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Addition of Me_2CuLi to *ortho*-Substituted Methyl Cinnamates
An NMR Study of the π-Complex Formation

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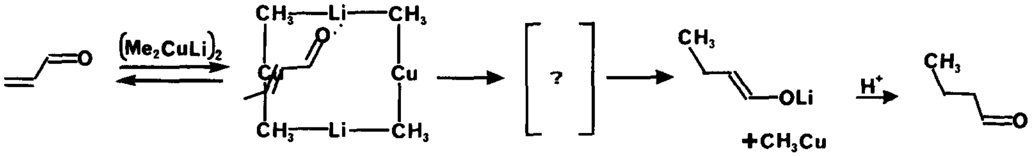
Abstract ^1H and ^{13}C NMR spectra of solutions obtained by mixing Me_2CuLi, **1**, or Ph_2CuLi, **2**, with methyl 3-[2-(1-methoxyethyl)phenyl]propenoate, **3**, labelled in C2 (99% ^{13}C), **3***, methyl 3-(2-methoxymethylphenyl)propenoate, **4**, methyl (S)-3-[2-(1-dimethylaminoethyl)phenyl]propenoate, **5**, and methyl 3-(2-dimethylaminomethylphenyl)-propenoate, **6**, in CD_2Cl_2/THF in the temperature range -90° - +20°C have shown the formation of more than one copper-alkene π-complex from each enoate. The ^{13}C labelled enoate **3*** on addition to **1** forms at least four isomeric π-complexes as proved by the presence of four C2 signals around 52 ppm in the ^{13}C NMR spectrum. Two dynamic processes have been observed, interconversion of different π-complexes and the reversible formation of the π-complexes, that lead to equilibrium mixtures of the copper-enoate species before carbon-carbon bond formation.

Knowledge about the mechanism(s) and the structure of intermediates in the cuprate addition reaction to α,β-unsaturated carbonyl compounds is a necessary prerequisite to obtain control of and to improve the enantioselectivity of reactions with chiral cuprates.[1] Although mechanistic studies were initiated quite a few years ago and many suggestions have been made no definite mechanism has as yet been generally accepted.

It is generally agreed that the formation of a complex between the reacting cuprate and enone/enoate is the first step in the reaction. This complex has been thought of as a lithium-carbonyl complex as suggested by House and coworkers.[2] The formation of this complex and the kinetics for its monomolecular transformation to the conjugate addition product have been investigated.[3] However, the rate expression obtained is also compatible with the alkene-copper π-complex suggested by several groups[4,5] or with a charge transfer complex.[6] Three alternative routes have been suggested for the transformation of the initial complex to the observable enolate conjugate addition product.[2,5,7,8,9]

We have recently demonstrated that the complex initially formed in the addition of lithium dimethylcuprate, Me_2CuLi, to α,β-unsaturated carbonyl compounds is a copper-alkene π-complex.[10]



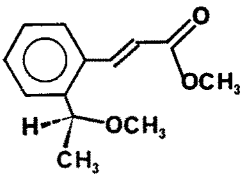
The complex can be studied by ^1H and ^{13}C NMR spectroscopy at temperatures below -40°C, when it exists in equilibrium with the reactants. As the temperature is increased the conjugate addition product is formed in concert with the disappearance of the π-complex.

Our suggestion is supported by observations made by Corey and Boaz who isolated a solid complex, that after addition of diethyl ether or THF in the presence of trimethylchlorosilane afforded the conjugate addition product.[11] These authors have also discussed possible frontier molecular orbital interactions in an initially formed d-π^* copper alkene complex.[12]

We have also shown that certain *ortho*-substitutents on the phenyl ring of cinnamic acid esters increase the rate of the conjugate addition of Me_2CuLi to the enoate significantly. This is true for a dimethylaminomethyl or methoxymethyl group when diethyl ether is used as solvent while in THF no rate increase is observed. The rate enhancement can be understood in terms of intramolecular coordination within the copper-alkene π-complex of the built-in ligand to a lithium atom in the dimeric cuprate.[13]

We have now extended our mechanistic investigation of the addition of cuprates to enoates with two objectives in mind. Firstly, we want to verify our suggestion of an initially formed copper-alkene π-complex from carbonyl substituted alkenes and organic cuprates. For this purpose we have prepared an *ortho*-substituted methyl cinnamate labelled with ^{13}C (99% enriched) in the C2 position. This labelling will allow the definite assignment of the alkene carbons of the proposed π-complex. Secondly we wish to study the effect of *ortho*-substituents in the phenyl ring of the methyl cinnamate and their potential as built-in ligands in intramolecular coordination in a copper-alkene π-complex. The introduct-ion of chiral *ortho*-substituents should provide diastereoselectivity in the addition reactions.

Results from an NMR investigation of the reactions between lithium dimethylcuprate, Me_2CuLi, **1**, or lithium diphenylcuprate, Ph_2CuLi, **2**, and four *ortho*-substituted methyl cinnamates are reported in this paper. The cinnamates under study were methyl 3-[2-(1-methoxyethyl)phenyl]propenoate, **3**, labelled in C2 (99% ^{13}C), **3***, methyl 3-(2-methoxymethylphenyl)propenoate, **4**, methyl (S)-3-[2-(1-dimethylaminoethyl)phenyl]propenoate, **5**, methyl 3-(2-dimethylaminomethylphenyl)propenoate, **6**, as well as methyl cinnamate, **7**, which was included for comparison. The results of the corresponding chemical study will be reported in a forthcoming paper.[14]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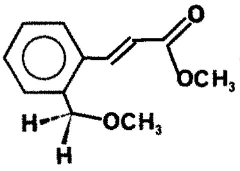
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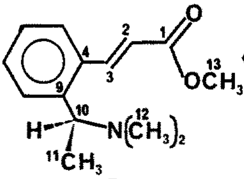

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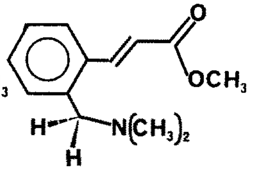
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Procedures

Solutions of Me_2CuLi, **1**, (written as a monomer for simplicity) were prepared by addition of methyllithium (4 mmol) to a slurry of copper(I) iodide (2.2 mmol) in diethyl ether, Et_2O, at 0°C. The diethyl ether was evaporated under reduced pressure. A few equivalents of ether were, however, retained in the solid as revealed by the NMR spectra. The solid **1** was suspended in dichloromethane-d_2, CD_2Cl_2, the solvent evaporated and 1 ml of fresh CD_2Cl_2 added. Alternatively, the solid **1** was dissolved in tetrahydrofuran-d_8, THF, the solvent evaporated followed by addition of 1 ml CD_2Cl_2. In these samples the coordinating Et_2O molecules are replaced by THF. No attempts were made to remove lithium iodide formed in the preparation. Me_2CuLi is only partly soluble in CD_2Cl_2 even with THF as a ligand and is obtained as a slurry. The sample was divided into two equal portions and transferred to NMR tubes, cooled to -78°C, ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded at low temperatures before addition of *ca* 0.25 mmol of enoate dissolved in 0.2 ml THF. The slurry dissolves on addition of THF, the solution thus obtained normally has an orange colour and is typically *ca* 1.4 M in Me_2CuLi (counted as a monomer), the cuprate to substrate ratio is 4:1, and the solvent system is CD_2Cl_2/THF 3:1. In one case, with cinnamic ester **6**, toluene-d_8 was used instead of CD_2Cl_2. Samples with Ph_2CuLi, **2**, were prepared analogously.

^1H and ^{13}C NMR spectra were recorded alternately for the same solutions at temperatures from -90°C to +20°C. The first spectra were normally recorded at -70°C, the temperature lowered to -90°C and then increased stepwise by 10 to 15°. The reversibility of the observed processes was checked by alternately increasing and decreasing the temperature of the sample.

The *ortho*-substituted methyl cinnamates were synthesized as described elsewhere[14] and their ^1H and ^{13}C NMR spectra recorded using the relevant solvent mixtures toluene/THF or dichloromethane/THF in 3:1 ratios. The chiral enoate **3*** was obtained labelled with ^{13}C on carbon C2 by a procedure starting with malonic-2-^{13}C acid (99% enriched).

Results and discussion

Selected data from the ^{13}C NMR investigation of the labelled enoate **3*** are collected in Table 1 and for enoates **4**, **5**, **6** and **7** in Table 2. The corresponding ^1H NMR data for **3***, **5** and **6** are found in Table 3. The ^1H NMR spectra of **4** were analogous to those recorded for **3** and **3***. Solvent signals (CD_2Cl_2 or CH_3 in toluene) were used as reference to measure chemical shifts. However, it was found that the chemical shifts of all species were slightly dependent on the composition of the solutions. Thus, small variations in the reported chemical shifts (*ca* 0.2 ppm and *ca* 1-2 ppm in the ^1H and ^{13}C NMR respectively) are due to slight shifts of the solvent signals.

Our original observation of a stable π-complex formed by a bonding interaction between copper in Me_2CuLi and the C=C double bond of the cinnamic ester is fully supported by results from a ^{13}C NMR study of the labelled, chiral enoate **3***, Fig. 1, and Table 1. The signal from the C2 carbon of **3*** itself appears at 119.7 ppm, Fig 1a. On addition of Me_2CuLi, (^{13}C NMR in Fig. 1b) at -70°C this signal disappears and instead several closely spaced signals are observed initially around 52 ppm. After 30 min at

Table 1. Selected ^{13}C NMR data for solutions of cinnamate **3*** (labelled with ^{13}C in the C2 position) and Me_2CuLi, **1**, or Ph_2CuLi, **2**, in the temperature range -90 to +20°C, cuprate:enoate ratio 4:1, solvent CD_2Cl_2:THF-d_8, 4:1. Chemical shifts were measured using the CD_2Cl_2 signal at 54.2 ppm as reference. C2 refers to free **3*** in solution; C2 in π-complexes refer to C2 of the ligand enoate.

Reactants	Temp °C	C2	C2 in π-complexes				Cuprate	Comments
1	-70						-8.9	
1+3*	-70	-	53.7	52.6	51.0	49.9	-5.5,-6.5,-9 -11, -13	no free **3***, 3 C4 signals
	-50	-	54	53	52	50	-6,-6.5,-9, -10,-12,-13M	
	-45	-	one broad signal 45-58				broadening	
	0	90-120					-12	sharp signals except C2
	+20	104-120					-12	C2 in products at 104 and 62 ppm
2+3*	-84	119	54.1	54.0	53	-	-	
	-73	119	54.1	54.0	53	-	-	THF at 66 ppm broad
	-52	119b	52 - 56 one broad signal					
	-35	114-120 very broad	50 - 60 very broad					coalescence at -30°C
	-25	110 - 122 very broad						sharp signals except C2
	0	116-120b						product C2 peaks at 100.8 and 60.2 ppm

M = major component, b = broad.

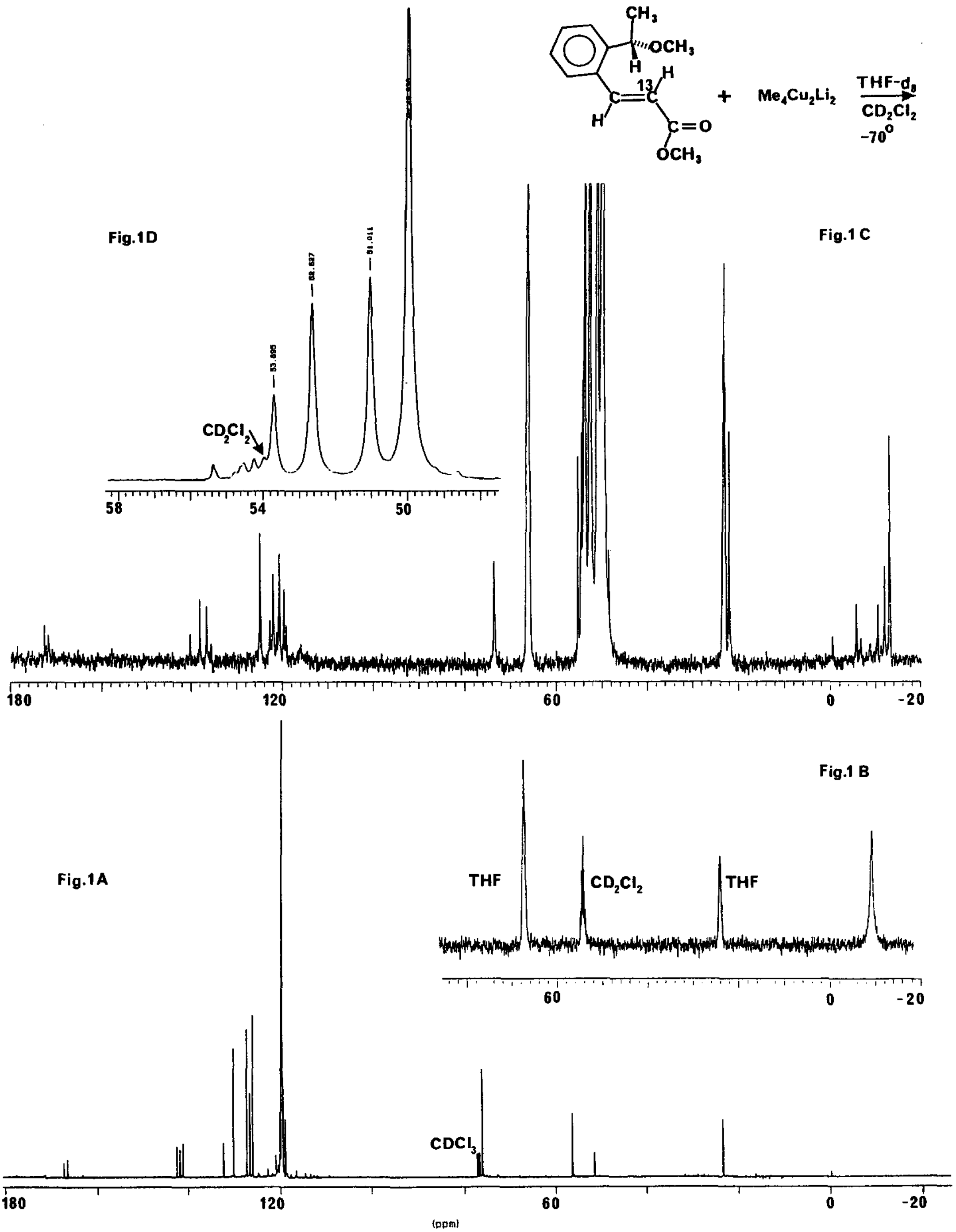


Figure 1. ^{13}C NMR spectra recorded at -70°C for solutions of a, ^{13}C labelled enoate 3* ($CDCl_3$), b, Me_2CuLi, 1, (CD_2Cl_2/THF), c, enoate 3* + 1, d, expansion of the shift region 48 - 54 ppm in Fig. 1c.

-70 to -60°C the relative intensities have changed, four signals remain, *cf.* Fig. 1c, and one of the major components has almost disappeared. In the expanded spectrum, Fig. 1d, the four C2 signals are observed at 53.7, 52.6, 51.0 and 49.9 ppm in the relative ratio 1 : 2.1 : 2.4 : 5.9. They appear as doublets, J_{CH} = 160 Hz, in the proton-coupled spectrum. In the corresponding ^{13}C NMR spectrum of the non-labelled enoate 3 all carbons except C3 are easily identified. Three signals at 172.1, 172.8 and 173.0 ppm are assigned to the C=O carbon while a group of three signals at 135.6, 136.6 and 138.2 ppm all are attributed to benzene C4. Thus, several slightly different alkene-copper π-complexes are formed on addition of 3 or 3* to Me_2CuLi.

Addition of the enoate 3* to Ph_2CuLi in CD_2Cl_2/THF again gives rise to a strong shielding of the C2 carbon. Three signals can be observed at 54.1, 53.8 and 52.8 ppm together with some remaining enoate 3* at 120 ppm. The C2 and the C=O signals, 166, 171 and 173 ppm, in the ^{13}C NMR spectra of 2 + 3* become broader at temperatures above -70°C and at -45°C coalescence of the C=O signals has occured. The three lines around 50 ppm then have merged into one very broad signal at 50 - 58 ppm. After coalescence of this signal and the C2 signal from the free enoate (119 ppm) at *ca* -30°C a new very broad peak appears between 100 - 120 ppm at -25°C. On further increasing the temperature to 0°C, C2 signals

Table 2 Selected ^{13}C NMR data for solutions of methyl cinnamates, 4, 5, 6 and 7 in the presence of Me_2CuLi, 1, in the temperature range -70°C to +10°C, cuprate:enoate ratio 4:1, solvent CD_2Cl_2:THF-d_8, 4:1. Chemical shifts are obtained by using the ^{13}C signals for CD_2Cl_2 at 54.2 ppm or toluene at 21.3 ppm as the reference. When several species are observed, their shifts are given on different lines.

Reactants	Temp°C	C1	C2	C3	C11	C12	C13	$(CH_3)_2CuLi$	Comments
1	-30							-8.1	
4	-70	168.7	119.9	142.6	-	59.6	53.7	-	
1+4	-70	174.4M	52.1	h	-	59.0	52.3	-2.2,-6,-8,	2 sets of peaks,
		173.6m	h	h		57.9	53.2	-9.7,-10.5M	no signals from 4
1	-90							-8.5,-9.3,-9.5	THF added
1+4	-90	175.0	52.6	h	-	59.6	52.9	-1.4,-6,-7.1	
		174	h	h		58.6	52.6	-9.6,-9.8	
1	-50							-9.5 b	THF C2 broad
5	-50	169.2	120.8	144.4	21.7	45.4	54.0	-	
1+5	-70	175M	54	64	25	47	54	-2,-3,-3.5	
		174m	h	h	18	44	58	-6,-9	+ signals from 5
	-50	175b	h	h	25b	47b	53b	-2 - -6b	signals for 5 sharp
		174b	h	h	18b	44b	56b		
	-45	c	c	c				-9 b	signals for 5 broad
	-10	170b	120vb	144vb	22	45	54	-8 - -9b	
	+10	170sh	120b	144b	21sh	45sh	54sh	-10b	
1	-55							-8.0	toluene-d_8/THF-d_8
6	-50	167.6	118.9	143.6	-	45.8	52.1	-	" "
1+6	-60	174.5M	*ca*52	58 d	-	46	52	-1.5,-6, -9	" "
		173.8m	h	h					+ signals from 6
	-30	c	52 b	58 b	-	46 b	53 b	-9 b	
	-10	170	in baseline		-	46sh	53sh	-9	
1	-70							-8.8	
1+7	-80	173	52	63	-	52	-	-2, -12	no free 7

M = major component, m = minor component, b = broad, vb = very broad, sh = sharp, c = coalescence, h =hidden.

due to addition products start to appear at 100.8 and 60.2 ppm but the C2 signal of **3*** is still present as a broad peak at 114-120 ppm.

The same type of temperature dependence is observed for **1** + **3*** with merging of the signals around 50 ppm at -50°C and coalescence of this signal and the C2 signal of free **3*** around -10°C. On further increase of the temperature signals assigned to product C2 carbons at 104 and 60 ppm (at 0°) are observed. At +20°C the C2 carbon appears as a broad signal at 114-120 ppm and a single cuprate peak is observed at -12 ppm. All other signals are sharp at this temperature.

These two experiments firmly establish the assignment of signals around 50 - 55 ppm to C2 carbons in a species that is best understood as a copper-alkene π-complex, as discussed previously. The possible formation of a lithium-carbonyl complex as a rationale for the large upfield shift of C2 was ruled out by addition of LiI to solutions of **4** in CD_2Cl_2/THF. No effect on the chemical shifts of any of the carbons was observed.

The solutions of Me_2CuLi with **4**, **5** (CD_2Cl_2/THF) and **6** ($C_6D_5CD_3$/THF) all show signals due to several species in their ^{13}C NMR spectra, Table 2. The two achiral enoates **4** and **6** give at least two carbonyl C1 signals, *ca* 174 and 175 ppm, in the presence of Me_2CuLi, that can be assigned to π-complexes at -70°C. The signals from C2 and C3 are partially hidden by overlap with other carbon signals. The chiral enoate **5** also gives rise to at least two new C1 signals attributed to π-complexes, Table 2. The carbonyl C1 signals are often difficult to distinguish from the baseline noise.

In the ^1H NMR spectra of **3**, **4**, **5** and **6** large shifts of the H2 and H3 protons to *ca* 4 ppm are observed together with a smaller upfield shift, Δδ *ca* -0.6 ppm, of the aromatic protons. The H2 protons are often difficult to identify since they are hidden under signals from other groups while two signals attributed to the H3 protons of two π-complexes can be readily identified, *cf* Table 3.

The formation of at least four copper-alkene π-complexes on mixing the chiral enoate **3*** with Me_2CuLi raises the question of how many π-complexes can be formed on mixing the enoate with a cuprate in a CD_2Cl_2/THF solution. The formation of two diastereomeric π-complexes on mixing a cuprate with a chiral enoate is a straight-forward basis for the presence of two C2 signals in the ^{13}C NMR spectrum but the discussion of further possible complexes is more speculative. However, several possibilities should be considered: firstly, the presence of several cuprate species each giving rise to a unique π-complex; secondly, different conformations of the chiral enoate **3** can approach a cuprate again giving rise to discrete π-complexes due to hindered rotation around formal single bonds in the π-complex. Thirdly, intra-molecular coordination within a π-complex of a heteroatom in the enoate side chain to lithium in the cuprate might lead to the observation of separate signals for π-complexes with and without intramolecular coordination at low temperatures.

Cuprate composition

The spectrum of Me_2CuLi (with LiI) in CD_2Cl_2 with coordinating THF, *i e* a minimum amount of THF, shows only one signal at -9 ppm (^{13}C NMR in Fig. 1b) and -1.2 ppm (^1H) respectively for the cuprate methyl groups over the temperature range studied in this investigation, -90° to -30°C, *cf* Tables 2 and 3. These signals are attributed to the dimeric cuprate $(Me_2CuLi)_2$.[15] However, a very fast equilibration of two or more cuprate species can not be entirely ruled out. The ^{13}C NMR signal for C2 in THF is slightly shifted and broadened in all spectra below -50°C indicating exchange between coordinated and free THF molecules.

It has recently been shown that Ph_2CuLi (also in the presence of LiI from its formation) in dimethyl sulfide exists as two different complexes that can be studied by ^{13}C NMR at -90°C.[16] The two sets of signals coalesce to one set of four lines at *ca.* -80°C with chemical shifts in good agreement with those reported previously by us for a solution of Ph_2CuLi (+LiI) in CD_2Cl_2 with coordinating diethyl ether.[17] The two sets of signals are attributed to $(Ph_2CuLi)_2$ in equilibrium with a LiI containing species, the latter one being the major species in dimethyl sulfide solution.

The composition of the cuprate solution is strongly solvent dependent as observed on addition of 4 dissolved in THF to $Me_2CuLi(THF)_x$ in CD_2Cl_2. In the first experiment the cuprate solution shows the normal signal attributed to the cuprate methyl groups at -1.2 ppm, -80°C. After addition of 4 dissolved in THF the mixture is still a slurry. The NMR spectra at -70°C show the presence of at least two π-complexes (two C=O carbons at 173 and 174 ppm, two sets of H3 at 4.3 and 3.9 ppm respectively, H2 hidden). In the cuprate region of the spectrum two broad signals are observed in the ^1H NMR spectrum at -1.2 ppm (major peak) and -1.4 ppm. After 30 min at -70°C a clear solution is obtained, the NMR spectra of which show only minor changes in the enoate region (sharpening of signals) but some major changes in the cuprate region showing signals at -0.21 (broad), -0.9, -0.95, -1.13 (major peak), and -1.4 ppm.

In the second experiment a clear solution was obtained by addition of THF to the slurry of $Me_2CuLi(THF)_x$ in CD_2Cl_2. The NMR spectra obtained for this solution show three signals at -90°C, -0.22, -1.15, -1.38 ppm (^1H) and -8.5, -9.3 and -9.5 ppm (^{13}C), respectively. The signals at -0.22 and -1.15 ppm integrated in an approximately 1 : 2 ratio and was assigned to a Me_3Cu_2Li species after comparison with the ^1H NMR spectrum obtained by Ashby and Watkins for a mixture of Me_3Cu_2Li and $(Me_2CuLi)_2$ in THF or dimethyl ether (LiI removed from solutions).[15b] The signal at -1.38 ppm is assigned to $(Me_2CuLi)_2$. Ashby *et al.*[15b] as well as Lipshutz *et al*[18] have discussed the equilibrium observed for the reagents dissolved in THF or dimethyl ether:

$$1/4\ (MeLi)_4 + Me_3Cu_2Li \rightleftharpoons (Me_2CuLi)_2$$

We have not observed any signal attributable to MeLi. However, considering the slight excess of copper iodide used in the preparation of $(Me_2CuLi)_2$ the observation of Me_3Cu_2Li can be rationalized by the following reaction taking place in the presence of THF:

$$(MeCu)_x + (Me_2CuLi)_2 \longrightarrow Me_3Cu_2Li$$

On addition of 4 to this cuprate mixture at -90°C signals assigned to two π-complexes appears, together with new signals in the cuprate region. In the ^1H NMR spectrum at -90°C the signals from Me_3Cu_2Li appear as sharp singlets at -0.21 and -1.13 ppm. The $(Me_2CuLi)_2$ signal at -1.38 ppm has almost disappeared and instead two new signals are observed at -0.92 and -0.96 ppm, in good agreement with our observations in the previous experiment. When the temperature is raised to -70°C the two signals -0.21 and -1.13 become very broad while all other signals remain sharp including the ones at -0.92 and -0.96 ppm. On further increasing the temperature to -45°C a single broad peak at -0.9 ppm is observed in the cuprate region of the spectrum. The H3 protons of the two π-complexes are broadened and coalescence of these signals and the H3 signal of the free 4 occurs at -30°C. Thus equilibration of the methyl groups within Me_3Cu_2Li is a faster process than the equilibration of methyl groups between different cuprate structures. The two signals at -0.92 and -0.96 ppm are assigned to methyl groups in cuprates interacting with the C=C double bond, *i e* the π-complexes. It is concluded from this experiment that the cuprate normally described as $(Me_2CuLi)_2$ is taking part in the formation of copper-alkene π-complexes as illustrated by the disappearance of the signal at -1.38 ppm while Me_3Cu_2Li is unaffected by the presence of the enoate.

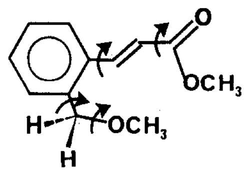
Furthermore, if coordination of different cuprate structures to the enoate were the cause for the observation of more than one π-complex from 4 and 6 or more than two from 3 or 5 it would be expected that formation of more than one π-complex on addition of methyl cinnamate, 7, to Me_2CuLi would be possible. This has, however, not been observed as only one set of signals are obtained on mixing Me_2CuLi with methyl cinnamate in CD_2Cl_2/THF, *cf* Table 2 or in CD_2Cl_2/Et_2O, *cf* ref. 10.

Pending new results we disregard the possible presence of different cuprate structures as the cause for formation of more than one π-complex on addition of achiral enoates to Me_2CuLi in CD_2Cl_2/THF solutions.

Conformational effects

In the free enoates rotation around single bonds in the two side chains on the benzene ring can be assumed to be relatively unhindered. However, on coordination of the cuprate to the C=C double bond rotational barriers around single bonds can be expected to increase substantially due to steric interactions in the complex, to coordination effects and to electronic effects, thus giving rise to π-complexes differing in the conformation of the enoate.

Enones and enoates can normally exist as an equilibrium of two conformers, *s-trans* and *s-cis*, corresponding to rotation around the C1-C2 bond. It has recently been demonstrated that solid copper-alkene π-complexes from CuCl and unsaturated carbonyl compounds can be isolated and their structures determined. The carbonyl compounds show a strong preference for either the *s-trans* or the *s-cis* conformation as methyl acrylate adopts a *s-trans* conformation contrary to the favoured *s-cis* conformation of the free ligand, while ethyl vinyl ketone adopts a *s-cis* conformation on bonding to CuCl.[19] The chemical shifts observed for the π-complexes formed on addition of **4** or **6** to Me_2CuLi are compatible with the formation of *s-cis* and *s-trans* isomeric π-complexes but can probably be equally well accounted for by assuming the formation of isomeric complexes due to hindered rotation around the C3-C4 or C9-C10 single bonds. The deshielding of the C=O carbons, *ca* 5 ppm, in the π-complexes relative to the free enoates as well as the shielding of the aromatic protons, *ca* 0.6 ppm, observed for all π-complexes suggest that conjugation in the delocalized π electron system has been reduced. Structures having the enoate side chain twisted relative to the benzene ring are in agreement with observed shifts. Bonding of Me_2CuLi to some of these conformers creates isomeric complexes that can be interconverted by rotation around single bonds. The complexes could be studied at low temperatures but should be indistinguishable at higher temperatures when rotation around the single bonds is fast on the NMR time scale.



Intramolecular coordination

On the formation of a π-complex by the bonding of the cuprate copper to the C=C double bond, there is also the possibility of further coordination of the side chain hetero atom to lithium or another copper in the dimeric cuprate. If, for example, the dimethylamino group of **5** or **6** is coordinated to lithium within the cuprate, the two methyl groups would experience different chemical environments and thus give rise to two new, equally large methyl signals in the ^{13}C and ^{1}H NMR spectra of **5** or **6**, in agreement with observations by van Koten and Noltes.[20] They reported that in the ^{1}H NMR spectrum of the dimeric cuprate $(2\text{-}Me_2NCH_2C_6H_4)_4Cu_2Li_2$ in toluene-d_8 the two methyl groups and the methylene protons each give rise to two distinct sets of signals at -60°C due to coordinative bonding of the dimethylamino group to the lithium atoms of the cuprate.

In the recorded ^{13}C NMR spectra of **5**, Table 2, three signals assigned to the methyl carbons of the dimethylamino group are observed. However, the major peak at 45 ppm is assigned to the free enoate **5** while the two signals at 44 and 47 ppm of different intensities are attributed to two different π-complexes. The presence of two C=O signals in approximately the same ratio supports this hypothesis. In the methoxymethyl substituted enoate **4** as well as in the dimethylamino substituted **6**, Table 3, the two methylene protons appear as broad singlets only slightly shifted from their original position. In the competition between the oxygen or the nitrogen of the side chain in the cinnamate and the surrounding THF for coordination on lithium, the THF oxygens obviously win, thus preventing intramolecular coordination in the solvent mixture CD_2Cl_2/THF. Likewise, no effect of intramolecular coordination of the C=O oxygen to lithium could be observed.

In order to study the reaction between cuprates and enoates under conditions as close as possible to ordinary synthetic conditions, we originally chose to study the addition of Me_2CuLi to enoates in CD_2Cl_2/Et_2O solution in the temperature range -90°C to +20°C. These conditions gave good results in our NMR investigation of the addition of Me_2CuLi to methyl cinnamate itself.[10] When the methoxymethyl substituted enoate **4** is added to $Me_2CuLi(Et_2O)_x$ in CD_2Cl_2 some product enolate is rapidly formed upon mixing as signals assigned to the enolate (163.3, C1, 151.5, C4, 33.7, C3 and 26.1, added CH_3) are observed together with signals attributed to free **4** as well as to a copper-alkene π-complex at -90°C. Similar results were obtained on addition of the dimethylaminomethyl substituted **6** to $Me_2CuLi(Et_2O)_x$ in CD_2Cl_2. In contrast to these experiments the enolate formation on addition of **4** to $Me_2CuLi(THF)_x$ in CD_2Cl_2 is very slow even when the temperature has been increased to -10°C. The observed fast reaction of the methoxymethyl substituted enoate **4** in CD_2Cl_2/Et_2O as well as the observed solvent/ligand effect on the rate of conjugate addition in the NMR experiments corroborate the observations made previously.[10] The high reaction rate obtained in Et_2O on introduction of the methoxy-

Table 3 Selected ^1H NMR data for solutions of methyl cinnamates, **3***, **5**, and **6** in the presence of Me_2CuLi, **1**, in the temperature range -90°C to +20°C, cuprate:enoate ratio 4:1, solvent CD_2Cl_2:THF-d_8, 4:1. Chemical shifts are obtained by using the ^1H signals for CD_2Cl_2 at 5.3 ppm or toluene at 2.3 ppm as the reference. When several species are observed in solution, their chemical shifts are given on separate lines.

Reactants	Temp°C	H2	H3	H11	H12	H13	$(CH_3)_2CuLi$	Comments
1	-70						-1.28	
3 *	-84	6.4dd	8.00	1.27d	3.12s	3.70s	-	
1+3*	-70	h	3.5M	0.90	2.88	3.22	-0.69,-1.28,-1.40,	aromatic protons
		3.0	3.6m	1.0	2.70	3.13	-1.62,-1.87	shielded
	-90	same peaks but broader						
	-50	h	3.6M	1.0	2.9	3.3	-0.6vb,-1.2,-1.3,	no free 3 in soln
		3.1b	3.7m	1.1	2.8b	3.2	-1.5,-1.7sh,-1.75	
	-30	c	c	1.0b	2.9b	3.3b	-1.4vb,-1.7sh	
	0	vb	vb	1.1sh,d	2.95sh	3.5sh	-1.2	H2, H3 in baseline
	+10	5.7vb	h	1.12d	3.0sh	3.55sh	-1.2	
	+20	6.1dd,b	7.8b	1.15d	3.0sh	3.6sh	-1.1sh	
1	-50						-1.27	
5	-50	6.27d	8.20d	1.18d	2.08s	3.68s	-	
1+5	-70	3.24	3.9	0.80b	1.71b	3.17	-1.30sh,-1.41bM	arom. protons shielded
		h	3.7	h	h	3.08	-1.82sh	
		6.0d	7.9b	h	h	3.36		free **5**
	-45	c	c					
	-30	6.0vb	8.0vb	0.93d	1.83	3.45	-1.24bM,-1.7b	
	-10	5.9vb	7.9vb	0.97d	1.87sh	3.51sh	-1.19M,-1.6b	2 broad arom. H
	0	6.0b	8.0b	1.00d	1.87sh	3.51sh	-1.15sh	arom. protons sharp
1	-55						-0.25sh	toluene-d_8 +coord. THF
6	-50	6.68d	8.78d	-	2.16s	3.65s	-	toluene-d_8
1+6	-60	4.25M	4.7M	-	2.36b	3.75b	0.1,-0.2M,	toluene-d_8/THF
		4.1m	5.0m	-	-	-	-0.3,-0.6,-0.8	3 species in soln
		6.7d	8.6d	-	2.2b			free **6**
	-30	c	c	-	2.3b	3.8b	-0.2b,-0.5shoulder	
	-10	6.3vb	8.3vb	-	2.30	3.80	-0.2	
	+10	6.4b	8.2vb	-	2.30sh	3.75sh	-0.2sh	+ product signals

M = major component, m = minor component, h = hidden, b = broad, vb = very broad, sh = sharp, c = coalescence, d = doublet, s = singlet.

methyl group in methyl cinnamate is consistent with a model including intramolecular coordination within a π-complex in weakly coordinating solvents. The activating chelating effect of an alkoxy or an amino group has also been described by Reetz *et al* for the addition of methyltitanium reagents to carbonyl compounds.[21]

Dynamic NMR spectra

The temperature dependence of the ^{1}H NMR spectra of the enoates **3** - **6** in the presence of Me_2CuLi is in good agreement with results obtained previously for **7**[10], *cf* Table 3. At -50°C a broadening of the H2 and H3 signals in the 4 ppm region as well as the H2, H3 signals from the free enoates is observed followed by coalescence around -30°C. On further increase of the temperature new very broad signals appear in an intermediate region (H2 at *ca* 5 to 6 ppm) reflecting the equilibrium

$$\text{cuprate + enoate} \rightleftharpoons \pi\text{-complexes} \qquad \text{(eq 1)}$$

These signals move downfield when the temperature is raised further (0 to +20°C) and H2 and H3 are observed as broad signals at 6.0 and 8.0 ppm respectively, close to the chemical shift values observed for the free enoates. The equilibrium average shifts for H2 and H3 at 0°C indicate that the equilibrium has been shifted towards the free reactants at this temperature in contrast to observations at -70°C when the π-complexes are the major species in solution and no or very low concentrations of the free enoates are observed.

On inspection of the ^{13}C NMR spectra of **5** there appears an interesting difference in the temperature dependence of the signals attributed to the C1 carbons in π-complexes relative to the C1 carbon signal of the free enoate **5**. The signals at 175.2 and 174.2 ppm are broadened at -50°C while the signal at 170.0 ppm is still sharp. At -40°C the two C1 signals attributed to the π-complexes have coalesced while the C1 signal from **5** has become slightly broadened. At -10°C a broad average C1 signal is observed at 170 ppm, which becomes sharp at +10°C. A similar behaviour is observed for the dimethylamino carbon signals. The average signals for the C2 and C3 carbons are still very broad at +10°C in accord with the larger shift difference, Δv *ca* -70 ppm, between the species in equilibrium.

The temperature dependence of the C1 signals is best explained by invoking at least two dynamic processes, *i e* equilibration of π-complexes at low temperatures followed by an equilibrium between reactants and the π-complexes, eq. 1, observed at higher temperatures. The first process probably is the interconversion of π-complexes by rotation around single bonds within the π-complex while the second process involves breaking of the copper-alkene bonding interaction.

This conclusion is in good agreement with the observed temperature dependence of the C2 signals in the spectra of **1** + **3*** or **2** + **3*** where equilibration of the different π-complexes (seen as one signal at -50 to -45°C) is fast on the NMR time scale at temperatures when the free **3*** is still unaffected.

We can thus conclude that the π-complexes present in solution are in equilibrium via two dynamic processes and that equilibration is fast at temperatures at which carbon-carbon bond formation starts. Thus the diastereoselectivity of the conjugate addition will be decided by the relative rates for the different π-complexes in the subsequent carbon-carbon bond forming step of the reaction rather than by their relative concentrations, dictated by the preferred binding of the ligand enoate to the cuprate. This is analogous to the mechanism found for the asymmetric hydrogenation of 2-aminoacrylic acids.[22]

Bonding in the π-complexes

The major contribution to bonding in the π-complexes formed from cuprates in contrast to Cu^+ or CuCl has been ascribed to interactions between filled copper d-orbitals and empty π*-orbitals of the enoates on the basis of the large shielding effect on H2, H3 and C2, C3 respectively on formation of the π-complexes.[10] Investigations of $Cu(alkene)^+$ complexes have shown maximum shielding of the C=C carbons on bonding to Cu^+ of the order 29 ppm in the ^{13}C NMR spectra[23] which should be compared with the upfield shift of *ca* 70 ppm observed for the cuprate-enoate complexes.

Recent HFS calculations for the $Cu(C_2H_4)^+$ and $CuX(C_2H_4)$ (X=F,Cl) have demonstrated that the main metal-ligand interactions in the ground state are ethene π to Cu 4s donation and Cu 3d to ethene π^* backdonation.[24] Whereas in $Cu(C_2H_4)^+$ the contribution of the backdonation is minor it constitutes more than half of the electronic interaction energy in $CuX(C_2H_4)$. Extending these results to the copper-enoate complexes studied by NMR it can be argued that the increase of electron density on copper, best described as a Me_2Cu^- anion, and the lowering of the energy of the LUMO of the ligand by introducing a carbonyl substituent on the alkene will further increase the contribution of backbonding from copper to the ligand to the total electronic interaction energy.

Conclusions

The previous assignment of carbon signals in the 50 - 60 ppm shift range to carbons C2 and C3 of cinnamic acid esters involved in the formation of a copper-alkene π-complex has been confirmed by the observation of four lines around 52 ppm for the C2 carbon of the ^{13}C labelled **3*** in the presence of Me_2CuLi.

A simple model for the observed formation of more than one copper-alkene π-complex on addition of cuprates to enoates **3** - **6** has been suggested. The model is based on the hypothesis that rotation around single bonds in the enoate ligand in the π-complexes is hindered. Conformational isomers of the enoates will give rise to different π-complexes that can interconvert at higher temperatures. Chiral enoates open up the possibility of the formation of diastereomeric π-complexes.

This simple model is sufficient to rationalize the presence of four closely spaced signals in the ^{13}C NMR spectrum of **3*** in the presence of Me_2CuLi. The model does not rule out the presence of more than four species, some of which can be present in very low concentrations. However, a more complicated model might be necessary in order to explain future experimental results.

The copper-alkene π-complexes observed as separate species at low temperatures interconvert. This reaction is faster than the equilibration of reactants and the π-complexes.

Intramolecular coordination within the π-complexes is claimed to be the reason for the increased reactivity of **4** and **6** compared to methyl cinnamate in their reactions with Me_2CuLi in Et_2O,[13] but is not observed in the π-complexes of **3**, **4**, **5** and **6** in the presence of THF.

At low temperatures (i e -90 to -70°C) the formation of the π-complexes is favoured, while the equilibrium is displaced towards reactants at higher temperatures, (-10 to 0°C).

The relative concentrations of diastereomeric π-complexes does not determine the diastereoselectivity of the addition reaction. The isomeric alkene-copper complexes exist in rapid equilibrium and thus the diastereoselectivity of the conjugate addition must be determined by their relative reaction rates in the following step of the reaction.

Experimental

All handling of organometallic reagents and NMR samples was carried out under argon and with dried equipment. Diethyl ether was distilled from sodium/benzophenone. Commercial deuterated solvents were used without further purification. We used commercial methyllithium in diethyl ether and phenyllithium in cyclohexane/ether (Aldrich). Copper (I) iodide was recrystallized[25] prior to use. ^1H and ^{13}C NMR spectra were recorded on a Varian XL 400.

3-[2-(1-methoxyethyl)phenyl]propenoic acid labelled in C2 (99% ^{13}C). 2-(1-Methoxyethyl)benzaldehyde[14] (ca 3.3 mmol) and malonic-2-^{13}C acid (179 mg, 1.7 mmol, C2 99% ^{13}C, ICN Biomedicals, Inc) were dissolved in pyridine (0.6 ml, 7.4 mmol).[26] After addition of piperidine (0.3 ml) the mixture was heated to 80°C, kept with stirring for 1 h followed by reflux at 110°C for 3 h. After cooling, the reaction mixture was poured into cold water and conc. HCl was added to pH <1. The crude crystals were solved in NaOH (1M), washed with diethyl ether and finally HCl (conc) was added and the crystals were filtered off. (248 mg, 70%). mp: 148-150°C. IR: 1675, 1600 cm-1. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, d, J 6.5 Hz) 3.27 (1H, s) 4.71 (1H, q, J 6.5 Hz) 6.37 (1H, dd, $J_{^{13}CH}$ 163.4 Hz, J 15.8 Hz) 7.32

7.44 (1+1H, t, J 7.4 Hz, aromatic) 7.49 7.59 (1+1H, d, J 7.7 Hz, aromatic), 8.23 (1H, dd, $J_{^{13}CCH}$ 3.3 Hz, J 15.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 56.6, 76.5, 119.2, 120.9, 126.6, 127.6, 130.7, 132.1, 142.9, 143.9 (d, J_{CC} 70 Hz), 171.8 (d, J_{CC} 74 Hz).

Methyl 3-[2-(1-methoxyethyl)phenyl]propenoate labelled in C2 (99% ^{13}C) 3*. A solution of the acid from the previous step (226 mg, 1.1 mmol) in methanol (20 ml) containing traces of conc. H_2SO_4 was refluxed for 12 h. The solvent was evaporated under reduced pressure, the residue flash chromatographed (elution with dichloromethane) and 200 mg of 3* isolated, 82%. IR: 1715, 1615 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, d, J 6.5 Hz) 3.25 (3H, s) 3.82 (3H, s) 4.70 (1H, q, J 6.6 Hz) 6.34 (1H, dd, $J_{^{13}CH}$ 162.7 Hz, J 16 Hz) 7.48 7.54 (1+1H, t, J 7.7 Hz, aromatic) 7.77 7.89 (1+1H, d, J 7.5 Hz aromatic) 8.10 (1H, dd, $J_{^{13}CCH}$ 3.34 Hz, J 16 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 51.6, 56.5, 76.1, 119.7, 126.1, 126.7, 127.5, 130.2, 132.4, 141.6 (d, J_{CC} 72 Hz), 142.7, 167.1 (d, J_{CC} 74 Hz).

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