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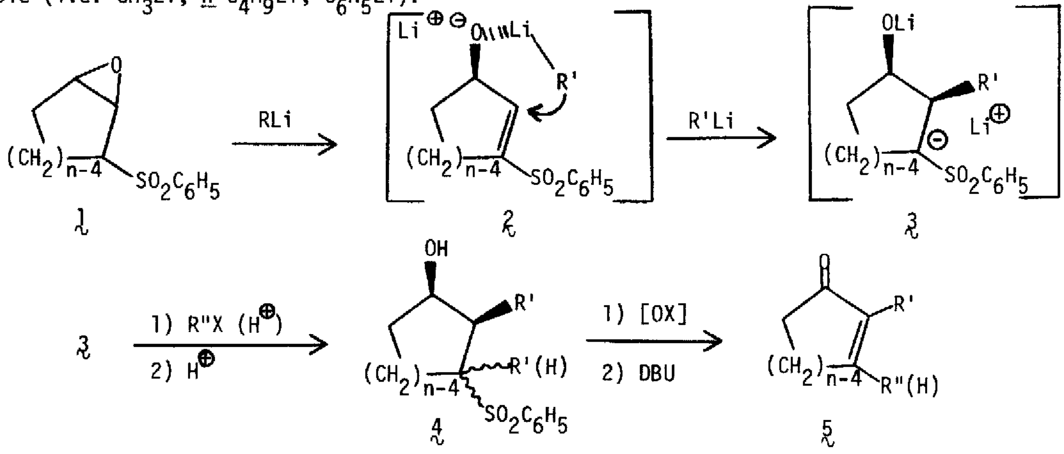
CONJUGATE-ADDITION REACTIONS OF HIGHLY-FUNCTIONALIZED ARYL LITHIUM REAGENTS TO γ-SILYLOXY-α,β-UNSATURATED SULFONES: CONSEQUENCES OF THE STRUCTURE OF THE SULFONE MOIETY.

D. L. Barton,[2] P. C. Conrad,[3] P. L. Fuchs*[4]
Department of Chemistry
Purdue University
West Lafayette, Indiana 47907

Summary. The effect of sulfone structure (phenyl vs t-butyl) is compared in the conjugate-addition reactions of ortho substituted and ortho, ortho disubstituted aryl lithium reagents with γ-silyloxy-α,β-unsaturated sulfones.

Our earlier reports on the use of γ-oxido-α,β-unsaturated sulfones (2, n=5,6,7) in the synthesis of α,β-difunctionalized enones (5) have shown that intermediate 2 gives good to excellent yields of conjugate-addition product 4 when the organometallic reagents are relatively simple (i.e. CH_3Li, n-C_4H_9Li, C_6H_5Li).[5]

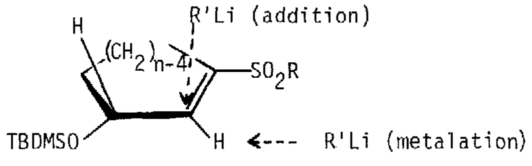


The addition reaction apparently takes place via intramolecular-assisted delivery of the organometallic reagent as in 2.[6] We now wish to report on our studies with more complex organometallics, particularly those ortho and diortho substituted.

Reactions carried out with **2** and highly substituted organometallics gave only poor yields of adducts **4**. Presumably many of these organometallics (Table I) are intramolecularly chelated, and as such, would not be expected to be complexed with **2**. Intramolecular-assisted delivery is less probable and the rate of the addition reaction becomes very slow as dipolar repulsion of the two charged species in solution becomes dominant. A partial solution to this problem has been the use of γ-silyloxy-α,β-unsaturated phenylsulfone **6a** in which dipolar repulsion factors are negated.[5] Unfortunately, although organolithiums like phenyllithium reacted even more facilely with **6a** than with **2**,[8] more substituted reagents still gave unacceptable yields (Table I). We found the reaction mixtures contained adduct, recovered vinylsulfone **6a**, and the compounds resulting from proton quench of the organometallics.

Since quenching experiments (C_6H_5CHO and CH_3OD) indicated the proton was not being abstracted from solvent (at least at low temperatures), non-metalated starting material, or n-butyl bromide (formed when using n-BuLi as the metalating agent) we surmised **6a** was the source of the proton. It was felt there were three sites on **6a** which were possible sources: The allylic hydrogen α to the silyloxy group, the vinylic hydrogen, and the ortho hydrogens of the phenyl group. Abstraction of the allylic proton seemed unlikely on the basis of the protection afforded by the silyloxy group and on a recent report of the conditions needed for this type of deprotonation.[9] Ortho metalation seemed even less likely because of the short times and low temperatures involved in our reactions.[10] This indicated the vinylic hydrogen to be the source of our trouble. Treatment of **6a** with LDA (30 min at -78°C) followed by quenching with CH_3OD (TMSCl) does in fact give deuturated (silylated) **6a** in which the incorporation is completely at the vinylic position.[17]

Since conjugate-addition takes place perpendicular to the plane of the vinylsulfone and deprotonation occurs in the same plane, an increase in the size of the sulfone group should retard the deprotonation reaction more strongly than the conjugate-addition reaction. Consistent with this analysis, additions to t-butylsulfone **6b**[12] afford substantially higher yields of conjugate-addition product in reactions with complex organometallics (Table I).

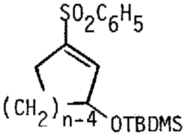


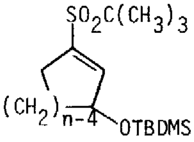
6a, $R=C_6H_5$
6b, $R=t\text{-}C_4H_9$

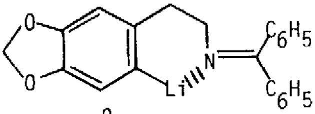
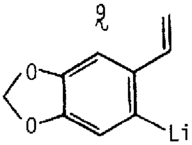
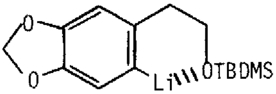
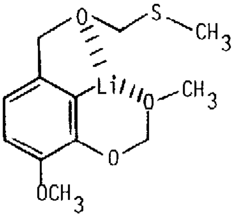
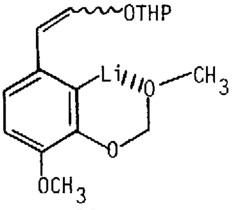
In summary, we have found that for the organometallic reagents examined, γ-silyloxy-α,β-unsaturated-t-butylsulfones (**6b**) are most suitable for conjugate-addition reactions. Conversion of the adducts to enones has been carried out in good yields (typically 60-75% overall). For example, the conjugate-addition adduct **7** from **12** and **6b** (n=6) was desilylated (2 equiv TBAF/THF,[14] 24 h, 25°C, 98%) to yield an alcohol which was oxidized ("TFAA activated" DMSO[15]) and eliminated (2 equiv DBU/Et_2O, 24 h, 25°C, 75% for the last two steps) to give the desired enone **8** after chromotography.[16] This procedure with few modifications has been used successfully in a number of cases.[17]

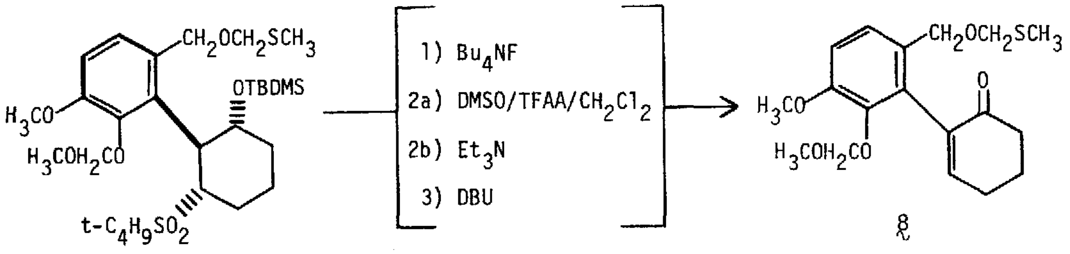
Table I

Comparison of Addition/Quenching Ratios for Phenyl vs. t-Butyl Vinylsulfones.


6a


6b

	Solvent	(n=5)	(n=5)
		Yield Adduct/Yield Quenching	
 9	THF	60-70/40-30	85-95/15-5
 10	Et$_2$O 3:1 THF/hexane	26/74 ---	95/5 90/10
 11	3:1 THF/hexane	60/40	75/25
	Solvent	(n=6)	(n=6)
		Yield Adduct/Yield Quenching	
 12	THF 3:1 THF/hexane Et$_2$O	25/75 --- 30/70	65/35 85/15 (78% isolated) 85/15 (77% isolated)
 13	THF	15/85	40/60



7

8

Overall Yield 73%

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References and Notes

1. Synthesis Via Vinyl Sulfones-3. For papers 1 and 2 see reference 5.
2. Postdoctoral Research Associate, 1978-1980.
3. Graduate Research Associate, David Ross Fellow.
4. A. P. Sloan Fellow 1977-1979.
5. P. C. Conrad and P. L. Fuchs, J. Am. Chem. Soc., 100, 346 (1978). J. C. Saddler, P. C. Conrad, and P. L. Fuchs, Tetrahedron Lett., 5079 (1978).
6. For a similar intramolecular delivery see: M. Isobe, M. Kitamura, and T. Goto, Tetrahedron Lett., 3465 (1979).
7. Prepared by heating epoxysulfone **1**[5] at 80-85°C for 3-4 h in DMF with 10 mole % of DBU followed by treatment with imidazole and t-butyldimethylsilyl chloride.[14]
8. Addition occurs instantaneously at -78°C for **6a** as opposed to 30 min at -20°C for **2**.
9. J. J. Eisch and J. E. Galle, J. Org. Chem., 44, 3279 (1979).
10. Typically conjugate-addition is complete after 15-30 min at -78°C while several hours at -78°C are needed for *ortho* metalation.[11]
11. H. E. Zieger and G. Wittig, J. Org. Chem., 27, 3270 (1962).
12. Prepared in the same manner as **6a**.
13. As Table I indicates we have observed a preference for less polar solvents for the conjugate-addition. Experimentally it is necessary to determine which solvent or solvent-pair is most suitable for both metalation and conjugate-addition.
14. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 6190 (1972).
15. K. Omura and D. Swern, Tetrahedron, 34, 1651 (1978).
16. All new compounds have IR, HMR, CMR and MS in accord with assigned structures.
17. Abbreviations used in this discussion are: LDA (lithium diisopropylamide); TMSCl (trimethylchlorosilane); TBDMS (t-butyldimethylsilyloxy); TBAF (tetrabutylammonium fluoride); TFAA (trifluoroacetic anhydride); DMSO (dimethyl sulfoxide); DBU (diazabicycloundecene).

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