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DIASTEREOSELECTIVE ADDITION OF THE 2-PHENYLSULFONYL-SUBSTITUTED ALLYLIC BROMIDES TO ALDEHYDES IN THE PRESENCE OF ZINC OR CHROMIUM (II) CHLORIDE

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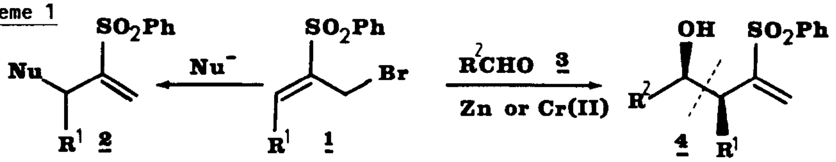
Summary : The 2-phenylsulfonyl allylic bromides 1 add diastereoselectively to various aldehydes 3 in the presence of zinc or of in situ generated chromium (II) salts to give mainly the syn-hydroxy sulfones 4 in high yields. The sulfone 4b can be easily transformed into the diastereomerically pure γ-pivaloyloxy ketone 14 allowing a complete control of the stereochemistry of four adjacent chiral centers in an acyclic compound.

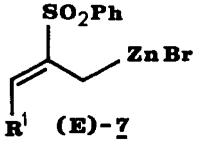
Scheme 1



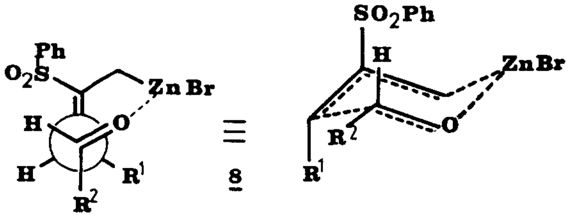
Recently we have reported that the easily available bromo-sulfones[1] of type 1 react regioselectively with nucleophiles (Nu) to produce the highly functionalized sulfones of type 2. We report now that the sulfones of type 1 are also able to react regioselectively with the aldehydes 3 in the presence of a metal[2], or a metallic salt, to furnish the hydroxysulfones of type 4 (see scheme 1).

Thus the reaction of the bromo sulfones 1a-c (1.0eq.) with the aldehydes 3a-f (1.5eq.) in the presence of zinc[3] (7eq. ; THF ; 0.5hr ; 30°-40°) or of the in situ generated chromium (II) salts[4,5] (2.0eq. ; THF ; 1.5hr ; 25°) gives in excellent yields (83-99%) and high diastereoselectivity (generally over 90:10) the *syn* -hydroxy sulfones 4a-j (see the table and scheme 2). It is remarkable[6] that the zinc mediated reaction shows such a high diastereoselectivity (see entries 1, 2, 3 and 8 of the table). We assign this high selectivity to the presence of the phenylsulfonyl group which highly favors the (E)-configuration[7] for the intermediate allylic zinc compound 7. Thus a chair transition state of type 8 is favored and explains the formation of the *syn* -diastereoisomer 4 for the following reasons :

(i) the steric interaction between the $PhSO_2$- and the R^2 groups are minimized ;
(ii) the R^2 group occupies an equatorial position in the chair transition state ;
(iii) the 109° angle (Bürgi-Dunitz angle[8]) approach of the allylic reagent is sterically highly favored.



(E)-7



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Scheme 2

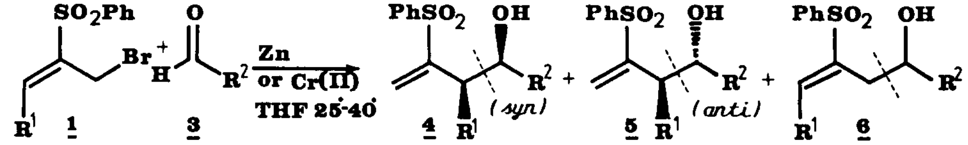


Table : Synthesis of the *syn* hydroxy sulfones 4a-j by the zinc, bismuth or chromium chloride mediated addition of the bromo-sulfones 1a-c to the aldehydes 3a-e

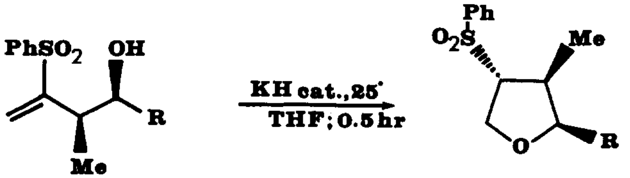
Entry	Bromo-sulfone 1	R^1	Aldehyde 3	R^2	Metal or Metal salt	Products(%) 4	5	6	Yield (%)[a]
1	1a	Me	3a	Ph-	Zn	4a:100	5a: 0	6a: 0	95
2	1a	Me	3b	cyclo-Hex-	Zn	4b:100	5b: 0	6b: 0	99
3	1a	Me	3c	Pent-	Zn	4c: 88	5c:12	6c: 0	91
4	1a	Me	3d	tert-Bu-	Zn	4d: 83	5d: 0	6d:17	99
5	1a	Me	3d	tert-Bu-	$CrCl_2$	4d: 81	5d: 0	6d:19	92
6	1a	Me	3e	iso-Bu-	$CrCl_2$	4e: 99	5e: 1	6e: 0	93
7	1a	Me	3f	(E)-CH_3-CH=CH-	$CrCl_2$	4f: 90	5f:10	6f: 0	83
8	1b	Pr	3a	Ph-	Zn	4g:100	5g: 0	6g: 0	95
9	1b	Pr	3c	Pent-	Zn	4h: 67	5h:33	6h: 0	98
10	1b	Pr	3c	Pent-	$CrCl_2$	4h: 94	5h: 6	6h: 0	93
11	1b	Pr	3c	iso-Bu-	$CrCl_2$	4i: 96	5i: 4	6i: 0	95
12	1c	iso-Bu	3c	Pent-	$CrCl_2$	4j: 90	5j:10	6j: 0	89
13	1b	Pr	3c	Pent-	Bi	4h: 0	5h:50	6h:50	37

a/ The given yields are those of flash chromatographically purified materials (in all cases the isomers of type 4, 5 and 6 could be separated). The reactions are performed on a 10mmol scale. All the spectroscopic datas (I.R., ^{1}H-NMR and ^{13}C-NMR) are compatible with the structure shown.

Similar discussions can be made for the chromium salts mediated reactions which show even better diastereoselectivities (compare entries 9 and 10 of the table). A preliminary result indicated that bismuth[9] leads, although in low yield, only to the *anti*- diastereo isomer of type 5 (see entry 13). The regioisomer of type 6 is only obtained if a bulky aldehyde or if bismuth are used (see entries 4, 5 and 13). The relative stereochemistry assigned to our major isomer (of type 4) is confirmed by X-ray structures[10] of compounds 4d and 9a. The functionalized tetrahydrofurans 9a and 9b are each obtained in high yields (scheme 3) as a sole isomer by a 5-Endo-Trig ring closure[11] respectively of the sulfones 4a and 4c.

Scheme 3

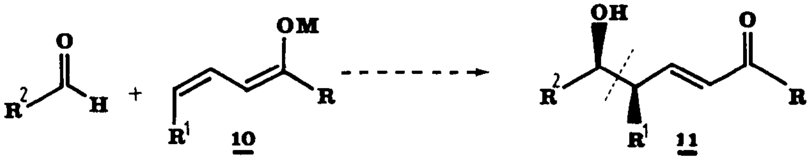
4a : R=Ph
4c : R=Pent



9a : R=Ph ; 80%
9b : R=Pent ; 89%

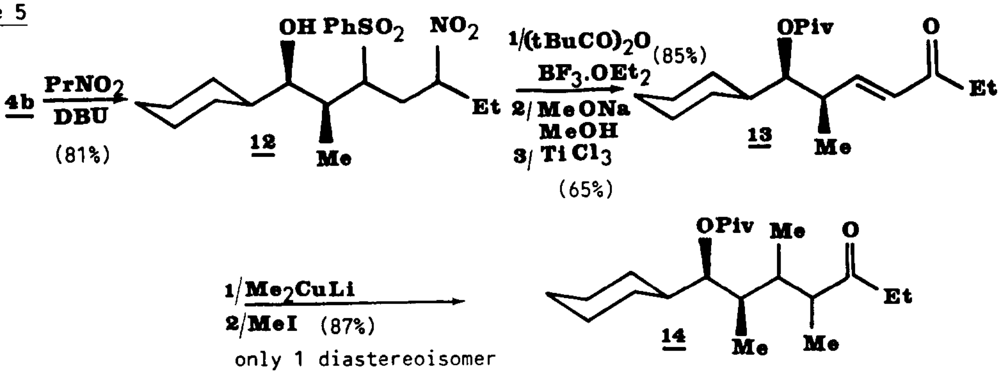
The hydroxy sulfones of type 4 are very useful intermediates and allow the synthesis of products of type 11 resulting from a formal diastereoselective and regiospecific γ-hydroxyalkylation[12] of a dienolate of type 10 (see scheme 4). Thus, the addition of an excess of nitropropane to the sulfone 4b in the presence of DBU[13] gives the hydroxy

Scheme 4



nitrosulfone 12 in 81% yield. Transformation into the pivaloyloxy derivative ($(tBuCO)_2O$ excess ; $BF_3.OEt_2$ cat.[14] ; 1 hr ; 60° ; 85%) followed by a Nef reaction[15] (MeONa(1.5eq.); MeOH ; then $TiCl_3$(4eq.) ; NH_4OAc(24eq.) ; 2hr ; 25°) gives, after a spontaneous elimination of $PhSO_2H$, the diastereoisomerically pure γ-pivaloyloxy enone 13 in 65% yield.

Scheme 5



Addition of Me_2CuLi (1.5eq. ; ether ; -15° ; 0.75 hr) followed by the addition of an excess of iodomethane (10eq. CH_3I ; HMPT/THF ; 0.25 hr ; 25°) leads to only one diastereoisomer[16] of the ketone 14 in 87% yield.

The scope of this method, which allows a complete control of the stereochemistry of four adjacent chiral centers in an acyclic compound (1a → 14) as well as the determination of the relative stereochemistry of all four centers in ketone 14 are currently investigated in our laboratory.

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3. In a typical reaction, 606mg (2mmol) of the sulfone 1b in 4ml THF are slowly added (within 15min) to a THF solution of PhCHO (318mg ; 3mmol ; 2ml THF) and activated zinc (1g ; 15mmol ; for the zinc activation see ref. 2d) at 30°-40° in a flask immersed in a common laboratory ultrasonic cleaner (48kHz ; 30w). After 0.5hr, the reaction mixture is cooled to 0° and quenched with an NH_4Cl solution. After the usual work-up and a flash-chromatography, the pure hydroxy-sulfone 4g is isolated (630mg ; 95%).
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5. In a typical reaction, a THF solution of $LiAlH_4$ (76mg ; 2mmol) is added to a suspension of $CrCl_3$ (630mg ; 4mmol ; 5ml THF) at -15°. The resulting dark solution is stirred 15min at 20° and 606mg (2mmol) of the bromo sulfone 1b in 5ml of THF and then a THF solution of hexanal (336mg ; 3mmol ; 5ml THF) are successively added. After 1.5hr at 25°, the reaction mixture is cooled to 0° and quenched with an NH_4Cl solution. After the usual work-up and a flash-chromatography, two pure products are isolated : 570mg of the *syn* -hydroxy sulfone 4h and 35mg of the *anti* -hydroxy sulfone 5h (total yield : 93%).
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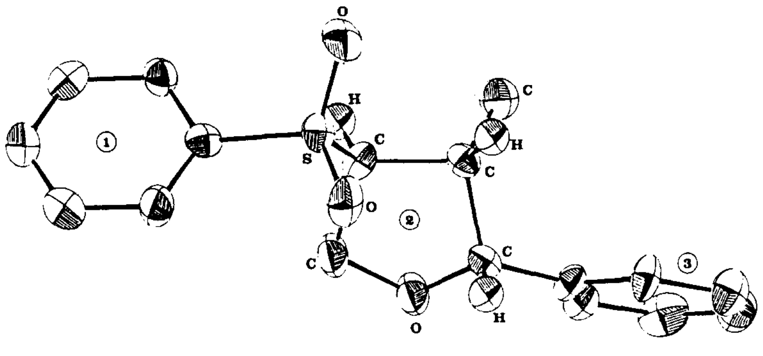
10. ORTEP representation of compound 9a :



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12. For a regiospecific γ-alkoxy alkylation of aldehyde dienolate equivalents see : A. Ishida and T. Mukaiyama, Bull. Chem. Soc. Japan, 50, 1161 (1977) and references cited therein ; see also T. Mukaiyama, Org. React. 28, 203 (1982). For γ-hydroxyalkylation of zinc ester dienolates see : M.W. Rathke, Org. React. 22, 423 (1975) ; M. Gaudemar, Organomet. Chem. Rev. A, 8, 183 (1972) ; L.E. Rice, M.C. Boston, H.O. Finklea, B.J. Suder, J.O. Frazier and T. Hudlicky, J. Org. Chem. 49, 1845 (1984) ; T. Hudlicky, M.G. Natchus, L.D. Kwart and B.L. Colwell, J. Org. Chem. 50, 4300 (1985).
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16. A 52.32MHz ^{13}C spectrum shows only one diastereoisomer of 14 (purity > 95%). Compare with W.R. Roush and B.M. Lesur, Tetrahedron Lett. 24, 2231 (1983). For the methylation see: R.K. Boeckman Jr, J. Org. Chem. 38, 4450 (1973).

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