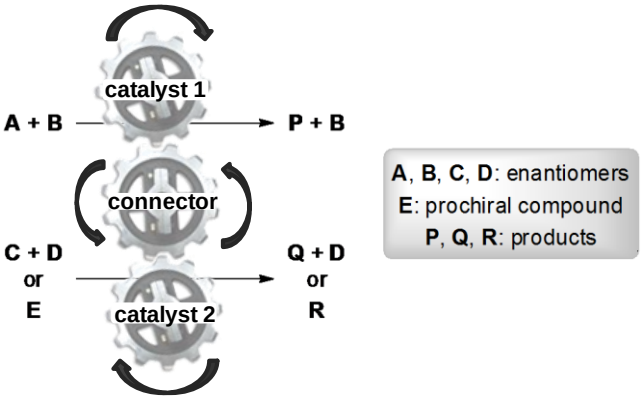
DOI: 10.1002/cctc.200((will be filled in by the editorial staff))

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

Fabricio R. Bisogno,[a] Ana Rioz-Martínez,[a] Cristina Rodríguez,[a] Iván Lavandera,[a] Gonzalo de Gonzalo,[a] Daniel E. Torres Pazmiño,[b] Marco W. Fraaije[b] and Vicente Gotor*[a]

Oxidoreductases are an important class of enzymes that catalyse 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 protocols. 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 catalyse the oxidation of ketones, sulfides and other heteroatoms employing atmospheric oxygen.[3] Besides all the advantages that biocatalysed oxidations present over chemical methods, the requirement of the expensive nicotinamide NADPH cofactor neccesitates effective cofactor regeneration by e.g. chemical, electrochemical, photochemical or enzymatic methods.[4] The methodology most often exploited is the 'enzyme-coupled' approach in which a second (and 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, where the coenzyme 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 *via* internal cofactor recycling.[8] By this, it was possible to obtain simultaneously up to three enantioenriched derivatives starting either from two racemic mixtures or a racemate plus a prochiral compound, maximising 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 using micromolar concentrations of the NADP connector.



Scheme 1. Concurrent obtaining of enantioenriched derivatives through PIKAT methodology.

Firstly, the enzymatic resolution of (±)-2-octanol (**1a**, 2 equiv.) catalysed by two commercially available ADHs (LBADH from *Lactobacillus brevis*[11] and ADH-T from *Thermoanaerobacter* sp.)[12] was coupled to the sulfoxidation of different sulfides (**4a-e**, 1 equiv.) 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 summarised in Table 1. For these reactions PAMO and M446G were used at 30ºC and HAPMO at 20ºC.[16]

[a] *F. R. Bisogno, A. Rioz-Martínez, C. Rodríguez, Dr. I. Lavandera, Dr. G. de Gonzalo, Prof. Dr. V. Gotor*
Departamento de Química Orgánica e Inorgánica
Instituto Universitario de Biotecnología de Asturias, Universidad de Oviedo
C/ Julián Clavería 8, 33006 Oviedo, Spain
Fax: (+34) 985 103448
E-mail: vgs@fq.uniovi.es
[b] *Dr. D. E. Torres Pazmiño, Prof. Dr. M. W. Fraaije*
Laboratory of Biochemistry
Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen
Nijenborgh 4, 9747 AG Groningen, The Netherlands

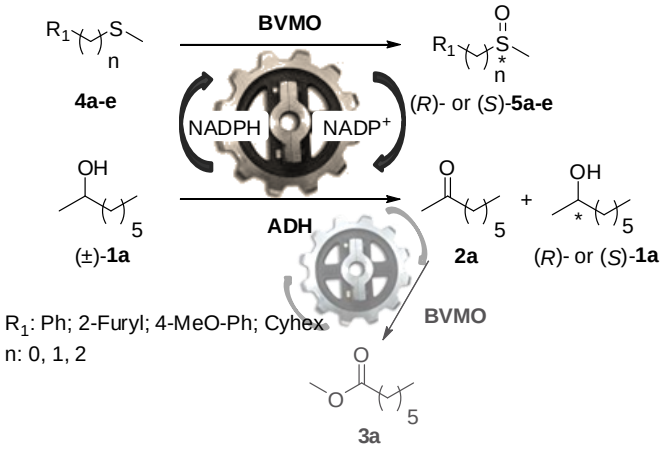
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.200xxxxxx.

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

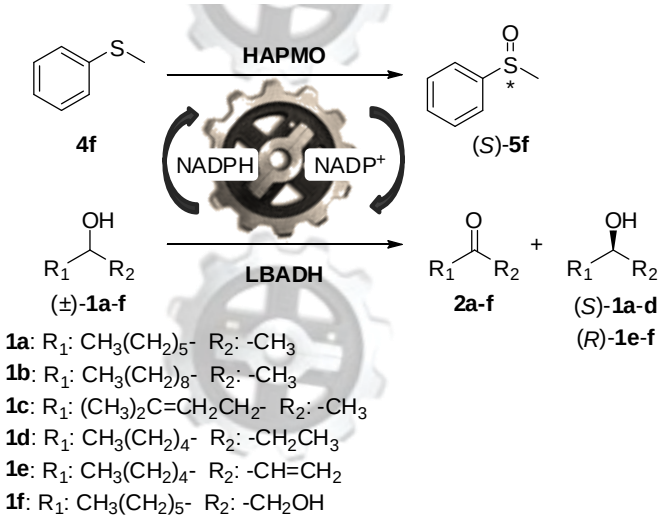
[a] For reaction conditions, see Supporting Information. [b] Determined by GC. [c] Referred to the quantity of sulfoxide formed. [d] Determined by HPLC.

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



Scheme 2. Parallel interconnected kinetic asymmetric transformation combining prochiral sulfides **4a**-**e** and (±)-2-octanol catalysed by BVMOs and ADHs.

We also applied this biocatalytic approach to the concurrent synthesis of enantioenriched **5d** (R_1=2-furyl, n=1) and **1a** (entries 6 and 7). The use of HAPMO led to enantiopure (*R*)-**5d** while (*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 which yielded sulfoxide (*S*)-**5e** with complete conversion and perfect selectivity using HAPMO (entries 8 and 9) while enantiopure **1a** was obtained in combination with ADH-T or LBADH.



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

Next, we explored the PIKAT approach for the concurrent resolution of (±)-**1a** and the preparation of different chiral sulfoxides. For this, HAPMO-catalysed sulfoxidation of thioanisole **4f** was coupled with the oxidative kinetic resolution of several racemic secondary alcohols catalysed by LBADH, as shown in Scheme 3 and Table 2. In all cases, enantiopure (*S*)-**5f** was recovered with good to excellent conversions (71-97%) depending on the alcohol employed. Thus, the use of aliphatic substrates **1a**-**c** (entries 1-3) led to excellent processes obtaining the remaining enantiopure (*S*)-alcohols. When alcohols in position 3 (**1d**-**e**) or diol **1f** were selected as substrates, the remaining alcohols were achieved with lower enantiomeric excesses (entries 4-6) because these oxidations were less favoured, 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** formation was observed 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.

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

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

[a] For reaction conditions, see 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 (CIP).

For an effective larger-scale application, the optimisation of the coenzyme amount is essential. Thus, the kinetic resolution of (±)-2-octanol **1a** catalysed by LBADH, combined with the asymmetric oxidation of thioanisole **4f** catalysed 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), this is moles of product (*S*)-**5f** formed per mol of cofactor used in the reaction, and as (2) the turnover frequency (TOF), which is the TON per unit of time (Figure 1). As can be seen, the performance of this system was maximal when the cofactor concentration was only 5 μM. At this concentration the efficiency is 10-fold higher than at 200 μM.

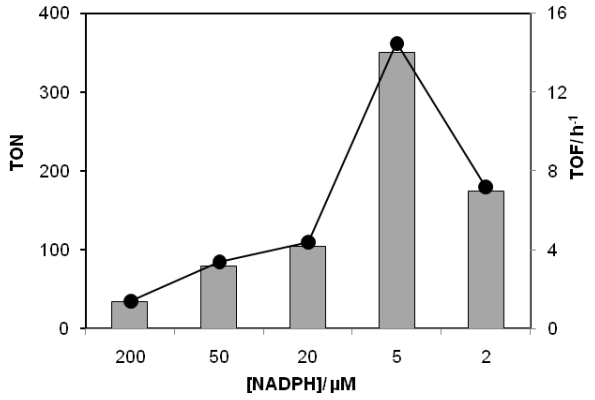


Figure 1. Effect of NADPH concentration on the TON (grey bars) and TOF (black dots) in the concurrent biooxidation of **4f** and (±)-**1a** employing HAPMO and LBADH.

The cofactor concentration was also optimised when this system was employed for the concurrent kinetic resolution of two racemic substrates. Previously,[10] it has been described that (±)-**1a** 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 optimising 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 for HAPMO (K_M=64 μM).[15b] It is worth noting that the selectivities of both biocatalysts remained unchanged independent of the employed cofactor concentration.

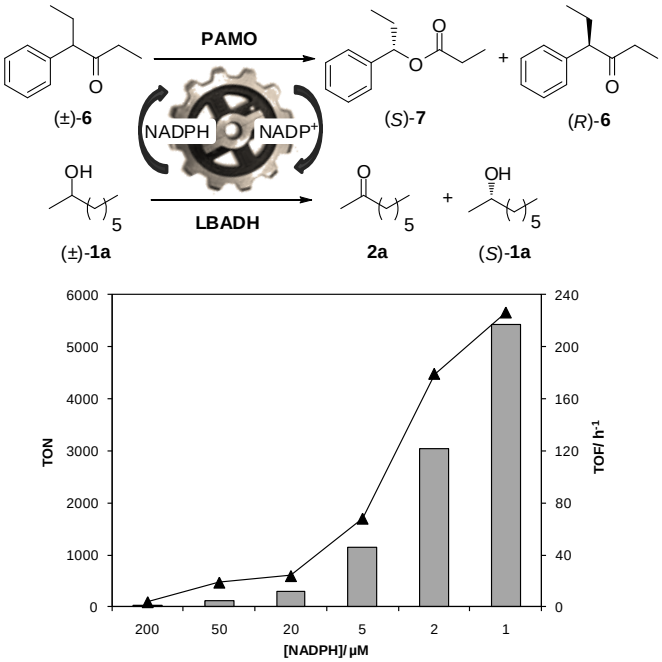


Figure 2. Effect of NADPH concentration on the TON (grey bars) and TOF (black triangles) in the PIKAT transformation of ketone (±)-**6** and alcohol (±)-**1a** using LBADH and PAMO.

The combination of biocatalysts to achieve concurrent catalytic processes is gaining more relevance in the last few years.[17] Recently we described the potential application of parallel interconnected kinetic asymmetric transformations in order 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 methodologies, 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 micromolar concentrations. More challenging chemical functionalities might be prepared by this process when broader substrate-accepting enzymes become available.

Acknowledgements

F.R.B. is supported by the Programme Alβan, the European Union Program of High Level Scholarships for Latin America (scholarship No. E07D402519AR). A.R.-M. (FPU program) thanks the Spanish Ministerio de Ciencia e Innovación (MICINN) for her predoctoral fellowship which is financed by the European Social Fund. C.R. thanks the Principado de Asturias for her predoctoral fellowship. I.L. (Ramón y Cajal Program) and G.d.G. (Juan de la Cierva Program) thank MICINN for personal funding. Financial support from MICINN (Project CTQ2007-61126) is gratefully acknowledged. We thank John K. Chondhu for his technical assistance. M.W.F. and D.E.T.P. receive support from the EU-FP7 "Oxygreen" project.

Keywords: biocatalysis redox processes turnover number alcohols sulfoxides

[1] a) *Modern Biooxidation. Enzymes, Reactions and Applications*; R. D. Schmid, V. B. Urlacher, Eds.; Wiley-VCH, Weinheim, **2007**; b) K. Faber, *Biotransformations in Organic Chemistry*; 5th ed., Springer, Berlin, **2004**.

[2] Recent bibliography: a) K. Nakamura, T. Matsuda, in *Asymmetric Organic Synthesis with Enzymes*; V. Gotor, I. Alfonso, E. García-Urdiales, Eds.; Wiley-VCH, Weinheim, **2008**, pp 193-228; b) S. Buchholz, H. Gröger, in *Biocatalysis in the Pharmaceutical and Biotechnology Industry*; R. N. Patel, Ed.; CRC Press, Boca Raton, **2007**, pp 757-790; c) S. M. A. de Wildeman, T. Sonke, H. E. Schoemaker, O. May, *Acc. Chem. Res.* **2007**, *40*, 1260-1266; d) J. C. Moore, D. J. Pollard, B. Kosjek, P. N. Devine, *Acc. Chem. Res.* **2007**, *40*, 1412-1419; e) K. Goldberg, K. Schroer, S. Lütz, A. Liese, *Appl. Microbiol. Biotechnol.* **2007**, *76*, 237-248; f) W. Kroutil, H. Mang, K. Edegger, K. Faber, *Adv. Synth. Catal.* **2004**, *346*, 125-142; g) W. Kroutil, H. Mang, K. Edegger, K. Faber, *Curr. Opin. Chem. Biol.* **2004**, *8*, 120-126.

[3] a) M. M. Kayser, *Tetrahedron* **2009**, *65*, 947-974; b) D. E. Torres Pazmiño, M. W. Fraaije in *Future Directions in Biocatalysis*; T. Matsuda, Ed.; Elsevier, Dordrecht, **2007**, pp 107-127; c) M. W. Fraaije, D. B. Janssen, in *Modern Biooxidation. Enzymes, Reactions and Applications*; R. D. Schmid, V. B. Urlacher, Eds.; Wiley-VCH, Weinheim, **2007**, pp 77-97; d) M. D. Mihovilovic, *Curr. Org. Chem.* **2006**, *10*, 1265-1287; e) N. M. Kamerbeek, D. B. Janssen, J. H. Van Berkel, M. W. Fraaije, *Adv. Synth. Catal.* **2003**, *345*, 667-678; f) M. D. Mihovilovic, B. Müller, P. Stanetty, *Eur. J. Org. Chem.* **2002**, 3711-3730.

[4] Recent examples: a) J. Liang, J. Lalonde, B. Borup, V. Mitchell, E. Mundorff, N. Trinh, D. A. Kochrekar, R. N. Cherat, G. G. Pai, *Org. Process Res. Dev.* **2010**, *14*, 193-198; b) M. M. Grau, J. C. van der Toorn, L. G. Otten, P. Macheroux, A. Taglieber, F. E. Zilly, I. W. C. E. Arends, F. Hollmann, *Adv. Synth. Catal.* **2009**, *351*, 3279-3286; c) M. Kurina-Sanz, F. R. Bisogno, I. Lavandera, A. A. Orden, V. Gotor, *Adv. Synth. Catal.* **2009**, *351*, 1842-1848; d) S. Aksu, I. W. C. E. Arends, F. Hollmann, *Adv. Synth. Catal.* **2009**, *351*, 1211-1216; e) F. Hildebrand, S. Lütz, *Chem. Eur. J.* **2009**, *15*, 4998-5001; f) S. H. Lee, D. H. Nam, J. H. Kim, J.-O. Baeg, C. B. Park, *ChemBioChem* **2009**, *10*, 1621-1624; g) M. M. Musa, N. Lott, M. Laivenieks, L. Watanabe, C. Vieille, R. S. Phillips, *ChemCatChem* **2009**, *1*, 89-93; h) M. Katzberg, K. Wechler, M. Müller, P. Dünkelmann, J. Stohrer, W. Hummel, M. Bertau, *Org. Biomol. Chem.* **2009**, *7*, 304-314; i) I. Lavandera, A. Kern, M. Schaffenberger, J. Gross, A. Glieder, S. de Wildeman, W. Kroutil, *ChemSusChem* **2008**, *1*, 431-436.

[5] Recent bibliography: a) J. Liang, E. Mundorff, R. Voladri, S. Jenne, L. Gilson, A. Conway, A. Krebber, J. Wong, G. Huisman, S. Truesdell, J. Lalonde, *Org. Process Res. Dev.* **2010**, *14*, 188-192; b) H. Ankati, D. Zhu, Y. Yang, E. R. Biehl, L. Hua, *J. Org. Chem.* **2009**, *74*, 1658-1662; c) S. Broussy, R. W. Cheloha, D. B. Berkowitz, *Org. Lett.* **2009**, *11*, 305-308; d) A. Rioz-Martínez, G. de Gonzalo, D. E. Torres Pazmiño, M. W. Fraaije, V. Gotor, *Eur. J. Org. Chem.* **2009**, 2526-2532; e) C. Rodríguez, G. de Gonzalo, D. E. Torres Pazmiño, M. W. Fraaije, V. Gotor, *Tetrahedron: Asymmetry* **2009**, *20*, 1168-1173; f) H. Ankati, Y. Yang, D. Zhu, E. R. Biehl, L. Hua, *J. Org. Chem.* **2008**, *73*, 6433-6436; g) B. Kosjek, J. Nti-Gyabaah, K. Telari, L. Dunne, J. C. Moore, *Org. Process Res. Devel.* **2008**, *12*, 584-588; h) I. Lavandera, A. Kern, B. Ferreira-Silva, A. Glieder, S. de Wildeman, W. Kroutil, *J. Org. Chem.* **2008**, *73*, 6003-6005; i) M. D. Mihovilovic, P. Kapitan, P. Kapitánová, *ChemSusChem* **2008**, *1*, 143-148; j) C. Rodríguez, G. de Gonzalo, D. E. Torres Pazmiño, M. W. Fraaije, V. Gotor, *Tetrahedron: Asymmetry* **2008**, *19*, 197-203.

[6] a) D. E. Torres Pazmiño, A. Riebel, J. de Lange, F. Rudroff, M. D. Mihovilovic, M. W. Fraaije, *ChemBioChem* **2009**, *10*, 2595-2598; b) D. E. Torres Pazmiño, R. Snajdrova, B.-J. Baas, M. Ghobrial, M. D. Mihovilovic, M. W. Fraaije, *Angew. Chem.* **2008**, *120*, 2307-2310; *Angew. Chem. Int. Ed.* **2008**, *47*, 2275-2278; c) T. Ema, S. Ide, N. Okita, T. Sakai, *Adv. Synth. Catal.* **2008**, *350*, 2039-2044; d) H. Gröger, C. Rollmann, F. Chamouleau, I. Sebastien, O. May, W. Wienand, K. Drauz, *Adv. Synth. Catal.* **2007**, *349*, 709-712; e) H. Gröger, F. Chamouleau, N. Orologas, C. Rollmann, K. Drauz, W. Hummel, A. Weckbecker, O. May, *Angew. Chem.* **2006**, *118*, 5806-5809; *Angew. Chem. Int. Ed.* **2006**, *45*, 5677-5681.

[7] a) R. A. Sheldon, *Pure Appl. Chem.* **2000**, *72*, 1233-1246; b) B. M. Trost, *Science* **1991**, *254*, 1471-1477.

[8] There are other examples where a BVMO and an ADH were combined to achieve cofactor recycling: a) F. Zambianchi, P. Pasta, G. Carrea, S. Colonna, N. Gaggero, J. M. Woodley, *Biotechnol. Bioeng.* **2002**, *78*, 489-496; or cascade processes: b) A. J. Willetts, C. J. Knowles, M. S. Levitt, S. M. Roberts, H. Sandey, N. F. Shipston, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1608-1610; c) R. Gagnon, G. Grogan, S. M. Roberts, R. Villa, A. J. Willetts, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1505-1511.

[9] N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896-2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.

[10] A. Rioz-Martínez, F. R. Bisogno, C. Rodríguez, G. de Gonzalo, I. Lavandera, D. E. Torres Pazmiño, M. W. Fraaije, V. Gotor, *Org. Biomol. Chem.* **2010**, *8*, 1431-1437.

[11] This (*R*)-selective enzyme shows a high preference for NADPH/$NADP^+$. See, for instance: M. Wolberg, W. Hummel, C. Wandrey, M. Müller, *Angew. Chem.* **2000**, *112*, 4476-4478; *Angew. Chem. Int. Ed.*, **2000**, *39*, 4306-4308.

[12] This (*S*)-selective biocatalyst shows a clear preference for NADPH/$NADP^+$. See: Z. Findrik, D. Vasić-Racki, S. Lütz, T. Daussmann, C. Wandrey, *Biotechnol. Lett.* **2005**, *27*, 1087-1095.

[13] M. W. Fraaije, J. Wu, D. P. H. M. Heuts, E. W. van Hellemond, J. H. Lutje Spelberg, D. B. Janssen, *Appl. Microbiol. Biotechnol.* **2005**, *66*, 393-400.

[14] D. E. Torres Pazmiño, R. Snajdrova, D. V. Rial, M. D. Mihovilovic, M. W. Fraaije, *Adv. Synth. Catal.* **2007**, *349*, 1361-1369.

[15] a) N. M. Kamerbeek, A. J. J. Olsthoorn, M. W. Fraaije, D. B. Janssen, *Appl. Environ. Microbiol.* **2003**, 419-426; b) N. M. Kamerbeek, M. J. H. Moonen, J. G. M. van der Ven, W. J. H. van Berkel, M. W. Fraaije, D. B. Janssen, *Eur. J. Biochem*. **2001**, *268*, 2547-2557.

[16] C. Rodríguez, G. de Gonzalo, M. W. Fraaije, V. Gotor, *Tetrahedron: Asymmetry* **2007**, *18*, 1338-1344.

[17] Recent examples: a) V. Resch, W. M. F. Fabian, W. Kroutil, *Adv. Synth. Catal.* **2010**, *352*, 993-997; b) F. R. Bisogno, I. Lavandera, W. Kroutil, V. Gotor, *J. Org. Chem.* **2009**, *74*, 1730-1732; c) C. V. Voss, C. C. Gruber, K. Faber, T. Knaus, P. Macheroux, W. Kroutil, *J. Am. Chem. Soc.* **2008**, *130*, 13969-13972; d) C. V. Voss, C. C. Gruber, W. Kroutil, *Angew. Chem.* **2008**, *120*, 753-757; *Angew. Chem. Int. Ed.* **2008**, *47*, 741-745; e) B. Boonstra, D. A. Rathbone, C. E. French, E. H. Walker, N. C. Bruce, *Appl. Environ. Microbiol.* **2000**, *66*, 5161-5166.

[18] a) M. C. Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun*. **2009**, 6129-6144; b) H. Pellissier, *Tetrahedron* **2006**, *62*, 5559-5601; c) J. Legros, J. R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19-31.

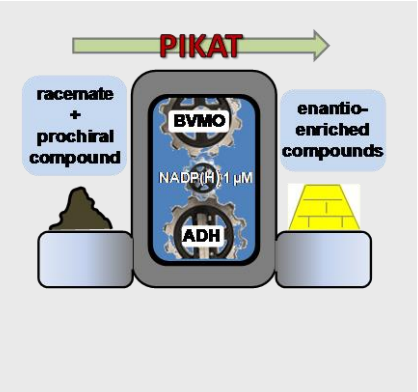
[19] M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kesseler, R. Stürmer, T. Zelinski, *Angew. Chem.* **2004**, *116*, 806-843; *Angew. Chem. Int. Ed.* **2004**, *43*, 788-824.

Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

Entry for the Table of Contents

COMMUNICATION

Combination of the stereoselective oxidation of several sulfides linked to the enantioselective oxidation of different *sec*-alcohols in a parallel interconnected kinetic asymmetric transformation fashion is shown. Furthermore, we focus on the cofactor concentration employed in these processes, demonstrating a high capacity of performance even at micromolar concentrations of the mediator



*Fabricio R. Bisogno, Ana Rioz-Martínez, Cristina Rodríguez, Iván Lavandera, Gonzalo de Gonzalo, Daniel E. Torres-Pazmiño, Marco W. Fraaije and Vicente Gotor**

Page No. – Page No.

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