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Oxidoreductases Working Together: Concurrent Obtaining of Valuable Derivatives by Employing the PIKAT Method

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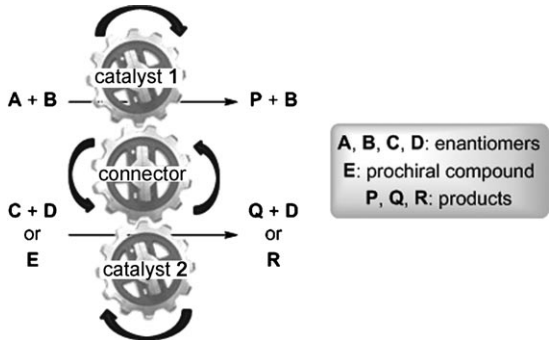
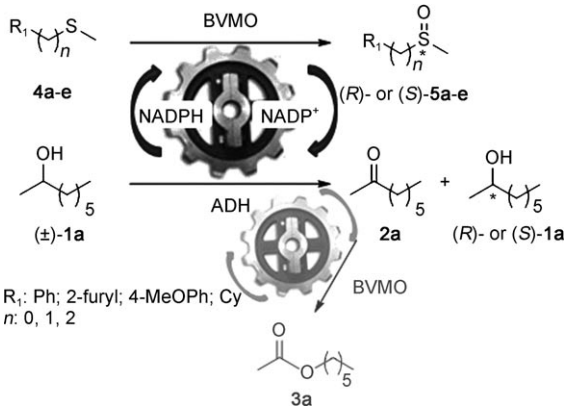
Oxidoreductases are an important class of enzymes that catalyze redox processes, transferring electrons from a reductant to an oxidant.[1] These biocatalysts are widely applied due to their usually exquisite chemo-, regio-, and stereoselectivities through mild and environmentally friendly procedures. Probably the oxidoreductases most often employed are the alcohol dehydrogenases (ADHs, EC 1.1.1.x.), which are able to perform stereoselective carbonyl reductions or enantioselective alcohol oxidations.[2] Another type of redox biocatalysts are Baeyer–Villiger monooxygenases (BVMOs; EC 1.14.13.x.) that catalyze the oxidation of ketones, sulfides, and other heteroatoms by atmospheric oxygen.[3] Besides all the advantages that biocatalyzed oxidations present over chemical methods, the requirement of the expensive nicotinamide NADPH cofactor necessitates effective cofactor regeneration by, for example, chemical, electrochemical, photochemical, or enzymatic methods.[4] The methodology most often exploited is the 'enzyme-coupled' approach, in which a second, preferably irreversible, enzymatic reaction is used to shift the equilibrium towards the desired product.[5] Recently, "designer bugs," whole cells containing the overexpressed genes of the desired enzymes (ADH/BVMO plus enzyme for the recycling system), or "self-sufficient" BVMOs, in which the recycling enzyme has been covalently linked to the monooxygenase, have been developed with very promising results.[6] Nevertheless, such enzyme-coupled transformations depend on a sacrificial coupled reaction which lowers the atom-efficiency environmental factor, *E*,[7] of the overall process.

We have recently developed a system in which two productive redox reactions are connected through internal cofactor recycling.[8] In this manner , it was possible to obtain simultaneously up to three enantioenriched derivatives starting either from two racemic mixtures or a racemate plus a prochiral compound, maximizing the redox efficiency[9] of the whole process and allowing parallel interconnected kinetic asymmetric transformations (PIKAT; Scheme 1).[10] Herein we have broadened the scope of the system combining the stereoselective oxidation of several sulfides with the enantioselective oxidation of different *sec*-alcohols. The cofactor concentration employed in these processes was optimized, which resulted in good performance, even when using micromolar concentrations of the NADP connector.



Scheme 1. Concurrent obtaining of enantioenriched derivatives through parallel interconnected kinetic asymmetric transformation (PIKAT) method.

Firstly, the enzymatic resolution of (±)-2-octanol (**1a**, 2 equivalents) catalyzed by two commercially available ADHs (LBADH from *Lactobacillus brevis*[11] and ADH-T from *Thermoanaerobacter* sp.)[12] was coupled with the sulfoxidation of different sulfides (**4a**–**e**, 1 equivalent) in the presence of the Baeyer–Villiger monooxygenases PAMO from *Thermobifida fusca*,[13] its M446G mutant[14] or HAPMO from *Pseudomonas fluorescens* ACB (Scheme 2).[15] The results are summarized in Table 1. For these reactions, PAMO and M446G were used at 30 °C and HAPMO at 20 °C.[16]



Scheme 2. Use of PIKAT method to oxidize prochiral sulfides **4a**-**e** and (±)-2-octanol, catalyzed by BVMOs and ADHs.

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Table 1. BVMO-catalyzed oxidation of sulfides **4a-e** coupled to the kinetic resolution of (±)-**1a** in the presence of LBADH or ADH-T ($t = 24$ h).[a]

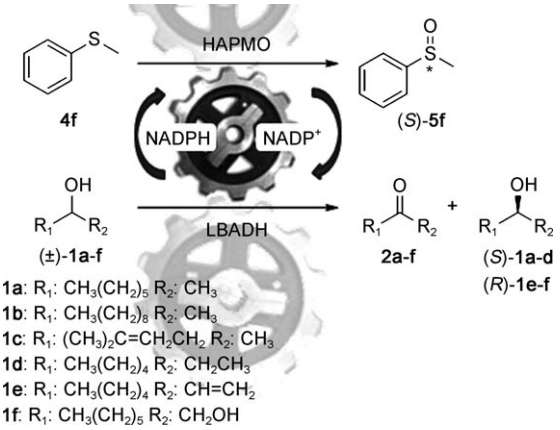
Entry	BVMO	ADH	Sulfide	c [%][b,c]	*ee* [%]		Yield [%]		
					5a–e[d]	**1a**[b]	**1a**[b]	**2a**[b]	**3a**[b]
1	HAPMO	ADH-T	**4a**	59	90 (*S*)	85 (*R*)	54	29	17
2	PAMO	LBADH	**4a**	55	≥99 (*S*)	94 (*S*)	51	27	22
3	HAPMO	ADH-T	**4b**	54	≥99 (*S*)	97 (*R*)	52	26	22
4	M446G	LBADH	**4b**	80	≥99 (*S*)	≥99 (*S*)	50	44	6
5	HAPMO	LBADH	**4c**	46	≥99 (*S*)	≥99 (*S*)	51	26	23
6	HAPMO	ADH-T	**4d**	65	≥99 (*R*)	85 (*R*)	54	36	10
7	PAMO	LBADH	**4d**	58	41 (*S*)	96 (*S*)	51	30	19
8	HAPMO	ADH-T	**4e**	≥99	≥99 (*S*)	97 (*R*)	51	46	3
9	HAPMO	LBADH	**4e**	≥99	≥99 (*S*)	97 (*S*)	51	46	3

[a] For reaction conditions, see the Supporting Information; [b] determined by GC; [c] referred to the quantity of sulfoxide formed; [d] determined by HPLC.

Several aromatic sulfides were combined with **1a** (Table 1, entries 1–5). Thus, benzyl methyl sulfide **4a** (R_1 = Ph, $n = 1$), methyl phenylethyl sulfide **4b** (R_1 = Ph, $n = 2$) and thioanisole derivative **4c** (R_1 = 4-MeO-Ph, $n = 0$), were oxidized to the corresponding sulfoxides (*S*)-**5a–c** with moderate to good conversions and excellent selectivities in the presence of the three BVMOs, whereas LBADH and ADH-T oxidized (*R*)-**1a** and (*S*)-**1a**, respectively, affording ketone **2a**. In most cases, a high amount of ester **3a** was formed due to the BVMO-catalyzed oxidation of **2a** (Scheme 2, gray) leading to an improvement in the optical purity of the remaining alcohol.

We also applied this biocatalytic approach to the concurrent synthesis of enantioenriched **5d** (R_1 = 2-furyl, $n = 1$) and **1a** (Table 1, entries 6 and 7). The use of HAPMO led to enantiopure (*R*)-**5d** whereas (*S*)-**5d** could be obtained with moderate optical purity when using PAMO. Finally, an aliphatic derivative (**4e**; R_1 = cyclohexyl, $n = 0$) was also tested. It yielded sulfoxide (*S*)-**5e** with complete conversion and perfect selectivity using HAPMO (Table 1, entries 8 and 9) whereas enantiopure **1a** was obtained in combination with ADH-T or LBADH.

Next, we explored the PIKAT approach for the concurrent preparation of (*S*)-**5f** and different chiral secondary alcohols. For this study, HAPMO-catalyzed sulfoxidation of thioanisole **4f** was coupled with the oxidative kinetic resolution of several racemic secondary alcohols catalyzed by LBADH (Scheme 3 and Table 2). In all cases, enantiopure (*S*)-**5f** was recovered with good to excellent conversion (71–97%), depending on the alcohol employed. Thus, the use of aliphatic substrates **1a–c** (Table 2, entries 1–3) led to excellent processes affording the remaining enantiopure (*S*)-alcohols. When alcohols in position 3 (**1d–e**) or diol **1f** were selected as substrates, the remaining alcohols were formed with lower enantiomeric excesses (Table 2, entries 4–6) because these oxidations were less favored. The oxidation of (±)-**1f** led to 1-hydroxyoctan-2-one **2f** with complete regioselectivity. β-Tetralol (±)-**1g** was also tested, but no β-tetralone **2g** was formed even after long reaction times (data not shown). As expected, no formation of sulfoxide **5f** was detected, highlighting that both transformations must work in order to achieve an appropriate system.



Scheme 3. LBADH-catalyzed kinetic resolution of racemic alcohols (±)-**1a-f** coupled with the stereoselective sulfoxidation of thioanisole **4f** catalyzed by HAPMO.

Table 2. Concurrent preparation of (*S*)-**5f** and alcohols **1a-f** employing HAPMO and LBADH.[a]

Entry	Alcohol	t [h]	c [%][b,c]	*ee* [%]		Yield [%]		
				5f[d]	**1a–f**[b]	**1a–f**[b]	**2a–f**[b]	**3a–f**[b]
1	(±)-**1a**	24	97	≥99 (*S*)	≥99 (*S*)	50	47	3
2	(±)-**1b**	24	76	≥99 (*S*)	≥99 (*S*)	49	40	11
3	(±)-**1c**	24	97	≥99 (*S*)	≥99 (*S*)	50	50	–
4	(±)-**1d**	48	87	≥99 (*S*)	72 (*S*)	58	42	–
5	(±)-**1e**	48	71	≥99 (*S*)	86 (*R*)[e]	54	37	9
6	(±)-**1f**	48	85	≥99 (*S*)	40 (*R*)[e]	60	40	–

[a] For reaction conditions, see the Supporting Information; [b] determined by GC; [c] referred to the quantity of sulfoxide formed; [d] determined by HPLC; [e] change in Cahn–Ingold–Prelog priority.

For an effective larger-scale application, the optimization of the coenzyme amount is essential. Thus, the kinetic resolution

of (±)-2-octanol **1 a** catalyzed by LBADH, combined with the asymmetric oxidation of thioanisole **4 f** catalyzed by HAPMO, was developed by employing different amounts of the NADP cofactor. The efficiency of the process regarding the cofactor was expressed as (1) the turnover number (TON), that is, moles of product (*S*)-**5 f** formed per mole of cofactor used in the reaction, and as (2) the turnover frequency (TOF), which is the TON per unit of time (Figure 1). The performance of this system was optimal when the cofactor concentration was only 5 μM. At this concentration the efficiency was ten times higher than at 200 μM.

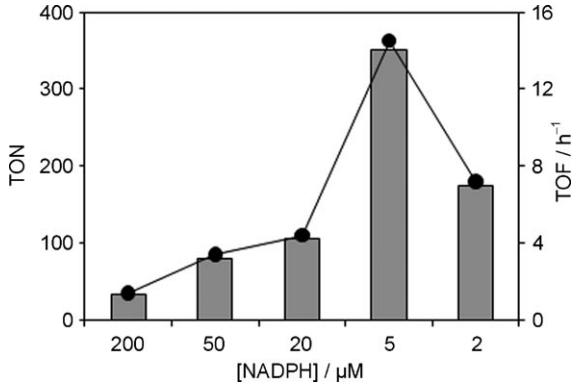


Figure 1. Effect of NADPH concentration on the TON (gray bars) and TOF (black dots) in the concurrent biooxidation of **4 f** and (±)-**1 a**, catalyzed by HAPMO and LBADH.

The cofactor concentration was also optimized when this system was employed for the concurrent kinetic resolution of two racemic substrates. Previously,[10] it has been described that (±)-**1 a** can concurrently be resolved in the presence of (±)-4-phenylhexan-3-one (±)-**6** using LBADH and PAMO in a process presenting excellent selectivity for both enzymatic reactions when employing 200 μM of NADPH concentration (Figure 2). Thus, we were interested in optimizing the NADPH concentration also for this system. Since ketone **6** was a very good substrate for PAMO,[16] even at 1 μM NADPH the coupled resolution worked, showing good possibilities for scaling up the processes. This fact can be explained since the NADPH affinity for PAMO ($K_M = 3$ μM)[13] is much better than that for HAPMO ($K_M = 64$ μM).[15b] The selectivities of both biocatalysts remained unchanged, independent of the employed cofactor concentration.

The combination of biocatalysts to achieve concurrent catalytic processes has garnered increasing interest in the last few years.[17] Recently we described the potential application of parallel interconnected kinetic asymmetric transformations to simultaneously obtain interesting enantioenriched organic compounds. Herein we have broadened the scope of this system, combining the stereoselective oxidation of several sulfides linked to the enantioselective oxidation of different *sec*-alcohols that can be separated using chromatographic techniques. Thus, in contrast to the conventional cofactor-recycling

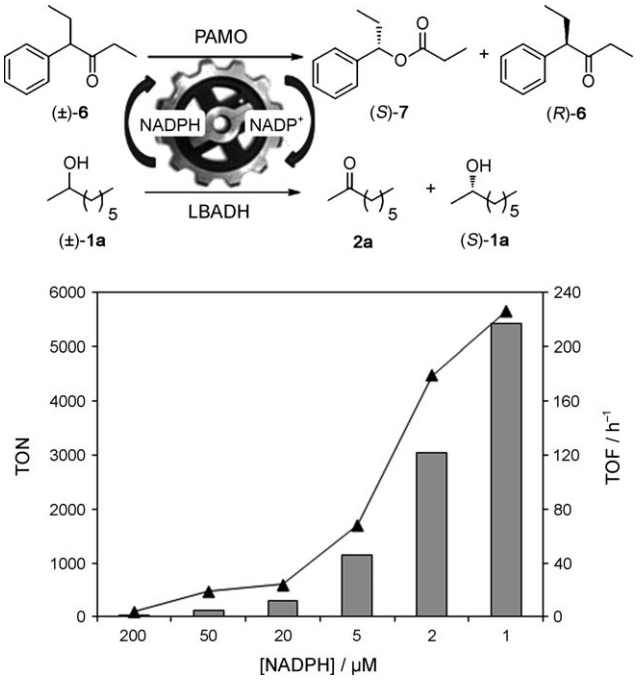


Figure 2. Effect of NADPH concentration on the TON (gray bars) and TOF (black triangles) in the PIKAT transformation of ketone (±)-**6** and alcohol (±)-**1 a**, catalyzed by LBADH and PAMO.

methods, it was possible to obtain in a one-pot process the corresponding enantioenriched sulfoxides[18] and secondary alcohols,[19] which represent valuable chiral building blocks in organic synthesis. Depending on the BVMO affinity towards sulfides, ester derivatives were also obtained due to the acceptance of the aliphatic ketones by these enzymes. Furthermore, we have focused on the cofactor concentration employed in these processes, showing a high performance even at 1–5 μM concentrations. More challenging chemical functionalities might be prepared by this process when broader substrate-accepting enzymes become available.

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Keywords: alcohols · biocatalysis · redox processes · sulfoxides · turnover number

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