Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2095–2098

TETRAHEDRON: *ASYMMETRY*

Enantioselective reduction of β-keto sulfones using the $NaBH_4/Me_3SiCl$ system catalyzed by polymer-supported chiral sulfonamide

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Received 21 July 2002; accepted 10 September 2002

Abstract—In the presence of 25 mol% of polymer-supported chiral sulfonamide, a variety of β-keto sulfones can be reduced into the corresponding β-hydroxy sulfones in excellent yields and with high enantioselectivities using the reducing system of $NaBH_4/Me_3SiCl$. © 2002 Elsevier Science Ltd. All rights reserved.

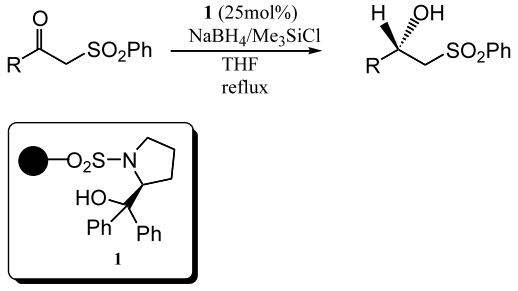
1. Introduction

Optically active β-hydroxy sulfones are useful chiral synthons for the asymmetric synthesis of biologically active molecules such as γ-butenolides,[1] γ-butyrolactones,[1,2] 2,5-disubstituted tetrahydrofuran[3] and δ-valeroactones.[4] Many methods have been developed for the enantioselective synthesis of optically active β-hydroxy sulfones, including kinetic resolution of racemic β-hydroxy sulfones,[5] Ru(II)-catalyzed hydrogenation,[6] baker's yeast-mediated reduction,[7] and CBS–oxazaborolidine-catalyzed borane reduction of β-keto sulfones.[8] However, these methods suffer from inherent drawbacks: For example, the yields of kinetic resolution of β-hydroxy sulfones are never above 50%,[5] while CBS–oxazaborolidine-catalyzed borane reduction of β-keto sulfones involves the use of toxic borane and the need for expensive catalysts.[8] Thus, the development of an efficient, economical and environmentally friendly methodology for the synthesis of optically active β-hydroxy sulfones is still required.

In the past decade, several groups have reported the preparation and application of polymer-supported catalysts derived from chiral amino alcohols for enantioselective reductions.[9] Recently, we have developed a new class of polymer-supported sulfonamides and applied them to the enantioselective reduction of prochiral ketones via $BH_3{\cdot}SMe_2$[10] or $NaBH_4/Me_3SiCl$ (or $BF_3{\cdot}OEt_2$).[11] In these studies we found that the reducing systems of $NaBH_4/Me_3SiCl$ and $NaBH_4/BF_3{\cdot}OEt_2$ could provide an efficient, economical and environmental friendly methodology for the synthesis of optically active secondary alcohols. Herein, we would like to report the enantioselective synthesis of optically active β-hydroxy sulfones by the polymer-supported sulfonamide catalyzed asymmetric borane reduction of β-keto sulfones.

2. Results and discussion

As shown in our previous paper, the enantioselective reduction of prochiral ketones with $NaBH_4/Me_3SiCl$ could be achieved with best results when the reactions were carried out in refluxing THF with 25 mol% polymer-supported sulfonamide **1** (200–400 mesh, 2% DVB, 2.29 mmol/g N) as catalyst.[11] In the same manner, the asymmetric reduction of β-keto sulfones was investigated (Scheme 1) and these results are shown in Table 1.



Scheme 1.

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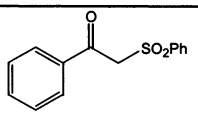
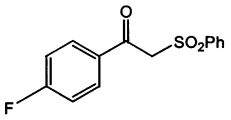
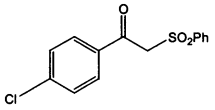
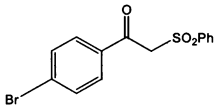
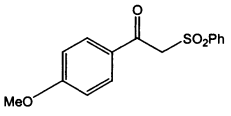
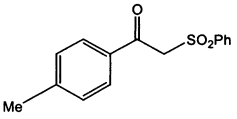
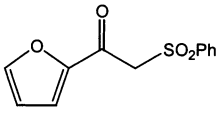
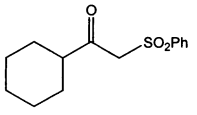
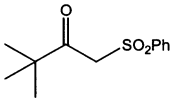
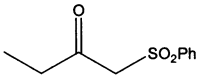
PII: S0957-4166(02)00546-3

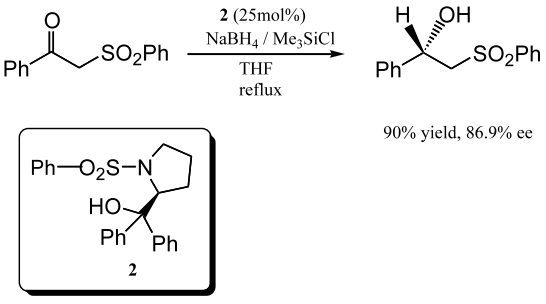
Table 1. Asymmetric reduction of β-keto sulfones[a]

Entry	β-Keto sulfones	Yield (%)[b]	Ee (%)[c]	Config.[d]
1		98	94	*S*
2		99	97	*S*
3		98	94	*S*
4		98	94	-
5		97	94	*S*
6		98	94	*S*
7		96	93	*S*
8		97	87	*S*
9		98	97	*S*[e]
10		98	56	*S*[e]

[a] Experiments were performed at 1 mmol scale; Molar ratio: β-keto sulfone/ $NaBH_4$/ Me_3SiCl/ cat. = 1:1.2:1.2:0.25; [b] Isolated yield after column purification or distillation; [c] Determined by chiral HPLC; [d] The absolute configurations were determined by comparison of reported specific rotations; [e] Analytical samples were converted to 3-chlorophenylcarbamates.

In all cases, the reductions afforded the corresponding β-hydroxy sulfones in excellent chemical yields. It is noteworthy that aromatic β-keto sulfones were reduced with excellent enantioselectivities (94–97% e.e.). To gain insight on the effect of the electron density of the aromatic ring, a series of β-keto sulfones bearing a different substituent at the *para* position on the phenyl group was studied. The results show that the electron density of the aromatic ring has little effect on the enantioselectivity. Notably, higher enantioselectivity could be obtained when the reduction occurred at the more hindered carbonyl group.

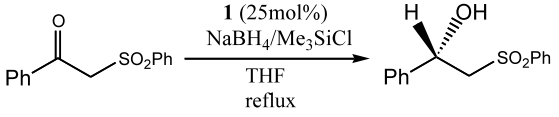
Under the above optimal reaction conditions, homogeneous sulfonamide **2** promoted the reduction of 2-(phenylsulfonyl)actophenoneacetophenone to give 86.9% e.e.—less than the polymer-supported sulfonamide **1** (Scheme 2).



Scheme 2.

Significantly, after the reduction was complete the polymer-supported sulfonamide **1** could be recovered by simple filtration followed by washing with water, and methanol. Recycling of the chiral polymer catalyst was tested by the reduction of 2-(phenylsulfonyl)acetophenone (Table 2). The results showed that the chiral polymeric catalyst could be reused at least five times with little or no loss of performance.

Table 2. The recycling of polymer-supported sufonylamide **1**



Run (No.)	Yield (%)[a]	E.e. (%)[b]
1	98	94
2	97	95
3	99	96
4	98	94
5	98	97

[a] Isolated yield after column purification or distillation.
[b] Determined by chiral HPLC.

3. Conclusion

The results reported here offer a simple and highly enantioselective methodology for the synthesis of optically active β-hydroxyl sulfones. Due to the efficiency, low-cost and high enantioselectivity observed, the method represents a very useful alternative to previously reported procedures.

4. Experimental

4.1. General

All reactions were carried out under a dry Ar atmosphere. THF was freshly distilled over sodium/benzophenone ketyl before use. β-Keto sulfones were prepared according to the reported procedure and further purified by crystallization.

4.2. Typical procedure for the asymmetric reduction of β-keto sulfones

Me_3SiCl (0.132 mg, 1.2 mmol) was added to a suspension of $NaBH_4$ (45 mg, 1.2 mmol) in THF (10 mL). The suspension was heated under reflux and stirred for 1 h. The polymeric catalyst **1** (98 mg, 0.25 mmol) was added and the reaction mixture was heated under reflux for a further 0.5 h. Then a THF (10 mL) solution of 2-(phenylsulfonyl)acetophenone (260 mg, 1 mmol) was added at a rate of 3 mL/h by syringe pump. After the addition was complete, the mixture was treated with water and filtered. The polymeric catalyst was washed several times with EtOAc and water. The resulting aqueous solution was extracted with EtOAc (3×10 mL) and dried with $MgSO_4$. The solution was evaporated and purified by Silica gel chromatography to give a white solid (258 mg, 98% yield); mp 93–94°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.25 (1H, dd, $J=14.3$ and 2.0 Hz), 3.40 (1H, dd, $J=14.3$ and 10.0 Hz), 3.69 (1H, s, CHOH), 5.19 (1H, dd, $J=10.0$ and 2.0 Hz), 7.29–7.73 (10H, m, 2Ph); IR: 3343 (OH), 1286–1135 (SO_2) cm^{-1}; $[\alpha]_D^{20}=+31.8$ (*c* 2.15, $CHCl_3$) {lit.[6b] $[\alpha]_D^{27}=+29.0$ (*c* 1.0, $CHCl_3$)}. The optical yield was determined to be 94% by chiralcel AD column chromatography (eluent: $V_{Hexane}:V_{i\text{-}PrOH}=4:1$).

Acknowledgements

We are grateful to the Ministry of Sciences and Technology, the State Key Project of Basic Research (Project 973, No. G 2000048007) and the National Natural Science Foundation of China for financial support.

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