Chiral Organolithium Complexes: The Structure of β-Lithiated β-Phenylcarboxamides and the Mechanism of Asymmetric Substitution in the Presence of (−)-Sparteine

Donald J. Gallagher, Hua Du, Scott A. Long, and Peter Beak*

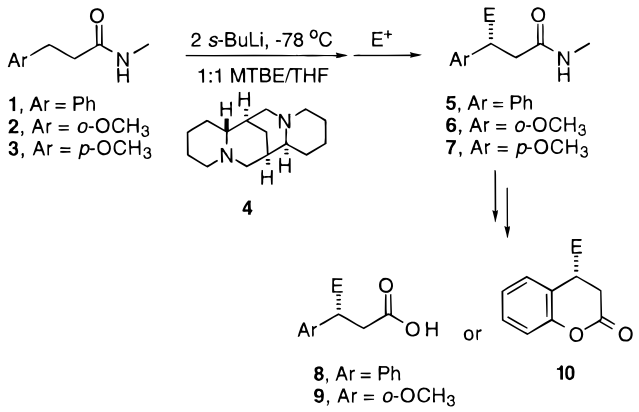
Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

Received July 15, 1996[⊗]

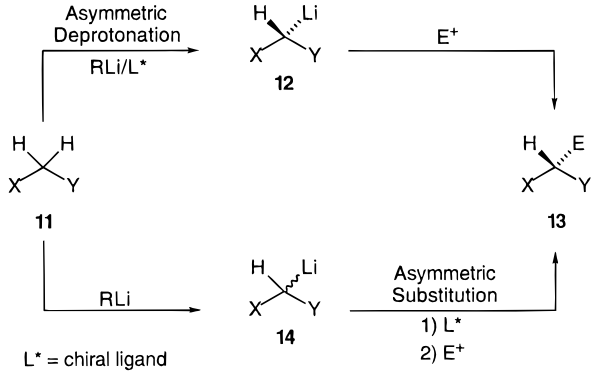
Abstract: Investigation of the structure and reactivity of β-lithiated β-phenylcarboxamides is reported. NMR spectroscopic investigations of β-lithiated amides **15** and **24** establish that the benzylic lithium is complexed by the nitrogen of the amide. The β-lithiated *N*-methyl amide **15** forms a complex with (−)-sparteine (**4**) which undergoes electrophilic substitution to provide enantioenriched products. The β-lithiated *N*-isopropyl amide **24** does not form a complex with **4**, so there is no asymmetric induction. The enantioselectivity of the reaction is shown to arise by the pathway of asymmetric substitution in which asymmetry is induced in a postdeprotonation step. Asymmetric induction in this lithiation−substitution sequence is suggested to occur via a dynamic thermodynamic resolution.

Introduction

Asymmetric lithiation−substitution methodology that provides highly enantioenriched products has been the focus of recent work.[1−4] We have communicated our initial observation that treatment of amides **1**−**3** with *sec*-BuLi in the presence of (−)-sparteine (**4**) followed by electrophilic substitution provides the enantioenriched products **5**−**10** in 60−94% ee.[5] We have recently reported synthetic applications of this methodology which afford enantioenriched amides, acids, and lactones.[6] We now report the results of structural and mechanistic studies that provide understanding of this asymmetric lithiation−substitution sequence.



Origin of Asymmetric Induction. The formation of enantioenriched products from an asymmetric lithiation−substitution sequence can result from either of the two limiting reaction pathways shown below.[7] One pathway is asymmetric deprotonation, in which a hydrogen is removed stereospecifically from a prochiral substrate, **11**, to provide a configurationally stable species, **12**, which undergoes electrophilic substitution to provide the enantioenriched product **13**.[2,8] The other pathway, which we refer to as asymmetric substitution, involves initial formation of a racemic organolithium species, **14**, complexation with a chiral ligand, and reaction with an electrophile to provide an enantioenriched product, **13**.[5] In the asymmetric substitution pathway, asymmetric induction occurs in a postdeprotonation step.



Results and Discussion

Reaction Pathway. In order to determine the source of asymmetric induction in the lithiation−substitution sequence from **1** to **5**, we have carried out a series of reactions to differentiate the two possible pathways. The dilithio species **15** was generated by lithiation of **1** with *sec*-BuLi in THF at −78 °C for 1.5 h, followed by addition of (−)-sparteine (**4**). After 20 min, trimethylsilyl chloride (TMSCl) was added. The

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

(1) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Aherns, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure & Appl. Chem.* **1994**, *66*, 1479. Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1459.

(2) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

(3) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

(4) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685.

(5) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516.

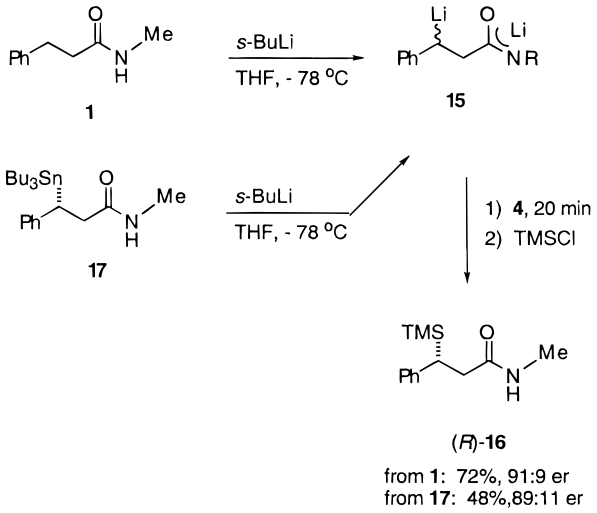
(6) Lutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 4542.

(7) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.*, in press.

(8) For examples of asymmetric deprotonation reactions, see: (a) Hoppe, D.; Zchage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. (b) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422. (c) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (d) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (e) Wu, S.; Lee, S. P.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.

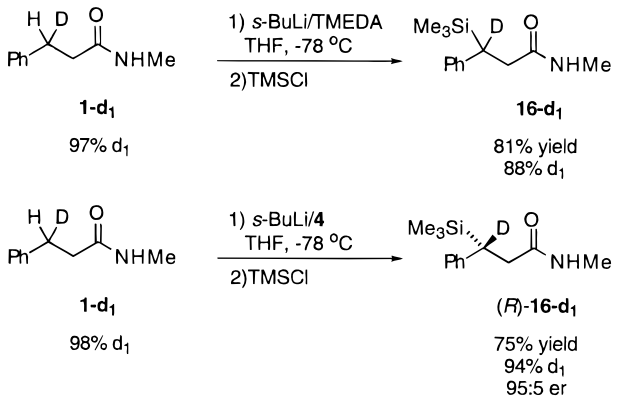
S0002-7863(96)02430-4 CCC: $12.00

TMS-substituted product (*R*)-**16** isolated in 78% yield had an enantiomeric ratio (er) of 91:9.[9] Similar results were obtained by treating the racemic tributyltin compound **17** with *sec*-BuLi in THF at −78 °C, followed by addition of **4** and reaction with TMSCl. The product **16** was obtained in 48% yield and 89:11 er.[10] The enantiomeric ratios of **16** found in these experiments in which (−)-sparteine is added after deprotonation are comparable to those found when the chiral ligand is present during the lithiation step. These results demonstrate that the racemic dianion **15** can be converted to enantioenriched products in the presence of (−)-sparteine, consistent with an asymmetric substitution pathway.



For reasons of operational simplicity in synthetic sequences, (−)-sparteine is present during the deprotonation step of the asymmetric lithiation−substitution of amides **1**−**3**.[6] A study of lithiation of the racemic β-deuterated amide **1-*d*$_1$** by *sec*-BuLi/TMEDA and *sec*-BuLi/(−)-sparteine was carried out to examine the possibility that an asymmetric deprotonation occurs when (−)-sparteine is initially present.[11] The racemic β-deuterated amide **1-*d*$_1$** (97% d_1) was treated with *sec*-BuLi/TMEDA at −78 °C for 1.5 h. Subsequent addition of chlorotrimethylsilane afforded the β-silyl substituted product **16-*d*$_1$** in 81% yield with 88% d_1, indicating a high isotope effect. A similar experiment in the presence of (−)-sparteine also indicated a high intramolecular isotope effect, providing (*R*)-**16-*d*$_1$** in 75% yield, 95:5 er, and 94% d_1. The yield is comparable to the 78% observed for the reaction of **1** in the same sequence.

If an asymmetric deprotonation pathway were operative, one enantiomer of **1-*d*$_1$**, the matched enantiomer, would be expected to be deprotonated at the same rate as undeuterated **1**.[8d−f,12] The other enantiomer of **1-*d*$_1$**, the mismatched enantiomer, would require removal of deuterium during a putative asymmetric deprotonation and be expected to react more slowly than the matched enantiomer because of a high isotope effect. In this case a lower yield of (*R*)-**16** would be expected relative to the

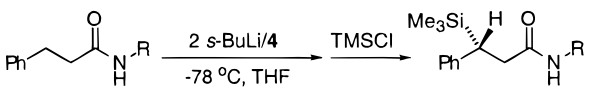


reaction of **1-*d*$_1$** with TMEDA because in the limiting case the mismatched enantiomer would not react. If asymmetric deprotonation were occurring and the isotope effect was not very large, comparable yields and enantiomeric excesses would be observed in the reaction with both TMEDA and (−)-sparteine, but deuterium incorporation in (*R*)-**16** would be lower in the latter case.

On the other hand, if the pathway involves an initial nonselective deprotonation followed by an asymmetric substitution, both enantiomers of **1-*d*$_1$** would be expected to lose the β-hydrogen preferentially because of a high kinetic isotope effect. The yield of the substitution product using (−)-sparteine as the ligand should be comparable to that of the reaction using TMEDA. The levels of enantioselectivity with **4** present should be similar to those found in the normal asymmetric lithiation−substitution of **1**. Since good yields, high deuterium incorporations, and high enantioselectivities are observed for the reaction of **1-*d*$_1$**, it appears that the asymmetric deprotonation pathway is not operative when (−)-sparteine is present during the lithiation step.[8e,12]

The experiments described above establish that asymmetric induction in the lithiation−substitution sequence of **1** with *sec*-BuLi/(−)-sparteine occurs during a postdeprotonation process. We have carried out additional studies in an effort to learn more about the intermediates in this asymmetric substitution process.

Structural Effects on Asymmetric Induction. We have found that alteration of the alkyl group on the amide nitrogen has a dramatic effect on the enantioselectivity of the asymmetric substitution reaction. In the normal synthetic sequence, lithiation of **1** with *sec*-BuLi/**4** in THF followed by electrophilic substitution with TMSCl provides **16** with a 94:6 er. Substitution of the methyl group with an ethyl group by using **18** in the same lithiation−substitution sequence provides amide **19** with only 60:40 er.[13] Reaction of the corresponding *N*-isopropyl amide **20** under the same conditions provides product **21** as a racemate.



The dramatic effect of the *N*-alkyl group on enantioselectivity prompted an investigation of the structures of the lithiated intermediates by NMR spectroscopy in order to elucidate the effect of these substituents on the course of the asymmetric substitution reaction.

(9) In this paper enantiomeric ratios (er) are reported as a measure of the enantioselectivity of the reaction.

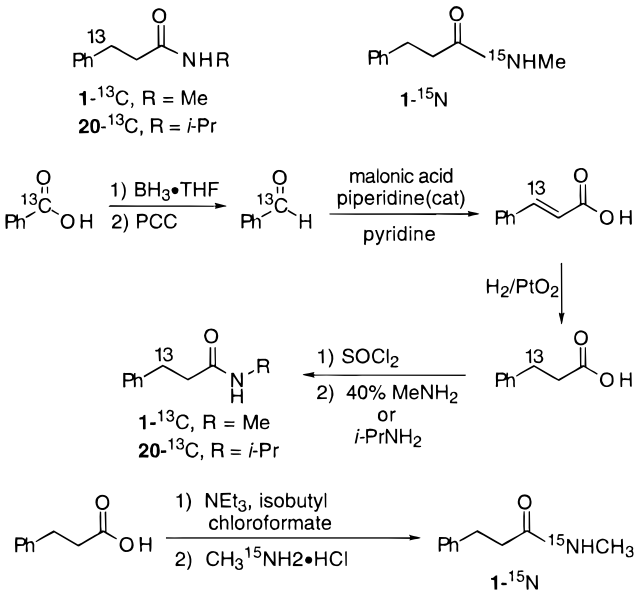
(10) The lower yield of **16** in this experiment was accompanied by isolation of amide **1** in 32% yield, suggesting some protonation of **15** may have occurred during this reaction.

(11) Schlosser and co-workers have shown that an asymmetric deprotonation/epimerization/asymmetric substitution process is operative during the lithiation of *N*-Boc-*N*-methylbenzylamine. Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342.

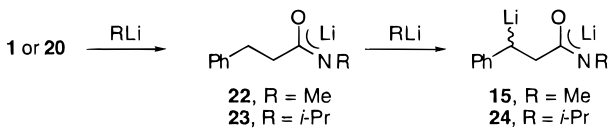
(12) (a) We have used this methodology for the detection of a diastereoselective deprotonation. Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 4938. (b) For an application to an asymmetric sulfur dipole-stabilized carbanionic reaction, see: Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323.

(13) Relatively small differences in an *N*-Me vs *N*-Et group have been found to influence an asymmetric reaction: Shimaro, M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7445.

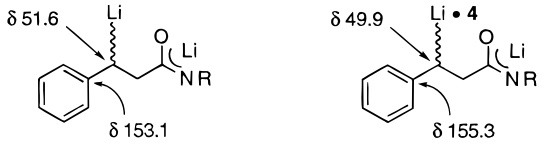
NMR Spectroscopic Studies. A multinuclear NMR spectroscopic investigation of the structures of lithiated intermediates was carried out using the ^{13}C-, ^{6}Li-, and ^{15}N-isotopically labeled-compounds **1**-^{13}***C***, **1**-^{15}***N***, and **20**-^{13}***C*** which were synthesized using established methodology.



Solutions of the labeled monoanionic amides **22** and **23** and dianionic amides **15** and **24** were generated by reaction of **1** or **20** with 1 or 2 equiv of *i*-Pr^{6}Li for 1.5 h in THF at −78 °C. The dianionic species were studied in the presence and absence of (−)-sparteine. The ^{13}C NMR spectrum of **15**-^{13}***C***-^{6}***Li*****$_2$** contains one predominant peak at 51.6 ppm that is assigned as the lithiated benzylic carbon. The peak is somewhat broad, but no ^{6}Li−^{13}C splitting could be observed at temperatures between −78 and −115 °C.[14] There are also two very small signals at 51.1 and 50.1 ppm that are unassigned. Addition of (−)-sparteine (2.5 equiv) gives rise to a major peak at 49.9 ppm while a smaller signal remains at 51.6 ppm.[15] The shift of the major signal for the benzylic carbon upon addition of (−)-sparteine strongly suggests that **4** is complexed to **15** in solution. The residual signal at 51.6 ppm is assigned to uncomplexed **15**. Since we can definitively assign only one signal in the ^{13}C NMR spectrum of **15**/**4**, it is not possible to determine whether the benzylic center exists in solution as one predominant epimer, a pair of epimers that rapidly interconverts on the NMR time scale, or a mixture of epimers with coincident NMR resonances.



The shifts of the benzylic and phenyl resonances in the ^{13}C NMR spectra of **15** and **15**/**4** relative to the unlithiated starting material can be used to estimate the hybridization of the lithiated benzylic center. A shift of approximately 35 ppm is expected for a planar anionic species, while a shift of approximately 10 ppm is expected for a pyramidalized carbanion.[16,17] Diagnostic shifts are also expected for the ipso carbons, which shift approximately 15 ppm for a pyramidalized carbanion and approximately −5 ppm for a planar carbanion. As shown below, the relative shifts of **15** and **15**/**4** for the benzylic centers are 19.1 and 17.3 ppm and the shifts in the ipso carbon resonances are 10.4 and 12.5 ppm, respectively. These values are consistent with a pyramidal benzylic carbon center with some delocalization into the phenyl ring.



Carbon	Δ(δ**15** - δ**1**) ppm	Δ(δ**15**/**4** - δ**1**) ppm
benzylic	19.1	17.3
ipso	10.4	12.5

The structures of **22** and **15** were also studied by ^{6}Li NMR spectroscopy. The ^{6}Li NMR spectrum of the monolithio species **22** contained a very broad peak centered around −0.3 ppm.[18] Addition of a second equivalent of *i*-Pr^{6}Li provides an orange solution of the dianion **15** that contains signals in the ^{6}Li NMR spectrum at −0.3 and 1.0 ppm as shown in Figure 1a. The signal at −0.3 ppm in the ^{6}Li NMR spectrum is assigned to the lithium associated with the amide anion, and the signal at 1.0 ppm is assigned to the lithium atom of the carbanionic center.

Addition of (−)-sparteine (2.4 equiv) to **15** provided the ^{6}Li NMR spectrum shown in Figure 1b. The spectrum has a signal at −0.3 ppm, assigned to the lithium amide resonance, and another signal at 1.3 ppm, which is assigned to the carbanionic lithium atom. The signal assigned to the carbanionic lithium atom has shifted +0.3 ppm relative to that in the spectrum shown in Figure 1a. Incremental addition of **4** to a solution of **15** results in the gradual formation of the peak at 1.3 ppm and the disappearance of the peak at 1.0 ppm. The signal at −0.3 ppm does not change. The shift of the signal from 1.0 to 1.3 ppm is interpreted as the result of complexation of (−)-sparteine with the lithium of the carbanionic center of **15**. The signal remaining at 1.0 ppm is considered to be residual uncomplexed **15**.

The ^{6}Li NMR spectrum of **15**/**4** as shown in Figure 1b was generated using customary line broadening techniques. When this line broadening is not applied, the ^{6}Li NMR signal at −0.3 ppm appears to be a collection of 2−3 overlapping peaks. The signal at 1.3 ppm appears to consist of two closely overlapping peaks of similar intensities. The differentiation between these two peaks is very small and is only observable with well-shimmed homogeneous solutions of **15**/**4**.[18] The possible causes of these multiple peaks will be addressed below.

The ^{1}H-decoupled ^{6}Li NMR spectrum of a solution of **15**-^{15}***N*****/4** in THF-d_8 at −78 °C contained a doublet (J = 5.3 Hz) at

(14) The lack of observable splitting prevents the determination of the aggregation state of this benzylic organolithium species. Splitting between the lithium and carbon atoms of benzylic lithium species is very difficult to observe. Fraenkel, G.; Martin, K. V. *J. Am. Chem. Soc.* **1995**, *117*, 10336.

(15) ^{13}C NMR spectra of **15** and **15/4** are provided as Supporting Information.

(16) These parts per million ranges were found from studies of the ^{13}C NMR shifts of (7-phenylnorbornyl)lithium and (7-phenylnorbornyl)potassium relative to 7-phenylnorbornane. Peoples, P. R.; Grutzner, J. B *J. Am. Chem. Soc.* **1980**, *102*, 4709.

(17) We have used a similar analysis in the study of *N*,*N*-diisopropyl-2-methyl-3-phenyl-3-lithiopropionamide. See ref 12a.

(18) The ^{6}Li NMR spectra are referenced to a solution of ^{6}LiBr in THF-d_8 solution contained in a 5 mm tube coaxially anchored in the 10 mm NMR tube containing the sample solutions.

(19) It proved to be experimentally challenging to shim these samples because of the presence of the coaxially-held standard tube and also because some precipitation often occurred in the sample during the acquisition of the NMR spectra.

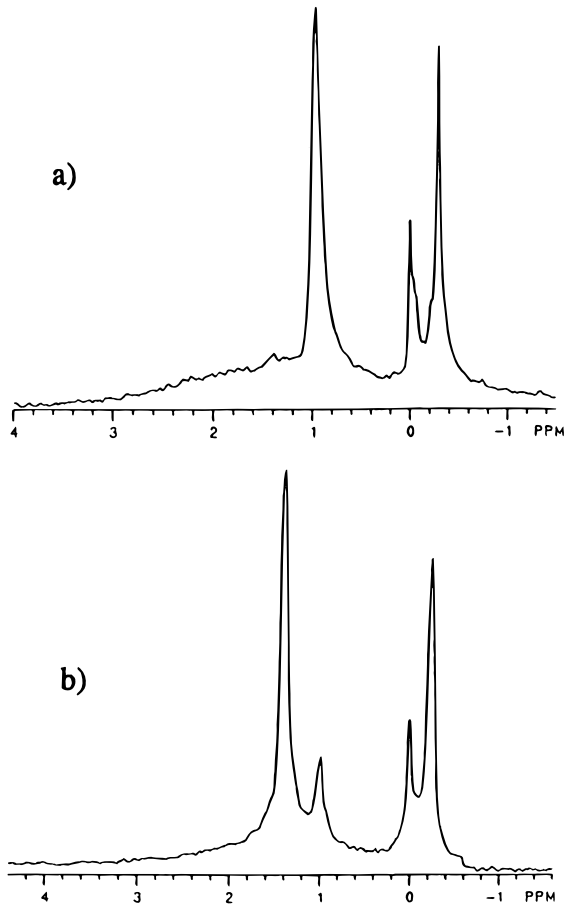
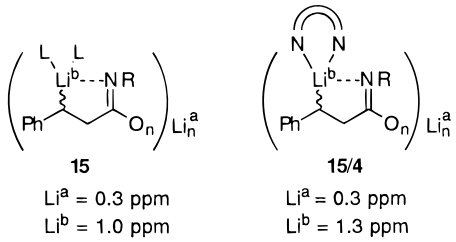


Figure 1. (a) ^{6}Li NMR spectrum of **15** in THF-d_8, 0.05 M, −78 °C. (b) ^{6}Li NMR spectrum of **15**/**4** in THF-d_8 (2.5 equiv of **4**), 0.05 M, −78 °C.

1.3 ppm, demonstrating scalar coupling between the amide nitrogen and the lithium of the carbanion. Application of ^{15}N-decoupling collapsed this doublet to a single peak. The lithium signal at −0.3 ppm did not show any coupling or broadening. The ^{1}H-decoupled ^{15}N NMR spectrum contained one major triplet (J = 5.3 Hz) with several other minor resonances. This spin interaction indicates contact between the amide nitrogen and the lithium of the carbanion in the dilithiated species.

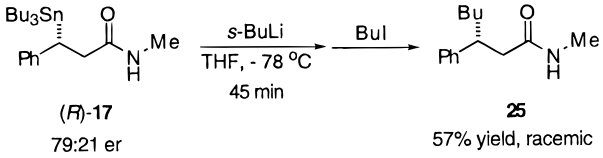
On the basis of the NMR data presented above, partial structures for the dianion **15** and the complex with (−)-sparteine **15**/**4** are proposed as shown below. The lithium of the benzylic carbanion is chelated with the nitrogen of the amide as shown by the ^{15}N−^{6}Li splitting. The lithium associated with the deprotonated amide is proposed to be bonded to the oxygen in accordance with the lack of splitting between ^{15}N and the ^{6}Li NMR signal at −0.3 ppm. This general type of structure is consistent with the structure of lithio-*N*-isopropylbenzamide found by Seebach and co-workers.[20] The anionic oxygen is most likely incorporated into dimers, tetramers, or other higher order aggregates.[21] The several overlapping peaks for Li^{a} may be a result of the presence of one or more diastereomeric aggregates.

The dilithio-*N*-isopropyl amide **24** was also investigated by ^{13}C and ^{6}Li NMR spectroscopy. The ^{13}C NMR spectrum of **24**-^{13}***C*** shows one major benzylic carbon signal at 50.8 ppm with two minor signals at 51.0 and 52.2 ppm. Addition of 2.5 equiv of **4** has little effect on the NMR spectrum. The signals at 50.8 and 52.2 ppm are unaffected. The ^{6}Li NMR spectrum of **24** contains signals at −0.3 and 1.0 ppm, which are assigned as the amidic lithium and benzylic lithium, respectively. Addition of (−)-sparteine has no effect on the signals in the ^{6}Li NMR spectrum. The fact that there are no changes in the ^{13}C NMR or ^{6}Li NMR spectra upon addition of (−)-sparteine suggests that no detectable complex between **24** and **4** is formed in solution.



These NMR studies indicate that the dramatic difference in enantioselectivity in the lithiation−substitution reactions of **15** and **24** is due to the formation of a complex between **15** and (−)- sparteine and the lack of a complex between **24** and (−)-sparteine. The structures of both **15** and **24** have been shown to involve a single Li bridging the benzylic and nitrogen atoms, a factor which places the *N*-alkyl group in proximity to the site of ligand complexation. The larger steric requirements of the isopropyl group in **24** apparently prevent complexation of (−)-sparteine.

Configurational Stability. The configurational stabilities of the organolithium species **15** and **15/4** were investigated by several techniques. Treatment of the enantioenriched tin compound (*R*)-**17** (78:22 er) with *sec*-BuLi for 45 min in THF at −78 °C, followed by addition of butyl iodide, resulted in the formation of racemic **25**. Similar results were obtained using TMSCl as the electrophile. These results indicate that the uncomplexed lithiated benzylic center of **15** is not configurationally stable over a time period of 45 min. As noted above, treatment of the racemic tin compound **17** with *sec*-BuLi followed by addition of (−)-sparteine (**4**) and electrophilic substitution with TMSCl provided **16** with an 89:11 er. This result shows that, over the time period of the experiment, the benzylic carbanion does not maintain its configuration in the presence of **4** at −78 °C.

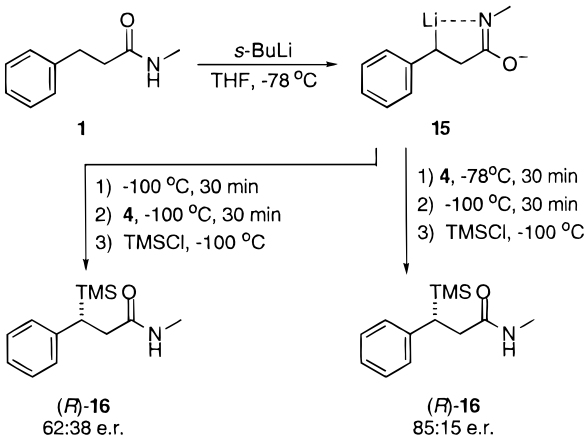


The configurational stability of the organolithium **15**/**4** at −100 °C has also been investigated by generating two solutions of the racemic dianionic species **15** at −78 °C. One of the solutions was cooled to −100 °C for 30 min, (−)-sparteine (2.0 equiv) was added, and the reaction was stirred at −100 °C for 30 min, followed by addition of TMSCl. The product (*R*)-**15** was obtained with a 62:38 er. (−)-Sparteine (2 equiv) was introduced to another solution of **15** at −78 °C which was stirred for 30 min and cooled to −100 °C for 30 min, and then TMSCl was added. The product (*R*)-**15** obtained in this manner had a significantly higher 85:15 er. These results suggest that epimerization of the benzylic stereogenic center of **15/4** is slower at −100 °C than at −78 °C.

The experiments discussed above addressed the configurational stability of the organolithium species over a 30 min to 1

(20) Maetzke, T.; Hidber, C. P.; Seebach, D. *J. Am. Chem. Soc.* **1990**, *112*, 8248. Maetzke, T.; Seebach, D. *Organometallics* **1990**, *9*, 3032.

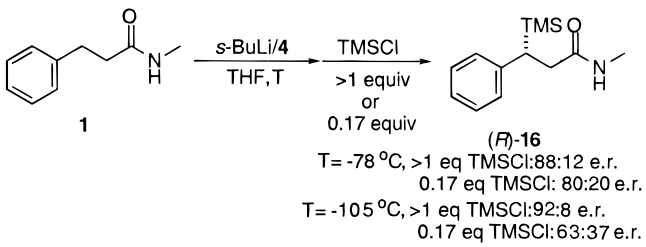
(21) For studies of alkoxide aggregation, see: Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 4101. McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805.



h time period. We also wished to determine the configurational stability of the species over the time period of the electrophilic trapping reaction. We have recently reported a method to determine the configurational stability of a diastereomeric organolithium complex with respect to electrophilic trapping based on the use of substoichiometric amounts of electrophile.[22] This method is based on the pioneering work of Hoffmann and co-workers on the rates of equilibration of chiral organolithium compounds.[23] If a mixture of two configurationally stable diastereomeric complexes is reacted with an electrophile, the product ratio will reflect the population of the two complexes. However, if the reaction with the electrophile is carried out with a deficient amount of electrophile, then the enantiomeric ratio may be different because each diastereomeric complex may react with electrophile at a different rate, i.e., possess different activation energies. Thus, if different enantiomeric ratios are observed using substoichiometric amounts of electrophile compared to using >1 equiv, this demonstrates configurational stability on the time scale of the electrophilic trapping reaction.[24]

Reactions using substoichiometric amounts of electrophile were carried out side by side with a reference reaction using >1 equiv of electrophile to ensure as similar conditions as possible for comparison.[25] Amide **1** was lithiated at −78 °C with 1.75 equiv of *sec*-BuLi/(−)-sparteine followed by reaction at −78 °C with either 0.17 equiv or 1.75 equiv of TMSCl. The reference reaction using >1 equiv of TMSCl provided an 88:12 er. The reaction using 0.17 equiv of TMSCl provided an er of 80:20. This modest difference in enantiomeric ratio suggests some measure of configurational stability on the time scale of reaction with the electrophile.[25,26] In this case, the minor diastereomeric complex has a lower activation energy of reaction with TMSCl. The calculated difference in transition state energies for the two complexes is 0.24 kcal/mol.

The same test of configurational stability was also performed at −105 °C since larger differences in enantiomeric ratios might



be expected at lower temperatures. The results of the macroscopic configurational stability test at −100 °C discussed above also suggested enhanced stability at lower temperature. Amide **1** was lithiated at −78 °C and cooled to −105 °C for 15 min, followed by the electrophilic reaction protocol as described above. An er of 92:8 was obtained using >1 equiv of TMSCl, while use of 0.17 equiv of TMSCl resulted in an er of 63:37. These very different enantiomeric ratio values strongly suggest that the **15/4** complex is configurationally stable at −105 °C over the time scale of reaction with TMSCl. The minor diastereomeric complex also has a lower activation energy of reaction with TMSCl at −105 °C. The difference in activation energies between the two complexes at −105 °C is calculated to be 0.64 kcal/mol.

Origin of Enantioselectivity in the Lithiation−Substitution Reaction of 1. There are several pathways of asymmetric induction that can account for the observed asymmetric substitution process. One operative mechanism that has been demonstrated by Hoppe and co-workers is that of selective crystallization,[28] in which an equilibrium between two diastereomeric complexes in solution is disturbed by selective crystallization of one of the complexes. Subsequent electrophilic substitution of the residual organolithium substrate provided good enantiomeric excesses in the products. We believe that this pathway is not operative in the lithiation−substitution of **1** because the reaction can be carried out under homogeneous reaction conditions to provide good yields and high enantioselectivities.[29]

There are two limiting cases that can be considered as the source of postdeprotonation asymmetric induction in the homogeneous lithiation−substitution of **1**.[7] One possibility is that there are two diastereomeric complexes, (*S*)-**15**/**4** and (*R*)-**15**/**4**, which interconvert rapidly on the time scale of the electrophilic substitution reaction. In this case, as Figure 2a shows, the enantioselectivity will reflect the difference in transition state energies ($\Delta\Delta G^{\ddagger}$) for the reaction of the diastereomeric complexes with an electrophile. This pathway has been termed dynamic kinetic resolution.[30,31]

The second possibility is that the carbanion is configurationally stable during the time of the electrophilic substitution reaction. As shown in Figure 2b, the enantiomeric ratio of the product should then reflect the energy difference ($\Delta\Delta G$) between the two diastereomeric complexes (*S*)-**15**/**4** and (*R*)-**15**/**4**. We have termed this process dynamic thermodynamic resolution because the two diastereomeric complexes can thermodynamically equilibrate to a favored complex, but not on the time scale of reaction with the electrophile.

(22) Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718.

(23) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frezen, G. *Tetrahedron* **1994**, *50*, 6049. Hoffmann, R. W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* **1992**, 719. Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975.

(24) Interpretation of the reverse observation cannot be made. If the same enantiomeric ratio is observed between the two reactions, no definitive conclusion can be drawn.

(25) The temperature of each reaction flask was monitored by a Teflon-coated internal thermocouple. Care was taken to make certain that the internal temperature of each solution was the same at the time of reaction with the electrophile.

(26) We estimate the error in enantiomeric ratio determination by CSP HPLC to be 2%.

(27) One possibility for different er values is that some lithiation of the product **16** could occur in situ. The reactions were quenched with CH_3OD, and the product **16** was analyzed for deuterium content. No deuterium incorporation was found, indicating that in situ lithiation of the product is not the cause of the different er values.

(28) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657.

(29) In addition, we have also performed the lithiation of **1** at higher concentrations which results in the formation of precipitates. The mixture was filtered at −78 °C, and the solution and solid reacted separately with TMSCl. Generally high enantiomeric excesses (70−88% ee) in the products were found from both the solution and solid, indicating that selective precipitation is not the source of enantioselectivity in this reaction.

(30) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

(31) The reactivity in this potential pathway is governed by the Curtin−Hammett principle. Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. For a full treatment of Curtin−Hammett−Winstein−Holness kinetics, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

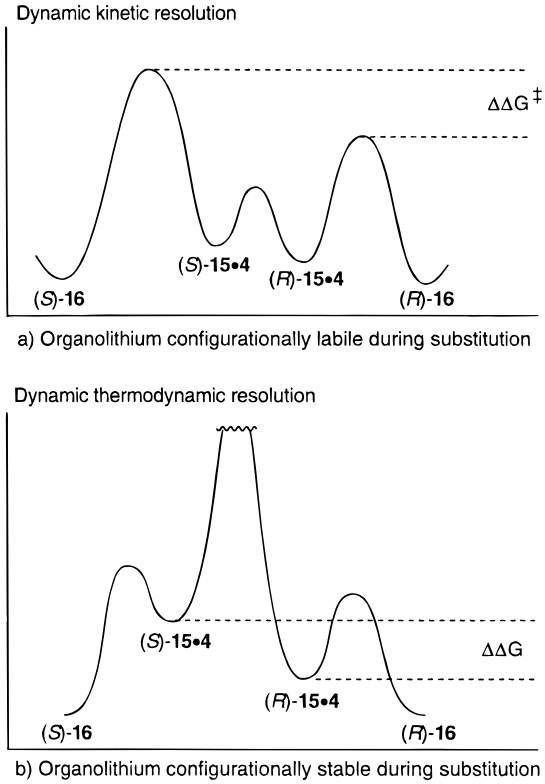
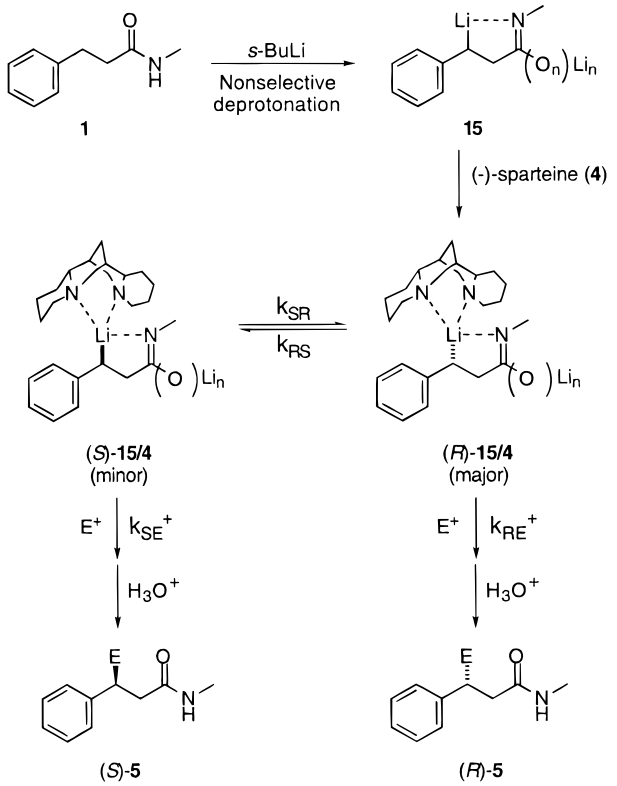


Figure 2. Energy level diagrams for the reaction of diastereomeric complexes (*R*)-**15/4** and (*S*)-**15/4** with electrophiles.

Both of the reaction profiles discussed above have been demonstrated with benzylic organolithium substrates.[32] In these figures we have assumed the substitutions proceed with retention of configuration, but reaction with inversion is also possible. The principles illustrated in the figures are independent of the stereochemistry of the substitution. The evidence for configurational stability at −105 °C presented above indicates that enantioinduction is occurring through a dynamic thermodynamic resolution in which reaction with an electrophile occurs faster than equilibration between two diastereomeric complexes. Therefore, the enantiomeric ratio obtained under these conditions represents the ground state population of the two diastereomeric complexes.

The evidence for one enantiodetermining mechanistic pathway is less clear for the electrophilic substitution reaction at −78 °C. While the difference using the substoichiometric test for configurational stability does indicate that the diastereomeric complexes have stability on the time scale of the reaction, the calculated activation energy difference between the two complexes is substantially smaller that that observed at −105 °C. Theoretically these energy differences should be similar. One explanation for this energy difference is that at −78 °C there is some competition occurring between the pathways of dynamic thermodynamic resolution and dynamic kinetic resolution. However, it is also possible that the discrepancies between the activation energy differences may result from mechanical factors such as the rate of mixing. It seems reasonable to suggest that the primary source of enantioinduction in this reaction is dynamic thermodynamic resolution, but a contribution from a dynamic kinetic resolution process cannot be discounted.

A mechanistic scheme summarizing the data presented is shown below. The amide **1** is lithiated nonselectively by 2 equiv of *sec*-BuLi to form the dianion **15**, which is complexed to (−)-sparteine.[33] Over the period of the reaction an equilibrium between the two diastereomeric organolithium complexes (*R*)-**15/4** and (*S*)-**15/4** is established which favors (*R*)-**15/4**. Addition of the electrophile provides the chiral products (*S*)-**5** and (*R*)-**5**.[33] At −100 °C the rate of reaction with the electrophile (k_{RE}^+ and k_{SE}^+) is much greater than the rate of equilibration (k_{SR} and k_{RS}) between the two diastereomeric complexes. At −78 °C the same process is occurring, except that the rate of reaction with the electrophile could be somewhat competitive with the rate of equilibration. At either temperature we believe that the primary pathway of asymmetric induction is a dynamic thermodynamic resolution in which the enantioselectivity is determined by the equilibrium which partitions between (*S*)-**15/4** and (*R*)-**15/4**.



Conclusion

The asymmetric lithiation−substitution of the *N*-methyl amide **1** by *sec*-BuLi/(−)-sparteine has been shown to proceed through a pathway of asymmetric substitution in which the enantioselectivity of the reaction is induced in a postdeprotonation step. NMR spectroscopic studies of **15**/**4** show this species to be a complex in which the amide nitrogen and (−)-sparteine are complexed to the benzylic lithium. The absence of asymmetric induction when the *N*-isopropyl amide **20** is used in the lithiation−substitution sequence is due to the steric hindrance by the isopropyl group that prevents (−)-sparteine from complexing to the lithiated amide. The enantioselectivity of the

(32) For cases in which the enantioselectivity reflects differences in ground state energies of diastereomeric organolithium complexes, see: Klute, W.; Kruger, M.; Hoffman, R. W. *Chem. Ber.* **1996**, *129*, 633.; Basu, A., Beak, P. *J. Am. Chem. Soc.* **1996**, *188*, 1575. For cases in which the enantioselectivity reflects the difference in transition state energies, $\Delta\Delta G^{\ddagger}$, see: Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem.* **1992**, 725. Thayumanaman, S.; Lee, S. P.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755.

(33) We have found that *i*-PrLi does not form an observable complex with (−)-sparteine in THF solution and assume that applies to *sec*-BuLi as well. Long, S. A.; Beak, P. Unpublished result.

reaction at −78 °C arises primarily from a dynamic thermodynamic resolution although a contribution from a dynamic kinetic resolution process is possible. Current work is aimed at understanding these processes and applying this methodology to other systems.

Experimental Section

All reactions involving organometallic reagents were carried out under a nitrogen or argon atmosphere in glassware that was either flame dried or dried in an oven and cooled under a nitrogen atmosphere. All solvents and reagents were obtained from commercial sources and were used without further purification except where noted. Benzoic acid (carboxyl-^{13}C, 99%) and methylamine-^{15}N·HCl (99%) were purchased from Cambridge Isotope Laboratories. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under a nitrogen atmosphere before use. The *sec*-BuLi solutions were titrated using the method of Suffert.[34]

High-pressure liquid chromatography (HPLC) was performed using Rainin HPXL pump systems. Preparative scale HPLC was performed on a Dynamax 60-A 8 μm silica column (Rainin Instrument Co., Woburn, MA 01801, 25 cm × 21.4 mm i.d.). Flash chromatography was performed with Merck 50−200 μm silica gel. Medium-pressure liquid chromatography (MPLC) was performed using columns of different sizes packed with Merck silica gel (32−63 mesh) whose length and diameter depended on the amount of material and the difficulty of the separation.

Enantiomeric Purity Analyses. Enantiomeric purity analyses were carried out with both racemic and enantioenriched compounds. Analytical chiral stationary phase (CSP) HPLC was performed on Pirkle-concept chiral columns (Regis Chemical Co., Morton Grove, IL 60053-9975, 25 cm × 4.6 mm i.d.): (*R*,*R*)-Beta-Gem 1, D-phenylglycine, and (*S*,*S*)-Whelk-O1 columns using mixtures of 2-isopropanol (*i*-PrOH) and hexane. Diastereomeric purity analyses determined by GC were performed on an HP-5 fused silica column.

Generation of 15 by Deprotonation, Followed by Addition of (−)-Sparteine and Electrophilic Substitution with TMSCl. To *N*-methyl-3-phenylpropanamide (**1**) (142 mg, 1.04 mmol) in THF (4 mL) and *t*-BuOMe (4 mL) at −78 °C was added *sec*-BuLi (2.0 mL, 2.18 mmol). The solution was stirred for 50 min, and then (−)-sparteine (**4**) (1 mL, 4.36 mmol) was added. The reaction mixture was stirred for 20 min, and then trimethylsilyl chloride (0.22 mL, 1.74 mmol) was added. The mixture was allowed to stir for 1 h, and then 5% HCl (20 mL) and Et_2O (20 mL) were added. The solution was allowed to warm to ambient temperature, and then the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography (3:1 hexane/EtOAc) to provide 146 mg (72%) of (*R*)-**16** as a colorless oil, whose chromatographic and spectral characteristics were identical to those of a previously characterized compound.[6] The enantiomeric ratio of (*R*)-**16** was determined directly by CSP HPLC analysis ((*S*,*S*)-Whelk-O1 column, 10% *i*-PrOH/hexane, 2.0 mL/min) to be 91:9 er. The major enantiomer (*R*)-**16** had a retention time of 13.5 min, and the minor enantiomer (*S*)-**16** had a retention time of 9.0 min.

Generation of 15 by Tin−Lithium Exchange, Followed by Addition of 4 and Electrophilic Substitution with TMSCl. To *N*-methyl-3-(tributylstannyl)-3-phenylpropanamide (**17**) (242 mg, 0.6 mmol) in THF (7 mL) was added *sec*-BuLi (1.44 mL, 1.55 mmol) at −78 °C. The reaction mixture was stirred for 30 min, and then (−)-sparteine (0.40 mL, 1.71 mmol) was added at −78 °C. The mixture was stirred for 20 min, and then trimethylsilyl chloride (0.16 mL, 1.24 mmol) was added. The resulting solution was stirred for 1 h, and then 5% HCl (15 mL) and Et_2O (20 mL) were added. The mixture was allowed to warm to ambient temperature, the layers were separated, and the aqueous layer was extracted with ether (2 × 20 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by MPLC (30% EtOAc/hexane) to give (*R*)-**16** (63 mg, 48%) as a colorless oil and **1** (56 mg, 36%) as a white solid. The enantiomeric ratio of (*R*)-**16** was determined to be 89:11 by CSP HPLC as described above.

(34) Suffert, J. *J. Org. Chem.* **1989**, *54*, 510.

Lithiation−Substitution of 1-d_1 with *sec*-BuLi/TMEDA. To a solution of **1-d_1** (0.109 g, 0.66 mmol) and TMEDA (0.24 mL, 1.61 mmol) in THF (10 mL) cooled to −78 °C was added *sec*-BuLi (1.1 M, 1.3 mL, 1.46 mmol). The reaction was stirred for 1 h, then TMSCl (0.11 mL, 0.86 mmol) was added, and the reaction was stirred for 1.5 h. Et_2O (10 mL) and 5% HCl (10 mL) were added and the layers separated. The aqueous layer was washed with additional Et_2O (2 × 10 mL), and the combined Et_2O layers were dried over $MgSO_4$. Filtering and removal of solvent provided an oil which was purified by MPLC (30% EtOAc/hexane) to give **16** as a clear oil (0.127 g, 0.54 mmol, 81%). FIMS analysis relative to an undeuterated standard indicated the product consisted of 88% d_1 material.

Lithiation−Substitution of 1-d_1 with *sec*-BuLi/(−)-Sparteine. To a solution of **1-d_1** (0.103 g, 0.63 mmol) in THF (8 mL) cooled to −78 °C was added a precooled solution of *sec*-BuLi (1.1 M, 1.2 mL, 1.39 mmol) and (−)-sparteine (0.36 mL, 1.58 mmol) in THF (5 mL). The reaction was stirred for 1 h, then TMSCl (0.10 mL, 0.82 mmol) was added, and the reaction was stirred for 1.5 h. Et_2O (10 mL) and 5% HCl (10 mL) were added and the layers separated. The aqueous layer was washed with additional Et_2O (2 × 10 mL), and the combined Et_2O layers were dried over $MgSO_4$. Filtering and removal of solvent provided an oil which was purified by MPLC (30% EtOAc/hexane) to give **16** as a clear oil (0.110 g, 0.468 mmol, 75%). FIMS analysis relative to an undeuterated standard indicated the product consisted of 94% d_1 material. The enantiomeric ratio of (*R*)-**16** was determined to be 95:5 by CSP HPLC as described above.

Preparation of (*R*)-*N*-Ethyl-3-phenyl-3-(trimethylsilyl)propanamide (19). To (−)-sparteine (0.40 mL, 1.65 mmol) in THF (4 mL) at −78 °C was added *sec*-BuLi (1.4 mL, 1.50 mmol). The reaction mixture was stirred for 20 min at −78 °C and then was transferred to a solution of *N*-ethyl-3-phenylpropanamide (**18**) (120 mg, 0.68 mmol) in THF (8 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 50 min, and then trimethylsilyl chloride (0.12 mL, 0.88 mmol) was added. This mixture was then allowed to stir for 50 min at −78 °C. Et_2O (20 mL) and 5% HCl (15 mL) were added. The mixture was allowed to warm to ambient temperature, and then the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by MPLC (25% EtOAc/hexane) to give **19** as an oil (120 mg, 71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.05 (s, 9H, $Si(CH_3)_3$), 0.82 (t, 3H, J = 7.3 Hz, CH_3), 2.49−2.63 (m, 3H, $CHCH_2$), 3.02−3.11 (m, 2H, CH_2), 5.42 (br s, 1H, NH), 7.02−7.22 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −3.12, 14.49, 33.17, 34.08, 36,89, 124.91, 127.27, 124.36, 142.32, 172.25. Anal. Calcd for $C_{14}H_{23}NOSi$: C, 67.41; H, 9.25; N, 5.62. Found: C, 67.48; H, 9.30; N, 5.59. The enantiomeric ratio of (*R*)-**16** was determined directly by CSP HPLC analysis ((*S*,*S*)-Whelk-O1 column, 4% *i*-PrOH/hexane, 2.0 mL/min) to be 60:40 er. The major enantiomer (*R*)-**19** had a retention time of 30.3 min, and the minor enantiomer (*S*)-**19** had a retention time of 18.9 min.

Preparation of *N*-Isopropyl-3-phenyl-3-(trimethylsilyl)propanamide (21). To (−)-sparteine (0.66 mL, 2.88 mmol) in THF (2 mL) and *t*-BuOMe (2 mL) at −78 °C was added *sec*-BuLi (1.3 mL, 1.44 mmol). The reaction mixture was stirred for 20 min at −78 °C and then was transferred to a solution of *N*-isopropyl-3-phenylpropanamide (**20**) (110 mg, 0.58 mmol) in THF (4 mL) and *t*-BuOMe (4 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 60 min, and then trimethylsilyl chloride (0.11 mL, 0.86 mmol) was added. This mixture was then allowed to stir for 60 min at −78 °C. Et_2O (20 mL) and 5% HCl (5 mL) were added. The mixture was allowed to warm to ambient temperature, and then the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL). The combined ether layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by MPLC (25% EtOAc/hexane) to give **21** as a white solid (77 mg, 51%): mp 64−68 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 6H, $Si(CH_3)_3$), 0.69 (d, 3H, J = 6.5 Hz, CH_3), 0.75 (d, 3H, J = 6.5 Hz, CH_3), 2.40−2.60 (m, 3H, $CHCH_2$), 3.74 (m, 1H, CH), 5.45 (br d, 1H, NH), 6.90−7.00 (m, 3H, Ar), 7.10−7.20 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −3.16, 22.30, 22.39, 33.25, 36.97, 40.86, 124.86, 127.30, 124.25, 142.25, 171.48. Anal. Calcd for $C_{15}H_{25}NOSi$: C, 68.39; H, 9.56; N,

5.32. Found: C, 68.66; H, 9.72; N, 5.30. The enantiomeric ratio of **21** was determined directly by CSP HPLC analysis ((*S*,*S*)-Whelk-O1 column, 10% *i*-PrOH/hexane, 2.0 mL/min) to be 50:50 er. The enantiomers had retention times of 13.5 and 9.0 min.

Representative Procedure of Organolithium NMR Sample Preparation. A solution of **1** (0.027 g, 0.16 mmol) and (−)-sparteine (**4**) (0.092 g, 0.39 mmol) in 3 mL of dry THF was cooled to −78 °C. In another flask 0.41 mL of a 0.80 M solution of isopropyllithium-^{6}*Li* was added, and the solvent was removed in vacuo. The organolithium-containing flask was then cooled to −78 °C, and the THF solution of **1** and **4** was then transferred via cannula to the organolithium flask with constant stirring. The substrate was allowed to lithiate for 1 h and was then transferred by cannula to a 10 mm NMR tube with a sealed 5 mm insert containing the reference solution.

Configurational Stability Study of (*R*)-15 at −78 °C. A solution of the tributyltin-substituted amide (*R*)-**17** (78:22 er) (0.2101 g, 0.467 mmol) in THF (4.7 mL) was cooled to −80 °C, and *sec*-BuLi (1.45 M, 0.64 mL, 0.93 mmol) was added.[6] The orange homogeneous reaction solution was stirred for 45 min, butyl iodide (0.053 mL, 0.467 mmol) was added, and the orange color disappeared. The reaction mixture was stirred for 10 min, and then 1 mL of MeOH/$H_2$0 was added. After warming to room temperature, 5 mL of 5% HCl and 10 mL of Et_2O were added. The layers were separated, and the aqueous layer was extracted with additional Et_2O (2 × 10 mL). The combined ether layers were washed with 10% $Na_2S_2O_3$, dried over $MgSO_4$, and filtered. The solvent was removed to provide an oil which was purified by MPLC (50% EtOAc/hexane) to provide *N*-methyl-3-phenylheptanamide (**25**) as a clear oil (0.0580 g, 0.227 mmol, 57%), whose chromatographic and spectral characteristics matched those reported earlier (synth ref). Analysis by CSP HPLC ((*S*,*S*)-Whelk-O1 column, 10% *i*-PrOH/hexane, 2.0 mL/min) indicated a racemic mixture. The two enantiomers had retention times of 8.6 and 10.5 min.

Comparative Configurational Stability Study of 15 at −100 °C. To a solution of **1** (0.1207 g, 0.740 mmol) in THF (7.5 mL) cooled to −78 °C under N_2 was added *sec*-BuLi (1.1 mL, 1.4 M, 1.48 mmol). The reaction was stirred for 1 h and then immersed in a −100 °C bath for 30 min. (−)-Sparteine (0.22 M in THF, 6.7 mL, 1.48 mmol) was added slowly, and the reaction was stirred for 30 min. TMSCl (0.25 mL, 2.0 mmol) was added, and the reaction was stirred at −100 °C for 10 min, followed by addition of CH_3OH/H_2O to quench the reaction. After warming to room temperature, the mixture was poured into 5% HCl (10 mL) and extracted with 3 × 10 mL of Et_2O. The ether layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to provide a pale yellow oil which was purified by column chromatography (40% EtOAc/hexane) to provide (*R*)-**16** as a clear oil (0.1358 g, 0.578 mmol, 78%). The enantiomeric ratio of (*R*)-**16** was determined to be 62:38 by CSP HPLC as described above.

To a solution of **1** (0.1276 g, 0.783 mmol) in THF (8 mL) cooled to −78 °C under N_2 was added *sec*-BuLi (1.2 mL, 1.4 M, 1.57 mmol). The reaction was stirred for 1 h, (−)-sparteine (0.22 M in THF, 7.1 mL, 1.57 mmol) was added slowly, and the reaction was stirred for an additional 30 min. The reaction was immersed in a −100 °C bath for 30 min, TMSCl (0.25 mL, 2.0 mmol) was added, and the reaction was stirred at −100 °C for 10 min, followed by addition of CH_3OH/H_2O to quench the reaction. After warming to room temperature, the mixture was poured into 5% HCl (10 mL) and extracted with 3 × 10 mL of Et_2O. The ether layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to provide a pale yellow oil which was purified by column chromatography (40% EtOAc/hexane) to provide (*R*)-**16** as a clear oil (0.1458 g, 0.620 mmol, 79%). The enantiomeric ratio of (*R*)-**16** was determined to be 85:15 by CSP HPLC as described above.

Test for Configurational Stability with Substoichiometric Electrophile: Representative Procedure at −105 °C. The reaction temperatures reported were determined by an internal Teflon-coated thermocouple. To a solution of **1** (0.1239 g, 0.760 mmol) and **4** (0.356 g, 1.52 mmol) in THF (8 mL) cooled to −78 °C under N_2 was added *sec*-BuLi (1.0 mL, 1.3 M, 1.33 mmol). The reaction was stirred for 1 h, then cooled to −105 °C, and stirred for 15 min. TMSCl (0.19 mL, 1.50 mmol) was added, and the reaction was stirred for 30 s, followed by addition of CH_3OH to quench the reaction. The reaction mixture was allowed to warm to room temperature, poured into 5% HCl (10 mL), and extracted with Et_2O (3 × 10 mL). After drying ($MgSO_4$), filtering, and removal of solvent the pale yellow oil obtained was purified by MPLC (50% EtOAc/hexane) to provide (*R*)-**16** as a clear oil (0.0708 g, 0.301 mmol, 54%). The enantiomeric ratio of (*R*)-**16** was determined to be 92:8 by CSP HPLC as described above.

This reaction was carried out alongside the experiment reported in the previous paragraph. To a solution of **1** (0.6876 g, 4.22 mmol) and **4** (1.98 g, 8.44 mmol) in THF (42 mL) cooled to −78 °C under N_2 was added *sec*-BuLi (5.7 mL, 1.3 M, 7.39 mmol). The reaction was stirred for 1 h, then cooled to −105 °C, and stirred for 15 min. TMSCl (0.094 mL, 0.739 mmol) was added, and the reaction was stirred for 30 s, followed by addition of CH_3OH to quench the reaction. The reaction mixture was allowed to warm to room temperature, poured into 5% HCl (40 mL), and extracted with Et_2O (3 × 40 mL). After drying ($MgSO_4$), filtering, and removal of solvent the pale yellow oil obtained was purified by MPLC (50% EtOAc/hexane) to provide (*R*)-**16** as a clear oil (0.0708 g, 0.301 mmol, 54%). The enantiomeric ratio of (*R*)-**16** was determined to be 63:37 by CSP HPLC as described above.

Acknowledgment. We thank the National Science Foundation and National Institutes of Health for support of this work. We are grateful to Dr. Amit Basu for extremely helpful discussions and to Professor G. B. Schuster for a gift of ^{6}Li metal.

Supporting Information Available: Preparation of ^{13}C-, ^{15}N-, and ^{6}Li-labeled compounds and ^{13}C NMR spectra of **15** and **15**/**4** (7 pages). See any current masthead page for ordering and Internet access instructions.

JA962430O