recrystallization from acetonitrile: ^{1}H NMR ($CDCl_3$) δ 7.35–8.0 (m, 8 H), 3.87 (s, 3 H), 3.29 and 3.15 (q, AB, 2 H, J = 18.2 Hz), 2.49 (br s, 1 H). ^{1}H NMR of **7b** ($CDCl_3$): δ 7.35–8.0 (m, 8 H), 4.33 (q, 2 H), 3.32 and 3.19 (q, AB, 2 H, J = 18.2 Hz), 2.71 (br s, 1 H), 1.29 (t, 3 H).

Preparation of 2,3-Dihydro-2-oxo-1*H*-cyclopenta[*l*]phenanthrene (8). Compound 8 was obtained from treatment of **7a** or **7b** with hydroiodic acid followed by sodium bisulfite solution.[16] From several attempts to synthesize 8 in this way, we found it necessary to modify the published workup procedure in order to get an acceptable purity of the compound. The dark greenish material was air-dried, ground in a mortar, and mixed with Celite (0.4 g per gram of crude product). The mixture was then Soxhlet extracted with absolute ethanol. Care was taken to avoid overheating and charring of precipitated material. After the first 20–25 extraction cycles, the brown solution was replaced with pure solvent, and the extraction was continued for 24 h. The light green material so obtained melted around 206 °C. After recrystallization from dioxane, the material melted at about 217 °C (lit.[16] mp 223–223.6 °C): ^{1}H NMR ($CDCl_3$) δ 8.65–8.71 (m, 2 H), 7.50–7.72 (m, 6 H), 3.63 (s, 4 H).

Preparation of the Tosylhydrazone 9 of Ketone 8. To a gently boiling stirred solution of 8 (0.70 g, 3.0 mmol) in a mixture of 70 mL of absolute ethanol and 30 mL of dioxane was added a lukewarm solution of (*p*-tolylsulfonyl)hydrazine (0.59 g, 3.4 mmol) in 30 mL of absolute ethanol, followed by 1 mL of glacial acetic acid. The product rapidly precipitated from the boiling solution. The mixture was allowed to cool while still being stirred. The precipitate was filtered, washed with ethanol, and air-dried. The off-white **9** weighed 1.02 g (85%) and melted with rapid decomposition at about 208 °C: ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1 H), 8.77–8.92 (m, 2 H), 7.43–8.00 (m, 10 H), 4.08 (s, 2 H), 4.02 (s, 2 H), 2.45 (s, 3 H).

Preparation of 5. This synthesis (a Shapiro reaction)[17] is an alternative to an earlier described method for the preparation of **5**.[16] To a stirred suspension of **9** (1.0 g, 2.5 mmol) in 40 mL of dry THF was added under argon 5 mL (ca. 7.5 mmol) of *n*-BuLi (ca. 1.5 M in hexane) at room temperature during 0.5 h. After an additional hour, the brown-red reaction mixture was carefully quenched with water. After ether extraction, the organic phase was washed with water and dried with $MgSO_4$. The solid material obtained on evaporation was column chromatographed on silica gel 60 with CCl_4. The white crystalline material obtained after removal of the CCl_4 was dissolved in a small amount of CH_2Cl_2 and passed through a small pad of silica gel supported on glass wool in a Pasteur pipet. The solvent was evaporated with a stream of argon, giving 140 mg (26%) of white crystals of **5**. The yield for this synthesis represents nonoptimal conditions: ^{1}H NMR ($CDCl_3$) δ 8.7–8.8 (m, 2 H), 8.0–8.3 (m, 2 H), 7.5–7.8 (m, 5 H), 6.7–6.8 (m, 1 H), 3.86 (t, 2 H, J = 1.7 Hz).

Preparation of Carbanions. The ether solutions of the different compounds in NMR tubes were initially degassed and subsequently disconnected from the vacuum line in an argon atmosphere. Typically, 2–4 equiv of concentrated *n*-BuLi (8–10 M) was added to cooled samples. The NMR tubes were then again evacuated and finally sealed off from the vacuum line. The NMR spectra of the carbanions were obtained on a Bruker WM-250 spectrometer, except for the 2D inverse relayed coherence transfer and inverse long-range shift-correlated assignment experiments which were performed on a Bruker AM-500 instrument. The chemical shifts were measured relative to internal cyclohexane and adapted to the TMS scale with δ ^{1}H (cyclohexane) = 1.43 ppm and δ^{13}C (cyclohexane) = 27.70 ppm. The reported NMR data refer to room temperature measurements with sample concentrations of 0.05–0.2 M.

Acknowledgment. We gratefully acknowledge support from the Swedish Natural Science Research Council to B.E. and U.E. and from the Fund of Basic Research, administered by the Israel Academy of Science and Humanities, to M.R.

Registry No. **4**, 29045-70-3; **4**$^-$, 117775-62-9; **5**, 235-92-7; **5**$^-$, 117775-63-0; **6**$^-$, 117775-64-1; **7a**, 117775-59-4; **7b**, 117775-60-7; **8**, 37913-11-4; **9**, 117775-61-8; 1,3-bis(triphenylphosphonio)propane dibromide, 7333-67-7; biphenyl-2,2′-dicarbaldehyde, 1210-05-5; (*p*-tolylsulfonyl)hydrazine, 1576-35-8.

(17) For reviews on the Shapiro reaction, see: (a) Shapiro, R. H. *Org. React. (N.Y.)* **1976**, *23*, 405. (b) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

Chiral Dipole-Stabilized Anions: Experiment and Theory in Nonbenzylic Systems. 100% Stereoselective Deprotonation and Two-Electron vs Single-Electron Transfer in the Chemistry of Lithium and Copper Piperidinooxazolines

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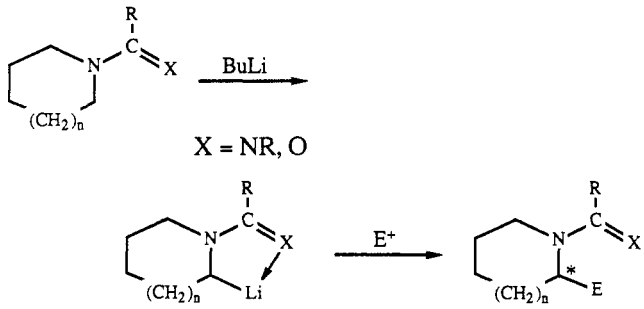
A chiral oxazoline derived from valine mediates the 100% stereoselective deprotonation of the 2-position of piperidine, forming a single diastereomer organolithium, which is dipole-stabilized. The organolithium species undergoes either two electron or single electron transfer processes, but the latter predominate for most electrophiles. The corresponding cuprates undergo only single electron transfer processes. MNDO calculations indicate little difference in energy between most of the conformational and stereoisomers of the organolithium, suggesting that the single organolithium diastereomer is formed under kinetic control. Mechanistic rationales for the unprecedented deprotonation, as well as the single electron transfer processes, are presented.

Dipole-stabilized anion mediated alkylation of carbons bearing heteroatoms is a useful process for the elaboration of a number of systems.[1] One such application is the α-alkylation of a nitrogen heterocycle. Among the more versatile functional groups for mediation of this process via dipole stabilization of the intermediate carbanion are aliphatic or aromatic amides and formamidines. The generalized process illustrated below generates a stereocenter, and so a stereoselective process aimed at the preparation of homochiral compounds would be highly desirable. The first example of such a process was reported

(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.

0022-3263/89/1954-0175$01.50/0

by Meyers for the α-alkylation of tetrahydroisoquinoline, but the process was quickly extended to β-carbolines and other allylically activated systems.[2]

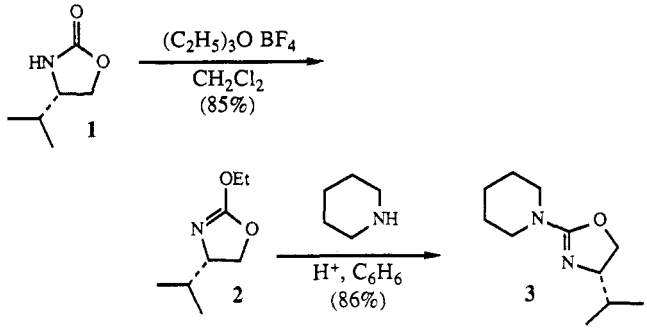


Unfortunately, the formamidine chiral auxiliaries that work so well when the metalated carbon is allylic or benzylic fail completely when it is not.[3] This failure has been attributed to a complex induced proximity effect, whereby bidentate chelation in the formamidine coordinates the alkyllithium base and prevents approach by the base to the "acidic" protons.[4] More vigorous conditions lead to destruction of the formamidine by addition across the C=N bond.

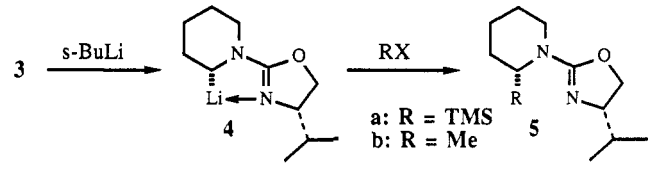
We recently introduced[5] an oxazoline auxiliary whose performance is comparable to the formamidines in benzylically activated systems,[6] *but which also mediates the deprotonation of nonactivated positions.* We now report the details of our initial investigation into the chemistry of these species as mediators for the metalation of piperidine and the reactions of the derived organolithium and organocopper species with alkyl halides.[7]

Results

Synthesis and Attachment of the Chiral Auxiliary. Alkylation[8] of the well-known[9] oxazolone **1** with Meerwein's reagent[10] afforded ethoxyoxazoline **2** in 85% yield. Condensation of **2** with piperidine afforded **3** in 86% yield.

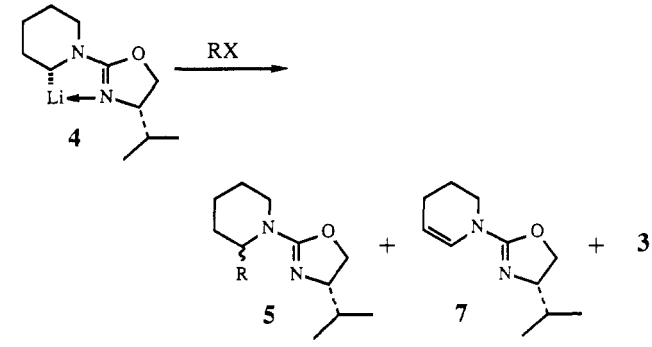


Lithiation and Alkylations. Metalation of **3** is best achieved by treating a mixture of **3** (0.5M) and 0.1 equiv of tetramethylethylenediamine (TMEDA) with 1.1–3.0 equiv of *sec*-butyllithium in 9/1 ether/tetrahydrofuran (THF) for 1 h at −23 °C (CCl_4/CO_2 slush). Quenching this anion with trimethylsilyl chloride affords a 96% yield of **5a**, indicating complete deprotonation under the stated conditions.



Capillary gas chromatography (50 m, 5% phenyl methyl siloxane) indicates that **5a** is a single diastereomer,[11] but attempts to remove the auxiliary and confirm the presence of a single enantiomer or assign its configuration resulted in destruction of the silylated heterocycle. Methylation of **4** with methyl iodide affords a 30% yield of **5b**. Again, capillary GC indicates a single diastereomer. Condensation of racemic 2-methylpiperidine with ethoxyoxazoline **2** affords a 1:1 mixture of the two possible diastereomers, and comparison with **5b** obtained by alkylation confirms that, within the limits of detection, *the alkylation is 100% stereoselective.* Removal of the chiral auxiliary and Pirkle analysis[12] indicate that the absolute configuration is *R*, as drawn.

Whereas the quenching of the organolithium with trimethylsilyl chloride afforded an excellent yield of coupled product (**5a**), the same reaction afforded only a 30% yield of **5b**. The rest of the reaction mixture consisted of roughly equal amounts of starting material, **3**, and an oxidation product, **7**. Propyl bromide afforded a mixture of starting material, **3**, coupling product, **5c**, and oxidation product, **7**, while hexyl bromide, undecyl bromide, and allyl bromide yielded only **3** and **7**. However, in all cases *except* methyl iodide and trimethylsilyl chloride, the coupling product **5** was obtained in <2% de.



c: R = $(CH_2)_2CH_3$
d: R = $(CH_2)_4CH{=}CH_2$
e: R = CH_2-c-C_5H_9

Transmetalation to Copper. Reaction of **4** with cuprous cyanide (1 equiv) followed by methyl iodide afforded a 53% yield of **5a**, with none of the oxidation product present, but the stereoselectivity was gone: the diastereomer ratio was 1/1. A few other electrophiles were reacted with this mixed lower order cuprate (propyl bromide,

(2) For reviews, see: (a) Meyers, A. I. *Aldrichimica 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.

(3) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974-7978.

(4) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363.

(5) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076–3078.

(6) Gawley, R. E.; Smith, G. A. *Tetrahedron Lett.* **1988**, *29*, 301–2.

(7) Taken in part from the Ph.D. Dissertation of Georgina C. Hart, University of Miami, 1988.

(8) Coppola, G. M. *J. Heterocycl. Chem.* **1981**, *18*, 767–770.

(9) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(10) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 1080–1082.

(11) The presence of a single chromatographic peak does not, in and of itself, constitute proof of a single diastereomer. However, in extensive work with aminooxazolines, we have never encountered a 2-substituted heterocyclic system in which the two diastereomers are inseparable by this method. Thus we are confident of this assertion, which is substantiated by the proof of a single diastereomer of **5b**.

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

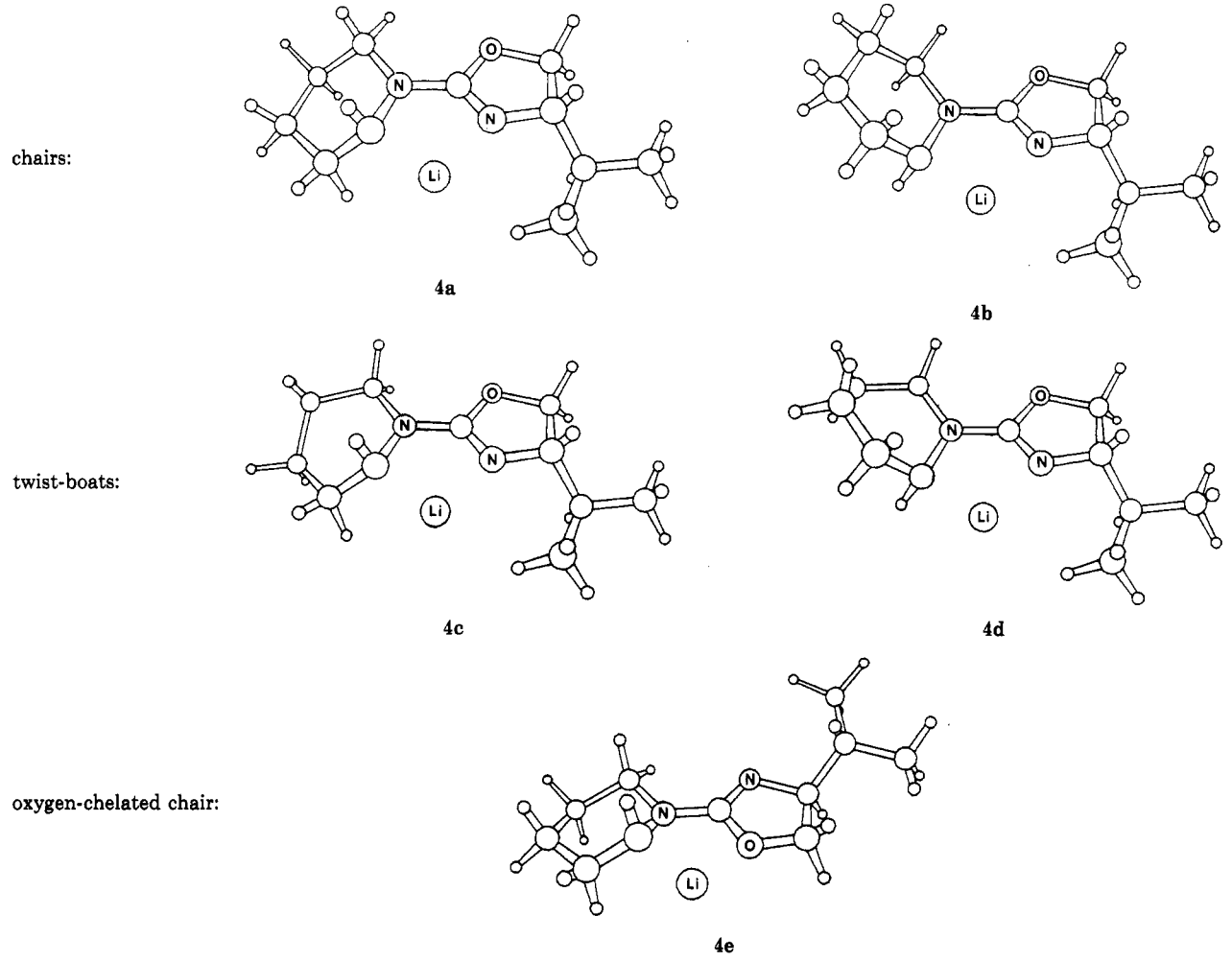


Figure 1. MNDO geometry-optimized organolithium stereoisomers.

iodide, and tosylate, hexyl bromide), but none gave coupling products. In all cases, the reaction contained only mixtures of **7** and **3** in varying amounts. Other nontransferring ligands were tried as well: PhS,[13] $CH_3OC(CH_3)_2C{\equiv}C$,[14] $CH_3SO_2CH_2$,[15] and **3**. When treated with either propyl bromide or methyl iodide, all of the mixed cuprates gave only mixtures of **7** and **3**, again in varying amounts.

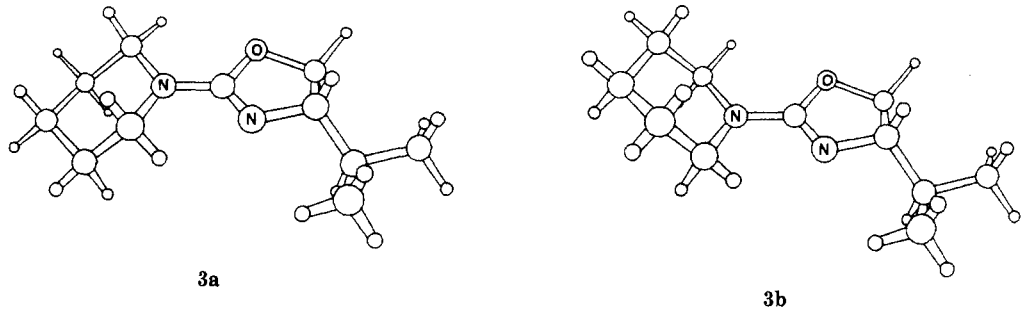
Theoretical Considerations. There are two chair conformations of piperidinooxazoline **3**, which semiempirical (MNDO) calculations reveal to be isoenergetic: $\Delta H < 0.1$ kcal/mol. Four diastereomeric organolithium species (**4a–d**) having the lithium syn to the oxazoline nitrogen are also estimated (MNDO) to be isoenergetic: $\Delta H < 0.1$ kcal/mol. Two of these are chairs, and two are twist-boats (Figure 1). A fifth possible organolithium, **4e** (Figure 1), has the lithium syn to the oxazoline oxygen and arises by 180° rotation around the horizontal N–C bond in **4a**. Calculations indicate that this structure is 11 kcal/mol less stable than **4a–d**.

Discussion

Chiral Auxiliary Design. The first goal of this project was the design of a chiral auxiliary that would mediate the deprotonation of a nonallylic (i.e., unactivated) site. Both amides[16] and *tert*-butylformamidines[17] are capable of this, but *the crucial difference between these activating groups and the chiral formamidines is the presence of a second ligating atom in the latter.* This ether oxygen was introduced in the chiral formamidine specifically to impart rigidity to the intermediate lithiated species in the hopes of achieving high stereoselectivity in the alkylation of a site five atoms removed from the existing stereocenter.[2a] *But its presence precludes metalation of a saturated heterocycle.*[3] Our chiral auxiliary was designed by modifying the formamidine auxiliary as follows. First, the ligating oxygen atom was removed to give species A, which can only bond in a monodentate fashion. In order to restrict rotation of the bond between the nitrogen and the stereocenter[18] (circled), a bond is needed between the two centers indicated in A. If the atom indicated in B (*) is a carbon, it would have to be disubstituted to prevent deprotonation there. An easier alternative is to substitute

(13) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788–7800.
(14) Corey, E. J.; Floyd, D. M.; Lipschutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418–20.
(15) Johnson, C. R.; Dhanoa, D. S. *J. Chem. Soc., Chem. Commun.* **1982**, 358.
(16) (a) Beak, P.; McKinnie, B. G.; Reitz, D. B. *Tetrahedron Lett.* **1977**, 1839–42. (b) Schlecker, R.; Seebach, D.; Lubosch, W. *Helv. Chim. Acta* **1978**, *61*, 512–26. (c) Seebach, D.; Wykpiel, W.; Lubosch, W.; Kalinowski, H. O. *Helv. Chim. Acta* **1978**, *61*, 3100–2. (d) Beak, P.; Brubaker, G. R.; Farney, R. *J. Am. Chem. Soc.* **1976**, *98*, 3621–27. (e) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrashekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4108–4110.
(17) (a) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270–3276. (b) Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E., Jr. *J. Org. Chem.* **1985**, *50*, 1019–1026.
(18) A chiral formamidine lacking bidentate chelation and therefore having free rotation around this bond affords poor stereoselectivity: Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361–70.

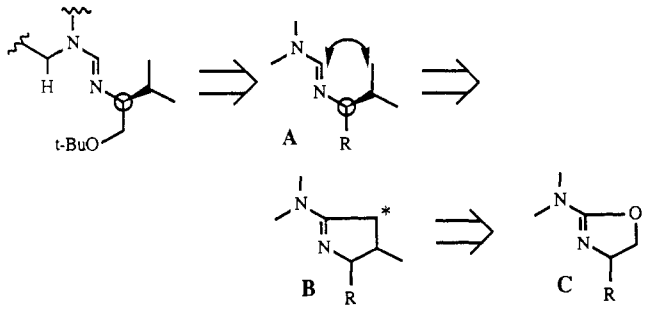
chairs:



3a 3b

Figure 2. Molecular mechanics calculated structures for piperidinooxazoline 3.

a heteroatom, either oxygen or sulfur. Since amino acids are easily reducible to chiral amino alcohols,[19] an oxazoline seemed preferable, as in C.[20]



Mechanism of the Deprotonation. It has already been shown for conformationally rigid piperidine amides[16] and formamidines[17] that alkylation occurs in the equatorial position, and ab initio calculations on model systems suggest that the lone pair or carbon–lithium bond is orthogonal to the π-system of the amide.[16e,21] Thus, it has been generally assumed on both theoretical and experimental grounds, that the organolithium species does not undergo pyramidal inversion and that the lithium is equatorial in piperidine systems. Although we have recently shown that lithiated tetrahydroisoquinolyloxazolines *do* undergo pyramidal inversion at very low temperatures, this phenomenon is due to the fact that the organolithium is benzylic.[22]

We base our conclusions regarding the piperidinooxazoline deprotonation on the following facts: 1. MNDO calculations reveal no differences in the energies of four stereoisomeric organolithiums, **4a–d**. 2. Previous studies have shown that lithiated piperidines alkylate equatorially and do not invert.[16c,e,17a,21] 3. The alkylation of the organolithium with methyl iodide is 100% selective, and the absolute configuration is *R*. Alkylation with trimethylsilyl chloride also appears to be 100% selective.

Since the alkylation is 100% stereoselective, and since **4** cannot invert, *it follows that the deprotonation is 100% stereoselective, and that 4 is a single epimer.* Dipole stabilization dictates that the lithium be equatorial, so it is impossible for the alkylation to occur with inversion of configuration.[23] Therefore **4** must be *R* and *the* C_2-α *hydrogen of the piperidine must have been removed selectively.*

3a•BuLi complex **3b**•BuLi complex

Figure 3. Coordination complex of *sec*-butyllithium and **3**.

Stereoelectronic considerations also dictate that an equatorial proton be removed.[16c,e] By analogy with other systems, coordination of the alkyllithium probably precedes deprotonation, and we propose that prior coordination occurs at the oxazoline nitrogen rather than oxygen (vide infra). Examination of the two chair conformers suggests a reason for the selective C_2-α-proton removal. Figure 2 illustrates the MM2-calculated chair structures, in which the equatorial hydrogens syn to the oxazoline nitrogen are blackened.

The C_2-α-proton is equatorial in **3a**. The selectivity can be rationalized by assuming prior coordination of the alkyllithium to the oxazoline nitrogen and orientation of the alkyl group anti to the isopropyl (see Figure 3). In **3a**, this would place the butyl group on the convex face of the molecule, while in **3b**, the butyl group would be on the concave face, severely crowded by the axial hydrogens of the piperidine. Thus, steric effects dictate a preference for the **3a**·BuLi complex. A similar coordination complex was recently postulated to account for the stereoselectivity of deprotonation of tetrahydroisoquinolyloxazolines.[22] *Thus, the stereoselectivity observed in this sequence is a product of kinetic control in the deprotonation and is directed by the stereoelectronic requirements for dipole stabilization and steric effects in the coordination complex.*

Lithiation and alkylation of **5b** is consistent with this hypothesis. Only one dialkylated product is formed, as indicated by NMR[24] and GC analysis, namely the trans isomer **6**. Assuming the methyl group in **5b** is more stable in the axial conformation (to avoid the oxazoline) and that the deprotonation occurs via a coordination complex similar to that postulated above, deprotonation would be expected to yield the lithium species shown, and alkylation should give *trans*-**6**, as it does.

As outlined above, we contend that the nitrogen is the site of alkyllithium complexation on the oxazoline, and we

(19) Smith, G. A.; Gawley, R. E. *Org. Synth.* **1984**, *63*, 136–9. 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, in press (Collect. Vol. VII).

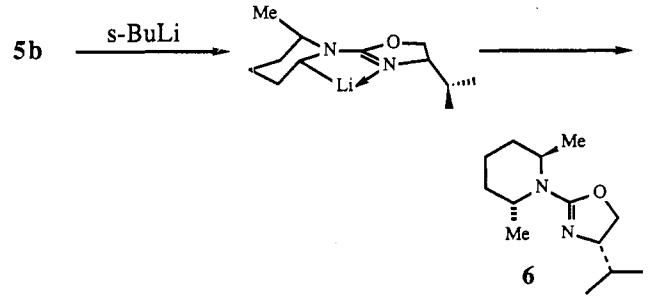
(20) It is coincidental and perhaps ironic that this analysis of Meyers' *formamidine* chemistry led us to design an *oxazoline* auxiliary.

(21) Bach, R. D.; Braden, M. L.; Wolber, G. J. *J. Org. Chem.* **1983**, *48*, 1509–14.

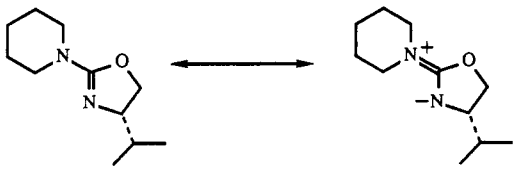
(22) Gawley R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265–6. Rein, K. R.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G.; Smith, G. A.; Gawley, R. E., submitted for publication in *J. Am. Chem. Soc.*

(23) The asymmetric alkylation of chiral tetrahydroisoquinolylformamidines has been postulated to occur with inversion, but again this system is benzylic: Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263–5.

(24) In the trans isomer, the symmetry-related atoms in the piperidine are homotopic, whereas in the cis isomer, they are diastereotopic. At 500 MHz, the methyl protons are isochronous, leaving little doubt as to the assignment.



predicate our mechanistic rationale on this hypothesis. Simple valence bond theory suggests that this is the case, by delocalization of the piperidine–nitrogen electrons as shown:

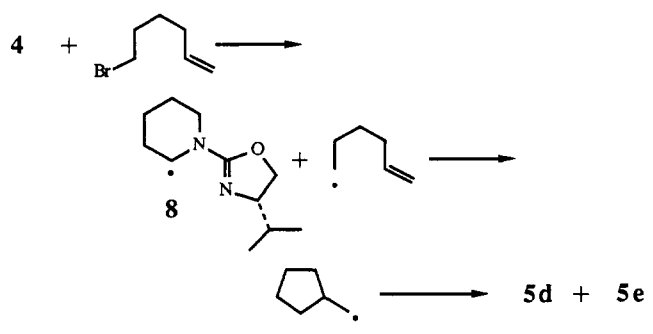


This contention is verified by density functional theory as well. It was recently shown that condensed fukui functions obtained using ab initio methods, which reflect the site reactivity, may be used to explain the gas-phase basicities of amines.[25] In the present instance, we use the condensed fukui function

$$f^-_i = q_i(n-1) - q_i(n)$$

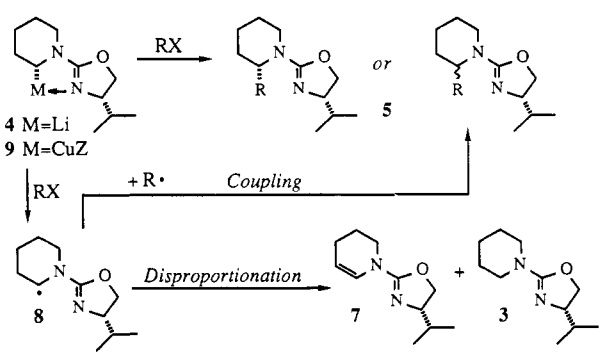
which indicates susceptibility to electrophilic attack. Here q_i are the Mulliken gross charges as calculated using the MNDO program, and n represents the total number of electrons in the molecule. The ratio of f^-_i for two atoms expresses the relative susceptibility to attack by an electrophile. The f^-_i values calculated with the MNDO structures **3a** and **3b** indicate that the oxazoline nitrogen is the most basic atom in the molecule and that it is significantly more prone to electrophilic attack than the oxazoline oxygen. For structure **3a**, $f^-_N/f^-_O = 4.0$, while for **3b**, $f^-_N/f^-_O = 5.1$, indicating an ≥4-fold difference in basicity for the two atoms.

Mechanisms of the Coupling with Alkyl Halides. Different mechanisms give rise to the 100% stereoselective products vs the nonselective products. That a single electron transfer process is responsible for the latter is shown by quenching **4** with the radical probe 5-hexenyl bromide. A mixture of **5d** and **5e** was formed, each as a 1:1 mixture of diastereomers. Formation of these products is consistent with a radical pathway, with consumption of the 5-hexenyl radical competing with cyclization to cyclopentylmethyl radical followed by coupling with 8, as shown below.[26]



(25) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708–5711.

Scheme I



Single-electron transfer also accounts for the presence of both the oxidation product, **7**, and the starting material, **3**, by disproportionation of radical **8**.[27] The loss of stereochemistry and the presence of oxidation product **7** in the cuprate reactions also suggests single-electron transfer (SET), but we were unable to verify SET in the same way since coupling was not observed with 5-hexenyl bromide. To our knowledge, this is the only example of a single electron transfer mechanism in an organocuprate cross-coupling detected by a change in stereochemistry of the transferring ligand.

A summary of the pathways observed are outlined in Scheme I. Metalation of **3** efficiently produces a single epimer of an organolithium, **4**. Transmetalation gives a cuprate, **9**. When treated with an alkyl halide the metalated piperidinooxazolines either couple in a two-electron transfer to give **5** in 100% de or undergo single-electron transfer to a mixture of radicals. Radical coupling affords **5** in 0% de, while disproportionation of **8** gives a mixture of starting material, **3**, and the oxidation product **7**.

The lithiated species, **4**, undergoes two-electron coupling with methyl iodide but simultaneously disproportionates as well. Although the disproportionation products must certainly have arisen from **8**, it is not clear why **8** does not couple with methyl radical. Possibly the methyl iodide radical anion decomposes by a pathway different than the other radical anions, or perhaps it just has a longer lifetime than **8**, which disproportionates faster than it can react with either methyl iodide radical or radical anion. With other alkyl halides, **4** undergoes only single electron transfer processes (both coupling and disproportionation). *We suggest that whether the metalated species undergoes single-electron transfer or two-electron coupling is a function of both the reduction potential of the alkyl halide and the oxidation potential of the organometallic.* Similar trends have been observed in the cross-coupling of organocuprates with alkyl halides: those alkyl halides whose reduction potentials are less negative are *more* prone to undergo single-electron transfer.[28]

Lipschutz has measured the reduction potential of a number of alkyl halides in THF and noted that the reduction potential varies with both the structure of the alkyl group and the identity of the halide.[29] Secondary alkyl

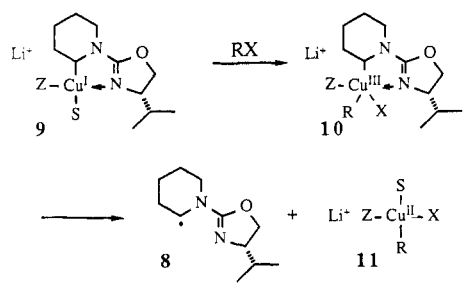
(26) A similar result was obtained in the alkylation of lithiated piperidine *N-tert*-butylformamidines, although it was of no stereochemical consequence since the substrate was achiral, and no rationale was given for the oxidation. See ref 17a.

(27) Previously, we attributed the presence of **3** to an unknown proton source, ref 5.

(28) (a) Lipschutz, B. H.; Wilhelm, R. S. Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038. (b) Lipschutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696–8. (c) Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251–4.

(29) Lipschutz, B. H.; Wilhelm, R. S.; Nugent, S. T.; Little, R. D.; Baizer, M. M. *J. Org. Chem.* **1983**, *48*, 3306–8.

Scheme II



iodides show a reduction potential slightly less negative than primary alkyl iodides. Although it was not measured, it is reasonable to assume that methyl iodide's reduction potential follows the trend and is more negative than a primary alkyl iodide. Thus cuprates undergo single-electron transfer when the alkyl halide reduction potential is less negative, but SET only has a stereochemical consequence when the alkyl halide is chiral and nonracemic. We observe the same trend with the lithiated piperidino-oxazolines: primary alkyl iodides give exclusive single-electron transfer (*detected in the piperidine*) while methyl iodide, with a presumably more negative reduction potential, exhibits both SET (disproportionation to 7 + 3) and two-electron coupling (5 in 100% de).

When transmetalated to copper (i.e., 9), only single electron transfer processes are observed. The proposed mechanism for the cuprate single electron transfer process is outlined in Scheme II. Oxidative addition of an alkyl halide produces a copper(III) complex, 10. This species is probably highly unstable and may not even be at an energy minimum. Homolytic cleavage of the carbon–copper bond gives radical 8 and a copper(II) species, 11. The relative lifetimes and reactivities of 8 and 11 then determine whether disproportionation or coupling is observed.

Studies of other transmetalations in this and related systems are under way and will be reported in due course.

Experimental Section

General Procedures. Molecular mechanics calculations were facilitated by the MACROMODEL program, version 1.5, developed by Professor W. Clark Still, Columbia University, Copyright 1986. The MM2 force field in this program is that of Allinger,[30] the parameters are from QCPE Program 395. Semiempirical (MNDO[31]) calculations were accomplished by using the MOPAC program.[32]

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 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 with 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). All compounds were routinely purified by radially accelerated preparative thin layer-chromatography with a Harrison Research Model 7924T Chromatotron and plates that were deactivated with 10% triethylamine in hexane followed by hexane immediately prior to use. Analytical samples were also distilled in a Kugelrohr apparatus. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Infrared (IR) spectra were recorded on a Perkin-Elmer 599 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Hitachi Perkin-Elmer R-600 spectrometer (60 MHz) in deuteriochloroform solution, unless otherwise noted. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian FT-80A NMR spectrometer (20 MHz), unless otherwise noted. High-pressure liquid chromatographic (HPLC) analyses were performed on a Varian 5000 chromatograph equipped with a variable-wavelength ultraviolet (UV) detector and Bakerbond chiral phase (*R*)-DNPG (covalent) Pirkle column with a film thickness of 5 μm and column dimensions of 4.6 × 250 mm. Peak areas and retention times for GC and HPLC were calculated with a Hewlett-Packard 3392A electronic integrator.

(*S*)-4-(1-Methylethyl)-2-oxazolidinone (1). The following is adapted from a procedure for the preparation 2-oxazolidinone.[33] Diethy carbonate (142 g, 1.2 mol), *S*-valinol[19] (100 g, 0.969 mol), and 0.7 g of NaOEt (from 0.22 g of sodium and 0.5 g of ethanol) were placed in a three-neck flask fitted with a thermometer, N_2 inlet, and a Vigreaux column with a distillation head. The mixture was heated in a 125 °C oil bath. Ethanol begins to distill when the internal temperature reaches 95 °C. After about 8 h, the internal temperature reaches 125 °C, and the ethanol ceases to distill (110–115 mL collected). The reaction mixture is cooled to 65 °C and poured into 200 mL of cold (≤0 °C) ether. The product precipitates (80–85%) and is isolated by filtration. No further purification is necessary. Mp: 71–72 °C (lit.[9] mp 71–72 °C). Concentration of the mother liquor yields a second crop. Total yield: 84–87%.

(*S*)-2-Ethoxy-4,5-dihydro-4-(1-methylethyl)oxazole (2). To a solution of 100 g of 1 (0.775 mol) in 1.2 L of methylene chloride at 0 °C was added dropwise a solution of 167 g of triethyloxonium tetrafluoborate[10,34] in 440 mL of methylene chloride. The solution was allowed to warm slowly to room temperature overnight. The reaction mixture was then slowly poured into 2 L of cold, saturated sodium carbonate. The organic layer was separated, and the aqueous layer was extracted with three 800-mL portions of methylene chloride. The combined organic phases were dried over anhydrous magnesium sulfate and condensed in vacuo. The product was obtained in 85% yield and distilled, bp 59 °C (2.5 mm). $[\alpha]_D$: −23.40° (*c* = 5.15, $CHCl_3$). ^{1}H NMR: δ 0.9 (d of d, 6 H, *J* = 6 Hz, $(CH_3)_2CH$), 1.3 (t, 3 H, *J* = 7 Hz, CH_3CH_2), 1.65 (m, 1 H, $(CH_3)_2CH$), 3.75 (m, 1 H, NCH), 3.9–4.45 (m, 4 H, OCH_2CH_3, OCH_2). ^{13}C NMR: δ 162.03, 68.78, 66.05, 32.64, 18.34, 18.08, 17.24, 13.90. IR: 1685 (C=N). Anal. ($C_8H_{15}NO_2$) C, H.

(*S*)-1-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]piperidine (3). A solution of 2.7 g (0.031 mol) of piperidine, 5 g (0.032 mol) of 2, and 0.1 g of *p*-toluenesulfonic acid in 100 mL of benzene was refluxed for 4 h. The reaction mixture was concentrated in vacuo to $^1/_3$ of its original volume and washed with saturated sodium bicarbonate and brine. The organic phase was dried with magnesium sulfate and concentrated to afford the product in 86% yield. Before use in the alkylations, it was distilled from calcium hydride, bp 78 °C (1.0 mm). $[\alpha]_D$: −33.6° (*c* = 5.1, $CHCl_3$). ^{1}H NMR: δ 0.9 (d of d, 6 H, *J* = 7 Hz, $(CH_3)_2CH$), 1.55 (br, 7 H, $CH(CH_3)_2$, $CH_2CH_2CH_2$), 3.30 (br, 4 H, CH_2NCH_2), 3.80 (m, 1 H, NCH), 3.85–4.25 (m, 2 H, CH_2O). ^{13}C NMR: δ 144.12, 71.31, 71.23, 52.38, 41.80, 35.36, 34.55, 34.27, 30.24, 29.25. IR: 1665 (C=N). Anal. ($C_{11}H_{20}N_2O$) C, H.

General Procedure for the Metalation of 3. To a stirring solution of 3 (0.5 mmol/mL, freshly distilled from calcium hydride) in 9/1 ether/THF and 0.1 equiv of TMEDA at −78 °C was added 1.1–3.0 equiv of *sec*-butyllithium (1.3 M in cyclohexane). The reaction mixture was then stirred for 1 h at −23 °C (CCl_4/CO_2 slush) and then cooled to −100 °C. The electrophile was added dropwise via syringe, and the reaction was warmed slowly to room temperature. The mixture was diluted with brine, and the layers were separated. The aqueous layer was extracted with ether; the combined organic layers were dried with sodium sulfate and concentrated in vacuo.

(*S*)-1-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-2(*R*)-(trimethylsilyl)piperidine (5a). Yield: 96%. The product was purified by radial chromatography and distilled, bp 130 °C (0.05 mm). $[\alpha]_D$: −37.6° (*c* = 1.58, $CHCl_3$). ^{1}H NMR: δ 0.1 (s, 9 H, $SiCH_3$), 0.9 (dd, 6 H, $CH(CH_3)_2$), 1.62 (m, 7 H, $(CH_2)_3CH_2N$,

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(31) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907.
(32) Stewart, J. J. P. QCPE Program No. 455.
(33) Scholz, K.-H.; Heine, H.-G.; Hartmann, W. *Org. Synth.* **1984**, *62*, 149–157.
(34) Commercially available solutions of this reagent are not recommended, but we have prepared and stored the crystalline solid at −20 °C under nitrogen for several months.

$(CH_3)_2CH$), 2.95 (m, 1 H, TMSC*H*), 3.5 (m, 2 H, NCH_2), 3.65–4.25 (m, 3 H, OCH_2, NC*H*). ^{13}C NMR: δ 160.74, 70.12, 69.91, 69.69, 46.97, 44.95, 33.29, 25.38, 22.84, 18.56, 17.61, −1.0. IR: 1655 (C=N). Anal. ($C_{14}H_{28}N_2OSi$) C, H.

(*S*)-1-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-2(*R*)-methylpiperidine (5b). The product was obtained in 30% yield, isolated by radial chromatography and purified by distillation, bp 105 °C (0.5 mm). ^1H NMR: δ 0.9 (dd, 6 H, J = 7 Hz, $(CH_3)_2CH$), 1.15 (d, 3 H, J = 8 Hz, $NCHCH_3$), 1.55 (br, 7 H, $CH(CH_3)_2$, $NCH_2(CH_2)_3$), 3.3 (br, 3 H, NCH_2, NC*H*), 3.65 (m, 1 H, C=NC*H*), 3.84–4.25 (m, 2 H, OCH_2). ^{13}C NMR: δ 161.11, 69.83, 47.90, 40.50, 33.24, 29.87, 25.41, 18.72, 18.54, 17.55, 17.33, 14.69. IR: 1650 (C=N). Anal. ($C_{12}H_{22}N_2O$) C, H.

(*R*)-1-(1-Naphthoyl)-2-methylpiperidine. To a solution of 603 mg of **5b** (2.87 mmol) in 8 mL of THF was added dropwise 1.26 g (5 equiv) of acetic formic anhydride.[35] The mixture was refluxed for 48 h and concentrated under reduced pressure. The crude *N*-formylpiperidine was then dissolved in 4 mL of 50% NaOH and refluxed for 18 h. The reaction mixture was cooled to room temperature and diluted with 10 mL of chloroform. 1-Naphthoyl chloride (5 equiv was then added dropwise to the two-phase solution. The mixture was shaken for 20–30 min, and then the layers were separated. The aqueous layer was extracted with chloroform. The combined organic layers were dried over magnesium sulfate, condensed in vacuo. The crude product was purified by radial chromatography. HPLC analysis on a Pirkle column showed this material to be the *R* enantiomer by co-injection with an authentic sample of racemic naphthamide independently prepared from racemic 2-methylpiperidine.[12]

(*S*)-1-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-2(*R*,*S*)-(6-hexenyl)piperidine (5d) and (*S*)-1-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-2(*R*,*S*)-(cyclopentylmethyl)-piperidine (5e). Yield: 51% of a 1:1.3 mixture of the two structural isomers, each obtained as a 1:1 mixture of diastereomers. The four isomers were preparatively inseparable but were purified by radial chromatography and distilled from calcium hydride, bp 160 °C (0.05 mm). Anal. ($C_{17}H_{30}N_2O$) C, H. GC–MS confirmed the presence of two pairs of stereoisomers.

(*S*)-1-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-2(*R*),6-(*R*)-dimethylpiperidine (6). Yield: 46%. The product was isolated by radial chromatography and purified by bulb-to-bulb distillation: bp 93.5 °C (0.1 mm). 500-MHz ^1H NMR: δ 0.9 (dd, 6 H, $(CH_3)_2CH$), 1.7 (m, 1 H, $(CH_3)_2CH$), 1.23 (d, 6 H, CH_3CHN), 1.45 (m, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 1.85 (m, 2 H, CH_2), 3.87 (m, 3 H, C=NC*H*, NC*H*), 4.0–4.2 (m, 2 H, OCH_2). 75-MHz ^{13}C NMR: δ 161.8, 70.89, 69.68, 69.12, 48.90, 33.10, 30.01, 19.50, 18.99, 18.46, 17.98, 17.85, 16.15. IR: 1650 (C=N). Anal. ($C_{13}H_{24}N_2O$) C, H.

(*S*)-1-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-1,4,5,6-tetrahydropyridine (7). This compound was obtained as a side product from several alkylations of **3**. It was isolated by radial chromatography and purified by bulb-to-bulb distillation: bp 100–103 °C (0.3 mm). ^1H NMR: δ 0.9 (dd, 6 H, J = 7 Hz, $(CH_3)_2CH$), 1.85 (m, 1 H, $CH(CH_3)_2$), 2.05 (m, 4 H, $NCH_2CH_2CH_2$), 3.65 (br t, 2 H, NCH_2), 4.8 (m, 1 H, NCH=C*H*), 6.65 (br d, 1 H, NC*H*=CH). ^{13}C NMR: δ 157.88, 125.82, 103.26, 70.76, 70.11, 43.57, 33.23, 21.48, 21.05, 18.80, 17.70. IR: 1675 (C=C), 1690 (C=N). Anal. ($C_{11}H_{18}NO_2$) C, H.

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Registry No. 1, 17016-83-0; 2, 102922-29-2; 3, 102922-36-1; 5a, 102922-43-0; 5b, 102922-42-9; 5d (isomer 1), 102922-39-4; 5d (isomer 2), 102922-46-3; 5e (isomer 1), 102922-47-4; 5e (isomer 2), 102922-40-7; 6, 102922-38-3; 7, 102922-37-2; (*R*)-1-(1-naphthoyl)-2-methylpiperidine, 90132-88-0; diethyl carbonate, 105-58-8; (*S*)-valinol, 2026-48-4; triethyloxonium tetrafluoroborate, 368-39-8; piperidine, 110-89-4; trimethylsilyl chloride, 75-77-4; 1-naphthoyl chloride, 879-18-5.

(35) Krimen, L. I. *Org. Synth.* **1970**, *50*, 1–3.

Bromination of (1*RS*,2*RS*,5*RS*)-2,3-Dibromo-6,7-benzobicyclo[3.2.1]octa-3,6-diene. A New and Convenient Synthesis of Disubstituted Benzobarrelenes

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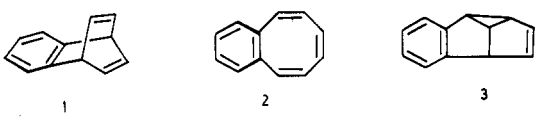
Bromination of (1*RS*,2*RS*,5*RS*)-2,3-dibromo-6,7-benzobicyclo[3.2.1]octa-3,6-diene (**1**) at −20 °C has been found to give only one product, the tetrabromide **10** via Wagner–Meerwein rearrangement with accompanying aryl migration. Radicalic bromination at room temperature produced nonrearranged tetrabromides, the rearranged tetrabromide **10**, the ketones **13** and **14**, and addition–elimination products **11** and **12**. Structures of the products were determined by ^1H and ^{13}C NMR data and chemical means. The double dehydrobromination of **10** was achieved by using potassium *tert*-butoxide to give 2,3-dibromobenzobarrelene (**20**). Reaction of **20** with *n*-BuLi and subsequent quenching with CH_3I, CO_2, and H_2O afforded the corresponding substituted benzobarrelenes.

Introduction

Benzobarrelene (**1**) is a molecule of considerable potential mechanistic interest. Zimmerman et al.[1] have reported that benzobarrelene (**1**) undergoes two types of photochemical reactions, one leading to benzocyclooctatetraene (**2**) proceeding from the singlet state of **1** via (2π + 2π)-cycloaddition and the other leading to semibulvalene (**3**) from the triplet excited state via di-π-methane rearrangement. Furthermore, deuterium labeling studies revealed that of the two bonding routes; vinyl–vinyl bridging and vinyl–aryl bridging, the last one is mainly utilized. However, di-π-methane rearrangement was uniquely provided by the vinyl–vinyl bridging. By the



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