Lithium–Selenium Exchange. Stereochemistry of α-Lithio Selenides and Sulfides

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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,α-alkoxalkyl,β-cyclopropyl) or which show strong thermodynamic preferences for one stereoisomer because of chelation or for stereoelectronic reasons (1,3-dithian-2-yl). We report here the results of a stereochemical study of an α-SeR and α-SR lithium reagents using the cis-3,5-diphenylcyclohexyl system I–2. Results that parallel some of ours have been obtained for several (γ-oxo-α(phenylthio)propyl)lithium reagents3a,b and for (4-tert-butyl-1-arylselenocyclohexyl)lithium.6c

Lithium reagents of this type are readily prepared by Li-Se exchange of selenoketals and selenothioketals.5a,b Compound 3a


The stereoelectivity of the cleavage was also determined, using ToSe/PhSe compound 3b. The products of cleavage and protonation were 93.3% 4-H, 5% 5-H, and 1.7% of the axially protonated cis H/ToSe compound. Thus the kinetic preference in favor of cleavage of the axial TolSe group (~98/2) 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-SiMe3/5-SiMe3 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,5 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. The interesting behavior summarized in Figure 1 was observed. A maximum of 91% of equatorial silane IFSiMe3 was present, the fraction being a smooth function of [Me2SiCl]. Thus the Li–Se exchange occurs with high retention of configuration, and trapping of 2a and equilibration of 2a to 1a are competitive.

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Lithium–selenium exchange is substantially faster than lithium–sulfur exchange.5,11 We can therefore study the fate of
kinetically formed equatorial α-methylthio (2b) and α-thiothylithio (2e) reagents. The sequential experiment using 6a (1) n-BuLi; (2) EtCO₂H) 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 with \([\text{Me}_3\text{SiCl} / \text{Bu-Me} / \text{Li}] \) and/or reaction with other electrophiles such as \(\text{Me}_3\text{SiCl} \) or \(\text{Me}_3\text{SiCH}_2\text{LH} \); the second is faster than reaction with trimethylchlorosilane; the second is the preferred pathway in the Li-Se exchange occurred with retention of configuration at carbon. An interesting and significant difference was seen when the p-tert-butyllithium 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 nature of the fast component is not clear. It could represent a radical pathway in the formation of indole. A maximum of 62% of the equatorially quenched product to axial lithium reagent has two rate components. One is faster than reaction with trimethylchlorosilane; the second is slower and there is a striking reversal of stereochemistry, which now occurs with a 30/1 preference for the equatorial selenium when in situ quenching was used just as 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 \(-7 \text{ min at } -78 \text{ °C} \) 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 presented by structures A and B.

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 \(-78 \text{ °C} \). The spiroselenoketal 10, in contrast to the noncyclic analogues 3a and 3b, cleaved the equatorial selenium with high stereoelectivity on treatment with tert-butyllithium.

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**Stereoelectronic Synthesis of Highly Substituted Tetrahydrofurans through Acid-Catalyzed Ring Closure of Selenyl Diols**

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Despite extensive research efforts directed toward the stereocontrolled production of substituted tetrahydrofurans from olefinic precursors, few studies have addressed the feasibility of directed ring closures of homoallylic alcohols.\(^3\) Endo-cyclization modes, such as the one shown in the top line of Scheme I, are generally considered to be energetically unfavorable.\(^1\) We envisioned the successful implementation of this strategy using an olefinic selenium species which would be generated from epoxy alcohols\(^4\) as shown in Scheme I. Nucleophilic ring opening\(^5\) leading to regioisomers III and IV would then be followed by a stereoconvergent elimination of water to provide V via the intermediate IV. We report herein the stereoelective 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.\(^6\) Ring opening of 1 with sodium phenyl selenide\(^7\)

\(^{(1)}\) The ratio of second-order rate constants for reaction of TolLi with PhSe and PhS to give TolYPh (THF, \(-78 \text{ °C}) is 250:1. Reich, I. L., unpublished results.


\(^{(6)}\) The MM2 energy of the compound is 4 kcal higher than that of the gauche conformation

\(^{(7)}\) The X-ray crystal structure of 4-tert-butyl-1-(methylthio)-1-(phenylthio)eclohexane shows it to be in conformation II.


