Chemoenzymatic asymmetric synthesis of 1,4-benzoxazine derivatives. Application in the synthesis of a Levofloxacin precursor

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Abstract

A versatile and general route has been developed for the asymmetric synthesis of a wide family of 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines bearing different pattern substitutions in the aromatic ring. While hydrolases were not suitable for the resolution of these racemic cyclic nitrogenated amines, alternative chemoenzymatic strategies were designed through independent pathways leading to both amine antipodes. On one hand, the bioreduction of 1-(2-nitrophenoxy)propan-2-ones allowed the

recovery in high yields of the enantiopure (*S*)-alcohols using the alcohol dehydrogenase from *Rhodococcus ruber* (ADH-A), while the evo-1.1.200 ADH led to their counterpart (*R*)-enantiomers with also complete selectivity and quantitative conversions. Alternatively, lipase-catalyzed acetylation of these racemic alcohols and the complementary hydrolysis of the acetate analogues gave access to the corresponding optically enriched products with high stereodiscrimination. Particularly attractive was the design of a chemoenzymatic strategy in 6 steps for the production of (*S*)-(–)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo-[*b*][1,4]oxazine, which is a key precursor of the antimicrobial agent Levofloxacin.

Keywords: Alcohol dehydrogenases/ Asymmetric synthesis/ Benzoxazine/ Levofloxacin / Lipases / Stereoselective synthesis

Introduction

Benzoxazines are privileged cyclic subunits found in a wide range of biologically active molecules with antibacterial, anticancer, antifungal and antimicrobial properties,[1] but also serve as synthetic building blocks for the formation of more complex structures with relevant medical applications.[2] The synthesis of achiral and racemic benzoxazines has been extensively reported in the literature,[3] particularly for those bearing the 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine fragment (Figure 1),[4] while less examples have appeared regarding the development of asymmetric routes towards enantioenriched benzoxazines. Optically active 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines have been mostly synthesized through asymmetric metal-catalyzed transfer hydrogenation[5] or hydrosilylation of imines,[6] organocatalytic additions[7] and broadly by using chemical kinetic resolutions of the racemic benzoxazines with optically active acyl chlorides[8] or palladium catalyzed couplings.[9]

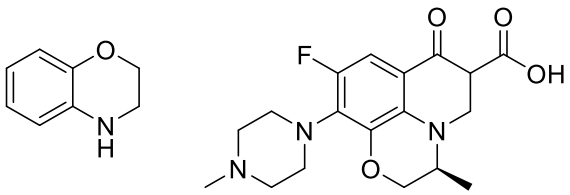


Figure 1. Chemical structure of the 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine subunit (left) and Levofloxacin, (right).

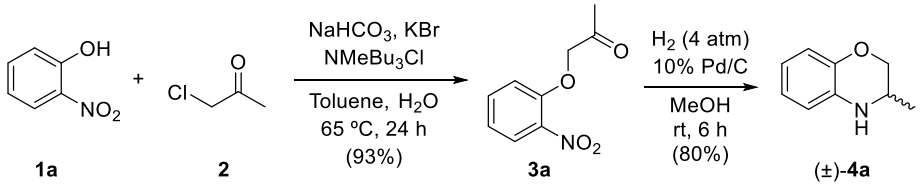
Certainly, one of the most targeted benzoxazine derivatives is Levofloxacin (Figure 1), which is a potent fluoroquinolone antibacterial agent, currently approved for the treatment of different human diseases such as pneumonia, acute bacterial sinusitis, urinary tract infections and acute pyelonephritis.[10] Chemical asymmetric strategies have been successfully carried out for the synthesis of this drug and other related non fluorinated analogues,[5a,11] the main efforts focused in the production of (*S*)-(–)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, which serves as adequate synthetic building block for the total synthesis of Levofloxacin.

Biocatalytic methods represent elegant and sustainable strategies for the production of enantiopure compounds under mild reaction conditions. In the last decades many organic chemists have incorporated the use of enzymes in their toolbox,[12] lipases and alcohol dehydrogenases being currently the most employed catalysts for their use in industrial applications, although other such as transaminases are nowadays receiving great attention.[13] Enzymes have been identified as particularly useful for the design of valuable synthetic routes towards the synthesis of enantiopure amines by means of the use of lipases, transaminases, monoamine oxidases and imine reductases among others.[14] In this context, hydrolases are valuable hydrolytic enzymes which can also catalyzed acylation reaction for the selective formation of amines through kinetic resolution processes.[15] Among the hydrolytic enzymes, lipases have attracted great attention due to their selective action in the asymmetric synthesis of a wide range of heterocyclic nitrogenated compounds.[16] Surprisingly, the production of optically enriched benzoxazine derivatives is limited to pig liver esterase-catalyzed hydrolytic approaches, finding moderate selectivity values.[17]

Herein, we wish to report the versatility of enzymes for the production of benzoxazine derivatives by the development of robust chemoenzymatic methods, lipases and oxidoreductases being satisfactorily used for the production of target cyclic nitrogenated compounds with good yields and excellent enantiomeric excess values. Special attention will be paid to the asymmetric synthesis of a valuable precursor of Levofloxacin.

Results and discussion

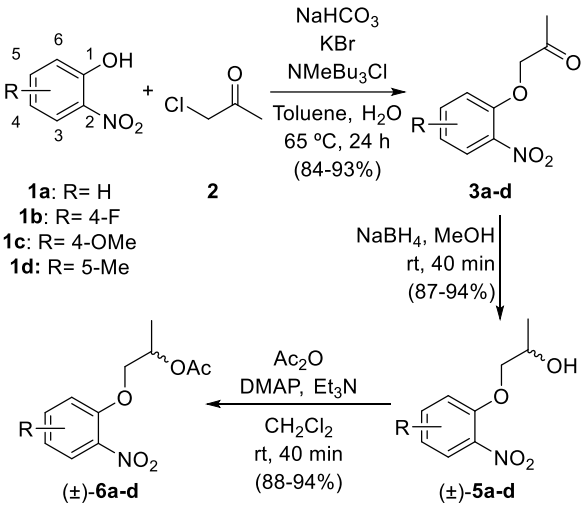
To explore new asymmetric routes for the synthesis of benzoxazine derivatives, the 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**4a**) was selected as a model for enzymatic activity screening. The synthesis of the racemate was performed by *O*-alkylation of 2-nitrophenol (**1a**) using chloroacetone (**2**) in the presence of potassium bromide, sodium hydrogencarbonate and tributylmethylammonium chloride, followed by a palladium catalyzed hydrogenation-cyclization sequence of the nitro ketone **3a** that allowed the isolation of (±)-**4a** in 75% overall yield. Because of the good levels of activity and stereoselectivity found for lipases in the classical kinetic resolution of secondary cyclic amines,[18] a panel of commercially available lipases (*Candida antarctica* lipase types A and B, porcine pancreas lipase, *Candida rugosa* lipase and *Pseudomonas cepacia* lipase) was used for the alkoxycarbonylation of **4a**. Unfortunately, no significant activity was observed when using different allyl carbonates in methyl *tert*-butyl ether (MTBE) as solvent.



Scheme 1. Synthesis of racemic benzoxazine **4a** for the study of its kinetic resolution.

Searching for an alternative strategy, we decided to take advantage from the previous preparation of

nitro ketone **3a**. Then, three independent strategies were undertaken (a) the non selective reduction of the ketone **3a** to the racemic alcohol **5a** followed by its classical kinetic resolution through lipase-catalyzed acylative processes; (b) the chemical acetylation of the so-obtained racemic alcohol to analyze in depth the complementary lipase-catalyzed hydrolytic process; (c) the selective bioreduction of the prochiral ketone **3a** using alcohol dehydrogenases. For these studies, a series of benzoxazine precursors bearing different pattern substitutions such as a fluorine atom, a methoxy group or a methyl functionality along the aromatic ring were chemically prepared through an efficient chemical route as depicted in Scheme 2. This includes the *O*-alkylation of 2-nitrophenols (**1a-d**), reduction of ketones **3a-d** with sodium borohydride and later acetylation with acetic anhydride in the presence of DMAP and triethylamine, affording the corresponding racemic acetates **6a-d** in good overall yields.

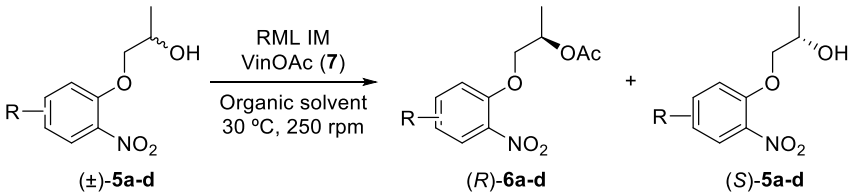


Scheme 2. Chemoenzymatic synthesis of nitro ketones **3a-d**, alcohols **5a-d** and acetates **6a-d**.

The lipase-catalyzed acetylation of alcohols **5a-d** was firstly considered, searching for a suitable lipase that was able to produce the corresponding alcohols and acetates in high optical purity (Table S1). The alcohol **5a** was selected as model substrate finding *Rhizomucor miehei* lipase in immobilized form (RML IM) as an ideal candidate leading to a 48% conversion in MTBE after 5 h with a 94% *ee* for the (*R*)-acetate and 89% *ee* for the remaining (*S*)-alcohol. Other lipases such as *Candida antarctica* lipase type A (CAL-A) and *Pseudomonas cepacia* (PSL-C I) displayed poor selectivities while *Candida*

antarctica lipase type B (CAL-B) did not shown significant activity. From a set of solvents the best results were found with MTBE and toluene (Table 1, entries 1 and 2), so next the extension to alcohols **5b-d** was performed. A similar trend was observed achieving the highest rates for the reactions carried out in MTBE (entries 3, 5 and 7), while the better selectivities were attained in toluene (entries 4, 6 and 8). MTBE was revealed to be the solvent of choice since the conversion values were lower in toluene (27-49%), and in addition the acetate optical purity begins to decrease at longer periods of time (data not shown).

Table 1. Enzymatic kinetic resolution of alcohols **5a-d** using RML IM (1:1 w/w) and 3 equivalents of vinyl acetate (**7**) in dry MTBE or toluene at 30 ºC and 250 rpm.



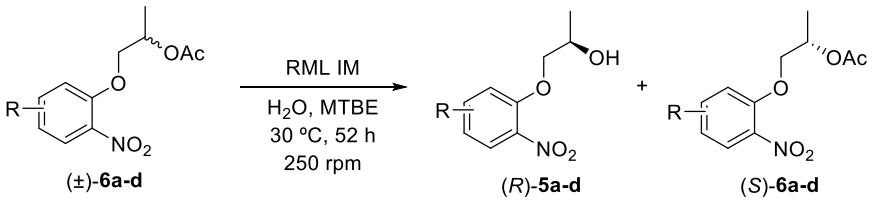
Entry	R[a]	Solvent	t (h)	ee_p (%)[b]	ee_s (%)[b]	c (%)[c]	E[d]
1	**5a** (H)	MTBE	5	94 (45)	89 (44)	48	103
2	**5a** (H)	Toluene	29.5	97	92	49	188
3	**5b** (4-F)	MTBE	5	95 (47)	91 (48)	49	117
4	**5b** (4-F)	Toluene	20	99	37	27	>200
5	**5c** (4-OMe)	MTBE	5	94 (47)	93 (48)	50	102
6	**5c** (4-OMe)	Toluene	20	>99	73	42	>200
7	**5d** (5-Me)	MTBE	7	93 (46)	94 (48)	50	103
8	**5d** (5-Me)	Toluene	20	>99	45	31	>200

[a] Substitution in brackets.
[b] Determined by HPLC. Isolated yields in parentheses.
[c] $c = ee_s/(ee_s + ee_p)$.
[d] $E = \ln[(1-c)(1-ee_p)]/\ln[(1-c)(1+ee_p)]$.[19]

Alternatively, we decided to study the lipase-catalyzed hydrolysis of the corresponding acetates. The results are summarized in Table 2. Since the water content is a decisive parameter for the enzymatic activity, the amount of water was studied using as reference the substrate **6a** without substitutions in the

aromatic ring (entries 1-3). In all cases, an excellent selectivity was observed, obtaining the complementary alcohol (*R*)-**5a** and the acetate (*S*)-**6a** in comparison with the lipase-catalyzed acetylation reaction. The reaction with 5 equivalents of hydrolytic agent led to a 48% conversion (entry 1) while notably, an increase in the amount of water led to slower kinetics but also with excellent stereoselectivity (21-35%, entries 2 and 3). Similar good results were obtained when extending the methodology to other substituted benzoxazine derivatives using 5 equivalents of water (entries 4-6).

Table 2. Enzymatic kinetic resolution of acetates **6a-d** using RML IM (1:1 w/w) in the presence of water using MTBE as solvent at 30 ºC and 250 rpm after 52 h.



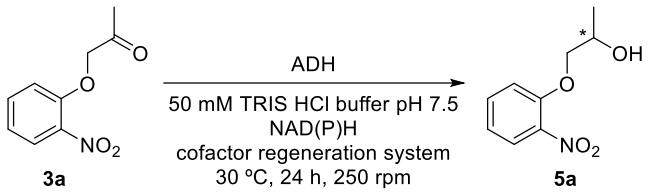
Entry	Substrate[a]	H_2O (equiv)	ee_p (%)[b]	ee_s (%)[b]	c (%)[c]	E[d]
1	**6a** (H)	5	98 (44)	92 (41)	48	>200
2	**6a** (H)	10	99	53	35	>200
3	**6a** (H)	20	>99	27	21	>200
4	**6b** (4-F)	5	96 (44)	97 (48)	50	>200
5	**6c** (4-OMe)	5	>99 (46)	91 (47)	48	>200
6	**6d** (5-Me)	5	>99 (47)	94 (48)	49	>200

[a] Substitution in brackets.
[b] Determined by HPLC. Isolated yields in parentheses.
[c] $c = ee_s/(ee_s + ee_p)$.
[d] $E = \ln[(1-c)(1-ee_p)]/\ln[(1-c)(1+ee_p)]$.[19]

Finally, bioreduction experiments were considered based on the access towards the final product in theoretically 100% yield. Oxidoreductases with opposite stereopreferences were employed in order to develop suitable routes for both alcohol antipodes. Thus, a set composed of Prelog alcohol dehydrogenases[20] as the one from ADH-A from *Rhodococcus ruber* (ADH-A), *Candida parapsilosis*

(ADH-CP) and Baker′s yeast (BY), but also anti-Prelog enzymes like *Lactobacillus brevis* (ADH-LB), *Lactobacillus kefir* (ADH-LK) and evo-1.1.200 ADH were screened in a 50 mM TRIS·HCl buffer pH 7.5 using a suitable cofactor recycling system when required (Table 3). For the Prelog enzymes high to excellent selectivities were found towards the formation of the (*S*)-alcohol **5a** (entries 1-3), notably the ADH-A showed a complete conversion and complete selectivity after 24 h (entry 1). On the other hand, for the synthesis of (*R*)-**5a**, the ADH-LK reduced completely the ketone obtaining the alcohol with very high enantiomeric excess (entry 4), while a 91% conversion was achieved in the production of the enantiopure alcohol when using ADH-LB (entry 5). The best result for the production of (*R*)-**5a** was observed with the evo-1.1.200 ADH (entry 6), obtaining the target alcohol in quantitative conversion.

Table 3. Bioreduction of nitro ketone **3a** for the production of optically active alcohol **5a** in TRIS·HCl buffer pH 7.5 after 24 h at 30 ºC.



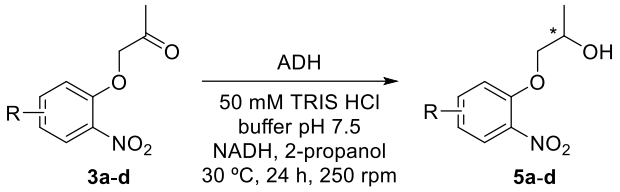
Entry	Enzyme	Cofactor	*c* (%)[a]	*ee* (%)[a]
1	ADH-A	NADH	>99	99 (*S*)
2	ADH-CP	NADH	8	99 (*S*)
3	BY	----	>99	86 (*S*)
4	ADH-LK	NADPH	>99	96 (*R*)
5	ADH-LB	NADPH	91	>99 (*R*)
6	evo-1.1.200	NADH	>99	>99 (*R*)

[a] Conversion and enantiomeric excess values calculated by ^{1}H NMR or HPLC measurements of the reaction crude. Absolute configurations appear in parentheses.

An efficient scale-up of the optimum ADH-catalyzed processes was successfully achieved for both a Prelog (ADH-A) and an anti-Prelog enzyme (evo-1.1.200 ADH), leading to the desired (*S*)- and (*R*)-alcohol in quantitative conversion and 85% and 99% isolated yields, respectively after a simple

extraction protocol (Table 4, entries 1 and 2). This methodology was satisfactorily extended to the bioreduction of ketones **3b-d** (entries 3-8). Both alcohol dehydrogenases led to full conversions, the ADH-A producing the enantiopure alcohols (*S*)-**5b-d** with very high yields (88-93% yield, entries 3, 5 and 7), while the evo-1.1.200 ADH led to the enantiopure (*R*)-alcohols in 78-88% yield (entries 4, 6 and 8). In this manner, the isolated yields were improved in comparison with the lipase-catalyzed transformations that are limited to a theoretically 50% yield due to the inherent limitations of kinetic resolution procedures.

Table 4. Bioreduction of nitro ketones **3a-d** in TRIS·HCl buffer pH 7.5 after 24 h at 30 ºC.



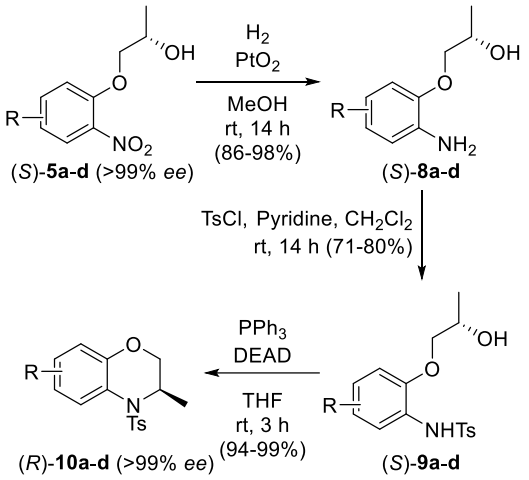
3a-d **5a-d**

Entry	Enzyme	**3**	*c* (%)[a]	*ee* (%)[a]
1	ADH-A	**3a**	>99 (85)	99 (*S*)
2	evo-1.1.200	**3a**	>99 (99)	>99 (*R*)
3	ADH-A	**3b**	>99 (89)	>99 (*S*)
4	evo-1.1.200	**3b**	>99 (87)	>99 (*R*)
5	ADH-A	**3c**	>99 (88)	>99 (*S*)
6	evo-1.1.200	**3c**	>99 (88)	>99 (*R*)
7	ADH-A	**3d**	>99 (93)	>99 (*S*)
8	evo-1.1.200	**3d**	>99 (78)	>99 (*R*)

[a] Conversion and enantiomeric excess values calculated by ^{1}H NMR or HPLC measurements of the reaction crude. Absolute configurations and isolated yields appear in parentheses.

A four-step sequence was designed for the production of racemic and enantiopure benzoxazines **10a-d**, occurring without any racemization of the intermediates or the final products (Scheme 3). Starting from the (*S*)-alcohols **5a-d**, the proposed synthesis began with the palladium catalyzed hydrogenation of the nitro functionality forming the corresponding amino alcohol (*S*)-**8a-d**, which was activated prior to

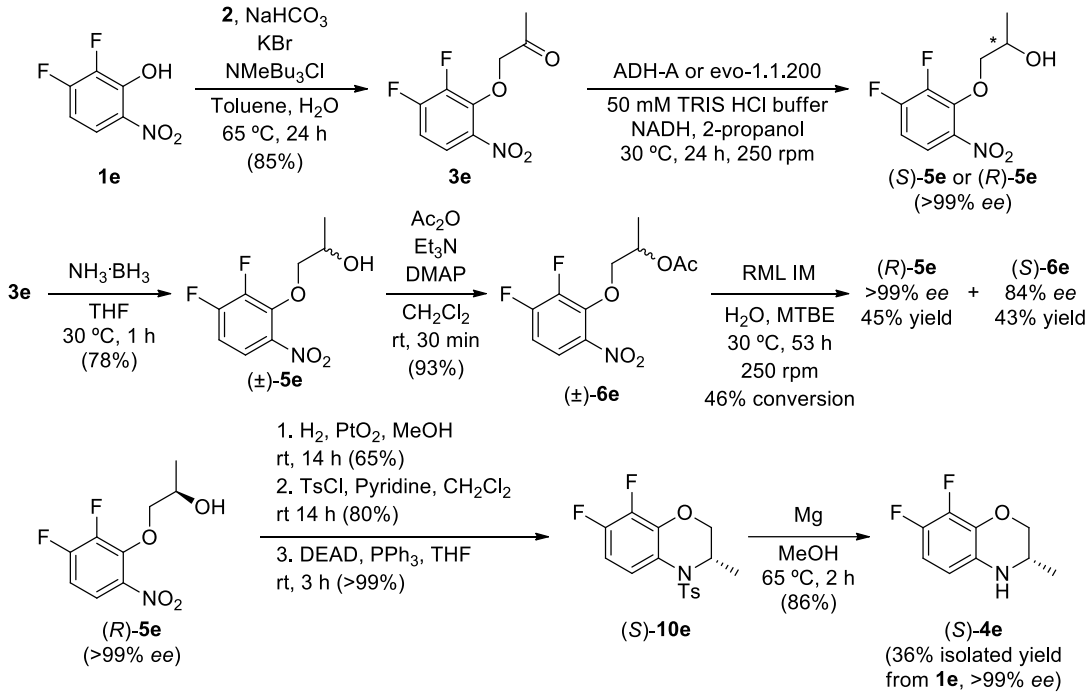
the cyclization under Mitsunobu condition reactions to avoid mixture of products as occurs using the free amine or when additional catalysts were employed as $ZnCl_2$ with related amino alcohols, for example **8e**.[21] This process occurred with inversion of the absolute configuration, yielding the tosylated benzoxazine derivative (*R*)-**10a-d**. As an example, the final deprotection of the activated amine **10a** with the tosyl group using magnesium in refluxing methanol allowed the recovery of the (*R*)-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**4a**) in 80% isolated yield after 2 h.



Scheme 3. Chemical synthesis of protected enantiopure benzoxazines **10a-d**.

Once that a powerful chemoenzymatic strategy was developed for the asymmetric synthesis of a representative number of 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine derivatives, efforts were focused on the development of an efficient and selective preparation of the Levofloxacin precursor (**4e**, 7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine). For that reason, a similar route was attempted starting from commercially available 2,3-difluoro-6-nitrophenol (**1e**) as depicted in Scheme 4. Its *O*-alkylation proceeded in 85% yield for the formation of the nitro ketone **3e**, which was subjected to the ADH-A catalyzed bioreduction leading to enantiopure (*S*)-**5e** after 24 h in 91% isolated yield using a TRIS·HCl buffer pH 7.5. For the preparation of its counterpart (*R*)-**5e** the use of evo-1.1.200 was attempted, finding a complete selectivity although its structural isomer 2-(2,3-difluoro-6-nitrophenoxy)propan-1-ol (**11**) was also found as a side product. For that reason, the bioreduction was

carried out at different pHs, minimizing the formation of **11** at lower pH values (6-6.5), yielding the alcohol (*R*)-**5e** in 94% isolated yield after 24 h at 30 ºC in a TRIS·HCl buffer pH 6. It must be mentioned that a (*R*)-configuration is required for the formation of the Levofloxacin, so the use of evo-1.1.200 seems to be an excellent tool for the introduction of the desired chirality.



Scheme 4. Chemoenzymatic synthetic alternatives for the production of the enantiopure alcohol (*R*)-**5e** and the corresponding Levofoxacin precursor (*S*)-**4e**.

In addition, the lipase-catalyzed hydrolysis of the racemic acetate **6e** was attempted, which would give direct access to the desired (*R*)-alcohol **5e**. Firstly, the chemical reduction of the ketone **3e** was initially performed with sodium borohydride. In this case, the unexpected formation of a (61:39) mixture of the desired alcohol (±)-**5e** and the structural isomer 2-(2,3-difluoro-6-nitrophenoxy)propan-1-ol (**11**) was observed. The formation of this side-product was almost suppressed using a mild reducing agent as the ammonia borane complex,[22] thus avoiding a basic reaction medium but also a basic work-up in the reaction, recovering **5e** in 78% yield after 1 h at 30 ºC. Then, the alcohol was chemically acetylated in 93% yield using acetic anhydride, to later explore its RML IM-catalyzed hydrolysis. After

53 h a total selectivity towards the formation of the (*R*)-alcohol was attained, obtaining the (*S*)-acetate **6e** in 84% *ee* and the desired enantiopure (*R*)-alcohol **5e** in 45% isolated yield.

Finally, taking the alcohol (*R*)-**5e**, a four step sequence was carried out involving the reduction of the nitro functionality, protection of the free amine, cyclization reaction in Mitsunobu condition and *N*-tosyl deprotection, leading to the valuable enantiopure Levofloxacin precursor (*S*)-**4e** in good overall yield (36%).

Conclusions

Two different classes of enzymes have efficiently served for the development of the asymmetric synthesis of both 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines enantiomers. Alcohol dehydrogenases and lipases have been identified as good catalysts for the synthesis of valuable optically active precursors as key independent features of the synthetic route. The alcohol dehydrogenase from *Rhodococcus ruber* has allowed the selective bioreduction of 1-(2-nitrophenoxy)propan-2-ones with complete selectivity towards the quantitative conversion into the (*S*)-alcohols, while the evo-1.1.200 led to the corresponding enantiopure (*R*)-enantiomers. On the other hand a lipase screening has been carried out, finding *Rhizomucor miehei* lipase as a versatile hydrolase for the development of classical kinetic resolutions through complementary acylative and hydrolytic processes. The chemoenzymatic route has also served to synthesize a valuable Levofloxacin precursor, which has been isolated in enantiopure form after a six-step sequence in good overall yield.

Experimental section

General procedure for the synthesis of ketones 3a-e. To a solution of the corresponding nitrophenol **1a-e** (3.02 mmol) in toluene (1 mL) chloroacetone (481 μL, 6.04 mmol), potassium bromide (43 mg, 0.36 mmol), sodium hydrogencarbonate (279 mg, 3.32 mmol) and tributylmethylammonium chloride solution (75% weight in water, 16 μL, 0.065 mmol) were successively added. The mixture was stirred

and heated at 65 ºC for 6 h and then additional chloroacetone (120 μL, 1.51 mmol) was added. The reaction was further heated at 65 ºC for 18 h and after this time water (1 mL) was added. The pH of the mixture was adjusted to 6.5-7 at 55-60 ºC by the addition of HCl 1N (between 7-15 drops). The layers were separated in a separatory funnel, and the aqueous phase was discarded. Then, an aqueous 5% NaCl solution (2 mL) was added to the organic phase and transferred to a round-bottom flask. The resulting mixture was vigorously stirred at 55-60 ºC for 10 min. The layers were again separated in a separatory funnel, the organic layer was collected, dried over Na_2SO_4, filtered and the solvent removed by distillation under reduced pressure. The resulting crude was washed with toluene to assure the complete chloroacetone removal, affording the corresponding pure ketones **3a-e** (84-93%).

1-(2-Nitrophenoxy)propan-2-one (3a). White solid (548 mg, 93% Yield). R_f (40% EtOAc/Hexane): 0.31. Mp: 68-70 ºC. IR (KBr): 3055, 2987, 2306, 1739, 1724, 1608, 1528, 1357, 1166, 1052, 860 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.62 (s, 2H), 6.94 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 0.9 Hz, 1H), 7.03-7.10 (m, 1H), 7.53 (ddd, $^3J_{HH}$ = 8.6, 7.5 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.87 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.0 (CH_3), 73.8 (CH_2), 114.7 (CH), 121.7 (CH), 126.1 (CH), 134.4 (CH), 140.1 (C), 151.1 (C), 204.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_9NNaO_4)^+$ $(M+Na)^+$: 218.0424 found: 218.0402.

1-(4-Fluoro-2-nitrophenoxy)propan-2-one (3b). Light yellow solid (592 mg, 92% Yield). R_f (40% EtOAc/Hexane): 0.21. Mp: 82-83 ºC. IR (KBr): 3055, 2987, 2343, 1740, 1723, 1538, 1498, 1420, 1360, 1204, 1049, 815 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 2.33 (s, 3H), 4.62 (s, 2H), 6.96 (dd, $^3J_{HH}$ = 9.2 Hz, $^4J_{FH}$ = 4.2 Hz, 1H), 7.28 (ddd, $^3J_{HH}$ = 9.3 Hz, $^3J_{FH}$ = 7.4, $^4J_{HH}$ = 3.1 Hz, 1H), 7.63 (dd, $^3J_{FH}$ = 7.7 Hz, $^4J_{HH}$ = 3.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.9 (CH_3), 74.6 (CH_2), 113.4 (d, $^2J_{FC}$ = 27.5 Hz, CH), 116.7 (d, $^3J_{FC}$ = 7.8 Hz, CH), 121.4 (d, $^2J_{FC}$ = 23.0 Hz, CH), 139.9 (d, $^3J_{FC}$ = 6.8 Hz, C), 147.8 (C), 156.1 (d, $^1J_{FC}$ = 245.6 Hz, C), 204.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_8FNNaO_4)^+$ $(M+Na)^+$: 236.0330 found: 236.0335.

1-(4-Methoxy-2-nitrophenoxy)propan-2-one (3c). Yellow solid (578 mg, 85% Yield). R_f (40%

EtOAc/Hexane): 0.38. Mp: 80-81 ºC. IR (KBr): 3055, 2987, 2348, 1739, 1718, 1534, 1499, 1430, 1360, 1224, 1052, 1035, 896, 811 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.80 (s, 3H), 4.57 (s, 2H), 6.92 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 7.07 (dd, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 3.1 Hz 1H), 7.39 (d, $^4J_{HH}$ = 3.1 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.0 (CH_3), 56.3 (CH_3), 75.1 (CH_2), 110.4 (CH), 117.2 (CH), 121.0 (CH), 140.4 (C), 145.5 (C), 154.1 (C), 204.9 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}NNaO_5)^+$ $(M+Na)^+$: 248.0529 found: 248.0540.

1-(5-methyl-2-nitrophenoxy)propan-2-one (3d). Light yellow solid (531 mg, 84% Yield). R_f (40% EtOAc/Hexane): 0.41. Mp: 98-99 ºC. IR (KBr): 3056, 1724, 1723, 1608, 1521, 1419, 1348, 1179, 1097, 1051, 896, 820 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.41 (s, 3H), 4.60 (s, 2H), 6.73 (s, 1H), 6.90 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.85 (d, $^3J_{HH}$ = 8.3 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.8 (CH_3), 26.8 (CH_3), 73.7 (CH_2), 115.2 (CH), 122.2 (CH), 126.1 (CH), 137.4 (C), 146.3 (C), 151.2 (C), 204.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}NNaO_4)^+$ $(M+Na)^+$: 232.0580 found: 232.0581.

1-(2,3-Difluoro-6-nitrophenoxy)propan-2-one (3e). Light yellow solid (593 mg, 85% Yield). R_f (40% EtOAc/Hexane): 0.69. Mp: 43-45 ºC. IR (KBr): 3059, 2987, 2924, 1741, 1627, 1597, 1541, 1496, 1358, 1217, 1070, 813 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.80 (d, $^5J_{FH}$ = 1.3 Hz, 2H), 7.05 (ddd, $^3J_{HH}$ = 9.3 Hz, $^3J_{FH}$ = 8.8 Hz, $^4J_{FH}$ = 7.2 Hz, 1H), 7.72 (ddd, $^3J_{HH}$ = 9.4 Hz, $^4J_{FH}$ = 5.2, $^5J_{FH}$ = 2.4 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.4 (CH_3), 78.1 (d, $^4J_{FC}$ = 5.3 Hz, CH_2), 111.7 (d, $^2J_{FC}$ = 19.3 Hz, CH), 120.8 (dd, $^3J_{FC}$ = 9.0 Hz, $^4J_{FC}$ = 4.0 Hz, CH), 140.0 (d, $^3J_{FC}$ = 3.7 Hz, C), 142.6 (dd, $^2J_{FC}$ = 10.9 Hz, $^3J_{FC}$ = 2.9 Hz, C), 144.7 (dd, $^1J_{FC}$ = 252.9 Hz, $^2J_{FC}$ = 14.7 Hz, C), 154.1 (dd, $^1J_{FC}$ = 259.6 Hz, $^2J_{FC}$ = 11.6 Hz, C), 203.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_7F_2NNaO_4)^+$ $(M+Na)^+$: 254.0235 found: 254.0249.

Synthesis of racemic 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (4a). Pd/C (10% weight loading, 100 mg) was added to a solution of ketone **3a** (2.05 mmol, 400 mg) in methanol (0.02 M, 102.5 mL) placed in the reaction vessel of a Parr hydrogenator. The air was evacuated and hydrogen was

introduced into the system until 4 atm of pressure. The suspension was stirred for 6 h at room temperature and afterwards the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O (20 mL) and the metal catalyst was filtered off through a diatomaceous earth plug. The reaction crude was obtained after solvent evaporation and purified by column chromatography on silica gel (20% Et_2O/Hexane), affording the racemic benzoxazine **4a** (245 mg, 80% Yield). Spectroscopical data are in agreement with those previously reported in the literature using a different procedure.[23]

General procedure for the synthesis of racemic nitro alcohols 5a-d. Sodium borohydride (19 mg, 0.50 mmol) was added to a solution of the corresponding ketone **3a-d** (1.00 mmol) in dry MeOH (3.8 mL) at 0 ºC. The solution was stirred at room temperature for 45 min, quenching the reaction by the addition of water (10 mL). MeOH was removed by distillation under reduced pressure and the aqueous residue extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried and the solvent removed by distillation under reduced pressure, affording the corresponding nitro alcohols **5a-d** (87-94%).

1-(2-Nitrophenoxy)propan-2-ol (5a). Yellow oil (172 mg, 87% Yield). R_f (40% EtOAc/Hexane): 0.19. IR (NaCl): 3586, 3440, 3055, 2985, 2937, 2307, 1609, 1526, 1354, 1166, 1020, 860 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 3.03 (br s, 1H), 3.88 (dd, $^2J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 7.5 Hz, 1H), 4.07 (dd, $^2J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 4.12-4.24 (m, 1H), 6.98-7.15 (m, 2H), 7.46-7.61 (m, 1H), 7.80 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.5 (CH_3), 65.8 (CH), 75.0 (CH_2), 115.0 (CH), 120.8 (CH), 125.8 (CH), 134.5 (CH), 139.6 (C), 152.2 (C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_{11}NNaO_4)^+$ $(M+Na)^+$: 220.0580 found: 220.0609.

1-(4-Fluoro-2-nitrophenoxy)propan-2-ol (5b). Yellow solid (202 mg, 94% Yield). R_f (40% EtOAc/Hexane): 0.26. Mp: 74-76 ºC. IR (KBr): 3586, 3441, 3055, 2984, 2935, 2340, 1534, 1499, 1354, 1203, 1141, 1022, 815, 786 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.28 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.98

(br s, 1H), 3.90 (dd, $^{2}J_{HH}$ = 9.0 Hz, $^{3}J_{HH}$ = 7.4 Hz, 1H), 4.10 (dd, $^{2}J_{HH}$ = 9.0 Hz, $^{3}J_{HH}$ = 3.2 Hz, 1H), 4.15-4.26 (m, 1H), 7.08 (dd, $^{3}J_{HH}$ = 9.2 Hz, $^{4}J_{FH}$ = 4.3 Hz, 1H), 7.28 (ddd, $^{3}J_{HH}$ = 9.4 Hz, $^{3}J_{FH}$ = 7.3 Hz, $^{4}J_{HH}$ = 3.1 Hz, 1H), 7.60 (dd, $^{3}J_{FH}$ = 7.8 Hz, $^{4}J_{HH}$ = 3.1 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.5 (CH_3), 65.9 (CH), 75.8 (CH_2), 113.0 (d, $^{2}J_{FH}$ = 27.5 Hz, CH), 116.6 (d, $^{3}J_{FH}$ = 7.7 Hz, CH), 121.5 (d, $^{2}J_{FH}$ = 22.8 Hz, CH), 139.3 (d, $^{3}J_{FC}$ = 8.3 Hz, C), 148.9 (d, $^{4}J_{FC}$ = 3.0 Hz, C), 155.5 (d, $^{1}J_{FC}$ = 244.3 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_{10}FNNaO_4)^+$ $(M+Na)^+$: 238.0486 found: 238.0500.

1-(4-Methoxy-2-nitrophenoxy)propan-2-ol (5c). Light orange solid (211 mg, 93% Yield). R_f (40% EtOAc/Hexane): 0.18. Mp: 75-77 ºC. IR (KBr): 3576, 3431, 3058, 2964, 2922, 2840, 2343, 1527, 1496, 1346, 1216, 1040, 817 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.25 (d, $^{3}J_{HH}$ = 6.4 Hz, 3H), 2.76 (br s, 1H), 3.80 (s, 3H), 3.81-3.91 (m, 1H), 4.07 (dd, $^{2}J_{HH}$ = 9.1 Hz, $^{3}J_{HH}$ = 3.1 Hz, 1H), 4.12-4.27 (m, 1H), 7.01 (d, $^{3}J_{HH}$ = 9.1 Hz, 1H), 7.09 (dd, $^{3}J_{HH}$ = 9.1 Hz, $^{4}J_{HH}$ = 3.0 Hz, 1H), 7.37 (d, $^{4}J_{HH}$ = 3.0 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.5 (CH_3), 56.1 (CH_3), 66.0 (CH), 76.1 (CH_2), 110.0 (CH), 117.1 (CH), 121.3 (CH), 139.8 (C), 146.6 (C), 153.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{13}NNaO_5)^+$ $(M+Na)^+$: 250.0686 found: 250.0711.

1-(5-Methyl-2-nitrophenoxy)propan-2-ol (5d). Light orange solid (186 mg, 88% Yield). R_f (40% EtOAc/Hexane): 0.18. Mp: 53-54 ºC. IR (KBr): 3583, 3435, 3055, 2985, 2935, 1609, 1592, 1517, 1347, 1182, 1093, 1031, 841 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.26 (d, $^{3}J_{HH}$ = 6.4 Hz, 3H), 2.37 (s, 3H), 3.02 (br s, 1H), 3.86 (dd, $^{2}J_{HH}$ = 9.0 Hz, $^{3}J_{HH}$ = 7.6 Hz, 1H), 4.08 (dd, $^{2}J_{HH}$ = 9.0 Hz, $^{3}J_{HH}$ = 3.2 Hz, 1H), 4.12-4.25 (m, 1H), 6.79 (d, $^{3}J_{HH}$ = 8.3 Hz, 1H), 6.84 (s, 1H), 7.76 (d, $^{3}J_{HH}$ = 8.3 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.5 (CH_3), 22.0 (CH_3), 66.0 (CH), 75.2 (CH_2), 115.7 (CH), 121.7 (CH), 126.2 (CH), 137.4 (C), 146.4 (C), 152.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{13}NNaO_4)^+$ $(M+Na)^+$: 234.0737 found: 234.0727.

Synthesis of racemic 1-(2,3-difluoro-6-nitrophenoxy)propan-2-ol (5e). Ammonia borane complex (24 mg, 0.76 mmol) was added to a solution of ketone **3e** (1.51 mmol) in dry THF (4.6 mL) and the

mixture was stirred at 30 ºC for 1 h. After this time the reaction was stopped by careful addition at 0 ºC of an aqueous HCl 2 M solution until an acidic pH (pH < 3) was achieved. Then, the mixture was extracted with CH_2Cl_2 (3 x 10 mL), the organic layers were combined, dried, filtered and the solvent was removed by distillation under reduced pressure. The crude was purified by column chromatography on silica gel (10% EtOAc/Hexane), affording the nitro alcohol **5e** (275 mg, 78% Yield). Yellow oil. R_f (40% EtOAc/Hexane): 0.51. IR (NaCl): 3569, 3439, 3054, 2987, 2360, 2307, 1653, 1539, 1355, 1163, 1022, 852, 665 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.83 (d, $^3J_{HH}$ = 3.7 Hz, 1H), 4.10 (ddd, $^2J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 7.7 Hz, $^5J_{FH}$ = 1.9 Hz, 1H), 4.15-4.28 (m, 1H), 4.38 (dt, $^2J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 2.4 Hz, $^5J_{FH}$ = 2.4 Hz, 1H), 7.01 (ddd, $^3J_{HH}$ = 9.4 Hz, $^3J_{FH}$ = 8.8 Hz, $^4J_{FH}$ = 7.2 Hz, 1H), 7.72 (ddd, $^3J_{HH}$ = 9.4 Hz, $^4J_{FH}$ = 5.3, $^5J_{FH}$ = 2.4 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.2 (CH_3), 66.5 (CH), 81.2 (d, $^4J_{FC}$ = 5.7 Hz, CH_2), 111.1 (d, $^2J_{FC}$ = 19.3 Hz, CH), 120.9 (dd, $^3J_{FC}$ = 9.2 Hz, $^4J_{FC}$ = 4.0 Hz, CH), 139.5 (d, $^3J_{FC}$ = 1.9 Hz, C), 143.8 (dd, $^2J_{FC}$ = 10.9 Hz, $^3J_{FC}$ = 2.8 Hz, C), 144.7 (dd, $^1J_{FC}$ = 253.0 Hz, $^2J_{FC}$ = 14.3 Hz, C), 154.4 (dd, $^1J_{FC}$ = 259.6 Hz, $^2J_{FC}$ = 11.6 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_9F_2NNaO_4)^+$ $(M+Na)^+$: 256.0392, found: 256.0390.

General procedure for the synthesis of racemic acetates 6a-e. 4-Dimethylaminopyridine (12 mg, 0.1 mmol), triethylamine (198 μL, 1.42 mmol) and acetic anhydride (90 μL, 0.95 mmol) were successively added to a solution of the corresponding alcohol **5a-e** (0.47 mmol) in dry CH_2Cl_2 (3.2 mL). The reaction was stirred at room temperature for 30 min and after this time the solvent removed by distillation under reduced pressure. The crude was purified by column chromatography on silica gel (EtOAc/Hexane mixtures), affording the corresponding acetates **6a-e** (88-94%).

1-(2-Nitrophenoxy)propan-2-yl acetate (6a). Intense yellow oil (106 mg, 94% Yield). R_f (40% EtOAc/Hexane): 0.41. IR (NaCl): 3055, 2986, 2940, 2343, 1734, 1609, 1528, 1355, 1239, 1091, 1035, 992, 860 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.38 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.06 (s, 3H), 4.12 (d, $^3J_{HH}$ = 5.1 Hz, 2H), 5.14-5.53 (m, 1H), 6.96-7.17 (m, 2H), 7.51 (ddd, $^3J_{HH}$ = 9.0, 7.5 Hz, $^4J_{HH}$ = 1.7 Hz, 1H),

7.82 (dd, $^{3}J_{HH}$ = 8.1 Hz, $^{4}J_{HH}$ = 1.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.6 (CH_3), 21.2 (CH_3), 68.3 (CH), 71.4 (CH_2), 114.9 (CH), 121.0 (CH), 125.8 (CH), 134.2 (CH), 140.2 (C), 151.9 (C), 170.7 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{13}NNaO_5)^+$ $(M+Na)^+$: 262.0686 found: 262.0708.

1-(4-Fluoro-2-nitrophenoxy)propan-2-yl acetate (6b). White solid (106 mg, 88% Yield). R_f (40% EtOAc/Hexane): 0.67. Mp: 63-64 ºC. IR (KBr): 3055, 2987, 2307, 1738, 1537, 1499, 1373, 1357, 1241, 1203, 1142, 1083, 1034, 943, 814, 788 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.37 (d, $^{3}J_{HH}$ = 6.5 Hz, 3H), 2.05 (s, 3H), 4.11 (d, $^{3}J_{HH}$ = 5.0 Hz, 2H), 5.18-5.30 (m, 1H), 7.06 (dd, $^{3}J_{HH}$ = 9.2 Hz, $^{4}J_{FH}$ = 4.3 Hz, 1H), 7.26 (ddd, $^{3}J_{HH}$ = 9.3 Hz, $^{3}J_{FH}$ = 7.4, $^{4}J_{HH}$ = 3.1 Hz, 1H), 7.57 (dd, $^{3}J_{FH}$ = 7.7 Hz, $^{4}J_{HH}$ = 3.1 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.6 (CH_3), 21.2 (CH_3), 68.2 (CH), 72.3 (CH_2), 113.0 (d, $^{2}J_{FH}$ = 27.4 Hz, CH), 116.7 (d, $^{3}J_{FH}$ = 7.9 Hz, CH), 121.1 (d, $^{2}J_{FH}$ = 22.9 Hz, CH), 139.3 (d, $^{3}J_{FC}$ = 9.6 Hz, C), 148.5 (d, $^{4}J_{FC}$ = 2.6 Hz, C), 155.7 (d, $^{1}J_{FC}$ = 244.6 Hz, C), 170.6 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{12}FNNaO_5)^+$ $(M+Na)^+$: 280.0592 found: 280.0613.

1-(4-Methoxy-2-nitrophenoxy)propan-2-yl acetate (6c). Yellow solid (116 mg, 92% Yield). R_f (40% EtOAc/Hexane): 0.46. Mp: 55-56 ºC. IR (KBr): 3055, 2986, 2307, 1734, 1533, 1499, 1373, 1354, 1243, 1041, 812 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.35 (d, $^{3}J_{HH}$ = 6.5 Hz, 3H), 2.06 (s, 3H), 3.80 (s, 3H), 4.07 (d, $^{3}J_{HH}$ = 4.8 Hz, 2H), 5.16-5.28 (m, 1H), 7.01 (d, $^{3}J_{HH}$ = 9.1 Hz, 1H), 7.07 (dd, $^{3}J_{HH}$ = 9.1 Hz, $^{4}J_{HH}$ = 3.0 Hz, 1H), 7.34 (d, $^{4}J_{HH}$ = 2.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.6 (CH_3), 21.2 (CH_3), 56.2 (CH_3), 68.5 (CH), 72.6 (CH_2), 109.9 (CH), 117.4 (CH), 120.8 (CH), 140.5 (C), 146.2 (C), 153.6 (C), 170.7 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{15}NNaO_6)^+$ $(M+Na)^+$: 292.0792 found: 292.0796.

1-(5-Methyl-2-nitrophenoxy)propan-2-yl acetate (6d). White solid (107 mg, 90% Yield). R_f (40% EtOAc/Hexane): 0.63. Mp: 76-77 ºC. IR (KBr): 3054, 2987, 2306, 1734, 1609, 1521, 1423, 1093, 1040 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.39 (d, $^{3}J_{HH}$ = 6.5 Hz, 3H), 2.06 (s, 3H), 2.40 (s, 3H), 4.11 (d, $^{3}J_{HH}$ = 5.1 Hz, 2H), 5.22-5.31 (m, 1H), 6.83 (dd, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 0.7 Hz, 1H), 6.86 (s, 1H), 7.77 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.7 (CH_3), 21.2 (CH_3), 22.0 (CH_3), 68.4 (CH),

71.4 (CH_2), 115.5 (CH), 121.7 (CH), 126.0 (CH), 137.9 (C), 145.9 (C), 152.2 (C), 170.7 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{12}H_{15}NNaO_5)^+$ $(M+Na)^+$: 276.0842 found: 276.0856.

1-(2,3-Difluoro-6-nitrophenoxy)propan-2-yl acetate (6e). Intense yellow oil (120 mg, 93% Yield). R_f (40% EtOAc/Hexane): 0.68. IR (NaCl): 3447, 3059, 2988, 2942, 2886, 2343, 1739, 1627, 1541, 1495, 1357, 1237, 1020, 813 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.33 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 2.03 (s, 3H), 4.23 (ddd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 5.9 Hz, $^5J_{FH}$ = 0.9 Hz, 1H), 4.33 (ddd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 3.4 Hz, $^5J_{FH}$ = 1.0 Hz, 1H), 5.16-5.28 (m, 1H), 7.01 (td, $^3J_{HH}$ = 9.1 Hz, $^3J_{FH}$ = 9.1 Hz, $^4J_{FH}$ = 7.2 Hz, 1H), 7.66 (ddd, $^3J_{HH}$ = 9.4 Hz, $^4J_{FH}$ = 5.2 Hz, $^5J_{FH}$ = 2.4 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.1 (CH_3), 21.0 (CH_3), 68.8 (CH), 77.2 (d, $^4J_{FC}$ = 5.2 Hz, CH_2), 111.4 (d, $^2J_{FC}$ = 19.4 Hz, CH), 120.4 (dd, $^3J_{FC}$ = 9.1 Hz, $^4J_{FC}$ = 4.1 Hz, CH), 140.3 (d, $^3J_{FC}$ = 2.2 Hz, C), 143.4 (dd, $^2J_{FC}$ = 9.7 Hz, $^3J_{FC}$ = 4.41 Hz, C), 144.9 (dd, $^1J_{FC}$ = 253.6 Hz, $^2J_{FC}$ = 14.2 Hz, C), 154.0 (dd, $^1J_{FC}$ = 259.0 Hz, $^2J_{FC}$ = 11.3 Hz, C), 170.5 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{11}F_2NNaO_5)^+$ $(M+Na)^+$: 298.0497 found: 298.0528.

General procedure for the synthesis of racemic and optically active amino alcohols 8a-e. A hydrogen atmosphere was done using a hydrogen balloon connected to a round-bottom flask, which contains a suspension of the corresponding nitro alcohol **5a-e** (2.50 mmol) and PtO_2 (150 mg, 0.66 mmol) in dry MeOH (14 mL). The resulting suspension was stirred at room temperature overnight and then the reaction was stopped by filtering the mixture through a diatomaceous earth plug. The solvent was removed by distillation under reduced pressure and the crude purified by column chromatography on silica gel (EtOAc/Hexane mixtures), affording the corresponding amino alcohols **8a-e** (65-98%).

1-(2-Aminophenoxy)propan-2-ol (8a). White solid (397 mg, 95% Yield). R_f (40% EtOAc/Hexane): 0.16. Mp: 66-67 ºC. IR (KBr): 3391, 3054, 2986, 2924, 2340, 1653, 1558, 1506, 1219, 1154 cm^{-1}. ^1H NMR (300.13 MHz, CD_3OD): δ 1.30 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 3.83 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 6.9 Hz, 1H), 3.94 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 3.7 Hz, 1H), 4.16 (dquint, $^3J_{HH}$ = 6.5, 3.7 Hz, 1H), 4.91 (br s, 3H), 6.66-6.75 (m, 1H), 6.75-6.90 (m, 3H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 19.5 (CH_3), 67.1 (CH), 74.7

(CH_2), 112.9 (CH), 117.0 (CH), 119.8 (CH), 122.3 (CH), 137.8 (C), 148.4 (C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_{14}NO_2)^+$ $(M+H)^+$: 168.1019 found: 168.1020. $[\alpha]_D^{20}$ +37.0 (*c* 0.3, EtOH) [for (*S*)-**8a** in >99% *ee*].

1-(2-Amino-4-fluorophenoxy)propan-2-ol (8b). Brown solid (444 mg, 96% Yield). R_f (40% EtOAc/Hexane): 0.16. Mp: 119-121 ºC. IR (KBr): 3391, 3054, 2985, 2933, 2341, 1623, 1513, 1218, 1160, 1035, 970, 842 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 3.77 (br s, 3H), 3.78 (dd, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.8 Hz, 1H), 3.90 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 3.0 Hz, 1H), 4.06-4.25 (m, 1H), 6.36 (ddd, $^3J_{HH}$ = 8.6 Hz, $^3J_{FH}$ = 8.6 Hz, $^4J_{HH}$ = 2.9 Hz, 1H), 6.43 (dd, $^3J_{FH}$ = 9.8 Hz, $^4J_{HH}$ = 2.9 Hz, 1H), 6.68 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{FH}$ = 5.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.0 (CH_3), 66.4 (CH), 75.1 (CH_2), 102.6 (d, $^2J_{FH}$ = 26.7 Hz, CH), 103.9 (d, $^2J_{FH}$ = 23.0 Hz, CH), 113.6 (d, $^3J_{FH}$ = 10.0 Hz, CH), 138.0 (d, $^3J_{FC}$ = 11.0 Hz, C), 142.5 (C), 158.2 (d, $^1J_{FC}$ = 237.3 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_9H_{13}FNO_2)^+$ $(M+H)^+$: 186.0925 found: 186.0941. $[\alpha]_D^{20}$ +21.6 (*c* 0.7, EtOH) [for (*S*)-**8b** in >99% *ee*].

1-(2-Amino-4-methoxyphenoxy)propan-2-ol (8c). Light yellow solid (483 mg, 98% Yield). R_f (40% EtOAc/Hexane): 0.10. Mp: 75-76 ºC. IR (KBr): 3583, 3391, 3054, 2986, 2340, 1623, 1516, 1419, 1220, 1168, 962 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.22 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 3.68 (br s, 3H), 3.70 (s, 3H), 3.75 (dd, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.8 Hz, 1H), 3.87 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 4.07-4.22 (m, 1H), 6.22 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.9 Hz, 1H), 6.30 (d, $^4J_{HH}$ = 2.9 Hz, 1H), 6.69 (d, $^3J_{HH}$ = 8.7 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.9 (CH_3), 55.5 (CH_3), 66.3 (CH), 74.4 (CH_2), 102.5 (CH), 102.6 (CH), 114.2 (CH), 137.8 (C), 140.9 (C), 155.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{16}NO_3)^+$ $(M+H)^+$: 198.1125 found: 198.1135. $[\alpha]_D^{20}$ +23.2 (*c* 0.5, EtOH) [for (*S*)-**8c** in >99% *ee*].

1-(2-Amino-5-methylphenoxy)propan-2-ol (8d). Light pink solid (421 mg, 93% Yield). R_f (40% EtOAc/Hexane): 0.15. Mp: 76-78 ºC. IR (KBr): 3402, 3054, 2985, 2929, 2523, 2307, 1592, 1520, 1420, 1152, 1132, 1041, 812 cm^{-1}. ^1H NMR (400.13 MHz, CD_3OD): δ 1.26 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.21 (s, 3H), 3.78 (dd, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 6.9 Hz, 1H), 3.88 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 3.7 Hz, 1H), 4.11

(dquint, $^3J_{HH}$ = 6.5, 3.8 Hz, 1H), 4.86 (br s, 3H), 6.56 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 6.64 (s, 1H), 6.66 (d, $^3J_{HH}$ = 7.8 Hz, 1H). ^{13}C NMR (100.6 MHz, CD_3OD): δ 19.5 (CH_3), 21.1 (CH_3), 67.1 (CH), 74.7 (CH_2), 113.8 (CH), 117.2 (CH), 122.5 (CH), 129.6 (C), 134.8 (C), 148.4 (C). HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{16}NO_2)^+$ $(M+H)^+$: 182.1176 found: 182.1173. $[\alpha]_D^{20}$ +12.5 (*c* 0.6, EtOH) [for (*S*)-**8d** in >99% *ee*].

1-(6-Amino-2,3-difluorophenoxy)propan-2-ol (8e). Yellow solid (330 mg, 65% Yield). R_f (40% EtOAc/Hexane): 0.25. Mp: 56-58 ºC. IR (KBr): 3398, 3054, 2986, 1653, 1559, 1507, 1490, 1419, 1165, 1047, 896 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.19 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 3.61 (br s, 3H), 3.83 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.8 Hz, 1H), 4.03-4.16 (m, 2H), 6.39 (ddd, $^3J_{HH}$ = 9.0 Hz, $^4J_{FH}$ = 4.8, $^5J_{FH}$ = 2.3 Hz, 1H), 6.70 (ddd, $^3J_{FH}$ = 9.9 Hz, $^3J_{HH}$ = 9.0 Hz, $^4J_{FH}$ = 8.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.5 (CH_3), 66.6 (CH), 79.3 (d, $^4J_{FC}$ = 3.3 Hz, CH_2), 109.6 (dd, $^3J_{FC}$ = 6.9 Hz, $^4J_{FC}$ = 3.2 Hz, CH), 111.4 (d, $^2J_{FC}$ = 17.8 Hz, CH), 135.5 (dd, $^2J_{FC}$ = 10.4 Hz, $^3J_{FC}$ = 1.3 Hz, C), 136.8 (dd, $^3J_{FC}$ = 2.7 Hz, $^4J_{FC}$ = 1.2 Hz, C), 144.7 (dd, $^1J_{FC}$ = 239.0 Hz, $^2J_{FC}$ = 11.3 Hz, C), 144.9 (dd, $^1J_{FC}$ = 247.1 Hz, $^2J_{FC}$ = 14.6 Hz, C). HRMS (ESI$^+$, *m/z*): calcd for $(C_9H_{12}F_2NO_2)^+$ $(M+H)^+$: 204.0831 found: 204.0857. $[\alpha]_D^{20}$ -22.4 (*c* 0.7, EtOH) [for (*R*)-**8e** in >99% *ee*].

General procedure for the synthesis of racemic and optically active sulfonamides 9a-e. Pyridine (56 μL, 0.69 mmol) and *p*-toluensulfonyl chloride (134 mg, 0.70 mmol) were added to a solution of the corresponding amino alcohol **8a-e** (0.54 mmol) in dry CH_2Cl_2 (13.5 mL). The solution was stirred at room temperature for 12 h until complete disappearance of the starting material was observed by TLC analysis. Almost all the solvent was removed by distillation under reduced pressure, and the resulting residue dissolved in EtOAc (20 mL) and washed firstly with an aqueous saturated NH_4Cl solution (2 x 20 mL), an aqueous HCl 1 M solution (2 x 20 mL) and finally an aqueous saturated NaCl solution (2 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated by distillation under reduced pressure. The crude was purified by column chromatography on silica gel (EtOAc/Hexane mixtures), affording the corresponding sulfonamides **9a-e** (71-80%).

***N*-(2-(2-Hydroxypropoxy)phenyl)-4-methylbenzenesulfonamide (9a).** White solid (135 mg, 78% Yield). R_f (40% EtOAc/Hexane): 0.25. Mp: 166-167 ºC. IR (KBr): 3545, 3297, 3054, 2985, 2920, 2343, 1596, 1501, 1404, 1340, 1156, 1114, 1088, 934, 819 cm^{-1}. ^1H NMR (300.13 MHz, $(CD_3)_2CO$): δ 1.13 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.34 (s, 3H), 3.61 (dd, $^2J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 7.6 Hz 1H), 3.71 (dd, $^2J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 3.2 Hz, 1H), 3.90-4.03 (m, 1H), 4.50 (br s, 1H), 6.84-6.97 (m, 2H), 7.05 (td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.23-7.34 (m, 2H), 7.51 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.58-7.69 (m, 2H), 8.46 (br s, 1H). ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$): δ 19.2 (CH_3), 21.3 (CH_3), 66.0 (CH), 75.4 (CH_2), 113.4 (CH), 121.7 (CH), 123.7 (CH), 126.6 (CH), 127.4 (C), 127.9 (2xCH), 130.1 (2xCH), 138.2 (C), 144.2 (C), 151.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{19}NNaO_4S)^+$ $(M+Na)^+$: 344.0927 found: 344.0941. $[\alpha]_D^{20}$ +15.1 (*c* 1.0, $CHCl_3$) [for (*S*)-**9a** in >99% *ee*].

***N*-(5-Fluoro-2-(2-hydroxypropoxy)phenyl)-4-methylbenzenesulfonamide (9b).** Colorless viscous oil (147 mg, 80% Yield). R_f (60% Et_2O/Hexane): 0.14. IR (NaCl): 3342, 3054, 2986, 2934, 2362, 1616, 1506, 1419, 1339, 1170, 1153, 1091, 1034, 812 cm^{-1}. ^1H NMR (300.13 MHz, $(CD_3)_2CO$): δ 1.15 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.34 (s, 3H), 3.61 (dd, $^2J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 3.77 (dd, $^2J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 3.0 Hz, 1H), 3.94-4.07 (m, 1H), 4.69 (br s, 1H), 6.78 (ddd, $^3J_{HH}$ = 9.0 Hz, $^3J_{FH}$ = 8.3 Hz, $^4J_{HH}$ = 3.1 Hz, 1H), 6.91 (dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{FH}$ = 5.1 Hz, 1H), 7.19-7.39 (m, 3H), 7.66-7.74 (m, 2H), 8.74 (br s, 1H). ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$): δ 19.1 (CH_3), 21.3 (CH_3), 66.0 (CH), 76.3 (CH_2), 109.5 (d, $^2J_{FC}$ = 27.8 Hz, CH), 111.6 (d, $^2J_{FC}$ = 23.0 Hz, CH), 114.9 (d, $^3J_{FC}$ = 9.4 Hz, CH), 127.9 (2xCH), 129.0 (d, $^3J_{FC}$ = 11.0 Hz, C), 130.3 (2xCH), 137.8 (C), 144.6 (C), 146.8 (d, $^4J_{FC}$ = 2.2 Hz, C), 157.6 (d, $^1J_{FC}$ = 237.0 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{18}FNNaO_4S)^+$ $(M+Na)^+$: 362.0833 found: 362.0847. $[\alpha]_D^{20}$ +16.0 (*c* 1.0, $CHCl_3$) [for (*S*)-**9b** in >99% *ee*].

***N*-(2-(2-Hydroxypropoxy)-5-methoxyphenyl)-4-methylbenzenesulfonamide (9c).** White solid (135 mg, 71% Yield). R_f (40% EtOAc/Hexane): 0.18. Mp: 132-133 ºC. IR (KBr): 3339, 3054, 2935, 2356, 1504, 1420, 1340, 1159, 1088, 956, 816 cm^{-1}. ^1H NMR (300.13 MHz, $(CD_3)_2CO$): δ 1.14 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.35 (s, 3H), 3.54 (dd, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.7 Hz, 1H), 3.69-3.75 (m, 1H), 3.71 (s, 3H), 3.92-

4.07 (m, 1H), 4.53 (d, $^3J_{HH}$ = 4.1 Hz, 1H), 6.58 (dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 3.0 Hz, 1H), 6.83 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 7.13 (d, $^4J_{HH}$ = 3.0 Hz, 1H), 7.23-7.32 (m, 2H), 7.67-7.72 (m, 2H), 8.58 (br s, 1H). ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$): δ 19.3 (CH_3), 21.3 (CH_3), 55.8 (CH_3), 66.1 (CH), 76.7 (CH_2), 108.9 (CH), 110.2 (CH), 115.4 (CH), 128.1 (2xCH), 128.9 (C), 130.2 (2xCH), 138.1 (C), 144.4 (C), 144.6 (C), 155.1 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{17}H_{21}NNaO_5S)^+$ $(M+Na)^+$: 374.1033 found: 374.1050. $[\alpha]_D^{20}$ +24.2 (*c* 1.0, $CHCl_3$) [for (*S*)-**9c** in >99% *ee*].

***N*-(2-(2-Hydroxypropoxy)-4-methylphenyl)-4-methylbenzenesulfonamide (9d).** Light pink solid (136 mg, 75% Yield). R_f (40% EtOAc/Hexane): 0.27. Mp: 139-141 ºC. IR (KBr): 3337, 3054, 2986, 2928, 2307, 1596, 1507, 1419, 1339, 1164, 1123, 1092, 815 cm^{-1}. ^{1}H NMR (400.13 MHz, $(CD_3)_2CO$): δ 1.14 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.22 (s, 3H), 2.31 (s, 3H), 3.60 (dd, $^2J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 3.67 (dd, $^2J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 3.2 Hz, 1H), 3.90-4.01 (m, 1H), 4.54 (d, $^3J_{HH}$ = 4.2 Hz, 1H), 6.69-6.74 (m, 2H), 7.23 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.38 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.61 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 8.37 (br s, 1H). ^{13}C NMR (100.6 MHz, $(CD_3)_2CO$): δ 19.2 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 66.1 (CH), 75.1 (CH_2), 114.0 (CH), 122.1 (CH), 124.1 (CH), 124.6 (C), 127.9 (2xCH), 130.0 (2xCH), 136.6 (C), 138.2 (C), 144.0 (C), 151.0 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{17}H_{21}NNaO_4S)^+$ $(M+Na)^+$: 358.1083 found: 358.1096. $[\alpha]_D^{20}$ +9.2 (*c* 1.0, $CHCl_3$) [for (*S*)-**9d** in >99% *ee*].

***N*-(3,4-Difluoro-2-(2-hydroxypropoxy)phenyl)-4-methylbenzenesulfonamide (9e).** Colorless viscous oil (154 mg, 80% Yield). R_f (40% EtOAc/Hexane): 0.41. IR (NaCl): 3349, 3054, 2986, 2359, 1653, 1559, 1507, 1490, 1419, 1265, 1165, 1047, 896, 738, 705 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.20 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.36 (s, 3H), 3.30 (br s, 1H), 3.59 (dd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 8.1 Hz, 1H), 3.93 (dd, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 2.3 Hz, 1H), 4.04-4.18 (m, 1H), 6.83 (td, $^3J_{HH}$ = 9.4 Hz, $^3J_{FH}$ = 9.4, $^4J_{FH}$ = 8.1 Hz, 1H), 7.22 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.30 (ddd, $^3J_{HH}$ = 9.4 Hz, $^4J_{FH}$ = 5.2, $^5J_{FH}$ = 2.4 Hz, 1H), 7.69 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 8.69 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.0 (CH_3), 21.7 (CH_3), 66.7 (CH), 79.8 (d, $^4J_{FC}$ = 3.6 Hz, CH_2), 111.8 (d, $^2J_{FC}$ = 18.1 Hz, CH), 116.5 (dd, $^3J_{FC}$ = 11.4 Hz, $^4J_{FC}$ = 3.8 Hz, CH), 127.5 (2xCH), 127.9 (dd, $^3J_{FC}$ = 3.2 Hz, $^4J_{FC}$ = 1.9 Hz, C), 129.8 (2xCH), 136.3 (C), 139.7 (dd,

$^{2}J_{FC}$ = 10.6 Hz, $^{3}J_{FC}$ = 2.0 Hz, C), 144.2 (C), 144.6 (dd, $^{1}J_{FC}$ = 248.7 Hz, $^{2}J_{FC}$ = 14.3 Hz, C), 148.4 (dd, $^{1}J_{FC}$ = 247.0 Hz, $^{2}J_{FC}$ = 11.1 Hz, C). HRMS (ESI^{+}, *m/z*): calcd for $(C_{16}H_{17}F_2NNaO_4S)^{+}$ $(M+Na)^{+}$: 380.0739 found: 380.0736. $[\alpha]_D^{20}$ -21.5 (*c* 0.6, EtOH) [for (*R*)-**9e** in >99% *ee*].

General procedure for the synthesis of racemic and optically active tosylated benzoxazines 10a-e. Triphenylphosphine (89 mg, 0.34 mmol) was added to a solution of the corresponding sulfonamide **9a-e** (0.28 mmol) in dry THF (3.1 mL). Next, diethyl azadicarboxylate (53 μL, 0.34 mmol) was added dropwise and stirred at room temperature for 2 h. After this time, the solvent was removed by distillation under reduced pressure and the crude purified by column chromatography on silica gel (EtOAc/Hexane mixtures), affording the corresponding tosylated benzoxazines **10a-e** (94-100%).

3-Methyl-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (10a). Colorless oil (84 mg, 99% Yield). R_f (40% EtOAc/Hexane): 0.72. IR (NaCl): 3054, 2986, 2340, 1599, 1559, 1490, 1350, 1170, 1072, 1015, 815 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.22 (d, $^{3}J_{HH}$ = 6.9 Hz, 3H), 2.38 (s, 3H), 3.20 (dd, $^{2}J_{HH}$ = 11.1 Hz, $^{3}J_{HH}$ = 2.2 Hz, 1H), 3.79 (dd, $^{2}J_{HH}$ = 11.1 Hz, $^{3}J_{HH}$ = 1.3 Hz, 1H), 4.27-4.63 (m, 1H), 6.80 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H), 6.95 (t, $^{3}J_{HH}$ = 7.7 Hz, 1H), 7.08 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H), 7.21 (dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 0.5 Hz, 2H), 7.46 (d, $^{3}J_{HH}$ = 7.9 Hz, 2H), 7.89 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.1 (CH_3), 21.7 (CH_3), 48.7 (CH), 66.1 (CH_2), 117.2 (CH), 121.3 (CH), 122.0 (C), 126.1 (CH), 126.3 (CH), 127.3 (2xCH), 130.0 (2xCH), 135.5 (C), 144.3 (C), 146.1 (C). HRMS (ESI^{+}, *m/z*): calcd for $(C_{16}H_{17}NNaO_3S)^{+}$ $(M+Na)^{+}$: 326.0821 found: 326.0814. $[\alpha]_D^{20}$ +164.8 (*c* 1.0, EtOH) [for (*R*)-**10a** in >99% *ee*].

6-Fluoro-3-methyl-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (10b). White solid (85 mg, 94% Yield). R_f (60% EtOAc/Hexane): 0.64. Mp: 81-83 ºC. IR (KBr): 3054, 2987, 2929, 2341, 1616, 1597, 1499, 1419, 1353, 1212, 1169, 970, 936, 814 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.22 (d, $^{3}J_{HH}$ = 6.9 Hz, 3H), 2.39 (s, 3H), 3.16 (dd, $^{2}J_{HH}$ = 11.1 Hz, $^{3}J_{HH}$ = 2.6 Hz, 1H), 3.80 (dd, $^{2}J_{HH}$ = 11.1 Hz, $^{3}J_{HH}$ = 1.5 Hz, 1H), 4.37-4.47 (m, 1H), 6.73-6.88 (m, 2H), 7.24 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H), 7.51 (d, $^{3}J_{HH}$ = 8.3 Hz,

2H), 7.69 (dd, $^{3}J_{FH}$ = 10.5 Hz, $^{4}J_{HH}$ = 2.7 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.1 (CH_3), 21.7 (CH_3), 48.8 (CH), 66.1 (CH_2), 112.1 (d, $^{2}J_{FC}$ = 27.7 Hz, CH), 113.0 (d, $^{2}J_{FC}$ = 23.5 Hz, CH), 117.8 (d, $^{3}J_{FC}$ = 9.0 Hz, CH), 122.5 (d, $^{3}J_{FC}$ = 10.9 Hz, C), 127.3 (2xCH), 130.1 (2xCH), 135.3 (C), 142.1 (d, $^{4}J_{FC}$ = 2.5 Hz, C), 144.5 (C), 156.8 (d, $^{1}J_{FC}$ = 238.2 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{16}FNNaO_3S)^+$ $(M+Na)^+$: 344.0727 found: 344.0742. $[\alpha]_D^{20}$ +171.7 (*c* 1.0, EtOH) [for (*R*)-**10b** in >99% *ee*].

6-Methoxy-3-methyl-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (10c). White solid (88 mg, 94% Yield). R_f (40% EtOAc/Hexane): 0.66. Mp: 150-152 ºC. IR (KBr): 3734, 3054, 2986, 2360, 2342, 1761, 1646, 1559, 1506, 1420, 1363, 1168, 933, 814 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.22 (d, $^{3}J_{HH}$ = 6.9 Hz, 3H), 2.37 (s, 3H), 3.12 (dd, $^{2}J_{HH}$ = 11.0 Hz, $^{3}J_{HH}$ = 2.5 Hz, 1H), 3.74 (dd, $^{2}J_{HH}$ = 11.0 Hz, $^{3}J_{HH}$ = 1.5 Hz, 1H), 3.80 (s, 3H), 4.34-4.50 (m, 1H), 6.66 (dd, $^{3}J_{HH}$ = 9.0 Hz, $^{4}J_{HH}$ = 2.8 Hz, 1H), 6.72 (d, $^{3}J_{HH}$ = 8.9 Hz, 1H), 7.21 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H), 7.44-7.54 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.1 (CH_3), 21.7 (CH_3), 48.9 (CH), 55.9 (CH_3), 65.9 (CH_2), 109.8 (CH), 110.1 (CH), 117.6 (CH), 122.2 (C), 127.3 (2xCH), 130.0 (2xCH), 135.4 (C), 140.1 (C), 144.3 (C), 153.7 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{17}H_{19}NNaO_4S)^+$ $(M+Na)^+$: 356.0927 found: 356.0944. $[\alpha]_D^{20}$ +333.9 (*c* 1.0, EtOH) [for (*R*)-**10c** in >99% *ee*].

3,7-Dimethyl-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (10d). Light brown viscous oil (88 mg, 99% Yield). R_f (40% EtOAc/Hexane): 0.57. IR (NaCl): 3032, 2981, 2934, 2892, 2340, 1918, 1598, 1577, 1500, 1349, 1321, 1219, 1167, 1069, 917, 813 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.20 (d, $^{3}J_{HH}$ = 6.9 Hz, 3H), 2.28 (s, 3H), 2.37 (s, 3H), 3.16 (dd, $^{2}J_{HH}$ = 11.0 Hz, $^{3}J_{HH}$ = 2.5 Hz, 1H), 3.75 (dd, $^{2}J_{HH}$ = 11.1 Hz, $^{3}J_{HH}$ = 1.4 Hz, 1H), 4.34-4.46 (m, 1H), 6.61 (d, $^{4}J_{HH}$ = 1.2 Hz, 1H), 6.76 (dd, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 1.4 Hz, 1H), 7.21 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H), 7.46 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H), 7.75 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.1 (CH_3), 21.0 (CH_3), 21.7 (CH_3), 48.7 (CH), 66.0 (CH_2), 117.4 (CH), 119.3 (C), 122.2 (CH), 125.9 (CH), 127.3 (2xCH), 129.9 (2xCH), 135.5 (C), 136.4 (C), 144.1 (C), 145.9 (C). HRMS (ESI^+, *m/z*): calcd for $(C_{17}H_{19}NNaO_3S)^+$ $(M+Na)^+$: 340.0978 found: 340.0990. $[\alpha]_D^{20}$ +210.1 (*c c* 1.0, EtOH) [for (*R*)-**10d** in >99% *ee*].

7,8-Difluoro-3-methyl-4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (10e). White solid (95 mg, >99% Yield). R_f (30% EtOAc/Hexane): 0.42. Mp: 85-87 ºC. IR (KBr): 3054, 2987, 2343, 1598, 1508, 1484, 1361, 1183, 1166, 1038, 815 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.21 (d, $^3J_{HH}$ = 7.0 Hz, 3H), 2.39 (s, 3H), 3.17 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 2.6 Hz, 1H), 3.92 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 0.9 Hz, 1H), 4.43-4.50 (m, 1H), 6.78 (td, $^3J_{HH}$ = 9.6 Hz, $^3J_{FH}$ = 9.6, $^4J_{FH}$ = 8.2, 1H), 7.24 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.44 (d , $^3J_{HH}$ = 8.3 Hz, 2H), 7.64 (ddd, $^3J_{HH}$ = 9.5 Hz, $^4J_{FH}$ = 5.2, $^5J_{FH}$ = 2.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.0 (CH_3), 21.7 (CH_3), 48.3 (CH), 66.4 (CH_2), 108.3 (d, $^2J_{FC}$ = 18.4 Hz, CH), 119.4 (d, $^3J_{FC}$ = 3.0 Hz, C), 120.4 (dd, $^3J_{FC}$ = 7.8 Hz, $^4J_{FC}$ = 4.2 Hz, CH), 127.3 (2xCH), 130.2 (2xCH), 135.0 (C), 136.7 (dd, $^2J_{FC}$ = 10.1 Hz, $^3J_{FC}$ = 3.4 Hz, C), 140.0 (dd, $^1J_{FC}$ = 247.4 Hz, $^2J_{FC}$ = 15.6 Hz, C), 144.8 (C), 148.6 (dd, $^1J_{FC}$ = 245.7 Hz, $^2J_{FC}$ = 10.1 Hz, C). HRMS (ESI^+, *m/z*): calcd for $(C_{16}H_{15}F_2NNaO_3S)^+$ $(M+Na)^+$: 362.0633, found: 362.0628. $[\alpha]_D^{20}$ -183.2 (*c* 0.5, EtOH) [for (*S*)-**10e** in >99% *ee*].

General procedure for the synthesis of racemic and optically active benzoxazines 4a,e. Magnesium turnings (22 mg, 0.88 mmol) was added to a solution of the corresponding tosylated benzoxazine **10a**,**e** (0.18 mmol) in dry MeOH (0.9 mL). The mixture was stirred under reflux for 2 h until complete deprotection of the tosyl group. Then, the solvent was removed by distillation under reduced pressure and the crude purified by column chromatography on silica gel (10% EtOAc/Hexane), affording the corresponding benzoxazines **4a**,**e** (79-86%).

3-Methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (4a). 21 mg, 79% Yield. R_f (10% EtOAc/Hexane): 0.24. The spectroscopical data have been included previously in this experimental section. $[\alpha]_D^{20}$ -17.6 (*c* 0.5, $CHCl_3$) [for (*R*)-**4a** in 99% *ee*]. [lit. $[\alpha]_D^{20}$ -19 (*c* 1.3, $CHCl_3$) for (*S*)-**4a** in 99% *ee*].[8a]

7,8-Difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (4e). 29 mg, 86% Yield. R_f (40% EtOAc/Hexane): 0.43. $[\alpha]_D^{20}$ -8.6 (*c* 1.3, $CHCl_3$) [for (*S*)-**4e** in 99% *ee*]. [lit. $[\alpha]_D^{20}$ -9.1 (*c* 1.3, $CHCl_3$) for (*S*)-**4e** in 99% *ee*].[11c]

Bioreduction of 1-(2-nitrophenoxy)propan-2-one (3a) with ADH-LK. In an eppendorf tube containing the ketone **3a** (2.3 mg, 0.012 mmol) in a 50 mM TRIS·HCl buffer pH 7.5 (450 μL), glucose-6-phosphate (40 μL), glucose-6-phosphate dehydrogenase (3 U, 10 μL), 10 mM NADPH solution in 50 mM TRIS·HCl buffer pH 7.5 (50 μL) and ADH-LK (3 U, 2 mg) were successively added. The reaction was shaken at 250 rpm and 30 ºC for 24 h. Then, the mixture was extracted with EtOAc (2 x 500 μL) and dried over Na_2SO_4, analyzing the reaction crude by NMR (conversion) and HPLC (enantiomeric excess).

Bioreduction of 1-(2-nitrophenoxy)propan-2-one (3a) with ADH-CP. In an eppendorf tube containing the ketone **3a** (2.3 mg, 0.012 mmol) in a 50 mM TRIS·HCl buffer pH 7.5 (450 μL), 2-propanol (25 μL), a 10 mM NADH solution in 50 mM TRIS·HCl buffer pH 7.5 (50 μL) and ADH-CP (3 U, 7.5 μL) were successively added. The reaction was shaken at 250 rpm and 30 ºC for 24 h. Then, the mixture was extracted with EtOAc (2 x 500 μL) and dried over Na_2SO_4, analyzing the reaction crude by NMR (conversion) and HPLC (enantiomeric excess).

Bioreduction of 1-(2-nitrophenoxy)propan-2-one (3a) with Baker′s yeast. Baker′s yeast (1.3 g) was added to a solution of glucose (165 mg) in H_2O (11 mL) stirring the resulting suspension for 15 min at 30 ºC and 250 rpm. After this time, the ketone **3a** (33 mg, 0.17 mmol) was added and the suspension was shaken at 30 ºC and 250 rpm for 24 h. Then, the reaction was centrifuged and the supernatant was extracted with EtOAc (3 x 20 mL). Organic layers were combined, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure, analyzing the reaction crude by NMR (conversion) and HPLC (enantiomeric excess).

General procedure for the bioreduction of ketones 3a-e with ADH-LB. In an eppendorf tube containing the corresponding ketone **3a-e** (0.018 mmol) and 2-propanol (38 μL) in a 50 mM TRIS·HCl

buffer pH 7.5 (555 μL), a 10 mM $MgCl_2$ solution in 50 mM TRIS·HCl buffer pH 7.5 (75 μL), a NADPH 10 mM solution in 50 mM TRIS·HCl buffer pH 7.5 (75 μL) and ADH-LB (4.5 U, 15 μL) were successively added. The reaction was shaken at 30 ºC and 250 rpm for 24 h and then extracted with EtOAc (2 x 500μL). Organic layers were combined and dried over Na_2SO_4, analyzing the reaction crude by NMR (conversion) and HPLC (enantiomeric excess).

General procedure for the bioreduction of ketones 3a-e with ADH-A. In an eppendorf tube containing the corresponding ketone **3a-e** (0.012 mmol) and 2-propanol (25 μL) in a 50 mM TRIS·HCl buffer pH 7.5 (425 μL), a NADH 10 mM solution in 50 mM TRIS·HCl buffer pH 7.5 (50 μL) and *E. coli*/ADH-A cells (15 mg) were successively added. The reaction was shaken at 30 ºC and 250 rpm for 24 h. After this time, the mixture was extracted with EtOAc (2 x 500 μL), the organic layers combined and dried over Na_2SO_4, analyzing the reaction crude by NMR (conversion) and HPLC (enantiomeric excess).

General procedure for the bioreduction of ketones 3a-e with evo-1.1.200. In an eppendorf tube containing the corresponding ketone **3a-e** (0.015 mmol) and 2-propanol (25 μL) in 50 mM TRIS·HCl buffer pH 7.5 (400 μL), a 10 mM $MgCl_2$ solution in 50 mM TRIS·HCl buffer pH 7.5 (60 μL), a 10 mM NADH solution in 50 mM TRIS·HCl buffer pH 7.5 (60 μL) and evo-1.1.200 (60 μL of a solution composed by 1 mg of pure evo-1.1.200 in 760 μL of a 50 mM TRIS·HCl buffer pH 7.5 and 240 μL of a 10 mM $MgCl_2$ solution) were successively added. The reaction was shaken at 30 ºC and 250 rpm for 24 h. Then, the mixture was extracted with EtOAc (2 x 500 μL), the organic layers combined and dried over Na_2SO_4, analyzing the reaction crude by GC (conversion) and HPLC (enantiomeric excess). For the ketone **3e** better results were found at slight acid pHs (6-6.5), suppressing the appearance of the side-product **11** at an optimal pH 6 value.

General procedure for the scale up of bioreduction of ketones 3a-e with ADH-A. *E. coli*/ADH-A cells (ratio 20:1 in weight ketone/crude enzyme) were rehydrated in a 50 mM TRIS·HCl buffer pH 7.5 (22 mL) by shaking the mixture at 30 ºC and 250 rpm for 5 min. The corresponding ketones **3a-e** (0.94 mmol), 2-propanol (1.5 mL) and NADH (10 mg) were successively added. The suspension was shaken at 30 ºC and 250 rpm until no starting material was detected by TLC analysis (24 h). Then, the mixture was extracted with EtOAc (3 x 20 mL), combining the organic layers, which were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure, affording the corresponding alcohols (*S*)-**5a-e** (85-93%, ≥99% *ee*).

General procedure for the scale up of bioreduction of ketones 3a-e with evo-1.1.200. To a suspension of ketone **3a-e** (0.15 mmol) in a mixture of 2-propanol (250 μL) and a 50 mM TRIS·HCl buffer pH 7.5 (4 mL), a 10 mM $MgCl_2$ solution in 50 mM TRIS·HCl buffer pH 7.5 (600 μL), a 10 mM NADH solution in 50 mM TRIS·HCl buffer pH 7.5 (600 μL) and evo-1.1.200 (600 μL of a solution composed by 1 mg of pure evo-1.1.200 in 760 μL of a 50 mM TRIS·HCl buffer pH 7.5 and 240 μL of a 10 mM $MgCl_2$ solution) were successively added. The reaction was shaken at 30 ºC and 250 rpm for 24 h. The mixture was extracted with EtOAc (3 x 10 mL), the organic layers were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure, affording the corresponding alcohol (*R*)-**5a-e** (78-99% yield, >99% *ee*). As mentioned before, for the ketone **3e** better results were found at slight acid pHs (6-6.5), suppressing the appearance of the side-product **11** at an optimal pH 6 value.

General procedure for the enzymatic kinetic resolution by acylation of racemic alcohols 5a-e. Vinyl acetate (**7**, 140 μL, 1.52 mmol) and RML IM (ratio 1:1 in weight alcohol/enzyme) were added to a suspension containing the corresponding racemic alcohol **5a-e** (0.51 mmol) in dry MTBE (5.1 mL) under nitrogen atmosphere. The reaction was shaken at 30 ºC and 250 rpm for the necessary time to

achieve a good kinetic resolution (see Tables 1 and S1). The reaction was followed by HPLC analysis until around 50% conversion was reached. The enzyme was filtered off, washed with CH_2Cl_2 (3 x 5 mL) and the solvent evaporated under reduced pressure. The crude reaction was purified by column chromatography on silica gel (eluent gradient 20-40% EtOAc/Hexane), affording the corresponding optically active acetates (*R*)-**6a-e** (45-47% yield, 93-95% *ee*) and alcohols (*S*)-**5a-e** (44-48% yield, 89-94% *ee*).

General procedure for the enzymatic kinetic resolution by hydrolysis of racemic acetates 6a-e. Water (39 μL, 2.16 mmol) was added to a suspension containing the corresponding racemic acetate **6a-e** (0.43 mmol) and RML IM (ratio 1:1 in weight acetate/enzyme) in MTBE (4.3 mL). The reaction was shaken at 30 ºC and 250 rpm for the necessary time to achieve a good kinetic resolution (see Table 2). The reaction was followed by HPLC analysis until around 50% conversion was reached. The enzyme was filtered off, washed with CH_2Cl_2 (3 x 5 mL) and the solvent was evaporated under reduced pressure. The crude reaction was purified by column chromatography on silica gel (eluent gradient 20-40% EtOAc/Hexane), affording the corresponding optically active alcohols (*R*)-**5a-e** (44-47% yield, 96->99% *ee*) and acetates (*S*)-**6a-e** (41-48% yield, 91-97% *ee*).

The following optical rotation values of alcohols **5a-e** and acetates **6a-e** were found after selected biocatalyzed transformations: (*S*)-**5a**: $[\alpha]_D^{20}$ +6.0 (*c* 0.6, EtOH) (>99% *ee*); (*S*)-**5b**: $[\alpha]_D^{20}$ +7.0 (*c* 0.5, EtOH) (>99% *ee*); (*S*)-**5c**: $[\alpha]_D^{20}$ +4.0 (*c* 0.75, EtOH) (>99% *ee*); (*S*)-**5d**: $[\alpha]_D^{20}$ +3.2(*c* 0.65, EtOH) (>99% *ee*); (*R*)-**5e**: $[\alpha]_D^{20}$ -4.8 (*c* 0.4, EtOH) (>99% *ee*); (*S*)-**6a**: $[\alpha]_D^{20}$ -74.3 (*c* 1.0, $CHCl_3$) (93% *ee*); (*R*)-**6b**: $[\alpha]_D^{20}$ -58.8 (*c* 0.75, $CHCl_3$) (91% *ee*); (*S*)-**6c**: $[\alpha]_D^{20}$ -49.7 (*c* 0.7, $CHCl_3$) (80% *ee*); (*S*)-**6d**: $[\alpha]_D^{20}$ -63.8 (*c* 0.8, $CHCl_3$) (85% *ee*); (*S*)-**6e**: $[\alpha]_D^{20}$ -18.5 (*c* 0.6, $CHCl_3$) (63% *ee*).

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Supporting Information Available. Copies of HPLC chiral analyses, and ^{1}H, ^{13}C and DEPT NMR spectra for described organic compounds are available free of charge via the Internet at http://pubs.acs.org.

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