Chiral Dipole-Stabilized Anions: Experiment and Theory in Benzylic and Allylic Systems. Stereoselective Deprotonations, Pyramidal Inversions, and Stereoselective Alkylations of Lithiated (Tetrahydroisoquinolyl)oxazolines

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Abstract: The stereoselective alkylation of chiral (tetrahydroisoquinolyl)oxazolines has been investigated. We report the details of this investigation, including an examination of the effect of both temperature and oxazoline substituent structure on the alkylation diastereoselectivity, a comparison of monodentate vs bidentate chelation of the organolithium, an evaluation of the effect of solvent and chelating solvent additives, the regiochemistry of alkylation of (3,4-dehydropiperidino)oxazolines, lithiation–alkylation experiments on stereoselectively deuterated monodentate and bidentate isoquinolinolyloxazolines, and semiempirical molecular orbital calculations on the organolithium diastereomers **13a,b**. There are two distinct stereoselective processes involved in the overall transformation. The proposed mechanism includes an oxazoline–alkyllithium coordination complex that controls the selectivity of the deprotonation step, whereas the selectivity of the electrophilic quench is governed by effects that are as yet undetermined.

Dipole-stabilized anion-mediated alkylation of carbons bearing heteroatoms is a useful process for the elaboration of a number of heterocyclic systems.[1] Among the more versatile functional groups for mediation of this process are aliphatic or aromatic amides, formamidines, and oxazolines. Since the alkylation sequence generates a stereocenter, a chiral auxiliary mediated alkylation would be highly desirable. The first example of such a process was a formamidine derived from a chiral amino alcohol for the α-alkylation of tetrahydroisoquinoline,[2] but the process was quickly extended to β-carbolines[3] and other allylically activated systems.[4] These elegant processes, reported from Meyers' laboratories over the past 5 years, have been the subject of several reviews.[5]

Unfortunately, the formamidine chiral auxiliaries that work so well when the metalated carbon is allylic or benzylic fail completely when it is not.[6] This failure has been attributed to a complex-induced proximity effect, whereby bidentate chelation in the formamidine coordinates the alkyllithium base and prevents approach by the base to the "acidic" protons.[7] We recently introduced a monodentate oxazoline auxiliary[8] which was specifically designed to activate both allylic and nonallylic positions on a heterocycle.[9]

This system mediates the 100% stereoselective deprotonation of piperidine and also mediates the stereoselective alkylation of tetrahydroisoquinolines, illustrated in Scheme I, with diastereomer ratios in the range of 15–40/1. Yields routinely exceed 90% for the alkylation step; the chiral auxiliary is readily available, easily attached and removed, and recoverable. Its use in the asymmetric synthesis of the isoquinoline alkaloids laudanosine and *O*-methylflavinantine in 94% enantiomeric excess was recently reported.[10]

The high yields and stereoselectivities of this sequence have prompted us to undertake an extensive investigation of the mechanisms of the processes involved. We now report the details of this investigation, which includes an examination of the effect of both temperature and oxazoline substituent structure on the alkylation diastereoselectivity, a comparison of intramolecular monodentate vs bidentate chelation of the organolithium by the chiral auxiliary, an evaluation of the effect of solvent and chelating solvent additives, the regiochemistry of alkylation of (3,4-dehydropiperidino)oxazolines, and lithiation–alkylation experiments on stereoselectively deuterated monodentate and bidentate isoquinolinolyloxazolines. On the basis of these experiments and the results of extensive *semiempirical* molecular orbital calculations, we offer a mechanism that is consistent with the chemistry of chiral auxiliary mediated dipole-stabilized anion alkylations at benzylic and allylic carbons.[11]

Results

Several chiral ethoxyoxazolines were prepared as illustrated in Scheme II and summarized in Table I. For entries 1, 3, 4, and 5, the requisite amino alcohols were prepared by lithium aluminum hydride reduction of the corresponding amino acid.[12] For entries 6 and 7, the benzyloxycarbonyl-protected amino alcohols were used. Cyclization with diethyl carbonate[13] or phosgene[14] afforded the oxazolidones **1**, which were *O*-alkylated with triethyloxonium tetrafluoroborate.[15] The methoxymethyl- (**2f**) and methoxypropyl-substituted (**2g**) oxazolines were synthesized by functional group manipulation as outlined in Scheme II. A similar planned synthesis of a methoxyethyl-substituted oxazoline failed due to an unavoidable intramolecular addition of the side-chain hydroxyl across the C=N bond, producing **3** instead (Scheme II). Details for the synthesis of these compounds and their properties may be found in the supplementary material.

The oxazolines were condensed with tetrahydroisoquinoline and the oxazolyltetrahydroisoquinolines, **4**, were lithiated and alkylated

(1) (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275–316. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Ibid.* **1984**, *84*, 471–523.
(2) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117–118.
(3) Loewe, M. F.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3291–3294.
(4) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974–7978.
(5) For reviews, see: (a) Meyers, A. I. *Aldichimica Acta* **1985**, *18*, 59–68. (b) Meyers, A. I. *Lect. Heterocycl. Chem.* **1984**, *7*, 75–81. (c) Meyers, A. I.; Fuentes, L. M.; Boes, M.; Dickman, D. A. *Chem. Scr.* **1985**, *25*, 25–31. For a recent leading reference to other work, see: (d) Meyers, D. A.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095–5108.
(6) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974–7978.
(7) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363.
(8) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076–3078.
(9) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175–181.
(10) Gawley, R. E.; Smith, G. A. *Tetrahedron Letters* **1988**, *29*, 301–302.
(11) Preliminary reports of portions of this work have appeared: Reference 8 and Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265–1266.
(12) Smith, G. A.; Hart, G.; Chemburkar, S.; Goicoechea-Pappas, M.; Rein, K.; Anklekar, T. V.; Smith, A. L.; Gawley, R. E. *Organic Syntheses*; Wiley: New York, Collect. Vol. VII, in press.
(13) Scholz, K.-H.; Heine, H.-G.; Hartmann, W. *Org. Synth.* **1984**, *62*, 149–157.
(14) Available as a 20% solution in toluene from Fluka.
(15) Meerwein, H. In *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 1080–1082. We have stored the crystalline solid for several months at −20 °C; commercially available solutions of this reagent are not recommended.

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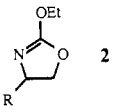
Table I. Oxazoline Chiral Auxiliaries

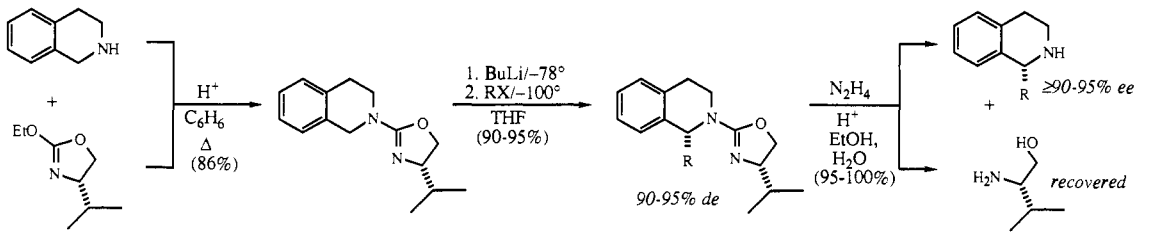


2

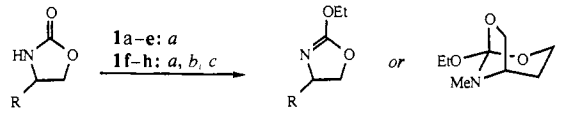
entry	"chiral pool" source	(*)-R	$[\alpha]_D$ (c)[a]	Scheme II yield, %
1	(S)-alanine	(S)-CH_3	−25.9 (1.4)	83
2	(R)-2-amino-1-butanol[b]	(R)-CH_2CH_3	+20.9 (1.4)	57
3	(S)-valine	(S)-$CH(CH_3)_2$	−23.4 (5.2)[c]	85
4	(R)-phenylglycine	(S)-C_6H_5	−24.6 (0.9)	61
5	(S)-phenylalanine	(S)-$CH_2C_6H_5$	+17.5 (1.7)[d]	84
6	(S)-serine	(R)-CH_2OCH_3	+29.0 (3.2)	13[e]
7	(S)-glutamic acid	(S)-$(CH_2)_3OCH_3$	−41.7 (1.6)[c]	22[e]

[a] Methanol, unless noted. [b] Aldrich Chemical Co., 70% ee. [c] Chloroform. [d] Ethanol. [e] Three steps.

Scheme I



Scheme II[a]



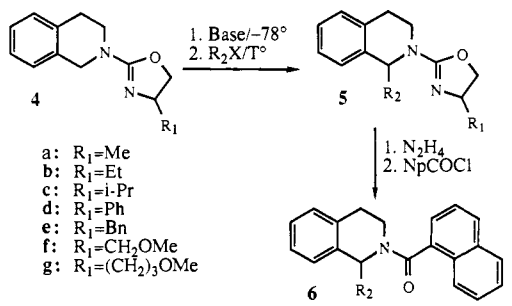
1a: R=Me
1b: R=Et
1c: R=i-Pr
1d: R=Ph
1e: R=Bn
1f: R=CO_2Me
1g: R=$(CH_2)_2CO_2Me$
1h: R=CH_2CO_2Et

2a: R=Me
2b: R=Et
2c: R=i-Pr
2d: R=Ph
2e: R=Bn
2f: R=CH_2OMe
2g: R=$(CH_2)_3OMe$

3 (from 1h)

[a] Conditions: (a) Et_3OBF_4, CH_2Cl_2; (b) $LiAlH_4$, THF; (c) KH, MeI.

Scheme III

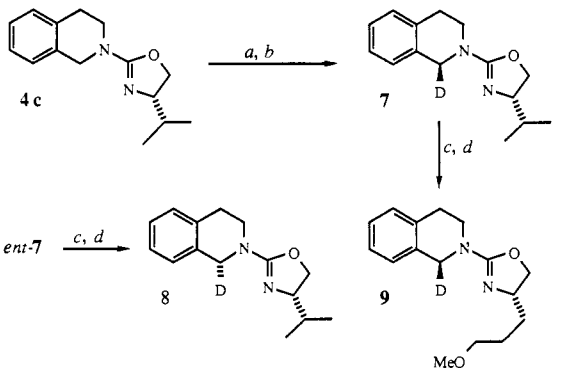


a: R_1=Me
b: R_1=Et
c: R_1=i-Pr
d: R_1=Ph
e: R_1=Bn
f: R_1=CH_2OMe
g: R_1=$(CH_2)_3OMe$

at the 1-position under a variety of conditions. A summary of these experiments is given in Table II. In all cases, the diastereomer ratios were determined by capillary gas chromatography. Determination of absolute configuration was achieved by conversion of the alkylated aminooxazolines (**5**) to the corresponding naphthamides, **6**, (Scheme III), and Pirkle column HPLC analysis.[16]

Stereoselective deuteration of the 1-position of tetrahydroisoquinoline was accomplished as shown in Scheme IV. Valinol-derived isoquinolyloxazoline **4c** was lithiated at −78 °C; addition of DMSO-d_6 and warming to room temperature afforded (1-β-deuteriotetrahydroisoquinolyl)oxazoline **7** (100% deuterium in-

Scheme IV[a]



[a] Conditions: (a) n-BuLi, THF, −78 °C; (b) DMSO-d_6, −78 to 25 °C; (c) $N_2H_4 \cdot H_2O$, H^+, EtOH-H_2O, reflux; (d) **2g**, C_6H_6, H^+, reflux.

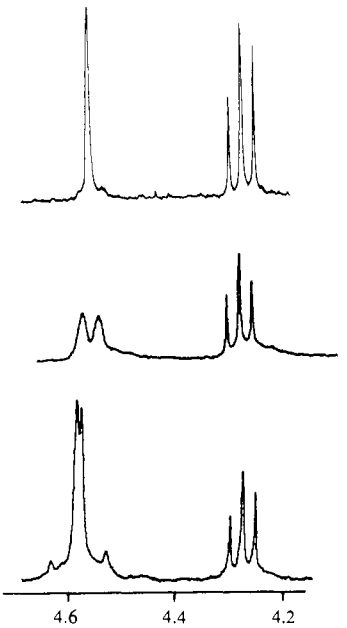
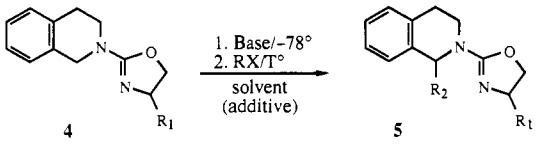


Figure 1. Partial 360-MHz ^{1}NMR spectrum of **4c** (bottom), 7 + 8 (middle), and 7 (top, with gated decoupling of deuterium).

(16) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504-2506.

Table II. Alkylation of (Tetrahydroisoquinolyl)oxazolines[a]



4 5

entry	R_1	base	solvent	additive	R_2X	T, °C	% de
1	Me	*n*-BuLi	THF	none	*n*-BuBr	−78	79
2	Et	*n*-BuLi	THF	none	*n*-BuBr	−78	80
3	*i*-Pr	*n*-BuLi	THF	none	*n*-BuBr	−78	82
4	Ph	*n*-BuLi	THF	none	*n*-BuBr	−78	82
5	Bn	*n*-BuLi	THF	none	*n*-BuBr	−78	55
6	Bn	*n*-BuLi	THF	none	*n*-BuBr	−100	68
7	*i*-Pr	*n*-BuLi	THF	none	*n*-PrBr	−78	84
8	*i*-Pr	*s*-BuLi	THF	none	*n*-PrBr	−78	86
9	*i*-Pr	*t*-BuLi	THF	none	*n*-PrBr	−78	85
10	*i*-Pr	*t*-BuLi	THF	none	*n*-PrI	−78	80
11	*i*-Pr	*t*-BuLi	THF	none	*n*-PrCl	no reaction	
12	*i*-Pr	*t*-BuLi	THF	none	BnCl	−78	86
13	*i*-Pr	*t*-BuLi	THF	none	BnCl	−90	90
14	Bn	*n*-BuLi	THF	none	BnCl	−100	83
15	*i*-Pr	*t*-BuLi	THF	none	BnBr	−78	48
16	*i*-Pr	*t*-BuLi	THF	none	BnBr	−100	65
17	*i*-Pr	*n*-BuLi	THF	none	2-$MeOC_6H_4CH_2Cl$	−78	62
18	*i*-Pr	*n*-BuLi	THF	none	3,4-$(MeO)_2C_6H_3CH_2Cl$	−78	76
19	*i*-Pr	*n*-BuLi	THF	none	MeI	−78	84
20	*i*-Pr	*t*-BuLi	THF	none	MeI	−100	90
21	*i*-Pr	*t*-BuLi	THF	none	MeI	−124	92
22	*i*-Pr	*t*-BuLi	THF	TMEDA[b]	*n*-BuBr	−78	82
23	Bn	*t*-BuLi	THF	TMEDA[b]	*n*-BuBr	−78	55
24	*i*-Pr	*t*-BuLi	ether	none	*n*-BuBr	−78	19
25	*i*-Pr	*t*-BuLi	ether	TMEDA[b]	*n*-BuBr	−78	35
26	CH_2OMe	*t*-BuLi	THF	none	*n*-BuBr	−78	25[c]
27	$(CH_2)_3OMe$	*t*-BuLi	THF	none	MeI	−78	71
28	$(CH_2)_3OMe$	*t*-BuLi	THF	none	MeI	−100	75
29	*i*-Pr	*n*-BuK	THF	none	*n*-BuBr	−78	32

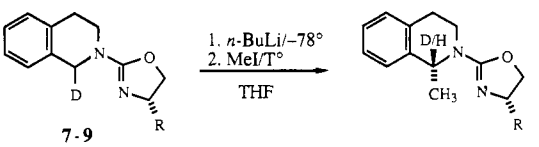
[a] The relative stereochemistry of the two stereocenters in syn as drawn, unless otherwise noted. Reactions were typically run at 0.1 M concentration. [b] One equivalent. [c] Relative stereochemistry is anti.

corporation by mass spectroscopy). A similar sequence using CH_3OD resulted in nonselective deuteration. The selectivity of the DMSO-d_6 deuteration was evaluated by NMR, as shown in Figure 1. At 360 MHz, the C_1 protons of **4c** are an AB quartet. The nonselectively deuterated species shows deuterium quadrupole-broadened singlets at δ 4.535 and 4.575, whereas **7** exhibits only the latter. Gated decoupling of the deuterium resonance sharpened the C_1 H signals and permitted accurate integration. Integration of the two signals indicates that the deuteration selectivity was 24/1 [92% diastereomeric excess (de)]. The absolute configuration was determined by comparison with an independently synthesized sample of (*R*)-1-deuteriotetrahydroisoquinoline.[17] Synthesis of the enantiomer of **7** (from D-valinol) and chiral auxiliary exchange with **2c** afforded (1-α-deuteriotetrahydroisoquinolyl)oxazoline **8**; similar exchange of chiral auxiliaries from **7** with **2g** gave (1-β-deuteriotetrahydroisoquinolyl)oxazoline **9**, having an alkoxy ligand on the side arm of the oxazoline (Scheme IV).

The three selectively deuterated isoquinolyloxazolines **7–9** were lithiated and alkylated with methyl iodide. The products were analyzed for deuterium content by NMR or mass spectroscopy and for diastereoselectivity by capillary GC; the results are summarized in Table III.

Condensation of **2c** with 1,2,3,6-tetrahydropyridine afforded (3,4-dehydropiperidino)oxazoline **10**, which may be lithiated and alkylated under conditions similar to those described for saturated piperidinooxazolines[9] or for the (tetrahydroisoquinolinolyl)oxazolines (Scheme V). However, the major, if not exclusive, products arise from substitution at the 4-position (i.e., **11**) of the piperidine. The diastereomer ratio of **11** could not be determined, but the 2-substituted product **12**, when present, was found to be ≥95% de. The results are summarized in Table IV.

Table III. Deprotonation and Alkylation of Deuterated (Tetrahydroisoquinolyl)oxazolines

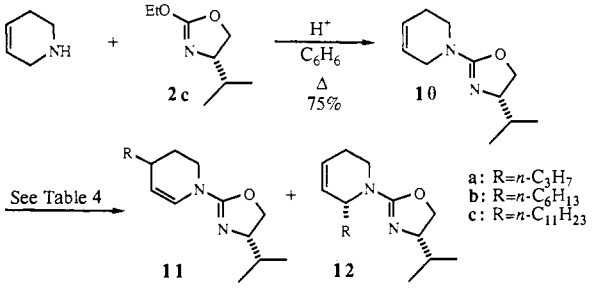


7-9

substr	R	D	C_1 *R*/*S* ratio (% de)	T, °C	D/H
7	(*S*)-*i*-Pr	β	12/1 (84)	−78	1.01/1[a]
8	(*S*)-*i*-Pr	α	10/1 (82)	−78	34.5/1[a]
9	(*S*)-$(CH_2)_3OMe$	β	7.3/1 (75)	−100	1/2[b]

[a] Determined by mass spectroscopy. [b] Determined by NMR.

Scheme V



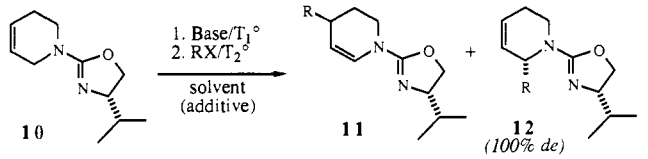
2c 10 11 12

Discussion

There are two potentially stereoselective processes involved in the conversion of isoquinolyloxazoline **4** to **5**: the deprotonation and the alkylation of the intermediate organolithium. Among the experiments described below are several which indicate that both

(17) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263–1265.

Table IV. Alkylation of (3,4-Dehydropiperidino)oxazoline



entry	T_1, °C	base	solvent	additive	RX	T_2, °C	11/12	yield, %
1	−23	*s*-BuLi	ether/THF[a]	TMEDA[b]	*n*-propyl-Br	−100	5/1	58
2	−23	*s*-BuLi	ether/THF[a]	TMEDA[b]	*n*-hexyl-Br	−100	2/1	87
3	−23	*s*-BuLi	ether/THF[a]	TMEDA[b]	*n*-undecyl-Br	−100	1/0	28
4	−78	*n*-BuLi	THF	none	*n*-propyl-Br	−78	1.5/1	93

[a] 9/1. [b] 0.1 equiv.

processes are indeed selective, but which reveal unequivocally that it is only the selectivity of the alkylation step that is important in the diastereoselection of the overall process. Table II details the results of a systematic study of the effects of oxazoline substituent, base, quench temperature, electrophile structure, solvent, and solvent additive. For convenience, most of the reactions were run at −78 °C.

To our suprise, in the series (**4**, R_1 =) methyl, ethyl, isopropyl, phenyl, there was only a slight increase in the selectivity of alkylation with *n*-butyl bromide: the selectivity ranged from 79 to 82% de (entries 1–4). When R_1 = benzyl, the selectivity dropped precipitously, to 55% de (entry 5). Another factor that had little effect was the structure of the alkyllithium base: deprotonation with *n*-butyl-, *sec*-butyl-, or *tert*-butyllithium and alkylation with *n*-propyl bromide afforded 85 ± 1% de in each case (entries 7–9).

The temperature at which the electrophile was added did have a significant effect. As shown by entries 5 vs 6, 12 vs 13, 15 vs 16, and 19 vs 20 vs 21, lowering the temperature to ≤−90 °C results in a significant increase in the selectivity. Taking entries 19–21 as examples, the increase from 84 to 92% de corresponds to an increase in the diastereomer ratio from 11.5/1 to 24/1, more than doubling the selectivity.

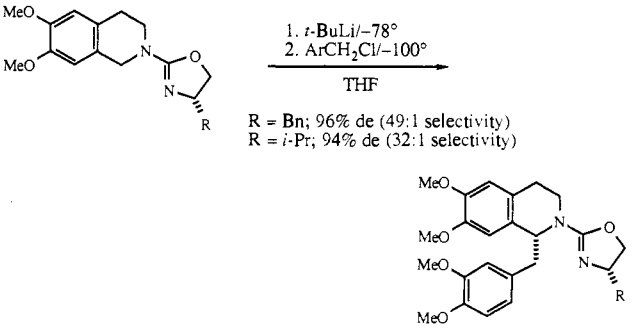
The electrophile also has an effect. By comparing entries 7 vs 10 vs 11, it is seen that *n*-propyl chloride is unreactive while *n*-propyl bromide gives slightly better selectivity than *n*-propyl iodide. The effect of the electrophile is more pronounced for benzylic halides: **4c** is alkylated in 86% de with benzyl chloride but only 48% de with benzyl bromide (entries 12 vs 15). 3,4-Dimethoxybenzyl chloride affords **5** in 76% de, whereas 2-methoxybenzyl chloride gives **5** in only 62% de (entries 17 and 18). These differences are most easily interpreted in terms of electrophile reactivity.

As stated above, the effect of the oxazoline substituent was not great except in the case of **4e** (R_1 = Bn). Although this auxiliary afforded poor selectivity with *n*-alkyl bromides (entries 5 and 6), the selectivity with benzyl chloride is much better (entry 6 vs 14). Moreover, we have also made the qualitative observation that the two diastereomers, **5**, are often more easily separable when R_1 is benzyl, a potentially important observation for the preparation of enantiomerically pure compounds.

When the tetrahydroisoquinoline ring is oxygenated, as in the case of the laudanosine precursors[10] shown in Scheme VI, the selectivity is increased substantially: 94–96% de vs 83% de for the unoxygenated analogue (Table II, entry 14). This change is interpreted as a decrease in the degree of delocalization of the negative charge into the aromatic ring (vide infra).

Comparison of entries 3 and 24 reveals that virtually all selectivity is lost when the solvent is changed from THF to ether. If aggregation is greater in ether, as seem reasonable, then alkylation of the higher aggregate affords lower selectivity. As shown by entries 3 vs 22, 5 vs 23, and 24 vs 25, the addition of 1 molar equiv of tetramethylethylenediamine (TMEDA)[18] had

Scheme VI



no effect on the selectivity in THF, but the selectivity was significantly enhanced in ether. The TMEDA effect suggests that aggregation is altered only in ether solvent.[19]

The effect of an additional ligand (as a substituent on the oxazoline) was evaluated by examining two auxiliaries with methoxy groups, **4f** and **4g**. Methoxymethyl-substituted oxazoline **4f** exhibited anomalous behavior (entry 26) in that the sense of asymmetric induction is reversed from all other compounds we have examined to date, including the examples in Table II and several other systems. Note that the asymmetric induction is quite low (19% de). The oxygen is almost certainly involved in chelating the lithium, since if it was not, we would expect a stereoselectivity comparable to the methyl- (**4a**) or ethyl-substituted (**4b**) species (entries 1 and 2). Note, however, that a species lithiated at C_1 of the tetrahydroisoquinoline and chelated by both the oxazoline nitrogen and the ether oxygen would be highly strained. We speculate that these two ligands compete for monodentate chelation, and that the two resultant species are quite different in their behavior toward an electrophile. Because of the anomalous behavior of **4f**, and because the selectivity is poor, we have not investigated its chemistry further. The bishomologue, (methoxypropyl)oxazoline **4g**, gave higher asymmetric induction (entry 27), but still not as high as the monodentate oxazolines. It is not obvious from the diastereomer ratio whether the oxygen is chelating the lithium, but proximity suggests that bidentate chelation is likely. Furthermore, deprotonation studies suggest that the alkoxy group is involved in a coordination complex with the alkyllithium base prior to deprotonation (vide infra).

The results outlined in Table II suggest, but do not prove, that the two possible stereoselective processes mentioned above (deprotonation and alkylation) are not related. The analysis of product diastereomers yields information on the selectivity of the overall process, but cannot distinguish between the deprotonation and the alkylation as the source. The two processes were "decoupled" simply by executing the sequence in such a way as to leave evidence in the alkylated product of the selectivity (if any) in the deprotonation step. Thus the stereoselectively deuterated

(18) For the use of TMEDA in enhancements of kinetic acidity, presumably by deaggregation, see: Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331–334, and 1640.

(19) TMEDA need not be a bidentate chelating agent. It might also be monodentate and may even serve as a bridging ligand between aggregates: Bauer, W.; Klusener, P. A. A.; Harder, S.; Kanters, J. A.; Duisenberg, A. J. M.; Brandsma, L.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 552–555.

substrates **7–9** were deprotonated with *n*-butyllithium and alkylated. The deuterium content of the product reveals the selectivity of the deprotonation, as expressed by the relative rates of deprotonation of the C_1 β- and the C_1 α-protons: k_β/k_α. Qualitatively, it is apparent from the data in Table III that *there is no relation between the deprotonation selectivity (D/H ratio) and the diastereomer ratio (R/S)*. Quantitatively, the magnitude of both the deprotonation selectivity and the kinetic isotope effect is easily calculated.[20] The deprotonation selectivity, k_β/k_α, is 5.8. The isotope effect, IE, is 5.9. The only assumption necessary is that the isotope effect is the same for **7** and **8**.[21] Removal of the C_1 β- or the C_1 α-protons produces two diastereomeric organolithiums, and the data suggest that the two are interconvertible, even at −78 °C. This point is further discussed later.

The related valinol-derived formamidines show a highly selective deprotonation following a rate-limiting prior coordination of the formamidine with the butyllithium base. The rate-limiting prior coordination of the bidentate formamidine with the butyllithium results in a deprotonation that is 100% stereoselective and that shows no kinetic isotope effect: deuterium is removed selectively.[17] This is the only mechanistic difference between the *bidentate* formamidines and the *monodentate* oxazolines. In order to determine the effects of bidentate chelation in the oxazoline system,[22] the selectively deuterated isoquinolyloxazoline **9** was prepared as shown in Scheme IV. The deprotonation is not 100% selective, but like the formamidines *there is a 2/1 preference for removal of deuterium*. Moreover, *there is no relation between the deprotonation selectivity and the diastereomer ratio*. We conclude that bidentate chelation does not preempt pyramidal inversion of the lithiated diastereomers.[23]

Theoretical studies have shown that the lone pair of a dipole-stabilized anion is not likely to orient in such a way as to overlap with the π-orbitals of the nitrogen amide (or amidine in this case), and experiments have shown that pyramidal inversion does not occur in conformationally rigid lithiated piperidine amides.[24] However, the carbon–lithium bond in this case is also benzylic, and benzyllithiums have been shown to undergo pyramidal inversion, even at low temperature.[25] The ^{1}H NMR of lithiated **4c** at −80 °C shows a one-proton triplet at δ 5.6, assigned to the hydrogen on position 6 of the tetrahydroisoquinoline. This shift is in the same range as the para hydrogens of several pyramidal benzylic carbanions (δ 5.5–6.0); it is clearly out of the chemical shift range of planar benzylic carbanions (δ 4.4–4.7).[26]

Finally, the effect of the cation was examined by conducting the deprotonation with *n*-butylpotassium (entry 29). It is known from NMR studies of alkali metal benzylic carbanions that the lithium derivatives are usually pyramidal while the potassium compounds are always planar.[25–27] The precipitous drop in selectivity for the potassium anion implicates a pyramidal benzylic carbanion with a tightly bound lithium as a prerequisite to high selectivity. As discussed below, we postulate an equilibrating mixture of (pyramidal) diastereomeric organolithiums, alkylation of which affords the two diastereomeric products.

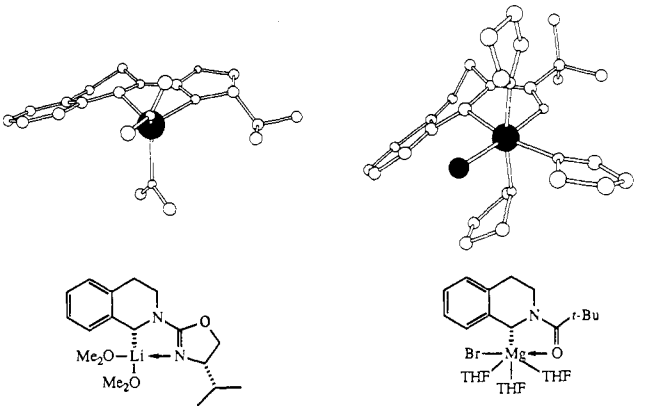
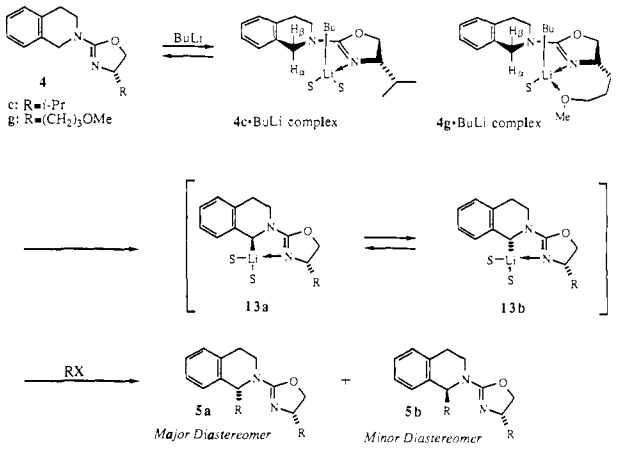


Figure 2. Left: One of the four MNDO-minimized organolithium diastereomers, showing flat chelated metallocyclic ring. Right: Similar view of a pivaloylisoquinoline Grignard crystal.[28]

Scheme VII



To gain insight into the structure of the organolithium species, we have conducted *semiempirical* MNDO calculations on four organolithium stereoisomers (each organolithium diastereomer in half-chair and half-boat conformations). The four isomers are not far apart in energy. The calculations indicate only ~2 kcal/mol between the most and least stable isomers, a spread that we judge to be insignificant for this method. The calculated geometries do have some pertinent features, however. All four have significant pyramidalization of the benzylic carbon, and all have an almost flat metallocyclic ring, with the C–Li bond in or very near the nodal plane of the N—C=N π-system. One of the isomers is shown in Figure 2, with the lithium solvated by methyl ether. Also shown in Figure 2 is an X-ray crystal structure of a pivaloyltetrahydroisoquinoline Grignard, which shows striking similarity as regards the pyramidalized benzylic position and the flat metallocycle.[28]

We believe that the high degree of selectivity observed in the organolithium alkylations described in this paper is most readily accounted for by a highly covalent C–Li bond. Although many organolithiums are regarded as ionic, and pyramidal inversion requires an ionic bond, the distinction between a tight ion pair and a polar covalent bond may be quite subtle. Indeed, Seebach has shown that three different organolithium species show covalent character at low temperature, as evidenced by the appearance of $^1J_{C-Li}$ coupling as the solution is cooled.[29] Consistent with a C–Li bond with significant covalent character, a comparison of calculated bond lengths and angles around the N—C=N group for

(20) The isotope effect is given by IE = $(D/H)_7^{1/2}(D/H)_8^{1/2}$ while the relative rates for the abstraction of the C_1 β- and the C_1 α-protons are given by $k_\beta/k_\alpha = (D/H)_8^{1/2}/(D/H)_7^{1/2}$, where $(D/H)_7$ and $(D/H)_8$ are the deuterium to hydrogen ratios in the methylated product obtained from **7** and **8** respectively.

(21) Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807–1816.

(22) The converse situation, namely a chiral monodentate formamidine, exhibits poor asymmetric induction. See: Reference 2.

(23) A dependence of asymmetric induction on the temperature of the alkyl halide quench of a lithiated bidentate formamidine has been noted (ref 2), raising the likelihood of lithium diastereomer interconversion in that system as well.

(24) (a) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4108–4110. (b) Bach, R. D.; Braden, M. L.; Wolber, G. J. *Ibid.* **1983**, *48*, 1509–1514. (c) Bartolotti, L. J.; Gawley, R. E. *Ibid.*, in press.

(25) Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709–4715.

(26) Hoell, D.; Lex, J.; Müllen, K. *J. Am. Chem. Soc.* **1986**, *108*, 5983–5991.

(27) Keys, B. A.; Eliel, E. L.; Juaristi, E. *Isr. J. Chem.* in press.

(28) The drawings in Figure 2 were made with the Macintosh program CHEM3D, Cambridge Scientific Computing, Inc. The fractional coordinates for the crystal structure are from: Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1–13.

(29) Heinzer, J.; Oth, J. F. M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1848–1862.

the lithiated structure in Figure 2 and **4c** indicates <0.01 Å difference in bond lengths and <0.5° difference in the bond angles. An ionic lithium coordinated to the oxazoline nitrogen would be expected to alter these values.[30]

The results discussed above implicate carbon–lithium covalency in the transmission of stereochemical information in the crucial alkylation step and may also explain the lower selectivity at higher temperature (more ionic character). Further work necessary to experimentally confirm this point is in progress.

The occurrence of pyramidal inversion as a result of overlap between the C–Li bond and adjacent aromatic π-orbitals is a phenomenon that is also evident in a related system: the dehydropiperidinooxazoline shown in Scheme V. The data in Table IV indicate that, *in all cases, the major product of alkylation arises from alkylation at the 4-position*, revealing significant overlap with the π-orbitals. Several related allylic systems also show predominant or exclusive γ-alkylation.[31] Thus, in the absence of an aromatic ring, the preferred site of alkylation is at the γ-position, implicating significant delocalization away from the amide function.

Mechanism. The mechanism we postulate to account for our observations is shown in Scheme VII. The first step is the formation of a coordination complex. Scheme VII illustrates the complex with monodentate oxazoline **4c** and bidentate oxazoline **4g**. In both cases, the butyl group is oriented anti to the substituent on the oxazoline and is positioned for selective removal of the H_β proton. It is the configuration of this coordination complex that accounts for the stereoselectivity of the deprotonation. Proton loss then produces an equilibrating pair of organolithium diastereomers, **13a** and **13b**, each of which is conformationally mobile and may exist in more than one conformation. Upon addition of an electrophile, **13a,b** is converted to the mixture of product diastereomers **5a,b**. The available evidence reveals neither the mechanism of the alkylation nor the structure of organolithium (position of the equilibrium, degree of aggregation, C–Li covalency). Although it is not known whether the preferred path of alkylation entails retention of configuration at C_1 of the organolithium (i.e., **13a** → **5b** and **13b** → **5a**) or inversion (i.e., **13a** → **5a** and **13b** → **5b**), the fact that all alkyl halides afford **5a** as the major diastereomer whereas DMSO-d_6 affords **5b** (R = D) suggests that one mode of electrophilic attack occurs with retention while the other occurs with inversion. If both sides of the organolithium diastereomer equilibrium are reasonably well populated, the product distribution in the alkylations might be determined by Curtin–Hammett kinetics.[32,33]

The experiments described in this paper offer unique insight into the processes governing the stereoselective deprotonation and alkylation of benzylic and allylic "dipole-stabilized anions", but do not furnish enough evidence to elucidate the organolithium structure or support a mechanism for its reaction with electrophiles. Further mechanistic investigations and synthetic applications of chiral dipole-stabilized anion alkylations are in progress in isoquinoline, isoindoline, and other systems and will be reported in due course.[34]

Experimental Section

General Procedures. Molecular mechanics and MNDO calculations were facilitated by the MacroModel program, version 1.5, developed by Professor W. Clark Still, Columbia University (copyright 1986). Semiempirical (MNDO[35]) calculations were accomplished with the MOPAC program.[36]

Tetrahydrofuran and diethyl ether were distilled immediately prior to use from sodium benzophenone ketyl. Tetramethylethylenediamine (TMEDA) was distilled from calcium hydride immediately prior to use. All other solvents were distilled before use. All reactions were run under an inert atmosphere of nitrogen. Gas chromatography was accomplished on a Varian 2440-10 chromatograph using either a J&W 45-m DB-5 or a SGE 50-m BP-5 vitreous silica capillary column (both are 5% phenyl methyl silicone).

General Procedure A. Synthesis of Oxazolidinones 1a–e. The following is adapted from a procedure for the preparation of 2-oxazolidinone.[37] The amino alcohol, diethyl carbonate (1.25 equiv), and NaOEt (0.01 equiv generated from sodium and 0.012 equiv of ethanol) were placed in a three-necked flask fitted with a thermometer, N_2 inlet, and a Vigreux column with a distillation head. The mixture was heated in a 125 °C oil bath. Ethanol began to distill when the internal temperature reached 95 °C. After ~8 h, the internal temperature reached 125 °C and the ethanol ceased to distill. The reaction mixture was cooled to 65 °C and poured into cold (0 °C) ether. The product precipitated and was isolated by filtration. No further purification was necessary.

General Procedure B. Synthesis of Oxazolines 2a–g. To a solution of the oxazolidinone (**1a–g**) in methylene chloride at 0 °C was added dropwise a solution of 1.1 equiv of triethyloxonium tetrafluroborate[15] in methylene chloride. The solution was allowed to warm slowly to room temperature overnight. The reaction mixture was then slowly poured into cold, saturated sodium carbonate. The organic layer was separated and the aqueous layer extracted with methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate and condensed in vacuo. The products were purified by vacuum distillation.

General Procedure C. Condensation of the Ethoxyoxazolines with Amines (4a–g and 10). A mixture of the ethoxyoxazoline, the corresponding amine (1.1 equiv), and a catalytic amount of *p*-toluenesulfonic acid was refluxed in benzene for 3–4 h (reaction progress was followed by TLC developed with 10% ethyl acetate in hexane). After being cooled, the reaction mixture was washed with saturated sodium bicarbonate and brine. The organic phase was dried over magnesium sulfate and concentrated to afford the crude product. The aminooxazolines were purified by radial chromatography and were distilled from calcium hydride immediately prior to use.

General Procedure D. Metalation and Alkylation of (Tetrahydroisoquinolyl)oxazolines 4. To a solution containing the isoquinoline (**4a–g**) (0.1–0.15 M) and TMEDA if specified (see Table II) in THF or ether at −78 °C was added dropwise (via syringe) 1.1 equiv of the specified base. The reaction mixture was stirred at −78 °C for 10–30 min, whereupon the solution was either maintained at −78 °C or cooled to the specified temperature. The electrophile (1.5–4 equiv) was added via syringe. This mixture was stirred for 20 min, then allowed to warm to room temperature, and diluted with brine. The aqueous phase was extracted with methylene chloride or chloroform, and the combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by radial chromatography followed by Kugelrohr distillation.

General Procedure E. Alkylation of Dehydropiperidinooxazolines. Compound **10** may be alkylated by general procedure D or by the following method, which is taken from ref 9. The piperidinooxazoline (0.5 mmol/mL of 90% ether–THF) and TMEDA (0.1 equiv) were stirred for 5 min at −78 °C under an inert atmosphere of nitrogen. *s*-BuLi, 1.3 M in hexane (1.1–3 equiv), was added via syringe, and the reaction mixture was allowed to warm to −23 °C. Stirring at this temperature continued for 30–45 min. After the mixture was cooled to −100 °C, the electrophile was added dropwise via syringe and the reaction mixture warmed slowly to room temperature. The reaction was quenched with brine and the layers separated. The aqueous layer was extracted with ether, and the organic layers were combined. Drying with sodium sulfate and removal of the solvent under reduced pressure gave the crude products, which were separated by chromatography and purified by distillation.

General Procedure F. Removal of the Chiral Auxiliary by Hydrazinolysis. The aminooxazoline was refluxed in a solution of hydrazine hydrate (approximately 0.5 mL/mmol) in ethanol containing a catalytic amount of *p*-toluenesulfonic acid. The reaction was monitored by TLC and required 4–6 h for completion. The solution was concentrated in vacuo and 10% KOH added to the residue. The mixture was extracted with methylene chloride, dried over $MgSO_4$, filtered, and evaporated in

(30) For a similar interpretation of the bonding in the pivaloyl Grignard shown in Figure 2, see: Reference 28.

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(32) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.

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(34) For an example of stereo- and regioselective sequential α,α'-dialkylation of isoindoline, see: Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.* **1988**, *53*, 5381–5383. For a mechanistic study of piperidinooxazolines, see: Reference 9.

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vacuo. The crude product was purified by radial chromatography.

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Supplementary Material Available: Details of the preparation and physical and spectral data for compounds **1-5**, **10**, and **11** (14 pages). Ordering information is given on any current masthead page.

Photophysical Analysis of Ion Pairing of β-Naphtholate in Medium Polarity Solvents: Mixtures of Contact and Solvent-Separated Ion Pairs

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Abstract: Absorption and emission properties of β-naphtholate are analyzed including lifetime measurements. It is shown that, in solvents of medium polarity, the broad absorption and emission bands of the β-naphtholate anion consist of overlapping spectra of contact (CIP) and solvent-separated (SSIP) ion pairs. In spite of the absence of spectral resolution, this is demonstrated by the following: (1) The shift of the emission maximum with excitation wavelength. (2) The biexponential decay measured by single photon counting. (3) The dependence of the decays on the excitation and emission wavelengths and on the nature of the cation used. (4) The dependence of Stern-Volmer quenching constants on the cations and on the excitation and emission wavelength. The ground-state equilibrium and the dynamics of the excited state are characterized. The estimated exchange rates are of the same order of magnitude and of about 2.10^7 s^{-1} in the excited state. NMR measurements have shown that the lifetimes of CIP and SSIP in the ground state are much shorter than 6.10^{-5} s.

Ion properties are strongly solvent dependent, and their reactivity may differ greatly according to the strength of their interactions with the surrounding molecules. In weakly polar solvents interionic interactions may dominate, and ion pairs will result. This ion pair concept was introduced by Bjerrum[1] and has been critically reviewed by Szwarc.[2] The definition of ion pairs is based on the mutual geometry of ions and solvent. Winstein[3] and Sadek[4] suggested the existence of "loose" and "tight" ion pairs. It is now of common use to speak about solvent-separated ion pairs (SSIP) or of contact ion pairs (CIP). Even more subtle distinctions were made by Y. Marcus: solvent-separated and solvent-shared ion pairs are distinguished according to the number (two or one, respectively) of solvent molecules separating the two paired ions.[5]

Predictions concerning ion pairs in solution are always delicate since many factors must be accounted for. Coulombic interionic interactions must be considered in competition with ion-dipole (solvent) interactions.[6] The dielectric constant will play a role, but it is not expected as a relevant parameter since it reflects macroscopic properties of the solvent, while the considered interaction clearly does not. Specific ion-solvent interactions may take a part in solvation, and a marked difference between hydroxylic and nonhydroxylic solvents is often expected.[7] Temperature will influence the status of ions in solution: when the thermal energy kT decreases, ion pair formation is of course favored, but it is not easy to predict in which direction the equilibrium between SSIP and CIP will change. In general, SSIP are favored by lowering the temperature.[8-10] Other factors like charge delocalization which favors SSIP,[11] steric effects, and aggregation phenomena[12-14] will also play a role.

Among other techniques like EPR, NMR, IR, or Raman measurements, spectrophotometric results were often reported as a proof for ion pairing. The effects of ion pairing on the reactivities and spectral properties of carbanions[6,8,15] and oxyanions[16] have been reviewed. It is for instance well known that a decrease of the cation radius shifts the absorption peak of anions to shorter wavelengths.[8,16] This hypsochromic shift is attributed to the higher association of the ion pair in the ground state when compared to the excited state and to an increasing association when the cation becomes smaller.

Absorption frequencies of ion pairs are shifted when the solvent changes: the direction of the shift depends on the change (increase

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