cation below 60 K. The estimated enthalpy difference between **1** and **2** in solid $SbF_5$ is very small. The barrier for interconversion of **1** and **2** cannot be determined, but it, too, must be very small to accommodate the observations.

The CPMAS NMR experiments and high-level ab initio calculations agree in major respects.[2] $C_4H_7^+$ is a mixture dominated by two structural isomers, the bicyclobutonium ion and the cyclopropylcarbinyl cation. Their energies are nearly identical, and the barrier to interconversion is very low. Characterized by experiment and theory, $C_4H_7^+$ is a molecular will-o'-the-wisp.

**Acknowledgment**. We thank Ray Kendrick for technical support. This research was supported by NSF Grant CHE-8519522. We gratefully acknowledge the Dreyfus New Grant Program for postdoctoral support for G.G.W. NSF Instrumentation Grants CHE-8551436 and CHE-8419266 and grants from the Dreyfus Foundation and Research Corporation provided funding for the 200-MHz NMR apparatus used in synthesis and analysis of the labeled precursors. The samples of $^{13}C$-labeled (chloromethyl)cyclopropane used in this study were prepared by Ms. Camilynn Brannan.

## Lithium–Selenium Exchange. Stereochemistry of α-Lithio Selenides and Sulfides[1]

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*Received June 5, 1990*

The preparation of organolithium reagents with stereochemical control at the C–Li center is generally successful only for a few structural types which are either configurationally very stable (vinyl,[2a] α-alkoxyalkyl,[2b] cyclopropyl[2c]) or which show strong thermodynamic preferences for one stereoisomer because of chelation[3,4,5a] or for stereoelectronic reasons (1,3-dithian-2-yl[5b]). We report here the results of a stereochemical study of α-SeR and α-SR lithium reagents using the *cis*-3,5-diphenylcyclohexyl system **1–2**. Results that parallel some of ours have been obtained for several (γ-oxy-α-(phenylthio)propyl)lithium reagents[3a,4a,b] and for (4-*tert*-butyl-1-(arylseleno)cyclohexyl)lithium.[6]

**1** **2**

a. YR = SePh
b. YR = SMe
c. YR = STol-*p*
d. YR = $SeCH_2CMe_2CH_2SeBu$-*t*
e. YR = H

Lithium reagents of this type are readily prepared by Li–Se exchange of selenoketals and selenothioketals.[6,7] Compound **3a** is cleaved rapidly by *n*-butyllithium to give lithium reagent **1a**, which can be quenched in excellent yield with a variety of electrophiles. The axial/equatorial product ratio was 92/8 within experimental error for the following electrophiles (% yield): $EtCO_2H$ (E = H, 96), $Me_2S_2$ (93), *p*-$Tol_2S_2$ (72), *p*-$Tol_2Se_2$ (75), $Me_3SiCl$ (91), $Me_2iPrSiCl$, $CO_2$ (77), $CH_3CHO$ (81), pivaldehyde (78). Since these substrates differ greatly in reactivity and steric demands (note especially the pairs of silanes and aldehydes), we conclude that the 92/8 ratio represents the equilibrium mixture of axial/equatorial lithium reagents **1a**/**2a** and that these are being trapped faster than they can equilibrate.[8]

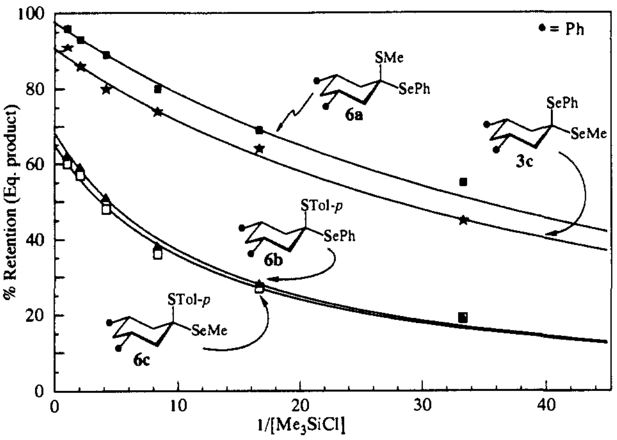
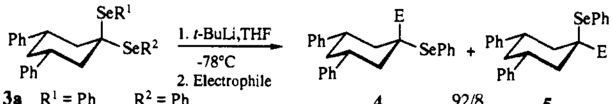


**Figure 1**. Product ratios for cleavage of selenides (0.01 M) by Li–Se exchange using *tert*-butyllithium in THF at −78 °C with in situ trimethylchlorosilane. The lines represent simulations using two parameters: the ratio of second-order reaction of **2** with $Me_3SiCl$ and first-order isomerization of **2** to **1** ($k_2/k_1$), and the initial stereospecificity (% equatorial formed initially): **6a** (■, $k_2/k_1$ = 44, 98%), **3c** (★, 39, 91%), **6b** (▲, 12, 69%), and **6c** (□, 13, 65%).



**3a** $R^1$ = Ph $R^2$ = Ph
**3b** $R^1$ = *p*-Tol $R^2$ = Ph
**3c** $R^1$ = Ph $R^2$ = Me

**4** **5**

The stereoselectivity of the cleavage was also determined, using TolSe/PhSe compound **3b**.[9] The products of cleavage and protonation were 93.3% **4**-H, 5% **5**-H, and 1.7% of the axially protonated cis H/TolSe compound. Thus the kinetic preference in favor of cleavage of the axial TolSe group (~98/2)[6a] is even larger than the thermodynamic ratio. The same conclusion can be reached from a different experiment. When **3a** was cleaved with *t*-BuLi in the presence of 48 equiv of trimethylchlorosilane, a 98/2 ratio of **4**-$SiMe_3$/**5**-$SiMe_3$ was obtained (dimethyl sulfate gave similar results). We believe that under these conditions we are trapping the kinetic product ratio of **1a**/**2a**.

Support for the above interpretations was provided by studies of the PhSe/MeSe compound **3c**,[9] using an in situ trimethylchlorosilane trap. The ratio of MeSe to PhSe cleavage was 4/1, so we were able to prepare the unstable equatorial lithium reagent **2a**.[10] The interesting behavior summarized in Figure 1 was observed. A maximum of 91% of equatorial silane **5**-$SiMe_3$ was formed when 96 equiv of trimethylchlorosilane was present, the fraction being a smooth function of [$Me_3SiCl$]. Thus the Li–Se exchange occurs with high retention of configuration, and trapping of **2a** and equilibration of **2a** to **1a** are competitive.

Lithium–selenium exchange is substantially faster than lithium–sulfur exchange.[7,11] We can therefore study the fate of

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(8) Trapping of nonequilibrium ratios of (α-(phenylthio)alkyl)lithium[4] and (α-bromoalkyl)lithium reagents[3b] with in situ carbonyl compounds or $Me_3SiCl$ has been reported.

(9) This compound was prepared in isomerically pure form (>99%) by crystallization. This is an important advantage of the 3,5-diphenylcyclohexyl system over the traditional 4-*tert*-butylcyclohexyl locked cyclohexane.

(10) This effect was discovered by Krief[6b] and has been used to prepare the less stable of two diastereomeric lithium reagents.[3,6c]

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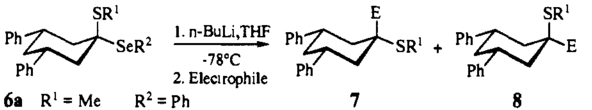
kinetically formed equatorial α-methylthio (**2b**) and α-tolylthio (**2c**) lithium reagents. The sequential experiment using **6a**[9] ((1) *n*-BuLi; (2) $EtCO_2H$) gave a 97/3 ratio of **7a**/**8a** (E = H), even when the electrophile was added less than 1 min after the *n*-butyllithium. Very similar ratios were also observed for cleavage

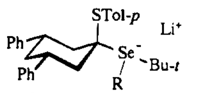


**6a** $R^1$ = Me $R^2$ = Ph
**6b** $R^1$ = *p*-Tol $R^2$ = Ph
**6c** $R^1$ = *p*-Tol $R^2$ = Me

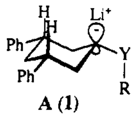
**7** Inversion

**8** Retention

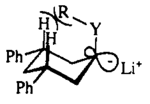
with *tert*-butyllithium and/or reaction with other electrophiles ($Me_3SiCl$, $EtMe_2SiCl$, $iPrMe_2SiCl$, $Ph_2Se_2$, $Me_2SO_4$). The behavior with in situ trimethylchlorosilane is summarized in Figure 1. As much as 96% of equatorial silane **8a** (E = $SiMe_3$) was formed, showing again that the Li–Se exchange occurred with retention of configuration at carbon. An interesting and significant difference was seen when the *p*-tolylthio compound **6b** was treated in a similar way. A maximum of 62% of the equatorially quenched product was obtained at high concentrations of silyl chloride. The shape of the curve suggests that equilibration of equatorial cleavage product to axial lithium reagent has two rate components. One is faster than reaction with trimethylchlorosilane; the second is competitive with the trapping rate. The nature of the fast component is not clear. It could represent a radical pathway in the Li–Se exchange, as for the Li/Br exchange,[12] or perhaps the exchange produces a transient aggregate or ion-pair structure that has a very low inversion barrier compared to the equilibrium structure of the lithium reagent. The ratio of products was identical within experimental error whether a phenylseleno (**6b**) or a methylseleno (**6c**[9]) was cleaved. These experiments argue against the direct reaction of possible intermediate ate complexes[1b] (**9**) giving retention products, since the two ate complexes should have different reactivities.



**9** R = Me, Ph



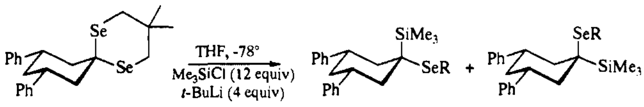
**A (1)**



**B (2)**

Ordinary cyclohexyllithium reagents (e.g., (4-*tert*-butylcyclohexyl)lithium[13] and **1e**–**2e**) give predominantly equatorial products (>10/1). There must therefore be a significant stereoelectronic factor that stabilizes the axial lithium reagents studied here, and the same effect may operate to direct nucleophilic attack to the normally more hindered axial substituent in compounds **3a** and **3b**. We suggest that this effect involves steric inhibition of carbanion lone pair/S–C bond (n–σ*) hyperconjugation. In conformation A of the axial isomer **1**, the carbanion lone pair and S–C σ* orbitals are antiperiplanar and, hence, properly aligned for optimal n–σ* interaction.[14] However, in the equatorial α-lithio selenide or sulfide (**2**), there are severe steric interactions in the conformation (B) in which the n–σ* interaction is most effective.[15]

To test this explanation, we have examined the spiroselenoketal **10**, in which the above stereoelectronic effect is absent during the cleavage, since the key n–σ* interaction is now gauche (and unfavorable) for both seleniums. In, fact, the cleavage is much slower and there is a striking reversal of stereochemistry, which now occurs with a 30/1 preference for the *equatorial* selenium when an in situ quench was used (as judged by the formation of **12**). The isomerization of the equatorial lithium reagent **2d** to the more stable axial isomer **1d** was much slower than for **1a**, **1b**, or **1c**, so that equatorial products could be obtained even in a sequential experiment. The isomerization **2d** to **1d** occurred with a half-life of ~7 min at −78 °C and proceeded to a 24/1 ratio in favor of the axial isomer, just like the other systems examined. We feel that this provides support for the arguments represented by structures A and B.



**10** R = $CH_2CMe_2CH_2SeBu$-*t* **11** **12**

| | | | |
|---|---|---|---|
| *in situ* | 1. $Me_3SiCl$ 2. *t*-BuLi | | 3:97 |
| sequential | 1. *t*-BuLi 2. time 3. $Me_3SiCl$ | (2 min) | 20:89 |
| | | (8 min) | 55:45 |
| | | (32 min) | 91:9 |
| | | (60 min) | 96:4 |

**Summary**. Cyclohexyl α-lithio sulfides and selenides **1** and **2** show a strong stereoelectronic preference for the axial lithium reagent. The equatorial α-thio and α-seleno reagents **2** can be produced and trapped with some stereospecificity, but they equilibrate to the more stable axial isomers **1** in 30 s or less (**1a**–**c**) or a few minutes (**1d**) at −78 °C. The spiroselenoketal **10**, in contrast to the noncyclic analogues **3a** and **3b**, cleaved the equatorial selenium with high stereoselectivity on treatment with *tert*-butyllithium.

**Acknowledgment**. We thank the National Science Foundation for generous support of our research and Mike Neeb for help with the preparative work.

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[11] The ratio of second-order rate constants for reaction of TolLi with $Ph_2Se$ and $Ph_2S$ to give TolYPh (THF, −78 °C) is 250/1: Reich, I. L., unpublished results.

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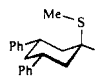
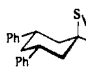
[15] The MM2 energy of conformation i is 4 kcal higher than that of the gauche conformation ii. The X-ray crystal structure of 4-*tert*-butyl-1-(methylseleno)-1-(phenylseleno)cyclohexane shows it to be in conformation ii.[6a]



i



ii

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# Stereoselective Synthesis of Highly Substituted Tetrahydrofurans through Acid-Catalyzed Ring Closure of Selenyl Diols

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*Received July 30, 1990*

Despite extensive research efforts directed toward the stereocontrolled production of substituted tetrahydrofurans from olefinic precursors,[1] few studies have addressed the feasibility of directed ring closures of homoallylic alcohols.[2] Endo-cyclization modes, such as the one shown in the top line of Scheme I, are generally considered to be energetically unfavorable.[3] We envisioned the successful implementation of this strategy using an electrophilic selenium species which would be generated from epoxy alcohols II[4] as shown in Scheme I. Nucleophilic ring opening[5] leading to regioisomers III and III′ would then be followed by a stereoconvergent elimination of water to provide V via the intermediate IV. We report herein the stereoselective synthesis of tri- and tetrasubstituted tetrahydrofurans based on such a homoallylic precursor system.

Epoxy alcohols **1**–**4** (Chart I) were chosen to develop the methodology.[4,6] Ring opening of **1** with sodium phenyl selenide[5]

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