Mechanism of 1,6-Addition Reactions of Organocuprates: Detailed NMR Spectroscopic Study of a Cuprate – Enyne π Complex

Johannes Canisius,[a] T. Andrew Mobley,[b] Stefan Berger,[b] and Norbert Krause*[a]

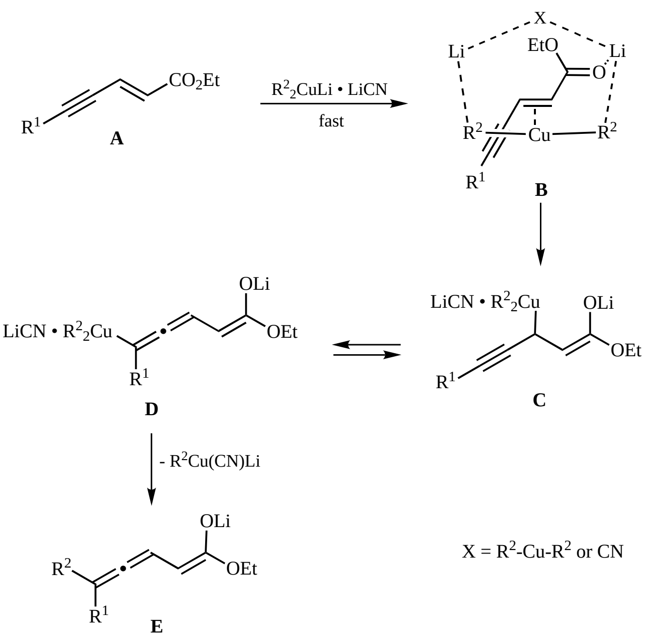
Abstract: A detailed NMR-spectroscopic study of the multiply ^{13}C-labeled cuprate π complexes **2**, **2a** and **2b** was carried out. The $^{13}C,^{13}C$ coupling constants observed were interpreted in terms of a deformation of the cuprate – alkene complex from the expected idealized square plane. This conclusion is in agreement with NOESY and ROESY data acquired with unlabeled material.

Keywords: cuprates · enynes · NMR spectroscopy · pi complexes

Introduction

The conjugate addition of organocuprate reagents to α,β-unsaturated carbonyl compounds belongs to the basic carbon – carbon forming reactions.[1] Among the different classes of Michael additions, the 1,4-addition to enones, enoates, and acetylenic esters is still the most noted, but recent developments expand the reaction to 1,6-, 1,8-, 1,10-, and 1,12-additions to Michael acceptors that bear a conjugated system of double and triple bonds.[2]

Examining the reactivity of cuprates and the mechanism of the conjugate addition reactions is, therefore, a matter of great interest. While the structures of organocuprate reagents have been successfully studied by X-ray diffraction methods,[3] the most promising method for studying the mechanism of copper-mediated reactions is NMR spectroscopy at low temperatures. In all cases examined so far, π complexes of the cuprate at the C=C double bond adjacent to the carbonyl function are formed, as has been shown by different groups for 1,4-addition[4] and by us for 1,6- and 1,8-addition reactions.[5] This and quantum-chemical calculations[6] as well as the determination of activation parameters by kinetic studies[7] indicate that a common reaction pathway of conjugate additions of organocuprate reagents is likely. In the case of the 1,6-addition, which shows strong similarities to 1,4-additions in terms of π-complex structure and activation parameters, the enyne **A** reacts with a cyano-Gilman cuprate $R_2CuLi \cdot LiCN$ at low temperature to form π complex **B**;[8] this then decomposes through an oxidative addition into the σ copper(III) species **C**, which could be in equilibrium with the allenic copper compound **D**. Both species seem also to contain lithium cyanide, and reductive elimination of the lower order cyanocuprate RCu(CN)Li from the latter intermediate then produces the 1,6-adduct **E**.[9]



In this paper, we present a detailed NMR spectroscopic study of multiply ^{13}C-labeled cuprate π complexes of type **B**. The observed $^{13}C,^{13}C$ coupling constants allow an insight into structural details of the cuprate – alkene; this is corroborated with NOESY and ROESY experiments.

---

[a] Prof. Dr. N. Krause, Dr. J. Canisius
Organic Chemistry II, Dortmund University
44221 Dortmund (Germany)
Fax: (+49) 231-7553884
E-mail: nkrause@pop.uni-dortmund.de

[b] Prof. Dr. S. Berger, Dr. T. A. Mobley
Institute of Analytical Chemistry, Leipzig University
Linnéstrasse 3, 04103 Leipzig (Germany)
Fax: (+49) 341-9736101
E-mail: stberger@rz.uni-leipzig.de

Results and Discussion

As one of our groups has previously described,[5] in π complex **B** the cuprate is coordinated to the C=C double bond adjacent to the carbonyl function. This conclusion was based on the decrease of the C–C coupling constant between the double bond carbon atoms from 74 to 53 Hz upon cuprate complexation of **1** (Figure 1). In addition, when using ^{13}C-labeled enynoates **1a/b**, a coupling of 12 Hz between C-3 and one of the copper-bound methyl groups was observed. These data, along with an absence of evidence for interaction of the cuprate with the triple bond led us to believe that the cuprate interacts with the double bond moiety of the substrate exclusively. An enolate type addition product is considered unlikely because there is no change in the $^{1}J_{CH}$ coupling constants at the 2- and 3-positions (162 Hz) compared with the free enynoate.

C,C Coupling constants	
$J_{2,3}$	53 Hz
$J_{a,b}$	≤ 4 Hz
$J_{2,a}$	0 Hz
$J_{2,b}$	~ 0 Hz
$J_{3,a}$	12 Hz
$J_{3,b}$	0 Hz

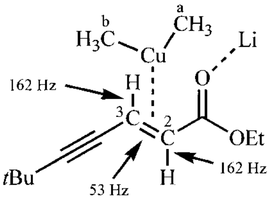
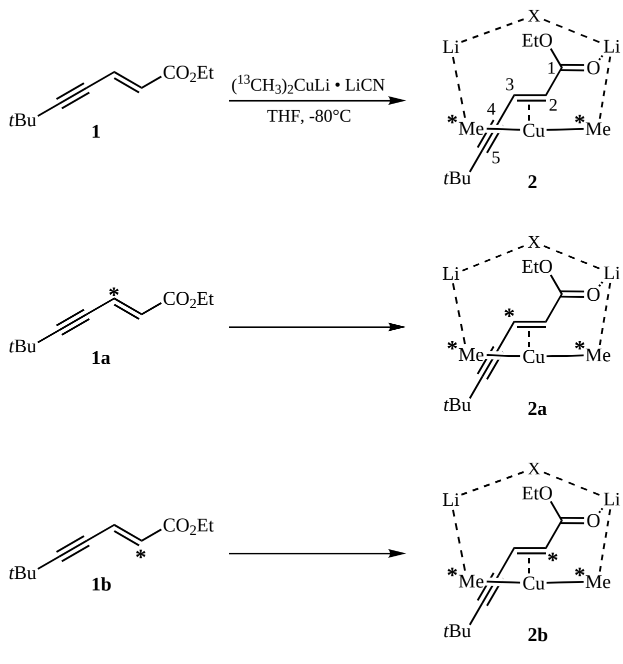


Figure 1. Coupling constants of π complex **2**.

In order to gain additional information about the structure of cuprate π complexes **B**, we generated complex **2**[8] by treatment of 2-en-4-ynoate **1** with $(^{13}CH_3)_2CuLi\cdot LiCN$ in [D$_8$]THF at –80 °C. This complex is particularly well-suited for detailed structural studies as the chemically nonequivalent methyl groups of the cuprate are "static" on the NMR timescale. Spectroscopic studies of ^{13}C-labeled cuprate complex **2** support the conclusions reached above. The additional coupling information obtained in conjunction with NOE studies has allowed us to develop a more detailed description of the environment around the coordinated cuprate. As shown in Figure 2, the ^{13}C NMR spectrum reveals characteristic high-field shifts of the signals for C-2 ($\Delta\delta = -68.1$ ppm) and C-3 ($\Delta\delta = -84.6$ ppm) as well as a low-field shift of the carbonyl resonance ($\Delta\delta = 9.0$ ppm); this is typical for a lithium–oxygen interaction.[4, 5]



X = Me-Cu-Me or CN

As can be seen in Figure 3a, the two methyl group carbons are observed as doublets with a 4 Hz coupling constant. This coupling constant is on the order of the linewidth of these resonances, however, and is so only observable when a strong gaussian window function is applied (LB = –2.0 Hz, GB = 0.6). In contrast when C-3 is also labeled with ^{13}C (π complex **2a**), the high-field methyl carbon is split into a doublet (Figure 3b) with the much larger coupling constant of 12 Hz. The C-3 resonance is also split into a doublet with the same coupling constant. A homonuclear ^{13}C,^{13}C COSY spectrum with ^{1}H decoupling shows a crosspeak between these two resonances, confirming the two as coupling partners. However, upon labeling of the C-2 of the alkene (π complex **2b** in Figure 3c), no similar coupling is observed to the methyl groups. This stands in agreement with the previous results.

^{1}H,^{1}H NOESY and ROESY spectra were acquired of unlabeled material (Figure 4). These data further differentiate between the two methyl groups. Only the high-field methyl has NOE crosspeaks with the diastereotopic AB protons of the ethyl ester methylene group. In addition, NOE crosspeaks between the vinylic protons on C-2 and C-3 are evident for

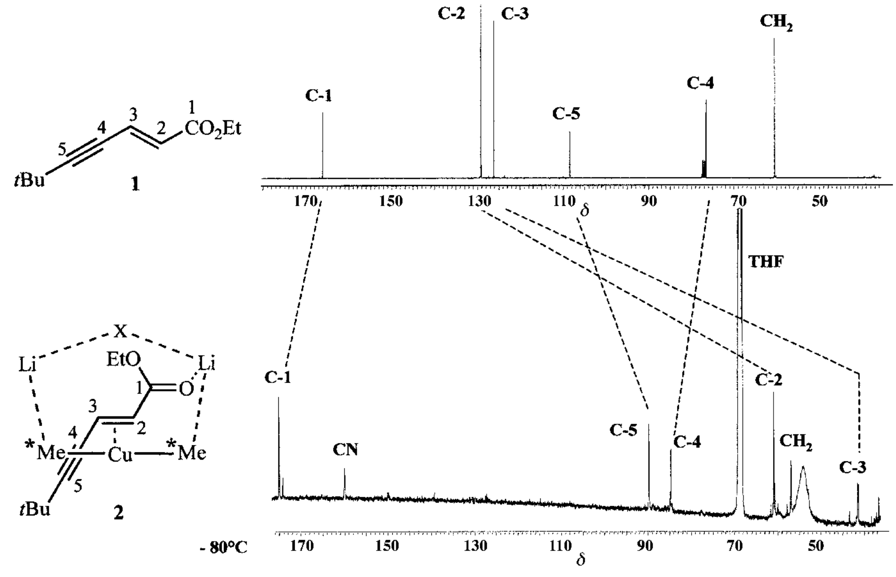


Figure 2. ^{13}C NMR spectra of the Michael acceptor **1** and the π complex **2** in [D$_8$]THF.

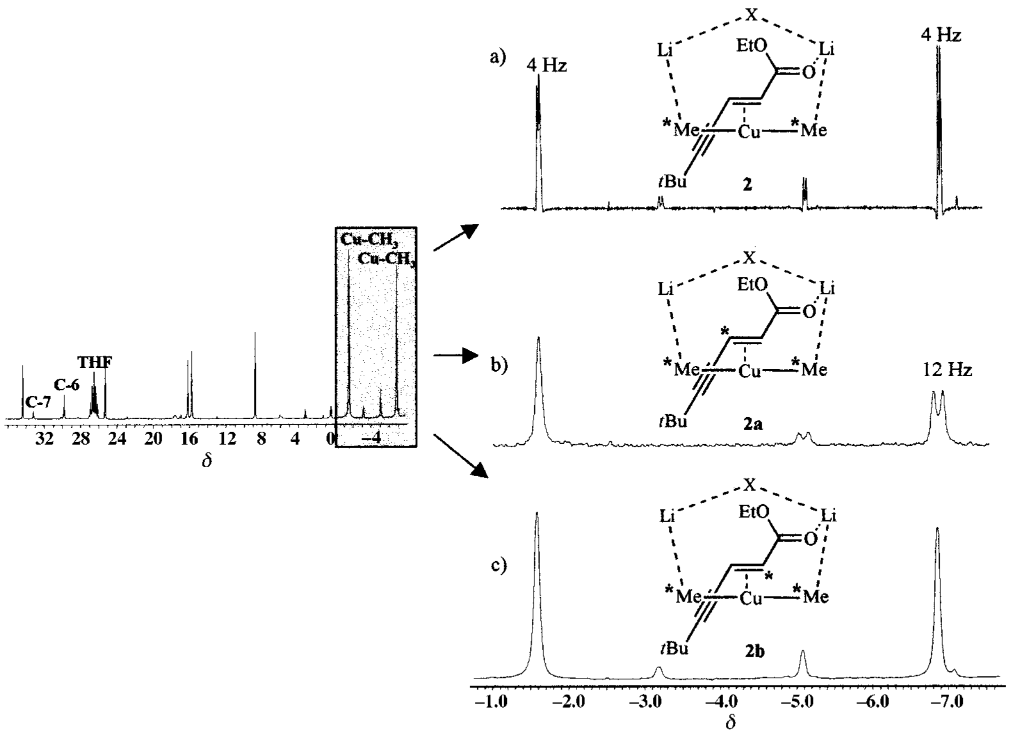


Figure 3. ^{13}C NMR spectra of π complexes **2**.

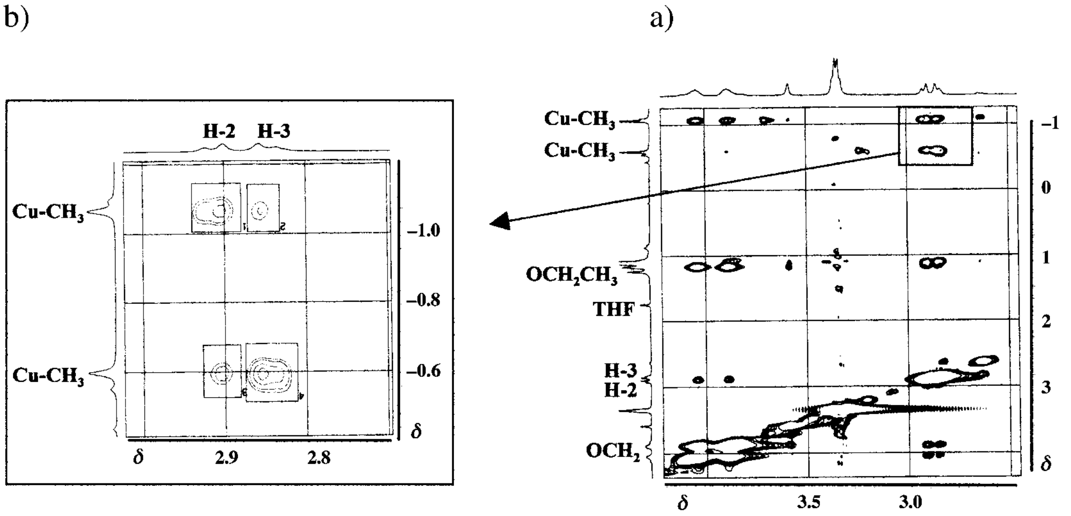


Figure 4. a) NOESY spectrum and b) ROESY spectrum of unlabeled π complex **2**.

both of the copper-bound methyl groups, although the relative integrations indicates that the C-2 proton has a stronger interaction with the upfield methyl, while the C-3 proton has a stronger interaction with the downfield methyl group (Figure 4b). There is also a crosspeak between the two methyl groups which in the ROESY spectrum has a relative sign opposite to the diagonal; this indicates that the mechanism in action is indeed dipolar relaxation rather than exchange (NOESY shown in Figure 4a, ROESY data not shown). The methylene of the ethyl ester also "sees" both of the vinyl protons on C-2 and C-3 (Figure 4a).

The studies of π complexes **2** from ^{13}C-labeled cuprate allow greater insight into the environment surrounding the copper in the π complex. For instance, the coupling constant of 4 Hz between the two methyl group carbons in **2** is drastically reduced from that observed in the free cuprate (21 Hz).[10] This indicates a change in the bonding geometry and electronic situation with respect to the free cuprate, for example, a drastic change in the Me-Cu-Me angle from the linear structure expected for the free cuprate. Perhaps of more primary concern, one can also be certain that each methyl resonance consists of a single methyl group owing to the absence of higher order coupling when a proton-coupled spectrum is taken. This conclusion is also supported by the fact that the vinylic C-3 is split into only a doublet (as opposed to a triplet) by the high-field methyl resonance at $\delta = -6.9$.

The unique large coupling between the high-field methyl carbon and vinylic C-3 of 12 Hz and the absence of couplings between both of the methyl carbons and C-2 also holds structural information. Based upon previous theoretical treatments,[6a] the expected structure for an alkene binding to the dimethylcuprate moiety would have a square-planar arrangement with the copper atom centered above the double bond. The various C-Cu-C angles would be geometrically similar and no large differences in the coupling constants would be expected. However, this is not the situation observed here; thus, one expects some deformation of the cuprate–alkene complex from the expected idealized square plane. To achieve a large methyl carbon C-3 coupling constant of 12 Hz, the CH_3-Cu-C-3 angle should be nearly linear. Combining this idea with the CH_3-Cu-CH_3 angle described above leads to the structure shown in Figure 5. One can see that one of the methyl groups is indeed practically *trans* with respect to C-3. The rest of the angles are all close to right angles; from these one would expect small coupling constants as observed experimentally. In addition, the structure in Figure 5 better explains the observed NOE data, in which the upfield methyl group interacts more strongly with the proton on C-2,while the downfield methyl interacts more strongly with the proton on C-3.

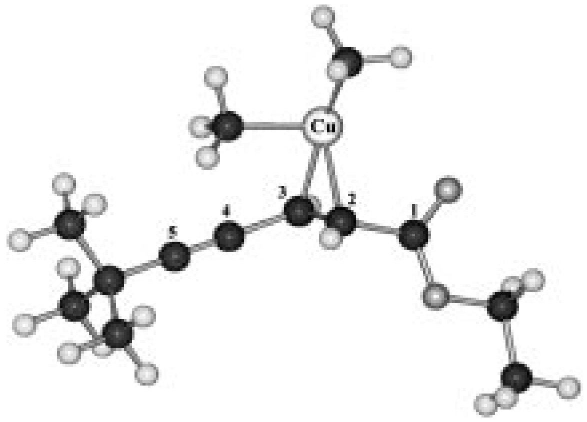


Figure 5. Proposed structure of π complex **2** (Li cation omitted).

In conclusion, we have shown that a precise structural description of an organocuprate π omplex can be derived from detailed NMR pectroscopic investigations. Implications of the structural features established here for the mechanistic course of 1,6-addition reactions to acceptor-substituted enynes are subject of further experimental and theoretical studies.

Experimental Section

Synthesis of ^{13}C-labeled π complexes 2, 2a, and 2b: In a dry, septum-capped 50mL centrifuge tube *n*BuLi (1.2 mL, 1.66 M in hexane, 2 mmol) was added to dry, degassed hexane (2 mL) under argon. MeI (^{13}C, 99%; 0.13 mL, 0.28 g, 2 mmol) was added to the cold (0 °C) solution; this resulted in a white precipitate within 10 min. The suspension was centrifuged, the supernatant hexane was removed, and the solid washed with dry, oxygen-free hexane (2 mL). This procedure was repeated three times, and the residual hexane was removed under slight vacuum. The solid MeLi was dried in vacuum and dissolved in cold $[D_8]$THF (1 mL). Standardization of the alkyllithium compounds was carried out by titration with *N*-pivaloyl-*o*-toluidine in THF at 0 °C.[11]

In a three-necked round-bottom flask with attached 5 mm NMR tube, a suspension of CuCN (45 mg, 0.5 mmol) in $[D_8]$THF (0.5 mL) was treated with of a solution of $^{13}CH_3Li$ (1.74 M, 1 mmol) in $[D_8]$THF (0.57 mL) at −30 °C. The mixture was stirred at −30 °C for 30 min, then cooled to −80 °C, and a solution of of Michael acceptor **1** , **1a** or **1b**[5] (81 mg, 0.45 mmol) in $[D_8]$THF (0.3 mL) was added dropwise. The yellow solution was stirred for 15 minutes at −80 °C and degassed by three freeze-pump-thaw cycles; during thawing the temperature was kept below −80 °C. The solution was transferred into a precooled (−80 °C) NMR tube, which was flame-sealed under vacuum at liquid nitrogen temperature.

The NMR spectra of the complexes were recorded at −80 °C in $[D_8]$THF (typical concentration: 0.7 M) with a Bruker DRX500 spectrometer at 500.13 MHz (^{1}H) and 125.8 MHz (^{13}C), by using a 5 mm broad-band triple resonance gradient probe and a Bruker BVT3000 unit for temperature control. The proton spectra were referenced to residual THF ($\delta = 1.75$) and the carbon spectra to $[D_8]$THF ($\delta = 26.5$). The typical ^{1}H 90° pulse was 13 μs. The spectral resolution in the ^{13}C NMR spectra was 0.5 Hz per point. The ^{13}C NMR spectrum of **2** was obtained by using exponential multiplication with LB = −2.0 Hz and GB = 0.6. The ^{1}H,^{1}H ROESY and NOESY experiments were performed with the unlabeled π complex **2** by using a spectral window of 8 × 8 ppm (1024 points in the f_2 dimension, 256 increments and 8 scans for each increment, mixing time of 600 ms and 2 s relaxation delay). The data were processed with the Bruker WINNMR software.

Acknowledgements

Financial support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Volkswagen-Stiftung is gratefully acknowledged.

---

[1] a) Y. Yamamoto in *Stereoselective Syntheses, Vol. 4* (Ed.: Y. Yamamoto), Thieme, Stuttgart, **1995**, pp. 2041–2057; b) B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135–631.

[2] Reviews: a) N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194–213; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186–204; b) N. Krause, S. Thorand, *Inorg. Chim. Acta* **1999**, *296*, 1–11; c) N. Krause, C. Zelder in *The Chemistry of Dienes and Polyenes, Vol. 2* (Ed.: Z. Rappoport), Wiley, New York, **2000**, pp. 645–691.

[3] a) G. Boche, F. Bosold, M. Marsch, K. Harms, *Angew. Chem.* **1998**, *110*, 1779–1781, *Angew. Chem. Int. Ed.* **1998**, *37*, 283–285; b) C. M. P. Kronenburg, J. T. B. H. Jastrzebski, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **1998**, *120*, 9688–9689.

[4] 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) S. H. Bertz, R. A. J. Smith, *J. Am. Chem. Soc.* **1989**, *111*, 8276–8277; f) S. Sharma, A. C. Oehlschlager, *Tetrahedron* **1989**, *45*, 557–568; g) A. S. Vellekoop, R. A. J. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 2902–2913.

[5] a) N. Krause, *J. Org. Chem.* **1992**, *57*, 3509–3512; b) N. Krause, R. Wagner, A. Gerold, *J. Am. Chem. Soc.* **1994**, *116*, 381–382.

[6] a) S. Mori, E. Nakamura, *Chem. Eur.* J, **1999**, 5, 1534–1543; b) E. Nakamura, S. Mori, K. Morokuma, *J. Am. Chem. Soc.* **1997**, *119*, 4900–4910; c) J. P. Snyder, S. H. Bertz, *J. Org. Chem.* **1995**, *60*, 4312–4313; d) J. P. Snyder, *J. Am. Chem. Soc.* **1995**, *117*, 11025–11026; Review: e) E. Nakamura, S. Mori, *Angew. Chem.* **2000**, *112*, 3902–3924; *Angew. Chem. Int. Ed.* **2000**, *39*, 3750–3771.

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

[8] Free cyano cuprates exist in ethereal solution either as homo- or heterodimer: R. M. Gschwind, P. R. Rajamohanan, M. John, G. Boche, *Organometallics* **2000**, *19*, 2868–2873; M. John, C. Auel, C. Behrens, M. Marsch, K. Harms, F. Bosold, R. M. Gschwind, P. R. Rajamohanan, G. Boche, *Chem. Eur. J.* **2000**, *6*, 3060–3068. The same is assumed for π complexes **B** and **2**, wherein X corresponds to R^2-Cu-R^2 for the homodimer and to CN for the heterodimer.

[9] For the 1,4-cuprate addition to enones, both theoretical[6a] and experimental studies (determination of kinetic isotope effects: D. E. Frantz, D. A. Singleton, J. P. Snyder, *J. Am. Chem. Soc.* **1997**, *119*, 3383–3384) indicate that the reductive elimination of a copper(III) species is the rate-determining step. Analogous investigations have not been carried out to date for the 1,6-addition to acceptor-substituted enynes.

[10] a) T. A. Mobley, F. Müller, S. Berger, *J. Am. Chem. Soc.* **1998**, *120*, 1333–1334; b) S. H. Bertz, *J. Am. Chem. Soc.* **1991**, *113*, 5470–5471.

[11] J. Suffert, *J. Org. Chem.* **1989**, *54*, 509–510.

Received: September 29, 2000
Revised: February 16, 2001 [F2764]