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The Mechanism of Organocuprate 1,4-Addition Reactions with α,β-Unsaturated Ketones: Formation of Cuprate–Enone Complexes with Lithium Dimethylcuprate

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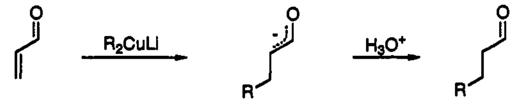
Abstract: Colored complexes can be obtained from some enones on addition to ethereal $Me_2CuLi{\cdot}LiI$ at −78 °C. The unreacted enone can be recovered from these mixtures in high yield by low-temperature protonation. When 2,2,5-trimethyl-4-hexen-3-one was added to $Me_2CuLi{\cdot}LiI$ at −80 °C, cuprate–olefin and lithium–carbonyl complexes were formed and observed by ^{13}C NMR. On warming this reaction solution to −55 °C, only the lithium–carbonyl complex was detectable which slowly ($t_{1/2} \approx 2.5$ h) converted into the β-alkylated enolate. Implications of these observations on the description of the mechanism of the 1,4-addition reaction are presented.

Introduction

The 1,4-addition reaction of lithium diorganocuprates with α,β-unsaturated carbonyl compounds has proven to be an extremely valuable reaction for creating a new carbon–carbon bond at the β position relative to the carbonyl group:[1]



(1)

Investigations of the mechanism of the 1,4-addition reaction of diorganocuprates with α,β-unsaturated carbonyl compounds have been undertaken over an extended period of time.[2] However, despite considerable effort, the formulation of a detailed mechanism remains incomplete. In some cases even elementary information regarding the nature of the reactive cuprate species is not available.[3]

The most popular current mechanistic view is that 1,4-addition reactions of organocuprates proceeds *via* an organocopper(III) adduct[4] attached to the β-carbon which subsequently undergoes reductive elimination to the primary enolate product. Direct observation of the proposed organometallic copper(III) intermediate[5] has not been reported, and predictions are that if such a species was on the reaction pathway then it would have a very short lifetime.

The steps preceding a possible copper(III) intermediate have been investigated by several groups over more than a decade, and in many instances, because of the sensitive nature of the reagents, the information obtained is of an indirect nature. The most consistent scenario for 1,4-addition of lithium diorganocuprates to α,β-unsaturated carbonyl compounds is that the reaction is initiated by some form of electron transfer from the organometallic species to the unsaturated substrate. This electron-transfer idea received substantial reinforcement when a correlation between one-electron reduction potentials of the α,β-unsaturated carbonyl systems with cuprate reactivity was recognized.[6] Direct evidence for one-electron transfer in at least some reactions involving organocuprates was obtained from the observation of ESR active species in the reaction of $Me_2CuLi{\cdot}LiI{\cdot}2LiBr$[7] with 9-fluorenone at low temperature.[8] The notion that organocuprate 1,4-addition proceeds by one-electron transfer *via* long-lived radical anion intermediates has been substantially refuted by subsequent studies, but the electron-transfer ability of organocuprates has been clearly demonstrated in studies with molecules specifically designed to trap any electron-rich enone system.[9] The relationship between reduction potential and organocuprate reactivity does not require that 1,4-addition reactions must proceed by a one-electron-transfer pathway, but the correlation must be recognized and accounted for in any credible mechanistic scheme.

Kinetic studies have been made on mixtures of selected β,β-disubstituted α,β-unsaturated ketones and methylcuprates in diethyl ether at 25 °C.[10] An intermediate species, which could be detected by absorption at 380 nm, was rapidly and reversibly formed, and this species then collapsed unimolecularly to a β-alkylated enolate. These observations lead to a general scheme:

$$\text{enone} + \mathrm{Me_2CuLi} \overset{K}{\rightleftarrows} \text{intermediate} \overset{k}{\rightleftarrows} \text{enolate product}$$

From appropriate model studies and infrared measurements it was concluded that the intermediate was a lithium-coordinated complex of the α,β-unsaturated ketone substrate. The electron-deficient lithium was presumed to be available even from the cuprate cluster if necessary as this species was detected in reactions with formally halide-free lithium dimethylcuprate *viz.* Me_2CuLi.[7] The equilibrium constants which were obtained from these experiments reflected the steric bulk about the carbonyl oxygen, although a preference for *syn* or *anti* coordination at oxygen with respect to the double bond could not be ascertained. This concept of prior coordination at the carbonyl oxygen, presumably by

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[•] Abstract published in *Advance ACS Abstracts,* March 1, 1994.

[1] Reviews: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992,** *41,* 135–631. Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; John Wiley & Sons: New York, 1980.

[2] Review: Smith, R. A. J.; Vellekoop, A. S. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Connecticut; Vol. 3, *Mechanism of Reactions of Importance in Synthesis*, in press.

[3] For a recent review of organocuprate structures, see: Power, P. P. *Prog. Inorg. Chem.* **1991,** *39,* 75–112.

[4] For example: Johnson, C. R.; Herr, R. W.; Wieland, D. M. *J. Org. Chem.* **1973,** *38,* 4263–4268.

[5] Isolatable organocopper(III) species are usually associated with stabilizing ligands, e.g., $(CF_3)_2CuSC(S)NEt_2$: Willert-Porada, M. A.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc., Chem. Commun.* **1989,** 1633–1634.

[6] House, H. O. *Acc. Chem. Res.* **1976,** *9,* 59–67.

[7] Lithium dimethylcuprates will be shown as monomers in this paper for simplicity; however, low halide Me_2CuLi has been shown to exist as a dimer in diethyl ether: Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976,** *98,* 4098-4104. Ashby, E. C.; Watkins, J. J. *J. Am. Chem. Soc.* **1977,** *99,* 5312–5317. The aggregration states of the other methylcuprates in diethyl ether are not known.

[8] House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966,** *31,* 3128–3141.

[9] Smith, R. A. J.; Hannah, D. J. *Tetrahedron* **1979,** *35,* 1183–1189.

[10] Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981,** *103,* 141–148.

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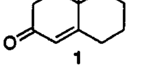
lithium, has some indirect support from studies of organocuprate reactions with α,β-unsaturated ketones having similar electronic arrangements but substantially different steric features.[9]

The kinetic evidence for the equilibrium between one or more intermediate species on the reaction pathway was further enhanced by the direct, spectroscopic observation of intermediates in mixtures of some organocuprates and unsaturated esters under conditions where the 1,4-addition proceeded at a relatively slow rate. Infrared spectra were obtained from stable, colored solutions produced at low temperatures by mixing unsaturated esters with methylcuprates in diethyl ether.[11] The unsaturated esters could be recovered unchanged from these solutions by low-temperature protonation. The infrared spectra showed significant shifts in the carbon–carbon double bond stretching frequency from that of the unsaturated substrate and this was interpreted as indicating some type of olefin–copper complexation.

Direct low-temperature NMR observation of solutions produced by mixing lithium dimethylcuprate and the enone 10-methyl-1(9)-octal-2-one (**1**) in diethyl ether[12] or cinnamate esters (**2**) in either THF/toluene or diethyl ether/CH_2Cl_2[13–15] has been made.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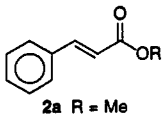

2a R = Me
2b R = ^tBu

The resonances detected were interpreted in terms of cuprate-*d* → enone-π* and lithium cation–carbonyl complexes. Cuprate-*d* → enone-π* complexes were characterized by large upfield shifts of the olefinic resonances of ~40 and ~80 ppm for the α- and β-carbons, respectively, compared with the starting unsaturated carbonyl compound, while the carbonyl carbon resonance was relatively unperturbed. The lithium–carbonyl complex showed chemical shifts in accord with those observed from the addition of a lithium salt to the unsaturated carbonyl compound in diethyl ether. The significantly greater upfield shifts observed for the β carbon resonance appears to indicate that the copper–β-carbon interaction was stronger than that of the copper–α-carbon interaction.

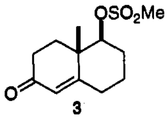
It could be argued that the cuprate-*d* → π*-complexes observed at low temperature with **1**, a rigid, β,β-disubstituted unsaturated ketone with the β-carbon at a ring junction, and cinnamate esters (**2**) are special cases and do not truly relate to the broad range of α,β-unsaturated ketones used in reactions with diorganocuprates. In addition, the interpretation of spectra obtained from mixtures of Me_2CuLi and **1** were generally complicated by the stereochemical features of **1** which resulted in the production of several sets of minor resonances assigned to diastereoisomeric *exo* and *endo* π-complexes with monomeric and dimeric organocuprates. The aim of this study was to investigate the generality of the formation of metal-π complexes from the interaction of simple α,β-unsaturated ketones with lithium dimethylcuprate in diethyl ether at low temperatures. The solvent of choice was dictated by the dominant use of diethyl ether for successful 1,4-addition reactions with diorganocuprates.

Results and Discussion

The influence of the substitution pattern on the reaction of a set of enones with lithium dimethylcuprates at low temperature was examined, using a range of enones. Several restrictions were imposed on the choice of enones to assist in the determination of suitable candidates for subsequent NMR study. It was desirable that the enone should be such as to avoid the stereochemical complications observed in the reaction of Me_2CuLi with **1**. Conformational flexibility of the enone substrates was also desired as this would allow comparison with the results obtained with the more rigid molecule **1**. The substrates were also required to be amenable to ^{13}C isotope labeling so as to assist in the structural assignment of intermediate species using ^{13}C NMR.

Low-Temperature Interaction of Methylcuprates with Enones. A series of methyl-substituted 2-cyclohexenones and acyclic enones were chosen for investigation with $Me_2CuLi{\cdot}LiI$[7] and $Me_2CuLi{\cdot}(LiX)_3$[7] (prepared from CuI and 2 equiv of MeLi·LiBr) at −78 °C. The appearance of each reaction mixture was noted on admixture, and, after low-temperature protonation, the reaction mixtures were assayed for product(s). The results that were obtained are summarized in Table 1.

The reaction of *cis*-5-(mesyloxy)-10-methyl-1(9)-octal-2-one (**3**) with various organocopper species to produce the internal displacement product 6-methyltricyclo[4.4.0.0^{1,5}]-9-decanone (**4**) has been effectively used as a measure of cuprate reactivity.[16,17] Reaction of **3** with $Me_2CuLi{\cdot}LiI$ or $Me_2CuLi{\cdot}(LiX)_3$ at −78 °C showed similar results (Table 1, entries 1 and 2) indicating that the additional lithium salts in the second reagent had no influence on cuprate ability to induce intramolecular alkylation.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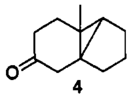
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In contrast, the type of MeLi used for the preparation of the cuprate did have a marked influence on the appearance of the reaction mixture as was demonstrated by the reaction with **1**. As noted previously,[12] an orange solution was obtained when **1** was added to $Me_2CuLi{\cdot}LiI$ (Table 1, entry 3), while with $Me_2CuLi{\cdot}(LiX)_3$ an orange precipitate was observed (Table 1, entry 4). In both cases **1** was effectively recovered by protonation. These results indicated that $Me_2CuLi{\cdot}LiI$ was useful for obtaining homogeneous solutions and hence suitable for NMR studies, while colored precipitates could be more readily achieved with $Me_2CuLi{\cdot}(LiX)_3$, perhaps suitable for solid-state structural analysis.

Inspection of the results (Table 1) allowed the enones to be divided into three categories depending on whether the observed change was 1,4-addition, formation of a soluble complex, or formation of an insoluble complex when mixed with $Me_2CuLi{\cdot}LiI$ at −78 °C. Overall it is clear that colored complexes can be obtained from a variety of enones under conditions which allow recovery of the unreacted enone in high yield and thus the *general nature* of the cuprate–enone interaction has been established.

Addition of 3-methyl-2-cyclohexenone (**5**) to $Me_2CuLi{\cdot}LiI$ at −78 °C (Table 1, entry 5) resulted in the formation of the 1,4-addition product. When **5** was added to the cuprate at −100 °C, a yellow solution initially formed which subsequently yielded a yellow precipitate (Table 1, entry 6). Protonation of this reaction mixture at −100 °C gave the starting enone in high recovery. Reaction of **5** with $Me_2CuLi{\cdot}(LiX)_3$ at −100 °C gave similar results (Table 1, entry 7). 5,5-Dimethyl-2-cyclohexenone (**6**) also underwent 1,4-addition at −78 °C (Table 1, entries 8 and 9). These two enones would appear to have similar reactivity at −78 °C to that of 2-cyclohexenone (**7**), which is highly reactive under these experimental conditions. The reaction of 3-penten-2-one (**8**) with either methylcuprate at −78 °C (Table 1, entries 10 and 12) gave a moderate amount of the 1,4-addition product. Repetition of the reaction with $Me_2CuLi{\cdot}LiI$ at −100 °C reduced

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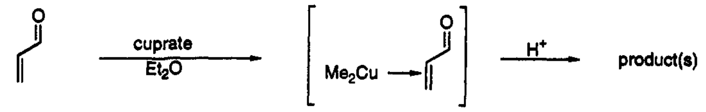
(17) Smith, R. A. J.; Vellekoop, A. S. *Tetrahedron* **1989**, *45*, 517–522.

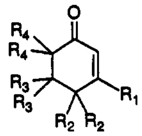
Table 1. Interaction of Methylcuprates with Enones at −78 °C



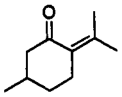
entry	enone	cuprate[a]	reaction mixture appearance	product(s)[b] % enone	product(s)[b] % 1,4-addition
1	**3**[c]	$Me_2CuLi{\cdot}LiI$	yellow precipitate	35[d]	58[d,e]
2	**3**[c]	$Me_2CuLi{\cdot}(LiX)_3$	yellow precipitate	35[d]	56[d,e]
3	**1**	$Me_2CuLi{\cdot}LiI$	orange solution	95[d]	
4	**1**	$Me_2CuLi{\cdot}(LiX)_3$	orange solution → orange precipitate	94[d]	
5	**5**	$Me_2CuLi{\cdot}LiI$	yellow precipitate	16	80
6	**5**	$Me_2CuLi{\cdot}LiI$[f]	yellow solution → yellow precipitate	96	
7	**5**	$Me_2CuLi{\cdot}(LiX)_3$[f]	yellow precipitate	93	3
8	**6**	$Me_2CuLi{\cdot}LiI$	yellow/orange precipitate	2	95
9	**6**	$Me_2CuLi{\cdot}(LiX)_3$	yellow/orange precipitate		96
10	**8**	$Me_2CuLi{\cdot}LiI$	yellow precipitate	55[d]	45[d]
11	**8**	$Me_2CuLi{\cdot}LiI$[f]	yellow precipitate	65[d]	35[d]
12	**8**	$Me_2CuLi{\cdot}(LiX)_3$	yellow precipitate	45[d]	45[d]
13	**9**	$Me_2CuLi{\cdot}LiI$	orange solution	93	
14	**9**	$Me_2CuLi{\cdot}(LiX)_3$	orange solution	91	
15	**10**	$Me_2CuLi{\cdot}LiI$	yellow/orange solution	91	5
16	**10**	$Me_2CuLi{\cdot}(LiX)_3$	yellow/orange solution → yellow precipitate	97	
17	**11**	$Me_2CuLi{\cdot}LiI$	orange solution	91	5
18	**11**	$Me_2CuLi{\cdot}(LiX)_3$	orange solution → yellow precipitate	98	
19	**12**	$Me_2CuLi{\cdot}LiI$	yellow solution	95	
20	**12**	$Me_2CuLi{\cdot}(LiX)_3$	yellow/orange solution	97	
21	**13**	$Me_2CuLi{\cdot}LiI$	orange solution	89[d]	4[d]
22	**13**	$Me_2CuLi{\cdot}(LiX)_3$	yellow/orange solution	90[d]	5[d]
23	**14**	$Me_2CuLi{\cdot}LiI$	yellow precipitate	95	
24	**14**	$Me_2CuLi{\cdot}LiI$[f]	yellow precipitate	97	
25	**14**	$Me_2CuLi{\cdot}(LiX)_3$	yellow precipitate	98	
26	**15**	$Me_2CuLi{\cdot}LiI$	yellow solution → yellow precipitate	87	10
27	**15**	$Me_2CuLi{\cdot}(LiX)_3$	orange solution → fine orange precipitate	92	

[a] $Me_2CuLi{\cdot}(LiX)_3$ represents $Me_2CuLi{\cdot}LiI{\cdot}2LiBr$. [b] Determined by capillary GC analysis unless stated otherwise. [c] Enone **3** was added in CH_2Cl_2 solution. [d] Determined by ^1H NMR. [e] Product is 6-methyltricyclo[4.4.0.0^{1,5}]-9-decanone (**4**). [f] Reaction carried out at −100 °C.

the amount of 1,4-addition but did not completely inhibit the reaction (Table 1, entry 11). Enones **5**–**8** clearly represent a group of compounds which are quite receptive to reaction with cuprates, but any distinctive common electronic or structural features are not readily discernable.



5. $R_1 = Me$; $R_2, R_3, R_4 = H$
6. R_1, R_2, R_4, H; $R_3 = Me$
7. $R_1, R_2, R_3, R_4 = H$
9. $R_1, R_2 = Me$; $R_3, R_4 = H$
10. $R_1, R_3 = Me$; $R_2, R_4 = H$
11. $R_1, R_4 = Me$; $R_2, R_3 = H$
14. $R_1, R_3, R_4 = H$; $R_2 = Me$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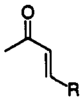
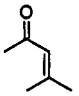
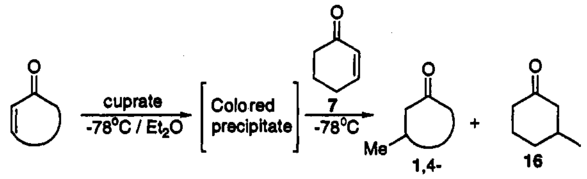

8. R = Me
15. R = Ph


13

Reaction of $Me_2CuLi{\cdot}LiI$ with 3,4,4-trimethyl-2-cyclohexenone (**9**) (Table 1, entry 13), 3,5,5-trimethyl-2-cyclohexenone (**10**) (Table 1, entry 15), 3,6,6-trimethyl-2-cyclohexenone (**11**) (Table 1, entry 17), (+)-pulegone (**12**) (Table 1, entry 19), or 4-methyl-3-penten-2-one (**13**) (Table 1, entry 21) gave homogeneous yellow-orange colored solutions at −78 °C. Low-temperature protonation of each of these mixtures gave the original enone in high recovery.

Table 2. Reaction of 2-Cyclohexenone (**7**) with the Colored Precipitates Obtained from **1** and **14** and Lithium Dimethylcuprates at −78 °C



enone	cuprate	products[a] (%) enone	products[a] (%) 1,4-	products[a] (%) 7	products[a] (%) 16
1	$Me_2CuLi{\cdot}(LiX)_3$	95[b]	0	<5	60
14	$Me_2CuLi{\cdot}LiI$	92	5	0	95

[a] GC yields unless stated otherwise. [b] NMR yield.

Similar recoveries were obtained with $Me_2CuLi{\cdot}(LiX)_3$ and **9**–**13**. A common but not unique feature of all these enones is *β,β*-disubstitution. This type of substitution may hamper the formation of polymeric cuprate–enone complexes and thus prevent precipitation of the intermediates and also inhibit the 1,4-addition reaction.

Both 4,4-dimethyl-2-cyclohexenone (**14**) (Table 1, entry 23) and *trans*-4-phenyl-3-buten-2-one (**15**) (Table 1, entry 26) gave yellow precipitates when exposed to $Me_2CuLi{\cdot}LiI$ at low temperatures which, after protonation at −78 °C, returned mostly unchanged enone. Precipitates were also observed with $Me_2CuLi{\cdot}(LiX)_3$. The reactivity of the solid precipitates was probed using the reactive enone 2-cyclohexenone (**7**). Product analysis of the reaction of **7** with mixtures produced from **1** and $Me_2CuLi{\cdot}(LiX)_3$ and also from **14** and $Me_2CuLi{\cdot}LiI$ are presented in Table 2.

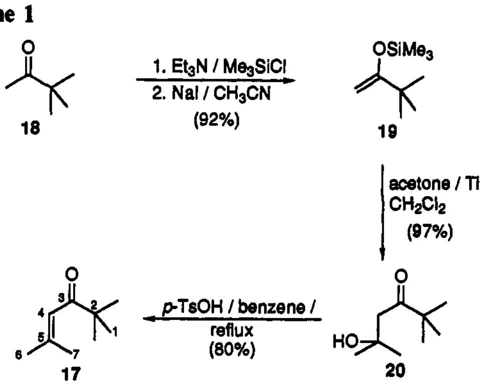
In both instances the original enone substrate was recovered in high yield together with appreciable amounts of 3-methylcyclohexanone (**16**) resulting from 1,4-addition to **7**. These results provide convincing evidence for the *reversible formation* of a cuprate–enone complex which allows a more reactive enone, *viz.* **7**, to effectively compete for the organocuprate and preferentially undergo 1,4-addition. These observations are related to those reported[18] for the reaction of 1-oxaspiro[4,5]-dec-6-en-8-one with lithium dimethylcuprate where a yellow solid was obtained at low temperatures. Activation of this complex was examined by warming a diethyl ether suspension, and the 1,4-addition product was obtained albeit nonstereoselectively. Stereoselective 1,4-addition was observed following resuspension of the yellow solid in THF containing TMSCl, at −78 °C.

Of the enones, **9–13**, which gave homogeneous solutions with $Me_2CuLi{\cdot}LiI$ at −78 °C 4-methyl-3-penten-2-one (**13**) was clearly the simplest and therefore appeared most attractive for direct NMR observation of any intermediate species. The focus on ^{13}C NMR in preference to ^{1}H NMR for these direct studies was based on the increased chemical shift scale with ^{13}C which was expected to reflect even minor electronic changes. This feature required ^{13}C enriched substrates, and **13** was clearly amenable to selective ^{13}C isotope incorporation. Previously **13** had been shown to undergo 1,4-addition with lithium dimethylcuprate in high yield (93%) in diethyl ether[19] confirming that **13** was indeed a normal substrate for cuprate 1,4-addition. A potential difficulty in the use of **13** in slow, 1,4-addition reactions is that the initial enolate can undergo α′-enolization. This type of enolate isomerization has previously been observed[20] with related potassium and sodium enolates at room temperature. α′-Enolization was also observed during mechanistic studies involving the reaction of Me_2CuLi with **1**.[12] Any enolization of this type would necessarily complicate interpretation of the NMR spectra of the 1,4-addition reaction system. In addition the α′-enolate would be less sterically hindered and thus could be expected to be more reactive with electrophiles than the initial α-enolate. As low-temperature NMR experiments involve the observation of the 1,4-addition reaction over an extended period of time a particularly clean reaction was required, and hence the enolate generated must be unreactive especially toward the unreacted enone in order to avoid complications resulting from Michael or aldol addition reactions.

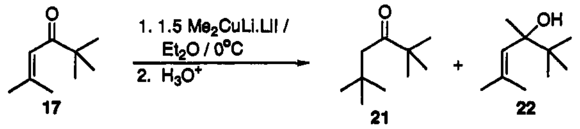
To overcome these potential difficulties a nonenolizable, bulky group adjacent to the carbonyl was required. 2,2,5-Trimethyl-4-hexen-3-one (**17**) satisfied these requirements and still retained the desired features necessary for ^{13}C NMR studies. It had previously been shown that **17** underwent efficient 1,4-addition with methylcuprates.[21] In this work **17** [For clarity in the following discussion, the letters **a**, **b**, and **c**, are suffixed to structure numbers **17**, **24**, **25**, or **26** and denote compounds with natural abundance ^{13}C 7.5% ^{13}C at C-5 or 14.9% ^{13}C at C-3, respectively.] was prepared in high yield by a modification of the classical Claisen reaction involving a silyl enol ether derived from 3,3-dimethyl-2-butanone (**18**) (Scheme 1).

The silyl enol ether 3,3-dimethyl-2-(trimethylsiloxy)butene[22] (**19**) underwent $TiCl_4$-promoted condensation[23] with acetone to give 5-hydroxy-2,2,5-trimethyl-3-hexanone (**20**). Acid catalyzed dehydration of **20** gave **17a** in high overall yield. The preparation of **17** with ^{13}C incorporated at the β-carbon, *viz.* 2,2,5-trimethyl-[5-^{13}C]-4-hexen-3-one (**17b**), was achieved as per Scheme 1 using partially enriched [2-^{13}C]acetone. Comparison of the relative intensities of the ^{13}C NMR resonances of **17a** and **17b** indicated a 7.5% ^{13}C isotope loading specifically at the β carbon of **17b**. Preparation of **17** with ^{13}C at the carbonyl carbon, *viz.* 2,2,5-trimethyl-4-hexen[3-^{13}C]-3-one (**17c**), was also undertaken. Reaction of [1-^{13}C]acetyl chloride with *t*-BuMgCl[24] gave impure 3,3-dimethyl[2-^{13}C]-2-butanone in 61% yield, which was isolated as a Et_3N solution. Further reaction as per Scheme 1 gave impure 5-hydroxy-2,2,5-trimethyl[3-^{13}C]-3-hexanone which after purification by column chromatography and dehydration gave **17c**. Comparison of the relative intensities of the ^{13}C NMR resonances of **17a** and **17c** indicated a 15% ^{13}C isotope loading at the carbonyl carbon.

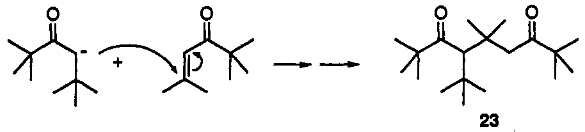
Scheme 1



Scheme 2



Scheme 3



With 2,2,5-trimethyl-4-hexen-3-one and its various ^{13}C labeled derivatives (**17a–c**) in hand attention was then focused on the investigation of cuprate reactivity of $Me_2CuLi{\cdot}LiI$ toward **17a**. Reaction of **17a** with $Me_2CuLi{\cdot}LiI$, prepared from purified MeLi,[25] at −78 °C, gave an orange solution which after low temperature protonation afforded unreacted **17a** in 98% yield. The 1,4-addition product, 2,2,5,5-tetramethyl-3-hexanone[26] (**21**), was obtained from the reaction of **17a** with $Me_2CuLi{\cdot}LiI$ at 0 °C in high yield (≈90%)(Scheme 2).

If the MeLi used for cuprate preparation contained a significant (>10%) level of residual base then small amounts of the 1,2-addition product, 2,2,3,5-tetramethyl-4-hexen-3-ol[19] (**22**), were also isolated. Some reactions also produced a small amount of a third product which could not be obtained in a pure form. Based on ^{1}H NMR and infrared spectral data, the structure for this compound was tentatively assigned as **23** and can be envisaged as resulting from Michael addition of the enolate to **17a** (Scheme 3). Only a relatively small amount of **23** was produced even when the cuprate 1,4-addition reaction was carried out in the presence of excess **17a**. The low Michael reactivity of the enolate and **17a** is presumably related to steric effects which are inherent in the reactants.

The effect of cuprate concentration on the efficiency of the 1,4-addition reaction of **17a** with $Me_2CuLi{\cdot}LiI$ was also investigated to cover the anticipated typical concentration range of

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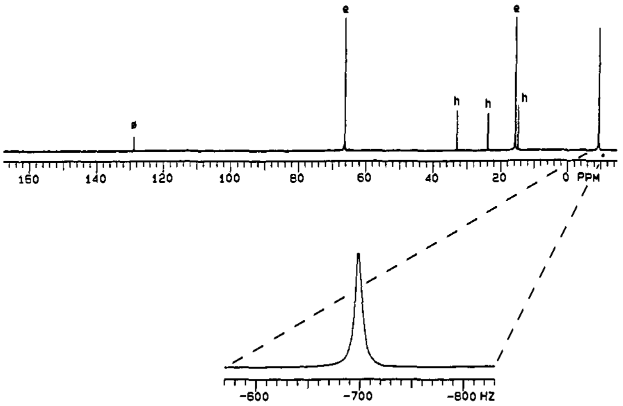


Figure 1. ^{13}C NMR spectrum of [^{13}C]Me$_2$CuLi·LiI in diethyl ether at −80 °C, with expansion of the upfield resonance.

NMR studies. At a high initial concentration (0.15 M) of Me$_2$CuLi·LiI the 1,4-addition product (**21**) was produced in high yield, while reactions containing lower cuprate concentration (0.033 M) produced some **22** and unreacted **17a** at the expense of **21**. Overall the effect of concentration was not found to be highly significant.

^{13}C NMR Investigation of the Reaction of 2,2,5-Trimethyl-4-hexen-3-one with Methylcuprates in Diethyl Ether. With the 1,4-addition reactivity of **17a** toward Me$_2$CuLi·LiI clearly demonstrated attention was directed toward an indepth NMR investigation. This effort was assisted by the preparation of Me$_2$CuLi·LiI from appropriately purified MeLi[25] which displayed a narrow line width ^{13}C NMR resonance. An advantage of using Me$_2$CuLi·LiI, rather than the halide free variety used in previous studies,[12] was that the cuprate more closely resembles the typical reagent used for 1,4-addition reactions, and hence any mechanistic data has relevance to the general synthetic community. A bonus from the studies of preparing narrow NMR line width cuprates was the availability of ^{13}C enriched Me$_2$CuLi·LiI as a consequence of a MeLi preparation involving ^{13}CH$_3$I.

Direct NMR examination of the reaction of Me$_2$CuLi·LiI with the enone **17a**, and its ^{13}C enriched variants (**17b,c**) was undertaken. The general experimental procedure involved the preparing of an ethereal methylcuprate solution at 0 °C and transferring this solution into an NMR tube. The cuprate solution was cooled to −80 °C in the probe of the NMR spectrometer, and then the enone was added at this temperature. This procedure gave reproducible results. The reaction mixture was observed by ^{13}C NMR at various temperatures over a period of time. A typical run lasted for approximately 7 h. After the spectroscopic observations were complete, the NMR tube was allowed to warm to room temperature, and the contents were isolated in the usual way. Analysis of the organic products from various runs with **17** consistently gave high yields of the 1,4-addition product, comparable with benchtop experiments.

The assignments of the ^{13}C NMR resonances of **17** in diethyl ether at −80 °C were made (Table 3) by comparison with the chemical shifts established in CDCl$_3$. Assignments of C-6 and C-7 in **17** were made by ^{1}H–^{13}C correlation following ^{1}H assignment by nuclear Overhauser enhancement experiments.

A typical spectrum of the methylcuprate, [^{13}C]Me$_2$CuLi·LiI, in diethyl ether-*d*$_{10}$ at − 80 °C is shown in Figure 1. The upfield resonance is assigned to [^{13}C]Me$_2$CuLi·LiI and the other resonances e, h, and ϕ are assigned to diethyl ether, *n*-hexane (from MeLi preparation), and benzene (internal standard) respectively. The presence of a single, narrow methylcuprate resonance is clearly demonstrated in the expansion of the upfield resonance.

A solution prepared from **17a** and Me$_2$CuLi·LiI at −80 °C showed only several small, broad resonances in the region 45–20 ppm together with the methylcuprate resonance (Figure 2a). The lack of any isolated resonances for **17a** indicated that rapid mixing and interaction had indeed taken place and was consistent with the results observed for **1**.[12] When the sample temperature was increased sequentially from −70 °C to −50 °C clear resonances at 99.0, 32.3, 29.9, 28.4, 27.1, and 21.9 ppm developed (Figure 2b-d). In addition a very broad, low intensity resonance at *ca.* 120 ppm was discernable on some occasions. Repetition of this reaction at −55 °C for an extended period of time gave a series of spectra in which the resonances at 99.0, 37.9, 32.3, 31.6, and 29.9 ppm gradually increased in intensity (Figure 3a-e).

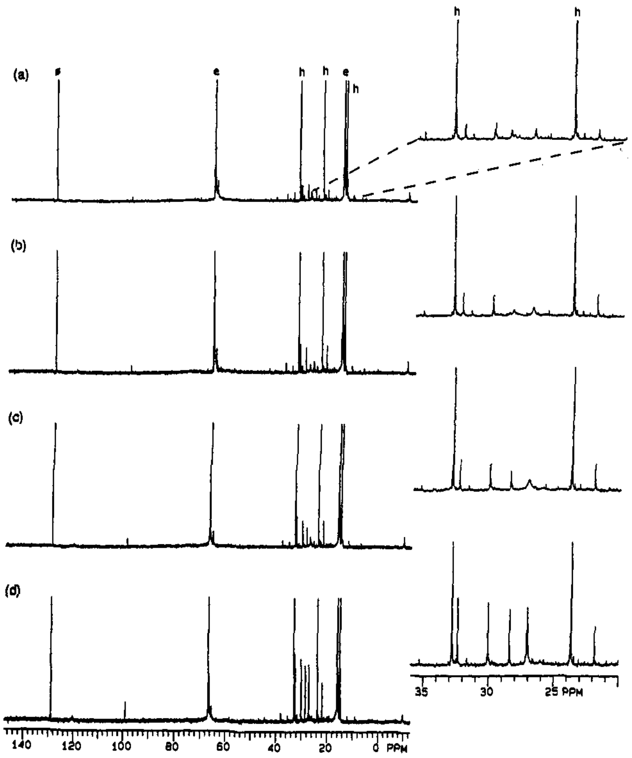


Figure 2. ^{13}C NMR spectra of the reaction of **17a** with Me$_2$CuLi·LiI in diethyl ether at (a) −80, (b) −70, (c) −60, and (d) −50 °C.

As subsequent chemical analysis of this reaction mixture showed a high yield of the 1,4-addition product **21** these resonances were assigned to the enolate **24a** resulting from 1,4-addition. A coupled spectrum showed the resonance at 99.0 ppm as a doublet, $^1J_{CH}$ = 145 Hz, typical for an sp^2 carbon[27] and is thus assigned to C-4 in **24a**. The high field aliphatic resonances were assigned as either methyl or quaternary carbons on the basis of their relative intensities. Subsequent experiments with **17b,17c**, and [^{13}C]Me$_2$CuLi·LiI (*vide infra*) allowed complete assignment of the enolate resonances (Table 3). The resonances which were initially observed, at 28.4, 27.1, and 21.9 ppm (Figure 3a) decreased during the course of the reaction which indicated that they were derived from reaction intermediate(s). No resonances attributable to C-3 or C-5 were detectable in the studies utilizing **17a**.

Reaction of the β-carbon labeled enone **17b** with Me$_2$CuLi·LiI at −80 °C showed two relatively intense, broad resonances at 158.9 ($W_{h/2}$ = 37 Hz) and 67.7 ppm ($W_{h/2}$ = 23 Hz) in an approximate ratio of 1:2 (Figure 4a). These two resonances were not detected in comparable experiments with **17a** and are therefore attributed to C-5 of two intermediate species. The small downfield shift (3.8 ppm) observed for the minor resonance compared with **17b** was consistent with the changes noted for the C-5 carbon of **17b** in the presence of a lithium salt (Table 3). Similar small downfield shifts resulting from lithium coordination had been observed by others.[12,13,15] This similarity suggested that the minor intermediate species at −80 °C was the lithium coordinated enone **25b**. The major C-5 resonance observed at 67.7 ppm reflects a large upfield shift of 87.4 ppm compared with **17b** and was assigned

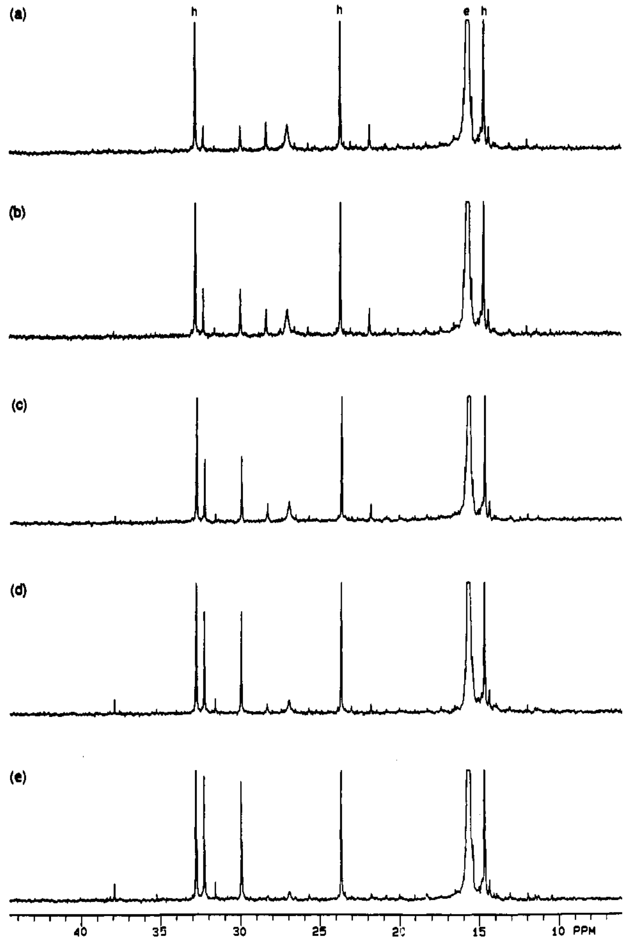


Figure 3. ^{13}C NMR spectra of the reaction of **17a** with $Me_2CuLi{\cdot}LiI$ in diethyl ether at -55 °C after (a) 1, (b) 43, (c) 114, (d) 275, and (e) 427 min.

to C-5 in a lithium coordinated cuprate-*d* → π*-complex **26b**. This dramatic upfield shift for **26b** compared with **17b** was consistent with that previously observed for cuprate-*d* → π*-complexes for enones and enoates. As the temperature of the solution was raised to -70 °C the resonance at 67.7 ppm broadened and decreased in intensity (Figure 4b). At -60 °C this resonance was no longer detectable, but the C-5 resonance of **25b** had correspondingly increased in intensity with some broadening (Figure 4c). Recooling this mixture to -80 °C resulted in the regeneration of the initial **25b**:**26b** ratio of approximately 1:2 (Figure 4d). It appears therefore that **25** and **26** are in an equilibrium situation with higher temperatures favoring **25**. At temperatures below -60 °C, negligible enolate **24b** could be detected, and this lack of reaction was consistent with benchtop experiments. On warming a mixture of **17b** and $Me_2CuLi{\cdot}LiI$ from -80 °C to -10 °C, further significant broadening and eventual disappearance of the C-5 resonance of **25b** was observed together with the steady growth of the C-5 resonance of the **24b** at 31.6 ppm (Figure 8, supplementary material). The enolate resonance at 31.6 ppm was clearly enhanced in intensity compared with the enolate obtained from the reaction with **17a** and hence could be unambiguously assigned to C-5. This firm assignment allowed, by default, the assignment of the remaining quaternary carbon of **24** resonance at 37.9 ppm as C-2 (Table 3). The lithium coordinated enone **25b** was the only intermediate detectable at -50 °C and hence the aliphatic resonances observed at 28.3, 27.1, and 21.9 ppm were attributed to this intermediate (Table 3). Integration of the components in the reaction mixture over the temperature range of -80 to -55 °C indicated that the total relative amounts of **24**, **25**, and **26** remained constant within experimental error (Figure 9, supplementary material).

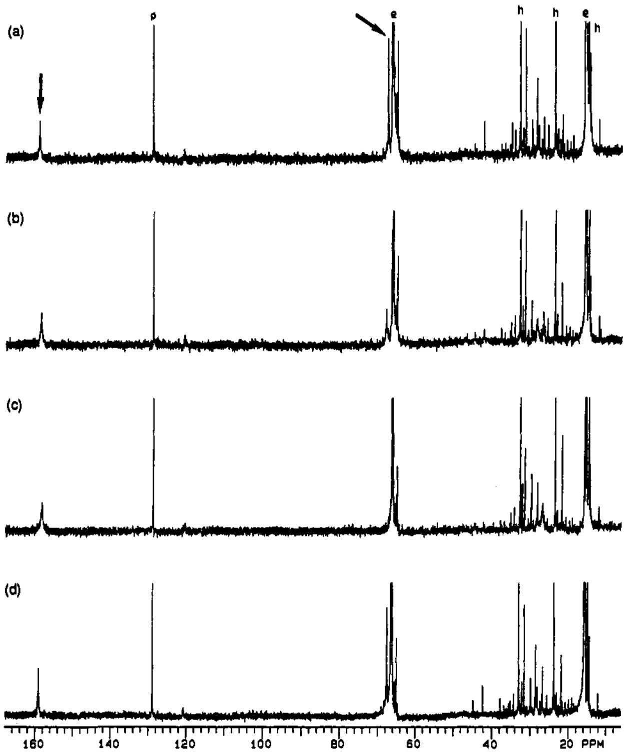


Figure 4. ^{13}C NMR spectra of the reaction of **17b** with $Me_2CuLi{\cdot}LiI$ in diethyl ether at (a) -80, (b) -70, (c) -60, and (d) -80 °C.

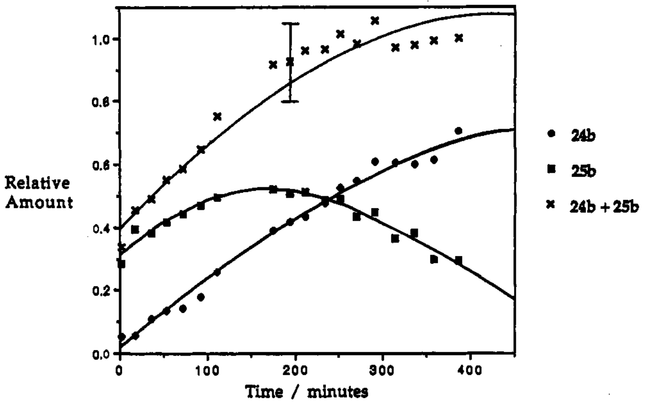


Figure 5. Time dependence of the amounts of lithium complex **25b** and enolate **24b** in a reaction of $Me_2CuLi{\cdot}LiI$ with **17b** in diethyl ether at -55 °C.

Observation of the reaction of **17b** with $Me_2CuLi{\cdot}LiI$ isothermally at -55 °C over a period of time showed an increase in the intensity of the resonances assigned to the lithium coordinated enone **25b** over the first half-life (~2.5 h) of the reaction followed by a decrease as the reaction proceeded (Figure 5). Steady formation of the enolate **24b** was observed throughout the reaction. The combined intensity of the C-5 resonance from **24b** and **25b** appeared to increase initially until a relatively constant value was attained. The observation of a net initial increase in intensity can be attributed to the conversion of some spectroscopically transparent species into the lithium complex **25b** as enolate production increased. This species may be an initially insoluble lithiated species which slowly dissolves as the chemical environment of the cuprate solution changes or alternatively the formation of an aggregate of lithiated enones may be involved in which the T_1 and/or NOE values for the C-5 resonance are significantly different from **25b**. A small chemical shift variation with time of the C-5 resonance assigned to **25b** was also noted (Figure 10, supplementary material), and this supports the idea of an alteration of the average composition of the lithium complex as

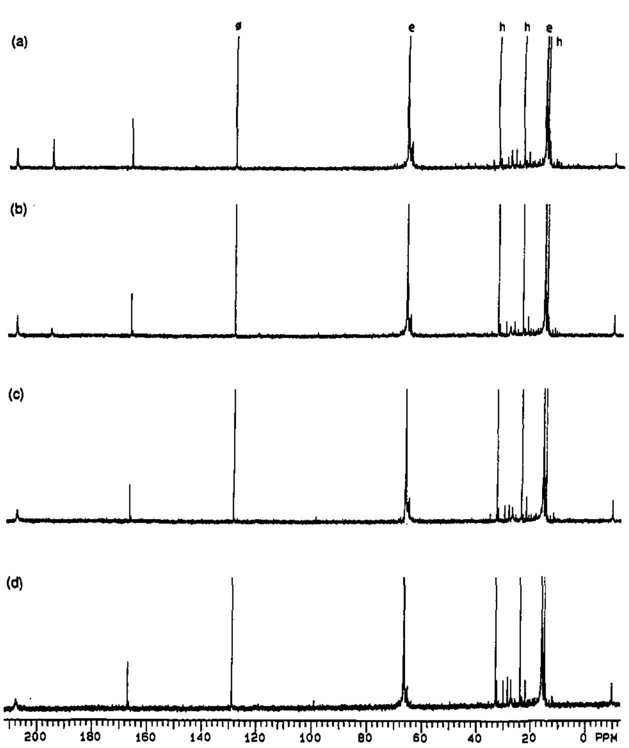


Figure 6. ^{13}C NMR spectra of the reaction of **17c** with $Me_2CuLi{\cdot}LiI$ in diethyl ether at (a) −80, (b) −70, (c) −60, and (d) −55 °C.

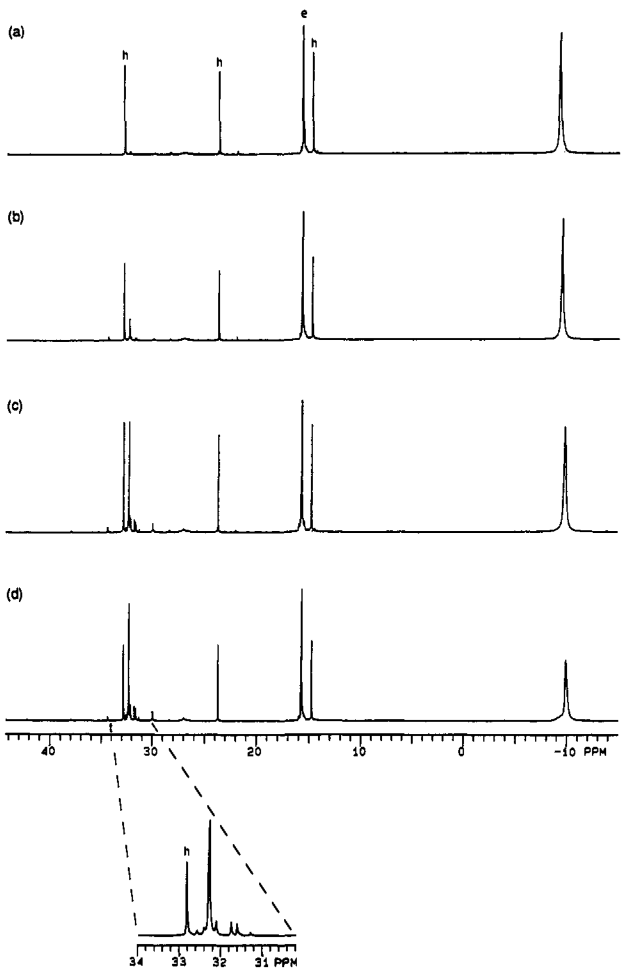


Figure 7. ^{13}C NMR spectra of the reaction of **17b** with $[^{13}C]Me_2CuLi{\cdot}LiI$ in diethyl ether at −55 °C after (a) 2, (b) 56, (c) 209, and (d) 413 min.

Table 3. ^{13}C NMR Chemical Shifts of **17** and Derived Complexes in Diethyl Ether

	carbon chemical shift, ppm						
	C-1	C-2	C-3	C-4	C-5	C-6	C-7
17	26.5	43.8	203.5	119.7[a]	155.1	28.1	20.7
17 + LiI	26.6	44.1	204.8	120.0	156.1	28.2	21.1
17 + $LiClO_4$	26.5	44.2	205.9	120.0	157.9	28.3	21.2
24	29.9	37.9	166.8	99.0[b]	31.6	32.3	
25	27.1[c,d]	*e*	209.0[c]	120[c]	158.9[c,f]	28.4[c,d]	21.9[c,d]
26	*e*	*e*	195.8[c]	*e*	67.7[c,g]	*e*	*e*
27	29.9	37.9	166.7	99.1[h]	31.6	32.3	

[a] $^1J_{CH}$ = 153 Hz. [b] $^1J_{CH}$ = 145 Hz. [c] Broad resonance. [d] Assignments interchangeable. [e] Not observed. [f] 158.3 ppm when low halide Me_2CuLi used. [g] 67.3 ppm when low halide Me_2CuLi used. [h] $^1J_{CH}$ = 148 Hz.

the reaction proceeds. It is also compatible with a gross dielectric change within the sample during the reaction.

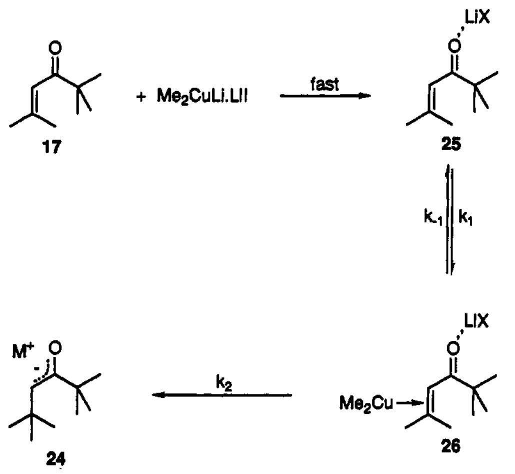
Reaction of **17b** with low-halide Me_2CuLi[12,25] at −80 °C showed at best minor spectral differences when compared with the reaction involving $Me_2CuLi{\cdot}LiI$. The two enhanced C-5 resonances were observed to be slightly upfield by *ca.* 0.5 ppm from the situation with $Me_2CuLi{\cdot}LiI$ but displayed a comparable ratio (2:5). Comparison of the spectra obtained at −55 °C with those from the reaction of **17b** with $Me_2CuLi{\cdot}LiI$ also showed only minor differences and thus it seems that reactions with $Me_2CuLi{\cdot}LiI$ or Me_2CuLi are essentially identical as far as the ^{13}C NMR is concerned.

Reaction of the carbonyl labeled enone **17c** with $Me_2CuLi{\cdot}LiI$ at −80 °C showed two previously unobserved, relatively intense, broad resonances at 209.0 ($W_{h/2}$ = 25 Hz) and 195.8 ppm ($W_{h/2}$ = 21 Hz). These resonances together with a sharp resonance at 166.8 ppm were in a ratio of 2:3:1 (Figure 6a). On warming the reaction mixture to −70 °C a significant reduction in intensity of the resonance at 195.8 ppm was observed, and at −60 °C it was not observable (Figure 6b,c). This temperature variation was consistent with that previously noted with **17b** and hence this resonance was assigned to C-3 of **26c**. The resonance at 209.0 ppm, 5.5 ppm downfield from that of **17c**, was consistent with a carbonyl carbon coordinating with a lithium salt (Table 3) and was therefore assigned to C-3 of **25c**. The resonance at 166.8 ppm was assigned to C-3 of the enolate **24c** (*vide infra*) and showed no intensity nor width variation on warming the reaction mixture from −80 to −60 °C. When the reaction was allowed to proceed at −55 °C this resonance increased in intensity (Figure 6d), consistent with the formation of the enolate.

During these NMR reaction studies the high field methyl carbon resonance was observed to move further upfield by *ca.* 1 ppm over the course of the reaction at −55 °C. In concert with this shift to higher field a significant broadening of this resonance was also noted making accurate detection and study of this peak difficult. Utilization of ^{13}C labeled methylcuprate in a reaction with **17b** allowed effective monitoring of this methyl carbon resonance. Addition of **17b** to $[^{13}C]Me_2CuLi{\cdot}LiI$ at -80 °C resulted in an immediate 18% reduction of the intensity of the cuprate carbon resonance at −9.28 ppm. On warming the reaction mixture to −60 °C only the methylcuprate and C-5 resonance of **25b** showed significant enhancement. As the reaction proceeded at −55 °C two relatively high intensity aliphatic resonances were observed at 32.3 and 31.6 ppm (Figure 7) both of which had previously been attributed to the enolate **24**. The enolate methyl resonance at 32.3 ppm was significantly larger than that observed when unlabeled $Me_2CuLi{\cdot}LiI$ was utilized and this feature allowed assignment of C-6 and, by default, C-1 of **24** (Table 3).

Throughout the period of the reaction of **17b** with $[^{13}C]Me_2CuLi{\cdot}LiI$ a single organometallic methyl resonance was observed which slowly broadened and decreased in intensity as it moved further upfield. All reaction systems using [^{13}C] enriched methylcuprate with **17** displayed only two enhanced methyl resonances, one at high field and enolate (**24**). Integration of these two methyl resonances against an internal standard showed

Scheme 4

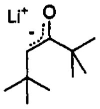


slow, regular formation of the enolate with a corresponding decrease in intensity of the organometallic methyl resonance. The combined intensity of these two resonances remained constant over ~2.5 half-lives at −55 °C (Figure 11, supplementary material). This feature discounts the possibility of formation of significant amounts of other organometallic species containing the migrating methyl group having broad or otherwise undetermined resonances.

The half-life of the reaction was found to be approximately 2.5 h at −55 °C. The relative intensities and line widths of all the resonances in the spectra taken at intervals during the reaction showed no unusual intensity variation nor line broadening hence the formation of paramagnetic species during the reaction seems extremely unlikely. A mechanistic plan which accommodates the observations is given in Scheme 4.

At −80 °C the two intermediate complexes **25** and **26** were observed with no detectable conversion into the enolate provided an adequate setup protocol was followed. Warming to −55 °C leads to the production of **24**, and the amount of **26** is substantially decreased. The initial dynamic equilibrium situation between **25** and **26** can be reestablished by recooling to −80 °C. In terms of Scheme 4, the situation at −80 °C is consistent with $k_1/k_{-1} \approx 1.5$, $k_2 \ll k_{-1}$. At −55 °C, slow formation of enolate **24** is observed indicating a situation where $k_2 > k_{-1}$, or k_2 (and/or k_{-1}) $> k_1$.

A brief study of the enolate **24** was also undertaken. The purpose of this effort was to attempt to further define the metal cation which is associated with the ambient anion. Reactivity studies[28] with the enolates derived from organocuprate 1,4-addition reactions have shown differences from the apparently equivalent lithium enolates. These results appeared to contrast with those from a study[19] of the reaction of 3-phenyl-2-cyclohexenone with $Me_2CuLi{\cdot}LiI$ at 0 °C which showed quantitative precipitation of all the involved copper as $(MeCu)_n$ leaving by default a lithium enolate in solution. Repetition of this reaction at lower temperatures however had shown that a significant amount of the enolate was also present in the precipitate.[19] It was considered that comparison of the now defined ^{13}C NMR of **24** with that of the independently prepared lithium enolate **27** may show spectral differences reflecting a difference in the cation.



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In addition the ^{13}C NMR results from the reaction of **17b** with $[^{13}C]Me_2CuLi{\cdot}LiI$ showed that the reduction in the intensity of the methylcopper resonance was smaller than anticipated. If all the methylcopper produced after the 1,4-addition was in the insoluble form of $(MeCu)_n$, no residual high field resonance was expected. After complete reaction at 0 °C *ca.* 50% of the methylcopper resonance remained visible. This tended to indicate that some type of soluble methylcopper species was part of the immediate reaction product prior to addition of an electrophile. Preparation of the lithium enolate **27** *via* α-proton abstraction from 2,2,5,5-tetramethyl[5-^{13}C]-3-hexanone using the hindered alkyllithium *t*-BuLi was investigated.[29] The success of the enolate formation was assayed by GC analysis of the crude reaction mixture after acetylation. This enolate trap was shown to be effective as quantitative acetylation of the cuprate-generated enolate **24** was achieved using acetic anhydride. ^{13}C NMR analysis of the reaction mixture gave chemical shifts for the enolate which can only have lithium as the cation (Table 3). From these results it can be seen that the ^{13}C NMR resonances observed for the two enolates are identical as far as this analytical method is concerned. This would indicate that either the primary product from cuprate 1,4-addition is actually the ether solvated lithium enolate **27** or another, undetermined cation is involved whose influence on the ^{13}C NMR of the anionic component is minimal. It may well be that the observed difference in chemical reactivity between the lithium enolate and that formed from 1,4-addition is a result of a small amount of copper being associated with a more reactive, albeit minor, enolate species or alternatively the coordination situation and/or the aggregation state of the same cation may be different in the two systems.

Conclusion

These results enhance the notion that the mechanism of cuprate 1,4-addition proceeds *via* a lithium coordinated enone and a cuprate *d*-enone → π*-complex which then gives rise to an enolate. In addition there is clear evidence for an equilibrium between these intermediate species. One of the remaining undetermined pieces of the mechanism is related to how the π-complex(es) are transformed into the β-alkylated enolate. The formation of a β-copper(III) species appears to be a real possibility and is often promoted; however, no direct evidence for such an intermediate is currently available. Alternatively, conversion of the π-complex into a β-methyl-α-cuprio ketone and then ultimately into an enolate[11] cannot be discounted given the available facts.

The correlation between the one-electron reduction potentials and useful cuprate reactivity is a useful guide although an indication of the amount of electron transfer involved in the 1,4-addition process remains an elusive target. Whilst reasonably long-lived species containing unpaired electrons are clearly not involved in these reactions, the formation of π-complexes appears to be important. The ease of one-electron transfer to an α,β-unsaturated ketone is closely related to the energy of the π* LUMO. The necessity of lithium coordination to the carbonyl group for 1,4-addition results in a lowering of the energy of the π* LUMO which in turn would facilitate *d* → π* complexation. This orbital has been rationally incorporated into an explanation of the significant increase in electron density at the alkenyl carbons following complexation with an organocuprate.[30] It may well be that the ease of electrochemical reduction and the cuprate reactivity of various α,β-unsaturated ketones are related by virtue of the commonality of the π* orbital energy although at this stage mechanistically the two reactions seem different in many respects.

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Experimental Section

IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrometer. NMR spectra were performed on a Varian VXR 300 instrument equipped with variable temperature probe operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts, in $CDCl_3$ solutions, are reported downfield from TMS (0 ppm) for ^{1}H and relative to the central $CDCl_3$ resonance (77.08 ppm) for ^{13}C spectra. In diethyl ether, the ^{13}C chemical shifts are reported relative to TMS (0 ppm). ^{1}H NMR spectra are reported according to the convention: chemical shift, integrated area, multiplicity, homonuclear coupling constant (J), or band width at half the peak height ($W_{h/2}$), proton assignment. Nuclear Overhauser enhancements are reported as NOE followed by the irradiated peak. Carbons types were determined by the DEPT pulse sequence. ^{1}H–^{13}C correlations are reported in the ^{13}C data list as HC followed by the chemical shift of the correlating proton. Gas chromatography (GC) analyses were carried out on a Perkin Elmer 8420 gas chromatograph fitted with a flame ionization detector on a 10 m × 0.25 mm OV-1 fused silica column using helium carrier gas (6 psi). The samples were introduced in ether solutions at an oven temperature of 40 °C, and the column was maintained at 40 °C for 5 min, then heated to 110 °C at a rate of 5 °C min^{-1}, and further heated to 250 °C at 20 °C min^{-1}. Dodecane was used as the internal standard unless otherwise stated. Retention times (t_R), in minutes, were determined from the injection point.

Solvents and Materials. Diethyl ether and hexane were distilled from $LiAlH_4$ and stored over sodium wire. For organometallic reactions, the solvent was then deoxygenated by alternate application of vacuum and argon. Commercial solutions (Aldrich) of low halide MeLi (1.4 M in diethyl ether), MeLi·LiBr (1.6 M in diethyl ether), *n*-BuLi (1.6 M in hexanes), and *t*-BuLi (1.7 M in pentane) were analyzed by the Gilman double titration[31] with 3-bromopropene. Commercial CuI (Fluka) was purified by continuous extraction using THF.[32] Purified ethereal MeLi was prepared from solid MeLi as detailed elsewhere.[25] Diethyl ether-d_{10} was obtained from Cambridge Isotope Laboratories and dried over molecular sieve 4Å ($^1/_{16}$ in. beads) before use. Commercial samples of MeI (^{13}C, 99%) and [1-^{13}C]acetyl chloride (99%) were obtained from Aldrich. [2-^{13}C]Acetone (99%) was obtained from Cambridge Isotope Laboratories.

3-Methyl-2-cyclohexenone (**5**), 2-cyclohexenone (**7**), 3-penten-2-one (**8**), 3,5,5-trimethyl-2-cyclohexenone (**10**), (+)-pulegone (**12**), 4-methyl-3-penten-2-one (**13**) and *trans*-4-phenyl-3-buten-2-one (**15**) were commercial samples. 10-Methyl-1(9)-octal-2-one (**1**) was prepared[33] from 3-buten-2-one and 2-methyl-cyclohexanone in benzene with *p*-TsOH as catalyst. *cis*-5-(Mesyloxy)-10-methyl-1(9)-octal-2-one (**3**) was prepared by mesylation of *cis*-5-hydroxy-10-methyl-1(9)-octal-2-one in pyridine.[34] 5,5-Dimethyl-2-cyclohexenone (**6**) was prepared *via* 5,5-dimethyl-1,3-cyclohexanedione.[35] 3,4,4-Trimethyl-2-cyclohexenone (**9**) and 3,6,6-trimethyl-2-cyclohexenone (**11**) were prepared by reaction of 3-buten-2-one with 3-methyl-2-butanone.[36] 4,4-Dimethyl-2-cyclohexenone (**14**) was prepared from 3-buten-2-one and 1-pyrrolidinyl-2-methylpropane.[37]

Reactions involving organometallic reagents were performed under a positive pressure atmosphere of dry argon in Schlenk tubes, equipped with rubber septa. The Schlenk tubes were flame dried under vacuum and then cooled under dry argon. Reagent transfers were performed using cannula techniques.

Low-Temperature Interaction of Enones with Methylcuprates. Typical Reaction. Dry CuI (0.190 g, 1.00 mmol) was placed in a dry Schlenk tube containing a Teflon-coated magnetic stirrer bar under argon. Degassed dry diethyl ether (8 mL) was then added, and the mixture stirred at 0 °C. Ethereal MeLi (2.00 mmol) was then added to give a clear solution which was stirred for 5 min at 0 °C prior to use. The ethereal $Me_2CuLi·LiI$ (~10 mL, 1.00 mmol) was then cooled to −78 °C, unless otherwise stated. A solution of enone (1.00 mmol) in diethyl ether (1 mL), unless otherwise stated, was added to the cuprate solution, and the appearance of the reaction mixture was monitored while stirring for 45 min at −78 °C.

Repetition of the above but using ethereal MeLi·LiBr in place of MeLi gave $Me_2CuLi·LiI·2LiBr$ [$Me_2CuLi·(LiX)_3$] which was also used for reactions.

The following reactions are reported according to the convention: cuprate (mmol), reaction temperature if applicable, enone (g, mmol), solvent of enone addition if applicable, state of reaction mixture, workup, and subsequent ^{1}H NMR or GC analysis. Entry refers to Table 1.

***cis*-5-(Mesyloxy)-10-methyl-1(9)-octal-2-one (3).** Entry 1: $Me_2CuLi·LiI$ (0.53 mmol), **3** (0.13 g, 0.53 mmol), CH_2Cl_2, a yellow precipitate formed immediately on addition of the enone. After 45 min at −78 °C, a solution of NH_4Cl/NH_3 (15 mL), prepared by mixing a saturated aqueous solution of NH_4Cl (15 mL), methanol (10 mL), and 25% aqueous NH_3 (4 mL), was poured into the reaction mixture at −78 °C. The total reaction mixture was then poured into a separating funnel, and the reaction Schlenk tube was washed consecutively with NH_4Cl/NH_3 solution (15 mL) and ether (10 mL). The total mixture was shaken until a deep blue color developed, and all the solids had dissolved. The mixture was separated, the aqueous layer was ether extracted (3 × 10 mL), the combined ether extract was washed with H_2O (15 mL) and then dried ($MgSO_4$), and the solvent evaporated *in vacuo*. ^{1}H NMR analysis of the residue indicated **3** (35%) and 6-methyltricyclo[4,4,0,0^{1,5}]-9-decanone[9] (**4**) (58%).

Entry 2: $Me_2CuLi·(LiX)_3$ (0.53 mmol), **3** (0.13 g, 0.53 mmol), CH_2Cl_2, a yellow precipitate formed immediately. Workup as described for entry 1 and ^{1}H NMR analysis of the residue indicated **3** (35%) and **4** (56%).

10-Methyl-1(9)-octal-2-one (1). Entry 3: $Me_2CuLi·LiI$ (1.03 mmol), **1** (0.17 g, 1.06 mmol), an orange solution was produced immediately. Workup as for entry 1 and ^{1}H NMR analysis of the residue indicated only **1** (95%).

Entry 4: $Me_2CuLi·(LiX)_3$ (1.04 mmol), **1** (0.17 g, 1.06 mmol), immediate orange solution which, after 5 min, yielded an orange precipitate. Workup as for entry 1 and ^{1}H NMR analysis of the residue indicated only **1** (94%).

3-Methyl-2-cyclohexenone (5). Entry 5: $Me_2CuLi·LiI$ (1.02 mmol), **5** (0.11 g, 1.02 mmol), a yellow precipitate formed immediately on addition of the enone. After 45 min at −78 °C the reaction mixture was quenched by injection of NH_4Cl/NH_3 solution (5 mL), followed by dodecane (0.17 g, 1.00 mmol), t_R 12.50, dissolved in diethyl ether (1 mL) at −78 °C. The mixture was warmed to room temperature and further NH_4Cl/NH_3 solution (15 mL) was added. The total mixture was stirred until a deep blue color developed and all the solids had dissolved. The mixture was then separated and ether extracted (3 × 10 mL). GC analysis of the combined ether extract indicated **5**, t_R 6.30 (16%), and 3,3-dimethylcyclohexanone,[38] t_R 4.50 (80%), by comparison with authentic material.

Entry 6: $Me_2CuLi·LiI$ (1.01 mmol), −100 °C, **5** (0.12 g, 1.08 mmol), a yellow solution formed immediately on the addition of the enone which, after 5 min, yielded a fine yellow precipitate. Workup as for entry 5 and GC analysis indicated only **5** (96%).

Entry 7: $Me_2CuLi·(LiX)_3$ (1.03 mmol), −100 °C, **5** (0.11 g, 1.01 mmol), a fine yellow precipitate formed immediately. Workup as for entry 5 and GC analysis indicated **5** (93%) and 3,3-dimethylcyclohexanone (3%).

5,5-Dimethyl-2-cyclohexenone (6). Entry 8: $Me_2CuLi·LiI$ (1.03 mmol), **6** (0.12 g, 0.99 mmol), a yellow/orange precipitate formed immediately. Workup as for entry 5 and GC analysis indicated **6**, t_R 5.27 (2%) and 3,3,5-trimethylcyclohexanone,[39] t_R 6.22 (95%), by comparison with authentic material.

Entry 9: $Me_2CuLi·(LiX)_3$ (1.02 mmol), **6** (0.12 g, 0.97 mmol), a yellow/orange precipitate formed immediately. Workup as for entry 5 and GC analysis indicated the formation of 3,3,5-trimethylcyclohexanone (96%).

3-Penten-2-one (8). Entry 10: $Me_2CuLi·LiI$ (1.02 mmol), **8** (0.084 g, 0.99 mmol), a yellow precipitate formed immediately. After 45 min at −78 °C, NH_4Cl/NH_3 solution (10 mL) was added to the reaction mixture. The reaction Schlenk tube was washed consecutively with NH_4Cl/NH_3 solution (10 mL) and then ether (10 mL). The total reaction mixture was shaken until a deep blue color developed and all solids had dissolved. The mixture was separated, and the aqueous layer was extracted with CCl_4 (3 × 10 mL). The combined organic extract was distilled using a Vigreux column at atmospheric pressure up to a head temperature of 50 °C. ^{1}H NMR analysis of the residual CCl_4 solution indicated **8** (55%) and 4-methyl-2-pentanone (45%).

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Entry 11: $Me_2CuLi{\cdot}LiI$ (1.02 mmol), −100 °C, **8** (0.088 g, 1.05 mmol), a yellow precipitate formed immediately. Workup as for entry 10 and ^1H NMR analysis indicated **8** (65%) and 4-methyl-2-pentanone (35%).

Entry 12: $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol), **8** (0.086 g, 1.02 mmol), a yellow precipitate formed immediately. Workup as for entry 10 and ^1H NMR analysis indicated **8** (45%) and 4-methyl-2-pentanone (45%).

3,4,4-Trimethyl-2-cyclohexenone (9). Entry 13: $Me_2CuLi{\cdot}LiI$ (1.01 mmol), **9** (0.12 g, 0.85 mmol), an orange solution formed immediately. Workup as for entry 5 and GC analysis indicated only **9**, t_R 10.62 (93%).

Entry 14: $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol), **9** (0.11 g, 0.81 mmol), an orange solution formed immediately. Workup as for entry 5 and GC analysis indicated only **9** (91%).

3,5,5-Trimethyl-2-cyclohexenone (10). Entry 15: $Me_2CuLi{\cdot}LiI$ (1.01 mmol), **10** (0.13 g, 0.93 mmol), a yellow/orange solution formed immediately. Workup as for entry 5 and GC analysis indicated **10**, t_R 8.80 (91%), and 3,3,5,5-tetramethylcyclohexanone,[40] t_R 7.91 (5%), by comparison with authentic material.

Entry 16: $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol), **10** (0.13 g, 0.96 mmol), a yellow/orange solution formed immediately on the addition of the enone which, after 15 min, yielded a fine yellow precipitate. Workup as for entry 5 and GC analysis indicated only **10** (97%).

3,6,6-Trimethyl-2-cyclohexenone (11). Entry 17: $Me_2CuLi{\cdot}LiI$ (1.02 mmol), **11** (0.14 g, 0.99 mmol), an orange solution formed immediately. Workup as for entry 5 and GC analysis indicated **11**, t_R 8.71 (91%), and 2,2,5,5-tetramethylcyclohexanone,[41] t_R 7.27 (5%), by comparison with authentic material.

Entry 18: $Me_2CuLi{\cdot}(LiX)_3$ (1.01 mmol), **11** (0.14 g, 0.99 mmol), an orange solution formed immediately on the addition of the enone which, after 15 min, yielded a fine yellow precipitate. Workup as for entry 5 and GC analysis indicated only **11** (98%).

(+)-Pulegone (12). Entry 19: $Me_2CuLi{\cdot}LiI$ (1.02 mmol), **12** (0.16 g, 1.02 mmol), a yellow solution formed immediately. Workup as for entry 5, but using tetradecane, t_R 17.55, in place of dodecane, and GC analysis indicated only **12**, t_R 12.41 (95%).

Entry 20: $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol), **12** (0.16 g, 1.02 mmol), a yellow/ orange solution formed immediately. Workup as for entry 19 and GC analysis indicated only **12** (97%).

4-Methyl-3-penten-3-one (13). Entry 21: $Me_2CuLi{\cdot}LiI$ (1.02 mmol), **13** (0.10 g, 1.03 mmol), an orange solution formed immediately. Workup as for entry 10 and ^1H NMR analysis indicated **13** (89%) and 4,4-dimethyl-2-pentanone[42] (4%).

Entry 22: $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol), **13** (0.098 g, 1.00 mmol), a yellow/orange solution formed immediately. Workup as for entry 10 and ^1H NMR analysis indicated **13** (90%) and 4,4-dimethyl-2-pentanone (5%).

4,4-Dimethyl-2-cyclohexenone (14). Entry 23: $Me_2CuLi{\cdot}LiI$ (1.01 mmol), **14** (0.12 g, 1.00 mmol), a yellow precipitate formed immediately. Workup as for entry 5 and GC analysis indicated only **14**, t_R 5.58 (95%).

Entry 24: $Me_2CuLi{\cdot}LiI$ (1.01 mmol), −100 °C, **14** (0.14 g, 1.10 mmol), a yellow precipitate formed immediately. Workup as for entry 5 and GC analysis indicated only **14** (97%).

Entry 25: $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol), **14** (0.13 g, 1.02 mmol), a yellow precipitate formed immediately. Workup as for entry 5 and GC analysis indicated only **14** (98%).

***trans*-4-Phenyl-3-buten-2-one (15).** Entry 26: $Me_2CuLi{\cdot}LiI$ (1.01 mmol), **15** (0.15 g, 0.99 mmol), a yellow solution formed immediately on addition of the enone which, after 20 min, yielded a yellow precipitate. Workup as for entry 5 and GC analysis indicated **15**, t_R 15.40 (87%), and 4-phenyl-2-pentanone,[43] t_R 13.27 (10%), by comparison with authentic material.

Entry 27: $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol), **15** (0.15 g, 0.99 mmol), an orange solution formed immediately on the addition of the enone which, after 15 min, yielded a fine orange precipitate. Workup as for entry 5 and GC analysis indicated only **15** (92%).

Reaction of 2-Cyclohexenone (7) with Enone–Cuprate Complexes. 10-Methyl-1(9)-octal-2-one (1). Repetition of the reaction of entry 4 using $Me_2CuLi{\cdot}(LiX)_3$ (1.02 mmol) and **1** (0.17 g, 1.05 mmol) eventually gave an orange precipitate. After stirring for 30 min at −78 °C, a solution of 2-cyclohexenone (**7**) (0.10 g, 1.05 mmol) in diethyl ether (1 mL) was added to the reaction mixture which resulted in the immediate formation of a yellow precipitate. After stirring the reaction mixture for 1 h at −78 °C, workup by protonation at −78 °C as described previously followed by GC analysis indicated **15**, t_R 4.65 (<5%), and 3-methylcyclohexanone[44] (**16**), t_R 5.22 (60%). The ether extract was then dried ($MgSO_4$), and the solvent evaporated *in vacuo*. ^1H NMR analysis of the residue indicated **1** (95%).

4,4-Dimethyl-2-cyclohexenone (14). Repetition of the reaction of entry 23 using $Me_2CuLi{\cdot}LiI$ (1.02 mmol) and **14** (0.13 g, 1.03 mmol) resulted in the immediate formation of a yellow precipitate. After stirring for 30 min, a solution of **7** (0.099 g, 1.03 mmol) in diethyl ether (1 mL) was added to the reaction mixture. No visible changes were observed on the addition of **7**. After stirring for 1 h at −78 °C, workup at −78 °C as described previously and GC analysis indicated **14** (92%), 3,4,4-trimethylcyclohexanone,[45] t_R 8.19 (5%), and **16** (95%).

Preparation of 2,2,5-Trimethyl-4-hexen-3-one (17). 3,3-Dimethyl-2-((trimethylsilyl)oxy)butene[22] (19). Me_3SiCl (15.8 mL, 0.12 mol) was added dropwise over 10 min to a stirred solution of 3,3-dimethyl-2-butanone (**18**) (10.1 g, 0.10 mol) and Et_3N (17.3 mL, 0.12 mol) under nitrogen at room temperature. A solution of NaI (18.8 g, 0.13 mol) in MeCN (125 mL) was then added dropwise over 20 min. When the addition was complete, stirring was maintained for 4 h at room temperature, then cold pentane (100 mL) and ice-cold H_2O (100 mL) were added consecutively. The mixture was separated, and the aqueous layer was extracted with pentane (3 × 100 mL). The combined organic extract was washed with H_2O until neutral and dried (Na_2SO_4), and the solvents distilled using a Vigreux column at atmospheric pressure under nitrogen to give **19** (16.02 g, 92%): IR ν_{max}/cm^{-1} 1618 (C=C); ^1H NMR/ppm 4.09 (1H, d, J = 1.3 Hz, H-1), 3.94 (1H, d, J = 1.3 Hz, H-1), 1.05 (9H, s, H-4), 0.22 (9H, s, $SiMe_3$); ^{13}C NMR/ppm 167.3 (C-2), 85.9 (C-1), 36.5 (C-3), 29.2 (C-4), 0.21 ($SiMe_3$).

5-Hydroxy-2,2,5-trimethyl-3-hexanone (20). A solution of **19** (4.03 g, 0.023 mol) in CH_2Cl_2 (50 mL) was added dropwise, over 15 min, to a stirred, yellow solution of $TiCl_4$ (2.85 mL, 0.026 mol) and acetone (2.00 mL, 0.027 mol) in CH_2Cl_2 (100 mL) at room temperature under argon.[23] On completion of the addition, the solution became opaque, and a yellow suspension formed. Stirring was continued for 5 h at room temperature. The reaction mixture was hydrolyzed with H_2O (50 mL), and the aqueous layer extracted with ether (3 × 100 mL). The combined organic extract was washed with H_2O (50 mL), dried (Na_2SO_4), and filtered, and the solvents were distilled through a Vigreux column at atmospheric pressure to leave, as a residue, **20**[46] (3.60 g, 97%): IR ν_{max}/cm^{-1} 3493 (OH), 1692 (C=O); ^1H NMR/ppm 2.65 (2H, s, H-4), 1.24 (6H, s, H-6), 1.14 (9H, s, H-1); ^{13}C NMR/ppm 218.8 (C-3), 69.7 (C-5), 46.7 (C-4), 44.8 (C-2), 29.2 (C-6), 25.9 (C-1).

2,2,5-Trimethyl-4-hexen-3-one (17a). A mixture of p-TsOH·H_2O (0.14 g) and **20** (2.85 g, 0.018 mol) in benzene (10 mL) was refluxed for 1.75 h with molecular sieve 4Å (1 g, $^1/_8$ in. beads) suspended in the base of the condenser. The mixture was allowed to cool, and anhydrous K_2CO_3 (1 g) was added. The liquid was transferred to a round bottom flask with ether (20 mL), and the solvents were distilled *in vacuo* (40 mmHg) to give **17a**[47] (2.02 g, 80%): IR ν_{max}/cm^{-1} 1681 (α,β-unsaturated C=O), 1621 (conjugated C=C); ^1H NMR/ppm 6.31 (1H, heptet, J = 1.4 Hz, H-4, NOE 1.91), 2.11 (3H, d, J = 1.3 Hz, H-7, NOE 1.91), 1.91 (3H, d, J = 1.2 Hz, H-6, NOE 6.31, 2.11), 1.14 (9H, s, H-1); ^{13}C NMR/ppm 206.2 (C-3), 155.2 (C-5), 119.7 (C-4), 43.6 (C-2), 27.9 (C-6, *HC* 1.91), 26.6 (C-1), 20.8 (C-7, *HC* 2.11).

5-Hydroxy-2,2,5-trimethyl[5-^{13}C]-3-hexanone. A solution of **19** (4.02 g, 0.023 mol) in CH_2Cl_2 (50 mL) was added dropwise, over 15 min, to a yellow solution of $TiCl_4$ (2.85 mL, 0.026 mol), acetone (1.69 mL, 0.023 mol) and [2-^{13}C]acetone (0.22 mL, 0.003 mol) in CH_2Cl_2 (100 mL) at room temperature under argon. On completion of the addition, the solution became opaque, and a yellow suspension formed. The mixture was stirred for 5 h at room temperature, then H_2O (50 mL) was added dropwise to the reaction mixture, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extract was washed with H_2O (50 mL), dried (Na_2SO_4), and filtered. The solvents were distilled at atmospheric pressure using a Vigreux column to leave 5-hydroxy-2,2,5-trimethyl[5-^{13}C]-3-hexanone (3.27 g, 88%): ^1H NMR as previously described for **20**; ^{13}C NMR/ppm 218.8 (C-3), 69.7 (C-5), 46.7 (C-4), 46.7 (d, $^1J_{CC}$ = 32.5 Hz, C-4), 44.8 (C-2), 29.2 (C-6), 29.2 (d, $^1J_{CC}$ =

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39.8 Hz, C-6), 25.9 (C-1). The ^{13}C resonance at 69.7 ppm was 6.8 times more intense relative to the other resonances than the corresponding resonance in **20** indicating a 7.5% isotope level.

2,2,5-Trimethyl [5-^{13}C]-4-hexen-3-one (17b). A mixture of *p*-TsOH·H_2O (0.17 g) and 5-hydroxy-2,2,5-trimethyl[5-^{13}C]-3-hexanone (3.27 g, 0.021 mol) in benzene (15 mL) was refluxed for 2 h with molecular sieve 4Å (1 g, $^1/_8$ in. beads) suspended in the base of the condenser. The mixture was allowed to cool, and anhydrous K_2CO_3 (1 g) was added. The liquid was transferred to a round-bottom flask with ether (20 mL), and the solvents were distilled *in vacuo* (40 mmHg) to give **17b** (2.29 g, 79%): ^{1}H NMR and ^{13}C NMR as previously described for **17a**, except the ^{13}C resonance at 155.2 ppm, was 6.8 times more intense than the corresponding resonance in **17a** indicating a 7.5% isotope level.

3,3-Dimethyl[2-^{13}C]-2-butanone. A solution of [1-^{13}C]acetyl chloride (0.22 mL, 3.15 mmol) and acetyl chloride (0.68 mL, 9.55 mmol) in diethyl ether (5 mL) was added dropwise to a stirred solution of *t*-BuMgCl (30 mL, 25 mmol) at 0 °C.[24] After the addition was complete, the pale yellow mixture was stirred for 3 h at 0 °C. H_2O (15 mL) was then added to the reaction mixture followed by 10% aqueous HCl until pH < 2. The mixture was ether extracted (4 × 10 mL), and the combined ether extract washed with H_2O (10 mL), dried ($MgSO_4$), and filtered. Et_3N (4 mL) was added to the filtrate, and the solvents were distilled through a Vigreux column at atmospheric pressure, until the temperature at the top of the column reached 70 °C. ^{1}H NMR analysis of the residual Et_3N solution showed it contained 3,3-dimethyl[2-^{13}C]-2-butanone (0.78 g, 61%): ^{1}H NMR/ppm 2.14 (2.25H, s, H-1), 2.14 (0.75H, d, $^2J_{CH}$ = 5.1 Hz, H-1), 1.15 (6.75 H, s, H-4), 1.15 (2.25H, d, $^3J_{CH}$ = 4.1 Hz, H-4) together with three unidentified ^{1}H resonances at 0.90, 0.89, and 0.86 ppm, in a relative ratio of 3:3:13.

3,3-Dimethyl-2-((trimethylsilyl)oxy)[2-^{13}C]-1-butene. Me_3SiCl (2.54 mL, 20 mmol) was added dropwise to a stirred solution of 3,3-dimethyl-[2-^{13}C]-2-butanone (0.78 g, 7.8 mmol) in Et_3N (4.27 g, 42 mmol), prepared as described above, and Et_3N (1.0 mL, 7.2 mmol), at room temperature under nitrogen. A solution of NaI (3.52 g, 24 mmol) in MeCN (20 mL) was added dropwise over 5 min and the mixture was stirred for 4 h at room temperature. Cold pentane (15 mL) and ice/H_2O (10 mL) were added successively to the reaction, and the aqueous layer was extracted with pentane (3 × 15 mL). The combined organic extract was washed consecutively with H_2O (10 mL), ice cold 1% aqueous HCl (5 mL), ice cold saturated aqueous $NaHCO_3$ (5 mL), H_2O (2 × 5 mL), then dried (Na_2SO_4), and filtered. Benzene (5 mL) was added to the filtrate, and the solvents were distilled through a Vigreux column at atmospheric pressure until the top of the column reached 60 °C. The residual benzene solution contained impure 3,3-dimethyl-2-((trimethylsilyl)oxy)[2-^{13}C]-1-butene (1.30 g, 96%): ^{1}H NMR/ppm 4.08 (1H, d, J = 1.3 Hz, H-1), 3.93 (1H, d, J = 1.3 Hz, H-1), 1.05 (7.90H, s, H-4), 1.05 (1.10H, d, $^3J_{CH}$ = 3.9 Hz, H-4), 0.21 (9H, s, $SiMe_3$) and two unidentified ^{1}H resonances at 0.90 and 0.86 ppm, in a relative ratio of 5:1. ^{13}C NMR as previously described.

5-Hydroxy-2,2,5-trimethyl[3-^{13}C]-3-hexanone. A solution of 3,3-dimethyl-2-((trimethylsilyl)oxy)[2-^{13}C]-1-butene (1.30 g, 7.50 mmol) in benzene (5 mL) and CH_2Cl_2 (25 mL) was added dropwise, over 5 min, to a stirred solution of acetone (1.00 mL, 0.014 mol) and $TiCl_4$ (1.40 mL, 0.013 mol) in CH_2Cl_2 (50 mL) under argon at room temperature.[23] The resultant mixture was stirred for 5 h at room temperature, then H_2O (15 mL) was added to the mixture, and the mixture was extracted with ether (4 × 10 mL). The combined organic extract was washed with H_2O (10 mL), dried (Na_2SO_4), and filtered. Benzene (5 mL) was added to the filtrate, and the solvents evaporated *in vacuo* (50 mmHg), up to 40 °C, to give a residual benzene solution of impure 5-hydroxy-2,2,5-trimethyl-[3-^{13}C]-3-hexanone (1.03 g, 86%). The ^{1}H NMR spectrum of this solution revealed two unidentified resonances (0.90 and 0.89 ppm) together with resonances assigned to silane byproducts. Crude 5-hydroxy-2,2,5-trimethyl[3-^{13}C]-3-hexanone (0.32 g) was chromatographed on a short column of dry silica gel (20 g) with fractions of ether/pentane mixtures (25 mL). GC analysis of each fraction showed pure 5-hydroxy-2,2,5-trimethyl[3-^{13}C]-3-hexanone present in the 20% and 50% ether/pentane fractions which were then combined, and the solvents were carefully distilled *in vacuo* (50–100 mmHg) to give pure 5-hydroxy-2,2,5-trimethyl-[3-^{13}C]-3-hexanone (0.22 g): ^{1}H NMR/ppm 2.65 (1.5H, s, H-4), 2.65 (0.5H, d, $^2J_{CH}$ = 5.1 Hz, H-4), 1.23 (6H, s, H-6), 1.14 (6.75H, s, H-1), 1.14 (2.25H, d, $^3J_{CH}$ = 4.1 Hz, H-1). The ^{13}C NMR as previously described for **20**, except the ^{13}C resonance at 218.8 ppm, was 15.6 times more intense than the corresponding resonance in **20** indicating a 17% isotope level.

2,2,5-Trimethyl-4-hexen[3-^{13}C]-3-one (17c). A mixture of *p*-TsOH·H_2O (0.020 g) and 5-hydroxy-2,2,5-trimethyl[3-^{13}C]-3-hexanone (0.22 g, 1.41 mmol) in benzene (4 mL) was refluxed for 2 h with molecular sieve 4Å (1 g, $^1/_8$ in. beads) suspended in the base of the condenser. The mixture was cooled and applied to a short dry silica gel (10 g) column. Elution with 5% ether/pentane gave fractions containing pure **17c** which were combined, and benzene (2 mL) was added. The solvents were carefully distilled *in vacuo* (60 mmHg) using a Kugelrohr apparatus to give pure **17c** (0.099 g): ^{1}H NMR/ppm 6.31 (1H, heptet, J = 1.3 Hz, H-4), 2.11 (3H, d, J = 1.2 Hz, H-7), 1.91 (3H, d, J = 1.3 Hz, H-6), 1.14 (6.25H, s, H-1), 1.14 (2.75H, d, $^3J_{CH}$ = 3.9 Hz, H-1); ^{13}C NMR/ppm 206.3 (C-3), 155.3 (C-5), 119.8 (C-4), 119.8 (d, $^1J_{CC}$ = 53.6 Hz, C-4), 43.6 (C-2), 43.6 (d, $^1J_{CC}$ = 40.1 Hz, C-2), 28.0 (C-6, *HC* 1.91), 26.6 (C-1), 20.9 (C-7, *HC* 2.11). The ^{13}C resonance at 206.3 ppm was 13.6 times more intense than the corresponding resonance in **17** indicating a 15% isotope level.

2,2,3,5-Tetramethyl-4-hexen-3-ol[19] (22). MeLi (1.50 mmol, 1.30 mL) was added to a stirred solution of **17a** (0.140 g, 1.00 mmol) in diethyl ether (7 mL) at room temperature and stirred for 30 min. Workup and GC analysis indicated the formation of **22**, t_R 6.35 (84.7%). The solvents were distilled *in vacuo* (60 mmHg) to leave **22**; IR ν_{max}/cm^{-1} 3496 (OH), 1673 (C=C); ^{1}H NMR/ppm 5.34 (1H, m, $W_{h/2}$ = 3.7 Hz, H-4), 1.87 (3H, d, J = 1.2 Hz, H-6 or H-7), 1.71 (3H, d, J = 1.2 Hz, H-6 or H-7), 1.27 (3H, s, 3-Me), 0.94 (9H, s, H-1).

Reaction of 2,2,5-Trimethyl-4-hexen-3-one (17a) with Methylcuprates. **(a)** Repetition of the procedure described above in entry 5, using $Me_2CuLi·LiI$ (1.01 mmol) and **17a** (0.142 g, 1.01 mmol) in diethyl ether (10 mL) resulted in the immediate formation of an orange solution. No further changes were observed during stirring at −78 °C for 1 h. Workup at −78 °C as described previously and GC analysis indicated only **17a**, t_R 4.00 (98%).

(b) Repetition of **(a)** using $Me_2CuLi·LiI$ (1.51 mmol) and **17a** (0.139 g, 0.99 mmol) in diethyl ether at 0 °C gave an orange solution immediately which, after 2 min, transformed into a yellow precipitate. After 45 min, GC analysis indicated **17a** (8.5%), 2,2,5,5-tetramethyl-3-hexanone[26] (**21**), t_R 3.36 (89.9%), and an unidentified compound, t_R 13.00 (1.6%). Evaporation of the solvents gave crude **21**: IR ν_{max}/cm^{-1} 1709 (C=O); ^{1}H NMR/ppm 2.38 (2H, s), 1.11 (9H, s), 1.02 (9H, s). Distillation of the crude product left a residue containing **23**: IR ν_{max}/cm^{-1} 1709 (C=O); ^{1}H NMR/ppm 2.37 (s), 1.15 (s), 0.97 (s).

(c) Repetition of **(b)** using $Me_2CuLi·LiI$ (1.01 mmol) and **17a** (0.284 g, 2.03 mmol) produced an orange solution immediately and a yellow precipitate after 20 s. GC analysis indicated **17a** (44.0%), **21** (45.6%), **22** (9.9%), and **23** (0.5%).

(d) Repetition of **(b)** in dilute solution, using diethyl ether (20 mL), produced an orange solution immediately and a yellow precipitate after 5 min. GC analysis indicated **17a** (8.2%) and **21** (89.4%).

(e) Repetition of **(d)** using diethyl ether (30 mL) gave similar results and GC analysis indicated **17a** (12.7%), **21** (83.8%), **22** (2.6%), and **23** (0.9%).

Low-Temperature ^{13}C NMR Studies of Cuprate–Enone Mixtures. To a stirred suspension of CuI (1.0 mmol) in diethyl ether (2 mL), at 0 °C under argon, was added purified MeLi[25] (2.0 mmol). The resultant solution was stirred for 5 min, and then the precipitate was allowed to settle. The cuprate solution (≈0.170 mmol) was then transferred, using a cannula, into a dry septum-capped 5-mm NMR tube held at 0 °C containing diethyl ether-d_{10} (0.09 mL) for locking and benzene (15 μL) as internal standard. The tube was then cooled to −80 °C in the NMR probe. Once adequate resolution had been achieved at −80 °C, the tube was ejected and held suspended in the cold gas plume within the insertion barrel of the NMR, while a solution of **17** (≈0.170 mmol) in diethyl ether (≈25 μL) was injected using an 11-cm syringe needle. The tube was then rapidly inserted into the probe, and, after sample spinning was reestablished, the field homogeneity was adjusted. The ^{13}C NMR spectra were obtained at various temperatures as required. After completion of the NMR studies, the NMR tube was warmed to room temperature, and then, after workup, GC analysis as described previously was undertaken. The reactions are reported according to the convention: methylcuprate, amount of enone, temperature (time/min) conditions; GC analysis of the final reaction mixture. **(a)** $Me_2CuLi·LiI$ (0.170 mmol), **17a** (0.026 g, 0.189 mmol), variable temperature; -80 °C (60), −70 °C (15), −60 °C (30), −50 °C (60); **17a** (10%) and **21** (85%); **(b)** $Me_2CuLi·LiI$ (176 mmol), **17a** (0.0233 g, 0.170 mmol), isothermal; −55 °C (440); **21** (97%) and **22** (2%). **(c)** $Me_2CuLi·LiI$ (0.180 mmol), **17b** (0.0243 g, 0.173 mmol), variable temperature; -80 °C (10), −70 °C (20), −60 °C (10), −80 °C (15), −60 °C (60), −80 °C (10), −60 °C (15), -50 °C (15), −40 °C (15), −30 °C (10), −20 °C (15), −10 °C (10); **17b** (2%), **21** (96%), and **23** (2%). (**d**) Me$_2$CuLi·LiI (0.180 mmol), **17b** (0.0259 g, 0.185 mmol), isothermal; –55 °C (400); **17b** (2%), **21** (94%), and **23** (4%). (**e**) Me$_2$CuLi[12] (0.170 mmol), **17b** (0.0234 g, 0.167 mmol), isothermal; –55 °C (390); **17b** (1.1%), **21** (98.2%), and **23** (0.7%). (**f**) [^{13}C]Me$_2$CuLi·LiI, (0.173 mmol), prepared from [^{13}C]MeLi, **17b** (0.0238 g, 0.170 mmol), isothermal; –55 °C (425); **21** (88%), **22** (4%), and **23** (8%). (**g**) Me$_2$CuLi·LiI (0.175 mmol), **17c** (0.0244 g, 0.172 mmol), isothermal; –55 °C (440); **17c** (2%), **21** (96%), and **22** (2%).

^{13}C NMR of Ethereal 2,2,5-Trimethyl[5-^{13}C]-4-hexen-3-one (17b) with Lithium Salts. Anhydrous LiI (0.21 g, 1.58 mmol) was dissolved in diethyl ether (7 mL) under argon at room temperature. This solution (0.7 mL) was transferred into a NMR tube precooled to 0 °C containing diethyl ether-d_{10} (0.09 mL) and benzene (15 μL). A solution of **17b** (0.021 g, 0.153 mmol) in diethyl ether (10 μL) was added to the NMR tube. The ^{13}C NMR spectrum was obtained, and the chemical shifts observed at –80 °C were reported in Table 3. A similar experiment was carried out with anhydrous LiClO$_4$ (0.15 g, 1.37 mmol).

2,2,5,5-Tetramethyl[5-^{13}C]-3-hexanone and 3-Acetoxy-2,2,5,5-tetramethyl[5-^{13}C]-3-hexene. A solution of 2,2,5-trimethyl[5-^{13}C]-4-hexen-3-one (**17b**) (1.12 g, 7.98 mmol) in diethyl ether (4 mL) was added to a stirred solution of Me$_2$CuLi·LiI (11.07 mmol, 58 mL) in ether at –78 °C. The mixture was then warmed to 0 °C, and after 2 min a yellow precipitate formed. After stirring for 1 h at 0 °C GC analysis of an aliquot, quenched with NH_4Cl/NH_3 solution, showed only 2,2,5,5-tetramethyl[5-^{13}C]-3-hexanone. A sample (5 mL) of the reaction solution was reserved for acetylation. The remainder of the reaction mixture was quenched with NH_4Cl/NH_3 solution (40 mL). The total mixture was shaken until a deep blue color developed, and all the solids had dissolved. The mixture was separated, and the aqueous layer was ether extracted (4 × 30 mL). The combined ether extract was washed with H_2O (2 × 10 mL) and dried ($MgSO_4$), and the solvents evaporated at atmospheric pressure through a Vigreux column to give a residue of 2,2,5,5-tetramethyl-[5-^{13}C]-3-hexanone (1.06 g, 85%): ^{1}H NMR/ppm 2.37 (1.8H, s, H-4), 2.37 (0.2H, d, $^2J_{CH}$ = 2.0 Hz, H-4), 1.05 (9H, s, H-1), 1.02 (8.1H, s, H-6), 1.02 (0.9H, d, $^2J_{CH}$ = 1.9 Hz, H-6). The solution generated by the cuprate reaction above (5 mL, 0.89 mmol) was added to a solution of acetic anhydride (1.0 mL, 10.6 mmol) in ether (5 mL), at 0 °C under argon. The resultant mixture was stirred for 1 h at 0 °C, by which stage GC analysis of an aliquot, quenched with NH_4Cl/NH_3 solution, showed only acetylated enolate (t_R 6.65). The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL) and diluted with ether (20 mL). The ethereal layer was washed with NH_4Cl/NH_3 solution (5 mL), H_2O (5 mL) and dried ($MgSO_4$), and solvents evaporated carefully *in vacuo* using Kugelrohr apparatus to leave a residue of 3-acetoxy-2,2,5,5-tetramethyl-[5-^{13}C]-3-hexene:[21] ^{1}H NMR/ppm 4.97 (1H, s, H-4), 2.15 (3H, s, O$_2$CMe), 1.05 (9H, s, H-1), 1.04 (8.1H, s, H-6), 1.04 (0.9H, d, $^2J_{CH}$ = 1.9 Hz, H-6).

Lithium Enolate (27). A pentane solution of *t*-BuLi (1.00 mL, 1.35 mmol) was added to a stirred solution of 2,2,5,5-tetramethyl[5-^{13}C]-3-hexanone (0.200 g, 1.28 mmol) in diethyl ether (3.5 mL) at –78 °C under argon. The resultant mixture was stirred for 15 min at –78 °C. A sample (0.5 mL) was added to a solution of acetic anhydride (0.25 mL) in ether (2 mL) and allowed to stand for 15 min and then quenched with H_2O (5 mL). GC analysis of the ethereal layer showed 2,2,5,5-tetramethyl-[5-^{13}C]-3-hexanone (6%), 3-acetoxy-2,2,5,5-tetramethyl[5-^{13}C]-3-hexene (31%), and two unidentified products (t_R 11.24, 10%; t_R 11.65, 38%). A second sample (0.5 mL) was added to H_2O (2 mL). GC analysis of the ethereal layer showed 2,2,5,5-tetramethyl[5-^{13}C]-3-hexanone (39%) and an unidentified product, t_R 11.65 (46%). The mixture was then warmed to 0 °C and 0.7 mL of the solution was transferred to a NMR tube, containing diethyl ether-d_{10} (0.09 mL) and benzene (15 μL) precooled to 0 °C, as previously described. The ^{13}C NMR spectrum was obtained as before at –80 °C, and the chemical shifts are listed in Table 3.

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Supplementary Material Available: Figures showing ^{13}C NMR spectra of the reaction of **17b** with Me$_2$CuLi·LiI in diethyl ether and graphs of reaction parameters (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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