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# Stereoselective Access to 1-[2-Bromo(het)aryloxy]propan-2-amines Using Transaminases and Lipases; Development of a Chemoenzymatic Strategy Toward a Levofloxacin Precursor

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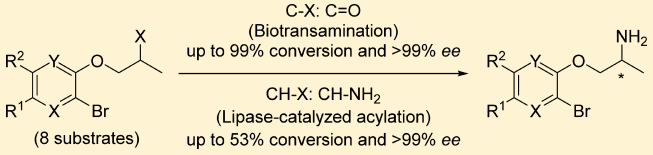
Supporting Information

**ABSTRACT:** Two independent enzymatic strategies have been developed toward the synthesis of enantioenriched 1-[2-bromo(het)aryloxy]propan-2-amines. With that purpose a series of racemic amines and prochiral ketones have been synthesized from commercially available 2-bromophenols or brominated pyridine derivatives bearing different pattern substitutions in the aromatic ring. Biotransamination experiments have been studied using ketones as starting materials, yielding both the (*R*)- and (*S*)-amine enantiomers with high selectivity (91−99% *ee*) depending on the transaminase source. In a complementary approach, the classical kinetic resolutions of the racemic amines have been investigated using *Candida antarctica* lipase type B as biocatalyst. Ethyl methoxyacetate was found as a suitable acyl donor leading to the corresponding (*S*)-amines (90−99% *ee*) and (*R*)-amides (88−99% *ee*) with high selectivity in most of the cases. A preparative biotransamination process has been developed for the synthesis of (2*S*)-1-(6-bromo-2,3-difluorophenoxy)propan-2-amine in 61% isolated yield after 24 h, a valuable precursor of the antimicrobial agent Levofloxacin.




## INTRODUCTION

Chiral amines are attractive building blocks for the synthesis of biologically active and high added-value products with interest in different chemical industrial sectors.[1] Remarkably, the use of biotransformations provides nowadays a plethora of possibilities for the design of stereoselective routes toward enantiopure amines and their derivatives.[2] Optically active 1-aryloxy-propan-2-amines (Scheme 1, $R^2$= $NH_2$) are particularly attractive nitrogenous compounds, the absolute configuration of their chiral center having a remarkable importance in their biological profiles.[3] From this family, 1-(2,6-dimethylphenoxy)propan-2-amine, also called as mexiletine, has attracted great attention for clinical purposes due to its properties as antiarrhythmic agent.[4] In past years, the versatility of biocatalytic reactions have been demonstrated toward the asymmetric synthesis of the non substituted 1-phenoxy-propan-2-amine by means of lipase-catalyzed resolutions,[5] and more recently biotransamination reactions from the corresponding propanones.[6] Remarkably, Turner and co-workers reported the conversion of racemic alcohols into enantiopure amines through a redox self-sufficient enzymatic cascade using an alcohol dehydrogenase and an amine dehydrogenase, yielding among other chiral amines, the enantiopure (*R*)-1-phenoxy-propan-2-amine in 84% conversion.[7]

The introduction of additional functionalities provides new opportunities in medicinal and synthetic chemistry. In this context, we have recently described the versatility of 1-(2-nitroaryloxy)propan-2-ones for the synthesis of benzoxazine fragments (Scheme 1), including the preparation of (*S*)-(−)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine, a key precursor of the antimicrobial agent Levofloxacin (Figure 1).[8] On the one hand, lipase from *Rhizomucor miehei* was able to catalyze with excellent selectivity the resolution of racemic alcohols and acetates through acylation and hydrolysis reactions, respectively. On the other hand, various alcohol dehydrogenases (ADHs) led to the production of both (*R*) and (*S*)-1-(2-nitroaryloxy)propan-2-ols with different pattern substitution in the aromatic ring using the evo-1.1.200 ADH and the ADH from *Rhodococcus ruber* (ADH-A), respectively.

Herein, we have carried out a chemoenzymatic route toward benzoxazine precursors, identifying 1-[2-bromo(het)aryloxy]-propan-2-ones as key compounds. First, biotransamination experiments have been investigated for the production of the corresponding amine enantiomers depending on the transaminase source. Alternatively, the reductive amination of the ketones can provide access to the corresponding racemic amines, which will be used as starting materials in lipase-catalyzed resolutions. The presence of the amino and bromo substitutions in the aromatic ring opens up the possibility of developing metal-catalyzed intramolecular cyclization for the production of optically active benzoxazine derivatives such as (*S*)-(−)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]-oxazine, a valuable precursor of Levofloxacin.

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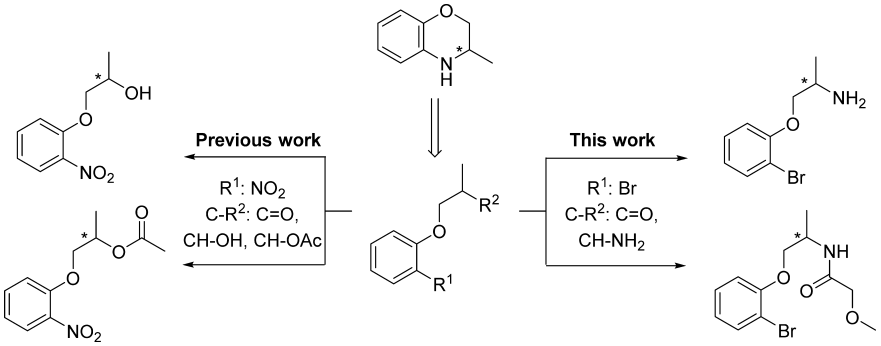
**Scheme 1. Chemoenzymatic Routes Toward Valuable Benzoxazine Precursors from 1-(2-Nitrophenoxy)propan-2-ones (left) and 1-(2-Bromophenoxy)propan-2-ones (right)**



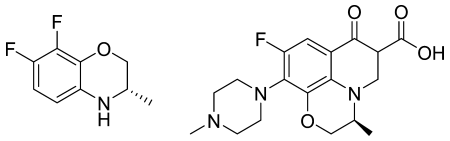



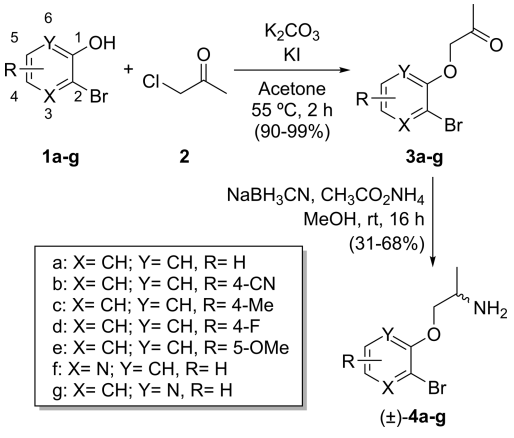
**Figure 1.** Structures of (*S*)-(−)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (left) and the antimicrobial agent Levofloxacin (right).

## RESULTS AND DISCUSSION

Two independent strategies were undertaken for the production of enantiopure 1-[2-bromo(het)aryloxy]propan-2-amines: (a) the transaminase-catalyzed amination of the corresponding 1-[2-nitro(het)aryloxy]propan-2-ones; and (b) the lipase-catalyzed resolution of the racemic amines. Bearing this in mind, a general and convergent route to prepare the prochiral ketones **3a−g** and racemic amines **4a−g** was performed starting from the corresponding commercially available 2-bromophenols **1a−d** and pyridinols **1f** and **1g** (Scheme 2), requiring a previous selective bromination of 3-methoxyphenol at the C-2 position with *N*-bromosuccinimide in the case of the non commercially available methoxy derivative **1e**.[9]

Substrates **1a−g** were alkylated using an equimolecular amount of chloroacetone (**2**) in the presence of 2 equiv of potassium carbonate and catalytic amounts of potassium iodide in refluxing acetone, obtaining after 2 h the ketones **3a−g** in high to quantitative yields. Prochiral ketones **3a−g** served as substrates for biotransamination reactions, but also as starting materials for the synthesis of the racemic amines through reductive amination using 2 equiv of sodium cyanoborohydride in combination with a large excess of ammonium acetate in methanol. Thus, racemic amines **4a−g** were obtained after 16 h at room temperature in low to moderate yields after purification by column chromatography on silica gel. The use of longer reaction times or alternatively the palladium-catalyzed reductive aminations in the presence of ammonium formate did not provide better results.

**Scheme 2. Chemical Synthesis of Prochiral Ketones 3a−g and Racemic Amines 4a−g**




Biotransamination experiments were initially explored as they allow the synthesis of (*S*)- or (*R*)-amines depending on the enzyme selectivity. In the last decades transaminases (TAs) have emerged as powerful enzymes for the synthesis of chiral amines starting from racemic amines, but more importantly from prochiral ketones as they provide access to a desired amine enantiomer in theoretically 100% yield.[10] The most structurally simple ketone was selected as the model compound for an initial enzyme screening, this is 1-(2-nitrophenoxy)-propan-2-one (**3a**) using a 50 mM substrate concentration. Different amine donors (L/D-alanine or isopropylamine) and cofactor recycling systems were used depending on the transaminase acceptance, which are described in the Experimental Section and Supporting Information. The temperature was kept at 30 °C and the reactions were shaken at 250 rpm in a phosphate buffer 100 mM pH 7.5. Based on our previous experience with the commercially available transaminases,[11] a 2.5% v/v of DMSO was added in the biotransaminations with these TAs to favor the solubility of the ketone **3a** in the reaction medium.

A set of 37 commercially available transaminases and 4 enzymes overexpressed in *Escherichia coli* were tested, including the (*S*)-selective *Arthrobacter citreus*[12] and *Chromobacterium violaceum* TAs,[13] and the (*R*)-selective *Arthrobacter* species[14] and *Aspergillus terreus* TAs.[15] The best results are shown in Table 1, while the results with the total 41 transaminases appear in the Supporting Information (Table S1). From the entire transaminase set, only 12 displayed complete selectivity toward the formation of single enantiomers, 10 for the (*S*)-**4a** and 2 for its antipode (Table S1). From all these selective enzymes, 10 of them led to the amine in more than 40% conversion (Table 1). Remarkably, the (*S*)-selective enzymes ATA-200 and ATA-256 gave the (*S*)-**4a** with excellent conversions (entries 2 and 5, > 96% conversion), obtaining the maximum value in the (*R*)-**4a** formation with the TA from *Aspergillus terreus* (At, 70% conversion, entry 10). For the At TA, an optimization study of the reaction conditions was



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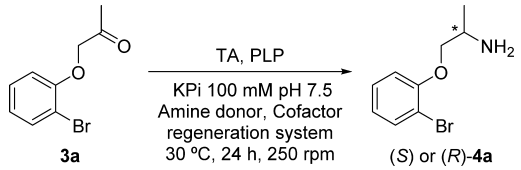
**Table 1. Biotransamination of Ketone 3a in Phosphate Buffer 100 mM pH 7.5 after 24 h at 30 °C**




| entry | TA | amine donor[a] | c (%)[b] | ee (%)[b] |
|---|---|---|---|---|
| 1 | TA-P1-G06[c] | IPA | 67 | > 99 (*S*) |
| 2 | ATA-200[c] | IPA | 97 | > 99 (*S*) |
| 3 | ATA-251[c] | IPA | 66 | > 99 (*S*) |
| 4 | AT1-254[c] | IPA | 89 | > 99 (*S*) |
| 5 | ATA-256[c] | IPA | 99 | > 99 (*S*) |
| 6 | ATA-260[c] | IPA | 53 | > 99 (*S*) |
| 7 | ATA-P1-B04[c] | IPA | 94 | > 99 (*S*) |
| 8 | Cv | L-Ala | 77 | > 99 (*S*) |
| 9 | ArR sp. | D-Ala | 45 | > 99 (*R*) |
| 10 | At | D-Ala | 70 | > 99 (*R*) |
| 11 | At[c] | D-Ala | 65 | > 99 (*R*) |
| 12 | At[d] | D-Ala | 96 | > 99 (*R*) |

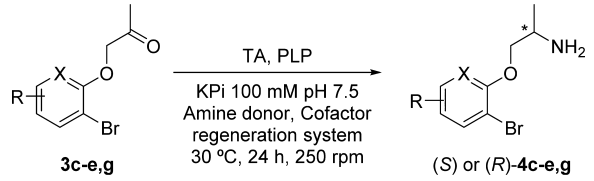
[a]Isopropylamine (IPA) or alanine (L- or D-Ala) was used as amine donors. [b]Conversion and enantiomeric excess values were calculated by GC analysis after derivatization of the amines in the reaction crude with $Ac_2O$. Absolute configurations appear in parentheses. [c]DMSO was added as cosolvent (2.5% v/v). [d]Double amount of enzyme was used (see Experimental Section).

performed, which showed that the use of DMSO as cosolvent led to a slightly lower conversion (65%, entry 11), while a significant improvement was achieved when doubling the amount of enzyme (96%, entry 12).

The scale-up of the process was performed for 100 mg of ketone **3a** employing the enzyme ATA-256 as biocatalyst, obtaining the enantiopure amine (*S*)-**4a** in 60% isolated yield after a purification by column chromatography (Scheme 3). The absolute configuration of the resulting enantiopure amine (*S*)-**4a** was assigned by its transformation into the 3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine using palladium(II) acetate and xantphos, yielding the benzoxazine (*S*)-**5** in 66% isolated yield without loss of the optical purity. Its optical rotation value was compared with the one previously described in the literature,[16] assigning the (*S*)-configuration for the amine **4a** obtained through the ATA-256 biotransformation.

With these results in hand, the transaminase-catalyzed reactions were performed over the aryloxypropanones **3b**–**e** and hetaryloxypropanones **3f** and **3g** (Table S2). It must be highlighted that a low reactivity was observed with all the TAs tested when ketones **3b** bearing a cyano functionality in the C-4 position and the pyridine derivative **3f** were tested as substrates (<45% conversion). In addition, the formation of side-reaction products was detected in some cases when performing the biotransamination over **3b**. The non heteroaromatic ketones bearing the methyl and the fluoro substitutions on the C-4 position (**3c** and **3d**) led to the best selectivities (Table 2,

**Table 2. Biotransamination of Ketone 3c–e,g (50 mM) in Phosphate Buffer 100 mM pH 7.5 after 24 h at 30 °C[a]**




| entry | substrate | R | X | TA | c (%)[a] | ee (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **3c** | 4-Me | CH | ATA-200[b] | 77 | > 99 (*S*) |
| 2 | **3c** | 4-Me | CH | ATA-254[b] | 77 | > 99 (*S*) |
| 3 | **3c** | 4-Me | CH | ATA-256[b] | 68 | > 99 (*S*) |
| 4 | **3c** | 4-Me | CH | ATA-P1-B04[b] | 64 | > 99 (*S*) |
| 5 | **3c** | 4-Me | CH | At | 91 | > 99 (*R*) |
| 6 | **3d** | 4-F | CH | ATA-200[b] | 76 | > 99 (*S*) |
| 7 | **3d** | 4-F | CH | ATA-254[b] | 87 | > 99 (*S*) |
| 8 | **3d** | 4-F | CH | ATA-256[b] | 98 | > 99 (*S*) |
| 9 | **3d** | 4-F | CH | ATA-P1-B04[b] | 95 | > 99 (*S*) |
| 10 | **3d** | 4-F | CH | At | 57 | > 99 (*R*) |
| 11 | **3e** | 5-OMe | CH | ATA-251[b] | 97 | 93 (*S*) |
| 12 | **3e** | 5-OMe | CH | ATA-256[b] | 87 | 93 (*S*) |
| 13 | **3e** | 5-OMe | CH | ATA-P1-B04[b] | 72 | 89 (*S*) |
| 14 | **3e** | 5-OMe | CH | TA-P1-G06[b] | > 99 | 91 (*S*) |
| 15 | **3g** | H | N | ATA-251[b] | 93 | 95 (*S*) |
| 16 | **3g** | H | N | ATA-254[b] | 88 | 97 (*S*) |
| 17 | **3g** | H | N | TA-P1-G06[b] | 97 | 97 (*S*) |

[a]Conversion and enantiomeric excess values were calculated by GC analysis after derivatization of the amines in the reaction crude with $Ac_2O$. Absolute configurations appear in parentheses. [b]DMSO was added as cosolvent (2.5% v/v).

entries 1–10), obtaining both amine enantiomers depending on the transaminase source. From the set of commercially available transaminases the best results were found with the ATA-200, ATA-254, ATA-256, and ATA-P1-B04, which led to the (*S*)-amines **4c** and **4d**, the fluoro substituted one leading in some cases to almost quantitative conversions (entries 8 and 9). In fact, the 100-mg preparative biotransamination of ketone **3d** with the ATA-256 led to the enantiopure (*S*)-**4d** in 66% isolated yield and very high purity. For the 5-methoxy derivative **3e**, good to quantitative conversions were achieved although none of the enzymes provided access to the (*S*)-**4e** in enantiopure form (entries 11–14). This amine was obtained in 91% *ee* and 74% isolated yield in the preparative biotransformation when using the TA-P1-G06. Finally, the pyridine ketone **3g** led to the (*S*)-**4g** in 95–97% *ee* and high to excellent conversion values (88–97%, entries 15–17). Unfortunately,

**Scheme 3. Chemoenzymatic Synthesis of (*S*)-3-Methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (5) for the Absolute Configuration Assignment of the Amine 4a**

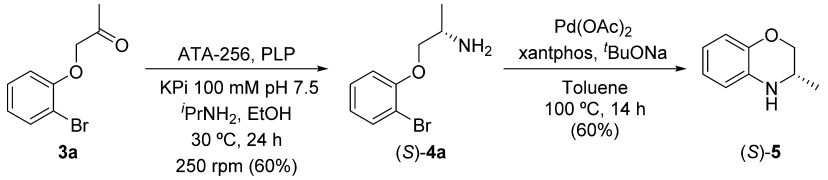





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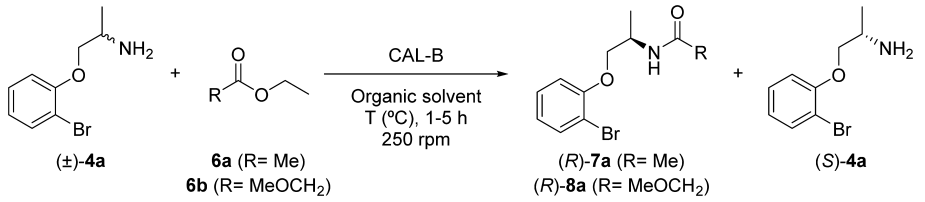
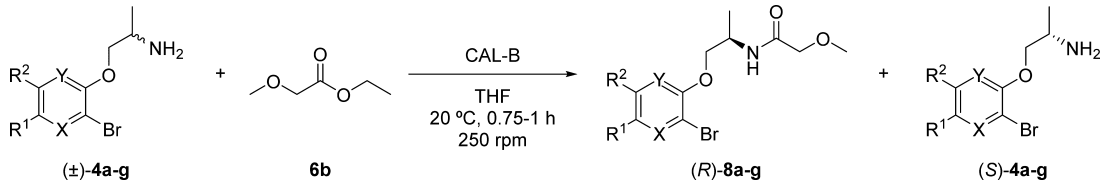
**Table 3. Lipase-Catalyzed Kinetic Resolution of 1-(2-Bromophenoxy)propan-2-amine (4a) Using CAL-B[a]**




| entry | CAL-B[b] | solvent | ester[c] | $T$ (°C) | $t$ (h) | $ee_p$ (%)[d] | $ee_s$ (%)[d] | $c$ (%)[e] | $E$[f] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1:1 | THF | **6a** (3 equiv) | 30 | 5 | 95 | 38 | 28 | 57 |
| 2 | 1:1 | THF | **6b** (3 equiv) | 30 | 5 | 83 | 99 | 54 | 56 |
| 3 | 1:1 | THF | **6b** (1 equiv) | 30 | 2.5 | 95 | 95 | 50 | 154 |
| 4 | 1:1 | THF | **6b** (2 equiv) | 30 | 1.5 | 93 | > 99 | 52 | 156 |
| 5 | 1:1 | MTBE | **6b** (2 equiv) | 30 | 1.5 | 69 | > 99 | 59 | 72 |
| 6 | 1:1 | THF | **6b** (2 equiv) | 4 | 1 | 97 | 92 | 49 | > 200 |
| 7 | 1:1 | THF | **6b** (2 equiv) | 4 | 2 | 96 | 99 | 51 | > 200 |
| 8 | 1:1 | THF | **6b** (2 equiv) | 20 | 1 | 95 | 99 | 51 | > 200 |
| 9 | 0.5:1 | THF | **6b** (2 equiv) | 20 | 1 | 97 | 86 | 47 | 195 |
| 10 | 0.5:1 | THF | **6b** (2 equiv) | 20 | 2 | 96 | 96 | 50 | 193 |

[a]Reaction conditions: **4a** (100 mM in THF or MTBE), CAL-B (ratio w/w), **6a**–**b** (1–3 equiv), 4–30 °C, 1–5 h at 250 rpm. [b]Ratio amine **4a**: CAL-B (w/w). [c]Equivalents of ester in parentheses. [d]Determined by HPLC. Isolated yields in parentheses. [e]$c = ee_s/(ee_s + ee_p)$. [f]$E = \ln[(1 - c)(1 - ee_p)]/\ln[(1 - c)(1 + ee_p)]$.[21]

**Table 4. Lipase-Catalyzed Kinetic Resolution of 1-[2-Bromo(het)aryloxy]propan-2-amines (4a–g) Using CAL-B and Ethyl Methoxyacetate (6b) in Dry THF[a]**




| entry | amine | $R^1$ | $R^2$ | X | Y | $t$ (h) | $ee_p$ (%)[b] | $ee_s$ (%)[b] | $c$ (%)[c] | $E$[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | H | H | CH | CH | 1 | 95 | 99 | 51 | > 200 |
| 2 | **4b** | CN | H | CH | CH | 1 | 93 | 90 | 50 | 91 |
| 3 | **4c** | Me | H | CH | CH | 1 | 97 | > 99 | 51 | > 200 |
| 4 | **4d** | F | H | CH | CH | 1 | 95 | > 99 | 51 | > 200 |
| 5 | **4e** | H | OMe | CH | CH | 0.75 | 88 | > 99 | 53 | 115 |
| 6 | **4f** | H | H | N | CH | 0.75 | 99 | > 99 | 50 | > 200 |
| 7 | **4g** | H | H | CH | N | 0.75 | 98 | > 99 | 50 | > 200 |

[a]Reaction conditions: **4a**–**g** (100 mM in THF), CAL-B (ratio 1:1 in weight), **6b** (2 equiv), 20 °C, 0.75–1 h at 250 rpm. [b]Determined by HPLC. Isolated yields in parentheses. [c]$c = ee_s/(ee_s + ee_p)$. [d]$E = \ln[(1 - c)(1 - ee_p)]/\ln[(1 - c)(1 + ee_p)]$.[21]

none of the commercially available TAs gave good activities for the preparation of the (*R*)-amines, the synthesis of (*R*)-**4c** and (*R*)-**4d** in enantiopure form being achieved with 91% and 57% conversion, respectively, when using the At-TA (entries 5 and 10).

In the search of an alternatively methodology for the synthesis of enantiopure amines, the hydrolase-catalyzed kinetic resolution of the racemic amines **4a**–**g** was attempted. Lipase-catalyzed acylation is a common strategy for the resolution of racemic amines and alcohols under mild reaction conditions,[17] mainly using esters as acyl donors.[18] So at this point, an initial screening of the reaction conditions was performed with the less hindered substrate, 1-(2-bromophenoxy)propan-2-amine (**4a**) as the model substrate (Table 3). *Candida antarctica* lipase type B (CAL-B)[19] was the enzyme of choice based on its capability to selectively produce nitrogenous compounds, and tetrahydrofuran was used as solvent since it allows a complete solubility of the amine **4a** in 100 mM concentration. Two non activated esters, such as ethyl acetate (**6a**) and ethyl methoxyacetate (**6b**), were initially assayed as acyl donors, which resulted in a similar selectivity but higher reactivity for **6b** after 5 h (entries 1 and 2). A notable decrease of the enantioselectivity was observed over the time when using **6b**, so the biotransformations were carried out with lower amount of the ester (1 or 2 equiv, entries 3 and 4), which led to conversions close to the ideal 50% and very high selectivity in short reaction times. Similarly, the reaction with methyl *tert*-butyl ether (MTBE) as solvent occurred very quickly but with less selectivity in comparison with THF. At this point, the reaction temperature was decreased, leading to both the (*R*)-amide and the (*S*)-amine with excellent selectivity at both 4 and 20 °C (entries 6–8), while reducing the loading of the enzyme did not provide additional benefits (entries 9 and 10). The reaction at 20 °C and 2 equiv of **6b** (entry 8) was performed at a 200 mg-scale, finding similar results in a highly stereoselective process that allowed the recovery of the (*R*)-amide **8a** and the remaining amine (*S*)-**4a** in 49% and 47% isolated yield, respectively (see Experimental Section).



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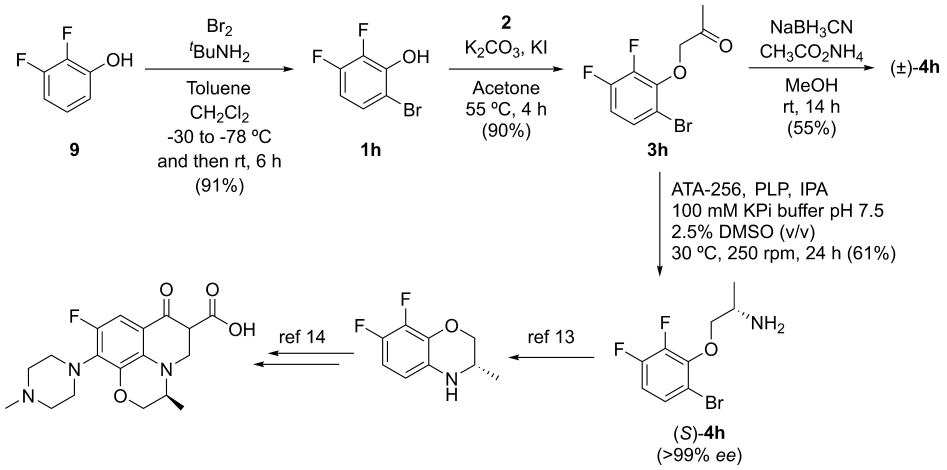
**Scheme 4. Chemoenzymatic Synthesis of the Levofloxacin Precursor (*S*)-4h**




The assignments of the absolute configurations for the optically active amide **8a** and the remaining amine **4a** were performed by measuring the optical rotation of **4a**, which was compared with the one obtained through transaminase-catalyzed reactions. It was concluded that the lipase-catalyzed reaction led to the (*R*)-**8a** and the (*S*)-**4a**, which is also in agreement with the expected configurations considering the Kazaluskas' rule.[20]

Once adequate reaction conditions were found for the resolution of the racemic amine **4a**, these are 100 mM substrate concentration in THF, 2 equiv of **6b**, CAL-B as enzyme in ratio 1:1 (w/w) with respect to the substrate, and 20 °C, the kinetic resolution was extended to a significant panel of amines bearing different pattern substitutions in the phenyl ring (**4b**–**e**) but also including pyridine derivatives, such as **4f** and **4g**. The results are shown in Table 4 and in all cases close to 50% conversion values were reached (additional information is given in Table S4). The corresponding (*R*)-amides **8a**–**g** and the remaining amines (*S*)-amines **4a**–**g** were isolated with very high to excellent selectivities in just 45 min for the most reactive substrates, such as the one with the methoxy substitution in the C-5 position and the pyridine derivatives (entries 4–7). Interestingly, the lipase-catalyzed approach provide an efficient stereoselective access to all the tested amines, allowing the isolation of enantioenriched **4b** and **4f** that were not obtained through transaminase-catalyzed reactions. The optical rotation values for the remaining amines were measured and later compared with the ones obtained through biotransamination experiments with transaminases of known stereospecificity, concluding that the CAL-B catalyzed acylations led to the (*R*)-methoxyacetamides **8a**–**g** and the (*S*)-amines **4a**–**g**.

Once that the versatility of CAL-B and transaminases was demonstrated in the synthesis of valuable optically active 1-[2-bromo(het)aryloxy]propan-2-amines, we expanded the possibilities of this chemoenzymatic strategy toward the synthesis of (*S*)-**4h**. This amine can be effectively cyclized to the corresponding benzoxazine precursor,[22] which is a valuable precursor of the antimicrobial agent Levofloxacin.[23] The synthetic pathway is depicted in Scheme 4 starting from the commercially available 2,3-difluorophenol (**9**). First, a selective bromination of the aromatic ring was performed using 2 equiv of *tert*-butylamine and equimolecular amount of bromine in toluene at low temperature, yielding after column chromatography the 2-bromo-5,6-difluorophenol (**1h**) in 91% isolated yield.[22a] This procedure improves the results using NBS, which led to a mixture of polybrominated products. Next, the *O*-alkylation proceeded smoothly after 4 h providing the ketone **3h** in 90% yield, which was subjected to the reductive amination reaction with sodium cyanoborohydride and ammonium acetate to yield the racemic amine **4h**. On the one hand, an initial attempt of the stereoselective lipase-catalyzed acylation was performed, but this amine resulted to be quite unstable in the reaction medium, both in the absence or presence of the enzyme. On the other hand, from a set of transaminases (see Table S3) the ATA-256 provided the best results yielding the Levofloxacin precursor (*S*)-**4h** in 99% conversion and 61% isolated yield after purification by column chromatography on silica gel.

## CONCLUSIONS

The chemoenzymatic synthesis of optically active 1-[2-bromo(het)aryloxy]propan-2-amines, which are valuable precursors of benzoxazine derivatives have been explored by using transaminases or *Candida antarctica* lipase type B for the stereoselective reaction step. Starting from commercially available 2-bromophenols or pyridine derivatives, prochiral ketones have been obtained through a simple alkylation reaction in good yields. The chemical reductive amination have provided access to the corresponding racemic amines, using both ketones and amines for extensive biocatalytic reaction studies. Transaminases have catalyzed the amination of ketones with especially good results in terms of conversion and selectivity when (*S*)-selective enzymes were considered. In a complementary approach starting from the corresponding racemic amines, their lipase-catalyzed resolution was studied, finding high to excellent selectivity values for the formation of the remaining (*S*)-amines and the (*R*)-methoxyacetamides in close to 50% conversion value.

The applicability of this synthetic strategy has been demonstrated in the production of a valuable precursor of the antimicrobial agent Levofloxacin. Therefore, the (*S*)-1-(6-bromo-2,3-difluorophenoxy)propan-2-amine has been prepared with complete selectivity and a global 50% yield, starting from 2,3-difluorophenol through a three-step sequence that involves a selective bromination reaction, alkykation step, and final biotransamination process using the commercially available ATA-256 enzyme.



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## EXPERIMENTAL SECTION

**Synthesis of 2-Bromo-5-Methoxyphenol (1e).**[9] *N*-bromosuccinimide (811 mg, 4.55 mmol) was added in one portion to a solution of 3-methoxyphenol (500 μL, 4.55 mmol) in dry $CH_2Cl_2$ (90 mL) under inert atmosphere. The reaction mixture was stirred at room temperature for 2 h and then washed with water (30 mL). The organic layer was dried over $Na_2SO_4$, subjected to filtration, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (10% $Et_2O$/hexane), to afford the bromophenol **1e** as a colorless oil (693 mg, 75%). Physical and spectral data were found to be consistent with those previously reported in the literature.[9]

**General Procedure for the Synthesis of Ketones 3a−g.** Chloroacetone (**2**, 82 μL, 1.03 mmol) was added to a mixture of potassium carbonate (238 mg, 1.72 mmol), potassium iodide (41 mg, 0.25 mmol), and the corresponding bromophenol **1a−g** (0.86 mmol) in acetone (3 mL) at room temperature, and the mixture was stirred and heated at 55 °C for 2 h. After this time, the solution was added to water (5 mL) and the product was extracted with $Et_2O$ (4 × 10 mL). The organic layers were combined, washed with water (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo, isolating the bromacetophenones **3a−g** with high purity without further purification (90−99%).

*1-(2-Bromophenoxy)propan-2-one (**3a**).* White solid (195 mg, 99% yield). $R_f$ (40% EtOAc/hexane): 0.61. mp: 67−68 °C. IR (NaCl): $\nu$ 3450, 3066, 3007, 2919, 1732, 1586, 1575, 1478, 1444, 1431, 1360, 969, 932, 863, 830 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.37 (s, 3H), 4.54 (s, 2H), 6.77 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.3 Hz, 1H), 6.89 (td, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz, 1H), 7.25 (ddd, $^3J_{HH}$ = 8.4, 7.5 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.58 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.6 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 27.0 ($CH_3$), 73.8 ($CH_2$), 112.1 (C), 113.1 (CH), 122.9 (CH), 128.6 (CH), 133.7 (CH), 154.1 (C), 205.5 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_9H_9BrNaO_2)^+$ $(M+Na)^+$ 250.9678; found 250.9691.

*3-Bromo-4-(2-oxopropoxy)benzonitrile (**3b**).* Yellowish solid (216 mg, 99% yield). $R_f$ (20% $Et_2O$/hexane): 0.33. mp: 109−110 °C. IR (KBr): $\nu$ 3364, 3054, 2987, 2306, 1731, 1601, 1440, 1377, 1322, 923, 896 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.39 (s, 3H), 4.66 (s, 2H), 6.81 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 7.60 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.0 Hz, 1H), 7.88 (d, $^4J_{HH}$ = 2.0 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 26.9 ($CH_3$), 73.4 ($CH_2$), 106.4 (C), 112.7 (CH), 112.8 (C), 117.4 (C), 133.1 (CH), 137.1 (CH), 157.6 (C), 203.4 (C) ppm. HRMS (ESI$^+$, $m/z$): calcd for $(C_{10}H_8BrNNaO_2)^+$ $(M+Na)^+$ 275.9631; found 275.9625; calculated for $(C_{10}H_9BrNO_2)^+$ $(M+H)^+$ 253.9811; found 253.9813.

*1-(2-Bromo-4-methylphenoxy)propan-2-one (**3c**).* Yellowish solid (207 mg, 99% yield). $R_f$ (20% $Et_2O$/hexane): 0.26. mp: 47−49 °C. IR (KBr): $\nu$ 3055, 2925, 1724, 1606, 1496, 1359, 1290, 947, 882 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.28 (s, 3H), 2.36 (s, 3H), 4.51 (s, 2H), 6.66 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.03 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.0 Hz, 1H), 7.39 (d, $^4J_{HH}$ = 2.0 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 20.3 ($CH_3$), 27.1 ($CH_3$), 74.1 ($CH_2$), 112.0 (C), 113.2 (CH), 129.1 (CH), 132.9 (C), 134.2 (CH), 152.2 (C), 206.1 (C) ppm. HRMS (ESI$^+$, $m/z$): calcd for $(C_{10}H_{11}BrNaO_2)^+$ $(M+Na)^+$ 264.9835; found 264.9827.

*1-(2-Bromo-4-fluorophenoxy)propan-2-one (**3d**).* White solid (195 mg, 92% yield). $R_f$ (20% $Et_2O$/hexane): 0.26. mp: 67−68 °C. IR (KBr): $\nu$ 3401, 3055, 2306, 1730, 1722, 1594, 1489, 1361, 947, 866 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.36 (s, 3H), 4.52 (s, 2H), 6.75 (dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{FH}$ = 4.6 Hz, 1H), 6.98 (ddd, $^3J_{HH}$ = 9.0 Hz, $^3J_{FH}$ = 7.7 Hz, $^4J_{HH}$ = 3.0 Hz, 1H), 7.34 (dd, $^3J_{FH}$ = 7.7 Hz, $^4J_{HH}$ = 3.0, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 27.0 ($CH_3$), 74.5 ($CH_2$), 112.6 (d, $^3J_{FC}$ = 9.9 Hz, C), 114.2 (d, $^3J_{FC}$ = 8.6 Hz, CH), 115.0 (d, $^2J_{FC}$ = 22.9 Hz, CH), 121.0 (d, $^2J_{FC}$ = 25.8 Hz, CH), 151.0 (d, $^4J_{FC}$ = 2.6 Hz, C), 157.4 (d, $^1J_{FC}$ = 244.5 Hz, C), 205.3 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_9H_8BrFNaO_2)^+$ $(M+Na)^+$ 268.9584; found 268.9578.

*1-(2-Bromo-5-methoxyphenoxy)propan-2-one (**3e**).* White solid (205 mg, 92% yield). $R_f$ (50% EtOAc/hexane): 0.68. mp: 62−64 °C. IR (KBr): $\nu$ 2840, 1734, 1722, 1586, 1488, 1421, 1360, 1307, 1201, 1169, 1067, 1025 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.32 (s, 3H), 3.73 (s, 3H), 4.47 (s, 2H), 6.30 (d, $^4J_{HH}$ = 2.7 Hz, 1H), 6.41 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.7 Hz, 1H), 7.39 (d, $^3J_{HH}$ = 8.7 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 26.9 ($CH_3$), 55.6 ($CH_3$), 73.6 ($CH_2$), 101.1 (CH), 102.7 (C), 107.2 (CH), 133.5 (CH), 154.8 (C), 160.2 (C), 205.4 (C) ppm. HRMS (ESI$^+$, $m/z$): calcd for $(C_{10}H_{11}BrNaO_3)^+$ $(M+Na)^+$ 280.9784, found: 280.9792.

*1-[(2-Bromopyridin-3-yl)oxy]propan-2-one (**3f**).* White solid (178 mg, 90% yield). $R_f$ (20% $Et_2O$/hex): 0.38. mp: 73−74 °C. IR (KBr): $\nu$ 3054, 2986, 1738, 1565, 1415, 1362, 967, 896, 793, 749, 704 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.40 (s, 3H), 4.60 (s, 2H), 7.05 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.23 (dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 8.06 (dd, $^3J_{HH}$ = 4.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 26.9 ($CH_3$), 73.5 ($CH_2$), 120.0 (CH), 123.4 (CH), 133.0 (C), 142.4 (CH), 151.3 (C), 204.1 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_8H_9BrNO_2)^+$ $(M+H)^+$ 229.9811; found 229.9812; calculated for $(C_8H_8BrNNaO_2)^+$ $(M+Na)^+$ 251.9631; found 251.9624.

*1-[(3-Bromopyridin-2-yl)oxy]propan-2-one (**3g**).* Brown solid (192 mg, 97% yield). $R_f$ (20% $Et_2O$/hex): 0.20. mp: 101−103 °C. IR (KBr): $\nu$ 3055, 2987, 1738, 1656, 1603, 1527, 1422, 1406, 1371, 970, 856 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.31 (s, 3H), 4.76 (s, 2H), 6.14 (t, $^3J_{HH}$ = 7.0 Hz, 1H), 7.18 (dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.9 Hz, 1H), 7.78 (dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.9 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 27.7 ($CH_3$), 58.9 ($CH_2$), 106.1 (CH), 116.4 (C), 137.6 (CH), 142.2 (CH), 158.8 (C), 200.1 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_8H_8BrNNaO_2)^+$ $(M+Na)^+$ 251.9631; found 251.9630.

**General Procedure for the Synthesis of Racemic 1-[2-Bromo(het)aryloxy]propan-2-amines 4a−g.** To a solution of the corresponding ketone **3a−g** (0.43 mmol) in dry MeOH (1.4 mL), ammonium acetate (335 mg, 4.34 mmol) and sodium cyanoborohydride (55 mg, 0.87 mmol) were successively added under inert atmosphere. The mixture was stirred at room temperature for 16 h, and after this time $H_2O$ (15 mL) was added to quench the reaction. The solution was acidified with a few drops of concentrated aqueous HCl and extracted with $Et_2O$ (3 × 15 mL). The organic layers were discarded and the aqueous phase basified with 2−3 pellets of NaOH, and extracted with $Et_2O$ (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated in vacuo. The reaction crude was purified by column chromatography on silica gel (10% MeOH/$CH_2Cl_2$), to afford the racemic amines (31−68%).

*1-(2-Bromophenoxy)propan-2-amine (**4a**).* Yellowish oil (36 mg, 36% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.28. IR (NaCl): $\nu$ 3356, 2965, 2929, 2227, 1658, 1614, 1597, 1487, 1369, 1295, 975, 855, 730 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.22 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 2.25 (brs, 2H), 3.22−3.57 (m, 1H), 3.74 (dd, $^2J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 7.4 Hz, 1H), 3.96 (dd, $^2J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 6.75−6.92 (m, 2H), 7.24 (td, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.53 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.6 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 19.4 ($CH_3$), 46.5 (CH), 75.2 ($CH_2$), 112.3 (C), 113.4 (CH), 122.1 (CH), 128.5 (CH), 133.3 (CH), 155.1 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_9H_{13}BrNO)^+$ $(M+H)^+$ 230.0175; found 230.0178.

*4-(2-Aminopropoxy)-3-bromobenzonitrile (**4b**).* Yellowish oil (44 mg, 40% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.33. IR (NaCl): $\nu$ 3364, 3358, 3104, 2227, 1750, 1596, 1494, 1461, 1398, 1397, 886, 816, 751, 715, 672 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.24 (d, $^2J_{HH}$ = 6.6 Hz, 3H), 2.12 (brs, 2H), 3.42−3.53 (m, 1H), 3.82 (dd, $^2J_{HH}$ = 8.8, $^3J_{HH}$ = 7.3 Hz, 1H), 4.01 (dd, $^2J_{HH}$ = 8.8, $^3J_{HH}$ = 4.1 Hz, 1H), 6.93 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.58 (dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 2.1 Hz, 1H), 7.83 (d, $^4J_{HH}$ = 2.1 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 19.5 ($CH_3$), 46.1 (CH), 75.5 ($CH_2$), 105.3 (C), 112.7 (C), 112.8 (CH), 117.7 (C), 133.1 (CH), 136.6 (CH), 158.6 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{10}H_{12}BrN_2O)^+$ $(M+H)^+$ 255.0128; found 255.0139.

*1-(2-Bromo-4-methylphenoxy)propan-2-amine (**4c**).* Yellowish oil (33 mg, 31% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.35. IR (NaCl): $\nu$ 3355, 2925, 2932, 1663, 1486, 1373, 1287, 933, 796, 782, 685 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.22 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 2.27 (s, 3H), 2.60 (brs, 2H), 3.37−3.48 (m, 1H), 3.72 (dd, $^2J_{HH}$ = 8.9, $^3J_{HH}$



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= 7.4 Hz, 1H), 3.94 (dd, $^2J_{HH}$ = 8.9, $^3J_{HH}$ = 4.0 Hz, 1H), 6.78 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 7.03 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.1 Hz, 1H), 7.35 (d, $^4J_{HH}$ = 2.1 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 19.3 ($CH_3$), 20.2 ($CH_3$), 46.4 (CH), 75.3 ($CH_2$), 112.0 (C), 113.5 (CH), 128.9 (CH), 131.8 (C), 133.6 (CH), 152.9 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{10}H_{15}BrNO)^+$ $(M+H)^+$ 244.0332; found 244.0322.

*1-(2-Bromo-4-fluorophenoxy)propan-2-amine (**4d**).* Yellowish oil (42 mg, 39% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.23. IR (NaCl): $\nu$ 3410, 3012, 2979, 1687, 1433, 1326, 1290, 947, 867, 753, 701 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.22 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 2.43 (brs, 2H), 3.33−3.53 (m, 1H), 3.71 (dd, $^2J_{HH}$ = 8.8, $^3J_{HH}$ = 7.4 Hz, 1H), 3.93 (dd, $^2J_{HH}$ = 8.8, $^3J_{HH}$ = 4.0 Hz, 1H), 6.83 (dd, $^3J_{HH}$ = 9.1, $^4J_{HF}$ = 4.8 Hz, 1H), 6.93−7.00 (m, 1H), 7.28 (dd, $^3J_{HF}$ = 7.8, $^4J_{HH}$ = 3.0 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 19.2 ($CH_3$), 46.4 (CH), 75.8 ($CH_2$), 112.4 (d, $^3J_{FC}$ = 9.9 Hz, C), 114.1 (d, $^3J_{FC}$ = 8.5 Hz, CH), 114.8 (d, $^2J_{FC}$ = 22.6 Hz, CH), 120.3 (d, $^2J_{FC}$ = 25.8 Hz, CH), 151.7 (d, $^4J_{FC}$ = 2.4 Hz, C), 156.7 (d, $^1J_{FC}$ = 243.3 Hz, C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_9H_{12}BrFNO)^+$ $(M+H)^+$ 248.0081; found 248.0085.

*1-(2-Bromo-5-methoxyphenoxy)propan-2-amine (**4e**).* Colorless oil (74 mg, 66% yield). $R_f$ (50% EtOAc/hexane): 0.38. IR (NaCl): $\nu$ 3368, 2330, 2174, 1591, 1489, 1467, 1306, 1283, 1203, 1170, 1061, 1023, 828 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.24 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 2.68 (brs, 2H), 3.39−3.52 (m, 1H), 3.70−3.79 (m, 1H) overlapped signal with 3.77 (s, 3H), 3.95 (dd, $^2J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 6.39 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.7 Hz, 1H), 6.49 (d, $^4J_{HH}$ = 2.7 Hz, 1H), 7.38 (d, $^3J_{HH}$ = 8.7 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 15.3 ($CH_3$), 48.4 (CH), 55.9 ($CH_3$), 69.9 ($CH_2$), 102.1 (CH), 103.1 (C), 108.8 (CH), 133.3 (CH), 154.5 (C), 160.3 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{10}H_{15}BrNO_2)^+$ $(M+H)^+$ 260.0281, found: 260.0275.

*1-[(2-Bromopyridin-3-yl)oxy]propan-2-amine (**4f**).* Yellowish oil (32 mg, 32% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.28. IR (NaCl): $\nu$ 3330, 3321, 2960, 2929, 2227, 1645, 1596, 1563, 1538, 1494, 1447, 1416, 849, 795, 726, 680 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.19 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.78 (brs, 2H), 3.35−3.48 (m, 1H), 3.72 (dd, $^2J_{HH}$ = 8.6, $^3J_{HH}$ = 7.5 Hz, 1H), 3.93 (dd, $^2J_{HH}$ = 8.6, $^3J_{HH}$ = 4.1 Hz, 1H), 7.11 (dd, $^3J_{HH}$ = 8.1, $^4J_{HH}$ = 1.6 Hz, 1H), 7.18 (dd, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 4.6 Hz, 1H), 7.96 (dd, $^3J_{HH}$ = 4.6, $^4J_{HH}$ = 1.6 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 19.8 ($CH_3$), 46.2 (CH), 75.7 ($CH_2$), 119.9 (CH), 123.5 (CH), 133.2 (C), 141.5 (CH), 152.3 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_8H_{12}BrN_2O)^+$ $(M+H)^+$ 231.0128; found 231.0123.

*1-[(3-Bromopyridin-2-yl)oxy]propan-2-amine (**4g**).* Yellowish oil (67 mg, 68% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.21. IR (NaCl): $\nu$ 3419, 3093, 2345, 2177, 1706, 1648, 1583, 1530, 1427, 1396, 1327, 976, 866, 855 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.16 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.15 (brs, 2H), 3.39−3.52 (m, 1H), 3.70 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 8.1 Hz, 1H), 4.08 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 6.08 (t, $^3J_{HH}$ = 7.0 Hz, 1H), 7.37 (dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.9 Hz 1H), 7.74 (dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.9 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 20.9 ($CH_3$), 45.8 (CH), 58.4 ($CH_2$), 105.8 (CH), 116.7 (C), 138.1 (CH), 141.7 (CH), 159.3 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_8H_{11}BrN_2NaO)^+$ $(M+Na)^+$ 252.9947; found 252.9945.

*Synthesis of Racemic N-[1-(2-bromophenoxy)propan-2-yl]-acetamide (**7a**).* 4-Dimethylaminopyridine (8.0 mg, 0.066 mmol), triethylamine (72.2 $\mu$L, 0.983 mmol), and acetic anhydride (72.2 $\mu$L, 0.655 mmol) were successively added to a solution of the racemic amine **4a** (75 mg, 0.328 mmol) in dry $CH_2Cl_2$ (2 mL). The reaction was stirred at room temperature for 1 h and after this time the solvent was removed by distillation under reduced pressure. The crude was purified by column chromatography on silica gel (5% MeOH/$CH_2Cl_2$), to afford the racemic acetamide **7a** as a white solid (86 mg, 96%). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.65. mp: 67−68 °C. IR (KBr): $\nu$ 3053, 2987, 1768, 1662, 1608, 1498, 1267, 914, 896, 761, 721 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.37 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 2.01 (s, 3H), 3.97−4.07 (m, 2H), 4.35−4.47 (m, 1H), 6.13 (d, 1H, $^3J_{HH}$ = 7.7 Hz), 6.82−6.93 (m, 2H), 7.26 (ddd, $^3J_{HH}$ = 8.2, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.6 Hz, 1H), 7.53 (dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.6 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 18.0 ($CH_3$), 23.8 ($CH_3$), 45.0 (CH), 72.1 ($CH_2$), 112.7 (C), 114.0 (CH), 127.8 (CH), 129.1 (CH), 133.7 (CH), 155.3 (C), 170.4 (C) ppm. HRMS (ESI$^+$, $m/z$): calcd for $(C_{11}H_{15}BrNO_2)^+$ $(M+H)^+$: 272.0281 found: 272.0287; calcd for $(C_{11}H_{14}BrNNaO_2)^+$ $(M+Na)^+$: 294.0100 found: 294.0103.

**General Procedure for the Synthesis of Racemic Methoxyacetamides 8a−g.** 4-Dimethylaminopyridine (1.5 mg, 0.012 mmol), triethylamine (25 $\mu$L, 0.18 mmol), and methoxyacetyl chloride (11 $\mu$L, 0.12 mmol) were successively added to a solution of the corresponding racemic amine **4a−g** (0.06 mmol) in dry $CH_2Cl_2$ (2.1 mL). The reaction was stirred at room temperature for 1 h and after this time the solvent was removed by distillation under reduced pressure. The crude was purified by column chromatography on silica gel (5% MeOH/$CH_2Cl_2$), to afford the corresponding methoxyacetamide **8a−g** (85−99%).

*N-[1-(2-Bromophenoxy)propan-2-yl]-2-methoxyacetamide (**8a**).* White solid (18 mg, 98% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.79. mp: 52−53 °C. IR (KBr): $\nu$ 3409, 3054, 2983, 2937, 2829, 1678, 1586, 1574, 1483, 1266, 986, 932, 896, 738, 704, 555 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.32−1.60 (m, 3H), 3.42 (s, 3H), 3.89−3.92 (m, 2H), 4.03−4.05 (m, 2H), 4.43−4.51 (m, 1H), 6.77−6.93 (m, 3H), 7.18−7.33 (m, 1H), 7.45−7.59 (m, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 18.1 ($CH_3$), 44.4 (CH), 59.6 ($CH_3$), 72.0 ($CH_2$), 72.3 ($CH_2$), 112.8 (C), 113.8 (CH), 122.7 (CH), 129.0 (CH), 133.7 (CH), 155.2 (C), 169.5 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{12}H_{17}BrNO_3)^+$ $(M+H)^+$ 302.0386; found 302.0381; calculated for $(C_{12}H_{16}BrNNaO_3)^+$ $(M+Na)^+$ 324.0206; found 324.0204.

*N-[1-(2-Bromo-4-cyanophenoxy)propan-2-yl]-2-methoxyacetamide (**8b**).* White solid (17 mg, 87% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.63. mp: 102−103 °C. IR (KBr): $\nu$ 3417, 3012, 2182, 1696, 1669, 1605, 1510, 1456, 1298, 1267, 965, 868, 852 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.42 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 3.43 (s, 3H), 3.85−3.97 (m, 2H), 4.07−4.16 (m, 2H), 4.45−4.53 (m, 1H), 6.75 (d, 1H, $^3J_{HH}$ = 6.9 Hz), 6.97 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 7.60 (dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 2.1 Hz, 1H), 7.85 (d, $^4J_{HH}$ = 2.1 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 17.8 ($CH_3$), 43.7 (CH), 59.2 ($CH_3$), 71.7 ($CH_2$), 71.8 ($CH_2$), 105.6 (C), 112.9 (C), 113.0 (CH), 117.7 (C), 133.2 (CH), 136.7 (CH), 158.4 (C), 169.3 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{13}H_{16}BrN_2O_3)^+$ $(M+H)^+$ 327.0339; found 327.0335; calculated for $(C_{13}H_{15}BrN_2NaO_3)^+$ $(M+Na)^+$ 349.0158; found 349.0164.

*N-[1-(2-Bromo-4-methylphenoxy)propan-2-yl]-2-methoxyacetamide (**8c**).* White solid (16 mg, 85% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.67. mp: 64−65 °C. IR (KBr): $\nu$ 3419, 3093, 2345, 2177, 1698, 1623, 1597, 1419, 1265, 896, 751, 706 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.41 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 2.29 (s, 3H), 3.43 (s, 3H), 3.85−3.97 (m, 2H), 4.00−4.04 (m, 2H), 4.58−4.35 (m, 1H), 6.80 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 6.95 (d, 1H, $^3J_{HH}$ = 7.9 Hz), 7.00−7.13 (m, 1H), 7.37 (d, $^4J_{HH}$ = 2.0 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 17.7 ($CH_3$), 20.2 ($CH_3$), 44.0 (CH), 59.3 ($CH_3$), 71.8 ($CH_2$), 71.9 ($CH_2$), 112.1 (C), 113.5 (CH), 128.9 (CH), 132.1 (C), 133.7 (CH), 152.8 (C), 169.1 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{13}H_{19}BrNO_3)^+$ $(M+H)^+$ 316.0543, found: 316.0532; calculated for $(C_{13}H_{18}BrNNaO_3)^+$ $(M+Na)^+$ 338.0362, found 338.0360.

*N-[1-(2-Bromo-4-fluorophenoxy)propan-2-yl]-2-methoxyacetamide (**8d**).* White solid (19 mg, 99% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.64. mp: 80−81 °C. IR (KBr): $\nu$ 3409, 3054, 2986, 1733, 1678, 1527, 1492, 1265, 985, 909, 896, 865, 748, 705 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.41 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 3.43 (s, 3H), 3.91 (m, 2H), 4.01 (m, 2H), 4.38−4.54 (m, 1H), 6.86 (dd, $^3J_{HH}$ = 9.1, $^4J_{HF}$ = 4.7 Hz, 1H), 6.99 (m, $^3J_{HH}$ = 9.1, $^3J_{HF}$ = 7.8, $^4J_{HH}$ = 3.0 Hz, 1H), 7.26−7.34 (m, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 17.6 ($CH_3$), 44.0 (CH), 59.2 ($CH_3$), 71.9 ($CH_2$), 72.4 ($CH_2$), 112.5 (d, $^3J_{FC}$ = 9.5 Hz, C), 114.0 (d, $^3J_{FC}$ = 8.5 Hz, CH), 114.8 (d, $^2J_{FC}$ = 22.6 Hz, CH), 120.4 (d, $^2J_{FC}$ = 26.3 Hz, CH), 151.5 (C), 156.8 (d, $^1J_{FC}$ = 243.8 Hz, C), 169.2 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{12}H_{16}BrFNO_3)^+$ $(M+H)^+$ 320.0292, found 320.0287; calculated for $(C_{12}H_{15}BrFNNaO_3)^+$ $(M+Na)^+$ 342.0112, found 342.0117.

*N-[1-(2-Bromo-5-methoxyphenoxy)propan-2-yl]-2-methoxyacetamide (**8e**).* White solid (17 mg, 87% yield). $R_f$ (10% MeOH/



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$CH_2Cl_2$): 0.71. mp: 67−68 °C. IR (KBr): $\nu$ 3420, 2934, 2401, 2111, 1670, 1639, 1589, 1423, 1257, 1023, 934, 829 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.41 (d, $^3J_{HH}$= 6.8 Hz, 3H), 3.43 (s, 3H), 3.79 (s, 3H), 3.91 (d, $^3J_{HH}$ = 5.6 Hz, 2H), 4.02−4.12 (m, 2H), 4.36−4.61 (m, 1H), 6.43 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.7, 1H), 6.50 (d, $^4J_{HH}$ = 2.7 Hz, 1H), 6.91 (d, 1H, $^3J_{HH}$ = 7.3 Hz), 7.41 (d, $^4J_{HH}$ = 8.6 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 17.7 ($CH_3$), 43.9 (CH), 55.6 ($CH_3$), 59.3 ($CH_3$), 71.8 ($CH_2$), 71.9 ($CH_2$), 100.9 (CH), 103.0 (C), 106.9 (CH), 133.1 (CH), 155.5 (C), 160.2 (C), 169.2 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{13}H_{18}BrNNaO_4)^+$ $(M+Na)^+$ 354.0311, found 354.0316.

*N-{1-[(2-Bromopyridin-3-yl)oxy]propan-2-yl}-2-methoxyacetamide (**8f**).* White solid (18 mg, 99% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.57. mp: 70−80 °C. IR (KBr): $\nu$ 3400, 2933, 1667, 1651, 1563, 1530, 1447, 1418, 1294, 796, 727 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.43 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 3.44 (s, 3H), 3.85−3.97 (m, 2H), 4.03−4.12 (m, 2H), 4.44−4.54 (m, 1H), 6.85 (d, 1H, $^3J_{HH}$ = 7.9 Hz), 7.17−7.25 (m, 2H, $H_4$), 8.02 (dd, $^3J_{HH}$ = 4.4, $^4J_{HH}$ = 1.8 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 17.6 ($CH_3$), 43.7 (CH), 59.3 ($CH_3$), 71.6 ($CH_2$), 71.9 ($CH_2$), 119.9 (CH), 123.5 (CH), 133.2 (C), 141.7 (CH), 152.0 (C), 169.3 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{11}H_{15}BrN_2NaO_3)^+$ $(M+Na)^+$ 325.0158, found: 325.0145.

*N-{1-[(2-Bromopyridin-3-yl)oxy]propan-2-yl}-2-methoxyacetamide (**8g**).* White solid (16 mg, 89% yield). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.65. mp: 138−139 °C. IR (KBr): $\nu$ 3478, 3319, 2922, 1649, 1596, 1537, 1494, 1378, 1297, 975, 848, 760, 657 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.30 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 3.39 (s, 3H), 3.86−3.96 (m, 2H), 3.97−4.08 (m, 2H), 4.21−4.39 (m, 1H), 6.10 (t, $^3J_{HH}$ = 7.2 Hz, 1H), 6.95 (d, 1H, $^3J_{HH}$ = 6.9 Hz), 7.25−7.37 (m, 1H), 7.73 (dd, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.9 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 18.1 ($CH_3$), 45.9 (CH), 53.9 ($CH_2$), 59.4 ($CH_3$), 71.8 ($CH_2$), 106.2 (CH), 116.6 (C), 137.3 (CH), 141.8 (CH), 159.6 (C), 169.9 (C) ppm. HRMS (ESI$^+$, $m/z$): calculated for $(C_{11}H_{16}BrN_2O_3)^+$ $(M+H)^+$ 303.0339, found 303.0342; calculated for $(C_{11}H_{15}BrN_2NaO_3)^+$ $(M+Na)^+$ 325.0158, found: 325.0165.

**General Procedure for the Enzymatic Kinetic Resolution by Acylation of Racemic Amines 4a−g.** Ethyl methoxyacetate (**6b**, 23.5 $\mu$L, 0.20 mmol) and CAL-B (ratio 1:1 in weight amine/enzyme) were added to a suspension containing the corresponding racemic amine **4a−g** (0.10 mmol) in dry THF (0.1 M, 1 mL) under inert atmosphere. The reaction was shaken at 20 °C and 250 rpm for the necessary time (0.75−1 h) to achieve a good kinetic resolution (see Tables 3 and 4). The reaction was followed by HPLC analysis until around 50% conversion was reached. The enzyme was filtered off, 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 5−10% MeOH/$CH_2Cl_2$), to afford the corresponding optically active methoxyacetamides (*R*)-**8a−g** (88−99% *ee*) and amines (*S*)-**4a−g** (90 → 99% *ee*).

Optical rotation values for the (*R*)-methoxyacetamides **8a−g**: $[\alpha]_D^{20}$ + 35.4 (*c* 1, EtOH) for (*R*)-**8a** in 93% *ee*; $[\alpha]_D^{20}$ + 36.4 (*c* 1, EtOH) for (*R*)-**8b** in 93% *ee*; $[\alpha]_D^{20}$ + 31.8 (*c* 1, EtOH) for (*R*)-**8c** in 96% *ee*; $[\alpha]_D^{20}$ + 25.3 (*c* 0.5, EtOH) for (*R*)-**8d** in 93% *ee*; $[\alpha]_D^{20}$ + 12.6 (*c* 1, EtOH) for (*R*)-**8e** in 88% *ee*; $[\alpha]_D^{20}$ + 19.8 (*c* 1, EtOH) for (*R*)-**8f** in 99% *ee*; $[\alpha]_D^{20}$ − 50.6 (*c* 1, EtOH) for (*R*)-**8g** in 83% *ee*.

Optical rotation values for the (*S*)-amines **4a−g**: $[\alpha]_D^{20}$ + 6.4 (*c* 0.5, EtOH) for (*S*)-**4a** in >99% *ee*; $[\alpha]_D^{20}$ − 30.5 (*c* 0.5, EtOH) for (*S*)-**8b** in 90% *ee* obtained by chemical derivatization of (*S*)-**4b**; $[\alpha]_D^{20}$ + 6.4 (*c* 1, EtOH) for (*S*)-**4c** in >99% *ee*; $[\alpha]_D^{20}$ + 2.5 (*c* 1, EtOH) for (*S*)-**4d** in >99% *ee*; $[\alpha]_D^{20}$ + 13.6 (*c* 1, EtOH) for (*S*)-**4e** in 91% *ee*; $[\alpha]_D^{20}$ + 4.2 (*c* 1, EtOH) for (*S*)-**4f** in >99% *ee*; $[\alpha]_D^{20}$ + 31.3 (*c* 0.5, EtOH) for (*S*)-**4g** in >99% *ee*.

**Scale-Up of the Enzymatic Kinetic Resolution by Acylation of Racemic Amine 4a.** Ethyl methoxyacetate (**6b**, 204.0 $\mu$L, 1.74 mmol) and CAL-B (200 mg, ratio 1:1 in weight amine/enzyme) were added to a suspension containing the corresponding racemic amine **4a** (200 mg, 0.87 mmol) in dry THF (0.1 M, 8.7 mL) under inert atmosphere. The reaction was shaken at 20 °C and 250 rpm for 45 min to achieve a 51% conversion with excellent selectivity. The enzyme was filtered off, washed with $CH_2Cl_2$ (3 × 15 mL) and the solvent evaporated under reduced pressure. The crude reaction was purified by column chromatography on silica gel (eluent gradient 5−10% MeOH/$CH_2Cl_2$), to afford the corresponding optically active methoxyacetamide (*R*)-**8a** (93% *ee*, 49% isolated yield) and amine (*S*)-**4a** (>99% *ee*, 47% isolated yield).

**General Procedure for the Biotransamination of Ketones 3a−h Employing Isopropylamine as Amino Donor.** A solution of ketone **3a−h** (0.025 mmol, 50 mM) in DMSO (12.5 $\mu$L) was added to a suspension of a commercial TA (2 mg) in phosphate buffer 100 mM pH 7.5 (500 $\mu$L) containing PLP (1 mM) and isopropylamine (1 M). The mixture was shaken at 30 °C and 250 rpm for 24 h. Then, the reaction was quenched by adding an aqueous NaOH 4 M solution (400 $\mu$L) and extracted with EtOAc (3 × 500 $\mu$L). The organic phases were combined and dried over $Na_2SO_4$. Reaction crude was analyzed through GC to determine conversion values, and later the enantiomeric excess after an *in situ* derivatization. For the methoxy derivative **4e**, HPLC was employed to determine de *ee* value of the enantioenriched amine.

**General Procedure for the Biotransamination of Ketones 3a,c,d Employing Alanine as Amino Donor and Alanine Dehydrogenase as Regeneration System.** To a suspension of ketones **3a−d** (0.05 mmol, 50 mM) in a 100 mM phosphate buffer pH 7 (440 $\mu$L) were successively added ammonium formate (100 $\mu$L of 1.5 M solution in a 100 mM phosphate buffer pH 7; final concentration 150 mM), alanine (250 $\mu$L of 1 M solution in phosphate buffer 100 mM pH 7; final concentration 250 mM), $NAD^+$ (100 $\mu$L of 10 mM solution in a 100 mM phosphate buffer pH 7; final concentration 1 mM), PLP (100 $\mu$L of 10 mM solution in a 100 mM phosphate buffer pH 7; final concentration 1 mM), lyophilized cells of *E. coli* containing overexpressed transaminases (20 mg), formate dehydrogenase (FDH, 2.6 mg, 11 U), and alanine dehydrogenase (AlaDH, 10 $\mu$L, 11 U). D- or L-alanine were used as amine donor depending on the (*R*) or (*S*)-transaminase selectivity, respectively. The resulting mixture was shaken at 30 °C and 250 rpm for 24 h. After this time the reaction was quenched by adding aqueous NaOH 4 M (400 $\mu$L), extracted with ethyl acetate (3 × 500 $\mu$L), and organic phases were combined and dried with $Na_2SO_4$. Reaction crude was analyzed through GC to determine conversion values and, after an *in situ* derivatization, the enantiomeric excess was calculated.

*Synthesis of 6-Bromo-2,3-difluorophenol (**1h**).*[22a] Bromine (119 $\mu$L, 2.31 mmol) was added dropwise over 3 min to a cooled (−30 °C) solution of $^tBuNH_2$ (485 $\mu$L, 4.61 mmol) in dry toluene (5.8 mL) until formation of a yellow solution. The mixture was cooled to −78 °C and after 10 min, a solution of 2,3-difluorophenol (**9**, 300 mg, 2.31 mmol) in dry $CH_2Cl_2$ (0.6 mL) was added dropwise over 5 min. The mixture was allowed to warm slowly to room temperature over 4 h, stirring the resulting mixture for additional 1.5 h at this temperature. The mixture was diluted with EtOAc (10 mL) and washed with an aqueous HCl 1 M solution (2 × 10 mL). The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The reaction crude was purified by column chromatography on silica gel (15% $Et_2O$/hexane), to afford the bromophenol **1h** as a colorless oil (439 mg, 91%). Physical and spectral data were found to be consistent with those previously reported in the literature.[22a]

*Synthesis of 1-(6-Bromo-2,3-difluorophenoxy)propan-2-one (**3h**).* Chloroacetone (82 $\mu$L, 1.03 mmol) was added to a mixture of potassium carbonate (238 mg, 1.72 mmol), potassium iodide (41 mg, 0.25 mmol), and the bromophenol **1h** (111.9 mg, 0.86 mmol) in acetone (3 mL) at room temperature, and the mixture was stirred and heated at 55 °C for 2 h. After this time the solution was added to water (5 mL) and the product was extracted with $Et_2O$ (4 × 10 mL). The organic layers were combined, washed with water (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo, isolating the bromacetophenone **3h** as an orangish oil (205 mg, 90%). $R_f$ (20% EtOAc/hexane): 0.44. IR (NaCl): $\nu$ 3461, 3094, 2921, 1741, 1724, 1612, 1588, 1485, 1462, 1429, 1360, 1297, 1208, 1179, 1058, 1019, 991, 975, 881, 801 $cm^{-1}$. $^1H$ NMR (300.13 MHz, $CDCl_3$): $\delta$ 2.35 (s, 3H), 4.64 (d, $^5J_{FH}$ = 0.9 Hz, 2H), 6.74−6.92 (m, 1H), 7.26 (ddd, $^3J_{HH}$ = 9.2 Hz, $^4J_{FH}$ = 5.4, $^5J_{FH}$ = 2.4 Hz, 1H) ppm. $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 26.7 ($CH_3$), 77.5 (d, $^4J_{FC}$ = 4.8 Hz, $CH_2$), 111.1 (d, $^3J_{FC}$ = 3.6 Hz, C), 112.9 (d, $^2J_{FC}$



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= 18.4 Hz, CH), 127.2 (dd, $^3J_{FC}$ = 7.4 Hz, $^4J_{FC}$ = 4.2 Hz, CH), 144.5 (dd, $^1J_{FC}$ = 251.8 Hz, $^2J_{FC}$ = 14.8 Hz, C), 144.8 (d, $^2J_{FC}$ = 7.3 Hz, C), 150.8 (dd, $^1J_{FC}$ = 250.3 Hz, $^2J_{FC}$ = 11.5 Hz, C), 204.1 (C) ppm. HRMS (ESI$^+$, *m*/*z*): calcd for $(C_9H_7BrF_2NaO_2)^+$ $(M+Na)^+$ 286.9490, found: 286.9480.

*Synthesis of 1-(6-Bromo-2,3-difluorophenoxy)propan-2-amine (**4h**).* To a solution of the ketone **3h** (80.0 mg, 0.43 mmol) in dry MeOH (1.4 mL), ammonium acetate (335 mg, 4.34 mmol) and sodium cyanoborohydride (55 mg, 0.87 mmol) were successively added under inert atmosphere. The mixture was stirred at room temperature for 14 h. The reaction crude was purified by column chromatography on silica gel (10% MeOH/$CH_2Cl_2$), to afford the racemic **4h** as a colorless oil (63 mg, 55%). $R_f$ (10% MeOH/$CH_2Cl_2$): 0.41. IR (NaCl): $\nu$ 3243, 3091, 2335, 1613, 1489, 1457, 1294, 1209, 1055 cm$^{-1}$. $^1$H NMR (300.13 MHz, $CDCl_3$): $\delta$ 1.26 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 3.28 (brs, 2H), 3.42−3.57 (m, 1H), 3.90−4.02 (m, 1H), 4.16 (ddd, $^2J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 3.9 Hz, $^5J_{FH}$ = 1.3 Hz, 1H), 6.82 (dt, $^3J_{FH}$ = 9.2 Hz, $^3J_{HH}$ = 7.6, $^4J_{FH}$ = 7.6 Hz, 1H), 7.25 (ddd, $^3J_{HH}$ = 7.6 Hz, $^4J_{FH}$ = 4.9, $^5J_{HF}$ = 2.5 Hz, 1H) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 15.1 ($CH_3$), 48.7 (CH), 74.3 (d, $^4J_{FC}$ = 4.6 Hz, $CH_2$), 111.7 (d, $^3J_{FC}$ = 3.8 Hz, C), 113.8 (d, $^2J_{FC}$ = 18.4 Hz, CH), 127.2 (dd, $^3J_{FC}$ = 7.4 Hz, $^4J_{FC}$ = 4.2 Hz, CH), 144.3 (dd, $^2J_{FC}$ = 10.1 Hz, $^3J_{FC}$ = 1.8 Hz, C), 145.0 (dd, $^1J_{FC}$ = 252.5 Hz, $^2J_{FC}$ = 14.5 Hz, C), 150.7 (dd, $^1J_{FC}$ = 250.8 Hz, $^2J_{FC}$ = 11.3 Hz, C) ppm. HRMS (ESI$^+$, *m*/*z*): calcd for $(C_9H_{11}BrF_2NO)^+$ $(M+H)^+$ 265.9987, found: 265.9989.

*Preparative Biotransamination of Ketones **3a,d,e,h**.* In a Falcon tube, the TA (35 mg, ATA-256 for ketones **3a,d,h** and TA-P1-G06 for **3e**) was suspended in a phosphate buffer 100 mM pH 7.5 (8.8 mL) containing PLP (1 mM) and isopropylamine (1 M). Then, a solution of ketones **3a**, **3d**, **3e**, or **3h** (0.44 mmol, 50 mM) in EtOH (220 $\mu$L) was added. The mixture was shaken at 30 °C and 250 rpm for 24 h. Then, the reaction was quenched by adding an aqueous NaOH 4 M solution until pH ≈ 10 (~2 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were combined, dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The reaction crude was purified by column chromatography (MeOH/$CH_2Cl_2$ mixtures), yielding the amines (*S*)-**4a,d,e,h** in moderate to good yields (60−74%) and good to excellent enantiomeric excess (91 → 99% *ee*). $[\alpha]_D^{20}$= +4.8 (*c* 0.4, EtOH) [for (*S*)-**4h** in >99% *ee*].

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01828.

Enzyme activity screenings, biotransformation reaction course, analytical separations, and $^1$H, $^{13}$C and DEPT NMR spectra for described organic compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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