trolling complex formation; (b) rapid, proton removal from the α-face; and (c) alkylation with inversion of the C-Li bond.

It is noteworthy that a related system, described by Gawley in the accompanying report,[16] does not show stereospecific proton removal but proceeds to a thermodynamic lithiated species which alkylates in a similar fashion. The bidentate C described herein, as opposed to a monodentate species in Gawley's system, is probably responsible for the difference in deprotonation behavior, since strong chelation of organolithiums with chiral formamidines inhibits metalation of piperidines and pyrrolidine derivatives,[17] an event not observed with the oxazoline chiral auxiliary.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this program.

(16) Gawley, R. E. *J. Am. Chem. Soc.*, following paper in this issue.
(17) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.

Thermodynamic Control in the Asymmetric Alkylation of the Dipole-Stabilized Anions of Chiral Aminooxazolines†

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The alkylation of dipole-stabilized anions has become an increasingly important methodology for carbon-carbon bond formation adjacent to heteroatoms, especially nitrogen.[1] In recent years, *asymmetric* alkylation of nitrogen heterocycles using formamidines as chiral auxiliaries has shown tremendous potential.[2] Generally, dipole-stabilized anions are believed to exist in a conformation in which the carbanion lone pair (or the carbon-lithium bond) is orthogonal to the π-system, with a calculated 22.3 kcal/mol preference.[3] Moreover, dipole-stabilized anions are thought to be configurationally stable.[3a] Relatively little is known about the processes governing the asymmetric alkylation of chiral dipole-stabilized anions, although chiral tetrahydroisoquinoline and β-carboline formamidines undergo highly stereoselective deprotonations as the first step of an efficient asymmetric alkylation sequence.[4]

In our initial study of the asymmetric alkylation of (tetrahydroisoquinolyl)oxazolines, the diastereomer ratio (**2**/**3**, Scheme I) was not significantly affected by either the structure of the base (*n*-BuLi, *sec*-BuLi, or *t*-BuLi) or the deprotonation temperature, whereas the temperature of the alkyl halide quench did exert an effect.[5] These results are inconsistent with a seteroselective deprotonation as the source of the asymmetric induction. Evidence is now provided that *the β-proton at C_1 is indeed removed stereoselectively but that the resulting anion is equilibrated to a thermodynamic mixture of diastereomeric lithiated species and that the latter process accounts for the stereoselectivity observed in the overall process.*

Quenching of lithiated formamidines with CH_3OD has been shown to produce a mixture of deuteriated diastereomers, whereas

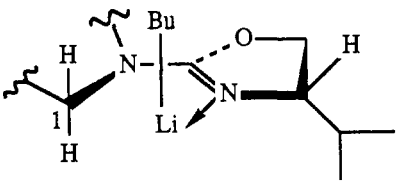
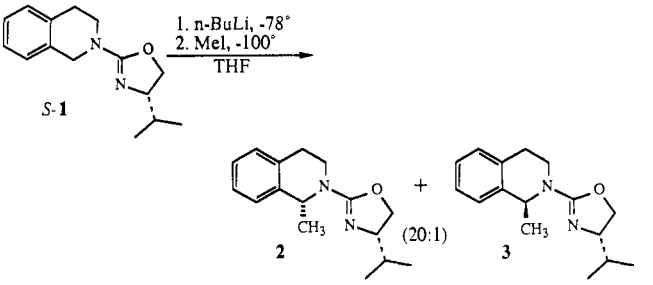
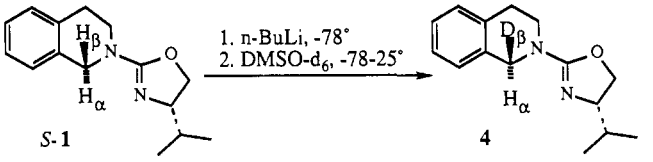


Figure 1. Coordination complex of (*S*)-**1** and butyllithium.

Scheme I



Scheme II



quenching with Me_2SO-d_6 is highly stereoselective.[4] The same behavior is exhibited by (tetrahydroisoquinolyl)oxazolines. Thus, when isoquinoline (*S*)-**1** is lithiated and quenched with CH_3OD, workup affords a 1:1 mixture of deuteriated epimers.[6] Quenching lithiated (*S*)-**1** with Me_2SO-d_6 at −78 °C and warming to room temperature afford a 96:4 mixture of the two 100% deuteriated[7] epimers, **4** (Scheme II). The absolute configuration of the major epimer at C_1 is *S*, as determined by comparison with an authentic sample.[8] It is noteworthy that the absolute configuration of the major deuteriated isomer at C_1 in **4** is opposite that in **2**. Furthermore, the stereoselective deuteriation does not occur until the reaction mixture is warmed up, conditions which afford poor asymmetric induction with methyl iodide.

When (β-deuterioisoquinolyl)oxazoline **4** was deprotonated at −78 °C and quenched with methyl iodide at the same temperature, the methylated product, **6**, was obtained in 84% de but contained 50% deuterium (Scheme III). Since the D/H ratio (1/1) is not the same as the diastereomer ratio (12/1), *the stereoselectivity observed in the overall alkylation cannot be due to stereoselectivity in the deprotonation.* In contrast, deprotonation and methylation of (α-deuterioisoquinolyl)oxazoline **5**[9] at −78 °C afforded about the same degree of asymmetric induction (82% de), but the products contained 97% deuterium.

Thus, *the deprotonation is stereoselective, but the selectivity of the deprotonation cannot account for the stereoselectivity observed in the overall process.* The selectivity of the deprotonation can be explained by a conformational preference of the

† Dedicated to Professor Ernest Eliel on the occasion of his 65th birthday.
(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) For reviews, see: Meyers, A. I. *Lect. Heterocycl. Chem.* **1984**, *7*, 75-81. Meyers, A. I. *Aldricimica Acta* **1985**, *18*, 59-68. Meyers, A. I.; Fuentes, L. M.; Boes, M.; Dickman, D. A. *Chem. Scr.* **1985**, *25*, 25-31.
(3) (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.
(4) (a) Loewe, M. F.; Boes, M.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3295-3298. (b) For a more recent study, see: Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.*, preceding paper in this issue.
(5) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076-3078.

(6) The ratio of deuteriated epimers was determined by 360-MHz NMR. The C_1 proton of **4** (Scheme II) resonates at δ 4.575, whereas the C_1 proton of **5** (Scheme III) resonates at δ 4.535. Accurate integration was accomplished by simultaneous gated decoupling of the deuterium resonance.
(7) Deuterium incorporation was determined from mass spectroscopic data. At 40 eV, the molecular ions of compounds **1**-**3** are <5% abundant. The base peak for all three components is at M − 43, arising from loss of isopropyl, and the deuterium content is readily available by analysis of the M − 43 fragment ions of **4**-**6**.
(8) (*R*)-1-Deuteriotetrahydroisoquinoline has been synthesized independently from (*R*)-1-deuteriobenzylamine by D. A. Dickman and A. I. Meyers, see the preceding paper in this issue. A comparison has revealed that the 1-deuteriotetrahydroisoquinoline obtained by hydazinolysis of the mirror image of **4** also has the *R* configuration.
(9) Compound **5** was synthesized from (*R*)-**1**, by exchange of chiral auxiliaries from the enantiomer of **4** (Scheme II).

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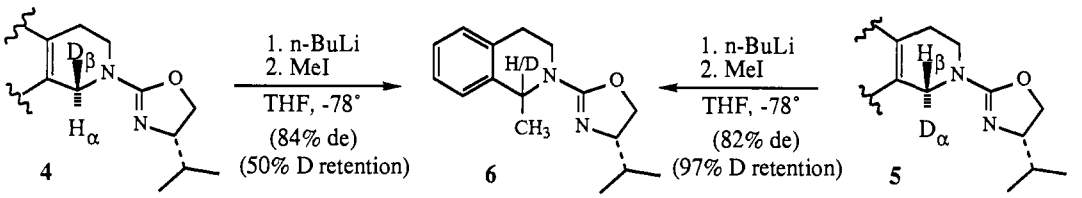
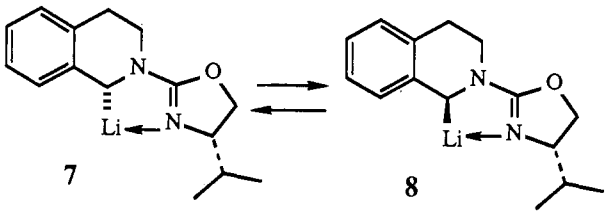
Scheme III



coordinated alkyllithium whereby the butyl group is anti to the isopropyl (Figure 1).

The stereoselectivity in the deprotonation is determined quantitatively by the relative rates of abstraction of the two protons, H_α and H_β (Scheme II). This quantity, as well as the isotope effect, can be calculated from the ratios of 6D/6H obtained from **4** and **5**.[10] The calculations yield a relative rate of 5.8 and an isotope effect of 5.9.[11] Thus, when the deuterium is up (as in **4**, Scheme III), the stereoselectivity of the deprotonation (loss of D_β favored) is opposed by the kinetic isotope effect, which directs the base to H_α. The result is deprotonation at both sites. In contrast, when the deuterium is down (as in **5**, Scheme III), both the stereoselectivity of the deprotonation and the isotope effect work in concert, directing the base to H_β, and virtually complete retention of deuterium is observed.

I believe that since both deuteriated epimers give the same diastereomeric product ratios while at the same time deprotonating via different mechanisms, a set of equilibrating lithiated aminooxazolines such as **7** and **8** are implicated. It also is possible that



there are equilibrating ion-pair aggregates, but further work is required on this point. It is interesting that the stereochemical sense by which these equilibrating anions are quenched is a function of the electrophile. Most intriguing is the opposite configuration obtained when the lithiated oxazolines are quenched with RX and Me_2SO-d_6. Two possibilities seem to be the most likely explanations: (1) that the position of the equilibrium is reversed when Me_2SO is added or (2) the organolithium is quenched with retention of configuration in one case and inversion in the other. The two possibilities cannot be distinguished with the presently available data.[12]

These results are consistent with those reported by Meyers and Dickman in the accompanying paper.[4b] The difference between the formamidines and the oxazolines is the lack of an isotope effect in the deprotonation of the formamidines. A dependence of asymmetric induction on the temperature of the alkyl halide quench of lithiated formamidines has been noted,[13] raising the possibility of thermodynamic control of equilibrating organolithiums in that system as well. It is noteworthy that bidentate chelation of the lithium by the chiral auxiliary is not necessary for high levels of asymmetric induction (cf., Scheme I). However, a "monodentate" formamidine derived from α-methylbenzylamine gives only moderate selectivity (10–52%).[13] What *is* required for good asymmetric induction is a nonrotating bond between the ligating nitrogen and the stereocenter of the chiral auxiliary. In the oxazolines, this is provided by the ring. In the formamidines, bidentate chelation serves the same purpose.

Summary. The experiments descibed herein clearly demonstrate that the stereoselectivity which exists in the deprotonation to form dipole-stabilized anions of aminooxazolines is not the source of the stereoselectivity observed for the overall process. The relative rates of deprotonation indicate that **8** is the diastereomer formed initially, consistent with a coordinated alkyllithium base preferring to a adopt a conformation anti to the isopropyl. The stereochemical sense of the reaction has the lithiated isoquinolyloxazolines (when drawn as in either **7** or **8**) being quenched by alkyl halides from the same side as the isopropyl but from the opposite side with Me_2SO.

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(10) Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807–1816. The only assumption involved is that the isotope effect is the same for H_α and H_β. The isotope effect is given by IE = $(6D/6H)_4^{1/2}(6D/6H)_5^{1/2}$ while the relative rates are given by k_β/k_α = $(6D/6H)_5^{1/2}/(6D/6H)_4^{1/2}$, where $(6D/6H)_4$ and $6D/6H)_5$ are the deuterium to hydrogen ratios in both stereoisomers of **6**, obtained from **4** and **5**, respectively. The actual values are $(6D/6H)_4$ = 1.01 and $(6D/6H)_5$ = 34.5.

(11) The results are subject to some error due to the less than 100% stereoselectivity in the Me_2SO-d_6 deuteriation but clearly indicate that the kinetic isotope effect and the stereoselectivity of the deprotonation are of comparable magnitude.

(12) We have recently learned that in a related system (isoindolyloxazolines), the stereochemical preference for alkylation is reversed when the solvent is changed from THF to ether: Chemburkar, S., unpublished results. **Note Added in Proof.** In side-by-side experiments at −78 °C, the ratio of **2** to **3** (Scheme I) was 9/1 in THF and 2/1 in ether.

(13) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117–118.

Magnetic Interaction of Two Diphenylcarbene Units Linked with an Ethylenic Double Bond

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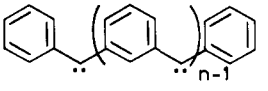
In 1967, Itoh and Wasserman et al. established independently that the dicarbene **1**, consisting of two phenylcarbene units attached to the meta positions of a benzene ring, had a quintet ground state.[1] The finding awoke both the experimental[2] and



1: n = 2
2: n = 4

theoretical[3] interests in organic high-spin molecules and partic-

(1) (a) Itoh, K. *Chem. Phys. Lett.* **1967**, *1*, 235. (b) Wasserman, E.; Murray, R. W.; Yager, W. A.; Trozzolo, A. M.; Smolinsky, G. *J. Am. Chem. Soc.* **1967**, *89*, 5076.

(2) (a) Wasserman, E.; Schueller, K.; Yager, W. A. *Chem. Phys. Lett.* **1968**, *2*, 259. (b) Brickman, J.; Kothe, G. *J. Chem. Phys.* **1973**, *59*, 2807. (c) Takui, T.; Itoh, K. *Chem. Phys. Lett.* **1973**, *19*, 120. (d) Itoh, K. *Pure Appl. Chem.* **1978**, *50*, 1251. (e) Teki, Y.; Takui, T.; Yagi, H.; Itoh, K.; Iwamura, H. *J. Chem. Phys.* **1985**, *83*, 539.

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