as can be seen from the amide I and III frequency shifts.[15] The diminished amide II and III resonance enhancement, due to transition dipole alignment in α-helices, has already been noted.[3] At the same time the amide S band vanishes completely in the α-helical form. While hypochromism can account for some of the intensity loss, the reason for its disappearance is uncertain; possibly the NH out-of-plane force constant is unaltered in the excited state for α-helix, in contrast to unordered peptide. In any event the marked intensity dependence makes amide S a promising marker for α-helical content in proteins. We note that there is no evidence for *cis*-amide links in the polylysine spectra nor in published protein spectra,[3] but the possibility of photoinduced isomerization in UVRR studies of proteins or peptides should be kept in mind.

Acknowledgment. We thank Dan Melamed for synthesizing the CD_3 labeled NMA and Marina Molina for the caprolactam spectra. This work was supported by NIH Grant GM 25158 (TGS) and by a grant from the Italian Consiglio Nazionale delle Ricerche (RP).

---

(15) Krimm, S.; Vandekar, J. *Adv. Protein Chem.* **1986**, *38*, 181.

(16) Fodor, S. P. A.; Rava, R. P.; Copeland, R. A.; Spiro, T. G. *J. Raman Spectrosc.* **1986**, *17*, 471-475.

Mechanism of Organocuprate Conjugate Addition: Observation of Cuprate-Olefin Complexes and Li-Coordinated Intermediates in the Reaction of Lithium Dimethylcuprate(I) with 10-Methyl-$\Delta^{1,9}$-2-octalone[1a]

Steven H. Bertz* and Robin A. J. Smith*,[1b]

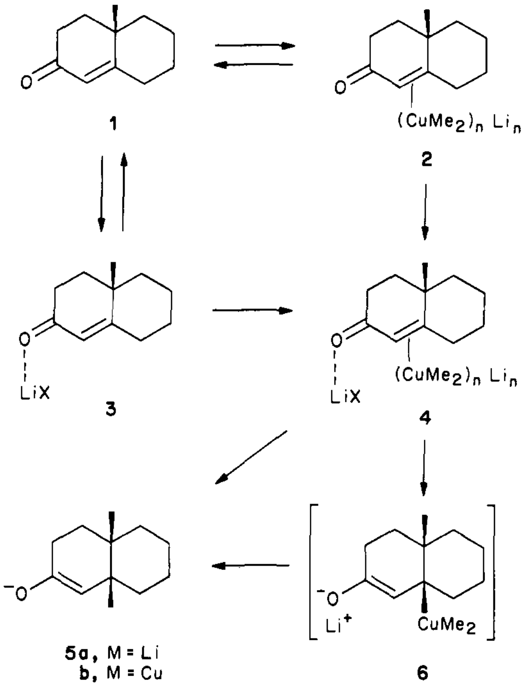
AT&T Bell Laboratories
Murray Hill, New Jersey 07974

Received May 5, 1989

Organocuprates react with α,β-unsaturated ketones to yield the enolates of the corresponding β-alkylated ketones.[2] Paradoxically, this reaction is both one of the most useful of those mediated by transition-metal reagents and yet one of the least understood. We have discovered that treatment of 10-methyl-$\Delta^{1,9}$-2-octalone (**1**) with halide-free lithium dimethylcuprate(I), $(Me_2CuLi)_2$,[3] at low temperatures in diethyl ether-d_{10} allows the intermediates in the sequence from **1** via **2** and **4** to enolate **5** (Scheme I) to be observed by using ^{13}C NMR spectroscopy.

When 0.25 M $(Me_2CuLi)_2$ in diethyl ether-d_{10} at -78 °C is treated with 2 equiv of **1** (1 equiv of **1** vs Me_2CuLi as it is usually written), it assumes a deep orange color, and three sets of lines attributable to cuprate-olefin π-complexes of general structure **2** are observed by ^{13}C NMR (Figure 1b). With 1 equiv of **1**, a small amount of a fourth π-complex is also observed. We tentatively assign the four complexes **2** to exo and endo isomers of monomeric and dimeric cuprates (Scheme I, $n = 1, 2$). The major olefin complex (50%) is characterized by lines with chemical shifts of 191.0, 82.5 ($J_{CH} = 149$ Hz), and 80.9 ppm for the carbonyl C and the olefinic α-C and β-C, respectively.[4] The corresponding lines for (uncomplexed) **1** are at 196.9, 125.1 ($J_{CH} = 159$ Hz), and 168.1 ppm (Figure 1a). The relatively unperturbed carbonyl C and the dramatic upfield shifts (42.6 and 87.2 ppm, respectively) of the olefinic α-C and β-C atoms are precisely what is expected for the change in bonding upon transformation of **1** into a h^2-olefin complex.[5] For comparison, the α and β olefinic C atoms of *tert*-butyl cinnamate are shifted upfield by 67.2 and 82.6 ppm, respectively, upon complexation by $Me_2CuLi{\cdot}LiI$.[6]

Scheme I



A significant amount of lithium-carbonyl complex **3** is also present: 15% with 1 equiv of **1** and 30% with 2 equiv at -78 °C (Figure 1b).[7] The ^{13}C lines characteristic of **3** are 204.2 ppm (carbonyl C), 124.8 ppm ($J_{CH} = 162$ Hz, olefin α-C), and 176.1 ppm (olefin β-C), in accord with the observed effects of adding Li salts to α,β-unsaturated ketones.[8] With 2 equiv of **1**, the proportion of **3** increases to 45% when the temperature is raised to -60 °C. When the sample is returned to -78 °C, the original ratio of **2**/**3** is restored. In their cuprate-cinnamate system Ullenius et al. also observed a lithium-carbonyl complex, which is "the major component when the ester is present in excess and also at higher temperatures...".[6a] In their system the lines due to the copper-olefin and lithium-carbonyl complexes coalesce before enolate appears. In our system exchange processes are apparently much slower, and we have been able to observe all the species **2**-**5** in a single spectrum (see Figure 2, Supplementary Material; see Figure 1d for **3**-**5** in a single spectrum).

With 1 equiv each of **1** and $(Me_2CuLi)_2$, three new species are present in addition to the complexes **2** and **3** discussed above (see Figure 1c). Two are proposed to be Li-coordinated copper-olefin complexes of general structure **4**, based on the downfield shifts of the olefinic resonances compared to those of **2**. One of these has broad signals at 188.3, 87.0, and 86.7 ppm, and the other has sharp lines at 188.0 (carbonyl C), 87.2 ($J_{CH} = 148$ Hz, olefinic α-C), and 87.4 ppm (olefinic β-C). Such lithium-carbonyl/copper-olefin complexes were proposed by Berlan to be the antepenultimate intermediate in the reaction of cuprates with enones.[9] The greater upfield shift of the β-C (>2× that of the α-C) indicates that the Cu-C_β bond is significantly stronger than the Cu-C_α interaction and suggests that conversion of **4** to the σ-allylcuprate(III) **6** is a plausible path to enolate **5**.

---

(1) (a) New Copper Chemistry, Part 16. For part 15 see: *Tetrahedron* **1989**, *45*, 425. (b) Visiting Scientist (1988), permanent address: Department of Chemistry, University of Otago, Dunedin, New Zealand.

(2) (a) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1. (c) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

(3) Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 4098.

(4) With a 1:1 ratio of **1**:$(Me_2CuLi)_2$, other carbonyl ^{13}C lines are at 190.8 and 185.4 ppm, α-olefinic ^{13}C lines at 85.2 (8%), 84.8 (21%), and 82.7 (21%) ppm, and β-olefinic ^{13}C lines at 81.2 (20%), 80.3 (6%), and 80.1 (24%) ppm.

(5) Salomon, R. G.; Kochi, J. K. *J. Organomet. Chem.* **1974**, *64*, 135.

(6) (a) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133. (b) Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523.

(7) With 1 equiv of **1**, the 176.1 ppm peak is not prominent due to broadness.

(8) House, H. O.; Chu, C.-Y. *J. Org. Chem.* **1976**, *41*, 3083. An ethereal solution that is 0.1 M in **1** and $LiClO_4$ has sp^2 ^{13}C lines at 203.7, 124.9, and 174.5 ppm.

(9) Berlan, J.; Battioni, J.-P.; Koosha, K. *Bull. Soc. Chim. Fr.* **1979**, II-183.

0002-7863/89/1511-8276$01.50/0

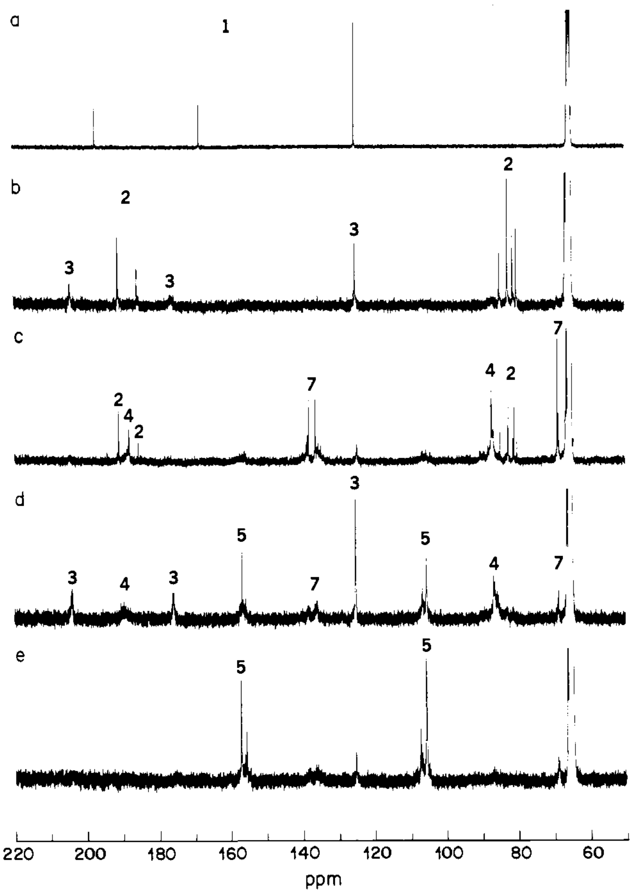
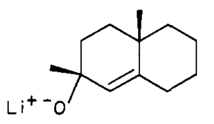
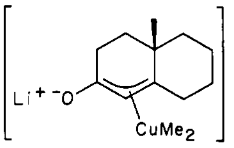


Figure 1. ^{13}C NMR spectra (220 to 50 ppm vs TMS) in diethyl ether-d_{10}: a. 10-methyl-$\Delta^{1,9}$-2-octalone (**1**) (−78 °C); b. (Me$_2$CuLi)$_2$ + **1** (2 equiv, −78 °C) gives rise to **2** and **3**; c. (Me$_2$CuLi)$_2$ + **1** (1 equiv, −78 °C) yields **4** and **7** in addition to **2**; d. (Me$_2$CuLi)$_2$ + **1** (2 equiv, −50 °C for ~0.2 h) shows **3–5** and **7**; e. Me$_2$CuLi·LiI + **1** (1 equiv, −50 °C for 1.5 h) affords **5a** and a minor amount of regioisomeric enolate.

The third new species has olefin resonances at 136.2 (J_{CH} = 148 Hz) and 138.1 ppm and a singlet at 68.9 ppm attributable to a quaternary C bearing an OLi substituent, consistent with 1,2-adduct **7**.[10] Product **7** appears immediately, before the 1,4-adduct **5** appears; therefore, **5** and **7** are not the result of partitioning a π-allylcuprate(III) intermediate such as **8** between alkylation at C-2 and C-9 (octalone numbering).



7



8

With 1 equiv of Me$_2$CuLi·LiI, an enolate (157.1, 105.6 ppm, Figure 1e) is observed at −50 °C along with minor amounts of regioisomeric enolate (155.6, 107.2 ppm),[11] since the reaction is slow under our conditions. Following House and Wilkins,[11c] we believe the primary product from Me$_2$CuLi·LiI and **1** to be the Li enolate **5a**; however, its precise nature remains to be established. With 1 equiv of **1** and halide-free (Me$_2$CuLi)$_2$, the conversion of **4** to enolate mixture **5** occurs at a significant rate when the temperature is increased to −60 °C.[12] Under these conditions **5** increases monotonically at the expense of **3** and **4** (Figure 3, supplementary material). With 2 equiv of **1**, the temperature must be raised to −50 °C for **5** to appear at an appreciable rate.

If a mixture of cuprate and **1** (i.e., **2** and **3**) that has been kept at −78 °C for as long as 1 h is quenched (aqueous NH$_4$Cl), **1** is recovered quantitatively. Workup of the reaction mixtures after warming yields a single 1,4-addition product, *cis*-9,10-dimethyl-2-octalone and minor amounts of 1,2-product.[10]

House and Umen[13,14] proposed that the reaction of α,β-unsaturated ketones with organocuprates such as (Me$_2$CuLi)$_2$ proceeds by single electron transfer to give an organic radical anion and an oxidized cuprate cluster, which combine to form a σ-allylcuprate(III) (e.g., **6**) without the intermediacy of copper–olefin complexes. They stated, "Although various π-complexes of the enone and cuprate might be envisioned to precede either process [electron transfer or nucleophilic addition[15]], we are aware of no compelling evidence for their presence...".[13] The ^{13}C NMR observations reported herein constitute compelling evidence for h^2-olefin cuprate and Li-coordinated copper–olefin complexes (**2** and **4**, respectively) on the mechanistic pathway of the conjugate addition reaction of (Me$_2$CuLi)$_2$ and **1**. Since the reaction conditions used in this study are typical of organocuprate conjugate additions, our results are deemed to be particularly relevant to the general synthetic reaction.

Acknowledgment. We thank Dr. Peter Mirau (AT&T Bell Laboratories) for helpful advice concerning NMR spectroscopy and Dr. J. San Filippo (Rutgers University) for useful suggestions about the preparation of lithium dimethylcuprate.

Supplementary Material Available: Experimental details and figures giving ^{13}C NMR spectra of (Me$_2$CuLi)$_2$ + **1** in diethyl ether-d_{10} (3 pages). Ordering information is given on any current masthead page.

---

(10) The major product from the addition of 1 equiv of MeLi to **1** has peaks at 68.8, 133.9, and 141.3 ppm. Upon quenching (aqueous NH$_4$Cl) GLC analysis revealed that for a 1:1 ratio of (Me$_2$CuLi)$_2$:**1**, the yield of 1,2-product was 25%. For a 1:2 ratio of (Me$_2$CuLi)$_2$:**1** it was 10%, and for a 1:1 ratio of Me$_2$CuLi·LiI:**1** it was 5%.

(11) For typical enolate ^{13}C NMR shifts: (a) House, H. O.; Prabhu, A. V.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209. (b) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954. (c) For a good model: House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1976**, *41*, 4031.

(12) A number of peaks (104.4, 104.6, 105.2, 157.2, 158.1, and 158.2 ppm) close to those of **5a** are attributable to Cu enolates **5b**, where the Cu atoms are part of different aggregates. Minor peaks in the enolate region (e.g., 105.4, 105.9, 106.6; 156.0, 156.8, and 157.3 ppm) may be due to regioisomeric Cu enolates corresponding to the regioisomeric Li enolate.

(13) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.

(14) See also: (a) House, H. O.; Fischer, W. F. *J. Org. Chem.* **1968**, *33*, 949. (b) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

(15) Casey, C. P.; Cesa, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4236.

A Highly Efficient Eight-Membered-Ring Cyclization for Construction of the Taxane Carbon Framework

Yoshiaki Horiguchi, Takashi Furukawa, and Isao Kuwajima*

Department of Chemistry
Tokyo Institute of Technology
Meguro, Tokyo 152, Japan

Received May 12, 1989

Members of the taxane family with their unique tricyclo[9.3.1.0^{3,8}]pentadecane skeleton[1] and important biological activities[2] have become important targets in synthetic organic chem-

---

(1) Review: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425. Taxusin: (a) Miyazaki, M.; Shimizu, K.; Mishima, N.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546. (b) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1966**, 923. Taxol: (c) Wani, M. C.; Taylor, M. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. (d) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr. *J. Org. Chem.* **1981**, *46*, 1469.

(2) (a) Riondel, J.; Jacrot, M.; Picot, F.; Beriel, H.; Mouriquand, C.; Potier, P. *Cancer Chemother. Pharmacol.* **1986**, *17*, 137. (b) Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83. (c) Hamel, E.; Lin, C. M.; Johns, D. G. *Cancer Treat. Rep.* **1982**, *66*, 1381. (d) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561. (e) Suffness, M.; Douros, J. D. *Methods Cancer Res.* **1979**, *16*, 73. (f) Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219.

0002-7863/89/1511-8277$01.50/0