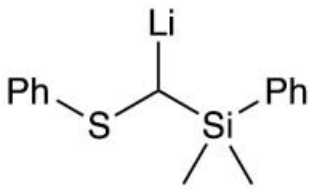
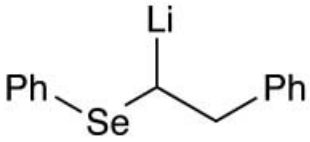
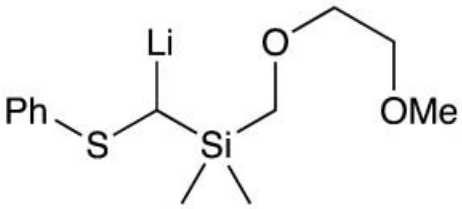
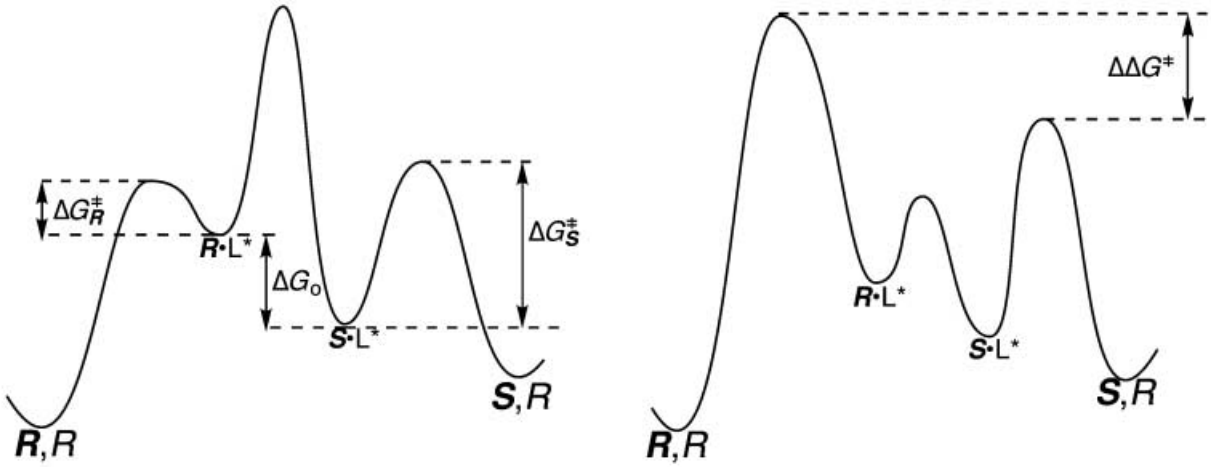


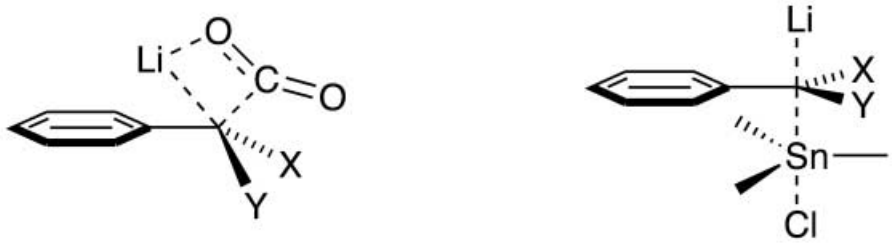
Examples of organolithium structures which have contributed to our understanding of configurational inversion pathways







Relative rates of inversion and electrophilic substitution can be probed by using the Hoffmann test for configurational stability



Retentive vs. invertive electrophilic substitution determines product stereochemistry

Configurational Stability and Transfer of Stereochemical Information in the Reactions of Enantioenriched Organolithium Reagents

Amit Basu* and S. Thayumanavan*

The conversion of a prochiral methylene group into a stereogenic center by means of a lithiation/substitution sequence has emerged as a powerful synthetic transformation over the past 15 years. This reaction proceeds via a chiral organolithium intermediate, and the stereochemical fidelity of the overall reaction sequence is intimately dependent on the stereochemical behavior of the chiral organolithium as well as on the rate and stereochemical sense of the electrophilic substitution step. Chiral organolithium reagents were first reported by Letsinger, Curtin, and Applequist half a century ago. The lithiated intermediates in these early studies were not highly configurationally stable, and applications in stereoselective synthesis were not immediately forthcoming. The two decades that followed the 1980 report by Still and Sreekumar of a configurationally stable α-oxyorganolithium were marked by an increased interest in these reagents. As the synthetic applications of chiral organolithium reagents have grown, so have accompanying mechanistic studies of these intermediates which serve as the basis for this review.

Keywords: asymmetric synthesis · configuration determination · enantioselectivity · electrophilic substitution · lithium

1. Introduction

The synthetic utility of chiral organolithium intermediates continues to provide the impetus for the development of new pathways for the stereoselective generation and subsequent reactions of these reagents. The synthesis (Scheme 1) involves conversion of an achiral starting material **R1** into one of two enantiomeric products **P1** or *ent*-**P1**. The stereoselectivity of the transformation is dependent on three factors:

a) the selectivity of formation of the stereoisomeric intermediates **C1** and *epi*-**C1**;
b) the rates of epimerization of **C1** and *epi*-**C1** relative to their rate of reaction with electrophiles;
c) the stereochemical course of the electrophilic substitution.

Changes in these variables can alter the stereochemical outcome of the reaction. Three limiting pathways are available for the transfer of stereochemical information:

a) *asymmetric deprotonation*: the selective formation of either **C1** or *epi*-**C1** by enantioselective proton abstraction from **R1** to generate a configurationally stable intermediate;
b) *dynamic kinetic resolution*: the lithiated intermediate is configurationally labile (i.e. **C1** and *epi*-**C1** are in rapid equilibrium), and stereoselectivity arises as a result of the differences in the transition state energies of electrophilic substitution for each diastereomeric intermediate;
c) *dynamic thermodynamic resolution*: the configurational stability of the diastereomeric intermediates is dependent on temperature, and stereoselectivity is dependent on the ratio of the two complexes.

Knowledge of the configurational behavior of the diastereomeric intermediates is crucial for identifying and understanding the reaction pathway. However, a detailed understanding of the origins of configurational stability remains unclear. The extent of the configurational stability and the mechanisms of inversion are very much dependent on the particular substrate. We are not aware of any example of an acyclic, sp^3-hybridized, nonheteroatom-containing organolithium compound that exhibits synthetically useful configurational stability under standard reaction conditions. The presence of a heteroatom within the molecule, whether it is adjacent to the lithium-bearing carbon atom or at some distal center, can significantly influence the stereochemical properties of the organolithium compound. A large variety of highly functionalized and synthetically useful chiral organolithium reagents have been developed in the past two decades.

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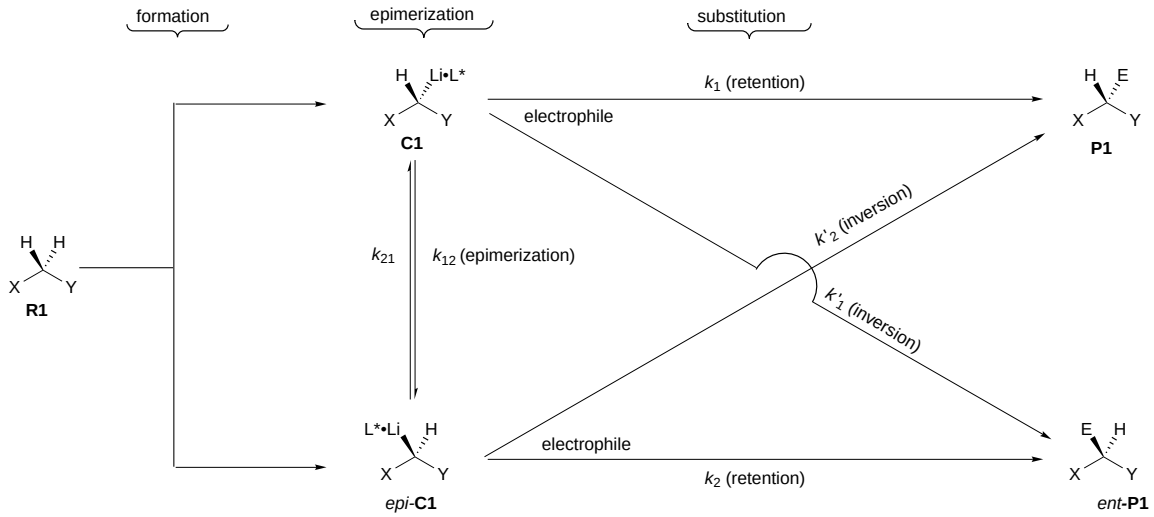

Scheme 1. Overview of steps involved in the lithiation and substitution of prochiral methylene groups.

In this review, we discuss these intermediates, their configurational stability, as well as the stereochemistry of the electrophilic substitution step. Initially (Section 2), we focus on the chemical and physical techniques that are used to probe the epimerization of enantiomeric/diastereomeric intermediates. Section 3 is a compendium of recent developments that involve the use of chiral organolithium reagents, and is organized on the basis of the substitution pattern adjacent to the organolithium center. We have restricted our focus in this section primarily to enantiomeric organolithium species. However, we mention diastereoselective reactions insofar as they provide unique and interesting examples of mechanistic phenomena that can be extended to the reactions of enantiomeric organolithium species. We conclude (Section 4) with a reexamination of the stereochemical irregularities that are frequently associated with the electrophilic substitution step.

We do not explicitly discuss the various methods for the selective generation of stereoisomeric intermediates **C1** and *epi*-**C1**, except for a few examples and relevant references. Although (−)-sparteine features prominently throughout the article, this is not a review of (−)-sparteine-mediated chemistry. The reader who is specifically interested in (−)-sparteine-assisted methodologies or coverage of synthetic applications is referred to several recent reviews.[1–4] Furthermore, the synthetic applications of these organolithium intermediates are beyond the scope of this article.

2. Spectroscopic and Chemical Methods for Determining Configurational Stability and Mechanisms of Inversion

2.1. Nuclear Magnetic Resonance Spectroscopy

Much of our understanding of the mechanism of configurational inversion derives from NMR spectroscopy studies of

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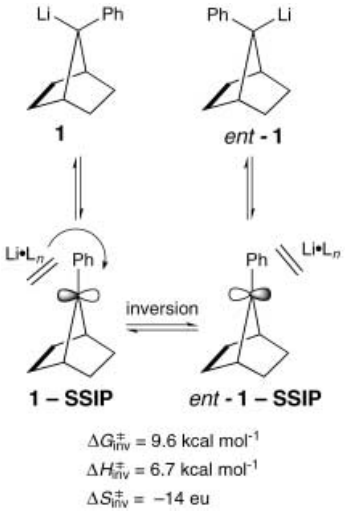
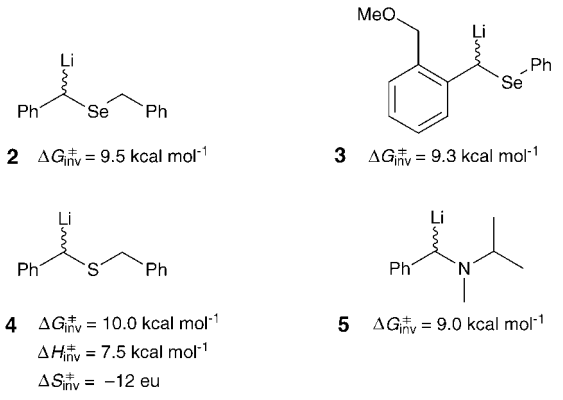
chiral organolithium intermediates, originally performed with primary organolithium reagents that contain diastereotopic marker groups.[5–7] NMR spectroscopy provides a quantitative description of the barriers for inversion and allows mechanistic information about the process to be inferred. Furthermore, enantioenriched samples are not required, because inversion can be detected by monitoring the dynamic behavior of diastereotopic signals in the molecule of interest. A variety of nuclei, including ^{1}H, ^{13}C, ^{6}Li, ^{7}Li, and ^{31}P have been used to provide structural and mechanistic information on the organolithium intermediate.

Thermodynamic parameters for the inversion of the achiral organolithium **1** (in [D_8]THF) were determined by means of NMR spectroscopy (Scheme 2).[8] It has been postulated that inversion occurs by the formation of a solvent-separated ion pair (SSIP) and planarization of the carbanion, followed by rotation of the ring and subsequent ion-pair recombination. The magnitude of the entropy of inversion is consistent with ion separation prior to or during the rate-limiting step.



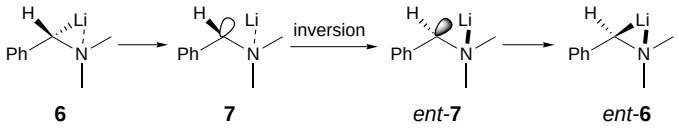
Scheme 2. Inversion of **1** through SSIP formation.

The α-heterobenzyllithium compounds **2**–**5** have remarkably homogenous inversion barriers despite several structural differences (Scheme 3).[9] The similar inversion energies of **2** and **3** indicate that the potential coordination of the lithium center to the heteroatom is not a crucial component of the inversion barrier. Consistent with this hypothesis, the inversion barrier for **4** is not affected by the addition of chelating amines such as pentamethyldiethylenetriamine (PMDTA). Even though there is restricted rotation around the C_{α}–C_{ipso} bond of α-lithio sulfide **4**, the organolithium compound is best characterized as an η^1 species on the basis of the temperature independence of the NMR spectroscopy signals, as well as the absence of a detectable NOE interaction between the lithium atom and the *ortho* hydrogen atom.[9] In contrast, both the *alpha* and *ipso* carbon atoms of the α-amino organolithium **5** exhibit temperature-dependent chemical shifts which suggests that the η^1 and η^3 structures are in equilibrium. Contrary to the case with **3** and **4**, addition of PMDTA or tetramethylethylenediamine (TMEDA) to **5** increases the inversion barrier. These comparisons reveal that despite the similarities in the magnitudes of the inversion barriers for a variety of α-heteroatom-substituted organolithium compounds, the mechanisms of the configurational inversion can differ. The entropies of activation observed for the inversion of **1** and **4** are consistent with an increased solvation of the lithium atom as it dissociates from the carbanion to form an ion pair. Hoffmann and co-workers have referred to this process as an increased "electrostriction" of the surrounding bulk solvent, that is, an increased solvent organization as a result of the increased dipole of the ion pair.[9]



Scheme 3. Inversion barriers of α-heteroatom-substituted benzylic organolithium compounds.

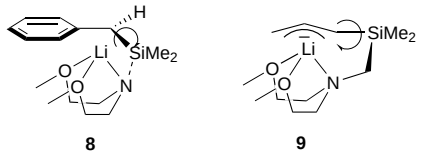
The process of inversion requires the lithium atom to move from one enantioface of a chiral organolithium compound to the other. A possible pathway involves the formation of a separated ion pair, followed by the rotation of the anion prior to reassociation of the lithium, as suggested by Peoples and Grutzner for **1**.[8] An alternative pathway is a conducted tour mechanism, originally suggested by Cram and Gosser, in which the lithium ion is coordinated to a Lewis basic site in the molecule, and is subsequently delivered to the opposite face of the carbanion.[10] The crystal structure of α-lithio-*N*,*N*-dimethylbenzylamine (**6**) indicates that the lithium ion bridges the carbon and nitrogen atoms. This bridged motif has also been observed in additional α-lithio amines by means of NMR spectroscopy.[11] Such a structure might represent the first step in a "conducted tour" process for an α-hetero organolithium compound which proceeds via the ion pair **7** (Scheme 4).[12]



Scheme 4. Nitrogen atom facilitated inversion of α-lithio-*N*,*N*-dimethylbenzylamine.

Fraenkel et al. have unambiguously identified an example of the conducted tour mechanism in the dynamic behavior of the benzylic and allylic organolithium reagents **8** and **9**.[13, 14] Rotation about the C–Si bond places the lithium ion on the other face of the carbanion, formally inverting the configuration of the planar carbanionic center. However, the similarity of the inversion barriers for **2**–**5**, along with the

lack of a heteroatom effect for the selenides **3** and **4** suggests that intramolecular Lewis base coordination of the lithium ion need not be a dominant factor during inversion (Scheme 5).

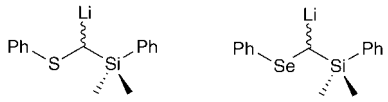


8 $G^{\ddagger}$ = 9.9 kcal mol^{-1}, $H^{\ddagger}$ = 6.6 kcal mol^{-1}, $S^{\ddagger}$ = –13 eu

9 $G^{\ddagger}$ = 11.9 kcal mol^{-1}, $H^{\ddagger}$ = 7.9 kcal mol^{-1}, $S^{\ddagger}$ = –15 eu

Scheme 5. Chelation-assisted configurational inversion of **8** and **9**.

A very different mechanism for the inversion of α-heteroatom-substituted organolithium reagents was reported independently by Hoffmann and co-workers and by Reich et al. in 1993.[15, 16] The addition of hexamethyl phosphoramide (HMPA) to organolithium compounds **10** and **11** generates spectroscopically characterizable contact ion pairs (CIPs). Titration of the contact ion pairs with additional HMPA generates SSIPs, which were identified by retention of Li–P coupling and the disappearance of Li–H and Li–C coupling in the NMR spectra. Remarkably, the inversion barriers of the SSIPs of **10** and **11** were significantly higher than those of the parent organolithium species themselves (Scheme 6). This observation is inconsistent with a model that involves lithium dissociation and solvation as the rate-determining step.



10 **11**

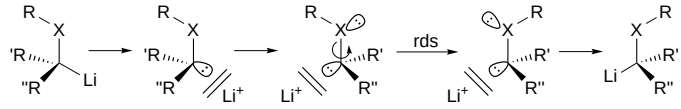
$\Delta G^{\ddagger}$ [kcal mol^{-1}]

RLi	SSIP	RLi	SSIP
8.0	9.1	8.2	9.5

Scheme 6. Differential inversion barriers for α-thio and α-selenoorganolithium compounds: covalent and SSIP intermediates.

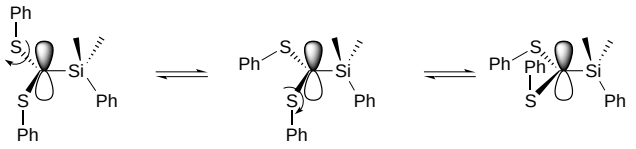
α-Thio-substituted organolithium compounds had long been suggested to be stabilized by n–σ* overlap, thus it was postulated that the rate-determining step for the inversion of **10** and **11** actually involved rotation around the C–S and C–Se bonds, respectively (Scheme 7).[17] The increased rotation barrier of the SSIP could arise from the repulsion between the carbanion and hetereoatom lone pairs, an interaction which is alleviated by the lithium atom in both the contact ion pair and the covalent organolithium species.

Dynamic NMR spectroscopic analysis of related organolithium **12** exhibited coalescence of the signals for the methyl



Scheme 7. C–X bond rotation as the rate-determining step (rds) for the inversion of α-thio and α-seleno organolithium compounds.

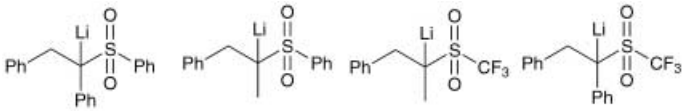
group, which corresponds to a $\Delta G^{\ddagger}_{inv}$ of 13.3 kcal mol^{-1}.[16] Diastereotopic methyl groups on silicon can be observed only if rotamer interconversion is slow on the NMR time scale, since **12** is achiral if C–S bond rotation is rapid (Scheme 8).



12a **12b** **12c**

Scheme 8. Formal configuration inversion through sequential C–S bond rotations of **12a**.

Increasing the steric bulk of the aryl group on the sulfur atom raised the inversion barrier, which is consistent with bond rotation as the rate-determining step. This phenomenon had been documented earlier with chiral α-lithio sulfones by Gais et al.[18, 19] Trifluoromethyl sulfones **15** and **16** have an inversion barrier which is almost twice as high as that for phenylsulfones **13** and **14**. As before, the higher activation energy is attributed to increased n–σ* overlap caused by the lower energy σ* orbital of the trifluoromethyl group (Scheme 9).[20]



13 $\Delta G^{\ddagger}_{inv}$ = 9.6 [kcal mol^{-1}]

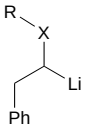
14 $\Delta G^{\ddagger}_{inv}$ = 9.6

15 $\Delta G^{\ddagger}_{inv}$ = 17.8, $\Delta H^{\ddagger}_{inv}$ = 16.7, $\Delta S^{\ddagger}_{inv}$ = –1.9 eu

16 $\Delta G^{\ddagger}_{inv}$ = 16.0

Scheme 9. Inversion barriers of tertiary lithiated sulfones.

Hoffmann et al. carried out an extensive NMR study of α-thio-, α-seleno-, α-telluro-, and α-silyl-substituted organolithium compounds **17** (Scheme 10).[21] In the chalcogen series, an increase in the steric bulk of the aryl group results in a decrease in the rates of inversion, consistent with C–X bond rotation as the rate-determining step. The inversion of α-deuterated **17e** does not exhibit an observable secondary isotope effect, and the inversion barrier for **17e** is not dependent on the solvent. The former indicates that configurational inversion of the organolithium is not the rate-determining step, and the latter result is inconsistent with the formation of a SSIP in the rate-determining step (Table 1).



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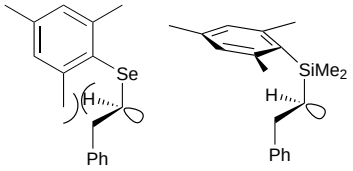
Scheme 10. α-Thio, α-seleno, α-telluro, and α-silyl organolithium compounds (X = S, Se, Te, Si).

In contrast, the inversion barriers of the silyl-substituted organolithium compounds do not vary with steric modifications.[21] This is attributed to the ability of the aryl group to rotate about the C_{ipso}–Si bond, thus minimizing the steric impact of the *ortho* substituents. However, when the heteroatom X is sulfur, tellurium, or selenium, n–σ* overlap between the heteroatom lone pair and the aryl ring requires

Table 1. Inversion barriers for α-chalcogen organolithium intermediates.

17	X	R	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	$\Delta H^{\ddagger}$ [kcal mol^{-1}]	$\Delta S^{\ddagger}$ [eu]
a	S	phenyl	11.3	10.6	−2.7
b	S	*m*-$CF_3C_6H_4$	11.4	9.3	−8
c	S	*p*-$MeOC_6H_4$	11.4	10.2	−4.5
d	S	duryl	>13.9		
e	Se	phenyl	12.4	11.7	−2.9
f	Se	*o*-tolyl	12.7		
g	Se	*p*-tolyl	12.3		
h	Se	mesityl	>14.3		
i	Se	duryl	>14.5		
j	Te	phenyl	11.8	10.0	−6.8
k	Te	duryl	13.9	14.7	3.0
l	$SiMe_2$	methyl	12.6	11.3	−5
m	$SiMe_2$	phenyl	11.8	12.4	2.0
n	$SiMe_2$	mesityl	11.8	11.1	−2.6
o	SiPhMe	phenyl	11.7	9.7	−7.9
p	$SiMe_2$	phenyl	11.9	7.0	−18.4

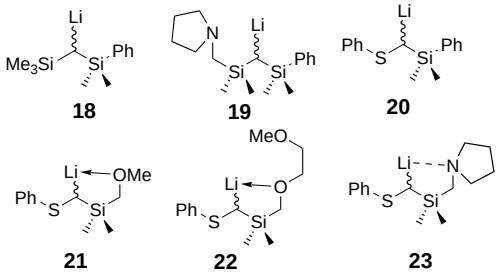
that the carbanion lone pair be positioned in a synclinal orientation to the nonbonded electrons on the heteroatom ring in the transition state of enantiomerization. This back-bonding type of interaction alleviates the energy cost of eclipsing the lone pairs, but imposes rotational restrictions on the C_{ipso}–X bond. In contrast, the arylsilane can twist out of the plane and avoid unfavorable steric interactions (Scheme 11).



17h **17n**

Scheme 11. Steric interactions in the inversion of α-thio and α-silyl organolithium compounds.

The effect of heteroatom substitutions on the inversion barriers of α-silyl and α-thio organolithium compounds has been examined by using similar NMR spectroscopy methods.[22] The bis-silyl organolithium compound **18** has a $\Delta G^{\ddagger}_{inv}$ of 11.2 kcal mol^{-1}, whereas the SSIP formed upon addition of 4 equivalents of HMPA has a corresponding barrier which is less than 7 kcal mol^{-1}. The presence of a coordinating heteroatom as in **19** does not have a significant effect on the inversion enthalpy $\Delta G^{\ddagger}_{inv}$ of the CIP, but significantly reduces the $\Delta S^{\ddagger}_{inv}$ term. Formation of the SSIP upon addition of 4 equivalents of HMPA reduces the barrier of **19** to less than 7.0 kcal mol^{-1}. These results are consistent with a model of inversion that involves the dissociation and solvation of the lithium atom in the transition state of inversion. Coordination of the lithium ion to a nitrogen atom slightly decreases the value of $\Delta G^{\ddagger}_{inv}$, but the entropic contribution is significantly reduced. The small values of $\Delta S^{\ddagger}_{inv}$ suggest that the nitrogen atom plays a role in delivering the lithium ion to the correct face of the newly inverted carbanion. In contrast, the $\Delta G^{\ddagger}_{inv}$ values for the thio-substituted organolithium compounds **20**–**23** (Scheme 12, Table 2) increase when intramolecular coordination is possible. Since the transition state for the inversion of **22** and **23** involves bond rotation and not lithium



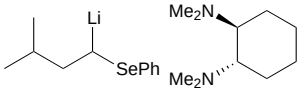
Scheme 12. Effect of coordinating heteroatoms on the inversion barriers of α-silyl and α-thio organolithium compounds.

coordination, the increased $\Delta G^{\ddagger}_{inv}$ values relative to **20** may represent better stabilization of the ground state in these species. In cases where $\Delta S^{\ddagger}_{inv}$ was determined, the values were found to be low which is consistent with a rate-determining step that involves bond rotation.

Table 2. Effects of the heteroatom on the inversion barriers of α-silyl organolithium intermediates.

Compound	RLi $\Delta G^{\ddagger}$ [kcal mol^{-1}]	$\Delta H^{\ddagger}$ [kcal mol^{-1}]	$\Delta S^{\ddagger}$ [eu]	SSIP $\Delta G^{\ddagger}$ [kcal mol^{-1}]
18	$\Delta G^{\ddagger}=11.2$	$\Delta H^{\ddagger}=10.1$	$\Delta S^{\ddagger}=-6.3$	<7.0
19	$\Delta G^{\ddagger}=10.7$	$\Delta H^{\ddagger}=10.5$	$\Delta S^{\ddagger}=-1.3$	<7.0
20	$\Delta G^{\ddagger}=8.0$	$\Delta H^{\ddagger}=7.9$	$\Delta S^{\ddagger}=-0.5$	9.5
21	$\Delta G^{\ddagger}=10.0$			9.4
22	$\Delta G^{\ddagger}=9.3$			9.6
23	$\Delta G^{\ddagger}=10.5$	$\Delta H^{\ddagger}=9.8$	$\Delta S^{\ddagger}=-3.6$	≥9.4

The effect of an intermolecular chelating ligand on the barrier of inversion of an α-seleno organolithium compound has been investigated.[23] The $\Delta G^{\ddagger}_{inv}$ for **24** was found to be 12.1 kcal mol^{-1}, both in the absence or presence of diamine **25**, which is consistent with C–Se bond rotation as the rate-determining step (Scheme 13).



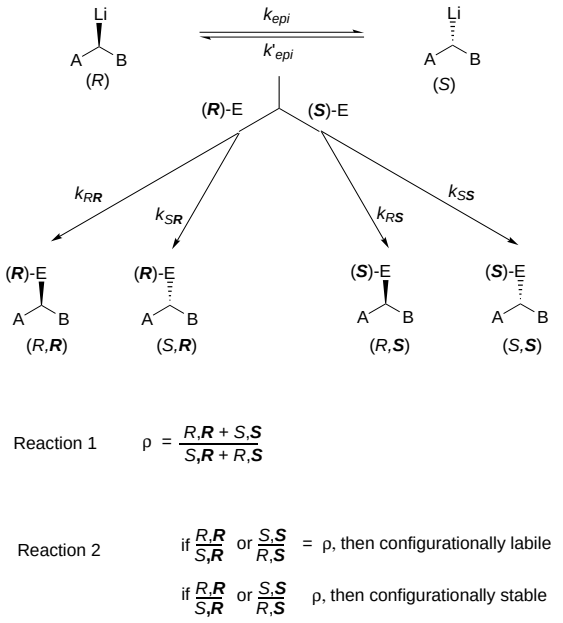
24 **25**

Scheme 13. α-Lithioselenide **24** is also configurationally labile in the presence of chelating diamine **25**.

In summary, the use of NMR spectroscopy as a probe for configurational behavior has provided a wealth of mechanistic information about the inversion process. The technique has broad scope and utility because of the ability to use achiral or racemic organolithium reagents. This technique has led to the identification of three types of mechanisms for inversion: a) a classical dissociative mechanism that involves the separation of the lithium atom from the organolithium carbon atom, followed by configurational inversion and recombination; b) a mechanism in which the dissociation process is facilitated by inter- or intramolecular Lewis base coordination; c) a final mechanism which does not involve dissociation in the rate-determining step—in this case, a bond rotation provides the highest energy barrier, usually as a result of some steric or stereoelectronic interaction. Thus, although several details of the inversion process have been clarified, it is clear that no single factor dominates the configurational behavior of organolithium species studied to date.

2.2. Determination of Configurational Stability Based on Kinetic Resolution (Hoffmann Test)

For our understanding of the mechanism and rates of inversion to be synthetically meaningful, this knowledge needs to be related to the rate of the reaction of the organolithium compound with an electrophile. Thus, an appreciation of configurational stability during an electrophilic substitution step can be of great value when developing synthetic methods that require chiral organolithium reagents. With this aim in mind, Hoffmann and coworkers have developed a chemical test of configurational stability based on kinetic resolution during the electrophilic substitution step.[24–26] The Hoffmann test consists of the two reactions, as outlined in Scheme 14. In the first reaction, which is a control reaction, the racemic organolithium compound is allowed to react with a racemic mixture of a chiral electrophile. It is desirable that the diastereomeric ratio of the resulting products lies between 1.5 and 3.0. In the second reaction, the racemic organolithium compound is treated with enantiopure electrophile. If the diastereomeric ratio of the products is the same as that obtained with the racemic electrophile, the organolithium is configurationally labile with respect to the rate of reaction with that particular electrophile. However, if the ratio of products from the second reaction differs from that observed in the control reaction, the organolithium is at least partially configurationally stable. In the case of an organolithium compound that is completely configurationally stable on the time scale of the reaction, the diastereomeric ratio from the second reaction should be equal to one. Although, in principle, any electrophile that meets the Hoffmann test criteria can be used, the vast majority of the reactions to date have involved the use of the Reetz aldehyde, *N*,*N*-dibenzylalaninal.[27]



Reaction 1 $\rho = \frac{R,\mathbf{R} + S,\mathbf{S}}{S,\mathbf{R} + R,\mathbf{S}}$

Reaction 2 if $\frac{R,\mathbf{R}}{S,\mathbf{R}}$ or $\frac{S,\mathbf{S}}{R,\mathbf{S}}$ = ρ, then configurationally labile

if $\frac{R,\mathbf{R}}{S,\mathbf{R}}$ or $\frac{S,\mathbf{S}}{R,\mathbf{S}}$ ρ, then configurationally stable

Scheme 14. Outline of the Hoffmann test for the determination of configurational stability. Reaction 1 is carried out with a racemic electrophile (E). Reaction 2 is carried out with an enantioenriched electrophile. If ρ for Reaction 1 is between 1.5 and 3.0, the electrophile is suitable for the Hoffmann test.

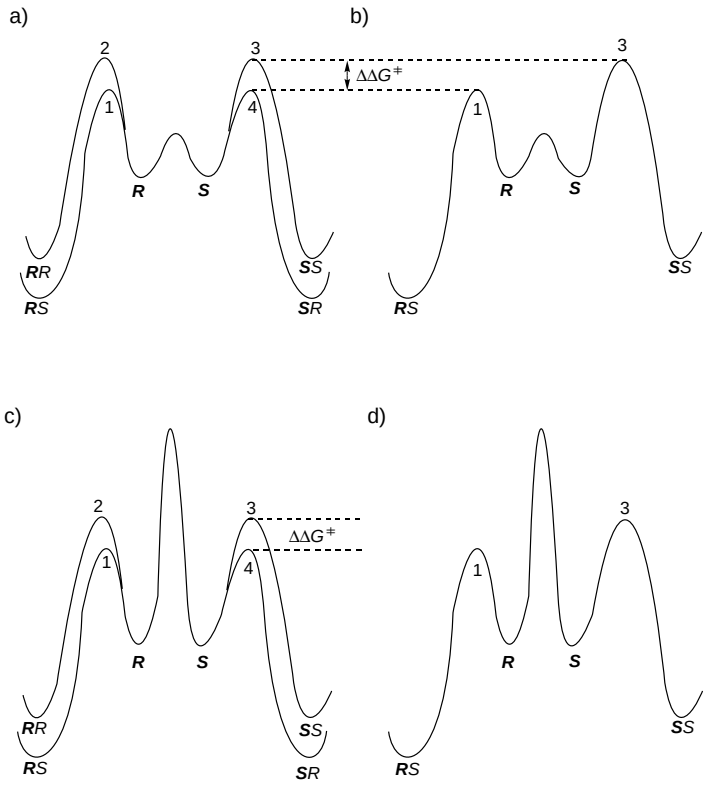


Figure 1. Energy diagram of the reaction kinetics of the Hoffmann test: a) and b) Reactions of a configurationally labile intermediate with the racemic electrophile or the pure *S* enantiomer. The product ratios are dependent on $\Delta\Delta G^{\ddagger}$; c) and d) Reactions of a configurationally stable intermediate with the racemic electrophile or the pure *S* enantiomer. The product ratios in c) are dependent on $\Delta\Delta G^{\ddagger}$, whereas d) shows that the product ratio is independent of $\Delta\Delta G^{\ddagger}$ in limiting cases.

The kinetic basis for the Hoffmann test can be understood by considering the energy diagrams in Figure 1. Figures 1a and 1b represent the reactions of a configurationally labile intermediate with the racemic and with the *S* enantiomer of an electrophile, respectively. In the reaction with the racemic electrophile, four different pathways are available for the equilibrating racemic organolithium intermediates. Since pathways 1 and 2 are enantiomeric to pathways 4 and 3, the overall diastereoselectivity of the product is determined by the diastereomeric transition state energy difference $\Delta\Delta G^{\ddagger}$ (Figure 1a). In the reaction with only the *S* enantiomer of the electrophile, trajectories 1 and 3 are the only pathways available for the equilibrating organolithium intermediate. However, since equilibration of the enantiomers is faster than the reaction with the electrophile, the overall diastereoselectivity of this reaction will still be determined by the diastereomeric transition state energy difference $\Delta\Delta G^{\ddagger}$ (Figure 1b). Thus, the diastereoselectivity of the reaction of a configurationally labile organolithium intermediate should be the same, regardless of whether the electrophile is racemic or enantiomerically pure. This situation represents a classic Curtin–Hammett situation.[28]

Figures 1c and 1d represent the reaction of a configurationally stable intermediate with the racemic and with the *S*

enantiomer of the electrophile, respectively. In the reaction with the racemic electrophile, pathways 1 and 2 are available for the *R* enantiomer of the organolithium intermediate, whereas pathways 3 and 4 are available for the *S* enantiomer of the organolithium intermediate. As before, pathways 1 and 2 are enantiomeric to pathways 4 and 3, respectively, and the overall diastereoselectivity of the product is still determined by the energy difference $\Delta\Delta G^{\ddagger}$ of the transitions states of the diastereomers.

However, the results of the reaction with an enantioenriched electrophile would differ for configurationally stable and configurationally labile intermediates. For configurationally stable intermediates, in the reaction with only the *S* enantiomer of the electrophile, the only available pathway for the *R* enantiomer of the organolithium compound is pathway 1 and the only available pathway for the *S* enantiomer of the organolithium compound is pathway 3. Since the intermediates are not at equilibrium, the diastereomeric ratio of the products will reflect the ground-state enantiomeric ratio of the organolithium intermediate, provided that the reaction is allowed to go to completion. Therefore, in the ideal case of a racemic configurationally stable organolithium intermediate, the diastereoselectivity of the products from the reaction represented by Figure 1 d would be equal to one.

It is critical that the reaction with the enantioenriched electrophile proceeds with high conversion; excess electrophile is usually used. Furthermore, if the intrinsic diastereoselectivity of the reaction is excessively large, the amount of "mismatched" reaction product from pathways 2 and 3 may be too small to be detected. The fact that racemic organolithium species can be used, as well as the requirement for low intrinsic diastereoselectivity allows one to conduct the Hoffmann test even with organolithium reagents and/or electrophiles that do not exhibit synthetically useful stereoselectivities. Furthermore, since the ratio obtained from the control reaction is the kinetic ratio, it can also be obtained by using the enantioenriched electrophile at very low conversions or by using it in substoichiometric amounts.

A modification of the Hoffmann test allows one to probe the rates of interconversion of organolithium species that are complexed to a chiral ligand.[29] Complexation renders the two interconverting species diastereomeric instead of enantiomeric, thereby disrupting the energy symmetry of the configurational inversion process. In this case, two experiments that are very similar to the original Hoffmann test, are conducted, except that only enantioenriched electrophile is used. The reactions are carried out by using stoichiometric and substoichiometric amounts of this electrophile. If the product stereoisomer ratios are different in the two cases, then the organolithium compound is configurationally stable on the timescale of the experiment. However, with diastereomeric organolithium complexes, the observation of identical product ratios does not necessarily imply configurational lability, and further experiments are required. Figure 2 shows an energy diagram for a case in which diastereomeric complexes (or diastereomers, as the test can be applied to both) do not rapidly interconvert relative to the rate of their reaction with the electrophile. The reaction with a stoichiometric amount of electrophile reflects the starting ratio of complexes $R\cdot$L and

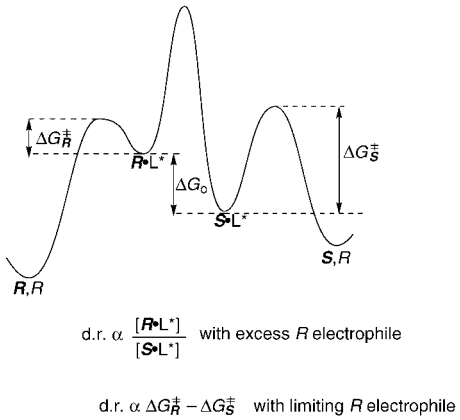


Figure 2. Kinetics of the modified Hoffmann test with non-equilibrating diastereomeric complexes. In the case of excess *R* enantiomer of the electrophile, the product ratio is dependent on the concentration ratio of the complex. When the *R* enantiomer is the limiting reagent,, the product ratio is dependent on the difference in the activation enthalpies.

$S\cdot$L. If the system is allowed to reach thermodynamic equilibrium, the product ratio reflects the ground-state energy difference ΔG_o. Once again, it is important to ensure that the reaction proceeds to completion; excess electrophile is generally used. In the reaction with small amounts of electrophile (very low conversion), the product ratio will reflect the differences between the activation energies, $\Delta G_S^{\ddagger} - \Delta G_R^{\ddagger}$, corrected for the relative population of the diastereomeric intermediates. At higher conversions, the ratio will of course shift towards the value obtained in the first reaction.

Identical ratios of stereoisomeric products in the two reactions can arise from two possible scenarios: a) the system is configurationally labile, and the product ratios in both reactions are the result of a dynamic kinetic resolution (Figure 3); b) the system is configurationally stable, but the activation energies for electrophilic substitution are identical ($\Delta G_S^{\ddagger} = \Delta G_R^{\ddagger}$). In the first case, the product ratio for both reactions will be determined by $\Delta\Delta G^{\ddagger}$. To distinguish between the two cases, one needs to be able to determine the starting ratio of diastereomeric complexes. If this ratio is not the same as the product ratio, then the system is configurationally labile. However, if the ratios are the same, then no kinetic resolution has occurred, and the configurational behavior cannot be determined—different electrophiles or reaction conditions must be tried.

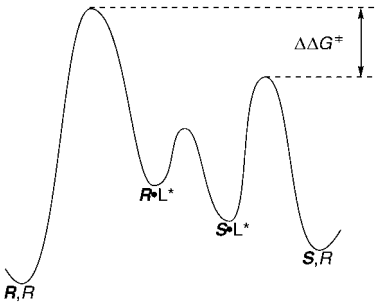


Figure 3. Kinetics of the modified Hoffmann test with rapidly equilibrating diastereomeric complexes. The product ratio is dependent on the activation enthalpies, both when the *R* enantiomer is in excess or when it is the limiting reagent.

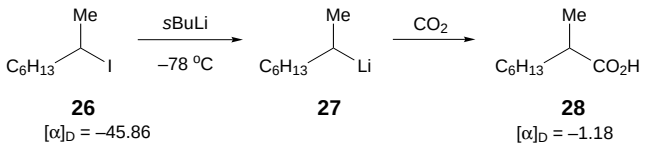
The Hoffmann test for diastereomeric complexes has been modified further to enable the use of achiral electrophiles.[30–32] The transition states that result from these complexes are diastereomeric as a result of the chiral ligand, and thus the electrophile no longer requires a stereocenter. In the modified test, the products are enantiomeric instead of diastereomeric, and the enantiomer ratio is determined instead of the diastereomer ratio.

The Hoffmann test and its variations have been applied to a wide variety of organolithium reagents. Although the successful interpretation of the results from a Hoffmann test does not require knowledge of the stereochemical course of the electrophilic substitution step in reactions of enantiomeric organolithium compounds, this is not the case with diastereomeric intermediates. Regardless of the actual invertive/retentive partition during electrophilic substitution of a given enantiomer of an organolithium compound, the other enantiomer must, by necessity, react with the same partition ratio because the pathways are isoenergetic. However, the stereochemical course of electrophilic substitution for two diastereomeric intermediates, which can differ in energy, need not be identical. While Ockhams's razor has led to the assumption of the more simple theory (identical stereochemical behavior for both diastereomers), this is an issue that may need to be examined more carefully in some cases.

3. Chiral Organolithium Reagents

3.1. Nonheteroatom α-Substituted Organolithium Compounds

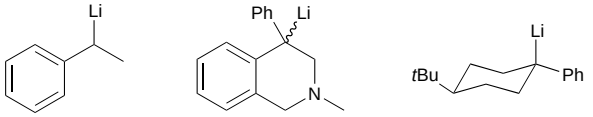
To the best of our knowledge, the first enantiomerically enriched organolithium compound was reported by Letsinger in 1950, who prepared the organolithium intermediate **27** by treating (−)-2-iodooctane (**26**) with *sec*-butyllithium (*s*BuLi) at −70 °C in a petroleum ether/diethyl ether mixture.[33] The organolithium intermediate retained approximately 20 % of its original configuration to provide optically active (−)-2-methyloctanoic acid (**28**) after treatment with CO_2 (Scheme 15). Higher reaction temperatures or use of polar solvents afforded the product with diminished optical activity, presumably as a result of racemization of the organolithium intermediate.[34]



26 $[\alpha]_D = -45.86$ **27** **28** $[\alpha]_D = -1.18$

Scheme 15. The first enantioenriched organolithium compound **27**, which was used in the synthesis of optically active (−)-2-methyloctanoic acid (**28**).

Nozaki et al. reported that deprotonation of ethylbenzene with *n*BuLi/(−)-sparteine followed by electrophilic substitution provided enantioenriched products, albeit with poor selectivities.[35] The resulting benzyllithium compound **29** was subsequently established to be configurationally labile under the conditions of the Hoffmann test.[36] The related benzyllithium intermediate **30** also undergoes electrophilic substitution under dynamic resolution, but it is not known whether it is under kinetic or thermodynamic conditions (Scheme 16).[37]

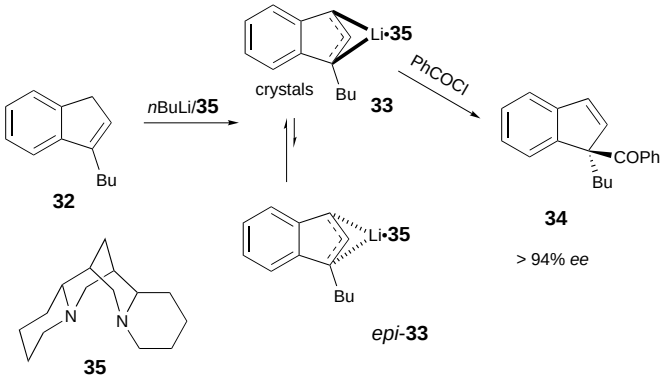


29 **30** **31**

Scheme 16. Earlier benzyllithium intermediates used in the first studies of configurational stability.

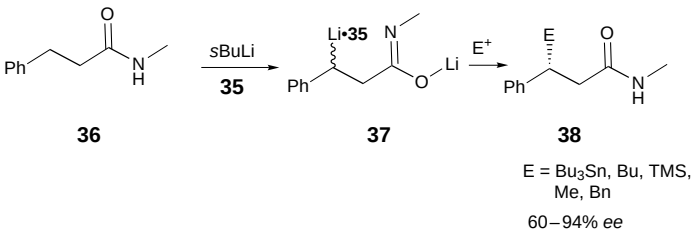
In contrast, protonation of benzyllithium compound **31** with deuterated water or dihydronaphthalene provides products with different *cis*/*trans* ratios in each case.[38] This result is taken to indicate that epimerization of **31** is competitive with the rate of protonation. Alternatively, the different diastereomeric ratios could arise from different amounts of retentive and invertive protonation.

A single enantiomer of a benzyllithium compound can be selectively stabilized by crystallization in a chiral environment.[39] Treatment of 1-butylindene (**32**) with a mixture of *n*BuLi and (−)-sparteine (**35**) provided the organolithium intermediate **33** as a single crystalline diastereomer. Treatment of **33** with benzoyl chloride occurred with retention of configuration to afford **34** (*ee* > 94 %; Scheme 17).



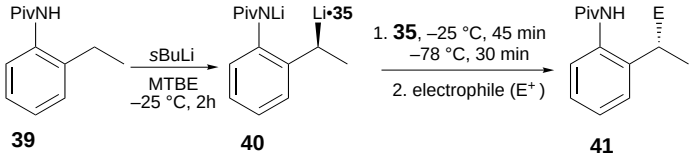
Scheme 17. Stereoselective crystallization/substitution of **33** in the presence of (−)-sparteine (**35**).

The (−)-sparteine-mediated substitution of enantiomeric β-lithiated amides has been reported. Treatment of secondary amide **36** with *s*BuLi/**35** afforded the organolithium intermediate **37**, which reacted with electrophiles to afford the substituted products **38** with good to excellent enantiomeric excesses (Scheme 18).[40] The configurational stability of the organolithium intermediate in the absence of diamine was established by using Sn/Li exchange experiments.[40, 41] However, in the presence of (−)-sparteine, the intermediate **37** exhibits a rate of epimerization that is comparable with that of the electrophilic substitution with trimethylsilyl chloride (TMSCl) at −78 °C, as determined by means of a modified Hoffmann test. At −100 °C the rate of epimerization is sufficiently slow to result in a dynamic thermodynamic resolution.[41]

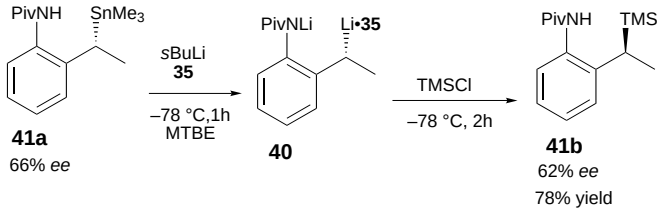


Scheme 18. (−)-Sparteine-mediated dynamic resolution of **37**.

Stereoselective (−)-sparteine-mediated lateral lithiation reactions of *N*-pivaloyl aniline **39** and *o*-ethyl-*N*,*N*-diisopropylbenzamide have been carried out.[42–44] In the case of the lithiated aniline **40**, highly enantioenriched products were obtained by allowing the diastereomeric organolithium intermediate to reach thermodynamic equilibrium at −25 °C. Subsequent cooling to -78 °C followed by electrophilic substitution provided products with high enantiomeric ratios (Scheme 19). Intermediate **40** was shown to be configurationally stable in the presence of *N*,*N*′-dibutylbispidine, an achiral (−)-sparteine mimic. Lithio-destannylation of the enantioenriched organostannane **41a** at −78 °C in the presence of (−)-sparteine followed by reaction with electrophiles provided an enantiomeric series of products (Scheme 20). The Sn/Li exchange is presumed to proceed with retention of configuration, followed by invertive electrophilic substitution.

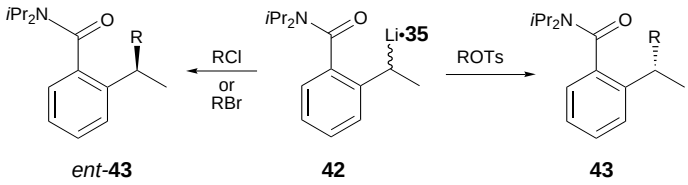


Scheme 19. Enantioselective (−)-sparteine-mediated lithiation/substitution of **39**.



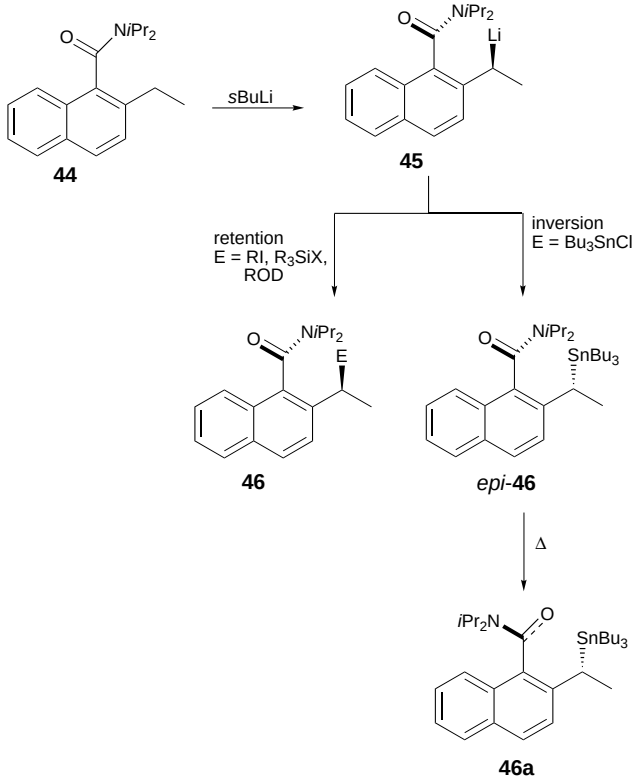
Scheme 20. Stereoinversion in the lithiation/substitution of stannane **41a**.

In contrast, lithiated benzamide **42** is configurationally labile at −78 °C. A modified Hoffmann test was carried out with allyl tosylate as the electrophile, and provided results consistent with a dynamic kinetic resolution pathway. Remarkably, the reaction of the organolithium compound with alkyl halides provided products with absolute configurations opposite to those of the products obtained from the reaction with alkyl tosylates (Scheme 21). It was suggested that retentive electrophilic substitution is favored by the slower reacting tosylates, thus allowing the sulfonyl oxygen atom to coordinate to the lithium cation.[43] Highly reactive electrophiles such as triflates, and electrophiles without Lewis basic sulfonyl oxygen atoms such as alkyl halides are proposed to react through an invertive transition state without precoordination to the lithium atom.



Scheme 21. Lithiation of the side chain and stereodivergent substitution of **42**.

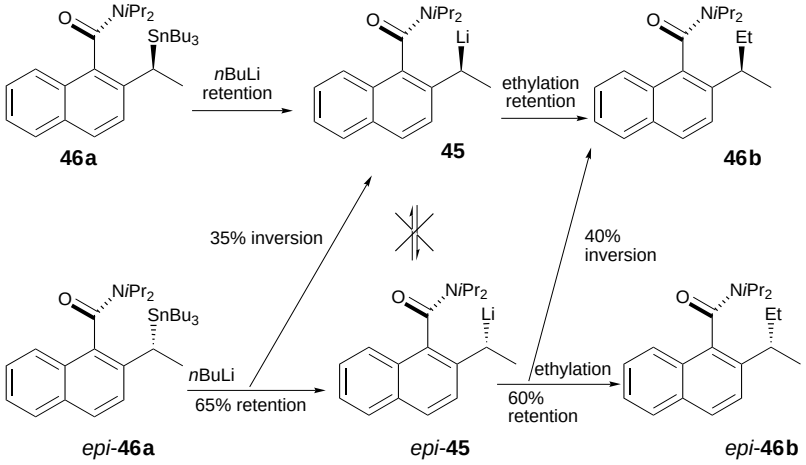
A related diisopropyl naphthamide **44** undergoes highly atroposelective reactions to provide benzylic substitution products **46** with high diastereoselectives.[45–48] Lateral lithiation of the naphthamide occurs stereoselectively to provide a single diastereomeric intermediate, presumed to be the *syn* diastereomer **45**.[49] This intermediate undergoes reaction with alkyl and silyl halides and methanol with retention of configuration, but stannylation occurs with inversion (Scheme 22). The *anti* stannane *epi*-**46** can be epimerized to **46** upon prolonged heating. The lithiated intermediates are configurationally stable at −40 °C.[47]



Scheme 22. Atroposelective lithiation/substitution at the side chain of **44**.

The lithiated naphthamide exhibits unique stereochemical behavior in its electrophilic substitution. The thermodynamically favored *syn* atropisomer **45** can be formed readily either by deprotonation of **44** or by Sn/Li exchange of the *syn*

stannane **46a**. The epimeric organolithium compound *epi*-**45** is formed by lithio-destannylation of the *anti* stannane *epi*-**46a**. The *anti* organolithium compound *epi*-**45** is also configurationally stable, and retains its configuration even after two hours at $-40\,^{\circ}C$. The Sn/Li exchange of *epi*-**46a** also proceeds partially with inversion, since both diastereomeric organolithium species were detected by means of NMR spectroscopy. However, the final product ratio after ethylation does not correspond to the organolithium ratio observed in the NMR spectra, thus indicating a lack of stereoselectivity in the electrophilic substitution of the *anti* organolithium. It is proposed that the inversion occurs during the actual lithio-destannylation step, but alternative mechanisms such as the formation of different "ate" complexes may also be operative (Scheme 23).[50, 51]

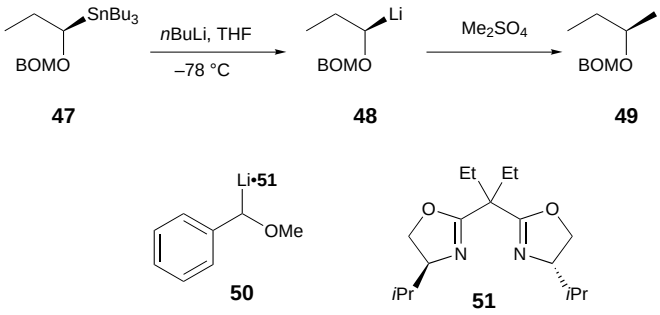


Scheme 23. Stereodivergent lithio-destannylation and substitution of **46a**.

3.2. α-Alkoxy-Substituted Organolithium Compounds

3.2.1. Nondipole-Stabilized Compounds

Organolithium intermediates with α-alkoxy substituents have attracted considerable interest since Still and Sreekumar's seminal report in 1980.[52] In that work, they reported the preparation of the enantioenriched α-benzyloxymethyl (BOM) organolithium compound **48** through lithio-destannylation of the enantioenriched tributyltin-substituted precursor **47**. Alkylation of the organolithium with dimethyl sulfate afforded BOM-protected (*R*)-2-butanol **49** with overall retention of configuration at the carbanion center and no detectable racemization. The configuration of **48** was maintained at temperatures as high as $-30\,^{\circ}C$ (Scheme 24). This methodology has been expanded by improved procedures for the preparation of enantioenriched α-alkoxy stannanes.[53, 54] Similarly, application of the modified Hoffmann test to the benzylic organolithium intermediate **50** established its configurational stability in the presence of the bisoxazoline ligand **51**.[55, 56]



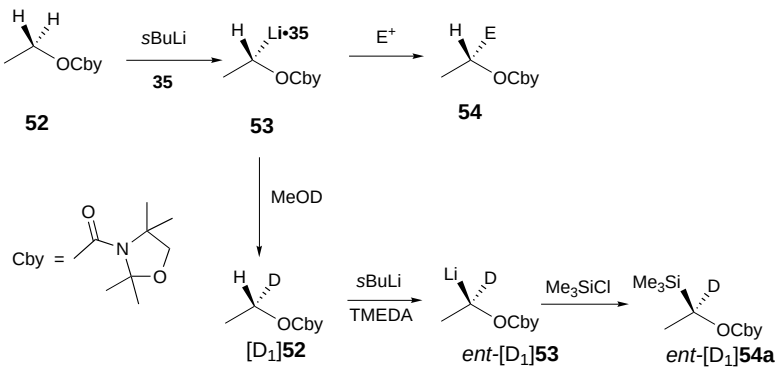
Scheme 24. Enantioselective lithiation/substitution of α-oxyorganolithium compounds **48** and **50** (BOM = benzyloxymethyl).

3.2.2. Dipole-Stabilized Compounds

The protection of an alcohol as a hindered carbamate activates the α-carbon atom towards lithiation as a result of dipole stabilization as well as of the directing-group ability of the carbamate moiety. These umpolung synthons provide a powerful method for the synthesis of chiral alcohols. Hoppe and coworkers have extensively developed the lithiation/substitution reaction sequence in the presence of (−)-sparteine to prepare enantioenriched alkyl carbamates. This work has been reviewed recently.[1]

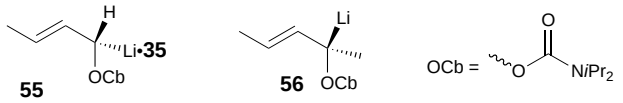
Carbamates such as **52**, which are derived from primary alcohols, undergo enantioselective deprotonation by alkyllithium compounds in the presence of (−)-sparteine to provide configurationally stable organolithium intermediates (Scheme 25). A large kinetic isotope effect was measured for the deprotonation step, and the lithiated intermediates react with electrophiles with retention of configuration in most instances. These two features have been elegantly combined by employing deuterium as a "protecting group"; both enantiomers of a product were obtained from a single enantiomer of the chiral ligand.[57, 58]

Modification of the substrate structure has a significant effect on the behavior of the organolithium intermediate. In the case of the secondary crotyllithium, selective crystalliza-



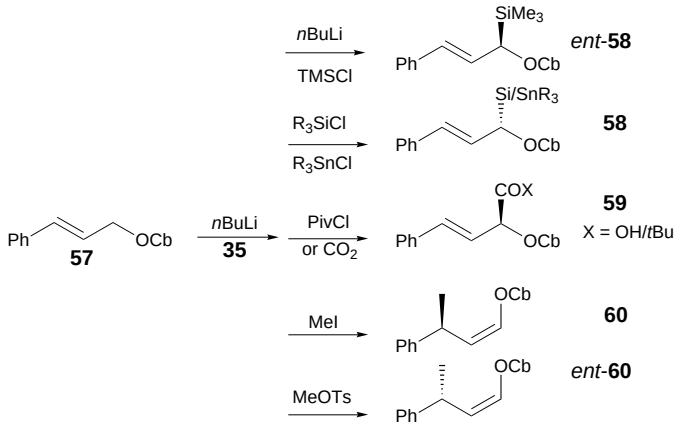
Scheme 25. (−)-Sparteine-mediated enantioselective deprotonation of carbamates derived from primary alcohols.

tion of a single diastereomer provided **55**, which reacts with $(OiPr)_4Ti$ with inversion of configuration.[59–62] The related tertiary crotyl intermediate **56** was configurationally stable and underwent substitution with either retention or inversion, depending on the electrophile (Scheme 26).[63, 64]



Scheme 26. Configurationally stable allylic α-oxyorganolithium reagents.

The stereo- and regioselectivity of the cinnamyl intermediate **57** depends on the nature of the electrophile (Scheme 27). When the deprotonation was carried out in the presence of TMSCl, (*R*)-**58** was isolated with 58% *ee*. Similarly, when

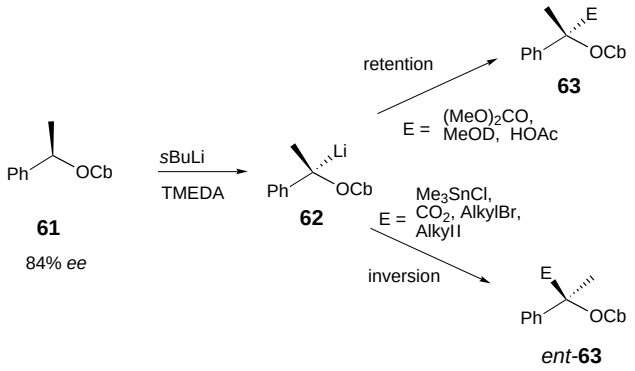


Scheme 27. Regio-and stereodivergent lithiation/substitution of cinnamyl intermediate **57**.

methyl iodide was added to the organolithium solution six minutes after deprotonation, the γ-substituted product **60** was obtained with 34% *ee*, whereas methylation after thirty minutes or at any time thereafter resulted in an *ee* value of 50%. These results suggest that the diastereomeric complex which is formed upon deprotonation epimerizes within thirty minutes in a thermodynamic ratio. A modified Hoffmann test with methyl iodide as the electrophile confirmed that a dynamic thermodynamic resolution was operative, and that the minor diastereomer reacted faster.

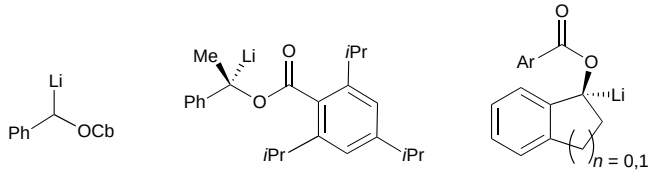
Previous studies of the deprotonation of alkyl carbamates with *n*BuLi/(−)-sparteine have established a strong preference for the abstraction of the pro-*S* proton followed by electrophilic substitution with retention of configuration.[65] Thus, deprotonation of **57** is presumed to initially generate an *S*-configured organolithium compound, which epimerizes over time to the *R* complex, unless TMSCl is present. In this scenario, silylation must occur with inversion of configuration. Reaction with methyl iodide also occurs with inversion in an *anti*-$S_{E'}$ fashion, whereas methyl tosylate reacts via a *syn*-$S_{E'}$ transition structure.

Tertiary lithium intermediates derived from benzyl carbamates also undergo electrophile-dependent stereodivergent substitution.[66–68] Carbamate **61**, which is derived from (*R*)-1-phenylethanol, was deprotonated with *s*BuLi/TMEDA at −78 °C. The reaction of intermediate **62** with acetic acid, [D]methanol, or dimethyl carbonate occurred with retention of configuration, whereas reaction with carbon dioxide or alkyl halides provided products with inversion of configuration (Scheme 28). These results indicate that the organolithium **62** is configurationally stable under the reaction conditions. The invertive substitution of Me_3SnCl can be exploited to access either enantiomer of the products.[69] A Hoffmann test on the related secondary organolithium compound **64** (Scheme 29) indicated that it was configurationally stable on the time scale of reaction with the Reetz aldehyde.[70]



Scheme 28. Stereodivergent electrophilic substitution of configurationally stable tertiary benzyllithium compound **62**.

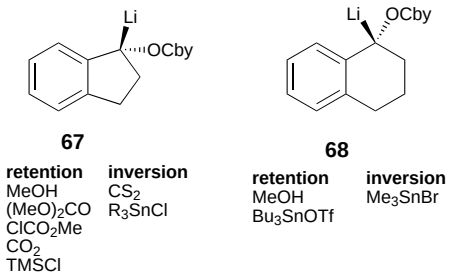
Hammerschmidt and Hanninger observed identical behavior with **65**, which has a triisopropylbenzoate instead of a carbamate as the directing group.[71] The absolute configuration of the stannylated intermediate was determined by means of crystallographic analysis, and indicated that stannylation does, in fact, occur with inversion of configuration.[69] This principle was further extended to cyclic benzyl lithium intermediates **66a**,**b**, which are derived from tetralol and indanol (Scheme 29).[72] The related carbamate derivatives **67** and **68** exhibit increased configurational stability relative to



Scheme 29. Benzylic α-oxyorganolithium reagents.

their ester counterparts.[72, 73] Again, the reaction between the diisopropyl carbamate and electrophiles in general occurs with retention of configuration, whereas trimethyltin bromide provides the product of invertive substitution. Notably, reaction with tributyltin triflate occurs with retention of configuration (Scheme 30).

Lithiated α-alkoxy species, particularly dipole-stabilized intermediates, are amongst the most widely used organo-



Scheme 30. Stereodivergent electrophilic substitution of carbamate derivatives **67** and **68**.

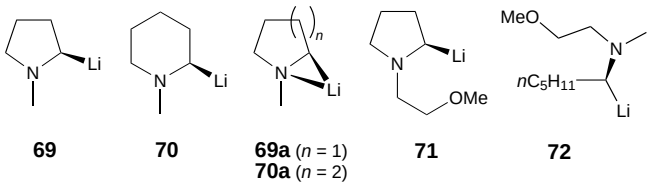
lithium reagents. Thus, it is not surprising that considerable effort has been devoted to the development of asymmetric reactions with these reagents. The preparation of configurationally stable α-alkoxy species, initially by Sn/Li exchange of enantioenriched stannanes and later by (−)-sparteine-mediated deprotonation of alkyl carbamates, are both general and powerful methodologies. Even intermediates with little or no configurational stability, such as allyl and benzyllithium compounds, undergo highly selective reactions, often through dynamic resolution pathways.

3.3. α-Amino-Substituted Organolithium Compounds

Chiral α-amino carbanions are of great synthetic value owing to their use in the stereoselective syntheses of natural and non-natural amino acids and alkaloid natural products.[74–76] α-Amino organolithium compounds are most frequently generated by Sn/Li exchange, following Peterson's method for the preparation of dialkylaminomethyllithium.[77, 78] However, the formation of many secondary organolithium compounds through this route can be problematic. Thus, there is little information about the configurational stability of chiral acyclic α-amino organolithium compounds that are not dipole-stabilized or chelated.[79–82]

3.3.1. Nondipole-Stabilized Compounds

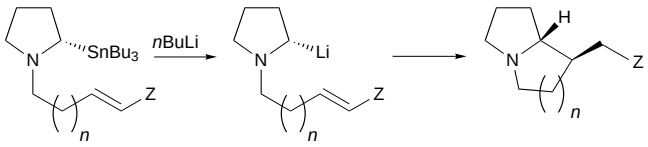
The cyclic nonstabilized 2-lithio-*N*-methylpyrrolidine (**69**) and 2-lithio-*N*-methylpiperidine (**70**) were generated from the corresponding enantioenriched organostannanes.[83] Both **69** and **70** are configurationally stable for at least 45 min at $-40\,^{\circ}C$, but significant decrease in the enantiopurity was observed at $-20\,^{\circ}C$. It was also observed that **71**, which has a potential internal coordination site, is configurationally less stable than **69**, although **71** is more stable than the acyclic analogue **72** (Scheme 31). The increased stability of **69** is attributed to structure **69a**. Recent NMR spectroscopic studies have shown that **69** exists as a dimer in solution, whereas **70** remains monomeric. The existence of the bridged structure **69a** was confirmed by the observation of $^{15}N-^{6}Li$ coupling in the NMR spectra.[11] Whereas a conformationally locked structure in **69a** increases the barrier to racemization, the presence of a coordinating methoxy group in **71** facilitates epimerization, presumably through a conducted-tour mechanism.[84] Acceleration of epimerization as a result of the coordinating ability of the pendant group has been observed with several dipole-stabilized organolithium intermediates. The reactions of **69** and **70** with alkyl halides occur with inversion of configuration, whereas retention is observed in reactions with carbonyl electrophiles.[85]



69 **70** **69a** (n = 1) **70a** (n = 2) **71** **72**

Scheme 31. α-Lithioamines examined for configurational stability.

The configurational stability of acyclic α-amino organolithium reagents that can be stabilized by chelation have been reported.[81] The enantioenriched organolithium intermediate **72** is configurationally stable at $-95\,^{\circ}C$ in THF. However, higher temperatures or the presence of chelating solvents such as dimethoxyethane resulted in a significant decrease in enantiopurity. The influence of the rate of electrophilic substitution on the rate of configurational inversion is highlighted by the anionic cyclization shown in Scheme 32. Lithiodestannylation of the enantioenriched organostannane **73a** (94% *ee*) followed by cyclization provided the [5,5] ring system **75a** in high yield and with complete retention of



73 **74** **75**

a: n = 1, Z = H
b: n = 2, Z = H
c: n = 2, Z = SPh

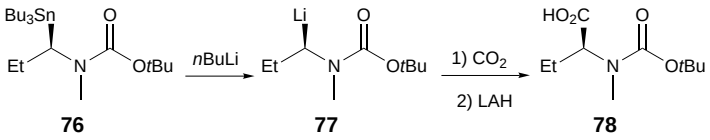
n = 1,2 n = 1,2

Scheme 32. Stereoselective cyclization of a chiral α-lithioamine.

configuration.[86] In contrast, cyclization of the organolithium onto the pentenyl side chain ($n = 2$) provided the product with poor stereoselectivity.[87] The rate of cyclization to form the six-membered ring was approximately sixteen times slower than that for the five-membered ring formation, thus slowing down the substitution step enough for it to be competitive with the rate of racemization. Introduction of an anion-stabilizing thiophenyl group (e.g. **73c**) increased the rate of cyclization and afforded the bicyclic product with good stereoselectivity (72% *ee*).[87]

3.3.2. Dipole-Stablized Compounds

The dipole stabilization of the lithiated intermediate has a significant effect on the configurational stability. Sn/Li exchange of **76** affords the organolithium intermediate **77**, which is moderately configurationally stable at $-78\,^{\circ}C$.[88] Higher temperatures or the presence of coordinating solvents such as dimethoxyethane or HMPA decreases the configurational stability (Scheme 33).

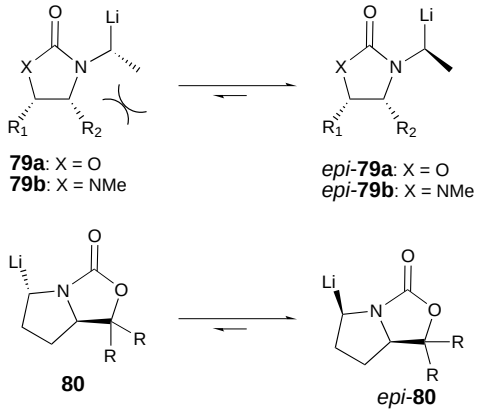


76 **77** **78**

T [°C]	solvent	*t* [min]	*ee* [%]
–78	THF	10	92
–78	THF	180	80
–55	THF	120	24
–78	DME	180	68
–78	THF/HMPA	180	0

Scheme 33. Configurational stability of the acyclic dipole-stabilized α-lithioamine **77**.

Studies of related diastereomeric species have also provided evidence for configurational stability of dipole-stabilized intermediates.[80, 89] The lithiated oxazolidinones **79a/b** and **80** rapidly epimerize at $-78\,^{\circ}C$ to diastereomers which are more configurationally stable (Scheme 34). The faster epimerization of the carbamate was ascribed to the poorer coordinating ability of a carbamate oxygen atom relative to the urea oxygen atom. This indicates that the dissociation of the lithium ion from the heteroatom is important for inversion.[79, 80] The organolithium intermediates were prepared by Sn/Li exchange of the appropriate organostannane precursors.



79a: X = O
79b: X = NMe

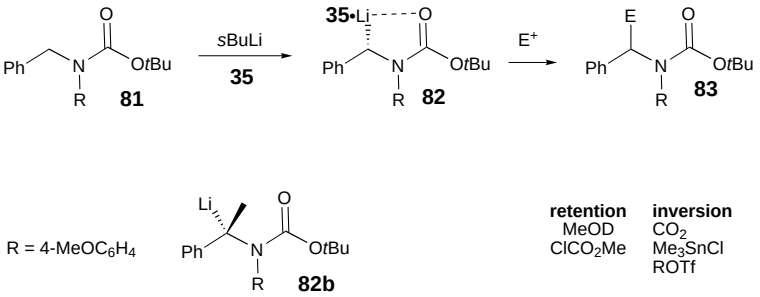
epi-**79a**: X = O
epi-**79b**: X = NMe

80 *epi*-**80**

Scheme 34. Epimerization of diastereomeric α-lithioamines.

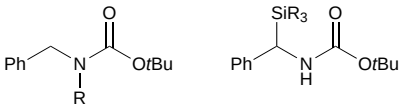
The benzylic organolithium intermediate **82** is configurationally stable in the presence of (−)-sparteine, but it is labile in the presence of TMEDA or in the absence of any chelating diamine.[90, 91] The (−)-sparteine/intermediate complex was characterized by means of NMR spectroscopy and found to be monomeric, with the lithium ion complexed to both the carbamate and (−)-sparteine.[90] A modified Hoffmann test with methyl triflate as the electrophile identified the major diastereomeric complex as marginally more reactive towards methylation. The intermediate **82** reacts with acyl halides with retention of configuration, whereas inversion is observed in the reactions with alkyl triflates (Scheme 35). Stannyl chlorides react with inversion and Sn/Li exchange occurs with retention of configuration, thus this methodology allows access to both enantiomers of the products. The corresponding tertiary organolithium **82b** is configurationally stable in the presence of TMEDA, and also undergoes stereodivergent electrophilic substitution, as observed with **82**.

The lithiation/substitution of the related **84a** proceeds through an asymmetric deprotonation, followed by racemization and diastereoselective precipitation of a single (−)-sparteine complex.[92] The lithiated intermediate was configurationally labile in the presence of TMEDA, but the configurational stability in the presence of (−)-sparteine was not determined. In contrast, the intramolecular cyclization reaction of **84c** proceeds through an asymmetric deprotonation pathway, as illustrated by Sn/Li exchange and isotope



Scheme 35. Stereodivergent (−)-sparteine mediated lithiation/substitution of **82**.

effect experiments.[93] Lithiation of the related *N*-silyl-*N*-Boc-benzylamine **84b** (Boc = *tert*-butoxycarbonyl) with *n*BuLi/(−)-sparteine is followed by anionic rearrangement to provide benzylic silane **85** with moderate enantioselectivities (Scheme 36).[94]

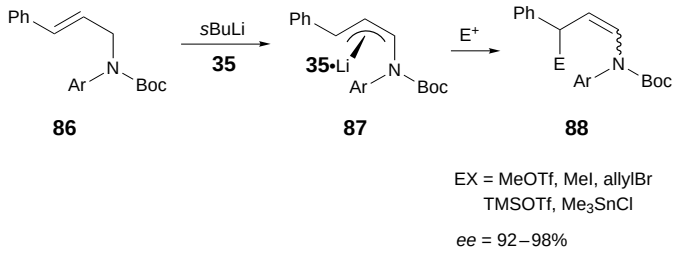


84 **85**

a: R = Me
b: R = Me_3Si
c: R = $(CH_2)_3Cl$

Scheme 36. Benzylamine derivatives **84** and **85**, which undergo stereoselective lithiation/substitution.

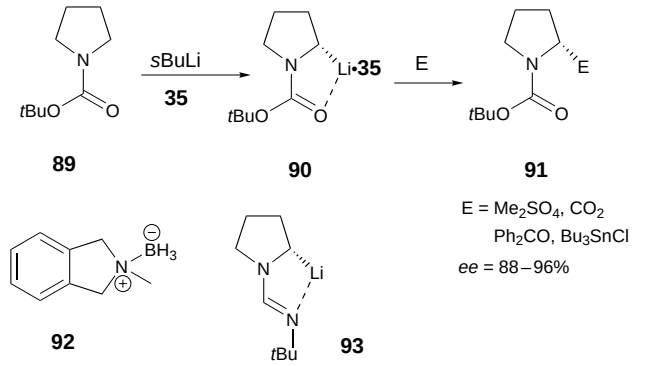
Beak and co-workers have reported the lithiation/substitution of cinnamylamine derivative **86**.[31, 95, 96] Treatment of **86** with *n*BuLi in the presence of (−)-sparteine followed by electrophilic substitution provided products **88** with high *ee* values (Scheme 37). The major organolithium intermediate was identified to be *endo-syn-anti*-**87** by means of both NMR spectroscopic and solid-state studies.[97] Under the standard reaction conditions of lithiation at $-78\,^{\circ}C$ followed by electrophilic substitution at the same temperature, the major pathway involved asymmetric deprotonation to provide a configurationally stable intermediate. However, when the reaction sequence was conducted at $-25\,^{\circ}C$, both dynamic kinetic and dynamic thermodynamic resolution pathways were operative.[31] Both enantiomers of the products are accessible by invertive substitution reactions of the enantiomeric organolithium intermediate or by a retentive Sn/Li exchange of the enantioenriched organostannane.



86 87 88

Scheme 37. Enantioselective lithiation/substitution of cinnamylamine derivative **86**.

The lithiation of *N*-Boc-pyrrolidine (**89**) in the presence of (−)-sparteine followed by electrophilic substitution affords 2-substituted pyrrolidines **91** with high *ee* values.[98, 99] Results from deuterium substitution and Sn/Li exchange experiments showed that the formation of the configurationally stable intermediate **90** was the critical step in the determination of the stereochemistry. The enantioselective deprotonation and substitution of the related isoindoline–borane complex **92** has also been reported (Scheme 38).[100] The configurational



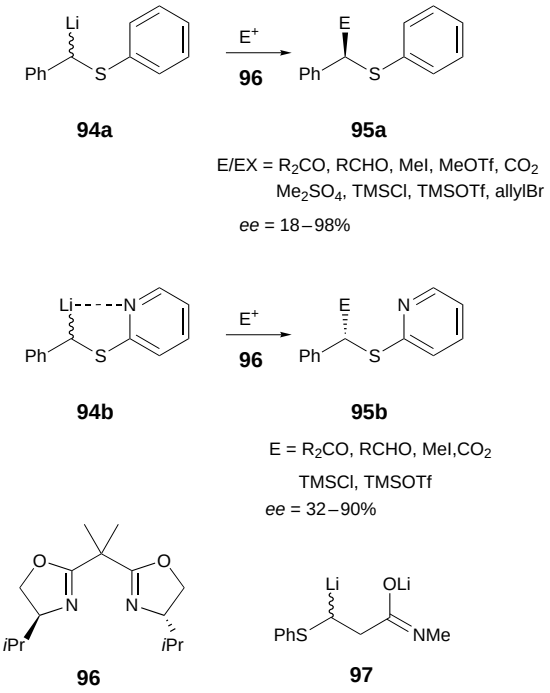
89 90 91 92 93

Scheme 38. Enantioselective lithiation/substitution of pyrrolidine derivatives.

stability of **90** and related organolithium intermediates depends on the nature of the dipole-stabilizing group and its geometry. Meyers and Elworthy have compared the configurational stability of **90** with the formamidine derivative **93** and found the latter to be more configurationally stable.[101] The difference was attributed to the better coordinating ability of the oxygen atom relative to the nitrogen atom, thus facilitating a conducted-tour pathway for inversion.

3.4. Sulfur-Containing Compounds

α-Lithio sulfides have been studied extensively because of the utility of lithiated dithianes as acyl anion equivalents. Studies of α-lithio sulfides have revealed novel mechanisms for configurational inversion which can be attributed to the n–σ* interaction with the sulfur atom. Many diastereoselective reactions of α-lithio sulfides have been reported and reviewed.[102, 103] Highly enantioselective lithiation/substitution sequences of α-lithio sulfides are known. The benzylic α-thio organolithium compound **94** undergoes enantioselective lithiation/substitution in the presence of the bisoxazoline **96**.[104, 105] A Hoffmann test indicated that the organolithium was configurationally labile both in the presence and absence of TMEDA.[70] The configurational lability of **94a** in the presence of the chiral ligand was studied with a modified Hoffmann test.[104] The reaction of **94a** with both 0.2 equivalents as well as with excess benzophenone provided the product with an *ee* value of 92% in both cases, which suggests the operation of a dynamic kinetic resolution. Consistent with this hypothesis, the enantiomeric ratios of the products were found to be highly dependent on the electrophile (Scheme 39). However, very different results were observed when the same reaction sequence was carried out with the pyridyl analogue **94b**.[105] The absolute configurations of the thiopyridyl substitution products were opposite to those of the thiophenyl products. Furthermore, the highest enantiomeric ratios were obtained after a "warm-cool" sequence, thus suggesting a dynamic thermodynamic resolution as the reaction pathway which was confirmed by using a modified Hoffmann test.

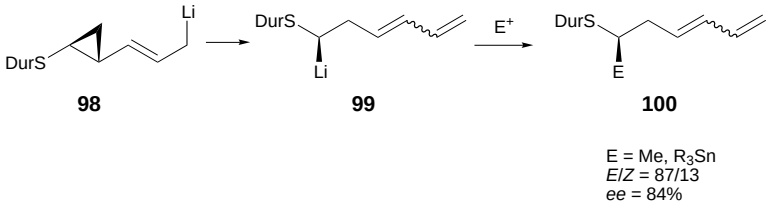


94a 95a 94b 95b 96 97

Scheme 39. Enantioselective substitution of α-lithiophenyl and pyridyl sulfides **94a**, **94b**, and **97**.

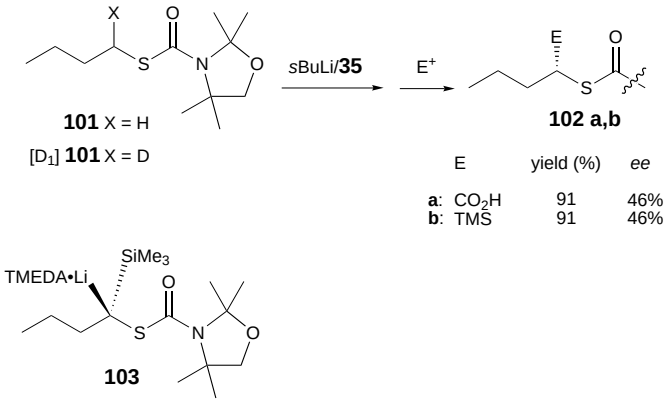
Based on molecular modeling, the authors proposed a retentive electrophilic substitution for **94a** and an invertive process for **94b**. Simultaneous coordination of the lithium cation by both the pyridyl nitrogen atom and the chelating ligand is believed to block the front face of **94b**. In contrast, the back face of carbanion **94a** is hindered as a result of the *anti* orientation of the thiophenyl group relative to the C–Li bond which is necessary for maximizing n-σ* overlap. Enantioenriched α-lithio sulfides have also been generated by a retrocarbolithiation of a cyclopropyl group.[106] The lithiated intermediate **99** can be trapped with methyl iodide or stannylating agents to provide products **100** with retention of

configuration (Scheme 40, Dur = 2,3,5,6-tetramethylphenyl). The ring opening occurs with retention of configuration to provide a lithiated intermediate, which is configurationally stable at $-105\,^{\circ}C$ but racemizes at $-78\,^{\circ}C$ (half-life = 90 min). This corresponds to an inversion barrier of 13.3 kcal mol^{-1}, similar to that measured for other lithiated duryl sulfides.[21]



Scheme 40. Cyclopropane ring-opening to provide a configurationally stable α-thio organolithium compound.

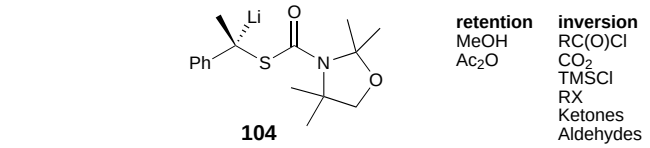
The enantioselective lithiation/substitution of thiocarbamate **101** provides products with a moderate enantiomeric excess.[107] Treatment of **101** with *s*BuLi/**35** followed by reaction with carbon dioxide or TMSCl provided **102a** or **102b** in excellent yields and moderate enantioselectivities. Treatment of [D_1]**101** with TMSCl under the same reaction conditions provided [D_1]**102b** with complete retention of deuteration and an *ee* value of 34%, which indicates that the deprotonation is not stereoselective. The configurational behavior of the secondary lithiated intermediate is unknown. The related tertiary lithiated carbamate **103** is configurationally stable at $-78\,^{\circ}C$ (Scheme 41).[108]



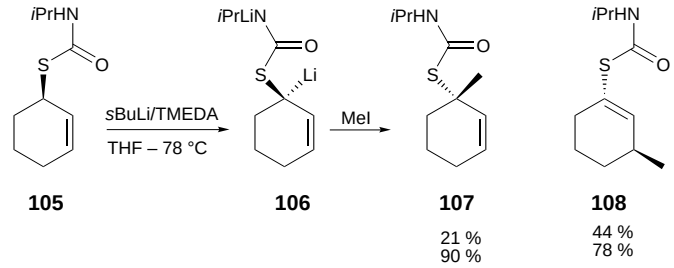
Scheme 41. Enantioselective lithiation/substitution of α-thiocarbamates.

The tertiary benzylic organolithium **104**, generated by deprotonation of the enantioenriched thiocarbamate, is configurationally stable at $-78\,^{\circ}C$, and even at $0\,^{\circ}C$ for up to ten minutes.[108] The reactions of the organolithium compound with methanol and acid anhydrides occur with retention of configuration, whereas acyl chlorides, aldehydes, ketones, alkylating agents, carbon dioxide, and TMSCl all provide the products of invertive substitution (Scheme 42).[109]

The allylic dilithio intermediate **106**, obtained by deprotonation of the enantioenriched precursor **105**, exhibits interesting solvent-dependent configurational stability.[110] Racemization occurs readily at $-78\,^{\circ}C$ in diethyl ether and toluene, but the organolithium compound is stable for 4.5 hours in THF at the same temperature. Methylation is not completely regioselective, and affords both α- and γ-substitution products derived from invertive and *anti*-$S_{E'}$ alkylation, respectively. Rotation about the C–S bond is believed to be the rate-determining step. By analogy to other α-lithio sulfides, which have been studied in detail by means of NMR spectroscopy, the configurational stability is highest under conditions that favor increased ion-pair formation (Scheme 43).



Scheme 42. Stereodivergent substitution of configurationally stable lithiated thiocarbamate **104**.



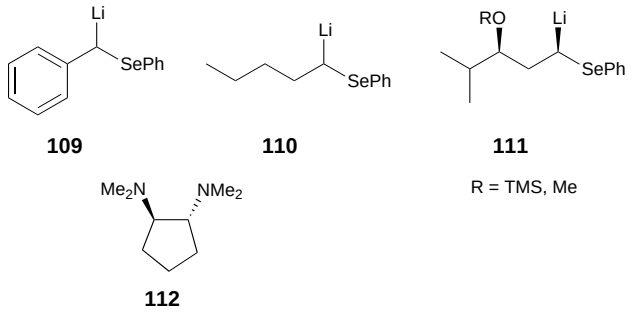
Scheme 43. Lithiation/substitution of chiral allylic thiocarbonate **105**.

Despite the extensive use of diastereomeric α-thio organolithium reagents as probes for studying configurational stability and inversion, until recently there have been very few synthetic applications of enantioenriched α-lithio sulfides. Chiral ligand mediated lithiation/substitution of α-lithio thioethers and thiocarbamates have illustrated the potential for carrying out stereoselective transformations with these reagents, and further developments and applications of chiral α-lithio sulfides can be expected.

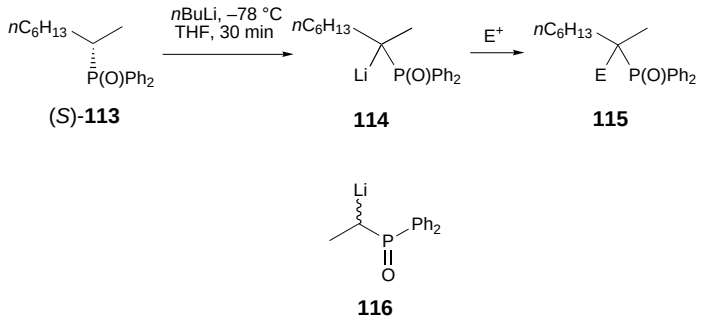
3.5. Selenium-Containing Compounds

The configurational stability of chiral acyclic selenides have been studied by using the Hoffmann test, with varying results.[9, 25] Benzyllithium compound **109** inverts faster than it reacts with aldehydes at $-78\,^{\circ}C$ in THF, but alkyllithium **110** is configurationally stable in a mixture of THF and diethyl ether at $-105\,^{\circ}C$. Organolithium compound **111** rapidly isomerizes to diastereomers (9:1) at $-78\,^{\circ}C$, but epimerization is competitive with the rate of electrophilic substitution at lower temperatures ($-100\,^{\circ}C$) (Scheme 44).[111]

Although organolithium compound **24** (Scheme 13) is configurationally labile, the presence of chiral diamine ligand **112** favors the formation of diastereomeric complexes (9:1) that react with electrophiles at a faster rate than they undergo



Scheme 44. α-Lithioselenides studied for configurational stability.



Scheme 45. Configurationally labile enantiomeric α-lithio phosphane oxides.

inversion. Competition experiments showed that uncomplexed **24** reacted faster with electrophiles than either of the diastereomeric complexes.[112] However, complexation of **24** with cyclohexyldiamine **25** afforded diastereomeric complexes (7:3) that reacted with electrophiles faster than the uncomplexed organolithium compound. These results indicate that an external ligand can be used to modulate the reactivity of organolithium compounds.

3.6. Phosphorus-Containing Compounds

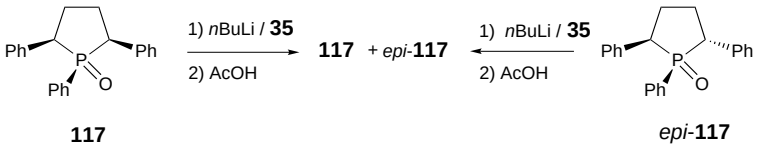
Phosphorus-stabilized organolithium compounds are of interest owing to their potential application in the stereoselective preparation of alkenes and in other aspects of asymmetric synthesis.[113, 114] Structural and mechanistic investigations indicate that the lithium ion in most α-lithiophosphonates, α-lithiophosphonamides, and α-lithiothiophosphonamides are not in contact with the carbon atom.[115–119] There are only a few examples in which such carbon–lithium contacts were observed by means of NMR spectroscopy or X-ray crystallography.[120, 121] In general, these carbanions are nearly planar and are considered to be formally sp^2 hybridized at the carbon center.[118, 122]

O'Brien and Warren have studied the configurational stability of enantioenriched phosphane oxides. Treatment of (*S*)-**113** (95% *ee*) with *n*BuLi or lithiumdiisopropylamide (LDA) followed by reaction with electrophiles afforded the product **115** as a racemic mixture, even when trimethylsilyl chloride was used as an internal electrophile.[123] The Hoffmann test was carried out with the secondary organolithium **116** and the Reetz aldehyde as the electrophile, and the lithiated intermediate was found to be configurationally labile under the reaction conditions (Scheme 45).[124]

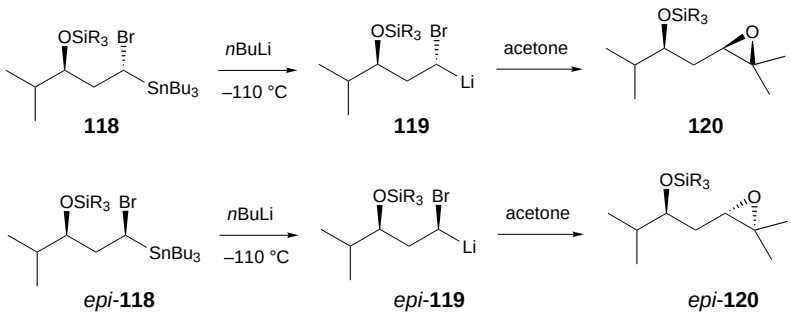
The α-lithio derivative of 1,2,5-triphenylphospholane **117** is configurationally stable in the presence of (−)-sparteine.[125] Treatment of **117** with *n*BuLi/(−)-sparteine followed by reaction with acetic acid afforded the products **117** and *epi*-**117** (1:2, 45% *ee* for the latter). When *epi*-**117** was used as the starting material for the reaction, the products were obtained in >99:1 ratio, and the product *epi*-**117** was racemic. The different product stereoselectivities from **117** and *epi*-**117** indicate that the organolithium intermediate is not configurationally labile.[126] The diastereoselectivity of the reaction and the facial selectivity of electrophilic substitution was dependent on the protonating agent (Scheme 46).

3.7. Halogen-Containing Compounds

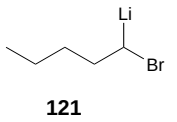
α-Halo organolithium reagents, which are useful intermediates for the synthesis of epoxides and cyclopropanes, are usually prepared by Li/Sn or Li/halogen exchange.[127–131] The epimeric intermediates **119** and *epi*-**119** were generated by the former route and provided diastereomeric epoxides upon reaction with acetone, thus demonstrating useful configurational stability under the reaction conditions (Scheme 47).[132] These conclusions were consistent with the results of a modified Hoffmann test.[133] Dibromide precursors also undergo diastereoselective Li/halogen exchange to provide stereoisomerically enriched intermediates. Enantiomeric α-halolithium reagents have not been as extensively studied. A Hoffmann test was conducted on racemic α-bromoalkyllithium **121** generated by Li/halogen exchange of the dibromide.[25] The organolithium **121** underwent addition to the Reetz aldehyde faster than it underwent configurational inversion, thus demonstrating functionally useful configura-



Scheme 46. After lithiation of **117** and *epi*-**117** and treatment of the resulting phosphane oxide with acetic acid, a mixture of epimers was obtained.



Scheme 47. Configurationally stable diastereomeric α-halo organolithium compounds.



121

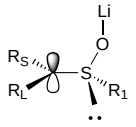
Scheme 48. Chiral α-bromo organolithium studied by means of the Hoffmann test.

tional stability at $-110\,^{\circ}C$ which could make α-haloorganolithium compounds important intermediates in stereoselective synthesis (Scheme 48).

4. Stereochemistry of Electrophilic Substitution

The preceding material illustrates the diverse organolithium structures that undergo highly stereoselective lithiation/substitution reactions. The lithiated intermediates range widely in their configurational stabilities, but it is also clear that configurational stability is not a prerequisite for highly stereoselective substitution reactions, since highly enantioenriched products can also be obtained by means of dynamic kinetic resolutions. However, the frequency of invertive and stereodivergent electrophilic substitution, both in configurationally labile and configurationally stable organolithium compounds, is noteworthy.

Electrophile-dependent stereochemistry in electrophilic substitution has been observed with a variety of diastereomeric organolithium intermediates, especially lithiated sulfoxides.[134] α-Lithio sulfoxides exhibit a propensity to undergo electrophilic substitution to provide products in which the incoming electrophile is *syn* to the sulfoxide oxygen atom when the incoming reagent has an electrofugal group that can coordinate to the lithium atom. Addition of lithium salts or other Lewis acids often perturbs this selectivity, presumably by altering the coordination environment of either the organolithium compound or of the electrofuge.[135–138] Crystallographic and spectroscopic studies indicate that α-lithio sulfoxides are best represented by structure **122**.[103] Electrofugal groups that can coordinate to the lithium atom are believed to deliver the electrophile to the top face, whereas all other species react from the bottom face. Large R^1 groups increase the steric hindrance towards bottom face alkylation, and a decrease in stereoselectivity is observed (Scheme 49).

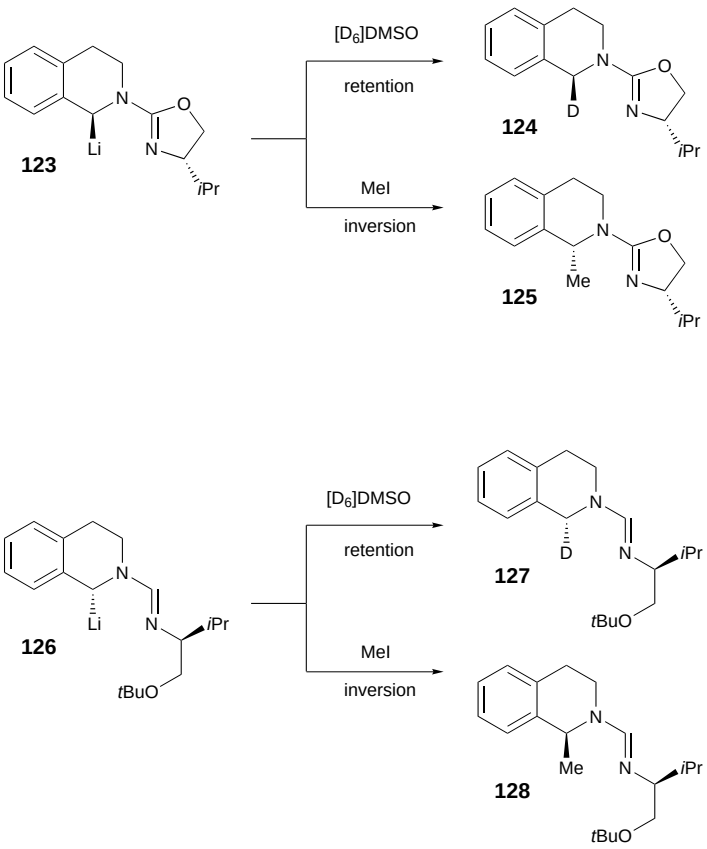


122

Scheme 49. Planar α-lithio sulfoxides permit stereodivergent electrophilic substitution.

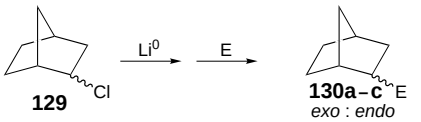
The coordination of a lithium atom to a sulfoxide has also been invoked to rationalize the stereochemistry of deuteration reactions with $[D_6]$DMSO. In the alkylations of α-lithio tetrahydroisoquinoline derivatives **123** and **126**, Meyers/Dickman and Gawley independently found that deuteration with $[D_6]$DMSO gave the opposite stereochemistry to that observed in the alkylation with methyl iodide (Scheme 50).[139, 140] Retentive deuteration was proposed to occur through the coordination of the sulfoxide oxygen atom to the lithium cation. The configurations of **123** and **126** were inferred from other experiments directed at addressing the selectivity of the deprotonation.

Stereodivergence based on the electrophile was first identified in the late 1960s in the earliest studies of chiral organolithium reagents.[141, 142] A series of experiments demonstrated that the stereochemistry of the lithiation/substitution of norbornyl chloride (**129**) was dependent on the choice



Scheme 50. Diastereodivergent substitution of lithiated tetrahydroisoquinolines.

of electrophile.[141] Substitution of 2-norbornyllithium afforded products with electrophile-dependent *exo/endo* ratios. These ratios were independent of the stereochemistry of **129**. When the organolithium compound was generated from the *exo* chloride at 20 instead of at 36 °C, the selectivities were higher. Remarkably, the reaction of bromine with the organolithium compound derived from the *endo* chloride at 20 °C provided *exo* bromide **130c** as the major product (Scheme 51). If a predominantly retentive Li/halogen exchange at 20 °C is assumed, these results are consistent with a



SM isomer	$MeCO_2Cl$	CO_2	Br_2
endo+exo	2.5 : 1	5.1 : 1	1 : 1.6
exo, 20 °C	3.6 : 1	11.2 : 1	1 : 2.7
endo, 20 °C			1.6 : 1

Scheme 51. Diastereodivergent substitution of norbornyllithium.

pathway that involves retentive electrophilic substitution of carbon dioxide and methyl chloroformate and invertive substitution of bromine. Although the configurational stability of the norbornyllithium was not independently examined, the observation that the product ratio is dependent on the

temperature of organolithium formation suggests that complete equilibration does not occur at 20 °C or below.

Despite these early results, the retentive pathway remained the paradigm for electrophilic substitution of organolithium reagents until fairly recently. In large part this is a result of the historical scarcity of organolithium reagents whose absolute configurations were known; hence the stereochemical course of the electrophilic substitution could not be determined. Thus, in the absence of experimental evidence suggesting otherwise, retentive substitution remained the simplest explanation consistent with the facts. Electrophilic substitution of allylic carbamates **56** and **55** (Scheme 26) provided examples of invertive processes, but since there is substantial precedent for *anti*-$S_{E'}$ processes, these results are not extraordinary. However, the electrophile-dependent stereodivergent substitution of benzyllithium **62** (Scheme 28) provided a clear example of an anomalous pathway, and one which was not restricted to an allylic system.

Table 3 highlights the diversity of organolithium reagents for which enough information about the configuration of the lithiated intermediate is known such that a reasonable hypothesis about the steric course of the substitution step can be made. Entries 2,3,7–9,11, and 17 are tertiary organolithium compounds which are generated by deprotonation of an enantioenriched precursor, and their configuration is assigned by assuming a retentive deprotonation. The configuration of the structures in entries 5 and 6 have been assigned on the basis of X-ray crystallography. The configuration of the remaining organolithium compounds shown in the table are not unequivocally established, but are reasonable hypotheses based on additional mechanistic information available in each case. With a few exceptions, a large number of the cases involve benzyl, allyl, or cinnamyl organolithium reagents which are capable of delocalizing the negative charge over several atoms. Although such intermediates are usually distorted from an ideal tetrahedral geometry, the X-ray crystal structures of **55** (Scheme 26) and **87** (Scheme 37) indicate that the carbanion center retains a small degree of pyramidalization and is not completely planar.[61, 97] Planarization serves to reduce the steric difference between the front and back faces of the carbanion, although the presence of an external ligand perturbs that symmetry.

Beyond this simple correlation, few prominent trends emerge. Of the organolithium reagents that undergo invertive or stereodivergent substitution, reactions with alkyl and trialkyltin halides always provide products of invertive substitution. Notably, in the lone case where tributyltin triflate was used as an electrophile (Table 3, entry 9), the reaction occurred with retention of configuration, which suggests that stannylation may also be subject to nucleofuge-dependent electrophilic substitution.[72] However, despite these anomalous results, stannylation reactions of most configurationally defined organolithium reagents occur with retention of configuration. The α-lithio pyrrolidine and piperidine derivatives (Table 3, entry 1) are not delocalized organolithium compounds, and Gawley et al. has suggested that invertive electrophilic substitution is actually the "default" pathway for the reactions of **69** and **70** (Scheme 31).[143] Alkyl halides react through this "standard" invertive pathway, whereas electrophiles that are capable of coordinating to the lithium atom, provide products with retention of configuration. In this case, retentive substitution with alkylating agents is believed to become a competitive pathway only when unfavorable steric interactions interfere with the invertive process.

A variety of explanations have been put forward to rationalize the stereochemical course of the electrophilic substitution step. It has been suggested that HOMO/LUMO interactions control the partitioning between retentive and invertive substitutions in the case of benzylic organolithium compound **62** (Table 3, entry 8; Scheme 28).[67] It was proposed that the increased planarization of **62** increases electron density on the rear face of the C–Li bond, thus increasing the probability for an approaching electrophile to interact with the back face. A similar explanation has been put forward for the invertive substitution of the pyridyl sulfide **94b** (Scheme 39).[105] Electrophiles that have a low-energy LUMO react rapidly with the carbanion through an invertive pathway. Electrophiles that are not very Lewis basic and cannot coordinate to the lithium atom are also suggested to undergo the invertive substitution. Electrophiles that can coordinate effectively to the lithium atom or have a higher energy LUMO and react slowly with the organolithium compound undergo retentive substitution. Similar rationalizations have been proposed for the substitution of the α-amino benzyllithium **82** (Table 3, entries 10 and 11; Scheme 35) and benzamide **42** (Table 3, entry 13; Scheme 21).[43, 90]

There have been a few attempts to study this issue by using theoretical techniques. The structure of $CH_3Li_2^+$ was calculated by using ab initio methods, which indicated that the D_{3h} isomer **132** was favored over the C_s structure **133** by 2.5 kcal mol^{-1} (Scheme 52).[146] The authors of the study noted that the D_{3h} structure is a potential model for invertive electrophilic substitution, as well as an intermediate in an intra-aggregate configurational inversion process that involves lithium atom exchange. Computational methods have been used to study the stereochemical pathways for the electrophilic substitution of the indanyl and benzylic organolithium compounds **134** and **135**.[73] The ground-state structures of the lithiated intermediates were calculated and optimized by using semiempirical methods. The sum of bond angles at the lithiated carbon atom of **135** was calculated to be 333.1°, consistent with partial planarization of the carbanion, although far from the 360° expected for an ideal planar structure. In contrast, the sum of angles of **134** was 323.8°, representative of increased puckering of the tetrahedral center (Scheme 53). Calculated energies for the completely planar organolithium compounds, which are possible transition states for an invertive substitution, indicated that the barrier to planarization for **134** was 4.1 kcal mol^{-1} higher than that for **135**. Although these results provide a rationale for why the benzyllithium compound undergoes invertive substitution more readily than the indanyl species, they do not account for the intrinsic preference for invertive over retentive substitution.

Qualitatively, these are all reasonable explanations, but they are nevertheless retroactive rationalizations. A model that can reliably predict the stereochemical course of an electrophilic substitution has yet to be formulated. For

Table 3. Configurationally defined organolithium intermediates that undergo stereodivergent substitution.

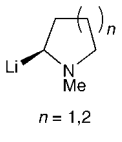
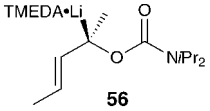
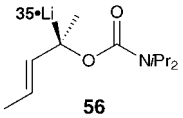
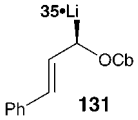
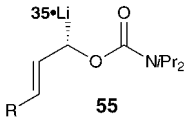
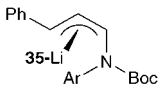
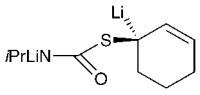
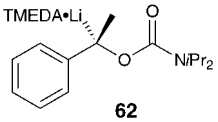
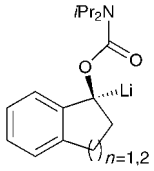
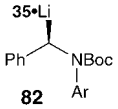
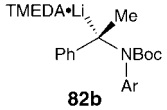
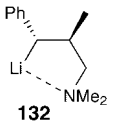
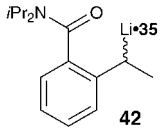
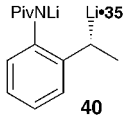
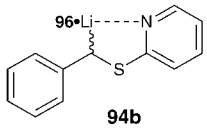
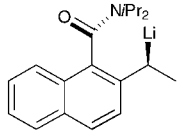
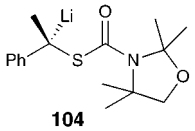
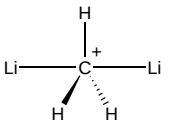
Entry	Lithiated Intermediate	Electrophiles which react with retention	inversion	Ref
1	 **69/70**	CO_2, $ClCO_2Me$, $(MeO)_2CO$, RCHO, R^1COR^2	RX (X = Cl, Br, I)	[85, 143]
2	 **56**	$Ti(OiPr)_4$	$TiCl(NEt_2)_3$, Me_3SnCl	[144]
3	 **56**		$Ti(OiPr)_4$, CO_2, $ClCO_2Me$, Bu_3SnCl	[144]
4	 **131**	MeOTs (δ)	TMSCl, R_3SnCl, PivCl, CO_2, MeI (δ)	[32]
5	 **55**		$Ti(OiPr)_4$, CO_2, R_3SnCl	[63]
6	 **87**	MeOD, Michael acceptors (δ), R^1COR^2, $ClCO_2Me$	Me_3SnCl, (α und δ), TMSOTf, CO_2, R-X, (X = Cl, Br, I)	[31]
7	 **106**		MeI	[110]
8	 **62**	MeOH, R^1COR^2, RCHO, $(MeO)_2CO$	HOAc, Me_3SnCl, RNCO, RCOCl, CO_2, R-X , (X = Cl, Br, I), CS_2, $ClCO_2Me$	[66, 67]
9	 **67/68**	MeOH, $(MeO)_2CO$, Bu_3SnOTf, $ClCO_2Me$	Me_3SnBr, Bu_3SnCl, Bu_3SnBr, CS_2	[73]
10	 **82**	MeOH, $ClCO_2Me$	Me_3SnCl, CO_2, ROTf	[90]
11	 **82b**	MeOH, $ClCO_2Me$	Me_3SnCl, CO_2, ROTf	[90]
12	 **132**	MeOH	$ZnBr_2$	[145]

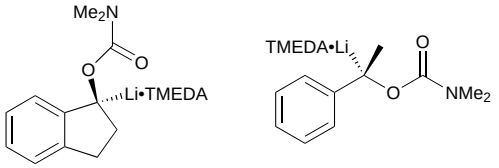
Table 3. (Continued)

Entry	Lithiated Intermediate	Electrophiles which react with retention	inversion	Ref
13	 **42**	ROTs	RX	[43]
14	 **40**		RCHO, ROTs, RX, Me_3SnCl, R^1COR^2	[43]
15	 **94b**	R^1COR^2, CO_2, MeI, TMSCl, TMSOTf		[105]
16	 **45**	RX, TMSX, MeOD	Bu_3SnCl	[47]
17	 **104**	MeOH, $(RCO)_2O$	RCOCl, CO_2, TMSCl, R-X, RCHO, R^1COR^2	[108, 109]



132 - D_{3h} **133** - C_s

Scheme 52. Two calculated structures for $CH_3Li_2^+$, which represent retentive (**133**-C_s) and invertive (**133**-D_{3h}) electrophilic substitution.



134 **135**

Scheme 53. Calculated structures of planar benzylic organolithium intermediates.

example, the electrophile methyl chloroformate reacts with inversion as well as with retention of configuration, depending on the particular organolithium compound (Table 3, entries 8 and 9). One of the biggest challenges towards understanding the nature of electrophilic substitution derives from the scarcity of structural information on the organolithium reagents. Only two of the organolithium species in Table 3 (entries 5 and 6) have been characterized structurally by means of X-ray crystallography.[61, 97] Both crystallize as monomers bound to the bulky (−)-sparteine ligand, which effectively blocks the *syn* face of the organolithium compound. However, structures such as **69** and **70** (Table 3,

entry 1; Scheme 31), which undergo stereodivergent substitution in the absence of any ligands, are likely to exist as more aggregated complex structures.[143]

These aggregation states of the organolithium compound may influence the stereochemical course of the reaction. A D_{3h}-like arrangement of lithium atoms with an Li-C-Li angle of 168° has been observed crystallographically in the solid-state structure of benzyllithium, thus suggesting that either face of the organolithium compound can undergo electrophilic substitution readily.[147] Thus, although a reaction may appear invertive in a unimolecular context, it may very well be that aggregation positions lithium atoms on both faces of the carbanion, thereby providing a four-centered transition state for both invertive and retentive substitutions. However, the extended angle observed in the benzyllithium is the exception rather than the rule, and most crystallographically observed Li-C-Li angles are significantly smaller. What is clear at this stage is that the stereochemical course of the electrophilic substitution of an organolithium compound cannot be generally assumed to occur through a retentive process. But, to be forewarned is to be forearmed, and it is imperative that each case be examined carefully. As additional examples are discovered and more structural information becomes available, we shall undoubtedly develop a better understanding of the factors that dictate the stereochemical pathway of electrophilic substitution.

5. Summary and Outlook

The important role of organolithium reagents in various synthetic transformations continues to provide the impetus for studies of the mechanisms of stereoselective reactions of organolithium compounds with a variety of physical organic tools. For example, NMR spectroscopy has provided information on the thermodynamic parameters involved in the inversion process and the solution structures of key organolithium intermediates. In many instances, factors that facilitate the dissociation of the lithium ion from the carbanion center, such as polar solvents, additives, or internal Lewis bases, are found to enhance the rate of epimerization. However, neither the dissociation of the lithium ion nor the configurational inversion is always the rate-determining step, particularly in the case of α-lithio sulfides and some dipole-stabilized carbanions.

Further data were derived from chemical reactivity and other mechanistic experiments. Hoffmann's test based on kinetic resolution has been an invaluable tool since it does not require inherently high stereoselectivities in reactions to obtain information on configurational stability. The test provides information about the relative rates of epimerization and substitution. Sn/Li exchange and deuterium labeling experiments provide information about the configurational stability as well as mechanism of formation of the chiral organolithium intermediate, and they complement the information afforded by the Hoffmann test. These experiments also provide information about the organolithium intermediate prior to the addition of an electrophile, and therefore represent the configurational stability on the timescale of standard reaction conditions, that is, the time the organolithium spends in the reaction mixture during the lithiation step. The configurational stability depends on solvent, temperature, the nature of the neighboring heteroatom, intra- or intermolecular coordination of Lewis bases, and whether or not the anion is conjugated with a π system.

Another important step in lithiation/substitution sequences is the facial selectivity of the approach of the electrophile during substitution. Electrophile-dependent retentive or invertive substitutions have now been observed for many cases. With a few exceptions, the carbanion in these cases is conjugated with a π system. There have been much speculation on the reasons for the observed trend. However, the lack of structural information has restricted opportunities for systematically expanding the scope of such reactions. Only in very few cases do we have a clear structure/function relationship for the stereochemical behavior of organolithium compounds. The solvent plays an important role in the configurational stability, often by providing a Lewis base site for lithium coordination, but it also affects the aggregation state of the organolithium compound. The connection between aggregation state and chemical behavior has not been as thoroughly studied with organolithium reagents as it has with lithium amides, and recently, lithiated alkynes. Substantial advances have been made in correlating the solution structures of these intermediates with their chemical behavior.[148–150]

What are the future opportunities and challenges in this field? We believe that the first of these challenges is the development of a systematic structure–function relationship for the stereochemical behavior of organolithium compounds. There have only been a few instances in which structural information about organolithium aggregates have been used as the starting point for the design of stereoselective lithiation/substitution sequences.[151, 152] A second and more challenging goal is the development of catalytic processes that use organolithium reagents. Ligand-catalyzed methodologies for the addition of organolithium reagents to imines have been reported.[153, 154] However, this has not been extended to other lithiation/substitution sequences that involve chiral organolithium reagents. A catalysis reaction requires either a ligand accelerated substitution step or a method for suppressing the rate of the uncatalyzed reaction. Furthermore, release of the ligand from the product is needed to ensure ligand turnover. A recent report of the ligand-accelerated electrophilic substitution of an α-seleno organolithium compound is a promising development in this direction.[29]

Rational design of such processes should be preceded by a thorough mechanistic understanding of each step in the reaction pathway. Although the challenge of developing catalytic methodologies in this area is not trivial, further advances in asymmetric ligand design and an increased fundamental understanding of reaction pathways should outline possible approaches. Given the wealth and diversity of the noncatalytic chiral organolithium chemistry described herein, it appears that it is a goal worth pursuing.

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