

# Chemical and Spectroscopic Studies on Copper Iodide Derived Organocuprates: New Insight into the Composition of Gilman's Reagent

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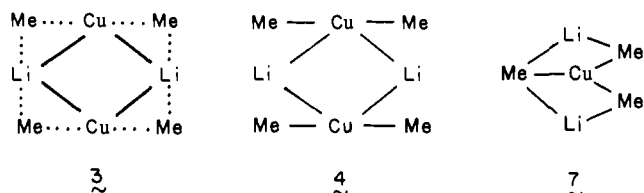
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**Abstract:** Both  $^1\text{H}$  and  $^7\text{Li}$  NMR spectroscopy at high field have served to reveal that the addition of ethereal  $\text{MeLi}$  to  $\text{MeCu}/\text{THF}$ , in the absence of  $\text{LiI}$ , leads to unprecedented equilibria ( $K_{\text{eq}} \sim 11$ ) between  $\text{Me}_2\text{CuLi}$  and  $\text{MeLi}$  plus  $\text{Me}_3\text{Cu}_2\text{Li}$ . From a series of spectra at  $-70^\circ\text{C}$ , a scheme is proposed to account for the signals observed in solutions of varying  $\text{MeLi}:\text{MeCu}$  ratios. These data lead to the conclusion that not only Gilman's reagent but also " $\text{Me}_3\text{CuLi}_2$ " and " $\text{Me}_5\text{Cu}_3\text{Li}_2$ " are not discrete, but rather are composed of differing percentages of the same components. In the presence of  $\text{LiI}$ , or in  $\text{Et}_2\text{O}$  solutions alone, however, this equilibrium does not exist for  $\text{MeLi}:\text{MeCu}$  ratios up to 1:1. Chemical tests on both ketones and esters, as well as a series of Gilman tests, fully corroborate the existence of various forms of Gilman's reagent.

Close to half a century ago, Gilman and Straley described the first reactions of an organocuprate,  $\text{RCu}$ , with organic functional groups (e.g., acid chlorides, allylic halides, aldehydes, etc.).<sup>1</sup> It was not until some 16 years later that this same school reported on the first organocuprate, " $\text{Me}_2\text{CuLi}$ " (**1**), commonly referred to today as "Gilman's reagent", prepared from 2 equiv of methyl lithium plus 1 equiv of cuprous iodide.<sup>2</sup> An appreciation for the synthetic attributes of this latter new class of reagents, however, was not forthcoming until the mid-1960's. Following recognition of the extensive carbon-carbon bond-forming potential of these "lower order" (LO) cuprates of general formula  $\text{R}_2\text{CuLi}$  (**2**), an overwhelming surge in methodological developments and their applications took place which continue unabated to this day.<sup>3</sup>

Clearly, the advances in the synthetic arena attract most of the attention. Nonetheless, it is generally acknowledged that, while cuprates **2** may convert an educt **A** to product **B**, very little is actually known about the species involved. In fact, although organocuprates are by far the most popular organotransition-metal-containing reagents for structural elaboration,<sup>4</sup> it would not be unfair to classify the reactions of these organometallic reagents as "black box" phenomena. Utilization of " $\text{R}_2\text{CuLi}$ ", in reality, implies nothing more than a stoichiometric representation of the precursors from which it has been prepared. The present state of affairs is such that, in solution, **1** is routinely accepted as a symmetrical, dimeric cluster, as put forth by Pearson and illustrated in **3**.<sup>5</sup> Recently, this concept has been challenged by Whangbo on the basis of extended Hückel calculations which suggest that dimer **4**, devoid of bridging alkyl ligands, is energetically preferred.<sup>6</sup>

In addition to these LO cuprate complexes, the so-called "higher order" (HO) reagents, " $\text{R}_3\text{CuLi}_2$ " (**5**)<sup>7</sup> and " $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$ " (**6**),<sup>8</sup> derived from copper halides (i.e.,  $3\text{RLi} + \text{CuX}$ ) and  $\text{CuCN}$ , respectively, have also begun to vie for a share of the cuprate market. Such species are differentiated from counterparts **2** simply on the basis of formal charge associated with the copper-containing center; hence, LO cuprates are monoanionic, while HO cuprates are  $\text{Cu}(\text{I})$  dianions. Reagents **5** have been assigned monomeric structure **7**,<sup>7a</sup> while information regarding the HO cyanocuprates has only recently begun to accrue.<sup>9</sup> The chemistry of each HO



cuprate, albeit of far more recent vintage, is certainly distinct and often leads to results superior to those realized under the influence of **2** or their congeners (i.e., mixed homo- or heterocuprates,  $\text{RR}'\text{CuLi}$ ).<sup>8</sup> However, as with **1**, assumptions regarding **5** have prevailed and the true composition and reactive component(s) which account for the chemistry observed,<sup>7</sup> prior to this report, had yet to be elucidated.

This contribution, to our knowledge, represents the first joint  $^1\text{H}$  and  $^7\text{Li}$  NMR spectroscopic study at high field (300 and 117 MHz, respectively) on organocuprates,<sup>10,11</sup> coupled with extensive supporting chemical data. We disclose herein that in  $\text{THF}$ , in the absence of lithium halide salts, several "well-known" copper reagents, including the very cornerstone of modern cuprate chemistry,  $\text{Me}_2\text{CuLi}$ , exist not as discrete complexes, but rather as an equilibrium mixture<sup>12</sup> of three distinct entities.<sup>13</sup>

## Results and Discussion

From the combination of  $0.5\text{MeLi}$ <sup>14</sup> and  $\text{MeCu}$  (as a slurry in  $\text{THF}$ ), which is known to afford  $\text{Me}_3\text{Cu}_2\text{Li}$ ,<sup>7a,b</sup> a single peak

- (1) Gilman, H.; Straley, J. M. *Recl. Trav. Chim. Pays-Bas* **1936**, *55*, 821.
- (2) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.
- (3) Posner, G. H. "An Introduction to Synthesis Using Organocupper Reagents"; Wiley: New York, 1980. Posner, G. H. *Org. React.* **1972**, *19*, 1. Posner, G. H. *Ibid.* **1975**, *22*, 253.
- (4) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, 1980.
- (5) Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 4098.
- (6) Stewart, K. R.; Lever, J. R.; Whangbo, M.-H. *J. Org. Chem.* **1982**, *47*, 1472.
- (7) (a) Ashby, E. C.; Watkins, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 5312. (b) Ashby, E. C.; Watkins, J. J. *Chem. Commun.* **1976**, 784. (c) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *Org. Chem.* **1977**, *42*, 1099. (d) Ashby, E. C.; Lin, J. J. *Ibid.* **1977**, *42*, 2805. (e) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. (f) Still, W. C.; Macdonald, T. L. *Tetrahedron Lett.* **1976**, 2659.
- (8) For a recent review on HO cuprates, see: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.
- (9) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3928, 3938, 3943.
- (10) Kleft, R. L.; Brown, T. L. *Organomet. Chem.* **1974**, *77*, 289.
- (11) Scherr, P. A.; Hogan, R. J.; Oliver, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 6055.
- (12) The proposed equilibrium does not rule out the possibility that more than three species may be present in minute quantities in solution. Hence, our equilibrium expression may not be a unique description of all possible equilibria, but it is consistent within the framework of our simple model. As expected, changing the concentration of the sample from 0.35–0.39 M (see Table II) to 0.21 M afforded the same relative percentages of two peaks at ca. the same chemical shifts.
- (13) Interestingly, this was first alluded to a decade ago, cf.: House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.
- (14) All solutions of varying  $\text{MeLi}:\text{MeCu}$  ratios were prepared with  $\text{MeLi}$  (low halide) purchased from the Aldrich Chemical Co. The  $\text{MeLi}$  was freshly titrated with each use.  $\text{MeCu}$ , free of lithium salts, was obtained by the method of House.<sup>15</sup>

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**Table I.** Equilibrium Data for CuI-Derived Organocuprates in THF/Et<sub>2</sub>O

Entry	MeLi : MeCu	Observed <sup>7</sup> Li NMR ratios, Cuprates : MeLi	K <sub>calc</sub>	Calculated % comp. MeLi / Me <sub>3</sub> Cu <sub>2</sub> Li / (Me <sub>2</sub> CuLi) <sub>2</sub>	Observed <sup>1</sup> H NMR ratios, Cuprates : MeLi	Calculated <sup>1</sup> H NMR ratios, Cuprates : MeLi
A	0.50 (Me <sub>3</sub> Cu <sub>2</sub> Li)	100 : 0	—	0 / 100 / 0	100 : 0	—
B	0.75	93 : 7	10	18 / 59 / 23	large : small	94 : 6
C	1.00 (Me <sub>2</sub> CuLi) <sub>2</sub>	83 : 17	16	34 / 34 / 32	83 : 17	87 : 13
D	1.50	60 : 40	10	57 / 13 / 30	73 : 27	74 : 26
E	2.00 (Me <sub>3</sub> CuLi <sub>2</sub> )	47 : 53	10	69 / 6 / 25	66 : 34	63 : 37
F	∞	0 : 100	—	100 / 0 / 0	0 : 100	—

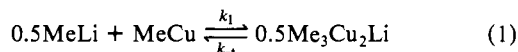
$K_{ave} = 11 \pm 3 M^{-1}$

**Table II.** Spectral data for CuI-Based Organocuprates in THF/Et<sub>2</sub>O<sup>a</sup>

	Me <sub>2</sub> CuLi	Me <sub>3</sub> CuLi <sub>2</sub>	Me <sub>3</sub> Cu <sub>2</sub> Li	MeCu + 0.75 MeLi	Me <sub>2</sub> CuLi + LiI	Me <sub>3</sub> CuLi <sub>2</sub> + LiI
<sup>7</sup> Li, δ (25°C) <sup>b</sup>	0.752	1.669	-0.372	-0.122	0.495	1.18
<sup>7</sup> Li, δ (-70°C) <sup>b</sup>	2.25 -0.38	2.31 -0.26	-0.405	-0.456	0.00	2.20 -0.12
<sup>1</sup> H, δ (25°C) <sup>c</sup>	-1.45 (bs)	-1.55 (bs)	-1.25 (s)	-1.44 (s)	-1.46 (s) <sup>d</sup>	-1.657 (bs)
<sup>1</sup> H, δ (-70°C) <sup>c</sup>	-1.56 (s) -2.09 (s)	-1.55 (s) <sup>e</sup>	-1.29 (s) -1.58 (s)	-1.55 (s)	-1.55 (s)	-1.54 (s) -2.02 (s)

<sup>a</sup>The concentration of each sample was between 0.35 and 0.39 M. <sup>b</sup>A 0.80 M solution of LiCl in CD<sub>3</sub>OD, within a capillary insert, was used as reference. <sup>c</sup>Values are referenced relative to the center peak of the Et<sub>2</sub>O triplet, 1.07 ppm. <sup>d</sup>Obtained at +7 °C. <sup>e</sup>Recorded at -50 °C, as MeLi precipitated out at -70 °C at these concentrations.

is observed in the <sup>7</sup>Li NMR spectrum over a -70 to +25 °C temperature range (Figure 1). This is consistent with the equilibrium shown in eq 1, where  $k_1 \gg k_{-1}$ . As a result, and in the absence of other processes, combining equal quantities of MeLi and MeCu, the expected outcome would be formation of



0.5Me<sub>3</sub>Cu<sub>2</sub>Li plus 0.5MeLi.<sup>16</sup> However, the <sup>7</sup>Li NMR spectrum for the 1:1 combination at -70 °C (Figure 1) shows *two resonances of unequal intensity*, which can be attributed to MeLi (downfield) and both Me<sub>3</sub>Cu<sub>2</sub>Li and Me<sub>4</sub>Cu<sub>2</sub>Li<sub>2</sub> (upfield). The

spectra for this 1:1 ratio at various temperatures are illustrated in Figure 2. Under these conditions, both copper-containing species appear at about the same chemical shift seen for Me<sub>3</sub>Cu<sub>2</sub>Li alone.<sup>18</sup> Such an observation, which invokes an averaging of signals due to rapid methyl and lithium exchange between Me<sub>3</sub>Cu<sub>2</sub>Li and Me<sub>2</sub>CuLi, is well-precedented for other organometallics (e.g., MeLi/Me<sub>2</sub>Zn,<sup>19a</sup> MeLi/Me<sub>2</sub>Mg,<sup>19a</sup> MeLi/Me<sub>2</sub>Cd.)<sup>19b</sup>

From the series of spectra in Figure 1, an equilibrium constant,  $K_{eq}$ ,<sup>12</sup> reflecting the admixture of various MeLi to MeCu ratios could be calculated, including that for the relationship shown in eq 2<sup>20</sup> (i.e., Gilman's reagent). The results listed in Table I clearly



(15) House, H. O.; Fischer, W. F. *J. Org. Chem.* **1968**, *33*, 949.

(16) Of course, if equal quantities of MeLi and Me<sub>3</sub>Cu<sub>2</sub>Li give complete conversion to (Me<sub>2</sub>CuLi)<sub>2</sub> as assumed from <sup>1</sup>H and <sup>13</sup>C NMR data,<sup>5,7a,b,17</sup> a single peak in the lithium spectrum is anticipated.

(17) House, H. O.; Chu, C. Y. *J. Org. Chem.* **1976**, *41*, 3083. House, H. O.; Respass, W. L.; Whitesides, G. M. *Ibid.* **1966**, *31*, 3128.

(18) Increasing the MeLi:MeCu ratio does not significantly alter the <sup>7</sup>Li NMR chemical shift of the upfield copper-containing peak. This observation suggests that the proposed two components have similar chemical shifts.

(19) (a) Seitz, L. M.; Brown, T. L. *J. Am. Chem. Soc.* **1966**, *88*, 4140. (b) Seitz, L. M.; Little, B. F. *J. Organomet. Chem.* **1969**, *18*, 227.

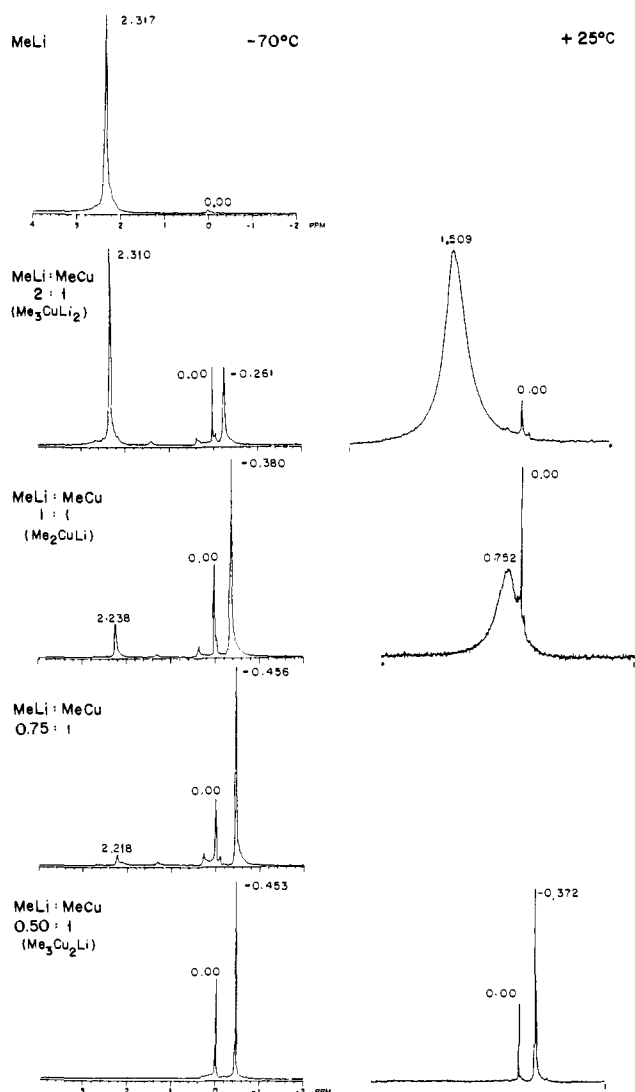


Figure 1.  $^7\text{Li}$  NMR spectra for various MeLi:MeCu ratios in THF/Et<sub>2</sub>O at -70 and 25 °C.

demonstrate that  $K_{\text{eq}} = 11 \pm 3$  is effectively described by eq 2.<sup>21</sup> Moreover, it necessitates that *no other species be involved in the consumption of MeLi* (e.g. "Me<sub>3</sub>CuLi<sub>2</sub>") to any significant degree.<sup>22,23</sup>

(20) The equilibrium constants were calculated from  $^7\text{Li}$  NMR integral ratios with the expression  $R = A + X/B - X$ , where  $R$  = the observed ratio of  $^7\text{Li}$ -containing cuprates to MeLi,  $A$  = initial concentration of Me<sub>3</sub>Cu<sub>2</sub>Li,  $B$  = concentration of MeLi following reaction with the MeCu present, and  $X$  = amount of lithium which changes its chemical environment upon exchange. Rearranging gives  $X = (RB - A)/(1 + R)$ . The equilibrium expression can be formulated as

$$K = [\text{Me}_4\text{Cu}_2\text{Li}_2]/\{[\text{MeLi}][\text{Me}_3\text{Cu}_2\text{Li}]\}$$

Since the Gilman cuprate formed contains two  $^7\text{Li}$  atoms, it can be expressed as

$$K = \frac{1}{2} X / \{([\text{MeLi}] - X)([\text{Me}_3\text{Cu}_2\text{Li}] - X)\}$$

The values calculated for all cases were averaged, giving  $K = 11 \pm 3$ , which reproduced the data shown in Table I.

(21) From this equilibrium,<sup>12</sup> the issue of aggregation state arises. All of the data upon which this treatment is based were collected under constant conditions of solvent(s) and temperature. While the extent of aggregation of any species (i.e., RLi, cuprate) in solution may vary with temperature, whatever the level of aggregation in THF/Et<sub>2</sub>O at -70 °C, it is highly likely to be constant for each component. Thus, this issue does not alter the treatment described herein.

(22) Should any significant quantity of Me<sub>3</sub>CuLi<sub>2</sub> be present as part of the upfield peak at  $\delta$  -0.38, this MeLi-consuming species would need to be included in the calculation of  $K_{\text{eq}}$ .<sup>20</sup> Hence, the resulting  $K$  value, with this addition, should be inconsistent with those where the ratio of MeLi:MeCu is  $\leq 1:1$ .

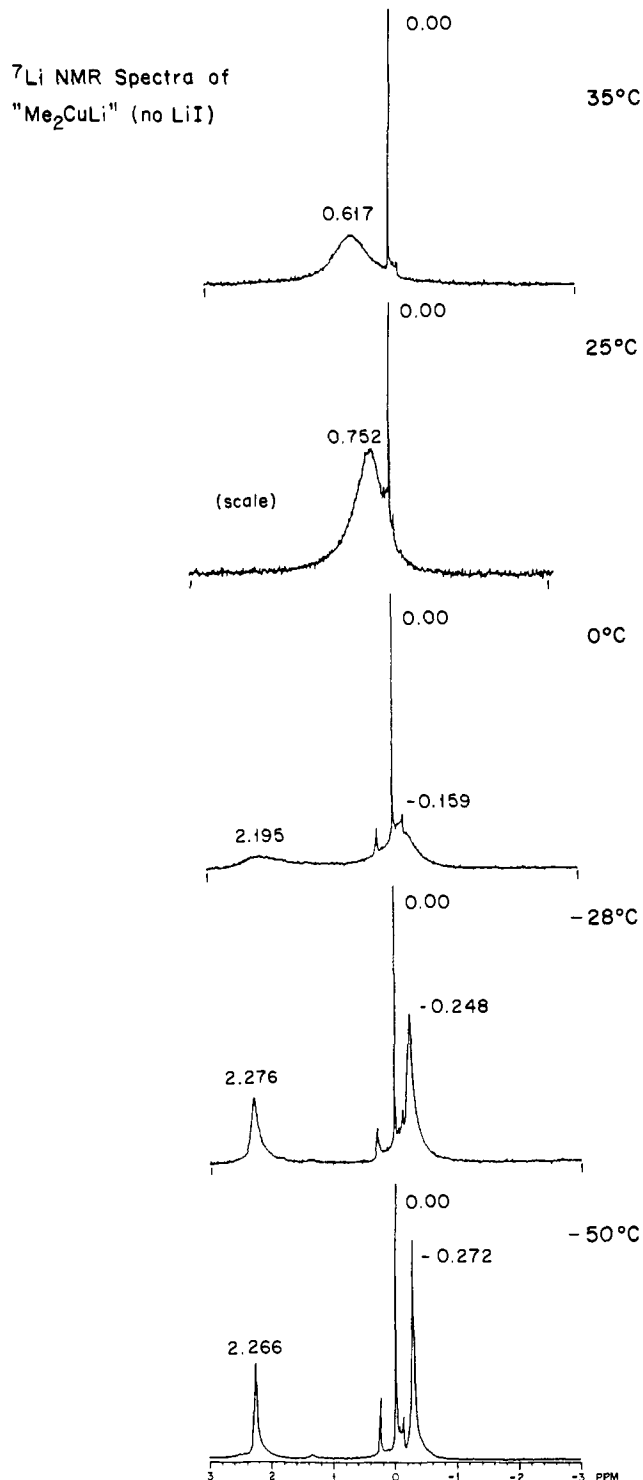


Figure 2.

With use of the same equilibrium expression in eq 2,<sup>12</sup> calculated intensities for the corresponding  $^1\text{H}$  signals for each MeLi to MeCu ratio can be arrived at,<sup>24</sup> which should fully corroborate the  $^7\text{Li}$  NMR data above. Both the  $^7\text{Li}$  and  $^1\text{H}$  NMR spectral data are summarized in Table II. The calculated values obtained

(23) Interestingly, Riviere et al. have suggested on the basis of chemical studies that the combination of  $2\text{RMgX} + \text{CuI}$  also affords three species in Et<sub>2</sub>O solution, cf.: Four, P.; LeTri, Ph.; Riviere, H. *J. Organomet. Chem.* 1977, 133, 385.

(24) The equilibrium concentration of each species is multiplied by the number of methyl groups it contains, followed by normalization of this ratio to 100%.

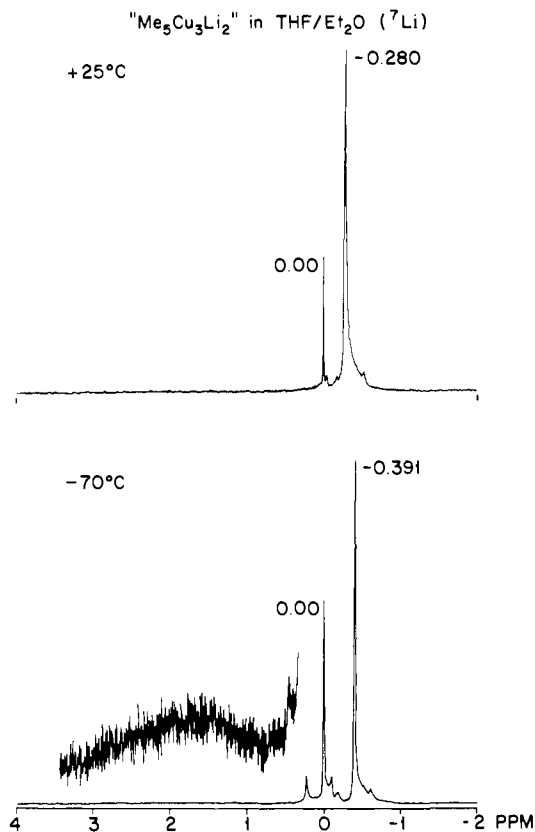


Figure 3.

(Table I) are in excellent agreement with those measured from peak integrations.<sup>25</sup>

The observation that various ratios of MeLi:MeCu > 0.5:1 subscribe to the equilibrium expressed in eq 2 raises the intriguing thought that other lithiocuprates derived from similar ingredients (i.e., CuI +  $x$ RLi, with the LiI removed) might also contain  $R_3Cu_2Li$  as the fundamental species in a THF/Et<sub>2</sub>O medium. One case in point concerns "Me<sub>5</sub>Cu<sub>3</sub>Li<sub>2</sub>", well-known to be the reagent of choice for effecting 1,4-delivery of a methyl group to  $\alpha,\beta$ -unsaturated aldehydes.<sup>26</sup> This aggregate is composed of a 0.66:1 ratio of MeLi:MeCu, which by <sup>7</sup>Li NMR, we find gives *the same two signals* at -70 °C corresponding to MeLi ( $\delta \sim 2.0$ ) and [Me<sub>4</sub>Cu<sub>2</sub>Li<sub>2</sub> + Me<sub>3</sub>Cu<sub>2</sub>Li] ( $\delta -0.39$ ) with  $K_{eq} \sim 9 M^{-1}$  (Figure 3). Hence, it appears that eq 2 is representative of all of the data obtained thus far (Table I), and that any addition of RLi to RCu in THF which exceeds the 0.5:1 mark (i.e.,  $R_3Cu_2Li$ ) is not totally consumed in Gilman cuprate formation, but rather enters into an equilibrium with both the aggregate  $R_3Cu_2Li$  and the lower order cuprate.

**Solvent Effects.** Having recognized the equilibrium in eq 2 associated with "Me<sub>2</sub>CuLi" in THF/Et<sub>2</sub>O (without LiI), it became immediately apparent that the 1:1 combination of MeLi:MeCu in Et<sub>2</sub>O alone must necessarily afford a solution of different composition. It is well-known,<sup>7</sup> and we have likewise found, that Me<sub>3</sub>Cu<sub>2</sub>Li does not form in Et<sub>2</sub>O. Hence, the subtleties associated with these various MeLi:MeCu ratios come into focus upon the realization that while a 0.5:1 ratio (i.e., Me<sub>3</sub>Cu<sub>2</sub>Li) cannot be used in Et<sub>2</sub>O,<sup>7</sup> only an additional 0.16 equiv of MeLi (i.e., 0.66:1, "Me<sub>5</sub>Cu<sub>3</sub>Li<sub>2</sub>") is sufficient to generate a totally different, soluble species.<sup>26,27</sup>

The <sup>7</sup>Li NMR of "Me<sub>2</sub>CuLi" in Et<sub>2</sub>O (Figure 4) reflects the absence of the equilibrium seen in THF/Et<sub>2</sub>O, as only a single peak is observed at  $\delta$  0.08 (i.e., no free MeLi is present). This

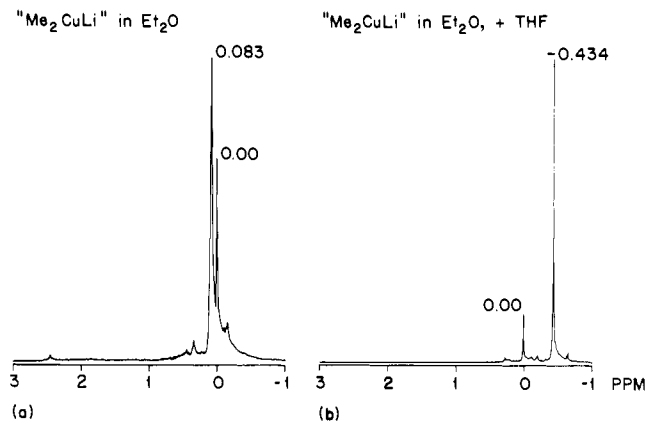
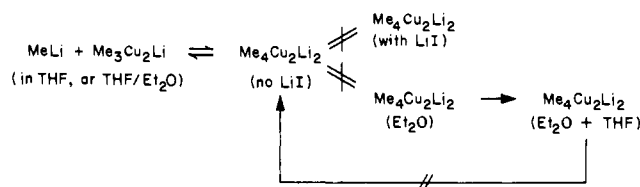


Figure 4. <sup>7</sup>Li NMR of (a) "Me<sub>2</sub>CuLi" in Et<sub>2</sub>O at -70 °C; (b) <sup>7</sup>Li NMR of "Me<sub>2</sub>CuLi" in Et<sub>2</sub>O, to which has been added THF; spectrum was taken at -70 °C.

## Scheme I



chemical shift is close to one-half ppm downfield of the cuprate peak seen in THF/Et<sub>2</sub>O ( $\delta -0.38$ ), both taken at similar concentrations at -70 °C. Considering that <sup>7</sup>Li NMR spans only ca. 4–6 ppm, this seems too large a shift to be attributed solely to a change in ethereal solvent.

Far more startling and certainly unexpected was the result obtained when THF was added to "Me<sub>2</sub>CuLi" prepared initially in pure Et<sub>2</sub>O. By introducing THF such that the final cuprate concentration and ratio of solvents were identical to those used in the formation of "Me<sub>2</sub>CuLi" in THF/Et<sub>2</sub>O, it was anticipated that cooling to -70 °C would result in loss of the singlet at  $\delta$  0.08 and appearance of the now familiar two peaks indicative of the equilibrium seen previously (vide supra). Irrespective of time and temperature, *this does not happen*. Rather, a *single new peak* at  $\delta -0.43$  appears, again too large a difference in chemical shift ( $\Delta\delta$  0.52 ppm) to be solely due to a change from Et<sub>2</sub>O to THF:Et<sub>2</sub>O (~3:1).<sup>30</sup> The only conclusion, therefore, that can be drawn from these spectroscopic experiments (Figure 4), which is fully consistent with chemical tests (vide infra), is that *the makeup of "Me<sub>2</sub>CuLi" is extremely dependent upon the solvent(s) in which it is originally formed*. Moreover, evidence for *four* unique species originating from CuI designated as "Me<sub>2</sub>CuLi" has been provided, the relationship between these being as summarized in Scheme I.

Clive's reagent<sup>26</sup> was also looked at in Et<sub>2</sub>O, as "Me<sub>5</sub>Cu<sub>3</sub>Li<sub>2</sub>" is most effective in this solvent. Competing 1,2-additions with enals can now be easily understood in light of this reagent's <sup>7</sup>Li NMR spectrum in THF/Et<sub>2</sub>O. In Et<sub>2</sub>O, however, only a single peak is present over a 130 °C temperature range (+25 to -105 °C). The line width of the peak remained surprisingly constant, suggesting that a discrete species may well be involved (Figure 5). Similar observations were noted in the proton spectra, lending further support to Clive's chemical results<sup>26</sup> which concluded that a 0.66:1 MeLi to MeCu ratio in Et<sub>2</sub>O forms a valuable reagent

(25) The <sup>7</sup>Li NMR spectra for ratios of MeLi:MeCu  $\leq 1$  (where LiI is present) reveals only a *single* peak at temperatures between -90 and 25 °C where a single peak was also noted. This may explain why attempts to do experiments of this type over a decade ago were not completely successful.<sup>10,11</sup>

(26) Clive, D. L. J.; Farina, V.; Beaulieu, P. L. *J. Org. Chem.* **1982**, *47*, 2572.

(27) In light of these fundamentally different species, each of which requires a less than 1:1 ratio of RLi:RCu, it is instructive to reconsider some of the early organocopper chemistry which assumed, based on Gilman's initial report,<sup>4</sup> that a full equivalent of RLi is needed to solubilize RCu.<sup>28,29</sup> Thus, as these workers "titrated" RLi by RCu, anticipating that complete dissolution implied cuprate (R<sub>2</sub>CuLi) formation, in reality, since this was done in Et<sub>2</sub>O, "Me<sub>5</sub>Cu<sub>3</sub>Li<sub>2</sub>" was the species actually prepared and subsequently used for couplings. Hence, care must be exercised in interpreting and extending these earlier results.

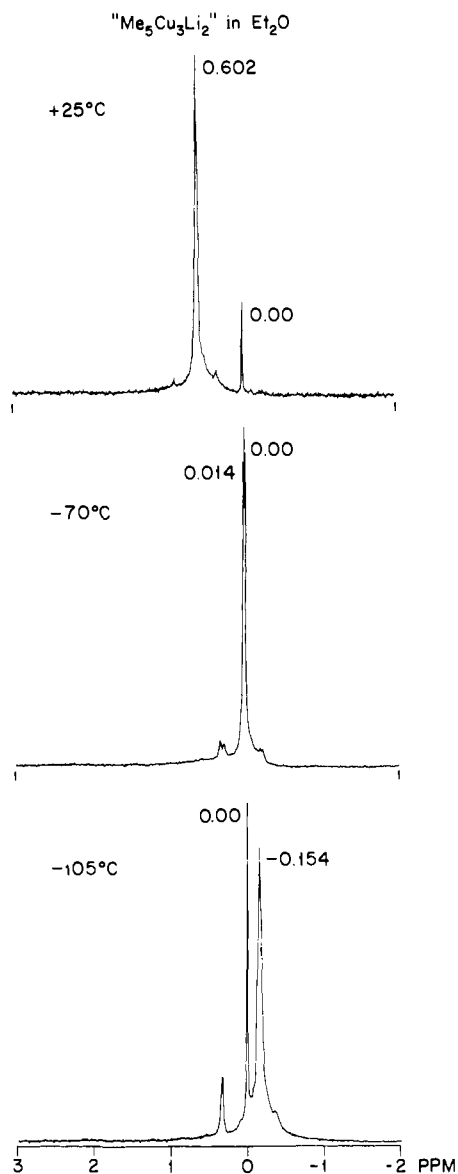


Figure 5.

for carrying out Michael additions to unsaturated aldehydes.

Increasing the MeLi to MeCu ratio to 2:1 (i.e., "Me<sub>3</sub>CuLi<sub>2</sub>") in Et<sub>2</sub>O at 0 °C (no LiI) gives a <sup>7</sup>Li NMR spectrum which consists of a broad singlet at δ 1.85. Cooling to -70 °C, however, gives rise to two singlets at δ 0.05 and 2.43 in roughly a 1.3:1 ratio (Figure 6). Hence, unlike "Me<sub>2</sub>CuLi", "Me<sub>3</sub>CuLi<sub>2</sub>" is composed of a very healthy quantity of "free" MeLi in solution regardless of solvent(s). The <sup>1</sup>H NMR spectrum at -70 °C likewise showed two signals (δ -1.14, -2.03) of similar ratio, the upfield peak characteristic of free MeLi.

A THF/Et<sub>2</sub>O solution containing this same 2 MeLi:MeCu combination, but under the influence of 1 equiv LiI, gives again two peaks (δ 2.20 and -0.12) in the <sup>7</sup>Li NMR spectrum at -70 °C. Factoring out the LiI, which comes together with the cuprate singlet, leaves a ca. 1:1 ratio for the MeLi:cuprate signal. Likewise, the proton spectrum displays the necessary 2:1 cuprate:MeLi ratio. These are the expected results based on the spectrum of "Me<sub>2</sub>CuLi" + LiI, to which has been added an equivalent of MeLi, and further substantiate the conclusion that "Me<sub>3</sub>CuLi<sub>2</sub>" is not a discrete entity.

One final comment with regard to solvent effects seems appropriate. It is especially noteworthy to point out that *observation of these dramatic variations in reagents as a function of solvent is in stark contrast to the commonly held view that the composition of Gilman's reagent is solvent independent.* Most of the evidence which has led to this reasonable deduction is spectro-

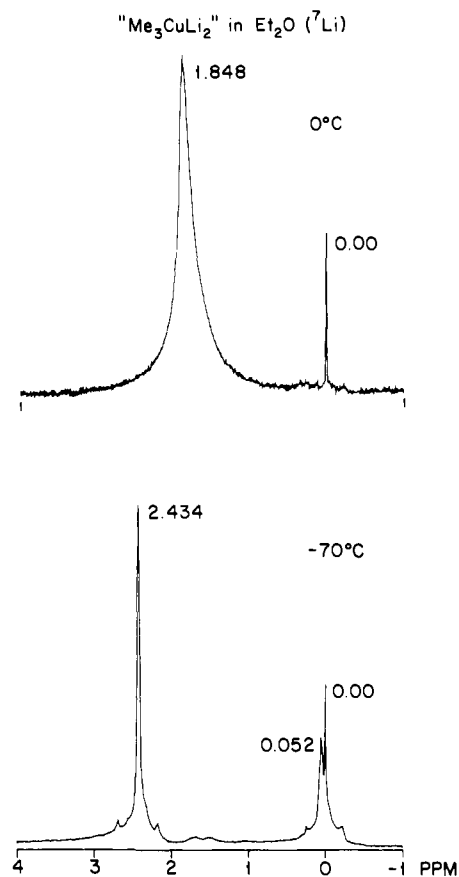
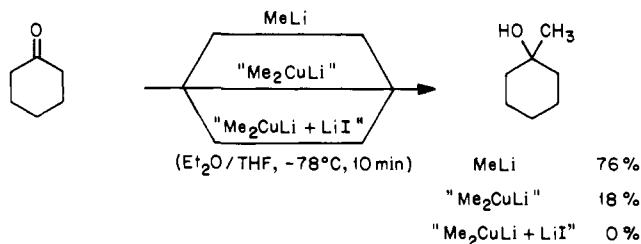


Figure 6.

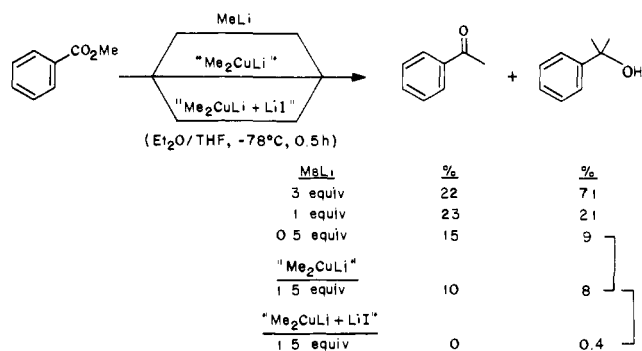
## Scheme II



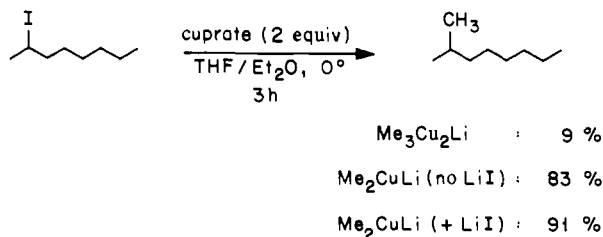
scopic;<sup>7,17</sup> however, differences between the various species shown to exist by combined <sup>7</sup>Li/<sup>1</sup>H NMR experiments are not readily detected by standard (<sup>1</sup>H, <sup>13</sup>C) NMR techniques in samples containing LiI.

**Chemical Tests.** Perhaps the single most intriguing question which arises from the <sup>7</sup>Li and <sup>1</sup>H NMR data with respect to Gilman's reagent in THF/Et<sub>2</sub>O is "If there is so much MeLi (ca. 34%) in "Me<sub>2</sub>CuLi", why doesn't it interfere with the reactions of this cuprate?" It is important at this point to recall that the presence of MeLi can only be detected spectroscopically when the LiI is removed from solution. Moreover, it is technique-wise far more expedient to simply leave the lithium salt formed in the reaction flask, thereby avoiding an additional operation (i.e., isolation of (RCu)<sub>n</sub>). Thus, since LiI has a pronounced effect on the spectroscopy of "Me<sub>2</sub>CuLi",<sup>10,11</sup> it was anticipated that this salt, along with the choice of solvent, may well be the keys to understanding the reactivity patterns of lower order cuprates. To test these concepts, side-by-side reactions were conducted on two substrates, cyclohexanone and methyl benzoate, each being treated with 1.5 equiv of MeLi, "Me<sub>2</sub>CuLi" without LiI, and "Me<sub>2</sub>CuLi" with LiI in THF/Et<sub>2</sub>O. The results are summarized in Schemes II and III. In line with existing experimental dogma,<sup>3</sup> we found that Gilman's reagent (+LiI) essentially did not react with either electrophile under the conditions indicated. The absence of LiI, however, led to substantial quantities of products formally<sup>3</sup> attributable to 1,2-addition of MeLi. When the amount

## Scheme III



## Scheme IV



of MeLi used was reduced from 1.5 to 0.5 equiv relative to ester, based on the determination that MeLi comprises roughly one-third of "Me<sub>2</sub>CuLi", about the same results were obtained as for the case of "Me<sub>2</sub>CuLi" alone (i.e., 10% acetophenone + 8% tertiary carbinol; 15% ketone + 9% carbinol; see Scheme III).

Thus, these chemical and spectroscopic data suggest that LiI in stoichiometric proportions radically alters the nature of Gilman's reagent prepared in the presence of THF.<sup>33</sup> What is also clear is that any RLi which may be present is no longer "free" to behave as one would anticipate given the functional groups routinely exposed to "Me<sub>2</sub>CuLi".

Considering that so many cuprate couplings are conducted in THF,<sup>3</sup> we wondered whether the "Me<sub>2</sub>CuLi" component of a one-to-one MeLi-to-MeCu mixture was actually the species responsible for the chemistry attributed to "Me<sub>2</sub>CuLi". 2-Iodo-octane, therefore, was treated independently with Me<sub>3</sub>Cu<sub>2</sub>Li, "Me<sub>2</sub>CuLi", and "Me<sub>2</sub>CuLi" + LiI. As shown in Scheme IV, the reagent prepared from 0.5:1 MeLi:MeCu is relatively inert, while "Me<sub>2</sub>CuLi" affords ca. 83% 2-methyloctane. Not surprisingly, the LiI encourages even a better coupling<sup>34</sup> as competing elimination and reduction are minimized due to the loss of "free" MeLi.

(28) San Filippo, J. *Inorg. Chem.* **1978**, *17*, 275.

(29) House, H. O.; Chu, C.-Y.; Wilkens, M. J.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

(30) Support for this statement comes in the form of comparison of  $T_1$  values for numerous lithium salts in Et<sub>2</sub>O vs. THF/Et<sub>2</sub>O (~3:1). For example, LiI in both media gives essentially the same  $T_1$  values (1.29 vs. 2.37 s) under otherwise identical conditions of concentration and temperature. By contrast, "Me<sub>2</sub>CuLi" in Et<sub>2</sub>O afforded a  $T_1$  value of 0.28 s, while the "same" cuprate in THF/Et<sub>2</sub>O (3:1) showed  $T_1$  = 2.56 s. Thus, on the basis of both chemical shift and  $T_1$  variations, we suspect that a unique species is present.

Somewhat related observations have been noted by van Koten and Noltes, cf.: van Koten, G.; Noltes, J. G. In "Comprehensive Organometallic Chemistry"; Pergamon Press: New York, 1984; Vol. 14, p 109. See also: van Koten, G.; Jastrzebski, J. T. B. H.; Muller, F.; Stam, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 697.

(31) The possibility that R<sub>2</sub>Cu<sup>-</sup> is the species which adds to the carbonyl group, followed by reductive elimination, however unlikely,<sup>32</sup> cannot be ruled out.

(32) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

(33) In a separate experiment, the supernatant (containing LiI) formed from generation of MeCu was measured following its removal, and 25% of this volume was reintroduced along with 1 equiv of MeLi. The <sup>7</sup>Li NMR spectrum (-70 °C) of this sample displayed the same equilibrium seen for "Me<sub>2</sub>CuLi", indicating that less than stoichiometric amounts of LiI are insufficient to bring rapid lithium exchange.

(34) Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

## Scheme V

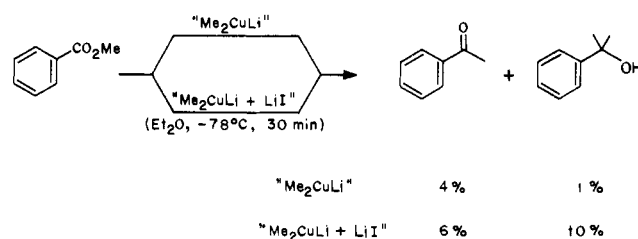
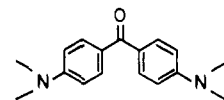


Table III. Gilman Tests on CuI-Derived "Gilman Reagents"

Cuprate	Solvent	Result
Me <sub>2</sub> CuLi (+ LiI)	THF/Et <sub>2</sub> O	-
Me <sub>2</sub> CuLi	THF/Et <sub>2</sub> O	+
Me <sub>2</sub> CuLi (+ LiI)	Et <sub>2</sub> O	-
Me <sub>2</sub> CuLi	Et <sub>2</sub> O	-
Me <sub>2</sub> CuLi	Et <sub>2</sub> O, then Et <sub>2</sub> O/THF	-



≡ Michler's Ketone

Related chemical tests on "Me<sub>2</sub>CuLi" in Et<sub>2</sub>O have also been carried out. The <sup>7</sup>Li NMR of this cuprate shows a single peak irrespective of the LiI content. Treatment of PhCO<sub>2</sub>Me with both "Me<sub>2</sub>CuLi" and "Me<sub>2</sub>CuLi" + LiI in Et<sub>2</sub>O at -78 °C for 30 min afforded, in the former case, 4% ketone and 1% carbinol, while with LiI present, 6% acetophenone and 10% tertiary alcohol resulted (Scheme V). Thus, *more* 1,2-addition takes place with LiI in solution with Et<sub>2</sub>O as solvent. This most likely is attributable to the lower Lewis basicity of Et<sub>2</sub>O relative to THF, which accentuates the carbonyl activating effect of the extra equivalent of lithium ions. Given the absence of a more reactive electrophilic center, 1,2-addition is encouraged.<sup>13,31</sup>

Further corroboration of both these chemical and spectroscopic observations can be acquired from the results of a series of Gilman tests, summarized in Table III. As originally reported by Gilman in 1925,<sup>35</sup> addition of a solution containing Michler's ketone to the organocuprate at room temperature followed by quenching with H<sub>2</sub>O and then introduction of I<sub>2</sub>/HOAc gives an intense blue coloration signaling the presence of free RLi. There seems to be a discrepancy in the literature concerning this protocol where cuprates are concerned, as Gilman claims that "Me<sub>2</sub>CuLi" gives a strong positive test,<sup>2</sup> contrary to that stated in a recent review.<sup>3</sup> It is easy to see the origins of the conflict, as the solvent(s) is not always specified, a factor which we now know plays a crucial role in cuprate constitution. In our hands, in concert with the <sup>7</sup>Li and <sup>1</sup>H NMR data, as well as the 1,2-addition and substitution chemistry described herein, the outcome in THF/Et<sub>2</sub>O is a function of LiI: when absent, a strong positive test is noted; when present in solution, a negative result is seen.

From the <sup>7</sup>Li NMR of "Me<sub>2</sub>CuLi" in Et<sub>2</sub>O (i.e., no "free" MeLi), the Gilman test<sup>35</sup> should be negative for both cases with and without LiI. This is precisely what is found (Table III). The critical test, however, comes in the case of "Me<sub>2</sub>CuLi" (no LiI) in Et<sub>2</sub>O to which THF has been added. As already discussed, the <sup>7</sup>Li NMR shows a new *singlet*<sup>30</sup> which does not revert to the equilibrium ratio for "Me<sub>2</sub>CuLi" formed originally in THF/Et<sub>2</sub>O.

(35) Gilman, H.; Schulze, F. *J. Am. Chem. Soc.* **1925**, *47*, 2002.

Consistent with this remarkable finding, the Gilman test is indeed *negative*.

### Summary

Both  $^1\text{H}$  and  $^7\text{Li}$  NMR spectral studies support the presence of an equilibrium-like situation associated with halide-free THF/Et<sub>2</sub>O solutions of varying MeLi:MeCu ratios. Both "lower" and "higher" order cuprates derived from CuI and MeLi consist of MeLi, Me<sub>2</sub>CuLi, and Me<sub>3</sub>Cu<sub>2</sub>Li. In the presence of LiI, however, this situation is not observed, in particular for MeLi:MeCu = 1, where a different form of Gilman's reagent exists. In Et<sub>2</sub>O, regardless of the LiI content, no equilibrium is noted, although in this medium "Me<sub>2</sub>CuLi" appears to be a unique species relative to that formed in THF (with LiI). Remarkably, "Me<sub>2</sub>CuLi" prepared in Et<sub>2</sub>O (no LiI) and diluted with THF does not revert over time or with changes in temperature to the equilibrium seen when THF is initially present. Chemical studies on two different substrate types, as well as Gilman tests for free RLi, are fully consistent with all of the spectroscopic data.

### Final Comments/Conclusions

Our original goal for initiating a program on  $^7\text{Li}$  NMR spectroscopy of lower (and higher) order organocuprates was to gain a better understanding as to why HO cyanocuprates are oftentimes superior in their reactions with organic substrates relative to LO Gilman cuprates. Early spectra of "Me<sub>2</sub>CuLi" were (naively) intended to serve as our point of reference with which to contrast those arrived at with CuCN-derived cuprates.<sup>36</sup> Although we were well aware of what appeared to be conflicting spectral accounts in the literature<sup>5,7a,b,17</sup> regarding LO systems, we had no idea that this tool for analysis would uncover such a rich deposit of fundamental information.

On the basis of the insight gained from this work, it now appears that Gilman's reagent, "Me<sub>2</sub>CuLi", surely the most popular and extensively utilized of any organocuprate known to date, is far more complex a species than its straightforward preparation would have us believe. Its formation in THF (with or without Et<sub>2</sub>O but minus LiI) in reality has an equal population of Me<sub>3</sub>Cu<sub>2</sub>Li in solution, while in Et<sub>2</sub>O, it behaves spectroscopically as a discrete entity. MeLi-to-MeCu ratios greater than 0.66:1 but less than 1:1 contain Me<sub>3</sub>Cu<sub>3</sub>Li<sub>2</sub> as a solution component in Et<sub>2</sub>O. Ratios in excess of 1:1, rather than forming a "higher order" derivative, simply build up the concentration of free MeLi, regardless of the solvent(s) present.

Finally, in our view, the real contribution here comes in the added flexibility inherently available to the synthetic practitioner, now that copper halide based cuprates can be more accurately thought of as RLi-to-RCu ratios. "Me<sub>2</sub>CuLi", "Me<sub>3</sub>Cu<sub>3</sub>Li<sub>2</sub>", and "Me<sub>3</sub>CuLi<sub>2</sub>" are simply three well-established examples. Thus, there is every reason to believe, for a specific molecule in question, that slightly more or less RLi to RCu might give considerably different results as compared with the "better known" ratios (vide supra). In other words, one should consider the opportunity for fine-tuning cuprate chemistry via this ratio, a general concept heretofore only rarely considered. Usually, reaction parameters such as solvent, concentration, temperature, and equivalents of cuprate are concerns. This work suggests that, in addition, the cuprate makeup itself may constitute an important variable worthy of attention. Indeed, there are cases in the literature where the traditional ratios have been modified to afford significantly improved results.<sup>37</sup> For sure, all copper halide catalyzed processes<sup>38</sup> containing excess RLi, which are clearly reactions of R<sub>2</sub>CuLi, fit this description.<sup>3</sup> The "extra" RLi may serve many roles,<sup>39</sup> not

the least of which is to rapidly convert the (polymeric) RCu formed back to the reactive R<sub>2</sub>CuLi. Further investigations which make use of Li NMR spectroscopy as a tool for addressing lingering questions in organocopper chemistry will be described in future reports from these laboratories.

### 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. Methylolithium was purchased from Aldrich and titrated according to the method of Watson and Eastham.<sup>41</sup> Cuprous iodide was purchased from Fisher and purified by the method of Floyd.<sup>42</sup>

All variable-temperature  $^1\text{H}$  and  $^7\text{Li}$  NMR experiments were performed on a Nicolet NT-300 spectrometer at 300.06 and 116.61 MHz, respectively. As reference, a capillary insert containing 0.8 M LiCl/MeOH-*d*<sub>4</sub>, held in a Teflon plug, was inserted into each 5-mm tube used.

**Preparation of Me<sub>3</sub>Cu<sub>2</sub>Li in THF/Et<sub>2</sub>O (No LiI).** CuI (190 mg, 1.0 mmol) was placed in a centrifuge tube, equipped with a t-tube and magnetic stir bar. The tube was evacuated with a vacuum pump and then purged with Argon, with the process repeated 3×. THF (1.5 mL) was injected, followed by cooling to -78 °C and dropwise addition of methylolithium (0.77 mL, 1.0 mmol). The solution was warmed to room temperature, where the flocculent yellow precipitate was allowed to settle. The t-tube was replaced with a septum under a stream of Argon, and the tube was spun in a centrifuge. The clear yellow supernatant solution was removed with a syringe and replaced with an equal volume of THF. The methylcopper was then stirred, with the washing repeated 3×. THF (1.5 mL) was injected, and the slurry was cooled to -78 °C where methylolithium (0.35 mL, 0.5 mmol) was added. Warming to 0 °C resulted in formation of a clear solution. An aliquot was then transferred via cannula under Argon to a dry NMR tube. The tube was then fitted with a Teflon plug from which a capillary insert containing MeOH-*d*<sub>4</sub>/LiCl (0.8 M) was suspended. The same technique was applied to all samples.

**Preparation of Me<sub>2</sub>CuLi in THF/Et<sub>2</sub>O (No LiI).** Methylcopper (1 mmol) was prepared and washed as outlined above, followed by addition of THF (1.4 mL), and at -78 °C methylolithium (0.74 mL, 1 mmol). Warming to 0 °C gave a water-clear solution.

**Formation of Me<sub>3</sub>Cu<sub>3</sub>Li<sub>2</sub>: MeCu + 0.66 equiv of MeLi in THF/Et<sub>2</sub>O (No LiI).** Methylcopper (1 mmol) was prepared and washed as above followed by addition of THF (1.5 mL) and methylolithium (0.43 mL, 0.66 mmol). Warming to 0 °C gave a clear solution.

**MeCu + 0.75 equiv of MeLi in THF/Et<sub>2</sub>O (No LiI).** Methylcopper (1 mmol) was prepared and washed as above, followed by addition of THF (2.0 mL) and methylolithium (0.48 mL, 0.75 mmol). Warming to 0 °C gave a clear solution.

**MeCu + 1.5 equiv of MeLi in THF/Et<sub>2</sub>O (No LiI).** Methylcopper was prepared and washed as above followed by the addition of THF (1.4 mL) and methylolithium (0.96 mL, 1.5 mmol). Warming to 0 °C gave a clear solution.

**Preparation of Me<sub>3</sub>Cu<sub>2</sub>Li in THF/Et<sub>2</sub>O (with LiI).** Cuprous iodide (190 mg, 1.0 mmol) was placed in a 15-mL, 2-necked, round-bottomed flask, equipped with t-tube and a magnetic stir bar. The flask was evacuated and then purged with Argon with the sequence repeated 3×. THF (1.5 mL) was injected, followed by cooling to -78 °C where methylolithium (1.15 mL, 1.5 mmol) was added dropwise. Warming to 0 °C produced a clear solution.

**Formation of Me<sub>2</sub>CuLi in THF/Et<sub>2</sub>O (with LiI).** Me<sub>2</sub>CuLi was prepared as a clear solution as described above. The following amounts of reagents were used: CuI (190 mg, 1 mmol), THF (2.5 mL), methylolithium (1.28 mL, 2 mmol).

**Preparation of Me<sub>3</sub>CuLi<sub>2</sub> in THF/Et<sub>2</sub>O (with LiI).** Me<sub>3</sub>CuLi<sub>2</sub> was prepared as a clear solution as described above. The following amounts of reagents were used: CuI (190 mg, 1 mmol), THF (1.1 mL), methylolithium (1.92 mL, 3.0 mmol).

**Formation of Me<sub>3</sub>Cu<sub>3</sub>Li<sub>2</sub>, Me<sub>2</sub>CuLi, and Me<sub>3</sub>CuLi<sub>2</sub> in Et<sub>2</sub>O.** These were all prepared precisely as described above by substituting Et<sub>2</sub>O for THF.

**Chemical Studies. Reaction of Me<sub>3</sub>Cu<sub>2</sub>Li (no LiI) with 2-Iodo-octane in THF/Et<sub>2</sub>O.** The aggregate Me<sub>3</sub>Cu<sub>2</sub>Li (1.0 mmol) was prepared as described above, followed by cooling to -78 °C and injection of 2-iodo-octane (91 μL, 0.5 mmol). The temperature was raised to 0 °C, with stirring continued for 3 h followed by quenching with 5 mL of a 10%

(36) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M., unpublished observations.

(37) For one case involving 2-lithiofuran plus CuI, see: Kojima, Y.; Kato, N. *Tetrahedron Lett.* **1980**, *21*, 4365.

(38) Copper halide catalyzed reactions involving excess organolithium (as opposed to Grignard reagents) are rare. For some examples see: Corey, E. J.; Wiegel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439. Miller, R. B.; Al-Hassan, M. I. *Tetrahedron Lett.* **1983**, *24*, 2055. Erdik, E. *Tetrahedron* **1984**, *40*, 641; Knudsen, M. J.; Schore, N. E., *J. Org. Chem.* **1984**, *49*, 5025.

(39) A recent synthesis of (±)-δ-citromycinone by Hauser and Mal<sup>40</sup> utilized a HO cyanocuprate to effect epoxide opening. However, the MeLi:CuCN ratio required was 6:1, rather than the usual<sup>8</sup> 2:1. The excess MeLi presumably occupied the oxygen-containing sites of complexation, thereby freeing the cuprate to effect substitution.

(40) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1862.

(41) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(42) Floyd, D. M. Ph.D. Thesis, University of Michigan, 1976, p 152.

concentrated  $\text{NH}_4\text{OH}/90\%$  saturated  $\text{NH}_4\text{Cl}$  solution. VPC analysis indicated formation of 2-methyloctane to the extent of 9%.

**Reaction of  $\text{Me}_2\text{CuLi}$  (No LiI) with 2-Iodoctane in THF/ $\text{Et}_2\text{O}$ .** The procedure above was duplicated, using  $\text{Me}_2\text{CuLi}$  prepared as described earlier. VPC analysis indicated formation of 2-methyloctane to the extent of 83%.

**Reaction of  $\text{Me}_2\text{CuLi-LiI}$  with 2-Iodoctane in THF/ $\text{Et}_2\text{O}$ .** The procedure above was duplicated with  $\text{Me}_2\text{CuLi-LiI}$  as prepared herein. VPC analysis indicated formation of 2-methyloctane to the extent of 91%.

**Reaction of MeLi with Cyclohexanone in THF/ $\text{Et}_2\text{O}$ .** Methylolithium (0.72 mL, 1 mmol) was dissolved in THF (5 mL) at  $-78^\circ\text{C}$ , followed by addition of cyclohexanone (52  $\mu\text{L}$ , 0.5 mmol). After 10 min the reaction was quenched with 5 mL of a 10% concentrated  $\text{NH}_4\text{OH}/90\%$  saturated  $\text{NH}_4\text{Cl}$  solution. VPC analysis indicated formation of 1-methylcyclohexanol to the extent of 76% (vs. 2-octanol as internal standard).

**Reaction of  $\text{Me}_2\text{CuLi-LiI}$  with Cyclohexanone in THF/ $\text{Et}_2\text{O}$ .** Cuprous iodide (190 mg, 1 mmol) was placed in a 15-mL, 2-necked, round-bottomed flask, evacuated, and purged with Argon (repeat 3 $\times$ ). THF (5 mL) was injected, followed by addition of methylolithium (1.48 mL, 2 mmol) at  $-78^\circ\text{C}$ . Warming to  $0^\circ\text{C}$  gave a clear solution which was recooled to  $-78^\circ\text{C}$  where cyclohexanone (52  $\mu\text{L}$ , 0.5 mmol) was added. After 10 min the reaction was quenched with 5 mL of a 10% concentrated  $\text{NH}_4\text{OH}/90\%$  saturated  $\text{NH}_4\text{Cl}$  solution. VPC analysis indicated no formation of 1-methylcyclohexanol.

**Reaction of  $\text{Me}_2\text{CuLi}$  (No LiI) with Cyclohexanone in THF/ $\text{Et}_2\text{O}$ .** Cuprous iodide (190 mg, 1 mmol) was placed in a 15 mL, 2-necked, round-bottomed flask, evacuated, and purged with Ar (repeat 3 $\times$ ). THF (5 mL) was injected, followed by cooling to  $-78^\circ\text{C}$  where methylolithium (0.72 mL, 1 mmol) was added. Warming to room temperature gave a yellow solid which was allowed to settle. The supernatant was removed with a syringe and replaced with an equal volume of THF. The washing was repeated 3 $\times$ . THF (5 mL) was added to the  $(\text{MeCu})_n$  and cooled to  $-78^\circ\text{C}$  where methylolithium (0.72 mL, 1 mmol) was injected. Warming to  $0^\circ\text{C}$  gave a clear solution. Cyclohexanone (52  $\mu\text{L}$ , 0.5 mmol) was added at  $-78^\circ\text{C}$ , and the reaction was quenched after 10 min with 5 mL of a 10% concentrated  $\text{NH}_4\text{OH}/90\%$   $\text{NH}_4\text{Cl}$  saturated solution. VPC analysis indicated formation of 1-methylcyclohexanol to the extent of 18% (vs. 2-octanol as internal standard).

**Reaction of  $\text{Me}_2\text{CuLi-LiI}$  with Methyl Benzoate in THF/ $\text{Et}_2\text{O}$ .**  $\text{Me}_2\text{CuLi-LiI}$  (0.5 mmol) was prepared in THF (2.5 mL) according to the above procedure. Methyl benzoate (41  $\mu\text{L}$ , 0.33 mmol) was injected at  $-78^\circ\text{C}$ , with stirring continued for 0.5 h followed by quenching with 5 mL of a 10% concentrated  $\text{NH}_4\text{OH}/90\%$  saturated  $\text{NH}_4\text{Cl}$  solution.

**Reaction of  $\text{Me}_2\text{CuLi}$  (No LiI) with Methyl Benzoate in THF/ $\text{Et}_2\text{O}$ .**  $\text{Me}_2\text{CuLi}$  (no LiI) was prepared in THF (2.5 mL) according to the above procedure. Methyl benzoate (41  $\mu\text{L}$ , 0.33 mmol) was injected at  $-78^\circ\text{C}$ , with stirring continued for 0.5 h. Quenching as above was followed by VPC analysis.

**Reaction of 0.5 equiv MeLi with Methyl Benzoate in THF/ $\text{Et}_2\text{O}$ .** Methylolithium (0.107 mL, 0.165 mmol) was dissolved in THF (6.9 mL) at  $-78^\circ\text{C}$ , followed by addition of methyl benzoate (41  $\mu\text{L}$ , 0.33 mmol). Stirring was continued for 0.5 h, followed by quenching with saturated  $\text{NH}_4\text{Cl}$  and VPC analysis.

**Reaction of 1 equiv of MeLi with Methyl Benzoate in THF/ $\text{Et}_2\text{O}$ .** Methylolithium (0.214 mL, 0.33 mmol) was dissolved in THF (6.8 mL) at  $-78^\circ\text{C}$ , followed by addition of methyl benzoate (41  $\mu\text{L}$ , 0.33 mmol). After the mixture was stirred for 0.5 h, the reaction was quenched with saturated  $\text{NH}_4\text{Cl}$ .

**Reaction of 3 equiv of MeLi with Methyl Benzoate in THF/ $\text{Et}_2\text{O}$ .** Methylolithium (0.65 mL, 1 mmol) was dissolved in THF (7 mL) at  $-78^\circ\text{C}$ , followed by addition of methyl benzoate (41  $\mu\text{L}$ , 0.33 mmol). Stirring was continued for 0.5 h, followed by quenching with saturated  $\text{NH}_4\text{Cl}$ .

**Reaction of  $\text{Me}_2\text{CuLi}$  (No LiI) in  $\text{Et}_2\text{O}$  with Methyl Benzoate.** Methylcopper (0.5 mmol) was prepared in  $\text{Et}_2\text{O}$  in a centrifuge tube as described earlier, then washed with  $\text{Et}_2\text{O}$  ( $3 \times 1$  mL).  $\text{Et}_2\text{O}$  (2.5 mL) was injected and the slurry cooled to  $-78^\circ\text{C}$  where methylolithium (0.32 mL, 0.5 mmol) was added dropwise. Warming to  $0^\circ\text{C}$  gave a clear, colorless solution which was recooled to  $-78^\circ\text{C}$ . Methyl benzoate (41  $\mu\text{L}$ , 0.33 mmol) was injected with stirring continued for 0.5 h followed by quenching with 3 mL of a 90%  $\text{NH}_4\text{Cl}$  (saturated)/10%  $\text{NH}_4\text{OH}$  (concentrated) solution.

**Reaction of  $\text{Me}_2\text{CuLi-LiI}$  in  $\text{Et}_2\text{O}$  with Methyl Benzoate.** Gilman's reagent (0.5 mmol) was prepared in  $\text{Et}_2\text{O}$  (2.5 mL) as described above. Methyl benzoate (41  $\mu\text{L}$ , 0.33 mmol) was injected at  $-78^\circ\text{C}$ , stirring was continued for 0.5 h, and then the reaction was quenched.

**Gilman Tests.** All cuprates used in these tests were prepared in a centrifuge tube as described herein (vide supra). An equal volume of Michler's ketone (1% solution) in dry benzene was added to the cuprate at  $0^\circ\text{C}$ .  $\text{H}_2\text{O}$  (1 mL) was introduced after ca. 5 min, with the temperature raised to room temperature. After stirring vigorously, a 0.2% solution of  $\text{I}_2$  in glacial acetic acid was added dropwise. A blue color which persists in the organic layer is considered a positive test.<sup>35</sup>

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**Registry No.**  $\text{Me}_2\text{Cu}_2\text{Li}$ , 61303-82-0; CuI, 1335-23-5; MeLi, 917-54-4; MeCu, 1184-53-8; LiI, 10377-51-2;  $\text{Me}_2\text{CuLi}$ , 15681-48-8;  $\text{Me}_3\text{CuLi}_2$ , 61278-42-0;  $\text{Me}_3\text{Cu}_3\text{Li}_2$ , 61701-36-8; 2-iodooctane, 557-36-8; 2-methyloctane, 3221-61-2; cyclohexanone, 108-94-1; 1-methylcyclohexanol, 590-67-0; methyl benzoate, 93-58-3; acetophenone, 98-86-2;  $\alpha,\alpha$ -dimethylbenzenemethanol, 617-94-7.