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Graphical Abstract

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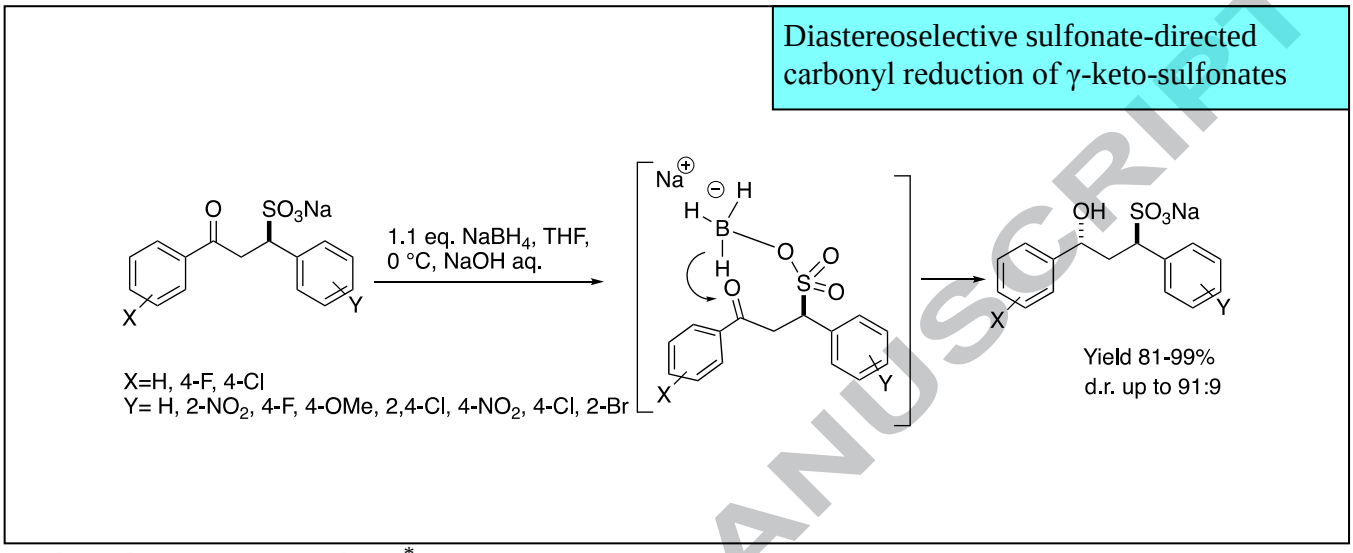

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Diastereoselective sulfonate-directed carbonyl reduction of γ-keto-sulfonates

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ABSTRACT

The diastereoselective reduction of γ-keto-sulfonates to afford α,γ-substituted γ-hydroxy sulfonates has been investigated. Herein we report the first example of a diastereoselective carbonyl reduction whereby hydride attack is directed *via* chelation of a neighbouring sulfonate group to a boron atom, thus affording prevalently *trans* γ-hydroxy sulfonates.

The development of efficient synthetic methods for controlling relative stereochemistry in small molecules remains an active area of great importance for organic chemistry. The stereoselective reduction of ketones is a powerful route for the installation of chiral centres. There are many powerful examples of stereoselective reduction of carbonyl groups using metal catalysts with chiral ligands – where chiral information is conveyed intermolecularly.[1] There are fewer examples where the diastereoselective reduction of a carbonyl group is influenced intramolecularly by a chiral centre *within* the substrate itself.

The stereochemical outcome of a ketone reduction is commonly accepted to occur through several potential models dictating selectivity. The exact details of which model prevails has been a matter of heated debate over the years and has been reviewed several times.[2–6] However, where the carbonyl substrate contains a heteroatom substituent capable of an effective coordination with the reducing agent, Cram chelate control is said to predominate. If chelation of a metal cation occurs between the carbonyl group and one heteroatom substituent of a fixed stereocenter within the substrate, the substrate will be locked into conformation and thus the reducing agent is capable of delivering a nucleophile diastereoselectively to the carbonyl carbon. A common example of Cram chelate control is the diastereoselective reduction of β-hydroxyketones using metal hydrides such as $Zn(BH_4)_2$, $LiAlH_4$ or $NaHB(OAc)_3$. This area has been studied extensively, with some notable examples from the groups of Evans[7] and Paterson.[8,9] Where a strongly chelating metal cation (such as Zn^{2+} or Mg^{2+}) is absent, it is possible for β-hydroxyketones to interact with boron. However, borohydride typically does not reduce β-hydroxyketones with good diastereoselectivity due to their weak interaction prior to the reduction step.[7,10] Normally, to achieve good diastereoselectivity, such interactions require a boron reagent which can effectively form an interaction with β-hydroxyketones. Alkoxydialkylboranes[10] have been used to preform an effective interaction with the substrate before reducing with $NaBH_4$; whereas triacetoxyborohydrides[7] are an effective reagent which can interact with the substrate, as well as deliver hydride, thus reducing the carbonyl moiety.

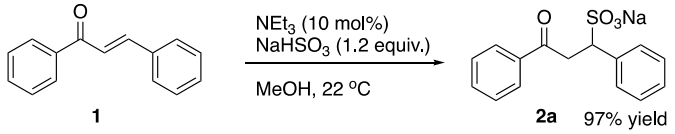
Apart from β-hydroxyketones, there are limited examples of Cram chelate controlled reduction of carbonyl compounds where the other boron-chelating heteroatom is not an ethereal or alkoxy oxygen atom. An example where the heteroatom is not oxygen was reported by Keck and co-workers where chiral β-amido ketones were diastereoselectively reduced with SmI_2.[11]

Marcantoni and co-workers have shown sulfones can be used as a directing group for the diastereoselective reduction of carbonyl moieties.[12] However, their methodology still relies on the addition of a Lewis acid additive, i.e. a strong chelator, to achieve diastereoselective reduction. Marcantoni and co-workers also reviewed the diastereoselective reduction of β-keto phosphine oxides and β-keto sulfones using hydride reducing agents and Lewis acid additives.[13] Ruano and co-workers reported the diastereoselective reduction of δ-ketosulfoxides.[14] Other related examples include the stereoselective addition of Gilman reagents (R_2CuLi) to olefins where chiral information is conferred by the coordination of sulfinylimine[15] or thioether[16,17] groups contained within the substrates.

Following our ongoing research in the enantioselective addition of sodium bisulfite to electrophilic alkenes,[18,19] we posed the question of whether the carbonyl functionality could be further elaborated in a stereoselective fashion. If this were found to be a feasible, then the range of enantioenriched sulfonic acids currently available for organic synthesis could be significantly extended. Herein we report the first example of the diastereoselective reduction of γ-keto-sulfonates **2** (Scheme 2) to

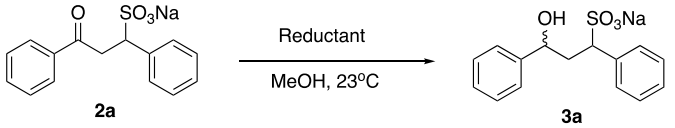
γ-hydroxy sulfonates **3** using $NaBH_4$. This reaction progressed without the need of an added Lewis acid or a strongly coordinating metal; in fact, the stereochemical outcome was found to rely on the coordination provided by the sulfonate moiety within the substrate to the reducing agent.

The study began with the preparation of compound **2a** (Scheme 1) following a variation of the procedure previously described.[18] Reaction of chalcone **1** in the presence of catalytic amounts of triethylamine in methanol provided – after evaporation of the solvent and subsequent recrystallisation from tetrahydrofuran – compound **2a** in 97% isolated yield.



Scheme 1. Synthesis of γ-keto-sulfonate **2a**.

With compound **2a** in hand, we then ran a preliminary screening using $LiAlH_4$, BH_3•THF, BH_3•$S(CH_3)_2$, and $NaBH_4$ as the reductants; tetrahydrofuran as the solvent; and reaction temperature kept at 0 °C (Scheme 2).



Scheme 2. Preliminary screening of reduction of **2**.

This study revealed the following facts: (*a*) $LiAlH_4$ provided full conversion of **2a** to **3a**, which was obtained as a 56:47 mixture of diastereoisomers; (*b*) both BH_3•THF and BH_3•$S(CH_3)_2$ showed no conversion to **3a**, with only unreacted **2a** isolated in both cases;

Table 1. Optimisation of reaction conditions for the diastereoselective reduction of **2a**

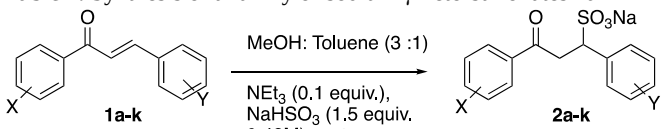
Entry	Solvent	$NaBH_4$ (eq.)	T (°C)	Time (h)	Conc. (M)	*dr*[a]
1	MeOH	1.2	23	16	0.3	66:33
2	H_2O	3	23	3	0.3	50:50
3	THF	3	23	3	0.3	62:38
4	CH_2Cl_2	3	23	16	0.3	59:61
5[c]	MeOH	1.1	0	1.5	0.3	65:35
6[c]	**THF**	**1.1**	**0**	**1.5**	**0.3**	**84:16**
7	THF	1.1	0	1.5	0.3	82:18
8[b]	THF	1.1	–20	24	0.3	77:33
9[b]	THF	1.1	–20	24	0.1	75:25
10[b]	THF	1.1	–20	24	0.05	75:25
11[b,c]	THF	1.1	–78	4	0.3	86:14
12[c]	THF	1.1	0	1.5	0.1	82:18
13	THF	1.1	0	1.5	0.1	75:25
14	THF	1.1	0	1.5	1.0	82:18
15[b]	THF/Tol (2:1)	1.1	0	1.5	0.1	87:13
16	THF/Tol (2:1)	1.1	0	16	0.1	83:17

[a] Diastereoselective ratio (*dr*) was calculated *via* ^{1}H NMR analysis of the crude reaction material at nominally full conversion. [b] Conversion ≤ 50%. [c] 0.1 mL of 1 M NaOH added to maintain basic pH to avoid $NaBH_4$ decomposition.

(*c*) reaction of **2a** with 1.1 equiv of $NaBH_4$ in THF provided full conversion to **3a** after just 1.5 hours and with a modest degree of diastereoselectivity (66:33). At this point, we hypothesised that the borohydride anion may have formed a complex with the sulfonate moiety of the substrate, thereby facilitating directed hydride addition to a preferred face of the carbonyl group. If that was the case, then the use of different solvents, impacting the interaction between the sulfonate and borohydride anion, would provide an opportunity to improve the diastereoselectivity.

Reaction conditions including solvent, temperature, reaction time and concentration were screened to maximise diastereoselectivity (Table 1). Water was used as a racemic control experiment (Table 1, entry 2) since it was expected to form a strong complex with the reducing agent, thereby preventing coordination to the chiral sulfonate; no diastereoselectivity was observed in this case, supporting this hypothesis. Aprotic solvents, expected to favour the desired activation of the borohydride (Table 1, entries 3-4), did not afford significant improvement to the diastereoselectivity at room temperature. Lowering the temperature to 0 °C, combined with the addition of catalytic amounts of NaOH, increased the *dr* up to 84:16 in THF (Table 1, entry 6). Further decreasing the temperature afforded only slightly better *dr* at the expense of longer reaction times and lower conversion of the starting materials. A concentration/temperature screening was also performed (Table 1, entries 9–15) revealing a substantial independence on the final outcome in terms of diastereomeric ratio. An apolar aprotic co-solvent – i.e. toluene – proved ineffective, affording only slightly better diastereoselectivity but at the expense of lower conversions and longer reaction times (Table 1, entry 16).

Table 2. Synthesis of a family of sodium γ-keto-sulfonates **2a-k**[a]



Entry	Product	X	Y	Yield (%)[b]
1	**2a**	H	H	97
2	**2b**	4-F	H	99
3	**2c**	H	2-NO_2	91
4	**2d**	H	4-F	96
5	**2e**	H	4-OMe	99
6	**2f**	4-F	4-OMe	99
7	**2g**	H	2,4-Cl	99
8	**2h**	H	4-NO_2	97
9	**2i**	H	4-Cl	94
11	**2j**	4-Cl	H	93
12	**2k**	H	2-Br	99

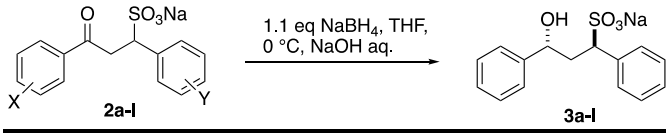
[a] Experimental procedure for the preparation of compounds **2a-l** and their characterisation is reported in the Electronic Supplementary Information. [b] Isolated yield.

In order to study the substrate scope of the reduction, we have prepared a small library of sulfonate salts (**2a-k**, Table 2). The

preparation of **2a-k** was adapted from a protocol already reported by us[18] – where the work-up was adapted to isolate the sodium sulfonate salts (see ESI).

Having identified the best carbonyl reduction conditions (1.1 eq $NaBH_4$, THF, 0 °C, NaOH aq.), we explored the reaction scope by submitting sulfonates **2a-k** to the optimised conditions (Table 3). It is possible to notice that a variety of substituents on the aromatic rings were tolerated, affording compounds **3a-k** with consistently good diastereoselectivities.

Table 3. Scope of the reaction for the reduction of **2a-k** to **3a-k**.



Entry	Product	X	Y	Conv. (%)[a]	Yield (%)[b]	*dr*[a]
1	**3a**	H	H	>99	98	84:16
2	**3b**	4-F	H	>99	89	80:20
3	**3c**	H	2-NO_2	>99	81	83:17
4	**3d**	H	4-F	>99	92	76:24
5	**3e**	H	4-OMe	>99	96	76:24
6	**3f**	4-F	4-OMe	>99	94	85:15
7	**3g**	H	2,4-Cl	>99	99	85:15
8	**3h**	H	4-NO_2	>99	78	79:21
9	**3i**	H	4-Cl	>99	91	85:15
11	**3j**	4-Cl	H	>99	98	81:19
12	**3k**	H	2-Br	>99	82	91:9

[a] Conversion and diastereoselective ratio (*dr*) was calculated *via* ^{1}H NMR analysis of the crude reaction material. [b] Isolated yield.

The absolute configuration of the hydroxyl stereocenter was determined by single crystal X-ray analysis of the *N*-(2-bromobenzyl)-*N*,*N*,*N*-triethylammonium salt **4**, derived from **3k**, as shown in Figure 1.

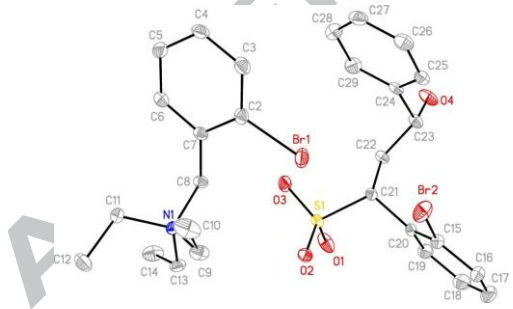
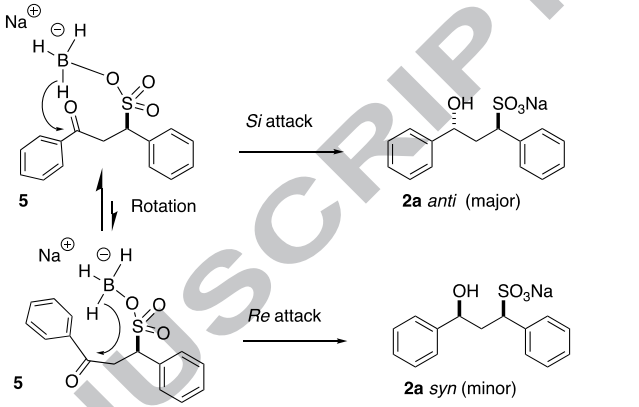


Figure 1. ORTEP plot for ammonium salt **4**, derived from γ-hydroxy sulfonate **3k**

The relative proximity of the ion pair revealed by the X-ray crystal structure of **4** may provide information regarding the reduction mechanism (Scheme 3). Our mechanistic hypothesis reasons that the reaction of $NaBH_4$ and water may form borane (BH_3) *in situ*, which could in turn form a charge-transfer complex with the sulfonate anion, producing intermediate **5**. Nucleophilic hydride can attack either the *Si* or the *Re* face of the carbonyl group due to the rotation around the C_1-C_2 or C_2-C_3 axis. However, *Si*-attack is thought to predominate as the major product of the reduction is the *anti* γ-hydroxy sulfonate.[20] Charge-transfer complexes with borane have been noted with several Lewis bases, including: amines,[21] phosphines,[22] and *N*-heterocyclic carbenes.[23] The latter have been shown capable of forming discrete sulfonate borohydrides.[23] The reaction of **2a** with commercially available 1M BH_3•THF provided desired **3a** in similar (79: 21) diastereomeric ratio, demonstrating that for the formation of intramolecular charge transfer complexes of borane, the solvent media is crucial. Seven membered transition states are unusual compared to the most common Zimmerman Traxler (six membered); however these have been precedented in a number of reports.[24]



Scheme 3. Proposed mechanism explaining the formation of the major *anti* diastereomer **2a** *via* charge-transfer complex **5**.

In conclusion, we have developed a convenient synthetic strategy to access α,γ-substituted γ-hydroxy sulfonates in good yield and stereoselectivity by reduction of γ-keto-sulfonates. The interaction of the sulfonate group to boron was able to direct the hydride attack predominantly at the *Si* face of the carbonyl, thus affording predominantly the *anti* γ-hydroxy sulfonates. The use of sulfonate as a directing group in reduction of carbonyls and in other reactions is hitherto unreported. This new reaction and the diastereoselectivity provided will be of interest for those studying the preparation of hydroxy sulfonic acids and their use in organic synthesis and medicinal chemistry.

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Supplementary Material

Experimental procedures for the preparation of compounds **2a-l**, **3a-l** and compound **4** and their characterisation; copies of representative ^{1}H/^{13}C NMR spectra can be found in the supplementary information.

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Highlights

A new hitherto unreported directing group for diastereoseelctive synthesis is reported

A method for the preparation of hydroxyl sulfonates in high yield and diastereoselectivity is provided

Data for a family of 12 ketosulfonates and 12 γ-hydroxysulfonates is reported