Alkylation of 2-Lithio-*N*-Methylpiperidines and -pyrrolidines: Scope, Limitations, and Stereochemistry

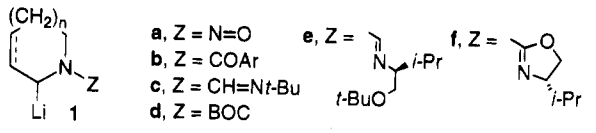
Robert E. Gawley* and Qianhui Zhang

Department of Chemistry, University of Miami, Coral Gables, Florida 33124-0431

Received May 31, 1995[⊗]

The scope and limitations of the alkylation of racemic and nonracemic 2-lithiopiperidines and -pyrrolidines, obtained by transmetalation of the corresponding stannanes, is reported. These organolithiums react with a variety of electrophiles to afford 2-substituted pyrrolidines and piperidines in excellent yield. With primary alkyl halides the reaction proceeds with net inversion of configuration at the metal-bearing carbon in the piperidines; in the pyrrolidines there is a mixture of inversion and retention, with the former predominating. With most carbonyl electrophiles (carbon dioxide, dimethyl carbonate, methyl chloroformate, pivaloyl chloride, benzaldehyde, and dialkyl ketones), retention is observed in both cases. Electrophiles such as benzophenone, benzyl bromide, and *tert*-butyl bromoacetate afford racemic coupling products. A mechanistic interpretation is presented.

The alkylation of saturated heterocycles α to nitrogen has been a focus of attention for synthetic chemists for over 20 years.[1] Deprotonation of the protons α to nitrogen is facilitated by nitroso groups (**1a**),[2] amides (**1b**),[3] formamidines (**1c**),[4] and urethanes (**1d**).[5]



All of these α-amino anions are stabilized by the group on nitrogen, but these groups also affect the stability and reactivity of the derived lithiated heterocycle. In some cases, the reaction of the α-aminoorganolithium species with alkyl halides is problematic due to the intervention of single electron (SET) processes.[6] In others, reported examples include a limited variety of electrophiles.[7] For the preparation of nonracemic compounds, chiral formamidines (**1e**) work well if the α-proton is allylic or benzylic[8] and BOC pyrrolidine can be enantioselectively deprotonated in the presence of sparteine, but again, few examples of reactions with alkyl halides were reported[7] and a similar strategy in the piperidine series has yet to emerge.[9] Chiral piperidinooxazolines (**1f**) can be stereoselectively deprotonated and the derived organolithiums are configurationally stable, but they are not good reagents for stereoselective alkylation due to the intervention of SET processes.[10]

We have recently reported the preparation of 2-lithio-*N*-methylpiperidines and -pyrrolidines in enantiomerically enriched form.[11] In both cases, the lithium compounds were obtained by transmetalation of the corresponding stannane, a process that is extremely facile in the heterocycle series, in contrast to some acyclic secondary α-aminostannanes.[12,13] Lithiated piperidines and pyrrolidines are remarkable in that their configurational stability exceeds their chemical stability: they are more prone to decomposition than racemization! We now report that these compounds are versatile nucleophiles, reacting with a variety of electrophiles to afford alkylation products in excellent yields and with a high degree

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1995.

(1) Reviews: (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–573. (c) Gawley, R. E.; Rein, K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.2.

(2) (a) Keefer, L. K.; Fodor, C. H. *J. Am. Chem. Soc.* **1970**, *92*, 5747–5748. (b) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 301.

(3) (a) Fraser, R. R.; Boussard, G.; Postescu, D.; Whiting, J. J.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 1109. (b) Beak, P.; Farney, R. *J. Am. Chem. Soc.* **1973**, *95*, 4771–4772.

(4) (a) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270. (b) Shawe, T. T.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2751–5. (c) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652–60.

(5) (a) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197–1200. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578–80. (c) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109–1117.

(6) For example, lithiated piperidino *tert*-butylformamidines are prone to oxidation by alkyl halides, affording poor (<30%) yields of coupling products with alkyl halides. The problem can be circumvented by transmetalation to a cuprate, however.[4a] In the pyrrolidine series, reaction of lithiated *tert*-butylformamidines with alkyl halides affords good yields (60–75%) with unactivated alkyl halides but modest yields (20–40%) with allyl and benzyl bromide.[4a]

(7) Reported examples of the reaction of lithiated BOC piperidines are limited to methyl and allyl halides.[5a] To our knowledge, no examples of lithiated BOC pyrrolidines reacting with alkyl halides have been reported by the Beak group. In our hands, alkylation of lithiated BOC pyrrolidine with, for example, allyl bromide affords low yields of alkylation product.

(8) (a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974–78. Recent reviews: ref 1c and (b) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589–2612. (c) Highsmith, T. K.; Meyers, A. I. in *Advances in Heterocyclic Natural Product Synthesis;* Pearson, W. H., Ed.; JAI: Greenwich, CT, 1991.

(9) (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708–10. (b) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.

(10) (a) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076–8. (b) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *Ibid.* **1989**, *54*, 175–81.

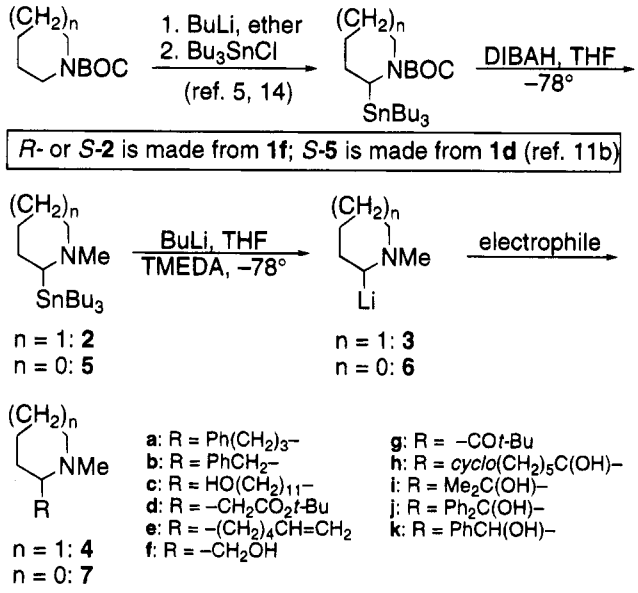
(11) (a) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515–6. (b) Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077–6088.

(12) Peterson demonstrated the utility of tin–lithium exchange for the preparation of [(dialkylamino)methyl]lithiums over 20 years ago: (a) Peterson, D. J. *J. Organomet. Chem.* **1970**, *21*, P63–4. (b) Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027–31. (c) Peterson, D. J.; Ward, J. F. *J. Organomet. Chem.* **1974**, *66*, 209–17.

(13) Two recent reports indicate that *unchelated, acyclic* secondary α-aminoorganolithiums are not available by transmetalation: (a) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.; Itô, S. *Tetrahedron Lett.* **1991**, *32*, 1975–78. (b) Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51–54. These authors successfully transmetalated an acyclic secondary α-aminostannane that could be chelated by an *N*-methoxyethyl group. (c) In contrast, Pearson has shown that dipole-stabilized, acyclic, secondary α-aminoorganolithiums are available by tin–lithium exchange: Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622–36.

0022-3263/95/1960-5763$09.00/0

Scheme 1



of stereoselectivity in most cases. Analysis of the stereochemical course of the reaction of nonracemic stannanes suggests that a mechanistic dichotomy may exist, depending on the electrophile.

Results

The initial evaluation of 2-lithiopiperidine and 2-lithiopyrrolidine as nucleophiles was conducted on racemic material, but no differences in product yield or reactivity were observed between the racemic and nonracemic organolithiums under the standard conditions described in the Experimental Section. The racemic stannanes are conveniently prepared from the *N*-BOC heterocycle by stannylation according to Beak's method,[5a,c,14] followed by reduction with DIBAH (Scheme 1).[11b] Nonracemic **2** and **5** were prepared (from **1f** and **1d**, respectively) as described previously.[11b]

Transmetalation with butyllithium in THF/TMEDA occurred smoothly at −78 °C in 15 min. The derived organolithiums were then allowed to react with a variety of electrophiles. The results of these evaluations are summarized in Table 1 for the piperidines and Table 2 for the pyrrolidines. These data are notable because of the uniformly high yields of coupling products, virtually independent of the electrophile. In fact, almost all the electrophiles tested reacted cleanly with either racemic or nonracemic organolithiums to afford coupling products in excellent yield.

With primary alkyl halides, coupling products are obtained in excellent yields in both the pyrrolidine and piperidine series. By adding an extra equivalent of butyllithium before the electrophile, ω-hydroxyalkyl halides can be used as electrophiles without protecting the hydroxyl group (*cf.* **4c**, **7c**).

The 2-lithiopiperidine **3** also reacts equally well with carbon dioxide, methyl chloroformate, and dimethyl carbonate. 2-Lithiopyrrolidine **6** reacts with carbon dioxide, but the reaction with methyl chloroformate and dimethyl carbonate did not afford the anticipated proline ester. Other carbonyl electrophiles work equally well with both the piperidines and pyrrolidines. Examples tested include an acid chloride lacking an α hydrogen (pivaloyl chloride) and ketones (cyclohexanone, acetone, and benzophenone). Benzaldehyde affords good yield of adducts, but no diastereoselectivity was observed.

Enantiopure lithiopiperidine (*R*)-**3** (≥99% ee) and enantioenriched (92−95% ee) lithiopyrrolidine (*S*)-**6** were found to have reactivities similar to the racemic compounds in the presence of TMEDA.[15] The absolute configurations of compounds **4c**, **4f**, **7f**, **7j**, and **7k** were determined by comparison to literature data,[16] while the configurations of compounds **4a**, **4i**, **7a**, **7g**, and **7i** were determined by independent synthesis from either proline or pipecolic acid derivatives (see supporting information). The absolute configuration assigned to all other compounds is inferred. Enantiomer ratios of most products were determined by rotation or NMR analysis using *(R)*-mandelic acid as a chiral solvating agent.[17] The enantiomer ratios of alcohols **4f** and **7f** were determined by Mosher analysis,[18] as described previously, and **4a** was determined by chiral stationary phase GC (see Experimental Section). Enantiomeric excesses listed as 99% ee means that the minor enantiomer was not visible by NMR or GC and that they are minimum values; values below 99% are probably accurate to ±5%. The relative configuration of the product is expressed as either retention or inversion, relative to the stannane educt.

Several transmetalations were investigated. The tin → lithium transmetalation is assumed to take place with retention; the reaction of lithiopiperidine (*R*)-**3** with tributyltin chloride occurs with 100% retention, as indicated by rotation. Transmetalation of lithiopyrrolidine (*S*)-**6** with zinc chloride afforded a species that failed to react with benzaldehyde, cyclohexanone, or pivaloyl chloride. Treatment of lithiopyrrolidines and lithiopiperidines with magnesium chloride afforded a species that failed to react with either CO_2 or cyclohexanone. Lithiopiperidine (*R*)-**3**, after treatment with magnesium chloride at −78 °C in THF, was treated with pivaloyl chloride to afford (*R*)-**4g** in 56% yield and 73% ee. Since the piperidinostannane (*R*)-**2** had an enantiomeric purity of 99% ee, this indicates approximately 87% inversion and 13% retention of configuration. In contrast, lithiopyrrolidine (*S*)-**6** afforded (*R*)-**7g** (75% yield, 60% ee) after similar treatment. Since the pyrrolidinostannane had an enantiomeric purity of 94% ee, this indicates approximately 83% retention and 17% inversion. Thus, the reaction of lithiated heterocycles with magnesium chloride occurs with predominant retention in the pyrrolidine series and inversion in the piperidine series.[19]

Discussion

The most notable feature of the data presented in Tables 1 and 2 is the uniformly high yields of alkylation

(14) The yield for the stannylation of BOC pyrrolidine in ref 5a was 25%. In our hands, the yield is 77% (see Experimental Section). The yield for the stannylation of BOC piperidine in ref 5a is 100%.

(15) This need not necessarily be true: in two preliminary experiments, we have observed different reactivity for enantioenriched and racemic lithiopyrrolidine **6** in the absence of TMEDA. After transmetalation at −78 °C, waiting for 45 min, and then quenching with carbon dioxide, the yield of adduct is 20% from the enantioenriched stannane (94% ee), but >90% with the racemic stannane.

(16) References for known compounds: (a) **4c** and **4f**: Craig, J. C.; Lee, S.-Y. C.; Pereira, W. E., Jr.; Beyerman, H. C.; Maat, L. *Tetrahedron* **1978**, *34*, 501−4. (b) **7f**: Aldrich Chemical Co. (c) **7j** and **7k**: Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111−15.

(17) Benson, S. C.; Cai, P.; Coilon, M.; Tokles, M. A.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335−41.

(18) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−49. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−19.

Table 1. Reaction of 2-Lithio-*N*-methylpiperidine (3) with Electrophiles. The Enantiomeric Purity of (*R*)-2 was ≥99% ee

electrophile	product	% yield[a]	configuration from (*R*)-**2**	configuration relative to (*R*)-**2**	% ee
$Ph(CH_2)_3Br$	4a	75–76	S	inversion	99[b]
$PhCH_2Br$	4b	89–91	racemic		0[c]
$LiO(CH_2)_{11}Br$	4c	78	S	inversion	90[d,e]
$BrCH_2CO_2$-*t*-Bu	4d	75	(from *rac* **2**)		
$MeOCO_2Me$	**4f**[f]	82–84	S	retention	99[g]
CO_2	**4f**[f]	83–84	S	retention	99[g]
$ClCO_2Me$	**4f**[f]	76	S	retention	99[g]
t-BuCOCl	4g	85	S	retention	99[c]
cyclohexanone	4h	78–79	S	retention	99[c]
acetone	4i	70	S	retention	95[d,h]
benzophenone	4j	49–52	racemic		0[c]
PhCHO	4k	67[i]	2-*S*	retention	92[c]
Bu_3SnCl	2	81	R	retention	99[d]

[a] Yields or yield range is from at least two experiments and includes one in the racemic series and one in the nonracemic series, unless noted. [b] Determined by chiral stationary phase GC. [c] Determined by NMR using (*R*)-mandelic acid as chiral solvating agent. [d] Determined by rotation. [e] Compared to literature value. [f] After LAH reduction. [g] Determined by Mosher analysis. [h] Compared to independently synthesized sample. [i] Mixture of *u* and *l* stereoisomers.

Table 2. Reaction of 2-Lithio *N*-methylpyrrolidine (6) with Electrophiles. The Enantiomeric Purity of (*S*)-5 Varied from 92 to 95% ee

electrophile	product	% yield[a]	configuration from (*S*)-**5**	configuration relative to (*S*)-**5**	% ee
$Ph(CH_2)_3Br$	7a	75	R	inversion	51[b,c]
$PhCH_2Br$	7b	60–72	racemic		0[d]
$PhCH_2Cl$	7b	59	S	inversion	15[d]
$LiO(CH_2)_{11}Br$	7c	52–53	R	inversion	not det.
$BrCH_2CO_2$-*t*-Bu	7d	77	racemic		0[d]
$Br(CH_2)_4CH{=}CH_2$	7e	70	S	retention	46[e]
CO_2	7f[f]	83–84	R	retention	93,[b] 94[g]
t-BuCOCl	7g	50–55	R	retention	62[d]
cyclohexanone	7h	86	R	retention	95[d]
acetone	7i	80–92	R	retention	95[b,c]
benzophenone	7j	70–72	racemic		0[d]
PhCHO	*l*-7k	75[h]	RR	retention	89[d]
	u-7k		RS	retention	89[d]

[a] Yields or yield range is from at least two experiments and includes one in the racemic series and one in the nonracemic series. [b] Determined by rotation. [c] Compared to independently synthesized sample. [d] Determined by NMR using (*R*)-mandelic acid as chiral solvating agent. [e] Determined by chiral stationary phase GC. [f] After LAH reduction. [g] Determined by Mosher analysis. [h] Mixture of *u* and *l* stereoisomers.

and addition products obtained, virtually independent of the electrophile. Comparison of the configuration of the stannane with the products of reaction reveals that primary alkyl halides that are not benzylic or α to a carbonyl react with inversion at the lithium-bearing carbon. In the piperidine series, the best data is for **4a**, which showed a base-line separation of the two enantiomers of the racemate on a β-cyclodextrin capillary GC column and appears to be in ≥99% ee. In the pyrrolidine series, **7a** (prepared from **5** of about 92–95% ee) is in 51% ee, indicating about 21–22% retention and 78–79% inversion of configuration. Similarly, **7e** is obtained in 46% ee. Activated alkyl halides such as benzyl bromide or chloride and *tert*-butyl bromoacetate afford racemic adducts, while tributyltin chloride reacts with piperidine (*R*)-**3** with 100% retention. The reaction of the nonracemic lithio heterocycles in both the pyrrolidine and piperidine series with most carbonyl electrophiles (*i.e.*, carbon dioxide, dimethyl carbonate, methyl chloroformate, pivaloyl chloride, cyclohexanone, acetone, and benzaldehyde) proceeds with virtually complete retention of configuration at the lithium-bearing carbon. The only exceptions are benzophenone, which affords racemic adduct, and pivaloyl chloride in combination with **6**, which shows about 10% inversion.

We speculate that the racemic products **4b**, **4j**, **7b**, **7d**, and **7j** obtained with activated alkyl halides and benzophenone are probably the result of a competing SET process. The partial racemization observed with pivaloyl chloride is more likely due to racemization of the ketone product during workup, however. Evidence for SET in the reactions with benzophenone is the appearance of a blue color and detection of the benzophenone ketyl by ESR.[20] Regarding the activated alkyl halides reacting by SET, note that Haberfield has recently observed SET in the reaction of phenacyl bromide (an α-halocarbonyl, not unlike *tert*-butyl bromoacetate) with bromide ion.[21]

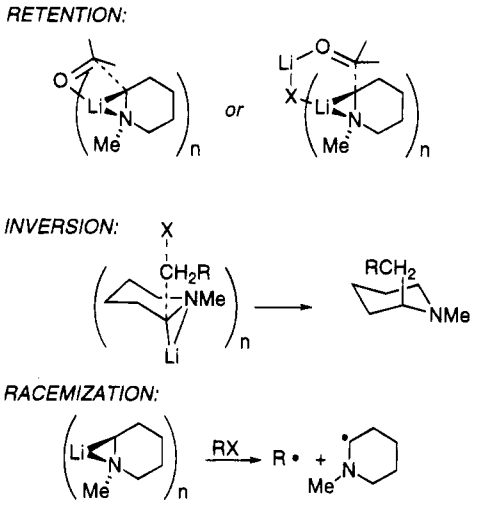
We must point out that the observations outlined above stand in contrast to the observations of Still and Hoppe regarding α-oxyorganolithiums.[22] As Hoppe notes,[22c] "Non-mesomerically stabilized α-oxyalkyllithium derivatives, being sp^3-hybridized, react with all investigated

(19) An alternative explanation might have been that transmetalation occurred with inversion of configuration and that the reaction was incomplete (to differing extents) for the two heterocycles. The mixture of lithio and magnesio heterocycles then reacting with the pivaloyl chloride with retention would afford the same result. This possibility is discounted by the fact that the species obtained upon $MgCl_2$ treatment does not react with either CO_2 or cyclohexanone. Had any lithio species been present, it would have reacted to give **4g** and **7g**.

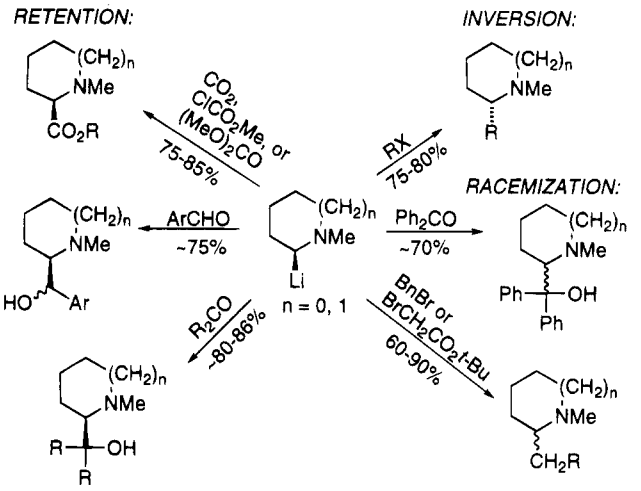
(20) We are grateful to Yuhong Zuo and Luis Echegoyen for this experiment. This is similar to evidence obtained previously in the reaction of lithiated isoquinolines with benzophenone: Rein, K. S.; Chen, Z.-H.; Perumal, P. T.; Echegoyen, L.; Gawley, R. E. *Tetrahedron Lett.* **1991**, *32*, 1941–1944.

(21) Haberfield, P. *J. Am. Chem. Soc.* **1995**, *117*, 3314–3315.

Scheme 2



Scheme 3



electrophiles [with] stereoretention." Thus, the observation of inversion of configuration in these systems has no precedent in α-oxyorganolithium chemistry. Hoppe observes that esters and anhydrides react with lithiated benzylic carbamates with retention of configuration at the lithium-bearing carbon, whereas acid chlorides react with inversion, and he has suggested that the stereochemical preference may be related to the presence of a low-energy LUMO in the electrophile.[22c] Note, however, that in our examples (Tables 1 and 2) all carbonyl electrophiles react with either 100% retention or 100% racemization.

Theory predicts that the lithium atom of α-aminomethyllithium bridges the carbon and nitrogen atoms,[23] a prediction that is confirmed by X-ray analysis of α-lithiated *N,N*-dimethylbenzylamine.[24] The same X-ray data indicate that the metal-bearing carbon is strongly pyramidalized. Compounds **3** and **6** are exceptionally stable toward racemization (pyramidal inversion), which argues for a very tight ion pair and a pyramidal carbon in solution. We are working under the assumption that the lithium atom of **3** and **6** bridges both carbon and nitrogen[11b] and that the hybridization state of the lithiated carbon is sp^3. Scheme 2 summarizes our mechanistic hypotheses (which are not predicated on any assumptions regarding aggregation state): (1) with carbonyl-containing electrophiles having relatively large (negative) reduction potentials, coordination of the electrophile and addition through a cyclic transition state results in net retention of configuration; (2) with difficultly reducible alkyl halides, the preference is for reaction through an S_E2(back) transition state, inverting the configuration of the carbanionic carbon; (3) oxidation of the organolithium by an electrophile having a less negative reduction potential affords racemic products by a radical coupling mechanism.

The dichotomy of reactivities toward inversion *vs* retention of configuration may have to do with the ability of the electrophile to coordinate the lithium prior to reaction (*i.e.*, Lewis basicity). The partial retention of configuration observed with alkyl halides in the pyrrolidine series is probably related to simple steric effects. Note that the bulky tributyltin chloride alkylates **3** with retention of configuration. These effects may differ depending on the aggregation state, but we have no data on the aggregation state of these species. It is interesting to note, however, that α-lithiated *N,N*-dimethylbenzylamine is a heterochiral dimer in the solid state[24] but a monomer in THF solution.[25] Regarding possible aggregation of **3** and **6**, it may be significant that, in the absence of TMEDA (conditions that are not conducive to the chemical stability of these organolithiums), lithiopyrrolidine **6** is considerably more stable when it is racemic than when it is enantiomerically enriched.[15]

In summary (Scheme 3), 2-lithiopiperidines and 2-lithiopyrrolidines appear to be very versatile nucleophiles for the elaboration of these heterocyclic systems, affording a variety of 2-substituted heterocycles in excellent yields. The stereoselectivity of the reaction is near 100% in the piperidine series with most carbonyl electrophiles (retention of configuration) and alkyl halides (inversion of configuration). In the pyrrolidine series, the selectivity is also near 100% with carbonyl electrophiles (retention), but there is some racemization (inversion predominates) with alkyl halides.

Experimental Section

General. Ethereal solvents were distilled from benzophenone–sodium. All glassware was oven dried and cooled in a desiccator or a nitrogen atmosphere, and all reactions were run under a nitrogen balloon. Reagents were transferred using standard syringe techniques. Proton NMRs were recorded at 400 MHz and carbon NMRs were recorded at either 100 or 23 MHz. *J* values are in hertz. Molecular ions of mass spectra run in EI mode are reported as M^+, while those run in chemical ionization or FAB mode are reported as MH^+. Chiral stationary phase (CSP) GC was conducted using a β-cyclodextrin capillary column (J&W Scientific). Diastereomer analysis by ^{19}F NMR of Mosher esters was done in $CDCl_3$ solution containing 1–3% trifluoroacetic acid. Enantiomer ratios determined using (*R*)-(−)-mandelic acid as a chiral solvating agent (CSA) were done in $CDCl_3$ solution (containing an excess of the CSA) by integration of the *N*-methyl protons. The nonracemic stannylpiperidines and -pyrrolidines were prepared as described previously.[11b]

(22) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1990**, *102*, 1201–1202. (b) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *50*, 1424–1425. (c) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097–6108.

(23) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467–75.

(24) Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887–94.

(25) Albrecht, H.; Harbach, J.; Hauck, T.; Kalinowski, H.-O. *Chem. Ber.* **1992**, *125*, 1753–1762.

***rac*-N-BOC-2-(tributylstannyl)pyrrolidine.** Following the procedure of Beak,[5a] *s*-BuLi (24 mmol) was added to a solution of *N*-BOC-pyrrolidine (3.4 g, 20.0 mmol) in ether (40 mL) at −78 °C containing TMEDA (4.3 mL, 24 mmol). The mixture was stirred for 1.5 h at −78 °C and then treated with Bu_3SnCl. The mixture was warmed to room temperature, and the reaction was quenched with 10 mL of brine. The aqueous layer was extracted with ether (3 × 15 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated. The colorless liquid product (7.0 g, 77%) was obtained after flash chromatography (hexane/ethyl acetate 20/1).

***N*-Methyl-2-(tributylstannyl)piperidine (*rac*-2).** Following the published procedure for the preparation of **5**,[11b] *N*-BOC-2-(tributylstannyl)piperidine [5c](10.0 g, 21.1 mmol) in THF (70 mL) was cooled to −78 °C and treated dropwise with DIBAH (13.1 mL, 73.7 mmol) by syringe. The mixture was slowly warmed to room temperature and stirred for 75 h. The mixture was then cooled to 0 °C, and the reaction was carefully quenched with water (5 mL). After 30 min of stirring the mixture was filtered and the cake was washed with ether (3 × 10 mL). The filtrate was dried with $MgSO_4$, filtered, and concentrated to give the crude product which was purified by flash chromatography on silica gel (hexane/ethyl acetate/EtOH 5/1/0.5) to give 5.8 g of product (72%). The product was identical in all respects except rotation to that reported previously for the enantiopure material.[11b]

General Procedure for Transmetalation−Alkylation. Under nitrogen, stannane **2** or **5** in THF (0.1 M) and TMEDA (1.3 equiv) was cooled to −78 °C and treated with BuLi (1.6 M in hexanes, 1.3 equiv). The yellow solution was stirred at −78 °C for 20 min. The electrophile was added, and the reaction was kept at −78 °C for 1 h. The reaction was quenched with 2 M HCl, and the solution was extracted with ether three times to remove any neutral compounds. The aqueous solution was basified with powdered Na_2CO_3 and extracted with ether four times. The combined ether solutions were dried with Na_2CO_3. After filtration, the solvent was removed in vacuo.

***N*-Methyl-2-(3′-phenylpropyl)piperidine (4a)** was prepared from **2** and 3-bromo-1-phenylpropane according to the general procedure. After purification by flash chromatography on silica gel with hexane/EtOAc/EtOH (5/1/0.5) as eluent and bulb-bulb distillation (180−185 °C/0.5 mmHg), a colorless liquid product was obtained in 76% yield: ^{1}H NMR ($CDCl_3$) 1.24 (2H, m), 1.42 (1H, m), 1.50−1.79 (8H, m), 1.84 (1H, m), 2.05 (1H, m), 2.20 (3H, s), 2.60 (2H, m), 2.83 (1H, m) 7.19 (3H, m), 7.25 (2H, m); ^{13}C NMR ($CDCl_3$) 142.44, 128.30, 128.14, 125.59, 63.67, 57.27, 42.98, 36.26, 32.52, 30.79, 26.99, 25.86, 24.39; MS (M^+) 217. Anal. Calcd for $C_{15}H_{23}N$: C, 82.95; H, 10.60. Found: C, 82.73; H, 10.70. **(*S*)-*N*-Methyl-(3′-phenylpropyl)piperidine ((*S*)-4a)** was prepared from (*R*)-**2**. CSP GC analysis showed a 99% enantiomer excess (base-line separation). $[\alpha]_D$ +25.0 (*c* 0.3, CH_2Cl_2). The absolute configuration was determined by comparison with a sample synthesized from (*S*)-**4f** by the sequence (i) Swern oxidation, (ii) Wittig olefination with $PhCH_2CH_2{=}PPh_3$, and (iii) reduction (see supporting information for details).

***N*-Methyl-2-(phenylmethyl)piperidine (4b)** was prepared from **2** and benzyl bromide according to the general procedure. After purification by flash chromatography on silica gel with hexane/EtOAc/EtOH (5/1/0.5) as eluent and bulb-to-bulb distillation (145−150 °C/0.5 mmHg), a colorless liquid was obtained in 91% yield: ^{1}H NMR ($CDCl_3$) 1.16 (2H, m), 1.38 (1H, m), 1.52 (3H, m), 2.07 (2H, m) 2.32 (1H, m), 2.35 (3H, s), 2.78 (1H, m), 3.13 (1H, dd, J_1 = 4.05, J_2 = 13.07), 7.10 (3H, m), 7.21 (2H, m); ^{13}C NMR ($CDCl_3$) 139.73, 129.27, 128.03, 125.70, 65.08, 56.74, 43.41, 39.13, 30.30, 25.75, 23.75; MS (M^+) 189. Anal. Calcd for $C_{13}H_{19}N$: C, 82.54; H, 10.05. Found: C, 82.33; H, 10.15. When (*R*)-**2** was used for the preparation, racemic **4b** was obtained, as indicated by CSP GC and CSA analysis.

***N*-Methyl-2-(11′-hydroxyundecyl)piperidine (4c).** Under nitrogen, *N*-methyl-2-(tributylstannyl)piperidine (**2**) (0.13 g, 0.34 mmol) in THF (3.4 mL) and TMEDA (0.065 mL, 0.44 mmol) were cooled to −78 °C and treated with *n*-BuLi (0.28 mL, 0.44 mmol, 1.6 M in hexane). The yellow solution was stirred at −78 °C for 20 min. A second equivalent of *n*-BuLi was added, followed immediately by the addition of 11-bromo-1-undecanol (0.31 mL, 0.40 mmol). The mixture was kept at −78 °C for 1 h. The workup procedure was the same as in the the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained (0.070 g) in 78% yield: ^{1}H NMR ($CDCl_3$) 1.20−75 (17H, m), 1.82 (1H, m), 2.05 (1H, m), 2.25 (3H, s), 2.85 (1H, m), 3.65 (2H, m); MS (MH^+) 270. **(*S*)-*N*-Methyl-2-(11′-hydroxyundecyl)piperidine ((*S*)-4c)** was prepared from (*R*)-**2**. The enantiomeric purity was determined to be 90% ee by comparison with the reported specific rotation; $[\alpha]_D$ +19.0 (*c* 0.35, 95% EtOH); lit.[16a] $[\alpha]_D$ +21 (*c* 0.2−2.0, 95% EtOH) for *S*-enantiomer.

***tert*-Butyl *N*-methyl-2-piperidineacetate (4d)** was prepared from **2** and *tert*-butyl bromoacetate according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 75% yield: ^{1}H NMR ($CDCl_3$) 1.20−1.72 (6H, m), 1.43 (9H, s), 2.15 (3H, m), 2.26 (3H, s), 2.59 (1H, dd, J_1 = 4.8, J_2 = 14.8). 2.79 (1H, m); ^{13}C NMR ($CDCl_3$) 172.02, 80.36, 60.31, 56.20, 43.25, 39.73, 31.93, 28.08, 25.86, 23.59; MS (MH^+) 214. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.61; H, 10.80. Found: C, 67.64; H, 10.85. When (*R*)-**2** was used for the preparation, racemic **4d** was obtained, as indicated by CSA analysis.

***N*-Methyl-2-piperidinemethanol (4f)** was prepared from methyl *N*-methylpipecolate which was made from **2** and dimethyl carbonate according to the general procedure. The crude methyl *N*-methylpipecolate (0.154 g, 0.96 mmol) was dissolved in ether (9.6 mL) and treated with LAH (0.055 g, 1.43 mmol). After being refluxed for 2 h, the reaction solution was cooled to 0 °C, and the reaction was quenched with water (1 mL), 15% NaOH solution (1 mL), and water (1 mL) sequentially. After filtration, the cake was washed with ether (3 × 5 mL). The ether solution was dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The crude *N*-methyl-2-piperidinemethanol was purified by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15) to give 0.089 g of **4f** (82%). The ^{1}H NMR and ^{13}C NMR of **4f** matched the spectra from a sample obtained from Aldrich. **(*S*)-*N*-Methyl-2-piperidinemethanol ((*S*)-4f)** was prepared from (*R*)-**2**. The enantiomeric purity of (*S*)-**4f** was determined to be 99% by Mosher analysis; $[\alpha]_D$ −15 (*c* 0.70, 95% EtOH); lit.[16a] $[\alpha]_D$ +14.6 (*c* 0.2−2.0, 95% EtOH) for *R*-isomer. **(*R*)-*N*-Methyl-2-piperidinemethanol ((*R*)-4f)** was prepared from (*S*)-**2**: $[\alpha]_D$ +14 (*c* 0.65, 95% EtOH). The enantiomeric purity of (*R*)-**4f** was determined to be 96% by Mosher analysis.

***N*-Methyl-2-(trimethylacetyl)piperidine (4g)** was prepared from **2** and pivaloyl chloride according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 85% yield: ^{1}H NMR ($CDCl_3$) 1.18 (9H, s), 1.23−1.76 (6H, m), 2.06 (1H, m), 2.10 (3H, s), 2.96 (1H, m), 3.18 (1H, dd, J_1 = 10.8, J_2 = 2.0); ^{13}C NMR ($CDCl_3$) 215.52, 68.35, 56.13, 44.42, 30.44, 26.67, 25.37, 23.55; MS (MH^+) 184. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.13; H, 11.48. Found: C, 72.34; H, 11.44. **(*S*)-*N*-Methyl-2-(trimethylacetyl)piperidine ((*S*)-4g)** was prepared from (*R*)-**2**: $[\alpha]_D$ −32 (*c* 0.1, CH_2Cl_2). The enantiomeric purity of (*S*)-**4g** was determined to be 99% by the CSA method.

***N*-Methyl-2-(1′-hydroxycyclohexyl)piperidine (4h)** was prepared from **2** and cyclohexanone according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 79% yield: ^{1}H NMR ($CDCl_3$) 1.16−1.80 (16H, m), 2.27 (2H, m), 2.49 (3H, s), 2.67 (1H, m), 2.91 (1H, m); ^{13}C NMR ($CDCl_3$) 72.45, 69.09, 53.43, 41.95, 37.07, 33.99, 25.97, 22.82, 22.39, 22.13, 19.79, 19.19. MS (MH^+) 198; $[\alpha]_D$ −19 (*c* 0.2, CH_2Cl_2). Anal. Calcd for $C_{12}H_{23}NO$: C, 73.10; H, 11.68. Found: C, 73.23; H, 11.53. **(*S*)-*N*-Methyl-2-(1′-hydroxycyclohexyl)piperidine ((*S*)-4h)** was prepared from (*R*)-**2**. The enantiomeric purity of (*S*)-**4h** was determined to be 99% by the CSA method.

***N*-Methyl-2-(2′-hydroxy-2′-propyl)piperidine (4i)** was prepared from **2** and acetone according to the general procedure. After purification by flash chromatography on silica gel

with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 70% yield: ^1H NMR ($CDCl_3$) 1.21 (6H, s), 1.40 (2H, m), 1.56 (3H, m), 1.78 (1H, m), 2.33 (1H, m), 2.52 (3H, s), 2.59 (1H, m), 2.94 (1H, m), 4.18 (1H, br); ^{13}C NMR ($CDCl_3$) 70.87, 68.60, 53.38, 44.14, 28.73, 24.12, 22.06; MS (MH^+) 158. Anal. Calcd for $C_9H_{19}NO$: C, 68.79; H, 12.10. Found: C, 68.74; H,.12.33. **(*S*)-*N*-Methyl-2-(2′-hydroxy-2′-propyl)piperidine ((*S*)-4i)** was prepared from (*R*)-**2**; $[\alpha]_D$ −8.4 (*c* 2, CH_2Cl_2). The enantiomeric purity was determined to be 99% by comparing the rotation with that of (*S*)-**4i** which was synthesized from (*S*)-methyl *N*-BOC-pipecolate by addition of methylmagnesium iodide (see supporting information).

Diphenyl(*N*-methyl-2-piperidyl)methanol (4j) was prepared from **2** and benzophenone according to the general procedure. After purification by flash chromatography on silica gel with hexane/EtOAc/EtOH (5/1/0.5) as eluent, the product was obtained in 49% yield: mp 88.5−88.9 °C; ^1H NMR ($CDCl_3$) 1.177 (3H, m), 1.50 (1H, m), 1.60 (2H, m), 1.93 (3H, s), 2.39 (1H, m), 2.87 (1H, m), 3.25 (1H, m), 7.05−7.30 (6H, m), 7.47 (2H, d, J = 7.6), 7.70 (2H, d, J = 7.6); ^{13}C NMR ($CDCl_3$) 150.19, 146.83, 128.03, 127.82, 125.76, 125.00, 77.38, 67.36, 57.50, 46.72, 28.14, 24.99, 24.02; MS (M^+) 283. Anal. Calcd for $C_{19}H_{23}NO$: C, 80.85; H, 8.51. Found: C, 80.59; H, 8.72. When (*R*)-**2** was used for the preparation, racemic product was obtained; $[\alpha]_D$ 0 (*c* 0.4, CH_2Cl_2). Two equal peaks were detected for the *N*-methyl protons by the CSA method.

1′-Phenyl-*N*-methyl-2-piperidinemethanol (4k) was prepared from **2** and benzaldehyde according to the general procedure. After purification by flash chromatographyon silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 65% yield. The two diastereomers (*u* and *l*) were not separated. **4k:** ^1H NMR ($CDCl_3$) 1.05 (1H, m), 1.40 (2H, m), 1.61 (3H, m), 2.30 (1H, m), 2.60 (3H, s, *l*), 2.70 (3H, s, *u*), 2.89 (1H, m), 3.05 (1H, m, l), 3.19 (1H, m, *u*), 4.63 (1H, d, J = 8.4, *u*), 5.23, (1H, s, *l*), 7.20−7.41 (5H, m); ^{13}C NMR ($CDCl_3$) 141.75, 141.02, 128.36, 128.01, 127.84, 127.70, 126.84, 125.80, 72.23, 70.06, 68.98, 66.64, 57.28, 51.95, 42.63, 38.34, 24.99, 23.48, 22.65, 21.87, 20.61, 19.10; MS (MH^+) 206. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.10; H, 9.27. Found: C, 76.32; H, 9.54. Nonracemic (*R*)-**4k** was prepared from (*R*)-**2**. The enantiomeric purity was determined to be 92% by the CSA method.

***N*-Methyl-2-(3′-phenylpropyl)pyrrolidine (7a)** was prepared from **5** and 3-bromo-1-phenylpropane by the the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 75% yield: ^1H NMR ($CDCl_3$) 1.24 (1H, m), 1.42 (1H, m), 1.70 (5H, m), 1.96 (2H, m), 2.11 (1H, q, J = 8.8), 2.28 (3H, s), 2.63 (2H, m), 3.04 (1H, m), 7.18 (3H, m), 7.27 (2H, m); ^{13}C NMR ($CDCl_3$) 142.55, 128.37, 128.24, 125.64, 66.21, 57.29, 40.45, 36.29, 33.56, 30.76, 28.62, 21.79; MS (MH^+) 204; $[\alpha]_D$ −35 (*c* 0.12, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}N$: C, 82.76; H, 10.34. Found: C, 82.62; H, 10.43. **(*R*)-*N*-Methyl-2-(3′-phenylpropyl)pyrrolidine ((*R*)-7a)** was prepared from (*S*)-**5**. A 51% enantiomeric excess of (*R*)-**7a** was determined by comparing the rotation data with that of (*R*)-**7a** which was synthesized from *N*-methylprolinol by the sequence: (i) Swern oxidation, (ii) Wittig olefination with $PhCH_2CH_2{=}PPh_3$, and (iii) reduction (see supporting information for details).

***N*-Methyl-2-(phenylmethyl)pyrrolidine (7b)** was prepared from **5** and benzyl bromide according to the General procedure. After purification by flash chromatography on silica gel with hexane/EtOAc/EtOH (5/1/0.5) as eluent and bulb-to-bulb distillation (155−116 °C/1.5 mmHg), the colorless liquid product was obtained in 72% yield: ^1H NMR ($CDCl_3$) 1.40−1.80 (5H, m), 2.20 (1H, m), 2.30 (1H, m), 2.40 (3H, s), 3.10 (2H, m), 7.20 (3H, m), 7.25 (2H, m); ^{13}C NMR ($CDCl_3$) 140.00, 129.06, 128.19, 125.86, 67.73 (2C), 57.28, 50.69, 30.84, 21.68; MS (MH^+) 176. Anal. Calcd for $C_{12}H_{17}N$: C, 82.29; H, 9.71. Found: C, 82.31; H, 9.81. When (*S*)-**5** was used for the preparation, racemic **7b** was obtained (determined by the CSA method).

***N*-Methyl-2-(11′-hydroxyundecyl)pyrrolidine (7c)** was prepared from **5** and 11-bromo-1-undecanol according to the same procedure used for the preparation of **4c**. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 52% yield: ^1H NMR ($CDCl_3$) 1.18−2.00 (25H, m), 2.10 (1H, dd), 2.28 (3H, s), 3.04 (1H, t), 3.58 (2H, t, J = 6.4); ^{13}C NMR ($CDCl_3$) 66.54, 62.86, 57.23, 40.33, 33.61, 32.79, 30.79, 29.92, 29.48 (4C), 29.38, 26.67, 25.69, 21.74; MS (M^+) 255; $[\alpha]_D$ −11.8 (*c* 1.85, CH_2Cl_2). Anal. Calcd for $C_{16}H_{33}NO$: C, 75.29; H, 12.94. Found: C, 75.10; H, 12.98. **(*R*)-*N*-Methyl-2-(11′-hydroxyundecyl)pyrrolidine ((*R*)-7c)** was prepared from (*S*)-**5**. Analysis by the CSA method indicated that (*R*)-**7c** was not racemic, but an accurate enantiomeric purity could not be determined due to peak overlap.

***tert*-Butyl *N*-methyl-2-pyrrolidineacetate (7d)** was prepared from **5** and *tert*-butyl bromoacetate according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 77% yield: ^1H NMR ($CDCl_3$) 1.43 (9H, s), 1.55 (1H, m), 1.77 (2H, m), 2.05 (1H, m), 2.20 (2H, m), 2.33 (3H, s), 2.50 (1H, m), 2.60 (1H, m), 3.05 (1H, m); ^{13}C NMR ($CDCl_3$) 171.50, 80.38, 62.78, 56.88, 40.45, 40.28, 31.098, 28.08, 21.94; MS (MH^+) 200; $[\alpha]_D$ 0 (*c* 0.2, CH_2Cl_2). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.33; H, 10.55. Found: C, 66.24; H, 10.39. When (*S*)-**5** was used for the preparation, racemic **7d** was obtained (determined by the CSA method).

***N*-Methyl-2-(5′-hexenyl)pyrrolidine (7e)** was prepared from **5** and 6-bromo-1-hexene by the the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 70% yield: ^1H NMR ($CDCl_3$) 1.20−1.57 (6H, m), 1.60−1.90 (3H, m), 2.00 (4H, m), 2.17 (1H, m), 2.30 (3H, s), 3.13 (1H, t), 4.94 (2H, m), 5.80 (1H, m); ^{13}C NMR ($CDCl_3$) 138.97, 114.33, 66.49, 57.33, 40.43, 33.72, 33.55, 30.78, 29.27, 26.13, 21.79; GC-MS (M^+) 167. Anal. Calcd for $C_{11}H_{21}N$: C, 79.04; H, 12.57. Found: C, 79.32; H, 12.33. **(*R*)-*N*-Methyl-2-(5′-hexenyl)-pyrrolidine ((*R*)-7e)** was prepared from (*S*)-**5**. CSP GC analysis showed a 46% enantiomeric excess. $[\alpha]_D$ −16 (*c* 0.4, CH_2Cl_2).

***N*-Methylpyrrolidine-2-methanol (7f).** *N*-Methyl-2-(tributylstannyl)pyrrolidine (**5**) (0.13g, 0.35 mmol) was dissolved in THF (3.50 mL, 0.1M) and TMEDA (0.07 mL, 0.45 mmol). The solution was cooled to −78 °C and treated with *n*-BuLi (0.30 mL, 1.5 M in hexane). The reaction mixture was stirred at −78 °C for 15 min and treated with a stream with CO_2 for 5 min. The mixture was stirred at −78 °C for 1 h and then diluted with ether (3 mL), and the reaction was quenched with saturated Na_2CO_3 (0.5 mL). The organic layer was removed by pipet, and the white solid was washed with ether (2 × 3 mL) and dried under vacuum. The *N*-methylproline was suspended in THF (7 mL) and cooled to 0 °C. LAH (0.10 g) was added in one portion to the THF suspension, and the reaction mixture was refluxed overnight. The solution was then cooled to 0 °C and diluted with 5 mL of ether, and the reaction was quenched with 0.1 mL of water. The mixture was filtered, and the cake was washed with ether (3 × 5 mL). The organic solution was dried over Na_2CO_3 and then concentrated to give the crude product. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was collected (0.033 g, 83% overall). ^1H NMR and ^{13}C NMR of **7f** matched that of a commercial sample (Aldrich). **(*R*)-*N*-Methyl-2-pyrrolidinemethanol ((*R*)-7f)** was prepared from (*S*)-**5**. The enantiomeric purity of (*R*)-**7f** was determined to be 94% by Mosher analysis; $[\alpha]_D$ +46 (*c* 0.75, CH_3OH); $[\alpha]_D$ −49.5 (*c* 5, CH_3OH), for the *S*-enantiomer from Aldrich.

***N*-Methyl-2-(trimethylacetyl)pyrrolidine (7g)** was prepared from **5** and pivaloyl chloride according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 55% yield: ^1H NMR ($CDCl_3$) 1.16 (9H, s), 1.65 (1H, m), 1.79 (1H, m), 1.95 (1H, m), 2.11 (1H, m), 2.25 (1H, m), 2.25 (3H, s), 3.18 (1H, m), 3.37 (1H, t, J = 8.4); ^{13}C NMR ($CDCl_3$) 215.62, 68.88, 56.05, 43.75, 40.31, 30.92, 26.12, 23.30; MS (MH^+) 170. Anal. Calcd for $C_{10}H_{19}NO$: C, 71.01; H, 11.24. Found: C, 71.25; H, 11.12. **(*R*)-*N*-Methyl-2-(trimethylacetyl)pyrrolidine ((*R*)-7g)** was prepared from (*S*)-**5**. The CSA method indicated an enantiomeric purity of 62% ee; $[\alpha]_D$ +85.0 (*c* 0.3, $CHCl_3$). The absolute configuration was established by comparison with a sample synthesized from (*R*)-BOC-

prolinal by addition of *tert*-butylmagnesium chloride followed by Swern oxidation (see supporting information for details).

***N*-Methyl-2-(1′-hydroxycyclohexyl)pyrrolidine (7h)** was prepared from **5** and cyclohexanone according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 86% yield as a colorless liquid: ^1H NMR ($CDCl_3$) 1.17−1.80 (14H, m), 2.40 (2H, m), 2.46 (3H, s), 3.01 (1H, m); ^{13}C NMR ($CDCl_3$) 73.69, 72.77, 58.64, 46.34, 36.80, 33.55, 27.11, 25.97, 25.21, 21.96 (2C); MS (MH^+) 184; $[\alpha]_D$ +37 (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{11}H_{21}NO$: C, 72.13; H, 11.48. Found: C, 72.32; H, 11.44. ***(R)*-*N*-Methyl-2-(1′-hydroxycyclohexyl)pyrrolidine ((*R*)-7h)** was prepared from (*S*)-**5**. The enantiomeric purity of (*R*)-**7h** was determined to be 94% by the CSA method.

***N*-Methyl-2-(2′-hydroxy-2′-propyl)pyrrolidine (7i)** was prepared from **5** and acetone (distilled from CaH_2) according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15), the product was obtained in 85% yield as a colorless liquid: ^1H NMR ($CDCl_3$) 1.12 (3H, s), 1.19 (3H, s), 1.70 (3H, m), 1.80 (1H, m), 2.35 (2H, m), 2.48 (3H, s), 2.61 (1H, br), 3.05 (1H, m); ^{13}C NMR ($CDCl_3$) 74.24, 72.48, 58.66, 45.89, 28.595, 27.96, 25.26, 24.93; MS (M^+) 143; $[\alpha]_D$ +5.75 (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_8H_{17}NO$: C, 67.17; H, 11.89. Found: C, 66.90; H, 11.84. ***(R)*-*N*-Methyl-2-(1′-methyl-1′-hydroxyethyl)pyrrolidine ((*R*)-7i)** was prepared from (*S*)-**5**. The enantiomeric purity of (*R*)-**7i** was determined to be 95% by comparing the rotation data with that of (*S*)-**7i** which was independently synthesized from BOC-L-proline by the sequence (i) esterification, (ii) addition of MeMgI, and (iii) LAH reduction (see supporting information for details).

Diphenyl(*N*-methyl-2-pyrrolidinyl)methanol (7j) was prepared from **5** and benzophenone according to the general procedure. After purification by flash chromatography on silica gel with CH_2Cl_2/EtOH (85/15) as eluent, the product was obtained in 70% yield. Spectral data matched those in the literature.[16c]

1′-Phenyl-*N*-methyl-2-pyrrolidinemethanol (7k) was prepared from **5** and benzaldehyde according to the general procedure. The product was obtained in 75% yield. The *u* and *l* diastereomers were separated by flash chromatography on silica gel with CH_2Cl_2/CH_3OH as eluent (85/15). ***u* diastereomer (*u*-7k)**: ^1H NMR ($CDCl_3$) 1.28 (1H, m), 1.70 (3H, m), 2.36 (1H, m), 2.45 (3H, s), 2.52 (1H, m), 3.15 (1H, m), 4.85 (1H, m), 7.70−7.41 (5H, m); ^{13}C NMR ($CDCl_3$) 141.68, 128.08, 126.73, 125.48, 70.93, 69.68, 57.55, 39.94, 23.91, 22.93. ***(1′S,2R′)*-7k** was prepared from (*S*)-**5**; $[\alpha]_D$ +59.6 (*c* 0.75, $CHCl_3$). The enantiomeric purity was determined to be 89% by the CSA method, and the absolute configuration was determined by comparison with literature data.[16c] ***l* diastereomer:** ^1H NMR ($CDCl_3$) 1.76 (3H, m), 1.91 (1H, m), 2.22 (3H, s), 2.39 (1H, m), 2.78 (1H, m), 3.12 (1H, m), 4.35 (1H, d, $J = 5.2$), 7.27 (5H, m); ^{13}C NMR ($CDCl_3$) 143.85, 128.14, 126.95, 126.08, 75.25, 71.53, 57.61, 43.90, 29.60, 24.40. ***(1R,2R′)*-7k** was prepared from (*S*)-**5**; $[\alpha]_D$ −13.0 (*c* 0.5, CH_3OH). The enantiomeric purity was determined to be 89% by the CSA method, and the absolute configuration was determined by comparison with literature data.[16c]

Acknowledgment. The authors thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. R.E.G. also thanks the NIH for a Fogarty Senior International Fellowship and Professor Dieter Seebach (ETH−Zürich) for his hospitality during a sabbatical leave, 1993−1994. We are also grateful to our colleagues Professor Luis Echegoyen and Mr. Yuhong Zuo for help with an ESR experiment.

Supporting Information Available: Details for the preparation of **4a**, **4i**, **7a**, **7g**, and **7i** from proline and pipecolic acid and proton and carbon NMR spectra of all new compounds (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information.

JO9509925