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# Three-Carbon Homologating Agents

JOHN C. STOWELL

*Department of Chemistry, University of New Orleans, Lake Front, New Orleans, Louisiana 70148*

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## Contents



John C. Stowell was born in Passaic, NJ, in 1938, and received his B.S. degree in chemistry from Rutgers University in 1960. His Ph.D. degree in organic chemistry was granted by Massachusetts Institute of Technology in 1964 where he worked with Dr. Frederick D. Greene on free-radical termination reactions and prepared the first diaziridinone. He joined the Central Research division of 3M Company in St. Paul, MN, for 4 years. In 1969 he became a postdoctoral fellow at The Ohio State University with Dr. Leo A. Paquette. He prepared and studied various $(CH)_{12}$ and benzo $(CH)_{10}$ compounds including thermal and silver-catalyzed rearrangements. In 1970 he joined the faculty of the University of New Orleans, then known as Louisiana State University in New Orleans. His research there included three-carbon homologating agents, three- and four-membered ring heterocycles, formimidoyl halides, sterically hindered amines and nitroso compounds, and heterogeneous concurrent strong acid and base catalysis.

## I. Introduction

There are over 100 reagents useful for the extension of organic molecules by three carbons with some functionality at the new terminus. The literature on this subject is not indexed as such, therefore a thorough search is not possible and I expect there are other useful reagents unintentionally omitted here. Nevertheless this review will make the surprisingly large number of alternative reagents more readily accessible to the synthetic organic chemist.

The reagents selected here carry only three carbons but there are many other closely related reagents carrying methyl groups or other structures that operate by the same principles found here. Thus the reader may use this review in planning incorporation of branched extensions.

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The subject consists of two fundamental classes, the nucleophilic and the electrophilic reagents. Within these two categories the organization is based on the degree of unsaturation in the chain and the level of oxidation in the functional group. One should therefore keep in mind that a reagent in any part of the review might be useful for a certain synthesis if it is followed with an oxidation or reduction reaction.

## II. Nucleophilic Reagents

The choice of functionality that may be placed on the third carbon of a nucleophilic reagent is limited owing to the facile intramolecular attack leading to cyclopropanes. Groups that would ordinarily be stable toward intermolecular attack by Grignard or lithium reagents may not withstand the intramolecular attack under similar conditions. For example, simple alkyl ethers are stable while phenyl ethers are not. However, many useful reagents have been devised where the electrophilic character of the $\beta$-functionality is reduced or where the nucleophilic site is rendered less potent by delocalization either allylically in the chain or outward to other temporary substituents. In other cases the three carbons are delivered with a double or triple bond in the chain that geometrically prevents three-membered ring formation. These may be reduced to the saturated chain at a later stage.

### A. Reagents Providing Functional Chains with Saturated $\alpha$-, $\beta$-, and $\gamma$-Carbons

#### 1. Ethers and Alcohols

In 1904 Hamonet[1] showed that a Grignard reagent could be prepared from 3-iodopropyl *n*-pentyl ether and that it would couple with bromomethyl *n*-pentyl ether to give a diether. 1,4-Dimethoxybutane could be prepared similarly. Yields and other details were not given.

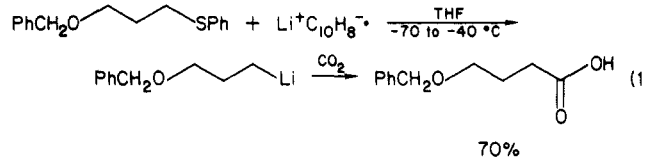
Where a hydroxyl group is the desired functionality, various protecting groups have been used during the nucleophilic step. Some ethers were suitable while others were not. 3-Bromopropyl phenyl ether as well as the iodo compound gave prompt 1,3-elimination to afford cyclopropane plus the phenoxide salt when treated with magnesium in ether.[2,3] A Grignard reagent could be prepared from the methyl ether, however, and it was added to a nitrile to afford a keto ether in low yield. In this case the ether was cleaved with hot concentrated hydrobromic acid at a later stage and ultimately used to prepare a pyrrolidine ring. Even the alkyl ethers show instability at higher temperatures. For example, the Grignard reagent from 3-bromopropyl ethyl ether gives cyclopropane when heated to about 75 °C in benzene.[4]

A tertiary ether is more readily removed. Thus *tert*-amyl 3-bromopropyl ether gave the Grignard reagent in ether in about 80% yield. This could be carbonated to give 4-(*tert*-amyloxy)butyric acid (53% yield) or added to benzaldehyde, acetone, or cyclohexanone in 90% yields.[5] Heating the hydroxy ether products with *p*-toluenesulfonic acid cleaves the ether but also causes cyclization to the corresponding tetrahydrofurans in 70–90% yields.

A benzyl ether can be removed by mild hydrogenolysis but again the Grignard reagent shows some instability. The benzyl ether of 3-bromo-2-methyl-1-propanol was converted to the Grignard reagent in THF while cooling to 30–40 °C. This was added to cyclododecanone and cleaved with hydrogen to give 3-(1-hydroxycyclododecyl)-2-methylpropanol in 65% yield.[6]

The phenylthio group, in contrast to the oxygen ethers, does not undergo a 1,3-elimination. Thus, 3-bromopropyl phenyl sulfide and magnesium in THF or ether gives the Grignard reagent which could be acylated with a mixed anhydride at low temperature or added to an aldehyde or ketone to give alcohols. The phenylthio group may then be removed by $\alpha$-halogenation and hydrolysis with CuO and $CuCl_2$ to give a $\gamma$-keto or $\gamma$-hydroxy aldehyde.[7-9]

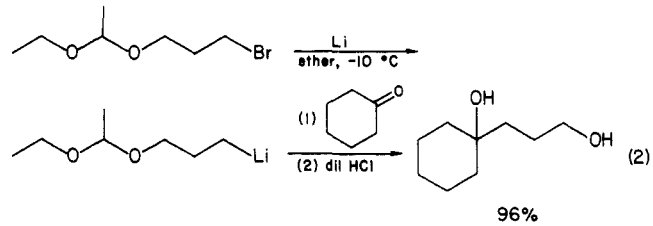
The analogous lithium reagents containing benzyl or phenylthio ether groups can be prepared using lithium dispersion or lithium naphthalene.[10] 3-Chloropropyl phenyl sulfide gives [3-(thiophenoxy)propyl]lithium, and 3-(benzyloxy)propyl phenyl sulfide gives [3-(benzyloxy)propyl]lithium (eq 1).




(1)

70%

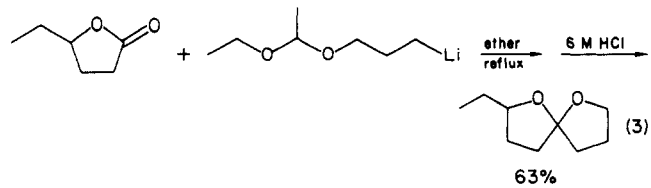
Acetal protection of an alcohol function may be removed easily with mild acid. Eaton[11,12] used ethyl vinyl ether to protect 3-bromo- and 3-chloropropanol. Both of these halo acetals react rapidly with lithium metal in ether, starting at room temperature and then cooling to between −15 and −5 °C for most of the reaction. The organolithium reagent is stable at −30 °C for months but at room temperature it slowly decomposes to cyclopropane and other products. The lithium reagent adds readily to ketones,[11-14] and the acetal may be hydrolyzed rapidly at room temperature with dilute aqueous ethanolic hydrochloric acid to afford 1,4-diols in high yield (eq 2). This hydrolysis is mild enough to




(2)

96%

leave the tertiary alcohol function undisturbed. This reagent also reacts with $\gamma$-lactones to give spiroketals (eq 3).[15]



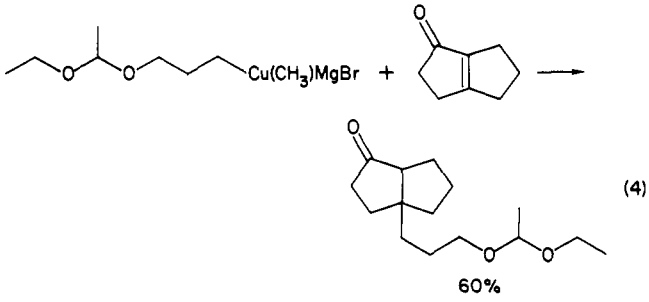

(3)

63%

The corresponding Grignard reagent would not form in ether[11] but it could be prepared from magnesium turnings in THF at 0–10 °C in about 65% yield.[16]

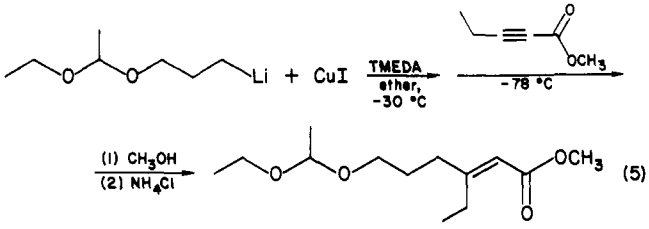
Catalytic or larger amounts of copper salts were used with the lithium or magnesium reagent to give coupling and Michael reactions. For instance cuprous iodide and the lithium reagent gave conjugate addition to cyclopentenone (50%). It is not effective with highly $\beta$-

substituted substrates but a mixed magnesium cuprate will serve as shown in eq 4.[17] The mixed cuprate from



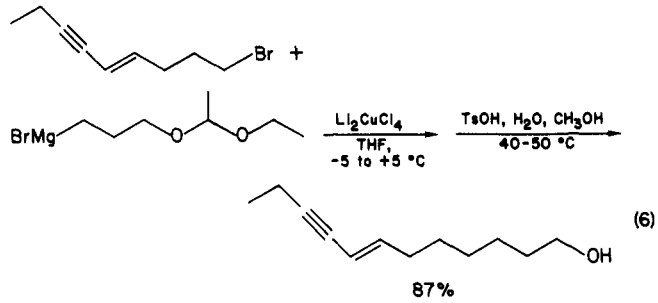

(4)

copper *tert*-butylacetylide was used in a conjugate addition to an $\alpha,\beta$-unsaturated lactone (56%).[18] The polymeric complex prepared from lithium reagent and an equivalent amount of cuprous iodide and TMEDA gave syn addition to an acetylenic ester (eq 5).[19] The



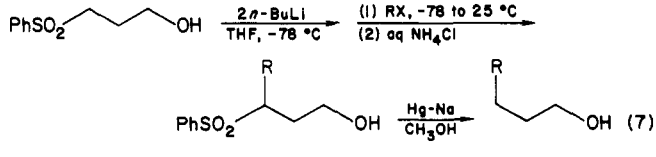

(5)

mixed cuprate from copper *tert*-butoxide was used similarly in additions to dimethyl acetylenedicarboxylate (75%) and dimethyl allenedicarboxylate (80%).[20] Coupling with alkyl halides[16] was carried out using copper salt catalysis (eq 6).[21] This same coupling was also performed with the lithium reagent in 50% yield.[22]




(6)

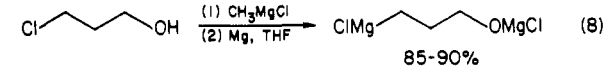
The sensitivity of the foregoing acetals and esters toward intramolecular attack by the nucleophilic site requires maintaining low temperatures. A simple alternative is to leave the alcohol unprotected but use a base to convert it to the alkoxide. A temporary sulfone group allows generation of the carbanion also by removal of a proton by a base. Two equivalents of *n*-butyllithium gave the C,O dianion which was then C-alkylated as shown in eq 7.[23]




(7)

| RX | alkylation yield, % | redn yield, % |
|---|---|---|
| *n*-butyl iodide | 90 | 80 |
| *n*-hexyl bromide | 90 | 86 |
| *n*-octyl iodide | 100 | 57 |
| 1-chloro-3-methyl-2-butene | 54 | - |
| benzyl chloride | 80 | 83 |

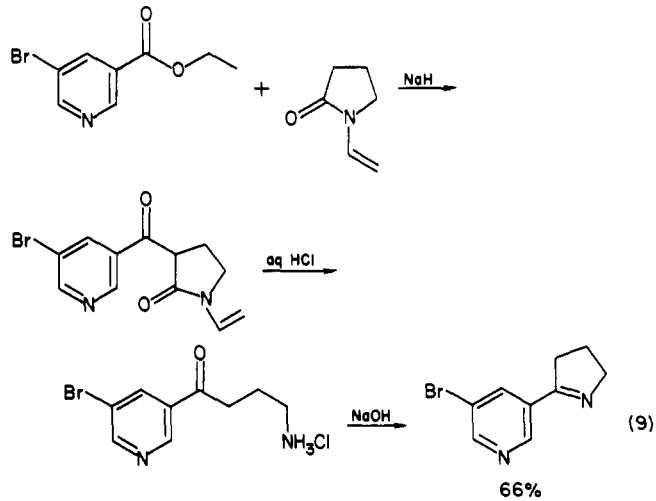
A remarkably simple alternative is now available with the discovery that the Grignard reagent can be prepared directly from the chloroalkoxide. Methyl or isopropyl magnesium chloride gives the alkoxide from 3-chloro-1-propanol at −20 °C in THF. This salt is soluble enough to give 0.3 N solutions at room temperature. It will react with magnesium in refluxing THF with the aid of a small amount of 1,2-dibromoethane to give the Grignard reagent (eq 8). This reagent gives all the usual reactions[24] including addition to ketones, coupling with allylic halides,[25] copper-catalyzed conjugate addition[26] and alkylation in 75–90% yields.




(8)

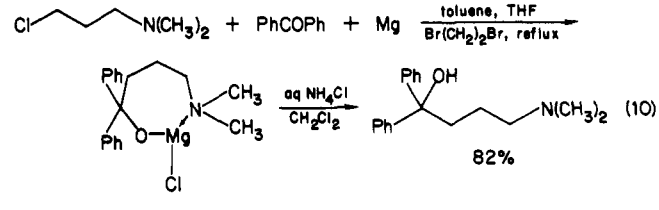
### 2. Amines

The enolate of *N*-vinylpyrrolidone may be acylated with esters. Hydrolysis of the resulting pyrrolidone with accompanying decarboxylation affords a keto amine. Thus three of the ring carbon atoms and the nitrogen constitute the homologation (eq 9).[27]




(9)

A dimethylamino group may be carried on the third carbon of a Grignard reagent if a highly modified procedure is used. The Grignard reagent is unstable so it is generated in the presence of a ketone electrophile so that it can be trapped as formed. The solvent of choice is toluene with a small amount of THF. The very stable magnesium alkoxide product precipitates and is filtered and washed with toluene before hydrolyzing in aqueous ammonium chloride (eq 10).[28]



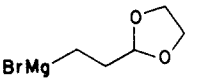

(10)

### 3. Bromides

1-Lithio-3-bromopropane is too unstable to be useful. Thus House et al. found that *n*-butyllithium and 1-bromo-3-iodopropane gave exchange at −110 °C as evidenced by formation of 1-iodobutane but protonation did not give any 1-bromobutane. Presumably cyclopropane formation is fast even at −110 °C.[29]

Magnesium leads to somewhat different results.[30] 1,3-Dibromopropane reacts with triply sublimed mag-

Table I. Reactions of



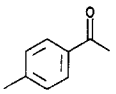
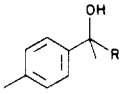
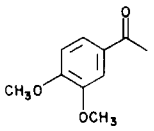
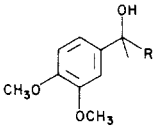
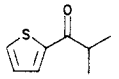
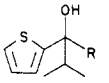
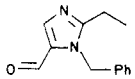
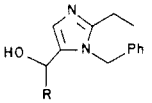
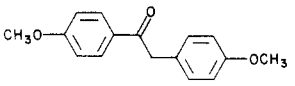
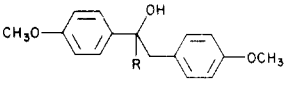
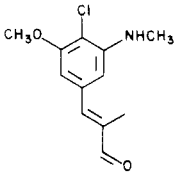
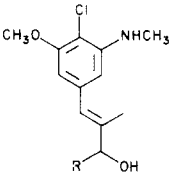
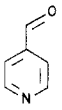
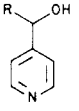
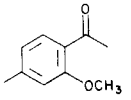
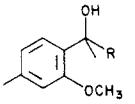
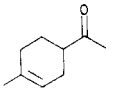
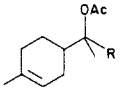
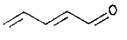
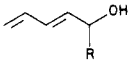
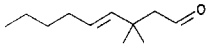
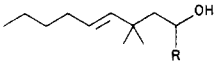
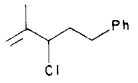
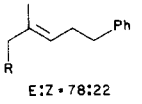
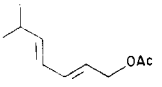
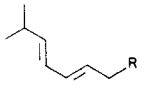
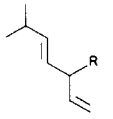
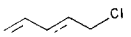
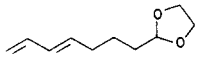
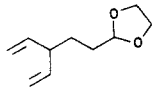
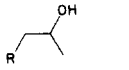
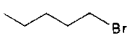
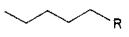
| electrophile | product[a] | yield, % | catalyst | ref |
|---|---|---|---|---|
|  |  | >55 | | 33 |
|  |  | 80 | | *c* |
|  |  | 90 | | *d* |
|  |  | 85 | | *e* |
|  |  | 90 | | *f* |
|  |  | 94 | | *g* |
|  |  | 95 | | *h* |
|  |  | 90 | | *i* |
|  |  | 78 | | *j* |
|  |  | 66-81 | | *k* |
|  |  | | | *l* |
|  |  E:Z = 78:22 | 83 | *b* | *m* |
|  |  | 65 | *b* | *k*, *n* |
| |  | 10 | | |
|  |  | 66 | | *o* |
| |  | 12 | | |
|  |  | 54 | *b* | 34 |
|  |  | 88 | *b* | *p* |

Table I (*Continued*)

| electrophile | product[a] | yield, % | catalyst | ref |
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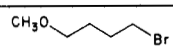
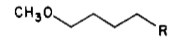
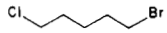
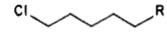
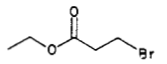
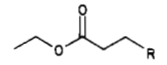
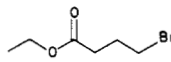
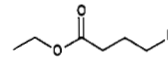
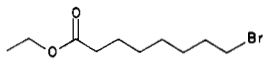
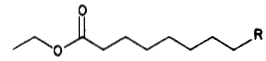
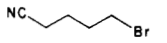
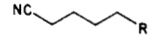
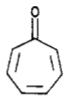
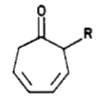
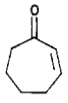
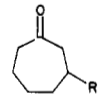
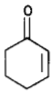
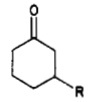
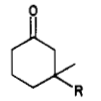
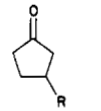
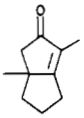
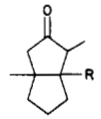
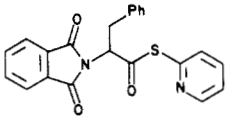
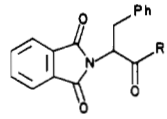
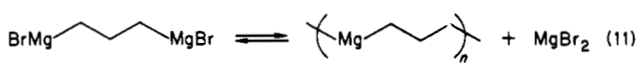
|  |  | 49 | *b* | *p* |
|  |  | 89 | *b* | *p* |
|  |  | 28 | *b* | *p* |
|  |  | 66 | *b* | *p* |
|  |  | 74 | *b* | *p* |
|  |  | 81 | *b* | *p* |
|  |  | 85 | | *q* |
|  |  | (87) | *b* | 34 |
|  |  | (85) | *b* | 34 |
|  |  | (74) | *b* | 34 |
|  |  | (77) | *b* | 34 |
|  |  | 68 | *b* | 103 |
|  |  | 35 | | *r* |

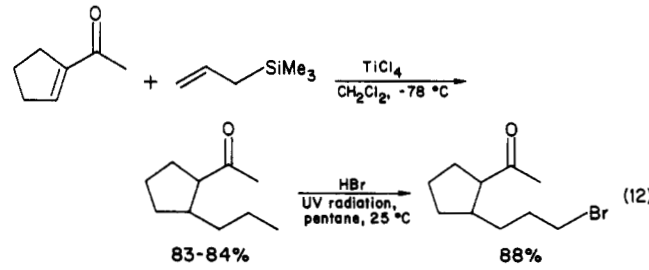
[a] R = 2-(1,3-dioxolanyl)ethyl. [b] $Li_2CuCl_4$ or CuBr·$Me_2S$. [c] Loozen, H. J. J. *J. Org. Chem.* **1975**, *40*, 520. [d] Loozen, H. J. J.; Godefroi, E. F. *J. Org. Chem.* **1973**, *38*, 1056. [e] Loozen, H. J. J.; Godefroi, E. F. *J. Org. Chem.* **1973**, *38*, 3495. [f] Hatam, N. A. R.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 461. [g] Gotschi, E.; Schneider, F.; Wagner, H.; Bernauer, K. *Helv. Chim. Acta* **1977**, *60*, 1416. [h] Loozen, H. J. J.; Godefroi, E. F.; Besters, J. S. M. *J. Org. Chem.* **1975**, *40*, 892. [i] Goldberg, O.; Driding, A. S. *Helv. Chim. Acta* **1977**, *60*, 964. [j] Feldstein, G.; Kocienski, P. J. *Synth. Commun.* **1977**, *7*, 27. [k] Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. [l] Pattenden, G.; Whybrow, D. *Tetrahedron Lett.* **1979**, 1885. [m] Macdonald, T. L.; Narayanan, B. A.; O'Dell, D. E. *J. Org. Chem.* **1981**, *46*, 1504. [n] Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1930**, *45*, 4264. [o] Gras, J-L.; Bertrand, M. *Tetrahedron Lett.* **1979**, 4549. [p] Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Org. Chem.* **1983**, *48*, 1767. [q] Rigby, J. H. *Tetrahedron Lett.* **1982**, *23*, 1863. [r] Almquist, R. G.; Chao, W-R.; Ellis, M. E.; Johnson, H. L. *J. Med. Chem.* **1980**, *23*, 1392.

nesium in ether at room temperature to give the bis(bromomagnesio)propane in about 30% yield. The reagent was purified by precipitating the organomagnesium reagent upon changing from ether to THF solvent, and then reconstituting the Grignard with magnesium bromide (eq 11). The double Grignard reagent may be protonated, carbonated, or exchanged with $HgBr_2$ to give the expected products.



(11)

A bromopropyl group may be introduced indirectly. Allyltrimethylsilane will give conjugate addition to $\alpha,\beta$-enones in the presence of titanium tetrachloride,[31] and the product may be treated with hydrogen bromide under free radical conditions (eq 12).[29]



(12)

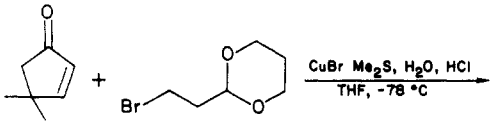
### 4. Propionaldehyde Homoenolate Equivalents

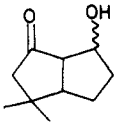
The highly susceptible aldehyde function must be protected in these nucleophilic reagents. Three com-

mon hydrolyzable derviatives are the acetals, enol ethers, and vinyl halides. One may also generate the aldehyde by oxidation after the carbon–carbon bond formation. Oxidation of the alcohols generated as in section IIA1 or oxidative cleavage of an alkene are useful examples.

Feugeas[32] showed that under ordinary conditions acyclic β-halo acetals or cyclic β-halo ketals do not give stable Grignard reagents. As with the ether reagents, cyclopropyl ring closure occurs. Büchi[33] found that a Grignard reagent could actually be made from 2-(2-bromoethyl)-1,3-dioxolane in THF if the temperature is kept below 35 °C. An important interference is the formation of up to 30% of the Wurtz coupling product during Grignard reagent formation.[34] This may be minimized by using freshly reduced magnesium powder or more conveniently by using freshly ground excess magnesium turnings. Eaton[12] observed that this Grignard reagent polymerized readily above 35 °C and decomposed slowly even at room temperature. The corresponding lithium reagent decomposed directly upon formation. With careful control of temperature, the Grignard reagent has been used successfully with a variety of electrophiles. The reactions include addition to aldehydes and ketones, coupling with allylic halides, copper-catalyzed coupling with primary halides, and copper-catalyzed conjugate addition (Table I). The resulting acetals were hydrolyzed to produce a wide variety of aldehydes.

The thermal instability of the Grignard reagent from 2-(2-bromoethyl)-1,3-dioxolane may be avoided altogether by using the corresponding dioxane instead. This gives a Grignard reagent with ordinary magnesium turnings in THF at reflux with no cyclopropyl ether formation, Wurtz coupling, or polymerization.[35] At −78 °C it reacts selectively with acid chlorides to give ketones in high yield with no appreciable attack on the product to give any tertiary alcohols (Table II). At room temperature, the Lewis acid character of the solution catalyzes the ring opening of the THF solvent with the acid chloride. The low reactivity toward carbonyl compounds is similar to that found by Ponaras[36] for the Grignard reagent from 2-methyl-2-(2-bromoethyl)-1,3-dioxolane. Hydrolysis of the acetal provides γ-keto aldehydes which are of use in the synthesis of cyclopentenones and pyridazines. The dioxane reagent gives coupling reactions with halides and tosylates under copper catalysis.[37,38] In some cases the yields are best when the coupling is finished at reflux in THF taking advantage of the thermal stability of the reagent, and in one case the lack of reactivity toward an ester function (Table II). Copper catalysis also leads to conjugate addition to α,β-unsaturated ketones as in eq 13.[39] The chloro Grignard was used similarly on (+)-carvone.[40]



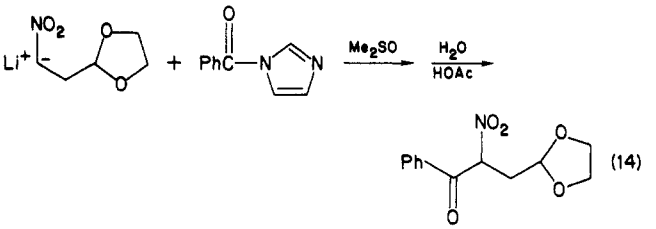



(13)

78%

The aqueous hydrolysis of the dioxane protection is an unfavorable equilibrium but acetone–aqueous HCl gives 70% yields of aldehydes.[38] Conversion to the dimethyl acetal followed by aqueous acid hydrolysis gives aldehydes in high yield.[41,42] Other methods have been devised[35,41] including using a subsequent reaction to drain the aldehyde from the equilibrium as in eq 13.[39,40,43]

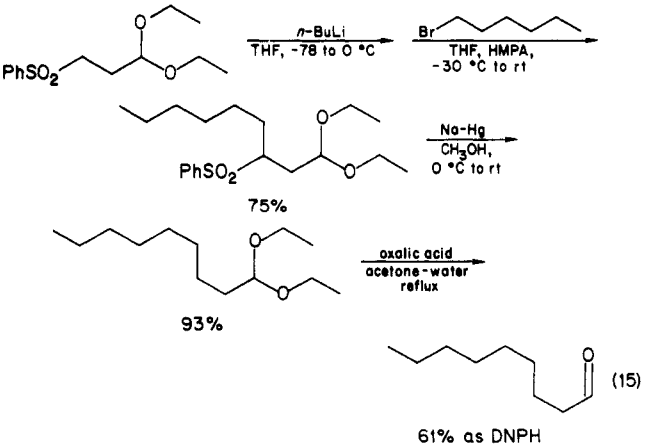
Nitro or sulfonyl groups in the β-position of acetals of propionaldehyde allow generation of the carbanion by use of a base. These delocalized carbanions do not give cyclopropyl byproducts but do react with a variety of electrophiles. Corey showed that 3-nitropropanal dimethyl acetal gives conjugate addition to 9-cyano-2-nonenal in the presence of base. The product was ultimately converted to $PGE_1$ and other prostaglandins. At a later stage the nitro group was reduced to the amine and still later converted to a keto group via N-bromination and dehydrobromination.[44,43] The similar 2-(2-nitroethyl)-1,3-dioxolane was converted to the lithio salt with lithium ethoxide and acylated in $Me_2SO$ solution with acylimidazoles (eq 14).[46] THF is not suitable because the lithio salt appears to be insoluble. An analogous 1,3-oxathiolane was used in further prostaglandin syntheses.[47]




(14)

95%

The phenylsulfonyl group is less stabilizing than a nitro group, therefore *n*-butyllithium is required as base. The carbanion from either cyclic or acyclic acetals of β-(phenylsulfonyl)propionaldehyde is readily alkylated with various primary halides in 75–92% yields. Isopropyl halides give 42–61% yields in the presence of HMPA.[48,49] Reductive cleavage of the phenylsulfonyl group with sodium amalgam followed by acetal hydrolysis provides the β-alkylated propionaldehydes (eq 15).[49] The anion may also be alkylated with epoxides

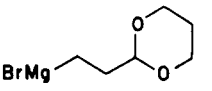


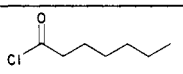
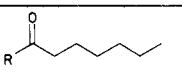
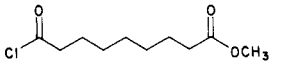
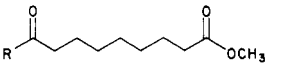

(15)

61% as DNPH

in 61 to 79% yields. Reductive removal of the phenylsulfonyl group and hydrolysis gives δ-lactols.[50] Esters will acylate the anion. In this case reduction gives the acetals of γ-keto aldehydes[51] (eq 16).[52] Two equivalents

Table II. Reactions of



| electrophile | product[a] | yield, % | catalyst | ref |
|---|---|---|---|---|
|  |  | 92 | | 37 |
|  |  | 91 | | c |
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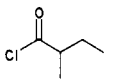
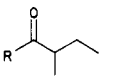
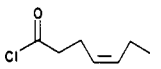
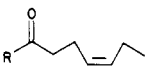
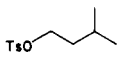
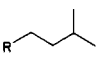
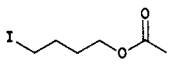
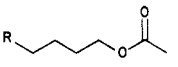
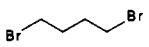
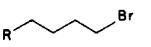
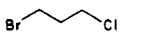
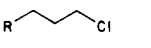
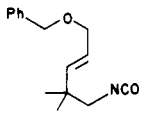
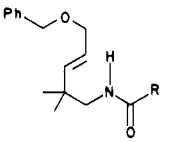
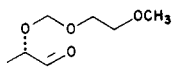
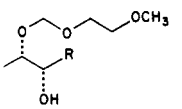
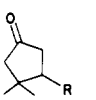
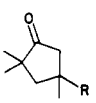
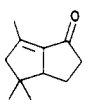
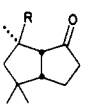
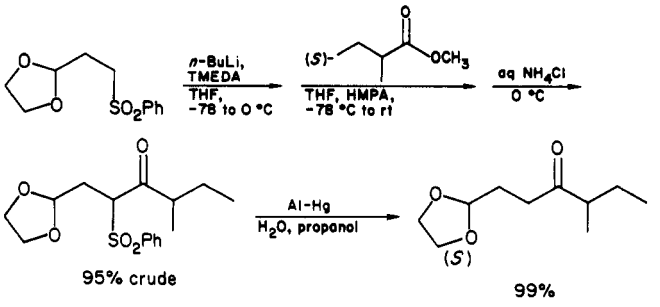
|  |  | 64 | | |
|  |  | >68 | | e |
|  |  | 77 | b | 37 |
|  |  | 77 | b | 37 |
|  |  | 86 | b | 38 |
|  |  | 81 | b | 38 |
|  |  | >62 | | f |
|  |  | 75 | | g |
|  |  | 79 | b | h |
|  |  | 48 | b | h |
|  |  | 68 | b | h |

[a] R = 2-(1,3-dioxan-2-yl)ethyl. [b] CuI, $Li_2CuCl_4$, or CuBr·$Me_2S$. [c] Stowell, J. C., unpublished results. [d] Dodge, J.; Hedges, W.; Timberlake, J. W.; Trefonas, L. M.; Majeste, R. J. *J. Org. Chem.* **1978**, *43*, 3615. [e] Sato, T.; Kawara, T.; Sakata, K.; Fujisawa, T. *Bull. Soc. Chem. Jpn.* **1981**, *54*, 505. [f] Hart, D. J.; Yang, T-K. *Tetrahedron Lett.* **1982**, *23*, 2761. [g] Kelly, T. R.; Kaul, P. N. *J. Org. Chem.* **1983**, *48*, 2775. [h] Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352.

of *n*-butyllithium must be used here since the β-ketosulfone product is more acidic than the starting material.




(16)

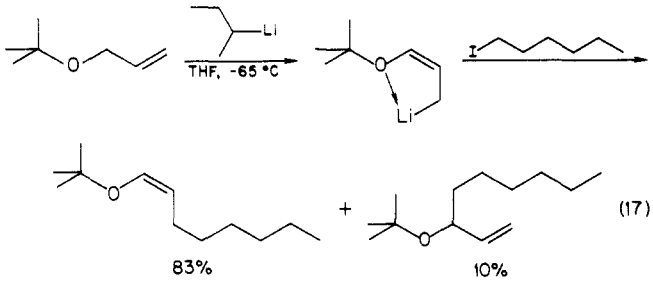
The sulfone acetals may be prepared by the reaction of sodium thiophenoxide with β-chloropropionaldehyde diethyl acetal to give the sulfide which may be oxidized to the sulfone.[49,48] Treatment of acrolein with *p*-toluenesulfinic acid and ethylene glycol gives the dioxolane sulfone directly in 67% yield.[53]

If the reductive cleavage of the sulfone group is replaced with elimination by base, the method gives α,β-unsaturated aldehydes.

Enol derivatives are alternatives to acetals for the protection of aldehydes. They have the advantage of giving resonance-stabilized carbanions that are available by proton removal by a base. However this is also a disadvantage because electrophiles may react at either

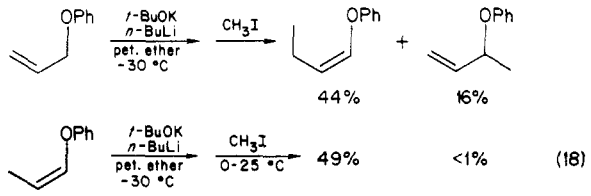
of the sites of delocalized carbanionic charge. Reaction $\gamma$ to the heteroatom gives three-carbon homologation but with most reagents attachment $\alpha$ to the heteroatom occurs in significant amounts. Variation of the heteroatom group affects the $\alpha$ to $\gamma$ product ratio, some cases being highly $\gamma$-selective.

Allyl ethers are rapidly deprotonated by *sec*-butyllithium in THF at −65 °C. The resulting carbanions react with alkyl halides at $\alpha$- and $\gamma$-positions to give mixtures of enol ethers and allyl ethers. If *tert*-butyl allyl ether is used, $\gamma$-alkylation is favored. Thus 1-iodohexane gave the *tert*-butyl enol ether of nonanal in 83% yield along with a 10% yield of the $\alpha$-alkylated allyl ether (eq 17).[54] Allyl triethylsilyl ether gave similar results,[55] while smaller groups give more of the $\alpha$-alkylation product.



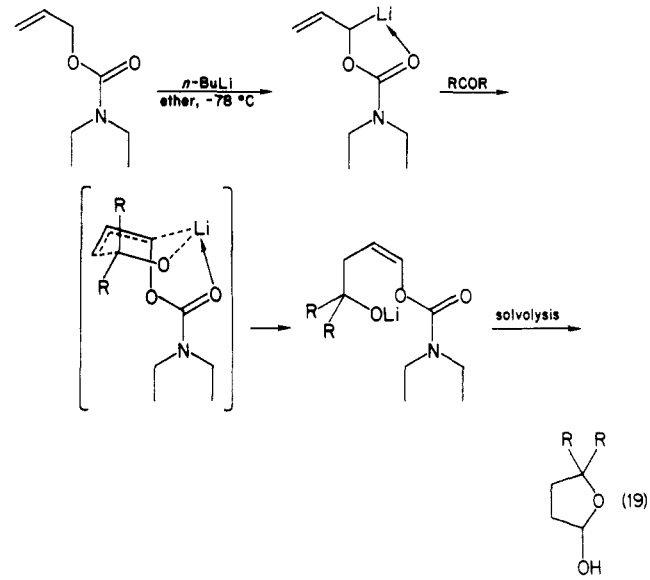

(17)

Alkylation may be occurring via a four-membered cyclic transition state at the site of lithium cation coordination which in the above case is determined by steric hindrance. Five-membered ring chelation in the $\gamma$-lithio reagent may explain the *Z* stereochemistry of the enol ether product (eq 17). If a tetrahydropyranyl allyl ether is used, the lithium is probably chelated at the preferred $\alpha$-position and nearly all the alkylation is $\alpha$-product.[56] Further indication of the importance of chelation is seen in the fact that alkylation of phenyl allyl ether and of phenyl (*Z*)-1-propenyl ether give different product ratios (eq 18).[57] The latter may give all (*Z*)-chelated lithium ions while the former may give some (*Z*)-chelated plus some (*E*)-nonchelated intermediates.




(18)

Addition to carbonyl groups gives largely the opposite result. The trimethylsilyl ether gives almost exclusively addition at the $\alpha$-position and the *tert*-butyl ether gives mostly $\alpha$-reaction. The best yield of $\gamma$-product occurs when the smallest group is present in the ether, that is with methyl allyl ether but even here 28% of the product was from reaction at the $\alpha$-position.[58] The $\alpha$-chelating anion from allyl *N,N*-diethylcarbamate ester gives better than 95% $\gamma$ selectivity in most cases to afford $\gamma$-hydroxyenol carbamates (eq 19).[59,60] This high selectivity may be the result of a six-membered ring transition state including the $\alpha$-chelated lithium. This too leads to (*Z*)-enol derivatives. Solvolysis of the enol carbamate gives a lactol which is readily oxidized to a lactone.

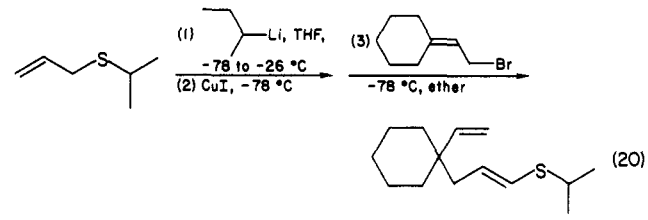



(19)

Other heteroatoms may temporarily serve in place of the oxygen of allyl ethers. These include sulfur, silicon, and nitrogen. Allyl thioethers have been deprotonated and treated with electrophiles to give various ratios of $\alpha$- and $\gamma$-products. The subsequent removal of sulfur may be done in ways that give aldehydes or $\alpha,\beta$-unsaturated alcohols or iodides.

Phenyl allyl thioether was converted to the anion with potassium *tert*-butoxide and *n*-butyllithium and then treated with methyl iodide. Up to 55% of $\gamma$-alkylation was possible but much $\alpha$-alkylation always accompanied this.[57] Chelating allyl thio compounds all gave largely $\alpha$-alkylation and were not used for aldehyde preparation.[61]

If the electrophile is an allyl halide and the cation is copper a highly selective $S_N2'$ alkylation occurs at the $\gamma$-position (eq 20).[62] However the organocopper reagent again adds to carbonyl groups at the $\alpha$-position.

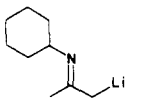
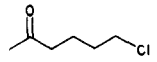
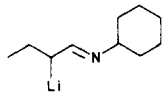
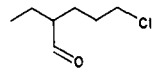
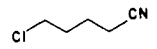
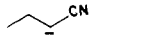
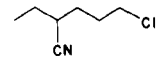
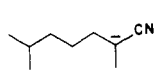
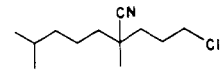
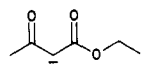
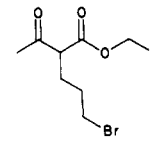
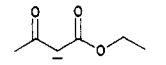
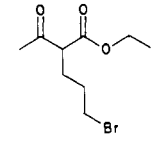



(20)

The addition of the lithio compound to carbonyl groups may be directed to the $\gamma$-position by high steric hindrance at the $\alpha$-position and the use of HMPA. The anion from 1-(phenylthio)-1-(trimethylsilyl)-2-propene in the presence of HMPA adds to *p*-anisaldehyde to give a 72% yield of the $\gamma$-product and only 1% of the $\alpha$-product.[63] This reagent also gives exclusive $\gamma$-addition to $\alpha,\beta$-unsaturated ketones but this consists of substantial amounts of both $\gamma$/1,2- and $\gamma$/1,4-addition. If copper is present in this case, the relative amount of 1,2-addition increases, in contrast with the effect of copper on non-sulfur containing carbanions.

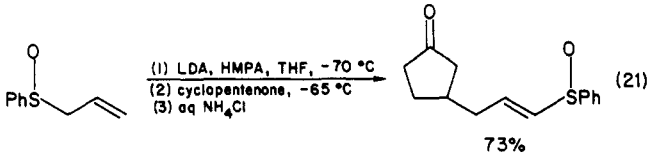
The lithio reagents derived from methyl, *tert*-butyl, and phenyl allyl thioethers will give only conjugate addition to cyclopentenone if HMPA is present. The organocopper reagent likewise gives conjugate addition. However, in both cases the attachment is $\alpha$ to the sulfur atom.[65] In contrast with this, the lithio anion from allyl

Table III. Halopropylation of Enolates

| nucleophile | dihalopropane | product | yield, % | ref |
|---|---|---|---|---|
|  | $Cl(CH_2)_3Br$ |  | 80[a] | c |
|  | $Cl(CH_2)_3Br$ |  | 54[a] | d |
| $^-CH_2CN$ | $Cl(CH_2)_3Br$ |  | 70 | e |
|  | $Cl(CH_2)_3Br$ |  | 57 | e |
|  | $Cl(CH_2)_3Br$ |  | 78 | f |
|  | $Br(CH_2)_3Br$ |  | 50[b] | g |
|  | $Br(CH_2)_3Br$ |  | 26[b] | g |

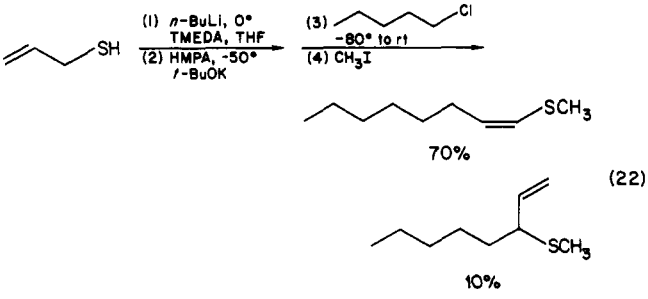
[a] Yield after hydrolysis of imine. [b] The keto esters were hydrolyzed and cyclized to the dihydropyrans (overall yield given). [c] Cuvigny, T.; Larcheveque, M.; Normant, H. *Liebigs Ann. Chem.* **1975**, 719. [d] Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. *J. Org. Chem. Chem.* **1979**, *44*, 1063. [e] Larcheveque, M.; Mulot, P.; Cuvigny, T. *J. Organomet. Chem.* **1973**, *57*, C33. [f] Larcheveque, M.; Cuvigny, T. *Tetrahedron Lett.* **1975**, 3851. [g] Weber, G.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 364.

phenyl *sulfoxide* gives conjugate addition to cyclopentenone exclusively at the γ-position (eq 21).[66]




(21)

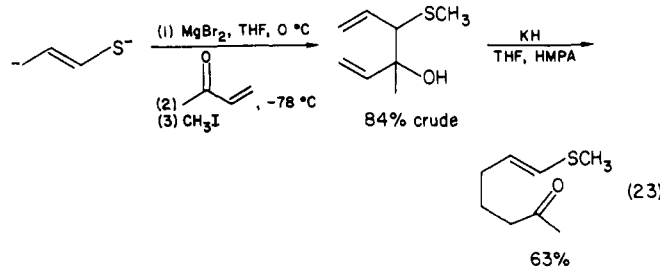
The dianion from allyl mercaptan gives somewhat better selectivity toward γ-alkylation, compared to the thioether anions, when HMPA and potassium *tert*-butoxide are present.[67] For example, alkylation with 1-chlorobutane followed by S-methylation gave a good yield of the cis thioenol ether (eq 22). The dianion




(22)

likewise gives addition reactions with good γ-selectivity. Benzophenone gave a 76% yield of adduct where the γ:α ratio was 90:10. The enol thioether products may be converted to dimethyl acetals by treatment with mercuric chloride in methanol. Octanal dimethyl acetal was obtained in 88% distilled yield.

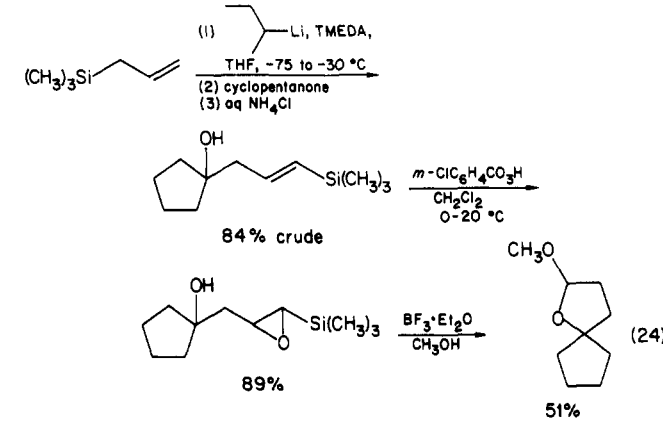
If the dianion from allyl mercaptan is associated with a magnesium cation, addition to carbonyl compounds gives greater than 90% α-products. If the carbonyl compound is α,β-unsaturated, a Cope rearrangement of the initial product gives reattachment at the original γ-position (eq 23).[68] This combination of steps




(23)

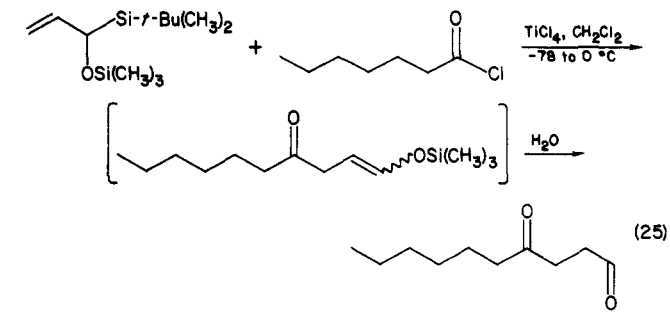
amounts to conjugate addition of the propionaldehyde homoenolate to the α,β-unsaturated carbonyl compound. The initial adduct is a 3-hydroxy 1,5-diene (diastereomers) the alkoxide of which undergoes rearrangement to the thioenol ether of an ε-keto aldehyde. The thioenol ether was converted to the dimethyl acetal, hydrolyzed, and cyclized to methyl cyclopentenyl ketone in 25% overall yield.

Allyltrimethylsilane may be deprotonated with *sec*-butyllithium and the resulting carbanion will add to ketones and aldehydes to give exclusively the γ-product (eq 24).[69] The resulting vinyl silane may be raised to



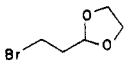
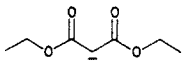
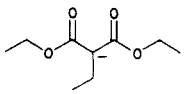
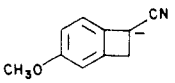
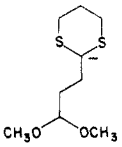
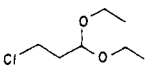
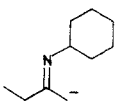
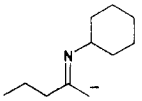
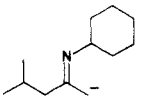
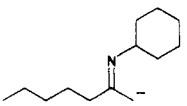
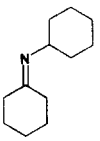

(24)

the aldehyde level of oxidation by epoxidation and $BF_3{\cdot}OEt_2$ catalyzed ring opening in methanol to afford lactol ethers. These may be further oxidized to lactones if desired. If an oxygen is already present in the allylsilane, hydrolysis gives the aldehyde directly. (α-Siloxyallyl)silane (eq 25) is nucleophilic toward the acyl carbonium ion and leads in this case to a γ-keto aldehyde.[70]



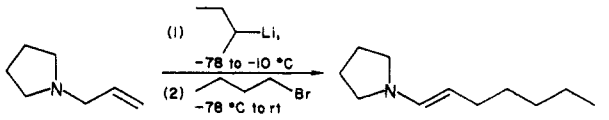

(25)

Table IV. Alkylation of Carbanions by β-Halopropionaldehyde Acetals

| carbanion | acetal | alkylation yield, % | free aldehyde yield, % | ref |
|---|---|---|---|---|
| $PhC{\equiv}C^-$ |  | 82 | 78 | *a* |
|  | | >78 | | *b* |
|  | | 53-55 | | *c* |
|  | | 96 | | *d* |
|  | | 90 | | *e* |
|  |  | 75 | | *f* |
|  | | 58 | 94 | 193 |
|  | | 61 | 96 | 193 |
|  | | 68 | 96 | 193 |
|  | | 64 | 95 | 193 |
|  | | 72 | 95 | 193 |

[a] Johnson, W. S.; Hughes, L. R.; Kloek, J. A.; Niem, T.; Shenvi, A. *J. Am. Chem. Soc.* **1979**, *101*, 1279. [b] Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. [c] Rouch, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. [d] Kametani, T.; Matsumoto, H.; Honda, T.; Fukumoto, K. *Tetrahedron Lett.* **1980**, *21*, 4847. [e] Ellison, R. A.; Lukenbach, E. R.; Chiu, C. *Tetrahedron Lett.* **1975**, 499. [f] Larcheveque, M.; Cuvigny, T. *Tetrahedron Lett.* **1975**, 3851.

The enamine function is very easily hydrolyzed, therefore the anion derived from an allyl tertiary amine should be another useful aldehyde homoenolate anion equivalent. *N*-Allylpyrrolidine is deprotonated by *sec*-butyllithium in THF. Reaction with 1-bromobutane gives the γ-alkylated product selectively (eq 26).[71] The




(26)

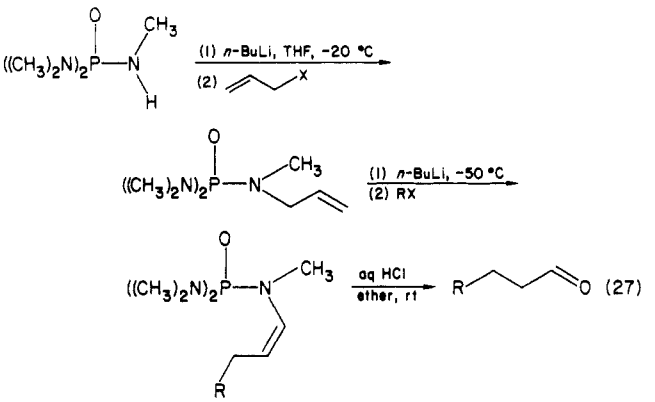
50% yield
> 95% γ alkylation

enamine product could be used for further elaboration at the β-position or hydrolyzed directly to the aldehyde. Addition to aldehydes and ketones once again gave substantial amounts of α-attachment. In fact with zinc cations almost exclusive α-addition occurred.

*N*-Phenyl-*N*-methyl-*N*-allylamine required the stronger base combination potassium *tert*-butoxide and *tert*-butyllithium but gave similar results.[72] Alkylation with 1-bromobutane gave a 69% yield of product which was 94% from γ-alkylation. Isobutylene oxide gave a 70% yield of exclusive γ-alkylation product, isolated as the cyclic aminal. With nonenolizable aldehydes almost equal amounts of α- and γ-product were produced, while enolizable ketones were simply deprotonated.

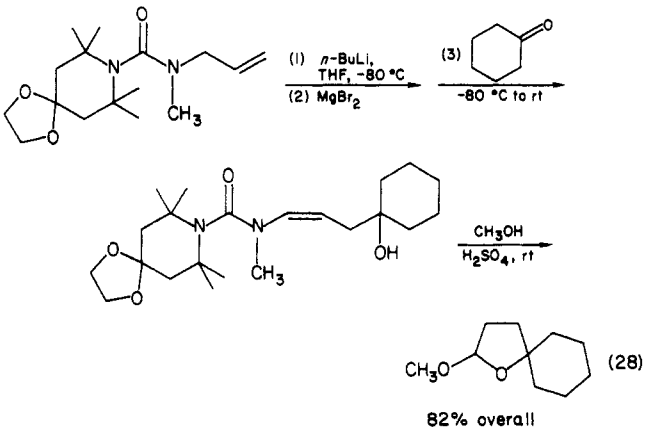
*N*-Allylcarbazole also gave high γ-selectivity in alkylation (93–96%) in somewhat higher yield (80–86%). Hydrolysis in aqueous hydrochloric acid–acetonitrile gave the aldehydes in good yield.[73] Addition to ketones again gives mostly reaction at the α-position.

Like the above amines, an *N*-allylphosphonamide may be deprotonated and alkylated. The bulky groups on phosphorus lead to clean γ-alkylation with various primary chlorides and bromides (eq 27).[74] As with enamines the products are very readily hydrolyzed to the aldehydes in 35–76% overall yields.




(27)

The magnesium compound derived from the bulky urea shown in eq 28 gives almost exclusively γ-reactivity with carbonyl compounds and alkylating agents in yields of 62–87%.[75] Mild acidic methanolysis gives the acetals of the aldehydes.

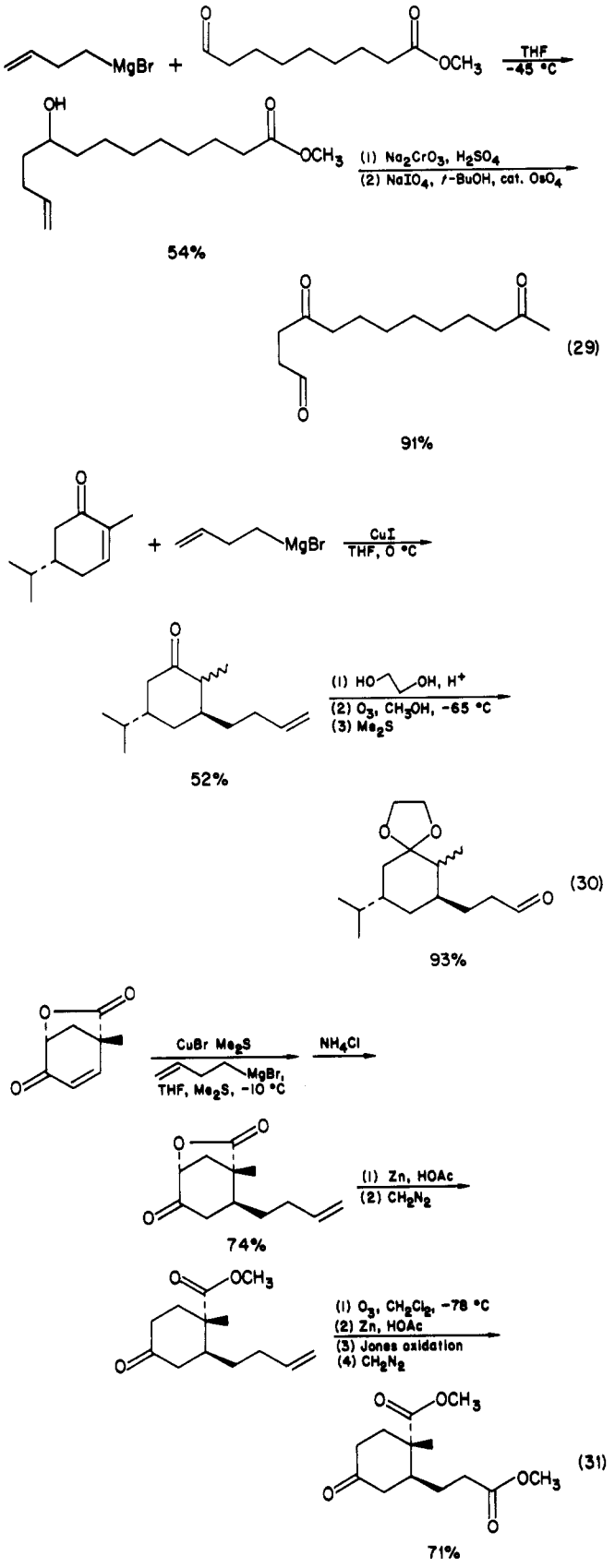



(28)

82% overall

The aldehyde function, or any other oxidation level at the terminal carbon, may be introduced with the stable, simple Grignard reagent from 4-bromo-1-butene. The initial adduct is oxidatively cleaved to introduce the functionality (eq 29–31).[76,40,77] A similar sequence

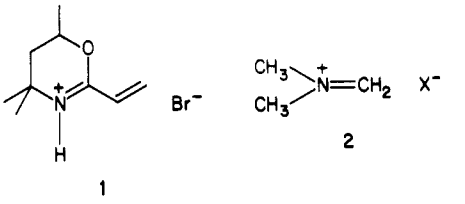
was also used in the synthesis of demethylgorgosterol.[78]




Acrolein itself will react with organoboranes to give aldehydes via an intermediate which is likely to be the enol borinate. Although the aldehydes are difficult to isolate, gas chromatography shows high yields. For example tricyclohexylborane and aqueous acrolein gave 3-cyclohexylpropanal in 77% yield after 1 h at room temperature.[79]

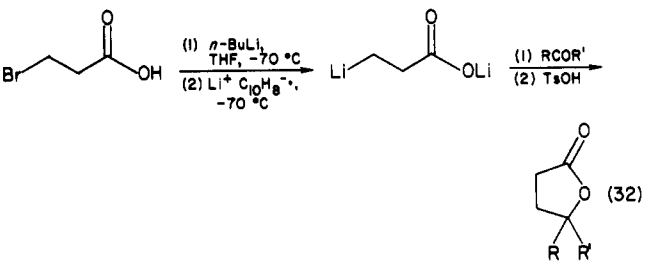
### 5. *Propionate Homoenolate Equivalents*

Protection of β-bromopropionic acid should make it possible to prepare Grignard or lithium reagents in analogy to those from β-bromopropionaldehyde. Attempts to convert this acid to a bicyclic ortho ester or to a dihydro-1,3-oxazine were unsuccessful.[12] In fact we[80] have found that the oxazine exists as the fully ionized tautomer 1 which is reasonable since it is a vinylogous relative of Eschenmoser's salt 2.[81]



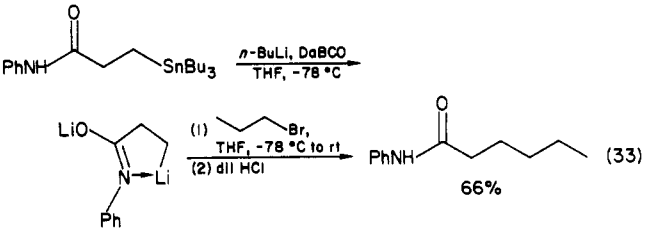

1 2

Caine found that the acid function is well enough protected if it is simply present as the carboxylate anion.[82] Treating β-bromopropionic acid with *n*-butyllithium and then lithium naphthalenide gave the O,β-dianion which was used in a γ-lactone synthesis as shown in eq 32.

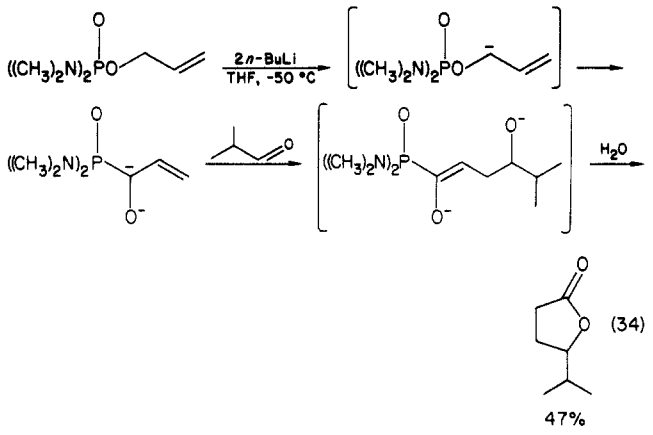



| aldehyde or ketone | lactone yield crude (isolated) |
|---|---|
| benzaldehyde | 56 (44) |
| isobutyraldehyde | 57 (43) |
| 2-octanone | 53 (40) |
| cyclopentanone | 35 (26) |
| cyclohexanone | 51 (41) |

A number of acid derivatives and other reagents provide similar overall results but require hydrolysis or oxidation to reach the substituted propionate. The anilide dianion may be prepared via lithium–tin exchange and deprotonation (eq 33).[83] Alkylation with halides or addition to ketones gives the expected products. For example benzophenone gives *N*,γ,γ-triphenyl-γ-hydroxybutyramide in 80% yield.

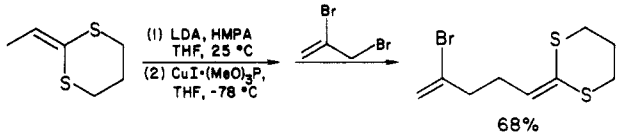



When allyl tetramethylphosphorodiamidate is deprotonated, the phosphorus migrates from oxygen to carbon. A second deprotonation then occurs to give a dianion. This may be alkylated with 1-iodopropane and hydrolyzed to give hexanoic acid in 45% yield.[84] Addition to aldehydes and ketones followed by hydrolysis gives γ-lactones (eq 34).[85] By this method adrenolactone was prepared from the corresponding steriodal ketone in 78% yield.[86]



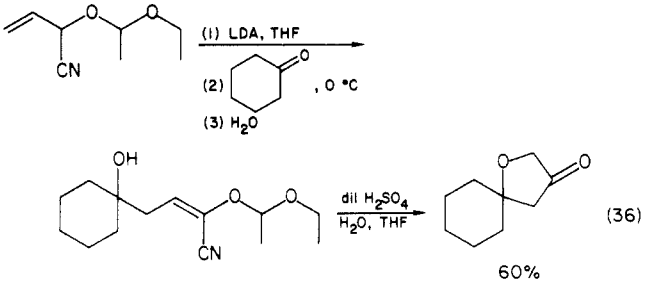

(34)

Ketene dithioacetals and ketene cyanohydrin acetals may be hydrolyzed to carboxylic acids or esters. These may be made from methylketene derivatives or the isomeric acrolein derivatives. For example, 2-ethylidene-1,3-dithiane was deprotonated with LDA–HMPA and complexed with cuprous iodide. This reagent gave exclusive $\gamma$-allylation where most of the product is the result of $S_N2'$ reaction (eq 35).[87] Simple alkylating agents and the lithium reagent give mostly $\alpha$-attack. Aqueous alcoholic mercuric chloride converts some ketene dithioacetals to esters.[88]



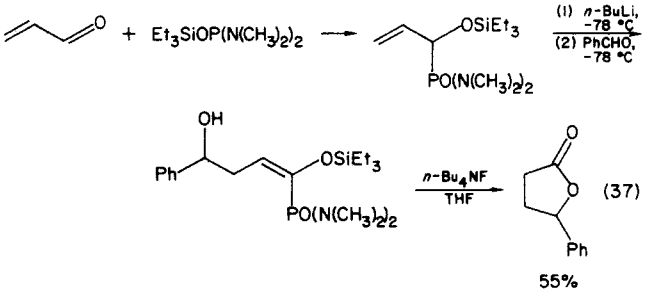

(35)

The carbanion from acrolein cyonohydrin ethoxyethyl ether gives exclusive $\alpha$-addition to ketones at −78 °C but at 0 °C the thermodynamic product, that from $\gamma$ addition, is cleanly formed (eq 36).[89] The $\gamma$-product is a ketene derivative and hydrolysis gives a $\gamma$-hydroxy acid which cyclizes to the $\gamma$-lactone in acid solution.



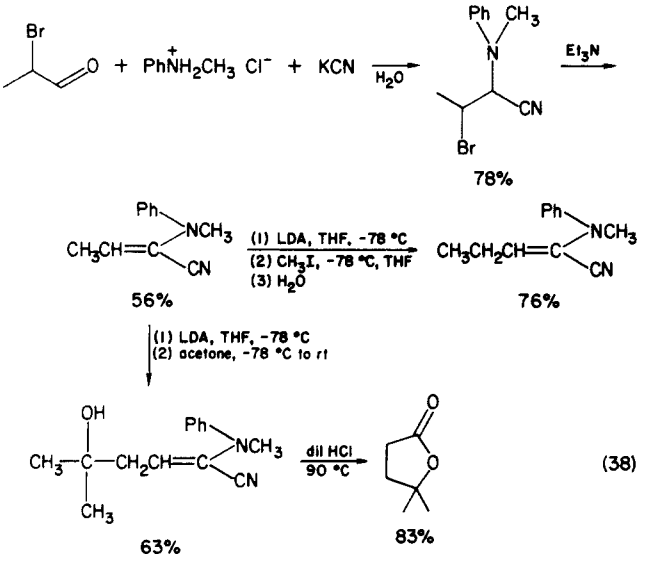

(36)

A similar acrolein derivative is prepared by treating with triethylsilyl *N,N,N',N'*-tetramethylphosphorodiamidate (eq 37).[90] The deprotonated form of this derivative is thermally unstable even at −78 °C, thus alkylation proceeds in low yield but addition to aldehydes followed by solvolysis gives $\gamma$-lactones.



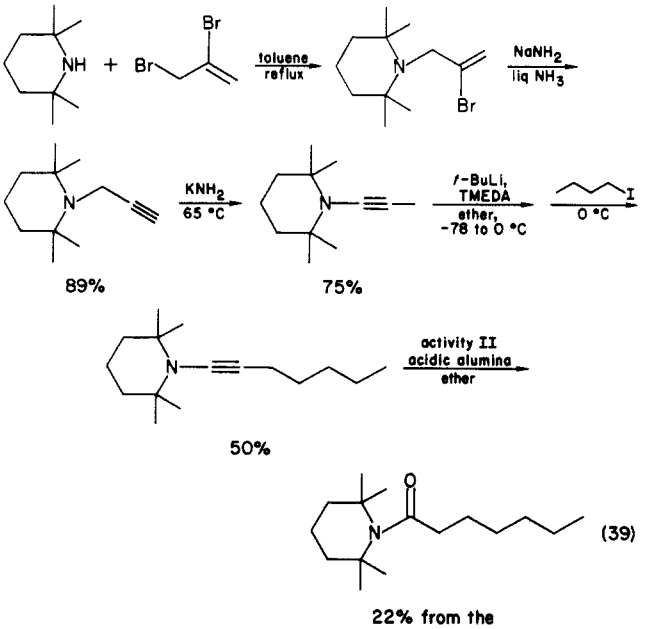

(37)

Better results are found with the nitrogen analogue of the above reagent. The anion from deprotonation of an $\alpha$-cyano enamine reacts selectively at the $\gamma$-site with alkylating agents as well as ketones and aldehydes (eq 38).[91,92] The extended $\alpha$-cyano enamines are then hydrolyzed to carboxylic acids or $\gamma$-lactones.



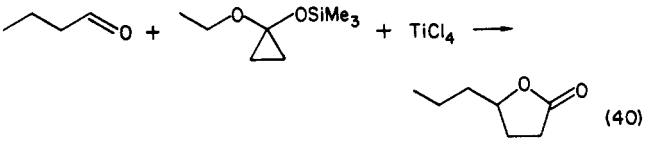

(38)

If the elements of HCN were missing from the above $\alpha$-cyano enamine, we would have any ynamine. This too should form an anion and react with electrophiles. 1-(Diethylamino)propyne was deprotonated and treated with an alkylating agent but no isolable products were obtained. Spectral data suggest that unstable products were formed by $\alpha$-alkylation. More steric hindrance on the nitrogen should direct alkylation to the $\gamma$-position and this was found with 1-propynyl-2,2,6,6-tetramethylpiperidine which gave up to 62% yields of alkylated product (eq 39).[93] Hydration and hydrolysis of the hindered ynamine products in solution proved difficult, however passage through a column of acidic hydrated alumina gave the amide which could be converted to acid by heating with potassium hydroxide in ethylene glycol.



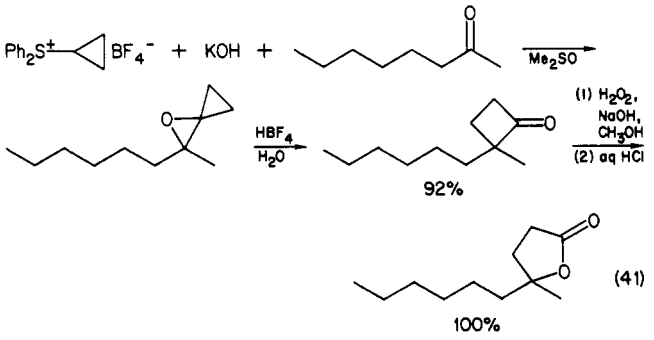

(39)

1-Ethoxy-1-(trimethylsiloxy)cyclopropane with titanium tetrachloride will add to aldehydes to afford γ-lactones (eq 40).[94] Although ketones fail to give adducts, ketals give γ-alkoxy esters. The cyclopropane starting material is available in 78% yield by treatment of ethyl 3-chloropropanoate with sodium and trimethylchlorosilane.[95]



(40)

γ-Lactones may also be prepared by adding the three carbons of diphenylsulfonium cyclopropylide to aldehydes or ketones. This gives the spiro epoxides which are rearranged to cyclobutanones and finally oxidized to the lactones as shown in eq 41.[96]



(41)

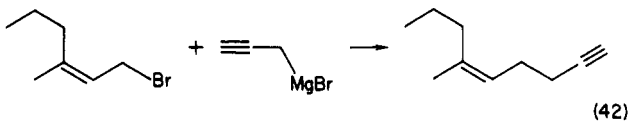
## B. Reagents Providing the Terminal Acetylene Function

Gaudemar[97] found that propargyl bromide reacts readily with magnesium and a trace of mercuric chloride in ether to give propargylmagnesium bromide. Hydrolysis of the reagent gives a mixture of propyne and allene. Carbonation similarly provides a mixture of the acetylenic and allenic acids. However, addition to aldehydes and ketones gives only the acetylenic alcohols. For example addition to acetone affords 4-methyl-1-pentyn-4-ol in 61% yield. The Grignard reagent must be prepared and kept below 20 °C in order to avoid rearrangement and disproportionation. When heated at reflux in ether, propyne and allene are evolved with the formation of $BrMgCH_2C{\equiv}CMgBr$. Also some $CH_3C{\equiv}CMgBr$ is formed.

The dimagnesium compound may be prepared intentionally by treating the propargylmagnesium bromide with ethylmagnesium bromide at lower than 20 °C. This dianionic reagent can then be used in addition reactions. For example, reaction with 2 equiv of acetone affords 2,6-dimethyl-3-heptyne-2,6-diol in 65% yield. Hydrogenation of this product gives 2,6-dimethylheptane-2,6-diol. The use of this dimagnesium reagent together with hydrogenation thus serves as the equivalent of the difficult reagent $BrMgCH_2CH_2CH_2MgBr$.

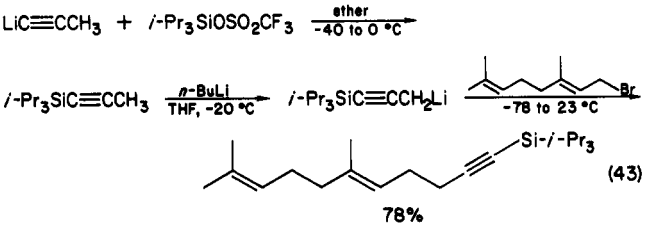
Propargyl bromide also reacts with aluminum turnings to give an organometallic that behaves the same way as the magnesium compound in the preparation of alcohols.

Propargylmagnesium bromide couples with allylic bromides to give the acetylenes along with some of the allene product (eq 42).[98-100] It couples similarly with 2-chlorodioxane to give both types of product.[101]



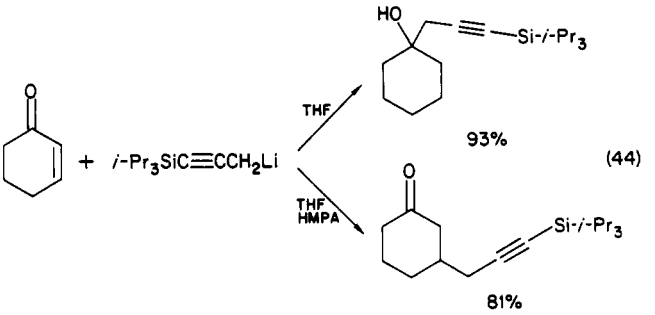
(42)

If the hydrogen on the sp-hybrid carbon of propyne is replaced temporarily with a trialkylsilyl group, the propargyl anion may be prepared by deprotonation with *n*-butyllithium. In this way rearrangement and disproportionation are prevented, and the steric bulk of the silyl group disfavors the formation of allenic products. The trimethylsilyl group allows alkylation with primary halides to give acetylenes in 50–55% yields, containing only 5–10% of the allene.[102] The silyl group is removed by treatment with silver nitrate followed by sodium cyanide or with potassium fluoride in DMF.[103] The triisopropylsilyl group is necessary in reactions with aldehydes to avoid formation of allenes. This more hindered reagent also gives only acetylenes upon treatment with benzyl and allyl bromides (eq 43).[104]



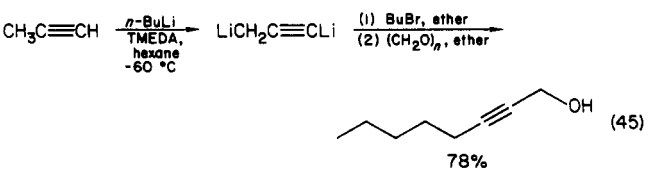
(43)

Addition to cyclohexanone gives the β-hydroxy acetylene in 63% yield. Alkylation with cyclohexene oxide gives an 82% yield of the *trans*-γ-hydroxy acetylene along with 4.5% of the allene. With cyclohexanone, either 1,2- or 1,4-addition may be had by appropriate choice of solvent (eq 44).



(44)

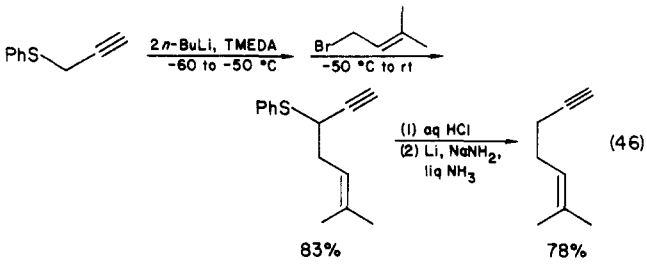
Instead of protecting the sp-hybrid site with a silyl group, one may use the 1,3-dianion from propyne. This gives preferential alkylation at the propargylic site to afford terminal acetylenes. 1-Bromobutane followed by dilute hydrochloric acid gave 1-heptyne in 39% yield.[105] The monoanion, that remains from alkylation of the dianion, may be treated with any of a wide variety of electrophiles to give bond formation to both ends of the original propyne. Examples include iodine, ethylene oxide, 1-bromobutane, chalcone, and formaldehyde (eq 45).



(45)

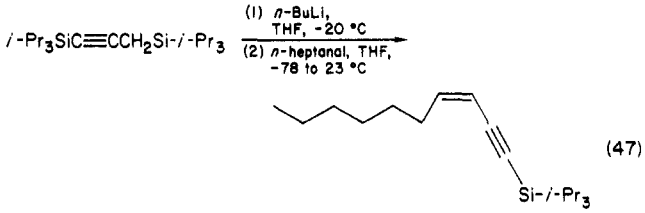
Clean propargyl–allyl coupling could not be obtained with the simple dianion but the phenylthio reagent is

quite suitable. The phenylthio group may be removed reductively (eq 46).[106]



(46)

The anion from 1,3-bis(triisopropylsilyl)propyne gives addition–elimination reactions with aldehydes to afford conjugated enynes (eq 47).[104] The cis isomer is obtained if the temperature is allowed to rise to 23 °C, but using HMPA and quenching quickly at −78 °C gave the trans enynes.

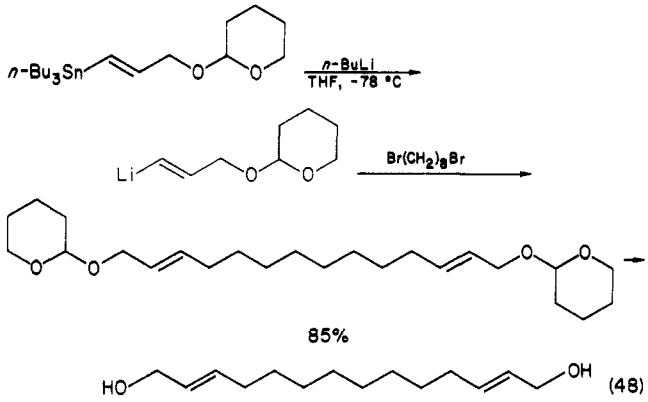


(47)

## C. Reagents Providing α,β-Unsaturated Functionality

### 1. Allylic Alcohols and Halides

Reaction of an electrophile with a vinyllithium reagent containing a protected alcohol on the third carbon leads to protected allyl alcohols. The trans isomers are available if tri-*n*-butyltin hydride is added to propargyl tetrahydropyranyl ether and exchanged with *n*-butyllithium (eq 48). This trans reagent reacts

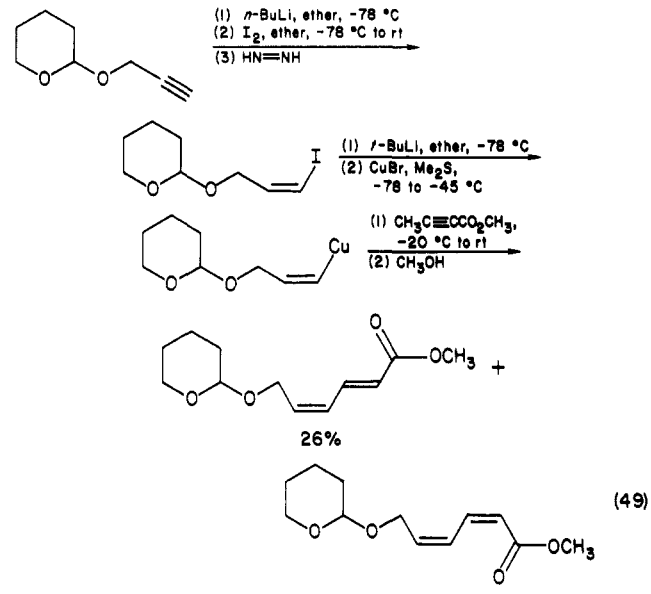


(48)

sterospecifically with organohalides to give the trans alkenes.[107] In combination with 1-pentynylcopper it gives conjugate addition to cyclohexenones and cyclopentenones in 80–85% yields.

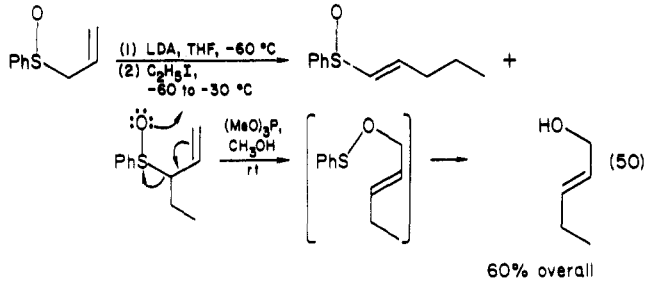
An alternative trans reagent was prepared from the tetrahydropyranyl ether of 3-(trimethylsilyl)-2-propyn-1-ol by hydroalumination–bromination. Halogen metal exchange with *sec*-butyllithium and treatment with 1-iodobutane gave a 75% yield of the butylated product with better than 99% stereospecificity. The tetrahydropyranyl protection was removed with dilute methanolic hydrochloric acid and the vinylsilyl group was cleaved with potassium fluoride in $Me_2SO$ at 150 °C to give the pure *trans*-2-hepten-1-ol in 70–80% yield.[108] This was then oxidized to the aldehyde.

The simple cis reagent was prepared from the propargyl tetrahydropyranyl ether by iodination, diimide reduction to the cis iodide, and lithium–iodine exchange (eq 49).[109] In this case the lithium reagent was converted to the copper reagent which was used in a conjugate addition. The cis stereochemistry was preserved throughout at the final γ,δ-position but both cis and trans α,β-unsaturation appeared owing to equilibration of the vinyl enolate at the temperature used for the conjugate addition.



(49)

The vinyl reagents above give the allyl alcohols directly but they can also be prepared from allyl reagents with rearrangement. The anion of an allyl sulfoxide gives mostly α-alkylation but addition of a thiophile leads to the allylic alcohol as shown in eq 50.[110] Addition of the anion to aldehydes is less useful because there is little site selectivity even at −100 °C.

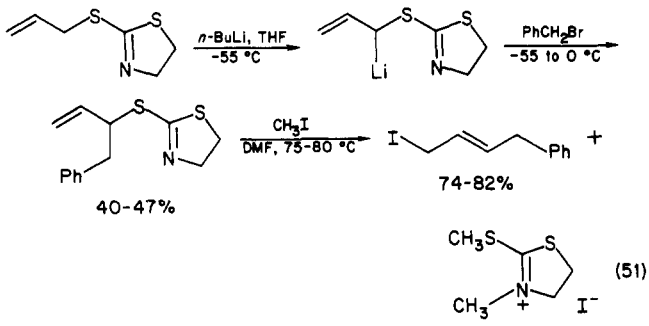


(50)

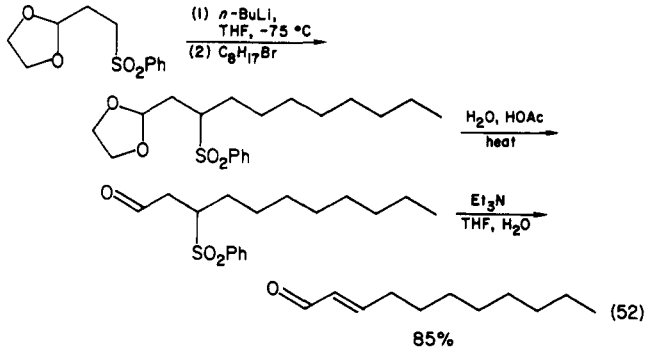
Allyl halides may be prepared from the α-alkylation product from a thioallyl ether in a way analogous to the rearrangement in eq 50. As pointed out in section A4, the anions from thioallyl ethers, especially chelating cases, give much α-alkylation. Subsequent $S_N2'$ displacement of the thioether function by iodide ion is shown in eq 51.[61] These allylic halides may then be oxidized to α,β-unsaturated aldehydes or converted to Wittig reagents.

### 2. α,β-Unsaturated Aldehydes

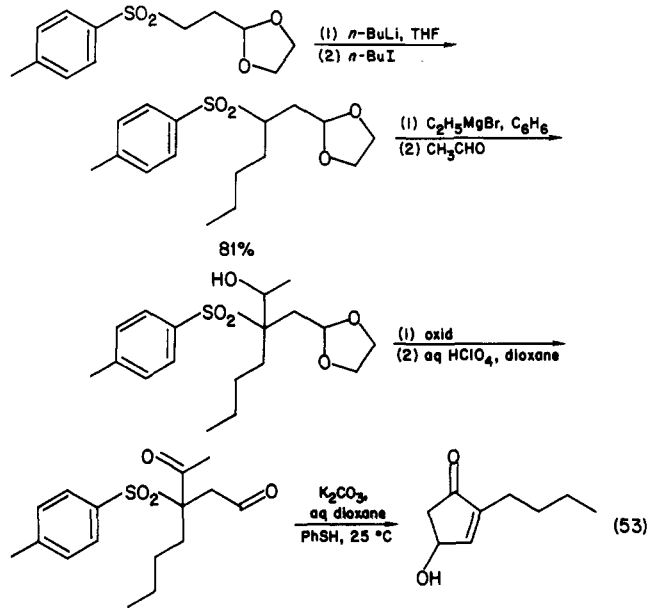
The β-(phenylsulfonyl)propionaldehyde acetals discussed in section A4 may be used to prepare α,β-unsaturated aldehydes if, after alkylation, benzenesulfenic




acid is eliminated with aqueous hydroxide, triethylamine, or dry sodium carbonate (eq 52).[48,49]

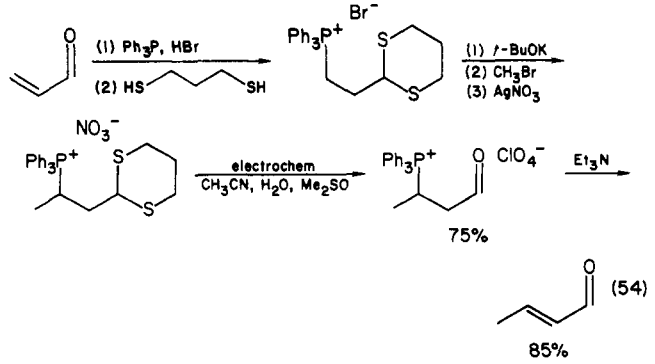



γ-Keto-α,β-unsaturated aldehydes may also be prepared if the alkylation step is followed by an addition at the same site and the resulting alcohol is oxidized (eq 53). Elimination of the sulfenic acid with base gives

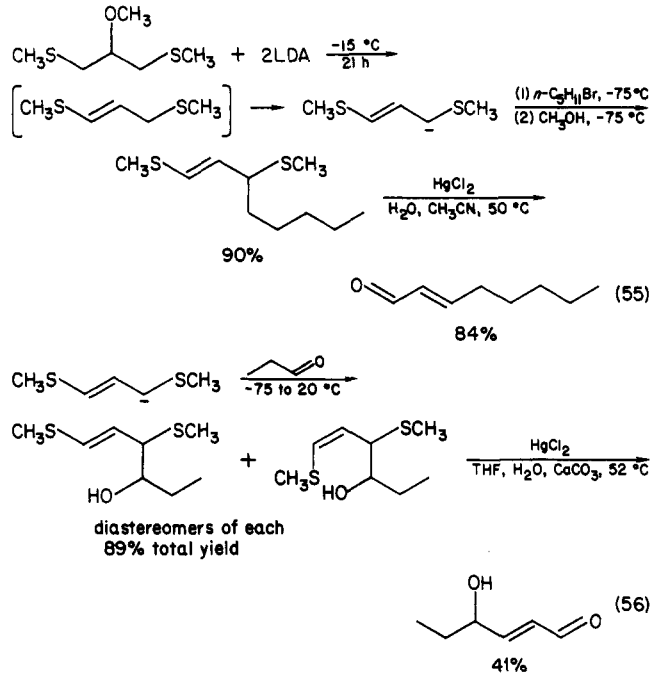



(*E*)-3-acetyl-2-heptenal but if thiophenol is added to catalyze the trans–cis isomerization, the base step proceeds to a hydroxycyclopentenone (eq 53).[111] The prostaglandin intermediate 2-(6-carbomethoxyhexyl)-4-hydroxycyclopent-2-en-1-one was prepared by this method.

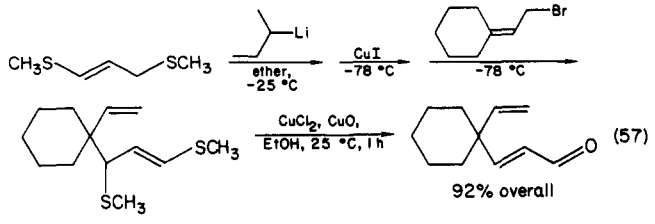
A β-phosphonium group may be used to activate the β-position for deprotonation. The aldehyde function was protected as a dithioacetal in the case shown in eq 54. Potassium *tert*-butoxide gave deprotonation and the ylide was alkylated with for example bromomethane. The dithiane was removed electrochemically from the nitrate salt. Finally elimination of triphenylphosphine gave the α,β-unsaturated aldehyde.[112]




In the above cases the aldehyde function was protected as the acetal. If it is protected as the thioenol ether, the carbanionic charge will be stabilized by allylic resonance. 1,3-Bis(methylthio)propene contains both the protected aldehyde, and a group that may be eliminated to give the α,β-unsaturation. Furthermore the symmetry of the anion leaves no question of site selectivity. Elimination and deprotonation of the methoxy precursor gives the delocalized sulfur-stabilized carbanion which may be alkylated with halide or epoxides or added to carbonyl compounds in high yield (eq 55, 56).[113] The hydrolysis and elimination of sulfur




functionality may be accomplished with thiophilic metals including mercuric chloride or silver nitrate in aqueous acetonitrile or aqueous THF, or better cupric chloride and cupric oxide in ethanol.[62] The corresponding copper reagent gives $S_N2'$ reactions with allylic halides (eq 57).[62]

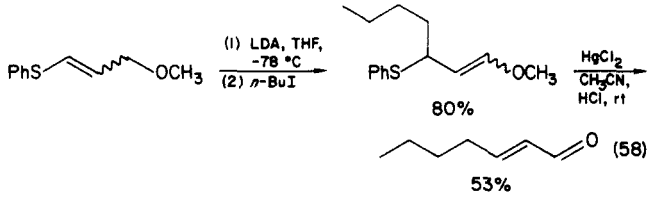



The starting material, 1,3-bis(methylthio)-2-methoxypropane, is prepared from epichlorohydrin by first treating with sodium methanethiolate and then sodium

hydride and methyl iodide.

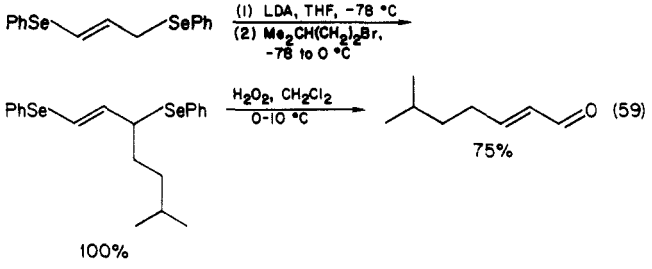
The similar bis(phenylthio) compound can be prepared from phenyl allyl sulfide by chlorination and then treatment with thiophenoxide. The anion is generated with *sec*-butyllithium, and then alkylated in high yield. Mercuric chloride in wet acetonitrile gives the $\alpha,\beta$-unsaturated aldehydes.[114]

3-Methoxy-1-(phenylthio)-1-propene may be used likewise. Deprotonation $\alpha$ to sulfur, alkylation, and mercuric chloride assisted hydrolysis again gives the $\alpha,\beta$-unsaturated aldehydes in good yields (eq 58).[115]



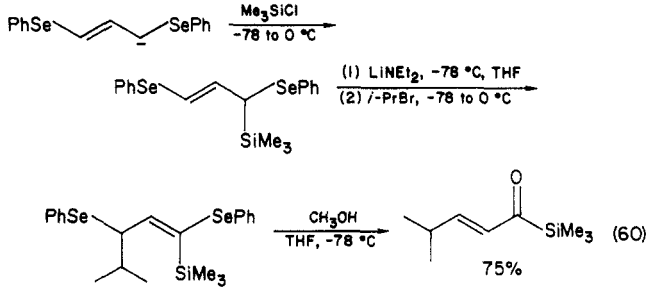
(58)

The use of selenium in place of sulfur retains the high nucleophilicity but allows removal of the selenium groups under very mild oxidative conditions (eq 59).[116]



(59)

Addition of the carbanion to 3-pentanone followed by oxidative removal of the selenium gave *trans*-4-ethyl-4-hydroxy-2-hexenal in 77% yield. Treatment of the anion with trimethylsilyl chloride gives another reagent that can be deprotonated and used with various electrophiles to prepare vinyl silyl ketones (eq 60).[116]

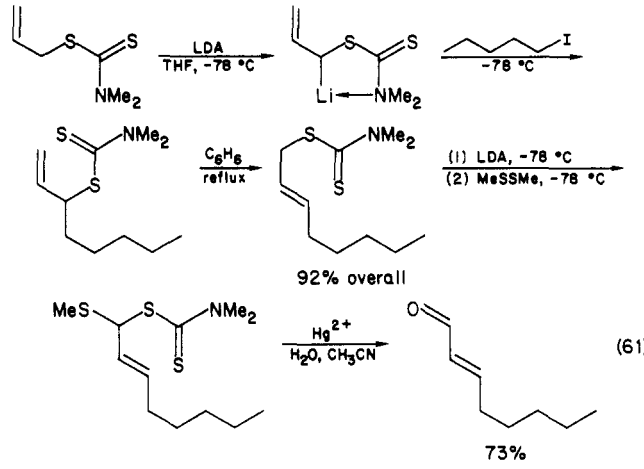


(60)

An alternative to the 1,3-bis(thio)propenes involves placing both sulfur groups on the 3-carbon. The anion from allyl *N,N*-dimethyldithiocarbamate may be $\alpha$-sulfenylated (dimethyl disulfide) and then alkylated, or preferably the sulfenylation may follow the alkylation. Although the alkylation occurs at the $\alpha$-position as seen for other chelated thioallyl cases, a [3.3] sigmatropic rearrangement favors the $\gamma$-product (eq 61). Hydrolysis then affords $\alpha,\beta$-unsaturated aldehydes in high overall yield.[117]

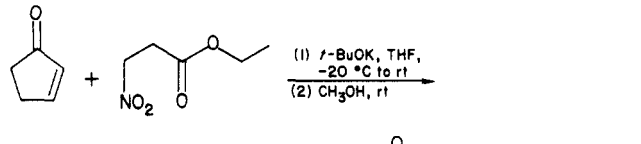
### 3. $\alpha,\beta$-Unsaturated Carboxylic Acids, Esters, and Lactones

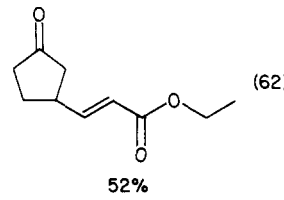
A proton is readily removed from the $\beta$-position of ethyl $\beta$-nitropropionate and the resulting carbanion will give addition or conjugate addition. The base also gives



(61)

a slower elimination of nitrous acid leading to $\alpha,\beta$-unsaturation (eq 62, 63).[9]



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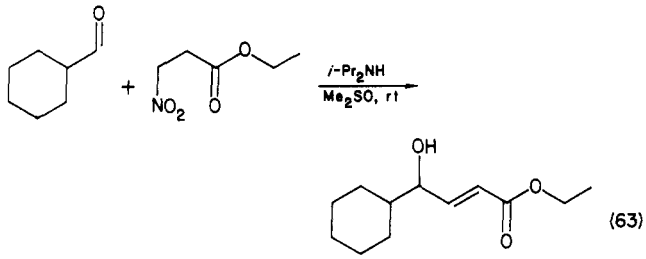
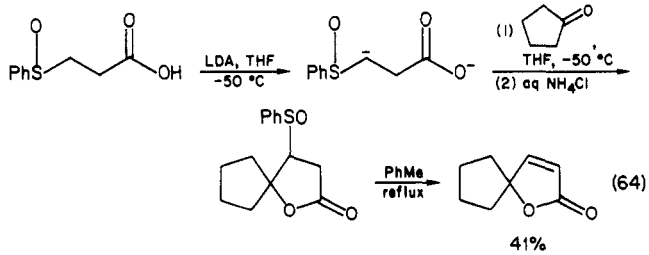


(63)

A phenylsulfonyl or phenylsulfenyl group in the $\beta$-position of propionic acid allows formation of the O,$\beta$-dianion. Addition to a ketone followed by thermal elimination of benzenesulfenic acid gave a butenolide (eq 64).[118] The dianion may also be $\beta$-alkylated with

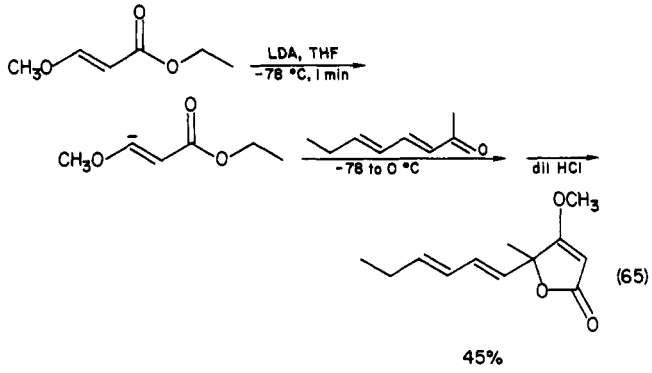


(64)

1-bromopropane, affording (after elimination) 2-heptenoic acid in 25% yield. The starting material is prepared from ethyl $\beta$-bromopropionate by treatment with sodium thiophenolate, hydrolysis, and oxidation with sodium periodate.

One may begin with the $\alpha,\beta$-unsaturation in place if a substituent is present on the $\beta$-position that will lead to kinetic $\beta$-deprotonation. A $\beta$-methoxy or pyrrolidino group serves this purpose in acrylonitrile, ethyl acrylate, or *N,N*-diethylacrylamide. The vinyl carbanions are prepared at low temperature and used promptly to

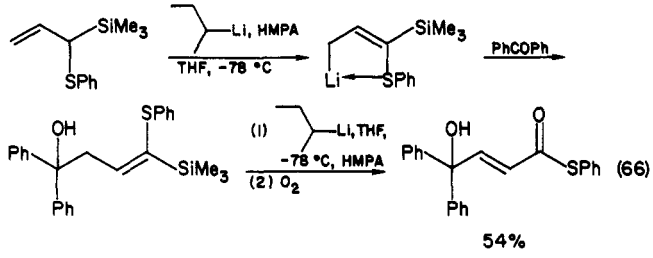
avoid rearrangement to the $\alpha$-anion.[119,120] This process was used in the synthesis of a tetronic acid derivative as shown in eq 65.[121] Addition to a ketone or aldehyde gives an alkoxide which promptly affords the lactone.




45%

The $\beta$-unsubstituted case may be prepared by metal halogen exchange of *n*-butyllithium (2 equiv) with $\beta$-bromoacrylic acid at −78 °C. Addition to cyclohexanone gave the butenolide in 48% yield.[121a]

As pointed out earlier, the anions from thioallyl ethers react with carbonyl compounds at the $\alpha$-position. Incorporation of an $\alpha$-(trimethylsilyl) group reverses this tendency and gives reaction at the $\gamma$-site. The resulting allylic alcohol can be converted to an O,C-dianion and then oxidized to afford $\alpha,\beta$-unsaturated phenylthio esters (eq 66).[122]



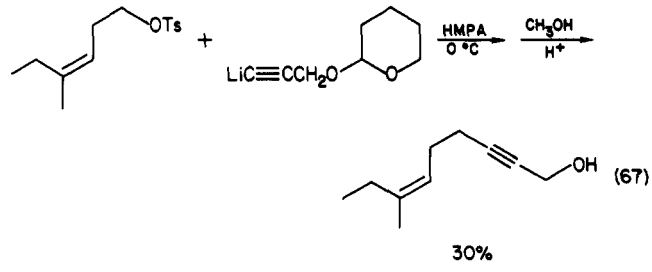

54%

## D. Reagents Providing $\alpha,\beta$-Acetylenic Functionality

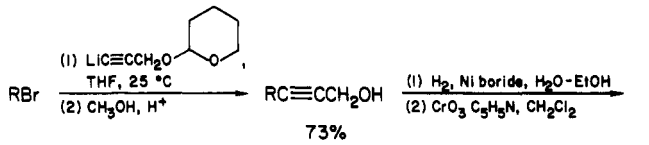
In part IA the problem of intramolecular attack of the nucleophilic site on the functional third carbon to give cyclopropyl compounds was often seen. Earlier workers avoided this problem by using a nonflexible, linear three-carbon chain, that is, the acetylene compounds. This choice also allows deprotonation of the $\beta$-carbon without using temporary activating groups. In most cases the extended molecule was hydrogenated to give the saturated compounds similar to those prepared directly by the methods in section A.

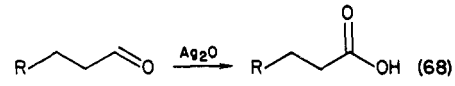
### 1. $\alpha,\beta$-Acetylenic Alcohols

Propargyl alcohol reacts exothermally with dihydropyran in the presence of *p*-toluenesulfonic acid to give the protected compound in 90% yield.[123] It may also be protected with ethyl vinyl ether but the product is not stable toward distillation and must be used in situ.[124] The proton on sp-hybrid carbon is then removed with Grignard reagents, alkyllithiums, or lithium amide, and the resulting acetylide ion is treated with various electrophiles including tosylates and allylic bromides (eq 67, 68).[125,126] In the first case the acetylenic linkage was converted to a trisubstituted double bond stereospecifically and in the second case it was hydrogenated and the aldehyde function oxidized to the

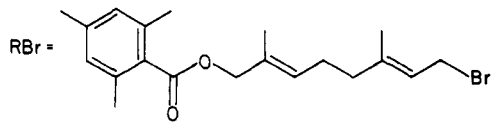



30%



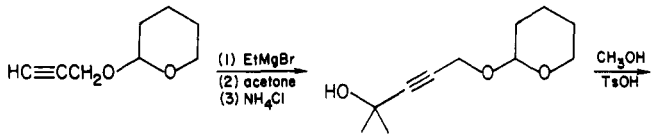




76%

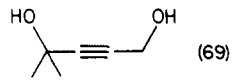



acid. The sequence in eq 68 was also carried out with geranyl bromide.[127] Various aryl iodides were coupled with the copper acetylide to give the propargyl alcohols after hydrolysis.[128]

Addition of the acetylide anion to aldehydes and ketones leads to 1,4-diols in good yields (eq 69).[123]



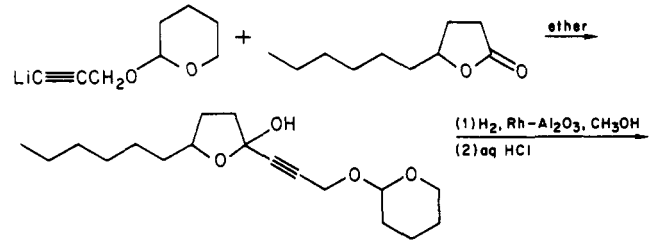

82%




89%

Those carbonyl compounds include acetaldehyde, propionaldehyde, acetone, 2-butanone, and 4-*tert*-butylcyclohexanone.[129,130] In many cases the triple bond was hydrogenated to the cis alkene or to the saturated diol.

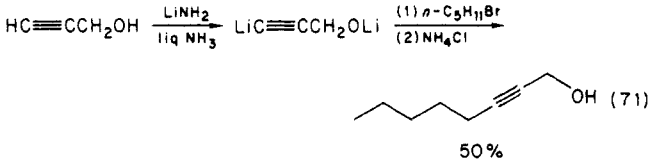
One equivalent of the lithium acetylide reacts with $\gamma$-lactones to give, after hydrogenation and acid treatment, dioxaspiro compound (eq 70).[124,131] Two equiv-




77%

alents of the lithium acetylide combined with 3,5-dimethoxybenzoate gave the tertiary alcohol in 90% yield.[132] The magnesioacetylide and methyl chloroformate gave methyl $\gamma$-hydroxytetrolate in 60–65% yield after methanolysis of the tetrahydropyranyl group.[133,134]

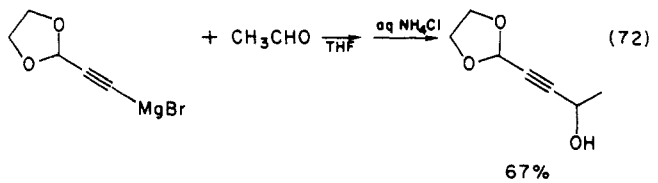
The O,C-dianion of propargyl alcohol ought to serve these purposes without the necessity of protecting the alcohol. Early attempts at addition to ketones with the dilithio and disodio compound in liquid ammonia, and the dimagnesium bromide dianion in THF were unsuccessful. However Karpf and Dreiding[135] found that the dilithio compound from propargyl alcohol and lithium amide in liquid ammonia gave a 90% yield of addition to cyclododecanone after 24 h of reflux in THF. With this ketone the THP-protected reagent gave only a 52% yield of the corresponding adduct. The dianion was also suitable for alkylation as shown in eq 71.[136] The product was then oxidized with manganese dioxide to the $\alpha,\beta$-acetylenic aldehyde.




(71)

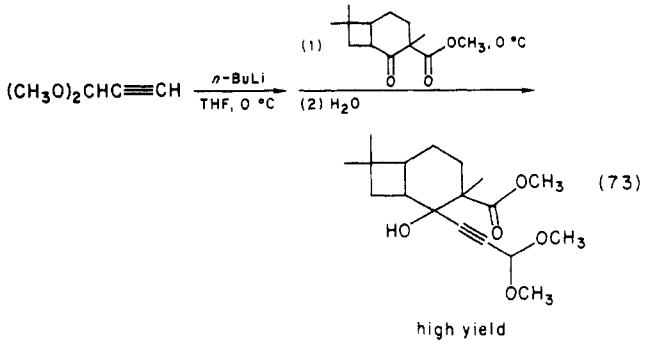
### 2. $\alpha,\beta$-Acetylenic Aldehydes

Acrolein was converted to 2,3-dibromopropanal, protected with ethylene glycol, and then dehydrobrominated to give the acetylene. This could be deprotonated to give the sodium, lithium, or magnesium bromide acetylide which adds to various aldehydes and ketones in 57–70% yields (eq 72).[137] The anion may also be methylated (64%) or ethylated (70%) with the respective sulfates.




(72)

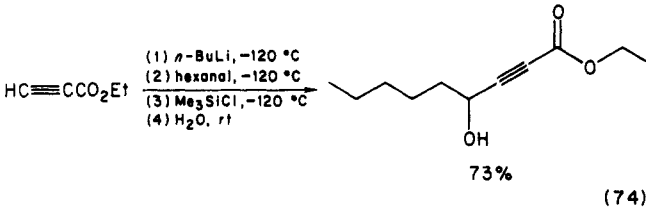
Corey utilized the dimethyl acetal in the synthesis of caryophyllene (eq 73).[138] The same dimethyl acetal was deprotonated with ethylmagnesium chloride and acylated with methyl chloroformate to afford methyl 4,4-dimethoxytetrolate in 40% yield.[139] Copper 3,3-diethoxyprop-1-ynide was coupled with several aryl iodides and then hydrolyzed to the highly reactive aldehydes.[128]




(73)

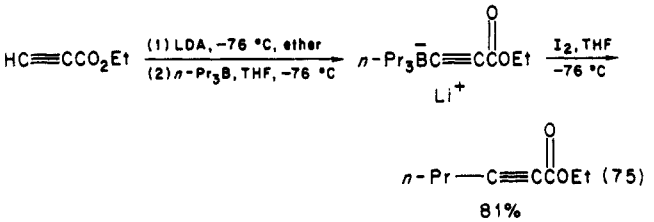
### 3. $\alpha,\beta$-Acetylenic Carboxylic Acids and Esters

Even the ester function may be present in an acetylide reagent if it is kept at low temperatures. Ethyl propiolate may be deprotonated and used at −78 °C while methyl propiolate requires temperatures below −100 °C. Addition to aldehydes and ketones is rapid and must be quenched with acetic acid or trimethylsilyl chloride while still cold (eq 74).[140–142] This affords 4-hydroxy-2-alkynoates in 59–91% isolated yields.




(74)

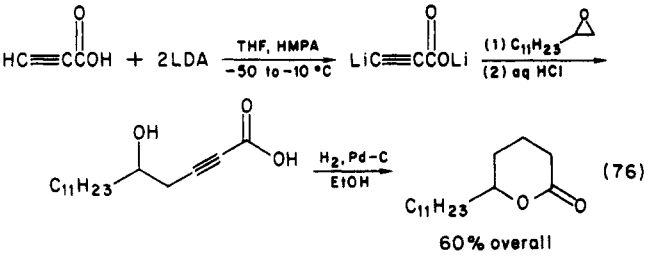
The alkylation products are available via reaction of the lithium reagent with trialkylboranes (eq 75).[143]




(75)

This is not limited to primary alkyl groups as is the usual alkylation of simple acetylides with organohalides. *sec*-Butyl and cyclohexyl groups were transferred similarly in 73 and 74% yield, respectively.

The propiolate ester anions are not reactive toward epoxides below −50 °C and they decompose above −50 °C so simple alkylation with epoxides is not possible. However the dianion of propiolic acid itself is stable for days at room temperature and reacts with epoxides to give 5-hydroxy-2-alkynoic acids in 30–60% yields.[144] This process was applied to the synthesis of a proposed pheromone of the oriental hornet (eq 76),[145] and of (+)-(6*R*,1′*R*)-pestaloin.[146]




(76)

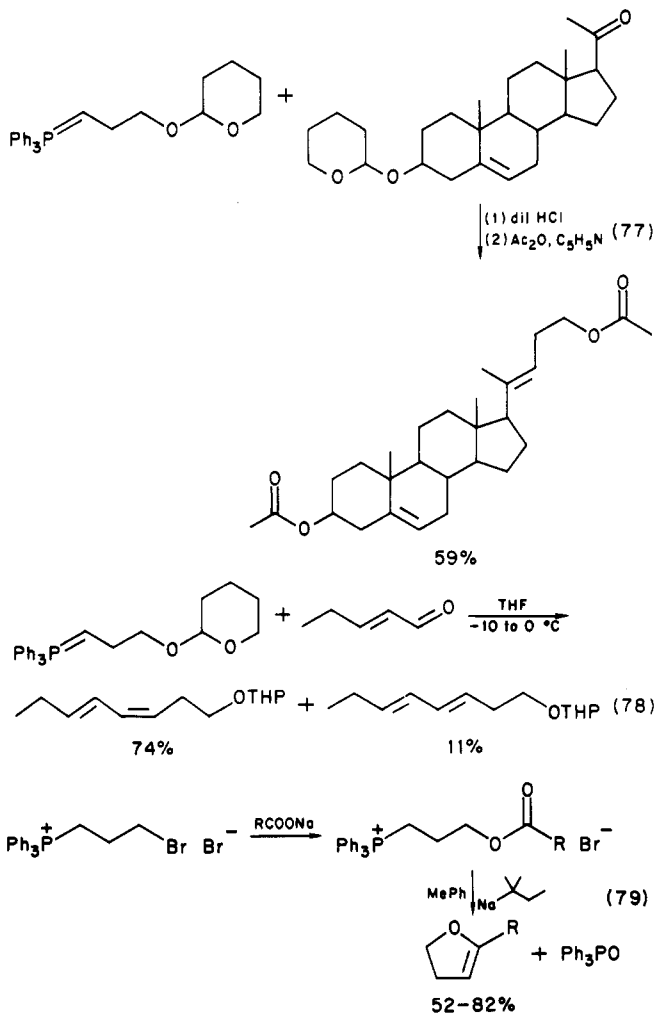
## E. Reagents Providing $\beta,\gamma$-Unsaturated Functionality

Aldehydes are the usual substrates when the new chain of three carbons is to be attached by a double bond. The three carbons are introduced as a Wittig reagent or as a cyclopropyl compound which is subsequently ring opened.

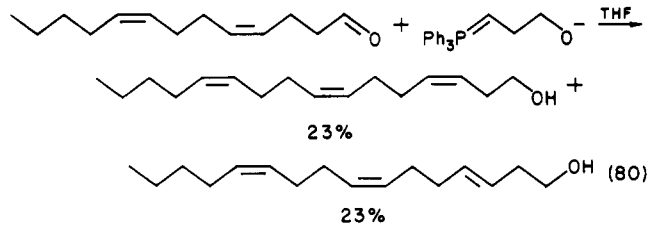
### 1. $\beta,\gamma$-Unsaturated Alcohols

3-Bromo-1-propanol was protected as the tetrahydropyranyl ether and then converted to the phosphonium salt. Potassium *tert*-amylate then gave the ylide which was condensed with pregnenolone tetrahydropyranyl ether to give the $\beta,\gamma$-unsaturated alcohol (eq 77).[147] The same Wittig reagent generated with *n*-butyllithium gave cis and trans products upon reaction with an aldehyde (eq 78).[148]

If the ylide contains not a tetrahydropyranyl ether function but an ester, the nucleophilic carbon attacks the ester carbonyl group intramolecularly to give a dihydrofuran (eq 79).[149]




Camps et al.[150] found it unnecessary to protect the alcohol function and simply used 2 equiv of base on the phosphonium salt from 3-bromo-1-propanol to give the alkoxide ylide. This was applied to the preparation of $\beta,\gamma$-unsaturated alcohols of interest in the insect pheromone area (eq 80).[150] This alkoxide ylide as well

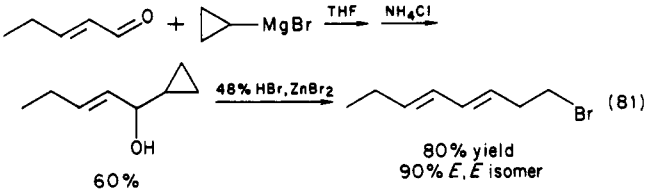



as the tetrahydropyranyl-protected one was used in another pheromone synthesis where the ylide was first methylated, again deprotonated and then condensed with an aldehyde to give *Z* and *E* isomers of a trisubstituted olefin. In yet another variation the order was reversed, that is, the tetrahydropyranyl-protected ylide was condensed with an aldehyde, again deprotonated, and alkylated to give trisubstituted $\beta,\gamma$-unsaturation.[151]

### 2. $\beta,\gamma$-Unsaturated Halides

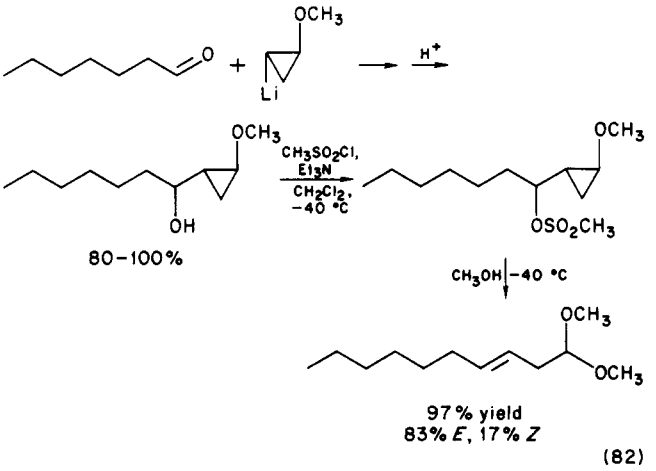
(3-Bromopropyl)triphenylphosphonium bromide has not yet been used to prepare $\beta,\gamma$-unsaturated bromides but it does react slowly with sodium ethoxide to give cyclopropyltriphenylphosphonium bromide. This is commonly used to prepare cyclopropylidene compounds from ketones or aldehydes.[152]

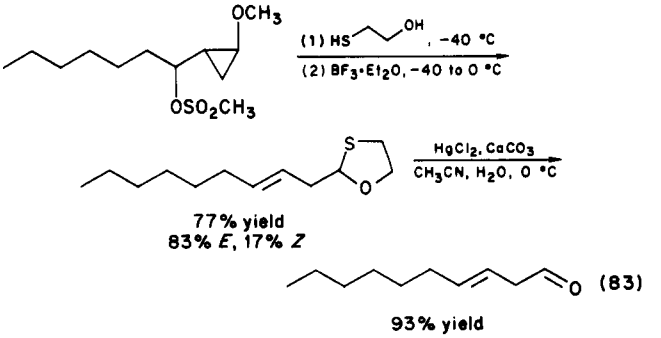
The standard route to trans-$\beta,\gamma$-unsaturated halides is the Julia reaction which involves ring opening of cyclopropylcarbinols. Where those compounds were prepared from cyclopropylmagnesium bromide, overall three-carbon homologation has been effected, for example see eq 81.[21,153] In more recent work it appears that magnesium bromide or iodide in anhydrous ether are superior reagents for the ring-opening step.[154]




### 3. $\beta,\gamma$-Unsaturated Aldehydes

Trans-$\beta,\gamma$-unsaturated aldehydes may be prepared from ketones and aldehydes using *cis*- or *trans*-(2-methoxycyclopropyl)lithium. Addition of one of these isomeric reagents gives a cyclopropylcarbinol which may be converted to a mesylate to be solvolyzed in methanol to afford the ring-opened dimethyl acetal of the *trans*-$\beta,\gamma$-unsaturated aldehyde (eq 82).[155] If the original aldehyde was branched at the $\alpha$-position, the stereoselectivity is greater than 97% *E*. Hydrolysis of the mesylate or the dimethyl acetal to the free aldehyde (acetone–water–oxalic acid, 45 °C)[156] gives some isomerization to the more stable $\alpha,\beta$-unsaturated aldehyde.[155,41] This isomerization may be kept to less than 2% by avoiding acid in the hydrolysis step. This was done by converting the cyclopropylcarbinol mesylate to a hemithioacetal and then removing that group with mercuric ion (eq 83), or with S-methylation and hydrolysis.[155]

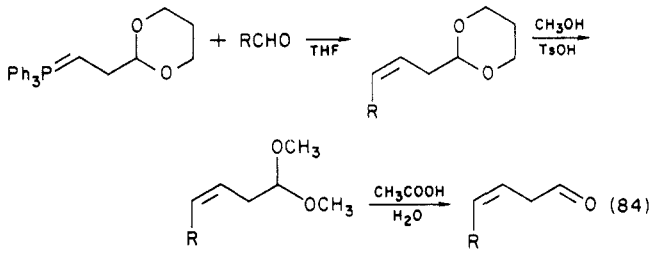


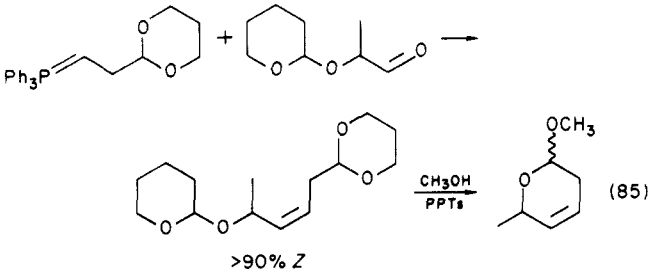

The three-carbon lithium reagents used in this sequence are prepared by a methoxy- or halocarbene

addition to vinyl bromide or methyl vinyl ether followed by metal–halogen exchange. Overall the process is an example of the Julia method at a higher oxidation level.

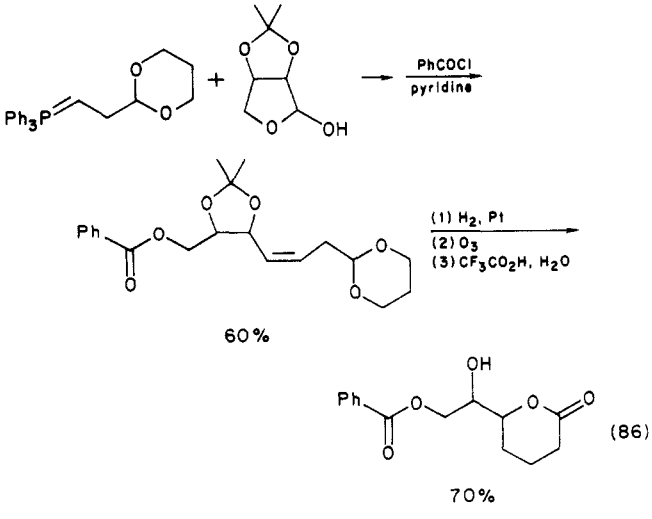
The cis-β,γ-unsaturated aldehydes may be prepared simply using the Wittig reagent shown in eq 84. Re-




action under lithium free conditions gives the dioxane derivatives of *cis*-β,γ-unsaturated aldehydes in up to 72% yields with greater than 95% cis selectivity.[41] Although the dioxanes are not readily hydrolyzed, they are easily converted to the dimethyl acetals which then give the free aldehyde in aqueous acetic acid at room temperature with no double-bond migration. Several of these aldehydes are major flavor components in foods. This method was also used to prepare an intermediate in the synthesis of (–)-sarracenin (eq 85).[157] Intentional isomerization of course makes the α,β-unsaturated aldehydes available from this reagent as well. The isopropyl acetal was used similarly to prepare (*Z*)-3-heptenal.[157a]




The same Wittig reagent was used to extend 2,3-*O*-isopropylidene-D-erythrose by three carbons, wherein the β,γ-unsaturation was reduced and the dioxane oxidized to the carboxylic acid level (eq 86).[158] Thus the

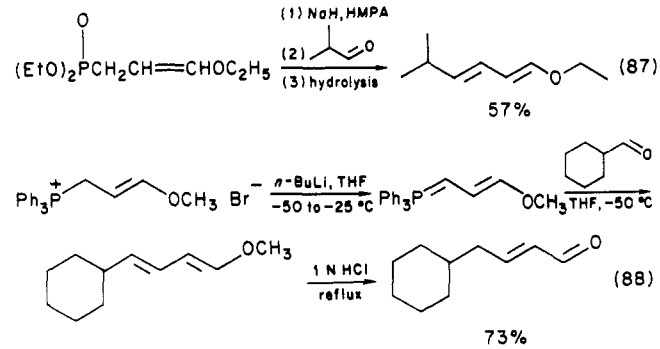



reagent was used as a propionate homoenolate.

The dithiane ylide analogous to the dioxane reagent above was prepared in three steps. Acrolein was treated with triphenylphosphine and HBr to give the phosphonium salt. This was protected using 1,3-propanedithiol and HBr, and finally potassium *tert*-butoxide gave the ylide. This is readily alkylated or acylated with primary bromides and iodides or acetic anhydride. The ylide also gave Wittig products upon treatment with ketones or aldehydes. The products may be hydrolyzed with aqueous cerium(IV) catalysis.[159]

Iwamoto et al.[160] showed that the cis-β,γ-unsaturated aldehydes could also be prepared using the Wittig reagent derived from 2-(2-iodoethyl)-1,3-dioxolane. In this case the dioxolane could be hydrolyzed to the free aldehyde using aqueous acetic acid.

Phosphorus ylides and phosphonate ester carbanions have been prepared wherein an aldehyde function is protected as the enol ether. Condensation of these with ketones and aldehydes gives alkoxybutadienes (eq 87, 88),[161,162] useful in their own right, but also hydrolyzable.




Mild hydrolytic conditions did not give any appreciable β,γ-unsaturated aldehydes but did give good yields of the α,β-unsaturated aldehydes.[161] Similar phosphonates have been used where the aldehyde function is protected as the thioenol ether or as an enamine.[162] The phosphonate in eq 87 was prepared from 1,3-dibromopropene by treatment with triethyl phosphite (90% yield) followed by sodium ethoxide (66% yield).[163] The phosphonium salt in eq 88 was prepared from methoxyallene by treatment with triphenylphosphine hydrobromide (68% yield).[161] The methoxyallene was prepared by isomerization of propargyl methyl ether with potassium *tert*-butoxide at 70 °C (82%). The propargyl methyl ether was in turn prepared from the alcohol and dimethyl sulfate.

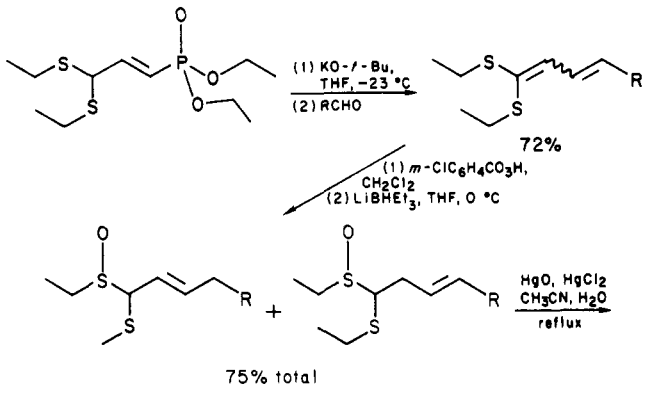
### 4. β, γ-Unsaturated Acids and Derivatives

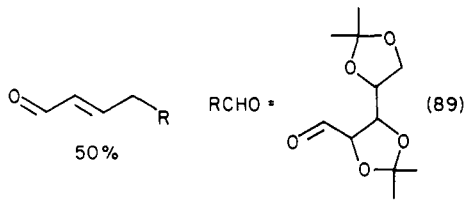
The phosphobetaine prepared from triphenylphosphine and β-chloropropionic acid may be used to prepare β,γ-unsaturated acids, but the ketone and betaine must be added together to sodium hydride at 0 °C.[163a] Attempts to prepare the ylide first led to elimination of triphenylphosphine leaving acrylic acid. Condensation with cyclohexanone gave cyclohexylidenepropionic acid in 66% yield. With *m*-methoxyacetophenone the *Z* and *E* isomers of the corresponding β,γ-unsaturated acid were formed in 53–69% yield.

β,γ-Unsaturated nitriles, amides, and esters were prepared in 8–45% yields by heating triphenylphosphine, the acrylic derivative, and an aldehyde directly.[163b]

A ketene dithioacetal (or tautomer thereof) is a protected form of an acid. The phosphonate in eq 89 affords the dithioketal derivatives of unsaturated acids

but all attempts to hydrolyze them failed. A reduction of the corresponding sulfoxide did lead to a synthesis of $\alpha,\beta$-unsaturated aldehydes.[164]




(89)

## III. Electrophilic Reagents

Electrophilic three-carbon homologating agents often have electrophilic character at both ends and therefore do not undergo internal attack as is the case with some nucleophilic reagents. Thus rather than stability problems, here we find questions of selectivity toward one group and not the other.

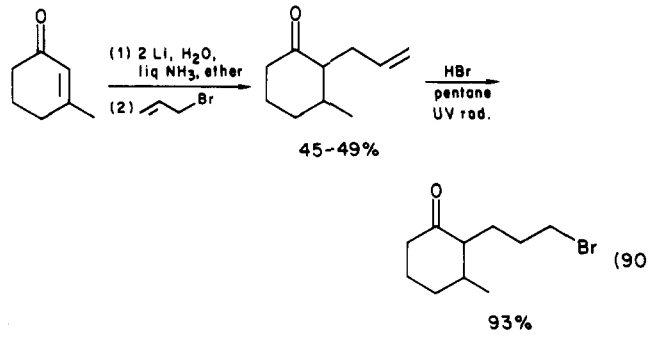
### A. Chloro- and Bromopropylation

A wide variety of carbanions will react with 1,3-dihalopropanes or halopropyl tosylates to give three-carbon extension with a halide at the new terminus.

Rossander and Marvel found that Grignard reagents containing six carbons or more will react with 3-chloropropyl tosylate to give displacement of the tosylate group, affording the extended chloro compounds in about 50% yield.[165,166] Two equivalents of chloro sulfonate are needed to allow for competing displacement of tosylate by the halide ion from the Grignard reagent. Higher yields may be obtained by adding the Grignard reagent to 1,3-dihalopropanes in the presence of lithium tetrachlorocuprate.[167] Isopropylmagnesium chloride and 1,3-dibromopropane gave 1-bromo-4-methylpentane in 68% yield, while isoamylmagnesium bromide and 1-bromo-3-chloropropane gave 1-chloro-6-methylheptane in 80% yield. (2-Methyl-1-butenyl)-copper and 1-chloro-3-iodopropane gave 3-methyl-7-chloro-3-heptene in 46% yield.[168] The higher order cuprate *sec*-$Bu_2Cu(CN)Li_2$ reacts selectively and efficiently even at −78 °C with 1-bromo-3-chloropropane to give 1-chloro-4-methylhexane in 89% yield.[168a] 1-Lithio-1-butyne and 1-bromo-3-chloropropane gave 7-chloro-3-heptyne in only 15% yield.[169]

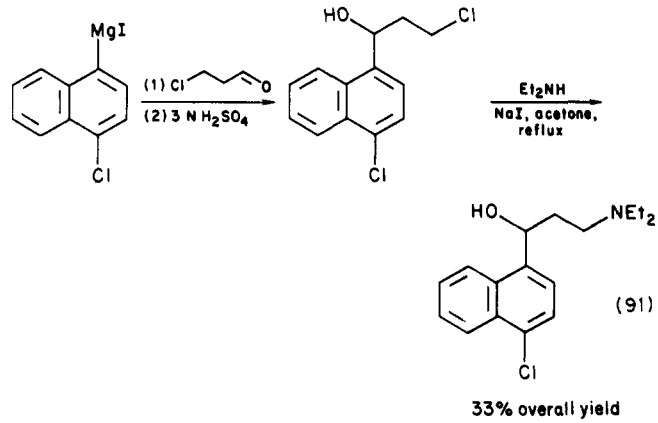
Various enolate-type nucleophiles were alkylated with 1,3-dihalopropanes as listed in Table III.

As noted earlier (eq 12) the allyl function may be introduced and then converted to other groups. Regiospecific allylation of a ketone enolate[170] followed by free-radical addition of HBr[171] gives overall bromopropylation (eq 90).



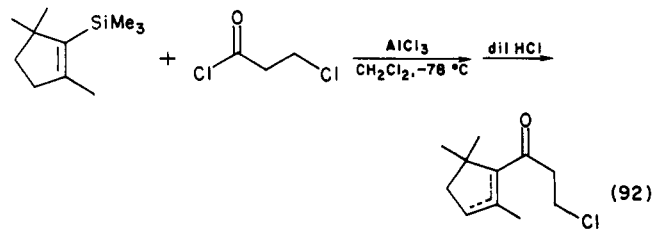

(90)

Other functionality may reside on the three carbons besides the terminal chlorine or bromine. These include alcohols and ketones. Grignard reagents add to $\beta$-chloropropionaldehyde to give the $\beta$-hydroxy chloropropylated products (eq 91).[172]




(91)

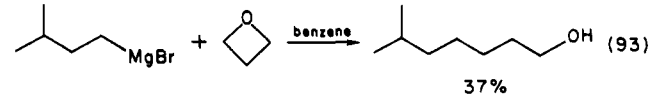
$\beta$-Chloropropionyl chloride reacts with a silane under Lewis acid catalysis to give the $\beta$-keto chloropropylated product (eq 92).[173]




(92)

### B. Hydroxypropylation

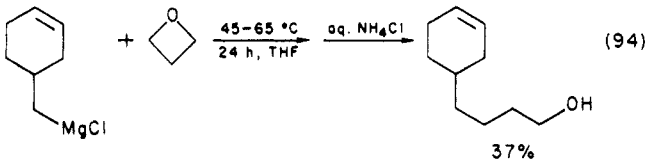
The ring opening of oxetane by carbanions is a direct route to the hydroxypropyl products. Grignard and lithium reagents require prolonged heating and generally give low yields. Combining an ether solution of a Grignard reagent with oxetane gives a precipitate. If the ether is then replaced with benzene and the suspension heated at reflux for 4 h, the alcohols are obtained in 28–84% yields (eq 93).[174,175] Aryl organo-




(93)

metallics give the best yields while secondary and tertiary Grignard reagents give much 3-halo-1-propanol from competing nucleophilic attack by the halide anion. The Grignard reagent may also be prepared and heated with oxetane in THF (eq 94).[176] Catalysis with cuprous iodide obviates the need for heating and gives higher

yields with either lithium[177] or Grignard[178] reagents (eq 95 and 96).

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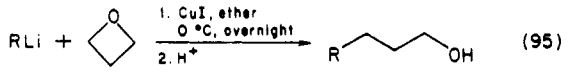
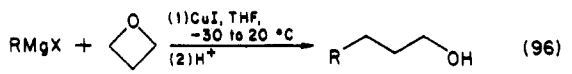



(95)

R (% yield) = *n*-Bu (78); Ph (55); 2-propenyl (50); $Me_2C{=}C{=}CH$ (41).

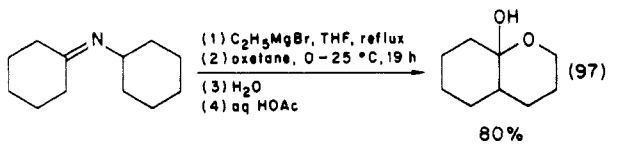



(96)

R (% yield) = *n*-Bu (75); Ph (52); allyl (50).

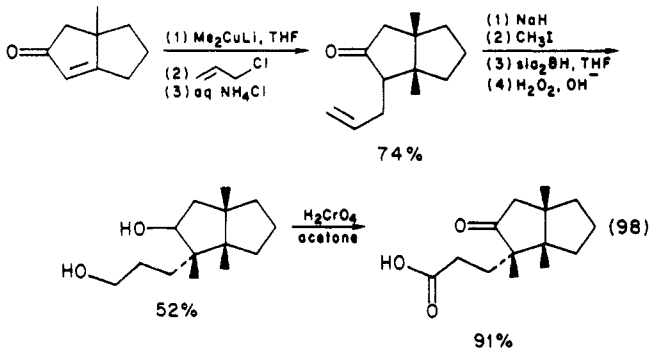
Lithiodithiane reacts with oxetane at −20 °C over a 1 week period to give the hydroxypropylated dithiane in 80% yield.[179]

Delocalized anions have been used similarly, for instance the $\alpha$-anion of acetonitrile (generated with phenyllithium) was alkylated with oxetane in refluxing either for 16 h to afford 2-phenyl-5-hydroxypentanenitrile in 51% yield.[180] The lithium and bromomagnesium enolates of cyclohexanone do not give alkylation with oxetane (the magnesium reagent gave 3-bromopropanol) but the imine enolates do. The hydroxypropylation product appears as the hemiketal after hydrolysis in aqueous acetic acid (eq 97).[181]




(97)

As seen before, the allyl group may be introduced and then coverted to another functionality. For example in the synthesis of (±)-gymnotriol a copper enolate was allylated and the resulting keto alkene hydrated using disiamylborane and oxidation (eq 98). This product was further oxidized to give the three-carbon extended acid.[182]

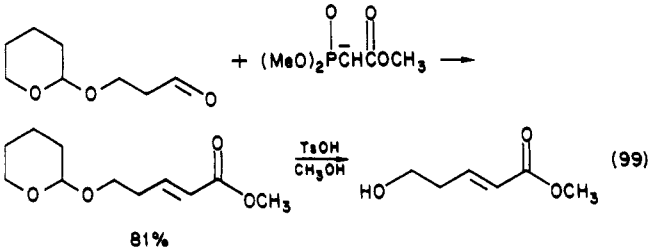



(98)

The hydroxypropyl group may be attached by a double bond if the electrophile is the tetrahydropyranyl-protected $\beta$-hydroxypropionaldehyde. A phosphonate or Wittig reagent gives the homologated product as shown in eq 99.[183]

## C. $\beta$-Electrophilic Equivalents of Propionaldehyde

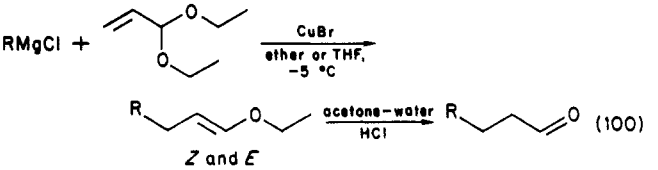
The electrophiles that furnish hydrolyzable derivatives of $\beta$-substituted propionaldehydes include acetals




(99)

of acrolein and $\beta$-bromo- or $\beta$-chloropropionaldehyde, 1,3-dichloropropene, and 1-(thiophenoxy)-3-chloropropene. Again other electrophiles may be used which require an oxidation or reduction step to reach the aldehyde state.

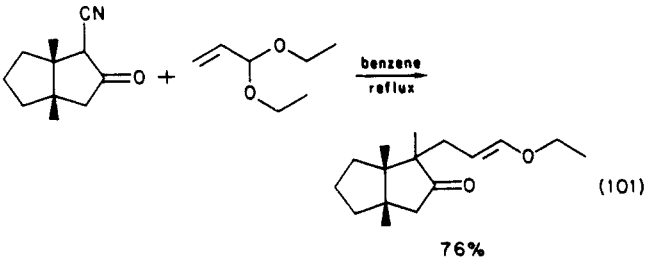
In the presence of cuprous bromide, Grignard reagents will attack the $\beta$-position of the diethyl acetal of acrolein giving the readily hydrolyzable enol ethers (eq 100).[184] Lithium reagents in pentane, and also butyl-




(100)

R (yield of enol ether, *Z* + *E*, %) = *n*-Bu (82.5); *n*-$C_7H_{15}$ (89); *sec*-Bu (53.5); *t*-Bu (83); Ph (65).

copper associated with $BF_3$ in ether do likewise. An enolizable nitrile attacked similarly to again give an enol ether (eq 101). In this case the product was converted to the dioxolane (92%) and eventually hydrolyzed to the aldehyde at a later stage in the synthesis.[185] A similar reaction was observed at the ortho position of a phenol in basic solution.[186]

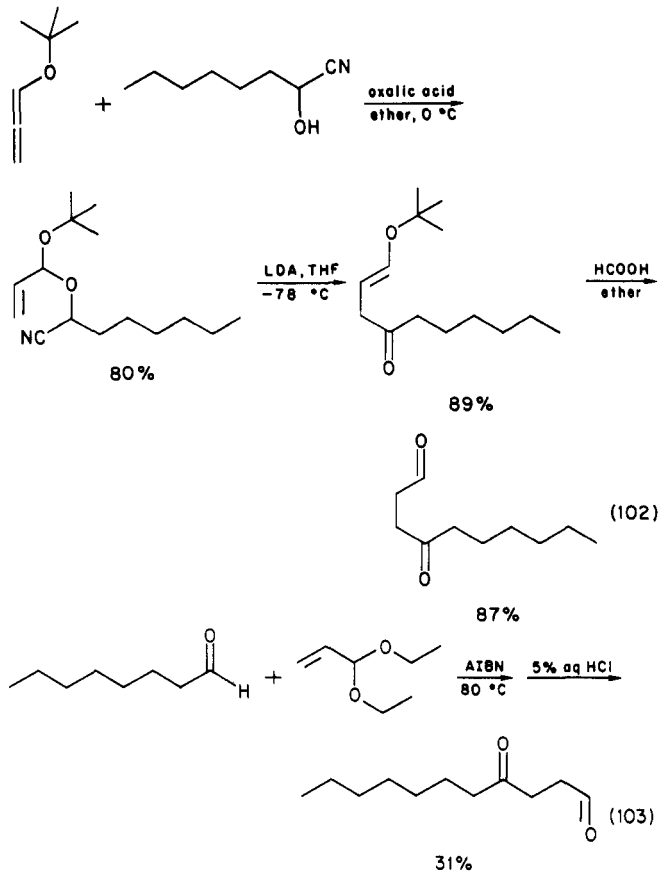



(101)

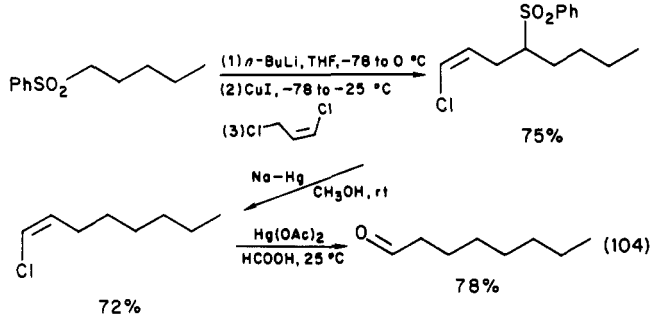
An aldehyde may be extended to a $\gamma$-keto aldehyde by preparing the cyanohydrin and adding it to *tert*-butyl allenyl ether to give an acrolein acetal. Treatment of this product with 2 equiv of a lithium dialkylamide leads to a [2.3] sigmatropic shift and elimination of HCN to give the enol ether a $\gamma$-keto aldehyde. This is hydrolyzed with formic acid (eq 102).[187] The same overall result may be obtained in lower yield but with only two steps using acyl radical attack on acrolein diethyl acetal (eq 103).[188] Here again, hydrolysis gives the $\gamma$-keto aldehyde.[189]

Acyclic and cyclic acetals of $\beta$-chloro and $\beta$-bromopropionaldehyde serve to alkylate a wide variety of carbanions (Table IV). In most cases the acetal is hydrolyzed to the free aldehyde.

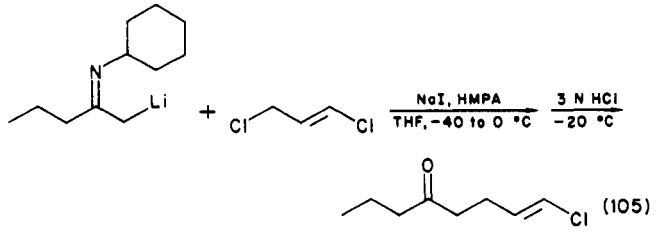
Nucleophilic substitution for the allylic chlorine in 1,3-dichloropropene gives a vinyl chloride which may be hydrolyzed to an aldehyde. Allylmagnesium bromide gives 1-chloro-1,5-hexadiene in 78% yield.[190] Unfortunately, simple Grignard reagents give mostly elimination and coupling byproducts.[191] A sulfone group gives a stabilized carbanion that behaves well as a nucleophile



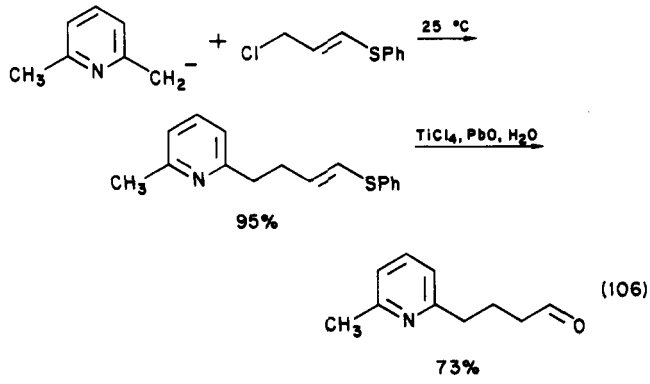

toward 1,3-dichloropropene, and the sulfone group may be removed later by reduction (eq 104).[192] The cuprous iodide was added to prevent dialkylation which otherwise may be up to 20% of the product. The vinyl halide is then hydrolyzed with mercuric acetate in formic acid.



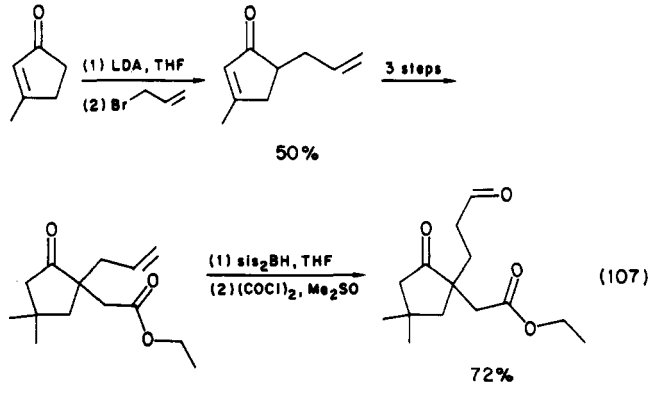

Ketone imine enolates will give good yields of chloroallylation if the carbanion is added to a THF solution of 1,3-dichloropropene, sodium iodide, and HMPA.[193] The imines are hydrolyzed to the ketones (eq 105) in dilute HCl and may be further hydrolyzed to the δ-ketoaldehydes using the mercuric acetate method shown in eq 104.



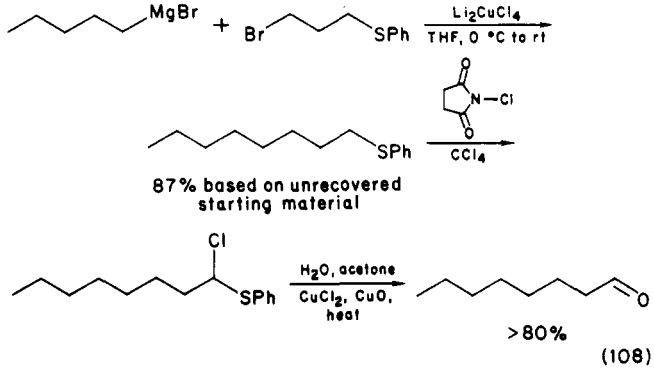

1-(Thiophenoxy)-3-chloropropene is a close analogue to 1,3-dichloropropene. The allylic chloride is again readily displaced and the enol thioether may be hydrolyzed[194] to the substituted propionaldehyde (eq 106).[195] The reagent is available by chlorination of allyl phenyl thioether with trichloroisocyanuric acid.




Several routes involve three-carbon reagents that require oxidation or reduction to reach the aldehyde state. Once again allyl bromide gives an allyl product which was hydroborated and oxidized (eq 107).[196]

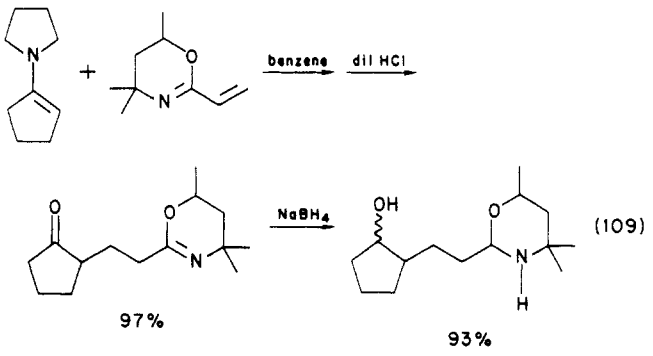



3-Bromopropyl phenyl sulfide will give coupling products with Grignard reagents in the presence of copper. Halogenation adjacent to sulfur followed by copper-assisted hydrolysis gives the homologated aldehyde (eq 108).[197]



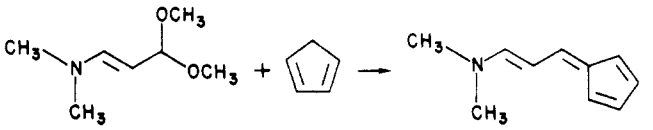

2-Vinyldihydro-1,3-oxazine (made from acrylonitrile) is polymerized by Grignard reagents but does give the conjugate addition product with an enamine. Sodium borohydride reduction of the dihydrooxazine gives the aldehyde precursor (eq 109). The original ketone function may be protected from the sodium borohydride as the ketal.[198]

The three-carbon electrophiles shown in eq 110[199] and 111[200] react with nucleophiles to give the enamines of β,γ-unsaturated aldehydes. Half-protected malon-

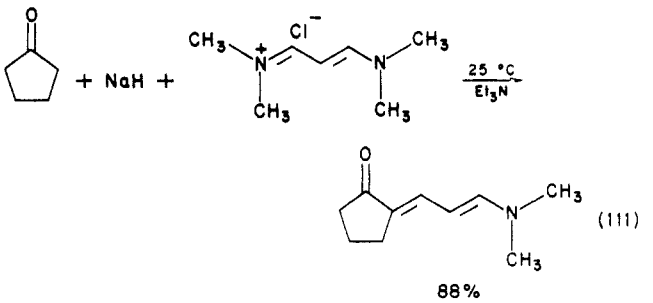



(109)

aldehyde reacts with Wittig reagents to give acetals of $\beta,\gamma$-unsaturated aldehydes.[42]

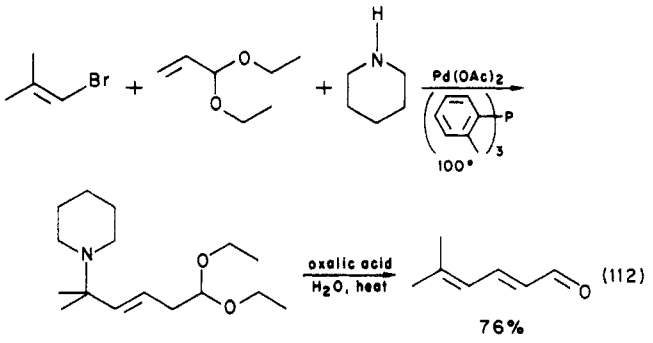



(110)




(111)

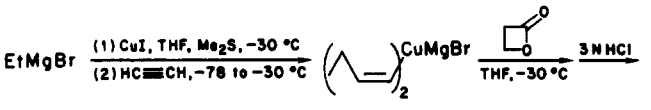
Finally, $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes are available from treatment of acrolein dimethyl acetal with vinyl palladium complexes in the presence of amines (eq 112).[201]




(112)

## 4. β-Electrophilic Equivalents of Propionic Acid, Propionic Ester, or Propionitrile

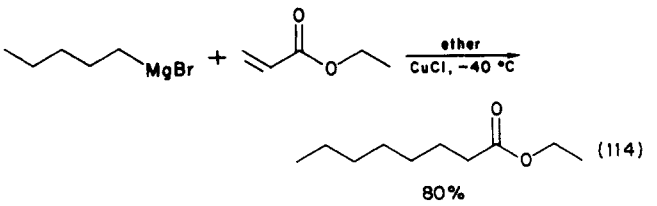
Propiolactone is a reactive electrophile which gives various products depending on the choice of nucleophile. Grignard reagents give mostly β-halopropionic acid along with some carbon attack at both the carbonyl and β-sites. Lithium reagents attack mostly at the carbonyl group. The preferred attack at the β-position occurs under the influence of copper or with lithium dialkylcuprates. Alkyl- and arylmagnesium chlorides are likewise selective in the presence of a catalytic amount of cuprous bromide. Thus isopropylmagnesium chloride with 10% CuBr at −5 °C reacted with butyrolactone to give after acidification 4-methylpentanoic acid in 82% yield.[202] Allyl- and vinylmagnesium chlorides do well if a stoichiometric amount of cuprous salt is used.[203,204] (Z)-Divinylcuprates may be prepared by the addition of dialkylcuprates to acetylene and then used to open propiolactone to give (Z)-4-alkenoic acids (eq 113).[205,206]




(113)

The perfume component 15-pentadecanolide (exaltolide) was made from 1,12-dodecanediol by conversion to 1-bromo-12-methoxydodecane, Grignard formation, and then copper catalyzed β-attack on propiolactone.[207]

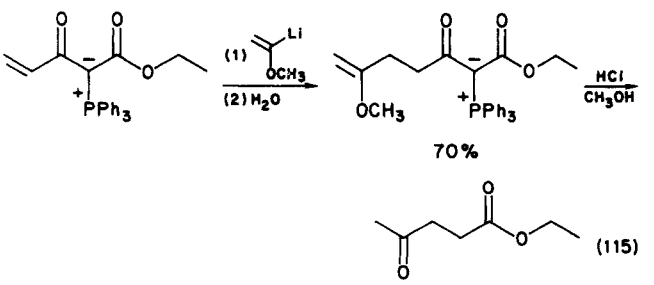
Ethyl acrylate is susceptible to conjugate addition of Grignard reagents if cuprous chloride is used and the temperature is kept at −40 °C to prevent polymerization (eq 114).[208] The Grignard reagents from bromo-




(114)

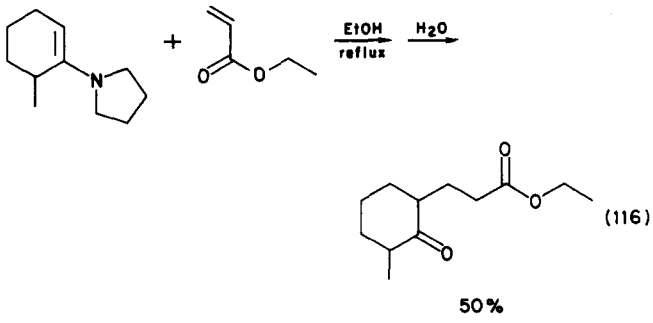
benzene, vinyl bromide, 6-bromo-1-hexene, benzyl chloride, and cyclohexyl bromide gave the corresponding extended esters in 41–73% yields. Lithium di-*sec*-butylcuprate was used in the same way to prepare ethyl 4-methylhexanoate in 57% yield.[209a] Triethyl orthoacrylate and Grignard reagents react in THF with copper catalysis at 5–15 °C to give ketene acetals. Subsequent hydrolysis gives the esters in 66–76% overall yields.[209b]

Without copper, lithium reagents attack the carbonyl group of acrylate esters. This may be prevented by incorporation of a partial negative charge in conjugation with the carbonyl group, and the attack of the alkyllithium reagent will then occur at the β-position. An acyl ylide serves this purpose and is then readily removed by alcoholysis to give the substituted propionic acid (eq 115).[210]



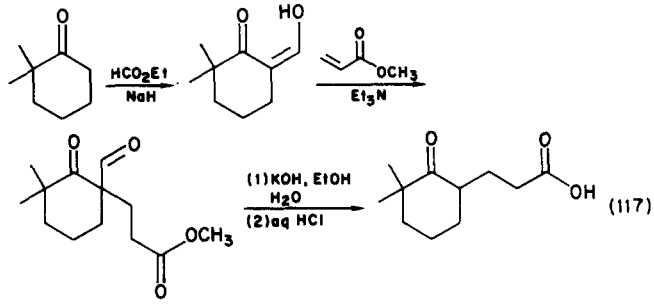

(115)

Enamines (eq 116)[211] and many resonance-stabilized carbanions will give Michael addition to acrylate esters. This area has been reviewed by House.[212] For example, with temporary activation, a cyclohexanone was added to methyl acrylate and then hydrolyzed to the substituted propionic acid (eq 117).[213] Angelicalactone anion adds similarly (eq 118).[214] Heating 2-methylcyclopentane-1,3-dione with triethyl orthoacrylate gives the homologated ortho ester in 85% yield.[185]



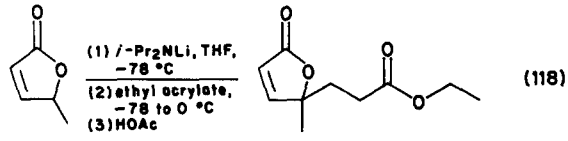

(116)

50%




(117)

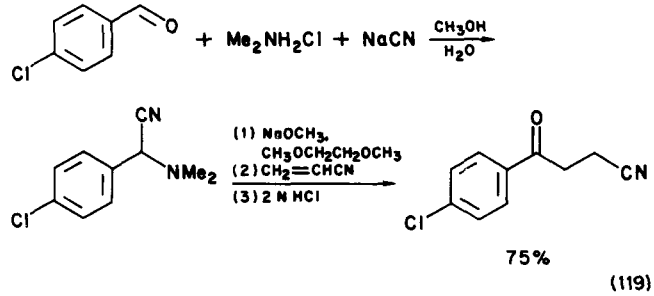
62%




(118)

60%

Acrylonitrile accepts Michael addition of resonance-stabilized carbanions (eq 119)[215] or enamines to give cyanoethylation. If more than one enolizable hydrogen is available, polycyanoethylation usually occurs. This process has been reviewed.[216] Cyanide ion catalyzes the addition of aldehydes to acrylonitrile, affording γ-keto nitriles. Thiazolium ion catalysts will cause addition of aldehydes to acrylate esters but the yields are usually low.[217]

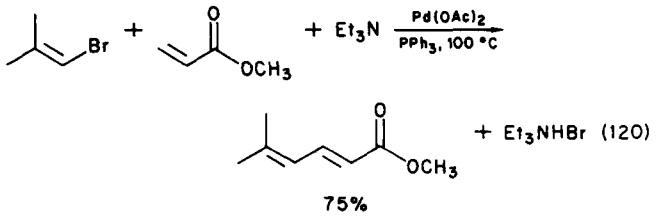



75%

(119)

α,β-Unsaturated homologated esters are available from conjugate addition to methyl propynoate. Vinylcopper adds at −78 °C and with methanol quenching (−78 °C) affords (*E*)-methyl penta-2,4-dienoate in 85% yield.[140] Lithium 1-pentynyl-*tert*-butylcuprate,[218] allylcopper, and lithium (3-methyl-1,2-butadienyl)-cuprate[219] also give conjugate addition to methyl propynoate. The syn stereoselectivity can also be obtained at higher temperatures if a boron complex of the copper reagent is used. Thus *n*-butylcopper(I)–triethylborane adds to ethyl propynoate at −55 °C to give a 67% yield of ethyl (*E*)-2-heptenoate. Propynoic acid at −70 °C gives (*E*)-2-heptenoic acid.[220,221]

α,β,γ,δ-Unsaturated esters are available from the reaction of methyl acrylate with vinyl palladium complexes in the presence of amines (eq 120).[222] This is the




75%

same process as shown in eq 112 for generating unsaturated aldehydes.

Abbreviations

| | |
|---|---|
| Ac | acetyl |
| Bu | butyl |
| Dabco | 1,4-diazabicyclo[2.2.2]octane |
| Et | ethyl |
| HMPA | hexamethylphosphoric triamide |
| LDA | lithium diisopropylamide |
| Me | methyl |
| $Me_2SO$ | dimethyl sulfoxide |
| Ph | phenyl |
| Pr | propyl |
| rt | room temperature |
| THF | tetrahydrofuran |
| TMEDA | tetramethylethylenediamine |
| Ts | *p*-tolylsulfonyl |

## References


(1) Hamonet, J.; Lemoine, M. G. *Compt. Rend.* **1904**, *138*, 975.
(2) Erlenmeyer, H.; Marbet, R. *Helv. Chim. Acta* **1946**, *29*, 1946.
(3) Paul, R. *Ann. Chim. (Paris)* **1932**, *18*, 311.
(4) Rabjohn, N.; Cohen, M. S. *J. Am. Chem. Soc.* **1952**, *74*, 6290.
(5) Renfrow, W. B.; Oakes, D.; Lauer, C.; Walter, T. A. *J. Org. Chem.* **1961**, *26*, 935.
(6) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *60*, 925.
(7) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1977**, *42*, 2362.
(8) Monti, S. A.; Chen, S.-C.; Yang, Y.-L.; Yuan, S.-S.; Bourgeois, O. P. *J. Org. Chem.* **1978**, *43*, 4062.
(9) Bakuzis, P.; Bakuzis, M. L. F.; Weingartner, T. F. *Tetrahedron Lett.* **1978**, 2371.
(10) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064. Dimitriadis, E.; Massey-Westropp, R. A. *Austr. J. Chem.* **1984**, *37*, 619.
(11) Eaton, P. E.; Cooper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947.
(12) Eaton, P. E.; Mueller, R. H.; Carlson, G. R.; Cullison, D. A.; Cooper, G. F.; Chou, T.-C.; Krebs, E.-P. *J. Am. Chem. Soc.* **1977**, *99*, 2751.
(13) Salaün, J.; Bennani, F.; Compain, J.-C.; Fadel, A.; Ollivier, J. *J. Org. Chem.* **1980**, *45*, 4129.
(14) Haslouin, J.; Rouessac, F. *Tetrahedron Lett.* **1976**, 4651.
(15) Jacobson, R.; Taylor, R. J.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1982**, *47*, 3140.
(16) Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327.
(17) Leyendecker, F.; Drouin, J.; Debesse, J. J.; Conia, J. M. *Tetrahedron Lett.* **1977**, 1591.
(18) Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1977**, *42*, 3630.
(19) Anderson, R. J.; Corbin, V. L.; Cotterell, G.; Cox, G. R.; Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 1197.
(20) Bryson, T. A.; Smith, D. C.; Kreuger, S. A. *Tetrahedron Lett.* **1977**, 525.
(21) Descoins, C.; Samain, D.; Lalanne-Cassou, B.; Gallois, M. *Bull. Soc. Chim. Fr.* **1977**, 941.
(22) Labovitz, J. N.; Henrick, C. A.; Corbin, V. L. *Tetrahedron Lett.* **1975**, 4209.
(23) Julia, M.; Uguen, D.; Callipolitis, A. *Bull. Soc. Chim. Fr.* **1976**, 519.
(24) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.
(25) Alexakis, A.; Cahiez, G.; Normant, J. F. *Tetrahedron Lett.* **1978**, 2027.
(26) Godleski, S. A.; Valpey, R. S. *J. Org. Chem.* **1982**, *47*, 381.
(27) Jacob, P. III. *J. Org. Chem.* **1982**, *47*, 4165.
(28) Miodownik, A.; Kreisberger, J.; Nussim, M.; Avnir, D. *Synth. Commun.* **1981**, *11*, 241.
(29) House, H. O.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1978**, *43*, 2153.

(30) Seetz, J. W. F. L.; Hartog, F. A.; Böhm, H. P.; Blomberg, C.; Akkerman, O. S.; Bickelhaupt, F. *Tetrahedron Lett.* **1982**, *23*, 1497.
(31) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.
(32) Feugeas, Cl. *Bull. Soc. Chim. Fr.* **1963**, 2568.
(33) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.
(34) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.
(35) Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560. Stowell, J. C.; Keith, D. R.; King, B. T. *Org. Synth.* **1984**, *62*, 140.
(36) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105.
(37) Stowell, J. C.; King, B. T. *Synthesis* **1984**, 278.
(38) Sato, T.; Naruse, K.; Fujisawa, T. *Tetrahedron Lett.* **1982**, *23*, 3587.
(39) Leone-Bay, A.; Paquette, L. A.; *J. Org. Chem.* **1982**, *47*, 4173.
(40) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165.
(41) Stowell, J. C.; Keith, D. R. *Synthesis* **1979**, 132.
(42) Bertrand, M.; Leandri, G.; Meou, A. *Tetrahedron* **1981**, *37*, 1703.
(43) Stowell, J. C.; Hauck, H. F. Jr. *J. Org. Chem.* **1981**, *46*, 2428.
(44) Corey, E. J.; Vlattas, I.; Andersen, N. H.; Harding, K. *J. Am. Chem. Soc.* **1968**, *90*, 3247.
(45) Corey, E. J.; Vlattas, I.; Harding, K. *J. Am. Chem. Soc.* **1969**, *91*, 535.
(46) Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1982**, *47*, 4040.
(47) Corey, E. J. *Ann. N. Y. Acad. Sci.* **1971**, *180*, 24.
(48) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1007.
(49) Julia, M.; Badet, B. *Bull. Soc. Chim. Fr.* **1975**, 1363.
(50) Kondo, K.; Saito, E.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 2275.
(51) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1397.
(52) Menicagli, R.; Wis, M. L.; Lardicci, L.; Botteghi, C.; Caccia, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 847.
(53) Janssen, C. G. M.; van Lier, P. M.; Buck, H. M.; Godefroi, E. F. *J. Org. Chem.* **1979**, *44*, 4199.
(54) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560.
(55) Still, W. C.; Macdonald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561.
(56) Hartmann, J.; Stähle, M.; Schlosser, M. *Synthesis* **1974**, 888.
(57) Hartmann, J.; Muthukrishnan, R.; Schlosser, M. *Helv. Chim. Acta* **1974**, *57*, 2261.
(58) Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620.
(59) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1024.
(60) Hoppe, D.; Brönneke, A. *Tetrahedron Lett.* **1983**, *24*, 1687.
(61) Hirai, K.; Kishida, Y. *Org. Synth.* **1977**, *56*, 77.
(62) Oshima, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn* **1975**, *48*, 1567.
(63) Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1981**, *46*, 5182.
(64) Kyler, K. S.; Netzel, M. A.; Arseniyadis, S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 383.
(65) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790.
(66) Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. R. *Aust. J. Chem.* **1981**, *34*, 2465.
(67) Geiss, K.-H.; Seebach, D.; Seuring, B. *Chem. Ber.* **1977**, *110*, 1833.
(68) Pohmakotr, M.; Geiss, K.-H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420.
(69) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004.
(70) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, *43*, 2551.
(71) Martin, S. F.; DuPriest, M. T. *Tetrahedron Lett.* **1977**, 3925.
(72) Ahlbrecht, H.; Eichler, J. *Synthesis* **1974**, *672*.
(73) Julia, M.; Schouteeten, A.; Baillarge, M. *Tetrahedron Lett.* **1974**, 3433.
(74) Coutrot, P.; Savignac, P. *J. Chem. Res., Synop.* **1977**, 308. *J. Chem. Res., Miniprint* **1977**, 3401.
(75) Hassel, T.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 399.
(76) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1978**, *43*, 4247.
(77) Stork, G.; Logusch, E. W. *Tetrahedron Lett.* **1979**, 3361.
(78) Ishiguro, M.; Akaiwa, A.; Fujimoto, Y.; Sato, S.; Ikekawa, N. *Tetrahedron Lett.* **1979**, 763.
(79) Brown, H. C.; Rogić, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1967**, *89*, 5709.
(80) Stowell, J. C.; Harry-O'Kuru, R., unpublished results.
(81) Bryson, T. A.; Bonitz, G. H.; Reichel, C. J.; Dardis, R. E. *J. Org. Chem.* **1980**, *45*, 524.
(82) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 883.
(83) Goswami, R.; Corcoran, D. E. *Tetrahedron Lett.* **1982**, *23*, 1463.
(84) Sturtz, G.; Corbel, B. *C. R. Acad. Sci. Ser. C* **1973**, *277*, 395.
(85) Sturtz, G.; Corbel, B.; Paugam, J.-P. *Tetrahedron Lett.* **1976**, 47.
(86) Sturtz, G.; Yaouanc, J.-J. *Synthesis* **1980**, 289.
(87) Ziegler, F. E.; Tam, C. C. *J. Org. Chem.* **1979**, *44*, 3428.
(88) Schubert, U. *Synthesis* **1978**, 364.
(89) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395.
(90) Evans, D. A.; Takacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371.
(91) Ahlbrecht, H.; Vonderheid, C. *Synthesis* **1975**, 512.
(92) Costisella, B.; Gross, H. *Tetrahedron* **1982**, *38*, 139.
(93) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1970**, *35*, 3405.
(94) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360.
(95) Rühlmann, K. *Synthesis* **1971**, 236.
(96) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.
(97) Gaudemar, M. *Ann. Chim. (Paris)* **1956**, 161.
(98) Bowlus, S. B.; Katzenellenbogen, J. A. *J. Org. Chem.* **1973**, *38*, 2733.
(99) Bowlus, S. B.; Katzenellenbogen, J. A. *Tetrahedron Lett.* **1973**, 1277.
(100) Ireland, R. E.; Dawson, M. I.; Lipinski, C. A. *Tetrahedron Lett.* **1970**, 2247.
(101) Gouin, L.; Faroux, M.-C.; Riobé, O. *Bull. Soc. Chim. Fr.* **1966**, 2320.
(102) Corey, E. J.; Kirst, A. *Tetrahedron Lett.* **1968**, 5041.
(103) Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831.
(104) Corey, E. J. Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719.
(105) Bhanu, S.; Scheinmann, F. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1218.
(106) Negishi, E.; Rand, C. L.; Jadhav, K. P. *J. Org. Chem.* **1981**, *46*, 5041.
(107) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265.
(108) Miller, R. B.; Al-Hassan, M. I. *Tetrahedron Lett.* **1983**, *24*, 2055.
(109) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1982**, *47*, 725.
(110) Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Tetrahedron Lett.* **1973**, 1385.
(111) Cooper, G. K.; Dolby, L. J. *Tetrahedron Lett.* **1976**, 4675.
(112) Cristau, H. J.; Chabaud, B.; Niangoran, C. *J. Org. Chem.* **1983**, *48*, 1527.
(113) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724.
(114) Cohen, T.; Bennett, D. A.; Mura, A. J., Jr. *J. Org. Chem.* **1976**, *41*, 2506.
(115) Wada, M.; Nakamura, H.; Taguchi, T.; Takei, H. *Chem. Lett.* **1977**, 345.
(116) Reich, H. J.; Clark, M. C.; Willis, W. W., Jr. *J. Org. Chem.* **1982**, *47*, 1618.
(117) Nakai, T.; Shiono, H.; Okawara, M. *Tetrahedron Lett.* **1974**, 3625.
(118) Iwai, K.; Kosugi, H.; Miyazaki, A.; Uda, H. *Synth. Commun.* **1976**, *6*, 357.
(119) Schmidt. R. R.; Talbiersky, J.; Russegger, P. *Tetrahedron Lett.* **1979**, 4273.
(120) Schmidt, R. R.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 204.
(121) Clemo, N. G.; Pattenden, G. *Tetrahedron Lett.* **1982**, *23*, 585. (a) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 5167.
(122) Bauer, P. E.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 34.
(123) Montijn, P. P.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 129.
(124) Phillips, C.; Jacobson, R.; Abrahams, B.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1980**, *45*, 1920.
(125) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.
(126) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318.
(127) Corey, E. J.; Achiwa, K. *Tetrahedron Lett.* **1969**, 1837.
(128) Atkinson, R. E.; Curtis, R. F.; Jones, D. M.; Taylor, J. A. *J. Chem. Soc. C* **1969**, 2173.
(129) Picard, P.; Moulines, J. *Bull. Soc. Chim. Fr.* **1974**, 2256.
(130) Boeckman, R. K., Jr.; Thomas, E. W. *Tetrahedron Lett.* **1976**, 4045.
(131) Smith, L. R.; Williams, H. J.; Silverstein, R. M. *Tetrahedron Lett.* **1978**, 3231.
(132) James, K.; Raphael, R. A. *Tetrahedron Lett.* **1979**, 3895.
(133) Earl, R. A.; Townsend, L. B. *Org. Synth.* **1981**, *60*, 81.
(134) Warrener, R. N.; Cain, E. N. *Aust. J. Chem.* **1971**, *24*, 785.
(135) Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 1226.
(136) Rickards, G.; Weiler, L. *J. Org. Chem.* **1978**, *43*, 3607.
(137) Giusti, G. *Bull. Soc. Chim. Fr.* **1972**, 753.
(138) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485.
(139) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.
(140) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* **1972**, *94*, 4395.
(141) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.
(142) Caine, D.; Smith, T. L., Jr. *Synth. Commun.* **1980**, *10*, 751.

(143) Yamada, K.; Miyaura, N.; Itoh, M.; Suzuki, A. *Synthesis* **1977**, 679.
(144) Carlson, R. M.; Oyler, A. R.; Peterson, J. R. *J. Org. Chem.* **1975**, *40*, 1610.
(145) Coke, J. L.; Richon, A. B. *J. Org. Chem.* **1976**, *41*, 3516.
(146) Mori, K.; Oda, M.; Matsui, M. *Tetrahedron Lett.* **1976**, 3173.
(147) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760.
(148) Iwamoto, M.; Takagi, Y.; Kogami, K.; Hayashi, K. *Agric. Biol. Chem.* **1983**, *47*, 117.
(149) Hercouet, A.; Le Corre, M.; *Tetrahedron Lett.* **1979**, 5.
(150) Camps, F.; Coll, J.; Canela, R.; Guerrero, A.; Riba, M. *Chem. Lett.* **1981**, 703.
(151) Heath, R. R.; Doolittle, R. E.; Sonnet, P. E.; Tumlinson, J. H. *J. Org. Chem.* **1980**, *45*, 2910.
(152) Utimoto, K.; Tamura, M.; Sisido, K. *Tetrahedron* **1973**, *29*, 1169.
(153) Descoins, C.; Henrick, C. A. *Tetrahedron Lett.* **1972**, 2999.
(154) McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566.
(155) Corey, E. J.; Ulrich, P. *Tetrahedron Lett.* **1975**, 3685.
(156) Winter, M. *Helv. Chim. Acta* **1963**, *46*, 1792.
(157) Baldwin, S. W.; Crimmins, M. T. *J. Am. Chem. Soc.* **1982**, *104*, 1132. (a) Battersby, A. R.; Buckley, D. G.; Staunton, J.; Williams, P. J. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2550.
(158) Cohen, N.; Banner, B. L.; Lopresti, R. J. *Tetrahedron Lett.* **1980**, *21*, 4163.
(159) Cristau, H. J.; Vors, J. P.; Beziat, Y.; Niangoran, C.; Christol, H. *ACS Symp. Ser.* **1981**, *171*, 59.
(160) Iwamoto, M.; Kubota, N.; Takagi, Y.; Kogami, K.; Hayashi, K. *Agric. Biol. Chem.* **1982**, *46*, 2383.
(161) Martin, S. F.; Garrison, P. J. *Tetrahedron Lett.* **1977**, 3875.
(162) Lavielle, G.; Sturtz, G. *Bull. Soc. Chim. Fr.* **1970**, 1369.
(163) Lavielle, G.; Sturtz, G., Normant, H. *Bull. Soc. Chim. Fr.* **1967**, 4186. (a) Corey, H. S.; McCormick, J. R. D.; Swensen, W. E. *J. Am. Chem. Soc.* **1964**, *86*, 1884. (b) Oda, R.; Kawabata, T.; Tanimoto, S. *Tetrahedron Lett.* **1964**, 1653.
(164) Just, G.; Potvin, P.; Hakimelahi, G. H. *Can. J. Chem.* **1980**, *58*, 2780.
(165) Rossander, S. S.; Marvel, C. S. *J. Am. Chem. Soc.* **1928**, *50*, 1491.
(166) Harmon, J.; Marvel, C. S. *J. Am. Chem. Soc.* **1932**, *54*, 2515.
(167) Friedman, L.; Shani, A. *J. Am. Chem. Soc.* **1974**, *96*, 7101.
(168) Normant, J. F.; Chaiez, G.; Chuit, C.; Villieras, J. *Tetrahedron Lett.* **1973**, 2407. (a) Lipshutz, B. H.; Parker, D.; Kozlowski, J. A.; Miller, R. D. *J. Org. Chem.* **1983**, *48*, 3334.
(169) Bauer, D.; Kobrich, G. *Chem. Ber.* **1976**, *109*, 2185.
(170) Caine, D.; Chao, S. T.; Smith, H. A. *Org. Synth.* **1977**, *56*, 52.
(171) House, H. O.; Chu, C.-Y., *Phillips*, W. V.; Sayer, T. S. B., Yau, C.-C. *J. Org. Chem.* **1977**, *42*, 1709.
(172) Jacobs, T. L.; Winstein, S.; Linden, G. B.; Seymour, D. *J. Org. Chem.* **1946**, *11*, 223.
(173) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.
(174) Searles, S. *J. Am. Chem. Soc.* **1951**, *73*, 124.
(175) Bestmann, H. J.; Vostrowsky, O.; Stransky, W. *Chem. Ber.* **1976**, *109*, 3375.
(176) Marvell, E. N.; Sturmer, D.; Knutson, R. S. *J. Org. Chem.* **1968**, *33*, 2991.
(177) Millon, J.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, 1095.
(178) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503.
(179) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.
(180) Darko, L. L.; Cannon, J. G. *J. Org. Chem.* **1967**, *32*, 2352.
(181) Hudrlik, P. F.; Wan, C.-N. *J. Org. Chem.* **1975**, *40*, 2963.
(182) Welch, S. C.; Chayabunjonglerd, S.; Prakasa Rao, A. S. C. *J. Org. Chem.* **1980**, *45*, 4086.
(183) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037.
(184) Normant, J. F.; Commercon, A.; Bourgain, M.; Villieras, J. *Tetrahedron Lett.* **1975**, 3833. Mioskowski, C.; Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 519. Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3079.
(185) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765. Coates, R. M.; Hobbs, S. J. *J. Org. Chem.* **1984**, *49*, 140.
(186) Clarke, D. G.; Crombie, L.; Whiting, D. A. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1007.
(187) Cazes, B.; Julia, S. *Bull. Soc. Chim. Fr.* **1977**, 931.
(188) Mondon, A. *Angew. Chem.* **1952**, *64*, 224.
(189) Jones, T. H.; Blum, M. S.; Fales, H. M.; Thompson, C. R. *J. Org. Chem.* **1980**, *45*, 4778.
(190) Spangler, C. W.; Woods, G. F. *J. Org. Chem.* **1965**, *30*, 2218.
(191) Pourrat, H. *Compt. Rend.* **1949**, *228*, 1031.
(192) Julia, M.; Blasioli, C. *Bull. Soc. Chim. Fr.* **1976**, 1941.
(193) Larchevêque, M.; Valette, G.; Cuvigny, Th. *Tetrahedron* **1979**, *35*, 1745.
(194) Mura, A. J., Jr.; Majetich, G.; Grieco, P. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4437.
(195) Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4433.
(196) Smith, A. B., III; Wexler, B. A.; Slade, J. *Tetrahedron Lett.* **1982**, *23*, 1631.
(197) Bakuzis, P.; Bakuzis, M. L. F.; Fortes, C. C.; Santos, R. *J. Org. Chem.* **1976**, *41*, 2769.
(198) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36.
(199) Bredereck, H.; Effenberger, F.; Zeyfang, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 242.
(200) Nair, V.; Cooper, C. S. *J. Org. Chem.* **1981**, *46*, 4759. Nair, V.; Jahnke, T. S. *Synthesis* **1984**, 424.
(201) Patel, B. A.; Kim, J. I.; Bender, D. D.; Kao, L.-C.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1061.
(202) Sato, T.; Kawara, T.; Kawashima, M.; Fujisawa, T. *Chem. Lett.* **1980**, 571.
(203) Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1980**, *21*, 935.
(204) Fujisawa, T.; Sato, T.; Kawara, T.; Kawashima, M.; Shimizu, H.; Ito, Y. *Tetrahedron Lett.* **1980**, *21*, 2181.
(205) Sato, T.; Kawara, T.; Sakata, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn* **1981**, *54*, 505.
(206) Fujisawa, T.; Sato, T.; Kawara, T.; Naruse, K. *Chem. Lett.* **1980**, 1123.
(207) Sato, T.; Kawara, T.; Kokubu, Y.; Fujisawa, T. *Bull. Chem. Soc. Jpn* **1981**, *54*, 945.
(208) Liu, S.-H. *J. Org. Chem.* **1977**, *42*, 3209.
(209) (a) Casey, C. P.; Cyr, C. R.; Grant, J. A. *Inorg. Chem.* **1974**, *13*, 910. (b) Gendreau, Y.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1979**, 305.
(210) Cooke, M. P., Jr.; Goswami, R. *J. Am. Chem. Soc.* **1977**, *99*, 642.
(211) Claus, P. K.; Vierhapper, F. W.; Willer, R. L. *J. Org. Chem.* **1977**, *42*, 4016.
(212) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin, Inc.: Menlo Park, CA, 1972.
(213) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1978**, *31*, 1809.
(214) Kraus, G. A.; Roth, B. *Tetrahedron Lett.* **1977**, 3129.
(215) Reutrakul, V.; Nimgirawath, S.; Panichanun, S.; Ratananukul, P. *Chem. Lett.* **1979**, 399.
(216) Bruson, H. A. *Org. React. (N.Y.)* **1949**, *5*, 79.
(217) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.
(218) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(219) Michelot, D.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, 275.
(220) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1979**, *44*, 1744.
(221) Yamada, K.; Miyaura, N.; Itoh, M.; Suzuki, A. *Bull. Chem. Soc. Jpn* **1977**, *50*, 3431.
(222) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.