Chemical and Spectroscopic Observations on the Properties and Composition of Higher Order, Mixed Organocuprates, R₂Cu(CN)Li₂

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The nature of organocuprates of general formula R₂Cu(CN)Li₂, derived from CuCN and 2RLi, is described in terms of their structural integrity in solution. A combination of chemical and spectroscopic tests conclusively demonstrates facile dissociation-reassociation of alkyl groups on copper. Data derived from both IR and variable temperature NMR spectra suggest that different aggregation states between Et₂O and THF based solutions of these reagents exist.

Introduction

In the course of our work on the development of new higher order, mixed organocuprate reagents 1,² formed

$$CuCN + 2RLi \rightarrow R_2Cu(CN)Li_2$$

from copper cyanide and 2 equiv of an alkyl, aryl, or vinyllithium species, we were cognizant of the recent pioneering work of Ashby et al.³ which indicated an apparent equilibrium between the higher order species Me₃CuLi₂ and the Gilman reagent, Me₂CuLi, along with free MeLi (eq 1). The occurrence of free methyllithium in solution

$$Me_3CuLi_2 \rightleftharpoons Me_2CuLi + MeLi$$
 (1)

suggests that limitations on the use of Me_3CuLi_2 might exist which are not generally associated with lower order reagents (e.g., 1,2-addition to ketones⁴). Whether such an equilibrium exists in the case of 1, however, remained to be elucidated. Herein we present details of our the study employing both chemical and spectroscopic means of analysis designed to probe the solution phenomena associated with higher order mixed systems of general formula R₂Cu(CN)Li₂. In view of the apparent broad synthetic value of these novel reagents,⁵ the insight gained from such a study might further define the scope of the chemistry involved and explain the chemical differences observed between lower and higher order organocuprates.

Results and Discussion

Chemical Tests. Although the value of reagents 1 to the synthetic practitioner has been reported and continues to show promise,² the possibility arises of forming still more highly mixed systems $RR'Cu(CN)Li_2$, 2, and presents an opportunity for defining the selectivity of ligand transfer.⁶ Furthermore, one of our original goals^{7a} has been to develop an alternate protocol incorporating a second nontransferable (i.e., "dummy") ligand (2, $R' = R_R = R_{residual}$) thereby necessitating use of only one potentially valuable lithiated species (2, $R = R_T = R_{transferable}$).⁵

Toward these ends we devised a series of experiments which would ultimately shed light on the integrity of both reagents 1 and their second generation counterparts 2. Having already examined the substitution reactions of epoxides with 1,^{7b} we chose 3 as the substrate. Reaction of 3 with (presumably) $Me(n-Bu)Cu(CN)Li_2$, formed by sequential addition of 1 equiv of each alkyllithium to CuCN,⁸ is to be compared with the results from reaction of 3 with the reagent(s) obtained by combining into one pot 0.5 equiv each of Me₂Cu(CN)Li₂ and (n-Bu)₂Cu-(CN)Li₂. If complete ligand scrambling occurs, the product ratio observed from this latter experiment should parallel that of the former reaction. Such a comparison would represent an unequivocal test of reagent solidarity. Hence, both 1 R = Me and R = n-Bu were prepared and 1 equiv of 3 was added to each, the results of which are shown in Table I. After 2 h at -40 °C there was obtained ca. 55%⁹ and ca. 83%¹⁰ alcohols 4 and 5, respectively. Formation of the highly mixed species 2, R = Me, R' = n-Bu, followed by introduction of 1 equiv of 3 led to both 4 (ca. 8%) and 5 (ca. 63%).¹¹ Thus, the selectivity of transfer of an

n-butyl over a methyl group took place in a ratio of ca. 8:1. Similar control experiments for 1, R = Me and R = n-Bu, were next carried out by using 0.5 equiv of reagent relative to epoxide. The former gave 4 in ca. 31% yield,¹² the latter afforded the tertiary carbinol 5 to the extent of ca. 39%.^{12,13}

Two additional control reactions, however, remained to be carried out. Assuming that delivery of one R group from 1 initially takes place, the resulting organocopper species so formed might be the lower order reagent RCu-(CN)Li, 6 (vide infra), itself a reactive reagent.¹⁴ Therefore, to determine the maximum contribution of 6. R = Me and R = n-Bu, to oxirane cleavage, 1 equiv of 3 was added to each. Under otherwise identical conditions of time, solvent, and temperature, 6, R = Me, led to ca. 6% of 4, while 6, R = n-Bu, afforded only 3-4% of 5.¹² Thus, under the experimental parameters (THF, -40 °C, 2 h) surrounding epoxide opening with 1, the corre-

⁽¹⁾ Recipient of an American Cancer Society Junior Faculty Research Award, 1981-1983. A. P. Sloan Foundation Fellow, 1984-1986.

⁽²⁾ For a review, see: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J.

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(b) A. Tetrahedron Rep., in press.
(c) Ashby, E. C.; Watkins, J. J. J. Am. Chem. Soc. 1977, 99, 5312.
(d) Macdonald, T. L.; Still, W. C. J. Am. Chem. Soc. 1975, 97, 5280.
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(973, 95, 7788. (b) Corey, E. J.; Beames, D. J. Ibid 1972, 94, 7210. (c) House, H. O.; Umen, M. J. J. Org. Chem. 1973, 38, 3893. (d) Corey, E. J.; Floyd, D. M.; Lipshutz, B. H. Ibid. 1978, 43, 3418.

^{(7) (}a) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. J. Am. Chem. Soc. 1981, 103, 7672. (b) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. Ibid 1982, 104, 2305.

⁽⁸⁾ The order in which the RLi and R'Li are introduced is of no consequence in reactions of 2.

⁽⁹⁾ Obtained along with 20% recovered starting material.

⁽¹⁰⁾ Approximately 4% of 3 was recovered.

⁽¹¹⁾ In this case, 13% starting material remained.

⁽¹²⁾ The remainder of the material was epoxide 3.

⁽¹³⁾ Similar studies on 1-methylcyclopentene oxide showed the same trends in product distribution.

Marino, J. P.; Abe, H. J. Am. Chem. Soc. 1981, 103, 2907. Marino,
 J. P.; Kelly, M. G. J. Org. Chem. 1981, 46, 4389. Marino, J. P.; Floyd,

D. M. Tetrahedron Lett. 1979, 675.



sponding reactions of 6 have a negligible impact on product distribution. These control studies are also summarized in Table I (columns e and f).

At this point, the stage was set for the key experiment. One half equiv of both 1, R = Me, and 1, R = n-Bu, were prepared in separate flasks and then combined via cannula into a single vessel. 3 (1 equiv) was introduced and the reaction was allowed to proceed in the usual fashion. In principle, should no mixing of alkyl groups take place, the results would be similar to those obtained previously wherein 1/2 equiv of each reagent had been used independently (i.e., columns c and d). If on the other hand, the individuality of each cuprate has been compromised, then up to 1 full equiv of 2 ($\mathbf{R} = \mathbf{Me}, \mathbf{R'} = n-\mathbf{Bu}$) could be formed according to eq 2. The variation in yields of 4 and $\frac{1}{2}Me_2Cu(CN)Li_2 + \frac{1}{2}(n-Bu)_2Cu(CN)Li_2 \rightarrow \frac{7}{8}$

$${}^{8}_{1} \text{ Me}(n-\text{Bu})\text{Cu}(\text{CN})\text{Li}_{2} (2)$$

5 reflect the relative percentages of 7, 8, and 9. Complete conversion of 7 and 8 to 9 (i.e., total mixing) could be inferred if the product yields of 4 and 5 are very similar to those seen using preformed 9 (column g). The results of this particular experiment are cited in Table I, column h. Remarkably, these data essentially match that garnered with CuCN/MeLi/n-BuLi (column g) and quite cogently attest to the ease with which alkyl groups on copper can dissociate and reassociate in solutions of 2. These early observations served to further whet our curiosity as to the composition of 1, as more informative data were to follow utilizing IR and, in particular, NMR spectroscopic techniques.

Spectroscopic Analyses. From the outset we anticipated that substitution of a nitrile for methyl ligand on copper would engender significant differences in the solution properties of 1 compared with Me₃CuLi₂. While CuCN is well-known to form mixed homocuprates 6,^{14,15} the question as to whether the second R group (of RLi) is directly attached to the copper center remained unanswered. Conceivably RLi could be adding to the nitrile ligand giving rise to metaloimine 10. However unlikely



(15) Hornemann, U.; Aikman, M. J. Chem. Commun. 1973, 88. Hamon, L.; Levisalles, J. J. Organomet. Chem. 1983, 251, 133.

this may seem, it could not a priori be eliminated as a possible structure for 1. Hence, 1, R = Me, was prepared and its solution (Et_2O) infrared spectrum recorded. As expected, the nitrile stretch was visible, absorbing at 2105 cm⁻¹ (Figure 1, Supplementary Material), while an imine stretch was not observed. Interestingly, 6, R = Me (in Et_2O), likewise gave a cyanide stretch at the identical position. On the basis of this data the nitrile group is intact, thus, 10 can be safely ruled out as a structural candidate for 1.

Considerably more illuminating information was secured by a series of variable temperature NMR experiments. We were surprised to find upon perusal of the literature that only a few scattered reports dealing with NMR studies on traditional Gilman-type reagents are available.¹⁶ In addition to Ashby's contribution³ which significantly extends the earlier NMR experiments of House^{16a,b} on Me₂CuLi, there appears to be but one report dealing in part with NMR data on the mixed homocuprate Me(t-Bu)CuLi.¹⁷ Unfortunately, little discussion is devoted to the spectroscopic results. The key point made, however, regards the combination of $[Me_2CuLi + (t-Bu)_2CuLi]$, where a unique methyl singlet is observed (δ -1.25) from this mix which contrasts with that $(\delta -1.70)$ derived from the one pot formulation using CuI/MeLi/t-BuLi. Both were recorded under similar conditions of temperature (-20 °C), solvent ratio (2:1 ether-pentane), and concentration (0.33 M). Hence, the conclusion that can be drawn from this work is that alkyl groups once affixed to copper in *lower order* reagents do not scramble (eq 3). An equilibrium of this

2 Me(t-Bu)CuLi
$$\#$$
 Me₂CuLi + (t-Bu)₂CuLi (3)

type had been proposed previously for both lithium^{6a} and magnesium based¹⁸ cuprates to explain differences in reactivity and selectivity between ligands. This result (eq 3) is in marked contrast to those recorded using chemical tests on CuCN based higher order reagents 1 discussed earlier (vide supra).

Variable low temperature NMR studies at 100 MHz were initially conducted on Me₂Cu(CN)Li₂ in THF/Et₂O by using an external capillary tube containing CH₂Cl₂ as reference. Varying the temperature between -95 and +5

^{(16) (}a) House, H. O.; Chu, C. Y. J. Org. Chem. 1976, 41, 3083. (b) House, H. O.; Respess, W. L.; Whitesides, G. M. Ibid. 1966, 31, 3128. (c) San Filippo, J. Inorg. Chem. 1978, 17, 275. (17) Berlan, J.; Koosha, K.; Battioni, J.-P. Bull. Chim. Soc. Fr. 1978,

^{575.}

⁽¹⁸⁾ Sjoholm, R.; Backlund, P. Finn. Chem. Lett. 1980, 28.

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8 1.0

Figure 2. NMR study of higher order, mixed organocuprates in THF at -20 °C.

°C gave a single, somewhat sharp signal at δ -1.50.¹⁹ That this was indeed due to a discrete species was shown by the series of spectra (recorded at -20 °C) illustrated in Figure 2. Initial generation of the mixed reagent MeCu(CN)Li gave a clean singlet at δ -1.40. Sequential addition of MeLi (initially <0.5 equiv, then >0.5 equiv but <1.0 equiv) gave rise to a new peak at δ -1.50 which gradually increased in size at the expense of the signal at δ -1.40. When precisely 1 additional equiv of MeLi had been added, only a single peak (at δ -1.50) was visible in the spectrum. Addition of >1 equiv of MeLi gave rise to a new broad signal (δ -2.07) which is characteristic of free MeLi.³ Therefore, since both 6. R = Me, and free MeLi are not seen when the CuCN:MeLi ratio is exactly 1:2, an equilibrium (eq 4)

$$R_2Cu(CN)Li_2 \Longrightarrow RCu(CN)Li + RLi$$
(4)

analogous to eq 1, should it exist, must lie far to the left. The appearance of free MeLi in the spectrum of $[Me_2Cu(CN)Li_2 + MeLi]$ indicates that any exchange of MeLi with 1, R = Me, is slow on the NMR time scale. Furthermore, the chemical shift of both 1 and 6, R = Me, is essentially invariant, in spite of the continuous change in solvent ratio (THF:Et₂O) and concentration as more MeLi (in Et₂O) is added.

The ease with which the higher order and lower order mixed reagents 1 and 6, R = Me, could be distinguished by NMR encouraged us to examine the copper-containing species formed following delivery of (presumably) one R group from 1. The logical byproduct of ligand transfer is the homocuprate 6 which should be observable over time upon treatment of 1 with a suitable substrate. Thus, reaction of 1-methylcyclopentene oxide with Me₂Cu(CN)Li₂ in THF at 0 °C was monitored by NMR after 0.75, 3, and 6 h (Figure 3, Supplementary Material). The appearance and gradual increase in the peak at δ -1.40, corresponding to 6, R = Me, at the expense of 1, R = Me (δ -1.50) is readily discerned. After 6 h, the reaction was guenched. Analysis by VPC indicated that 37% product²⁰ (cis-1.2dimethylcyclopentan-1-ol)^{7b} was present, a quantity which compares quite favorably with the extent of formation of the lower order mixed cuprate (32% as judged by integration).

We next focused on the more highly mixed reagent Me(n-Bu)Cu(CN)Li₂, 9. Earlier chemical tests (vide supra) indicated that the stoichiometry represented by 9 is arrived at either by sequential addition of MeLi and n-BuLi to CuCN or upon admixture of Me₂Cu(CN)Li₂ with (n-Bu)₂Cu(CN)Li₂. Hence, we fully expected the NMR spectrum of 9 to show a methyl singlet as well as an ABX₂ pattern characteristic of diastereotopic protons on the methylene group attached to copper (as in 11).²¹ The



spectrum, taken at -27 °C, of the preformed reagent (CuCN + MeLi + n-BuLi) is shown in Figure 4c. Sur-

⁽¹⁹⁾ The 300-MHz proton spectrum of Me₂Cu(CN)Li₂ at -30 °C likewise gave a single peak.

⁽²⁰⁾ The remaining material was the starting oxirane.

⁽²¹⁾ For a somewhat analogous example in a tetrahedral iridium species, see: Hoyano, J. K.; Graham, W. A. G. J. Am. Chem. Soc. 1982, 104, 3723.



Figure 5.

prisingly, not one but two very close peaks (δ -1.53 and δ -1.56) are visible, in addition to what is seemingly a doublet of triplets centered at δ -0.38, suggesting at least two different methyl and methylene signals. For verification of our chemical tests, the same spectrum should result from the 1:1 combination of 1, R = Me, plus 1, R = *n*-Bu. Indeed, the spectrum of [Me₂Cu(CN)Li₂ + (*n*-Bu)₂Cu(CN)Li₂] did not show a CH₃ singlet and CH₂ triplet characteristic of the individual reagents (Figure 4, parts a and b, respectively) but rather gave the same multiple absorptions seen earlier (Figure 4, parts c and d). Thus, while lower order cuprates supposedly maintain their integrity in solution,¹⁷ higher order, highly mixed systems (i.e., RR'Cu(CN)Li₂, 2) irrespective of the mode of preparation revert to the same chemical blend.

Further support for this loss of initial constitution was accrued by recording the NMR spectrum of Me₂Cu(CN)Li₂ to which had been added 1 equiv of *n*-BuLi. The singlet originally present for 1, R = Me (Figure 4a), was replaced by the two now characteristic singlets at δ -1.53 and δ -1.56 of equal intensity. In addition, there appeared a broad singlet at δ -2.07 due to free MeLi and an apparent doublet of triplets (centered at δ -0.37) corresponding to at least two methylene units (of *n*-Bu ligands) attached to copper.

The facility with which these reagents (e.g., 7 and 8)appear to exchange ligands, as also noticed by Ashby concerning Me₃CuLi₂ (vide supra), suggested that results from the earlier French work¹⁷ were most atypical. In repeating their study, which involved treatment of CuI with MeLi (1 equiv) followed by t-BuLi (1 equiv), we obtained a 300-MHz NMR spectrum, illustrated in Figure 5, which is clearly (and reproducibly) different from the reported data.¹⁷ Moreover, in our hands, the admixture of $Me_2CuLi + t$ - Bu_2CuLi , initially prepared in separate flasks, afforded the identical spectrum. To insure the generality of ligand mobility, the same series of experiments was conducted by using *n*-BuLi in place of *t*-BuLi. As anticipated, the spectra from both reagent combinations (i.e., CuI/MeLi/n-BuLi vs. $Me_2CuLi + n$ -Bu₂CuLi) were superimposable (Figure 6, Supplementary Material). Hence, the conclusion, therefore, which may be drawn from

these studies is that *both* lower and higher order organocuprates have common ground with respect to their tendencies to readily exchange ligands between copper centers. While such a practice involving copper(I) dianions (i.e., higher order cuprates) can be mechanistically envisioned to proceed via the corresponding lower order species, the related pathway between lower order species may invoke either (a) an RCu intermediate, which, in sufficient quantities at least, would be expected to assume its polymeric state and drop out of solution, or (b) an equilibrium between dimer and monomer forms.

Most significant of these NMR experiments on 9 is the occurrence of more than one distinct CH_3 singlet in the spectrum of $Me(n-Bu)Cu(CN)Li_2$. This spectroscopic observation, taken together with the common assumption that Cu(I) clusters are of a tetrahedral nature,^{22,23} implies that 2 (and hence, most likely 1) cannot be monomeric. That is, it is difficult to see how a monomeric species of formula $Me(n-Bu)Cu(CN)Li_2$ may give rise to what appears to be two sharp singlets, neither one of which corresponds in chemical shift to $Me_2Cu(CN)Li_2$ (Figure 4a). This would be an especially noteworthy assessment since it contrasts with the nature of Me_3CuLi_2 , for which evidence of its monomeric state has been described.³

To further substantiate that the assignment as two "singlets" is, in fact, due to magnetically dissimilar methyl groups, a ¹³C NMR experiment was also performed at 75.45 MHz on Me(n-Bu)Cu(CN)Li₂ to eliminate the possibility of multiple peaks arising from spin coupling. If two magnetically unique methyls are present, two key peaks would be expected in the carbon spectrum. The cyanide carbon was anticipated to be broad and of little information.²⁴ The spectrum (Figure 7, Supplementary Material), recorded at -30 °C, reveals a poorly defined nitrile carbon absorption at ~161 ppm and two distinct singlets of roughly equal intensity at -11.103 and -10.998 ppm. Hence, it would appear that the data are consistent with the hypothesis that two individual methyl ligands are present.

Additional insight as to the effect of varying the Cu(I) salt precursor on the spectroscopic properties of higher order cuprates was secured from a brief study using CuSCN. That is, addition of MeLi (2 equiv) to CuSCN in THF gives rise to a tan colored solution believed to contain Me₂Cu(SCN)Li₂.²⁵ The low temperature (-30 °C) NMR spectrum of this higher order, mixed reagent, as with the CuCN analogue, affords a single peak at δ -1.50. Upon cooling to -65 °C, however, this absorption splits into two well-resolved peaks at δ -1.32 and δ -1.59 in a ratio of ca. 1:4 (Figure 8, Supplementary Material).

In light of the dependence of spectral properties of 1 and 2 on both the alkyl ligands involved as well as the source of the Cu(I) salt (CuCN vs. CuSCN), it was of great interest to consider the effect of varying the composition of 2. Hence, in addition to a methyl group (i.e., 2, $R = CH_3$), a second ligand, R' = Ph was selected to reflect the more closely related basicities of the parent organolithium species (i.e., MeLi vs. PhLi) as compared with that of MeLi vs. *n*-BuLi. The NMR spectrum of Me(Ph)Cu(CN)Li₂ in THF (at -30 °C) is illustrated in Figure 9 (Supplementary Material). Substitution of a phenyl for *n*-butyl group on copper affords a spectrum again showing two methyl

⁽²²⁾ Cotton, F. A.; Wilkison, G. "Advanced Inorganic Chemistry"; Wiley: New York, 1972.

⁽²³⁾ For an alternative, see: Stewart, K. R.; Lever, J. R.; Whangbo, M.-H. J. Org. Chem. 1982, 47, 1472.

⁽²⁴⁾ Pesek, J. J.; Mason, W. R. Inorg. Chem. 1979, 18, 924.

⁽²⁵⁾ Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. J. Org. Chem. 1983, 48, 546.

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resonances at δ -1.38 and δ -1.50 in a ratio of ca. 2:1, in contrast to the 1:1 ratio for those at δ -1.53 and δ -1.56 for 9. Whether these absorptions parallel those described earlier for 9 or connote a major electronic perturbation due to the aromatic ring (i.e., with its potential for $d\pi^*$ backbonding) remains to be clarified. It would appear, however, with four distinct higher order organocuprates [Me₂Cu-(CN)Li₂, Me(*n*-Bu)Cu(CN)Li₂, Me(Ph)Cu(CN)Li₂, and Me₂Cu(SCN)Li₂] providing closely interrelating NMR data that strong evidence as to the similarities in reagent geometry is now in hand.

To further probe the structural features of CuCN derived organocuprates, the role of solvent in determining the aggregation state of R₂Cu(CN)Li₂ was next considered. With lower order Gilman reagents, solvent can be a controlling reaction parameter,²⁶ although it is of little influence on the dimeric nature of R_2CuLi .²⁷ In the case of Me₃CuLi₂, a monomeric species exists regardless of the ethereal medium (THF, Et₂O, Me₂O).³ Although the chemical shifts for cuprates prepared from CuCN in varying percentages of THF/Et₂O (and in some cases, hexane, from *n*-BuLi) did not change, it was anticipated that the total absence of THF from solutions of 1 or 2 would have a profound impact on the copper complex, as detected by NMR. In the event, the spectrum of 7 in Et_2O displayed a singlet at δ -1.28, while that of 9 (from CuCN/MeLi/ *n*-BuLi) in Et_2O /hexane showed, in addition to a poorly resolved CH₂ triplet (now at δ -0.35), a solo broad singlet also at $\delta -1.28$! This dramatic change in both line shape (compare with Figure 4c) and chemical shift (ca. 0.25 ppm) is far too great to be credited to a simple exchange of ethereal solvents.³ Instead, we favor an altered aggregation state which is in response to the poorer Lewis basicity of Et₂O vs. THF.³ The loss in peak definition, seen in the IR spectrum of 7 (Figure 1, Supplementary Material), can be accounted for by the reagent adopting an oligomeric structure such as in 12. Notice here that the nitrile ligand serves both as occupant of the fourth coordination site and as a means of bridging monomers.²²

$$\left\{ \begin{array}{c} R^{R} & R^{H} \\ -CN - Cu - CN - Cu - CN - Cu - CN \\ R^{H} & R^{H} \\ R^{H} & R^{H} \end{array} \right\}$$

Interestingly, sequential lowering of the temperature at which the spectrum of 9 was taken (i.e., $-20 \rightarrow -30 \rightarrow -45$ $\rightarrow -65$ °C) gave demonstrably different data from that seen in THF (vide supra). In Et₂O, an apparent equilibrium between Me(*n*-Bu)Cu(CN)Li₂ and MeCu(CN)Li plus free MeLi could be detected.²⁸ The initially broad signal seen





at -20 °C (δ -1.28) splits into two peaks, best seen at -65 °C, one at δ -1.36, the other at δ -1.38, in addition to a broad signal for MeLi at δ -2.03. These spectra are illustrated in Figure 10 and serve to manifest the variation in reagents 1 or (or 2) as a function of solvent.

To further highlight the differences in reagent composition in THF vs. Et_2O , the spectrum for 9 in Et_2O /hexane should be convertible to that seen previously (Figure 4c), simply by the addition of THF. Dilution of the sample, which gave rise to the spectra shown in Figure 10, with an equal volume of THF rapidly led to the identical spectrum of 9, as if the reagent had been prepared originally in THF.

One aspect of this discussion which has not been addressed thus far concerns the role (if any) of the gegenion in solution. It is difficult to ascertain with confidence in what way lithium affects the structure of the reagent in ethereal media and hence, the spectroscopy realized to date. We have, however, confirmed that a dilithium salt is critical to the success of the coupling between higher order cuprates and secondary unactivated alkyl halides. As examples, substitution of 2 equiv of *n*-BuMgCl for 2 equiv of *n*-BuLi in the formation of $R_2Cu(CN)M_2$ followed by addition of cyclopentyl iodide (0 °C, 30 min) or 2bromopentane (0 °C, 1 h) afforded only 18% and 5% of the corresponding hydrocarbons, respectively. By way of comparison, each of the anticipated products of coupling

⁽²⁶⁾ Posner, G. H. Org. React. (N.Y.) 1972, 19, 1; 1975, 22, 253.

⁽²⁷⁾ Pearson, R. G.; Gregory, G. D. J. Am. Chem. Soc. 1976, 98, 4098.
(28) The additional n-Bu containing species (i.e., n-BuLi, n-BuCu-(CN)Li, and 9) were presumably present within the complex pattern at

⁽C.N.L.), and 9) were presumably present within the complex pattern at δ -0.47 which is not readily interpreted.

⁽²⁹⁾ Unfortunately, not all of the spectral data amassed on 7, 8, and 9 is consistent, as yet, with the discussion presented. Following the observation of structure dependence on solvent, more detailed IR studies³⁰ were performed on these three cuprates in both Et₂O and THF (see supplementary material). In Et₂O, the IR spectrum for each over time underwent only subtle changes. The corresponding spectra in THF, however, which in all cases showed two sharp nitrile stretches after 5 min at 0 °C, changed to essentially a single, sharp absorption after ca. 2 h. One logical deduction is that two isomers, initially present for 7-9 in THF as seen on the IR time scale, can only be detected for 9 on the NMR time frame. Thus, both 7 and 8 are seen as reagents with rapidly exchanging ligands, each giving an averaged signal in the NMR spectrum (Figure 4a,b). The discrepancy arises in the case of 9. The IR spectrum suggests that, as with 7 and 8, one of two species is increasing at the expense of the second isomer. The NMR spectrum of 9 (Figure 4c), however, over the same 2-h period, remains unchanged.

⁽³⁰⁾ Each cuprate was freshly prepared and then stored at 0 °C under Ar over the 2-h period. Fresh aliquots were drawn after 5 min, 1 h, and 2 h of which the IR spectrum was recorded. As the stability of these reagents has been amply measured and demonstrated,³¹ the spectral changes observed are almost certainly real and not a reflection of reagent decomposition.

 ⁽³¹⁾ Bertz, S. H.; Dabbagh, G. Chem. Commun. 1982, 1030. Bertz, S.
 H.; Dabbagh, G.; Villacorta, G. M. J. Am. Chem. Soc. 1982, 104, 5824.

from these reactions have been obtained by using 1 or 2 in yields exceeding 85%.⁵



It should also be acknowledged that, perhaps, more questions have been raised by this work than have been answered.²⁹ For example, it is still not obvious why the thermodynamic sink for the admixture of 7 with 8 lies so heavily, if not completely, on the side of $9^{.32}$ Although Et₂O solutions of 1 appear to be highly complexed, THF as solvent promotes lower states of aggregation, at least as suggested by the spectral data recorded herein. Whether these cuprates are monomeric or, more likely, dimeric in THF remains to be established. Clearly, should a monomeric reagent be involved, the NMR spectrum of, e.g., 9 argues against a tetrahedral array. Hence, to accommodate the data, one can consider the interesting possibilities of a planar arrangement or an alternative tricoordinate Cu(I) formed according to the equilibrium shown below. While the former suggestion is unprecedented, so was a linear, unconstrained dicoordinated Cu(I) species unknown until just recently.³³ The latter proposal

$$CuL_3$$
(solvent) \Rightarrow CuL_3 + solvent

is unlikely since the relative peak intensities for the methyl signals in 9 remain unchanged between -95 and 5 °C. A dimeric species, on the other hand, may be either cyclic or acyclic (or both). The cyclic reagent must contend with the planarity requirements of two nitrile ligands. A linear dimer, which cannot be ruled out, nonetheless raises serious concerns over existing opportunities for further associations via the free nitrile ligand, a situation suggested to be occurring in Et_2O (vide supra). Still more curious is the location of two lithium ions within the copper cluster. While these may be solvated by THF, in relatively nonpolar ethereal media the gegenion is likely to be associated with the copper dianion. Hence, placement of the two Li⁺ on a tetrahedral array could impart an element of asymmetry into the complex. Whatever the structure of these higher order cyanocuprates, it would appear that the cyano group is responsible for generating a most atypical reagent. in terms of both their synthetic potential and structural classification.³⁴ Thus, it is appreciated that studies of this type are not in themselves a definitive means of structure elucidation. Other potentially informative experiments include use of ebullioscopic,³ EXAFS, and Li NMR³⁵ techniques. In addition, we are continuing to look for the proper combination of ligands, solvent, and genenion which

will ultimately lead to a crystalline derivative for subsequent X-ray analysis.

Summary

The facility with which ligands may dissociate and reassociate from one copper center to another in R₂Cu- $(CN)Li_2$ has been demonstrated by using both chemical and spectroscopic means of analysis. In the former case, reactions of a 1,1-disubstituted epoxide with cuprates prepared from either sequential addition of MeLi and n-BuLi to CuCN (i.e., Me(n-Bu)Cu(CN)Li₂) or by mixing Me₂Cu(CN)Li₂ with (n-Bu)₂Cu(CN)Li₂ afforded essentially the same product distributions. By means of variable low temperature NMR experiments, these chemical studies were corroborated. Further NMR analyses on Me₂Cu-(CN)Li₂ in THF revealed no detectable equilibrium between this higher order species and the lower order reagent MeCu(CN)Li and free MeLi. With the more highly mixed cuprate $Me(n-Bu)Cu(CN)Li_2$, two unique methyl signals are present in THF, an observation further substantiated by ¹³C NMR spectroscopy. In Et₂O, a poorer Lewis base than THF, the aggregation state changes markedly, with spectral studies suggesting an oligomeric nature, presumably bridging via the cyano ligands. Introduction of THF to this soution completely converts the complex back to the identical species normally formed in THF, as evidenced by NMR techniques.

Experimental Section

All glassware and syringes were dried in an oven overnight at 120 °C prior to use. Solvents were freshly distilled from sodium/benzophenone ketyl. Methyllithium (low halide) was purchased from Aldrich, and *n*-butyllithium from Ventron. Both were titrated according to the method of Watson and Eastham.³⁶ Copper cyanide was obtained from MCB as a tan powder and stored in an Abderhalden over KOH under vacuum at 56 °C.

Most variable temperature ¹H NMR experiments were conducted on a Varian XL-100 spectrometer. ¹³C NMR measurements were made on a Nicolet NT-300 instrument. As reference, a capillary insert was used containing ca. 10% CH₂Cl₂ in acetone- d_6 . Infrared spectra was recorded in solution using a Perkin-Elmer Model 283 spectrophotometer. VPC analyses were carried out on a Hewlett-Packard Model 5880A gas chromatograph containing a 6 ft × ¹/₈ in. column of 20% SE-30 Chromsorb W.

Representative Procedure for Reactions of 1 and 6 with Epoxide 3 (Reaction of 7). Cuprous cyanide (44.8 mg, 0.50 mmol) was placed in a two-neck 25-mL round-bottom flask equipped with a magnetic stir bar. The salt was dried azeotropically with toluene $(1 \times 1.0 \text{ mL})$ under vacuum at room temperature and then purged with dry argon. Dry THF (1.0 mL) was added via syringe and the slurry was cooled to -78 °C. Methyllithium (0.63 mL, 1.0 mmol, 1.58 M in Et₂O) was added dropwise producing a light yellow-tan solution. The cuprate was warmed to -40 °C where the epoxide 3 (59 μ L, 0.50 mmol) was introduced neat via microliter syringe. Stirring was continued for 2 h at -40 °C before quenching with 5 mL of a 90% saturated NH₄Cl/10% concentrated NH₄OH solution. Further stirring for ca. 30 min at room temperature was allowed before the two-phase mixture was transferred to a separatory funnel and extracted with Et₂O (2×5 mL). VPC analysis indicated a 66.5% yield of 4, isolated as a clear, colorless liquid.³⁷ IR (neat) cm⁻¹ 3400, 2980, 2880, 1455, 1375, 1155, 950, 920, 785; NMR (CDCl_3) δ 1.45 (6 h, q, J = 8 Hz), 1.15 (1 H, s), 0.85 (9 H, t, J = 8 Hz).

Reaction of 8. The same procedure given above for the use of 7 was employed, using *n*-butyllithium (0.40 mL, 1.0 mmol, 2.50 M). Following workup, VPC analysis indicated that 5 had formed to the extent of 81.3%, isolated as a clear, colorless liquid: IR (neat) cm⁻¹ 3415, 2940, 2880, 1460, 1379, 1150, 975, 945, 930; NMR (CDCl₃) δ 1.30 (12 H, m), 0.85 (9 H, m); mass spectrum, m/e

⁽³²⁾ We have also observed by integration of the NMR spectrum that treatment of 9 with 1 equiv of n-BuLi at -25 °C leads to a mixture of 8 and 9 with liberation of free MeLi, in a ratio of 30:5:19. The area assigned to 8 must therefore contain some residual n-BuLi which did not completely replace the methyl ligand in 9. (33) Sorrell, T. N.; Jameson, D. L. J. Am. Chem. Soc. 1983, 105, 6013.

⁽³³⁾ Sorrell, T. N.; Jameson, D. L. J. Am. Chem. Soc. 1983, 105, 6013. (34) While Ashby's work,³ to our knowledge, is the only directly related spectroscopic investigation on organocopper dianions, there are many other literature reports of a similar nature involving other metals which have afforded data quite analogous to our findings. One very recent case in point concerns the reactions of organolithium reagents with [PdR₂L₂)-type square planar complexes; cf. Nakazawa, H.; Ozawa, F.; Yamamoto, A. Organometallics 1983, 2, 241. Within the Group IB series, elegant and highly elucidating observations, in particular, by the Kochi group on (monomeric) square planar gold(III) complexes are in many respects remarkably similar to a number of observations described herein on copper(I) species, cf. Komiya, S.; Kochi, J. K. J. Am. Chem. Soc. 1976, 98, 7599.

⁽³⁵⁾ Lipshutz, B. H., Kozlowski, J. K.; Breneman, C. M., submitted for publication.

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(relative intensity) 143 (3.3), 129 (55.5), 110 (9.7), 98 (31.1), 87 (100), 69 (51.2), 55 (38.1), 45 (44.1), 41 (41.4), 29 (43.7), high-resolution mass spectrum, calcd for $C_{10}H_{22}O - C_2H_5$ 129.1280, found 129.1260.

Reaction of 6, R = Methyl. The same procedure with 7 was followed, except 1.0 equiv of MeLi (0.32 mL, 0.50 mmol, 1.58 M) was added to CuCN. VPC analysis showed formation of 4 in 6% yield.

Reaction of 6, R = n-Butyl. The procedure given for the preparation of 8 was followed except 1.0 equiv of n-BuLi (0.20 mL, 0.50 mmol, 2.50 M) was added to CuCN. GC analysis indicated that 5 had been formed to the extent of ca. 3%.

Preparation and Reaction of 9 with Epoxide 3. Copper cyanide (44.8 mg, 0.50 mmol) was placed in a 25-mL two-neck round-bottom flask which contained a magnetic stir bar. The salt was dried azeotropically with toluene $(1 \times 1.0 \text{ mL})$ under vacuum at room temperature and then purged with dry argon. Dry THF (1.0 mL) was introduced producing a slurry which was cooled to -78 °C. Methyllithium (0.32 mL, 0.50 mmol, 1.58 M) was added dropwise which resulted in a light tan solution after ca. 10 min. Subsequent addition of n-butyllithium (0.20 mL, 0.50 mmol, 2.50 M) produced no visible change. After warming the solution to -40 °C, the oxirane 3 (59 μ L, 0.50 mmol) was added neat via syringe. Stirring was maintained at this temperature for 2 h after which time the reaction was quenched with 5 mL of a 90% saturated $NH_4Cl/10\%$ concentrated NH_4OH solution. After stirring for an additional 30 min at room temperature, the mixture was transferred to a separatory funnel and extracted with Et_2O (2 × 5 mL). VPC analysis indicated both 4 and 5 were present in yields of 8.1% and 61.8%, respectively, with 13% starting material remaining.

Preparation, Mixing, and Reaction of 7 and 8 with Epoxide 3. Cuprous cyanide (22.4 mg, 0.25 mmol) was placed in a 25-mL two-neck round-bottom flask equipped with a magnetic stir bar. After the salt was dried azeotropically with toluene ($1 \times 1.0 \text{ mL}$) under vacuum at ambient temperature, the vessel was purged with and maintained under dry argon. THF (0.50 mL) was added and the slurry was cooled to -78 °C where *n*-BuLi (0.20 mL, 0.50 mmol, 2.5 M) was introduced dropwise generating a light tan solution within 10 min.

In a separate flask, the above procedure was duplicated substituting methyllithium (0.32 mL, 0.50 mmol, 1.58 M) for *n*-BuLi, which likewise produced a light tan solution.

Reagent 7 (Me₂Cu(CN)Li₂), precooled to -78 °C, was transferred via cannula into cuprate 8, which was also maintained at -78 °C. The resulting solution was stirred for 5 min before warming to -40 °C. Epoxide 3 (54 µL, 0.50 mmol) was then added dropwise with stirring upon completion of which the reaction was continued for 2 h before quenching with 5 mL of a 90% saturated NH₄Cl/10% concentrated NH₄OH solution. Following an additional 30-min period of stirring at room temperature, extractive workup (Et₂O, 2×5 mL) was followed by VPC analysis which showed that both products 4 and 5 were present in 8.6% and 60.3% yields, respectively.

Representative Procedure for NMR Sample Preparation. Me₂Cu(CN)Li₂. Following the generation of 7 as outlined above, the cold (-78 °C) solution was transferred under Ar via cannula to a dry, cold NMR tube. The tube was then fitted with a teflon plug from which a capillary insert containing $CH_2CH_2/acetone-d_6$ was suspended. The spectrum was then immediately recorded. The same technique was applied to both 9 (prepared from sequential addition of MeLi and *n*-BuLi) and 9 (prepared by mixing 1 equiv each of 7 and 8).

Preparation of 7 Containing 1 Equiv of n**-BuLi.** To cuprate 7 formed as described above and cooled to -78 °C was added 1.0 equiv of n-BuLi. The solution was then transferred via cannula to an NMR tube in the usual fashion and the spectrum immediately taken.

NMR Analysis of Reaction of 7 with 1-Methylcyclopentene Oxide. To reagent 7, cooled to 0 °C and prepared as described above, was added 1.0 equiv of 1-methylcyclopentene oxide³⁸ heat via syringe. Aliquots were transferred to an NMR tube during the course of the reaction (after 0.75, 3, and 6 h) in the usual fashion.

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Registry No. 3, 1192-17-2; 4, 597-49-9; 5, 2051-32-3; 6 (R = Me), 41753-78-0; 6 (R = n-Bu), 41742-63-6; 7, 80473-70-7; 8, 80473-69-4; 9, 86250-96-6; t-BuLi, 594-19-4; Me₂CuLi, 15681-48-8; t-Bu₂CuLi, 24406-16-4; CuSCN, 1111-67-7; Me₂Cu(SCN)Li₂, 91606-28-9; PhLi, 591-51-5; Me(Ph)Cu(CN)Li₂, 91328-62-0; n-BuMgCl, 693-04-9; MeLi, 917-54-4; n-BuLi, 109-72-8; n-Bu₂Cu(CN)(MgCl)₂, 91606-30-3; cyclopentyl iodide, 1556-18-9; 2-bromopentane, 107-81-3; cuprous cyanide, 544-92-3; 1-methyl-cyclopentene oxide, 16240-42-9.

Supplementary Material Available: Figures 1, 3, 6–9, and IR data for ref 29 (7 pages). Ordering information is given on any current masthead page.

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New Nitrogenous Sesquiterpenes from the Marine Sponge Axinella cannabina

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In addition to acanthellin-1 (1), an isonitrile previously found in *Acanthella acuta*, five new nitrogenous sesquiterpenes (2-6) have been isolated from the Mediterranean sponge *Axinella cannabina* and their structures elucidated on the basis of chemical and spectral data. These metabolites form two new isocyanide-isothio-cyanate-formamide series thus confirming the biogenetical relationship between these three classes of compounds.

The marine sponge Axinella cannabina is a fertile source of sesquiterpenes with diverse and often unusual carbocyclic skeleton, carrying isocyanide, isothiocyanate, or formylamine functionalities.¹⁻⁵ In view of the potential