Synthetic and Mechanistic Implications of Ligand Mixing in Higher Order Mixed (Trialkylsilyl)- and (Trialkylstannyl)cuprates

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Low-temperature ^{119}Sn, ^{29}Si, ^{13}C, and ^{1}H NMR spectroscopic techniques were used to probe the nature of cuprates derived from CuCN, MeLi, and R_3MLi (M = Si or Sn) in THF. These studies conclusively demonstrate facile dissociation–reassociation of R_3M and alkyl groups on copper which results in preferential formation of mixed (trialkylsilyl)- or (trialkylstannyl)cuprates of the general formula $R_3M(Me)Cu(CN)Li_2$ (M = Si or Sn) and $R_3M(Me)_2CuLi_2$ (M = Sn). These mixed metallocuprates preferentially transfer R_3M moieties (M = Si or Sn) in reactions with α,β-unsaturated enones and 1-alkynes.

(Trialkylsilyl)- and (trialkylstannyl)copper reagents are invaluable tools for the construction of carbon–silicon and carbon–tin bonds. In general, reactions of these reagents occur under relatively mild conditions and tolerate polar functional groups. Indeed, one has a myrid of literature examples from which to choose in deciding upon reaction parameters.[1,2] Most commonly sought are lithium-based cuprates, $(R_3M)_nCuLi_{n-1}\cdot LiX$ (M = Si or Sn, n = 1 or 2, X = Br or CN) prepared stoichiometrically from cuprous salts and 1 to 2 equiv of R_3MLi.[1,2] While homo (trialkylsilyl)- and (trialkylstannyl)cuprates serve admirably as donors of R_3M anions, problems attend the use of these reagents in that not all the metal anions bound to copper are transferred in these processes. Consequently, workup of these reactions afford R_3MH, R_3M-MR_3, and R_3MOH, all of which complicate product isolation.[1,3]

The possibility arises that the mixed metallocuprates, i.e., $R_3Si(R')CuLi\cdot LiX$ (1) or $R_3Sn(R')CuLi\cdot LiX$ (2) would preferentially transfer R_3M anions and thereby increase ligand efficiency of these reagents and offer opportunities for design of new (chiral) reagents. The ability of methyl to serve as an efficient nontransferrable ligand in mixed organoalkylcuprates[4] and trialkylsilylcuprates[1] led us to determine the composition of mixed (trialkylsilyl)- and (trialkylstannyl)cuprates derived from CuCN with methyl serving as the second or third anionic ligand.

In the present study we provide spectroscopic evidence that novel mixed (trialkylsilyl)-, $(R_3Si)(Me)Cu(CN)Li_2$, and (trialkylstannyl)cuprates, $(R_3M)(Me)_nCuLi_n\cdot LiCN$ (M = Sn, n = 1 or 2) are formed from several combinations of methyl and trialkylsilyl or trialkylstannyl anions in the presence of cuprous cyanide. These NMR studies also suggest that in the mixed metallocuprates containing one alkyl anion per copper cation $[(R_3M)(Me)Cu(CN)Li_2]$, the nitrile ligand is bound to copper as has been recently advanced for HO cyanocuprates.[5] These species react rapidly with conjugated enones and other unsaturated organic substrates[1,2,6-8] to transfer R_3M in preference to alkyl ligands.

Results and Discussion

Silicon-29 and Carbon-13 NMR Studies of Mixed (Trialkylsilyl)cuprates. (Dimethylphenylsilyl)lithium (3) in THF was prepared by reaction of $PhMe_2SiCl$ and lithium metal (therefore containing LiCl).[9] Solutions of this reagent at −5 °C gave a ^{29}Si NMR signal at −28.5 ppm (Figure 1a).[9] Solutions of mixed (trialkylsilyl)(methyl)-cuprates[1] were generated by addition of THF solutions of 3 to equimolar THF solutions of MeLi and CuCN at −70 °C. This combination, as well as addition of 1 equiv of MeLi to 1 equiv of $PhMe_2SiCu(CN)Li$,[9] (4, Figure 1b) and

Scheme I

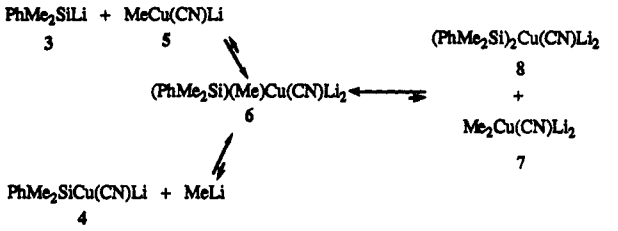

Table I. ^{13}C Chemical Shifts of Methyl Groups in Metallocuprates

$R_3Si(Sn)-M$	Si(Sn)–Me	Cu–Me
$PhMe_2SiLi$	7.5	
$PhMe_2SiCu(CN)Li$	6.3	
$(PhMe_2Si)_2Cu(CN)Li_2$	5.1	
$(PhMe_2Si)_3CuLi_2$	8.1	
$PhMe_2Si(Me)Cu(CN)Li_2$	6.0	−5.0
Me_4Sn	−9.5	
Me_3SnLi	−3.7	
$Me_3SnCu(CN)Li$	−4.5	
$(Me_3Sn)_2Cu(CN)Li_2$	−0.04	
$(Me_3Sn)_3Cu_2Li$	1.67	
$(Me_3Sn)_3CuLi_2$	−1.13	
$Me_3Sn(Me)Cu(CN)Li_2$	−2.0	−9.3
$Me_3Sn(Me)_2CuLi_2$	−1.7	−9.3
$Bu_3Sn(Me)Cu(CN)Li_2$		−9.3

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(1) (a) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805. (b) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2527.

(2) (a) Piers, E.; Chong, J. M. *Tetrahedron* **1989**, *45*, 363 (and references cited therein). (b) Cox, S. D.; Wüdl, F. *Organometallics* **1983**, *2*, 184. (c) Westmijze, H.; Ruitenberg, K.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1983**, 2797. (d) Hudec, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1020.

(3) (a) Sharma, S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1986**, 6161. (b) Sharma, S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1988**, 261. (c) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064.

(4) (a) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943. (b) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1985**, 5911.

(5) Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4302.

(6) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, 2065.

(7) Oehlschlager, A. C.; Hutzinger, M. W.; Aksela, R.; Sharma, S.; Singh, S. M. *Tetrahedron Lett.* **1990**, 165.

(8) Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.*, in press.

(9) (a) Sharma, S.; Oehlschlager, A. C. *Tetrahedron* **1989**, *45*, 557. (b) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5383. (c) Solutions containing R_3SiLi–Me–Cu at ratios different than 1:1:1 give mixtures of species and will be the subject of forthcoming publication.

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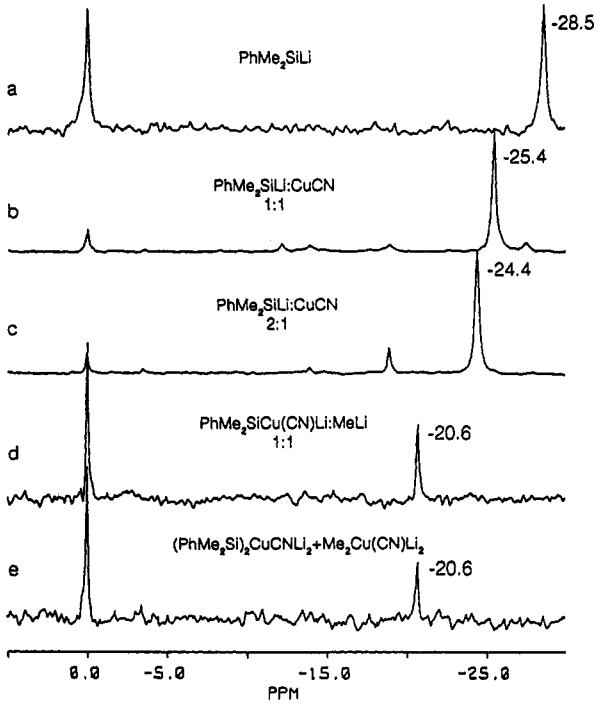


Figure 1. ^{29}Si NMR spectra of (a) $PhMe_2SiLi$, (b) $PhMe_2SiCu(CN)Li$, (c) $(PhMe_2Si)_2Cu(CN)Li_2$, (d) $PhMe_2SiCu(CN)Li$ + MeLi, (e) $(PhMe_2Si)_2Cu(CN)Li_2$ + $Me_2Cu(CN)Li_2$; spectra were run at −50 °C.

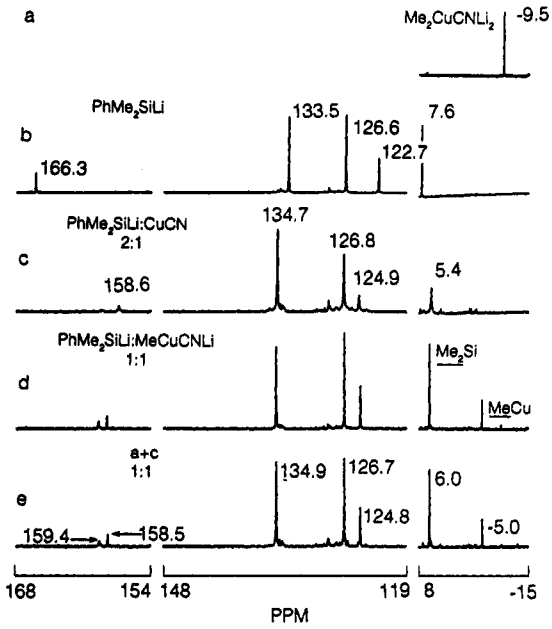
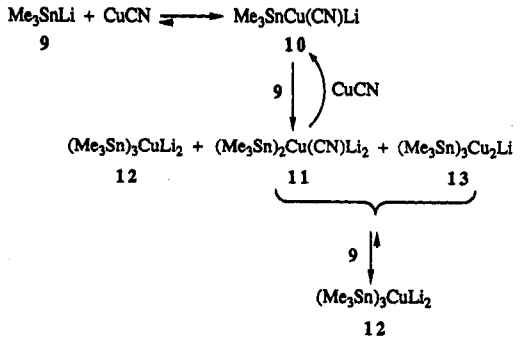


Figure 2. ^{13}C NMR spectra of (a) $Me_2Cu(CN)Li_2$, (b) $PhMe_2SiLi$, (c) $(PhMe_2Si)_2Cu(CN)Li_2$, (d) $PhMe_2SiLi$ + $MeCu(CN)Li$, (e) $(PhMe_2Si)_2Cu(CN)Li_2$ + $Me_2Cu(CN)Li_2$; spectra were run at −70 °C.

addition of **3** to preformed MeCu(CN)Li[4a] (**5**) yielded solutions that exhibited a single ^{29}Si signal at −20.6 ppm (Figure 1d) attributable to $(PhMe_2Si)(Me)Cu(CN)Li_2$ (**6**), implying that any equilibria of the types shown in Scheme I must lie heavily toward **6**. To establish that **6** could be produced by mutual alkyl and silyl anion exchange, equivalent amounts of $Me_2Cu(CN)Li_2$[4a] (**7**) and $(PhMe_2Si)_2Cu(CN)Li_2$[9] (**8**, Figure 1c) were prepared separately and then combined via a cannula. These solutions gave ^{29}Si NMR spectra (Figure 1e) identical with those obtained previously (Figure 1d), indicating the same species (**6**) had been formed (Scheme I).

Scheme II



The ^{13}C NMR spectrum (Figure 2d) of $(PhMe_2Si)(Me)Cu(CN)Li_2$ (**6**) at −70 °C, prepared from a THF solution of MeCu(CN)Li (**5**) and $PhMe_2SiLi$ (**3**, Figure 2b),[9] consisted of seven lines: four in the phenyl region (δ 158.5, ipso; 134.9, ortho; 126.7, meta; 124.8, para), one nitrile (δ 159.4), and two high field signals at 6.0 and −5.0 ppm. The latter two signals were assigned to a methyl bound to silicon (6.0 ppm) and a methyl bound to copper (−5.0 ppm) in **6** (Table I). Likewise, the ^{13}C NMR spectra (Figure 2e) of solutions resulting from mixing $Me_2Cu(CN)Li_2$ (**7**, Figure 2a) and $(PhMe_2Si)_2Cu(CN)Li_2$ (**8**, Figure 2c)[9] did not show signals characteristic of the individual reagents. Rather, these solutions gave the same spectra obtained previously from solutions derived from the combination of $PhMe_2SiLi$ (**3**) and MeCu(CN)Li (**5**, Figure 2d). Thus, mixed (trialkylsilyl)(methyl)cuprates as well as homo (trialkylsilyl)cuprates and alkylcuprates, irrespective of the mode of preparation, revert to the same species, **6**, when the ratio of silyl anion to alkyl anion to cuprous ion is 1:1:1 (Scheme I).[9c] The ^{13}C NMR spectra of solutions of **6** revealed one signal for the nitrile carbon at 159.4 ppm. This chemical shift is indicative of a coordinated nitrile.[5,9a] Corroborating evidence for the bound nitrile comes from infrared analysis of solutions of **6** which show an absorption at ν_{CN} 2123 cm^{-1}.[9,10] Free LiCN exhibits an absorption at ν_{CN} 2085 cm^{-1}.[5] These observations suggest that nitrile is coordinated with copper in **6**.

Tin-119, Carbon-13, and Hydrogen-1 NMR Studies on Mixed (Trialkylstannyl)cuprates. We next focused on preparation of reagents containing equimolar ratios of trialkylstannyl and alkyl anions coordinated with copper. Our recent studies of homo (trialkylstannyl)cuprates revealed a strong parallel between the homo trialkylsilyl and trialkylstannyl systems (Scheme II).[9,11] Thus, at a 1:1 ratio of **9** to CuCN, $Me_3SnCu(CN)Li$ (**10**) was formed almost exclusively. When the ratio was increased to 2:1, mixtures of $(Me_3Sn)_2Cu(CN)Li_2$ (**11**) and $(Me_3Sn)_3CuLi_2$ (**12**) as well as $(Me_3Sn)_3Cu_2Li$ (**13**) were formed. At 3:1 ratios of Me_3Sn to CuCN, **12** becomes the predominant species just as $(PhMe_2Si)_3CuLi_2$ is the predominant species in THF solutions containing three equivalents of **3** to 1 equiv of CuCN.[9,11]

The ^{13}C NMR spectrum (Figure 3d) of a solution containing 1 equiv each of MeLi and $Me_3SnCu(CN)Li$ (**10**, Figure 3b) at −70 °C revealed three signals at −2.0, −9.3, and −9.5 ppm. The resonances at −2.0 and −9.3 ppm were assigned to carbons of the methyls bound to tin and copper, respectively, in $(Me_3Sn)(Me)Cu(CN)Li_2$ (**14**) whereas the signal at −9.5 ppm is attributable to Me_4Sn. The same

(10) CuCN/2LiCl complex in THF shows an infrared absorption at ν_{CN} 2148 cm^{-1}. The IR spectra were recorded on solutions warming to room temperature. No visible decomposition was observed within 0.5 h.

(11) Sharma, S.; Oehlschlager, A. C., submitted for publication in *J. Org. Chem.*

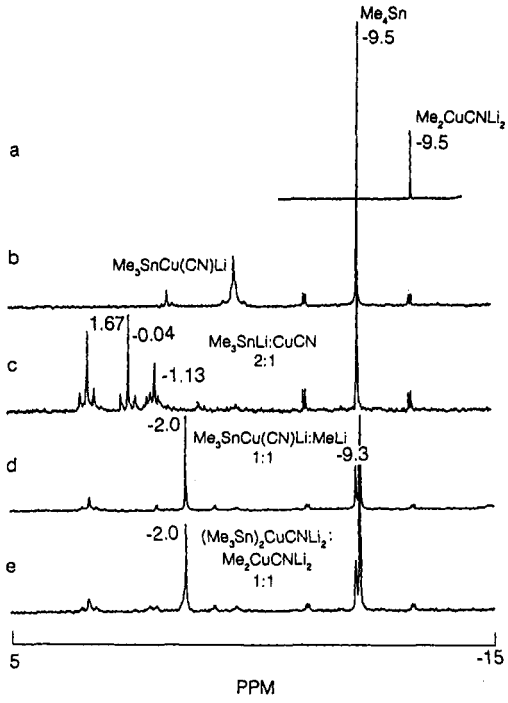
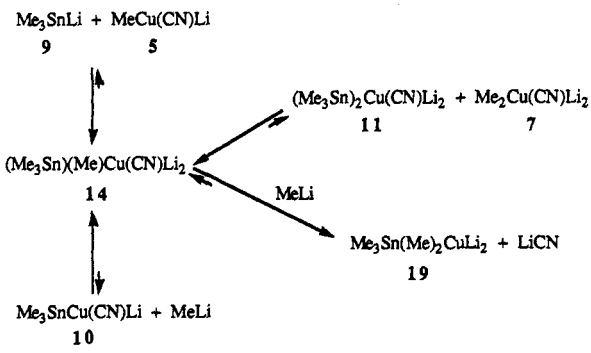


Figure 3. ^{13}C NMR spectra of (a) $Me_2Cu(CN)Li_2$, (b) 1.0 Me_3SnLi + CuCN, (c) 2.0 Me_3SnLi + CuCN, (d) $Me_3SnCu(CN)Li$ + MeLi, (e) $(Me_3Sn)_2Cu(CN)Li_2$ + $Me_2Cu(CN)Li_2$; the spectra were run at −70 °C.

Scheme III



spectrum was obtained when equimolar amounts of **9** and **5** were combined. The intensities of the satellites of the signal at −2.0 ppm are as expected for $^1J(^{119}Sn-^{13}C$, 182.0 Hz) coupling to a single tin nucleus. No $^2J(^{119}Sn-^{13}C)$ coupling was observed between the methyl bound to copper and the Me_3Sn moiety. This is attributed to rapid intermolecular exchange between methyls on copper. Since no signals due to $(Me_3Sn)_2Cu(CN)Li_2$ (**11**), $Me_2Cu(CN)Li_2$ (**7**), $Me_3SnCu(CN)Li$ (**10**), Me_3SnLi (**9**), MeCu(CN)Li (**5**), or MeLi are observable when the **9**:MeLi:CuCN ratio is 1:1:1, equilibria in Scheme III must favor **14** just as **6** is favored in Scheme I.

That ligand mixing is also facile in the mixed (trialkylstannyl)cuprates was revealed by the clean generation of **14** from mixing equimolar amounts of solutions containing 2:1 ratios of Me_3SnLi:CuCN (containing **11**–**13**, Figure 3c, Scheme II) and $Me_2Cu(CN)Li_2$ (**7**, Figure 3a). The ^{13}C NMR spectrum, taken at −70 °C, of the reagent formed in this experiment (Figure 3e) is identical with the one obtained previously (Figure 3d) from the mixture of MeLi and $Me_3SnCu(CN)Li$.

In support of our interpretation of the ^{13}C NMR spectrum of **14**, the ^1H spectrum (Figure 4b) of this reagent at −70 °C (prepared as for Figure 3e) and by mixing a 1:1:1 ratio of Me_3SnLi (**9**, Figure 4a), MeLi and CuCN showed

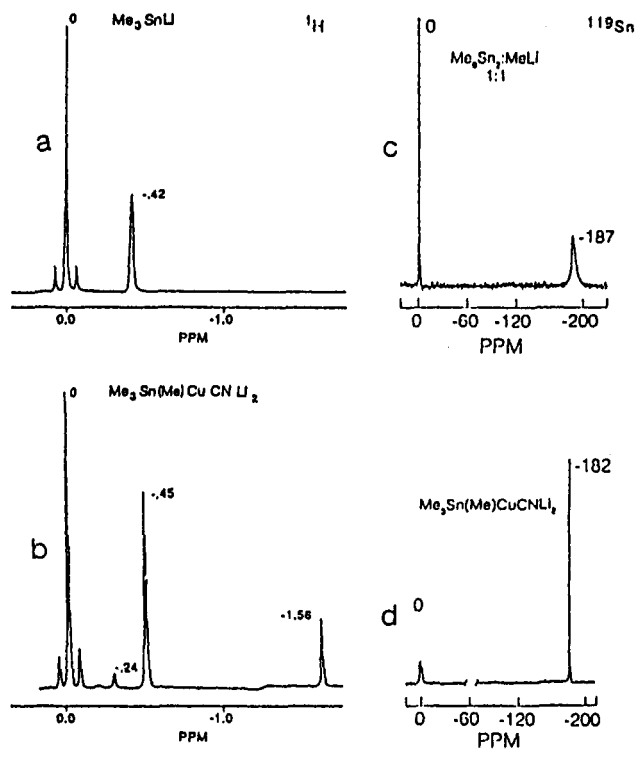


Figure 4. ^1H NMR spectra of (a) Me_3SnLi, (b) $(Me_3Sn)_2Cu(CN)Li_2$ + $Me_2Cu(CN)Li_2$; ^{119}Sn NMR spectra of (c) Me_3SnLi, (d) Me_3SnLi + MeCu(CN)Li; the spectra were run at −70 °C.

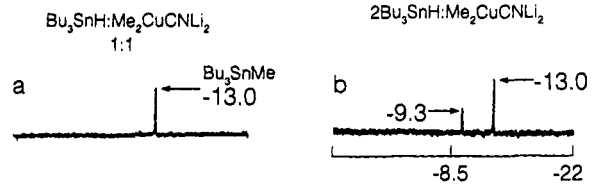
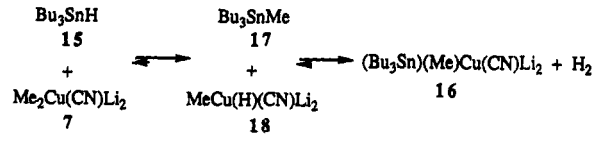


Figure 5. ^{13}C NMR spectra of (a) Bu_3SnH + $Me_2Cu(CN)Li_2$, (b) 2.0 Bu_3SnH + $Me_2Cu(CN)Li_2$; the spectra were run at −70 °C.

Scheme IV



two resonances in a 3:1 ratio at −0.45 (Me on tin) and −1.56 ppm (Me on copper) along with a minor peak due to **11** at −0.24 ppm.[11] The ^{119}Sn NMR spectra (Figure 4d) of these solutions showed a singlet at −182.0 ppm, indicative of a single species. This signal is attributed to **14** and is slightly upfield and sharper than that of Me_3SnLi (**19**, Figure 4c, −187.0 ppm). Corroborating evidence for this formulation comes from infrared analyses of these solutions which show a bound nitrile at 2108 cm^{-1}.[5,9a]

Encouraged by the formation of $(Me_3Sn)(Me)Cu(CN)Li_2$ (**14**) we examined the low-temperature ^{13}C NMR spectra of solutions generated from the mixture of 1 equiv of Bu_3SnH (**15**) and $Me_2Cu(CN)Li_2$ (**7**). This combination, which has been suggested[12] to produce $Bu_3Sn(Me)Cu(CN)Li_2$ (**16**), gave a species that exhibited a single peak at −13.0 ppm (Figure 5a) corresponding to the methyl in Bu_3Sn*Me* (**17**, Scheme IV). The stoichiometry of this

(12) Lipshutz, B. H.; Ung, C. S.; Sengupta, S. *Syn. Lett.* **1989**, *1*, 64.

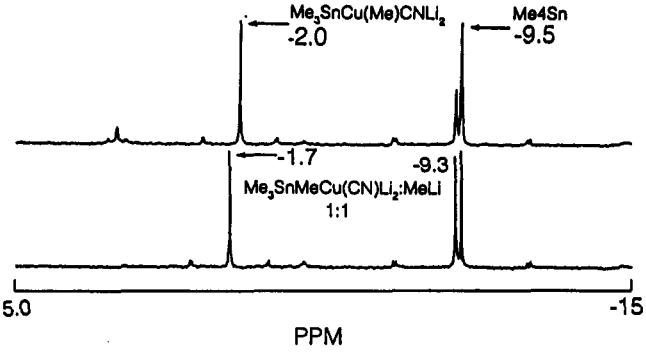
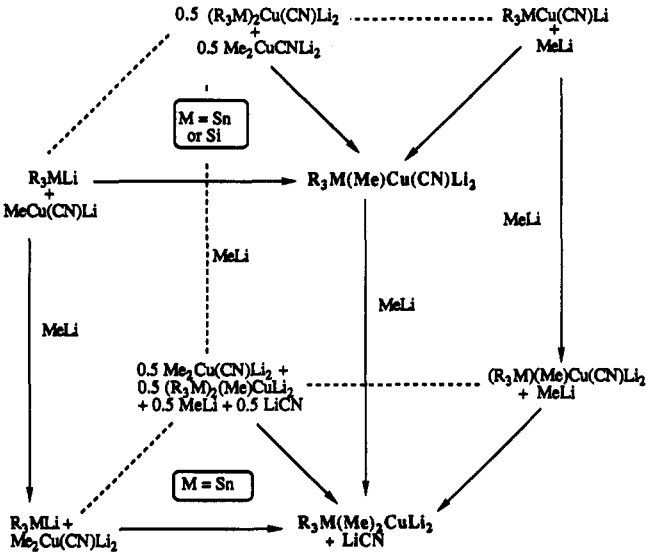


Figure 6. ^1H NMR spectra of (a) $(Me_3Sn)_2Cu(CN)Li_2$ + $Me_2Cu(CN)Li_2$, (b) $(Me_3Sn)Cu(Me)(CN)Li_2$ + MeLi; the spectra were run at −70 °C.

Scheme V



reaction requires the formation of $Me(H)Cu(CN)Li_2$ (**18**).

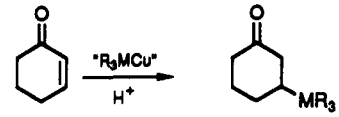
Addition of a further equivalent of Bu_3SnH (**15**) to the above solution resulted in immediate release of a gas and appearance of a new signal at −9.3 ppm (Figure 5b). Since this signal is similar to the one observed earlier (−9.3 ppm) for methyl bound to copper in $(Me_3Sn)(Me)Cu(CN)Li_2$ (**14**), it is attributed to the analogous methyl in $(Bu_3Sn)(Me)Cu(CN)Li_2$ (**16**). The stoichiometry of the conversion of an equivalent of Bu_3SnH (**15**) and $Me(H)Cu(CN)Li_2$ (**18**) to produce $(Bu_3Sn)(Me)Cu(CN)Li_2$ (**16**) requires the evolved gas to be hydrogen (Scheme IV).[12]

Since trialkylstannyl and alkyl anions appeared to exchange rapidly on copper, no impediments were envisioned to the preparation of mixed reagents containing a total of 3 equiv of trialkylstannyl and alkyl anions per equivalent of copper ion. Solutions containing 2 equiv of methyl anion and 1 equiv each of stannyl anion and copper ion were prepared by addition of 1 equiv of MeLi to preformed $(Me_3Sn)(Me)Cu(CN)Li_2$ (**14**, Figure 6a, containing Me_4Sn, −9.5 ppm), at −70 °C. This experiment yielded a solution that exhibited two ^{13}C NMR signals at −1.7 ppm $^1J(^{119}Sn-^{13}C$, 189 Hz), and −9.3 ppm which were attributed to $(Me_3Sn)(Me)_2CuLi_2$ (**19**, Figure 6b, Table I). This assignment was based on the increase in the intensity of the signal assigned to the copper bound methyls at −9.3 ppm relative to the signal at −1.7 ppm assigned to the tin-bound methyls in this solution compared to that observed for solutions of **14** (Figure 6a). Signals corresponding to other (trialkylstannyl)cuprates were not apparent in solutions of **19** containing 1:2:1 ratios of stannyl anion to alkyl anion to copper cation (Figure 6b). Thus, just as for the formation of **14**, **23** appears to be cleanly formed and represents a thermodynamic sink in the equilibria shown in Scheme III. Again, no $^2J(^{119}Sn-^{13}C)$ was observed in **19**, presumably due to rapid intermolecular exchange between methyls bound to copper.

In spite of the significant difference between the basicities of the methyl anion (MeH, $pK_a \sim 40$) and trialkylsilyl or trialkylstannyl anions (R_3MLi, $pK_a \sim 23$; M = Si, Sn), solutions containing equimolar amounts of these anions and cuprous ion revert cleanly to mixed cuprates, $R_3M(Me)Cu(CN)Li_2$ (Scheme V). When the proportion of methyl anion is increased in solutions containing trialkylstannyl anion to the cuprous cation ratios of 1:1 to give compositions wherein the R_3Sn:Me:Cu ratio is 1:2:1, a new species $R_3Sn(Me)_2CuLi_2$ (Scheme V) is again cleanly formed. In each case the new mixed (trialkylmetallo)(alkyl)cyanocuprate or (trialkylstannyl)(dialkyl)cuprate represent thermodynamic sinks with respect to other species that could be formed at these stoichiometries.

As shown in Tables II and III both $(PhMe_2Si)(Me)Cu(CN)Li_2$ (**6**) and $(Me_3Sn)(Me)Cu(CN)Li_2$ (**14**) efficiently transfer their silyl and stannyl ligands to cyclohex-2-en-1-one and 3-butyn-1-ol in preference to methyl.[1,2,6-8,13] Product yields are generally as good as or higher than for the classical homo (trialkylsilyl)- and (trialkylstannyl)-cuprates because of simplification in isolation procedures since methane is the hydrolysis product whereas R_3M-MR_3, R_3MH, and R_3MOH are the side products obtained on workup of homo (trialkylsilyl)- or (trialkylstannyl)-cuprates. Recent work has shown that preferential transfer of R_3M to a variety of unsaturated organic substrates occurs with $R_3Sn(R')Cu(CN)Li_2$ reagents.[6-8] The preferential migration of the R_3M ligands to the organic substrates can be rationalized as being due to the weaker bond between

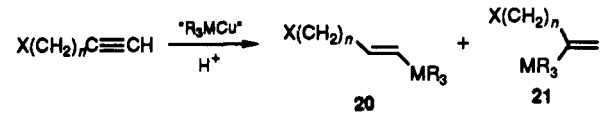
Table II. Reaction of Metallocuprates with Cyclohexenone



M = Si; R_3 = $PhMe_2$
M = Sn; R = Bu or Me

reagent	% yield
$PhMe_2SiCu(CN)Li$	58
$(PhMe_2Si)_2Cu(CN)Li_2$	65
$(PhMe_2Si)_3CuLi_2$	70
$PhMe_2Si(Me)Cu(CN)Li_2$	94
$Me_3SnCu(Me)(CN)Li_2$	92
$Bu_3SnCu(Me)(CN)Li_2$	96

Table III. Reaction of Metallocuprates with 1-Alkynes



X = H, n = 6; M = Si; R = $PhMe_2$
X = OH, n = 2; M = Sn; R = Bu or Me

reagent used	20	21	% yield
$PhMe_2SiCu(CN)Li$	60	40	62
$(PhMe_2Si)_2Cu(CN)Li_2$	>98	<2	92
$(PhMe_2Si)_3CuLi_2$	>98	<2	90
$PhMe_2Si(Me)Cu(CN)Li_2$	>98	<2	94
$Me_3SnCu(Me)(CN)Li_2$	10	90	80
$Bu_3SnCu(Me)(CN)Li_2$	50	50	85

(13) Still, W. C.; Macdonald, T. L. *Tetrahedron Lett.* **1976**, 2659.

R_3Si and R_3Sn anions and copper cation compared to methyl anion together with a far longer Si/Sn–Cu bond being formed. According to this explanation the ligand that migrates is the one which is least tenaciously bound to copper.

Experimental Section

All glassware and syringes were dried in an oven overnight at 120 °C, and glassware was flame-dried under vacuum and flushed with argon immediately prior to use. Syringes were flushed with argon and kept under positive argon pressure until use. Transfer of reagents was performed by syringes equipped with stainless steel needles. Reactions were carried out in three-necked round-bottom flasks equipped with filtration units and Teflon-coated magnetic stirring bars.

Transfer of CuCN took place in a glovebag. All alkyllithiums were freshly titrated before use.[14]

Tetrahydrofuran was freshly distilled over potassium benzophenone ketyl. Unless otherwise stated, other chemicals obtained from commerical sources were used without further purification.

Low-temperature ^{119}Sn NMR experiments were conducted on a Bruker WM-400 spectrometer with an operating frequency of 149.197 MHz. A typical set of parameters utilized a spectral width of 50 000 Hz, 8K of memory, 11 Hz/data point, an acquisition time of 0.09 s, and a 55° pulse of 35 μs. The decoupler was turned on during acquisition and off during the relaxation delay (4 s) in order to supress the negative NOE of ^{119}Sn. A line broadening of 20 Hz was applied to all spectra. Spectra were recorded in THF that contained Me_4Sn as internal reference.

Low-temperature ^{29}Si NMR experiments were conducted on a Bruker WM-400 spectrometer with an operating frequency of 79.495 MHz. A typical set of parameters utilized a spectral width of 20 000 Hz, 8K of memory, 2.44 Hz/data point, an acquisition time of 0.204 s, and a 15° pulse of 10 μs. The decoupler was turned on during acquisition and off during the relaxation delay (4 s) in order to supress the negative NOE of ^{29}Si. A line broadening of 20 Hz was applied to all spectra. Spectra were recorded in THF that contained Me_4Si as internal reference.

^{13}C NMR spectra were obtained on Varian XL-300 spectrometer with an operating frequency of 75.46 MHz. Parameters for the ^{13}C spectral acquisition typically involved a spectral width of 15 000 Hz, 32K of memory, an acquisition time of 0.4 s, and a 60° pulse of 12 μs. The spectra were recorded on THF solutions unless otherwise specified and were referenced to THF, α = 25.3 ppm, β = 67.41 ppm.

Low-temperature ^1H NMR spectra were recorded on a Varian XL-300 spectrometer in THF-d_8. The peaks are referenced to Me_4Sn (δ 0) as internal reference.

A vacuum-jacketed, glass dewar measuring 7.5 × 16.0 cm (i.d. 5.5 cm) was designed with a tapering bottom to fit in the cup of the vortex mixer. All NMR samples were stirred while cooling at the indicated temperatures in this dewar.

Preparation of (Trialkylsilyl)cuprates. ^{29}Si NMR Sample Preparations: Preparation of $PhMe_2SiLi$ in THF. Dimethylphenylsilyl chloride was stirred with small pieces of lithium in THF (20 mL) at −5 °C in an ice/salt bath as described in ref 9. (Dimethylphenylsilyl)lithium was titrated according to the procedure of Fleming et al.[1b]

Preparation of $PhMe_2SiCu(CN)Li$ and $(PhMe_2Si)_2Cu(CN)Li_2$. These homosilylcuprates were prepared in THF at the concentrations described in ref 9 in 10-mm NMR tubes, each equipped with an argon inlet. The solutions were stirred on the vortex mixer at −50 °C for 20 min before recording the NMR spectra.

Preparation of $PhMe_2Si(Me)Cu(CN)Li_2$ by Reaction of $PhMe_2SiLi$ and $MeCu(CN)Li$. CuCN (0.18 g, 2.0 mmol) was added to a 10-mm NMR tube, equipped with an argon inlet. The solution was cooled to −50 °C, and MeLi (1.4 mL, 2.0 mmol) in Et_2O was added via a syringe. The reaction mixture was stirred on the vortex mixer at −50 °C for 10 min. (Dimethylphenylsilyl)lithium (3) in THF (1.8 mL, 2.0 mmol) was added dropwise to this clear solution at −50 °C at which time it turned deep red in color. The NMR spectrum was recorded after stirring for 20 min.

Preparation of 6 by Reaction of $PhMe_2SiCu(CN)Li$ and MeLi. MeLi (1.4 mL, 2.0 mmol) was added to a solution of 4 (2.0 mmol) at −50 °C. The reaction mixture was stirred on the vortex mixer at −50 °C for 20 min. The NMR spectrum was then recorded.

Preparation of 6 by Reaction of $(PhMe_2Si)_2Cu(CN)Li_2$ and $Me_2Cu(CN)Li_2$. CuCN (0.09 g, 1.0 mmol) was added to a flask, equipped with an argon inlet. The solution was cooled to −50 °C where MeLi (1.4 mL, 2.0 mmol) was introduced dropwise to generate a clear solution of 7. After 10 min this solution was transferred via a precooled cannula into cuprate 8 (2.0 mmol),[9a] which was also maintained at below −50 °C. The resulting deep red solution was stirred for 20 min before recording the NMR spectrum.

^{13}C and ^1H NMR Sample Preparation: Preparation of CuCN·2LiCl. THF (11.0 mL) was added to a mixture of CuCN (0.98 g, 11.0 mmol) and LiCl (0.95 g, 22.0 mmol) in a round-bottomed flask under argon. A clear faint, yellow solution was obtained after 0.5 h of stirring. This solution was used as the CuCN source for all the ^{13}C and ^1H NMR sample preparations unless otherwise specified.

Preparation of 6 by Reaction of 3 and 5. CuCN in THF (0.25 mL, 0.25 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −50 °C, and MeLi (0.18 mL, 0.25 mmol) in Et_2O was added via a syringe. The reaction mixture was stirred on the vortex mixer for 10 min. Upon addition of (dimethylphenylsilyl)lithium in THF (0.3 mL, 0.25 mmol) dropwise to this clear solution at −78 °C the reaction turned deep red. The NMR spectrum were recorded after stirring for 20 min.

Preparation of 6 by Reaction of 4 and MeLi. CuCN in THF (0.25 mL, 0.25 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −70 °C and (dimethylphenylsilyl)lithium in THF (0.3 mL, 0.25 mmol) was added dropwise. The reaction mixture was stirred on the vortex mixer for 10 min. MeLi (0.18 mL, 0.25 mmol) in Et_2O was added via a syringe at −78 °C. The spectra were recorded immediately.

Preparation of 6 by Reaction of 7 and 8. CuCN in THF (0.25 mL, 0.25 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −78 °C and (dimethylphenylsilyl)lithium in THF (0.6 mL, 0.5 mmol) added dropwise. The reaction mixture was stirred on the vortex mixer for 20 min. In a separate vial, MeLi (0.36 mL, 0.5 mmol) was added to a THF solution of CuCN (0.25 mL, 0.25 mmol) at −50 °C. After 10 min of stirring, the solution of 7, precooled to −78 °C, was transferred via a cannula into cuprate 8, which was also maintained at −78 °C. The resulting deep red solution was stirred for 20 min before recording the NMR spectrum.

Preparation of (Trialkylstannyl)cuprates. ^{119}Sn NMR Sample Preparation: Preparation of Me_3SnLi. According to the procedure of Still et al.,[15] MeLi (7.15 mL, 10.0 mmol) was added dropwise at −45 °C to Me_6Sn_2 (3.27 g, 10.0 mmol) in THF (10 mL) under argon. The resulting pale yellow solution was stirred for 0.5 h and titrated according to procedure of Gilman[16] before using in the preparations of cuprates.

Preparation of $Me_3Sn(Me)Cu(CN)Li_2$ by Reaction of Me_3SnLi and $MeCu(CN)Li$. CuCN in THF (0.09 g, 1.0 mmol) was added to a 10-mm NMR tube, equipped with an argon inlet. The solution was cooled to −50 °C, and MeLi (0.71 mL, 1.0 mmol) in Et_2O was added via a syringe. The reaction mixture was stirred on a vortex mixer for 10 min. Trimethyltin lithium in THF (2.0 mL, 1.0 mmol) was added dropwise to this clear solution at −78 °C. The reaction turned clear yellow in color. The spectra were recorded immediately.

^1H and ^{13}C NMR Sample Preparation: Preparation of 10. A THF solution of Me_3SnLi (0.5 mL, 0.25 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −78 °C, and a solution of CuCN in THF (0.25 mL, 0.25 mmol) was added dropwise. The reaction mixture was stirred

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on the vortex mixer for 20 min. The spectra were recorded immediately. Inverse addition of the reagents gave similar spectral results.

Preparation of 11. A THF solution of Me_3SnLi (0.5 mL, 0.25 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −78 °C, and a solution of CuCN in THF (0.125 mL, 0.125 mmol) was added dropwise. The reaction mixture was stirred on the vortex mixer for 20 min. The spectra were recorded immediately. Similar spectral results were obtained when the order of mixing of reagents was reversed.

Preparation of 14 by Reaction of 9 and 5. CuCN in THF (0.4 mL, 0.4 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −50 °C, and MeLi (0.3 mL, 0.4 mmol) in Et_2O was added via a syringe. The reaction mixture was stirred on the vortex mixer for 10 min. Trimethyltin lithium in THF (1.0 mL, 0.4 mmol) was added dropwise to this clear solution at −78 °C. The reaction turned yellow. The spectra were recorded immediately.

Preparation of 14 by Reaction of 7 and 11. CuCN in THF (0.2 mL, 0.2 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −78 °C, and trimethyltin lithium in THF (1.0 mL, 0.4 mmol) was added dropwise. The reaction mixture was stirred on the vortex mixer for 20 min. In a separate vial, 7 (0.2 mmol, prepared as above), precooled to −78 °C, was transferred via a cannula into cuprate 11, which was also maintained at −78 °C. The resulting yellow solution was stirred for 20 min before recording the NMR spectrum.

Reaction of 15 with 7: Generation of 18. Bu_3SnH (0.13 mL, 0.5 mmol) was added dropwise at −85 °C to $Me_2Cu(CN)Li_2$ (0.5 mmol). NMR was recorded on the resulting yellow solution after stirring for 10 min.

Reaction of 15 with 7: Generation of 16. Bu_3SnH (0.13 mL, 0.5 mmol) was added dropwise at −85 °C to a solution of $Me_2Cu(CN)Li_2$ (0.25 mmol) in THF. After the evolution of H_2 subsided (5 min), NMR was recorded on the resulting yellow solution.

Preparation of $Me_3Sn(Me)_2CuLi_2$ by Reaction of 10 and MeLi. CuCN in THF (0.4 mL, 0.4 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −78 °C, and Me_3SnLi (1.0 mL, 0.4 mmol) in THF was added via a syringe. The reaction mixture was stirred on the vortex mixer for 10 min. MeLi (0.6 mL, 0.8 mmol) in Et_2O was added dropwise to this orange suspension at −78 °C. The reaction turned clear yellow in color. The spectra were recorded immediately.

Preparation of 19 by Reaction of 14 and MeLi. CuCN in THF (0.4 mL, 0.4 mmol) was added to a 5-mm NMR tube, equipped with an argon inlet. The solution was cooled to −50 °C, and MeLi (0.3 mL, 0.4 mmol) in Et_2O was added via a syringe. The reaction mixture was stirred on the vortex mixer for 10 min. Trimethyltin lithium in THF (1.0 mL, 0.4 mmol) was added dropwise to this clear solution at −78 °C. The reaction turned yellow. MeLi (0.3 mL, 0.4 mmol) in Et_2O was then added via a syringe to yield a clear yellow solution. The reaction mixture was stirred for 20 min before recording the spectra.

Typical Procedure for Reactions of $PhMe_2SiLi$/MeLi/CuCN Solutions with Cyclohex-2-en-1-one. $PhMe_2SiLi$ (1.25 mL, 1.0 mmol) was added dropwise at −70 °C to a solution of MeCu(CN)Li [1.0 mmol, prepared from the addition of MeLi in Et_2O (0.7 mL, 1.0 mmol) and CuCN (0.089 g, 1.0 mmol in THF (2 mL) at −50 °C] in THF (2 mL) under argon. The resulting deep red solution was stirred for 0.5 h after which cyclohexenone (0.08 mL, 0.82 mmol) was added via a syringe. Reactions were stirred for a further 0.5 h and then quenched with saturated NH_4Cl/10% NH_4OH. Workup involved extraction of the organic phase with Et_2O (2 × 2 mL) and washing with brine (2 × 2 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Column chromatography (4:1 hexanes–EtOAc) yielded 3-(dimethylphenylsilyl)cyclohexanone in >90% isolated yield and >95% purity as judged by gas chromatographic analysis using dodecane as an internal standard. The ^1H NMR and IR data for the 1,4-adduct matched those reported by Fleming et al.[1] for this compound: $^{13}C\{^1H\}$ ($CDCl_3$) δ 212.5 (C=O), 136.6 (ipso), 133.8, 129.2, 127.8, 42.3, 41.8, 29.7, 27.5, 26.0, −5.4 ($SiCH_3$), −5.5 ($SiCH_3$); MS *m/e* 232 (M^+); mass calcd for $C_{14}H_{20}OSi$ 232.1283, found 232.1282.

Typical Procedure for Reactions of R_3SnLi/MeLi/CuCN Solutions with Cyclohex-2-en-1-one. Me_3SnLi (2.0 mL, 1.0 mmol) was added dropwise at −78 °C to a solution of MeCu(CN)Li [1.0 mmol, generated from the reaction of MeLi in Et_2O (0.75 mL, 1.0 mmol) and CuCN (0.089 g, 1.0 mmol) in THF (2 mL)] under argon. The resulting yellow solution was stirred for 0.5 h, after which cyclohexenone (0.08 mL, 0.82 mmol) was added via a syringe. The reaction was stirred for a further 0.5 h and then quenched with saturated NH_4Cl/10% NH_4OH. Standard workup followed by column chromatography (4:1 hexanes–EtOAc) yielded 3-(trimethylstannyl)cyclohexanone in >90% isolated yield and >95% purity as judged by gas chromatographic analysis using dodecane as an internal standard. The ^1H NMR and IR data matched those reported by Still[13] for this compound: $^{13}C\{^1H\}$ ($CDCl_3$) δ 212.2 (C=O), 45.8, 42.1, 30.8, 29.4, 25.2, −11.7 ($SnCH_3$); MS *m/e* 246 (M^+ − 15); mass calcd for $C_9H_{18}OSn$ 246.1283, found 246.1282.

Typical Procedure for Silylcupration of 1-Alkynes Using R_3SiLi/MeLi/CuCN. CuCN (0.197 g, 2.2 mmol) was placed in a flask equipped with an argon inlet. The flask was repeatedly (3×) evacuated and purged with argon. THF (5 mL) was injected, the reaction was cooled to −50 °C, and MeLi in Et_2O (1.65 mL, 2.2 mmol) was added dropwise. The reaction was stirred for 0.5 h to yield a water clear solution. (Dimethylphenylsilyl)lithium in THF (2.6 mL, 2.2 mmol) was then added dropwise. The resulting deep red solution was stirred for 0.5 h after which 1-octyne (0.24 g, 2.2 mmol) was added dropwise. The reaction was stirred for additional 0.5 h and then quenched with H_2O (5 mL). The reactions were warmed gradually to room temperature. The usual workup followed by column chromatography (hexanes) yielded 92% of the vinyl silane in >97% purity as determined by gas chromatographic analysis with respect to dodecane as an internal standard: IR (NaCl) 1620, 1440, 1250, 1120, 995 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 7.1–7.5 (m, 5 H, Ph), 6.17 (dt, *J* = 18, 6 Hz, 1 H, HC=CSi), 5.85 (dt, *J* = 18, 1.5 Hz, 1 H, C=CHSi), 2.7 (tdd, *J* = 7, 6, 1.5 Hz, 2 H, allylic), 1.2–1.42 (m, 8 H, CH_2), 0.95 (t, *J* = 7 Hz, 3 H, CH_3), 0.3 (s, 6 H, $SiCH_3$); $^{13}C\{^1H\}$ ($CDCl_3$) δ 149.5 (C=CSi), 139.4 (C=CSi), 133.8 (ipso), 128.7, 127.6, 127.2, 36.8, 36.7, 31.7, 28.8, 28.6, 22.5, 13.9 ($SiCH_3$); MS *m/e* 246 (M^+); mass calcd for $C_{16}H_{26}Si$ 246.1803, found 246.1809.

Typical Procedure for Stannylcupration of 1-Alkynes Using R_3SnLi/MeLi/CuCN. Me_3SnLi (2.0 mL, 1.0 mmol) was added dropwise at −78 °C to a solution of MeCu(CN)Li [1.0 mmol, generated from the reaction of MeLi in Et_2O (0.75 mL, 1.0 mmol) and CuCN (0.089 g, 1.0 mmol) in THF (2 mL)] under argon. The resulting yellow solution was stirred for 0.5 h after which 3-butyn-1-ol (0.063 g, 0.9 mmol) was added via a syringe followed by MeOH (2.0 mL). The reaction turned immediately red in color. The reaction was stirred for a further 0.5 h and then allowed to warm to room temperature. The usual workup followed by column chromatography (hexanes–ethyl acetate, 8:1, as eluant) yielded 72% of 4-hydroxy-2-(trimethylstannyl)-1-butene and 8.0% of 4-hydroxy-1-(trimethylstannyl)-1-butene. Gas chromatographic analysis revealed a purity of >97% for both isomers. 4-Hydroxy-2-(trimethylstannyl)-1-butene: IR (NaCl) 3350 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 5.7 (d, *J* = 2 Hz, $^3J_{Sn-H}$ = 147 Hz, 1 H, HC=CSn), 5.35 (d, *J* = 2 Hz, $^3J_{Sn-H}$ = 69 Hz, 1 H, SnC=CH), 3.6 (q, 2 H, OCH_2), 2.5 (t, 2 H, allylic), 1.34 (t, 1 H, OH), 0.14 (s, $^2J_{Sn-H}$ = 54 Hz, 9 H, $SnCH_3$); MS *m/e* 219 (M^+ − 15); mass calcd for $C_6H_{13}SnO$ 219.9895, found 219.9960. 4-Hydroxy-1-(trimethylstannyl)-1-butene: IR (NaCl) 3350 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 6.1 (d, *J* = 20 Hz, $^3J_{Sn-H}$ = 32 Hz, 1 H, *H*CSn=CH), 5.9 (dt, *J* = 20, 6 Hz, $^3J_{Sn-H}$ = 60 Hz, 1 H, SnCH=C*H*), 3.7 (q, 2 H, OCH_2), 2.4 (t, 2 H, allylic), 1.36 (t, 1 H, OH), 0.10 (s, $^2J_{Sn-H}$ = 54 Hz, 9 H, $SnCH_3$); MS *m/e* 219 (M^+ − 15); mass calcd for $C_6H_{13}SnO$ 219.9895, found 219.9971.

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Registry No. 3, 3839-31-4; 4, 75583-56-1; 6, 130326-25-9; 8, 110769-32-9; 9, 17946-71-3; 10, 112083-87-1; 11, 123322-23-6; 12,

130326-23-7; **13**, 130350-27-5; **14**, 127837-47-2; **16**, 122539-76-8; **19**, 130326-24-8; **20** (M = Si, n = 6, R_3 = $PhMe_2$, X = H), 116488-00-7; **20** (M = Sn, n = 2, R = Bu, X = OH), 107399-01-9; **20** (M = Sn, n = 2, R = Me, X = OH), 76077-09-3; **21** (M = Si, n = 6, R_3 = $PhMe_2$, X = H), 87437-03-4; **21** (M = Sn, n = 2, R = Bu, X = OH), 122229-78-1; **21** (M = Sn, n = 2, R = Me, X = OH), 76077-30-0; $(PhMe_2Si)_3CuLi_2$, 122343-28-6; Me_4Sn, 594-27-4; $H(CH_2)_6C{\equiv}CH$, 629-05-0; $HO(CH_2)_2C{\equiv}CH$, 927-74-2; ^{119}Sn, 14314-35-3; ^{29}Si, 14304-87-1; MeCu(CN)Li, 41753-78-0; CuCN, 544-92-3; 2-cyclohexenone, 930-68-7; 3-(dimethylphenylsilyl)-cyclohexanone, 67262-98-0; 3-(tributylstannyl)cyclohexanone, 63831-51-6; 3-(trimethylstannyl)cyclohexanone, 63831-50-5.

Regioselective Synthesis of Imidazo[4,5-*g*]quinazoline Quinone Nucleosides and Quinazoline Amino Nucleosides. Studies of Their Xanthine Oxidase and Purine Nucleoside Phosphorylase Substrate Activity

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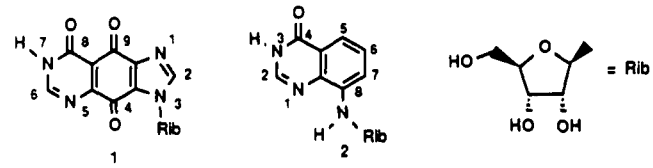
The regioselective synthesis of 3-ribofuranosylimidazo[4,5-*g*]quinazoline-4,8,9(3*H*,7*H*)-trione (**1**) (benzoquinone-stretched-out inosine) and 8-(ribofuranosylamino)quinaozlin-4(3*H*)-one (**2**) was carried out in conjunction with the design of reductive alkylating nucleosides and new purine nucleoside mimics, respectively. The preparation of **1** was carried out by regioselective ribosylation of 4-nitroimidazo[4,5-*g*]quinazolin-8(3*H*,7*H*)-one (**3**) followed by nitro group reduction, Fremy oxidation, and deacetylation. Regiocontrol of ribosylation has steric origions: the 4-nitro group of **3** directs silylation to the N(1) position, which results in ribosylation exclusively at the N(3) position under Vorbrüggen reaction conditions. Regiocontrol during the preparation of **2** was possible by generating a stabilized ribofuranosyl carbocation, which selectively reacts with the amine group of the base. Nucleoside **1** is a purine-like quinone by virtue of its oxidation by xanthine oxidase. The potential inosine mimic **2** does not undergo phosphorolysis by purine nucleoside phosphorylase (PNPase), but the base form (8-aminoquinazolin-4(3*H*)-one) does bind to the PNPase active site as tightly as hypoxanthine. Factors which contribute to this binding behavior are discussed.

Imidazo[4,5-*g*]quinazolines and quinazolines can mimic purines in a number of enzymatic systems. Leonard and co-workers[2] found that imidazo[4,5-*g*]quinazolines, and their nucleoside and nucleotide derivatives, act as substrates and cofactors for certain purine-utilizing enzymes. Work in this laboratory showed that quinone analogues of imidazo[4,5-*g*]quinazolines can be functionalized as enzyme-directed reductive alkylating agents.[3-5] Like many naturally occurring reductive alkylating agents,[6] quinone reduction is followed by leaving group elimination to afford an alkylating quinone methide species. Finally, quinazolines are substrates for the purine-utilizing enzyme xanthine oxidase,[7] and it was possible to design quinazoline-based reductive alkylating agents of this enzyme.[8]

The findings cited above have prompted investigations of nucleoside reductive alkylating agents based on imidazo[4,5-*g*]quinazolines and of purine nucleoside mimicks based on aminoquinazolines. These investigations required the efficient regioselective ribosylation of these ring systems. Described herein are the regioselective ribosylation studies which led to the synthesis of the nucleosides in Chart I and the results of enzyme binding studies with xanthine oxidase and purine nucleoside phosphorylase.

Chart I



1 2

The synthetic methodologies employed to prepare nucleoside **1** could be applied to the preparation of analogues bearing a leaving group (i.e., reductive alkylating agents). Enzymatic studies with **1** indicate it is oxidized by xanthine oxidase. Amino nucleoside **2** was designed as an inosine mimic, wherein the ribofuranosyl and fused pyrimidone groups are in nearly the same relative positions as found in the inosine. Nucleoside **2** weakly binds to the active site of purine nucleoside phosphorylase (PNPase), but it is not a substrate. The free base of **2**, 8-aminoquinazolin-4-(3*H*)-one, is a good inhibitor of PNPase, however. A mechanism is presented for PNPase binding by the free base.

Results and Discussion

Nucleoside Reductive Alkylating Agents. The strategy for preparing imidazo[4,5-*g*]quinazoline quinone nucleosides was to carry out regioselective ribosylation of **3** in Scheme I and then elaborate the quinone moiety by reduction of the nitro group and Fremy oxidation of the resulting amine. Leonard and co-workers have prepared structurally related nucleosides by mercury-catalyzed ribosylation of the imidazo[4,5-*g*]quinazoline ring[9] as well

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