4β-,5β-Diphenyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9j) was prepared from *cis*-stilbene. Purified by MPLC (Lobar A column, 5% EtOAc/hexane) to give a white solid: mp 87-88 °C (MeOH); ^{1}H NMR δ 7.06 (8 H, m), 6.88 (1 H, s), 6.86 (1 H, s), 5.73 (1 H, d, J = 9.5 Hz), 4.51 (1 H, d, J = 9.5 Hz), 1.60 (3 H, s), -0.02 (9 H, s); IR 1600, 1490, 1450, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{20}H_{24}NO_2Si$(M - CH_3) 338.1576, found 338.1575.

5β-Methyl-4β(2-propyl)-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9m) was prepared from *cis*-4-methyl-2-pentene and purified by semipreparative HPLC (3% EtOAc/hexane): ^{1}H NMR δ 3.79 (1 H, dd, J = 10.0 Hz, 2.25 Hz), 3.09 (1 H, m), 2.01 (1 H, m), 1.57 (3 H, s), 1.51 (3 H, s), 1.12 (3 H, d, J = 6.75 Hz), 1.09 (3 H, d, J = 6.75 Hz), 0.95 (3 H, d, J = 6.75 Hz), 0.16 (9 H, s); IR 1480, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{12}H_{24}NO_2Si$(M - CH_3) 242.1576, found 242.1573.

Dihydropyran cycloadducts 9n (major) and 9n′ (minor) were separated by flash chromatography (7.5% EtOAc/hexane). **9n**: ^{1}H NMR δ 5.70 (1 H, d, J = 6.87 Hz), 3.81 (1 H, m), 3.64 (1 H, m), 3.21 (1 H, q, J = 6.48 Hz), 2.21 (1 H, m), 1.93 (1 H, m), 1.68 (2 H, m), 1.60 (3 H, s), 1.52 (3 H, s), 0.16 (9 H, s); ^{13}C NMR δ 2.44, 19.7, 20.8, 29.0, 30.0, 44.3, 60.3, 73.0, 101.8, 166.9; IR (neat) 2960, 1470, 1385, 1365 cm^{-1}; MS, m/e calcd for $C_{11}H_{20}NO_3Si$(M - CH_3) 242.1212, found 242.1212. **9n′**: ^{1}H NMR δ 4.72 (1 H, d, J = 4.5 Hz), 4.08 (1 H, m), 3.74 (1 H, m), 3.40 (1 H, m), 2.30-1.40 (4 H, m), 1.59 (3 H, s), 1.53 (3 H, s), 0.14 (9 H, s); ^{13}C NMR δ 165.9, 78.63, 77.97, 72.56, 63.11, 30.12, 29.12, 21.31, 20.02, 2.42; IR (neat) 2960, 1460, 1440, 1380, 1360, 1255 cm^{-1}; MS, m/e calcd for $C_{11}H_{20}NO_3Si$(M - CH_3) 242.1212, found 242.1212.

4,5,5-Trimethyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9o) was prepared from 2-methyl-2-butene. Purified by Kugelrohr distillation [bp 90 °C (2.2 mm)]; ^{1}H NMR δ 2.92 (1 H, q, J = 7.88 Hz), 1.57 (3 H, s), 1.52 (3 H, s), 1.28 (3 H, s), 1.26 (3 H, s), 1.18 (3 H, d, J = 7.88 Hz), 0.16 (9 H, s); IR 1450, 1380, 1365 cm^{-1}; MS, m/e 228, 200, 131. Anal. calcd for ($C_{12}H_{25}NO_2Si$): C, 59.21; H, 10.35. Found: C, 58.98; H, 10.40.

3-Methylcyclopentenone adduct 9p was purified by flash chromatography (14% EtOAc/hexane): ^{1}H NMR δ 3.51 (1 H, s), 2.7-2.3 (3 H, m), 1.98 (1 H, m), 1.53 (3 H, s), 1.50 (3 H, s), 1.48 (3 H, s), 0.13 (9 H, s); IR 1730, 1600, 1440, 1400 cm^{-1}; MS, m/e calcd for $C_{12}H_{20}NO_3Si$(M - CH_3) 254.1212, found 254.1212. Anal. Calcd for ($C_{13}H_{23}NO_3Si$): C, 57.96; H, 8.60. Found: C, 58.11; H, 8.55.

3-Methylcyclohexenone adduct 9q was purified by flash chromatography (10% EtOAc/hexane) to give 32 mg (23%) of product: ^{1}H NMR δ 3.71 (1 H, d, J = 1 Hz), 2.62 (1 H, m), 2.29 (1 H, m), 2.03 (2 H, m), 1.66 (2 H, m), 1.60 (3 H, s), 1.48 (3 H, s), 1.46 (3 H, s), 0.13 (9 H, s); IR 1710, 1460, 1380, 1365 cm^{-1}; MS, m/e calcd for $C_{14}H_{25}NO_3Si(M^+)$ 283.1604, found 283.1603.

2-Methylcyclopentenone adduct (9r) was purified by flash chromatography: ^{1}H NMR δ 3.64 (1 H, dd, J = 8.00, 2.50 Hz), 2.38 (3 H, m), 2.07 (1 H, m), 1.61 (3 H, s), 1.53 (3 H, s), 1.38 (3 H, s), 0.14 (9 H, s); IR 1760, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{13}H_{23}NO_3Si(M^+)$ 269.1447, found 269.1447.

5α-Carbomethoxy-5β,4a-dimethyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9s) was purified by Kugelrohr distillation [bp 90 °C (0.2 mm)]: ^{1}H NMR δ 3.76 (3 H, s), 3.63 (1 H, q, J = 6.75 Hz), 1.56 (3 H, s), 1.51 (3 H, s), 1.47 (3 H, s), 1.25 (3 H, d, J = 6.75 Hz), 0.15 (9 H, s); IR 1725, 1440, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{12}H_{22}NO_2Si$(M - CH_3) 272.1318, found 272.1314.

4,4,5,5-Tetramethyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9t) was purified by semipreparative HPLC followed by MPLC (Lobar A column, 3% EtOAc/hexane): ^{1}H NMR δ 1.58 (6 H, s), 1.18 (6 H, s), 1.17 (6 H, s), 0.18 (9 H, s); IR 1380, 1360, 1040 cm^{-1}; MS, m/e calcd for $C_{12}H_{24}NO_2Si$(M - CH_3) 242.1576, found 242.1584.

3,4-Bis(1,1-dimethylethyl)furoxan[20] (Di-*tert*-butylfuroxan, 10). To a solution of 2,2-dimethylpropanaldoxime chloride[22] (542 mg, 4.00 mmol) in benzene (10 mL) was added triethylamine (572 μL, 4.10 mmol). The reaction mixture was refluxed for 18 h, diluted with ether, and filtered through a column of florisil. The resulting solution was concentrated under reduced pressure and the solid obtained was recrystallized from methanol to give 265 mg of **10** (67%) as a white solid, mp 68.5-69 °C: ^{1}H NMR δ 1.50 (9 H, s), 1.48 (9 H, s).

5-Methyl-5-(1-propyl)-3-(2-methylprop-2-yl)-2-isoxazoline (13b) was prepared with 2-methyl-1-pentene and purified by Kugelrohr distillation: ^{1}H NMR δ 2.69 (2 H, AB quartet), 1.7-1.25 (4 H, m), 1.32 (3 H, s), 1.18 (9 H, s), 0.93 (3 H, t, J = 7.88 Hz); IR 1450, 1360, 910 cm^{-1}; MS, m/e calcd for $C_{11}H_{21}NO$ 183.1623, found 183.1624.

4,5,5-Trimethyl-3-(2-methylprop-2-yl)-2-isoxazoline (13d) was prepared from 2-methyl-2-butene and purified by semipreparative HPLC (5% EtOAc/hexane): ^{1}H NMR δ 2.76 (1 H, q, J = 6.75 Hz), 1.29 (3 H, s), 1.25 (9 H, s), 1.24 (3 H, s), 1.13 (3 H, d, J = 6.75 Hz), IR 1450, 1375, 1355 cm^{-1}; MS, m/e calcd for $C_{10}H_{19}NO(M^+)$ 169.1467, found 169.1470. Anal. Calcd for ($C_{10}H_{19}NO$): C, 70.96; H, 11.31. Found: C, 71.09; H, 11.30.

3-Methylcyclopentenone adduct 13e was purified by flash chromatography (15% EtOAc/hexane): ^{1}H NMR δ 3.38 (1 H, s), 2.61 (1 H, m), 2.43 (2 H, m), 1.99 (1 H, m), 1.47 (3 H, s), 1.24 (9 H, s); IR 1740, 1440, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{11}H_{17}NO_2(M^+)$ 195.1259, found 195.1261.

3,4-Bis[2-[(trimethylsilyl)oxy]cyclohex-1-yl]furoxan (14) was prepared in the same manner as furoxan **7**: mp 85-86 °C (MeOH); ^{1}H NMR δ 2.45 (4 H, m), 2.02 (4 H, m), 1.72 (4 H, m), 1.40 (8 H, m), 0.11 (9 H, s), 0.56 (9 H, s); IR 1560, 1430, 1210, 1030 cm^{-1}; MS, m/e calcd for $C_{19}H_{35}N_2O_4Si_2$(M - CH_3) 411.2134, found 411.2135.

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α-Deuterium and Carbon-13 Kinetic Isotope Effects Associated with the S_N2 Displacement of Iodide and Tosylate by Lithium Organocuprates[1a]

Cong-yuan Guo,[1b] Marilyn L. Brownawell, and Joseph San Filippo, Jr.*

Contribution from the Department of Chemistry, Rutgers, the State University of New Jersey, New Brunswick, New Jersey 08903. *Received July 26, 1984*

Abstract: The secondary α-deuterium and ^{13}C isotope effects associated with the competitive methylation of two cuprates, (n-C_8H_{17})$_2$CuLi(PBu_3) and (n-C_8H_{17})$_4$CuLi$_3$(PBu_3), by CH_3X-CD_3X and $^{12,13}CH_3X$ (X = I or OTs) together with their related temperature dependences are reported.

The significance of the temperature dependence of primary hydrogen kientic isotope effects has recently received increased attention.[2] The corresponding influence on α-secondary hydrogen kinetic isotope effects is widely held to be less significant. In fact,

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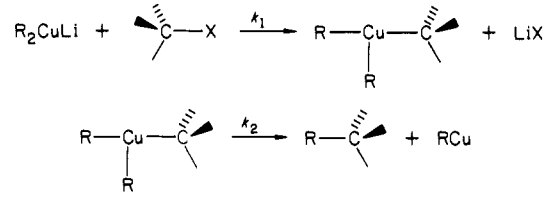
Table I. α-Deuterium and Carbon-13 KIE for Reactions of $(n\text{-}C_8H_{17})_2CuLi(n\text{-}Bu_3P)$ and $(n\text{-}C_8H_{17})_4CuLi_3(n\text{-}Bu_3P)$

reagent	solv	substrate	temp, °C	k_L/k_H[a]	A_H/A_D	$[\Delta E_a]^D_H$, cal/mol
$(n\text{-}C_8H_{17})_2CuLi(L)$	THF	$^{12}CH_3I$–$^{13}CH_3I$	−17	1.062 ± 0.003[b]	0.98 ± 0.04[c]	39
			−31	1.068 ± 0.004		
			−45	1.068 ± 0.004		
			−60	1.080 ± 0.002		
$(n\text{-}C_8H_{17})_2CuLi(L)$	THF	CH_3I–CD_3I	−16	1.111 ± 0.006	0.89 ± 0.07	104
			−48	1.113 ± 0.004		
			−63	1.164 ± 0.004		
			−81	1.188 ± 0.003		
$(n\text{-}C_8H_{17})_4CuLi_3(L)$	THF	$^{12}CH_3OTs$–$^{13}CH_3OTs$	−40	1.022 ± 0.002		
$(n\text{-}C_8H_{17})_4CuLi_3(L)$	THF	CH_3OTs–CD_3OTs	−14	1.157 ± 0.003	0.82 ± 0.03[d]	175
			−22	1.164 ± 0.007		
			−42	1.204 ± 0.004		
			−58	1.318 ± 0.005		

[a] Values for CH_3X–CD_3X systems represent k_{3H}/k_{3D}. Assuming that each isotopic center contributes an equal and additive increment to the isotopic difference in energies of activation, the value per isotopic center can be obtained by taking $^1/_3$ of this value. All reactions were carried out under pseudo-first-order conditions, employing a ≥10-fold excess of methyl iodide or tosylate. The isotopic composition of the isolated *n*-nonane was determined by high-precision, whole-molecule (cf. ref 2 and 13) mass spectrometry, employing ca. 20000 scans while monitoring the M, M + 1, M + 2, and M + 3 ions. High-precision, whole-molecule mass spectrometry was also employed to establish the ratio of the starting reagents $[CH_3X]/[CD_3X]$ and $[^{12}CH_3X]/[^{13}CH_3X]$, determined as [*n*-nonane-d_0]/[*n*-nonane-d_3] and [*n*-nonane-$^{12}C_1$]/[*n*-nonane-$^{13}C_1$] obtained from the quantitative reaction of $(n\text{-}C_8H_{17})_4CuLi_3(L)$ with CL_3X (10:1). An ionizing voltage of 70 eV and a constant source pressure of between 6×10^{-7} and 8×10^{-7} mmHg were employed. [b] These error limits were derived from a single experiment. They represent the deviation from the same KIE value which was determined by collecting the intensity data (ca. 20000 scans) in blocks of 1000 scans and subjecting the collective KIE values to standard statistical analysis. [c] These error limits represent standard deviations derived from linear regression treatment of the mean KIE values. [d] This value and its standard deviation were calculated after omitting the datum point obtained at −58 °C.

it has been concluded, based on the limited data so far available, that the temperature dependence in such instances is "normal" with all the effect in the exponential factor and the preexponential factor equal to unity.[3,4] Recognizing that previous studies have focused largely on reactions occurring over a relatively narrow temperature range involving, in general, temperatures at or above ambient, we elected to examine the influence of temperature on a system that would permit investigation over an appreciable range of subambient temperatures.

Because of the extraordinary nucleophilicity of certain organometallic complexes, an investigation employing one of these reagents seemed a fruitful avenue. A host of such reactions is known;[5] however, the alkylation of lithium organocuprates has been by far the most intensely investigated. Their reaction with alkyl tosylates and most alkyl halides is stereospecific and purported to proceed by a two-step process in which the first step involves an S_N2 displacement at carbon by copper(I) leading to an unstable copper(III) intermediate which subsequently decomposes (undergoes reductive elimination) with concomitant formation of a C–C bond and alkylcopper(I).[6] This mechanism is



consistent with (i) the observed inversion of stereochemistry at the carbon bonded to X, (ii) the observed retention of stereochemistry at the carbon bonded to copper, (iii) the observed kinetics of the reaction, and (iv) the influence of X on the relative reactivity profile, i.e., I > Br > Cl ≥ OTs. This last point is particularly significant in that it suggests that $k_1 < k_2$, i.e., that the S_N2 step is rate limiting.

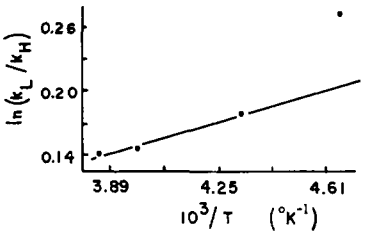


Figure 1. Plot of ln (k_L/k_H) vs. $1/T$ for reaction of $(n\text{-}C_8H_{17})_4CuLi_3(L)$ with CH_3OTs–CD_3OTs in THF (entry 4, Table I).

The need for high-precision rate determinations and the chemical nature of lithium organocuprates placed limits on the scope of our investigation. The high-precision measurements which temperature-dependent KIE studies require necessitated the use of intermolecular competition techniques. This requirement limited our investigation to pseudo-first-order reaction conditions. Under these conditions, however, the reaction of simple cuprates, i.e., $R_2CuLi(L)$, with tosylates is prohibitively slow.[6b] By comparison, the corresponding reaction using the higher cuprate $R_4CuLi_3(L)$ occurs at a reasonable rate, and for this reason, alkylation studies with methyl tosylate could reasonably be conducted with only the higher cuprate. Also, because the lower cuprate $R_2CuLi(L)$ is quite reactive toward methyl iodide, the corresponding reaction of $R_4CuLi_3(L)$ with methyl iodide was not studied because the formation of $R_2CuLi(L)$ during the course of the reaction of $R_4CuLi_3(L)$ with CH_3I would lead to ambiguity regarding the identity of the actual nucleophile.

Table I summarizes the α-deuterium secondary isotope effects as well as the carbon 13 isotope effects observed for the reaction of two lithium organocuprates, $R_2CuLi(n\text{-}Bu_3P)$ and $R_4CuLi_3(n\text{-}Bu_3P)$, with methyl iodide and tosylate, respectively (Figure 1). These data are informative in several ways. Consider, for example, the carbon isotope effect which is large (6–7%) for the methylation with methyl iodide, but significantly smaller (ca. 2%) for the related reaction with methyl tosylate. Carbon isotope effects for S_N2 reactions are expected[7,8] to be maximal when the

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bonds between the attacking nucleophile, the reacting carbon center, and the departing group are about equal. As the symmetry of this process is disrupted, the value of the carbon isotope effect decreases toward unity. The observed values (X = I) are at the higher end of the spectrum reported for carbon 13 isotope effects and are probably near the effective maximum. It seems likely, therefore, that the transition state for this process has a "symmetrical" structure. By comparison, the transition state for the similar reaction involving methyl tosylate is judged to have a significantly less symmetrical structure. We note, too, that the carbon isotope effect shows a normal temperature dependence.[4]

Finally, the magnitude of the preexponential term, A_H/A_D, does not differ significantly from unity (ca. 0.95–0.99 per deuterium), and the observed value of zero-point energy is reasonable for the zero-point-energy difference associated with the out-of-plane bending mode leading to an S_N2 transition state.

Traditionally, a spectrum of "tight–loose" character has been attributed to S_N2 transition states based on the magnitude of the α-secondary deuterium isotope effect observed for a series of reactions.[9] Unqualified extrapolation of these conclusions to the studies presented here would suggest that the abnormally large normal isotope effect that characterizes these reactions results from a very "loose" transition state, presumably as consequence of the formation of a rather long copper–carbon bond in the transition state, making the transition state more reactant-like which in turn relieves some of the steric strain associated with a "tighter" transition state. However, if consideration is given to the influence of temperature in determining the magnitude of the KIEs listed in Table I, then it becomes apparent that at ambient or higher temperatures, these nucleophilic displacements would be expected to exhibit more-or-less typical α-secondary kinetic isotope effects. These findings point out the potential importance of temperature considerations when interpreting secondary isotope effects.

The last entry in Table I deserves brief comment. It is apparent that this point falls well outside of the estimated experimental error limits. At least two explanations may be responsible for this behavior. One is that at this temperature, we are beginning to observe a mechanistic complexity, e.g., branching, that results in anomalous behavior. The other is that such anomalous behavior is a reflection of hydrogen tunneling during the C–H bending motions associated with this particular nucleophilic displacement.[10–12]

Experimental Section

General. Subambient temperature control was maintained to within ±0.1 °C by using either a Neslab RTE-8 refrigerated cooling bath or a Lauda Ultra-Kryostat Model UK-50SDW. Preparative GLPC was performed on Varian Model 80-P gas chromatographs.

Mass spectral determinations were performed on a Hewlett-Packard Model 5985 GC/MS. The isotopic composition of each isotopically enhanced product mixture [i.e., n-$C_8H_{17}CH_3$–n-$C_8H_{17}CD_3$ and n-$C_8H_{17}{}^{12}CH_3$–n-$C_8H_{17}{}^{13}CH_3$] was determined by high-precision, whole-molecule mass spectrometry[2,13] employing ca. 20000 scans while monitoring the M, M + 1, M + 2, and M + 3 ions. High-precision, whole-molecule mass spectrometry was also employed to establish the ratio of the starting reagents $[CH_3X]/[CD_3X]$ and $[{}^{12}CH_3X]/[{}^{13}CH_3X]$, determined as a mixture of [n-nonane-d_0]/[n-nonane-d_3] and [n-nonane-^{12}C]/[n-nonane-$^{13}C_1$] obtained from the reaction of 10-fold excess of $(n\text{-}C_8H_{17})_4CuLi_3(L)$ with CL_3X and $^{12,13}CH_3X$.

Preparation and Reaction of Oganometallic Reagents. All reactions involving organometallic reagents were carried out under an inert atmosphere of prepurified nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride immediately before use and was transferred under nitrogen by using hypodermic syringes or stainless steel cannulas. Dioxane was distilled from sodium benzophenone dianion.

Analyses of lithium reagents were carried out by using the Gilman double-titration procedure[14a] or by titration with a standard solution of 2-butanol in xylene with bipyridyl as an indicator.[14b]

***n*-Octyllithium.** Into a flame-dried, three-necked 500-mL flask equipped with a Teflon-coated stirrer bar, condenser, and dropping funnel was placed ~200 mL of olefin-free hexane, freshly distilled under nitrogen from a blue solution of benzophenone ketyl. Under a flush of helium, lithium dispersion (1.1% Na, 200 μm, 0.43 g-atom; Alfa-Ventron) was added. This mixture was heated at gentle reflux with efficient stirring before slowly adding 34 g (mmol) of n-octyl chloride in 50 mL of hexane over a 5-h period. Stirring and refluxing was maintained for an additional 4 h. GLPC analysis of a hydrolyzed aliquot of the reaction mixture indicated that no n-octyl chloride remained; however, there were significant quantitites of 1-octene (~10%) and n-hexadecane (~10%). Attempts to eliminate these side products by further dilution of the octyl chloride or by using a 2–3-fold excess of lithium did not appreciably alter these results.

The tri-*n*-butylphosphine complexes of copper(I) iodide were prepared as described previously.[15] Copper(I) iodide was purified by using a literature procedure.[16] Typically, solutions of lithium di-n-octylcuprate containing tri-n-butylphosphine (represented in this paper as $R_2CuLi\cdot PBu_3$) were prepared by placing $ICu\cdot PBu_3$ (0863 g, 2.20 mmol) in a flame-dried, nitrogen-flushed, 40-mL centrifuge tube. The tube was capped with a rubber septum and flushed with nitrogen before adding THF (8–10 mL) by syringe. The centrifuge tube was placed in a dry ice bath and a solution of n-octyllithium (3.85 mL, 1.17 N) in hexane injected. The contents of the vessel were thoroughly mixed before adding 0.6 mL of dioxane. The resulting mixture was shaken vigorously and the vessel transferred to a centrifuge bucket precooled to −78 °C and packed with crushed dry ice. After centrifuging, the vessel was placed in a dry ice bath, and the clear, halide-free supernatant liquid was transferred by cannula to a waiting 50-mL flask equipped with a Teflon-coated stirring bar and a sealed ampule containing a mixture (ca. 1:1) of CH_3I–CD_3I (5.743 g, ca. 40 mmol) in THF (2–3 mL). The flask was placed in a cooling bath at the desired reaction temperature and the mixture allowed to equilibrate for 15–30 min. At this point, the ampule was broken and the contents of the flask were mixed. The resulting homogeneous mixture was stirred for an appropriate time (>24 h) before adding methanolic hydrogen chloride (1 mL, 10% v/v) followed by water (6 mL). The organic layer was separated and the aqueous layer extracted 3 times with diethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated on a steam bath. The resulting mixture of n-$C_8H_{17}CH_3$ and n-$C_8H_{17}CD_3$ was isolated by preparative GLPC by using a 12-ft, 0.25-in. column of SE-30 on Chromosorb W.

An analogous procedure was used in carrying out the reactions of $R_4CuLi_3(L)$ with methyl tosylate.

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(11) The related phenomenon of hydrogen tunneling during the bending motion that accompanies the pyramidal inversion of free ammonia is, of course, well-known (cf.: Gordy, W.; Cook, R. L., "Microwave and Molecular Spectroscopy"; Wiley-Interscience: New York, 1970; pp 149–154. Bell, R. P. "The Tunnel Effect in Chemistry"; Chapman and Hall: New York, 1980; pp 150–154).

(12) Based on model vibrational-analysis calculations, Huskey and Schowen[17] reached a similar conclusion in their recent study of a hydride-transfer reaction.

(13) For additional discussion of the details related to this technique, see: Klapper, M. H., et al. *J. Am. Chem. Soc.* **1980**, *102* 1221. Caprioli, R. M.; Fies, T. F.; Story, M. S. *Anal. Chem.* **1974**, *46*, 453A. Reimschussel, W.; Peneth, P. *Org. Mass. Spectrom.* **1980**, *15*, 302.

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