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CONJUGATE-ADDITION REACTIONS OF ORGANOMETALLIC REAGENTS TO γ-OXYGENATED-α,β-UNSATURATED SULFONES: CONTROL OF STEREOCHEMISTRY AT THE β-POSITION[1]

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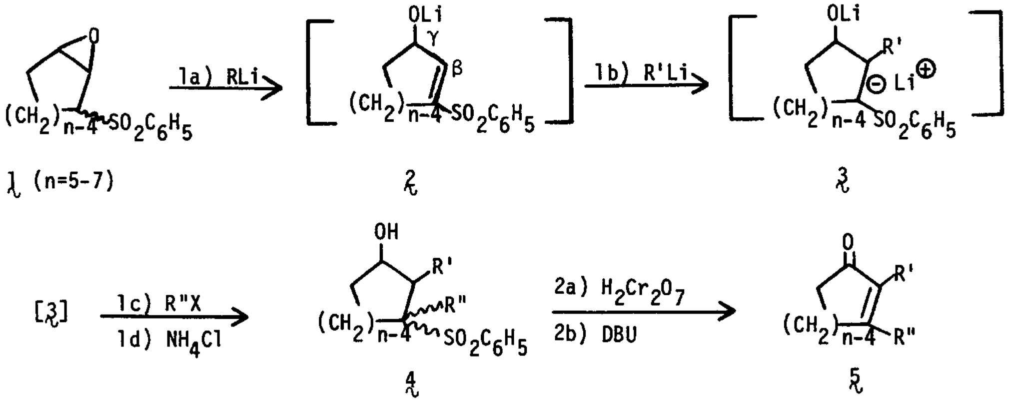
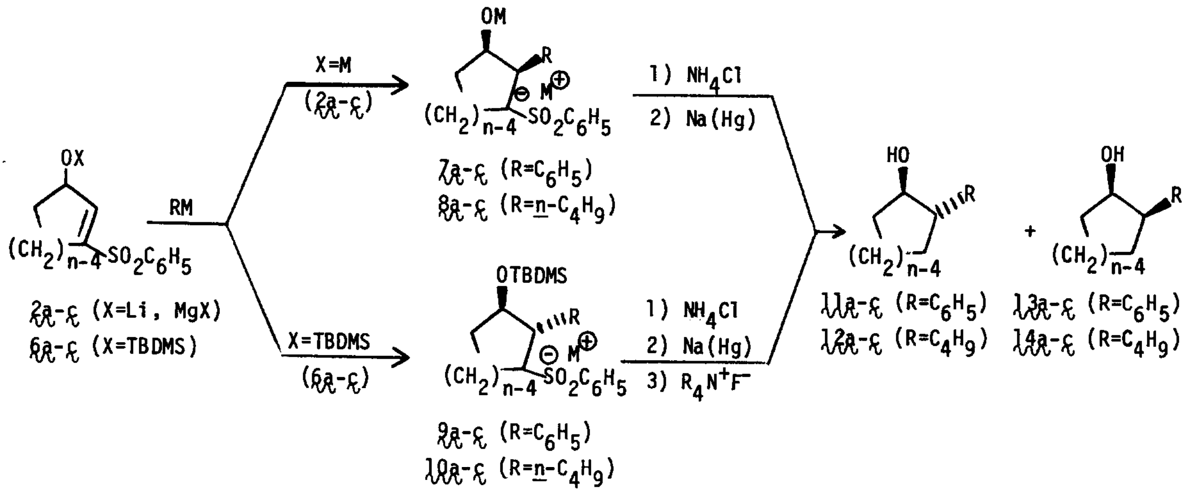
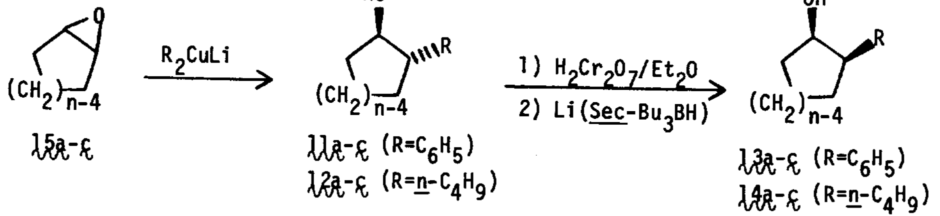
The key step in our recently developed synthesis of α,β-difunctionalized enones (**5**) from β-epoxysulfones (**1**) involves the conjugate-addition reaction of organolithium reagents to γ-oxido-α,β-unsaturated sulfones (**2**).[4]



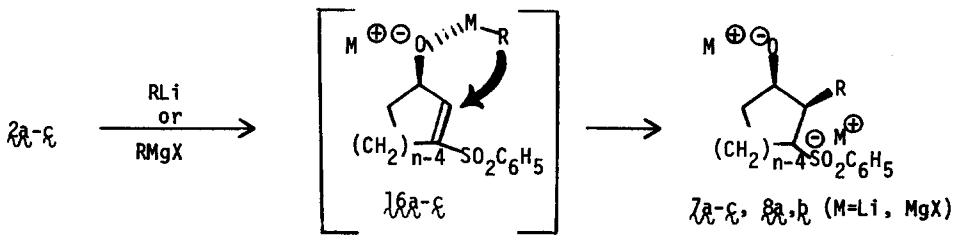
In preparation for further development of this conjugate-addition reaction for the synthesis of natural products, we wished to delineate those factors responsible for stereochemical control of the incoming organometallic reagent. This study details the addition of phenyl and butyl lithium (as well as the corresponding Grignard reagents in several instances) to two series of γ-oxygenated vinylsulfones (**2a**-**c**, **6a**-**c**). The stereochemistry of the addition process was determined by conversion of the resulting adducts **7**-**10** to cycloalkanols **11**-**14** which were compared to authentic samples prepared by an alternate route (**15**→**11**→**13**; **15**→**12**→**14**).[5-11]



[M = Li, MgX]; [(a) n=5; (b) n=6; (c) n=7]; [TBDMS = t-butyldimethylsilyl]

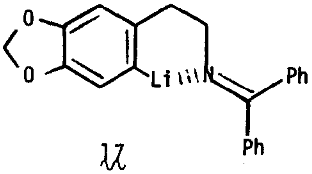


The results can be generalized very simply. With two exceptions[12] (entries 13,23 Table I), γ-oxido vinylsulfones (2a-c) yield cis adducts (13a-c, 14a,b) whereas γ-siloxy vinylsulfones (6a-c)[13] afford trans products (11a-c, 12a,b). While the trans additions to the γ-siloxy vinylsulfones (6a-c) are in accord with expectations based upon a steric approach model, the cis additions to the γ-oxido vinylsulfones (2a-c) apparently require intramolecular-assisted delivery of the organometallic via the intermediacy of an alkoxide-organometallic complex (16a-c).



Our recent experience with conjugate-additions of more highly-functionalized organolithium reagents 17,18 to γ-oxido vinylsulfones 2a,2b suggests that the presence of complex 16 is required for successful bond formation. Organolithium reagents 17,18 presumably are both already intramolecularly chelated and would not be expected to be appreciably stabilized by further complexation to the alkoxide moiety of vinylsulfones **2a**,**b**. Without the intramolecular assist provided by complex **15**, the dipolar repulsion terms apparently become dominant in solution and make the addition rate of **17**,**18** to **2a**,**b** impossibly slow.

Fortunately, this limitation can be easily circumvented, since reagents **16** and **17** both add instantaneously to the corresponding *silyloxy* vinylsulfones **6a**,**b** at -78°C and -100°C.



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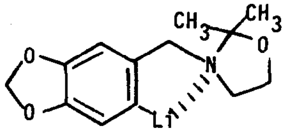

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Footnotes and References

1. Synthesis via vinyl sulfones-2. For paper 1 see reference 4.
2. Graduate Research Associate, David Ross Fellow.
3. Alfred P. Sloan Fellow, 1977-1979.
4. P. C. Conrad, P. L. Fuchs, *J. Amer. Chem. Soc.*, *100*, 346 (1978).
5. The hydroxysulfones **7**,**8** were desulfonylated by the method of M. Julia and D. Arnould, *Bull. Soc. Chim. Fr.*, 743 (1973).
6. Siloxysulfones **9**,**10** were reduced[5] and then deprotected by the method of E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, *94*, 6190 (1972).
7. For cuprate-epoxide reactions see: R. W. Herr, D. M. Wieland, C. R. Johnson, *J. Amer. Chem. Soc.*, *92*, 3813 (1970).
8. For specific reductions with L-Selectride see: H. C. Brown, S. Krishnamurthy, *J. Amer. Chem. Soc.*, *94*, 7159 (1972).
9. All new compounds have IR, HMR, CMR and MS in accord with their assigned structures.
10. In the proton NMR for all six pairs of alcohols, the absorption of the carbinol hydrogen occurred at higher field in the *trans* isomer (**11**,**12**) than did the corresponding absorption for the *cis* isomer (**13**,**14**). [See E. L. Eliel, M. H. Gianni, Th. H. Williams, J. B. Stothers, *Tet. Lett.*, 741 (1962).]
11. In the carbon NMR for all six pairs of alcohols, the absorption of the carbinol carbon occurred at lower field in the *trans* isomer (**11**,**12**) than did the corresponding absorption for the *cis* isomer (**13**,**14**). [See J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, H. J. Reich, *J. Amer. Chem. Soc.*, *92*, 1338 (1970)].
12. The factors responsible for the lack of stereocontrol in the butyl additions to the cycloheptenyl substrates are not clear. In the case of **2c**, models suggest that the greater flexibility of the seven-membered ring could allow intramolecular delivery of an organolithium from a pseudo-equatorial alkoxide (The phenyllithium pseudo-equatorial alkoxide complex suffers more severe non-bonded interactions and could well prefer to deliver the organometallic from the axial direction, especially at the higher reaction temperature where ring interconversions would be facilitated). The 50/50 ratio in additions to **6c** may be a consequence of diminished axial interactions in the larger ring system with the "small" organolithium reagent.

13. Similar alkoxide directing effects have been previously observed: P. L. Fuchs, J. Org. Chem., 41, 2935 (1976); A. Alexakis, J. F. Normant, J. Villieras, J. Molec. Cat., 1, 43 (1975).

14. Silyl ethers 6a-c were prepared as follows: β-Epoxysulfones 1a-c were dissolved in DMF (0.2 M), 0.1 eq. of DBU was added, and the reaction mixture was heated at 80-90° until the epoxide had been completely converted to the γ-hydroxy-α,β-unsaturated sulfone (∿2 hrs, TLC: 40% Et_2O-$CHCl_3$/SiO_2). The reaction mixture was then cooled to 25°C, 2.2 equivalents of imidazole and 1.1 equivalents of t-butyldimethylsilyl chloride were added and the reaction allowed to stir at 25°C for ∿1 hr. Work-up in the normal manner[6] afforded the pure siloxyvinylsulfones[9] (6a, 87%, oil; 6b, 90%, m.p. 59-61°C; 6c, 91% oil).

TABLE I

Entry	Substrate ⓐ,ⓑ	Organometallic	Conditions ⓒ	Products ⓓ (trans)/(cis) Ratio	Overall Yield ⓔ
1	2a	n-C_4H_9Li	THF, -78°	12a(13)/14a(87)	61%
2	2a	n-C_4H_9Li	20% HMPA/THF, -78°	12a (5)/14a(95)	36%
3	2a	n-C_4H_9Li	20% Hex/THF, -100°	12a (6)/14a(94)	61%
4	2a	C_6H_5Li	THF, -20°	11a (9)/13a(91)	72%
5	2a	C_6H_5Li	10% 12-Crown-4/THF, -20°	11a(13)/13a(87)	65%
6	2a	C_6H_5Li	20% HMPA/THF, -20°	11a (3)/13a(97)	71%
7	2b	n-C_4H_9Li	THF, -78°	12b(14)/14b(86)	60%
8	2b	n-C_4H_9Li	20% HMPA/THF, -78°	12b (5)/14b(95)	47%
9	2b	n-C_4H_9Li	20% Hex/THF, -100°	12b (6)/14b(94)	70%
10	2b	n-C_4H_9MgBr	THF, -78°	12b(11)/14b(89)	39%
11	2b	C_6H_5Li	THF, -20°	11b (0)/13b(100)	59%
12	2b	C_6H_5MgBr	THF, -20°	11b (1)/13b(99)	76%
13	2c	n-C_4H_9Li	THF, -78°	12c(83)/14c(17)	82%
14	2c	n-C_4H_9Li	20% HMPA/THF, -78°	12c(87)/14c(13)	51%
15	2c	n-C_4H_9Li	20% Hex/THF, -100°	12c(79)/14c(21)	64%
16	2c	C_6H_5Li	THF, -20°	11c (0)/13c(100)	77%
17	6a	n-C_4H_9Li	THF, -78°	12a(99)/14a(1)	48%
18	6a	C_6H_5Li	THF, -78°	11a(98)/13a(2)	44%
19	6b	n-C_4H_9Li	THF, -78°	12b(100)/14b(0)	69%
20	6b	n-C_4H_9MgBr	THF, -78°	12b(88)/14b(12)	54%
21	6b	C_6H_5Li	THF, -78°	11b(99)/13b(1)	59%
22	6b	C_6H_5MgBr	THF, -20°	11b(83)/13b(17)	36%
23	6c	n-C_4H_9Li	THF, -78°	12c(50)/14c(50)	50%
24	6c	C_6H_5Li	THF, -78°	11c(95)/13c(5)	50%

ⓐSubstrates 2a-c are prepared in situ by reaction of β-epoxysulfone 1a-c with an extra equivalent of organometallic reagent (R=R^1 for the 1→3 transformation). ⓑSubstrates 6a-c are prepared as per footnote 14. ⓒThe addition of the phenyl organometallics occurred at ca. -20° whereas all the other reactions to 2a-c occurred at -78°C or lower. ⓓThe response-factor corrected yields and trans/cis product ratios were determined by VPC on a 150' capillary OV210 column at between 100-190°C for all products except 12c and 14c. The latter two products were assigned by integration of the carbinol proton in the HMR spectra on the isolated material. ⓔThe overall yields are based upon β-epoxysulfone for the 2a-c series and upon γ-silyloxysulfones for the 6a-c series. No attempt was made to maximize the yield of any of these reactions.

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