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Reaction Intermediates

Intermediates Formed in the Reactions of Organocuprates with α,β-Unsaturated Nitriles

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Abstract: Conjugate additions of organocuprates are of outstanding importance for organic synthesis. To improve our mechanistic understanding of these reactions, we have used electrospray ionization mass spectrometry for the identification of the ionic intermediates formed upon the treatment of $LiCuR_2{\cdot}LiCN$ (R = Me, Bu, Ph) with a series of α,β-unsaturated nitriles. Acrylonitrile, the weakest Michael acceptor included, did not afford any detectable intermediates. Fumaronitrile (FN) yielded adducts of the type $Li_{n-1}Cu_nR_{2n}(FN)_n^-$, $n = 1–3$. When subjected to fragmentation in the gas phase, these adducts were not converted into the conjugate addition products, but re-dissociated into the reactants. In contrast, the reaction with 1,1-dicyanoethylene furnished the products of the conjugate addition without any observable intermediates. Tri- and tetracyanoethylene proved to be quite reactive as well. The presence of several cyano groups in these substrates opened up reaction pathways different from simple conjugate additions, however, and led to dimerization and substitution reactions. Moreover, the gas-phase fragmentation behavior of the species formed from these substrates indicated the occurrence of single-electron transfer processes. Additional quantum-chemical calculations provided insight into the structures and stabilities of the observed intermediates and their consecutive reactions.

Introduction

Conjugate additions of organocuprates continue to be one of the most important methods for C–C bond formation in organic synthesis.[1] The mechanism of these reactions has always aroused keen interest. Early studies suggested the operation of single-electron transfer (SET) processes between the organocuprate and the Michael acceptor substrate.[2] As evidence for such processes has not materialized, however, they are no longer considered as likely reaction pathways, except for the most electrophilic Michael acceptors.[3] Instead, conjugate additions of organocuprates are now generally believed to proceed through addition/elimination sequences.[4] The central intermediate of this mechanism corresponds to an adduct of the two reactants, in which the copper center interacts with the C=C double bond of the Michael acceptor (Scheme 1). Experimental support for such species mainly comes from low-temperature NMR spectroscopy, which finds large upfield shifts of the resonances of the α- and β-carbon atoms of the Michael acceptor and a decrease in their coupling constants upon mixing with the organocuprate.[5–13] When α,β-unsaturated carbonyl compounds are used as substrates, NMR spectroscopy also points to secondary interactions between the oxygen atom of the carbonyl group and the Li^+ counterion of the organocuprate.[6,7,9–11] The formation of these adducts is reversible,[8,12] which suggests that the interaction between the π electrons of the C=C double bond and the Cu^I center is relatively weak. Accordingly, these adducts are often referred to as π complexes and considered intermediates distinct from the β-cuprio(III) enolates, in which the cuprate moiety forms a σ bond to the β-carbon atom. Quantum-chemical calculations suggest, however,[4,14,15] that this distinction is probably artificial and that the π complex, the cuprio enolate, as well as the cupracyclopropane should better be viewed as different resonance structures describing one and the same intermediate (Scheme 1).[16] Depending on the substituents of the organocuprate and the substrate, the relative weight of these three resonance structures will differ.[11]

The transfer of one of the organyl groups from the copper center to the β-carbon atom (often referred to as reductive elimination) furnishes a lithium enolate in the rate-limiting step of the overall sequence (Scheme 1).[4b] The lithium enolate gives the final addition product after aqueous work-up or can be trapped by another electrophile. For the adducts of α,β-unsaturated carbonyl compounds, the activation energy of the reductive elimination is relatively small ($E_A \approx 80\ \mathrm{kJ\,mol^{-1}}$),[17] which explains the need for low temperatures to intercept these fleeting intermediates.

Although the main features of the mechanism of conjugate additions of organocuprates are known, several important aspects require further attention. For instance, the reaction intermediates have been shown to form higher aggregates in diethyl ether, the solvent used most commonly for this type of reaction.[10b] So far, only a limited number of these aggregates have been characterized.[10] Likewise, the microscopic reactivity

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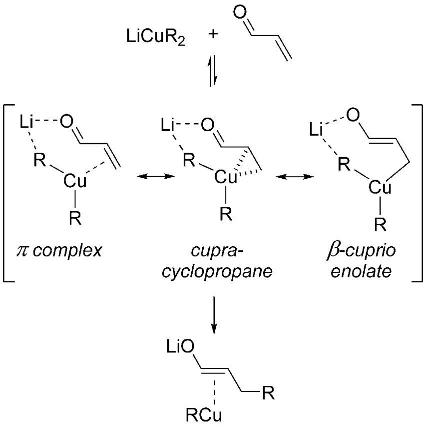

Scheme 1. Generally accepted mechanism for the conjugate addition of lithium organocuprates to acrolein. For simplification, only a single bridging Li center is drawn although the actual intermediates presumably contain polynuclear Li bridges.

of the intermediates has only been studied theoretically, but not experimentally. To shed more light on these problems, we here turn to electrospray ionization (ESI) mass spectrometry, which can provide information on organocuprates complementary to that obtained by NMR spectroscopy by selectively probing the charged species present in solution. Previous work has shown that this method is well-suited to detect and characterize even highly reactive organocopper ions.[18–20] Gas-phase experiments on mass-selected organocopper ions, moreover, make it possible to probe their intrinsic reactivity in unprecedented detail and without any interference from dynamic equilibria,[19–21] which severely complicate their analysis in solution.[22]

As the addition of organocuprates to α,β-unsaturated carbonyl compounds proceeds too fast to intercept the involved intermediates by ESI mass spectrometry, we employed the less reactive α,β-unsaturated cyanoethylenes ($C_2H_{4-n}(CN)_n$, $n=1$–4; Figure 1) as Michael acceptors. The systematic variation of the number and position of the cyano groups in these substrates permits us to fine-tune their electronic properties and probe the resulting effects on their reactivity toward prototypical cyanocuprates $LiCuR_2{\cdot}LiCN$ (R = Me, Bu, Ph) in THF as well as, for selected cases, in Et_2O. To aid in the interpretation of the ESI-mass spectrometric data, we also performed quantum-chemical calculations. The goal of these calculations was to obtain qualitative insight into the structures and stabilities of relevant complexes in the gas phase, but not to model the full reaction sequence of the probed systems.

Results

ESI mass spectrometry

Reactions of diorganylcuprates with acrylonitrile

Upon the addition of 1 equivalent of acrylonitrile, ethereal solutions of $LiCuR_2{\cdot}LiCN$ (THF: R = Me, Bu, Ph; Et_2O: Bu) turned yellow and yielded precipitates.[23] For the case of $LiCuMe_2{\cdot}LiCN$, negative-ion mode ESI mass spectrometry showed

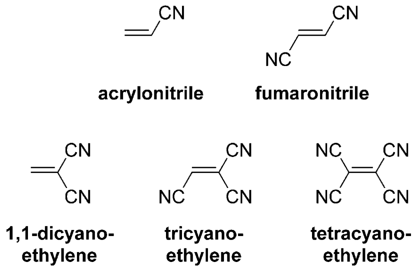

Figure 1. Substrates considered in the present work.

the partial consumption of the dimethylcuprate reactant and the formation of product ions with decreased Me/Cu ratios, such as $LiCu_2Me_3(CN)^-$ and $LiCu_2Me_2(CN)_2^-$ (Figure S1 in the Supporting Information). No reaction intermediates could be observed, however. In all other cases, only $Li_{n-1}Cu_nR_{2n}^-$ anions characteristic of solutions of the reactant diorganylcuprates were detected (Figures S2–S4 in the Supporting Information). In the positive-ion mode, exclusively $Li(solv)_n^+$ and $Li_2CN(solv)_n^+$ were found ($n=2$, 3 for solv = THF and $n=1$, 2 for solv = Et_2O, Figures S5 and S6 in the Supporting Information).

Reactions of diorganylcuprates with fumaronitrile

The reactions of $LiCuR_2{\cdot}LiCN$ (THF: R = Me, Bu, Ph; Et_2O: Bu) with 1 equivalent of fumaronitrile (FN) afforded dark-brown solutions. Their analysis by negative-ion mode ESI mass spectrometry showed the presence of several complexes of the type $Li_{n-1}Cu_nR_{2n}(FN)_n^-$, besides the organocuprate anions already known and mentioned above (Figure 2 and Figures S7–S13 in the Supporting Information). The fumaronitrile-containing complexes displayed a very limited macroscopic stability, which decreased in the order of Bu > Me > Ph. In line with their relatively higher stability, the complexes derived from dibutylcuprate, that is, $Li_{n-1}Cu_nBu_{2n}(FN)_n^-$, were particularly abundant and formed aggregates with $n=1$–3 (Figure 2). Upon changing the solvent from THF to Et_2O, the signal intensity of the largest aggregate ($n=3$) strongly increased, whereas that of the medium one ($n=2$) remained rather small (Figure 2). The reactions of $LiCuR_2{\cdot}LiCN$, R = Me and Ph, only produced the mononuclear complexes $CuR_2(FN)^-$ (Figures S7, S8, S12, and S13).

Gas-phase fragmentation of the complexes $Li_{n-1}Cu_nR_{2n}(FN)_n^-$ resulted in the liberation of fumaronitrile in all cases [Figure 3 and Figures S14–S17 in the Supporting Information; Eq. (1)]. For the lithium-containing species, $n=2$, 3 and R = Bu, these processes were accompanied by the hydrolysis of one or two butyl substituents in ion–molecule reactions involving traces of water present in the vacuum system of the mass spectrometer [Eq. (2) with $n=2$, 3, $x=0$–n, and $z=1$, 2]:

$$Li_{n-1}Cu_nR_{2n}(FN)_n^- \rightarrow Li_{n-1}Cu_nR_{2n}(FN)_{n-1}^- + FN \qquad (1)$$

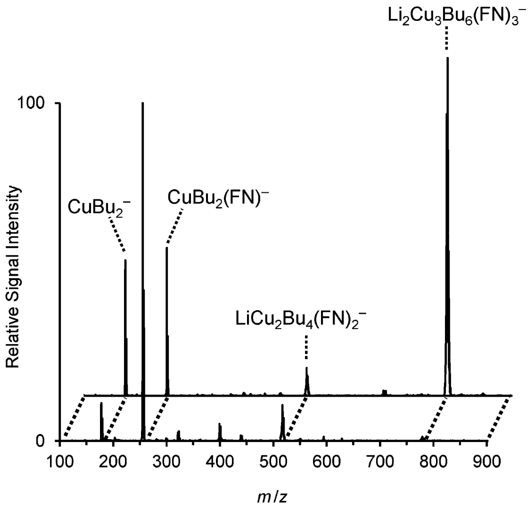

Figure 2. Negative-ion mode ESI mass spectrum of solutions of the products formed in the reaction of $\mathrm{LiCuBu_2{\cdot}LiCN}$ with fumaronitrile (FN) in THF (front) and $\mathrm{Et_2O}$ (back).

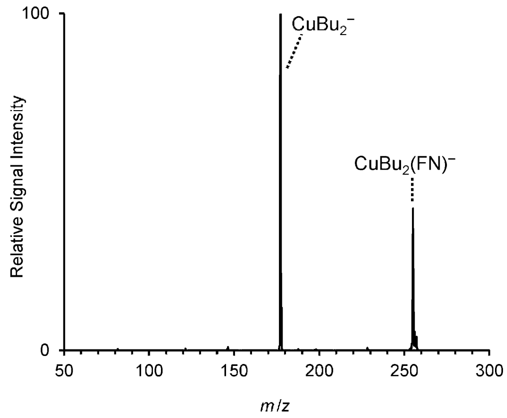

Figure 3. Mass spectrum of mass-selected $\mathrm{CuBu_2(FN)^-}$ (*m/z* 255) and its fragment ion produced upon collision-induced dissociation ($V_{\mathrm{exc}} = 0.21$ V).

$$\mathrm{Li}_{n-1}\mathrm{Cu}_n\mathrm{Bu}_{2n}(\mathrm{FN})_x^- + z\,\mathrm{H_2O} \rightarrow \mathrm{Li}_{n-1}\mathrm{Cu}_n\mathrm{Bu}_{2n-z}(\mathrm{OH})_z(\mathrm{FN})_x^- + z\,\mathrm{BuH} \tag{2}$$

In the positive-ion mode, mainly $\mathrm{Li(solv)}_n^+$ and $\mathrm{Li_2CN(solv)}_n^+$ ($n = 2$, 3 for solv = THF and $n = 2$ for solv = $\mathrm{Et_2O}$, Figures S18 and S19 in the Supporting Information), but also a few organocopper cations, such as $\mathrm{Li_2CuBu(OH)(Et_2O)_2^+}$ and $\mathrm{Li_2CuBu(CN)(Et_2O)_2^+}$ (Figure S19), were found.

Reactions of diorganylcuprates with 1,1-dicyanoethylene

When neat 1,1-dicyanoethylene was added to organocuprate solutions in THF or $\mathrm{Et_2O}$, a bead of solid material was formed instantly, thus already pointing to the high reactivity of this substrate. To overcome this difficulty, 1,1-dicyanoethylene was first dissolved in THF or $\mathrm{Et_2O}$, respectively, before its addition to the organocuprates. Upon analysis by negative-ion mode ESI mass spectrometry, the solutions in THF showed the complete or partial consumption of the reactant organyl-rich cuprates and the formation of their cyanide-containing counterparts (Figures S20–S24 in the Supporting Information), whereas no anions indicative of a reaction were found in $\mathrm{Et_2O}$ (Figure S25 in the Supporting Information). For the reaction of $\mathrm{LiCuBu_2{\cdot}LiCN}$ in THF, we detected complexes that we assigned as $\mathrm{LiCu_2Bu_2(C(CN)_2{-}CH_2Bu)(CN)^-}$ and $\mathrm{Li_2Cu_2Bu_2(C(CN)_2{-}CH_2Bu)(CN)_2^-}$ (Figures S21–S23). These assignments were based on their gas-phase fragmentation, which led to the loss of CuBu and $\mathrm{Li_2(C(CN)_2{-}CH_2Bu)(CN)}$ [Eqs. (3) and (4); Figures S26 and S27 in the Supporting Information], respectively. The reaction of the organocuprates with 1,1-dicyanoethylene, thus, apparently proceeded all the way to the addition products with the formation of new carbon–carbon bonds.

$$\mathrm{LiCu_2Bu_2(C(CN)_2{-}CH_2Bu)(CN)^-} \rightarrow \mathrm{LiCuBu(C(CN)_2{-}CH_2Bu)(CN)^-} + \mathrm{CuBu} \tag{3}$$

$$\mathrm{Li_2Cu_2Bu_2(C(CN)_2{-}CH_2Bu)(CN)_2^-} \rightarrow \mathrm{Cu_2Bu_2(CN)^-} + \mathrm{Li_2(C(CN)_2{-}CH_2Bu)(CN)} \tag{4}$$

The inferred presence of addition products was also clear from the positive-ion mode ESI mass spectra. Besides cations of the type $\mathrm{Li(solv)}_n^+$ and $\mathrm{Li_2(CN)(solv)}_n^+$, $n = 2$, 3, these spectra showed complexes of the composition $\mathrm{Li_2(C(CN)_2{-}CH_2R)(solv)_2^+}$ (THF: R = Me, Bu, Ph; $\mathrm{Et_2O}$: R = Bu; Figure 4 and Figures S28–S34 in the Supporting Information). The observation of these ions unambiguously proved the occurrence of carbon–carbon bond formation. Upon fragmentation in the gas phase, the $\mathrm{Li_2(C(CN)_2{-}CH_2R)(solv)_2^+}$ cations mainly lost one solvent molecule or exchanged it for one water molecule (Figures S35–S38 in the Supporting Information).[24]

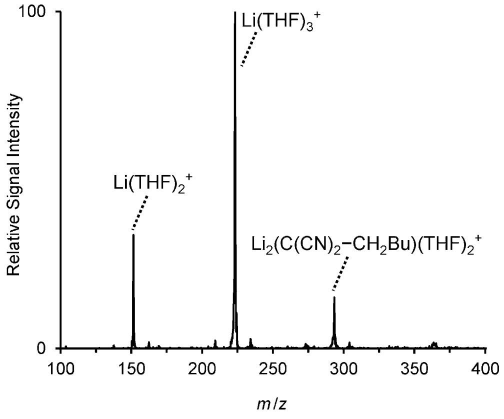

Figure 4. Positive-ion mode ESI mass spectrum of a solution of the products formed in the reaction of $\mathrm{LiCuBu_2{\cdot}LiCN}$ with 1,1-dicyanoethylene in THF.

Reactions of diorganylcuprates with tricyanoethylene

Reactions of diorganylcuprates with tricyanoethylene in THF afforded orange-brown solutions (the analogous experiments in $\mathrm{Et_2O}$ could not be performed because the corresponding sample solutions caused immediate clogging of the ESI capillary). Analysis by negative-ion mode ESI mass spectrometry first identified cyanide-containing organocuprates, such as

$Cu_2R_2(CN)^-$ and $LiCu_2R_2(CN)_2^-$ (R = Me, Bu, Ph), which indicated the consumption of the reactant diorganylcuprates (Figures S39–S45 in the Supporting Information). In addition, the reactions with the dialkylcuprates $LiCuR_2{\cdot}LiCN$, R = Me, Bu, afforded copper-free anions $X_R^- = [HC_4(CN)_5R]^-$, which must have originated from dimerization of the substrate. For the reaction of $LiCuBu_2{\cdot}LiCN$, we also observed an organocuprate complex that incorporated the X_R^- species, namely $LiCuBu(CN)X_{Bu}^-$. Upon gas-phase fragmentation, this ion afforded a multitude of fragment ions (Figure S46 in the Supporting Information). Besides the formation of smaller cuprate(I) anions as well as free X_{Bu}^-, the fragmentation also resulted in the loss of a butyl radical [Eq. (5) with R = Bu]. To confirm this unusual type of reactivity, we conducted control experiments with $LiCuHex_2{\cdot}LiCN$. These experiments afforded analogous ESI mass spectra, including $LiCuHex(CN)X_{Hex}^-$ (Figures S47–S49 in the Supporting Information), which also expelled a hexyl radical upon gas-phase fragmentation [Eq. (5) with R = Hex], among other fragmentation channels (Figure S50 in the Supporting Information).

$$LiCuR(CN)X_R^- \rightarrow LiCu(CN)X_R^- + R^{\bullet} \tag{5}$$

Positive-ion mode ESI mass spectrometry of solutions of diorganylcuprates treated with tricyanoethylene resulted in the detection of $Li(THF)_n^+$ and $Li_2(CN)(THF)_n^+$, $n = 2, 3$ (Figure S51 in the Supporting Information).

Reactions of diorganylcuprates with tetracyanoethylene

Organocuprates dissolved in THF or Et_2O reacted with tetracyanoethylene to afford light-yellow solutions, along with precipitates. Negative-ion mode ESI mass spectrometry again detected a multitude of cyanide-containing cuprate anions, indicating the consumption of the diorganylcuprate reagents (Figure 5 and Figures S52–S60 in the Supporting Information). Moreover, additional ions assigned as Y_R^- (R = Me, Bu, Ph), $LiCuR(CN)Y_R^-$ (R = Bu, Ph), and $LiCuR_2Y_R^-$ (R = Bu in THF) were observed. The measured *m/z* ratios and isotope patterns of the ions Y_R^- upon first sight seemed to point to their identities as simple adducts of the organocuprate anions $LiCuR_2(CN)^-$ and tetracyanoethylene (Figure 6, top). Gas-phase fragmentation of Y_R^- did not result in the release of tetracyanoethylene, as one would expect in this case, however, but instead led to the loss of $R(NC)C{=}C(CN)_2$ [Figures S61–S63 in the Supporting Information; Eq. (6)]:

$$Y_R^- \rightarrow LiCuR(CN)_2^- + R(NC)C{=}C(CN)_2 \tag{6}$$

This finding suggested that the formation of Y_R^- involved the cleavage of one of the C–CN bonds of the original tetracyanoethylene. Thus, Y_R^- could be an adduct of a cuprate anion with a $R(NC)C{=}C(CN)_2$ moiety (Figure 6, bottom left) or the product of the insertion of the cuprate into one of the C–CN bonds of the substrate (Figure 6, bottom right). In the first case, the observed release of $R(NC)C{=}C(CN)_2$ would simply correspond to the dissociation of the adduct whereas in the second case, it would be brought about by a reductive elimination.

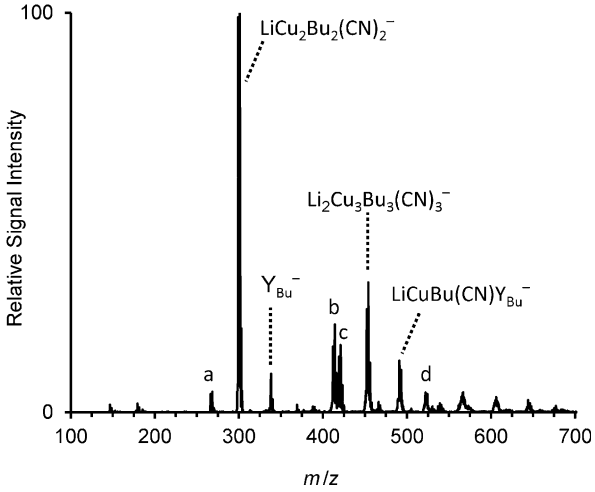

Figure 5. Negative-ion mode ESI mass spectrum of a solution of the products formed in the reaction of $LiCuBu_2{\cdot}LiCN$ with tetracyanoethylene in THF, a = $Cu_2Bu_2CN^-$, b = $Li_2Cu_3Bu_2(OH)(CN)_3^-$ (resulting from in-trap hydrolysis of $Li_2Cu_3Bu_3(CN)_3^-$), c = $LiCu_3Bu_3(CN)_2^-$, d = $LiCuBu_2Y_{Bu}^-$. For possible structural assignments of Y_{Bu}^-, see Figure 6.

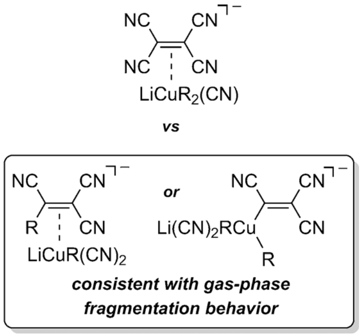

Figure 6. Possible structures of Y_R^-.

The higher homologues $LiCuR(CN)Y_R^-$ (R = Bu and Ph) showed analogous reactivity and mainly produced $Li_2Cu_2R_2(CN)_3^-$ upon gas-phase fragmentation [Figures S64 and S65 in the Supporting Information; Eq. (7) with R = Bu or Ph, respectively]. In the case of the butyl-containing species, the expulsion of a butyl radical again was also observed, however, among other decomposition channels (Figure S64 in the Supporting Information). Control experiments with the analogous hexyl-containing complex (Figures S66–S68 in the Supporting Information) showed a very similar behavior (Figures S69 and S70 in the Supporting Information).

$$LiCuR(CN)Y_R^- \rightarrow Li_2Cu_2R_2(CN)_3^- + R(NC)C{=}C(CN)_2 \tag{7}$$

In the positive-ion mode, only $Li(solv)_n^+$ cations were detected ($n = 2, 3$; Figures S71 and S72 in the Supporting Information).

Quantum-chemical calculations

Adducts of dimethylcuprate and α,β-unsaturated nitriles

In all the cases examined, the quantum-chemical calculations found the reactions of the dimethylcuprate anion with the α,β-unsaturated nitriles to afford adducts without the involvement of any barriers. The stability of these adducts increased as a function of the number of cyano groups present in the Michael acceptor (Table 1). For acrylonitrile, that is, the substrate with only a single cyano group, the reaction enthalpy was calculated to be only moderately negative such that the adduct formation was predicted to be slightly endergonic at room temperature. Given its apparent low stability, we did not consider the adduct of $\mathrm{CuMe_2^-}$ and acrylonitrile any further. In the case of tricyanoethylene, the calculations identified two different isomers of the adduct with $\mathrm{CuMe_2^-}$, which were quite similar, however, differing mainly in the orientation of the methyl groups (Figure S73 in the Supporting Information).

Table 1. Reaction energies, enthalpies, and Gibbs enthalpies (in kJ mol^{-1}, relative to the separated reactants) of the adduct formation from $\mathrm{CuMe_2^-}$ and the α,β-unsaturated nitrile substrates calculated at the B3LYP/6-31G*/MDF level.

Substrate	ΔE (0 K)	ΔH (298 K)	ΔG (298 K)
acrylonitrile	−22.0	−23.1	20.6
fumaronitrile	−85.4	−86.4	−44.2
1,1-dicyanoethylene	−86.2	−86.5	−43.7
tricyanoethylene[a]	−142.5	−142.9	−98.0
tetracyanoethylene	−195.4	−195.8	−151.3

[a] Values calculated for first isomer (values calculated for second isomer: −142.7/−143.3/−96.2 kJ mol^{-1}).

The formation of the adducts was accompanied by a bending of the $\mathrm{CuMe_2^-}$ unit (the free anion is linear) and significant increases in the C1–C2 bond lengths (Figure 7 and Table 2). These increases varied only little among the adducts derived from the different substrates. In the cases of fumaronitrile and tetracyanoethylene, the two carbon atoms C1 (the α-carbon) and C2 (the β-carbon) of the Michael acceptor interacted with the copper center in identical ways. In contrast, the two other substrates bound the copper in an asymmetric fashion in that the more highly substituted carbon atom, that is, C1, was at a larger distance to the metal center than the other. This asymmetry was particularly pronounced for the adduct of $\mathrm{CuMe_2^-}$ and 1,1-dicyanoethylene.

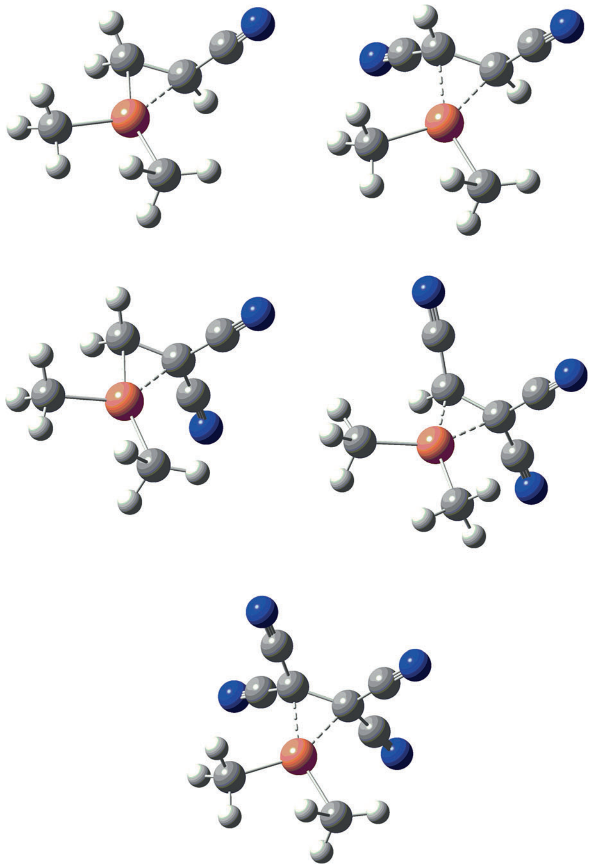

Figure 7. Structures of the adducts formed from $\mathrm{CuMe_2^-}$ and the α,β-unsaturated nitriles calculated at the B3LYP/6-31G*/MDF level.

The weakening of the C1–C2 bonds of the Michael acceptors upon adduct formation was also reflected in a marked decrease in the bond orders according to our NBO (natural-bond order) analysis (Table 3). The bond orders of approximately 1 determined for the adducts suggest that the π bond between the two carbon atoms is largely broken. Moreover, the carbon atoms C1 and C2 do not interact with the copper center equally, but the latter one binds to it more strongly. Again, this asymmetry is particularly conspicuous for the adduct of 1,1-dicyanoethylene, in which the C2–Cu bond almost equals a full single bond, whereas the C1–Cu bond is virtually non-existent.

Table 2. Bond lengths r [pm] of selected bonds of free substrates and their $\mathrm{CuMe_2^-}$ adducts calculated at the B3LYP/6-31G*/MDF level.

Substrate	Free substrate	Adduct of $\mathrm{CuMe_2^-}$ and substrate			Difference
	r(C1–C2)	r(C1–C2)	r(C1–Cu)	r(C2–Cu)	Δr(C1–C2)
fumaronitrile	135	146	201	201	11
1,1-dicyanoethylene	135	146	212	195	11
tricyanoethylene	136	148[a]	207[a]	199[a]	12
tetracyanoethylene	137	150	204	204	13

[a] Identical values calculated for both isomers.

Table 3. Atom–atom net linear NLMO/NPA bond order of selected bonds of the free substrates and their $CuMe_2^-$ adducts derived from NBO analysis at the B3LYP/6-31G*/MDF level.

Substrate	Free substrate	Adduct of $CuMe_2^-$ and substrate		
	C1–C2	C1–C2	C1–Cu	C2–Cu
fumaronitrile	1.90	1.06	0.32	0.41
1,1-dicyanoethylene	1.71	1.03	0.13	0.91
tricyanoethylene	1.74	1.00[a]	0.22[b]	0.33[a]
tetracyanoethylene	1.79	1.01	0.20	0.19

[a] Identical values calculated for both isomers. [b] 0.21 calculated for the other isomer.

Consecutive reactivity

For a successful conjugate addition, the reaction must not halt at the stage of the adduct between $CuMe_2^-$ and the Michael acceptor, but continue and transfer one of the methyl groups to the latter. As exemplified for the reaction with 1,1-dicyanoethylene in the gas phase (Figure 8), the transition structure associated with this transfer features a loosened Cu–Me bond. Energetically, this transition structure still is more favorable than the separated reactants because the electron-poor Michael acceptor benefits from the interaction with the anionic cuprate. Entropically, however, the transition structure is less favorable owing to its geometric constraints. The following intermediate marks the successful transfer of the methyl group to the β-carbon atom of the Michael acceptor, whereas the copper center binds to its α-carbon atom. This complex is significantly more stable than the primary adduct between $CuMe_2^-$ and 1,1-dicyanoethylene. Elimination of neutral CuMe finally leads to the anionic conjugate addition product.

For the reactions involving the other substrates, qualitatively similar reaction paths and transition structures (Figure S74 in the Supporting Information) were found. As the entropic contributions were comparable in all cases, the relative energies of the transition structures associated with the transfer of the methyl group were largely determined by energetic factors and the strength of the initial interaction between the cuprate and the α,β-unsaturated nitrile. Accordingly, the Gibbs enthalpy calculated for this decisive transition structure strongly decreased upon adding more cyano groups to the ethylene core of the substrates (Table 4). At the same time, the substitution pattern also played a role, the transition structure derived from 1,1-dicyanoethylene being more stable than that derived from fumaronitrile.

Table 4. Energies, enthalpies, and Gibbs enthalpies (in kJ mol^{-1}, relative to the separated reactants) of the transition structures associated with the transfer of the methyl group from $CuMe_2^-$ to the α,β-unsaturated nitrile substrates calculated at the B3LYP/6-31G*/MDF level.

Substrate	$\Delta E^{\neq}$	$\Delta H^{\neq}$ (298 K)	$\Delta G^{\neq}$ (298 K)
acrylonitrile	62.8	60.1	106.7
fumaronitrile	27.6	25.2	72.5
1,1-dicyanoethylene	−21.7	−23.7	23.8
tricyanoethylene[a]	−45.0	−46.9	1.7
tetracyanoethylene	−62.4	−63.9	−17.1

[a] Identical values calculated for both isomers.

As the experiments demonstrated, alternative consecutive reaction pathways are feasible and apparently predominate for the reactions with tri- and tetracyanoethylene. To understand the inferred cleavage of one of the C–CN bonds in the latter case, we considered two different mechanisms. The first one involves the transfer of one of the methyl groups to the β-carbon atom of the substrate, as it also occurs for a regular Michael-type addition, followed by the 1,2-elimination of $MeCu(CN)^-$ and the formation of an adduct (Figure S75 in the Supporting Information). The barrier of this elimination was predicted to be smaller than that of the initial transfer of the methyl group, suggesting that it indeed would be relatively facile. The second mechanism involves the insertion of the $CuMe_2^-$ unit into one of the C–CN bonds of the substrate to afford a Cu^{III} complex (Figure S76 in the Supporting Information). The barrier of this reaction was calculated to be similar to that of the transfer of one methyl group of $CuMe_2^-$ to the

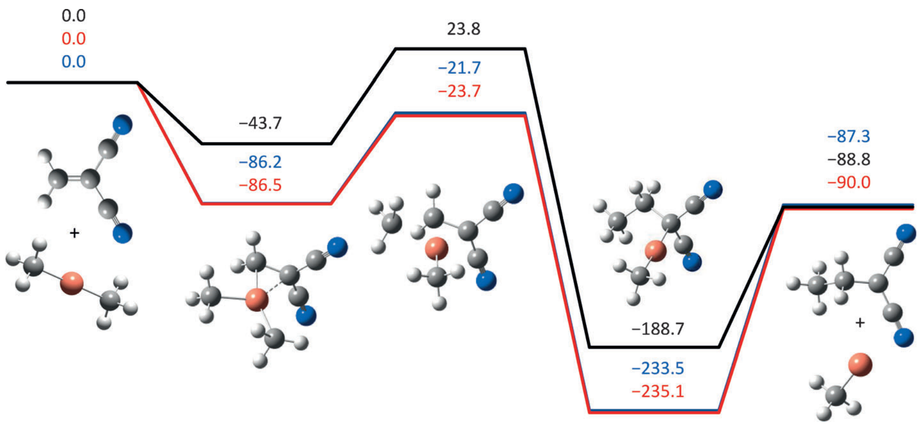

Figure 8. Schematic potential energy surfaces (blue: energy at 0 K, red: enthalpy at 298 K, black: Gibbs enthalpy at 298 K) together with the structures of the reactants, transition states, intermediates, and products of the reaction of $CuMe_2^-$ with 1,1-dicyanoethylene calculated at the B3LYP/6-31G*/MDF level and their relative stabilities [kJ mol^{-1}].

β-carbon atom of the Michael acceptor, indicating that it could well compete with this transfer reaction. The resulting Cu^{III} complex could also undergo a reductive elimination to afford the same adduct that is produced by the 1,2-elimination of $MeCu(CN)^-$ (Figure S77 in the Supporting Information). This adduct is apparently rather unstable and may spontaneously dissociate into $Me(NC)C{=}C(CN)_2$ and free $MeCu(CN)^-$.

Discussion

Primary adducts of diorganylcuprates and α,β-unsaturated nitriles

The present quantum-chemical calculations show that $CuMe_2^-$ and α,β-unsaturated nitriles spontaneously form adducts even without the stabilizing effect of secondary interactions via bridging Li^+ counterions. As mentioned above, such secondary interactions are considered to be a prerequisite for the conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds (Scheme 1).[4] Presumably, they are less important for the addition to the corresponding nitriles because nitrogen has a lower Li^+ affinity than oxygen.[25] However, adducts stable at room temperature are predicted to form only if at least two cyano groups are attached to the carbon–carbon double bond of the Michael acceptor, in line with previous NMR spectroscopic experiments.[11c]

The calculated changes in the bond lengths and orders upon adduct formation can be well understood as the result of the transfer of electron density from the $CuMe_2^-$ moiety to the Michael acceptor. As expected, the adducts can thus be viewed as π complexes, cupracyclopropanes, or β-cuprio nitrile anions (Figure 9). For the symmetric Michael acceptors, the former two descriptions are more appropriate, whereas for the asymmetric ones and among these, in particular, for 1,1-dicyanoethylene, the latter description better captures the bonding situation in the adduct.

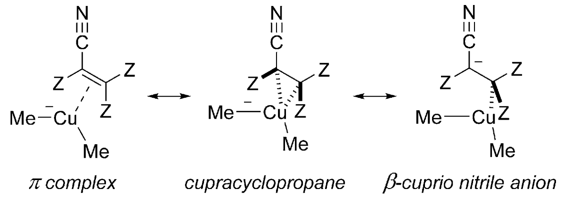

Figure 9. Different possible descriptions of the adducts of $CuMe_2^-$ and α,β-unsaturated nitriles (Z = H, CN).

The experimentally observed adducts between the organocuprate anions and fumaronitrile include not only mononuclear, but also di- and trinuclear complexes with exactly one molecule of fumaronitrile per copper center. The relative abundances of the adducts $Li_{n-1}Cu_nBu_{2n}(FN)_n^-$ closely resembled those of the free butylcuprate complexes $Li_{n-1}Cu_nBu_{2n}^-$ (high relative ESI signal intensities for the mono- and trinuclear complexes in THF, low signal intensity for the dinuclear ones).[19] This finding suggests that the structures of the organocuprate aggregates are not strongly perturbed by the coordination of fumaronitrile, but that they preserve the chain-like and trigonal-prismatic geometries previously deduced for free $LiCu_2R_4^-$ and $Li_2Cu_3R_6^-$ anions, respectively (Figure 10).[19d]

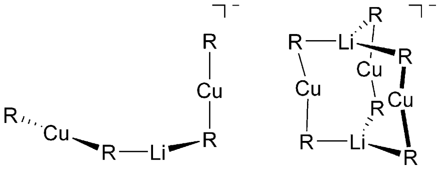

Figure 10. Putative structures of $LiCu_2R_4^-$ and $Li_2Cu_3R_6^-$ anions observed by ESI mass spectrometry.[19d]

Like the free organocuprate complexes $Li_{n-1}Cu_nR_{2n}^-$,[19b] the adducts $Li_{n-1}Cu_nBu_{2n}(FN)_n^-$ show a pronounced solvent effect. As for the former, the shift toward higher aggregation states observed upon changing the solvent from THF to the less polar Et_2O can be explained by the poorer ability of the latter to solvate Li^+ ions and the resulting prevalence of contact ion pairs.[19b] This parallel again highlights the close similarities between free organocuprates and their adducts with fumaronitrile.

Consecutive reactions

Once the primary adducts of organocuprates and α,β-unsaturated nitriles are formed, they can either undergo the back reaction and re-dissociate into the reactants or they can transfer one organyl substituent to the β-carbon atom of the substrate. Clearly, the back reaction becomes less favorable if the cuprate anion interacts with the Michael acceptor more strongly. The gas-phase fragmentation experiments unambiguously demonstrate that for the fumaronitrile adducts the re-dissociation completely wins over the organyl transfer and further consecutive reactions. According to the calculations, the barrier associated with the transfer of a methyl group from $CuMe_2^-$ to the β-carbon atom of the substrate is significantly lower for the case of 1,1-dicyanoethylene than for that of fumaronitrile. This assessment is fully supported by the experiments, which proved the occurrence of the organyl transfer to 1,1-dicyanoethylene by detecting the final conjugate addition products. Presumably, the lower barrier associated with the reaction of 1,1-dicyanoethylene is related to better stabilization of the resulting product complex, in which the high negative charge density at the carbon atom bound to the copper center can be well delocalized by two neighboring electron-withdrawing cyano groups. The higher (electrophilic) reactivity of 1,1-dicyanoethylene in comparison to fumaronitrile has also been noted for other reaction types and analyzed theoretically.[26]

For tri- and tetracyanoethylene, the stronger interactions with the organocuprate anions further favor organyl transfer reactions over the re-dissociation of the primary adducts. As the experiments show, these reactions are no simple conjugate additions, but correspond to more complicated pathways involving the release of one cyano group from the substrate. For the reaction of $CuMe_2^-$ with tetracyanoethylene in the isolated gas phase, the calculations identified two feasible mechanisms for the replacement of a cyano group by a methyl substituent. In solution, aggregation, counterion, and solvation effects may possibly open additional pathways for this substitution.

Finally, several of the intermediates formed in the reactions of $CuBu_2^-$ and $CuHex_2^-$ with tri- and tetracyanoethylene lost butyl and hexyl radicals, respectively, upon gas-phase fragmentation. This behavior differs from that of all of the cuprate complexes that we have investigated previously and points to a specific effect of tri- and tetracyanoethylene. Most likely, these electron-poor substrates can withdraw single electrons from the alkylcuprate reagents, thus producing reactive alkylcopper(II) intermediates, which can then re-form organocopper(I) complexes by the expulsion of alkyl radicals.[27] Indeed, SET processes are believed to occur in the reactions of organocuprates with highly activated alkenes.[3,14a] The present results are fully in line with this hypothesis.

Conclusions

By using ESI mass spectrometry and quantum-chemical calculations, we have identified and characterized several intermediates formed in the reactions of organocuprates $LiCuR_2{\cdot}LiCN$ (R = Me, Bu, Ph) with α,β-unsaturated nitriles in THF and Et_2O. Of particular interest was the observation of adducts containing up to three copper centers and the same number of fumaronitrile molecules. The relative abundance of these species resembled those of the free organocuprate reagents, suggesting that their structures were largely retained upon coordination of the substrate. Moreover, the adducts showed a similar solvent dependence as the free organocuprates, with larger aggregation states predominating in the less polar Et_2O. The interaction between $CuMe_2^-$ and fumaronitrile can be described either as the binding in a π complex or in a cupracyclopropane. Its strength is calculated to be relatively low such that the adduct more easily re-dissociates into the reactants than undergoes a methyl transfer from the cuprate to the Michael acceptor. In line with this prediction, gas-phase fragmentation of the adducts resulted in the loss of fumaronitrile.

According to the theoretical calculations, the reactions of the organocuprates with 1,1-di-, tri-, and tetracyanoethylene also proceeded via analogous primary adducts, but did not halt at this stage, as the ESI mass spectrometric experiments also suggested. Whereas 1,1-dicyanoethylene underwent a simple conjugate addition, tri- and tetracyanoethylene lost one of their cyano groups in a dimerization or a substitution by one of the organyl residues of the cuprate reagent, respectively. In addition, the reactions of these highly activated Michael acceptors apparently also involved SET processes.

By varying the number and position of cyano groups attached to a carbon–carbon double bond, it is thus possible to fine-tune the reactivity of prototypical Michael acceptors. The use of these substrates in organocuprate conjugate addition reactions makes it possible to intercept intermediates at various stages along the reaction coordinate and thereby helps to complete our mechanistic understanding of these extraordinarily important transformations.

Experimental and Theoretical Section

Sample preparation

Standard Schlenk techniques were employed in all cases. THF and Et_2O were distilled from sodium/benzophenone. Copper cyanide was dried by repeated heating under vacuum at 350 °C. Solutions of MeLi (1.54 м) in Et_2O, BuLi (2.20–2.64 м) in cyclohexane, PhLi (1.76 м) in Bu_2O, and HexLi (2.1 м) in hexane were used as purchased. Their exact concentrations were determined by titration with 1,3-diphenyl-2-propanone tosylhydrazone.[28] Solutions of $LiCuR_2{\cdot}LiCN$ were prepared by treating suspensions of CuCN in THF or Et_2O, respectively, with 2 equivalents of RLi under argon at −78 °C. After stirring at this temperature for 0.2–1 h, the CuCN was completely dissolved. The α,β-unsaturated nitriles were added either neat or as an ethereal solution.

ESI mass spectrometry

Sample solutions of $c \approx 25$ mм were filled into a gas-tight syringe and continuously administered into the ESI source of an HCT quadrupole ion trap mass spectrometer (Bruker Daltonik) by a syringe pump (17–67 μL min^{-1}). The ESI source was operated with N_2 as the sheath and drying gas (0.7 bar backing pressure and 5 L min^{-1} flow rate, respectively) at a voltage of ±3000 V. To minimize decomposition reactions during the ESI process and facilitate comparison with previous results,[19,29] we applied mild conditions identical to those reported previously (60 °C drying gas temperature and low potential differences along the path of the ions). The helium-filled quadrupole ion trap ($p(\mathrm{He}) \approx 0.3$ Pa) was operated at a trap drive of 20. This low value, although introducing some mass discrimination in favor of lighter ions, proved to be ideal for the simultaneous detection of different ions in the m/z 50–1000 range. In the gas-phase fragmentation experiments, the mass-selected ions (isolation widths of 1–4 u) were subjected to excitation voltages of amplitudes of V_{exc} and allowed to collide with the He gas before detecting the resulting fragment ions. Peak assignments given are based on the measured m/z values, the observed isotope patterns, and/or the gas-phase fragmentation behavior.

Quantum-chemical calculations

Density functional theory (DFT) calculations were performed with the program package Gaussian 03[30] and used the B3LYP hybrid functional[31] with an effective core potential of 10 core electrons for the Cu atoms (B3LYP/6-31G*/MDF)[32] as an economical method, similar to some previous theoretical work on organocuprates.[19c,33] Stationary points were classified as local minima (zero imaginary frequencies) or transition states (one imaginary frequency) by means of vibrational analyses. All given energies are zero-point corrected. Selected systems were further characterized by natural bond orbital analyses.[34] All calculations refer to the gas phase.

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Keywords: cuprates · density functional calculations · mass spectrometry · Michael additions · reactive intermediates

[1] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, New York, **1992**.

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

[3] Y. Yamamoto, S. Nishii, T. Ibuka, *J. Am. Chem. Soc.* **1988**, *110*, 617–618.

[4] a) E. Nakamura, S. Mori, *Angew. Chem. Int. Ed.* **2000**, *39*, 3750–3771; *Angew. Chem.* **2000**, *112*, 3902–3924; b) N. Yoshikai, E. Nakamura, *Chem. Rev.* **2012**, *112*, 2339–2372.

[5] a) G. Hallnemo, T. Olsson, C. Ullenius, *J. Organomet. Chem.* **1985**, *282*, 133–144; b) E.-L. Lindstedt, M. Nilsson, T. Olsson, *J. Organomet. Chem.* **1987**, *334*, 255–261; c) C. Ullenius, B. Christenson, *Pure Appl. Chem.* **1988**, *60*, 57–64; d) B. Christenson, T. Olsson, C. Ullenius, *Tetrahedron* **1989**, *45*, 523–534; e) K. Nilsson, C. Ullenius, N. Krause, *J. Am. Chem. Soc.* **1996**, *118*, 4194–4195; f) K. Nilsson, T. Andersson, C. Ullenius, A. Gerold, N. Krause, *Chem. Eur. J.* **1998**, *4*, 2051–2058.

[6] S. H. Bertz, R. A. J. Smith, *J. Am. Chem. Soc.* **1989**, *111*, 8276–8277.

[7] N. Krause, R. Wagner, A. Gerold, *J. Am. Chem. Soc.* **1994**, *116*, 381–382.

[8] A. S. Vellekoop, R. A. J. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 2902–2913.

[9] J. Eriksson, Ö. Davidsson, *Organometallics* **2001**, *20*, 4763–4765.

[10] a) R. M. Gschwind, *Chem. Rev.* **2008**, *108*, 3029–3053; b) W. Henze, T. Gärtner, R. M. Gschwind, *J. Am. Chem. Soc.* **2008**, *130*, 13718–13726.

[11] a) S. H. Bertz, R. A. Hardin, M. D. Murphy, C. A. Ogle, J. D. Richter, A. A. Thomas, *Angew. Chem. Int. Ed.* **2012**, *51*, 2681–2685; *Angew. Chem.* **2012**, *124*, 2735–2739; b) S. H. Bertz, K. L. Browder, R. A. Hardin, M. D. Murphy, C. A. Ogle, A. A. Thomas, *Organometallics* **2012**, *31*, 7809–7811; c) S. H. Bertz, S. K. Cope, R. A. Hardin, M. D. Murphy, C. A. Ogle, D. T. Smith, A. A. Thomas, T. N. Whaley, *Organometallics* **2012**, *31*, 7827–7838; d) S. H. Bertz, R. A. Hardin, M. D. Murphy, C. A. Ogle, J. D. Richter, A. A. Thomas, *J. Am. Chem. Soc.* **2012**, *134*, 9557–9560.

[12] For an IR spectroscopic study of the in-situ formed intermediates, see: S. R. Krauss, S. G. Smith, *J. Am. Chem. Soc.* **1981**, *103*, 141–148.

[13] For an X-ray absorption spectroscopic study of the in-situ formed intermediates, see: T. M. Barnhart, H. Huang, J. E. Penner-Hahn, *J. Org. Chem.* **1995**, *60*, 4310–4311.

[14] a) E. Nakamura, S. Mori, K. Morokuma, *J. Am. Chem. Soc.* **1997**, *119*, 4900–4910; b) S. Mori, E. Nakamura, *Chem. Eur. J.* **1999**, *5*, 1534–1543; c) M. Yamanaka, E. Nakamura, *Organometallics* **2001**, *20*, 5675–5681.

[15] M. Ahlquist, T. E. Nielsen, S. Le Quement, D. Tanner, P.-O. Norrby, *Chem. Eur. J.* **2006**, *12*, 2866–2873.

[16] Distinct and observable species of the β-cuprio(III) enol type do form upon consecutive reactions with silyl chlorides or cyanides: see ref. [11 d] and, S. H. Bertz, S. Cope, M. Murphy, C. A. Ogle, B. J. Taylor, *J. Am. Chem. Soc.* **2007**, *129*, 7208–7209.

[17] J. Canisius, A. Gerold, N. Krause, *Angew. Chem. Int. Ed.* **1999**, *38*, 1644–1646; *Angew. Chem.* **1999**, *111*, 1727–1730.

[18] B. H. Lipshutz, H. Keith, D. J. Buzard, *Organometallics* **1999**, *18*, 1571–1574.

[19] a) A. Putau, K. Koszinowski, *Organometallics* **2010**, *29*, 3593–3601; addition/correction: A. Putau, K. Koszinowski, *Organometallics* **2010**, *29*, 6841–6842; b) A. Putau, K. Koszinowski, *Organometallics* **2011**, *30*, 4771–4778; c) A. Putau, H. Brand, K. Koszinowski, *J. Am. Chem. Soc.* **2012**, *134*, 613–622; d) A. Putau, M. Wilken, K. Koszinowski, *Chem. Eur. J.* **2013**, *19*, 10992–10999.

[20] A. Tsybizova, J. Roithová, *Mass Spectrom. Rev.* **2016**, *35*, 85–110.

[21] a) P. F. James, R. A. J. O'Hair, *Org. Lett.* **2004**, *6*, 2761–2764; b) N. Rijs, G. N. Khairallah, T. Waters, R. A. J. O'Hair, *J. Am. Chem. Soc.* **2008**, *130*, 1069–1079; c) N. J. Rijs, B. F. Yates, R. A. J. O'Hair, *Chem. Eur. J.* **2010**, *16*, 2674–2678; d) N. J. Rijs, N. Yoshikai, E. Nakamura, R. A. J. O'Hair, *J. Am. Chem. Soc.* **2012**, *134*, 2569–2580; e) N. J. Rijs, N. Yoshikai, E. Nakamura, R. A. J. O'Hair, *J. Org. Chem.* **2014**, *79*, 1320–1334.

[22] S. Woodward, *Chem. Soc. Rev.* **2000**, *29*, 393–401.

[23] For the reaction of simple carbanions with acrylonitrile in the gas phase, see: C. F. Bernasconi, M. W. Stronach, C. H. DePuy, S. Gronert, *J. Am. Chem. Soc.* **1990**, *112*, 9044–9052.

[24] The vacuum system of the quadrupole-ion trap mass spectrometer contained inevitable traces of background water.

[25] For a comparison of theoretically calculated Li$^+$ affinities of ketones and imines, see: L. M. Costa, L. W. C. Paes, J. W. M. Carneiro, *J. Braz. Chem. Soc.* **2012**, *23*, 648–655.

[26] a) J. Sauer, H. Wiest, A. Mielert, *Chem. Ber.* **1964**, *97*, 3183–3207; b) K. N. Houk, L. L. Munchausen, *J. Am. Chem. Soc.* **1976**, *98*, 937–946.

[27] The absence of analogous gas-phase fragmentation reactions of the corresponding intermediate derived from CuPh$_2^-$ suggests that the latter is not a sufficiently strong electron donor or that the resulting Ph$^•$ radical is not stable enough for its release upon gas-phase fragmentation.

[28] M. F. Lipton, C. M. Sorensen, A. C. Sadler, R. H. Shapiro, *J. Organomet. Chem.* **1980**, *186*, 155–158.

[29] K. Koszinowski, *J. Am. Chem. Soc.* **2010**, *132*, 6032–6040.

[30] Gaussian 03, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**.

[31] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.

[32] T. Leininger, A. Nicklass, H. Stoll, M. Dolg, P. Schwerdtfeger, *J. Chem. Phys.* **1996**, *105*, 1052–1059.

[33] a) H. Hu, J. P. Snyder, *J. Am. Chem. Soc.* **2007**, *129*, 7210–7211; b) T. Gärtner, N. Yoshikai, M. Neumeier, E. Nakamura, R. M. Gschwind, *Chem. Commun.* **2010**, *46*, 4625–4626.

[34] E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold, *NBO*, Version 3.1, University of Wisconsin, Madison WI, **1993**.

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FULL PAPER

Reaction Intermediates

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■■–■■

Intermediates Formed in the Reactions of Organocuprates with α,β-Unsaturated Nitriles

Intercepted intermediates: Electrospray ionization mass spectrometry (ESI MS) permits the interception of elusive intermediates of conjugate addition reactions between organocuprates and α,β-unsaturated nitriles. The intermediates are further characterized by gas-phase fragmentation experiments and quantum-chemical calculations.