Communications to the Editor

The Role of Me_3SiCl in Gilman Cuprate 1,4-Addition Reactions

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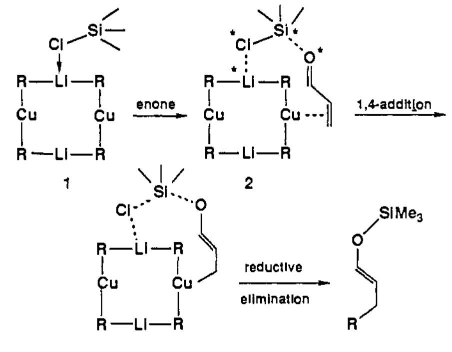
Some years ago, the remarkable effects of Me_3SiCl on Gilman cuprate conjugate addition reactions in THF[1] were brought to attention by reports from a number of groups throughout the world.[2–6] Not only can the presence of this additive significantly enhance yields of 1,4-adducts, but dramatic rate accelerations are normally observed.[2–6] Even substrates which are totally unreactive as Michael acceptors can oftentimes be used when TMS-Cl is in the medium.[3] Not surprisingly, therefore, considerable debate surrounds the manner in which this particular silyl chloride acts. An early, seminal study attributes the phenomenon to the ability of TMS-Cl to trap an initial cuprate–substrate (d–π^*) complex, thus shifting the equilibrium toward product silyl enol ether.[2a] A second scenario invokes a TMS-Cl–substrate interaction in a Lewis acid–Lewis base sense, with subsequent addition of the cuprate to this *in situ* derived complex.[7] We now present data based on low-temperature heteronuclear NMR and related chemical experiments that shed new light on the interactions between the three species involved, which ultimately allow for a melding of the above scenarios into a single unified role for TMS-Cl in lower order cuprate 1,4-additions.[8]

The Corey and Boaz proposal[2a] is predicated on ^{1}H NMR experiments which show no change in the position of the singlet due to Me_2CuLi upon exposure to Me_3SiCl.[2b] Horiguchi, Komatsu, and Kuwajima claim that Me_3SiCl must be acting as a Lewis acid toward an enone carbonyl oxygen.[7] Although unsubstantiated by physical means,[9] the inference regarding Lewis acidity was deemed necessary to account for the stereochemical results realized in their 1,4-additions of R_2CuLi to substituted cyclohexenones. There is, however, the possibility of a third combination of events involving these three species. That is, an interaction between TMS-Cl and R_2CuLi may exist where TMS-Cl acts as a Lewis *base* toward the cuprate (*cf.* **1**).[10] Hence, with chlorine acting in this capacity, the "Lewis acidity" of TMS-Cl is expected to increase, with the Me_3Si residue well-positioned within the cuprate cluster to create an enhanced "push–pull" effect generally regarded as essential for cuprate Michael donor reactivity[11] (shown pictorially in Scheme I). Note that the O, Si, Cl, and Li (starred) atoms in **2** involve all hard–hard interactions.[12]

Scheme I. Proposed Sequence of Events for Me_3SiCl-Accelerated Cuprate 1,4-Addition Reactions



To establish that an interaction between Li^+ in the cuprate and TMS-Cl may be involved, both ^{7}Li and ^{35}Cl NMR[13] experiments were conducted at low temperatures on THF solutions of various lower order cuprates in the presence of this additive. The ^{7}Li NMR spectrum of 0.10 M $Me_2CuLi{\cdot}LiI$[14] (**3**) in THF at −80 °C shows a single peak at δ +0.171 (*vs* LiCl/MeOH as δ 0.00). Addition of 1 equiv of TMS-Cl, which is tantamount to a 1.5% change in total volume of the sample, moves the signal to δ +0.041 (Figure 1).[15] Mixed cuprate $R(2\text{-}Th)CuLi{\cdot}LiI$ (**4**, R = Me) was also examined *via* a series of spectra recorded using 0.00, 0.50, 1.00, and 1.50 equiv of TMS-Cl relative to cuprate. The initial signal at δ −0.063 shifts significantly to δ +0.003 (and then less so with additional amounts of silyl chloride), again indicating an impact of non-lithium-containing TMS-Cl on the cuprate (Figure 2 see supplementary material).[16,17]

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(1) The effects of TMS-Cl in Et_2O are usually far less impressive than in THF solutions of Gilman reagents.[2b]

(2) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015; (b) **1985**, *26*, 6019.

(3) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

(4) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.

(5) Linderman, R. J.; Godfrey, A. *Tetrahedron Lett.* **1986**, *27*, 4553.

(6) For more recent studies, see: Bertz, S. H.; Smith, R. A. J. *Tetrahedron* **1990**, *46*, 4091. See also: Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Ibid.* **1989**, *45*, 349. Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Ibid.* **1988**, *44*, 2055. Bergdahl, M.; Lindstedt, E.-L.; Olsson, T. *J. Organomet. Chem.* **1989**, *365*, C11. Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. On the other hand, there are reports where TMS-Cl has been observed to *suppress* cuprate reactivity, *e.g.*, see: Wurster, J. A.; Wilson, L. J.; Morin, G. T.; Liotta, D. *Tetrahedron Lett.* **1992**, *33*, 5689.

(7) Horiguchi, Y.; Kamatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087.

(8) For a recent review on organocopper chemistry, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* (*New York*) **1992**, *41*, 135.

(9) We are unaware of any physical evidence suggesting a Lewis acid–base interaction between TMS-Cl and a carbonyl derivative.

(10) There are many examples of halides acting as Lewis bases toward organometallic species, see, *e.g.*: Fernandez, J. M.; Gladysz, J. A. *Organometallics* **1989**, *8*, 207. Stalke, D.; Whitmire, K. H. *J. Chem. Soc., Chem. Commun.* **1990**, 833. Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189.

(11) Ouannes, C.; Dressaire, G.; Langlois, Y. *Tetrahedron Lett.* **1977**, 815. Hallnemo, G.; Ullenius, C.; *Ibid.* **1986**, *27*, 395.

(12) Ho, T. L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977. Pearson, R. G. *Hard and Soft Acids and Bases*; Dowden, Hutchinson, & Ross, Inc.: Stroudsburg, PA, 1973. Pearson, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 7684.

(13) Lambert, J. B.; Schiff, W. *J. Am. Chem. Soc.* **1988**, *110*, 6364. Prakash, G. K. S.; Keyaniyan, S.; Aniszfeld, R.; Heiliger, L.; Olah, G. A.; Stevens, R. C.; Choi, H-K.; Bau, R. *Ibid.* **1987**, *109*, 5123.

(14) (a) The rate of exchange of LiI with R_2CuLi is extremely rapid on the NMR time scale.[14b] In addition, evidence is mounting which suggests that the halide ion is actually part of the cuprate cluster (*i.e.*, $R_2Cu(X)Li_2$, a "higher order" cuprate.[14c] (b) Kleft, R. L.; Brown, T. L. *J. Organomet. Chem.* **1974**, *77*, 289. Scherr, P. A.; Hogan, R. J.; Oliver, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 6055. (c) X-ray study: Hope, H.; Olmstead, M. M.; Power, P. P.; Sandell, J.; Xu, X. *Ibid.* **1985**, *107*, 4337. (d) NMR data: Bertz, S. H.; Dabbagh, G. *Ibid.* **1988**, *110*, 3668.

(15) (a) ^{7}Li NMR spectroscopy spans only about 4 ppm.[15b] Hence, $\Delta\delta$s of the magnitude observed for these spectra are quite significant. Moreover, the $\Delta\delta$s observed for $Me_2CuLi{\cdot}LiI$ have been reproduced (±0.07 ppm) on >3 independently prepared samples. (b) Brevard, C.; Granger, P.; *Handbook of High Resolution Multinuclear NMR*; Wiley: New York, 1981. Coleman, B. *NMR of Newly Accessible Nuclei*; Academic Press: New York, 1983.

(16) The aggregate Me_3Cu_2Li (from 3MeLi + 2CuI) in THF[17b] was also examined by ^{7}Li NMR at −78 °C alone (δ 0.10) and in the presence of 1 equiv of TMS-Cl (δ −0.06). Thus, the same phenomenon was observed with this species as well ($\Delta\delta = 0.16$), although the direction of change in this spectrum is different, as is the cuprate itself (*e.g.*, the ^{1}H NMR of Me_3Cu_2Li in THF is totally unlike that of Me_2CuLi).

(17) Whether the interaction observed is the same for both cuprate types, therefore, cannot be stated with certainty. (b) Ashby, E. C.; Watkins, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 5312.

(18) Complexation of symmetrical chloride ion causes a broadening in its line width, *cf.*: Sugawara, T.; Yudasaka, M.; Yokoyama, Y.; Fujiyama, T.; Iwamura, H. *J. Phys. Chem.* **1982**, *86*, 2705.

0002-7863/93/1515-9283$04.00/0

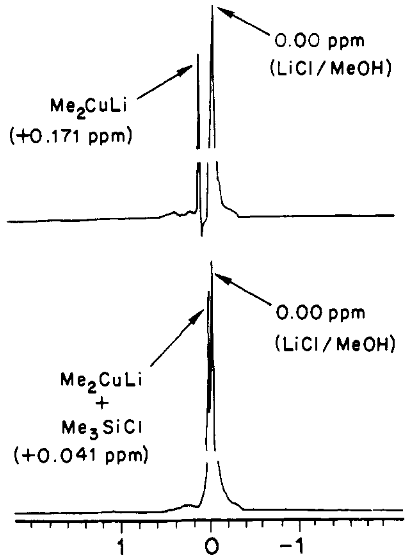


Figure 1. ^{7}Li NMR spectra of (top): Me_2CuLi in THF, 0.10M, -80°; (bottom): same sample containing 1.0 equiv Me_3SiCl.

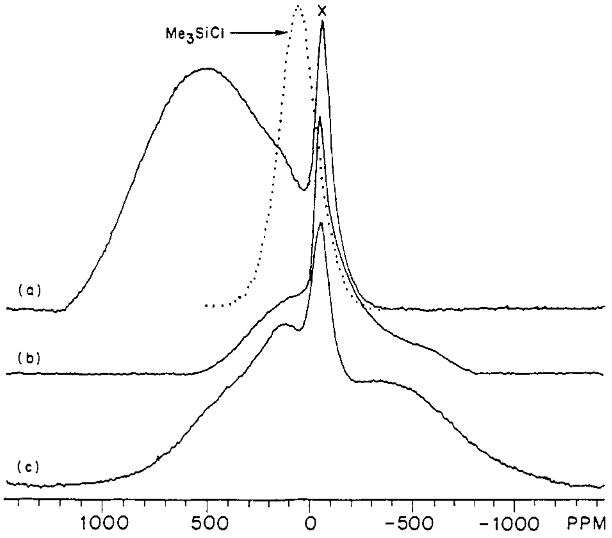
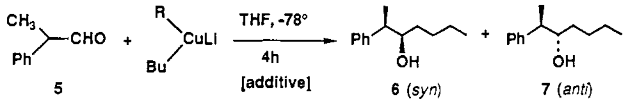


Figure 3. ^{35}Cl NMR spectra of TMS-Cl in THF at -60° taken in the presence of (a) Me(2-Th)CuLi; (b) $Me(MeO(Me_2)CC{\equiv}C)CuLi$; (c) Me_2CuLi *vs.* TMS-Cl alone (top spectrum). Peaks marked by an x represent LiCl generated from gradual decomposition of each species over the 2-3 h required for data acquisition.

In order to ascertain whether an association of TMS-Cl with the cuprate through the chlorine atom exists (*cf.* **1**), ^{35}Cl solution NMR experiments were expected to reveal, by assessment of peak shape (*i.e.*, line broadening), a loss in symmetry for the environment surrounding this nucleus relative to that seen for TMS-Cl alone.[18] That is, although the signal for Me_3SiCl is very broad (*ca.* 11 kHz) due to the large quadrupolar moment associated with ^{35}Cl,[13] dative coordination of chlorine to a metal (*e.g.*, the Li^+)[18] in R_2CuLi should further broaden the initially obtained signal. This is indeed what has been found for three different species: (a) Me(Th)CuLi·LiI, (b) $Me(MeOC(Me_2)$-$C{\equiv}C)CuLi{\cdot}LiI$, and (c) $Me_2CuLi{\cdot}LiI$ (Figure 3).[19] Control experiments, *e.g.*, where Me_4Si (rather than Me_3SiCl) was added to **3**, showed no change in the ^{7}Li NMR spectrum; likewise, the ^{35}Cl NMR spectrum of TMS-Cl remained unaltered upon addition of 2-cyclopentenone.[9]

Scheme II



	Ratio (6:7)
Bu_2CuLi	1.7 : 1
Bu_2CuLi + TMS-Cl	9 : 1
Bu(2-Th)CuLi	no reaction
Bu(2-Th)CuLi + TMS-Cl	12-19 : 1

The picture that begins to emerge points to a rapid association of some quantity of TMS-Cl to the Gilman cuprate dimer,[20,21] which, in addition to impacting on the Lewis acidity of silicon,[22] (1) increases the net size of the reagent and simultaneously (2) decreases the number of available coordination sites on Li^+ within this newly formed complex. The former effect is supported by studies on cuprate·TMS-Cl 1,2-additions,[23] where Cram selectivities are predicted to increase. In the event, while treatment of aldehyde **5** (Scheme II) with Bu_2CuLi affords a very modest preference for *syn* product **6**, the ratio goes up to 9:1 simply upon addition of TMS-Cl. More striking is the case of cuprate **4** (R = *n*-Bu), which by itself is unreactive toward **5** at -78 °C over 4 h but proceeds to add smoothly under these conditions in the presence of TMS-Cl, providing adducts **6** and **7** in up to a 19:1 ratio! The latter occurrence helps to formulate an explanation as to how TMS-Cl can change the stereochemical outcome in cuprate 1,4-additions to enones which bear proximate chelating heteroatom functionality.[2a,24]

In conclusion, these results provide *prima facie* evidence that an interaction between a Gilman cuprate and TMS-Cl does exist.[20,25] They strongly suggest that an alternative sequence of events may well be involved in TMS-Cl induced[26] cuprate conjugate additions, which represents the confluence of insightful hypotheses as originally put forth by the Corey[2a] and Kuwajima[7] groups. Moreover, from a practical standpoint, given the potential stereochemical impact of TMS-Cl on a 1,2- or 1,4-cuprate addition, such a role for this additive encourages its use where reaction rates and/or yields are *not* problematic.[24g,26]

Supplementary Material Available: Figure of ^{7}Li NMR of Me(2-Th)CuLi in THF at -60 °C containing 0.0, 0.5, 1.0, and 1.5 equiv of TMS-Cl (1 page). Ordering information is given on any current masthead page.

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(19) The spectrum in Figure 3c could be viewed as suggestive of *two* species being present. This may well be the case since Me_2CuLi and TMS-Cl are *not* fully compatible at -60 °C over the 3-h time period required to obtain this ^{35}Cl NMR spectrum at these concentrations. Hence, Me_3Cu_2Li is unequivocally present, and as noted in its ^{7}Li NMR spectrum,[17] it is likely to have a different chemical shift upon complexation with TMS-Cl.

(20) (a) It is appreciated that complexation of TMS-Cl with a cuprate does not unequivocally establish that the association is between Cl^- and Li^+. However, if the alternative Cu···Cl interaction is involved to any significant degree, the initial Cu(d)–olefin(π^*) complexation[20b] might actually be retarded, which is obviously contrary to experimental findings. (b) Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988**, *60*, 57.

(21) van Koten, G.; Jastrzebski, J. T. B. H.; Muller, F.; Stam, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 697. Olmstead, M. M.; Power, P. P. *Ibid.* **1990**, *112*, 8008. Lorenzen, N. P.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 300.

(22) Unfortunately, several ^{29}Si NMR experiments on Me_2CuLi + TMS-Cl at -78 °C showed no change in chemical shift for this additive.

(23) For a review on cuprate 1,2-additions, see: Lipshutz, B. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1992; Vol. 1; see, also: Matsugawa, S.; Isaka, M.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 1975.

(24) (a) Alexakis, A.; Sedrani, R.; Mangeney, P. *Tetrahedron Lett.* **1990**, *31*, 345. (b) Smith, A. B.; Dunlop, N. G.; Sulikowski, G. A. *Ibid.* **1988**, *29*, 439. (c) Alexakis, A. *Pure Appl. Chem.* **1992**, *64*, 387. (d) Marek, I.; Alexakis, A.; Mangeney, P.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1992**, *129*, 171. (e) Courtemanche, G.; Alexakis, A.; Vaissermann, J.; Normant, J.-F. *J. Organomet. Chem.* **1992**, *423*, 281. (f) Arai, M.; Nemoto, T.; Ohashi, Y.; Nakamura, E. *Synlett* **1992**, 309. (g) For a particularly striking example in total synthesis, see: Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Hartmann, M. *J. Org. Chem.* **1992**, *57*, 1070.

(25) Prior suggestions along these lines can be found in the work of Nilsson: Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1989**, *45*, 535. Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *J. Organomet. Chem.* **1987**, *334*, 255.

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