Stereospecificity and Stereoselectivity in Electrophilic Substitution Reactions of Non-α-Heterosubstituted Organolithiums and Stannanes: A Rotationally Restricted Amide as an Internal Stereochemical Marker

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Abstract: The complete stereochemical course of a tin−lithium exchange/electrophilic quench sequence has been unambiguously determined by stereochemical characterization (using X-ray crystallography or NOE studies) at every step. Pairs of diastereoisomeric stannanes of known stereochemistry bearing atropisomeric amide substituents undergo tin−lithium exchange with alkyllithiums to give diastereoisomeric benzylic organolithiums whose stereochemistry can be assigned by NMR. For one atropisomer of the stannanes, the tin−lithium exchange is fully stereospecific and proceeds with retention of stereochemistry. The other atropisomer undergoes nonstereospecific tin−lithium exchange: the first reported example of a lack of stereospecificity in electrophilic substitution of tin for lithium. One of the diastereoisomeric atropisomeric organolithiums produced by the tin−lithium exchange is deuterated and alkylated with retention but stannylated with inversion of stereochemistry. The other is alkylated nonstereospecifically but stannylated with retention.

Introduction

The conversion of C−Sn to C−Li bonds by electrophilic substitution (tin−lithium exchange) is the most important general way of making configurationally defined organolithiums, in particular those α to oxygen. Stereochemically pure α-alkoxystannanes may be transmetalated to organolithiums which react with electrophiles without erosion of stereochemical purity and with overall retention of stereochemistry.[1−3] The first demonstration of this stereospecificity was provided by Still in his seminal paper of 1980.[1a] His sequence of reactions started with stannane (±)-**2**, formed by purification of the major product of nucleophilic addition of Bu_3SnLi to aldehyde **1**. The stannane transmetalates stereospecifically to an organolithium presumed to be (±)-**3** which reacts stereospecifically with electrophiles, and the *overall* course of the reaction was proved to proceed with retention by re-stannylation with Bu_3SnI (Scheme 1).

That overall retention in similar systems is the norm later received firmer confirmation from studies of compounds where the stereochemistry of both stannane and final product could be unambiguously assigned.[1b,c] This has been widely assumed to imply that each individual step (transmetalation and quench) is retentive, but the same result could arise from a double inversion. This possibility may not withstand the more vigorous slicings of Ockham's razor,[4] but it must be borne in mind as a conceivable mechanistic pathway in some instances. It is now well-known that the stereospecificity of the reaction of a number of organolithiums with electrophiles is erratic, with many reported examples of organolithiums reacting with some electrophiles with retention and with others with inversion.[5]

Still was careful not to make any claims for the stereochemistry of the intermediate organolithium,[1a] but subsequent workers have frequently cited this paper in support of assumptions of retention in the tin−lithium exchange step. Statements such as "the method of Still and Sreekumar leads to α-lithio ethers with

(1) For representative examples of stereospecific tin−lithium exchange/electrophilic quench in α-alkoxystannanes, see: (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 3376. (c) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842. (d) Lesimple, P.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1985**, 894. (e) Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 4399. (f) Lindermann, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491. (g) Tomooka, K.; Igarishi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795. (h) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 8939.

(2) For representative examples of stereospecific tin−lithium exchange/electrophilic quench in other α-heterosubstituted stannanes, see: (a) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515. (b) Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077. (c) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546. (d) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (e) Beak, P.; Kerrick, S. T. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (f) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (g) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (h) Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679. (i) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. (j) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607. (k) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941. (l) Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089. (m) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (n) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322. (o) Brickmann, K.; Brückner, R. *Chem. Ber.* **1993**, *126*, 1227.

(3) For examples of stereospecific tin−lithium exchange/electrophilic quench in non-α-heterosubstituted stannanes, see: (a) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415. (b) Newman-Evans, R. H.; Carpenter, B. K. *Tetrahedron Lett.* **1985**, *26*, 1141. (c) Tanaka, K.; Minami, K.; Funaki, I.; Suzuki, H. *Tetrahedron Lett.* **1990**, *31*, 2727. (d) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.

(4) Hoffmann, R. *Bull. Soc. Chim. Fr.* **1996**, *133*, 117.

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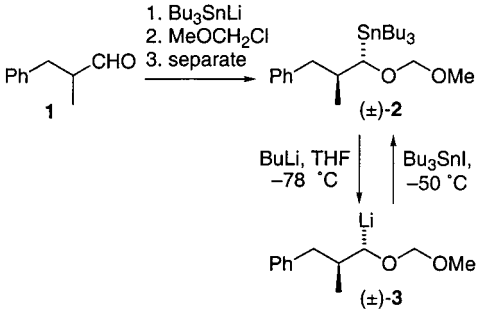
Scheme 1. Stereospecific Tin−Lithium Exchange

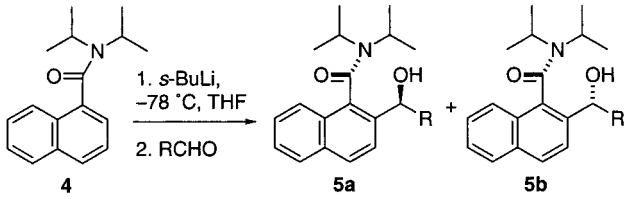


retention",[1e] "retention of stereochemistry is well-known for the generation of α-heterosubstituted organometallics",[2c] "the lithium−tin transmetalation proceeds with retention of configuration at carbon",[6] and "enantiomerically defined α-alkoxyorganolithiums ... can be generated stereospecifically (retention of configuration) from easily obtainable enantio-enriched stannanes"[1h] are common. They are probably correct in most cases, but they remain unproven.

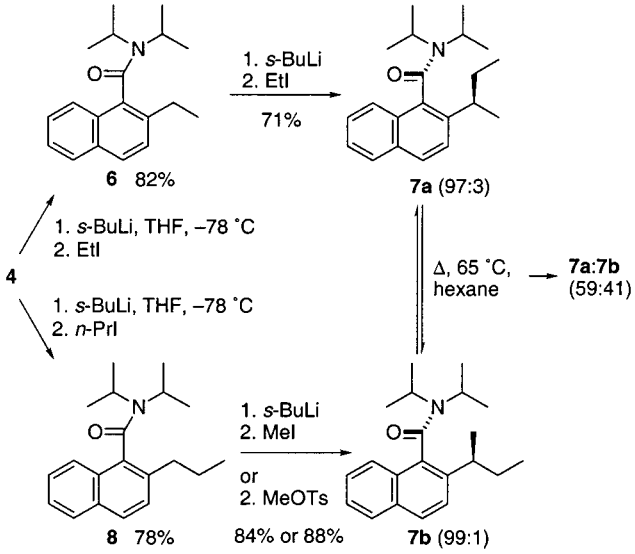
The missing piece of evidence is the stereochemistry of the intermediate organolithium. Retention of two-dimensional stereochemistry during a tin−lithium exchange is, by contrast, proven beyond doubt by direct spectroscopic assignment of geometry to both vinylstannanes and vinyllithiums.[7] Absolute or relative three-dimensional stereochemistry in an organolithium is much harder to prove spectroscopically, and the firmest evidence for a retentive tin−lithium exchange is Hammerschmidt's[5l] demonstration that the same α-heterosubstituted organolithium is formed both by deprotonation of a hindered aryl ester of known absolute configuration and by transmetalation of a stannane of crystallographically proven stereochemistry.

In this paper,[8] we provide clarification of the stereochemical course of a series of electrophilic substitutions of stannanes and their derived organolithiums lacking an α-heterosubstituent. We describe (a) the first direct spectroscopic observation of the stereochemistry of an organolithium produced by tin−lithium exchange, allowing us for the first time to assess the stereospecificity of the reaction; (b) the first example of a tin−lithium exchange which is demonstrably not stereospecific; and (c) the varying stereospecificity of the reaction of the organolithiums with electrophiles.

Scheme 2. Atropisomeric Tertiary 1-Naphthamides



Scheme 3. Atroposelective Lateral Alkylation



Results and Discussion

We used for our investigations some tertiary 1-naphthamides, typified by **6**, which have two important characteristics worth highlighting. First, they are chiral compounds,[9,10] with the amide perpendicular to the aromatic ring.[11] The barrier to rotation about the Ar−CO bond is sufficiently high that **6**, for example, can be resolved into enantiomers which racemize over a period of days in solution at ambient temperature,[12] and the addition of lithiated *N*,*N*-diisopropyl-1-naphthamide **4** to aldehydes gives a mixture of stable diastereoisomeric atropisomers **5a** and **5b** (Scheme 2).[10,13] This reaction illustrates the second important feature of these compounds: their ease of construction via lithiation at an ortho[14] or a lateral[15] position.

On two successive treatments with *s*-BuLi and EtI, **4** gave **6** and then **7a** (Scheme 3). The second lithiation−quench reaction was highly stereoselective, and **7a** was produced almost as a single diastereoisomer (97:3 by HPLC) whose structure was determined by X-ray crystallography (Figure 1). The other diastereoisomer, **7b**, was made from **4** using a different pair of lithiation−quench reactions, first with propyl iodide to give **8**, and then by methylation. Diastereoisomer **7b** was formed

(5) References 2i, 3d, and the following: (a) Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297. (b) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344. (c) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763. (d) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed.* **1990**, *29*, 1424. (e) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (f) Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149. (g) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed.* **1995**, *34*, 2158. (h) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141. (i) Behrens, K.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Eur. J. Org. Chem.* **1998**, *2397*, 7. (j) Derwing, C.; Frank, H.; Hoppe, D. *Eur. J. Org. Chem.* **1999**, 3519. (k) Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 1069. (l) Hammerschmidt, F.; Hanninger, A.; Völlenkle, H. *Chem.—Eur. J.* **1997**, *3*, 1728. (m) Hammerschmidt, F.; Hanninger, A.; Simov, B. P.; Völlenkle, H.; Werner, A. *Eur. J. Org. Chem.* **1999**, 3511. (n) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (o) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem.—Eur. J.* **1999**, *5*, 2055.

(6) Reich, H. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577.

(7) Seyferth, D.; Vaughan, L. G. *J. Am. Chem. Soc.* **1964**, *86*, 883. It is revealing to compare the methods available for determining stereospecificity in the transmetalation of vinylmetals prior to 1964 with those generally used for determining three-dimensional stereospecificity in present-day studies of tin−lithium exchange: Curtin, D. Y.; Crump, J. W. *J. Am. Chem. Soc.* **1958**, *80*, 1922. Nesmeyanov, A. N.; Borisov, A. E. *Tetrahedron* **1957**, *1*, 158.

(8) Preliminary communications: (a) Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *39*, 2561. (b) Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565.

(9) (a) Cuyegkeng, M. A.; Mannschreck, A. *Chem. Ber.* **1987**, *120*, 803. (b) Clayden, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 949.

(10) Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2607.

(11) Bond, A. D.; Clayden, J.; Wheatley, A. E. H. *Acta Cryst. E* **2001**, *57*, 291.

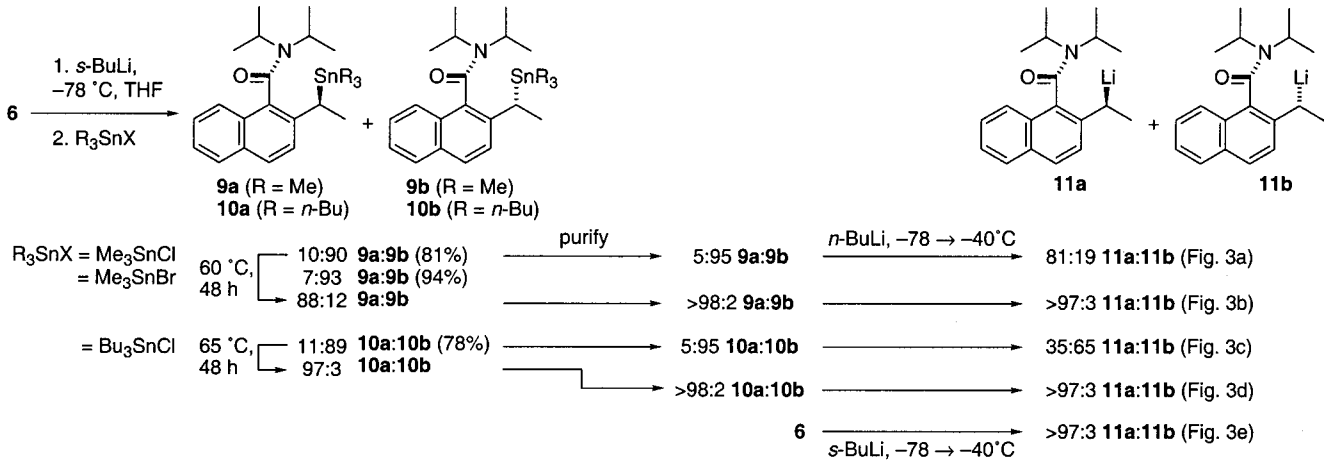
(12) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.

(13) Bowles, P.; Clayden, J.; Tomkinson, M. *Tetrahedron Lett.* **1995**, *36*, 9219.

(14) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(15) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.

Scheme 4. Formation and Transmetalation of Diastereoisomeric Pairs of Stannanes **9** and **10**



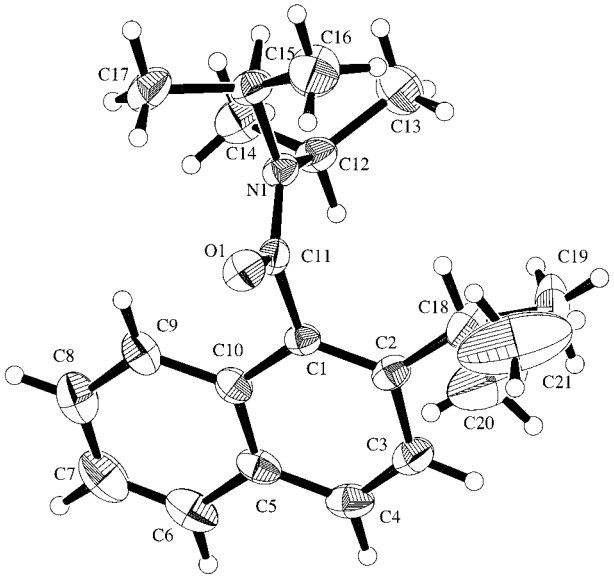


Figure 1. X-ray crystal structure of **7a**.

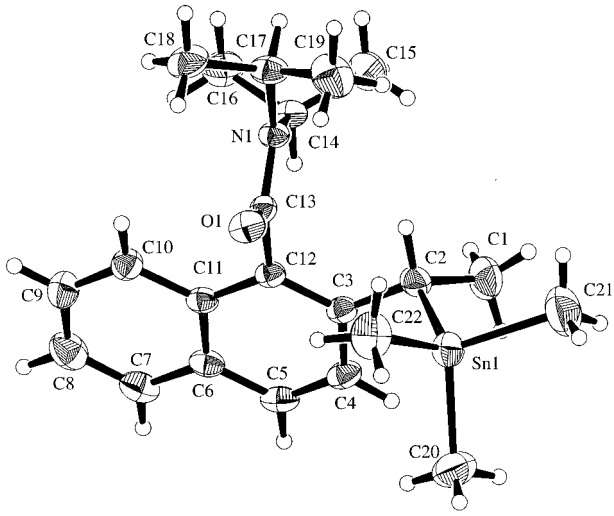


Figure 2. X-ray crystal structure of **9a**.

with 99:1 stereoselectivity (Scheme 3) using either methyl iodide or methyl tosylate. The two atropisomers **7a** and **7b** could be interconverted by heating to 65 °C: after 48 h at this temperature, each diastereoisomer had equilibrated to a 59:41 mixture of **7a**:**7b** which remained unchanged on further heating.[12,16]

For our tin−lithium exchange work, we needed pairs of diastereoisomeric stannanes **9a** and **9b**, and **10a** and **10b**. These were easily made from **6**, which was lithiated and quenched with Me_3SnCl or Me_3SnBr to give mainly **9b** or with Bu_3SnCl to give mainly **10b** as shown in Scheme 4. These samples of **9b** and **10b** could be enriched to 95% purity by rapid, cold flash chromatography. Alternatively, the samples could be epimerized to **9a** and **10a**. Thermodynamic equilibrium was attained after 48 h at 60−65 °C, and fortunately, equilibration more or less reversed the diastereoisomeric ratios of **9** and **10**: the equilibrated mixtures contained 88% **9a** and 97% **10a**, respectively (equilibration begins to occur even at room temperature, hence the difficulties in purifying **9a** and **10a**). Residual **9b** and **10b** could be removed by flash chromatography to give pure samples of **9a** and **10a**. Stereochemistry was unambiguously assigned to **9a** (and hence **9b**) by an X-ray crystal structure (Figure 2); the stereochemistry of **10a** and **10b** is assigned by analogy.

We treated the purified stannanes **9a**, **9b**, **10a**, and **10b** with *n*-BuLi at −78 °C in d_8-THF in an NMR tube. For comparison, **6** was lithiated at −78 °C with *s*-BuLi, and the ^{1}H NMR spectrum of all five solutions was run at −40 °C. Figure 3 shows portions of the spectra we obtained, which were unchanged when they were run a second time after 1 h at −40 °C. Each spectrum shows one or both of two species, which we assume to be organolithiums **11a** and **11b**, in ratios quantified in Scheme 4.

We can immediately draw several conclusions from these spectra. First, because the spectra in Figure 3 are not all the same and remain not the same after 1 h at −40 °C, organolithiums **11a** and **11b** must be configurationally stable[17] at −40 °C. This is of itself remarkable: most benzylic organolithiums are configurationally unstable unless they are α-heterosubstituted,[18] and indeed, the otherwise very similar organolithium **12** has been shown to be configurationally unstable even at −78 °C.[5n] There are two possible reasons for this difference in configurational stability: one is that a difference in Ar−CO dihedral angle between the benzamide

(16) Of course, epimerization interconverts the two racemic diastereoisomers of **7** through rotation about the Ar−CO bond. To simplify later discussions, one diastereoisomer is pictured as its enantiomer with respect to this interconversion.

(17) "Configurational stability" here refers to the stereogenic center bearing Li and not to the rotationally restricted amide. The amide's barrier to rotation is such that at −78 °C we expect the half-life for interconversion of diastereoisomers to exceed 1 000 000 years (ref 12).

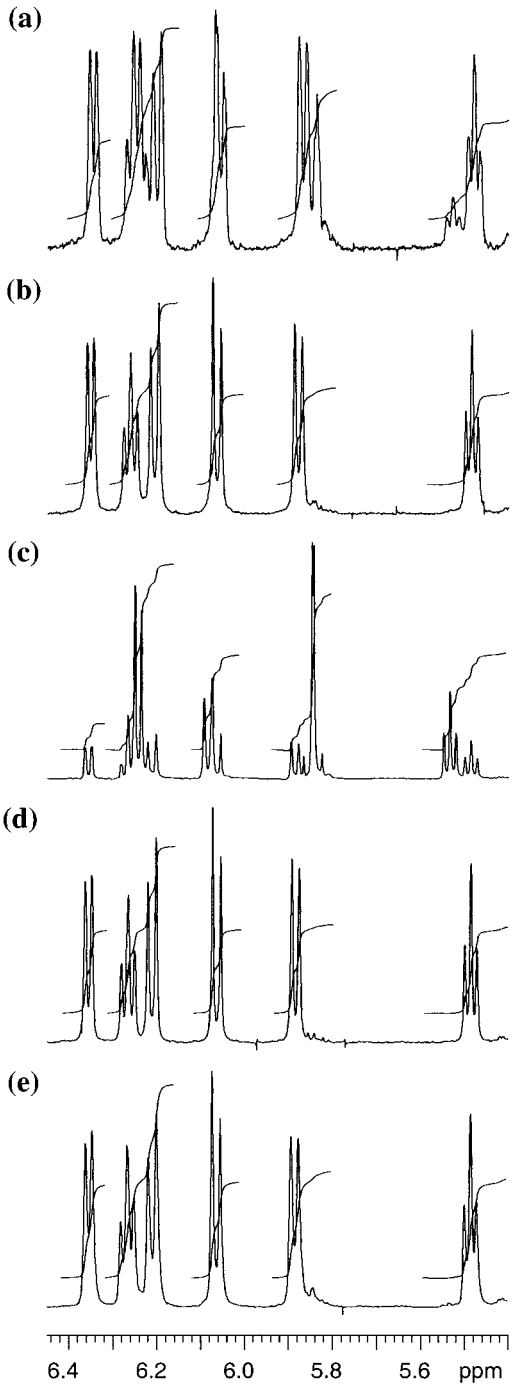


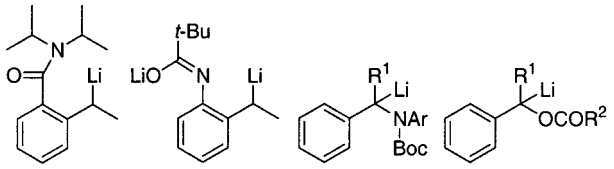
Figure 3. ^{1}H NMR spectra of mixtures of **11a** and **11b**: (a) transmetalation of **9b**, (b) transmetalation of **9a**, (c) transmetalation of **10b**, (d) transmetalation of **10a**, and (e) lithiation of **6**.

and the naphthamide leads to very different anion structures. The benzamide **12**, for example, may be able to keep the amide and ring more nearly coplanar, stabilizing a conjugated trigonal (planar) anion as well as permitting a greater degree of intramolecular O−Li coordination. The more perpendicular amide group of the naphthamide **11**, by contrast, might lead to a less delocalized, more tetrahedral (and therefore more configurationally stable) organolithium, with less O−Li coordination.[19] An alternative explanation is simply that the solvents are different: Beak's work was carried out in *tert*-butyl methyl ether and pentane in the presence of (−)-sparteine; ours is in THF.[20] Later results (see Table 1) allowed us to show that **11** has configurational stability even in *t*-BuOMe/pentane.

Table 1. Stereospecificity of Reactions of **11a** and **11b**

entry	stannane[a]	RLi	E^+, product	expected ratio of **11a**:**11b** on transmetalation[b]	product ratio *d*-**6**, **7**, or **9**; **a**:**b**
1	**9a**	*n*-BuLi	EtI, **7**	>97:3	97:3
2	**8a**	*n*-BuLi	EtI, **7**	>97:3	98:2
3	**9a**	*n*-BuLi	Me_3SnCl, **9**	>97:3	10:90
4	**9b**	*n*-BuLi	EtI, **7**	81:19	91:9
5	**10b**	*n*-BuLi	EtI, **7**	35:65	60:40
6	**9b**	*n*-BuLi	Me_3SnCl, **9**	81:19	<2:98
7	**10a**	*n*-BuLi[c]	EtI, **7**		98:2
8	**10b**	*n*-BuLi[c]	EtI, **7**		60:40
9	**10b**	*n*-BuLi[d]	EtI, **7**		64:36
10	**10a**	*n*-BuLi[e]	D_2O, *d*-**6**		92:8
11	**10b**	*n*-BuLi[e]	D_2O, *d*-**6**		18:82
12	**9a**	MeLi	EtI, **7**		98:2
13	**9b**	MeLi	EtI, **7**		98:2
14	**9a**	PhLi	EtI, **7**		98:2
15	**9b**	PhLi	EtI, **7**		93:7

[a] Chromatographically purified stannanes were used: **9a** and **10a** were >99% pure by HPLC; **9b** and **10b** contained 4−5% of **9a** and **10a**, respectively. [b] Values obtained from the spectra in Figure 1. [c] Organolithium warmed to −40 °C for 1 h prior to quenching at −78 °C. [d] Organolithium warmed to −25 °C for 5 min prior to quenching at −78 °C. [e] Reaction carried out in *t*-BuOMe/pentane.



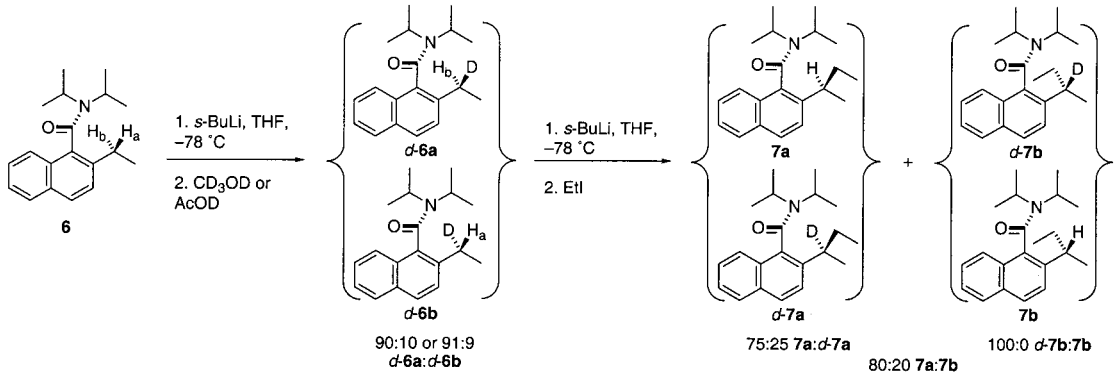
12 **13** **14** **15**

Second, because spectra b, d, and e in Figure 3 are almost identical and clearly contain only one species, tin−lithium exchange of **9a** and **10a** must give a single, clean organolithium, and that organolithium is identical to the one produced simply by deprotonating **6** with *s*-BuLi, a reaction which is itself highly diastereoselective. The transmetalation of **9a** and **10a** is therefore fully stereospecific, though at this stage we could not be sure that it goes with 100% retention and not 100% inversion.

Third, *neither **9b** nor **10b** transmetalate stereospecifically*. Compound **9b** transmetalated largely to **11a**, the same organolithium as that produced from **9a**, giving only 19% **11b**. Transmetalation of **10b** is somewhat more stereospecific, giving only 35% **11a** and 65% **11b**. To our knowledge, these are the first nonstereospecific tin−lithium exchanges ever reported.

(18) Non-α-heterosubstituted *secondary* benzyllithiums are configurationally unstable: (a) Hoffmann, R. W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* **1992**, 719. (b) Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210. (c) Kato, T.; Marumoto, S.; Sato, T.; Kuwajima, I. *Synlett* **1990**, 671. One notable exception: (d) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209. Non-α-heterosubstituted *tertiary* benzyllithiums have slightly greater configurational stability: (e) Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709. (f) Paquette, L. A.; Ra, C. S. *J. Org. Chem.* **1988**, *53*, 4978. (g) Hoell, D.; Lex, J.; Müllen, K. *Angew. Chem., Int. Ed.* **1983**, *22*, 243. (h) Bousbaa, J.; Ooms, F.; Krief, A. *Tetrahedron Lett.* **1997**, *38*, 7625. α-Alkoxy benzyllithiums are typically configurationally stable when tertiary, less so when secondary; see refs 5d−f,i,k, and (i) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed.* **1989**, *28*, 69. α-Amino benzyllithiums may have low configurational stability: (j) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5505. (k) Ahlbrecht, H.; Harbach, J.; Hoffmann, R. W.; Ruhland, T. *Liebigs Ann. Chem.* **1995**, 211. (l) Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem.* **1992**, 725. When the nitrogen is acylated, configurational stability is the norm; see ref 2i and (m) Hara, O.; Ho, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537 but see also ref 2g. Lithiated benzylsulfoxides and sulfones are configurationally stable, but lithiated benzylsufides, selenides, and silanes are not; see ref 16k,l and (n) Tanikaga, R.; Hamamura, K.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1988**, 817.

Scheme 5. Proving the Stereochemistry of the Organolithium



The X-ray crystal structure of **9a** (Figure 2) lends certainty to our assignment of stereochemistry of starting stannanes **9** and **10**,[21] but in order to clarify fully the stereochemical course of the transmetalation, we needed to be equally certain about the stereochemistry of organolithiums **11a** and **11b**. The lack of stereospecificity in some similar reactions[5] warned us to avoid jumping to hasty conclusions about the sense of stereospecificity (inversion or retention) in any of the electrophilic substitutions, so we aimed to rely on firm correlations with crystallographically or spectroscopically proven stereochemistry for our assignments.

Although we had a crystal structure of the product of **11a** (formed by lithiation of **6**) with ethyl iodide (Scheme 3), the erratic stereospecificity of the reactions of alkyl halides with benzylic organolithiums[5] prevents us from drawing firm conclusions about the stereochemistry of **11a**. However, **11a** also reacted stereoselectively with CD_3OD and with AcOD (Scheme 5). In C_6D_6 solution, the ^{1}H NMR spectrum of **6** (Figure 4a) shows a clear ABX_3 system for the 2-ethyl group. Lithiation and deuteration gave, in quantitative yield, a mixture of diastereoisomers of *d*-**6** in whose ^{1}H NMR spectrum (Figure 4b) the downfield signal of the AB part of the system is diminished to only 10% of one proton. We therefore conclude that **11a** is deuterated by both reagents with ~90:10 stereoselectivity.

All known deuterations of organolithiums with deuterated alcohols proceed with retention of stereochemistry,[22] and we were able to confirm that the deuteration of **11a** is no exception by *re-lithiating* deuterated product *d*-**6**.[23] Had the major deuterated diastereoisomer of *d*-**6** been formed with *inversion*, we would expect this re-lithiation to proceed much as did the first lithiation reaction, subject perhaps to a small *secondary* kinetic isotope effect; certainly, we would expect an ethyl iodide quench to give back the same diastereoisomer **7a** as we obtained from **6** (Scheme 3) and for this diastereoisomer to be largely

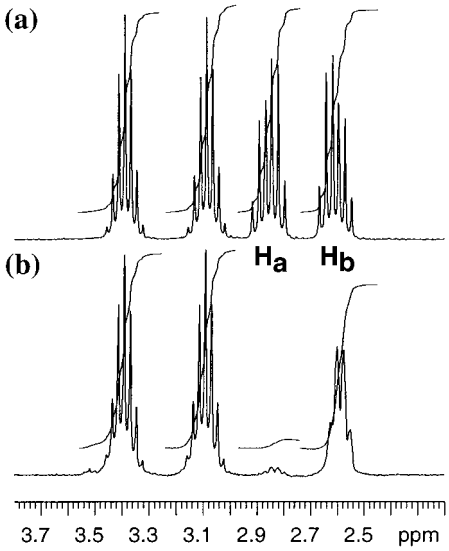


Figure 4. Deuteration of **6**: (a) ^{1}H NMR spectrum of **6** and (b) ^{1}H NMR spectrum of the 90:10 mixture of *d*-**6a** and *d*-**6b**.

deuterated. Instead, when we re-lithiated *d*-**6** and quenched with ethyl iodide, we obtained the product mixture shown in Scheme 5. Most of the product was indeed **7a**, but there was a severe erosion of stereoselectivity to give only a 80:20 ratio of diastereoisomers **7a**:**7b**. Moreover, most of the **7a** which was formed was no longer deuterated, meaning that, notwithstanding any primary kinetic isotope effect, re-lithiation has largely removed the deuterium from *d*-**6**. We are thus forced to conclude that the major diastereoisomer of *d*-**6** has the relative stereochemistry as **11a**: in other words, the deuteration proceeds with retention of stereochemistry.

The loss of stereospecificity compared to the lithiation−EtI quench of undeuterated **6** arises because now a *primary* kinetic isotope effect is operative. The rate of removal of the deuterium from *d*-**6a** is now slowed sufficiently that the rate of removal of proton H_b from *d*-**6a** is competitive. Removal of H_b gives diastereoisomeric organolithium **11b** in deuterated form and, hence, ethylated and deuterated diastereoisomer *d*-**7b**. We can in fact assign an approximate magnitude to this kinetic isotope effect by assuming the rate of removal of H_b from *d*-**6a** is the same as the rate of removal of the same proton H_b from **6**: we shall call this rate k_{H_b}. Similarly, call the rate of removal of H_a from **6** k_{H_a} and the rate of removal of D from *d*-**6a** k_D. The ratio of deuterated **7** (both diastereoisomers) to nondeuterated **7** (both diastereoisomers) from Scheme 5 is 60:40, but 10% of this total material will be *d*-**7a** arising from *d*-**6b**, so the true ratio of k_{H_b} to k_D must be close to 1. The ratio of k_{H_a} to k_{H_b} is >95:5, as shown by Figure 3e, so k_{H_a}/k_D (the primary kinetic

(19) We have recently described just such a difference between an ortholithiated benzamide and naphthamide in the solid state: Clayden, J.; Davies, R. P.; Hendy, M. A.; Snaith, R.; Wheatley, A. E. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1238.

(20) The difference is made even more surprising by the fact that THF can lower configurational stability (ref 5k) and that a 2-naphthylmethyllithium has been reported to be less configurationally stable than a comparable benzyllithium (ref 5f).

(21) The relative thermodynamic stabilities of the atropisomers of **9** and **10** support the expectation that both Me_3SnCl and Bu_3SnCl react with the same sense of stereospecificity. Spectroscopic evidence is also consistent: the $^2J_{Sn-H}$ coupling constants in **9a** and **10a** are consistently larger than those in **9b** and **10b**.

(22) Earlier reports (ref 5e) that deuteration using deuterated carboxylic acids or their ammonium salts proceeds with inversion have been corrected (ref 5k,f) but there is still some uncertainty in this area; see ref 5o.

(23) For comparable proof of organolithium stereochemistry, see: Kopach, M. E.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 6764.

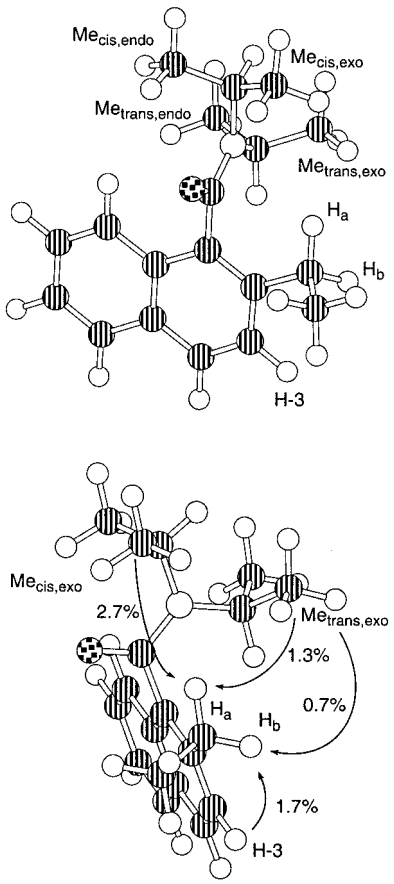


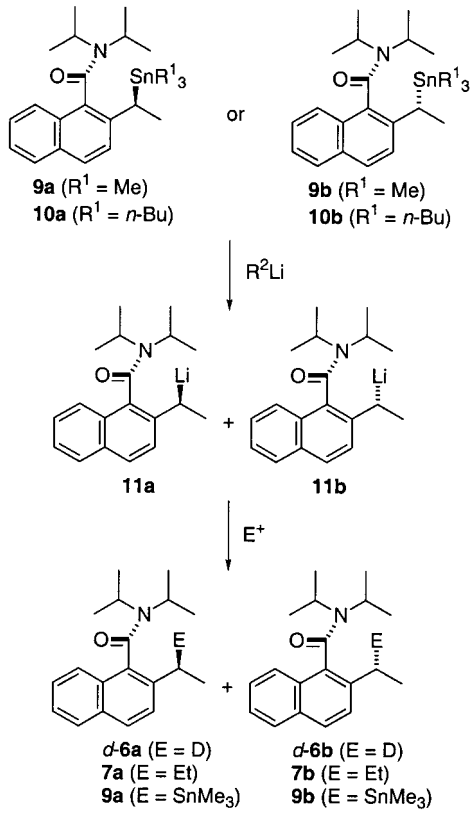
Figure 5. Assignment of stereochemistry to H_a and H_b of **6** by NOE.

isotope effect for lateral deprotonation) must therefore exceed 20 at −78 °C.[24]

In summary, Scheme 4 tells us that organolithium **11a** has the same stereochemistry as the deuterated amide *d*-**6a**. To determine the stereochemistry of *d*-**6a**, we carried out some NOE experiments. Tertiary aromatic amides typically have well-defined conformations, which we have been able to exploit in a series of stereocontrolled reactions,[25] and these precedents, along with molecular modeling (MM2), indicated that the lowest energy conformation of **6** approximates that shown in Figure 5. The aromatic region of the spectrum of **6** was assigned by COSY and NOESY. NOE experiments then allowed the assignment of stereochemistry to H_a and H_b. Irradiation of H-3 gave a clear enhancement of H_b (1.7%, <0.2% NOE of H_a), and irradiation of the two *exo* methyl doublets enhanced H_a to a greater extent than H_b. These NOEs allowed us to assign H_a and H_b in Scheme 5 as the upfield and downfield protons of Figure 4, respectively, and hence allow the assignment of stereochemistry to *d*-**6a** and hence **11a**.

Proof of the stereochemistry of **11a** allows us to be sure of the following: lithiation of **6** removes proton H_a to give configurationally stable organolithium **11a**, which reacts with

Scheme 6. Investigating the Stereospecificity of the Reactions of **11**



CD_3OD or with EtI (we already know the stereochemistry of **7a** from its crystal structure, Figure 1) with retention of stereochemistry. Organolithium **11a** reacts, however, with Me_3SnCl, Me_3SnBr, and Bu_3SnCl with predominant *inversion*, giving **9b** and **10b**.

We also investigated the stereospecificity of the reactions of both **11a** and **11b** by treating the mixture of organolithiums formed by transmetallating **9** or **10** with an electrophile (Scheme 6). The results of transmetallating mixtures of diastereoisomers of **9** or **10** with alkyllithiums and quenching with electrophiles are given in Table 1.

From Figure 3, we know that both **9a** and **10a** transmetalate with full stereospecificity to give **11a**, and the results presented in entries 1−3 of Table 1 are in full accord with reactions of **11a** identical to those already presented in Scheme 4: full retention with EtI (entries 1 and 2) to give **7a** and 90% inversion with Me_3SnCl to give 10:90 **9a**:**9b** (entry 3). Figure 3 also showed that **9b** and **10b** transmetalate nonstereospecifically, giving **11a** and **11b** in 35:65 and 81:19 ratios, respectively. Entries 4−6 reveal the result of reacting these mixtures of **11a** and **11b** with electrophiles. In entry 4, an 81:19 mixture of **11a** and **11b** generates a 91:9 mixture of **7a** and **7b**, while, in entry 5, a 35:65 mixture of **11a** and **11b** generates a 60:40 mixture of **7a** and **7b**. Because **11a** is known to give only **7a**, **11b** must react with EtI nonstereospecifically, giving a ratio of between 1:1 and 2:1 **7a** and **7b**. On quenching with Me_3SnCl, the 81:19 mixture of **11a** and **11b** generates solely **9b** (entry 6). Because **11a** typically transmetalates to 10:90 **9a**:**9b**, this result can be explained only if **11b** reacts with Me_3SnCl with complete *retention*. Entries 7−9 confirm that transient warming of **11** to −40 °C (entries 7 and 8) or −25 °C (entry 9) has no appreciable effect on the stereochemical outcome of the reactions, confirming the configurational stability of **11**. Entries 10 and 11 show that changing from THF to

(24) See also: (a) Clayden, J.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1998**, *39*, 8377. Values for k_H/k_D for lithiation reactions at low temperature may have very large kinetic isotope effects. See, for example: (b) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed.* **1993**, *32*, 394. (c) Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553.

(25) (a) Clayden, J. *Synlett* **1998**, 810. (b) Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998**, *39*, 105. (c) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033. (d) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556. (e) Clayden, J.; Lai, L. W. *Tetrahedron Lett.* **2001**, *42*, 3163. (f) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1999**, *40*, 3331.

Table 2. Stereospecificity in the Reactions of Benzylic Organolithiums

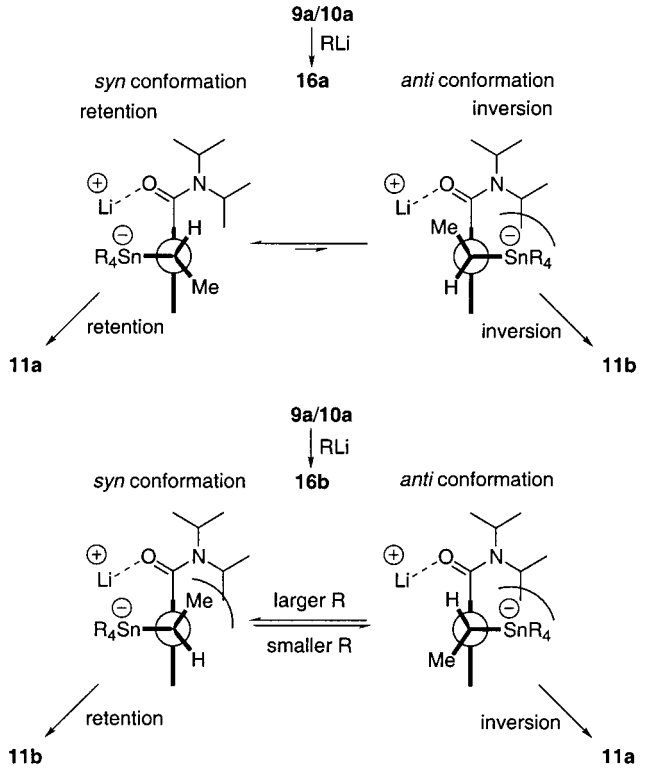
	electrophile				
	ROD	$ROSO_2R'$	RI	R_3SiCl	Me_3SnCl
11a or **8**-Li	retention	retention	retention	retention	inversion
11b			mixture		retention
13			inversion	inversion	inversion
14	retention	inversion			inversion
15	retention	inversion	inversion	inversion	inversion

t-BuOMe−pentane still permits the stannanes to react stereospecifically, ruling out solvent as the factor conferring greater configurational stability on **11** than **12**. Entries 12−15 are discussed below.

That organolithiums **11** react with some electrophiles with retention and some with inversion is to be expected: erratic stereospecificity is well precedented in the reactions of benzylic organolithiums.[5] For comparison, Table 2 summarizes the reactions of **11** (or lithiated **8**) along with those of comparable benzylic organolithiums **13**,[3d] **14**,[2i] and **15**.[5d−f,j−m]

Knowing the stereochemistry of every compound in the sequence from stannane through organolithium to product of electrophilic quench enables us to be absolutely certain that (a) stannanes **9a** and **10a** undergo stereospecific tin−lithium exchange with complete retention of stereochemistry and (b) stannanes **9b** and **10b** undergo nonstereospecific tin−lithium exchange, with **9b** giving predominant inversion and **10b** giving predominant retention. Entries 12−15 of Table 1 indicate that stereospecificity of tin−lithium exchange with **9b** is dependent on the organolithium used. Comparison of entries 4, 13, and 15, for example, shows that the highest degree of *invertive* tin−lithium exchange is obtained with MeLi, followed by PhLi and then *n*-BuLi. The reason for the lack of stereospecificity in these transmetalations is far from clear but is perhaps a more general feature of nonheterosubstituted organolithiums than so far appreciated, because stereospecificity has been studied in detail only for α-heterosubstituted organolithiums.[3] The transmetalation probably proceeds via stannate intermediate **16**[26] which may collapse to give either diastereoisomeric organolithium depending on the direction of attack on the C−Sn bond by Li^+.[27] Likely conformations[22] of the ate complexes **16a** and **16b** derived from **9a**/**10a** and **9b**/**10b** are shown in Scheme 7. In the absence of data on the relative rates of formation, conformational change, and collapse of the ate complexes, it is impossible to propose a detailed rationale for the variation in stereospecificity. However, we expect that **16a**, in common with **9a** and **10a**, unambiguously prefers the syn conformation shown in Scheme 7, in which delivery of either RLi or Li^+ can take place in such a way that retentive transmetalation occurs. The preferred conformation of **16b** (and **9b** and **10b**), on the other hand, is presumably less clear-cut: either the tin or the methyl substituent must lie close to the bulky NR_2 group on the amide, and population of the anti conformer could lead to invertive transmetalation. It is interesting to note that a higher proportion of inversion was observed in the transmetalation of **9b** than in the transmetalation of **10b**, and more inversion was observed with smaller organolithiums RLi, perhaps because of a shift of the conformational equilibrium of **16b** to the right with smaller tin substituents or preferential attack by larger organolithiums on the less crowded tin substituent in the syn conformation.

Scheme 7. Rationale for Varying Stereospecificity



Experimental Section

The synthesis of amides **4**[10] and **6**[12] has been described previously. Flash chromatography was performed by the method of Still, Kahn, and Mitra.[28] HPLC analyses were performed on a Phenosphere 100 × 8.00 mm 5 μm silica column, 80 Å, using a Perkin-Elmer LC-480 diode array system with 0.5% ethanol in hexane as eluant, a 2 mL/min flow rate, and UV detection at 280 nm. The workup of atroposelective reactions was performed with cool solvents which were evaporated at room temperature or below.

***N,N*-Diisopropyl-2-propyl-1-naphthamide 8.** *sec*-Butyllithium (1.66 mL, 1.3 M solution in cyclohexane, 2.15 mmol) was added dropwise to a solution of *N,N*-diisopropyl-1-naphthamide **4**[10] (0.50 g, 1.96 mmol) in THF (60 mL), cooled to −78 °C under an atmosphere of nitrogen. The solution was stirred at −78 °C for 1 h. Propyl iodide (0.38 mL, 3.92 mmol) was added, and the solution was allowed to warm to room temperature over 30 min, by which time the solution had turned colorless. Water (30 mL) was added, and the THF was removed under reduced pressure. The aqueous phase was then extracted with dichloromethane (3 × 20 mL), the combined organic extracts were washed with water (30 mL), dried over magnesium sulfate, and filtered, and the solvent was evaporated. The residual off-white solid was purified by flash chromatography [5% ethyl acetate in light petroleum (R_f 0.43, 10% ethyl acetate)] to afford amide **8** as a white solid (0.45 g, 78%); mp 120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.86−7.76 (3H, m, ArH), 7.54−7.42 (2H, m, ArH), 7.41 (1H, d, J = 8.5, ArH), 3.72−3.50 (2H, m, 2 × NCH), 2.87−2.61 (2H, m, $ArCH_2$), 1.97−1.60 (2H, m, $ArCH_2CH_2$), 1.82 (3H, d, J = 6.7, $NCHCH_3$), 1.73 (3H, d, J = 6.7, $NCHCH_3$), 1.12 (3H, d, J = 6.7, $NCHCH_3$), 1.05 (3H, t, J = 7.3 Hz, CH_2CH_3), 1.02 (3H, d, J = 6.6, $NCHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.5 (s, CO), 135.3 (s, Ar), 134.2 (s, Ar), 131.8 (s, Ar), 129.7 (s, Ar), 127.8 (d, Ar), 127.6 (d, Ar), 127.1 (d, Ar), 126.3 (d, Ar), 125.3 (d, Ar), 124.8 (d, Ar), 50.9 (d, NCH), 46.0 (d, NCH), 35.5 (t, $ArCH_2$),

(26) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1290. (c) Reich, H. J.; Phillips, N. H. *J. Am. Chem. Soc.* **1986**, *108*, 2102. (d) Ashe, A. J.; Lohr, L. L.; Al-Taweel, S. M. *Organometallics* **1991**, *10*, 242.

(27) There is evidence that the stereospecificity of the transmetalation changes as the reaction proceeds, perhaps because of a buildup of lithium salts. For example, repeating the reaction in entry 5 of Table 1, but with EtI added after only 5 min, gave 72% of recovered **10b**, but the 28% of **7** was formed in a 79:21 ratio of **7a**:**7b**. After 20 min, a 59% yield of **7** was formed in a ratio of 78:22 of **7a**:**7b**.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2943.

24.2 (t, $ArCH_2CH_2$), 21.1 (q, $NCHCH_3$), 20.1 (q, $NCHCH_3$), 20.6 (q, $NCHCH_3$), 20.4 (q, $NCHCH_3$), 14.3 (q, CH_2CH_3); IR (Nujol mull) ν_{max} 1615 cm^{-1}; *m/z* (CI^+) 298 (100%), 256 (5%), 197 (3%); M^+ 297.2093 ($C_{20}H_{27}NO$ requires 297.2090). Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71%. Found: C, 80.40; H, 9.40; N, 4.58%.

(*aR*,S)-2-(But-2-yl)-*N*,*N*-diisopropyl-1-naphthamide 7a.** *sec*-Butyllithium (0.18 mL, 0.233 mmol) was added dropwise to a solution of amide **6** (60 mg, 0.212 mmol) in THF (30 mL), cooled to −78 °C under an atmosphere of nitrogen. The resultant dark green solution was stirred at −78 °C for 1 h. Ethyl iodide (34 μL, 0.424 mmol) was added. The solution was allowed to warm to 0 °C, water (20 mL) was added, and the THF was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 15 mL), the combined organic layers were washed with water (20 mL), dried over magnesium sulfate, and filtered, and the solvent was evaporated to give amide **7a** as a white solid (78 mg, 71%); mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.86−7.78 (3H, m, ArH), 7.54−7.41 (3H, m, ArH), 3.69−3.55 (2H, m, 2 × NCH), 2.98−2.83 (1H, m, ArCH), 1.82 (3H, d, J = 6.9, $NCHCH_3$), 1.72 (3H, d, J = 7, $NCHCH_3$), 1.80−1.55 (2H, m, CH_2), 1.35 (3H, d, J = 6.7, $CHCH_3$), 1.14 (3H, d, J = 6.7, $NCHCH_3$), 1.02 (3H, d, J = 6.9, $NCHCH_3$), 0.84 (3H, t, J = 8, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.5 (s, CO), 140.3 (s, Ar), 133.7 (s, Ar), 132.1 (s, Ar), 129.8 (s, Ar), 128.1 (d, Ar), 127.9 (d, Ar), 126.4 (d, Ar), 125.5 (d, Ar), 125.2 (d, Ar), 123.8 (d, Ar), 50.8 (d, NCH), 46.1 (d, NCH), 37.8 (d, ArCH), 31.8 (t, CH_2), 21.1 (q, $NCHCH_3$), 20.9 (q, $NCHCH_3$), 20.6 (q, $NCHCH_3$), 20.6 ($CHCH_3$), 20.5 (q, $NCHCH_3$), 12.2 (q, CH_2CH_3); IR (evaporated film) ν_{max} 1621 cm^{-1}; *m/z* (CI^+) 312 (M + H, 100%), 211 (11%), 210 (3%); M^+ 311.2249 ($C_{21}H_{29}NO$ requires 311.2247). Recrystallization from EtOAc gave crystals suitable for X-ray analysis, see in a following section.

HPLC analysis of the crude product mixture showed t_R = 8.28 min (96.9%) for **7a** and 9.36 min (3.1%) for **7b**. When the reaction was carried out at −40 °C, with cooling to −78 °C prior to ethyl iodide quench, the ratio was 96.5:3.5% **7a**:**7b**.

An identical reaction using deuterated amide *d*-**6** (see below) as the starting material gave the yields and results shown in Scheme 5.

(*aR*,R)-2-(But-2-yl)-*N*,*N*-diisopropyl-1-naphthamide 7b.** In a similar way, amide **8** (70 mg, 0.235 mmol) was treated with *sec*-butyllithium (0.20 mL, 1.3 M solution in cyclohexane, 0.259 mmol) and methyl iodide (20 μL, 0.471 mmol) to give *amide* **7b** as a white solid (88 mg, 84%); mp 99−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.91−7.78 (3H, m, ArH), 7.57−7.39 (3H, m, ArH), 3.74−3.56 (2H, m, 2 × NCH), 2.96−2.79 (1H, m, ArCH), 1.88−1.70 (2H, m, CH_2), 1.83 (3H, d, J = 6.9, $NCHCH_3$), 1.73 (3H, d, J = 6.7, $NCHCH_3$), 1.33 (3H, d, J = 6.7, $ArCHCH_3$), 1.13 (3H, d, J = 6.7, $NCHCH_3$), 1.05 (3H, t, J = 7.4, CH_2CH_3), 1.03 (3H, d, J = 6.5, $NCHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.5 (s, CO), 140.9 (s, Ar), 133.4 (s, Ar), 131.9 (s, Ar), 129.7 (s, Ar), 128.2 (d, Ar), 127.8 (d, Ar), 126.2 (d, Ar), 125.4 (d, Ar), 125.0 (d, Ar), 123.8 (d, Ar), 50.8 (d, NCH), 46.0 (d, NCH), 38.4 (d, ArCH), 29.3 (t, CH_2), 21.9 (q, $CHCH_3$), 21.0 (q, $NCHCH_3$), 20.9 (q, $NCHCH_3$), 20.6 (q, $NCHCH_3$), 20.5 (q, $NCHCH_3$), 12.6 (q, CH_2CH_3); *m/z* (CI^+) 312 (M + H, 100%), 211 (11%), 171 (8%); M^+ 311.2255 ($C_{21}H_{29}NO$ requires 311.2249).

HPLC analysis of the crude reaction mixture gave t_R = 7.34 min (1.3%) for **7a** and 8.51 min (98.7%) for **7b**. With methyl tosylate as the electrophile, a ratio of 0.6:99.4% **7a**:**7b** was obtained.

Heating **7b** in hexane at 65 °C for 2 days led to an unchanging equilibrated mixture of **7a** and **7b** in a ratio of 58.6:41.4%. The rate of interconversion of the atropisomers has been published.[12]

2-(1-Deuterioethyl)-*N*,*N*-diisopropyl-1-naphthamide *d*-6. In a similar way, amide **6** (70 mg, 0.235 mmol) was treated with *sec*-butyllithium (0.20 mL, 1.3 M solution in cyclohexane, 0.259 mmol) and deuteriomethanol (0.5 mL, excess) to give *deuterated amide d*-**6** as a white solid (70 mg, 100%). ^{1}H NMR (300 MHz, C_6D_6) correlates with **6**:[12] δ_H 8.17 (1H, d, J = 8.5, ArH^8), 7.73 (1H, d, J = 8, ArH^5), 7.67 (1H, d, J = 8, ArH^4), 7.42 (1H, t, J = 8), 7.40 (1H, t, J = 8) (ArH^6 and ArH^7), 7.30 (1H, d, J = 8, ArH^3), 3.56 (1H, sept, J = 6.5, NCH), 3.26 (1H, sept, J = 6.5, NCH), 2.98 (0.1H, br q, J = 7, H_a [1H, dq, J = 14, 7 in **6**]), 2.88 (0.9H, br q, J = 7, H_b [1H, dq, J = 14, 7 in **6**]), 1.89 (3H, d, J = 6.5, $CHMe$), 1.83 (3H, d, J = 6.5, $CHMe$), 1.42 (3H, d, J = 6.5, $CHDMe$ [3H, t, J = 7 in **6**]), 0.78 (3H, d, J = 6.5, $CHMe$), 0.71 (3H, d, J = 6.5, $CHMe$); *m/z* (CI^+) 285 (M + H, 100%), 254 (8%), 184 (26%); M^+ 284.2000 ($C_{19}H_{34}DNO$ requires 284.1999).

(*aR*,S)-*N*,*N*-Diisopropyl-2-(1-(trimethylstannyl)ethyl)-1-naphthamide 9a and (*aR*,R**)-*N*,*N*-Diisopropyl-2-(1-(trimethylstannyl)-ethyl)-1-naphthamide 9b.** In a similar way, amide **6** (188 mg, 0.66 mmol) in THF (45 mL) was treated with *sec*-butyllithium (0.56 mL, 1.3 M solution in hexanes, 0.73 mmol) and trimethyltin chloride (1.33 mL of a 1 M solution in THF, 1.33 mmol). Rapid workup using cold solvents gave the crude product as a colorless oil. The partially epimerized crude product was purified by flash chromatography on silica gel [15:1 petrol (bp 40−60 °C)−EtOAc] to afford *stannane* **9a** (66 mg, 22%) as a white solid; mp 113−115 °C; R_f 0.35 [7:1 petrol (bp 40−60 °C)−EtOAc]; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.42 (2H, m, ArH), 7.67 (1H, d, J = 8.4, ArH), 7.45 (1H, t, J = 6.9, ArH), 7.35 (1H, t, J = 8.0, ArH), 7.29 (1H, d, J = 8.7, ArH), 3.61 (2H, m, 2 × NCH), 2.75 (1H, q, J = 7.4, $CHSnMe_3$, with satellites due to ^{119}Sn−H coupling, $^2J_{Sn-H}$ = 66), 1.74 (3H, d, J = 6.9, $NCHCH_3$), 1.67 (3H, d, J = 6.9, $NCHCH_3$), 1.64 (3H, d, J = 7.6, $SnCHMe$), 1.07 (3H, d, J = 6.7, $NCHCH_3$), 0.98 (3H, d, J = 6.6, $NCHCH_3$), 0.00 (9H, s, $SnMe_3$, with satellites due to ^{119}Sn−H coupling, $^2J_{Sn-H}$ = 54); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.9, 141.6, 130.5, 130.0, 127.8, 126.4, 124.4, 124.3, 123.8, 50.6, 45.9, 24.4, 20.9, 20.8, 20.6, 17.2, and −10.0; IR (film) υ_{max} 3054, 2966, 2928, 2864, 1625 cm^{-1}; *m/z* (CI^+) 447 (4%, M^+), 432 (100%, M − CH_3), and 284 (21%, M − $Sn(CH_3)_3$); M^+, 447.1584 ($C_{22}H_{33}NOSn$ requires 447.1583). Slow recrystallization from cool petroleum ether afforded crystals suitable for X-ray analysis (see below). Also obtained was *stannane* **9b** (174 mg, 59%) as a white solid; mp 109−112 °C; R_f 0.25 [7:1 petrol (bp 40−60 °C)−EtOAc] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.78−7.68 (3H, m, ArH), 7.47−7.34 (2H, m, ArH), 7.16 (1H, d, J = 8.5, ArH), 3.61 (2H, m, 2 × NCH), 2.74 (1H, q, J = 7.4, $CHSn$, with satellites due to ^{119}Sn−H coupling, $^2J_{Sn-H}$ = 46), 1.77 (3H, d, J = 6.9, $NCHCH_3$), 1.67 (3H, d, J = 6.9, $NCHCH_3$), 1.59 (3H, d, J = 7.6, $SnCHMe$), 1.06 (3H, d, J = 6.6, $NCHCH_3$), 1.02 (3H, d, J = 6.6, $NCHCH_3$), 0.10 (9H, s, $Sn(CH_3)_3$, with satellites due to ^{119}Sn−H coupling, $^2J_{Sn-H}$ = 51); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.5, 142.0, 132.3, 131.1, 130.0, 128.1, 127.9, 127.3, 126.3, 124.9, 124.6, 50.8, 46.0, 26.4, 21.7, 20.9, 20.8, 20.7, 20.5, and −9.6; IR (film) υ_{max} 2971, 2927, 2861, 1627 cm^{-1}; UV−vis λ_{max}, nm (ϵ_{max}) (CH_2Cl_2) 244 (5059), 286 (1018); *m/z* (CI) 448 (5%, M + H^+), 432 (100%, M − Me), and 284 (M − $SnMe_3$); M^+, 447.158 ($C_{22}H_{33}NOSn$ requires 447.1583). Anal. Calcd for $C_{22}H_{33}NOSn$: C, 59.2; H, 7.4; N, 3.1%. Found: C, 59.44; H, 7.54; N, 3.11%.

HPLC analysis of the crude product mixture gave t_R = 5.3 min (10%) for **9b** and 8.9 min (90%) for **9a**. A similar reaction using trimethyltin bromide as the electrophile afforded a crude product containing a 93:7 ratio of **9b** and **9a** in 94% yield. Heating a solution of stannane **9b** in $CDCl_3$ for 48 h at 60 °C returned a mixture of **9a**:**9b** in a ratio of 88:12.

(*aR*,R)-*N*,*N*-Diisopropyl-2-(1-(tributylstannyl)ethyl)-1-naphthamide 10b.** In a similar way, amide **6** (0.250 g, 0.882 mmol) in THF (60 mL) was treated with *sec*-butyllithium (0.75 mL, 1.3 M solution in cyclohexane, 0.970 mmol) and tributyltin chloride (0.48 mL, 1.76 mmol). Rapid workup using cold solvents gave the crude product as a colorless oil. Purification by column chromatography (5% ethyl acetate in light petroleum) gave *stannane* **10b** as a waxy white solid (0.394 g, 78%); mp 61−62 °C; R_f 0.19; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.89−7.71 (3H, m, ArH), 7.51−7.38 (2H, m, ArH), 7.22 (1H, d, J = 8.7, ArH), 3.66 (2H, sept, J = 6.8, 2 × NCH), 2.86 (1H, q, J = 7.4, ArCH, with satellites due to ^{119}Sn−H coupling, J_{Sn-H} = 43), 1.81 (3H, d, J = 6.8, $NCHCH_3$), 1.72 (3H, d, J = 6.8, $NCHCH_3$), 1.64 (3H, d, J = 7.4, $ArCHCH_3$), 1.58−1.26 (12H, m, CH_2's), 1.11 (3H, d, J = 6.7, $NCHCH_3$), 1.08 (3H, d, J = 6.7, $NCHCH_3$), 1.00−0.80 (6H, m, 3 × CH_2), 0.91 (9H, t, J = 7.3, 3 × $(CH_2)_3CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.6 (s, CO), 142.4 (s, Ar), 132.4 (s, Ar), 131.1 (s, Ar), 130.1 (s, Ar), 128.2 (d, Ar), 128.0 (d, Ar), 127.9 (d, Ar), 126.3 (d, Ar), 124.8 (d, Ar), 124.6 (d, Ar), 51.0 (d, NCH), 46.0 (d, NCH), 29.2, 27.5, 26.4, 21.9, 21.7, 20.9, 20.6, 20.5, 13.6, 9.6; IR (Nujol mull) ν_{max} 1621 cm^{-1}; *m/z* (CI^+) 573 (3%), 521 (5%), 520 (18%), 517 (30%), 516 (100%), 515 (47%), 514 (73%), 513 (34%), 512 (47%), 308 (11%), 284 (57%), 282 (26%), 256 (18%); [M^+ − Bu] 516.2295 ($C_{27}H_{42}NOSn$ requires 516.2287).

Also obtained was **10a** as a colorless oil (0.721 g, 14%).

HPLC analysis of the crude product mixture gave $t_R = 2.34$ min (10.9%) for **10b** and 5.46 min (89.1%) for **10a**.

(*aR*,S)-*N,N*-Diisopropyl-2-(1-(tributylstannyl)ethyl)-1-naphthamide 10a.** A sample of crude stannane **10b** was dissolved in hexane and heated to 65 °C for 48 h. The solution was concentrated to give a crude product which was purified by column chromatography (5% ethyl acetate in light petroleum) to yield *stannane* **10a** as a colorless oil, M^+ 573.2981 ($C_{31}H_{51}NOSn$ requires 573.2991); R_f 0.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.80−7.29 (6H, m, ArH), 3.65 (1H, sept, $J = 6.7$, NCH), 3.60 (1H, sept, $J = 6.7$, NCH), 2.84 (1H, q, $J = 7.4$, ArCH, with satellites due to SnH coupling, $^2J_{Sn-H} = 61$), 1.79 (3H, d, $J = 6.7$, NCHCH_3), 1.72 (3H, d, $J = 6.7$, NCHCH_3), 1.70 (3H, d, $J = 7.4$, ArCHCH_3), 1.48−1.17 (12H, m CH_2's), 1.11 (3H, d, $J = 6.7$, NCHCH_3), 0.99 (3H, d, $J = 6.7$, NCHCH_3), 0.92−0.78 (6H, m, 3 × CH_2), 0.82 (9H, t, $J = 7.2$, 3 × CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.8 (s, CO), 141.9 (s, Ar), 130.5 (s, Ar), 130.0 (s, Ar), 129.8 (s, Ar), 127.6 (2 × d, Ar), 126.3 (d, Ar), 124.5 (d, Ar), 124.4 (d, Ar), 124.3 (d, Ar), 50.5 (d, NCH), 45.8 (NCH), 28.9, 27.3, 24.3, 20.9, 20.8, 20.7, 20.7, 18.0, 13.6, 9.3; *m*/*z* (CI^+) 573 (3%), 521 (4%), 520 (17%), 517 (26%), 516 (100%), 515 (45%), 514 (71%), 513 (31%), 512 (40%), 284 (28%); IR (thin film) ν_{max} 1628 cm^{-1}.

HPLC analysis of the crude equilibrated mixture indicated a ratio of 97.0:3.0 **10a**:**10b**.

(*aR*,R)-*N*,N-Diisopropyl-2-(1-lithioethyl)-1-naphthamide 11a and (*aR*,S**)-*N*,N-Diisopropyl-2-(1-lithioethyl)-1-naphthamide 11b.** In separate experiments, each of **9a**, **9b**, **10a**, **10b**, and **6** (20 mg) were dissolved in d_8-THF (0.5 mL) under a nitrogen atmosphere in an NMR tube (8 inches × 0.5 mm) stoppered with a septum. The solution was cooled to −78 °C, and *n*-butyllithium (*sec*-butyllithium for **6**) was added (4 equiv). The mixture was agitated with the syringe needle, and after 20 min, the tube was transferred to the NMR spectrometer whose probe had been precooled to −40 °C. After 10 min, a ^{1}H NMR spectrum was acquired (Figure 3) which showed a mixture of organolithiums **11a** and **11b** in the ratios indicated in Scheme 4. A second ^{1}H NMR spectrum was acquired 1 h later; the ratios from both spectra were identical within experimental error. *Organolithium* **11a** was the sole product from **9a**, **10a**, and **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.08 (1H, d, $J = 7.0$, ArH), 5.98 (1H, t, $J = 8.0$, ArH), 5.93 (1H, $J = 9.5$, ArH), 5.78 (1H, d, $J = 9.5$, ArH), 5.60 (1H, d, $J = 8.5$, ArH), 5.20 (1H, $J = 7.0$, ArH), 4.20 (1H, septet, $J = 7.0$, NCH), 3.13 (1H, septet, $J = 6.5$, NCH), 2.55 (1H, q, $J = 6.5$, CHLi), 1.5−0.5 (multiplet obscured by solvent peaks). *Organolithium* **11b** was identified as the major component from the transmetalation of **10b** and the minor component from the transmetalation of **9b**.^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.00 (2H, m, ArH), 5.80 (1H, m, ArH), 5.59 (2H, m, ArH), 5.27 (1H, t, $J = 6.5$, ArH), 4.53 (1 H, septet, $J = 7.0$, NCH), 3.15 (1 H, septet, $J = 6.5$, NCH) 2.92 (1 H, q, $J = 7.0$, CHLi), 1.5−0.5 (multiplet obscured by solvent peaks).

Transmetalation/Electrophilic Quench of 9a. A solution of **9a** (32 mg, 0.07 mmol) in THF (10 mL) at −78 °C under an atmosphere of nitrogen was treated with *n*-butyllithium (0.05 mL, 0.08 mmol; 1.46 M solution in hexanes). The dark green solution was stirred for 1 h. Ethyl iodide (0.01 mL, 0.13 mmol) was added, and the resulting colorless solution was allowed to warm to ambient temperature. Water (10 mL) was added, and the THF was removed under reduced pressure at ambient temperature. The aqueous residue was extracted with dichloromethane (4 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude product as a white solid. Purification by flash chromatography on silica gel [15:1 petrol (bp 40−60 °C)−EtOAc] afforded amides **7a** and **7b** (combined yield 20 mg, 89%). Analytical HPLC showed a ratio of 97:3 **7a**:**7b**.

Reactions using methyllithium or phenyllithium as the nucleophile, or with trimethyltin chloride as the electrophile, were carried out in an identical manner, and the outcomes are presented in Table 1.

Transmetalation/Electrophilic Quench of 9b. In the same way, a solution of **9b** (4:96; 117 mg, 0.27 mmol) in THF (36 mL) at −78 °C was treated with *n*-butyllithium (0.18 mL, 0.29 mmol; 1.6 M solution in hexanes) and ethyl iodide (0.04 mL, 0.50 mmol). After workup in the usual manner, analytical HPLC of the crude product showed a mixture of 91:9 **7a**:**7b**. Purification by flash chromatography on silica gel [15:1 petrol (bp 40−60 °C)−EtOAc] afforded stannanes **7a** and **7b** (combined yield 63 mg, 77%). Also obtained was naphthamide **6** (13 mg, 17%).

Reactions using methyllithium or phenyllithium as the nucleophile, or with trimethyltin chloride as the electrophile, were carried out in an identical manner, and the outcomes are presented in Table 1.

Transmetalation/Electrophilic Quench of 10a and 10b. In the same way, **10a** and **10b** were treated with *n*-butyllithium and ethyl iodide to give mixtures of **7a** and **7b**. The results are detailed in Table 1.

X-ray Crystal Structures. 7a: Colorless crystal, $C_{19}H_{29}NO$, $M_r = 311.47$, monoclinic, $P2_1/n$, $a = 7.638(4)$ Å, $b = 13.286(4)$ Å, $c = 18.879(3)$ Å, $\beta = 92.61(3)°$, data collection at 292 K, $Z = 4$, residual $R = 0.064$. Full details may be found in the Supporting Information.

9a: Colorless crystal, $C_{22}H_{33}NOSn$, $M_r = 446.18$, monoclinic, $P2_1/n$, $a = 7.694$ Å, $b = 13.465$ Å, $c = 22.077$ Å, $\beta = 97.10°$, data collection at 292 K, $Z = 4$, residual $R = 0.0365$. Full details may be found in the Supporting Information.

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Supporting Information Available: Spectra (^{1}H and ^{13}C NMR) of **6**, *d*-**6a**, **7a**, **7b**, **9a**, **9b**, **10a**, **10b**. ^{1}H NMR spectra of **11a** and **11b**; X-ray crystallographic data for **7a** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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