Aldrichimica Acta

Volume 14, Number 1, 1981

Synthesis and Applications of Vinylic Organoboranes
Chemical Reactions of Newly Available Pyridines

Special — Deuterated Solvent Brochure

chemists helping chemists in research & industry

aldrich chemical co.

Aldrichimica Acta

Volume 14, Number 1, 1981
A publication of the ALDRICH CHEMICAL COMPANY

Main Sales Office:
P.O. Box 355
Milwaukee, Wisconsin 53201
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6300
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo, Japan
Telephone: 03-258-0155.0156
TWX: 2222518

In Israel:
Sigma Israel Chemical Co.
P.O. Box 37673
Tel Aviv, Israel 61360
Telephone: 03-612315
Telex: (922) 35645

About Our Cover:

This moving depiction of *Jesus and the Samaritan Woman at the Well* (John *4*) is one of the great puzzles in our chemist's collection. The subject was a favorite of Rembrandt and several of his students have been suggested as the artist, for instance, Carel Fabritius, probably Rembrandt's ablest and most inventive student, and Gerbrand van den Eeckhout who became Rembrandt's great friend. Our chemist believes it is by neither but has, as yet, no plausible solution—beauty in search of its creator is no less beautiful because of our ignorance.

The painting is a symphony of colors and shadows. The dominant colors are very unusual—violets and blues, and the concentration on shadow dominates the work: her shadow and the shadow of Jesus' hand, the focus of the whole.

This large work (oil on canvas, 43-1/4 x 33-1/2") was probably painted in the 1640's. It is unusual not only for its color, composition and the breathtaking psychological relationship—Jesus' great care for the woman—but also its execution: part of the foliage was painted with the brush handle cutting into the paint film. This technique was used by Rembrandt and his last student, Aert de Gelder, in the second half of the 17th century and may, in time, provide a clue to the artist of this masterpiece.

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

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

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

Lab Notes

We have found that one of the frequent causes of poor resolution in routine NMR work is the presence of paramagnetic particles adhering to the inside of the tube from the washing process. If a cotton plug is placed in the bottom of the inlet of a tube washer (such as your Z10,724-7) and samples are always filtered through a cotton plug, the tubes never come in contact with unfiltered solvent and remain free of these particles.

Douglas A. Livingston
Department of Chemistry
Columbia University
New York, NY 10027

Did you ever leave a water-cooled condenser on overnight then find water all over the floor the next morning because the latex tubing popped off the joint of the condenser? A cable tie, a piece of plastic approximately 1/8" x 3-1/2" used to tie electrical wires together, can prevent this occurence. To install, place latex tubing over inlet/outlet to condenser. Pull cable tie tightly around tubing and joint. To remove cable tie, slit the tie with a razor blade.

Becky Eubank
Commercial Lab Application
POLAROID
Assonet, MA 02702

Editor's Note: Aldrich offers a tie for this application.

A common problem inherent with the daily usage of gas chromatographs is the eventual breakage or deactivation of the ignition filament incorporated within its self-contained detector unit. Replacement usually necessitates the inconvenience and expense of a service call by a factory representative. Alternatively, flame ignition may be brought about directly by using a match — a dangerous procedure which usually contaminates the detector — or by implementing a commercially available "Electric Match" or other portable spark source.

However, in our laboratory, a simple, inexpensive and readily available soldering gun has been employed effectively and safely over the past several years to ignite various self-contained flame-ionization detectors. The soldering gun is a "pistol" type, Model 199 manufactured by Wen with replaceable tips and is available at a very nominal price. Detector ignition is accomplished in the usual manner except for the external placement of the hot probe over the detector port. The tip geometry of this soldering gun is easily modified to adapt to various detector designs.

This type of external flame ignitor offers several advantages. Its construction is extremely durable and safe as well as simple and convenient to operate. The physical thickness of the ignition probe effectively eliminates the need for frequent tip replacements while clean ignitions are achieved without imparting contaminating residues to the detector. Most significantly, this approach appears to be independent of detector design and can be used without causing electrical damage to the internal circuitry of the detector unit.

Peter D. Frade, Ph.D.
Annetta R. Kelly, Ph.D.
Department of Pathology
Division of Pharmacology and Toxicology
Henry Ford Hospital
Detroit, Michigan 48202

The violent "bumping" of certain liquids during vacuum distillation may be effectively prevented by merely packing the distillation flask with glass wool and distilling as usual. This method is effective even when the addition of boiling stones has proven useless.

David J. Eickhoff
Laboratory Technician
Procter & Gamble Co.
Miami Valley Labs
Cincinnati, Ohio 45247

P.S. Credit for this technique goes to Dr. E.D. Mihelich who first showed it to me.

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

"Please Bother Us."

by Ronald Bader.

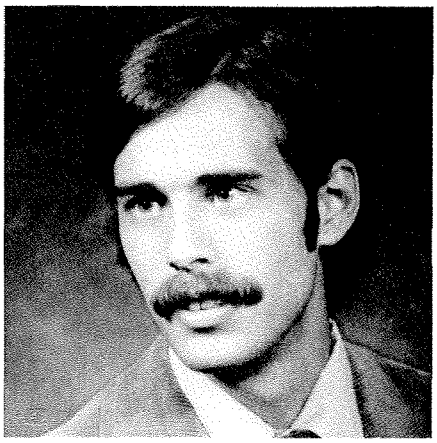
Mr. John Fulmer of the General Electric Company Plastics Division wrote to me recently to suggest that we synthesize 2-methylbenzofuran as an analytical standard. Mr. Fulmer explained that this "is a byproduct impurity in the commercial synthesis of phenol from cumene. Almost three billion pounds of phenol is produced annually in the U.S. All of the major industrial phenol producers (Monsanto, Allied, Dow, General Electric, Georgia Pacific, USS Chemicals, Shell Chemical) require gram quantities of 2-methylbenzofuran on a continuing basis for gas chromatograph and UV standardizations. No one in the *world* offers it."

Naturally, we made it.

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

Synthesis and Applications of Vinylic Organoboranes*

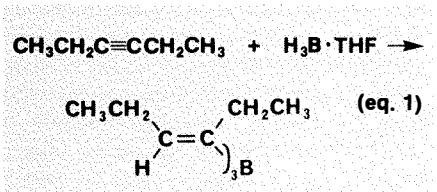
Herbert C. Brown
and James B. Campbell, Jr.
R.B. Wetherill Chemistry Laboratory
Purdue University
West Lafayette, Indiana 47907



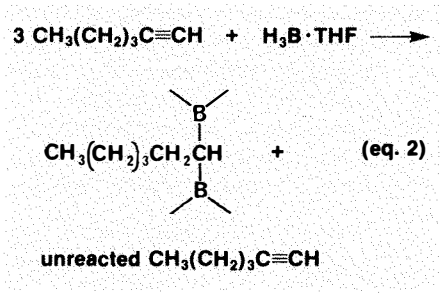
I. INTRODUCTION

The hydroboration of olefins with diborane in ether solvents provides a convenient synthesis of aliphatic and alicyclic organoboranes.[1] The resulting organoboranes have proven to be exceptionally useful synthetic reagents.[2]

Early work which attempted to extend hydroboration with borane to alkynes as a route to the vinylic organoboranes, met with limited success. While the reaction of internal alkynes with diborane provides the trialkenylboranes in moderate yields (eq. 1), terminal alkynes yield little or none of

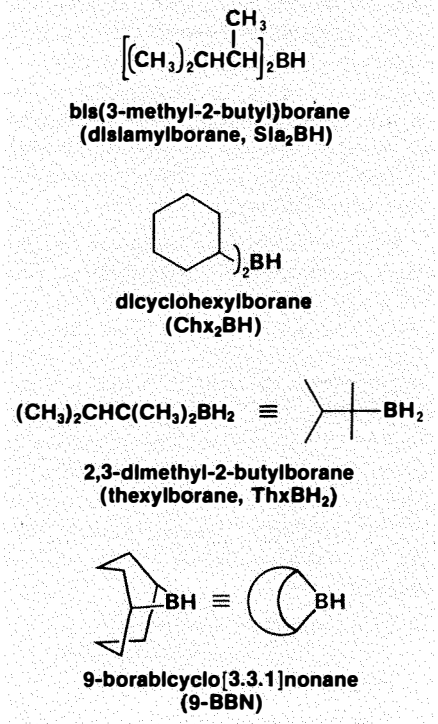


the desired alkenylborane.[3] Apparently dihydroboration competes with monohydroboration in the case of internal acetylenes, becoming the predominant reaction in the case of terminal acetylenes (eq. 2).



The large steric requirements of certain olefins apparently hinder reaction with $H_3B\cdot THF$ beyond the formation of the corresponding mono- or dialkylboranes.[2c,d] This feature makes possible the convenient synthesis of several mono- and dialkylboranes and their utilization as desirable hydroborating reagents. Many of these reagents exhibit highly selective behavior in the hydroboration of olefins. Consequently, they appeared attractive as precursors for the controlled monohydroboration of acetylenes for the synthesis of the desired vinylic boranes. In fact, all of the mono- and dialkylborane reagents indicated in Fig. 1 have demonstrated utility for such monohydroboration of alkynes. The later introduction of several other heterosubstituted boranes as hydroborating reagents further expanded the availability of reagents for preparing vinylic boranes from acetylenes (Fig. 2).

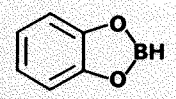
FIGURE 1. MONO- AND DIALKYLBORANE HYDROBORATING AGENTS



All the reagents illustrated permit the controlled monohydroboration of both terminal and internal alkynes to provide the corresponding vinylic boranes. The mildness of the reagents tolerates the

*Based in part upon lectures presented at the Symposium on Synthesis and Chemistry of Acetylenic Compounds, Division of Petroleum Chemistry, Meeting of the American Chemical Society, Honolulu, Hawaii, April 1-6, 1979, and the International Symposium on Metallo-Organics in Organic Synthesis, Perkin Division, The Royal Society of Chemistry, University College, Swansea, Wales, UK, July 14-17, 1980.

FIGURE 2. HETEROSUBSTITUTED BORANES AS HYDROBORATING AGENTS



1,3,2-dioxabenzoborole (catecholborane, CtO_2BH)

$H_2BCl \cdot OEt_2$ monochloroborane-ethyl etherate

$HBCl_2 \cdot OEt_2$ dichloroborane-ethyl etherate

$H_2BCl \cdot SMe_2$ monochloroborane-methyl sulfide

$HBBr_2 \cdot SMe_2$ dibromoborane-methyl sulfide

presence of a wide variety of functional groups, such as ester, ether, halogen, and nitrile. The stereospecific *cis* nature of hydroboration gives exclusively the *trans*-alkenylboranes, often also in high regioisomeric purity. Subsequent reactions of the alkenylboranes usually proceed by stereodefined pathways, thus allowing highly stereo- and regiospecific syntheses.

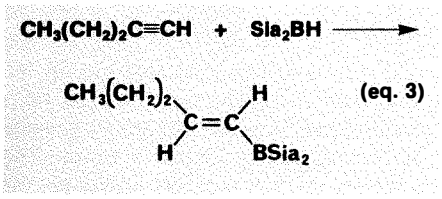
Many of the mono- and difunctional hydroborating reagents exhibit diverse reactivity characteristics toward different unsaturated substrates. Thus, the availability of an array of hydroborating reagents to convert alkynes to the alkenylboron compounds expands the synthetic capability immensely. A wide spectrum of possible selective transformations of an alkyne in the presence of various functional groups, alkenes, or even structurally different alkynes may then be conducted *via* hydroboration.

With the evolution of each new reagent came an advance in the capability of performing selective transformations of alkynes by hydroboration. Thus, each new reagent will be discussed in a more or less chronological perspective. A separate section will examine directive effects in the hydroboration of several unsymmetrically substituted alkynes. Finally, representative transformations of the vinylic boranes or the diboraalkanes, readily available now *via* the hydroboration of alkynes, will be presented.

II. HYDROBORATION OF ALKYNES WITH BORANE DERIVATIVES

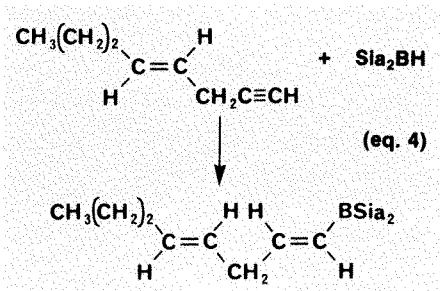
A. Disiamylborane

Reaction of either terminal or internal alkynes with disiamylborane at 0° proceeds rapidly to form the alkenyldisiamylboranes[3] (eq. 3). Competing dihydroboration is insignificant even with an excess of the borane present, thus overcoming the difficulties associated with $H_3B \cdot THF$ as the hydroborating agent. Apparently the high steric requirements of disiamylborane minimize further reaction with the alkenylborane.



(eq. 3)

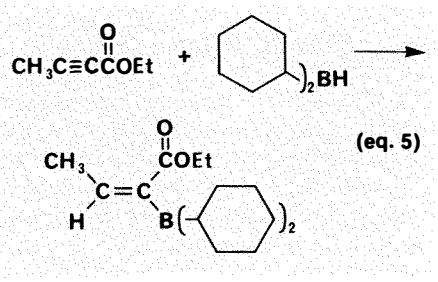
While diborane in THF is fairly nondiscriminating among unsaturated substrates, disiamylborane reveals a far more selective reactivity. In fact, an internal or terminal alkyne can be selectively hydroborated with disiamylborane in the presence of all but unhindered terminal olefins[4,5a] (eq. 4).



(eq. 4)

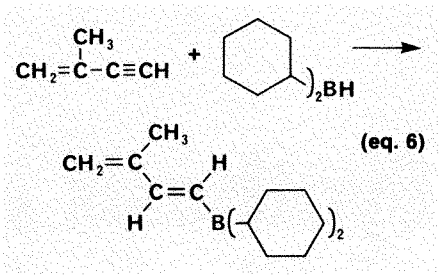
B. Dicyclohexylborane

In many cases, dicyclohexylborane may be substituted for disiamylborane. However, the slightly lower steric requirements of dicyclohexylborane may allow dihydroboration of the alkyne,[6] but careful control of the reaction conditions affords the corresponding alkenyldicyclohexylboranes in excellent yields[7] (eq. 5).



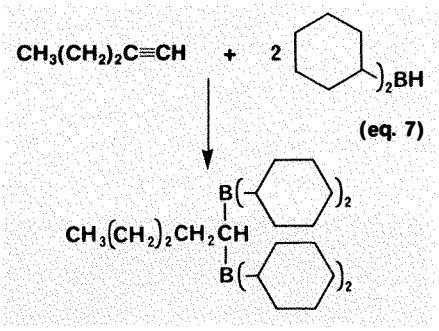
(eq. 5)

Although the relative reactivity of olefinic and acetylenic substrates toward dicyclohexylborane has not been quantitatively established, selective hydroborations are also achievable[8] (eq. 6).



(eq. 6)

Hydroboration of 1-alkynes with two equivalents of dicyclohexylborane results in exclusive formation of the 1,1-diboraalkanes[6] (eq. 7). Thus, direct access to such

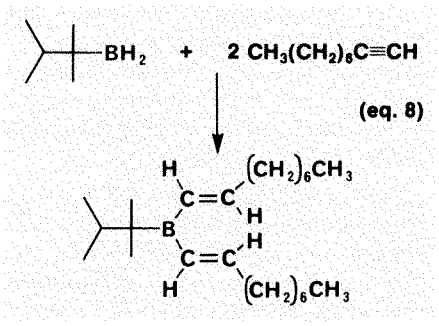


(eq. 7)

geminal organometallics can be accomplished virtually quantitatively from any 1-alkyne and dicyclohexylborane.

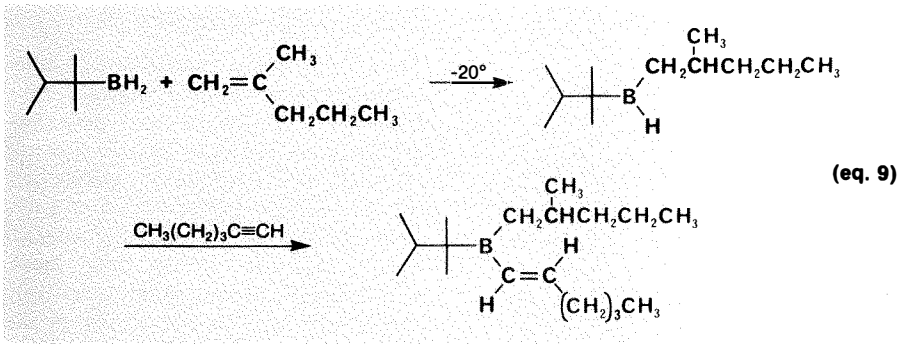
C. Thexylborane and Thexylmonoalkylboranes

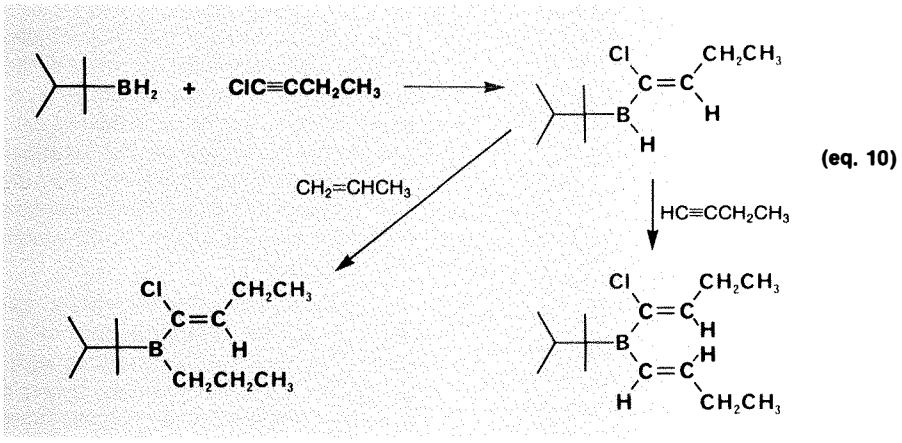
Thexylborane is unique among the available alkylborane hydroborating reagents because of its difunctional nature.[5a] Reaction of two equivalents of a 1-alkyne with thexylborane cleanly produces the thexyldialkenylborane[9] (eq. 8). With the exception of simple terminal



(eq. 8)

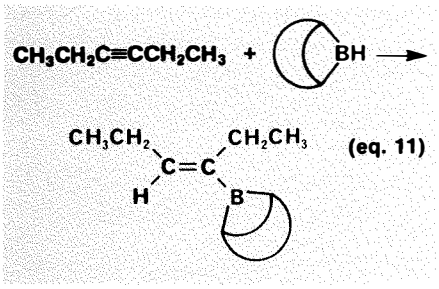
olefins, the controlled low-temperature hydroboration of all other olefins with thexylborane provides the corresponding thexylmonoalkylboranes in nearly quantitative yield. Subsequent addition of an alkyne gives the mixed thexyldialkenylborane[10] (eq. 9). Although reaction of thexylborane with one equivalent of a 1-alkyne does not cleanly afford the thexylmonoalkenylborane, reaction with either a 1-chloro- or 1-bromoalkyne does provide the thexyl-1-halo-1-alkenylborane[11] (eq. 10). This monofunctional alkenylborane may then be used to prepare either mixed thexyldialkenyl- or thexylalkylalkenylboranes.



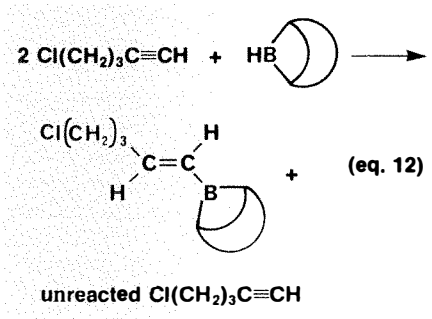


D. 9-BBN

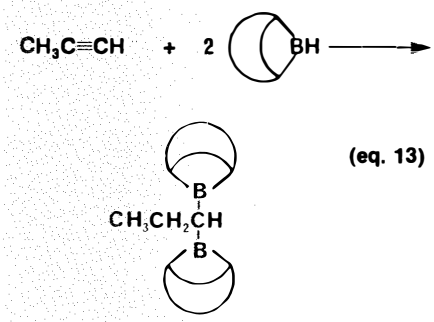
Of the alkyl-substituted hydroboration reagents, 9-BBN possesses by far the greatest thermal and oxidative stability.[12] The reagent, a crystalline solid, may be stored for long periods of time under nitrogen and is in fact commercially available.[5b] Reaction of 9-BBN with internal alkynes affords the *B*-alkenyl-9-BBN derivatives in good yields[13] (eq. 11).



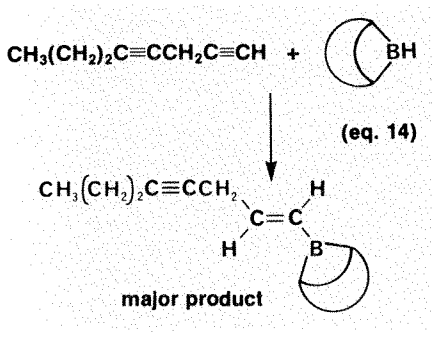
However, addition of 9-BBN to a 1-alkyne in stoichiometric quantities leads to the formation of substantial amounts of the dihydroboration product along with the desired alkenylborane. Presumably the openness of the boron atom in the 9-BBN moiety permits further reaction with the intermediate alkenylborane to give the 1,1-diboraalkane. However, use of a considerable excess of 1-alkyne, usually 100%, suppresses dihydroboration, yielding the desired alkenylborane in excellent yield[13] (eq. 12). The excess alkyne is generally easily recovered. The resulting *B*-alkenyl-9-BBN derivative is stable and can be isolated by vacuum distillation, if desired, to obtain the pure alkenylborane.



Addition of two equivalents of 9-BBN to the 1-alkyne readily produces the 1,1-diboraalkane in nearly quantitative yield (eq. 13), providing an alternative route to such derivatives.[14]

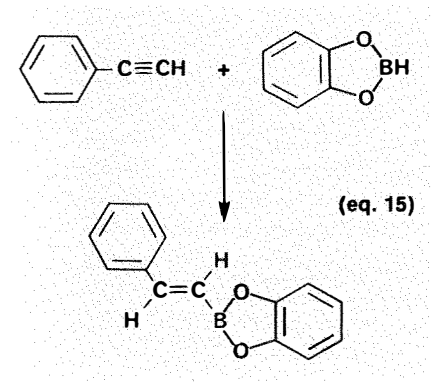


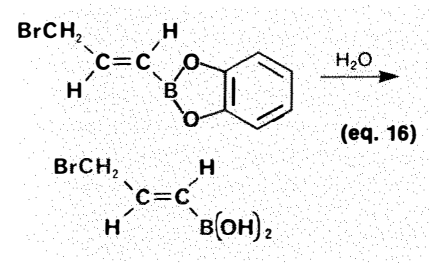
Unlike many of the other dialkylborane hydroborating reagents, 9-BBN demonstrates a significantly different reactivity toward unsaturated substrates. In general, unhindered terminal olefins react more readily than terminal and internal alkynes, while terminal alkynes react more readily than internal alkynes[15] (eq. 14).



E. Catecholborane

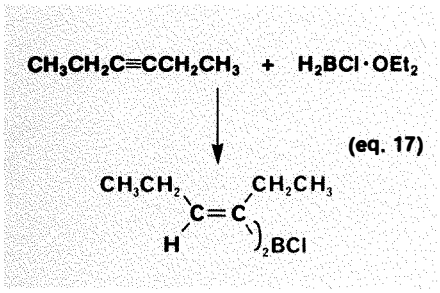
Addition of one equivalent of catechol to an equivalent of borane in THF gives the monofunctional reagent, catecholborane.[16,5b] The reaction of alkynes with catecholborane proceeds quite sluggishly at room temperature. However, at elevated temperatures, in refluxing tetrahydrofuran, the reaction proceeds smoothly to give the alkenylcatecholboranes in excellent yields[17] (eq. 15). These alkenylboranes are quite stable to air and can be isolated by simple distillation or recrystallization. Such access to the alkenylcatecholboranes also allows direct entry into the class of stereodefined alkenylboronic acids and esters *via* hydroboration (eq. 16).



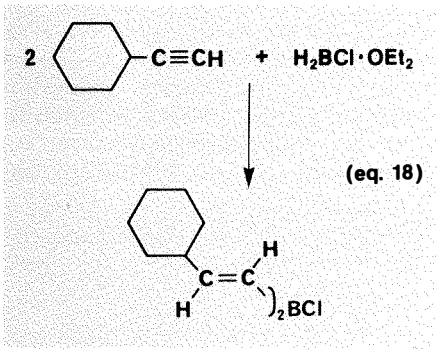


F. Mono- and Dichloroborane-Ethyl Etherates

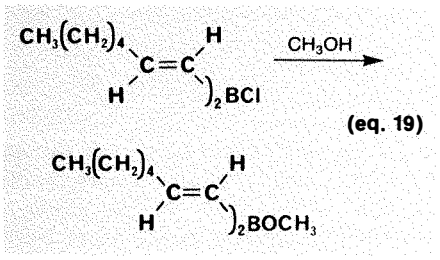
The preparation of mono- and dichloroborane-ethyl etherates and their use as hydroborating reagents for olefins subsequently led to their development as precursors to the alkenylchloroboranes. Reaction of monochloroborane-etherate[18] with two equivalents of an internal alkyne cleanly affords the dialkenylchloroboranes in excellent yields[19] (eq. 17). Attempts to



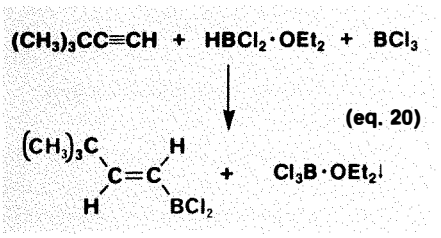
extend the reaction to 1-alkynes incur complications due to competing dihydroboration. However, use of an excess (~40%) of the 1-alkyne gives quantitative yields of the desired bis(1-alkenyl)chloroboranes[19] (eq. 18). Hydrolysis or alcohol-



ysis of these boranes then provides a simple, direct synthesis of dialkylborinic acids or esters of known stereochemistry (eq. 19).



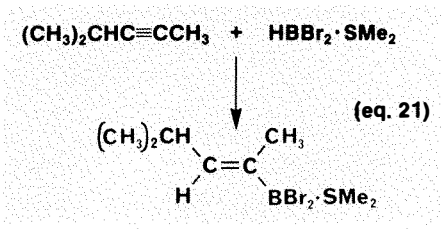
The reaction of dichloroborane-ethyl etherate with alkynes proceeds slowly. Apparently the strong bond between the ether and the Lewis acid, dichloroborane, impedes the reaction. However, addition of one equivalent of boron trichloride to a mixture of dichloroborane-etherate and alkyne results in rapid hydroboration with deposition of the $Cl_3B \cdot OEt_2$ adduct[20] (eq. 20). Presumably, the stronger Lewis acid,[21]



BCl_3, effectively removes the complexing ethyl ether, permitting the liberated dichloroborane to undergo immediate reaction. Hydrolysis or alcoholysis of the resultant alkenyldichloroborane then provides a simple preparation of the desired alkenylboronic acid or esters *via* hydroboration.

G. Dibromoborane-Methyl Sulfide

Quite recently, dibromoborane-methyl sulfide was prepared[22] and demonstrated to react directly with olefins without addition of a stronger Lewis acid.[23] This is puzzling since one would expect dibromoborane to form an especially strong adduct which should exhibit a diminished reactivity. Nevertheless, reaction of dibromoborane-methyl sulfide with alkynes cleanly affords the corresponding alkenyldibromoboranes in excellent yields[24] (eq. 21). For-



tunately, with 1-alkynes, the reaction proceeds readily to the alkenylborane stage, with no significant complications arising from competitive dihydroboration.

Moreover, dibromoborane-methyl sulfide exhibits an unusually rapid reaction with internal alkynes, far faster than the reaction of the reagent with terminal double or triple bonds. This offers considerable promise. The relative reactivity data suggest that selective hydroboration of internal alkynes in the presence of 1-alkynes or any olefin should be feasible. The markedly different selectivity of 9-BBN[15] and $HBBr_2 \cdot SMe_2$[24] should be noted (eq. 22).

III. DIRECTIVE EFFECTS

Availability of the considerable number of different hydroborating reagents for the preparation of alkenyl- and dialkenylboranes permits various valuable selective hydroborations. For example, 9-BBN permits the selective hydroboration of a terminal alkene in the presence of an internal alkyne[15] (eq. 22). On the other hand, dibromoborane-methyl sulfide selectively hydroborates an internal alkyne in the presence of a terminal alkene[24] (eq. 22).

The various hydroborating reagents also provide a regioselectivity spectrum in the hydroboration of unsymmetrically substituted alkynes. Nearly all of the reagents place boron exclusively at the terminal position in 1-alkynes. However, many internal alkynes involve a balance between steric and electronic effects in the placement of the boron.

In Table I, the directive effects encountered in the hydroboration of 2-hexyne and 4-methyl-2-pentyne are summarized for the hydroborating reagents discussed. Clearly, all of the reagents show some sensitivity to steric effects, placing boron predominantly at the least hindered position. Both 9-BBN and $HBBr_2 \cdot SMe_2$ appear to be even more selective than the highly hindered reagents, disiamylborane and dicyclohexylborane.

The effect of a phenyl group, which alters the electronic requirements of the triple bond, is significant, as is evidenced by a comparison of the data for 1-phenyl-1-propyne with those for 1-cyclohexyl-1-propyne (Table II).

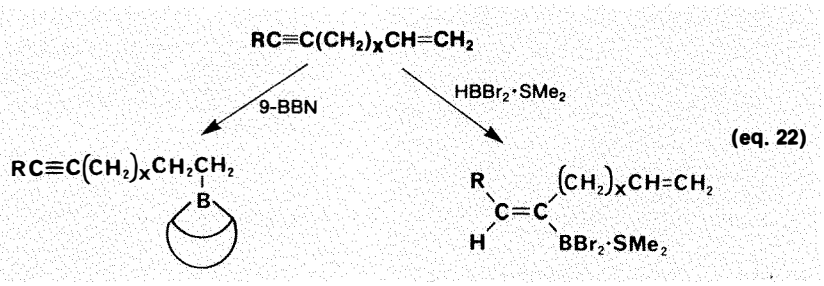
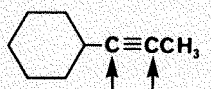
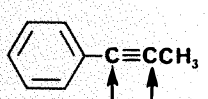


TABLE I. DIRECTIVE EFFECTS IN THE HYDROBORATION OF 1-SUBSTITUTED PROPYNES[a]

Hydroborating Reagent	$CH_3(CH_2)_2C{\equiv}CCH_3$		$(CH_3)_2CHC{\equiv}CCH_3$	
	↑	↑	↑	↑
Diborane	40	60	25	75
Thexylborane[b]	39	61	19	81
Disiamylborane[b]	39	61	7	93
Dicyclohexylborane[b]	33	67	8	92
$HBBr_2 \cdot SMe_2$[c]	25	75	4	96
9-BBN[d]	22	78	4	96

[a] Determined by oxidation of the alkenylboranes to the carbonyls.
[b] Data from reference 8.
[c] Data from reference 24.
[d] Data from reference 13.

TABLE II. DIRECTIVE EFFECTS IN 1-CYCLOHEXYL- AND 1-PHENYL-1-PROPYNE[a]

Hydroborating Reagent				
Disiamylborane[b]	9	91	19	81
Dicyclohexylborane[b]	8	92	29	71
$HBBr_2 \cdot SMe_2$[c]	9	91	64	36
9-BBN[d]	4	96	65	35

[a,b,c,d] Same as in Table I

In 1-cyclohexyl-1-propyne, all of the reagents show a marked tendency to place boron at the least hindered position. However, the presence of the phenyl group directs both 9-BBN and $HBBr_2 \cdot SMe_2$ primarily to the position adjacent to the ring. Contrariwise, both dicyclohexylborane and disiamylborane still show a large preference to locate next to the smaller methyl group. Both 9-BBN and $HBBr_2 \cdot SMe_2$ appear to be sensitive to electronic and steric effects, and can be strongly influenced by electronic effects. On the other hand, disiamylborane and dicyclohexylborane apparently are controlled mainly by steric effects, with considerably smaller sensitivity to electronic factors.

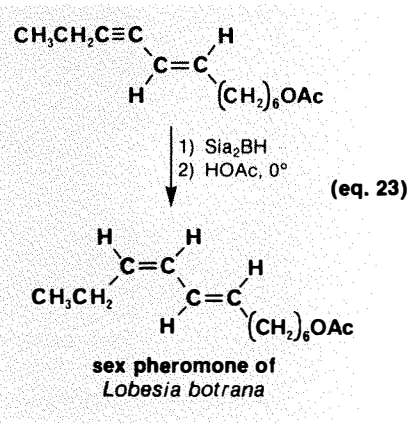
The diverse regioselectivity exhibited by the several hydroborating reagents has important implications for the regioselective transformations of alkynes. Based upon the steric and electronic environment of an alkyne, the appropriate choice of hydroborating reagent could provide a range of regiospecific hydroborations.

IV. REPRESENTATIVE APPLICATIONS OF VINYLIC BORANES

All of the resulting classes of vinylic boranes prepared by the hydroboration of alkynes have demonstrated considerable utility in organic synthesis.[2] Many of the reactions are, in fact, extensions of known alkylborane chemistry. However, the vinylic boranes also exhibit their own unique characteristics in many cases. Moreover, since the hydroboration of an alkyne produces the *trans*-alkenylborane solely, the stereodefined nature of many of the subsequent reactions often permits the precise prediction of the stereochemistry of the product. Representative transformations of vinylic organoboranes are reviewed below.

A. Protonolysis

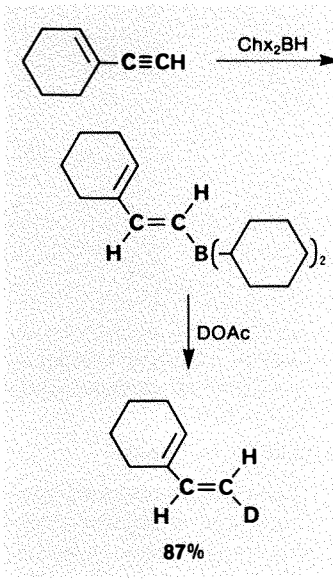
Addition of acetic acid to an alkenylborane results in mild protonolysis of the boron-carbon bond to yield the corresponding alkenes.[3] The reaction proceeds stereospecifically with retention of configuration[25] (eq. 23). Thus, hydroboration-



sex pheromone of *Lobesia botrana*

(eq. 23)

protonolysis of an alkyne provides a noncatalytic hydrogenation of triple to double bonds. In the case of internal alkynes, this procedure provides a valuable route to the pure *cis*-alkenes. The mildness and selectivity allow the presence of many functional groups and ready adaptability to the synthesis of many natural products. Deuterioacetic acid provides a simple, stereospecific preparation of deuterated olefins[8] (eq. 24).

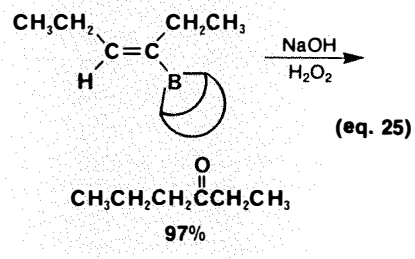


87%

(eq. 24)

B. Oxidation

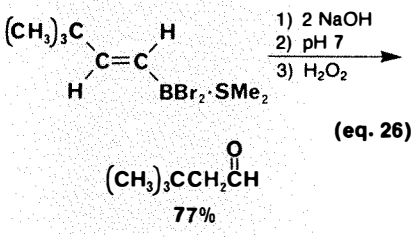
Oxidation of alkenylboranes can be easily achieved with alkaline hydrogen peroxide to produce the corresponding carbonyl compounds[3,13] (eq. 25). For oxidation of 1-



97%

(eq. 25)

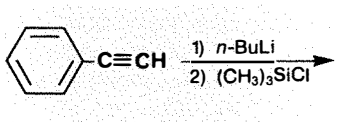
alkenylboranes, the addition of a pH 7 buffer is desirable to minimize base-promoted condensations of the resulting aldehydes[3,24] (eq. 26). Hydroboration of 1-



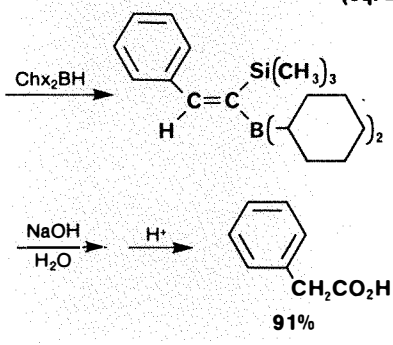
77%

(eq. 26)

trimethylsilylacetylenes, followed by oxidation, provides a method of converting 1-alkynes to the corresponding carboxylic acids[26] (eq. 27). The 1-trimethylsilylacetyl-



(eq. 27)

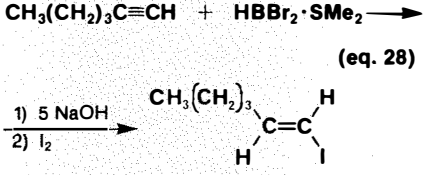


91%

enes may be prepared and used directly *in situ* to prepare the carboxylic acids.

C. Halogenation

A variety of stereochemically pure alkenyl halides may be prepared from alkenylborane precursors. Iodination of an alkenylboronic acid in the presence of base gives excellent yields of the *trans*-1-alkenyl iodide.[27a] Use of $HBBr_2 \cdot SMe_2$ permits a simple one-pot conversion of 1-alkynes to stereodefined alkenyl iodides without isolation of any intermediates[24] (eq. 28).

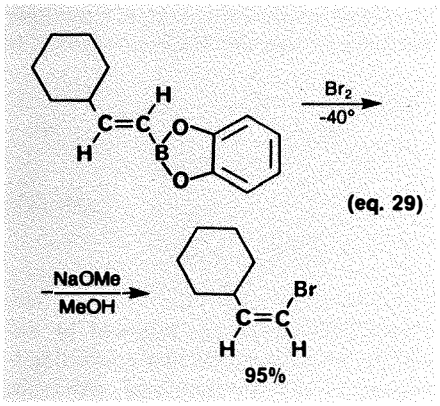


(eq. 28)

67% isolated yield

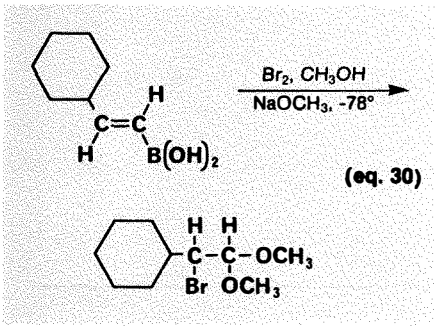
The corresponding *cis*-alkenyl iodide may be prepared by first treating the alkenylboronic acid with excess iodine, allowing sufficient time to form the diiodo derivative, followed by the addition of base.[27b]

The faster addition of bromine to the double bond makes the preparation of *cis*-1-bromoalkenes easier by a process involving the reaction of bromine with the alkenylcatecholborane, followed by addition of sodium methoxide[28] (eq. 29).



(eq. 29)

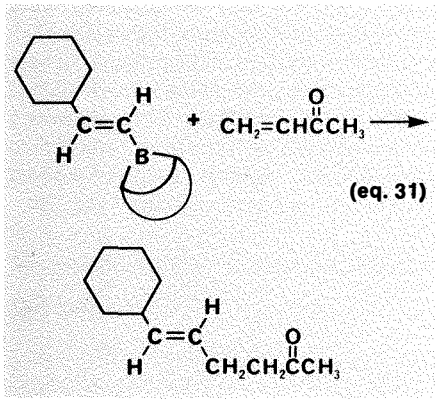
The reaction of such alkenylboronic acids with bromine in methanol at -78°, in the presence of sodium methoxide, provides a convenient synthesis of α-bromo acetals[29] (eq. 30).



(eq. 30)

D. Conjugate Addition

B-Alkenyl-9-BBN derivatives undergo 1,4-addition of the alkenyl group to acyclic enones, yielding γ,δ-unsaturated ketones[30] (eq. 31). The addition occurs with strict

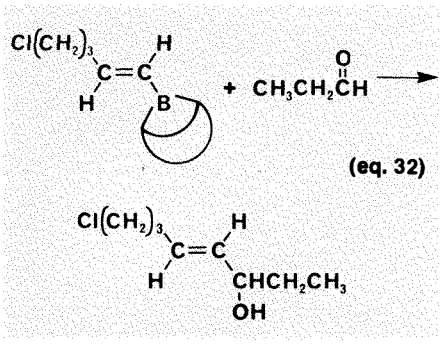


(eq. 31)

retention of configuration in the initial vinylic borane. The reaction evidently proceeds through a cyclic transition state, so that transoid enones, such as 2-cyclohexenone, cannot be utilized. On the other hand, cisoid enones, including very sensitive and easily polymerized derivatives, such as methyl vinyl ketone, react without difficulty.

E. 1,2-Addition to Aldehydes

Unlike alkylboranes, *B*-alkenyl-9-BBN derivatives add across the carbonyl group of aldehydes to produce stereochemically pure allylic alcohols[31] (eq. 32). Since many

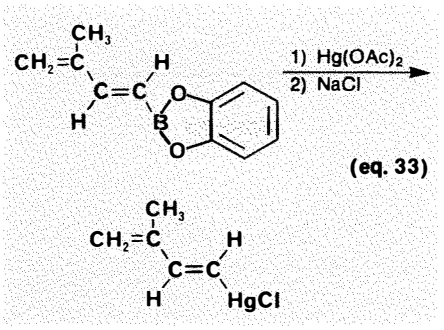


(eq. 32)

functional groups, such as ester, halogen, and nitrile, are tolerated by hydroboration, a "Grignard-like" synthesis of such allylic alcohols with reactive substituents present in the organometallics is now possible.

F. Mercuration

The mercuration of alkenylboranes provides easy access to stereochemically defined alkenylmercurials.[32] Addition of mercuric acetate to an alkenylcatecholborane results in clean formation of the alkenylmercuric compound in excellent yields[32b] (eq. 33). The resulting organo-

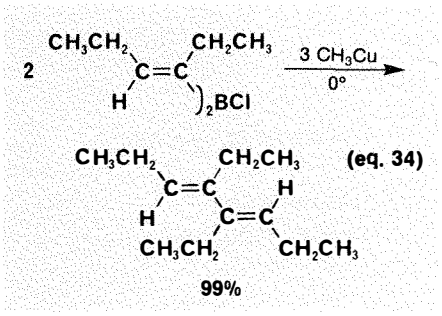


(eq. 33)

mercurials have since been shown to be exceptionally useful synthetic reagents, undergoing a variety of carbon-carbon bond-forming reactions.[33]

G. Transmetallation to Copper

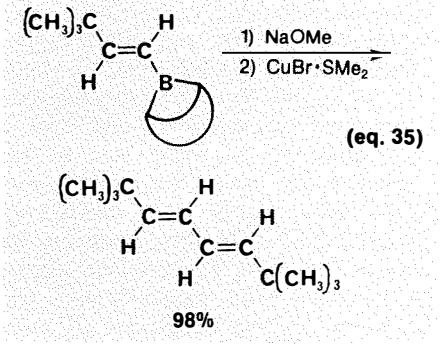
Recently, dialkenylchloroboranes were reported to undergo methylcopper-induced coupling to give *trans,trans*-1,3-dienes in excellent yields and high stereochemical purity[34] (eq. 34). The reaction presumably involves initial formation of an alkenylcopper reagent which undergoes thermal dimerization with retention of configuration to give the 1,3-diene. An



(eq. 34)

99%

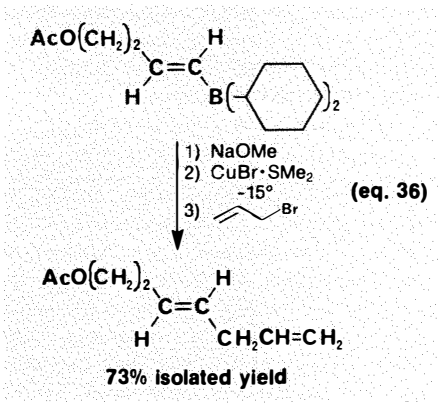
alternative procedure employing milder conditions proceeds *via* the sodium methoxide addition compound of an alkenyldialkylborane[35a] (eq. 35). The



(eq. 35)

98%

stability of the vinylic copper intermediate should be greater at lower temperatures. Indeed, by working at -15°, the decomposition of the copper intermediate is retarded and it can be trapped by allylic halides to afford a stereochemically defined synthesis of 1,4-dienes[35b] (eq. 36).



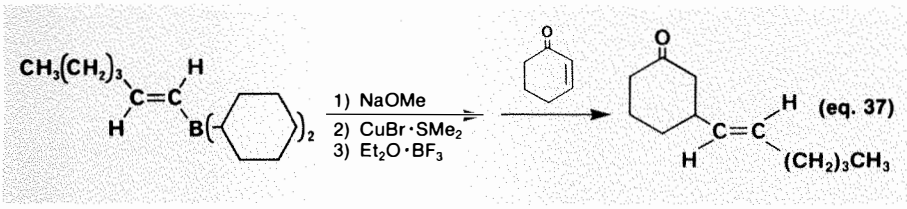
(eq. 36)

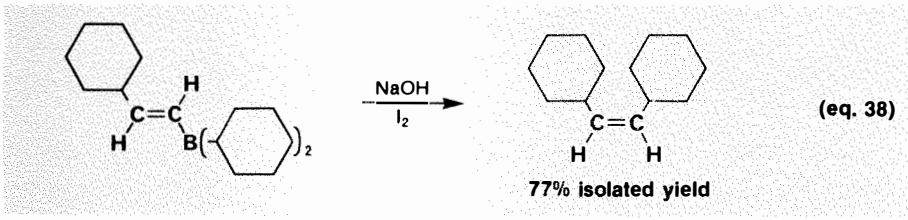
73% isolated yield

Again, the mildness of the reaction allows a wide variety of functional groups to be tolerated. Finally, conjugate addition of the copper reagent to cyclic enones can be effected,[35c] supplementing the 1,4-addition reaction of *B*-alkenyl-9-BBN derivatives (Section D) (eq. 37).

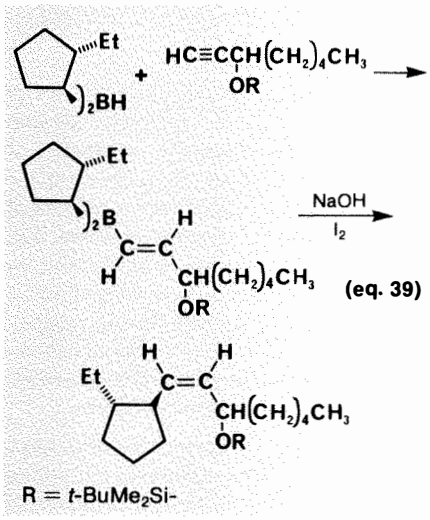
H. *cis*-Olefin Synthesis

Addition of iodine to an alkenyldialkylborane in the presence of base results in the exclusive formation of a *cis*-olefin derived from transfer of an alkyl group from boron to the adjacent carbon[36] (eq. 38). Migration of the alkyl group from boron occurs with strict retention of configuration,



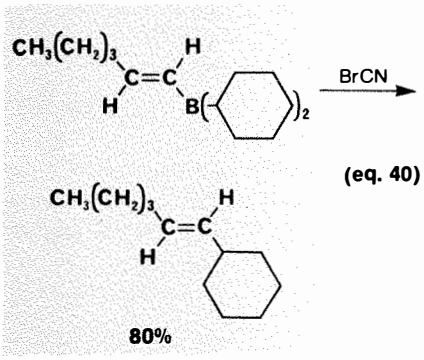


defined in the hydroboration step. Because of the known stereochemical outcome, the reaction has proven to be of value in the preparation of prostaglandin analogs[37] (eq. 39).

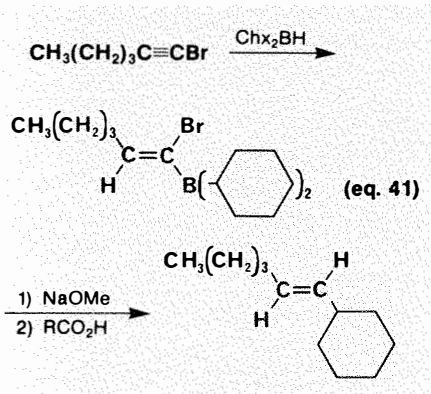


I. *trans*-Olefin Synthesis

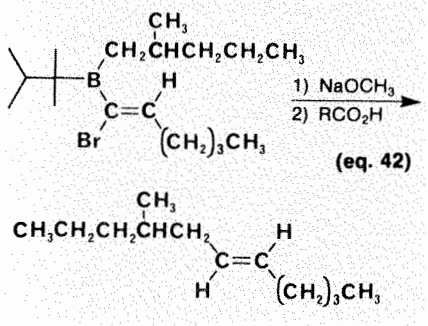
Reaction of an alkenyldialkylborane with cyanogen bromide produces the *trans*-olefin, again derived from alkyl-group transfer from boron[38] (eq. 40).



Alternatively, hydroboration of 1-halo-1-alkynes with a dialkylborane followed by treatment with sodium methoxide provides *trans*-olefins[39] (eq. 41). Unfortunately, these reactions are limited by the availability of dialkylborane hydroborating reagents. Also, only one of the two available groups on boron transfers.



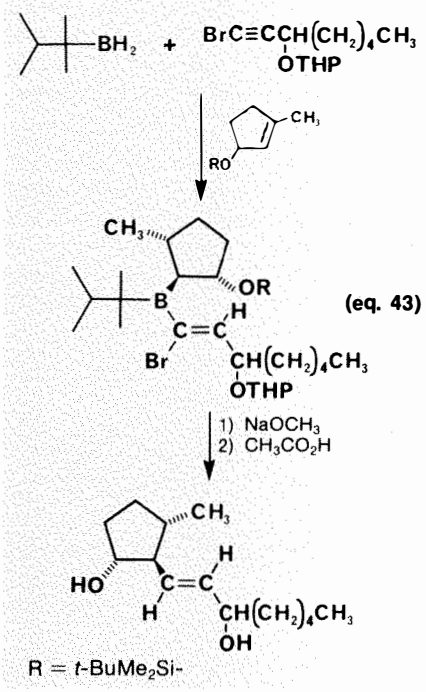
Use of the thexylmonoalkylboranes, readily synthesized from thexylborane, overcomes these difficulties, allowing the introduction of many alkyl groups. An alkyl-1-haloalkenylthexylborane[10] is perfectly set up for an alkyl group migration, and indeed, treatment with sodium methoxide, followed by protonolysis, releases the desired *trans*-olefin (eq. 42).

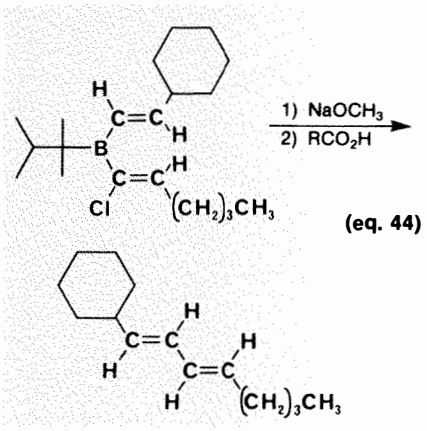


The application of such a stereodefined reaction to the synthesis of natural products is again illustrated by the preparation of a prostaglandin model[40] (eq. 43).

J. Synthesis of Conjugated *trans,trans*-Dienes

Reaction of thexylborane, first with a 1-haloalkyne followed by addition of a second alkyne, gives the mixed dialkenylthexylborane.[11] Treatment first with sodium methoxide followed by protonolysis provides the conjugated *trans,trans*-diene in good yields[11] (eq. 44). This

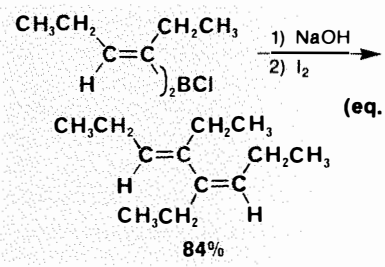




procedure also permits the synthesis of unsymmetrical *trans,trans*-dienes. An alternative preparation of symmetrical *trans,trans*-dienes has been discussed earlier (Section G).

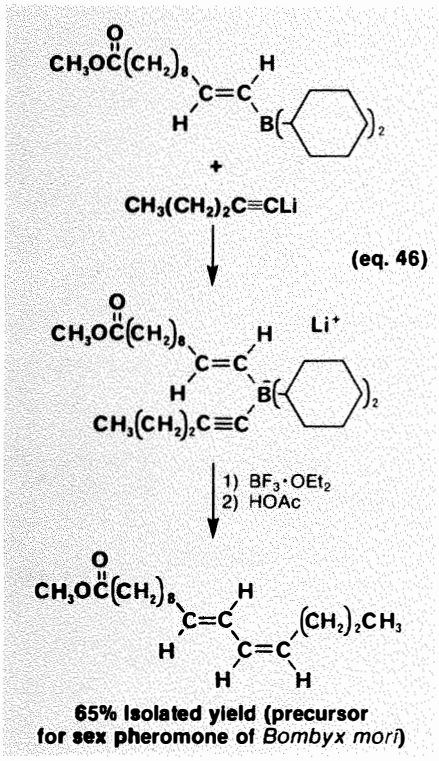
K. Synthesis of Conjugated *cis,trans*-Dienes

Preparation of symmetrical *cis,trans*-dienes may be performed by iodination of dialkenylboronic acids in the presence of base, a procedure analogous to that described for the synthesis of *cis*-olefins[41] (eq. 38). The requisite dialkenylborinic acids are most conveniently formed by basic hydrolysis of the dialkenylchloroboranes (eq. 45), readily produced by



hydroboration of alkynes with chloroborane etherate.[42] Thus, hydroboration of alkynes with $H_2BCl \cdot OEt_2$, followed by sequential treatment with base and iodine, provides a direct route to such dienes.

Another more general procedure for preparing *cis,trans*-dienes, which can be utilized for the synthesis of unsymmetrical derivatives, involves stepwise treatment of an alkenyldialkylborane with a lithium alkynylide, followed by boron trifluoride etherate[43] (eq. 46). Protonolysis of the intermediate releases the isomerically pure unsymmetrical *cis,trans*-diene in good yield.

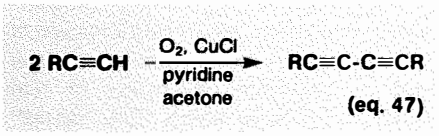


(eq. 46)

65% Isolated yield (precursor for sex pheromone of *Bombyx mori*)

L. Synthesis of Conjugated *cis,cis*-Dienes

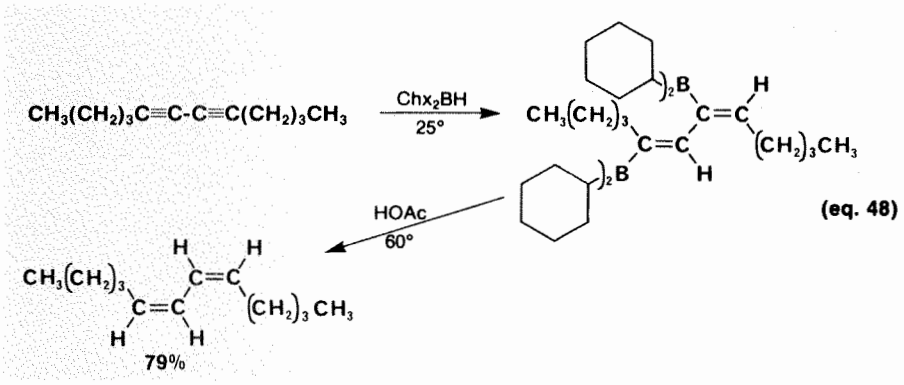
The oxidative coupling of 1-alkynes in the presence of copper salts provides a convenient route to the symmetrical conjugated diynes[44] (eq. 47). Hydroboration-protonolysis of such diynes makes readily available the symmetrical conjugated *cis,cis*-dienes[45] (eq. 48).



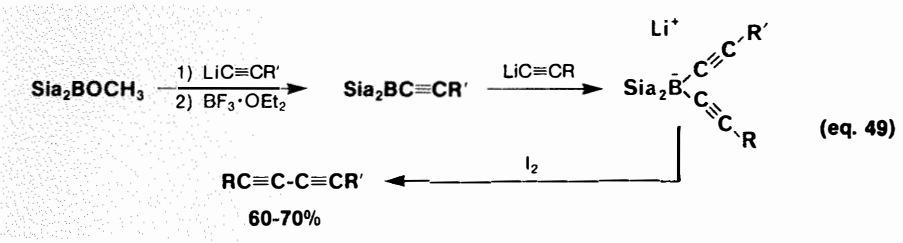
(eq. 47)

Borane chemistry now provides two synthetic routes to the synthesis of unsymmetrical conjugated diynes, one proceeding through dicyclohexylmethylthioborane[46] and the other proceeding through disiamylmethoxyborane.[47] The latter will be illustrated here (eq. 49), although both appear equally satisfactory.

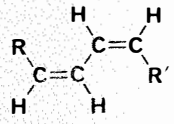
Hydroboration-protonolysis of this unsymmetrical conjugated diyne by the Zweifel-Polston procedure[45] should provide the corresponding conjugated *cis,cis*-diene.



(eq. 48)

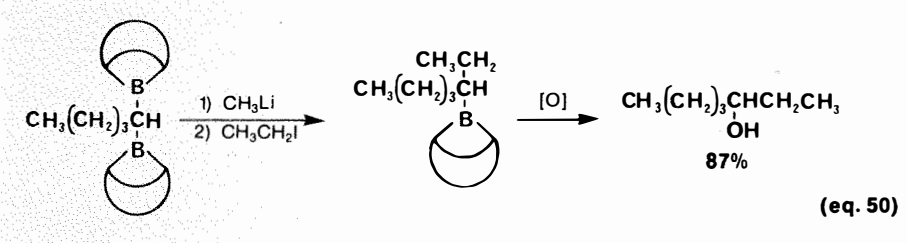


(eq. 49)

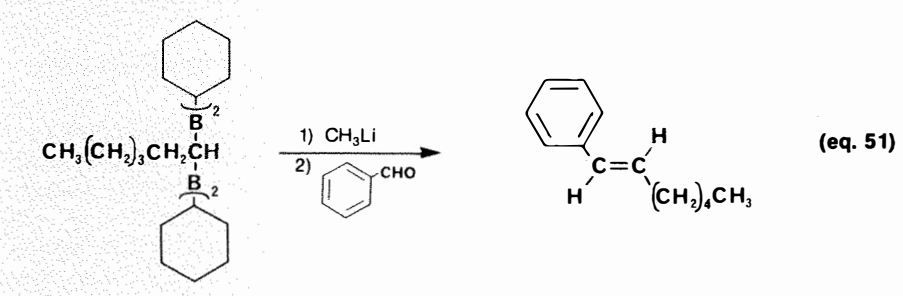


M. 1,1-Dibora Compounds

The often troublesome 1,1-dibora compounds accompanying the hydroboration of alkynes have themselves, in fact, revealed some interesting synthetic potential. Treatment of a 1,1-diboraalkane with one equivalent of CH_3Li,[48] followed by excess of an alkyl halide, gives a substituted secondary alcohol upon oxidation[14] (eq. 50). Additions of the organometallic reagent derived from 1,1-diboraalkanes and methyllithium to carbonyl compounds give a "Wittig-like" olefination[49] (eq. 51).



(eq. 50)



(eq. 51)

V. CONCLUSION

The controlled monohydroboration of both internal and terminal alkynes provides a stereospecific synthesis of vinylic organoboranes. In some cases the reaction can be directed to the formation of 1,1-diboraalkanes. Highly selective and regiochemically distinct transformations of alkynes are possible depending upon the proper choice of hydroborating reagent. The alkenylboranes thus produced can undergo a variety of stereoselective reactions with defined stereochemical results.

Undoubtedly, the chemistries of alkenylboranes and 1,1-diboraalkanes are still in their infancy, awaiting further exploitation of the remarkably versatile derivatives made available by the hydroboration of acetylenes. Further development of novel hydroborating reagents and of convenient synthetic routes to the *cis*-vinylic organo-

boranes will greatly expand the horizons, allowing many more selective transformations of acetylenes.

VI. ACKNOWLEDGEMENT

The support of the National Science Foundation (Grants CHE 76-20846 and CHE 79-18881) is gratefully acknowledged.

VII. LITERATURE CITED

1) H.C. Brown, "Hydroboration," W.A. Benjamin, New York, NY, 1962.
2) (a) H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, NY, 1972; (b) G.M.L. Cragg, "Organoboranes in Organic Synthesis," Marcel Dekker, New York, NY, 1973; (c) T. Onak, "Organoborane Chemistry," Academic Press, New York, NY, 1975;(d) H.C. Brown, G.W. Kramer, A.B. Levy, and M.M. Midland, "Organic Syntheses via Boranes," Wiley-Interscience, New York, NY, 1975.
3) H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83,** 3834 (1961).
4) H.C. Brown and A.W. Moerikofer, *ibid.*, **85,** 2063 (1963).
5) (a) Kits are available from Aldrich Chemical Company; (b) The reagent is available from Aldrich Chemical Company.
6) G. Zweifel and H. Arzoumanian, *J. Am. Chem. Soc.*, **89,** 291 (1967).
7) J. Plamondon, J.T. Snow, and G. Zweifel, *Organomet. Chem. Synth.*, **1,** 249 (1971).
8) G. Zweifel, G.M. Clark, and N.L. Polston, *J. Am. Chem. Soc.*, **93,** 3395 (1971).
9) G. Zweifel and H.C. Brown, *ibid.*, **85,** 2066 (1963).
10) E. Negishi, J.-J. Katz, and H.C. Brown, *Synthesis,* 555 (1972).
11) E. Negishi and T. Yoshida, *Chem. Commun.*, 606 (1973).
12) (a) E.F. Knights and H.C. Brown, *J. Am. Chem. Soc.*, **90,** 5280 (1968); (b) C.G. Scouten and H.C. Brown, *J. Org. Chem.*, **38,** 4092 (1973).
13) H.C. Brown, C.G. Scouten, and R. Liotta, *J. Am. Chem. Soc.*, **101,** 96 (1979).
14) L. Brener, Final Report, Purdue University, 1976.
15) C.A. Brown and R.A. Coleman, *J. Org. Chem.*, **44,** 2329 (1979).
16) H.C. Brown and S.K. Gupta, *J. Am. Chem. Soc.*, **93,** 1816 (1971).
17) (a) H.C. Brown and S.K. Gupta, *ibid.*, **94,** 4370 (1972); (b) H.C. Brown and S.K. Gupta, *ibid.*, **97,** 5249 (1975).
18) H.C. Brown and P.A. Tierney, *J. Inorg. Nucl. Chem.*, **9,** 51 (1959).
19) H.C. Brown and N. Ravindran, *J. Am. Chem. Soc.*, **98,** 1785 (1976).
20) H.C. Brown and N. Ravindran, *ibid.*, **98,** 1798 (1976).
21) H.C. Brown and R.R. Holmes, *ibid.*, **78,** 2173 (1956).
22) (a) K. Kinberger and W. Siebert, *Z. Naturforsch. B,* **30,** 55(1975);(b) H.C. Brown and N. Ravindran, *Inorg. Chem.*, **16,** 2938 (1977).
23) N. Ravindran and H.C. Brown, *J. Am. Chem. Soc.*, **99,** 7097 (1977).
24) H.C. Brown and J.B. Campbell, Jr., *J. Org. Chem.*, **45,** 389 (1980).
25) E. Negishi and A. Abramovitch, *Tetrahedron Lett.*, 411 (1977).
26) G. Zweifel and S.J. Backlund, *J. Am. Chem. Soc.*, **99,** 3184 (1977).
27) (a) H.C. Brown, T. Hamaoka, and N. Ravindran, *ibid.*, **95,** 5786 (1973); (b) T. Hamaoka, unpublished results.
28) H.C. Brown, T. Hamaoka, and N. Ravindran, *ibid.*, **95,** 6456 (1973).
29) T. Hamaoka and H.C. Brown, *J. Org. Chem.*, **40,** 1189 (1975).
30) P. Jacob III and H. C. Brown, *J. Am. Chem. Soc.*, **98,** 7832 (1976).
31) P. Jacob III and H.C. Brown, *J. Org. Chem.*, **42,** 579 (1977).
32) (a) R.C. Larock and H.C. Brown, *J. Organomet. Chem.*, **36,** 1 (1972); (b) R.C. Larock, S.K. Gupta, and H.C. Brown, *J. Am. Chem. Soc.*, **94,** 4371 (1972).
33) (a) D. Seyferth, Ed., *J. Organomet. Chem., Library 1,* 257-303 (1976); (b) R.C. Larock, *Angew. Chem., Int. Ed. Engl.*, **17,** 27 (1978).
34) H.C. Brown and N. Ravindran, *J. Am. Chem. Soc.*, **98,** 1785 (1976).
35) (a) J.B. Campbell, Jr. and H.C. Brown, *J. Org. Chem.*, **45,** 549 (1980); (b) J.B. Campbell, Jr. and H.C. Brown, *ibid.*, **45,** 550 (1980); (c) J.B. Campbell, Jr., unpublished results.
36) G. Zweifel, H. Arzoumanian, and C.C. Whitney, *J. Am. Chem. Soc.*, **89,** 3652 (1967).
37) D.A. Evans, T.C. Crawford, R.C. Thomas, and J.A. Walker, *J. Org. Chem.*, **41,** 3947 (1976).
38) G. Zweifel, R.P. Fisher, J.T. Snow, and C.C. Whitney, *J. Am. Chem. Soc.*, **94,** 6560 (1972).
39) G. Zweifel and H. Arzoumanian, *ibid.*, **89,** 5086 (1967).
40) E.J. Corey and T. Ravindranathan, *ibid.*, **94,** 4013 (1972).
41) G. Zweifel, N.L. Polston, and C.C. Whitney, *ibid.*, **90,** 6243 (1968).
42) H.C. Brown and N. Ravindran, *J. Org. Chem.*, **38,** 1617 (1973).
43) G. Zweifel and S.J. Backlund, *J. Organomet. Chem.*, **156,** 159 (1978).
44) I.D. Campbell and G. Eglinton, *Org. Syn.*, **45,** 39 (1965).
45) G. Zweifel and N.L. Polston, *J. Am. Chem. Soc.*, **92,** 4068 (1970).
46) A. Pelter, R. Hughes, K. Smith, and M. Tabata, *Tetrahedron Lett.*, 4385 (1976).
47) J.A. Sinclair and H.C. Brown, *J. Org. Chem.*, **41,** 1078 (1976).
48) G. Zweifel and H. Arzoumanian, *Tetrahedron Lett.*, 2535 (1966).
49) G. Cainelli, G. Dal Bello, and G. Zubiani, *ibid.*, 4315 (1966).

Chemical Reactions of Newly Available Pyridines

Helmut Beschke
Degussa

INTRODUCTION

During the last few decades pyridine derivatives have become steadily more important in the fields of medicinal and herbicide chemistry. The structures of the pyridine derivatives on the market are as varied as their fields of application. A few structural derivatives of importance are: quaternary, dimeric, halogenated, and vinyl compounds, as well as carbinols, ketones, mercaptans, carboxylic acids, and polycyclics. Research and development teams are seeking new variants steadily and often the feasibility of an economic synthesis of an intermediate determines the commercial viability of the end product.

In this connection a new method of synthesis of substituted pyridines is of interest.[1] Substituted aldehydes or ketones are reacted with acrolein or formaldehyde and ammonia in heterocatalytic gas-phase reactions to yield products which, until now, could be made only by multi-step syntheses. Many of these newly available pyridine derivatives are offered by Aldrich (Scheme 1). To show the many possibilities offered by these 12 selected compounds, we have summarized their reactions in this essay.

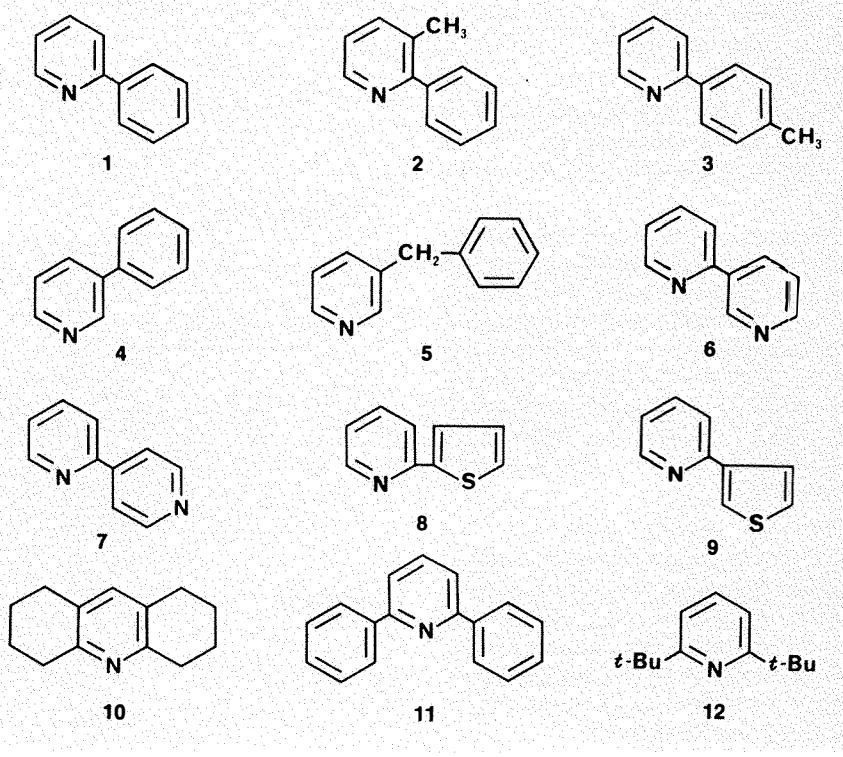
CHEMICAL TRANSFORMATIONS OF PYRIDINES

Among the newly offered compounds are five aryl pyridines, two bipyridines, two thienylpyridines and three symmetrically substituted pyridines. The known reactions of these products will be enumerated in the same order. In each case, the first reaction determined the order of the ensuing conversions.

CHEMICAL TRANSFORMATIONS OF ARYLPYRIDINES 1 - 5

2-Phenylpyridine (1) has been the starting material in a great many reactions (Scheme 2). Quaternization with chloro-

Scheme 1
Pyridine Derivatives



acetaldoxime leads to oxime **13** (X = NOH, R = H) which is transformed with HBr and perchloric acid into benzo[*a*]quinolizinium perchlorate **(14)**.[2] Analogously, reaction with methyl δ-bromolevulinate yields ketoester **13** (X = O, R = $CH_2CH_2COOCH_3$) and from that, the corresponding substituted compound **14**.[3]

N-Oxidation of 2-phenylpyridine yields the N-oxide **15** from which one obtains the *m*-nitrophenyl derivative **16**, and by reduction, 2-(*m*-nitrophenyl)pyridine **(17)**.[4-6]

Hydrogenation with nickel yields 2-phenylpiperidine **(18)**,[7] and with platinum, 2-cyclohexylpiperidine (**19**, R = H).[8] 2-Cyclohexylpiperidine has been used for the preparation of various antiinflammatories (**19**, R as shown).[9-11]

Amination of 2-phenylpyridine, employing Tschitschibabin reaction with sodium amide, leads to 2-amino-6-phenylpyridine (**20**, X = NH_2) from which one obtains, in the usual manner, 2-bromo-6-phenylpyridine (**20**, X = Br), the 2-cyano derivative as well as 6-phenylpyridine-2-carboxylic acid.[12-14]

Reaction with *p*-methoxyphenyllithium yields the diphenyl derivative **21** which can be hydrogenated with sodium in ethanol to a *cis*/*trans* mixture of piperidine **22**. Both isomers can be converted to the *N*-nitroso compound **23**; the *cis* isomer is then reduced to the hydrazine derivative **24** and converted with mercuric oxide to a mixture of the conjugated olefins **25** and **26**.[15]

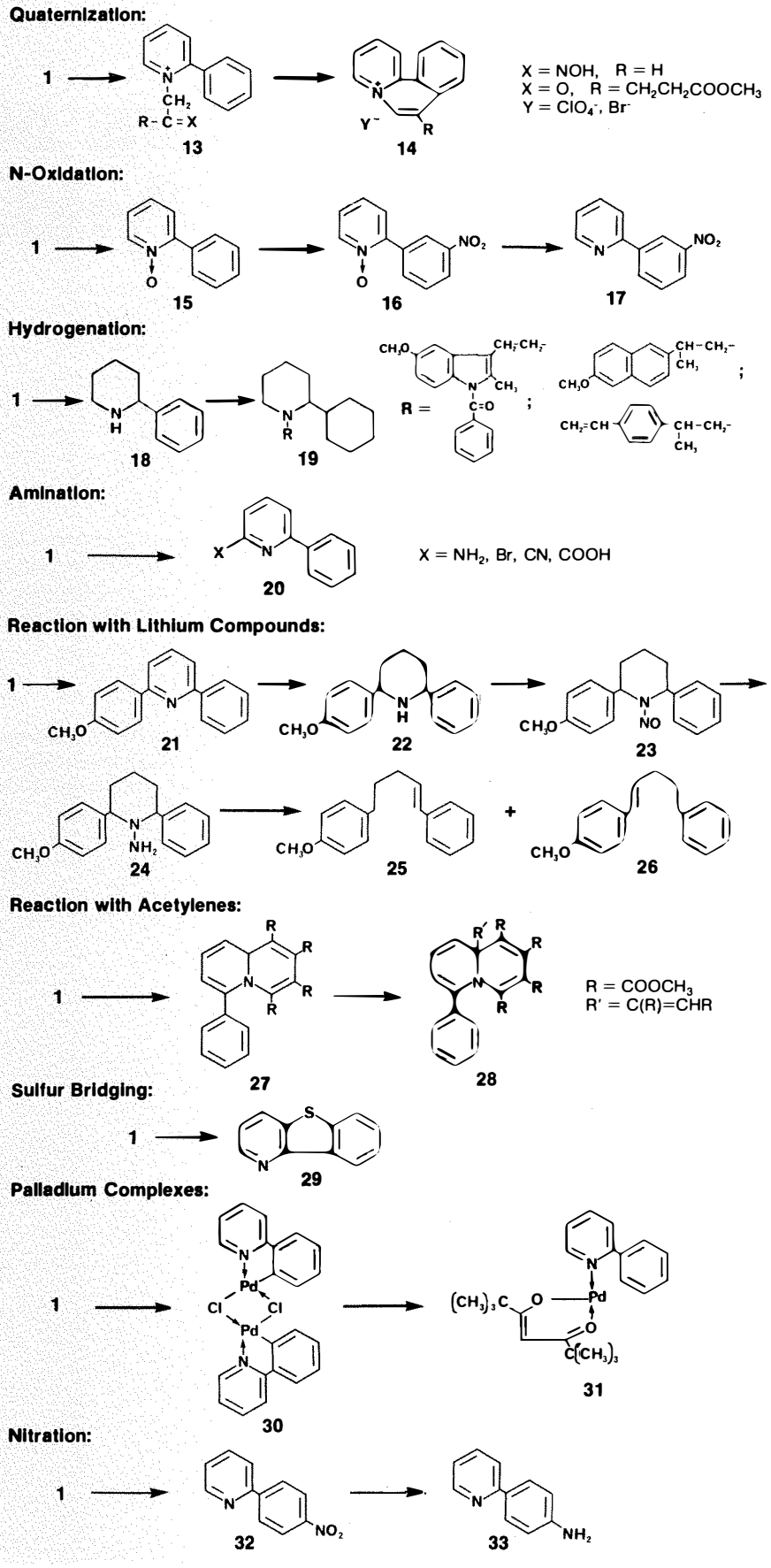
Addition of dimethyl acetylenedicarboxylate to 2-phenylpyridine yields the quinolizine derivative **27** and, after further reaction with the acetylene derivative, compound **28**.[16]

Reaction of 2-phenylpyridine with hydrogen sulfide/alumina at 630° C yields the ring-closed product, thienopyridine **(29)**.[17]

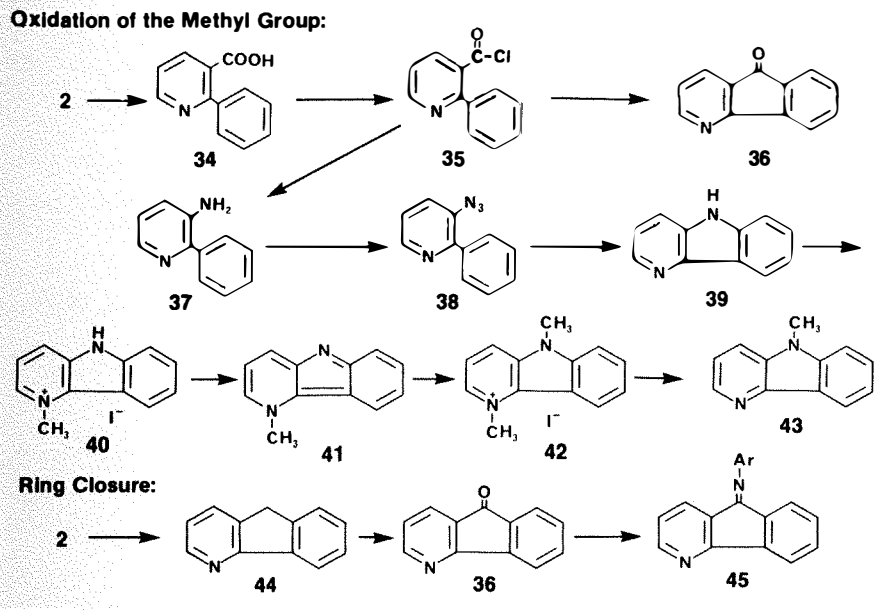
Palladium complexes are obtained by reaction with $PdCl_2$. Thus was formed the dimeric 2-(2-pyridyl)phenylpalladium(II) chloride **(30)** which, upon treatment with 2,2,6,6-tetramethyl-3,5-heptanedione, yielded 2,2,6,6-tetramethyl-3,5-heptanedionato-2-(2-pyridyl)phenylpalladium(II) **(31)**. These complexes are useful in the production of palladium coatings on glass or ceramics.[18]

The only reaction which has been described that involves the benzene ring is nitration. In contrast to the nitration of N-oxide **15** in which the main product is the *m*-nitro derivative **16**, nitration of 2-phenylpyridine results in substantial quantities of 2-(*p*-nitrophenyl)pyridine **(32)** as well as the *m*-derivative **17**.[4]

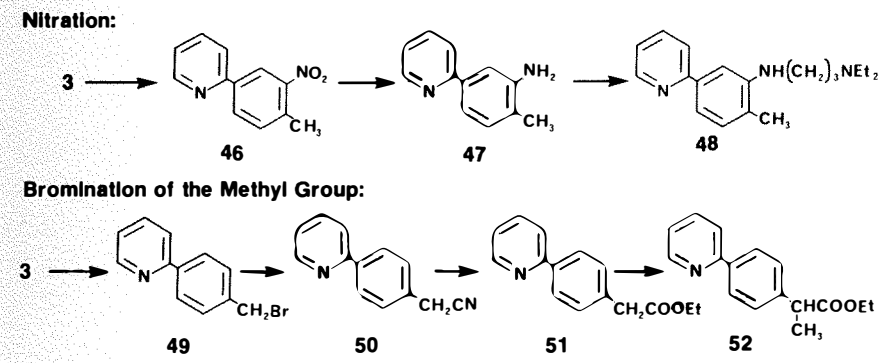
Scheme 2
Reactions of 2-Phenylpyridine (1)



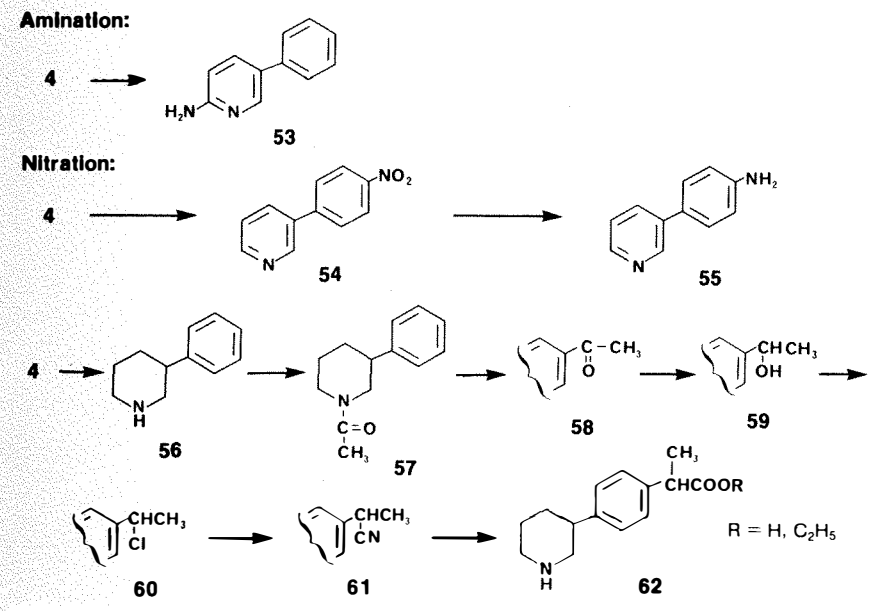
Scheme 3
Reactions of 3-Methyl-2-phenylpyridine (2)



Scheme 4
Reactions of 2-(*p*-Tolyl)pyridine (3)



Scheme 5
Reactions of 3-Phenylpyridine (4)



3-Methyl-2-phenylpyridine (2) has been used to make the polycyclics 4-azafluorene and δ-carboline (Scheme 3).

Oxidation affords carboxylic acid **34** which leads to 4-azafluorenone **(36)** *via* the acid chloride **35**.[19] Curtius degradation through the azide converts **35** to 3-amino-2-phenylpyridine **(37)**, from which one obtains the δ-carboline **39** *via* 3-azido-2-phenylpyridine **(38)**. The quaternary salt **40**, the anhydro base **41**, the quaternary dimethyl derivative **42** and *N*-methylcarboline **(43)** have been described.[20]

With a catalyst, direct ring closure of **2** to 4-azafluorene **(44)** can be effected. Oxidation yields 4-azafluorenone **(36)**, which reacts with aniline to yield the imine **45**.[21]

With **2-(*p*-tolyl)pyridine (3)** only reactions with the phenyl moiety have been described (Scheme 4).

Nitration of **3** yields the *m*-nitro compound **46**, which has been converted to the 3-diethylaminopropylamino derivative **48** *via* the amine **47**.[22] These compounds were made in a search for new antimalarials.

The bromo derivative **49**, obtained by bromination of the methyl group, can be converted to the nitrile **50** and the esters **51** and **52**. The ester **52** possesses analgesic and antiinflammatory properties.[23]

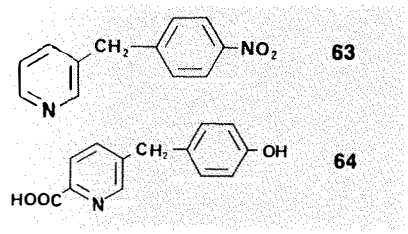
3-Phenylpyridine (4) (Scheme 5) has been described as an antimicrobial,[24] as well as an anti-corrosion agent for steel, zinc and aluminum.[25]

Amination of **4** using the Tschitschibabin reaction yields 2-amino-5-phenylpyridine **(53)**.[26]

Nitration yields the *p*-nitrophenyl derivative **54** which upon hydrogenation affords 3-(*p*-aminophenyl)pyridine **(55)**.[27]

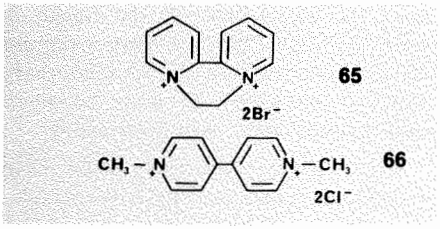
Hydrogenation of **4** yields 3-phenylpiperidine **(56)**, from which the acetyl derivative **57**, and thence the diacetyl compound **58**, the carbinol **59**, the chloride **60**, the cyanide **61** and the anti-inflammatory α-[*p*-(3-piperidyl)phenyl]propionic acid **(62)** and its ethyl ester were prepared.[28]

3-Benzylpyridine (5) has been nitrated to the *p*-nitro derivative **63**.[29] Further transformations have not been described. It should be noted that 3-benzylpyridine is structurally related to the anti-hypertensive phenopicolinic acid **(64)**.[30]



REACTIONS OF BIPYRIDINES 6 AND 7

Thus far, only two of the six bipyridines, namely 2,2′-bipyridine and 4,4′-bipyridine, have found technical applications. From these two, the herbicides Diquat **(65)** and Paraquat **(66)** have been made on a large scale.[31]



2,3′-Bipyridine and 2,4′-bipyridine, inaccessible up to now, can be made by our new pyridine synthesis.

2,3′-Bipyridine (6) (Scheme 6) can be quaternized preferentially in the pyridine ring which is substituted in the 3-position. With methyl bromide the quaternary bipyridine **67** is obtained, which has been hydrogenated to the piperidine **68**.[32]

N-Oxidation with peracetic acid yields the di-N-oxide **69**, from which the nitro dioxide **70**, the ethoxy dioxide **71** (by exchange), and the ethoxybipyridine **72** (by reduction with phosphorus trichloride) have been made.[33] The dioxide **69** can be converted to the bromobipyridine **78**.[34] With hydrochloric acid the nitro dioxide **70** can be converted to the chloro dioxide **73** from which 4-chloro-2,3′-bipyridine **(74)** can be obtained by reduction with phosphorus trichloride. This can be converted to the quaternary product **75**.[35]

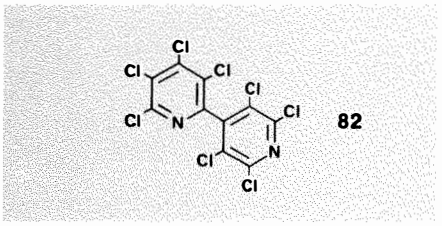
Amination of 2,3′-bipyridine yields a mixture of **76** and **77**.[36]

Bromination yields 5′-bromo-2,3′-bipyridine **(78)** which can be hydrolyzed with potassium hydroxide under pressure to the hydroxybipyridine **79**.[37]

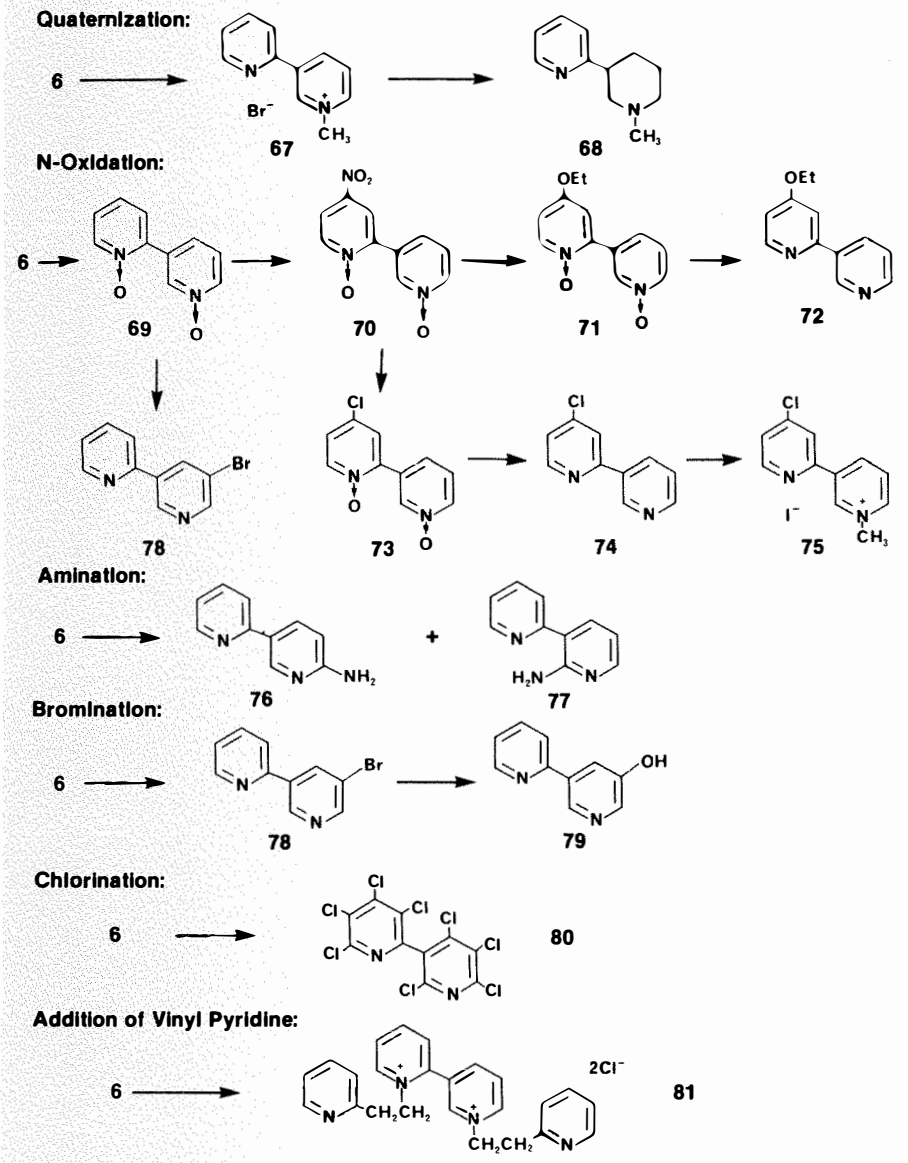
Chlorination in the gas phase yields the herbicide octachloro-2,3′-bipyridine **(80)**.[38]

Addition of 2-vinylpyridine to 2,3′-bipyridine dihydrochloride yields the diquaternary chloride **81** which has been reported to have fungicidal, insecticidal, herbicidal and germicidal activity; it is also a corrosion inhibitor.[39]

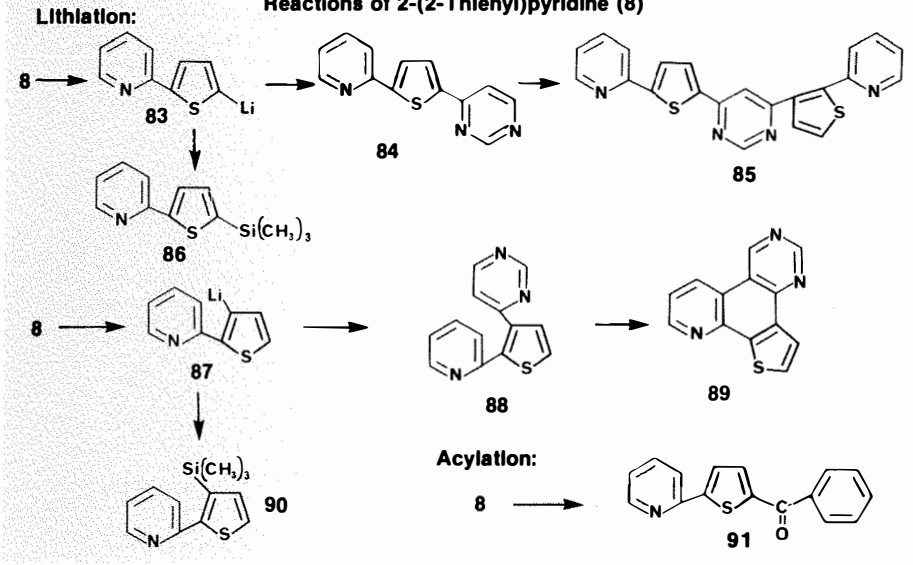
2,4′-Bipyridine (7) can be chlorinated to octachloro-2,4′-bipyridine **(82)**.[38]



Scheme 6
Reactions of 2,3′-Bipyridine (6)



Scheme 7
Reactions of 2-(2-Thienyl)pyridine (8)



CHEMICAL REACTIONS OF THIENYLPYRIDINES 8 AND 9

Because of the reactivity of the thiophene ring, interesting polyheterocyclics have been made from thienylpyridines.

2-(2-Thienyl)pyridine (8) (Scheme 7), on treatment with butyllithium, yields preferentially either the lithium derivative **83** or **87** depending on the solvent. With chlorotrimethylsilane either **86** or **90** is obtained. Reaction with pyrimidine affords either the triheterocyclic **84** or **88**.[40] The 2-isomer **84** can react with the lithium derivative **87** to yield the pentaheterocyclic **85**. Irradiation of **88** leads to the interesting thieno[3,2-*e*]pyrido[2,3-*g*]quinazoline **(89)**.[41]

Acylation of 2-(2-thienyl)pyridine with benzoyl chloride yields the benzoyl derivative **91**.[42]

Heavy metal complexes of 2-(2-thienyl)-pyridine with Ni^{++}, Cu^{++} and Zn^{++} have been described.[43-45]

2-(3-Thienyl)pyridine (9) (Scheme 8) reacts with butyllithium to form the lithium derivative **92** which has been converted with pyrimidine to the triheterocyclic **93**, and to thieno[2,3-*e*]pyrido[2,3-*g*]quinazoline **(94)** by irradiation. The tetraheterocyclic **95** was made from **92** by treatment with $CuCl_2$.[41]

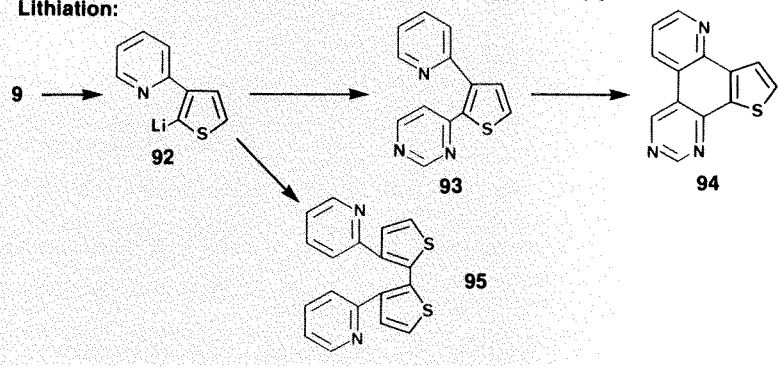
REACTIONS OF SYMMETRICALLY SUBSTITUTED PYRIDINES 10 - 12

1,2,3,4,5,6,7,8-Octahydroacridine (10) (Scheme 9) can be hydrogenated with nickel to perhydroacridine **(96)**, the configuration of which has not been determined.[46] Reduction with sodium in ethanol gives *trans-syn-trans*-perhydroacridine **(96a)** in high yield.[47,48] Electrochemical reduction yields a mixture of products with stereoselectivity dependent on the cathode potential.[49]

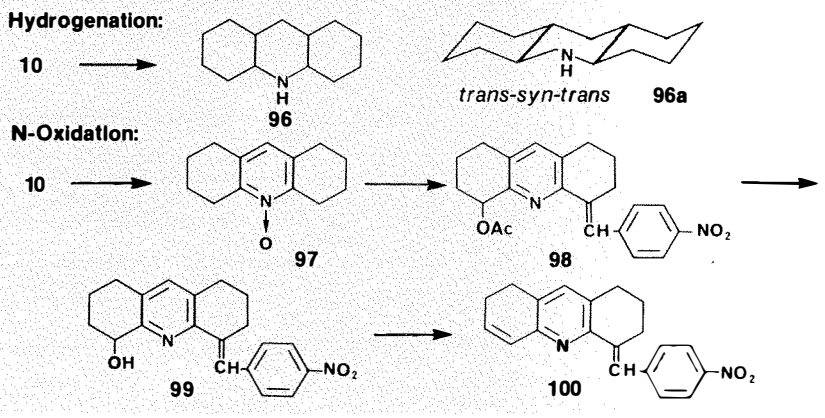
N-Oxidation of **10** yields the N-oxide **97** which has been converted and rearranged with *p*-nitrobenzaldehyde and acetic anhydride to the benzylidene acetic ester **98**. Acid hydrolysis yields the carbinol **99**, and dehydration with polyphosphoric acid yields the vinyl derivative **100**.[50]

2,6-Diphenylpyridine (11) (Scheme 10) can be reduced with sodium in ethanol to a mixture of *cis*- and *trans*-2,6-diphenylpiperidine **(101)** which, because of differences in their physical properties, can be separated then converted to the *cis*- and *trans*-nitrosopiperidines **(102)** and to the *cis*- and *trans*-hydrazines **(103)**. Oxidative degradation of these hydrazines leads to a mixture of *cis*- and *trans*-1,2-diphenylcyclopropane and 1,5-diphenyl-1-pentene respectively.[51]

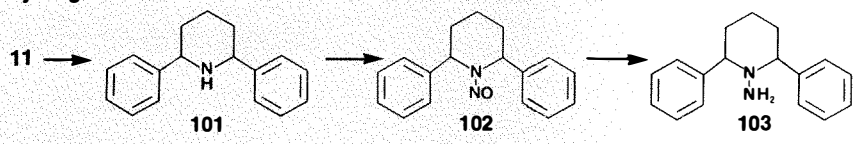
Scheme 8
Reactions of 2-(3-Thienyl)pyridine (9)



Scheme 9
Reactions of 1,2,3,4,5,6,7,8-Octahydroacridine (10)



Scheme 10
Reactions of 2,6-Diphenylpyridine (11)

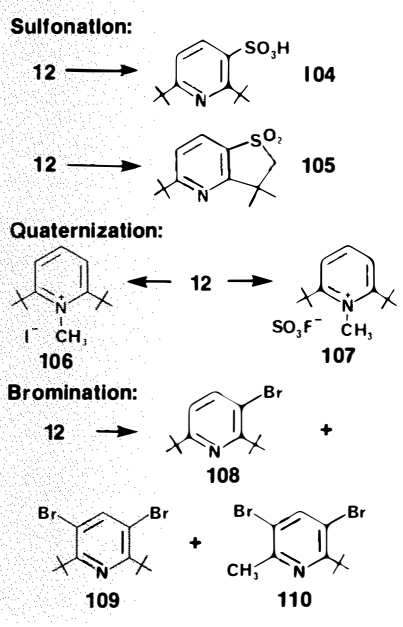


2,6-Diphenylpyridine acts as a catalyst in the side-chain chlorination of ring-chlorinated toluenes.[52]

2,6-Di-*t*-butylpyridine (12) (Scheme 11) has been investigated particularly because of its extraordinary properties as a sterically hindered base. It is a weaker base than pyridine; it reacts with proton acids, but not with electrophilic compounds such as methyl iodide or boron trifluoride under the usual conditions. Also, 2,6-di-*t*-butylpyridine displays a different reactivity than most pyridines. Thus, it can be sulfonated with sulfur trioxide at low temperature to obtain 2,6-di-*t*-butylpyridine-3-sulfonic acid **(104)**,[53] while at high temperature 2,3-dihydro-3,3-dimethyl-5-*t*-butylthieno-[3,2-*b*]pyridine 1,1-dioxide **(105)** is obtained.[54]

The quaternization of **12** with methyl iodide and with methyl fluorosulfonate has been accomplished recently to yield the quaternary compounds **106** and **107**. A pressure of 5,000-6,000 bars over a period

Scheme 11
Reactions of 2,6-Di-*t*-Butylpyridine (12)



of 10-15 hours at 90° was required.[55] Reaction occurs only when the pressure is higher than 4,000 bars.[56]

Bromination of **12** with bromine and sulfuric acid yields a mixture of the bromine derivatives **108**, **109** and **110**.[57]

SUMMARY

This overview demonstrates the interesting chemistry of twelve pyridine derivatives. Since it is now possible to produce these compounds by heterocatalytic gas-phase syntheses, they have become commercially available, and this is likely to lead to much new research. The important aim of this review is to challenge the reader's imagination for new derivatives that he can make from these pyridines.

References:

1) Degussa, Belgian Patent 858,388 (1976). Degussa, U.S. Patent 4,169,951 (1977). Degussa, U.S. Patent 4,171,444 (1977). Degussa, Belgian Patent 858,391 (1977). Degussa, Ger. Offen. 2,819,196 (1978).
2) R.W.L. Kimber and J.C. Parham, *J. Org. Chem.*, **28**, 3205 (1963).
3) C.K. Bradsher and N.L. Yarrington, *ibid.*, **28**, 81 (1963).
4) A.R. Hands and A.R. Katritzky, *J. Chem. Soc.*, 1754 (1958).
5) A.R. Katritzky and M. Kingsland, *J. Chem. Soc. (B)*, 862 (1968).
6) D.E. Butler, *et al., J. Med. Chem.*, **14**, 575(1971).
7) H. Adkins and H.J. Cramer, *J. Am. Chem. Soc.*, **52**, 4349 (1930).
8) J. Overhoff and J.P. Wibaut, *Recl. Trav. Chim.*, **50**, 957 (1931).
9) Sterling Drug, U.S. Patent 4,021,431 (1972).
10) Sterling Drug, U.S. Patent 4,028,366 (1975).
11) Sterling Drug, U.S. Patent 4,008,276 (1975).
12) M. Goshaev, *et al., Khim. Geterotsikl. Soedin.*, 1642 (1972).
13) M. Goshaev, *et al., Izv. Akad. Nauk Turkm. SSR, Ser. Fiz.-Tekh., Khim. Geol. Nauk,* 108 (1973).
14) F.H. Case and T.I. Kasper, *J. Am. Chem. Soc.*, **78**, 5842 (1956).
15) C.G. Overberger and L.P. Herin., *J. Org. Chem.*, **27**, 2423 (1962).
16) R.M. Acheson, M.W. Foxton, and A.R. Hands, *J. Chem. Soc. (C)*, 387 (1968).
17) L.H. Klemm, *et al., J. Heterocycl. Chem.*, **8**, 383 (1971).
18) Du Pont, U.S. Patent 3,876,675 (1971).
19) R.A. Abramovitch, A.D. Notation, and Giam Choo Seng, *Tetrahedron Lett.*, **1** (1959).
20) R.A. Abramovitch, K.A.H. Adams, and A.D. Notation, *Can. J. Chem.*, **38**, 2152 (1960).
21) N.S. Prostakov, *et al., Zh. Org. Khim.*, **13**, 1484 (1977); *Chem. Abstr.*, **87**, 151983v (1977).
22) H. Gilman and I.T. Edward, *Can. J. Chem.*, **31**, 457 (1953).
23) Yoshitomi Pharmaceuticals, Japan. Patent 9094680 (1973).
24) Fujinaga Pharmaceuticals, Japan. Patent 74125538 (1973).
25) Standard Oil, U.S. Patent 3,514,458 (1967).
26) Fujinaga Pharmaceuticals, Japan. Patent 74125366 (1973).
27) A.R. Katritzky and P. Simmons, *J. Chem. Soc.*, 1511 (1960).
28) Ciba-Geigy, Swiss Patent 565,761 (1969).
29) F. Bryans and F.L. Pyman, *J. Chem. Soc.*, 549 (1929).
30) Takara Shuzo Co., Ltd.; Nippon Shinyaku Co. Ltd., Ger. Offen. 2,602,340 (1976); *Chem. Abstr.*, **85**, 142995g (1976). Takara Shuzo Co., Ltd.; Nippon Shinyaku Co. Ltd., Ger. Offen. 2,524,574 (1975).
31) W.R. Boon, *Chem. Ind.*, 782 (1965).
32) R. Lukes and J. Pliml, *Chem. Listy,* **49**, 1836 (1955).
33) Y.V. Kurbatov, *et al., Tr. Samarkand. Gos. Univ.*, 43 (1969); *Chem. Abstr.*, **75**, 48836c (1971).
34) S.V. Abdullaev, *et al., Ref. Zh. Khim.*, Abstr. No. 10Zh320 (1973); *Chem. Abstr.*, **80**, 108322x (1974).
35) S.V. Abdullaev, *et al., Tr. Samarkand. Gos. Univ.*, 52 (1969).
36) D.A. Inoyatova, *et al., Ref. Zh. Khim.*, Abstr. No. 5Zh491 (1970); *Chem. Abstr.*, **74**, 125364f (1971).
37) O.S. Otroshchenko, *et al., Nauchn. Tr., Tashkentsk. Gos. Univ.*, 24 (1964); *Chem. Abstr.*, **63**, 3007h (1965).
38) Imperial Chemical Industries, British Patent 1,276,253 (1970).
39) Reilly Tar, U.S. Patent 3,049,547 (1961).
40) T. Kauffmann and A. Mitschker, *Tetrahedron Lett.*, 4039 (1973).
41) A. Mitschker, U. Brandl, and T. Kauffmann, *ibid.*, 2343 (1974).
42) T. Kauffmann, A. Mitschker, and H.-J. Streitberger, *Angew. Chem.*, **84**, 829 (1972).
43) K. Kahmann, H. Sigel, and H. Erlenmeyer, *Helv. Chim. Acta,* **47**, 1754 (1964).
44) H. Sigel, *et al., ibid.*, **55**, 610 (1972),
45) K. Kahmann, H. Sigel, and H. Erlenmeyer, *ibid.*, **48**, 295 (1965).
46) H. Adkins and H.L. Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).
47) F.W. Vierhapper and E.L. Eliel, *J. Org. Chem.*, **40**, 2734 (1975).
48) I.v. Braun, A. Petzold, and A. Schultheiss, *Ber.*, **56**, 1347 (1923).
49) Z.A. Batyrbekova, *Deposited Doc.*, VINITI 61 (1974); *Chem. Abstr.*, **86**, 179467h (1977).
50) G.A. Klimov and M.N. Tilichenko, *Khim. Geterotsikl. Soedin.*, 175 (1969); *Chem. Abstr.*, **70**, 114984z (1969).
51) C.G. Overberger, I.G. Lombardino, and R.G. Hiskey, *J. Am. Chem. Soc.*, **79**, 6430 (1957).
52) Hoechst AG, Ger. Patent 2,139,779 (1971); *Chem. Abstr.*, **78**, 97292t (1973).
53) H.C. Brown and B. Kanner, *J. Am. Chem. Soc.*, **88**, 986 (1966).
54) H.C. Van der Plas and T.H. Crawford, *J. Org. Chem.*, **26**, 2611 (1961).
55) Y. Okamoto and K.J. Lee, *J. Am. Chem. Soc.*, **97**, 4015 (1975).
56) W.I. le Noble and Y. Ogo, *Tetrahedron,* **26**, 4119 (1970).
57) L. Van der Does, A. Van Veldhuizen, and H.J. den Hertog, *Recl. Trav. Chim. Pays-Bas,* **93**, 61 (1974).

Page intentially blank

Page intentially blank

Aldrichimica Acta

Volume 14, Number 2, 1981

Polymeric Dyes

Bromotrimethylsilane and Iodotrimethylsilane — Versatile Reagents for Organic Synthesis

chemists helping chemists in research & industry

aldrich chemical co.

Aldrichimica Acta

Volume 14, Number 2, 1981
A publication of the ALDRICH CHEMICAL COMPANY

Main Sales Office:
P.O. Box 355
Milwaukee, Wisconsin 53201
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6300
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo, Japan
Telephone: 03-258-0155.0156
TWX: 2222518

In Israel:
Sigma Israel Chemical Co.
P.O. Box 37673
Tel Aviv, Israel 61360
Telephone: 03-612315
Telex: (922) 35645

About Our Cover:

We have asked our chemist-collector about his criteria for including a given painting in his collection, and he has told us that he prefers Dutch 17th century portraits and "histories", especially Biblical and of the school of Rembrandt, well-drawn and strong in color. He had first seen this large (oil on canvas, 41 × 46-1/2 inches) *Baptism of the Eunuch* (Acts 8) many years ago in the living room of a great collector in England, Dr. Efim Schapiro, who had simply called it "Rembrandt School." The most stunning feature of this "history" is its contrast of colors, the cherry red of the little boy's dress and the shining gold of the eunuch's coat. Charming, also, is the blue Delft dish held by the little boy, a charm enhanced by the incongruity of a Delft dish in a New Testament story.

Our chemist believes that this was painted by Jacob Backer, generally thought to have been a Rembrandt student in Amsterdam in the early 1630's. There is no definite proof, although Backer and Rembrandt occasionally used the same models. For instance, the head of Democritus in Backer's painting of *Democritus Visited by Hippocrates* (Fig. 1) which we used on the cover of our biochemical catalog is of the same model used by Rembrandt for St. Paul in his painting of *St. Peter and St. Paul in Discussion* (Fig. 2) of 1628, now in Melbourne.

This *Baptism of the Eunuch* is not particularly "Rembrandtesque" and so may be an early work, before Backer became influenced by Rembrandt. The fourth figure from the right, the young man who looks so out of place in this New Testament story, may be a self-portrait.

Fig. 1

Fig. 2

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

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

Lab Notes

When the seal (vacuum gasket) in our Büchi Rotavapor R recently developed a leak necessitating a seal replacement, we learned that the current (mid-1980) cost of the required tool for seal removal was $85. We wished to avoid this expense, if possible. A new-style fluorocarbon seal does not require use of such a tool, but the removal of the original piece still posed a problem. The following comments are applicable to the models R and RE.

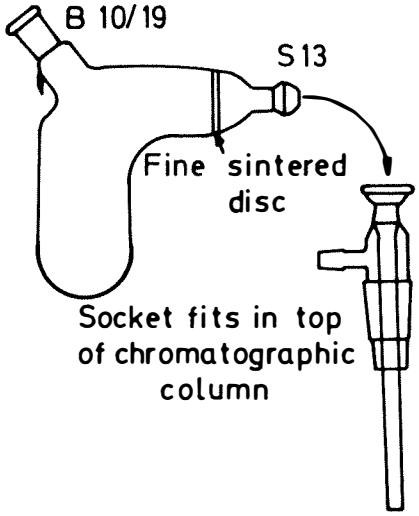
An easy solution was obtained by first removing the large coil spring and plastic screw coupling from the outside of the condenser and then carving away all the exposed rubber from the old seal. This exposed the metal washer which is responsible for the very tight pressfit of the original seal. The base of the condenser was immersed in aqua regia overnight. This resulted in complete solution of the washer and permitted easy removal of the residue the next day. Thorough cleaning should precede installation of the newer fluorocarbon seal.

Robert Rothchild
Assistant Professor, Science Department
John Jay College of Criminal Justice
City University of New York
445 West 59th St., New York, NY 10019

It is always convenient to eliminate as many steps in experimental procedures as possible, especially when dealing with difficult samples. The following apparatus has proved useful for loading dissolved asphaltene derived from coal-to-oil conversion processes onto chromatographic columns.

Powdered asphaltene is accurately weighed into the apparatus *via* the B10/19 socket and a known volume of solvent is introduced (*e.g.*, by pipette) as shown in the figure. When as much of the sample as possible has dissolved (the lower bulb of the apparatus can be immersed in hot water to aid dissolution, if necessary) the apparatus is turned 90°, seated on the suction column, and the solution is sucked through gently, directly onto the chromatographic support. In dealing with solvents having low boiling points (*e.g.*, diethyl ether) suction causes the solvent to bubble up from the column, in which case the application of slight pressure to the sample holder is preferred.

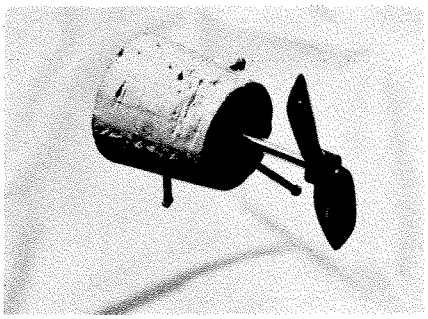
When the solution has been drained off, the apparatus is dried and weighed. The concentration of the solution added to the chromatographic column can then be calculated.



The apparatus eliminates some transfer steps and therefore cuts down on sample loss, for example, that remaining on glassware surfaces, sockets, taps, etc.

Dr. R. D. Davies
Fuel Research Institute
P.O. Box 217
Pretoria, South Africa 0001

It is often advantageous to have an airflow monitor in a fume hood. A simple monitor consists of a model airplane propeller (from a hobby shop) mounted on a needle stuck in a cork, with a short length of plastic tubing between the cork and the



propeller. Three nails can provide the legs of the airflow monitor which, when placed at the back of the hood, spins for years, unless airflow is interrupted.

Charles E. Gragg
Research Scientist
Burroughs Wellcome Co.
3030 Cornwallis Rd.
Research Triangle Park, NC 27709

One of life's minor irritations is the weighing of small quantities of statically charged peptide/protein material from lyophilization. Under normal circumstances, the light, fluffy, material flies everywhere.

We have found that using a commercial laundry antistatic cloth (Bounce) to wipe the outside of the receiving vessel, the glass balance doors, the containing vessel and the balance knobs, eliminates this problem.

Lucila Licate
Larry Taylor
Lafayette Clinic
951 East Lafayette
Detroit, Michigan 48207

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

"Please Bother Us."

by Alfred Bader.

Recently Professor J. C. Stowell at the University of New Orleans suggested that we offer dicinnamalacetone, an indicator for detecting excess hydrogen halides in many organic solvents (acetic acid, acetone, chloroform, dichloromethane, toluene, but not alcohols). It turns from yellow to a brilliant red. It is a very useful indicator, because so often, when a product is in contact with HCl or HBr for any length of time, yields decline. For example, Professor Stowell uses it in the addition of HBr to acrolein. Naturally, we made dicinnamalacetone right away.

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

Polymeric Dyes

D. J. Dawson
Dynapol
Palo Alto, CA 94304

I. INTRODUCTION

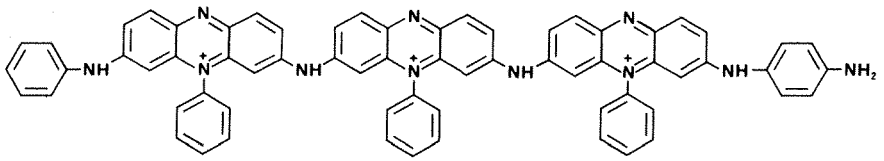
The origins of polymeric dyes are no doubt lost in antiquity along with the name of the first chemist to synthesize one. In the broadest sense of the word, a polymeric dye is a "high-molecular-weight" colored compound composed of a number of repeating units. This type of definition would include Aniline Black (**1**), a black dye discovered over a century ago and prepared by the oxidation of aniline with copper or vanadium salts. The broad definition of polymeric dye given above would also include many polymers, synthetic or natural, soluble or cross-linked, since few of these compounds are stark white. For the purpose of further discussion, the definition of polymeric dye will be considerably restricted to include only those compounds which are "useful" polymers (a molecular weight of at least 1,000 daltons), "useful" dyes (a high tinctorial strength), and soluble in one or more solvents.

With this working definition in hand, our experience in the field of polymeric dyes can now be described. Dynapol was founded in 1972 with one main objective: to develop new food additives which would be nontoxic by virtue of being nonabsorbable from the gastrointestinal (GI) tract; from this overall objective the polymeric food-dye project was born. At that time, twelve food dyes were approved for use in the United States. Of the twelve dyes, three comprised the vast majority of the market: Tartrazine (**2**), Sunset Yellow (**3**, actually an orange dye), and Amaranth (**4**).

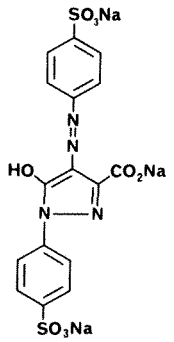
Clearly, then, our first goal was to prepare polymeric dyes to either duplicate these colors or to cover the same color range. This undertaking was all the more ambitious when the full list of product specifications was considered. These polymeric dyes must:

- be water-soluble to give sparkling clear solutions
- have a high tinctorial strength
- be inexpensive to produce on a multimillion lb/yr scale
- be anionic or uncharged (a cationic polymer would be precipitated by any number of typical food constituents)
- be stable to all the various stresses of food preparation, sterilization, storage, shipping, and use
- be stable to all forms of digestive and microbiological attacks in the GI tract so that no species small enough to be absorbed would be cleaved from the polymer.

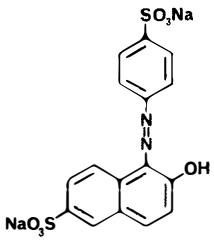
These were the most critical specifications; others covering product identity and performance numbered in the dozens. The successful synthesis of these and other polymeric dyes is described here.



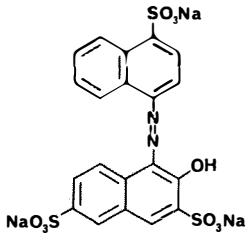
1



2
Tartrazine
FD & C Yellow #5



3
Sunset Yellow
FD & C Yellow #6



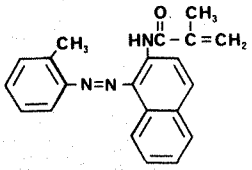
4
Amaranth
FD & C Red #2

II. SYNTHETIC APPROACHES; Polymeric Azo Dyes

At least four different strategies have been followed to prepare polymeric dyes.

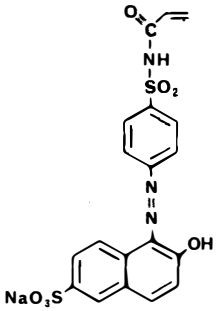
1. Polymerization of colored monomers

This approach has been reported[1] by several workers to be a viable one. Often this route takes the form of derivatizing a commercially available dye with a polymerizable group; an example is making acrylate esters or methacrylamide derivatives such as **5**.

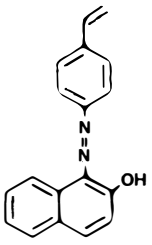


5

Concerned that neither ester nor amide links were sufficiently stable for food-dye use, Dynapol prepared dye monomers such as **6** and **7** by multistep procedures only to find that the combination of multiple nonquantitative reaction steps and mediocre polymerization properties rendered the entire route uneconomical.



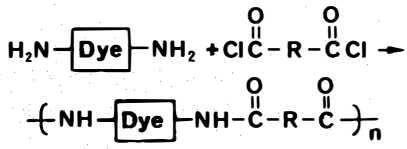
6



7

2. Polycondensation

Polycondensation was another route popular in the literature.[2] In its usual form, a dye containing two amino groups is condensed with a bis-acid chloride or a bis-isocyanate to afford a colored condensation polymer:



This approach was not pursued by Dynapol because the dyes with which we were working lacked the diamino functionality, the resulting polymers are held together by amide groups, and finally because the polydye molecular-weight specifications would put stringent requirements on starting-material purity which would, in turn, adversely affect the production economics.

3. High-molecular-weight derivatives of a single chromophore

One of the first commercially available polymeric dyes was marketed ten years ago by Milliken Chemicals. Called Versatint® dyes, these materials were prepared by the graft polymerization of ethylene oxide onto a commercial dye; the resulting product was simply a dye molecule with one or more poly(ethylene oxide) chains attached to it. In this fashion, the molecular weight of the polymeric dye could be adjusted to any desired size. These dyes were produced at the time for the textile fugitive dye market and were indeed of sufficiently high molecular weight that they were not retained by the textiles. Again, Dynapol chose not to pursue this approach because of a lack of suitable functionality on our target dyes, a severe tinctorial strength problem if only one chromophore was present on a polymer chain, and the potential difficulties of reproducible manufacture and effective quality control needed for food additives.

4. Polydyes made from preformed polymers

This approach was the one ultimately chosen by Dynapol. Although it has the disadvantage of a multistep process, the advantages inherent in the separation of the polymer-formation chemistry from the dye chemistry were more than adequate compensation. Once this decision was made, the next consideration was the multitude of possible routes to make polymeric dyes. One way to look at the options was to recognize that general nucleophile-electrophile reactions (alkylations, acylations, and many others) are some of the most reliable and high-yield synthetic processes known. The next question, then, was to decide whether the polymer should be the electrophile or the nucleophile. Figure 1 illustrates the two options with some known polymers.

One of our earlier routes to a polymeric version of Sunset Yellow is depicted in Figure 2. This route, which involved the nucleophilic attack of sulfonamide anion **9** on poly(epichlorohydrin) (**10**), followed by elaboration of the adduct **11** to the polydye **14**, was successful — usually. However, the problems that were encountered with crosslinking (and therefore insolubilization) taught us two valuable lessons:

- it does not take very much crosslinking to ruin the solubility of a polymer, and
- a polyelectrophile is crosslinked by a polynucleophile and *vice versa.*

Nature abounds in polynucleophiles (*e.g.*, water, many solvents, reagents, food components), but there are very few polyelectrophiles. Therefore, choosing a polynucleophile as a polymer backbone would virtually eliminate crosslinking as a serious side reaction. Although a few other dyes were built on poly(epichlorohydrin) and poly(chloromethylstyrene), the majority of our efforts was directed toward polynucleophiles.

Figure 1. Typical Electrophilic and Nucleophilic Polymers

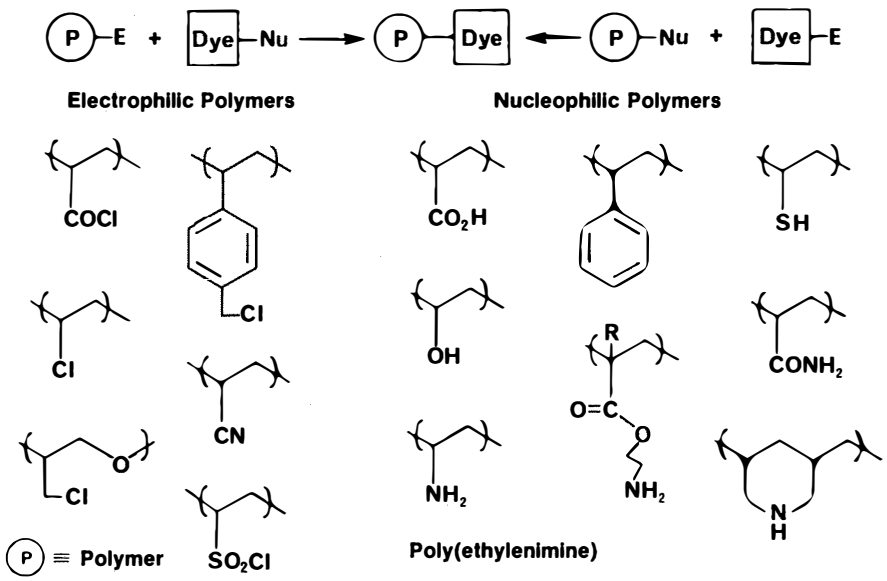
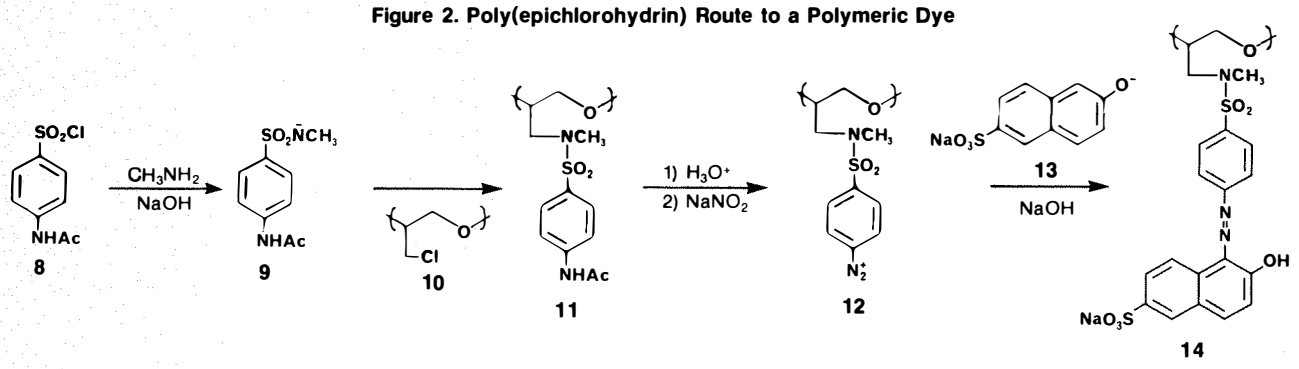


Figure 2. Poly(epichlorohydrin) Route to a Polymeric Dye



After much careful consideration, and for reasons too detailed to discuss here, polymeric amines were chosen as having the best combination of availability, reactivity, and product stability. Of the polyamines, poly(ethylenimine) was selected first since it was inexpensive and commercially available. The scheme used to prepare our first polyamine-based polydye is shown in Figure 3.

The sheer simplicity and the reproducibility of the synthetic process convinced us that we were on the right track. Unfortunately, the polydye **18** obtained from poly(ethylenimine) was soluble only at high pH. The neutral pH insolubility was clearly due to the poly(ethylenimine) which is a highly branched structure containing 1°, 2°, and 3° amines in the ratio of 1:2:1. The primary and secondary amines reacted completely with the sulfonyl chloride **8** but the tertiary amines could not. As a result, they were carried through the sequence unchanged and provided cationic sites in the final polydye at pH values below 11; the combination of scores of cationic and anionic sites in the same molecule caused the insolubility. The solution to this problem was to switch to a polyamine with only primary (or secondary) amines but no tertiary amines. Despite its cost and lack of availability,[3] poly(vinylamine) was chosen as the ideal backbone; the high density of amine functionality was a key factor in this choice. Since none of the known syntheses appeared to be commercially feasible, a new route to poly(vinylamine) was developed[4] and scaled up to provide the polydye program with literally thousands of moles of polyamine. With both an ample supply of polymer backbone and an economical method of converting it to polymeric azo dyes, the synthesis of Poly S™-119[4,5] and Poly T™-128[4,5] became a reality (Figure 4).[6] Over the last several years, this route to polymeric azo dyes has been used, with some development and slight modification, to prepare many other azo polydyes covering a wide range of hues. The syntheses of two of these dyes with outstanding color properties, Poly A™-133[5]

Figure 3. Poly(ethylenimine) Route to a Polymeric Dye

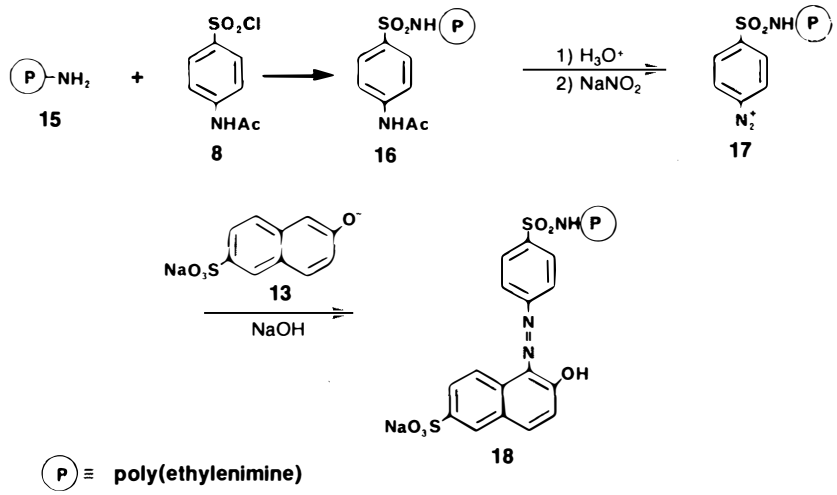
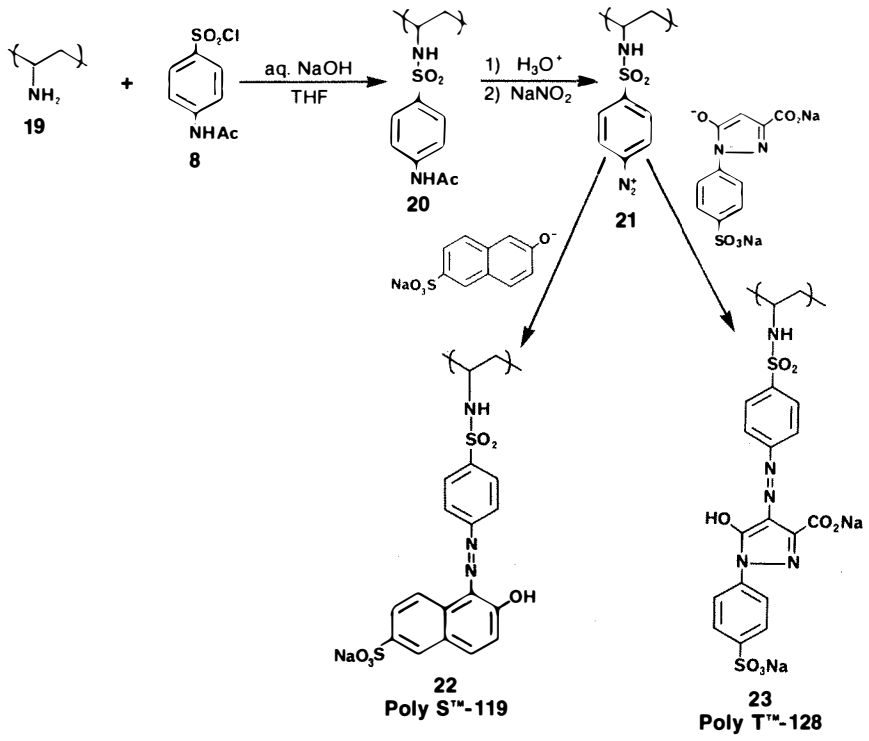


Figure 4. Syntheses of Two Polymeric Azo Dyes



and Poly Blk™-863[5] are shown in Figure 5.

Poly A™-133 is a bluish red dye similar, although not identical, to Amaranth. Poly Blk™-863 is coal black; its visible absorption spectrum (Figure 6) indicates a multitude of broad absorption modes, some of which may be due to the close packing of the chromophores along the polymer backbone.

This approach to polymeric azo compounds has been shown clearly to be flexible and adaptable to a wide variety of coupling agents. Over 110 polymeric azo dyes have been prepared as well as a number of polymeric drugs.

The success of the polymeric azo dyes **22** and **23** as food-dye candidates was short-lived; attachment of chromophores to the high-molecular-weight polymer (30,000-200,000 daltons) in no way guarantees biological inertness. In this case, azo-bond reduction and accompanying chromophore cleavage were found[7] to occur readily in the GI tract, presumably due to the presence of reductive cofactors of low molecular weight known to be present. Polyazo dyes were abandoned as food additives and the search then turned to other chromophore classes which were not susceptible to reductive cleavage. Polymeric dyes were prepared from many chromophore classes including nitroaniline, triarylmethane, xanthene, anthraquinone, phthalocyanine, benzanthrone, naphthalimide, and others. Obviously, new methods of attachment were required for each chromophore class; with few exceptions, amine polymers were found to make superior backbones. Our results with two of these chromophore classes, nitroaniline and anthraquinone, will be discussed below.

III. POLYMERIC NITRO-ANILINE DYES

As the search for polymeric food dyes turned away from the azo class, the goal became one of finding acceptable colors (particularly yellow and red) that would satisfy the needs of the food-processing industry; exact spectral matches to the existing food colors were no longer necessary. The nitroaniline chromophore class seemed ideal because it would provide a direct C-N-C link between chromophore and backbone *via* simple nucleophilic displacement (see Figure 7). The chromophore precursors were relatively inexpensive and a wide range of colors from yellow to red was potentially feasible. In practice, the most success was obtained in making yellow dyes.

Since good water solubility is necessary for a polymeric food dye, the chromophore should contain at least one sulfonic acid

Figure 5. Syntheses of Red and Black Polymeric Azo Dyes

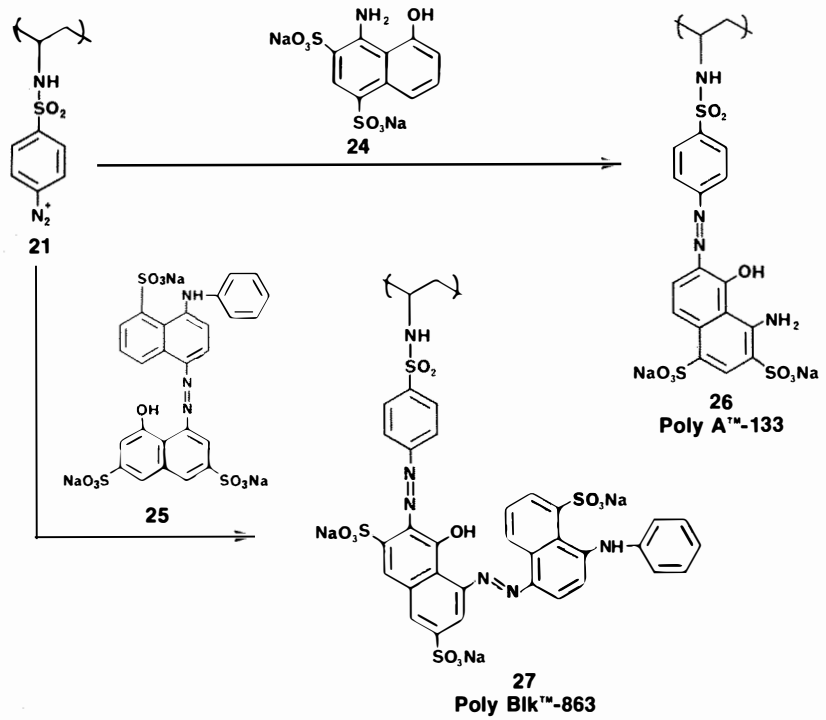


Figure 6. Visible Spectrum of Poly Blk™-863

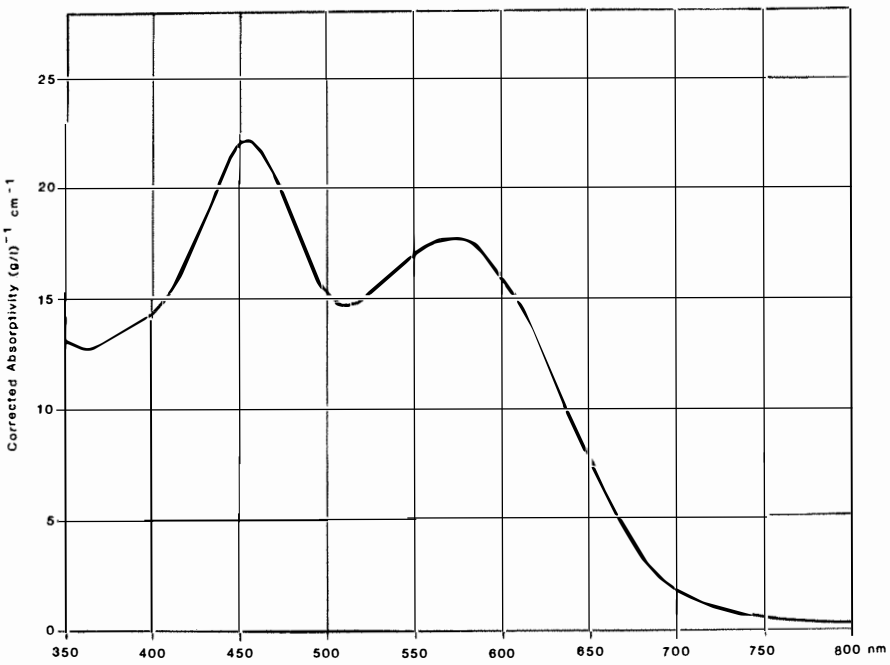
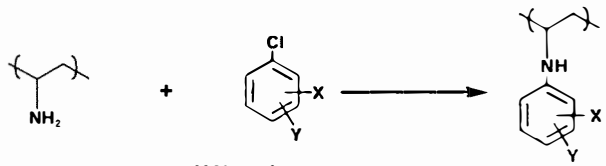


Figure 7. Generic Route to Nitroaniline Polydyes



X,Y ≡ electron-withdrawing groups

group. Synthesis of the polydyes made from several commercially available chloronitrobenzene derivatives soon led to the selection of sodium 4-chloro-3-nitrobenzenesulfonate (**28**) as the ideal chromophore precursor. Figure 8 depicts the synthesis of Poly Y™-606.[5]

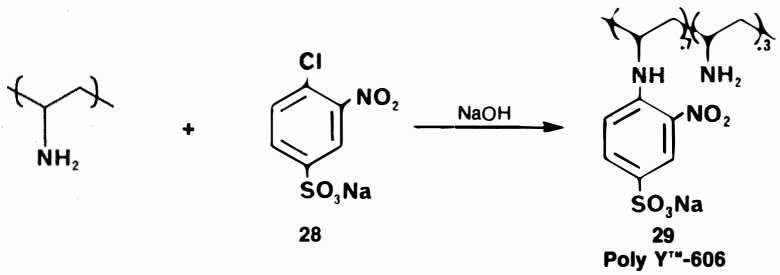
Unlike the preparation of the azo polydyes, chromophore substitution could not be pushed easily to completion; however, since the tinctorial strength of the polydye increased only slightly when the chromophore substitution was forced above 70 mer%,* 60-70 mer% was chosen as the specification. A further minor modification was made to the polydye structure to obtain Poly Y™-607, which was selected as the yellow food-dye candidate.

Research along other nonfood lines suggested that there might be a use for a purely cationic dye. Purely anionic dyes such as the azo dyes Poly S™-119 and Poly T™-128 were generally quite fugitive and would not adhere strongly to many solid substrates. Poly Y™-606, with both anionic and cationic character, was considered to be ampholytic and, under some pH conditions, would adhere strongly to substrates such as paper pulp. A completely cationic dye should adhere even more strongly to a wide variety of substrates. The most obvious route to a cationic dye is to start with a cationic polymer, such as poly(vinylamine), and partially substitute it with an uncharged chromophore. A number of these cationic polydyes were made in both the nitroaniline and anthraquinone chromophore classes. These polydyes generally exhibited lower solubility than their anionic counterparts but were still truly soluble in mildly acidic water. The synthesis of one of the best of these polydyes, Poly Y™-636,[5] is illustrated in Figure 9.

IV. POLYMERIC ANTHRAQUINONE DYES

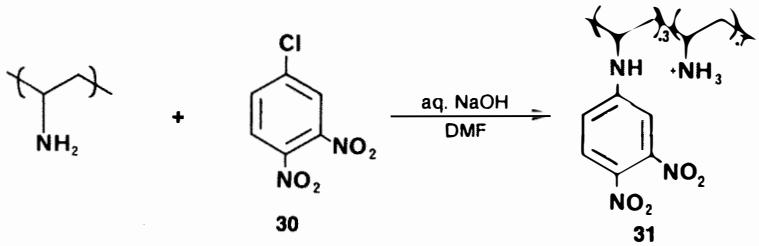
The search for a good bluish red polymeric dye soon turned toward the anthraquinone class. Many red anthraquinone dyes are known and most can be represented by the general structure **32**; a closely related class, the anthrapyridones, is illustrated by structure 33.

Figure 8. Synthesis of a Yellow Polymeric Nitroaniline Dye

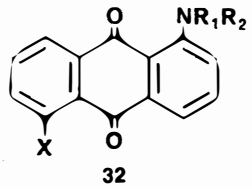


28 **29** **Poly Y™-606**

Figure 9. Preparation of a Yellow Cationic Polydye

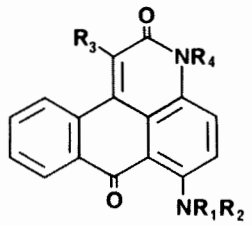


30 **31** **Poly Y™-636**



32

R_1, R_2 = H, alkyl, or aryl
X = H or NR_1R_2

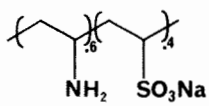


33

R_1, R_2, R_3, R_4 = H, alkyl, or aryl

Since the red color of these dyes requires an amino group at the 1-position of anthraquinones or the 6-position of anthrapyridones, a polymeric amine appeared to fit this chemistry well. These amino derivatives are usually prepared from the corresponding bromo compounds by a copper(I)-catalyzed Ullmann condensation. At the onset, it was not obvious that this kind of reaction would occur readily and cleanly with a polymeric amine; in practice, the Ullmann reaction proceeded very smoothly with poly(vinylamine).

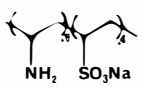
A feature which is conspicuously absent in almost all of the red anthraquinone precursors is a sulfonate solubilizing group. Some sulfonated derivatives were prepared but the final colors lacked the brilliance of some of the other, non-sulfonated chromophores. The solution to this dilemma was to prepare a copolymer (**34**) containing both amine and sulfonate.[8]



34

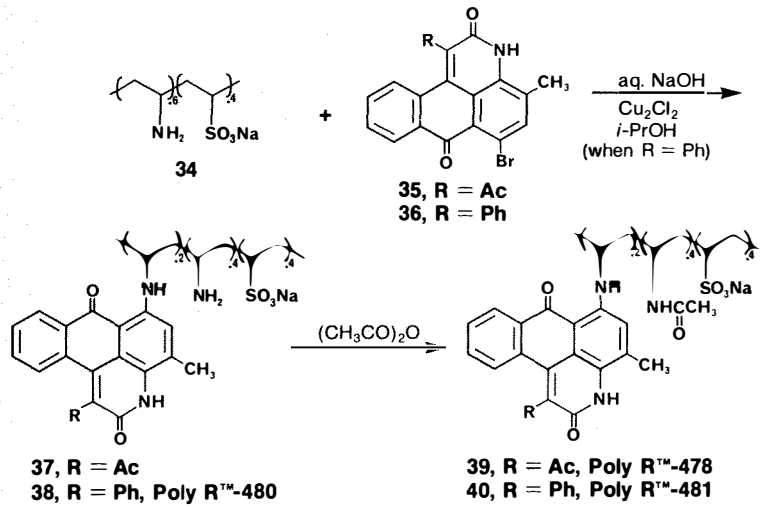
By using this copolymer, even the most hydrophobic of chromophores could be brought into aqueous media to afford sparkling clear solutions. With this polymer and the Ullmann condensation, several polymeric red and blue dyes were developed as food-dye candidates. The syntheses of four of these dyes are described in Figures 10 and 11. For reasons apparently independent of the size of the chromophore and perhaps related to the copper ion's need for two adjacent amines for ligands, the chromophore attachment could not be readily forced beyond 30 mer%; a more economical 20% was eventually chosen. The residual amines (40 mer%) of ampholytic polydyes like Poly R™-480[5] (**38**) were acetylated to prevent precipitation of the polydyes under strong acid conditions such as those found in soft drinks. Both Poly R™-478[5] (**39**, violet) and Poly R™-481[5] (**40**, magenta) were developed concurrently as substitutes for FD & C Red #2, with Poly R™-481 eventually being chosen for its closer color match. The polymeric blue dye, Poly B™-41 I[5] (**41**), is unique in that it employs both chromophore and backbone sulfonates for

*The term "mer%" expresses the fraction of repeating backbone units (in this case, two-carbon units) substituted by any given moiety; it is analogous to "mole%" except that the units are covalently bound together instead of being individual molecules. As an example, the polymer depicted as:



can be described as 60 mer% amine and 40 mer% sulfonate. Neither the structure drawn above nor its mer% description implies any specific sequence of the groups.

Figure 10. Synthesis of Red Polymeric Anthrapyridone Dyes



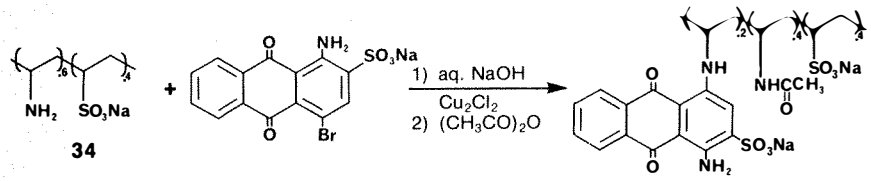
34

35, R = Ac
36, R = Ph

37, R = Ac
38, R = Ph, Poly R™-480

39, R = Ac, Poly R™-478
40, R = Ph, Poly R™-481

Figure 11. Preparation of a Blue Polymeric Anthraquinone Dye



34

41
Poly B™-411

solubilization; unlike the azo dyes, the chromophore sulfonate alone was unable to provide more than marginal water solubility.

V. GENERAL PROPERTIES

The ten polymeric dyes described above were selected to illustrate the flexibility of Dynapol's approach to these polymer-bound species. A great many other polydyes have been prepared using these methods; at present, the total is 320 and still growing. All of these polydyes are water-soluble, some as high as 30% by weight; they also have some solubility in nonaqueous but polar solvents such as DMSO, DMF, glycols and formic acid. The molecular weights of the backbone polymers range from 40,000-60,000 daltons for the copolymer and 100,000-160,000 daltons for poly(vinylamine); accordingly, the polydye weights are somewhat higher. Viscosities are noticeable above 5 wt %, but solutions are deeply colored to the point of opacity at far lower concentrations. Other properties of the polydyes include:

- very low diffusion rate
- nonvolatility
- insolubility in most organic solvents
- generally no surface activity except in the case of backbone-solubilized polydyes containing a very hydrophobic chromophore, such as Poly R™-481
- readily precipitated by multivalent cations, *e.g.*, Al^{+++}, Ca^{++}
- nonfluorescent at normal chromophore loadings.

The specific spectral properties of the ten polydyes discussed in this article are listed in Table I.

VI. USES

The properties listed above for Dynapol's polymeric dyes suggest that they could find a great many applications beyond the original food-additive use. A number of these uses have already been demonstrated; others are speculative.

A. Known Uses

- Nontoxic additives for food and drugs (when approved).
- Bulk paper dyeing — properly formulated polydyes have demonstrated complete exhaustion (retention) in bulk paper fibers to very high loading levels with subsequent very strong bleed resistance.
- Inks — polydyes can be highly purified, form stable solutions, and do not crystallize. These properties are advantageous in ink applications where clogging of orifices is a concern. In addition, due to the hundreds of binding sites, properly formulated polydyes exhibit very low bleed from paper after drying, even when subjected to water immersion.
- Hair dyes — several of the polydyes in each of the charge classes have been formulated to make excellent temporary or permanent hair dyes; lack of skin absorptivity is an obvious advantage of polydyes in this application. Further, the polymeric properties of the dyes give superior control in the use of temporary hair dyes.
- Fugitive dyes — like the Versatint® dyes, unformulated polydye solutions exhibit little or no attraction to most textiles; not only is this useful to the textile industry but it is a joy to the chemists working with the dyes.
- Ultrafiltration membrane testing and calibration — UF membranes are often tested only by the water flux through them; this test does not distinguish between many

Table I. Comparison Data for Ten Selected Polydyes[5]

Name	Color	Chromophore	Charge	λmax, nm	Approx. absorptivity, corr. $[(g/l)^{-1}cm^{-1}]$
Poly A™-133	Red	Azo	Anionic	530	48
Poly B™-411	Blue	Anthraquinone	Anionic	593	13
Poly Blk™-863	Black	Disazo	Anionic	456	23
Poly R™-478	Violet	Anthrapyridone	Anionic	519	13
Poly R™-480	Magenta	Anthrapyridone	Ampholytic	513	15
Poly R™-481	Magenta	Anthrapyridone	Anionic	513	14
Poly S™-119	Orange	Azo	Anionic	475	34
Poly T™-128	Yellow	Azo	Anionic	430	39
Poly Y™-606	Yellow	Nitroaniline	Ampholytic	430	14
Poly Y™-636	Yellow	Nitroaniline	Cationic	425	11

small holes and a few large holes, nor does it detect small membrane ruptures. Dynapol's polydyes are purified by UF techniques and, in turn, have been used to monitor the membranes for leaks. Likewise, a mixture of polydyes of different colors and molecular weights could be used as a rapid membrane calibrator by simply measuring the color of the transported dye.

- Gel-permeation chromatography standards — blue dextran, which is a high-molecular-weight polymeric dye itself, has been used for years to determine the exclusion volume of GPC systems. Polydyes could function in the same way or even as varicolored nonexclusion-limit calibrators.
- Superior lakes — dyes containing sulfonate groups are often precipitated with an aluminum hydroxide gel to form insoluble pigments known as lakes. Lakes are used in food and cosmetics where dye migration is undesirable and clarity unimportant (*e.g.*, cake frosting). Polydyes have literally hundreds of sulfonate groups per molecule; lakes made with these dyes are extremely stable, even to dilute hydrochloric acid, which will dissolve normal lakes.[9]
- GI tract studies — polymers such as Carbowax™ are often used as markers in the GI tract to measure absorption of other species or clearance rates. Since polydyes are highly colored, they make visible markers.

B. Other Possible Uses

- Biological stains — the high molecular weight of the polydyes should exclude them from certain regions of tissues and cells while the multiplicity of charged sites could allow stronger binding to other sites.
- Diffusion-restricted uses, photography, printing — due to their large molecular size, polydyes have a very low diffusion rate in water and a virtually zero rate in structured media such as gelatin.[10] This property could prove to be valuable in certain cases such as color films and multidye color printing where previously only pigments exhibited low diffusion rates.
- Water-flow studies — the very low diffusion rate of polydyes in water could be used in engineering studies of water flow; they would provide highly visible demonstrations of laminar *vs.* turbulent flow, vortices, and water-flow patterns around fixed or moving objects.
- Studies of polymer-diffusion rates — although the diffusion rate is low, it probably is not absolutely zero; studies on polymer-diffusion rates which heretofore required UV or radiolabelled polymers might well be aided by such visible polymers.
- Uses where total insolubility in organic solvents is important — like most polymers, polydyes are absolutely insoluble in solvents with a solubility parameter and polarity much different from those of the polymer. Although the solubility parameters of all the polydyes have not been measured, their solubility in water and insolubility in ethanol suggest that they will be insoluble in most organic solvents such as ether, THF, chloroform, toluene, hexane, ethyl acetate, and acetone. As a result, substrates (paper, cloth, Drierite®, alumina, etc.), would lose none of their color in these solvents.

Dynapol's polymeric dyes represent a completely unique class of compounds unlike any polymer or dye previously known. The above lists of applications should be just a starting point for interested readers many of whom, it is hoped, will think of other uses in their own field of interest. Although the syntheses of several of these dyes have been published,[4,8] they are somewhat lengthy for the individual who has no access to some of the key intermediates. Now that ten of these polydyes are available from Aldrich for evaluation, those who are interested in these dyes will find them readily accessible.

References and Notes:

1) (a) Ida, T.; Takahashi, S.; Utsumi, I. *Yakugaku Zasshi* **1969**, *89*, 517; (b) Ida, T.; Watanabe, T.; Takahashi, S.; Utsumi, I. *ibid.* **1969**, *89*, 524; (c) Utsumi, I.; Ida, T.; Watanabe, T.; Takahashi, S.; Hasimoto, T. *Kogyo Kagaku Zasshi* **1970**, *73*, 1151; (d) Blackhall, A.; Boyd, V.; Fishwick, B.R.; Macheta, Z.; Robinson F. Brit. Patent 1 269 627, 1972.
2) (a) Nagashima, S.; Tsuchiya, K.; Tsuneda, T. Japan. Patent 73 08 562, 1973; (b) Eijima, S.; Tsuchiya, Y.; Tsuneta, T. Japan. Patent 73 25 667, 1973; (c) Shiba, M.; Hiramasu, H.; Nakano, H.; Kawano, Y.; Shigeri, Y.; Kondo, T. *Polym. J.* **1973**, *4*, 366; (d) Gangneux, P.; Marechal, E. *Bull. Soc. Chim. Fr.* **1973**, 1466.
3) In 1973, poly(vinylamine) was available only from Polysciences for $600/100g.
4) Dawson, D.J.; Gless, R.D.; Wingard, Jr., R.E. *J. Am. Chem. Soc.* **1976**, *98*, 5996.
5) This is one of ten polymeric dyes now available from Aldrich.
6) Although the structures of these azo polydyes as drawn indicate that the compounds are homopolymers, this is not strictly true. There are small amounts of other units: primary aliphatic amines from incomplete Schotten-Baumann reaction with the sulfonyl chloride **8** as well as diazotization side products such as polymer-bound phenols and anilines. The sum of these units will vary but rarely exceeds 5-10 mer%.
7) (a) Brown, J.P. *Abstracts of the Annual Meeting, Am. Soc. Microbiol.* **1976**, 123; (b) Honohan, T.; Enderlin, F.E.; Ryerson, B.A.; Parkinson, T.M. *Xenobiotica* **1977**, *7*, 765.
8) Dawson, D.J.; Otteson, K.M.; Wang, P.C.; Wingard, Jr., R.E. *Macromolecules* **1978**, *11*, 320.
9) Bellanca, N.; Furia, T.E. U.S. Patent 4 167 422, 1979.
10) Bellanca, N.; Furia, T.E. U.S. Patent 3 937 851, 1976.

About the Author

Dr. Daniel Dawson obtained his B.S. degree in Chemistry from the University of North Carolina at Chapel Hill in 1967 and his Ph.D. from the California Institute of Technology in 1971. After 1-1/2 years of postdoctoral work for Professor E. J. Corey at Harvard University, Dr. Dawson joined the staff of Dynapol in 1972 where he is now the Director of Chemical Research and Development.

Dr. Dawson's research group at Dynapol has been responsible for the discovery, development, and scale-up of two polymeric food colors and one polymeric antioxidant as well as the basic chemistry and process development behind the production of *N*-vinylacetamide and the polymeric amines used as backbones for the polymeric dyes.

Drying of tert-Butyl Hydroperoxide

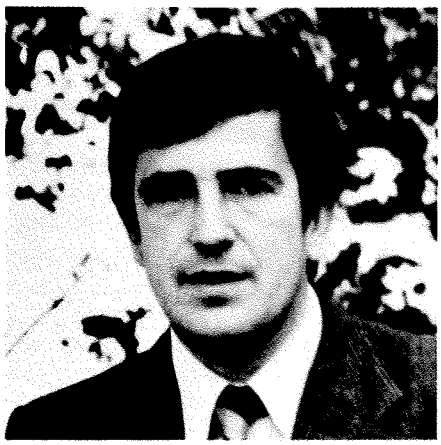
A recent Acta article[1] described the practical consideration of handling the potentially hazardous *tert*-butyl hydroperoxide (TBHP) which is most often used as an aqueous solution. Caution must be exercised when drying concentrated solutions of TBHP.

13X molecular sieves (pore size ~9Å) must not be used under any circumstances to dry TBHP (heat of absorption of TBHP causes ignition),[1] but 4A[1] and 3A[2] sieves have been reported to be effective and safe in the preparation of small quantities of absolute TBHP (may have less than 0.01 mol/l H_2O).

1) Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* **1979**, *12*, 63.
2) Langhals, H.; Fritz, E.; Mergelsberg, I. *Chem. Ber.* **1980**, *113*, 3665.

Bromotrimethylsilane and Iodotrimethylsilane — Versatile Reagents for Organic Synthesis[1]

Arthur H. Schmidt
Abteilung für Organische Chemie und Biochemie
Fachhochschule Fresenius
6200 Wiesbaden, West Germany



INTRODUCTION

In the mid-seventies several research groups independently started investigations on the synthetic use of bromotrimethylsilane and iodotrimethylsilane. Within a short period of time it became evident that the reactivity of both reagents differed dramatically from that of chlorotrimethylsilane and that numerous standard procedures of organic synthesis may be effected by bromo- and iodotrimethylsilane under extremely mild conditions. Furthermore, it became clear that bromo- and iodotrimethylsilane should offer a variety of novel functional group transformations. Thus, both compounds have rapidly become important reagents for the organic chemist.

PREPARATION

The methods for the generation of bromo- and iodotrimethylsilane on a preparative scale are based on the cleavage of a Si-Y bond by means of bromine or iodine, respectively, or by a halogenation reagent MX_n. Thus, bromotrimethylsilane was prepared in 73% yield by the treatment of hexamethyldisiloxane with phosphorus tribromide in the presence of a catalytic amount of ferric chloride hexahydrate (eq. 1).[2] The yield of bromotrimethylsilane was improved to 81% by using a mixture of phosphorus tribromide/bromine,[3] to 87% by the use of catechyl phosphorus tribromide,[3] and to 86% by the treatment of hexamethyldisiloxane with aluminum tribromide.[4] The following physical data[2] have been reported: clear, colorless liquid; bp 79.9°C/754 torr; d_4^{20} 1.188; air- and moisture-sensitive. Analogously, iodotrimethylsilane is prepared by treatment of hexamethyldisiloxane with aluminum triiodide, generated *in situ* from the elements (eq. 2).[5-7] According to Voronkov[5] iodotrimethylsilane is thus obtained in 93% yield as a colorless liquid; bp 107°C/760 torr; d_4^{20} 1.422;[4] 1.470.[5] The compound is extremely sensitive to light, moisture, and air.

An excellent alternative procedure[8] for the preparation of bromo- and iodotrimethylsilane consists of the treatment of a mixture of 1,4-bis(trimethylsilyl)-1,4-dihydronaphthalene and the 1,2-isomer[9] with bromine and iodine, respectively (eq. 3). This preparation procedure was recently optimized by us,[10] affording bromotrimethylsilane and iodotrimethylsilane in 94% and 92% yield, respectively.

IN SITU GENERATION

Despite the ready availability of iodotrimethylsilane, routine application in organic synthesis may be difficult due to its marked instability toward hydrolysis. This has prompted several groups to devise suitable methods for the *in situ* generation of iodotrimethylsilane. Though bromotrimethylsilane is less sensitive several of these procedures have also been extended to its *in situ* preparation. Table 1 gives a summary of these methods.

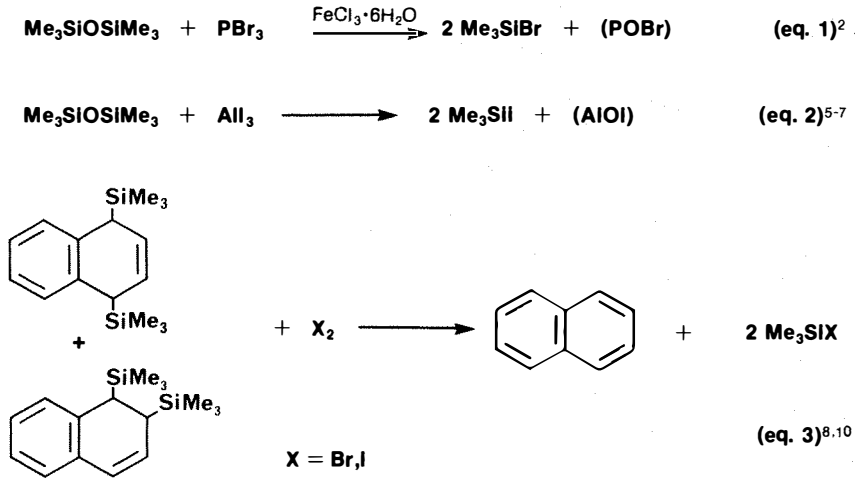
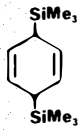
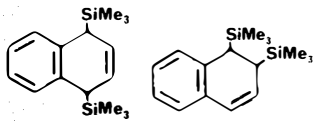
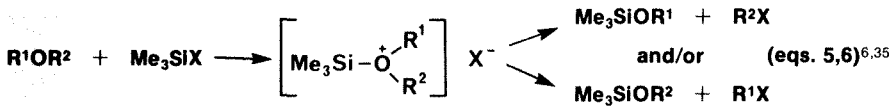


Table 1. Methods for the *in situ* Generation of Bromotrimethylsilane and Iodotrimethylsilane

Reagents	Products	Solvent	Ref.
$2\ Me_3SiCl + MgBr_2$	$2\ Me_3SiBr + MgCl_2$	diethyl ether (as solvate)	11
$2\ Me_3SiCl + MgI_2$	$2\ Me_3SiI + MgCl_2$	xylene	11
$Me_3SiCl + NaI$	$Me_3SiI + NaCl$	a) neat or excess substrate	12,13,14
		b) CH_2Cl_2	12
		c) MeCN	12,15
$Me_3SiCl + LiI$	$Me_3SiI + LiCl$	a) CH_2Cl_2	12,14
		b) CCl_4	16
$Me_3SiCl + NaBr$	$Me_3SiBr + NaCl$	a) MeCN	17,18,19
		b) neat or excess substrate	19
$Me_3SiPh + I_2$	$Me_3SiI + PhI$	a) neat	20
		b) nitromethane	21
$Me_3SiCH_2CH{=}CH_2 + I_2$	$Me_3SiI + CH_2{=}CHCH_2I$	aprotic solvents	22
 $+ I_2$	$2\ Me_3SiI + PhH$	aprotic solvents	22
mixture of $+ 2\ X_2$	$4\ Me_3SiX$ a) X = Br; b) X = I	a) neat or excess substrate	23
		b) MeCN	24
		c) CCl_4	25
$Me_3SiSiMe_3 + I_2$	$2\ Me_3SiI$	a) neat	26
		b) CCl_4	26,27
		c) $CHCl_3$	28
$Me_3SiSiMe_3 + Br_2$	$2Me_3SiBr$	neat or PhH	45

(eq. 4)[34]



(eqs. 5,6)[6,35]

Table 2. Cleavage of Ethers by Means of Iodotrimethylsilane

R^1	R^2	Solvent	Temp./Time	Yield[a]	Ref.
Ph	Me	neat	*ca.* 130°/21h	99%	34
2-MePh	Me	neat	*ca.* 130°/30h	97%	34
4-MePh	Me	neat	*ca.* 130°/18h	99%	34
4-BrPh	Me	neat	*ca.* 130°/36h	98%	34
Hexyl	Me	$CDCl_3$	25°/6h	95%	6
Hexyl	Et	$CDCl_3$	25°/12h	48.7%	6
Hexyl	*t*-Bu	CCl_4	25°/0.1h	100%	6
Ph	Me	$CDCl_3$	25°/48h	100%	6
4-BrPh	Me	$CDCl_3$	25°/120h	100%	6

[a]The yields refer to the trimethylsilyl ethers R^1OSiMe_3

USE IN ORGANIC SYNTHESIS

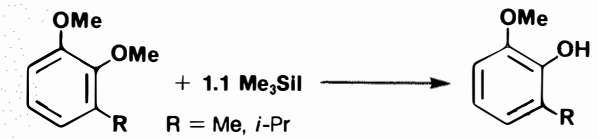
Ether Cleavage

Several early investigations have dealt with the cleavage of various ethers by means of bromo- and iodotrimethylsilane.[11,29-33] However, the great preparative value of this method and its general applicability were not clearly realized for a long time. In 1976 Voronkov[34] demonstrated that the heating of 16 differently substituted aryl methyl ethers with iodotrimethylsilane to 120-130°C for 20-50hrs afforded the corresponding aryloxytrimethylsilanes in practically quantitative yields (eq. 4). Investigations on the same topic were independently carried out by others.[6,35] The experimental results summarized by Jung indicated the possibility of cleaving ethers selectively in the presence of structurally different ethers and of other compounds with various functional groups under surprisingly mild conditions (eqs. 5 and 6, Table 2).

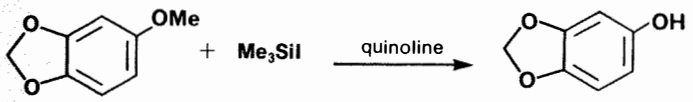
Numerous examples have been reported on the dealkylation of ethers with iodotrimethylsilane, demonstrating the tremendous preparative value of this method. Furthermore, several variations of the standard procedure have been found useful and have been proposed for the dealkylation of specific ethers. Such examples are:

The regiospecific mono-O-demethylation of substituted catechol methyl ethers (eq. 7),[36] the selective O-demethylation of the methyl ether function leaving the methylenedioxy group intact as in the cases of sesamol methyl ether (eq. 8)[37] and 1,2-methylenedioxy-3-methoxybenzene (eq. 9).[37] To effect these demethylations it was necessary to use quinoline as the solvent. The methoxy group in the isoquinoline alkaloid hydrocotarnine was cleaved selectively with iodotrimethylsilane in boiling *o*-dichlorobenzene in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) affording hydrocotarnoline (eq. 10).[38] An interesting reaction sequence was observed when the demethylation of 1,4-dimethoxyphenanthrene with iodotrimethylsilane was attempted. Heating of the reactants in CCl_4 for 48hrs effected demethylation and subsequently oxidation to 1,4-phenanthroquinone (eq. 11).[39] Furthermore, iodotrimethylsilane smoothly dealkylates 2,4-dialkoxypyrimidines to give uracils in high yield (eq. 12, $R^1{=}CH_3$, $R^2{=}SO_3H$, 40-45°C in sulfolane, 15 min., quantitative yield).[40] Dealkylation of alkoxyalkynes with iodotrimethylsilane, prepared ***in situ*** from hexamethyldisilane and iodine, afforded trimethylsilylketenes in moderate yield (eq. 13).[26]

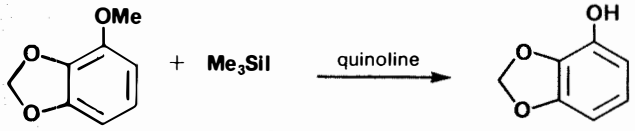
Removal of the urethane and the benzyl ether blocking groups from peptides is



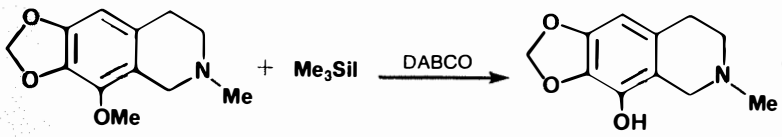
(eq. 7)[36]



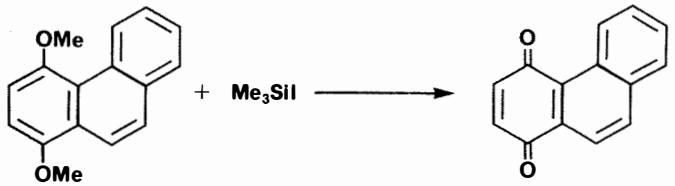
(eq. 8)[37]



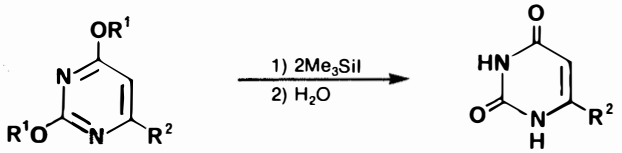
(eq. 9)[37]



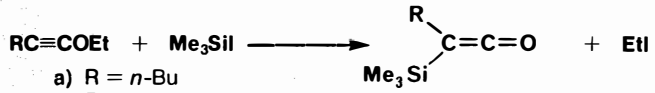
(eq. 10)[38]



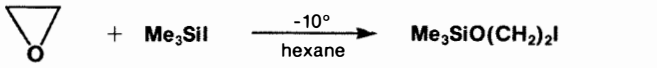
(eq. 11)[39]



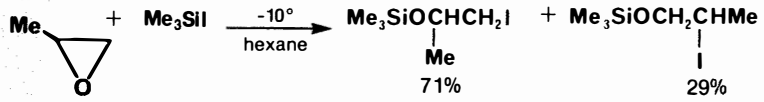
(eq. 12)[40]



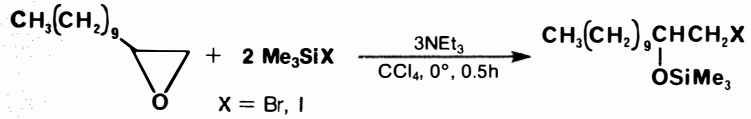
(eq. 13)[26]



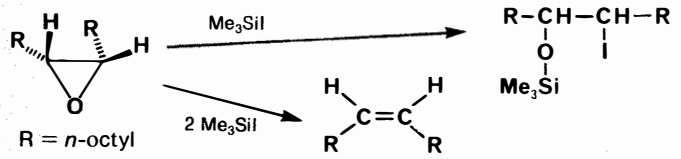
(eq. 14)[42]



(eq. 15)[42]

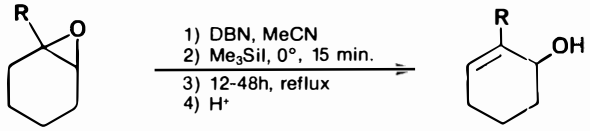


(eq. 16)[43]



(eq. 17)[43]

(eq. 18)[43]



(eq. 19)[44]

readily accomplished by treatment with iodotrimethylsilane. The method seems to be particularly useful for the debenzylation of *O*-benzyltyrosine peptides since no troublesome side products are formed in this reaction.[41]

Some of the results obtained so far from studies of the reactions of epoxides with bromo- and iodotrimethylsilane are shown in eqs. 14-16.[42,43]

Simple epoxide ring opening was also observed on adding an equimolar amount of iodotrimethylsilane to *cis*-9,10-oxidooctadecene (eq. 17). The reverse addition of this epoxide to a twofold equimolar amount of iodotrimethylsilane, however, effects deoxygenation and affords 9-*Z*-octadecene in 83% yield (eq. 18).[43]

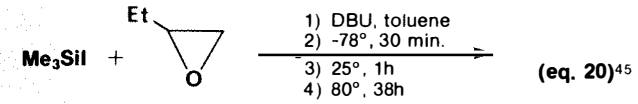
The generation of allylic alcohols from epoxides by treatment with iodotrimethylsilane and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[44] or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)[45] has been reported recently (eqs. 19, 20).

Dealkylation of Acetals, Ketals and Related Compounds

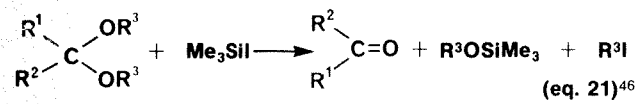
Dealkylation of acetals and ketals to the corresponding carbonyl compounds is one of the most useful transformations in organic chemistry. This reaction is usually carried out under aqueous, acidic conditions. Jung's group[46] discovered that treatment of acetals and ketals with iodotrimethylsilane (CH_2Cl_2, 25°C, 15 min.) afforded the corresponding carbonyl compounds (eq. 21). It is particularly noteworthy that this transformation proceeds under extremely mild, neutral, and nonaqueous conditions and that the products are obtained in very high yield (Table 3). Surprisingly, treatment of ethylene ketals with iodotrimethylsilane results in the formation of a mixture of products (eq. 22).[46]

In the context of deacetalization and deketalization two further examples of the synthetic applicability of iodotrimethylsilane need be mentioned. Treatment of trialkyl orthoformates with an equimolar amount of iodotrimethylsilane[46] or bromotrimethylsilane[19,47] affords the corresponding alkyl formates in high yield (eq. 23). The formation of Mannich salts from the reaction of tetraalkylaminals with iodotrimethylsilane (eq. 24)[48] is of great preparative value and awaits further investigation with respect to its scope and limitations.

Various α-iodoethers and α-iodothioethers have been made easily accessible by means of iodotrimethylsilane. Thus, iodomethyl methyl ether is generated conveniently by reacting dimethoxymethane



(eq. 20)[45]

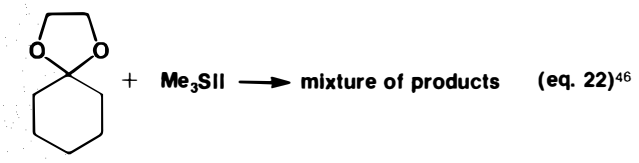


(eq. 21)[46]

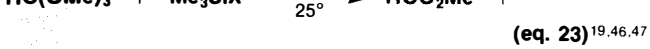
Table 3. Conversion of Ketals to Ketones by Means of Iodotrimethylsilane[46]

R¹	R²	R³	Solvent[a]	Yield[b]
-(CH₂)₄-		Me	$CHCl_3$/propene	87%
-(CH₂)₅-		Me	$CHCl_3$/propene	90%
C_6H_{13}	Me	Me	CH_2Cl_2	87%
C_5H_{11}	H	Me	$CHCl_3$/propene	85%
-(CH₂)₅-		Et	$CHCl_3$/propene	84%

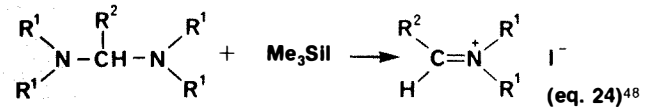
[a]Conditions: 25°C/15 min.
[b]Yields refer to isolated product



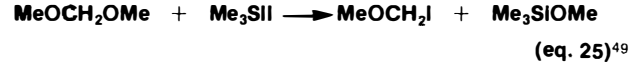
(eq. 22)[46]



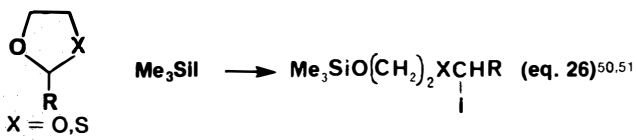
(eq. 23)[19,46,47]



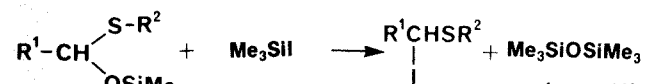
(eq. 24)[48]



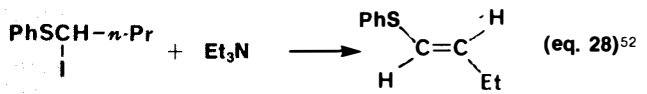
(eq. 25)[49]



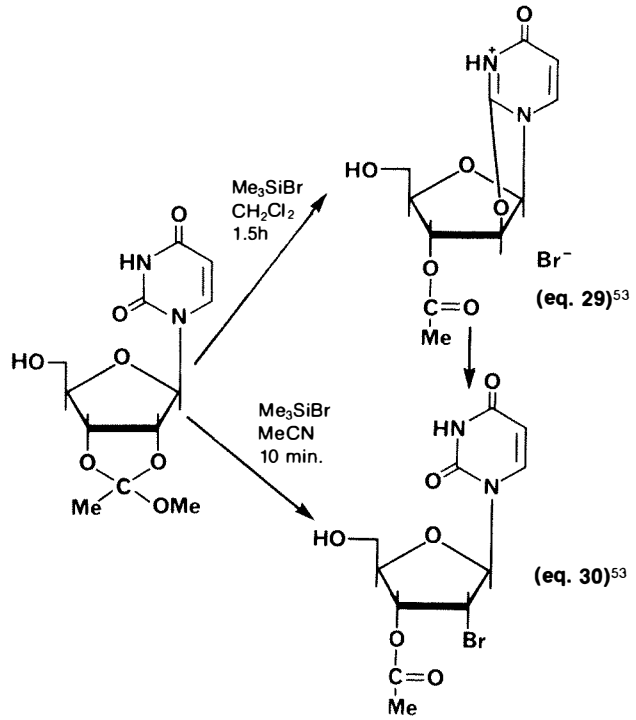
(eq. 26)[50,51]



(eq. 27)[52]

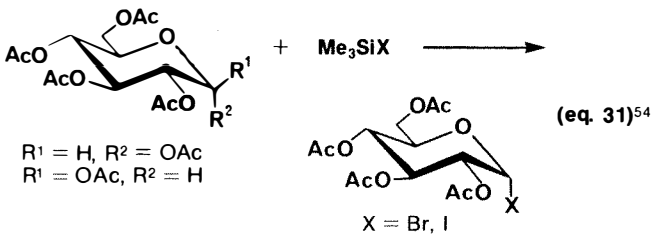


(eq. 28)[52]

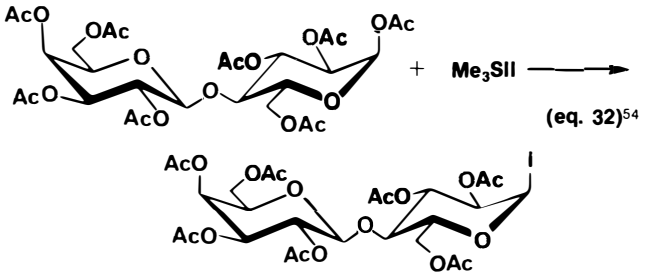


(eq. 29)[53]

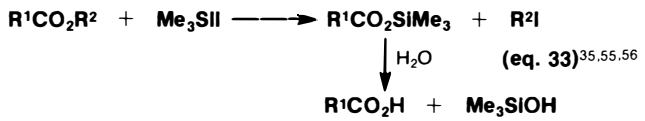
(eq. 30)[53]



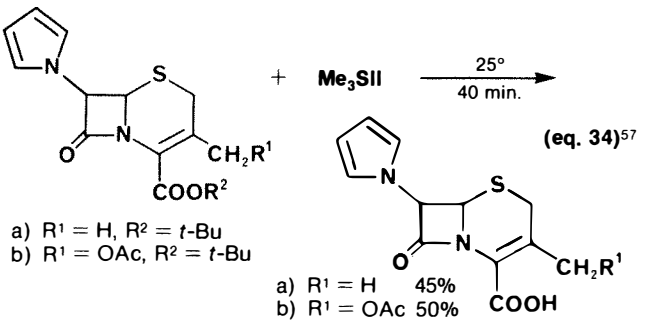
(eq. 31)[54]



(eq. 32)[54]



(eq. 33)[35,55,56]



(eq. 34)[57]

(methylal) with iodotrimethylsilane at room temperature (eq. 25).[49] This method is amenable to large-scale synthesis, and yields as high as 93% have been realized. Another important advantage of this procedure is that it does not produce the potentially carcinogenic bis(iodomethyl) ether. Iodomethyl methyl ether has been found useful for the methoxymethylation and iodomethylation of various organic substrates.

The α-iodoethers and the α-iodothioether obtained from the reaction of iodotrimethylsilane with 1,3-dioxolanes and 1,3-oxathiolane respectively (eq. 26) are highly reactive species and have been used successively for the alkylation of purines and pyrimidines.[50,51]

Other α-iodothioethers were obtained by the reaction of *O*-(trimethylsilyl)hemithioacetals with iodotrimethylsilane (eq. 27).[52] Treatment of these α-iodothioethers with an appropriate base (*e.g.*, triethylamine) provided an easy access to vinyl sulfides. In cases where geometric isomers were possible, the products with *E* geometry were obtained (eq. 28).

The first synthetic applications of bromo- and iodotrimethylsilane in the nucleoside and saccharide fields have been reported. On treatment of a (methoxyethylidene)uridine with bromotrimethylsilane, the 2,2′-anhydrouridine (eq. 29) or the 2′-bromouridine (eq. 30) is obtained, depending on the solvent and the reaction time.[53] Both compounds are useful for further modification of the nucleoside sugar moiety. Primary and secondary acetoxy-substituted saccharides react with bromo- and iodotrimethylsilane to effect exclusive formation of glycosyl iodides. Accordingly, pentaacetyl hexapyranoses afford the corresponding glycosyl halides in high yield (eq. 31).[54] In the disaccharide series, α-octaacetyllactose was treated with iodotrimethylsilane. The product was found to be α-heptaacetyllactosyl iodide; no monosaccharide formation was observed (eq. 32).[54]

Transesterification and Cleavage of Carboxylic Esters

In 1976 Olah[35,55] reported the cleavage of methyl, ethyl, and benzyl carboxylic esters by treatment with iodotrimethylsilane (100°C, 2-4 hrs) and subsequent hydrolysis of the trimethylsilyl esters (eq. 33). The yields of free carboxylic acids were found to be in the range of 55-90%. Independently, Jung[56] demonstrated that for the ester cleavage much milder conditions were sufficient. The reaction was carried out in CCl_4 or $CHCl_3$. In the case of methyl, ethyl, and isopropyl carboxylic esters, temperatures of 50°C were found to be adequate. The dealkylation of *tert*-butyl and benzyl carboxylic esters proceeded rapidly at 25°C. A survey is given in Table 4.

The preparative value of this method has been demonstrated by the dealkylation of a *tert*-butyl ester in the 7-pyrrolocephalosporin series to the corresponding acid (eq. 34a).[57] The great selectivity of this method was shown by the removal of the *tert*-butyl group leaving an acetate group intact (eq. 34b).[57]

It was found recently that ester cleavage by introduction of iodotrimethylsilane is strongly catalyzed by free iodine.[58]

Treatment of carboxylic esters with bromotrimethylsilane under similar conditions effected the desired dealkylation only in low yields.[20,47] Consistent with this, ring opening of lactones by iodotrimethylsilane is an easy process (eq. 35)[59,60] while the analogous process with bromotrimethylsilane requires drastic reaction conditions.[17,19,60]

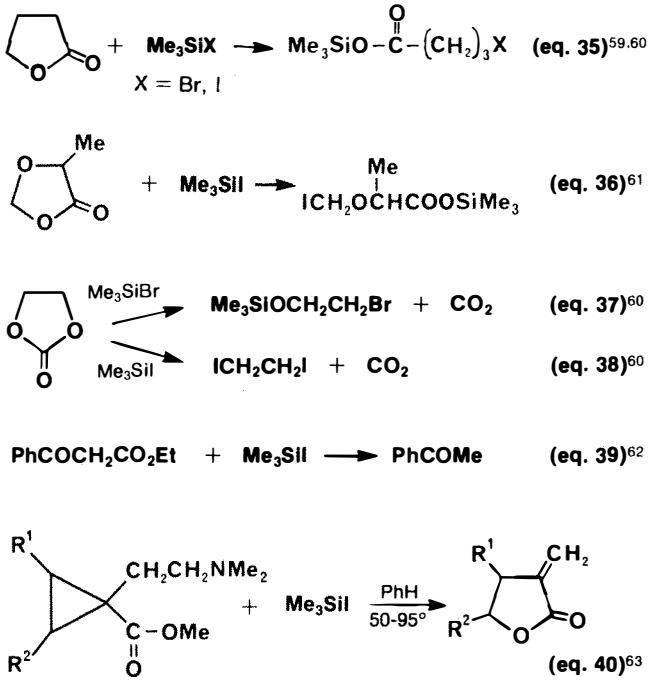
In a similar fashion, the treatment of 5-methyl-1,3-dioxolan-4-one with iodotrimethylsilane afforded a trimethylsilyl ester (eq. 36).[61] In contrast, the reaction of ethylene carbonate with bromo- or iodotrimethylsilane proceeded with decarboxylation to give the β-bromoethyl trimethylsilyl ether (eq. 37) or 1,2-diiodoethane (eq. 38).[60] Decarboxylation in connection with ester dealkylation has also been observed in the treatment of β-ketocarboxylic esters and *gem*-dicarboxylic esters such as dialkylmalonates with iodotrimethylsilane (eq. 39).[62] A new method for the construction of the α-methylene-γ-butyrolactone moiety consists of the treatment of 1-(2-dimethylaminoethyl)cyclopropanecarboxylates with iodotrimethylsilane (eq. 40).[63]

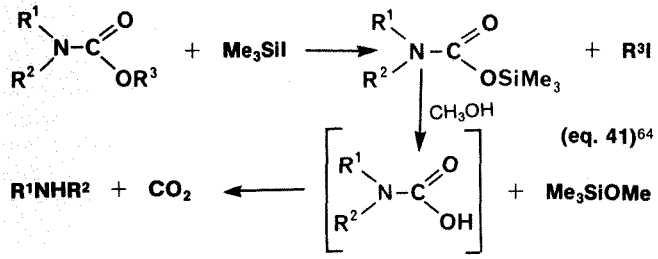
In this context the conversion of carbamates to amines by means of iodotrimethylsilane (60°C, 1-2.5 hrs) deserves special mention (eq. 41).[64] This procedure has been applied successfully in the removal of the benzyloxycarbonyl and the *tert*-butyloxycarbonyl group in N-protected peptides[28,41] as well as in the synthesis of spectroscopically pure azepine (eq. 42).[65]

Table 4. Cleavage of Carboxylic Esters with Iodotrimethylsilane

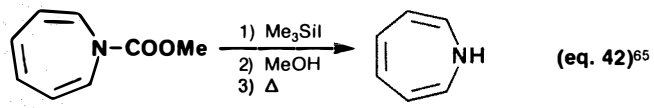
R^1	R^2	Solvent	Time/Temp.	Yield[a]	Ref.
n-Octyl	Me	CCl_4	35h/50°	85[b]	56
Ph	Me	CCl_4	6h/50°	b	56
Ph	Me	- - -	2h/100°	80[c]	35
2-BrPh	Me	- - -	2h/100°	81[c]	35
Ph	Et	CCl_4	48h/50°	b	56
Ph	Et	- - -	4h/100°	72[c]	35
Me	*i*-Pr	CCl_4	10.5h/50°	b	56
Me	*t*-Bu	CCl_4	1/6h/25°	b	56
Ph	*t*-Bu	CCl_4	0.5h/25°	90[b]	56
Ph	Bz	CCl_4	1.5h/25°	b	56
Ph	Bz	- - -	2h/100°	86[c]	35
c-Hexyl	Bz	- - -	2h/100°	85[c]	35

[a]The numbers refer to yields of isolated product.
[b]Product: trimethylsilyl ester of the carboxylic acid. Yields determined by ^1H NMR are *ca.* 100%.
[c]Product: carboxylic acid.

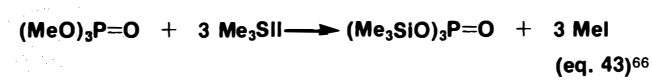




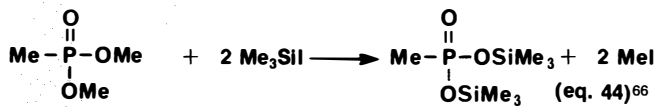
(eq. 41)[64]



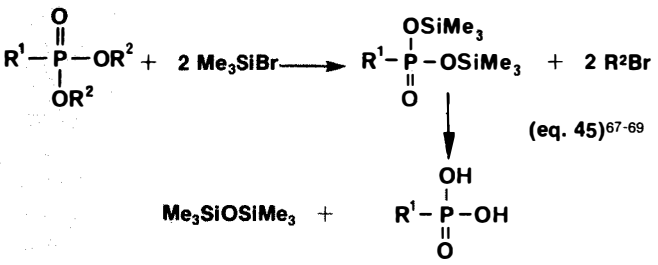
(eq. 42)[65]



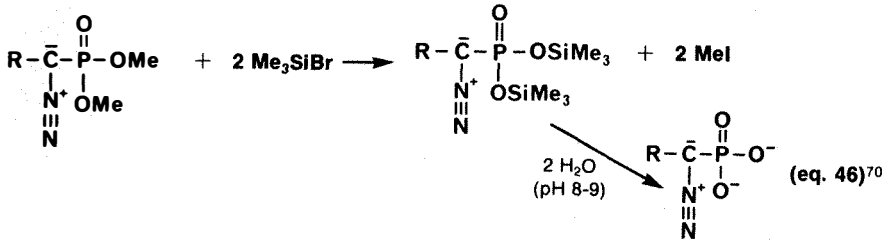
(eq. 43)[66]



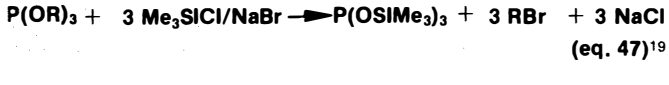
(eq. 44)[66]



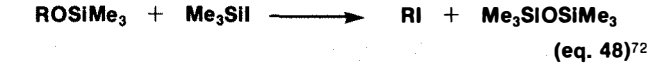
(eq. 45)[67-69]



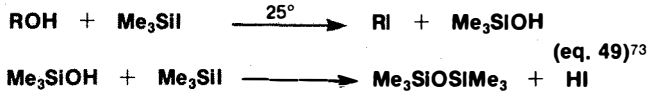
(eq. 46)[70]



(eq. 47)[19]



(eq. 48)[72]



(eq. 49)[73]

Table 5. Conversion of Alcohols to Alkyl Iodides and Alkyl Bromides by Means of Iodo- and Bromotrimethylsilane

R	Time/Temp.	Alkyl Iodide	Alkyl Bromide	Ref.
Me	0.5h/25°	100%[a]		73
	19h/25°		95%[a]	47
Et	5h/25°	99%[a]		73
	307h/25°		100%[a]	47
i-Pr	24h/25°	96%[a]		73
	46h/50°		100%[a]	47
t-Bu	0.2h/25°	100%[a]		73
	<1/6h/25°		100%[a]	47
Bz	24h/25°	85%[b]		73
	<1/6h/25°		95%[b]	47
c-Hexyl	24h/25°	81%[b]		73
	14h/50°		90%[b]	47

[a]Yields were determined by ^{1}H NMR.
[b]Yields refer to isolated product.

Transesterification and Ester Cleavage of Trialkyl Phosphates, Phosphonic Acid Dialkyl Esters, and Trialkyl Phosphites

One of the most valuable applications of bromo- and iodotrimethylsilane is the mild and selective dealkylation of trialkyl phosphates and dialkyl phosphonates. On addition of iodotrimethylsilane to a solution of trimethyl phosphate or dimethyl methylphosphonate Schmidbaur[66] obtained, after 1hr at 25°C, a 98% yield of tris(trimethylsilyl) phosphate (eq. 43) and bis(trimethylsilyl) methylphosphonate (eq. 44), respectively. Only a little later the groups of Rudinskas[67] and Mc Kenna[68] reported the dealkylation of dialkyl phosphonates by means of bromotrimethylsilane and were the first to clearly recognize the synthetic potential of this deesterification procedure. The general applicability of the method has been demonstrated, in the meantime, using a large number of phosphonic esters (eq. 45).[69]

Two interesting applications of this procedure have been reported: the synthesis of α-diazophosphonic acids[70] (eq. 46) and the synthesis of enol phosphates.[71]

The treatment of trialkyl phosphites with chlorotrimethylsilane/NaBr afforded tris(trimethylsilyl) phosphite in 67% yield (eq. 47).[19]

Synthesis of Alkyl Bromides and Alkyl Iodides

In the early experiments on the reaction of ethers with bromo- and iodotrimethylsilane, alkyl halides were usually obtained as side or main products. These results suggested the formation of trimethylsilyl ethers as intermediates, which reacted with more halotrimethylsilane to give alkyl halides. In agreement with this Voronkov[72] showed that the treatment of trimethylsilyl ethers with iodotrimethylsilane afforded alkyl iodides in practically quantitative yields (eq.48). Further investigation showed that alkyl iodides are easily obtained in good yields by the direct treatment of alcohols with iodotrimethylsilane (eq. 49).[73] The silicon-containing byproducts are a mixture of trimethylsilanol and hexamethyldisiloxane. A drawback of the method is the formation of free hydrogen iodide. Similarly, treatment of alcohols with 1.5-4.0 equivalents of bromotrimethylsilane afforded the expected bromides (Table 5).[47]

Reaction with Carbonyl Compounds

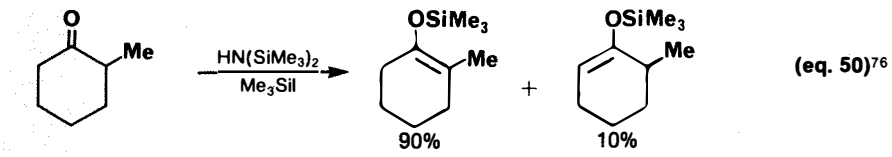
The reaction of aldehydes and ketones with halotrimethylsilanes has been examined in depth with respect to the formation of trimethylsilyl enol ethers.[74,75] Recently the use of the hexamethyldisilazane/iodotrimethylsilane system was proposed as a highly effective silylating reagent.[76] The reactions are carried out at room temperature and usually afford a very good yield of the thermodynamically more stable product (eq. 50).

Since 1975 we have been exploring the reactions of carbonyl compounds with halotrimethylsilanes in the absence of a base. On the addition of iodotrimethylsilane to acetone, or on the addition of chlorotrimethylsilane to a suspension of NaI in excess acetone, we observed an ex-

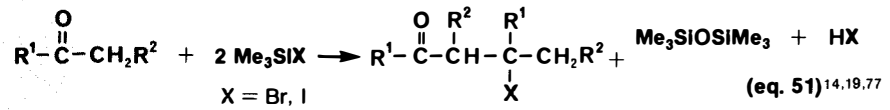
othermic reaction which afforded 4-iodo-4-methylpentan-2-one.[14] The corresponding β-bromoketone was obtained in a similar way.[14,19] This aldol-like reaction has been observed in the meantime for numerous other carbonyl compounds (eq. 51).[77,78] During the course of these investigations the iodotrimethylsilane/zinc system was introduced by us.[77,79]

It has been proposed[80] that the formation of the β-haloketones may proceed through an α-halotrimethylsilyl ether. The formation of such a species was suggested by the formation of α,α-diiodotoluene when excess iodotrimethylsilane was added to benzaldehyde.[81]

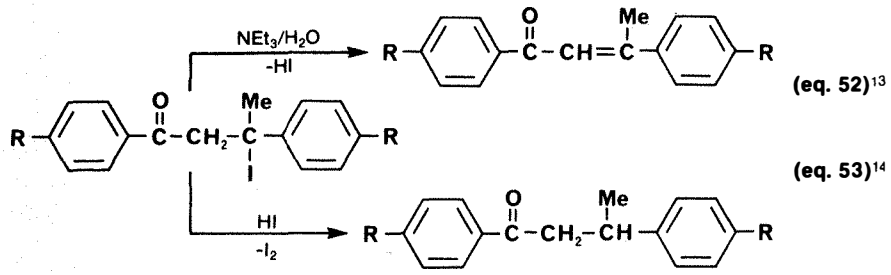
Depending upon the work-up conditions the reaction of aryl methyl ketones with iodotrimethylsilane afforded α,β-unsaturated ketones (eq. 52) or the corresponding saturated ketones (eq. 53).[13,14] The generation of both types of products may be explained by the intermediacy of β-iodoketones.



(eq. 50)[76]

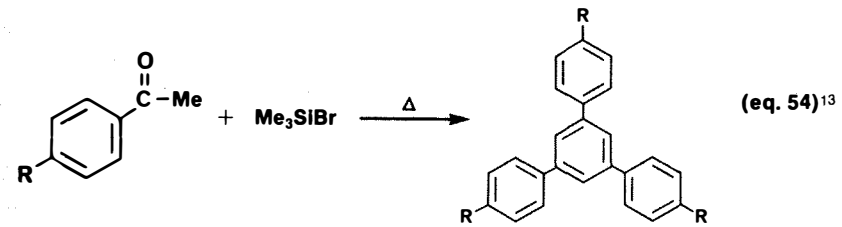


(eq. 51)[14,19,77]

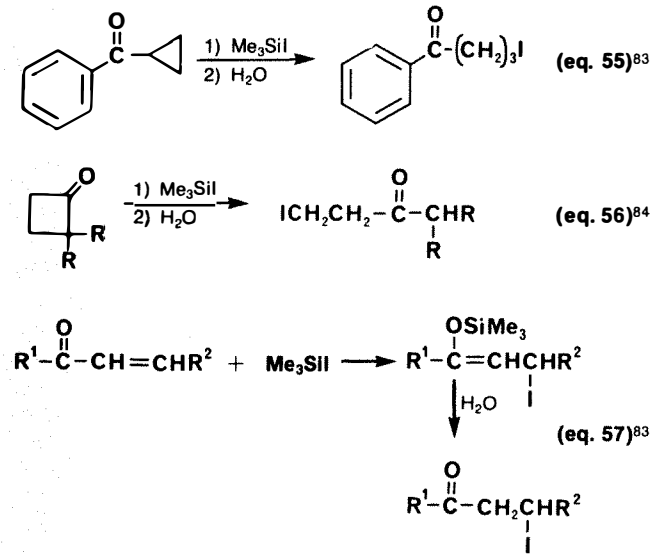


(eq. 52)[13]

(eq. 53)[14]



(eq. 54)[13]



In addition to the results shown in eq. 53 the conversion of α-hydroxyketones to ketones by means of iodotrimethylsilane needs to be mentioned.[82]

When aryl methyl ketones or cyclopentanone were heated with bromotrimethylsilane three molecules of ketone were condensed to form a benzene nucleus (eq. 54).[13]

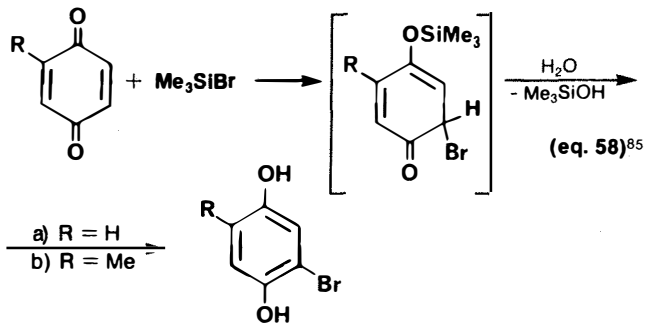
The reactions of bromo- and iodotrimethylsilane with unsaturated ketones, quinones, and several specially substituted ketones are summarized in eqs. 55-58.[83-85]

Miscellaneous Reactions

Several reports are available dealing with the addition of bromo- and iodotrimethylsilane to various pentavalent phosphorus compounds.(eq. 59, 60).[66,86,87]

The deoxygenation of sulfoxides to sulfides may be accomplished easily by means of iodotrimethylsilane[21] and bromotrimethylsilane (eq. 61).[21] For this purpose both reagents may also be generated *in situ*.[19,21,88] The procedure has been found useful in the selective deoxygenation of an α,β-unsaturated sulfoxide.[89] Similarly, sulfonyl halides can be deoxygenated with iodotrimethylsilane to yield disulfides.[90]

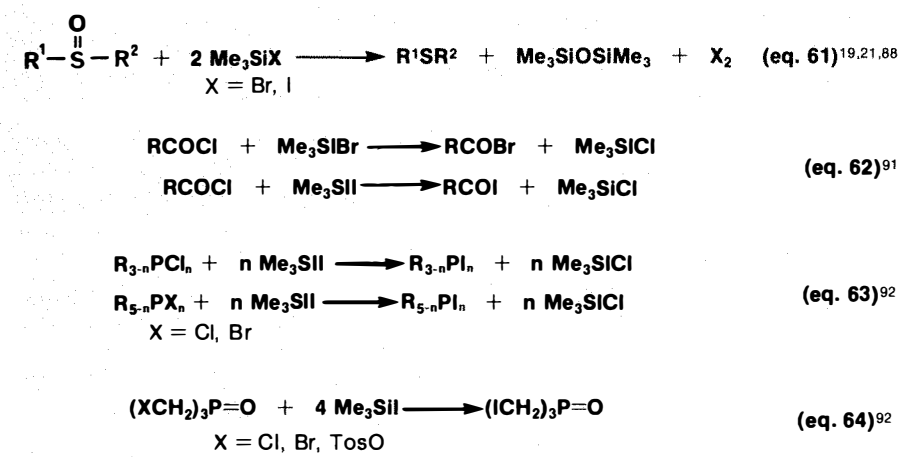
Recently bromo- and iodotrimethylsilane have been found useful in halogen-exchange reactions. Thus, acid chlorides were easily converted under very mild conditions to acid bromides and acid iodides (eq. 62).[1,91] Furthermore, chlorophosphines and chlorophosphoranes have been converted to the corresponding iodides by means of iodotrimethylsilane (eq. 63).[92] Surprisingly, iodotrimethylsilane also brings about chlorine or bromine/iodine exchange in bis- and tris(halomethyl)-phosphine oxides. In the same way the tosyloxy group may be exchanged (eq. 64).[92]



(eq. 58)[85]

(eq. 59)[86]

(eq. 60)[66,87]



ACKNOWLEDGEMENTS

I wish to thank the following coworkers for contributing to our research in this field: Manuel Russ, A. Sartorius, D. Grosse, and P. Wiesert. Furthermore, I am grateful to Dr. R. Lantzsch, Leverkusen, for stimulating discussions and to Dr. T. W. Flechtner of Cleveland State University for perusal of this review.

References and Notes:

I) Based in part on the comprehensive review: "Bromtrimethylsilan und Iodtrimethylsilan — Darstellung und Anwendung in der organischen Synthese," Schmidt, A.H. *Chem.-Ztg.* **1980**, *104*, 253.
2) Gilliam, W.F.; Meals, R.N.; Sauer, R.O. *J. Am. Chem. Soc.* **1946**, *68*, 1161.
3) Gross, H.; Böck, C.; Costisella, B.; Gloede, J. *J. Prakt. Chem.* **1978**, *320*, 344.
4) Voronkov, M.G.; Dolgov, B.N.; Dmitrieva, N.A. *Proc. Acad. Sci. USSR* **1952**, *84*, 959, and references cited therein.
5) Voronkov M.G.; Khudobin, Y.I. *Izvest. Sibirsk. Otdel. Akad. Nauk. Ser. Khim. Nauk.* **1956**, 713.
6) Jung, M.E.; Lyster, M.A. *J. Org. Chem.* **1977**, *42*, 3761.
7) Jung, M.E.; Lyster, M.A. *Organic Syntheses* **1979**, *59*, 35.
8) Birkofer, L.; Krämer, E. *Chem. Ber.* **1967**, *100*, 2776.
9) Weyenberg, D.R.; Thoporcer, L.H. *J. Org. Chem.* **1965**, *30*, 943.
10) Schmidt, A.H.; Russ, M. *Synthesis* **1981**, 67.
11) Krüerke, U. *Chem. Ber.* **1962**, *95*, 174.
12) Russ, M. Ingenieurarbeit Fachhochschule Fresenius, Wiesbaden, 1976.
13) Schmidt, A.H.; Russ, M. *Chem.-Ztg.* **1978**, *102*, 26.
14) Schmidt, A.H.; Russ, M. *ibid.* **1978**, *102*, 65.
15) Morita, T.; Okamoto, Y.;Sakurai, H. *Tetrahedron Lett.* **1978**, 2523.
16) Machida, Y.; Nomomoto, S.; Saito, I. *Synth. Commun.* **1979**, *9*, 97.
17) Scheibye, S.; Thomsen, I.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1979**, *88*, 1043.
18) Olah, G.A.; Gupta, B.G.B.; Malhotra, R.; Narang, S.C. *J. Org. Chem.* **1980**, *45*, 1638.
19) Schmidt, A.H.; Russ, M. *Chem. Ber.* **1981**, *114*, 1099.
20) Ho, T.-L.; Olah, G.A. *Synthesis* 1977, 417.
21) Olah, G.A.; Gupta, B.G.B.; Narang, S.C. *ibid.* **1977**, 583.
22) Jung, M.E.; Blumenkopf, T.A. *Tetrahedron Lett.* **1978**, 3657.
23) Schmidt, A.H.; Russ, M.; Grosse, D., unpublished results.
24) Grosse, D., Diplomarbeit Fachhochschule Fresenius, Wiesbaden, 1980.
25) Schmidt, A.H.; Russ, M., unpublished results.
26) Sakurai, H.; Shirakata, A.; Sasaki, K.; Hosomi, A. *Synthesis* **1979**, 740.
27) Seitz, D.E.; Ferreira, L. *Synth. Commun.* **1979**, *9*, 931.
28) Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 612.
29) Kumada, M.; Hattori, H. *J. Inst. Polytechn. Osaka City, Univ. Ser. C3* **1952**, 77; *Chem. Abstr.* **1954**, *48*, 7542a.
30) Kumada, M.; Hattori, H. *J. Chem. Soc. Jpn., Ind. Chem. Sect.* **1953**, *56*, 269.
31) Zakharkin, L.I.; Stanko, V.I.; Brattsev, V.A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1961**, 2079.
32) Voronkov, M.G.; Puzanova, V.E.; Pavlov, S.F.; Dubinskaya, E.I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1975**, 448.
33) Voronkov, M.G.; Dubinskaya, E.I.; Komarov, V.G.; Pavlov, S.F. *Zh. Obshch. Khim.* **1976**, *46*, 1908.
34) Voronkov, M.G.; Dubinskaya, E.I.; Pavlov, S.F.; Gorokhova, V.G. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1976**, 2355.
35) Ho, T.-L.; Olah, G.A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 774.
36) Vickery, E.H.; Pahler, L.F.; Eisenbraun, E.J. *J. Org. Chem.* **1979**, *44*, 4444.
37) Minamikawa, J.; Brossi, A. *Tetrahedron Lett.* **1978**, 3085.
38) Minamikawa, J.; Brossi, A. *Can. J. Chem.* **1977**, *57*, 1720.
39) Rosen, B.J.; Weber, W.P. *J. Org. Chem.* **1977**, *42*, 3463.
40) Silverman, R.B.; Radak, R.E.; Hacker, N.P. *ibid.* **1979**, *44*, 4970.
41) Lott, R.S.; Chaukan, V.S.; Stammer, C.N. *Chem. Commun.* **1979**, 495.
42) Voronkov, M.G.; Komarov, V.G.; Albanov, A.I.; Dubinskaya, E.I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978**, 2623.
43) Denis, J.N.; Magnane, R.; van Eenoo, M.; Krief, A. *Nouv. J. Chim.* **1979**, *3*, 705.
44) Kraus, G.A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 2579.
45) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1980**, 2329.
46) Jung, M.E.; Andrus, W.A.; Ornstein, P.L. *ibid.* 1977, 4175.
47) Jung, M.E.; Hatfield, G.L. *ibid.* **1978**, 4483.
48) Bryson, T.A.; Bonitz, G.H.; Reichel, C.J.; Dardis, R.E. *J. Org. Chem.* **1980**, *45*, 524.
49) Jung, M.E.; Mazurek, M.A.; Lim, R.M. *Synthesis* **1978**, 588.
50) Keyser, G.E.; Bryant, J.D.; Barrio, J.R. *Tetrahedron Lett.* **1979**, 3236.
51) Bryant, J.D.; Keyser, G.E.; Barrio, J.R. *J. Org. Chem.* **1979**, *44*, 3733.
52) Aida, T.; Harpp, D.N.; Chan, T.H. *Tetrahedron Lett.* **1980**, 3247.
53) Logue, M.W. *Carbohydr. Res.* **1975**, *40*, C9.
54) Thiem J.; Meyer, B. *Chem. Ber.* **1980**, *113*, 3075.
55) Ho, T.-L.; Olah, G.A. *Proc. Nat. Acad. Sci., USA* **1978**, *75*, 4.
56) Jung, M.E.; Lyster, M.A. *J. Am. Chem. Soc.* **1977**, *93*, 968.
57) Nudelman, A.; Braun, F.; Karoly, E. *J. Org. Chem.* **1978**, *43*, 3788.
58) Benkeser, R.A.; Mozdzen, E.C.; Muth, C.L. *ibid.* **1979**, *44*, 2185.
59) Voronkov, M.G.; Komarov, V.G.; Albanov, A.I.; Kositsina, E.I.; Dubinskaya, E.I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978**, 1692.
60) Kricheldorf, H.R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 689.
61) Muchmore, D.C.; Dahlquist, F.W. *Biochem. Biophys. Res. Commun.* **1979**, *86*, 599.
62) Ho, T.-L. *Synth. Commun.* **1979**, *9*, 233.
63) Hiyama, T.; Saimoto, H.; Nishio, K.; Shinoda, M.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1979**, 2043.
64) Jung, M.E.; Lyster, M.A. *Chem. Commun.* **1978**, 315.
65) Vogel, E.; Altenbach, H.J.; Drossard, J.M.; Schmickler, H.; Stegelmeier, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1016.
66) Schmidbaur, H.; Seeber, R. *Chem. Ber.* **1974**, *107*, 1731.
67) Rudinskas, A.J.; Hullar, T.L. *J. Med. Chem.* **1976**, *19*, 1367.
68) McKenna, C.E.; Higa, M.T.; Cheung, N.H., Contribution No. 149 at the Pacific Conference on Chemistry and Spectroscopy, October 28-30, 1975, Hollywood, California (Private communication: C.E. McKenna).
69) (a) McKenna, C.E.; Higa, M.T.; Cheung, N.H.; McKenna, M.C. *Tetrahedron Lett.* **1977**, 155; (b) McKenna, C.E.; Schmidhauser, J. *Chem. Commun.* **1979**, 739.
70) Bartlett P.A.; Long, K.P. *J. Am. Chem. Soc.* **1977**, *99*, 1267.
71) Hata, T.; Yamada, K.; Futatsugi, T.; Sekine, M. *Synthesis* **1979**, 189.
72) Voronkov, M.G.; Pavlov, S.F.; Dubinskaya, E.I. *Dokl. Akad. Nauk. SSSR* **1976**, *227*, 607.
73) Jung, M.E.; Ornstein, P.L. *Tetrahedron Lett.* **1977**, 2659.
74) Rasmussen, J.K. *Synthesis* **1977**, 91.
75) Aringer, L.; Eneroth, P.; Gustafsson, J.A. *Steroids* **1971**, *17*, 377.
76) Miller, R.D.; Kean, D.R. *Synthesis* **1979**, 730.
77) Schmidt, A.H.; Russ, M. *Chem.-Ztg.* **1979**, *103*, 183.
78) Schmidt, A.H.; Russ, M., unpublished results.
79) A further application of this system has been described recently by others: Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 32.
80) Schmidt, A.H.; Russ, M. *Chem.-Ztg.* **1979**, *103*, 285.
81) Jung, M.E.; Mossman, A.B.; Lyster, M.A. *J. Org. Chem.* **1978**, *43*, 3698.
82) Ho, T.-L. *Synth. Commun.* **1979**, *9*, 665.
83) Miller, R.D.; McKean, D.R. *Tetrahedron Lett.* **1979**, 2305.
84) Miller, R.D.; McKean, D.R. *ibid.* **1980**, 2639.
85) Miller, L.L.; Stewart, R.F. *J. Org. Chem.* **1978**, *43*, 3078.
86) (a) Seyferth, D. *Angew. Chem.* **1961**, *72*, 36; (b) Seyferth, D.; Grim, S.O. *J. Am. Chem. Soc.* **1961**, *83*, 1610.
87) Romanenko, V.D.; Tovstenko, V.I.; Markovski, L.N. *Zh. Obshch. Khim.* **1979**, *49*, 1907.
88) Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *Synthesis* **1979**, 61.
89) Nicolaou, K.C.; Barnette, W.E.; Magolda, R.L. *J. Am. Chem. Soc.* **1978**, *100*, 2567.
90) Olah, G.A.; Narang, S.C.; Field, L.D.; Salem, G.F. *J. Org. Chem.* **1980**, *45*, 4792.
91) Schmidt, A.H.; Russ, M.; Grosse, D. *Synthesis* **1981**, 216.
92) Romanenko, V.D.; Tovstenko, V.I.; Markovski, L.N. *ibid.* **1980**, 823.

About the Author

Dr. Arthur H. Schmidt was educated at the University of Frankfurt/Main, West Germany, where he received his Ph.D. (Dr. phil. nat.) in 1970. After postdoctoral studies at the University of Frankfurt/Main, at Columbia University, New York, and at the Université de Paris-Sud, Orsay, France, he joined Bayer AG at Leverkusen. Since 1975 he has been on the staff of the Fachhochschule Fresenius at Wiesbaden, West Germany. His research interests encompass organometallic compounds, heterocyclic compounds, and small-ring chemistry.

Page intentially blank

Page intentially blank

Aldrichimica Acta

Volume 14, Number 3, 1981

Transition-Metal Templates for Selectivity in Organic Synthesis
Isobenzofuran and Related o-Quinonoid Systems

chemists helping chemists in research & industry
aldrich chemical co.

Aldrichimica Acta

Volume 14, Number 3, 1981
A publication of the ALDRICH CHEMICAL COMPANY

Main Sales Office:
P.O. Box 355
Milwaukee, Wisconsin 53201
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6304
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo, Japan
Telephone: 03-258-0155.0156
TWX: 2222518

In Israel:
Sigma Israel Chemical Co.
P.O. Box 37673
Tel Aviv, Israel 61360
Telephone: 03-612315
Telex: (922) 35645

About Our Cover:

Our chemist-collector first saw this almost mystical landscape (oil on panel, 27-$^1/_2$ × 41 inches) after giving a talk on Chemistry in Art at an A.C.S. meeting in Rochester, New York some time ago. A collector there inquired whether he might be interested in purchasing it, which he did. The painting appears to be by a mid-seventeenth-century painter strongly influenced by two of the greatest Dutch painters, Hercules Seghers and Rembrandt. Our chemist knows of several similar works by the same hand, generally misattributed to other Rembrandt students such as Govaert Flinck and Roland Roghman.

Fig. 1

This painting is signed (Fig. 1), but the signature is hard to decipher. Could it be that of the artist, van Terlee, born in Dordrecht in 1636 and died there in 1687, who is reported to have been a Rembrandt student? If so, this would be the first known signed work of van Terlee, and the other very similar works could then be attributed to him. What a pleasure to resurrect an able artist from oblivion.

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

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

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

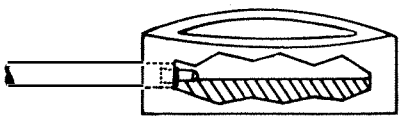
Lab Notes

In our laboratory we occasionally need to protect our vacuum pumps from volatile acid gases such as HCl or HBr. We have found that these gases are effectively removed by bubbling through a mixture of approximately 10% triethylenetetramine and 90% ethylene glycol. At pressures as low as 0.1mm Hg, very little ethylene glycol boils away, and is easily collected in the usual cold trap (-78°C).

Lauren R. Brown, Ph.D.
JBL Chemical Company
825 Capitolio Way
San Luis Obispo, CA 93401

In many small-scale chemical reactions it is necessary to maintain the temperature of the reaction mixture at 0°C (usually by means of an ice bath) for several hours. Pyrex recrystallization dishes are often used as containers for such baths. These dishes are inefficient insulators, requiring painstaking siphoning of water from the ice bath in order to add more ice.

Styrofoam containers are quite efficient insulators and can usually be obtained by modification of styrofoam crates used for shipping one-gallon bottles of mineral acids. A styrofoam crate is dissected diagonally and the edges smoothened with a sharp knife. The resulting 5.5-inch-diameter container (itself a good storage chamber for ice or Dry Ice) can be shortened to the desired height. A drain is easily added by boring a hole through one side using a 0.25-inch-diameter cork borer. Tygon



tubing (0.25 inch) is forced through the opening and is secured with a tubing "quick disconnect." The ice bath is now ready for use and will generally maintain 0°C for seven to eight hours with one filling of ice.

Dale E. O'Dell
J.S. Sawyer
D.R. Reagan
Department of Chemistry
Vanderbilt University
Nashville, TN 37235

Recovering mercury from the bulb end of a broken thermometer is a frequently encountered problem. Since it is usually difficult to break the bulb without scattering mercury droplets, the following procedure is offered as a solution.

Slowly immerse the bulb of the thermometer in a Dry Ice/acetone slush to contract all the mercury into the bulb. Freeze the mercury completely by keeping it in the bath for approximately 1 min., then rapidly plunge the bulb end into a warm-water bath. The thermal shock will crack the glass and the mercury will fall neatly to the bottom. Mercury thus obtained can be stored under water in a closed jar until needed for a manometer, etc.

This procedure can also be used to coalesce a broken mercury column in a thermometer. After freezing all the mercury into the bulb, allowing the thermometer to reach room temperature slowly will give a column of mercury with no separations.

Jim Sarafin
Aldrich-Boranes, Inc.

It is often very handy to have solvents in polyethylene squeeze bottles, but these tend to drip if the solvents are volatile and the temperature fluctuates. We overcome this problem by punching a small vent hole near the top of the bottle by means of a hot glass rod. Simply place a finger over the hole to use the bottle.

We often use Parafilm® to cover the mouths of flasks and test tubes. Unfortunately, it is sometimes difficult to separate the film from the backing. Pulling on a corner of a piece of film and backing stretches the film but not the paper backing, making it easy to separate film from paper.

George Chang
Department of Nutritional Sciences
Agricultural Experiment Station
College of Natural Resources
University of California, Berkeley
Berkeley, CA 94720

* *Editor's note*:
For our customers' convenience, we now offer Parafilm® as follows:

●Registered trademark of the American Can Company

Whenever I receive a moisture-sensitive reagent from Aldrich, it is my practice to use the labeled metal can as a desiccator. The can is opened, the bottle is removed from the plastic bag, and Drierite is added to the can. The bottle is then replaced in the can, which is sealed under dry N_2 gas using the plastic bag and a rubber band to secure the system around the can. With this cheap desiccator and the Aldrich Sure/Seal™ bottle, an air-sensitive reagent is effectively protected from the atmosphere.

Ronald J. Mattson
College of Pharmacy
University of South Carolina
Columbia, SC 29208

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

"Please Bother Us."

by Ofpid Bader.

Recently, Dr. Malcolm R. Bell at the Sterling-Winthrop Research Institute suggested that we offer tris(4-bromophenyl)aminium hexachloroantimonate. Nathan L. Bauld and coworkers at the University of Texas at Austin have shown (*J. Am. Chem. Soc.* **1981,** *103,* 718) that this radical cation effectively catalyzes Diels-Alder reactions involving neutral or electron-rich dienophiles, precisely those cases in which Lewis-acid catalysis is not very effective.

Naturally, we made it.

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

Transition-Metal Templates for Selectivity in Organic Synthesis

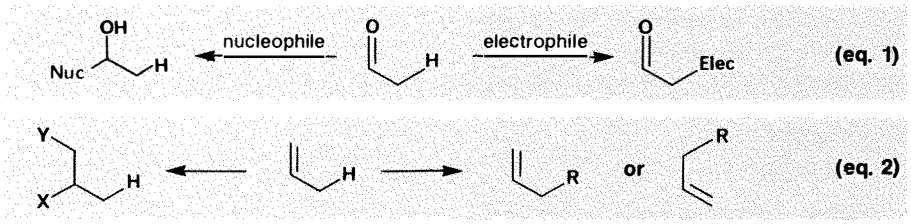
Barry M. Trost
McElvain Laboratories of Organic Chemistry
Department of Chemistry
University of Wisconsin
1101 University Avenue
Madison, WI 53706

A key aspect of synthetic design is efficiency — the ability to transform readily available starting materials into target compounds *via* the shortest possible routes. Synonymous with efficiency is selectivity, which may be divided into three major classes: (1) chemoselectivity — functional group differentiation, (2) regioselectivity — orientational control in the reaction of an unsymmetrical functional group and/or an unsymmetrical reagent, and (3) stereocontrol — control of relative stereochemistry (diastereoselectivity) and/or control of absolute stereochemistry (enantioselectivity).

The unique position of the carbonyl group in synthetic design stems from the selective formation of bonds at the carbonyl carbon atom or the alpha carbon atom according to eq. 1. The corresponding reactions of the π-isoelectronic olefin, especially with respect to allylic functionalization, has proven much less useful because low selectivity frequently plagues such processes (eq. 2). In our search for chemoselective allylic alkylation procedures, we focused on the ability of palladium salts to achieve activation of the allylic system and to permit subsequent alkylation in the presence of other functional groups — especially the carbonyl group. In the course of these studies, we delved into the palladium-catalyzed alkylation of allylic systems in which palladium templates exercise an extraordinary degree of control over the behavior of organic molecules.[1] In this report, I wish to consider the application of these concepts in four different problems, but first to outline the basic principles.

GENERAL CONSIDERATIONS

As a general introduction of the basic process, we can consider the alkylation of 2-methylcyclopentane-1,3-dione. Such systems are notorious for their tendency to suffer O- *vs.* C-alkylation. Allylation of 2-methylcyclopentane-1,3-dione with allyl bromide proceeded in only 30% yield; however, with allyl acetate and a palladium(0) catalyst, the yield of **2** (R = H) jumped dramatically to 94%.[2] Use of **1** (R = OC_2H_5) gave **2** (R = OC_2H_5) which permitted development of a cyclopentenone annulation as illustrated in eq. 3. The bicyclic ketone 3, a bis-nor analog of the Wieland-Miescher ketone, can prove pivotal as a general intermediate towards polycondensed cyclopentanoid natural products — such as coriolin and hirsutic



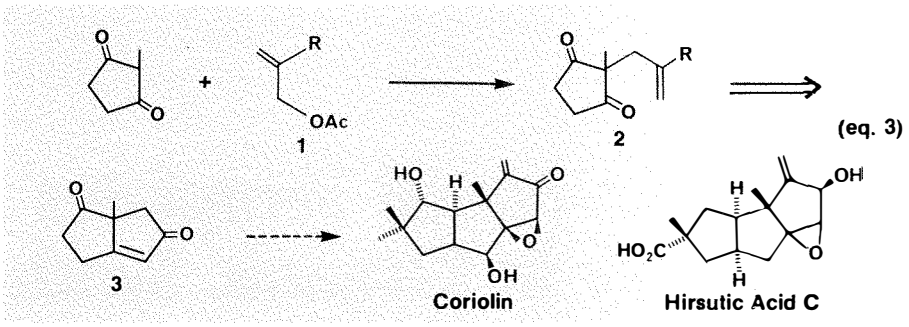
Professor Barry M. Trost (right) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

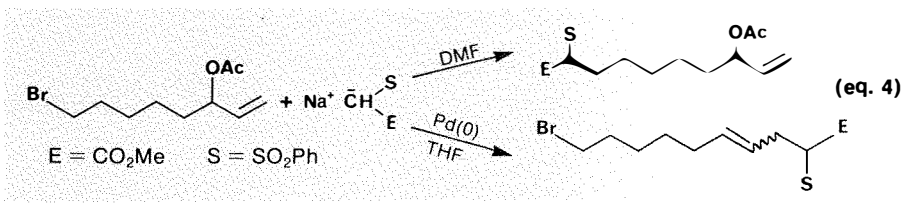
acid C — in a fashion similar to the pivotal role the Wieland-Miescher ketone has played in cyclohexanoid natural products. A total synthesis of coriolin using this strategy nears completion.[3]

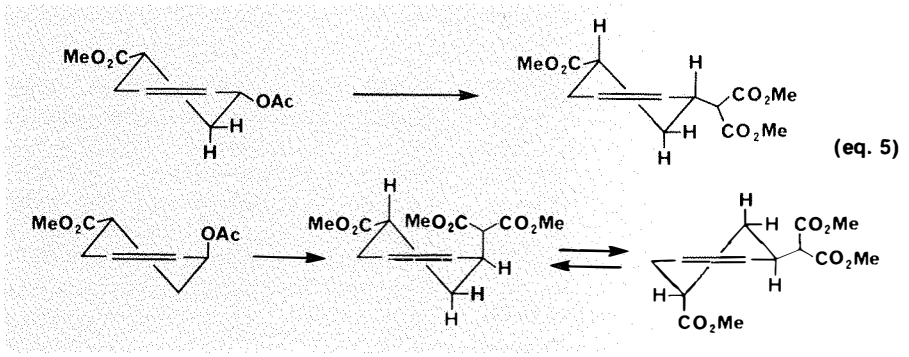
Eq. 4 illustrates the reordering of reactivity of two functional groups.[4] In the absence of the transition-metal catalyst, only the bromide would be expected to react, as is observed. However, addition of a Pd(0) catalyst allows selective alkylation of the allylic acetate without any attack at the bromide.

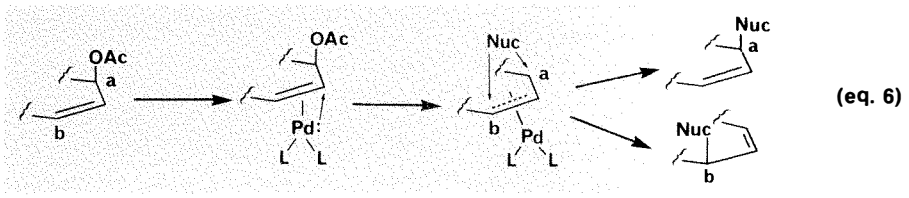
Normally, displacement reactions in organic chemistry are accompanied by inversion of configuration. As shown in eq. 5, this alkylation involves displacement with retention of configuration.[4]

Eq. 6 represents a convenient working hypothesis. When coordination of the Pd(0) catalyst occurs on the face of the double bond opposite the acetate, it induces ionization of the acetate to give a π-allylpalladium intermediate. The position identity of the acetate, *i.e.*, whether it was originally located at C(a) or C(b), is lost at this stage. Thus, the choice of substrate with acetate at either C(a) or C(b) can depend only on synthetic expediency — a real benefit of this methodology. The regioselectivity depends upon: (1) the nature of the nucleophile, (2) the nature of the substitution on the allyl unit, and (3) the nature of the ligands on Pd.



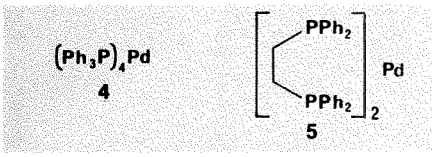






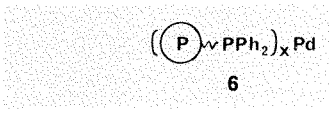
CATALYSTS

Pd(0) is required as a catalyst for these reactions. Soluble palladium catalysts which are sensitive to oxygen normally bear phosphine ligands. The most common catalysts are **4**[5] and **5**.[6,7] In some cases, to



preserve catalyst lifetime and increase turnover, 1-2 equivalents of additional phosphines are added. Rate retardation normally accompanies such a modification. To avoid handling such oxygen-sensitive materials, the catalyst can be generated *in situ* from Pd(II) salts by reduction with DIBAL or, in the case of $Pd(OAc)_2$, with an olefin (typically the substrate) in the presence of phosphine ligands. For small-scale reactions, 1-10 mol % of catalyst has been employed. The amount of catalyst decreases as the scale of the reaction increases; as little as 0.01 mol % has been employed.

An insolubilized version of the catalyst has been produced.[8,9] Either silica gel or crosslinked polystyrene can be phosphinylated and the modified support exchanged with **4** to give **6**. Besides facilitating



recovery and recycling of the catalyst, such insolubilized versions do show modified selectivities as a result of the modified ligands.

STEREO-RELAY

In Fig. 1, we consider the question of control of stereochemistry at a reaction site relative to a remote chiral center. In a conformationally well defined system, such as a six-membered ring, this problem is minimized. The presence of substituents on the ring normally fixes the conformation in one of the two possible chair forms as shown in 7. Thus, the two faces of the carbonyl group are quite distinct and reaction is expected to occur preferentially on one of the two faces — most frequently from the equatorial direction as shown. Cleavage of bond "a" in 7 creates **8** where the interconnecting chain between the chiral

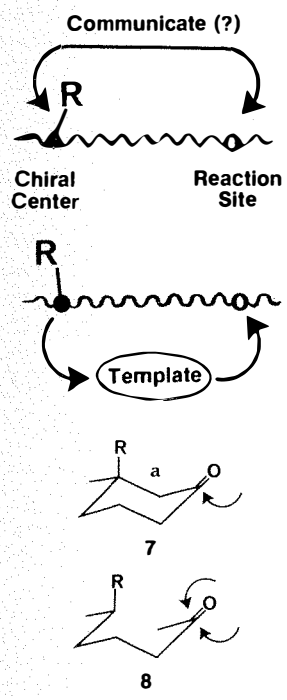
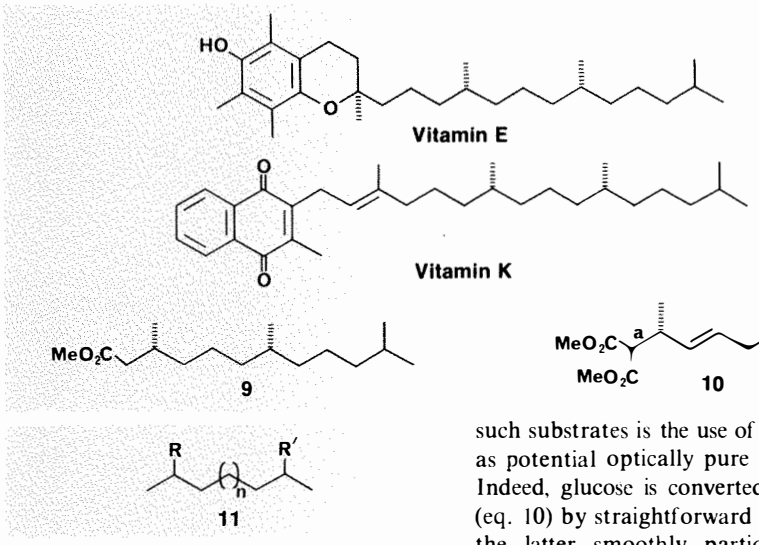


Figure 1

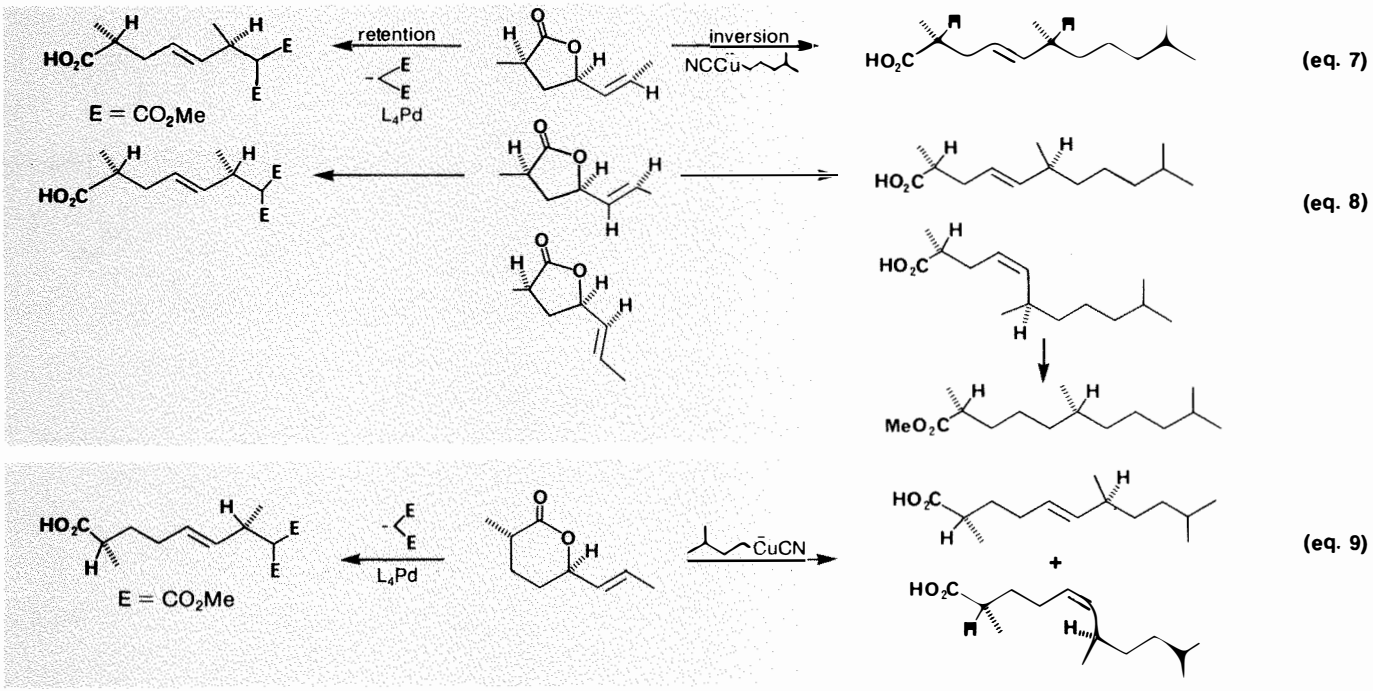
center and the reaction site no longer exhibits a conformational bias. Here reaction on the two faces of the carbonyl group occurs with equal probability. Thus, in conformationally non-rigid systems — acyclic or macrocyclic ones — a mechanism to communicate between these two sites needs to be found. One approach is to design a substrate that permits temporary complexation of a normally non-rigid chain onto a template, thereby inducing conformational rigidity. We chose to examine this question in terms of the creation of the side chains of Vitamins E and K for which **9**, which possesses the two chiral centers, provides a logical target.[10] In terms of allylic alkylation, **9** translates into **10** in which bond "a" creates the second chiral center relative to the existing one.[11,12]

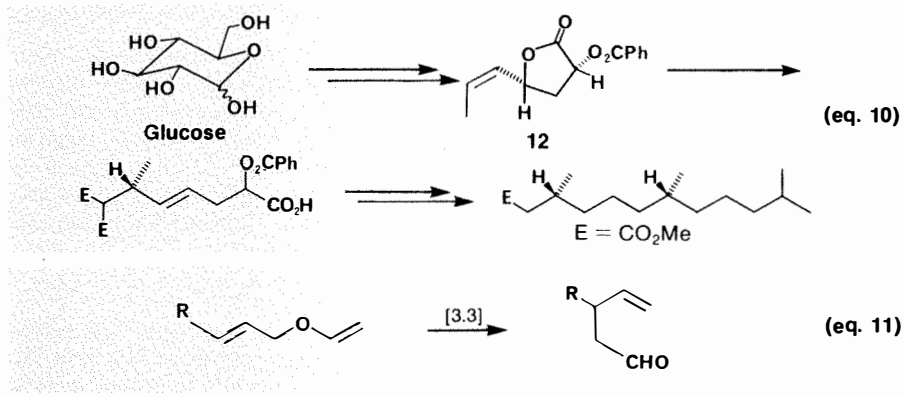


Vinyl lactones represent ideal choices for this stereo-relay process in which the ring geometry will be transmitted down the chain. Eqs. 7 and 8 illustrate the success of this approach where Pd(0)-catalyzed alkylation leads to S_N2' reaction with clean **retention** of configuration regardless of the olefin geometry.[11] This reaction complements cuprate chemistry, shown in eqs. 7 and 8, which also proceeds with allyl transposition but with **inversion** of configuration.[12] Unfortunately, the cuprate chemistry does not exhibit as high a degree of stereochemical control with the *E* olefin series (eq. 8) as do the palladium templates, demonstrating the superiority of the palladium reaction in this case.

Variation of the separation between the chiral centers as in **11** can be achieved by varying the position of the substituents on the vinyl lactone or, as shown in eq. 9, by varying the size of the lactone ring.[13] Here, too, the higher degree of control exhibited by the palladium template is obvious.

While the products of the reactions illustrated in eqs. 7 and 8 have been converted to the target for the vitamin side chains, this approach only controls relative stereochemistry. One reason for choosing such substrates is the use of carbohydrates as potential optically pure raw materials. Indeed, glucose is converted to lactone **12** (eq. 10) by straightforward chemistry and the latter smoothly participates in the palladium-initiated reaction (95% yield) to give a single homogeneous product which is converted to the side-chain fragment where both relative and absolute stereochemistry have been fully controlled.[14]





[1,3] REARRANGEMENT

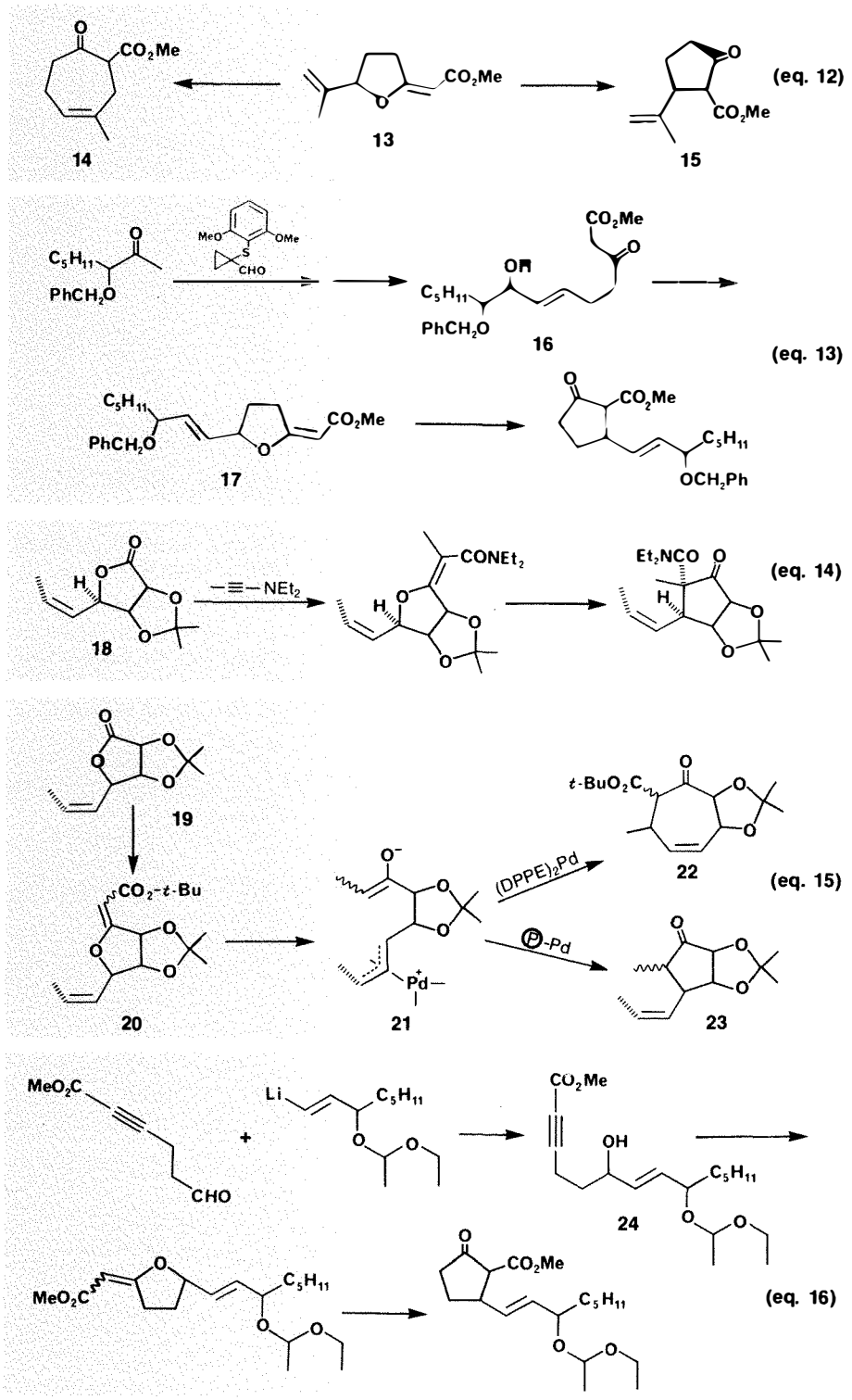
The chemistry of allyl vinyl ethers in-

variably becomes integrated with [3.3] sigmatropic rearrangements (eq. 11). In cases such as **13**, the cycloheptenone **14** is produced (eq. 12). For many natural products, an alternative pathway, a [1.3] rearrangement, to produce a 3-vinylcyclopentanone would be the desired course. Indeed, a reordering of the "expected" reactivity profile of **13** is available using a palladium template in which the exclusive product is indeed the cyclopentanone **15**.[6]

This process takes on added importance due to the cyclization proclivity of β-ketoesters such as **16** (eq. 13) for O- rather than C-alkylation. Indeed, all attempts to cyclize **16** lead only to the alkylidenevinyltetrahydrofuran **17**. However, this tendency no longer presents a problem since **17** smoothly isomerizes to the desired cyclopentanone with a Pd(0) catalyst; in this case, an approach to prostaglandin analogs.

The utility of this cyclopentanone synthesis depends upon the availability of the requisite alkylidenetetrahydrofurans. Eq. 13 illustrates their accessibility from ketones through use of the new conjunctive reagent 1-(2,6-dimethoxyphenylthio)-cyclopropanecarboxaldehyde.[15] Especially valuable are vinyl lactones such as **18** (eq. 14) and **19** (eq. 15) which are, in turn, available from carbohydrates.[16] Ynamines smoothly effect olefination of a lactone (87% yield) and the product rearranges to the cyclopentanone in 93% yield with complete regio- and stereocontrol upon subjection to **5** as the palladium template. Alternatively, **19** reacts with *t*-butyl lithioacetate followed by dehydration to give **20** in 91% yield. In this case, rearrangement can be controlled to give either the cycloheptenone **22** or the cyclopentanone **23** by judicious choice of catalyst. The regioselectivity depends upon the rate of *syn-anti* interconversion in the intermediate **21**. With the sterically demanding polymeric catalyst, such interconversion is inhibited and only the normal [1.3] product is seen. With a sterically small ligand, such interconversion is fast and only the seven-membered ring is observed. Such rational control of reactivity is a decided advantage of transition-metal-catalyzed reactions.

An alternative approach employs methyl 6-oxo-2-pentynoate as a conjunctive reagent for cyclopentanone synthesis.[17] Chemoselective addition of vinyl organometallics produces the alcohol **24** (eq. 16). Surprisingly, conjugate addition of the alcohol proved particularly troublesome. An efficient solution to this perplexing problem evolved from organosulfur chemistry. Addition of sodium benzenesulfinate to a warm alcoholic solution of **24** smoothly triggered cyclization to the desired alkylidenevinyltetrahydrofuran. Isomerization with the palladium catalyst completed an additional entry into the family of prostanoids. Thus, the availability of alkylidenevinyltetrahydrofurans of type **25** from many different types of substrates suggests great versatility for this cyclopentanone synthesis (eq. 17).



CYCLOPENTANE ANNULATION

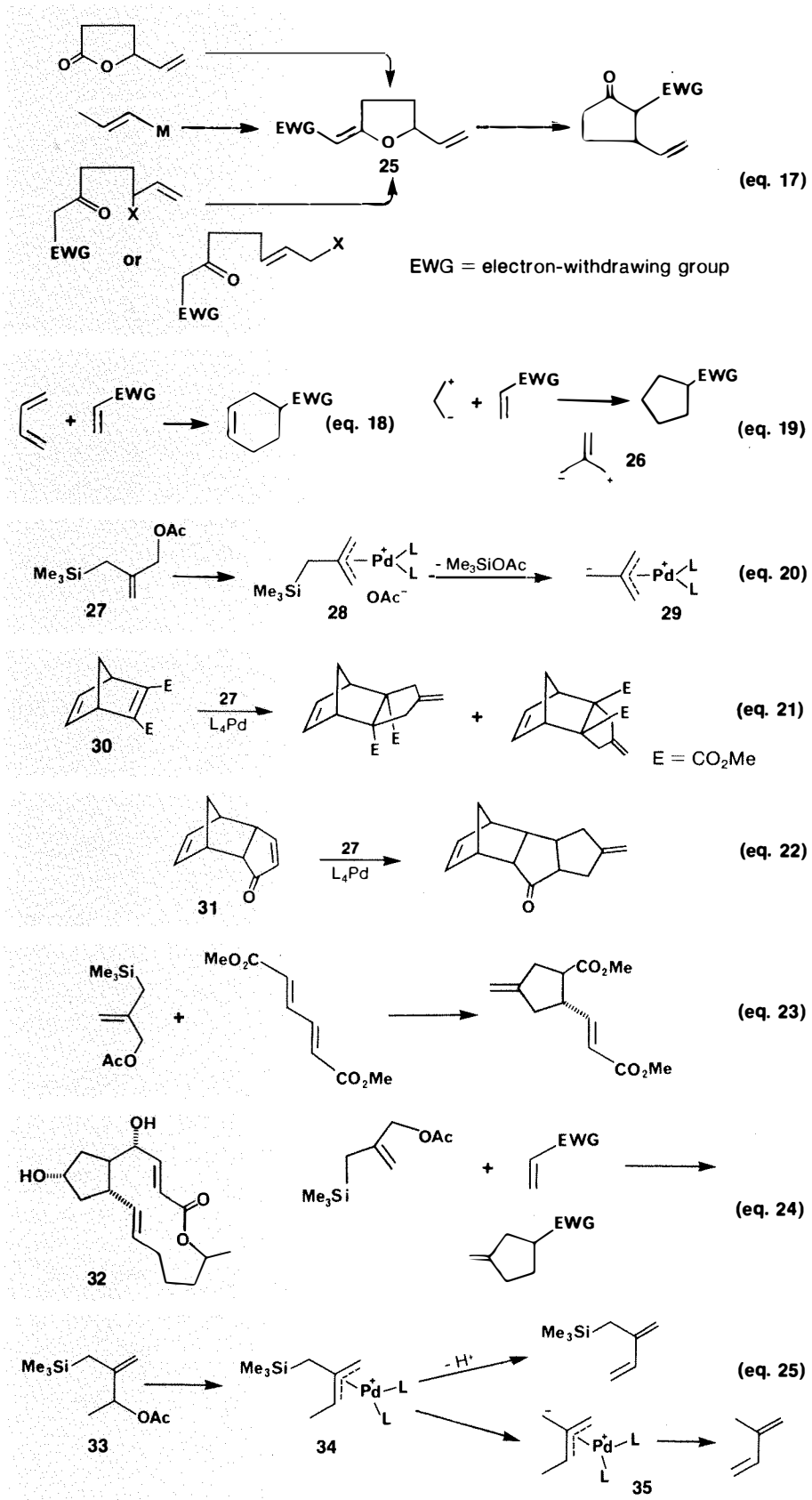
The increasing importance of cyclopentanoid natural products heightens the demand for increased flexibility in synthetic approaches to them. The [1.3] isomerization of alkylidenevinyltetrahydrofurans contributes to that flexibility. In cyclohexanoid chemistry, the Diels-Alder reaction (eq. 18) holds a special position. The virtues of such a cycloaddition approach are lacking for the case of five-membered carbon rings for which the analog might be a 1,3-dipolar cycloaddition as illustrated in eq. 19. Initiating an investigation into such an area draws our attention to trimethylenemethane, shown in a dipolar form in **26**, a reactive in-

termediate which has been studied from a physical point of view but whose use in synthesis is precluded because of very low yields.

Combining the virtues of organosilicon chemistry with palladium templates led us to propose that a bifunctional conjunctive reagent such as **27** (eq. 20) would be ideal since the π-allylpalladium intermediate **28** could suffer desilylation by acetate to generate not trimethylenemethane itself, but its palladium complex **29** where the only by-product is trimethylsilyl acetate.[18-20] Of course, the reactivity of an intermediate such as **29** was not known.[21] For example, iron complexes of trimethylenemethane are notorious for their lack of reactivity.[22] Hoping that cycloaddition would occur, we employed traps such as **30** and **31** (eqs. 21 and 22) which contain both electron-rich and electron-poor olefins. Both reacted smoothly and chemoselectively with **27** in the presence of a Pd(0) catalyst to give cycloaddition-like products with the electron-poor olefin. The cycloaddition to dimethyl *E,E*-muconate produces a methylenecyclopentane (eq. 23) which possesses structural features that naturally lead to application of this methodology to a total synthesis of brefeldin A, **32**. The chemistry as well as Fenske-Hall calculations[20,23,24] lead to the conclusion that this complex indeed behaves as a zwitterion as represented in structure **29** (eq. 20). Thus, the cycloaddition can be generalized as in eq. 24, in which the trap must bear at least one electron-withdrawing group (EWG).

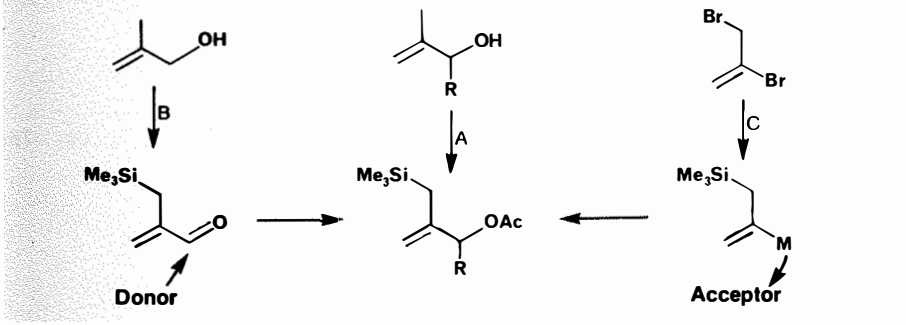
The utility of such a cycloaddition approach depends upon the accessibility of the requisite bifunctional reagents such as **27** and the extension to substituted analogs. Such an extension is not trivial. Consider the case of the methyl derivative **33** where, at every stage, proton transfer can compete with the desired process as illustrated (eq. 25).

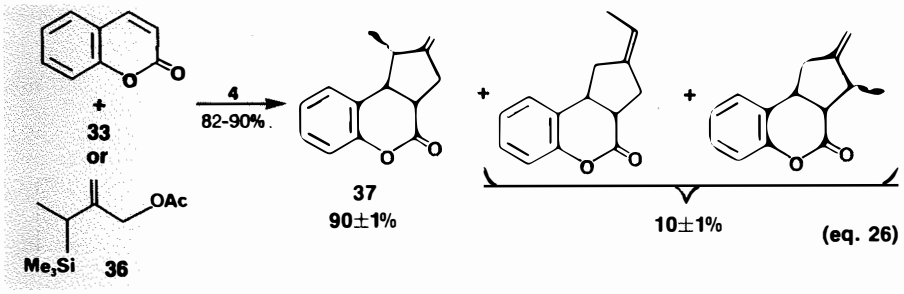
Scheme 1 outlines three of the four approaches we have developed to the requisite substrates.[25] The direct metallation (path A) is very general for methallyl alcohols. 2-Trimethylsilylmethylpropenal, available from methylallyl alcohol by the metallation-silylation procedure of path A followed by oxidation, represents an acceptor conjunctive reagent where organometallics serve as the source of the R group (path **B**). Alternatively, the lithium or magnesium derivative of 2-bromoallyltrimethylsilane, available from 2,3-dibromopropene, represents a donor conjunctive reagent where electrophiles such as aldehydes serve as the source of the R group (path C).

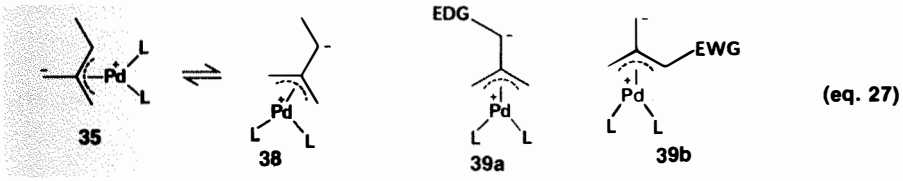


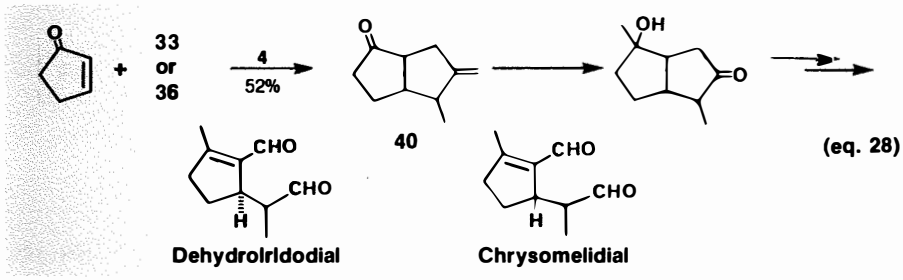
The aspirations for the generality of this cycloaddition were fulfilled. Using coumarin as a trap (eq. 26), a single major product resulted. Thus, an extraordinary event occurred. Desilylation of **34** to give reactive intermediate **35** competes favorably with simple proton loss to give a stable molecule (eq. 24)! Whereas use of **33** initially generates **35**, the regioisomer **36** generates **38**. Yet, the same product mixture emerges. Using the simple notion that the reaction is initiated by nucleophilic at-

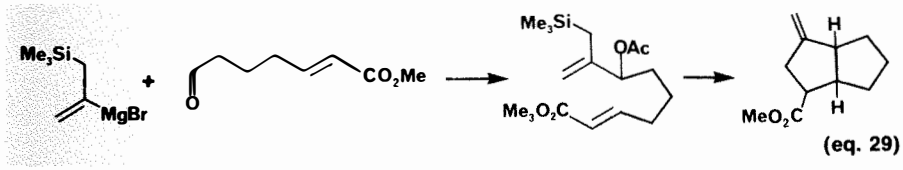
Scheme 1. Synthetic Approaches to Bifunctional Conjunctive Reagents for Cycloaddition



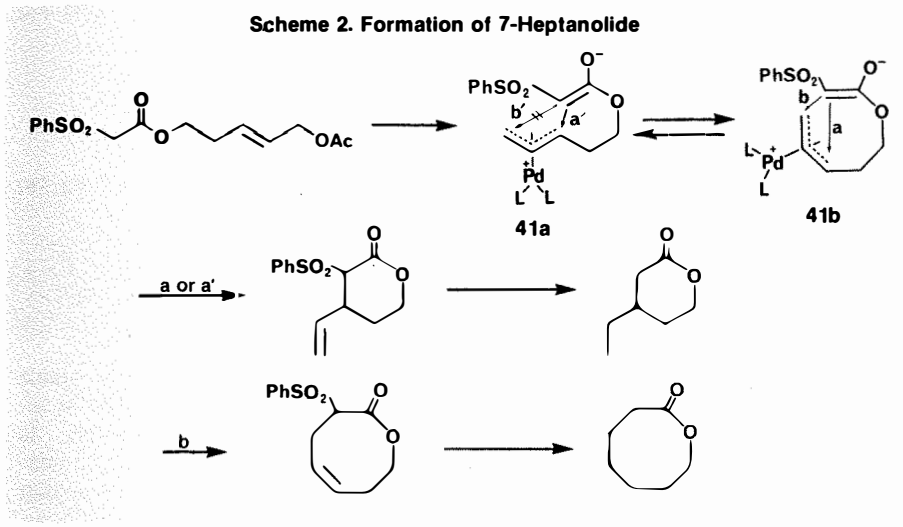








Scheme 2. Formation of 7-Heptanolide

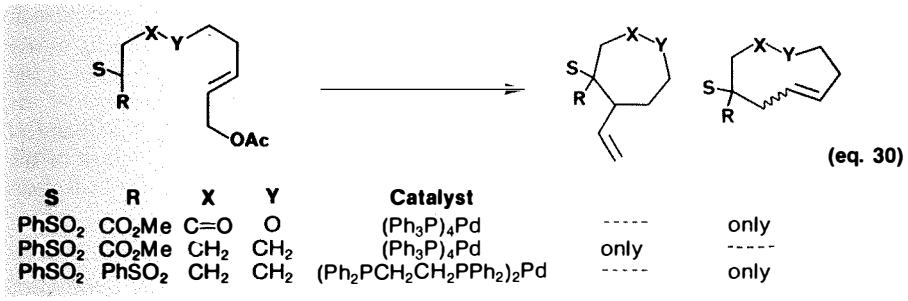


tack of the most anionic carbon of the complex, the predominant cycloadduct **37** is derived from **38**. Indeed, calculations predict **38** to be more stable than **35**. The electron-releasing methyl group prefers to be on the most electron-rich carbon — the antithesis of normal behavior in organic chemistry! Thus, the transition-metal template imposes a level of control that leads to new selectivity. The factors that lead to placing the electron-donating group (EDG) on the most electron-rich carbon of the TMM system (*i.e.*, **39**) can suggest that the EWG be placed on the least electron-rich carbon as in **39b**.

Cyclopentanone reacts smoothly with either **33** or **36** to give **40** virtually exclusively (>20:1 in regioisomers) — an intermediate towards loganin[26] as well as the insect pheromones dehydroiridodial and chrysomelidial[27] as shown in eq. 28. The availability of a donor reagent to create the requisite structural unit particularly facilitates the synthesis of a substrate for an intramolecular reaction as shown in eq. 29. The promise of a family of reagents for cycloaddition-like approaches to cyclopentanoid natural products appears fulfilled.

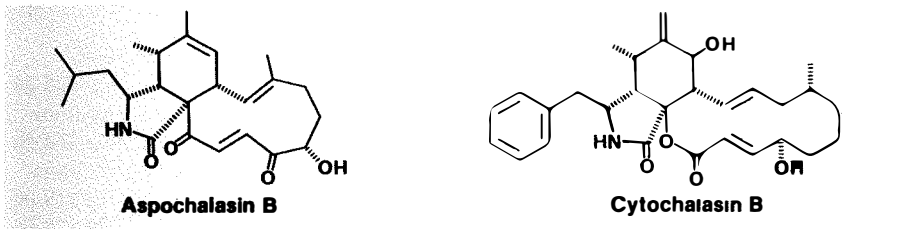
MACROCYCLIZATION

Thus far, the utility of these templates for ring formation dealt only with the more normal ring sizes — five-, six- and seven-membered rings. Macrolides and all carbon macrocycles represent major synthetic challenges. Techniques that focus on formation of such rings by C-C bond formation represent the most flexible methods. Our initial attention[28] focused on macrolides where palladium-initiated cyclization to rings of ten or more members culminated in syntheses of phoracantholides I and J,[28,29] recifeiolide,[28,30] and exaltolide.[28,31] Most striking is the regioselectivity in formation of medium-size rings. For example, cyclization of the substrate shown in Scheme 2 can proceed to either a six- or an eight-membered ring. In addition to the 10^5 kinetic preference for formation of six-membered rings, the higher stability of *syn* complexes such as **41a** should reinforce the preference for six-membered ring formation. In spite of all this, eight-membered ring formation dominates (93%). As shown in eq. 30, nine-membered ring formation dominates over seven. Once again the normal rules for reactivity are violated — the normally difficultly available eight- and nine-membered rings are now preferred! As eq. 30 summarizes, variation of the nature of the nucleophiles, of the substitution in the chain, and of the ligands on the palladium permit complete control of regiochemistry and thus, ring size — truly a remarkable



(eq. 30)

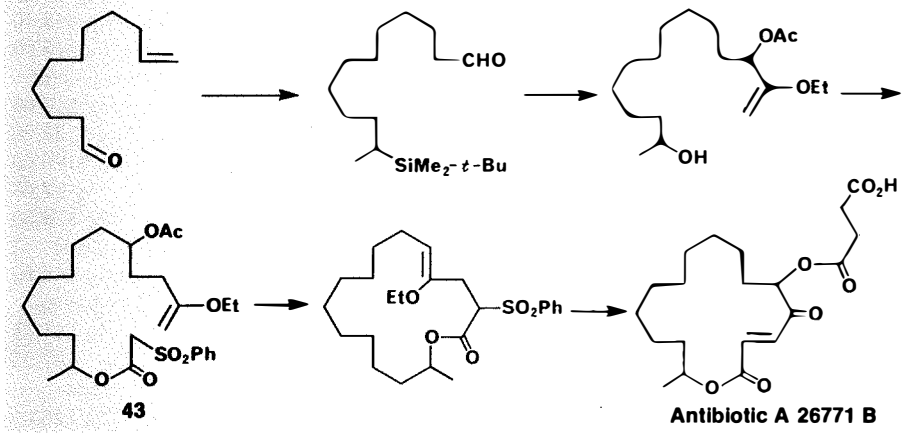
S	R	X	Y	Catalyst		
$PhSO_2$	CO_2Me	C=O	O	$(Ph_3P)_4Pd$	-----	only
$PhSO_2$	CO_2Me	CH_2	CH_2	$(Ph_3P)_4Pd$	only	-----
$PhSO_2$	$PhSO_2$	CH_2	CH_2	$(Ph_2PCH_2CH_2PPh_2)_2Pd$	-----	only



Aspochalasin B

Cytochalasin B

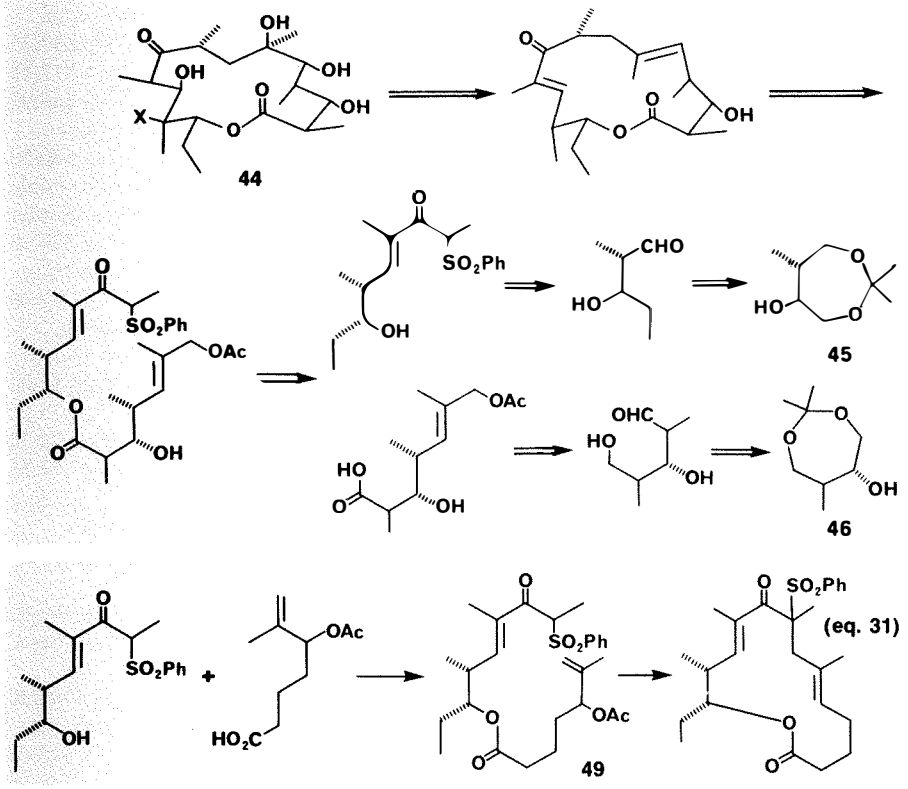
Scheme 3. Synthesis of Antibiotic A 26771 B



43

Antibiotic A 26771 B

Scheme 4. Retrosynthetic Analysis of Erythrynolide Synthesis



44

45

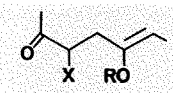
46

49

(eq. 31)

level of control of reactivity.[32]

The challenge of the synthesis of complex natural products offers an ideal testing ground for this method. The cytochalasin family of natural products consists of a highly substituted cyclohexyl ring fused to a macrolide as in cytochalasin B or to an all-carbon macrocycle as in aspochalasin B. A common feature of both is the highly oxygenated pattern in the macrocycle, a type of pattern found in other natural products such as antibiotic A 26771 B (see Scheme 3). An ideal precursor to all of these is the fragment shown in structure **42**,

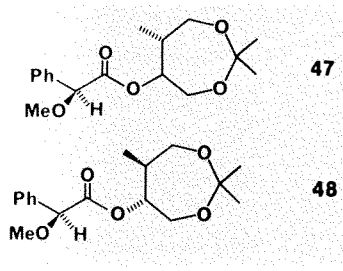


42

where the enol ether can serve as an easy entry into the simple alcohol as in cytochalasin B or an α-hydroxy ketone as in aspochalasin B and antibiotic A 26771 B. This fragment becomes an obvious target of allylic alkylation.

Scheme 3 illustrates the ready availability of the requisite substrate **43** from 10-undecenal. Treatment of **43** with a Pd(0) catalyst and *N*,*O*-bis(trimethylsilyl)acetamide in refluxing THF gave the requisite macrocycle in 55-61% yield, a much higher yield than obtained by any lactonization approach.[33] Hydroxylation using a catalytic amount of osmium tetroxide followed by esterification with succinic anhydride completes the sequence. The soundness of this strategy for cytochalasin synthesis is established.

Equally challenging targets are the erythrynolides A (**44**, X=OH) and B (**44**, X=H) as shown in Scheme 4. The retrosynthetic analysis utilizing this macrocyclization principle converges to **45** and **46** — a pair of enantiomers! Thus, the problem of control of absolute as well as relative stereochemistry is resolved as long as both enantiomers are available in a simple operation. A simple solution emerged. The *O*-methylmandelate esters **47** and **48** revealed two well-resolved peaks by HPLC and permitted large-scale separation on a Waters Prep 500 instrument.[34] A second advantage of this approach is the ability to assign stereochemistry. Using the Mosher model, the stereochemistry depicted in **47**



47

48

and **48** corresponds to the less and more polar isomers, respectively. Further correlation was provided by comparison of the regenerated optically pure **45** and **46** whose absolute configurations were established by Horeau's method.

With the strategy developed, the elaboration of **45** into the desired alcohol is complete, and the corresponding elaboration of **46** into the carboxylic acid is nearing completion. However, establishment of the critical ring closure remains to be accomplished. Comfortingly, subjection of a model **49** (eq. 26), which possesses a fully elaborated alcohol half and a stripped version of the carboxylic acid portion, to the normal cyclization conditions creates the correct fourteen-membered macrolide ring of the erythrynolides.

CONCLUSION

An appreciation of the intricacies of transition-metal chemistry in the design and application of new reactions is emerging. The fact that insight based upon traditional thinking is challenged offers an unprecedented opportunity to expand the rules of selectivity. Indeed, such an expansion is critical if we are to mount a successful campaign to have chemistry better serve the needs of man by instilling efficiency and bringing to application more sophisticated materials. We hope the above will contribute to this task.

ACKNOWLEDGMENTS

Our work on the use of transition-metal templates in organic synthesis represents the collaborative effort of an enthusiastic group of graduate and postdoctoral students. The four thrusts which have been the focus of this report were derived principally from the efforts of Mr. Thomas P. Klun (stereo-relay), Dr. Thomas A. Runge (1,3-rearrangement), Mr. Dominic M.T. Chan (cyclopentane annulation), and Dr. Thomas R. Verhoeven, Dr. Steven J. Brickner and Dr. John L. Belletire (macrocyclization). To them and to the rest of the group I am most indebted. We are especially grateful for the continuing financial support of the National Science Foundation, the General Medical Sciences Institute and the National Cancer Institute of the National Institutes of Health, and the University of Wisconsin.

References:

1) Trost, B.M. *Acc. Chem. Res.* **1980**, *13*, 385.
2) Trost, B.M.; Curran, D.P. *J. Am. Chem. Soc.* **1980**, *102*, 5699.
3) Curran, D.P., unpublished work in these laboratories.
4) Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.
5) Coulson, D.R. *Inorg. Syn.* **1972**, *13*, 121.
6) Trost, B.M.; Runge, T.A.; Jungheim, L.N. *J. Am. Chem. Soc.* **1980**, *102*, 2840.
7) Rosevear, D.T.; Stone, F.G.A. *J. Chem. Soc. (A)* **1968**, 164.
8) Trost, B.M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779.
9) Springer, S., unpublished work in these laboratories.
10) Cohen, N.; Lopresti, R.J.; Neukom, C.; Janez, G. *J. Org. Chem.* **1980**, *45*, 582.
11) Trost, B.M.; Klun, T.P. *J. Am. Chem. Soc.* **1979**, *101*, 6756.
12) Trost, B.M.; Klun, T.P. *J. Org. Chem.* **1980**, *45*, 4256.
13) Klun, T.P., unpublished work in these laboratories.
14) Trost, B.M.; Klun, T.P. *J. Am. Chem. Soc.* **1981**, *103*, 1864.
15) Trost, B.M.; Jungheim, L.N. *ibid.* **1980**, *102*, 7910.
16) Trost, B.M.; Runge, T.A. *ibid.*, in press.
17) Trost, B.M.; Runge, T.A., submitted for publication in *J. Am. Chem. Soc.*
18) Trost, B.M.; Chan, D.M.T. *J. Am. Chem. Soc.* **1979**, *101*, 6429.
19) Trost, B.M.; Chan, D.M.T. *ibid.* **1979**, *101*, 6432.
20) Trost, B.M.; Chan, D.M.T. *ibid.* **1980**, *102*, 6359.
21) *Cf.* Binger, P.; Schuchardt, V. *Chem. Ber.* **1980**, *113*, 3334; Inoue, Y.; Hibi, T.; Kawashima, Y.; Hashimoto, H. *Chem. Lett.* **1980**, 1521.
22) Day, A.C.; Powell, J.T. *Chem. Commun.* **1968**, 1240; Ehrlich, K.; Emerson, G.F. *J. Am. Chem. Soc.* **1972**, *94*, 2464.
23) Gordon, D.; Nanninga, T., unpublished work.
24) Albright, T.A. *J. Organomet. Chem.* **1980**, *198*, 159.
25) Chan, D.M.T., unpublished work in these laboratories.
26) Kon, K.; Isoe, S. "Abstracts of Papers," 23rd Symposium on the Chemistry of Natural Products, Japan, 1980, 49.
27) Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399.
28) Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
29) Trost, B.M.; Verhoeven, T.R. *ibid.* **1979**, *101*, 1595.
30) Trost, B.M.; Verhoeven, T.R. *Tetrahedron Lett.* **1978**, 2275.
31) Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1977**, *99*, 3867.
32) Verhoeven, T.R.; Martina, D., unpublished work in these laboratories.
33) Asaoka, M.; Yanagida, N.; Takei, H. *Tetrahedron Lett.* **1980**, *21*, 4611; Tatsuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. *ibid.* **1980**, *21*, 1479; Hase, T.A.; Nylund, E.-L. *ibid.* **1979**, 2633.
34) Belletire, J.L., unpublished work in these laboratories.

About the Author

Professor Barry M. Trost was born on June 13, 1941. He received the B.A. degree from the University of Pennsylvania in 1962 and the Ph.D. degree (Professor H.O. House) from the Massachusetts Institute of Technology in 1965. He was appointed Assistant Professor of Chemistry at the University of Wisconsin in 1965 and was promoted to Associate Professor, Professor, and Evan P. and Marion Helfaer Professor in 1968, 1969 and 1976, respectively.

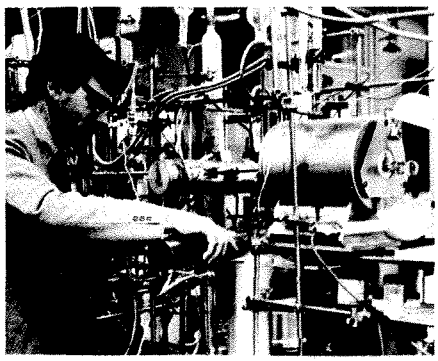
Dr. Trost has developed transition-metal-assisted synthetic methodologies including allylic alkylation, cyclopentanone annulation, and medium-to-large ring cyclization reactions. Natural-product chemistry to his credit include the total syntheses of juvenile hormone, grandisol, methyldesoxypodocarpate, juvabione, ibogamine, recifeiolide, exaltolide, and phoracantholides I and J.

Among his many awards and distinctions are the 1977 ACS Award in Pure Chemistry, the 1981 Baekeland Award, and election to the National Academy of Sciences in 1980. Dr. Trost has delivered 50 plenary lectures in the U.S. and abroad, has served as editor of numerous books and journals, and is the author of over 200 scientific papers. He is a member of the American Chemical Society, the Chemical Society (London), and is a Fellow of the American Association for the Advancement of Science.

Isobenzofuran and Related *o*-Quinonoid Systems

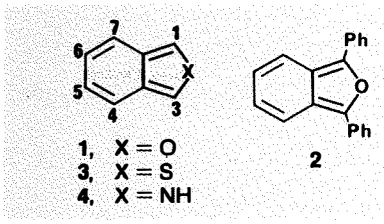
A New Group of Synthetic Intermediates

U.E. Wiersum
AKZO Research Laboratories
Corporate Research Department
Velperweg 76
Arnhem, The Netherlands



INTRODUCTION

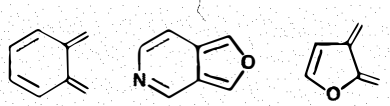
Isobenzofuran (IBF) or benzo[*c*]furan (**1**) has long been an elusive species[1,2] and, until very recently, its chemistry has been underdeveloped. Only 1,3-diphenylisobenzofuran (**2**) is well known[3] as a standard trapping agent for olefins.[4]



The fundamental question, whether isobenzofuran and the related isothianaphthene (**3**, benzo[*c*]thiophene) and isoindole (**4**, benzo[*c*]pyrrole) are aromatic or *o*-quinonoid systems, makes these compounds naturally attractive to organic chemists. Theoretical studies have been published in recent years.[5-7]

Despite their relatively recent isolation, the chemistry of the parent isothianaphthene **3**[8,9] and isoindole **4**[10,11] was developed[12,13] earlier than that of isobenzofuran. Isobenzofuran is only very briefly treated in heterocyclic textbooks. In 1978, Haddadin wrote an excellent review on isobenzofuran and related isoannelated heteroaromatics.[14] Recently a comprehensive review covering the literature up to mid-1978 was published by Friedrichsen.[15] However, since these reviews, new methods for the generation of isobenzofurans have been found. Their application in the Diels-Alder synthesis of polycyclic systems, including natural products, has become recognized.

This development is paralleled by the use of other *o*-quinonoid systems, *e.g.*, *o*-quinodimethane (**5**),[16] furo[3,4-*c*]pyridine (**6**),[17] or 2,3-dimethylene-2,3-dihydrofuran (**7**).[18] Like isobenzofuran, these systems are conveniently prepared by flash-vacuum thermolysis (FVT).[19]

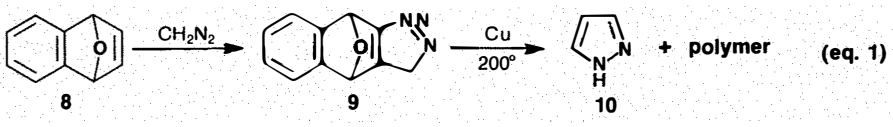


The aim of this review is to present the title compounds as a complementary set of synthetic intermediates, which also have potential application in the natural-product area.

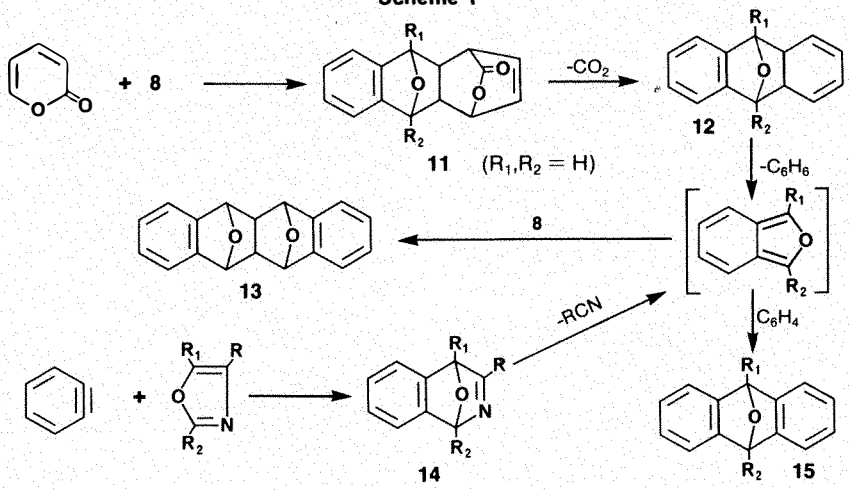
ISOBENZOFURAN. GENERATION AND REACTIONS

In 1956, Wittig and Pohmer,[20] while developing the chemistry of benzyne, prepared 1,4-epoxy-1,4-dihydronaphthalene (**8**). The double bond in **8**, like in norbornene, is quite reactive as a dienophile.[21] With diazomethane the pyrazoline **9** (eq. 1) was formed which, on thermal decomposition, yielded pyrazole **10** and a polymer indicated as polyisobenzofuran.[20]

Isobenzofuran was first demonstrated to exist as a transient intermediate by Fieser and Haddadin.[22] They reacted **8** with α-pyrone to form Diels-Alder adduct **11** (Scheme 1), which spontaneously loses car-



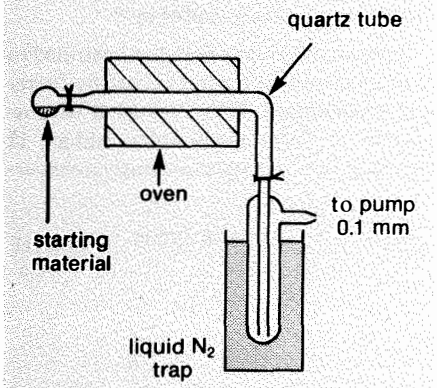
Scheme 1



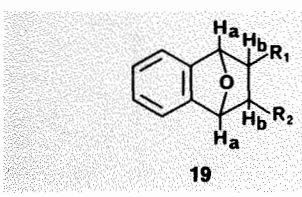
bon dioxide to give product **12**, the formal Diels-Alder adduct of isobenzofuran and benzene, decomposing above 60°C. Isobenzofuran is trapped *in situ* by dienophiles added to the reaction mixture, or by an excess of **8** to give an *exo-endo* mixture of diepoxide **13**. Isobenzofurans are also transient intermediates in the reaction of benzyne with oxazoles.[23] The initial adduct **14** decomposes into isobenzofuran and a nitrile.[24] Another molecule of benzyne traps the isobenzofuran to give adduct **15**.

Isobenzofuran was isolated simultaneously by three different groups, *via* retro-Diels-Alder reaction with derivatives of **8**. Warrener[25] applied 3,6-di(2'-pyridyl)-*s*-tetrazine (Scheme 2) as the diene component with **8** to prepare adduct **16**, which loses nitrogen to form **17**. By decomposing **17** under reduced pressure at 120°C, **1** and dipyridylpyridazine were trapped on a cold finger. Wege[26] isolated isobenzofuran in a similar experiment with lactone **11**. The simplest and most rapid route to relatively large quantities of **1** involved flash-vacuum thermolysis (FVT) of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**18**).[1] When this compound is evaporated at 0.1 mm Hg into an unpacked quartz tube (25 cm long, 0.8 in. diam) heated at 650°C, ethylene is expelled and a quantitative amount of colorless crystals of pure **1** is collected in a cold trap connected to the tube (see Figure 1), at a

Figure 1

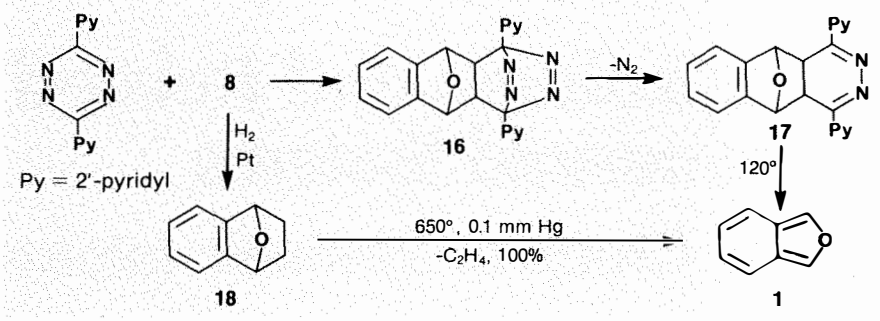


rate of 5-10 g/h. In organic solvents, **1** homopolymerizes at room temperature but it can be stored in the refrigerator for longer periods. These solutions react instantaneously and quantitatively with dienophiles such as maleic anhydride and methyl vinyl ketone to produce mixtures of *exo*- and *endo*-adducts **19**.[1,15] With less



19

Scheme 2



reactive olefins such as styrene or cyclohexene, homopolymerization of **1** starts to compete with the Diels-Alder addition.[1] The *exo*- and *endo*-isomers **19** are nicely distinguishable by NMR:[21] the bridgehead methine protons H_a in the *exo*-isomers show no coupling with the H_b protons, while in the *endo*-isomers, J_{ab} is about 5 Hz.[27] In most of the adducts, the 1,4-oxygen bridge can be easily eliminated under mildly acidic conditions to naphthalene derivatives, or to naphthols with adducts of acetylenic dienophiles.[2,20,28]

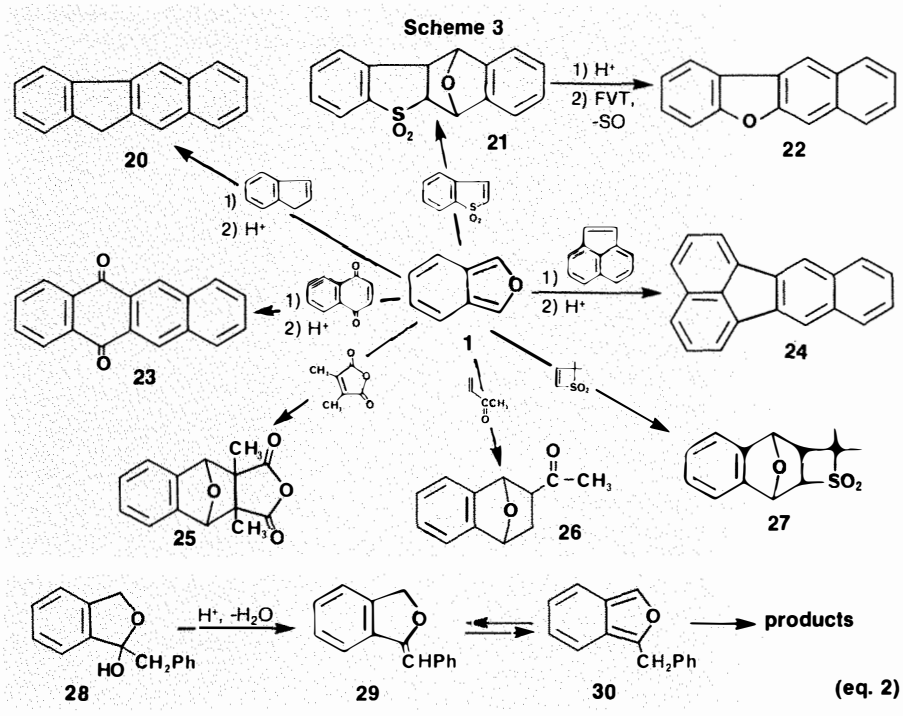
Several condensed aromatic compounds are rapidly prepared *via* isobenzofuran (Scheme 3), *e.g.* 2,3-benzofluorene (**20**), benzonaphthofuran (**22**), 5,12-naphthacenedione (**23**), and benzo[*k*]fluoranthene (**24**).[29] 3,4-Dimethylmaleic anhydride does not react with furan to give the Spanish fly component cantharidin;[30] however, its benzo analog **25** is rapidly formed with **1**.[29] Some adducts could not be dehydrated to the corresponding naphthalenes, *e.g.*, those of methyl vinyl ketone[29] and benzothiete-1,1-dioxide[31] gave deviant reactions.[32]

The reactivity of the isobenzofuran moiety in Diels-Alder reactions and its versatility as a synthetic intermediate are also illustrated with numerous reactions of 1,3-diphenylisobenzofuran (**2**).[14,15,33] A new synthesis[34] and new reactions[35] of **2** were very recently reported. The photochemistry and the reaction of **2** with singlet oxygen have also been well studied.[15]

1,3-Dialkylisobenzofurans and some 4-, 5-, 6-, or 7-substituted isobenzofurans are prepared by the FVT method of Wiersum and Mijs.[1] This method was developed independently by Heaney and coworkers,[36] who prepared 4,5,6,7-tetrafluoro- and 4,5,6,7-tetrachloroisobenzofuran which, as their isoindole analogs, [37] are considerably more stable than the parent systems.

The FVT method was also applied to the preparation of 1-benzylisobenzofuran (**30**).[38] It was demonstrated[39] earlier that **30** shows an interesting tautomerism with benzalphthalan (**29**), formed *via* dehydration of hemiketal **28** (eq. 2). In the presence of dienophiles, the equilibrium shifts towards **30** and the Diels-Alder adducts are

Scheme 3



formed. Several adducts of **30** and their conversion to naphthalenes have been reported.[28]

Isobenzofuran synthesis *via* a hemiketal precursor goes back to the formation of 1-benzoyl-3-phenylisobenzofuran[40] and 1,3-diphenylisobenzofuran (**2**).[41] The linearly annelated 1,3-diphenylnaphtho[2,3-*c*]-furan (**32**), less stable and more reactive than **2**, was also prepared[42] *via* the corresponding hemiketal **31** (eq. 3). Nevertheless, isobenzofuran generation at ambient temperatures from hydroxy- or alkoxyphthalan derivatives was only recognized as general in 1980.[2,28,43] Methoxyphthalan (**34**), rapidly prepared from phthalyl alcohol (**33**), gives the parent isobenzofuran (**1**) in quantitative yield by treatment with lithium diisopropylamide or by refluxing in toluene (eq. 4).[2]

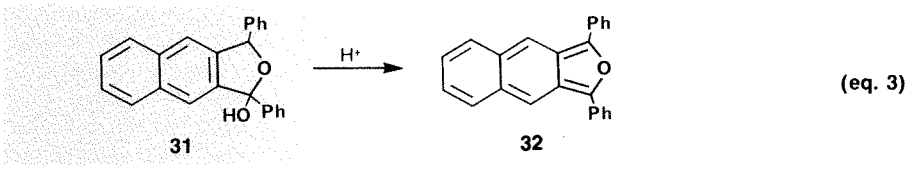
Essentially similar in the final step is the generation of 5,6-dimethoxyisobenzofuran (**37**).[43] 6-Bromoveratraldehyde (**35**) is converted in a number of steps to 1,5,6-trimethoxyphthalan (**36**) which spontaneously yields **37** *in situ* which, in turn, is trapped by dienophiles to yield adducts **38** (Scheme 4).

Methoxy- or alkoxy-substituted isobenzofurans are of special interest for application in natural-product synthesis. An ingenious route (Scheme 5) to 1-arylnaphthalide ligands **40** was reported by Plaumann, Smith and Rodrigo.[44] Piperonal and **35** provide the ketal **39**, the precursor to the isobenzofuran derivative that is reacted with dimethyl acetylenedicarboxylate to give the Diels-Alder adduct which is hydrolyzed to the naphthol and then reduced to **40**.

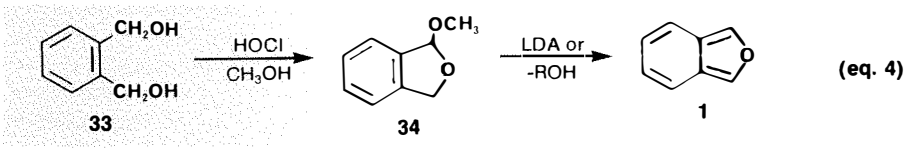
In another application, Kende and coworkers[45] generated 4-methoxyisobenzofuran (**41**) *via* the α-pyrone method,[22] as an intermediate in the construction of the tetracyclic skeleton of the aglycone part (**42**) of daunorubicin, used in cancer chemotherapy (eq. 5).

1-Phenylisobenzofuran (**44**) is generated from 2-methylbenzophenone *via* photobromination to **43**, and subsequent elimination of hydrogen bromide by boiling in carbon tetrachloride (eq. 6). **44** is trapped by dienophiles and the adducts **45** are, under the acidic reaction conditions, converted directly to naphthalenes **46**.[46] With methyl vinyl ketone as dienophile, only 1-phenyl-2-acetylnaphthalene was formed in this sequence.

o-Carbonylated phenylcarbenes yield isobenzofurans; for example, the photolysis of 1,4-diphenylphthalazine-*N*-oxide to 1,3-diphenylisobenzofuran is thought to proceed *via* *o*-benzoyldiphenylcarbene.[47] 1-methoxyisobenzofurans **49**[2] are

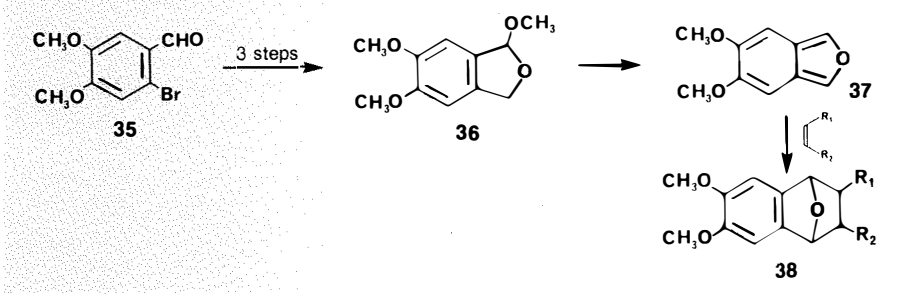


(eq. 3)

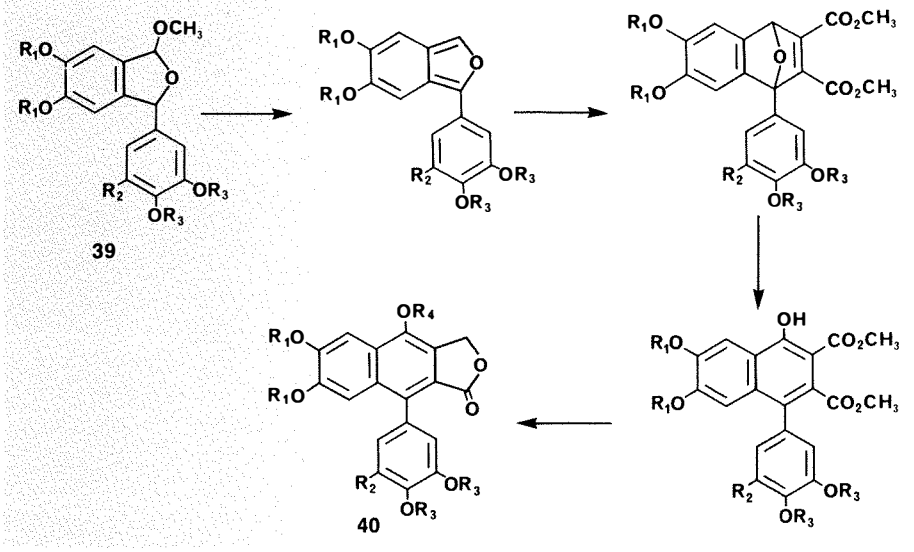


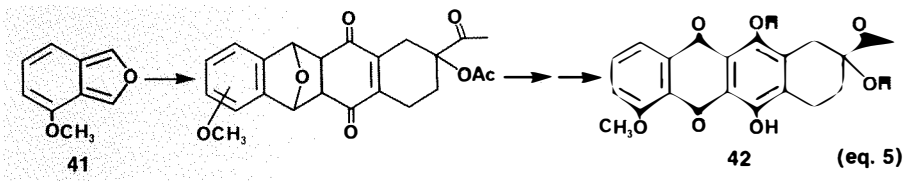
(eq. 4)

Scheme 4

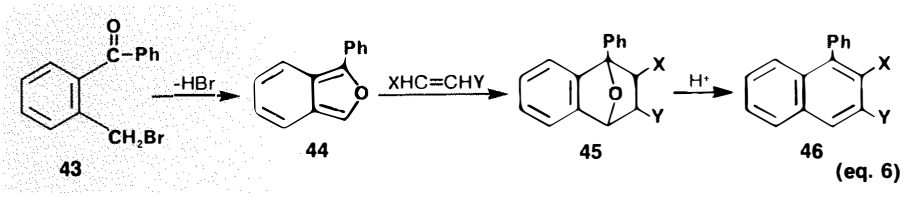


Scheme 5

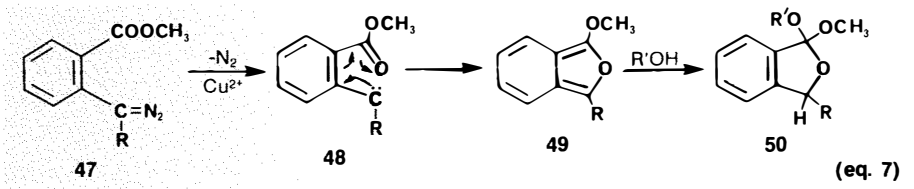




(eq. 5)



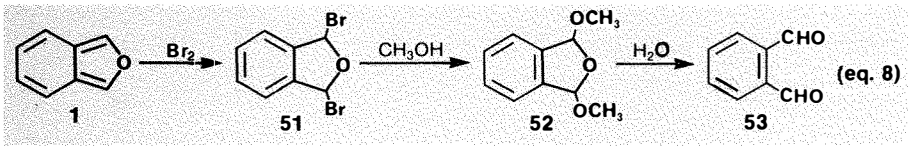
(eq. 6)



(eq. 7)

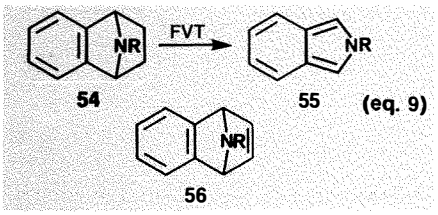
generated and trapped[48,49] in the copper-catalyzed decomposition of *o*-diazomethylbenzoates **47**, *via* the carbene **48** (eq. **7**). In the absence of a trapping dienophile, the cyclic orthoester **50** was formed by the addition of alcohols. It was not discussed if this ester reversibly forms **49**. The question of whether the addition of alcohols to isobenzofurans is reversible and the possible existence of equilibria like **1** ⇌ **34** or **36** ⇌ **37** remain to be further investigated.[2]

Bromine reacts instantaneously with isobenzofuran (eq. 8).[50] Work-up in the presence of methanol gives phthalaldehyde (**53**), presumably *via* intermediates **51** and **52**.[50] 1-Hydroxyphthalan can be prepared *via* autooxidation of phthalan.[41] The free-radical chemistry of 1-methoxyphthalan (**34**) has been studied.[51]



GENERATION OF RELATED *o*-QUINONOIDS BY FLASH-VACUUM THERMOLYSIS

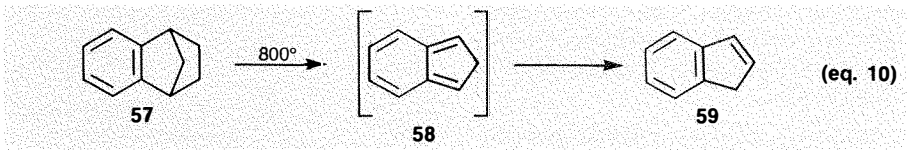
Several reactive *o*-quinonoid intermediates have been generated and characterized by FVT procedures. FVT has expanded the scope of the retro-Diels-Alder reaction enormously.[52] Expulsion of ethylene from tetrahydronaphthalenes, analogous to the procedure for isobenzofuran,[1] is rather general. Isoindoles **55** (eq. **9**) are obtained from 1,4-imino-1,2,3,4-tetrahydronaphthalenes **54**.[11,36,37] The iminodihydronaphthalenes **56** are good dienophiles.[53,54] Isoindole chemistry continues to grow.[55]

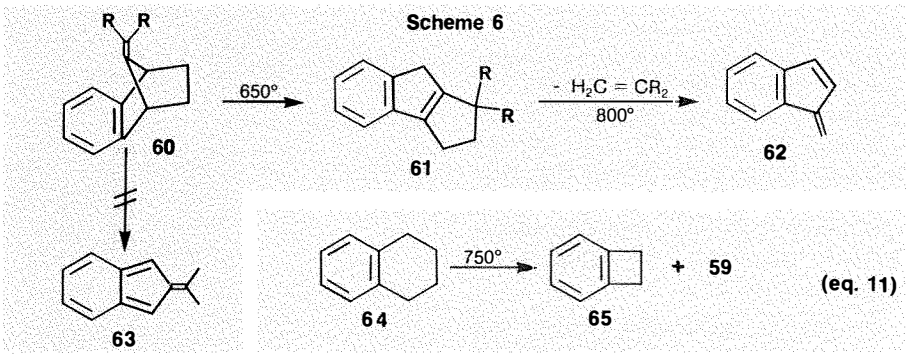


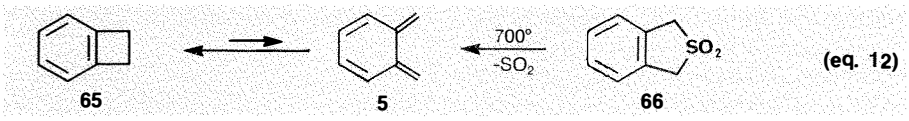
1,4-Methano-1,2,3,4-tetrahydronaphthalene (**57**) yields indene (**59**) quantitatively (eq. 10).[1] The intermediacy of isoindene (**58**) as a discrete species in this reaction could not be firmly established with photoelectron spectroscopy.[56] This method,[57] in addition to matrix isolation,[58] is a good tool for the characterization of reactive intermediates. Indenes thermally equilibrate to isoindenes[59] and can be trapped with olefins.[60]

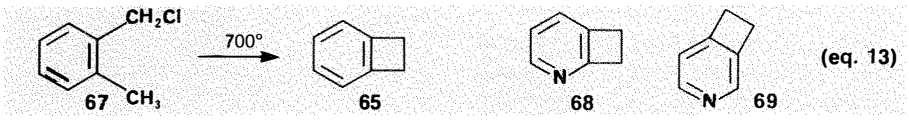
Methylene-methanotetrahydronaphthalenes **60** show a deviant reaction (Scheme 6) to form cyclopentaindenes **61**,[36] which ultimately form benzo[*a*]fulvene (**62**) in good yield.[61] No isobenzofulvene (**63**) was found.

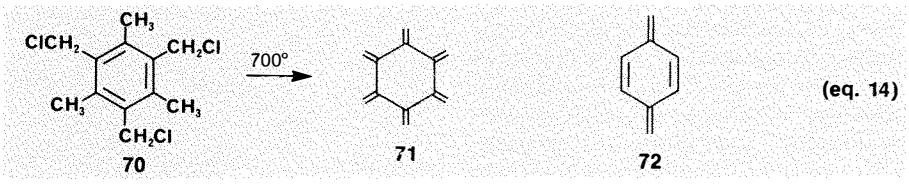
Tetralin (**64**) itself was intensively studied as a hydrogen donor in coal technology.[62] Laser-induced decomposition experiments (eq. 11) indicate that benzocyclobutene (**65**) is the primary product,[63] but under FVT conditions, styrene, indene and naphthalene are major products.[50,63] Benzocyclobutene (**65**) undergoes thermal ring opening (eq. 12) to *o*-quinodimethane (**5**). *o*-Quinodimethanes are highly reactive dienes that enable a similar annelation approach, as *via* isobenzofurans. The field, opened by Cava[64] who trapped **5** in the pyrolysis of 1,3-dihydroisothianaphthene-2,2-dioxide (**66**), has been extensively reviewed.[16,65,66] A large number of preparative approaches to benzocyclobutenes, including many FVT procedures, have been found.[16,59]

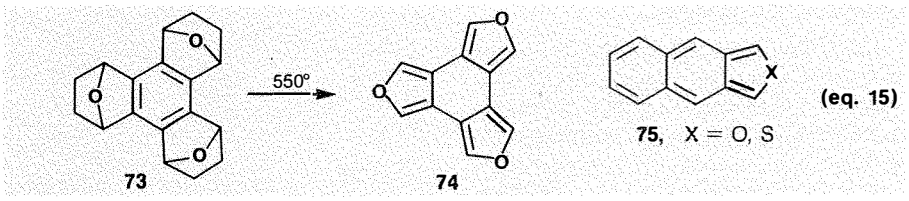












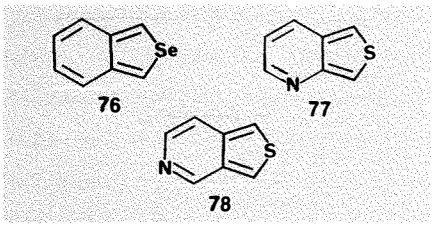
Intramolecular Diels-Alder cyclization, *via* benzocyclobutene ⇌ *o*-quinodimethane intermediates, has been applied to natural-product synthesis by Oppolzer[66] and Kametani.[67] Cava prepared 4-demethoxydaunomycinone[68] (**42**) similarly. His method for the generation of benzocyclobutenes from sulfones of type **66** (eq. 12) was recently applied to the total synthesis of steroids,[69] an alternative to the cobalt-catalysis method of Vollhardt.[69]

FVT of *o*-methylbenzyl chloride (**67**) is an excellent method of preparation of **65** (eq. 13).[70] Cyclobutapyridines **68** and **69** are prepared in a similar way.[71]

The mechanism of the pyrolysis of **67** was studied by deuterium labeling.[72] FVT of 2,4,6-tris(chloromethyl)mesitylene (**70**, eq. 14) gives hexamethylenecyclohexane (**71**, hexaradialene) in good yield.[16,73,74] *p*-Quinodimethane (**72**) can be isolated by FVT of [2.2]paracyclophane.[75] Boekelheide[74] applied benzocyclobutene pyrolysis to the preparation of multibridged

cyclophanes. Hexaradialene (**71**) is structurally related to triphenylene and its heterocyclic analogs, *e.g.*, benzo[1,2-*c*:3,4-*c'*:5,6-*c''*]trifuran (**74**). Several isoannelated furans, including **74**, have been prepared (eq. 15) from the corresponding epoxy precursors[76] such as **73**, *via* retro-Diels-Alder FVT reaction. Non-linear annelation stabilizes the isobenzofuran structural system.[76]

Naphtho[2,3-*c*]furan (**75**, X = O) is expected to be much more unstable and is still unknown. However, the thiophene analog (**75**, X = S), much less stable than 3,[77] was isolated *via* FVT of the corresponding 1,3-dihydrosulfoxide,[78] according to Cava's dehydration method.[9] This route was also successful for the synthesis of benzo[*c*]-selenophene (**76**),[79] thieno[3,4-*b*]pyridine (**77**), and thieno[3,4-*c*]pyridine (**78**).[80,81]

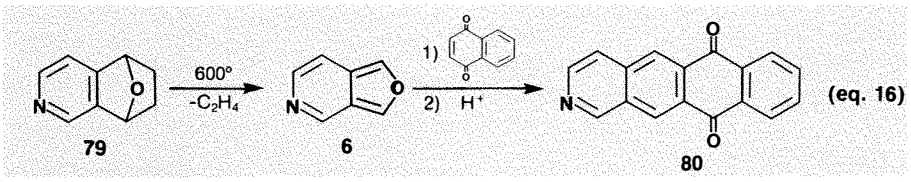


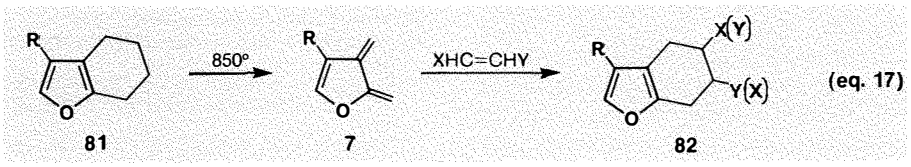
Furo[3,4-*c*]pyridine (**6**) was prepared (eq. 16) by FVT of 5,8-epoxy-5,6,7,8-tetrahydroisoquinoline (**79**).[17] **6** has synthetic potential similar to isobenzofuran, as illustrated by the preparation of 8-aza-5,12-naphthacenedione (**80**).[17]

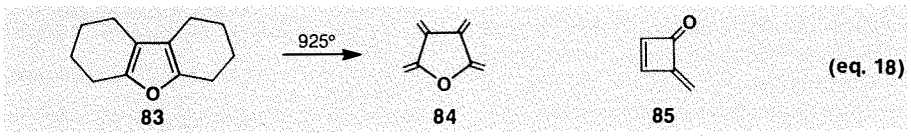
Tetrahydrobenzofurans **81** produce 2,3-dimethylene-2,3-dihydrofurans **7**, which form a mixture of Diels-Alder adducts (**82**) with activated olefins (eq. 17).[18] **7** is also obtained by FVT of 2-methyl-3-acetoxymethylfurans.[82] Hexaradialene (**71**) has a heterocyclic counterpart in furanoradialene (**84**), formed in a two-step retro-Diels-Alder reaction (eq. 18) of octahydrodibenzofuran (**83**).[83] Another interesting FVT preparation of a furan is the formation of methylenecyclobutenone (**85**) from furfuryl benzoate.[84]

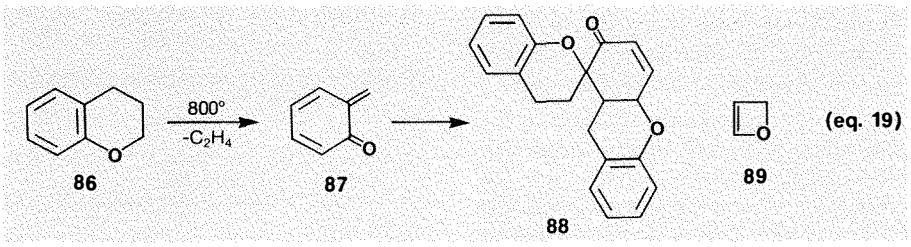
Heteroanalogs of *o*-quinodimethane (**5**) have also been characterized and are expected to have good synthetic potential as well.[74] *o*-Quinonemethide (**87**), usually isolated as the trimer **88**,[85] can be generated from various precursors.[58] FVT of chroman (**86**)[50] gives trimer **88** above 800° (eq. 19), but other fragmentations occur at lower temperatures.[86] In contrast to the *o*-quinodimethane series, *o*-quinonemethides definitely exist in the open form (**87**). The parent oxetene (**89**), however, was isolated at low temperature *via* FVT, although it rearranges rapidly to acrolein at room temperature.[87]

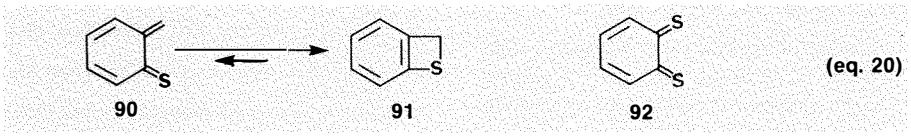
In the sulfur series, benzo[*b*]thiete (**91**) is obtained in good yield as a relatively stable

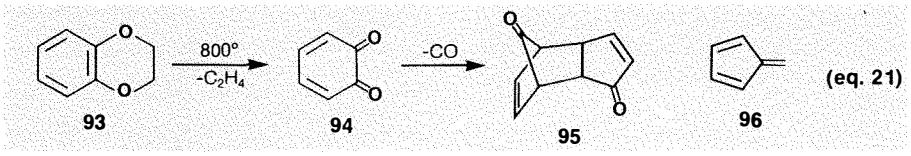


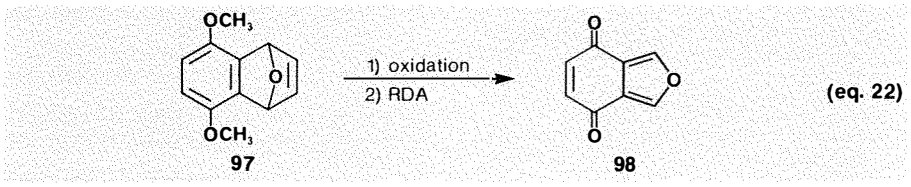


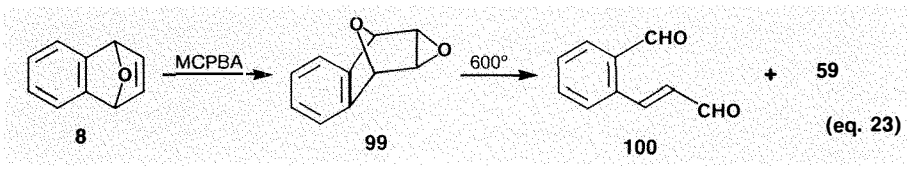












compound,[88] but it dimerizes and undergoes Diels-Alder reaction[74] *via* the open thio-*o*-quinonemethide **90** (eq. 20). The formation of **91** in the high-temperature pyrolysis of thianaphthene-1,1-dioxide[89] is mechanistically interesting, in comparison to the SO extrusion[90] in the conversion **21** → **22**.[29] Dithio-*o*-benzoquinone (**92**) is reported as an FVT intermediate.[91] Preparatively interesting is the FVT reaction (eq. 21) of benzodioxane (**93**) which shows a genuine retro-Diels-Alder reaction.[92] The primary product *o*-benzoquinone (**94**) is unstable at the applied temperature, and, contrary to *p*-benzoquinone,[93] loses one molecule of CO to yield cyclopentadienone, ultimately isolated as its dimer (**95**) in good yield. At temperatures above 800°, *o*-quinonemethide (**87**) also begins to decarbonylate, thus representing a simple preparation of fulvene (**96**).[94]

Many more FVT reactions, as summarized here, can be run with the simple apparatus shown in Figure 1.[95] In connection with isobenzofuran chemistry, the preparation of isobenzofuran-4,7-quinone (**98**, eq. 22) *via* 1,4-epoxy-5,8-dimethoxy-1,4-dihydronaphthalene (**97**) must be recalled.[96] Diepoxide **99** (eq. 23) is the major metabolite of **8** in rats.[97] It is rapidly

prepared from **8** by *m*-chloroperoxybenzoic acid oxidation and yields *o*-formylcinnamaldehyde (**100**) and indene (**59**) in equal amounts,[98] when subjected to FVT.

CONCLUSION

Isobenzofurans have become readily available synthetic intermediates which can add two rings at an olefinic bond in one step. The presence of the oxygen bridge in the adducts implies aromatization to naphthalene derivatives or hydroxyl functionalization as further strategic possibilities. In the complementary case of benzocyclobutene addition, a tetralin unit is constructed. Heterocyclic analogs of isobenzofuran such as furopyridines, thia-*o*-quinonemethides and dimethylenedihydrofurans allow, in a similar way, the construction of, for example, isoquinoline, thiachroman, or benzofuran units.

The recent abundance of data on the generation of a great variety of the title intermediates certainly enables new approaches in natural-product synthesis. The FVT method is a synthetic means of great value for the title compounds.

Another important conclusion is that FVT is a synthetic method of general utility[95] which encompasses many areas of organic chemistry.[19,99] Isotope labeling of the starting materials in FVT experiments makes these unimolecular, clean, gas-phase reactions likewise suited for mechanistic studies.

References:

I) Wiersum, U.E.; Mijs, W.J. *Chem. Commun.* **1972**, 347.
2) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061; Makhlouf, M.A.; Rickborn, B. *ibid.* **1981**, *46*, 2734.
3) Elderfield, R.C. "Heterocyclic Compounds"; Vol. II; John Wiley: New York, 1951; p 68.
4) Fieser, L.F.; Fieser, M. "Reagents for Organic Synthesis"; Vol. I-III; John Wiley: New York, 1967-1979.
5) Dewar, J.S.; Harget, A.J.; Trinajstic, N.; Worley, S.D. *Tetrahedron* **1970**, *26*, 4505.
6) Palmer, M.H.; Kennedy, S.M.F. *J. Chem. Soc., Perkin Trans. 2* **1976**, 81.
7) Chacko, E.; Bornstein, J.; Sardella, D.J. *J. Am. Chem. Soc.* **1977**, *99*, 8248.
8) Mayer, R.; Kleinert, H.; Richter, S.; Gewald, K. *J. Prakt. Chem.* **1963**, *20*, 244.
9) Cava, M.P.; Pollack, N.M. *J. Am. Chem. Soc.* **1966**, *88*, 4112.
10) Bonnett, R.; Brown, R.F.C. *Chem. Commun.* **1972**, 393.
11) Bornstein, J.; Remy, D.E.; Shields, J.E. *ibid.* **1972**, 1149.
12) For a review on isothianaphthene, see: Iddon, B. *Advan. Heterocycl. Chem.* **1972**, *14*, 331.
13) For a review on isoindole, see: White, J.D.; Mann, M.E. *ibid.* **1969**, *10*, 113.
14) Haddadin, M.J. *Heterocycles* **1978**, *9*, 865.
15) Friedrichsen, W. *Advan. Heterocycl. Chem.* **1980**, *26*, 135.
16) Thummel, R.P. *Acc. Chem. Res.* **1980**, *13*, 70.
17) Wiersum, U.E.; Eldred, C.D.; Vrijhof, P.; van der Plas, H.C. *Tetrahedron Lett.* **1977**, 1741.
18) Jullien, J.; Pechine, J.M.; Perez, F.; Piade, J.J. *ibid.* **1979**, 3079.
19) Brown, R.F.C. "Pyrolytic Methods in Organic Chemistry", Vol. 41, Organic Chemistry Monographs; Academic Press: New York, 1980.
20) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.
21) Wittig, G.; Reuther, W. *Justus Liebigs Ann. Chem.* **1972**, *761*, 20
22) Fieser, L.F.; Haddadin, M.J. *J. Am. Chem. Soc.* **1964**, *86*, 2081; *Can. J. Chem.* **1965**, *43*, 1599.
23) Kost, A.N.; Moscou State University, personal communication.
24) Reddy, G.S.; Bhatt, M.V. *Tetrahedron Lett.* **1980**, *21*, 3627.
25) Warrener, R.N. *J. Am. Chem. Soc.* **1971**, *93*, 2346.
26) Wege, D. *Tetrahedron Lett.* **1971**, 2337.
27) Takeshita, H.; Mori, A.; Sano, S.; Fujise, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1661.
28) Smith, J.G.; Welankiwar, S.S.; Schantz, B.S.; Lai, E.H.; Chu, N.G. *J. Org. Chem.* **1980**, *45*, 1817.
29) Wiersum, U.E.; Scharp, J.; 't Lam, P., unpublished results.
30) Stork, G.; van Tamelen, E.E.; Friedman, L.J.; Burgstahler, A.W. *J. Am. Chem. Soc.* **1953**, *75*, 384.
31) Paquette, L.A.; Phillips, T.R. *J. Org. Chem.* **1965**, *30*, 3883.
32) Fétizon, M.; Trong Anh, N. *Bull. Soc. Chim. Fr.* **1965**, 3208.
33) Onishchenko, A.S. "Diene Synthesis," Academy of Sciences of the USSR, Engl. Transl., 1964, p 566.
34) Oida, T.; Tanimoto, S.; Sugimoto, T.; Okano, M. *Synthesis* **1980**, 131.
35) Smith, J.G.; McCall, R.B. *J. Org. Chem.* **1980**, *45*, 3982.
36) Heaney, H; Ley, S.V.; Price, A.P.; Sharma, R.P. *Tetrahedron Lett.* **1972**, 3067.
37) Bornstein, J.; Remy, D.E.; Shields, J.E. *ibid.* **1974**, 4247.
38) Chacko, E.; Sardella, D.J.; Bornstein, J. *ibid.* **1976**, 2507.
39) Smith, J.G.; Wikman, R.T. *J. Org. Chem.* **1974**, *39*, 3648.
40) Allen, C.F.H.; Gates, Jr., J.W. *J. Am. Chem. Soc.* **1943**, *65*, 1230.
41) Rieche A.; Schulz, M. *Justus Liebigs Ann. Chem.* **1962**, *653*, 32.
42) Cava, M.P.; VanMeter, J.P. *J. Org. Chem.* **1969**, *34*, 538.
43) Keay, B.A.; Lee, D.K.W.; Rodrigo, R. *Tetrahedron Lett.* **1980**, *21*, 3663.
44) Plaumann, H.P.; Smith, J.G.; Rodrigo, R. *Chem. Commun.* **1980**, 354.
45) Kende, A.S.; Curran, D.P.; Tsay, Y.; Mills, J.E. *Tetrahedron Lett.* **1977**, 3537.
46) Faragher, R.; Gilchrist, T.L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 336.
47) Tomer, K.B.; Harrit, N.; Rosenthal, I.; Buchardt, O.; Kumler, P.L.; Creed, D. *J. Am. Chem. Soc.* **1973**, *95*, 7402.
48) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287.
49) Kraus, G. Iowa State University, personal communication.
50) Wiersum, U.E.; Nieuwenhuis, T., unpublished results.
51) Rynard, C.M.; Thankachan, C.; Tidwell, T.T. *J. Am. Chem. Soc.* **1979**, *101*, 1196.
52) Ripoll, J.L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19.
53) Anderson, P.S.; Christy, M.E.; Engelhardt, E.L.; Lundell, G.F.; Ponticello, G.S. *J. Heterocycl. Chem.* **1977**, *14*, 213.
54) Sasaki, T.; Manabe, T.; Nishida, S. *J. Org. Chem.* **1980**, *45*, 476, 479.
55) Kreher, R.; Schmitt, D.; Herd, K.J. *Tetrahedron Lett.* **1980**, *21*, 3471.
56) Schweig, A.; Vermeer, H., University of Marburg, personal communication.
57) Müller, C.; Schweig, A.; Thiel, W.; Grahn, W.; Bergman, R.G.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* **1979**, *101*, 5579.
58) McIntosh, C.L.; Chapman, O.L. *Chem. Commun.* **1971**, 771.
59) McCullough, J.J. *Acc. Chem. Res.* **1980**, *13*, 270.
60) Noland, W.E.; Landucci, L.L.; Kameswaran, V. *J. Org. Chem.* **1980**, *45*, 3456.
61) Warrener, R.N.; Gell, K.I.; Paddon-Row, M.N. *Tetrahedron Lett.* **1977**, 53.
62) Collins, C.J.; Roark, W.H.; Raaen, V.F.; Benjamin, B.M. *J. Am. Chem. Soc.* **1979**, *101*, 1877.
63) Berman, M.R.; Comita, P.B.; Moore, C.B.; Bergman, R.G. *ibid.* **1980**, *102*, 5692.
64) Cava, M.P.; Deana, A.A. *ibid.* **1959**, *81*, 4266.
65) Klundt, I.L. *Chem. Rev.* **1970**, *70*, 471.
66) Oppolzer, W. *Synthesis* **1978**, 793.
67) Spangler, R.J.; Beckmann, B.G.; Kim, J.H. *J. Org. Chem.* **1977**, *42*, 2989.
68) Kerdesky, F.A.J.; Cava, M.P. *J. Am. Chem. Soc.* **1978**, *100*, 3635.
69) Oppolzer, W.; Roberts, D.A. *Helv. Chim. Acta* **1980**, *63*, 1703; Funk, R.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* **1980**, *102*, 5245, 5253.
70) Loudon, A.G.; Maccoll, A.; Wong, S.K. *ibid.* **1969**, *91*, 7577.
71) Thummel, R.P.; Kohli, D.K. *J. Org. Chem.* **1978**, *43*, 4882.
72) Morello, M.J.; Trahanovsky, W.S. *Tetrahedron Lett.* **1979**, 4435.
73) Schiess, P.; Heitzmann, M. *Helv. Chim. Acta* **1978**, *61*, 844.
74) Boekelheide, V. *Acc. Chem. Res.* **1980**, *13*, 65.
75) Pearson, J.M.; Six, H.A.; Williams, D.J.; Levy, M. *J. Am. Chem. Soc.* **1971**, *93*, 5034.
76) Stringer, M.B.; Wege, D. *Tetrahedron Lett.* **1980**, *21*, 3831.
77) MacDowell, D.W.H.; Jeffries, A.T.; Meyers, M.B. *J. Org. Chem.* **1971**, *36*, 1416.
78) Bornstein, J.; Hardy, R.P.; Remy, D.E. *Chem. Commun.* **1980**, 612.
79) Saris, L.E.; Cava, M.P. *J. Am. Chem. Soc.* **1976**, *98*, 867.
80) Klemm, L.H.; Johnson, W.O.; White, D.V. *J. Heterocycl. Chem.* **1972**, *9*, 843.
81) Barker, J.M. *Advan. Heterocycl. Chem.* **1977**, *21*, 65.
82) Trahanovsky, W.S., Iowa State Univ., personal communication.
83) Jullien, J.; Pechine, J.M.; Perez, F.; Piade, J.J. *Tetrahedron Lett.* **1980**, *21*, 611.
84) Trahanovsky, W.S.; Park, M.-G. *J. Am. Chem. Soc.* **1973**, *95*, 5412.
85) Cavitt, S.B.; Sarrafizadeh R. H.; Gardner, P.D. *J. Org. Chem.* **1962**, *27*, 1211.
86) Loudon, A.G.; Maccoll, A.; Wong, S.K. *J. Chem. Soc. (B)* **1970**, 1727.
87) Martino, P.C.; Shevlin, P.B. *J. Am. Chem. Soc.* **1980**, *102*, 5429.
88) Schulz, R.; Schweig, A. *Tetrahedron Lett.* **1980**, *21*, 343.
89) van Tilborg, W.J.M.; Plomp, R. *Chem. Commun.* **1977**, 130.
90) For SO versus SO_2 extrusion, see: ref. 19, p 196.
91) Sato, M.; Lakshmikantham, M.V.; Cava, M.P.; Garito, A.F. *J. Org. Chem.* **1978**, *43*, 2084.
92) Hageman, H.J.; Wiersum, U.E. *Chem. Brit.* **1973**, *9*, 206.
93) Hageman, H.J.; Wiersum, U.E. *Tetrahedron Lett.* **1971**, 4329.
94) Wentrup, C. *Chimia* **1977**, *31*, 258.
95) Wiersum, U.E. *Recl. Trav. Chim. Pays-Bas*, in press.
96) Cragg, G.M.L.; Giles, R.G.F.; Roos, G.H.P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1339.
97) Sims, P. *Biochem. J.* **1965**, *95*, 608.
98) Lewars, E.G.; Young, A.B. *Tetrahedron Lett.* **1979**, 4799.
99) Seybold, G. *Angew. Chem.* **1977**, *89*, 377.
100) Wentrup, C. *Top. Curr. Chem.* **1976**, *62*, 173.

About the Author

Dr. Ulfert E. Wiersum is a senior chemist at AKZO Corporation, based in Arnhem, The Netherlands. He received his Ph.D. in 1968 at the University of Groningen, The Netherlands, working with Prof. H. Wynberg. He did postdoctoral work with Prof. F.G. Bordwell at Northwestern University prior to joining the AKZO group in 1970.

At the AKZO Corporate Research Department, Dr. Wiersum did pioneering work in the area of flash-vacuum thermolysis, with special emphasis on synthetic utility. His research activities include studies in polymer-degradation mechanisms in relation to polymer additives as flame retardants, polymerization initiators and antioxidants.

Page intentially blank

Aldrichimica Acta

Volume 14, Number 4, 1981

The Role of Silver Salts in Organic Processes
A Compilation of References on Formyl and Acyl Anion Synthons

chemists helping chemists in research & industry
aldrich chemical co.

Aldrichimica Acta

Vol. 14, No. 4, 1981
A publication of the ALDRICH CHEMICAL COMPANY

Main Sales Office:
P.O. Box 355
Milwaukee, Wisconsin 53201
Telephone: (414) 273-3850
Order Desk: (800) 558-9160 Toll-free
TWX: (910) 262-3052
Telex: 26 843

East Coast Service and Distribution Center:
159 Forrest Street
Metuchen, New Jersey 08840
Telephone: (201) 549-6304
TWX: (710) 998-0575

In Canada:
Aldrich Chemical Co. (Canada), Ltd.
1500 Stanley Street, Suite 405
Montreal, Quebec H3A 1R3
Telephone: (514) 845-9289
Eastern & Atlantic: (800) 361-6141 Toll-free
TWX: (610) 421-4608

In Great Britain:
Aldrich Chemical Company, Ltd.
The Old Brickyard, New Road
Gillingham, Dorset
SP8 4JL, England
Telephone: 074-76 2211
Telex: (851) 417238

In West Germany/Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany
Telephone: (07329) 6011
Telex: (841) 714838

In Belgium/Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium
Telephone: 014/611431
Telex: (846) 32540

In Japan:
Aldrich Japan
c/o Kyodo Bldg. Shinkanda
10 Kanda-Mikuracho
Chiyoda-Ku, Tokyo, Japan
Telephone: 03-258-0155.0156
TWX: 2222518

In Israel:
Sigma Israel Chemical Co.
P.O. Box 37673
Tel Aviv, Israel 61360
Telephone: 03-612315
Telex: (922) 35645

About Our Cover:

Sometimes we wonder whether our chemist-collector buys old master paintings more because of their quality or for the problems of authorship and iconography they present. In the case of the large (44 × 55 inches) painting on our cover, surely it was both. When he was offered this painting by a dealer in London last summer, it was called "Christ Disputing with the Doctors" by Jan Lievens. Some years earlier, Christie's in London had sold it under the same title, as by Gerrit Willemsz. Horst, a Rembrandt student.

Our chemist-collector is certain that it depicts Joseph explaining his dreams, and believes it is a work of Jan Victors, influenced more by Lievens than Rembrandt, although Victors was a Rembrandt student. Compare it, for instance, with Lievens' "Feast of Esther" (Fig. 1). That painting, in the North Carolina Museum of Art in Raleigh, is so similar to this work that our chemist has wondered whether that famous work might possibly be by Victors, rather than by Lievens.

Jesus' disputation with the Pharisees is always depicted in the Temple — not in a bedroom as in the painting on our cover. Victors may have intended the old woman to be Rachel, but, if so, simply overlooked that Rachel, in the Biblical account, had died years earlier. Rembrandt made the same mistake in his representation of this subject (Fig. 2), now in the Rijksmuseum.

Victors painted a great many Biblical subjects; none depicts an episode from the life of Jesus. The rich colors make this painting one of his most beautiful.

Fig. 1

Fig. 2

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

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

Lab Notes

I was prompted to write by the Lab Note in Vol. 14, No. 2 of *Aldrichimica Acta* which described a method for eliminating the problem of statically charged peptides.

We, too, have long suffered this problem. The commercially available anti-static devices that contain a radioactive strip have been marginally successful in our hands. Several years ago we bought an anti-static pistol (*ca.* $20) from the local stereo store. The unit operates on the piezoelectric effect to emit a stream of charged ions which completely neutralizes all surface static over a 30-cm area. This unit has worked extremely well and the only trouble that we have experienced is trying to keep track of it as many co-workers borrow it.

Paul D. Gesellchen, Ph.D.
Biochemistry Research Department
Lilly Research Laboratories
307 East McCarty St.
Indianapolis, Indiana 46285

Editor's note: We believe that such an anti-static device will be very useful in many laboratories, so, for the convenience of our customers, we now offer the Zerostat anti-static pistol.

The following three shortcuts have proven useful in our laboratory:

1) A discarded square plastic bottle (of the type several chemical manufacturers use to distribute their products), after being cut down to size and notched at opposite ends, is very convenient for cooling the receiver flasks in Kugelrohr distillations. This device stands up well to both wet ice and Dry-Ice/acetone.

2) A polyethylene squeeze bottle with a pinhole in its side is an excellent container for running anhydrous HF reactions. After adding the substrate to the bottle, HF is introduced from an inverted pre-cooled lecture cylinder. Upon capping the squeeze bottle, the HF which boils off displaces any remaining air. From 10-25ml of HF (a suitable volume for typical-scale Friedel-Crafts reactions involving 0.1-5g of substrate) can be handled in a 100-ml bottle without danger of bursting. The HF will evaporate overnight allowing the reaction mixture to be worked up in the usual fashion.

3) A simple procedure for the purification of tosyl chloride consists of placing the crude material in an extraction thimble for overnight extraction with reagent-grade hexane in a Soxhlet extraction apparatus. Seeding of the cooled hexane solution results in a beautiful snow-like crystallization. Decantation of the hexane under a dry atmosphere followed by pumping at high vacuum affords tosyl chloride of excellent purity.

John L. Belletire
Assistant Professor of Chemistry
University of Cincinnati
Cincinnati, Ohio 45221

Dissolving hard clumps of crude solid in a minimal amount of solvent, such as in sample preparation for NMR analysis or MPLC, is often difficult and time-consuming.

This problem can often be overcome easily by placing the tube, flask or vial containing the undissolved solid in the water bath of an ultrasonic cleaner for a few seconds.

Peter K. Trumper
Department of Chemistry
University of Minnesota
207 SE Pleasant St.
Minneapolis, Minnesota 55455

A frequent problem with gas chromatographs used for routine analysis is septum failure. The down time for this is usually at least an hour, particularly if an electron-capture detector or other gas-flow-sensitive detector is being used.

We have found that two things can be done to prevent this. First of all, be sure that there are no microscopic burrs on the syringe needle point. These can usually be felt by drawing the needle point between the nails of your thumb and forefinger. If a burr is found, remove it with a very fine-grit crocus cloth. Secondly, daily cleaning and lubrication of the syringe needle greatly reduces septum wear and also makes insertion and withdrawal of the needle easier. This is accomplished by wiping the needle with a 10% solution of SE30 (a GLC liquid phase) in toluene. The excess is removed with a clean dry tissue. We have been using SE30 as a needle lubricant for at least four years on various kinds of GLC columns and have never encountered any interference or column degradation that

Cont'd. on page 77.

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

"Please Bother Us."

by Jessica Bader.

Recently, Dr. James W. Miles of the Center for Infectious Diseases in Atlanta called us with an interesting problem. *m*-Diphenoxybenzene is used worldwide as an internal standard in the GLC analysis of malathion. The only supplier known to Dr. Miles was a laboratory supply house whose smallest package was 25 grams priced at more than a hundred dollars. That may not seem excessive to some U.S. laboratories, but it does to us. Also, 25 grams is such a large quantity for that application. Would Aldrich help?

Of course, we would. Some years ago, we perfected an elegant preparation of *m*-phenoxybenzaldehyde, of great importance in the synthesis of pyrethroids, and that technology was applicable here. We made a small batch of *m*-diphenoxybenzene and were able to cut the price by more than half. And, of course, we offer a 5-gram unit. For bulk quantities, we could lower the price much further.

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

The Role of Silver Salts in Organic Processes

John R. Long
Aldrich Chemical Company, Inc.

INTRODUCTION

In the early 1970's, topical reviews[1a-e] and resources such as the Fiesers' *Reagents for Organic Synthesis* highlighted many uses of silver compounds in organic synthesis. This article extends that perspective by supplementing earlier citations with reports of recent applications such as rearrangements and isomerizations, cycloadditions and ring expansions, oxidative cleavages and couplings, and alkylations.

Despite its wide range of applications, silver chemistry has remained rather specialized, an inference readily drawn from literature of the mid-seventies. Ozin[2] described some rather selective silver chemistry (including the use of silver supported on silica in the catalytic oxidation of ethylene) in his account of metal-ion-matrix chemistry; however, Kozikowski and Wetter[3] reviewed transition metals in organic synthesis with great emphasis on first-row (Group B) elements and platinum-group metals but made no mention of silver.

SILVER CARBONATES AND CARBOXYLATES

McKillop and Young[4] recently reviewed the use of supported reagents in organic preparations and highlighted numerous applications of the Fetizon reagent (silver carbonate on Celite) including: 1) general, selective and unusual oxidations; 2) fragmentation reactions; 3) rearrangements of bromohydrins; and 4) oxidations of nitrogen compounds (see Fig. 1).

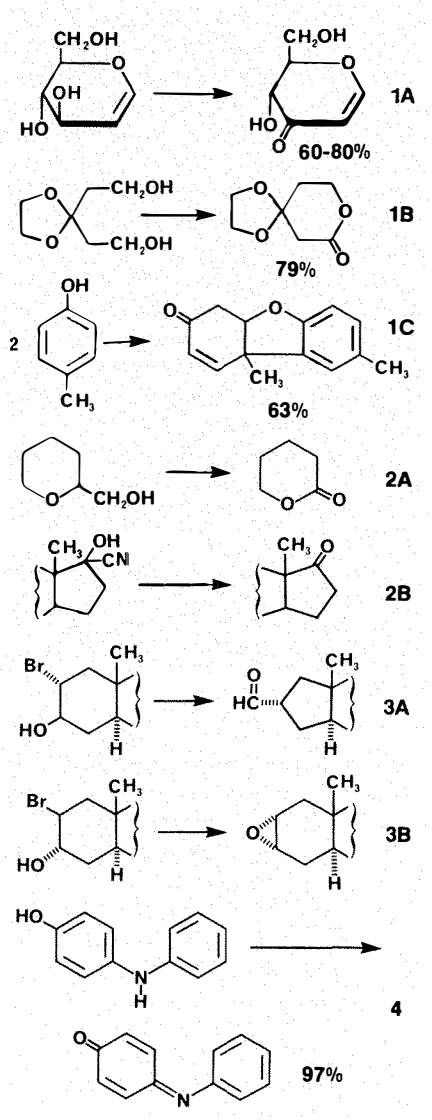
The Fetizon reagent is most effective when prepared immediately before use; the Fiesers described its role in the oxidative coupling of phenols and anilines (eq. 1)[5] and in the oxidation of 1,4-diols to lactones.[6]

In the course of the recent synthesis of (±)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol, **2**, an intermediate in the synthesis of anthracyclinones, the Fetizon reagent was the only suitable means of oxidizing **1** to **2** (eq. 2).[7] Attempts to effect the conversion with Collins reagent, pyridinium chlorochromate, pyridinium dichromate, or NCS/Me_2S/Et_3N were unsuccessful.

Examination of some reactions characteristic of unsupported silver carbonate shows that the elimination of silver halide, the driving force for a large number of silver-induced transformations, is frequently utilized; eq. 3 is an example.

Work on glycoside synthesis showed that, relative to the Konigs-Knorr synthesis, improvements in reaction conditions and yield could be achieved by treating gluco-

Figure 1



pyranosyl bromides with appropriate silver salts of dicarboxylic acids or hydrocarboxylic acids.[8] Extended to alcohols of various types, the reaction sequence seems to follow a trimolecular synchronous mechanism (eq.4).

A variety of tertiary alkyl chlorides have been converted to di-*t*-alkyl ethers by a slight excess of silver carbonate in pentane at 20°C (eq. 5).[9] The yield of the hindered ether decreased as the alkyl groups became bulkier. Silver oxide was not as effective in promoting the conversion as shown by comparative data (Table 1). It was suggested that calcium hydride suppressed the formation of the alcohol by reacting with a postulated silver hydroxide intermediate. Preparations of these hindered ethers using HgO, ZnO, $ZnCO_3$, PbO_2 and Tl_2O_3 were not satisfactory.

Silver carbonate was found to be the most effective of a variety of silver salts used as catalysts in novel syntheses of enol esters from carboxylic acids and acetylenic compounds (eq. 6).[10]

Another transformation attributed to the chemists who popularized the reagent is the Prévost-Woodward[1b] reaction which utilized silver acetate and iodine in tandem. In wet acetic acid, the reagent converted the olefinic diketone **3** (eq. 7) to the diacetate **4** as part of a stereocontrolled total synthesis[11] of the triacetate precursor of 20-hydroxyecdysone, a highly oxidized crustacean molting hormone.

The Prévost reagent is also commonly known as the silver benzoate-iodine combination; Gunstone[12] described this reagent and its variations in conjunction with trans-hydroxylation of olefins as a function of reaction stoichiometry (eq. 8).

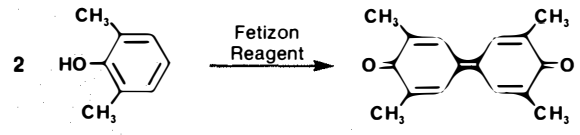
The reagent also cleaves α-glycols to carbonyls[13] and may be effective in transformations where complications from free iodine are negligible.

A recent report on the synthesis of α-acyloxy carbonyl compounds featured a study of the oxidation of enol silyl ethers by seven different silver carboxylate-iodine combinations.[14]

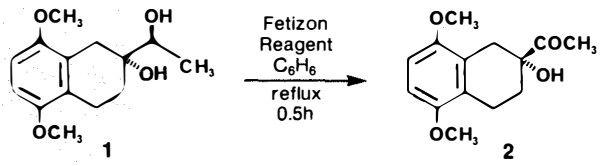
PRINCIPAL ACTIVE AREAS

A few selected topics which represent areas of most active research involving silver salts in organic processes are:

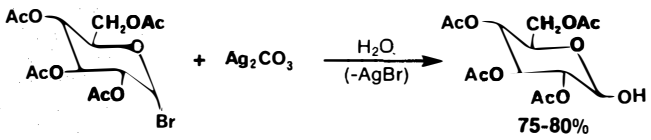
1) general synthetic procedures which are "silver-assisted"
2) oxidative processes, also frequently described as "silver-assisted"
3) rearrangements and ring contractions
4) cycloadditions and ring expansions
5) alkylations and dealkylations
6) protecting-group removal and other specialized uses.



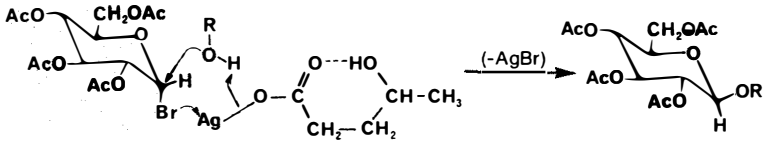
(eq. 1)



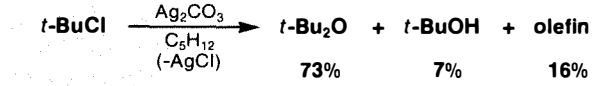
(eq. 2)



(eq. 3)



(eq. 4)

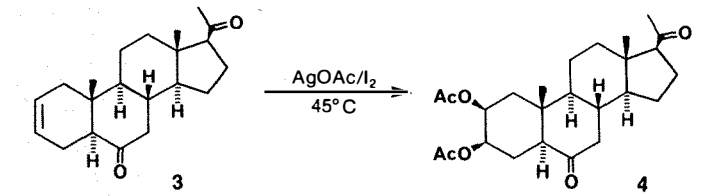


(eq. 5)

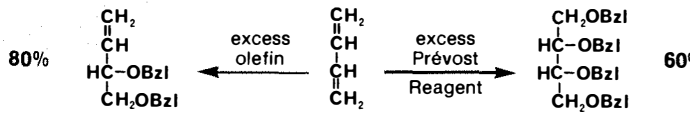
TABLE 1

SUBSTRATES	CONDITIONS	YIELD (%) [Et(Me)₂C]₂O	Et(Me)₂COH	olefin
$Et(Me)_2CCl$; Ag_2CO_3	hexane/20°/20h	47	21	32
$Et(Me)_2CCl$; Ag_2O	hexane/35°/20h	34	27	39
$Et(Me)_2CCl$; Ag_2O/CaH_2	hexane/35°/40h	16	1	83

(eq. 6)

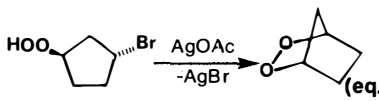


(eq. 7)



(eq. 8)

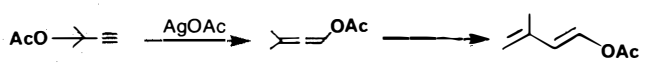
(eq. 9)



(eq. 10)

(eq. 11)

where R = alkyl, aryl; (M)(X) = $AgNO_3$, AgOAc, $HgCl_2$



(eq. 12)

Silver-Assisted Transformations

There are many ways in which the silver ion assists in organic transformations to yield unique products. Its solubility property is exploited in eqs. 9[15] and 10.[16]

Equation 11 depicts the synthesis of sulfenamides, important intermediates in organic synthesis. Their preparation is greatly simplified in a one-pot synthesis[17] in which, compared to eqs. 9 and 10, more direct interaction of the silver ion with substrate occurs. Mercuric chloride is preferred where silver nitrate reacts with the amine; however, somewhat lower yields and diminished product stability are obtained with the mercury salt.

A formidable synthetic problem involving Diels-Alder routes to potential trichothecene precursors was solved by the use of silver acetate as shown in eq. 12.[18]

Silver cyanide has a catalytic effect in the reaction between acid chlorides and alcohols to form hindered esters. The data appear to rule out acyl cyanide intermediates although precise definition of the mechanism is complicated by the fact that silver trifluoroacetate or carbonate as well as copper cyanide are ineffective for this transformation.[19]

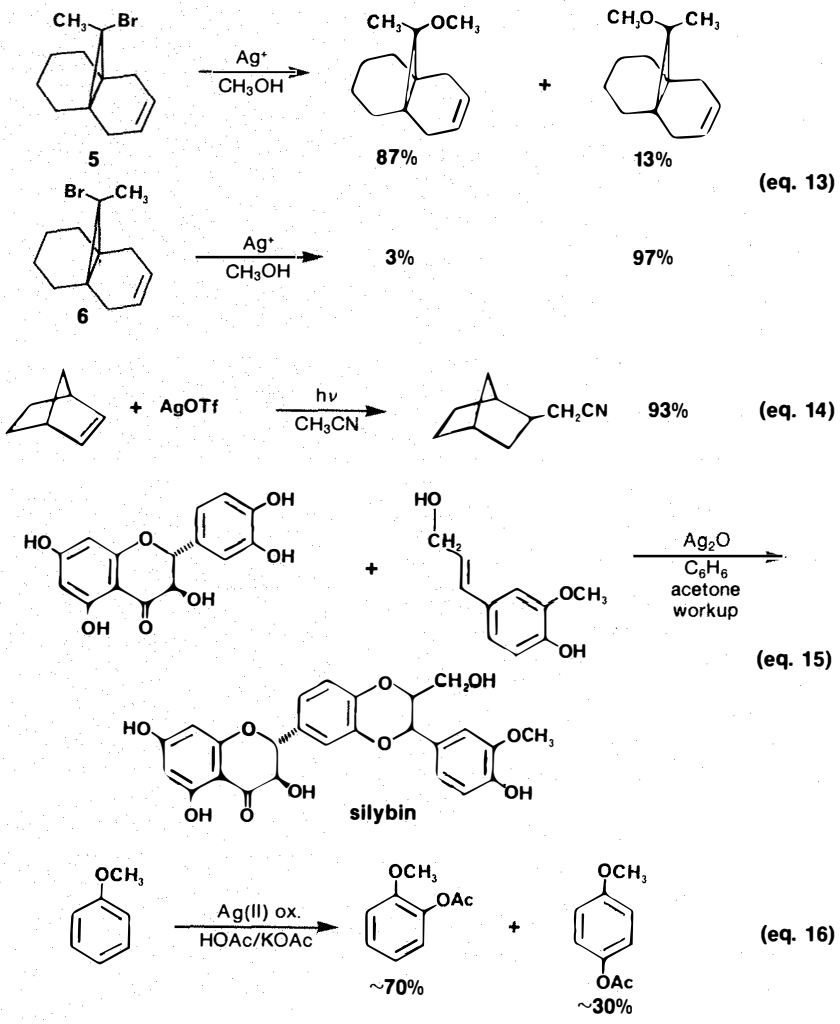
Silver ion can be used to activate 2-pyridylthiol esters by complexation to promote lactonization.[20]

The silver-assisted methanolyses of **5** and **6** (eq. 13) are particularly interesting because in **5** the silver ion is subject to a concerted interaction involving both π-complexation with the double bond and the attraction leading to bromide displacement. Ensuing rearrangement results in an unexpectedly great proportion of secondary product (13%) in comparison with methanolysis of **6** which favors the halide displacement with minimal competition from the Ag-π interaction.[21]

Irradiation of an acetonitrile solution of norbornene and silver trifluoromethanesulfonate (AgOTf, silver triflate) effects a conversion (eq. 14) involving a surprisingly complex mechanism.[22]

Mechanisms have been proposed for a number of silver-assisted transformations. The reaction of terminal alkynes with iodine in methanol may produce diiodoalkenes *via* a molecule-induced homolytic radical mechanism, but in the presence of silver ion, diiodoketones and substitution products are also formed in considerable yield, presumably *via* an ionic mechanism.[23]

A mechanistic study of the reactions of methylallyl chlorides with silver nitrate in acetonitrile has been reported,[24] and the stereoelectronic control in the S_N1 mechanism of the silver(I) ion-catalyzed acetolysis of



various bromo-4-en-3-oxo steroids was recently discussed.[25]

The determination of mechanisms in transformations involving natural product derivatives is a complex exercise. The oxidative coupling of substituted catechols with isoeugenol or coniferyl alcohol in the presence of Ag_2O is highly regioselective when the catechol bears an alkyl substituent.[26] While a free-radical coupling mechanism has been proposed similar to that suggested for the biosynthesis of silybin,[27] the possibility that a π-silver complex is assisting the reaction warrants further investigation. Evaluation of the system is made more interesting in that the best route to a simple biomimetic synthesis of silybin involved oxidation with equimolar amounts of silver(I) oxide (eq. 15).[26] The reaction seemed to be fairly general in scope.

The coupling of selectively blocked bromosaccharides can be effected with either silver triflate or $Ag_2CO_3/AgClO_4$.[28]

Selected Oxidations

As part of a series on metal-ion oxidations, Nyberg and Wistrand[29] discussed the oxidative acetoxylation of aromatic compounds in acetic acid by silver(II) complexes with nitrogen-containing ligands. Such high-yield catalytic reactions can be initiated either by presynthesized $Ag(bpy)_2S_2O_8$ or by a AgOAc/2,2'-bipyridine/$K_2S_2O_8$ mixture. The procedure may be useful for the preparation of alkoxy- and hydroxy-substituted derivatives of aromatic acetates (eq. 16).

Comparative studies were carried out with Ag(II) complexes having non-oxidizing counterions, *viz.* silver(II) dipicolinate and $Ag(bpy)_2(OTf)_2$. The reaction proceeded independently of the anion *via* a mechanism involving removal by Ag(II) of one electron from the aromatic substrate to form a radical cation. Previous studies have shown that the primary oxidant is indeed Ag(II), formed by the action of $S_2O_8^{2-}$ (or $SO_4^{\cdot}$) on Ag(I).[30] The authors also reported catalyst efficiencies of between 1,500 and almost 10,000%.

Silver dipicolinate has also been shown to act as a highly selective oxidant in the synthesis of novel quinones (eq. 17).[31]

Persulfate-silver ion oxidations of numerous substrates have been reported recently, along with much discussion on the

mechanism. The development of this area bears considerable potential for new selective synthetic procedures.

In order to better define the role of the silver ion, Caronna *et al.* used protonated quinoline to trap nucleophilic free-radical intermediates formed during the oxidation of various alcohols.[32] The authors concluded that alkoxy radicals were formed in all cases (eq. 18).

Drawing similar conclusions, Walling and Camaioni emphasized that both the oxidants $SO_4^{\cdot}$ and Ag(II) are present in such systems and may show different selectivity patterns yielding very different products.[33]

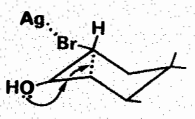
Clerici[34] reported new types of selective homolytic aromatic substitutions involving protonated heteroaromatic bases. The reaction shown in eq. 19 occurs in lower yield in the absence of Ag^+.

Clerici and Porta[35] showed that unsaturated aliphatic and arylalkyl alcohols were oxidized by $S_2O_8^{2-}/Ag^+$ to cyclic ethers through different pathways. Contributing factors included chain length and heteroatom influence; the primary step is the formation of the alkoxy radical and hydrogen abstraction.

Silver ion has also assisted pyridinium chlorochromate in the oxidation of tertiary 2-alkylcyclopropylcarbinols to corresponding β,γ-unsaturated ketones (eq. 20),[36] a synthetically useful method for 1,4-carbonyl transposition.

Rearrangements/ Ring Contractions

Silver-ion-induced ring contraction of steroidal bromohydrins is both stereospecific and highly dependent upon the conformation of the bromine atom.[37] As in eq. 3A (Figure 1), ring contraction occurs if the

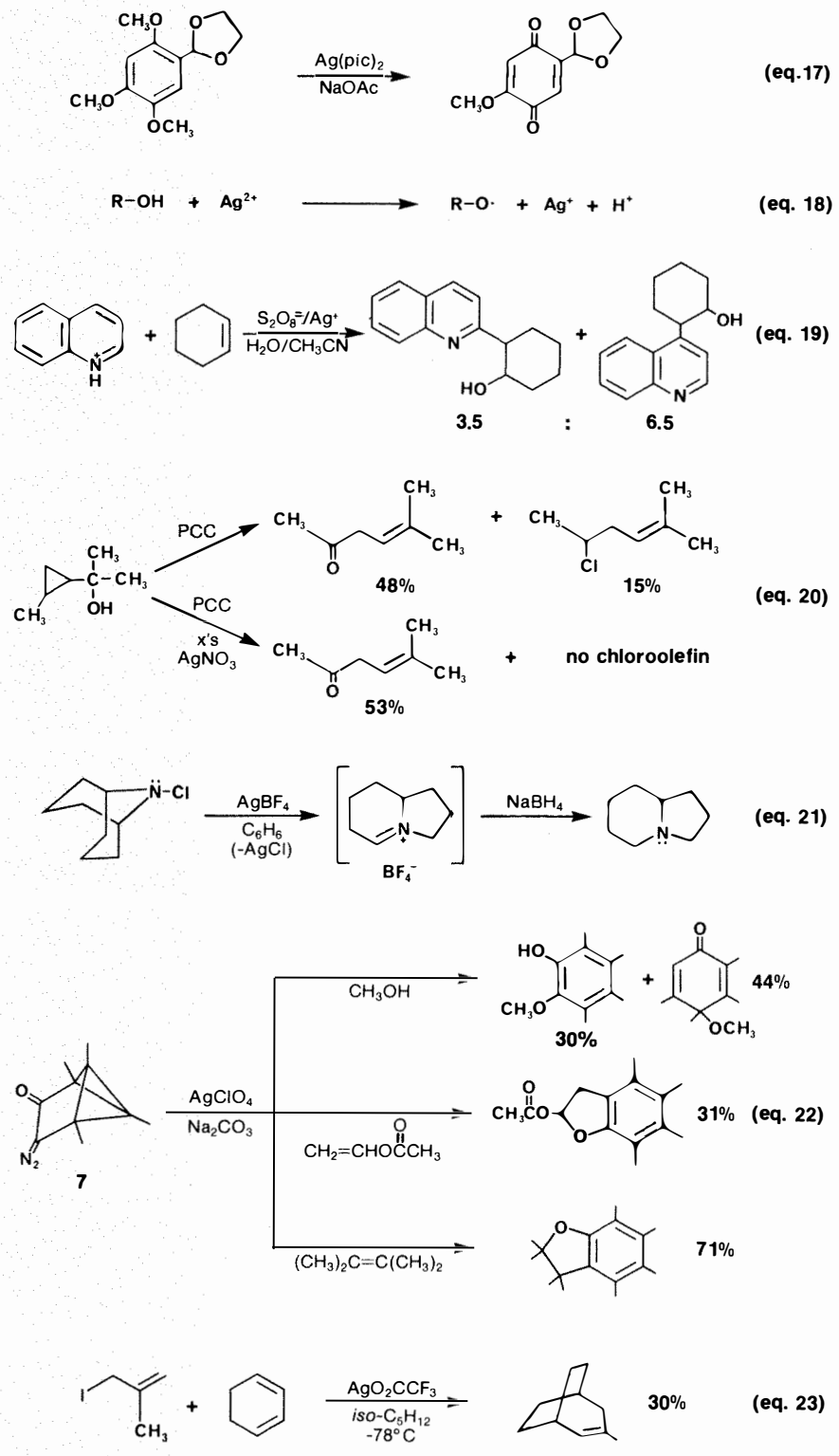


bromine atom is equatorial; if the bromine is axial, oxide or ketone formation (*via* hydride shift) occurs.

Schell[38] recently reported the first ionic rearrangement product isolated from a silver-ion-induced reaction of a chloramine (eq. 21) as part of a continuing model study for the synthesis of alkaloids containing a bridgehead nitrogen.

The procedure allows the isolation of primary products in good yield by preventing oxidation of immonium-ion-rearrangement products and minimizing production of secondary amines.

Silver perchlorate catalyzes loss of nitrogen from the strained-ring diazoketone **7** to yield an α-ketocarbene which undergoes



further rearrangement (eq. 22).[39] Sodium carbonate prevented possible acid catalysis, but its presence raised the possibility that silver carbonate might have been a participating entity.

A similar study has shown that only appropriate substitution of the benzotricycloheptene framework with labilizing substituents permits silver-ion-induced skeletal rearrangement.[40]

Cycloadditions/Ring Expansions

Several studies by Hoffmann and coworkers[41] on cycloadditions of allyl cations to conjugated dienes have provided data pertaining to both reaction conditions and the role of various silver counterions in the process. The authors stated that the most important factor in optimizing the yield of a reaction such as shown in eq. 23 is the nature of the silver counterion.

The authors were also able to initiate the first cycloaddition of an open-chain diene (eq. 24).

If silver tetrafluoroborate is used in the reaction, the BF_4^- ion is not effective in stabilizing postulated intermediates, and can cause the untimely production of HBF_4 which promotes the polymerization of reactants and products. Electrophilic catalysts such as silver benzoate or silver acetate give only allylic esters, even with the reactive cyclopentadiene.

Silver trifluoroacetate seemed to be even more effective than the trichloroacetate because it is soluble in both ether and water, it bears considerable thermal and photochemical stability, and it liberates little if any trifluoroacetic acid. Silver trifluoroacetate supported on diatomite resulted in little change in product yield or distribution, indicating that the reaction can proceed in either a homogeneous or heterogeneous mode.

Silver trifluoroacetate has been used more recently to promote the reaction of allenyl cations with dienes (eq. 25).[42]

Jendralla[43] has been able to isolate thermally stable, moderately light-sensitive *trans*-cycloheptene derivatives with $AgClO_4$ and $AgOSO_2CF_3$, and carry out cycloadditions with several dienes (eq. 26).

Both $AgBF_4$ and $AgPF_6$ have been applied to the cycloaddition of vinyl bromides to various olefins in methylene chloride.[44] The method gives high yields and appears to be widely applicable.

Loozen[45,46] has investigated the silver-ion-assisted ring expansion of geminal dibromobicycloalkanes, and has discussed the application of silver perchlorate, silver tosylate and silver nitrate to complex transformations such as shown in eq. 27. The method enables the stereospecific synthesis of medium-sized rings apparently *via* a free cationic intermediate.

Alkylations/Dealkylations

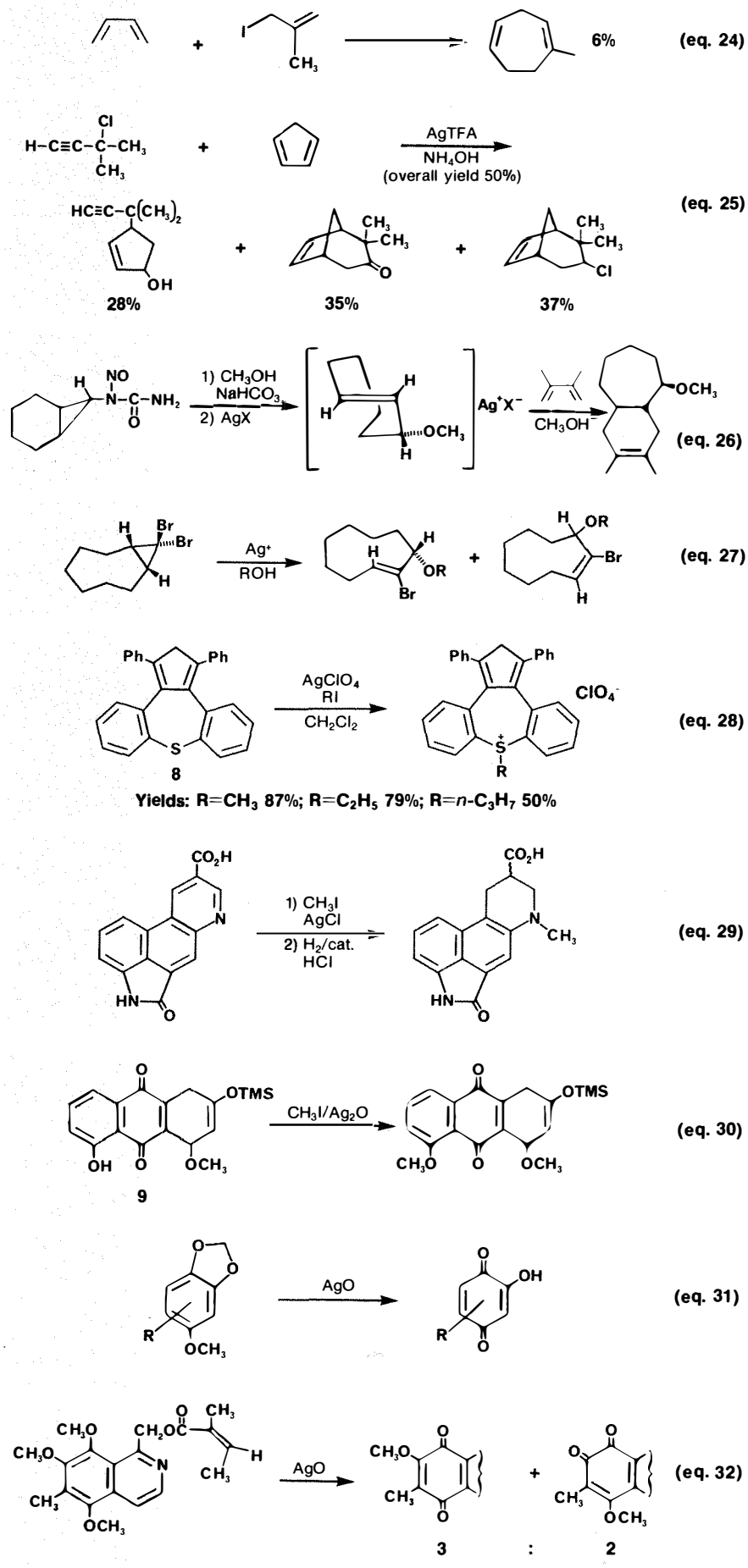
Silver perchlorate promotes the reaction of alkyl iodides with the thiazulene 8 to give thiazulenium salts in various yields (eq. 28).[47]

Silver chloride/methyl iodide was used recently to methylate at nitrogen in the ergoline ring system of ergot alkaloids (eq. 29).[48]

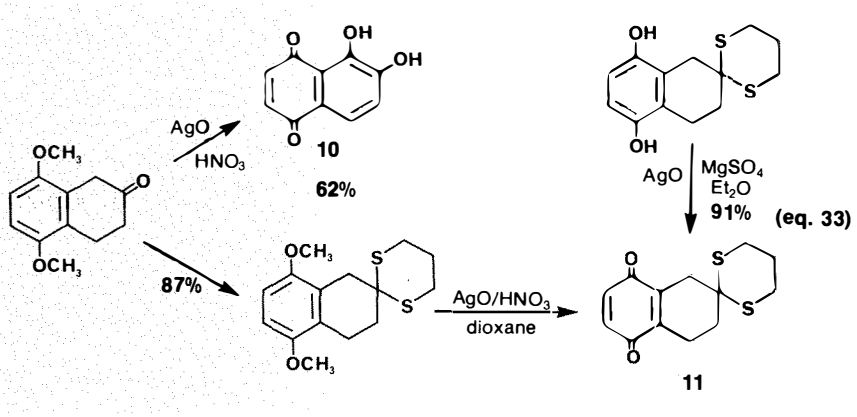
A silver(I) oxide/CH_3I methylation of a hydroxyl group of the anthraquinone 9 was carried out in chloroform (eq. 30).[49]

Oxidative demethylations[50-52] are commonly carried out with AgO (eqs. 31 and 32).

Both Ag_2O and AgO have been used by Farina and Torres[53] in the synthesis of naph-



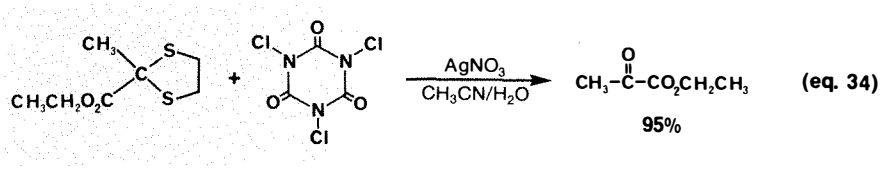
thoquinone derivatives which are valuable intermediates in the preparation of antitumor anthracyclines. An unexpectedly convenient synthesis of *o*-naphthazarin (5,6-dihydroxy-1,4-naphthoquinone), **10**, arose from an attempt to prepare the thioacetal **11** from 5,8-dimethoxy-2-tetralone (eq. 33).



(eq. 33)

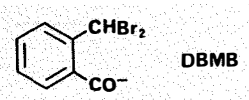
Specialized Applications

Olah[54] has used the industrial chemical trichloroisocyanuricacid inplaceof*N*-chlorosuccinimide in the cleavage of ethanediyl S,S-acetals, a reaction which can be carried out quickly at room temperature in the presence of silver nitrate (eq. 34).



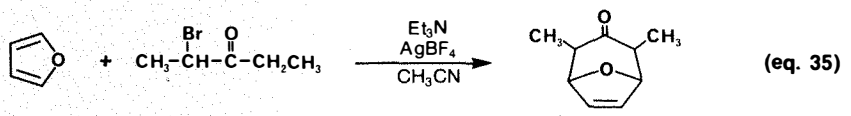
(eq. 34)

Removal of the protecting group DBMB from 2-dibromomethylbenzoate esters has

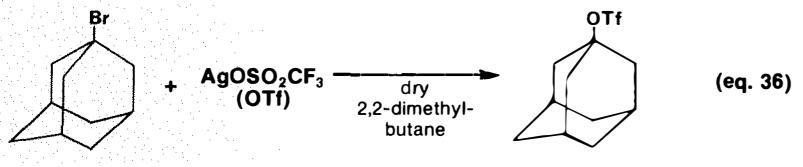


DBMB

been carried out under exceptionally mild conditions with silver perchlorate/lithium bromide.[55] This technique should be useful in transformations involving sensitive compounds such as oligonucleotides; its application in the synthesis of adenylyl-(2′→5′)-adenylyl-(2′→5′)-adenosine has been described.[56]

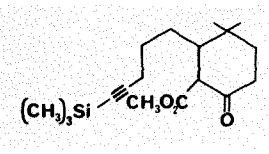


(eq. 35)



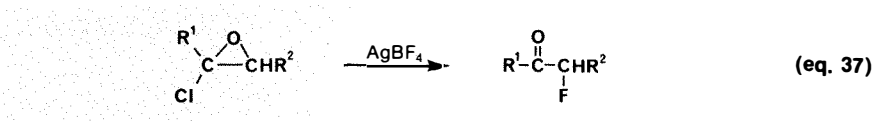
(eq. 36)

Deprotection of the acetylenic intermediate

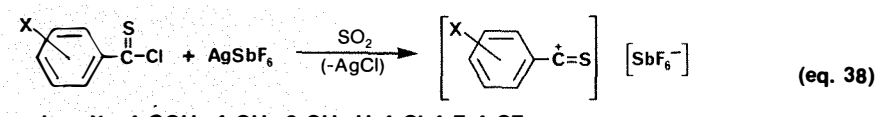


was carried out with $AgNO_3$-KCN because KF/DMF/H_2O led to aldol condensation products.[57]

A new method for generating oxyallyls from α-bromoketones uses silver tetrafluoroborate/NEt_3 to promote the reaction in the presence of various furans.[58] This produces cycloadducts useful in the synthesis of biologically active analogs of α-multistriatin (eq. 35).

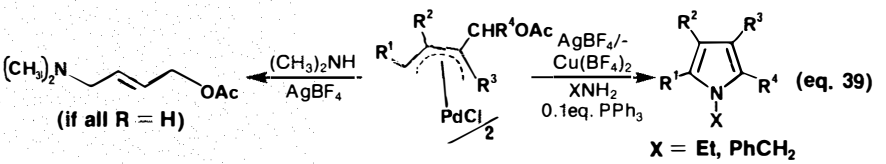


(eq. 37)



(eq. 38)

where X = 4-OCH_3, 4-CH_3, 2-CH_3, H, 4-Cl, 4-F, 4-CF_3



(eq. 39)

Studies on the thermal decomposition of silver salts of aryldinitromethanes in the presence of unsaturated systems[59] and of arenesulfinates[60] have shed additional light on a relatively unexploited area of silver chemistry.

The specialized reactions of other simple and complex fluoride salts of silver merit discussion. Zweig[61] and co-workers described a new method for selective monofluorination of aromatics using silver difluoride as a strong oxidant and fluoride source. Oxidative fluorination of diaryl diselenides has also been reported.[62]

Silver ion catalysis of fluoroxysulfate oxidations has demonstrated surprising selectivity toward certain inorganic substrates, and the system may bear considerable potential as a chemical reagent in organic processes.[63]

Silver(I) fluoride was required to induce fluorine exchange with di-, tri-, and tetrabromoadamantanes, providing the respective fluoroadamantanes in about 70% yield.[64]

Recently, the first reported preparation of 1-adamantyl triflate using silver triflate was described (eq. 36).[65]

Silver triflate[66] and silver methanesulfonate[67] are also convenient precursors to a number of alkylmethanesulfonate derivatives useful as alkylating agents for aromatic compounds.

Silver tetrafluoroborate reacts with chlorinated oxiranes to produce α-fluorinated carbonyl compounds (eq. 37).[68]

Olah has shown that silver hexafluoroantimonate, $AgSbF_6$, is an electrophilic bromination catalyst[69] and is useful in promoting chlorination of reactive alkanes.[70] A later report has shown the salt useful in the generation of thiobenzoyl cations (eq. 38).[71]

There seems to be great potential in the area of silver-assisted transformations of complexes stabilized by other metals. For example, $AgBF_4$ plays an important role in

the palladium-promoted 1,4-cycloamination of 1,3-dienes to pyrroles (eq. 39),[72] a significant class of compounds to which simple synthetic approaches are lacking.

Vermeer *et al.* have extended the chemistry of lithium bromide-stabilized alkyl silver complexes ($RAg{\cdot}3LiBr$)[73] to include the synthesis of alkylated butatrienes, $RCH_2C(R')=C=C=CR^2R^3$, from the enynylmethanesulfinates $H_2C=C(R')C\equiv C\text{-}CR^2R^3OSOCH_3$.[74]

Such transformations may follow mechanisms which utilize the silver ion in both σ and π bonding modes; they are also interesting because of the parallels and contrasts that can be drawn with organocopper chemistry.

A similar magnesium-stabilized complex was recently reported for the *trans*-addition shown in eq. 40.[75]

A brief examination of the use of silver compounds in some recent preparations of organometallic and coordination compounds is also instructive because such studies may pertain to complex catalytic processes.

The preparation of the first structurally characterized alkoxyplatinum compound employed silver ion (as $AgNO_3$) to effect chloride displacement from $Pt(COD)Cl_2$ and provide an intermediate susceptible to the base-induced methoxidation shown in eq. 41.[76]

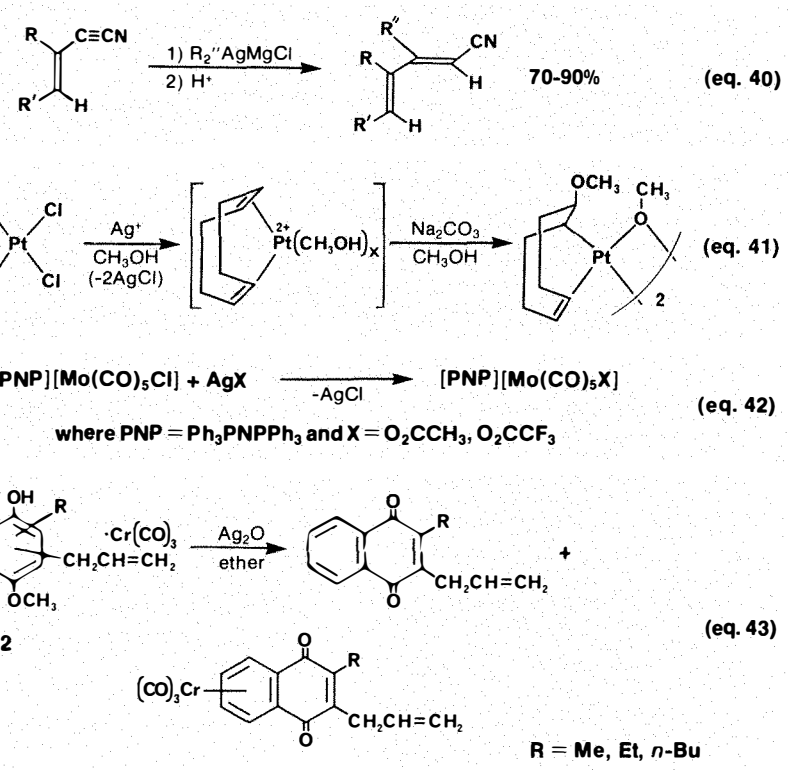
Alkoxy and hydroxy complexes of Pt(II) may be intermediates in the preparation of hydridoplatinum complexes[77,78] and in catalytic processes such as the hydration of nitriles.[79]

Salts such as $AgBF_4$, $AgPF_6$, $AgOSO_2CF_3$ and $AgOSO_2C_6H_4CH_3$ have the capacity to serve a dual function in some synthetic procedures: the introduction of a complex anion to assist in the stabilization of the desired product, and the generation of unique intermediates by chloride displacement.

Silver hexafluorophosphate has been used in preparations of adducts formed with neutral diamagnetic organometallics; these derivatives can function as controlled sources of highly reactive radical cations.[80] An example is $Ag[Rh(CO)PPh_3(C_5H_5)]_2[PF_6]$ which contains Ag-Rh bonds and is a stable source of the reactive radical cation $[Rh(CO)PPh_3(C_5H_5)]^{\cdot +}$.

Cotton *et al.*[81] found both silver acetate and silver trifluoroacetate useful in the synthesis of novel aceto complexes of molybdenum and chromium which exhibit a monodentate acetate group which may be a strongly labilizing ligand (eq. 42).

Some interesting chemistry has been demonstrated by Doetz and Pruskil[82] in complex reactions between silver(I) oxide



and **12**, the condensation product of pentacarbonyl(methoxyphenylcarbene)chromium(0) and selected enynes (eq. 43).

Yields are low, the reaction likely complicated by the fluxional interaction between the tricarbonylchromium moiety and the delocalized aromatic groups.

While we acknowledge the omission of the specifics of numerous traditional applications of silver salts to organic processes (such as Lewis acid-catalyzed nitrations using $AgNO_3$),[83] we are interested in keeping new applications in a high profile for our readership. Please feel free to submit any new, unusual, or overlooked reports of such usage to our editor for future updated reviews.

References:

1) a) Syper, L. *Tetrahedron Lett.* **1967**, 4193; b) Wilson, C.V. *Organic Reactions* **1957**, *9*, 332; c) Paquette, L.A. *Acc. Chem. Res.* **1971**, *4*, 280; d) Paquette, L.A. *Synthesis* **1975**, 347; e) Beak, P. *Acc. Chem. Res.* **1976**, *9*, 230.
2) Ozin, G.A. *ibid.* **1977**, *10*, 21.
3) Kozikowski, A.P.; Wetter, H.F. *Synthesis* **1976**, 561.
4) McKillop, A; Young, D.W. *ibid.* **1979**, 401.
5) Fieser, L.F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley-Interscience: New York; Vol. 2, p 363; Vol. 3, p 247; Vol. 4, p 425; Vol. 5, p 577; Vol. 6, p 511.
6) Fieser, M. "Reagents for Organic Synthesis"; Wiley-Interscience: New York, 1980; Vol. 8, p 441.
7) Terashima, S.; Tanno, N.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2749.
8) Wulff, G.; Roehle, G.; Krueger, W. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 455.
9) Masada, H.; Sakajiri, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 866.
10) Ishino, Y.; Nishiguchi, I.; Nakao, S.; Hirashima, T. *Chem. Lett.* **1981**, 641.
11) Kametani, T.; Tsubuki, M.; Nemoto, H. *Tetrahedron Lett.* **1980**, *21*, 4855.
12) Gunstone, F.D. *Advances in Organic Chemistry, Methods and Results* **1960**, *1*, 122.
13) Luening, B.; Paulsson, L. *Acta Chem. Scand.* **1967**, *21*, 829.
14) Rubottom, G.M.; Mott, R.C.; Juve, Jr., H.D. *J. Org. Chem.* **1981**, *46*, 2717.
15) Tada, M.; Miura, K.; Okabe, M.; Seki, S.; Mizukami, H. *Chem. Lett.* **1981**, 33; see also Saimoto, H.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1981**, *103*, 4975.
16) Porter, N.A.; Gilmore, D.W. *ibid.* **1977**, *99*, 3503; for related techniques, see Bloodworth, A.J.; Eggelte, H.J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1375.
17) Davis, F.A.; Friedman, A.J.; Kluger, E.W.; Skibo, E.B.; Fretz, E.R.; Milicia, A.P.; LeMasters, W.C.; Bentley, M.D.; Lacadie, J.A.; Douglass, I.B. *J. Org. Chem.* **1977**, *42*, 967.
18) Banks, R.E.; Miller, J.A.; Nunn, M.J.; Stanley, P.; Weakley, T.J.R.; Ullah, Z. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1096.
19) Takimoto, S.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2335.
20) Haslam, E. *Tetrahedron* **1980**, *36*, 2409.
21) Engbert, T.; Kirmse, W. *Justus Liebigs Ann. Chem.* **1980**, 1689.
22) Bruno, J.W.; Marks, T.J.; Lewis, F.D. *J. Am. Chem. Soc.* **1981**, *103*, 3608.
23) Heasley, V.L.; Shellhamer, D.F.; Heasley, L.E.; Yaeger, D.B.; Heasley, G.E. *J. Org. Chem.* **1980**, *45*, 4649.
24) Kevill, D.N.; Degenhardt, C.R. *J. Am. Chem. Soc.* **1979**, *101*, 1465.
25) Koga, T.; Nogami, Y. *Tetrahedron Lett.* **1981**, *22*, 3075.
26) Merlini, L.; Zanarotti, A.; Pelter, A.; Rochefort, M.P.; Haensel, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 775.
27) Pelter, A.; from Haensel, R.; Rimpler, H. *Deutsche Apothek. Zeit.* **1968**, *108*, 1985.
28) Paulsen, H.; Buensch, A. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 902.
29) Nyberg, K.; Wistrand, L.-G. *J. Org. Chem.* **1978**, *43*, 2613.
30) Anderson, J.M.; Kochi, J.K. *J. Am. Chem. Soc.* **1970**, *92*, 1651.
31) Kloc, K.; Mlochowski, J.; Syper, L. *Chem. Lett.* **1980**, 725.
32) Caronna, T.; Citterio, A.; Grossi, L.; Minisci, F.; Ogawa, K. *Tetrahedron* **1976**, *32*, 2741.
33) Walling, C.; Camaioni, D.M. *J. Org. Chem.* **1978**, *43*, 3266.

34) Clerici, A.; Minisci, F.; Ogawa, K.; Surzur, J.-M. *Tetrahedron Lett.* **1978**, 1149.
35) Clerici, A.; Porta, O. *J. Chem. Soc., Perkin Trans.2* **1980**, 1234.
36) Wada, E.; Okawara, M.; Nakai, T. *J. Org. Chem.* **1979**, *44*, 2952.
37) Nace, H.R.; Crosby, G.A. *ibid.* **1979**, *44*, 3105.
38) Schell, F.M.; Ganguly, R.N. *ibid.* **1980**, *45*, 4069.
39) Elzinga, J.; Hogeveen, H.; Schudde, E.P. *ibid.* **1980**, *45*, 4337.
40) Padwa, A.; Rieker, W.F. *Tetrahedron Lett.* **1981**, *22*, 1487; for a related study, see Padwa, A.; Blacklock, T.J.; Loza, R. *J. Am. Chem. Soc.* **1981**, *103*, 2404.
41) Hoffmann, H.M.R.; Kernaghan, G.F.P.; Greenwood, G. *J. Chem. Soc. B* **1971**, 2257 and references cited therein.
42) Mayr, H.; Grubmueller, B. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 130.
43) Jendralla, H. *ibid.* **1980**, *19*, 1032.
44) Hanack, M.; Harder, I.; Bofinger, K.-R. *Tetrahedron Lett.* **1981**, *22*, 553.
45) Loozen, H.J.J.; Robben, W.M.M.; Richter, T.L.; Buck, H.M. *J. Org. Chem.* **1976**, *41*, 384.
46) Loozen, H.J.J.; de Haan, J.W.; Buck, H.M. *ibid.* **1977**, *42*, 418.
47) Hori, M.; Kataoka, T.; Shimizu, H.; Okitsu, M. *Tetrahedron Lett.* **1980**, *21*, 4287.
48) Horwell, D.C. *Tetrahedron* **1980**, *36*, 3123.
49) Manning, W.B.; Kelly, T.P.; Muschik, G.M. *Tetrahedron Lett.* **1980**, *21*, 2629.
50) Snyder, C.D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.
51) Kraus, G.A.; Neuenschwander, K. *Synth. Commun.* **1980**, *10*, 9.
52) Danishefsky, S.; Berman, E.; Cvetovich, R.; Minamikawa, J. *Tetrahedron Lett.* **1980**, *21*, 4819.
53) Farina, F.; Torres, T. *Synthesis* **1980**, 753.
54) Olah, G.A.; Narang, S.C.; Salem, G.F. *ibid.* **1980**, 659.
55) Chattopadhyaya, J.B.; Reese, C.B.; Todd, A.H. *Chem. Commun.* **1979**, 987.
56) Chattopadhyaya, J.B. *Tetrahedron Lett.* **1980**, *21*, 4113.
57) Jackson, W.P.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1516.
58) Mann, J.; Usmani, A.A. *Chem. Commun.* **1980**, 1119.
59) Coutouli-Argyropoulou, E.; Alexandrou, N.E. *J. Org. Chem.* **1980**, *45*, 4158.
60) Fields, E.K.; Meyerson, S. *ibid.* **1977**, *42*, 1691; *ibid.* **1976**, *41*, 916.
61) Zweig, A.; Fischer, R.G.; Lancaster, J.E. *ibid.* **1980**, *45*, 3597.
62) Maxwell, W.M.; Wynne, K.J. *Inorg. Chem.* **1981**, *20*, 1707.
63) Thompson, R.C.; Appelman, E.H. *ibid.* **1981**, *20*, 2114.
64) Bhandari, K.S.; Pincock, R.E. *Synthesis* **1974**, 655.
65) Takeuchi, K.; Moriyama, T.; Kinoshita, T.; Tachino, H.; Okamoto, K. *Chem. Lett.* **1980**, 1395.
66) Booth, B.L.; Haszeldine, R.N.; Laali, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2887.
67) Moe, G.R.; Sayre, L.M.; Portoghese, P.S. *Tetrahedron Lett.* **1981**, *22*, 537.
68) Griesbaum, K.; Keul, H.; Kibar, R.; Pfeffer, B.; Spraul, M. *Chem. Ber.* **1981**, *114*, 1858.
69) Olah, G.A.; Schilling, P. *J. Am. Chem. Soc.* **1973**, *95*, 7680.
70) Olah, G.A.; Renner, R.; Schilling, P.; Mo, Y.K. *ibid.* **1973**, *95*, 7686.
71) Olah, G.A.; Surya Prakash, G.K.; Nakajima, T. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 812.
72) Baeckvall, J.-E.; Nystroem, J.-E. *Chem. Commun.* **1981**, 59.
73) Westmijze, H.; Kleijn, H.; Vermeer, P. *J. Organometal. Chem.* **1979**, *172*, 377.
74) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *ibid.* **1980**, *192*, 275.
75) *Idem ibid.* **1981**, *206*, 257.
76) Giordano, F.; Vitagliano, A. *Inorg. Chem.* **1981**, *20*, 633.
77) Chatt, J.; Shaw, B.L. *J. Chem. Soc.* **1962**, 5075.
78) Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134.
79) Bennett, M.A.; Yoshida, T. *ibid.* **1973**, *95*, 3030.
80) Connelly, N.G.; Lucy, A.R.; Galas, A.M.R. *Chem. Commun.* **1981**, 43.
81) Cotton, F.A.; Darensbourg, D.J.; Kolthammer, B.W.S. *J. Am. Chem. Soc.* **1981**, *103*, 398.
82) Doetz, K.H.; Pruskil, I. *Chem. Ber.* **1980**, *113*, 2876.
83) Olah, G.A.; Fung, A.P.; Narang, S.C.; Olah, J.A. *J. Org. Chem.* **1981**, *46*, 3533.

About the Author

Dr. John Long received the B.S. degree from the University of Toledo in 1967 and the Ph.D. degree in 1973 from the Ohio State University where he worked with Professor Sheldon Shore in the area of boron hydride chemistry. Postdoctoral appointments at the Ames Laboratory (Iowa State University) and the National Bureau of Standards afforded him the opportunity to investigate the chemistry of rare-earth water-splitting cycles and the synthetic potential of laser-induced chemistry, respectively. Dr. Long's arrival at Aldrich coincided with the company's expansion of the Inorganics Division into a highly successful product line.

A Compilation of References on Formyl and Acyl Anion Synthons

Tapio A. Hase and Jorma K. Koskimies
University of Helsinki, Department of Chemistry
Vuorikatu 20, Helsinki 10
Finland

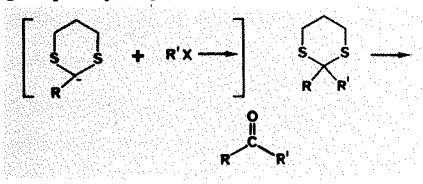
This compilation is intended to include acyl synthons which yield carbonyl compounds by direct alkylation

$$RCO^- + R'-X \longrightarrow R-CO-R'$$

or addition

$$RCO^- + R'-CHO \longrightarrow RCO-CHOH-R'$$

requiring the unmasking of the carbonyl group only, *e.g.*,



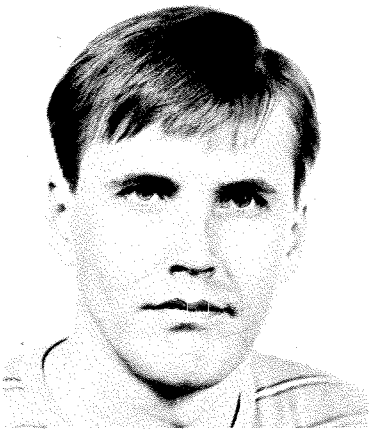
Thus, the various homologative reactions, *e.g.*,

$$R-CHO \longrightarrow RCH_2-CHO$$

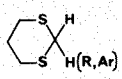
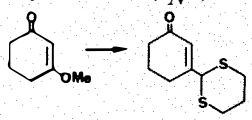
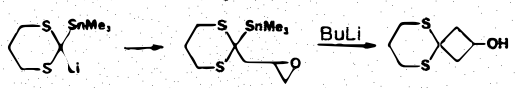
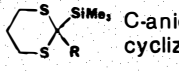
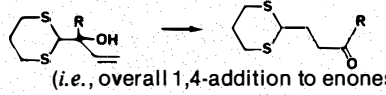
(such as use of $Ph_3P{=}CH{-}OR$) are excluded although these are often somewhat loosely cited as examples of nucleophilic acylation.

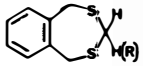
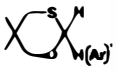
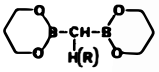
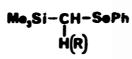
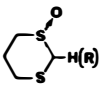
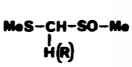
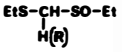
Note that RCHO (or RCDO) will be obtained on quenching a RCO^- synthon with water (or D_2O). This trivial solution is omitted from the Table, but other electrophiles are given as originally reported. Expressions such as C=C–C=O are used to cover both aldehydes and ketones, and imply generality in regard to double-bond substitution. A direct or Michael addition to such species is indicated by "1,2-" or "1,4-", respectively, in parentheses. Individual compounds (*e.g.*, $CH_2{=}CHCH_2OAc$) are only shown when generality is lacking or was not reported. Although many of the acyl anion reagents listed can accommodate functionality in R (or Ar) such as unsaturation, ether groups, etc., it is intended that a compilation of R-functional RCO^- synthons be presented later. Similarly, synthons such as ^-COOH and derivatives, $^-C{-}OH$, $^+C{-}C{=}O$, etc., fall outside the scope of the present tabulation.

Dr. Hase



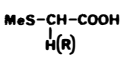
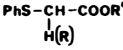
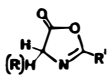
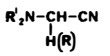
Dr. Koskimies

Equivalence	Reagent	Electrophile	Ref.
HCO^- (RCO^-, $ArCO^-$)		RX, ROTs (cyclic or tertiary unreactive), aldehydes, ketones	1
		$ROSO_2Ph$ (primary only)	2
		oxiranes, oxetanes	1,3,4
		RCOCl, RCOOR', ArCN	1
		$HCOOEt$, $(COOEt)_2$ for aryl dithianes	5
		C=C–C=O (1,2- *vs.* 1,4-addition)	6-10
		$C{=}C{-}CONR_2$ (1,4-)	11
		$C{=}C{-}NO_2$ (1,4-)	12
		$C{=}N^+R_2$	13
		$ArC{\equiv}N \rightarrow O$ (→ α-oximinodithiane)	14
		RSSR	15
		Me_3SiCl, Me_3GeBr, Ph_3SnCl	16-18
		allylic alcohol (S_N2')	19,20
			21
			18
		 C-anion generation with F^-; for cyclization [R = $(CH_2)_nCHO$ or enal]	22
		 (*i.e.*, overall 1,4-addition to enones)	23,24

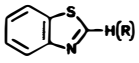
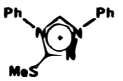
Equivalence	Reagent	Electrophile	Ref.
		selective reaction with ArCHO *vs.* ketones	25
		stereochemistry of the anion	26
		stereoselective addition to cyclohexanones	27
HCO^- (RCO^-)		primary RBr, RI, ketones, oxiranes, ClCOOEt	28
HCO^-		RBr, RI, ketones	29
HCO^- (RCO^-)		oxiranes	30
HCO^-		primary RX, ketones, oxiranes, enones (1,2-)	31
RCO^-	$(R'S)_2CHR$	RCl	32
		Me_3SiCl	16
		oxiranes	33,34
		ketones, CO_2, ClCOOEt	35
		enones (1,4-)	10,35,36
RCO^-	$(PhS)_2CHR$	RBr, RI	37,38
		Me_3SiCl	16
		ketones	39-41
		enones, enoic esters (1,2- and 1,4-)	10,42,43
HCO^-	$(R_2NCS\text{-}S)_2CH_2$	RI (primary)	43,44
HCO^-	$MeS\text{-}CH_2\text{-}S\text{-}CSNMe_2$	RBr, RI (primary)	45
HCO^-	$PhS\text{-}CH_2OMe$	RBr, ketones, lactones	46,47
HCO^-		RBr, RI (primary)	48
HCO^- ($ArCO^-$)		MeI, ketones, ArCOOEt chiral anion	49-51
HCO^-	$PhS\text{-}CH_2SiMe_3$	RBr, RI, oxiranes	52-54
HCO^- (RCO^-)		RBr, RI, ROTs; PhCHO ⟶ $PhCH_2COR$ and PhCOOMe ⟶ $PhCOCH_2R$	55
HCO^- (RCO^-)		RBr, RI (primary)	56,57
		ketones	57,58
RCO^-	$(PhSe)_2CHR$	RX, Me_3SiCl, oxiranes, ketones	59
		enones, enoic esters (poor 1,2- *vs.* 1,4-selectivity)	10
RCO^-		intramolecular rearrangement of the ylid	60,61
HCO^- (RCO^-)		RX, ketones, RCOOR'	62,63
HCO^- (RCO^-)		RBr, RI, ROTs	64-66
		dialkylation with RX	67
		with α,ω-dihalide	68-70
		2-Br-pyridine	64
		$C{=}N^+R_2$	13
		ketones	71
		RCOOR'	72
		PhCHO, RCN⟶abnormal products	73-75
		Cyclopentenone 1,4- but cyclohexenone unselective	76
		rearrangement	66
HCO^- (RCO^-)		RBr, RI (primary), ketones, RCOOR', RCOCl, C=C-COOR (1,4-) unselective for enones	77-80

References:

1) Seebach, D.; Corey, E.J. *J. Org. Chem.* **1975**, *40*, 231.
2) Seebach, D.; Wilka, E.M. *Synthesis* **1976**, 476.
3) Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* **1975**, 2643.
4) Jones, J.B.; Grayshan, R. *Can. J. Chem.* **1972**, *50*, 810; *ibid.* **1972**, *50*, 1407; *ibid.* **1972**, *50*, 1414.
5) Weintraub, P.M. *J. Heterocycl. Chem.* **1979**, *16*, 1081.
6) Ostrowski, P.C.; Kane, V.V. *Tetrahedron Lett.* **1977**, 3549.
7) Brown, C.A.; Yamaichi, A. *Chem. Commun.* **1979**, 100.
8) El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* **1977**, 2897.
9) Seebach, D.; Locher, R. *Angew. Chem.* **1979**, *91*, 1024.
10) Lucchetti, J.; Krief, A. *J. Organometal. Chem.* **1980**, *194*, C49.
11) Mpango, G.B.; Mahalanabis, K.K.; Mahdavi-Damghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823.
12) Seebach, D.; Leitz, H.F.; Ehrig, V. *Chem. Ber.* **1975**, *108*, 1924; Seebach, D.; Ehrig, V.; Leitz, H.F.; Henning, R. *ibid.* **1975**, *108*, 1946.
13) Duhamel, L.; Duhamel, P.; Mancelle, N. *Bull. Soc. Chim. Fr.* **1974**, 331.
14) Yamamori, T.; Adachi, I. *Tetrahedron Lett.* **1980**, *21*, 1747:
15) Ellison, R.A.; Woessner, W.D.; Williams, C.C. *J. Org. Chem.* **1972**, *37*, 2757.
16) Seebach, D.; Kolb, M.; Groebel, B.T. *Chem. Ber.* **1973**, *106*, 2277.
17) Brook, A.G.; Duff, J.M.; Jones, P.F.; Davis, N.R. *J. Am. Chem. Soc.* **1967**, *89*, 431; Corey, E.J.; Seebach, D.; Freedman, R. *ibid.* **1967**, *89*, 434.
18) Seebach, D.; Willert, J.; Beck, A.K.; Groebel, B.T. *Helv. Chim. Acta* **1978**, *61*, 2510.
19) Tanigawa, Y.; Kanamaru, H.; Sonoda, A.; Murahashi, S.I. *J. Am. Chem. Soc.* **1977**, *99*, 2361.
20) Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S.I. *ibid.* **1978**, *100*, 4610.
21) Grosserode, R.S.; Tobin, P.S.; Wheeler, D.M.S. *Synth. Commun.* **1976**, *6*, 377.
22) Grotjahn, D.B.; Andersen, N.H. *Chem. Commun.* **1981**, 306.
23) Wilson, S.R.; Misra, R.N. *J. Org. Chem.* **1978**, *43*, 4903.
24) Wilson, S.R.; Misra, R.N.; Georgiadis, G.M. *ibid.* **1980**, *45*, 2460.
25) Weidemann, B.; Widler, L.; Olivero, A.G.; Maycock, C.D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 357.
26) Eliel, E.L.; Hartmann, A.A.; Abatjoglou, A.G. *J. Am. Chem. Soc.* **1974**, *96*, 1807.
27) Juaristi, E.; Eliel, E.L. *Tetrahedron Lett.* **1977**, 543.
28) Seebach, D.; Corey, E.J.; Beck, A.K. *Chem. Ber.* **1974**, *107*, 367.
29) Balanson, R.D.; Kobal, V.M.; Schumaker, R.R. *J. Org. Chem.* **1977**, *42*, 393.
30) Rozen, S.; Shahak, I.; Bergmann, E.D. *Tetrahedron Lett.* **1972**, 1837.
31) Ncube, S.; Pelter, A.; Smith, K.; Blatcher, P.; Warren, S. *ibid.* **1978**, 2345.
32) Feuglas, C.; Galy, J.P. *C. R. Acad. Sci.* **1970**, *270*, C 2157.
33) Braun, M.; Seebach, D. *Chem. Ber.* **1976**, *109*, 669.
34) Seebach, D.; Braun, M. *Angew. Chem.* **1972**, *84*, 60.
35) Meyers, A.I.; Tait, T.A.; Comins, D.L. *Tetrahedron Lett.* **1978**, 4657.
36) Buerstinghaus, R.; Seebach, D. *Chem. Ber.* **1977**, *110*, 841.
37) Schill, G.; Merkel, C. *Synthesis* **1975**, 387.
38) Ager, D.J. *Tetrahedron Lett.* **1980**, *21*, 4763.
39) Blatcher, P.; Grayson, J.I.; Warren, S. *Chem. Commun.* **1976**, 547.
40) Cohen, T.; Kuhn, D.; Falck, J.R. *J. Am. Chem. Soc.* **1975**, *97*, 4749.
41) Blatcher, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1074.
42) Mukaiyama, T.; Narasaka, K.; Furusato, M. *J. Am. Chem. Soc.* **1972**, *94*, 8641.
43) Smith, R.A.J.; Lal, A.R. *Aust. J. Chem.* **1979**, *32*, 353.

Equivalence	Reagent	Electrophile	Ref.
HCO^-	*p*-tolyl-S-CH_2-SO-*p*-tolyl	chiral products from RCHO, cyclopentenone (1,4-)	81-82
HCO^-	Me_3SiCH_2-SO-Ph	MeI	83-84
		PhCOOEt	85
		ketones (→ R_2C=CH-SO-Ph)	85
HCO^-		RBr, RI, Me_3SiCl, ketones	86
HCO^-	$TsCH_2$-pyridinium	maleic anhydride (1,4-)	87
HCO^-	$PhSO_2$-CH_2NO_2	RX (primary), CH_2=$CHCH_2OAc$(Pd)	88
HCO^-	$PhSO_2$-CH_2O-CHMe-OEt	RX, ketones	89
HCO^-		RBr, RI	90-93
(RCO^-)		MeSSMe	91
HCO^-		RX, ketones, enones (1,2-)	94-96
(RCO^-)			
HCO^-		ketones; enones and enoic esters (1,4-)	95
(RCO^-)			
HCO^-	NC-CH_2S-CS-NMe_2	RX (primary), α,ω-dihalides	97
HCO^-		RX	98-100
(RCO^-)		CH_2=CHCN, HC≡CCOOMe (1,4-)	101,102
RCO^-	PhCH=N-CHR-COOEt	RX; enones and enoic esters (1,4-)	103
HCO^-		RX (primary, secondary)	104-106
(RCO^-)		ketones, oxiranes	104,107
		enones (1,4-)	104
		enoic esters (1,4-)	108
$ArCO^-$	Ar-CH(NR'_2)CN	RX	109,110
		C=C-CN (1,4-)	111-113
		enoic esters (1,4-)	111
RCO^-	R-CH(OR')-CN	RCl, RBr, RI, ROTs (primary, secondary)	114-117
		ketones	115-119
		enones (1,4-)	118,119
		preparation	120-126
$ArCO^-$	Ar-CH(OR')-CN	RX, R_2SO_4, ROTs	127,128
		ketones	129,130
		cyclohexenone (1,2- or 1,4- selectively)	131
		acyclic enones (dependence on substituents in Ar)	132
		quinoline N→O (attack at C-2)	133
$ArCO^-$	PhCH = N-CH_2-Ar	RBr (primary), RI, ClCOOEt	134
HCO^-	N-(phthalimide)-CH_2NO_2	enones, enoic esters (1,4-)	135
RCO^-	X_2PO-CH($OSiMe_3$)-R (-Ar)	RBr, RI (primary)	136-138
($ArCO^-$)		ketones	139-140
		PhSSPh	136
RCO^-	RCH_2COOH	RX (and decarboxylation)	141
HCO^-	*p*-tolyl-CH_2NC	ketones	142
RCO^-	RCH_2CN	RX	143
$ArCO^-$	$ArCH_2CN$	enoic esters (1,4-)	144
RCO^-	RCH_2NO_2	ClCOOEt, $(RO)_2CO$, PhCHO, ketones, esters, anhydrides	145-154

44) Nakai, T.; Okawara, M. *Chem. Lett.* **1974**, 731.
45) Hori, I.; Hayashi, T.; Midorikawa, M. *Synthesis* **1974**, 705.
46) Trost, B.M.; Miller, C.H. *J. Am. Chem. Soc.* **1975**, *97*, 7182.
47) de Groot, A.; Jansen, B.J.M. *Tetrahedron Lett.* **1981**, *22*, 887.
48) Fuji, K.; Ueda, M.; Fujita, E. *Chem. Commun.* **1977**, 814.
49) Eliel, E.L.; Koskimies, J.K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614.
50) Eliel, E.L.; Frazee, W.J. *J. Org. Chem.* **1979**, *44*, 3598.
51) Koskimies, J.K., Ph.D. Dissertation, University of North Carolina; *Diss. Abstr. Int.* **1977**, *38*, 692-B.
52) Ager, D.J.; Cookson, R.C. *Tetrahedron Lett.* **1980**, *21*, 1677.
53) Ager, D.J. *ibid.* **1980**, *21*, 4759.
54) Kocienski, P.J. *ibid.* **1980**, *21*, 1559.
55) Matteson, D.S.; Moody, R.J. *J. Am. Chem. Soc.* **1977**, *99*, 3196.
56) Sachdev, K.; Sachdev, H.S. *Tetrahedron Lett.* **1976**, 4223.
57) Van Ende, D.; Dumont, W.; Krief, A. *J. Organometal. Chem.* **1978**, *149*, C10.
58) Dumont, W.; Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1979**, 485.
59) Van Ende, D.; Cravador, A.; Krief, A. *J. Organometal. Chem.* **1979**, *177*, 1.
60) Hunt, E.; Lythgoe, B. *Chem. Commun.* **1972**, 757.
61) Corey, E.J.; Walinsky, S.W. *J. Am. Chem. Soc.* **1972**, *94*, 8932.
62) Carlson, R.M.; Helquist, P.M. *J. Org. Chem.* **1968**, *33*, 2596.
63) Bryan, R.F.; Carey, F.A.; Dailey, Jr., O.D.; Maher, R.J.; Miller, R.W. *ibid.* **1978**, *43*, 90.
64) Newkome, G.R.; Robinson, J.M.; Sauer, J.D. *Chem. Commun.* **1974**, 410.
65) Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1971**, 3151.
66) Ogura, K.; Katoh, N.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 889.
67) Schill, G.; Jones, P.R. *Synthesis* **1974**, 117.
68) Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1974**, 3653.
69) Ogura, K.; Yamashita, M.; Furukawa, S.; Suzuki, M.; Tsuchihashi, G. *ibid.* **1975**, 2765.
70) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *ibid.* **1976**, 759.
71) Ogura, K.; Tsuchihashi, G. *ibid.* **1972**, 2681.
72) Okura, K.; Furukawa, S.; Tsuchihashi, G. *Chem. Lett.* **1974**, 659.
73) Ogura, K.; Tsuchihashi, G.; *Tetrahedron Lett.* **1972**, 1383.
74) Ogura, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 1960.
75) Ogura, K.; Katoh, N.; Yoshimura, I.; Tsuchihashi, G. *Tetrahedron Lett.* **1978**, 375.
76) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *ibid.* **1978**, 1303.
77) Richman, J.E.; Herrmann, J.L.; Schlessinger, R.H. *ibid.* **1973**, 3267.
78) Herrmann, J.L.; Richman, J.E.; Schlessinger, R.H. *ibid.* **1973**, 3271.
79) Herrmann, J.L.; Richman, J.E.; Schlessinger, R.H. *ibid.* **1973**, 3275.
80) Herrmann, J.L.; Richman, J.E.; Wepplo, P.J. Schlessinger, R.H. *ibid.* **1973**, 4707.
81) Colombo, L.; Gennari, C.; Scolastico, C.; Guanti, G.; Narisano, E. *Chem. Commun.* **1979**, 591.
82) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *Synthesis* **1981**, 74.
83) Brook, A.G.; Anderson, D.G. *Can. J. Chem.* **1968**, *46*, 2115.
84) Vedejs, E.; Mullins, M. *Tetrahedron Lett.* **1975**, 2017.
85) Carey, F.; Hernandez, O. *J. Org. Chem.* **1973**, *38*, 2670.
86) Gokel, G.W.; Gerdes, H.M.; Miles, D.E.; Hufnal, J.M.; Zerby, G.A. *Tetrahedron Lett.* **1979**, 3375.
87) Abramovich, R.A.; Mathur, S.S.; Saunders, D.W.; Vanderpool, D.P. *ibid.* **1980**, *21*, 705.
88) Wade, P.A.; Hinney, H.R.; Amin, N.V.; Vail, P.D.; Morrow, S.D.; Hardinger, S.A.; Saft, M.S. *J. Org. Chem.* **1981**, *46*, 765.
89) Tanaka, K.; Matsui, S.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3619.

Equivalence	Reagent	Electrophile	Ref.
HCO^- (RCO^-)	$(EtOOC)_2CH$-H (-R)	RX, ROTs	155
RCO^- ($ArCO^-$)	$TsCH_2$-R (-Ar)	RBr, RI	156,157
HCO^- (RCO^-)		PhCN, PhCOCl	158-160
HCO^-		RX (primary)	161
RCO^-	RCHO	thiazolium salt-catalyzed addition: R'CHO	162-165
		enones, enoic esters (1,4)	166-170
$MeCO^-$	CH_2=CH-$SiMe_3$	RX, ketones, PhCOBr	171-172
		enones (1,4- with Cu^+)	173-174
$MeCO^-$	CH_2=CH-OR'	RBr, ketones, esters	175-180
		enones (1,4- with Cu^+)	174,177, 180
R_2CHCO^-	R_2C=CH-SR'	RI (primary)	172,181-184
		Me_3SiCl, PhSeBr, Bu_3SnCl, RSSR, PhCOBr	172,185, 186
		ketones, CO_2, oxiranes	181,183, 185,187
		vinyl cuprates→cumulenes	188
$PhCH_2CO^-$	PhCH=CH-SePh	PhCOBr	172
$MeCO^-$	Bu_3Sn-CH=CH_2	enones (1,4-)	189
R_2CHCO^-	R_2C=CH-NC	MeI, Me_3SiCl, Me_2CO	190
RCO^-	R'NC+RLi	RX, Me_3SiCl, aldehydes, oxiranes, CO_2, ClCOOEt	191,192
HCO^-	CH_2Cl_2	ketones	193-197
HCO^-	CH_2Br_2	RX, ketones, CO_2, RCOOR'	198
HCO^- (RCO^-)	$Na_2Fe(CO)_4$	RCl, RBr, RI, ROTs (primary), RCOCl (esters unreactive)	199-205
RCO^-	$NaRFe(CO)_4$	RX, ketones, RCOCl	200,201, 206-208
		enones, enoic esters (1,4-)	208
HCO^-	$NaCo(CO)_4$	RX (primary)	209
RCO^-	Me_3SiO-CR=CR-$OSiMe_3$	RX (primary, secondary)	210
RCO^- ($ArCO^-$)	R'CO-CHOH-R (Ar'CO-CHOH-Ar)	RX (but allylic halides give acyl oxiranes), enoic esters and amides (1,4-)	211
$ArCO^-$	ArCO-CHOH-Ar	RX (allylic, benzylic only)	212
$ArCO^-$	ArCOCH=CH-Me	MeI, PhSeBr	213
$ArCO^-$	$ArCOSiMe_3$	RBr, RI (primary)	214
$MeCO^-$	MeCOCN	ketones	215

90) Trost, B.M.; Tamaru, Y. *Tetrahedron Lett.* **1975**, 3797.
91) Trost, B.M.; Tamaru, Y. *J. Am. Chem. Soc.* **1975**, *97*, 3528.
92) Trost, B.M.; Tamaru, Y. *ibid.* **1977**, *99*, 3101.
93) Trost, B.M.; Crimmin, M.J.; Butler, D. *J. Org. Chem.* **1978**, *43*, 4549.
94) Grieco, P.A.; Wang, C.L.J. *Chem. Commun.* **1975**, 714.
95) Yamagiwa, S.; Hoshi, N.; Sato, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 214.
96) Nokami, J.; Kawada, M.; Okawara, R.; Torii, S.; Tanaka, H. *Tetrahedron Lett.* **1979**, 1045.
97) Masuyama, Y.; Ueno, Y.; Okawara, M. *ibid.* **1976**, 2967.
98) Kuebel, B.; Gruber, P.; Heernaus, R.; Steglich, W. *Chem. Ber.* **1979**, *112*, 128.
99) Lohmar, R.; Steglich, W. *ibid.* **1980**, *113*, 3706.
100) Lohmar, R.; Steglich, W. *Angew. Chem.* **1978**, *90*, 493.
101) Steglich, W.; Gruber, P. *ibid.* **1971**, *83*, 727.
102) Wegmann, H.; Schulz, G.; Steglich, W. *Justus Liebigs Ann. Chem.* **1980**, 1736.
103) Stork, G.; Leong, A.Y.W.; Touzin, A.M. *J. Org. Chem.* **1976**, *41*, 3491.
104) Stork, G.; Ozario, A.A.; Leong, A.Y.W. *Tetrahedron Lett.* **1978**, 5175.
105) Albrecht, H.; Raab, W.; Vonderheid, C. *Synthesis* **1979**, 127.
106) Buechi, G.; Liang, P.H.; Wueest, H. *Tetrahedron Lett.* **1978**, 2763.
107) Reutrakul, V.; Ratananukul, P.; Nimgirawath, S. *Chem. Lett.* **1980**, 71.
108) Schick, H.; Theil, F.; Jablokoff, H.; Schwarz, S. *Z. Chem.* **1981**, *21*, 68.
109) Dyke, S.F.; Tilly, E.P.; White, A.W.C.; Gale, D.P. *Tetrahedron* **1975**, *31*, 1219.
110) McEvoy, F.J.; Albright, J.D. *J. Org. Chem.* **1979**, *44*, 4597.
111) Albright, J.D.; McEvoy, F.J.; Moran, D.B. *J. Heterocycl. Chem.* **1978**, *15*, 881.
112) Leete, E.; Chedekel, M.R.; Bodem, G.B. *J. Org. Chem.* **1972**, *37*, 4465.
113) Reutrakul, V.; Nimgirawath, S.; Panichanum, S.; Ratananukul, P. *Chem. Lett.* **1979**, 399.
114) Deuchert, K.; Hertenstein, U.; Huenig, S. *Synthesis* **1973**, 777.
115) Huenig, S.; Wehner, G. *ibid.* **1975**, 181.
116) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286.
117) Stork, G.; Depezay, J.C.; d'Angelo, J. *Tetrahedron Lett.* **1975**, 389.
118) Aufderhaar, E.; Baldwin, J.E.; Barton, D.H.R.; Faulkner, D.J.; Slaytor, M. *J. Chem. Soc. C* **1971**, 2175.
119) Huenig, S.; Oeller, M. *Chem. Ber.* **1981**, *114*, 959.
120) Evans, D.A.; Truesdale, L.K. *Tetrahedron Lett.* **1973**, 4929.
121) Evans, D.A.; Truesdale, L.K.; Carroll, G.L. *Chem. Commun.* **1973**, 55.
122) Evans, D.A.; Hoffman, J.M.; Truesdale, L.K. *J. Am. Chem. Soc.* **1973**, *95*, 5822.
123) Evans, D.A.; Carroll, G.L.; Truesdale, L.K. *J. Org. Chem.* **1974**, *39*, 914.
124) Lidy, W.; Sundmeyer, W. *Chem. Ber.* **1973**, *106*, 587.
125) Neef, H.; Mueller, R. *J. Prakt. Chem.* **1973**, *315*, 367.
126) Parham, W.E.; Roosevelt, C.S. *J. Org. Chem.* **1972**, *37*, 1975.
127) Deuchert, K.; Hertenstein, U.; Huenig, S.; Werner, G. *Chem. Ber.* **1979**, *112*, 2045.
128) Kalir, A.; Balderman, D. *Synthesis* **1973**, 358.
129) Huenig, S.; Werner, G. *Chem. Ber.* **1979**, *112*, 2062.
130) Hamana, M.; Endo, T.; Saeki, S. *Tetrahedron Lett.* **1975**, 903.
131) Huenig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 302.
132) Huenig, S.; Wehner, G. *ibid.* **1980**, *113*, 324.
133) Endo, T.; Saeki, S.; Hamana, M. *Heterocycles* **1975**, *3*, 19.
134) Arrowsmith, J.E.; Cook, M.J.; Hardstone, D.J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2364.
135) Cowherd, F.G.; Doria, M.C.; Galeazzi, E.; Muchowski, J.M. *Can. J. Chem.* **1977**, *55*, 2919.
136) Hata, T.; Hashizuma, A.; Nakajima, M.; Sekine, M. *Tetrahedron Lett.* **1978**, 363.
137) Sekine, M.; Nakajima, M.; Kune, A.; Hata, T. *ibid.* **1979**, 4475.
138) Evans, D.A.; Takacs, J.M.; Hurst, K.M. *J. Am. Chem. Soc.* **1979**, *101*, 371.
139) Koenigkramer, R.E.; Zimmer, H. *Tetrahedron Lett.* **1980**, *21*, 1017.
140) Koenigkramer, R.E.; Zimmer, H. *J. Org. Chem.* **1980**, *45*, 3994.
141) Wasserman, H.H.; Lipshutz, B.H. *Synthesis* **1975**, 4611.
142) Oldenziel, D.H.; van Leusen, A.M. *ibid.* **1974**, 167.
143) Selikson, S.J.; Watt, D.S. *J. Org. Chem.* **1975**, *40*, 267.
144) Parker, K.A.; Kallmerten, J.L. *Tetrahedron Lett.* **1977**, 4557.
145) Ho, T.L.; Wong, C.M. *Synthesis* **1974**, 196.
146) Lehr, F.; Gonnermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258.
147) Shechter, H.; Williams, Jr., F.T. *J. Org. Chem.* **1962**, *27*, 3699.
148) Pagano, A.H.; Shechter, H. *ibid.* **1970**, *35*, 295.

149) Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. *J. Am. Chem. Soc.* **1974**, *96*, 5261.
150) Kornblum, N.; Wade, P.A. *J. Org. Chem.* **1973**, *38*, 1418.
151) McMurray, J.E.; Melton, J.; Padgett, H. *ibid.* **1974**, *39*, 259.
152) Black, D.S.C. *Tetrahedron Lett.* **1972**, 1331.
153) Jacobson, R.M. *ibid.* **1974**, 3215.
154) McMurray, J.E. *Acc. Chem. Res.* **1974**, *7*, 281.
155) Nokami, J.; Yamamoto, T.; Kawada, M.; Izumi, M.; Ochi, N.; Okawara, R. *Tetrahedron Lett.* **1979**, 1047.
156) Little, R.D.; Myong, S.O. *ibid.* **1980**, *21*, 3339.
157) Kotake, H.; Inomata, K.; Kinoshita, H.; Sakamoto, Y.; Kaneto, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3027.
158) Gilman, H.; Beel, J.A. *J. Am. Chem. Soc.* **1949**, *71*, 2328.
159) Boger, D.L. *J. Org. Chem.* **1978**, *43*, 2296.
160) Corey, E.J.; Boger, D.L. *Tetrahedron Lett.* **1978**, 5; *ibid.* **1978**, 9; *ibid.* **1978**, 13.
161) Dobschall, G. *ibid.* **1975**, 1889.
162) Stetter, H.; Schlenker, W. *ibid.* **1980**, *21*, 3479.
163) Stetter, H.; Basse, W.; Nienhaus, J. *Chem. Ber.* **1980**, *113*, 690.
164) Novák, L.; Baán, G.; Marosfalvi, J.; Szántay, C. *ibid.* **1980**, *113*, 2939.
165) Novák, L.; Majoros, B.; Szántay, C. *Heterocycles* **1979**, *12*, 369.
166) Stetter, H.; Base, W.; Wiemann, K. *Chem. Ber.* **1978**, *111*, 431.
167) Novák, L.; Baán, G.; Marosfalvi, J.; Szántay, C. *Tetrahedron Lett.* **1978**, 487.
168) Stetter, H.; Mohrmann, K.H.; Schlenker, W. *Chem. Ber.* **1981**, *114*, 581.
169) Stetter, H.; Hilboll, G.; Kuhlmann, H. *ibid.* **1979**, *112*, 84.
170) Trost, B.M.; Shuey, C.D.; DiNinno, Jr., F.; McElvain, S.S. *J. Am. Chem. Soc.* **1979**, *101*, 1284.
171) Groebel, B.T.; Seebach, D. *Angew. Chem.* **1974**, *86*, 102.
172) Groebel, B.T.; Seebach, D. *Chem. Ber.* **1977**, *110*, 867.
173) Huynh, C.; Linstrumell, G. *Tetrahedron Lett.* **1979**, 1073.
174) Boeckman, Jr., R.K.; Bruza, K.J. *J. Org. Chem.* **1979**, *44*, 4781.
175) Baldwin, J.E.; Lever, Jr., O.W.; Tzodikov, N.R. *ibid.* **1976**, *41*, 2312.
176) Baldwin, J.E.; Hoefle, G.A.; Lever, Jr., O.W. *J. Am. Chem. Soc.* **1974**, *96*, 7125.
177) Chavdarian, C.G.; Heathcock, C.H. *ibid.* **1975**, *97*, 3822.
178) Schoellkopf, U.; Haenssle, P. *Justus Liebigs Ann. Chem.* **1972**, *763*, 208.
179) Hartmann, J.; Staehle, M.; Schlosser, M. *Synthesis* **1974**, 888.
180) Boeckman, Jr., R.K.; Bruza, K.J.; Baldwin, J.E.; Lever, Jr., O.W. *Chem. Commun.* **1975**, 519.
181) Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, Y.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694.
182) Muthukrishnan, R.; Schlosser, M. *Helv. Chim. Acta* **1976**, *59*, 13.
183) Schaumann, E.; Walter, W. *Chem. Ber.* **1974**, *107*, 3562.
184) Cohen, T.; Matz, J.R. *Synth. Commun.* **1980**, *10*, 311.
185) Cohen, T.; Weisenfeld, R.B. *J. Org. Chem.* **1979**, *44*, 3601.
186) Harirchian, B.; Magnus, P. *Chem. Commun.* **1977**, 522.
187) Cookson, R.C.; Parsons, P.J. *ibid.* **1978**, 821.
188) Westmijze, H.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1975**, 2923.
189) Corey, E.J.; Wollenberg, R.H. *J. Am. Chem. Soc.* **1974**, *96*, 5581.
190) Schoellkopf, U.; Stafforst, D.; Jentsch, R. *Justus Liebigs Ann. Chem.* **1977**, 1167.
191) Niznik, G.E.; Morrison III, W.H.; Walborsky, H.M. *J. Org. Chem.* **1974**, *39*, 600.
192) Hirowatari, N.; Walborsky, H.M. *ibid.* **1974**, *39*, 604.
193) Koebrich, G. *Angew. Chem.* **1972**, *84*, 557.
194) Grosser, J.; Koebrich, G. *Chem. Ber.* **1975**, *108*, 328.
195) Koebrich, G.; Werner, W. *Tetrahedron Lett.* **1969**, 2181.
196) Blumbergs, P.; LaMontagne, M.P.; Stevens, J.I. *J. Org. Chem.* **1972**, *37*, 1248.
197) Buechi, G.; Minster, D.; Young, J.C.F. *J. Am. Chem. Soc.* **1971**, *93*, 4319.
198) Villieras, J.; Bacquet, C.; Normant, J.F. *Bull. Soc. Chim. Fr.* **1975**, 1797.
199) Cooke, Jr., M.P. *J. Am. Chem. Soc.* **1970**, *92*, 6081.
200) Collman, J.P.; Winter, S.R.; Clark, D.R. *ibid.* **1972**, *94*, 1788.
201) Collman, J.P.; Hoffman, N.W. *ibid.* **1973**, *95*, 2689.
202) Cooke, Jr., M.P.; Parlman, R.M. *ibid.* **1975**, *97*, 6863.
203) Mérour, J.Y.; Roustan, J.L.; Charrier, C.; Collin, J.; Benaim, J. *J. Organometal. Chem.* **1973**, *51*, C24.
204) Kimura, Y.; Tomita, Y.; Nakanishi, S.; Otsuji, Y. *Chem. Lett.* **1979**, 321.
205) Carnelli, G.; Manescalchi, F.; Umani-Ronchi, A.; Panunzio, P. *J. Org. Chem.* **1978**, *43*, 1598.
206) Watanabe, Y.; Mitsudo, T.; Tanaka, M.; Yamamoto, K.; Okajima, T.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2569.
207) Sawa, Y.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* **1970**, *35*, 4183.
208) Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* **1969**, *91*, 4926.
209) Ungváry, F.; Markó, L. *J. Organometal. Chem.* **1980**, *193*, 379.
210) Wakamatsu, T.; Akasaka, K.; Ban Y. *Tetrahedron Lett.* **1974**, 3879; *ibid.* **1974**, 3883.
211) Hase, T. *Synthesis* **1980**, 36.
212) Ueno, Y.; Okawara, M. *ibid.* **1975**, 268.
213) Hase, T.A.; Kukkola, P. *Synth. Commun.* **1980**, *10*, 451.
214) Degl'Innocenti, A.; Pike, S.; Walton, D.R.M. Seconi, G.; Ricci, A.; Fiorenza, M. *Chem. Commun.* **1980**, 1201.
215) Kraus, G.A.; Shimagaki, M. *Tetrahedron Lett.* **1981**, *22*, 1171.

About the Authors

Dr. Hase was born in Helsinki in 1937. He received the M.Sc. degree from the Helsinki University of Technology in 1962, and obtained the Ph.D. in 1969 from Imperial College (London) where he worked under Prof. D.H.R. Barton. In 1974-1975 he visited Harvard University as a research fellow, working in Prof. E.J. Corey's group. Dr. Hase is now an Associate Professor at the University of Helsinki, with research interests in synthetic organic chemistry.

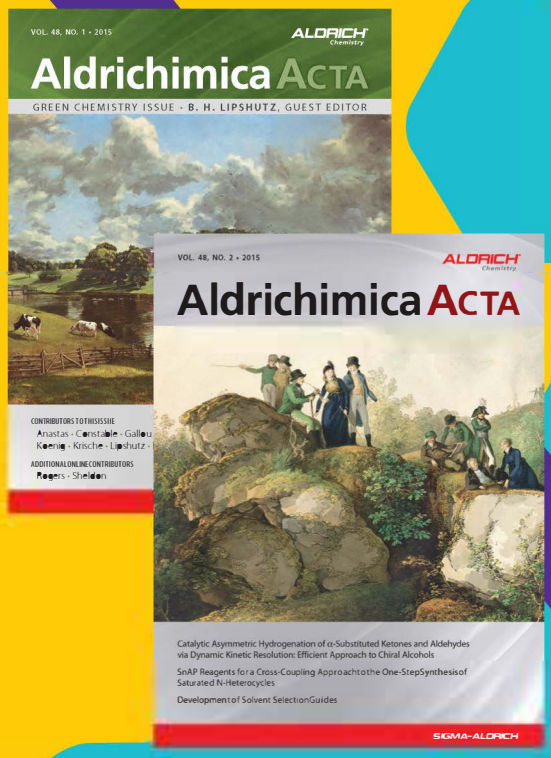
Jorma Koskimies was born in Finland in 1946. He received his candidate in philosophy from the University of Helsinki and his Ph.D. degree from the University of North Carolina in 1976 where he studied with E.L. Eliel. He then returned to the University of Helsinki where he is currently a lecturer in organic chemistry.

Lab Notes, *cont'd. from page 62.*

could be attributed to its use. We found that regular needle lubrication would often double or even triple the septum life. Lubrication also helps prevent needle bending or breakage.

Norman A. Buck
Research Assistant
Department of Entomology
College of Agriculture
The University of Arizona
Tucson, Arizona 85721

Acta Archive Indexes



The Acta Archive Indexes document provides easy access to all of the Acta content; 1968 to the present.

The volumes, issues, and content are sorted as follows:

- Chronological
- Authors
- Titles
- Affiliations
- Painting Clues (by volume)

From this index, you can jump directly to a particular volume. Using the sorted sections, you can locate reviews by various authors or author affiliation. Additionally, the content is fully searchable, allowing you to look for a particular key word from the various data available.

To access the index, **click here**.

2017-02521
02/17