

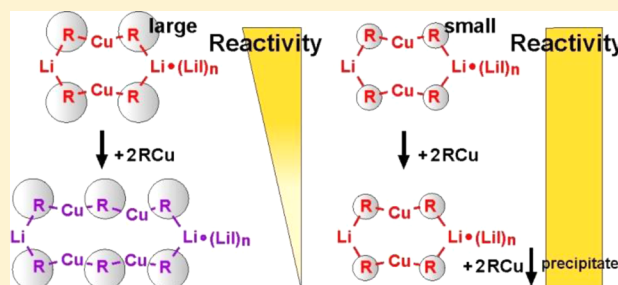
Elongated Gilman Cuprates: The Key to Different Reactivities of Cyano- and Iodocuprates

Maria Neumeier¹ and Ruth M. Gschwind*

Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, D-93053 Regensburg, Germany

S Supporting Information

ABSTRACT: In the past the long-standing and very controversial discussion about a special reactivity of cyano- versus iodocuprates concentrated on the existence of higher-order cuprate structures. Later on numerous structural investigations proved the structural equivalence of iodo and cyano Gilman cuprates and their sequential intermediates. For dimethylcuprates similar reactivities were also shown. However, the reports about higher reactivities of cyanocuprates survived obstinately in many synthetic working groups. In this study we present an alternative structural difference between cyano- and iodocuprates, which is in agreement with the results of both sides. The key is the potential incorporation of alkyl copper in iodo but not in cyano Gilman cuprates during the reaction. In the example of cuprates with a highly soluble substituent ($R = \text{Me}_3\text{SiCH}_2$) we show that in the case of iodocuprates during the reaction several copper-rich complexes are formed, which consume additional iodocuprate and provide lower reactivities. To confirm this, a variety of highly soluble copper-rich complexes were synthesized, and their molecular formulas, the position of the equilibria, their monomers and their aggregation trends were investigated by NMR spectroscopic methods revealing extended iodo Gilman cuprates. In addition, the effect of these copper-rich complexes on the yields of cross-coupling reactions with an alkyl halide was tested, resulting in reduced yields for iodocuprates. Thus, this study gives an explanation for the thus far confusing results of both similar and different reactivities of cyano- and iodocuprates. In the case of small substituents the produced alkyl copper precipitates and similar reactivities are observed. However, iodocuprates with large substituents are able to incorporate alkyl copper units. The resulting copper-rich species have less polarized alkyl groups, i.e. gradually reduced reactivities.



INTRODUCTION

The long-standing and very controversial scientific discussion about a special reactivity of cyanocuprates seemed to be solved during the past decade.¹ In addition, the structures of all relevant copper complexes seemed to be elucidated.² Only two crystal structures showed the principal existence of homoleptic higher-order structures $[\text{R}_3\text{Cu}]^{2-}$ in the solid state.^{3,4} All others reported for $\text{R}_2\text{CuLi}\cdot\text{LiCN}$ systems exclusively cyano Gilman type cuprates in their monomeric^{5–9} as well as dimeric structures.^{10,11} The aggregation levels of the supramolecular oligomers of cyano- and iodocuprates were found to differentiate slightly¹² and correlated to reactivity.¹³ But all the structural studies on Cu(I) and Cu(III) cuprate intermediates did not reveal any significant deviations for cyano- and iodocuprates.^{14–22} In addition, Bertz et al. found in a direct comparison of the reactivity profiles of $\text{R}_2\text{CuLi}\cdot\text{LiI}$ and $\text{R}_2\text{CuLi}\cdot\text{LiCN}$ ($R = \text{Me}, \text{Bu}$) in Michael addition reactions that cyanocuprates have similar or even reduced reactivities compared to iodocuprates.^{23,24} Hence, the early e.g. Alexakis,²⁵ Nakamura,²⁶ van Koten²⁷ and later on persistent but often oral reports of better performances of cyanocuprates from various groups in the synthetic community were attributed to variations in the experimental conditions.

However, the iodocuprates gave us a surprise while varying the cuprate substituents in our investigations of Cu(III) intermediates^{18,22} from methyl groups to the larger, highly soluble Me_3SiCH_2 moieties and using substoichiometric amounts of organolithium compounds. With Me_3SiCH_2 substituents we suddenly detected copper rich Cu(I) complexes consisting of combinations of Gilman cuprates and uncharged copper alkyl species in diethyl ether. The corresponding $\text{Me}_3\text{Cu}_2\text{Li}$ complexes had been detected previously in reactions of methyl copper with less than one equivalent of methyl lithium in Me_2O or THF.²⁸ But in diethyl ether methyl copper is known to be not soluble because of the formation of extended aggregates^{29,30} and we never had detected such complexes for dimethylcuprates during nearly a decade of NMR measurements in diethyl ether. In principle, this is nothing unexpected, because it is well-known that uncharged homoleptic organocopper compounds R_nCu_n often exist as highly aggregated species in the solid state and are insoluble in common organic solvents in case of small substituents (e.g., $R = \text{Me}$).^{29,30} Furthermore, it is well established that disaggregation of these polymers can be achieved by bidentate ligands (e.g., 2-

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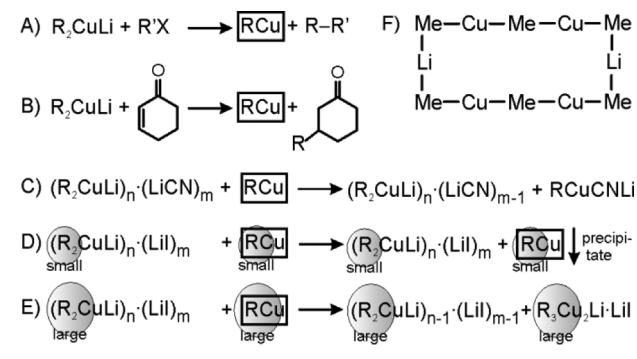
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(dimethylamino)phenyl ligands³¹), bulky substituents^{32–34} (e.g., $R = \text{mesityl}$, Me_3SiCH_2) or coordinating solvents^{3,32,33} (e.g., dimethyl sulfide, tetrahydrothiophene). Thus, clearly a gradual better solubility of copper rich iodocuprate complexes is expected for $R = \text{Me}_3\text{SiCH}_2$ compared to $R = \text{Me}$. However, to our surprise we found an extreme situation: not detectable signals for copper rich cuprates for $R = \text{Me}$ compared to a quantitative formation in the case of $R = \text{Me}_3\text{SiCH}_2$.

This raised two main questions: First, does the presence of copper rich iodocuprates influence the reactivity of iodocuprates and thus lead potentially to differences compared to cyanocuprates? Second, can the large solubility differences of copper rich iodocuprates depending on the size of their substituents explain the confusions in the various reports about better or equal performances of cyano- versus iodocuprates?

In principle an influence is highly probable (see Scheme 1): In both conjugate addition reactions as well as cross coupling

Scheme 1. Formation of RCu in Cross-Coupling (A) and Conjugate Addition Reactions (B); Further Reaction of RCu Depending on the Salt and Substituent Used (C, D, E); (F) Schematic Structure of $[\text{R}_3\text{Cu}_2\text{Li}]_2$ ²⁸



reactions of iodo and cyano Gilman cuprates alkyl copper compounds (**RCu**) are formed as byproducts (see Scheme 1A, B).^{29,35} Next the fate of **RCu** depends on the salt used. In case of cyano Gilman cuprates, **LiCN** and **RCu** form an heteroleptic cuprate and the remaining cyanocuprates are unaffected (see Scheme 1C). For iodo Gilman cuprates the size of the substituent is decisive. **RCu** with small substituents precipitates. Again the remaining iodo Gilman cuprates are unaffected (see Scheme 1D). However, **RCu** with large substituents can form soluble copper rich complexes with an additional iodo Gilman cuprate (see Scheme 1E). As a result the respective iodo Gilman cuprate is overstoichiometrical consumed during the reaction and the reactivity of the copper rich complexes becomes more and more important during the course of the reaction. This should reduce the reactivity of such iodocuprates, because copper rich complexes (see Scheme 1F) have less polarized i.e. less reactive alkyl groups. To sum up, for small substituents (e.g., dimethylcuprates) the reactivities of iodo and cyano Gilman cuprates are expected to be similar, whereas for large substituents the reactivity and possibly also the selectivity of iodocuprates compared to that of cyanocuprates should be significantly affected by the formation of copper-rich complexes. This should be evident mainly in reactions requiring maximal cuprate reactivities, e.g. cross-coupling reactions with sterical hindered reaction partners.

Having this filter at hand, we searched again the literature results for reactivity differences between cyano and iodo Gilman cuprates. Thus, Liphutz initially reported enhanced

reactivities of cyanocuprates,^{36–39} i.e. yields between 82 to 100% in reactions of $(n\text{-Bu})_2\text{CuLi}\cdot\text{LiCN}$ with unactivated secondary alkyl halides in THF, while previous reports of reactions with $(n\text{-Bu})_2\text{CuLi}$ and Me_2CuLi led only to yields between 12 and 21%^{29,40,41} and also, later on, better stereoselectivities using cyano- instead of iodocuprates were published.⁴² Indeed, the reactivity differences reported were dependent of the size of the cuprate substituent. While for $\text{Me}_2\text{CuLi}\cdot\text{LiX}$ ($X = \text{I}, \text{SCN}$) similar yields were found, significantly improved yields were reported for $(n\text{-Bu})_2\text{CuLi}\cdot\text{LiSCN}$ and $(n\text{-Pr})_2\text{CuLi}\cdot\text{LiSCN}$.⁴³ Furthermore, primary alkyl iodides were observed to react readily with $\text{R}_2\text{CuLi}\cdot\text{LiCN}$, and for substitution reactions with poorer leaving groups (Br, Cl) extremely mild reaction conditions could be applied, i.e. lower temperatures than required for R_2CuLi .⁴⁴ Van Koten reported higher reactivities for cyanocuprates with aminoaryl ligands in substitution reactions van Koten²⁷ and Alexakis obtained the highest yields in the boron fluoride-promoted opening of epoxides using *n*-butyl-cyanocuprates, e.g. Alexakis.²⁵ Furthermore, House published a reactivity of $\text{Ph}_2\text{CuLi}\cdot\text{PhLi}$ higher than that of Ph_2CuLi in coupling reactions with aryl iodide,⁴⁵ which would be in agreement with a regeneration of Gilman cuprate from copper-rich complexes. Drawbacks of all of these relative reactivity reports are potential deviations in the experimental conditions between cyano- and iodocuprates. Therefore, Bertz and Ogle reported a direct comparison of reactivity profiles for $\text{R}_2\text{CuLi}\cdot\text{LiI}$ and $\text{R}_2\text{CuLi}\cdot\text{LiCN}$ ($R = \text{Me}, \text{Bu}$).^{23,24} In Michael addition reactions, similar or even reduced reactivities of cyanocuprates were found. However, in the substitution reaction of $\text{R}_2\text{CuLi}\cdot\text{LiX}$ ($R = \text{Bu}; X = \text{I}, \text{CN}$) with cyclohexyl iodide, the reaction which initialized the higher-order discussion, Bertz and Ogle initially reported higher reactivities for the cyano Gilman cuprate compared to the iodo Gilman cuprate,²⁴ which were later on brought into line by several renormalization procedures taking side reactions into account.⁴⁶

In order to clarify whether the existence of copper-rich iodo **Cu(I)** complexes in the case of a large cuprate substituent are the reason for the puzzling and long-standing reports about reactivity differences between cyano- and iodocuprates, we synthesized a variety of highly soluble copper-rich complexes $\text{R}_{1-4}\text{Cu}_{1-3}\text{Li}_{0,1}\text{X}_{0,1}$ ($R = \text{Me}_3\text{SiCH}_2; X = \text{I}, ^{13}\text{CN}$) and investigated their structures and reactivity in cross-coupling reactions with methyl iodide.

RESULTS AND DISCUSSION

Model System. To test the influence of subsequently formed copper-rich complexes on the reactivity and selectivity of organocuprate reactions, Gilman cuprates $\text{R}_2\text{CuLi}\cdot\text{LiX}$ with large substituents ($R = \text{Me}_3\text{SiCH}_2; X = \text{I}, ^{13}\text{CN}$) were used. Furthermore, organocopper complexes derived from varying **RLi**:**CuX** ratios less than 2:1 were synthesized to yield copper-rich complexes. Et_2O was chosen as the solvent to be able to apply in our over-the-years developed approach for the structure elucidation of organocuprates in this solvent.^{2,10–13,18,19} In order to compensate the low solubility of copper-rich complexes in Et_2O , the extended substituent $R = \text{Me}_3\text{SiCH}_2$ was chosen. To reveal the influence of copper-rich complexes on the reactivity of organocuprate reactions, as a test system the cross-coupling reaction between the Gilman cuprates $\text{R}_2\text{CuLi}\cdot\text{LiX}$ ($R = \text{Me}_3\text{SiCH}_2; X = \text{I}, ^{13}\text{CN}$) and methyl iodide was chosen.⁴⁷ As discussed above, reactivity differences between cyano- and iodocuprates were reported

mainly in substitution reactions with sterically hindered alkyl halides (critical reactivity) combined with coordinating solvents or larger cuprate substituents (improved solubility). To mimic such a sterical hindered substitution reaction providing both critical reactivity and sufficiently high solubility of copper-rich complexes, we chose a small alkyl halide (CH_3I) and a large relatively unreactive cuprate substituent ($\text{R} = \text{Me}_3\text{SiCH}_2$), which is usually used as a dummy ligand.⁴⁸ In addition, all NMR spectroscopic measurements were performed at low temperatures between 170 and 185 K, to resolve the different copper-rich complex species. At typical synthetic conditions²⁸ (195–273 K) only broad or averaged signals are observed (for details see SI).

Formation of Copper-Rich Iodocopper(I) Complexes.

Copper-rich iodocopper(I) complexes were synthesized by adding seven different ratios of $\text{Me}_3\text{SiCH}_2\text{Li}$ (**RLi**) to an ethereal suspension of **CuI** at 170 K. The formation of the respective soluble copper(I) complexes started immediately, which was visible by specific color changes (vide infra) and was spectroscopically investigated by NMR at 170 K (see, e.g., the ^1H spectra in Figure 1).

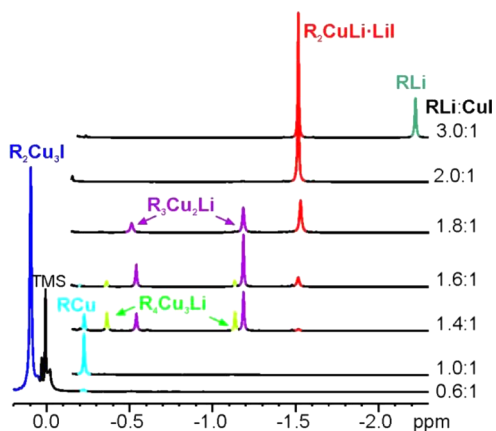
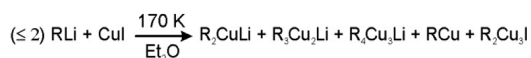


Figure 1. Multiple copper-rich complexes are detectable at ratios smaller than 2:1 using $\text{Me}_3\text{SiCH}_2\text{Li}$ (**RLi**) and **CuI** from their CH_2 -signals in the high-field section of ^1H spectra in d_6 -diethyl ether at 170 K.

The signals of **RLi** and the Gilman cuprate $\text{R}_2\text{CuLi}\cdot\text{LiI}$ were assigned on the basis of previous investigations.¹² The molecular formulas of the copper-rich complexes were determined by integral analysis of the signals downfield from the Gilman cuprate (for details see SI). The monomeric structures were determined with ^1H , ^{13}C hetero multi bond correlation (HMBC) spectra and aggregation trends were studied with diffusion ordered spectroscopy (DOSY) measurements. With these techniques, not only the Gilman cuprate $\text{R}_2\text{CuLi}\cdot\text{LiI}$ ($\text{R} = \text{Me}_3\text{SiCH}_2$) but also overall four copper-rich complexes with the formal monomers $\text{R}_3\text{Cu}_2\text{Li}\cdot 2\text{LiI}$, $\text{R}_4\text{Cu}_3\text{Li}\cdot 3\text{LiI}$, $\text{RCu}\cdot\text{LiI}$, and $\text{R}_2\text{Cu}_3\text{I}\cdot 2\text{LiI}$ were detected (see Scheme 2). Regarding the formal stoichiometries of these complexes our previous¹² as well as actual (see below) DOSY investigations show that the **LiI** units are at least partially separated from the

Scheme 2. Formation of Copper-Rich Iodocuprates



copper complex, and the determination of their exact number is not feasible. Therefore, in Scheme 2 and in the following text the **LiI** units are omitted.

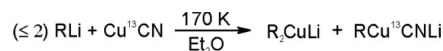
At overstoichiometric amounts of **RLi** (see **RLi:CuI** = 3.0:1 in Figure 1), clear and colorless samples are formed containing R_2CuLi and the excess of **RLi** unreacted in solution.⁴⁹ In the colorless sample with **RLi:CuI** = 2.0:1 exclusively R_2CuLi was detected. In the clear and pale-brown solution with **RLi:CuI** = 1.8:1, additionally the first copper-rich complex $\text{R}_3\text{Cu}_2\text{Li}$ (purple in Figure 1), was observed with two chemically nonequivalent organic moieties in a 1:2 ratio. Lowering further the organolithium to copper salt ratio to **RLi:CuI** = 1.6:1 a clear and yellow sample indicated the formation of $\text{R}_3\text{Cu}_2\text{Li}$ and additionally $\text{R}_4\text{Cu}_3\text{Li}$ ($\text{R} = \text{Me}_3\text{SiCH}_2$) (light green in Figure 1), with two chemically nonequivalent organic moieties in a 1:1 ratio. In addition, small amounts of the alkyl copper compound **RCu** ($\text{R} = \text{Me}_3\text{SiCH}_2$) were detected (light blue in Figure 1). From the ratio **RLi:CuI** = 1.4:1 onward, only negligible amounts of R_2CuLi were detected, and exclusively the copper-richer complexes $\text{R}_3\text{Cu}_2\text{Li}$, $\text{R}_4\text{Cu}_3\text{Li}$ and **RCu** were observed. At **RLi:CuI** = 1.0:1 was **RCu** exclusively detected. Below a 1:1 ratio (**RLi:CuI** = 0.6:1), the solution was still clear and yellow, but **CuI** partly remained at the bottom of the NMR tube and a signal of an additional complex (dark blue in Figure 1) was observed, which fits very well to an X-ray structure reported by van Koten et al.,⁵⁰ for $\text{R}_2\text{Cu}_3\text{I}$. However, an independent, exact determination of the stoichiometry of $\text{R}_2\text{Cu}_3\text{I}$ is obscured by severe spectral overlap.

In summary, in seven different mixtures of **RLi** and **CuI**, a variety of different **Cu(I)** complexes with the general molecular formula $\text{R}_{1.4}\text{Cu}_{1.3}\text{Li}_{0.1}\text{I}_{0.1}$ were observed. At ratios of **RLi** to **CuI** larger than 2:1, exclusively R_2CuLi ($\text{R} = \text{Me}_3\text{SiCH}_2$) was present. By reducing the content of **RLi**, the position of the equilibrium was shifted toward several copper-richer complexes. The more **RCu** units are incorporated in these complexes the more downfield shifted appear their proton signals compared to those of R_2CuLi . This indicates a stepwise-reduced polarization as well as reactivity in the row R_2CuLi , $\text{R}_3\text{Cu}_2\text{Li}$, $\text{R}_4\text{Cu}_3\text{Li}$, **RCu**, and $\text{R}_2\text{Cu}_3\text{I}$, which is well-known for R_2CuLi and **RCu** from the introduction of the Gilman cuprates.

Formation of Cyanocuprate(I) Complexes in Diethyl Ether.

Next, the complex formation of $\text{Me}_3\text{SiCH}_2\text{Li}$ (**RLi**) with Cu^{13}CN was studied, to solve the question whether copper-rich complexes are also formed in the case of cyano copper complexes but remained undetected so far. Therefore, six samples were prepared with **RLi** to Cu^{13}CN ratios from 3.0:1 to 0.3:1. These samples were investigated by ^1H as well as DOSY experiments at 170 K in diethyl ether (see Scheme 3 and Figure 2, for details see SI).

Scheme 3. Formation of Heteroleptic Cyanocuprates



Depending on the stoichiometric ratio, exclusively **RLi**, homoleptic cyanocuprate $\text{R}_2\text{CuLi}\cdot\text{Li}^{13}\text{CN}$ ($\text{R} = \text{Me}_3\text{SiCH}_2$, orange in Figure 2), and the soluble heteroleptic cyanocuprate $\text{RCu}^{13}\text{CNLi}$ (magenta in Figure 2) were detected, but not any trace of additional copper-rich complexes or higher-order cuprates. Thus, in accordance with previous studies³⁶ no copper-rich complexes are detected in the case of cyano copper complexes.

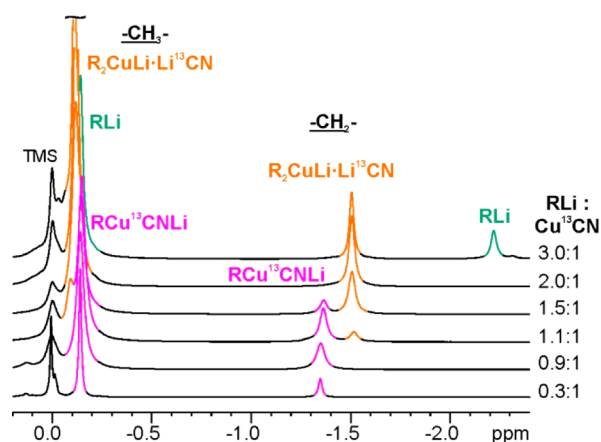


Figure 2. Heteroleptic cyanocuprate but no copper-rich complexes are detectable at ratios smaller than 2:1 using $\text{Me}_3\text{SiCH}_2\text{Li}$ (RLi) and Cu^{13}CN from their CH_2 - (<-1 ppm) and CH_3 -signals (>-0.5 ppm) in the ^1H spectra in d_6 -diethyl ether at 170 K.

Structures of Iodocopper(I) Complexes in Diethyl Ether. Next, the structures of the copper-rich iodocopper(I) complexes were addressed. From various NMR spectroscopic investigations on organocuprates,^{5,6} π -complexes⁵¹ as well as $\text{Cu}(\text{III})$ complexes^{18,22} and in agreement with theoretical calculations,^{52–55} it is known that the partly covalent copper–alkyl bond allows for a magnetization transfer via scalar coupling, whereas the predominantly electrostatic lithium–alkyl interaction acts as a spin system barrier. Accordingly, the existence or lack of cross signals in $^1\text{H},^{13}\text{C}$ HMBC spectra indicate the kind of metal in between the two groups revealing the monomeric structure of these copper-rich complexes. In addition, DOSY measurements can be used to elucidate the hydrodynamic ratios of organocuprate aggregates including salt- and solvent-coordination.¹² Therefore, the structures of the copper-rich complexes $\text{R}_3\text{Cu}_2\text{Li}$, $\text{R}_4\text{Cu}_3\text{Li}$, and RCu were investigated by $^1\text{H},^{13}\text{C}$ HMBC, and DOSY measurements at 185 and 170 K. To avoid extended supramolecular aggregates,^{12,13} samples with low concentrations were used ($c = 0.07$ – 0.13 mol/L).

In the $^1\text{H},^{13}\text{C}$ HMBC spectrum of $\text{R}_3\text{Cu}_2\text{Li}$, cross signals between the chemically nonequivalent CH_2 groups and to their corresponding Me_3Si moieties were detected but none between the two chemically equivalent CH_2 groups (see Figure 3). This $^1\text{H},^{13}\text{C}$ HMBC coupling pattern is in perfect agreement with an “extended” Gilman cuprate monomer shown in Figure 3, which was first proposed by Ashby²⁸ merely on the basis of ^1H chemical shifts. In this “extended” Gilman cuprate monomer the two chemically equivalent CH_2 groups show a cross peak to the single CH_2 moiety ($^3J_{\text{H,C}}$) but no cross peak among themselves ($^5J_{\text{H,C}}$). Adducts of Gilman cuprates with RCu and LiI units can be excluded on the basis of this scalar coupling pattern.

Accordingly, the complex $\text{R}_4\text{Cu}_3\text{Li}$ was investigated (for details see SI), and a similar structure was determined, which is elongated by one more RCu moiety (for the dimeric core structure see Figure 4). For $(\text{RCu})_n$ the monomeric structure is evidently RCu . Thus, the structures $\text{R}_3\text{Cu}_2\text{Li}$ and $\text{R}_4\text{Cu}_3\text{Li}$ can be derived from R_2CuLi by gradual elongation of the homocuprate by one and two RCu units, respectively, and may be considered as charged organocuprate analogue structures, whereas $(\text{RCu})_n$ is an uncharged alkyl copper structure.

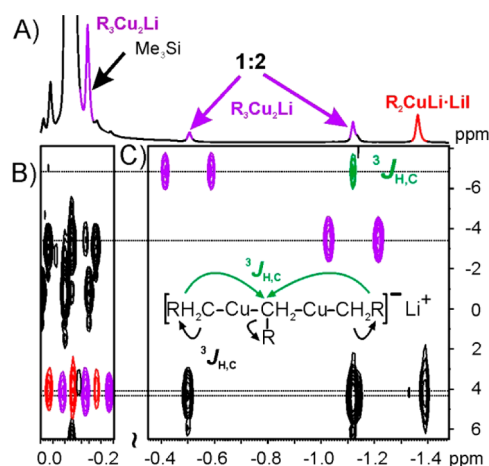


Figure 3. Structure identification of $\text{R}_3\text{Cu}_2\text{Li}$ as Gilman cuprate extended by one RCu unit based on the high field sections of ^1H (A) and $^1\text{H},^{13}\text{C}$ HMBC spectra (B,C) of a 1.8:1 mixture of RLi and CuI at 185 K in Et_2O (Me_3Si region (B) scaled down for the sake of clarity). The signals of $\text{R}_3\text{Cu}_2\text{Li}$ and $\text{R}_2\text{CuLiLiI}$ in the ^1H spectrum as well as their $^3J_{\text{H,C}}$ cross signals are depicted in purple and red, respectively. The decisive cross signals are color coded according to the inset.

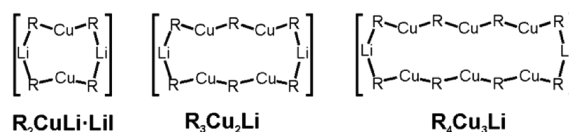


Figure 4. Schematic structures of $\text{RCuR}(\text{CuR})_n\text{LiLiI}$ ($\text{R} = \text{Me}_3\text{SiCH}_2$, $n = 0, 1$, and 2) based on $^1\text{H},^{13}\text{C}$ HMBC, and ^1H -DOSY measurements at 185 and 170 K. For details see text and SI.

Diffusion Measurement on Iodo- and Cyanocuprate(I) Complexes in Diethyl Ether. The aggregation level of the iodocopper complexes $\text{R}_2\text{CuLiLiI}$, $\text{R}_3\text{Cu}_2\text{Li}$, $\text{R}_4\text{Cu}_3\text{Li}$, RCu and of the cyano copper complexes $\text{R}_2\text{CuLiLiCN}$ and RCuCNLi was determined by ^1H DOSY investigations, similar to our previous studies of $\text{R}_2\text{CuLiLiX}$ ($\text{X} = \text{I}, \text{CN}$) in Et_2O .¹² There, in highly concentrated samples (0.6 mol/L) of RCuLiLiI in Et_2O at 240 K slightly larger aggregates than dimers were found with a high number of solvent molecules attached ($[(\text{R}_2\text{CuLi})_2(\text{LiI})_2(\text{Et}_2\text{O})_{7.5}]_{1.3}$). In order to avoid extended oligomeric structures at 185 and 170 K the concentrations of the samples were drastically reduced to $c = 0.07$ – 0.13 mol/L, at which a comparable aggregation number of 1.3 was found for $[(\text{R}_2\text{CuLi})_2(\text{LiI})_2(\text{Et}_2\text{O})_{7.5}]$.

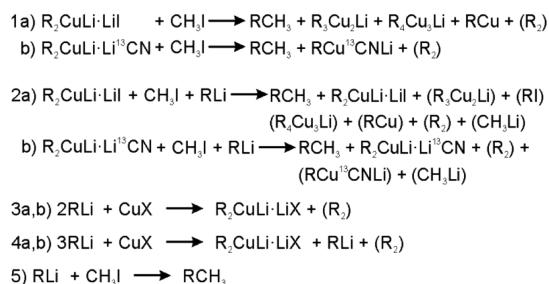
The DOSY study revealed for $\text{R}_3\text{Cu}_2\text{Li}$ and $\text{R}_4\text{Cu}_3\text{Li}$ similar dimeric core structures and aggregation trends as previously found for the Gilman cuprates R_2CuLi (for details see SI). Just the amounts of LiI units and solvent molecules are slightly reduced, which goes along with the reduced polarity of the alkyl groups in these extended cuprates. For RCu , the experimental diffusion coefficient excludes a monomer as well as the tetrameric structure reported in X-ray studies³⁴ but indicates a higher aggregation, which would fit an octameric linear aggregate or a corresponding cyclic system. For visualization, the dimeric core structures for R_2CuLi , $\text{R}_3\text{Cu}_2\text{Li}$, and $\text{R}_4\text{Cu}_3\text{Li}$ are schematically shown in Figure 4.

For $\text{R}_2\text{CuLiLi}^{13}\text{CN}$ and $\text{RCu}^{13}\text{CNLi}$, the corresponding DOSY investigations indicate the formation of moderately higher aggregates than dimers. This is in accordance with the known slightly higher aggregation trends for cyanocuprates

compared to iodocuprates¹² and the low concentration of the actual samples (for details see SI).

Reactivity of Iodo- and Cyanocupper(I) Complexes in Cross-Coupling Reactions with Methyl Iodide. The more RCu units are integrated within the copper-rich iodo complexes, the larger ppm values are found for the ¹H signals of their CH₂ groups (see Figure 1). This indicates a decreased polarization of these organic moieties compared to the Gilman cuprates and suggests a lower reactivity of copper-rich iodo complexes in C–C bond formations. In addition, during a reaction the more reactive Gilman cuprate is overstoichiometrically consumed at the moment copper rich complexes are formed. Both effects are expected to reduce the reactivity of iodocuprates compared to cyanocuprates, in case copper-rich iodo complexes are soluble. In order to observe such reactivity differences in the yields of typical cuprate reactions and in a NMR spectrometer without a rapid injection unit, two main conditions have to be met. First, the copper-rich iodo complexes have to be soluble, e.g. due to large alkyl substituents or by a good coordinating solvent. Second, the reactivity required for the reaction has to be critical for cuprates, i.e. the slightly reduced reactivity of the copper-rich complexes should be not sufficient for this reaction. Such reactivity differences were mainly reported for substitution reactions using sterical hindered substrates (vide supra), and the use of diethylether for substitution reactions reduces further the reactivity. To be able to transfer directly all of our structural investigations and in addition to meet both criteria, here an “inverse” setup was used: The highly soluble but inactive cuprates $R_2CuLi \cdot LiI$ and $R_2CuLi \cdot Li^{13}CN$ ($R = Me_3SiCH_2$) were tested in cross-coupling reactions with methyl iodide in diethylether at low temperatures without and with an excess of RLi (see Scheme 4 (1) and (2)). In addition, several blind reactions were performed to validate the results (see Scheme 4 (3), (4), and (5)).

Scheme 4. Educts and Products of Cross-Coupling and Blind Reactions at 170 K in Et₂O; Side Products up to 5% Are Given in Brackets



First an exact one-to-one stoichiometry of Gilman cuprate and alkyl halide ($R_2CuLi \cdot LiI/R_2CuLi \cdot Li^{13}CN:CH_3I:CH_3Li = 1.0:1.0:0.0$) was selected for both iodo- and cyanocuprate to elucidate the possible influence of the copper-rich Cu(I) complexes on the reactivity. Second, the reaction was performed additionally in the presence of one equivalent excess of the MeLi ($R_2CuLi \cdot LiI/R_2CuLi \cdot Li^{13}CN:CH_3I:CH_3Li = 1.0:1.0:1.0$) to enable the regeneration of the reactive Gilman cuprates during the reaction. For both conditions two concentrations (0.05 and 0.13 mol/L) were chosen to test the influence of the aggregate size. Each mixture was reacted 20 min at 170 K, then ¹H NMR spectroscopy was used to

detect the existent copper species and to determine the reaction yields by integration.⁵⁶

In Figure 5 sections of representative ¹H spectra of these reactions are presented, the reaction equations are given in

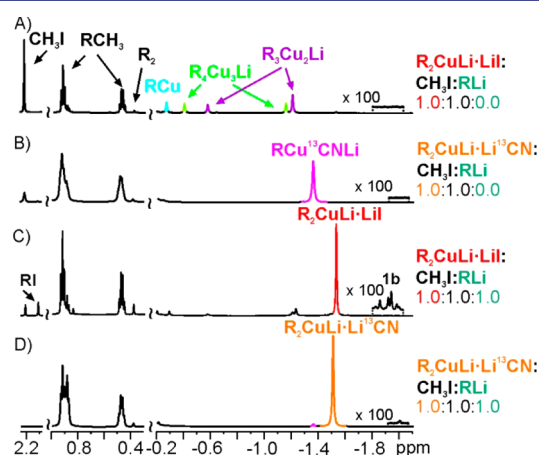


Figure 5. Cross-coupling reactions with stoichiometric amounts of iodocuprates $R_2CuLi \cdot LiI$ ($R = Me_3SiCH_2$) and CH_3I show the formation of copper-rich complexes and reduced yields of RCH_3 (A). Cyanocuprates (B) as well as both cuprates plus excess of RLi (C, D) show higher yields of RCH_3 (For exact yields see Table 1). ¹H spectra at $c = 0.05$ – 0.06 mol/L $R_2CuLi \cdot LiX$ ($X = I, ^{13}CN$) at 170 K in Et₂O-*d*₆.

Table 1. Yields of Iodo and Cyano Gilman Cuprates in Cross-Coupling Reactions with CH₃I without and with Excess of Me₃SiCH₂Li; the Corresponding Reactions Are Given in Scheme 4

cuprate	ratio $R_2CuLi \cdot LiX:CH_3I:RLi$	yields [%] ^{a,b}	
		$Me_3SiCH_2CH_3$	$(Me_3SiCH_2)_2$
X = I	1a	57 (31)	1 (1)
	2a	95 (91)	5 (2)
	3a	–	1 (<1)
	4a	–	3 (1)
X = CN	1b	95 (81)	2 (–)
	2b	97 (99)	4 (–)
	3b	–	1 (–)
	4b	–	3 (–)
blind reaction	5	17	

^a $c = 0.05$ – 0.06 mol/L. ^b $c = 0.13$ mol/L in brackets, of $R_2CuLi \cdot LiX$ ($X = I, ^{13}CN$) in diethylether at 170 K. All yields were determined by integral analysis of the corresponding proton spectra.

Scheme 4, and the yields are summarized in Table 1. After the stoichiometric reactions of $R_2CuLi \cdot LiI$ with CH_3I , indeed substantial amounts of the copper-rich complexes R_3CuLi , R_4CuLi , and RCu are detected (see Figure 5A). As expected, the identical reaction with $R_2CuLi \cdot Li^{13}CN$ leads only to $RCuCNLi$ (see Figure 5B). Surprisingly, considering the long reactivity discussion about iodo- and cyanocuprates but in accordance with our considerations about the influence of soluble copper-rich complexes, the integrals of the main product 2,2-dimethyl-2-silabutane RCH_3 (see Scheme 4) show a formidable higher yield for the cyanocuprate $R_2CuLi \cdot$

Li^{13}CN (95%) than for the reaction with the iodocuprate $\text{R}_2\text{CuLi}\cdot\text{LiI}$ (57%).

Bertz and Ogle reported in their reactivity study of iodo- and cyanocuprates⁴⁶ high amounts of the side products for the iodocuprates and low amounts for cyanocuprates formed during the cuprate preparation. Therefore, they renormalized the reactivities of both cuprates to their effective concentrations.⁴⁶ In our investigation, besides RCH_3 , only small amounts of the side product 2,2,5,5-tetramethyl-2,5-disilabutane R_2 were detected (2% for $\text{R}_2\text{CuLi}\cdot\text{Li}^{13}\text{CN}$ and 1% for $\text{R}_2\text{CuLi}\cdot\text{LiI}$). All other possible side products⁴⁶ were below the detection limit. In general R_2 can be generated on two pathways, first during the cuprate preparation (see e.g. reaction 3 in Scheme 4) and second by metal–halide exchange and subsequent substitution reaction (see e.g. reaction 2a and 2b in Scheme 4). Therefore, in Table 1 the amount of R_2 before (see reaction 3a and 3b) and after the reaction with CH_3I (see reaction 1a and 1b) is given. In our case the concentrations of R_2 before the reaction are negligible for both cuprates (both 1%). Therefore, a renormalization is not necessary, and the yields can be directly correlated with the reactivity. Next, the influence of the concentration, i.e., larger aggregates, was tested using the identical reactions at higher cuprate concentrations (0.13 mol/L). Again, a significantly higher yield was observed for $\text{R}_2\text{CuLi}\cdot\text{Li}^{13}\text{CN}$ (81%) than for $\text{R}_2\text{CuLi}\cdot\text{LiI}$ (31%). As expected for substitution reactions, which are faster in THF than in diethyl ether, the absolute yields decreased for both cuprates at higher concentrations, i.e., the formation of larger aggregates.

These results raised the question whether the reduced reactivity of the copper-rich complexes $\text{R}_3\text{Cu}_2\text{Li}$, $\text{R}_4\text{Cu}_3\text{Li}$, and RCu cause this drastic reactivity difference, which only occurs in the case of iodocuprates in combination with large, highly soluble cuprate substituents. To prove this, additional experiments with one equivalent excess of RLi were performed, which enable the regeneration of the Gilman cuprates during the reaction. Under these overstoichiometric conditions the yield with $\text{R}_2\text{CuLi}\cdot\text{LiI}$ increased dramatically from 57% to 95%, whereas in the case of $\text{R}_2\text{CuLi}\cdot\text{Li}^{13}\text{CN}$ only a slight increase from 95% to 97% yield was observed. Also for the higher concentrated samples a similarly pronounced trend was found (for spectra see SI Figure 6). There, the yield for $\text{R}_2\text{CuLi}\cdot\text{LiI}$ increased by 60% up to 91% and in the case of $\text{R}_2\text{CuLi}\cdot\text{Li}^{13}\text{CN}$ also a pronounced effect (+18%) with the highest yield of all (99%) was detected. In order to exclude that these increased yields are only achieved by the direct reaction between RLi and CH_3I , a blind reaction (RLi : 0.07 mol/L; CH_3I : 0.13 mol/L) using 2 equiv of CH_3I was investigated at 162 K to ensure that the effects of this blind reaction are not underestimated (see reaction 5 in Table 1). As an upper limit for this direct reaction of RLi and CH_3I , thus, a yield of 17% of RCH_3 could be determined. This blind reaction yielded also the products of metal–halide exchange CH_3Li and RI (see SI Figure 7). In the case of the iodocuprate, $\text{R}_2\text{CuLi}\cdot\text{LiI}$, indeed also these products of metal–halide exchange CH_3Li and RI are detected (see Figure 5C), indicating that the blind reaction plays a role. However, for iodocuprates plus one equivalent of RLi the yields of RCH_3 increase by far higher (+38% and +60%) than the upper limit yield of the blind reaction (17%). This demonstrates impressively that the formation of copper-rich complexes leads to a reduced reactivity.

In case of the cyanocuprate, $\text{R}_2\text{CuLi}\cdot\text{Li}^{13}\text{CN}$, the increased yields of RCH_3 (by 2% and 18%) are in the range of the blind

reaction (17% RCH_3). Therefore, all interpretations have to be made cautiously. However, only traces of the metal–halide exchange are detected (see Figure 5D), suggesting that the blind reaction plays a minor role in this case. In addition, the absolute yields observed for cyanocuprates are higher than those for iodocuprates, especially for the higher concentrated sample. According to the structural investigations and the theoretical calculations in this field there are two possible explanations. First, Nakamura postulated a MeLi -bridged species $\text{MeCu}(\text{CN})\text{Li}\cdot\text{MeLi}$ as a possible approach to explain the special reactivity of cyanocuprates.^{48,57} The overstoichiometric use of an alkyl lithium compound in reaction 2b is expected to favor the formation particularly of such structures, and exactly this combination leads to the highest yields observed (see entry 2b in Table 1). Second, mixed supra-molecular aggregates of R_2CuLi and RCuCNLi units could decrease the reactivity. In accordance with the experimental results both effects of mixed aggregates are expected to be more pronounced at higher concentrations. Therefore, the reactivity of cyanocuprates may be fine-tuned by the formation of such alkyl lithium-bridged cyanocuprates or mixed aggregates with heteroleptic cuprates, whereas the reactivity of iodocuprates is strongly reduced in case soluble copper-rich complexes can be formed.

CONCLUSIONS

More than three decades ago Lipshutz reported higher reactivities of cyano- versus iodocuprates especially for large substituents, and later on many synthetic chemists used cyanocuprates very successfully. Lipshutz's structural explanation, the existence of higher-order cuprates, was based on an assumption of Ashby and later on disproven by numerous structural investigations showing cyano Gilman cuprates in solution. For the structural model system, the dimethylcuprates, also nearly identical reactivities were shown for iodo- and cyanocuprates. Therefore, better performances of other cyanocuprates observed in syntheses remained reports without structural explanation.

Here we present an alternative explanation, which is, to our knowledge, in agreement with all of the fundamental statements of both sides and, we feel, the solution to this Gordian knot. The key to different reactivities of cyano- and iodocuprates is not mainly the structure of the cuprates before the reaction but the fate of the alkyl copper side product of the iodocuprates after the reaction. In the case of cyanocuprates always heteroleptic cuprates are formed. However, for iodocuprates the situation differs, depending on the solubility of the alkyl copper. In the case of small substituents, e.g. methyl copper, this side product precipitates and does not affect the further reaction. As a result the reactivities of cyano- and iodocuprates are very similar. However, in the case of large substituents, e.g. $\text{R} = \text{Me}_3\text{SiCH}_2$, as in this study, the neutral alkyl copper side product is incorporated into the remaining iodocuprate and forms "extended" Gilman cuprates (only detectable at temperatures far below those usually applied in synthesis). These copper-rich complexes not only have reduced polarities of their alkyl groups and therefore a reduced reactivity, but in addition, consume overstoichiometrically the higher reactive iodo Gilman cuprate. As a result both situations are possible and true: very similar reactivities of cyano- and iodocuprates and substantially reduced reactivities for iodocuprates. Key is the solubility and incorporation of the alkyl copper in iodocuprates. This incorporation, which is detrimental to

reactivity, can be modulated by the size of the substituent (i.e., small substituent precipitation/full reactivity, large substituent complete incorporation/reduced reactivity as shown in this study and all intermediate levels for medium-sized substituents) as well as most probably also by variations of solvent properties, additives, or temperature. In addition, our reactivity and structural study shows that, to a minor extent, also the well-known aggregation and proposed mixed aggregate effects of the cuprates overlay these reactivities, which may have led to further confusion.

As a rule of thumb this study shows that, in reactions requiring critical reactivities and large cuprate substituents, cyanocuprates are expected to perform better than iodocuprates.

EXPERIMENTAL SECTION

Sample Preparation. The $\text{Me}_3\text{SiCH}_2\text{Li}$ solution (1.0 M in pentane) was purchased from Sigma-Aldrich. $\text{Et}_2\text{O}-d_{10}$ was freshly distilled over K/Na alloy. All manipulations during the synthesis were done under exclusion of moisture and air. All cuprate samples were prepared by a method described by John et al.¹⁰ The synthesis was directly done in $\text{Et}_2\text{O}-d_{10}$ to exclude protonated Et_2O . The pentane from the $\text{Me}_3\text{SiCH}_2\text{Li}$ solution was removed before the addition to the Cu salt suspension. The conversions with methyl iodide were performed at 170 K. The NMR titrations were performed at 0.2–0.06 mol/L, DOSY measurement at 0.07–0.18 mol/L, and reactions with CH_3I at 0.05–0.06 and 0.13 mol/L.

NMR Data Collection and Processing. The NMR spectra were recorded on a Bruker Avance 600 MHz spectrometer equipped with a 5 mm broadband triple resonance Z-gradient probe. ^1H , ^{13}C HMBC measurements were carried out with a standard Bruker pulse program (hmbcetgp12nd) using 64 scans, 16 dummy scans, $\text{TD}(\text{F2}) = 4\text{k}$ and $\text{TD}(\text{F1}) = 400$ with a relaxation delay of 2 s. All diffusion measurements were performed with a convection-suppressing pulse program⁵⁸ in pseudo-2D mode and processed with Bruker software package t1/t2. For each experiment, 2 dummy scans and 8 actual scans were used, with a relaxation delay of 10 s and a diffusion delay of 50 ms. The shape of the gradients was sinusoidal, with a length of 4 ms, and the strength was varied in 24 increments (5–95%) of the gradient ramp created by Bruker software DOSY. The temperature for all measurements was controlled by a Bruker BVTE 3900 temperature unit.

Determination of Diffusion Coefficients. The diffusion coefficients were determined using the Bruker software package t1/t2 to fit the measured decline of intensity. The diffusion coefficients given in SI Table 2 and SI Table 4 are the average results of 1–6 experiments of each measurement with sample concentrations between 0.07 and 0.18 mol/L. Due to the low concentration range, the experimental diffusion coefficient show higher experimental errors than usual for DOSY measurements: 9% ($\text{R}_2\text{CuLi}\cdot\text{LiI}$, 3 experiments, 1×0.07 mol/L, 2×0.13 mol/L), 9% ($\text{R}_3\text{Cu}_2\text{Li}$, 4 experiments, 2×0.07 mol/L, 2×0.13 mol/L), 11% ($\text{R}_4\text{Cu}_3\text{Li}$, 4 experiments, 2×0.07 mol/L, 2×0.13 mol/L), 7% (RCu , 4 experiments, 2×0.07 mol/L, 2×0.13 mol/L), 5% ($\text{R}_2\text{CuLi}\cdot\text{Li}^{13}\text{CN}$, 1 experiment, 0.18 mol/L), and 6% ($\text{RCuLi}^{13}\text{CN}$, 3 experiments, 3×0.07 mol/L).

Internal Viscosity Reference. Since we noticed a strong dependence of the viscosity on the concentration, the temperature, and the kind of Cu(I) complexes, a trace (2–3 drops) of benzene (C_6H_6) was used as an internal reference.⁵⁹ By a comparison of the diffusion coefficients of the reference measured in pure $\text{Et}_2\text{O}-d_{10}$ and in the cuprate sample, the viscosity correction factors for the Cu(I) complex samples were determined, in order to get comparable experimental diffusion coefficients.

Integral Analysis of the Reactions between $\text{R}_2\text{CuLi}\cdot\text{LiX}$ ($\text{X} = \text{I}$, ^{13}CN) and MeI. For the determination of yields (%), the sum of integrals of the CH_3 groups, which correspond to unreacted MeI, the main product RCH_3 , and the product of metal–halide exchange, H_3CLi , were correlated to the added amount of MeI and set to 100%.

Accordingly, the integral of the side product R_2 was correlated to this sum, and the yields of R_2 (%) were calculated.

ASSOCIATED CONTENT

Supporting Information

Assignments, diffusion coefficients, additional spectra, interpretations and details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

Ruth.Gschwind@ur.de

Present Address

¹Dr. Maria Neumeier, Eicherstraße 2, 85123 Karlskron, Germany.

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Notes

The authors declare no competing financial interest.

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temperatures is not possible due to the close melting point of Et₂O (157 K) and relatively small line widths necessary for reliable spectra integration. In addition, extensive reactivity investigations of Bertz and Ogle showed that it is extremely difficult to obtain reliable and highly reproducible kinetic data for substitution reactions of organocuprates. Bertz, S. H.; Chopra, A.; Eriksson, M.; Ogle, C. A.; Seagle, P. *Org. Chem. Eur. J.* **1999**, *5*, 2680. Bertz, S. H.; Human, J.; Ogle, C. A.; Seagle, P. *Org. Biomol. Chem.* **2005**, *3*, 392. Murphy, M. D.; Ogle, C. A.; Bertz, S. H. *Chem. Commun.* **2005**, 854. Therefore, in this study only yields are discussed.

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