It's on lithium! An answer to the recent communication which asked the question: 'If the cyano ligand is not on copper, then where is it?'

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In this paper we answer the question recently posed by Lipshutz and James (see title), and we present a mechanism which explains why the cuprates prepared from CuCN have a greater product-forming ability in many reactions.

A recent communication by Lipshutz and James reports "new ^{1}H and ^{13}C NMR spectral data on 'higher order' cyanocuprates" and asks the rhetorical question, 'If the cyano ligand is not on copper, then where is it?'[1] While these workers now appear to accept our point of view that organocuprates prepared from 2 equiv. of lithium reagent and 1 equiv. of CuCN are not true higher-order cuprates, we disagree with the statement of the 'intriguing possibility that would seem to accommodate both schools of thought'.

The basis for disagreement is threefold: (*i*) a copper–cyano π-complex also containing σ-bonded alkyl or aryl groups would be expected to give rise to a coupling ^2J between the cyano-C and C1 of the σ-bonded groups. (*ii*) EXAFS should reveal Cu–C and Cu–N distances for a side-bound CN, as it did for the end-bound CN in the so-called 'lower-order' cyanocuprates. (*iii*) Calculations for LiCN side-bound to a Gilman reagent fail to arrive at a stable minimum due to electron repulsion. Points (*ii*) and (*iii*) have been treated in companion communications by Penner-Hahn[2] and Snyder.[3]

'Reactivity' continues to be a persistent theme of the 'higher-order cyanocuprate' school, *e.g.* the paper in question contends that 'Such an orientation might explain the seemingly contrasting phenomena of higher-order cuprate stability and yet oftentimes greater reactivity (due to the increase in negative charge in the cyanocuprate) relative to monoanionic R_2CuLi'.[1] In this communication we briefly discuss the NMR data and then present the results of a new paradigm for comparing cuprate reactivity by using logarithmic reactivity profiles. We also report the dramatic effect of pyridine on organocuprate conjugate addition.

In 1990, Bertz reported that the ^{13}C NMR spectrum of $R_2CuLi{\cdot}LiCN$ prepared from recrystallized RLi (R = Ph, Et) and CuCN in [$^2H_8$]-thf was identical to that of the reagent prepared from CuI, except for the CN resonance, of course.[4] In 1991 he demonstrated that two-bond couplings ^2J across Cu^I could be observed and used to prove that CN was σ-bonded to Cu in 'lower-order cyanocuprates' RCu(CN)Li.[5] No coupling of CN to R was observed for $R_2CuLi{\cdot}Li^{13}CN$. The issue of cuprate aggregation has also been addressed.[6] Finally, a *bona fide* higher-order cuprate has been characterized by NMR spectroscopy[7] and X-ray crystallography.[8]

Krause *et al.* have used this method to show that ^{13}C in a (side-bound) copper–olefin complex couples to a methyl group on the same Cu.[9] Thus, if side-bound CN were present in $R_2CuLi{\cdot}LiCN$, the ^2J experiment should have detected it.

In his 1990 paper, Bertz pointed out that the NMR observations were more consistent with a complex between R_2Cu^- and $CNLi_2^+$.[4] A growing body of experimental[10] and theoretical[11–14] results suggests that the bonding in organocuprates is principally ionic in nature. For example, Snyder *et al.* calculated the energetics of the Me_3CuLi_2 system,[11] and they concluded that it is best described as a complex between Me_2CuLi and MeLi (Fig. 1, **VI**, R = R′ = Me), not a higher-order cuprate with three methyls bonded to Cu. There are several ways a CN^- could bridge between two Li^+ cations (Fig. 1, **I–IV**). Snyder[12] and Frenking[14] have calculated representative structures. Higher-order structures are 20–30 kcal (cal = 4.184 J) higher in energy!

The main experimental point of the new communication by Lipshutz and James is that the addition of LiCN to $Me_2CuLi{\cdot}LiI$ affords a new species: "What is clear is that 'LiCN', as $(LiCN)_n$ or as the solvent separated salt, is not present."[1] This has been asserted previously,[15] and it is not disputed by us; however, we disagree as to the structure of the new species, rather than the fact that a new one is formed.

The confusion over 'reactivity' arises because judgements about it have been based upon the yield of a desired synthetic target rather than kinetic data. The yield from an organocopper reaction is often dependent upon the competition between three fundamental processes: (*i*) the desired reaction, (*ii*) thermal decomposition, and (*iii*) transmetallation. In 1982 Bertz showed that $Bu_2CuLi{\cdot}LiCN$ is significantly more stable than $Bu_2CuLi{\cdot}LiI$, as far as thermal decomposition is concerned.[16] In 1991 he demonstrated that transmetallation is one of the main reasons that the yield of butylcyclohexane from iodocyclohexane is lower with $Bu_2CuLi{\cdot}LiI$ than with $Bu_2CuLi{\cdot}LiCN$.[17]

With a suitably reactive substrate, comparisons can be made at a temperature (−78 °C) where thermal decomposition is negligible. Table 1 summarizes the logarithmic reactivity profiles (LRPs) for the reactions of Bu(Th)CuLi·LiI (Th = 2-thienyl)[18] and Bu(Th)CuLi·LiCN[19] with cyclohex-2-enone **1** to afford 3-butylcyclohexanone **2**. A logarithmic reactivity profile is generated by finding where a reaction plateaus and then decreasing the reaction time by orders of magnitude to follow how the yield drops off. Surprisingly, the reagent prepared from CuI gives results that are comparable to those from CuCN. In fact, the yield from CuI is significantly better after 1 h at −78 °C in thf, the solvent used by Lipshutz *et al.*[19]

The reaction of $Bu_2CuLi{\cdot}LiCN$ with **1** yielded 99% of **2** in diethyl ether after 1 h at −78 °C.‡ No 1,2-adduct was observed

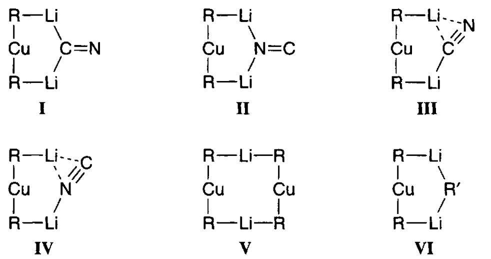


Fig. 1 Organocuprate structures (solvation omitted) calculated by Snyder[12] and Frenking[14]

Table 1 Logarithmic reactivity profiles for selected organocopper reagents with **1**[a]

	Yield of **2**[b]			
	Bu(Th)CuLi·LiI		Bu(Th)CuLi·LiCN	
t[c]/h	ether	thf	ether	thf
1	94	99	99	89
0.1	86	80	99	74
0.01	71	41	89	57
0.001	62	29	64	32

[a] **1** = Cyclohex-2-enone. Th = 2-thienyl. Reactions run on a 1 mmol scale at a concentration of 0.1 mol dm^{-3}. [b] **2** = 3-butylcyclohexanone, measured by GLC using the internal standard method. [c] 1 h = 60.0 min, 0.1 h = 6.0 min, 0.01 h = 36 s, 0.001 h = 4 s.

with the cuprates prepared from CuCN. For comparison, the reaction of $Bu_2CuLi·LiI$ with **1** in ether afforded 66% of **2**, 32% of recovered starting material, and 2% of 1,2-adduct after 1 h at −78 °C. Purified CuI was used.[20] In this case, 'recovered' is not necessarily synonymous with 'unreacted', as hydrolysis of the intermediate copper–enone complex returns starting enone.[21]

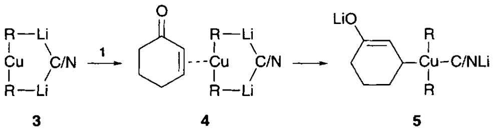
We have discovered that a way to drive the reaction of $Bu_2CuLi·LiI$ with **1** to completion at −78 °C is to add pyridine. When a 0.1 h reaction mixture was quenched with aqueous bicarbonate just 4 s after the addition of 1 equiv. of pyridine, the yield improved from 67% of **2** in ether to essentially quantitative (99%).‡ When triethylamine was substituted for pyridine, the yield of **2** was 97%; however, 2% of 1,2-adduct was also formed.§.

Dorigo *et al.* calculated the energy of trimethylcopper and showed that it is stabilized by ethers or amines.[22] Although they modelled ammonia, we find that triethylamine can also promote 1,2-addition. We chose pyridine because, like 2-thienyl, it has a π system that can help stabilize a positive charge on Cu.

The important observation is that the yields from the CuI-based reagents in the presence of a 2-thienyl ligand or upon the addition of pyridine (or dioxygen§) to the reaction mixtures are as good at those from the CuCN-based cuprates. $Bu_2CuLi·LiI$ may well be as reactive as $Bu_2CuLi·LiCN$ as far as the formation of the cuprate–enone π complex is concerned,[23] but thereafter the intermediates have different reactivities.

We explain the enhanced product-forming ability of $R_2CuLi·LiCN$ in terms of the mechanism of Scheme 1.¶ The key concept is that CN is set up in the olefin complex **4** to form the square-planar intermediate **5** by a least-motion backside attack. Reductive elimination then yields **2** and BuCu(CN)Li.‖ Intermediates analogous to **4**[11] and **5**[24] have been calculated, and one corresponding to **5** has been proposed previously.[17]** It has recently been shown that $SiMe_3Cl$ can accelerate cuprate reactions by a similar mechanism.[25]

Bertz *et al.* showed that in ethereal solvents the methyl homocuprate from CuI consists primarily of the dimer $(Me_2CuLi)_2$ plus free LiI, and not the iodine-bridged structure **VI** (R = Me, R′ = I) corresponding to CN-bridged **3**.[13] Thus, in the reaction of $R_2CuLi·LiI$ with α-enones, an intermediate analogous to **4** is not formed.¶ A coordinated pyridine can stabilize an intermediate analogous to **5**. Copper–pyridine complexes are well known for Cu^I and Cu^{II},[26] and Snyder has calculated that the Cu in the so-called 'Cu^{III} intermediate' is actually closer to Cu^I.[24] In the mixed thienyl cuprates R(Th)CuLi·LiX (X = I, CN) the stabilizing π system is built into the reagent, and as a result, the difference in reactivity is relatively small.



Scheme 1

In conclusion, there is no *prima facie* evidence for 'higher-order cyanocuprates'—either with σ- or π-bound CN and the spectroscopic data apparently characterizing these species can be accommodated by cyclic bridged aggregates which contain a 'lower-order' cuprate centre. Therefore, the more conventional formula $R_2CuLi·LiCN$ should be used instead of $R_2Cu(CN)Li_2$ and the compounds are more appropriately named cyano-Gilman reagents.

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Footnotes

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‡ The remainder of the mass balance was starting material.

§ We have also found that bubbling dioxygen (0.1 h, −78 °C) through these reaction mixtures drives them to completion. See Y. Chounan, T. Ibuka and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1994, 2003.

¶ N.B., C/N symbolizes C≡N or N≡C (*cf.* **I–IV**). Also, a seven-membered ring in which C is bonded to one Li and N is bonded to the other is also possible.

‖ The transition state for reductive elimination must be stabilized more than the ground state (**5**) for a rate acceleration to be observed.

** An alternative explanation involves coordination of the stabilizing ligand to the π-olefin complex, which then inserts the olefin into a C–Cu bond, *i.e.* R–Cu adds across the double bond.

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