Two Different Pathways of Stereoinformation Transfer: Asymmetric Substitutions in the (−)-Sparteine Mediated Reactions of Laterally Lithiated *N*,*N*-Diisopropyl-*o*-ethylbenzamide and *N*-Pivaloyl-*o*-ethylaniline

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Abstract: Highly enantioenriched substitution products can be obtained by the (−)-sparteine mediated lithiation−substitution reactions of the laterally lithiated intermediates **3·1** and **14·1** derived from the amides **2** and **13**. Either enantiomer of the products can be obtained with high enantioenrichment using (−)-sparteine as the ligand by appropriate choice of the protocol. The enantiodetermining step in both sequences occurs after deprotonation. Enantioenrichment in the sequence with **3·1** arises from a dynamic kinetic resolution, whereas enantioenrichment in the sequence with **14·1** arises from a dynamic thermodynamic resolution.

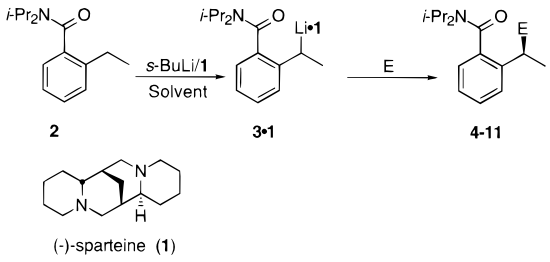
Introduction

Enantioselective lithiation−substitution sequences mediated by (−)-sparteine have been shown to provide efficient methodology for asymmetric synthesis. A quarter century ago, Nozaki first reported the use of (−)-sparteine as a chiral ligand in a lithiation−substitution sequence.[1] Hoppe's more recent application of this ligand to asymmetric deprotonations of carbamates to afford oxygen dipole stabilized carbanions with high enantioselectivities has stimulated interest in (−)-sparteine mediated lithiations.[2,3]

Asymmetry can be introduced in a lithiation−substitution sequence by energy differences in either the formation or reaction of the diastereomeric lithiated intermediates.[4] The pathway of asymmetric deprotonation is well recognized, but transfer of stereoinformation in a post-deprotonation step, the pathway of asymmetric substitution, while known, is less developed. Asymmetric substitutions can be more permissive than asymmetric deprotonations. The substitutions are applicable to organolithium intermediates regardless of their mode of formation and can involve configurationally labile carbanions.[4,5] We have communicated preliminary studies of enantioselective (−)-sparteine induced lithiation−substitutions of two benzylic organolithium species.[6] We now report full studies of the stereoinformation transfer in these asymmetric substitutions which establish that the reactions proceed by mechanistically different pathways.[4]

Results

Methodology. Lateral lithiation of the *N*,*N*-diisopropyl(*o*-ethyl)benzamide(**2)** effected by *s*-BuLi in the presence of (−)-sparteine (**1**) at −78 °C affords the putative organolithium complex **3·1**. Treatment of **3·1** with the variety of electrophiles provides the products **4**−**11** with a enantiomeric ratios (er) and yields shown in Table 1.



Alkylation, stannylation, and silylation provide products with high enantiomeric ratios (ers) in useful yields. The use of chlorides afford higher enantiomeric ratios and yields than bromide or iodide. Acetone as an electrophile provides the tertiary alcohol **12** with poor enantioselectivity. The absolute configuration of (*R*)-**8** was determined by independent synthesis from (*R*)-3-phenylbutyric acid.[7,8] The absolute configuration of **11** was determined by Tamao−Fleming oxidation and

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(4) For a recent discussion of the different pathways, see: Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, 29, *29*, 552.

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(8) Experimental details are provided as Supporting Information.

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Table 1. Yields and Enantiomeric Ratios of Products from the (−)-Sparteine Mediated Enantioselective Lithiation−Substitution of **2**

electrophile	solvent	product	yield (%)	er
p-$MeOC_6H_4CH_2Cl$	MTBE/pentane	(*R*)-**4**	79	96:4
$PhCH_2Cl$	MTBE/pentane	(*R*)-**5**	52	84:16
$CH_2{=}CHCH_2Cl$	pentane	(*R*)-**6**	89	96:4
$CH_2{=}CHCH_2Br$	pentane	(*R*)-**6**	48	76:24
$CH_3(CH_2)_3Cl$[a]	pentane	(*R*)-**7**	95	90:10
$CH_3(CH_2)_3Br$	pentane	(*R*)-**7**	45	87:13
$CH_3(CH_2)_3I$	MTBE/pentane	(*R*)-**7**	71	64:36
$CH_3(CH_2)_2Cl$[a]	MTBE/pentane	(*R*)-**8**	32	88:12
n-Bu_3SnCl	pentane	(*S*)-**9**	78	94:6
Me_3SiCl	MTBE/pentane	(*S*)-**10**	79	96:4
$Me_2PhSiCl$	MTBE/pentane	**11**	76	66:34[b]
CH_3COCH_3	MTBE/pentane	**12**	64	70:30

[a] Reaction with the electrophile is carried out at −5 to 0 °C. [b] This value is obtained from the sequence to the 3-methylphthalide and is taken to represent a lower limit. See footnote 10a.

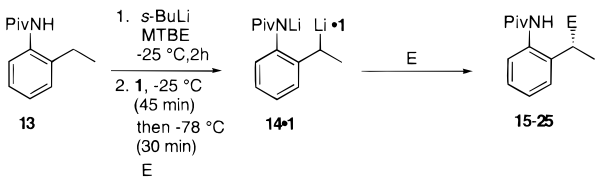
Table 2. Yields and Enantiomeric Ratios of Products from (−)-Sparteine Mediated Enantioselective Lithiation−Substitution of **13**

electrophile	product	yield (%)	er
Me_3SiCl[a]	(*R*)-**15**	72	95:5
$PhMe_2SiCl$	(*R*)-**16**	6[b]	89:11
Me_3GeCl	(*R*)-**17**	62	89:11
Me_3SnCl	(*R*)-**18**	77	83:17
Bu_3SnCl[a]	(*R*)-**19**	71	65:35
allyl bromide[c]	(*S*)-**20**	67	91:9
allyl chloride[a]	(*S*)-**20**	78	88:12
allyl tosylate	(*R*)-**20**	53	86:14
benzyl bromide	(*S*)-**21**	56	90:10
iodoundecane	(*S*)-**22**	62	89:11
cyclohexanone	(*R*)-**23**	80	89:11
cyclohexane carboxaldehyde	(*R*)-**24**	31[d]	74:26
		55[e]	95:5
benzaldehyde	(*R*)-**25**[f]	67	91:9

[a] Reaction conducted in diethyl ether. [b] The yield of impure material was 85% but only 6% could be separated from **13** on chromatography. [c] Reaction conducted in MTBE/pentane (1/1 v/v). [d] Less retained diastereomer on chromatography. Relative configuration not assigned. [e] More retained diastereomer on chromatography. Relative configuration not assigned. [f] 2:1 ratio of diastereomers. Enantiomeric ratio determined by deoxygenation to (*S*)-**21**.

cyclization to the resulting alcohol to 3-methylphthalide of known configuration.[9,10] The absolute configurations of other compounds are assigned by analogy to **8** and **12** is unassigned.

Metalation of the anilide **13** is effected with *s*-BuLi at −25 °C to generate a dilithio intermediate **14**. Optimal conditions were found to require a 45 min incubation period of **14** with **1** at −25 °C to give the putative intermediate **14·1**. Subsequent cooling to −78 °C followed by the addition of electrophiles affords the products **15-25** with the ers and yields shown in Table 2. High enantioselectivities can be achieved also when the electrophile is added at −25 °C.

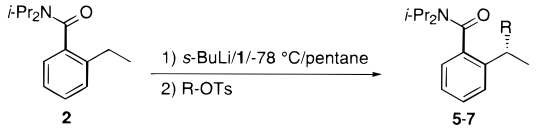


The absolute configuration of (*R*)-**16** was determined by oxidation to the corresponding alcohol, which was independently synthesized.[6b] The absolute configuration of (*S*)-**20** was determined through independent chemical synthesis.[6b] The configuration of (*R*)-**25** was correlated to that of (*S*)-**21** via deoxygenation.[6b] These results indicate that reactions of **14·1** with an aldehyde, silyl chloride, and alkyl halide provide products with the same sense of chirality at the benzylic carbon.

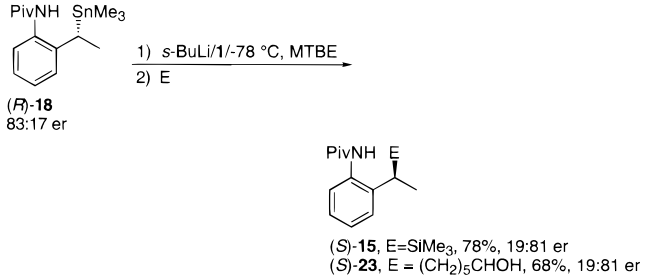
Table 3. Yields and Enantiomeric Ratios of Products from the (−)-Sparteine Mediated Enantioselective Lithiation−Substitution of **2** with Alkyl Tosylates

R-	product	yield (%)	er
$PhCH_2$-	(*S*)-**5**	26	11:89
allyl-	(*S*)-**6**	46	6:94
n-Bu-	(*S*)-**7**	52	1:99

Either enantiomer of the products can be obtained selectively from **2** and **13** with (−)-sparteine as the only source of stereochemical information. For the lithiation−substitution of **2**, the use of alkyl tosylates as electrophiles provides products with a configuration opposite to that obtained with alkyl halides with good ers, as shown for the preparations of (*S*)-**5**, (*S*)-**6**, and (*S*)-**7** in Table 3.[11]



Access to the products from **13** with configurations opposite to that obtained from the chlorides can be achieved *via* the organostannane (*R*)-**18**. Lithio-destannylation of (*R*)-**18** in the presence of **1** at −78 °C followed by reactions with electrophiles provides (*S*)-**15** and (*S*)-**23**.[19b]



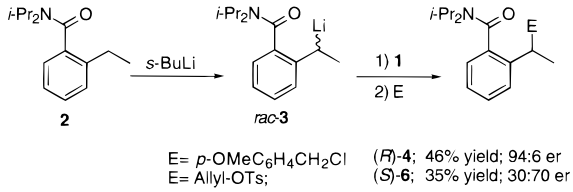
Mechanistic Studies. Our preliminary work established that the high enantioselectivities observed in the (−)-sparteine mediated lithiation−substitutions of **2** and **13** are introduced after the deprotonation.[6] We have carried out experiments to verify this and to distinguish between the reaction pathways of dynamic kinetic resolution and dynamic thermodynamic resolution.[4,6]

Asymmetric Substitutions. When (−)-sparteine is added to a solution of *rac*-**3** followed by reaction with electrophiles, the products are formed with enantioenrichments similar to the reactions in which *s*-BuLi and **1** were premixed. These results show that the enantioselectivity in the lithiation−substitution of **2** can be established after the deprotonation.

(9) The er of **12** was not determined due to the poor resolution of the enantiomers on CSP-HPLC columns. However, comparison of the optical rotation of 3-methylphthalide with the literature values suggests that the product phthalide is obtained with 66:34 er. Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 3136.

(10) (a) The reaction of **3·1** with phenyldimethylsilyl chloride to obtain **12** was not optimized for enantioselectivities. Therefore, even though the enrichment appears to be different than for trimethylsilyl chloride, the reaction is assumed to have the same sense of facial selectivity as **10**. (b) The lithiation had to be carried out in MTBE:pentane, because **2** could not be lithiated in pentane in the absence of (−)-sparteine. The reaction in Table 3 was carried out in pentane, and the difference in the enantiomeric ratios is attributed to the solvent difference.

(11) The *S*-enantiomers of the products **5**−**7** can also be obtained in moderate selectivities by the reaction of methyl chloride with appropriately substituted, laterally lithiated intermediate in the presence of (−)-sparteine.[6a]



However, the results above do not rule out the possibility of an initial asymmetric deprotonation followed by an asymmetric substitution. To test for such a possibility, the racemic monodeuterated amide *rac*-**2**-d_1 was subjected to lithiation−substitution sequences.

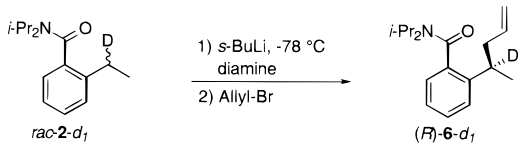


Table 4 provides comparison of the results of the lithiation−substitutions of **2** and *rac*-**2**-d_1. From the reaction *rac*-**2**-d_1 with *s*-BuLi/TMEDA, a deuterium isotope effect of 19 can be calculated for the deprotonation. The kinetic isotope effect and the facial selectivity of the deprotonation by the chiral base (*s*-BuLi/**1**) are the two competing factors in the reaction of *rac*-**2**-d_1 with *s*-BuLi/**1**. One enantiomer of **2**-d_1 will behave similar to the diprotio compound, while the other enantiomer will have the deuterium removed only if the enantioselectivity of the deprotonation overrides the isotope effect.[12] Comparison of entries 2 and 3 for reaction of **2** and rac **2**-d_1 with *s*-BuLi/(−)sparteine shows a loss of 22% deuterium in the latter reaction despite a large isotope effect. This result indicates that the deprotonation step is highly enantioselective. If we assume that the value of the isotope effect for the reaction with (−)-sparteine is similar for reactions with TMEDA, the facial selectivity of the deprotonation can be calculated to be 96:4.[13] A similar seqence of asymmetric deprotonation followed by racemization and asymmetric substitution has been reported by Schlosser.[5c]

The effect of temperature on the asymmetric substitution was investigated. When the reaction is carried out at −40 °C in MTBE/pentane (*R*)-**6** is obtained with 88:12 er, which is lower than the 96:4 er obtained at −78 °C. At −25 °C, the selectivity degraded further, providing (*R*)-**6** with a 69:31 er.

When *rac*-**14** was generated in the absence of diamines and then treated with (−)-sparteine followed by TMSCl, the product **15** was obtained with high enantioenrichment. The enantiomeric ratio was comparable to that obtained with (−)-sparteine present during the lithiation. This result establishes that enantioselectivity can be introduced in the lithiation−substitution of **13** subsequent to dilithiation. However, the reaction conditions used for complexation of **14** with (−)-sparteine have significant effects on the enantiomeric ratios of **15** as shown in Table 5. Entry 1 shows that when the organolithium is complexed at −78 °C with (−)-sparteine, **15** is obtained in a very poor enantiomeric ratio. If (−)-sparteine is added at −25 °C and the solution is allowed to stir at that temperature for only 5 min prior to cooling to −78 °C, the er is still very poor as shown by entry 2. However, with the standard reaction sequence in which **1** is stirred with **14** for 45 min at −25 °C before cooling to −78 °C, (*R*)-**15** is obtained with very high enantioselectivity as shown in entry 3. Clearly an incubation period is required for the diastereomeric complexes to equilibrate prior to reaction with the electrophile. We refer to the protocol involving incubation at −25° followed by cooling to −78 °C as a warm/cool sequence.

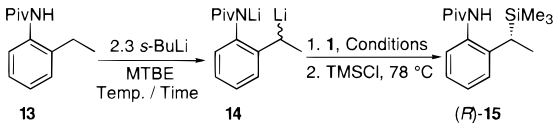
Table 4. Yields of Products from the Lithiation−Allylation of *rac*-**2**-d_1

% d_1 of **2**	*s*-BuLi (equiv)	diamine	ratio (**6**:**2**)	% d_1 of (*R*)-**6**	er
99	0.7	TMEDA	62:38	94	
0	1.0	(−)-sparteine	90:10		74:26
99	1.0	(−)-sparteine	76:24	77	73:27

Table 5. Effect of Metalation Conditions with (−)-Sparteine on the Enantioselectivity of **15**

entry	metalation temp (°C)	time (h)	(−)-sparteine temp (°C) init/final	time at temp (min) init/final	yield[a] (%)	er
1[b]	−25	2	−78	30	88	56:44
2[c]	−25	2	−25/−78	5/10	65[d]	69:31
3	−25	2	−25/−78	45/30	63[d]	91:9
4	−25	2	−25/−40	45/30	87	93:7
5	−25	2	−25	45	95	93:7
6	−25	2	−25/0	45/30	98	93:7
7	23	1	23	75	46[d]	92:8

[a] Yields are from GC data and are uncorrected. [b] A solution of (−)-sparteine in MTBE was cooled to −78 °C prior to addition to the solution of organolithium at −78 °C. [c] Reaction conducted in Et_2O. [d] Yield of isolated (*R*)-**15**.



We have found that the reaction of **14** can be carried out at higher temperatures without an adverse effect on the stereoselectivity. Conducting the "cooler" portion of the warm/cool sequence at −40 °C provides a product with slightly higher enantiomeric ratios as seen by comparison of entries 3 and 4. The product is obtained with equally high ers when the "cool" portion of the sequence is omitted as shown in entry 5 or even when the electrophilic substitution is carried out at a higher temperature as shown for entry 6. In fact, conducting the entire reaction sequence at ambient temperature provides the product **15** with 92:8 er, in effect unchanged from the standard warm/cool sequence. However, under these conditions **15** is accompanied by more uncharacterized side products than in the lower temperature reactions.

Configurational Stabilities. The enantioselectivities in these reactions could arise through either a dynamic thermodynamic resolution or a dynamic kinetic resolution.[4] To distinguish these pathways the configurational stabilities at the benzylic positions of **3·1** and **14·1** must be determined with respect to their rates of reactions with electrophiles. We have used two approaches to obtain this information. The first involves lithio-destannylation of the enantioenriched organostannanes, and the second involves a variant of the Hoffmann test of configurational stability.[6c,14]

The tin−lithium exchange reactions of the enantioenriched stannyl derivatives (*S*)-**9** or (*R*)-**18** without ligand or in the

(12) (a) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715. (b) Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 4938. (c) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394.

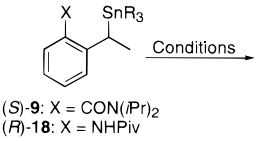
(13) The enantioenrichment of the product is not taken into account, since the organolithium intermediate is configurationally labile and enantiodetermination occurs after deprotonation. The details of the calculations are provided as Supporting Information.

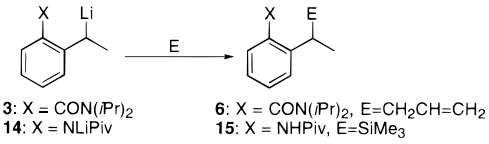
(14) (a) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975. (b) Hoffmann, R. W; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721. (c) Hoffmann, R. W.; Klute, W. *Chem. Eur. J.* **1996**, *2*, 694. (d) Hoffmann, R. W.; Ruhl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* **1992**, 719.

Table 6. Products from Lithio-Destannylations of (*S*)-9 and (*R*)-17

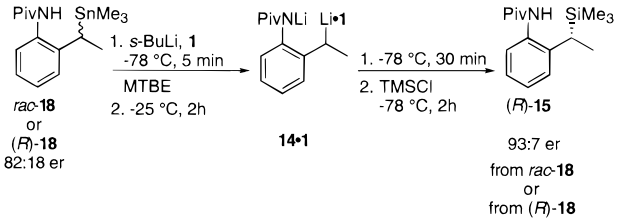
reactant	er	conditions	E	product	er
(*S*)-**9**	94:6	*n*-BuLi, MTBE/pentane, 1.5 h, −78 °C	allyl chloride	**6**	52:48
(*S*)-**9**	94:6	*n*-BuLi/TMEDA, MTBE/pentane, 1.5 h, −78 °C	allyl chloride	**6**	50:50
(*R*)-**18**	82:18	*s*-BuLi, MTBE, 1 h, −78 °C	TMSCl	**15**	51:49
(*R*)-**18**	85:15	*s*-BuLi/TMEDA, MTBE, 1 h, −78 °C	TMSCl	**15**	52:48

presence of TMEDA provide the substitution products **6** and **15**, respectively, as racemic mixtures under the conditions shown in Table 6. We conclude that the organolithium species **3** and **14** are configurationally labile with respect to the rates of their reactions with allyl chloride and trimethylsilyl chloride under these conditions. The organolithium intermediate **3** was also found to be configurationally labile with respect to the rate of its reaction with allyl tosylate.



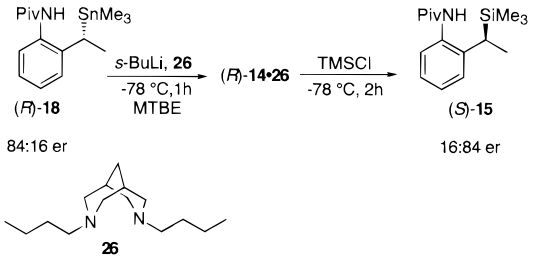


When lithio-destannylation of (*R*)-**18** was carried out in the presence of (−)-sparteine, reactions with TMSCl and cyclohexanone gave (*S*)-**15** and (*S*)-**23** with configurations opposite to those of products obtained in the warm/cool protocol (vide supra). However when the solution of **14** generated by lithio-destannylation of racemic or enantioenriched **18** was warmed to −25 °C and stirred at that temperature for 2 h prior to cooling to −78 °C and reaction with TMSCl, (*R*)-**15** was obtained with enantiomeric ratios comparable to those obtained using the conventional warm/cool sequence.

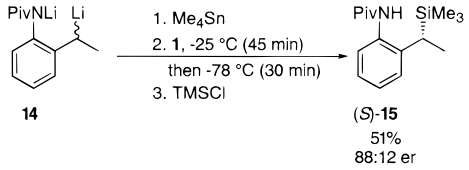


Since the configurational stability of **14** in the presence of (−)-sparteine is different from that in the presence of the TMEDA, we investigated dibutylbispidine (**26**) as a ligand. The diamine **26** was selected because it has the same ring scaffold as the central rings of (−)-sparteine. We observed that (*S*)-**15** is obtained from (*R*)-**18** with an 16:84 er in the presence of **26**. The results with **1** and **26** are consistent with formation of diastereomeric complexes **14·1** and enantiomeric complexes **14·26** which are configurationally stable at −78 °C. Equilibration of the diastereomeric complexes of **14·1** can take place at −25 °C to give the enantiomeric ratio with the warm/cool sequence. Clearly **26** is a better achiral mimic for (−)-sparteine than is TMEDA.[3d,15]

The solutions of **3·1** and **14·1** appear homogeneous although colored. To definitively rule out selective crystallization of one diastereoisomer as the stereoselective step a filtered solution of **14·1** was treated with TMSCl and found to give the same er of (*R*)-**15** as unfiltered material.[2] Moreover if stereoinformation transfer were driven by crystallization the enantioinversion in the lithio destannylation would not be observed.



A possible rationale for the observation of enantioinversion in the lithio-destannylation sequence of (*R*)-**18** is that different reactive species are involved than those which are produced by deprotonation of **13**.[16] To evaluate if an "ate" complex could be such a species, tetramethyltin was added to a solution of the racemic organolithium **14** prior to the warm/cool sequence, and reaction with TMSCl was found to afford (*R*)-**15**. Moreover when tetramethyltin was added to a solution of the diastereomeric complexes at −78 °C, no effect on stereoselection for (*R*)-**15** was observed. If an ate complex is the reactive species, and the above experiments could generate such a complex, then the observation of enantioinversion would be expected. These experiments, while not definitive, suggest that ate complexes are not the species responsible for the enantioinversion in the lithio-destannylation of **18**.[17]



We formulate a pathway of retentive lithio-destannylation for the conversion of (*R*)-**18** to (*R*)-**14**, followed by an invertive electrophilic substitution to afford (*S*)-**15** and (*S*)-**23**.[2,3,18] Results from our and Hoppe's labs have shown benzylic organolithium reagents can undergo electrophilic substitution with retention or inversion of configuration at the carbanionic

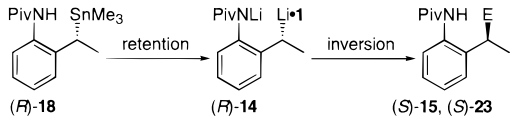
(15) Collum has recently reported that sparteine binds more strongly to LiHMDS than to TMEDA. Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10704.

(16) (a) Reich, H. J.; Phillips, N. H. *J. Am. Chem. Soc.* **1986**, *108*, 2102. (b) Reich, H. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577.

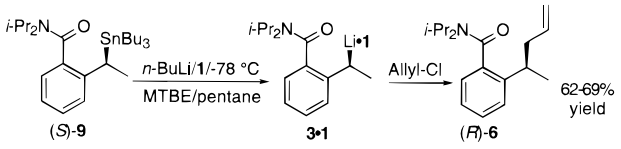
(17) If lithio-destannylation of **18** were producing ate complexes as reactive intermediates, the lithium would be not be localized at the stereogenic benzylic carbon of the organometallic. In such a case it seems less likely that the stereochemical behavior of the ate complex would be significantly affected by the nature of the ligand for lithium. The observations that the ligands **1** and **26** are involved suggests that the intermediates generated from the lithio-destannylation sequence are the same diastereomeric organolithium complexes that are formed in the warm/cool sequence.

(18) Lithio-destannylations with retention of configuration at the carbon bearing tin are usually observed, see: Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 3376. However, Clayden has recently reported a case of partial inversion: Clayden, J.; Pink, J. H., *Tetrahedron Lett.* **1997**, *29*, 552.

carbon.[3b,19] While there is precedent for invertive electrophilic substitutions, the facial selectivities in those cases are electrophile dependent.[20] The electrophilic substitutions of **14·1** appears to provide an invertive electrophilic substitution which is independent of the nature of the electrophile.[21]



Treatment of the stannyl compound (*S*)-**9**, of varying enantiomeric ratios with *n*-BuLi in the presence of (−)-sparteine (**1**) at −78 °C followed by reaction with allyl chloride provided (*R*)-**6** with high enantioenrichments, independent of the enantioenrichment of (*S*)-**9.** When these reactions were carried out with allyl tosylate as electrophile (*S*)-**6** was the product. Experiments which establish that neither lithium chloride nor lithium tosylate in the reaction medium affect the enantiomeric ratios were also carried out (*vide infra*).

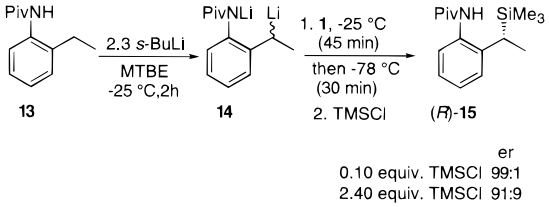


er	er
50:50	94:6
67:33	92:8
82:18	92:8
91:9	91:9

If the diastereomeric complexes of **3·1** were nonequilibrating at −78 °C, the enantioenrichments of the product would be expected to be dependent on the initial enantioenrichment of the organostannane. The observation that the enantioenrichment of (*R*)-**6**, or (*S*)-**6** using allyl tosylate as the electrophile, is independent of the enantioenrichment of **9** suggests that the diastereomeric complexes are equilibrating more rapidly than they react with the electrophile and the enantioselectivity of the reaction is the result of a dynamic kinetic resolution.[4]

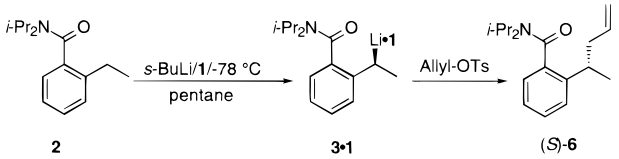
R. W. Hoffmann has provided an elegant method for determining the configurational stabilities of carbanions relative to the rates of their reaction with electrophiles. The Hoffmann Test takes advantage of the kinetic resolution of diastereomers in a reaction of a racemic organolithium reactant with a chiral electrophile in racemic and enantioenriched forms.[14] We have recently applied a variant of the Hoffmann Test in which organolithium species which are diasteriomeric by virtue of complexation with a chiral ligand undergo reaction with an achiral electrophile via diasteriomeric transition states.[6c] We refer to this as the "poor man's Hoffmann Test", as it does not require a chiral enantioenriched electrophile.[4] The tests can be carried out either by determining the stereoselectivity with a deficiency and excess of the electrophile or by monitoring the stereoselectivity of the substitution product as a function of the extent reaction and both approaches have been utilized here. If reaction with an excess and a deficiency of electrophile gives the product with different enantioselectivity or if the enantioselectivity near the beginning of the reaction is different from the enantioselectivity at later stages nonequilibrating diasteriomeric complexes which react at different rates with the electrophile are present.[4] In cases where non-equilibrating diasteriomeric complexes can be equilibrated under different conditions the reaction offers the opportunity for dynamic thermodynamic resolution.[4]

We have reported application of the test to the reaction of **13**, in which silylation of **14·1** with 0.1 equiv of TMSCl provided (*R*)-**15** with 99:1 er, in contrast to the 91:9 er obtained with 2.4 equiv of TMSCl.[22] This result clearly establishes the existence of two nonequilibrating diastereomeric complexes which react with the electrophile at different rates. We have used this approach to determine the relative reactivities of the complexes with TMSCl as well as to establish the ratio of the diastereomeric complexes to be 92:8.[23]



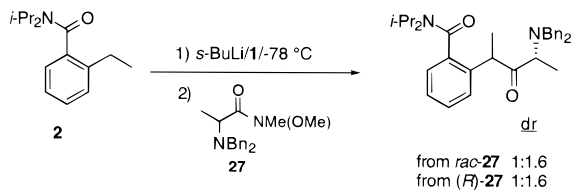
er	
0.10 equiv. TMSCl	99:1
2.40 equiv. TMSCl	91:9

The enantioselectivity of the reaction of **3·1** with allyl tosylate was monitored over the course of a reaction. The er of the product (*S*)-**6** was found to be independent of the extent of conversion. This observation is consistent with a mechanism of rapidly equilibrating diastereomeric complexes of **3·1** in a dynamic kinetic resolution.[24]



time (h)	**6**:**2**	er
1	13:87	80:20
2	23:77	81:19
4	35:65	80:20

The classic Hoffmann Test for **3** using the chiral electrophile **27** has been reported.[6a] The observation of a product diastereomeric ratio of 1:1.6 in reactions of **3** with both racemic and enantioenriched **27** also indicated that the organolithium **3** undergoes equilibration more rapidly than it adds to the amide **27**.[25]



(19) (a) Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424. (b) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (c) Derwing, C.; Hoppe. D. *Synthesis* **1996**, 149.

(20) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.

(21) The absolute configurations to the organostannanes are inferred by comparison of CSP-HPLC chromatographic profiles and signs of optical rotation which correspond to organosilanes. These assignments and those to the organolithium intermediates are provisional and used to show the suggested pathways of invertive substitutions of **14·1** and specific retentive substitution of **3·1** with tosylate and related nucleophiles.

(22) When the test is conducted by carrying out the electrophilic substitution at −25 °C, reaction with 0.1 equiv of TMSCl affords (*R*)-**15** with 98:2 er, while reaction with excess TMSCl provides (*R*)-**15** with 92:8 er.

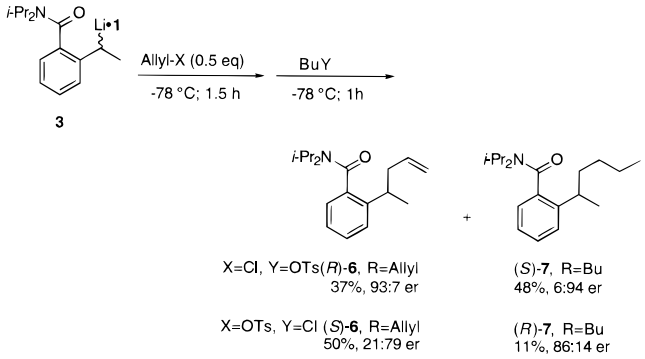
(23) The use of electrophiles other than TMSCl in the test with **14·1** afforded identical enantiomeric ratios in reactions with excess and deficient electrophile. This may be attributed to indistinguishable rates of reaction of each diastereomeric complex with the electrophile.

(24) Similar results were observed when allyl chloride was used as the electrophile.

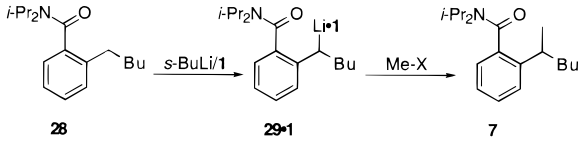
Table 7. Yields and Enantiomeric Ratios of **7** Obtained from (−)-Sparteine Mediated Enantioselective Lithiation−Substitution of **29** with Selected Methylating Agents

MeX	yield (%)	er	absolute configurtn
MeI	84	62:38	*S*
MeCl	75	84:16	*S*
$MeOSO_2CF_3$	53	79:21	*S*
$MeOSO_2C_6F_5$	<5	78:22	*S*
$(MeO)_3PO$	52	61:39	*S*
Me_2SO_4	51	38:62	*R*
$MeOSO_2$-*p*-$Me-C_6H_4$	50	17:83	*R*
$MeOSO_2$-*p*-$OMeC_6H_4$	38	12:88	*R*
$MeOSO_2C_6H_5$	56	11:89	*R*
$MeOSO_2$-*m*-$CF_3C_6H_4$	<10	5:95	*R*

Electrophile Dependence for 3·1. The dependence of the stereochemistry of alkylation of **3·1** upon the electrophile is an intriguing result. In order to determine if the lithium salts generated during the reaction affect the stereochemical outcome, reactions of **3·1** with alkyl tosylate in the presence of in situ generated lithium chloride and reactions of **3·1** with alkyl chloride in the presence of lithium tosylate were carried out.[26] Lithium chloride was generated by addition of 0.5 equiv of allyl chloride to **3·1** as the electrophile.[27] After 90 min, addition of butyl tosylate provided the product (*S*)-**7** with 6:94 er. A control reaction in which the addition of allyl chloride was omitted, afforded (*S*)-**7** with 7:93 er. An experiment using 0.5 equiv of allyl tosylate as the first electrophile followed by butyl chloride as the electrophile gave (*R*)-**7** with an 86:14 er, while omission of allyl tosylate also afforded (*R*)-**7** with 86:14 er. These results indicate that the presence of lithium chloride or lithium tosylate in the reaction mixture does not influence the stereochemistry of the alkylations.



An investigation of selected electrophiles has been carried out for **29·1** obtained by reaction of with *N*,*N*-diisopropyl-*o*-pentylbenzamide (**28**) with *s*-BuLi/(−)-sparteine at −78 °C in MTBE/pentane. Reaction of **29·1** with different methylating electrophiles provides **7** with the different absolute configurations and enantiomeric ratios shown in Table 7. The electrophiles methyl chloride, methyl iodide, methylpentafluorobenzene sulfonate, methyl triflate, and trimethyl phosphate, provided (*S*)-**7** with ers ranging from 61:39 to 84:16. With dimethyl sulfate, methyl tosylate, methyl-*p*-methoxybenzene sulfonate, methylbenzene sulfonate, or methyl-*m*-trifluoromethylbenzene sulfonate, (*R*)-**7** was obtained with ers from 38:62 to 5:95.



These results show that sulfonate leaving groups can provide either enantiomer of the product. The electrophiles methyl tosylate, methylbenzene sulfonate, methyl-*p*-methoxybenzene sulfonate, methyl-*m*-trifluoromethylbenzene sulfonate, and dimethyl sulfate, which favor the R isomer, appear to be slower reacting than methyl triflate and methylpentafluorobenzene sulfonate which favor the S isomer. This fact was substantiated by the treatment of **29·1** with a 1:1.2 ratio of $CH_3OSO_2CF_3$ to CD_3OSO_2Ph in the presence of **1** to provide (*S*)-**7** with 77:23 er and less than 5% d_3 incorporation.

Discussion

The amide-directed lateral lithiations of the benzamide **2** and the anilide **13** provide **3** and **14** which form complexes with (−)-sparteine that afford highly enantioenriched products on further reactions with electrophiles. The complex **14·1** affords products with high enantioselectivities with the same sense of configuration at the anionic carbon with a variety of electrophiles. The confirgurations of the products derived from the complex **3·1** are dependent on the electrophile.[28]

It has been demonstrated that stereoinformation transfer in the reactions of the benzylic organolithium species **3·1** and **14·1** occurs after deprotonation. Two limiting cases can be identified for asymmetric substitutions.[4] The pathways are distinguished by the rate of configurational epimerization at the benzylic carbon of the diastereomeric organolithium/ligand complexes with respect to the rate of the reaction of the complexes with an electrophile. In a dynamic thermodynamic resolution, the enantiodetermining step occurs prior to electrophilic substitution, and the complexes are nonequilibrating on the time scale of reaction with the electrophile. The enantioselectivity is then determined by the ratio of diastereomeric complexes for reactions with at least 1 equiv of the electrophile. In a dynamic kinetic resolution, the diastereomeric complexes are in rapid equilibrium with respect to their rate of reaction with the electrophiles. In this case, the enantioselectivity is determined by the difference in the transition state energies for reaction of each diastereomeric complex with the electrophile. The latter corresponds to a Curtin−Hammett situation.[4]

A variant of the Hoffmann Test of configurational stability of the lithiated benzamide **3·1** indicates that the complexes equilibrate more rapidly than they react with electrophiles.[29] The observation of highly enantioenriched product upon lithiodestannylation and substitution of (*S*)-**9** beginning with different enantioenrichments supports the hypothesis of rapid equilibration of the diastereomeric complexes under the reaction conditions. The reaction pathway of **3·1** is considered to be a dynamic kinetic resolution. The observation that lower enantioselectivities are observed at higher temperatures is consistent with the operation of this pathway.

(25) A potential concern is that the diastereomeric ratio of the product was determined by equilibration of the acidic benzylic position. This was shown to be unlikely by the failure of the products to equilibrate under the reaction conditions. Lee, S.; Beak, P. Unpublished results.

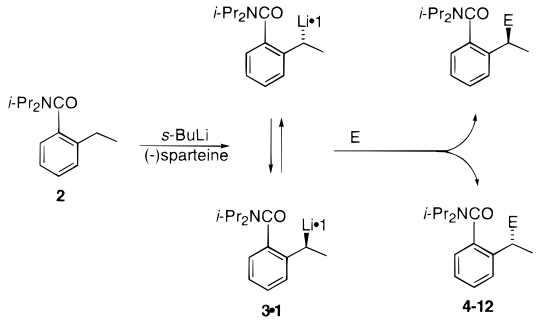
(26) (a) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533. (b) Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc., Perkin Trans. I* **1993**, 3113. For review on LiX salt effects, see: (c) Ruck, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433. (d) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227. (e) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(27) When the reaction is stopped before the addition of butyl tosylate, a significant amount of (*R*)-**6** is obtained. This confirms that allyl chloride has reacted with the organolithium to provide lithium chloride in solution prior to the addition of butyl tosylate.

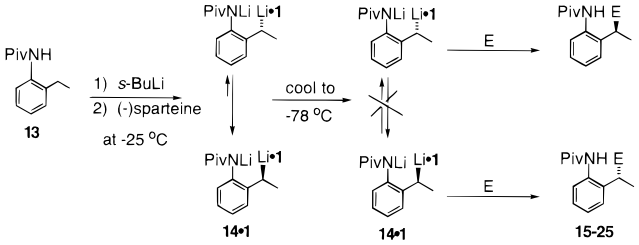
(28) Reaction of **3·1** with carbonyl electrophiles results in much poorer enantioenrichment than products derived from alkylation.

(29) While coincidental equivalence of transtion state energies remains a possibility for reactions of **3·1**, the observation of different enantioselectivities with different electrophiles suggests that this is not the case.

Scheme 1. Dynamic Kinetic Resolution



Scheme 2. Dynamic Thermodynamic Resolution



The reaction of the anilide **13** can take place under conditions where the diastereomeric complexes do not equilibrate faster than their rate of reaction with electrophiles. A thermodynamic ratio of diastereomeric complexes is established by equilibration at −25 °C and is the controlling factor in the transfer of stereochemical information. The result of the Hoffmann test at −25 °C as well as the observation that it requires longer than 5 min to establish the equilibrium indicates that the rate of epimerization of the **14·1** complexes at −25 °C is slow with respect to the rates of the electrophilic substitutions.[20] Equilibration does not occur on this time scale at −78 °C is also established by the lithio-destannylations of **18** in the presence of **1** and **26**.[6c]

It is interesting that the alkylations of **3·1** with alkyl halides occur with the opposite stereochemical sense to that observed with alkyl tosylates. The difference persists even with sulfonates; methyl triflate provides (*S*)-**7** with an er of 79:21 while methyl benzene sulfonate affords (*R*)-**7** with an er of 11:89. Our hypothesis is that the noncomplexing halides and the more reactive electrophiles approach the carbanion from the sterically less encumbered face resulting in an invertive substitution product.[30] The slower reacting sulfonates and the sulfates of Table 7 coordinate to the lithium of the organolithium intermediate to form an ion pair prior to carbon−carbon bond formation. This process could allow delivery of the alkyl group to the carbanionic center on the same face as the lithium and result in a net retentive substitution.[31] These pathways are consistent with the earlier suggestions of Hoppe.[19b]

The electrophilic substitution pattern for **14·1** does not follow that of **3.1**. Allyl chloride and allyl tosylate give (*S*)-**20** and of all the substitution reactions are suggested to occur consistently with inversion. In this case, the presence of the second lithium in the complex may play a role in coordination with the electrophile. Similar speculative rationales have been offered, and further work will be needed to delineate the stereochemical course of these reactions.[3b,19,20,32,33]

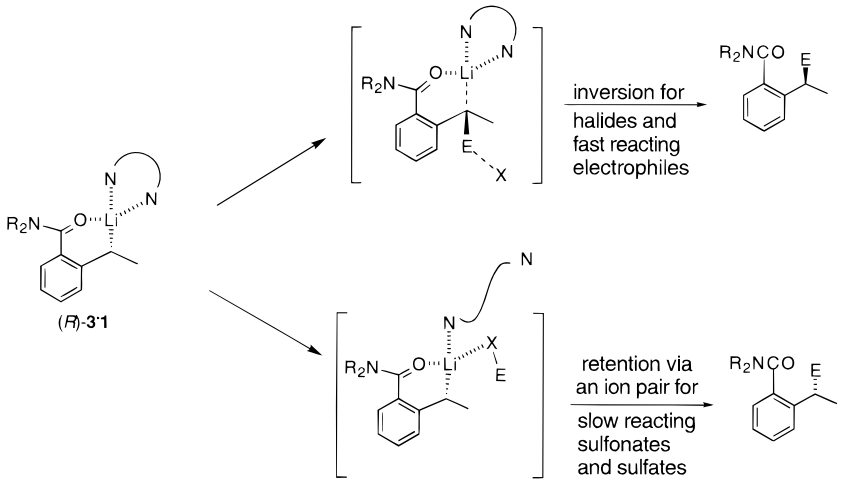
In summary, both **3·1** and **14·1** give significantly enantioenriched products by asymmetric substitutions in the presence of (−)-sparteine. However, the stereoinformation transfer occurs from the diastereomeric complexes by different pathways. The lithiated benzamide diastereomeric complexes **3·1** are rapidly equilibrating, and asymmetric induction occurs via a dynamic kinetic resolution. The anilide forms configurationally stable diastereomeric complexes **14·1** which equilibrate at −25 °C, and the reaction involves a dynamic thermodynamic resolution. In both cases, only one antipode of the chiral ligand provides access to enrichment in either enantiomer of the products. These reactions illustrate two general diastereoselective pathways which are available for enantioenrichment by asymmetric substitutions.

Experimental Section[34,35]

All solvents were obtained from commercial sources and used without further purification unless otherwise indicated. Diethyl ether (Et_2O), *tert*-butyl methyl ether (*t*-BuOMe), and tetrahydrofuran (THF) were distilled from sodium/benzophenone under a nitrogen atmosphere. Pentane was distilled from sodium/benzophenone under a nitrogen atmosphere with tetraglyme as cosolvent. Hexanes used for flash chromatography were distilled from bulk solvent over anhydrous $CaSO_4$. TMEDA was distilled over CaH_2. (−)-Sparteine was liberated from commercially available (−)-sparteine sulfate pentahydrate and distilled over calcium hydride under nitrogen atmosphere. *s*-BuLi in cyclohexane was titrated according to the method of Suffert.[36]

General Lithiation Procedure for *N,N*-Diisopropyl-*o*-ethylbenzamide (2): To a solution of (−)-sparteine (128.8 mg, 0.55 mmol) in 15 mL of solvent at −78 °C was added *s*-BuLi (0.52 mL, 1.06 M solution in cyclohexane, 0.55 mmol). The reaction mixture was stirred for 10 min −78 °C and then added to a precooled solution of **2** (116.7 mg, 0.5 mmol) in 15 mL of the solvent. The resulting purple reaction mixture was stirred for 1.5 h at −78 °C, and then 1.5 equivs of the electrophile was added. After the reaction was complete, methanol

Scheme 3



was added to the resulting colorless solution followed by extractive workup with water and diethyl ether. The aqueous layer was extracted twice with diethyl ether. The combined organic layer was washed with 0.5 M H_3PO_4. The organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide the crude product mixture. Purification by flash column chromatography using hexane/ethyl acetate mixture as the mobile phase provided pure product.

General Lithiation Procedure for *N*-Pivaloyl-*o*-ethylaniline (13). To a solution of pivanilide **13** (564 mg, 2.75 mmol) in ether (19 mL) at −25 °C was added *s*-BuLi (4.66 mL, 1.24 M in cyclohexane, 5.78 mmol), and the resultant bright orange solution was stirred at this temperature for 2 h. (−)-Sparteine (1.86 g, 7.94 mmol) was added, and the solution was stirred at −25 °C for 45 min, followed by cooling to −78 °C for 30 min. The electrophile was added, and the resultant solution was stirred at −78 °C until completion. The reaction was quenched with excess aqueous methanol, washed (5% H_3PO_4), dried ($MgSO_4$), and concentrated in vacuo. Purification of the mixture by chromatography provided product in pure form.

Acknowledgment. We are grateful to the National Institutes of Health, Institutes of General Medical Sciences and the National Science Foundation for support of this work.

Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **6**, **8**, **11**, **17**, **19**, and **24**, tests for configurational stability, and the effect of lithium chloride and lithium tosylate and the determination of absolute configuration of the compound **8** (17 pages). See any current masthead page for ordering and Internet access instructions.

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(30) In an alternate possibility, either enantiomer of the products can be obtained through a retentive substitution reaction in a dynamic kinetic resolution. In this case, the reactive diastereomeric complex would be different for different electrophiles.

(31) The ion pair formation with the sulfonates can be accommodated either by allowing the carbonyl group of the benzamide or one of the nitrogens of (−)-sparteine to move out of ligation with lithium.

(32) Meyers, A. I.; Knaus, G.; *J. Am. Chem. Soc.* **1974**, *96*, 6508. Chassaing, G.; Lett, R.; Marquet, A. *Tetrahedron Lett.* **1978**, *5*, 471. Beak, P.; Hunter, J. E.; Jun, Y. M.; Wallin, A. P. J. Am. Chem. Soc. **1987**, *109*, 5403.

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

(34) Other details of the general experimental prcoedures are provided as Supporting Information.

(35) Experimental procedures and characterization data for compounds **2**−**7**, **9**, **10**, **12**, **13**−**16**, **18**, **20**−**23**, **25**, and **28** as well as the experimental procedures for the determination of absolute configuration of **12**, **16**, and **20** are available as Supporting Information in refs 6a and 6b.

(36) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.