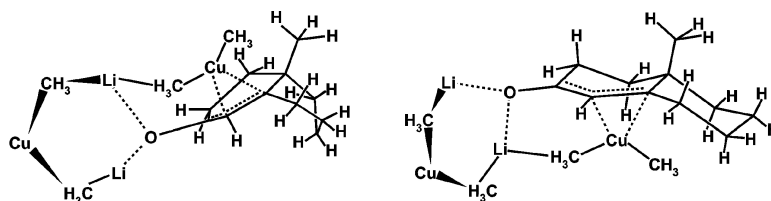


Organocuprate Conjugate Addition: Structural Features of Diastereomeric and Supramolecular π -Intermediates

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Organocuprate Conjugate Addition: Structural Features of Diastereomeric and Supramolecular π -Intermediates

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Abstract: In the reaction pathway of conjugate additions with organocuprate reagents, Cu(I) π -complexes and Cu(III) σ -complexes have been identified as central, NMR-detectable intermediate species. However, no experimental evidence for the structures of π -intermediates with extensive chiral enones or the principal aggregation level and aggregate structure of π -complexes in diethyl ether has been available so far. Furthermore, the structural characteristics of π -complexes which are essential for their high reactivities and diastereoselectivities have not yet been rationalized experimentally. Therefore, the π -intermediates of 4,4a,5,6,7,8-hexahydro-4a-methyl-naphthalen-2(3H)-one and Me₂CuLi or Me₂CuLi·LiX (X = I, CN) in diethyl ether are investigated in detail. For the first time, the formation of two intermediate cuprate enone π -complexes on both sides of the double bond is observed. In addition, the conformation of the enone adopted in the major β -face π -complex rationalizes the exclusive syn addition observed in the synthetic product. For the investigation of the aggregation level and structure, a NMR screening of π -complexes with Me₂CuLi·LiX (X = I, CN) and three achiral enones is performed, which simplifies the spectra by the generation of enantiotopic π -complexes. Thus, NMR diffusion experiments on cuprate intermediates and the detection of scalar couplings across copper without isotope labeling are possible for the first time. Extensive NMR studies, including those of cyclohexanone complexes, show that, in principle, salt-free dimethylcuprate is able to complex the carbonyl group. However, in the presence of salt, the carbonyl-complexing aggregates are composed of salt and cuprate moieties. These mixed aggregates cause the formation of large supramolecular π -intermediate structures which control their reactivity. The π -complexing cuprate units show a bent geometry as a general structural feature that is unaffected by the presence or kind of salt and the type of enone. Thus, the high diastereoselectivity and the reactivity of organocuprate 1,4-addition reactions are for the first time rationalized on the basis of structural characteristics of selected π -intermediates.

Introduction

Organocopper reagents are among the most frequently applied transition metal reagents for the formation of C–C bonds in organic synthesis.^{1–4} Despite their important role in organic reactions, the complicated structure of organocopper complexes in solution, their potential self-aggregation, and their sensitivity to solvent, salt, and concentration have hindered experimental structure elucidation so far. Therefore, a rational design capable of tapping the full potential of copper reagents remains elusive. However, in the case of organocuprates, which are generally accepted as mechanistic models for organocopper chemistry, a number of experimental investigations have allowed insight into

their monomer and aggregate structures and have identified organocuprate enone π -complexes as intermediates in 1,4-addition reactions.^{5–8} Very recently, the first Cu(III) intermediates were detected by NMR spectroscopic studies in conjugate addition and substitution reactions of organocuprates.^{9–12} In addition to these experimental studies, various theoretical calculations provide insight into the reaction pathways of organocopper reagents. These calculations reveal open cluster structures and transition states in these impressively complex mechanisms.^{13–15}

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For the synthetically important 1,4-addition reactions of organocuprates to enones, combined NMR investigations and kinetic studies show that, in ethereal solutions, the aggregation level of these reagents is crucial for their reactivity.^{16,17} Thus, tetrahydrofuran (THF) as solvent leads to a rigorous reduction of the reactivity in 1,4-additions to enones, because it supports the formation of solvent-separated ion pairs,¹⁸ and only a small amount of the reactive contact ion pairs remains.^{16,19} In contrast, in diethyl ether, dimethylcuprates form oligomeric structures that are composed of homodimers connected by salt and solvent bridges,^{20,21} which promote conjugate addition reactions. Recently, the aggregation degree and the composition of the supramolecular structures of the organocuprate reagents were correlated with the reactivities obtained in 1,4-addition reactions to cyclohexenones.¹⁷ In the case of $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$ ($2\cdot\text{LiCN}$) in diethyl ether, the addition of a certain number of equivalents of THF leads to a disaggregation of its oligomeric structure into dimers with salt units attached. Along with the disaggregation, the reactivity decreases, which corroborates the importance of the aggregated species in 1,4-addition reactions of organocuprates. In agreement with these experimental results, theoretical calculations suppose that the reactivity and the synthetic potential of organocuprate clusters are based on their ability to form supramolecular assemblies allowing for cooperative interactions within the polymetallic clusters.¹³ However, despite the impressive progress in the theoretical calculations of supermolecules, the computable cluster sizes have been small compared to the supramolecular organocuprate clusters which are experimentally observed in diethyl ether.

Some of the intermediate species in conjugate addition reactions in the reaction pathway of 1,4-, 1,6-, and 1,8-addition reactions of cuprates have been observed previously.^{22–34} However, despite the importance of aggregates in 1,4-addition

reactions, most of these NMR studies have been performed in THF, which only allows for the observation of minimum cluster sizes as the main species. These studies congruently reveal one cuprate unit attached to the π -system next to the carbonyl moiety. With the aid of isotopically labeled compounds, two types of scalar couplings across copper were observed, indicating a bent geometry of the cuprate unit in the π -complex.^{23,33} Studies done in solvents which, in principle, support the formation of contact ion pairs or higher aggregates have been reported only for one cuprate unit directly attached to the π -system.^{22,30,35} The aggregation level and aggregate structure of the π -intermediates in diethyl ether, which are expected to be crucial for their reactivities, as well as the influence of the kind of enones or the type of salt on these intermediates, are entirely unknown at present. In addition, the experimental intermediate studies published so far have not yet addressed the structural or conformational reasons for the high diastereoselectivities observed in many 1,4-addition reactions of cuprates. Such structural or conformational factors should be related to the formation of α - or β -face π -complex intermediates. One of the famous examples in this respect is the 1,4-methylation of methyl octalones by organocuprates, which yields exclusively the syn addition product, i.e., β -methyl octalones.³⁶

Therefore, in this study the structures and aggregation trends of the intermediate π -complexes of 4,4a,5,6,7,8-hexahydro-4a-methyl-naphthalen-2(3H)-one (synonym: 10-methyl- $\Delta^{1,9}$ -2-octalone) (**1**) and Me_2CuLi (**2**) or $2\cdot\text{LiX}$ ($X = \text{I}, \text{CN}$) in diethyl ether are investigated in detail. For the first time, structural details of two intermediate cuprate enone π -complexes are elucidated, and the diastereoselectivity of the reaction is rationalized experimentally. Furthermore, a NMR screening of intermediate π -complexes with $2\cdot\text{LiX}$ ($X = \text{I}, \text{CN}$) and three achiral enones is presented. The resulting enantiotopic π -complexes simplify the spectra to such an extent that it is possible, for the first time, to investigate the aggregate structure, the aggregation level of cuprate enone π -complexes, and the influence of the type of salt on these intermediates.

Results and Discussion

π -Complexes of 4,4a,5,6,7,8-Hexahydro-4a-methyl-naphthalen-2(3H)-one (1**).** To investigate the structures of intermediate cuprate π -complexes with sterically hindered chiral enones, compounds **1** (see Figure 1a) and **2** or $2\cdot\text{LiI}$ in diethyl ether was chosen as a model system. The synthetic approaches, the NMR spectroscopic results, and the theoretical calculations known for this system allow for a detailed interpretation of the NMR spectroscopic data to rationalize the high stereocontrol of 1,4-addition reactions of organocuprates to chiral, cyclic enones experimentally. Actually, 1,4-addition reactions of **1** with copper species yielded β -methyl octalones exclusively, and without further additives, diethyl ether is the best solvent for this reaction.^{36–40} In order to explain this syn addition with respect to the methyl substituent, an enolate-like geometry of the transition state was postulated,^{36,38–40} in which **1** adopts a

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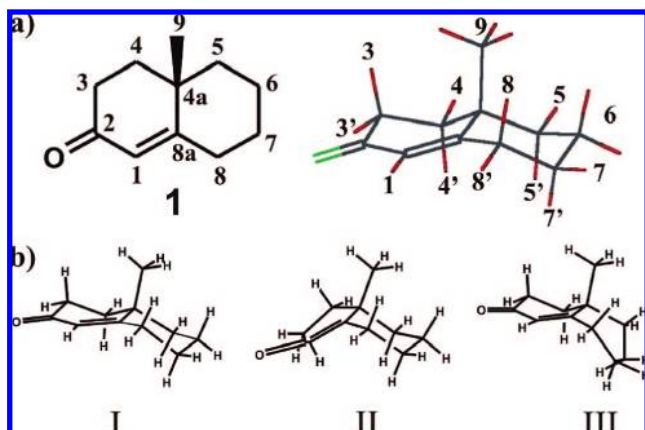


Figure 1. (a) Schematic representation of 4,4a,5,6,7,8-hexahydro-4a-methyl-naphthalen-2(3H)-one (synonym: 10-methyl- $\Delta^{1,9}$ -2-octalone) (**1**) and major conformation with the diastereoselective labeling of the protons; no diastereoselective assignment of the protons 6 is possible. (b) DFT structures of conformations I, II, and III of **1** according to Aamouche et al.⁴¹

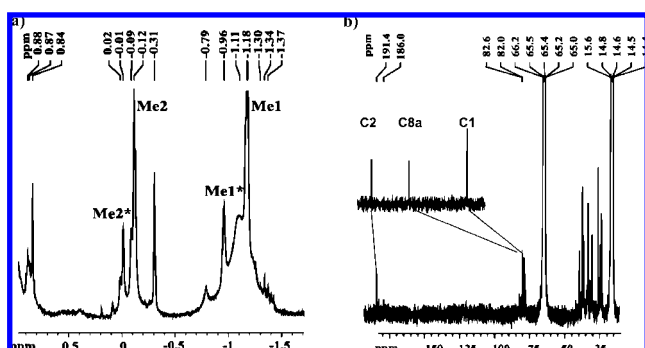


Figure 2. (a) Cuprate section of the ¹H spectrum and (b) enone section of the ¹³C spectrum of the intermediate π -complexes composed of **1** and 2 equiv of **2**·LiI in diethyl ether at 170 K. In panel b), the ¹³C spectrum of free **1** is given as an inset to show the chemical shift changes upon π -complexation. The minor intermediate is labeled with an asterisk.

conformation similar to II in Figure 1b. In contrast, theoretical calculations of pure **1** proposed three conformations, “trans-chair” (I), “cis-chair” (II), and “trans-boat” (III), showing relative energies I < II < III (see Figure 1).⁴¹ Furthermore, in the vibrational spectra of **1**, only conformation I was observed, which was attributed to the predicted energy difference of ~ 1.8 kcal/mol between I and II. This reveals that conformation I is preferred for free **1** and conformation II does not contribute significantly in CCl₄ or CS₂. From NMR investigations, the stabilization of several unspecified cuprate π -complexes in a mixture of **1** and **2** in diethyl ether was reported,²² showing the existence of different π -complex conformations as possible indications of the stereocontrol mechanism of this reaction.

In order to optimize the experimental conditions, the different cuprate enone complex species of **1** and **2**, reported previously as mixtures,²² were prepared individually and their assignment reconfirmed. For example, typical ¹H and ¹³C spectra of **1** complexed with 2 equiv of **2** are shown in Figure 2. The formation of π -complexes is directly indicated by the characteristic upfield shifts ($\Delta\delta^{13}\text{C}$) of C1, C2, and C8a of the enone.^{6,22} Despite the optimization procedure and the exclusive formation of cuprate olefin π -complexes (see Figure 2b), the

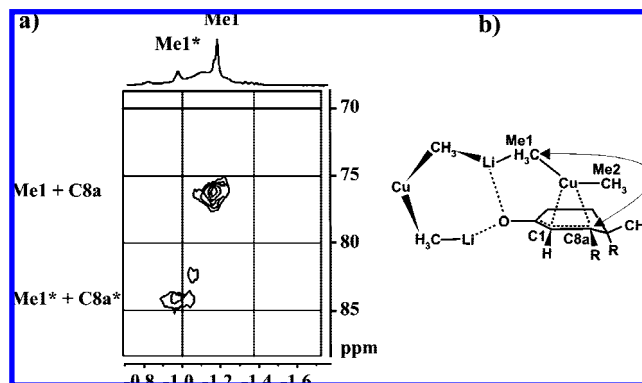


Figure 3. (a) Section of a ¹H,¹³C INEPT-INADEQUATE spectrum of **1** at natural abundance and ¹³C-labeled **2**·LiI in diethyl ether at 180 K. The cross signals appearing at ¹³C chemical shifts equal to $\delta^{13}\text{C}_{\text{Me1}^*} + \delta^{13}\text{C}_{\text{C8a}^*}$ are the result of ¹³C,¹³C scalar couplings across copper, as indicated by the arrow in panel b).

cuprate section of the ¹H spectrum is still very overcrowded (see Figure 2a). Thus, the splitting of each presented ¹³C signal of free **1** into at least two signals and the appearance of multiple proton signals in the cuprate section indicate the formation of several intermediate species (see Figure 2b).

Interestingly, with 2 equiv of the lower order cyanocuprate MeCu(CN)Li, no π -complexes, but only lithium carbonyl complexes, are observable. Similar results are obtained for enone **4** (see below). In contrast, the NMR detection of a π -complex of *t*-BuCu(CN)Li attached to the alkyne moiety of methyl phenylpropiolate in THF is reported,²⁸ and active substrate control was observed in the treatment of 5-oxygen-substituted cyclohexenones with the heteroleptic cuprates MeCu(CN)Li and *t*-BuCu(CN)Li.^{42,43} These results reflect the higher thermodynamic stability of π -complexes between electron-poor transition metal complexes and alkynes. In the case of alkyl-substituted enones and electron-poor heteroleptic cuprates, the resulting π -complexes are not sufficiently stabilized to allow for NMR observation.

In the case of the π -complex formation of **1** with 2 equiv of dimethyl cuprate, two differently populated π -complexes were identified and their ¹H and ¹³C chemical shifts assigned with the aid of ¹H,¹³C HMQC, ¹H,¹³C HMBC, ¹H,¹H NOESY, and ¹H,¹³C INEPT-INADEQUATE spectra as well as ¹³C isotopically labeled dimethyl cuprates (for ¹H and ¹³C chemical shift assignments, see Tables S1–S3 in the Supporting Information). Due to severe line broadening of the proton signals, it was not possible to use ¹H,¹H scalar coupling constants to identify the individual methylene protons. Therefore, the diastereotopic assignment is based on nuclear Overhauser effect (NOE) signals. For both π -complexes, the orientation of the two methyl groups named Me1/Me1* and Me2/Me2* (see Figure 3b) has been assigned by various NOESY cross peaks to the enone system. In addition, using INEPT-INADEQUATE^{44,45} spectra, it was possible to detect, for the first time, ¹³C,¹³C scalar coupling interactions between the cuprate moiety and an enone without ¹³C labeling of the enone. The exclusive detection of scalar

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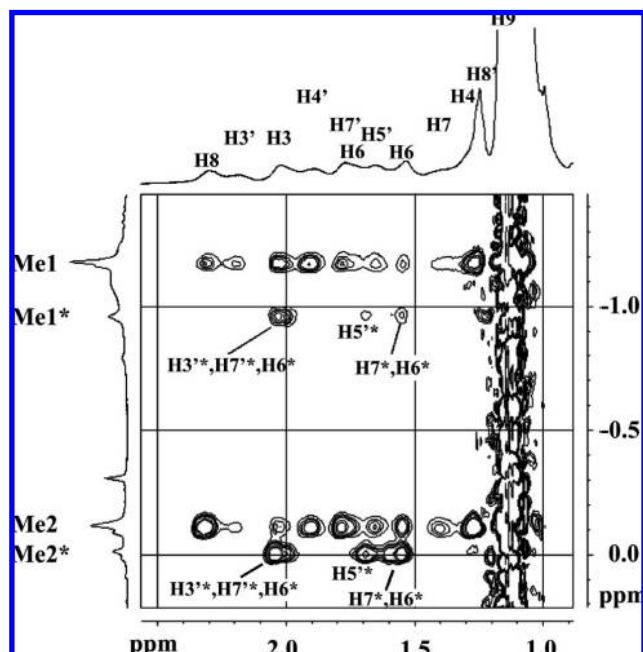
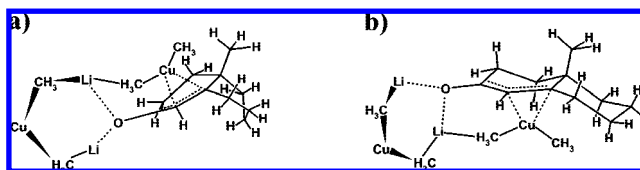


Figure 4. Section of a $^1\text{H},^1\text{H}$ NOESY spectrum of the π -complexes composed of **1** and $2\cdot\text{LiI}$ in diethyl ether at 180 K. The different patterns of the cross signals of the two π -complexes indicate considerably different structures. All signals of the minor intermediate are labeled with an asterisk; for a visualization of the numbers, see Figures 1a and 3b.

couplings between Me1/C8a and Me1*/C8a* (see Figure 3a) indicates a bent cuprate unit in both π -complexes (see Figure 3b), which is in accordance with previous NMR investigations of cuprate enyne π -complexes^{23,33} and theoretically predicted reaction pathways.^{13–15}

The similarity of the cuprate units attached to the double bond in both conformations raises questions about their structural differences. For this purpose, information is gained from the different cross peak patterns in the NOESY spectrum (see Figure 4). In the major conformation, the NOE cross peak between Me1 and H3' is smaller than that between Me1 and H8, and the cross peaks Me1/H3 and Me1/H4' show similar intensities. In addition, medium to weak cross signals Me1/H7' and Me1/H6 are detected. In principle, this pattern resembles a β -face π -complex for the major conformation. However, for a β -face π -complex with **1** in conformation I, one would expect a very strong NOE contact between Me1 and H3 and very weak or no NOE cross peaks for Me1/H7' and Me1/H6. In contrast, Me1/H3 shows intensity similar to that of Me1/H4', and Me1/H3' is very small. Thus, the actual NOE pattern of the major conformation fits well to a β -face π -complex, in which the enone part of **1** has a conformation of type II and the cyclohexyl ring adopts a conformation similar to III (for schematic representations of **1** in the conformations I, II, and III, see Figure 1b; for a schematic representation of the β -face π -complex with the conformational mixture of II and III, see Scheme 1a). In the case of the minor conformation, the observed NOE patterns differ significantly from those of the major π -complex. Despite the fact that severe signal overlaps complicate the interpretation, some cross peaks are very informative: Even for the low signal intensities of the minor conformation, a cross signal between Me1* and H7*/H6* is detected. Furthermore, the cross signal Me2*/(H7*/H6*) is very strong and the cross signal Me2*/H5* even stronger in the case of the minor conformation than in the major conformation. This NOE pattern indicates an α -face

Scheme 1. Schematic Representations of (a) the Major Conformation and (b) the Minor Conformation of the π -Complexes Composed of **1** and **2** or $2\cdot\text{LiI}$ in Diethyl Ether (See Text for Details)



complexation of the double bond in the case of the minor conformation (see Scheme 1b). Due to the severe signal overlaps, experimental differentiation of the three conformational states is not possible; however, minimization of steric hindrance between the α -face cuprate and **1** makes conformation I more probable than II or III.

The presented NOE data provide insight into the structural arrangement of π -complexes composed of cuprates and sterically demanding enones (see Scheme 1): (a) in the case of **1**, β -face as well as α -face π -complexes can be observed as intermediates, with the β -face complex being the major species; (b) the structural arrangement of the cuprate unit relative to the double bond is very similar in both intermediates, as indicated by identical scalar coupling patterns across copper; (c) upon π -complexation, the conformational preference of **1** in the major conformation changes in favor of structure II for the enone part and III for the cyclohexyl part. These results rationalize for the first time experimentally the observed stereochemistry of 1,4-methylations of methyloctalones by copper species, which exclusively yield β -methyloctalones.^{36,38,40} The exclusive formation of β -methyloctalones in combination with the β -face π -intermediate as the major species leads to the conclusion that, in the case of **1**, the more stable intermediate is also related to the energetically lower transition states, which was often doubted in cuprate reaction pathways. In addition, the energetic differences in the remaining reaction pathway, including several transition states around the Cu(III) intermediate, are sufficiently pronounced to suppress the conversion of the less populated α -face π -intermediate completely. Furthermore, the presented structure of the major β -face π -complex explains the previously reported effects of different substitution patterns of **1** on the yield of 1,4-methylation of **1**:^{37–40} e.g., substitution in position 7 reduces the yield of the product considerably; however, with substituents in position 7', no 1,4-methylation product is obtained.

Influence of Salt on π -Complexes of **1.** In the first NMR observation of π -complexes of **1**, Bertz and co-workers reported that, with 1 equiv of $2\cdot\text{LiI}$, the formation of π -complexes was not observed in diethyl ether at $-50\text{ }^\circ\text{C}$. Two isomeric enolates were detected, but their precise nature remained to be established.²² In later studies using rapid-injection NMR and 2-cyclohexenone, a ratio of 2 equiv of cuprate to 1 equiv of enone was reported for the formation of the observed π -complexes in THF.^{27,46} This is in striking contrast to the heterodimeric structure as a decisive reactive core for 1,4-addition reactions, which was many times proposed in theoretical studies and also in NMR spectroscopic investigations in THF.^{27,46} For heterodimers, it was also stated that the LiXLi^+ moiety ($\text{X} = \text{I}, \text{CN}$) has better carbonyl-complexing properties than $\text{Li}-\text{MeCuMe}-\text{Li}^+$. As a consequence, it should be possible to

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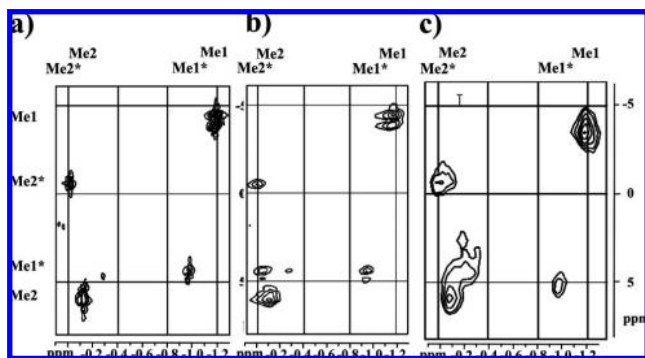


Figure 5. Sections of ^1H , ^{13}C HMQC spectra of the π -complexes composed of **1** and 2 equiv of (a) $2\cdot\text{LiI}$, (b) **2**, and (c) $2\cdot\text{LiCN}$ in diethyl ether at 180 K. The similarity of the chemical shift patterns indicates similar π -complexing cuprate units in all three cases. The increasing line widths (a < b < c) hint at different aggregation levels in solution.

detect appropriate π -intermediates at 1:1 ratios of enone to $2\cdot\text{LiX}$ (X = I, CN), with MeCuMe as π -complexing unit and LiXLi as carbonyl-complexing unit. However, in accordance with the experimental results reported by Bertz and Ogle in diethyl ether and THF,^{22,27,46} only small traces of cuprate enone π -complex were detected using **1** and 1 equiv of $2\cdot\text{LiX}$ (X = I, CN) in diethyl ether. With the enones **3a**, **3b**, and **4** (see below), no π -complex formation was observed at all with 1 equiv of $2\cdot\text{LiX}$ (X = I, CN).

In the case of 2 equiv of $2\cdot\text{LiX}$ (X = I, CN) reacting with **1**, π -complexes are observed which show signal patterns of the π -complexing cuprate units in their ^1H , ^{13}C HMQC spectra which are extremely similar to those of salt-free **2** (see Figure 5). Direct comparison of the three HMQC spectra shows that the positions of the four cross signals assigned to the major and minor conformations of the π -complexes are nearly identical in all spectra. In addition, the relative intensities of the four cross peaks remain stable upon varying the cuprate from **2** over $2\cdot\text{LiI}$ to $2\cdot\text{LiCN}$. Both observations indicate that, in the case of 2 equiv of **2** per enone, neither the presence of an additional equiv of salt nor the type of salt affects the structures of the π -complexing units of both conformations. Furthermore, the ratio between the two conformations is not affected.

In contrast to the stability of the chemical shifts, the presence and the type of salt severely influence the line widths of the signals. In general, broad line widths indicate either different aggregation levels in the three samples or different amounts of deviating conformations in fast exchange on the NMR time scale. But the previously reported different aggregation levels of cuprate reagents in diethyl ether^{17,20,47,48} and the diffusion measurements on the π -complexes with **3a**, **3b**, and **4** (see below) make the interpretation of the line widths in terms of aggregation levels highly probable. Since the short transversal relaxation times of the proton signals in the salt-containing sample do not allow for the measurement of reliable diffusion coefficients by NMR experiments, only a qualitative estimation of the aggregation of these π -intermediates with **1** in diethyl ether is possible. A comparison of the line widths in the three HMQC spectra suggests that the aggregation level of the intermediate with LiI is the lowest. The salt-free intermediate shows an increased aggregation level, and the intermediate with

LiCN exhibits by far the broadest line widths, hinting at the highest aggregation level within the three samples. Interestingly, these observations fit exactly to the aggregation behavior of the sterically hindered cuprate $(\text{Me}_3\text{SiCH}_2)_2\text{CuLi}$ in diethyl ether.²⁰ Furthermore, the disaggregation of the supramolecular structures or the composition of these higher aggregates could be connected to their reactivity in 1,4-addition reactions to enones.¹⁷

In THF, which supports the formation of solvent-separated ion pairs, considerably reduced aggregation levels are reasonable, and in the case of the free cuprate reagents, it was shown that the contact ion pairs exist only in very low concentrations.^{16,18} Thus, it is not in contrast to the results reported here that, recently, in THF, smaller aggregates were proposed as the main species for π -complexes of $2\cdot\text{LiX}$ (X = I, CN, MeCuMe) and cyclohexenone.⁴⁶ Interestingly, in this study in THF, no evidence for homodimeric π -complexes was found, despite the necessary 2:1 ratio of cuprate to enone. Therefore, a heterodimeric π -complex is explicitly stated with a Li–I–Li⁺ or a Li–CN–Li⁺ moiety as the carbonyl-complexing unit. An investigation of this open question for the π -intermediates in diethyl ether was not possible with the π -complexes composed of **1** and **2** or $2\cdot\text{LiX}$ (X = I, CN) due to overlapping signals in the region of the cuprate reagents, the existence of the two π -complex conformers, and the broad line widths. Therefore, it was necessary to simplify the intermediate spectra in order to investigate the carbonyl-complexing unit and to determine the aggregation tendencies of the salt-containing π -intermediates in diethyl ether.

Spectrum Simplification by Enantiomeric Intermediates. As outlined above, the complexation of the enone from the β -face and the α -face creates two diastereomeric cuprate enone π -complexes which appear in the NMR spectra as two sets of signals and complicate the interpretation of the spectra. A solution to this problem is the use of achiral enones. The β - and α -face complexation of achiral enones results in enantiomeric π -complexes that are not distinguishable by NMR spectroscopy in achiral solvents. This results in a simple but effective reduction of the intermediate signals, as shown in the HMQC spectra on the cuprate section of the π -complexes with chiral **1** and achiral **4** in Figure 6.

The ^{13}C spectra of the π -complexes also reveal, in the fingerprint region of the enone, that the number of π -complexes is reduced to one NMR-detectable type in the case of achiral enones (see Figure 7d compared to Figure 2a). By using structurally simple achiral enones and conventional low-temperature NMR, it is essential, for the observation of π -intermediates in diethyl ether, to reduce the reaction rate by substituent effects. Therefore, the sterically hindered and achiral enones **3a**, **3b**, and **4** (see Scheme 2) were chosen to investigate the structure of the carbonyl-complexing unit and the aggregation level of π -intermediates in 1,4-addition reactions. The π -complexes of **3a**, **3b**, and **4** with $2\cdot\text{LiX}$ (X = I, CN) were found to be stable for days, even in diethyl ether, by applying conventional low-temperature NMR spectroscopy at 170 K. In contrast, the sterically less hindered enones 3-methylcyclohexenone and cyclohexenone reacted too fast to allow for extensive two-dimensional NMR investigations. These results show that not only substituents in positions 3 and 4^{22,28,30,35} but also in position 6 support the stability of π -complexes. Furthermore, multiple substitution allows for the use of the small methyl groups as substituents and enones as substrates, even in diethyl ether. This solvent shows high reaction rates in 1,4-additions, supporting the formation of the reactive cuprate contact ion pairs

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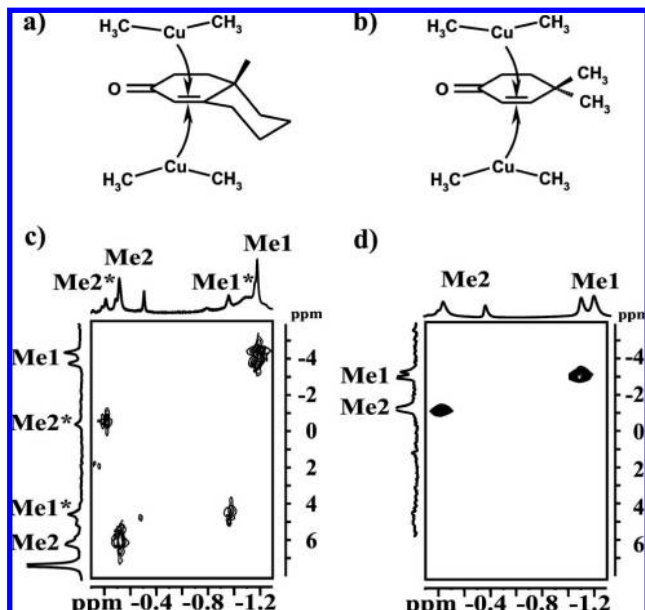


Figure 6. Schematic representations of the β - and α -face complexation of chiral (a) and achiral enones (b) and cuprate sections of the corresponding ^1H , ^{13}C HMQC spectra of the π -complexes composed of **1** and 2 equiv of **2** (c) or 4 and 2 equiv of **2**·LiI (d) in diethyl ether at 180 K. With achiral enones (shown as an example on **4**), enantiomeric π -complexes are formed which produce only one set of signals in the NMR spectra.

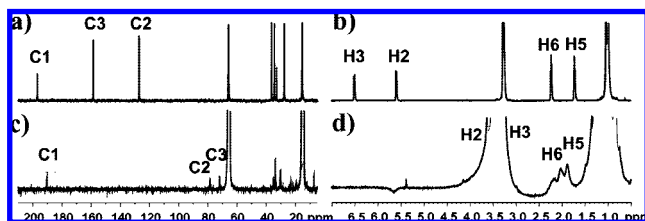
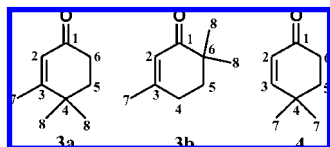


Figure 7. Typical change of ^{13}C spectra (a,c) and ^1H spectra (b,d) of free enones (a,b) upon π -complexation with 2 equiv of **2**·LiX (X = I, CN) (c, d), shown as an example for **4** and **2**·LiI in diethyl ether at 170 K.

Scheme 2. Selected Sterically Hindered, Achiral Enones That Build NMR-Observable, Enantiomeric Cuprate Enone π -Complexes in Diethyl Ether at 173 K



and aggregates. In THF, which provides slower reaction rates for 1,4-additions due to the preference for solvent-separated ion pairs,^{16,19} π -complexes of **2**·LiX (X = I, CN), even with unsubstituted cyclohexenone, were observed with the aid of rapid injection NMR.^{27,46}

In a small screening using the achiral enones **3a**, **3b**, and **4** and the salt-containing cuprates **2**·LiX (X = I, CN), for each combination only one set of π -complex signals was detected, as shown in Figure 7. In order to also detect the minor conformations or long-range NOE contacts, very high concentrations of **2**·LiX (0.7 M) were used initially. Due to the high aggregation tendency of **2**·LiCN in diethyl ether,²⁰ this concentration produced a gel-like consistency of the π -complexes at 170 K, unsuitable for NMR investigations. Therefore, following the procedure previously reported for the free reagent

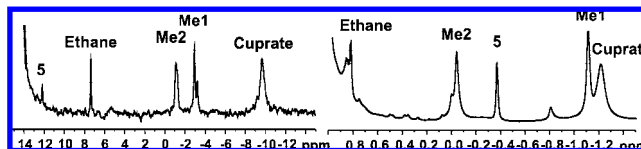


Figure 8. Characteristic signal patterns of the cuprates in π -intermediates, as shown, for example, on the ^{13}C spectrum (left) and ^1H spectrum (right) of **4** and 2 equiv of **2**·LiI in diethyl ether at 170 K.

2·LiCN,¹⁷ 6 equiv of THF was added to disaggregate the π -intermediates of **2**·LiCN. The resulting π -complexes were found to be appropriate for NMR studies and showed an aggregation level like those of **2**·LiI. In all six combinations, the formation of the resulting π -complexes can be easily seen on the basis of the characteristic changes of the chemical shift patterns in the ^1H and ^{13}C spectra of the enones (see Figure 7). For all π -complexes composed of **3a**, **3b**, and **4** and **2**·LiI or **2**·LiCN, upfield shifts $\Delta\delta^{13}\text{C}$ of about -12 , -44 , and -85 ppm were observed for the carbon signals of C1, C2, and C3, respectively. The corresponding changes in $\Delta\delta^1\text{H}$ are about 2.1 ppm for H2 and H3 (for the exact ^1H and ^{13}C chemical shifts of all six π -complexes, see Tables S4–S7 in the Supporting Information). Furthermore, there is no difference in the chemical shifts of any of the three enones depending on the cuprate **2**·LiI or **2**·LiCN. But the intermediate is only built in a 2:1 ratio (cuprate:enone) without any additional species like pure carbonyl complexes.

The cuprate signals of the six π -complexes also reveal some characteristic features. The cuprate chemical shift sections of the ^1H and the ^{13}C spectra in Figure 8 show that, in every complex, the typical methyl group signals of the π -complexing cuprate unit (Me1, Me2) are observed. Furthermore, a signal labeled “cuprate” is detected in each sample, its intensity depending strongly on the exact 2:1 ratio between cuprate and enone. The chemical shifts of these cuprate signals are, in principle, similar to the chemical shifts of the free reagents **2**·LiX (X = I, CN), respectively, but show deviations depending on the kind of enone (see Carbonyl-Complexing Moiety, below). Furthermore, in every intermediate spectrum, signals of substitution side reactions are observed which are caused by traces of methyl halides in the commercial MeLi solutions used for the synthesis of **2**·LiX (X = I, CN).¹² Thus, ethane is detected in each spectrum, and a transient symmetrical species **5**, whose unusual ^1H and ^{13}C chemical shift combination of ~ -0.3 and ~ 14 ppm, respectively, fits to the tetraalkyl Cu(III) species reported recently.^{10–12}

Aggregation Level of π -Intermediates. Recently, a direct correlation between the reactivity of cuprates in 1,4-addition reactions to enones and the aggregation level (for **2**·LiCN) or the aggregate structure (for **2**·LiI) of the free cuprate reagents was revealed.¹⁷ Therefore, the question of whether the trend of LiCN-containing cuprates forming larger oligomers²⁰ is also valid for the π -intermediates or whether the addition of enones leads to a disaggregation is very interesting in terms of structure–reactivity correlations.

The already mentioned gel-like consistency of π -complexes with **2**·LiCN shows the distinct tendency of LiCN-containing π -complexes to form higher aggregates. Regrettably, with the gel-like consistency, it was not possible to quantify the degree of aggregation. However, in accordance with our previous results for the free cuprates, a disaggregation of these larger aggregates is possible upon addition of THF. By using 6 equiv of THF, the aggregate sizes of the π -intermediates with **2**·LiCN were

Table 1. Average Diffusion Coefficients D ($\times 10^{-9}$ m²/s) of the Compounds Observed in the Spectra of the π -Complexes Composed of **2**·LiI or **2**·LiCN and **3a**, **3b**, or **4** in Diethyl Ether at 170 K

cuprate	Me1	Me2	enone	ethane
0.12 (± 0.08)	0.15 (± 0.03)	0.15 (± 0.04)	0.29 (± 0.09)	0.6 (± 0.2)

reduced, similar to those of π -complexes with **2**·LiI. These experimental results confirm the previous observation that the salt is involved in the connection of the different aggregate units.

In order to analyze which of the compounds observed in the intermediate spectra really participate in the π -complex aggregate, ¹H-diffusion measurements of the different intermediates were performed. Despite the improved sample preparation, the broad line widths and sometimes overlapping signals still hampered a detailed interpretation of the data. While clearly different and reproducible diffusion coefficients were found for the individual compounds, any trends reflecting the kind of salt or the type of enone were within the error range. Therefore, for each compound the average diffusion coefficient of all intermediates is given in Table 1.

The very similar diffusion coefficients of 0.12-, 0.15-, and 0.15×10^{-9} m²/s for cuprate, Me1, and Me2 in Table 1 clearly show that, in diethyl ether, all cuprate moieties in the intermediate samples participate in a large π -complex aggregate. A comparative diffusion experiment on pure **2**·LiCN under otherwise identical experimental conditions, particularly the addition of 6 equiv of THF, yielded a considerably larger diffusion coefficient of $(0.22 \pm 0.01) \times 10^{-9}$ m²/s. This indicates that the addition of enone does not disaggregate the oligomeric structures of the cuprate reagents but increases the size of the whole aggregate species.

In comparison to the cuprate signals, those of the enones show a larger average D value of 0.29×10^{-9} m²/s, with an error range of $\pm 0.09 \times 10^{-9}$ m²/s. At first glance this is surprising, since scalar couplings indicate covalent bonding between Me1/Me2 and the enone (see below). However, baseline-separated proton signals representing exclusively enones bound in the π -complex are not available. Therefore, contributions of the free enone or product falsify this D value, explaining the large error range. Furthermore, the significantly larger diffusion constant of 0.6×10^{-9} m²/s of ethane is appropriate to its size and confirms that ethane exists as individual species separated from the large π -complex aggregate, in agreement with the missing cross peaks in the NOESY spectra.

π -Complexing Moiety. In the π -complexes of **1**, the mixture of conformations necessitates ¹³C labeling of the cuprates and measurement of INEPT-INADEQUATE spectra to detect ¹³C, ¹³C scalar couplings between Me1/C3 and Me1*/C3*, respectively. This already represents progress compared to the previous two-fold labeling of cuprate and enone.^{23,33} The simplification of the spectra by using achiral enones and, in the case of **2**·LiCN, disaggregation by THF improved the quality of the spectra so much that, even without any isotope labeling, ¹H, ¹³C scalar couplings between the π -complexing cuprate moieties and the enones could be observed in ¹H, ¹³C HMBC spectra (see Figure 9a). The bent arrangement of the π -complexing cuprate unit in each sample was proved by cross signals between Me1 and C3, and the orientation of the two methyl groups was confirmed by ¹H, ¹H NOESY spectra (see Figure S1 in the Supporting Information). This shows the bent geometry of the π -complexing cuprate unit to be a general structural feature of these complexes that is unaffected by the

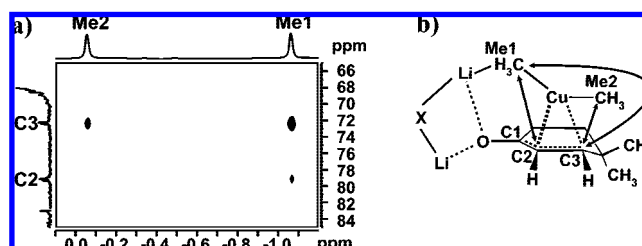


Figure 9. Section of a ¹H, ¹³C HMBC spectrum of **4** and **2**·LiCN, both at natural abundance, in diethyl ether at 170 K. The cross signals indicate ¹H, ¹³C scalar couplings across copper, as indicated by the arrows in panel b.

presence or kind of salt and the type of enone. Furthermore, for the π -complex composed of **4** and **2**·LiCN, additional cross peaks of reduced intensities were detected between Me2 and C3 and between Me1 and C2 for the first time, indicating additional but smaller scalar couplings across copper (see Figure 9). Previous investigations of ¹³C-labeled π -complexes with ynoates in THF reported only one observed $J_{C,C} = 12$ Hz between Me1 and C3; the other coupling constants were found to be below the spectral resolution.^{23,33} Since the relative signal intensities in HMBC spectra are proportional to the coupling constant, the improved sample preparation enables, without ¹³C labeling, the detection of additional structural parameters within the π -complexes. This allows for refining the structure of these π -complexes by theoretical calculations, as shown for Cu(III) intermediates.⁴⁹

Carbonyl Complexing Moiety. Considering the requirement of 2 equiv of MeCuMeLi per enone as a prerequisite for the detection of π -complexes, in addition to the π -complexing cuprate unit (Me1, Me2), an additional equivalent of MeCuMeLi is present in solution. The respective signals of these second cuprate units are labeled “cuprate”, and in principle their chemical shifts are similar to those observed for the free cuprate reagents in diethyl ether. Despite this similarity, the diffusion coefficients obtained for these species indicate unambiguously the participation of this moiety in the π -complex aggregate (see above). Now the question arises whether the species labeled “cuprate” is really the carbonyl-complexing moiety or otherwise included into the π -complex aggregate.

Table 2. ¹H and ¹³C (in Parentheses) Chemical Shift Differences $\Delta\delta$ (ppm)^a of the Cuprate Species Compared to the Free Cuprate Reagents at 170 K in Diethyl Ether

	3a	3b	4
2 ·LiI	0.09 (−0.1)	−0.19 (+0.1)	−0.01 (−0.1)
2 ·LiCN	0.03 (+0.3)	−0.12 (+1.0)	−0.01 (0.0)

^a $\Delta\delta$ (ppm) = $\delta(\text{free reagents } \mathbf{2}\cdot\text{LiX (X = I, CN)}) - \delta(\text{cuprate in } \pi\text{-intermediates})$.

In case the cuprate species is spatially close to the carbonyl group, the chemical shifts of the cuprate species should be affected by the type of enone, and especially steric hindrance around the carbonyl should lead to chemical shift deviations. The respective chemical shift differences observed for the six π -intermediates are given in Table 2, and they correspond very well to the steric demand of **3a**, **3b**, and **4**. The largest chemical shift perturbations are observed for **3b** with the two methyl substituents next to the carbonyl group (see Scheme 2). In contrast, the two methyl groups of **4**, which are oriented in the

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opposite direction of the carbonyl unit, cause nearly no deviations, and **3a** leads to medium chemical shift changes.

Surprisingly, neither NOE cross peaks nor exchange cross peaks between Me1/Me2 and cuprate have been detected in any of the six intermediates. In many samples this can be explained by the low intensity and the large line widths of the two signals in combination with the small chemical shift differences, leading to potential cross peaks very close to the diagonal. But also in samples with chemical shift differences of 0.29 ppm, no cross signals were detected. Furthermore, no NOE interactions between the cuprate moiety and an enone were detected in any of the intermediates. This might be explained by the large distances between cuprate protons and those of the enones. For instance, even in π -complexes with **3b**, which show the highest chemical shift differences and have a methylation pattern pointing roughly in the direction of the carbonyl group, the through-space distance between the methyl protons of **3b** and those of cuprate is still around 4.4 Å, according to model structures. This distance is quite large in terms of observable NOE contacts in the presence of quadrupole nuclei such as copper and lithium. Even in small peptides without additional leakage terms for cross-relaxation pathways, structural evidence from missing NOE contacts is taken into account only for distances lower than 3.5 Å.⁵⁰ Due to this discrepancy and the fact that, in previous experimental NMR investigations of π -complexes composed of **2**·LiX (X = I, CN) and cyclohexanone in THF, no evidence of a homodimeric π -complex was found,^{27,46} we investigated the principal carbonyl complexation properties of **2**, **2**·LiI, and **2**·LiCN on cyclohexanone.

Carbonyl Complexes of Cyclohexanone. A 1:1 ratio of **2** to cyclohexanone was chosen to generate competitive conditions for the salt and the cuprate units in terms of carbonyl complexation, comparable to the situation in the π -complexes. Besides this, identical experimental conditions were used, such as addition of 6 equiv of THF in the case of **2**·LiCN. In all three resulting complexes, a downfield shift of about 6 ppm, to 219.0 ppm, is observed for the carbon signal of the carbonyl group, in agreement with previous investigations of the influence of carbonyl complexation on ¹³C chemical shifts.^{22,51,52} The ¹H and ¹³C chemical shifts of the cuprate moieties in these complexes with cyclohexanone and as free reagents are given in Table 3.

Table 3. ¹H and ¹³C Chemical Shifts δ (ppm) of **2**, **2**·LiI, and **2**·LiCN as Free Reagents and as Complexes with Cyclohexanone in Diethyl Ether (Plus 6 Equiv of THF in the Case of **2**·LiCN) at 170 K

	2		2 ·LiI		2 ·LiCN	
	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$
complex	-1.13	-9.3	-1.17	-9.1	-1.06	-9.3
free reagent	-1.14	-9.6	-1.20	-9.5	-1.27	-9.9

Comparison of the chemical shifts in Table 3 provides additional information. Upon carbonyl complexation, significant chemical shift changes are observed for all three types of cuprates, with the largest chemical shift differences detected for **2**·LiCN. In the case of the salt units in **2**·LiI and **2**·LiCN, which complex the carbonyl groups of cyclohexanone exclusively, this would result in chemical shifts of the cuprate moiety

of **2**·LiI and **2**·LiCN similar to those of the free reagent **2**. The other extreme would be that the salt does not contribute at all to the aggregate around the carbonyl. The chemical shifts of **2**·LiI and **2**·LiCN would then be expected to be similar to those of the complex with **2**. The chemical shifts experimentally detected for the complexes with **2**·LiI and **2**·LiCN indicate a mixture of both extreme scenarios and suggest mixed aggregates composed of cuprate and salt units.

Furthermore, the aggregate sizes of the three complexes with cyclohexanone were investigated with the aid of diffusion experiments. Again, the diffusion coefficients obtained for the three complexes varied only within the error range. The average diffusion coefficient for the cuprate units is $(0.15 \pm 0.02) \times 10^{-9} \text{ m}^2/\text{s}$, and that of the cyclohexanone is $(0.13 \pm 0.06) \times 10^{-9} \text{ m}^2/\text{s}$. Interestingly, in these complexes, which are not able to perform 1,4-addition reactions and show only a small amount of 1,2-addition products in their spectra, the two diffusion coefficients of the cuprate and the enone are very similar. This corroborates the suggestion that, in the case of enone complexes, the deviating diffusion coefficients of the enones are caused by the free enone and/or product of the 1,4-addition reaction (see above).

The diffusion coefficients of the cyclohexanone complexes are very similar to those obtained for the cuprate species in the π -complexes. This result indicates that the absence of the double bond does not affect the aggregation level of the complexes significantly and that carbonyl-complexing aggregates are responsible for the formation of higher aggregates in diethyl ether. In this context, the identical chemical shift of 219.0 ppm for all three cuprate cyclohexanone complexes indicates two points: first, the salt-free cuprate **2** is able to complex the carbonyl group properly, and second, the strength of the carbonyl complexation is not affected by the presence or absence of salt in diethyl ether if the size of the aggregates is similar. These experimental observations are in excellent agreement with our previously proposed correlation between aggregate size and composition and reactivity of the cuprates.¹⁷

The combined results of diffusion coefficients, chemical shift data, and NOE investigations clearly show the potential of cuprate units to complex carbonyl groups. Furthermore, the cuprate moieties are shown to participate in the carbonyl-complexing aggregate which is responsible for the formation of higher aggregates in diethyl ether. However, carbonyl complexation exclusively by simple homodimeric units, as shown in theoretically calculated structures, is not supported by the experimental data. The sum of the presented experimental data indicates rather more complicated mixed aggregates composed of salt and cuprate moieties.

Conclusion

In order to rationalize the high diastereoselectivities of organocuprates in conjugate addition reactions to sterically demanding enones, the structural features of π -intermediates composed of Me₂CuLi or Me₂CuLi·LiX (X = I, CN) and 10-methyl- $\Delta^{1,9}$ -2-octalone in diethyl ether were investigated in detail. The formation of two intermediate cuprate enone π -complexes on both sides of the double bond is observed for the first time, with the β -face π -complex as the major species. In this major π -complex conformation, the steric hindrance between the cuprate moieties and the enone is minimized by a change of the preferred conformation of 10-methyl- $\Delta^{1,9}$ -2-octalone supporting the formation of the β -face π -complex. Furthermore, neither the structures nor the relative population

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of the two π -complexes is affected by the presence or the type of salt in the cuprate reagents, and the more stable intermediate is related to the stereochemistry of the product observed. These results rationalize, for the first time, the exclusive formation of β -methylcatalones experimentally.

Also in this work, a small NMR screening of intermediate π -complexes with $\text{Me}_2\text{CuLi}\cdot\text{LiX}$ ($X = \text{I}, \text{CN}$) and three different enones is presented to investigate the aggregate structure and the aggregation level of cuprate enone π -complexes as well as the influence of the type of salt on these intermediates. For this study, achiral enones are chosen, since the resulting enantiotopic π -complexes appear as single species in the NMR spectra and simplify the spectra so far that, for the first time, NMR diffusion experiments on cuprate intermediates are possible. The observed diffusion coefficients show that, in diethyl ether, all cuprate moieties in the intermediate samples participate in a large π -complex aggregate. Compared to pure cuprate reagents, the addition of the enone increases the size of the whole aggregate species. Similar aggregation trends of the free cuprate reagents and the π -complex species corroborate the previously proposed importance of the supramolecular structure for the reactivity of organocuprates. Comparative studies on all six cuprate enone intermediates and on carbonyl complexes with cyclohexanone and salt-free or salt-containing cuprates were performed to investigate the structure and the role of the π - and the carbonyl-complexing moieties. The refined π -complex preparation allowed for the detection of additional scalar couplings across copper, even in intermediates without any isotope labeling. The resulting screening shows that the bent geometry of the π -complexing cuprate unit is a general structural feature of these complexes, unaffected by the presence or kind of salt and the type of enone. Furthermore, diffusion experiments on cyclohexanone complexes show that the carbonyl-complexing aggregates are responsible for the formation of higher aggregates in diethyl ether. In principle, salt-free dimethylcuprate is able to complex the carbonyl group properly, and the participation of cuprate moieties in the carbonyl-complexing aggregate part is shown. However, the experimental data do not support a simple cuprate moiety for the carbonyl complexation but rather more complex mixed aggregates composed of salt and cuprate moieties. These results give, for the first time, an insight into the supramolecular structures of π -intermediates which are crucial for the reactivities of organocuprates in conjugate addition reactions.

Experimental Section

Synthesis and Sample Preparation of the π -Complexes. The samples were prepared using Schlenck technique with argon as inert

gas. The respective cuprate (0.4 mmol) was synthesized following the known procedure,^{53,54} and a trace (2–3 drops) of benzene was added as viscosity reference.¹⁷ The apparatus was then cooled to $-110\text{ }^\circ\text{C}$, and the enone (0.2 mmol in 0.4 mL of $\text{Et}_2\text{O}-d_{10}$) was added very slowly with stirring. The colorless cuprate solution turned orange and was poured into the NMR tube. In the case of the cyanocuprate samples, 6 equiv of THF was added prior to the transfer. At $-110\text{ }^\circ\text{C}$, the samples of the π -complexes are stable for 1–2 days; for longer storage, they should be frozen in liquid nitrogen. It is essential to constantly keep to temperatures below $-100\text{ }^\circ\text{C}$ while handling the NMR tubes. All enones **1**, **3a**, **3b**, and **4** build π -complexes which can clearly be recognized by the change of the color from colorless to orange.

NMR Data Collection and Processing. The NMR spectra were recorded on Bruker DRX500 and DMX500 spectrometers equipped with a 5 mm broadband triple-resonance Z-gradient probe (maximum gradient strength, 53.6 G/cm). All diffusion measurements were performed with a convection-suppressing pulse sequence⁵⁵ in pseudo-2D mode and processed with the Bruker software package t1/t2. For each experiment, 16 dummy scans and 32 actual scans were used, with a relaxation delay of 2 s and a diffusion delay of 60 ms. The shape of the gradients was sinusoidal, with a length of 2 ms, and the strength was varied in 10 increments (5–95%) of the gradient ramp created by Bruker software DOSY. The INEPT-INADEQUATE was assembled using an INEPT-transfer and an INADEQUATE-sequence. The spectra were carried out with 256 dummy scans and 128 actual scans, $\text{TD}(\text{F}2) = 2\text{k}$, $\text{TD}(\text{F}1) = 300$, and 1.5 s of relaxation delay for acquisition. The data were processed with $\text{SI}(\text{F}2) = 2\text{k}$ and $\text{SI}(\text{F}1) = 512$. The $^1\text{H}, ^1\text{H}$ NOESY measurements were carried out using 16 scans, $\text{TD}(\text{F}2) = 4\text{k}$, $\text{TD}(\text{F}1) = 300$, 8 s of relaxation delay for acquisition, and a mixing time of 1 s. The data were processed with $\text{SI}(\text{F}2) = 4\text{k}$ and $\text{SI}(\text{F}1) = 512$. The $^1\text{H}, ^{13}\text{C}$ HMQC spectra were recorded with 4 scans, $\text{TD}(\text{F}2) = 4\text{k}$, $\text{TD}(\text{F}1) = 256$, and a relaxation delay of 8 s. The data were processed with $\text{SI}(\text{F}2) = 4\text{k}$ and $\text{SI}(\text{F}1) = 512$. The $^1\text{H}, ^{13}\text{C}$ HMBC spectra were measured using 32 scans with $\text{TD}(\text{F}2) = 16\text{k}$ and $\text{TD}(\text{F}1) = 400$ and a relaxation delay of 6 s. Data were processed with $\text{SI}(\text{F}2) = 2\text{k}$ and $\text{SI}(\text{F}1) = 512$. The temperatures for all measurements were calibrated with methanol as internal temperature standard and were controlled by a Bruker BVT 3000 temperature unit.

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Supporting Information Available: Tables S1–S7 with the ^1H and ^{13}C chemical shift assignments of the π -complexes; $^1\text{H}, ^1\text{H}$ NOESY and $^1\text{H}, ^{13}\text{C}$ HMBC spectra showing the orientation of the π -complexing cuprate unit and its connectivity. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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