Origins of Stereoselectivity in Asymmetric Syntheses Using Chiral Oxazolines

M. A. Hoobler,[1] David E. Bergbreiter,* and Martin Newcomb*

Contribution from the Department of Chemistry, Texas A&M University, College Station, Texas 77843. Received May 15, 1978

Abstract: The structures of chiral oxazoline lithio anions enriched in ^{13}C have been studied by ^{13}C NMR spectroscopy. No rotation about the carbon–carbon bond in the lithio azaallyl anion (**5**) from (4*S*,5*S*)-2-(1-methylethyl)-4-methoxymethyl-5-phenyl-2-oxazoline was observed in 2 h at −50 °C. The ratio of the *E* (**2**) and *Z* (**3**) isomers formed by deprotonation of (4*S*,5*S*)-2-ethyl-4-methoxymethyl-5-phenyl-2-oxazoline varied as a function of the base used for deprotonation (base-solvent, 2:3; lithium diisopropylamide-tetrahydrofuran, 96:4; lithium diisopropylamide-dimethoxyethane, 96:4; *n*-butyllithium–tetrahydrofuran, 69:31; lithium diisopropylamide-hexamethylphosphoric triamide-tetrahydrofuran, 67:33; lithium diphenylamide-tetrahydrofuran, 80:20). Asymmetric syntheses employing chiral oxazoline lithio anions are discussed in terms of the stereoselectivity of the deprotonation reaction as well as that of the alkylation reaction.

Asymmetric syntheses of carbon–carbon bonds are of considerable importance to synthetic organic chemistry.[2] In recent years, significant progress has been made toward this objective through the use of chiral enamines[3] and lithio anions derived by lithium diisopropylamide deprotonation of chiral hydrazones,[4] chiral imines,[5] chiral imino esters,[6] and chiral oxazolines[7] which act as nucleophiles in reactions with electrophilic alkyl halides. This report describes and clarifies the factors underlying successful asymmetric syntheses using nucleophilic lithio anions formed by lithium diisopropylamide deprotonation of chiral oxazolines. The results detailed below show that this asymmetric synthesis and by analogy other asymmetric syntheses employing intermediate nonequilibrating lithio anions proceed first by stereoselective deprotonation leading to configurationally stable lithio anions followed by a stereoselective electrophilic attack on one diastereotopic face of these chiral nucleophiles by an alkyl halide.

Results and Discussion

A reaction scheme and mechanism for asymmetric syntheses using chiral oxazoline lithio anions based on that proposed by Meyers[7a,d] is shown in Scheme I. In Meyers' mechanism the overall stereoselectivity of this asymmetric synthesis was ascribed to different rates of stereospecific alkylation of lithio anions **2** and **3** which were claimed to be in rapid equilibrium. An alternative explanation is that the deprotonation step is essentially stereospecific and leads to almost entirely lithio anion **2** or **3** which does not equilibrate.[8] A subsequent stereoselective alkylation of these lithio anions would then explain the observed asymmetric synthesis. Our first studies showed that oxazoline lithio anions do not rapidly equilibrate.
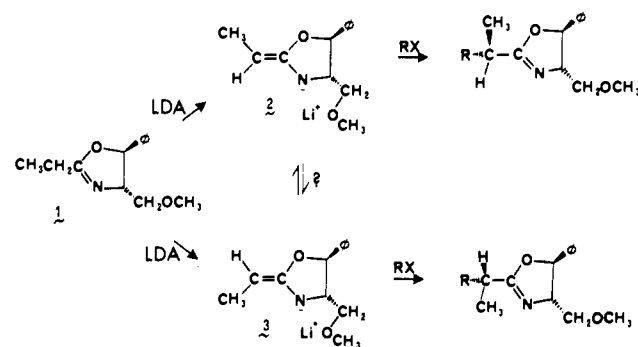
Dimethyloxazoline **4** labeled with $^{13}CH_3$ was prepared according to eq 1. Product **4** was ca. 35% enriched in ^{13}C and was

Scheme I
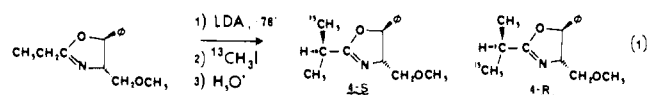
a diastereomeric mixture by virtue of isotopic substitution.[9] However, spectral examination of this oxazoline by ^1H decoupled 50.2-MHz ^{13}C NMR failed to show any difference between the diastereomeric methyl groups of **4**. By analogy to Meyers' results[7a] in other alkylations at −78 °C, we presume that the major diastereomer formed in this syntheses is **4**-*S* with *S* configuration at the new chiral carbon as shown in eq 1. Although the percent asymmetric synthesis in preparation of this isotopically substituted oxazoline was not directly measurable, a lower limit of 50% is reasonable.

When these $^{13}CH_3$-labeled dimethyloxazolines were de-

protonated and the resulting dimethyloxazoline lithio anions examined by ^1H decoupled 25.1-MHz ^{13}C NMR, two upfield methyl peaks corresponding to the labeled methyl groups of lithio anions **5** and **6** were observed at δ 17.6 and 19.4 in a ratio of 64:36 (Figure 1a). The nonequivalence and unchanging nature of the labeled methyl peaks in this NMR spectrum at −50 °C for over 2 h indicate that rapid rotation was not occurring and rotation is slower than alkylation of similar species. At higher temperatures, these lithio anion solutions decomposed as reported previously.[7]

The ^{13}C NMR of lithio anions **5** and **6** shows a preponderance of one isomer. We have assigned structure **5** to this major isomer. This assignment is based on the assumption that the diastereomeric mixture of oxazolines leading to **5** and **6** was predominantly *S* at the α carbon as shown in eq 1 and 2. If deprotonation then occurs mainly from the -CH_2OCH_3 side of the oxazoline as shown in eq 2, **5** would be the major product
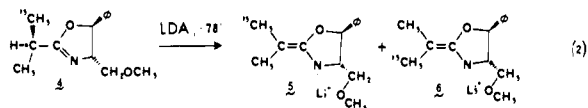
and the upfield peak in Figure 1a would be due to the methyl group trans to the nitrogen.[10] These assignments correlate with our other results described below and are in agreement with arguments presented by Meyers for electrophilic substitution of similar lithio anions. However, it should be noted that the alternative of topside deprotonation cannot be rigorously excluded by our data. Indeed, the stereoselectivity of 36% observed for formation of the disubstituted oxazoline lithio anions **5** and **6** from **4** is lower than the ca. 50% asymmetric synthesis expected in preparation of the neutral oxazoline **4**. This suggests that some topside deprotonation does occur.
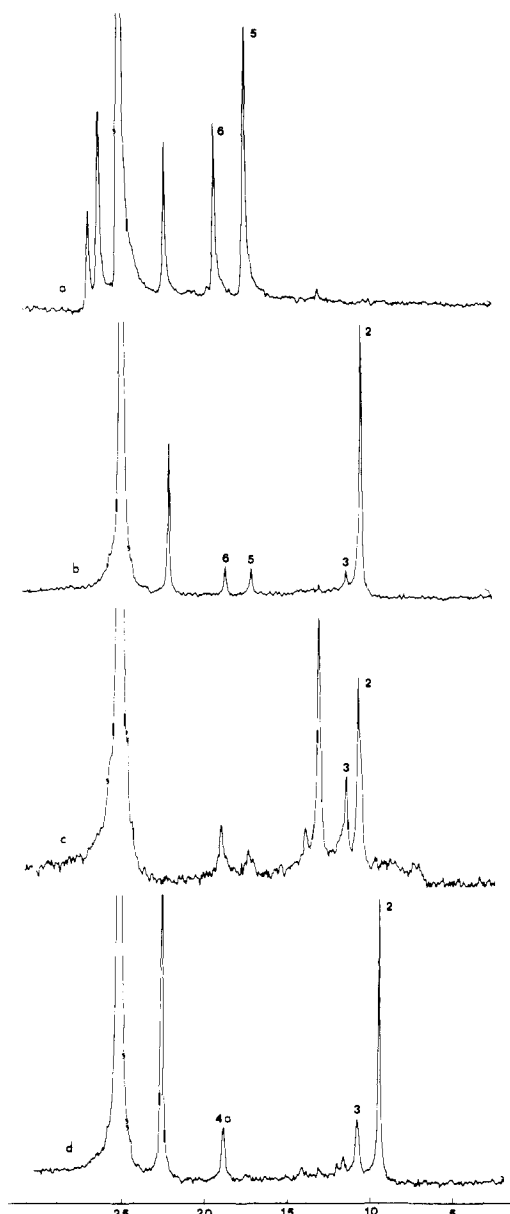
Figure 1. ^1H decoupled ^{13}C NMR spectra of oxazoline lithio anions in THF at -50 ± 4 °C. (a) Spectrum of lithio anions **5** and **6** prepared by LDA deprotonation of **4**. Additional peaks in the spectrum at δ 22.3, 26.2, and 26.8 are due respectively to diisopropylamine, lithium diisopropylamide, and oxazoline containing three methyl groups, two of which are labeled with ^{13}C. The large peak at δ 25.0 is due to the β-THF carbons. (b) Spectrum of lithio anions **2** and **3** prepared by LDA deprotonation of a mixture of **1** and **4a**. In addition to diisopropylamine, small peaks at δ 18.8 and 17.4 are present from deprotonation of **4a**. (c) Spectrum of lithio anions **2** and **3** prepared by deprotonation of a mixture of **1** and **4a** with *n*-butyllithium in THF. The tall peak at δ 13.3 and the other small peaks between δ 13.0 and 25.0 are due to excess base which is partially overlapping peaks due to the dimethyloxazoline lithio anion from deprotonation of **4a**. (d) Spectrum of lithio anions **2** and **3** prepared by lithium diphenylamide deprotonation of a mixture of **1** and **1a**. The peak at δ 22.6 is due to diisopropylamine and the peak at δ 18.8 is due to **4a**.

In order to examine the mechanism proposed by Meyers in Scheme I, we also prepared labeled oxazoline **1** as shown in eq 3. This preparation yielded oxazoline **1** contaminated by a
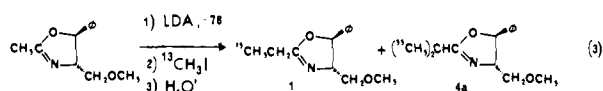
small amount of the dimethyloxazoline **4a** (ca. 5–10%) which was a mixture of mono- and dilabeled material. On depro-
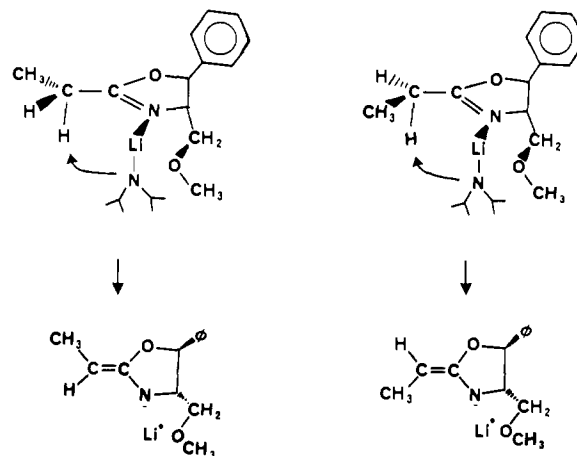

Figure 2. Possible transition states for deprotonation of oxazoline by LDA with σ coordination of LDA to the oxazoline. π coordination of LDA to the oxazoline is shown in Figure 3.
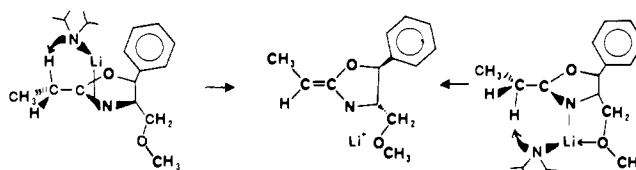

Figure 3. Topside and bottomside deprotonation via a closed transition state leads to the same stereochemical result. Only π coordination of base to the oxazoline is shown.

tonation of this mixture of **1** and **4a** below -40 °C in THF with LDA we obtained a solution of lithio anions which gave the ^{13}C NMR spectrum of Figure 1b. In addition to a small equal intensity doublet for lithio anions **5** and **6** at δ 17.4 and 18.8, respectively, a large peak assigned to lithio anion **2** was observed at δ 10.9. The small peak at δ 11.7 was assigned to lithio anion **3**. These assignments of stereochemistry are consistent with subsequent electrophilic attack by an alkyl halide predominantly from the bottomside of this lithio anion to give the *S* configuration at the new chiral carbon observed by Meyers.[7] The relative chemical shifts of the methyl groups in anions **2** and **3** are in accord with arguments above for the anions **5** and **6**.[10] These assignments are further consistent with the general observation that deprotonation of monosubstituted carbonyl compounds or derivatives with lithium diisopropylamide in THF produces lithio anion solutions in which the predominant geometrical isomer is the isomer in which the substituent is trans to the former sp²-hybridized heteroatom.[11] This general observation can be rationalized by a six-membered transition state in which lithium coordinates in either a π fashion to a heteroatom or a σ fashion to the lone pair of a heteroatom (Figure 2). In either case, an alkyl group would prefer a pseudoequatorial position in these transition states for steric reasons. Similar arguments have been presented previously by Ireland for the stereoselectivity observed in ester enolate formation by LDA/THF.[11] It should be noted that in a closed transition state like that shown in Figure 2, either topside or bottomside deprotonation yields the same stereochemical result (Figure 3).

Solvation is known to have a dramatic effect in deprotonations of esters, ketones, dimethylhydrazones, and chiral aldehyde hydrazones.[11] When a mixture of **1** and **4a** was deprotonated with lithium diisopropylamide in dimethoxyethane, the same mixture of **2** and **3** was observed as was seen in LDA/THF deprotonation. Addition of 2 equiv of hexamethylphosphoric triamide (HMPA) per lithium ion had a more dramatic effect. In this latter case, we observed two peaks

at δ 12.7 and 12.2 (ratio 2:1). In this case the downfield peak was larger but alkylation with 1-iodobutane and hydrolysis of the product oxazoline gave (*S*)-2-methylhexanoic acid (30% ee, vide infra),[12] which is the product obtained by alkylation of the lithio anion mixture formed by deprotonation of **1** by LDA.[7a] Although a reversal of the deprotonation stereoselectivity *and* a reversal of the predominant direction of electrophilic attack could be occurring in this reaction in the presence of HMPA, a simpler explanation of our data would be that HMPA addition is simply not as effective in changing oxazoline deprotonation stereoselectivity as it is in changing deprotonation stereoselectivity in other systems.

The observation of substantial stereoselectivity in deprotonation of oxazoline **1** and of slow carbon–carbon bond rotation in lithio anions **5–6** and **2–3** relative to electrophilic substitution (vide supra) established that the overall stereoselectivity in asymmetric syntheses using oxazoline anions is dependent on both the chiral barrier in the alkylation step *and* the stereoselectivity of the deprotonation step. This premise is further supported by the deprotonation experiments using other bases. Meyers had previously reported that replacement of lithium diisopropylamide with *n*-butyllithium leads to lower overall stereoselectivity in these asymmetric syntheses.[7] According to our results, this corresponds to a lower stereoselectivity in the deprotonation step and a similar stereoselectivity in the alkylation step. The ^{13}C NMR spectrum (Figure 1c) of a lithio anion mixture prepared by deprotonation of **1** with excess *n*-butyllithium supports this explanation since it clearly shows that the ratio of **2:3** is lower.

Assuming that the relative intensities of the methyl signals from **2** and **3** in the ^{1}H decoupled ^{13}C spectra are accurate measures of the relative lithio anion populations, then deprotonation of **1** with lithium diisopropylamide occurred with a stereoselectivity of 96:4 to give predominantly **2**. Qualitative evidence from ^{13}C NMR spectra of **5** and **6** support the assumption that Overhauser effects and T_1 values are nearly equal for the labeled methyl groups of **2** and **3**. Specifically, we observed an equal intensity doublet for the labeled methyl groups of the dimethyllithio anion derived from oxazoline **4a**. Statistically **4a** consists of an equal population of two mono-[13]CH$_3$-labeled diastereomeric oxazolines (in the absence of an unusually large ^{13}C/^{12}C isotope effect) and a small amount of di-[13]CH$_3$-labeled oxazoline. This mixture of mono- and dilabeled oxazolines would give equal amounts of **5** and **6** on deprotonation. The experimental observation of equal peak intensities for **5** and **6** after deprotonation of this oxazoline mixture at −78 °C therefore requires similar T_1 and Overhauser effects for the [13]CH$_3$ groups of **5** and **6**. Another assumption, that the stereoselectivities in the alkylations of **2** and **3** with 1-iodobutane at −78 °C are identical, leads to the conclusion that alkylation of this 96:4 mixture of **2** and **3** occurred with a 6:1 stereoselectivity to give 66% optically pure (*S*)-2-methylhexanoic acid after hydrolysis as observed by Meyers.[7a] Using the above assumptions and the 6:1 stereoselectivity in alkylation, one estimates that the mixture of **2** and **3** produced by deprotonation with *n*-butyllithium (2/3 = 69/31) would produce after alkylation at −78 °C and hydrolysis 28% optically pure (*S*) acid in excellent agreement with Meyers' observed 28% optically pure (*S*) acid obtained experimentally after aging the mixture for 20 h at −30 °C.[7a] Similarly, the mixture of **2** and **3** formed by deprotonation of **1** by LDA in the presence of HMPA would be expected to yield, upon alkylation with 1-iodobutane at −78 °C followed by hydrolysis, 25% optically pure (*S*) acid. In agreement with this prediction we obtained 30% optically pure (*S*)-2-methylhexanoic acid. This agreement between the predicted and observed optical purity supports our assignments of chemical shifts in the spectrum of **2** and **3** formed in the presence of HMPA. We infer from the alkylation results that, although

changes in the base may have dramatic effects in the stereoselectivity of the deprotonation step, changes in solvation of the intermediate lithio anions have little effect on alkylation stereoselectivity.

When the mixture of **1** and **4a** was treated with lithium diphenylamide (from LDA and diphenylamine) in THF, the spectrum[8] shown in Figure 1d was obtained. Under these conditions **4a** was not deprotonated, but **1** was deprotonated to give a mixture of **2** and **3** wherein the methyl peaks of each occur in the ratio of 80:20, respectively, in the ^{1}H decoupled ^{13}C NMR spectrum. Since diphenylamine is substantially more acidic than diisopropylamine and since **4a** was not deprotonated, this reaction probably gave a mixture of **2** and **3** equilibrated by a protonation–deprotonation process. Previous results obtained by Whitesides et al.[11] in preparation of aldehyde enolates from 3,3-dimethylbutanal and lithium diphenylamide could also be rationalized by equilibration catalyzed by weakly acidic diphenylamine.

Conclusions

The results described above have implications for other systems besides oxazoline lithio anions. Since the overall stereoselectivity in reactions of this general type depends on the stereoselectivity in both the deprotonation and electrophilic substitution steps, attempted mechanistic studies in which the steric demands of the substituents on a chiral anion are changed but no measure of the stereoselectivity in the deprotonation step is obtained are meaningless.

It is clear that much previous work has been directed toward control of this electrophilic substitution stereoselectivity.[3-7] A new emphasis on the understanding and control of the initial deprotonation step of these two-step asymmetric syntheses is now warranted. Our current research is directed toward realization of this goal and the possibility of combining diastereoselective deprotonation reactions with stereoselective electrophilic substitution in order to synthesize two different enantiomers from a single chiral precursor.

Experimental Section

General Methods. All reactions of air- and water-sensitive organometallic reagents were carried out in flame-dried glassware under nitrogen atmospheres using standard techniques.[13] Nitrogen was dried by passage through a drying tower of calcium chloride. Tetrahydrofuran and other ethereal solvents were distilled from a purple solution or suspension of disodium benzophenone dianion prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from sodium at reduced pressure. Polarimetry was accomplished using a Perkin-Elmer Model 141 polarimeter and a quartz sample cell (path length 10 mm, 0.1 mL). ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded using a JEOL FT-100 spectrometer. Probe temperatures in the ^{13}C NMR experiments were measured periodically with a Leeds and Northrup Numatron Model 913 and varied by less than 1 °C. IR spectra were taken using sodium chloride plates or sodium chloride cells on a Beckman IR-8 spectrometer. All organic chemicals were purchased from Aldrich Chemical Co. or other commercial sources in reagent quality and were used as supplied.

Preparation of ^{13}C-Labeled Oxazoline. ^{13}C-Labeled 4. (4*S*,5*S*)-2-Ethyl-4-methoxymethyl-5-phenyl-2-oxazoline (unlabeled **1**) was prepared by the method of Meyers, Knaus, Kamata, and Ford.[7a] A solution of 11 mmol of LDA (from *n*-butyllithium and diisopropylamine) in 18 mL of THF–hexane under nitrogen was cooled to −78 °C. To this solution was added 2.19 g (10 mmol) of unlabeled **1** in 20 mL of THF. The reaction mixture was stirred for 1 h at −78 °C, and 15.3 mL of a 0.78 M solution of ca. 35% ^{13}C-enriched iodomethane in THF was added dropwise. The reaction mixture was allowed to warm to 25 °C and was stirred for 12 h. The mixture was poured into saturated sodium chloride solution and diluted with ether. The ethereal phase was dried (MgSO$_4$) and concentrated in vacuo to give a residue which contained labeled **4** by ^{1}H NMR. GC analysis (6 ft × ⅛ in., 3% Carbowax 20M) showed that the residue contained **4** and (4*S*,5*S*)-2-(1,1-dimethylethyl)-4-methoxymethyl-5-phenyl-2-oxazoline in a

ratio of 9:1. The ^{1}H decoupled ^{13}C NMR spectrum of this product contained only peaks consistent with enriched **4** and the trimethyloxazoline impurity. This mixture was used without further purification.

^{13}C-Labeled 1. In a similar manner (4*S*,5*S*)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline[7a] was deprotonated at −78 °C with LDA in THF and subsequently treated with 35% ^{13}C-enriched iodomethane. GC analysis of the crude product showed the desired labeled **1** and dilabeled **4a** in a 15:1 ratio. The ^{1}H decoupled ^{13}C NMR spectrum of this crude product showed only peaks consistent with labeled **1** and dilabeled **4a**. This mixture was used without further purification.

In each case, the observed ^{13}C NMR spectra and GC retention times matched those of the pure, unlabeled oxazolines prepared by the method of Meyers.[7a]

Samples for ^{13}C NMR spectra were made in the following manner. Solvents were distilled from a solution of base (LDA or *n*-butyllithium) in an all-glass vacuum system. Pure solvents (THF or DME) and the appropriate additives (HMPA, diphenylamine) were than added to the residues to give base solutions which showed only small ^{13}C NMR signals in the region δ 0–20. Solutions of the base were added to the oxazolines in tubes at −78 °C, and the mixtures were subsequently stirred (vortex stirrer) and allowed to warm to ca. −40 °C. The ^{1}H decoupled ^{13}C NMR spectra were recorded on a JEOL ^{13}C NMR (25.1 MHz) at ca. −50 °C using an external CDCl₃ lock signal. Chemical shifts are reported in δ values relative to the β-THF signal which we define as δ 25.0. This β-THF signal exhibited small shifts relative to external Me₄Si (in CDCl₃) as a function of the base identity and concentration. Meyers[12] reports chemical shifts relative to *internal* Me₄Si which are about 0.9 δ units smaller than ours. ^{13}C NMR spectra were identical in different runs with substrate concentrations from 0.1 to 0.5 M.

(*S*)-2-Methylhexanoic acid was obtained from alkylation of the anion of **1** formed by deprotonation with LDA in the presence of HMPA. The base solution was prepared by generating 22 mmol of LDA in 35 mL of THF-hexane at −78 °C, stirring for 1 h, and adding 7.7 mL (44 mmol) of HMPA. This solution was then added dropwise to a solution of 4.3 g (20 mmol) of unlabeled oxazoline **1** in 40 mL of THF at −78 °C. The resulting orange solution was stirred at −78 °C for 2 h and a solution of 2.7 mL (24 mmol) of 1-iodobutane in 8 mL of THF was added dropwise. The mixture was allowed to warm to 25 °C and was stirred for 12 h. After workup as described above, the crude product was purified by bulb to bulb distillation (bp ca. 150 °C, 2.5 Torr). The distillate was treated with 4 N sulfuric acid as described by Meyers[7a] to give 2-methylhexanoic acid which was purified by bulb to bulb distillation and had $[\alpha]^{25}{}_D$ 5.6° (neat).

Acknowledgment.

References and Notes

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(8) Meyers had considered this possibility but dismissed it because the deprotonation temperature had no significant effect on the observed asymmetric synthesis.[7a]
(9) It is interesting to note that hydrolysis of this oxazoline would produce isobutyric acid which is chiral by virtue of isotopic carbon substitution.
(10) In the absence of extensive data for chemical shifts in lithio anions like **2**, **3**, **5**, and **6**, we believe that chemical reasoning is the best approach for assignments of stereochemistry in these lithio anion spectra. If our stereochemical assignments are wrong, alkylation and deprotonation would have to be occurring from the topside of these oxazolines (see equations). It should be noted that in one reported oxazoline anion alkylation topside attack by the electrophile may be occurring (ref 7e). If the stereoselectivity of the deprotonation in Hansen's oxazoline is similar to those we have observed, then his observed overall stereoselectivity is explained by preferential topside alkylation. Details of this reaction sequence could be obtained by studies similar to those described in this report.
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