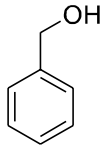
Table of contents

S1 Overview of compound numbers



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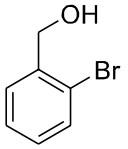

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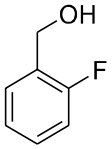

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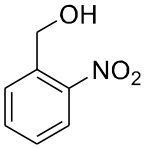

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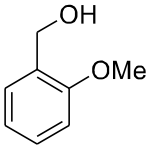

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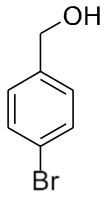

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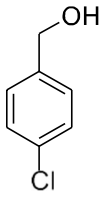

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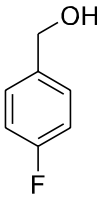

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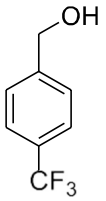

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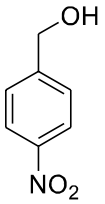

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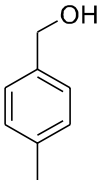

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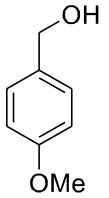

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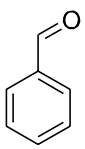

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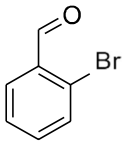

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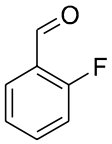

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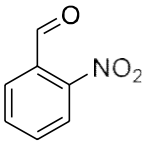

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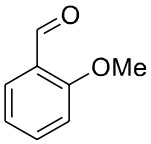

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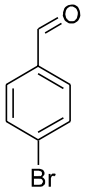

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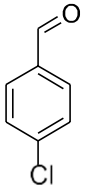

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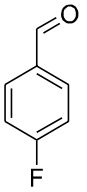

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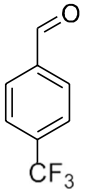

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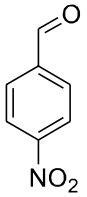

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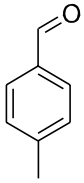

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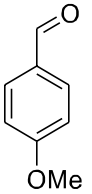
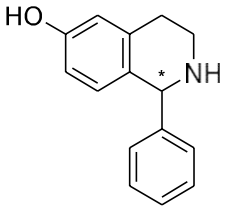


Fehler! Verweisquelle konnte nicht gefunden werden.**l**

Figure S1: Overview of the used benzylic alcohols Fehler! Verweisquelle konnte nicht gefunden werden.**a–l** and aldehydes Fehler! Verweisquelle konnte nicht gefunden werden.**a–l**.



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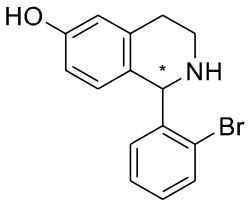

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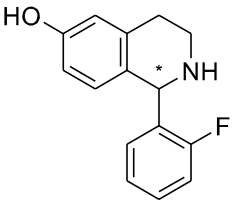

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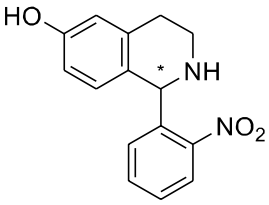

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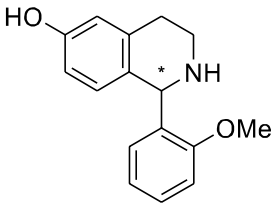

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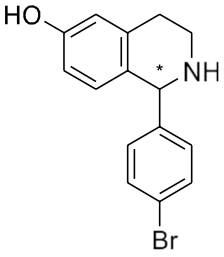

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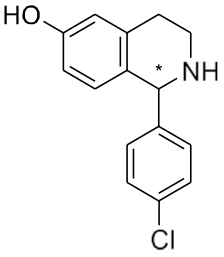

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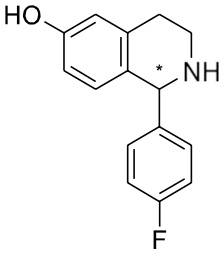

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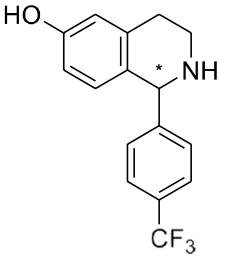

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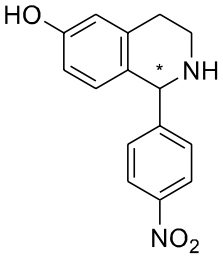

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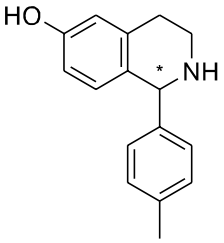

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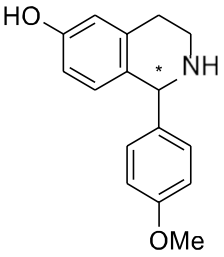

Fehler! Verweisquelle konnte nicht gefunden werden.**l**

Figure S2: Overview of the produced 1-phenyl-1,2,3,4-tetrahydroisoquinolines (THIQs) Fehler! Verweisquelle konnte nicht gefunden werden.**a–l**.

S2 General methods

Names are in accordance with the IUPAC nomenclature.

TLC staining: Reactions were monitored by thin layer chromatography (TLC) on pre-coated plastic sheets (Polygram SIL G/UV254, *Macherey–Nagel*, Düren, Germany) with detection by UV-light at 245 nm or ninhydrin staining (ninhydrin staining solution: 0.2 g ninhydrin, 100 mL EtOH) followed by brief heating with a heat gun.

Mass spectrometry: GC-MS analysis was performed on a Thermo Scientific Trace 1310 gas chromatograph (*Thermo Scientific,* Waltham, MA, USA) equipped with an Optima 5MS column (30 m x 0.25 mm, 0.25 µm, *Macherey-Nagel*, Düren, Germany) and coupled with a ISQ™ QD Single Quadrupole Mass Spectrometer (*Thermo Scientific,* Waltham, MA, USA). The temperatures of the injector and the detector were fixed at 250 °C and 230 °C, respectively. Helium was used as the carrier gas. Mass spectra were collected in the electron impact mode at 70 eV. The column temperature was initially 60 °C for 1 min, then raised to 185 °C at a rate of 15 °C min^{-1}, subsequently raised to 280 °C at a rate of 120 °C min^{-1} and maintained at that temperature for 5 min.

NMR spectroscopy: ^{1}H- and ^{13}C-NMR spectra were recorded on an Advance/DRX 600 nuclear magnetic resonance spectrometer (*Bruker,* Billerica, USA) at ambient temperature in $CDCl_3$ at 600 and 151 MHz, respectively. The chemical shifts are given in ppm relative to the solvent [^{1}H: δ(CD_3OD) = 3.31 ppm; ^{13}C: δ(CD_3OD) = 49.00 ppm; ^{1}H: δ(DMSO-d_6) = 2.50 ppm; ^{13}C: δ(DMSO-d_6) = 39.52 ppm]. Signals were assigned by means of DEPT-135° Puls-, ^{1}H-^{1}H-COSY-, ^{1}H-^{13}C-HSQC- and ^{1}H-^{13}C-HMBC-experiments; splitting patterns are given as singlet (s), doublet (d), triplet (t), quartett (q), doublet of doublet (dd), doublet of doublet of doublet (ddd), multiplet (m) and broad singlet (brs) plus coupling constants (*J*) are reported in Hz.

IR spectroscopy: IR data were recorded on a *SpectrumTwo* instrument (*PerkinElmer,* Waltham, MA, USA) as thin film. Absorbance frequencies are reported in cm^{-1}.

LC-MS (achiral stationary phase): Analytes were separated and analyzed using a LC-MS *Agilent* 1100 series (*Agilent Technologies*, Santa Clara, CA, USA) equipped with a diode array and API electrospray mass detector. Substances were separated by the reversed phase stationary phase Atlantis T3 (1 m x 3.0 mm, 3 µm). Water + 0.1% (*v*/*v*) formic acid and methanol + 0.1% (*v*/*v*) formic acid were used as eluents for the following gradient program: 0.00 min: water + 0.1% (*v*/*v*) formic acid : methanol + 0.1% (*v*/*v*) formic acid (90:10), 4.00 min: water + 0.1% (*v*/*v*) formic acid : methanol + 0.1% (*v*/*v*) formic acid (40:60), 6.00 min: 100% methanol + 0.1% (*v*/*v*) formic acid. The program was stopped after 10.00 min. Flow rate was set to 0.6 ml/min. The column temperature was kept at 30 °C. Detection wavelengths were 250 nm and 286 nm, 3D field (190 nm–800 nm). 10 µL of each sample were injected. MS detection was set to positive mode with a range of *m*/*z* = 100–1000. Substances were identified by their UV absorption spectra and their mass to charge ratio (*m*/*z*).

S3 Methods in biology

S3.1 Bacterial strains and culture conditions

Cultivation of *Escherichia coli* (*E. coli*) BL21(DE3) strains was either carried out in LB (lysogeny broth) liquid medium (10 g/L tryptone, 5 g/L yeast extract, 10 g/L sodium chloride), LB agar plates (addition of 2% agar) or in TB (terrific broth) liquid medium (*Carl Roth*, Karlsruhe, Germany: 12 g/L casein, 24 g/L yeast extract, 12.54 g/L K_2HPO_4, 2.31 g/L KH_2PO_4, 4 mL/L glycerol) at 37 °C. Ampicillin was added as antibiotic to the culture medium in a final concentration of 100 µg/mL.

All cultivation media were prepared using distilled water and sterilized by autoclaving.

S3.2 Vector map, DNA sequence and protein sequence of the laccase

S3.2.1 Vector map of pET22b(+) empty vector

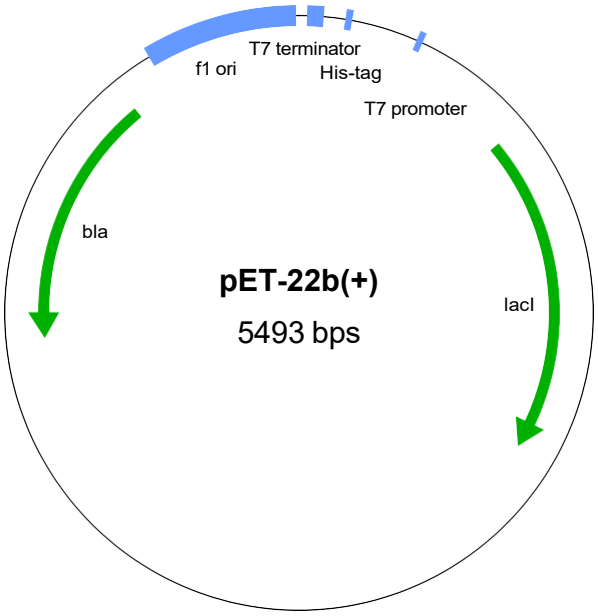

Figure S3. Vector map of pET22b(+) empty vector.

S3.2.2 Laccase Ssl1 from *Streptomyces sviceus*

Vector map of pET22b(+) containing the gene *6xhis:ssl1*.

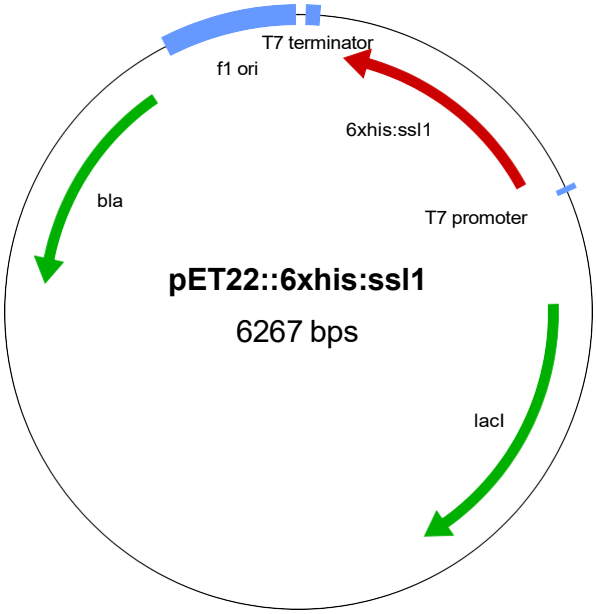

Figure S4. Vector map of pET22b(+) containing the gene *6xhis:ssl1*.

The vector was kindly provided by the group of Prof. Dr. *Vlada Urlacher* (Institute of Biochemistry II, Heinrich Heine University Düsseldorf) [1,2].

Amino acid sequence of 6xHis:Ssl1

MHHHHHHAPGGEVRRIKLYAERLADGQMGYGLEKGRATIPGPLIELNEGDTLHIEFENTMDVRASLHVH
GLDYEVSSDGTTLNKSDVEPGGTRTYTWRTHAPGRRSDGTWRAGSAGYWHYHDHVVGTEHGTGGIRK
GLYGPVIVRRKGDVLPDATHTIVFNDMLINNRPAHSGPNFEATVGDRVEFVMITHGEYYHTFHMHGHR
WADNRTGMLTGPDDPSQVVDNKIVGPADSFGFQVIAGEGVGAGAWMYHCHVQSHSDMGMVGLFL
VKKTDGTIPGYEPHEHSGQRAEHHH

DNA sequence of *6xhis:ssl1*

ATGCATCATCATCATCATGCCCCGGGCGGCGAGGTCAGGCGCATCAAGCTGTACGCCGAGAGG
CTCGCCGACGGGCAGATGGGCTACGGCCTGGAGAAGGGCAGGGCGACGATCCCCGGCCCGCTCAT
CGAGCTCAACGAGGGCGACACCCTGCACATCGAGTTCGAGAACACCATGGACGTCCGGGCGAGCCT
GCACGTCCACGGCCTGGACTACGAAGTCTCCAGCGACGGCACGACGTTGAACAAGAGTGACGTCGA
GCCGGGCGGCACCCGCACCTACACCTGGCGCACCCACGCGCCGGGCCGCCGGAGCGACGGCACCTG
GCGGGCGGGCAGCGCGGGCTACTGGCACTACCACGACCACGTCGTCGGCACGGAACACGGCACCG
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CGACGCACACGATCGTCTTCAACGACATGCTCATCAACAACAGGCCGGCGCACTCGGGGCCCAACTT
CGAGGCCACCGTGGGCGATCGGGTCGAGTTCGTGATGATCACGCACGGCGAGTACTACCACACCTT
CCATATGCACGGTCACCGCTGGGCGGACAACCGCACGGGCATGCTCACGGGGCCCGACGACCCGAG
CCAGGTCGTCGACAACAAGATCGTGGGCCCGGCGGACTCCTTCGGCTTCCAGGTGATCGCGGGGGA
GGGGGTCGGGGCGGGCGCGTGGATGTACCACTGCCATGTGCAGAGCCACTCCGACATGGGGATGG
TGGGCCTGTTCCTGGTGAAGAAGACGGACGGGACGATCCCGGGGTACGAGCCGCACGAGCACAGC
GGGCAGCGGGCCGAACACCACCACTGA

S3.3 Heterologous expression of the laccase gene *6xhis:ssl1*

A baffled 3 L *Fernbach* flask containing TB medium (1 L), ampicillin (100 µg/mL) and $CuSO_4$(2 mM) was inoculated to an OD_{600} of 0.05 with a pre-culture of *E. coli* BL21(DE3) harbouring the pET22::6xhis:ssl1 vector. The culture was incubated at 37 °C (130 rpm, orbit diameter 2.5 cm) and induced with IPTG (40 µM) at an OD_{600} of approx. 0.6. Directly after induction of protein expression, the temperature was lowered to 25 °C and incubation was carried out for additional 16 h (130 rpm, orbit diameter 2.5 cm). Cells were harvested by centrifugation (20 min, 7,100 rcf, 4 °C) and stored at -20 °C as wet or freeze-dried cell pellet

For a negative control of the expression *E. coli* BL21(DE3) cells harboring the pET22b(+) empty vector were used.

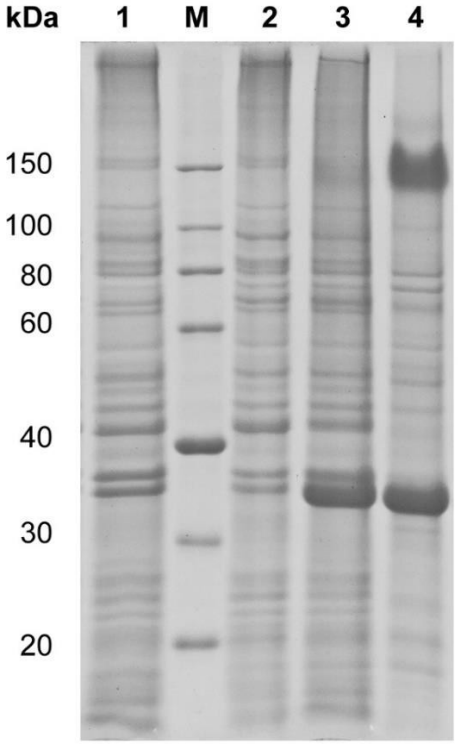


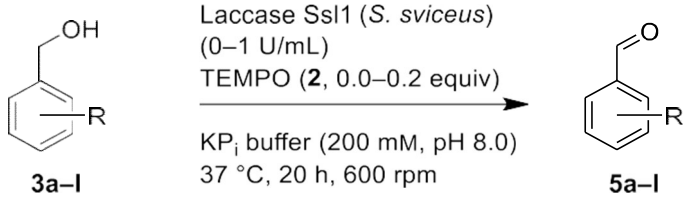
Figure S5. SDS-PAGE of the expression of the laccase gene *6xhis:ssl1* and empty vector control. [M: Marker (Roti®-Mark 10–150), 1: *E. coli* pET-22b(+) empty vector, 2: *E. coli* pET22::6xhis:ssl1 before induction, 3: *E. coli* pET22::6xhis:ssl1 after induction (6xHis:Ssl1, 32.5 kDa), 4: Heat-treated supernatant of *E. coli* pET22::6xhis:ssl1 after induction (6xHis:Ssl1, 32.5 kDa)].

Preparation of laccase solution: Frozen cell pellet was thawed and resuspended in potassium phosphate buffer (KP_i buffer, 200 mM, pH 8.0; 0.5 g cells per mL) containing $CuSO_4$ (0.3 mM). The cells were lysed *via* sonication using a SONOPULS Ultrasonic homogenizer (*Bandelin*, Berlin, Germany; 3 x 5 min and five cycles, 40% power). The lysate was treated with heat at 65 °C for 20 min to deactivate non-specific enzyme activities. After centrifugation (10 min, 7,100 rcf, 4 °C) the clarified cell supernatant was used for the determination of the laccase activity.

For the one-pot process, unless otherwise stated, one batch of laccase solution was prepared, diluted, aliquoted and frozen in liquid nitrogen. Before an experiment, the solution was thawed on ice, the volumetric activity measured and the solution diluted to 0.6 U/mL.

Laccase activity assay: The determination of the laccase activity was performed as described before by *Gunne* and *Urlacher* (2012) using 2,6-dimethoxyphenol (2,6-DMP, 0.5 mM) as substrate in KP_i buffer (200 mM, pH 8.0; 1 mL) [1]. The oxidation of 2,6-DMP was followed spectrophotometrically at 468 nm (Ɛ = 49.6/mM·cm) at 25 °C for 1 min.

S3.4 Oxidation of benzylic alcohols Fehler! Verweisquelle konnte nicht gefunden werden.a–l using the laccase/TEMPO (Fehler! Verweisquelle konnte nicht gefunden werden.) system



Analytical scale: The oxidation of benzylic alcohols **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** was performed in glass vials fitted with a PTFE/silicon septum perforated with a cannula for oxygen exchange. The benzylic alcohol **Fehler! Verweisquelle konnte nicht gefunden werden.** (0.12 mmol, 1.00 equiv) and TEMPO (**Fehler! Verweisquelle konnte nicht gefunden werden.**, 0.0–0.2 equiv) were added to a freshly prepared laccase solution (0–1 U/mL*; vide supra* S3.3) in KP_i buffer (1 mL, 200 mM or 1 M, pH 8.0). The reaction mixture was shaken with 600 rpm on an orbital shaker for microtiterplates for 20 h at 37 °C. For GC-MS analysis the reaction mixture was extracted with MTBE (1 mL). The organic phase was dried over $MgSO_4$ and 20 µL of the sample was diluted in 240 µL MTBE.

For a negative control without laccase the oxidation was performed using freshly prepared cell lysate of *E. coli* BL21(DE3) cells containing the pET22b(+) empty vector. Expression, protein preparation and reaction handling were carried out as described before (*vide supra*).

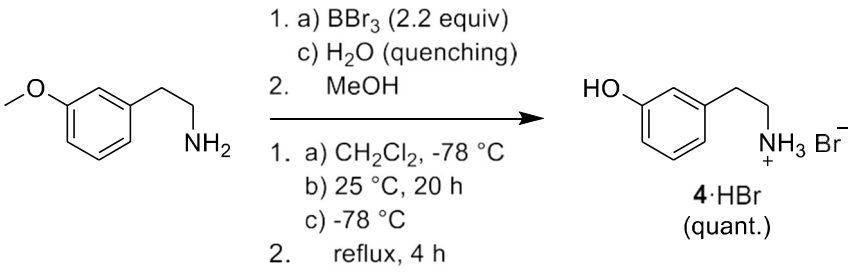
Preparative scale: The oxidation of 2-bromobenzyl alcohol (**Fehler! Verweisquelle konnte nicht gefunden werden.b**) was performed in a 100 mL *Schott®* flask fitted with a PTFE/silicon septum perforated with a cannula for oxygen exchange. 2-bromobenzyl alcohol (**Fehler! Verweisquelle konnte nicht gefunden werden.b**, 224 mg, 1.20 mmol, 1.00 equiv) and TEMPO (**Fehler! Verweisquelle konnte nicht gefunden werden.**, 37.5 mg, 0.24 mmol, 0.2 equiv) were added to a freshly prepared laccase solution (1 U/mL*; vide supra* S3.3) in KP_i buffer (10 mL, 200 mM, pH 8.0). The reaction mixture was shaken with 500 rpm on an orbital shaker for culture flasks for 20 h at 37 °C. For GC-MS analysis the reaction mixture was extracted with MTBE (10 mL). The organic phase was dried over $MgSO_4$ and 20 µL of the

sample was diluted in 240 µL MTBE. For NMR analysis the aqueous phase was acidified and extracted.

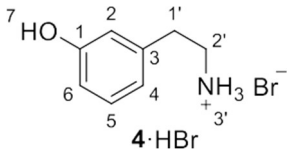
S4 Chemical syntheses

General chemical syntheses: All reactions under inert atmosphere were performed under usage of oven-dried glassware, under an atmosphere of dry nitrogen and applying standard *Schlenk* techniques. Reactions were monitored by thin layer chromatography (TLC) on pre-coated plastic sheets (Polygram SIL G/UV254, *Macherey–Nagel*, Düren, Germany) with detection by UV-light at 245 nm or ninhydrin staining (S2). Removal of solvent was performed at 40 °C *in vacuo*. Preparative column chromatography was performed using silica gel 60 (particle size 0.040–0.063 mm, 230–240 mesh, *Macherey–Nagel*, Düren, Germany). The solvents ethyl acetate (EtOAc), diethyl ether and dichloromethane were distilled prior to use. All other chemicals and solvents were used as purchased without further purification. Analytics [(liquid chromatography)-mass spectrometry, NMR spectroscopy, IR spectroscopy] were performed as described in S2.

S4.1 Synthesis of 3-(2′-aminoethyl)phenol hydrobromide (Fehler! Verweisquelle konnte nicht gefunden werden., *m*-tyramine·HBr)



The synthesis of *m*-tyramine hydrobromide (**Fehler! Verweisquelle konnte nicht gefunden werden.**·HBr) was achieved according a modified protocol of *Pesnot et al* [3]. The reaction was performed in a *Schlenk* flask under nitrogen atmosphere. To a solution of 2-(3-methoxyphenyl)ethylamine (5.00 mL, 34.4 mmol, 1 equiv) in dry dichloromethane (160 mL) boron tribromide in hexane (75.7 mL, 75.7 mmol, 1.00 M, 2.20 equiv) was slowly added at -78 °C. The reaction mixture was warmed to room temperature (25 °C) and stirred for 20 h. Afterwards, the reaction mixture was quenched by adding water (200 mL) dropwise at -78 °C; the aqueous layer was extracted with dichloromethane (3 x 100 mL) and lyophilized to give a light brownish solid. The reaction product was dissolved without further purification in methanol (40 mL) and was heated to reflux for 4 h. The resulting mixture was distilled to remove trimethyl borate and methanol. Removing the solvent under reduced pressure over night provided *m*-tyramine hydrobromide (**Fehler! Verweisquelle konnte nicht gefunden werden.**·HBr, 7.5 g, 34.4 mmol, quant.) as white solid.



^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm] = 2.77 (t, $^3J_{1',2'}$ 8.0 Hz, 2H, 1′-H), 3.01 (t, $^3J_{2',1'}$ 8.0 Hz, 2H, 2′-H), 6.60–6.69 (m, 3H, 2,4,6-H) 7.11 (dd, $^3J_{5,4}$ = 7.6 Hz, $^3J_{5,6}$ = 7.6 Hz 1H, 5-H), 7.72–7.91 (m, 3H, NH_3), 9.41 (s, 1H, OH); **13C-NMR** (151 MHz, DMSO-d_6): δ [ppm] = 32.9

(C-1'), 40.0 (C-2'), 113.7 (C-6), 115.5 (C-2), 119.2 (C-4), 129.6 (C-5), 138.6 (C-3), 157.5 (C-1); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2977, 1589, 1460, 1364, 1260, 1153, 1134, 922, 865, 784, 751, 694; **LC-MS** (API-ES, 70 eV): t_R = 1.068 min, *m*/*z* = 218 $[M+H]^+$/220 $[M+H]^+$.

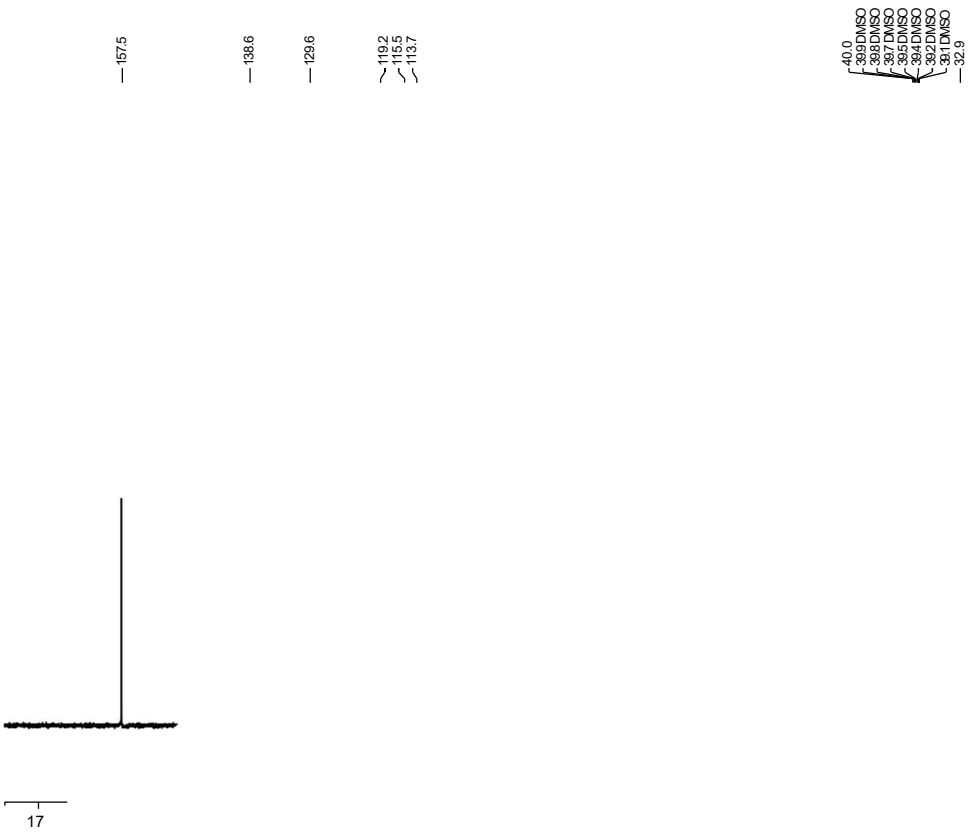
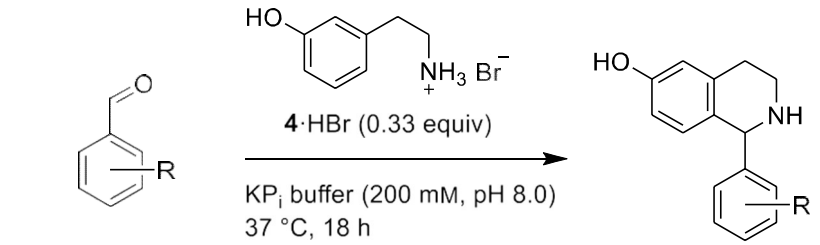


Figure S6. ^{1}H- and ^{13}C-NMR-spectra of *m*-tyramine·HBr (Fehler! Verweisquelle konnte nicht gefunden werden.·HBr) in $CDCl_3$ (600 MHz/151 MHz).

S4.2 Phosphate salt-mediated *Pictet-Spengler* reaction towards THIQs Fehler! Verweisquelle konnte nicht gefunden werden.**a–l**

S4.2.1 General procedure



5a–l (1.00 equiv) **1a–l**

The phosphate salt-mediated *Pictet-Spengler* reaction towards THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** was performed in a round-bottom flask equipped with a magnetic stirrer under oxygen atmosphere. The reaction mixture consisting of *m*-tyramine hydrobromide (**Fehler! Verweisquelle konnte nicht gefunden werden.**·HBr, 100 mg, 0.46 mmol, 0.33 equiv) and an aldehyde **Fehler! Verweisquelle konnte nicht gefunden werden.** (1.38 mmol, 1.00 equiv) in KP_i buffer (10 mL, 200 mM, pH 8.0) was stirred for 18 h at 37 °C. Afterwards, the solution was cooled to room temperature (25 °C) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** were precipitated by adding small amounts of cold HCl solution indiethyl ether (1 M) to the residue. The resulting solid was washed with cold diethyl ether, filtered, and resuspended in MeOH. The solvent was removed under reduced pressure and the THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** were purified *via* chromatography on silica with dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1% (*v*/*v*)] using a column (length = 5–12 cm, diameter = 3 cm). The THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** were obtained as free amines and racemic mixtures. The yields are related to the quantity of *m*-tyramine hydrobromide (**Fehler! Verweisquelle konnte nicht gefunden werden.**·HBr) used.

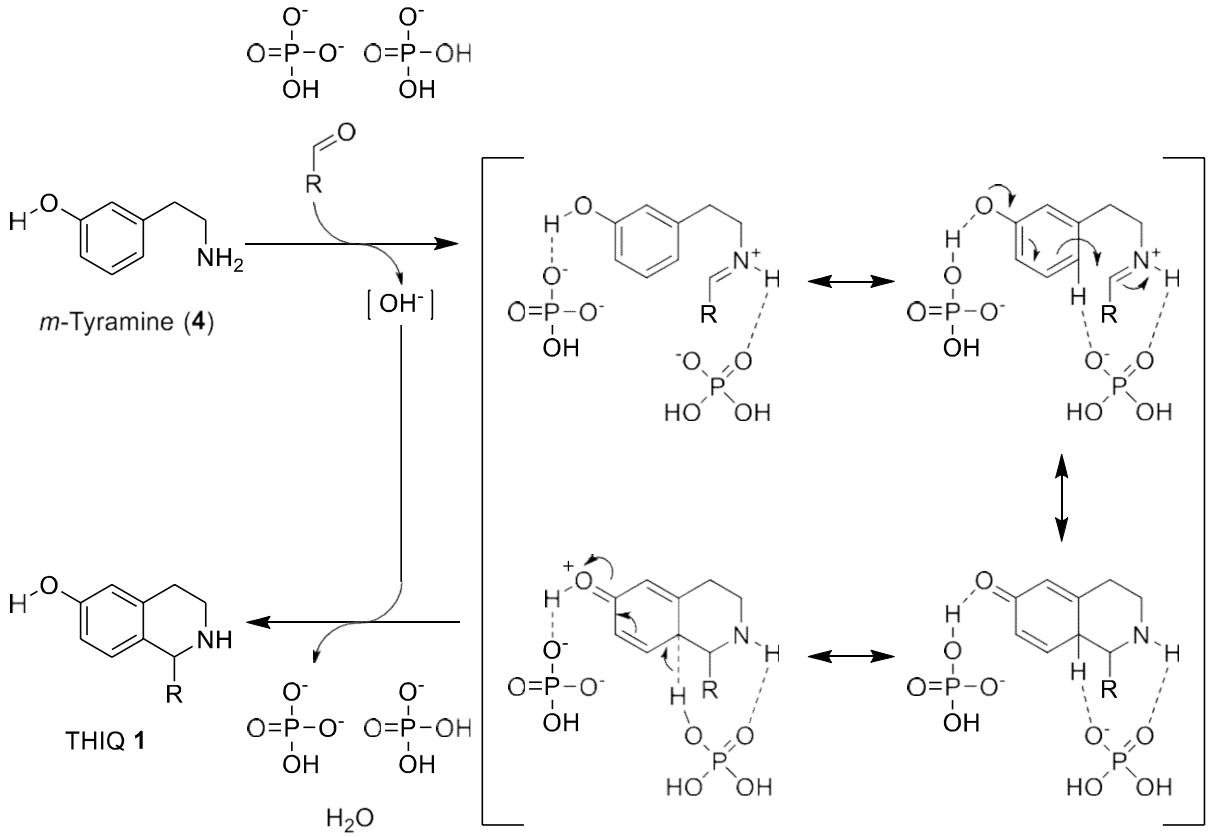
S4.2.2 Additional procedures for the phosphate salt-mediated *Pictet-Spengler* reaction regarding reaction conditions

Additional procedures for the phosphate salt-mediated *Pictet-Spengler* reaction towards THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** were performed with following alternative reaction conditions:

- Nitrogen atmosphere instead of oxygen atmosphere
- Addition of ascorbic acid (1 equiv) as antioxidant
- 60 °C instead of 37 °C
- KP_i buffer at pH 5.0 and 7.0 instead of 8.0

- Addition of TEMPO (**Fehler! Verweisquelle konnte nicht gefunden werden.**, 0.067–0.20 equiv)

S4.2.3 Suggested mechanism of phosphate salt-mediated *Pictet-Spengler* reaction

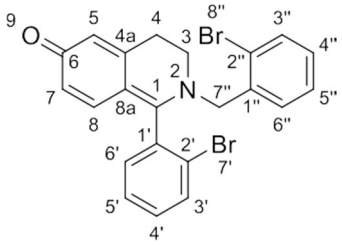


Scheme S1. Suggested KP_i buffer-mediated *Pictet-Spengler* reaction at a slightly alkaline pH of 8.0 in the presence of HPO_4^{2-} and $H_2PO_4^-$ ions. Parts of the scheme were adopted from *Parra* & *Maresh* (2016) [4].

S4.2.4 By-product Fehler! Verweisquelle konnte nicht gefunden werden. of the phosphate salt-mediated Pictet-Spengler reaction

Compound characterization of the by-product Fehler! Verweisquelle konnte nicht gefunden werden.

2-(2″-bromobenzyl)-1-(2′-bromophenyl)-3,4-dihydroisoquinolin-6(2*H*)-one (Fehler! Verweisquelle konnte nicht gefunden werden.**)**



6

The by-product **Fehler! Verweisquelle konnte nicht gefunden werden.** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a yellow solid after KP_i mediated *Pictet-Spengler* reaction with *m*-tyramine hydrobromide (**Fehler! Verweisquelle konnte nicht gefunden werden.**·HBr) and 2-bromobenzaldehyde (**Fehler! Verweisquelle konnte nicht gefunden werden.b**) in KP_i buffer (200 mM, pH 8.0): **^{1}H-NMR** (600 MHz, DMSO-d_6): δ [ppm] = 2,90 (ddd, $^2J_{4a,4b}$ = 16.3 Hz, $^3J_{4a,3a}$ = 9.7 Hz, $^3J_{4a,3b}$ = 6.0 Hz, 1H, 4a-H), 3.00 (ddd, $^2J_{4b,4a}$ = 16.5 Hz, $^3J_{4b,3b}$ = 10.3 Hz, $^3J_{4b,3a}$ = 6.0 Hz, 1H, 4b-H), 3.66–3.80 (m, 2H, 3a-H, 3b-H), 4.38 (d, $^2J_{7''a,\ 7''b}$ = 16.3 Hz, 1H, 7″a-H), 4.62 (d, $^2J_{7''b,\ 7''a}$ = 16.3 Hz, 1H, 7″b-H), 5.90 (dd, $^3J_{7,8}$ = 9.4 Hz, $^4J_{7,5}$ = 2.1 Hz, 1H, 7-H), 6.02 (d, $^4J_{5,7}$ = 2.2 Hz, 1H, 5-H), 6.30 (d, $^3J_{8,7}$ = 9.4 Hz, 1H, 8-H), 7.26 (dd, $^3J_{4',3'}$ = 7.9 Hz, $^3J_{4',5'}$ = 7.9 Hz, 1H, 4′-H), 7.39–6.57 (m, 5H, 5′-H, 6′-H, 4″-H, 5″-H, 6″-H), 7.58 (d, $^3J_{3',4'}$ = 8.0 Hz, 1H, 3′-H), 7.78 (dd, $^3J_{3'',4''}$ = 7.0 Hz, $^4J_{3'',5''}$ = 1.4 Hz, 1H, 3″-H); **13C-NMR** (151 MHz, DMSO-d_6): δ [ppm] = 27.4 (C-4), 48.4 (C-3), 56.3 (C-7″), 108.0 (C-8a), 120.9 (C-5), 122.0 (C-2′), 122.2 (C-2″), 122.5 (C-7), 128.0, 128.4, 129.2, 129.9 (C-4′), 130.6, 132.2, 132.7 (C-1″), 132.8 (C-3″), 132.9 (C-3′), 134.4 (C-1′), 135.5 (C-8), 140.4 (C-4a), 161.4 (C-1), 182.5 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 1614, 1512, 1486, 1416, 1332, 1196, 1150, 1099, 1024, 896, 861, 830, 804, 754, 669, 589, 499, 469; **HRMS** (ESI-FTMS, positive-ion): Calculated for $[M+H]^+$ = 469.9750, 470.9783, 471.9729, 472.9763, 473.9709, 474.9742, found = 469.9748, 470.9778, 471.9730, 472.9759, 473.9711, 474.9738.

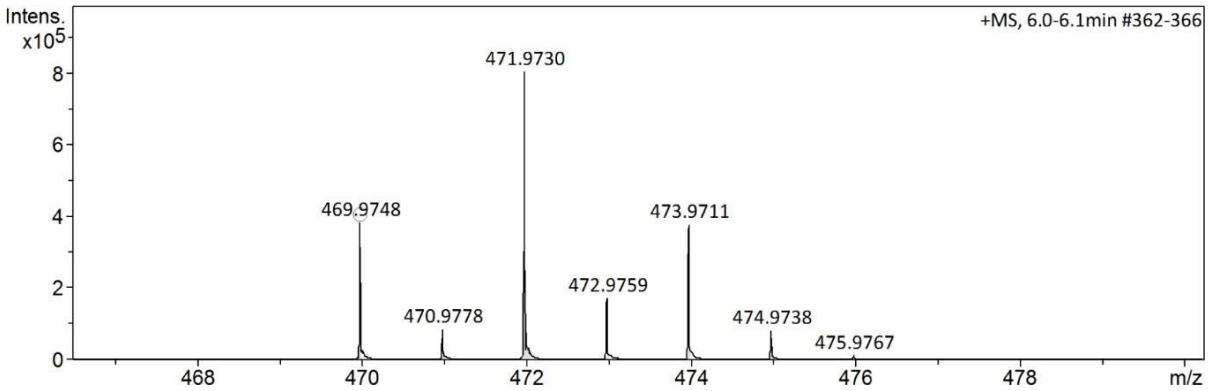


Figure S7. HRMS mass spectrum of by-product Fehler! Verweisquelle konnte nicht gefunden werden.. [ESI-FTMS, positive-ion]

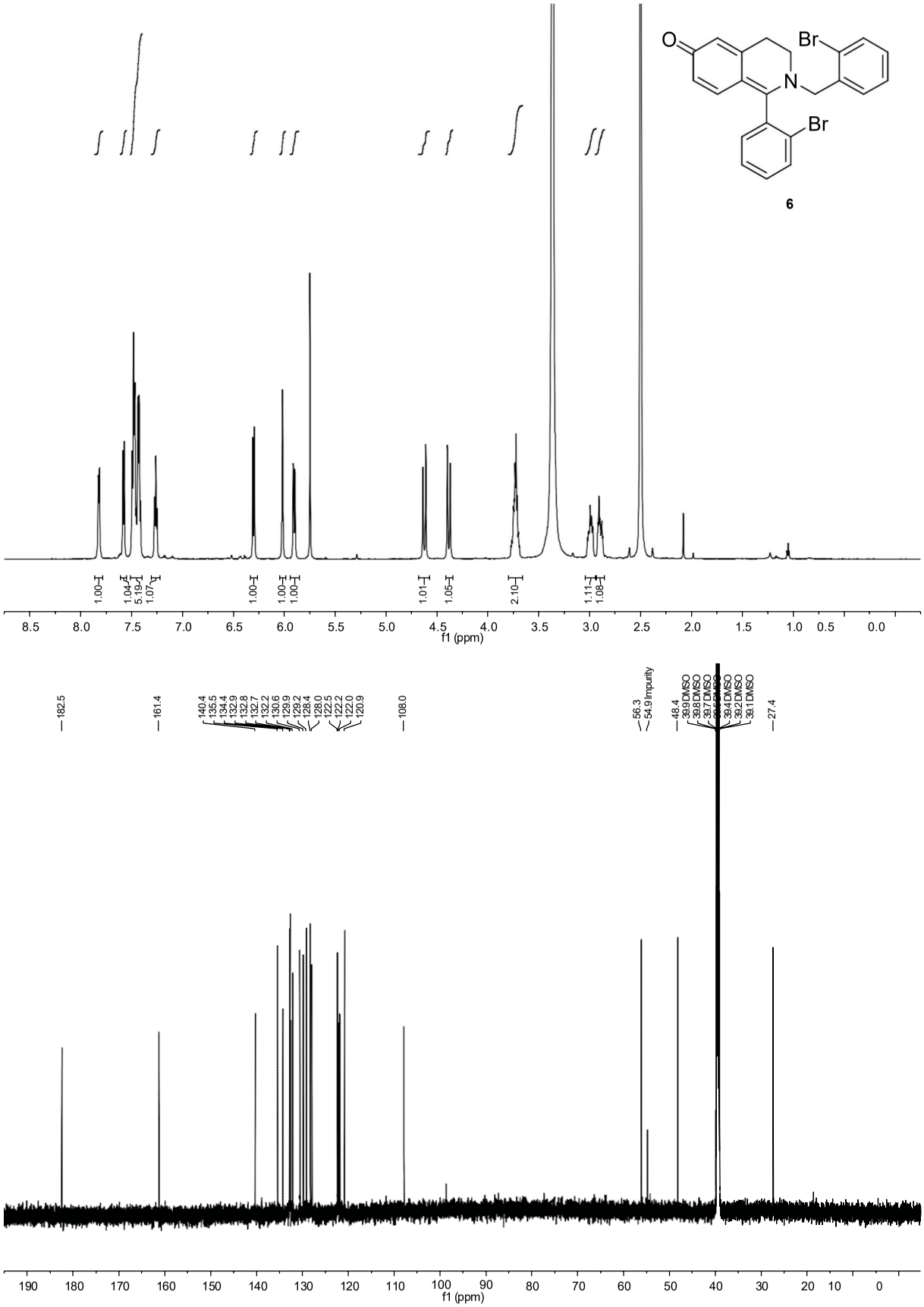
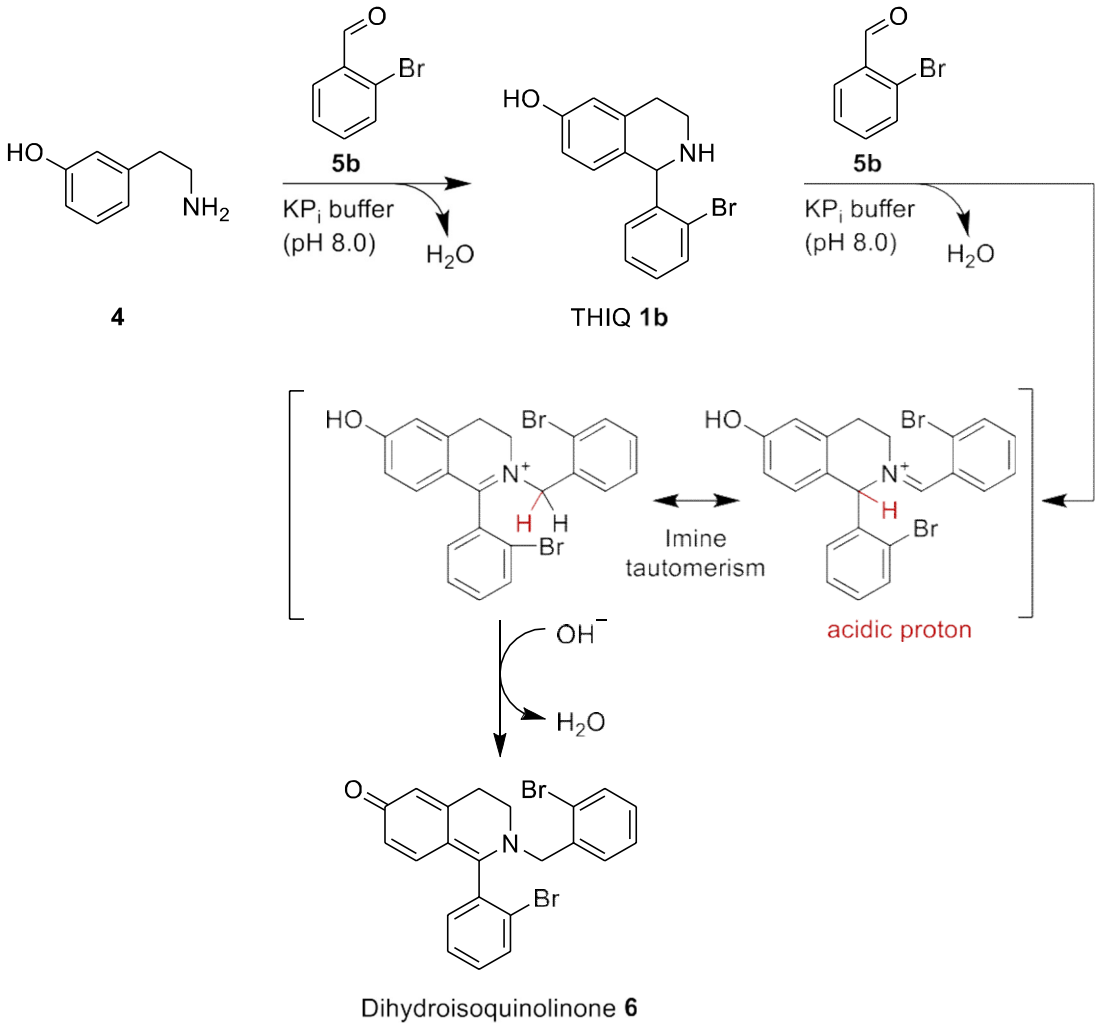


Figure S8. ^{1}H- and ^{13}C-NMR-spectra of by-product Fehler! Verweisquelle konnte nicht gefunden werden. in DMSO-d_6 (600 MHz/151 MHz).

Suggested reaction mechanism towards the by-product Fehler! Verweisquelle konnte nicht gefunden werden.



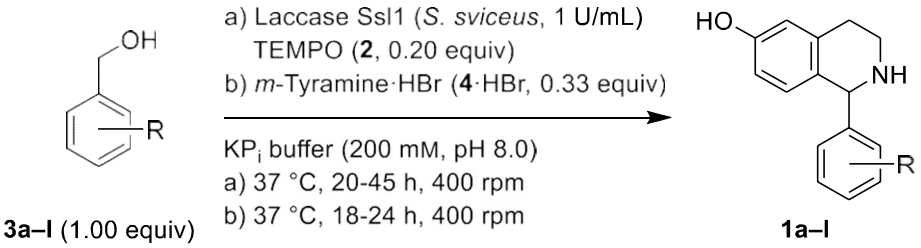
Scheme S2. Suggested reaction mechanism towards the by-product Fehler! Verweisquelle konnte nicht gefunden werden. *via* imine tautomerism and alkaline reaction conditions.

(a) visible light (b) UV light

Figure S9. Solution of by-product **Fehler! Verweisquelle konnte nicht gefunden werden.** in MeOH irradiated by visible-(a) and UV-light (b, λ = 254 nm).

S5 Chemoenzymatic one-pot cascade towards THIQs Fehler! Verweisquelle konnte nicht gefunden werden.a–l

The chemoenzymatic one-pot process was performed in a 100 mL *Schott®* flask fitted with a PTFE/silicon septum perforated with a cannula for oxygen exchange under constant shaking at 400 rpm on an orbital shaker for culture flasks at 37 °C.



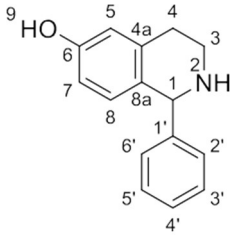
3a–l (1.00 equiv) **1a–l**

The benzylic alcohol **Fehler! Verweisquelle konnte nicht gefunden werden.** (1.38 mmol, 1.00 equiv) and TEMPO (**Fehler! Verweisquelle konnte nicht gefunden werden.**, 32 mg, 0.21 mmol, 0.15 equiv, unless otherwise stated) were added to a laccase solution (0.6 U/mL*; vide supra* S3.3) in KP_i buffer (10 mL, 200 mM, pH 8.0) with 0.3 mM $CuSO_4$. The reaction mixture was shaken for 20–45h at 37 °C. To follow the reaction, a 100 µL sample was taken for GC-MS analysis and analyzed (*vide supra* S3.4). For conversions and individual reaction times, see Supplementary Table S1. Afterwards, *m*-tyramine hydrobromide (**Fehler! Verweisquelle konnte nicht gefunden werden.**·HBr, 100 mg, 0.46 mmol, 0.33 equiv) in KP_i buffer (10 mL, 200 mM, pH 8.0) was added to the reaction mixture and shaken for another 18–24h. The solution was then cooled to room temperature (25 °C) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** were precipitated by adding small amounts of cold HCl solution in diethyl ether (1 M) to the residue. The resulting solid was washed with cold diethyl ether, filtered, and resuspended in MeOH. The solvent was removed under reduced pressure and the THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** were purified *via* column (length = 10–
16 cm, diameter = 3 cm) chromatography on silica with dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)] providing the THIQs **Fehler! Verweisquelle konnte nicht gefunden werden.a–l** as free amines as racemic mixtures. The yields are related to the quantity of *m*-tyramine hydrobromide (**Fehler! Verweisquelle konnte nicht gefunden werden.**·HBr) used.

Figure S10: Exemplary reaction set-up consisting of 100 mL *Schott*® flasks with a PTFE septum and a cannula at the start of the second reaction step and at the end of the reaction.

S6 Compound characterization of THIQs Fehler! Verweisquelle konnte nicht gefunden werden.a–l

1-Phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**a)**

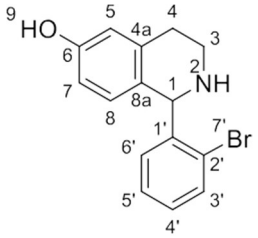


1a

The product Fehler! Verweisquelle konnte nicht gefunden werden.**a** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 96.4 mg, 0.43 mmol, 93%; one-pot process: 33 mg, 15 mmol, 32%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.73–2.81 (m, 1H, 4a-H), 2.91–2.96(m, 1H, 4b-H), 2.96–3.01 (m, 1H, 3a-H), 3.12–3.20 (m, 1H, 3b-H), 4.98 (s, 1H, 1-H), 6.46–6.52 (m, 2H, 7-H, 8-H), 6.58 (d, $^4J_{5,7}$ = 2.3 Hz, 1H, 5-H), 7.21–7.24 (m, 2H, 5'-H, 3'-H), 7.24–7.28 (m, 1H, 4'-H), 7.29–7.33 (m, 2H, 6'-H, 2'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 42.5 (C-3), 62.4 (C-1), 114.4 (C-7), 115.8 (C-5), 128.5 (C-4'), 129.4 (C-6', C-2'), 129.8 (C-8a), 130.2 (C-8), 130.2 (C-5', C-3'), 137.5 (C-4a), 145.6 (C-1'), 156.9 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2910, 1602, 1430, 1362, 1347, 1299, 1236, 1181, 1157, 1106, 1000, 949, 877, 858, 817, 776, 744, 695, 649, 610, 594, 558, 532, 494; **LC-MS** (API-ES, 70 eV): t_R = 4.19 min, *m*/*z* = 226 $[M+H]^+$.

The ^{1}H-NMR- und ^{13}C-NMR data are in accordance to literature [5].

1-(2'-Bromophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**b)**

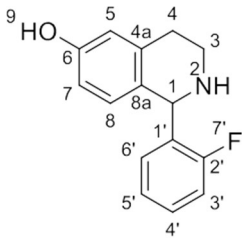


1b

The product Fehler! Verweisquelle konnte nicht gefunden werden.**b** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 95.0 mg, 0.31 mmol, 68%; one-pot process: 69 mg, 0.23 mmol, 49%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.83 (ddd, $^2J_{4a,4b}$ = 16.5 Hz, $^3J_{4a,3a}$ = 6.1 Hz, $^3J_{4a,3b}$ = 5.5 Hz, 1H, 4a-H), 2.91 (ddd, $^2J_{4b,4a}$ = 16.6 Hz, $^3J_{4b,3b}$ = 6.2 Hz, $^3J_{4b,3a}$ = 5.4 Hz, 1H, 4b-H), 2.97 (ddd, $^2J_{3a,3b}$ = 12.0 Hz, $^3J_{3a,4a}$ = 6.8 Hz, $^3J_{3a,4b}$ = 5.2 Hz, 1H, 3a-H), 3.09 (ddd, $^2J_{3b,3a}$ = 11.9 Hz, $^3J_{3b,4b}$ = 6.7 Hz, $^3J_{3b,4a}$ = 5.0 Hz, 1H, 3b-H), 5.51 (s, 1H, 1-H), 6.47–6.55 (m, 2H, 7-H, 8-H), 6.61 (d, $^4J_{5,7}$ = 2.2 Hz, 1H, 5-H), 6.97 (dd, $^3J_{6',5'}$ = 7.7 Hz, $^4J_{6',4'}$ = 1.7 Hz, 1H, 6'-H), 7.17 (ddd, $^3J_{4',3'}$ = 8.1 Hz, $^3J_{4',5'}$ = 7.7 Hz, $^4J_{4',6'}$ = 1.7 Hz, 1H, 4'-H), 7.21–7.27 (m, 1H, 5'-H), 7.64 (dd, $^3J_{3',4'}$ = 8.1 Hz, $^4J_{3',5'}$ = 1.3 Hz, 1H, 3'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 41.4 (C-3), 60.5 (C-1), 114.7 (C-7), 115.9 (C-5), 125.6 (C-2'), 128.5 (C-5'), 128.6 (C-8a), 130.1 (C-8), 130.2 (C-4'), 132.3 (C-6'), 134.0 (C-3'), 137.8 (C-4a), 144.4 (C-1'), 157.2 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2977, 1588, 1461, 1260, 1153, 1135, 936, 922, 866, 783, 751, 694, 639; **LC-MS** (API-ES, 70 eV): t_R = 4.68 min & t_R = 6.84 min, *m*/*z* = 304 $[M+H]^+$ & *m*/*z* = 306 $[M+H]^+$.

The mass data is in accordance to literature [6].

1-(2'-Flurophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**c)**

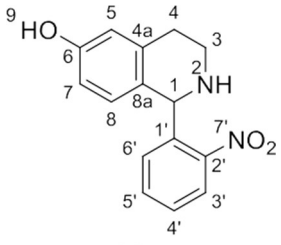


1c

The product Fehler! Verweisquelle konnte nicht gefunden werden.**c** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 103.3 mg, 0.42 mmol, 92%; one-pot process: 72 mg, 0.30 mmol, 64%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.80 (ddd, $^2J_{4a,4b}$ = 16.5 Hz, $^3J_{4a,3a}$ = 7.6 Hz, $^3J_{4a,3b}$ = 5.4 Hz, 1H, 4a-H), 2.91 (ddd, $^2J_{4b,4a}$ = 16.4 Hz, $^3J_{4b,3b}$ = 7.7 Hz, $^3J_{4b,3a}$ = 5.5 Hz, 1H, 4b-H), 2.98 (ddd, $^2J_{3a,3b}$ = 12.4 Hz, $^3J_{3a,4a}$ = 7.6 Hz, $^3J_{3a,4b}$ = 5.2 Hz, 1H, 3a-H), 3.13 (ddd, $^2J_{3b,3a}$ = 12.4 Hz, $^3J_{3b,4b}$ = 6.4 Hz, $^3J_{3b,4a}$ = 5.6 Hz, 1H, 3b-H), 5.37 (s, 1H, 1-H), 6.47–6.57 (m, 2H, 7-H, 8-H), 6.60 (d, $^4J_{5,7}$ = 2.4 Hz, 1H, 5-H), 7.02 (m_c, 1H, 6'-H), 7.08 (dd, $^3J_{5',6'}$ = 7.5 Hz, $^3J_{5',4'}$ = 7.5 Hz, 1H, 5'-H), 7.13 (m_c, 1H, 3'-H), 7.25–7.35 (m, 1H, 4'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 29.9 (C-4), 42.0 (C-3), 54.9 (C-1), 54.9 (C-1), 114.6 (C-7), 116.0 (C-5), 116.3 (C-3'), 116.4 (C-3'), 125.1 (C-5'), 125.1 (C-5'), 128.6 (C-8a), 129.7 (C-8), 130.3 (C-4'), 130.3 (C-4'), 132.0 (C-6'), 132.0 (C-6'), 132.3 (C-1'), 132.4 (C-1'), 137.8 (C-4a), 157.1 (C-6), 161.7 (C-2'), 163.3 (C-2'); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2923, 1580, 1481, 1455, 1423, 1367, 1320, 1285, 1260, 1220, 1155, 1061, 1033, 850, 827, 800, 762, 642, 576, 559, 527; **LC-MS** (API-ES, 70 eV): t_R = 5.63 min, *m*/*z* = 244 $[M+H]^+$.

The mass data is in accordance to literature [6].

1-(2'-Nitrophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**d)**



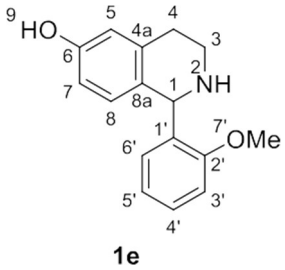
1d

The product Fehler! Verweisquelle konnte nicht gefunden werden.**d** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 94.5 mg, 0.35 mmol, 76%; one-pot process: 59 mg, 0.22 mmol, 47%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.83 (ddd, $^2J_{4a,4b}$ = 16.5 Hz, $^3J_{4b,3b}$ = 7.0 Hz, $^3J_{4b,3a}$ = 5.9 Hz, 1H, 4a-H), 2.89–2.95 (m, 1H, 4b-H), 2.98 (ddd, $^2J_{3a,3b}$ = 11.9 Hz, $^3J_{3a,4a}$ = 6.8 Hz, $^3J_{3a,4b}$ = 5.1 Hz, 1H, 3a-H), 3.13 (ddd, $^2J_{3b,3a}$ = 11.8 Hz, $^3J_{3b,4b}$ = 6.8 Hz, $^3J_{3b,4a}$ = 4.9 Hz, 1H, 3b-H), 5.49 (s, 1H, 1-H), 6.49–6.54 (m, 2H, 7-H, 8-H), 6.62 (s, 1H, 5-H), 7.16 (dd, $^3J_{6',5'}$ = 7.7 Hz, $^4J_{6',4'}$ = 1.6 Hz, 1H, 6'-H), 7.45–7.52 (m, 1H, 4'-H), 7.51–7.59 (m, 1H, 5'-H), 7.92 (dd, $^3J_{3',4'}$ = 8.3 Hz, $^4J_{3',5'}$ = 1.5 Hz, 1H, 3'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 41.3 (C-3), 56.5 (C-1), 114.8 (C-7), 116.0 (C-5), 125.3 (C-3'), 128.1 (C-8a), 129.6 (C-4'), 130.3 (C-8), 133.3 (C-6'), 133.6 (C-5'),

138.1 (C-4a), 139.5 (C-2′), 151.7 (C-1′), 157.3 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2938, 1606, 1520, 1347, 1057, 1033, 786, 745, 644; **LC-MS** (API-ES, 70 eV): t_R = 4.93 min, *m/z* = 271 [M+H]$^+$.

The IR and mass data are in accordance to literature [7].

1-(2′-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**e)**

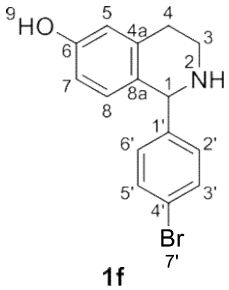


1e

The product Fehler! Verweisquelle konnte nicht gefunden werden.**e** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP$_i$-mediated *Pictet-Spengler* reaction: 100.8 mg, 0.39 mmol, 86%; one-pot process: 67 mg, 0.26 mmol, 57%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.84 (dd, $^3J_{4,3a}$ = 5.9 Hz, $^3J_{4,3b}$ = 6.3 Hz, 2H, 4-H), 2.92 (dt, $^2J_{3a,3b}$ = 12.1 Hz, $^3J_{3a,4}$ = 5.8 Hz, 1H, 3a-H), 3.03 (dt, $^2J_{3b,3a}$ = 12.4 Hz, $^3J_{3b,4}$ = 6.2 Hz, 1H, 3b-H), 3.86 (s, 3H, 8′-H), 5.40 (s, 1H, 1-H), 6.52 (dd, $^3J_{7,8}$ = 8.4 Hz, $^4J_{7,5}$ = 2.5 Hz, 1H, 7-H), 6.57 (d, $^3J_{8,7}$ = 8.4 Hz, 1H, 8-H), 6.59 (d, $^4J_{5,7}$ = 2.4 Hz, 1H, 5-H), 6.80 (dd, $^3J_{6',5'}$ = 7.6 Hz, $^4J_{6',4'}$ = 1.8 Hz, 1H, 6′-H), 6.84 (dd, $^3J_{5',6'}$ = 7.5 Hz, $^3J_{5',4'}$ = 7.8 Hz, 1H, 5′-H), 7.02 (d, $^3J_{3',4'}$ = 8.2 Hz, 1H, 3′-H), 7.26 (dd, $^3J_{4',5'}$ = 7.7 Hz, $^3J_{4',3'}$ = 8.3 Hz, 1H, 4′-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 29.9 (C-4), 41.0 (C-3), 55.8 (C-1), 55.9 (C-8′), 111.9 (C-3′), 114.5 (C-7), 115.8 (C-5), 121.1 (C-5′), 128.8 (C-8a), 129.8 (C-4′), 130.1 (C-8), 131.4 (C-6′), 132.8 (C-1′), 137.6 (C-4a), 157.0 (C-6), 158.8 (C-2′); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 1600, 1487, 1456, 1237, 1098, 1025, 828, 753, 648, 587; **LC-MS** (API-ES, 70 eV): t_R = 6.79 min, *m/z* = 256 [M+H]$^+$.

The mass data is in accordance to literature [7].

1-(4′-Bromophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**f)**



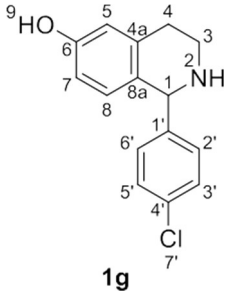
1f

The product Fehler! Verweisquelle konnte nicht gefunden werden.**f** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP$_i$-mediated *Pictet-Spengler* reaction: 110.5 mg, 0.36 mmol, 75%; one-pot process: 98 mg, 0.32 mmol, 70%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.73–2.81 (m, 1H, 4a-H), 2.89–3.00 (m, 2H, 3a-H, 4b-H), 3.11–3.17 (m, 1H, 3b-H), 4.98 (s, 1H, 1-H), 6.47–6.53 (m, 2H, 7-H, 8-H), 6.58 (d, $^4J_{5,7}$ = 1.8 Hz, 1H, 5-H), 7.12–7.18 (m, 2H, 6′-H, 2′-H), 7.44–7.49 (m, 2H, 5′-H, 3′-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 42.4 (C-3), 61.7 (C-1), 114.5 (C-7), 115.9 (C-5), 122.2 (C-8), 129.3 (C-8a), 130.1 (C-1′), 132.1 (C-6′, C-2′), 132.4 (C-5′, C-3′), 137.6 (C-4a), 144.9 (C-4′), 157.1 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2923,

1587, 1487, 1244, 1153, 1100, 1069, 1010, 811, 714, 534; **LC-MS** (API-ES, 70 eV): t_R = 7.16 min, *m*/*z* = 304 $[M+H]^+$ & *m*/*z* = 306 $[M+H]^+$.

The mass data is in accordance to literature [6,7].

1-(4'-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**g)**

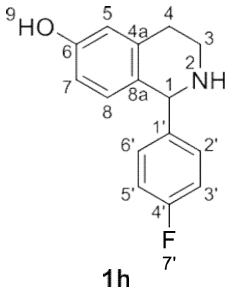


1g

The product Fehler! Verweisquelle konnte nicht gefunden werden.**g** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 99.9 mg, 0.38 mmol, 84%; one-pot process: 66 mg, 0.25 mmol, 55%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.73–2.80 (m, 1H, 4a-H), 2.89–3.00 (m, 2H, 3a-H, 4b-H), 3.09–3.18 (m, 1H, 3b-H), 4.99 (s, 1H, 1-H), 6.50 (d, $^4J_{5,7}$ = 1.5 Hz, 1H, 5-H), 6.58 (s, 1H, 5-H), 7.21 (d, $^3J_{6',5'/2',3'}$ = 8.2 Hz, 2H, 6'-H, 2'-H), 7.31 (d, $^3J_{5',6'/3',2'}$ = 8.4 Hz, 2H, 5'-H, 3'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 42.4 (C-3), 61.6 (C-1), 114.5 (C-7), 115.9 (C-5), 129.4 (C-8a), 129.4 (C-5', C-3'), 130.1 (8), 131.8 (C-6', C-2'), 134.2 (C-1'), 137.6 (C-4a), 144.5 (C-4'), 157.0 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2923, 1588, 1489, 1243, 1154, 1090, 1056, 1033, 1014, 814, 719, 537; **LC-MS** (API-ES, 70 eV): t_R = 5.18 min, *m*/*z* = 260 $[M+H]^+$.

The mass data is in accordance to literature [6].

1-(4'-Fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**h)**

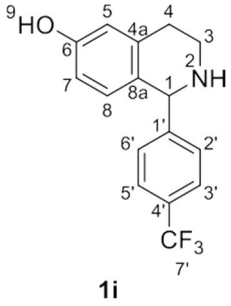


1h

The product Fehler! Verweisquelle konnte nicht gefunden werden.**h** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 99.9 mg, 0.38 mmol, 84%; one-pot process: 81 mg, 0.33 mmol, 71%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.72–2.82 (m, 1H, 4a-H), 2.90–3.02(m, 2H, 3a, 4b-H), 3.09–3.19 (m, 1H, 3b-H), 4.99 (s, 1H, 1-H), 6.50 (s, 2H, 7-H, 8-H), 6.58 (s, 1H, 5-H), 7.04 (m_c, 2H, 6'-H, 2'-H), 7.24 (m_c, 2H, 5'-H, 3'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 42.4 (C-3), 61.6 (C-1), 114.5 (C-7), 115.9 (C-6', C-2'), 115.9 (C-6', C-2'), 116.0 (C-5), 129.7 (C-8a), 130.1 (C-8), 132.0 (C-5', C-3'), 132.0 (C-5', C-3'), 137.6 (C-4a), 141.7 (C-1'), 141.7 (C-1'), 157.0 (C-6), 162.7 (C-4'), 164.4 (C-4'); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2938, 1603, 1505, 1221, 1156, 1056, 1033, 1015, 824, 551; **LC-MS** (API-ES, 70 eV): t_R = 4.52 min, *m*/*z* = 244 $[M+H]^+$.

The mass data is in accordance to literature [6].

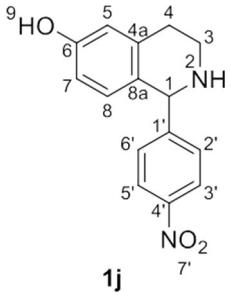
1-(4'-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**i)**



1i

The product Fehler! Verweisquelle konnte nicht gefunden werden.**i** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 69.5 mg, 0.24 mmol, 52%; one-pot process: 50 mg, 0.17 mmol, 37%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.75–2.83 (m, 1H, 4a-H), 2.91–3.03(m, 2H, 3a, 4b-H), 3.11–3.18 (m, 1H, 3b-H), 5.09 (s, 1H, 1-H), 6.44–6.55 (m,2H, 7-H, 8-H), 6.60 (d, $^4J_{5,7}$ = 2.2 Hz, 1H, 5-H), 7.43 (d, $^3J_{6',5'/2',3'}$ = 8.0 Hz, 2H, 6'-H, 2'-H), 7.62 (d, $^3J_{5',6'/3',2'}$ = 8.1 Hz, 2H, 5'-H, 3'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 42.3 (C-3), 61.8 (C-1), 114.6 (C-7), 116.0 (C-5), 123.0 (C-7'), 124.8 (C-7'), 126.2 (C-5', C-3'), 126.2 (C-5', C-3'), 126.2 (C-5', C-3'), 126.3 (C-5', C-3'), 126.6 (C-7'), 129.0 (C-8a), 130.1 (C-8), 130.5 (C-1'), 130.7 (C-1'), 130.9 (C-6', C-2'), 137.7 (C-4a), 150.2 (C-4'), 157.2 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 3269, 2938, 1607, 1456, 1415, 1322, 1251, 1153, 1124, 1106, 1062, 1033, 1020, 967, 945, 847, 824, 802, 768, 712, 667, 626, 606, 594, 572, 531, 469, 460; **LC-MS** (API-ES, 70 eV): t_R = 5.53 min, *m*/*z* = 294 $[M+H]^+$.

1-(4'-Nitrophenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**j)**

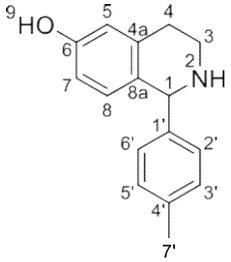


1j

The product Fehler! Verweisquelle konnte nicht gefunden werden.**j** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 69.5 mg, 0.24 mmol, 52%; one-pot process: 108 mg, 0.40 mmol, 87%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.76–2.84 (m, 1H, 4a-H), 2.91–3.04(m, 2H, 3a-H, 4b-H), 3.10–3.18 (m, 1H, 3b-H), 5.14 (s, 1H, 1-H), 6.46–6.54 (m, 2H, 7-H, 8-H), 6.61 (d, $^4J_{5,7}$ = 2.1 Hz, 1H, 5-H), 7.44–7.52 (m, 2H, 6'-H, 2'-H), 8.16–8.24 (m, 2H, 5'-H, 3'-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 42.3 (C-3), 61.6 (C-1), 114.6 (C-7), 116.1 (C-5), 124.4 (C-5', C-3'), 128.6 (C-8a), 130.1 (C-8), 131.3 (C-6', C-2'), 137.7 (C-4a), 148.7 (C-4'), 153.3 (C-1'), 157.3 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2981, 1605, 1510, 1343, 1250, 1057, 1033, 844, 803, 751, 704, 540, 467; **LC-MS** (API-ES, 70 eV): t_R = 4.45 min & t_R = 4.60 min, *m*/*z* = 271 $[M+H]^+$.

The IR and mass data are in accordance to literature [7].

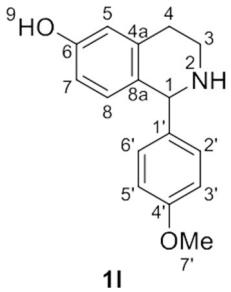
1-(4′-Methylphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**k)**



1k

The product Fehler! Verweisquelle konnte nicht gefunden werden.**k** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 65.8 mg, 0.27 mmol, 60%; one-pot process: 64 mg, 0.27 mmol, 58%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.32 (s, 3H, 7′-H), 2.70–2.83 (m, 1H,4a-H), 2.88–3.03 (m, 2H, 3a-H, 4b-H), 3.10–3.21 (m, 1H, 3b-H), 4.94 (s, 1H,1-H), 6.44–6.54 (m, 2H, 7-H, 8-H), 6.57 (d, $^4J_{5,7}$ = 2.4 Hz, 1H, 5-H), 7.12 (m_c, 4H, 6′-H, 5′-H, 3′-H, 2′-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 21.1 (C-7′), 30.0 (C-4), 42.5 (C-3), 62.1 (C-1), 114.4 (C-7), 115.8 (C-5), 130.0 (C-6′, C-2′), 130.0 (C-8a), 130.1 (C-5′, C-3′), 130.2 (C-8), 137.5 (C-4a), 138.2 (C-4′), 142.6 (C-1′), 156.9 (C-6); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2939, 1601, 1431, 1360, 1308, 1238, 1105, 1033, 1002, 891, 859, 813, 766, 698, 604, 551, 535, 494; **LC-MS** (API-ES, 70 eV): t_R = 5.15 min, *m*/*z* = 240 $[M+H]^+$.

1-(4′-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (Fehler! Verweisquelle konnte nicht gefunden werden.**l)**



1l

The product Fehler! Verweisquelle konnte nicht gefunden werden.**l** was obtained after column chromatography {dichloromethane/MeOH [4% (*v*/*v*)]/ammonia in MeOH (7 N) [1%(*v*/*v*)]} as a light yellow solid (KP_i-mediated *Pictet-Spengler* reaction: 76.7 mg, 0.30 mmol, 65%; one-pot process: 51 mg, 0.20 mmol, 43%). **^{1}H-NMR** (600 MHz, CD_3OD): δ [ppm] = 2.72–2.81 (m, 1H, 4a-H), 2.89–3.01(m, 2H, 3a, 4b-H), 3.12–3.21 (m, 1H, 3b-H), 3.78 (s, 3H, 7′-H), 4.94 (s, 1H, 1-H), 6.48 (dd, $^3J_{7,8}$ = 8.4 Hz, $^4J_{7,5}$ = 2.5 Hz, 1H, 7-H), 6.52 (d, $^3J_{8,7}$ = 8.4 Hz, 1H, 8-H), 6.57 (d, $^4J_{5,7}$ = 2.4 Hz, 1H, 5-H), 6.84–6.90 (m, 2H, 6′-H, 2′-H), 7.11–7.17 (m, 2H, 5′-H, 3′-H); **13C-NMR** (151 MHz, CD_3OD): δ [ppm] = 30.0 (C-4), 42.5 (C-3), 55.7 (C-7′), 61.8 (C-1), 114.4 (C-7), 114.7 (C-6′, C-2′), 115.8 (C-5), 130.1 (C-8a), 130.2 (C-8), 131.2 (C-5′, C-3′), 137.4 (C-4a), 137.6 (C-1′), 156.9 (C-6), 160.5 (C-4′); **IR** (ATR-Film): $\tilde{\nu}$ [cm^{-1}] = 2941, 1611, 1514, 1433, 1362, 1306, 1281, 1242, 1177, 1103, 1055, 1033, 1001, 887, 860, 817, 779, 605, 559; **LC-MS** (API-ES, 70 eV): t_R = 4.61 min & t_R = 4.80 min, *m*/*z* = 256 $[M+H]^+$.

The IR and mass data are in accordance to literature [7].

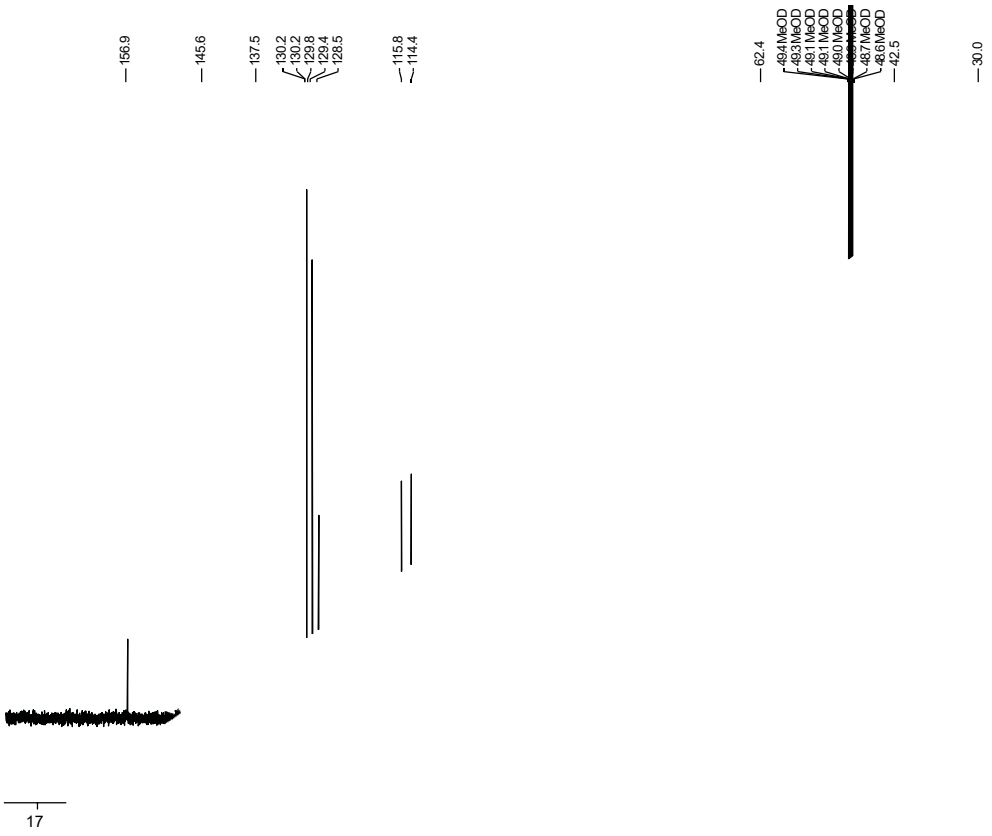


Figure S11. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**a** in CD_3OD (600 MHz/151 MHz).

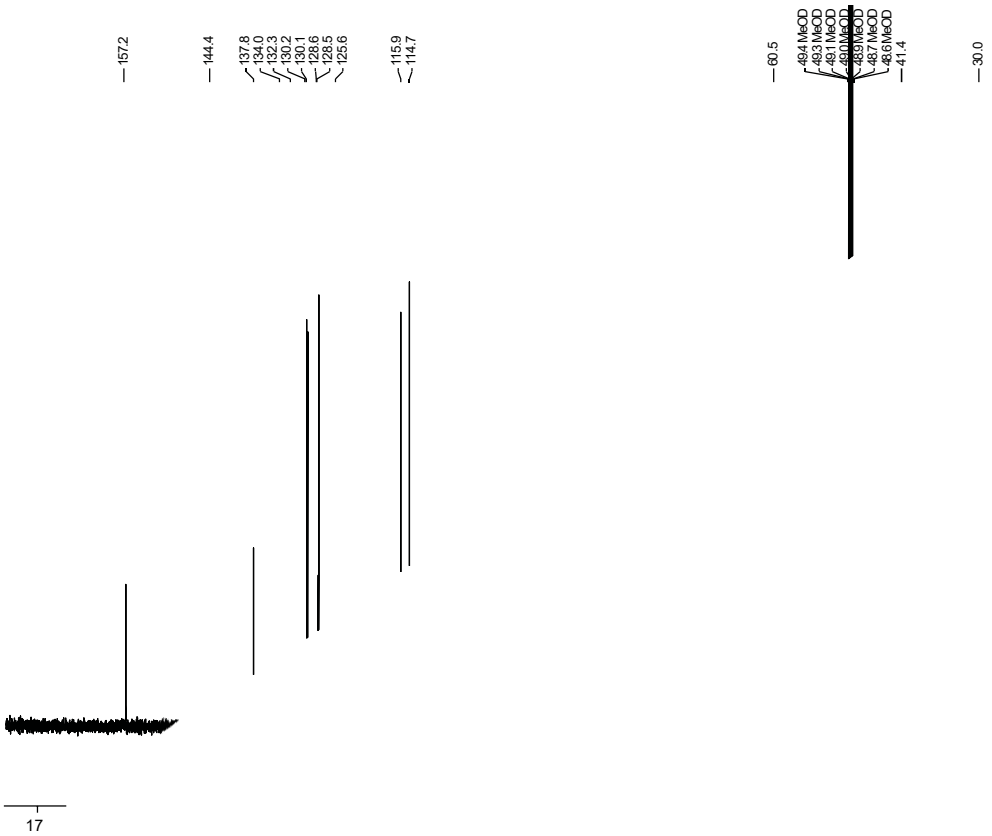


Figure S12. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**b** in CD_3OD (600 MHz/151 MHz).

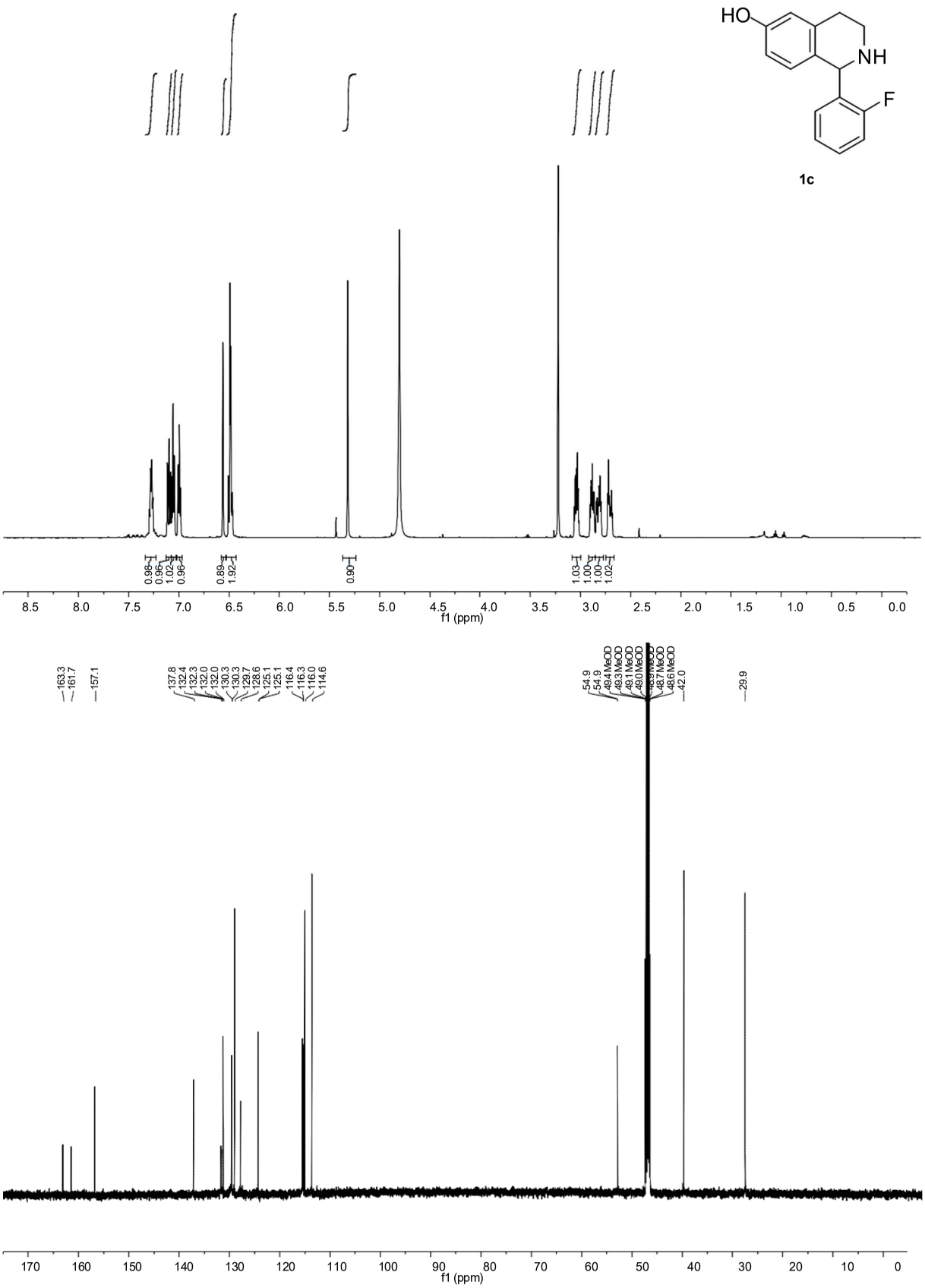


Figure S13. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**c** in CD_3OD (600 MHz/151 MHz).

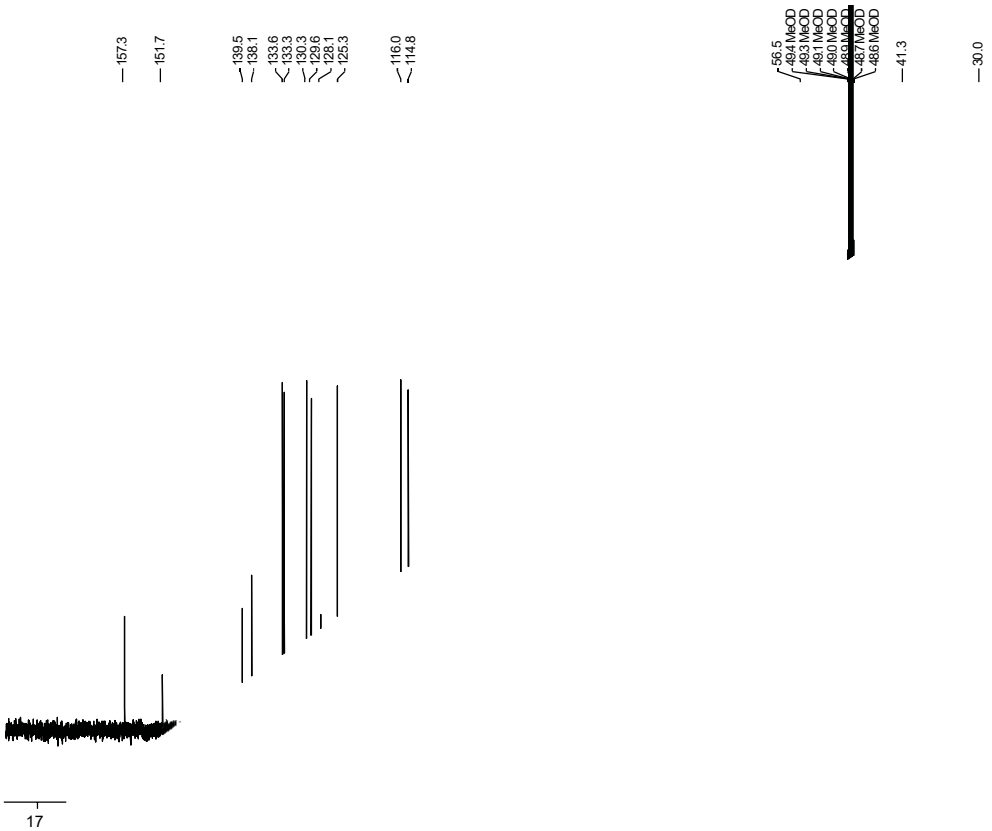


Figure S14. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**d** in CD_3OD (600 MHz/151 MHz).

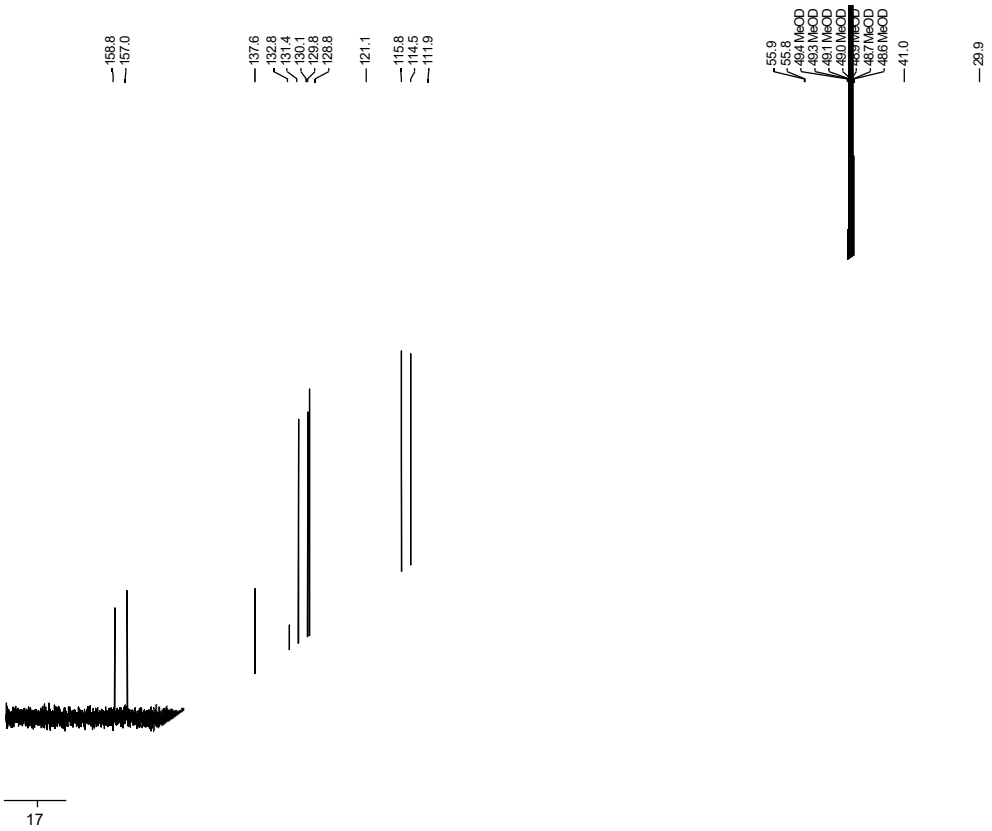


Figure S15. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**e** in CD_3OD (600 MHz/151 MHz).

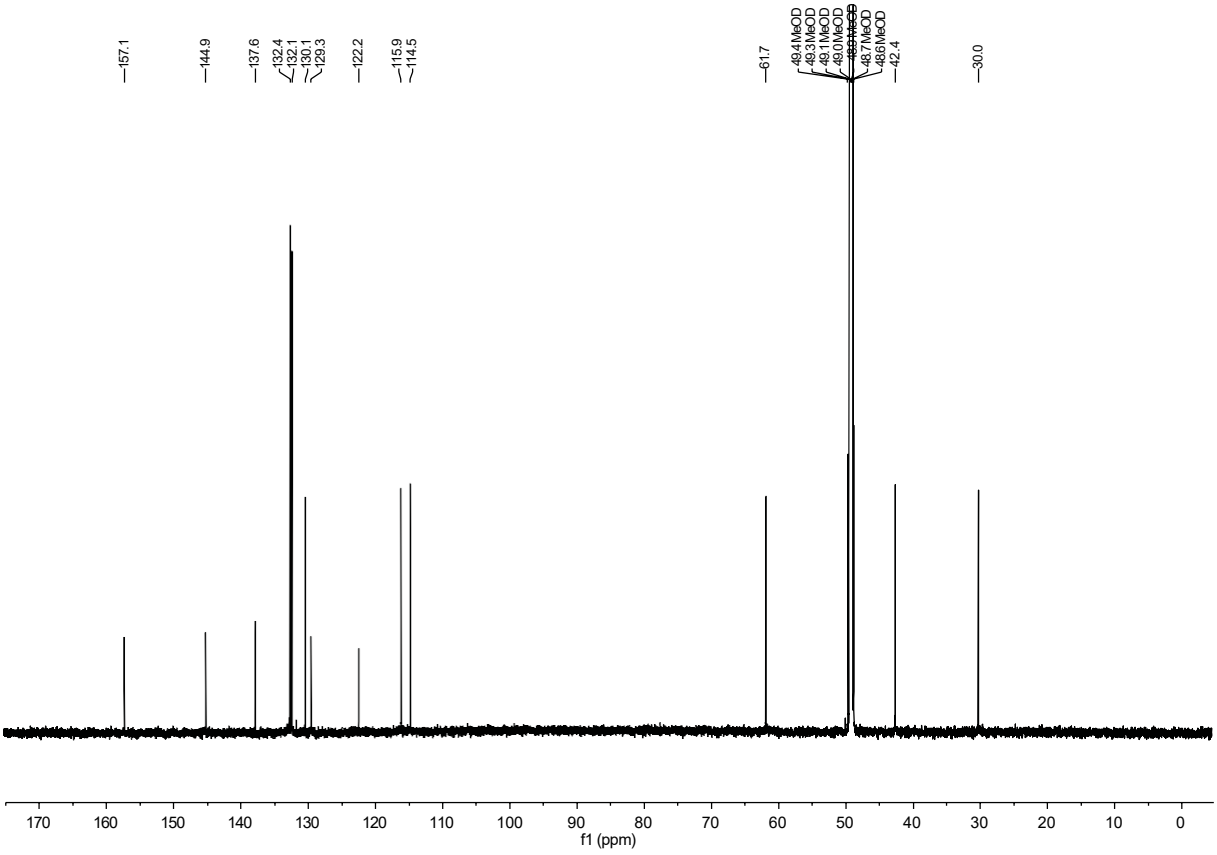


Figure S16. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**f** in CD_3OD (600 MHz/151 MHz).

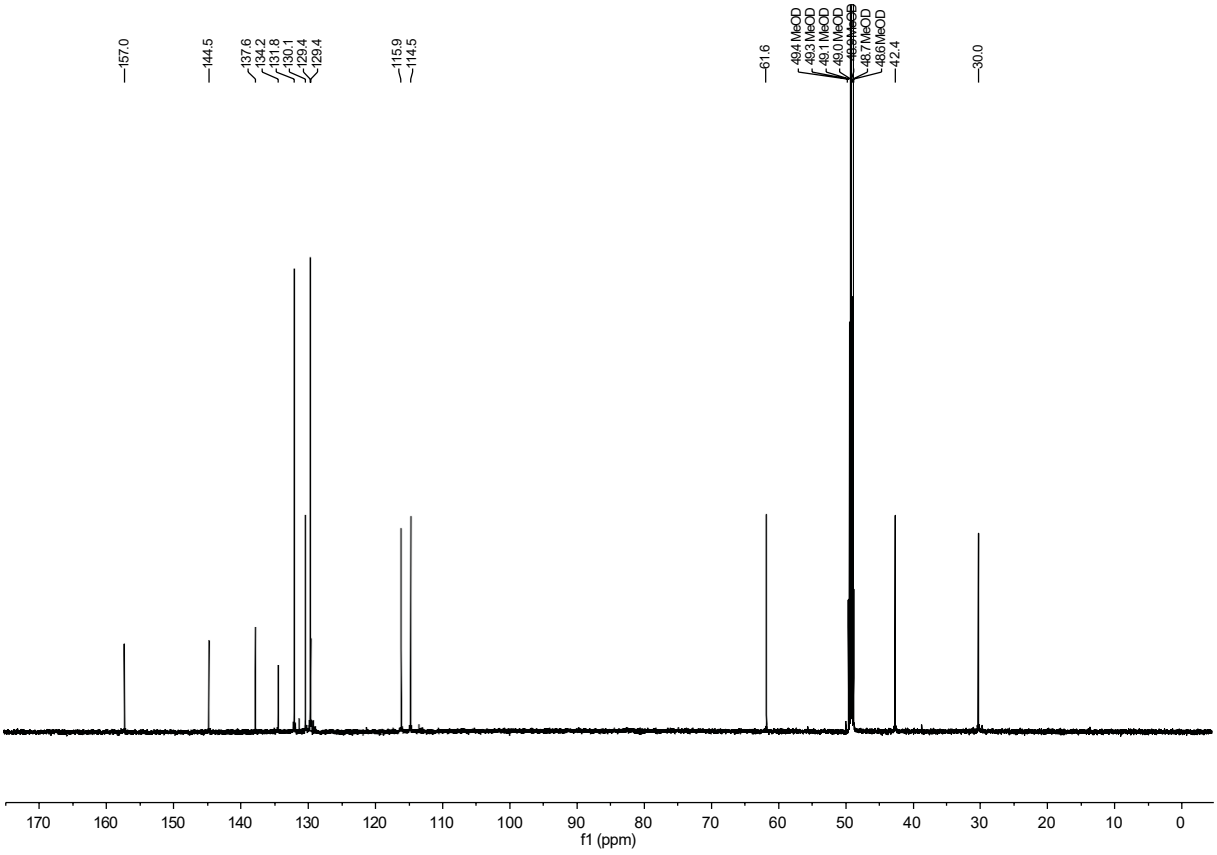


Figure S17. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**g** in CD_3OD (600 MHz/151 MHz).

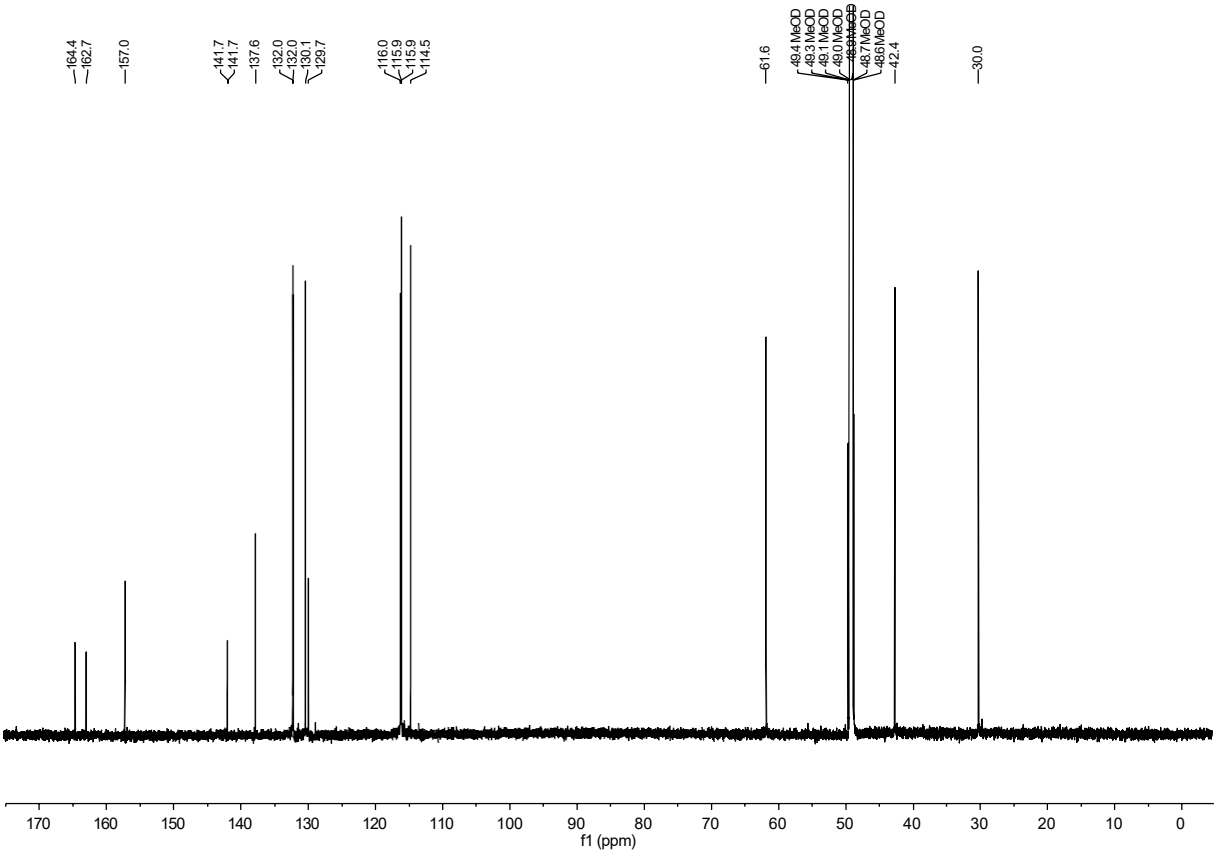


Figure S18. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**h** in CD_3OD (600 MHz/151 MHz).

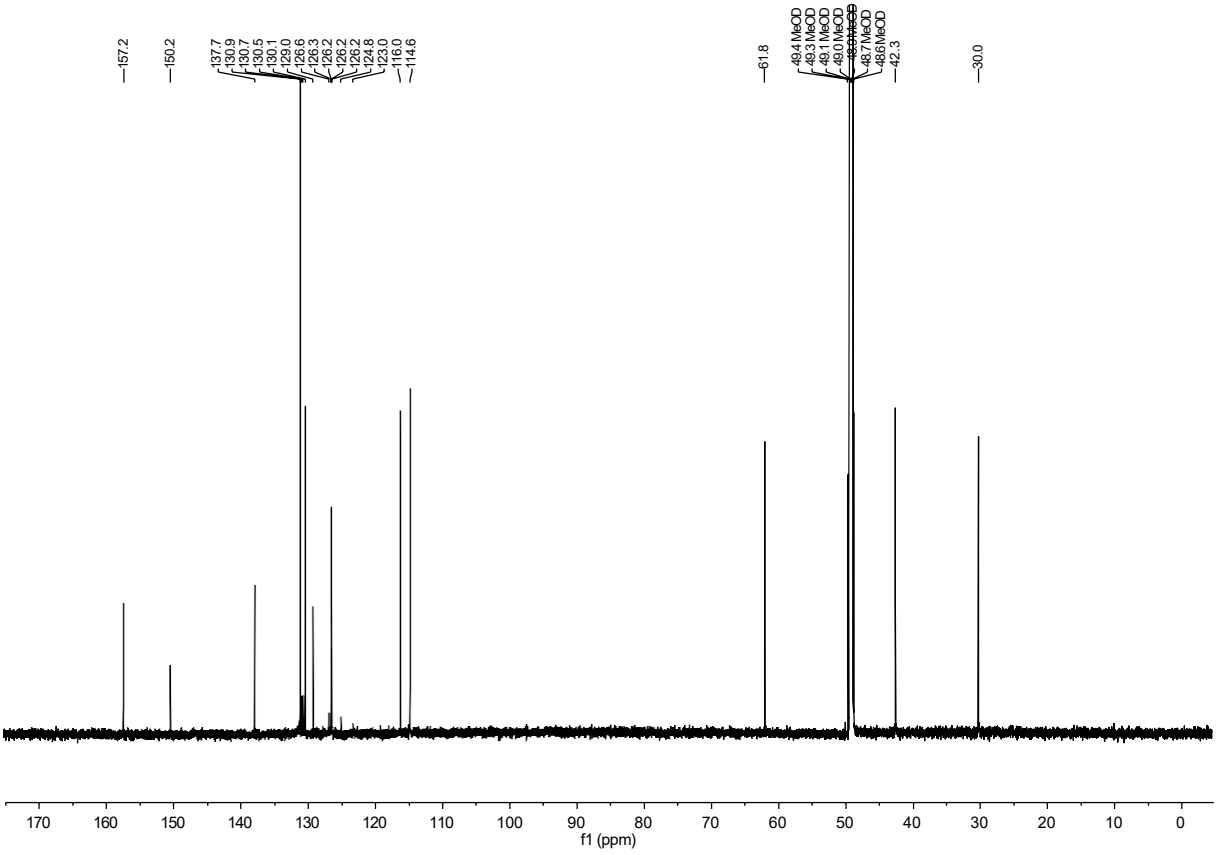


Figure S19. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**i** in CD_3OD (600 MHz/151 MHz).

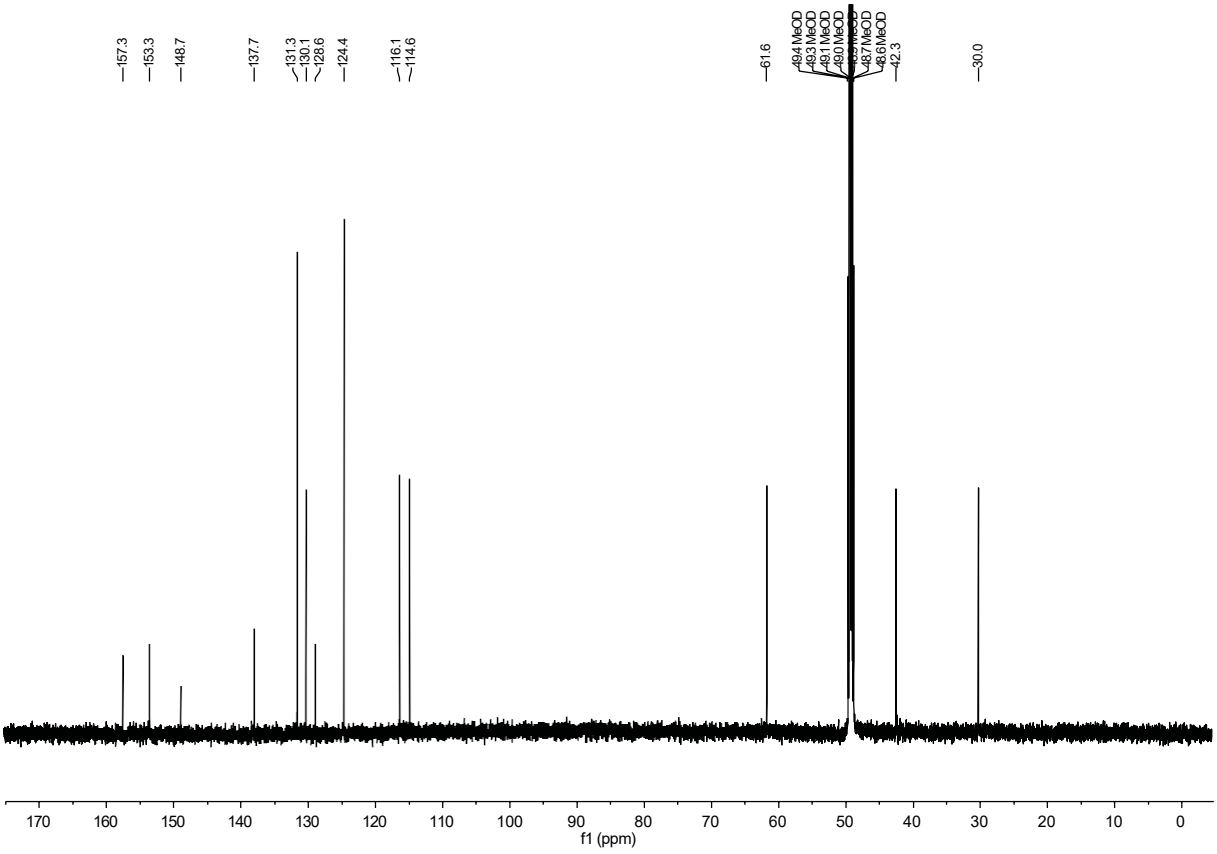


Figure S20. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**j** in CD_3OD (600 MHz/151 MHz).

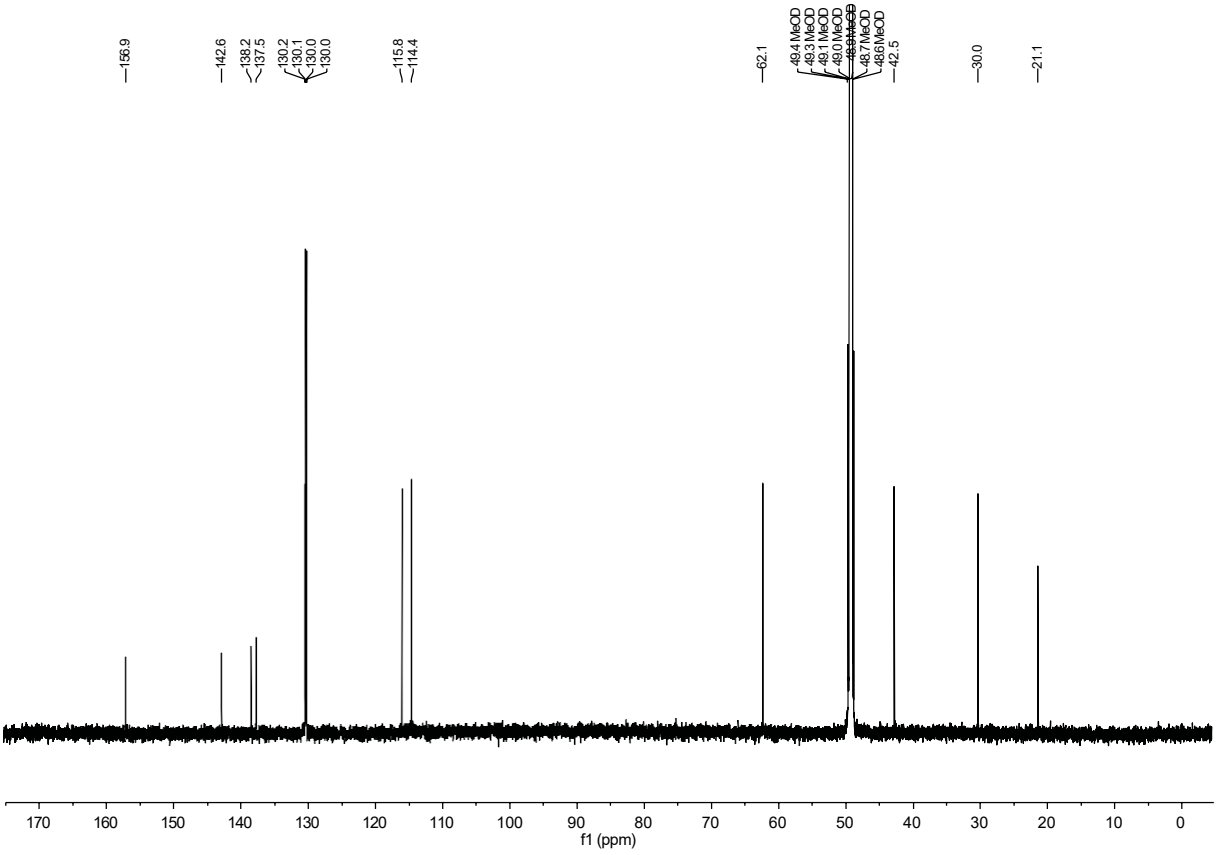


Figure S21. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**k** in CD_3OD (600 MHz/151 MHz).

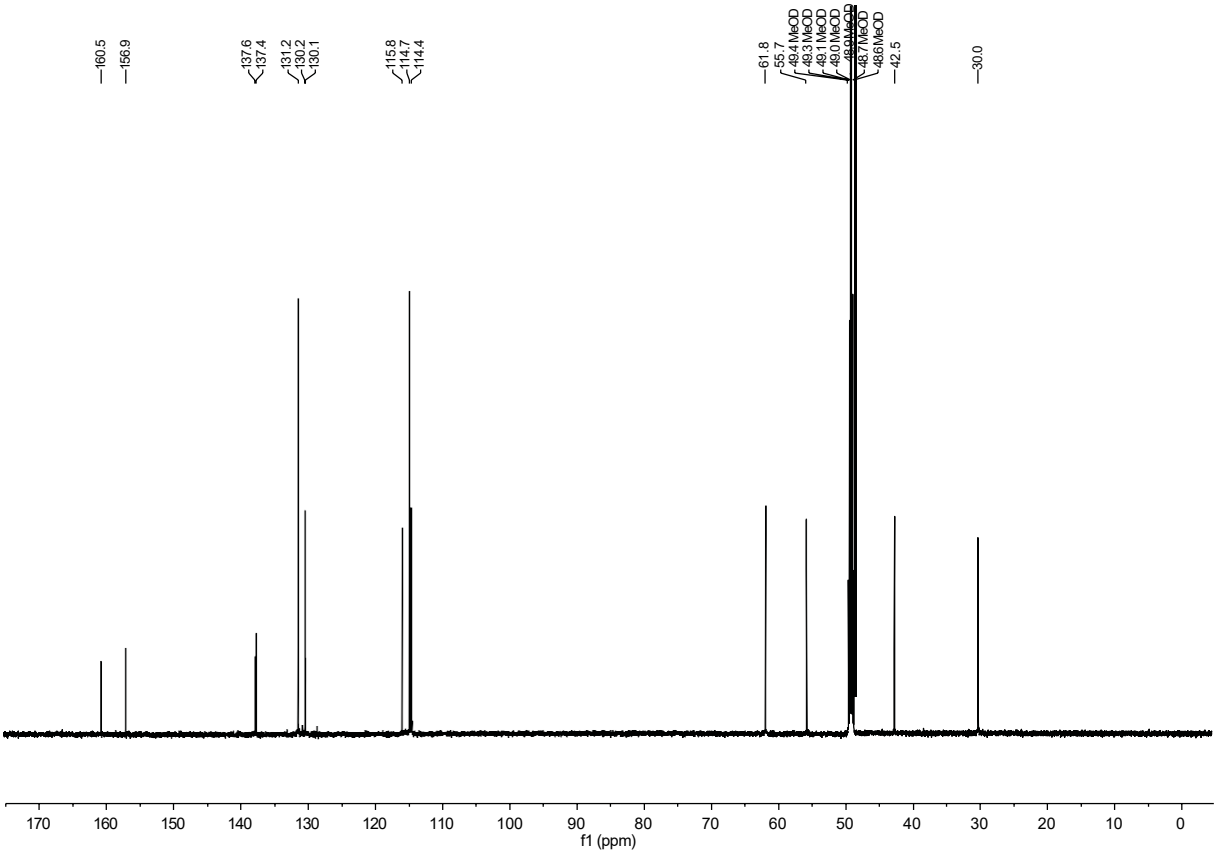


Figure S22. ^{1}H- and ^{13}C-NMR-spectra of THIQ Fehler! Verweisquelle konnte nicht gefunden werden.**l** in CD_3OD (600 MHz/151 MHz).

S7 Reaction monitoring

To follow the progress of the first reaction step in the cascade setup at 0.15 equiv of TEMPO (**2**), GC-MS analysis was performed on a 100 µL sample from the reaction solution as described (see S3.4).

Supplementary Table S1: Reaction monitoring via GC-MS analysis for the first step of the one-pot process, including reaction time and conversion.

R	1st step: Reaction time [h]	1st step: Conversion[1] [%]	Yield[2] cascade [%]	THIQ
H	41	100	32	Fehler! Verweisquelle konnte nicht gefunden werden.a
2-Br	20	n.m.	49	Fehler! Verweisquelle konnte nicht gefunden werden.b
2-F	22	92	64	Fehler! Verweisquelle konnte nicht gefunden werden.c
2-NO_2	20	n.m.	47	Fehler! Verweisquelle konnte nicht gefunden werden.d
2-OMe	44	93	57	Fehler! Verweisquelle konnte nicht gefunden werden.e
4-Br	24	100	70	Fehler! Verweisquelle konnte nicht gefunden werden.f
4-Cl	40	100	55	Fehler! Verweisquelle konnte nicht gefunden werden.g
4-F	24	97	71	Fehler! Verweisquelle konnte nicht gefunden werden.h
4-CF_3	25	100	37	Fehler! Verweisquelle konnte nicht

				gefunden werden.i Fehler! Verweisquelle
4-NO_2	45	94	87	konnte nicht gefunden werden.j Fehler! Verweisquelle
4-Me	20	n.m.	58	konnte nicht gefunden werden.k Fehler! Verweisquelle
4-OMe	24	97	43	konnte nicht gefunden werden.l

[1] The conversion is derived from the ratio (benzylic alcohol:benzaldehyde) by GC.
[2] The yields are related to the quantity of *m*-tyramine hydrobromide (4·HBr) used.
(n.m.: not measured)

S8 References

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