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Lipase-promoted dynamic kinetic resolution of racemic β-hydroxyalkyl sulfones

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Abstract—A series of racemic aryl β-hydroxyalkyl sulfones have been successfully transformed into the corresponding optically active *O*-acetyl derivatives in high yields (up to 80%) with enantiomeric excesses more than 99% using a dynamic kinetic resolution procedure, in which a lipase-promoted kinetic resolution is combined with a concomitant ruthenium-catalysed racemization of the substrates.

1. Introduction

Sulfones are an interesting class of compounds, which are widely used in organic synthesis due to the ability of the sulfonyl group to stabilise an adjacent carbanionic centre,[1] with sulfones with a stereogenic carbon atom being of particular interest. Optically active β-hydroxyalkyl sulfones, for example, have been used as building blocks in the synthesis of a variety of enantiopure cyclic compound classes, such as lactones,[2–4] tetrahydrofurans[5] and furanones.[2] So far, these optically active β-hydroxyalkyl sulfones have been synthesized both by chemical methods, for example, via oxidation of chiral β-hydroxyalkyl sulfoxides,[3] and by biocatalytic approaches. The latter comprise of baker's yeast-mediated reduction of β-oxo sulfones leading to the (*S*)-enantiomers of the corresponding β-hydroxyalkyl sulfones,[6] and a lipase-catalysed acylation of racemic β-hydroxyalkyl sulfones, performed under kinetic resolution conditions.[7] Although the kinetic resolution procedure allowed both enantiomers of α-, β- and γ-hydroxyalkyl sulfones to be obtained, only one lipase (*Porcine pancrease* lipase) was found effective with the enantiomeric excesses of the products low to moderate.[7]

Over the course of our investigations on the enzyme-promoted syntheses of chiral heteroorganic compounds,[8,9] we became interested in the preparation of β-hydroxyalkyl sulfones of high enantiomeric purity. Taking into account the well-known drawback of kinetic resolutions, in which the yield of the desired product is limited to 50%, we focussed our attention on one of the deracemization techniques,[10] namely the dynamic kinetic resolution,[11] which combines kinetic resolution with an in situ racemization of the starting material.[12] As the products of interest are secondary alcohols, we decided to adopt the procedure, which utilizes enzyme-catalysed acetylation combined with ruthenium-catalysed racemization.[13,14] This procedure has recently been applied for the dynamic kinetic resolution of α-hydroxy acid esters[15] and α- and β-hydroxyalkanephosphonates,[16] which in both cases gave the desired *O*-acyl derivatives in high yields and excellent ee's (over 99%). In this contribution we report on the dynamic kinetic resolution of a series of racemic β-hydroxyalkyl sulfones **1**.

2. Results and discussion

2.1. Kinetic resolution of β-hydroxyalkyl sulfones

Since the previous publication[7] concerning enzyme-promoted kinetic resolutions of hydroxyalkyl sulfones

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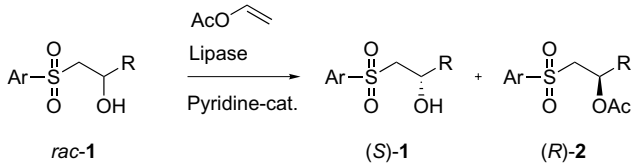
reported only a single example of a β-hydroxyalkyl sulfone in combination with a single effective enzyme, we decided to begin our studies by screening several lipases for the enantioselective acetylation of selected β-hydroxy sulfones *rac*-**1**. Thus, β-hydroxyalkyl sulfones *rac*-**1a** and **b** were treated with an excess of vinyl acetate in the presence of various lipases (Scheme 1). It should be emphasized that the addition of catalytic amounts of pyridine to the reaction medium proved crucial,[17] since in the absence of pyridine, the reaction was very slow or did not proceed at all. The resulting β-acetoxyalkyl sulfones **2a** and **2b** were separated from the unreacted substrates using column chromatography with the results summarized in Table 1. On inspection of Table 1 it can be seen that the best results were obtained when *Candida antarctica* lipase B (CAL-B) was applied (E >100), although lipases AK and PS also exhibited a reasonable stereoselectivity (E >50). In all cases, the preferential formation of the esters derived from the (*R*)-enantiomers of the substrates has been observed, which is in agreement with the literature data.[7]

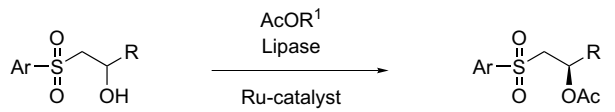


a: Ar = Ph, R = Me
b: Ar = *p*-Tol, R = Me

Scheme 1.

2.2. Dynamic kinetic resolution of β-hydroxyalkyl sulfones 1

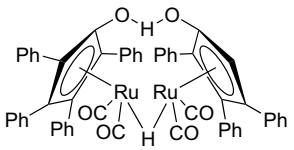
On the basis of the aforementioned results, we decided to combine the enzyme-promoted kinetic resolution of β-hydroxyalkyl sulfones **1** with a ruthenium-catalysed racemization of the substrates using catalyst **3**, originally prepared by Menasche and Shvo[18] and later investigated and used by Pamies and Bäckvall.[16] Since the dynamic kinetic resolution results in the formation of only one product enantiomer, which on the basis of our results (Scheme 1) is (*R*)-**2**, this approach is complementary to the baker's yeast-promoted reduction of the corresponding β-oxo sulfones, which leads to (*S*)-**2**.[6] A general procedure, which is described in the Experimental, was applied to the substrates shown in Scheme 2 with the results shown in Table 2.



a: Ar = Ph, R = Me
b: Ar = *p*-Tol, R = Me
c: Ar = *p*-Tol, R = Et

R^1 = *p*-ClC_6H_4 **4**, $CH=CH_2$ **5**

Scheme 2.



3

The reactions were performed in toluene (or in some cases in benzene with comparable results) at 30 °C in the presence of a catalytic amount of pyridine. In the first set of experiments, we used *p*-chlorophenyl acetate **4** as an acetylating agent, following the suggestion of Pamies and Bäckvall[16] that this reagent, in contrast to the commonly used vinyl acetate **5**, is more compatible with the ruthenium hydride catalyst **3** and gives better yields of the acetylated products. However, we encountered severe difficulties in separating the desired products from the excess of **4** and the resulting *p*-chlorophenol via chromatography. Therefore, in a later stage, we started using vinyl acetate **5** as the acetylating agent and found out that the product yields and enantioselectivities of both reactions were comparable. The enantioselectivity depended on the lipase used and generally ranged from very good to excellent. As expected on the basis of kinetic resolution experiments, the best results were obtained with the lipase from *C. antarctica B* (CAL-B).

Table 1. Kinetic resolution of *rac*-**1**

Entry	Substrate	Lipase	c[c] (%)	(*R*)-**2**		(*S*)-**1**			
				Yield[b] (%)	$[\alpha]_D$[a]	Yield[b] (%)	$[\alpha]_D$[a]	ee (%)	E[d]
1	**1a**	AK	41	38	+0.5	59	+8.5	65	58
2		CAL	47	47	+0.6	52	+10.2	85	127
3		LPL	43	41	+0.45	51	+9.0	65	26
4		PS	35	30	+0.5	65	+6.1	51	62
5	**1b**	AK	39	36	+0.5	58	+9.0	60	58
6		CAL	46	46	+0.6	38	+10.0	82	137
7		LPL	43	43	+0.55	49	+9.3	66	30
8		PS	35	35	+0.4	53	+7.2	50	45

[a] In chloroform.
[b] Isolated yield, relative to the racemic compound.
[c] Conversion (determined by ^{1}H NMR).
[d] $E = [\ln(1 - c)(1 - ee_s)]/[\ln(1 - c)(1 + ee_s)]$.

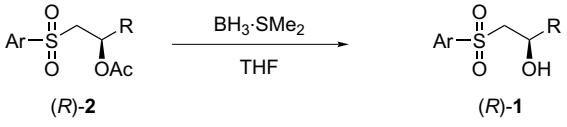
Table 2. Dynamic kinetic resolution of *rac*-**1**

Entry	Substrate	Enzyme	Yield (%) of **2**	$[\alpha]_D$[a] of **2**	$[\alpha]_D$[a] of **1**[c]	ee (%)[b] of **1**[c]
1	**1a**	AK	66	−0.8	−9.6	90
2		CAL	70	−1.0	−12.0	>99
3		LPL	68	−0.8	−9.5	90
4		PS	64	−1.1	−11.8	>99
5	**1b**	AK	75	−1.0	−10.2	90
6		CAL	79	−1.1	−11.6	>99
7		LPL	70	−0.6	−6.5	50
8		PS	75	−0.9	−10.3	90
9	**1c**	AK	30	−3.6	−5.7	85
10		CAL	42[d]	−4.4	−9.2	>99
11		LPL	30	−4.0	−8.8	90
12		PS	34	−4.4	−9.2	>99

[a] In chloroform.
[b] Determined by ^{1}H NMR.
[c] Obtained via reduction of **2** with $BH_3{\cdot}Me_2S$ in THF.
[d] Vinyl acetate was used as the acetyl donor.

Surprisingly, much lower yields and enantioselectivities were observed in the acetylation of **1c**, although it differs from **1b** only by one methylene group in the alkyl chain. Nevertheless, it must be stressed that under these circumstances, we were never able to obtain the β-acetoxyalkyl sulfones **2** in quantitative yields. In all cases, unusual by-products were isolated in low yields, which are probably complexes of **1** with the ruthenium catalyst **3**. These products were yellow and upon treatment with acids gave unreacted **1** and decomposition products of the catalyst **3**. It is noteworthy that similar findings were reported by Pamies and Bäckvall.[16]

Finally, the ee values of the β-hydroxyalkyl sulfones **1** were determined by ^{1}H NMR using (*R*)-1,1′-bi-2-naphthol as a chiral solvating agent. However, this method could not be directly applied to the β-acetoxyalkyl sulfones **2**, since no separation of the NMR peaks was observed. Therefore, they had to be transformed into the corresponding hydroxy derivatives. Attempts aimed at a straightforward hydrolysis or methanolysis failed, despite the fact that Chinchilla et al.[7] reported successful examples of this particular transformation, albeit with a certain degree of racemization. To accomplish this transformation in a satisfactory manner, we applied a borane/dimethyl sulfide complex, which proved to be very efficient in removing the acetyl group under mild conditions leading to the desired β-hydroxyalkyl sulfones **1** in quantitative yields without any racemization (Scheme 3).



(*R*)-**2** (*R*)-**1**

a: Ar = Ph, R = Me
b: Ar = *p*-Tol, R = Me
c: Ar = *p*-Tol, R = Et

Scheme 3.

3. Conclusions

An efficient dynamic kinetic resolution of racemic β-hydroxyalkyl sulfones has been achieved using lipase mediated acetylation with *p*-chlorophenyl acetate or vinyl acetate as the acyl donors and a ruthenium catalyst for the in situ racemization of the substrate.

4. Experimental

4.1. General

The enzymes were purchased from AMANO or FLUKA. NMR spectra were recorded on Bruker instruments at 200 MHz with $CDCl_3$ or C_6D_6 as solvents. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates. The enantiomeric excess (ee) values were determined by ^{1}H NMR, using (*R*)-1,1′-bi-2-naphthol as a chiral solvating agent. 4-Chlorophenyl acetate was prepared according to the procedure described by Persson et al.[13]

4.2. Synthesis of racemic 1—general procedure

A solution of a corresponding aryl methyl sulfone in THF was cooled to −78 °C. At this temperature, under argon, equimolar amounts of 2.5 M *n*-BuLi and, after 20 min of stirring, the corresponding aldehyde was added. The mixture was stirred and monitored by TLC. After 3 h, 5% aqueous NH_4Cl was added, the solution extracted with chloroform and dried over $MgSO_4$. The solvent was evaporated to yield pure β-hydroxyalkyl sulfone **1**. Other methods of preparation of **1** and their spectral data were described by Crumbie et al.[6]

4.3. Kinetic resolution of 1—general procedure

A mixture of racemic **1** (1 mmol), enzyme (20 mg), vinyl acetate (2 mL) and pyridine (five drops) was stirred in

isopropyl ether (5 mL) and chloroform (1 mL) at 30 °C. The reaction was monitored by TLC and stopped at ca. 50% conversion (after 48 h). The reaction mixture was filtered through a Dowex® 50 W, the solvent then evaporated and the crude mixture separated by column chromatography (ethyl acetate/petroleum ether in gradient from 1:100 to 1:1) to yield β-acetoxy-**2** and unreacted β-hydroxyalkyl sulfone **1**.

4.4. General procedure for the ruthenium and enzyme-coupled dynamic kinetic resolution of 1

Catalyst $[Ru(CO)_4(\mu\text{-}H)(C_4Ph_4\text{–}COHOCC_4Ph_4)]$ **3** (20 mg, 0.02 mmol) and enzyme (40 mg) were added to the mixture of racemic **1** (100 mg, 0.5 mmol), 4-chlorophenyl acetate **4** (250 mg, 1.5 mmol) or vinyl acetate **5** (1 mL) and pyridine (five drops) in toluene (preferably) or benzene (7–10 mL). The reaction was stirred at 30 °C and monitored by TLC. After 72 h, the reaction mixture was filtered through a Dowex® 50 W, the solvent then evaporated and the crude mixture separated by column chromatography (ethyl acetate/petroleum ether 1:1 in gradient from 1:100 to 1:1) or by TLC (ethyl acetate/petroleum ether 1:1) to yield the corresponding β-acetoxyalkyl sulfone **2**.

Acetate **2** was converted to the corresponding β-hydroxyalkyl derivative **1** by reduction with an equimolar amount of $BH_3{\cdot}Me_2S$ in THF (2.0 M), for 1 h at 65 °C. THF was then evaporated, 5% aqueous $KHCO_3$ added and the aqueous layer extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation of the solvent, pure β-hydroxyalkyl sulfone **1** was obtained in quantitative yield.

4.5. Phenyl 1-(2-acetoxy)propyl sulfone 2a

White solid, mp = 87–88 °C; ^{1}H NMR ($CDCl_3$): δ = 1.32 (d, J = 6.4, 3H), 1.74 (s, 3H), 3.17–3.55 (AB, 2H), 5.21–5.30 (m, 1H), 7.51–7.69 (m, 3H), 7.89 (d, J = 8.4, 2H); ^{13}C NMR ($CDCl_3$): δ = 20.29, 20.7, 60.6, 65.1, 128.1, 129.2, 133.8, 139.5, 169.6; MS (CI): *m/z* 243 (M+H); Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.74; H, 5.81; S, 13.47.

4.6. *p*-Tolyl 1-(2-acetoxy)propyl sulfone 2b

White solid, mp = 45–47 °C; ^{1}H NMR ($CDCl_3$): δ = 1.32 (d, J = 6.4, 3H), 1.80 (s, 3H), 2.44 (s, 3H), 3.15–3.53 (AB, 2H), 5.20–5.30 (m, 1H), 7.36 (d, J = 8.0, 2H), 7.78 (d, J = 8.1, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.2, 21.7, 22.56, 61.7, 66.1, 129.1, 130.8, 137.4, 145.8, 170.6; MS (CI): *m/z* 257 (M+H); Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.25; H, 6.25; S, 12.5. Found: C, 56.23; H, 6.22; S, 12.25.

4.7. *p*-Tolyl 1-(2-acetoxy)butyl sulfone 2c

Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 0.82–0.89 (t, 3H), 1.62–1.69 (m, 2H), 1.80 (s, 3H), 2.44 (s, 3H), 3.18–3.48 (AB, 2H), 5.12–5.29 (m, 1H), 7.36 (d, J = 8.5, 2H), 7.77 (d, J = 8.5, 2H); ^{13}C NMR ($CDCl_3$): δ = 10.9, 21.6, 23.1, 27.3, 59.9, 70.0, 129.1, 130.8, 137.4, 145.8, 170.8; MS (CI): *m/z* 271 (M+H); Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.96; H, 6.96; S, 11.73.

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References

1. Simpkins, N. S. *Sulphones in Organic Chemistry*; Pergamon: Oxford, 1993.
2. Tanaka, K.; Ootake, K.; Imai, K.; Tanaka, N.; Kaji, A. *Chem. Lett.* **1983**, 633–634.
3. Solladie, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912–1914.
4. Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Tetrahedron Lett.* **1986**, *27*, 4817–4820.
5. Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1799–1803.
6. Crumbie, R. L.; Deol, B. S.; Nemorin, J. E.; Ridley, D. D. *Aust. J. Chem.* **1978**, *31*, 1965–1980.
7. Chinchilla, R.; Najera, C.; Pardo, J.; Yus, M. *Tetrahedron: Asymmetry* **1990**, *1*, 575–578.
8. Kiełbasiński, P.; Mikołajczyk, M. In *Enzymes in Action: Green Solutions for Chemical Problems*; Zwanenburg, B., Mikołajczyk, M., Kiełbasiński, P., Eds.; Kluwer Academic: Dordrecht, 2000, pp 161–191.
9. Kiełbasiński, P.; Żurawiński, R.; Albrycht, M.; Mikołajczyk, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3379–3383, and references cited therein.
10. Strauss, U. T.; Faber, K. In *Enzymes in Action: Green Solutions for Chemical Problems*; Zwanenburg, B., Mikolajczyk, M., Kielbasinski, P., Eds.; Kluwer Academic: Dordrecht, 2000, pp 1–23.
11. Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321–331.
12. Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417–9476.
13. Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650, and references cited therein.
14. Pamies, O.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 5052–5058.
15. Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037–1040.
16. Pamies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 4815–4818.
17. Theil, F. *Tetrahedron* **2000**, *56*, 2906–2918.
18. Menasche, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885–3891.