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A Mechanistic and Structural Investigation of the (−)-Sparteine Mediated Asymmetric Benzylic Lithiation Substitution Reactions of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine

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Abstract: Mechanistic and structural studies show the high enantioenrichments in the products from lithiation−substitutions of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine (**1**) by *n*-BuLi/(−)-sparteine (**6**) arise from an enantioselective deprotonation of **1** to provide configurationally stable (*R*)-**2**/**6**. NMR spectroscopy establishes that ^{13}C, ^{6}Li labeled (*R*)-**2**/**6** and (*S*)-**2**/**6** are monomeric with lithium complexed to the benzylic position, the carbonyl of the Boc group and (−)-sparteine. Deprotonations of the tertiary protons in (*R*)- and (*S*)-*N*-Boc-*N*-(*p*-methoxyphenyl)-α-methylbenzylamine ((*R*)-**8** and (*S*)-**8**) with *n*-BuLi/TMEDA provide (*R*)-**9**/TMEDA and (*S*)-**9**/TMEDA, respectively, with high enantioenrichments. Absolute configurations assigned to (*R*)-**2** and (*R*)-**1**-d_1 allow analysis of the electrophile dependent stereochemistry of the reactions of these configurationally stable organolithium intermediates.

Introduction

Methods for asymmetric carbon−carbon bond formation are of considerable current interest. Understanding the pathways of these reactions should provide a basis for rational improvement of the methodology. Asymmetric lithiation−substitution sequences with (−)-sparteine as the chiral ligand have been shown to provide products with high enantiomeric ratios (ers).[1−8] We have reported enantioselective sequences beginning with *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine (**1**) which afford the mono- and disubstituted products **3** and **5**.[2a] In this sequence **1** is deprotonated with *n*-BuLi/(−)-sparteine (**6**) to generate an organolithium complex **2**, which reacts with alkylating and carbonyl electrophiles to provide the new carbon−carbon bonds of **3** with high enantioenrichments. The tertiary carbanion **4**, which can be generated subsequently from **3** with the achiral base *n*-BuLi/TMEDA at −78 °C, reacts with electrophiles stereoselectively to produce **5** also with high enantioenrichment. We now report investigations of the pathways and structures involved in these asymmetric lithiation−substitution sequences.

The formation of enantioenriched products **3** can arise from either of two limiting reaction pathways under the influence of a chiral diamine ligand L*.[8] One pathway is asymmetric deprotonation, in which one of the prochiral benzylic hydrogens

[⊗] Abstract published in *Advance ACS Abstracts*, November 1, 1997.

(1) (a) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141. (b) Hoppe, D.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158. (c) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479.

(2) (a) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757 (b) Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, in press. (c) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (d) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575. (e) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715. (f) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209.

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

(4) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **1995**, *117*, 8853.

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

(6) (a) Voyer, N.; Roby, J. *Tetrahedron Lett.* **1995**, *36*, 6627. (b) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342.

(7) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574.

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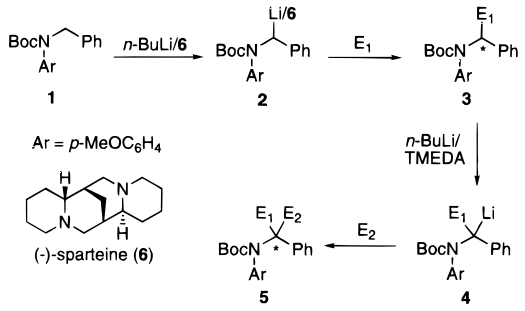
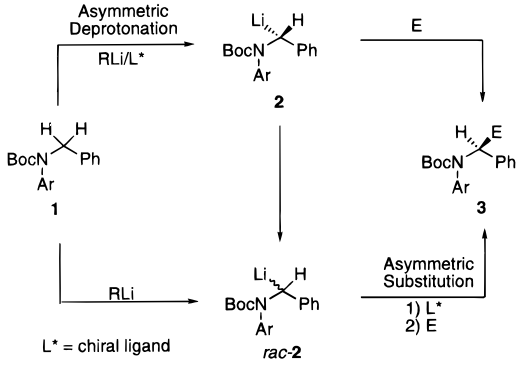


is preferentially abstracted by the chiral base RLi/L* from the substrate **1** to provide a configurationally stable species **2.** The organolithium intermediate **2** then undergoes stereoselective electrophilic substitution to provide the enantioenriched product **3**. The second pathway, which we refer to as asymmetric substitution, involves the formation of a racemic organolithium species *rac*-**2** either initially or by racemization of **2**. Complexation of *rac*-**2** with L* and reaction of the complex with an electrophile provides the enantioenriched product **3**. In the asymmetric deprotonation pathway the stereoinformation which is transferred to the products is introduced in the initial step, whereas in asymmetric substitutions the asymmetric induction leading to the products occurs in a post-deprotonation step.[8]



Results and Discussion

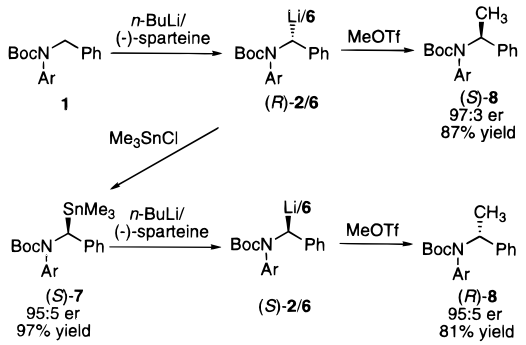
Reaction Pathways. Treatment of **1** with 1.2 equiv of *n*-BuLi/**6** in toluene at −78 °C provided after alkylation with methyl triflate (*S*)-**8** in 87% yield with a 97:3 er. The absolute configuration of (*S*)-**8** is assigned after oxidative cleavage of the *p*-methoxyphenyl group with ceric ammonium nitrate (CAN)[9] by comparison of CSP-HPLC retention times with that of the authentic compound. The tin derivative (*S*)-**7** was prepared in 97% yield with a 95:5 er using the same methodology as described for (*S*)-**8**.[2a] The absolute configuration assigned to (*S*)-**7** was determined by X-ray crystallography.[10] Reaction of the enantioenriched tin compound (*S*)-**7** with *n*-BuLi/**6** provides (*R*)-**8** in 81% yield and with a 95:5 er.[2a] Thus, a convenient route to either enantiomer of **8** is available via either the deprotonation−methylation of **1** or via the transmetalation−methylation of (*S*)-**7**. These results are consistent with an asymmetric deprotonation pathway as shown in Scheme 1. The assignments of absolute configuration of (*R*)-**2**/**6** and (*S*)-**2**/**6** are also obtained from these transformations (*vide infra*).

To further distinguish the two limiting pathways we generated the racemic intermediate *rac*-**2** via tin−lithium exchange under conditions which exposed it to the chiral ligand. Transmetalation of racemic **7** with *n*-BuLi/**6** in toluene at −78 °C followed by reaction with methyl triflate afforded racemic **8** in 83% yield

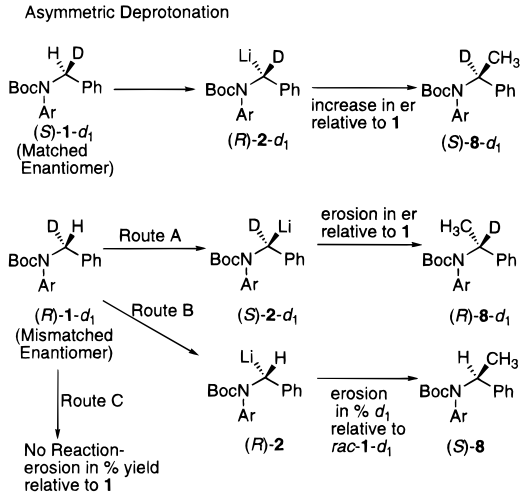
(9) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(10) We have previously deposited the X-ray data for (*S*)-**7**.[7]

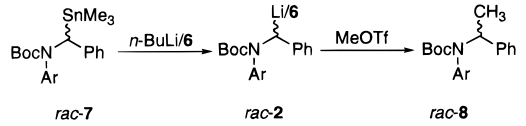
Scheme 1



Scheme 2



as shown in Table 2. If the same organolithium intermediate **2** is obtained from lithiodestannylation as from deprotonation, this result demonstrates that the racemic organolithium intermediate, *rac*-**2**, is not transformed into enantioenriched products in the presence of (−)-sparteine under the reaction conditions.



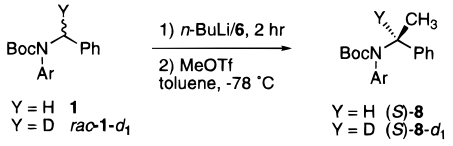
The two pathways can be distinguished also by submitting the racemic analogue *rac*-**1**-d_1 to the standard lithiation−substitution protocol and comparing the results to the reaction of **1**.[2e,6b,11,12] The synthesis of *rac*-**1**-d_1 was accomplished by treating **1** with *n*-BuLi/TMEDA at −78 °C. After 2 h, the reaction mixture was quenched with MeOD to furnish *rac*-**1**-d_1 with 99% d_1 according to FIMS, which was also confirmed by ^{1}H NMR. The pertinent comparisons are summarized in Table 1.

For asymmetric deprotonation, (*S*)-**1**-d_1 is termed the matched enantiomer as it has the proton in the favored position for abstraction with *n*-BuLi/**6**. The enantiomer (*S*)-**1**-d_1 should react with *n*-BuLi/**6** and methyl triflate essentially as does **1** to give (*S*)-**8**-d_1 as shown in Scheme 2. However, for the mismatched enantiomer, (*R*)-**1**-d_1, the deuterium is in the favored position for abstraction with *n*-BuLi/**6**, and its removal would be inhibited

(11) (a) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (b) Rein, K.; Pappas, M. G.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 2211. (c) Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807. (d) Curtin, D. Y.; Kellom, D. B. *J. Am. Chem. Soc.* **1953**, *75*, 6011.

(12) Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391.

Table 1. Reactions of **1** and *rac*-**1**-d_1 with *n*-BuLi/**6** in Toluene To Provide **(*S*)-8** and **(*S*)-8**-d_1



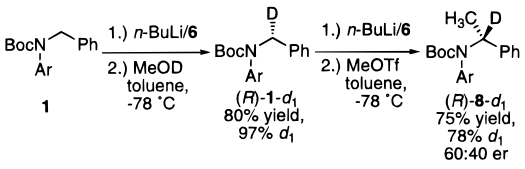
Y	reactant	yield (%)	*S*:*R* ratio[a]	d_1[a] (%)
Y = H	**1**	100	98:2	
Y = D (99% d_1)	*rac*-**1**-d_1	88	68:32	89

[a] The percent error is ±5%.

by a large deuterium isotope effect at −78 °C.[2e,6b,11a,13] As shown in Scheme 2, the mismatched enantiomer may follow three different paths in lithiation−methylation. If the proton is abstracted (Route A), the product (*S*)-**8**-d_1 would have an eroded er relative to the product from the reaction of **1** and have a net deuterium incorporation of the reactant *rac*-**1**-d_1. If the deuterium is removed (Route B), the product (*S*)-**8**-d_1 would have a decreased deuterium content, but the enantioenrichment would be comparable to that from the reaction of **1**. If both the deuterium kinetic isotope effect and the enantioselectivity are sufficiently high to prevent reaction (Route C), the product (*S*)-**8**-d_1 would be produced in decreased yield relative to that from **1** but shows similar deuterium content to that of *rac*-**1**-d_1 and enantioenrichment similar to that from **1**. In this case recovered **1**-d_1 would be enriched in (*R*)-**1**-d_1.

Lithiation of **1** with *n*-BuLi/**6** and subsequent reaction with methyl triflate after 2 h provided (*S*)-**8** in quantitative yield and 98:2 er. Reaction of *rac*-**1**-d_1 (99% d_1) under identical conditions provided (*S*)-**8**-d_1 (89% d_1) in 88% yield and 68:32 er. The observed decrease in er and deuterium incorporation in the product indicates that the reaction proceeds through an asymmetric deprotonation pathway in which Route A dominates but Route B is available. The deuterium kinetic isotope effect is more important than the inherent enantioselectivity in this case.

The conclusion that the asymmetric induction occurs through asymmetric deprotonation was further tested by submitting the enantioenriched (*R*)-**1**-d_1 (97% d_1) to the lithiation-substitution protocol. The absolute configuration of (*R*)-**1**-d_1 is based upon the assumption that the reaction of (*R*)-**2** with MeOD occurs with retention (*vide infra*).[14] Treatment of (*R*)-**1**-d_1 with *n*-BuLi/**6** and reaction with methyl triflate afforded (*R*)-**8** in 75% yield (78% d_1) and 60:40 er. A similar result was observed when carbon dioxide was used as electrophile. These results further support the asymmetric deprotonation pathway. The deuterium in (*R*)-**1**-d_1 is in the favored position for asymmetric deprotonation, and thus, due to the deuterium kinetic isotope effect, the formation of (*R*)-**2** is inhibited with the result that (*S*)-**2** is formed leading to (*R*)-**8**-d_1 with a 60:40 er. This rationale is consistent with an invertive reaction pathway for reaction of **2** with methyl triflate (*vide infra*).



(13) Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323.

(14) Hammerschmidt and Hoppe have found also that MeOD and AcOD react with retention of configuration in reactions of oxygen dipole stabilized carbanions which are similar to **2**. Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 1069.

Table 2. Transmetalation of **7** to Produce **8**

entry	er of reactant	ligand	reaction time (h)	yield[a] (%)	er of Product[b]
1	racemic	(−)-sparteine	10	83	racemic
2	95:5	(−)-sparteine	0.5	73	95:5
3	95:5	(−)-sparteine	10	81	95:5
4	95:5	TMEDA	0.5	75	70:30
5	95:5	TMEDA	10	79	56:44

[a] Isolated yield. [b] The error in er's is judged to be ±5%.

Configurational Stability and Reactivity. The data and the sequence in Scheme 1 show that the complexes of **2**/**6** are configurationally stable under the reaction conditions. The configurational stability of **2** and **2**/**6** under different conditions was investigated by subjecting the enantioenriched stannane (*S*)-**7** to tin−lithium exchange in the presence of (−)-sparteine and TMEDA as shown in Table 2. Treatment of (*S*)-**7** with *n*-BuLi/**6** for 0.5 and 10 h and subsequent reaction with methyl triflate provided (*R*)-**8** in 73% and 81% yields with 95:5 er, respectively, as shown in entries 2 and 3. However, reaction of (*S*)-**7** in the presence of the achiral ligand TMEDA gave (*R*)-**8** in 70:30 and 56:44 er, respectively, after the same transmetalation periods as shown by entries 4 and 5. In these lithiodestannylations we assume that tin−lithium exchange is occurring through a retentive pathway.[15,16] These results further demonstrate that **6** is a more effective ligand in maintaining configurations of these organolithium species than is TMEDA.[2f,17−19]

The configurationally stablility of **2**/**6** provides an opportunity to determine if the diastereomeric complexes react with electrophiles with sufficiently different activation energies to affect the enantiomeric ratio. In this variant of the Hoffmann test, reaction with a deficiency and an excess of the electrophile could reveal that possibility.[20]

Separate reactions were conducted in which an excess (1.5 equiv) and a deficiency (0.1 equiv) of methyl triflate was added to (*R*)-**2** after a 2 h lithiation period with *n*-BuLi/**6** to provide (*S*)-**8** as shown in Table 3. In these experiments the solvent methyl *tert*-butyl ether was used in order to provide a more observable change in er. In the reference reaction with excess electrophile, the methyl triflate was allowed to react with (*R*)-**2** for 1 h before the reaction was quenched with MeOD. However, in the reaction with a deficiency of electrophile, the methyl triflate was allowed to react with (*R*)-**2** for only 2 min before quenching with MeOD. This protocol was followed since the er of the initial (*S*)-**8** generated is of interest. In addition, we were concerned that (*S*)-**8** could undergo further lithiation, especially for the experiment using a deficiency of electrophile where there is a large excess of (*R*)-**2** relative to

(15) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (c) Reich, H. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577. (b) Aggarawal, V. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 175.

(16) In the only case that has been reported in which tin-lithium takes place with any inversion, retention still predominates. Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565.

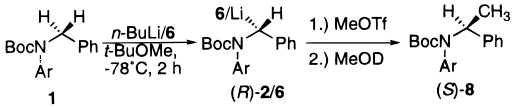
(17) The configurational stability of the carbanion in the absence of ligand could not be determined since the lithiodestannylation did not proceed with *n*-BuLi alone.

(18) An alternative possibility is that, in the presence of TMEDA, **2** may react nonstereoselectively with methyl triflate.

(19) Pearson and Chong have also observed for carbamate and urea stabilized α-aminoorganolithiums the addition of HMPA and TMEDA, respectively, significantly diminish configurational stability. Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220.

(20) In order to test for this possibility we used a variant of the Hoffmann test,[21] which we have termed the "poor man's" Hoffmann test since it does not require a chiral enantioenriched electrophile.[22] Since (*R*)-**2** is configurationally stable, a reaction with a deficiency of electrophile could provide an enantiomeric ratio different from that with an equivalent of electrophile.

Table 3. Reactions of (*R*)-**2** in *t*-BuOMe with an Excess or Deficiency of MeOTf To Yield (*S*)-**8**



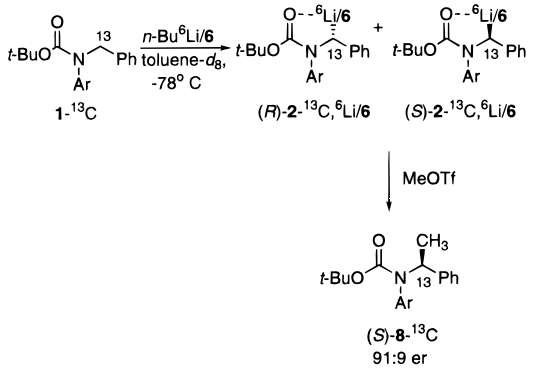
equiv of MeOTf	yield[a] (%)	*S:R*
1.5	93	92:8
0.1[b]	2.4	96:4

[a] The yield is relative to **1**. [b] Trapping time was 2 min.

methyl triflate. The ^{1}H NMR and field ionization mass spectra of (*S*)-**8** for both experiments showed no deuterium incorporation (i.e. <2%), and, therefore, we concluded that in both cases further lithiation of the product does not occur. The products of these reactions show a difference in er of 92:8 and 96:4 for (*S*)-**8**, a difference which is only slightly beyond experimental error. This result could be taken optimistically to indicate the major diastereomer (*R*)-**2**/**6** reacts faster with methyl triflate than does the minor diastereomer (*S*)-**2**/**6**. However, the results also show there is not an opportunity for substantial enantioenrichment by using a deficiency of methyl triflate as the electrophile.

NMR Spectroscopic Studies. The work of Fraenkel[23] and Seebach[24] provides the basis for the use of isotopic dipolar couplings in organolithium complexes to assign structure to the intermediates in this sequence. A ^{6}Li and ^{13}C NMR spectroscopic investigation of the structures of the lithiated intermediates (*R*)- and (*S*)-**2** was carried out with the appropriately labeled reactants **1**-^{13}C and *n*-Bu^{6}Li.[25−27] Compound **1**-^{13}C was prepared as described previously using labeled α-^{13}C benzyl bromide.[2a]

Generation of the organolithium intermediate **2**-^{13}C,^{6}Li was accomplished by reaction of **1**-^{13}C with 1.1 equiv of *n*-Bu^{6}Li/**6** in toluene-d_8 at −78 °C. As shown in Figure 1a, the ^{6}Li NMR spectrum contained two doublets at 1.29 and 1.18 ppm in an 89:11 ratio with each showing $^1J(^6\text{Li}, ^{13}\text{C}) = 3.7$ Hz. The data are consistent with the monomeric complexes (*R*)- **2**-^{13}C,^{6}Li/**6** and (*S*)-**2**-^{13}C,^{6}Li/**6** in which each ^{6}Li atom is bonded to only one ^{13}C atom. By imposing a 30 s delay between pulses to account for differences in T_1, the ratio of the two diastereomeric complexes is established to be 91:9 as shown in Table 4.[28] Two additional weak peaks observed at 0.81 and 1.66 ppm were absent in the subsequent generation of an equimolar mixture of the diastereomeric complexes (*vide infra*).



The structure of **2**-^{13}C,^{6}Li/**6** was also investigated by ^{13}C NMR spectroscopy. In addition to two peaks at 54.4 and 53.9 ppm which we assign to the two rotamers of **1**-^{13}C, the spectrum contained two strong absorptions at 71.1 and 71.9 ppm in a 90:10 ratio which we assign to the benzylic carbons of the intermediates (*R*)- and (*S*)-**2**-^{13}C,^{6}Li. Unfortunately, as shown in Figure 1b the coupling to ^{6}Li is only partially resolved. In support of the ^{6}Li NMR data, the ^{13}C NMR spectrum indicates a monomeric organolithium intermediate. In order to insure the measured integrals represented an accurate ratio of the two species, the ^{13}C NMR spectrum was acquired with a 100 s delay between pulses.[28] Further evidence of the assignments in the ^{13}C NMR spectrum was provided by the acquisition of a proton coupled ^{13}C NMR spectrum. The spectrum showed two doublets for the two benzylic carbons at 71.1 and 71.9 ppm indicative of two methine groups, ^{13}CH^{6}Li. After completion of the NMR spectroscopic study, the sample was allowed to react with methyl triflate to provide (*S*)-**8**-^{13}C in 91:9 er.

In order to generate an equimolar mixture of (*R*)- and (*S*)-**2**-^{13}C,^{6}Li, the racemic trimethyltin labeled compound *rac*-**7**-^{13}C was prepared.[2a] Transmetalation in toluene-d_8 at −78 °C with 1.5 equiv of *n*-Bu^{6}Li/**6** provided the ^{6}Li and ^{13}C NMR spectra shown in Figure 1c,d. The ^{6}Li NMR shows two doublets centered at 1.39 ppm ($^1J(^6\text{Li},^{13}\text{C}) = 3.9$ Hz) and 1.28 ppm ($^1J(^6\text{Li},^{13}\text{C}) = 3.7$ Hz) in a 51:49 ratio. There is also a weak broad absorption at 0.5 ppm which remains unassigned. The ^{13}C NMR spectrum contained, in addition to unreacted *rac*-**7**-^{13}C, two benzylic lithiated carbon absorptions at 71.9 and 71.2 ppm in a 50:50 ratio. As evident from Figure 1d, the one-bond ^{6}Li/^{13}C coupling is marginally resolved. Consistent with our previous assignments, the NMR data support the monomeric intermediates (*R*)- and (*S*)-**2**-^{13}C,^{6}Li with both the Boc group and (−)-sparteine simultaneously complexing to provide the normally encountered tetracoordinated lithium. The data indicate that the same organolithium intermediate is obtained from either the deprotonation of **1** or the lithiodestannylation of **7**.

The structure of **2**-^{13}C,^{6}Li was also investigated by carrying out a similar study in ether-d_{10}.[29] As shown in Figure 2a, the ^{6}Li NMR spectrum of (*R*)- and (*S*)-**2**-^{13}C,^{6}Li contained three peaks centered at 1.89 ppm. The above data indicate two partially overlapping doublets ($\Delta\delta = 3.9$ Hz, $^1J(^6\text{Li},^{13}\text{C}) = 3.9$ Hz) in a 71:29 ratio. A minor unassigned broad peak appears at approximately 0.8 ppm.

The lithiated intermediates were also studied by ^{13}C NMR spectroscopy. The spectrum possessed two peaks at 54.6 and

(21) (a) Hoffmann, R. W.; Lanz, J.; Metternich, R.; Tarara, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1145. (b) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975.

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

(23) Fraenkel, G; Fraenkel, A. M.; Geckle, M. J.; Schloss, F. *J. Am. Chem. Soc.* **1979**, *101*, 4745.

(24) (a) Seebach, D.; Siegel, H.; Gabriel, J.; Hässig, R. *Helv. Chim. Acta* **1980**, *63*, 2046. (b) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.

(25) For some recent examples using ^{6}Li and ^{13}C NMR spectroscopy in the characterization of organolithium compounds, see: (a) Lichtenfeld, C. M.; Ahlbrecht, H. *Tetrahedron* **1996**, *52*, 10025. (b) Sorger, K. Schleyer, P.v.R.; Stalke, D. *J. Am. Chem. Soc.* **1996**, *118*, 1086. (c) Fraenkel, G.; Martin, K. V. *J. Am. Chem. Soc.* **1995**, *117*, 10336. (d) Bauer, W.; Griesinger, C. *J. Am. Chem. Soc.* **1993**, *115*, 10871.

(26) For some recent examples using ^{6}Li or ^{7}Li NMR spectroscopy in the characterization of lithium amides, see: (a) Lucht, B.L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 3529. (c) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217. (d) Hilmersson, G.; Ahlberg, P.; Davidsson, Ö *J. Am. Chem. Soc.* **1996**, *118*, 3539. (e) Hilmersson, G.; Davidsson, Ö *J. Org. Chem.* **1995**, *60*, 7660. (f) Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273.

(27) For a review of the advantages of ^{6}Li versus ^{7}Li NMR spectroscopy, see: Günther, H. In *Advanced Applications of NMR to Organometallic Chemistry*; Gielen, M., Willem, R., Wrackmeyer, B., Eds.; John Wiley & Sons: New York, 1996; Chapter 9, pp 247−290.

(28) A similar delay was used in all subsequent spectra.

(29) We also conducted an NMR investigation in THF-d_8; however, the ^{6}Li spectrum showed a large singlet and several minor absorptions. Apparently, the increased ligating ability of THF alters the structure of the organolithium intermediate. This phenomenon may be the cause of the reduced enantioselectivity in THF.[2a]

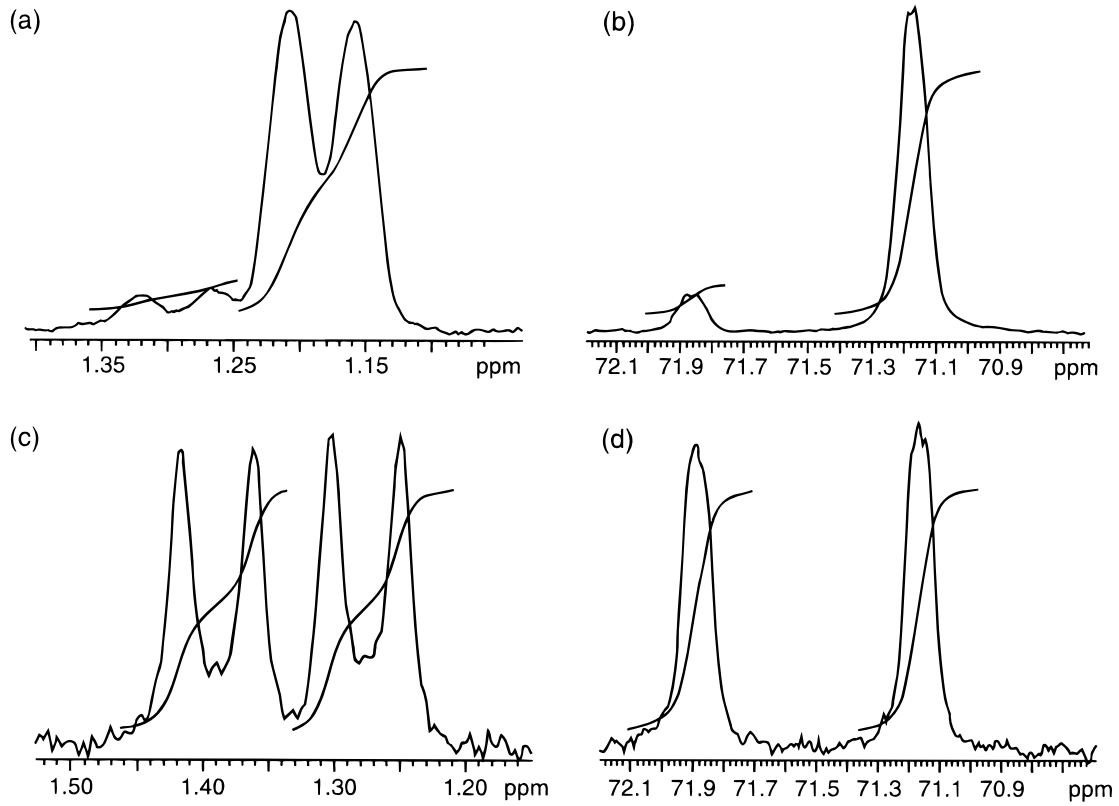


Figure 1. (a) 73.6 MHz ^{6}Li and (b) 125.7 MHz ^{13}C NMR spectra of **1**-^{13}C and *n*-Bu^{6}Li in toluene-d_8 (0.15 M) at −78 °C. (c) 73.6 MHz ^{6}Li and (d) 125.7 MHz ^{13}C NMR spectra of *rac*-**7**-^{13}C and *n*-Bu^{6}Li in toluene-d_8 (0.10 M) at −78 °C.

Table 4. Ratio of Diastereomeric Complexes Observed by NMR and upon Trapping with Methyl Triflate (−78 °C)

	(*R*)-**2**-^{13}C,^{6}Li:(*S*)-**2**-^{13}C,^{6}Li	
	ether-d_{10}	toluene-d_8
^{6}Li NMR	71:29	89:11
^{13}C NMR	73:27	90:10
trap with MeOTf	81:19	91:9

53.9 ppm which are assigned to the two rotamers of **1**-^{13}C. The spectrum also contained two strong absorptions at 71.5 and 70.4 ppm in a 73:27 ratio which we assign to the benzylic carbons of the intermediates (*R*)- and (*S*)-**2**-^{13}C,^{6}Li. Each peak showed coupling to ^{6}Li (^1J(^{6}Li,^{13}C) = 3.9 Hz for both absorptions) as indicated by the 1:1:1 triplet in Figure 2b. The proton coupled ^{13}C NMR spectrum showed two doublets of triplets for the benzylic carbons at 71.5 and 70.4 ppm indicative of two ^{13}-CH^{6}Li absorptions. As shown in Table 4, reaction with methyl triflate provided (*S*)-**8**-^{13}C in 81:19 er. Hence, in toluene-d_8 and ether-d_{10}, the ^{6}Li and ^{13}C NMR spectra are fully consistent with the monomeric structures (*R*)- **2**-^{13}C,^{6}Li/**6** and (*S*)-**2**-^{13}C,^{6}-Li/**6**.

The chemical shifts of the benzylic resonance in the ^{13}C NMR specrtra of **2**-^{13}C,^{6}Li relative to the unlithiated starting material **1**-^{13}C can be used to estimate the hybridization of the lithiated benzylic stereogenic center.[12,30] Previous studies by Peoples and Grutzner showed that the formation of the planar (7-phenylnorbornyl)potassium caused a 33.9 ppm downfield shift, while the pyramidal species (7-phenylnorbornyl)lithium caused only a 10.1 ppm downfield shift relative to unmetalated 7-phenylnorbornane.[31] The averaged downfield shifts for the ^{13}C signals of (*S*)-**2**-^{13}C,^{6}Li/**6** and (*R*)-**2**-^{13}C,^{6}Li/**6** in ether-d_{10} and toluene-d_8 are 16.7 and 17.4 ppm, respectively.[32] These values are consistent with a pyramidal benzylic carbon atom with some degree of delocalization into the benzene ring.[33]

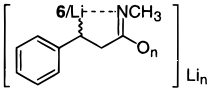
The NMR data reveal that the organolithium intermediate is monomeric, and the resulting diastereomeric complexes are configurationally stable consistent with an asymmetric deprotonation mechanism. In toluene-d_8, the observed ratio of diastereomeric complexes agrees well with the enantiomeric ratio of the products obtained on reaction with methyl triflate. However, in ether-d_{10} an increase in er in the products relative to the ratio of complexes observed by NMR may be a result of some background asymmetric substitution

Tertiary Benzyllithium Analogues. We have investigated the lithiation−substitution at the tertiary benzylic carbons of (*R*)-**8** and (*S*)-**8** with the results shown in Scheme 3 and Table 5.[2a] The reactant (*S*)-**8** was obtained by subjecting **1** to the standard lithiation−substitution protocol and carrying out a

(30) Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 4938.

(31) Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709.

(32) Interestingly, we observed almost an identical chemical shift change for our previous study on the dilithio-N-methyl amide shown below in THF-d_8.[12]



(33) For a large number of organolithium compounds, an empirical rule has emerged which usually correctly predicts the value of ^{1}J(^{6}Li,^{13}C) (see eq 1).[34] Thus despite differences in hybridization,[35] this rule predicts a value of approximately 17 Hz for monomers, 8.5 Hz for dimers, and 5.7 Hz for static tetramers or hexamers. Benzyllithiums represent a specific class of compounds which possess significantly lower coupling constants than that predicted by eq 1.[25c,36] For example, Fraenkel and Martin found for the parent monomeric benyllithium with 0.005 M TMEDA in THF-d_8, a coupling constant of 3.8 Hz.[25c] Fraenkel proposed that benyllithiums possess increased ionic character and thus, as derived by Karplus, Grant, and Litchman[37] for ^{1}J(^{13}C,^{1}H), the magnitude of ^{1}J(^{6}Li,^{13}C) decreases

$$^1J(^6\text{Li}, ^{13}\text{C}) \approx 17/n \text{ Hz} \quad (1)$$

where n = number of equivalently coupled ^{6}Li or ^{13}C nuclei.

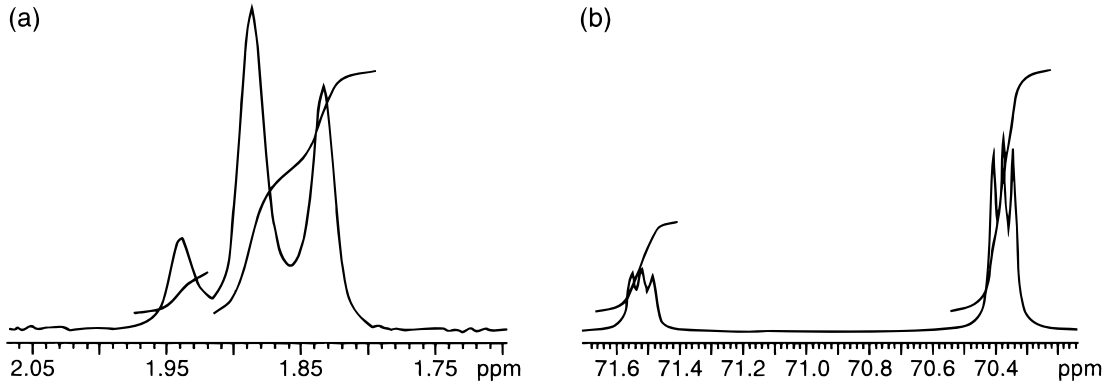


Figure 2. (a) 73.6 MHz ^{6}Li and (b) 125.7 MHz ^{13}C NMR spectra of **1**-^{13}C and *n*-Bu^{6}Li in ether-d_{10} (0.15 M) at −78 °C.

Scheme 3

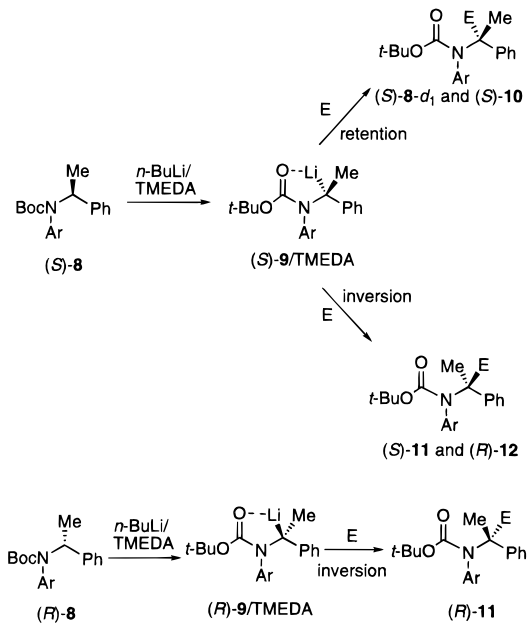


Table 5. Lithiation−Substitution at the Tertiary Benzylic Carbons of (*R*)-**8** and (*S*)-**8**

reactant (er)	E	product (er, yield)
(*S*)-**8** (97:3)	MeOD	(*S*)-**8**-d_1 (97:3, 80%)
(*S*)-**8** (97:3)	$ClCO_2CH_3$	(*S*)-**10** (95:5, 61%)
(*S*)-**8** (99:1)	allyl triflate	(*S*)-**11** (98:2, 96%)
(*S*)-**8** (99:1)	CO_2	(*R*)-**12** (70:30, 84%)
(*S*)-**8** (99:1)[a]	CO_2	(*R*)-**12** (99:1, 81%)
(*R*)-**8** (99:1)	allyl triflate	(*R*)-**11** (99:1, 92%)

[a] *n*-BuLi/**6** was used.

single recrystallization to afford (*S*)-**8** in 99:1 er. The reactant (*R*)-**8** was synthesized from (*S*)-**7** via a tin−lithium exchange-lithiation to provide (*R*)-**8** in 99:1 er after a single recrystallization.

When (*S*)-**8** of 97:3 er was treated with 1.2 equiv of *n*-BuLi/TMEDA in toluene at −78 °C for 8 h followed by addition of MeOD, (*S*)-**8**-d_1 (98%-d_1) was obtained in 80% yield with an er of 97:3 with retention of configuration.[14,38] With (*S*)-**8** as the reactant and methyl chloroformate as the electrophile, (*S*)-**10** was obtained in 61% yield and 95:5 er with retention. The absolute configuration of **10** is based on comparison of optical rotation to the *N*-benzoyl amides of previously assigned authentic enantiomers.[39]

Reaction of (*S*)-**8** of 99:1 er with *n*-BuLi/TMEDA and subsequent reaction with allyl triflate provided (*S*)-**11** in 96% yield and 98:2 er with inversion.[2a] The enantiomer (*R*)-**11** was prepared in 92% yield and 99:1 er from (*R*)-**8** using the same reaction sequence. The absolute configuration of **11** is based on comparison to the Mosher amides of previously assigned authentic enantiomers.[40] With (*S*)-**8** as the substrate, TMEDA as the ligand, and carbon dioxide as the electrophile, (*R*)-**12** was obtained in 84% yield with 70:30 er, while with (−)-sparteine as the ligand (*R*)-**12** was obtained in 81% yield and 99:1 er with inversion. The absolute configuration of **12** was assigned by comparing the CSP-HPLC retention times of the corresponding methyl ester with that of (*S*)-**10**. This result shows that the electrophilic substitution of the tertiary lithium intermediate (*S*)-**9**/TMEDA with CO_2 is highly stereoselective in the presence of sparteine but not in the presence of TMEDA. We also observed that, in the presence of TMEDA, allyl bromide and allyl iodide react with (*S*)-**9**/TMEDA nonstereoselectively to afford (*S*)-**11** in 67:33 and 53:47 er, respectively.[2b]

An alternative approach which provides both enantiomers at the quaternary center is to change the order of the substitution reactions. For example, compound (*S*)-**13** of 99:1 er was obtained in 89% yield by deprotonation−ethylation of (*S*)-**8** in toluene. The enantiomer (*R*)-**13** was obtained in 47% yield and 93:7 er by deprotonation−methylation of (*S*)-**14** in toluene which was obtained from **1** by a deprotonation−ethylation sequence.[41]

The capability of generating either enantiomer of **9** was investigated. An enantioenriched sample (99:1 er) of (*S*)-**8** was deprotonated with *n*-BuLi/TMEDA and then allowed to react with trimethyltin chloride to provide (*S*)-**15**. Lithiodestannylation of (*S*)-**15** was then carried out with *n*-BuLi/TMEDA to generate (*R*)-**9**/TMEDA and subsequently reacting with MeOD. The transmetalation was allowed to proceed for 8 h and provided (*R*)-**8**-d_1 with 99:1 er. Since (*R*)-**8**-d_1 was obtained with the same enantioenrichment as the initial substrate, (*R*)-**9**/TMEDA and (*S*)-**9**/TMEDA must be configurationally stable under these

(34) Bauer, W.; Schleyer, P. v. R. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 1, p 89.

(35) This unusual behavior has recently been concluded to arise from a simultaneous increase in s-character and decrease in lithium−carbon covalency. Lambert, C.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1129.

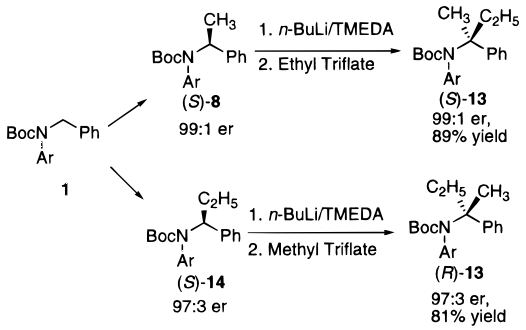
(36) (a) Hoell, D.; Lex, J.; Müllen, K. *J. Am. Chem. Soc.* **1986**, *108*, 5983. (b) Ruland, T.; Hoffmann, R. W.; Schade, S.; Boche, G. *Chem. Ber.* **1995**, *128*, 551.

(37) (a) Karplus, M.; Grant, D. M. *Proc. Natl. Acad. U.S.A.* **1959**, *45*, 1269. (b) Grant, D. M.; Litchman, W. M. *J. Am. Chem. Soc.* **1965**, *87*, 3994. (c) Litchman, W. M.; Grant, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 2228.

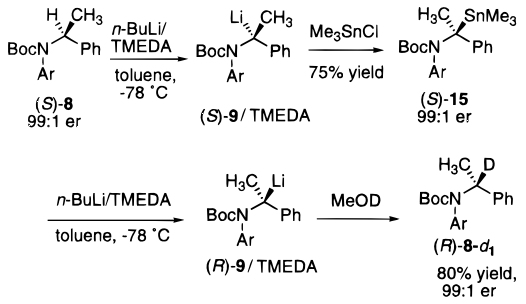
(38) When CH_3COOD was used as the electrophile, (*S*)-**8**-d_1 (99%-d_1) was obtained in 78% yield with a 92:8 er.

(39) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schonholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta.* **1995**, *78*, 563.

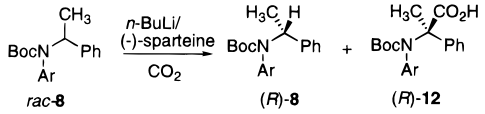
(40) Hua, D. H.; Miao, S. W.; Chen, J.-S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.



reaction conditions. Corresponding tertiary lithiated dipole-stabilized α-oxygen carbanions have been shown by Hoppe to be configurationally stable.[44]



We achieved a moderate kinetic resolution of *rac*-**8** with *n*-BuLi/**6**. Lithiation of **8** with 0.5 equiv of *n*-BuLi/**6** and reaction with CO_2 provided (*R*)-**8** and (*R*)-**12** in 55% and 22% yield and 75:25 and 87:13 er, respectively, as shown in Table 6. With 0.8 equiv of *n*-BuLi/**6** provided (*R*)-**8** and (*R*)-**12** in 12% and 66% yield and with 81:19 and 57:43 ers, respectively.



Reaction Pathway. Our experimental work establishes that the lithiation-substitutions of **1** at the benzylic position proceed by the pathway of asymmetric deprotonation. The lithiated intermediate (*R*)-**2**/**6** is a configurationally stable monomeric species with the carbonyl oxygen complexed to the lithium. The same species **2** is generated by deprotonation as by destannylation from the appropriate precursors. The absolute configuration of (*S*)-**7** is established, and lithiation−deuteration sequences at the tertiary benzylic carbon of (*R*)-**8** and (*S*)-**8** give net retention.

From well established precedents which show that tin−lithium exchange proceeds with retention, the configuration of (*R*)-**2** and (*S*)-**2** can be assigned with confidence.[15,16] Hence, the chiral base *n*-BuLi/**6** preferentially removes the pro-*R* proton from **1** to give (*R*)-**2**/**6**. The assignment of retention of configuration in the lithiation of **1** and **8** is consistent with the expectation

Table 6. Kinetic Resolution of (*R*)-**8**

n-BuLi/(−)-sparteine (equiv)	extent of reaction[a] (%)	er (yield) of (*R*)-**8**	er (yield) of (*R*)-**12**
0.5	30	75:25 (55%)	87:13 (22%)
0.8	83	81:19 (12%)	57:43 (66%)

[a] The extent of reaction was determined by proton NMR of the crude reaction mixture.

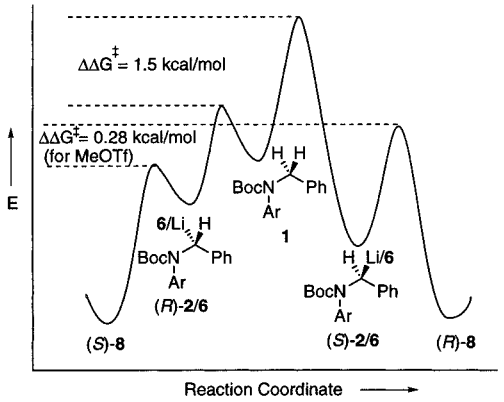


Figure 3. Energy diagram for asymmetric deprotonation.

that the proton would be removed by the organolithium associated with the carbonyl oxygen in the preequilibrium complex.[8,44] With these assignments, the stannylations of **2** and **9** must proceed with inversion.

Reactions of the benzylic lithiated species (*R*)-**2**/**6**, (*S*)-**2**/**6**, (*R*)-**9**/TMEDA, and (*S*)-**9**/TMEDA with electrophiles can occur with retention or inversion.[7,43,44] Both stereochemistries have been observed for reactions of a number of α-heteroatom organolithiums species with electrophiles.[42,43,44] The reaction pathways are shown in Scheme 4 for **1** and (*S*)-**8**. On the basis of above assignments, electrophilic substitutions of (*R*)-**2**/**6** and (*S*)-**9**/TMEDA proceed with inversion with methyl triflate, trimethyltin chloride, and carbon dioxide, while MeOD and methyl chloroformate proceed with retention.[45] The pattern that reactions of highly reactive and/or non-lithium coordinating electrophiles proceed with inversion and less reactive and/or lithium coordinating electrophiles proceed with retention is consistent with previous suggestions.[2f,44]

The energetics of the lithiation−methylation can be analyzed as shown in Figure 3 for the conversion of **1** to **3**. In the asymmetric deprotonation the pro-*R* hydrogen of **1** is preferentially abstracted with a $\Delta\Delta G^{\ddagger} = 1.5$ kcal/mol to provide (*R*)-**2**/**6** and (*S*)-**2**/**6** which are configurationally stable in a ratio of 98:2. With methyl triflate as the electrophile, the major diastereomer (*R*)-**2**/**6** reacts faster than does the minor diastereomer (*S*)-**2**/**6** with the difference in free energy between transition structures estimated as 0.28 kcal/mol at −78 °C.

Summary

The present work provides analysis of an asymmetric deprotonation−substitution pathway which provides products with high enantioselectivities in replacements of prochiral methylene protons with carbon−carbon bonds. Either enantiomer of products with one or two new carbon−carbon bonds can be obtained by proper choice of the electrophile or by use of lithiation−substitution−lithiation sequences. Application of this methodology and extensions to other systems are under further study.

(41) The loss of enantioenrichment and low conversion in toluene was improved by using ether as the solvent to give (*R*)-**12** in 81% yield and 97:3 er.

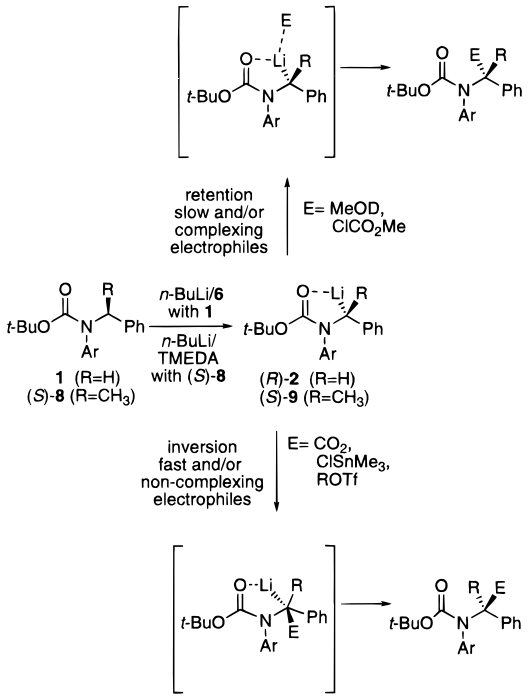
(42) The reaction of the secondary lithium intermediate (*R*)-**2** with $ClCO_2$-Me and CO_2 also provided the opposite configuration with $ClCO_2Me$ proceeding through a retentive pathway and CO_2 proceeding through an invertive pathway.

(43) For examples of both invertive and retentive electrophilic trapping of organolithium intermediates, see: (a) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (b) Derwig, C.; Hoppe, D. *Synthesis* **1996**, 149. (c) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.

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

(45) For the reaction with MeOD, we suggest that complexation with (*R*)-**2**/**6** and (*S*)-**9**/TMEDA occurs prior to deuterium transfer.

Scheme 4



Experimental Section

Preparation of NMR Samples. To a solution of (−)-sparteine (≈ 0.16 mmol) in 0.6 mL of toluene-d_8 or ether-d_{10} (previously distilled over CaH_2) at −78 °C was added *n*-Bu^{6}Li. The reaction mixture was stirred for 30 min and transferred via cannula to a solution of **1**-^{13}C or *rac*-**7**-^{13}C (≈ 0.14 mmol) in 0.3 mL of toluene-d_8 or ether-d_{10}. After 5 min, the resulting solution was transferred via cannula to a septum-capped 5 mm NMR tube (dried in oven at 120 °C overnight) immersed in a −78 °C bath.

Acquisition of NMR Spectra. The ^{6}Li and ^{13}C NMR spectra were recorded at −78 °C on a Varian UI500WB spectrometer operating at 73.6 MHz for ^{6}Li (delay = 30 s) and 125.7 MHz for ^{13}C (delay = 100 s). The ^{6}Li NMR spectra were referenced to a solution of ^{6}LiBr in THF-d_8 and the ^{13}C spectra to the residual solvent peaks in toluene-d_8 (137.5 ppm) or ether-d_{10} (65.3 ppm). Due to the relatively small difference in resonance between ^{6}Li and ^{2}H, the ^{6}Li NMR spectra were run unlocked. This protocol improved spectral quality.

Preparation of ^{6}Li-Butyllithium. ^{6}Li metal (rod) 2.90 g (482 mmol) in a drybox was hammered flat, cut into small pieces, and loaded into a Schlenk flask. The flask was removed from the drybox, and 80 mL of pentane and 25.2 mL (241 mmol) of 1-chlorobutane were then added. The reaction was sonicated overnight at ≈ 40 °C and filtered through Celite using stardard Schlenk apparatus to yield a yellow solution of *n*-Bu^{6}Li.

Enantiomeric Purity Analyses. Analytical HPLC was performed for both racemic and enantioenriched compounds using a Rainin HPXL Solvent Delivery System attached to a Rheodyne pump, a Rainin Dynamax absorbance detector (254 nm), and a computer equipped with Dynamax MacIntegrator. Either a Chiralcel OD column (0.5 mL/min flow rate, 5% MTBE in hexane), a (*S*)-*N*-naphthylleucine column (2.0 mL/min flow rate, 20% *i*-PrOH in hexane), a Whelk-O column (1.0 mL/min flow rate, 0.75% *i*-PrOH in hexane), or a Chiralpak AD column (0.8 mL/min flow rate, 1.5% *i*-PrOH in hexane) was used for the separation of enantiomers.

General Procedure for the Asymmetric Syntheses of *N*-Boc-*N*-(*p*-methoxyphenyl)-α-Substituted Benzylamines: Syntheses of (*S*)-7, (*S*)-8, (*R*)-1-d_1, and (*S*)-14. To a solution of (−)-sparteine (1.2 equiv) in toluene (*ca.* 0.1 M) at −78 °C was added *n*-BuLi (1.2 equiv). The reaction mixture was stirred for 30 min at −78 °C, and then a solution of **1** (1.0 equiv) in toluene (*ca*. 0.2 M) was transferred to the above solution at −78 °C. The resulting reaction mixture was stirred at −78 °C for 4 h, and then an electrophile (1.2 equiv) in toluene (*ca.* 0.2 M) was added after precooling. After stirring for 3 h at −78 °C, this mixture was allowed to slowly warm to room temperature. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether, extraction of the combined diethyl ether extracts with saturated NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude mixture purified by chromatography to give the pure product.

Removal of the *p*-Methoxyphenyl Group by CAN. The concentrated crude product mixture was dissolved in CH_3CN-H_2O (4:1; *ca.* 0.05 M), and CAN (ceric ammonium nitrate, 2.5 equiv) was added at 0 °C. After stirring at 0 °C for 0.5 h, the mixture was diluted with diethyl ether, poured into water, and extracted with diethyl ether. The extracts were combined, dried over $MgSO_4$, filtered through a pad of Celite, and concentrated *in vacuo*. The crude mixture was further purified by chromatography to give a pure product.

***N*-Boc-*N*-(*p*-methoxyphenyl)-α-trimethylstannylbenzylamine ((*S*)-7).** From 600 mg of **1** was obtained 887 mg (97%) of **7** as a white solid: mp 84−85 °C; $[\alpha]^{22}_D = -113.2$ (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−6.77 (m, 9H, *Ph* + *Ph*OMe), 4.06 (s, 1H, C*H*Ph), 3.78 (s, 3H, PhOCH_3), 1.49 (s, 9H, -C(CH_3)$_3$), 0.14 (s, ^2J (^{119}SnC*H*) = 26.4 Hz, 9H, Sn(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 156.6, 144.2, 137.9, 128.4, 128.2, 127.0, 124.3, 113.5, 80.0, 59.1, 55.2, 28.3, −6.8; EIMS (70 eV) *m/z* (rel intensity) 462 (5), 421 (5), 406 (30), 376 (54), 346 (4), 330 (7), 256 (24), 212 (100), 196 (68), 165 (100), 57 (99). Anal. Calcd for $C_{22}H_{31}NO_3Sn$: C, 55.49; H, 6.56; N, 2.94. Found: C, 55.48; H, 6.81; N, 2.85.

The enantiomeric ratio of **7** was determined to be 95:5 on a Chiralcel OD column (The major enantiomer had a retention time of 8.7 min, and the minor enantiomer had a retention time of 9.5 min.).

***N*-Boc-*N*-(*p*-methoxyphenyl)-α-methylbenzylamine ((*S*)-8).** From 619 mg of **1** was obtained 562 mg (87%) of **8** as a white solid: mp 95−96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−6.72 (m, 9H, *Ph* + *Ph*OMe), 5.70 (brs, 1H,C*H*Ph), 3.76 (s, 3H, PhOCH_3), 1.44 (d, J = 7.2 Hz, 3H, CHCH_3), 1.38 (brs, 9H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.0, 155.4, 142.2, 131.8, 130.8, 128.0, 127.5, 127.0, 113.3, 79.8, 55.2, 54.4, 28.3, 17.9; EIMS (70 eV) *m/z* (rel intensity) 327 (12, M^+), 271 (42), 227(10), 212 (23), 167 (100), 123 (170, 105 (37), 57 (29). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.20; H, 7.68; N, 4.21.

After removal of the *p*-methoxyphenyl group, the enantiomeric ratio of **(*S*)-8** was determined to be 97:3 in favor of the *S* enantiomer by chiral HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative on a (*S*)-*N*-naphthylleucine column. The absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-α-methyl-benzylamine (the *S*-enantiomer (major) had a retention time of 8.0 min, and the *R*-enantiomer (minor) had a retention time of 5.7 min). After one recrystallization from *n*-hexane, **(*S*)-8** of 99:1 er was obtained in 81% yield.

***N*-Boc-*N*-(*p*-methoxyphenyl)-α-ethyl-benzylamine ((*S*)-14).** From 239 mg of **1** was obtained 239 mg (92%) of **14** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62−6.25 (m, 9H, *Ph* + *Ph*OMe), 5.45 (brs, 1H,C*H*Ph), 3.74 (s, 3H, PhOCH_3), 1.83 (m, 2H, CHCH_2CH$_3$), 1.39 (brs, 9H, -C(CH_3)$_3$), 1.01 (t, J = 7.0 Hz, 3H, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.0, 155.6, 140.8, 131.6, 130.8, 128.3, 127.9, 127.1, 113.2, 79.7, 61.2, 55.1, 28.3, 24.4, 11.3; EIMS (70 eV) *m/z* (rel intensity) 341 (11, M^+), 285 (22), 240 (6), 212 (43), 167 (100), 134 (7), 123 (8), 119 (14), 91 (42), 57 (48). HRMS calcd for $C_{21}H_{27}NO_3$ ($M^+ + 1$) 341.1983, found 341.1991.

After removal of the *p*-methoxyphenyl group, the enantiomeric ratio of **14** was determined to be 97:3 er in favor of the *S* enantiomer by chiral HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative on a (*S*)-*N*-naphthylleucine column. The absolute configuration was assigned by conversion to a commercially available amino acid (The *S*-enantiomer (major) had a retention time of 7.3 min, and the *R*-enantiomer (minor) had a retention time of 5.3 min.).

General Procedure for the Tin−Lithium Exchange Reaction with *n*-BuLi/Ligand: Preparation of (*R*)-8 from (*S*)-7 and Preparation of (*R*)-8-d_1 from 15. To a solution of 1.2 equiv of (−)-sparteine (or TMEDA) in toluene (*ca.* 0.1 M) at −78 °C was added *n*-BuLi (1.2 equiv). The reaction mixture was stirred for 30 min at −78 °C, and then a solution of **7** (1.0 equiv) in toluene (*ca*. 0.2 M) was transferred to the above solution at −78 °C. The resulting reaction mixture was

stirred at −78 °C for 4 h, and then methyl triflate (1.2 equiv) in toluene (*ca.* 0.2 M) was added after precooling. After stirring for 3 h at −78 °C, this mixture was allowed to slowly warm to room temperature. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether twice, extraction of the combined diethyl ether extracts with saturated NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo.* The crude product was further purified by chromatography to give a pure product.

From 84 mg of **7** was obtained 84 mg (81%) of (*R*)-**8** as a white solid: mp 95−96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−6.72 (m, 9H, *Ph* + *Ph*OMe), 5.70 (brs, 1H, C*H*Ph), 3.76 (s, 3H, PhOCH_3), 1.44 (d, J = 7.2 Hz, 3H, CHCH_3), 1.38 (brs, 9H, -C(CH_3)$_3$).

After removal of the *p*-methoxyphenyl group, the enantiomeric ratio of **(*R*)-8** was determined to be 95:5 in favor of the *R* enantiomer by chiral HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative on a (*S*)-*N*-naphthylleucine column. The absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-α-methyl-benzylamine (The *R*-enantiomer (major) had a retention time of 5.5 min, and the *S*-enantiomer (minor) had a retention time of 7.6 min.). After one recrystallization from *n*-hexane, **(*R*)-8** of 99:1 er was obtained in 80% yield.

Transmetalation of 15 To Provide (*R*)-8-d_1. To a solution of **15** (152 mg, 0.310 mmol) and TMEDA (0.056 mL, 0.372 mmol) in toluene (5.3 mL) at −78 °C was added *n*-BuLi (0.248 mL, 0.372 mmol, 1.5 M). After 1 h, CH_3OD (3 mL) was added, and this mixture was allowed to warm to ambient temperature. This mixture was washed with 4 mL of NH_4Cl (aqueous), the two layers were separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The remainder was filtered through a short plug of silica with CH_2Cl_2 and concentrated. Purification by preparative HPLC (1−5% EtOAc in hexane; 10.0 to 12.5 mL/min; 25 cm × 21.4 mm i.d.) yielded (*R*)-**8**-d_1 as a white solid (56 mg, 57%). mp = 101−103 °C. The enantiomeric excess was determined to be 99:1 er in favor of the *R* enantiomer by CSP HPLC (Whelk-0 column; 0.75% *i*-PrOH in hexane; 1.0 mL/min; retention time for the *R* enantiomer: 19 min). The deuterium incorporation was determined to be >95% by ^{1}H NMR.

General Procedure for the Preparation of α,α-Disubstituted *N*-Boc Benzylamines. To a solution of 1.2 equiv of TMEDA in toluene (*ca.* 0.1 M) at −78 °C was added *n*-BuLi (1.2 equiv). The reaction mixture was stirred for 10 min at −78 °C, and then a solution of α-substituted benzylamine (1.0 equiv) in toluene (*ca*. 0.2 M) was transferred to the above solution at −78 °C. The resulting reaction mixture was stirred at −78 °C for 4 h, and then allyl triflate (1.2 eq) in toluene (*ca.* 0.2 M) was added after precooling. After being stirred for 3 h at −78 °C, this mixture was allowed to slowly warm to room temperature. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether twice, extraction of the combined diethyl ether extracts with saturated NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo.* The crude product was further purified by chromatography to give a pure disubstituted product.

***N*-Boc-*N*-(*p*-methoxyphenyl)-2-methyl-2-phenylglycine Methyl Ester ((*S*)-10) from (*S*)-8.** From 276 mg of **8** (97:3 er) was obtained 197 mg (61%) of **10** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57−6.74 (m, 9H, *Ph* + *Ph*OMe), 3.82 (s, 3H), 3.76 (s, 3H), 1.57 (s, 3H, C*Me*)1.39 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 158.3, 155.1, 132.6, 130.9, 127.6, 127.0, 114.1, 113.3, 80.6, 67.8, 55.2, 52.4, 28.0, 26.5; HRMS calcd for $C_{22}H_{27}NO_5$ 385.1889, found 385.1888.

In order to prepare the Boc deprotected methyl ester for the CSP-HPLC analysis, **10** was treated with 20% trifluoroaceticacid in methylene chloride at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58−6.39 (m, 9H, *Ph* + *Ph*OMe), 4.78 (brs, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 1.89 (s, 3H, C*Me*). The enantiomeric ratio of **10** was determined to be 95:5 in favor of the *S* enantiomer by chiral HPLC using racemic material as a standard (Chiralpak-AD column; 1.5% isopropyl alcohol in hexane; 0.8 mL/min; the *S* enantiomer (major) had a retention time of 18.0 min, and the *R* enantiomer (minor) had a retention time of 19.0 min.).

After removal of the *p*-methoxyphenyl group and the Boc group of (*S*)-**10**, the amine was treated with benzoyl chloride and Et_3N in THF to provide methyl-(*S*)-*N*-benzoyl-2-methyl-2-phenylglycinate: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84−7.26 (m, 11H, 2*Ph* + N*H*), 3.74 (s, 3H, O*Me*), 2.18 (s, 3H, C*Me*). The absolute configuration of (*S*)-**10** was determined by optical rotation of the amide by comparison to authentic compound: $[\alpha]^{22}_D$ = +20.1 (*c* 0.02, $CHCl_3$).

***N*-Boc-*N*-(*p*-methoxyphenyl)-α-allyl-α-methyl-benzylamine ((*S*)-11) from (*S*)-8.** From 197 mg of **(*S*)-8** (99:1 er) was obtained **11** as 212 mg of a colorless oil in 96% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51−6.71 (m, 9H, *Ph* + *Ph*OMe), 5.56 (m, 1H, C*H*═CH_2), 5.03 (m, 2H, CH═CH_2), 3.81 (s, 3H, PhOCH_3), 2.77 (brt, 1H, CH_2-CH═CH_2), 2.51 (dd, J = 6.0 Hz, 13.1 Hz, 1H, CH_2CH═CH_2), 1.37 (s, 3H, NCCH_3), 1.11 (brs, 9H, -C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2, 148.5, 134.4, 133.9, 131.4, 127.9, 125.8, 125.2, 125.1, 118.5, 113.7, 79.9, 63.7, 55.3, 45.3, 28.0, 27.1; EIMS (70 eV) *m/z* (rel intensity) 367 (2, M^+), 326 (1), 270 (2), 226 (26), 167 (100), 108 (9), 57 (17).

The enantiomeric ratio of **11** was determined to be 98:2 using racemic material as a standard by ^{1}H-NMR. The absolute configuration was assigned by comparison to the Mosher amides of previously assigned authentic enantiomers (300 MHz ^{1}H-NMR using chiral shift reagent (+)-Eu(hfc)$_3$ derivatives in benzene-d_6; PhOCH_3, (*S*) δ 3.58, (*R*) δ 3.68).

***N*-Boc-*N*-(4-methoxyphenyl)-α-allyl-α-methyl-benzylamine ((*R*)-11) from (*R*)-8.** The product **(*R*)-11** of 99:1 er was prepared in 92% yield from **(*R*)-8** of 99:1 er by the same procedure for the preparation of **(*S*)-11**. After removing *p*-methoxyphenyl group and Boc group of (*R*)-**11**, the amine was treated with (*R*)-Mosher acid chloride and Et_3N in THF. The absolute configuration of (*R*)-**11** was determined by ^{1}H-NMR of the (*R,R*)-Mosher amide by comparison to the authetic diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.22 (m, 10H, 2*Ph*), 5.56 (m, 1H, C*H*═CH_2), 5.14 (m, 2H, CH═CH_2), 3.45 (s, 3H, O*Me*), 2.90−2.60 (m, 2H, CH_2CH═CH_2), 1.76 (s, 3H, NCCH_3).

***N*-Boc-*N*-(*p*-methoxyphenyl)-2-methyl-2-phenylglycine ((*R*)-12) from (*S*)-8.** From 128 mg of **8** was obtained 122 mg (84%) of (*R*)-**12** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.73 (brs, 1H, CO_2H), 7.70−6.81 (m, 9H, *Ph* + *Ph*OMe), 3.78 (s, 3H, CH_3O), 1.54 (s, 3H, C*Me*), 1.41 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.6, 158.7, 157.0, 141.1, 132.3, 130.7, 128.0, 127.4, 126.1, 113.8, 82.1, 68.8, 55.4, 28.2, 28.1; HRMS calcd for $C_{21}H_{25}NO_5$ 371.1733, found 371.1731.

In order to prepare the ester for the CSP-HPLC analysis, (*R*)-**12** was refluxed for 2 h in MeOH containing excess thionyl chloride to give the corresponding Boc deprotected methyl ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58−6.39 (m, 9H, *Ph* + *Ph*OMe), (brs, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 1.89 (s, 3H, C*Me*). The enantiomeric ratio of (*R*)-**12** was determined to be 70:30 (99:1 with **6**) in favor of the *R* enantiomer by chiral HPLC. (Chiralpak-AD column; the *R*-enantiomer (major) had a retention time of 19.0 min, and the *S* enantiomer (minor) had a retention time of 18.1 min.).

***N*-Boc-*N*-(*p*-methoxyphenyl)-α-ethyl-α-methyl-benzylamine ((*S*)-13) from (*S*)-8.** From 244 mg of **(*S*)-8** was obtained 237 mg (89%) of **13** as a colorless oil: ^{1}H NMR (benzene-d_6, 300 MHz) δ 7.50−6.67 (m, 9H, *Ph* + *Ph*OMe), 3.24 (s, 3H, PhOCH_3), 1.87 (m, 1H, NCCH_aH$_b$), 1.53 (m, 1H, NCCH$_a$$H_b$), 1.51 (s, 3H, C$H_3$), 1.09 (brs, 9H, -C(C$H_3$)$_3$), 0.59 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 155.1, 148.1, 134.0, 131.2, 127.7, 125.6, 125.3, 113.7, 79.7, 64.5, 55.3, 35.7, 27.9, 24.6, 9.2; EIMS (70 eV) *m/z* (rel intensity) 355 (1, M^+), 254 (2), 223 (11), 167 (100), 133 (13), 123 (16), 91 (40), 57 (29); HRMS calcd for $C_{22}H_{29}NO_3$ 355.2147, found 355.2151.

The enantiomeric ratio of (*S*)-**13** was determined to be 99:1 using racemic material as a standard by ^{1}H-NMR. The absolute configuration was assigned by analogy to the formation of (*R*)-**11** (300 MHz ^{1}H-NMR using chiral shift reagent (+)-Eu(hfc)$_3$ derivatives in benzene-d_6; PhOCH_3, (*S*) δ 3.62, (*R*) δ 3.67).

***N*-Boc-*N*-(*p*-methoxyphenyl)-α-ethyl-α-methyl-benzylamine ((*R*)-13) from (*S*)-14.** From 194 mg of **(*S*)-14** was obtained 164 mg (81%) of (*R*)-**13** as a colorless oil: ^{1}H NMR (benzene-d_6, 300 MHz) δ 7.50−6.69 (m, 9H, *Ph* + *Ph*OMe), 3.24 (s, 3H, PhOCH_3), 1.87 (m, 1H, NCCH_aH$_b$), 1.55 (m, 1H, NCCH$_a$$H_b$), 1.51 (s, 3H, C$H_3$), 1.09 (brs, 9H, -C(C$H_3$)$_3$), 0.59 (t, J = 7.4 Hz, 3H, CH_2CH_3).

The enantiomeric ratio of (*R*)-**13** was determined to be 97:3 using racemic material as a standard by ^{1}H-NMR. The absolute configuration was assigned by analogy to the formation of (*R*)-**11** (300 MHz ^{1}H-NMR using chiral shift reagent (+)-Eu(hfc)$_3$ derivatives in benzene-d_6; PhOCH_3, (*S*) δ 3.39, (*R*) δ 3.44).

***N*-Boc-*N*-(*p*-methoxyphenyl)-α-methyl-α-trimethylstannyl-benzylamine (15) from (*S*)-8.** To a solution of **(*S*)-8** (145 mg, 0.443 mmol; 99:1 er) and TMEDA (0.080 mL, 0.532 mmol) in toluene (7.5 mL) at −78 °C was added *n*-BuLi (0.355 mL, 0.532 mmol). After 8 h, trimethyltin chloride (0.532 mL, 0.532 mmol, 1.0 M solution in hexanes) was added. After ca. 3 h at −78 °C, this mixture was allowed to warm to ambient temperature over ca. 4 h and then left at ambient temperature for ca. another 7 h. This mixture was washed with 5 mL of NH_4Cl (aqueous), the two layers were separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The remainder was filtered through a short plug of silica with CH_2Cl_2 and concentrated. Purification by preparative HPLC (1% EtOAc in hexane; 10.0 mL/min; 25 cm × 21.4 mm i.d.) yielded **15** as a clear, colorless oil (163 mg, 75%): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ −0.04 (t, J = 25.3, 9H, Me_3Sn), 1.36 (s, 9H, $C(CH_3)_3$), 1.46 (s, 3H, CH_3CN), 3.73 (s, 3H, OCH_3), 6.65−7.29 (m, 9H, Ar). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ −5.4 (t, J = 176.6 Hz, Me_3Sn); 22.7 (*C*H_3-CN); 28.3 (C(*C*H_3)$_3$); 55.2 (CH_3O); 56.6 (NCSn); 80.1 (*C*(CH_3)$_3$); 113.0, 124.2, 124.8, 127.98, 128.01, 129.7, 147.8, 157.4 (Ar); 157.7 (C═O); HRMS calcd for $C_{23}H_{33}NO_3{}^{116}$Sn (M^+) 487.1473, found 487.1477 (0.4 mDa).

Reaction of (*R*)-1-d_1 with *n*-BuLi/6. To a solution of **6** (0.13 mL, 0.576 mmol) in toluene (6.0 mL) at −78 °C was added *n*-BuLi (0.40 mL, 0.576 mmol). After 30 min, a solution of (*R*)-**1**-d_1 (151 mg, 0.480 mmol; 97% d_1) in toluene (4.0 mL) at −78 °C was added. After 1.5 h, methyl trifluoromethanesulfonate (0.065 mL, 0.576 mmol) was added. The resulting reaction mixture was then allowed to slowly warm to room temperature. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether, extraction of the combined diethyl ether extracts with saturated NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude mixture purified by column chromatography using EtOAc:petroleum ether (1:10) as eluent to give (*R*)-**8**-d_1 in 75% yield. The enantiomeric ratio was determined to be 60:40 by CSP HPLC (Whelk-O column; the *S* enantiomer (major) had a retention time of 21 min, and the *R* enantiomer (minor) had a retention time of 19 min.). The deuterium incorporation was determined to be 78% by FIMS.

Reaction of 1 with 1.5 and 0.1 Equiv of MeOTf in *t*-BuOMe To Provide (*S*)-8. To a solution of **6** (0.13 mL, 0.553 mmol) in *t*-BuOMe (6.0 mL) at −78 °C was added *n*-BuLi (0.38 mL, 0.553 mmol). After 30 min, a solution of **1** (144 mg, 0.460 mmol) in *t*-BuOMe (4.0 mL) at −78 °C was added. After 2 h, methyl trifluoromethanesulfonate (0.078 mL, 0.690 mmol) was added. After 1 h at −78 °C, 0.25 mL of CH_3OD was added and this mixture was allowed to warm slowly to ambient temperature. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether, extraction of the combined diethyl ether extracts with saturated NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude mixture purified by column chromatography using EtOAc:petroleum ether (1:10) as eluent to give (*S*)-**8** in 93% yield. The enantiomeric ratio was determined to be 92:8 by CSP HPLC (Whelk-O column; the *S* enantiomer (major) had a retention time of 21 min and the *R* enantiomer (minor) had a retention time of 19 min.). The deuterium incorporation was determined to be 1.1% by FIMS. The reaction with 0.1 equiv of MeOTf was carried out in a similar manner, except the reaction with 0.1 equiv of MeOTf was quenched with CH_3OD after 2 min to provide (*S*)-**8** in 2.4% yield (1.6% d_1, 96:4 er).

Preparation of *rac*-1-d_1. To a solution of TMEDA (0.30 mL, 1.98 mmol) in toluene (6.0 mL) at −78 °C was added *n*-BuLi (1.37 mL, 1.98 mmol). After 30 min, a solution of **1** (516 mg, 1.65 mmol) in toluene (4.0 mL) at −78 °C was added. After 2 h, MeOD (0.33 mL, 8.23 mmol) was added. The resulting reaction mixture was then allowed to slowly warm to room temperature. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether, extraction of the combined diethyl ether extracts with saturated NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude mixture purified by column chromatography using EtOAc:petroleum ether (1:10) as eluent to give rac-**1**-d_1 in 100% yield. The deuterium incorporation was determined to be 99% d_1 by FIMS.

Reaction of 1 and *rac*-1-d_1 with *n*-BuLi. To a solution of **6** (0.14 mL, 0.506 mmol) in toluene (6.0 mL) at −78 °C was added *n*-BuLi (0.42 mL, 0.607 mmol). After 30 min, a solution of *rac*-**1**-d_1 (159 mg, 0.506 mmol) in toluene (4 mL) at −78 °C was added. After 2 h, methyl trifluoromethanesulfonate (0.069 mL, 0.607 mmol) was added. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether, extraction of the combined diethyl ether extracts with saturated NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude mixture purified by column chromatography using EtOAc:petroleum ether (1:10) as eluent to give (*S*)-**8**-d_1 in 89% yield. The enantiomeric ratio was determined to be 68:32 by CSP HPLC (Whelk-O column; the *S* enantiomer (major) had a retention time of 21 min, and the *R* enantiomer (minor) had a retention time of 19 min.). The deuterium incorporation was determined to be 89% by FIMS. The reaction with **1** was carried out in a similar manner to provide (*S*)-**8** in 100% yield.

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