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ON THE STEREOSPECIFIC REDUCTION OF VINYLSULFOXIDES WITH THE POSSIBILITY OF DEUTERIUM LABELING

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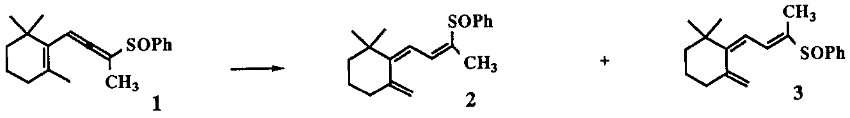
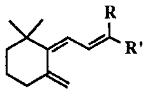
Abstract: Upon treating triene sulfoxide 2 or 3 in the presence of methanol (internal proton source) in ether with tert-butyllithium, the reduced product 4b or 4c, respectively, is obtained with retention of configuration. A deuterium label can be incorporated by using methanol-O-d_1 as the internal proton source.

Recently we reported a method whereby certain triene sulfoxides can be synthesized with high selectivity and specificity via pericyclic processes of allenic sulfoxides.[1] One particularly useful observation was that the phenylsulfinyl moiety can uniquely control the π-facial selectivity of the [1,5]-sigmatropic hydrogen shift.[1a] For example, near room temperature, vinylallene sulfoxide 1 isomerized primarily to 2 rather than 3. During the course of these investigations, it became of interest to explore the possibility of synthesizing vinyllithium reagents, or more particularly, trienyllithium and even higher order polyenyllithium reagents,[2] for further use in synthesis.

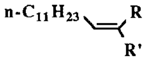


Reacting a sulfoxide RS(O)R' with an alkyllithium R"Li should afford RLi, R'Li and even recovered R"Li depending upon several factors including the relative stabilities of RLi, R'Li and R"Li.[3] Treatment of 2 with RLi was anticipated to afford trienyllithium 4a rather than the undesirable phenyllithium.[4,5] We observed however that treatment of 2 with a variety of alkyllithium reagents (MeLi, n-BuLi, s-BuLi or t-BuLi) in ether followed by proton quenching afforded a complex array of products and/or only modest yields of triene 4b. For example, with methyllithium, only the product of phenyl-methyl exchange (41%) was observed. By contrast, an optimum yield of 47% of 4b was obtained using 3-4 equivalents of t-BuLi/ether at -78°C followed by methanol post quench as the reducing conditions. We report now the remarkable finding that a close variant of this kind of reduction (2 → 4b)[6] can be effected efficiently and stereospecifically employing t-BuLi with MeOH as the internal quench.[7] Moreover, the finding that this process allows for incorporation of deuterium label renders the procedure described herein especially useful.

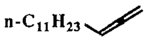
The procedure is very simple. For example, one merely adds tert-butyllithium (0.27 mL,



4a, R=Li; R'=CH_3
b, R=H; R'=CH_3
c, R=CH_3; R'=H
d, R=D; R'=CH_3
e, R=CH_3; R'=D
f, R=PhSO; R'=H
g, R=R'=H
h, R=H; R'=PhSO



5a, R=PhSO; R'=CH_3
b, R=CH_3; R'=PhSO
c, R=H; R'=CH_3
d, R=CH_3; R'=H
e, R=PhSO; R'=H
f, R=H; R'=PhSO
g, R=R'=H



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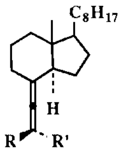


7a, R=SOPh; R'=CH_3
b, R=H; R'=CH_3
c, R=CH_3; R'=H
d, R=CH_3; R'=D
e, R=D; R'=CH_3

1.88 M solution in pentane) rapidly via syringe to a stirred solution of a mixture of 2 (0.13 mmol) and MeOH (0.32 mmol) in ether (2.5 mL) at −78 °C. After less than 10 min at −78 °C, MeOH (0.5 mL) post quench, work up at room temperature and then purification by chromatography provided **4b** in 72% yield. The sulfur containing by-product in these reductions was t-butyl phenyl sulfoxide, isolated in 92-95% of the amount of **4b** obtained.

The results of a number of such reductions carried out in this study are summarized in Table 1. The reductions of Z- (2) or E-sulfoxide (3) with MeOH (entries 1 and 2) or MeOD (entries 3 and 4) as the internal quench demonstrate stereospecificity for this process including label incorporation. For the simple mono-ene sulfoxides **5a** and **5b** (entries 5 and 6), the yields are attenuated and allene 6[8] is a significant by-product.[9] As evidenced by entries 7 through 10, the presence of a proton α to the sulfoxide, because of competing deprotonation, affords lowered yields. Fortunately, for some of these simpler systems, alternatives exist.[6]

In a study of possible mechanistic significance, the allene sulfoxide **7a** when subjected

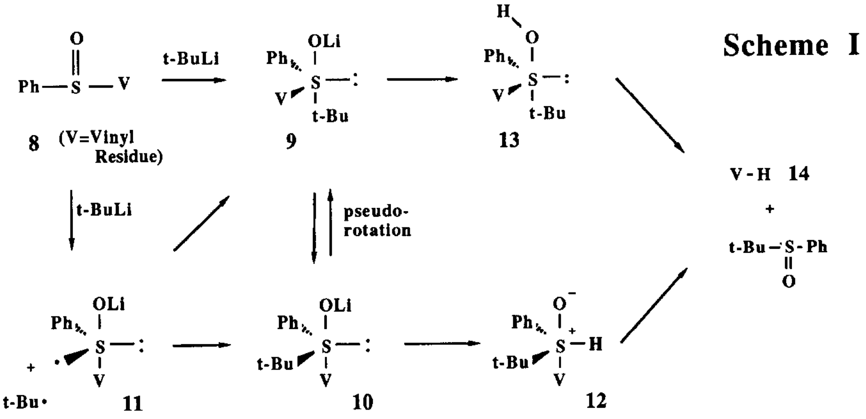
Table 1. Reduction of Vinylsulfoxides

Entry	Sulfoxide	Product	Yield, %[a]
1	2	4b	72
2	3	4c	70
3	2	4d[b]	72
4	3	4e[c]	65
5	5a	5c (plus 6)	52 (14)
6	5b	5d (plus 6)	28 (29)
7	5e	5g	40
8	5f	5g	29
9	4f	4g	28
10	4h	4g	19
11	7a	7b[d]	87
12	7a	7e[g]	93

[a] Isolated yields after HPLC or flash column chromatography. All new compounds exhibited satisfactory ^1H- and ^{13}C-NMR and other spectral data including MS data. [b] MeOD internal quench followed by MeOD post quench or MeOH post quench afforded 90.2% or 82.5% d_1 product, respectively. MeOH internal quench followed by MeOD post quench afforded only 2% d_1 product. [c] MeOD internal quench followed by MeOD post quench afforded 93.7% d_1 product. [d] The ratio of **7b**/**7c** was 97.3%/2.7%. [g] MeOD internal quench followed by MeOH post quench afforded 89.9% d_1 product with a 96.3%/3.7% ratio of **7e**/**7d**.

to the standard reduction conditions (entry 11) afforded 7b with high selectivity (7b/7c = 97.3%/2.7%). Similarily, the labeled allene 7e (entry 12) could be obtained with high selectivity (7e/7d = 96.3%/3.7%) with 90% deuterium incorporation. We have shown previously that deprotonation of 7b with strong base (n-BuLi, KOt-Bu, THF) followed by D_2O quench affords the deuterated inversion product 7d while similar deprotonation-D_2O quench of 7c also afforded 7d, the retention product.[4b] Thus the metallated allenic species are configurationally unstable.[4b] The fact that reduction of sulfoxide 7a affords mainly 7b with excellent retention (entry 11) supports the hypothesis that a free allenyllithium species is not involved. By implication, the mechanistic pathway for the reduction of the vinylsulfoxides may not involve a vinyllithium as an intermediate.[10] Moreover, in further studies with 2, internal or post quenching with other electrophiles (e.g., CH_3I, EtI, $ClCO_2Et$, $(MeO)_2SO_2$ and $(CH_3)_3SiCl$) afforded little or none of the desired alkylated or silylated products. These results could be a reflection of more complex pathways which ensue when electrophiles other than a proton is used to quench the putative sulfurane intermediate (either 9 or 10) hypothesized below. If vinyllithium intermediates are involved, significant alkylation or silylation should have occurred.

As a possible mechanistic hypothesis (Scheme I)[11] the t-butyllithium can be envisaged to initially attack 8 axially to afford 9, which rapidly pseudorotates[12] to another trigonal bipyramidal structure 10. Alternatively, (since t-butyllithium is the most effective of the alkyllithium reagents examined) the first step could involve a single electron transfer from t-BuLi affording the sulfuranyl radical species 11, which, if formed, must undergo formed combination with t-butyl radical before disproportionation of the latter to afford the same 9 or 10. Durst[3a] proposed a similar type sulfuranyl radical to account for the racemization of optically active t-butyl phenyl sulfoxide upon treatment with t-butyllithium. As discussed above, direct fragmentation of sulfurane 9, 10 or another pseudorotamer to a vinyllithium does not seem likely.[11] Rather, we propose direct protonation[13] of the putative sulfurane intermediate (e.g. 9 or 10) to afford species such as 13 or 12, which undergoes stereospecific coupling[14] of proton and the vinyl moiety to provide reduced olefin 14 and t-butyl phenyl



Scheme I

sulfoxide. As for the preferential coupling of proton with vinyl rather than phenyl, similar observations have been made by Trost[5] and by Neef.[4a,10]

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(9) In connection with other ongoing projects in this Laboratory, the method described in this study has proven effective for the stereospecific reduction of tetraene and even pentaene sulfoxides (H. Elnagar and A. de Lera, unpublished observations).

(10) The Schering group (Ref. 4a) has reported a desulfurization of allenic sulfoxides using MeLi (post quenching procedure) instead of t-BuLi. Curiously, when we attempted to incorporate deuterium using CD_3Li or post quenching with DCl/D_2O, only the unlabeled, desulfurized allene was obtained. This result may preclude the allenyl anion species hypothesized by the Schering group as an intermediate in their process (unpublished observations, E.M.G.A van Kruchten and P. Theobald).

(11) Alternative pathways, including direct protonation of vinyllithium within a methanol containing solvent cage, cannot be explicitly ruled out at this stage. However, if a vinyllithium species were produced, there should have been no advantage to the internal quench procedure described herein since vinyllithium compounds should be stable. It must of course be emphasized that any proposed pathway must accomodate the fact that up to >90% of the quenching of the intermediate is due to the methanol (see footnotes b-d of the Table) present in the reaction solution before work up.

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