A chemo-enzymatic synthesis of chiral secondary alcohols bearing sulfur-containing functionality†

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Received (in Montpellier, France) 12th November 2008, Accepted 17th December 2008
First published as an Advance Article on the web 12th January 2009
DOI: 10.1039/b820192g

A facile method for the preparation of chiral secondary alcohols bearing a sulfur-containing functionality using a chemo-enzymatic approach is described, with the aid of baker's yeast and *Candida Antarctica* lipase B. A complete set of four stereoisomers of two substituted phenylsulfinylpropan-2-ols were synthesized from β-sulfinyl ketones with excellent enantioselectivity for the first time.

In recent years, a variety of sulfur-containing chiral alcohols have been utilized as key chiral synthons in asymmetric synthesis.[1] Many transformations have been used in their preparation by employing whole-cell biocatalysts,[2] enzymatic transformations[3] and transition metal catalysis.[4] However, the drawbacks of these reactions are also obvious. For bioreduction in water, a relatively large volume of water is required as the solvent, which makes the work-up procedure more difficult, particularly since the product is difficult to isolate from the huge amounts of biomass.[2] For enzymatic kinetic resolution (KR), as a rule, no more than a 50% yield of the enantiomer needed can be obtained.[3a,b] Using transition metal complexes needs harsh conditions[4a,c–e] and expensive reagents,[4] or is less effective.[4b] Furthermore, because β-hydroxysulfoxides bear two chiral centers, four stereoisomers are thus expected. Unfortunately, none of the reported methods provide all of four stereoisomers of β-hydroxysulfoxides simultaneously with excellent enantioselectivity.[2,3c,d] Herein, we wish to report an alternative and convenient biotransformation system. With the aid of this system, both β-hydroxysulfones and β-hydroxysulfides were synthesized in medium-to-high yields and excellent enantioselectivities. Moreover, four stereoisomers of substituted phenylsulfinylpropan-2-ols were prepared with excellent enantioselectivities with the aid of *Candida Antarctica* lipase B (CALB).

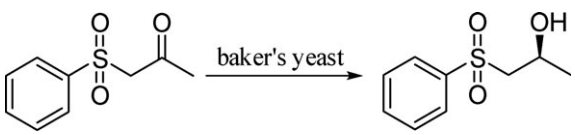
Due to the intrinsic limitations of biotransformations undertaken in water, a variety of organic solvents, such as benzene, petroleum ether, toluene and carbon tetrachloride, were used to replace water in yeast-catalyzed reactions.[5] Diisopropyl ether, as a substitute for water, worked well with enzymes in our previous studies.[6] Herein, we investigated whether it could be used as an appropriate organic solvent for the bioreduction of sulfur-containing ketones by baker's yeast. After trials, we found that 1 g of baker's yeast was most effective in a mixture of 10 mL diisopropyl ether and 0.7 mL water. (*S*)-Phenylsulfonylpropan-2-ol was obtained in 99% yield and 99% ee in 4 h (Scheme 1).

There have been reports concerning the baker's yeast-mediated reduction of 1-(phenylsulfonyl)propan-2-one in an aqueous system.[2a–c] The best result was obtained by using 6 g yeast per mmol substrate;[2a] while in our system, only 1 g yeast per mmol substrate was utilized, and the time for such a biotransformation was significantly shortened (Table 1). It is worth noting that the work-up was greatly simplified by avoiding a tedious extraction.

Recently, several protocols for the preparation of other chiral β-hydroxysulfones *via* enantioselective reduction have been documented (Scheme 2).[2f,4d,e] However, as shown in Table 2, as a non-popular enzyme, *P. minuta IAM 12215* is not easily available. Furthermore, this bioreduction system also suffers from the same intrinsic limitations of biotransformations in water. Nevertheless, enantioselective reductions catalyzed by transition metals such as Rh and Ru are highly efficient. However, expensive chiral metallic catalysts and harsh operating conditions for the removal of water and oxygen are usually required. Besides these operations with hydrogen under pressure are also inconvenient.

To further study the scope of this diisopropyl ether/limited water system, a variety of sulfur-containing ketones were prepared, as shown in Scheme 3. Various sulfur-containing ketones were reduced enantioselectively by baker's yeast in this system.

As shown in Table 3, when R^2 was methyl, all the sulfur-containing alcohols were obtained with excellent enantioselectivity. Electronic effects do not seem to have any significant influence on the enantioselectivity of the products. When R^2 was methyl, substituted phenylsulfonylpropan-2-ols were obtained in medium-to-high yield with excellent enantioselectivities, except for **1d**; this is probably due to the poor solubility of **1d** in diisopropyl ether (Table 3, entries 1–5). With the increasing steric hindrance of R^2, both the yield and ee dropped (Table 3, entries 6–7). When phenyl deactivated the carbonyl group, the reaction was blocked (Table 3, entry 8).



Scheme 1 The bioreduction of β-ketosulfones by baker's yeast.

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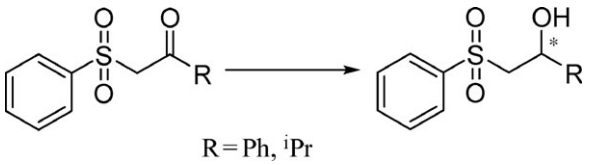
† Electronic supplementary information (ESI) available: Experimental procedures and data, and other material. See DOI: 10.1039/b820192g

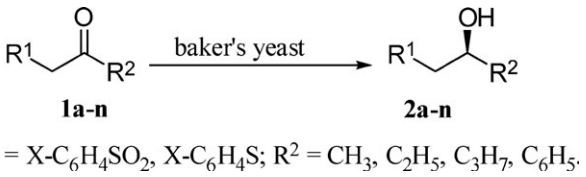
Table 1 The bioreduction of 1-(phenylsulfonyl)propan-2-one

Entry	Solvent	Yeast/g mmol^{-1}	Reaction time/h	Yield (%)	ee (%)
1[a]	$^{i}Pr_2O$	1	4	99	99
2[b]	H_2O	6	24	99	>95

[a] 1 g baker's yeast, 10 mL diisopropyl ether and 0.7 mL water with 1 mmol substrate. [b] 6 g baker's yeast and 6 g sucrose in 18 mL water with 1 mmol substrate.[2a]



Scheme 2 Transformations for the preparation of chiral β-hydroxysulfones.



Scheme 3 The enantioselective reduction of sulfur-containing ketones.

Enantiopure β-hydroxysulfides serve as synthons in asymmetric synthesis.[1] For substituted phenylthiopropan-2-ones, the baker's yeast in diisopropyl ether system also works well (Table 3, entries 9, 11–15) as smaller amounts of substrates can be reduced, and longer reaction times are required because of the poor electron-withdrawing ability of the phenylthio group. It has been reported that in an aqueous system, the baker's yeast-mediated reduction of phenylthiopropan-2-one (**1i**) occurs in only a 35% yield at low concentrations (Table 3, entry 10).[2b]

Compared with bioreductions in water,[2a–d,f] our biotransformation system has advantages. The procedure is easily undertaken, the product can be isolated efficiently and the reaction time is shorter. In addition, the biotransformation system can also be applied to larger reaction scales. What's more, the system developed by us is more atom-economical than the KR system (for KR, the yield is $\leq$50 %).[3a,b] Besides this, the method is economical and can be carried out under very mild conditions relative to transformations catalyzed by transition metal complexes.[4]

In recent years, many transformations for the preparation of chiral β-hydroxysulfoxides have been introduced; however, not all of the stereoisomers of β-hydroxysulfoxides can be obtained by one single method.[2,3c,d] Herein, we wish to report a novel method for the preparation of the four stereoisomers of β-hydroxysulfoxides based on a combination of baker's yeast and CALB with excellent enantioselectivities (Scheme 4).

As shown in Table 4, the four stereoisomers of two β-hydroxysulfoxides have been prepared by combining our biotransformation system with CALB, with excellent enantioselectivities and high *syn*/*anti* ratios. The absolute configuration of each stereoisomer was determined by comparisons of their specific rotations and ^{1}H NMR spectra with the literature,‡ in addition to HPLC with a chiral column.§ Compared with other reported methods,[2b–e,3c,d] our strategy is of unique significance since, for the first time, the four stereoisomers of two β-hydroxysulfoxides could be prepared simultaneously with excellent enantioselectivities by using commercial available reagents, rather than expensive or uncommon materials, or special skills in biology.[2c–e]

In summary, chiral β-hydroxysulfones and β-hydroxysulfides were prepared using baker's yeast in a diisopropyl ether/limited water solvent system with medium-to-high yields and excellent enantioselectivities. By combined this biotransformation system with CALB, a complete set of four stereoisomers of two substituted phenylsulfinylpropan-2-ols was prepared simultaneously for the first time with highly efficiency.

Experimental

General procedure for the bioreduction of sulfur-containing alcohols using baker's yeast in a diisopropyl ether/limited water solvent system

To a 25 mL round-bottomed flask equipped with a magnetic stirring bar was added 1 g baker's yeast, 10 mL diisopropyl ether and 0.7 mL water. The solution was stirred for 5 min, after which time each β-keto sulfone (**1a**) (198 mg, 1 mmol) was added. The mixture was stirred at 30 °C and monitored by TLC. 4 h later, the mixture was filtered, the filtrate removed under reduced pressure and the residue subjected to flash chromatography over silica gel (petroleum : EtOAc = 1 : 1) to afford a colourless oil (**2a**) (198 mg, yield: 99%, ee: 99%).

Table 2 Comparison of literature data related to the catalytic transformations leading to chiral β-hydroxysulfones

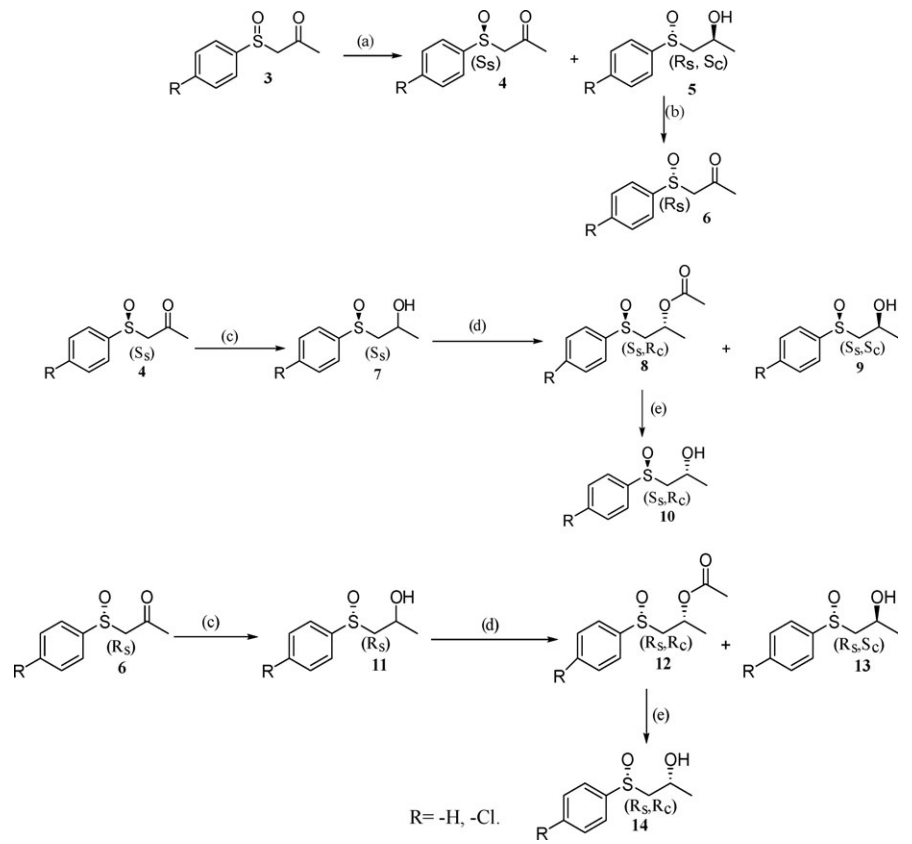
Entry	Solvent (1 mmol)	Catalyst (1 mmol)	Reaction time/h	Yield (%)	ee (%)
1	113 mL H_2O	2 g *P. minuta IAM 12215*	28	92[a]	97
2	4 mL EtOH	0.25% Ru*Cl_2/(H_2)	20	100[b]	99
3	4 mL ^{i}PrOH	1% Rh*SbF_6/(H_2)	24	99[b]	95

[a] (a) Isolated yield. [b] (b) Conversion. For more detailed information, please refer to 2*f*, 4*d* and *e*.

Table 3 The enantioselective reduction of sulfur-containing ketones

Entry	Substrates	R^1	R^2	Reaction time/h	Products	Yield (%)[a]	ee (%)[b]	Configuration[c]
1	**1a**	$C_6H_5SO_2$	CH_3	4	**2a**	99[f]	99	*S*
2	**1b**	4-$CH_3C_6H_4SO_2$	CH_3	5	**2b**	95	99	*S*
3	**1c**	4-$CH_3OC_6H_4SO_2$	CH_3	5	**2c**	85	99	*S*
4	**1d**	4-$NO_2C_6H_4SO_2$	CH_3	4	**2d**	47	96	*S*
5	**1e**	4-$ClC_6H_4SO_2$	CH_3	4	**2e**	77	99	*S*
6	**1f**	$C_6H_5SO_2$	C_2H_5	10	**2f**	91	92	*S*
7	**1g**	$C_6H_5SO_2$	C_3H_7	17	**2g**	74	70	*S*
8	**1h**	$C_6H_5SO_2$	C_6H_5	20[d]	**2h**	—	—	—
9	**1i**	C_6H_5S	CH_3	12	**2i**	97[e]	95	*S*
10	**1i**[g]	C_6H_5S	$-CH_3$	24	**2i**	35	—	—
11	**1j**	4-$CH_3C_6H_4S$	CH_3	12	**2j**	96[e]	99	*S*
12	**1k**	4-$CH_3OC_6H_4S$	CH_3	12	**2k**	86[e]	99	*S*
13	**1l**	4-ClC_6H_4S	CH_3	18	**2l**	67[e]	98	*S*
14	**1m**	4-$NO_2C_6H_4S$	CH_3	22	**2m**	92[e]	96	*S*
15	**1n**	4-BrC_6H_4S	CH_3	17	**2n**	73[e]	97	*S*

[a] Isolated yield. [b] Determined by HPLC with a chiral column. [c] Determined by comparison with the optical rotation of known compounds. [d] No reaction. [e] 1 g baker's yeast can only catalyze 0.2–0.3 mmol β-ketosulfides, which is also indicated in the Experimental section. [f] When the amount of **1a** was increased up to 10 mmol, the reaction also proceeded successfully. [g] 0.5 g **1i** in 600 mL baker's yeast suspension (water).[2b]



Scheme 4 Preparation of the four stereoisomers of substituted phenylsulfinylpropan-2-ols. *Reagents and reaction conditions:* (a) Baker's yeast/$^iPr_2O$/limited water. (b) Triacetoxyperiodinane/CH_2Cl_2. (c) $NaBH_4$/MeOH. (d) CALB, $CH_3COOCHCH_2$/$^iPr_2O$. (e) $BF_3{\cdot}Et_2O$/MeOH, reflux.

General procedure for the preparation of the four stereoisomers of substituted phenylsulfinylpropan-2-ols

To a 25 mL round-bottomed flask equipped with a magnetic stirring bar was added 3 g baker's yeast, 30 mL diisopropyl ether and 2.1 mL water. The solution was stirred for 5 min, after which time phenylsulfinylpropan-2-one (**3a**) (420 mg, 2.3 mmol) was added. The mixture was stirred at 30 °C and the reaction monitored by TLC. 80 min later, the mixture was filtered, the solvent removed under reduced pressure and the residue subjected to flash chromatography over silica gel (petroleum : EtOAc = 1 : 1 ~ 1 : 2) to afford the desired products (S_S)-phenylsulfinylpropan-2-one (**4a**) and

Table 4 Preparation of the four stereoisomers of substituted phenylsulfinylpropan-2-ols

Product	ee (%)[a]	*syn*/*anti*[a]
(S_S,S_C)-Phenylsulfinylpropan-2-ol (**9a**)	>99	26 : 1
(S_S,R_C)-Phenylsulfinylpropan-2-ol (**10a**)	99	1 : 38
(R_S,S_C)-Phenylsulfinylpropan-2-ol (**13a**)	99	1 : 29
(R_S,R_C)-Phenylsulfinylpropan-2-ol (**14a**)	>99	12 : 1
(S_S,S_C)-4-Chlorophenylsulfinylpropan-2-ol (**9b**)	>99	53 : 1
(S_S,R_C)-4-Chlorophenylsulfinylpropan-2-ol (**10b**)	>99	1 : 19
(R_S,S_C)-4-Chlorophenylsulfinylpropan-2-ol (**13b**)	93	1 : 8915
(R_S,R_C)-4-chlorophenylsulfinylpropan-2-ol (**14b**)	98	12 : 1

[a] The ee values and *syn*/*anti* ratios of **9a–14a** were determined by HPLC (WATERS) using a chiral column. The four stereoisomers of racemic phenylsulfinylpropan-2-ol were distinguished by HPLC (using a CHIRALPAK OD column, hexane : ^{i}PrOH = 90 : 10, 0.7 mL min^{-1}; retention times: 14.02, 18.14, 21.18 and 24.57 min). The ee values and *syn*/*anti* ratios of **9b–14b** were determined by HPLC (WATERS) using a chiral column. The four stereoisomers of racemic 4-chlorophenylsulfinylpropan-2-ol were distinguished by HPLC (using a CHIRALPAK OJ column, hexane : ^{i}PrOH = 98 : 2, 0.7 mL min^{-1}; retention times: 38.03, 43.24, 61.90 and 71.51 min).

(R_S,S_C)-phenylsulfinylpropan-2-ol (**5a**), respectively. Oxidation by triacetoxyperiodinane of compound (**5a**) gave (R_S)-phenylsufinylpropan-2-one (**6a**).

(S_S)-Phenylsulfinylpropan-2-ol (**7a**) was obtained by reducing (S_S)-phenylsulfinylpropan-2-one (**4a**) with $NaBH_4$. The CALB-catalyzed kinetic resolution of **7a** afforded acetate **8a** and (S_S,S_C)-phenylsulfinylpropan-2-ol (**9a**) (general procedure for the kinetic resolution of phenylsulfinylpropan-2-ol: 100 mg CALB, 5 mL $^iPr_2O$ and 1 mL $CH_3COOCHCH_2$ were used for 1 mmol substrate; 24 h later, acetate **8a** and alcohol **9a** were obtained). The transesterification of **8a** catalyzed by $BF_3{\cdot}Et_2O$ in methanol afforded (S_S,R_C)-phenylsulfinylpropan-2-ol (**10a**). Similarly, (R_S,S_C)-phenylsulfinylpropan-2-ol (**13a**) and (R_S,R_C)-phenylsulfinylpropan-2-ol (**14a**) were prepared.

This project was supported by the Chinese Academy of Sciences and the National Natural Science Foundation of China (Grant nos. 20672132 and 20872165).

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‡ A clear distinction between the two diastereomers could be observed from their ^{1}H NMR spectra (see ref. 3*c*); the methyl protons in **9a** resonate at δ 1.33, and in case of **10a** at δ 1.27. Therefore, **9a** was (S_S,S_C)-phenylsulfinylpropan-2-ol and **10a** was (S_S,R_C)-phenylsulfinylpropan-2-ol. The specific rotation of **9a** was −248° (*c* 1.00 in $CHCl_3$), while the specific rotation of **10a** was +317° (*c* 0.60 in $CHCl_3$), which also proved to be the absolute configuration of **9a** and **10a**. In the same way, the other two stereoisomers of phenylsulfinylpropan-2-ol also could be distinguished.

§ The retention time of each stereoisomer synthesized by the above method was in accordance with the value for the stereosiomer prepared by known methods.