Fieser
and
Fieser's

Reagents
for
Organic
Synthesis

VOLUME
EIGHT

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Mary Fieser

Reagents for Organic Synthesis

PREFACE

This volume of reagents includes references to papers published in 1977 and the first half of 1978. I am very grateful for the continuing advice and help of my colleagues. Professor Daniel Sternbach and Gary Amstutz have read portions of the manuscript. Professor John Cooper has given advice on nomenclature of organometallic compounds, particularly of metal carbonyls. The following chemists have been especially helpful in the proofreading—Professor William Roush, Professor Rick Danheiser, Dr. Mark A. Wuonola, Dr. William Moberg, Dr. James V. Heck, Professor Bruce Lipshutz, Dr. Ving Lee, Dr. Mary Lee, Dr. John Secrist, Professor Dale L. Boger, Stephen Kamin, Anthony Feliu, Jeffrey C. Hayes, Don Landry, Marcus A. Tius, John Maher, Jay W. Ponder, Paul Hopkins, John Munroe, Donald Wolanin, Charles Manley, Howard Simmons, III, Stuart Schreiber, Craig Shaefer, Stephen Hall, Stephen Pesceckis, John Morin, David Carini, Howard Sard, Stephen Brenner, Katharine Brightly, Chad G. Miller, Robert Wolf, Stephen Freilich, William Roberts, Jeffrey Howbert, and William McWhorter.

The picture of the Reagents group was taken by Professor Janice Smith.

MARY FIESER

Cambridge, Massachusetts
March 1980

Reagents for Organic Synthesis

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A

Acetic acid, 2, 5–7; **5,** 3; **7,** 1.

2-Alkyl-5-hydroxycyclopentene-2-ones (3). Epoxides (**1**) of 2-alkylcyclopen-tene-2-ones when heated in acetic acid rearrange to acetoxyenones (**2**), which can be hydrolyzed by sodium carbonate at room temperature to the hydroxy-enones (**3**). These can be rearranged by strong base or acid to **4**.[1]
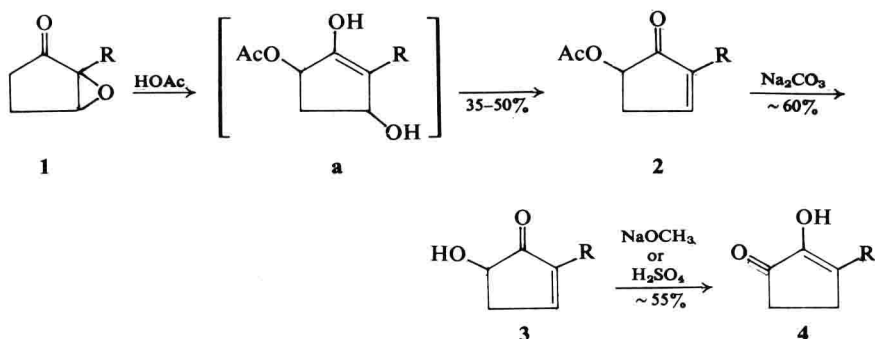
Cyclization. Treatment of the urea **1** with acetic acid at 50° results in cycliza-tion to **2**. Treatment with a stronger acid, such as trifluoroacetic acid, results in cyclization to a mixture of **3** and **2**. Since **2** and **3** are not interconvertible two different cyclizations are possible.[2] The ring system of **2** is present in the neuro-toxins related to saxitoxin, which are present in certain clams and mussels.
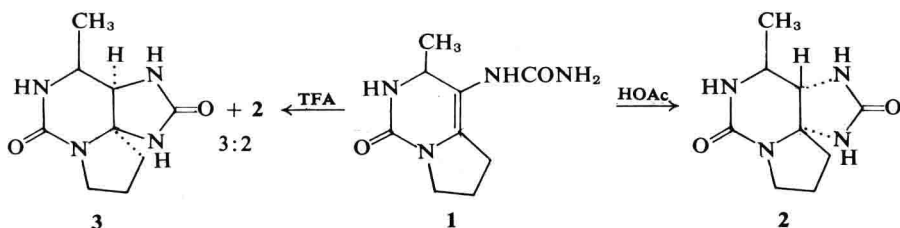
[1] M. P. L. Caton, G. Darnbrough, and T. Parker, *Syn. Comm.*, **8,** 155 (1978).
[2] H. Taguchi, H. Yazawa, J. F. Arnett, and Y. Kishi, *Tetrahedron Letters*, 627 (1977).

Acetic anhydride, 1, 3; **2,** 7–10; **5,** 3–4; **6,** 1–2; **7,** 1.

Enol lactonization. Acetic anhydride[1] is superior to acetyl chloride[2] for enol lactonization of **1** to give **2**. Prolonged treatment, particularly in the presence of sodium acetate, leads to **3**. The enol lactone **2** is a useful precursor to oxygenated γ-butyrolactones.

1
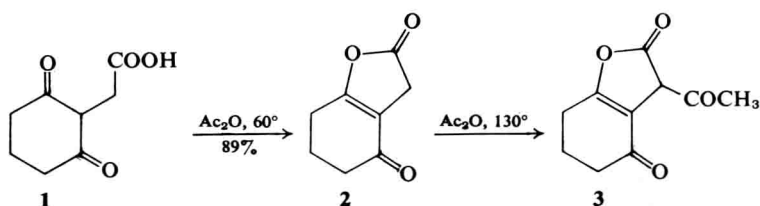
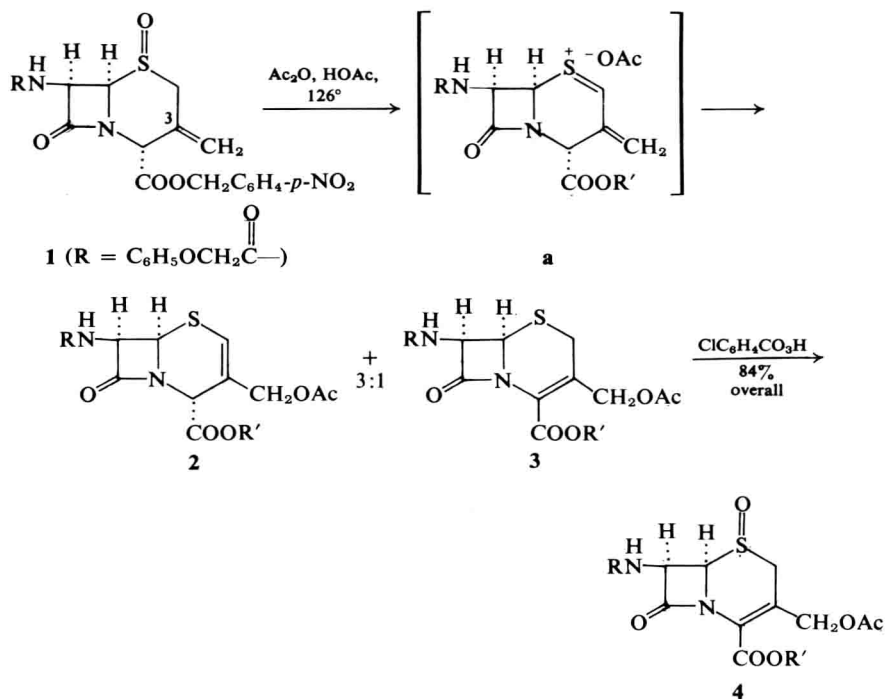[1] T. A. Eggelte, J. J. J. de Boer, H. de Koning, and H. O. Huisman, *Syn. Comm.*, **8**, 353 (1978).

[2] K. W. Rosenmund, H. Herzberg, and H. Schütt, *Ber.*, **87**, 1258 (1954).

Acetic anhydride–Acetic acid, 6, 1.

Pummerer reaction. The reaction of the 3-*exo*-methylenecepham sulfoxide **1** with Ac$_2$O–HOAc (2:1) at reflux gives a mixture of **2** and **3**, probably by way of

a 1,4-Pummerer type intermediate (**a**). Treatment of the mixture with *m*-chloro-perbenzoic acid at 0° gives the Δ^3-3′-acetoxycephem sulfoxide **4** in 84% overall yield.[1]

[1] G. A. Koppel and L. J. McShane, *Am. Soc.*, **100**, 288 (1978).

2-Acetoxyisobutyryl chloride, $(CH_3)_2\underset{\underset{OAc}{|}}{C}COCl$ **(1).** Mol. wt. 164.59, b.p. 55–56°/

6 mm. The material can be prepared on a kilogram scale by acetylation of 2-hy-droxyisobutyric acid (AcCl, 2 hours reflux) followed by reaction with thionyl chloride (100°, 2 hours); yield 84.6%.[1]

Reactions with diols. A few years ago Mattocks[2] reported a curious reaction of 2-acetoxy-2-methylbutyryl chloride (2) with the 1,4-diol 3 to give 4 and 5. The same paper reported other abnormal reactions of 2 with 1,2- and 1,3-diols.

3   2   4 (54%)   5 (20%)
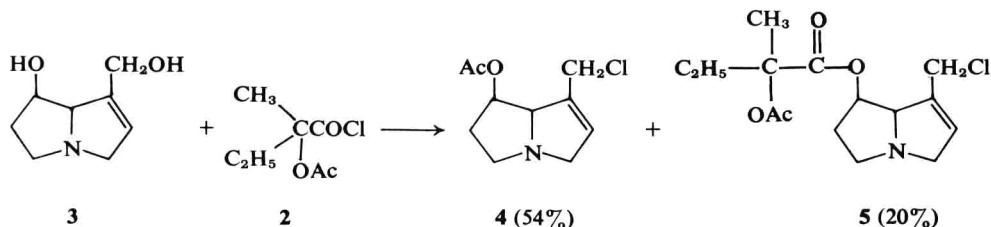
Greenberg and Moffatt[1] have confirmed and extended these results, but they used α-acetoxyisobutyryl chloride, which is not chiral, to simplify the reactions. These chemists first examined the reaction of 1 with a primary alcohol, *p*-nitro-benzyl alcohol (6). The reaction in acetonitrile and with added triethylamine (3 equiv.) gives the 1,3-dioxolane-4-one 7 in 84% yield. The reaction in pure triethylamine gives the crystalline ester 8 in 47% yield.


8   6

7
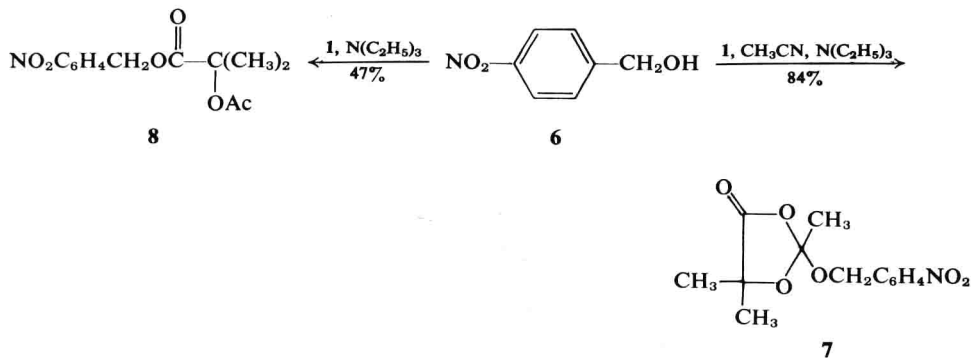
The reagent (1) reacts with *trans*-cycloalkane-1,2-diols to give a multitude of products. Reaction with *cis*-cycloalkane-1,2-diols gives *trans*-2-chlorocycloalkyl acetates in high yield. An example is formulated in equation (I). This reaction


(I)

(65%)
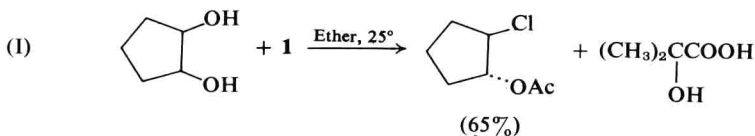
involves a cyclic acetoxonium ion, which can form only from a *cis*-1,2-diol.

Greenberg and Moffatt also examined the reaction of **1** with ribonucleosides, in particular, a protected form of uridine (**9**). In this case, chlorine is introduced
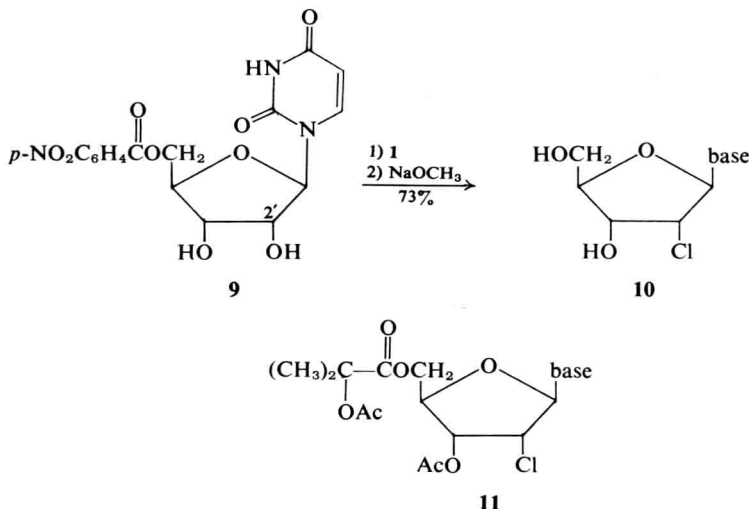
exclusively into the 2′-position with overall retention of configuration, presumably because of participation of the carbonyl group in the base. The major product (71% yield) of reaction of **1** with uridine itself (no solvent) is **11**. This reaction, however, is solvent dependent.

The reaction of **1** with pseudouridine (**12**), a C-nucleoside, differs from the reaction with uridine in that a mixture of 2′- and 3′-chlorodeoxynucleosides are formed. Thus the reaction of **1** with **12**, either neat or in acetonitrile, followed by hydrogenolysis with tri-*n*-butyltin hydride and deblocking gives about equal amounts of 2′- and 3′-deoxypseudouridine, (**13** and **14**).[3]
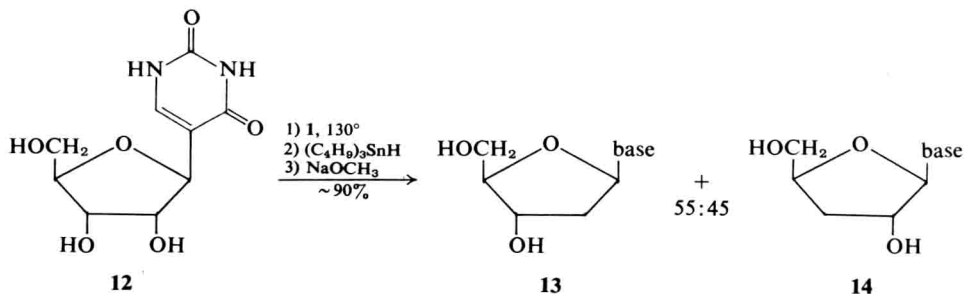
[1] S. Greenberg and J. G. Moffatt, *Am. Soc.*, **95**, 4016 (1973).
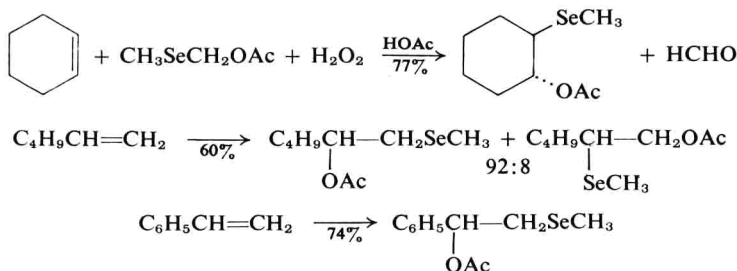
[2] A. R. Mattocks, *J. Chem. Soc.*, 1918, 4840 (1964).

[3] M. J. Robins and W. H. Muhs, *J.C.S. Chem. Comm.*, 677 (1978).

Acetoxymethyl methyl selenide, $CH_3SeCH_2OCOCH_3$. Mol. wt. 151.06, b.p. 51–52°/10 mm. The selenide is prepared by the Pummerer reaction of dimethyl selenoxide (**6**, 224) with acetic acid (29.2% yield).

Oxyselenation. In the presence of hydrogen peroxide the selenide reacts with alkenes to form acetoxyselenated products with loss of formaldehyde. The reaction apparently involves formation of the selenoxide, and indeed no reaction occurs in the absence of H_2O_2. Presumably the selenoxide then loses formaldehyde to form methaneselenenyl acetate, CH_3SeOAc, which is the actual reagent.[1]

Examples:

$C_4H_9CH{=}CH_2 \xrightarrow[60\%]{} C_4H_9\underset{OAc}{CH}{-}CH_2SeCH_3 + C_4H_9\underset{SeCH_3}{CH}{-}CH_2OAc$

92:8

$C_6H_5CH{=}CH_2 \xrightarrow[74\%]{} C_6H_5\underset{OAc}{CH}{-}CH_2SeCH_3$

[1] N. Miyoshi, S. Murai, and N. Sonoda, *Tetrahedron Letters*, 851 (1977).

Acetyl hexachloroantimonate, $CH_3CO^+SbCl_6^-$. Mol. wt. 374.51, colorless crystals sensitive to moisture. The salt is prepared from acetyl chloride and antimony(V) chloride.[1]

Acylation of alkenes. In the presence of a nonnucleophilic base (*e.g.*, ethyl-diisopropylamine), the reagent reacts with alkenes in CH_2Cl_2 at -50 to $-25°$ under kinetic control to form β,γ-unsaturated ketones in moderate to high yield.

Examples:

$(CH_3)_2C{=}CH_2 \xrightarrow[>90\%]{} CH_3COCH_2C\overset{CH_2}{\underset{CH_3}{\diagup\diagdown}}$
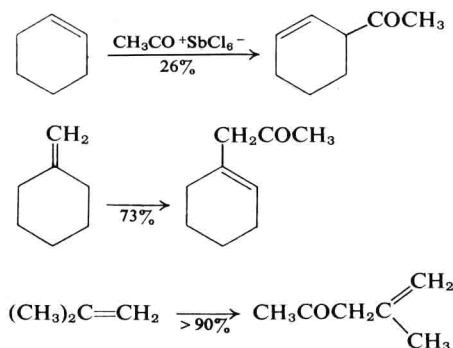
This acylation is considered to be an ene reaction, in which the acetyl cation abstracts an allylic hydrogen from the alkene in concerted fashion (equation I).[2]

(I)

$$\text{(structures showing reaction with CH}_2, \text{CH}_3, \text{C, O}^+, \text{H} \longrightarrow \text{H}_2\text{C} \quad \text{O}^+ \text{ with CH}_3 \quad \xrightarrow{-\text{H}^+} \quad \text{CH}_2 \quad \text{O with CH}_3)$$
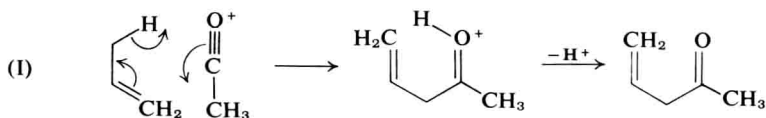

[1] G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *Am. Soc.*, **84**, 2733 (1962).
[2] H. M. R. Hoffmann and T. Tsushima, *ibid.*, **99**, 6008 (1977).

B-1-Alkenyl-9-borabicyclo[3.3.1]nonanes (1). These substances are prepared by hydroboration of alkynes with 9-BBN (**2**, 31; **3**, 24–29; **4**, 41; **5**, 46–47; **6**, 62–64).[1]

Allylic alcohols.[2] Usually reaction of organoboranes with carbonyl groups results in reduction. However, B-1-alkenyl-9-borabicyclo[3.3.1.]nonanes (**1**) add to simple aldehydes to give, after oxidation, allylic alcohols, with retention of configuration (equation I). The reaction is a Grignard-like synthesis and should be a useful route to allylic alcohols, even to those containing functional groups.
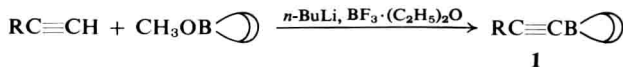
(I) $\text{R}^1\text{C}{\equiv}\text{CR}^2$ + 9-BBN $\xrightarrow{\text{THF}}$

(45–85%)
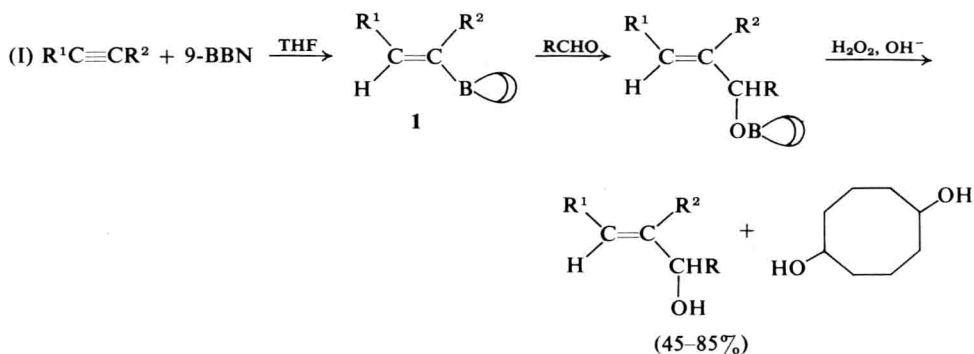
[1] H. C. Brown, E. F. Knights, and C. G. Scouten, *Am. Soc.*, **96**, 7765 (1974).
[2] P. Jacob III and H. C. Brown, *J. Org.*, **42**, 579 (1977).

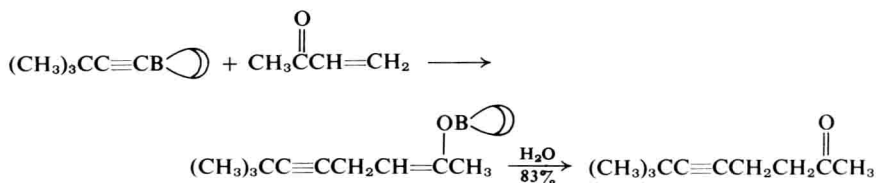**B-1-Alkynyl-9-borabicyclo[3.3.1]nonanes (1).**
Preparation[1]:

$$\text{RC}{\equiv}\text{CH} + \text{CH}_3\text{OB} \xrightarrow{\text{n-BuLi, BF}_3\cdot(\text{C}_2\text{H}_5)_2\text{O}} \text{RC}{\equiv}\text{CB}$$

1

Conjugate additions. The reagent undergoes conjugate addition to α,β-unsaturated ketones to form γ,δ-acetylenic ketones.[2]

Examples:

$$(\text{CH}_3)_3\text{CC}{\equiv}\text{CB} + \text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}{=}\text{CH}_2 \longrightarrow$$

$$(\text{CH}_3)_3\text{CC}{\equiv}\text{CCH}_2\text{CH}{=}\overset{\text{OB}}{\underset{}{\text{C}}}\text{CH}_3 \xrightarrow[83\%]{\text{H}_2\text{O}} (\text{CH}_3)_3\text{CC}{\equiv}\text{CCH}_2\text{CH}_2\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_3$$

$$CH_3(CH_2)_3C{\equiv}CB\text{\textcircled{\tiny)}} + (CH_3)_2C{=}CHCOCH_3 \xrightarrow[70\%]{} CH_3(CH_2)_3C{\equiv}C\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_2COCH_3$$

4-Methoxy-3-butene-2-one also undergoes rapid conjugate addition with B-1-alkynyl-9-borabicyclo[3.3.1]nonanes with elimination of B-methoxy-9-BBN to give a 4-*trans*-alkynyl-3-butene-2-one in almost quantitative yield.[3]

$$RC{\equiv}CB\text{\textcircled{\tiny)}} + \underset{CH_3O}{\overset{H}{}}\underset{}{}C{=}C\underset{H}{\overset{CCH_3}{}} \xrightarrow[98\%]{} \underset{RC{\equiv}C}{\overset{H}{}}C{=}C\underset{H}{\overset{CCH_3}{}} + \text{\textcircled{\tiny C}}BOCH_3$$
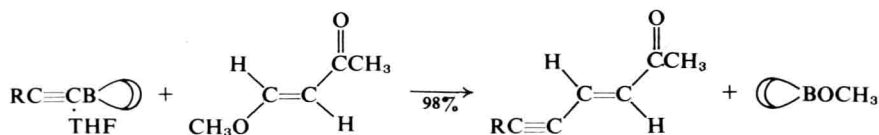
The reaction is general for other β-methoxy-α,β-unsaturated ketones that can assume the cisoid conformation and provides a useful synthesis of conjugated enynones.
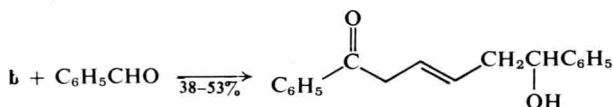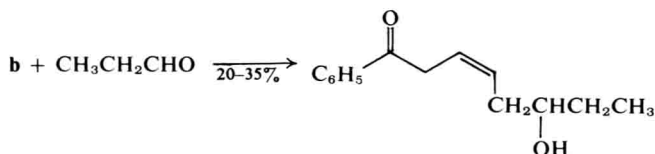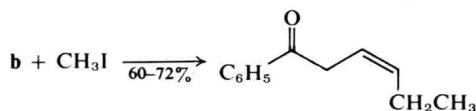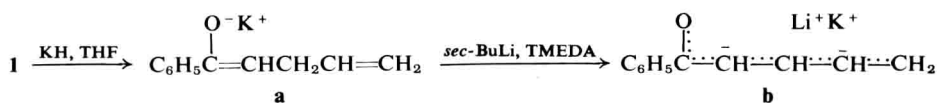
[1] J. A. Sinclair and H. C. Brown, *J. Org.*, **41**, 1078 (1976).
[2] J. A. Sinclair, G. A. Molander, and H. C. Brown, *Am. Soc.*, **99**, 954 (1977).
[3] G. A. Molander and H. C. Brown, *J. Org.*, **42**, 3106 (1977).

Allylacetophenone, $C_6H_5COCH_2CH_2CH{=}CH_2$ (1). Mol. wt. 160.21, b.p. 125–127°/16 mm. This compound can be prepared from acetophenone and allyl bromide in the presence of sodium *t*-amyloxide.[1]

The dianion (**b**) of this unsaturated ketone (**1**) can be obtained by depronation first with KH in THF at 0° and then with *sec*-butyllithium (TMEDA). The dianion reacts with electrophiles exclusively at the terminal position; in

$$1 \xrightarrow{KH,\,THF} \underset{\mathbf{a}}{C_6H_5\overset{\overset{O^-K^+}{|}}{C}{=}CHCH_2CH{=}CH_2} \xrightarrow{sec\text{-BuLi, TMEDA}} \underset{\mathbf{b}}{C_6H_5\overset{\overset{O}{\|}}{C}{\cdots}\bar{C}H{\cdots}CH{\cdots}\bar{C}H{\cdots}CH_2 \quad Li^+K^+}$$

$$\mathbf{b} + CH_3I \xrightarrow[60-72\%]{} C_6H_5$$

$$\mathbf{b} + CH_3CH_2CHO \xrightarrow[20-35\%]{} C_6H_5$$

$$\mathbf{b} + C_6H_5CHO \xrightarrow[38-53\%]{} C_6H_5$$

the reaction with alkyl halides, epoxides, and aliphatic aldehydes or ketones only the *cis*-compound is formed, whereas only *trans*-adducts are formed with aromatic carbonyl compounds.[2]

[1] G. Vavon and J. Conia, *Compt. rend.*, **223**, 245 (1946).
[2] M. Pohmakotr and D. Seebach, *Angew. Chem., Int. Ed.*, **16**, 320 (1977).

Allyl triflate, $CH_2=CHCH_2OSO_2CF_3$ (**1**). Mol. wt. 191.16, colorless liquid, must be stored at $-78°$ in a vented flask. This triflate can be prepared in pure form in 69% yield by the reaction of allyl alcohol with trifluoromethanesulfonic anhydride and pyridine in dichloromethane.[1]

Caution: Avoid contact with or inhalation of this volatile, very reactive alkylating reagent.

Ring expansion. Vedejs[2] and Schmid[3] have devised a repeatable ring expansion process involving successive [2,3]sigmatropic shifts as illustrated in scheme (I). An α-vinyl heterocycle such as 2-vinylthiacyclopentane (**2**) is alkylated with allyl triflate to give the salt **3**. On treatment with a base (DBU) in acetonitrile,
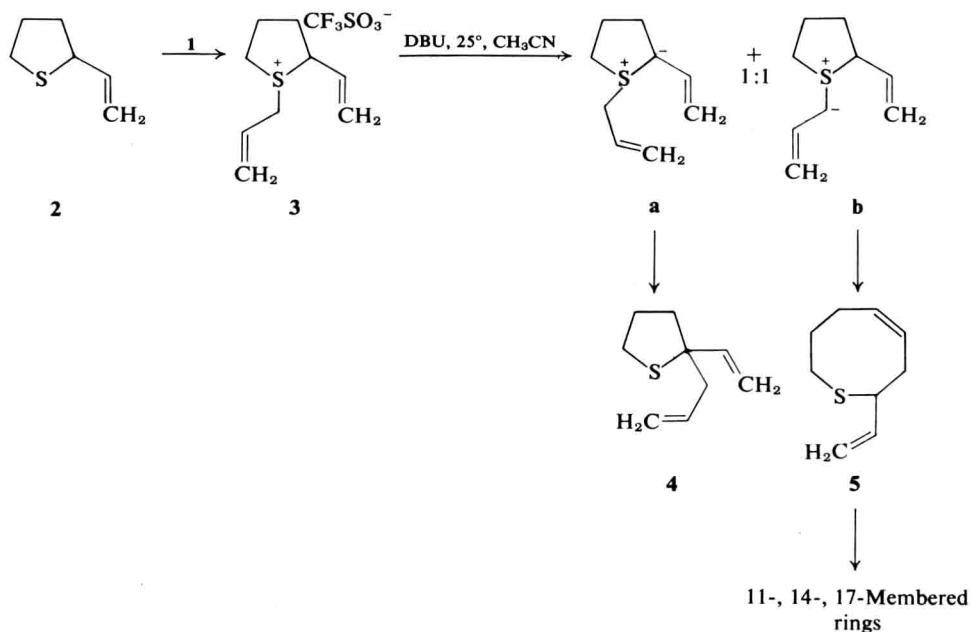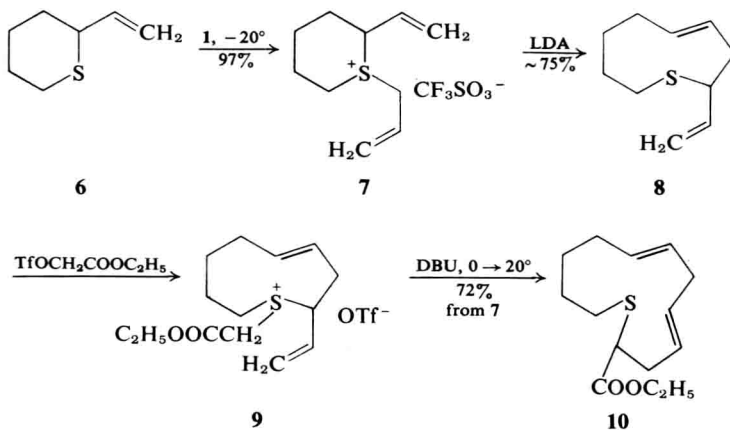

Scheme (I)

3 is converted into the endocyclic (**a**) and exocyclic (**b**) ylides in a 1:1 ratio. These ylides rearrange under the conditions of generation into **4** and **5**, respectively. The desired ring expanded cyclic sulfide **5** can be converted in the same

way into cyclic sulfides with 11-, 14-, and 17-membered rings. In these later ring expansions the undesired shifts to products such as **4** are not observed.

The same sequence has been applied to 2-vinylthiane (**6**). In this case formation of the undesired ylide was minimized by use of LDA in place of DBU (scheme II).

Scheme (II)

Conformational factors involved in these [2,3] sigmatropic shifts have been discussed.[4]

[1] E. Vedejs, D. A. Engler, and M. J. Mullins, *J. Org.*, **42**, 3109 (1977).
[2] E. Vedejs and J. P. Hagen, *Am. Soc.*, **97**, 6878 (1975); E. Vedejs, M. J. Mullins, J. M. Renga, and C. P. Singer, *Tetrahedron Letters*, 519 (1978).
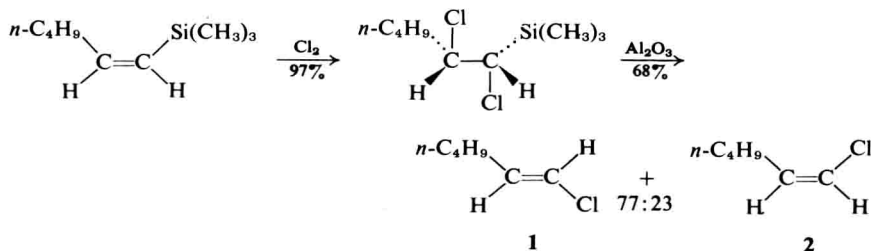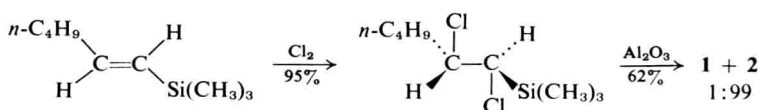[3] R. Schmid and H. Schmid, *Helv.*, **60**, 1361 (1977).
[4] E. Vedejs, M. J. Arco, and J. M. Renga, *Tetrahedron Letters*, 523 (1978).

Alumina, 1, 19–20; **2**, 17; **3**, 6; **4**, 8; **6**, 16–17; **7**, 5–7.

Vinyl halides. These compounds can be prepared from vinylsilanes by halogenation followed by elimination of $ClSi(CH_3)_3$ with sodium methoxide or neutral alumina.
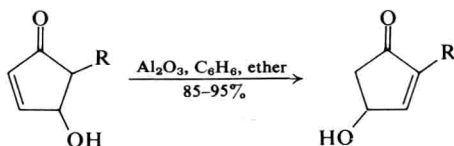
Examples:

The stereoselectivity is high with *trans*-vinylsilanes but somewhat lower with *cis*-vinylsilanes; the same selectivity is observed with both $NaOCH_3$ and Al_2O_3.[1]

2-Alkyl(aryl)-5-hydroxy-3-ketocyclopentenes.[2] These substances can be obtained in 85–95% yield by column chromatography of 4-alkyl(aryl)-5-hydroxy-3-ketocyclopentenes.[3]

Doped aluminas. Posner[4] has reviewed organic reactions on alumina surfaces (93 references). Although the exact role of alumina is not understood, alumina may activate both the substrate and the reagent by adsorption in the proper orientation for a chemical reaction. Some recent examples are discussed.

Complete details of nucleophilic opening of epoxides (**6**, 16–17) catalyzed by commercially available alumina (W-200-N) have been published.[5] Some generalizations can be drawn from the extensive investigations. The reactivity of symmetrical cycloalkene oxides decreases in the order of ring size: 6 > 8 > 12; and reactivity of the nucleophiles decreases in the order: ROH ~ HOAc > RNH_2. One great advantage of this method is that usually only one product is formed.

This reaction has also been applied to arene oxides. These oxides can be opened by alumina doped with alcohols and amines, but this reaction competes with 1,2-hydride shifts to give phenols.[6]

Examples: