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Chemoenzymatic Asymmetric Synthesis of 1,4-Benzoxazine Derivatives: Application in the Synthesis of a Levofloxacin Precursor

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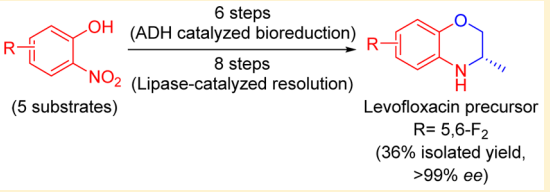
Supporting Information

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. Whereas hydrolases were not suitable for resolution of these racemic cyclic nitrogenated amines, alternative chemoenzymatic strategies were designed through independent pathways leading to both amine antipodes. On one hand, bioreduction of 1-(2-nitrophenoxy)-propan-2-ones allowed the recovery of the enantiopure (*S*)-alcohols in high yields using the alcohol dehydrogenase from *Rhodococcus ruber* (ADH-A), whereas evo-1.1.200 ADH led to their counterpart (*R*)-enantiomers also with complete selectivity and quantitative conversion. 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 six 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.



INTRODUCTION

Benzoxazines are privileged cyclic subunits found in a wide range of biologically active molecules with antibacterial, anticancer, antifungal, and antimicrobial properties,[1] but they 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 there are fewer examples regarding the development of asymmetric routes toward 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 using chemical kinetic resolutions of racemic benzoxazines with optically active acyl chlorides[8] or palladium-catalyzed couplings.[9]

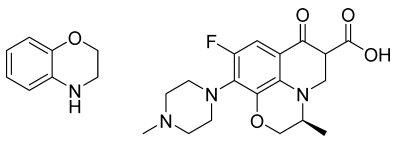


Figure 1. Chemical structure of the 3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine subunit (left) and Levofloxacin (right).

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, including pneumonia, acute bacterial sinusitis, urinary tract infections, and acute pyelonephritis.[10] Asymmetric chemical strategies have been successfully carried out for the synthesis of this drug and other related nonfluorinated analogues.[5a,11] The main efforts focused on the production of (*S*)-(−)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, which serves as an 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 couple of decades, many organic chemists have incorporated the use of enzymes into their toolbox,[12] with lipases and alcohol dehydrogenases currently being the most employed catalysts for use in industrial applications, although others, such as transaminases, are receiving significant attention as well.[13] Enzymes have been identified as particularly useful for the design of valuable synthetic routes toward 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 that can also catalyze acylation reactions for the selective formation of amines through kinetic resolution processes.[15] Among the hydrolytic enzymes, lipases have attracted significant attention due to their selective action in the asymmetric synthesis of a wide range of heterocyclic nitrogenated compounds.[16]

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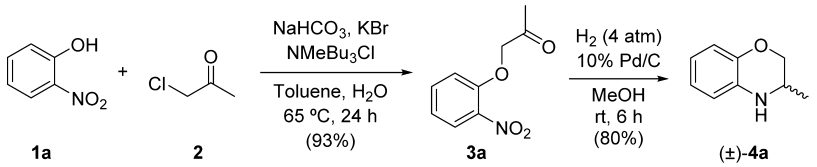
Scheme 1. Synthesis of Racemic Benzoxazine 4a for Studying its Kinetic Resolution



Surprisingly, the production of optically enriched benzoxazine derivatives is limited to pig liver esterase-catalyzed hydrolytic approaches, achieving moderate selectivity values.[17] Herein, we report the versatility of enzymes for the production of benzoxazine derivatives through 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.

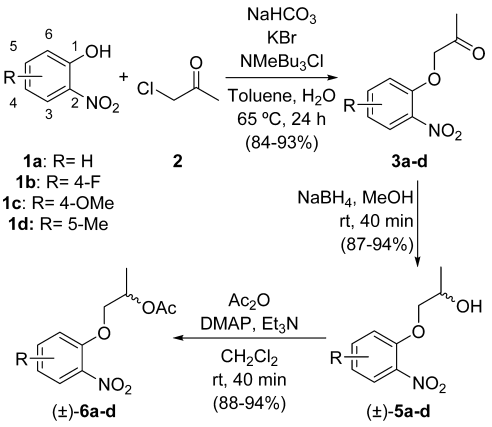
RESULTS AND DISCUSSION

To explore new asymmetric routes for the synthesis of benzoxazine derivatives, we selected 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**4a**) 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 hydrogen carbonate, and tributylmethylammonium chloride, followed by a palladium-catalyzed hydrogenation-cyclization sequence of nitro ketone **3a**, which 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) were 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.

Searching for an alternative strategy, we took advantage of the previous preparation of nitro ketone **3a**. Then, three independent strategies were undertaken: (a) nonselective reduction of ketone **3a** to racemic alcohol **5a** followed by classical kinetic resolution through lipase-catalyzed acylative processes, (b) chemical acetylation of the racemic alcohol obtained to analyze the complementary lipase-catalyzed hydrolytic process in depth, and (c) selective bioreduction of 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 *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.

The lipase-catalyzed acetylation of alcohols **5a**–**d** was considered first, searching for a suitable lipase that was able to produce the corresponding alcohols and acetates in high optical purity (Table S1 in the Supporting Information). Alcohol **5a** was selected as the model substrate, finding *Rhizomucor miehei* lipase in immobilized form (RML IM) as an ideal candidate, leading to 48% conversion in MTBE after 5 h

Scheme 2. Chemoenzymatic Synthesis of Nitro Ketones 3a–d, Alcohols 5a–d, and Acetates 6a–d



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

Alternatively, we decided to study lipase-catalyzed hydrolysis of the corresponding acetates. The results are summarized in Table 2. Because the water content is a decisive parameter for enzymatic activity, the amount of water was studied using substrate **6a** as reference without substitutions in the aromatic ring (entries 1–3). In all cases, excellent selectivity was observed, obtaining the complementary alcohol (*R*)-**5a** and acetate (*S*)-**6a** in comparison to the lipase-catalyzed acetylation reaction. The reaction with 5 equiv of hydrolytic agent led to 48% conversion (entry 1). Notably, increasing the amount of water led to slower kinetics but maintained excellent stereoselectivity (21–35%, entries 2 and 3). Similar good results were obtained when extending the methodology to other substituted benzoxazine derivatives using 5 equiv of water (entries 4–6).

Finally, bioreduction experiments were considered on the basis of accessing the final product theoretically at 100% yield. Oxidoreductases with opposite stereopreferences were employed to develop suitable routes for both alcohol antipodes. Thus, a set composed of Prelog alcohol dehydrogenases[20] from *Rhodococcus ruber* (ADH-A), *Candida parapsilosis* (ADH-CP) and Baker's yeast (BY) as well as anti-Prelog enzymes, including *Lactobacillus brevis* (ADH-LB), *Lactobacillus kefir* (ADH-LK), and evo-1.1.200 ADH, were screened in 50 mM

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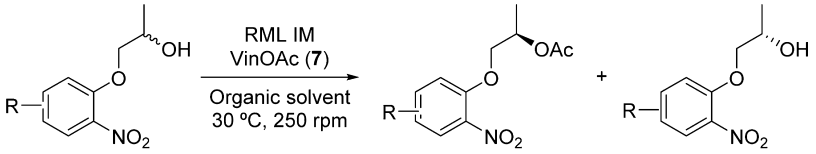
Table 1. Enzymatic Kinetic Resolution of Alcohols 5a–d using RML IM (1:1 w/w) and 3 Equiv of Vinyl Acetate 7 in Dry MTBE or Toluene at 30 °C and 250 rpm

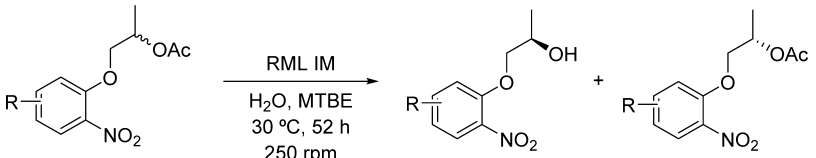


(±)-**5a-d** (*R*)-**6a-d** (*S*)-**5a-d**

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]As determined by HPLC with 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]

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 °C and 250 rpm after 52 h



(±)-**6a-d** (*R*)-**5a-d** (*S*)-**6a-d**

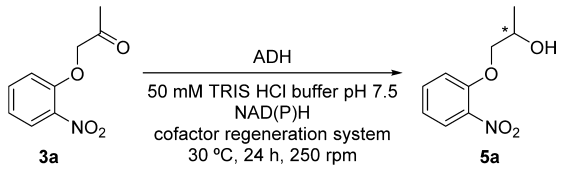
entry	substrate[a]	H_2O (equiv)	ee$_p$ (%)[b]	ee$_s$ (%)[b]	*c* (%)[c]	*E*[d]
1	**6a** (H)	5	98 (44)	92 (41)	48	>200
2	**6a** (H)	10	99	53	35	>200
3	**6a** (H)	20	>99	27	21	>200
4	**6b** (4-F)	5	96 (44)	97 (48)	50	>200
5	**6c** (4-OMe)	5	>99 (46)	91 (47)	48	>200
6	**6d** (5-Me)	5	>99 (47)	94 (48)	49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

[a]Substitution in brackets. [b]Determined by HPLC with 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]

Tris-HCl pH 7.5 buffer, using a suitable cofactor recycling system when required (Table 3). For the Prelog enzymes, high to excellent selectivities were found for the formation of (*S*)-alcohol **5a** (entries 1–3). Notably, ADH-A showed complete conversion and selectivity after 24 h (entry 1). On the other hand, for the synthesis of (*R*)-**5a**, ADH-LK completely reduced the ketone, obtaining the alcohol with very high enantiomeric excess (entry 4), and 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 evo-1.1.200 ADH (entry 6), obtaining the target alcohol in quantitative conversion.

Efficient scale-up of the optimal 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 with ADH-A producing the enantiopure alcohols (*S*)-**5b–d** with very high yields (88–93%, entries 3, 5, and 7),

Table 3. Bioreduction of Nitro Ketone 3a for the Production of Optically Active Alcohol 5a in Tris-HCl pH 7.5 Buffer after 24 h at 30 °C



3a **5a**

entry	enzyme	external 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 crude reaction and absolute configurations appear in parentheses.

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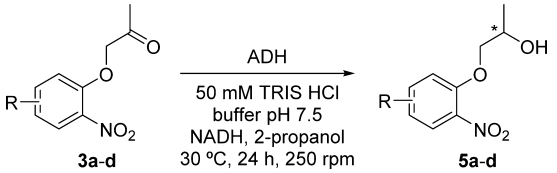
Table 4. Bioreduction of Nitro Ketones 3a–d in Tris-HCl pH 7.5 Buffer after 24 h at 30 °C



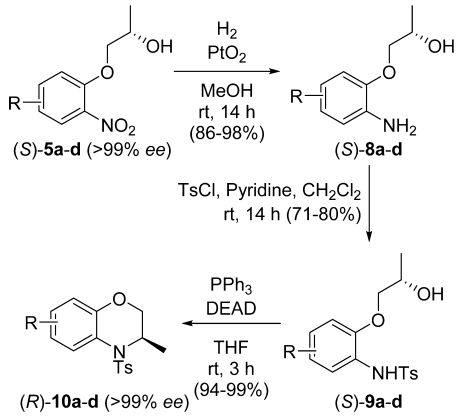
entry	enzyme	3	c (%)[a]	ee (%)[a]
1	ADH-A	**3a**	>99 (85)	99 (*S*)
2	evo-1.1.200	**3a**	>99 (99)	>99 (*R*)
3	ADH-A	**3b**	>99 (89)	>99 (*S*)
4	evo-1.1.200	**3b**	>99 (87)	>99 (*R*)
5	ADH-A	**3c**	>99 (88)	>99 (*S*)
6	evo-1.1.200	**3c**	>99 (88)	>99 (*R*)
7	ADH-A	**3d**	>99 (93)	>99 (*S*)
8	evo-1.1.200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

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

and 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 theoretical 50% yield due to the inherent limitations of kinetic resolution procedures.

A four-step sequence was designed for the production of racemic and enantiopure benzoxazines **10a–d**, which occur without any racemization of the intermediates or final products (Scheme 3). Starting from (*S*)-alcohols **5a–d**, the proposed

Scheme 3. Chemical Synthesis of Protected Enantiopure Benzoxazines 10a–d



synthesis began with platinum catalyzed hydrogenation of the nitro functionality, forming the corresponding amino alcohols (*S*)-**8a–d**, which were activated prior to cyclization under Mitsunobu reaction conditions to avoid the mixture of products as is seen using free amine or when additional catalysts were employed, such as $ZnCl_2$ with related amino alcohols, for example **8e**.[21] This process occurred with inversion of the absolute configuration, yielding tosylated benzoxazine derivatives (*R*)-**10a–d**. As an example, the final deprotection of activated amine **10a** with the tosyl group using magnesium in refluxing methanol allowed the recovery of (*R*)-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**4a**) in 80% isolated yield after 2 h.

Once 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 turned to focus 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 this reason, a similar route was attempted starting from commercially available 2,3-difluoro-6-nitrophenol (**1e**) as depicted in Scheme 4. *O*-alkylation proceeded in 85% yield for the formation of nitro ketone **3e**, which was subjected to ADH-A-catalyzed bioreduction, leading to enantiopure (*S*)-**5e** after 24 h in 91% isolated yield using a Tris-HCl pH 7.5 buffer. For the preparation of its (*R*)-**5e** counterpart, the use of evo-1.1.200 was attempted, which resulted in complete selectivity, though the structural isomer 2-(2,3-difluoro-6-nitrophenoxy)-propan-1-ol (**11**) was also found as a side product. For this reason, the bioreduction was carried out at different pHs, minimizing the formation of **11** at lower pH values (6–6.5), which yielded the alcohol (*R*)-**5e** in 94% isolated yield after 24 h at 30 °C in a Tris-HCl pH 6 buffer. It must be mentioned that the (*R*)-configuration is required for the formation of Levofloxacin; thus, the use of evo-1.1.200 seems to be an excellent tool for introducing a desired chirality.

In addition, the lipase-catalyzed hydrolysis of racemic acetate **6e** was attempted, which would give direct access to the desired (*R*)-alcohol **5e**. First, the chemical reduction of 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 mostly suppressed using a mild reducing agent, such as the ammonia borane complex,[22] thus avoiding basic reaction medium as well as a basic workup in the reaction, recovering **5e** in 78% yield after 1 h at 30 °C. Then, the alcohol was chemically acetylated in 93% yield using acetic anhydride to later explore its RML IM-catalyzed hydrolysis. After 53 h, total selectivity toward the formation of the (*R*)-alcohol was attained, obtaining (*S*)-acetate **6e** in 84% ee and the desired enantiopure (*R*)-alcohol **5e** in 45% isolated yield.

Finally, taking alcohol (*R*)-**5e**, a four step sequence was carried out, involving reduction of the nitro functionality, protection of the free amine, cyclization in Mitsunobu conditions, 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 in the development of asymmetric synthesis of both 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine 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 toward quantitative conversion to the (*S*)-alcohols, whereas evo-1.1.200 led to the corresponding enantiopure (*R*)-enantiomers. On the other hand, it was found that upon carrying out a lipase screen, *Rhizomucor miehei* lipase seems to be 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

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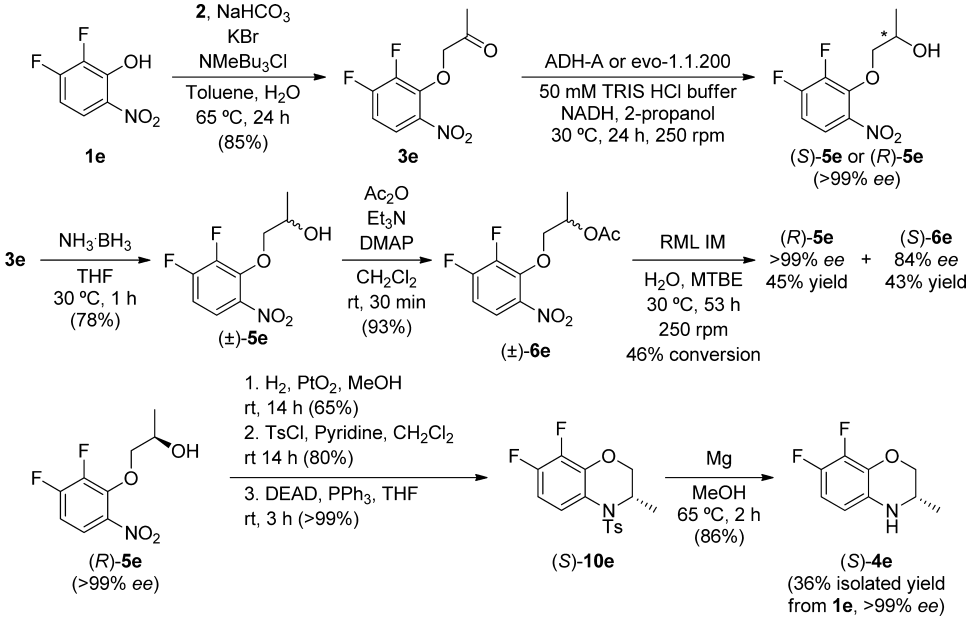
Scheme 4. Chemoenzymatic Synthetic Alternatives for the Production of the Enantiopure Alcohol (*R*)-5e and the Corresponding Levofoxacin Precursor (*S*)-4e



has been isolated in the 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) were added successively chloroacetone (481 μL, 6.04 mmol), potassium bromide (43 mg, 0.36 mmol), sodium hydrogen carbonate (279 mg, 3.32 mmol), and a tributylmethylammonium chloride solution (75% weight in water, 16 μL, 0.065 mmol). The mixture was stirred and heated at 65 °C for 6 h, and then additional chloroacetone (120 μL, 1.51 mmol) was added. The reaction was further heated at 65 °C 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 °C by the addition of 1N HCl (between 7 and 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 °C for 10 min. The layers were again separated in a separatory funnel, the organic layer was collected, dried over Na_2SO_4, and filtered and the solvent was removed by distillation under reduced pressure. The resulting crude product was washed with toluene to ensure 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 °C. 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 °C. 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 °C. 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 °C. 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 °C. 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 reaching 4 atm of pressure. The suspension was stirred for 6 h at room

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temperature, and afterward, the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O (20 mL), and the metal catalyst was filtered 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 racemic benzoxazine **4a** (245 mg, 80% yield). The spectroscopic 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 ketones **3a−d** (1.00 mmol) in dry MeOH (3.8 mL) at 0 °C. 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 was extracted with CH_2Cl_2 (3 × 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 °C. 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, $^2J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 7.4 Hz, 1H), 4.10 (dd, $^2J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 3.2 Hz, 1H), 4.15−4.26 (m, 1H), 7.08 (dd, $^3J_{HH}$ = 9.2 Hz, $^4J_{FH}$ = 4.3 Hz, 1H), 7.28 (ddd, $^3J_{HH}$ = 9.4 Hz, $^3J_{FH}$ = 7.3 Hz, $^4J_{HH}$ = 3.1 Hz, 1H), 7.60 (dd, $^3J_{FH}$ = 7.8 Hz, $^4J_{HH}$ = 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, $^2J_{FH}$ = 27.5 Hz, CH), 116.6 (d, $^3J_{FH}$ = 7.7 Hz, CH), 121.5 (d, $^2J_{FH}$ = 22.8 Hz, CH), 139.3 (d, $^3J_{FC}$ = 8.3 Hz, C), 148.9 (d, $^4J_{FC}$ = 3.0 Hz, C), 155.5 (d, $^1J_{FC}$ = 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 °C. IR (KBr): 3576, 3431, 3058, 2964, 2922, 2840, 2343, 1527, 1496, 1346, 1216, 1040, 817 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.76 (br s, 1H), 3.80 (s, 3H), 3.81−3.91 (m, 1H), 4.07 (dd, $^2J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 4.12−4.27 (m, 1H), 7.01 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 7.09 (dd, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 3.0 Hz, 1H), 7.37 (d, $^4J_{HH}$ = 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 °C. IR (KBr): 3583, 3435, 3055, 2985, 2935, 1609, 1592, 1517, 1347, 1182, 1093, 1031, 841 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.26 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.37 (s, 3H), 3.02 (br s, 1H), 3.86 (dd, $^2J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 4.08 (dd, $^2J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 3.2 Hz, 1H), 4.12−4.25 (m, 1H), 6.79 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 6.84 (s, 1H), 7.76 (d, $^3J_{HH}$ = 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 °C for 1 h. After this time, the reaction was stopped by careful addition at 0 °C of an aqueous 2 M HCl solution until an acidic pH (pH < 3) was achieved. Then, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried, and 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 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 added successively to a solution of the corresponding alcohols **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 was removed by distillation under reduced pressure. The crude product 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, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 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 °C. IR (KBr): 3055, 2987, 2307, 1738, 1537, 1499, 1373, 1357, 1241, 1203, 1142, 1083, 1034, 943, 814, 788 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.37 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.05 (s, 3H), 4.11 (d, $^3J_{HH}$ = 5.0 Hz, 2H), 5.18−5.30 (m, 1H), 7.06 (dd, $^3J_{HH}$ = 9.2 Hz, $^4J_{FH}$ = 4.3 Hz, 1H), 7.26 (ddd, $^3J_{HH}$ = 9.3 Hz, $^3J_{FH}$ = 7.4, $^4J_{HH}$ = 3.1 Hz, 1H), 7.57 (dd, $^3J_{FH}$ = 7.7 Hz, $^4J_{HH}$ = 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, $^2J_{FH}$ = 27.4 Hz, CH), 116.7 (d, $^3J_{FH}$ = 7.9 Hz, CH), 121.1 (d, $^2J_{FH}$ = 22.9 Hz, CH), 139.3 (d, $^3J_{FC}$ = 9.6 Hz, C), 148.5 (d, $^4J_{FC}$ = 2.6 Hz, C), 155.7 (d, $^1J_{FC}$ = 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 °C. IR (KBr): 3055, 2986, 2307, 1734, 1533, 1499, 1373, 1354, 1243, 1041, 812 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.35 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.06 (s, 3H), 3.80 (s, 3H), 4.07 (d, $^3J_{HH}$ = 4.8 Hz, 2H), 5.16−5.28 (m, 1H), 7.01 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 7.07 (dd, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 3.0 Hz, 1H), 7.34 (d, $^4J_{HH}$ = 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 °C. IR (KBr): 3054, 2987, 2306, 1734, 1609, 1521, 1423, 1093, 1040 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.39 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.06 (s, 3H), 2.40 (s, 3H), 4.11 (d, $^3J_{HH}$ = 5.1 Hz, 2H), 5.22−

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5.31 (m, 1H), 6.83 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 0.7 Hz, 1H), 6.86 (s, 1H), 7.77 (d, $^3J_{HH}$ = 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}. ^{1}H 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, $^3J_{FC}$ = 4.4 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 generated using a hydrogen balloon connected to a round-bottom flask, which contained a suspension of the corresponding nitro alcohols **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 was 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 °C. IR (KBr): 3391, 3054, 2986, 2924, 2340, 1653, 1558, 1506, 1219, 1154 cm^{-1}. ^{1}H 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 °C. IR (KBr): 3391, 3054, 2985, 2933, 2341, 1623, 1513, 1218, 1160, 1035, 970, 842 cm^{-1}. ^{1}H 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 °C. IR (KBr): 3583, 3391, 3054, 2986, 2340, 1623, 1516, 1419, 1220, 1168, 962 cm^{-1}. ^{1}H 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 °C. IR (KBr): 3402, 3054, 2985, 2929, 2523, 2307, 1592, 1520, 1420, 1152, 1132, 1041, 812 cm^{-1}. ^{1}H 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 °C. 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 alcohols **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 was dissolved in EtOAc (20 mL) and washed with an aqueous saturated NH_4Cl solution (2 × 20 mL), an aqueous HCl 1 M solution (2 × 20 mL), and finally an aqueous saturated NaCl solution (2 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated by distillation under reduced pressure. The crude product 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 °C. IR (KBr): 3545, 3297, 3054, 2985, 2920, 2343, 1596, 1501, 1404, 1340, 1156, 1114, 1088, 934, 819 cm^{-1}. ^{1}H 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}. ^{1}H 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),

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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 °C. IR (KBr): 3339, 3054, 2935, 2356, 1504, 1420, 1340, 1159, 1088, 956, 816 cm^{-1}. ^{1}H 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 °C. 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, $^2J_{FC}$ = 10.6 Hz, $^3J_{FC}$ = 2.0 Hz, C), 144.2 (C), 144.6 (dd, $^1J_{FC}$ = 248.7 Hz, $^2J_{FC}$ = 14.3 Hz, C), 148.4 (dd, $^1J_{FC}$ = 247.0 Hz, $^2J_{FC}$ = 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 product was 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-2H-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, $^3J_{HH}$ = 6.9 Hz, 3H), 2.38 (s, 3H), 3.20 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 2.2 Hz, 1H), 3.79 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 1.3 Hz, 1H), 4.27−4.63 (m, 1H), 6.80 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 6.95 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 7.21 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 0.5 Hz, 2H), 7.46 (d, $^3J_{HH}$ = 7.9 Hz, 2H), 7.89 (d, $^3J_{HH}$ = 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-2H-benzo[b][1,4]oxazine (**10b**).* White solid (85 mg, 94% yield). R_f (60% EtOAc/hexane): 0.64. Mp: 81−83 °C. 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, $^3J_{HH}$ = 6.9 Hz, 3H), 2.39 (s, 3H), 3.16 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 2.6 Hz, 1H), 3.80 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 1.5 Hz, 1H), 4.37−4.47 (m, 1H), 6.73−6.88 (m, 2H), 7.24 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.51 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.69 (dd, $^3J_{FH}$ = 10.5 Hz, $^4J_{HH}$ = 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, $^2J_{FC}$ = 27.7 Hz, CH), 113.0 (d, $^2J_{FC}$ = 23.5 Hz, CH), 117.8 (d, $^3J_{FC}$ = 9.0 Hz, CH), 122.5 (d, $^3J_{FC}$ = 10.9 Hz, C), 127.3 (2xCH), 130.1 (2xCH), 135.3 (C), 142.1 (d, $^4J_{FC}$ = 2.5 Hz, C), 144.5 (C), 156.8 (d, $^1J_{FC}$ = 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-2H-benzo[b][1,4]-oxazine (**10c**).* White solid (88 mg, 94% yield). R_f (40% EtOAc/hexane): 0.66. Mp: 150−152 °C. 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, $^3J_{HH}$ = 6.9 Hz, 3H), 2.37 (s, 3H), 3.12 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 3.74 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 1.5 Hz, 1H), 3.80 (s, 3H), 4.34−4.50 (m, 1H), 6.66 (dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.8 Hz, 1H), 6.72 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 7.21 (d, $^3J_{HH}$ = 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-2H-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, $^3J_{HH}$ = 6.9 Hz, 3H), 2.28 (s, 3H), 2.37 (s, 3H), 3.16 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 3.75 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 1.4 Hz, 1H), 4.34−4.46 (m, 1H), 6.61 (d, $^4J_{HH}$ = 1.2 Hz, 1H), 6.76 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.4 Hz, 1H), 7.21 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.46 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.75 (d, $^3J_{HH}$ = 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 1.0, EtOH) [for (R)-**10d** in >99% ee].

*7,8-Difluoro-3-methyl-4-tosyl-3,4-dihydro-2H-benzo[b][1,4]-oxazine (**10e**).* White solid (95 mg, >99% yield). R_f (30% EtOAc/hexane): 0.42. Mp: 85−87 °C. IR (KBr): 3054, 2987, 2343, 1598, 1508, 1484, 1361, 1183, 1166, 1038, 815 cm^{-1}. ^{1}H 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

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$(C_{16}H_{15}F_2NNaO_3S)^+$ [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 and 4e. Magnesium turnings (22 mg, 0.88 mmol) were added to a solution of the corresponding tosylated benzoxazines **10a** and **10e** (0.18 mmol) in dry MeOH (0.9 mL). The mixtures were stirred under reflux for 2 h until complete deprotection of the tosyl group occurred. Then, the solvents were removed by distillation under reduced pressure, and the crude products were purified by column chromatography on silica gel (10% EtOAc/hexane), affording the corresponding benzoxazines **4a** and **4e** (79−86%).

*3-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**4a**).* Twenty-one milligrams, 79% yield. R_f (10% EtOAc/hexane): 0.24. The spectroscopical data are listed above in the 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-2H-benzo[b][1,4]oxazine (**4e**).* Twenty-nine milligrams, 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 ketone **3a** (2.3 mg, 0.012 mmol) in 50 mM Tris-HCl pH 7.5 buffer (450 μL), glucose-6-phosphate (40 μL), glucose-6-phosphate dehydrogenase (3 U, 10 μL), 10 mM NADPH solution in 50 mM Tris-HCl pH 7.5 buffer (50 μL), and ADH-LK (3 U, 2 mg) were added successively. The reaction was shaken at 250 rpm at 30 °C for 24 h. Then, the mixture was extracted with EtOAc (2 × 500 μL) and dried over Na_2SO_4, and the reaction crude products were analyzed by NMR (conversion) and HPLC (enantiomeric excess).

Bioreduction of 1-(2-Nitrophenoxy)propan-2-one (3a) with ADH-CP. In an eppendorf tube containing ketone **3a** (2.3 mg, 0.012 mmol) in 50 mM Tris-HCl pH 7.5 buffer (450 μL), 2-propanol (25 μL), a 10 mM NADH solution in 50 mM Tris-HCl pH 7.5 buffer (50 μL), and ADH-CP (3 U, 7.5 μL) were added successively. The reaction was shaken at 250 rpm at 30 °C for 24 h. Then, the mixture was extracted with EtOAc (2 × 500 μL) and dried over Na_2SO_4, and the reaction crude products were analyzed 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), and the resulting suspension was stirred for 15 min at 30 °C and 250 rpm. After this time, ketone **3a** (33 mg, 0.17 mmol) was added, and the suspension was shaken at 30 °C and 250 rpm for 24 h. Then, the reaction was centrifuged, and the supernatant was extracted with EtOAc (3 × 20 mL). Organic layers were combined, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The reaction crude products were analyzed 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 ketones **3a−e** (0.018 mmol) and 2-propanol (38 μL) in 50 mM Tris-HCl pH 7.5 buffer (555 μL), a 10 mM $MgCl_2$ solution in 50 mM Tris-HCl pH 7.5 buffer (75 μL), a NADPH 10 mM solution in 50 mM Tris-HCl pH 7.5 buffer (75 μL), and ADH-LB (4.5 U, 15 μL) were added successively. The reaction was shaken at 30 °C and 250 rpm for 24 h and then extracted with EtOAc (2 × 500 μL). Organic layers were combined and dried over Na_2SO_4, and the reaction crude products were analyzed 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 ketones **3a−e** (0.012 mmol) and 2-propanol (25 μL) in 50 mM Tris-HCl pH 7.5 buffer (425 μL), a NADH 10 mM solution in 50 mM Tris-HCl pH 7.5 buffer (50 μL) and *E. coli*/ADH-A cells (15 mg) were added successively. The reaction was shaken at 30 °C and 250 rpm for 24 h. After this time, the mixture was extracted with EtOAc (2 × 500 μL), the organic layers combined and dried over Na_2SO_4, and the reaction crude products were analyzed 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 ketones **3a−e** (0.015 mmol) and 2-propanol (25 μL) in 50 mM Tris-HCl pH 7.5 buffer (400 μL), a 10 mM $MgCl_2$ solution in 50 mM Tris-HCl pH 7.5 buffer (60 μL), a 10 mM NADH solution in 50 mM Tris-HCl pH 7.5 buffer (60 μL) and evo-1.1.200 (60 μL of a solution composed of 1 mg of pure evo-1.1.200 in 760 μL of 50 mM Tris-HCl pH 7.5 buffer and 240 μL of 10 mM $MgCl_2$ solution) were added successively. The reaction was shaken at 30 °C and 250 rpm for 24 h. Then, the mixture was extracted with EtOAc (2 × 500 μL), and the organic layers were combined and dried over Na_2SO_4, analyzing the reaction crude products by GC (conversion) and HPLC (enantiomeric excess). For ketone **3e**, better results were found at slightly acidic pHs (6−6.5), suppressing the appearance of side-product **11** at an optimal pH value of 6.

General Procedure for the Scale up of Bioreduction of Ketones 3a−e with ADH-A. *E. coli*/ADH-A cells (20:1 weight ratio of ketone/crude enzyme) were rehydrated in 50 mM Tris-HCl pH 7.5 buffer (22 mL) by shaking the mixture at 30 °C and 250 rpm for 5 min. The corresponding ketones **3a−e** (0.94 mmol), 2-propanol (1.5 mL), and NADH (10 mg) were added successively. The suspension was shaken at 30 °C and 250 rpm until no starting material was detected by TLC analysis (24 h). Then, the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined and dried over Na_2SO_4 and filtered, and the solvent was 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 ketones **3a−e** (0.15 mmol) in a mixture of 2-propanol (250 μL) and 50 mM Tris-HCl pH 7.5 buffer (4 mL), a 10 mM $MgCl_2$ solution in 50 mM Tris-HCl pH 7.5 buffer (600 μL), a 10 mM NADH solution in 50 mM Tris-HCl pH 7.5 buffer (600 μL), and evo-1.1.200 (600 μL of a solution composed of 1 mg of pure evo-1.1.200 in 760 μL of 50 mM Tris-HCl pH 7.5 buffer and 240 μL of 10 mM $MgCl_2$ solution) were added successively. The reactions were shaken at 30 °C and 250 rpm for 24 h. The mixtures were extracted with EtOAc (3 × 10 mL). The organic layers were combined and dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, affording the corresponding alcohols (*R*)-**5a−e** (78−99% yield, >99% ee). As mentioned before, for ketone **3e**, better results were found at slightly acidic pHs (6−6.5), suppressing the appearance of side-product **11** at an optimal pH value of 6.

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 (1:1 weight ratio of alcohol/enzyme) were added to a suspension containing the corresponding racemic alcohols **5a−e** (0.51 mmol) in dry MTBE (5.1 mL) under nitrogen atmosphere. The reactions were shaken at 30 °C and 250 rpm for the necessary time to achieve good kinetic resolution (see Table 1 and Table S1 in the Supporting Information). The reaction was followed by HPLC analysis until ∼50% conversion was reached. The enzyme was filtered and washed with CH_2Cl_2 (3 × 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 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 acetates **6a−e** (0.43 mmol) and RML IM (1:1 weight ratio of acetate/enzyme) in MTBE (4.3 mL). The reaction was shaken at 30 °C and 250 rpm for the necessary time to achieve good kinetic resolution (see Table 2). The reaction was followed by HPLC analysis until ∼50% conversion was reached. The enzyme was filtered and washed with CH_2Cl_2 (3 × 5 mL), and the solvent was evaporated under reduced pressure. The crude reaction products were purified by column

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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).

■ ASSOCIATED CONTENT

Supporting Information

Copies of HPLC chiral analyses and ^1H, ^{13}C, and DEPT NMR spectra describing the organic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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