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A REACTIVITY UMPOLUNG ROUTE TO CYCLIC HOMOENOLATE ALDOL PRODUCTS VIA α-ALKOXYORGANOCUPRATE CONJUGATE ADDITIONS

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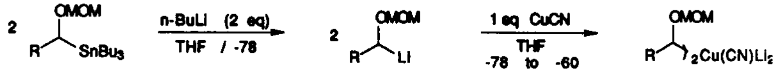
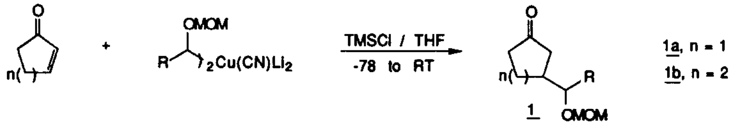
Abstract Substituted α-alkoxyorganocuprate reagents readily undergo conjugate addition reactions with cyclic enones to provide homoaldol products.

The development of homoenolate anions and their equivalents has received considerable attention for several decades.[1] Several successful approaches have been described for acyclic homoenolates[2] and for acyclic homoenolate anion equivalents.[3] In contrast to the achievements realized in acyclic systems, the generation and synthetic applications of cyclic homoenolate anions has not been realized. Chenard[4] has recently described an approach to the homoenolate of cyclohexanone. However, a regiochemical mixture of α- and γ- substitution products was obtained in condensation reactions of the intermediate γ-alkoxyallyl anion with aldehydes. We now wish to describe the general utility of α-alkoxyorganocuprate reagents[5] in the preparation of homoaldol products from cyclic ketones in synthetically useful yields.





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Several higher order cuprate[6] reagents were prepared from the corresponding α-alkoxyorganostannane[7] and employed in conjugate addition reactions with cyclohexenone and cyclopentenone in the presence of excess trimethylsilyl chloride.[5,8] The yields of the conjugate addition products 1 are given in the Table.[9] The cuprate reactions were routinely quenched and worked up using dilute aqueous acid to affect hydrolysis of the

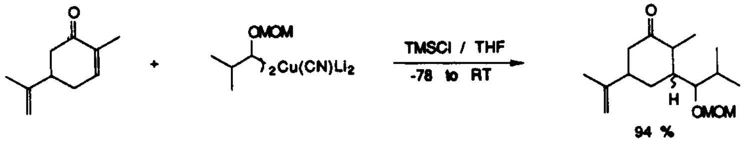
Table Homoaldol Products 1 of Cyclic Ketones by Conjugate Addition Reactions of α-Alkoxyorganocuprate Reagents

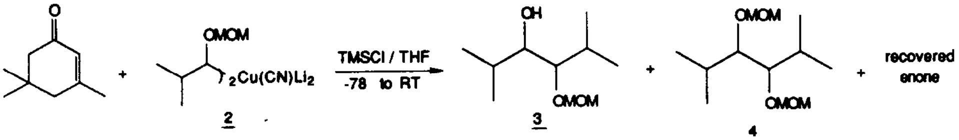
Cuprate Reagent	Enone Conjugate Addition Product % Yield[a]	
R=	n=1	n=2
i-Pr	73	96
n-Pent	68	86
t-Bu	94	96
cycl-Hex	75	84
Ph	43	71

[a] Yields reported are for chromatographed material, all new compounds exhibited correct spectral and elemental analyses.

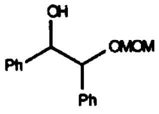
incipient trimethylsilyl enol ether produced in the reaction. Alternatively, the reaction could be worked up by the addition of an excess of triethylamine and dilution with ether followed by rapid filtration through a short column of silica gel pretreated with triethylamine. The yield of trimethylsilyl enol ether obtained in this fashion varied from 86-98% (R=*i*-Pr, *t*-Bu).

Aliphatic substituted α-alkoxyorganocuprate reagents efficiently react with cyclic enones substituted in the α position, but problems arise in conjugate addition reactions with β substituted cyclohexenones. For example, reaction of cuprate reagent 2 with carvone resulted in a 94% yield of the 1,4-addition product.[9] However, attempts to achieve1,4-alkylation of isophorone with cuprate 2 were unsuccessful. In this reaction, the major products isolated were the dimeric decomposition products, 3 and 4.[10] Aryl substituted α-alkoxyorganocuprates tend to produce more dimeric decomposition products (for R=Ph, 5 and 6), and reproducible yields of 1,4-addition products are difficult to obtain. It is interesting to note that silylation of the cuprate reagent is not a significant competing reaction, even though excess trimethylsilyl chloride is present in the addition reaction mixture. Only small amounts of 7, accounting for less than 10% of the α-alkoxystannane, could be isolated, while the protonated by-product 8 accounted for





the remainder of the stannane which had not been converted to the 1,4-addition product or 5 and 6. Nevertheless, a reasonable yield of 1b (R=Ph) was obtained.



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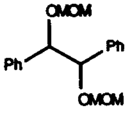

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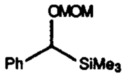

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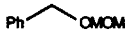

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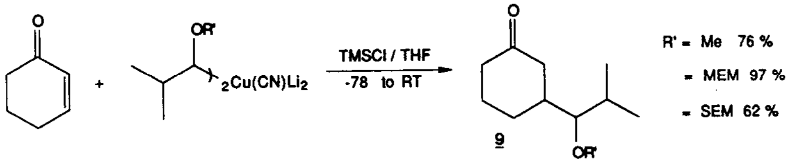
Several other alkoxy protecting groups are also tolerated in this reaction. The MEM[11], SEM[11], and methyl ether derivatives provided good yields of the cyclic homoaldol product 9. In contrast, the BOM[11] protected stannane (R=i-Pr), in attempted cuprate formation and addition to cyclohexenone, resulted in a complex mixture of products. BOM protected stannanes are commonly employed in the generation and reaction of α-alkoxylithio species; however, one research group has previously noted the inability to form a cuprate from [(benzyloxy)methyl]lithium.[12]



The yield of the reaction also depends on several additional factors. The α-alkoxyorganostannane must be very clean, typically 99% pure by GC analysis. Impure stannanes will not generate a clear, homogeneous solution of the cuprate reagent. A heterogeneous mixture of the cuprate reagent will result in a reduced yield of the conjugate addition product. Yields are also poor if the cuprate reaction is carried out without excess in-situ trimethylsilyl chloride.

The utility of α-alkoxyorganocuprate reagents in the synthesis of 5 and 6 membered ring cyclic homoaldol products is clearly demonstrated by these results. In all cases, none of the 1,2-addition products were detected in the crude reaction mixture by ^{1}H-NMR or GC analysis. Therefore the problem, of α,γ-regioisomeric mixtures discussed previously is removed by an application of reactivity umpolung.[13]

A general experimental procedure is as follows:

> The appropriate α-alkoxyorganostannane (1.0 mmol) was dissolved in anhydrous THF (5mL) and cooled to -78°C (CO_2/acetone) under an inert atmosphere. n-Butyllithium (1.25 mmol) was then added via syringe to the cold α-alkoxystannane solution and the solution was stirred for 15 minutes. The clear solution was then cannulated into a suspension of CuCN (0.5 mmol) in THF (2mL) at -78°C. The transmetallation flask was rinsed with cold (-78°C) THF (2.5 mL). The cuprate suspension was allowed to slowly warm to -60°C (bath temperature) over 30-60 minutes until a clear, homogeneous solution resulted. This cuprate solution was recooled to -78°C and cannulated into a

solution of the enone (0.5 mmol) containing trimethylsilyl chloride (2.5 mmol) in THF (3 mL) at -78°C. The cuprate flask was rinsed with cold (-78°C) THF (2.5 mL) to ensure complete transfer of the cuprate (final volume THF, 15 mL). The enone/cuprate mixture was maintained at -78°C for 30 minutes and then allowed to gradually warm to room temperature over a 3 hour period. The reaction mixture was then quenched by the addition of aqueous 1.0 N HCl or by adding excess triethylamine and ether.

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