FULL PAPER

Sequential Two-Step Stereoselective Amination of Allylic Alcohols through Combination of Laccases and Amine Transaminases

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Abstract: A sequential two-step chemoenzymatic methodology has been described for the stereoselective synthesis of (3*E*)-4-(het)arylbut-3-en-2-amines in a highly selective manner and under mild reaction conditions. The approach consists in the oxidation of the corresponding alcohol precursors using the catalytic system composed by the laccase from *Trametes versicolor* and the oxy-radical TEMPO, followed by the asymmetric biotransamination of the corresponding ketone intermediates. Optimisation of the oxidation reaction, exhaustive amine transaminase screening for the biotransaminations and the compatibility of both enzymatic reactions have been deeply studied, searching for the design of a compatible sequential cascade. This synthetic strategy has been successfully achieved, the combination of enzymes displaying a broad substrate scope as 16 chiral amines have been obtained in moderate to good isolated yields (29-75% isolated yield) and excellent enantiomeric excess (94->99). Interestingly, both amine enantiomers can be achieved depending on the selectivity of the amine transaminase employed in the system.

Introduction

The chemical preparation of allylic amines has traditionally attracted great attention,[1,2] due to the presence of this motif in numerous biologically active and natural products.[3-8] In addition, their versatility in chemical synthesis has been largely demonstrated based on their multiple applications for the preparation of valuable nitrogen-containing organic compounds.[9-11] In this context, the stereoselective synthesis of (3*E*)-4-arylbut-3-en-2-amine derivatives is particularly challenging, and it has been described through a series of metal-catalysed methodologies including kinetic resolutions through acylation[12] and alkylation processes,[13] or asymmetric synthesis via Claissen rearrangements,[14] dehydroxybenzotriazolylation,[15] hydrogenation,[16,17] hydroamination,[18] alkenylation reactions,[19] and azidation of allylic esters,[20] among others.

Biocatalytic methods have appeared as a sustainable solution for the synthesis of chiral amines by means of the single action of several enzyme classes including lipases, amine transaminases (ATAs), amine oxidases, amine dehydrogenases, imine reductases or reductive aminases,[21-26] but interestingly in recent years great devotion has been put towards the synthesis of chiral amines through chemo-, photo- and multienzymatic approaches.[27-33] As an example, the selective amination of racemic *sec*-alcohols has been described through elegant cascades via combination of an alcohol dehydrogenase-catalysed oxidation into ketones with a subsequent bioamination using ATAs[34,35] or amine dehydrogenases.[36-42] In spite of these efforts, the biocatalytic synthesis of (3*E*)-4-arylbut-3-en-2-amines has received little attention, the activity of a commercial amine transaminase being low for the biotransamination of (3*E*)-4-phenylbut-3-en-2-one towards optically active (3*E*)-4-phenylbut-3-en-2-amine (<30%).[43]

On the other hand, laccases display great potential for chemical synthesis but also pulp and paper industry applications.[44-46] These redox enzymes are blue multicopper oxidases able to catalyse the oxidation of low molecular weight phenols at the expense of the reduction of molecular oxygen into water through a four-electron transference.[47] However when attempting the oxidation of natural substrates, the enzyme requires the use of a chemical mediator, e.g. 2,2,6,6-tetramethylpiperidinoxyl radical (TEMPO).[48,49] In this manner, the oxidation of diols,[50] amino alcohols,[51] profenols,[52] benzylic[53,54] and allylic alcohols[55] has been fully exploited in our research group, in some cases being possible the development of sequential multienzymatic transformations by the proper modification of the reaction medium. These chemoenzymatic strategies include dynamic kinetic resolutions[52] and deracemisation of alcohols in combination with alcohol dehydrogenases,[53] the selective amination of benzylic alcohols by the use of amine transaminases,[54] or the redox isomerisation of allylic alcohols coupling the action of laccases with ene-reductases.[55]

Herein, we propose to extend the applicability of laccases to produce synthetically challenging optically active allylic amines via combination of a laccase-mediated oxidation of allylic alcohols and the subsequent stereoselective biotransamination of the resulting ketone intermediates using stereocomplementary ATAs (Scheme 1).

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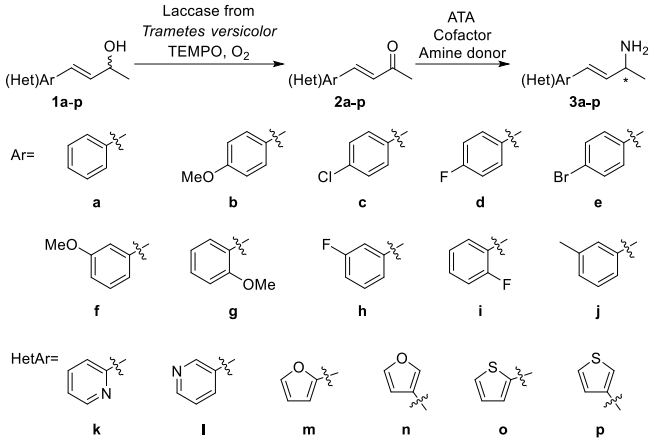
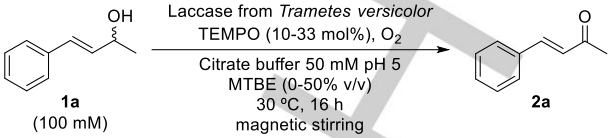


Scheme 1. Stereoselective chemoenzymatic amination of allylic alcohols **1a-p** combining the laccase/TEMPO system with an amine transaminase.

Table 1. Oxidation of **1a** (100 mM) with the L*Tv*/TEMPO system in the presence of different amounts of TEMPO and MTBE as cosolvent.



Entry	TEMPO (mol%)	MTBE (% v/v)	2a (%)[a]
1	33	----	7
2	33	20	8
3	33	50	>99
4	20	50	87
5	10	50	64

[a] Conversion values were measured by GC analyses.

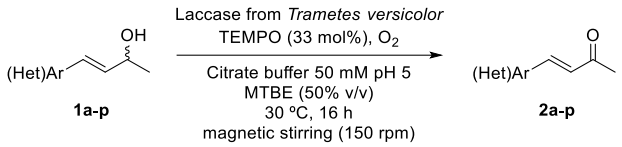
Results and Discussion

Following the methodology reported by Gladkowski and co-workers,[56] a series of (hetero)aromatic aldehydes were subjected to Claisen-Schmidt condensation with acetone under basic medium (Scheme S1), obtaining the corresponding unsaturated ketones **2b**-**p** in good to very high isolated yields (54-94%). Next, ketones **2a-p** were chemically reduced using sodium borohydride to afford the desired racemic allylic alcohols **1a**-**p** in 46-99% isolated yield.

At this point the study of the individual biooxidation and biotransamination steps were deeply analysed, trying first to find suitable conditions for the individual reactions, to later search for compatible conditions where both enzymes could act in a cascade or a sequential manner. Initially, (3*E*)-4-phenylbut-3-en-2-ol (**1a**) was selected as model substrate to study the applicability of commercially available laccase from *Trametes versicolor* (L*Tv*) in combination with different amounts of the oxy-radical TEMPO (10-33 mol%, Table 1). The reactions were carried out under previously optimised conditions in our research group.[51,53] This is, in a citrate buffer 50 mM pH 5 with a 100 mM substrate concentration at 30 ºC and in an open-to-air tube to assure the oxygen presence. Interestingly, only a 7% conversion into the ketone **2a** was observed with a high TEMPO concentration (33 mol%, entry 1) in the buffer system. Therefore, to favour the solubility of the substrate,[51-55] MTBE was employed as organic cosolvent (20-50% v/v, entries 2-5). Due to the low boiling point of MTBE, it evaporated from the medium after the first three hours leading to a monophasic system, and a complete conversion was attained when 50% v/v MTBE and 33 mol% TEMPO were employed (entry 3), although the use of lower TEMPO loadings did not allow the reaction get to completion (entries 4 and 5). Even at prolonged times using 20 mol% of TEMPO (94 and 98% conversion after 24 and 48 h, respectively) and 10 mol% of TEMPO (70 and 74% after 24 and 48 h, respectively).

The optimised reaction conditions found for **1a** (entry 3, Table 1) were then applied to the oxidation of the other allylic alcohols **1b**-**p**, gratifyingly finding excellent to complete conversions (>98%, Table 2), independently on the position and the electronic character of the substitution at the phenyl ring, and also for various heteroaromatic derivatives such as pyridyl, furyl and thienyl. Satisfyingly, no by-products were detected in any case, demonstrating the mildness and selectivity of the chemoenzymatic system here proposed.

Table 2. Oxidation of racemic allylic alcohols **1a**-**p** (100 mM) with the laccase/TEMPO system using MTBE as cosolvent.

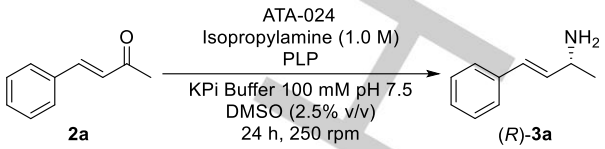


Entry	Alcohol 1a-p	R	Ketone 2a-p (%)[a]
1	**1a**	H	>99
2	**1b**	4-OMe	>99
3	**1c**	4-Cl	>99
4	**1d**	4-F	>99
5	**1e**	4-Br	>99
6	**1f**	3-OMe	98
7	**1g**	2-OMe	>99
8	**1h**	3-F	99
9	**1i**	2-F	99
10	**1j**	3-Me	98
11	**1k**	2-pyridyl	99
12	**1l**	3-pyridyl	>99
13	**1m**	2-furyl	99
14	**1n**	3-furyl	>99
15	**1o**	2-thienyl	>99
16	**1p**	3-thienyl	>99

[a] Conversion values were measured by GC analyses.

At this point the biotransamination experiments of the (3*E*)-4-(het)arylbut-3-en-2-ones **2a**-**p** were assayed, in order to find adequate reaction conditions but also suitable amine transaminases (ATAs) for each substrate to later attempt the stereoselective amination of the racemic alcohols in a concurrent approach. PLP-dependent ATAs have been found as ideal biocatalysts for the transformation of prochiral and racemic ketones into optically active amines using a molar excess of an amine donor, generally isopropylamine or alanine.[57-61] For simplicity, an initial assessment was developed using ketone **2a** and commercially available (*R*)-selective ATA-024, that is known to accept isopropylamine as amine donor. Reaction parameters such as the amount of pyridoxal-5'-phosphate (PLP), ketone concentration, temperature and ATA loading were considered (Table 3).

Table 3. Biotransamination of ketone **2a** using ATA-024 as biocatalyst and isopropylamine as amine donor.



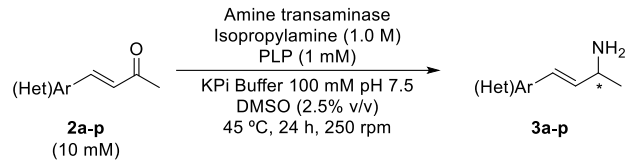
Entry	[2a] (mM)	[PLP] (mM)	T (ºC)	ATA-024 (mg/mL)[a]	*c* (%)[b]
1	25	0.25	30	4	45
2	25	0.5	30	4	46
3	25	1.0	30	4	46
4	10	0.25	30	4	56
5	5	0.25	30	4	61
6	10	0.25	30	8	56
7	10	0.25	45	4	63

[a] mg of lyophilised ATA-024 per mL of solvent. [b] Conversion values were measured by GC analyses.

The use of different cofactor amounts seemed to have not significant impact in the conversion when 25 mM of ketone **2a** was used (entries 1-3, 45-46% conversion), while higher conversions were reached at low substrate concentrations (5 and 10 mM, entries 4 and 5), although there was no change when using more enzyme loading (entry 6). For practical applications, the best conditions were found when increasing the temperature to 45 ºC reaching a promising 63% conversion at 10 mM ketone concentration (entry 7).

From this point, exhaustive screenings using ATAs overexpressed in *E. coli* cells and later lyophilised (*Chromobacterium violaceum*,[62] *Arthrobacter citreus*,[63] *Arthrobacter* species[64-66] and its evolved mutant ArRmut11[67]) and semipurified commercially available ATAs, also in lyophilised form, were developed for the sixteen unsaturated ketones considered in this study, and for a clear understanding all the results in terms of conversion and enantiomeric excess values have been included in the Electronic Supporting Information. The best results are highlighted in Table 4, observing low to very high conversion values (15-89%) and excellent selectivities (>97% *ee*). Remarkably the preparation of both amine enantiomers was possible depending on the ATA selectivity. Especially (*R*)-selective ATA-024, ATA-033 and ATA-415, and (*S*)-selective ATA-254, ATA-256 and ATA-260 enzymes proved to be the most efficient catalysts in these transformations.

Table 4. Biotransamination of ketones **2a**-**p** using amine transaminases and isopropylamine as amine donor.



2a-p (10 mM) → **3a-p**

Entry	Ketone	R	Enzyme	*c* (%)[a]	*ee* 3a-p (%)[b]
1	**2a**	H	ATA-033	56	99 (*R*)
2	**2a**	H	ATA-256	57	>99 (*S*)
3	**2b**	4-OMe	ATA-025	42	>99 (*R*)
4	**2b**	4-OMe	ATA-254	39	>99 (*S*)
5	**2c**	4-Cl	ATA-415	45	>99 (*R*)
6	**2c**	4-Cl	ATA-256	42	99 (*S*)
7	**2d**	4-F	ATA-033	50	>99 (*R*)
8	**2d**	4-F	ATA-254	49	>99 (*S*)
9	**2e**	4-Br	ATA-033	38	>99 (*R*)
10	**2e**	4-Br	ATA-254	43	>99 (*S*)
11	**2f**	3-OMe	ATA-024	34	>99 (*R*)
12	**2f**	3-OMe	ATA-256	38	99 (*S*)
13	**2g**	2-OMe	ATA-415	15	99 (*R*)
14	**2g**	2-OMe	TA-P1-G06	23	99 (*S*)
15	**2h**	3-F	ATA-025	56	>99 (*R*)
16	**2h**	3-F	ATA-254	59	>99 (*S*)
17	**2i**	2-F	ATA-033	77	>99 (*R*)
18	**2i**	2-F	ATA-256	76	>99 (*S*)
19	**2j**	3-Me	ATA-025	32	>99 (*R*)
20	**2j**	3-Me	ATA-256	39	>99 (*S*)
21	**2k**	2-pyridyl	ATA-415	59	>99 (*R*)
22	**2k**	2-pyridyl	TA-P1-G06	89	>99 (*S*)
23	**2l**	3-pyridyl	ATA-024	82	>99 (*R*)
24	**2l**	3-pyridyl	ATA-260	76	99 (*S*)
25	**2m**	2-furyl	ATA-024	56	>99 (*R*)
26	**2m**	2-furyl	TA-P1-A06	57	>99 (*S*)
27	**2n**	3-furyl	ATA-033	56	>99 (*R*)
28	**2n**	3-furyl	ATA-260	60	98 (*S*)
29	**2o**	2-thienyl	ATA-024	57	>99 (*R*)
30	**2o**	2-thienyl	ATA-260	58	99 (*S*)
31	**2p**	3-thienyl	ATA-024	63	>99 (*R*)
32	**2p**	3-thienyl	ATA-260	63	99 (*S*)

[a] Conversion values were measured by GC analyses. [b] Enantiomeric excess were measured by GC analyses after derivatisation of the corresponding amines with acetic anhydride.

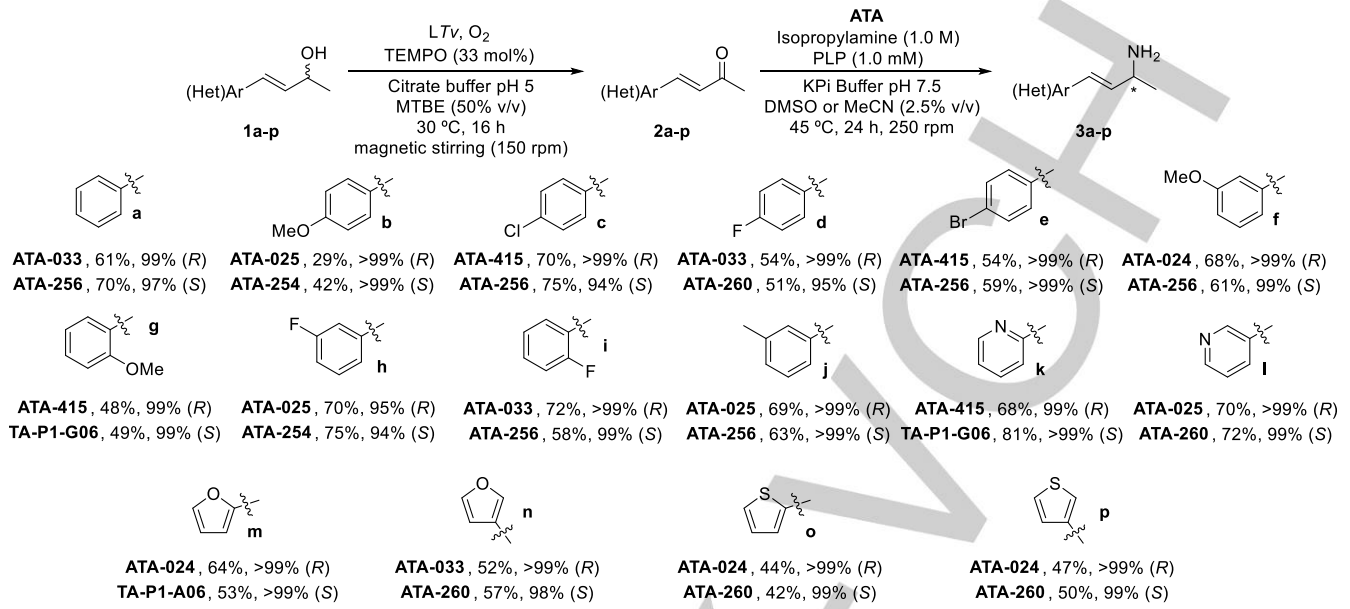
Finally, the two-step sequential process was attempted, so after the laccase-catalysed oxidation, optimal conditions in terms of pH, substrate concentration and temperature for the ATAs were provided in order to make feasible the biotransamination reaction. Thus, the pH of the solution was adjusted to a value of 7.5 diluting accordingly the solution until a 10 mM ketone intermediate concentration, 2.5% DMSO was added to solubilise the reactants and the temperature was increased up to 45 ºC. In this manner, the 16 amine enantiomer pairs of **3a**-**p** were obtained in high to excellent enantiomeric excess values (>93%). For the isolation of the optically active products, a simple liquid-liquid extraction protocol was required for allylic amines **3a-j** and **3m-p**, while for the pyridyl compounds **3k** and **3l** a column chromatography was necessary to isolate them in a pure form (4.1-10.5 mg, 29-81% isolated yield, Scheme 2). It must be mentioned that when the scale-up of the processes was achieved, the use of MeCN as cosolvent was applied as it simplified the isolation processes through liquid-liquid extraction, providing higher amine yields.

Conclusions

The design of chemoenzymatic and multienzymatic strategies for the synthesis of optically active compounds is one of the most demanding task pursuits nowadays in organic synthesis. Herein, a sequential two-step synthetic approach has been described for the synthesis of a series of optically active (3*E*)-4-(het)arylbut-3-en-2-amines starting from the corresponding racemic allylic alcohols. Individual biotransformations were studied and optimised, finding suitable conditions for the chemoselective oxidation of (3*E*)-4-(het)arylbut-3-en-2-ols, and the biotransamination of the corresponding (3*E*)-4-arylbut-3-en-2-ones.

The catalytic system composed by the laccase from *Trametes versicolor* and the chemical mediator TEMPO (33 mol%) has selectively oxidised 16 racemic allylic alcohols with excellent conversion (>98%) after 16 h at 30 ºC and using a 100 mM alcohol concentration, isolating the corresponding ketones with excellent purity just after a liquid-liquid extraction protocol. After amine transaminase screening, pairs of enzymes with opposite selectivity were found to give access to the corresponding optically active allylic amines in enantiopure form.

A sequential protocol employing both enzymatic methods was possible by simple changing the pH from 5.0 to 7.5 and diluting the ketone intermediate concentration to 10 mM, so after addition of the amine donor (isopropylamine) and the enzyme cofactor (PLP), a wide panel of optically active (3*E*)-4-arylbut-3-en-2-amines were obtained in >94% *ee* after 24 h at 45 ºC in moderate to good isolated yields (29-81%) after a simple extraction protocol, except for pyridyl-derived amines that required an additional column chromatography purification.



Scheme 2. Stereoselective amination of racemic alcohols **1a-p** through a sequential strategy. Isolated yields are shown after a liquid-liquid extraction protocol, requiring **3k** and **3l** an additional column chromatography purification.

Experimental Section

Material and methods

Ketone **2a** was acquired from Sigma-Aldrich. Laccase from *Trametes versicolor* (L*Tv*, 0.66 U/mg) and pyridoxal 5'-phosphate (PLP) were purchased from Sigma-Aldrich. Codex Transaminase ATA Screening Kit (ATASK-000250) was purchased from Codexis Inc. The lot numbers of the more active commercially available ATAs are: D101186 (ATA-024), 0907A (ATA-025), D15042 (ATA-033), PF282 (ATA-254), 01 (ATA-256), D11125 (ATA-260), D11130 (ATA-415), FER090326 (TA-P1-A06) and D15046 (TA-P1-G06). Lyophilised ATAs overexpressed in *E. coli* were obtained as previously reported in the literature.[62-67] All other reagents and solvents were obtained from Sigma-Aldrich or Acros and used as received.

Sequential reactions were performed in test tubes [(19 x 130 x 3) mm] and centrifuge tubes [(17 x 118 x 15) mm]. The oxidation step mediated by the laccase/TEMPO catalytic system was performed in an open-to-air test tube using magnetic stirring, while for the subsequent transamination step, the reaction media was transferred to the centrifuge tube, and shaken at 250 rpm and 45 ºC for the required time.

NMR spectra were recorded on a Bruker AV300 MHz spectrometer. All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. IR spectra were recorded on a Bruker ALPHA spectrophotometer on NaCl pellets. High resolution mass spectra (HRMS) were obtained in a Bruker Daltonics spectrometer using the ESI-TOF positive mode. Measurement of the optical rotation was carried out at 590 nm in a PerkinElmer 241 polarimeter. Thin layer chromatrographies (TLCs) were conducted with Merck Silica Gel 60 F254 precoated plates and visualised with UV and potassium permanganate stain. Column chromatographies were performed using Merck Silica Gel 60 (230-400 mesh).

Gas chromatrography (GC) analyses were performed on Agilent HP6890 and Agilent HP7820A gas chromatograph apparatus equipped with a FID detector for the measurement of conversion and enantiomeric excess values. High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph UV detector at a 210 nm wavelength for the measurement of enantiomeric excess values. Details of analytical methods, retention times and chromatograms have been included in the Electronic Supporting Information.

Typical procedure for the synthesis of ketones 2b-p

Ketones **2b**-**p** were synthesised following the procedure described by Gładkowski *et al.* for ketone **2a** as follows:[56] A solution of the corresponding aldehyde (3.3 mmol) in acetone (1 mL) and water (0.1 mL) was placed in a water bath. Then, a 10% NaOH aqueous solution (0.1 mL) was slowly added. The reaction mixture was stirred overnight at room temperature and acidified after this time with a HCl 2 M aqueous solution to pH 2. The product was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phases dried over anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (25% EtOAc/hexane except 83% EtOAc/hexane for pyridyl substrates), yielding the corresponding ketones **2b-p** (54-94% yield).

(*E*)-4-Phenylbut-3-en-2-one (2a) Yellow solid. R_f (25% EtOAc/hexane): 0.58. Mp: 38-40 ºC. IR (NaCl): 3060, 3028, 3003, 1668, 1610, 1359, 1279, 976, 750, 691 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.35 (s, 3H), 6.69 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 7.34-7.39 (m, 3H), 7.46-7.53 (m, 3H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.5 (CH_3), 127.1 (CH), 128.3 (2CH), 129.0 (2CH), 130.5 (CH), 134.4 (C), 143.4 (CH), 198.4 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}O)^+$ $(M+H)^+$ 147.0804, found: 147.0803.

(*E*)-4-(4-Methoxyphenyl)but-3-en-2-one (2b). Pale yellow solid (512 mg, 88% yield). R_f (25% EtOAc/hexane): 0.44. Mp: 66-68 ºC. IR (NaCl): 3288, 3048, 2941, 2916, 2844, 2774, 2241, 1896, 1683, 1601, 1512, 1251, 989, 854 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.76 (s, 3H), 6.54 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 6.82-6.88 (m, 2H), 7.38-7.44 (m, 3H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.5 (CH_3), 55.5 (CH_3), 114.6 (2CH), 125.1

(CH), 127.2 (C), 130.1 (2CH), 143.4 (CH), 161.7 (C), 198.5 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{13}O_2)^+$ $(M+H)^+$ 177.0910, found: 177.0917.

(*E*)-4-(4-Chlorophenyl)but-3-en-2-one (2c). Pale yellow solid (382 mg, 64% yield). R_f (25% EtOAc/hexane): 0.56. Mp: 56-57 ºC. IR (NaCl): 3286, 3044, 3021, 2972, 2922, 1946, 1661, 1092, 979, 810 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.62 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 7.27-7.32 (m, 2H), 7.36-7.43 (m, 3H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.6 (CH_3), 127.4 (CH), 129.2 (2CH), 129.4 (2CH), 132.9 (C), 136.3 (C), 141.8 (CH), 198.0 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{10}ClO)^+$ $(M+H)^+$ 181.0415, found: 181.0413.

(*E*)-4-(4-Fluorophenyl)but-3-en-2-one (2d). Pale yellow solid (293 mg, 54% yield). R_f (25% EtOAc/hexane): 0.54. Mp: 31-33 ºC. IR (NaCl): 3072, 3048, 3021, 2923, 2009, 1897, 1668, 1599, 1509, 1231, 977, 818 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.23 (s, 3H), 6.50 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 6.88-6.99 (m, 2H), 7.29-7.44 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.2 (CH_3), 115.8 (d, *J* = 22.0 Hz, 2CH), 126.6 (d, *J* = 2.2 Hz, CH), 130.0 (d, *J* = 8.5 Hz, 2CH), 130.5 (d, *J* = 3.2 Hz, C), 141.7 (CH), 163.7 (d, *J* = 251.3 Hz, C), 197.8 (C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –109.2 ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{10}FO)^+$ $(M+H)^+$ 165.0710, found: 165.0696.

(*E*)-4-(4-Bromophenyl)but-3-en-2-one (2e). White solid (424 mg, 57% yield). R_f (25% EtOAc/hexane): 0.57. Mp: 77-79 ºC. IR (NaCl): 3079, 3022, 2924, 1912, 1657, 1584, 1262, 978, 806 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.30 (s, 3H), 6.61 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 7.28-7.39 (m, 3H), 7.40-7.46 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.6 (CH_3), 124.6 (C), 127.4 (CH), 129.5 (2CH), 132.1 (2CH), 133.3 (C), 141.8 (CH), 197.9 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{10}BrO)^+$ $(M+H)^+$ 224.9910, found: 224.9920.

(*E*)-4-(3-Methoxyphenyl)but-3-en-2-one (2f). Yellow liquid (460 mg, 79% yield). R_f (25% EtOAc/hexane): 0.48. IR (NaCl): 3370, 3003, 2961, 2942, 2837, 2205, 2072, 2034, 1984, 1933, 1690, 1669, 1359, 1170, 1046, 978, 780, 752, 687 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.83 (s, 3H), 6.70 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 6.95 (ddd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 2.6, $^4J_{HH}$ = 1.0 Hz, 1H), 7.06 (apparent t, $^4J_{HH}$ = 2.6 Hz, 1H), 7.13 (d, $^3J_{HH}$ = 7.7 Hz ,1H), 7.31 (apparent t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.47 (d, $^3J_{HH}$ = 16.3 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.8 (CH_3), 54.6 (CH_3), 112.7 (CH), 115.8 (CH), 120.4 (CH), 126.8 (CH), 129.4 (CH), 135.3 (C), 142.7 (CH), 159.4 (C), 197.6 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{13}O_2)^+$ $(M+H)^+$ 177.0910, found: 177.0914.

(*E*)-4-(2-Methoxyphenyl)but-3-en-2-one (2g). Pale yellow solid (425 mg, 73% yield). R_f (25% EtOAc/hexane): 0.50. Mp: 49-51 ºC. IR (NaCl): 3003, 2940, 2888, 2838, 1666, 1598, 1488, 1466, 1246, 1026, 754 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.63 (s, 3H), 6.54 (d, $^3J_{HH}$ = 16.5 Hz, 1H), 6.69 (dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 0.8 Hz, 1H), 6.74 (apparent td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 0.8 Hz, 1H), 7.14 (ddd, $^3J_{HH}$ = 8.3, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.7 Hz, 1H), 7.30 (dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.7 Hz, 1H), 7.68 (d, $^3J_{HH}$ = 16.5 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.7 (CH_3), 54.9 (CH_3), 110.7 (CH), 120.3 (CH), 122.7 (C), 127.0 (CH), 127.7 (CH), 131.4 (CH), 138.0 (CH), 157.8 (C), 198.1 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{13}O_2)^+$ $(M+H)^+$ 177.0910, found: 177.0915.

(*E*)-4-(3-Fluorophenyl)but-3-en-2-one (2h). Pale yellow oil (309 mg, 57% yield). R_f (25% EtOAc/hexane): 0.57. IR (NaCl): 3066, 3043, 3006, 2922, 1944, 1873, 1804, 1672, 1615, 1583, 1439, 1360, 1259, 979, 783, 682 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.63 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 6.97-7.06 (m, 1H), 7.13-7.19 (m, 1H), 7.21-7.34 (m, 2H), 7.39 (d, $^3J_{HH}$ = 16.3 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.6 (CH_3), 114.3 (d, *J* = 21.8 Hz, CH), 117.2 (d, *J* = 21.4 Hz, CH), 124.2 (d, *J* = 2.7 Hz, CH), 128.1 (CH), 130.5 (d, *J* = 8.4 Hz, CH), 136.7 (d, *J* = 7.8 Hz, C), 141.7 (d, *J* = 2.7 Hz, CH), 162.9 (d, *J* = 246.8 Hz, C), 198.0 (C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –112.4 ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{10}FO)^+$ $(M+H)^+$ 165.0710, found: 165.0707.

(*E*)-4-(2-Fluorophenyl)but-3-en-2-one (2i). White solid (326 mg, 60% yield). R_f (25% EtOAc/hexane): 0.59. Mp: 41-42 ºC. IR (NaCl): 3105, 3040, 3012, 2924, 1943, 1816, 1669, 1645, 1487, 1465, 1365, 1228, 1098, 974, 762 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.70 (d, $^3J_{HH}$ = 16.5 Hz, 1H), 7.02 (ddd, *J* = 10.7, *J* = 8.2, *J* = 1.1 Hz, 1H), 7.10 (td, *J* = 7.6, *J* = 1.1 Hz, 1H), 7.25-7.33 (m, 1H), 7.48 (td, *J* = 7.6, *J* = 1.8 Hz, 1H), 7.59 (d, $^3J_{HH}$ = 16.5 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.4 (CH_3), 116.1 (d, *J* = 21.9 Hz, CH), 122.4 (d, *J* = 11.4 Hz, C), 124.5 (d, *J* = 3.6 Hz, CH), 128.6 (d, *J* = 3.0 Hz, CH), 129.1 (d, *J* = 5.4 Hz, CH), 131.9 (d, *J* = 8.7 Hz, CH), 135.5 (d, *J* = 3.5 Hz, CH), 161.2 (d, *J* = 253.9 Hz, C), 198.2 (C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –114.8 ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{10}FO)^+$ $(M+H)^+$ 165.0710, found: 165.0706.

(*E*)-4-(*m*-Tolyl)but-3-en-2-one (2j). Yellow liquid (445 mg, 84% yield). R_f (25% EtOAc/hexane): 0.61. IR (NaCl): 3022, 2921, 2864, 2735, 1946, 1881, 1819, 1790, 1691, 1667, 1613, 1585, 1359, 1257, 1229, 978, 779, 691, 561 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.04 (s, 3H), 6.40 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 6.84-7.04 (m, 4H), 7.17 (d, $^3J_{HH}$ = 16.3 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.4 (CH_3), 26.5 (CH_3), 124.7 (CH), 126.1 (CH), 128.0 (CH), 128.2 (CH), 130.5 (CH), 133.7 (C), 137.6 (C), 142.5 (CH), 196.9 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{13}O)^+$ $(M+H)^+$ 161.0961, found: 161.0944.

(*E*)-4-(Pyridin-2-yl)but-3-en-2-one (2k). Pale yellow liquid (340 mg, 70% yield). R_f (17% hexane/EtOAc): 0.60. IR (NaCl): 3052, 3005, 2921, 1692, 1669, 1620, 1582, 1432, 1359, 1250, 980, 767 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.38 (s, 3H), 7.11 (d, $^3J_{HH}$ = 16.0 Hz, 1H), 7.26 (ddd, $^3J_{HH}$ = 7.9, $^3J_{HH}$ = 4.8, $^4J_{HH}$ = 1.1 Hz. 1H), 7.43-7.54 (m, 2H), 7.70 (apparent td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8 Hz, 1H), 8.63 (ddd, $^3J_{HH}$ = 4.8, $^4J_{HH}$ = 1.9, $^5J_{HH}$ = 0.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.2 (CH_3), 124.3 (CH), 124.4 (CH), 130.3 (CH), 136.9 (CH), 142.0 (CH), 150.3 (CH), 153.2 (C), 198.6 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_9H_{10}NO)^+$ $(M+H)^+$ 148.0757, found: 148.0751.

(*E*)-4-(Pyridin-3-yl)but-3-en-2-one (2l). Pale yellow solid (383 mg, 79% yield). R_f (17% hexane/EtOAc): 0.37. Mp: 33-35 ºC. IR (NaCl): 3031, 3006, 2921, 1693, 1672, 1613, 1415, 1360, 1258, 980, 797, 705 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.37 (s, 3H), 6.74 (d, $^3J_{HH}$ = 16.4 Hz, 1H), 7.31 (dd, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 4.8 Hz, 1H), 7.47 (d, $^3J_{HH}$ = 16.4 Hz, 1H), 7.83 (apparent dt, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 2.0 Hz, 1H), 8.58 (dd, $^3J_{HH}$ = 4.8, $^4J_{HH}$ = 1.6 Hz, 1H), 8.72 (d, $^4J_{HH}$ = 2.3 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.8 (CH_3), 123.9 (CH), 128.8 (CH), 130.3 (C), 134.3 (CH), 139.5 (CH), 150.0 (CH), 151.3 (CH), 197.8 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_9H_{10}NO)^+$ $(M+H)^+$ 148.0757, found: 148.0751.

(*E*)-4-(Furan-2-yl)but-3-en-2-one (2m). Orange solid (323 mg, 72% yield). R_f (25% EtOAc/hexane): 0.50. Mp: 35-37 ºC. IR (NaCl): 3144, 3126, 2921, 1687, 1665, 1611, 1359, 1253, 1018, 969, 750 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.47 (dd, $^3J_{HH}$ = 3.4, $^3J_{HH}$ = 1.8 Hz, 1H), 6.60 (d, $^3J_{HH}$ = 16.0 Hz, 1H), 6.65 (d, $^3J_{HH}$ = 3.4 Hz, 1H), 7.26 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 7.49 (d, $^3J_{HH}$ = 1.4 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.0 (CH_3), 112.7 (CH), 115.8 (CH), 124.4 (CH), 129.5 (CH), 145.1 (CH), 151.0 (C), 197.9 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_8H_9O_2)^+$ $(M+H)^+$ 137.0597, found: 137.0596.

(*E*)-4-(Furan-3-yl)but-3-en-2-one (2n). Brown solid (409 mg, 91% yield). R_f (25% EtOAc/hexane): 0.45. Mp: 44-45 ºC. IR (NaCl): 3132, 3117, 2926, 1661, 1627, 1361, 1274, 1258, 1160, 1017, 971, 870, 798 cm^{-1}. ^{1}H NMR

(300.13 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.43 (d, $^3J_{HH}$ = 15.7 Hz, 1H), 6.57-6.60 (m, 1H), 7.37-7.45 (m, 2H), 7.67 (d, $^3J_{HH}$ = 0.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.4 (CH_3), 107.5 (CH), 122.9 (C), 127.3 (CH), 133.5 (CH), 144.7 (CH), 145.0 (CH), 198.2 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_8H_9O_2)^+$ $(M+H)^+$ 137.0597, found: 137.0593.

(*E*)-4-(Thiophen-2-yl)but-3-en-2-one (2o). Orange wax (312 mg, 62% yield). R_f (25% EtOAc/hexane): 0.50. IR (NaCl): 3104, 3085, 2920, 1664, 1595, 1423, 1254, 1200, 1046, 965, 707 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.03 (s, 3H), 6.23 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.77 (dd, $^3J_{HH}$ = 5.1, $^3J_{HH}$ = 3.6 Hz, 1H), 7.01 (d, $^3J_{HH}$ = 3.6 Hz, 1H), 7.13 (d, $^3J_{HH}$ = 5.1 Hz, 1H), 7.36 (d, $^3J_{HH}$ = 15.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.8 (CH_3), 125.1 (CH), 127.7 (CH), 128.4 (CH), 131.0 (CH), 135.0 (CH), 139.1 (C), 196.7 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_8H_8NaOS)^+$ $(M+Na)^+$ 175.0188, found: 175.0190.

(*E*)-4-(Thiophen-3-yl)but-3-en-2-one (2p). Pale yellow solid (474 mg, 94% yield). R_f (25% EtOAc/hexane): 0.45. Mp: 67-68 ºC. IR (NaCl): 3107, 3008, 2922, 1665, 1636, 1615, 1358, 1265, 1159, 975, 876, 784 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.34 (s, 3H), 6.54 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 7.30 (dd, $^3J_{HH}$ = 5.1, $^4J_{HH}$ = 1.1 Hz, 1H), 7.35 (dd, $^3J_{HH}$ = 5.1, $^4J_{HH}$ = 3.4 Hz, 1H), 7.46-7.55 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.5 (CH_3), 125.3 (CH), 127.1 (CH), 127.2 (CH), 128.7 (CH), 137.0 (CH), 137.8 (C), 198.7 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_8H_8NaOS)^+$ $(M+Na)^+$ 175.0188, found: 175.0181.

Typical procedure for the synthesis of alcohols 1a-p

Alcohols **1a-j** were synthesised following the procedure described by Gładkowski *et al.* for alcohol **1a** as follows:[56] A solution of $NaBH_4$ (170.2 mg, 4.5 mmol) in water (1 mL) was added dropwise to a stirring solution of the corresponding (3*E*)-4-(het)arylbut-3-en-2-one **2a-p** (3 mmol) in MeOH (10 mL) at 0 ºC. The reaction mixture was first stirred for 1 h in an ice bath and then 2 h at room temperature. Afterwards, hot water was added and the product was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phases were washed with brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The reaction crudes of allylic alcohols were purified by column chromatography on silica gel, yielding the corresponding alcohols **1a-j** (46-99% yield, eluent 50% Et_2O/hexane), **1k** and **1l** (87-91% yield, eluent 83% EtOAc/hexane) and **1m-p** (71-91% yield, eluent 25% EtOAc/hexane).

(*E*)-4-Phenylbut-3-en-2-ol (1a). White solid (445 mg, 99% yield). R_f (50% Et_2O/hexane): 0.44. Mp: 35-36 ºC. IR (NaCl): 3376, 3026, 2973, 2926, 2872, 1949, 1879, 1807, 1751, 1494, 1449, 1141, 1060, 967, 748, 693 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.38 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.81 (br s, 1H), 4.45-4.54 (m, 1H), 6.27 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.4 Hz, 1H), 6.57 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 7.22-7.27 (m, 1H), 7.30-7.40 (m, 4H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.5 (CH_3), 69.0 (CH_3), 126.6 (2CH), 127.8 (CH), 128.7 (2CH), 129.5 (CH), 133.7 (CH), 136.8 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{12}NaO)^+$ $(M+Na)^+$ 171.0780, found: 171.0785.

(*E*)-4-(4-Methoxyphenyl)but-3-en-2-ol (1b). White solid (469 mg, 88% yield). R_f (50% Et_2O/hexane): 0.31. Mp: 75-78 ºC. IR (NaCl): 3424, 2956, 2838, 1891, 1513, 1255, 1032, 808 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.69 (s, 1H), 3.81 (s, 3H), 4.42-4.51 (m, 1H), 6.12 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.6 Hz, 1H), 6.50 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.82-6.89 (m, 2H), 7.28-7.36 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.6 (CH_3), 55.4 (CH_3), 69.2 (CH), 114.1 (2CH), 127.8 (2CH), 129.1 (CH), 129.5 (C), 131.5 (CH), 159.4 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO_2)^+$ $(M+Na)^+$ 201.0886, found: 201.0875.

(*E*)-4-(4-Chlorophenyl)but-3-en-2-ol (1c). White solid (351 mg, 64% yield). R_f (50% Et_2O/hexane): 0.48. Mp: 63-65 ºC. IR (NaCl): 3375, 3052, 2975, 1492, 1265, 1092, 739 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.37 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.77 (br s, 1H), 4.44-4.52 (m, 1H), 6.23 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.4 Hz, 1H), 6.52 (dd, $^3J_{HH}$ = 15.9, $^4J_{HH}$ = 1.1 Hz, 1H), 7.28 (br s, 4H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.5 (CH_3), 68.9 (CH), 127.8 (2CH), 128.2 (CH), 128.9 (2CH), 133.3 (C), 134.3 (CH), 135.3 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}ClNaO)^+$ $(M+Na)^+$ 205.0391, found: 205.0394.

(*E*)-4-(4-Fluorophenyl)but-3-en-2-ol (1d). White solid (230 mg, 46% yield). R_f (50% Et_2O/hexane): 0.46. Mp: 38-40 ºC. IR (NaCl): 3430, 3071, 2977, 1891, 1601, 1508, 1372, 1227, 968, 857 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.87 (br s, 1H), 4.43-4.51 (m, 1H), 6.17 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.3 Hz, 1H), 6.52 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.96-7.03 (m, 2H), 7.29-7.36 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.6 (CH_3), 68.9 (CH), 115.6 (d, *J* = 21.6 Hz, 2CH), 128.1 (d, *J* = 8.3 Hz, 2CH), 128.3 (CH), 133.0 (d, *J* = 3.3 Hz, C), 133.4 (d, *J* = 1.9 Hz, CH), 162.4 (d, *J* = 246.5 Hz, C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –114.5 ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}FNaO)^+$ $(M+Na)^+$ 189.0686, found: 189.0687.

4-(4-Bromophenyl)but-3-en-2-ol (1e). White solid (387 mg, 57% yield). R_f (50% Et_2O/hexane): 0.38. Mp: 46-48 ºC. IR (NaCl): 3385, 2972, 1898, 1655, 1487, 1072, 1009, 805 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.77 (br s, 1H), 4.43-4.52 (m, 1H), 6.24 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.4 Hz, 1H), 6.50 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 7.21-7.24 (m, 2H), 7.40-7.45 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.5 (CH_3), 68.9 (CH), 121.5 (C), 128.1 (2CH), 128.3 (CH), 131.8 (2CH), 134.4 (CH), 135.8 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{10}Br)^+$ $(M-OH)^+$ 208.9960, found: 208.9971.

(*E*)-4-(3-Methoxyphenyl)but-3-en-2-ol (1f). Pale yellow liquid (417 mg, 78% yield). R_f (50% Et_2O/hexane): 0.37. IR (NaCl): 3425, 2971, 2836, 1926, 1719, 1599, 1288, 1047, 969, 779, 691 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.87 (br s, 1H), 3.78 (s, 3H), 4.41-4.50 (m, 1H), 6.25 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.4 Hz, 1H), 6.51 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.79 (dd, $^3J_{HH}$ = 6.4, $^4J_{HH}$ = 2.6 Hz, 1H), 6.91 (apparent t, $^3J_{HH}$ = 2.6, 1H), 6.96 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.22 (apparent t, $^3J_{HH}$ = 7.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3 (CH_3), 55.1 (CH_3), 68.6 (CH), 111.7 (CH), 113.2 (CH), 119.1 (CH), 129.0 (CH), 129.5 (CH), 134.0 (CH), 138.2 (C), 159.7 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO_2)^+$ $(M+Na)^+$ 201.0886, found: 201.0890.

(*E*)-4-(2-Methoxyphenyl)but-3-en-2-ol (1g). Pale yellow liquid (435 mg, 81% yield). R_f (50% Et_2O/hexane): 0.39. IR (NaCl): 3396, 2970, 2837, 1899, 1688, 1598, 1239, 974, 753 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.41 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 3.01 (br s, 1H), 3.83 (s, 3H), 4.47-4.56 (m, 1H), 6.31 (dd, $^3J_{HH}$ = 16.0, $^3J_{HH}$ = 6.4 Hz, 1H), 6.85-6.99 (m, 3H), 7.25 (ddd, $^3J_{HH}$ = 8.2, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.7 Hz, 1H), 7.46 (dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.7 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3 (CH_3), 55.2 (CH_3), 69.0 (CH), 110.7 (CH), 120.5 (CH), 123.9 (CH), 125.7 (C), 126.7 (CH), 128.5 (CH), 134.3 (CH), 156.5 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{14}NaO_2)^+$ $(M+Na)^+$ 201.0886, found: 201.0888.

(*E*)-4-(3-Fluorophenyl)but-3-en-2-ol (1h). Pale yellow liquid (354 mg, 71% yield). R_f (50% Et_2O/hexane): 0.52. IR (NaCl): 3371, 3075, 3037, 2974, 2928, 1935, 1857, 1585, 1488, 1447, 1265, 1144, 961, 781 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.41 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.49 (br s, 1H), 4.48-4.56 (m, 1H), 6.30 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.1 Hz, 1H), 6.56 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.93-7.00 (m, 1H), 7.10 (ddd, *J* = 10.2, *J* = 2.6, *J* = 1.6 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.27-7.34 (m, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.5 (CH_3), 68.8 (CH), 113.0 (d, *J* = 21.8 Hz, CH), 114.6 (d, *J* = 21.4 Hz, CH), 122.5 (d, *J* = 2.8 Hz, CH), 128.3 (d, *J* = 2.5 Hz, CH), 130.2 (d, *J* = 8.4 Hz, CH), 135.0 (CH), 139.2 (d, *J* = 7.8 Hz, C), 163.2 (d, *J* = 245.0 Hz, C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –113.5 ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{11}FNaO)^+$ $(M+Na)^+$ 189.0686, found: 189.0695.

(*E*)-4-(2-Fluorophenyl)but-3-en-2-ol (1i). White wax (380 mg, 76% yield). R_f (50% Et_2O/hexane): 0.56. IR (NaCl): 3431, 2976, 1488, 1457, 1229, 970, 756 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 3.01 (s, 1H), 4.44-452 (m, 1H), 6.34 (dd, $^3J_{HH}$ = 16.1, $^3J_{HH}$ = 6.3 Hz, 1H), 6.71 (d, $^3J_{HH}$ = 16.1 Hz, 1H), 6.97-7.08 (m, 2H), 7.14-7.21 (m, 1H), 7.41 (td, *J* = 7.7, *J* = 1.8 Hz) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3 (CH_3), 68.8 (CH), 115.7 (d, *J* = 22.4 Hz, CH), 121.5 (d, *J* = 3.7 Hz, CH), 124.1 (d, *J* = 3.5 Hz, CH), 124.5 (d, *J* = 12.2 Hz, C), 127.5 (d, *J* = 3.7 Hz, CH), 128.7 (d, *J* = 8.4

Hz, CH), 136.3 (d, J = 4.5 Hz, CH), 160.3 (d, J = 248.8 Hz, C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –118.1 ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{11}FNaO)^+$ $(M+Na)^+$ 189.0686, found: 189.0682.

(*E*)-4-(*m*-Tolyl)but-3-en-2-ol (1j). Pale yellow liquid (414 mg, 85% yield). R_f (50% Et_2O/hexane): 0.46. IR (NaCl): 3405, 2974, 2923, 2733, 1943, 1876, 1606, 1488, 1261, 970, 779, 694 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.40 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 2.38 (s, 3H), 2.90 (s, 1H), 4.45-4.54 (m, 1H), 6.28 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.4 Hz, 1H), 6.55 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 7.07-7.13 (m, 1H), 7.18-7.28 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.5 (CH_3), 23.5 (CH_3), 68.8 (CH), 123.7 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 129.3 (CH), 133.5 (CH), 136.8 (C), 138.1 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{14}NaO)^+$ $(M+Na)^+$ 185.0937, found: 185.0945.

(*E*)-4-(Pyridin-2-yl)but-3-en-2-ol (1k). Pale yellow liquid (389 mg, 87% yield). R_f (17% hexane/EtOAc): 0.40. IR (NaCl): 3375, 2971, 2926, 2869, 1656, 1588, 1565, 1471, 1432, 1367, 1300, 1143, 1062, 999, 854, 766 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.18 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 4.29-4.41 (m, 1H), 5.18 (br s, 1H), 6.46-6.62 (m, 2H), 6.81-6.90 (m, 1H), 7.04 (dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.2 Hz, 1H), 7.35 (apparent td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.6 Hz, 1H), 8.27 (d, $^3J_{HH}$ = 4.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.0 (CH_3), 67.2 (CH), 121.1 (CH), 121.7 (CH), 127.6 (CH), 136.4 (CH), 139.1 (CH), 148.7 (CH), 155.2 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_9H_{12}NO)^+$ $(M+H)^+$ 150.0913, found: 150.0913.

(*E*)-4-(Pyridin-3-yl)but-3-en-2-ol (1l). Pale yellow liquid (409 mg, 91% yield). R_f (17% hexane/EtOAc): 0.25. IR (NaCl): 3373, 2970, 2926, 2868, 1654, 1590, 1572, 1480, 1417, 1184, 1143, 1063, 969, 834, 794, 707 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.18-1.34 (m, 3H), 4.33-4.43 (m, 1H), 5.09 (br s, 1H), 6.13-6.31 (m, 1H), 6.40 (dd, $^3J_{HH}$ = 16.1, $^4J_{HH}$ = 3.3 Hz, 1H), 7.08 (dt, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 3.2 Hz, 1H), 7.50-7.56 (m, 1H), 8.17-8.44 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3 (CH_3), 67.6 (CH), 123.5 (CH), 124.5 (CH), 132.8 (C), 133.0 (CH), 137.0 (CH), 147.6 (2CH) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_9H_{12}NO)^+$ $(M+H)^+$ 150.0913, found: 150.0914.

(*E*)-4-(Furan-2-yl)but-3-en-2-ol (1m). Red liquid (369 mg, 89% yield). R_f (25% EtOAc/hexane): 0.36. IR (NaCl): 3347, 2972, 2927, 2872, 1656, 1563, 1490, 1257, 1150, 1058, 1013, 963, 798, 737 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.30 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 3.20 (br s, 1H), 4.35-4.44 (m, 1H), 6.13-6.23 (m, 2H), 6.32 (m, 2H), 7.30 (d, $^3J_{HH}$ = 1.2 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3 (CH_3), 68.1 (CH), 107.8 (CH), 111.2 (CH), 117.5 (CH), 132.4 (CH), 141.8 (CH), 152.5 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_8H_{10}NaO_2)^+$ $(M+Na)^+$ 161.0573, found: 161.0586.

(*E*)-4-(Furan-3-yl)but-3-en-2-ol (1n). Dark orange liquid (361 mg, 87% yield). R_f (25% EtOAc/hexane): 0.29. IR (NaCl): 3348, 2972, 2928, 2874, 1664, 1508, 1452, 1370, 1160, 1138, 1059, 1023, 965, 848, 779 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.28 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 3.26 (br s, 1H), 4.31-4.40 (m, 1H), 5.93 (dd, $^3J_{HH}$ = 15.8, $^3J_{HH}$ = 6.3 Hz, 1H), 6.35 (d, $^3J_{HH}$ = 15.8 Hz, 1H), 6.43-6.48 (s, 1H), 7.30-7.34 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.2 (CH_3), 68.4 (CH), 107.5 (CH), 118.8 (CH), 123.6 (C), 133.3 (CH), 140.4 (CH), 143.4 (CH) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_8H_{10}NaO_2)^+$ $(M+Na)^+$ 161.0573, found: 161.0570.

(*E*)-4-(Thiophen-2-yl)but-3-en-2-ol (1o). Brown liquid (423 mg, 91% yield). R_f (25% EtOAc/hexane): 0.38. IR (NaCl): 3372, 2971, 2925, 2870, 1648, 1449, 1369, 1138, 1058, 957, 853, 695 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.35 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 3.53 (s, 1H), 4.37-4.46 (m, 1H), 6.11 (dd, $^3J_{HH}$ = 15.7, $^3J_{HH}$ = 6.2 Hz, 1H), 6.68 (d, $^3J_{HH}$ = 15.7 Hz, 1H), 6.90-6.97 (m, 2H), 7.10-7.16 (m, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.2 (CH_3), 68.1 (CH), 122.2 (CH), 124.0 (CH), 125.5 (CH), 127.2 (CH), 133.2 (CH), 141.8 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_8H_{10}NaOS)^+$ $(M+Na)^+$ 177.0345, found: 177.0333.

(*E*)-4-(Thiophen-3-yl)but-3-en-2-ol (1p). White solid (328 mg, 71% yield). R_f (25% EtOAc/hexane): 0.31. Mp: 59-60 ºC. IR (NaCl): 3356, 2971, 2925, 2871, 1656, 1450, 1369, 1159, 1058, 965, 864, 830, 771 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.36 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.75 (s, 1H) 4.40-4.49 (m, 1H), 6.11 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.4 Hz, 1H), 6.58 (dd, $^3J_{HH}$ = 15.9, $^4J_{HH}$ = 0.6 Hz, 1H), 7.15 (dd, $^4J_{HH}$ = 2.9, $^4J_{HH}$ = 1.2 Hz, 1H), 7.20 (dd, $^3J_{HH}$ = 5.1, $^4J_{HH}$ = 1.1 Hz, 1H), 7.27 (dd, $^3J_{HH}$ = 5.0, $^4J_{HH}$ = 2.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.5 (CH_3), 69.0 (CH), 122.3 (CH), 123.8 (CH), 125.1 (CH), 126.2 (CH), 133.6 (CH), 139.4 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_8H_{10}NaOS)^+$ $(M+Na)^+$ 177.0345, found: 177.0333.

Typical procedure for the synthesis of amines 3a-j,m-p

Amines **3a**-**j**,**m-p** were synthesised following the procedure described by Schenck and Bosnich for amine **3a** as follows:[14] Solid NaOH (480 mg, 12 mmol) was added in portions to a solution of the corresponding ketone **2a**-**j**,**m-p** (1.2 mmol) and $NH_2OH{\cdot}HCl$ (134 mg, 1.92 mmol) in a mixture of EtOH (0.96 mL) and water (0.24 mL). The mixture was refluxed overnight, cooled to room temperature and then acidified with a HCl 6 M aqueous solution until pH 2. The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phases dried over anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure, obtaining the corresponding oxime intermediate, which was further used without additional purification. Then, zinc dust (393 mg, 6 mmol) was added in portions to an ice-cooled solution of the so-obtained oxime intermediate in EtOH (0.8 mL) and glacial acetic acid (0.8 mL). The mixture was allowed to warm up to room temperature and then gently warmed and stirred on a steam bath for 2 h. Afterwards, rests of zinc dust were filtered-off and the solvent evaporated under reduced pressure. The residue was dissolved in a HCl 6 M aqueous solution (10 mL) and washed with CH_2Cl_2 (3 x 15 mL). Then, the aqueous phase was treated with a NaOH 10 M aqueous solution until pH 12. The resulting aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the corresponding amines **3a**-**d,f-j**,**o-p** were obtained with high purity (21-54% yield), except amines **3e**, **3m** and **3n** that were additionally purified by column chromatography on silica gel (5% NH_3/MeOH, 21-54% yield).

(*E*)-4-Phenylbut-3-en-2-amine (3a). Pale yellow oil (92 mg 52% yield). R_f (5% NH_3/MeOH): 0.62. IR (NaCl): 3362, 3287, 2963, 1948, 1878, 1805, 1493, 1449, 1369, 967, 748, 694 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.67 (br s, 2H), 3.61-3.70 (m, 1H), 6.20 (dd, $^3J_{HH}$ = 15.8, $^3J_{HH}$ = 6.6 Hz, 1H), 6.45 (d, $^3J_{HH}$ = 15.8 Hz, 1H), 7.17-7.25 (m, 1H), 7.26-7.39 (m, 4H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.9 (CH_3), 49.3 (CH), 126.3 (2CH), 127.3 (CH), 127.8 (CH), 128.6 (2CH), 136.2 (CH), 137.2 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{14}N)^+$ $(M+H)^+$ 148.1121, found: 148.1119.

(*E*)-4-(4-Methoxyphenyl)but-3-en-2-amine (3b). Pale yellow wax (115 mg, 54% yield). R_f (5% NH_3/MeOH): 0.53. IR (NaCl): 3417, 3945, 2964, 2837, 1608, 1512, 1248, 737 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.24 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.06 (br s, 2H), 3.63 (m, 1H), 3.79 (s, 3H), 6.06 (dd, $^3J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 6.40 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.81-6.86 (m, 2H), 7.27-7.31 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.9 (CH_3), 49.5 (CH), 55.4 (CH_3), 114.1 (2CH), 127.5 (CH), 127.5 (2CH), 130.0 (C), 133.9 (CH), 159.1 (C) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{11}H_{16}NO)^+$ $(M+H)^+$ 178.1226, found: 178.1231.

(*E*)-4-(4-Chlorophenyl)but-3-en-2-amine (3c). Yellow wax (92 mg, 42% yield). R_f (5% NH_3/MeOH): 0.64. IR (NaCl): 3356, 3282, 2965, 2925, 1491, 1092, 808 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.21 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 2.04 (br s, 2H), 3.59-3.68 (m, 1H), 6.14 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.5 Hz, 1H), 6.37 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 7.23 (s, 4H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.8 (CH_3), 49.2 (CH), 126.7 (CH), 127.5 (2CH), 128.6 (2CH), 132.8 (C), 135.7 (C), 136.7 (CH) ppm. HRMS (ESI$^+$, *m/z*): calcd for $(C_{10}H_{13}ClN)^+$ $(M+H)^+$ 182.0731, found: 182.0739.

(*E*)-4-(4-Fluorophenyl)but-3-en-2-amine (3d). Yellow oil (75 mg, 38% yield). R_f (5% NH_3/MeOH): 0.60. IR (NaCl): 3355, 3287, 2967, 2925, 1928, 1602, 1509, 1226, 1158, 969, 817 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.10 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.70 (br s, 2H), 3.49 (m, 1H), 5.97 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.5 Hz, 1H), 6.27 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.80-6.89 (m, 2H), 7.13-7.20 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.5 (CH_3), 48.9 (CH), 115.1 (d, *J* = 21.6 Hz, 2CH), 126.3 (CH), 127.4 (d, *J* = 7.8 Hz, 2CH), 133.1 (d, *J* = 3.3 Hz, C), 135.6 (d, *J* = 2.2 Hz, CH), 161.8 (d, *J* = 246.1 Hz, C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –115.0 ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{13}FN)^+$ $(M+H)^+$ 166.1027, found: 166.1029.

(*E*)-4-(4-Bromophenyl)but-3-en-2-amine (3e). Yellow oil (58 mg, 21% yield). R_f (5% NH_3/MeOH): 0.64. IR (NaCl): 3357, 3288, 2962, 2925, 1487, 1359, 1176, 1008, 967, 809 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.24 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.61 (br s, 2H), 3.60-3.69 (m, 1H), 6.18 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.5 Hz, 1H), 6.39 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 7.19-7.23 (m, 2H), 7.38-7.43 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.0 (CH_3), 49.3 (CH), 121.0 (C), 126.8 (CH), 127.9 (2CH), 131.7 (2CH), 136.3 (C), 137.1 (CH) ppm. HRMS (ESI^+, m/z): calcd for $(C_{10}H_{13}BrN)^+$ $(M+H)^+$ 226.0226, found: 226.0221.

(*E*)-4-(3-Methoxyphenyl)but-3-en-2-amine (3f). Yellow oil (94 mg, 44% yield). R_f (5% NH_3/MeOH): 0.58. IR (NaCl): 3358, 3290, 2962, 2835, 1598, 1464, 1156, 1047, 970, 779, 691 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.21 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.97 (br s, 2H), 3.62 (m, 1H), 3.76 (s, 3H), 6.16 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.6 Hz, 1H), 6.39 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.74 (ddd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 2.6, $^4J_{HH}$ = 1.0 Hz, 1H), 6.88 (apparent t, $^4J_{HH}$ = 2.6 Hz, 1H), 6.93 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.18 (apparent t, $^3J_{HH}$ = 7.8 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.7 (CH_3), 49.2 (CH), 55.1 (CH_3), 111.5 (CH), 112.9 (CH), 118.9 (CH), 127.7 (CH), 129.5 (CH), 136.3 (CH), 138.6 (C), 159.7 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{16}NO)^+$ $(M+H)^+$ 178.1226, found: 178.1224.

(*E*)-4-(2-Methoxyphenyl)but-3-en-2-amine (3g). Brown oil (92 mg, 43% yield). R_f (5% NH_3/MeOH): 0.54. IR (NaCl): 3357, 3289, 2962, 2837, 1935, 1899, 1798, 1597, 1489, 1243, 1028, 975, 752 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 3.59-3.67 (m, 1H), 3.81 (s, 3H), 6.19 (dd, $^3J_{HH}$ = 16.0, $^3J_{HH}$ = 6.8 Hz, 1H), 6.74-6.93 (m, 3H), 7.18 (ddd, $^3J_{HH}$ = 9.1, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.7 Hz, 1H), 7.42 (dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.7 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.8 (CH_3), 49.5 (CH), 55.4 (CH_3), 110.7 (CH), 120.6 (CH), 122.4 (CH), 126.1 (C), 126.6 (CH), 128.3 (CH), 137.0 (CH), 156.5 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{16}NO)^+$ $(M+H)^+$ 178.1226, found: 178.1222.

(*E*)-4-(3-Fluorophenyl)but-3-en-2-amine (3h). Yellow oil (44 mg, 22% yield). R_f (5% NH_3/MeOH): 0.61. IR (NaCl): 3351, 3276, 2961, 2925, 2856, 1936, 1858, 1586, 1488, 1448, 1265, 1142, 969, 783 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.16 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.55 (br s, 2H), 3.52-3.61 (m, 1H), 6.12 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.5 Hz, 1H), 6.33 (d, $^3J_{HH}$ = 15.9 Hz, 1H), 6.81 (apparent tdd, *J* = 8.3, *J* = 2.6, *J* = 1.0 Hz, 1H), 6.97 (dt, *J* = 10.3, *J* = 2.2 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 7.12-7.19 (m, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.9 (CH_3), 49.2 (CH), 112.7 (d, *J* = 21.8 Hz, CH), 114.0 (d, *J* = 21.4 Hz, CH), 122.2 (d, *J* = 2.7 Hz, CH), 126.8 (d, *J* = 2.5 Hz, CH), 130.0 (d, *J* = 8.5 Hz, CH), 137.6 (CH), 139.7 (d, *J* = 7.8 Hz, C), 163.1 (d, *J* = 245.2 Hz, C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –113.6 ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{13}FN)^+$ $(M+H)^+$ 166.1027, found: 166.1014.

(*E*)-4-(2-Fluorophenyl)but-3-en-2-amine (3i). Pale yellow wax (52 mg, 26% yield). R_f (5% NH_3/MeOH): 0.64. IR (NaCl): 3356, 3269, 2963, 2925, 2855, 1946, 1912, 1799, 1581, 1488, 1455, 1375, 1229, 970, 755 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.61 (br s, 2H), 3.61-3.72 (m, 1H), 6.27 (dd, $^3J_{HH}$ = 16.0, $^3J_{HH}$ = 6.7 Hz, 1H), 6.61 (d, $^3J_{HH}$ = 16.0 Hz, 1H), 6.96-7.10 (m, 2H), 7.13-7.20 (m, 1H), 7.43 (apparent td, *J* = 7.7, *J* = 1.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.8 (CH_3), 49.8 (CH), 115.8 (d, *J* = 22.3, CH), 120.6 (d, *J* = 3.5, CH), 124.2 (d, *J* = 3.3 Hz, CH), 125.0 (d, *J* = 12.6 Hz, C), 127.4 (d, *J* = 3.7 Hz, CH), 128.7 (d, *J* = 8.3 Hz, CH), 138.6 (d, *J* = 4.3 Hz, CH), 160.3 (d, *J* = 249.1 Hz, C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –118.5 ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{10}H_{13}FN)^+$ $(M+H)^+$ 166.1027, found: 166.1028.

(*E*)-4-(*m*-Tolyl)but-3-en-2-amine (3j). Yellow oil (81 mg, 42% yield). R_f (5% NH_3/MeOH): 0.58. IR (NaCl): 3354, 3288, 2966, 2922, 1604, 1454, 1373, 968, 778, 695 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.25 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.79 (br s, 2H), 2.34 (s, 3H), 3.61-3.70 (m, 1H), 6.19 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.7 Hz, 1H), 6.43 (dd, $^3J_{HH}$ = 15.9, $^4J_{HH}$ = 1.2 Hz, 1H), 6.99-7.23 (m, 4H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.5 (CH_3), 23.9 (CH_3), 49.4 (CH), 123.5 (CH), 127.0 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 136.0 (CH), 137.2 (C), 138.1 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_{11}H_{16}N)^+$ $(M+H)^+$ 162.1277, found: 162.1278.

(*E*)-4-(Furan-2-yl)but-3-en-2-amine (3m). Yellow oil (64 mg, 39% yield). R_f (5% NH_3/MeOH): 0.61. IR (NaCl): 3354, 3287, 2966, 2927, 2870, 1651, 1594, 1453, 1374, 1255, 1012, 964, 926, 884, 800, 735 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.19 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.55 (br s, 2H), 3.53-3.62 (m, 1H), 6.08-6.18 (m, 2H), 6.26 (d, $^3J_{HH}$ = 16.0 Hz, 1H), 6.31 (dd, $^3J_{HH}$ = 3.3, $^3J_{HH}$ = 1.9 Hz, 1H), 7.29 (d, $^3J_{HH}$ = 1.8 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.9 (CH_3), 49.0 (CH), 107.2 (CH), 111.2 (CH), 116.4 (CH), 135.1 (CH), 141.6 (CH), 152.8 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_8H_{12}NO)^+$ $(M+H)^+$ 138.0913, found: 138.0910.

(*E*)-4-(Furan-3-yl)but-3-en-2-amine (3n). Yellow oil (68 mg, 41% yield). R_f (5% NH_3/MeOH): 0.52. IR (NaCl): 3411, 3405, 2970, 2929, 2872, 1658, 1508, 1452, 1374, 1160, 1073, 1023, 967, 871, 782, 731, 596 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.21 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.55 (br s, 2H), 3.56-3.65 (m, 1H), 5.93 (dd, $^3J_{HH}$ = 15.8, $^3J_{HH}$ = 6.6 Hz, 1H), 6.32 (d, $^3J_{HH}$ = 15.8 Hz, 1H), 6.50 (d, $^3J_{HH}$ = 1.7 Hz, 1H), 7.35 (m, 1H), 7.37 (s, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.0 (CH_3), 49.3 (CH), 107.7 (CH), 117.6 (CH), 124.1 (C), 136.0 (CH), 140.2 (CH), 143.6 (CH) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_8H_{12}NO)^+$ $(M+H)^+$ 138.0913, found: 138.0915.

(*E*)-4-(Thiophen-2-yl)but-3-en-2-amine (3o). Yellow oil (73 mg, 40% yield). R_f (5% NH_3/MeOH): 0.70. IR (NaCl): 3356, 3289, 2959, 2925, 2855, 1650, 1594, 1454, 1376, 957, 853, 810, 696 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.24 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 1.58 (br s, 2H), 3.58-3.67 (m, 1H), 6.06 (dd, $^3J_{HH}$ = 15.7, $^3J_{HH}$ = 6.6 Hz, 1H), 6.60 (d, $^3J_{HH}$ = 15.7 Hz, 1H), 6.88-6.97 (m, 2H), 7.12 (d, $^3J_{HH}$ = 4.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.9 (CH_3), 49.2 (CH), 121.3 (CH), 123.9 (CH), 125.3 (CH), 127.4 (CH), 136.1 (CH), 142.5 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_8H_{12}NS)^+$ $(M+H)^+$ 154.0685, found: 154.0684.

(*E*)-4-(Thiophen-3-yl)but-3-en-2-amine (3p). Yellow oil (63 mg, 34% yield). R_f (5% NH_3/MeOH): 0.60. IR (NaCl): 3405, 3392, 2965, 2925, 2868, 1649, 1451, 1372, 1261, 1084, 966, 773 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.19 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.44 (br s, 2H), 3.53-3.62 (m, 1H), 6.02 (dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 6.7 Hz, 1H), 6.43 (dd, $^3J_{HH}$ = 15.9, $^4J_{HH}$ = 0.5 Hz, 1H), 7.06 (dd, $^4J_{HH}$ = 3.0, $^4J_{HH}$ = 1.3 Hz, 1H), 7.16 (dd, $^3J_{HH}$ = 5.0, $^4J_{HH}$ = 1.2 Hz, 1H), 7.21 (dd, $^3J_{HH}$ = 5.1, $^4J_{HH}$ = 2.9 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.9 (CH_3), 49.2 (CH), 121.4 (CH), 122.0 (CH), 125.0 (CH), 125.9 (CH), 136.1 (CH), 139.7 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_8H_{12}NS)^+$ $(M+H)^+$ 154.0685, found: 154.0683.

Typical procedure for the synthesis of amines 3k and 3l[68]

An aqueous solution of conc. sulfuric acid (490 mg, 5 mmol) in dry acetonitrile (2 mL) was added to a stirred solution of the corresponding alcohol **1k** or **1l** (1 mmol) and Na_2SO_4 (142 mg, 1 mmol) in dry acetonitrile (3.1 mL) at 0 ºC. The mixture was allowed to reach room temperature, and the stirring was continued for 24 h. The mixture was concentrated under reduced pressure, and then cold water was added and the mixture extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the corresponding acetamides (1 mmol) were dissolved in a 6 M HCl aqueous solution (5.7 mL) and heated at 80 ºC for 16 h. The resulting solution was basified by addition of a 4 M NaOH aqueous solution to pH 10 and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the corresponding amines **3k** and **3l** were obtained with high purity in 47 and 58% yield, respectively.

(*E*)-4-(Pyridin-2-yl)but-3-en-2-amine (3k). Yellow oil (70 mg, 47% yield). R_f (5% NH_3/MeOH): 0.68. IR (NaCl): 3353, 3278, 3005, 2965, 2925, 2869, 1653, 1587, 1564, 1470, 1432, 1370, 1300, 1150, 974, 767, 742 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.07 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 1.64 (br s, 2H), 3.46-3.55 (m, 1H), 6.36 (dd, $^3J_{HH}$ = 15.7, $^4J_{HH}$ = 1.2 Hz, 1H), 6.54 (dd, $^3J_{HH}$ = 15.8, $^3J_{HH}$ = 6.3 Hz, 1H), 6.90 (ddd, $^3J_{HH}$ = 7.5, $^3J_{HH}$ = 4.9, $^4J_{HH}$ = 1.2 Hz, 1H), 7.07 (apparent dt, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.1 Hz, 1H), 7.40 (apparent td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8 Hz, 1H), 8.34 (ddd, $^3J_{HH}$ = 4.9, $^4J_{HH}$ = 1.9, $^5J_{HH}$ = 1.0 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.4 (CH_3), 48.7 (CH), 121.1 (CH), 121.6 (CH), 127.3 (CH), 136.2 (CH), 140.5 (CH), 149.1 (CH), 155.3 (C) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_9H_{13}N_2)^+$ $(M+H)^+$ 149.1073, found: 149.1076.

(*E*)-4-(Pyridin-3-yl)but-3-en-2-amine (3l). Yellow oil (86 mg, 58% yield). R_f (5% NH_3/MeOH): 0.62. IR (NaCl): 3351, 3275, 3029, 2967, 2926, 2869, 1663, 1587, 1570, 1480, 1453, 1416, 1371, 1024, 969, 847, 828, 709 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.12 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 1.46 (br s, 2H), 3.50-3.59 (m, 1H), 6.15 (dd, $^3J_{HH}$ = 16.0, $^3J_{HH}$ = 6.3 Hz, 1H), 6.31 (d, $^3J_{HH}$ = 16.0 Hz, 1H), 7.08 (dd, $^3J_{HH}$ = 8.0, $^3J_{HH}$ = 4.8 Hz, 1H), 7.54 (apparent dt, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.9 Hz, 1H), 8.29 (dd, $^3J_{HH}$ = 4.8, $^4J_{HH}$ = 1.6 Hz, 1H), 8.44 (d, $^4J_{HH}$ = 2.1 Hz, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.7 (CH_3), 49.0 (CH), 123.3 (CH), 124.0 (CH), 132.5 (CH), 132.6 (C), 138.4 (CH), 148.0 (CH), 148.1 (CH) ppm. HRMS (ESI^+, *m/z*): calcd for $(C_9H_{13}N_2)^+$ $(M+H)^+$ 149.1073, found: 149.1076.

General procedure for the laccase-catalysed oxidation of alcohols 1a-p

In an open-to-air test tube, TEMPO (4.1 mg, 33 mol%) was added to a solution of the corresponding racemic alcohol **1a**-**p** (0.08 mmol, 100 mM) in a biphasic mixture of oxygen-saturated citrate buffer 50 mM pH 5 and MTBE (50% v/v for a total volume of 800 μL). The reaction mixture was magnetically stirred for a few minutes to dissolve all the reagents and then the laccase from *Trametes versicolor* was added (7 mg, 4.6 U), and the mixture magnetically stirred (150 rpm) for additional 16 h at 30 ºC. After this time, the product was extracted with EtOAc (2 x 2 mL), the organic phases combined, dried over Na_2SO_4, filtered and an aliquot was taken for the determination of the conversion value by GC analysis (see Tables 1 and 2, >98% conversion into ketones **2a**-**p**).

General procedure for the biotransamination of ketones 2a-p

In an Eppendorf vial, the corresponding ketone **2a**-**p** (5 μmol, 10 mM) was dissolved in DMSO (2.5% v/v, 12 μL). Then, a phosphate buffer 100 mM pH 7.5 (485 μL) containing PLP (1 mM) and isopropylamine (1.0 M) and the corresponding commercially available ATA (2 mg) were added. The reaction was shaken at 45 ºC and 250 rpm for 24 h and then stopped by the addition of a NaOH 10 M aqueous solution (200 μL). The mixture was extracted with EtOAc (500 μL) and the organic layer was separated by centrifugation (2 min, 13,000 rpm). This extraction and centrifugation protocol was performed twice, and the organic layers were combined and dried over Na_2SO_4. Conversion and enantiomeric excess values were determined by GC (see Tables 3, 4 and others in the Supporting Information file).

Typical procedure for the sequential two-step synthesis of enantioenriched amines 3a-p from racemic alcohols 1a-p

In an open-to-air test tube, TEMPO (4.1 mg, 33 mol%) was added to a solution of the corresponding racemic alcohol **1a**-**p** (0.08 mmol, 100 mM) in a biphasic mixture of an oxygen-saturated citrate buffer 50 mM pH 5 and MTBE (50% v/v, for a total volume of 800 μL). The reaction mixture was stirred for a few minutes to dissolve all the reagents, and then the laccase from *Trametes versicolor* (7 mg, 4.6 U) was added. The reaction was stirred for 16 h at 30 ºC, observing the complete evaporation of MTBE along this time. This fact led to a volume reduction from the initial 800 μL to 400 μL, and as a consequence, the substrate concentration increased from the initial 100 mM to approximately 200 mM. The resulting reaction crude containing the ketone intermediate **2a**-**p** was transferred to a 15 mL centrifuge tube, and then DMSO (0.2 mL), phosphate buffer 100 mM pH 7.6 (7.4 mL) containing isopropylamine (1.08 M), and PLP (2 mg) were added, leading to a concentration approximately of 10 mM for the substrate, 1 M for isopropylamine, 1 mM for PLP and 2.5% v/v of DMSO. At the same time, the addition of this concentrated buffer to the reaction media, caused an increase in the pH from an initial value of 5 to approximately 7.5, therefore, further pH adjustment was not required for the biotransamination reaction. Finally, the corresponding commercially available amine transaminase (24 mg) was added. The centrifuge tube was closed and the reaction shaken at 45 ºC and 250 rpm for 24 h. After this time, the reaction was stopped by addition of a NaOH 10 M aqueous solution (3 mL). The mixture was extracted with EtOAc (5 mL) and the organic layer was separated by centrifugation (3 min, 4,900 rpm). This extraction and centrifugation protocol was performed twice and, finally, the organic layers were combined and dried over Na_2SO_4. Conversion values into the corresponding enantioenriched amines **3a-p** were determined by GC analyses. Derivatisation of the amines **3a-p** as acetamide derivatives with acetic anhydride in the presence of potassium carbonate was necessary for the measurement of their enantiomeric excess values.

Semi-preparative sequential two-step bioamination of alcohols 1a, b, g and o

In an open-to-air test tube, TEMPO (8.2 mg, 33 mol%) was added to a solution of the corresponding racemic alcohol **1a**, **b**, **g** or **o** (0.16 mmol, 100 mM) in a biphasic mixture of an oxygen-saturated citrate buffer 50 mM pH 5 and MTBE (50% v/v, for a total volume of 1.6 mL). The reaction mixture was stirred for a few minutes to dissolve all the reagents, and then the laccase from *Trametes versicolor* (14 mg, 9.2 U) was added. The reaction was stirred for 16 h at 30 ºC, observing the complete evaporation of MTBE along this time. This fact led to a volume reduction from the initial 1.6 mL to 800 μL, and as a consequence, the substrate concentration increased from the initial 100 mM to approximately 200 mM. The resulting reaction crude containing the ketone intermediate **2a**, **b**, **g** or **o** was transferred to a 50 mL centrifuge tube, and then acetonitrile (MeCN, 0.4 mL), phosphate buffer 100 mM pH 7.6 (14.8 mL) containing isopropylamine (1.08 M), and PLP (4 mg) were added, leading to a concentration approximately of 10 mM for the substrate, 1 M for isopropylamine, 1 mM for PLP and 2.5% v/v of MeCN. At the same time,

the addition of this concentrated buffer to the reaction media, caused an increase in the pH from an initial value of 5 to approximately 7.5, therefore, further pH adjustment was not required for the biotransamination reaction. Finally, the corresponding commercially available amine transaminase (48 mg) was added. The centrifuge tube was closed and the reaction shaken at 45 ºC and 250 rpm for 24 h. After this time, the reaction was stopped by addition of a NaOH 10 M aqueous solution (6 mL). The mixture was extracted with EtOAc (10 mL) and the organic layer was separated by centrifugation (3 min, 4,900 rpm). This extraction and centrifugation protocol was performed twice and, finally, the organic layers were combined and dried over Na_2SO_4. Conversion values into the corresponding enantioenriched amines **3a**, **b**, **g** or **o** were determined by GC analyses. Optical rotation of enantiopure amine **3a** was determined to confirm the amine absolute configuration: (*R*)**-3a**: $[\alpha]_D^{20}$= +21.5 (c= 1.0, $CHCl_3$, >99% *ee*). Lit: $[\alpha]_D^{20}$= +25.8 (c= 1.16, $CHCl_3$, >99% *ee*).[15] Then, the optical rotation values of novel optically active amines **3b**, **3g** and **3o** were also calculated: (*S*)**-3b**: $[\alpha]_D^{20}$= –34.6 (c= 1.0, $CHCl_3$, >99% *ee*); (*S*)**-3g**: $[\alpha]_D^{20}$= –23.5 (c= 1.0, $CHCl_3$, 99% *ee*); (*R*)-**3o**: $[\alpha]_D^{20}$= +20.8 (c= 1.0, $CHCl_3$, >99% *ee*). Derivatisation of these amines as acetamide derivatives with acetic anhydride in the presence of potassium carbonate was necessary for the measurement of their enantiomeric excess values, and the elution times were compared with those previously described[17] to assign the absolute configurations of the allylic amines obtained by this enzymatic approach.

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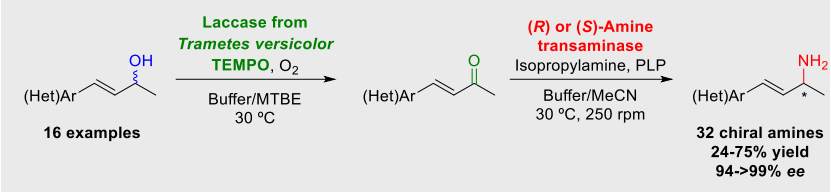

A sequential two-step amination of (3*E*)-4-(het)arylbut-3-en-2-alcohols has been described through a sequential cascade. The approach consists in their laccase *Trametes versicolor*/TEMPO-mediated oxidation to form the corresponding ketone intermediates, followed by asymmetric biotransamination using amine transaminases. Satisfyingly, 16 amine enantiomer pairs were obtained in very high to excellent stereoselectivity (94->99% *ee*) and moderate to good isolated yields (29-75% isolated yield).

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Sequential Two-Step Stereoselective Amination of Allylic Alcohols through Combination of Laccases and Amine