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Reactions of (2*S*)-1-Arenesulfonyl-2-alkanol Dianions with Aldehydes. Application to the Synthesis of Enantiomerically Pure (3*S*)-1-Alken-3-ols and (2*E*,4*S*)-4-Hydroxy-2-alkenenitriles[#]

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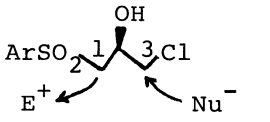
Enantiomerically pure (2*S*)-1-arenesulfonyl-2-alkanols (1) were prepared by yeast reduction of 1-arenesulfonyl-3-chloro-2-propanones, followed by epoxydation and alkylation. Reaction of dianions of 1 with aldehydes occurred at the *pro*(*R*) position of C(1) to give 1,3-diols, which were converted to (3*S*)-1-alken-3-ols or (2*E*,4*S*)-4-hydroxy-2-alkenenitriles in 100% e.e.

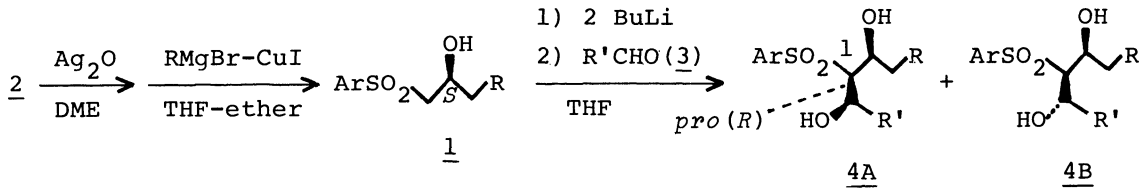
Asymmetric reduction of ketones with Baker's yeast is increasingly recognized as a valuable method for organic synthesis. In the synthetic strategy it is essential to prepare an enantiomerically-pure alcohol from a simple ketone with Baker's yeast and to achieve the subsequent conversions. The use of a β-sulfonyl-ketone as a substrate in yeast reduction has the following advantages; the asymmetric reduction might proceed efficiently,[1,2] and a sulfonyl group would be expected to facilitate the further carbon-carbon bond formation and functional-group transformation. Although the alkylation of chiral 1-arenesulfonyl-2-alkanol dianions can be carried out with reactive sodium iodoacetate[3] and allyl halides,[4] the reaction with aldehydes has not been reported. In the latter reaction the enantiomerical purity of the product may be lowered by fission and successive recombination of a C(1)-C(2) bond in its anion, or the competitive aldol reaction of aldehydes may occur through proton transfer from an aldehyde to a dianion.

Here we wish to report that dianions of enantiomerically pure (2*S*)-1-arene-sulfonyl-2-alkanols (1) obtained from (2*R*)-1-arenesulfonyl-3-chloro-2-propanols (2), react with aldehydes (3) selectively at the *pro*(*R*) position of their C(1) to give 1,3-diols (4), which are subsequently converted to (3*S*)-1-alken-3-ols (5) or (2*E*,4*S*)-4-hydroxy-2-alkenenitriles (6) with 100% e.e. Enantiomerically pure 2 were prepared in a large scale by reduction of the corresponding ketones with Baker's yeast.[5] After epoxidation with silver(I) oxide and alkylation with a Grignard reagent and copper(I) iodide[6] generally produced 1 in enantiomerically pure forms.[7,8]



2a, Ar = C_6H_5
2b, Ar = *p*-ClC_6H_4

[#]This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

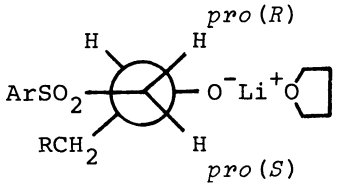


Aldehyde (or paraformaldehyde) (3) (1.5 equiv.) was added to a stirred solution of the dianion generated from 1 (or racemic 1) (1 equiv.) and butyllithium (2.2 equiv.) in tetrahydrofuran (THF) at -78 °C under argon atmosphere. After stirring for 30 min the solution was allowed to warm to room temperature, and quenched with an aqueous ammonium chloride. HPLC and TLC revealed that two diastereoisomeric 1,3-diols (4A and 4B) (one isomer when R'=H) were formed. These isomers were isolated easily by chromatography on silica gel as shown in Table 1.

Table 1. Preparation of 4

	Ar	R	R'	Yield/%[a]	4A/4B
a	C_6H_5	H[b]	n-$C_{11}H_{23}$	73	80/20
b	C_6H_5	n-C_7H_{15}[b]	n-C_3H_7	84	64/36
c	C_6H_5	C_6H_5	H	83	—
d	C_6H_5	n-C_5H_{11}[b]	H	80	—
e	C_6H_5	n-C_7H_{15}	H	78	—
f	C_6H_5	n-C_8H_{17}	H	88	—
g	C_6H_5	n-$C_{10}H_{21}$[b]	H	71	—
h	p-ClC_6H_4	n-C_8H_{17}	H	68	—

a) Isolated yield. b) Racemic 1 was used.



The structure of 4 was determined by ^1H NMR measurement after converting to acetone acetals.[9] Interestingly, carbon-carbon bond formation was found to occur only at the *pro*(*R*) position of C(1), while in alkylation reaction both *pro*(*R*) and *pro*(*S*) positions are reactive.[4] This finding may be explained as follows; bulky lithium alkoxide $-O^-Li^+$ coordinated with THF[10] rather than with a sulfonyl group, makes *pro*(*R*)-H more reactive towards a base than *pro*(*S*)-H, and the difference in reactivities between two carbanions generated is large in the reversible aldol-type reaction. A sulfonyl group enabled the diastereoisomeric 4A and 4B to be separated readily, and the ratio of 4A/4B would be made to vary by changes in reaction conditions because metal alkoxide $-O^-M^+$ seems to coordinate with a carbonyl group of an aldehyde rather than a sulfonyl group.

Since it is important to achieve the functional-group transformation without a loss of enantiomerical purity in the present strategy, we applied new methods to prepare 5 and 6, which might be rather difficult to be obtained in 100% e.e. by asymmetric reduction of the corresponding ketones.

Conventional treatment of 4c-h with *p*-toluenesulfonyl chloride and pyridine produced tosylates (7) in high yields. To a stirred solution of 7 (1 equiv.) and sodium hydrogenphosphate (4 equiv.) in dry methanol at 0 °C was added Na-Hg (5%) (*ca.* 4 equiv.). The resulting mixture was stirred at 0 °C for 1 h and quenched with water. After usual work-up chromatography on silica gel gave 5 with 100% e.e.

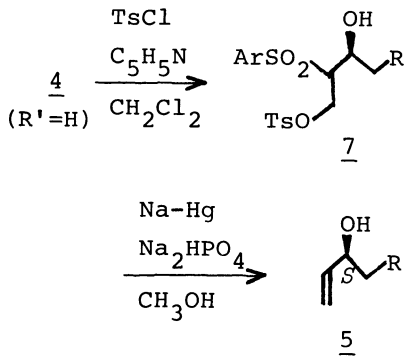


Table 2. Preparation of 5

	Ar	R	Yield/%[a]	e.e./%[b]
a	C_6H_5	C_6H_5	65	100
b	C_6H_5	n-C_8H_{17}	51	100
c	C_6H_5	n-$C_{10}H_{21}$	55	—[c]
d	p-ClC_6H_4	n-C_8H_{17}	45	—[c]

a) Isolated yield. b) Ref. 7. c) Racemic 7 was used.

A mixture of 7 (1 equiv.), sodium cyanide (5 equiv.), and tetrabutylammonium iodide (cat.) in water-benzene was refluxed for 3 h. After usual work-up chromatography on silica gel yielded 6 with 100% e.e.

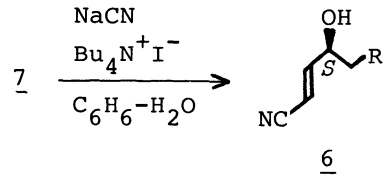


Table 3. Preparation of 6

	Ar	R	Yield/%[a]	e.e./%[b]
a	C_6H_5	C_6H_5	76	—[c]
b	C_6H_5	n-C_5H_{11}	71	—[c]
c	C_6H_5	n-C_7H_{15}	81	100[d]
d	p-ClC_6H_4	n-C_8H_{17}	84	100

a) Isolated yield. b) Ref. 7. c) Racemic 7 was used. d) Ref. 11.

The present strategy may be generally applicable for synthesis of a broad range of enantiomerically pure compounds from 1, which can be prepared in a large scale.

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References

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4) A. P. Kozikowski, B. B. Mugrage, C. S. Li, and L. Felder, Tetrahedron Lett., 27, 4817 (1986).

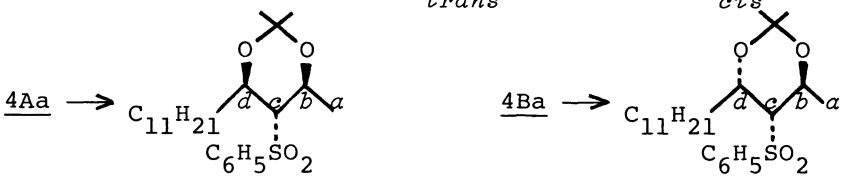
5) In a practical preparation a suspension of 1-phenylsulfonyl-3-chloro-2-propanone (23.2 g, 0.1 mol), Baker's yeast (Oriental Yeast Co.)(400 g), and sucrose (100 g) in water (2 l) was stirred for 48 h at room temperature. The solid was removed by filtration, and the filtrate was extracted with ethyl acetate. After evaporation of the solvent recrystallization of the residual solid twice from ethanol gave enantiomerically pure 2a in 60% yield.[7] The similar treatment of 1-(*p*-chlorophenylsulfonyl)-3-chloro-2-propanone gave 2b with 100% e.e. in 90% yield.[7] 2a; mp 89 °C, $[\alpha]_D^{24}$ +10.15° (c 1.00 CH_3OH). 2b; mp 98 °C, $[\alpha]_D^{24}$ +6.58° (c 1.20 CH_3OH).

6) R. Tanikaga, K. Hosoya, and A. Kaji, J. Chem. Soc., Chem. Commun., 1986, 836.

7) Enantiomeric excess of alcohols was determined by ^1H and ^{19}F NMR and/or HPLC analyses of the corresponding (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid esters. Racemic 1 were prepared by reaction with a dianion of aryl methyl sulfone with aldehydes.[12]

8) $[\alpha]_{365}^{22}$ (c 1.0 CH_3OH): 1a (Ar=C_6H_5, R=C_6H_5) -31.3°; 1b (Ar=C_6H_5, R=*n*-C_7H_{15}) -2.1°; 1c (Ar=C_6H_5, R=*n*-C_8H_{17}) -2.7°; 1d (Ar=*p*-ClC_6H_4, R=*n*-C_8H_{17}) -9.6°. $[\alpha]_D^{22}$: 1a-d; 0°. The chemical yields obtained were same as those from racemic 2.[3]

9) The structure of acetals of 4Aa and 4Ba is reasonably confirmed by the following J values, *i.e.*, J_{trans}= 7-8 Hz and J_{cis}= *ca.*4 Hz.



$J_{b,c}$= 7.6 Hz, $J_{c,d}$= 7.9 Hz

$J_{b,c}$= 7.0 Hz, $J_{c,d}$= 4.3 Hz

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11) Recently, 6c was obtained in 74% e.e. by another method: J. Nokami, T. Mandai, A. Nishimura, T. Takeda, and S. Wakabayashi, Tetrahedron Lett., 27, 5109 (1986).

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13) $[\alpha]_D^{21}$ (c 1.0 CH_3OH): 5a +9.4°; 5b +11.4°; 6c +31.0°; 6d +30.0°.

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