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Highly Enantioselective One-Pot Synthesis of Chiral β-Hydroxy Sulfones via Asymmetric Transfer Hydrogenation in an Aqueous Medium

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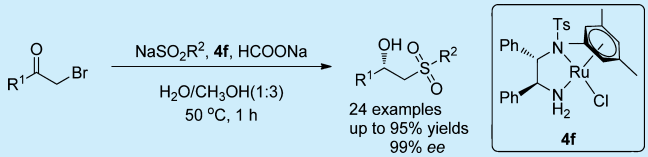
Supporting Information

ABSTRACT: A mild transformation in an aqueous medium for the one-pot synthesis of optically active β-hydroxy sulfones is described. The intermediates of β-keto sulfones obtained via a nucleophilic substitution reaction of α-bromoketones and sodium sulfinates in H_2O/MeOH (1:3, v/v) at 50 °C were reduced through Ru-catalyzed asymmetric transfer hydrogenation in one-pot using HCOONa as a hydrogen source providing a variety of chiral β-hydroxy sulfones with high yields and excellent enantioselectivities.



One-pot transformation, including one-pot tandem reaction and one-pot sequential reaction, is an efficient methodology for the construction of complex and high-value compounds from relatively simple, inexpensive, and accessible raw materials.[1] The desired products could be obtained with minimum workup and without the isolation of intermediates through this method, which minimizes production cycles and cost and decreases waste. So the increasing demands for environmentally and economically friendly synthetic processes have promoted the booming development of the one-pot synthetic method.

The increasing demand for optically pure compounds for pharmaceuticals, pesticides, and other fine chemicals has greatly accelerated the development of asymmetric catalytic methodologies.[2] Among these methods, asymmetric transfer hydrogenation (ATH), utilizing transition metals including iridium, rhodium, and ruthenium to enantioselectively reduce prochiral ketones and imines, has become one of the most efficient methods for constructing enantioenriched secondary alcohols and amines.[3] ATH has gained much attention and developed rapidly in recent years because of its significant advantages such as simple operation, mild reaction conditions, high yield, high enantioselectivity, and so on.

Chiral β-hydroxy sulfones are a type of important optically active alcohol that is an essential building block for several bioactive molecules. Because of the electron-withdrawing property of the sulfonyl group at the β-position, the α-carbon could be further functionalized and the sulfonyl group could be removed without racemization.[4] They have also been used for the synthesis of optically active compounds such as γ-butenolides,[5] δ-valerolactone,[6] etc. Because of the wide use of chiral β-hydroxy sulfones, several methods were developed for the synthesis of those compounds. Nageswar, Venkateswarlu and co-workers synthesized racemic β-hydroxy sulfones via opening of epoxides with sulfinates,[7] which could be transformed into the corresponding optically active *O*-acetyl derivatives using a lipase promoted dynamic kinetic resolution.[8] Carretero and colleagues recently obtained chiral β-hydroxy sulfones though asymmetric conjugate boration of α,β-unsaturated sulfones using nonracemic Cu(I)-diphosphine complexes as a catalyst in the presence of the strong base *t*-BuONa.[9] Asymmetric reduction of β-keto sulfones is a common way to obtain chiral β-hydroxy sulfones. The baker's yeast mediated reduction is a practical route. However, poor yields and enantioselectivities were obtained when the substrates were aryl ketones.[10] Chemical methods for asymmetric reduction of β-keto sulfones are one of the most efficient ways to provide chiral β-hydroxy sulfones. Currently, most of them are catalytic enantioselective hydrogenations.[11] Although high yields and enantioselectivities were attained, the high pressure of the reactions made them difficult to operate. There are also some works synthesizing chiral β-hydroxy sulfones via borane reduction in the organic solvent tetrahydrofuran (THF).[12] Despite ATH being an outstanding procedure to enantioselectively reduce ketones, only a few reports of chiral β-hydroxy sulfones synthesis employing this method in DMF were published.[13] Pure β-keto sulfones also must be obtained for most of reported processes (Scheme 1), which cause a long production cycle and high cost of products. Herein, we report a novel catalytic procedure for the one-pot, two-step synthesis of optically active β-hydroxy sulfones from α-bromoketones and sodium sulfinates in an aqueous medium (Scheme 1).

In the case of asymmetric synthesis, high enantioselectivity should be one of the most important objectives. Therefore, we started our studies with optimization of the conditions for ATH. As we know, the complexes of transition metals, such as

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Scheme 1. Synthesis of Chiral β-Hydroxy Sulfones from α-Bromoketones and Sodium Sulfinate

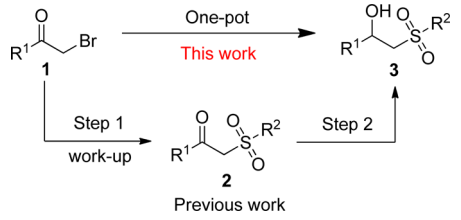
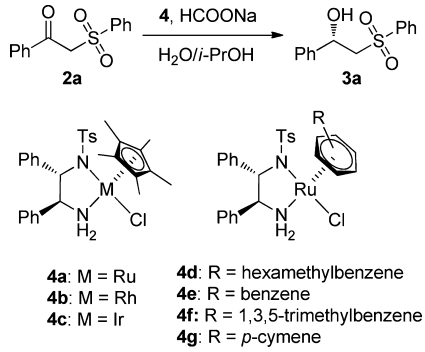


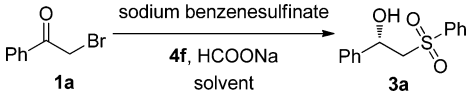
Table 1. Screening of Catalysts for the Synthesis of (*S*)-1-Phenyl-2-(phenylsulfonyl)ethanol via ATH[a]



entry	catalyst	conv (%)[b]	*ee* (%)[c]
1	**4a**	99	97
2	**4b**	99	97
3	**4c**	99	83
4	**4d**	99	98
5	**4e**	99	88
6	**4f**	99	99
7	**4g**	99	98

[a]Reaction conditions: **2a** (0.1 mmol), **4** (5 mol %), HCOONa (0.3 mmol), 4 mL of H_2O/*i*-PrOH (1:3, v/v). [b]Determined by HPLC with a Daicel Chiralpak column AD-H.

Table 2. Optimization of Reaction Conditions for the One-Pot Synthesis of the Chiral β-Hydroxy Sulfones[a]



entry	solvent	temp (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	H_2O	20	24	78	95
2	H_2O/CH_3OH (1:3)	20	9	89	98
3	H_2O/CH_3OH (1:3)	50	1	93	99
4	CH_3OH	50	1	85	96
5	*i*-PrOH	50	1	82	96
6	H_2O/CH_3OH (1:1)	50	1	86	95
7	H_2O/CH_3OH (1:5)	50	1	90	97
8	H_2O/*i*-PrOH (1:3)	50	1	88	98
9	H_2O/CH_3OH (1:3)	40	2	85	97
10	H_2O/CH_3OH (1:3)	60	0.5	80	95

[a]Reaction conditions: **2a** (0.1 mmol), **4f** (5 mol %), HCOONa (0.3 mmol), solvent (4 mL). [b]Isolated yield. [c]Determined by HPLC with a Daicel Chiralpak column AD-H.

ruthenium, rhodium, and iridium, with the ligand of *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) are efficient catalysts for the asymmetric reduction of ketones and imines.[3b,14] We are interested in the ATH of aromatic ketones

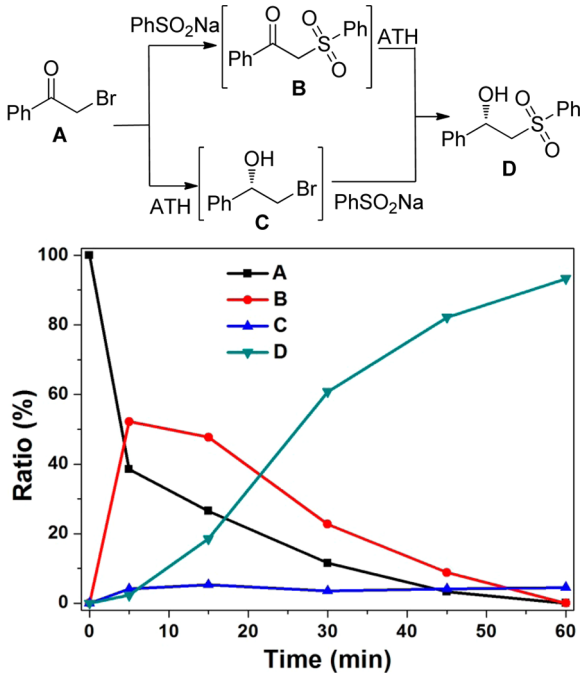


Figure 1. Kinetic investigation of the one-pot synthesis of β-hydroxy sulfone.

in aqueous solution and have done some work based on this type of catalysts.[15] Here, we chose the ATH of 1-phenyl-2-(phenylsulfonyl)ethanone **2a** for the synthesis of (*S*)-1-phenyl-2-(phenylsulfonyl)ethanol **3a** as a model reaction. The catalysts Cp*MTsDPEN (Cp* = pentamethylcyclopentadiene, M = Ru, Rh, and Ir) **4a**–**4c** and AreneRuTsDPEN **4d**–**4g** were screened to catalyze the model reaction under the reported conditions of H_2O/*i*-PrOH (1:3, v/v) with HCOONa as a hydrogen source.[16] We found that **2a** could be converted to **3a** smoothly in 4 h in the presence of all tested catalysts **4a**–**4g**, and **4f** provided the best enantioselectivity (Table 1).

After catalyst **4f** was designated, the conditions of a one-pot synthesis of β-hydroxy sulfones were investigated next. Here, we chose the reaction of 2-bromo-1-phenylethanone **1a** and sodium benzenesulfinate as a model reaction. As shown in Table 2, the reaction was conducted in water first, and the reaction rate was very slow (entry 1, Table 2). That was probably due to the poor solubility of 2-bromo-1-phenylethanone in water. So cosolvent H_2O–CH_3OH (1:3, v/v) was applied for this reaction, and the reaction rate significantly increased (entry 2). When the reaction temperature was increased from 20 to 50 °C, the reaction would be completed in 1 h (entry 3). However, the yield of the corresponding product decreased when the reaction was carried out in organic solvents, such as CH_3OH and *i*-PrOH (entries 4 and 5). Then the ratio of water and organic solvent was also evaluated (entries 6–8), and it was found that H_2O–CH_3OH (1:3, v/v) gave the best result. A decreased yield was obtained using H_2O–*i*-PrOH (1:3, v/v) as the solvent. Next, the optimal reaction temperature was determined to be 50 °C (entries 9 and 10).

A kinetic investigation of this model reaction was also carried out, and the result is shown in Figure 1. This reaction can be accomplished via two alternative routes. Nucleophilic substitution takes place in one pathway first involving the intermediate **B** followed by ATH. Another pathway includes

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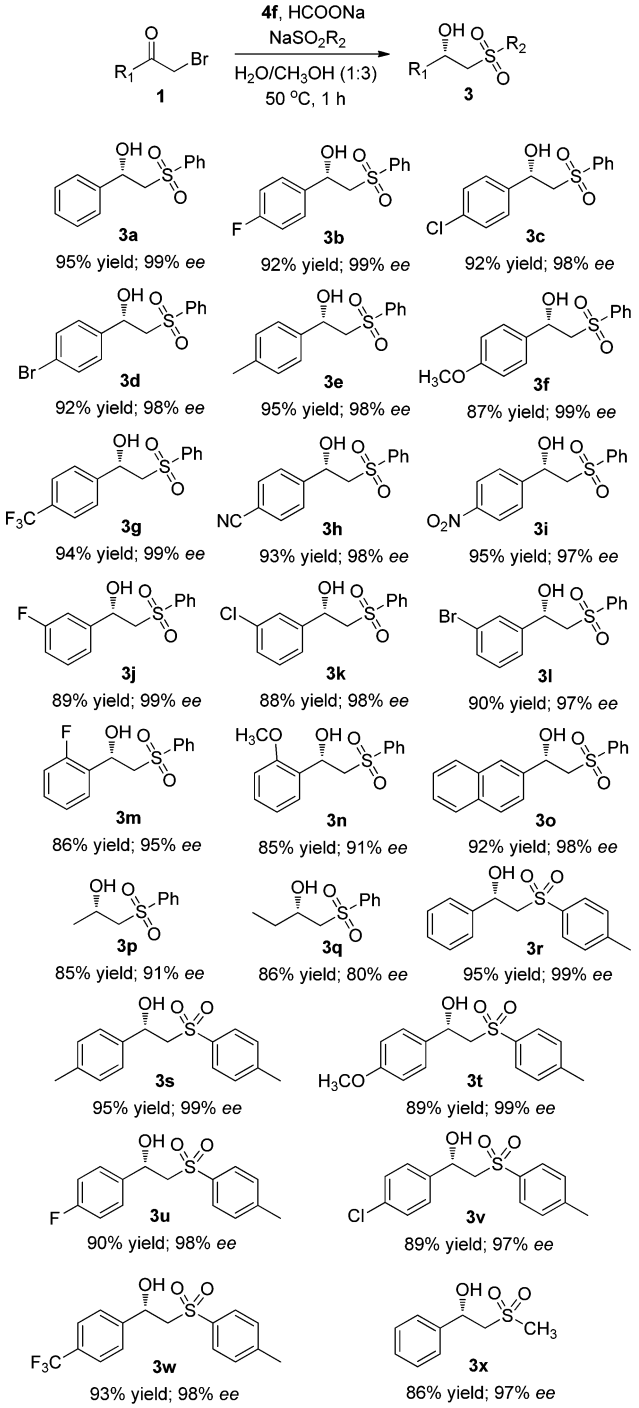
Scheme 2. One-Pot Synthesis of Chiral β-Hydroxy Sulfones[a]



[a]Reactions were performed with 0.1 mmol of α-bromoketone, 0.11 mmol of sodium sulfinate, 5 mol % of **4f**, and 0.3 mmol of HCOONa in 4 mL of H_2O/CH_3OH (1:3, v/v) at 50 °C for 1 h; isolated yield; *ee* values were determined by HPLC with a Daicel Chiralpak column AD-H or Daicel Chiralcel column OJ-H.

ATH which provides the intermediate **C** followed by nucleophilic substitution. As shown in the kinetic curve plot, 2-bromo-1-phenylethanone **A** decreases rapidly and 1-phenyl-2-(phenylsulfonyl)ethanone **B** increases quickly within the first 5 min. Then the ratio of product **D** increases gradually, and both **A** and **B** slowly disappear. In the process of this reaction, the concentration of 2-bromo-1-phenylethanol **C** is essentially constant, which indicates that the route of this reaction is through the nucleophilic substitution−ATH pathway. The resuling kinetic curves also demonstrate that the reaction is totally finished in 60 min.

Encouraged by the above good results, the scope of the one-pot synthetic reaction was investigated with a variety of α-bromoketones and sodium sulfinates, and the results are summarized in Scheme 2. It was found that all 4′-substituted α-bromoacetophenones, regardless of the electron-donating or -withdrawing property of the substituent, provided corresponding optically active β-hydroxy sulfones **3b−3i** in high yields and excellent enantioselectivities reacting with sodium benzenesulfinate. Very similar results were obtained using 3′-substituted α-bromoacetophenones as substrates **1j−1l**. When the reactions of 2′-substituted α-bromoacetophenones (**1m** and **1n**) and sodium benzenesulfinate were carried out, **3m** and **3n** were obtained with slighly decreased enantioselectivities (95% and 90% *ee*, respectively). That was probably due to the steric hindrance of the substituents. 2-Bromo-1-(2-naphthyl)-ethanone **1o** was also tested for the one-pot synthesis, and it afforded **3o** in 92% yield with 98% *ee*. The aliphatic α-bromoketones, **1p** and **1q**, were investigated for this transformation as well, which furnished the desired products in good yields (85% and 86%) with slightly declined enantioselectivities (91% and 80% *ee*). In addition, the one-pot transformations were successfully accomplished using sodium *p*-toluenesulfinate and sodium methanesulfinate providing **3r−3x** with high yields and enantioselectivities. To demonstrate the practicality of this reaction, a scale-up one-pot reaction with 1 mmol of 2-bromo-1-phenylethanone **1a** was carried out. The result showed that a longer reaction time (2 h) was needed and the same *ee* value with a slightly reduced yield (83%) was observed compared to the small-scale reaction. Furthermore, almost the same result (85% yield, 98% *ee*) was observed in this reaction with a lower catalyst loading (2 mol %), which demonstrated the high catalytic effectivity of catalyst **4f** for this one-pot procedure.

In summary, we have described a mild, ATH-based procedure for the one-pot synthesis of optically active β-hydroxy sulfones in an aqueous medium from α-bromoketones and sodium sulfinates. This reaction is carried out in a cosolvent of H_2O and CH_3OH at 50 °C, catalyzed with RuCl[(*S*,*S*)-TsDPEN)](mesitylene) using HCOONa as a hydrogen source. This transformation affords desired products in high yields with excellent enantioselectivities using a variety of α-bromoketones and sodium sulfinates as substrates.

■ ASSOCIATED CONTENT

Supporting Information

General information, typical experimental procedures, characterization, and HPLC spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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