Supporting Information

Stereoselective amination of racemic *sec*-alcohols through sequential application of laccases and transaminases

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I. General considerations

Racemic alcohols **1a**, **4a**, **5a**, **12a**, and **13a**, and prochiral ketones **1b-3b** and **10b-13b**, were obtained from Alfa-Aesar. Racemic alcohols **6a**, **7a**, and **14a**, ketones **4b-9b**, **14b**, **15b** and **17b** were purchased from Sigma-Aldrich. Ketone **16b** was acquired from Merck.

Racemic alcohols **2a**, **3a**, **8a-11a**, **15a**, and **17a**, and racemic amines **1c-13c**, **16c** and **17c** were synthesized and exhibited physical and spectral data in agreement with those reported.[1,2] Racemic alcohol **14a**, and racemic amines **14c** and **15c** were synthesized and conveniently characterized (*vide infra*). The absolute configurations for both enantiomers of **14c** and **15c** were assigned based on the well-known stereopreferences shown by transaminases towards similar propiophenone derivatives.

Laccase from *Trametes versicolor* (0.9 U/mg) was purchased from Sigma-Aldrich. Codex Transaminase ATA Screening Kit (ATASK-000250) and PLP were purchased from Codexis. All other reagents were obtained from commercial sources and used as received.

Sequential reactions were performed in a sealed tube [(19 x 130 x 3) mm], otherwise indicated. The oxidation step mediated by the laccase/TEMPO catalytic system was performed open-to-air using magnetic stirring, while for the transamination step, the sealed tube was closed, and orbital shaking (250 rpm) was used.

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 recorder on a Bruker ALPHA spectrophotometer on NaCl pellets. Gas chromatography (GC) analyses were performed on an Agilent HP7820 GC chromatographs equipped with a FID detector. High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph UV detector at 210 nm. High resolution mass spectra (HRMS) were obtained in a Bruker Daltonics spectrometer using the ESI-TOF mode Thin-layer chromatography (TLC) was conducted with Merck Silica Gel 60 F254 precoated plates and visualized with UV and potassium permanganate stain. Column chromatography was performed using Merck Silica Gel 60 (230-400 mesh). Measurement of the optical rotation was carried out at 590 nm in a PerkinElmer 241 polarimeter.

In addition to those specified above, the following abbreviations and designations are used throughout the Supporting Information: Ac_2O: acetic anhydride; NH_4OAc: ammonium acetate, EtOAc: ethyl acetate; MeOH: methanol; EtOH: ethanol, 2-PrOH: 2-propanol; MeCN:

acetonitrile; MTBE: methyl *tert*-butyl ether; DMSO: dimethyl sulfoxide; TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy radical; PLP: pyridoxal 5'-phosphate.

II. Compounds described in this contribution

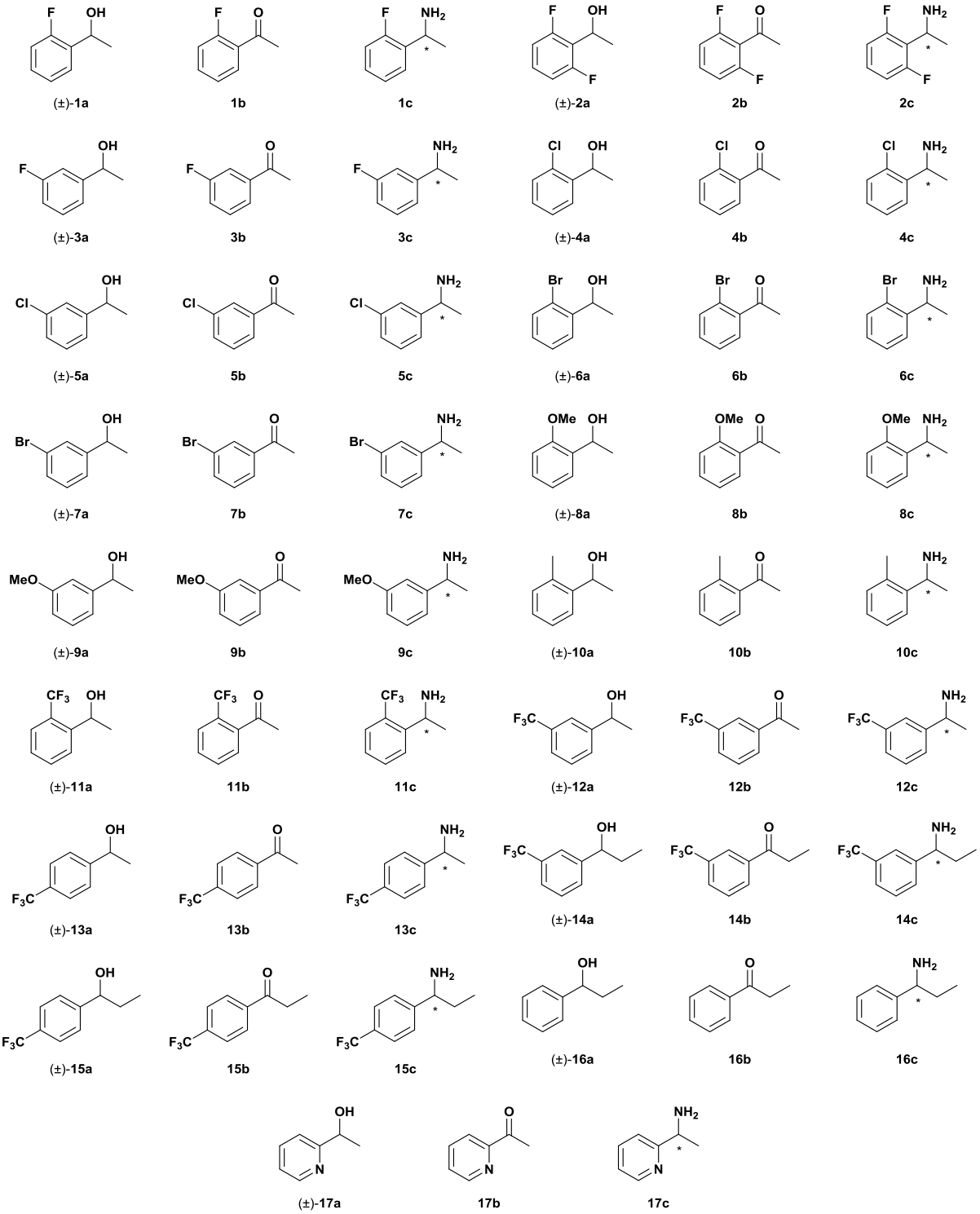


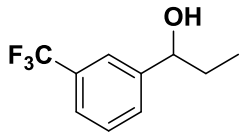
Figure S1. Structures of alcohols, ketones and amines under study in this manuscript.

III. General protocol for the synthesis of the non-commercial racemic alcohols

Sodium borohydride (265 mg, 7 mmol) was added to a solution of the corresponding ketone (3.5 mmol) in anhydrous methanol (11 mL, 0.32 M). The solution was stirred at room temperature and the reaction was monitored by TLC analysis until complete disappearance of the starting ketone. Then, the reaction was quenched by the addition of an aqueous HCl 1 M solution (3 mL). The solvent was evaporated and the remaining residue dissolved in distilled water (20 mL). The solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure affording the racemic alcohols without further purification.

Synthesized racemic alcohols **2a**, **3a**, **8a-11a**, **15a**, and **17a** exhibited physical and spectral data in agreement with those reported in the literature.[1] Characterization data of the non-previously described racemic alcohol **14a** are given below:

(±)-1-[3-(Trifluoromethyl)phenyl]propan-1-ol [(±)-14a]



(±)-**14a**

The title compound was obtained according to the general procedure as a colorless oil (694 mg, 3.4 mmol, yield 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.60 (*s*, 1H), 7.55-7.41 (*m*, 3H), 4.59 (*t*, 1H, *J*= 6.5 Hz), 3.13 (*br s*, 1H), 1.81-1.68 (*m*, 2H), 0.89 (*t*, 3H, *J*= 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 145.5, 130.6 (*q*, *J*= 31.9 Hz), 129.3, 128.7, 124.2 (*q*, *J*= 270.5 Hz), 124.1 (*q*, *J*= 3.8 Hz), 122.7 (*q*, *J*= 3.8 Hz), 75.2, 31.9, 9.8. ^{19}F-NMR (282 MHz, $CDCl_3$): δ (ppm) –62.6. IR (NaCl): ν 3346, 2971, 2937, 2880, 1452, 1329, 1267, 1126, 1163 cm^{-1}. HRMS (ESI^+, m/z) calcd $C_{10}H_{11}F_3ONa$ [$(M+Na)^+$] 227.0654; found, 227.0650.

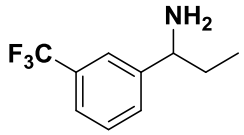
IV. General protocol for the synthesis of racemic amines

Ammonium acetate (2.691 g, 35 mmol) and sodium cyanoborohydride (438 mg, 7 mmol) were added to a solution of the corresponding ketone (3.5 mmol) in anhydrous methanol (11 mL, 0.32 M). The reaction was stirred for 24 h at room temperature. After this time the solvent was evaporated under reduced pressure and the remaining residue was dissolved in distilled water (20 mL). The solution was acidified to pH 1 with concentrated HCl and then washed with EtOAc (3 × 20 mL), discarding the organic layer. Then, the aqueous phase was

basified to pH 10 with an aqueous NaOH 10 M solution (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude amine was purified by column chromatography on silica gel (eluent gradient EtOAc/MeOH 99:1 to 90:10).

Racemic amines **1c-13c, 16c** and **17c** exhibited physical and spectral data in agreement with those reported in the literature.[2] Characterization data of the non-previously described racemic amines **14c** and **15c** are given below:

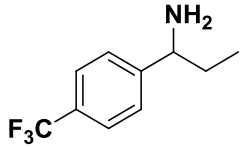
1-[3-(Trifluoromethyl)phenyl]propan-1-amine [(±)-(14c)]



(±)-14c

The title compound was obtained according to the general procedure and isolated after column chromatography on silica gel (EtOAc/MeOH 90:10) as a colorless oil (591 mg, 2.9 mmol, yield 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.59 (*s*, 1H), 7.50-7.40 (*m*, 3H), 3.87 (*t*, 1H, *J*= 6.8 Hz), 1.67 (*quint*, 2H, *J*= 7.3 Hz), 1.56 (*br s*, 2H), 0.85 (*t*, 3H, *J*= 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 147.4, 130.6 (*q*, *J*= 31.9 Hz), 129.9, 128.7, 124.5 (*q*, *J*= 270.6 Hz), 123.6 (*q*, *J*= 3.9 Hz), 123.2 (*q*, *J*= 3.9 Hz), 57.4, 32.4, 10.6. ^{19}F-NMR (282 MHz, $CDCl_3$): δ (ppm) –62.5. IR (NaCl): ν 3375, 3293, 2967, 2934, 2878, 1613, 1598, 1449, 1375, 1163, 1124, 1073 cm^{-1}. HRMS (ESI$^+$, m/z) calcd $C_{10}H_{13}F_3N$ [$(M+H)^+$] 204.0995; found, 204.0997.

1-[4-(Trifluoromethyl)phenyl]propan-1-amine [(±)-15c]



(±)-15c

The title compound was obtained according to the general procedure and isolated after column chromatography on silica gel (EtOAc/MeOH 90:10) as a colorless oil (569 mg, 2.7 mmol, yield 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.57 (*d*, 2H, *J*= 8.3 Hz), 7.43 (*d*, 2H, *J*= 7.8 Hz), 3.88 (*t*, 1H, *J*= 6.7 Hz), 1.68 (*quint*, 2H, *J*= 7.5 Hz), 1.53 (*br s*, 2H), 0.86 (*t*,

3H, *J*= 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 150.4, 129.1 (*q*, *J*= 31.7 Hz), 126.8 (2C), 125.2 (*q*, 2C, *J*= 3.9 Hz), 124.8 (*q*, *J*= 270.0 Hz), 57.4, 32.4, 10.6. ^{19}F-NMR (282 MHz, $CDCl_3$): δ (ppm) –62.4. IR (NaCl): ν 3375, 3292, 2967, 2934, 2861, 1619, 1462, 1420, 1327, 1124, 1068, 1017 cm^{-1}. HRMS (ESI^+, m/z) calcd $C_{10}H_{13}F_3N$ [$(M+H)^+$] 204.0995; found, 204.0996.

V. Optimization of the laccase/TEMPO reaction conditions

V.1. Effect of the stirring on the oxidation reaction (Magnetic vs *orbital stirring)*

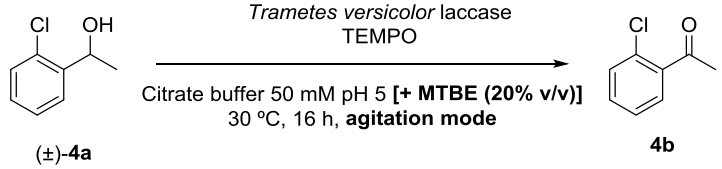
Magnetic stirring

In an open-to-air test tube, TEMPO (4.1 mg, 33 mol%) was added to a solution of the racemic alcohol **4a** (12 mg, 0.08 mmol, 50 mM) in an oxygen-saturated citrate buffer 50 mM pH 5 (1.6 mL), or to a biphasic mixture of oxygen-saturated citrate buffer 50 mM pH 5 and MTBE (20% 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* was added (5 U). The reaction was stirred for 16 h under magnetic stirring at 30 ºC. Then, it was extracted with EtOAc (2 x 2 mL). The organic layers were combined, dried over Na_2SO_4, and an aliquot was taken for the determination of the conversion value by GC analysis (Table S1).

Orbital stirring

In an open-to-air Erlenmeyer flask (10 mL), TEMPO (4.1 mg, 33 mol%) was added to a solution of the racemic alcohol **4a** (12 mg, 0.08 mmol, 50 mM) in an oxygen-saturated citrate buffer 50 mM pH 5 (1.6 mL), or to a biphasic mixture of oxygen-saturated citrate buffer 50 mM pH 5 and MTBE (20% 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* was added (5 U). The reaction was stirred for 16 h in an orbital shaker (250 rpm) at 30 ºC. Then, it was extracted with EtOAc (2 x 2 mL). The organic layers were combined, dried over Na_2SO_4, and an aliquot was taken for the determination of the conversion value by GC analysis (Table S1).

Table S1. Oxidation of (±)-**4a** with the laccase/TEMPO system using stirring or orbital shaking in the presence (or not) of MTBE as cosolvent.



(±)-**4a** **4b**

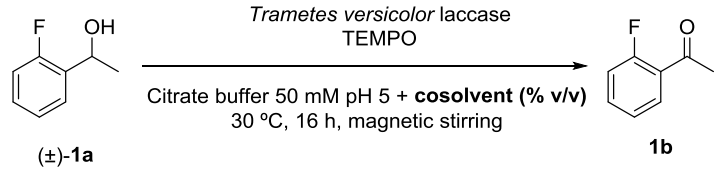
Entry	(% v/v) MTBE	**4b** (%)[a]	
		magnetic	orbital
1	-	80	42
2	20	98	65

[a] Conversion values measured by GC.

V.2. Effect of the organic solvent

In an-open-to-air test tube, TEMPO (4.1 mg, 33 mol%) was added to a solution of the racemic alcohol **1a** (11 mg, 0.08 mmol, 50 mM) in 1.6 mL of solvent (buffer/organic solvent were added in different ratios). The reaction mixture was stirred for a few minutes to dissolve all the reagents and then the laccase from *Trametes versicolor* was added (5 U). The reaction was magnetically stirred for 16 h at 30 ºC. It is noteworthy that when the reactions were carried out in the presence of MTBE as organic solvent, after the reaction time it was completely evaporated, leading to more concentrated reactions. Finally, it was extracted with EtOAc (2 x 2 mL). The organic layers were combined, dried over Na_2SO_4, and an aliquot was taken for the determination of the conversion values by GC analysis (Table S2).

Table S2. Effect of the organic cosolvent in the laccase/TEMPO-catalyzed oxidation of (±)-**1a**.



(±)-**1a** **1b**

Entry	(% v/v) cosolvent	**1b** (%)[a]
1	-	58
2	(5) DMSO	14
3	(20) MTBE	77
4	(50) MTBE	>99

[a] Conversion values measured by GC.

VI. Transaminase screenings

VI.1. General procedure for the enzymatic transamination reactions

VI.1.1. Enzymatic transamination reactions performed at analytical scale (0.0125 mmol of the substrate)

In a 1.5 mL Eppendorf vial, the corresponding ketone **1b**-**17b** (25 mM, 0.0125 mmol) was dissolved in DMSO (2.5% v/v, 12 µL). Then, phosphate buffer 100 mM pH 7.5 (485 µL, 1 mM PLP, 1 M isopropylamine) and the commercially available transaminase (2 mg) were added. The reaction was shaken at 30 ºC and 250 rpm for 24 h and stopped by the addition of an aqueous NaOH 10 M solution (200 µL). Then, the mixture was extracted with EtOAc (500 µL) and the organic layer was separated by centrifugation (2 min, 13,000 rpm). This centrifugation protocol was performed twice. The organic layers were combined and dried over Na_2SO_4. Conversions were determined by GC and enantiomeric excess by chiral GC or HPLC.

VI.1.2. Enzymatic transamination reactions performed at larger scale (0.08 mmol of the substrate)

In a second study, the transamination of some selected ketones was studied at larger scale.

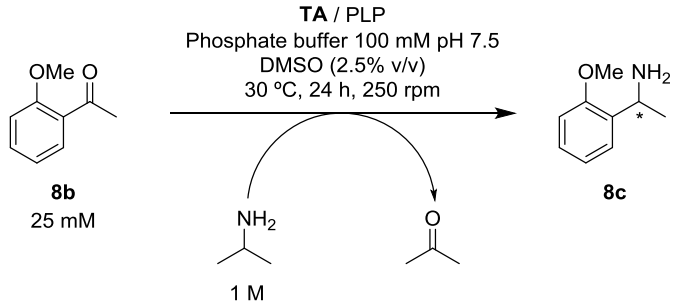
In a tube [(19 x 130 x 3) mm], the corresponding ketone **9b**, **11b**, **12b**, or **14b** (25 mM, 0.08 mmol) was dissolved in DMSO (2.5% v/v, 80 µL). Then, phosphate buffer 100 mM pH 7.5 (3.12 mL, 1 mM PLP, 1 M isopropylamine) and the commercially available transaminase (12 mg) were added. The reaction was shaken at 30 ºC and 250 rpm for 24 h and stopped by the addition of an aqueous NaOH 10 M solution (3 mL). Then, the mixture was extracted with EtOAc (5 mL) and the organic layer was separated by centrifugation (3 min, 4,900 rpm). This centrifugation protocol was performed twice. The organic layers were combined and dried over Na_2SO_4. Conversions were determined by GC and enantiomeric excess by chiral GC or HPLC.

The results from transaminase-catalyzed screenings with selected ketones are listed below.

*VI.2. Enzymatic screening for transaminase-catalyzed reactions of the prochiral ketone **8b***

The following conversions and enantiomeric excess were obtained following the procedures previously described (Table S3).

Table S3. Selected results obtained for the enzymatic transamination of **8b** using isopropylamine and commercially available transaminases. Transaminases later selected for the bienzymatic sequential strategy appear in bold font.



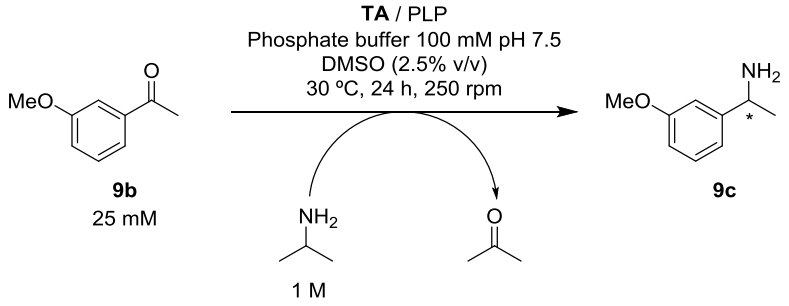
Entry[a]	Enzyme	*c* (%)[b]	*ee* (%)[c]
1	ATA-200	98	>99 (*S*)
2	ATA-237	98	>99 (*S*)
3	ATA-251	98	>99 (*S*)
4	ATA-254	98	>99 (*S*)
5	**ATA-256**	**98**	**>99 (*S*)**
6	ATA-260	98	>99 (*S*)
7	ATA-P1-B04	98	>99 (*S*)
8	ATA-013	97	87 (*R*)
9	ATA-025	98	96 (*R*)
10	ATA-113	98	96 (*S*)
11	ATA-P1-F03	97	>99 (*S*)
12	ATA-P1-G05	98	>99 (*S*)
13	ATA-024	98	96 (*R*)
14	**ATA-033**	**98**	**98 (*R*)**
15	ATA-P1-A06	99	90 (*S*)
16	ATA-P1-G06	98	95 (*S*)

[a] Transaminase-catalyzed reactions were performed at 0.0125 mmol scale.
[b] Conversions values measured by GC analysis.
[c] Enantiomeric excess values were determined by chiral HPLC analysis as the acetamide derivatives.

*VI.3. Enzymatic screening for transaminase-catalyzed reactions of the prochiral ketone **9b***

The following conversions and enantiomeric excess were obtained following the procedures previously described (Table S4).

Table S4. Selected results obtained for the enzymatic transamination of **9b** using isopropylamine and commercially available transaminases. Transaminase later selected for the bienzymatic sequential strategy appears in bold font.



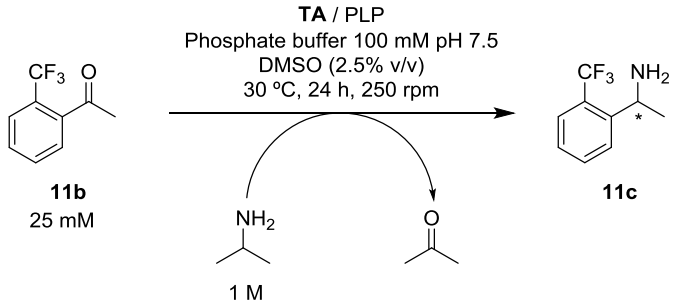
Entry	Enzyme	*c* (%)[a]	*ee* (%)[b]
1[c]	ATA-200	70	>99 (*S*)
2[c]	ATA-251	65	>99 (*S*)
3[c]	ATA-254	65	>99 (*S*)
4[c]	ATA-024	72	81 (*R*)
5[c]	ATA-P1-A06	72	73 (*S*)
6[d]	ATA-200	72	>99 (*S*)
7[d]	ATA-251	73	>99 (*S*)
8[d]	**ATA-254**	**74**	**>99 (*S*)**

[a] Conversions values measured by GC analysis.
[b] Enantiomeric excess values were determined by chiral GC analysis as the acetamide derivatives.
[c] Transaminase-catalyzed reactions were performed at 0.0125 mmol scale.
[d] Transaminase-catalyzed reactions were performed at 0.08 mmol scale.

*VI.4. Enzymatic screening for transaminase-catalyzed reactions of the prochiral ketone **11b***

The following conversions and enantiomeric excess were obtained following the procedures previously described (Table S5).

Table S5. Selected results obtained for the enzymatic transamination of **11b** using isopropylamine and commercially available transaminases. Transaminase later selected for the bienzymatic sequential strategy appears in bold font.



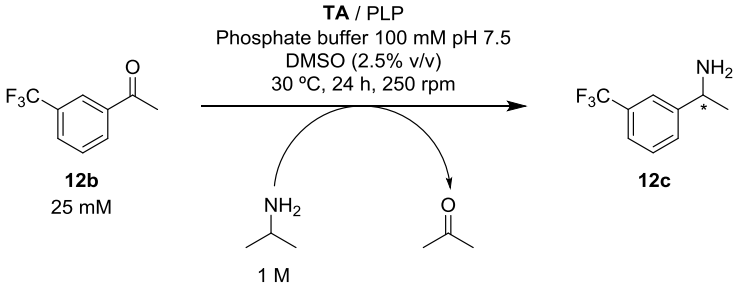
Entry	Enzyme	*c* (%)[a]	*ee* (%)[b]
1[c]	ATA-113	95	>99 (*S*)
2[c]	ATA-024	91	>99 (*R*)
3[c]	ATA-033	89	>99 (*R*)
4[d]	ATA-113	71	>99 (*S*)
5[d]	**ATA-024**	**96**	**>99 (*R*)**
6[d]	ATA-033	73	>99 (*R*)

[a] Conversions values measured by GC analysis.
[b] Enantiomeric excess values were determined by chiral HPLC analysis as the acetamide derivatives.
[c] Transaminase-catalyzed reactions were performed at 0.0125 mmol scale.
[d] Transaminase-catalyzed reactions were performed at 0.08 mmol scale.

*VI.5. Enzymatic screening for transaminase-catalyzed reactions of the prochiral ketone **12b***

The following conversions and enantiomeric excess were obtained following the procedures previously described (Table S6).

Table S6. Selected results obtained for the enzymatic transamination of **12b** using isopropylamine and commercially available transaminases. Transaminase later selected for the bienzymatic sequential strategy appears in bold font.



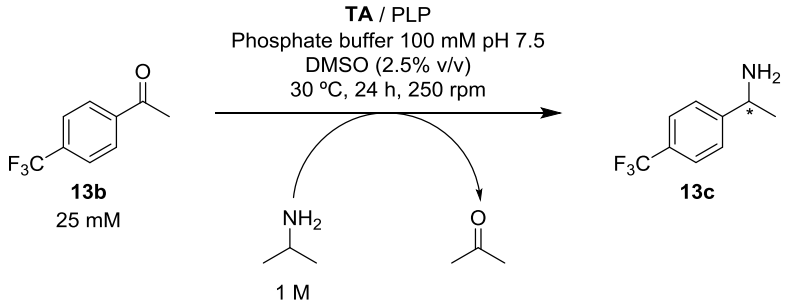
Entry	Enzyme	*c* (%)[a]	*ee* (%)[b]
1[c]	ATA-237	66	>99 (*S*)
2[c]	ATA-251	70	>99 (*S*)
3[c]	ATA-254	69	>99 (*S*)
4[c]	ATA-256	72	>99 (*S*)
5[c]	ATA-260	68	>99 (*S*)
6[c]	ATA-415	73	89 (*R*)
7[c]	ATA-P1-B04	66	71 (*S*)
8[c]	ATA-013	67	85 (*R*)
9[c]	ATA-025	74	96 (*R*)
10[c]	ATA-113	70	70 (*S*)
11[c]	ATA-024	74	92 (*R*)
12[c]	ATA-033	77	96 (*R*)
13[c]	ATA-P1-G06	74	87 (*S*)
14[d]	ATA-237	63	>99 (*S*)
15[d]	**ATA-251**	**71**	**>99 (*S*)**
16[d]	ATA-254	62	>99 (*S*)
17[d]	ATA-256	66	>99 (*S*)
18[d]	ATA-260	59	>99 (*S*)

[a] Conversions values measured by GC analysis.
[b] Enantiomeric excess values were determined by chiral GC analysis as the acetamide derivatives.
[c] Transaminase-catalyzed reactions were performed at 0.0125 mmol scale.
[d] Transaminase-catalyzed reactions were performed at 0.08 mmol scale.

*VI.6. Enzymatic screening for transaminase-catalyzed reactions of the prochiral ketone **13b***

The following conversions and enantiomeric excess were obtained following the procedure previously described (Table S7).

Table S7. Selected results obtained for the enzymatic transamination of **13b** using isopropylamine and commercially available transaminases. Transaminases later selected for the bienzymatic sequential strategy appear in bold font.



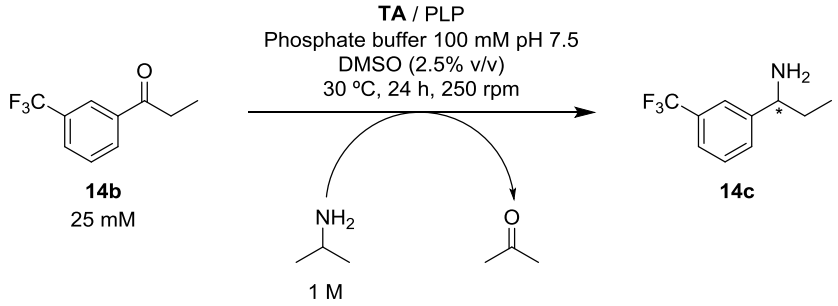
Entry[a]	Enzyme	*c* (%)[b]	*ee* (%)[c]
1	ATA-200	72	>99 (*S*)
2	ATA-237	81	>99 (*S*)
3	**ATA-251**	**86**	**>99 (*S*)**
4	ATA-254	85	>99 (*S*)
5	ATA-256	85	>99 (*S*)
6	ATA-303	86	85 (*R*)
7	ATA-412	79	93 (*R*)
8	ATA-415	84	>99 (*R*)
9	ATA-P1-B04	85	74 (*S*)
10	ATA-013	81	>99 (*R*)
11	**ATA-025**	**86**	**>99 (*R*)**
12	ATA-117	91	39 (*R*)
13	ATA-P2-A07	92	89 (*R*)
14	ATA-024	86	97 (*R*)
15	ATA-033	76	95 (*R*)
16	ATA-P1-A06	82	73 (*S*)
17	ATA-P1-G06	89	60 (*S*)

[a] Transaminase-catalyzed reactions were performed at 0.0125 mmol scale.
[b] Conversions values measured by GC analysis.
[c] Enantiomeric excess values were determined by chiral GC analysis as the acetamide derivatives.

*VI.7. Enzymatic screening for transaminase-catalyzed reactions of the prochiral ketone **14b***

The following conversions and enantiomeric excess were obtained following the procedures previously described (Table S8).

Table S8. Selected results obtained for the enzymatic transamination of **14b** using isopropylamine and commercially available transaminases. Transaminase later selected for the bienzymatic sequential strategy appears in bold font.

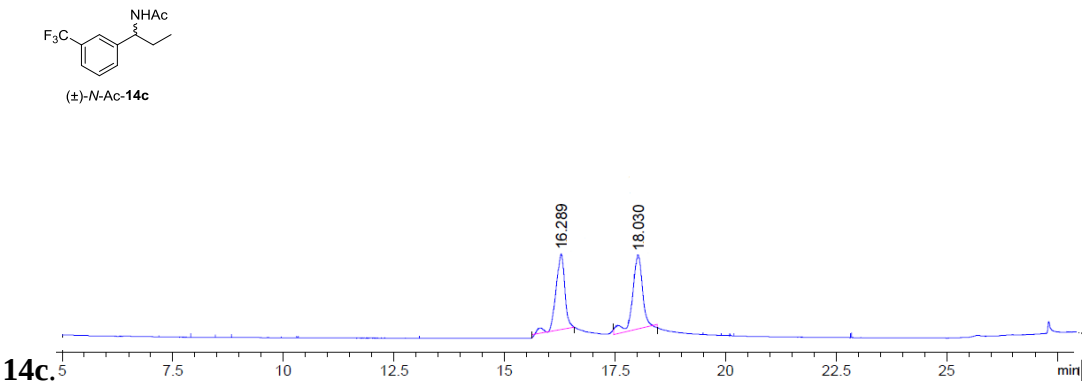


Entry	Enzyme	*c* (%)[a]	*ee* (%)[b]
1[c]	ATA-237	67	>99 (*S*)
2[c]	ATA-415	71	>99 (*R*)
3[c]	ATA-025	69	>99 (*R*)
4[d]	**ATA-237**	**71**	**>99 (*S*)**
5[d]	ATA-415	50	>99 (*R*)
6[d]	ATA-025	40	>99 (*R*)

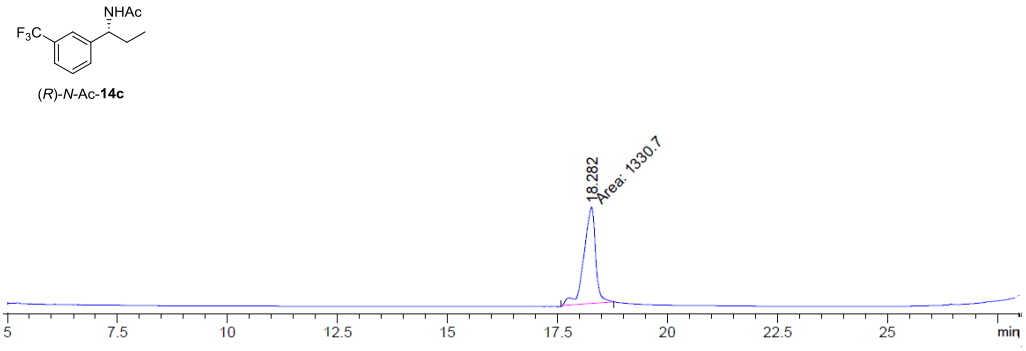
[a] Conversions values measured by GC analysis.
[b] Enantiomeric excess values were determined by chiral GC analysis as the acetamide derivatives.
[c] Transaminase-catalyzed reactions were performed at 0.0125 mmol scale.
[d] Transaminase-catalyzed reactions were performed at 0.08 mmol scale.

Figure S2. Analytical separation by chiral GC for: a) (±)-*N*-Ac-**14c**, b) (*R*)-*N*-Ac-**14c** obtained from the enzymatic transamination of ketone **14b** using ATA-025, and c) (*S*)-*N*-Ac-**14c** obtained using ATA-237.

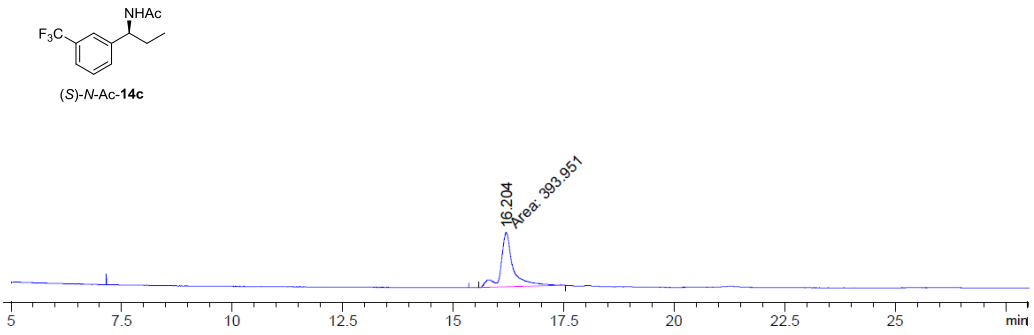
a) (±)-*N*-Ac-**14c**.



b) (*R*)-*N*-Ac-**14c**. Obtained from ATA-025-catalyzed reaction.



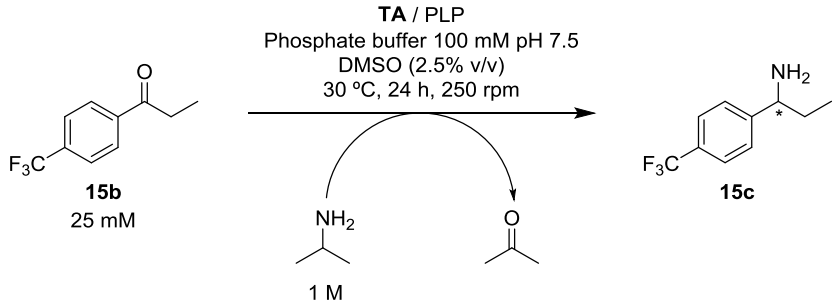
c) (*S*)-*N*-Ac-**14c**. Obtained from ATA-237-catalyzed reaction.



*VI.8. Enzymatic screening for transaminase catalyzed reactions of the prochiral ketone **15b***

The following conversions and enantiomeric excess were obtained following the procedures previously described (Table S9).

Table S9. Selected results obtained for the enzymatic transamination of **15b** using isopropylamine and commercially available transaminases. Transaminases later selected for the bienzymatic sequential strategy appear in bold font.

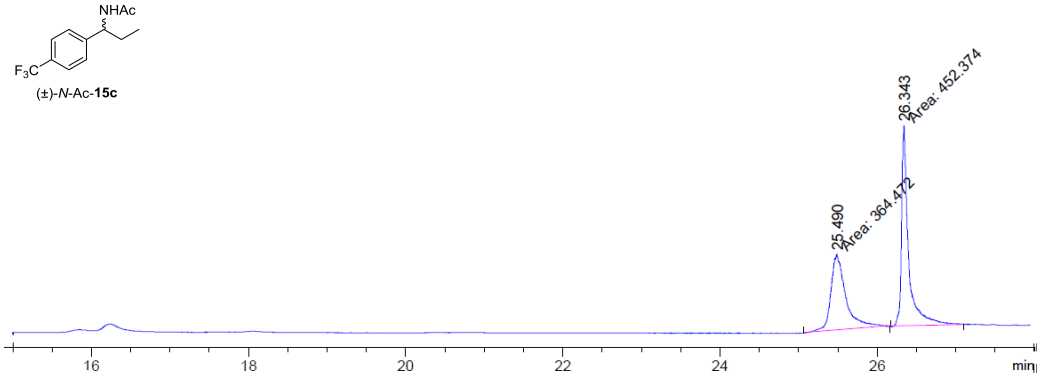


Entry[a]	Enzyme	*c* (%)[b]	*ee* (%)[c]
1	**ATA-237**	**74**	**>99 (*S*)**
2	ATA-415	70	96 (*R*)
3	**ATA-025**	**78**	**>99 (*R*)**

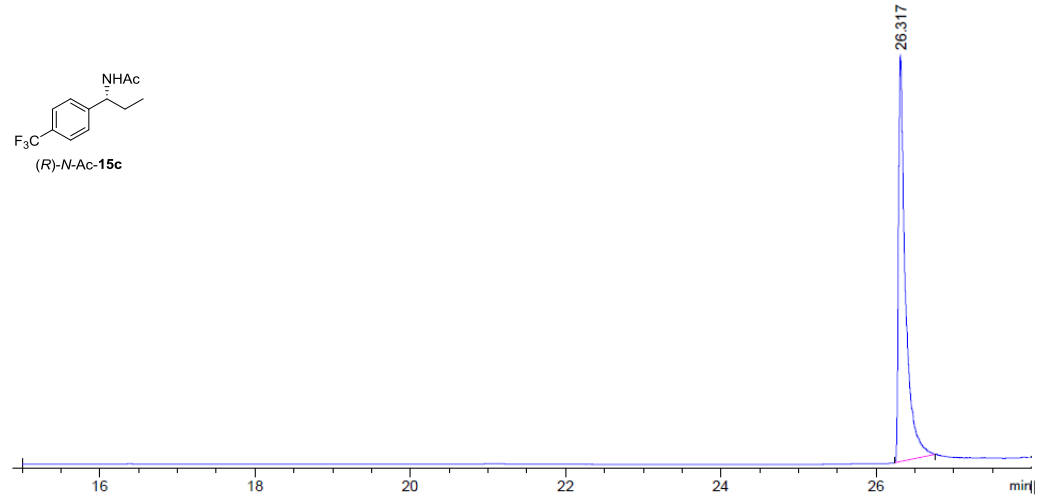
[a] Transaminase-catalyzed reactions were performed at 0.0125 mmol scale.
[b] Conversions values measured by GC analysis.
[c] Enantiomeric excess values were determined by chiral GC analysis as the acetamide derivatives.

Figure S3. Analytical separation by chiral GC for: a) (±)-*N*-Ac-**15c**, b) (*R*)-*N*-Ac-**15c** obtained from the enzymatic transamination of ketone **15b** using ATA-025, and c) (*S*)-*N*-Ac-**15c** obtained using ATA-237.

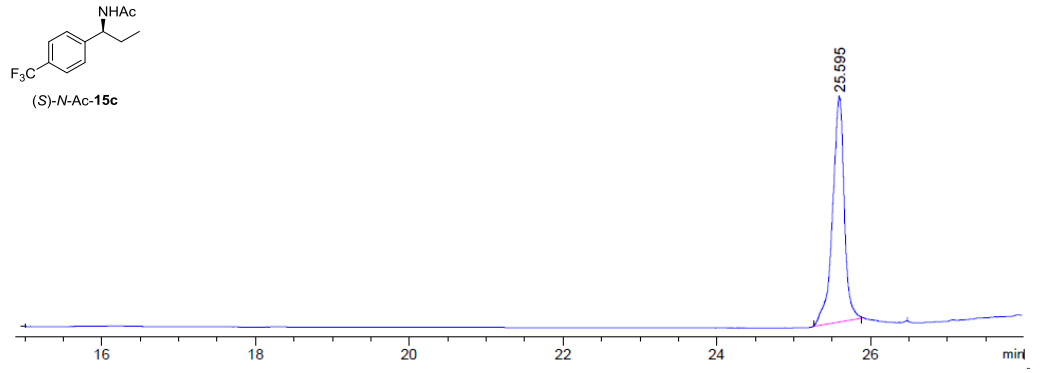
a) (±)-*N*-Ac-**15c**.



b) (*R*)-*N*-Ac-**15c**. Obtained from ATA-025-catalyzed reaction.

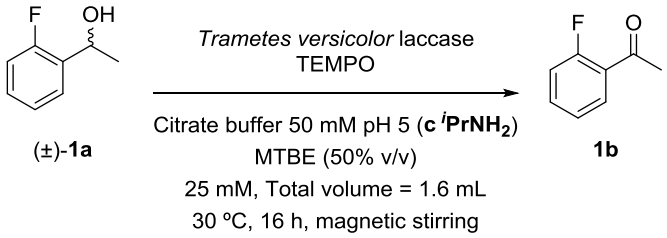


c) (*S*)-*N*-Ac-**15c**. Obtained from ATA-237-catalyzed reaction.



VII. Optimization of the bienzymatic process

VII.1. Influence of the presence of isopropylamine in the oxidation step

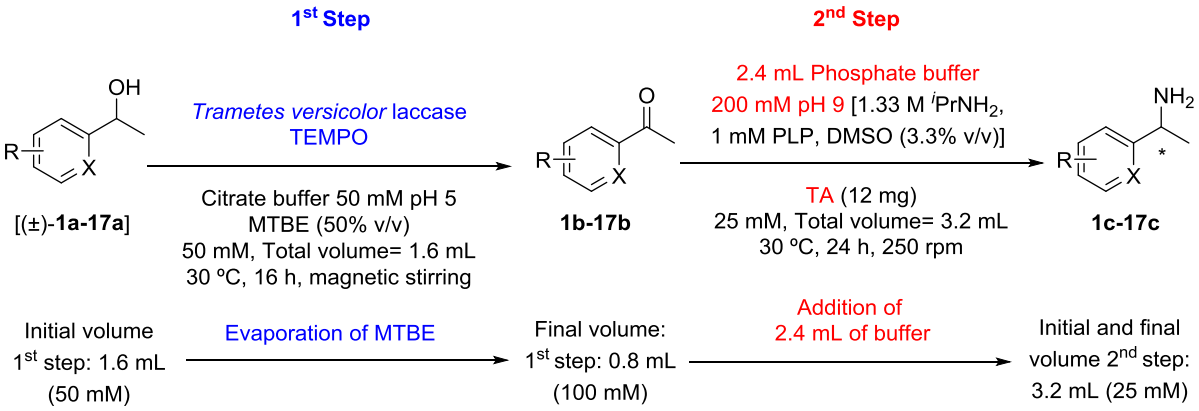


Scheme S1

Searching for adequate reaction conditions for the bienzymatic sequential process, the influence of the isopropylamine in the oxidation step was studied (Scheme S1).

A solution of citrate buffer 50 mM pH 5 containing different concentrations of isopropylamine [50-1000 mM] was prepared. Then, in an open-to-air sealed tube, the racemic alcohol **1a** (5.6 mg, 0.04 mmol, 25 mM) was dissolved in a biphasic media composed by the previously prepared citrate buffer (containing isopropylamine) and MTBE (50% v/v, for a total volume of 1.6 mL). Afterwards, TEMPO was added (2 mg, 33 mol%) to the solution. The mixture was stirred for a few minutes to dissolve all the reagents, and finally, the laccase (2.5 U) was added. The reaction mixture was stirred for 16 h at 30 ºC, observing the complete evaporation of MTBE along this time. Finally, it was extracted with EtOAc (2 x 2 mL). The organic layers were combined, dried over Na_2SO_4, and an aliquot was taken to determine the composition of the reaction mixture by GC analysis (Results are shown in Table 2 of the main manuscript).

VII.2. General procedure for the sequential one-pot two-step synthesis of enantioenriched amines from racemic alcohols



Scheme S2

The enantioenriched amines **1c-17c** were obtained according to the following procedure after two sequential reactions involving a laccase/TEMPO oxidation in the first step and a transaminase-catalyzed reaction in the second one, leading in a one-pot process to the desired optically active amines (*S*)- or (*R*)-**1c-17c** depending on the transaminase selectivity (Scheme S2):

In an open-to-air sealed tube, TEMPO (4.1 mg, 33 mol%) was added to a solution of the racemic alcohol **1a-17a** (0.08 mmol, 50 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* (5 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 0.8 mL, and in consequence, the substrate concentration increased from the initial 50 mM to approximately 100 mM. To the resulting reaction crude, phosphate buffer 200 mM pH 9 (2.4 mL) containing isopropylamine (1.33 M), PLP (1 mM) and DMSO (3.3% v/v) was added, leading to approximately 25 mM, 1 M, 0.75 mM, and 2.5% v/v as substrate, isopropylamine, PLP, and DMSO final concentrations, respectively. 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. Finally, the corresponding commercially available transaminase (12 mg) was added. The sealed tube was closed and the reaction was shaken at 30 ºC and 250 rpm for 24 h. After this time, the reaction was stopped by addition of an aqueous NaOH 10 M solution (3 mL).

Then, the mixture was extracted with EtOAc (5 mL) and the organic layer was separated by centrifugation (3 min, 4,900 rpm). This centrifugation protocol was performed twice and, finally, the organic layers were combined and dried over Na_2SO_4. Conversion and enantiomeric excess values into the corresponding enantioenriched amines **1-17c** were determined by GC analysis (Results are shown in Table 3 of the main manuscript).

*VII.3. Determination of the optical rotation of enantiopure **14c** and **15c***

The optical rotation of enantiopure amines (*S*)-**14c** and (*R*)-**15c** was determined for c= 1 in EtOH:

(*S*)-**14c**: $[\alpha]_D^{20} = -4.5$ (c= 1, EtOH), >99% *ee*

(*R*)-**15c**: $[\alpha]_D^{20} = +2.5$ (c= 1, EtOH), >99% *ee*

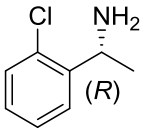
VIII. Scaling-up reactions

VIII.1. Using isopropylamine as amine donor for the transamination step

In an open-to-air sealed tube (30 x 140 x 5 mm), TEMPO (33 mol%) was added to a solution of the racemic alcohols **4a** or **9a** (100 mg, 50 mM) in a biphasic mixture of an oxygen-saturated citrate buffer 50 mM pH 5 and MTBE (50% v/v, total volume: 12.8 mL for **4a**; 13.1 mL for **9a**). The reaction mixture was stirred for a few minutes to dissolve all the reagents, and then the laccase from *Trametes versicolor* (40 U for **4a**; 41 U for **9a**) was added. The reaction was stirred for 16 h at 30 ºC, observing the complete evaporation of MTBE along this time. The resulting crude was diluted by the addition of phosphate buffer 200 mM pH 9 (19.2 mL for **4a**; 19.7 mL for **9a**) containing isopropylamine (1.33 M), PLP (1 mM), and MeCN (3.3% v/v), leading to approximately 25 mM, 1 M, 0.75 mM, and 2.5% v/v as substrate, isopropylamine, PLP, and MeCN final concentrations, respectively. The final pH of the reaction after the addition of the previously described phosphate buffer was approximately 7.5, therefore further pH adjustment was not required. Finally, ATA-025 (75 mg for **4a**) or ATA-254 (75 mg for **9a**) was added. The sealed tube was closed and the reaction was shaken at 30 ºC and 250 rpm for 24 h. The conversion to the corresponding amine was determined by taking a sample (200 µL) of the reaction mixture which was basified with an aqueous NaOH 10 M solution (100 µL) and extracted as shown above, leading to >99% and 67% conversion for **4c** and **9c**, respectively (measured by GC). At this

point, the solution was centrifuged at 4,900 rpm for 7 min. The supernatant was decanted, the crude was acidified with an aqueous HCl 3 M solution (5 mL) and extracted with EtOAc (3 x 25 mL) discarding the organic layer in order to eliminate the remaining starting material. Then, the aqueous phase was basified with an aqueous NaOH 10 M solution (8 mL) and extracted with EtOAc (3 x 35 mL). For (*R*)-**4c**, as a consequence of the total conversion observed, only the basic treatment was performed. The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure providing (*R*)-**4c** (93% yield, >99% *ee*) and (*S*)-**9c** (62% yield, 98% *ee*). Characterization data are given below:

(*R*)-1-(2-Chlorophenyl)ethanamine [(*R*)-4c].

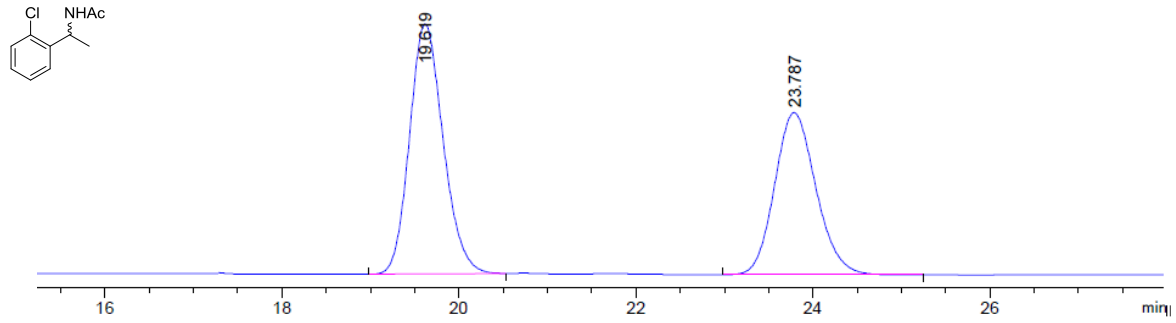


Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.52 (*dd*, 1H, *J*= 7.7, 1.9 Hz), 7.28 (*m*, 2H), 7.14 (*apparent td*, 1H, *J*= 7.7, 1.7 Hz), 4.53 (*q*, 1H, *J*= 6.5 Hz), 1.55 (*br s*, 2H), 1.38 (*d*, 3H, *J*= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 144.6, 132.6, 129.6, 127.8, 127.1, 126.3, 47.6, 23.7.

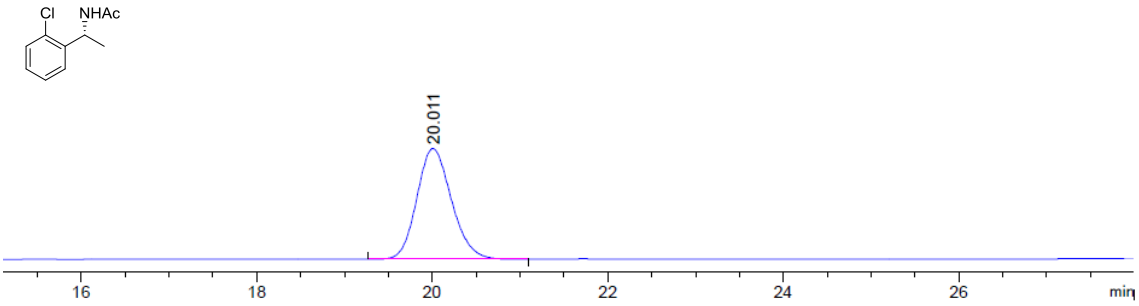
For determining the enantiomeric excess, the enantioenriched amine (*R*)-**4c** was acetylated using a standard procedure, and its HPLC chromatogram was compared to the one obtained from the acetylated racemic compound (Figure S4).

Figure S4. Analytical separation by HPLC for racemic (above) and enantiopure (below) *N*-Ac-**4c** obtained at 100-mg scale in the two-step sequential process starting from the racemic alcohol **4a**, and using ATA-025 and isopropylamine (1 M) as amine donor in the transamination step.

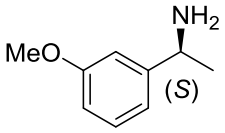
(±)-*N*-Ac-**4c**.



(*R*)-*N*-Ac-**4c**. Obtained after the one-pot two-step process using ATA-025 and isopropylamine in the transamination step.



(*S*)-1-(3-Methoxyphenyl)ethanamine [(*S*)-9c].

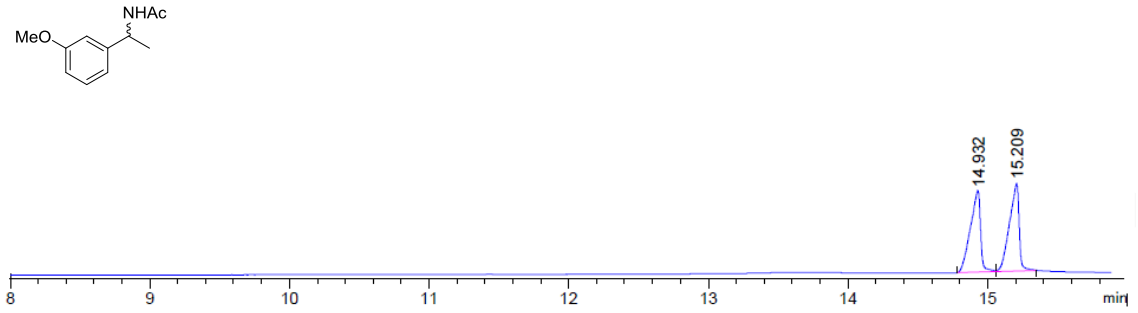


Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26 (*apparent t*, 1H, *J*= 8.2 Hz), 6.93 (*m*, 2H), 6.78 (*m*, 1H), 4.09 (*q*, 1H, *J*= 6.6 Hz), 3.82 (*s*, 3H), 1.80 (*br s*, 2H), 1.39 (*d*, 3H, *J*= 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.8, 149.4, 129.5, 118.0, 112.1, 111.4, 55.2, 51.3, 25.5.

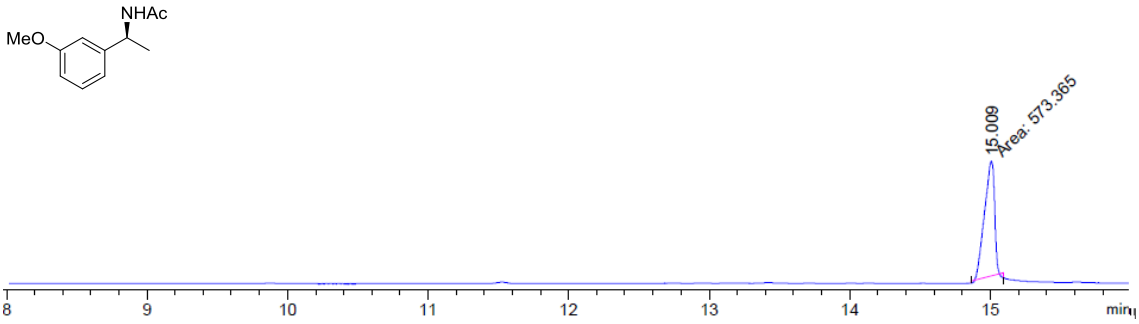
For determining the enantiomeric excess, the enantioenriched amine (*S*)-**9c** was acetylated using a standard procedure, and its GC chromatogram was compared to the one obtained from the acetylated racemic compound (Figure S5).

Figure S5. Analytical separation by GC for racemic (above) and enantiopure (below) *N*-Ac-**9c** obtained at 100-mg scale in the one-pot two-step sequential process starting from the racemic alcohol **9a**, and using ATA-254 and isopropylamine (1 M) as amine donor in the transamination step.

(±)-*N*-Ac-**9c**



(*S*)-*N*-Ac-**9c**. Obtained from the one-pot two-step process using ATA-254 and isopropylamine in the transamination step.



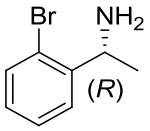
VIII.2. Using cis*-but-2-ene-1,4-diamine as amine donor for the transamination step*

According to the protocol previously described by us in the transaminase-catalyzed reactions using *cis*-but-2-ene-1,4-diamine as amine donor instead of isopropylamine,[3] 1.5 equivalents of this compound were used in the transamination step for the sequential transformation of the racemic alcohol **6a** into the enantiopure amine (*R*)-**6c** at 100 mg substrate scale:

In an open-to-air sealed tube (30 x 140 x 5 mm), TEMPO (16 mg, 0.09 mmol, 20 mol%) was added to a solution of the racemic alcohol **6a** (100 mg, 0.050 mmol, 50 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 9.9 mL). The reaction mixture was stirred for a few minutes to dissolve all the reagents, and then the laccase from *Trametes versicolor* (30 U) was added. The reaction was stirred for 16 h at 30 ºC, observing the complete evaporation of MTBE along this time. The resulting crude was diluted by the addition of phosphate buffer 200 mM pH 9 (15 mL), containing *cis*-but-2-ene-1,4-diamine (1.5 equivalents, 37.5 mM), PLP (1 mM), and MeCN (3.3% v/v), leading to approximately 25 mM, 0.75 mM, and 2.5% v/v as substrate, PLP, and MeCN final concentrations, respectively. The final pH of the reaction after the addition of the previously described phosphate buffer was approximately 7.5, therefore further pH adjustment was not required. Finally, ATA-033 (75 mg) was added. The sealed tube was closed and the reaction was shaken at 30 ºC and 250 rpm for 48 h. At the end, as previously described, the initial yellowish reaction turned completely into black color due to the formation of polypyrrole. The conversion to the amine was determined by taking a sample (200 µL) of the reaction mixture which was basified with an aqueous NaOH 10 M solution (100 µL) and extracted as shown above, leading to 97% (measured by GC). At this point, the solution was centrifuged at 4,900 rpm for 7 min. The supernatant was decanted, acidified with an aqueous HCl 3 M solution (5 mL), and extracted with EtOAc (3 x 25 mL) discarding the organic layer, in order to remove the small amount of the remaining starting material. Then, the aqueous phase was basified with an aqueous NaOH 10 M solution (8 mL) and extracted with EtOAc (3 x 35 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure, isolating (*R*)-**6c** (91% yield, >99% *ee*). Characterization data are given below:

(*R*)-1-(2-Bromophenyl)ethanamine [(*R*)-6c].

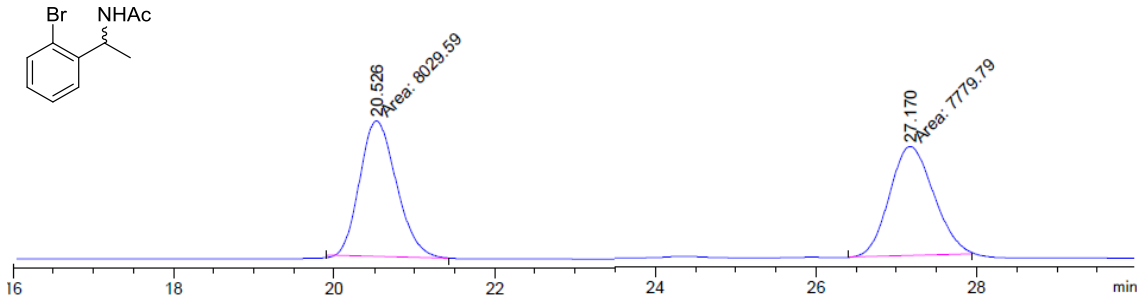


Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.53 (*d*, 2H, *J*= 7.7 Hz), 7.33 (*apparent t*, 1H, *J*= 7.4 Hz), 7.09 (*apparent t*, 1H, *J*= 7.2 Hz), 4.52 (*q*, 1H, *J*= 6.6 Hz), 1.71 (*br s*, 2H), 1.40 (*d*, 3H, *J*= 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.1, 132.9, 128.2, 127.8, 126.5, 123.1, 50.0, 23.7.

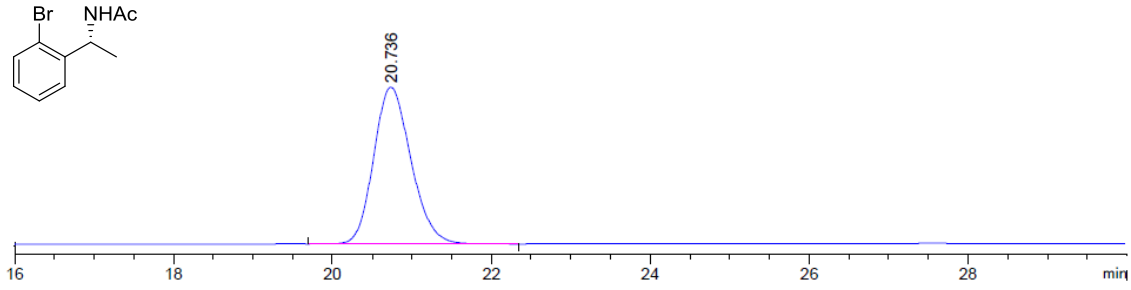
For determining the enantiomeric excess, the enantioenriched amine (*R*)-**6c** was acetylated using a standard procedure, and its HPLC chromatogram was compared to the one obtained from the acetylated racemic compound (Figure S6).

Figure S6. Analytical separation by HPLC for racemic (above) and enantiopure (below) *N*-Ac-**6c** obtained at 100-mg scale in the one-pot two-step sequential process starting from the racemic alcohol **6a** and using ATA-033 and 1.5 equivalents of *cis*-but-2-ene-1,4-diamine as amine donor in the transamination step.

(±)-*N*-Ac-**6c**.



(*R*)-*N*-Ac-**6c**. Obtained from the one-pot two-step process using ATA-033 and *cis*-but-2-ene-1,4-diamine in the transamination step.



IX. Environmental assessment using EATOS

E-factor calculations (Figure S7) were performed using the EATOS (v. 1.1) software tool.[4] All reactions were treated as proceeding to the corresponding isolated yields, hence all losses in yield are accounted for as 'unknown by-products'. The work-up protocols have not been taking into account for this comparison as it was assumed to be the same for all three methodologies. The Excel file used for these calculations is also available as ESI material.

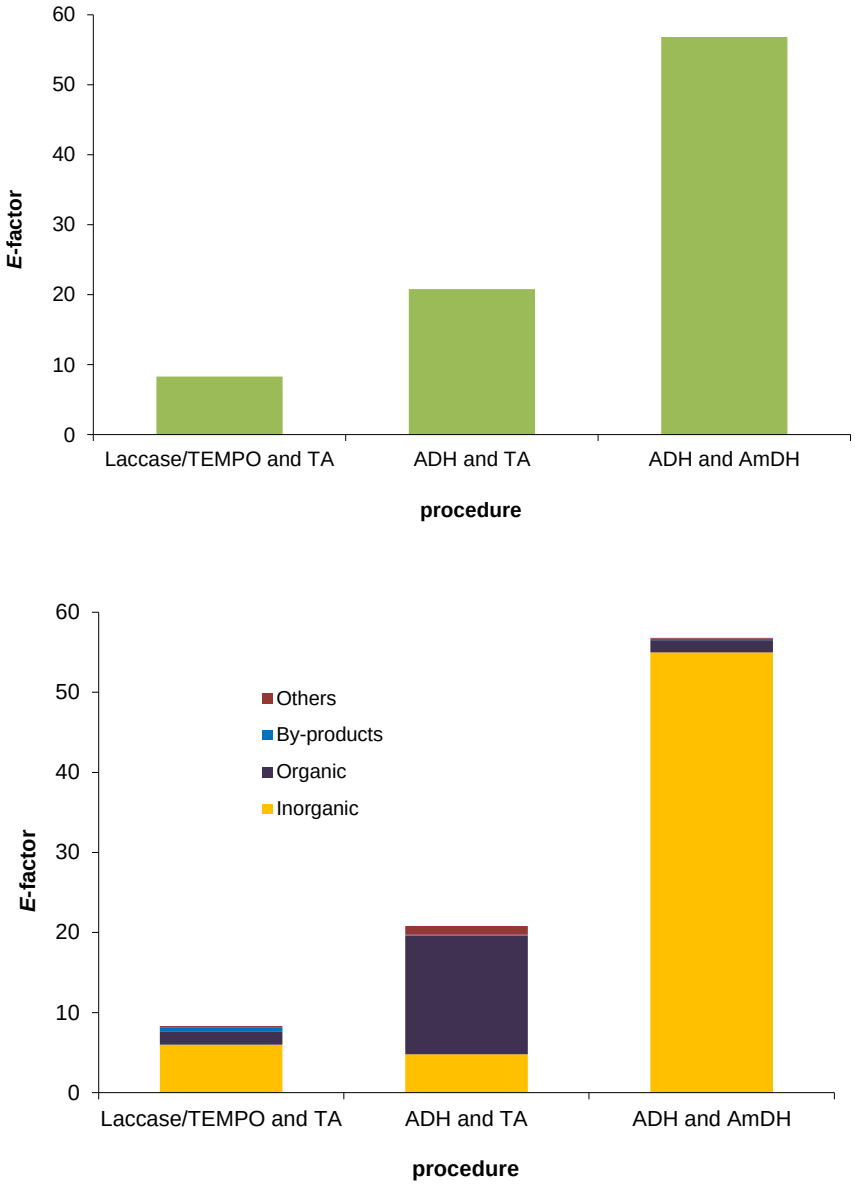


Figure S7. Contribution to *E*-factor (excluding solvents) for each procedure to synthesize an enantioenriched amine from a racemic alcohol.

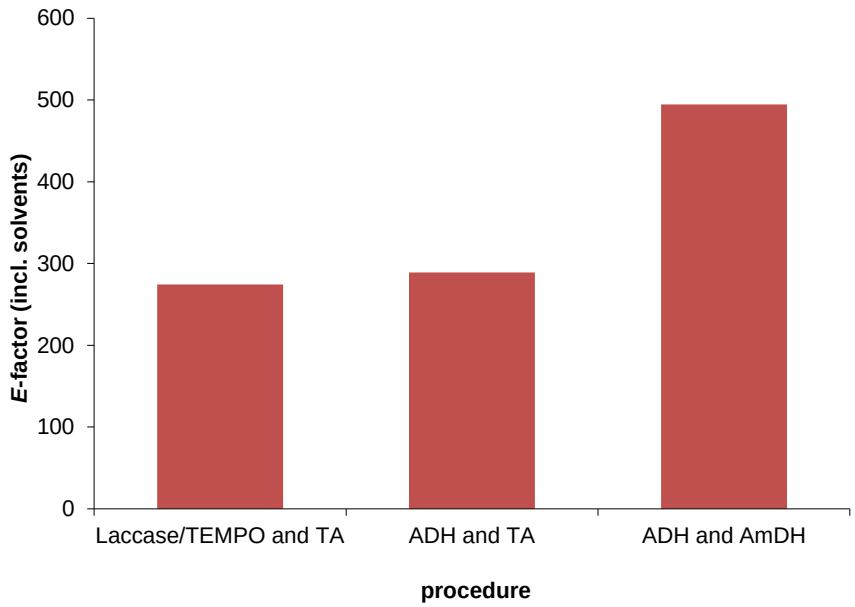


Figure S8. Contribution to *E*-factor (including solvents) for each procedure to synthesize an enantioenriched amine from a racemic alcohol.

X. Analytical data

X.1. GC analyses for the determination of conversion values

The following GC columns were used:

A: Hewlett Packard HP-1 (30 m x 0.32 m x 0.25 µm, 12.2 psi N_2).

B: CP-ChiraSil-DEX CB (25 m x 0.32 x 0.25 µm, 12.2 psi N_2).

C: RT-BetaDEXe (30 m x 0.25 m x 0.25 µm, 12.2 psi N_2).

Table S12. Retention times for compounds **1-17** obtained by GC analysis.

Compound	Column	Program[a]	Retention time (min)		
			alcohol	ketone	amine
1	**A**	60/10/20/180/5	4.8	3.5	4.2
2	**B**	80/26/40/200/3	27.7;27.9[b]	13.3	18.9;20.2[c]
3	**B**	70/10/20/180/5	15.0;15.1[b]	13.5	14.0
4	**A**	80/10/40/180/0	5.6	4.2	5.0
5	**A**	50/0/2/180/0	13.6	11.5	12.6
6	**A**	80/10/40/180/0	9.1	6.9	8.1
7	**A**	50/0/2/180/0	18.3	15.8	16.9
8	**C**	90/0/2.5/140/3/20/180/5	23.2;23.9[b]	20.9	19.5
9	**B**	130/5/5/135/6/20/180/0	13.9	8.5	9.2
10	**B**	110/0/2.5/135/0/10/180/4	12.3	6.3	8.4
11	**B**	110/0/2.5/135/0/10/180/4	9.2;9.5[b]	4.5	4.9
12	**B**	110/0/2.5/135/0/10/180/4	9.4;10.0[b]	4.3	5.6
13	**B**	110/0/2.5/135/0/10/180/4	10.8;11.4[b]	5.5	7.5
14	**A**	50/0/2.5/65/5/20/200/0	11.5	8.7	9.5
15	**A**	50/0/2.5/65/5/20/200/0	11.3	8.5	9.8
16	**B**	90/0/1/125/0/10/180/4	30.0	17.2	18.6
17	**B**	90/0/2.5/120/0/40/200/3	11.0	6.8	10.0

[a] GC programme: initial temp. (ºC) / time (min) / ramp (ºC/min) / temp. (ºC) / time (min) / ramp (ºC/min) / final temp. (ºC) / time (min).

[b] The enantiomers of these alcohols were separated when the total conversions were determined in the CP-ChiraSil-DEX CB column: **first enantiomer**;**second enantiomer**.

[c] The enantiomers of **2c** were separated when the total conversions were determined in the CP-ChiraSil-DEX CB column: **first enantiomer**;**second enantiomer**.

X.2. Analyses for the determination of enantiomeric excess

X.2.1. Product derivatization for *ee* determination

For the enantiomeric excess determination of the obtained amines, it was necessary to measure them as *N*-acetamide derivatives (otherwise indicated). Therefore, a chemical acetylation was carried out using the following procedure: the amine obtained in the biotransformation crude (1 mg) was dissolved in EtOAc (1 mL) and placed in a 1.5 mL Eppendorf vial, where K_2CO_3 (10 mg) and acetic anhydride (5 drops) were added. The mixture was shaken at 30 ºC and 900 rpm for 1 h, and then an aqueous NaOH 10 M solution (200 µL) was added. The organic layer was separated by centrifugation (2 min, 13,000 rpm), dried over Na_2SO_4 and transferred to a GC glass vial for analysis. When HPLC was used, EtOAc was evaporated using a continuous flow of nitrogen, and the remaining residue was re-dissolved in hexane/2-PrOH (90:10 v/v), filtered and then injected in the HPLC.

X.2.2. GC analyses for *ee* determination

The column CP-Chirasil-DEX CB (25 m x 0.32 x 0.25 μm, 12.2 psi N_2) was used in all cases for the determination of enantiomeric excess.

Table S13. Retention times for the two amine enantiomers measured by chiral GC.

Compound	Program[a]	Retention time (min)	
		(*R*)	(*S*)
1c	90/5/2/150/0/40/200/3	30.5	30.1
2c	80/26/40/200/3	18.9[b]	20.2[b]
3c	135/20/10/200/2	28.1	27.8
5c	135/20/10/200/2	25.8	25.5
7c	135/20/10/200/2	28.1	27.8
9c	140/5/5/180/5	15.3	14.9
10c	90/5/2/160/0/5/200/2	36.0	35.4
12c	140/5/5/180/5	9.8	9.4
13c	140/5/5/180/5	15.5	11.1
14c	135/25/25/190/1	18.3	16.2
15c	135/25/25/190/1	26.3	25.6
16c	135/25/25/190/1	23.5	21.8
17c	90/5/2/150/0/40/200/3	32.9	31.6

[a] GC programme: initial temp. (ºC) / time (min) / ramp (ºC/min) / temp (ºC) / time (min) / ramp (ºC/min) / final temp. (ºC) / time (min).
[b] Enantiomeric excess measured as free amine.

X.2.3. HPLC analyses for *ee* determination

The following HPLC conditions were used:

A: Column Daicel Chiralpak IC (25 cm x 4.6 mm, 5 µm particle size); eluent: *n*-hexane / 2-PrOH (90:10), 40 ºC, flow 0.8 mL/min.

B: Column Daicel Chiralpak IC (25 cm x 4.6 mm, 5 µm particle size); eluent: *n*-hexane / 2-PrOH (90:10), 30 ºC, flow 0.8 mL/min.

C: Column Daicel Chiralpak AD-H (25 cm x 4.6 mm, 5 µm particle size); eluent: *n*-hexane / 2-PrOH (95:5), 30 ºC, flow 1.0 mL/min.

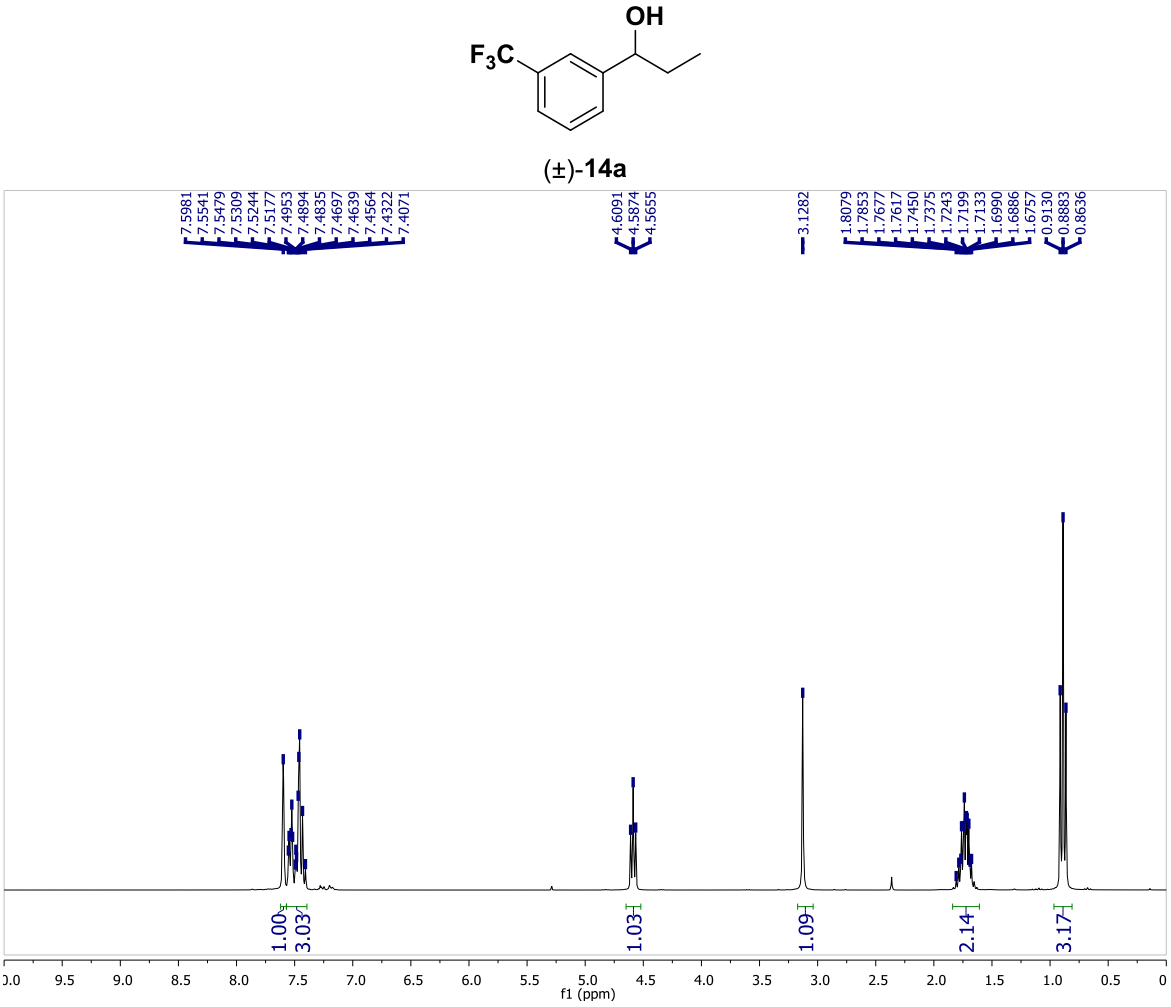
D: Column Daicel Chiralpak AD-H (25 cm x 4.6 mm, 5 µm particle size); eluent: *n*-hexane / 2-PrOH (95:5), 30 ºC, flow 0.8 mL/min.

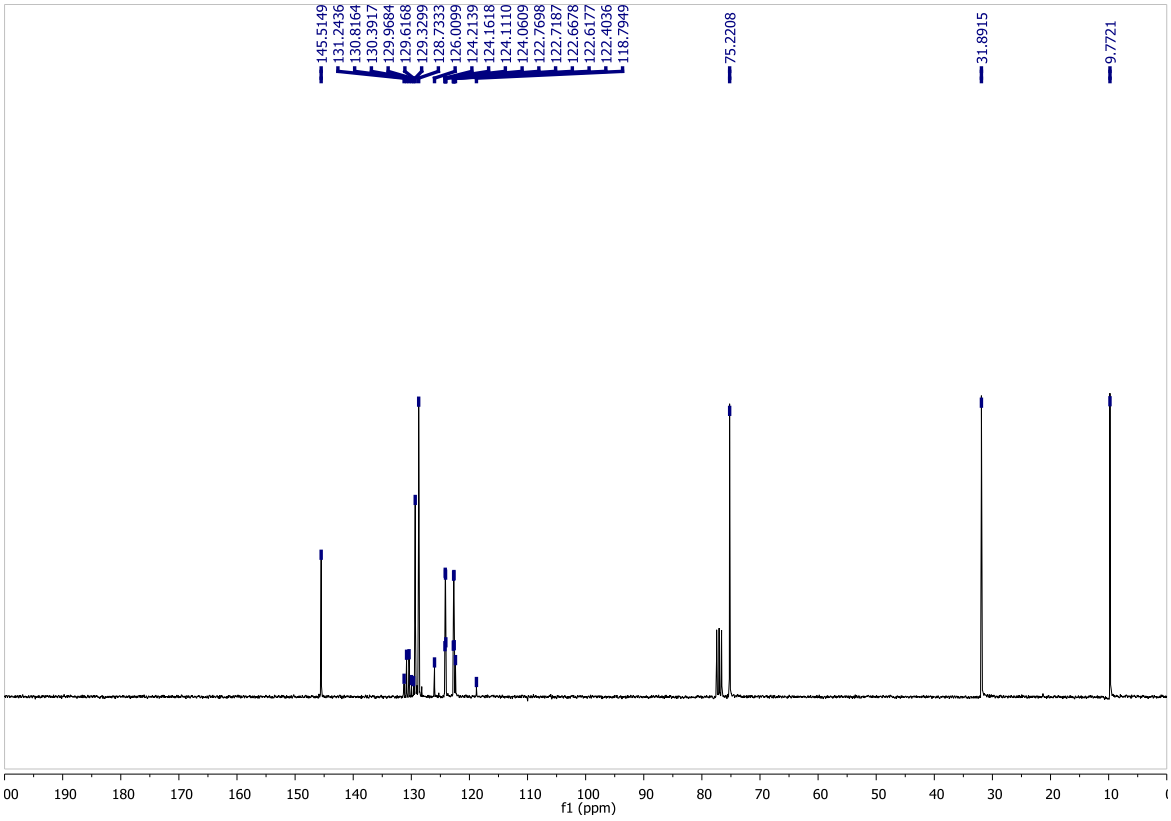
Table S14. Retention times for the two amine enantiomers measured by chiral HPLC.

Compound	Conditions	Retention time (min)[a]	
		(*R*)	(*S*)
4c	**A**	20.0	23.8
6c	**B**	20.5	27.1
8c	**C**	11.2	15.2
11c	**D**	9.1	12.1

[a] Measured as *N*-acetamide derivatives.

XI. NMR spectra

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124.1110
124.0609
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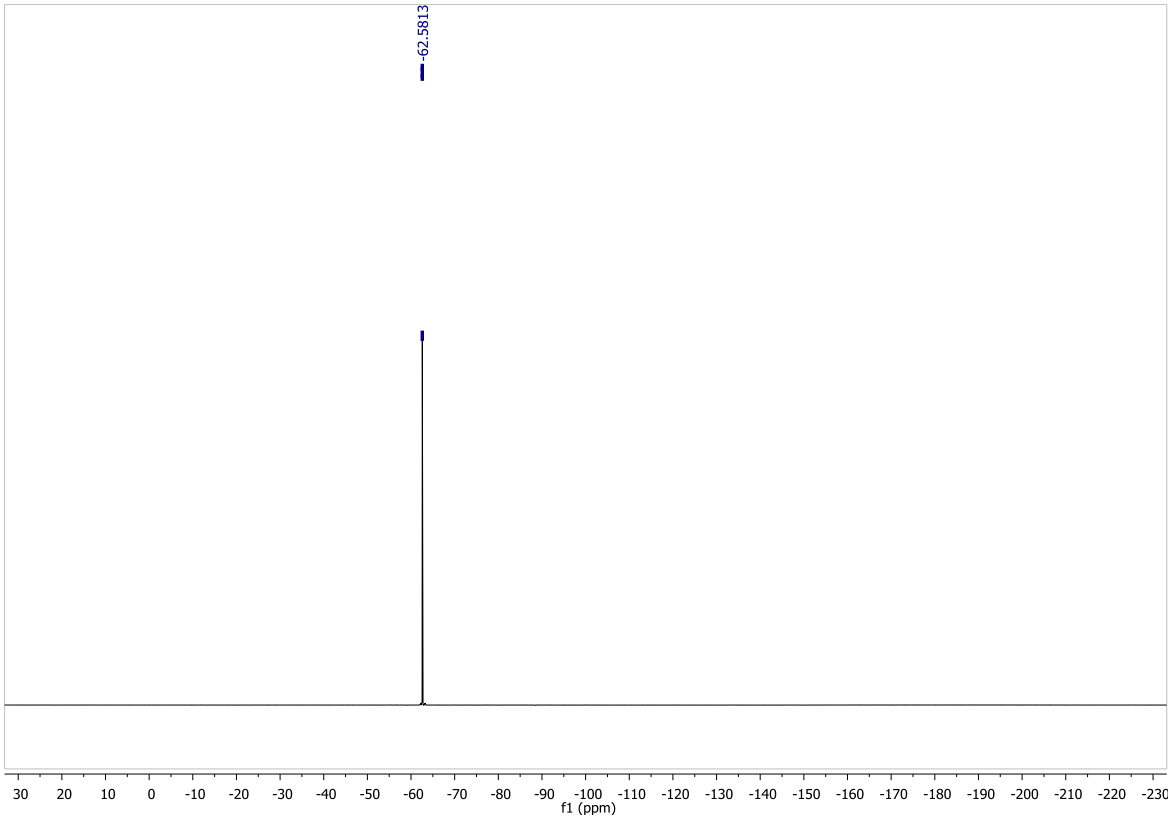
75.2208
31.8915
9.7721
f1 (ppm)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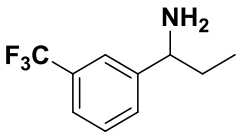
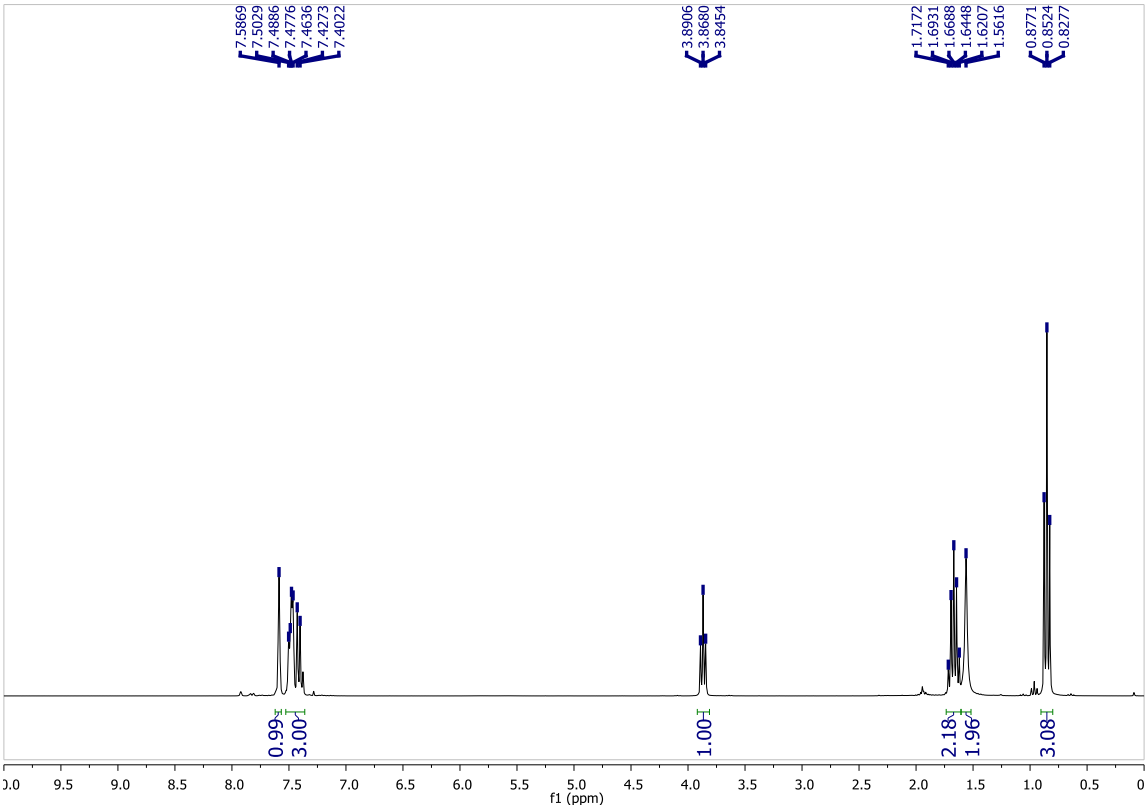

NH2
F3C

(±)-14c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1.6931
1.6688
1.6448
1.6207
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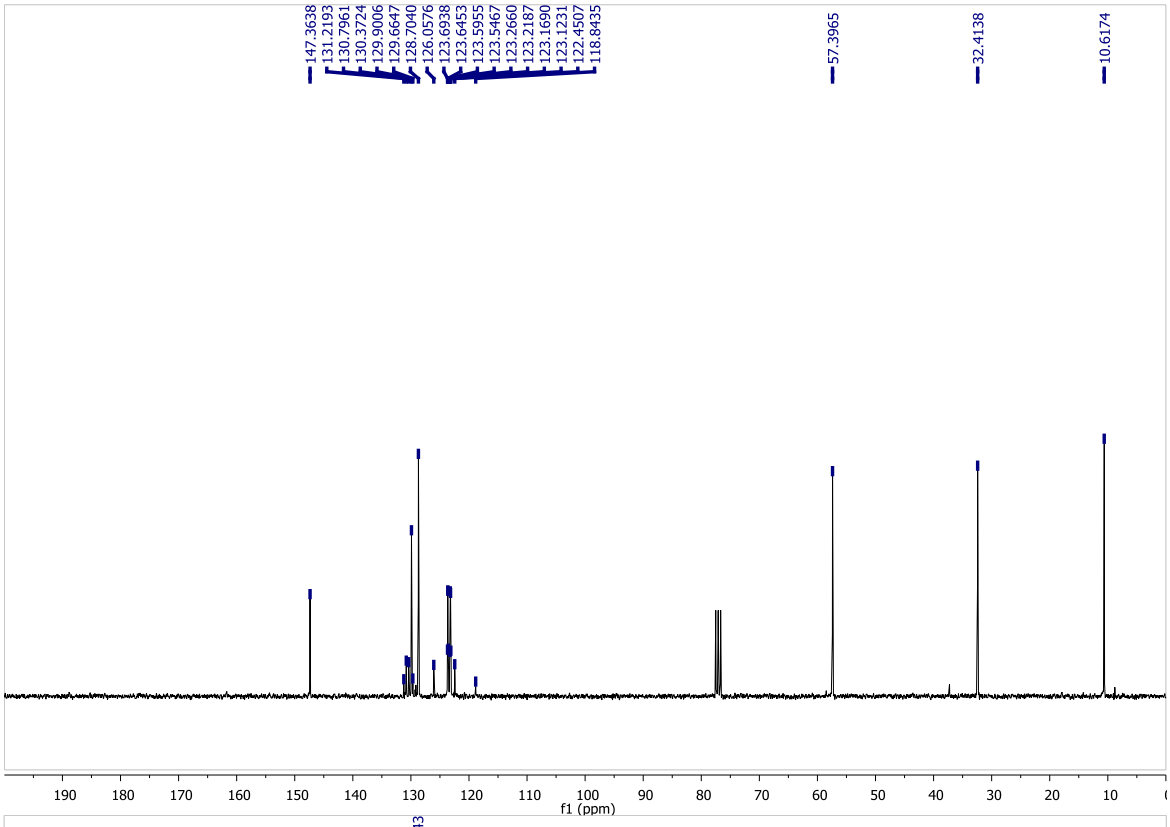
3.00
1.00
2.18
1.96
3.08
f1 (ppm)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123.5467
123.2660
123.2187
123.1690
123.1231
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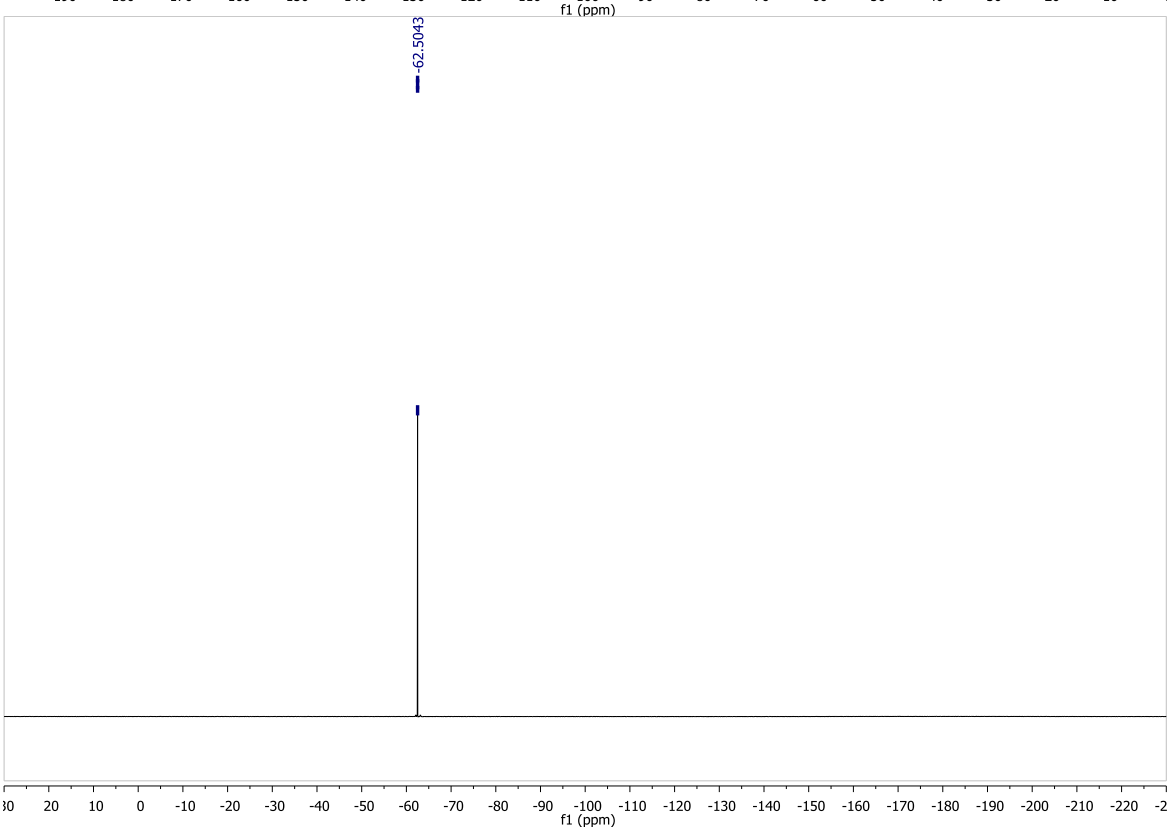
f1 (ppm)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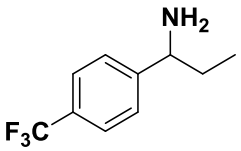
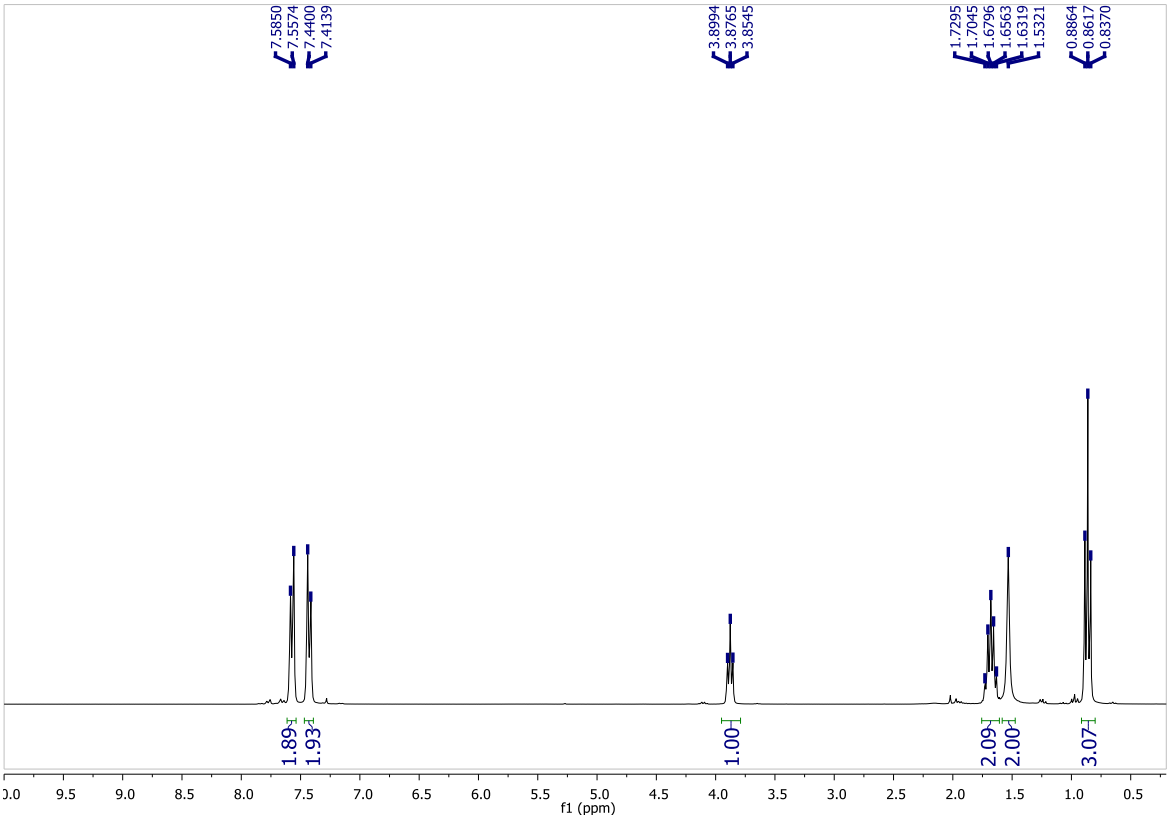

NH2
F3C

(±)-**15c**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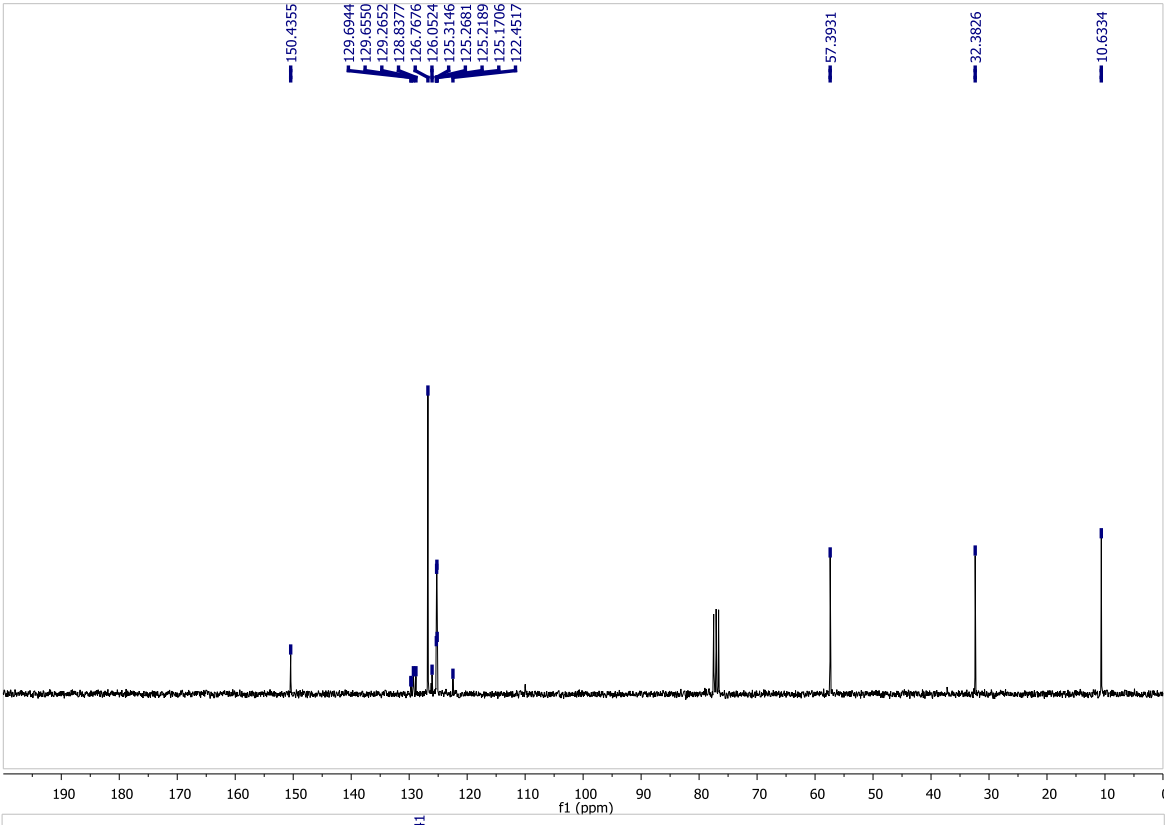
f1 (ppm)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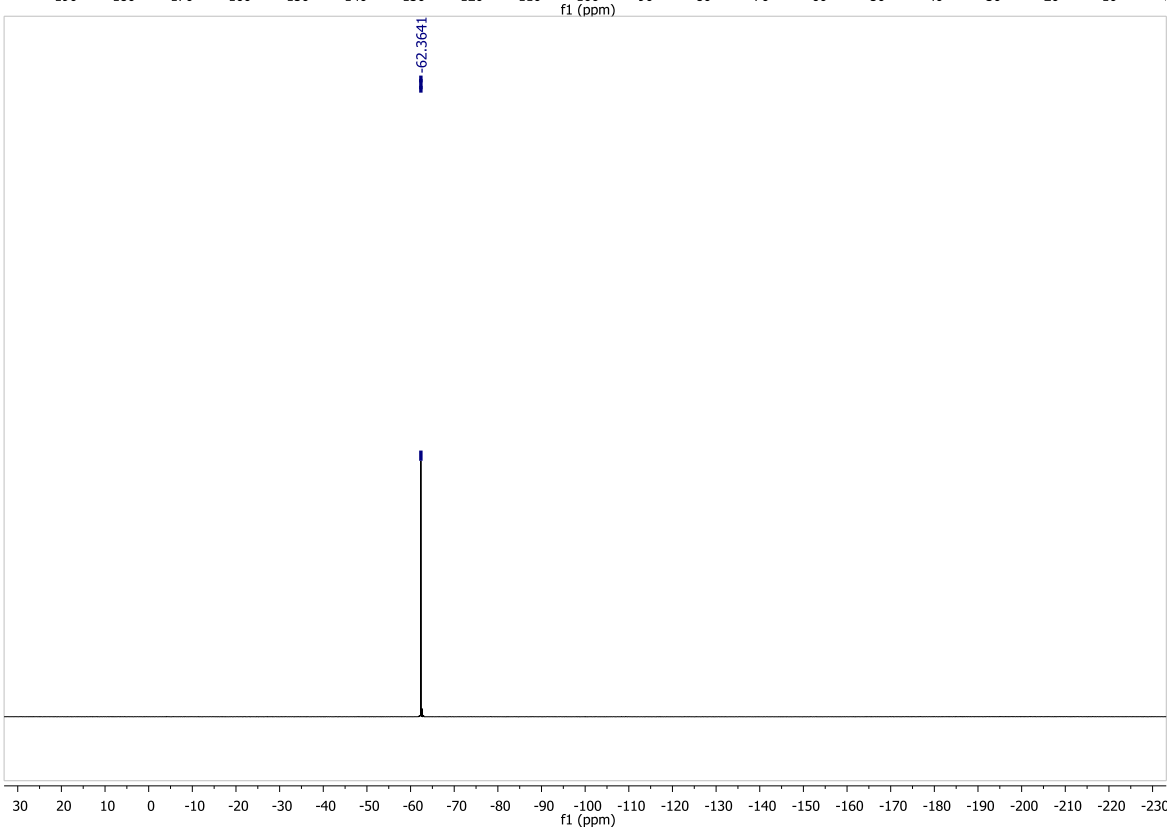
f1 (ppm)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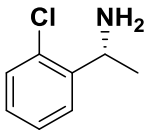
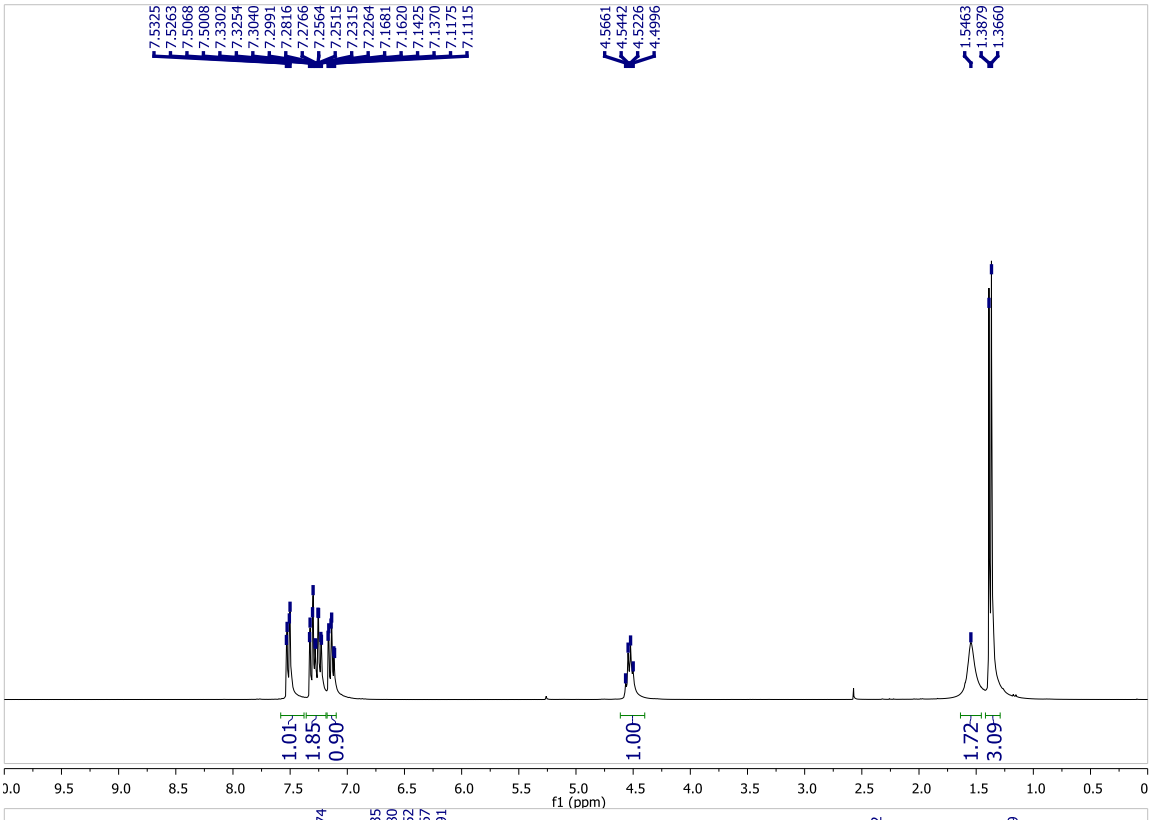

Cl
NH2

(*R*)-**4c**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7.2515
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7.1681
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7.1175
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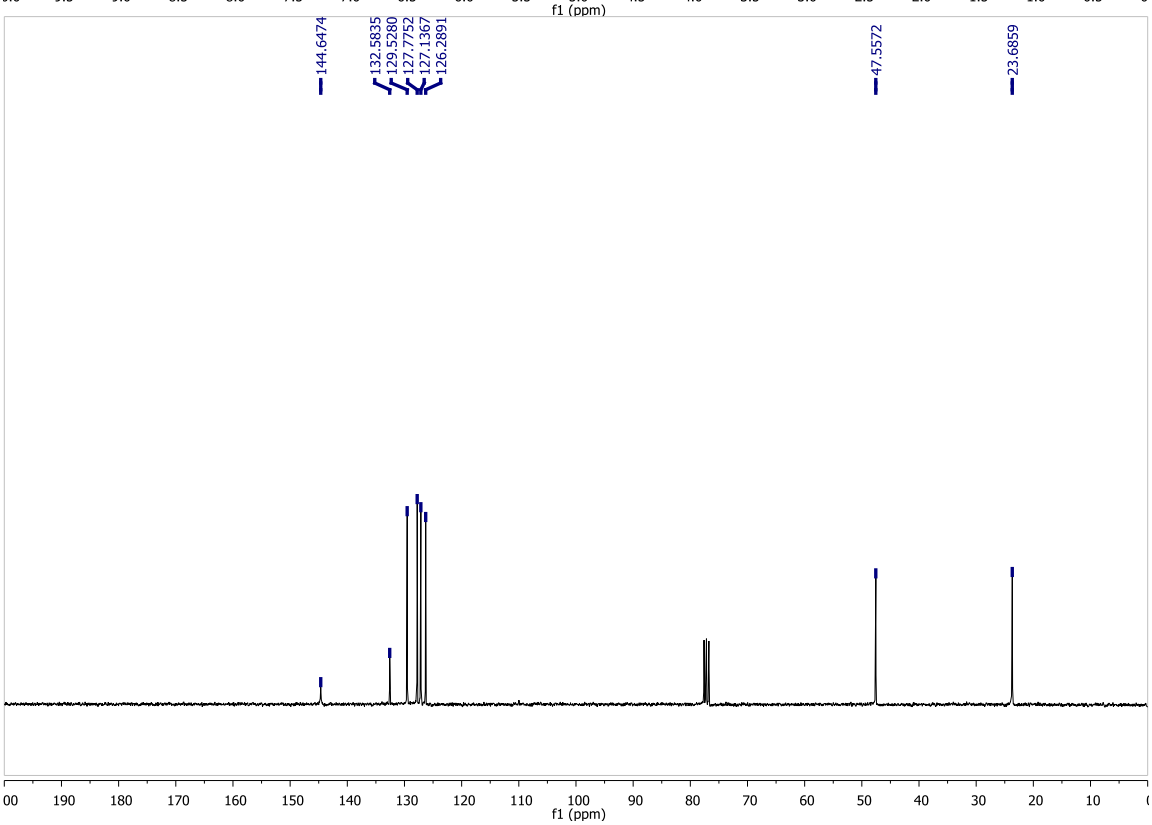
1.72
3.09
f1 (ppm)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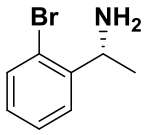
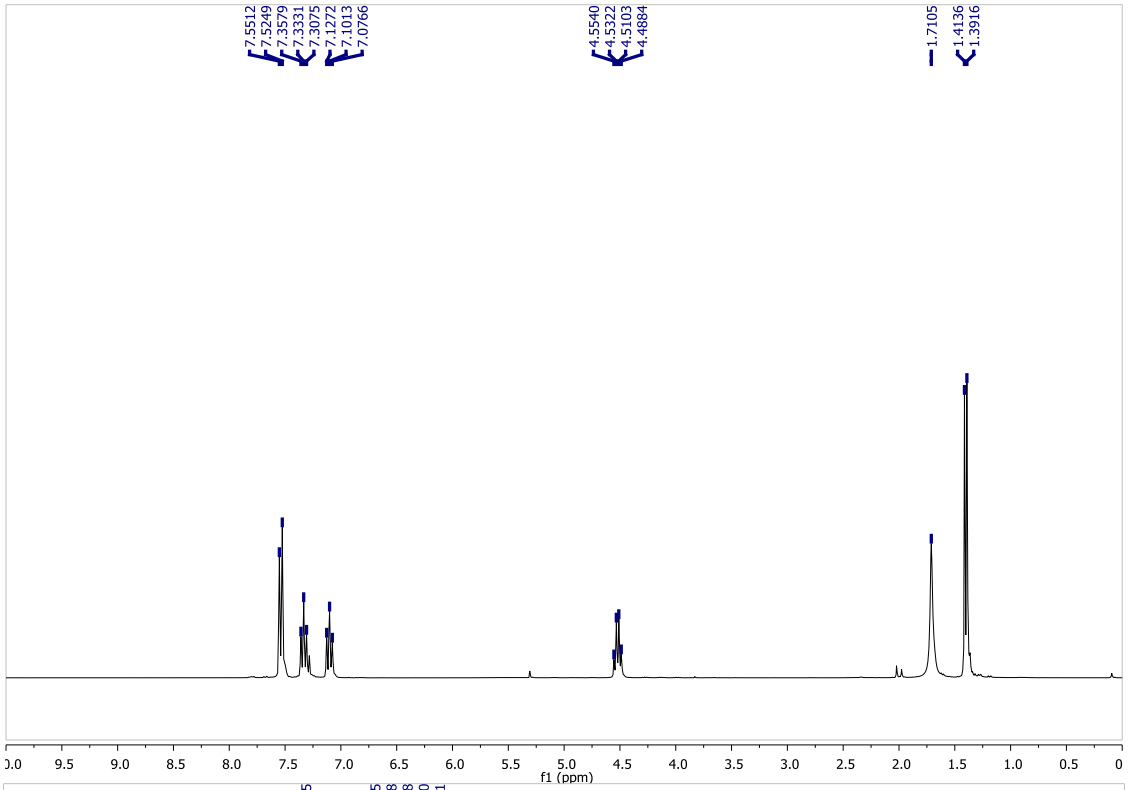

Br
NH2

(*R*)-**6c**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7.3331
7.3075
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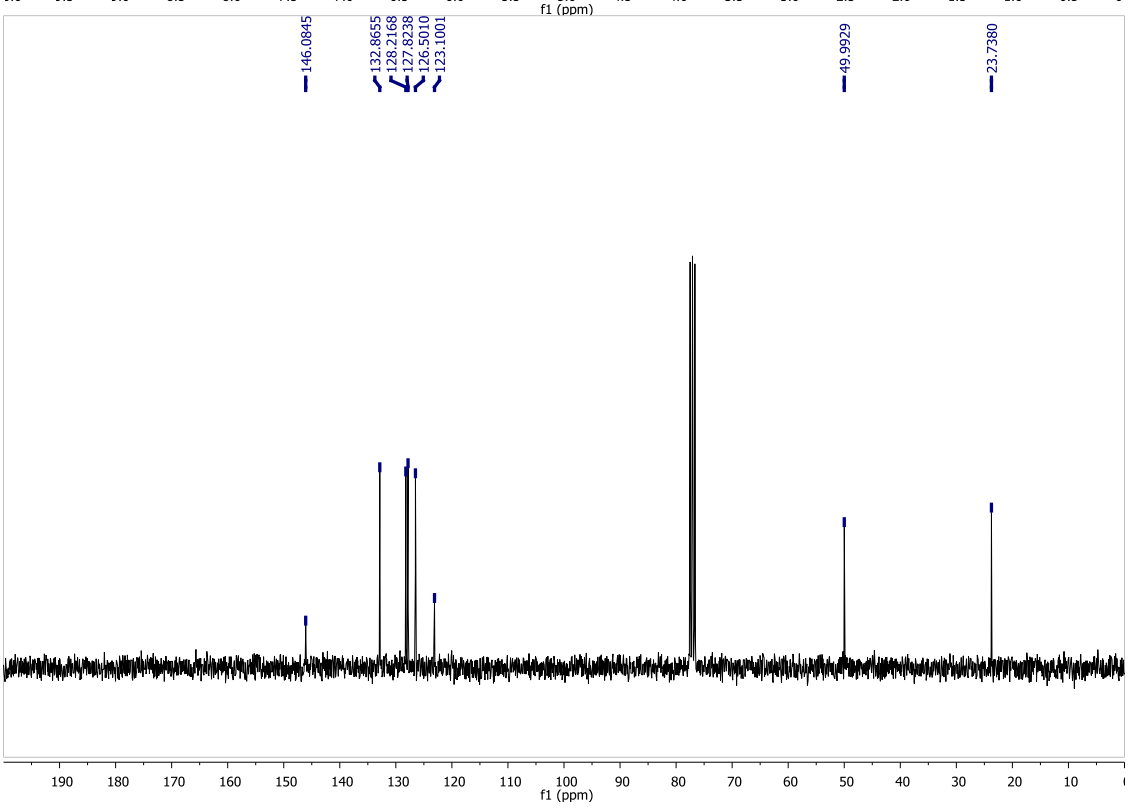
1.4136
1.3916
f1 (ppm)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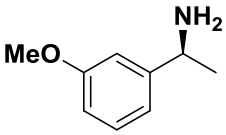
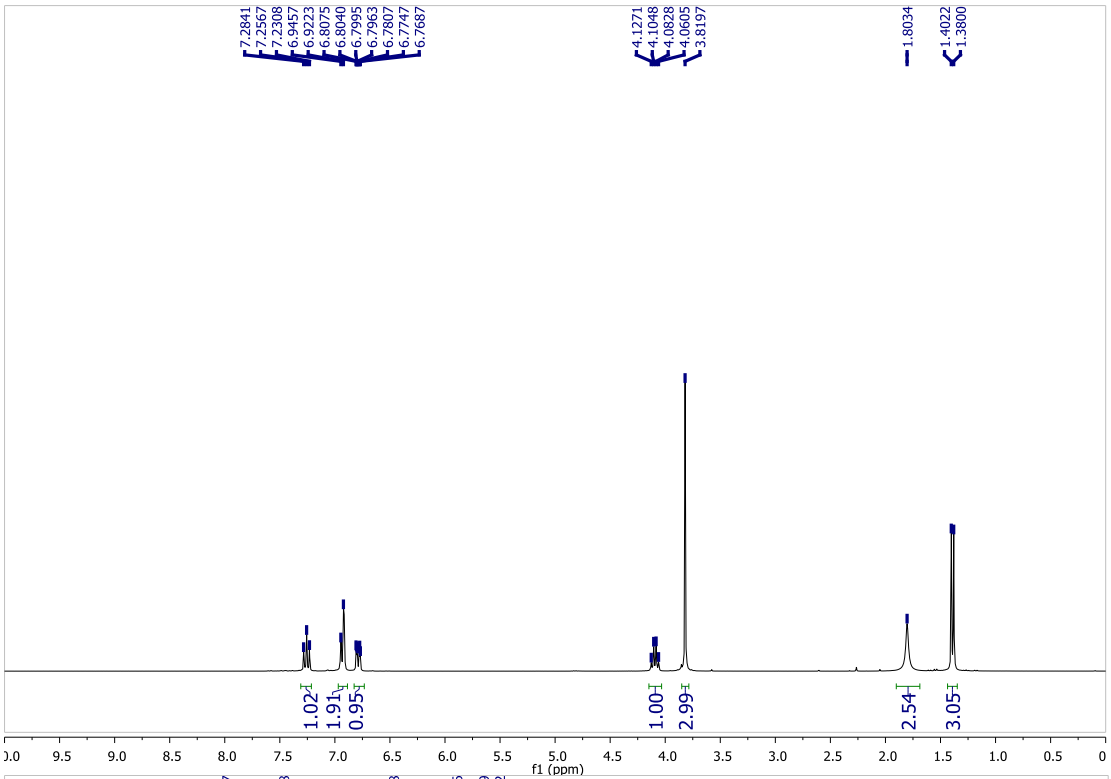
f1 (ppm)


NH2
MeO

(*S*)-**9c**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6.9223
6.8075
6.8040
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6.7963
6.7807
6.7747
6.7687
4.1271
4.1048
4.0828
4.0605
3.8197
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1.3800
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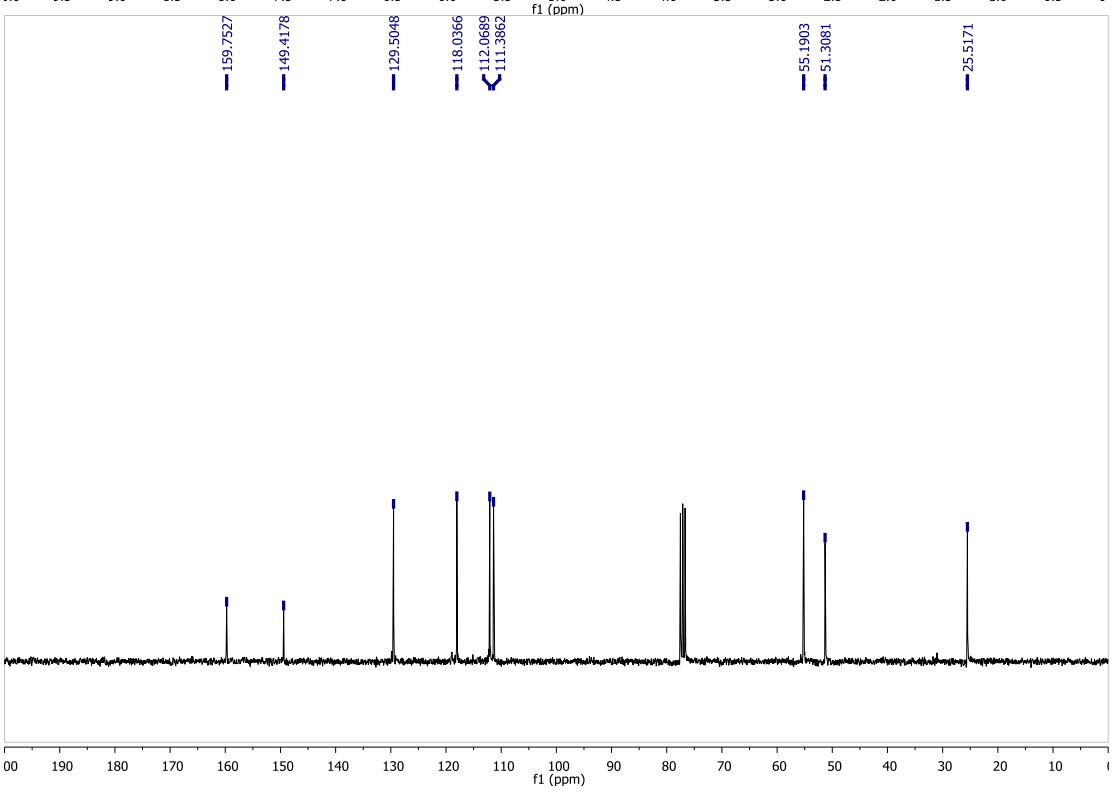
0.95
1.00
2.99
2.54
3.05
f1 (ppm)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129.5048
118.0366
112.0689
111.3862
55.1903
51.3081
25.5171
f1 (ppm)

XII. References

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4. a) M. Eissen and J. O. Metzger, *Chem.–Eur. J.*, 2002, **8**, 3580-3585; (b) EATOS: Environmental Assessment Tool for Organic Syntheses, http://www.metzger.chemie.uni-oldenburg.de/eatos/english.htm.