

New Copper Chemistry, Part 29<sup>[‡]</sup>

## Re-evaluation of Organocuprate Reactivity: Logarithmic Reactivity Profiles for Iodo- versus Cyano-Gilman Reagents in the Reactions of Organocuprates with 2-Cyclohexenone and Iodocyclohexane

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*Dedicated to Professor Martin Nilsson on the occasion of his 70th birthday*

**Abstract:** Iodo-Gilman reagents  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$ ,  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$ , and  $\text{BuThCuLi} \cdot \text{LiI}$  and cyano-Gilman reagents (née “higher order cyanocuprates”  $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$ ,  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN}$ , and  $\text{BuThCuLi} \cdot \text{LiCN}$ ) react with 2-cyclohexenone at various rates, which depend upon the R groups (Me, Bu, Th = thienyl), Li salt (LiI vs. LiCN), solvent (ether vs. THF), and amount of trimethylsilyl chloride (TMSCl) additive. The effect of the Li salt (CuI vs. CuCN precursor) is less than that of solvent or TMSCl. The

butylcuprate-iodocyclohexane reaction has also been examined as a function of Li salt, solvent, and TMSCl additive, and similar effects are observed. The reactivity matrix  $\mathbf{R}$  with elements  $r_{ij}$  is a convenient way to store and present a large amount of relative reactivity data. Entry  $r_{ij}$  is the ratio of the rate with

reagent  $i$  to the rate with reagent  $j$ , which we approximate by using yields measured after a short time (4 s). The logarithmic reactivity profile (LRP) provides an efficient means for determining yields under conditions where such comparisons are valid. The results of a large number of 4-point LRPs and related reactions are tabulated and analyzed to provide a clearer picture of organocuprate reactivity.

**Keywords:** aggregation · alkylations · cuprates · lithium · Si ligands

### Introduction

The first isolated organocopper compound was  $\text{PhCu}$ , prepared by Reich from  $\text{PhMgBr}$  and  $\text{CuI}$ .<sup>[1]</sup> The reagents prepared from two equivalents of  $\text{RLi}$  and a copper(I) salt are now commonly called Gilman reagents, since he first prepared the prototypical  $\text{Me}_2\text{CuLi}$  from  $\text{MeLi}$  and  $\text{MeCu}$ , and correctly concluded that it is an *ate* complex.<sup>[2]</sup> The  $\text{MeCu}$  was obtained from  $\text{MeLi}$  and  $\text{CuI}$ . In 1966 House, Respass, and Whitesides demonstrated that  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  gave effi-

cient 1,4-addition to  $\alpha$ -enones,<sup>[3]</sup> and shortly thereafter, Corey and Posner showed that  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  and  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  gave useful cross-coupling reactions with alkyl halides.<sup>[4]</sup>

As in these early investigations, virtually all the pioneering research on synthetic applications of organocuprates was done with  $\text{CuI}$ .<sup>[5, 6]</sup> In 1981 it was reported that the simple substitution of  $\text{CuCN}$  for  $\text{CuI}$  in the usual preparation of organocuprates gave new reagents “ $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$ ” of such superior reactivity that a new kind of structure was required: “higher order cyanocuprates”.<sup>[7]</sup> Several experimental techniques (NMR,<sup>[8–12]</sup> IR,<sup>[13]</sup> EXAFS<sup>[14]</sup>) and theoretical calculations<sup>[14c, 15]</sup> have recently converged on the conclusion that the reagents prepared from two equivalents of  $\text{RLi}$  and one equivalent of  $\text{CuCN}$  are not, in fact, higher order cyanocuprates, but rather cyanide-modified Gilman reagents (cyano-Gilman reagents), which consequently should be denoted as  $\text{R}_2\text{CuLi} \cdot \text{LiCN}$ .<sup>[16]</sup>

In light of these results, we have reinvestigated the reactivity issue. Our principal tool has been the logarithmic reactivity profile (LRP),<sup>[17–19]</sup> which is generated by quenching an archetypal reaction after times that span several orders of

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magnitude. Herein we report 4-point LRPs for the reactions of  $\text{Me}_2\text{CuLi} \cdot \text{LiX}$ ,  $\text{Bu}_2\text{CuLi} \cdot \text{LiX}$ , and  $\text{BuThCuLi} \cdot \text{LiX}$  ( $X = \text{I}, \text{CN}$ ) with 2-cyclohexenone **1** in THF and ether and for the reactions of  $\text{Bu}_2\text{CuLi} \cdot \text{LiX}$  ( $X = \text{I}, \text{CN}$ ) with CyI (Cy = cyclohexyl group) in THF. Many of these reactions have also been run in the presence of trimethylsilyl chloride (TMSCl). Based upon the results of 45 LRPs and a number of control experiments (>200 reactions total), we present a clearer picture of organocuprate reactivity that does not include higher order cyanocuprates.

## Results

**Methyl homocuprates:** Table 1 summarizes the LRPs for the reactions of the methyl iodo- and cyano-Gilman reagents with **1** in THF at  $-78^\circ\text{C}$ . The yields of 3-methylcyclohexanone **2** from the 4 s reactions of  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  ( $4.5 \pm 0.9\%$ ) and

Table 1. LRP data for reactions of  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  and  $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$  with **1** in THF.<sup>[a]</sup>

Reagent	Additive	Time [h]	Yield <b>2</b> [%]	Yield <b>3</b> [%]
$\text{Me}_2\text{CuLi} \cdot \text{LiI}$	none	1	73	–
	none	0.1	48	–
	none	0.01	20	–
	none	0.001	4.5	–
	1 TMSCl	1	0.7	90
	1 TMSCl	0.1	3.3	83
	1 TMSCl	0.01	1.2	81
	1 TMSCl	0.001	3.1	80
	0, 1 TMSCl <sup>[b]</sup>	1, 1	35	65
	0, 1 TMSCl <sup>[b]</sup>	1, 0.1	34	45
	0, 1 TMSCl <sup>[b]</sup>	1, 0.01	55	13
	0, 1 TMSCl <sup>[b]</sup>	1, 0.001	51	15
	0, 1 TMSCl <sup>[c]</sup>	2, 0.001	66	<0.1
	0, 1 TMSCl <sup>[d]</sup>	3, 0.001	65	<0.1
	$\text{Me}_2\text{CuLi} \cdot \text{LiCN}$	none	1	78
none		0.1	36	–
none		0.01	13	–
none		0.001	5.2	–
1 TMSCl		1	7.6	65
1 TMSCl		0.1	1.5	75
1 TMSCl		0.01	4.9	70
1 TMSCl		0.001	3.9	57

[a] Reactions were run at  $-78^\circ\text{C}$  on a 2 mmol scale at 0.1M in THF. Quench: 6 mL of sat. aq. sodium bicarbonate ( $3 \text{ mL mmol}^{-1} \text{ Cu}$ ). [b] Cuprate and **1** were stirred for 1 h at  $-78^\circ\text{C}$ ; 1 equiv of TMSCl was added, followed by 6 mL of sat. aq. bicarbonate after the usual LRP time. [c] Same as in [b], except cuprate and **1** were initially stirred for 2 h at  $-78^\circ\text{C}$ . [d] Same as in [b], except cuprate and **1** were initially stirred for 2 h at  $-78^\circ\text{C}$  and then allowed to warm slowly to  $0^\circ\text{C}$  over 0.9 h; after 0.1 h at  $0^\circ\text{C}$ , the reaction mixture was cooled to  $-78^\circ\text{C}$  for the addition of TMSCl.

$\text{Me}_2\text{CuLi} \cdot \text{LiCN}$  ( $5.2 \pm 1.0\% \approx 5 \pm 1\%$ ) are the same to within the estimated 20% relative error (see Discussion below). The iodocuprate appears to be modestly ahead of the cyanocuprate at the 36 s ( $20 \pm 4$  vs.  $13 \pm 3\%$ ) and 6 min marks ( $48 \pm 10$  vs.  $36 \pm 7\%$ ), but the error bars overlap. The 1 h yields from these reagents ( $73 \pm 15$  vs.  $78 \pm 16\%$ ) approach the same level. The ratios of yields calculated for the Gilman reagents  $\text{Me}_2\text{CuLi} \cdot \text{LiX}$  ( $X = \text{I}, \text{CN}$ ) are  $R_{\text{LiCN}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiX}/\text{THF}) = 0.87, 1.5, 1.3, 0.94$  (in the order of

increasing time,  $t >$ ). The average ratio is  $1.2 \pm 0.5$ , where the uncertainty has been calculated with 95% confidence limits (CL).<sup>[20a,b]</sup> Within experimental error, there is no significant effect of changing the Li salt (i.e., cuprate precursor).

With one equivalent of TMSCl in THF, the 4 s yields of 3-methyl-1-trimethylsilyloxycyclohexene **3** from both  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  and  $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$  ( $80 \pm 16$  and  $57 \pm 11\%$ , respectively) are substantially higher than the corresponding yields of ketone **2** without TMSCl (previous paragraph). The ratios of total yields with and without one equivalent of TMSCl for  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  are  $R_{\text{TMSCl}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiI}/\text{THF}) = 18.5, 4.1, 1.8, 1.2$  ( $t >$ ). For the cyanocuprate  $R_{\text{TMSCl}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiCN}/\text{THF}) = 12, 5.8, 2.1, 0.93$  ( $t >$ ); however, quantitative comparisons cannot be made in this case, since cyano-Gilman reagents react with TMSCl.<sup>[21]</sup> The resulting TMSCN also accelerates conjugate additions in THF.<sup>[22]</sup>

The TMSCl ratios ( $R_{\text{TMSCl}}$ ) approach one as the yields from the native reactions catch up to those from the TMSCl-accelerated ones. Therefore, the 4 s data give the most valid comparisons. Total yields are used to calculate TMSCl ratios ( $\% \mathbf{3} + \% \mathbf{2})/\% \mathbf{2}$ , based on the assumption that the small amounts of **2** from the reactions with TMSCl are due to hydrolysis of **3**. However, some of the **2** may arise from protonation of small amounts of enolate (see Discussion). If  $\% \mathbf{3}$  alone is used in the numerator, the ratios are the same to within experimental uncertainty.

The third LRP in Table 1 examines silylation of the enolate produced in the cuprate conjugate addition. After 1 h at  $-78^\circ\text{C}$ , four reaction mixtures from  $\text{Me}_2\text{CuLi} \cdot \text{LiI} + \mathbf{1}$  were treated with one equivalent of TMSCl; they were then quenched after the standard times to create the LRP. At the 4 s and 36 s times, the yields of TMS enol ether **3** are about 15%. At the 6 min and 1 h times, they are 45% and 65%, respectively. However, when the initial time before TMSCl addition was extended to 2 h, no **3** was observed at the 4 s mark. Therefore, the 15% yield of **3** observed with the 1 h initial time may be attributed to silylation of the intermediate  $\pi$  complex (see Discussion), which was gone after the 2 h initial time. The key observation is that silylation is much slower when the TMSCl is added at the end of the reaction, where it silylates the enolate, than at the beginning, where it silylates the  $\pi$  complex.

Table 2 summarizes the results for methyl cuprates in ether, including some with one equivalent of THF per Li. Two kinds of MeLi were used: low halide MeLi, freshly prepared in ether by the *Organic Syntheses* procedure,<sup>[23a]</sup> and MeLi·THF, crystallized from commercial MeLi solution in THF/cumene.<sup>[23b]</sup> These very pure lithium reagents were used to prepare  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  and  $\text{Me}_2\text{CuLi} \cdot \text{LiI} \cdot 2\text{THF}$ , respectively.

In ether  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  appears to be more reactive than  $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$  (4 s yields, 32 vs. 5.3%). However, the latter is not homogeneous in ether, as it is in THF. Consequently, the salt ratios for ether are not as accurate as for THF (above). With this caveat, they are  $R_{\text{LiCN}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiX}/\text{ether}) = 6.0, 2.2, 1.9, 2.2$  ( $t >$ ).

At short times, the yields with  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  in ether are much higher than in THF (4 s yields, 32 vs. 4.5%). The solvent ratios are  $R_{\text{ether/THF}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiI}) = 7.1, 2.3, 1.1, 1.1$  ( $t >$ ). The THF additive ratios for  $\text{Me}_2\text{CuLi} \cdot \text{LiI} \cdot 2\text{THF}$  in ether

Table 2. LRP data for the reactions of  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$ ,  $\text{Me}_2\text{CuLi} \cdot \text{LiI} \cdot 2\text{THF}$  and  $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$  with **1** in ether.<sup>[a]</sup>

Reagent	Additive	Time [h]	Yield <b>2</b> [%]	Yield <b>3</b> [%]
$\text{Me}_2\text{CuLi} \cdot \text{LiI}$	none	1	80	–
	none	0.1	52	–
	none	0.01	47	–
	none	0.001	32	–
	1 TMSCl	1	73	2.9
	1 TMSCl	0.1	59	1.9
	1 TMSCl	0.01	43	1.4
	1 TMSCl	0.001	36	2.4
	1 TMSCl/3py <sup>[b]</sup>	0.001	50	2.8
	$\text{Me}_2\text{CuLi} \cdot \text{LiI} \cdot 2\text{THF}$	none	1	81
none		0.1	83	–
none		0.01	69	–
none		0.001	47	–
1 TMSCl		1	86	3.4
1 TMSCl		0.1	75	3.2
1 TMSCl		0.01	40	2.1
1 TMSCl		0.001	38	2.2
6 TMSCl		1	71	< 0.1
6 TMSCl		0.1	59	0.4
$\text{Me}_2\text{CuLi} \cdot \text{LiCN}$	none	1	37	–
	none	0.1	27	–
	none	0.01	21	–
	none	0.001	5.3	–

[a] Reactions were run at  $-78^\circ\text{C}$  on a 1 mmol scale at 0.1M in ether. Quench: 3 mL of sat. aq. sodium bicarbonate, unless otherwise noted.

[b] Quench: 3 equiv of py and after 1 s, 3 mL of sat. aq. bicarbonate.

(2 mol % THF) vs.  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  in neat ether are  $R_{2\text{THF}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiI} / \text{ether}) = 1.47, 1.5, 1.6, 1.0 (t >)$ . Thus, a small amount of THF (1 equiv per Li) accelerates the reaction noticeably, whereas a large excess (neat THF) slows the reaction dramatically, as can be appreciated by calculating the reciprocal 4 s solvent ratio,  $R_{\text{THF/ether}} = 1/7.1 = 0.14$ .

After 4 s,  $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$  appears to have the same reactivity in ether (5.3 %, Table 2) and THF (5.2 %, Table 1). By 1 h, the yield in THF is definitely better than in ether (78 vs. 37 %). These comparisons are not conclusive, since the reagent in ether is not homogeneous.

The TMSCl ratios in neat ether are  $R_{\text{TMSCl}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiI} / \text{ether}) = 1.2, 0.94, 1.2, 0.95 (t >)$ ; average  $1.1 \pm 0.2$  (95 % CL). With one equivalent of THF per Li,  $R_{\text{TMSCl}}(0.1\text{M } \text{Me}_2\text{CuLi} \cdot \text{LiI} \cdot 2\text{THF} / \text{ether}) = 0.86, 0.61, 0.94, 1.1 (t >)$ ; average  $0.9 \pm 0.3$  (95 % CL). In both cases the averages = 1 to within experimental error, and it can be concluded that the effect of TMSCl in ether is negligible, even in the presence of one equivalent of THF. Obviously, more than one equivalent of THF per Li is required for the activating effect of TMSCl. It is important to note that ketone **2** is the predominant product from both reagents in ether, not TMS enol ether **3**.

The use of six equivalents of TMSCl appears to have a slightly negative effect, which may be attributed to the reaction between TMSCl and  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$ .<sup>[24, 25]</sup> (The resulting  $\text{MeCu/TMSCl}$  in ether is not as reactive as  $\text{BuCu/TMSCl}$  in THF—see next section.)

The addition of three equivalents of pyridine (py) to a 4 s reaction containing TMSCl in ether (Table 2, footnote [b]), followed 1 s later by saturated aqueous sodium bicarbonate,

gave  $50 \pm 10\%$  of **2** and  $2.8 \pm 0.6\%$  of **3**. When these results are corrected (decreased by 20 %) to account for the extra reaction time (5 s vs. 4 s), the yields are  $40 \pm 8\%$  and  $2.2 \pm 0.4\%$ , respectively. These are the same to within experimental error as the yields without py ( $36 \pm 7\%$  of **2** and  $2.4 \pm 0.5\%$  of **3**). Thus, the addition of py to the quench in ether has no apparent effect.

**Butyl homocuprates:** Table 3 contains data for the butyl homocuprates and mixed butyl thienylcuprates (next section) prepared from CuI and CuCN in THF and ether (0.1M and

Table 3. LRP data for the reactions of  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$ ,  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN}$ ,  $\text{BuThCuLi} \cdot \text{LiI}$  and  $\text{BuThCuLi} \cdot \text{LiCN}$  with **1** in THF and ether.<sup>[a]</sup>

Reagent	Time [h]	% <b>4</b> in	
		THF 0.1M (0.03M)	ether 0.1M (0.03M)
$\text{Bu}_2\text{CuLi} \cdot \text{LiI}$	1	97 (64, <sup>[b]</sup> 86)	97 (99 <sup>[b]</sup> )
	0.1	86 (35, <sup>[b]</sup> 68)	99 (99 <sup>[b]</sup> )
	0.01	34 ( 8, <sup>[b]</sup> 24)	99 (99 <sup>[b]</sup> )
	0.001	19 ( 4, <sup>[b]</sup> 10)	99 (99, <sup>[b]</sup> 92 <sup>[c]</sup> )
$\text{Bu}_2\text{CuLi} \cdot \text{LiCN}$	1	80 (65)	99 (100)
	0.1	75 (68)	99 (100)
	0.01	25 (46)	99 (96)
	0.001	14 (13)	99 (62, <sup>[c]</sup> 53)
$\text{BuThCuLi} \cdot \text{LiI}$	1	99 (40, <sup>[b]</sup> 75)	94 (92 <sup>[b]</sup> )
	0.1	80 (27, <sup>[b]</sup> 57)	86 (89 <sup>[b]</sup> )
	0.01	41 ( 6, <sup>[b]</sup> 32)	71 (84 <sup>[b]</sup> )
	0.001	29 (< 1, <sup>[b]</sup> 8.4)	62 (82, <sup>[b]</sup> 92 <sup>[c]</sup> )
$\text{BuThCuLi} \cdot \text{LiCN}$	1	89 (56)	99 (91)
	0.1	74 (37)	99 (87)
	0.01	57 (34)	89 (81)
	0.001	32 (14)	64 (63, <sup>[c]</sup> 65)

[a] Reactions were run at  $-78^\circ\text{C}$  on a 1 mmol scale at the concentrations in the solvents listed. Quench: 3 mL of sat. aq. sodium bicarbonate. CuI (Aldrich 99.999 %) was used, except as noted. [b] CuI purified by the procedure of ref. [26a] (not used in any calculations). [c] Used in calculations.

0.03M). The 0.1M iodocuprates were prepared from 99.999 % CuI. The 0.03M iodocuprate reactions were initially run with CuI purified by the *Organometallics in Synthesis (Ois)* method,<sup>[26a]</sup> but it was subsequently discovered that this material often gave poorer results. Therefore, the LRPs in THF and 4 s reactions in ether that had been run with *Ois* material (Table 3, footnote [b]) were repeated with 99.999 % CuI. The yields of 3-butylcyclohexanone **4** at all four times in THF were significantly higher. The 4 s results in ether were the same to within experimental error; therefore, the rest of the ether LRPs were not redone.

At 0.1M in THF,  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  appears to be slightly more reactive than  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN}$  (4 s yields,  $19 \pm 4$  vs.  $14 \pm 3\%$ ), and at 0.03M it appears to be slightly less reactive (4 s yields,  $10 \pm 2$  vs.  $13 \pm 3\%$ ). However, since the 20 % relative error bars overlap, it makes more sense to say that the yields are approximately equal at both concentrations. The salt ratios at 0.1M in THF are  $R_{\text{LiCN}}(0.1\text{M } \text{Bu}_2\text{CuLi} \cdot \text{LiX} / \text{THF}) = 1.4, 1.4, 1.1, 1.2 (t >)$ . The average is  $1.3 \pm 0.2$  with 95 % CL;<sup>[20a]</sup> thus, the iodocuprate appears to be slightly more reactive. However, with 99 % CL the average is  $1.3 \pm 0.4$ .

At 0.1M in ether, both iodo- and cyanocuprate reactions have reached their plateaus by 4 s, and the ratio of yields is not

a good indication of relative reactivity. By cutting down the concentrations to 0.03 M,  $R_{\text{LiCN}}(0.03 \text{ M Bu}_2\text{CuLi} \cdot \text{LiX/ether}) = 1.5$  is measured at 4 s.

The butylcuprates from CuI and CuCN are more reactive in ether than in THF. Since the 0.1 M ether reactions are essentially complete after 4 s, the solvent ratios at this concentration are lower limits:  $R_{\text{ether/THF}}(0.1 \text{ M Bu}_2\text{CuLi} \cdot \text{LiI}) = 5.2$  (lower limit) and  $R_{\text{ether/THF}}(0.1 \text{ M Bu}_2\text{CuLi} \cdot \text{LiCN}) = 7.1$  (lower limit). The 0.03 M reactions have not reached plateaus by 4 s:  $R_{\text{ether/THF}}(0.03 \text{ M Bu}_2\text{CuLi} \cdot \text{LiI}) = 9.2$  and  $R_{\text{ether/THF}}(0.03 \text{ M Bu}_2\text{CuLi} \cdot \text{LiCN}) = 4.8$ .

Comparison of the 0.1 M butyl results with the corresponding methyl data gives the group-transfer ratios ( $t >$ )  $R_{\text{Bu/Me}}(0.1 \text{ M R}_2\text{CuLi} \cdot \text{LiI/THF}) = 4.2, 1.7, 1.8, 1.3$ ;  $R_{\text{Bu/Me}}(0.1 \text{ M R}_2\text{CuLi} \cdot \text{LiCN/THF}) = 2.7, 1.9, 2.1, 1.0$ ;  $R_{\text{Bu/Me}}(0.1 \text{ M R}_2\text{CuLi} \cdot \text{LiI/ether}) = 3.1, 2.1, 1.9, 1.2$  (lower limits) and  $R_{\text{Bu/Me}}(0.1 \text{ M R}_2\text{CuLi} \cdot \text{LiCN/ether}) = 19, 4.7, 3.7, 2.7$  (inaccurate). The last series is inaccurate, owing to the insolubility of  $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$  in ether.

Tables 4 and 5 summarize the effects of TMSCl on  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  in THF and ether. The results with 99.999% CuI are much better than with CuI purified by the *Inorganic Syntheses* method (Tables 4 and 5, footnote [b]),<sup>[26b]</sup> which was

Table 4. LRP data for the reactions of  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  with **1** in THF.<sup>[a]</sup>

Reagent	Additive(s)	Time [h]	Yield <b>4</b> [%]	Yield <b>5</b> [%]
$\text{Bu}_2\text{CuLi} \cdot \text{LiI}$	none	1	97, 90, 91 (47 <sup>[b]</sup> )	–
	none <sup>[c]</sup>	0.1	86, 76, 80 (45 <sup>[b]</sup> )	–
	none	0.01	34, 41, 46 (46 <sup>[b]</sup> )	–
	none	0.001	19, 21, 23 (40 <sup>[b]</sup> )	–
	1 TMSCl	1	< 1	66
	1 TMSCl	0.1	< 1	65
	1 TMSCl	0.01	1	62
	1 TMSCl	0.001	3	47
	2 TMSCl	1	2	88
	2 TMSCl	0.1	1	89
	2 TMSCl	0.01	2	92
	2 TMSCl	0.001	2, < 1	82, 80
	6 TMSCl	0.001	99	< 1
	6 TMSCl <sup>[d]</sup>	0.001	5, 11, 5, 4, 5	58, 60, 62, 71, 72
	6 TMSCl/py <sup>[e]</sup>	0.001	10	80
	6 TMSCl/py <sup>[f]</sup>	0.001	3	93
6 TMSCl/py <sup>[g]</sup>	0.001	< 1	99	

[a] Reactions were run at  $-78^\circ\text{C}$  on a 1 mmol scale at 0.1 M in THF. CuI (Aldrich 99.999%) was used, except as noted. Quench: 3 mL of sat. aq. sodium bicarbonate, unless otherwise noted. [b] CuI purified by the method of ref. [26b] (not used in any calculations); reactions run by G. Miao (refs. [17, 18]). [c] Two additional 6 min reactions gave yields of 82 and 78%. [d] Quench: 6 mL of sat. aq. bicarbonate. [e] Quench: 1 equiv of py and after 1 s, 3 mL of sat. aq. bicarbonate. [f] Quench: 1 equiv of py and after 1 s, 6 mL of sat. aq. bicarbonate. [g] Quench: 1 equiv of py and 6 equiv of HMPA in 1 mL of THF and after 1 s, 3 mL of sat. aq. bicarbonate.

used for the communications.<sup>[17, 18]</sup> With one equivalent of TMSCl, the yields of 3-butyl-1-trimethylsilyloxycyclohexene **5** from  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  in THF level off at about 65% vs. 90% for the analogous methyl reagent. There appears to be significantly more reaction of the butyl reagent with TMSCl, presumably to afford  $\text{BuCu}$ .<sup>[25]</sup> With two equivalents of TMSCl, the yields from  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  in THF level off at about 90%. The excess TMSCl can promote the addition of  $\text{BuCu} \cdot \text{LiI}$  to  $\alpha$ -enones.<sup>[27]</sup>

Table 5. LRP data for the reactions of  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  with **1** in ether.<sup>[a]</sup>

Reagent	Additive	Time [h]	Yield <b>4</b> [%]	Yield <b>5</b> [%]
$\text{Bu}_2\text{CuLi} \cdot \text{LiI}$	none	1	97, 99 (66 <sup>[b]</sup> )	–
	none	0.1	99, 99 (67 <sup>[b]</sup> )	–
	none	0.01	99, 97 (69 <sup>[b]</sup> )	–
	none	0.001	99, 98 (54 <sup>[b]</sup> )	–
	1 TMSCl	1	97	3
	1 TMSCl	0.1	90	4
	1 TMSCl	0.01	91	3
	1 TMSCl	0.001	85	4

[a] Reactions were run at  $-78^\circ\text{C}$  on a 1 mmol scale at 0.1 M in ether. Quench: 3 mL of sat. aq. sodium bicarbonate, unless otherwise noted. [b] CuI purified by the method of ref. [26b] (not used in any calculations); reactions run by G. Miao (refs. [17, 18]).

The TMSCl ratios in THF are  $R_{\text{TMSCl}}(0.1 \text{ M Bu}_2\text{CuLi} \cdot \text{LiI/THF}) = 2.6, 1.9, 0.76, 0.68$  ( $t >$ ). The 4 s TMSCl ratio (2.6) is significantly less than the corresponding ratio for the methyl reagents in THF (18.5), as the native butyl reagent is more reactive than the native methyl one (see above). With two equivalents of TMSCl, the ratios are  $R_{2\text{TMSCl}}(0.1 \text{ M Bu}_2\text{CuLi} \cdot \text{LiI/THF}) = 4.4, 2.8, 1.0, 0.93$  ( $t >$ ), which are significantly higher.

The yields for  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  in ether (Table 5) are essentially quantitative with 99.999% CuI. In contrast to the results in THF, the TMS enol ether **5** is not the principal product with TMSCl (1 equiv) in ether, for example, the 4 s yields are 85% of ketone **4** and 4% of **5**. The TMSCl ratios are upper limits:  $R_{\text{TMSCl}}(0.1 \text{ M Bu}_2\text{CuLi} \cdot \text{LiI/ether}) = 0.90, 0.95, 0.95, 1.0$  ( $t >$ ); average  $0.95 \pm 0.06$  (95% CL). As in the methyl case, TMSCl does not accelerate the reaction of  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  with **1** in ether.

Without py or hexamethylphosphoramide (HMPA), the total yield (%**4** + %**5**) after 4 s from  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}/6 \text{ TMSCl}$  in THF is  $71 \pm 7\%$  (Table 4, footnote [d], see also Discussion). When this yield is corrected (increased by 20%) to account for the extra reaction time (1 s), the baseline for comparison of the reactions with these additives is  $85 \pm 8\%$ . The total yields are 90–96% with one equivalent of py and 99% with one equivalent of py and six equivalents of HMPA. It appears that these additives improve the total yields in THF, even though they are added at the end.

**Mixed thienylcuprates:** Butyl thienylcuprates (Table 3) were prepared by the procedure of Nilsson et al.,<sup>[28]</sup> who introduced these useful mixed cuprates. The salt ratios (4 s) are  $R_{\text{LiCN}}(0.1 \text{ M BuThCuLi} \cdot \text{LiX/THF}) = 0.91$ ,  $R_{\text{LiCN}}(0.03 \text{ M BuThCuLi} \cdot \text{LiX/THF}) = 0.60$ ,  $R_{\text{LiCN}}(0.1 \text{ M BuThCuLi} \cdot \text{LiX/ether}) = 0.97$  and  $R_{\text{LiCN}}(0.03 \text{ M BuThCuLi} \cdot \text{LiX/ether}) = 1.5$ . Neither reagent is dramatically more reactive in either solvent.

As with the homocuprates, the mixed thienylcuprates from both CuI and CuCN are more reactive in ether than in THF. The solvent ratios (4 s) are  $R_{\text{ether/THF}}(0.1 \text{ M BuThCuLi} \cdot \text{LiI}) = 2.1$ ,  $R_{\text{ether/THF}}(0.03 \text{ M BuThCuLi} \cdot \text{LiI}) = 11$ ,  $R_{\text{ether/THF}}(0.1 \text{ M BuThCuLi} \cdot \text{LiCN}) = 2.0$  and  $R_{\text{ether/THF}}(0.03 \text{ M BuThCuLi} \cdot \text{LiCN}) = 4.5$ . For both CuI and CuCN the ratios are higher at the lower concentration, where the yields in THF fall off but not those in ether.

At 0.1 M in THF, the thienylcuprates prepared from either CuI or CuCN are more reactive than the corresponding

homocuprates; the 4 s yields are  $29 \pm 6$  vs.  $19 \pm 4\%$  starting from CuI and  $32 \pm 6$  vs.  $14 \pm 3\%$  from CuCN. At 0.03 M in THF, both thienylcuprates and homocuprates have essentially the same reactivity independent of precursor; the respective 4 s yields are  $8 \pm 2$  vs.  $10 \pm 2\%$  from CuI and  $14 \pm 3$  vs.  $13 \pm 3\%$  from CuCN.

At 0.1 M in ether, the 4 s yields from the thienylcuprates (ca. 60%) are much lower than from the homocuprates (99%), regardless of precursor. At 0.03 M in ether, thienyl- and homocuprates both give approximately 90% yields from CuI and about 60% yields from CuCN.

**CuI purification:** To obtain the results in the initial communications,<sup>[17–18]</sup> we used CuI that had been purified by the *Inorganic Syntheses (IS)* method,<sup>[26b]</sup> then rigorously dried over phosphorus pentoxide in an Abderhalden apparatus (0.1 Torr, 110 °C). We subsequently found that this material gave much lower yields in THF (Table 4, footnote [b]) and ether (Table 5, footnote [b]) than commercial 99.999% CuI (Aldrich). The *IS* material also gave higher levels of 1,2-adduct.<sup>[18, 29]</sup>

We have also examined CuI that was purified by the *Organometallics in Synthesis (OiS)* procedure.<sup>[26a]</sup> It was dried at ambient temperature under vacuum (0.1 Torr). The *OiS* material gave significantly lower yields in THF than 99.999% CuI (Table 3, footnote [b]). In ether the yields were comparable (see section on butyl homocuprates). Since both purified batches tended to give lower yields of the 1,4-adduct, commercial ultrapure CuI (Aldrich 99.999%) was adopted for quantitative work.

It should be noted that the 99.999% purity refers to metals only. One explanation for the superiority of the 99.999% CuI, which was not rigorously dried, may be that small amounts of water are beneficial. This contrainuitive result was first demonstrated by Corey, Hannon and Boaz.<sup>[24c]</sup> Another factor may be different surface characteristics, as CuI is a semiconductor. Redox reactions between it and reactive species (BuLi, BuCu, Bu<sub>2</sub>CuLi) might account for the fact that

solutions of BuCu·LiI and Bu<sub>2</sub>CuLi·LiI are invariably gray to black, owing to the presence of colloidal copper.

**Reactions with CyI:** Table 6 summarizes the LRP for the reactions of iodocyclohexane **6** with Bu<sub>2</sub>CuLi·LiI or Bu<sub>2</sub>CuLi·LiCN in THF to afford principally butylcyclohexane **7**. At the concentration used here (0.12 M), the radical products (cyclohexane **8**, cyclohexene **9**, dicyclohexyl **10**)<sup>[30]</sup> are not as abundant as they were at the higher concentration (0.3 M) studied previously,<sup>[31]</sup> and the amounts of octane **11** are likewise lower. A salient feature of the yields, which were all measured in duplicate, is the prevalence of nonmonotonic LRPs (3 out of 4 for the reagents without TMSCl). For example, upon going from 4 s to 1 h, the percent yields of **7** in the first LRP drop from 9 to 6 (–33%), jump to 26 (+333%), and finally fall again to 15 (–42%). This apparently random aspect is suggestive of a radical chain reaction that is initiated by impurities or inhibited by them.<sup>[32]</sup>

Most of the cuprate-enone LRPs in Tables 1–5 are monotonic. The small declines (3% ave.) in the 1 h yields of major products for six of the enone LRPs (out of 35) are understandable in terms of the potential for side reactions with labile products such as enolates or TMS enol ethers. The products in the case of Table 6 are hydrocarbons, which are much more inert. There are only three enone LRPs in which a decrease (2% ave.) occurs before the end.

The addition of TMSCl (1 or 2 equiv) to the iodo-Gilman reagent makes its reaction with CyI less erratic, that is, the data within an LRP are much smoother. There are modest declines in two of the 1 h yields of **7**. Furthermore, the highest yield of **7** in every LRP with TMSCl is  $\geq 53\%$ , the best yield from the cyano-Gilman reagent. Similar effects were observed when the glassware was passivated with ammonia.<sup>[31]</sup> In ether the yield of **7** after 1 h at –78 °C was only 1%, with or without two equivalents of TMSCl.

The addition of TMSCl also increases the amount of **11** from Bu<sub>2</sub>CuLi·LiI. All sixteen reactions in the four LRPs with TMSCl (1 or 2 equiv) contain significant levels ( $\geq 10\%$ )

Table 6. LRP data for the reactions of Bu<sub>2</sub>CuLi·LiI and Bu<sub>2</sub>CuLi·LiCN with CyI.<sup>[a]</sup>

Reagent	Additive	Time [h]	Yield <b>7</b> <sup>[b]</sup> [%] ([%])	Yield <b>8</b> <sup>[c]</sup> [%] ([%])	Yield <b>9</b> <sup>[d]</sup> [%] ([%])	Yield <b>10</b> <sup>[e]</sup> [%] ([%])	Yield <b>11</b> <sup>[f]</sup> [%] ([%])	
Bu <sub>2</sub> CuLi·LiI	none	1	15 (31)	8 (6)	<1 (<1)	<1 (<1)	3 (1)	
	none	0.1	26 (18)	5 (5)	<1 (<1)	<1 (<1)	<1 (5)	
	none	0.01	6 (38)	5 (11)	<1 (5)	<1 (<1)	<1 (10)	
	none	0.001	9 (32)	4 (17)	<1 (12)	<1 (23)	<1 (19)	
	1 TMSCl	1	47 (59)	10 (14)	<1 (6)	8 (14)	17 (14)	
	1 TMSCl	0.1	54 (54)	13 (10)	5 (4)	13 (11)	14 (19)	
	1 TMSCl	0.01	42 (54)	14 (16)	4 (8)	9 (25)	13 (15)	
	1 TMSCl	0.001	18 (40)	15 (15)	4 (7)	7 (12)	14 (17)	
	2 TMSCl	1	53 (53)	8 (9)	3 (6)	4 (<1)	21 (31)	
	2 TMSCl	0.1	61 (47)	11 (7)	8 (7)	<1 (<1)	22 (26)	
	2 TMSCl	0.01	40 (31)	9 (9)	6 (6)	<1 (<1)	17 (31)	
	2 TMSCl	0.001	16 (6)	9 (9)	7 (8)	<1 (<1)	29 (49)	
	Bu <sub>2</sub> CuLi·LiCN	none	1	53 (46)	22 (7)	18 (<1)	32 (<1)	17 (<1)
		none	0.1	31 (20)	5 (4)	6 (<1)	<1 (<1)	21 (<1)
none		0.01	42 (2)	23 (3)	16 (<1)	31 (<1)	18 (<1)	
none		0.001	32 (<1)	24 (3)	21 (<1)	41 (<1)	21 (<1)	

[a] Reactions were run at –78 °C on a 1 mmol scale at 0.12 M in THF. Quench: 4 mL of sat. aq. ammonium chloride. Yields in parentheses are for duplicate runs. [b] Butylcyclohexane. [c] Cyclohexane. [d] Cyclohexene. [e] Dicyclohexyl. [f] Octane.

of **11**, whereas six of the eight reactions in the two LRPs without TMSCl contain negligible amounts. One of the LRPs with  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN}$  contains significant amounts of **11**, the other none. Thermal decomposition of butylcuprates does not afford **11**,<sup>[33]</sup> but small amounts of it might be the result of adventitious oxygen.<sup>[34]</sup>

In virtually every reaction the amount of **8** exceeds that of **9**, owing to transmetallation (formation of  $\text{CyCu}$ ).<sup>[31]</sup> Therefore,  $2 \times \% \mathbf{9}/\% \mathbf{10}$  is used to calculate the ratio of disproportionation to combination  $k_d/k_c$ , rather than  $(\% \mathbf{8} + \% \mathbf{9})/\% \mathbf{10}$ .<sup>[30]</sup> A number of the reactions give values in the usual range for cyclohexyl radical (1.1–1.5)<sup>[30]</sup> or close to it; for example, the 4 s reactions in the two LRPs with one equivalent of TMSCl give  $k_d/k_c = 1.1$  and 1.2.

The 4 s reactions in the two LRPs with two equivalents of TMSCl contain significant amounts of **8** (9%) and **9** (7–8%), but not **10** (<1%). These results are consistent with the thermal decomposition of an intermediate  $\text{CyCu}$  species through  $\beta$ -hydride elimination.<sup>[33]</sup>

## Discussion

**Background:** We date the modern era of organocopper chemistry from the seminal 1966 paper by House et al.,<sup>[3]</sup> who showed that  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  reacts with  $\alpha$ -enones to give 1,4-addition products in high yields. In 1973 House proposed that the mechanism of the conjugate addition reaction involves electron transfer from the cuprate to the  $\alpha,\beta$ -unsaturated substrate as the first step.<sup>[35]</sup> A prime piece of evidence was the reaction of cuprates with  $\beta$ -cyclopropyl- $\alpha,\beta$ -unsaturated ketones to afford ring-opened products.<sup>[36]</sup>

An alternative explanation based on the insertion of Cu into a *syn* cyclopropyl bond was proposed as part of a treatise on cuprate-cyclopropane reactivity.<sup>[37]</sup> Moreover, a Chalmers University team observed a cuprate-olefin  $\pi$  complex in the reaction of  $\text{Me}_2\text{CuLi}$  with a cinnamate ester,<sup>[38]</sup> and a Bell Labs group characterized two kinds of  $\pi$  complexes in the reaction of this cuprate with an  $\alpha$ -enone.<sup>[39]</sup> In the latter case it was possible to observe the appearance of enolate as the final  $\pi$  complex disappeared.

Corey and Posner<sup>[4]</sup> published a pair of classic communications in 1967 and 1968 that described the reactions of  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  and  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  with alkyl halides to give cross-coupled products. In 1969, the House–Whitesides collaboration published a full paper on this reaction, and they concluded that the mechanism involves an  $\text{S}_{\text{N}}2$ -like process in the cases of primary and secondary bromoalkanes.<sup>[40]</sup>

The first clear evidence for electron transfer in a cuprate reaction, other than oxidation,<sup>[34]</sup> was for  $\text{Bu}_2\text{CuLi} \cdot \text{LiI} + \text{CyI}$ , which gave both radical products from the substrate and octane from the cuprate.<sup>[31]</sup> The octane was attributed to oxidatively induced reductive elimination, since treatment of  $\text{R}_2\text{CuLi} \cdot \text{LiI}$  with dioxygen or nitroarenes gives rise to good yields of coupled products  $\text{R}-\text{R}$ .<sup>[34]</sup>

In 1981, Lipshutz et al. reported that the reaction of  $\text{CyI}$  with the reagent prepared from two equivalents of  $\text{BuLi}$  and one equivalent of  $\text{CuCN}$  gave a quantitative yield of butylcyclohexane.<sup>[7]</sup> It appeared much better than the liter-

ature yields of 25% quoted for  $\text{Bu}_2\text{CuLi} \cdot \text{LiI} + \text{CyBr}$ <sup>[40]</sup> and 21% for  $\text{Me}_2\text{CuLi} \cdot \text{LiI} + \text{CyI}$ ,<sup>[41]</sup> but in a footnote the authors mentioned a 75% yield for the latter.<sup>[41b]</sup> The control reaction  $\text{Bu}_2\text{CuLi} \cdot \text{LiI} + \text{CyI}$  was not done; nevertheless, it was claimed that the  $\text{CuCN}$ -derived reagents were a new kind of cuprate species: “higher order cyanocuprates”.<sup>[7]</sup>

The original conclusion was clearly a non sequitur and begged two questions: i) what is the yield of butylcyclohexane from  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$  under precisely the same conditions? And, ii) what is the optimal yield with  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}$ ? When the reaction  $\text{Bu}_2\text{CuLi} \cdot \text{LiI} + \text{CyI}$  was run under the same conditions that were found to be optimal for  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN} + \text{CyI}$ , the yield was 32% vs. 81% for the latter.<sup>[31]</sup> However, when the conditions for the former were optimized independently, the yield was 55%.<sup>[31]</sup> Therefore, a better ratio of yields of desired product is  $81/55 = 1.5$ , rather than  $81/32 = 2.5$ . The yield from  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN}$  was increased to 91% by bubbling dioxygen through the reaction mixture before the usual aqueous quench,<sup>[31]</sup> which implicated transmetallation.<sup>[40]</sup>

Such comparisons are predicated on the assumption that the ratio of yields from two reagents after a standard period of time is an approximation of their relative reactivity. The present study was undertaken to critically examine this assumption for the reactions of prototypical iodo- and cyano-Gilman reagents with archetypal substrates **1** and **6** and, if possible, to find conditions under which valid comparisons can be made.

Organocuprate reactions are competitions between three fundamental processes: the desired reaction, thermal decomposition, and transmetallation.<sup>[18, 33b]</sup> Thermal decomposition has been found to proceed by several possible mechanisms ( $\beta$ -hydride elimination,  $\text{Cu}-\text{C}$  bond homolysis, thermally induced reductive elimination), which depend upon the structure of the cuprate and experimental details such as the presence of coordinating ligands.<sup>[33]</sup> Transmetallation has been well-documented (see also Results).<sup>[31, 40]</sup> Thus, a complete mass balance is a necessary but not sufficient condition for comparison. Cuprate reactions, like many others, often plateau after an initial period during which yields increase continuously. Consequently, for a ratio of yields to be a valid approximation of the true reactivity ratio, it must be vouchsafed that neither reaction has reached a plateau when the yields are measured.

Thus, the logarithmic reactivity profile (LRP, operational definition given in the introduction) was conceived. It must be emphasized that this technique was never intended as a tool for splitting hairs, but rather one for sketching a rough outline of reactivity that affords information useful to synthetic as well as mechanistic chemists. In the communications that introduced this method,<sup>[17–19]</sup> we used 1, 0.1, 0.01, and 0.001 h (3600, 360, 36, and  $3.6 \approx 4$  s), and these are continued as the standard times here. Subsequent investigators added a 10 h reaction to span another order of magnitude.<sup>[42]</sup> For our purposes, the most valid comparisons are made at the shortest possible time (4 s).

**Quench conditions:** While most synthetic chemists have used two equivalents of TMSCl in conjunction with organocopper reagents, the preliminary mechanistic study of TMSCl acti-

vation by one of us employed six equivalents,<sup>[17]</sup> in order to more closely simulate the conditions of the original report by Corey and Boaz, who used five equivalents.<sup>[24]</sup> Some reactions were also run in the presence of HMPA, which requires at least three equivalents per Li for its effect to level off,<sup>[43a]</sup> and it was desired to use equimolar TMSCl and HMPA. However, with six equivalents of TMSCl in THF, the quench conditions become critical. The use of 3 mL of saturated aqueous sodium bicarbonate gave only ketone **4**, owing to hydrolysis of **5**. Doubling the amount of quench solution to 6 mL gave 65 ± 8% of **5** (see next section). Hydrolysis can also be suppressed by the addition of py (Table 4, footnotes [e], [f]); however, it appears that in THF the total yield is increased somewhat by this expedient (see section on butyl homocuprates). The addition of py does not affect the outcome in ether (see section on methyl homocuprates).

In control experiments these quench conditions did not hydrolyze solutions of **5** in THF or ether. Moreover, solutions of **4** were treated with TMSCl (6 equiv) and py (1 equiv in THF, 3 equiv in ether), followed by saturated aqueous sodium bicarbonate, and no **5** was observed after the usual work-up. Nevertheless, with py in THF, some of the **5** may be from py-catalyzed silylation of the enolate.<sup>[43b]</sup> Therefore, the best approach is to cut back the TMSCl to two equivalents, which can be quenched without the complications of added amine. Finally, the starting enone **1** recovered at the end of a reaction is not necessarily unreacted, since quenching the enone-cuprate  $\pi$  complex results in release of enone.<sup>[24a, 39b]</sup>

Some of the difficulties encountered upon quenching organocopper reactions have been described in a compendious practicum,<sup>[44]</sup> which also gives a good feel for the many nuances of organocopper chemistry.

**Experimental uncertainty:** In the reaction of **1** with methylcuprates, the Gilman reagent from CuI in THF appears to be slightly less reactive than the one from CuCN at the shortest time (4.5 vs. 5.2%, Table 1). On the other hand, in the reaction of **1** with butylcuprates, the Gilman reagent from CuI appears to be slightly more reactive at the same time and concentration (19 vs. 14%, Table 3). In fact, the corresponding yields are the same to within experimental uncertainty. A relative error of approximately 20% is obtained by repeating the same

reaction several times. The entire LRP for Bu<sub>2</sub>CuLi · LiI was run thrice in THF (Table 4) and twice in ether (Table 5); the first entry in each case is used to calculate ratios.

In THF the yields range from 19 to 97% and afford good statistics. Average yields (95% confidence limits, CL<sup>[20a]</sup>) are 21 ± 5%, 40 ± 15%, 81 ± 13% and 93 ± 9% ( $t >$ ). The relative errors are 24, 37, 16 and 10% (ave. 22%). The 6 min reaction was repeated two more times and the yields were 82% and 78%. The average of all five 6 min yields is 80 ± 5% (95% CL, 6% rel. error).<sup>[20b]</sup> Substituting these data, the average relative error is 19%. All the yields in ether (ave. 98 ± 1%, 95% CL) were essentially quantitative.

The 4 s reaction of Bu<sub>2</sub>CuLi · LiI/6TMSCl with **1** in THF was run five times (Table 4, footnote [d]). The average yield of **5** is 65 ± 8% (95% CL), which has 12% relative error. The total yields (% **4** + % **5**) have an average value of 71 ± 7% (95% CL, 10% rel. error).

While individual cases may be somewhat better or worse, we have adopted 20% relative error as the best overall estimate and used it to assign error bars in those cases where not enough yields were available for meaningful statistics. In good agreement, the five average ratios calculated with 95% CL in the Results section have 5–40% relative errors. A 40% relative error in a ratio of yields is the maximum expected for 20% relative errors in the yields.<sup>[20c]</sup>

**Reactivity matrices:** In order to minimize the effect of experimental uncertainty on the interpretation of the results, our conclusions are mainly based on trends in the data and ratios of yields, and not on absolute numbers. Several ratios of interest ( $R_{I/CN}$ ,  $R_{ether/THF}$ ,  $R_{TMSCl}$ ,  $R_{2TMSCl}$ ,  $R_{2THF}$ ,  $R_{Bu/Me}$ ) were introduced in the Results section. It is important to note that the 4 s ratios are an approximation of the true reactivity ratios calculated from accurate kinetic data, which would be much more difficult to amass.

It is convenient to summarize reactivity ratios as elements  $r_{ij}$  of a reactivity matrix  $R$ . Tables 7 and 8 are the methyl and butyl matrices, respectively. Two butyl reagents are included in the methyl matrix in order to enable comparisons between R groups. (A separate Me/Bu matrix could be constructed, but this would add another table.) For example, the group transfer ratio  $R_{Bu/Me}(0.1M R_2CuLi \cdot LiI/THF) = 4.2$  is entry  $r_{9,1}$ ,

Table 7. Reactivity matrix for 4 s data from Tables 1–3.<sup>[a]</sup>

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1)	1	0.87	0.14	0	0.054	0	0.096	0	0.24	0
(2)	<b>1.16</b>	1	0	0.98 <sup>[b]</sup>	0	0	0	0	0	0
(3)	<b>7.1</b>	0	1	<b>6.0</b> <sup>[b]</sup>	0.39 <sup>[c]</sup>	0.83	0.68	0.80	0	0.32
(4)	0	<b>1.02</b> <sup>[b]</sup>	0.17 <sup>[b]</sup>	1	0	0	0	0	0	0
(5)	<b>18.5</b>	0	2.6 <sup>[c]</sup>	0	1	2.16	0	2.1	0	0
(6)	0	0	1.2	0	0.46	1	0	0.955	0	0
(7)	10.4	0	1.47	0	0	0	1	1.17	0	0
(8)	0	0	1.26	0	0.48	1.05	0.855	1	0	0
(9)	4.2	0	0	0	0	0	0	0	1	0.192
(10)	0	0	3.1	0	0	0	0	0	5.2	1

[a] Entries  $r_{ij}$  (row  $i$ , column  $j$ ) are calculated by dividing the yield from reagent  $i$  by the yield from reagent  $j$  [ $i, j = (1)–(10)$ : (1) Me<sub>2</sub>CuLi · LiI/THF, (2) Me<sub>2</sub>CuLi · LiCN/THF, (3) Me<sub>2</sub>CuLi · LiI/ether, (4) Me<sub>2</sub>CuLi · LiCN/ether, (5) Me<sub>2</sub>CuLi · LiI/THF + TMSCl, (6) Me<sub>2</sub>CuLi · LiI/ether + TMSCl, (7) Me<sub>2</sub>CuLi · LiI · 2 THF/ether, (8) Me<sub>2</sub>CuLi · LiI · 2 THF/ether + TMSCl, (9) Bu<sub>2</sub>CuLi · LiI/THF, (10) Bu<sub>2</sub>CuLi · LiI/ether]. Three significant figures are given only in those cases where round-off error occurs with two. All reagents were 0.1 M. [b] Less accurate, owing to nonhomogeneity of reagent 4. [c] Changes more than one experimental variable, see Discussion.

Table 8. Reactivity matrix for 4 s data from Tables 3–5.<sup>[a]</sup>

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1)	1	<b>1.36</b>	0.109 <sup>[b]</sup>	0	0.38	0	0.655	0	0	0
(2)	0.74	1	0	0.21 <sup>[b]</sup>	0	0	0	0.44	0	0
(3)	<b>9.2</b> <sup>[b]</sup>	0	1	<b>1.5</b> <sup>[b]</sup>	1.98 <sup>[c]</sup>	1.11	0	0	1.6	0
(4)	0	<b>4.8</b> <sup>[b]</sup>	0.67 <sup>[b]</sup>	1	0	0	0	0	0	1.55
(5)	<b>2.6</b>	0	0.505 <sup>[c]</sup>	0	1	0.56	0	0	0	0
(6)	0	0	0.90	0	1.8	1	0	0	0	0
(7)	1.53	0	0	0	0	0	1	0.91	0.47	0
(8)	0	2.3	0	0	0	0	<b>1.1</b>	1	0	0.50
(9)	0	0	0.63	0	0	0	<b>2.14</b>	0	1	0.97
(10)	0	0	0	0.65	0	0	0	<b>2.0</b>	<b>1.03</b>	1

[a] Entries  $r_{ij}$  (row  $i$ , column  $j$ ) are calculated by dividing the yield from reagent  $i$  by the yield from reagent  $j$  [ $i, j = (1)–(10)$ : (1)  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}/\text{THF}$ , (2)  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN}/\text{THF}$ , (3)  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}/\text{ether}$ , (4)  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN}/\text{ether}$ , (5)  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}/\text{THF} + \text{TMSCl}$ , (6)  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}/\text{ether} + \text{TMSCl}$ , (7)  $\text{BuThCuLi} \cdot \text{LiI}/\text{THF}$ , (8)  $\text{BuThCuLi} \cdot \text{LiCN}/\text{THF}$ , (9)  $\text{BuThCuLi} \cdot \text{LiI}/\text{ether}$ , (10)  $\text{BuThCuLi} \cdot \text{LiCN}/\text{ether}$ ]. Three significant figures are given only in those cases where round-off error occurs with two. All reagents were 0.1 M, unless otherwise noted. [b] Reagents were 0.03 M, as 0.1 M ratios were limits. [c] Changes more than one experimental variable, see Discussion.

that is, its address is row 9, column 1.<sup>[20d]</sup> We use  $r_{ij} = 0$  to indicate those cases where the ratios do not appear to make chemical sense. Since this is to some extent a matter of judgment, the data needed to calculate any entry are given in Tables 1–5.

The values of  $r_{ij}$  ( $i = j$ ) on the main diagonal are all unity, for example,  $r_{1,1} = 1$ . Entry  $r_{2,1}(\text{Me}) = 1.16$  compares the methyl cyano- and iodo-Gilman reagents in THF (cf.  $1/R_{\text{LiCN}}$ ). Entry  $r_{3,1}(\text{Me}) = 7.1$  is the solvent ratio  $R_{\text{ether/THF}}(0.1\text{M Me}_2\text{CuLi} \cdot \text{LiI})$ . Entry  $r_{4,1}(\text{Me}) = 0$ , as two independent variables (solvent and Li salt) are changed at once. Entry  $r_{5,1}(\text{Me}) = 18.5$  compares  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  with and without TMSCl in THF (cf.  $R_{\text{TMSCl}}$ ). It is clear that the change of solvent from THF to ether and the addition of TMSCl in THF have larger effects on the classic Gilman reagent than the addition of cyanide.<sup>[45]</sup>

Entry  $r_{6,1}(\text{Me}) = 0$ , as it would compare  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  in ether with added TMSCl, which has no effect in this solvent, to the cuprate without TMSCl in THF. A ratio that changes two experimental variables at once yet has considerable interest is  $r_{5,3}(\text{Me}) = 2.6$ , which shows that addition of TMSCl to  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  in THF makes this cuprate significantly more reactive than it is in neat ether. Entry  $r_{7,1}(\text{Me}) = 10.4$  compares  $\text{Me}_2\text{CuLi} \cdot \text{LiI} \cdot 2\text{THF}$  in ether with  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  in THF (i.e., 2 vs. 100 mol % THF). Entries  $r_{8,1}$  and  $r_{10,1}$  are 0.

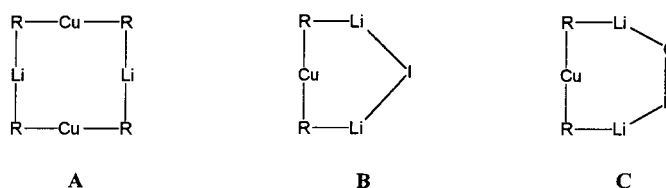
An advantage of collecting all the ratios in one place is the ease of identifying the major effects. The three largest ratios in Table 7 are in column 1, discussed in detail above. The two largest ratios in the butyl matrix,  $r_{3,1}(\text{Bu}) = 9.2$  and  $r_{4,2}(\text{Bu}) = 4.8$ , are the solvent ratios (0.03 M) for the iodo- and cyano-Gilman reagents, respectively. The third largest ratio  $r_{5,1}(\text{Bu}) = 2.6$  measures the effect of TMSCl (1 equiv) on  $\text{Bu}_2\text{CuLi} \cdot \text{LiI}/\text{THF}$ .

The fourth largest ratio is  $r_{8,2}(\text{Bu}) = 2.3$ , which compares the thienylcuprate with the homocuprate from  $\text{CuCN}$  in THF. The mixed cuprate from  $\text{CuI}$  in THF also appears to be more reactive than the related homocuprate, as  $r_{7,1}(\text{Bu}) = 1.53$ . Therefore, the conclusion that mixed cyanocuprates are less reactive than the corresponding homocuprates<sup>[6c]</sup> is clearly incorrect, as we also showed for the  $\beta$ -silylcuprates.<sup>[19]</sup>

It was previously discovered that the TMS enol ether is not formed with  $\text{R}_2\text{CuLi}/\text{TMSCl}$  in ether<sup>[17]</sup> or  $\text{RCu}/\text{TMSCl}$  in dimethyl sulfide (DMS),<sup>[46]</sup> and we find here that there is no

significant rate acceleration with TMSCl in ether:  $r_{6,3}(\text{Me}) = 1.2$  and  $r_{6,3}(\text{Bu}) = 0.90$ . (N.B.,  $r_{3,6}(\text{Bu}) = 1.1$ .) Thus, we have delineated a fundamental mechanistic dichotomy between ether and THF in the conjugate addition reaction of organocuprates according to the effect of TMSCl. Eriksson et al. found an analogous result for  $\text{BuCu}/\text{TMSCl}$ .<sup>[42]</sup>

**Structural considerations:** Before discussing mechanistic details, it is useful to introduce some information on the structures of organocuprates; for example, it has been conjectured that the cuprate-haloalkane reaction proceeds via a cuprate monomer and the cuprate-enone reaction via a dimer.<sup>[10]</sup> An early study by Pearson and Gregory concluded that halide-free  $\text{Me}_2\text{CuLi}$  is dimeric in ether.<sup>[47]</sup> The structure of  $\text{Me}_2\text{CuLi} \cdot \text{LiI}$  in solution has not been established; the Pearson–Gregory dimer **A** and the Bertz–Snyder heterodimer **B** are predicted to have essentially the same NMR shifts.<sup>[48]</sup> In 1990, it was asserted that organocuprates are mainly monomers in THF, based on NMR studies.<sup>[8]</sup> This conclusion has recently been confirmed by EXAFS,<sup>[49]</sup> and cryoscopy is consistent with it.<sup>[50]</sup>



NMR investigations also established that cuprates are dimers in DMS,<sup>[10]</sup> and X-ray crystal structures of unhindered cuprates prepared in ether<sup>[51, 52]</sup> or DMS<sup>[53, 54]</sup> reveal a dimer motif. The solution structure of the 2:1 cyanocuprate  $\text{R}_2\text{CuLi} \cdot \text{LiCN}$  has been proposed to be one of several possible heterodimers of  $\text{R}_2\text{CuLi}$  and  $\text{LiCN}$ ,<sup>[14c, 15]</sup> and <sup>15</sup>N NMR is consistent with **C**.<sup>[11]</sup> The X-ray crystal structures of  $\text{R}_2\text{CuLi} \cdot \text{LiCN}$  contain ionic subunits  $\text{R}_2\text{Cu}^-$  and  $\text{Li}_2\text{CN}^+$ ,<sup>[55, 56]</sup> as proposed by one of us in 1990.<sup>[8]</sup>

Finally, structural proposals must be based upon spectroscopic data or X-ray analysis, not reactivity data. For example, when  $\text{Ph}_3\text{CuLi}_2 \cdot \text{LiCuPh}_2$ —the first bona fide higher order



cuprate—was prepared in DMS, a Cu bonded to three Ph groups was proposed on the basis of  $^{13}\text{C}$  NMR spectroscopy.<sup>[57]</sup> This was confirmed by X-ray crystallography.<sup>[54]</sup>

**Mechanistic considerations:** Corey and Boaz suggested that TMSCl silylates the carbonyl O of the intermediate enone-cuprate  $\pi$  complex,<sup>[24]</sup> which induces faster formation of the putative  $\text{Cu}^{\text{III}}$  intermediate in their scheme. A modification in which the TMSCl simultaneously coordinates the Li of the cuprate and the O of the complexed enone has also been suggested.<sup>[58]</sup> The conclusion that the preliminary LRP data ruled out such a mechanism as the predominant one in THF is not correct,<sup>[17]</sup> owing to partial hydrolysis (see section on quench conditions above). The  $81 \pm 13\%$  average yield (95% CL) of **5** for the 4 s reactions with two equivalents of TMSCl (Table 4) provides the best estimate from LRP data for the amount of product from the Corey–Boaz mechanism or an equivalent.<sup>[59]</sup>

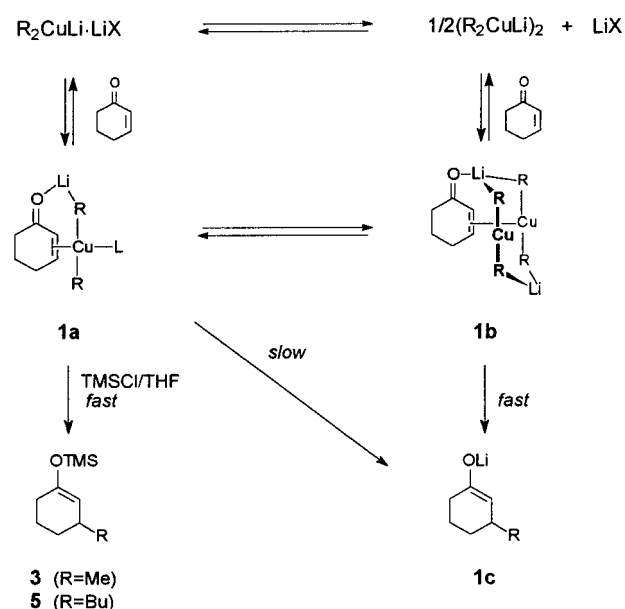
Bertz and Snyder proposed that coordination of TMSCl by Cu (through bridging Cl) could stabilize the transition state by the organometallic analogue of the Eaborn effect (carbenium ion stabilization by  $\beta$ -silicon<sup>[60]</sup>), which was supported by DFT calculations.<sup>[17]</sup> Subsequent *ab initio* calculations confirmed the ability of  $\beta$ -Si to stabilize a copper cation,<sup>[61]</sup> and they also discounted a TMSCl-enone interaction as a possible source of the rate acceleration, as had been suggested.<sup>[27]</sup>

There is little silylation and no appreciable rate increase for the cuprates studied in ether upon addition of TMSCl. Consequently, neither the Corey–Boaz nor the Bertz–Snyder mechanism is operative, and the reaction in ether appears to be the same with or without TMSCl. It is important to note that the Corey–Boaz and Bertz–Snyder mechanisms are not mutually exclusive, for example, coordination of TMSCl by Cu in the enone-cuprate  $\pi$  complex could precede *O*-silylation in THF.

TMSCl also has a beneficial effect on the  $\text{Bu}_2\text{CuLi} \cdot \text{LiI} + \text{CyI}$  reaction. To our knowledge this is the first demonstration of a significant effect of TMSCl on an organocopper reaction that does not involve silylation of oxygen. Of the proposals to date, only the Bertz–Snyder mechanism can account for this activation. Thus, the role of TMSCl could be to stabilize a  $\text{Cu}^{\text{II}}$  or  $\text{Cu}^{\text{III}}$  intermediate by the  $\beta$ -silyl effect discussed above. This reaction does not proceed at an appreciable rate in ether with or without TMSCl.

Scheme 1 summarizes our mechanistic proposals, which are based on enone-cuprate  $\pi$  complexes **1a** (from cuprate monomer) and **1b** (from cuprate dimer). The NMR evidence is consistent with a fast equilibrium between starting materials ( $\alpha,\beta$ -unsaturated carbonyl compound + cuprate) and cuprate-olefin  $\pi$  complexes.<sup>[38, 39]</sup> Calculations suggest both monomer and dimer  $\pi$  complexes are feasible,<sup>[62, 63]</sup> for example, in one study dimer **A** and heterodimer **B** were modeled.<sup>[63]</sup>

One explanation for the lack of a TMSCl effect on the cuprate-enone reaction in ether is that dimer complex **1b** goes rapidly to enolate **1c** in the absence of a good donor ligand (L). The crucial role of Li in reactions of lithiocuprates, such as  $\text{Bu}_2\text{CuLi}$ , is dramatically demonstrated by the much lower reactivity of the sodiocuprate  $\text{Bu}_2\text{CuNa}$  towards **1**.<sup>[29b]</sup> Activation by Li is much more effective in weakly coordinating



Scheme 1.

solvents, such as ether, dichloromethane, and DMS, than in strongly coordinating ones, like THF, HMPA, and  $\text{py}$ .<sup>[10b, 46]</sup> THF breaks down **1b** to the monomer complex **1a** ( $\text{L} = \text{THF}$ ), just as it breaks down cuprate dimer to monomer.<sup>[8, 10]</sup> Monomer complex **1a** may go to enolate **1c**, but more slowly than **1b** to **1c** in ether, which explains why cuprate conjugate addition is slower in THF. Another explanation is that conjugate addition only proceeds from the dimer complex **1b**, which has a much lower concentration in THF than in ether.

When TMSCl is present in THF, **1a** ( $\text{L} = \text{THF}$  or TMSCl) undergoes conversion to TMS enol ether faster than to enolate **1c**. Whether or not the formation of TMS enol ether (**3** or **5**) in THF is faster than the formation of **1c** in ether depends upon R (faster for  $\text{R} = \text{Me}$ , slower for Bu). Rapid-injection NMR confirms that the appearance of TMS enol ether upon addition of TMSCl to the  $\pi$  complex in THF is much faster than the appearance of the enolate without TMSCl.<sup>[59b]</sup>

A  $\text{Cu}^{\text{III}}$  species is not an obligatory intermediate for either the native or TMSCl-assisted reaction. All of the evidence adduced for it is indirect, for example, stereochemical studies<sup>[24]</sup> and calculations.<sup>[62–64]</sup> As an alternative, the reaction could proceed through intramolecular transfer of R from Cu to the  $\beta$ -carbon of the complexed enone or, in the presence of TMSCl in THF, its *O*-silylated derivative. Based on a study of kinetic isotope effects, the Cu does not become  $\sigma$ -bonded to the  $\alpha$ -carbon of the enone in the rate-determining step, as it would in the addition of  $\text{R}-\text{Cu}$  across the double bond.<sup>[65]</sup>

**Synthetic considerations:** Among the decisions the synthetic chemist must make about organocopper reactions are the copper(I) precursor ( $\text{CuI}$ ,  $\text{CuBr}$ ,  $\text{CuBr} \cdot \text{DMS}$ ,  $\text{CuCN}$ ), the active organometallic ( $\text{RLi}$ ,  $\text{RMgX}$ ,  $\text{RZnX}$ ,  $\text{RNa}$ ), the stoichiometry (catalytic Cu, 1:1, 2:1, > 2:1  $\text{RLi}$ ), the solvent (THF, ether, DMS, dichloromethane), the additive (TMSCl, HMPA,

phosphine, Lewis acid), and the dummy ligand (alkynyl, thienyl, hetero, trimethylsilylmethyl), in addition to experimental variables such as cuprate excess, temperature, time, and work-up.<sup>[5, 6, 44]</sup> Many of these factors are interrelated, and it is difficult if not impossible to predict with certainty which of the many kinds of organocopper reagents will be optimal for a particular substrate.

On top of all this, the results can depend upon the origin of the particular copper(I) salt, as discussed in the Results section for CuI. The source of CuCN has also proven to be problematic: an X-ray study of a novel phenylcuprate species found substantial amounts of CuCl in the lot of commercial CuCN used as starting material.<sup>[53b]</sup> There is now a vast literature on organocopper reagents and reactions, but it is of limited value because the starting copper(I) salts have not been well-characterized and side-by-side comparisons have not been made in most cases. The lack of control experiments for  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN} + \text{CyI}$  was discussed above, and this was also the pattern when the yields were reported for the reactions of “ $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$ ” and  $\alpha$ -enones,<sup>[66a,b]</sup>  $\alpha,\beta$ -unsaturated esters,<sup>[66c]</sup> epoxides,<sup>[66d]</sup> and primary alkyl halides,<sup>[66e]</sup> and when  $\text{RThCuLi} \cdot \text{LiCN}$  reagents were introduced.<sup>[66f]</sup>

As long as GLC or HPLC has been calibrated for the product of one cuprate reaction, it is a simple matter to run additional reactions to test the major factors under controlled conditions. We typically ran four to eight 1 mmol reactions simultaneously in 4 dram vials in two cold-baths on a large magnetic stirring plate,<sup>[67]</sup> for example, butylcuprates and phenylcuprates prepared from CuI, CuBr, CuBr · DMS, CuCl, CuOTf, CuCN, and CuSCN.<sup>[29]</sup> Another good model is provided by Persson and Bäckvall,<sup>[68]</sup> who investigated the use of CuCN, CuCl, CuBr, and CuI as precursors for cuprates and also studied both 1:1 and 2:1 cyanocuprates prepared from BuLi, BuMgBr, and BuMgI. When improved reactivity and thermal stability were claimed for trimethylsilylmethylcuprates, LRP and thermal stability studies were used to document their superiority.<sup>[19]</sup>

The LRPs reported here demonstrate the strong solvent dependence of cuprate reactions, as noted previously,<sup>[3, 10b, 46]</sup> and they also highlight the powerful influence of TMSCl (in THF), which has been studied by numerous investigators.<sup>[17, 24, 27, 28c]</sup> These effects have now been set on a firm quantitative basis, which also helps to put the 2:1 cyanocuprates in perspective.

Of all the reactivity ratios in Tables 7 and 8, five of them are most critical for synthetic chemists who are selecting reaction conditions. They are  $r_{1,2}$  (I vs. CN in THF),  $r_{3,4}$  (I vs. CN in ether),  $r_{3,1}$  (ether vs. THF for the iodocuprates),  $r_{4,2}$  (ether vs. THF for the cyanocuprates), and  $r_{5,1}$  (TMSCl vs. none in THF). These entries (or their reciprocals, whichever are  $>1$ ) are boldface in the reactivity matrices. The values for the methyl homocuprates are 1.16, (6.0), 7.1, (1.02), and 18.5, respectively. The ratios in parentheses are less accurate because of solubility problems (see Results section). Where the reagents are homogeneous, the salt ratio is much less than the solvent ratio and TMSCl ratio.

The ratios for the corresponding butyl homocuprates are 1.36, 1.5, 9.2, 4.8, and 2.6. The salt ratios (first two) are significantly less than the solvent ratios (third and fourth) and

TMSCl ratio. The mixed thienylcuprates were not treated with TMSCl here (see Lindstedt et al.<sup>[28c]</sup>); consequently, only the first four analogous ratios apply (boldface italics in Table 8): 1.1, 1.03, 2.14, and 2.0. As with the homocuprates, the thienylcuprates are affected less by the Li salt than by the solvent.

If the goal is to accelerate conjugate addition of methyl, the addition of TMSCl to a THF solution is recommended. This gave a rate enhancement of 18.5 ( $r_{5,1}$ ) over the rate in neat THF and 2.6 ( $r_{5,3}$ ) over the rate in neat ether. More importantly, these conditions also gave the best final yield (90% after 1 h at  $-78^\circ\text{C}$ , Table 1) in the form of the TMS enol ether. In contrast, if the group to be added is butyl, the best strategy is to use ether, as reaction in this solvent is faster than the TMSCl-assisted reaction in THF ( $r_{3,5} = 1.98$ ) and is essentially quantitative after 4 s at  $-78^\circ\text{C}$  (Table 5). If the TMS enol ether is desired, two equivalents of TMSCl in THF is recommended (Table 4).<sup>[24d]</sup>

For conjugate addition of more valuable R groups, the thienylcuprates from CuI in THF or CuCN in ether appear to be superior, judged by the virtually quantitative yields after 1 h at  $-78^\circ\text{C}$  (0.1M, Table 3). The reagents from CuI in ether and CuCN in THF are not far behind. In those cases where the competitive transfer of thienyl is a problem, the trimethylsilylmethylcuprates are recommended.<sup>[19]</sup>

The take-home lesson for synthetic chemists is simple: try several diverse kinds of organocopper reagents under carefully controlled conditions for any given transformation. Thus, it is advisable to do a breadth-first search of reagents,<sup>[5]</sup> rather than a depth-first search based on one reagent. A corollary is not to give up after trying several unsuccessfully. There is a plethora of reagents,<sup>[5, 6]</sup> and they can be screened efficiently by running four or more reactions at a time on a small scale.

## Summary

Organocopper reactions have a high level of complexity, both in terms of experimental execution and mechanistic explanation, and many mysteries remain. While the structures of organocopper reagents in solution<sup>[8–12]</sup> and in the solid state<sup>[51–56]</sup> are now understood to a good first approximation, not all aspects of their reactions have been elucidated. It is possible that the details of the reactions of iodo- and cyano-Gilman reagents are different, but it is now clear that their intrinsic reactivities are not very different. In fact, the difference between  $\text{R}_2\text{CuLi} \cdot \text{LiCN}$  and  $\text{R}_2\text{CuLi} \cdot \text{LiI}$  is less than one order of magnitude in the classic reactions studied here, including  $\text{Me}_2\text{CuLi} \cdot \text{LiI} + \mathbf{1}$ , which was one of the first organocuprate applications, and  $\text{Bu}_2\text{CuLi} \cdot \text{LiCN} + \text{CyI}$ , for which the claim of extraordinary reactivity was first made.

We conclude that the reagents prepared from two equivalents of RLi and CuI or CuCN are both Gilman reagents, which may be different in detail or degree, but not fundamentally in reactivity. The overarching truth is *neither the CuI- nor the CuCN-derived cuprate is extraordinarily more reactive*. “Higher order cyanocuprates” have been promoted as a revolutionary advance;<sup>[69]</sup> however, these results suggest that they should instead be viewed as an evolutionary development.

## Experimental Section

**General:** CuI (Aldrich 99.999%) and CuCN (Aldrich 99%) were used, unless otherwise noted. CuI (E. Merck 99%) was purified by the *Organometallics in Synthesis* procedure,<sup>[26a]</sup> and CuI (Aldrich 98%) was purified by the *Inorganic Syntheses* method.<sup>[26b]</sup> They were dried as described in the Results section. The clumps of CuI were crushed by means of a glass rod. (N.B. the use of a metal spatula contaminates the Cu salt with other metals.<sup>[31]</sup>) THF and ether were distilled from K/benzophenone.

Cyclohexyl iodide **6** (Aldrich 98%) was distilled and stored over silver wool. The 2-cyclohexen-1-one **1** (Aldrich 95+%) and chlorotrimethylsilane (TMSCl, Aldrich 98%) were used without further purification; they were stored under Ar in the freezer. Pyridine (Aldrich 99+%) and triethylamine (Aldrich 99%) were used as received. BuLi in hexanes (FMC 24% w/w, 2.38 M; Aldrich 2.5 M) was used for the enone reactions and BuLi in pentane (Aldrich 2.0 M) was used for the CyI experiments. MeLi (1.52 M, 0.20 M residual base) in ether was prepared by the *Organic Syntheses* procedure.<sup>[23a]</sup> MeLi·THF was crystallized from 1.0 M MeLi in THF/cumene (FMC),<sup>[23b]</sup> and the pure solid was dissolved in ether to give 1.15 M MeLi·THF in ether (0.16 M residual base). All lithium reagents were standardized by means of the Gilman double titration immediately before use.<sup>[31, 70]</sup> All reactions were run under an atmosphere of purified nitrogen.

Potentiometric titration of the sat. aq. sodium bicarbonate indicated that it was 1.04 M; therefore, a 6.00 mL aliquot contained 6.24 mmol of base. The concentration of residual base in the 2.38 M BuLi was 0.22 M; thus, the amount of residual base added in 0.84 mL (2.00 mmol BuLi) was 0.18 mmol. Then, the total amount of base added to a 1 mmol Bu<sub>2</sub>CuLi reaction quenched with 6.00 mL of sat. aq. sodium bicarbonate was 8.42 mmol, including BuLi.

Dry ice/acetone baths were used for low-temperature reactions; they were monitored by means of calibrated thermocouples. Disposable polypropylene syringes (Becton–Dickinson, plungers with double seals) or gas-tight glass syringes (Hamilton) were used for liquid transfers. They were filled with nitrogen and emptied three times before being filled with liquid and cooled with powdered dry ice. The tip of the needle was protected from the atmosphere, except for the brief period when it was between septa.

GLC analyses were performed on a Hewlett–Packard 5890 gas chromatograph equipped with FID detector and 30 m HP-5 capillary column (0.32 mm i.d., 0.25 μm film, crosslinked 5% diphenyl/dimethylsiloxane). It was calibrated before each use with authentic products and internal standard. A BuLi blank was quenched in the same manner as the reaction mixtures to measure the amount of octane in this reagent. For those entries in Tables 1–6 where the mass balance was <100%, the remainder was recovered starting material.

**Typical procedure for the LRP:** A portion of CuI (191.0 ± 0.2 mg, 1.003 ± 0.001 mmol) was weighed into a 25 mL flask, which had been dried overnight in an oven (110 °C) and blown out with Ar. After adding a magnetic stirring bar to the flask and sealing it with a rubber septum, the atmosphere in it was replaced with purified nitrogen (3 cycles of evacuation and filling). Decane internal standard (0.100 mL, 73.0 mg) was added with a tared syringe. A positive pressure of nitrogen was maintained throughout the rest of the experiment. Dry solvent (THF or ether) was added by syringe, rinsing down the walls of the flask to make sure all the CuI was suspended. The volume of solvent was adjusted so that after all additions, the final concentration would be 0.10 M for reactions of **1** (0.12 M for **6**). The nominally 0.03 M reactions of **1** were 0.033 M, as 1.00 mmol of cuprate was used and the final volume was 30.0 mL.

The flask was cooled to –78 °C for 6 min with stirring and BuLi in hexane (2.52 M, 0.79 mL, 1.99 mmol, 0.04 M residual base) was added slowly. (For the CyI reactions a 0.98 mL quantity of 2.04 M BuLi in pentane was used; the residual base was 0.19 M.) The suspension was stirred at –78 °C for 6 min and then annealed at 0 °C for 6 min.<sup>[29a]</sup> The resulting black solution was cooled to –78 °C for 6 min. For those reactions that involved TMSCl, it was added in 1 mL of cold solvent, a 127 μL portion (1.00 mmol) for each one equivalent. The reaction mixture was stirred for 6 min at –78 °C, and 2-cyclohexen-1-one **1** (96.1 mg, 1.00 mmol) was added in THF (1 mL) with a cold syringe. The stopwatch was started when the plunger was pushed. (For CyI reactions a 210 mg quantity of iodocyclohexane **6** was used.)

After the standard LRP time, the plunger was pushed on the syringe containing the quench solution. In the case of a 4 s reaction, the needle on

the syringe containing the quench solution was inserted through the septum before injection of the substrate. (Nitrogen was drawn into the inverted quench syringe before its needle was inserted into the reaction flask to make sure no water was introduced prematurely and no ice formed in the needle to clog it.) The stock solutions used in the quenches (sat. aq. sodium bicarbonate with **1** and sat. aq. ammonium chloride with **6**) were deoxygenated by sparging with nitrogen before each use.

The flask was removed from the dry ice/acetone bath and warmed by hand until the ice inside it melted. The aqueous layer was checked to make sure it had pH > 7. The organic layer was separated as quickly as possible and dried over anhydrous sodium sulfate. In the case of THF reactions, an equal volume of ether was added. The solutions were transferred to vials containing fresh anhydrous sodium sulfate and analyzed the same day by GLC. The vials were then sealed with Teflon<sup>®</sup> tape and stored in a freezer.

## Acknowledgment

We thank A. Slusher (UNCC) and G. Miao (ArQule) for technical assistance and J.P. Snyder (Emory University) for many helpful discussions. T. Rathman (FMC) generously provided lithium reagents used in this project.

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- $S/n^{1/2} = 1.73$ ; 95% confidence limits  $\pm CL_{0.95} = t_{0.05} \times SE_M = 2.776 \times 1.73 = 4.80 \approx 5$ , where  $t_{0.05} = 2.776$  is the value of Gosset's (Student's) distribution for  $n - 1 = 4$  degrees of freedom. N.B. we also use degrees of freedom in the formula for  $S^2$ , as we calculate the sample standard deviation  $S$  as an unbiased estimate of the population standard deviation  $\sigma$ ; c) The relative error in the product or quotient of two numbers is the sum of the relative errors in the numbers: F. Daniels, J. W. Williams, P. Bender, R. A. Alberty, C. D. Cornwell, J. E. Harriman, *Experimental Physical Chemistry*, 7th ed., McGraw-Hill, New York, **1970**, pp. 430–439; d) H. G. Hecht, *Mathematics in Chemistry*, Prentice-Hall, Englewood Cliffs, NJ, **1990**.
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Received: October 5, 1998

Revised Version: May 17, 1999 [F1371]