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VOLUME  
TEN

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CIENCE

**Fieser and Fieser's**  
**Reagents for**  
**Organic Synthesis**

**VOLUME TEN**

**Mary Fieser**  
**Harvard University**



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**Reagents for Organic Synthesis**

## PREFACE

This volume of reagents includes references to papers published during 1980 and the first half of 1981. I am indebted to many colleagues for advice and help. Alan E. Barton and Paul B. Hopkins have again read the manuscript. I am especially grateful for invaluable proofreading by Dr. James V. Heck, Dr. Ving Lee, Professor Bruce Lipshutz, Professor Dale Boger, Dr. Michael McMillan, Daniel Brenner, Jeffrey C. Hayes, Jay W. Ponder, John E. Munroe, William P. Roberts, Steven Freilich, Thomas Eckrich, Robert E. Wolf, Jr., Marco Pagnotta, Marifaith Hackett, William McWhorter, Judith Hartman, William L. Seibel, Andrew G. Myers, John C. Schmidhauser, Daniel F. Lieberman, Charles Manly, Donald Wolanin, J. Jeffrey Howbert, and, especially, Katharine Brighty, who read almost the entire galley proof. The proofreading was coordinated by Peter T. Lansbury, Jr. The picture of the group was taken by Alan Barton.

MARY FIESER

*Cambridge, Mass.  
April, 1982*



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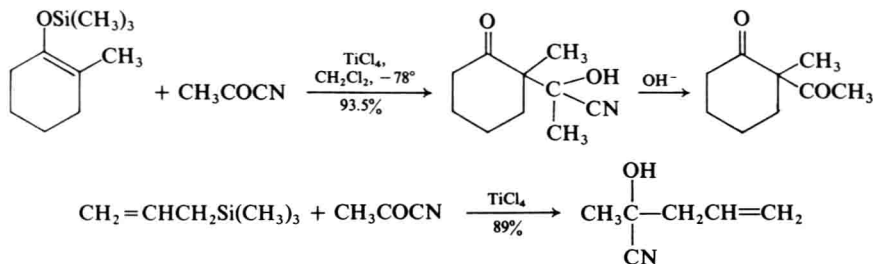
# A

**Acetyl cyanide**,  $\text{CH}_3\text{COCN}$ . Mol. wt. 69.16, b.p.  $90-92^\circ$ .

Acyl cyanides can be prepared by reaction of acid chlorides with cyanotrimethylsilane at  $60-70^\circ$ <sup>1</sup> or with copper cyanide.<sup>2</sup>

**Monocyanohydrins of  $\beta$ -diketones.**<sup>3</sup> In the presence of  $\text{TiCl}_4$ , acetyl cyanide reacts with enol silyl ethers of ketones at  $-78^\circ$  to afford monocyanohydrins of  $\beta$ -diketones in excellent yield. The corresponding reaction with enol silyl ethers of aldehydes proceeds in only about 35% yield. A low temperature is essential for this reaction. A similar reaction is possible with allyltrimethylsilane.

Examples:



<sup>1</sup> K. Herrman and G. Simchen, *Synthesis*, 204 (1979).

<sup>2</sup> J. F. Normant and C. Piechucki, *Bull. Soc.*, 2402 (1972).

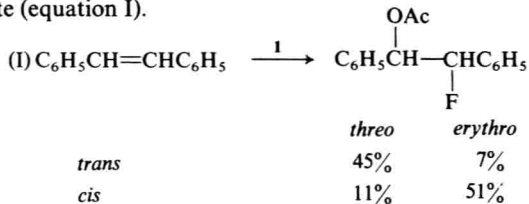
<sup>3</sup> G. A. Kraus and M. Shimagaki, *Tetrahedron Letters*, **22**, 1171 (1981).

**Acetyl hypofluorite (1).** Mol. wt. 78.04.

Preparation in  $\text{CH}_3\text{COOH}-\text{CFCl}_3$ :



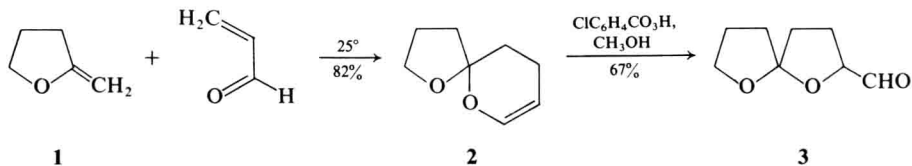
**Fluorination.**<sup>1</sup> The reagent reacts with *trans*- and *cis*-stilbene, preferentially by *syn*-addition. Only the *syn*-adducts are isolable in the reaction of **1** with ethyl *trans*- and *cis*-cinnamate (equation I).



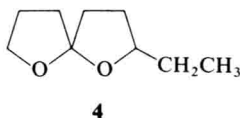
<sup>1</sup> S. Rozen, O. Lerman, and M. Kol, *J.C.S. Chem. Comm.*, 443 (1981).

Acrolein,  $\text{CH}_2=\text{CHCHO}$ , **2**, 15; **3**, 5.

**Hetero-Diels-Alder reaction.**<sup>1</sup> Acrolein undergoes a Diels-Alder reaction with furanoid and pyranoid exocyclic vinyl ethers at 25° (4–6 days). The spiroketal (**2**) obtained can be oxidized in  $\text{CH}_3\text{OH}$  by *m*-chloroperbenzoic acid to the ring



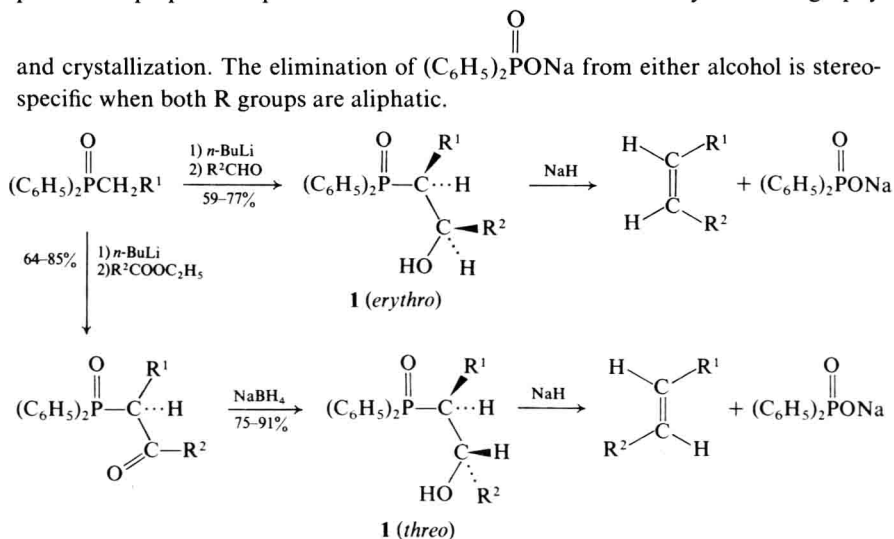
contracted aldehyde. The aldehyde (**3**) obtained in this way was used to synthesize racemic chalcogran (**4**), an aggregation pheromone of a beetle. Some polyether antibiotics contain similar subunits.



<sup>1</sup> R. E. Ireland and D. Habich, *Tetrahedron Letters*, **21**, 1389 (1980).

**Alkyl diphenyl phosphonates**,  $(\text{C}_6\text{H}_5)_2\text{PCH}_2\text{R}$ .

**(E)- and (Z)-Alkenes.** Both (Z)- and (E)-alkenes can be prepared stereoselectively by the Wittig-Horner reaction formulated in Scheme (I).<sup>1</sup> Thus it is possible to prepare the pure diastereoisomers of the alcohols **1** by chromatography



Scheme 1

<sup>1</sup> A. D. Buss and S. Warren, *J.C.S. Chem. Comm.*, 100 (1981).

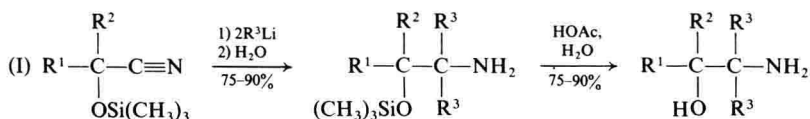


**Alkyl lithium reagents, 9, 5-8.**

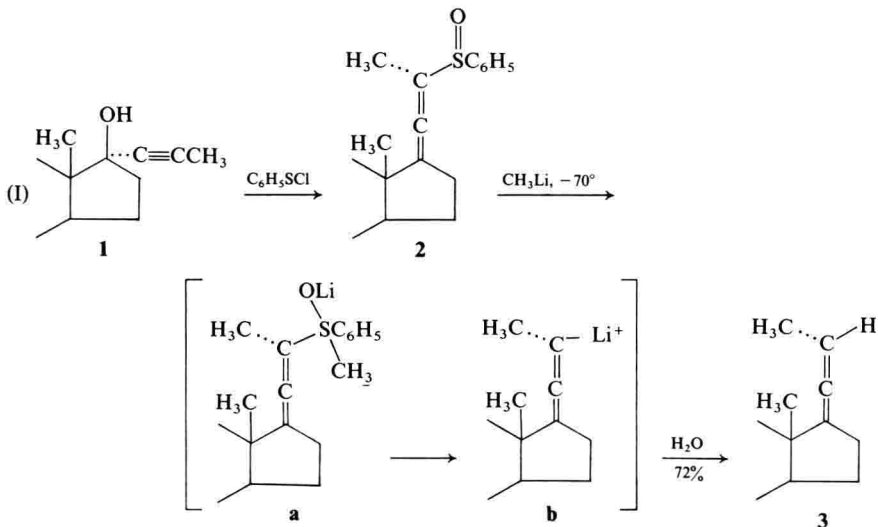
**Simplified preparation.**<sup>1</sup> Alkyl- and aryllithium reagents can be prepared readily and in high yield by reaction of alkyl or aryl bromides with lithium containing 2% sodium by irradiation for 10-30 minutes in an ultrasound laboratory cleaner. No initiation is necessary and the solvent (THF) can be technical grade, although yields are higher in the absence of water. Reagents prepared in this way can be used for addition to carbonyl compounds (Barbier reaction<sup>2</sup>) in 60-90% isolated yields.

**Determination of concentration.** Two laboratories<sup>3</sup> recommend 1,3-diphenyl-2-propanone tosylhydrazone (m.p. 185-186° dec.) for determination of the concentration of RLi in THF solutions. The dianion of the tosylhydrazone has an intense orange color.

**$\beta$ -Amino alcohols.**<sup>4</sup> Alkyl lithium reagents undergo double addition to  $\alpha$ -trimethylsilyloxy nitriles to form  $\beta$ -trimethylsilyloxy amines. These products are hydrolyzed by aqueous acetic acid to  $\beta$ -amino alcohols (equation I).

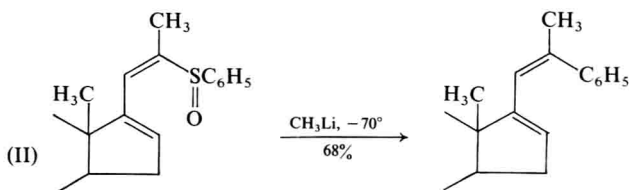


**Reaction with allene sulfoxides.**<sup>5</sup> Allenic sulfoxides are desulfurized by reaction with methyllithium. An example is the transformation shown in equation (I). The propynylcarbinol **1** is treated with benzenesulfonyl chloride to form the allene **2**,



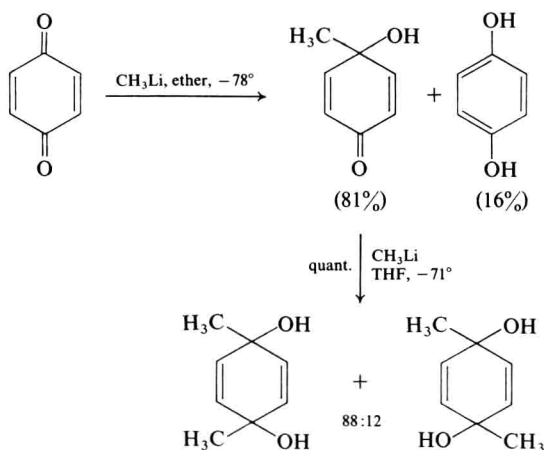
which undergoes cleavage to **3** on treatment with methyllithium. The reaction is stereospecific.

The same paper mentions a benzylic type rearrangement of a sulfoxide induced by methyllithium (equation II).

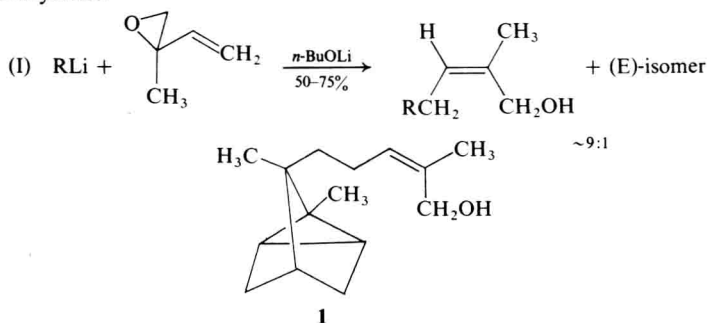


**Reaction with *p*-benzoquinones.**<sup>6</sup> Fischer and Henderson have found conditions that result in 1,2-addition of various RLi reagents to *p*-benzoquinone. The reaction when conducted in ether at  $-78^\circ$  results in 4-alkyl-4-hydroxycyclohexa-2,5-diene-1-ones. These products undergo further 1,2-addition with RLi in THF to give dialkylcyclohexa-2,5-diene-1,4-diols. Mixed dienediols can be obtained by use of two different RLi reagents.

Example:



**Reaction with isoprene epoxide.**<sup>7</sup> Alkyl lithium reagents undergo 1,4-addition to isoprene epoxide to give predominately (Z)-allylic alcohols, particularly in the presence of a base (equation I). The reaction was used to prepare  $\alpha$ -santalol (**1**) from  $\pi$ -bromotricyclene.



Phenyllithium reacts with the epoxide by 1,2- and 1,4-addition, with no stereoselectivity.

<sup>1</sup> J.-L. Luche and J.-C. Damiano, *Am. Soc.*, **102**, 7926 (1980).

<sup>2</sup> C. Blomberg and F. A. Hartog, *Synthesis*, 18 (1977).

<sup>3</sup> M. F. Lipton, C. M. Sorenson, A. C. Sadler, and R. H. Shapiro, *J. Organometal. Chem.*, **186**, 155 (1980).

<sup>4</sup> R. Amouroux and G. P. Axiotis, *Synthesis*, 270 (1981).

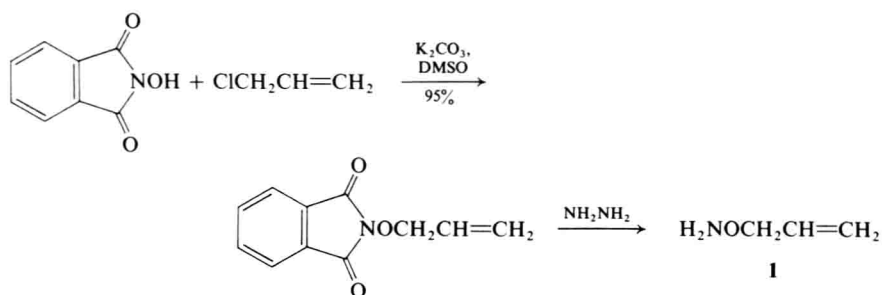
<sup>5</sup> G. Neef, U. Eder, and A. Seeger, *Tetrahedron Letters*, **21**, 903 (1980).

<sup>6</sup> A. Fischer and G. N. Henderson, *Tetrahedron Letters*, **21**, 701 (1980).

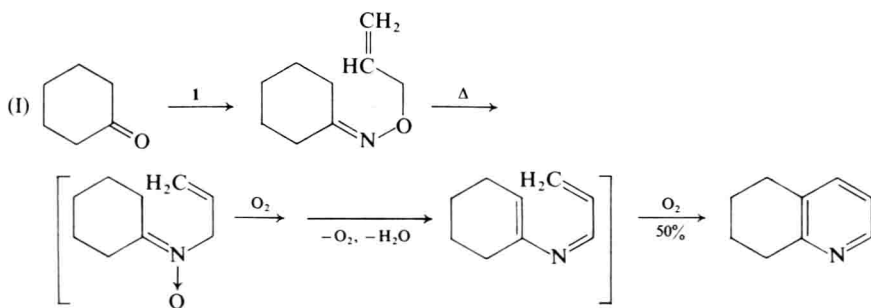
<sup>7</sup> M. Tamura and G. Suzukamo, *Tetrahedron Letters*, **22**, 577 (1981).

### O-Allylhydroxylamine (I). Mol. wt. 73.10.

Preparation:



**2,3-Disubstituted pyridines.**<sup>1</sup> A typical reaction is the synthesis of 5,6,7,8-tetrahydroquinoline (equation I). If the thermolysis is carried out in the absence of oxygen, the yield of the pyridine is 3%.

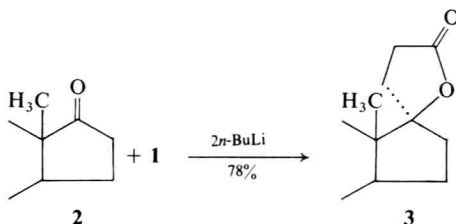


<sup>1</sup> H. Irie, I. Katayama, and Y. Mizuno, *Heterocycles*, **12**, 771 (1979).

**Allyltetramethylphosphorodiamidate**,  $[(\text{CH}_3)_2\text{N}]_2\text{P}(=\text{O})\text{CH}_2\text{CH}=\text{CH}_2$  (I). Mol. wt. 192.21, b.p. 57°/0.01 mm. The reagent is prepared by reaction of allyl alcohol and

tetramethylphosphorodiamidic chloride in the presence of benzyltriethylammonium chloride in  $\text{CH}_2\text{Cl}_2$  and aqueous  $\text{NaOH}$  (90% yield).

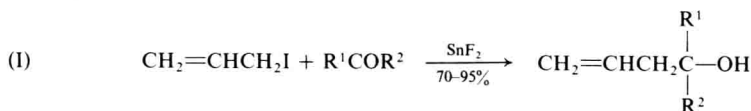
**Adrenolactone (3).**<sup>1</sup> A new synthesis of the lactone involves reaction of the tetrahydropyranyl derivative of 3 $\beta$ -hydroxy-17-ketoandrostene (2) with the dilithio derivative of 1.



<sup>1</sup> G. Sturtz and J.-J. Yaouane, *Synthesis*, 289 (1980).

**Allyltin difluoriodide**,  $\text{CH}_2=\text{CHCH}_2\text{SnIF}_2$ . The reagent is prepared *in situ* from allyl iodide and  $\text{SnF}_2$  (dried).

**Homoallylic alcohols.**<sup>1</sup> The reagent reacts with aldehydes and ketones to form derivatives of homoallylic alcohols in satisfactory yield (equation I). 1,3-Dimethyl-2-imidazolidinone is the most satisfactory solvent.

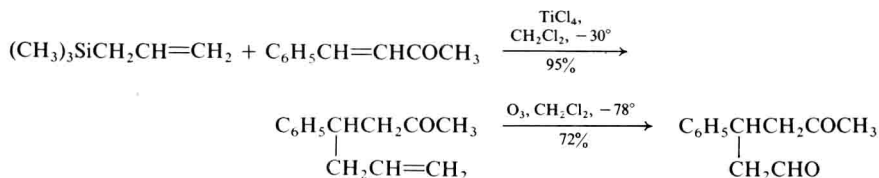


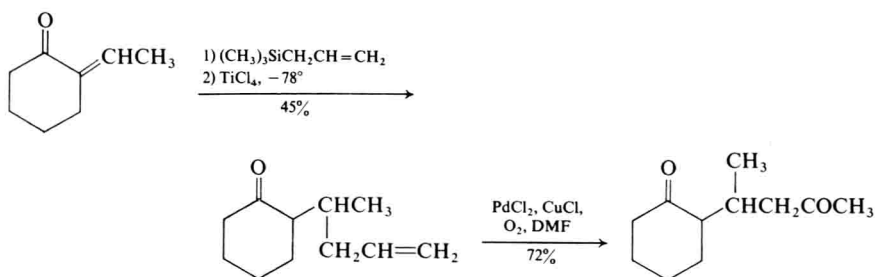
<sup>1</sup> T. Mukaiyama, T. Harada, and S. Shoda, *Chem. Letters*, 1507 (1980).

**Allyltrimethylsilane**,  $(\text{CH}_3)_3\text{SiCH}_2\text{CH}=\text{CH}_2$  (1). Mol. wt. 114.27, b.p. 84–88°. Suppliers: Aldrich, Petrarch Systems.

**Acetylation.**<sup>1</sup> In the presence of  $\text{TiCl}_4$  or  $\text{BF}_3$  etherate allyltrimethylsilane undergoes conjugate addition to  $\alpha,\beta$ -enones. The  $\delta,\epsilon$ -enones formed are converted by ozonation or  $\text{KMnO}_4$ – $\text{KIO}_4$  to  $\delta$ -keto aldehydes. Wacker oxidation can be used to obtain methyl ketones.

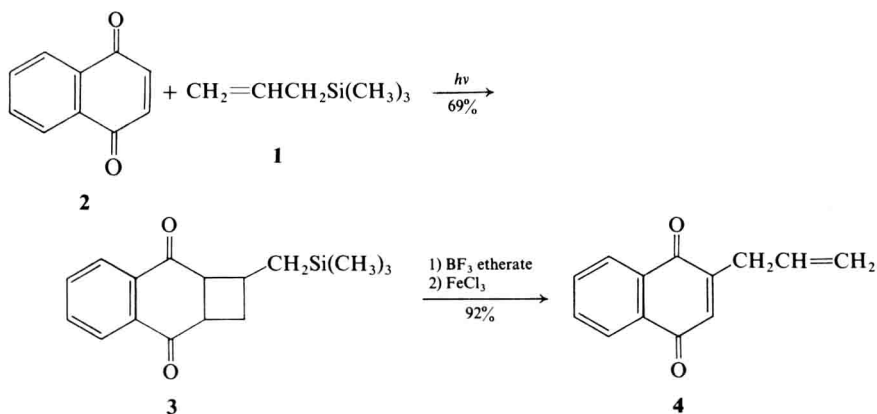
Examples:



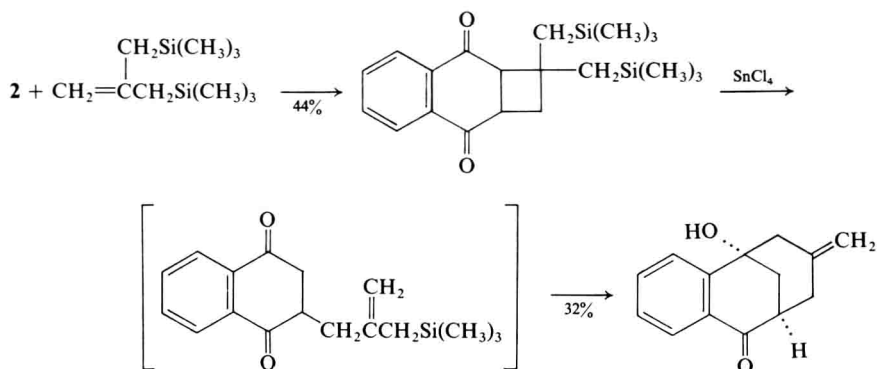


(2-Methyl-2-propenyl)trimethylsilane,  $(\text{CH}_3)_3\text{SiCH}_2\text{C}(\text{CH}_3)=\text{CH}_2$ , can be used in this sequence as a route to 1,5-diketones.

**Allylnaphthoquinones.**<sup>2</sup> Allyltrimethylsilane (**1**) undergoes irradiation-assisted cycloaddition to 1,4-naphthoquinone (**2**) to give a mixture of stereoisomers (**3**). Cleavage and subsequent oxidation of **3** gives allylnaphthoquinone (**4**) in high yield.



Another example:



**Trimethylsilyl ethers and esters.**<sup>3</sup> The reaction of alcohols and allyltrimethylsilane in acetonitrile with TsOH as catalyst (70–80°, 1–3 hours) results in trimethylsilyl ethers in 85–95% yield with elimination of propene. The same reaction with carboxylic acids results in trimethylsilyl esters. Phenols do not undergo this reaction.

*t*-Butyldimethylsilyl ethers can be prepared in the same way from allyl-*t*-butyldimethylsilane (b.p. 65–66°/47 mm).

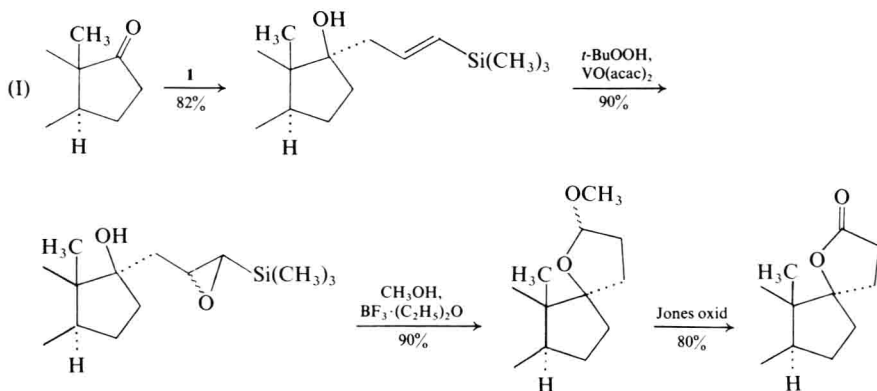
<sup>1</sup> A. Hosomi, H. Kobayashi, and H. Sakurai, *Tetrahedron Letters*, **21**, 955 (1980).

<sup>2</sup> M. Ochiai, M. Arimoto, and E. Fujita, *J.C.S. Chem. Comm.*, 459 (1981).

<sup>3</sup> T. Morita, Y. Okamoto, and H. Sakurai, *Tetrahedron Letters*, **21**, 835 (1980).

**Allyltrimethylsilylzinc chloride**,  $[(CH_3)_3SiCH=CH-CH_2]^-ZnCl^+$  (**1**). This nucleophile is prepared by reaction of allyltrimethylsilane with *sec*-butyllithium and TMEDA in THF at –70° and then with  $ZnCl_2$  at –40°.

**Spiro- $\gamma$ -lactones.**<sup>1</sup> This anion (**1**) has been used to prepare steroidal 17-spiro- $\gamma$ -lactones (equation I) by reaction of a 17-keto steroid at the  $\gamma$ -position. The Sharpless oxidation step can be conducted in the presence of a  $\Delta^4$ -3-keto group. When the



lithium anion of allyltrimethylsilane is used in the reaction some attack at the  $\alpha$ -position also occurs.

<sup>1</sup> E. Ehlinger and P. Magnus, *Tetrahedron Letters*, **21**, 11 (1980).

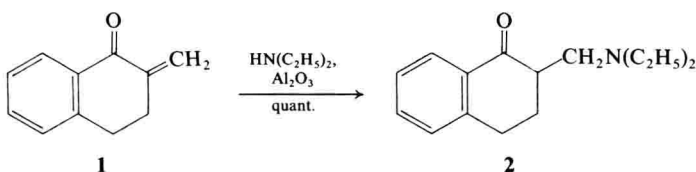
**Alumina**, **1**, 19–20; **2**, 17; **3**, 6; **4**, 8; **6**, 16–17; **7**, 5–7; **8**, 9–13; **9**, 8–11.

**Cleavage of epoxides** (**6**, 16–17; **8**, 10–12). Cleavage of epoxides catalyzed by Woelm neutral alumina is particularly useful in the case of medium-ring epoxides, which are generally rather unreactive and which are liable to undergo transannular reactions. For example, *cis*-cyclooctene oxide supported on neutral alumina is converted to *trans*-2-acetoxycyclooctanol in 78% yield by reaction with acetic acid at

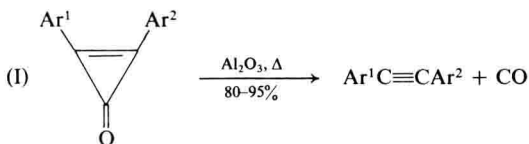
25° for 24 hours.<sup>1</sup> Acetolysis under homogeneous conditions at 60° for 22 hours proceeds in 21% yield.<sup>2</sup>

**Monoesterification of dicarboxylic acids.**<sup>3</sup> Chemiabsorption of a dicarboxylic acid on alumina or silica can be used to effect selective esterification of one acid group with diazomethane. The method was demonstrated by conversion of terephthalic acid,  $C_6H_4-1,4-(COOH)_2$ , into the monomethyl ester in quantitative yield.

**Michael reaction with exocyclic  $\alpha,\beta$ -enones.**<sup>4</sup> Conjugate addition of secondary amines to  $\alpha,\beta$ -enones proceeds readily unless the enone is exocyclic. In such a case the reaction is very slow unless alumina is added as catalyst. Thus the reaction of **1** and diethylamine in the presence of alumina proceeds in 2 hours to give **2** quantitatively.



**Diarylacetylenes.**<sup>5</sup> Thermal decarbonylation of diarylcyclopropenones in refluxing *o*-dichlorobenzene to give diarylacetylenes proceeds in high yield in the presence of alumina (equation I).



<sup>1</sup> G. H. Posner, M. Hulce, and R. K. Rose, *Org. Syn.* submitted (1980).

<sup>2</sup> A. C. Cope, S. Moon, and P. E. Peterson, *Am. Soc.*, **81**, 1650 (1959).

<sup>3</sup> T. Chihara, *J.C.S. Chem. Comm.*, 1215 (1980).

<sup>4</sup> S. W. Pelletier, A. P. Venkov, J. Finer-Moore, and N. V. Mody, *Tetrahedron Letters*, **21**, 809 (1980).

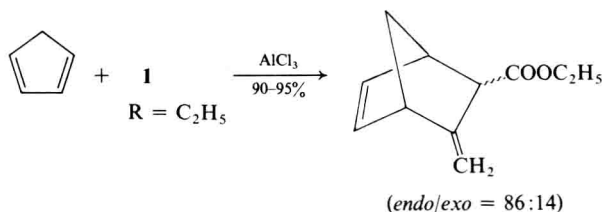
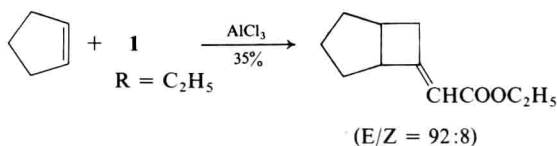
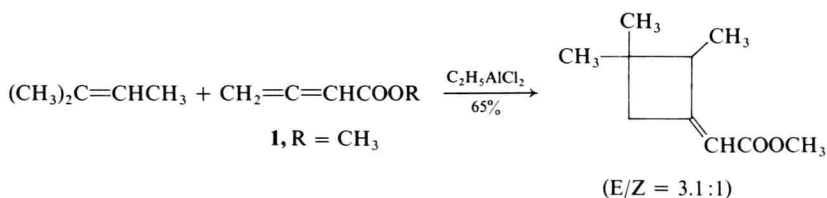
<sup>5</sup> D. H. Wadsworth and B. A. Donatelli, *Synthesis*, 285 (1981).

**Aluminum chloride**, **1**, 24–34; **2**, 21–23; **3**, 7–9; **4**, 10–15; **5**, 10–13; **6**, 17–19; **7**, 7–9; **8**, 13–15; **9**, 11–13.

**[2 + 2] Cycloaddition.** In the presence of either  $C_2H_5AlCl_2$ <sup>1</sup> or  $AlCl_3$ ,<sup>2</sup> esters of 2,3-butadienoic acid (**1**) undergo [2 + 2] cycloadditions at the 3,4-double bond with acyclic or cyclic alkenes to give cyclobutylideneacetic esters. The reaction is considered to involve the vinyl cation  $H_2C=\overset{+}{C}-CH=C(OR)O\bar{A}lCl_3$ . A mixture of

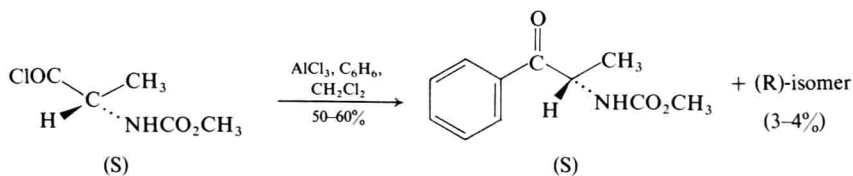
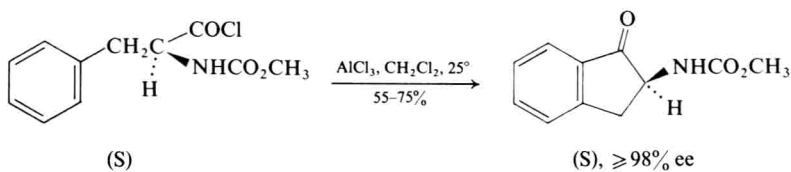
(E)- and (Z)-isomers is formed, but the (E)-isomer is favored. The ester undergoes Diels-Alder reactions (thermal and catalyzed) at the 2,3-double bond.

Examples:



**Chiral  $\alpha$ -amino ketones.**<sup>3</sup> N-Methoxycarbonyl-protected  $\alpha$ -amino acid chlorides undergo Friedel-Crafts reactions with high retention of chirality. Cbz-protected amino acids under the same conditions give intractable tars.

Examples:



Cyclic chiral  $\alpha$ -amino ketones are reduced by  $\text{BH}_3$ ,  $\text{NaBH}_4$ , or  $\text{LiAlH}_4$  predominantly to chiral *trans*- $\alpha$ -amino alcohols (80–90% yield).



<sup>1</sup> B. B. Snider and D. K. Spindell, *J. Org.*, **45**, 5017 (1980).

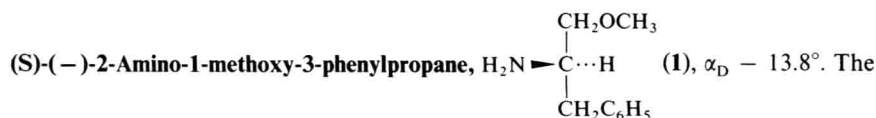
<sup>2</sup> H. M. R. Hoffmann, Z. M. Ismail, and A. Weber, *Tetrahedron Letters*, **22**, 1953 (1981).

<sup>3</sup> D. E. McClure, B. H. Arison, J. H. Jones, and J. J. Baldwin, *J. Org.*, **46**, 2431 (1981).

### Aluminum chloride–Ethanethiol, 9, 13.

**Dealkylation of esters.**<sup>1</sup> The combination of an aluminium halide and a dialkyl sulfide is more potent than the aluminum halide–ethanethiol system. Dealkylation of higher esters is possible with the newer system. The order of activity of sulfides is tetrahydrothiophene > (CH<sub>3</sub>)<sub>2</sub>S > (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>S.

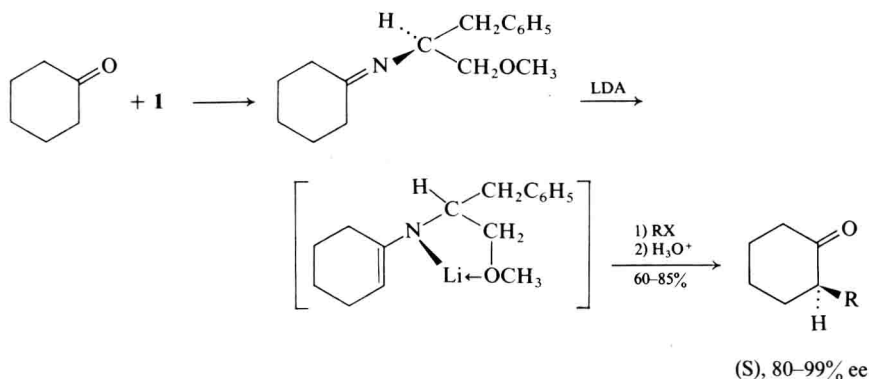
<sup>1</sup> M. Node, K. Nishide, M. Sai, K. Fuji, and E. Fujita, *J. Org.*, **46**, 1991 (1981).



methoxy amine is prepared from (S)-phenylalanine by NaBH<sub>4</sub> reduction followed by methylation.

**Enantioselective alkylation of ketones.** Chiral imines prepared from cyclic ketones and **1** on metalation and alkylation are converted to chiral 2-alkylcycloalkanones in 87–100% enantiomeric purity.<sup>1</sup> The high enantioselectivity is dependent on chelation of the lithium ion in the anion by the methoxyl group, which results in a rigid structure.

Example:



On double alkylation of cyclohexanone, (2S,6S)-2,6-dimethylcyclohexanone is obtained in 85% ee.

Enantioselective alkylation of acyclic ketones is also possible,<sup>2</sup> but in this case the enantioselectivity is dependent on the geometry of the chiral imine. Thus the product of thermodynamic alkylation (of the E-isomer) is the enantiomer of the