

nonanal to 8-ketononanal is detected; the hydroxy aldehyde is obtained in 55% yield after purification.

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Alkoxy Stabilization and Synthetic Utility of Tetrahedral Carbanions

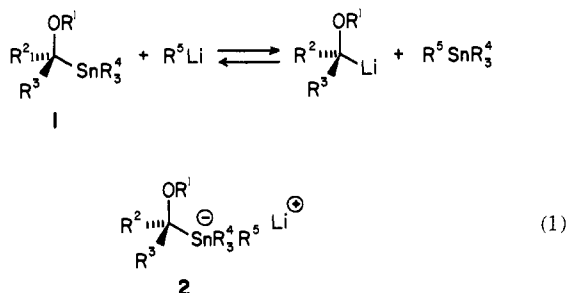
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Heteroatom-substituted carbanions have been intensively studied in efforts to understand substituent effects on carbon acidity and to exploit the broad synthetic utility of these reactive species. Enhancement of the thermodynamic and kinetic acidity of carbon acids by many second-, third-, and fourth-row elements has been well established.¹ In contrast, although calculations suggest that oxygen substitution considerably increases carbanion stability,² experimental efforts have not yet provided unambiguous documentation of this effect.^{1a,3} We report here a study supporting the considerable stabilizing influence of α -alkoxy groups upon lithium carbanions, as well as demonstration of the synthetic utility of some carbanions of this type.

A careful study of the tin-lithium exchange in eq 1 was un-



dertaken to ascertain the structural dependence of the position of this equilibrium.⁴ Low-temperature ¹H NMR spectroscopy demonstrated that exchange took place to afford discreet organolithium species, with no evidence of a stannylate complex, **2**, and was complete within 10 min at -60 °C in DME.^{5,6} By

(1) For reviews of heteroatom-substituted carbanions, see: (a) Krief, A. *Tetrahedron* **1980**, *36*, 2531. (b) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (c) Ahlbrecht, H. *Chimia* **1977**, *31*, 391. (d) Seebach, D.; Geiss, K.-H. In "New Applications of Organometallic Reagents in Organic Synthesis"; Seyferth, D., Ed.; Elsevier: Amsterdam, 1976, p 1.

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(3) (a) Cohen, T.; Matx, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900 and references therein. (b) Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*. (c) Hunter, D. H.; Lin, Y.-t.; McIntyre, A. L.; Shearing, D. J.; Zvagulis, M. *J. Am. Chem. Soc.* **1973**, *95*, 8327. (d) Shatenshtein, A. I.; Gvozdeva, H. A. *Tetrahedron* **1969**, *25*, 2749. (e) Slauch, L. H.; Bergman, E. J. *Org. Chem.* **1961**, *26*, 3158. (f) Dessy, R. E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* **1966**, *88*, 460.

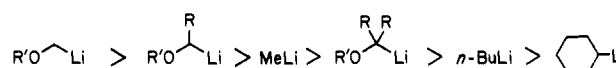
(4) For recent utility of this exchange reaction, see: (a) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5420. (b) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (c) Still, W. C. *Ibid.* **1978**, *100*, 1481. (d) For early work on this exchange process, see: Seyferth, D. *Ibid.* **1964**, *86*, 883.

Table I. Reactions of α -Alkoxy Organolithium **1** with Various Electrophiles

Electrophile:								
	EtCHO	PhCHO	Me	H ⁺ (MeOH)	MeI	Me ₂ SO	Allyl·Cl	<i>n</i> -BuI
	73%	86%	70%	88%	6, 69%	81%	5(R+H), 80%	5(R+H), 35% 6, 61%
	82%	—	—	89%	—	90%	—	—
	89% ^c	91% ^c	82%	90%	85%	—	86%	92%

^a R = SnBu₃ + BuLi → R = Li. ^b ~2:1 mixture of isomers.

examining competitive exchange reactions of several α -alkoxy tri-*n*-butyl- and trimethylstannanes with *n*-BuLi and MeLi, the following order of relative stabilities was established (R' = CH₂OMe):⁶



Since these competitive equilibration experiments completely favored a single organolithium species, as judged by ¹H NMR analysis, a minimum of 2 kcal/mol or 1.5 pK_a units separates each species in the above series. This demonstrates a substantial thermodynamic stabilizing influence of oxygen upon carbanionic centers which may be attributable to an inductive effect, an optimal orientation of the heteroatom lone pair, differences in the states of aggregation of the organolithium species, or a combination of these effects.²

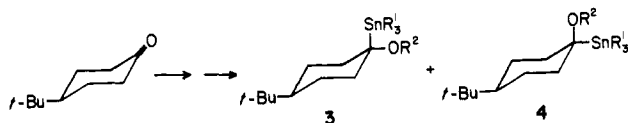
These tin-lithium exchange processes are subject to kinetic factors in addition to the above thermodynamic considerations. The rate of exchange is strongly dependent upon the solvent employed (DME > THF > Et₂O) and the steric environment about the trialkylstannyl group [Me₃Sn >> (*n*-Bu)₃Sn >> (c-C₆H₁₁)₃Sn] (c-C₆H₁₁ = cyclohexyl). In the present study, dialkylalkoxymethyl lithium species were conveniently generated only in DME. However, (phenylalkylalkoxymethyl)lithium species could be produced via tin-lithium exchange utilizing the trimethylstannyl moiety, rather than the tri-*n*-butylstannyl, in a variety of solvents (DME, THF, Et₂O). This contrasting behavior could be readily predicted through considerations of the thermodynamic stabilities of the relevant carbanions [e.g., **1** (R₂ = Me, R₃ = Ph > Me)].

Considerable utility is conferred upon these (dialkylalkoxy-methyl)lithium species by virtue of their stereospecific generation from the precursor stannane with retention of configuration and their stereospecific reaction with electrophiles with retention of configuration. This was demonstrated through a study of the α -alkoxy stannane species **3** and **4** derived from 4-*tert*-butylcyclohexanone. The ratio of axial to equatorial stannanes (**3** and

(5) Equilibration of the exchange reaction was judged complete when a stable ratio of integration values for the carbon-tin and carbon-lithium species were obtained. Integration values were reproducible to $\pm 5\%$ with a detection limit for the carbon-lithium species present (e.g., *n*-BuLi, MeLi) of at least 5% (of the theoretical amount of RLi introduced) at equilibrium. NMR data were confirmed by quantitative chromatographic and spectral analysis⁷ of the products derived from protonation of the reaction mixture.

(6) The following tetraalkyl stannanes were synthesized⁷ and analyzed for ligand exchange with methyllithium and *n*-butyllithium via low-temperature (-60 °C) NMR spectroscopy in deuterated solvents (THF, DME): Me₂Sn, *n*-BuSnMe₃, Me₃SnCH₂OMOM, Me₃SnCH(Me)OMOM, 1-Me₃Sn-(c-C₆H₁₁)-1-OMOM, 1-(*n*-Bu)₃Sn-1-(c-C₆H₁₁)-1-OMOM, *n*-Bu₃Sn-(c-C₆H₁₁) (MOM = methoxymethyl).

(7) Satisfactory spectral and analytical data was obtained for all new compounds. Compounds **5** (R = H, Me), **6** (R = H, Me, EtCHOH), and **7** (R = H, Me, *n*-Bu, allyl) were confirmed by independent synthesis.



4, $R^1 = n\text{-Bu}$ could be varied from 93:7 under thermodynamic conditions (e.g., reversible stannane addition in THF at -60°C) to 25:75 under kinetic conditions (e.g., Et_2O at -100°C). The configurations of the α -alkoxy stannanes (**3** and **4**, $R^2 = \text{CH}_2\text{OMe}$) were established by analysis of the ^{119}Sn - $\beta^{13}\text{C}$ coupling constants in each epimer⁸ and by correlation of the cyclohexyl ethers derived via protonation of the derived organolithium species with independently synthesized materials of known configuration. The reversibility of the (tri-*n*-butylstannyl)lithium addition was confirmed by subjecting the kinetic reaction mixture (**3** and **4**, $R^2 = \text{H}$) to *n*-BuLi in THF at -60°C to afford the thermodynamic ratio of products.⁹

Axial alkoxy cyclohexylstannanes (e.g., **3**) are extremely useful synthetic intermediates since carbanion generation and subsequent electrophile trapping contrasts sharply with the normal stereochemical mode of addition to cyclohexanones by carbon nucleophiles.¹⁰ This methodology provides unique entry to highly stereoselective axial substitution of cyclohexanones by relatively hindered carbon centers. Selected alkylation sequences are presented in Table I. It should be noted that the stereochemical integrity of **5** and **6** is completely maintained throughout the sequence. Also, while (arylalkylalkoxymethyl)lithium species (e.g., **7**) underwent smooth alkylation reactions in every case examined, the less stable dialkyl alkoxy lithium species appear to favor proton or hydride transfer reactions in preference to alkylation with alkyl halides. Although the reason for this behavior has yet to be defined, modification of the organometallic species in anticipation that a "softer" nucleophilic metal center might promote alkylation is currently being pursued.

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Registry No. **3** ($R^1 = n\text{-Bu}$; $R^2 = \text{MOM}$), 89726-83-0; **4** ($R^1 = n\text{-Bu}$; $R^2 = \text{MOM}$), 89746-17-8; **5** ($R = \text{CH}(\text{OH})\text{CH}_2\text{CH}_3$), 89726-84-1; **5** ($R = \text{CA}(\text{OH})\text{C}_6\text{H}_5$), 89726-85-2; **5** ($R = \text{C}(\text{CH}_3)_2\text{OH}$), 89726-86-3; **5** ($R = \text{H}$), 89726-87-4; **5** ($R = \text{CH}_3$), 89726-88-5; **6** ($R = \text{CH}(\text{OH})\text{CH}_2\text{CH}_3$), 89726-89-6; **6** ($R = \text{H}$), 89726-90-9; **6** ($R = \text{CH}_3$), 89726-91-0; **7** ($R = \text{CH}(\text{OH})\text{CH}_2\text{CH}_3$), 89726-92-1; **7** ($R = \text{CH}(\text{OH})\text{C}_6\text{H}_5$), 89726-93-2; **7** ($R = \text{C}(\text{CH}_3)_2\text{OH}$), 89726-94-3; **7** ($R = \text{CH}_3$), 24142-63-0; **7** ($R = \text{CH}_2\text{CH}=\text{CH}_2$), 89726-95-4; **7** ($R = n\text{-Bu}$), 89726-96-5; **8**, 89726-97-6; $\text{Me}_3\text{SnCH}(\text{OMOM})\text{CH}(\text{CH}_3)_2$, 89726-98-7; *n*-Bu₃SnCH(OMOM)-CH₂CH₃, 89726-99-8; Me_4Sn , 594-27-4; *n*-BuSnMe₃, 1527-99-7; $\text{Me}_3\text{SnCH}_2\text{OMOM}$, 89727-00-4; $\text{Me}_3\text{SnCH}(\text{Me})\text{OMOM}$, 89727-01-5; 1- $\text{Me}_3\text{Sn}(\text{c-C}_6\text{H}_{10})\text{OMOM}$, 89727-02-6; 1-(*n*-Bu)₃Sn(c-C₆H₁₀)OMOM, 89727-03-7; *n*-Bu₃Sn(c-C₆H₁₁), 40218-10-8; MeLi, 917-54-4; *n*-BuLi, 109-72-8; PhCHO, 100-52-7; MeCOMe, 67-64-1; H⁺(MeOH), 38684-25-2; MeI, 74-88-4; Me₂SO₄, 77-78-1; H₂C=CH-CH₂Cl, 107-05-1; *n*-BuI, 542-69-8; *n*-Bu₃SnLi, 4226-01-1; propionaldehyde, 123-38-6; 4-*tert*-butylcyclohexanone, 61203-82-5.

Supplementary Material Available: Representative experimental procedure and a listing of spectral and analytical data for selected new compounds (10 pages). Ordering information is given on any current masthead page.

(8) See the following and references therein: (a) Wickham, G.; Olszowy, H. A.; Kitching, W. *J. Org. Chem.* **1982**, *47*, 3788. (b) Kitching, W.; Olszowy, H. A.; Harvey, K. A. *Ibid.* **1982**, *47*, 1893. (c) Kitching, W.; Olszowy, H. A.; Waugh, J.; Doddrelly, D. *Ibid.* **1978**, *43*, 898.

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Novel Kinetic Profile of Zinc Ion Catalysis in Dihydroquinoline Reduction of 2-Pyridinecarbaldehyde in Aqueous Solution

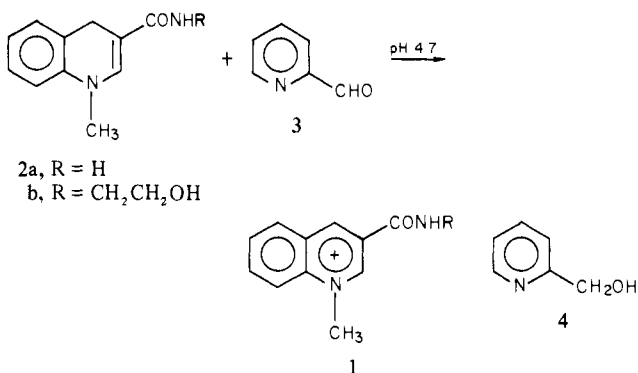
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Metal ion catalysis in the reduction of carbonyl compounds with 1,4-dihydropyridines have attracted much attention;¹ since zinc ion at the active site of alcohol dehydrogenase is suggested to play an important role in the reduction.² However, the kinetic studies on the reduction of carbonyl compounds with 1,4-dihydropyridines or related compounds reveal that the effect of metal ion on the rate is complicated, and nature or even existence of catalysis is not clear.³⁻⁶ We now wish to report the following new findings. (1) Zinc ion remarkably accelerates the reduction of 2-pyridinecarbaldehyde with dihydroquinoline derivatives in aqueous solution. (2) Kinetic complexities in catalysis disappears when the reaction is carried out under carefully deaerated, dark conditions. (3) A hydroxyl group on dihydroquinoline accelerates the rate appreciably.⁹

Two dihydroquinolines **2a** and **2b** were prepared.⁸ The reduction of 2-pyridinecarbaldehyde **3** with **2** was carried out in a carefully deaerated buffer solution¹⁰ (pH 4.7, 0.02 M AcOH-AcONa) at 50°C under Ar in the dark. At appropriate time



intervals, the decrease of absorption at 350 nm characteristic to **2** was measured. After the reduction was practically over, the reaction mixture was analyzed on HPLC (cation-exchange column, Toyo-Sotatsu, iex-230/0.02 M AcOH-AcONa pH 5.0). Formation of 2-pyridylmethanol (**4**) was confirmed by IR (3200, 1590, 1640, and 1430 cm^{-1}), electronic spectra, TLC ($\text{SiO}_2/\text{AcOEt}$), and HPLC (cation-exchange column).¹¹ The yields of **4** were

(1) (a) Creighton, D. J.; Sigman, D. S. *J. Am. Chem. Soc.* **1971**, *93*, 6314. Creighton, D. J.; Hajdu, J.; Sigman, D. S. *Ibid.* **1976**, *98*, 4619. (b) Shinkai, S.; Bruce, T. C. *Ibid.* **1972**, *94*, 8258; *Biochemistry* **1973**, *12*, 1750. (c) Shirai, M.; Chishina, T.; Tanaka, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1079.

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(3) Entirely different kinetics were reported for metal ion effect; one-half-order dependence followed by inhibition,^{4,5} zeroth-order dependence,⁶ and inhibition.⁷

(4) Gase, R. A.; Boxhoorn, G.; Pandit, U. K. *Tetrahedron Lett.* **1976**, 2889.

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(7) Shinkai, S.; Hamada, H.; Kusano, Y.; Manabe, O. *Ibid.* **1979**, *52*, 2600.

(8) Preparation of **1b** was carried out from 3-quinolinecarbonyl chloride with methyl iodide via 1-methyl-3-(chloroformyl)quinolinium iodide, followed by the treatment with ethanolamine. Reduction was performed with 1-methyl-1,4-dihydroquinoline.

(9) Tabushi, I.; Kugimiya, S.; Mizutani, T. *J. Am. Chem. Soc.* **1983**, *105*, 1658.

(10) Buffer solutions were deaerated by freeze-pump-thaw cycles before use. Sample solutions were prepared in a vacuum box filled with Ar.

(11) The product was identical with the authentic **4** on TLC and HPLC.