomerization are competitive reactions as shown by the kinetics.

Based on all these observations, the mechanism in **Scheme 7** is proposed in which the cyclobutane reversibly opens up to reform the zwitterionic tetramethylene. The zwitterionic species can exist in either the *gauche* or *trans* conformation. The former is favored due to Coulombic interaction, but the latter will competitively undergo a proton transfer to form the open chain isomer or react with another NVCz molecule to initiate the cationic homopolymerization. The anionic homopolymerization of the electrophilic olefin is not possible because it is tetrasubstituted.

In the NVCz-DDED system, the cyclobutane does not revert back to the olefins, as shown by the absence of the CT color once the cyclobutane adduct is formed. Therefore, neither the CT complex nor an ion-radical pair is the initiator for the observed cationic polymerization. If the NVCz cation-radical were formed, the NVCz dimer would be found,[24d] and it is not. NVCz is one of the most electron-rich olefins, and the fact that no cation-radicals are observed in this system makes it very unlikely that they would be generated in any other olefin-olefin combination.

We extended the proposed mechanism to further enhance the effectiveness of electrophilic olefins as cationic initiators. Specifically, we introduced a leaving group in the ß-position of the olefin. Expulsion of the leaving group in the proposed zwitterionic tetramethylene results in a cationic center with the leaving group as a more stable counterion. As shown in **Scheme 8**, olefins such as ß,ß-dicyanovinyl tosylate and ß-carbomethoxy-ß-cyanovinyl tosylate are effective initiators for cationic polymerization.



Scheme 8. *Acceptor olefins with a β-leaving group.*

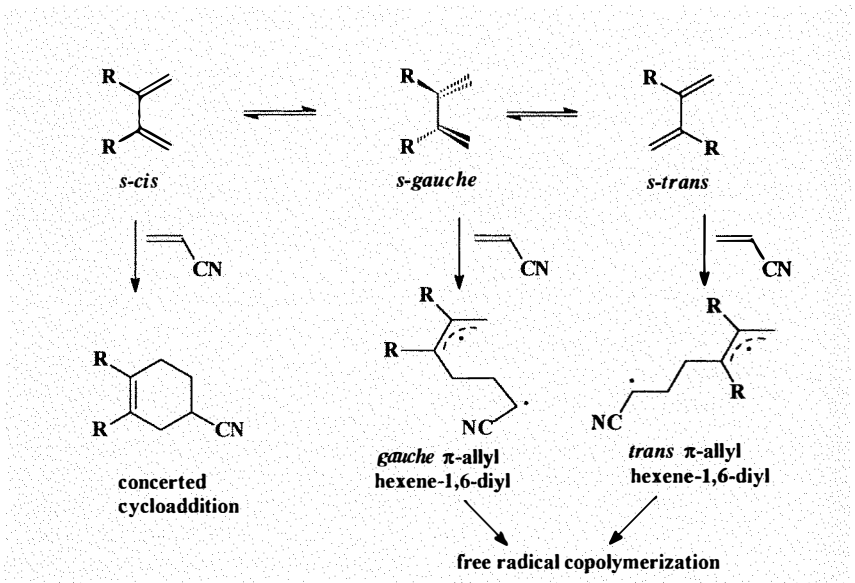
Detailed description of diene-olefin reactions

In reactions of electron-rich dienes with electron-poor olefins, the $4_s + 2_s$ Diels-Alder cycloadditions are the most obvious outcome and are highly favored. We again quote Professor Huisgen in mentioning that these reactions are dominant due to "the magic of the symmetry-allowed concerted cycloaddition!"[8] The case of these concerted reactions depends not only on the HOMO-LUMO energies of the diene and dienophile, but also on the conformation of the diene. The importance of the latter has been thoroughly investigated by Sustmann in the reactions of various dienes with TCNE.[26] The dienes in the *s-cis* conformation react substantially faster with the dienophile than the dienes that prefer the *s-trans* conformation.

As we mentioned in the introduction, we recently determined that spontaneous polymerizations also occur in these systems.[2] These polymerizations are reproducible and not due to impurities. They lead to extremely high molecular weight polymers. If the diene and dienophile are able to copolymerize by deliberately adding free radical initiators, then spontaneous copolymer formation during the Diels-Alder reaction can be taken as evidence for the presence of initiating (di)radicals in the reaction mixture.

A series of alkyl 1,3-dienes was reacted with acrylonitrile (AN). The dienes were divided into different groups according to their conformational equilibria. The dienes that exist freely in an *s-cis*/*s-trans* equilibrium include 2,3-dimethyl-1,3-butadiene (DMB), isoprene, and *E*-1,3-pentadiene. The reactions of DMB with AN were investigated in great detail.[2] Alternating copolymers are obtained along with the expected Diels-Alder cycloadduct at 80° and at 100 °C. The copolymerization and the cycloaddition proceed as two *independent* second order reactions. The proposed mechanism is depicted in **Scheme 9**. The proposed free radical initiating species is a *trans*-2-hexene-1,6-diradical formed by reaction of the *s-trans* conformer of the diene with AN, while the *s-cis* conformation undergoes the concerted cycloaddition. The conformation of the diene is an important factor in determining the outcome of the reactions. Even though the spontaneous polymerization is evidence for the presence of a 2-hexene-1,6-diradical in the reaction mixture, we do not propose any contribution of a stepwise mechanism to the observed [4+2]-cycloadditions. The cycloaddition and the formation of the initiating species result from different conformations of the diene with the acceptor olefin, whereas in the olefin-olefin reactions the cycloaddition and the initiation of the polymerization are the consequence of competitive reactions of the tetramethylene intermediate.

1,3-Cyclohexadiene (CHD) has a cyclic structure which, of course, excludes the *s-trans* conformer. Therefore, we were rather surprised to find a literature report that thermal reactions of CHD with AN lead to a mixture of copolymer and cycloadduct.[27] We confirmed this finding and again found independent second order



Scheme 9. *Proposed scheme for diene-olefin reactions.*

kinetics for both the copolymerization and the cycloaddition. This indicates that the *s-gauche* conformer of the diene can also form an initiating diradical as shown in **Scheme 9**. The competing concerted [4+2]-cycloaddition takes place from the *s*-cis form of the diene.

We confirmed these conclusions by using either *s-cis*-locked or *s-trans*-locked dienes. The former include 1,3-cyclopentadiene and 1,2-dimethylenecyclopentane, which in reactions with AN only undergo the concerted cycloaddition. In contrast, *s-trans*-locked dienes, such as 2,5-dimethyl-2,4-hexadiene and verbenene (2-methylene-6,6-dimethylbicyclo[3.1.1]-hept-3-ene), give exclusively copolymers in reactions with AN, still following the second order kinetics.

1-Methoxy-1,3-butadiene (MeOBD) is more electron-rich than the alkyldienes. Again, the *E*-isomer can freely rotate from the *s-cis* to the *s-trans* conformer. Therefore, based on our proposed reaction scheme, a competition between the concerted [4+2]-cycloaddition and the spontaneous copolymerization is predicted. MeOBD was reacted with a series of electron-poor olefins with increasing electrophilicity. With the least electrophilic olefin AN, only copolymerization is observed. With fumaronitrile, high yields of high molecular weight copolymer are obtained along with [4+2]-cycloadduct. In the reaction of the very electrophilic olefin methyl ß,ß-dicyanoacrylate with MeOBD, the [4+2]-cycloaddition dominates with a low yield of the alternating copolymer. The more electrophilic the olefin, the more [4+2]-cycloaddition predominates over the copolymerization and the higher the rates. The same mechanism as depicted in **Scheme 9** is proposed for these reactions.

1-Anisyl-1,3-butadiene (ABD) is an example of a nucleophilic diene which cannot homo- or copolymerize by a free radical mechanism owing to the excessive stabilization of the growing allylic free radical. However cationic homopolymerization is possible. In reactions with trisubstituted electrophilic olefins, such as trimethyl ethylenetricarboxylate, only extremely rapid [4+2] cycloaddition takes place. But, if reacted with electrophilic olefins containing a leaving group, cationic homopolymerization of the diene can compete with the cycloaddition. In these cases, more polymer is formed with increasing electrophilic character and with increasing leaving group ability. Thus 2-carbomethoxy-2-cyanovinyl chloride in reaction with ABD leads mostly to cycloadduct, while 2,2-dicyanovinyl tosylate with ABD leads exclusively to the homopolymer of the latter. This behavior is analogous to the reactions of nucleophilic olefins with electrophilic olefins containing a leaving group and an analogous mechanism is proposed as shown in **Scheme 8**.

Summary and conclusions

These systems represent an intersection of organic chemistry with polymer chemistry. A complete understanding of the mechanism requires identification of both small molecules and polymers formed by spontaneous reactions. Deliberate initiation or inhibition may direct the outcome toward polymers or small molecules, respectively.

Spontaneous polymerizations often accompany the cycloadditions of electron-rich olefins or dienes with electron-poor olefins. Such spontaneous polymerizations are particularly likely to occur in reactions of monosubstituted electron-rich olefins or dienes with mono-, 1,1-di-, or trisubstituted acceptor olefins. Moderate electron disparity, as indicated by yellow charge transfer complexes, leads with moderate rates to alternating copolymers, Strong electron disparity, indicated by red or blue CT complexes, leads by fast reactions to cationic homopolymerization of the donor olefin.

Representative reactions of these types were studied in detail. For the [2+2] case of moderate electron disparity, *p*-methoxystyrene and dimethyl cyanofumarate give an inverse-electron-demand hetero-Diels-Alder product and alternating copolymer. The postulated 1,4-tetramethylene diradical intermediate was supported by kinetics, free radical trapping, and lack of solvent effect. For the [2+2] case of strong electron disparity, NVCz and dimethyl 1,1-dicyanoethylene-2,2-dicarboxylate reacted via a 1,4-tetramethylene zwitterion, supported by kinetics, trapping, and strong acceleration by polar solvents. In this case, the tetramethylene intermediate is partitioned between the cycloadduct at low concentration and the polymer at high concentration.

1,3-Dienes and electrophilic olefins react spontaneously with electrophilic olefins to give copolymers along with the expected Diels-Alder cycloadducts. Both products form by second order kinetics, so dilution does not affect the product ratio. The small molecule and polymer are not formed by partitioning an intermediate, but by competing reactions of the *s-trans* and *s-cis* diene conformations. We postulate that the former undergoes bond formation with the acceptor olefin to form an intermediate 2-hexene-1,6-diyl initiating diradical, while the latter undergoes the concerted cycloaddition.

Finally, mention may be made that these processes apply to industrially important olefins as well as to specialty components.

We hope that this brief account may stimulate greater understanding and appreciation between organic and polymer chemists and that the combined use of both organic and polymer chemistry principles may be applied to other systems.

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About the authors

H.K. Hall, Jr. was born in New York City in 1924. He received his undergraduate training at Brooklyn Polytech, a Master's degree at Pennsylvania State University, and a PhD degree from the University of Illinois in 1949. Postdoctoral work followed, with Prof. P.J. Flory at Cornell and with Professors S. Winstein and W.G. Young at UCLA. After 17 years at DuPont, he moved in 1969 to the University of Arizona. His research interests have included the synthesis and ring-opening polymerization mechanisms of strained bicyclic molecules, the mechanisms of reactions of donor with acceptor olefins, the synthesis and polymerization of imines, and the synthesis of electrically conductive, piezoelectric, and nonlinear optical polymers.

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Polyfluorinated Alkenes, Alkynes, and Allenes

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Introduction

Nowhere is the fascination of organofluorine chemistry better exemplified than in unsaturated fluorocarbons. It is a chemistry of unusual rearrangements and novel products with a structural and mechanistic diversity that tests both the chemist's ingenuity and understanding. The aim of this article is to give an overview of this important area. References 1-3 provide a more detailed discussion of many of the aspects covered. Reviews are available on the chemistry of perfluoroalkyl(aryl)alkynes[4] and perfluoro-2-methylpropene.[5]

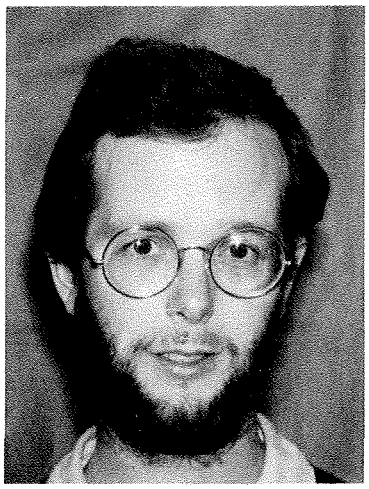
Synthesis

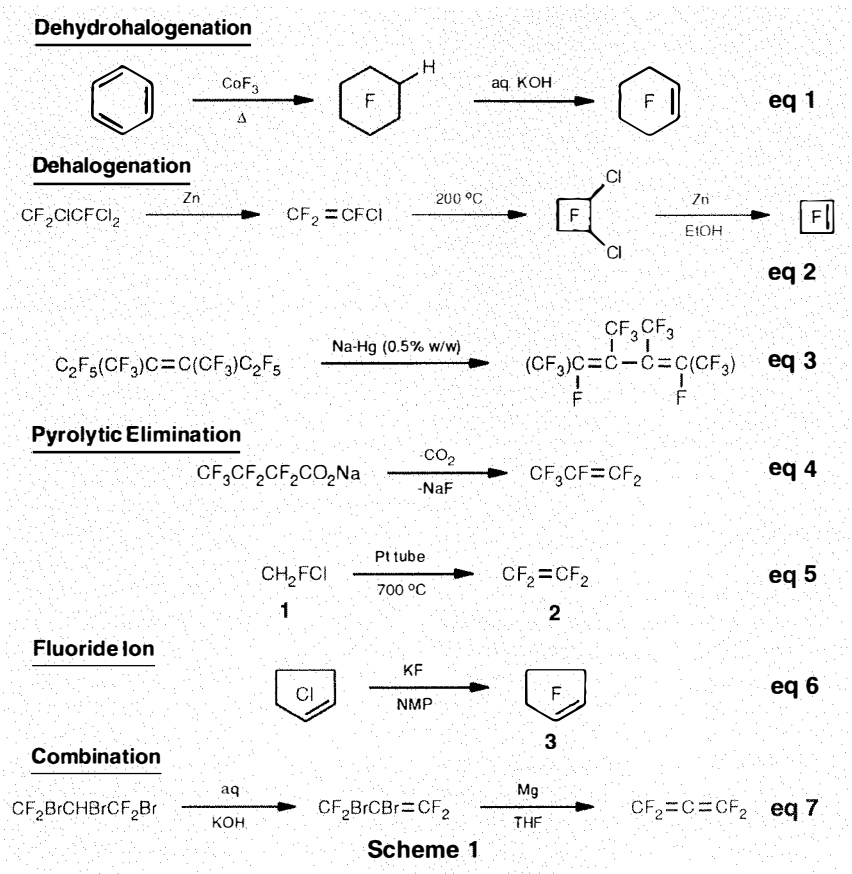
Unsaturated fluorocarbons have been prepared via several general approaches (**Scheme 1**)†; a combination of these is also possible, as in the synthesis of tetrafluoroallene (eq 7).[6]

One general approach is the β-elimination of hydrogen halide from a partially fluorinated precursor. Dehydrofluorination can be achieved using a variety of bases, including aqueous potassium hydroxide (eq 1).[7] The factors that influence the loss of HF from polyfluorocyclohexanes and -cyclopentanes have been extensively investigated.[8] Electronic and stereochemical influences are important, with the former being dominant. Use of a phase-transfer catalyst considerably improved the yield in the base-induced dehydroiodination of 1,2-bis(perfluoroalkyl)iodoalkenes to bis(perfluoroalkyl)-alkynes.[9]

Dimerisation of the carbene formed by α-elimination of HCl from chlorofluoromethane **(1)** forms the basis of the commercial production of tetrafluoroethylene **(2)** (eq 5).[10] Alkene **2** can also be produced by generation of difluorocarbene through the electrolysis of dichlorodifluoromethane.[11] Decomposition of hexafluoroisopropyl(pentafluoroethyl)diazomethane, in the presence of boron trifluoride-triethylamine, gives a perfluoroalkylated cyclopropene in high yield.[12]

Elimination of bromine or chlorine using zinc is another commonly used method (eq 2).[13] Electrolytic methods can also be used.[14] Mixed halogens can be eliminated, as in the case of IF from α,ω-diiodoperfluoroalkanes, to give perfluorodienes.[15] Defluorination is not widely used as a route to fluorinated alkenes. However, loss of fluorine from suitable substrates can occur using activated carbon[16] or sodium amalgam (eq 3).[17] The latter method is particularly useful for the synthesis of fluorinated dienes in good yield. Stereoselective defluorination of 1,4-bis(perfluoroalkyl)butatrienes to





Scheme 1

†An "F" in the middle of a ring denotes that all unmarked positions are occupied by fluorine.

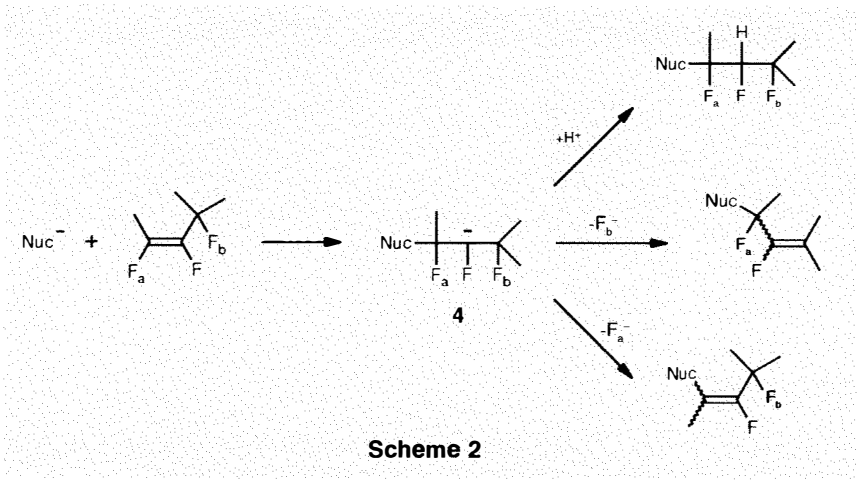
fluorinated divinylalkynes occurs under mild conditions using zinc.[18]

A method especially important for the synthesis of terminal polyfluoroalkenes is the β-elimination of fluoride ion in the pyrolysis of sodium polyfluoroalkylcarboxylates (eq 4).[19] Contact times must be kept short to avoid isomerisation of the product to the more stable internal alkene.[20]

Other species that can be eliminated to give unsaturated fluorocarbons include hexafluoroethane, from tetrafluoroethylene tetramer,[21] and nitrogen in the vacuum pyrolysis of triazines. The latter method has enabled the isolation and identification of the highly unstable difluoroacetylene.[22] Acetylenic fluorines are highly destabilising; however, replacement of fluorine with a perfluoroalkyl (R_F) group increases stability. A typical example is perfluoro-3-methylbut-1-yne which is thermally stable and can be readily stored. It is obtained by the pyrolysis of perfluoro-4,6-diisopropyl-1,2,3-triazine under vacuum.[23]

Exchange of chlorine with fluorine is a very common synthetic approach in fluoroaromatic chemistry, but it is rarely applied in the synthesis of fluorinated alkenes. One of the few examples is the formation of **3** from its perchloro analog. Allylic rearrangements ensure that all positions become reactive (eq 6).[24]

Other synthetic methods that can be applied include the transformation of CO_2H to CF_3 using sulfur tetrafluoride, as in the preparation of hexafluorobut-2-yne.[25] General application of this approach is restricted by the available acids as precursors. Perfluorocarboxylic acid anhydrides are useful raw materials for perfluoroalkyl-substituted 1,4-alkadienes through the Reformatsky reaction.[26] 2,2,2-Trifluoroethyl *p*-toluenesulfonate is a precursor for 1,1-difluoroalkenes[27] and 1,1-difluoro-1,3-enynes.[28] Reaction of 1,1,1-trichlorotrifluoroethane with aldehydes and subsequent dehydrochlorination is a useful route to 1-aryl-3,3,3-trifluoropropynes.[29]



Scheme 2

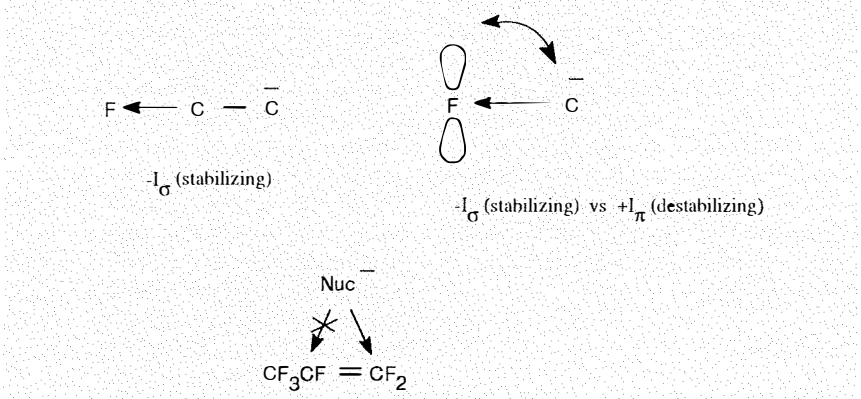
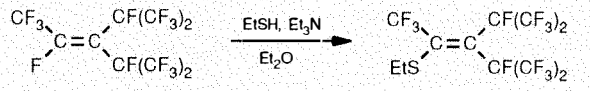


Diagram 1



eq 8

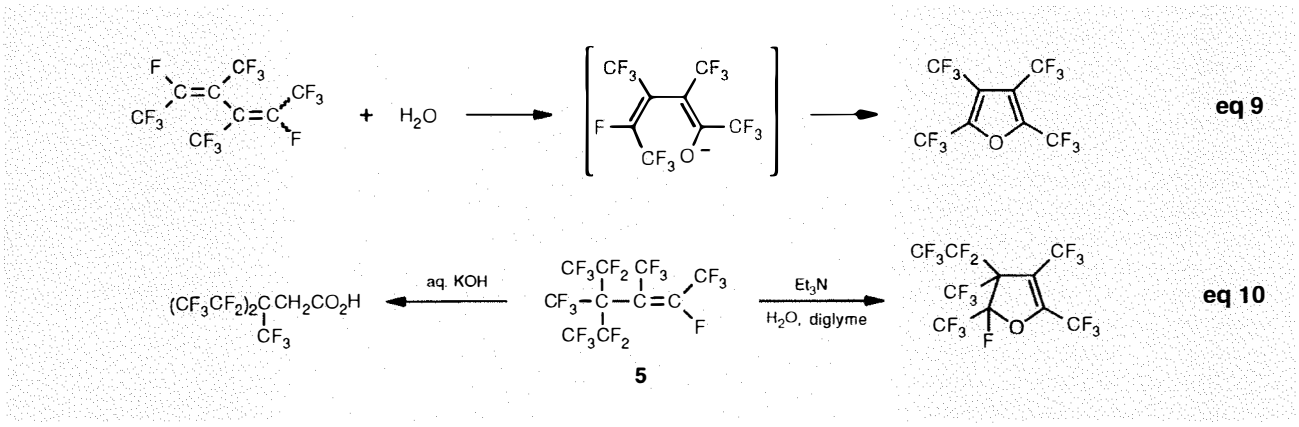
Reactions

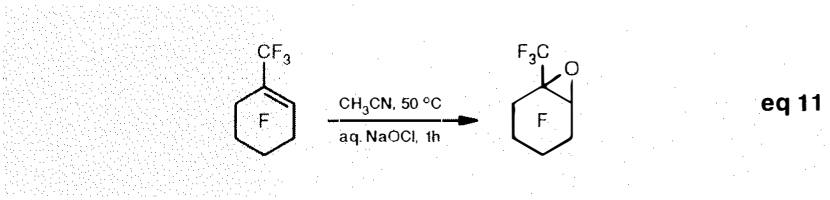
Nucleophilic chemistry

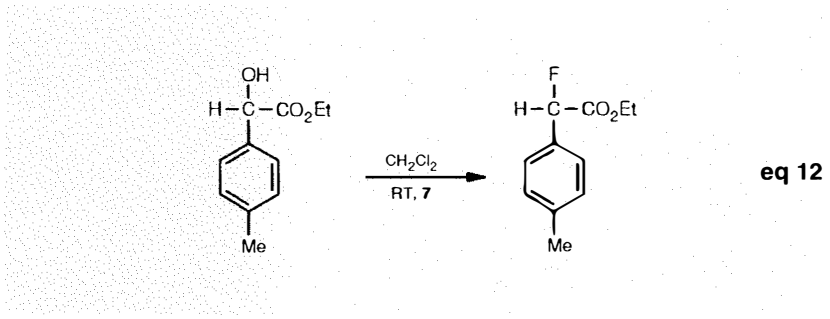
The chemistry of polyfluorinated alkenes, alkynes, and allenes is dominated by reactions with nucleophiles. Three possible outcomes for a reaction between a nucleophile and a fluoroalkene are shown in **Scheme 2**. As the stability of the intermediate carbanion **4** increases, there is a greater tendency for fluoride ion to be eliminated ($-F_a$ and/or $-F_b$). Alternatively, protonation of **4** occurs to give an addition product.

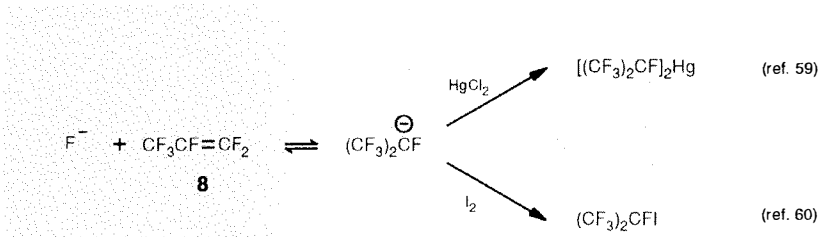
The orientation and reactivity of a fluoroalkene towards nucleophilic attack can be rationalised by considering the factors which influence the stability of **4** (**Diagram 1**).[30] Perfluoroalkyl groups are electron-withdrawing ($-I_\sigma$) and are strongly stabilising. The influence of fluorine is less straightforward as $-I_\sigma$ is countered by a geometry-dependent $+I_\pi$ effect that is destabilising. The latter is greater for an sp^2 than an sp^3 carbanion. Although consideration of these factors explains most observations, they do not account for the greater reactivity of $(CF_3)_2C{=}CF_2$ compared to $CF_3CF{=}CFCF_3$. This has led to an alternative explanation being proposed that is based on the effect of substituents on LUMO energies and HOMO-LUMO interactions between nucleophile and alkene.[30,31]

There are many examples of reactions of fluoroalkenes with O, N, S, C, and other nucleophiles,[32] and those of tetrafluoroethylene tetramer and pentamer have been reviewed.[33] Recent examples include reaction of perfluoro-2-methylpent-2-ene with thiourea,[34] diamines,[35] alcohols,[36] and hexafluoroacetone cyanohydrin;[37] hexafluoropropene oligomers with secondary amines[38] and thiols (eq 8);[39] 1,2-dichloroperfluoro-cyclic and -acyclic alkenes with amines;[40] and perfluorohept-1-ene with bifunctional nucleophiles.[41] Correct orientation and a suitable site for attack may lead to heterocyclic formation, as between perfluoro-3,4-dimethylhex-2,4-diene and water (eq 9), or potassium sulfide.[42]









Scheme 3

Unsaturated fluorocarbons are very reactive towards nucleophiles and even 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) will react.[43] In several instances the outcome is not as straightforward as expected. For example, tertiary aromatic amines can react at the ring carbon in preference to the nitrogen.[44] Tetrafluoroethylene pentamer (**5**) is hydrolysed to a pentanoic acid using aqueous potassium hydroxide, but with triethylamine a perfluorinated dihydrofuran is obtained (eq 10).[45]

Fluorinated epoxides are intermediates for fluoroketones and polyethers.[46] The usual method of synthesis is by reaction of alkaline hydrogen peroxide with the alkene. Cyclic[47,48] and acyclic[48,49] fluoroalkenes are also readily epoxidised by aqueous sodium hypochlorite.[50] It is interesting to note that the hypochlorite ion successfully competes with the hydroxide ion in this reaction (eq 11).

Nucleophilic substitution can be followed either by further attack at an unsaturated site or by elimination of HF. Fluorinated imines are formed by loss of HF from the product obtained between primary amines and polyfluoroalkenes.[51] Reaction of ammonia with suitable substrates offers a route to nitriles that can then trimerise to give triazines substituted with polyfluoroalkyl groups.[52]

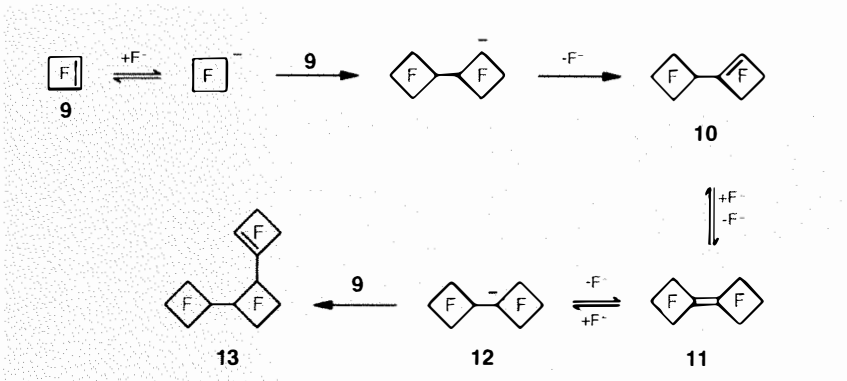
The synthetic utility of fluoroalkenes and alkynes is further enhanced through reaction with bifunctional nucleophiles.[53] This offers the opportunity for the synthesis of a wide range of heterocycles such as benzodioxoles and benzodioxepines.[53b] Enolate anions combine with cyclic and acyclic fluoroalkenes to give furans and/or pyrans, depending on the reactants.[54]

The fluorodehydroxylation reagents 2-chloro-1,1,2-trifluoroethyldiethylamine (**6**)[55] and *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropaneamine (**7**) are obtained by the addition of diethylamine to the relevant alkene. These reagents are used to prepare fluorinated amino acids and steroids under mild conditions.[56] Reaction can also occur in the presence of groups such as esters (eq 12).[57] Reagent **6** is also useful for the introduction of the CHClF group into benzoheterocycles.[55b]

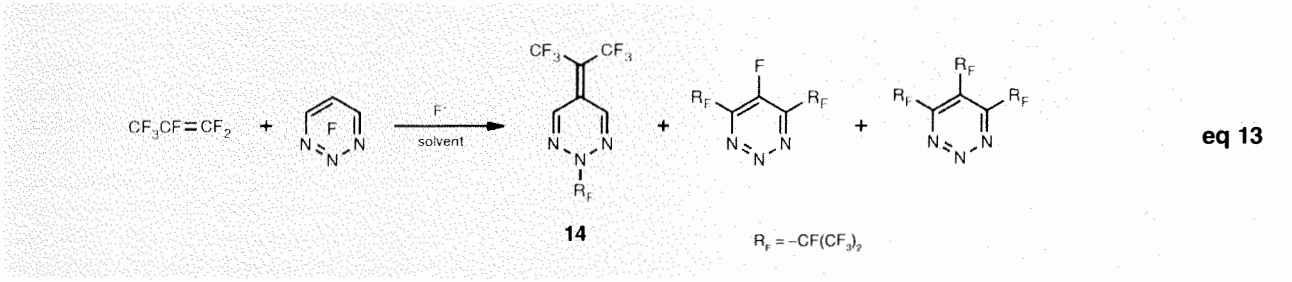
Fluoride ion chemistry

Miller showed that carbanions generated by fluoride ion could be trapped by various reagents.[58] This is a powerful technique for obtaining an extensive range of fluorinated compounds (**Scheme 3**). Fluoride ion induced oligomerisation is an important reaction for the synthesis of complex fluorinated alkenes.[30,61] The structure and distribution of the products are dependent on the alkene and reaction conditions; for example, with **8** it is possible to obtain a trimer while a hexamer is possible with **2**.[62] An important aspect is the preferential elimination of fluoride ion to give a branched alkene rather than polymerisation. An exception is the highly reactive hexafluorobut-2-yne that forms a white polymer.[63] The extended conjugation in this polymer is disrupted by the bulky trifluoromethyl groups twisting the chain into a spiral form.[64]

Oligomerisation is not restricted to acyclic systems (**Scheme 4**).[65] With cyclic compounds there is a competition between exo and endo products; a consideration of angle strain and eclipsing interactions can explain the observed distribution. Bases such as pyridine can also be used to initiate a reaction by an ylid-type process. Cooligomerisation opens up the prospect of multi-ring compounds which themselves undergo novel reactions. This synthetic approach has been extended to reactions of the nitranion derived from perfluoro-1-methyl-1,3-diazacyclopent-2- and -3-ene with cyclic fluoroalkenes.[66]



Scheme 4

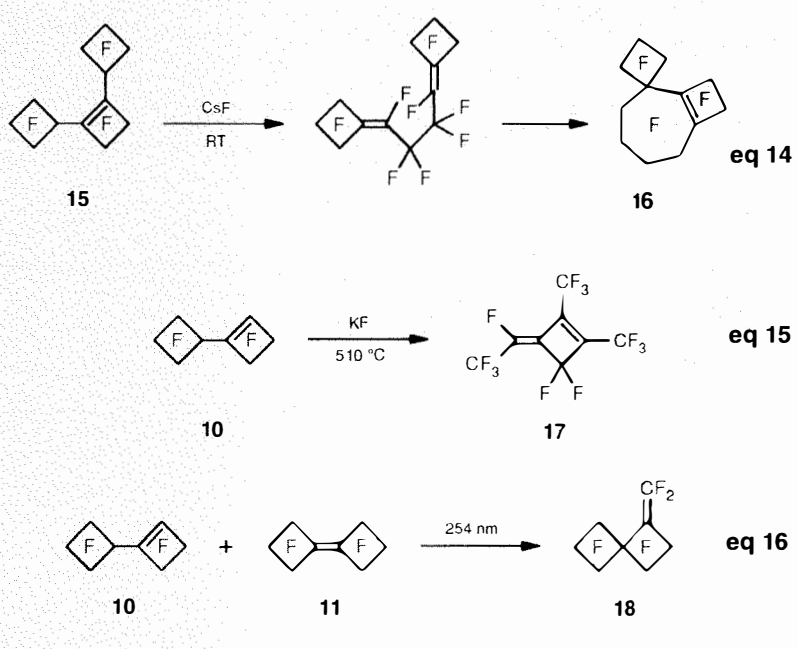


eq 13

Carbanion **4** (**Scheme 2**, Nuc = F⁻) will also react with sufficiently activated aromatics. This important reaction is known as polyfluoroalkylation and is the nucleophilic analog of the Friedel-Crafts alkylation. Side chains such as C_2F_5, $(CF_3)_2CF$, $(CF_3)_3C$, $CF_3(C_2F_5)CF$, CF_3CFCl, and $(CF_3)_2CH$[67] can be introduced using this method. Polysubstitution and rearrangement can also occur. Reaction of the heptafluoroisopropyl anion with trifluoro-1,2,3-triazine results in the unexpected isolation of **14** together with the anticipated di- and tri-substituted products. Formation of **14** is a rare example of nucleophilic attack at nitrogen, in this instance the N-2 of a triazine ring.[68]

The outcome of these reactions is dependent on the stability of the intermediate carbanion **4** (**Scheme 2**, Nuc = F⁻). Clearly, careful choice of the substrate and reaction conditions should make it possible to observe the carbanion spectroscopically. This is indeed the case and there are now several reports (e.g., **12**[69] and $[(CF_3)_3C^-]$[70] of direct observation by ^{13}C and ^{19}F-NMR.[30] Crystalline stable perfluoro-*tert*-alkylcarbanion salts can be isolated when tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) is used as the source of the fluoride ion.[71] The chemistry of the perfluoro-*tert*-butyl carbanion has been reviewed.[72]

A fluoride ion can also induce some amazing skeletal rearrangements. Examples of this include an acyclic triene to a diisopropylidenecyclobutene,[73] trimer **15** to cycloheptene **16** (eq 14),[74] and **10** to **17** (eq 15).[75] Isomerisation of perfluoro-1-alkenes to the thermodynamically more stable 2-alkenes readily occurs in the presence of fluoride ions.[20]



eq 14

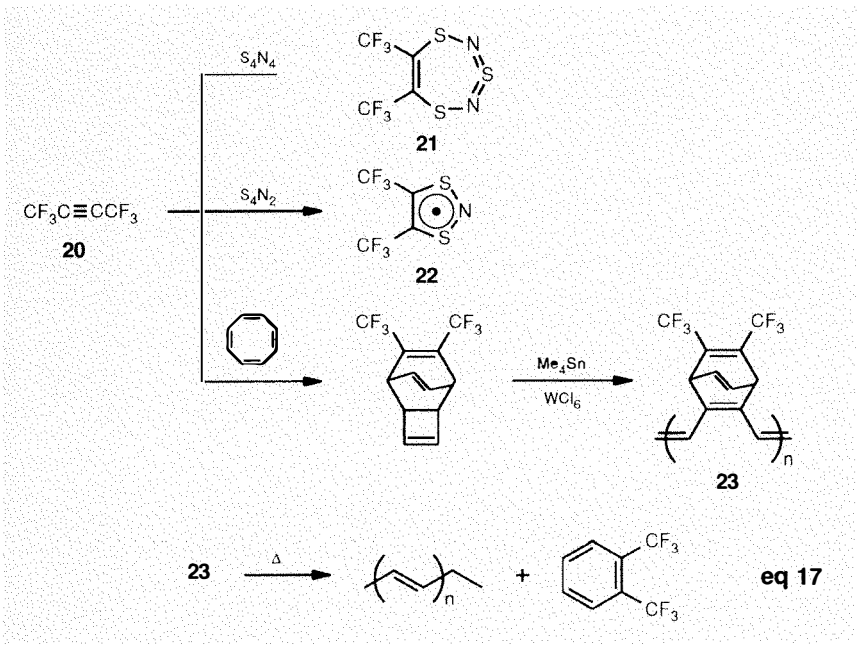
eq 15

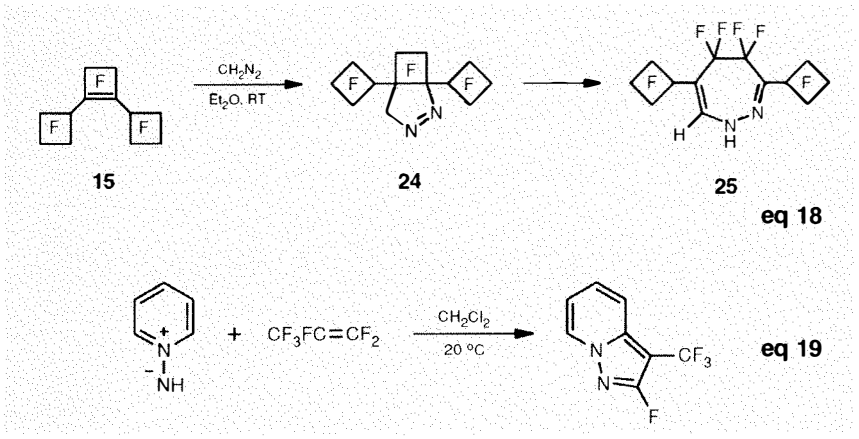
eq 16

Pentafluorophenylation of fluorinated alkenes occurs using trimethyl(pentafluorophenyl)silane and cesium fluoride.[76] Incorporation of silyl ether and R_F groups from silicon-containing precursors into cyclic fluoroalkenes is catalysed by fluoride ions. These products have potential applications as monomers and complexing agents.[77]

Rearrangements

Rearrangements involving the sigmatropic shift of fluorine[78] can be achieved by photolysis[79] or pyrolysis.[80] Spiro compound **18** is derived from **11**





when a mixture of **10** and **11** is photolysed (eq 16). The required photoequilibration of **10** and **11** necessitates a photochemical 1,3-shift of fluorine.[81]

In many instances, a fluorinated compound will undergo different chemistry relative to its hydrocarbon counterpart, enabling mechanistic subtleties to be explored. Photolysis of octafluoro-1,3,5-triene gives valence isomers, in contrast to its octahydro analog which does not.[82] A different mechanism is followed for the formation of the Cope product in the pyrolysis of fluorinated 1,5-hexadienes compared to the corresponding hydrocarbon analogs.[83]

Cycloaddition reactions

There is a great deal of interest in the cycloaddition chemistry of polyfluorinated alkenes containing the difluoromethylene group because of their readiness to undergo thermal 2+2 cycloaddition to form four-membered rings.[84] Indeed, the tendency is so great that in the electrocyclic ring opening of fluorinated cyclobutenes the equilibrium is shifted towards the cyclobutene.[85] These observations can be explained by the loss of destabilising vinylic fluorines and strengthening of the carbon-fluorine bond.

Cycloaddition can occur between two fluoro components or a fluoro and non-fluoro component in a stepwise free radical process. Terminal polyfluoroalkenes are more reactive than their internal counterparts, and the addition is usually very specific. In Diels-Alder type reactions there is the possibility of competition between 1,2- and 1,4- addition and, depending on the reactants, even the former can predominate.

The thermal cycloaddition reaction of hexafluorobuta-1,3-diene (**19**) with itself has been studied in great detail.[86] Adducts from 2+2 and 4+2 additions are found, together with products of further reaction (such as trimers). Much of the interest in **19** arises from its lack of planarity — in contrast to buta-1,3-diene. Addition of **19** to buta-1,3-diene[87] and phenylacetylene[88] has also been investigated, while reaction with substituted thiazyls offers a route to fluorinated thiazines.[89]

Pyrolysis of the adducts of tetrafluoroethylene[90] and other fluoroalkenes[91] with butadienes can lead to fluorinated aromatics with a specific substitution pattern.

Other examples of cycloaddition leading to heterocycle formation include reaction of *C,N*-diphenylnitrone with fluoroalkenes to give isoxazolidines,[92a] and oxazetidines by 1,2-cycloaddition of nitroso compounds.[92b]

Hexafluorobut-2-yne (**20**) is a highly reactive dienophile with reaction leading to many interesting products, including heterocycles. A typical example is the formation of trithiadiazepine (**21**) by addition of tetrasulfur tetranitride to **20**.[93] Reaction of tetrasulfur dinitride with **20** also gives a 1,3,2-dithiazolyl (**22**) which is stable up to 275 °C in the dark. Replacement of the trifluoromethyl groups with hydrogen or methyl considerably reduces its stability.[94] Alkyne **20** is also a precursor for the metathesis polymerization to good quality films of the conducting polymer poly(acetylene) (eq 17).[95]

Cycloaddition of perfluoro-3-methylbut-1-yne to pent-2-ene involves a rare stereospecific 2+2 thermal reaction.[23]

The influence of fluorine on orbital energies, arising from the opposing effects described earlier, has led to fluorinated compounds being used as models in studying the finer points of the cycloaddition mechanism. Reactions of fluoroallene and difluoroallene are of particular interest because the fluorine substituent affects C(1) - C(2) and C(2) - C(3) differently.[96,97] Furthermore, benefits can arise from their increased reactivity compared to allene and the low steric demand of fluorine. In general, it is found that frontier molecular orbital theory can be used to rationalize the observations. However, it was also found that in the reaction with diazoalkanes there is a competition between frontier orbital and steric control, resulting in a reversal of regiospecificity.[98]

1,3-Dipolar cycloaddition of diazomethane to perfluoroalkylalkenes yields Δ^1- and Δ^2-dihydropyrazoles. Alkenes with one or more fluorines are significantly less reactive than when four R_F groups are present. In the case of the pyrazole (**24**), formed initially by reacting **15** with diazomethane,

subsequent ring opening yields a dihydro-1*H*-1,2-diazepine (**25**) (eq 18).[99]

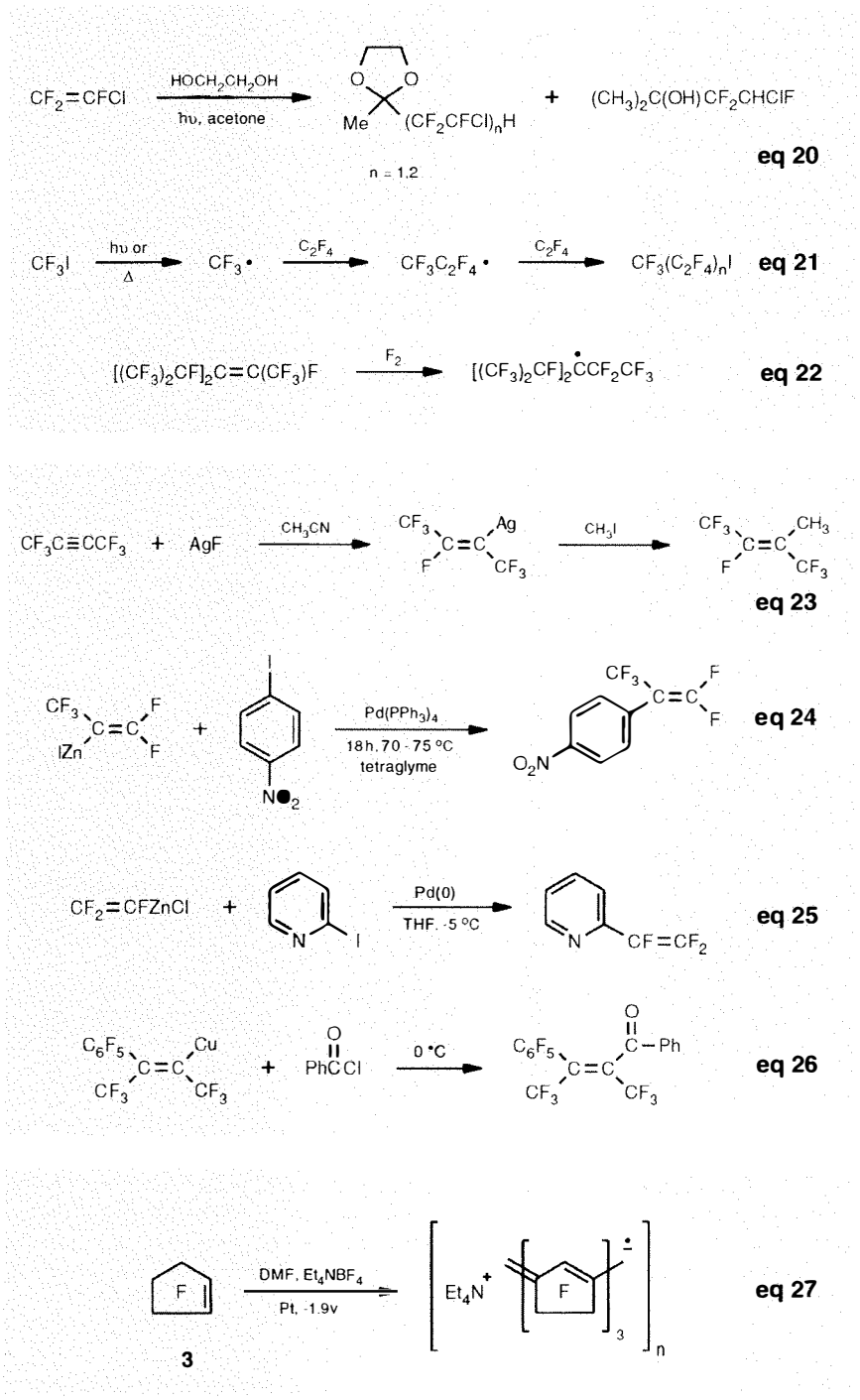
Other examples of addition include aryl azides and *N*-phenylsydnone with tetrafluoroallene[100] and ethyl diazoacetate with perfluoroalkylalkynes leading to pyrazoles.[101] Pyridinium ethoxycarbonyl and benzoyl methylides react with fluoroalkenes to give fluorinated indolizines.[102] Pyrazolo[1,5-*a*]pyridines are obtained using heteroaromatic imines (eq 19).[103]

Free radical chemistry

Free radical attack of a fluorinated double bond occurs readily, but in contrast to ionic attack, the addition can be non-regiospecific. The direction of addition is influenced by polar effects, bond strengths, and the relative stabilities of intermediate radicals. An investigation into the addition of ethers to fluoroalkenes has helped in the understanding of the mechanism of free radical reactions.[104,105] Perfluoroalkyl groups are found to influence further reaction by deactivating adjacent positions to the abstraction of hydrogen. These studies show that steric effects are more important than capto-dative influences in polyfluoroalkyl-containing systems. Interestingly, the free radical addition of tertiary amines to hexafluoropropene can occur in preference to nucleophilic attack.[105]

Radical reactions offer a practical route to numerous fluorinated derivatives. Mono-, di-, and tri-adducts are possible with ethers.[104] Simple adducts or cyclised products, such as dioxolanes, are obtained from reaction with diols (eq 20).[106] A particularly important reaction is that of telomerisation of fluorinated alkenes with perfluoroalkyl iodides (eq 21).[107] The extent of reaction can be determined by altering or changing the temperature, reactant ratios, and reactants. A detailed investigation into the influence of reaction conditions on the telomerisation of tetrafluoroethylene with iodine and hexafluoropropene with diiodoperfluoroalkanes has been carried out.[108] The method of initiation for the reaction between chloroperfluoroalkyl iodides and chlorotrifluoroethylene determined whether liquid telomers or solid polymers were formed.[109] Copper complexes are useful catalysts in the addition of carbon tetrachloride to 3,3,3-trifluoropropene[110] and trifluoroethylene,[111] affording products in high yield.

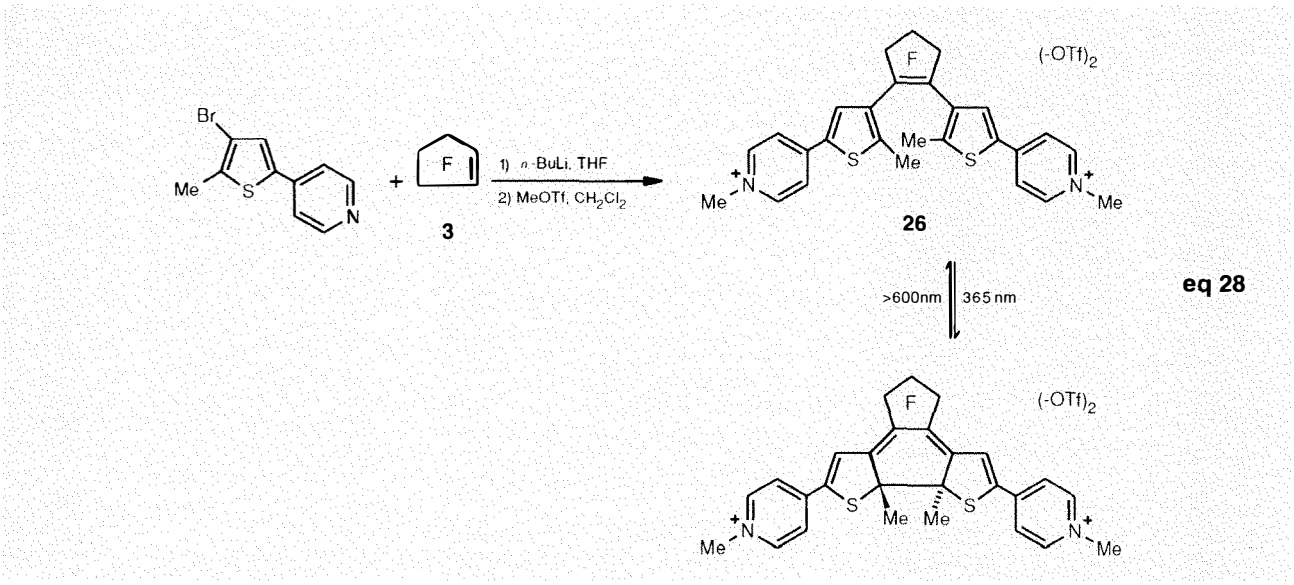
Fluorination of hexafluoropropene trimers leads to the isolation of a remarkably stable free radical (eq 22).[112] The bulky R_F groups shield the radical centre from reaction with, for example, oxygen. The radical is useful as a polymerisation initiator.[113]



Organometallic chemistry

Polyfluoroalkenyl- and alkynyl organometallics can be prepared by the usual synthetic procedures.[114] A process specific to organofluorine chemistry is the addition of a fluoride ion to an unsaturated fluorocarbon (eq 23). Silver fluoride will add to hexafluorobut-2-yne,[115] perfluoro-2-methylpropene,[116] perfluoro-2-methylpent-2-ene,[117] and tetrafluoroallene[118] to give the respective silver compounds. The following examples illustrate a few of the many applications of fluorinated organometallics in organic synthesis.

Trifluorovinyllithium is obtained by direct metallation[119] or halogen exchange.[120] Its widespread use in synthesis is limited by its instability to elimination of lithium fluoride. 2,2-Difluorovinyllithium is a useful reagent for the formation of compounds containing an allylic CF_2 group.[121] Fluorounsaturated alcohols are formed by the ring opening of oxiranes



and oxetanes with fluorovinyllithium in the presence of BF_3•OEt_2.[122] 3,3,3-Trifluoropropynyllithium, generated from trifluoropropyne, is used to obtain ynols[123] and 1,4-dialkynyl esters[124] containing the trifluoromethyl group. Ynols can also be isolated using 3,3,3-trifluoropropynylmagnesium bromide.[125]

In general, fluoroalkenyl organolithium and magnesium halide compounds need to be used at low temperature, stimulating interest in more stable reagents based on other metals. Perfluoroalkenylcadmium and zinc reagents can be prepared, at room temperature, by reaction of the bromo- or iodoalkene and the metal. These reagents can be used at temperatures up to 80 °C to synthesize fluorinated dienes and alkenyl ketones via palladium-catalysed coupling reactions.[126] Similarly, β,β-difluoro-α-(trifluoromethyl)styrenes are prepared from pentafluoropropen-2-yl zinc and aryl iodides (eq 24).[127] This is a useful route for aryl compounds substituted with nitro or ester groups and gives good yields under mild conditions. An alternative route to trifluorovinylzinc is by exchange of zinc for lithium (eq 25).[128]

Polyfluoroalkenylcopper reagents are obtained by metathesis of zinc and cadmium analogs with copper(I) salts and are of similar synthetic value.[129] For example, fluorinated α-bromo or α-chlorovinyl copper and zinc compounds dimerize to give buta-1,2,3-trienes.[130] Pentafluorophenylcopper adds stereospecifically across the triple bond of **20** to give $C_6F_5(CF_3)C{=}C(CF_3)Cu$. This reagent can be trapped with iodine, allyl bromides, and acyl chlorides (eq 26).[131] The stereochemistry of addition is *syn*, and the method is useful for the preparation of fluoroalkenes with a high degree of substitution. 2-Chloroperfluorocycloalkenylcopper reagents are useful for the introduction of a polyfluorocyclic group into, for example, acyl halides.[132]

α,β-Difluoroallyl alcohols can be synthesized from α,β-difluorovinyl triethylsilane derived from chlorotrifluoroethylene.[133] The α,β,β-trifluoro-analogous silane is a potential precursor for poly(difluoroacetylene) through fluoride ion catalysis.[134]

Unsaturated fluorocarbons are of considerable interest as ligands in organometallic chemistry. Much of this stems from their highly electron deficient nature that can lead to modification of chemistry or allow insights into the mechanism of catalysis.[135] For example, movement of ligands in a complex can have important consequences for the outcome of a reaction. The tetrafluoroethylene ligand in $[Ru(\eta^5\text{-}C_5Me_5)Cl\ (\eta^2\text{-}C_2F_4)]_2$ was found to have a very low barrier to rotation.[136]

Electrophilic chemistry

Although the chemistry of unsaturated fluoroorganics is dominated by nucleophilic chemistry, this does not mean that electrophilic reactions are precluded. Dimerisation[137] and isomerisation[137,138] of fluoroalkenes can be induced using antimony fluoride in a reaction analogous to the acid-catalysed oligomerisation of hydrocarbons. Electrophilic halofluorination[139] and reaction with, for example, mercury trifluoroacetate[140] and sulfur trioxide[141] are observed.

At first sight, it is remarkable that electrophilic chemistry and the most electronegative element can be associated. However, the *2p* orbital of fluorine is similar in size to that of carbon, and an α-fluorine actually stabilises a carbocation compared to hydrogen.[142]

A practical illustration of this is the observation that electrophiles add to 1,1-difluoroalkenes so that the positive charge develops on the 1-C.[143] In certain cases, it is possible to observe fluorinated carbocations by spectroscopy.[144] For example, substituted polyfluoroallyl cations, generated from the parent alkene using antimony pentafluoride, can be detected by ^{19}F-NMR.[144a] Similarly, the structure of the carbocation derived from perfluoro-β-methylstyrene has been analysed by ^{19}F-NMR.[144b]

Electrochemistry

Cathodic polymerisation of perfluorocyclopentene at platinum or mercury electrodes gives a blue-black conducting material (eq 27).[145] Perfluorocyclobutene behaves similarly, while reduction of perfluorocyclohexene gives hexafluorobenzene. Electrolysis of perfluorocyclohexadienes at a mercury cathode also gives hexafluorobenzene in high yield.[146] The mechanism involves stepwise electron transfer and loss of a fluoride ion. Dimerisation of perfluorocyclic alkenes can be achieved by electrochemical reduction.[147] Functionalisation, such as fluorosulfation of perfluoro-2-alkenes, is also possible.[148]

Commercial applications

The most important industrial use of fluorinated alkenes is in the synthesis of polymers and copolymers. Poly(tetrafluoroethylene) is the principal fluorinated polymer due to its unique combination of

high thermal and chemical stability and low surface energy.[149] The necessity for it to be processed by sintering has stimulated the development of polymers, such as fluoroelastomers,[150] which are more amenable to traditional methods of processing. Included amongst these are poly(chlorotrifluoroethylene), poly(vinylidene fluoride), and the copolymer of vinylidene fluoride and hexafluoropropene.[151] Poly(vinylidene fluoride) is also of great interest because of its pyro- and piezo-electric properties.[152] A novel application of the latter property is in the generation of electricity using the effect of wave motion on filaments of the polymer in the sea.[153]

Hexafluoropropene and tetrafluoroethylene can be photo oxidised to perfluoropolyethers that are used as fluids, for example, in vacuum technology.[154] Hexafluoropropene epoxide itself is an important monomer[155] for ion-selective membranes.[156] High-performance fluids and greases are obtained by telomerisation of chlorotrifluoroethylene.[157] Surfacecoating materials are obtained by radical reaction of hexafluoropropene with polyols.[158] Interest in these materials stems from the low surface energy conferred by the fluorocarbon group. Not surprisingly, fluorocarbon telomer iodides are intermediates in the synthesis of surfactants. Surface active agents can also be obtained via attack of suitable substrates on tetrafluoroethylene oligomers. A significant difference is that the former route leads to straight chain products while the latter process gives branched products.[159]

Octafluorocyclopentene (**3**) is used in the synthesis of some notable photochromic compounds[160,161] and, in particular, **26** (eq 28). Irradiation of **26** with light of different frequencies causes reversible ring opening/closing which confers the possibility of developing molecular switches for electronic applications. The fluorocarbon component enhances the ability of the system to withstand degradation under repeated irradiation.[160]

Fluoroalkenes also have potential applications as intermediates in drug[162] and agrochemical[162,163] synthesis, and as blowing agents.[164]

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About the author

Dr. Michael J. Silvester received his B.Sc. from the University of Durham, UK, in 1977. In 1981, he was awarded a PhD for investigations into the electro-organic chemistry of organofluorine compounds, under the supervision of Professor Richard D. Chambers.

After continuing his career as a Senior Research Assistant at Durham, he joined Aldrich Chemical Co. Ltd. (Bristol Organics Division) as a Senior Production Chemist in 1986. He also assists in new product development and the introduction of new fluorine technologies.

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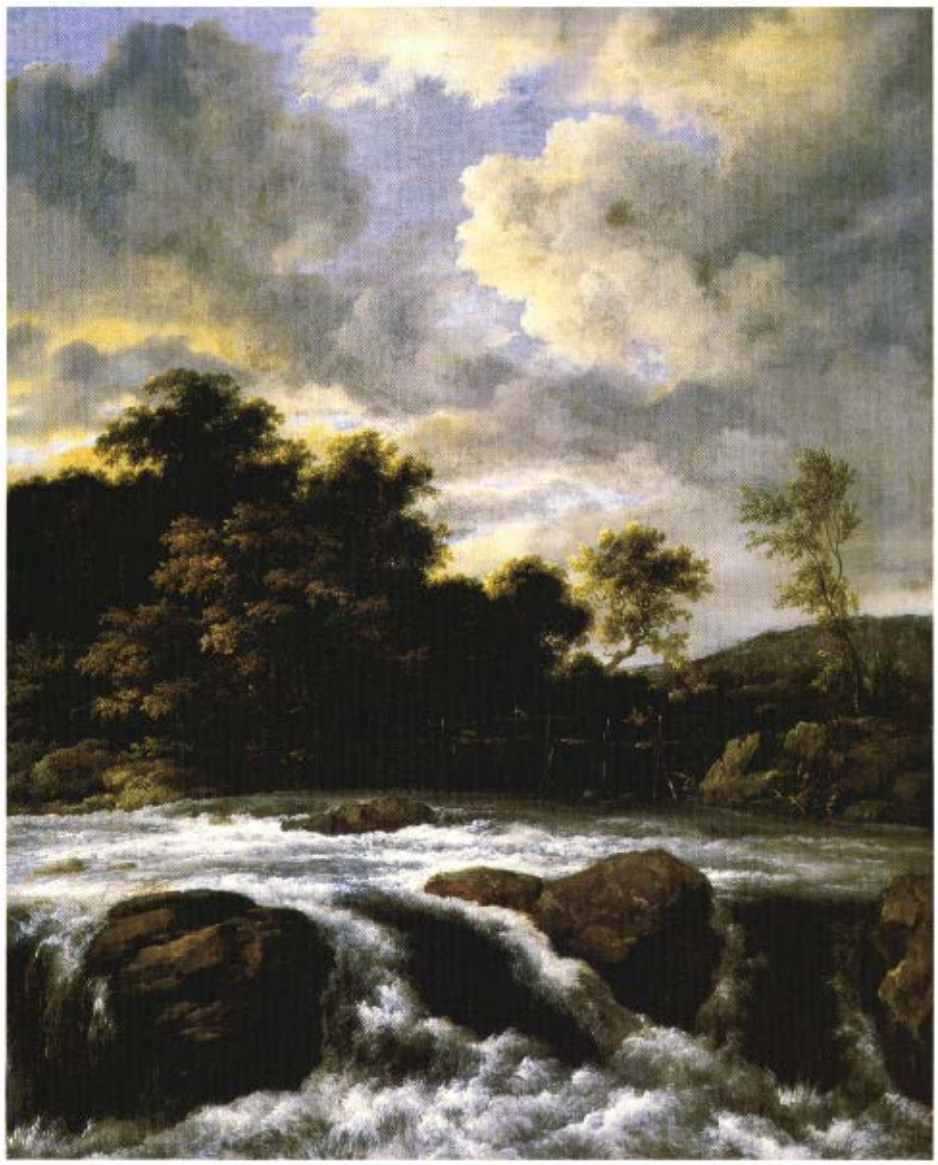

Organo Iodine(III) and Thallium(III) Reagents in Organic Synthesis: Useful Methodologies Based on Oxidative Rearrangements

Rare Earth Triflates in Organic Synthesis

The Intermediacy of Transition-Metal Silicon-Bonded Complexes: Recent Developments

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About our Cover:

Our cover displays a scenic masterpiece entitled *Landscape with Waterfall* (ca. 1665, oil on canvas, 69.4 x 56 cm) by Jacob van Ruisdael (1628/9-1682). Today, as in Goethe's time, Ruisdael is considered the undisputed master of Dutch landscape during its most heroic phase (1650-75). His subjects include scenery which he had never viewed firsthand. In the 1660s he painted a number of imaginary landscapes, all distinctly northern in character, along with waterfalls, all strongly inspired by the Scandinavian work of Allaert van Everdingen (1621-1675).

The upright format, low vantage point, expansive middleground, hills, and towering skies are very much Ruisdael's elements. However, Ruisdael's paintings have a greater power than the sum of these parts; they convey a vision that is at once romantic and grand, dark and melancholy. Like the example on our cover, many are twilight scenes, with weak and low light, transparent and grey shadow—a darkling world with transient and insignificant figures. As much as earlier Vanitas still-lifes, Ruisdael's painting bespeaks the impermanence of a passing world and the haunting grandeur of Nature.

The painting is in the collection of The Saint Louis Art Museum.

Lab Notes

In our lab we do a lot of ion chromatography. We use translucent polyethylene or propylene bottles for eluent and regenerant solutions. Determining the liquid level at a glance was always difficult. We tried many things, but a simple solution that works well is to put a handful of brightly colored Aldrich NMR tube caps in the polybottles. The caps show up really well through the bottle. They float. They are not attacked by most solutions. And they are both readily available and cheap!

J.G. Townsend, Sr. Chemist
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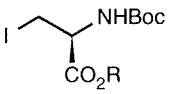
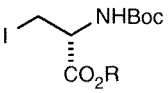
by

Jai Nagarkatti,
President



1a R = CH_2Ph
1b R = CH_3



2a R = CH_2Ph
2b R = CH_3

Professor R.F.W. Jackson at the University of Newcastle, UK, suggested that we offer the enantiomeric pairs of *N*-(*tert*-butoxycarbonyl)-3-iodoalanine methyl and benzyl esters. These chiral intermediates are readily converted into organozinc reagents that are useful for the preparation of enantiomerically pure α-amino acids[1] as well as 4-oxo- and 3-aryl-α-amino acids.[2] The organozinc reagents undergo Pd(0) catalyzed coupling to give phosphonomethylphenyl alanines[3] and also form zinc/copper reagents, useful for α-amino acid synthesis.[4-6]

(1) Jackson, R.F.W. et al. *J. Chem. Soc., Chem. Commun.* **1989**, 644. (2) Jackson, R.F.W. et al. *J. Org. Chem.* **1992**, *57*, 3397. (3) Dow, R.L.; Bechle, B.M. *Synlett* **1994**, 293. (4) Bajgrowicz, J.A. et al. *Tetrahedron* **1985**, *41*, 1833. (5) Idem *Tetrahedron Lett.* **1984**, *25*, 2759. (6) Dunn, M.J. et al. *J. Org. Chem.* **1995**, *60*, 2210.

Naturally, we made these useful protected amino acid derivatives. It was no bother at all, just a pleasure to be able to help.

Organo Iodine(III) and Thallium(III) Reagents in Organic Synthesis: Useful Methodologies Based on Oxidative Rearrangements

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1. Introduction

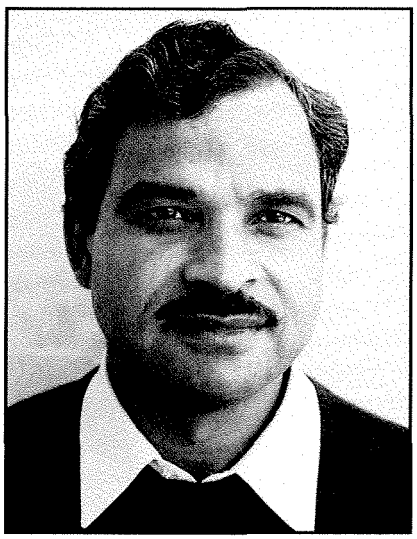
A similar and unique feature of both thallium(III) and organo iodine(III) reagents is their oxidizing ability, where the central hypervalent atom acts as an electrophile. These oxidations are termed oxythallation and oxyhyperiodination. Oxythallation and solvothallation are well established synthetic methodologies,[1-3] whereas analogous iodination processes are relatively new and less common.[4]

Several excellent publications dealing with the synthetic versatility of Tl(III)[1-3] and hypervalent iodine reagents[5-12] have appeared recently. The present article is intended to highlight the parallel nature and synthetic utility of Tl(III) and organo I(III) reagents. The discussion will focus only on oxidative rearrangements, one of the most fascinating and potentially useful areas of organic research. This choice excludes discussion of a considerable amount of work on the rearrangement of iodonium ylides/salts,[6a,12] a distinct feature of organo I(III) reagents. The common abbreviations of important reagents used in this review are given in **Table 1**.

2. Discussion

As a part of our broad program directed towards the development of hypervalent iodine oxidation reagents for α-functionalization of carbonyl compounds, we ventured into the area of acetophenone and chalcone oxidations with HTIB (in methanol).[4] However, instead of obtaining α-functionalized compounds, we observed products resulting from rearrangement. A reaction involving rearrangement was found to be of broader interest since similar oxidative rearrangements using Tl(III) salts had been reported.[2a]

In this context, Moriarty and co-workers[4] were the first to coin the term 'solvohyperiodination' for hypervalent iodine mediated reactions, analogous to the term solvothallation used to describe Tl(III) reactions. Furthermore, we predicted the possibility of providing a useful complement to the well-established Tl(III) mediated methods. Since then, a great deal of work based on the analogy between Tl(III) and I(III) reagents has revealed their increasing synthetic utility. Most of this work deals with rearrangement processes involving 1,2-aryl migration and forms the basis of this article. The discussion of these results has been divided into four parts, each part describing reactions with a different substrate. Subdivisions of these parts are based on the type of hypervalent reagent involved in the transformation.



2.1. Alkyl aryl ketone substrates: α-arylalkanoate and acid precursors

α-Arylalkanoic acids, such as ibuprofen and Naproxen-S, have found widespread use as anti-inflammatory agents.[13] In addition, these acids and their derivatives are extensively used as important synthetic intermediates. Among the various methods available for preparing α-arylalkanoates **2** and acids **1**, the oxidative rearrangement of alkyl aryl ketones[14] using Tl(III) or

Table 1. Thallium(III) and organo iodine(III) reagents.

Reagent	Formula	Abbreviation	Aldrich Cat. No.
Thallium(III) acetate	$Tl(O_2CMe)_3$	TTA	15,116-5
Thallium(III) nitrate trihydrate	$Tl(NO_3)_3 \cdot 3H_2O$	TTN	16,301-5
Thallium(III) perchlorate hydrate	$Tl(ClO_4)_3 \cdot xH_2O$	TTPC	40,376-8
Iodobenzene diacetate	$PhI(O_2CMe)_2$	IBD	17,872-1
Iodobenzene bis(trifluoroacetate) or [Bis(trifluoroacetoxy)iodo]benzene	$PhI(O_2CCF_3)_2$	IBTA	23,213-0
[Hydroxy(tosyloxy)iodo]benzene	PhI(OH)OTs	HTIB	30,103-5
[Hydroxy(mesyloxy)iodo]benzene	PhI(OH)OMs	HMIB	—

organo I(III) reagents is one of the most efficient and practical (eq 1). This elegant approach has been divided into the following two sections to allow for a more detailed discussion of Tl(III) and I(III) reagents.

2.1.1. Tl(III) oxythallations/ solvothallations

A variety of reaction conditions have been employed to achieve the transformation of **3** to **1**, depending on the nature of the substrate. McKillop[15] used TTN in methanol to effect transformation of acetophenone to methyl phenylacetate (94%). α-Methoxyacetophenone is formed as a by-product (6%). Although the reaction has been applied successfully to a wide range of acetophenones, it has two disadvantages. The reaction is unsuccessful for amino substituted substrates because of preferential oxidation of the amino group. Second, use of acetophenones in which the aromatic ring is strongly deactivated (i.e., EWG substituents) results in low yields of esters and high yields of α-substituted products **4**.

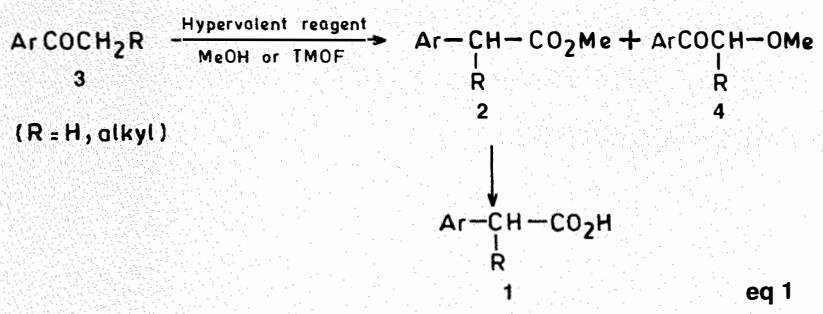
The formation of α-substituted products can be completely suppressed by utilization of TTN/K-10 (i.e., TTN on K-10 clay) reagents.[16] A few examples of alkyl aryl ketone rearrangements are depicted in equations 2,[15,16] 3,[17] 4,[18] and 5.[19,20]

Other alkyl aryl ketones, such as propiophenones (**3**, R = Me) also undergo an analogous rearrangement to give methyl α-propionates. However, the use of methanol alone as a solvent does not give satisfactory results because of the concomitant formation of α-methoxylated ketones. This side reaction is completely suppressed by employing the following reaction conditions: (i) a methanol and trimethyl orthoformate (TMOF) mixture as the solvent;[21] (ii) use of TTN/K-10 reagent;[16] or (iii) employing the corresponding enol ether as a substrate.[22] The latter modification is particularly useful since it allows a one-step preparation of the methyl ester **7** of ibuprofen from 4-isobutylpropiophenone via its enol ether **8** (eq 6).[22-24]

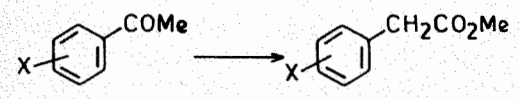
The possible mechanistic pathways of these Tl(III) mediated rearrangements have been investigated by McKillop,[15,16] Walker and Pillai,[22] and Higgins and Thomas.[25] Despite some minor discrepancies, a reasonable mechanism based on these studies is outlined in **Scheme 1**.

2.1.2. I(III) oxyhyperiodinations/ solvohyperiodinations

Hypervalent iodine(III) reagents provide a useful alternative to Tl(III)mediated

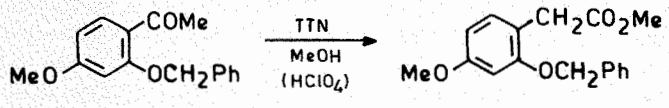


eq 1

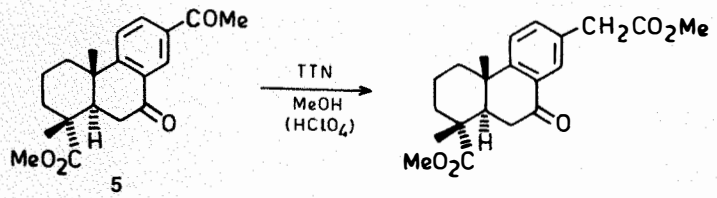


eq 2

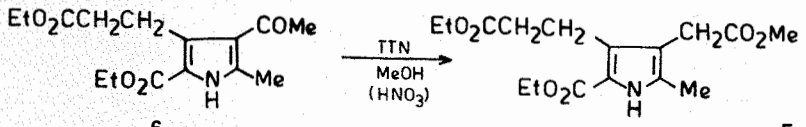
X	Yield (%)	
	TTN–$HClO_4$/MeOH	TTN, K-10
H	84	86
4-F	44	88
4-Me	86	84
4-Br	35	89
2-OMe	62	—
4-OMe	89	92



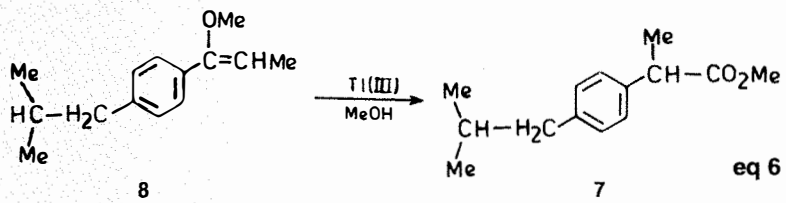
eq 3



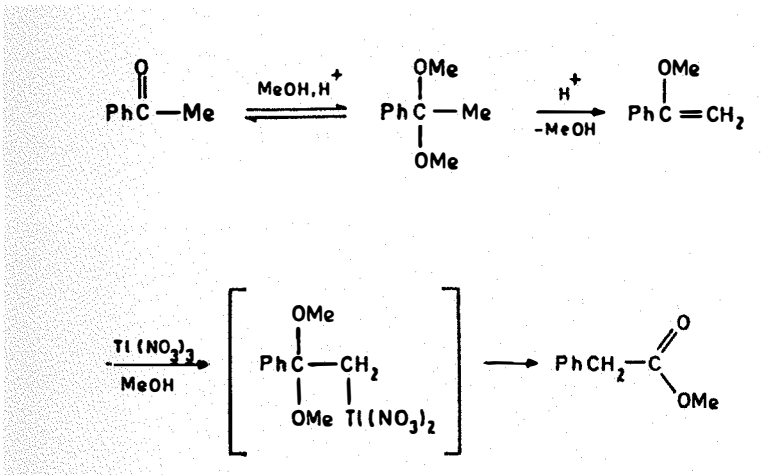
eq 4



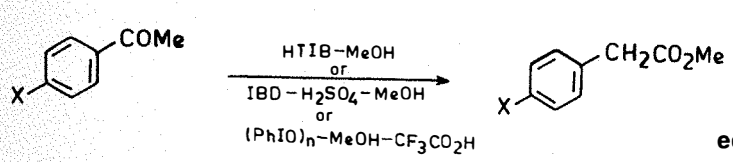
eq 5



eq 6

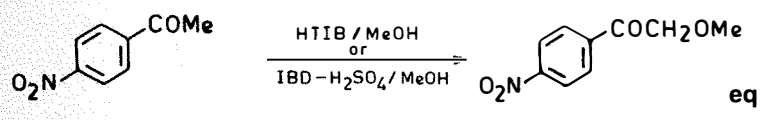


Scheme 1

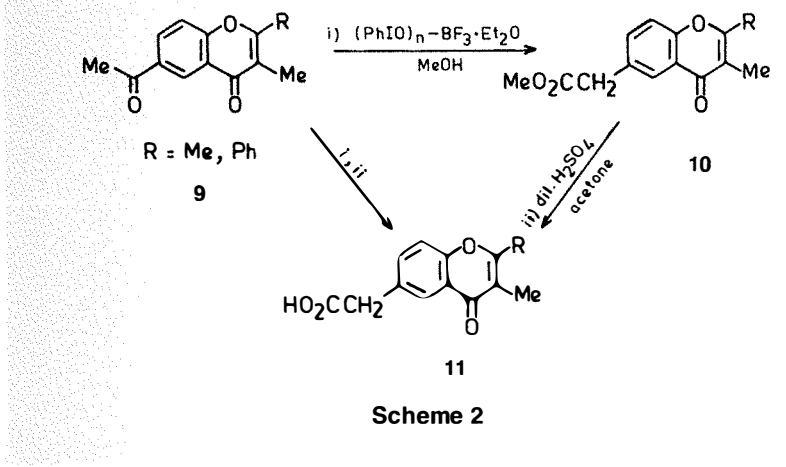


eq 7

X	Yield (%)	
	HTIB / MeOH	IBD–H_2SO_4 / MeOH
H	57	61
OMe	68	70
Me	62	63
Cl	55	53
F	41	—



eq 8



Scheme 2

methodology for the effective one-step conversion of **3** to **2**. For example, acetophenones, upon treatment with HTIB/IBD or iodosobenzene and concentrated sulfuric acid in methanol, afford methyl arylacetates (eq 7) in good yields, along with smaller amounts of α-methoxyacetophenones.[4,26,27] However, oxidation of *p*-nitroacetophenone under similar conditions mainly provides the α-methoxy derivative (eq 8). This reaction has successfully been applied to the synthesis of 2-substituted-3-methylchromon-6-ylacetic acids **11** starting from **9** (**Scheme 2**).[28]

The use of methanol as a solvent does not give a satisfactory result for rearrangement of propiophenones and related compounds. However, when TMOF is employed as the solvent, propiophenones are successfully transformed to α-arylpropionates (eq 9).

This method is also effective for synthesizing 2-(6-methoxy-2-naphthyl)-propanoic acid (**12**), whose (*S*)-enantiomer is a well-known anti-inflammatory drug (Naproxen S, **Scheme 3**),[26] as well as 2-substituted 3-methylchromon-6-ylpropanoic acids (**14**).[28]

A further advantage of the hypervalent iodine approach is that alkaline hydrolysis of the resultant ester can be performed directly without isolating the ester, thus yielding alkanoic acid in one step (**Scheme 3**; i.e., **13** to **12**).

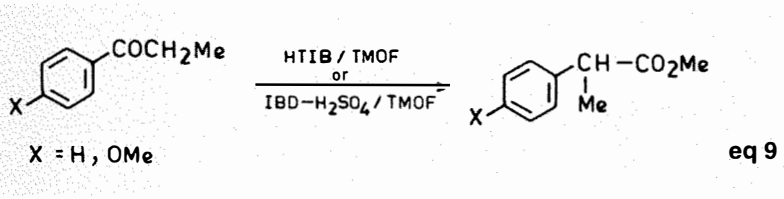
The results of the hypervalent iodine oxidative rearrangements of alkyl aryl ketones, under various reaction conditions, can be explained mechanistically in terms of initial enol ether formation, followed by solvohyperiodination, as shown in **Scheme 4**. In compounds substituted at the C-4 position with electron donating groups, the bridged phenonium ion **18** is stabilized, thus aryl migration occurs. In compounds substituted at this position with electron withdrawing groups, methoxy participation gives bridged ion **19** that subsequently undergoes ring opening to yield the α-methoxyketone **20**.[26]

2.2. Chalcone substrates

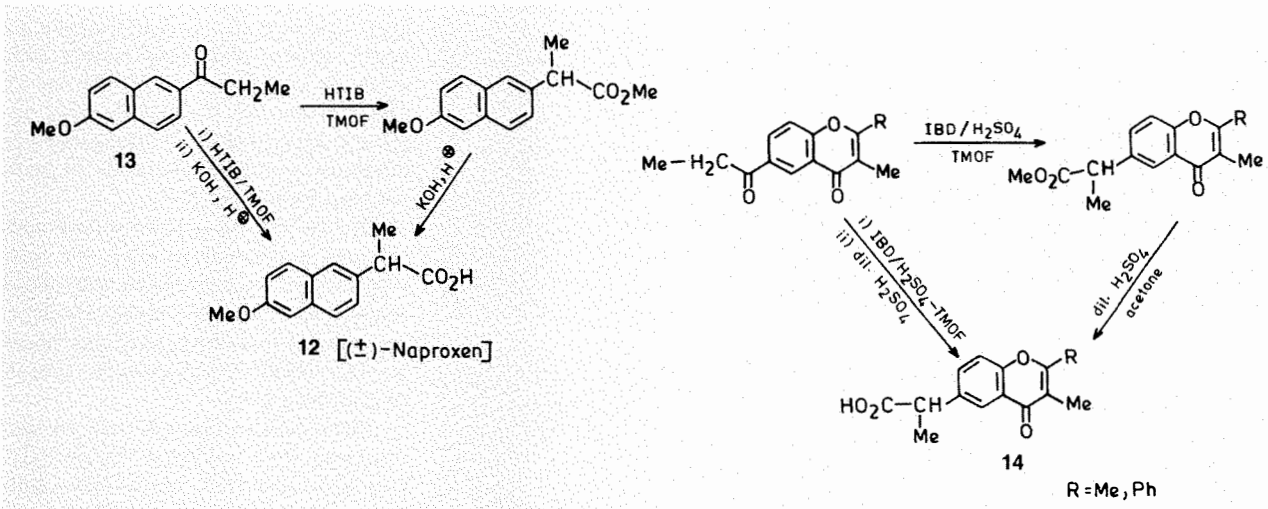
2.2.1. Tl(III) transformations

Chalcones **21**, a typical class of α,β-unsaturated ketones, are known to undergo oxidative 1,2-aryl migrations in the presence of either Tl(III) or I(III) reagents. Thallium(III) mediated oxidations of **21**, leading to convenient formation of 1,2-diaryl-3,3-dimethoxypropan-1-ones **22**, have been investigated in more detail than I(III) oxidations. Initially employed conditions involving the use of

TTA/MeOH[29] did not provide satisfactory results; however, replacement of TTA by TTN and use of a small amount of perchloric acid provided improved results.[30] These conditions furnished rearranged products at room temperature in moderate to high



eq 9



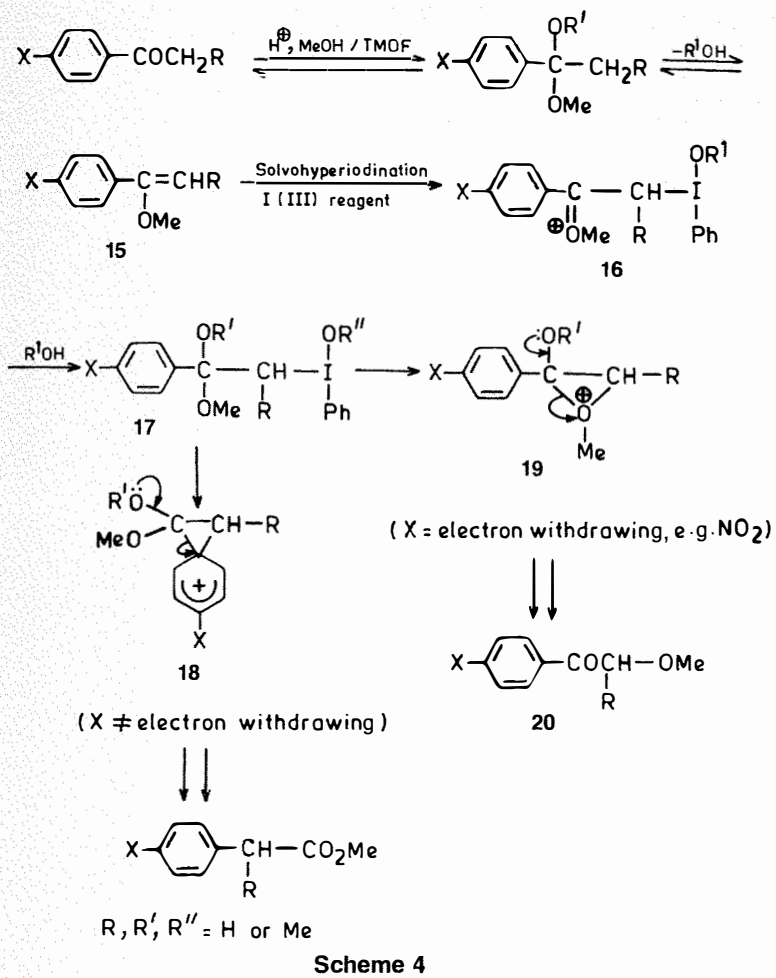
Scheme 3

yields. A probable mechanism is outlined in **Scheme 5**.

Oxidation of chalcone (**21**, Ar = Ar′ = Ph) with TTN in TMOF resulted in a 1:1 mixture of the expected 3,3-dimethoxy-1,2-diphenyl-propan-1-one (**22**) and methyl 2,3-diphenyl-3-methoxypropanoate (**23**, Ar = Ar′ = Ph). The latter product, **23**, resulted from a competing pathway involving migration of the Ar′ ring as shown in **Scheme 6**. TMOF, in the presence of acid, favors ketalization of the carbonyl group, leading to a competing process involving migration of the Ar′ ring.[31,32]

The rearrangement of chalcones using TTN/MeOH becomes especially important in synthesizing isoflavones **26** from suitably *o*-substituted chalcones **27**. Thus, when the Ar′ ring of a chalcone carries an *ortho*-hydroxyl group, the 1,2-diaryl-3,3-dimethoxypropan-1-one (**28**), the rearranged product resulting from solvothallation followed by Ar ring migration, should be capable of further transformation to an isoflavone (**26**) by intramolecular *trans*-ketalization (**28** to **29**) followed by loss of methanol (**29** to **26**, **Scheme 7**).[33,34] This approach, first recognized by Ollis and co-workers, has made isoflavones, including natural products, easily accessible.

From a practical point of view, it is necessary to protect the *ortho*-hydroxyl group before effecting the 1,2-aryl



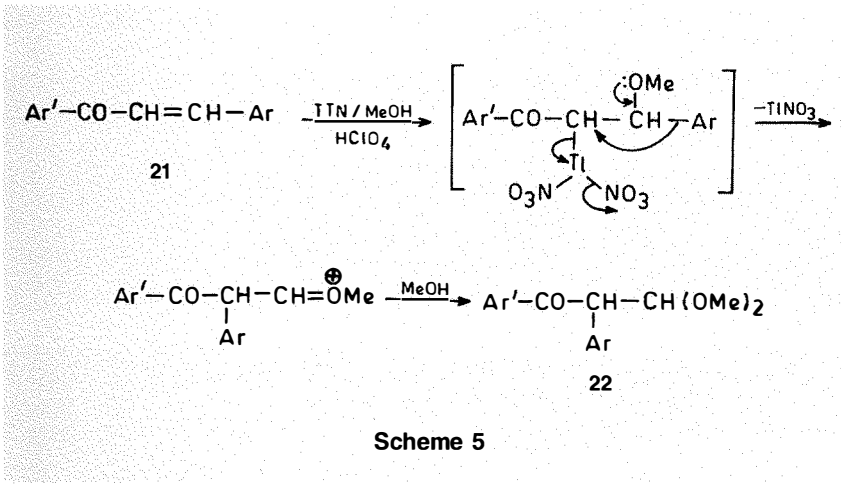
Scheme 4

migration. An example is the synthesis of retusin (**Scheme 8**).[35] Other examples of naturally occurring flavonoids synthesized using this methodology are illustrated in **Table 2** (cf. references 36-38).

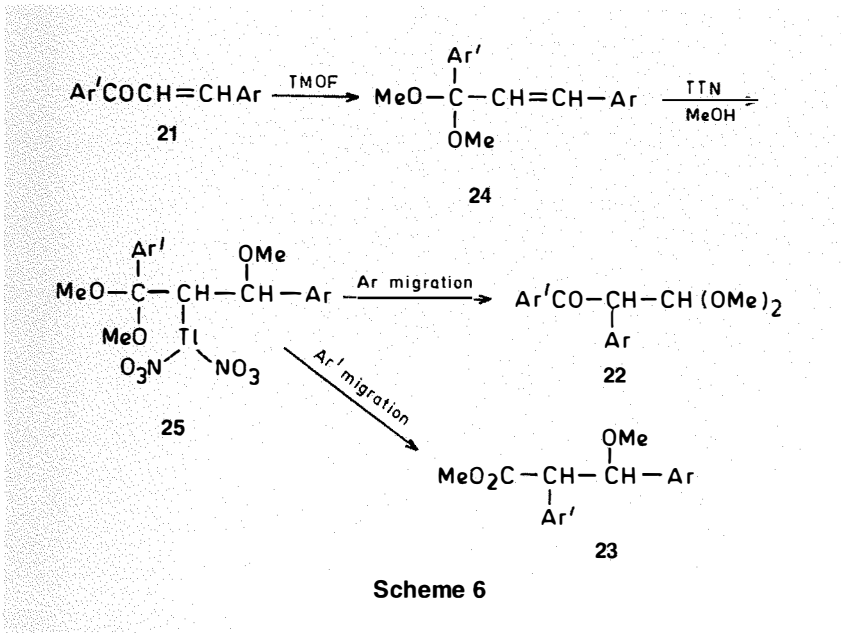
2.2.2. *I(III) transformations*

Hypervalent iodine reagents have also been employed to effect 1,2-aryl migration in chalcones.[39] Thus, treatment of **21** with HTIB/IBD or iodosobenzene in an acidic methanol solution affords rearranged products **22** (**Scheme 9**, route a).[4]

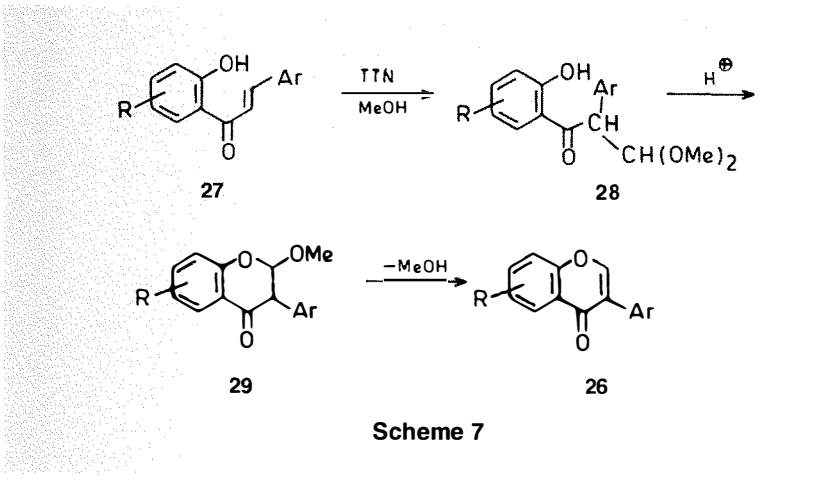
It is interesting to mention here in the context of hypervalent iodine chemistry that, depending on reaction conditions, various pathways can be followed in these oxidations. For instance, when chalcone is mixed with HTIB in dichloromethane, the *vic* tosylate (**30**) is obtained[40] (**Scheme 9**, route b). On the other hand, the treatment of chalcones (**21**) with IBD-KOH in methanol gives α-hydroxy-β-methoxydimethylketals (**31**, **Scheme 9**, route c).[41,42]



Scheme 5



Scheme 6



Scheme 7

2.3. *Flavanone substrates*

2.3.1. *I(III) transformations*

One of the most interesting and useful aspects of hypervalent iodine reagents is the oxidation of flavanones (**32**). Depending on the reaction conditions isoflavones (**26**), flavones (**33**), and methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates (**34**) can be prepared (**Scheme 10**).

The oxidation of flavanones with HTIB in boiling acetonitrile or propionitrile does not afford the expected α-functionalized products [i.e., 3-tosyloxyflavanone (**35**)]. Instead, a 1,2-shift of the C-2 aryl group occurs, thus providing a new and useful route to isoflavones (**26**, **Scheme 10**, route a).[43] The course of this oxidative rearrangement is greatly influenced by reaction conditions, resulting in **33** and **34** in addition to **26** or a mixture of several products.

Detailed experimental studies have established that it is indeed possible to choose reaction conditions giving a more selective process. For example, the other reaction conditions that can yield **26** as the major product in the oxidation of **32** are IBD/*p*-TsOH in MeCN, and iodosobenzene/methanesulfonic acid in CH_2Cl_2 or MeCN.

Replacement of acetonitrile or propionitrile with methanol in the oxidation of **32** with HTIB leads to entirely different results, producing flavones (**33**) as the major products (**Scheme 10**, route b).[44] Minor products include variable amounts of **34** and *cis*-3-methoxyflavanones (**36**). Similar results are obtained by using IBD/MeOH, IBD/AcOH, or $(PhIO)_n/BF_3{\cdot}Et_2O$. The use of IBD/$CF_3COOH$, iodobenzene bis-trifluoroacetate (IBTA) in MeCN, or IBD-H_2SO_4/MeCN affords a mixture of **26** and **33** in varying ratios.[45]

When TMOF is employed as a solvent in the previous oxidation a contraction of the pyran ring occurs. Methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates (**34**) are produced as major products, as well as minor amounts of

cis-3-methoxyflavanones (**36**) and **33** in variable ratios (**Scheme 10**).[46]

The mechanistic pathways for the transformations **32** to **26/33** and **32** to **34** are outlined in **Schemes 11** and **12**, respectively.

Salient features of these pathways are as follows:

(i) A common step to both the conversions is the electrophilic attack of the I(III) species (oxyhyperiodination) on the enol form of **32** at the face of the molecule *anti* to the C-2 aryl ring to provide intermediate **37**.

(ii) Pathways a and a′, involving a 2,3-aryl shift, lead to **26**. Pathway b, involving S_N2 attack of X^-/XH at the C-3 position of **37**, leads to **33** via **36**.

(iii) The nucleophilicity of X^-/XH plays a decisive role in effecting the course of the reaction.

(iv) The use of TMOF as a solvent provides strong acetalizing conditions (**32** to **38**) leading to **34** via enol ether **39**, as outlined in **Scheme 12**.

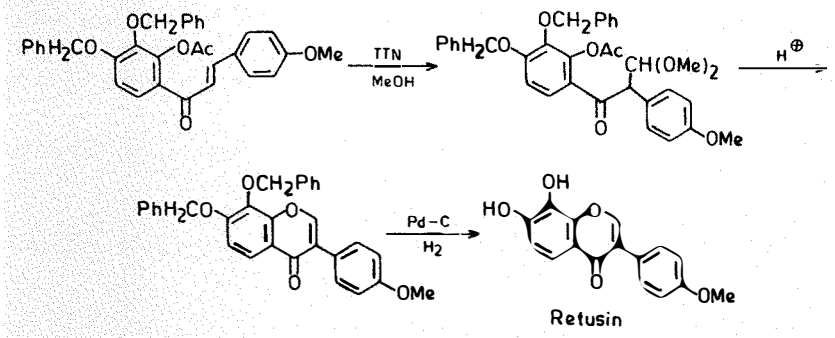
2.3.2. Tl(III) transformations

The oxidation of **32** using Tl(III) salts under a variety of reaction conditions has also provided effective methods for the formation of **26**,[47-50] **33**,[51,52] and **34**.[53] A particularly noteworthy feature is the efficient and general synthesis of **26**. The oxidation of **32** with TTN or TTA and 70% perchloric acid in MeCN or CH_2Cl_2 provides **26**. [A wide range of isoflavones can be prepared with substitution (electron withdrawing and electron releasing) at the *para*-position of the aryl ring.] Using MeCN/DME as solvent, thallium triperchlorate (TTPC) is generated in situ by exchanging acetate and nitrate with perchlorate anions.[50]

The mechanism for these transformations is similar to the pathways proposed for the hypervalent iodine methods as discussed in section 2.3.1 and depicted in **Scheme 11**. Since the nature of the C-2 aryl substituent in the TTPC mediated transformations of **32** to **26** has no affect on the course of the reaction, it has been suggested that the C-2 aryl migration presumably occurs via an oxonium ion (path a) rather than a bridged carbonium ion (path a′).

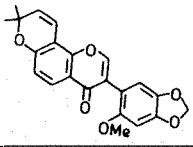
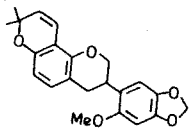
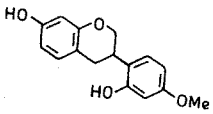
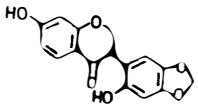
2.4. Miscellaneous substrates

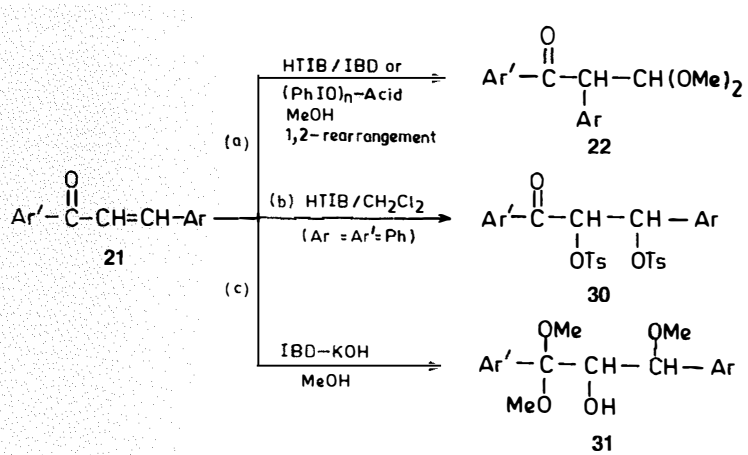
Other kinds of compounds that undergo oxidative rearrangement with Tl(III) and I(III) reagents include styrenes, alkynes, cinnamaldehydes, and allenes. Some examples of these reactions, which lead to a number of valuable products, are summarized in **Table 3**.



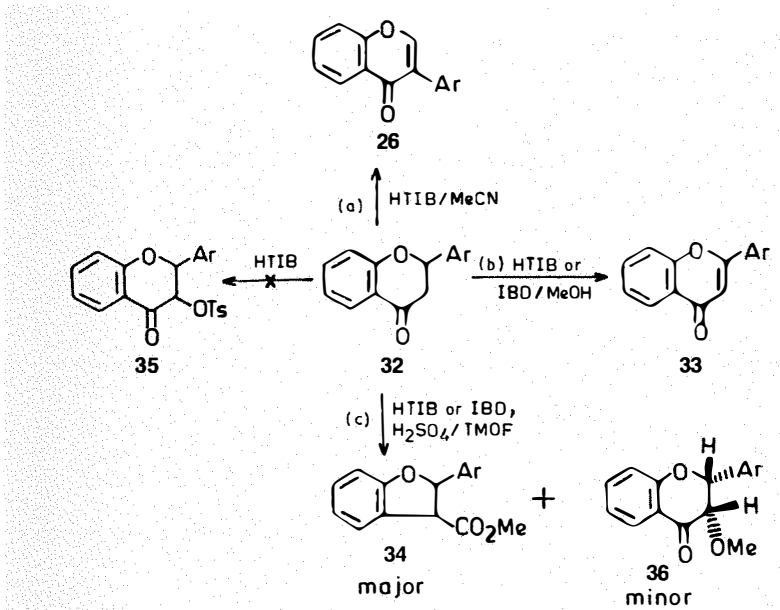
Scheme 8

Table 2. Some naturally occurring flavonoids synthesized according to the Tl(III) methodology depicted in **Schemes 7** and **8**.

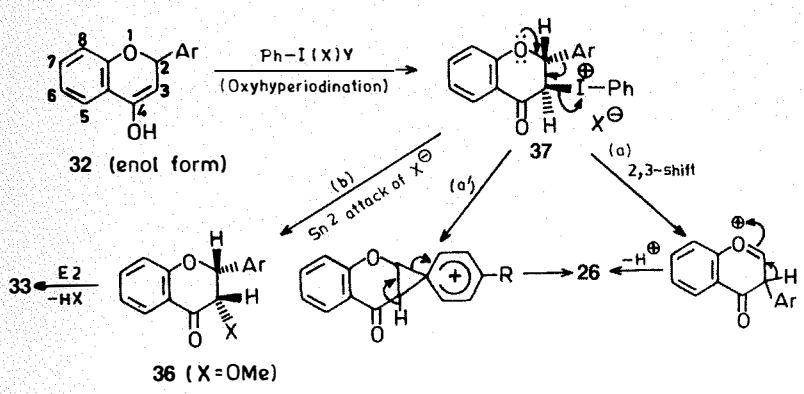
Flavonoid	Structure	Reference
Jamaicin		36
(±)-2′-O-Methylleiocin		37
(±)-Vestitol		38
(±)-Sophorol		38



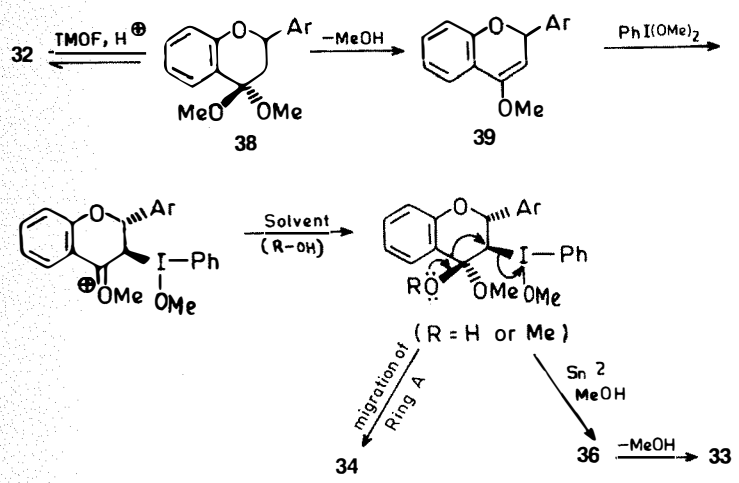
Scheme 9



Scheme 10



Scheme 11



Scheme 12

3. Conclusions

The preceding summary of oxidative rearrangements clearly indicates the close similarity between Tl(III) and I(III) reagents. A number of useful syntheses involving these oxidative rearrangements are receiving wider acceptance because of their simplicity, high yields, and use of readily available starting materials. The methodologies involving the two types of hypervalent reagents are complementary. Some concluding remarks on their comparative advantages/disadvantages are discussed below.

The advantages of Tl(III) over I(III) based methodology:

(i) The use of TTN and K-10 in the conversion of alkyl aryl ketones to α-aryl alkanoates suppresses the formation of α-substituted products (**4**).

(ii) The use of TTPC in MeCN or DME offers a general one-step synthesis of isoflavones from flavanones (**32** to **26**).

(iii) One fundamental difference between Tl(III) and I(III) is in the properties of their reduced products. Whereas thallium salts are generally water insoluble solids, organo iodine(I) compounds are generally water insoluble liquids making it somewhat easier to separate Tl(I) salts.

The advantages of I(III) over Tl(III) based methodology:

(i) A unique feature of organo I(III) reagents is their nontoxic nature. Tl(III) salts are usually highly toxic materials.

(ii) α-Arylalkanoic acids are obtained in a one-pot procedure, if the step for the isolation of the ester is omitted. Separation of iodobenzene is not problematic.

(iii) A remarkable point in the context of hypervalent iodine chemistry is that two (or more) distinct pathways are followed under acidic/neutral or basic conditions.

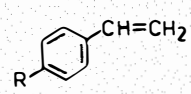
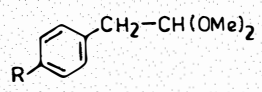
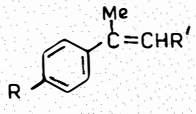
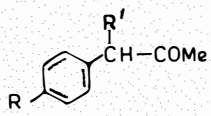
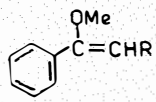
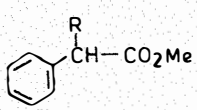
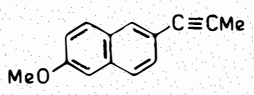
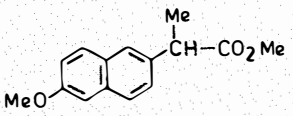
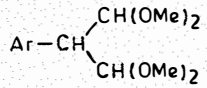
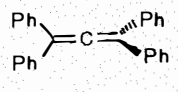
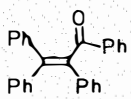
(iv) Although not discussed in this review, iodonium ylides/salts that are available only through I(III) reagents are important synthetic intermediates.[6a,12]

Finally, this review of hypervalent reagents will hopefully stimulate further synthetic and theoretical studies with a special emphasis on the following aspects: (i) synthesis of chiral molecules, (ii) synthesis of biologically important compounds, and (iii) quantitative comparison of the reactivity of Tl(III) and I(III) reagents.

Acknowledgments

Thanks are due to Professor Robert M. Moriarty, Chemistry Department,

Table 3. Miscellaneous substrates which undergo oxidative rearrangements using Tl(III) and I(III) reagents.

Substrate	Structure	Major product	Reaction condition	Reference
Styrenes			TTN/MeOH TTN, K-10 HTIB/MeOH	54-56 16 4
α-Methylstyrenes			TTN/MeOH	54,56
α-Methoxystyrenes			TTN/MeOH (R = H,Me) HTIB/MeOH IBD,H+ (R = H)	22 26
Alkynes	$R^1C{\equiv}CR^2$	$R^1CHR^2CO_2Me$	TTN/MeOH HTIB/MeOH	57 58
			TTN/MeOH	59
Cinnamaldehydes	$Ar-CH{=}CH-CHO$		TTN, TMOF/MeOH	21
Allenes			HTIB/CH_2Cl_2 -78°C to RT	60

University of Illinois, Chicago, and Ms. Neena Saini, Chemistry Department, K.U. Kurukshetra for their valuable discussions and other help during the preparation of this manuscript. Financial assistance provided by C.S.I.R., New Delhi, India is also greatly acknowledged.

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About the author

Dr. Om Prakash received a M.Sc. degree from Meerut University (S.D. College, Muzaffarnagar) in 1972. He received a PhD degree from the University of Roorkee, India in 1976 under the supervision of Professor V.K. Mahesh. After about one year of postdoctoral work with Professor S.P. Singh at Kurukshetra University (Kurukshetra) on the 'Synthesis of Heterocyclic Compounds of Potential Medicinal Interest', he joined the faculty at Meerut College as a Lecturer in 1977. In 1979, he joined the faculty of Kurukshetra University. He traveled to the University of Illinois at Chicago in 1983 and worked there as a postdoctoral research associate with Professor Robert M. Moriarty on the 'Synthesis of Acetylcholinesterase Reactivators.' During his stay at the University of Illinois-Chicago (1983-1986), he also explored the utility of hypervalent iodine reagents in organic synthesis. As a result of his efforts, applications of hypervalent oxidation reactions gained wider acceptance. He also developed novel applications of many new reagents. In 1986, he returned to Kurukshetra University as a faculty member and later revisited Professor Moriarty's laboratory in Chicago in 1988-1989. At present, Dr. Prakash is an Associate Professor at Kurukshetra University and his research group is working on the applications of newer reagents in organic synthesis and the use of these reagents in the synthesis of heterocyclic compounds.

Rare Earth Triflates in Organic Synthesis

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Introduction

Metal mediated bond formation plays an important role in organic chemistry. Recent discoveries indicate that rare earth trifluoromethanesulfonate complexes can substitute for traditional Lewis acids in a variety of organic transformations.

Hydrated forms of the lanthanide(III) trifluoromethanesulfonates (triflates) are prepared from the reaction of the corresponding oxide with triflic acid in water. Typically, the crude product contains eight or nine molecules of water. Extensive heating under vacuum is required to produce a compound that is water free. These anhydrous salts are air and water stable, hygroscopic, white to slightly colored powders—the color depending upon the lanthanide atom. For example, prascodymium(III) triflate is pale green.[1]

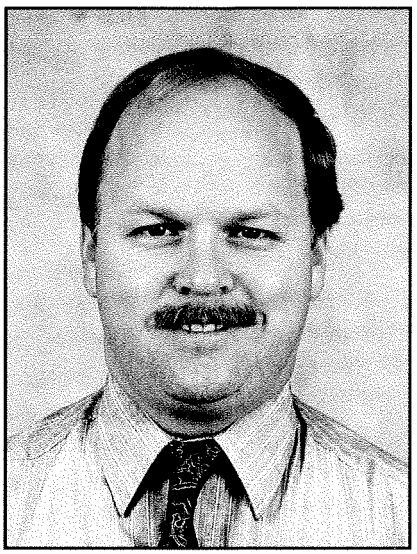
This article will discuss the use of these reagents in carbon-carbon bond forming processes such as aldol condensations, Diels-Alder reactions, Friedel-Crafts acylations, and in a variety of carbon-heteroatom bond forming processes including glycosylation and ring-opening reactions of epoxides and aziridines.

Carbon-carbon bond formation

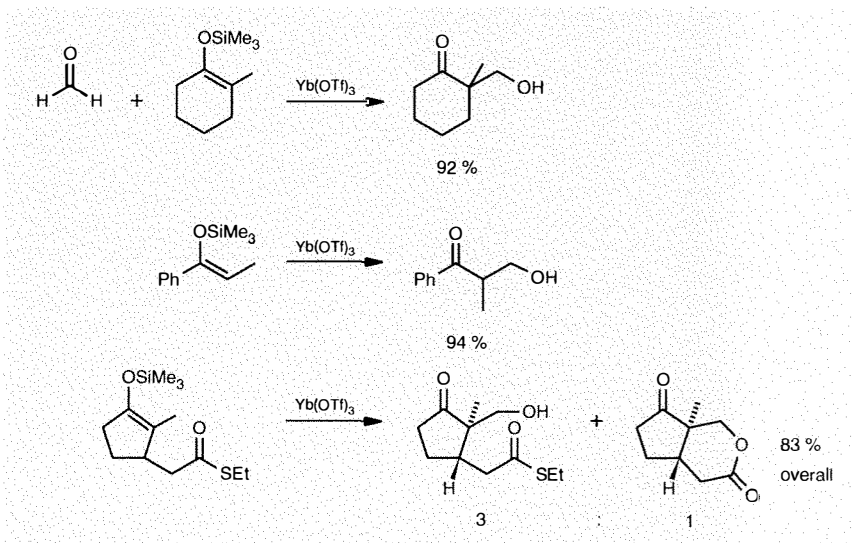
Aldol condensation. The Mukaiyama reaction is a Lewis acid catalyzed, cross-aldol involving the reaction of a silyl enol ether (silyl ketene acetal) with aldehydes or ketones. First reported by Mukaiyama in 1973,[2] this method overcomes traditional problems with cross-aldol reactions such as difficult to separate product mixtures. In the initial studies, $TiCl_4$ was found to be the best Lewis acid catalyst; however, use of this catalyst requires strictly nonaqueous conditions.

Kobayashi first reported the use of lanthanide(III) trifluoromethanesulfonates as catalysts for the Mukaiyama reaction using a commercially available formaldehyde solution to make hydroxymethyl adducts.[3] These reactions were performed in the presence of water! Kobayashi found that the silyl enol ether of 2-methylcyclohexanone reacts readily in the presence of ytterbium triflate to form 2-hydroxymethyl-2-methylcyclohexanone (**Scheme 1**). Ytterbium triflate appears to be the most effective catalyst for this reaction, but most other lanthanides work to some extent. The reactions were carried out in a 1:1 mixture of water and THF at room temperature and were complete after 24 to 30 hours. Yields ranged from 77 to 94% with various silyl enol ethers (**Scheme 1**). As little as 1 mol % of catalyst can be used without significantly reducing yields.[4] Arseniyadis and co-workers took advantage of this methodology in studies directed towards the total synthesis of an A-seco taxane (**Scheme 2**).[5]

Aqueous solutions can also be employed for the Mukaiyama reaction with



other aldehydes and ketones (**Scheme 3**). Yield optimization studies using the reaction of 1-trimethylsiloxycyclohexene with benzaldehyde showed that the highest



Scheme 1

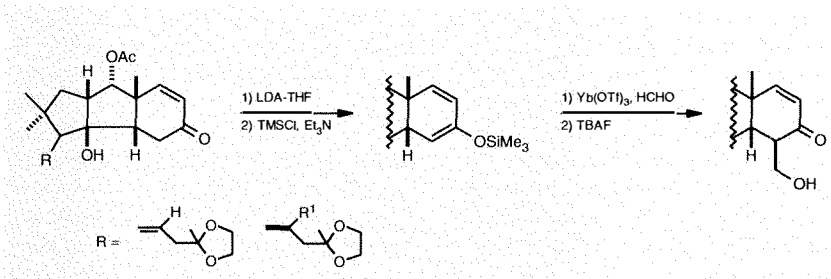
yields were obtained with $Yb(OTf)_3$, $Lu(OTf)_3$, and $Gd(OTf)_3$. Diastereoselectivities for the reaction were modest, averaging 75% *syn* and 25% *anti*. Water/THF (1:4) was found to be the most effective solvent.[6]

Interestingly, salicylaldehyde and 2-pyridinecarboxaldehyde can be used as substrates with lutetium triflate as the catalyst. Normally, metal enolates or Lewis acids are incompatible with salicylaldehyde because of the free hydroxy group. 2-Pyridinecarboxaldehyde is difficult to use with Lewis acids due to coordination of the metal with nitrogen which deactivates the catalyst.[6]

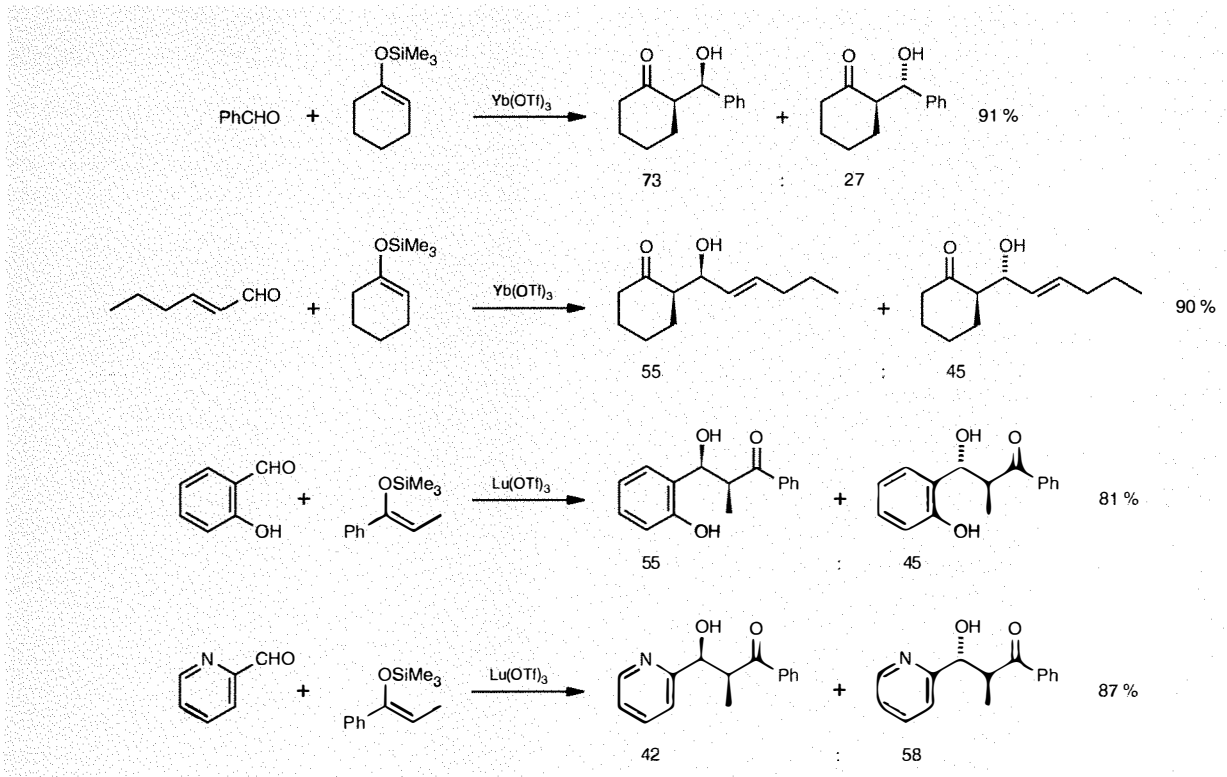
The use of lanthanide triflates as catalysts is not restricted to solutions containing water. An anhydrous organic solvent was employed by Kobayashi[7] to carry out lanthanum-catalyzed aldol reactions of silyl enolates with several aldehydes and acetals (**Scheme 4**). Even though these reactions in organic media are hetereogeneous, yields are generally good, ranging from 75 to 95%.

Reaction rates vary considerably between catalysts. In the previous study, approximately 16 hours at room temperature were required for complete reaction. Another study found that scandium triflate catalyzed the reaction of 1-trimethylsiloxycyclohexene with benzaldehyde at -78 °C in the same amount of time. At this temperature $Y(OTf)_3$ and $Yb(OTf)_3$ did not work as catalysts. A number of other aldehydes and acetals will react with silyl enol ethers at this temperature, with aldehydes more reactive than acetals.[8]

Some attempts have been made to prepare chiral Lewis acids capable of performing enantioselective Mukaiyama reactions (**Scheme 5**). One group of catalysts can be prepared by reacting lanthanide triflates with the deprotonated form of (1*S*,2*S*)-1,2-diphenylethylenediamine in THF. Evaporation of the solvent in vacuo and extraction of the residue with dichloromethane yields the active catalyst. Lanthanum, ytterbium, and europium catalysts were prepared in this manner. Catalyst effectiveness was studied by reacting benzaldehyde, *p*-nitrobenzaldehyde, and hydrocinnamaldehyde with the ketene silyl acetal derived from ethyl isobutryate. Yields ranged from 19 to 98% (*p*-nitrobenzaldehyde giving the best yield) with ee's of 33 to 47%. Using the ytterbium catalyst, it was found that slow addition of the substrate improved the enantioselectivity.[9] In another study, a variety of rare earth compounds, including ytterbium triflate, were used as catalytic or stoichiometric reagents in the reaction of (*E*)-silyl ketene acetals with benzaldehyde (**Scheme 5**). The best *anti/syn* ratio was obtained by using $Sm(O\text{-menthyl})_2$.[10] Mechanistic studies indicate that a silicon species, and not the metal complex, is the active catalyst in the system,[11] making it difficult to design a lanthanide-containing chiral catalyst for this reaction.[12]

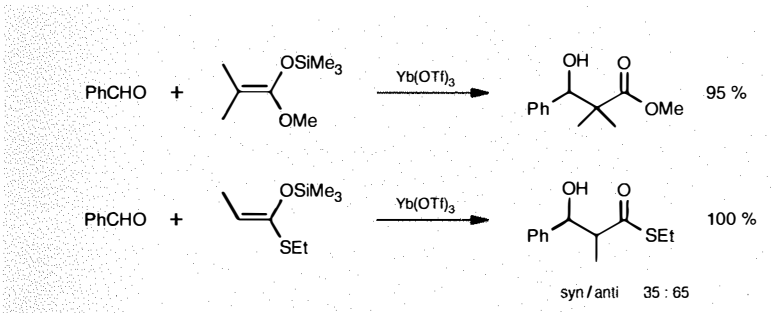


Scheme 2

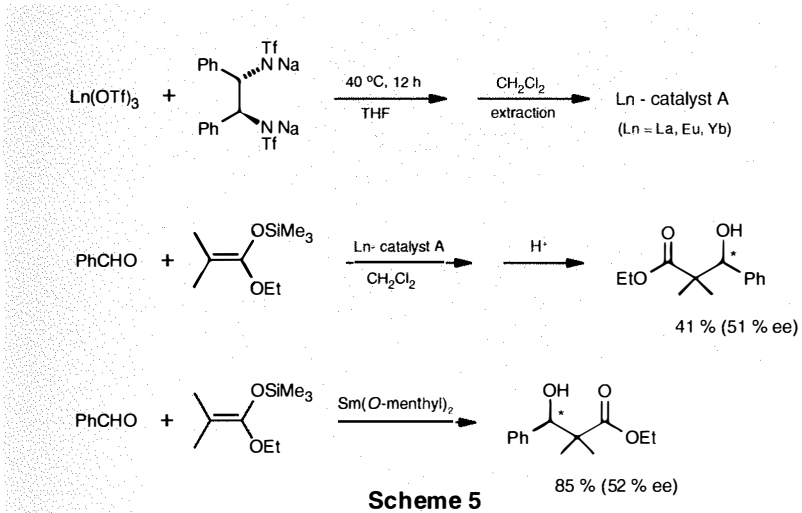


Scheme 3

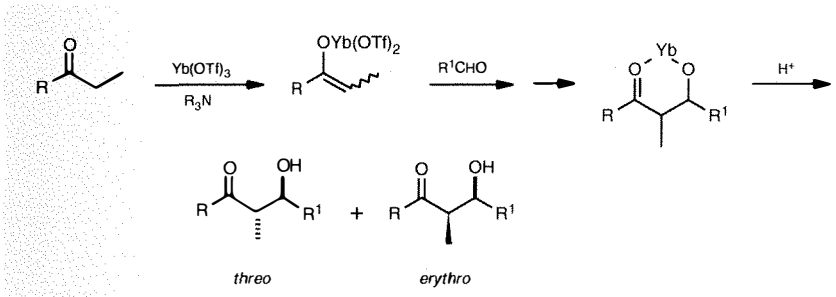
Recently, the use of ytterbium(III) triflate as a *stoichiometric* reagent in cross-aldol reactions between ketones and aldehydes was reported (**Scheme 6**).[13] To avoid unwanted side products, the reaction is done sequentially: ytterbium triflate and triethylamine are added to the ketone to form an intermediate ytterbium enolate complex, which is then quenched with the aldehyde. *Threo*-diastereoselectivity is favored with isobutyraldehyde and trimethylacetaldehyde, while products with benzaldehyde are predominantly *erthyro*.[13]



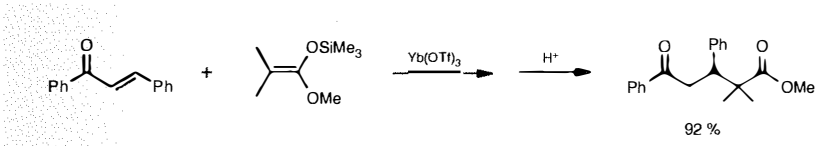
Scheme 4



Scheme 5



Scheme 6



Scheme 7

Michael reaction. Lanthanide triflates catalyze the conjugate addition of silyl enolates with α,β-unsaturated ketones to give the 1,5-dicarbonyl compounds (**Scheme 7**). Silyl enolates derived from ketones, esters, and thioesters can be used. These reactions are run at room temperature in methylene chloride followed by acidic workup.[14] Scandium triflate will also catalyze this reaction giving 1,5-dicarbonyl compounds in 80 to 88% yield with no 1,2-addition products.[8]

Diels-Alder reaction. Although not strictly necessary, Lewis acids are employed as catalysts in Diels-Alder reactions to improve regioselectivity and the extent of endo addition. Not surprisingly, rare earth triflates have found use in this reaction (**Table 1**). $Yb(OTf)_3$ catalyzes the Diels-Alder reaction of methacrolein, methyl vinyl ketone, or 1,4-naphthoquinone with cyclopentadiene. With methacrolein the exo isomer is favored, while the other two dienophiles provide predominantly the endo isomer.[14] Scandium triflate also acts as a catalyst. The reaction of 3-acryloyl-1,3-oxazolidin-2-ones or methyl vinyl ketone with dienes in dichloromethane, followed by water workup, gave the Diels-Alder product in good to excellent yields. Endo products are favored.[15] Scandium triflate was also examined as a possible catalyst in the synthesis of tetracyclic intermediates via the Diels-Alder reaction, resulting in good yields but a mixture of products.[16]

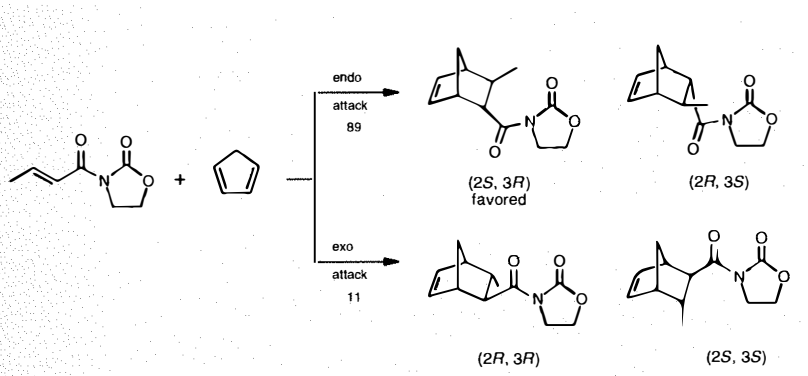
In contrast to the aldol condensation, considerably more success has been achieved in developing chiral triflate catalysts for asymmetric Diels-Alder reactions. For example, a catalyst prepared from ytterbium or scandium triflate, (*R*)-(+)-binaphthol, and a tertiary amine catalyzes the reaction of crotonoyl-1,3-oxazolidin-2-one with cyclopentadiene to produce the Diels-Alder adduct in 77% yield, with an endo to exo ratio of 89:11 and a 95% ee favoring the endo (2*S*,3*R*) adduct (**Scheme 8**). Trimethylpiperidine was the most effective amine for the reaction.[17,18]

The proposed structure for the catalyst, based on ^{13}C-NMR and IR data, shows both oxygens of the binaphthol coordinated to the metal, with a hydrogen bond between each of the binaphthol hydrogens and two molecules of *cis*-1,2,6-trimethylpiperidine. These interactions are indicated by changes in the ^{13}C chemical shifts of the *N*-methyl groups of the piperidine (**Scheme 9**). Aging of the catalyst occurs during the reaction and as

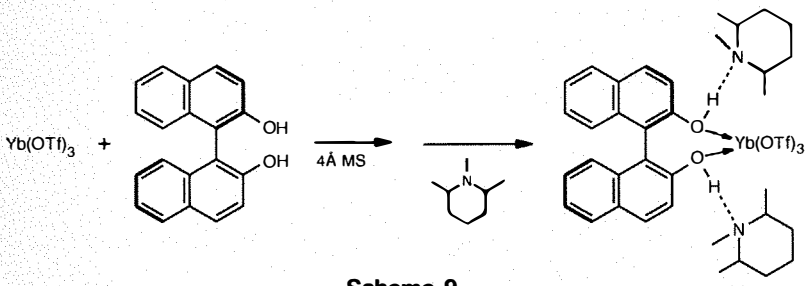
reaction times increase, selectivities decrease. Certain additives, such as 3-acetyl-1,3-oxazolidin-2-one and 3-phenylacetylacetone (PAA), prevent catalyst aging.[19]

With ytterbium triflate as the catalyst, enantioselectivities can be reversed depending upon the choice of additives. The addition of 3-acetyl-1,3-oxazolidin-2-one gives a 93% ee of the (2*S*,3*R*)-isomer, while PAA produces an 81% ee of the (2*R*,3*S*)-isomer. This is important because the same chiral source, (*R*)-(+)-binaphthol, is used to produce both enantiomers.[20]

Using the enantioselective catalyst system developed by Kobayashi, Markó was able to produce chiral bicyclic lactones in moderate to excellent enantiomeric purity (**Scheme 10**). On heating, these lactones lose CO_2 to form substituted cyclohexadienes. 3-Carbomethoxy-2-pyrone (3-CMP) was reacted with a variety of vinyl ethers and vinyl sulfides. It was found that enantioselectivity increases with the size of the substituent attached to the vinyl ether oxygen. An ethyl substituent gives 27% ee, while adamantyl gives 85% ee. The adamantyl product can be

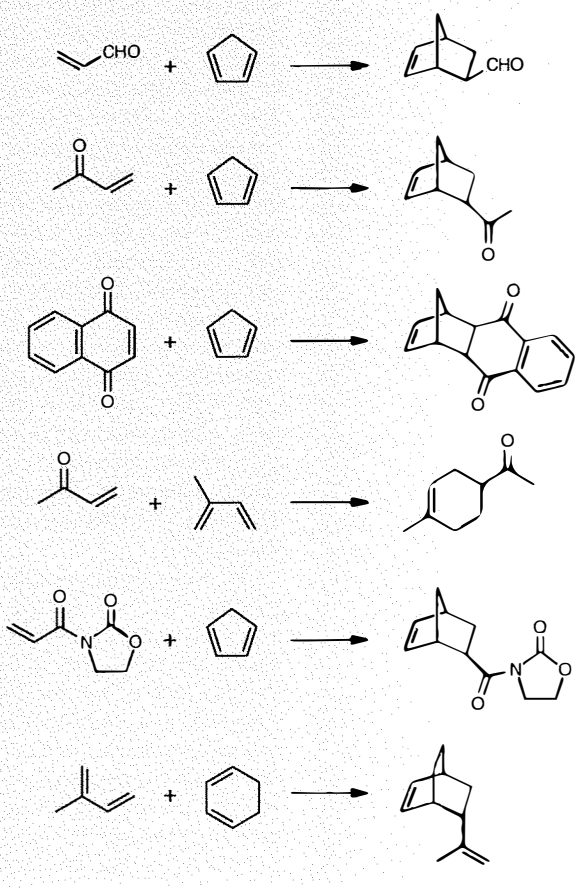


Scheme 8



Scheme 9

Table 1. Rare earth triflates used as catalysts in Diels-Alder reactions.



Yield	endo	exo	$M(OTf)_3$ M =
76 %	7	93	Yb
86 %	90	10	Yb
93 %, 89 %	100	0	Yb, Sc
91 %			Sc
95 %	87	13	Sc
83 %	> 95	< 5	Sc

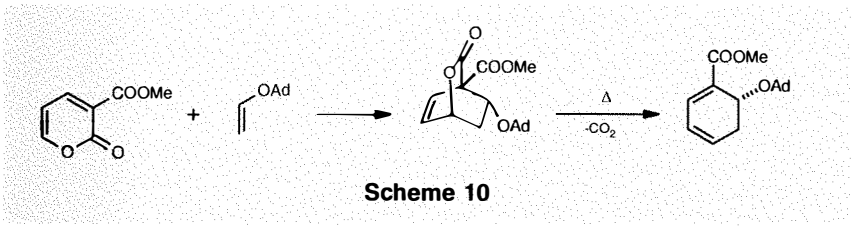
recrystallized once to give optically pure material. Product enantiomeric purity is usually higher with vinyl sulfides than with vinyl ethers.[21]

Acylation. Friedel-Crafts acylations normally employ a stoichiometric amount of aluminum chloride as the Lewis acid. A catalytic amount of $Yb(OTf)_3$ in nitromethane at 50°C promotes the acylation of anisole, thioanisole, and *N,N*-dimethylaniline to the corresponding acetophenones in good yield (**Scheme 11**). Unlike aluminum chloride, the catalyst is recoverable and can be reused.[22]

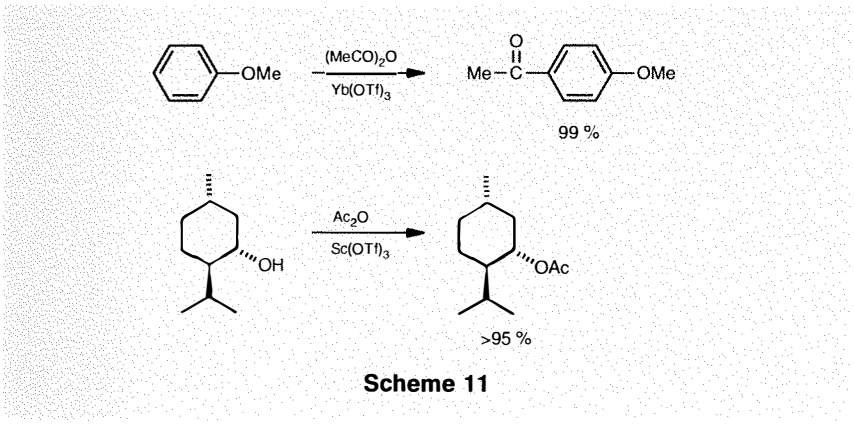
Scandium trifluoromethanesulfonate was found to catalyze the acylation of alcohols by acid anhydrides under mild conditions in quantitative yields (**Scheme 11**). A typical catalyst loading was 1%. Yields are better and reaction times shorter than with other acylation catalysts such as DMAP and Bu_3P. Secondary and tertiary alcohols are easily acylated and acid-sensitive substrates can be acylated at low temperatures.[23]

Allylation. Lewis acids are well known for promoting the allylation of aldehydes; however, stoichiometric quantities of Lewis acids are usually required. Scandium triflate catalyzes the reaction of carbonyl compounds with tetraallyltin in an aqueous medium (H_2O/THF = 1:9, **Scheme 12**) with yields ranging from 74 to 100%. Reactions with D-arabinose and 2-deoxy-D-ribose produce predominately the *anti* isomer, while the reaction with 2-deoxy-D-glucose produces a 1:1 mixture of enantiomers.[24] Ytterbium triflate (5 mol%) catalyzes the reaction of aldehydes with allyltributylstannane under mild conditions in dichloromethane (**Scheme 12**). Reactions are complete after 24 hours and give excellent yields.[25]

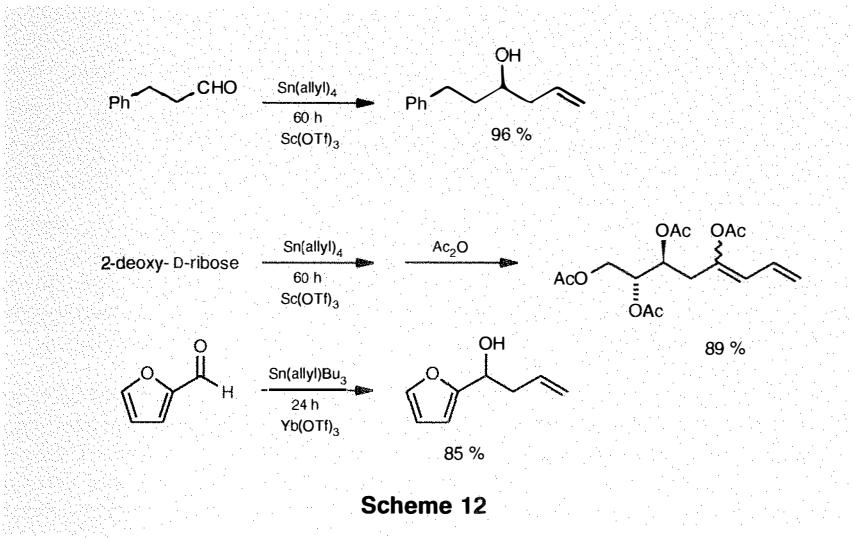
Pinacol coupling. A reduced lanthanide triflate, prepared from the reaction of either $Sm(OTf)_3$ or $Yb(OTf)_3$ with ethylmagnesium bromide at -78°C followed by warming to room temperature, promotes the reductive homocoupling of a variety of aldehydes and ketones to form the corresponding pinacols. This reagent is more efficient than SmI_2.[26] A similar reagent can be prepared from samarium(III) triflate with *sec*-butyllithium at room temperature in THF. On treatment with low valent samarium triflate, pinacol coupling of ketones and aldehydes proceeded smoothly.[27]



Scheme 10



Scheme 11



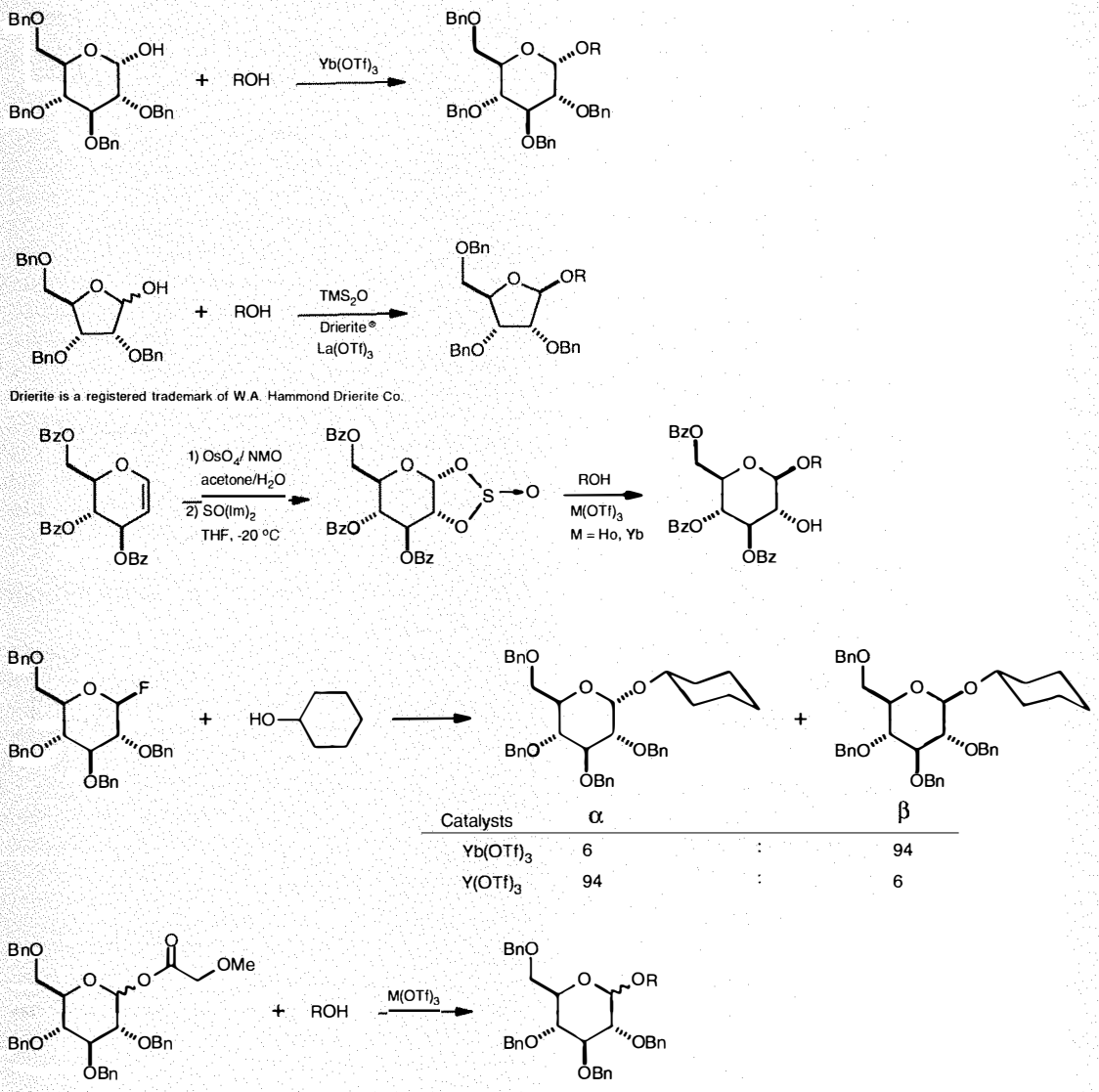
Scheme 12

Carbon-oxygen bond formation

Glycosylation. Stereoselective glycosylation is one of the most important reactions in carbohydrate chemistry, and, consequently, a number of methods have been developed. Several Lewis acids have been employed in this capacity. Recent studies have shown that lanthanide triflates are useful catalysts for glycosylation with free 1-hydroxy sugars and with 1-*O*-protected or masked glycosyl equivalents.

A combination of $Yb(OTf)_3$ and methoxyacetic acid serves as a catalyst for the reaction of a 1-hydroxy sugar with a variety of alcohols to form glycosides (**Scheme 13**). Most of the yields were quantitative with α:β ratios of 75:25. In one case, namely, the reaction of a ribofuranose with 2,3,4-tri-*O*-benzyl-5-methyl-D-glucopyranose produced only the β form.[28] Lanthanum triflate was found to be the most effective catalyst for the glycosylation reaction of 2,3,5-tri-*O*-benzyl-D-ribofuranose with a variety of glycosyl acceptors (**Scheme 13**). This reaction required hexamethyldisiloxane and anhydrous calcium sulfate. The β form of the glycoside is favored; however, addition of lithium perchlorate reverses the selectivity.[29]

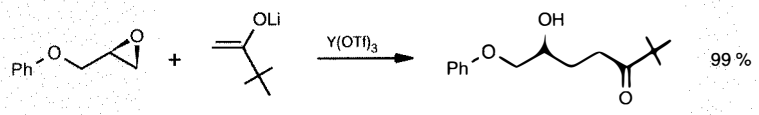
Cyclic sulfites are easily made by treating a glycal with osmium tetroxide and NMO to produce the *cis*-diol followed by reaction with thionyldiimidazole (**Scheme 13**). The sulfite, in turn, is treated with either allyl, benzyl, or cyclohexyl alcohol in the presence of ytterbium or holmium triflate to stereoselectively produce the glycoside. With the benzyl protection, the glucosyl sulfite produced only the β form.[30]



Scheme 13

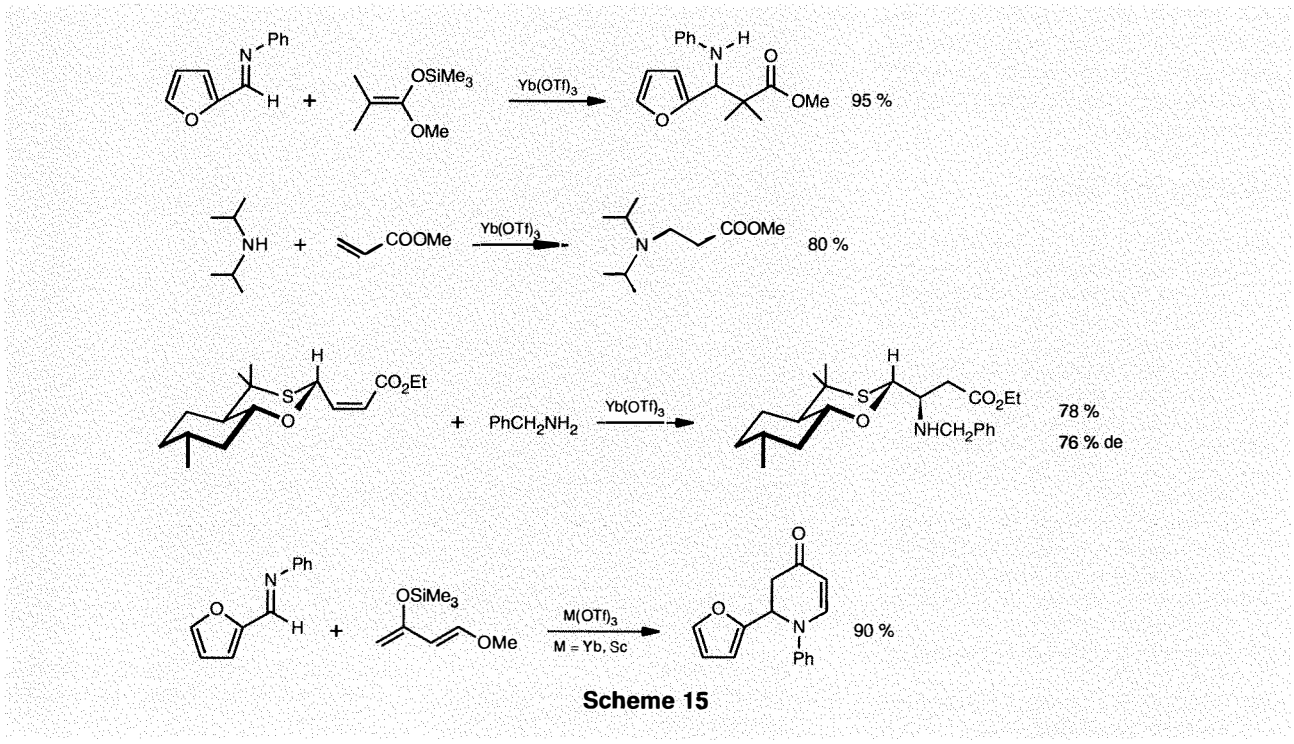
Glycosyl fluorides are often employed as glycosyl donors in the synthesis of complex sugar chains. Rare earth salts catalyze their reaction with glycosyl acceptors (**Scheme 13**). As the examples show, good α and β selectivity is possible. Lewis acid additives such as zinc chloride or barium perchlorate significantly reduce reaction times.[31]

Benzyl and acyl protected 1-*O*-methoxyacetyl sugars also act as glycosyl donors. A number of rare earth triflates were found to effectively catalyze their reactions with a variety of alcohols and thiols (**Scheme 13**).[32] In most cases, a mixture of α and β forms was observed, with the thermodynamically stable isomer predominating at elevated temperatures.[33] In the reaction of 1-*O*-methoxyacetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with 1-octanol, triflates of some heavy lanthanide(III) salts such as $Tb(OTf)_3$, $Ho(OTf)_3$, $Tm(OTf)_3$, and $Yb(OTf)_3$ were highly effective as catalysts. A combination of methoxyacetic acid and $Yb(OTf)_3$ will also catalyze the reaction.[34] Ytterbium triflate in nitromethane catalyzes the reaction of peracylated sugars such as 1,3,4,5,6-penta-*O*-acetyl-β-D-glucopyranose with trimethylsilyl azide to form glycosyl azides. While yields are slightly lower than with other Lewis acids, the catalyst is easily recoverable and can be reused. Solvents other than nitromethane are not effective for this reaction.[35]



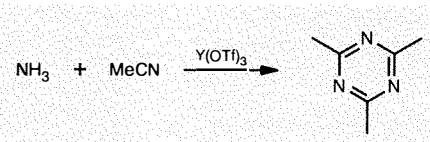
Scheme 14

Ring Opening. Yttrium triflate catalyzes the reaction of lithium enolates with epoxides to form γ-hydroxy ketones (**Scheme 14**). Lithium enolates derived from pinacolone and acetophenone react



Scheme 15

with either propylene oxide, 1,2-epoxyoctane, styrene oxide, or 1,2-epoxy-3-phenoxypropane to form the desired product. Attack at the least substituted epoxide carbon is favored for all but styrene epoxide.[36]



Scheme 16

Carbon-nitrogen bond formation

Enolates and unsaturated esters. Preparation of β-amino ketones and β-amino esters, which lead to β-lactam derivatives, can be accomplished by the reaction of imines with enolates (**Scheme 15**). Yttrium, ytterbium, and scandium triflates catalyze this reaction with yields ranging from 47 to 97%.[37] Ytterbium triflate was found to be the best catalyst for the high pressure synthesis of β-amino esters from α,β-unsaturated methyl esters. Using this method, it is possible to synthesize some very hindered amino esters that are of interest as β-lactam precursors (**Scheme 15**). The reaction of benzylamine with an ester containing a chiral 1,3-oxathiane produced the desired adduct with good diastereoselectivity.[38] Tetrahydropyridines can be prepared by the Diels-Alder reaction of imines. Scandium and ytterbium triflate catalyze the reaction of several imines with Danishefsky's diene to produce cycloaddition adducts in good yield (**Scheme 15**).[29]

Nitriles. Monoamines, primary diamines, and secondary amines react with nitriles to give amidines, cyclic amidines, and pyrimidines, respectively. Almost all lanthanide triflates are active catalysts for this reaction. Typically, 1-10 mol % of catalyst is used giving yields of approximately 90%.[39] At high temperature, ammonia reacts with acetonitrile and benzonitrile in the presence of yttrium triflate to form 2,4,6-trisubstituted-*s*-triazines (**Scheme 16**).[40]

Ring-opening reactions. The treatment of epoxides or oxetanes with amines is a useful method for the synthesis of amino alcohols. Commonly used methods suffer from limitations with sterically demanding amines. The high pressure mediated ring opening of epoxides with amines to give amino alcohols is catalyzed by $Yb(OTf)_3$. Cyclohexene oxide reacts with benzylamine, dibenzylamine, phenyl amines and pyrrolidine to form β-amino alcohols in good yields (**Scheme 17**).[41] Ytterbium, neodymium, and gadolinium triflates are effective catalysts for the preparation of β-amino alcohols by aminolysis of 1,2-epoxides at atmospheric pressure (**Scheme 17**). Reactions were performed at room temperature in nonpolar or slightly polar solvents and gave good yields (85 to 100%) using only a small amount of catalyst.[42] The same three catalysts are also useful for the aminolysis of oxetanes to form γ-amino alcohols (**Scheme 17**). $LiBF_4$ and $LiClO_4$ also serve as reagents in this reaction giving similar yields; however, reaction times are significantly longer.[43]

A complementary reaction is the treatment of aziridines with primary and secondary amines to form 1,2-diamines. Mono- or di-substituted *N*-protected aziridines react with amines in the presence of a catalytic amount of $Yb(OTf)_3$ to form the desired product (**Scheme 17**). Tri-substituted and unprotected aziridines gave unidentified polymers. Boc, tosyl, and benzyl protecting groups can be used to protect the aziridine nitrogen.[44]

Conclusion

Rare earth triflates are versatile Lewis acids that have been employed in a number of important reactions. One of the main advantages they offer over other Lewis acids is the ability to act as catalysts rather than stoichiometric reagents. Although somewhat hygroscopic in the solid

form, they are stable towards water and are effective as catalysts in solutions containing water. Additionally, they are easily recoverable and show no loss of catalytic activity upon reuse.

References and Notes

(1) Note that in the +3 oxidation state scandium, lanthanum, yttrium, and lutetium complexes are diamagnetic, while all other rare earths give paramagnetic complexes.
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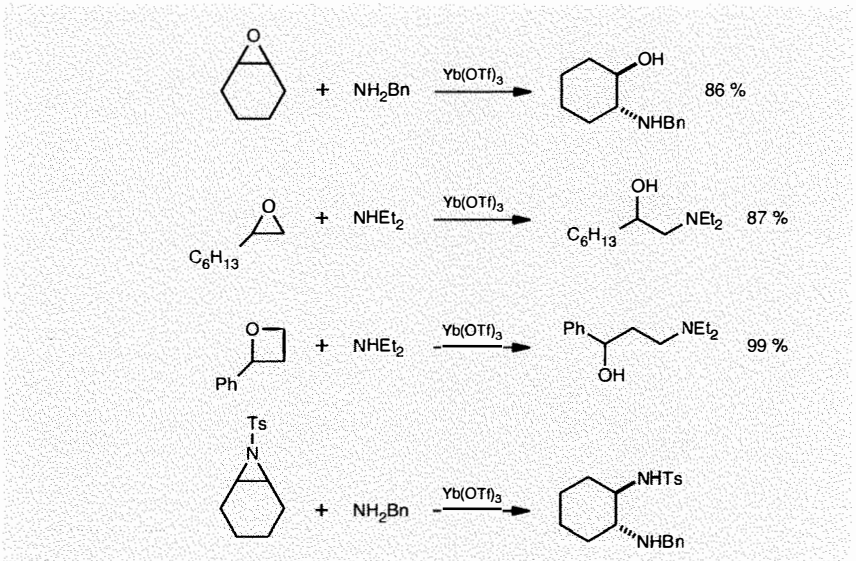

Scheme 17

About the author

Robert W. Marshman was born in Weymouth, MA in 1958. He received his BA in chemistry from the University of Chicago in 1981. After a brief stint as an EEG technician and a slightly longer one working as a laboratory technician for a pediatric surgeon, he entered graduate school and received a Master's degree in chemistry from the University of Illinois at Chicago in 1985. He earned his PhD in inorganic chemistry from the University of Illinois at Urbana/Champaign in 1990 working under the direction of Dr. Patricia Shapley. His thesis work involved the synthesis of high oxidation state osmium alkyl compounds. He worked for two years as a postdoctoral research associate for Dr. Debbie Crans at Colorado State University. His research there involved the interaction of vanadium with biological systems. He is presently employed at Aldrich Chemical Company as a Scientist in inorganic production where his duties include overseeing inorganic production and the development of new products.

For a listing of rare earth triflates offered by Aldrich, please see page 92.

The Intermediacy of Transition-Metal Silicon-Bonded Complexes: Recent Developments

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Introduction

The reactions of transition-metal complexes with silanes have long been an area of interest for both catalytic and stoichiometric transformations. The study of transition-metal silicon compounds began in 1956 with Wilkinson's preparation of $Cp(CO)_2FeSiMe_3$.[1]

Today, there exists a wide range of synthetic methods for the formation of metal-silicon bonds.[2a-d] Consequently, silyl derivatives of nearly all the transition metals are known. Methods involving both electrophilic[3a-b] and nucleophilic[4a-c] silicon reagents have been developed with the synthetic route of choice dependent on the type of transition-metal complex desired. At present, the most widely used method of preparing compounds containing transition-metal silicon bonds is the oxidative addition of Si-H and Si-Si bonds to the transition-metal center.

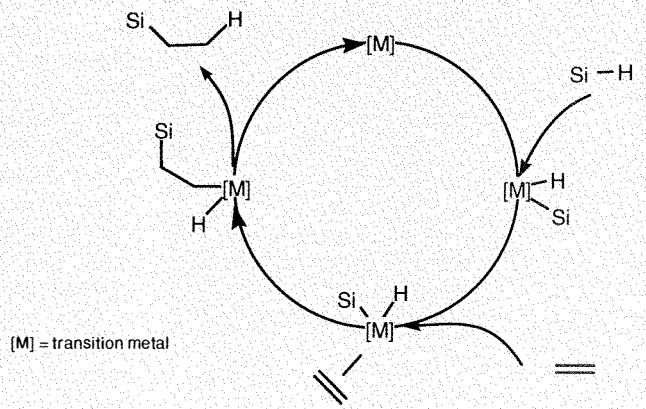
The majority of the material presented in this survey will discuss the occurrence of transition-metal silicon bonded compounds as reactive intermediates in a number of catalytic transformations. These include hydrosilylation, double silylation (or bis-silylation), dehydrogenative coupling, transition-metal catalyzed redistribution reactions, and ring opening metathesis polymerization. The intermediacy of singly and multiply bound transition-metal silicon compounds will be explored within the context of the above processes and stable examples of these reactive intermediates will be presented for clarity. Whenever possible, uses for the end products of these processes will be presented.

Hydrosilylation and bis-silylation

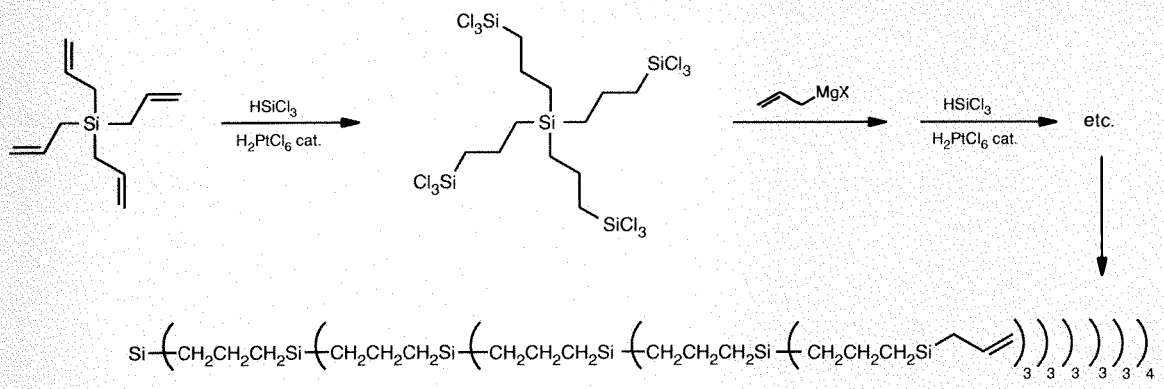
Hydrosilylation, the transition-metal mediated oxidative addition of an Si-H bond to an alkene, has been studied in detail for various transition-metal complexes. The driving force for this catalytic process results from the relative weakness of the Si-H bond (bond energy 88-92 kcal/mole). The mechanism of transition-metal catalyzed hydrosilylation, commonly referred to as the Chalk-Harrod mechanism,[5a-b] involves initial oxidative addition of an Si-H bond to the transition-metal center, followed by coordination of the unsaturated species to the metal center. This is followed by insertion of the unsaturated species into the transition-metal silicon bond and reductive elimination of the final product. A general catalytic pathway demonstrating the Chalk-Harrod mechanism is given in **Scheme 1**.

In the silicone industry, hydrosilation is used primarily to synthesize organofunctional silicon monomers, to crosslink silicone polymers, and to connect silicone and organic polymer blocks to form copolymers. A particularly exciting development in this area involves the hydrosilylation of tetravinylsilane and tetraallylsilane in the presence of platinum catalysts to form organosilicon dendrimers.[6a-c] The case for tetraallylsilane

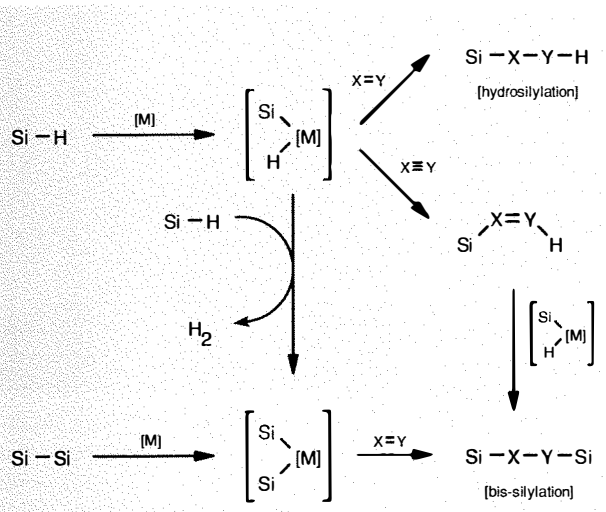
is given in **Scheme 2.** Since hydrosilylation is an established and well-documented area of silicon chemistry, the reader is encouraged to consult any of several excellent review articles on hydrosilylation for more details on catalyst selection, regio- and stereoselectivity, and reaction conditions.[7a-b]



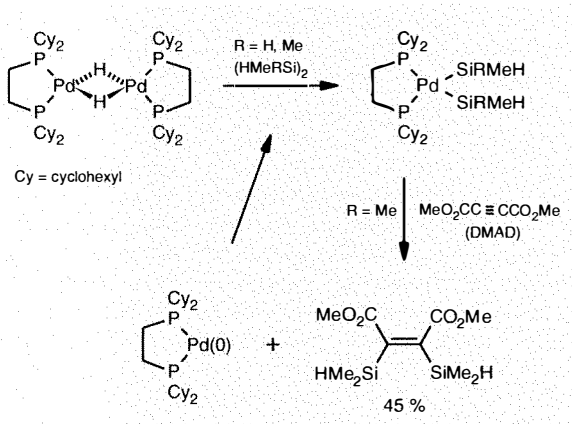
Scheme 1



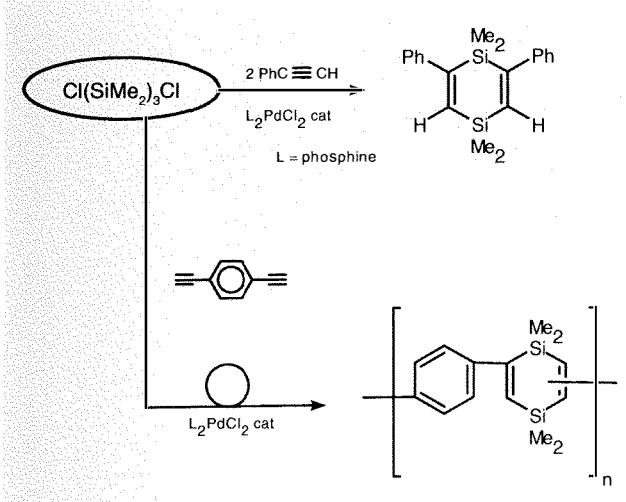
Scheme 2



Scheme 3



Scheme 5

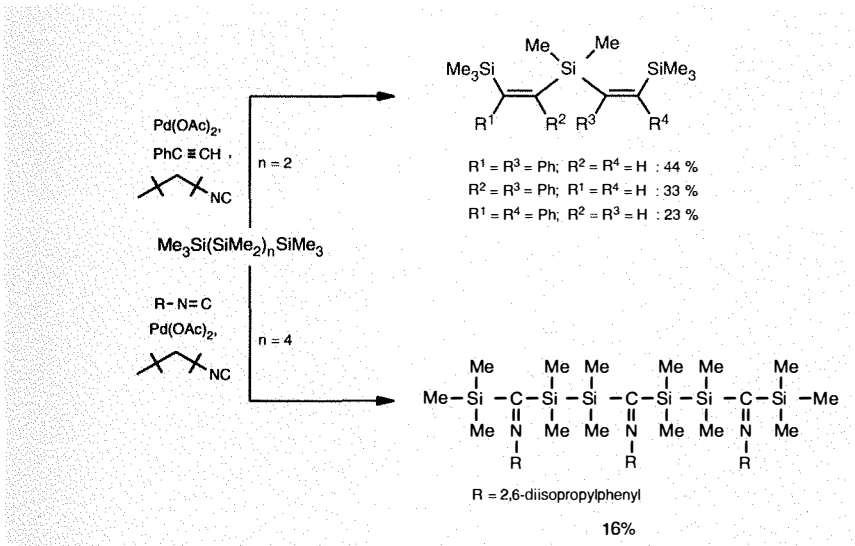


Scheme 4

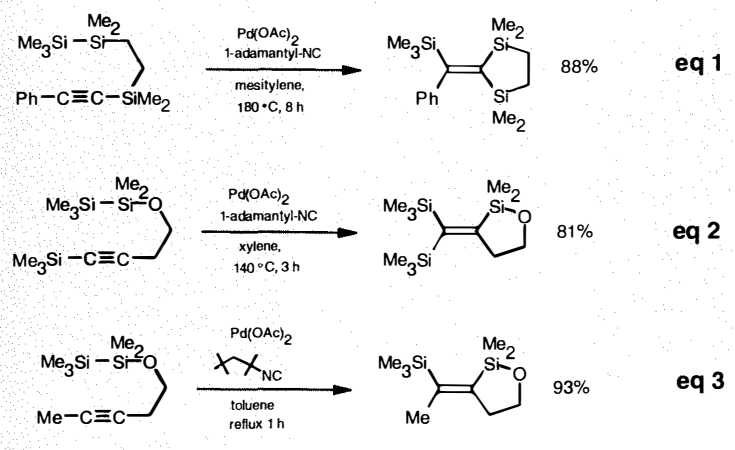
Of more recent interest is double silylation, commonly referred to as bis-silylation, of unsaturated species. Since the bond energy of the Si-Si bond (i.e., 74-80 kcal/mole) is similar to that of the Si-H bond, it is reasonable to assume that the oxidative addition of an Si-Si bond would also be a facile process. **Scheme 3** illustrates the intermediacy of transition-metal silicon compounds in both hydrosilylation and bis-silylation processes.

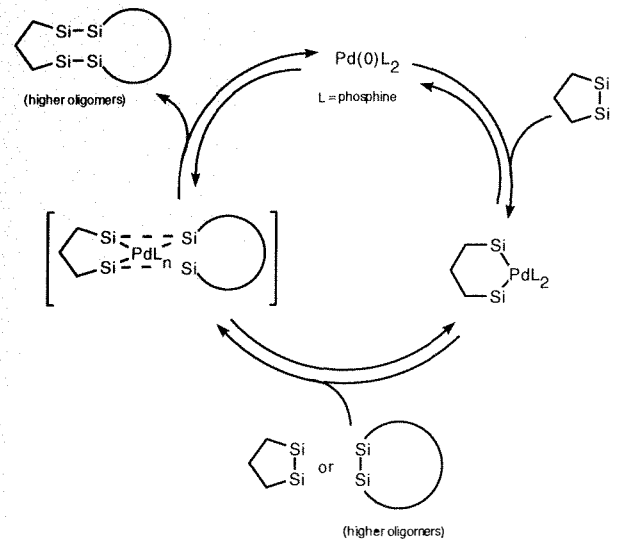
Interest in this area began with initial reports by Kumada on the oxidative addition of the Si-Si bond in 1,1,2,2-tetramethyldisilane to acetylenes.[8a-b] However, recent interest was sparked by reports from the Tanaka group concerning the use of tetrakis(triphenylphosphine)palladium to catalyze the addition of substituted disilanes to ethylene.[9a-b] The Tanaka group has also shown that the reaction of the trisilane $Cl(SiMe_2)_3Cl$ with acetylenes gives polymers containing 1,4-disilacyclohexa-2,5-dienylene rings in the presence of a variety of palladium catalysts of the form L_2PdCl_2 (L = phosphine).[10] Some representative examples are given in **Scheme 4**.

Since compounds containing palladium-silicon bonds are both thermodynamically and kinetically unstable, recent work by Fink's group has centered on the synthesis and isolation of stable variants. By using sterically encumbered chelating phosphine ligands, Fink and co-workers have successfully synthesized and characterized (X-ray crystallography) the first stable compound



Scheme 6





Scheme 7

containing palladium-silicon bonds (**Scheme 5**).[11] The unusually high thermal stability observed for this compound is attributed to kinetic protection afforded by the use of bulky substituents on the phosphine ligand. The Pd-Si bond is also strengthened by the high basicity of the phosphine ligand. Additionally, the chelate effect may impart some thermodynamic stability with respect to reductive elimination of disilane from the bis(silyl) complex. The stoichiometric reaction of this compound with dimethyl acetylenedicarboxylate (DMAD) gives the expected bis-silylation product.

Much attention has been directed toward the synthesis of silicon-containing polymers due to the unique chemical and physical properties associated with the silicon-silicon bond.[12a-b] One particularly intriguing example of bis-silylation is the consecutive addition of oligomeric silanes to isonitriles[13a-d] and acetylenes[13d] using a palladium(II) acetate-*tert*-alkyl isocyanide catalyst system (**Scheme 6**).

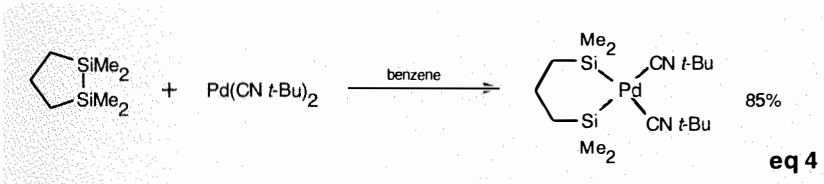
It is worthwhile to note that the insertion of the isonitrile group into the polysilane backbone occurs in a stereoregular fashion to give poly[sila(*N*-2,6-xylyl)imines]. This catalyst system also effects the *intra*molecular bis-silylation of alkynes, leading to the regioselective formation of cyclic organosilicon compounds in greater than 80% yield (eq 1-3). A general reaction pathway for this transformation is given in **Scheme 7**. Extension of this catalytic cycle using 1,1,2,2-tetramethyl-1,2-disilacyclopropane resulted in the formation of several novel macrocyclic organosilicon compounds.[13a]

These macrocycles, which contain Si-Si linkages in the rings, can undergo insertion of isocyanides. This is due to the high, but controllable, reactivity of the silicon-silicon bond toward transition-metal catalysts (**Scheme 8**). The intermediacy of the bis-silyl(palladium) complex is supported by the stoichiometric reaction of 1,1,2,2-tetramethyl-1,2-disilacyclopentane with bis(*tert*-butyl isocycanide)-palladium(0) to give the *cis*-bis(silyl) palladium complex that has been characterized spectroscopically (eq 4). This new catalyst system has made the bis-silylation of alkynes a synthetically useful reaction.

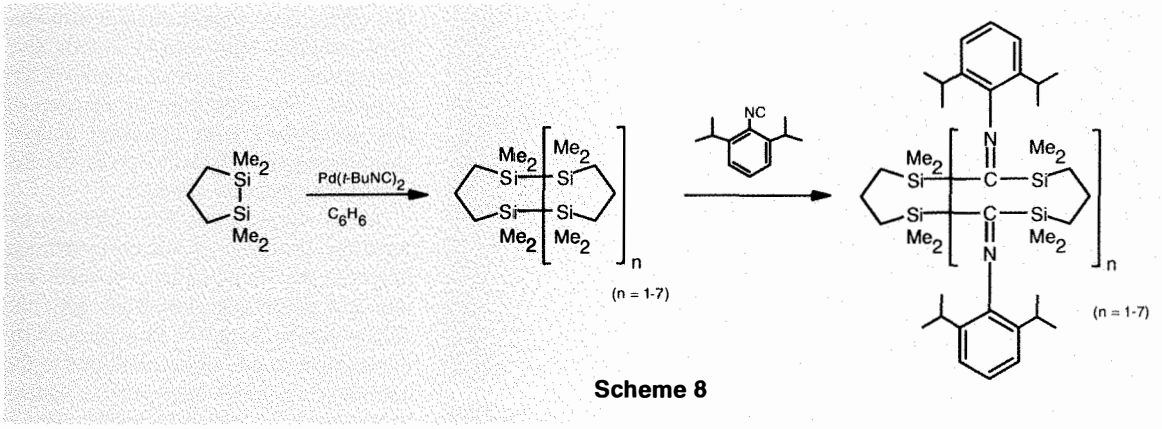
Dehydrogenative coupling

In 1987, work by Brown-Wensley demonstrated that many late transition-metal hydrosilylation catalysts also catalyzed the formation of Si-Si bonds from Si-H bonds depending on the reaction conditions

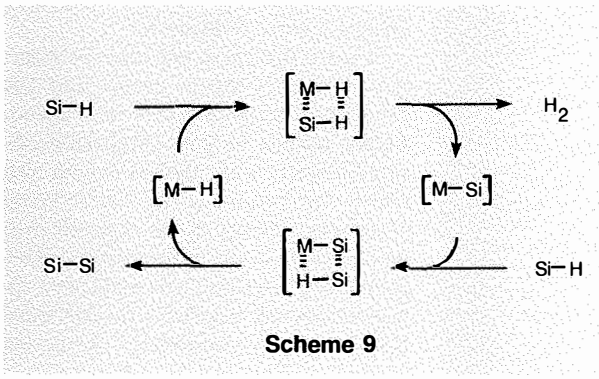
employed.[14] This reaction, known as dehydrocoupling, has been the focus of many studies into the transition-metal catalyzed formation of Si-Si bonds. Dehydrocoupling is a potentially useful route to catenated silicon compounds, known as polysilanes. Polysilanes have a variety of



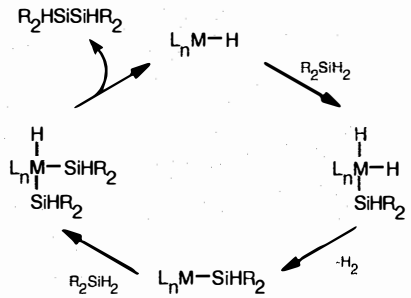
eq 4



Scheme 8



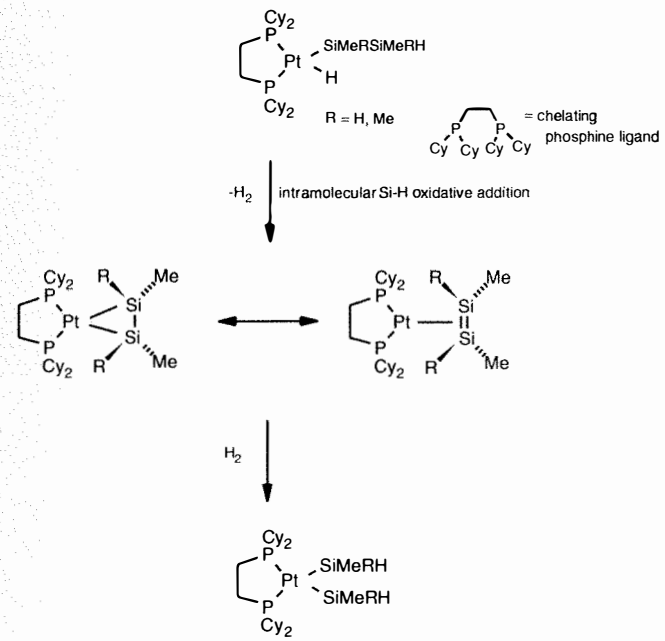
Scheme 9



Scheme 10

industrial uses,[15a-c] such as conversion to useful silicon carbide fibers, and use as materials for microlithography, semiconductors, and non-linear optics.

Dehydrocoupling via the early transition metals has been studied extensively.[16a-d, 17] Dehydrocoupling using early transition-metal catalysts resulted in polysilanes with chain lengths of up to 20 silicon atoms. A higher molecular weight polymer is not observed. This is due to the reversibility of the dehydrocoupling reaction, resulting in competing polymerization and depolymerization processes. Using cyclopentadienyl complexes of Ti, Zr, and Hf, Tilley has proposed a σ-bond metathesis mechanism to explain the formation of Si-Si bonds. A general reaction pathway is given in **Scheme 9**. Several dinuclear complexes containing transition-metal silicon bonds have been isolated from the reaction mixtures, although the role of these complexes in the dehydrocoupling reaction has not been determined conclusively.[18a-b]

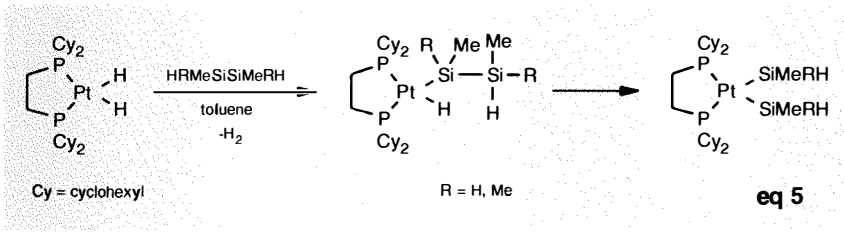


Scheme 11

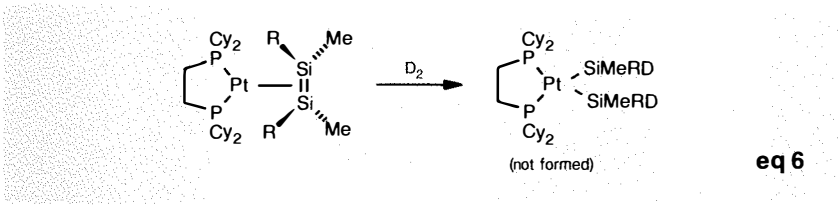
Recently, there has been much interest in the late transition-metal catalyzed dehydrocoupling reactions, where oxidative addition and reductive elimination are facile processes. A general catalytic pathway for dehydrocoupling via late transition metals is given in **Scheme 10**. The main feature of this mechanism is that one can account for the Si-Si bond formation via a series of oxidative addition/reductive elimination steps. While it is known that palladium silyl complexes are thermally unstable with respect to elimination of disilanes, there are few examples in the literature for a dehydrocoupling cycle based entirely on oxidative addition/reductive elimination steps.[19]

A serious drawback to the dehydrocoupling reaction is that redistribution, or the scrambling of constituents on silicon, appears to compete with Si-Si bond formation. However, in certain circumstances, redistribution reactions are advantageous because they lead to the formation of oligomeric or polymeric silanes.

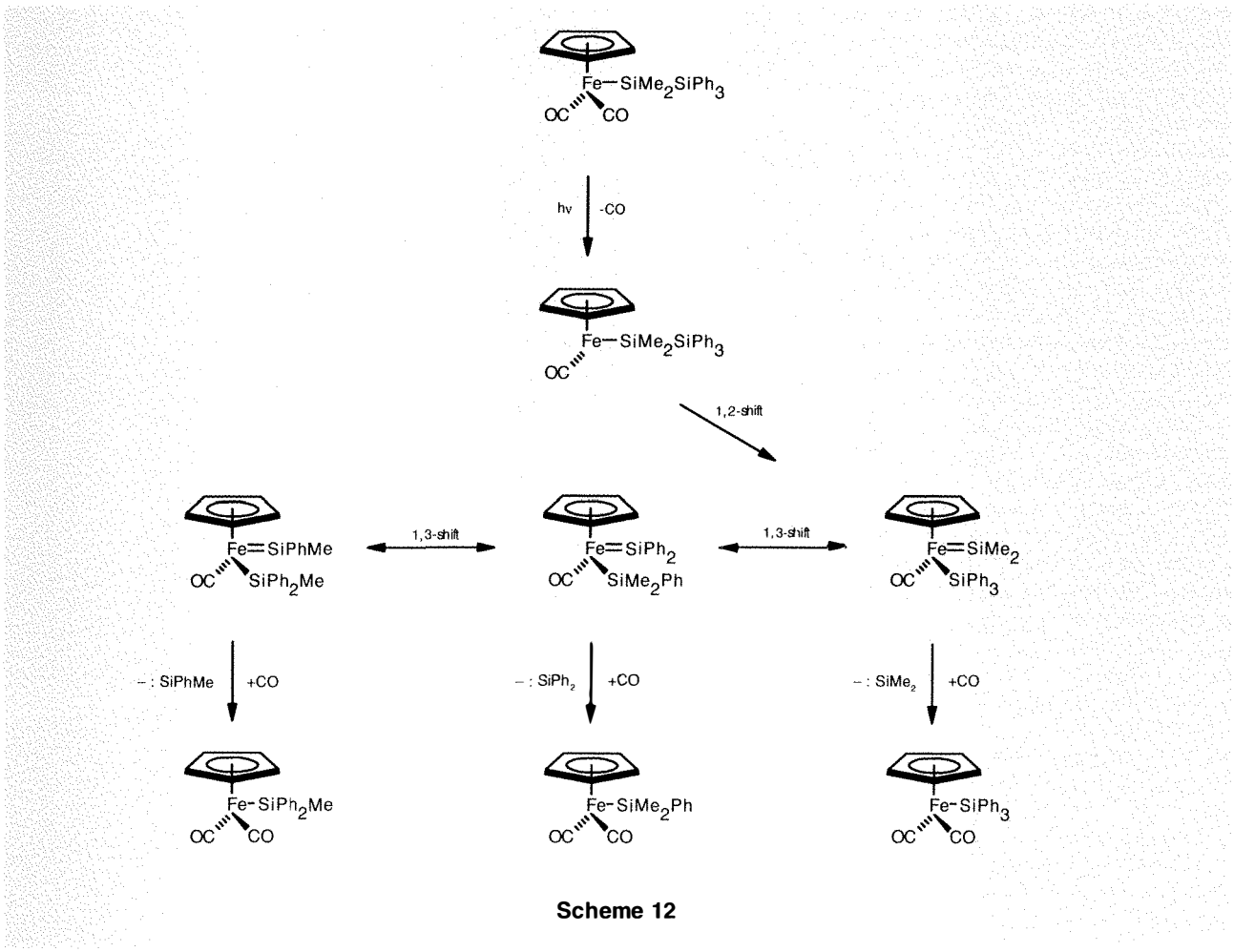
Recent work in this area has centered on the reaction of disilanes with transition metals. The groups of Fink and Michalczyk have shown that the reaction of disilanes with a *cis*-platinum hydride complex results in the apparent platinum-mediated cleavage of the Si-Si bond in the disilane, leading to the formation of a bis(silyl) platinum complex (eq 5).[20] There are two possible mechanisms that can account for this rearrangement. The first involves the intermediacy of metal-disilene species formed by intramolecular oxidative addition of the terminal Si-H bond on the disilane. Hydrogenolysis of the Si=Si bond leads to the formation of a bis(silyl) complex (**Scheme 11**). This mechanism has been proposed by Pham and West for the reaction of substituted disilanes with platinum complexes, although the intermediate platinum-disilene species has not been isolated.[21a-b] It is interesting to note that neither Tanaka[22] nor Fink[20] observed the intermediate platinum-disilene species for the reaction of similar platinum systems



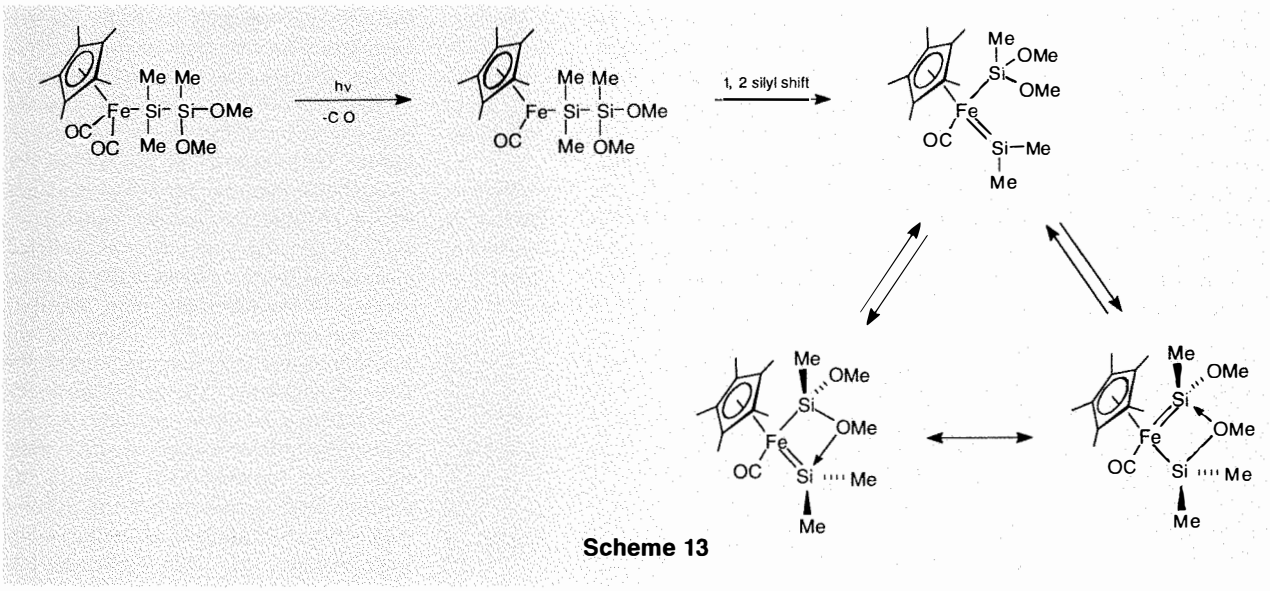
eq 5



eq 6



Scheme 12



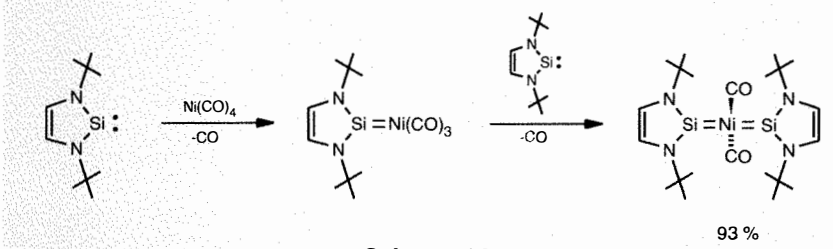
Scheme 13

with disilanes. Deuterium labelling experiments failed to give direct evidence for the intermediacy of a platinum-silylene species (eq 6).[23]

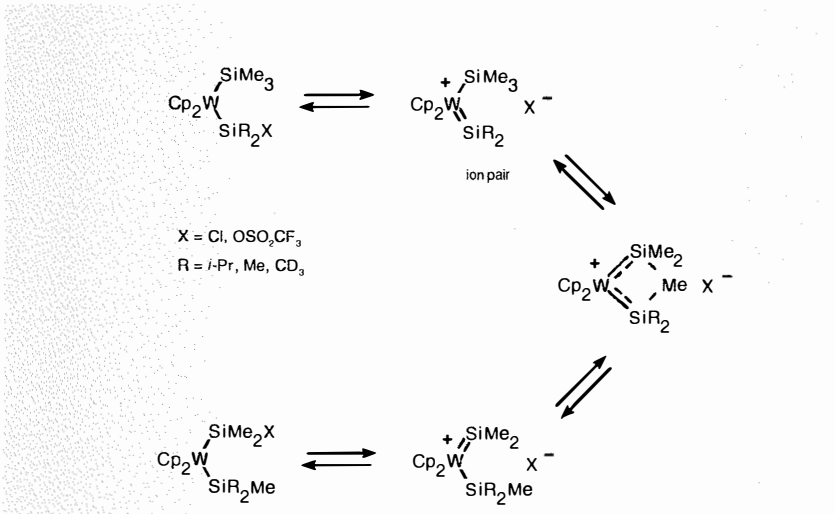
Another possible mechanistic pathway to explain redistribution reactions involves the intermediacy of metal-silylene species generated via 1,2-shifts between the metal and silicon or 1,3-shifts between silicon centers. The vast majority of recent work in this area centers on the photochemical deoligomerization of polysilyl iron complexes. Pannell,[24a-f] Ogino,[25a-f] and Turner[26] have reported convincing evidence for direct 1,3-shifts of substituents between silicon centers (**Scheme 12**). Ogino succeeded in trapping the iron-silylene species and has characterized the complex by X-ray crystallography.[25a,c] In this system, a lone pair of electrons from the oxygen donates electron density to the electrophilic silicon that stabilizes the iron-silylene species (**Scheme 13**).

Several donor stabilized metal-silylene complexes have been independently synthesized and characterized.[27a-g] Recent interest in this area concerns the synthesis and characterization of metal-silylene species that are not stabilized by Lewis base donors. This was accomplished by Denk in the synthesis of a stable silylene complex, which upon reaction with $Ni(CO)_4$ gave a "base free" bis(silylene) nickel complex (**Scheme 14**).[28a-c] Tilley has also reported the synthesis of "base free" cationic ruthenium-silylene complexes of the type $[Cp^*(PMe_3)_2Ru{=}SiR_2]^+BR'_4^-$, where R = Ph, Me, S(*p*-MePh) or O(*p*-MePh); R′ = Ph, or C_6F_5.[29a-b]

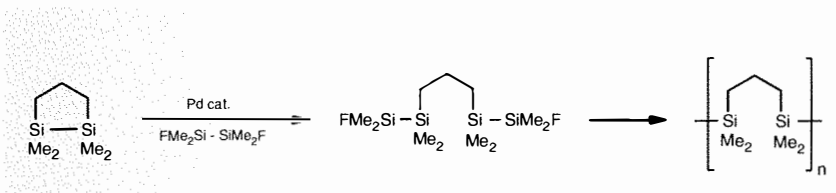
Intramolecular redistribution reactions also occur in cyclopentadienyl complexes of molybdenum and tungsten. The Berry



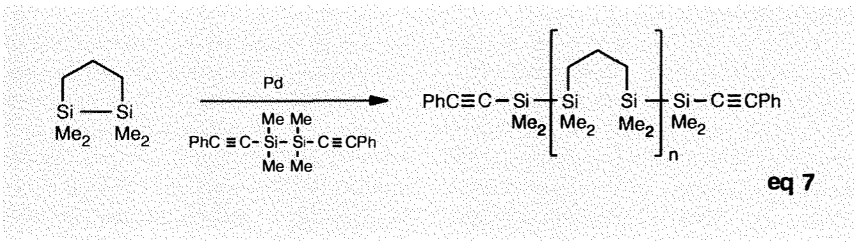
Scheme 14



Scheme 15



Scheme 16



eq 7

group has synthesized a series of bis(silyl) complexes that isomerize rapidly in the presence of trace amounts of Lewis acid catalysts (**Scheme 15**).[30a,b] A mechanism is proposed in which an electrophilic cationic tungsten-silylene intermediate is formed by dissociation of the electronegative group (X) followed by migration of a methyl group to the electrophilic silicon in the tungsten-silylene. Reassociation of X^- gives the rearranged product. This mechanism is consistent with the observed *intra*molecular scrambling of methyl groups in these complexes and *inter*molecular scrambling of X.

The intermediacy of transition-metal silylene complexes in redistribution reactions does explain why high molecular weight polysilanes are not observed using late transition-metal catalysts. Redistribution reactions can lead to termination of the growing polysilane chain by replacement of the Si-H functionality on the terminal silicon. Deoligomerization, similar to that observed in polysilyl iron complexes, also results in the formation of low molecular weight polysilanes. Although there is a rich and interesting chemistry associated with these two processes, they compete with the Si-Si bond forming dehydrocoupling process, thus limiting their usefulness.

Ring-Opening Metathesis Polymerization

The transition-metal catalyzed ring-opening metathesis polymerization (ROMP) of cyclic organodisilanes and cyclic polysilanes has only recently been studied. Tanaka has reported the ROMP of 1,1,2,2-tetramethyl-1,2-disilacyclopentane in the presence of a Pd catalyst and $FMe_2SiSiMe_2F$ leads to formation of the intermediate difluorotetrasilane (**Scheme 16**).[31] Successive reactions between the new Si-Si linkage activated by the fluorine substituent and 1,1,2,2-tetramethyl-1,2-disilacyclopentane result in formation of the observed polymer in 89% yield. The reaction of 1,2-bis(phenylethynyl)-1,1,2,2-tetramethyldisilane with 1,1,2,2-tetramethyl-1,2-disilacyclopentane gives the acetylene-terminated polymer in 61% yield (eq 7).[31]

The use of cyclic polysilanes in the ROMP process is a recent area of interest, although the transition-metal catalyzed route has not been studied in detail. Further work in this area may lead to the synthesis of stereoregular silicon polymers containing Si-Si linkages.[32]

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Craig A. Recatto was born in New Orleans, LA in 1966. He obtained a B.A. degree in chemistry from the University of New Orleans in 1988 and his PhD in chemistry from Tulane University in 1994 under the guidance of Professor Mark J. Fink. Dr. Recatto's research interests include general organosilicon chemistry, the role of transition-metal derivatives in the dehydrocoupling reaction and the synthesis of MOCVD precursors to platinum silicide. Dr. Recatto joined Aldrich as a scientist in 1994 and oversees process and product development for Aldrich's expanding line of silicon, germanium, and tin compounds.

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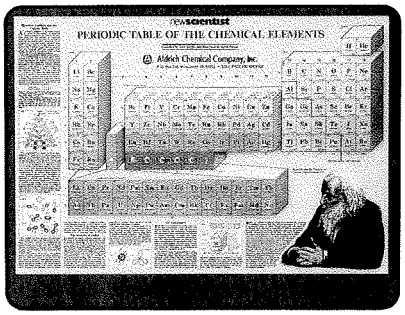

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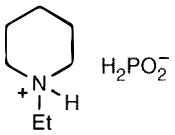
"Please Bother Us."

by

Jai Nagarkatti, President



Dr. Joseph Cs. Jaszberenyi of Professor D.H.R. Barton's research group at Texas A&M kindly suggested that we make this phosphorus-based hydrogen atom transfer reagent used with AIBN in radical deoxygenation, dehalogenation, and deamination.[1] The reagent is inexpensive and nontoxic as compared to the usual silicon- and tin-based reagents for deoxygenation. It also forms easily separable, water soluble by-products. The hypophosphite-AIBN method was found to be superior to traditional methods in a recently reported deoxygenation of the C-3 hydroxyl of a protected pyranose derivative.[2]

(1) Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (2) Azhayev, A.; Guzaev, A.; Hovinen, J.; Mattinen, J.; Silianpää, R.; Lönnberg, H. *Synthesis* **1994**, 396.

Polycyclic Cage Compounds: Reagents, Substrates, and Materials for the 21st Century

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Introduction

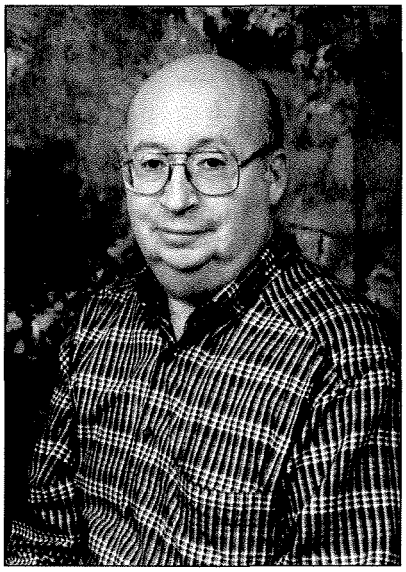
Polycarbocyclic "cage" compounds occupy a unique niche in the annals of synthetic organic chemistry. Compounds of this type collectively have been relegated to the category of "non-natural products".[1] Many cage compounds possess high molecular symmetry, and the artist that resides in the soul of many synthetic chemists finds beauty and challenge therein.

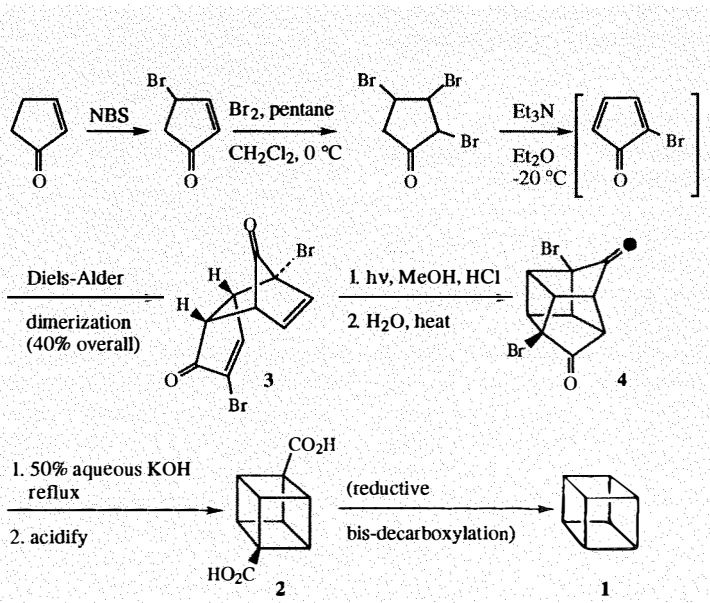
Certain structural restrictions are imposed upon cage molecules by their respective carbocyclic frameworks. Thus, cage compounds tend to possess rigid structures which lack the conformational mobility associated with simple medium-ring monocyclic compounds. When cage structures contain small rings (i.e., cyclopropanes and/or cyclobutanes) as components of their respective molecular frameworks, steric strain becomes an important factor. Thus, synthetic chemists who might initially have been attracted to a highly symmetrical but highly strained cage compound such as pentacyclo-[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane (C_8H_8, "cubane", **1**) might have second thoughts about pursuing a target molecule whose very existence seems to defy conventional wisdom. Thus, as with most things in life, a balance must be achieved between aesthetic attraction and other harsh realities, real or imagined.

The balance between aesthetics and potential practical limitations gradually has tipped in favor of the former. Thus, cubane yielded to Eaton and Cole's rational synthesis in 1964 (**Scheme 1**).[2] The remaining Platonic solid for which a hydrocarbon analog might exist, namely, pentagonal dodecahedrane ($C_{20}H_{20}$) was synthesized by Paquette and co-workers many years later.[3] Between the extremes of these C_nH_n "prismanes"[4] lie a host of other cage molecules which have yielded to rational synthesis.[5] The ability of modern synthetic organic chemists to access such unusual systems thus has been demonstrated.

The synthesis of cubane (**1**) provides an excellent object lesson in this regard. Despite its thermodynamic instability (i.e., its strain energy content has been estimated variously to be 166 kcal-mol^{-1} and 181 kcal-mol^{-1}),[6,7] "no kinetically viable paths exist for the thermal rearrangement of cubane".[8] Thus, in order to be successful, any attempt to synthesize cubane must necessarily rely upon kinetically accessible pathways; thermodynamic control must be avoided at all costs!

Eaton and Cole's[2] successful early synthesis of cubane-1,4-dicarboxylic acid (**2**, **Scheme 1**) is a marvel of economy and simplicity. With only minor modification, this procedure remains to this day the

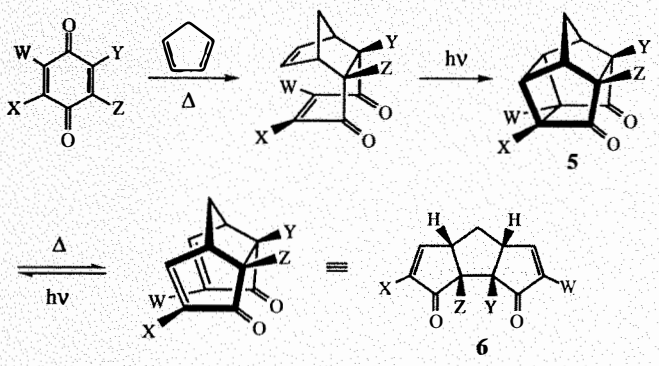




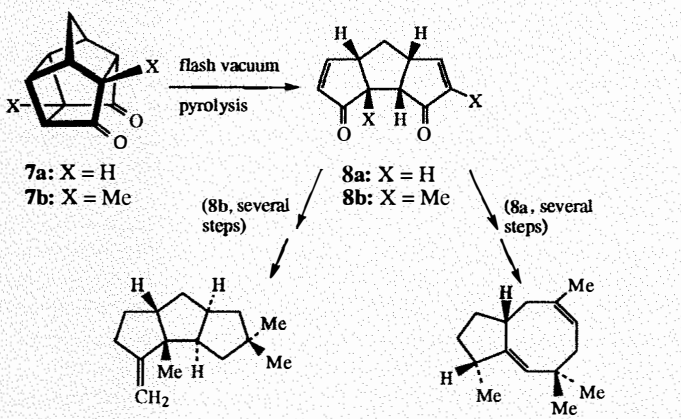
Scheme 1

best available method for large-scale synthesis of **2**. Key steps in the kinetically controlled synthesis involve: (i) stereospecific in situ [4 + 2] (Diels-Alder) cyclodimerization of 2-bromocyclopentadienone followed by (ii) intramolecular [2 + 2] photocyclization of the resulting *endo* Diels-Alder cycloadduct, **3**, and (iii) semibenzilic acid rearrangement performed on 5,9-dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (**4**). A recent improvement in the method for bis-decarboxylation of **2** to cubane which utilizes the Barton decarboxylation procedure has been published by Eaton and co-workers.[9]

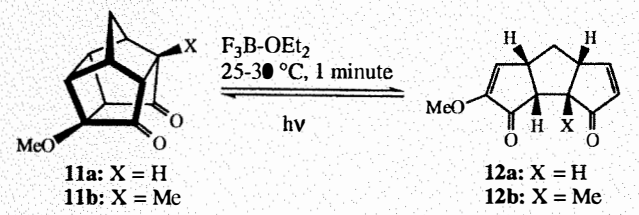
With rational syntheses of several such complex, rigid, and often highly strained systems now a *fait accompli*, the next progressive step in the development of polycarbocyclic cage compounds necessarily lies in the direction of their chemistry. Several questions immediately come to mind: Can relief of steric strain be "harnessed"; that is, can the stepwise breakdown of cage systems be controlled to produce ring-opened compounds which potentially can serve as useful synthetic intermediates? Can the polycarbocyclic frameworks inherent in cage molecules serve as "templates" upon which more advanced structures can be constructed? The answers to these and other related questions have been resoundingly affirmative. The purpose of this brief review is to examine some recent applications of cage compounds and their chemistry to a variety of problems which range from synthetic and mechanistic applications to materials and pharmaceutical/medicinal applications.



Scheme 2



Scheme 3



Scheme 4

Synthetic applications: Cage compounds as precursors to useful synthetic intermediates

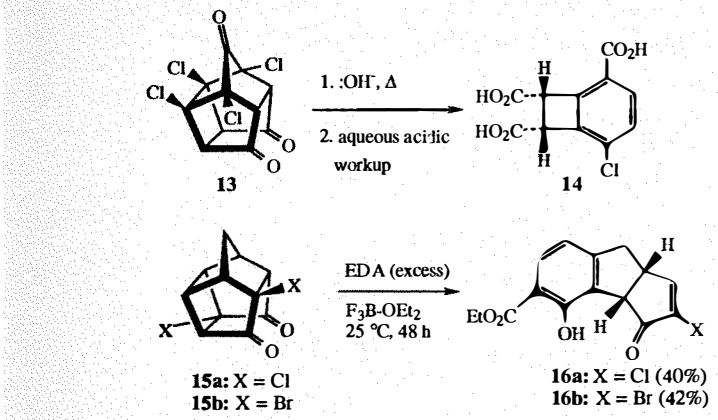
A. Controlled ring fragmentation of substituted PCU-8,11-diones: Applications to polyquinane synthesis

Mehta and co-workers[10] developed a "photothermal olefin metathesis" method which demonstrated that thermal [2 + 2] cycloreversion of substituted pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diones (i. e., "PCU-8,11-diones", **5**), can be controlled to afford the corresponding *cis,cisoid,cis* linear triquinanes (**6**, **Scheme 2**). Compounds derived from systems of the type **6** have been used productively as intermediates in the synthesis of a number of (racemic) natural products, for example, hirsutene (**9**, **Scheme 3**),[11] coriolin,[12] $\Delta^{9(12)}$-capnellene,[13] precapnelladiene (**10**, **Scheme 3**),[14] and a carbocyclic fragment of ikarugamycin.[15]

The foregoing discussion indicates how thermally induced ring fragmentation of PCU-8,11-diones has been employed as a key step in polyquinane synthesis. This type of ring fragmentation is particularly facile in PCU-8,11-diones which bear electron donating substituents at C(1) and/or C(7) (e.g., **11**, **Scheme 4**).[16] Such compounds are "push-pull" systems, that is, they contain electron-donating RO- groups which can hyperconjugate through the σ-bonded framework with distant C=O moieties in the cage. Such systems have been studied extensively in the past and are known to undergo facile thermal [2 + 2] cycloreversion and also to be highly sensitive to Lewis acid catalysts.[16]

B. Other ring fragmentation processes

Base-promoted ring fragmentation of 2,3,5,6-tetrachloro-PCU-4,8,11-trione (**13**) results in the formation of a substituted benzocyclobutenetricarboxylic acid (**14**, **Scheme 5**).[17] Similarly, ring



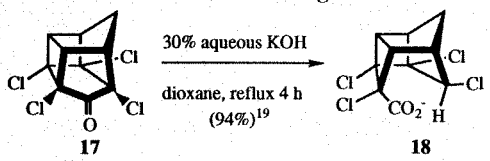
13 14

15a: X = Cl
15b: X = Br

16a: X = Cl (40%)
16b: X = Br (42%)

Scheme 5

Anomalous semibenzilic acid rearrangement:



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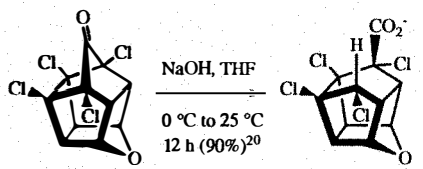
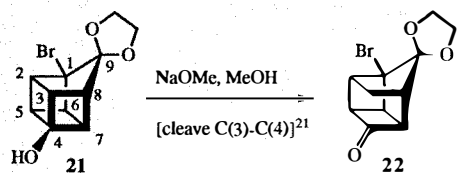


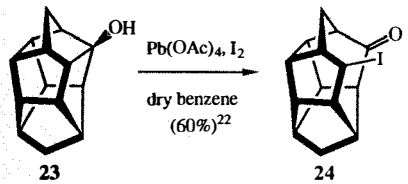
19 20

Homoketonization:



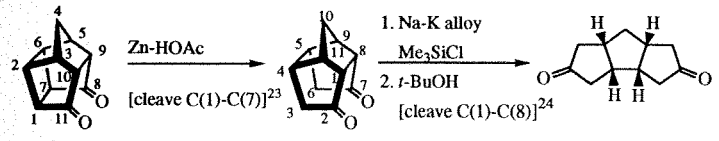
21 22

Oxidative C-C σ-bond cleavage:



23 24

Reductive C-C σ-bond cleavage:



25 26 27

Scheme 6

fragmentation with concomitant aromatization occurs when either 1,9-dichloro- or 1,9-dibromo-PCU-8,11-dione (**15a** or **15b**, respectively) is reacted with ethyl diazoacetate (EDA) in the presence of F_3B-OEt_2 (**Scheme 5**).[18]

Several additional examples of ring fragmentation processes are shown in **Scheme 6**. Thus, base promoted "anomalous semibenzilic acid rearrangement" of cage α-haloketones frequently result in ring fragmentation, particularly when Cl is employed as the leaving group.[19,20] Base promoted homoketonization has been employed to promote cleavage of carbon-carbon σ-bonds in cage systems.[21] Finally, both oxidative and reductive scission of carbon-carbon σ-bonds have been employed to promote ring fragmentation in carbocyclic cage systems.[22-24]

C. Ring contraction and ring expansion processes

Semibenzilic acid rearrangements have been used extensively to promote ring contractions in cage systems. Thus, ring contraction of **4** to **2** (**Scheme 1**) is a key step in the Eaton-Cole cubane synthesis. Numerous other examples of this type can be found, one of which is shown in **Scheme 7**.[25]

In addition, ring expansion processes have been extensively applied to cage systems to provide synthetic access to new "homologues". These include diazoester promoted ring expansions,[26] Tieffeneau-Demjanov rearrangements,[26] transition metal promoted carbonyl insertion reactions,[27] and Saegusa[28a] ring homologation,[28b] examples of which are shown in **Scheme 7**.

D. Lewis acid promoted cationic rearrangements in cage hydrocarbons

Lewis acid promoted rearrangements in polycyclic hydrocarbons provide a thermodynamic route to unusual cage molecules.[29] In such reactions, the most stable C_nH_m isomer, that is, the "stabilomer",[29a] is produced as the major rearrangement product. The prototype reaction in this regard is Schleyer's synthesis of adamantane, **40**, from a readily available tricyclic $C_{10}H_{16}$ precursor (**39**).[30] Similarly, D_3-trishomocubane (i.e., **42**, the $C_{11}H_{14}$ stabilomer),[29] can be prepared via cationic rearrangement of PCU (**41**).[31]

E. Other cationic rearrangements in functionalized cage systems

Numerous examples have been reported whereby cationic rearrangements have been employed in cage systems to provide

synthetic access to a variety of unusual molecules.[29b] Some examples in this regard are shown in **Scheme 9**.[32,33]

Physical-organic and mechanistic applications

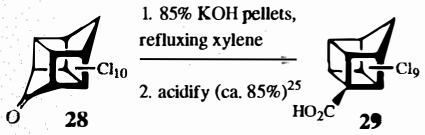
A. Studies of the mechanism of long-range electronic interactions

Long-range interactions between nonconjugated π-systems can be propagated via through-bond and/or through-space mechanisms.[34] In order to explore the relative importance of these mechanisms in, for example, the transmission of electronic substituent effects, long-range energy and/or electron transfer processes, and spin-density propagation, rigid carbocyclic frameworks have been constructed whose internuclear distances and internal geometries can be estimated simply and accurately.

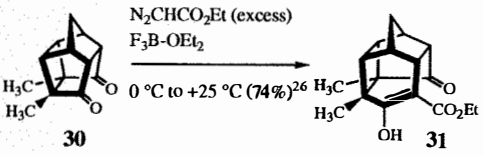
Photoelectron (PE) spectroscopy[34,35a] and ^{13}C nuclear magnetic resonance (NMR) chemical shifts[34] have been employed to study the transmission mechanism of transannular electronic effects in appropriately functionalized cage systems. Some examples in this regard are depicted in **Scheme 10**.[36-39] Depending upon the nature of the substituents X and Y in systems **49-51**, the available experimental evidence suggests that predominant through-bond or a mixture of through-bond and through-space modes of transmission of electronic substituent effects are operative.

In other examples, it has been advantageous to incorporate cage moieties as "rod-like spacers" into large, semi-rigid molecules. By taking advantage of a unique type of synthetic strategy referred to as "nanostructural architecture",[40] extended semirigid molecular systems have been devised in which both through-bond and through-space distances can be varied in a

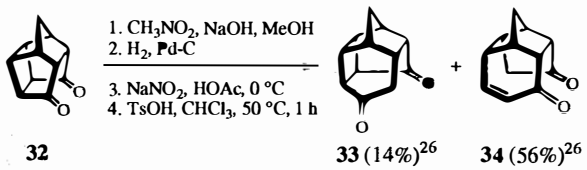
Semibenzilic Acid Promoted Ring Contraction:



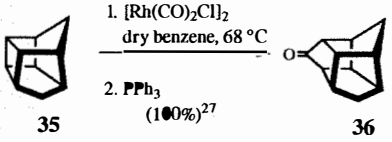
Diazoester Promoted Ring Expansion:



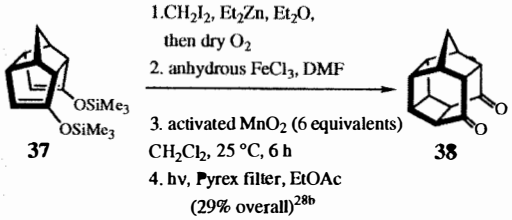
Tieffeneau-Demjanov Rearrangement:



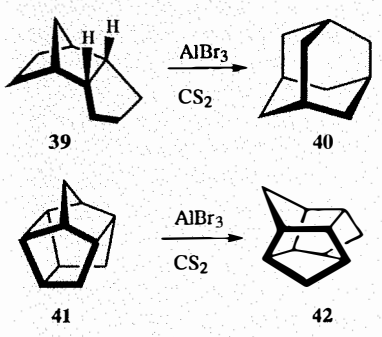
Transition Metal Promoted Carbonyl Insertion Reactions:



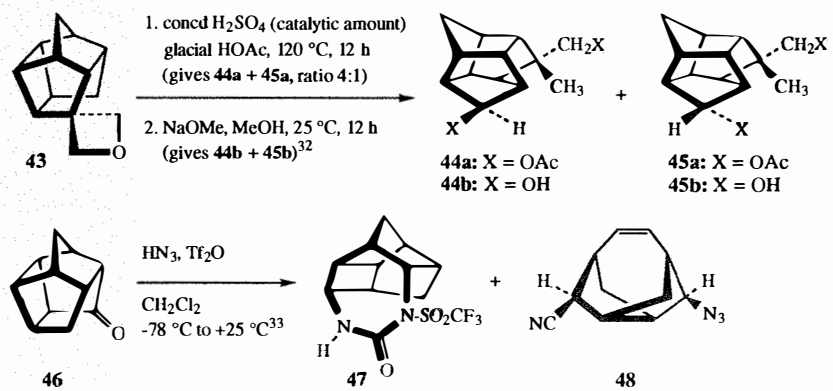
Saegusa[28a] Ring Homologation:



Scheme 7

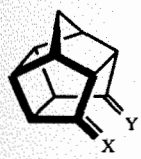


Scheme 8



Scheme 9

Photoelectron Spectroscopic Studies:



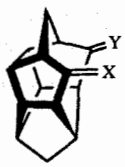
49a: X = Y = O[36]
49b: X = O, Y = CH_2
49c: X = Y = CH_2
49d: X = O, Y = CHCl
49e: X = O, Y = $CHSiMe_3$
49f: X = CH_2, Y = $CHSiMe_3$
49g: X = Y = $CHSiMe_3$

50a: X = Y = H_2[37]
50b: X = O, Y = H_2
50c: X = CH_2, Y = H_2
50d: X = Y = O
50e: X = Y = CH_2
50f: X = O, Y = CH_2
50g: X = OCH_2CH_2O, Y = O
50b: X = OCH_2CH_2O, Y = H_2

Carbon-13 NMR Chemical Shift Studies:

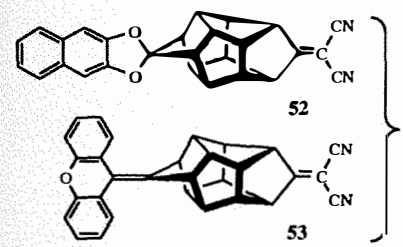
49[38]

50[39a]



51[39a,39b]

Scheme 10



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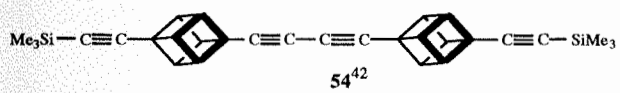
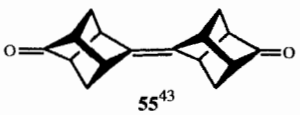
53

rigid donor-spacer-acceptor (DSA) molecules for use in the investigation of mechanisms of photoinduced electron transfer processes.[41]

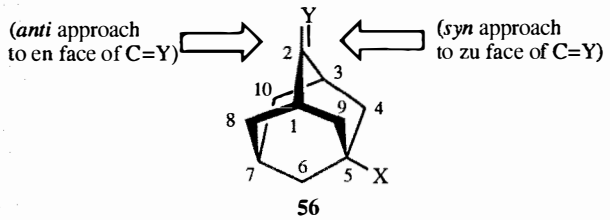


54[42]



55[43]

Scheme 11



56

Scheme 12

systematic manner. Spectral data obtained for these systems has provided a basis upon which the relative mechanistic importance of through-bond and through-space mechanisms can be gauged. Some examples in this regard are depicted in **Scheme 11**.

B. Diastereofacial selectivity studies

Appropriately functionalized adamantanes have been used extensively as a model system to investigate the theoretical basis of stereoselective reactions. Thus, the zu and en faces of the C=Y moiety in 2,5-disubstituted adamantanes of the type **56** (**Scheme 12**) are sterically equivalent, and observed differences in *syn*/*anti* product ratios are thought to reflect the electronic effect of the 5-substituent, X, upon the transition state for reaction at the distant C=Y center. Thus, a wide variety of reactions has been studied including, for example, nucleophilic attack on ketones (**56**, Y = O)[44] and electrophilic addition to alkenes (**56**, Y = CH_2),[45] among others.[46] The results thereby obtained have been explained variously in terms of substituent effects on σ-participation (transition state hyperconjugation, the so-called "Cieplak effect")[47] or, alternatively, the torsional strain transition state model that has been proposed by Felkin[48] and by Anh.[49] However, the interpretation of these often subtle effects continues to be a controversial topic.[50]

Cage compounds have also been employed as substrates in studies of π-facial selectivities in Diels-Alder cycloadditions.[51] Thus, hexacyclo-[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione (i.e., **57**, X = Y = O, **Scheme 13**) reacts as the diene component when undergoing [4 + 2] cycloaddition to methyl acrylate.[52] Substituent effects upon the zu vs. en and *syn* vs. *anti* selectivity of this process has been examined in detail.[53] Interestingly, **57** (X = Y = O) functions as the dienophile when undergoing [4 + 2] cycloaddition either to hexachlorocyclopentadiene or to 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (electron-poor dienes) in inverse electron demand[54] Diels-Alder reactions.[55]

C. Caged reactive intermediates

Cubane has provided a rigid polycarbocyclic cage framework upon which a variety of unusual and highly reactive species have been constructed. Thus, Eaton and co-workers have generated such "impossible" species as cubyl cation[56] [**60**, (**Scheme 14**), "the least likely carbocation"[8]], cubyl radical (**61**),[57]

cubylcarbinyl radical (**62**, "the least long-lived radical derived to date from any saturated hydrocarbon system"),[58] 1,4-cubadiyl (**63**),[59] 1,2-dehydrocubane (**64**,[60] "the most extreme example of a pyramidalized olefin"[8]), and 9-phenyl-1(9)-homocubene (**65**,[61] "the anti-Bredt olefin nonpareil...the most twisted olefin yet known"[8]).

Pharmaceutical/medicinal applications

1-Aminoadamantane [i.e., "amantadine", **66**, R = H (**Scheme 15**)] provides a familiar and important example of a medicinally important cage compound; it has found wide application both as an antiviral agent (against influenza A)[62] and for treatment of extrapyramidal disorders such as Parkinson's syndrome.[63] Thus, aminododecahedranes (**67**),[64] aminotrishomocubanes (**68**),[65] and aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (**69**),[66] like 1-aminoadamantane, all display antiviral activity toward influenza A. In addition, some closely related cage amines, for example **70**[67] and **71**,[68] have been employed as in vivo calcium antagonists.

Some functionalized cubanes and homocubanes have been reported to display useful pharmacological activity. Thus, 4-substituted cubylcarbinylamines of the type **72** have been demonstrated to possess the ability to inhibit monoamine oxidase-B irreversibly.[69] Several substituted cubane and homocubane carboxamides of the types **73** and **74** have been shown to inhibit stomach ulcer formation in rats.[70,71]

Materials applications

A. Energetic materials

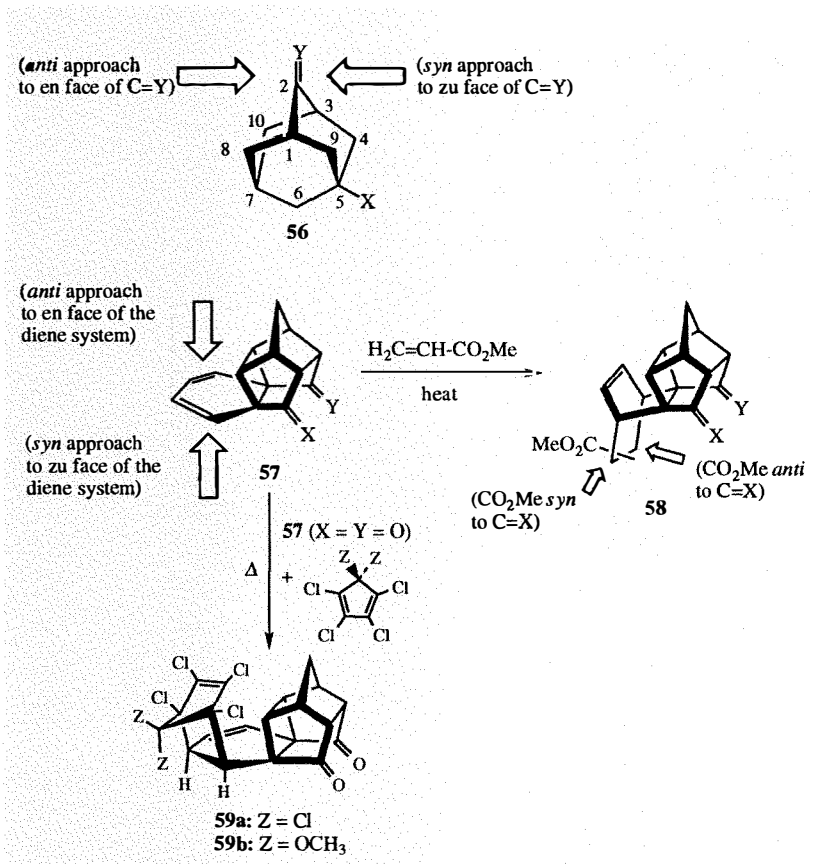
That highly strained carbocyclic systems can be synthesized routinely is now an established fact. Often, there is no kinetically accessible pathway by which such compounds might alleviate the steric strain that remains locked within their respective carbocyclic frameworks.[8] Thus, such compounds exist in the face of what might be described as "thermodynamic adversity".

Recently, a branch of materials science has emerged that takes advantage of the high strain energy content and highly compact structures which constitute the hallmarks of most polycarbocyclic cage systems. Military applications of cage molecules which seek to exploit these features have led to the development of new classes of high energy density fuels[72] and explosives.[73]

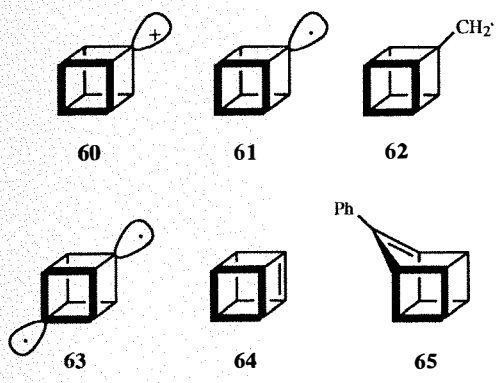
Since 1980, polynitropolycyclic compounds have occupied center-stage in the never-ending search for new, more powerful, stable explosives. The quest for compounds of this type began with the successful synthesis of 1,3,5,7-tetranitroadamantane (**75a**, **Scheme 16**).[74] Since that time, several polynitropolycyclic systems have been synthesized; some representative examples are shown in **Scheme 16**.

B. Polymers

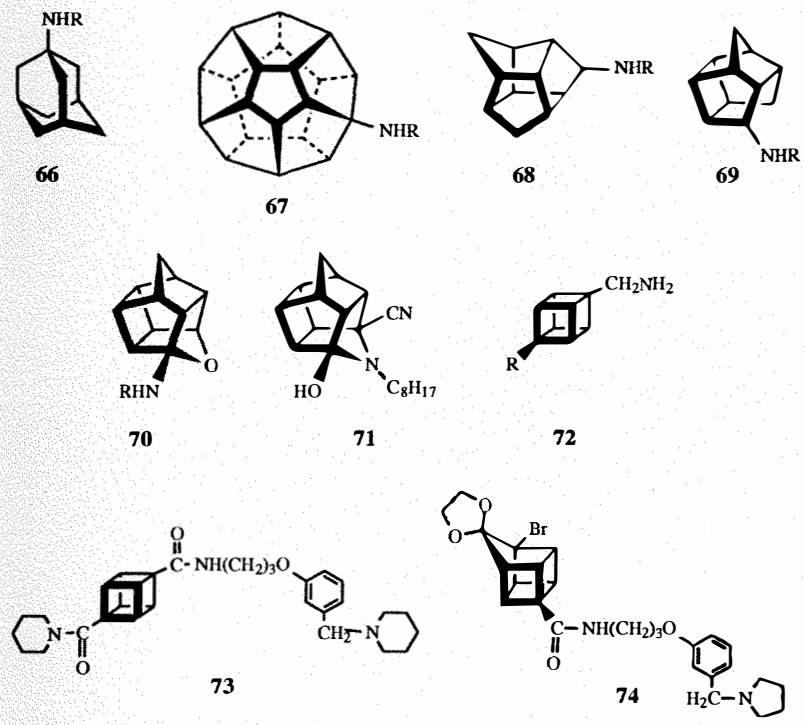
Cubane-derived polymers have been prepared via titanium-promoted cationic polymerization of 1,4-diallylcubane.[81] In addition, substituted 1,4-diiodocubanes (e.g., **80**, **Scheme 17**) have been



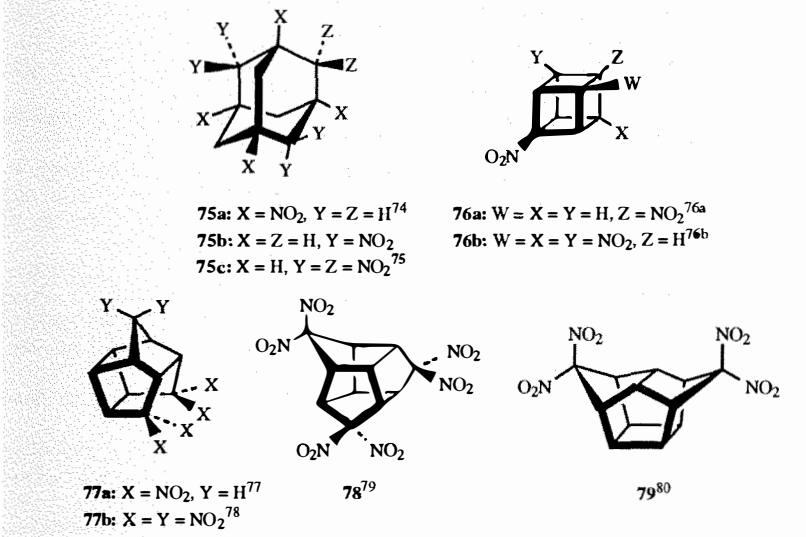
Scheme 13



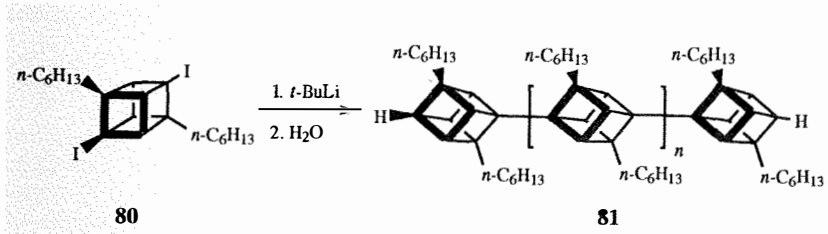
Scheme 14



Scheme 15



Scheme 16



Scheme 17

polymerized via their reaction with *t*-BuLi.[82] The resulting polymers are rigid structures composed of straight "rods". Other rigid polymers have been constructed which contain alternating energetic cage units and acetylene units that function as spool-like "connectors". The individual components of such systems have been likened to nanoscale analogs of Tinkertoys®, a popular children's construction play-set.[83]

C. Cage-derived crown ethers and molecular clefts

Worldwide efforts to study molecular recognition and inclusion phenomena have been aided by the use of cage and cage-derived compounds as a means to construct new types of molecular host systems. Thus, the introduction of 1,4-bridged cubyl moieties into crown ether ionophores (as in, e.g., **82**, **Scheme 18**)[84] confers both rigidity and lipophilicity upon the host macromolecule. The resulting crown ethers have been used productively in the construction of ion-selective electrodes. Other crowned cages, for example **83a** and **83b**, have also been synthesized.[85]

In another approach, cage molecules have been used as templates or "frameworks" for the construction of molecular clefts. Thus, several polyaza cavity-shaped *syn*-orthocyclophane clefts, for example **84-86** (**Scheme 18**), have been synthesized.[86,87]

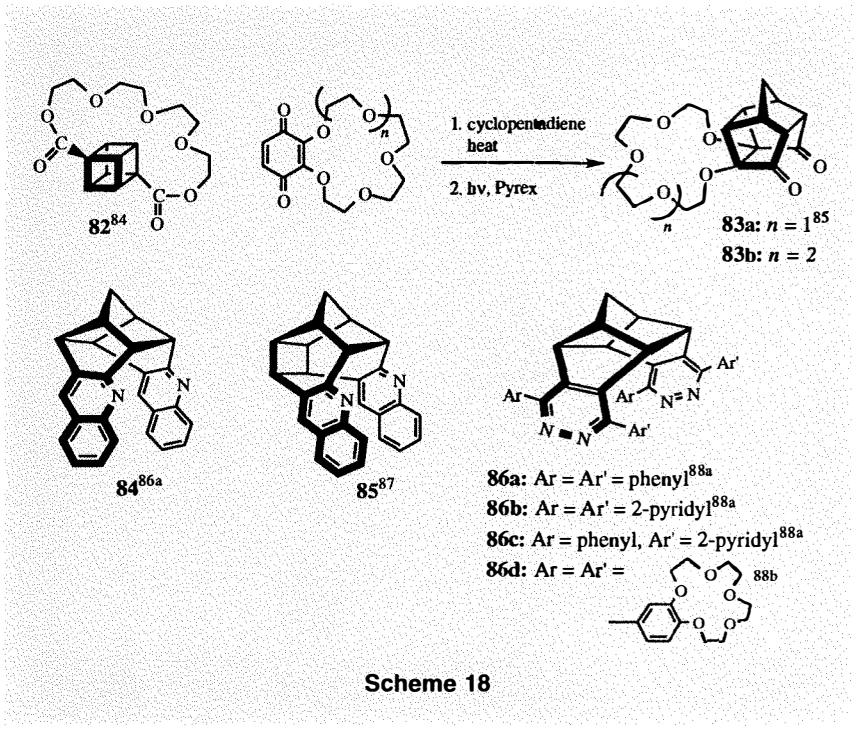
D. Fullerene-derived materials

Few compounds have generated as much excitement in recent years as have the cage allotropes of carbon that are collectively known as "Buckminsterfullerenes" (i.e., C_{60}, C_{70}, and related species).[89] In addition to their inherent theoretical interest, the materials aspects of fullerenes have attracted considerable attention in recent years.[90] Thus, doping of C_{60} with alkali metal vapors results in the formation of species of the type A_3C_{60} and A_6C_{60} which are among the first examples of three-dimensional organic conductors and superconductors.[91] Fullerenes also have been investigated as potential components of third-order nonlinear optical (NLO) materials.[92] Recently, functionalized fullerenes have been incorporated as pendant substitutents into "charm bracelet"[93] polymers.[94] The preparation of water-soluble fullerenes which possess HIV antiviral activity has also been reported.[95]

Concluding remarks

Cage molecules have carved an impressive niche for themselves in organic chemistry. They have been employed as intermediates in organic and natural product synthesis through stereo- and regiocontrolled ring expansion and fragmentation processes and as templates for nanoarchitectural construction of rigid molecular systems that possess ever-increasing levels of complexity. Appropriately functionalized cage molecules provide structurally well-defined systems of known molecular geometry that serve as precursors to "theoretically interesting molecules". Functionalized cages also have found extensive application for the study of mechanisms of transmission of electronic substituent effects and of long-range electron and energy transfer processes. Several new cage-containing medicinal and/or pharmacological agents have been produced. New materials applications of cage molecules and of cage-containing polymers are being announced with increasing regularity. Thus, the future of cage chemistry appears to be bright; these are, indeed, the reagents and substrates that will continue to define the directions of organic and physical-organic chemistry into the 21st century.

This brief exposition of cage chemistry is intended to provide a space-restricted overview of a broad and highly interdisciplinary field. Inevitably, this approach has resulted in the omission of much important work, a shortcoming for which the author apologizes.



Scheme 18

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About the author

Dr. Marchand received his B. S. degree in Chemistry from Case Institute of Technology in 1961. He completed his Ph.D. in Organic Chemistry in 1965 at the University of Chicago, where he worked under the aegis of Professor Michael J. S. Dewar. After one year as an NIH Postdoctoral Research Fellow at the University of California, Berkeley (1965-1966, with Professor Andrew Streitwieser), Dr. Marchand joined the faculty in the Department of Chemistry, at the University of Oklahoma. He was promoted to Associate Professor in 1970 and then to Professor of Chemistry in 1976. He received the 1976 Sigma Xi faculty research award at the University of Oklahoma. In 1982, Dr. Marchand moved to the Department of Chemistry, University of North Texas, where he presently holds the position of Regents' Professor of Chemistry.

Dr. Marchand was the 1989 Regents' Faculty Lecturer at the University of North Texas. He received the Wilfred T. Doherty Award of the Dallas-Fort Worth Section of the American Chemical Society in April, 1991. He was appointed Erskine Fellow in the Department of Chemistry, University of Canterbury, Christchurch, New Zealand during May-August, 1992. He was appointed Visiting Scientist at the University of Tokyo by the Japanese Ministry of Education during December, 1992 and January, 1993. Later in 1993, he was named Toulose Scholar at the University of North Texas. He presented the 1993 Henry Lardy Lecture at South Dakota State University in April, 1993.

Dr. Marchand is author or coauthor of six books, eighteen review articles, and approximately 200 research publications in peer-reviewed scientific journals. He edits a monograph series, "Methods in Stereochemical Analysis", which is published by VCH Publishers, New York. He is a member of the editorial boards of the *Journal of Energetic Materials* and *Structural Chemistry,* and he is also a member of the editorial advisory board of "Structure, Energy, and Reactivity in Chemistry" (monograph series edited by Joel F. Liebman and A. Greenberg, published by Chapman & Hall, New York).

New Reactions for Forming Heterocycles and Their Use in Natural Products Synthesis

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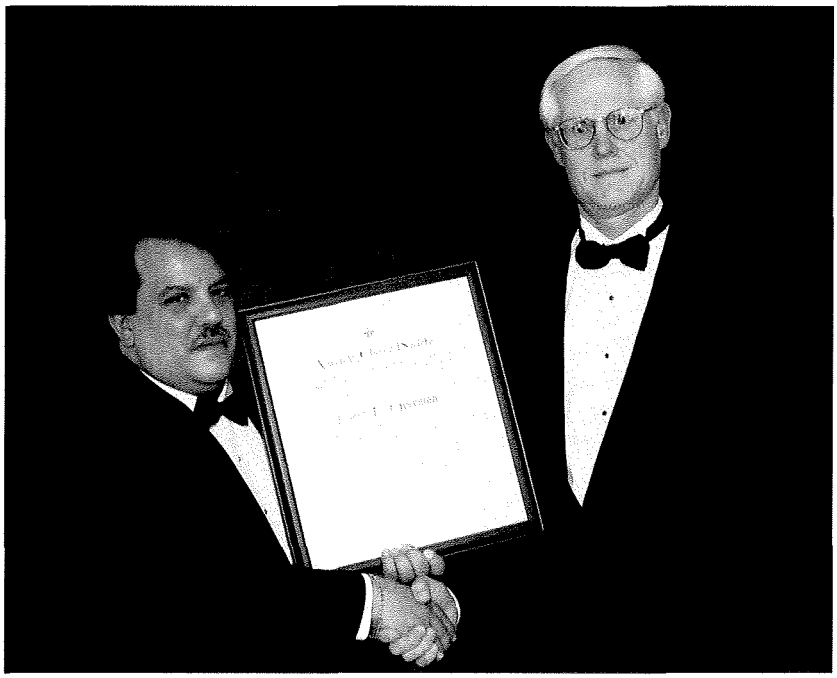


Professor Larry E. Overman (right) receiving the 1995 ACS Award for Creative Work in Synthetic Organic Chemistry from Dr. Stephen J. Branca, Vice-President, Aldrich Chemical Company, Inc.

Introduction

The past 50 years have witnessed extraordinary progress in synthetic organic chemistry.[1] A variety of reagents, reactions, and synthetic strategies have been developed which allow impressively intricate molecules to be assembled.[2] Yet, when confronted with the challenge of preparing even modestly elaborate target structures in a practical fashion on meaningful scales, the tools of synthetic organic chemistry are often found lacking. Future advances in our ability to achieve efficient syntheses of increasingly complex target structures will depend largely on the invention or discovery of new reactions. New reactions especially impact our ability to prepare complex molecules since they open new vistas in synthetic strategy.

Our capacity to synthesize polycyclic molecules is distinctively affected by the introduction of new methods for ring formation. Recognizing this fact, our laboratory has been engaged for a number of years in the invention and development of new cyclization reactions. In this article, highlights of our studies in the area of heterocyclic construction will be presented with particular emphasis given to the impact of new cyclization reactions on the synthesis of heterocyclic natural products. The ring-forming reactions that are the focus of this discussion are depicted in **Figure 1**. A common thread among these reactions is the assembly of the heterocyclic ring by carbon-carbon, rather than carbon-heteroatom, bond formation. Such construction allows unique opportunities for stereocontrol, which will be illustrated throughout this account.

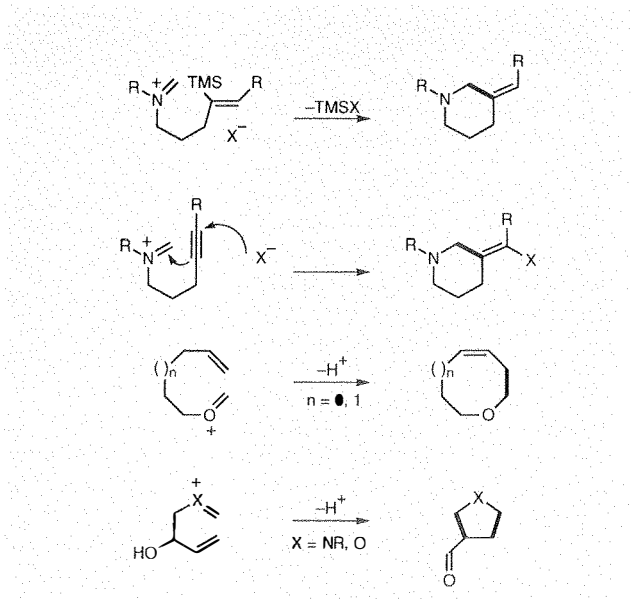


Figure 1. Syntheses of heterocycles by C–C bond-formation. The new C–C bonds formed are shown in bold.

Iminium Ion-Vinylsilane Cyclizations

Our involvement with silicon chemistry began in late 1979 when I learned from John Daly, one of the pioneers of amphibian natural products, that the structure of the pumiliotoxin A alkaloids had been revealed through Isabella Karle's recent X-ray analysis of the hydrochloride salt of pumiliotoxin 251D (**1**).[3] This result had prompted Daly to propose that pumiliotoxins A (**2**) and B (**3**), the parent members of this amphibian alkaloid group, differed from pumiliotoxin 251D only in having more elaborate side chains (**Figure 2**). Mindful that pumiliotoxins A and B exhibited important cardiotonic and myotonic properties

and that the rare Central American dendrobatid frogs from which they had been isolated were unlikely to provide significant quantities of these alkaloids, we decided to pursue their total syntheses.[4,5]

Controlling the stereochemistry of the exocyclic double bond appeared to be the most formidable challenge in developing a concise route to the pumiliotoxin A alkaloids. (*L*)-Proline was an obvious starting material and our attention was drawn immediately to a strategy in which formation of the piperidine ring and elaboration of the (*Z*)-alkylidene side chain would be realized in a coordinated way (**Scheme 1**). Since vinylsilanes had recently been shown to react stereospecifically with retention of configuration with simple electrophiles, we postulated that vinylsilane intermediate **7** might serve as an equivalent for zwitterionic synthon **6**. At that time the choice of a vinylsilane as a Mannich reaction component was adventurous, since neither intramolecular reactions of vinylsilanes with electrophiles nor bimolecular reactions of iminium ions with vinylsilanes had been documented. Our hope, of course, was that intramolecular juxtaposition would engage these weakly reactive cyclization partners.

The validity of these considerations was demonstrated a year later in our total synthesis of pumiliotoxin 251D (**1**).[6] Iminium ion-vinylsilane cyclizations were next employed to prepare pumiliotoxins A (**2**) and B (**3**) and in so doing clarify the complete stereostructure of these alkaloids.[7,8] The enantioselective total synthesis of pumiliotoxin A (**2**) is illustrative and is outlined in **Schemes 2** and **3**.[8]

Construction of the side chain component, silylalkyne **11**, began with (*S*)-2-methyl-1-penten-3-ol (**8**), which at the time was obtained by Sharpless kinetic resolution.[9] Ireland-Claisen rearrangement of propionate ester **9** was then employed to relate the C(11) and C(15) stereocenters.[10] As is discussed in more detail elsewhere,[5] the 7:1 stereoselection realized in the formation of **10** is notably high for an Ireland-Claisen rearrangement of a tertiary allylic ester.

Conversion of silylalkyne **11** to aluminate **12** followed by coupling with proline-derived epoxide **13** provided bicyclic oxazolidinone **14** in moderate yield (**Scheme 3**). This critical step joins the side chain and pyrrolidine fragments and stereospecifically establishes the *Z* configuration of the trisubstituted vinylsilane. The second pivotal step, stereospecific iminium ion-vinylsilane cyclization, proceeded in high yield when oxazolidine **15** was heated in weakly acidic methanol to provide **16**. Cleavage of the benzyl protecting group then provided 15(*S*)-pumiliotoxin A, whose comparison with the natural isolate established that the major isomer of the mixture of C(15) epimeric alcohols obtained from the amphibian source had the 15(*S*) configuration.

The total synthesis of 15(*S*)-pumiliotoxin A summarized in **Schemes 2** and **3** is the most efficient synthesis of a natural pumiliotoxin A alkaloid realized by this strategy. The longest linear sequence proceeds in 14 steps and 8% overall yield from pentenol **8**. The iminium ion-vinylsilane approach for accessing pumiliotoxin A alkaloids was sufficiently practical to allow a number of analogs to be prepared. Biological evaluation of these congeners and many natural

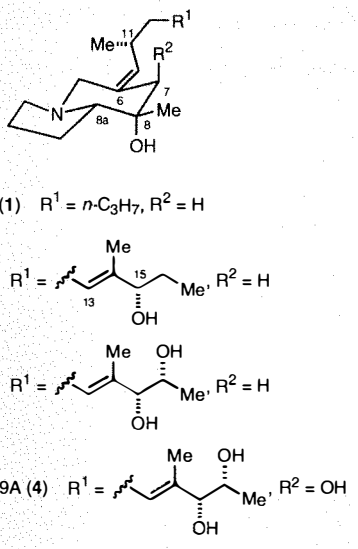
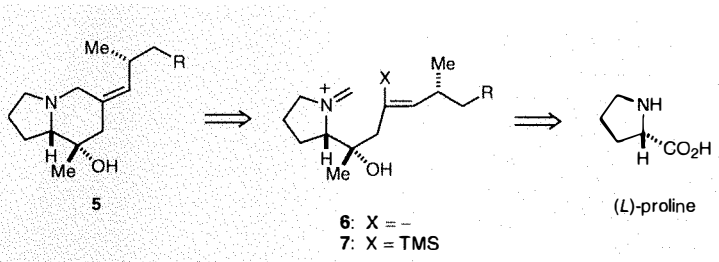
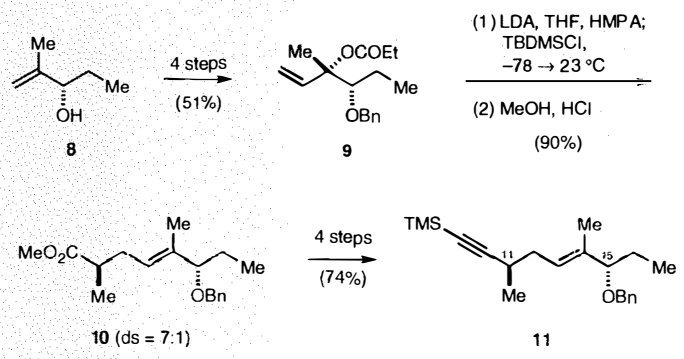


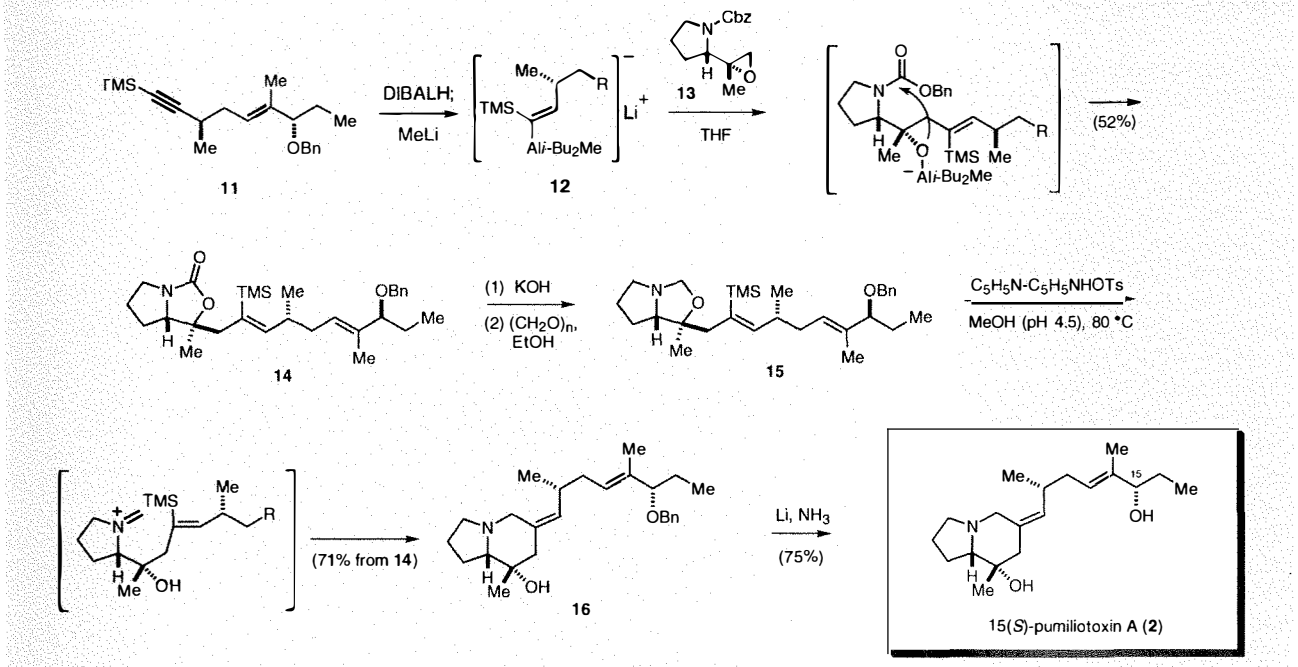
Figure 2. Representative pumiliotoxin A and allopumiliotoxin alkaloids.



Scheme 1



Scheme 2



Scheme 3

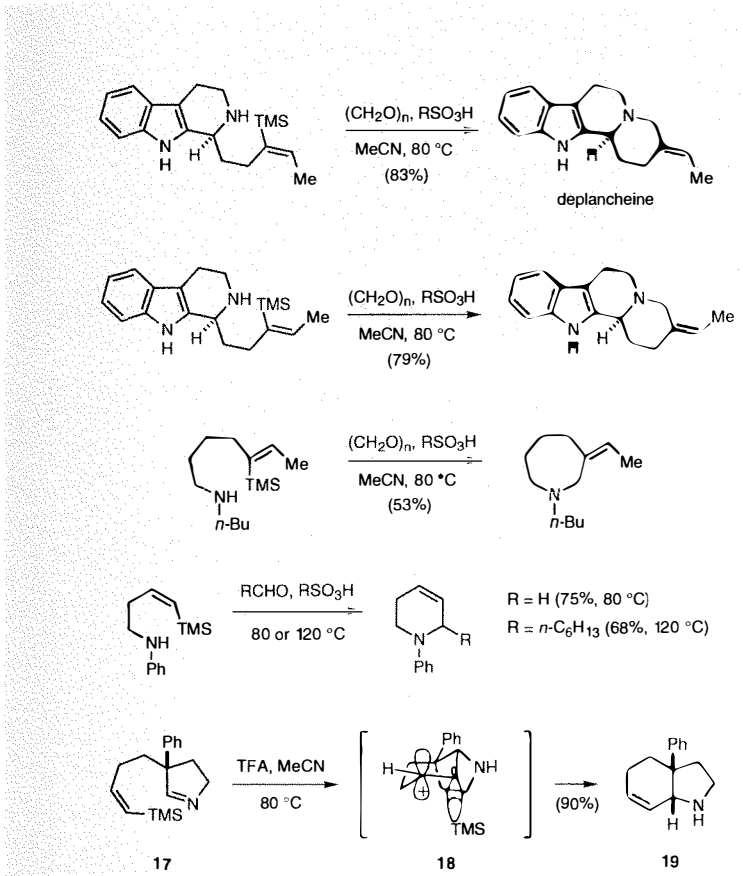


Figure 3. Representative iminium ion-vinylsilane cyclizations.

alkaloids defined structure-activity relationships in this area.[11]

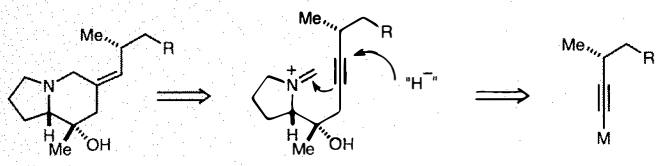
The scope of iminium ion-vinylsilane cyclizations can be gleaned from the examples depicted in **Figure 3**.[12,13] As in related transformations in the pumiliotoxin A series, cyclizations take place at near neutral pH, since <1 equivalent of acid was employed in the reactions summarized in **Figure 3**. Cyclizations proceeding in an exocyclic mode with respect to the vinylsilane nucleophile are highly stereospecific and can be employed to prepare either (*E*)- or (*Z*)-alkylidenepiperidines or alkylideneazepines. Related endocyclizations provide a general entry to substituted 1,2,5,6-tetrahydropyridines, but are not useful for forming unsaturated azacycles of other ring sizes. The smooth, acid-promoted conversion of pyrroline (*Z*)-vinylsilane **17** to *cis*-hexahydroindole **19** stands in marked contrast to the failure of the related cyclization of the (*E*)-vinylsilane stereoisomer.[13c] As suggested in **18**, this difference in reactivity is not surprising since the cation formed from chair topography cyclization of only the *Z* stereoisomer can be stabilized by conjugative electron release from the silyl substituent.[14] Iminium ion-vinylsilane cyclizations have been employed by us to prepare a number of other natural products including plant alkaloids of the *Corynanthe*,[13a,15] *Amaryllidaceae*,[13c,14] and

Elaeokarpus[13b,13d] families, as well as a *Streptomyces* antibiotic.[16]

Nucleophile-Promoted Iminium Ion-Alkyne Cyclizations

In our first syntheses of the pumiliotoxin A alkaloids the *Z* geometry of the exocyclic alkene was encoded in an acyclic vinylsilane precursor and the silyl group then was exploited to transfer stereochemistry to the alkylidene product. An alternative approach is suggested in **Scheme 4** in which antarafacial addition of an iminium electrophile and an external nucleophile to a tethered alkyne would fashion the (*Z*)-alkylideneindolizidine core of the pumiliotoxin A alkaloids. Besides the conceptual simplicity of this approach, the troublesome junction of the side chain and pyrrolidine fragments was expected to be improved by introduction of the side chain as an alkynyl nucleophile.

In 1987 when our investigations of this second approach to the pumiliotoxin A alkaloids began, we could find only one example of the reaction of a simple iminium ion with an alkyne.[17,18] Since this conversion was accomplished under aqueous conditions and, thus, did not reveal stereochemical features, we initially surveyed our prospects in model systems. Not surprisingly, the most direct rendition of this new strategy in which the external nucleophile would be a hydride was undermined by simple reduction of the formaldiminium ion to give an *N*-methylated product. However, halogens or pseudohalogens served admirably as cyclization components (**Figure 4**).[19,20]



Scheme 4

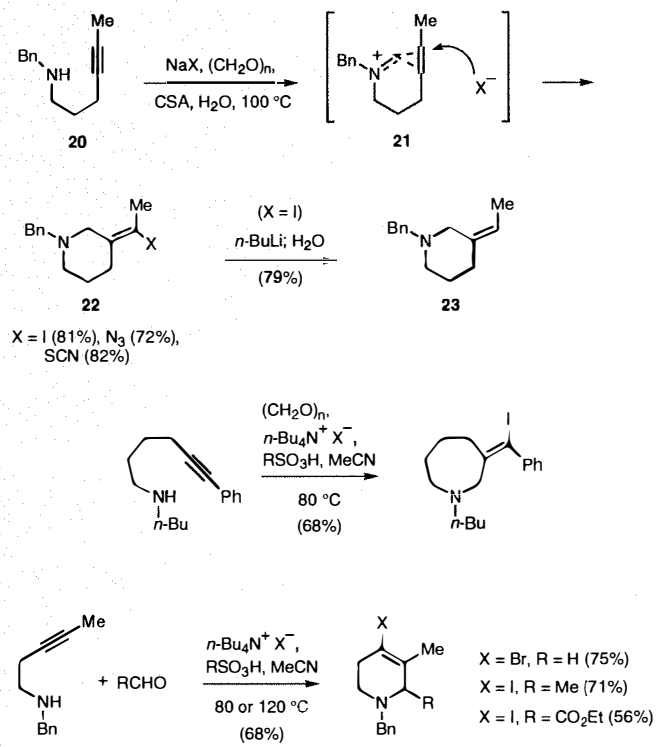
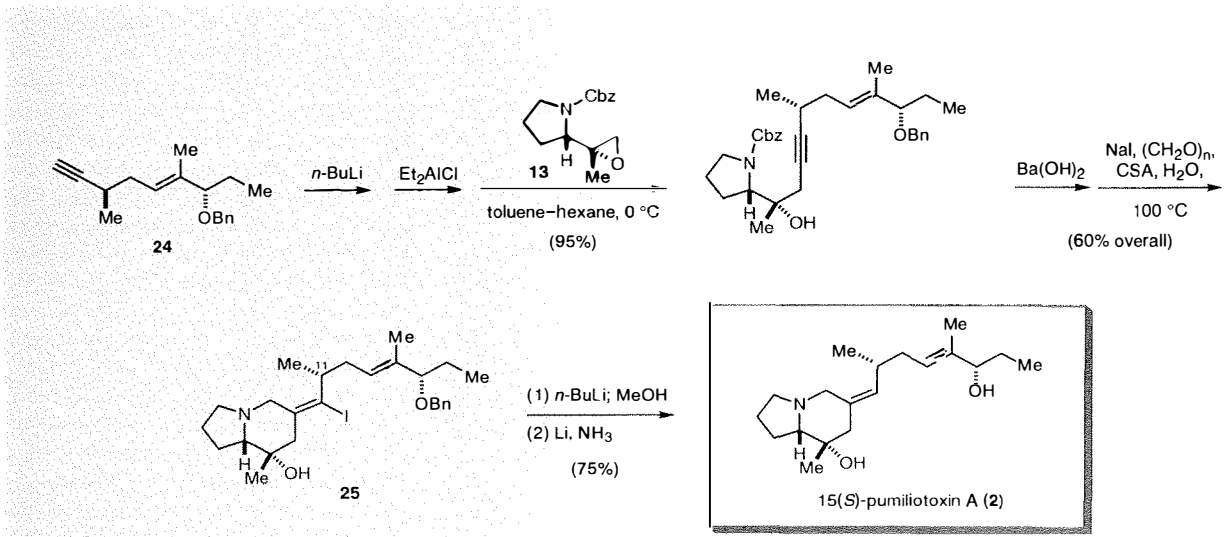
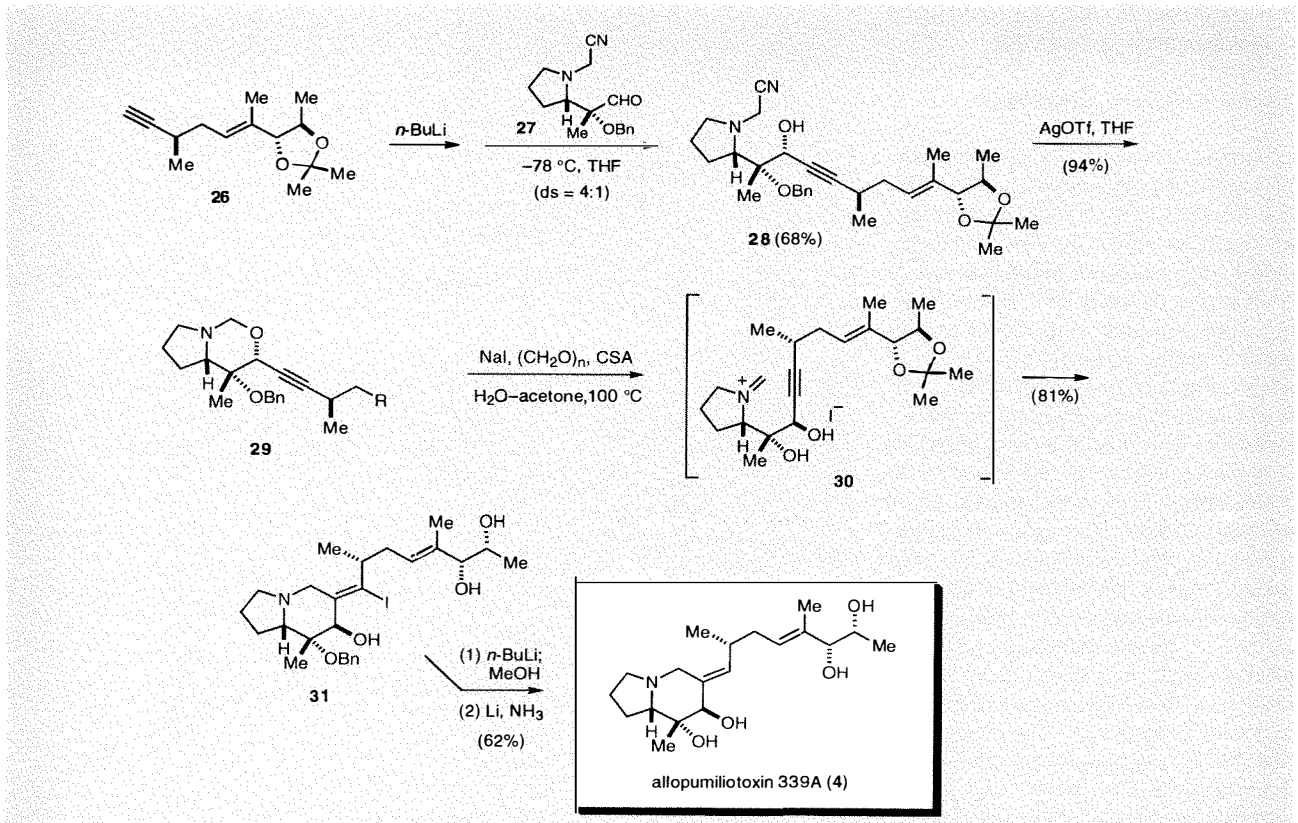


Figure 4. Representative nucleophile-promoted iminium ion-alkynecyclizations.



Scheme 5



Scheme 6

In the case most relevant to the proposed total synthesis endeavor, 4-alkynylamine **20** could be transformed *stereospecifically* to alkylidenepiperidine **22** in the presence of I^-, Br^-, N_3^-, or SCN^- under either aqueous or aprotic cyclization conditions. Similar to iminium ion-vinylsilane cyclizations, exocyclic nucleophile-promoted iminium ion-alkyne cyclizations occur in useful yields to form six- and seven-membered alkylidene azacycles. However, only tetrahydropyridines can be prepared efficiently by related endocyclizations.[19,20] Since the iodide product **22** (X = I) was easily reduced with retention of configuration to form **23**, a second potential solution to the pumiliotoxin A alkaloid synthesis problem was in hand.

Before briefly examining this total synthesis application, one singular feature of these cyclizations should be noted. When formaldiminium ion **21** is generated in a non-nucleophilic solvent (e.g., acetonitrile) in the absence of strong external nucleophiles, cyclization does not take place even at 100 °C.[19] Thus, the halide (or pseudohalide) nucleophile is not just trapping a vinyl cation intermediate, but is an intimate participant in the cyclization transition state. To stress this kinetic feature we have described these Mannich cyclization reactions of alkynes as *nucleophile-promoted*. Interestingly, the kinetic participation of external nucleophiles in related cyclizations of alkenes is less important.[19]

Iodide-promoted iminium ion-alkyne cyclizations were first employed to realize an improved construction of (+)-15(*S*)-pumiliotoxin A (**2**) (**Scheme 5**).[21] The two key steps of this synthesis were the efficient junction of epoxide **13** with the alkynylalane derivative of **24**, and the pivotal iodide-promoted Mannich cyclization which proceeded with perfect antarafacial stereoselectivity to afford **25**. The efficiency of the cyclization step was ~80%, since 15% of 11-epi-**25** (resulting from the minor C-11 epimer of **24**) was also isolated. This synthesis of pumiliotoxin A proceeded in 13 steps and 14% overall yield from (*S*)-2-methyl-1-penten-3-ol (**8**, **Scheme 2**), the precursor of alkyne **24**.

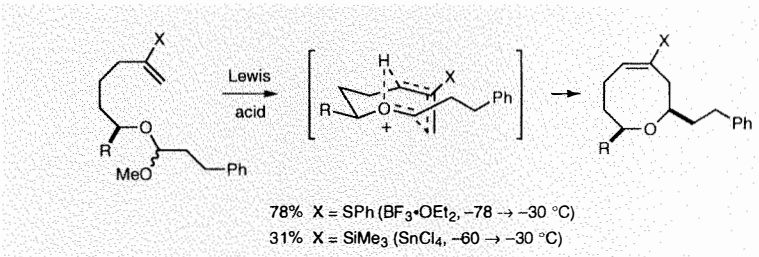
The best illustration to date of the utility of iodide-promoted iminium ion-alkyne cyclizations is provided by our recent enantioselective total synthesis of allopumiliotoxin 339A (**4**) (**Scheme 6**).[22,23] The rare allopumiliotoxins, which contain a more oxidized indolizidine core, are the most complex amphibian indolizidine alkaloids.[4] Allopumiliotoxin 339A (**4**) was an especially attractive synthetic target, since it is the only alkaloid of the pumiliotoxin A family to be more effective than pumiliotoxin B in stimulating sodium influx and phosphoinositide breakdown in guinea pig cerebral cortical synaptoneurosomes.[11c]

Construction of **4** from side chain and pyrrolidine fragments **26** and **27** is summarized in **Scheme 6**. The chemistry involved in the preparation of these components is discussed in a recent review and will not be reiterated here.[5] Addition of the alkynyllithium derivative of **26** to aldehyde **27** occurred with modest facial guidance from the adjacent benzyl ether to provide the major diastereomer **28** in 68% yield. Related alkynyl titanium and zinc nucleophiles, which would be expected to react with a higher degree of chelate organization, would not add to hindered aldehyde **27**. The critical ring-opening of oxazine **29** and iodide-promoted cyclization of formaldiminium ion intermediate **30** proceeded smoothly in aqueous acetone at 100 °C (with cleavage of the isopropylidene acetal) to afford alkylideneindolizidine **31** in 81% yield. Stereospecific de-iodination and careful cleavage of the benzyl protecting group

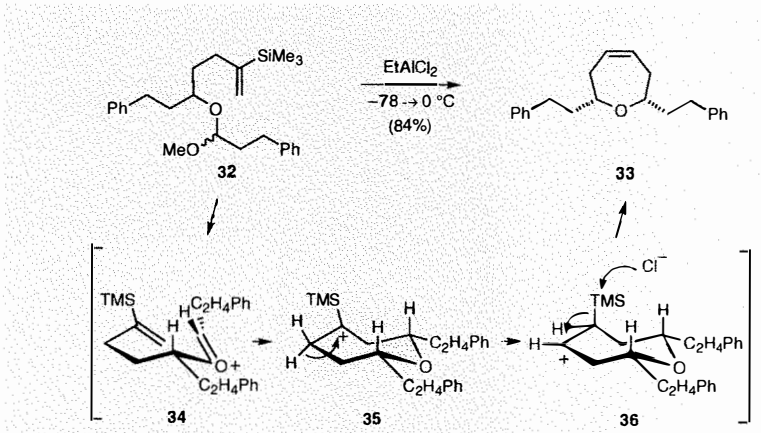
then completed this first total synthesis of (+)-allopumiliotoxin 339A (**4**).

Acetal-Alkene Cyclizations

During the course of a general survey of vinylsilane-terminated heterocyclization reactions,[12c,24] we discovered the surprising efficiency of the Lewis acid-promoted conversion of 5-hexenyl acetals to Δ^4-oxocenes (**Scheme 7**).[25] That demanding eight-membered rings could be prepared in useful yields by cyclizations of simple acyclic precursors that are not biased toward coiled conformations was remarkable. The yield of these cyclizations is markedly affected by the nature of the 5-substituent, with a thiophenyl group proving optimal.[25b] Our extensive investigations of this cyclization in the silyl series support an intramolecular ene mechanism (as suggested in **Scheme 7**) in which C–C bond formation and C–H bond cleavage occur in a synchronous fashion through a transition state resembling a bicyclo[3.3.1]nonane.[26] The reader is referred to the original literature for further discussion of mechanistic and stereochemical nuances of these reactions,[25,26] and to an earlier review for a discussion of the importance of the charged heteroatom in these reactions and the two five-membered heterocycle constructions we will examine subsequently.[27]



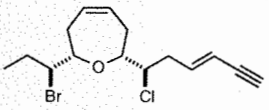
Scheme 7



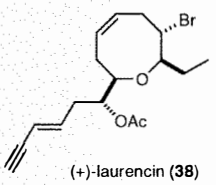
Scheme 8

Cyclizations of 4-alkenyl acetals to yield seven-membered ring ethers are, as expected, even more efficient.[28] We were, however, surprised to find that cyclizations of 4-(trimethylsilyl)-4-alkenyl acetals occur with loss of the silyl substituent to directly form Δ^4-oxepenes (**Scheme 8**). Although desilylation could conceivably have occurred after cyclization, this scenario was readily excluded by appropriate control experiments. Participation by the ring oxygen in the transfer of an allylic hydrogen is apparently unfavorable in this case, presumably since it would involve a more highly strained bicyclo[3.2.1]heptyl transition structure. As a result, a step-wise process ensues in which Prins cyclization of **32** occurs to form initially the tertiary α-silyl cation **35**, which undergoes a 1,2-hydride shift to yield the more stable β-silyl secondary carbenium ion **36**, the ultimate precursor of **33**. Three subtle effects are responsible for the high-yielding formation of Δ^4-oxepene **33**: (a) initial Prins cyclization occurs in an endocyclic sense as a result of the greater stability of a tertiary α-silyl cation over a primary β-silyl cation,[12] (b) cyclization of the more stable (*E*)-oxocarbenium ion occurs preferentially in a conformation **34** that minimizes destabilizing allylic interactions, and (c) electron-withdrawal by the ring oxygen controls regioselectivity of the hydride migration.

Secondary metabolites of red algae of the genus *Laurencia* have served as a testing ground for these new approaches to seven- and eight-membered cyclic ethers (**Figure 5**).[29-31] Our recent total syntheses of (+)-isolaurepinnacin (**37**)[30] and (+)-laurencin (**38**)[31] provide good illustrations of the utility and selectivity of acetal-alkene cyclizations. The synthesis of (+)-isolaurepinnacin (**37**) is summarized in **Scheme 9**.[30] Mixed acetal cyclization substrate **42** was assembled by silver-promoted coupling of alcohol **40** and α-bromoacetal **41**. The former intermediate was available in five steps from enantiopure epoxy alcohol **39**,[9,32] while **41** was formed in situ from Me_2BBr cleavage[33] of the corresponding (*R*)-α-chloroacetal. Successful cyclization of **42** requires selective activation of only the methoxy group in this substrate containing five distinct Lewis basic functional groups. Not surprisingly, many common Lewis acids were not up to this challenge. Boron trichloride, however, proved uniquely effective affording oxepene **44** in 90% yield, after desilylation. This key conversion was most simply accomplished by treating **42** with a slight excess of BCl_3 at -78 °C and slowly allowing the reaction to warm to 0 °C. At -78 °C, BCl_3 selectively cleaves the methoxy group to afford α,β-dichloroether **43**, an intermediate which can be isolated if the reaction is

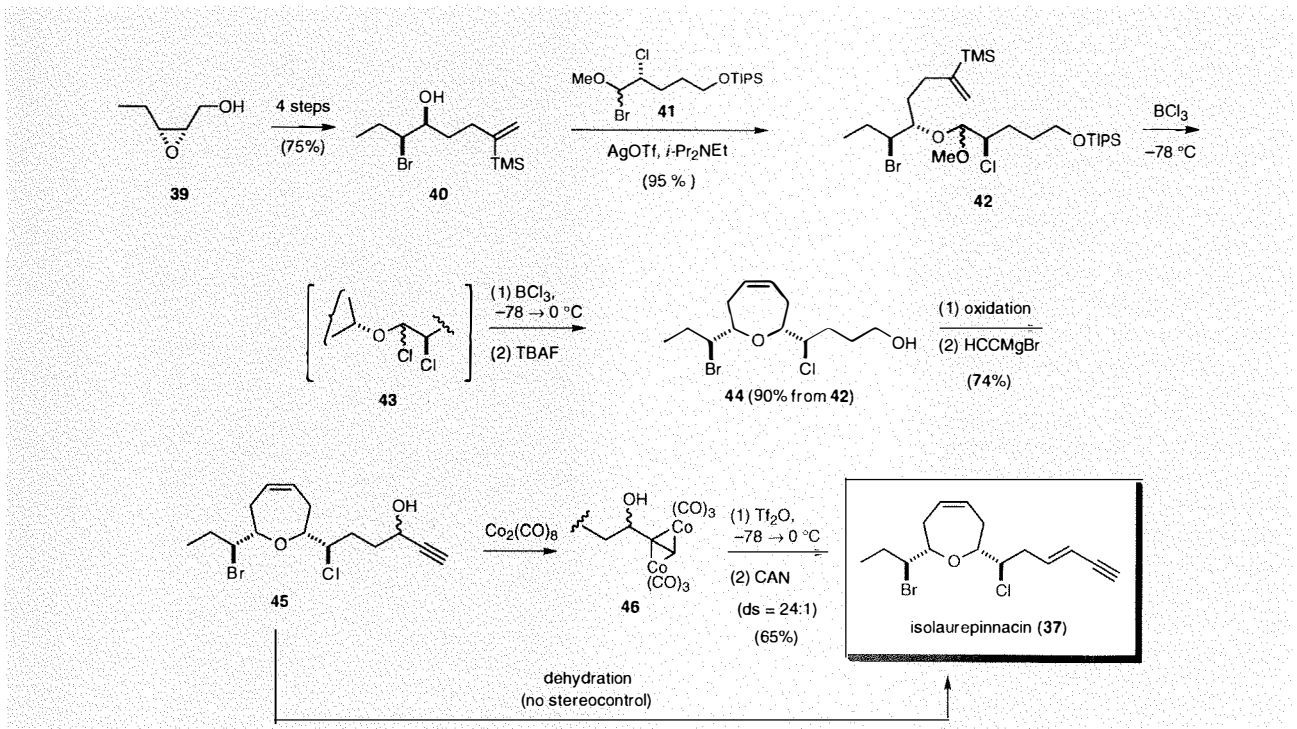


(+)-isolaurepinnacin (**37**)



(+)-laurencin (**38**)

Figure 5. Representative *Laurencia* metabolites synthesized by acetal-alkene cyclizations.



Scheme 9

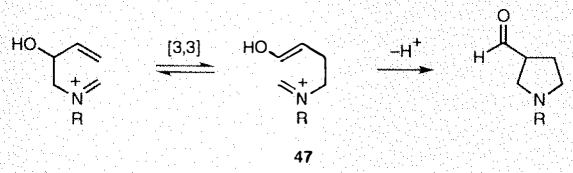
carefully quenched at low temperature. Upon warming in the presence of BCl_3, **43** is cleanly transformed to the TIPS ether precursor of **44**.

The synthesis of (+)-isolaurepinnacin (**37**) was concluded by way of propargylic alcohol **45**. Direct dehydration of this intermediate occurred with little stereocontrol. However, dehydration of the hexacarbonyldicobalt derivative **46**, as suggested by earlier work of Pettit and Nicholas,[34] took place with high selectivity to provide **37** in 65% overall yield from **45** after decomplexation.

This first total synthesis of (+)-isolaurepinnacin (**37**) was achieved in 12 steps and 15% overall yield from *cis*-2-penten-1-ol. The synthesis defined rigorously the *S* configuration of the bromide substituent of **37** which had previously been conjectured on biosynthetic grounds. The regioselective cleavage of the mixed acetal and integrity of the chlorine and bromine substituents realized in the central cyclization step highlight the remarkable selectivity that can be achieved in properly orchestrated acetal-alkene cyclizations.

Aza-Cope-Mannich Reaction

In 1979 when we were pursuing the total synthesis of perhydrogephyrotoxin, a hexahydro derivative of the lead member of another family of amphibian alkaloids,[4] we solved a troubling stereochemical problem by utilizing the [3,3]-sigmatropic rearrangement of unsaturated iminium cations to fashion a key bond.[35] The pyrrolidine synthesis we invented for this purpose is shown in **Scheme 10**.[36] This reaction, often termed the aza-Cope-Mannich reaction, exploits the facility of this charged sigmatropic equilibration and directs the course of the rearrangement by capturing the "product" sigmatropic isomer **47** by an exothermic Mannich cyclization.



Scheme 10

The aza-Cope-Mannich reaction has proven to be a powerful method for assembling a wide variety of nitrogen heterocycles. Several simple examples are illustrated in **Figure 6**.[37,38] The reaction can be accomplished by direct condensation of a homoallylic amine containing hydroxyl or alkoxyl substitution at the allylic site with an aldehyde (or acetal) in the presence of an equivalent or less of acid. Alternatively, aza-Cope-Mannich reorganization can be triggered by loss of cyanide from an appropriate cyanoalkylamine or from ring opening of a 5-vinyloxazolidine. All of these variations are illustrated in **Figure 6**. The reaction takes place under notably mild conditions: typically near room temperature and at neutral pH (basic amine and ≤ 1 equivalent of acid). These gentle conditions are undoubtedly responsible for the success of this reaction with labile aldehydes such as furfural and also for the reaction's compatibility with tertiary allylic alcohol functionality. Also apparent in the examples depicted in **Figure 6** is the wide variation possible in the alkene component, which can be unsubstituted or contain electron-donating or electron-withdrawing substituents. A hallmark of the aza-Cope-Mannich reaction is its superb stereoselectivity. The high

stereocontrol realized in the conversion of **48** to **49** (ds = 24:1), and the companion study of the corresponding *Z* stereoisomer, establishes that the iminium ion sigmatropic rearrangement occurs preferentially in a chair topography identical to Cope rearrangement of simple 1,5-dienes.[37g] If the vicinal amine and alcohol groups are located on a ring, the aza-Cope-Mannich reaction achieves an unusual construction in which pyrrolidine annulation is coupled with one-carbon expansion of the starting ring (e.g., the last three entries of **Figure 6**).

During the past 15 years we have employed the aza-Cope-Mannich reaction as the central strategic element in total syntheses of more than a dozen alkaloids.[35,39-45] Representative examples are shown in **Figure 7** in which the fragment that derives from the central 3-acylpyrrolidine unit of the aza-Cope-Mannich product is shown in boldface print.

Our recent enantioselective total syntheses of (–)- and (+)-strychnine provide an instructive benchmark of the utility of the aza-Cope-Mannich reaction to solve formidable problems in alkaloid construction.[45] The synthesis plan that evolved in our laboratory over the period of several years is summarized in **Scheme 11** for the preparation of natural (–)-strychnine (**50**). Aza-Cope-Mannich reaction of azabicyclooctane **53** was expected to provide tetracycle **52**, an intermediate which encodes the critical D, E, and F rings and the *Z* double bond of the heptacyclic strychnine skeleton. Tactics developed during our earlier synthesis of (±)-akuammicine, a much simpler *Strychnos* alkaloid, projected assembly of **53** from cyclopentenylstannane **54**, carbon monoxide, and an appropriately protected derivative of 2-iodoaniline.[43]

The synthesis of (–)-strychnine (**50**) begins with (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate (**56**), which is available in high enantiomeric purity from enantioselective hydrolysis of *meso* diacetate **55** with several enzyme preparations (**Scheme 12**).[46] Conversion of **56** to carbonate derivative **57** followed by selective palladium-catalyzed activation of the allylic carbonate unit[47] and coupling with β-ketoester anion **58** provided adduct **59**. Without separation, both stereoisomers of this intermediate were converted, by way of the (*E*)-α,β-unsaturated ester **60**, to cyclopentenylstannane **61**. Carbonylative cross coupling of **61** with 2-iodoaniline derivative **62** delivered cyclopentenyl aryl ketone **63**. The efficiency realized in this important step

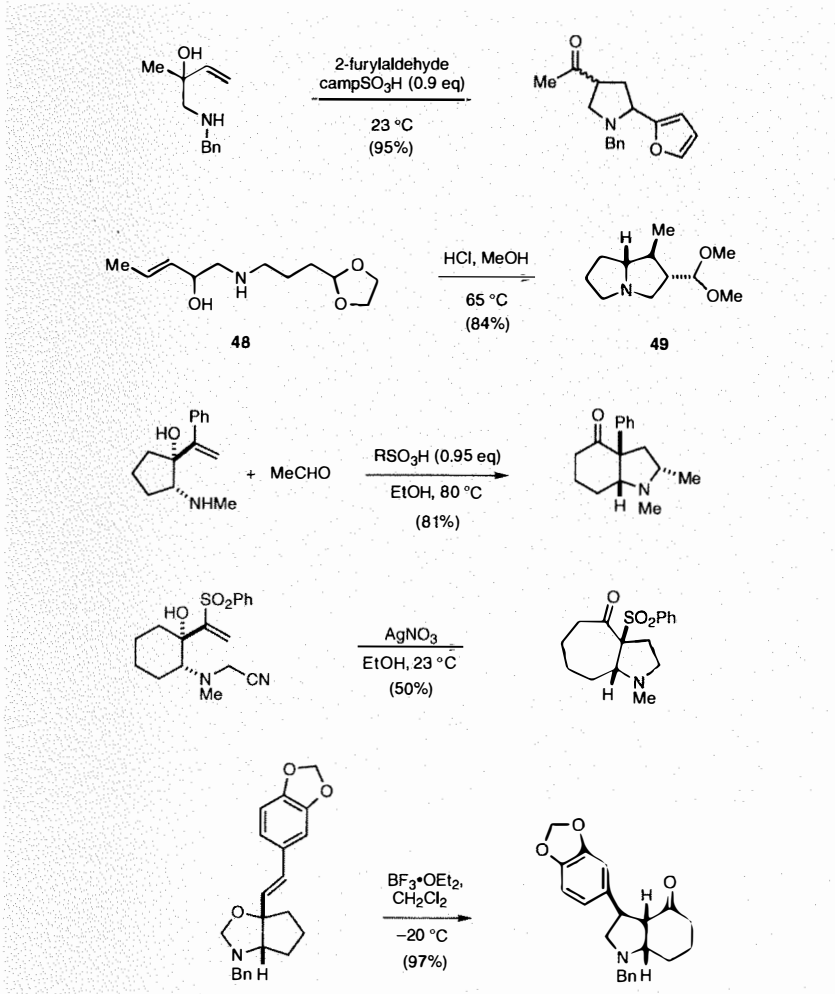


Figure 6. Representative aza-Cope-Mannich reactions.

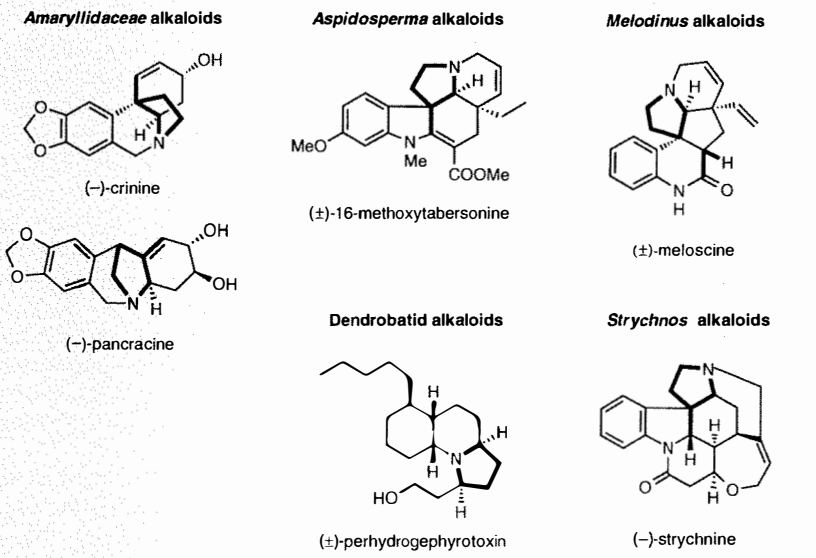
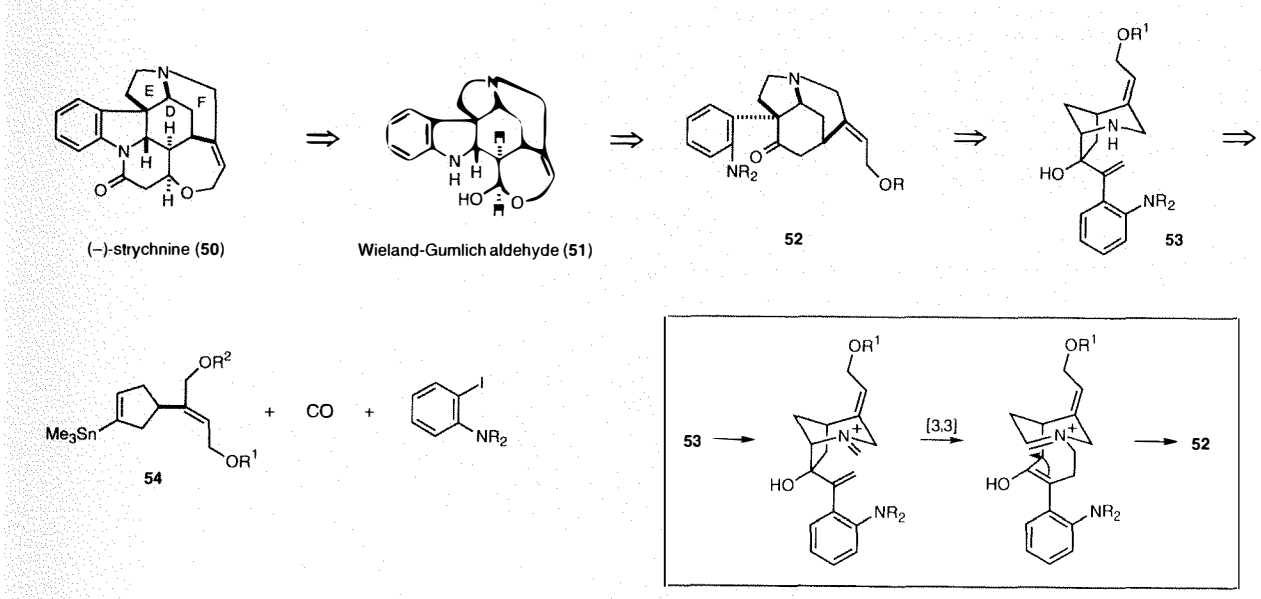
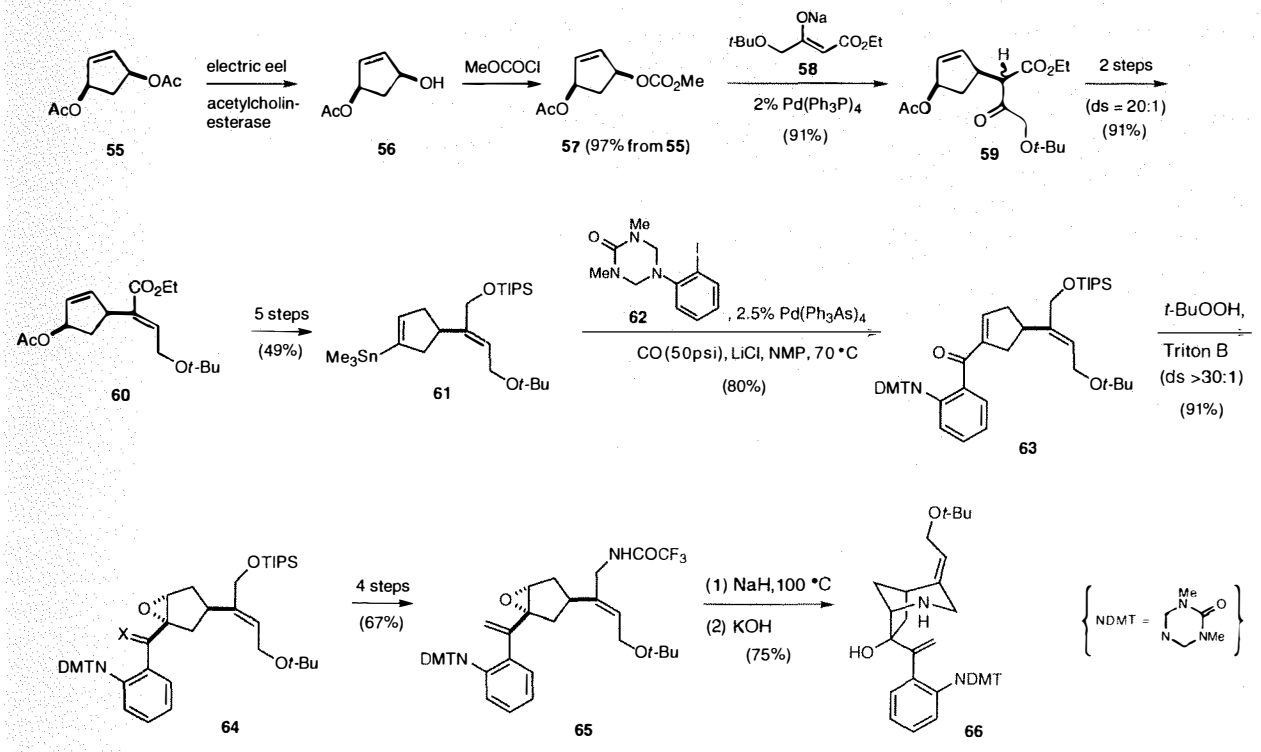


Figure 7. Representative alkaloid total syntheses accomplished using the aza-Cope-Mannich reaction as the key step. The 3-acylpyrrolidine subunit is shown in bold.



Scheme 11



Scheme 12

benefited greatly from Knapp's introduction of the triazone group for protecting primary amino groups[48] and recent optimizations of Stille cross-coupling procedures.[49] Stereoselective epoxidation of **63** yielded oxirane **64**, which was elaborated in four straightforward steps to trifluoroacetamide **65**. Finally, base-promoted intramolecular aminolysis of **65** and cleavage of the trifluoroacetyl group provided azabicyclooctane **66**.

The pivotal aza-Cope-Mannich conversion of **66** to tetracyclic intermediate **67** took place *stereoselectively in near quantitative yield* when **66** was heated in acetonitrile in the presence of paraformaldehyde and Na_2SO_4 (**Scheme 13**). Carbomethoxylation of **67** followed by heating the resulting β-ketoester in methanolic HCl resulted in cleavage of both the triazone and *t*-butyl protecting groups and dehydrative cyclization to yield 18-hydroxyakuammicine (**68**) in 70% overall yield. Following precedents

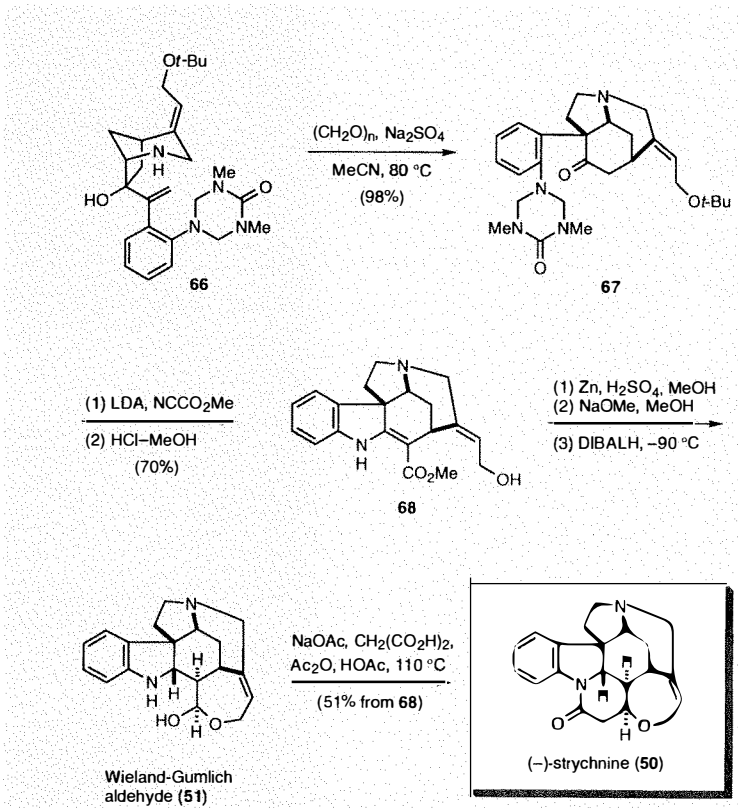
recorded during early structural studies of *Strychnos* alkaloids, the vinylogous urethane unit of **68** was saturated.[50] The resulting β-oriented methyl ester was then reduced at low temperature to provide the Wieland-Gumlich aldehyde (**51**). Classical Perkin condensation of **51** with malonic acid[51] then afforded enantiopure (–)-strychnine (**50**).

This first asymmetric total synthesis of (–)-strychnine (**50**) was achieved in 24 steps and 3% overall yield from *meso* diester **55**. Slight modification of this synthesis provided the first samples of *ent*-strychnine.[45] Biological studies of this unnatural enantiomer demonstrated, for the first time, that three-dimensional interactions are critical in the binding of (–)-strychnine to the inhibitory glycine receptor.[52]

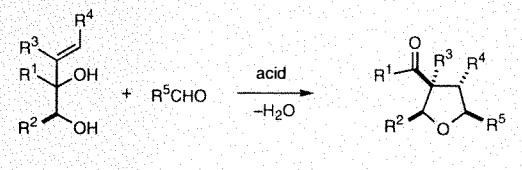
Synthesis of Cyclic Ethers by Prins-Pinacol Rearrangements

The condensation of allylic diols with carbonyl compounds to form 3-acyltetrahydrofurans would represent a logical extension of our acylpyrrolidine synthesis (**Scheme 14**). Not surprisingly, this tetrahydrofuran synthesis had been discovered by accident many years earlier during attempts to prepare acetals from allylic diols.[53] In recent years we have explored the scope of this reaction in some detail, and representative examples of this highly stereocontrolled synthesis of cyclic ethers are shown in **Figure 8**.[54,55] The rearrangement can be conveniently triggered at low temperature by treating an acetal intermediate with any of a number of Lewis acids, although we typically find that $SnCl_4$ is preferred. Alternatively, many aldehydes and some ketones can be directly condensed with allylic diols in the presence of acid. In these latter cases we find that BF_3•OEt_2 is optimal.

Several of the most characteristic features of this synthesis of cyclic ethers are illustrated in the transformations depicted in **Figure 8**. The reaction delivers tetrahydrofurans having a *cis* relationship of the substituents flanking oxygen and the 3-acyl substituent, while the alkene unit is incorporated in a suprafacial fashion. In most cases, both the *syn* and *anti* diol stereoisomers provide the same tetrahydrofuran product, as exemplified in the evolution of acetals **69** (a mixture of four diastereomers derived from a 1:1 mixture of diol stereoisomers) to a single tetrahydrofuran **70**. Tetrahydrofurans of high enantiomeric purity can be obtained from reactions of enantiopure allylic diols with



Scheme 13



Scheme 14

aldehydes and ketones, for example, the conversion of **71** to **72**. This enantioselective construction of substituted tetrahydrofurans has been made particularly attractive by recent advances in the synthesis of enantioenriched allylic diols.[56]

Analogous to the aza-Cope-Mannich reaction, we anticipated that this tetrahydrofuran synthesis would involve a sigmatropic rearrangement (in this case an unknown 2-oxonia[3,3]sigmatropic rearrangement) followed by an intramolecular aldol cyclization. However, mechanistic investigations suggest an alternative, Prins cyclization-pinacol rearrangement pathway (**Scheme 15**).[54b] In this description the observed stereochemical outcome follows from a preference for chair topographies in both the cyclization and pinacol rearrangement steps, for example, the conversion of **73** to **74** to **70**. Illustrated also in **Scheme 15** is an important feature that contributes to the success and utility of this tetrahydrofuran synthesis: only one mode of ring-opening of acetal **69** is productive. Thus, there is no need to engineer selective formation of a single oxonium ion intermediate.

A good illustration of the strategic use of this tetrahydrofuran synthesis in complex molecule construction is provided by our recent enantioselective total synthesis of 7-deacetoxyalcyonin acetate (**75**), a member of the eunicellin diterpenes which was isolated from the soft coral *Eunicella stricta* (**Figure 9**).[57] Eunicellin (**76**) was the first characterized member of this structurally distinctive marine natural products

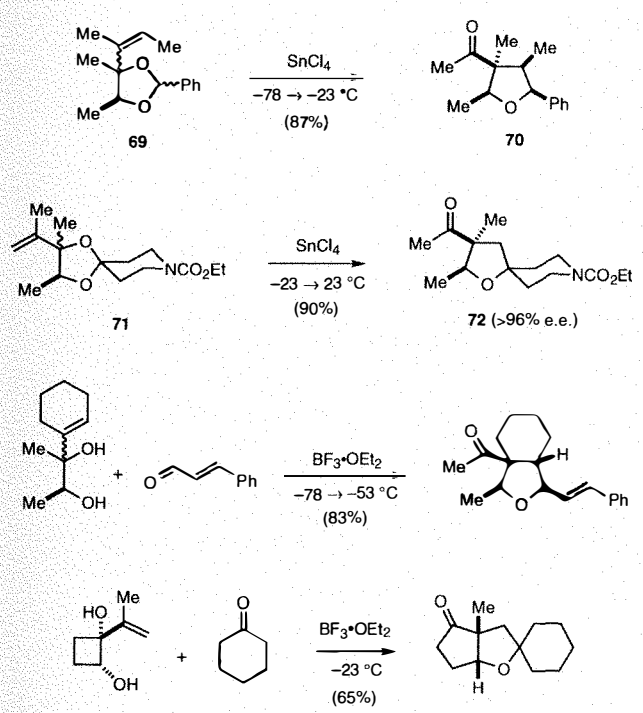


Figure 8. Preparation of representative 3-acyltetrahydrofurans by Prins-pinacol reactions.

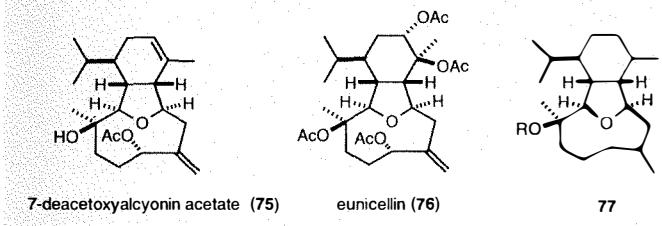


Figure 9. Representative eunicellin diterpenes and their common skeleton.

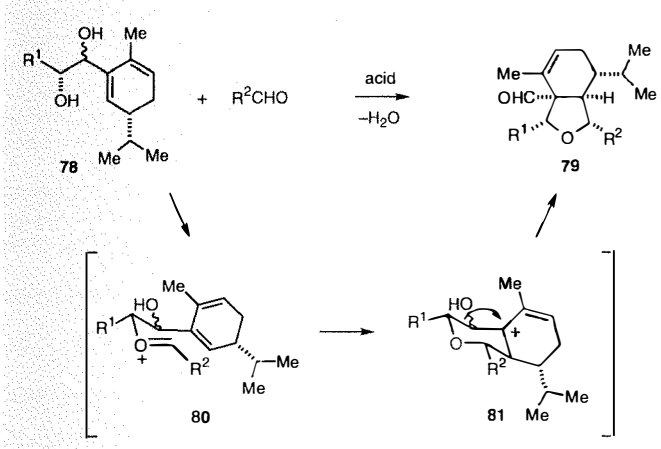
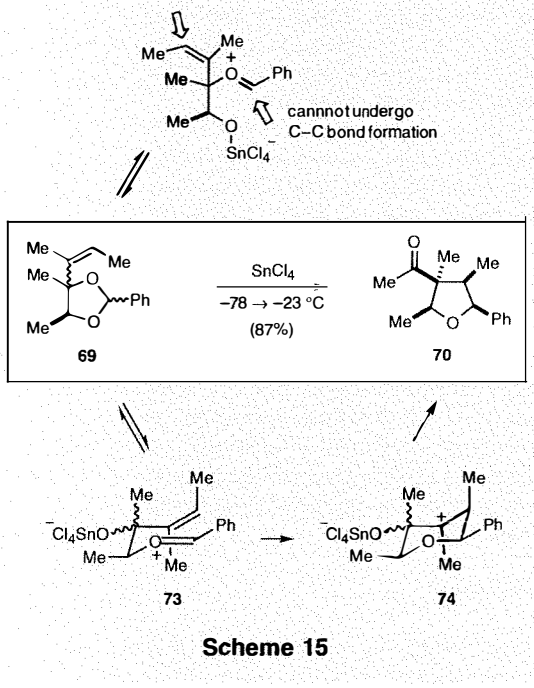


Figure 10. Stereochemical analysis of the key Prins-pinacol reaction.



Scheme 15

group which numbers ~50 members.[58] These diterpenes are characterized by a unique oxatricyclic ring system composed of hydroisobenzofuran and oxonane units. This skeleton and the six stereocenters that are believed to be common to this family of marine metabolites are depicted in structure **77**.

Our plan for preparing the eunicellin diterpenes was guided by the perception that Prins-pinacol condensation-rearrangement of a dienyl diol such as **78** and an aldehyde would assemble in one step the distinctive hexahydroisobenzofuran core **79** of these diterpenes (**Figure 10**). If the formyl group could be excised with retention of stereochemistry, this key reaction would also comprehensively deal with five of the six stereocenters common to the eunicellin diterpenes. The stereochemical outcome of this central reaction was anticipated to derive from chair topography cyclization of the more stable (*E*)-oxocarbenium ion intermediate **80** from the diene face opposite the isopropyl substituent to form allylic carbocation **81**. The preference for this cyclization conformer would be reinforced by the R^1 substituent, which adopts a favored equatorial orientation in **80**.

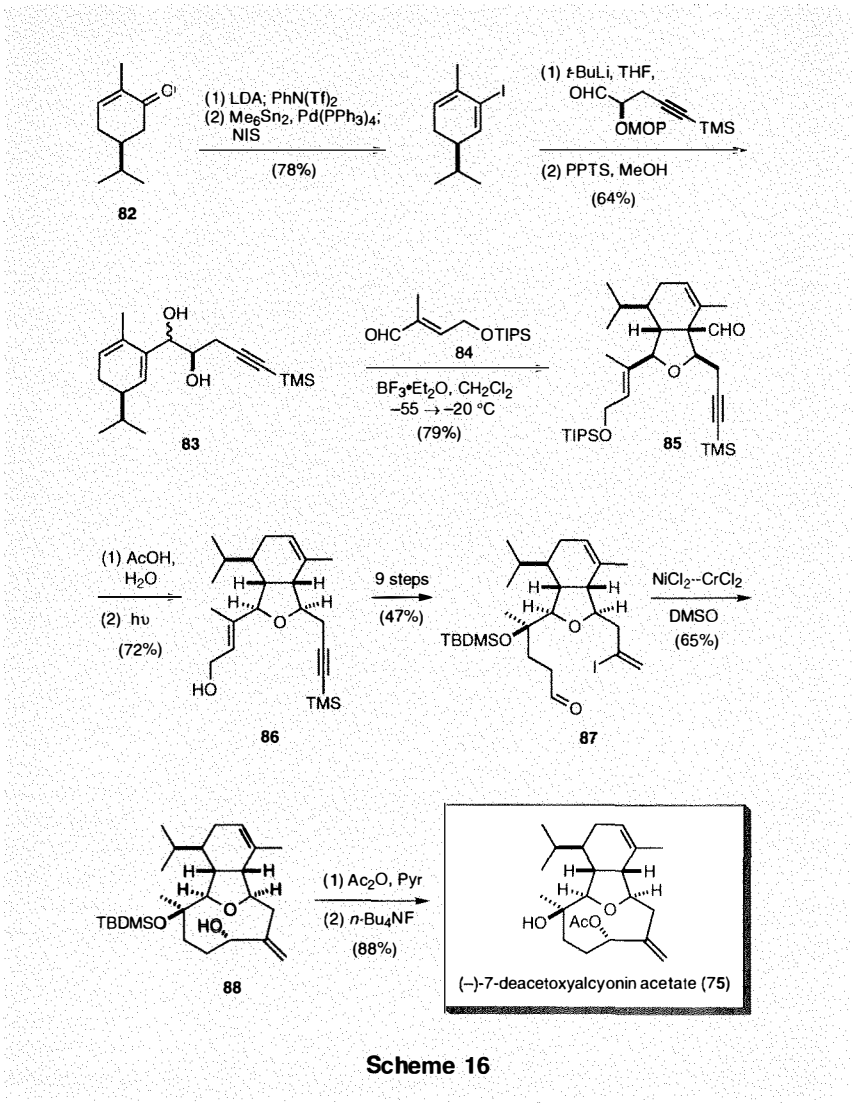
Our recent reduction of this scheme to practice resulted in the first total synthesis of an eunicellin diterpene and is summarized in **Scheme 16**. Rearrangement substrate **83** was assembled in four steps in 50% overall yield from dihydrocarvone (**82**). It was a 9:1 mixture of *anti* and *syn* stereoisomers and was taken directly into the central cyclization step. Exposure of **83** to an excess of readily available enal **84** and BF_3•OEt_2 at low temperature afforded hexahydroisobenzofuran **85** as a single stereoisomer in 79% yield. Cleavage of the TIPS ether followed by photolysis through a pyrex filter provided bicyclic ether **86** in 72% yield. That loss of carbon monoxide would proceed with retention of configuration and with minimal allylic rearrangement was expected from earlier studies of the

deformylation of β,γ-unsaturated aldehydes by Jeger and Schaffner.[59] Intermediate **86**, which contains the complete bicyclic core of 7-deacetoxyalcyonin acetate (**75**), is available in 8 steps and 28% overall yield from (*S*)-carvone.

The synthesis of **75** was completed by elaboration of **86** in a multistep, yet efficient, sequence to **87**. The final ring was then forged by Nozaki-Kishi cyclization[60] of **87** which proceeded with high (>20:1) stereoselection to afford **88** in good yield. The stereochemical outcome of this final key step is controlled by torsional and transannular interactions in the forming nine-membered oxacyclic ring. A brief analysis of this important stereochemical issue can be found in our original report.[57] Acetylation of **88** followed by desilylation then provided (−)-deacetoxyalcyonin acetate (**75**).

Conclusion

The reactions highlighted in this discussion allow a number of complex nitrogen and oxygen heterocycles to be synthesized in a concise fashion. High stereochemical selectivity and broad compatibility with intricate functionality are hallmarks of these transformations. Another distinctive and attractive feature of these heterocyclization reactions is their "low-tech" nature. Generation of solvated iminium or oxonium ion species is all that is required to initiate the ring-forming process. Finally, and of particular significance, these carbon-carbon bond-forming cyclization reactions allow new strategies to be employed in the synthesis of complex heterocycles and heterocyclic natural products.



Scheme 16

Acknowledgments

I express my special appreciation and admiration to my co-workers whose experimental skill and creativity have made our accomplishments in synthetic organic chemistry possible. Those who contributed to the programs reviewed here are cited in the references. To my teachers, Gerald Bakker, Howard W. Whitlock, Jr., and Ronald C. D. Breslow, I owe special thanks for provoking and nurturing my love affair with organic chemistry. To my colleagues at the University of California, Irvine I owe a special debt for their support and much lively discussion over the years. Finally, I would like to warmly thank Samuel J. Danishefsky, David A. Evans, Clayton H. Heathcock, and Gilbert Stork for their impeccable example, encouragement and support.

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About the author

Larry E. Overman was born in Chicago, Illinois in 1943 and raised in Hammond, Indiana where he attended public schools. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr. at the University of Wisconsin. After an NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine in 1971 where he is now Distinguished Professor of Chemistry. Professor Overman was chair of the Department of Chemistry at UCI from 1990-1993.

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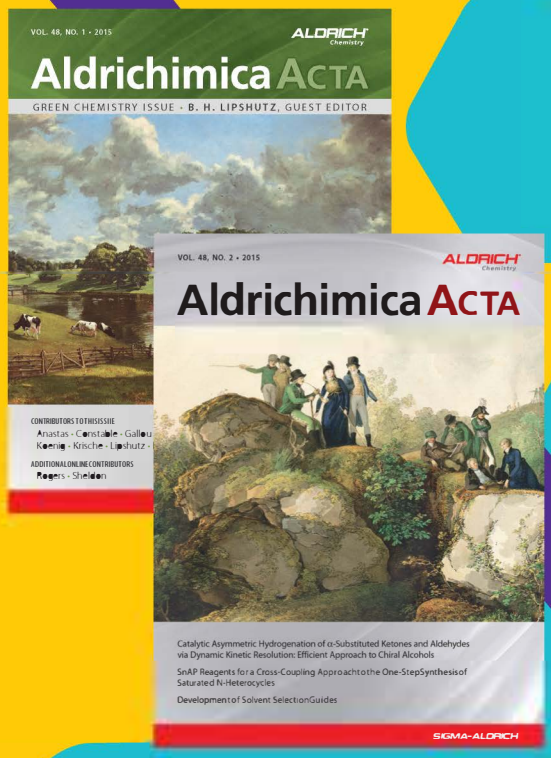

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