Stereochemistry of Metalation and Alkylation of Chiral Oxazolines. A ^{13}C Nuclear Magnetic Resonance Study of Lithio Oxazolines[1]

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Abstract: Low-temperature ^{13}C NMR spectra of lithiated chiral oxazolines **2** and **3** exhibit two isomers in ratios of 92 ± 3% Z and 8 ± 3% E. These ratios are indicative of kinetic products which do not equilibrate over the temperature range −106 to −28 °C and time ranging from 0.5 to 221 h. The studies were conveniently performed using enriched ^{13}C labeling in the lithio oxazolines. Alkylation of these lithio anions with incremental equivalents of alkyl halides indicated that the two metalated species are disappearing at the same rate supporting the contention that the high % ee of the chiral acids produced in this reaction are directly derived from the ratio of lithio anions in solution.

It has been previously demonstrated that chiral alkanoic acids **4** can be prepared in good chemical yields (65–88%) and in 60–83% enantiomeric excess (ee) from (4*S*,5*S*)-2-ethyl-4-methoxymethyl-5-phenyloxazoline (**1**) by the metalation-alkylation-hydrolysis sequence shown in Scheme I.[2] Several criteria were found to be essential for the optimization of the % ee of the acids including (a) the presence of the methoxymethyl and phenyl group in a trans-1,2 relationship,[2b] (b) the use of THF as a solvent, (c) the use of hindered nitrogen bases for metalation, and (d) alkylation temperature below −78 °C. On the other hand, metalation temperatures leading to **2** and **3** were found to be inconsequential since generating the lithio anions at all temperatures between −20 and −80 °C gave **4** in good enantiomeric excess. It was previously[2a] suggested that **2** and **3** were formed by statistical deprotonation and existed in mobile equilibrium such that alkylation of **2**, favored by fewer nonbonded interactions in the transition state, resulted in the observed chiral acid **4** containing the *S* configuration. This mechanism implied that the rate of isomerization of **3** to **2** was faster than the rate of alkylation taking place on **2**. This sequence was consistent with all the experimental data at hand, although no direct evidence was available concerning the nature and ratio of the lithio oxazolines (**2, 3**) and the relative rates of alkylation for these species. In order to support or correct this proposed mechanism, it was considered critical that these aspects of the reaction be examined.

The results of a low-temperature ^{13}C NMR study which addresses itself to these questions are now complete and cast strong doubt on the previously proposed mechanism. The current study shows that **2** and **3** are formed by deprotonation with a high degree of stereoselectivity (ca. 9:1) and remain in this kinetic ratio throughout a wide range of time and temperature. The ^{13}C NMR study was performed close to preparative conditions using the same base, solvent, temperature, and reaction times. In order to eliminate dynamic range difficulties associated with strong ^{13}C signals from large amounts of THF solvent, **1** was prepared using enriched ^{13}C in the β-methyl group. This would facilitate data accumulation and also provide strong signals for the Z- and E-methyl groups in **2** and **3**, respectively. The requisite ^{13}C-enriched oxazoline was prepared by metalation of **5**[2a,3] with LDA (THF, −78 °C) followed by treatment with 45–50% enriched [^{13}C]methyl iodide which furnished **1A** (55–66%), **6** (1–13%), and un-

(4*S*,5*S*)-**5** → **1A** + **6**
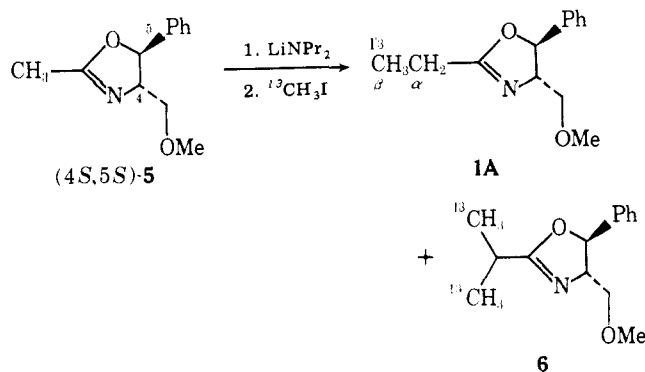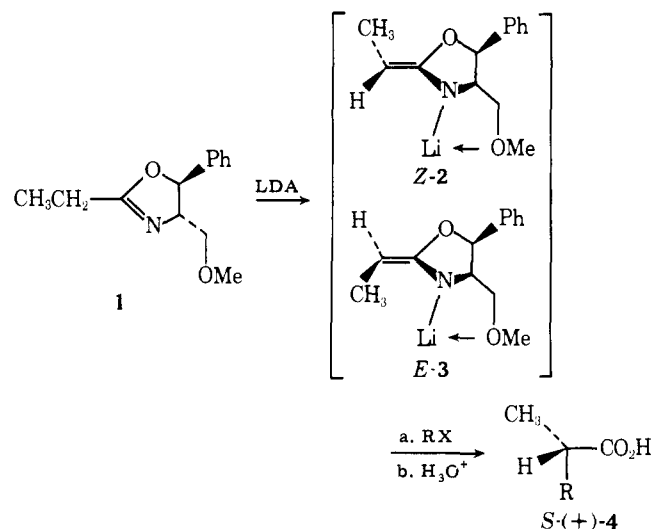
reacted starting material (30–40%). Although the three-component mixture could be separated by gas chromatography, it was not necessary, for the purpose at hand, to do so since the ^{13}C signals for the α and β carbons were sufficiently different to allow the study to proceed (Table I). Furthermore, the lack of ^{13}C-enriched carbon in **5** would preclude its interference in the signals of interest, namely, C-β in **2** and **3**.

Metalation of **1A** with hexane-free LDA in 0.5 M THF (preparative conditions) gave rise to ^{13}C-labeled **2** and **3** whose Z- and E-methyl groups were readily discernible in the spectrum (Figure 1a). Integration of these two signals, under quantitative conditions (see Experimental Section), showed that the signals at 12.1 and 12.9 ppm were in the ratio of 95:5. The sample temperature was allowed to rise and the spectrum recorded at various intervals (Table II, entries 1–3). Over this temperature range no change in the ratio of **2** to **3** occurred either in the presence or absence of NOE. That these signals were, indeed, due to the E- and Z-methyl groups was further confirmed by the off-resonance decoupled spectrum, which showed the two methyl signals at 12.1 and 12.9 ppm as quar-

Scheme I

Table I. ^{13}C NMR Chemical Shifts of Oxazolines and Lithiated Oxazolines in Tetrahydrofuran at 25 MHz[a,b]

structure	C-α	C-β	C-2	C-4	C-5	C-6	OCH₃	phenyl
1, 1A[c,d]	21.6	10.7	168.6	75.8	84.0	75.5	58.0	142.9 (i) 129.0 (o) 125.8 (m) 127.8 (p)
6[c,d]	28.5	20.0 19.8	170.9	74.6	83.0	75.2	58.8	142.5 (i) 128.7 (o) 125.1 (m) 127.7 (p)
2(3)	51.5	12.1 12.9	168.5	78.0	78.4	69.9	57.8	145.9 (i) 128.0 (o) 125.4 (m) 126.6 (p)
7		18.4 20.1						

[a] Chemical shifts (parts per million vs. Me₄Si) were recorded at 30 and −70 °C; variations on δ were less than 0.01%. [b] Concentrations were 0.5–2.0 M in THF. [c] Spectra in CDCl₃ gave chemical shifts which were within 0.05% of those observed in THF. [d] Chemical shift assignments for **1** and **6** were based on chemical shifts for similarly functionalized carbons in known compounds and by off-resonance decoupled spectra at 30 °C in THF.

tets. Aging studies at various temperatures to assess the kinetic and thermodynamic behavior of **2:3** were also performed over a wide range of time and temperature and little, if any, change was visible (Table II, entries 4–9).

It must be stated here that these spectral data are incapable of distinguishing whether the major or minor component in solution is **2** or **3**; however, the assignment of the major component to **2** is based on earlier work from this laboratory.[2b] It was shown that replacement of the topside phenyl in **1** by hydrogen results in virtually racemic acid **4**. Thus, by blocking entry of the alkyl halide from the topside of **2**, alkylation from the underside gives the observed *S* configuration of **4**. If **3** were
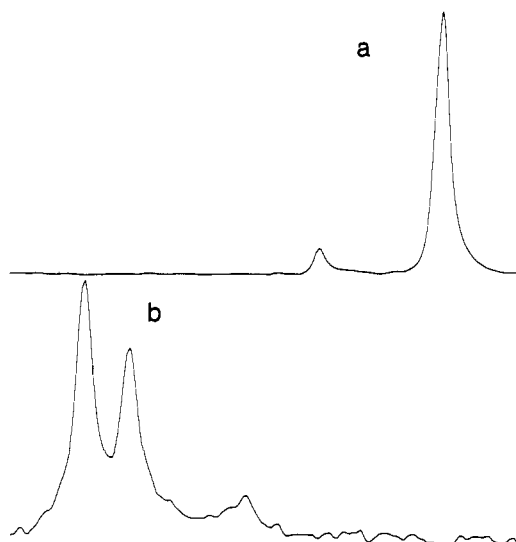
Figure 1. (a) ^{13}C NMR spectrum of Cβ in **2** and **3** at −30 °C in THF showing a minor peak at 12.9 ppm (**3**) and a major peak at 12.1 ppm (**2**). (b) ^{13}C NMR spectrum of Cβ in **2** and **3** at −78 °C in THF where metalation was performed in the presence of HMPA. The larger peak has a shift of 13.9 ppm (**2**) and the smaller peak a shift of 13.6 ppm (**3**). Both spectra were observed under conditions of gated decoupling to suppress NOE. Chemical shift assignments and experimental conditions are detailed in the text.

Table II. Lithio Oxazoline Ratios from ^{13}C NMR Spectra. Time, Aging, and Temperature Dependence

entry	post metalation time, h, of 1A[a]	aging, h[b] 2, 3	t, °C	lithio oxazolines[c] % 2 (Z)	% 3 (E)
1	0.5		−78	95	5
2	2.5		−40	95	5
3	4.0		−28	96	4
4		23.5	−106	94	6
5		27.5	−82	94	6
6		21.0	−28	88	12
7		100.0	−30	91	9
8		149.0	−60	95	5
9		221.0	−78	92	8

[a] Metalations with LDA performed at −78 °C and spectra examined after 15 min, at intervals and temperatures indicated. [b] Samples were metalated at the temperatures indicated and stored at these temperatures in NMR tubes for the intervals indicated. [c] Ratios are accurate to ±3%.

the major species in solution, then underside entry of the alkyl halide would lead to the *R* acid **4**.

The instability of the lithio oxazolines **2** and **3** above −25 °C precluded any attempts to observe their behavior and possible interconversion. Furthermore, the ^{13}C spectra were also taken of **2** and **3** generated by "kinetic" (addition of **1A** to LDA) or "thermodynamic" (addition of LDA to **1A**) conditions with no visible change in the 95:5 ratio of **2** to **3**. These spectral data were also consistent with preparative experiments leading to the chiral acid, *S*-(+)-**4**. The oxazoline **1**, metalated in either order, gave *S*-(+)-**4** in 66–68% ee.

These results indicate that, below −28 °C, there is little, if any, interconversion of the lithio oxazolines and this is in agreement with earlier observations[2a] which furnished chiral acids whose % ee was independent of the metalation temperature. The high degree of stereoselective deprotonation in **1** between −30 and −106 °C is further consistent with the results of Ireland[3] and Heathcock,[4] who reported that diastereomeric ratios of products, derived from lithio enolates, implied a high

ratio of isomeric (*E, Z*) enolates. Recently, Newcomb and Bergbreiter[5] reported a ^{1}H NMR study on lithiated dimethylhydrazones and concluded that the isomeric (*E, Z*) anions are also formed kinetically in a highly disproportionate ratio. None of these previous workers was able to observe any signs of equilibration of the *E,Z* isomers.

Both Ireland[3] and Newcomb and Bergbreiter[5] also reported that the addition of hexamethylphosphoramide (HMPA) prior to metalation of esters or dimethylhydrazones resulted in a drastic change in the *E,Z* ratios of the lithiated species. In fact, a reversal in the ratios was noted. In the present study, metalation of **1** (natural abundance) in 23% HMPA–THF gave, after alkylation, the *S*-(+) acid **4** (R = Bu) in 28% ee.[6] This amounts to a significant drop in stereoselective synthesis. On the other hand, addition of 2–3 equiv of HMPA *after* metalation gave, upon alkylation and hydrolysis, *S*-(+)-**4** (R = Bu) in 71% ee. The ^{13}C NMR spectrum of **2** and **3** (from **1A**) was examined in order to evaluate this behavior. The spectrum of ^{13}C-enriched **2** and **3**, derived from **1A** with HMPA added prior to metalation, gave a 64:36 ratio of **2** to **3** (Figure 1b). The degree of shielding for the *Z*- and *E*-methyl groups was found to be reversed, 13.9 and 13.6, respectively. In order to confirm this assignment, the sample was alkylated with butyl iodide (−78 °C) and gave, after hydrolysis, *S*-(+)-**4** (R = *n*-Bu) in 28–30% ee. This, therefore, is in good agreement with the 64:36 ratio observed in the ^{13}C NMR spectrum. With evidence of a kinetically "frozen" ratio of lithio oxazolines within the conditions examined, it was now of interest to assess the relative alkylation rates of the two isomers **2** and **3**. When an NMR sample of ^{13}C-labeled oxazoline **1A** was metalated (LDA, −78 °C, THF) and allowed to thermally equilibrate in the probe at −28 °C, the ratio of **2:3** was found to be 90:10. The solution was then treated, in increments, with methyl iodide, and the spectrum recorded 20 min after the addition of each increment of methyl iodide. The results, seen in Table III, indicate the ratio of **2:3** remaining after the addition of methyl iodide. Also present in the spectrum was the corresponding appearance of the dimethyloxazoline **6**. From the data in Table III it is clear that the ratio **2:3** remains essentially constant throughout the alkylation process. Further proof of this phenomena was gathered by isolating the products from the incremental methylations which showed (VPC) the ratios of starting material **1A** to products **6** in comparable ratios. In a parallel series of preparative experiments using *n*-butyl iodide to generate *S*-(+)-**4** (R = *n*-Bu), the % ee of the acid was virtually unchanged (64–66% ee) when 0.25, 0.50, and 1.0 equiv of *n*-butyl iodide were added at −78 °C. Thus, it may be concluded that the respective rates of alkylation on the "frozen" ratio of **2** to **3** at −28 and −78 °C are essentially the same and that the efficient asymmetric induction observed in this system is not due to selective alkylation, but instead to the high ratio of **2** over **3**. Based upon the information gathered in the ^{13}C NMR study and the collateral preparative experiments, the mechanism of the asymmetric synthesis of chiral acids **4** from chiral oxazolines **1** must be revised to include, as the critical step, the stereoselective formation of **2** and alkylation of the

latter from the underside to furnish, after hydrolysis, *S*-(+)-**4**. The earlier results,[2a,b] which exhibited a loss in asymmetric yield with higher alkylation temperature, can now be interpreted as increasing topside alkylation at higher temperatures and loss of selectivity to underside entry. To account for the high degree of stereoselective deprotonation, which appears to be temperature independent up to ca. −30 °C, it is tempting to propose a complex between the lithium ion of LDA and the methoxy group followed by deprotonation through a pseudo-six-membered transition state similar to that suggested by Ireland[3] for enolates. Thus, **8A** and **8B**, representing transition states leading to **2** and **3**, can be seen to have as their major difference the methyl group axial in **8A** and equatorial in **8B**.

3 (*E*-CH₃)   2 (*Z*-CH₃)
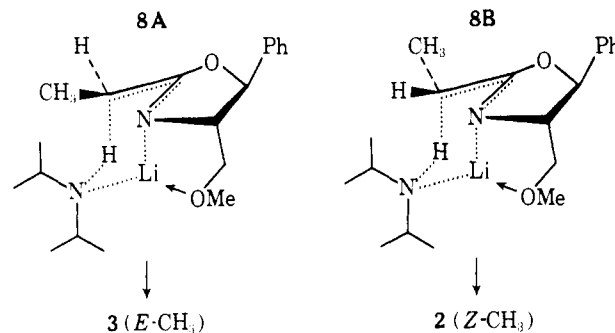
Serious 1,3 interaction would develop in **8A** between the axial methyl and the axial isopropyl groups thus making **8B** the more favorable pathway which generates the major lithio derivative **2**. This conclusion is also supported by CPK molecular models. When the metalation is performed in the presence of HMPA, this highly powerful solvating species may tend to compete in the complexation between the lithium cation and the methoxy group causing a decrease in the rigidity of the transition states **8A, 8B**. This would allow the methyl (or other R) group to rotate more freely prior to deprotonation and resulting in a decrease in the stereoselectivity of the process from 95:5 to 64:36 for **2** and **3**, respectively.

With regard to the rotational energy barrier for **2** and **3**, since equilibrium was not achieved, it is not profitable to discuss the magnitude of this barrier, although others[5,7] have assigned limits to the C=C rotation of approximately 16–18 kcal/mol. The $\Delta\delta$ of 29.9 ppm found from the ^{13}C NMR studies for C-α in **1** vs. **2** (and **3**) as well as the large degree of methyl nonequivalence observed for **7** (Table I) lend considerable support for a substantial degree of double bond character in **2** (and **3**).

Experimental Section

Oxazoline **1** was prepared as previously described,[2a] bp 77–80 °C (0.05 mm). [α]²³$_D$ −115.9° (*c* 10.5, CHCl₃). Oxazoline **5** was purchased from Aldrich Chemical Co., Milwaukee, Wis., or prepared as previously described,[2a] bp 82–90 °C (bulb to bulb) at 0.05 mm, [α]²³$_D$ −81.75° (*c* 10.3, CHCl₃). Methyl iodide (90% [13]C) was obtained from Stohler Isotope Co., Waltham, Mass., and used as received. Rotations were taken on a Perkin-Elmer 241 polarimeter and gas chromatography performed on a Hewlett-Packard 5750 instrument using 10% UCW-98 on Chromosorb W, 60–80 mesh. Diisopropylamine (Aldrich) was distilled from calcium hydride and stored over Linde 4A molecular sieves. *n*-Butyllithium (hexane) was purchased from Alfa-Ventron Co. and titrated with diphenylacetic acid[8] prior to use.

[13]**C NMR Measurements.** To assure quantitative conditions when performing pulsed Fourier transform ^{13}C NMR experiments, it is necessary to take into consideration both the spin–lattice relaxation time (T_1) and the nuclear Overhauser effect (NOE) for each resonance of interest. To this end, T_1 and NOE determinations were performed for C$_\beta$ in **2** and **3**. T_1 determinations were made at −25 and −78 °C using both the standard inversion recovery[9] and the fast inversion recovery[10] techniques. Within experimental error,[11] the relaxation times of C$_\beta$ for both **2** and **3** were identical and equal to 0.5

Table III. Incremental Alkylation of Lithio Oxazolines **2** and **3** in THF Monitored by ^{13}C NMR

MeI,[a] equiv	lithio oxazoline remaining[b]		alkylation (% **6**)
	% **2** (*Z*)	% **3** (*E*)	
0	90	10	0
0.4	88	12	39
0.8	89	11	61
1.2	89	11	95
1.8	0	0	100

[a] Methyl iodide added in THF solution to **2** and **3** at −28 °C.
[b] Ratios are ±3%.

s at −78 °C and 1.5 s at −25 °C. Similarly, the NOE for C_β of **2** and **3** was found to be identical with a value equal to the theoretical maximum of **3**.

In general, quantitative pulse Fourier transform NMR requires a delay time (τ) between excitation pulses that is $>5T_1$. In addition, suppression of any NOE by gated decoupling[12] is usually performed, but in view of the previously mentioned equality of relaxation times as well as NOE for C_β's, quantitative conditions for this system do not require a particular delay time (τ) or NOE suppression. This was verified by comparing ratios of integrated intensities obtained with and without $\tau > 5T_1$ and gated decoupling. In all cases, the ratios were identical. However, the majority of ^{13}C NMR experiments reported in this work were carried out with $\tau > 5T_1$ and using gated decoupling. Most ^{13}C NMR measurements were performed on a JEOL FX-100 operating at a frequency of 25.05 MHz. Usually, 16K data points were used with a bandwidth of 5 kHz. Samples were run in both 5- and 10-mm tubes using an external ^{2}H field frequency lock. Integrated intensities were obtained by expanding the appropriate portion of each spectrum and cutting and weighing the various peaks. The JEOL variable temperature controller was calibrated before use. Some earlier exploratory work was carried out on a highly modified Bruker HFX-90 spectrometer[13] interfaced to a Digilab FTS/NMR-3 data system.

All chemical shifts are reported as $\delta_i = (\nu_i - \nu_r)/\nu_r$ where δ_i is the chemical shift in parts per million of the ith spin isochromat, ν_i is the resonant frequency of the ith spin isochromat, and ν_r is the resonant frequency of the internal reference (Me$_4$Si). Using this convention, shifts to lower frequency are shifts to greater shielding.

(4S,5S)-^{13}C-β-2-Ethyl-4-methoxymethyl-5-phenyl-2-oxazoline (1A). A solution of lithium diisopropylamide (7 mmol) in THF (5 mL) was cooled to −78 °C and treated dropwise with a solution of **5** (1.43 g, 7 mmol) in 20 mL of THF over 20 min, and stirred at −78 °C for 1 h during which time the anion appeared as a suspension. To this mixture was added [^{13}C]methyl iodide 90% enriched^{13}C, 4 mmol). To obtain complete alkylation, natural abundance methyl iodide was added (4 mmol) at −78 °C and the mixture became homogeneous almost immediately. Stirring at −78 °C was continued for 6 h and then the mixture was allowed to warm to ambient. The reaction mixture was poured into 50 mL of ice-brine solution and extracted (3 × 100 mL) with ether, and the extracts were dried (Na$_2$SO$_4$), concentrated, and distilled, bulb to bulb, 85 °C (0.03 mm), to give 1.54 g of clear, colorless oil. VPC analysis indicated that the product contained 57% **1A**, 40% **5**, and 3% **6**. This mixture, of which only **1A** and **6** contained ^{13}C-enriched carbon, was utilized in the ^{13}C NMR study.

^{13}C Lithio Oxazolines 2 and 3. A solution of LDA (6.3 mmol) was prepared from equivalent amounts of butyllithium and diisopropylamine in THF at 0 °C. The THF and hexanes were then evaporated from the flask under vacuum until the LDA was a dry powder. To the LDA was added fresh anhydrous THF (5 mL) and the solution evaporated in vacuo to dryness leaving LDA again as a powder. The LDA was redissolved in THF (5 mL) and the solution cooled to −78 °C and **1A** (1.29 g, 6 mmol) in 5 mL of THF was added dropwise over 15 min. The reaction mixture was then cooled to −98 °C and aliquots (∼2 mL) were transferred via a cannula to precooled 10-mm NMR

tubes capped with a rubber septum. These various solutions were then examined at the intervals and temperatures given in Table II.

^{13}C Lithio Oxazolines 2 and 3 in HMPA–THF and Alkylation. A solution of LDA (5 mmol) in THF (10 mL) was prepared at room temperature and twice evaporated under vacuum to remove all hexanes. The LDA was redissolved in THF (5 mL) and HMPA (2.9 g, 16 mmol) and the solution cooled to −78 °C. A solution of **1A** (0.8 g, 3.8 mmol) in 5 mL of THF was added dropwise over 5 min and the solution stirred at −78 °C for 15 min. An aliquot (0.5 mL) of the anion solution was transferred via cannula to a 5-mm NMR tube which had been precooled to −78 °C. Me$_4$Si was added, and the ^{13}C NMR spectrum was recorded (Figure 1). The remaining solution was treated, at −78 °C, with 5 mmol of n-butyl iodide over a 5-min period and stirring continued for 1 h. The reaction mixture was quenched at −78 °C with 2 mL of 2-propanol and then poured into ice-brine, extracted with ether, dried, and concentrated to give an orange oil. Without further purification, the alkylated oxazoline was hydrolyzed in 6 M hydrochloric acid (50 mL) at reflux for 4 h. After cooling, the aqueous solution was extracted with ether, dried, and concentrated to give the crude 2-methylhexanoic acid. Distillation (bp 70–85 °C, 0.1 mm) gave ca. 200 mg of a colorless oil which was 80% 2-methylhexanoic acid and 20% 2,2-dimethylhexanoic acid, $[\alpha]^{23}_D$ +4.19° (c 7, CHCl$_3$), 24% ee. Correction for 80% purity^{2a} gave 2-methylhexanoic acid in 28% ee. $[\alpha]^{23}_D$ +5.24°.

References and Notes

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(14) After this manuscript was submitted, we learned that Bergbreiter and Newcomb had performed, independently, a similar study on the deprotonation of oxazolines. We thank these authors for their willingness to allow both studies to appear simultaneously; M. A. Hoobler, D. E. Bergbreiter, and M. Newcomb, *J. Am. Chem. Soc.*, preceding paper in this issue.