Stereoselective Sulfonate Aldol Reactions: Asymmetric Synthesis of α,β-Substituted β-Hydroxy Sulfonates

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Abstract: An efficient asymmetric synthesis of β-hydroxy sulfonates is described via stereocontrolled aldol reactions of sulfonates using 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as the chiral auxiliary. The aldol reactions with aromatic aldehydes yielded predominantly *syn* adducts in very good yields and excellent diastereo- and enantiomeric excesses (de, ee ≥98%).

Key words: asymmetric synthesis, sulfonates, aldol reaction, sugar auxiliary, hydroxy sulfonates

Derivatives of sulfonic acids are important constituents of living organisms and are involved in various physiological processes.[1] However, in many cases the physiological role of these sulfonic acid derivatives remains unclear. To get further insight into their mode of action a stereoselective access to these derivatives is desirable and compulsory for physiological tests. In our ongoing research concerning the chemistry of sulfonates we have now developed an efficient diastereo- and enantioselective approach to one class of these derivatives, namely the title β-hydroxy sulfonates. Hitherto, only a few synthetic routes for the asymmetric synthesis of these interesting compounds have been described. Optically active β-hydroxy sulfonates could be synthesized by nucleophilic opening of enantiomerically pure epoxides with either sodium sulfite[2] or sodium bisulfite[3] and by Ru–BINAP-catalyzed hydrogenation of β-keto sulfonates.[4]

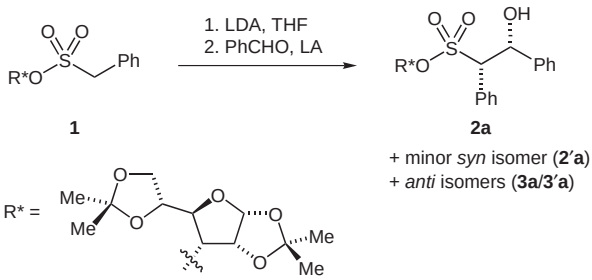
It is widely accepted that the aldol reaction is one of the most powerful tools for the stereoselective construction of new carbon–carbon bonds. In this respect, the asymmetric aldol reaction of sulfonate derivatives appears to be the most direct route to these title compounds. To the best of our knowledge, however, no method has been reported so far for an asymmetric aldol reaction utilizing chiral sulfonates. Furthermore, even reports about aldol reactions of α-metalated achiral sulfonates are very scarce.

Zwanenburg and Nkunya reported on the asymmetric Darzens reaction of L-menthyl chloromethanesulfonate with aldehydes and symmetrical ketones under phase-transfer conditions (PTC) leading to (*trans*-)epoxy sulfonates in moderate to good yields, but with only moderate diastereomeric excesses (9–17%).[5] In an attempt to synthesize α,β-epoxysulfonic acids via the Darzens reaction, Ghosez et al. described the reaction of the lithiated tetrabutylammonium chloromethanesulfonate with a D-alaninal derivative to afford the corresponding α-chloro-β-hydroxy sulfonate in 72% yield as a mixture of four diastereomers.[6]

In our previous work, we described a highly efficient asymmetric route towards a variety of different sulfonic acid derivatives employing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as the chiral auxiliary.[7–13] Therein we also reported an efficient asymmetric synthesis of substituted γ-hydroxy sulfonates by hydrolysis of enantiopure γ-sulfones[11] and by reduction of enantiopure β-alkoxycarbonyl sulfonates.[13] In this context, we now wish to describe a direct and efficient methodology for the asymmetric synthesis of α,β-substituted β-hydroxy sulfonates by performing stereocontrolled aldol reactions with enantiomerically pure sulfonates.

Our studies started with the model reaction between the enantiopure sulfonate **1** and benzaldehyde as outlined in Scheme 1. In the first test reaction, the enantiopure sulfonate **1** was deprotonated with one equivalent of LDA at –78 °C and treated with benzaldehyde at –78 °C for one hour. After aqueous workup, the desired aldol adduct could not be observed. Instead only the starting material **1** and a small amount of the cleaved chiral auxiliary could be identified by ^{1}H NMR analysis. A change of the reaction temperature to either –40 °C or –100 °C did not yield the desired product either.

We then examined the reaction in the presence of various Lewis acidic additives. For this purpose the aldehyde was complexed with the additive before its addition to the



Scheme 1 Asymmetric aldol reaction of the sulfonate **1** with benzaldehyde (LA = Lewis acid)

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lithiated sulfonate. When the lithiated sulfonate **1** was reacted with benzaldehyde precomplexed with *t*-$BuMe_2SiCl$ at –78 °C for two hours, the four diastereomeric aldol products **2a**:**2′a**:**3a**:**3′a** were obtained in 63% yield in a ratio of 58:6:30:6 (see Table 1, entry 2). The product ratio was determined by ^{1}H NMR analysis of the crude product by comparing the integrals of the four methine protons (C*H*OH) resonating as doublets at δ = 5.80, 5.82, 5.35 and 5.39 ppm, and comparing the order of these values with the order above, i.e. **2a**:**2′a**:**3a**:**3′a**, respectively, as shown in Figure 1. The assignment of the relative configuration of the aldol adducts was based on the comparison of the vicinal coupling constants ($J_{1,2}$ = 2.3 Hz for both *syn* isomers **2a** and **2′a**; $J_{1,2}$ = 9.6 and 9.5 Hz for the *anti* isomers **3a** and **3′a**, respectively).

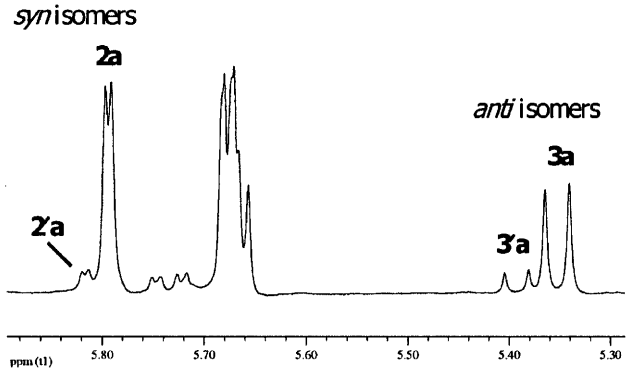


Figure 1 ^{1}H NMR spectrum (400 MHz) of the crude product of the aldol reaction between **1** and PhCHO (the region of the methine protons of the four diastereomers **2a**, **2′a**, **3a** and **3′a** is shown)

To further improve both yield and diastereoselectivity, we investigated the effects of a number of other Lewis acids, including $BF_3{\cdot}OEt_2$, Cy_2BCl, $MgCl_2$, ZnX_2 (X = Cl, Br, I) and $ZnEt_2$, as summarized in Table 1.

As can be seen in Table 1, the use of $ZnCl_2$ as the Lewis acid at –78 °C gave the best results in the aldol reaction of the sulfonate **1** regarding both yield and diastereoselectivity (entry 3). The aldol adduct was obtained in 88% yield as a 79:21 mixture of *syn* and *anti* isomers. The minor *syn* diastereomer **2′a** could not be detected in this case. Furthermore, we also observed that a lower reaction temperature had no significant influence on the *syn*/*anti* selectivity as shown in entry 4: carrying out the reaction at –100 °C gave a comparable diastereoselectivity but a lower yield. Using an excess of $ZnCl_2$ gave **2a** with a similar selectivity but with a lower overall yield (entries 6 and 7).

It should also be noted that only a trace of product was observed when the lithiated sulfonate **1** was subjected to a transmetalation with one of the Lewis acids ($ZnCl_2$ or $BF_3{\cdot}OEt_2$) prior to the addition of benzaldehyde (entries 5 and 9). These results strongly indicate that the Lewis acid acts as an indispensable activating agent for the carbonyl group. If a transmetalation, promoted by the addition of the Lewis acid to the lithiated sulfonate prior to the addition of the aldehyde, occurs, it appears to be a dead end.

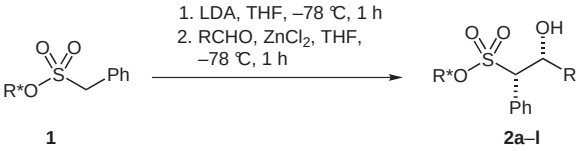
Table 1 Optimization of the Reaction Conditions of the Aldol Reaction of the Sulfonate **1** with Benzaldehyde

Entry	Lewis acid[a]	equiv	Temp.[b] (°C)	Yield[c] (%)	Ratio[d] *syn*/*anti*
1	none	0	–78	0	–
2	*t*-$BuMe_2SiCl$	1.5	–78	63	(58:6)/(30:6)
3	**$ZnCl_2$**	**1.2**	**–78**	**88**	**(79:0)/(18:3)**
4	$ZnCl_2$	1.2	–100	45	(82:0)/(15:3)
5	$ZnCl_2$[e]	2.5	–78	trace	–
6	$ZnCl_2$	3	–78	60	(76:0)/(20:4)
7	$ZnCl_2$	3	–100	52	(84:0)/(14:2)
8	$BF_3{\cdot}OEt_2$	1.2	–78	51	(62:7)/(25:6)
9	$BF_3{\cdot}OEt_2$[e]	1.2	–78	0	–
10	$MgCl_2$	1.2	–78	22	(65:0)/ (18:17)
11	Cy_2BCl	1.2	–78	18	(78:0)/ (11:11)
12	$ZnBr_2$	1.2	–78	39	(81:0)/ (17:2)
13	ZnI_2	1.2	–78	52	(65:0)/ (30:5)
14	$ZnEt_2$	1.2	–78	10	(39:6)/ (47:8)

[a] Unless stated otherwise, the lithiated sulfonate **1** was treated with PhCHO (2 equiv) precomplexed with the indicated Lewis acid.
[b] Temperature at which the reaction was performed for both the enolate formation and the addition of PhCHO.
[c] Yield after chromatography.
[d] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[e] The reaction was performed by adding the Lewis acid to the lithium enolate followed by stirring for 1 h and addition of PhCHO.

From these investigations, the best results in terms of both yield and diastereoselectivity arose from the experimental conditions shown in entry 3. We then proceeded to apply these conditions to a wide range of other aldehydes (Scheme 2). Therefore, the enantiopure sulfonate **1** was deprotonated with LDA (1 equiv) in THF at –78 °C, followed by the addition of the corresponding aldehyde (2 equiv) precomplexed with $ZnCl_2$ (1.2 equiv) at –78 °C, to furnish predominantly the *syn*-configured β-hydroxy sulfonates **2a**–**l**.[14] The results are illustrated in Table 2.

Obviously, the nature of the aldehyde had a profound influence on both the yield and the diastereoselectivity of the reaction. The reaction with aromatic aldehydes



Scheme 2 Asymmetric aldol reaction of sulfonate **1** with different aldehydes

afforded the corresponding aldol products in very good to excellent yields (84–96%) and with high diastereoselectivities (63–89%). In all of these cases, only three (i.e. one *syn* and two *anti* diastereomers) out of four possible diastereomers could be detected. Moreover, the major sulfonate could be easily obtained diastereomerically pure by flash column chromatography and recrystallization (de ≥98%) in all cases. In contrast, the reaction with aliphatic aldehydes resulted in low diastereoselectivities but still moderate to very good yields (entries 9–12).

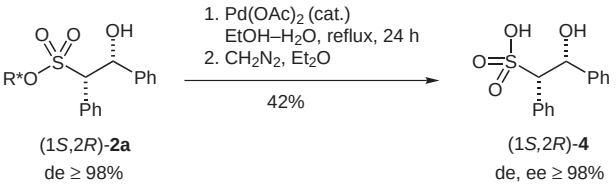
Table 2 Asymmetric Aldol Reaction of the Sulfonate **1** with Representative Aldehydes

Entry	Product	R	Yield[a] (%)	dr[b]
1	**2a**	Ph	88	79:0:18:3 (≥99)
2	**2b**	4-(*i*-Pr)C_6H_4	84	79:0:18:3 (≥99)
3	**2c**	2-$MeOC_6H_4$	89	83:0:9:8 (≥99)
4	**2d**	3-$MeOC_6H_4$	91	75:0:20:5 (≥99)
5	**2e**	2-$NO_2C_6H_4$	93	71:0:15:14 (≥99)
6	**2f**	4-$NO_2C_6H_4$	92	63:0:19:18 (≥99)
7	**2g**	2-ClC_6H_4	96	89:0:6:5 (≥99)
8	**2h**	4-ClC_6H_4	92	75:0:22:3 (≥99)
9	**2i**	Me	92	48:36:16[c]
10	**2j**	*i*-Pr	60	48:44:8[c]
11	**2k**	*n*-Pr	48	56:31:13[c]
12	**2l**	*n*-Bu	42	55:31:14[c]

[a] Yield of a diastereomeric mixture.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture. The value in parentheses shows the dr value after flash column chromatography and recrystallization.
[c] Diastereomeric ratio of all observed isomers.

In all examples employing aromatic aldehydes, the reaction predominantly gave the *syn* adduct **2a**–**h**. The relative configuration of **2b**–**h**/**2′b**–**h** was assigned by comparison of their ^{1}H NMR spectra to that of **2a**/**2′a** described above. The absolute configurations of the two newly formed stereogenic centers in the β-hydroxy sulfonates **2a**–**h** were assigned to be 1*S*,2*R* based on the results obtained from related reactions in previous reports using functionalized electrophiles.[8,13] Further evidence for this assumption was obtained from the fact that related electrophilic α-alkylations show the same relative topicity.[7,9] By assuming a uniform reaction mechanism, all examples described herein should possess the same absolute configuration.

In a first attempt, the removal of the chiral auxiliary to yield the corresponding sulfonic acids was successfully accomplished using a procedure that had been described previously:[7] refluxing the aldol adduct (1*S*,2*R*)-**2a** in an EtOH–H_2O mixture containing a catalytic amount of $Pd(OAc)_2$ for one day followed by treatment with diazomethane yielded the β-hydroxy sulfonic acid (1*S*,2*R*)-**4** in a nonoptimized yield of 42% as a single diastereoisomer showing that the cleavage reaction proceeded without epimerization and/or racemization (Scheme 3).[15,16] Accordingly, the ee value of the β-hydroxy sulfonic acid (1*S*,2*R*)-**4** is expected to be greater than 98% based on the de value of the corresponding aldol adduct. It should be noted that the attempted methylation of the sulfonic acid group did not furnish the corresponding methyl sulfonate, probably due to intramolecular H-bonding between the sulfonic acid moiety and the β-hydroxyl group.



Scheme 3 Removal of the chiral auxiliary to form the β-hydroxy sulfonic acid (1*S*,2*R*)-**4**

In summary, we have developed an efficient asymmetric access to α,β-substituted β-hydroxy sulfonates by performing stereocontrolled aldol reactions of enantiopure sulfonates using 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as the chirality auxiliary. A thoughtful study and optimization of the reaction conditions led to the conclusion that the best conditions regarding both yield and diastereoselectivity involve the reaction of the lithiated sulfonates with aldehydes precomplexed with zinc chloride. In addition, the reaction with aromatic aldehydes led to the corresponding aldol adducts in very good yields and with excellent diastereoselectivities. Studies towards a more efficient cleavage of the chiral auxiliary are currently underway in our laboratories.

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(13) Enders, D.; Adelbrecht, J.-C.; Harnying, W. *Synthesis* **2005**, 2962.
(14) **General Procedure for Aldol Reactions of the Sulfonate 1**: To a cooled (–78 °C) solution of freshly generated lithium diisopropylamide [prepared by treatment of diisopropylamine (1.1 mmol) in anhyd THF (3 mL) with *n*-BuLi (1 mmol) at –78 °C for 30 min] was added dropwise a solution of the sulfonate **1** (1 mmol) in THF (2 mL) under N_2. After stirring for 1 h, a mixture of aldehyde (2 mmol) and 1 M $ZnCl_2$ in THF (1.2 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h and then quenched with sat. NH_4Cl. The mixture was poured into an ice-cooled 1 N HCl solution (10 mL) and extracted with EtOAc. The combined organic layers were washed with H_2O, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product. The diastereomeric ratio was determined at this stage by ^{1}H NMR (400 MHz). The crude product was purified by flash column chromatography (SiO_2, EtOAc–hexane) to give the aldol product **2**. (1*S*,2*R*)-**2a**: colorless solid; de ≥ 98%; mp 103–104 °C; $[\alpha]_D^{29}$ +93.1 (*c* = 0.105, EtOH). IR (KBr): 3446 (s), 2986, 1630, 1375, 1344 (s), 1217, 1150 (s), 1059 (s), 1017 (s), 886, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29, 1.30, 1.37, 1.57 (4 × s, 12 H, 4 × Me), 3.65 (br s, 1 H, OH), 3.75 (dd, *J* = 6.6, 8.7 Hz, 1 H, C*H*H), 3.95 (dd, *J* = 6.7, 8.7 Hz, 1 H, CH*H*), 4.09 [dd, *J* = 4.1, 8.6 Hz, 1 H, CH_2CHCHO), 4.25 (dt, *J* = 4.1, 6.6 Hz, 1 H, CH_2CHCHO), 4.46 [t, *J* = 4.4 Hz, 1 H, $OCHCH(OC)_2$], 4.47 (d, *J* = 2.2 Hz, 1 H, $CHSO_3$), 4.81 (dd, *J* = 4.7, 8.6 Hz, 1 H, $CHOSO_2$), 5.71 [d, *J* = 3.7 Hz, 1 H, $CH(OC)_2$], 5.80 (br d, *J* = 1.8 Hz, 1 H, C*H*OH), 7.01–7.30 (m, 10 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 26.1, 26.6, 26.7 (4 × Me), 65.4 (CH_2), 72.1 (CHOH), 74.0 ($CHSO_3$), 74.6, 76.4, 76.9, 77.6 (4 × CHO), 103.8 (OCHO), 110.3, 113.8 [2 × $C(CH_3)_2$], 126.0 (Ar*C*H), 127.76 (Ar*C*), 127.83, 128.1, 128.2, 129.1, 131.3 (Ar*C*H), 139.2 (Ar*C*). MS (EI, 70 eV): *m*/*z* (%) = 520 (0.2)[M$^+$], 505 (22), 399 (16), 341 (23), 292 (17), 197 (31), 167 (31), 127 (51), 91 (100), 77 (33), 55 (17). Anal. Calcd for $C_{26}H_{32}O_9S$ (520.59): C, 59.99; H, 6.20. Found: C, 60.13; H, 6.19.
(15) (1*S*,2*R*)-**4**: colorless solid; de, ee ≥ 98%; mp 169–170 °C; $[\alpha]_D^{29}$ +122.0 (*c* = 0.115, EtOH). IR (KBr): 3467 (s), 1220, 1163 (s), 1049 (s), 795, 713, 651, 572 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 3.87 (br s, 1 H, OH), 4.02 (d, *J* = 1.8 Hz, 1 H, $CHSO_3$), 5.71 (d, *J* = 1.8 Hz, 1 H, C*H*OH), 6.93–6.97 (m, 2 H, ArH), 7.02–7.11 (m, 6 H, ArH), 7.17–7.21 (m, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD): δ = 71.7, 73.1 (2 × CH), 126.0, 127.0, 127.19, 127.22, 127.6, 130.7 (Ar*C*H), 132.5, 140.7 (2 × Ar*C*). MS (EI, 70 eV): *m*/*z* (%) = 179 (100)[PhCH=C(Ph)$^+$], 165 (55), 152 (20).
(16) *epi*-**4** obtained from the cleavage of the *anti* isomer **3a** under the same conditions exhibits a different ^{1}H NMR spectrum. ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD): δ = 3.67 (br s, 1 H, OH), 4.16 (d, *J* = 10.1 Hz, 1 H, $CHSO_3$), 5.29 (d, *J* = 10.1 Hz, 1 H, C*H*OH), 7.00–7.30 (m, 10 H, ArH).