The effects of in-situ trimethylsilyl chloride on the regioselectivity of the addition of α-alkoxy- and α-alkyl-substituted organocuprates to enals

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(Received June 3rd, 1988)

Abstract

The regioselectivity of the addition of α-substituted organocuprates to enals has been examined. The addition of trimethylsilyl chloride to both the enal and cuprate prior to the combination of the reactants improves the regioselectivity and the isolated yield for the 1,4-addition product.

The regioselectivity (1,2 vs. 1,4) of organocuprate additions to enals has been a long standing problem in organic synthesis. Normant and Clive [1] have extensively studied the reactions of alkyl, aryl, vinyl, and allyl organocuprates with enals having a variety of substitution patterns. The results of these studies indicated that α or β substitution of the enal substrate resulted in an increasing proportion of 1,2-addition as the steric constraints of the enal substituents increased. For a given enal substrate, primary alkylcuprates as well as phenyl and vinyl cuprate species provided the 1,4-addition product as the major regioisomer; however, allyl, acetylenic, and secondary alkyl cuprates resulted in poor selectivity, providing regioisomeric mixtures, or favoring the 1,2-addition product. Recently, reports on the beneficial effects of in-situ trimethylsilyl chloride (TMSCl) indicated very favorable regioselectivity in the addition of organocuprates to enals [2]. The presence of trimethylsilyl chloride accelerates the rate of cuprate conjugate addition to several classes of unsaturated carbonyl compounds and improves the yield of the conjugate addition product by minimizing competing side reactions [2,3]. We have been developing the chemistry of α-alkoxyorganocuprates [4a,b] and have encountered problems in the regioselectivity of the reaction of these α-heteroatom substituted organocuprate reagents with enals. In reviewing the previous studies of cuprate additions to enals, we noted that regioselective conjugate addition reactions of secondary alkyl cuprates with enals had not been fully addressed. We would now like to report our study of the 1,4-regioselectivity of α-alkoxy and α-alkyl substituted organocuprates in additions to cinnamaldehyde and heptenal. Improved regiocontrol for both classes of

1) BuLi

2) 0.5 eq. CuCN

)₂Cu(CN)Li₂

1

OMOM

SnBu₃

Ph̲⟶CHO

OMOM

CHO

Ph

2

1,4 - addition

OMOM

Ph

OH

3
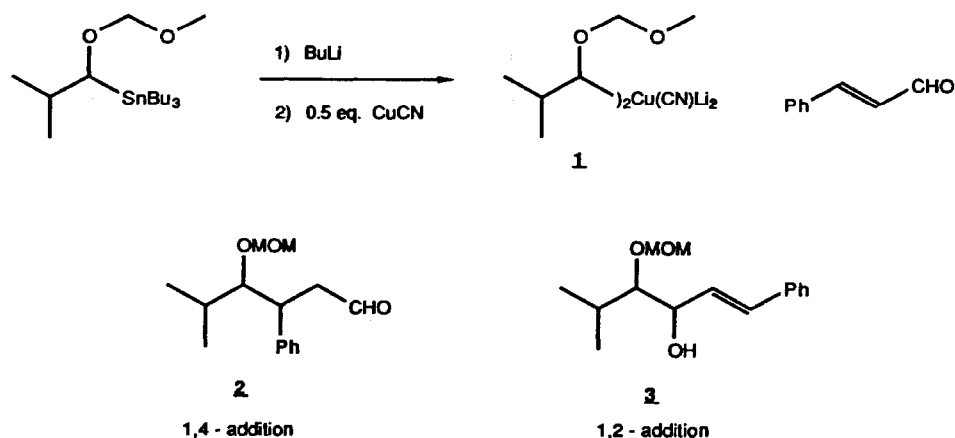
1,2 - addition

α-substituted organocuprates has been realized using a modified in-situ trimethyl-silyl chloride/cuprate addition reaction procedure.

Previous studies [4a,b] with α-alkoxyorganocuprates indicated that these steri-cally encumbered reagents were somewhat unreactive toward conjugate addition reactions. For efficient conjugate addition reactions with enones, higher order cyanocuprates [5] in conjunction with trimethylsilyl chloride (premixed with the enone) were required. In the reactions of the α-alkoxyorganocuprates with enones, only the 1,4-adduct was detected in the crude reaction mixture, while the corre-sponding α-alkoxylithio species provided only the 1,2-adduct. Upon reaction of cuprate **1** with a solution of cinnamaldehyde containing five equivalents of TMSCl in-situ, we were disappointed to note a 1/1 ratio of 1,4 to 1,2 addition products in moderate yield (31 and 33% for **2** and **3** respectively). This result contrasted with the previously reported complete 1,4-regioselectivity for the TMSCl mediated addition of lithium dimethylcuprate to cinnamaldehyde [2a]. In an attempt to improve the regioselectivity of the α-alkoxyorganocuprate reaction, a brief survey of the reaction of several other less reactive α-alkoxyorganocuprate species with cinnamaldehyde premixed with TMSCl was conducted. A thiophenoxy cuprate derivative of **1** was unreactive, providing only recovered cinnamaldehyde, while a hexynyl cuprate resulted in predominantly 1,2-addition (85% 1,2-adduct). The cyanocuprate gave improved regioselectivity (81/19 ot 1,4/1,2) while a tributylphosphine derived cuprate provided complete regiocontrol (100% 1,4). However, the yield of 1,4-adduct was less than 10% in each case examined.

Kuwajima et al. [2b,c] have demonstrated that alkyl organocuprates derived from copper(I) bromide-dimethyl sulfide complex react readily with enals in the presence of TMSCl and hexamethylphosphoric triamide (HMPA), providing the 1,4-addition product with excellent regiocontrol. HMPA or 4-N,N-dimethylaminopyridine (DMAP) [2c] served to enhance the beneficial regiocontrol aspects noted with TMSCl alone and excellent yields of the silyl enol ether derivative of the conjugate addition product were obtained. In the present study, the sterically demanding α-alkoxyorganocuprates derived from copper(I) cyanide gave the opposite results, apparently favoring 1,2-addition or providing no enhanced regiocontrol upon the addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU, a non-

Table 1

Additive effects on the regioselectivity of α-alkoxyorganocuprate reactions with cinnamaldehyde

Entry	i-PrC(OMOM)H$_n$X	Equivalents of TMSCl [a]	Additive [b]	2/3 [c] (1,4/1,2)
1	Cu(CN)Li [d]	0	none	NR [e]
2	Cu(CN)Li	5	none	81/19
3	Cu(CN)Li	5	TMEDA	3/97
4	Cu(CN)Li$_2$ [f]	0	none	NR
5	Cu(CN)Li$_2$	5	none	50/50
6	Cu(CN)Li$_2$	5	TMEDA	25/75
7	Cu(CN)Li$_2$	5	DMAP	43/57
8	Cu(CN)Li$_2$	5	DMPU	48/52

[a] Number of equivalents of TMSCl premixed with cinnamaldehyde in THF at −78°C prior to addition to the cuprate. [b] TMEDA = tetramethylethylene diamine, DMAP = 4-N,N-dimethylaminopyridine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. [c] Ratios given were determined by capillary GC analysis of the crude reaction product mixture. [d] One equivalent of the α-alkoxylithio species was employed to prepare the cyano cuprate, n = 1, entries 1–3. [e] NR = no reaction. [f] Two equivalents of the α-alkoxylithio species was employed to prepare the higher order cyano cuprate, n = 2, entries 4–8.

carcinogenic substitute for HMPA), DMAP, or tetramethylethylene diamine (TMEDA) [3c]. In these examples (Table 1), no variation in the regioselectivity was observed if the amine additive was initially combined with the enal/TMSCl mixture or the cuprate reagent. Therefore, the order of the combination of the amine additive and the cuprate reagent had no effect on the reaction.

Corey [2a] had reported that, in one instance, the beneficial aspects of TMSCl were also noted if TMSCl had been premixed with the cuprate reagent instead of the enone. In this earlier study [2a], lithium dimethylcuprate was shown to be minimally reactive towards TMSCl, even at 0°C. We sought to determine if the order of combination of the reagents (cuprate, TMSCl, enal) could possibly have any effect on the regioselectivity for the reaction of the higher order cyanocuprate 1 with cinnamaldehyde or heptenal. The results of this study are presented in Table 2. As noted earlier, the higher order α-alkoxy cyanocuprate reagent was unreactive towards addition to the enal without the addition of TMSCl (Table 2, entry 1). The addition of 5 or 10 equivalents of TMSCl to the enal allowed the cuprate addition reaction to proceed; however, the regioselectivity was virtually 1/1 for the 1,4 and 1,2 addition products. Therefore, the initial stoichiometry of the enal and TMSCl has no effect on the regioselectivity of the cuprate addition reaction. In contrast, an interesting result was noted if TMSCl was initially combined with the cuprate rather than the enal (Table 2, entry 4) in that the 1,4-regioselectivity of the reaction improved. Further experimentation determined that the optimum conditions for enhanced regioselectivity and yield of the 1,4-addition product were to add two equivalents of TMSCl to the cuprate and five equivalents of TMSCl to the enal prior to combining the reactants (the "2/5" procedure). Amounts of TMSCl added to the cuprate in excess of two equivalents had minimal impact on the 1,4-regioselectivity of the cuprate reaction, serving to neither improve nor diminish the selectivity obtained by using the "2/5" procedure. The regioselectivity for the addition of 1 to cinnamaldehyde increased to 4 to 1 in favor of the 1,4-adduct and an improvement in the isolated yield of the 1,4-addition product was also realized

Table 2

The effects of trimethylsilyl chloride on the regioselectivity of α-alkoxyorganocuprate addition to enals

Entry	OMOM R^1\C)$_2$Cu(CN)Li$_2$ /H R^1 =	R^2C(H)=C(H)CHO R^2 =	Equiv. TMSCl		Regioselectivity[c] 1,4/1,2	Isolated yield (%)	
			Cuprate[a]	Enal[b]		1,4	1,2
1	i-Pr	Ph	0	0	–	0	0
2	i-Pr	Ph	0	5	48/52	31	33
3	i-Pr	Ph	0	10	52/48	24	22
4	i-Pr	Ph	5	0	62/38	29	18
5	i-Pr	Ph	2	5	79/21	46	12
6	i-Pr	n-Bu	0	5	62/38	26	16
7	i-Pr	n-Bu	2	5	61/39	37	24
8	n-Bu	Ph	0	5	59/41	26	18
9	n-Bu	Ph	2	5	82/18	36	8
10	n-Bu	n-Bu	0	5	44/56	18	23
11	n-Bu	n-Bu	2	5	64/36	30	17

[a] TMSCl premixed with the cuprate at $-78\,^\circ$C in THF. [b] TMSCl premixed with the enal at $-78\,^\circ$C in THF. [c] Regioselectivity ratio determined from isolated, chromatographed material.

(Table 3, entry 5) using the "2/5" modification. This observation proved to not be an isolated case. Several other examples are given in entries 6–11 of Table 2. The reduced yields of products obtained (Table 2) were attributed to decomposition of
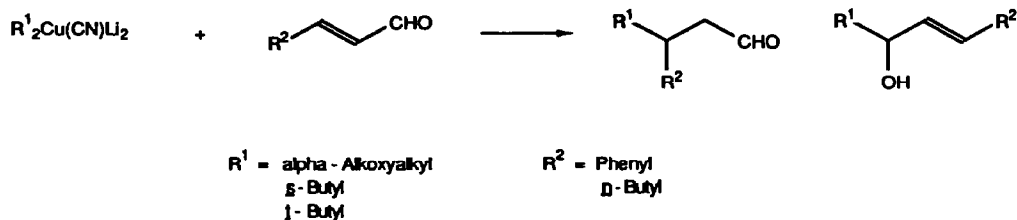
Table 3

The effects of in-situ trimethylsilyl chloride on the regioselectivity of α-substituted higher order cyano alkylcuprate addition to enals

Entry	α-Substituted cuprate reagent	Enal RC(H)=C(H)CHO	Equiv. TMSCl[a]		Regioselectivity[b] 1,4/1,2	Isolated yield (%) 1,4-product
			Cuprate	Enal		
1	t-BuLi	Ph	0	0	40/60	–
2	(t-Bu)$_2$Cu(CN)Li$_2$	Ph	0	0	12/88	–
3	(t-Bu)$_2$Cu(CN)Li$_2$	Ph	0	5	89/11	–
4	(t-Bu)$_2$Cu(CN)Li$_2$	Ph	2	5	56/44	28[c]
5	s-BuLi	Ph	0	0	59/41	–
6	(s-Bu)$_2$Cu(CN)Li$_2$	Ph	0	0	22/78	–
7	(s-Bu)$_2$Cu(CN)Li$_2$	Ph	0	5	52/48	–
8	(s-Bu)$_2$Cu(CN)Li$_2$	Ph	2	5	70/30	31[c]
9	t-BuLi	Bu	0	0	3/97	–
10	(t-Bu)$_2$Cu(CN)Li$_2$	Bu	0	0	86/14	–
11	(t-Bu)$_2$Cu(CN)Li$_2$	Bu	0	5	70/30	–
12	(t-Bu)$_2$Cu(CN)Li$_2$	Bu	2	5	98/2	61[d]
13	s-BuLi	Bu	0	0	3/97	–
14	(s-Bu)$_2$Cu(CN)Li$_2$	Bu	0	0	7/93	–
15	(s-Bu)$_2$Cu(CN)Li$_2$	Bu	0	5	79/21	76[d]
16	(s-Bu)$_2$Cu(CN)Li$_2$	Bu	2	5	92/8	81[d]

[a] TMSCl added to cuprate or enal prior to combination of the reactants. [b] Ratio determined by capillary GC of crude reaction product mixtures and were not corrected for response factors. [c] By flash chromatography on silica gel. [d] By Kugelrohr distillation.

the aldehyde or allylic alcohol during aqueous work-up and purification [1b]. A non-aqueous work-up using triethylamine gave a > 90% combined yield of silyl enol ether (from 1,4-addition) and silyl ether (from 1,2-addition) products. Unfortunately, these silylated compounds were not readily separable and this isolation technique could not be used to enhance the yields of isolated products.

R^1 = alpha - Alkoxyalkyl   R^2 = Phenyl
s - Butyl   n - Butyl
t - Butyl

The "2/5" procedure was then examined in more detail using higher order cyanocuprates prepared from t-butyllithium and s-butyllithium, Table 3. The same general trend observed for the α-alkoxyorganocuprates was also evident for these cuprate addition reactions. The 1,4-regioselectivity was enhanced using the "2/5" procedure over that observed for the "0/0" or "0/5" methods. For example, compare Table 3 entries 2 and 3, 7 and 8, and 15 and 16. In the reaction of cinnamaldehyde and lithium (di-t-butyl)cyanocuprate using the "0/5" procedure followed by an aqueous work-up, not only was the 1,4-adduct isolated, but the silyl enol ether derivative of the 1,4-addition product 4 and the silyl ether derivative of the 1,2-addition product 5 were also obtained. This result is in contrast to the report
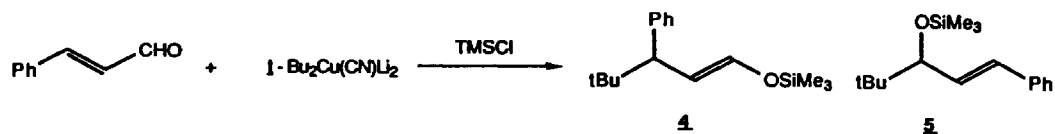
of Alexakis [3a] which indicated that the silyl enol ether products were not directly obtained from in-situ TMSCl/cuprate addition reactions, but required added base. The silyl enol ether 4 was identified by a strong absorption at 1650 cm^{-1} in the IR spectrum of the crude product mixture as well as by ^{1}H NMR. A GC/MS analysis confirmed the structural assignment. The same products (4 and 5) could also be isolated from the cuprate reaction if triethylamine was employed rather than saturated aqueous ammonium chloride in the work-up procedure. Interestingly, the silyl enol ether 4 obtained from the aqueous work-up procedure was a mixture of E and Z isomers (55/45 by capillary GC analysis), while that from the triethylamine work-up was obtained as a 68/32 stereoisomeric mixture. The silyl enol ether was not separated from the reaction by-products and the stereochemistry has not been unambiguously assigned. Kuwajima [2b,2] has noted that the in-situ TMSCl/cuprate addition reaction provides a stereoselective synthesis of silyl enol ethers from enals, up to 90% E. In contrast, addition of a tertiary amine base and TMSCl after the cuprate conjugate addition reaction produces a mixture of silyl enol ethers. The reaction with the higher order cyano-t-butyl cuprate seems to be an anomaly. Given the fact that both s-butyl- and t-butyl-lithium react with cinnamaldehyde to provide some 1,4-adduct, the substrate may be the cause of the apparent anomalous results. However, in the TMSCl mediated conjugate addition reactions of α-alkoxyorgano-cuprate 1 and cinnamaldehyde followed by a triethylamine work-up, GC analysis indicated greater than 90% stereoisomeric purity for the silyl enol ether obtained.

Discussion

The actual role of trimethylsilyl chloride in cuprate conjugate addition reactions is still not fully understood. Spectroscopic studies [2a,b,3a] have indicated that the silyl chloride is not simply functioning as a Lewis acid activator for the carbonyl compound. The rate acceleration also observed cannot be explained if the silyl chloride is only serving to trap the enolate species generated. Corey [2a] has postulated that the silyl chloride stabilizes the $d-\pi^*$ intermediate [6] of the conjugate addition reaction and subsequently drives the reaction forward due to the increased rate of conversion to the copper(III) intermediate. Nilsson [7a] has recently postulated a 3,4-addition mechanism in which a silyl halide (TMSCl or TMSI) forms a cyclic intermediate with an α-cuprio ketone adduct. The evidence presented by Corey [6a] on the existance of an a β-Cu^{III} intermediate seems to more adequately corroborate the data for both TMSCl mediated and non-TMSCl media-ted [8] organocuprate conjugate addition reactions. In any event, the present investigation seems to indicate that additional factors might also account for the results observed. Specifically, premixing a higher order cyano cuprate and trimethyl-silyl chloride apparently moderates the reactivity of the cuprate species. Perhaps a new species, which displays different reactivity than the "original" higher order cyanocuprate, is formed in solution. Nilsson [7b] has recently reported ^{29}Si NMR evidence that this may be the case for 2-thienyl cuprates, although no specific details were given. Lipshutz [9] has also presented ^{29}Si NMR evidence that a new species is apparently generated upon the mixture of a cuprate and TMSCl. It is unlikely that the TMSCl is serving to disrupt the α-alkoxyorganocuprate and liberate free RLi given the fact that the α-alkoxylithio species provides clean 1,2-addition, while the α-alkoxyorganocuprate shows no reactivity in the absence of TMSCl (Table 3 entry 1). Control reactions have shown that silylation of the α-alkoxylithio species by TMSCl is not a rapid reaction; therefore, the "removal" of free RLi from the cuprate solution by silylation is also quite unlikely. The amount of TMSCl initially present with the enal does not seem to be the deciding factor, compare for example Table 2 entries 2–5 and Table 3 entries 15 and 16. The presence of additional additives such as TMEDA, DMAP, or DMPU, actually interferes with the regiose-lectivity of cuprate addition. These additives may serve to disrupt the unique solution structure of the higher order cyano cuprate and TMSCl. Clearly a unique situation arises when TMSCl is present initially in both the cuprate and enal solutions. In summary, the method presented in this paper provides for improved yields and enhanced regioselectivity for the conjugate addition reactions of α-sub-stituted organocuprate reagents with enals.

Experimental

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 chromagraph equipped with an 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 [10] prior to use. Trimethylsilyl chloride was freshly distilled from CaH_2 prior to use. Copper(I) cyanide (tan colored) was purchased from Aldrich. Ultra-pure copper(I) iodide was purchased from Alfa. Additional organic reagents were purchased from Aldrich and distilled or recrystallized 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. Exact-mass mass spectroscopic analyses were carried out on a JEOL HMX-110 mass spectrometer. GC/MS analyses were carried out on a Hewlett-Packard 5895B GC/MS system.

Cuprate preparation, α-alkoxyorganocuprates

The α-alkoxyorganostannanes were prepared by a condensation reaction of lithium tributylstannylate and the appropriate aldehyde, followed by protection of the α-hydroxyorganostannane by chloromethyl methyl ether [11].

Thiophenoxy cuprate. A solution of 0.266 g (0.65 mmol) 1-methoxymethoxy-2-methyl-1-tributylstannylpropane in 3 ml of THF was cooled to $-78°C$ (CO_2/acetone). A 0.31 ml sample of a 2.6 M solution of n-butyllithium in hexane (0.82 mmol) was then added and the solution stirred for 20 minutes at $-78°C$. A second 25 ml round bottom flask containing 0.113 g (0.65 mmol) of thiophenoxy copper [12] suspended in 3 ml THF was then cooled to $-78°C$ (CO_2/acetone). The α-alkoxylithio species (generated from the stannane) was transferred via cannula to the suspension of thiophenoxy copper. The transmetallation flask was rinsed with an additional 1 ml of THF (cooled to $-78°C$) to ensure complete transfer of the lithio species. The cuprate mixture was gradually warmed to $-50°C$ (bath temperature) over a 1.5 h time period and then recooled to $-78°C$ (bath temperature). An 82 μl (0.65 mmol) sample of cinnamaldehyde was added to a third flask containing 3 ml THF. The solution of cinnamaldehyde was then cooled to $-78°C$ CO_2/acetone) and 0.42 ml (3.3 mmol) of freshly distilled (from CaH_2) TMSCl was added. After stirring the aldehyde/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 slightly heterogeneous mixture was stirred at $-78°C$ for 1 h, and then gradually warmed to $0°C$ (ice bath) over an additional 2.5 h time period. The reaction mixture was quenched by the addition of 1 ml 0.1 N HCl. The mixture was then diluted with 100 ml Et_2O, and extracted sequentially with 100 ml of a 1/1 solution of 0.1 N HCl/saturated aqueous NH_4Cl, 100 ml saturated aqueous $NaHCO_3$, and 50 ml saturated aqueous NaCl. The organic phase was separated and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product mixture. The products were then obtained by column chromatography.

Tributylphosphine cuprate. A solution of 0.27 g (0.68 mmol) 1-methoxymethoxy-2-methyl-1-tributylstannylpropane in 3 ml of THF was cooled to $-78°C$ (CO_2/acetone). A 0.33 ml sample of a 2.6 M solution of n-butyllithium in hexane (0.85

mmol) was then added and the solution stirred for 20 min at $-78°C$. A second 25 ml round bottom flask containing 0.266 g (0.68 mmol) of copper(I) iodide-tributylphosphine complex [13] suspended in 3 ml of THF was then cooled to $-78°C$ (CO_2/acetone). The α-alkoxylithio species was transferred via cannula to the suspension of copper iodide-tributylphosphine complex. The remainder of the procedure was identical to that described for the thiophenoxy cuprate, using in this case 85 μl (0.68 mmol) cinnamaldehyde and 0.43 ml (3.4 mmol) TMSCl. Work-up of the reaction was also identical to that described above.

Hexynyl cuprate. A solution of 71 μl (0.61 mmol) hexyne in 3 ml THF was cooled to $0°C$ (ice bath). A 0.26 ml sample of a 2.6 M solution of n-butyllithium in hexane (0.67 mmol) was then added dropwise and the resulting clear solution stirred for 1 h at $0°C$. A second 25 ml round bottom flask containing 0.115 g (0.67 mmol) copper(I) iodide suspended in 3 ml THF was then cooled to $0°C$ (ice bath). The hexynyllithium solution was then transferred via cannula to the copper iodide suspension. The bright yellow slurry of hexynyl copper was then stirred for 1 h at $0°C$, and then cooled to $-78°C$ (CO_2/acetone). The α-alkoxylithio species was prepared as described above and added to the hexynyl copper slurry at $-78°C$. The mixture was stirred at $-78°C$ for 10 min and then gradually warmed to $-65°C$ (bath temperature) over a period of 1 h. The slightly heterogeneous cuprate mixture was then cooled to $-78°C$ prior to the addition of the aldehyde/TMSCl mixture as described above. In this example, 84 μl (0.66 mmol) cinnamaldehyde and 0.42 ml (3.3 mmol) TMSCl were added. Work-up of the reaction was as described previously.

Cyano cuprate. A solution of 0.27 g (0.66 mmol) 1-methoxymethoxy-2-methyl-1-tributylstannylpropane in 3 ml THF was cooled to $-78°C$ (CO_2/acetone). A 0.31 ml sample of a 2.6 M solution of n-butyllithium in hexane (0.82 mmol) was then added and the solution stirred for 20 minutes at $-78°C$. A second 25 ml round bottom flask containing 0.059 g (0.66 mmol) copper(I) cyanide suspended in 3 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 $-78°C$. After stirring for 10 minutes at $-78°C$, the cuprate mixture was gradually allowed to warm to $-70°C$ (bath temperature) over a period of 1 h. A clear, slightly yellow homogeneous solution was obtained. After recooling the cuprate solution to $-78°C$ the addition of cinnamaldehyde/TMSCl followed the procedure described for the thiophenoxy cuprate. In this case, 84 μl (0.66 mmol) cinnamaldehyde and 0.42 ml (3.3 mmol), TMSCl were added. Work-up was then completed as described.

Higher order cyanocuprate. The higher order cyano cuprate was prepared in the same manner as the cyanocuprate with the exception that two equivalents of the α-alkoxylithio species were added to one equivalent of copper(I) cyanide. For example, 0.543 g (1.3 mmol) 1-methoxymethoxy-2-methyl-1-tributylstannylpropane was employed with 0.059 g (0.66 mmol) copper(I) cyanide. The aldehyde (0.66 mmol) and TMSCl (3.3 mmol) equivalents are the same as in the cyanocuprate reaction. Complete formation of the higher order cyano cuprate was noted by the complete dissolution of copper cyanide to form a clear, slightly yellow homogeneous solution. This standard procedure was employed for the preparation of higher order cyanocuprates from 1-methoxymethoxy-1-tributylstannylpentane also.

Higher order cyanocuprate / amine additives. *TMEDA*: The higher order cyanocuprate procedure was followed with the exception that TMEDA was combined

with the aldehyde/TMSCl solution prior to the addition of this tertiary mixture to the cuprate reagent. For a 0.63 mmol CuCN scale reaction 0.28 ml (1.88 mmol) TMEDA (freshly distilled from CaH_2) was employed. *DMAP*: The higher order cyanocuprate procedure was followed with the exception that DMAP was combined with the aldehyde/TMSCl solution prior to the addition of this tertiary mixture to the cuprate reagent. For a 0.66 mmol CuCN scale reaction, 0.153 g (1.25 mmol) DMAP was employed. *DMPU*: The DMPU mediated reaction was carried out in the same manner. For a 0.60 mmol CuCN scale reaction, 0.14 ml (1.2 mmol) DMPU was employed.

"2/5" procedure. The appropriate higher order cyanocuprate reagent was prepared as described. At the point in the procedure where the cuprate reagent had completely formed, producing a clear, slightly yellow homogeneous solution, the cuprate was cooled to $-78°C$ (CO_2/acetone) and two equivalents of TMSCl (based on mmol CuCN used) was then added. After stirring the cuprate/TMSCl mixture for 2 min, the aldehyde/TMSCl mixture was added via cannula. The resulting orange mixture was stirred at $-78°C$ for 1 h and then gradually warmed to $20°C$ over a period of 2 h. An aqueous work-up, as described for the thiophenoxy cuprate reaction, was then employed. *Non-aqueous work-up*: As an alternative work-up procedure for the isolation of silyl enol ether derivatives, triethylamine was substituted for the aqueous quench. After completion of the time period for the conjugate addition reaction, the mixture was cooled to $0°C$ (ice bath) and 1–2 ml of triethylamine was added. The ice bath was removed and the mixture was stirred vigorously for 20 min. The crude product mixture was diluted with 150 ml of anhydrous Et_2O and then filtered through a one inch pad of silica gel (pretreated with 2% Et_3N/Et_2O). The resulting clear ether layer was dried over anhydrous Na_2SO_4 and the solvent then removed under reduced pressure.

Cuprate preparation, α-alkylorganocuprates

The t-butyl and s-butyl higher order cyanocuprates were prepared in the same manner as the α-alkoxyorganocuprate reagents. Two equivalents of the alkyllithium reagent were employed per equivalent of copper(I) cyanide. The cuprate reagents were formed at $-78°C$, no warming was necessary, within 45 min. After combination of all reactants (cuprate/aldehyde/TMSCl) the reaction mixture was allowed to slowly warm from -78 to $0°C$ over a time period of 3 h. An aqueous work-up procedure was utilized as described previously.

Reaction of enals with RLi. The enal (1.2 mmol) was dissolved in 2.5 ml THF and then cooled to $-78°C$ (CO_2/acetone). The appropriate alkyllithium species (1.4 mmol) was then added dropwise and the reaction mixture was allowed to warm to $0°C$. The reaction was quenched by the addition of 1 ml 1.0 N HCL, diluted with 50 ml Et_2O and sequentially extracted with 25 ml saturated aqueous NH_4Cl, and 25 ml saturated aqueous NaCl. The layers were separated and the organic phase dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure.

1,4-products from α-alkoxyorganocuprate reactions

4-Methoxymethoxy-5-methyl-3-phenylhexanal. Purified by flash chromatography using a 1, 5, 10, 15% ethyl acetate/petroleum ether gradient eluent system. ^{1}H NMR ($CDCl_3$) δ 0.82–1.00 (m, 6H), 1.53–1.66 (m, 2H), 2.70–3.05 (m, 2H), 3.35–3.53 (m, 4H), 4.48–4.63 (m, 2H), 7.18–7.35 (m,5H), 9.65–9.67 (br t, 1H); [13]C

NMR (CDCl$_3$) δ 16.50, 18.51, 19.57, 20.05, 27.67, 29.98, 30.18, 31.13, 42.64, 44.16, 55.75 55.96, 87.88, 89.19, 98.74, 126.30, 126.45, 127.94, 128.41, 141.42, 142.43, 207.43 (mixture of diastereomers); IR (neat) (cm^{-1}) 1715; Analysis as the 2,4-di-nitrophenylhydrazone. Exact mass calcd. for C$_{12}$H$_{26}$N$_4$O$_6$: 430.1852. Found: 430.1842.

3-(1-(1-Methoxymethoxy-2-methyl)propyl)heptanal. Purified by flash chromatography using a 5, 10, 20% Et$_2$O/hexane gradient eluent system. ^{1}H NMR (CDCl$_3$) δ 0.66–2.73 (m, 19H), 3.12–3.19 (m, 1H), 3.36 (s, 3H), 4.53–4.69 (m, 2H), 9.76 (t, 1H); ^{13}C NMR (CDCl$_3$) δ 13.86, 18.91, 20.29, 27.82, 29.29, 29.85, 30.40, 45.90, 55.76, 87.04, 98.13, 205.10; IR (neat) (cm^{-1}) 1715; Analysis as the 2,4-dinitrophenyl-hydrazone. Exact mass calcd. for C$_{19}$H$_{30}$N$_4$O$_6$: 410.2165. Found: 410.2090.

4-Methoxymethoxy-3-phenyloctanal. Purified by flash chromatography using a 1, 5, 10, 15, 20% ethyl acetate/petroleum ether gradient eluent system. ^{1}H NMR (CDCl$_3$) δ 0.73–0.83 (m, 3H), 1.15–1.54 (m, 6H), 2.79–2.94 (m, 2H), 3.28–3.31 (d, 3H), 3.37–3.67 (m, 2H), 4.54–4.62 (m, 2H), 7.12–7.26 (m, 5H), 9.62 (t, 1H); ^{13}C NMR (CDCl$_3$) δ 13.76, 22.52, 27.88, 29.61, 30.90, 31.05, 35.23, 43.28, 44.96, 55.76, 80.83, 81.16, 96.36, 126.74, 128.15, 128.30, 140.11, 201.41; IR (neat) (cm^{-1}) 1720; Analysis as the 2,4-dinitrophenylhydrazone. Exact mass calcd. for C$_{22}$H$_{28}$N$_4$O$_6$: 444.2009. Found: 444.1247.

3-Butyl-4-methoxymethoxyoctanal. Purified by flash chromatography using a 1, 5, 7, 10% ethyl acetate/petroleum ether gradient eluent system. ^{1}H NMR (CDCl$_3$) δ 0.80–0.91 (m, 6H), 1.12–1.56 (m, 13H), 2.23–2.57 (m, 1H), 3.34–3.56 (m, 5H), 4.52–4.65 (dd, 2H), 9.74 (t, 1H); ^{13}C NMR (CDCl$_3$) δ 13.82, 13.90, 22.20, 22.64, 22.74, 28.42, 29.71, 30.57, 36.67, 44.64, 55.69, 79.66, 95.84, 202.59; IR (neat) (cm^{-1}) 1725; Analysis as the 2,4-dinitrophenylhydrazone. Exact mass calcd. for C$_{20}$H$_{32}$N$_4$O$_6$: 424.2322. Found: 424.2237.

1,2-products from α-alkoxyorganocuprate additons

3-Methoxymethoxy-2-methyl-6-phenylhex-5-en-4-ol. Purified by flash chromatography using a 1, 5, 10, 15% ethyl acetate/petroleum ether gradient eluent system. ^{1}H NMR (CDCl$_3$) δ 0.72–1.00 (br d, 6H), 1.66–1.92 (m, 1H), 3.05–3.15 (m, 1H), 3.25–3.47 (s, 3H), 3.49–4.35 (m, 1H, OH), 4.38–4.77 (q, 2H), 5.90–6.75 (m, 2H), 7.05–7.40 (m, 5H); IR (neat) (cm^{-1}) 3200–3600.

3-Methoxymethoxy-2-methyldec-5-en-4-ol. Purified by flash chromatography using a 5, 10, 20% Et$_2$O/hexane gradient eluent system. ^{1}H NMR (CDCl$_3$) δ 0.68–1.82 (m, 14H), 1.82–2.21 (br d, 2H), 2.95–3.25 (m, 1H), 3.35–3.48 (m, 4H, OH), 3.82–4.15 (m, 1H), 4.50–4.72 (q, 2H), 5.15–5.68 (m, 2H); IR (neat) (cm^{-1}) 3180–3640.

4-Methoxymethoxy-1-phenyloct-1-en-3-ol. Purified by flash chromatography using a 1, 5, 10, 15% ethyl acetate/petroleum ether gradient eluent system. ^{1}H NMR (CDCl$_3$) δ 0.55–1.53 (m, 9H), 3.18–3.37 (m, 4H), 3.43–3.54 (br d, 1H, OH) 3.96–4.15 (br d, 1H) 4.53–4.60 (m, 2H), 5.92–6.62 (m, 2H), 7.04–7.33 (m, 5H); IR (neat) (cm^{-1}) 3140–3600.

5-Methoxymethoxydodec-7-en-6-ol. Purified by flash chromatography using a 1, 5, 7, 10% ethyl acetate/petroleum ether gradient eluent system. ^{1}H NMR (CDCl$_3$) δ 0.75–1.10 (m, 6H), 1.10–1.62 (m, 10H), 1.95–2.19 (br d, 2H), 2.93–3.12 (m, 1H, OH), 3.36 (s, 3H), 3.80–4.17 (br d, 1H), 4.58–4.80 (m, 3H), 5.24–5.90 (m, 2H); IR (neat) (cm^{-1}) 3240–3600.

1,4-products from α-alkylorganocuprate additions

4,4-Dimethyl-3-phenylpentanal. Purified by flash chromatography using 3% ethyl acetate/petroleum ether as eluent. ^{1}H NMR (CDCl$_3$) δ 0.70 (s, 9H), 2.48–2.92 (m, 3H), 7.00–7.15 (m, 5H); IR (neat) (cm^{-1}) 1720; Analysis as the 2,4-dinitrophenylhydrazone, m.p. 156°C, from ethanol. Anal. Found: C, 61.49; H, 6.01. C$_{19}$H$_{22}$N$_4$O$_4$ calcd.: C, 61.61; H, 5.99%.

4-Methyl-3-phenylhexanal. Purified by flash chromatography using a 0–6% ethyl acetate/petroleum ether eluent system. ^{1}H NMR (CDCl$_3$) δ 0.70–1.05 (m, 6H), 1.05–1.78 (m, 3H), 2.70–2.90 (m, 2H), 2.95–3.30 (m, 1H), 7.10–7.48 (m, 5H), 9.65 (t, 1H); IR (neat) (cm^{-1}) 1720; Analysis as the 2,4-dinitrophenylhydrazone, m.p. 98°C, from ethanol. Anal. Found: C, 61.57; H, 6.02. C$_{19}$H$_{22}$N$_4$O$_4$ calcd.: C, 61.61; H, 5.99%.

3-(2-methylpropyl)heptanal. Purified by Kugelrohr distillation, b.p. 60–70°C/30 mmHg. ^{1}H NMR (CDCl$_3$) δ 0.50–1.72 (m, 18H), 2.10–2.45 (m, 3H), 7.00–7.15 (m, 5H), 9.82 (t, 1H); IR (neat) (cm^{-1}) 1710; Analysis as the 2,4-dinitrophenylhydrazone, m.p. 131°C, from ethanol. Anal. Found: C, 58.16; H, 7.52. C$_{17}$H$_{26}$N$_4$O$_4$ calcd.: C, 58.27; H, 7.48%.

3-(2-Butyl)heptanal. Purified by Kugelrohr distillation, b.p. 70–85°C/30 mmHg. ^{1}H NMR (CDCl$_3$) δ 0.74–1.05 (m, 9H), 1.05–1.53 (m, 9H), 1.85–2.13 (m, 1H), 2.17–2.44 (m, 2H), 9.81 (t, 1H); IR (neat) (cm^{-1}) 1725; Analysis as the 2,4-dinitrophenylhydrazone, m.p. 99°C, from ethanol. Anal. Found: C, 58.35; H, 7.50. C$_{17}$H$_{26}$N$_4$O$_4$ calcd.: C, 58.27; H, 7.48%.

1,2-Products from α-alkylorganocuprate additions

2,2-Dimethyl-5-phenylpent-4-en-3-ol. ^{1}H NMR (CDCl$_3$) δ 0.95 (s, 9H), 3.90 (d, 1H), 6.25–6.59 (m, 2H), 7.18–7.40 (m, 5H); IR (neat) (cm^{-1}) 3200–3600.

4-Methyl-1-phenylhex-1-en-3-ol. ^{1}H NMR (CDCl$_3$) δ 0.70–1.68 (m, 10H), 4.00–4.26 (m, 1H), 6.07–6.69 (m, 2H), 7.18–7.44 (m, 5H); IR (neat) (cm^{-1}) 3160–3600.

2,2-Dimethylnon-4-en-3-ol. ^{1}H NMR (CDCl$_3$) δ 1.00–1.34 (m, 4H), 1.60–1.80 (m, 12H), 1.78–2.05 (br d, 2H), 3.52 (d, 1H), 5.20–5.69 (m, 2H); IR (neat) (cm^{-1}) 3150–3615.

3-Methyldec-5-en-4-ol. ^{1}H NMR (CDCl$_3$) δ 0.7–1.0 (m, 9H), 1.00–1.36 (m, 7H), 1.78–2.03 (br d, 2H), 3.62–3.86 (m, 1H), 5.16–5.68 (m, 2H); IR (neat) (cm^{-1}) 3100–3600.

Acknowledgment

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