DOI: 10.1002/ejoc.201000890

Enzymatic Synthesis of Novel Chiral Sulfoxides Employing Baeyer–Villiger Monooxygenases

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Keywords: Biocatalysis / Monooxygenases / Oxidation / Sulfur / Enantioselectivity

Optically active sulfoxides are compounds of high interest in organic chemistry. Herein, we report the preparation of a set of chiral heteroaryl alkyl, cyclohexyl alkyl, and alkyl alkyl sulfoxides by using enantioselective sulfoxidation reactions employing three Baeyer–Villiger monooxygenases (BVMOs). Careful selection of the reaction conditions, starting sulfide, and biocatalyst can be used to achieve good to excellent enantiomeric excess values. Thus, valuable chiral synthons can be obtained by performing the reactions under mild and environmentally friendly conditions. The most promising biotransformations that employ a BVMO cell-free extract preparation have been developed on a 250-mg scale to give the chiral sulfoxides in high yields in most of the reactions.

Introduction

There are several examples of synthetic chiral sulfoxide targets, as many molecules with high biological activity contain the sulfinyl group with a defined configuration.[1] The increasing interest in these compounds extends even further than the molecules themselves into their use as chiral catalysts in chemistry.[2] Thus, the chirality of organic sulfoxides has been widely exploited in organic synthesis: enantiopure sulfoxides are important auxiliaries in asymmetric synthesis as well as chiral ligands in enantioselective catalysis. This is mainly due to their availability, high asymmetric induction, and the fact that chiral sulfoxides that induce optical activity can be removed from the target compound easily under mild conditions. Optically active heteroaryl alkyl sulfoxides offer an advantage over other sulfoxides by exhibiting chelating properties that present a potential interest in asymmetric synthesis.

Methods currently available to obtain the molecules of interest include: kinetic resolution of racemic sulfoxides by reduction or oxidation processes,[3] asymmetric oxidation of prochiral sulfides by employing different oxidants,[4] or the nucleophilic addition of different ligands to diastereochemically pure chiral sulfinates.[4a,5]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000890.

In the last few years, biocatalysis has emerged as a valuable synthetic tool for the preparation of high added-value compounds.[6] Some of the advantages of biocatalytic methods are that enzymes can afford high efficiencies and regio- and/or enantioselectivities working under mild reaction conditions and an increasing applicability due to the recent advances in biotechnology. There are two major groups of enzymes that can be used for the oxidation of prochiral sulfides to the corresponding optically active sulfoxides: peroxidases[7] and monooxygenases.[8] This latter family of enzymes catalyzes the transfer of one oxygen atom from molecular oxygen to an organic substrate by using various cofactors for the oxidative processes.

Baeyer–Villiger monooxygenases (BVMOs) are nicotinamide cofactor dependent flavoproteins able to perform the oxidation of carbonyl compounds (the Baeyer–Villiger oxidation) and the oxygenation of different heteroatoms, including sulfur.[9] Thus, BVMOs have been described in the enantioselective oxidation of sulfides, dithianes, sulfites, and racemic sulfoxides.[10] In the last few years, several BVMOs have been described and applied in biocatalytic processes.[11] Two well-known examples are phenylacetone monooxygenase (PAMO)[12] and 4-hydroxyacetophenone monooxygenase (HAPMO),[13] which are primarily active on aromatic compounds. Recently, mutagenesis studies have allowed the preparation of PAMO mutant (M-PAMO) that has shown a different substrate profile when compared to the wild-type.[14]

In previous work, the PAMO- and HAPMO-catalyzed oxidation of aryl alkyl sulfides gave high selectivities depending on the nature of the substrate and the biocatalyst employed.[15] Whereas PAMO was able to catalyze the oxidation of benzyl alkyl sulfides, HAPMO preferred to oxidize thioanisole derivatives. Herein, we describe the use of a

biocatalytic methodology for the preparation of different heteroaryl, cyclohexyl, alkyl, and cyclic sulfoxides by employing Baeyer–Villiger monooxygenases.

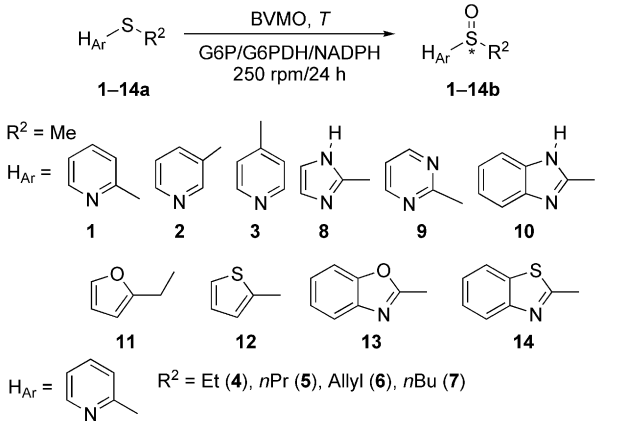
Results and Discussion

Unless otherwise stated, all enzymatic sulfoxidations were performed with purified enzymes. A second enzymatic system, glucose-6-phosphate/glucose-6-phosphate dehydrogenase, was used to regenerate the nicotinamide cofactor NADPH.[16]

BVMO-Catalyzed Oxidation of Heteroaryl Alkyl Sulfides

Initially, our experiments were devoted to the preparation of pyridine methyl sulfoxides containing the nitrogen atom at the 2-, 3-, or 4-position by employing the three available BVMOs. Reactions were performed in Tris-HCl 50 mM buffer (pH 9.0) at 30 °C for the two PAMO enzymes (PAMO and M-PAMO) and at 20 °C for HAPMO.[17] After 24 h, it was observed that HAPMO was able to catalyze the enzymatic sulfoxidation of the three derivatives with moderate to high conversions and excellent enantiomeric excess values. The best substrate for this enzyme was 2-(methylthio)pyridine (**1a**), as it was possible to obtain the corresponding enantiopure (*S*)-sulfoxide **1b** with complete conversion (Table 1, Entry 1). The use of substrates containing the nitrogen atom further away from the methylthio group led to lower conversions. Thus, (*S*)-3-(methylsulfinyl)pyridine (**2b**) was obtained with 95% conversion (*c*), whereas 4-(methylthio)pyridine (**3a**) was less effectively oxidized to the (*R*)-sulfoxide (*c* = 63%; Table 1, Entries 2 and 3, respectively). When wildtype PAMO and its M446G mutant were employed in the oxidation of these substrates, only (*R*)-3-(methylsulfinyl)pyridine was obtained, whereas compounds **1a** and **3a** showed no reactivity. The sulfoxidation performed in the presence of M-PAMO led to the formation of (*R*)-**2b** with 54% conversion and 88%*ee* (Table 1, Entry 4), whereas PAMO showed a lower activity (*c* = 26%) and selectivity (39%*ee*). It is important to highlight that both enantiomers of sulfoxide **2b** can be obtained with good to excellent optical purities by simply modifying the biocatalyst employed, as HAPMO displays opposite enantiopreference to PAMO enzymes. Due to the excellent results obtained in the HAPMO-catalyzed oxidation of **1a**, we decided to analyze the effect of the alkyl chain on the oxidation of the 2-pyridine derivative. This enzyme was able to catalyze the sulfoxidation of the ethyl, *n*-propyl, and allyl sulfides with complete enantioselectivity. Enantiopure (*S*)-2-(ethylsulfinyl)pyridine (**4b**) can be synthesized with total conversion after 24 h (Table 1, Entry 6). When the length of the alkyl chain was extended to a propyl group, enantiopure (*S*)-**5b** was recovered with a strong decrease in the enzymatic activity (*c* = 11%). This trend has been described previously for this biocatalyst in the oxidation of thioanisole derivatives.[15b] As depicted in Table 1, the oxidation of 2-(allylthio)pyridine (**6a**) led to (*S*)-**6b** with 99%*ee* and low conversion (*c* = 23%; Table 1, Entry 8). It seems that the presence of a double bond had a positive effect on HAPMO activity as compared to that observed for the propyl group. Finally, 2-(butylthio)pyridine (**7a**) was not oxidized by HAPMO. The 2-(alkylthio)pyridines were also tested in presence of PAMO and M-PAMO. Surprisingly, M-PAMO was able to transform sulfide **4a** into (*R*)-2-(ethylsulfinyl)-pyridine (**4b**) with 13% conversion and 76%*ee* after 24 h (Table 1, Entry 10). Again, this biocatalyst showed an opposite enantiopreference with respect to HAPMO. For all the BVMO-catalyzed oxidations, only small amounts (less than 8%) of sulfone formed by the over-oxidation of the obtained sulfoxide were detected for some substrates. This indicates that this second oxidation step could not influence the optical purity of the final sulfoxides to a great extent when starting from the prochiral sulfides. The BVMOs were also tested in the biooxidation of other nitrogen-containing heterocyclic sulfides such as 2-(methylthio)-1*H*-imidazole (**8a**), 2-(methylthio)pyrimidine (**9a**), and 2-(methylthio)-1*H*-

Table 1. BVMO-catalyzed oxidation of heteroaryl sulfides **1**–**14a**.[a]



Entry	Substrate	Enzyme	*c* [%][b]	*ee* [%][c]
1	**1a**	HAPMO	≥99	≥99 (*S*)
2	**2a**	HAPMO	95	≥99 (*S*)[d]
3	**3a**	HAPMO	63	≥99 (*R*)[d]
4	**2a**	M-PAMO	54	88 (*R*)[d]
5	**2a**	PAMO	26	39 (*R*)[d]
6	**4a**	HAPMO	≥99	≥99 (*S*)[d]
7	**5a**	HAPMO	11	≥99 (*S*)
8	**6a**	HAPMO	23	≥99 (*S*)[d]
9	**7a**	HAPMO	≤3	–
10	**4a**	M-PAMO	13	76 (*R*)[d]
11	**11a**	HAPMO	69	≥99 (*R*)[e]
12	**11a**	PAMO	92	81(*S*)[e]
13	**11a**	M-PAMO	64	25 (*S*)[e]
14	**12a**	HAPMO	71	≥99 (*S*)[e]
15	**12a**	PAMO	22	34 (*R*)[e]
16	**12a**	M-PAMO	7	–

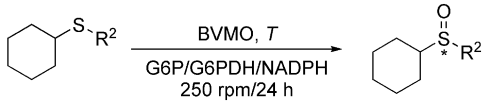
[a] For reaction conditions, see the Experimental Section. [b] Determined by using GC. [c] Determined by using HPLC, except for sulfoxide **2b**, which was determined by using GC. [d] Absolute configurations determined by comparison of the retention times for these compounds with those obtained in the asymmetric sulfoxidation of **2**–**4a** and **6a** by using the Kagan methodology. [e] Absolute configurations determined by comparison of the HPLC times with those published.

benzo[*b*]imidazole (**10a**), but no reaction was observed after long reaction times even after modification of some of the reaction parameters such as pH or temperature.[17,18] Finally, the heteroaryl oxygenated substrate 2-furfuryl methyl sulfide (**11a**) was oxidized in the presence of the three BVMOs. Enantiopure (*R*)-**11b** was obtained by employing HAPMO (Table 1, Entry 11), whereas the use of the two PAMO enzymes led to lower *ee* values in the preparation of the opposite enantiomer, especially when using M-PAMO. Compound (*S*)-**11b** can be achieved with high conversion and 81%*ee* by using PAMO (Table 1, Entry 12). A sulfur-containing heteroaryl sulfide such as 2-(methylthio)thiophene (**12a**) was also analyzed. HAPMO was able to transform **12a** into enantiopure sulfoxide (*S*)-**12b** with good conversion after 24 h, whereas PAMO showed lower activity and selectivity in the preparation of the opposite enantiomer, (*R*)-**12b** (*c* = 22% and 34%*ee*; Table 1, Entry 15). Its M446G mutant catalyzed the sulfoxidation with a very low activity (Table 1, Entry 16). Finally, none of the enzymes catalyzed the oxidation of benzo-fused derivatives **13a** and **14a**, oxygen- and sulfur-containing analogs of benzoimidazole **10a**.

Biocatalyzed Oxidation of Cyclohexyl Alkyl Sulfides

Both PAMO and HAPMO have been described as BVMOs that are primarily active on aromatic compounds.[15] We decided to extend the substrate range by testing nonaromatic sulfides. Initially, the biooxidation of different cyclohexyl alkyl sulfides was analyzed upon incubation with HAPMO, PAMO, and its mutant. As shown in Table 2, HAPMO was able to catalyze the sulfoxidation of cyclohexyl methyl sulfide (**15a**) and cyclohexyl ethyl sulfide (**16a**) to the corresponding (*S*)-sulfoxides with total conversion and excellent enantiomeric excess values after 1 d (Table 2, Entries 1 and 2). PAMO yielded (*S*)-cyclohexyl methyl sulfoxide (**15b**) after 24 h with 96% conversion and moderate optical purity (35%*ee*; Table 2, Entry 3), whereas this biocatalyst was not able to oxidize the ethyl derivative. Reactions performed in the presence of M-PAMO led to sulfoxide (*S*)-**15b** with moderate conversion and enantiomeric excess, whereas (*S*)-**16b** was obtained after 24 h with only 19% conversion and 31%*ee*. As expected from the previous results, M-PAMO was able to catalyze the oxidation of **16a** for which PAMO did not show activity due to the larger active site of the former. Cyclohexyl propyl sulfide (**17a**) was also subjected to BVMO-catalyzed sulfoxidation, but no reaction was detected in the presence of the three biocatalysts, indicating that the propyl group limits the activity of these enzymes when oxidizing cyclohexyl derivatives.

Table 2. Biocatalyzed oxidation of cyclohexyl alkyl sulfides **15**–**17a**.[a]



15–17a **15–17b**

R^2 = Me (**15**), Et (**16**), *n*Pr (**17**)

Entry	Substrate	Enzyme	*c* [%][b]	*ee* [%][c]
1	**15a**	HAPMO	≥99	≥99(*S*)
2	**16a**	HAPMO	≥99	96(*S*)[d]
3	**15a**	PAMO	96	35(*S*)
4	**16a**	PAMO	5	–
5	**15a**	M-PAMO	67	49(*S*)
6	**16a**	M-PAMO	19	31(*S*)[d]

[a] For reaction conditions, see the Experimental Section. [b] Determined by using GC. [c] Determined by using HPLC. [d] Absolute configuration was determined by comparing the retention times on HPLC for this compound with those obtained in the asymmetric sulfoxidation of **16a** by using the Kagan methodology.

The effect of pH on the enzymatic sulfoxidation of **15a** catalyzed by the three BVMOs was analyzed (Figure 1). HAPMO was able to catalyze the oxidation of **15a** with complete conversion and high enantiomeric excess regardless of the pH values studied (even at pH 10.5). For both PAMO enzymes, the optimum pH for sulfoxidation activity ranged from 9.0 to 10.0. Concerning the enzymatic selectivity, (*S*)-**15b** can be obtained with the highest enantiomeric excess at pH 10.5 (43%*ee*), whereas pH 9.0 was more adequate for M-PAMO catalyzed sulfoxidations (49%*ee*). Further increases in pH led to a gradual loss of enantioselectivity. This observation is different from that of previous work, which showed that this biocatalyst is capable of catalyzing Baeyer–Villiger oxidations with a high conversion for the synthesis of 1-isochromanone at pH 10.5.[19]

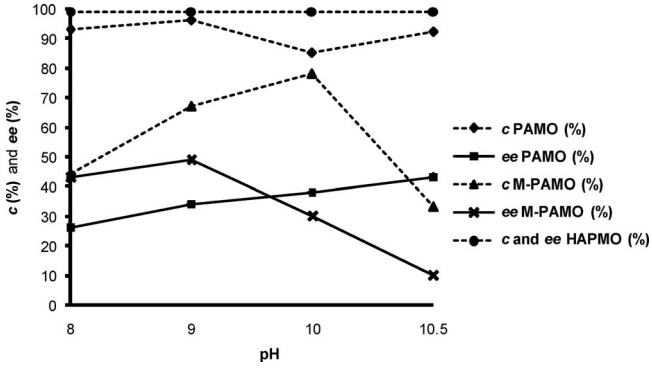


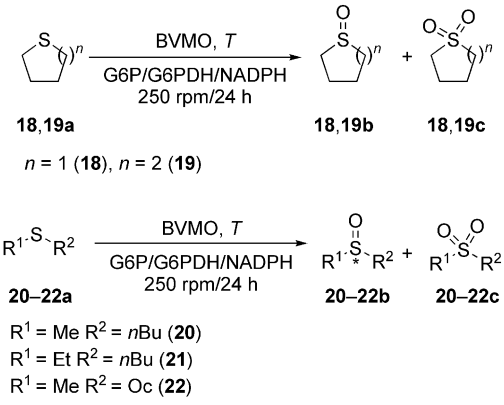
Figure 1. Effect of pH on the oxidation of cyclohexyl methyl sulfide (**15a**) catalyzed by the three BVMOs.

Biooxidation of Cyclic and Linear Aliphatic Sulfides

Other nonaromatic sulfides were employed as substrates for the three BVMOs. These enzymes have been employed in the sulfoxidation of cyclic sulfides tetrahydrothiophene (**18a**) and tetrahydro-2*H*-thiopyran (**19a**). No oxidation product was detected for both PAMO and M-PAMO at pH 9.0 and 30 °C. On the contrary, when both substrates were oxidized in the presence of HAPMO, high percentages (close to 80%) of final sulfoxides **18b** and **19b** were obtained (Table 3, Entries 1 and 2). Furthermore, no starting sulfides were detected, as a moderate amount of sulfone was formed

in both reactions (ca. 20%). Therefore, HAPMO was able to catalyze the first oxidation step (from the sulfide to the sulfoxide), and compounds **18**–**19b** were suitable substrates for conversion to the corresponding sulfones.

Table 3. Biooxidation of cyclic and linear aliphatic sulfides **18**–**22a**.[a]



Entry	Sulfide	Enzyme	Conversion			*ee* **b** [%]
			a [%]	**b** [%]	**c** [%]	
1	**18a**	HAPMO	–	76	24	–
2	**19a**	HAPMO	–	80	20	–
3	**20a**	HAPMO	–	≥99	–	≥99 (*S*)[b]
4	**21a**	HAPMO	–	≥99	–	≥99 (*S*)[c]
5	**22a**	HAPMO	13	75	12	≥99 (*S*)[d]
6	**20a**	PAMO	60	40	–	65 (*S*)[b]
7	**21a**	PAMO	66	34	–	50 (*S*)[c]
8	**20a**	M-PAMO	55	45	–	53 (*S*)[b]
9	**21a**	M-PAMO	61	39	–	36 (*S*)[c]

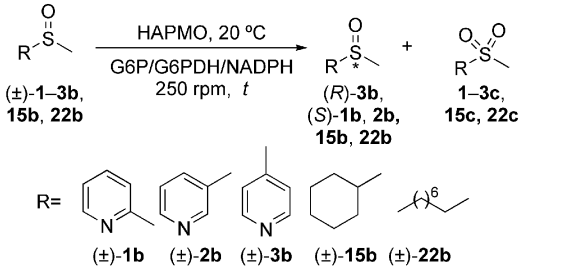
[a] For reaction conditions, see the Experimental Section. Conversions and enantiomeric excess values were determined by using GC. [b] Absolute configuration was determined by comparing the specific rotation value with published data. [c] Absolute configuration was established in a manner analogous to that used for *n*-butyl methyl sulfoxide (**20b**). [d] Absolute configuration determined by comparing the retention times on HPLC.

Finally, our efforts were devoted to develop the oxidation of linear aliphatic sulfides. As can be observed in Table 3, the best results were again obtained by using HAPMO as the biocatalyst. *n*-Butyl methyl and *n*-butyl ethyl sulfoxides (**20b** and **21b**, respectively) were achieved in enantiopure form and with complete conversion after 24 h (Table 3, Entries 3 and 4). HAPMO was then employed in the oxidation of a linear sulfide containing a longer alkyl chain such as methyl octyl sulfide (**22a**) to give 75% of enantiopure (*S*)-methyl *n*-octyl sulfoxide (**22b**) and 12% of corresponding sulfone **22c** (Table 3, Entry 5). PAMO and its M446G mutant were not able to transform this substrate, probably due to its size. Nevertheless, both enzymes were able to perform the oxidation of alkyl butyl sulfides **20a** and **21a** with moderate conversions (34–45%) and enantiomeric excess values (36–65%; Table 3, Entries 6–9).

HAPMO-Catalyzed Biooxidation of Racemic Sulfoxides

In general, sulfoxidations catalyzed by HAPMO led to the highest enantiomeric excess values and conversions. Moreover, this biocatalyst was able to catalyze the oxidation of sulfoxides to the corresponding sulfones in the kinetic resolution of some racemic sulfoxides by oxidation processes. The favored enantiomer will be converted into the corresponding sulfone, whereas the unreactive one will remain as an enantioenriched compound. As described in Table 4, the oxidation of sulfoxides is a really fast process, requiring short reaction times to achieve high conversions, as compared to sulfoxide formation. The oxidation of racemic alkyl pyridyl sulfoxides, for example, (±)-2-(methylsulfinyl)pyridine (**1b**), occurred with a 60% conversion after 0.5 h, leading to the (*S*)-sulfoxide with a good enantiomeric excess (Table 4, Entry 1). When the nitrogen atom was located further away from the sulfoxide moiety (compounds **2b** and **3b**), the reactions were still fast but the enzyme selectivity was much lower, giving enantiomeric excess values close to 20%. HAPMO-catalyzed oxidation of nonaromatic sulfoxides occurred with lower activity as compared to that of heteroaromatic analogs. It typically required 5 h to reach conversions of around 60% for (±)-cyclohexyl methyl sulfoxide (**15b**) and (±)-methyl *n*-octyl sulfoxide (**22b**), but with higher selectivity. Thus, (*S*)-**15b** can be recovered with 82%*ee*, whereas enantiopure (*S*)-**22b** was obtained.

Table 4. HAPMO-catalyzed biooxidation of racemic sulfoxides **1**–**3b**, **15b**, and **22b**.[a]



Entry	Substrate	*t* [h]	*c* [%][b]	*ee* [%][c]
1	(±)-**1b**	0.5	60	71 (*S*)
2	(±)-**2b**	0.6	67	21 (*S*)
3	(±)-**3b**	0.5	55	24 (*R*)
4	(±)-**15b**	5.0	60	82 (*S*)
5	(±)-**22b**	4.5	55	≥99 (*S*)

[a] For reaction conditions, see the Experimental Section. [b] Determined by using GC. [c] Determined by using HPLC, except for (±)-**2b**, which was determined by using GC.

Kinetic Parameters of HAPMO for the Oxidation of Prochiral Sulfides 1a, 2a, 11a, 15a, and 20a

To have a better knowledge of HAPMO as an oxidative biocatalyst of prochiral sulfides, the kinetic parameters for this biocatalyst were determined when catalyzing the sulfoxidation of substrates presenting different structures (Table 5).

Heteroaryl alkyl and alkyl alkyl sulfides that were tested showed good K_M values in the range 0.1–1.7 mM. All the sulfides that were tested presented similar k_{cat} values, with activities in the range of 0.3–2.9 s^{-1}, with the highest value being obtained for the oxidation of cyclohexyl methyl sulf-

Table 5. Kinetic parameters for the HAPMO-catalyzed sulfoxidation of prochiral sulfides.

Entry	Substrate	k_{cat} [s^{-1}]	K_M [mM]	k_{cat}/K_M [$s^{-1}mM^{-1}$]
1	**1a**	2.48 ± 0.26	1.7 ± 0.02	1.5
2	**2a**	0.32 ± 0.03	0.29 ± 0.01	1.1
3	**11a**	0.35 ± 0.03	0.15 ± 0.02	2.3
4	**15a**	2.87 ± 0.21	0.13 ± 0.01	22.1
5	**20a**	2.02 ± 0.16	0.40 ± 0.03	5.0

ide. These activities are 6 to 12 times lower than those obtained for the preferred substrates of this enzyme, acetophenones that have electron-withdrawing groups in the aromatic moiety.[13c] Better catalytic efficiencies were found for substrates with alkyl substituents (compounds **15a** and **20a**), whereas 10 to 20 times lower efficiencies were observed for the heteroaromatic-containing sulfides, as compared to **15a**.

Conclusions

The synthesis of a set of chiral heteroaryl alkyl, cyclohexyl alkyl, and alkyl alkyl sulfoxides by enantioselective sulfoxidation reactions catalyzed by three BVMOs is described. This work demonstrates the potential of BVMOs in the preparation of these high added-value compounds. HAPMO was able to perform the enzymatic oxidation of pyridine methyl sulfides with moderate to high conversions and excellent enantiomeric excess values, whereas PAMO and M-PAMO were only able to oxidize 3-(methylthio)pyridine. HAPMO was also able to oxidize a set of 2-(alkylthio)pyridines with complete selectivity and decreasing conversions for substrates with longer alkyl chains. Other nitrogen-containing heterocyclic sulfides as pyrimidine, imidazole, and benzoimidazole were not suitable substrates for the BVMOs. Oxidation of oxygen- and sulfur-containing heteroaryl alkyl sulfides catalyzed by HAPMO also led to good conversions and high optical purities. Cyclohexyl methyl and cyclohexyl ethyl sulfoxide were obtained with high and moderate conversions and enantiomeric excess values, respectively, in the oxidations catalyzed by HAPMO and M-PAMO, whereas no sulfoxidation was achieved with substrates containing longer alkyl chains. The HAPMO-catalyzed oxidation of cyclohexyl methyl sulfide was hardly affected by pH. Meanwhile, PAMO and its mutant were strongly influenced by pH. Cyclic and linear aliphatic sulfides were converted by HAPMO with excellent and good conversions, respectively. In contrast, PAMO and M-PAMO sulfoxidation of alkyl alkyl sulfides led to moderate conversion and enantiomeric excess. Kinetic resolution of racemic sulfoxides catalyzed by HAPMO was a faster process when compared to enzymatic sulfoxidation. This biocatalyst showed lower activity and higher enantioselectivity towards nonaromatic sulfoxides than aromatic ones. Scaling up of some of the biotransformations by using a cell-free extract afforded the chiral sulfoxides in moderate to good yields.

Experimental Section

General Methods: Recombinant histidine-tagged phenylacetone monooxygenase (PAMO),[20] its M446G mutant (M-PAMO),[14b] and recombinant 4-hydroxyacetophenone monooxygenase (HAPMO)[13c] were over-expressed and purified as described previously. One unit of BVMO will oxidize 1.0 μmol of thioanisole to methyl phenyl sulfoxide per minute at pH 9.0 and 25 °C in the presence of NADPH. Glucose-6-phosphate dehydrogenase from *Leuconostoc mesenteroides* was obtained from Fluka-Biochemika. Cell-free extract from over-expressed HAPMO on *E. coli* TOP10 was obtained by following a similar procedure as described previously.[21] Sulfides **11a** and **12a** were acquired from Alfa Aesar, substrate **15a** was supplied by Sigma–Aldrich–Fluka, compounds **14a** and **18**–**21a** were purchased from Acros Organics, and sulfide **22a** was obtained from TCI Europe. All other reagents and solvents were of the highest quality available and were obtained from Sigma–Aldrich–Fluka and Acros Organics. Chemical reactions were monitored by analytical TLC, which was performed on Merck silica gel 60 F254 plates and visualized by UV irradiation. Flash chromatography was carried out with silica gel 60 (230–240 mesh, Merck). Melting points were taken in open capillary tubes by using a Gallenkamp apparatus. IR spectra were recorded with a Perkin–Elmer 1720-X Fourier transform infrared spectrophotometer by using KBr pellets. ^{1}H NMR, ^{13}C NMR, and DEPT spectra were recorded with tetramethylsilane (TMS) as the internal standard with a Bruker AC-300 DPX (^{1}H: 300.13 MHz; ^{13}C: 75.5 MHz) spectrometer. EI+ mass spectra were recorded with a Hewlett Packard 5973 mass spectrometer. APCI+ and ESI+ mass spectra were measured with a chromatograph mass detector. High-resolution mass spectra were obtained with a Bruker Microtof-Q-spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. GC analyses were performed with a Hewlett Packard 6890 Series II chromatograph. For all the analyses, the injector and FID temperatures were 225 and 250 °C, respectively. HPLC analyses were performed with Hewlett Packard 1100 LC liquid chromatograph. Kinetic determinations were performed with a Varian Cary50Bio UV/Vis spectrophotometer.

Sulfides **1a**, **3a**, and **8**–**10a** were synthesized by reaction of the corresponding thiol and potassium carbonate with iodomethane and triethylamine in CH_2Cl_2 at 0 °C (yields ranged from 5 to 99%).[22]

Compound **2a** was prepared according to a known procedure[23] by treating 3-bromopyridine with isopropylmagnesium chloride and 1,2-dimethyldisulfane in dry THF at room temperature under a nitrogen atmosphere (83% yield).

Compounds **4**–**7a**, **16a**, and **17a** were synthesized by treating the corresponding thiol (250 mg) at 0 °C with sodium and ethyl or propyl iodide or allyl bromide in dry MeOH under a nitrogen atmosphere. The yields obtained ranged from 48 to 81%.[15b] Sulfide **13a** was prepared by treatment of 2-(methylthio)benzoxazole with methyl iodide by following the published procedure.[24]

Compounds **1a**,[23] **2a**,[23] **3a**,[25a] **4a**,[25b] **8a**,[25c] **9a**,[25d] **10a**,[25e] and **13a**[24] exhibit physical and spectral properties in accord with those reported.

2-(Propylthio)pyridine (5a): Yield: 203.3 mg (59%). Pale-brown liquid. IR (KBr): $\tilde{\nu}$ = 3050, 2929, 1579, 1454, 1124 cm^{-1}. ^{1}H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 1.21 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, CH_3), 1.85–1.92 (m, 2 H, CH_2CH_3), 3.27 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, SCH_2), 7.19–7.20 (m, 1 H, pCH_{ar}), 7.40 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, oCH_{ar}), 7.72–7.75 (m, 1 H, mCH_{ar}), 8.52 (d, $^3J_{H,H}$ = 4.2 Hz, 1 H, NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 14.0 (CH_3), 24.1 (CH_2), 33.4 (CH_2), 120.9 (CH_{ar}), 123.4 (CH_{ar}), 138.0

(CH_{ar}), 150.5 (CH_{ar}), 161.4 (C_{ar}) ppm. MS (ESI+): *m/z* (%) = 176 (100) $[M + Na]^+$. HRMS (ESI+): calcd. for $C_8H_{11}AgNS$ $[M + Ag]^+$ 259.9658; found 259.9654.

2-(Allylthio)pyridine (6a): Yield: 190.0 mg (56%). Pale-brown liquid. IR (KBr): $\tilde{\nu}$ = 3050, 2923, 1636, 1579, 1454, 1124 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 3.83 (d, $^3J_{H,H}$ = 6.8 Hz, 2 H, SCH_2), 5.10 (dd, $^2J_{H,H}$ = 0.9 Hz, $^3J_{H,H}$ = 10.1 Hz, 1 H, CH=CHH), 5.32 (dd, $^2J_{H,H}$ = 0.9 Hz, $^3J_{H,H}$ = 15.0 Hz, 1 H, CH=CHH), 5.89–6.03 (m, 1 H, CH=CH_2), 6.95–6.99 (m, 1 H, *p*CH_{ar}), 7.17 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, *o*CH_{ar}), 7.46 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, *m*CH_{ar}), 8.42 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 32.9 (CH_2), 117.5 (CH_2), 119.4 (CH), 122.1 (CH_{ar}), 133.7 (CH_{ar}), 135.9 (CH_{ar}), 149.3 (CH_{ar}), 158.4 (C_{ar}) ppm. MS (EI+): *m/z* (%) = 151 (21) $[M]^+$, 136 (100), 124 (15), 118 (36), 79 (35). HRMS (ESI+): calcd. for C_8H_9AgNS $[M + Ag]^+$ 257.9507; found 257.9503.

2-(Butylthio)pyridine (7a): Yield: 304.5 mg (81%). Colorless liquid. IR (KBr): $\tilde{\nu}$ = 3100, 2958, 1579, 1556, 1121 cm^{-1}. ^1H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 1.13 (t, $^3J_{H,H}$ = 6.0 Hz, 3 H, CH_3), 1.61–1.70 (m, 2 H, CH_2CH$_3$), 1.80–1.90 (m, 2 H, SCH$_2$CH_2), 3.31 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, SCH_2), 7.21–7.26 (m, 1 H, *p*CH_{ar}), 7.43 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, *o*CH_{ar}), 7.77 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, *m*CH_{ar}), 8.53–8.54 (m, 1 H, NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 14.3 (CH_3), 23.3 (CH_2), 31.1 (CH_2), 32.9 (CH_2), 120.9 (CH_{ar}), 123.5 (CH_{ar}), 138.0 (CH_{ar}), 150.5 (CH_{ar}), 168.5 (C_{ar}) ppm. MS (EI+): *m/z* (%) = 167 (28) $[M]^+$, 138 (72), 125 (100), 111 (72), 78 (64). HRMS (ESI+): calcd. for $C_9H_{13}AgNS$ $[M + Ag]^+$ 273.9820; found 273.9823.

Cyclohexyl Ethyl Sulfide (16a): Yield: 223.4 mg (72%). Pale-yellow liquid. IR (KBr): $\tilde{\nu}$ = 3010, 2928, 2852, 1448, 1262, 998 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 1.21–1.29 (m, 8 H, CH_3 and 5 CH), 1.59–1.62 (m, 1 H, CH), 1.74–1.76 (m, 2 H, CHHCHSCHH), 1.94–1.98 (m, 2 H, CHHCHSCHH), 2.15–2.65 (m, 3 H, SCH and SCH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 15.0 (CH_3), 23.9 (CH_2), 25.8 (2 CH_2), 26.1 (2 CH_2), 33.6 (CH_2), 43.0 (CH) ppm. MS (EI+): *m/z* (%) = 144 (5) $[M]^+$, 82 (7), 67 (7), 40 (100). HRMS (ESI+): calcd. for $C_8H_{16}NaS$ $[M + Na]^+$ 167.0865; found 167.0869.

Cyclohexyl Propyl Sulfide (17a): Yield: 136.2 mg (40%). Pale-yellow liquid. IR (KBr): $\tilde{\nu}$ = 3010, 2929, 2853, 1448, 1261 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 0.94 (t, $^3J_{H,H}$ = 4.1 Hz, 3 H, CH_3), 1.21–1.36 (m, 6 H, 6 CH), 1.53–1.65 (m, 2 H, 2 CH), 1.74–1.77 (m, 2 H, CHHCHSCHH), 1.93–2.03 (m, 2 H, CHHCHSCHH), 2.51 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, SCH_2), 2.58–2.63 (m, 1 H, SCH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 13.6 (CH_3), 23.3 (CH_2), 25.8 (CH_2), 26.1 (2 CH_2), 33.2 (2 CH_2), 33.7 (CH_2), 43.4 (CH) ppm. MS (EI+): *m/z* (%) = 158 (30) $[M]^+$, 115 (19), 82 (75), 67 (77), 55 (58), 40 (100). HRMS (ESI+): calcd. for $C_9H_{18}NaS$ $[M + Na]^+$ 181.1027; found 181.1022.

Racemic sulfoxides **1**–**6b**, **11b**, **12b**, **15b**, **16b**, **20b**, and **21b** were obtained by oxidation of the corresponding sulfides **1**–**6a**, **11a**, **12a**, **15a**, **16a**, **20a**, and **21a** (100 mg) with H_2O_2 in MeOH at room temperature (yields ranged from to 10 to 98%, as indicated for each of the compounds).

Compounds (±)-**11b**,[26a] (±)-**12b**,[26b] (±)-**16b**,[25c] (±)-**18b**,[26d] (±)-**19b**,[26e] (±)-**20b**,[26f] and (±)-**22b**[26g] also exhibit physical and spectral properties in accord with those reported.

General Method for the BVMO-Catalyzed Oxidation of Sulfides 1–22a or Sulfoxides (±)-1–3b, (±)-15b, and (±)-22b: In a typical experiment, starting sulfides **1**–**22a** (10 mM) or corresponding sulfoxides (±)-**1**–**3b**, (±)-**15b**, and (±)-**22b** were dissolved in Tris-HCl (50 mM, pH 8.0–10.5, 0.5 mL) containing 1% DMSO, glucose-6-phosphate (2.0 equiv.), glucose-6-phosphate dehydrogenase (5 units), NADPH (0.2 mM), and the corresponding Baeyer–Villiger monooxygenase (1.0 unit). The mixture was shaken at 250 rpm at the selected temperature in a rotary shaker for 24 h. Reactions were then stopped and extracted with ethyl acetate (2 × 0.5 mL). The organic layers were dried with Na_2SO_4 and analyzed directly by GC and/or HPLC to determine the conversion and the enantiomeric excess values of the final products.

Enzymatic Preparation of Chiral Sulfoxides (*S*)-1b, (*S*)-2b, (*R*)-3b, (*S*)-4–6b, (*S*)-15, (*S*)-20b, and (*S*)-21b by Employing Cell-Free Extract from HAPMO on a Multimilligram Scale: Sulfides **1**–**6a**, **15a**, **20a**, and **21a** (250 mg) were dissolved in Tris-HCl buffer (50 mM, pH 9.0, 40 mL) containing 1% DMSO, NADPH (0.2 mM), glucose-6-phosphate (2 equiv.), glucose-6-phosphate dehydrogenase (1250 units), and HAPMO cell-free extract (46 mL). The mixture was shaken at 250 rpm at 20 °C, and the reaction was monitored by TLC. After 24 h, the reaction was stopped and extracted with ethyl acetate (5 × 30 mL). The organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. The crude residues were purified by flash chromatography by using different concentrations of CH_2Cl_2/MeOH as eluent, (98:2) for **1b**, **5b**, and **6b**; (95:5) for **2b**, **3b**, and **4b**; and (90:10) for **15b**, **20b**, and **21b**, to obtain completely enantiopure (*S*)-**1b**, (*S*)-**2b**, (*R*)-**3b**, (*S*)-**4**–**6b**, (*S*)-**15b**, (*S*)-**20b**, (*S*)-**21b**.

(±)-2-(Methylsulfinyl)pyridine [(±)-1b]: Yield: 81.2 mg (72%). Pale-yellow oil. IR (KBr): $\tilde{\nu}$ = 2924, 1644, 1579, 1426, 1032 cm^{-1}. ^1H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 2.86 (s, 3 H, CH_3), 7.35–7.40 (m, 1 H, *p*CH_{ar}), 7.91–8.01 (m, 2 H, *o*CH_{ar} and *m*CH_{ar}), 8.61 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 41.2 (CH_3), 119.2 (CH_{ar}), 124.5 (CH_{ar}), 138.0 (CH_{ar}), 149.5 (CH_{ar}), 169.5 (C_{ar}) ppm. MS (EI+): *m/z* (%) = 141 (15) $[M]^+$, 124 (7), 93 (32), 78 (100), 51 (46). HRMS (ESI+): calcd. for C_6H_7NNaOS $[M + Na]^+$ 164.0141; found 164.0135. (*S*)-**1b**: Yield: 267.9 mg (95%).

(±)-3-(Methylsulfinyl)pyridine [(±)-2b]: Yield: 39.4 mg (35%). Pale-yellow oil. IR (KBr): $\tilde{\nu}$ = 2921, 1651, 1580, 1416, 1037 cm^{-1}. ^1H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 3.09 (s, 3 H, CH_3), 7.82–7.87 (m, 1 H, *m*CH_{ar}), 8.37–8.41 (m, 1 H, CH_{ar}CS), 8.92 (d, $^3J_{H,H}$ = 3.5 Hz, 1 H, CH_{ar}N), 9.04 (s, 1 H, NCH_{ar}CS) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 43.7 (CH_3), 126.3 (CH_{ar}), 134.1 (CH_{ar}), 143.7 (C_{ar}), 146.6 (CH_{ar}), 153.3 (CH_{ar}) ppm. MS (EI+): *m/z* (%) = 141 (100) $[M]^+$, 126 (65), 78 (81), 51 (84), 39 (32). HRMS (ESI+): calcd. for C_6H_7NNaOS $[M + Na]^+$ 164.0141; found 164.0140. (*S*)-**2b**: Yield: 253.8 mg (90%), $[\alpha]_D^{25}$ = –34.3 (*c* = 1.21, acetone), ≥99% *ee*.

(±)-4-(Methylsulfinyl)pyridine [(±)-3b]: Yield: 22.6 mg (20%). Yellow oil. IR (KBr): $\tilde{\nu}$ = 2921, 1620, 1579, 1408, 1037 cm^{-1}. ^1H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 2.91 (s, 3 H, CH_3), 7.78 (d, $^3J_{H,H}$ = 6.2 Hz, 2 H, CH_{ar}CSCH_{ar}), 8.80 (d, $^3J_{H,H}$ = 3.9 Hz, 2 H, CH_{ar}NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 43.4 (CH_3), 120.0 (2 CH_{ar}), 151.5 (2 CH_{ar}), 158.1 (C_{ar}) ppm. MS (EI+): *m/z* (%) = 141 (4) $[M]^+$, 125 (100), 92 (30), 79 (20), 51 (29). HRMS (ESI+): calcd. for C_6H_7NOS $[M + H]^+$ 142.0321; found 142.0338. (*R*)-**3b**: Yield: 141.0 mg (50%), $[\alpha]_D^{25}$ = +41.1 (*c* = 0.95, acetone), ≥99% *ee*.

(±)-2-(Ethylsulfinyl)pyridine [(±)-4b]: Yield: 11.2 mg (10%). Pale-yellow oil. IR (KBr): $\tilde{\nu}$ = 2963, 1650, 1580, 1449, 1012 cm^{-1}. ^1H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 1.35 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, CH_3), 3.10–3.19 (m, 1 H, CHHS), 3.22–3.43 (m, 1 H, CHHS), 7.70–7.74 (m, 1 H, *p*CH_{ar}), 8.10 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, *o*CH_{ar}), 8.27 (t, $^3J_{H,H}$ = 9.0 Hz, 1 H, *m*CH_{ar}), 8.85 (d, $^3J_{H,H}$ = 4.6 Hz, 1 H,

NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 5.8 (CH_3), 48.5 (CH_2), 121.8 (CH_{ar}), 126.7 (CH_{ar}), 139.9 (CH_{ar}), 151.5 (CH_{ar}), 164.1 (C_{ar}) ppm. MS (ESI+): *m*/*z* (%) = 178 (100) [M + Na]$^+$. HRMS (ESI+): calcd. for C_7H_9NNaSO [M + Na]$^+$ 178.0297; found 178.0310. (*S*)-**4b**: Yield: 279.0 mg (85%), $[\alpha]_D^{25}$ = –56.2 (*c* = 1.05, acetone), ≥99% *ee*.

(±)-2-(Propylsulfinyl)pyridine [(±)-5b]: Yield: 69.6 mg (63%). Pale-yellow oil. IR (KBr): $\tilde{\nu}$ = 2966, 1650, 1577, 1453, 1022 cm^{-1}. ^{1}H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 1.25 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CH_3), 1.73–1.99 (m, 1 H, CHHCH$_3$), 2.02–2.09 (m, 1 H, CHHCH$_3$), 3.07–3.17 (m, 1 H, CHHS), 3.26–3.35 (m, 1 H, CHHS), 7.70–7.74 (m, 1 H, *p*CH_{ar}), 8.08–8.14 (m, 1 H, *o*CH_{ar}), 8.22–8.31 (m, 1 H, *m*CH_{ar}), 8.85 (d, $^3J_{H,H}$ = 4.8 Hz, 1 H, NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 13.6 (CH_3), 16.8 (CH_2), 57.2 (CH_2), 121.4 (CH_{ar}), 126.7 (CH_{ar}), 140.1 (CH_{ar}), 151.4 (CH_{ar}), 164.8 (C_{ar}) ppm. MS (ESI+): *m*/*z* (%) = 192 (100) [M + Na]$^+$. HRMS (ESI+): calcd. for $C_8H_{11}NNaOS$ [M + Na]$^+$ 192.0454; found 192.0455. (*S*)-**5b**: Yield: 16.6 mg (6%).

(±)-2-(Allylsulfinyl)pyridine [(±)-6b]: Yield: 67.2 mg (61%). Yellow oil. IR (KBr): $\tilde{\nu}$ = 2928, 1637, 1578, 1425, 1036 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 3.58 (dd, $^2J_{H,H}$ = 13.1 Hz, $^3J_{H,H}$ = 7.4 Hz, 1 H, CHHS), 3.83 (dd, $^2J_{H,H}$ = 13.1 Hz, $^3J_{H,H}$ = 7.2 Hz, 1 H, CHHS), 5.15 (d, $^3J_{H,H}$ = 17.7 Hz, 1 H, CHH=CH), 5.26 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, CHH=CH), 5.57–5.69 (m, 1 H, CH$_2$=CHCH$_2$), 7.35 (t, $^3J_{H,H}$ = 4.3 Hz, 1 H, *p*CH_{ar}), 7.89–7.90 (m, 2 H, *o*CH_{ar} and *m*CH_{ar}), 8.60 (d, $^3J_{H,H}$ = 4.6 Hz, 1 H, NCH_{ar}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 57.5 (CH_2), 120.5 (CH), 123.7 (CH_2), 124.4 (CH_{ar}), 125.0 (CH_{ar}), 137.7 (CH_{ar}), 149.4 (CH_{ar}), 163.5 (C_{ar}) ppm. MS (ESI+): *m*/*z* (%) = 190 (100) [M + Na]$^+$. HRMS (ESI+): calcd. for C_8H_9NNaOS [M + Na]$^+$ 190.0303; found 190.0306. (*S*)-**6b**: Yield: 52.8 mg (19%), $[\alpha]_D^{25}$ = –39.8 (*c* = 0.75, acetone), ≥99% *ee*.

(±)-Cyclohexyl Methyl Sulfoxide [(±)-15b]: Yield: 110.1 mg (98%). Pale-yellow liquid. IR (KBr): $\tilde{\nu}$ = 2931, 1451, 1033 cm^{-1}. ^{1}H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 1.58–1.66 (m, 6 H, 6 CH), 1.91–1.94 (m, 2 H, CHHCHSCHH), 2.28–2.31 (m, 2 H, CHHCHSCHH), 2.84 (s, 3 H, SCH_3), 2.85–2.88 (m, 1 H, SCH) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 25.7 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 27.6 (CH_2), 35.1 (CH_3), 61.6 (CH) ppm. MS (EI+): *m*/*z* (%) = 146 (7) [M]$^+$, 83 (51), 67 (71), 55 (92), 40 (100). HRMS (ESI+): calcd. for $C_7H_{14}NaOS$ [M + Na]$^+$ 169.0658; found 169.0649. (*S*)-**15b**: Yield: 255.5 mg (91%).

(±)-*n*-Butyl Methyl Sulfoxide [(±)-20b]: Yield: 87.5 mg (76%). Yellow oil. IR (KBr): $\tilde{\nu}$ = 2960, 2937, 1652, 1038 cm^{-1}. ^{1}H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 1.18 (t, $^3J_{H,H}$ = 6.6 Hz, 3 H, butyl CH_3), 1.63–1.77 (m, 2 H, CH_2CH$_3$), 1.87–1.98 (m, 2 H, CH_2CH$_2$S), 2.82 (s, 3 H, methyl CH_3), 2.90–3.13 (m, 2 H, CH_2S) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 14.3 (CH_3), 23.2 (CH_2), 26.0 (CH_2), 38.4 (CH_3), 54.9 (CH_2) ppm. MS (ESI+): *m*/*z* (%) = 120 (9) [M]$^+$, 64 (100), 41 (88). (*S*)-**20b**: Yield: 249.0 mg (88%), $[\alpha]_D^{25}$ = +32.5 (*c* = 0.5 in ethanol), ≥99% *ee*.

(±)-*n*-Butyl Ethyl Sulfoxide [(±)-21b]: Yield: 72.6 mg (64%). Yellow oil. IR (KBr): $\tilde{\nu}$ = 2962, 2935, 1648, 1045 cm^{-1}. ^{1}H NMR (300.13 MHz, CD_3OD, 25 °C): δ = 1.18 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, butyl CH_3), 1.51 (t, $^3J_{H,H}$ = 7.6 Hz, 3 H, ethyl CH_3), 1.63–1.77 (m, 2 H, CH_2CH$_3$), 1.88–1.98 (m, 2 H, CH_2CH$_2$S), 2.86–3.11 (m, 4 H, CH_2SCH_2) ppm. ^{13}C NMR (75.5 MHz, CD_3OD, 25 °C): δ = 7.6 (CH_3), 14.5 (CH_3), 23.5 (CH_2), 26.3 (CH_2), 46.7 (CH_2), 52.4 (CH_2) ppm. MS (EI+): *m*/*z* (%) = 134 (6) [M]$^+$, 118 (26), 78 (100), 41 (81). HRMS (ESI+): calcd. for $C_6H_{14}NaOS$ [M + Na]$^+$ 157.0658; found 157.0668. (*S*)-**21b**: Yield: 252.7 mg (89%).

Determination of the Kinetic Parameters for the HAPMO Oxidation of Sulfides 1a, 2a, 11a, 15a, and 20a: Unless indicated otherwise, all activities measurements were performed in air-saturated 50 mM Tris-HCl buffer (pH 9.0). HAPMO concentration was measured photometrically by using a molar extinction coefficient of 12.4 mM^{-1} cm^{-1} at 440 nm for protein bound to FAD. Enzymes activities were determined spectrophotometrically at 30 °C by monitoring the decrease in absorbance at 340 nm due to the NADPH oxidation. For compounds **1a** and **2a**, measurements were performed at 370 nm. This wavelength was selected because these sulfides displayed significant absorbance at 340 nm, the λ_{max} of NADPH. The standard assay mixture contained stock solutions of sulfides in DMSO (1.0 M), 10 mM NADPH, and the biocatalyst (0.2–0.8 μM).

Supporting Information (see footnote on the first page of this article): Experimental data of sulfides **1**–**4a**, **8**–**10a** and sulfoxides **11b**, **12b**, **16b**, **18b**, **19b**, and **22b**; determination of absolute configurations of sulfoxides **2**–**4b**, **6b**, and **16b** by employing the Kagan methodology;[27] GC and HPLC data and ^{1}H and ^{13}C-NMR spectra of compounds **5a**, **6a**, **7a**, **16a**, **17a**, **1b**, **2b**, **3b**, **4b**, **5b**, **6b**, **15b**, and **21b**.

Acknowledgments

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. G.d.G. thanks MICINN by personal funding. This work was supported by the Ministerio de Educación y Ciencia (MEC) (Project CTQ 2007–61126). M.W.F. and D.E.T.P. received support from the EU-FP7 "Oxygreen" project.

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Received: June 21, 2010
Published Online: October 15, 2010

