Tetrahedron Vol. 45, No. 2, pp. 495 to 506, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

APPLICATIONS OF α-ALKOXYORGANOCUPRATE REAGENTS IN THE REGIOSPECIFIC SYNTHESIS OF CYCLIC HOMOALDOL PRODUCTS

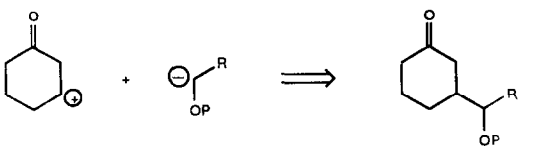
Russell J. Linderman*, Alex Godfrey, and Kelly Horne

Department of Chemistry
North Carolina State University, Raleigh, NC 27695-8204, USA

(*Received in USA* 27 *June* 1988)

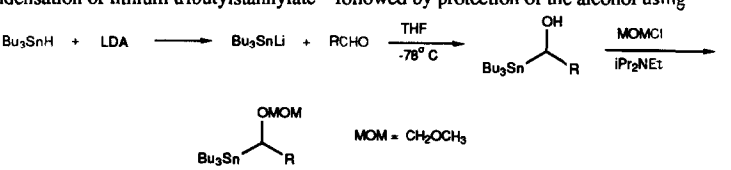
Abstract Cyclic homoaldol products have been prepared via conjugate addition of α-alkoxyorganocuprate reagents to enones. The reactions are regiospecific, providing the homoaldol products in good to excellent yields. The preparation of the cuprates from the α-alkoxyorganostannane precursor is described in detail. Best results were obtained with the higher order cyano cuprate reagent using in-situ trimethylsilyl chloride.

The preparation and study of synthetic equivalents to homoenolate anions has led to successful routes for the preparation of acyclic homoaldol products.[1] Recent efforts in this area have resulted in the generation of enantioselective reagents with relatively high degrees of asymmetric induction.[2] In comparison, efforts to prepare homoenolates from cyclic ketones have not progressed nearly as far.[3] A homoenolate equivalent for cyclohexanone, a β-tributylstannyl silyl enol ether derivative, has been prepared by Chenard.[4] Transmetallation of the stannane generated the homoenolate equivalent; however, condensation reactions with aryl aldehydes resulted in mixtures of α and γ alkylated products.[5] We have chosen to develop a general route to cyclic homoaldol products by employing the concept of reactivity umpolung[6] to circumvent the regioselectivity problems encountered with alkoxyalkyl anions. This approach required the regiospecific conjugate addition reaction of an α-alkoxyanion to a cyclic enone. α-Heteroatom substituted anions are well

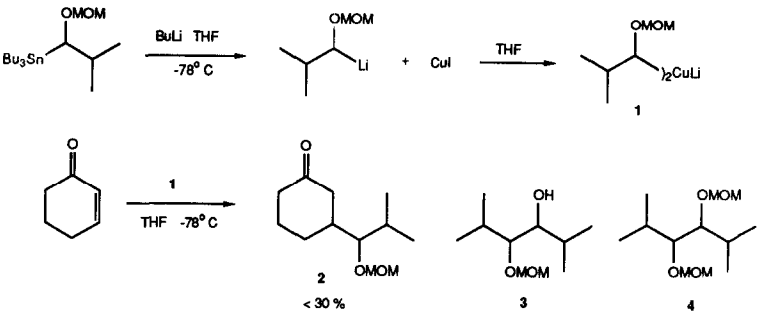


known[7] and α-alkoxylithio species are readily available from the corresponding α-alkoxystannane.[8] We have recently reported the preparation of α-alkoxyorganocuprates,[9] via the α-alkoxyorganostannane derived from aldehydes, and described the application of these reagents in the synthesis of cyclic homoaldol products in preliminary form.[10] We now present a full account of this work, and describe the preparation of ketone derived α-alkoxyorganocuprates.

A series of α-alkoxyorganostannanes were readily prepared from the corresponding aldehyde by condensation of lithium tributylstannylate[8a] followed by protection of the alcohol using

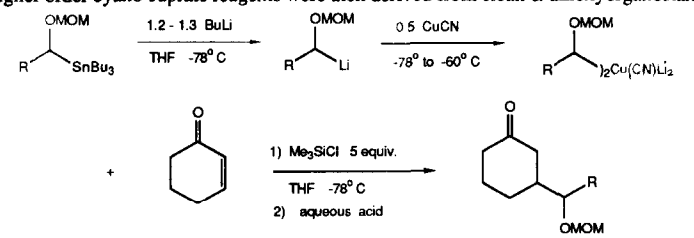


chloromethyl methyl ether and Hunig's base. Initial attempts to generate the homocuprate 1 from copper (I) iodide met with little success.[9a] Rather than the conjugate addition product from the reaction with cyclohexenone, 2, dimeric products 3 and 4 were obtained. Fuchs[10b] has also reported the isolation of dimeric by-products in attempts to form cuprate reagents from α-alkoxyorganostannanes. The dimers presumably were due to oxidative dimerization of the cuprate reagent catalyzed by traces of copper (II) salts present in commercially available copper (I) sources.



Indeed, these workers[10b] reported that this problem was especially significant when commercially available copper (I) cyanide was employed. In contrast to this report, our studies have indicated that higher order cyano cuprates[11] (from CuCN) are the reagents of choice for the conjugate addition of α-alkoxyorganocuprates to enones. The most critical feature to the success of the conjugate addition reaction of these species has been the purity of the α-alkoxyorganostannane precursor. The generation of α-alkoxyorganocuprates from a variety of copper (I) salts has been possible if the stannane employed was 99% pure from other tin contaminants. The major tin by-products present in crude α-alkoxystannane obtained from lithium tributylstannylate derived by deprotonation of tributyltin hydride by lithium diisopropylamide (LDA) have been identified as tributyltin hydride, hexabutylditin, and hexabutyldistannoxane. The hexabutylditin can be formed in relatively large proportions during the LDA deprotonation of tributyltin hydride if care is not exercised. Secondary amines are known to catalyze the dimerization of tin hydrides.[12] Higher molecular weight catenated tin compounds are also produced in small quantities. In separate experiments, we have also demonstrated that (α-hydroxyalkyl)tributylstannanes revert to the aldehyde and the stannyl anion in basic aqueous solution at room temperature. The reversibility of tin anion addition to aldehydes was also demonstrated by adding a catalytic amount of potassium hydride to a THF solution of an (α-hydroxyalkyl)tributylstannane at room temperature. Removal of the solvent at reduced pressure (no aqueous quench) revealed only tributyltin hydride and the aldehyde. The di-tin and tin oxide contaminants are not readily removed from the α-alkoxyorganostannane by simple distillation. In general, column chromatographic purification was carried out (flash chromatography on silica gel), and the purity of the α-alkoxyorganostannane assessed by capillary gas chromatography. Although the stannanes routinely employed were prepared via the tin hydride / LDA route, tributylstannylmagnesium chloride[13] can also be used for the initial aldehyde condensation step.

Higher order cyano cuprate reagents were then derived from clean α-alkoxyorganostannanes,



via the α-alkoxylithio species by transmetallation in THF. Best results were obtained using 1.2 - 1.3 equivalents of n-butyllithium for the preparation of the α-alkoxyorganolithio species. In reactions where transmetallation of the stannane was incomplete, some butyl transfer product (1,4-addition via butyl cuprate) was isolated. Greater difficulties with the transmetallation step were noted with α-alkoxyorganostannane which had been stored for several months. The best results

were obtained with fresh stannanes, or material which was less than one month old. The higher order cyano cuprate reagent forms readily below -65° C as evidenced by complete dissolution of copper (I) cyanide (Aldrich, tan colored, used without purification). A clear homogeneous solution of the cuprate was obtained. We had earlier warmed the cuprate solutions during the formation step[9a]; however, this is not necessary and may be detrimental to reproducible results. Turbid, colored solutions were indicative of impure α-alkoxystannane starting material and ultimately provided reduced yields of the cyclic homoaldol products. Optimal yields were obtained using five equivalents of trimethylsilyl chloride (TMSCl) premixed with the enone.[9a,10b,14] Examples of the preparation of several cyclic homoaldol products are shown in Table I.

TABLE I Homoaldol Products from α-Alkoxyorganocuprate Conjugate Addition Reactions

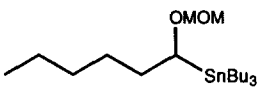
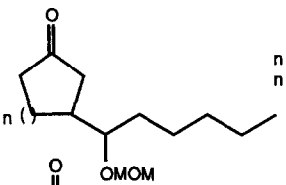
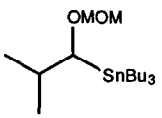
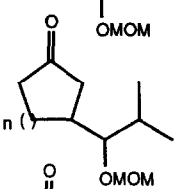
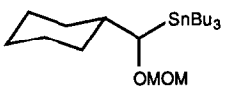
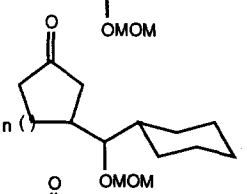
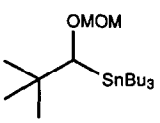
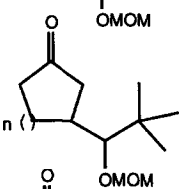
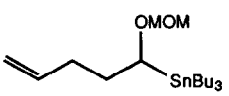
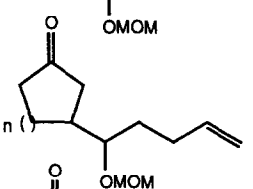
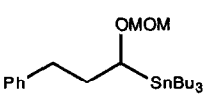
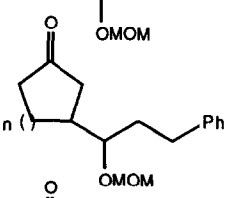
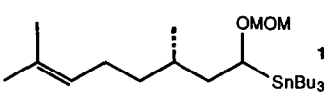
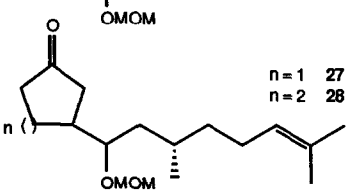
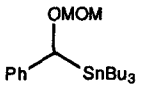
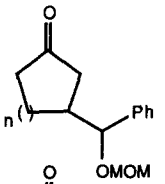
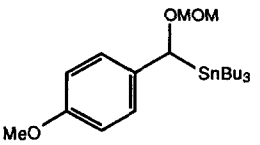
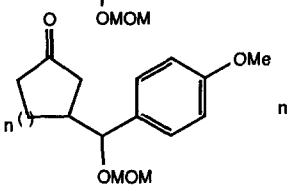
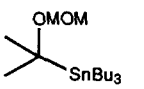
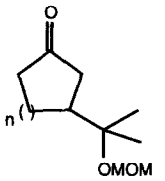
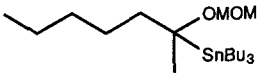
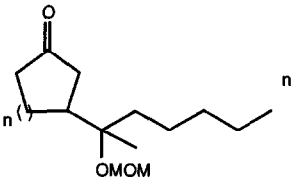
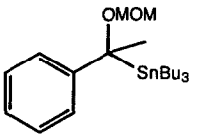
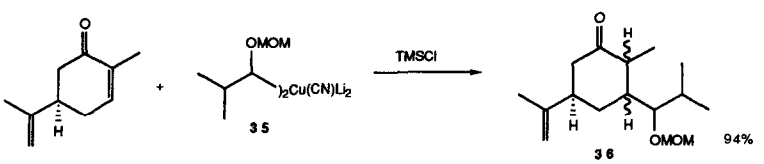
	α-Alkoxyorganostannane			Homoaldol Product		
Entry	Structure	Cmpd. No.	% Yield	Structure	Cmpd. No.	% Yield
1		5	57		n=1 17 n=2 18	68 86
2		6	78		n=1 19 n=2 2	73 96
3		7	60		n=1 20 n=2 21	75 84
4		8	62		n=1 22 n=2 23	94 96
5		9	35		n=2 24	78
6		10	57		n=1 25 n=2 26	34 40
7		11	74		n=1 27 n=2 28	75 67

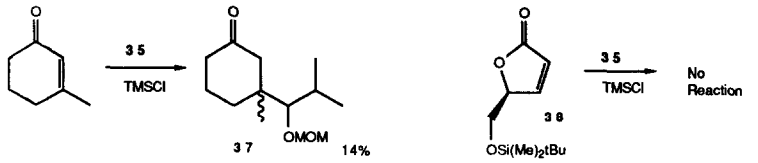
TABLE I continued

8		12	73		n = 1 29 43 n = 2 30 71	
9		13	48		n = 2 31 18	
10		14	24		n = 1 32 77 n = 2 33 73	
11		15	39		n = 2 34 43	
12		16	29	none obtained		

Cuprates derived from aldehydes (secondary α-alkoxyorganocuprates) readily undergo conjugate addition reactions with cyclohexenone and cyclopentenone, providing the 1,4-adducts in up to 97% yield. Steric bulk on the cuprate reagent does not seem to interfere with the reaction, note that the t-butyl substituted product (Table I, entry 4) is obtained in >94% yield. The alkoxy protecting group can also be varied from MOM to MEM, or SEM, or even the methyl ether derivative.[10a] However, the enone substitution pattern and steric demand did affect the reaction. Carvone readily underwent conjugate addition with cuprate 35 to provide 36 as a mixture of diastereomers. An



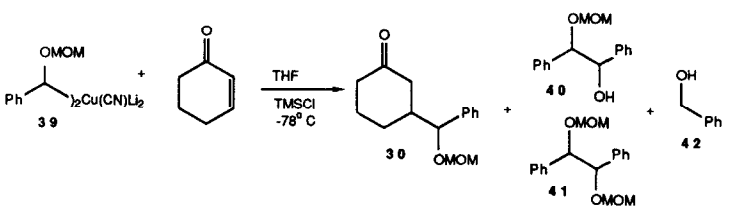
analogous reaction with isophorone at -78° C gave no reaction, while warming to 0° C led to only dimeric by-products (3 and 4) and recovered enone. 3-Methylcyclohexenone did undergo conjugate addition; however, the yield of 37 (14%) was substantially reduced relative to the 96% yield of 2 obtained upon reaction of 35 and cyclohexenone. Addition of Lewis acid activators, such as boron trifluoride etherate, led to complex reaction product mixtures due to decomposition of the methoxymethyl acetal protecting group. The optically active lactone 38[15] was completely unreactive under all experimental reaction conditions attempted.



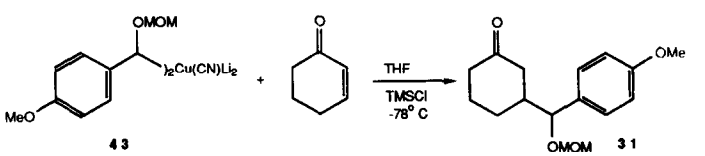
Although the α-alkoxyorganocuprate reagent 35 was apparently unstable when warmed to 0° C (note isophorone reaction above), the reagent does appear to be stable at temperatures up to -40° C for limited time periods. In reactions with cyclohexenone at -78° C, a 96% yield of the 1,4-adduct 2 was obtained. Allowing the cuprate solution to warm to -60° C prior to the addition of the enone/TMSCl mixture reduced the yield of the 1,4-adduct to 83%. Warming the cuprate solution from -78° C to -40° C over a 30 minute time period prior to the addition of the enone resulted in an 84% yield of the conjugate addition product. No increase in the amount of dimeric (oxidative coupling) by-products (2 and 3) was noted in these reactions.

Trimethylsilyl chloride greatly enhanced the conjugate addition reaction and was routinely employed; however, other trialkylsilylchlorides were also effective. For example, the yield of 2 from the reaction of cuprate 35 and cyclohexenone using triethylsilyl chloride was 80%. tert-Butyldimethylsilyl chloride provided a 76% yield of 2 using the same procedure. Since the silyl enol ether can be isolated from the reaction[10a,16], this procedure can directly provide several trialkylsilyl enol ethers regiospecifically.

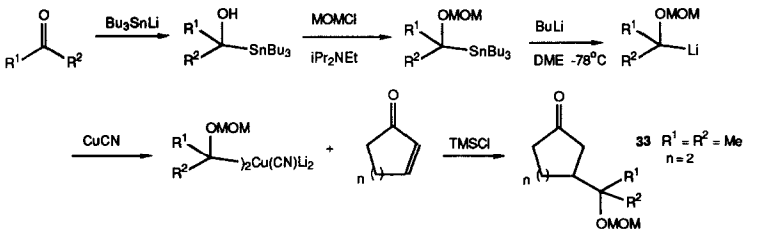
Benzylic substitution poses some problem in the generation and reaction of the α-alkoxyorganocuprate. The reagent derived from benzaldehyde, 39, was quite unstable at temperatures above -60° C, decomposing to dimeric products 40 and 41, as well as protonated material 42



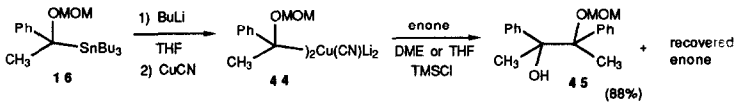
(obtained after aqueous work-up). Although reasonable yields of 1,4-adducts from reactions with cyclohexenone and cyclopentenone were obtained, Table I, the reaction was quite erratic, sometimes providing none of the conjugate addition product. The p-methoxysubstituted cuprate 43 was even more problematic, providing the 1,4-addition product 31 in only 18% yield.



Cuprates derived from ketones (tertiary substituted α-alkoxyorganostannanes) also underwent facile conjugate addition to cyclohexenone and cyclopentenone (see Table I). It is interesting to note that the cyclic homoaldol products obtained from these cuprate reagents contain a remote quaternary carbon. Transmetallation of tertiary substituted α-alkoxyorganostannanes generally cannot be carried out in THF[8a,b]. We were surprised to note that stannane 14, derived from acetone, readily underwent transmetallation in THF at -78°C and subsequent cuprate formation and conjugate addition in good yield. The reaction sequence could also be carried out in DME without any significant changes in the yield of the conjugate addition product 33. The stannane derived from 2-



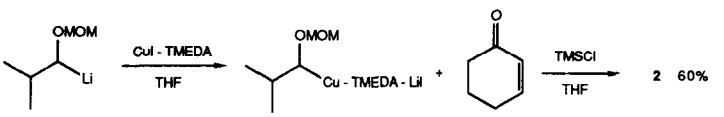
heptanone 15 could not be transmetallated in THF; however, transmetallation, cuprate formation, and cuprate addition, was accomplished in DME. The stannane derived from acetophenone 16 was also converted to the corresponding lithio species in THF. The benzylic stabilized α-alkoxylithio species derived from 16 had also been generated in THF by McGarvey and Macdonald[8b], and effectively underwent alkylation and condensation reactions. However, in our attempts to react the α-alkoxyorganocuprate 44 with cyclohexenone, none of the 1,4-addition product was observed, only the dimeric by-product 45 was obtained in 88% isolated yield. Changing to DME as solvent was ineffective in promoting the conjugate addition of 44. Therefore, an apparent limitation to this



methodology is the generation of aryl substituted tertiary α-alkoxyorganocuprates. Benzylic stabilization, note the problems discussed earlier with cuprates 39 and 43, may cause the cuprate to be unreactive towards 1,4-addition at low temperatures and decompose below the temperature necessary to affect a conjugate addition reaction. We have not assessed the possible role of the purity of the copper (I) salt[10b] employed in generating these reagents.

In all of the cases examined, the products were obtained as mixtures of diastereomers (capillary GC analysis). The degree of diastereoselectivity was dependent on several factors, including the substrate and cuprate steric requirements, and the type of cuprate reagent employed.[9a,16] These aspects of the chemistry of these novel functionalized organocuprates will be discussed in detail in a subsequent publication.

In an attempt to improve the synthetic efficiency of this process, several procedures for the addition of heterocuprates employing only one equivalent of the α-alkoxyorganostannane precur-



sor, rather than the two required for the higher order cyano cuprate, were investigated. In general,

these experiments were ineffective; however, the copper (I) iodide-tetramethylethylene diamine procedure, recently described by Johnson[14d], provided a very reasonable yield of the 1,4-addition product 2, 60%. This was significant for several reasons, only one equivalent of the α-alkoxylithio species was required, the addition reaction was more stereoselective than the higher order cyano cuprate reaction, and that reagent grade copper (I) iodide could be used. This variation of the cyclic homoaldol methodology described is therefore efficient from the viewpoint of both the enone substrate and the α-alkoxyorganostannane.

In conclusion, a general route for the preparation of cyclic enones has been realized. Secondary and tertiary substituted α-alkoxyorganocuprates undergo conjugate addition reactions with non-sterically demanding enones in very good to excellent yield. Further studies are in progress to define the factors controlling the diastereoselectivity of the reaction, and to more adequately define the stability and reactivity of these novel functionalized organocuprate reagents.

Experimental Section

General. Infrared spectra were recorded on either a Beckman Acculab I or a Perkin Elmer 1430 ratio recording spectrophotometer. ^{1}H NMR spectra were obtained on either a Varian EM360A, EM390 or Bruker 250 mHz spectrometer using tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on an IBM 100 or Bruker 250 mHz spectrometer using deuterochloroform as an internal standard. Capillary gas chromatographic analyses were carried out using a Hewlett-Packard 5890 gas chromatograph equipped with a FID detector. All GC analyses were carried out on a SE-30, 25 m fused silica capillary column using a temperature ramp program. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride. All reactions were carried out in flame-dried glassware under an inert atmosphere (Ar). Alkyllithium reagents were purchased from Aldrich and titrated[17] prior to use. Trimethylsilyl chloride was freshly distilled from CaH_2 prior to use. Copper (I) cyanide (tan colored) was purchased from Aldrich. Additional organic reagents were purchased from Aldrich and distilled prior to use. Flash chromatography was performed on silica gel 60, 230-400 mesh ASTM, obtained from American Scientific Products. Radial preparative chromatography was carried out on a Harrison Research Chromatotron. All chromatography solvents were distilled prior to use. Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia.

Preparation of α-alkoxyorganostannanes. Diisopropylamine (1.6 mL, 11 mmol) was dissolved in 20 mL of dry tetrahydrofuran (THF) and cooled to O° C (ice bath). A 3.75 mL sample of a 2.6M solution of n-butyllithium in hexane (10 mmol) was then added dropwise. The solution was stirred for 15 min at 0° C and then cooled to -78° C (CO_2/acetone). The aldehyde or ketone (10 mmol) was then added dropwise (neat) via syringe. Incident light was excluded by covering the reaction flask. The reaction mixture was stirred for 5 min at -78° C and then quenched by the addition of 1 mL saturated aqueous ammonium chloride. The slurry was allowed to warm to room temperature and the reaction mixture was then diluted with 100 mL petroleum ether. The layers were separated and the organic phase was washed with 40 mL of saturated sodium chloride. The organic phase was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to provide the crude (α-hydroxyalkyl)tributylstannane product. The crude product was then dissolved in 25 mL of dry methylene chloride (distilled from P_2O_5) and placed under an inert atmosphere. Diisopropylethylamine (8.7 mL, 50 mmol) and 4-N,N-dimethylaminopyridine (0.122 g, 1 mmol) were then added to the solution. After cooling to 0° C (ice bath), chloromethyl methyl ether (2.3 mL, 30 mmol) was added dropwise to the methylene chloride solution via syringe (CAUTION: Chloromethyl methyl ether should only be handled in a fume hood while wearing gloves.) The reaction mixture was then allowed to gradually warm to room temperature. Reaction progress was monitored by TLC until the (α-hydroxyalkyl)tributylstannane was totally consumed. The mixture was then diluted with 100 mL petroleum ether and washed successively with 0.5 N aqueous hydrochloric acid (2 x 40 mL), saturated aqueous sodium bicarbonate (1 x 40 mL). The organic phase was separated and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the α-alkoxyorganostannane was purified by flash chromatography on silica gel initially using 100% petroleum ether to remove tin by-products, followed by a 1-5% ethyl acetate/petroleum ether gradient elution. The purity of the α-alkoxyorganostannane was then assessed by capillary GC.

1-Methoxymethoxy-1-(tri-n-butylstannyl)hexane, 5 (57%): IR (neat) (cm^{-1}) 2900, 1455, 1140, 1090, 1025; ^{1}H-NMR ($CDCl_3$) δ 4.58 (s, 2H), 4.04 (t, 1H), 3.33 (s, 3H), 2.05-0.65 (m, 33H); ^{13}C-NMR ($CDCl_3$) δ 96.2, 73.9, 55.2, 35.0, 31.8, 29.0, 27.3, 22.5, 13.9, 13.5, 9.0; Anal. Calcd for $C_{20}H_{44}O_2Sn$: C, 55.19; H, 10.19. Found: C, 55.18; H, 10.21.

1-Methoxymethoxy-2-methyl-1-(tri-n-butylstannyl)propane, 6 (78%): IR (neat) (cm^{-1}) 2900, 1460, 1140, 1090, 1035; ^{1}H-NMR ($CDCl_3$) δ 4.56 (s, 2H), 3.91 (d, 1H, J = 5 Hz), 3.32 (s, 3H), 2.05 (m, 1H), 1.75-0.72 (m, 33H); ^{13}C-NMR ($CDCl_3$) δ 96.9, 82.1, 55.3, 32.7, 29.0, 27.3, 20.8, 19.8, 13.3, 9.7; Anal. Calcd for $C_{18}H_{40}O_2Sn$: C, 53.09; H, 9.90. Found: C, 53.20; H, 9.89.

(Cyclohexyl)(methoxymethoxy)(tri-n-butylstannyl)methane, 7 (60%): IR (neat) (cm^{-1}) 2900, 1450, 1140, 1025; ^{1}H-NMR ($CDCl_3$) δ 4.60 (s, 2H), 3.95 (d, 1H, J = 7 Hz), 3.31 (s, 3H), 1.90-0.9 (m, 38H); Anal. Calcd for $C_{21}H_{44}O_2Sn$: C, 56.39; H, 9.91. Found: C, 56.47; H, 9.92.

2,2-Dimethyl-1-methoxymethoxy-1-(tri-n-butylstannyl)propane, 8 (62%): IR (neat) (cm^{-1}) 2900, 1460, 1140, 1080, 1035; ^{1}H-NMR ($CDCl_3$) δ 4.56 (m, 2H), 3.72 (s, 1H), 3.36 (s, 3H), 1.80-0.65 (m, 33H); ^{13}C-NMR ($CDCl_3$) δ 97.8, 87.8, 55.9, 36.5, 29.0, 28.1, 27.4, 13.5, 10.6; Anal. Calcd for $C_{19}H_{42}O_2Sn$: C, 54.17; H, 10.05. Found: C, 54.25; H, 10.11.

1-Methoxymethoxy-1-(tri-n-butylstannyl)pent-4-ene, 9 (35%): IR (neat) (cm^{-1}) 3080, 2920, 1640, 1460, 1140, 1095; ^{1}H-NMR ($CDCl_3$) δ 5.80 (m, 1H), 4.98 (m, 2H), 4.55 (s, 2H), 4.02 (t, 1H, J = 6 Hz), 3.35 (s, 3H), 2.30-0.65 (m, 31H); ^{13}C-NMR ($CDCl_3$) δ 138.4, 114.4, 96.6, 73.4, 55.3, 34.6, 32.1, 29.1, 27.4, 13.5, 9.2; Anal. Calcd for $C_{19}H_{40}O_2Sn$: C, 54.44; H, 9.62. Found: C, 54.36; H, 9.68.

1-Methoxymethoxy-3-phenyl-1-(tri-n-butylstannyl)propane, 10 (57%): IR (neat) (cm^{-1}) 3090, 2920, 1600, 1495, 1455, 1140; ^{1}H-NMR ($CDCl_3$) δ 7.26 (m, 5H), 4.60 (s, 2H), 4.10 (t, 1H, J = 6 Hz), 3.40 (s, 3H), 2.71 (m, 2H), 2.12 (m, 2H), 1.74-0.70 (m, 27H); ^{13}C-NMR ($CDCl_3$) δ 142.3, 128.3, 125.6, 96.6, 73.7, 54.4, 37.3, 34.4, 29.1, 27.4, 13.5, 9.2; Anal. Calcd for $C_{23}H_{42}O_2Sn$: C, 58.87; H, 9.02. Found: C, 58.79; H, 9.04.

3(S),7-Dimethyl-1-methoxymethoxy-1-(tri-n-butylstannyl)oct-6-ene, 11 (74%): IR (neat) (cm^{-1}) 2920, 1455, 1140, 1090; ^{1}H-NMR ($CDCl_3$) δ 5.05 (m, 1H), 4.47 (s, 2H), 4.20 (m, 1H), 3.36 (s, 3H), 2.20-0.80 (m, 45H); ^{13}C-NMR ($CDCl_3$) δ 130.9, 124.8, 109.5, 96.5, 72.2, 71.7, 55.3, 42.8, 37.8, 36.4, 30.2, 29.1, 27.4, 25.5, 25.3, 20.0, 18.6, 17.4, 13.5, 9.0; Anal. Calcd for $C_{24}H_{50}O_2Sn$: C, 58.91; H, 10.30. Found: C, 58.84; H, 10.36.

(Methoxymethoxy)phenyl(tri-n-butylstannyl)methane, 12 (73%): IR (neat) (cm^{-1}) 2940, 2860, 1580, 1455, 1160, 1050, 920; ^{1}H-NMR ($CDCl_3$) δ 7.22 (m, 5H), 5.05 (s, 1H), 4.40 (s, 2H), 3.32 (s, 3H), 1.50-0.90 (m, 27H); ^{13}C-NMR ($CDCl_3$) δ 130.1, 129.7, 128.4, 127.9, 90.9, 58.0, 27.7, 26.9, 16.3, 13.5; Anal. Calcd for $C_{21}H_{38}O_2Sn$: C, 57.15; H, 8.68. Found: C, 57.04; H, 8.71.

Methoxymethoxy(4-methoxyphenyl)(tri-n-butylstannyl)methane, 13 (48%): IR (neat) (cm^{-1}) 3100, 2900, 1150, 1100, 1060; ^{1}H-NMR ($CDCl_3$) δ 7.2 (d, 2H, J = 8 Hz), 6.8 (d, 2H, J = 8 Hz), 5.43 (s, 1H), 3.85 (m, 2H), 3.82 (s, 3H), 3.50 (s, 3H), 1.6-0.9 (m, 27H); ^{13}C-NMR ($CDCl_3$) δ 131.9, 131.7, 113.5, 113.1, 90.4, 57.4, 55.2, 27.6, 27.4, 16.3, 13.4; Anal. Calcd for $C_{22}H_{40}O_3Sn$: C, 56.07; H, 8.55. Found: C, 56.14; H, 8.57.

2-Methoxymethoxy-2-(tri-n-butylstannyl)propane, 14 (24%): IR (neat) (cm^{-1}) 2940, 1135, 1120, 1090, 1030; ^{1}H-NMR ($CDCl_3$) δ 4.67 (s, 2H), 3.35 (s, 3H), 1.80-0.50 (m, 33H); ^{13}C-NMR ($CDCl_3$) δ 93.2, 76.9, 54.9, 28.8, 28.4, 27.2, 13.2, 9.2; Anal. Calcd for $C_{17}H_{38}O_2Sn$: C, 51.93; H, 9.74. Found: C, 51.78; H, 9.76.

2-Methoxymethoxy-2-(tri-n-butylstannyl)heptane, 15 (39%): IR (neat) (cm^{-1}) 2900, 1135, 1090, 1030; ^{1}H-NMR ($CDCl_3$) δ 4.62 (s, 2H), 3.32 (s, 3H), 1.64-0.77 (m, 41H); ^{13}C-NMR ($CDCl_3$) δ 93.6, 82.2, 55.3, 42.6, 32.4, 29.2, 27.5, 26.3, 25.4, 22.6, 13.9, 10.0; Anal. Calcd for $C_{21}H_{46}O_2Sn$: C, 56.14; H, 10.32. Found: C, 56.24; H, 10.35.

(Methoxymethoxy)phenyl(tri-n-butylstannyl)methane, 16 (29%): IR (neat) (cm^{-1}) 3020, 1150, 1100, 1060, 990; ^{1}H-NMR ($CDCl_3$) δ 7.25 (m, 5H), 4.72 (q, 2H), 3.4 (s, 3H), 2.0 (s, 3H), 1.7-1.2 (m, 18H), 0.93 (t, 9H, J = 7 Hz); ^{13}C-NMR ($CDCl_3$) δ 128.06, 124.45, 123.83, 92.97, 55.58, 28.80, 27.35, 23.98, 14.50, 9.61; Anal. Calcd for $C_{22}H_{40}O_2Sn$: C, 58.04; H, 8.86. Found: C, 58.19; H, 8.92.

Higher order cyano cuprate formation and reaction. A solution of the stannane (1.0 mmol) in 5 mL THF was cooled to -78° C (CO_2/acetone). A 0.50 mL sample of a 2.6 M solution of n-butyllithium in hexane (1.3 mmol) was then added and the solution was stirred for 5 min at -78° C. A second 25 mL round bottom flask containing 0.045 g (0.5 mmol) copper (I) cyanide suspended in 2 mL THF was then cooled to -78° C (CO_2/acetone). The α-alkoxylithio species was transferred via cannula to the suspension of copper cyanide at -78° C. The cuprate mixture was gradually allowed to warm to -60° C (bath temperature) over a period of 1/2 h. A clear, homogeneous solution was obtained. A third 25 mL round bottom flask containing a solution of the enone (0.5 mmol) in 3 mL THF was cooled to -78° C (CO_2/acetone). Trimethylsilyl chloride (0.32 mL, 2.5 mmol) was then added to the enone solution. The enone/TMSCl mixture was then added to the cuprate solution (at -78° C) via cannula. The resulting mixture was stirred for 1 h at -78° C, and then gradually warmed to 0° C (ice bath) over an additional 2.5 hour time period. The reaction mixture was quenched by the addition of 1 mL of 1.0 N aqueous hydrochloric acid, stirred for 10 min, and then diluted with 100 mL ether. The mixture was then washed sequentially with a 1:1 mixture of aqueous ammonium chloride/1.0 N hydrochloric acid (1 x 40 mL), saturated aqueous sodium chloride (1 x 40 mL), and saturated sodium bicarbonate (1 x 40 mL). The layers were separated and the organic phase was dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the crude reaction product was purified by flash chromatography on silica gel using 15-20% ethyl acetate/petroleum ether as eluent. The spectral data given is for the mixture of diastereomers obtained.

3-(1-Methoxymethoxy-2-methylpropyl)cyclohexanone, 2 (96%): IR (neat) (cm^{-1}) 2900, 1710, 1145, 1090; ^{1}H-NMR ($CDCl_3$) δ 4.56 (s, 2H), 3.32 (s, 3H), 2.90 (dd, 1H, J = 4.61, 6.01 Hz), 2.43-1.36 (m, 10H), 0.85 (d, 6H, J = 6.67 Hz); ^{13}C-NMR ($CDCl_3$) δ 211.7, 98.7, 88.3, 55.9, 45.7, 42.7, 41.2, 30.1, 29.1, 25.8, 25.0, 19.7, 17.9; Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.29; H, 10.38.

3-(1-Methoxymethoxyhexyl)cyclopentanone, 17 (68%): IR (neat) (cm^{-1}) 2900, 1735, 1140, 1090; ^{1}H-NMR ($CDCl_3$) δ 4.75 - 4.52 (m, 2H), 3.50 (m, 1H), 3.38 (s, 3H), 2.65 -0.70 (m, 20H); ^{13}C-NMR ($CDCl_3$) δ 219.0, 95.8, 80.2, 79.9, 55.6, 41.6, 40.8, 40.3, 40.0, 38.3, 32.3, 31.8, 25.7, 24.4, 22.4, 13.8; Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.09; H, 10.63.

3-(1-Methoxymethoxyhexyl)cyclohexanone, 18 (86%): IR (neat) (cm^{-1}) 2900, 1710, 1440, 1145, 1090; ^{1}H-NMR ($CDCl_3$) δ 4.66 (s, 2H), 3.42 (s, 4H), 2.60-0.75 (m, 20H); ^{13}C-NMR ($CDCl_3$) δ 211.8, 96.0, 80.5, 55.6, 44.2, 42.6, 41.8, 41.2, 31.8, 30.8, 27.7, 25.8, 25.0, 24.8, 22.4, 13.8; Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.46; H, 10.83.

3-(1-Methoxymethoxy-2-methylpropyl)cyclopentanone, 19 (73%): IR (neat) (cm^{-1}) 2900, 1735, 1050; ^{1}H-NMR ($CDCl_3$) δ 4.62 (s, 2H), 3.36 (s, 3H), 3.22 (m, 1H), 2.75-1.50 (m, 8H) 1.00 (d, 6H, J = 6 Hz); ^{13}C-NMR, ($CDCl_3$) δ 218.8, 98.1, 97.9, 86.9, 86.7, 55.9, 42.3, 41.5, 39.2, 38.3, 31.3, 31.1, 26.6, 25.6, 19.4, 19.2, 17.3; Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.06. Found: C, 65.86; H, 10.06.

3-[(Cyclohexyl)methoxymethoxymethyl]cyclopentanone, 20 (75%): IR (neat) (cm^{-1}) 2900, 1735, 1140, 1090, 1030; ^{1}H-NMR ($CDCl_3$) δ 4.6 (s, 2H), 3.35 (s, 3H), 3.30 (m, 1H), 2.4-1.2 (m, 18H); Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 69.89; H, 10.01.

3-[(Cyclohexyl)methoxymethoxymethyl]cyclohexanone, 21 (84%): IR (neat) (cm^{-1}) 2900, 1710, 1150, 1090, 1040; ^{1}H-NMR ($CDCl_3$) δ 4.61 (m, 2H), 3.29 (s, 3H), 3.05 and 2.94 (dd, 1H, J = 3.5, 5.2 Hz), 2.4-1.8 (m, 4H), 1.7-0.9 (m, 16H); ^{13}C-NMR ($CDCl_3$) δ 212.3, 212.0, 98.9, 98.3, 87.8, 87.4, 75.3, 74.5, 56.1, 45.8, plus additional signals upfield ; Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.94; H, 10.32.

3-(2,2-Dimethyl-1-methoxymethoxypropyl)cyclopentanone, 22 (94%): IR (neat) (cm^{-1}) 2920, 1735, 1145, 1095; ^{1}H-NMR ($CDCl_3$) δ 4.65 (s, 2H), 3.33 (s, 3H) 3.10 (s, 1H), 2.55-1.45 (m, 7H), 0.90 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 220.0, 219.2, 99.5, 89.9, 55.8, 43.9, 40.3, 38.4, 37.8, 37.6, 36.1, 28.0, 26.7, 24.9; Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.35; H, 10.40.

3-(2,2-Dimethyl-1-methoxymethoxypropyl)cyclohexanone, 23 (96%): IR (neat) (cm^{-1}) 2920, 1710, 1145, 1090; ^{1}H-NMR ($CDCl_3$) δ 4.62 (m, 2H), 3.38 (s, 3H), 3.00 & 2.78 (s, 1H), 2.58 - 1.50 (m, 9H), 0.87 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 212.0, 99.5, 91.5, 91.0, 56.0, 48.6, 44.0, 41.3, 39.8, 36.5, 32.2, 26.6, 25.3; Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.26; H, 10.63.

3-(1-Methoxymethoxypent-4-enyl)cyclohexanone, 24 (78%): IR (neat) (cm^{-1}) 2940, 1710, 1640, 1445, 1145, 1095; ^{1}H-NMR ($CDCl_3$) δ 5.85 (m, 1H), 5.03 (m, 2H), 4.64 (m, 2H), 3.44 (m, 4H), 2.55 -1.08 (m, 13H); ^{13}C-NMR ($CDCl_3$) δ 211.1, 137.8, 114.6, 96.2, 80.1, 55.5, 44.0, 42.6, 41.8, 41.1, 30.1, 29.2, 27.4, 25.8, 24.9; Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.87; H, 9.83.

3-(1-Methoxymethoxy-3-phenylpropyl)cyclopentanone, 25 (34%): IR (neat) (cm^{-1}) 2910, 1735, 1150, 1110, 1060; ^{1}H-NMR ($CDCl_3$) δ 7.5 (s, 5H), 4.7 (s, 2H), 3.5 (m, 1H), 3.4 (s, 3H), 3.1 (m, 2H), 2.8-0.9 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ 217.9, 141.8, 128.3, 128.1, 125.9, 97.3, 96.4, 80.4, 80.1, 72.2, 55.7, 41.6, plus 12 additional upfield signals; Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.20; H, 8.41.

3-(1-Methoxymethoxy-3-phenylpropyl)cyclohexanone, 26 (40%): IR (CH_2Cl_2) (cm^{-1}) 3020, 2900, 1710, 1600, 1490, 1140, 1090; ^{1}H-NMR ($CDCl_3$) δ 7.22 (m, 5H), 4.65 (m, 2H), 3.46 (m, 1H), 3.40 (m, 3H), 2.75-0.84 (m, 13H); ^{13}C-NMR ($CDCl_3$) δ 211.2, 141.7, 128.3, 128.1, 125.8, 96.5, 80.6, 55.7, 44.1, 43.0, 42.2, 41.3, 33.0, 31.6, 27.5, 26.1, 25.1; Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.67; H, 8.77.

3-(3(S),7-Dimethyl-1-methoxymethoxyoct-6-enyl)cyclopentanone, 27 (75%): IR (neat) (cm^{-1}) 1735, 1150, 1090, 910; ^{1}H-NMR ($CDCl_3$) δ 5.0 (m, 1H), 4.6 (m, 2H), 3.6 (m, 1H), 3.3 (s, 3H), 2.3 (m, 2H), 2.0-0.9 (m, 25H); Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.13; H, 10.76.

3-(3(S),7-Dimethyl-1-methoxymethoxyoct-6-enyl)cyclohexanone, 28 (67%): IR (neat) (cm^{-1}) 2930, 1710, 1450, 1150, 1035; ^{1}H-NMR ($CDCl_3$) δ 5.05 (m, 1H), 4.54 (s, 2H), 3.44 (m, 1H), 3.28 (s, 3H), 2.40-0.67 (m, 25H); ^{13}C-NMR ($CDCl_3$) δ 211.3, 130.9, 124.4, 109.6, 95.9, 78.5, 55.5, 44.3, 43.8, 42.7, 42.5, 42.1, 41.8, 41.2, 38.6, 38.3, 37.4, 36.8, 28.6, 27.8, 27.4, 26.0, 25.4, 25.1, 19.8, 19.3, 17.3; Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.79; H, 10.92.

3-[(Methoxymethoxy)(phenyl)methyl]cyclopentanone, 29 (43%): IR (neat) (cm^{-1}) 2980, 2880, 1735; ^{1}H-NMR ($CDCl_3$) δ 7.3 (s, 5H), 4.5 (m, 3H), 3.3 (s, 3H), 2.6-1.6 (m, 7H); Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.65; H, 7.68.

3-[(Methoxymethoxy)(phenyl)methyl]cyclohexanone, 30 (71%): IR (neat) (cm^{-1}) 2980, 2880, 1710; ^{1}H-NMR ($CDCl_3$) δ 7.3 (s, 5H), 4.6 (m, 3H), 3.4 (s, 3H), 2.6-1.3 (m, 9H); Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H, 8.10.

3-[(Methoxymethoxy)(4-methoxyphenyl)methyl]cyclohexanone, 31 (18%): IR (neat) (cm^{-1}) 2940, 1710, 1610, 1510, 1040; ^{1}H-NMR ($CDCl_3$) δ 7.1 (d, 2H, J = 3.3 Hz), 6.8 (d, 2H, J = 3.3 Hz), 4.44 (m, 2H), 4.34 (d, 1H, J = 5 Hz), 3.76 (s, 3H), 3.32 (s, 3H), 2.4-1.6 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ 211.3, 211.2, 159.2, 131.4, 131.1, 128.4, 113.6, 93.8, 93.7, 55.6, 55.0, 45.0, 44.5, 44.1, 41.2, 27.6, 27.0, 24.6.

3-(2-Methoxymethoxy-2-propyl)cyclopentanone, 32 (77%): IR (neat) (cm^{-1}) 1735, 1382, 1367, 1150; ^{1}H-NMR ($CDCl_3$) δ 4.7 (s, 2H), 3.3 (s, 3H), 2.4-1.8 (m, 7H), 1.2 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 219.0, 90.8, 75.7, 55.0, 48.0, 39.9, 38.7, 29.5, 23.9, 23.5; Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.55; H, 9.78.

3-(2-Methoxymethoxy-2-propyl)cyclohexanone, 33 (73%): IR (neat) (cm^{-1}) 2940, 2880, 1710, 1380, 1370, 1140, 1080; ^{1}H-NMR ($CDCl_3$) δ 4.69 (s, 2H), 3.33 (s, 3H), 2.59-1.34 (m, 9H), 1.22 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 212.0, 90.9, 55.1, 48.9, 43.0, 41.1, 25.7, 25.1, 23.6; Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.89; H, 10.10.

3-(2-Methoxymethoxy-2-heptyl)cyclohexanone, 34 (43%): IR (neat) (cm^{-1}) 2900, 1710, 1090, 1030; ^{1}H-NMR ($CDCl_3$) δ 4.61 (s, 2H), 3.35 (s, 3H), 2.45-0.75 (m, 23H) ; ^{13}C-NMR ($CDCl_3$) δ 211.9, 90.7, 79.1, 79.0, 55.3, 46.0, 45.8, 42.8, 42.5, 41.1, 36.7, 32.3, 25.5, 25.3, 25.1, 22.9, 22.8, 22.4, 20.6, 20.5, 13.8; Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.15; H, 11.01.

2-Methyl-3-(1-methoxymethoxy-2-methylpropyl)-5(S)-(prop-2-enyl)-cyclohexanone, 36 (94%): IR (neat) (cm^{-1}) 2900, 1700, 1640, 1450, 1145, 1085, 1025; ^{1}H-NMR ($CDCl_3$) δ 4.82-4.41 (m, 4H), 3.39-2.91 (m, 4H), 2.79-0.80 (m, 20H); ^{13}C-NMR ($CDCl_3$) δ 214.8, 211.6, 148.0, 146.7, 111.7, 110.6, 109.6, 98.7, 97.7, 86.0, 84.9, 56.0, plus 21 more closely packed upfield signals between 46.2 - 11.6; Anal. Calcd for $C_{16}H_{26}O_3$: C, 71.60; H, 10.51. Found: C, 71.48; H, 10.53.

Alkyl copper-TMEDA : A solution of 0.204 g (0.5 mmol) 1-methoxymethoxy-2-methyl-1-tributylstannylpropane in 5 mL THF was cooled to -78° C (CO_2/acetone). A 0.50 mL sample of a 2.6 M solution of n-butyllithium in hexane (1.3 mmol) was then added and the solution stirred for 5 min at -78° C. To a second 25 mL round bottom flask containing 0.095 g (0.5 mmol) of copper (I) iodide suspended in 2 mL THF was added 83 mL (0.55 mmol) of TMEDA (freshly distilled from CaH_2). The resulting homogeneous yellow-green CuI-TMEDA solution (will turn violet-red over time) was then cooled to -78° C (CO_2/Acetone) and the α-alkoxylithio species added via cannula. The mixture was stirred at -78° C for 10 min and then gradually warmed to -60° C (bath temperature) over a period of 1/2 h. A 48 μL (0.5 mmol) sample of cyclohexenone was added to a third flask containing 2 mL THF. The enone solution was cooled to -78° C (CO_2/acetone) and 0.32 mL (2.5 mmol) of TMSCl was then added. After stirring the enone/TMSCl mixture for 2 min at -78° C, the solution was transferred via cannula to the flask containing the cuprate at -78° C. The resulting mixture was stirred for 1 h at -78° C and then gradually warmed to 0° C (ice bath) over a period of 2 h. The reaction was quenched by the addition of 1 mL of a 50:50 mixture of 1.0 N HCl/saturated aqueous ammonium chloride. The work-up procedure followed that of the higher order cyano cuprate reaction. Compound 2 was obtained in 60% yield after chromatography.

Acknowledgments. We would like to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. We would also like to thank Joyce McKenzie and Brian Griedel for their assistance in some of the reactions described.

References and Footnotes

1. For reviews on the homoaldol reaction and homoenolate anion equivalents see (a) Hoppe, D. Angew. Chem. Int. Ed. Engl., 1984, 23, 932. (b) Werstiuk, N. H. Tetrahedron, 1983, 39, 205.
2. (a) Hoppe, D.; Kramer, T. Angew. Chem. Int. Ed. Engl., 1986, 25, 160. (b) Nakamura, E.; Sekuja, K; Kuwajima, I. Tetrahedron Lett., 1987, 28, 337. (c) Kramer T.; Hoppe, D. Tetrahedron Lett., 1987, 28, 5149.
3. Hoppe, D.; Hanko, R.; Bronneke, A.; Licheteberg, F. Angew. Chem. Int. Ed. Engl., 1981, 20, 1024.
4. Chenard, B. L. Tetrahedron Lett., 1986, 27, 2805.
5. Other α-alkoxyallyl anions also produce mixtures of α and γ alkylated products, see ref 1.
6. Seebach, D. Angew. Chem. Int. Ed. Engl., 1979, 18, 239.
7. For an earlier review of α-heteroatom substituted organometallics, see Krief, A. Tetrahedron, 1980, 36, 2531.

8. (a) Still, W. C.; Sreekumar, C. J. Am. Chem. Soc., 1980, 102, 1201. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. J. Am. Chem. Soc., 1988, 110, 842. (c) Duchene, A.; Quintard, J-P. J. C. S., Chem. Commun., 1987, 29. (d) Lesimple, P.; Beau. J-M.; Sinay, P. J. C. S., Chem. Commun., 1985, 894, and references given in these papers.
9. (a) Linderman, R. J.; Godfrey, A. Tetrahedron Lett., 1986, 27, 4553. (b) Linderman, R. J.; McKenzie, J. M. Tetrahedron Lett., 1988, in press.
10. (a) Linderman, R. J.; Godfrey, A.; Horne, K. Tetrahedron Lett., 1987, 28, 3911. (b) Hutchinson, D. K.; Fuchs, P. L. J. Am. Chem. Soc., 1987, 109, 4930. (c) Corey, E. J.; Eckrich, T. M. Tetrahedron Lett., 1983, 24, 3165.
11. For a review of the chemistry of higher order cuprates, see Lipshutz, B. H. Synthesis, 1987, 325.
12. Poller, R. C. The Chemistry of Organotin Compounds. Academic Press, New York. 1970.
13. Quintard, J-P.; Elissondo, B; Jousseaume, B. Synthesis, 1984, 495.
14. For examples of the utility of in-situ trimethylsilyl chloride in cuprate reactions, see (a) Corey, E. J.; Boaz, N. W. Tetrahedron Lett., 1985, 26, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. Tetrahedron Lett., 1986, 27, 1047. (c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. Tetrahedron Lett., 1986, 27, 4029. (d) Johnson, C. R.; Marren, T. J. Tetrahedron Lett., 1987, 28, 27. (e) Bergdahl, M.; Lindstedt, E-L.; Nilsson, M.; Olsson, T. Tetrahedron, 1988, 44, 2055.
15. Prepared by silylation of the alcohol. Camps, P; Font, J.; Cardellach, J.; Ortuno, R. M.; Ponsati, O. Tetrahedron, 1982, 38, 2395.
16. A. Godfrey and J. McKenzie, unpublished results from this laboratory.
17. Watson, S. C.; Eastham, K. E. J. Organomet. Chem., 1967, 9, 165.