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β-Silyl Organocuprates: The Grail of Organocuprate Chemistry?[1a]

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Organocuprates $R_2CuLi{\cdot}LiX$,[2] prepared from 2 equiv of lithium reagent and a copper(I) salt CuX (typically X = I, Br, CN), are indispensible reagents for selective carbon−carbon bond formation.[3] With few exceptions, only one of the two R groups in these "Gilman reagents" is utilized in synthetic applications.[4] A mixed cuprate $RR'CuLi{\cdot}LiX$ which is highly reactive yet selectively transfers only one group R has been the "holy grail" of organocuprate chemistry.

The two basic approaches to this problem have been the use of a nontransferred group R′ (i) bonded to Cu at an sp or sp^2 carbon (e.g., alkynyl[5] or 2-thienyl,[6,7] respectively) or (ii) attached to Cu via a heteroatom such as S,[8] N,[9,10] or P.[9−12] None of these has been ideal. Cyanocuprates RCu(CN)Li are convenient to prepare but are relatively unreactive.[13] Phosphidocuprates are thermally stable[9] and highly reactive,[10−12] but the precursor phosphines are expensive and toxic. The best solution to date appears to be RCu(Th)Li·LiI (Th = 2-thienyl), introduced by the Nilsson group.[6] The cyano analogs RCu(Th)Li·LiCN[7] appear to have fundamentally similar reactivities.[14]

In this paper we report a new approach to this problem derived from our work on the mechanism of TMSCl acceleration of organocuprate conjugate addition. We proposed a new mechanism in which coordination of TMSCl to Cu allows the transition state to be stabilized by a silicon atom in the β-position.[15a] Thus, we reasoned that by building a β-silicon into the auxiliary group R′, we would create a cuprate of unparalleled reactivity.

Table 1. Logarithmic Reactivity Profiles of Selected Organocopper Reagents: Yields (%) of **2**[a]

reagent	time (h)[b]			
	1	0.1	0.01	0.001
BuCu(TMSM)Li·LiI				
ether	100	99	99	98
THF	99	99	95	82
BuCu(TMSM)Li·LiCN				
ether	99	99	99	99
THF	99	98	96	84
BuCu(HMDS)Li·LiI				
ether	99	99	99	84
THF	55	13	10	3
BuCu(TMST)Li·LiI				
ether	94	89	85	61
THF	72	20	7	2
BuCu(Th)Li·LiCN				
ether	99	99	89	64
THF	89	74	57	32
$Bu_2CuLi{\cdot}LiCN$				
ether	97	97	95	94
THF	84	82	67	54

[a] Compound **2** = 3-butylcyclohexanone: measured by using GLC and the internal standard method. All reactions were run at −78 °C on a 1.00 mmol scale (0.10 M). [b] Time: 1 h = 60 min, 0.1 h = 6 min, 0.01 h = 36 s, 0.001 h = 4 s.

We have reduced this concept to practice in three ways. First, addition of RLi (1 equiv) to ((trimethylsilyl)methyl)copper(I), prepared by the procedure of Lappert *et al.*,[16] yields mixed cuprates $RCu(CH_2SiMe_3)Li$. We have prepared these new ((trimethylsilyl)methyl)cuprates from CuI as well as CuCN, and we find that they are extraordinarily reactive in both ether and THF (*vide infra*). They have the additional advantage of a most innocuous byproduct upon aqueous workup, viz. tetramethylsilane. We propose to name them TMSM-cuprates.

A second class of β-silylcuprates combines our new concept with our previous *N*-heterocuprates.[9,10] Thus, hexamethyldisilazidocuprates $RCu[N(SiMe_3)_2]Li$ are conveniently prepared from RLi and copper(I) bis(trimethylsilyl)amide.[17] In diethyl ether these new reagents are also extremely reactive, and their byproducts upon aqueous workup, NH_3 and TMSOTMS, are relatively benign. (Organocopper reactions are often quenched with aqueous ammonium salt.) We call them HMDS-cuprates.

The third class of β-silylcuprates combines our new concept with Posner's thiocuprates.[8] ((Trimethylsilyl)thio)cuprates $RCu(SSiMe_3)Li$ are prepared from RLi and $CuSSiMe_3$, which is formed *in situ* from CuI and $LiSSiMe_3$.[18] These ((trimethylsilyl)thio)cuprates (TMST-cuprates) also have excellent reactivity in ether. In addition to TMSOTMS, aqueous workup gives H_2S, which improves the yields of some organocuprate reactions.[4]

Logarithmic reactivity profiles[14,15a] (LRPs) for BuCu(TMSM)Li, BuCu(HMDS)Li, and BuCu(TMST)Li are compared to those for BuCu(Th)Li·LiCN and $Bu_2CuLi{\cdot}LiCN$ in Table 1. A LRP is generated by quenching an archtypal reaction after a series of times which span as many orders of magnitude as possible. The butyl((trimethylsilyl)methyl)cuprate is significantly more reactive toward 2-cyclohexenone (**1**) than the

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[1] (a) New Copper Chemistry, part 27. For part 26, see ref 14; for part 25, see ref 15a; for part 24, see ref 19. (b) Complexity Study Center. (c) Chalmers University of Technology. (d) Brigham Young University. (e) Emory University.

[2] For recent compendious reviews, see: Bertz, S. H.; Fairchild, E. H. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1995; Vol. 2, p 1312 (CuBr), 1324 (CuCl), 1341 (CuCN), 1346 (CuI).

[3] (a) For extensive tables of examples, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) See p 221 of ref 3a.

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Table 2. Thermal Stability of BuCu(TMSM)Li•LiI and BuCu(Th)Li•LiI: Yields (%) of **4** (and **5** or **6**)[a]

reagent	temp (°C) −78	0	25
BuCu(TMSM)Li•LiI			
ether	98 (1)[b]	98 (2)	94 (4)
THF	95 (3)	95 (3)	92 (3)
BuCu(Th)Li•LiI			
ether	74 (10)[c]	58 (12)	13 (17)
THF	85 (11)	61 (21)	3 (42)

[a] Compound **4** = butyl phenyl ketone, **5** = (trimethylsilyl)acetophenone, **6** = 2-benzoylthiophene: measured by using GLC and the internal standard method. All reactions were run on a 1.00 mmol scale (0.10 M). [b] Yields of **5** in parentheses. [c] Yields of **6** in parentheses.

corresponding 2-thienylcuprate in both ether and THF. The ((trimethylsilyl)methyl)cuprate is also more reactive than the cyano Gilman reagent: slightly more reactive in ether, considerably more in THF. In fact, the yields of 3-butylcyclohexanone (**2**) are quantitative or nearly so (99−100%) from BuCu(TMSM)Li•LiI and BuCu(TMSM)Li•LiCN in both ether and THF. Even at the shortest time we can reliably obtain (4 s), the yields in ether are virtually quantitative (98−99%). No 3-((trimethylsilyl)methyl)cyclohexanone was detected.

Within experimental error, the ((trimethylsilyl)methyl)cuprates prepared from CuI and CuCN have equal reactivities. The reactivities of the thienylcuprates prepared from CuI and CuCN are almost equal, which is attributable to stabilization of the transition state by the thienyl group.[14] We believe that the β-trimethylsilyl group exerts an even greater effect, since the yields from the ((trimethylsilyl)methyl)cuprates are higher and their dependence on the precursor salt is lower (negligible).

The BuCu(HMDS)Li•LiI reagent also has excellent reactivity in ether but not in THF. The yield from the BuCu(TMST)Li•LiI reagent is slightly lower than from the HMDS-cuprate in ether but significantly better in THF after 1 h (−78 °C). We note that all yields fall off faster in THF than in ether. In general, yields from conjugate addition reactions of cuprates are not as good in THF as in ether.[2,3] The difference between ether and THF is much less for the ((trimethylsilyl)methyl)cuprates than for any of the other reagents.

The butyl group was chosen for study because it has sufficient reactivity at −78 °C, where thermal decomposition is not a complicating factor. Nevertheless, it also has two β-hydrogen atoms, which make it susceptible to thermal decomposition at higher temperatures. Therefore, we studied the thermal decomposition of the ((trimethylsilyl)methyl)cuprates by using the paradigm introduced previously.[9]

The cuprates were aged at various temperatures (−78, 0, or 25 °C) for 0.5 h and then quenched with benzoyl chloride (**3**) at −78 °C. The amount of butyl phenyl ketone (**4**) present is then a measure of the (minimum) amount of viable reagent that remains. Table 2 summarizes the thermal stability data, which show that this new reagent is more stable than previous homocuprates or heterocuprates.[9] For example, in ether the corresponding yields for Bu$_2$CuLi•LiI are 96, 89, and 82%, and for Bu$_2$CuLi•LiCN they are 99, 95, and 84%, respectively.[9]

The yields of **4** were slightly lower than the yields of **2** (*vide supra*), since small amounts (1−4%) of (trimethylsilyl)acetophenone (**5**) were also formed with the excess (2.2 equiv) of **3**. With 1 equiv of **3**, the yields of **4** were 100% in ether and 96% in THF (along with 3% of **5**). Authentic samples of the side products were prepared via the reactions of (TMSM)$_2$CuLi•LiI with **1** and **3**, respectively.

For comparison, the corresponding data for the thienyl mixed cuprates are also summarized in Table 2. The contrast between the ((trimethylsilyl)methyl)cuprates and the thienylcuprates is especially stark at 25 °C, where the former retain almost all of their reactivity but the latter are defunct. Also, more of the side product (in this case 2-benzoylthiophene (**6**)) from the transfer of the "nontransferred" ligand is formed, especially in THF.

The thermal stabilities of the intermediates also deserve comment. While (TMS)CH$_2$Cu and (TMS)$_2$NCu are stable at 0 °C, (TMS)SCu is not and deposits Cu metal at this temperature. It is prepared at −20 °C; see the Supporting Information.

The composition of the reagent responsible for conjugate addition was probed by performing density functional theory (DFT)[19] geometry optimizations (B3LYP/LANL2DZ basis set)[19] for the TMSM and Me homocuprates and the mixed cuprate species, as summarized in eq 1. The calculated energy for this isodesmic reaction is 1.8 kcal/mol. This corresponds to Boltzmann distributions containing 99.1% mixed cuprate at −78 °C, 96.5% at 0 °C, and 95.4% at 25 °C. The results indicate that the mixed cuprate is strongly favored over the corresponding homocuprates at the temperatures used in our studies.

$$2[(\mathrm{TMSM})\mathrm{CuMe}]^- \rightleftharpoons [(\mathrm{TMSM})_2\mathrm{Cu}]^- + [\mathrm{Me}_2\mathrm{Cu}]^- \quad (1)$$

In conclusion, we have found that by building a β-silicon atom into an organocuprate, the resulting reagent is (i) highly reactive, (ii) thermally stable, and (iii) economical as far as the transferred group is concerned. We have demonstrated this for the two most important applications of organocopper reagents, conjugate addition and ketone formation,[20] although more work is needed to fully define the scope and limitations of these new reagents. As far as cyano Gilman reagents are concerned, it has been noted that "those prepared from 2 equivalents of the same organolithium and 1 equivalent of copper(I) cyanide are more reactive species relative to those containing a second residual ligand..."[3b] It would appear that we have invented the first mixed cuprate that is more reactive than the corresponding homocuprates. Finally, we believe that this work illustrates the extension of the Eaborn β-silyl effect[21] to metal centers.

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Supporting Information Available: Experimental details (1 page). See any current masthead page for ordering and Internet access instructions.

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