

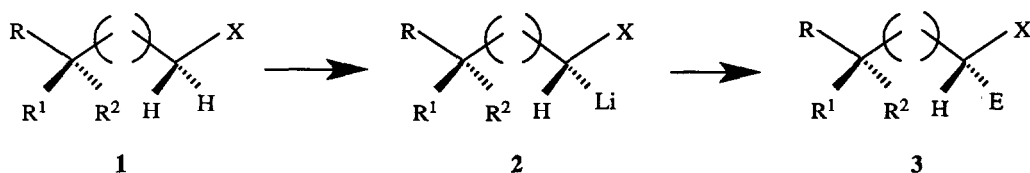
DIASTEREOSELECTIVE REACTIONS OF AN ACYCLIC α -LITHIATED SULFIDE: A CASE OF THERMODYNAMIC CONTROL

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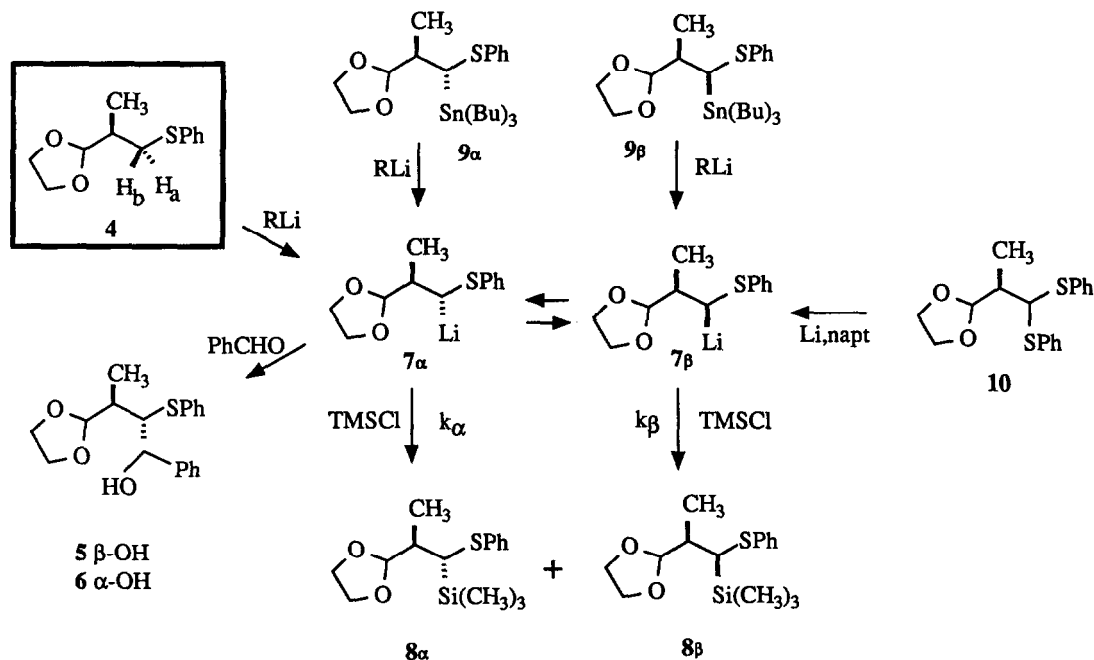
Summary: The C-Li bond α to sulfur in an acyclic sulfide thermodynamically favors one configuration (96:4). This allows for the diastereoselective functionalization of sulfide 4.

Direct replacement of a diastereotopic proton with an electrophile (1 \rightarrow 3) represents an efficient approach to the creation of asymmetric carbon atoms¹. In practice this is achieved most easily via an organometallic intermediate such as 2. Overall stereoselectivity can be achieved through either: (1) diastereoselective formation of one tetrahedral organometallic followed by stereoselective electrophilic addition; or (2) formation of a planar or functionally planar carbanion which undergoes selective electrophilic attack on one face. In the former scenario the formation of one organometallic diastereomer could arise from either a diastereoselective deprotonation (a kinetic process) or from a selective equilibration (a thermodynamic process). In this communication we would like to report on a highly stereoselective functionalization of an alkyl sulfide (1, X=SPh) in which the configuration of the intermediate organolithium 2 is thermodynamically controlled.



Our initial foray into this area involved the deprotonation and subsequent alkylation of sulfide 4 with benzaldehyde. This reaction produced the two diastereomers 5 and 6 in a 4 to 1 ratio. The identity of the major product 5 was proven by X-ray crystallography. The minor product could then be related to the major isomer by a simple oxidation/reduction sequence. Importantly the two diastereomers with a *syn* relationship between the methyl group and the new C-C bond were not observed. Hence the 1,2-asymmetric induction was complete while the 1,3-asymmetric induction was 80%². A reasonable explanation for the observed 1,2-stereoselectivity is that the intermediate organolithium has the α -configuration (see 7 α , Scheme 1) and that this diastereomer reacts with benzaldehyde with retention of configuration at the C-Li bond. In order to evaluate this hypothesis, especially as it relates to the configurational integrity of the intermediate organolithium, we have probed the stereoselectivity of this process in some detail.

As for this study we were interested in exploring only the 1,2-induction, we switched our electrophilic probe to trimethylsilyl chloride. Simple deprotonation and silylation of sulfide 4 yielded a 98:2 ratio of diastereomers



SCHEME 1

(Table 1, entry 1). In analogy with the benzaldehyde experiment we have assigned the major product to be **8 α** as shown in Scheme 1³. While at this point we suspected that preferred formation of **8 α** might arise from the diastereoselective deprotonation of H_a the results shown in entry 2 hinted that such was not the case. More specifically performing the deprotonation (-20) and silylation (25°) at higher temperatures (entry 2) did not lead to an increased production of **8 β** through either a decrease in the kinetic selectivity of deprotonation and/or an epimerization of the intermediate organolithium. That the critical factor for obtaining high stereoselectivity was a thermodynamic preference for **7 α** and not a diastereoselective deprotonation became apparent when alternative routes to the intermediate organolithium were explored.

In accord with literature results⁴ Sn/Li exchange on compound **9 α** should initially produce the α -organolithium **7 α** , while Sn/Li exchange on **9 β** should initially produce the β -organolithium **7 β** . If no epimerization was taking place the corresponding silylated epimers **8 α** and **8 β** should be produced. As seen in entries 4 and 5 the Sn/Li exchange of both **9 α** and **9 β** ⁵ lead to the same 98:2 ratio of **8 α** to **8 β** . Obviously epimerization had taken place and thus the stereochemistry of the product is independent of the initial stereochemistry of the organolithium⁶.

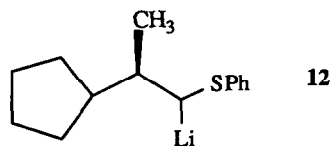
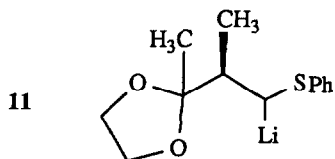
The Sn/Li exchange experiments did not allow one to evaluate whether the ratio of products obtained reflected the thermodynamic ratio of organolithiums. This would be the case if the rate of silylation was faster than the rate of epimerization. If on the other hand the rate of silylation is slow relative to epimerization, the ratio of products would be dependent on k_{α}/k_{β} (see Scheme 1). We believe that the results presented in entries 7 and 8 allow one to distinguish between these alternatives. Reductive desulfenylation⁷ of **10** should not discriminate between the two diastereotopic SPH groups, hence a near to equal mixture of **7 α** and **7 β** should be produced initially. In spite of this

TABLE 1: Stereoselectivity versus Reaction Conditions

| ENTRY | PREPARATION OF ORGANOLITHIUM 7 | RATIO 8 α /8 β ³ |
|-------|---|--|
| 1 | From 4,s-BuLi,-78 $^{\circ}$,THF | 98:2 |
| 2 | From 4,n-BuLi,-20 $^{\circ}$,THF | 98:2 |
| 3 | From 4,t-BuLi,-78 $^{\circ}$,THF,HMPA (2.0 X) | 73:27 |
| 4 | From 9 α ,n-BuLi,-78 $^{\circ}$,THF | 98:2 |
| 5 | From 9 β ,n-BuLi,-78 $^{\circ}$,THF | 97:3 |
| 6 | From 9 α ,n-BuLi,25 $^{\circ}$,pentane | 70:30 |
| 7 | From 10,Li,naph,-78 $^{\circ}$,THF | 95:5 |
| 8 | From 10,Li,naph,-78 $^{\circ}$,THF (in presence of TMSCl) | 61:39 |

fact subsequent silylation should result in the standard predominance of 8 α as seen in previous entries. Entry 7 gave just this result. If however the reductive desulfenylation was carried out in the presence of TMSCl (entry 8) a 61:39 mixture of stereoisomers was obtained indicating that the initially formed mixture of organolithiums was trapped. That the initially formed mixture of organolithiums could be trapped, strongly supports the contention that the rate of silylation is faster than the rate of epimerization. If so the high stereoselectivity observed in the other entries reflects the thermodynamic preference for 7 α over 7 β . Interestingly the stereoselectivity is negatively effected by switching the solvent to either a more polar (entry 3)⁸ or less polar (entry 6) solvent. One explanation for this result is that in these solvents epimerization has become competitive with silylation. In pentane this is accomplished by slowing down silylation relative to epimerization⁹, while in the presence of HMPA the rate of epimerization is accelerated relative to silylation.

In conclusion, the results discussed herein support the notion that C-Li bonds α to sulfur react in a stereospecific manner via a tetrahedral intermediate¹⁰. In essence then they are similar to their oxygen^{4a,4b} and nitrogen^{1d} counterparts and differ only in the fact that their rate of epimerization is seemingly faster. This low barrier to inversion forces one to rely on thermodynamics to achieve high stereospecificity in the reaction of α -lithiated sulfides. We believe that the same dynamics are present in the more well-studied α -lithiated sulfoxides and, as



others have concluded, it is the asymmetry at the sulfoxide center which often controls the thermodynamic configuration at the C-Li bond¹¹. This raises the interesting question as to the origin of the thermodynamic

preference for 7α over 7β . While we have yet to answer this question conclusively it is instructive to note that the diastereomeric ratio of silylated products for organolithiums **11** and **12** is 85:15¹². Since it was thought that internal coordination of the lithium atom to the dioxolane ring was an important element in the thermodynamic preference of 7α , we were not surprised at the decrease in stereoselectivity for **11** and **12**. We are mildly surprised that, even in the absence of a dioxolane ring, relatively high stereoselectivity is maintained by **12**.

Acknowledgements: We gratefully acknowledge the financial support of the National Science Foundation (CHE-8612735). A.M.L. thanks Coca Cola for a summer undergraduate fellowship.

References and Notes

- For related studies, see: (a) Meyers, A.I.; Dickman, D.A. *J. Am. Chem. Soc.* **1987**, *109*, 1263. (b) Gawley, R.E. *J. Am. Chem. Soc.* **1987**, *109*, 1265. (c) Beak, P.; Hunter, J.E.; Jun, Y.M.; Wallin, A.P. *J. Am. Chem. Soc.* **1987**, *109*, 5403. (d) Rondan, N.G.; Houk, K.N.; Beak, P.; Zajdel, W.J.; Chandrasekan, J.; Schleyer, P.v.R. *J. Org. Chem.* **1981**, *46*, 4110. (e) Williams, D.R.; Phillips, J.G.; Huffman, J.C. *J. Org. Chem.* **1981**, *46*, 4101. (f) Eliel, E.L. *Tetrahedron* **1974**, *30*, 1503.
- The selectivity parallels that reported by Williams (ref 1e) for a related sulfoxide system. The 1,3-stereoselectivity fits a transition state model proposed by McGarvey, wherein the dioxolane ring provides the necessary internal coordination, see: McGarvey, G.J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5420.
- The ratio of silylated isomers was determined by capillary gas chromatography. Except for entries 2 and 6 all silylations were performed at -78° . That methyl iodide also reacts with *anti* selectivity (4:1, 0°) lends further support to the silylation assignments.
- (a) Still, W.C.; Skeekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J.S.; MacDonald, T.L.; McGarvey, G.J. *J. Am. Chem. Soc.* **1984**, *106*, 3376. (c) Corey, E.J.; Eckdrick, T.M. *Tetrahedron Lett.* **1984**, *25*, 2415. (d) Newman-Evans, R.H.; Carpenter, B.K. *Tetrahedron Lett.* **1985**, *26*, 1141.
- 9α was produced in a 90:10 ratio of isomers by quenching **7** with $(\text{Bu})_3\text{SnCl}$. Reductive desulfenylation of 9α followed by resulfenylation with PhSSPh yielded 9β as the major diastereomer (70:30 mixture). 9α and 9β need not be diastereomerically pure to prove that prior equilibration of the organometallic intermediates was occurring.
- It may well be that the deprotonation is also stereoselective. However any such selectivity is irrelevant as far as the final stereoselectivity is concerned. For other examples where this is true, see: refs 1a, 1b and 1f.
- Cohen, T.; Weisenfeld, R.B. *J. Org. Chem.* **1979**, *44*, 3601.
- These are the original conditions reported for achieving α -lithiation in phenyl sulfides, see: Dolak, T.M.; Bryson, T.A. *Tetrahedron Lett.* **1977**, 1961.
- It takes 5 hrs at 25° to achieve complete silylation of the organolithium in pentane. We had originally explored the use of pentane in an effort to obtain a configurationally stable organolithium. Unfortunately epimerization occurs at the temperatures necessary (0° to 25°) to achieve Sn/Li exchange.
- Calculations, NMR studies and crystallography all support a tetrahedral structure for α -lithiated sulfides. For a leading reference, see: Seebach, D.; Gabriel, J.; Hässig, R. *Helv. Chim. Acta* **1984**, *67*, 1083.
- For a review on carbanions α to sulfur, see: Wolff, S. In *Organic Sulfur Chemistry*; Bernardi, F.; Csizmadia, I.G.; Mangini, A. Eds.; Elsevier: Amsterdam, **1985**, Chapter 3.
- The sense of the diastereoselectivity in these cases has not been determined.

(Received in USA 22 February 1988)