Temperature- and Electrophile-Dependent Stereocontrol: A Structural and Mechanistic Investigation of (−)-Sparteine-Mediated Asymmetric Lithiation−Substitution Sequences of *N*-Boc-*N*-(*p*-Methoxyphenyl)cinnamylamine

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Abstract: The reaction pathways for the highly enantioselective, (−)-sparteine-mediated, lithiation−substitution reactions of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine ((*E*)-**2**) have been investigated. The solution structure of the major allyllithium intermediate has been determined by ^{6}Li and ^{13}C NMR to be a monomeric η^3 species, *endo-syn-anti*-**8·1**. The complexes *exo-syn-anti*-**8·1**, *endo-syn-syn*-**8·1**, and *exo-syn-syn*-**8·1** are also shown to be present in solution. The enantiodetermining step in the lithiation−silylation or lithiation−alkylation of (*E*)-**2** can involve asymmetric deprotonation, dynamic kinetic resolution, or dynamic thermodynamic resolution. The results reported herein establish that each of these pathways can be operative. This information allows determination of the stereochemical course for each step of these reactions and permits preparation of either epimer at the new stereogenic carbon.

Introduction

Chiral ligand-mediated lithiation−substitution sequences which involve dipole-stabilized carbanions provide a new approach to asymmetric synthesis.[1,2] The asymmetry may be introduced either in a deprotonation step or in a post-deprotonation event. Three limiting cases, asymmetric deprotonation, dynamic thermodynamic resolution, and dynamic kinetic resolution, have been observed.[1−4] Determination of the relationships between structure, the reaction pathway, and the stereochemical consequences can afford a basis for rational improvement of the methodology.[5]

We now are able to provide an analysis of the structures and limiting mechanisms for the synthetically useful (−)-sparteine-mediated lithiation−substitution sequences of *N*-Boc-*N*-(*p*-methoxyphenyl)cinnamylamine.[6] This work shows, in detail, how changes in the reaction conditions can alter the reaction pathway and demonstrates how understanding the reaction mechanism can allow selection for either enantiomer of a desired product.

The limiting pathways for asymmetric replacement of a prochiral proton in the lithiation−substitution sequence of an *N*-Boc allylamine are shown in Scheme 1. The mechanism of asymmetric deprotonation, in which one of the prochiral protons of the *N*-Boc allylamine is selectively removed, proceeds via a configurationally stable, enantioenriched organolithium complex. Subsequent stereoselective electrophilic substitution, shown arbitrarily to proceed with inversion of configuration, provides an enantioenriched enecarbamate product. The alternative post-deprotonation pathways of enantioselection by asymmetric substitution involve a configurationally labile allyllithium intermediate. For a dynamic kinetic resolution, the rate of equilibration between the diastereomeric allyllithium complexes is greater than the rate of their reaction with electrophile.[3] For a dynamic thermodynamic resolution, the complexes are labile on the time scale of metalation but are configurationally stable on the time scale of reaction with an electrophile.[4,7]

We have communicated the fact that (−)-sparteine (**1**)-mediated lithiations of allylamine derivatives (*E*)-**2**, (*E*)-**3**, and (*E*)-**4** provide highly enantioenriched, configurationally stable allyllithiums at −78 °C.[6] Addition of alkylating reagents, acylating reagents, and α,β-unsaturated lactones to the organolithium derived from deprotonation of (*E*)-**2** at −78 °C provides the *Z* enecarbamates (*Z*)-**5** with high enantioselectivities as the major products, accompanied by 3−10% of the *E* isomers (*E*)-**5**. Addition of alkylating reagents to the organolithiums derived from deprotonation of (*E*)-**3** or (*E*)-**4** at −78 °C affords mixtures of the *Z* and *E* enecarbamates **6** and **7**, also with high enantioselectivities. Hydrolysis of the enecarbamate products

(1) (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282 and references therein.

(2) For recent cases, see: (a) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160−1165. (b) Behrens, K.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Eur. J. Org. Chem.* **1998**, 2397.

(3) (a) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209. (b) Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2.

(4) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.

(5) See, for example: (a) Fraenkel, G.; Cabral, J.; Lanter, C.; Wang, J. *J. Org. Chem.* **1999**, *64*, 1302. (b) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14.

(6) (a) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (b) Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537. (c) Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522. (d) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996.

(7) In a dynamic thermodynamic resolution, the dynamic step of equilibration to a thermodynamic ratio of isomers is slower than, and can be separated from, a subsequent product-forming step. This reaction profile provides a useful rationalization for the effects of reaction conditions, especially temperature and time, on many processes which may proceed via isomeric complexes.[1,4]

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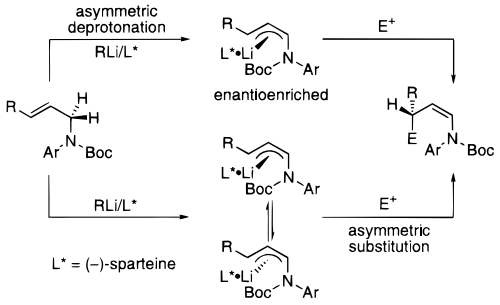
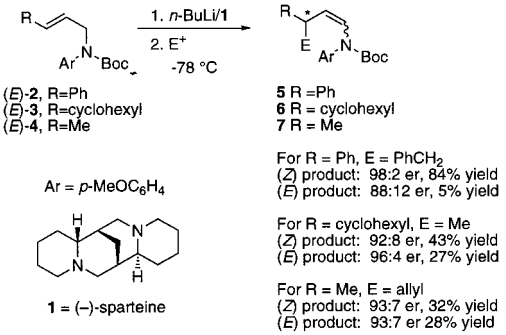
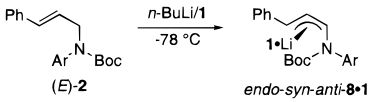
Scheme 1



to aldehydes or reduction to amines demonstrates that the intermediates are formally chiral homoenolate synthetic equivalents or chiral γ-lithioamine synthetic equivalents for displacements, 1,2-additions, and 1,4-additions.[6]

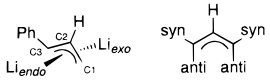


We have also recently reported the solid-state structure of the crystalline organolithium/(−)-sparteine complex derived from deprotonation of (*E*)-**2** at −78 °C in ether with *n*-BuLi/(−)-sparteine.[6c] This investigation revealed the crystalline species to be *endo-syn-anti*-**8·1**, with the lithium cation η^3-coordinated to the allyl unit.[8] Dissolution of *endo-syn-anti*-**8·1** into diethyl ether and subsequent reaction with benzyl bromide furnished nearly enantiopure (*Z*,*S*)-**5**.



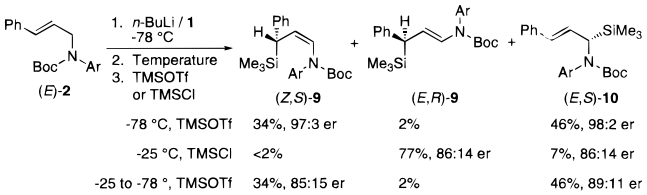
We have found that the absolute configurations of the products resulting from lithiation−substitution of cinnamylamine (*E*)-**2** are a function of the reaction temperature and the electrophile. The solution structures of the *N*-Boc allyllithium·(−)-sparteine complexes from (*E*)-**2** have been determined by NMR spectroscopy and related to the enantioselectivities of the product-forming reactions. We have experimentally established that, depending on the reaction conditions, transformations from (*E*)-**2** can proceed by each of the limiting mechanisms: asymmetric deprotonation, dynamic thermodynamic resolution, and dynamic kinetic resolution.[1,3,4,7] A practical consequence of these divergent pathways is the ability to rationally control the reaction variables to access either configuration at the newly formed stereogenic center.

(8) The allylic organolithium complexes described herein are designated according to (1) the face of the allyl unit which bears the lithium, *exo* or *endo*, and (2) the relationship between the H atom at C-2 of the allyl unit and the non-H substituents at C-3 and C-1, *anti* or *syn*.

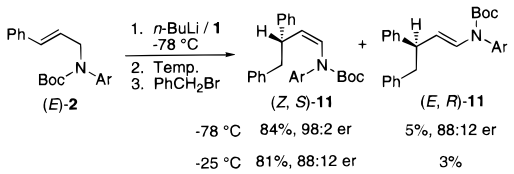


Results and Discussion

Temperature-Dependent Lithiation−Substitution of (*E*)-2. Lithiation of (*E*)-**2** with *n*-BuLi/**1** at −78 °C followed by addition of trimethylsilyl triflate at −78 °C afforded a mixture of *Z* enecarbamate (*Z*,*S*)-**9**, *E* enecarbamate (*E*,*R*)-**9**, and α-substituted *E* allylamine (*E*,*S*)-**10** in 34%, 2%, and 46% yields, respectively.[9] The products (*Z*,*S*)-**9** and (*E*,*S*)-**10** are obtained with enantiomeric ratios (er's) of 97:3 and 98:2, respectively. In a separate reaction, the intermediate carbanion was formed at −78 °C and then warmed to −25 °C. Treatment with trimethylsilyl chloride provided (*E*,*R*)-**9** with an 86:14 er in 77% yield, and (*E*,*S*)-**10** in 7% yield with an 86:14 er.[10] The enecarbamate (*Z*,*S*)-**9** was not observed. Thus, for formation of **9**, reaction at −78 °C with TMSOTf provides the (*S*)-epimer, while reaction at −25 °C with TMSCl provides the (*R*)-epimer. When the anion was formed at −78 °C, warmed to −25 °C for 1 h, and then recooled to −78 °C, addition of trimethylsilyl triflate at −78 °C provided a mixture of (*Z*,*S*)-**9** and (*E*,*S*)-**10** in 34% and 46% yields with 85:15 and 89:11 er's, respectively. The product (*E*,*R*)-**9** was obtained in 2% yield.



Lithiation of (*E*)-**2** with *n*-BuLi/**1** followed by treatment with benzyl bromide at −78 °C provided (*Z*,*S*)-**11** in 84% yield with a 98:2 er and (*E*,*R*)-**11** in 5% yield with an 88:12 er.[9] Reaction between the anion and benzyl bromide at −25 °C provided (*Z*,*S*)-**11** with an 88:12 er in 81% yield and 3% of (*E*)-**11**.



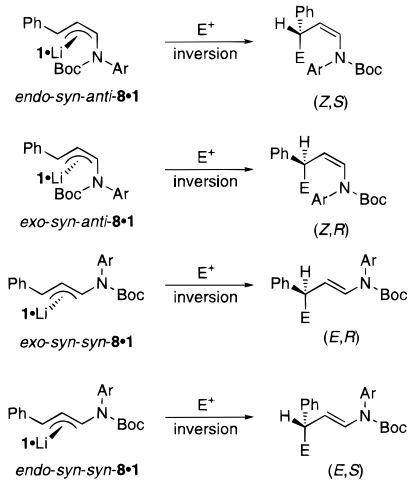
In a competition experiment at −25 °C, 1.0 equiv of lithiated (*E*)-**2** was treated with a precooled mixture of 1.1 equiv of both benzyl bromide and TMSCl. Analysis of the reaction product revealed only the benzylated product (*Z*,*S*)-**11**, with less than 1% of the silylated products (*Z*,*S*)-**9**, (*E*,*R*)-**9**, or (*E*,*S*)-**10**.

NMR Spectroscopic Studies of Lithiated (*E*)-2. Our previous structural analysis identified *endo-syn-anti*-**8·1** as the major intermediate leading to the highly enantioenriched products. However, the existence of three other allyllithium species could explain the changes in product distribution which are observed as a function of reaction temperature. The extant rationalization for the course of invertive silylation and alkylation reactions with *endo-syn-anti*-**8·1**, *exo-syn-anti*-**8·1**, *exo-syn-syn*-**8·1**, and *endo-syn-syn*-**8·1** is illustrated.

A ^{6}Li and ^{13}C NMR spectroscopic investigation has been carried out with (*E*)-**2**, ^{13}C-labeled at both allylic termini, and

(9) Absolute configurations for (*Z*,*S*)-**9** and (*Z*,*S*)-**11** were obtained through hydrolysis and conversion to the corresponding α-methylbenzylamine propionamides which are crystallographically known; see ref 3b.

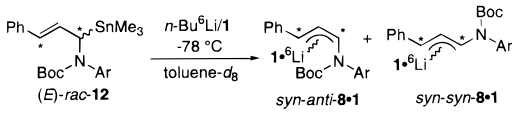
(10) The organolithium generated from (*E*)-**2** does not react with TMSCl at −78 °C.



n-Bu^{6}Li to address the structural issue. Treatment of isotopically labeled (*E*)-**2** with 0.9 equiv of n-Bu^{6}Li/**1** in toluene-d_8 at −78 °C provided a mixture of configurational and conformational organolithium isomers. As depicted in Figure 1a, the ^{6}Li NMR spectrum contains two singlets at −0.87 and −0.25 ppm in a 95:5 ratio.[11] These resonances are assigned to the diastereomeric complexes *endo-syn-anti*-**8·1** and *exo-syn-anti*-**8·1**.[6c,12a]

The ^{13}C NMR spectrum shows, in addition to reactant (*E*)-**2** at 80.0 ppm, two singlets at 90.9 and 84.8 ppm in a 95:5 ratio and two singlets at 74.0 and 80.7 ppm in a 93:7 ratio, as shown in Figure 1b. The major peaks at 90.9 and 74.0 ppm are assigned to the allylic terminal carbons of *endo-syn-anti*-**8·1**, and the minor peaks at 84.8 and 80.7 ppm are assigned to the allylic termini carbons of *exo-syn-anti*-**8·1**.[12b] Thus, taken together, the ^{6}Li NMR and ^{13}C NMR spectra show *endo-syn-anti*-**8·1** and *exo-syn-anti*-**8·1** to be present in a ratio of approximately 96:4. After acquisition of the NMR data, the sample was allowed to react with benzyl bromide at −78 °C to provide (*Z,S*)-**11** with a 91:9 er.[13]

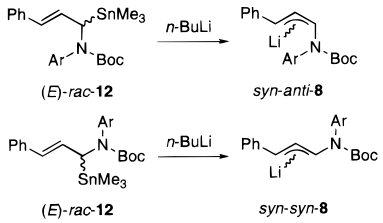
Further evidence for the assignments was provided by tin−lithium exchange between 1.0 equiv of *n*-Bu^{6}Li/**1** and the racemic trimethylstannane (*E*)-*rac*-**12**, which was ^{13}C doubly labeled at the allylic termini. The ^{6}Li NMR and ^{13}C NMR spectra of the diastereomeric complexes from this exchange are shown in Figure 1c and d.



The ^{6}Li NMR spectrum shows three major singlets at −0.84, −0.24, and 0.27 ppm, which are assigned to *endo-syn-anti*-**8·1**, *exo-syn-anti*-**8·1**, and *syn-syn*-**8·1**, respectively. Integration of the ^{6}Li NMR spectrum reveals an *endo-syn-anti*-**8·1**:*exo-syn-anti*-**8·1** ratio of 58:42 and a *syn-anti*-**8·1**:*syn-syn*-**8·1** ratio of 80:20. The ^{13}C NMR spectrum contains two singlets at 90.8 and 84.9 ppm in a 54:46 ratio and two singlets at 74.1 and 80.7 ppm in a 59:41 ratio. As before, these resonances are assigned to the allylic terminal carbons of *endo-syn-anti*-**8·1** and *exo-syn-anti*-**8·1**. An additional peak at 82.7 ppm is assigned to one of the terminal carbons of *syn-syn*-**8·1**, while the second labeled carbon resonates at 80.7 ppm.[14] In accord with the (*E*):(*Z*) product ratios observed upon treatment with electrophiles, the ^{6}Li and ^{13}C NMR spectra indicate a *syn-anti*-**8·1**: *syn-syn*-**8·1** ratio of approximately 79:21.[15] This work shows that the ratio of *endo-syn-anti*-**8·1** to *exo-syn-anti*-**8·1** depends on whether the lithiated intermediate **8·1** is generated by direct deprotonation or lithiodestannylation. Consistent with earlier work, *endo-syn-anti*-**8·1** must be configurationally stable at −78 °C and arise from (*E*)-**2** through asymmetric deprotonation.[6]

Although no $^1J(^6\text{Li},^{13}\text{C})$ coupling was observed,[16] a comparison of the chemical shifts of the allylic terminal carbons of *endo-syn-anti*-**8·1** and *exo-syn-anti*-**8·1** to those of known η^1 and η^3 allyllithium complexes suggests that the lithium is bound in an η^3 fashion.[17] The carbon shifts of *syn-syn*-**8·1** are also consistent with an η^3 structure.[17]

Reaction Pathways for Lithiation−Substitution of (*E*)-2 at −78 °C. To distinguish between asymmetric deprotonation and asymmetric substitution pathways, the racemic lithiated intermediates **8** were formed from the cinnamate (*E*)-**2**, the racemic γ-stannane (*Z*)-*rac*-**13**, and the racemic α-stannane (*E*)-*rac*-**12**. Generation of racemic **8** by reaction of (*E*)-**2** with *n*-BuLi in MTBE followed by addition of (−)-sparteine and, subsequently, benzyl bromide afforded (*Z*)-**11** in 70% yield with a 57:43 er. Generation of racemic **8** by tin−lithium exchange of (Z)-*rac*-**13** with *n*-BuLi followed by addition of (−)-sparteine and benzyl bromide afforded (*Z*)-**11** in 66% yield with a 57:43 er. Tin−lithium exchange of (*E*)-*rac*-**12** with *n*-BuLi followed by addition of (−)-sparteine and benzyl bromide provided (*Z*)-



(11) These and all subsequent integral ratios in the ^{6}Li and ^{13}C NMR spectra were obtained after imposing sufficient delays to account for differences in T_1 (see Supporting Information for details).

(12) (a) An additional weak absorption, present at 0.26 ppm, may be ascribed to one or both of the *syn-syn* isomers. (b) An additional weak absorption appears at 82.7 ppm. Based on evidence from our subsequent study on the lithiodestannylation of (*E*)-*rac*-**12** (Figure 1d), this peak is ascribed to one of the allylic terminal carbons of a *syn-syn*-**8·1** isomer. The other allylic *syn-syn* terminal peak is presumed to be at 80.7, accidentally equivalent with a peak from *exo-syn-anti*-**8·1**.

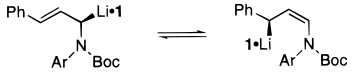
(13) The discrepancy between this enantiomeric ratio and that predicted by the ratio of complexes from the ^{6}Li and ^{13}C NMR data is attributed to partial equilibration of the diastereomeric complexes caused by warming during removal from the NMR spectrometer. The enantiomeric ratio of the minor product (*E,R*)-**11** was not determined.

(14) Apparent fine structure in the peak at 82.7 ppm may represent partial separation of *endo-syn-syn*-**8·1** and *exo-syn-syn*-**8·1**.

(15) Experimentally, at −78 °C, the *Z*/*E* product ratios are reduced when starting with (*E*)-**12** versus (*E*)-**2**. This suggests that (*E*)-*rac*-**12** undergoes transmetalation from two conformations competitively to give both racemic *syn-anti*-**8** and *syn-syn*-**8**.

(16) To increase the likelihood of observing coupling, a subsequent experiment using unlabeled *n*-BuLi/**1** was also carried out ($^1J(^7\text{Li},^{13}\text{C})/^1J(^6\text{Li},^{13}\text{C}) = 2.64$). However, neither ^{6}Li−^{13}C nor ^{7}Li−^{13}C coupling was observed.

(17) (a) The η^1 species (3-neopentylallyl)lithium has ^{13}C shifts of 20 and 101 ppm for the allylic terminal carbons: Fraenkel, G.; Halasa, A. F.; Mochel, V.; Stumpe, R.; Tate, D. *J. Org. Chem.* **1985**, *50*, 4563. (b) For the fully delocalized η^3 species 1,3-bis(trimethylsilyl)allyllithium, allylic carbons resonate at 67 ppm: Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 1382. (c) An additional possibility, which cannot be fully discounted, is that two η^1 species which equilibrate rapidly and stereoselectively are present.



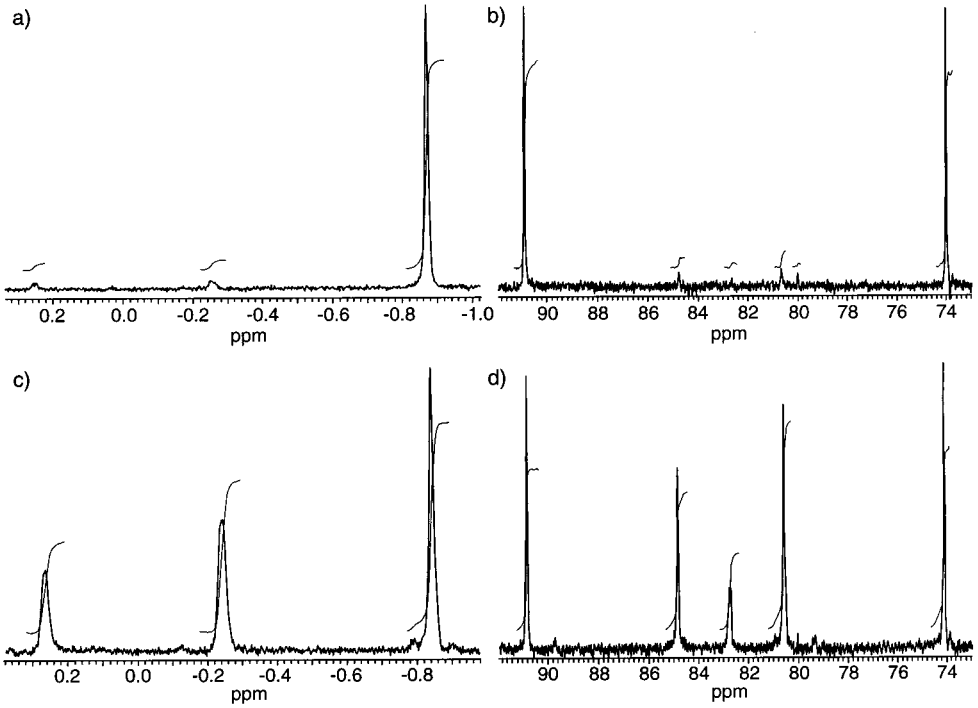
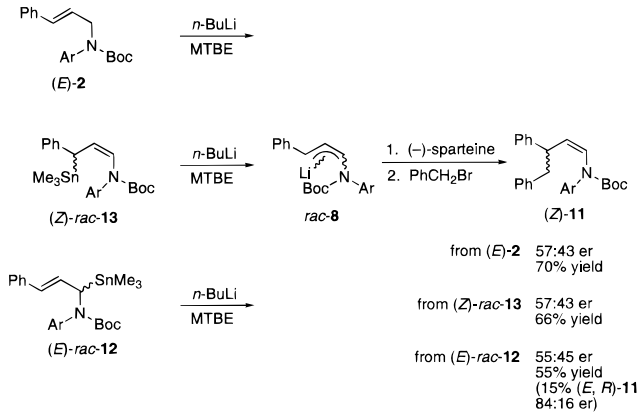
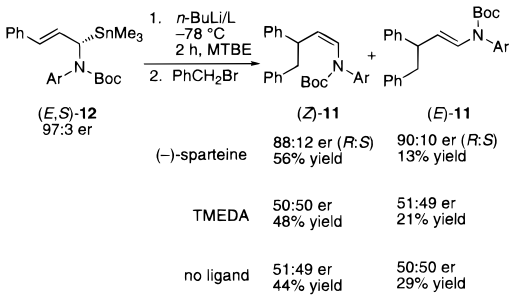


Figure 1. (a) 73.6-MHz ^{6}Li and (b) 125.7-MHz ^{13}C NMR spectra of ^{13}C/^{6}Li-labeled *endo-syn-anti*-**8·1** and *exo-syn-anti*-**8·1** (0.080 M) in toluene-d_8 at −78 °C (generated through deprotonation with *n*-Bu^{6}Li/(−)-sparteine). (c) 73.6-MHz ^{6}Li and (d) 125.7-MHz ^{13}C NMR spectra of ^{13}C/^{6}Li-labeled *endo-syn-anti*-**8·1**, *exo-syn-anti*-**8·1**, and *syn-syn*-**8·1** (0.10 M) in toluene-d_8 at −78 °C (generated through transmetalation of (*E*)-*rac*-**12**).

11 in 55% yield with a 55:45 er. In contrast to the reactions from (*E*)-**2** and (*Z*)-*rac*-**13**, the reaction from (*E*)-*rac*-**12** provides 15% of the *E* enecarbamate (*E*,*R*)-**11** with an enantiomeric ratio of 84:16.[15] Since the racemic organolithium **8** does not provide highly enantioenriched *Z* enecarbamate product after complexation with (−)-sparteine at −78 °C, these results suggest that the enantiodetermining step leading to (*Z*,*S*)-**11** from (*E*)-**2** is an asymmetric deprotonation. On the other hand, the enantiodetermining step for the formation of the minor *E* enecarbamate (*E*,*R*)-**11** must be an asymmetric substitution since the initially racemic organolithium *syn-syn*-**8** does provide enantioenriched product if (−)-sparteine is added prior to electrophile.



Configurational Stability of *syn-anti*-8·1 and Lability of *syn-syn*-8·1 at −78 °C. Because asymmetric deprotonation is the enantiodetermining step in the (−)-sparteine-mediated lithiation−substitution of (*E*)-**2** to give (*Z*,*S*)-**11**, the lithiated intermediate *endo-syn-anti*-**8·1** must be configurationally stable at -78 °C (vide supra). This implies that, if *exo-syn-anti*-**8·1** could be generated as the major species in solution, it would be configurationally stable and its invertive substitution with benzyl bromide would provide (*Z*,*R*)-**11**. Tin−lithium exchange of the enantioenriched α-stannane (*E*,*S*)-**12** with *n*-BuLi/**1** and addition of benzyl bromide afforded a mixture of (*Z*,*R*)-**11** and (*E*,*R*)-**11** isomers in 56% and 13% yields with er's of 88:12 and 90:10, respectively. Thus, a convenient route to the (*S*)-enantiomer of **11** is available through deprotonation−benzylation of (*E*)-**2**, while the (*R*)-enantiomer of **11** may be accessed by transmetalation−benzylation of (*E*,*S*)-**12**. These results are consistent with a pathway of retentive tin−lithium exchange to give *exo-syn-anti*-**8·1** from (*E*,*S*)-**12**. The observation of (*E*,*R*)-**11** from both the direct sequence and the transmetalation sequence is consistent with configurational lability of *syn-syn*-**8·1** and a pathway of asymmetric substitution.



The configurational stability of **8** was also investigated with TMEDA and without a ligand present. In both cases, **8** was found to be configurationally labile, as shown by the formation of racemic (*Z*)-**11** and (*E*)-**11** from highly enantioenriched (*E*,*S*)-**12**.[18]

In summary, the reaction pathway at −78 °C for asymmetric induction leading to the enecarbamates (*Z*,*R*)-**11** and (*Z*,*S*)-**11** involves an asymmetric deprotonation and a stereoselective substitution. The reaction profile is shown in Figure 2 for reaction with benzyl bromide. The chiral base, *n*-BuLi/(−)-

(18) For details on the effect of ligand on configurational stability, see the Supporting Information.

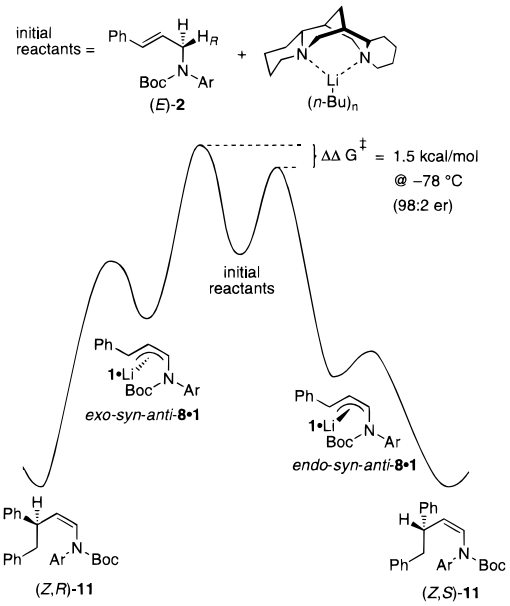
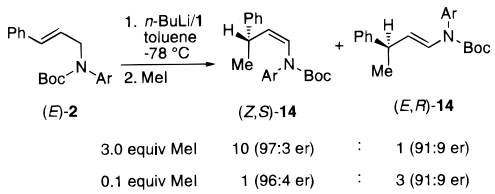


Figure 2. Reaction profile for the lithiation−substitution of (*E*)-**2** at −78 °C.

sparteine, selectively removes the *pro-R* proton from (*E*)-**2**, resulting in preferential formation of the configurationally stable, enantioenriched, η^3 allyllithium *endo-syn-anti*-**8·1**. The enantiomeric ratio is determined from the difference in transition-state energies for removal of the two prochiral protons. For an enantiomeric ratio of 98:2, $\Delta\Delta G^{\ddagger}$ is calculated to be 1.5 kcal/mol at −78 °C. Highly stereoselective electrophilic substitution of the allyllithium intermediate, which can occur with either retention or inversion of configuration, depending on the electrophile, leads to highly enantioenriched enecarbamates.[6]

Relative Reactivity of *syn-anti*-8·1 and *syn-syn*-8·1. (−)-Sparteine-mediated lithiation−substitution of (*E*)-**2** with benzyl bromide at −78 °C and (−)-sparteine-mediated transmetalation−substitution of (*E*,*S*)-**12** with benzyl bromide at −78 °C give different *E*/*Z* ratios of product **11**. Comparison of the products formed from these two sequences permits analysis of the configurational and conformational stability of organolithium intermediates **8·1**, as shown in Figure 3.

To test the validity of this analysis and determine the relative reactivities of *syn-anti*-**8·1** and *syn-syn*-**8·1**, we employed a derivative of the Hoffmann test for conformational stability.[3,4,19] Deprotonation of (*E*)-**2** with *n*-BuLi/**1** in toluene at −78 °C was carried out in two separate parallel reactions, followed by addition of 3 equiv of methyl iodide to one reaction and 0.1 equiv to the other. The enantiomeric ratios of the products (*Z*,*S*)-**14** and (*E*,*R*)-**14** from reaction with excess methyl iodide, 97:3 and 91:9, were experimentally identical to those from the reaction using 0.1 equiv of methyl iodide, 96:4 and 91:9. However, the reaction with excess methyl iodide afforded a 10:1 *Z*/*E* product ratio, while the reaction with 0.1 equiv of methyl iodide provided a 1:3 *Z*/*E* product ratio.



The *Z*/*E* product ratio for the reaction with 3.0 equiv of methyl iodide is determined from the relative populations of *syn-anti*-**8·1** and *syn-syn*-**8·1**, a ratio which is determined kinetically in the deprotonation step at −78 °C. The observation of a different *Z*/*E* selectivity with 0.1 equiv of methyl iodide is consistent with a kinetic resolution where the activation energy ($\Delta G^{\ddagger}_E$) for reaction of *syn-syn*-**8·1** with methyl iodide to give (*E*,*R*)-**14** is smaller than the activation energy ($\Delta G^{\ddagger}_Z$) for reaction of *syn-anti*-**8·1** with methyl iodide to give (*Z*,*S*)-**14**, as shown in Figure 4.

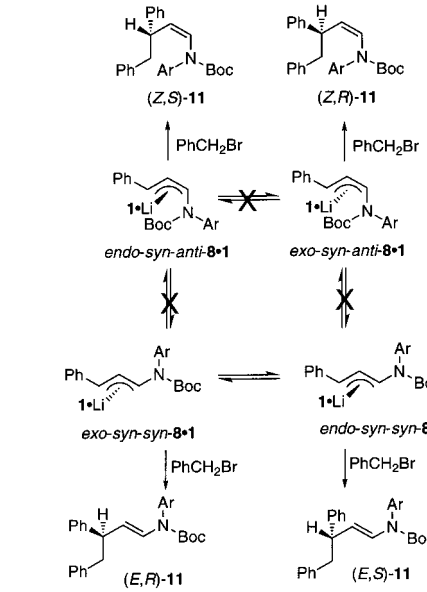


Figure 3. Configurational and conformational stability of **8·1** at −78 °C and reaction of **8·1** with benzyl bromide.

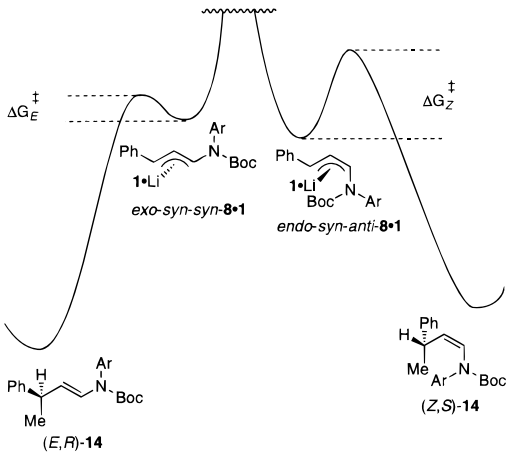


Figure 4. Reaction pathway for kinetic resolution of *syn-syn*-**8·1** and *syn-anti*-**8·1** on reaction with deficient methyl iodide.

Summary of Reaction Pathways for the Lithiation−Substitution of (*E*)-2 at −78 °C. Thus, at −78 °C, (*E*)-2 undergoes an asymmetric deprotonation to provide a kinetic ratio of the diastereomeric complexes *endo-syn-anti*-**8·1** and *exo-syn-anti*-**8·1**. The minor intermediates *exo-syn-syn*-**8·1** and *endo-syn-syn*-**8·1** also are formed from (*E*)-**2** under these conditions. The complexes react with electrophiles in a stereoselective fashion to give highly enantioenriched enecarbamates. A complete reaction profile is shown in Figure 5. The ratio of *syn-anti*-**8·1** and *syn-syn*-**8·1** intermediates must be established kinetically since equilibration between these species does not

(19) (a) Hoffmann, R. W.; Polachowski, A. *Chem. Eur. J.* **1998**, *4*, 1724. (b) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975. (c) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049. (d) Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1409.

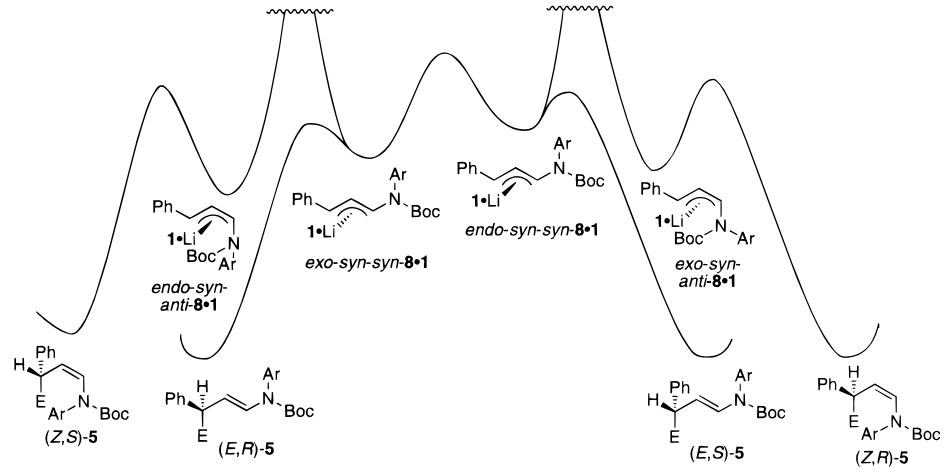
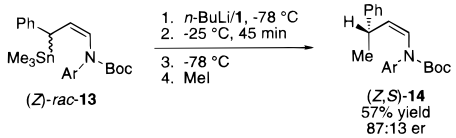


Figure 5. Complete reaction pathway for asymmetric lithiation−substitution of (*E*)-**2** at −78 °C.

occur at −78 °C. The population ratio of *syn-anti*-**8·1** to *syn-syn*-**8·1** can be estimated to be 10:1 from the *Z*/*E* product ratio obtained upon reaction of the complexes with excess methyl iodide. This ratio corresponds to a transition state energy difference of 1.1 kcal/mol at −78 °C. Equilibration provides a thermodynamic ratio of *endo-syn-syn*-**8·1** and *exo-syn-syn*-**8·1** at −78 °C, and thus the enantiomeric ratio of (*E*,*R*)-**14** from reaction with methyl iodide is established by either a dynamic kinetic resolution or a dynamic thermodynamic resolution.[1] Finally, the activation energy for reaction of *syn-syn*-**8·1** with methyl iodide to give (*E*)-**14** is smaller than the activation energy for reaction of *syn-anti*-**8·1** with methyl iodide to give (*Z*)-**14**.

Reaction Pathways of (*E*)-2 at −25 °C. The temperature and electrophile dependence of the product ratios for the lithiation−substitution of (*E*)-**2** with TMSCl and TMSOTf (vide supra) offers an opportunity for control of the absolute configuration of enecarbamate products. To provide a basis for rational development of procedures for stereocontrol, we have investigated the sequence at different temperatures. Formation of *syn-anti*-**8·1** was achieved by treatment of the racemic stannane (*Z*)-*rac*-**13** with *n*-BuLi/(−)-sparteine at −78 °C. Warming to −25 °C, then cooling to −78 °C before methyl iodide was added, provided (*Z*,*S*)-**14** with an 87:13 er in 57% yield. The sequence carried out entirely at −78 °C with benzyl bromide gives (*Z*,*S*)-**11** with an er of 57:43 (vide supra). These results suggest that the diastereomeric intermediates *endo-syn-anti*-**8·1** and *exo-syn-anti*-**8·1** are configurationally labile at −25 °C. The complexes equilibrate to a thermodynamic ratio of 87:13, which is maintained upon cooling to −78 °C. The formation of (*Z*,*S*)-**14** is consistent with equilibration of **8·1** at −25 °C to *endo-syn-anti*-**8·1**, the same major diastereomeric complex as that obtained kinetically through deprotonation at −78 °C.



Because the warm−cool sequence gives (*Z*,*S*)-**14** as the major product, *syn-anti*-**8·1** must be thermodynamically favored over *syn-syn*-**8·1** in the equilibration at −25 °C. Thus, we propose a dynamic kinetic resolution for the *E* selectivity observed for reaction of **8·1** with TMSCl at −25 °C. This profile is presented in Figure 6. Isomerization of *endo-syn-anti*-**8·1** to *exo-syn-syn*-**8·1** is faster than reaction of *endo-syn-anti*-**8·1** with TMSCl. Therefore, the preferred pathway is electrophilic substitution

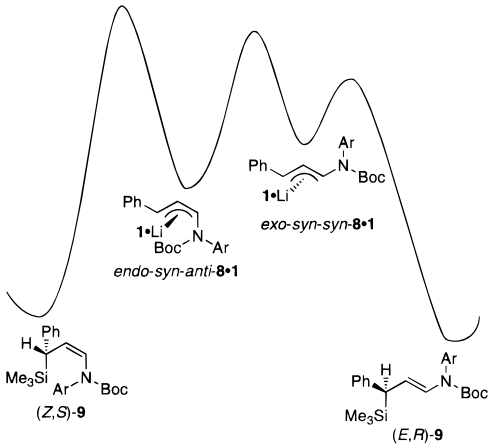


Figure 6. Reaction pathway for dynamic kinetic resolution of *exo-syn-syn*-**8·1** and *endo-syn-anti*-**8·1** at −25 °C.

of *exo-syn-syn*-**8·1** with TMSCl to provide the *E* product (*E*,*R*)-**9**. Note that the conformational isomerism is shown to be irreversible in the presence of TMSCl (vide infra).

Since the diastereomeric lithiated intermediates **8·1** equilibrate at −25 °C before electrophile is added, either a dynamic thermodynamic resolution or a dynamic kinetic resolution could be the operative mode for asymmetric induction. To distinguish between these possibilities, we carried out the reaction of (*E*)-**2** with *n*-BuLi/**1** in toluene at −78 °C in two separate parallel sequences.[1,3,4,19] Each solution was warmed to −25 °C, and then excess TMSCl was added to one reaction and 0.05 equiv was added to the other reaction. The product (*E*,*R*)-**9** was obtained with 86:14 and 73:27 er's, respectively.

These results suggest a dynamic thermodynamic resolution and are consistent with configurational stability (but conformational lability) of **8·1** on the time scale of reaction with electrophile. This suggests that, when excess TMSCl is used, the enantiomeric ratio is determined by the thermodynamic ratio (*endo-syn-anti*-**8·1** + *exo-syn-syn*-**8·1**):(*exo-syn-anti*-**8·1** + *endo-syn-syn*-**8·1**), as shown in Figure 7. When 0.05 equiv of TMSCl is used, the enantiomeric ratio presumably depends only on the concentrations of *exo-syn-syn*-**8·1** and *endo-syn-syn*-**8·1**, and on the difference in activation energies for their reaction with TMSCl.[20] Since the enantiomeric ratio decreased when a deficiency of TMSCl was used, there must be a smaller

(20) This interpretation assumes that, at thermodynamic equilibrium, the two *syn-syn* diastereoisomers of **8·1** are present in at least 5%.

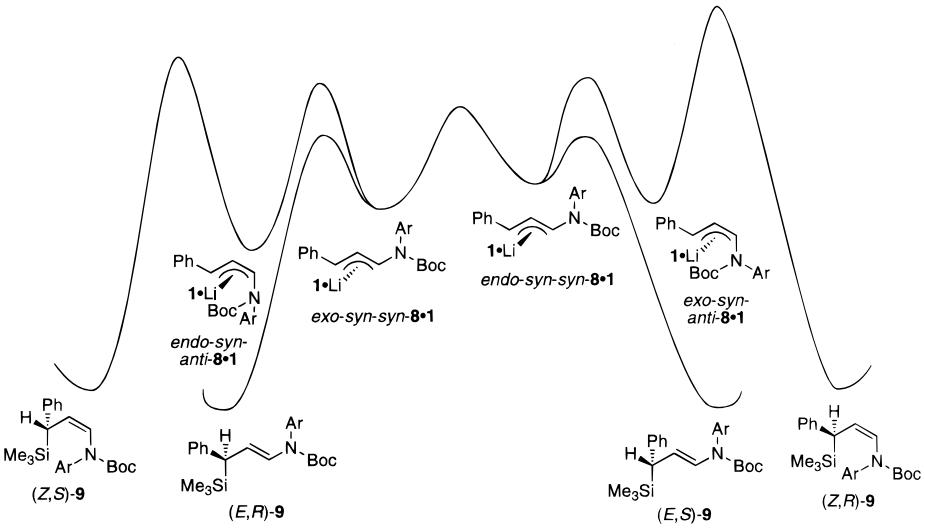


Figure 7. Reaction profile for interconversion of complexes of **8·1** and their reaction with TMSCl at −25 °C.

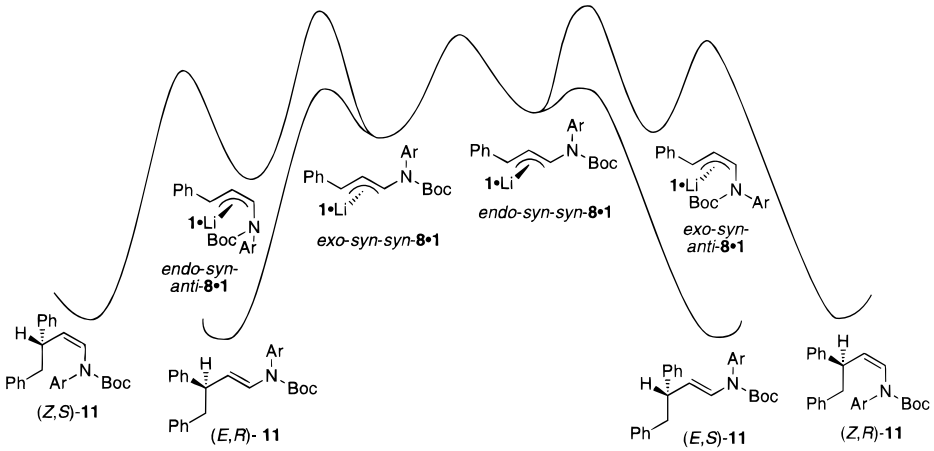
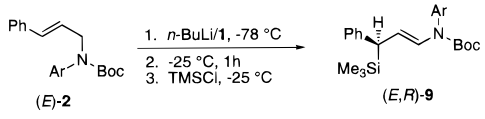


Figure 8. Reaction profile for interconversion of complexes of **8·1** and their reaction with benzyl bromide at −25 °C.

activation energy for reaction of the minor diastereomeric complex *endo-syn-syn*-**8·1**.



1.2 equiv TMSCl	86:14 77% yield
0.05 equiv TMSCl	73:27 er 3% yield

As mentioned previously, the conformational isomerisms between *endo-syn-anti*-**8·1** and *exo-syn-syn*-**8·1** and between *exo-syn-anti*-**8·1** and *endo-syn-syn*-**8·1** are shown as irreversible on the time scale of reaction with electrophile (Figure 6). Our analysis assumes, based on results at −78 °C, that *syn-syn* epimerization is faster than *syn-anti* epimerization at −25 °C. This assumption, coupled with the experimental evidence for dynamic thermodynamic resolution of *syn-syn*-**8·1** at −25 °C, permits the complete analysis shown in Figure 7.

Thus, at −25 °C, the complexes of the lithiated intermediate **8·1** undergo asymmetric substitution by both a dynamic kinetic resolution and a dynamic thermodynamic resolution. The relative energies of these complexes are shown in Figure 7. In reactions with TMSCl, *syn-anti*-**8·1** and *syn-syn*-**8·1** provide a kinetic *Z*/*E* product ratio which is established in the substitution step. The enantiomeric ratio of the *E* product, however, is controlled by the thermodynamic ratio, (*endo-syn-anti*-**8·1** + *exo-syn-syn*-**8·1**):(*exo-syn-anti*-**8·1** + *endo-syn-syn*-**8·1**), established prior to reaction with electrophile.

Reaction Pathways of 8·1 at −25 °C with Benzyl Bromide. The product differences observed for the reaction of *endo-syn-anti*-**8·1** with benzyl bromide are consistent with an activation energy for this substitution which is smaller than the activation energy for *Z*/*E* isomerization. Therefore, this asymmetric substitution involves a dynamic thermodynamic resolution, as shown in Figure 8. The lower activation energy for reaction of **8·1** with benzyl bromide versus TMSCl is consistent with the competition experiment between the two electrophiles at −25 °C, in which only the benzylated product was observed.

Stereochemical Analysis of the Lithiation−Substitution of (*E*)-2 at −78 °C. Stereochemical Course of Deprotonation. The reaction between (*E*)-**2** and *n*-BuLi/**1** at −78 °C to provide *endo-syn-anti*-**8·1** proceeds by selective removal of the *pro-R* proton, assuming retentive lithiation. We have also reported removal of the *pro-R* proton from an *N*-Boc benzylamine derivative.[21] In contrast, (−)-sparteine-mediated removal of the *pro-S* enantiotopic proton has been reported for most substrates whose methylene groups are not allylic or benzylic.[22] In addition, Hoppe has reported removal of the *pro-S* proton from (*E*)-cinnamyl *N*,*N*-diisopropylcarbamate using the same chiral

(21) (a) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (b) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561.

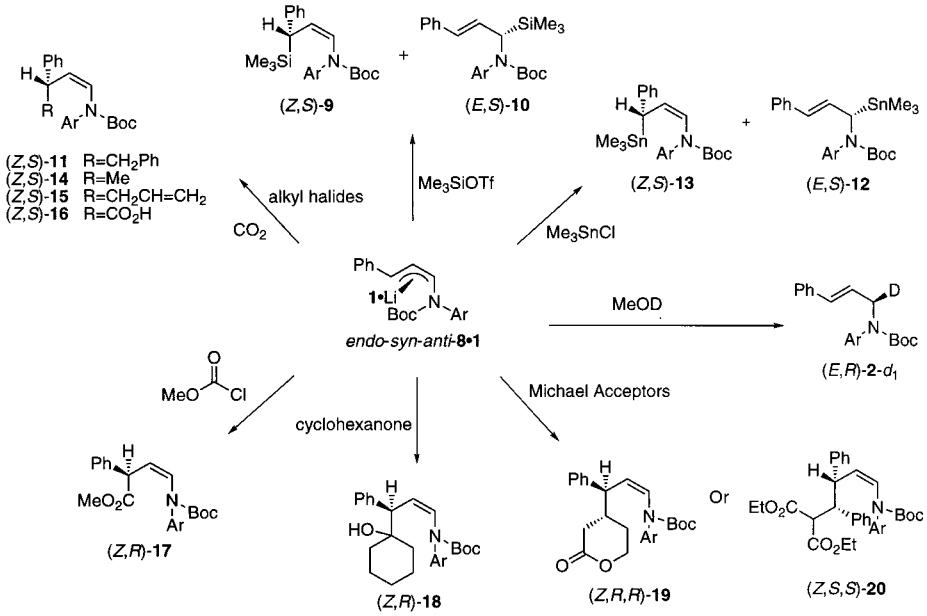
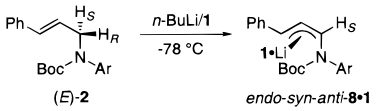


Figure 9. Stereochemical course of electrophilic substitutions of *endo-syn-anti*-**8·1**.

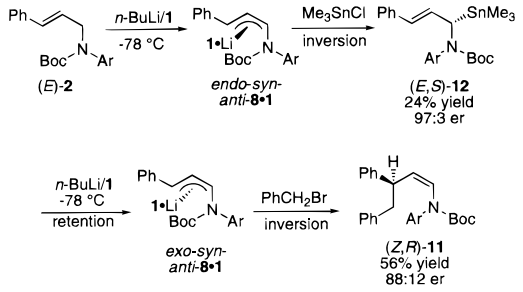
base.[2b] Interestingly, Hoppe also reports that, for reaction between *n*-BuLi/(−)-sparteine and a similar substrate, *rac*-(*E*)-crotyl 1-methyl-1-*N*,*N*-diisopropylcarbamate, a kinetic resolution is observed wherein only the *pro-R* proton is removed.[23]



Stereochemical Outcome of Electrophilic Substitutions of *endo-syn-anti*-8·1. The stereochemical course of electrophilic substitutions of *endo-syn-anti*-**8·1** with different electrophiles can be unambiguously assigned from its absolute configuration and the absolute configurations of the enecarbamate products. A summary of results obtained to the present time is shown in Figure 9. Methyl chloroformate, cyclohexanone, MeOD, and the Michael acceptor, 5,6-dihydro-2*H*-pyran-2-one, react with *endo-syn-anti*-**8·1** with retention of configuration to provide (*Z*,*R*)-**17**, (*Z*,*R*)-**18**, (*E*,*R*)-**2**-d_1, and (*Z*,*R*,*R*)-**19**, respectively. In contrast, benzyl bromide, methyl iodide, allyl bromide, carbon dioxide, diethyl benzalmalonate, trimethylsilyl triflate, and trimethyltin chloride react with *endo-syn-anti*-**8·1** with inversion of configuration to provide (*Z*,*S*)-**11**, (*Z*,*S*)-**14**, (*Z*,*S*)-**15**, (*Z*,*S*)-**16**, (*Z*,*S*,*S*)-**20**, (*Z*,*S*)-**9**, (*E*,*S*)-**10**, (*Z*,*S*)-**13**, and (*E*,*S*)-**12**, respectively.

These results suggest that reactions with non-lithium coordinating electrophiles, the halides and the triflates, or the highly reactive electrophiles, carbon dioxide and diethyl benzalmalonate, proceed with inversion of configuration; conversely, reactions with less reactive lithium coordinating electrophiles, the carbonyl compounds and deuteriomethanol, proceed with retention of configuration. Hoppe has offered a similar analysis for the stereochemical outcome of these reactions between planar anions and various electrophiles.[24]

Stereochemical Course of Tin−Lithium Exchange with (*E*,*S*)-12. Although tin−lithium exchange has generally been assumed to proceed with retention of configuration, relatively few cases have been unambiguously established.[25] In addition, a recent example which shows some inversion has been reported.[26] Deprotonation of (*E*)-**2** under the standard conditions followed by reaction with trimethyltin chloride as the electrophile provided the α-stannane (*E*,*S*)-**12** in 24% yield with a 97:3 er.[27] The absolute configuration of (*E*,*S*)-**12** was determined by X-ray crystallography using anomalous dispersion. Tin−lithium exchange of enantioenriched (*E*,*S*)-**12** with *n*-BuLi/**1** and addition of benzyl bromide afforded (*Z*,*R*)-**11** in 56% yield with an 88:12 er.[28] Since the absolute configurations of the allyllithium *endo-syn-anti*-**8·1**, the stannane (*E*,*S*)-**12**, and the product (*Z*,*R*)-**11** have been determined (vide supra), the retentive stereochemical pathway is unambiguous. Substitution of *endo-syn-anti*-**8·1** with trimethyltin chloride occurs with inversion of configuration, and transmetalation of (*E*,*S*)-**12** occurs with retention of configuration to afford *exo-syn-anti*-**8·1**. Invertive electrophilic substitution of *exo-syn-anti*-**8·1** with benzyl bromide provides (*Z*,*R*)-**11**.



(22) (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (c) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (d) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69.

(23) Zschage, O.; Schwark, J.-R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 296.

(24) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.

(25) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546.

(26) Clayden, J. *Synth. Lett.* **1998**, 810 and references therein.

(27) The γ-substituted stannane is formed in 49% yield with an er of 97:3.[6c]

(28) The erosion of er from 97:3 in (*E*,*S*)-**12** to 88:12 in (*Z*,*R*)-**11** could indicate that the reaction between benzyl bromide and *exo-syn-anti*-**8·1** is less stereoselective than that between benzyl bromide and *endo-syn-anti*-**8·1**. Alternatively, it might indicate that the lithiodestannylation does not occur with complete retention of configuration at carbon.

Summary

Analysis of the lithiation−substitution pathways for reactions of (*E*)-**2** with *n*-BuLi/**1** to afford enecarbamate products with high enantioenrichments shows that each of the three enantiodetermining processes can be operative. The reaction pathway may be selected by control of the reaction conditions. The understanding afforded by this analysis should allow rational development of this and related systems for asymmetric synthesis.

Experimental Section

General Procedures. All general procedures are documented in the Supporting Information section. *Standard workup* refers to dilution of the reaction mixture with Et_2O and water, separation of the organic layers, and drying of the organic layers with $MgSO_4$. Note that all NMR spectra for (*Z*)-enecarbamates are obtained in acetone-d_6 to prevent isomerization to the corresponding (*E*)-enecarbamates. This isomerization does occur in $CDCl_3$.

Representative Lithiation of *N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-phenyl-(*E*)-2-propen-1-amine ((*E*)-2) at −78 °C with Electrophilic Substitution at −78 °C: Preparation of (*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3,4-diphenyl-(*Z*)-1-buten-1-amine ((*Z*,*S*)-11). A solution of (*E*)-**2** (171 mg, 0.50 mmol) and (−)-sparteine (**1**) (0.13 mL, 0.55 mmol) in toluene (8 mL) was cooled to −78 °C. *n*-BuLi (0.37 mL, 1.4M, 0.55 mmol) was added, and the clear yellow solution was stirred for 1 h. Benzyl bromide (0.09 mL, 0.76 mmol) was added. The mixture was stirred for 1 h, and then the reaction was quenched at −78 °C with methanol. Standard workup and chromatography of the resultant oil (10:1 petroleum ether/ethyl acetate) afforded (*Z*,*S*)-**11** as a colorless oil (191 mg, 88%). Separation of the minor *E* isomer was achieved by preparative HPLC (2.5% ethyl acetate in hexane).

(*Z*,*S*)-**11**: ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.36 (s, 9H), 2.72 (s, 1H), 2.73 (s, 1H), 3.23−3.27 (m, 1H), 3.81 (s, 3H), 5.10 (t, J = 9.8 Hz, 1H), 6.58 (d, J = 9.2 Hz, 1H), 6.84−6.91 (m, 6H), 7.01 (d, J = 8.9 Hz, 2H), 7.04−7.16 (m, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 27.3, 42.9, 43.4, 54.8, 80.1, 113.8, 122.2, 125.6, 125.7, 126.8, 127.3, 127.6, 127.8, 128.3, 129.0, 134.7, 139.6, 143.7, 152.8, 157.9. Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.09; H, 7.30; N, 3.17. The enantiomeric ratio of (*Z*,*S*)-**11** was determined to be 98:2 by CSP−HPLC ((*R*,*S*)-Whelk-O column, 15% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer (*S*) had a retention time of 11.5 min, and the minor enantiomer (*R*) had a retention time of 9.0 min. $[\alpha]_D$ = +72.4 (c = 0.243, MeOH). The absolute configuration was determined by an X-ray crystal structure of an (*S*)-α-methylbenzamide derivative.[9]

Representative Lithiation of *N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-phenyl-(*E*)-2-propen-1-amine ((*E*)-2) at −78 °C with Electrophilic Substitution at −25 °C: Preparation of *N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-phenyl-3-trimethylsilyl-(*E*)-1-propen-1-amine ((*E*,*R*)-9). A solution of the cinnamylamine derivative (*E*)-**2** (145 mg, 0.427 mmol) and (−)-sparteine (**1**) (0.11 mL, 0.47 mmol) in toluene (10 mL) was cooled to −78 °C. *n*-BuLi (0.31 mL, 1.5 M, 0.47 mmol) was added, and the clear yellow solution was stirred for 1 h. The solution was then warmed to −25 °C and stirred an additional 1 h. During this time period, the solution became orange-brown. Trimethylsilyl chloride (0.07 mL, 0.51 mmol) was added, the solution was stirred for 1 h, and then the reaction was quenched at −25 °C with methanol. Standard workup and chromatography of the resultant oil (15:1 petroleum ether/ethyl acetate) afforded (*E*,*R*)-**9** as a colorless oil (135 mg, 77%) and (*E*,*S*)-**10** as a white solid, mp 85−87 °C (13 mg, 7%).

(*E*,*R*)-**9**: ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.12 (s, 9H), 1.36 (s, 9H), 2.99 (d, J = 10.4 Hz, 1H), 3.83 (s, 3H), 4.75 (dd, J = 14.4, 10.8 Hz, 1H), 6.92−7.22 (m, 10H); ^{13}C NMR (acetone-d_6, 100 MHz) δ −2.9, 28.3, 39.8, 55.6, 80.9, 111.1, 115.1, 125.2, 127.7, 128.9, 129.8, 130.5, 133.0, 144.2, 153.1, 159.5. Anal. Calcd for $C_{24}H_{39}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.07; H, 8.16; N, 3.51. The enantiomeric ratio of (*E*,*R*)-**9** was determined directly to be 88:12 by CSP−HPLC ((*R*,*S*)-Whelk-O column, 15% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer had a retention time of 6.3 min, and the minor enantiomer had a retention time of 5.0 min. The absolute configuration of (*E*,*R*)-**9** was determined by comparison of chiral stationary phase HPLC retention times with those of (*E*,*S*)-**9**, which was obtained from isomerization of (*Z*,*S*)-**9**. The absolute configuration of (*Z*,*S*)-**9** was determined from an X-ray crystal structure of an (*S*)-α-methylbenzamide derivative.[9]

(*E*,*S*)-**10** was identical spectroscopically (NMR) and chromatographically (TLC, HPLC) to the product obtained from reaction of (*E*)-**2** at −78 °C. The enantiomeric ratio of (*E*,*S*)-**10** was determined directly to be 84:16 by CSP−HPLC ((*R*,*S*)-Whelk-O column, 0.5% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer had a retention time of 7.6 min, and the minor enantiomer had a retention time of 6.9 min. The absolute configuration of (*E*,*S*)-**10** was assigned by analogy to (*Z*,*S*)-**9**.

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Supporting Information Available: General procedures for reactions, instrumentation, enantiomeric purity analyses, and NMR spectroscopic studies, as well as additional experimental details, covering mechanistic studies of (*E*)-**2**, the effect of ligand on configurational stability, synthesis and reactions of (*E*)-**4**, and synthesis of NMR substrate (*E*)-**2**-$^{13}C_2$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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