Synthesis of pharmaceutical drugs from waste cashew nut shell liquid

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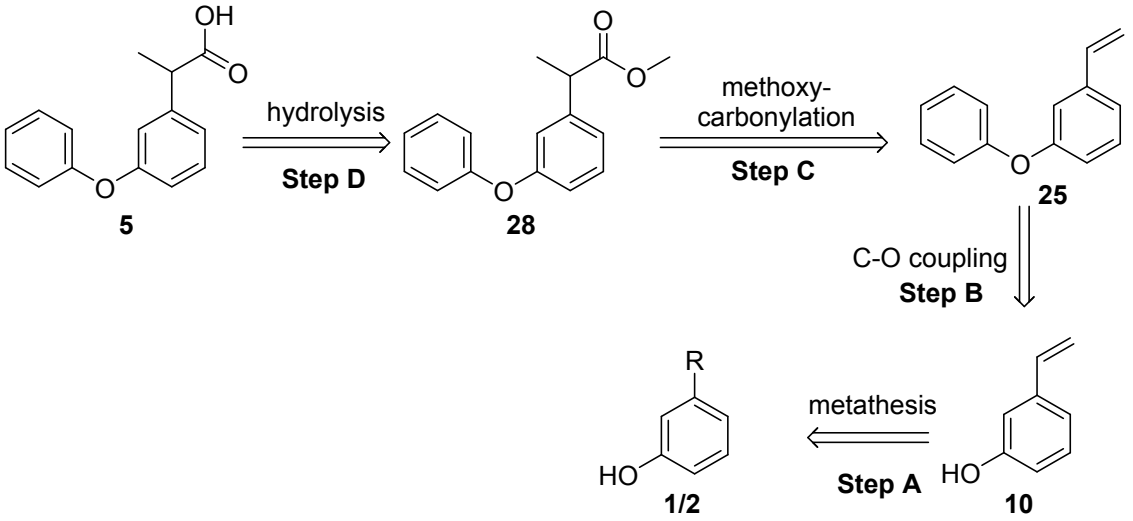
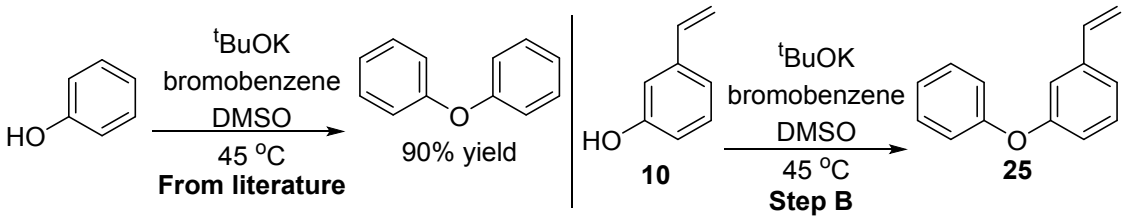
1 Tested reaction pathways for the synthesis of Fenoprofene

The initial retrosynthesis is shown in Scheme S1 which involves the conversion of the anacardic acid, **1**, or cardanol, **2**, to 3-vinyl phenol, **10**, followed by C-O coupling to diphenyl ether, **18**, which can then undergo branch selective methoxycarbonylation to the corresponding ester **28**, and a final hydrolysis step could afford the desired drug **5**.



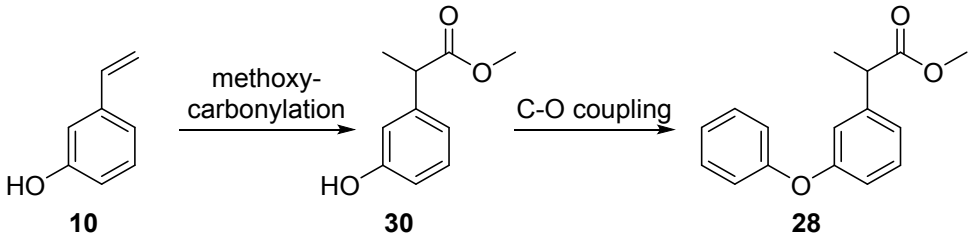
Scheme S1. Retrosynthesis of Fenoprofen from cashew nut shell liquid and derivatives.

Step A has been successfully achieved as discussed in the paper, it is then moved on to step B (C-O coupling). From the literature, it has been found that C-O coupling between phenol and bromobenzene can be achieved in the presence of potassium *tert*-butoxide to the corresponding O-Ph product in a good yield (90%) (Scheme S2).[1] However, when the same reaction conditions were applied using 3-vinyl phenol, **10**, as substrate, the expected product **25** was not obtained (Scheme S2). The starting material was fully converted to a complicated mixture of products, which was difficult to analyze.



Scheme S2. C-O coupling between alcohol and bromobenzene.

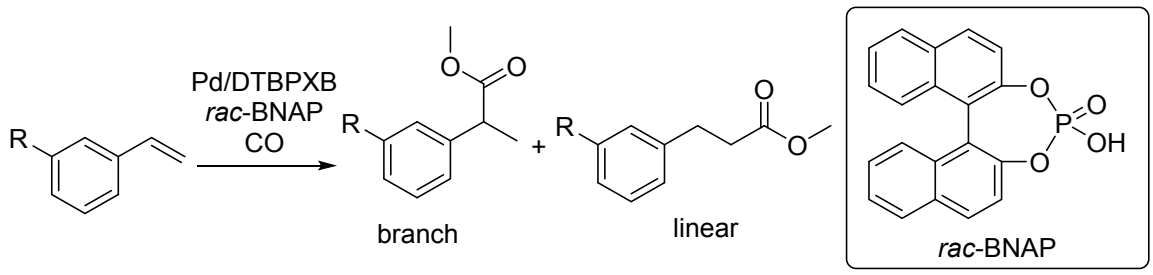
This is probably because of the instability of the styrene, so the second plan was to start with methoxycarbonylation of 3-vinylphenol, **10**, for the synthesis of methyl 2-(3-hydroxyphenyl)propanoate, **30**, to get rid of the double bond, and make the material more stable (Scheme S3).



Scheme S3. Second plan for the synthesis of fenoprofen.

Therefore, methoxycarbonylation was then studied. The conditions for branched selective methoxycarbonylation were initially optimised using styrene, **21**, as a model compound with conditions adopted from literature.[2] The branched product, methyl 2-phenylpropanoate, **31**, was obtained in 91% selectivity over the linear methyl 3-phenylpropanoate, **32** (Table S1, Entry 1). Although in the literature,[2] [$Pd(dba)_2$] was used as the catalyst, similar results were obtained when using [$Pd_2(dba)_3$] (Table S1, Entry 2). In the absence of racemic BINOL-phosphoric acid (*rac*-BNPA) no conversion of styrene was observed (Table S1, Entry 3).

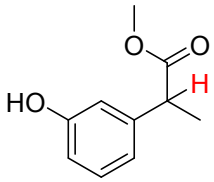
Table 1. Methoxycarbonylation of 3-vinyl phenol.[a]



Entry	R	Catalyst	Yield[b] (%)	Sel. Branch: linear[b] (%)
1	H	$[Pd(dba)_2]$	93 (92)	90.9 : 9.1
2	H	$[Pd_2(dba)_3]$	92	91.4: 8.6
3[c]	H	$[Pd(dba)_2]$	0	-
4	OH	$[Pd(dba)_2]$	92[d] (89)	89.9 : 10.1

[(a)]Substrate (1 mmol), catalyst (0.5 mol%), DTBPXB (2 mol%), *rac*-BNPA (7.5 mol%), anhydrous MeOH (0.25 mL), anhydrous DCM (0.75 mL), CO (5 bar), rt, 20 h. [(b)] Yield and selectivity was calculated by FID-GC based on calculated response factor, yield was a sum of linear and branch products. Numbers in parentheses are isolated yield. [(c)]no *rac*-BNPA [(d)]NMR yield using 1,4-dinitrobenzene as internal standard.

After optimizing the methoxycarbonylation conditions, the reaction was carried out using 3-vinyl phenol, **10**, as substrate, and 92% yield was obtained with 90% selectivity to the desired branched product, methyl 2-(3-hydroxyphenyl)propanoate, **30**, over the linear one, methyl 3-(3-hydroxyphenyl)propanoate, **33**, (Table S1, Entry 4). The isolated regioisomeric mixture was then used in the next C-O coupling step (Scheme S3) with bromobenzene. However, the expected O-Ph ester **28** did not form while a very complicated mixture was obtained instead, and its composition was difficult to analyse by GCMS, GC or NMR. This could possibly be explained by the nature of the starting material, methyl 2-(3-hydroxyphenyl)propanoate, **30**, which has more than one active side for the deprotonation (Figure S1). The proton adjacent to the carbonyl (coloured in red) could also be deprotonated by potassium *tert*-butoxide in the C-O coupling step, and therefore could lead to the formation of side products.



30

Figure S1. Structure of methyl 2-(3-hydroxyphenyl)propanoate.

2 Experimental

2.1 General methods

All the commercially available reagents were used without further purification unless specified otherwise. m-Cresol, *rac*-BNPA, 3-hydroxybenzaldehyde, 3-phenoxybenzaldehyde, methyltriphenylphosphonium bromide and ethyltriphenylphosphonium bromide were purchased from Alfa Aesar; Hoveyda-Grubbs catalyst 1st generation, Hoveyda-Grubbs catalyst

2nd generation, Grubbs catalyst 1st generation, Grubbs catalyst 2nd generation, dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]{[2-(1-methylacetoxy)phenyl]methylene}ruthenium(II), bis(dibenzylideneacetone)palladium(0) ([Pd(dba)$_2$]), anhydrous DMSO, potassium *tert*-butoxide, bromobenzene, n-BuLi, dichloro(1,5-cyclooctadiene)palladium(II), tri-*tert*-butylphosphine solution (1.0 M in toluene), pivalic anhydride and sodium borohydride were purchased from Sigma Aldrich; Tris(dibenzylideneacetone)dipalladium(0) ([Pd$_2$(dba)$_3$]) and *tert*-butyl hydroxycarbamate were purchased from Fluorochem. Iron phthalocyanine and styrene were purchased from Acros. Bis(ditertiarybutyl-phosphinomethyl)benzene was obtained from Digital Specialty Chemical Inc. Potassium *tert*-butoxide was freshly sublimed before use. Air sensitive or moisture sensitive reactions were carried out under argon in a fume hood using standard Schlenk techniques with oven-dried glassware. Flash column chromatography was performed manually using silica gel (pore size 60 Å, 70-230 mesh particle size, 40-63 μm particle size). Analytical TLC was performed on pre-coated polyester sheets of silica (60 F254 nm) and visualised by short-wave UV light at 254 nm. Permanganate TLC stain was used for compounds with no UV visible chromophore. Ninhydrin stain was also used for primary and secondary amines, which gave a dark purple spot for primary amines, and a yellow/orange spot for secondary amines. For the reactions carried out in microwave vials, Biotage 10 mL and 30 mL glass microwave vials were used. Mass spectra were recorded on a Micromass LCT with a TOF mass spectrometer coupled to a Waters 2795 HPLC and a Waters 2996 detector. NMR spectra were recorded on Bruker Avance II 400 and Bruker Avance II 500 spectrometers, ^{13}C spectra were measured with ^{1}H decoupling. Residual protio peaks from deuterated solvents were used as reference with TMS at 0 ppm. GCMS was carried out using a Thermo electron Corporaton DSQ II for the GC, and Trace GC ULTRA Thermo Electron Corporation mass spectrometer for the MS with a THERMO TR-5 (5% Phenyl Methylpolysiloxane) column. Method: 50-300 °C, ramp rate 15 °C/min, hold for 20 mins.

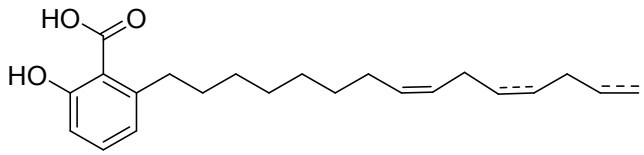
2.2 Experimental Procedures

2.2.1 Extraction of cashew nut shell liquid

Cashew nut shell liquid (CNSL) was extracted from cashew nut shells using a procedure adopted from the literature.[3] Clean dry shells (200 g) were soaked in petroleum ether (2 L) for four days. The shells were then separated from the solution by decantation followed by filtration to remove other solid particles. In order to increase the yield, the same procedure was

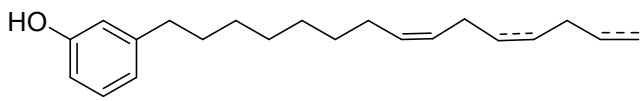
repeated to extract any remaining CNSL from the shells, and the cashew nut shell was further soaked in petrol ether for another 4 days, filtration and concentration under reduced pressure afforded cashew nut shell liquid as a brown oil (28 g, 14%).

Anacardic acid, 1



The isolation of anacardic acid from CNSL was performed using a literature procedure reported by Santos.[3] The CNSL (20 g) was dissolved in aqueous methanol (5%, 120 mL), calcium hydroxide (10 g) was then added into the solution in portions. The pinkish solution was heated at 50 °C for 3 hours. The calcium anacardate precipitated, was filtered and washed thoroughly with 5% methanol (3 × 30 mL). The crushed cake was then transferred into a flask containing HCl (6 M, 100 mL) and ethyl acetate (150 mL), and stirred for 1 hour. The organic layer was separated, washed with distilled water (3 × 50 mL), and dried over magnesium sulphate. Filtration and concentration under reduced pressure afforded anacardic acid as a brown oil (11 g, 55%). δ_H (500 MHz, $CDCl_3$) 0.88-0.96 (4H, m, CH_3/CH_2), 1.14-1.43 (27.9H, m, CH_2), 1.52-1.66 (4.3H, m, CH_2), 1.93-2.11 (6.6H, m, CH_2), 2.18-2.20 (2.3H, m, CH_2), 2.72-2.87 (4H, m, CH_2), 2.91-3.15 (3.6H, m, CH_2), 4.90-5.11 (1.6H, m, CH), 5.25-5.48 (6H, m, CH), 5.73-5.85 (0.8H, m, CH), 6.74-6.89 (3.6H, m, Ar-H), 7.35 (1.8H, t, J = 7.9 Hz), 11.1 (1.6H, br s, OH); δ_C (126 MHz, $CDCl_3$) 14.0, 14.3, 22.8, 22.9, 25.7, 25.8, 27.3, 27.4, 29.1, 29.3, 29.4, 29.5, 29.6, 29.8, 29.9, 31.7, 31.9, 32.1, 34.6, 36.6, 110.6, 112.4.8, 116.0, 122.9, 127.0, 127.7, 128.1, 128.3, 129.4, 130.0, 130.1, 130.3, 130.5, 135.4, 137.0, 147.8, 147.9, 163.7, 176.1. The uneven integral numbers in the proton NMR arise because anacardic acid is a mixture of saturated (3.9%), mono-ene (51.6%), di-ene (7%) and tri-ene (37.5%) compounds. *The spectroscopic properties of this compound were consistent with literature data*.[4]

Cardanol, 2

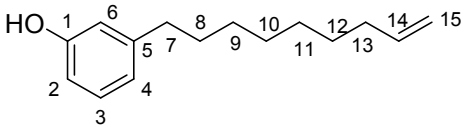


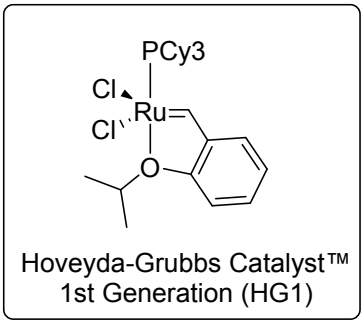
Heating anacardic acid (5 g, 14.4 mmol) at 200 °C afforded cardanol as brownish oil in a 98.6% yield (4.3 g, 14.2 mmol). δ_H (400 MHz, $CDCl_3$) 0.88-0.97 (4H, m, CH_3/CH_2), 1.26-1.48 (24.4

H, m, CH_2), 1.60 (4H, quint, J = 7.3 Hz), 1.96-2.14 (6.4H, m, CH_2), 2.52-2.61 (3.9H, m, CH_2), 2.73-2.90 (2.9H, m, CH_2), 4.97-5.14 (2.7H, m, CH), 5.24-5.51 (5.5H, m, CH), 5.76-5.93 (0.5H, m, CH), 6.63-6.71 (3.6H, m, Ar-H), 6.78 (1.9H, d, J = 7.5 Hz), 7.16 (1.8H, t, J = 7.7 Hz); δ_C (126 MHz, $CDCl_3$) 13.9, 14.3, 22.8, 22.9, 25.7, 25.8, 27.3, 29.1, 29.4, 29.5, 29.7, 29.8, 29.9, 31.4, 31.6, 31.9, 35.9, 112.6, 114.8, 115.4, 121.1, 127.0, 127.7, 128.1, 128.3, 129.4, 129.5, 130.0, 130.1, 130.3, 130.5, 155.5. The uneven integral numbers in the proton NMR arise because cardanol is a mixture of saturated, mono-ene, di-ene and tri-ene compounds. *The spectroscopic properties of this compound were consistent with literature data*.[4]

2.2.2 Synthesis of 3-vinylphenol

3-(non-8-en-1-yl)phenol, 11

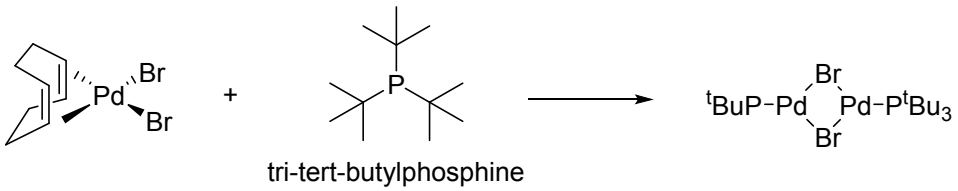




Reaction conditions adopted from literature.[5] In the glove box, Hoveyda-Grubbs 1st generation catalyst (21.6 mg, 36 μmol, 0.5 mol%) was weighed into a 30 mL microwave vial fitted with a stirrer bar. The microwave vial was sealed and removed from the glove box. Under a flow of Ar, cardanol (2.5 mL, 3.3 mmol, 1 equiv.) and anhydrous DCM (20 mL) or 2-methyl THF (20 mL) were introduced to the microwave vial by syringes. The microwave vial was introduced into a pre-purged 250 mL Hastelloy autoclave, and the cap of the microwave vial was removed under Ar flow. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (10 bar). The reaction mixture was stirred at room temperature for 16 hours. Afterwards, the reaction mixture was concentrated under reduced pressure. The product was obtained as a yellow oil (0.69 g, 96% yield when DCM was used as solvent; 0.68g, 94% yield when 2-methyl THF was used as solvent) after purification by flash column chromatography (20% ethyl acetate/ petroleum ether). δ_H (500 MHz, $CDCl_3$) 1.24-1.43 (8H, m, $H_{9\text{-}12}$), 1.60 (2H, qui, J = 7.3 Hz, H_8), 2.00-2.07 (2H, m, H_{13}), 2.56 (2H, t, J = 7.4 Hz, H_7), 4.81 (1H, s, OH), 4.91-4.96 (1H, m, H_{15}), 4.97-5.03 (1H, m, H_{15}), 5.82 (1H, ddt, J = 6.7, 10.1,

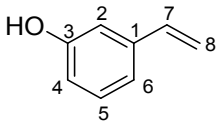
16.9, H_{14}), 6.62-6.69 (2H, m, ArH), 6.76 (1H, d, J = 7.5 Hz, ArH), 7.14 (1H, J = 7.7 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 29.1, 29.2, 29.4, 29.5, ($C_{9\text{-}12}$), 31.4 (C_8), 33.9 (C_{13}), 35.9 (C_7), 112.6, 114.3, 115.4, 121.1, 129.5 (ArC, C_{15}), 139.4 (C_{14}), 145.1 (C_5), 155.5 (C_1). *The spectroscopic properties of this compound were consistent with literature data.*[5]

Bromo(tri-tert-butylphosphine)palladium(I) dimer, 16



Reaction conditions adopted from literature.[6] A Schlenk flask was charged with [Pd(cod)$(Br)_2$] (375.5 mg, 1.0 mmol) and anhydrous toluene (2.5 mL), a solution of P^tBu_3 (1 M in toluene, 1.5 mL, 1.5 mmol) was added to the suspension. The reaction mixture was stirred at room temperature under Ar for 2 hours. Then anhydrous MeOH (7.5 mL) was added and the green reaction mixture stirred for another 20 minutes. The resulting green solid was isolated by filtration under argon, washed with anhydrous MeOH (5 × 2.5 mL) and dried *in vacuo* to afford the product as a dark green solid (325 mg, 84%). δ_H (400 MHz, C_6D_6) 1.32 (t, J = 6.2 Hz, 36H); $\delta_{P\ \{H\}}$ (162 MHz, C_6D_6) 86.2. It was stored under argon in a fridge and used within 14 d.

3-vinylphenol, 10



Method 1: Metathesis of 3-(non-8-en-1-yl)phenol

Reaction conditions adopted from literature.[5] In the glove box, Bromo(tri-tert-butylphosphine)palladium(I) dimer (5 mg, 6.5 μmol, 1.3 mol%) and **M1** (6.6 mg, 10 μmol, 2 mol%) were weighed into a 10 mL microwave vial fitted with a stirrer bar. 3-(Non-8-en-1-yl)phenol (125 mg, 0.5 mmol) in anhydrous THF (2 mL) was also added into the microwave vial. The microwave vial was sealed, removed from the glove box, and introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (5 bar). The reaction mixture was stirred

at 50 °C for 16 hours. After cooling to -78 °C, the pressure was slowly released. The reaction mixture was filtered through a plug of silica gel and the solvent was removed under reduced pressure. Under inert atmosphere, **M1** (6.6 mg, 10 μmol, 2 mol%), crude product and THF (2 mL) were added into a microwave vial with two needles in an autoclave, the autoclave was charged with ethylene gas again (5 bar). The reaction mixture was stirred at 50 °C for another 16 hours. Purification by flash column chromatography (20% ethyl acetate/ petroleum ether) afforded the product as a pale yellow oil (47 mg, 78% yield). 3-Vinylphenol is a very unstable compound and should be used on the same day of production. Otherwise, 3-vinylphenol should be diluted in DCM and stored in freezer for less than 2 days.

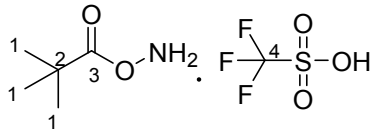
Method 2: Wittig reaction

Reaction conditions adopted from literature.[7] A Schlenk flask was charged with methyltriphenylphosphonium bromide (3.57 g, 10 mmol, 2 equiv.) and THF (50 mL, 0.2 M). The suspension was cooled to 0 ˚C and n-BuLi (4 mL, 10 mmol, 2.5 M in hexanes, 2 equiv.) was added dropwise. The yellow solution was then stirred for 2 h at 0 °C. Subsequently, 3-hydroxybenzaldehyde (0.61 g, 5 mmol, 1 equiv) in THF (4 mL, 1.25 M) was added dropwise, while a white precipitate started appearing. After allowing the solution to warm to room temperature, it was stirred for a further 16 hours. The solvent was evaporated under reduced pressure to afford the crude product, which was then purified by flash column chromatography (33% ethyl acetate/ cyclohexane) to afford the desired 3-vinylphenol as a pale yellow oil. (0.552 g, 92% yield).

δ_H (400 MHz, $CDCl_3$) 5.12 (1H, br s, OH), 5.26 (1H, dd, J = 0.8, 10.9 Hz, $H_{8\ cis\ to\ 7}$), 5.73 (1H, dd, J = 0.9, 17.5 Hz, $H_{8\ trans\ to\ 7}$), 6.67 (1H, dd, J = 10.9, 17.6 Hz, H_7), 6.75 (1H, ddd, J = 0.9, 2.6, 8.0 Hz, H_4), 6.90 (1H, dd, J = 1.6, 2.6 Hz, H_2), 7.00 (1H, ddt, J = 0.6, 1.5, 7.7 Hz, H_6), 7.21 (1H, t, J = 7.9 Hz, H_5); δ_C (101 MHz, $CDCl_3$) 112.9 (C_2), 114.5 (C_8), 115.0 (C_4), 119.3 (C_6), 129.9 (C_5), 136.5 (C_7), 139.5 (C_1), 155.7 (C_3). *The spectroscopic properties of this compound were consistent with literature data.*[7]

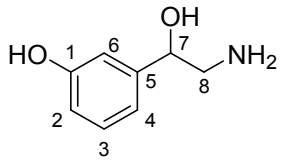
2.2.3 Synthesis of Norfenefrine

O-pivaloylhydroxylammonium triflate



Reaction conditions adopted from literature.[8] Pivalic anhydride (3.66 mL, 18.02 mmol, 1.2 equiv.) was added to a solution of *tert*-butyl hydroxycarbamate (2.00 g, 15.02 mmol, 1 equiv.) in DCM (40 mL). The reaction mixture was refluxed for 16 hours. The mixture was then quenched with sat. $NaHCO_3$ and diluted with DCM. The organic phase was washed 3 times with sat. $NaHCO_3$ after which it was dried over $MgSO_4$, filtered and evaporated under reduced pressure. 2-Methyl THF (40 mL) could also be used as solvent instead of DCM. When 2-methyl THF was used, after refluxing overnight, the mixture was concentrated under reduced pressure before the work up. The white solid obtained (3.77 g, 17.4 mmol) was dissolved in diethyl ether (40 mL) and triflic acid (1.54 mL, 17.4 mmol, 1 equiv.) was added dropwise at 0 °C. The reaction was allowed to reach room temperature and it was diluted with petroleum ether (40 mL) to precipitate the product. The mixture was filtered to obtain the desired product as a white solid (2.75 g, 69% over 2 steps). δ_H (500 MHz, d_6-DMSO) 1.22 (9H, s, H_1); δ_C (126 MHz, d_6-DMSO) 26.5 (C_1), 37.8 (C_2), 120.6 (1C, q, J = 322.8 Hz, C_4), 175.0 (C_3); δ_F (471 MHz, d_6-DMSO) -77.8. *The spectroscopic properties of this compound were consistent with literature data*.[8]

3-(2-amino-1-hydroxyethyl)phenol, 6

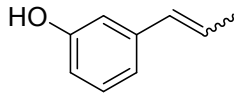


Reaction conditions adapted from literature.[9] A microwave vial fitted with a stirring bar was charged with iron (II) phthalocyanine (14.2 mg, 0.025 mmol), and degassed for 20 minutes with Ar. O-pivaloylhydroxylammonium triflate (0.33 g, 1.25 mmol) was dissolved in acetonitrile (1 mL) and water (0.5 mL), and degassed for 5 minutes. 3-Vinylphenol (60 mg, 0.5 mmol) in degassed acetonitrile (0.2 mL) and the solution of O-pivaloylhydroxylammonium triflate were added to the microwave vial containing the iron catalyst simultaneously. The reaction mixture was stirred at room temperature for 16 hours. Afterwards, the reaction mixture was diluted with methyl *tert*-butyl ether (15 mL) and extracted with a HCl solution (1 M, 3 × 15 mL). The combined water phases were concentrated under reduced pressure to afford the amine salt. Dioxane was used as internal standard for an NMR yield in deuterated water (74% yield). The free amine was obtained by dissolving the chloride salt in triethyl amine (1 equiv. to the salt) and DCM, and purified by flash column chromatography (100: 15 :1.5 of DCM: MeOH: Et_3N). The desired product was obtained as a pale yellow oil (54 mg, 71%). δ_H (500

MHz, d_6-DMSO) 2.52-2.2.56 (1H, m, H_8), 2.61-2.66 (1H, m, H_8), 4.33-4.38 (1H, m, H_7), 5.23 (1H, br s, OH), 6.58-6.62 (1H, m, ArH), 6.69-6.74 (2H, m, ArH), 7.05-7.10 (1H, m, ArH); δ_C (126 MHz, d_6-DMSO) 50.0 (C_8), 74.2 (C_7), 112.8 (ArC), 113.7 (ArC), 116.6 (ArC), 128.9 (ArC), 145.9 (C_5), 157.1 (C_1). *The spectroscopic properties of this compound were consistent with literature data*.[10]

2.2.4 Synthesis of Metaraminol

3-(prop-1-en-1-yl)phenol, 20

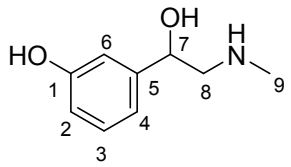


Reaction conditions adapted from literature.[7] A Schlenk flask was charged with ethyltriphenylphosphonium bromide (3.71 g, 10 mmol, 2 equiv.) and THF (50 mL, 0.2 M). The suspension was cooled to 0 ˚C and n-BuLi (4 mL, 10 mmol, 2.5 M in hexanes, 2 equiv.) was added dropwise. The yellow solution was then stirred for 2 h at 0 °C. Afterwards, 3-hydroxybenzaldehyde (0.61 g, 5 mmol, 1 equiv) in THF (4 mL, 1.25 M) was added dropwise. A white precipitate started appearing. After allowing the solution to warm to room temperature, it was stirred for further 16 hours. The solvent was evaporated under reduced pressure to afford the crude product, which was then purified by flash column chromatography (33% ethyl acetate/ cyclohexane) to afford the desired 3-prop-1-en-1-ylphenol as a colourless oil. (0.63 g, 94% yield).

A mixture of *E*- and *Z*- isomers was obtained. δ_H (400 MHz, $CDCl_3$) 1.84-1.94 (6H, m), 5.68 (2H, br s, OH), 5.77-5.85 (1H, m), 6.17-6.26 (1H, m), 6.31-6.42 (2H, m), 6.68-6.75 (2H, m), 6.80-6.86 (2H, m), 6.88-6.95 (2H, m), 7.14-7.25 (2H, m); δ_C (101 MHz, $CDCl_3$) 14.8, 18.6, 112.6, 113.6, 113.9, 115.8, 118.8, 121.7, 126.5, 127.4, 129.5, 129.5, 129.8, 130.65, 139.4, 139.8, 155.2, 155.6. *The spectroscopic properties of this compound were consistent with literature data.*[5,11]

This compound can also be prepared by isomerising ethenolysis of 3-non-1-enylphenol followed by elimination of the ethene and introduction of propene without changing the catalyst.[5]

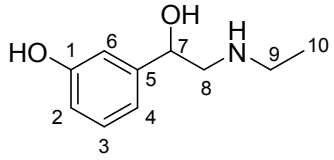
2.2.5 Synthesis of racemic Phenylephrine, 7



Reaction conditions adapted from literature.[12] Methyl triflate (164 ml, 1.5 mmol, 1.5 equiv.) was added to a solution of norfenefrine (153 mg, 1 mmol, 1 equiv.) in HFIP (1 mL) under stirring at room temperature. After 1 h, the reaction mixture was quenched by an aq. sol. of HCl (2 mol $dm^{-3,}$ 1 mL) and the reaction mixture was concentrated under reduced pressure. Dodecane was used as internal standard for an NMR yield in deuterated methanol (79% yield). A sample of the free amine for analysis was obtained by dissolving the hydrochloride salt in triethyl amine and DCM, and purified by prep-TLC (100: 10: 1 of DCM: MeOH: aq. NH_3). δ_H (500 MHz, MeOD) 2.39 (3H, s, H_9), 2.67 (1H, dd, J = 4.5 Hz, 12.1 Hz, H_8), 2.77 (1H, dd, J = 8.6 Hz, 12.1 Hz, H_8), 4.60 (1H, dd, J = 4.5 Hz, 8.6 Hz, H_7), 6.44 (1H, d, J = 7.4 Hz, ArH), 6.51-6.55 (1H, m, ArH), 6.62-6.63 (1H, m, ArH), 6.96 (1H, t, J = 7.7 Hz, H_3); δ_C (126 MHz, MeOD) 36.0 (C_9), 60.0 (C_8), 73.9 (C_7), 112.7 (C_6), 117.6 (C_2), 119.5 (C_4), 129.9 (C_3), 144.8 (C_5), 168.3 (C_1). *The spectroscopic properties of this compound were consistent with literature data.*[13]

2.2.6 Synthesis of Etilefrine

3-(2-(ethylamino)-1-hydroxyethyl)phenol; etilefrine, 8



Method 1: Reductive amination

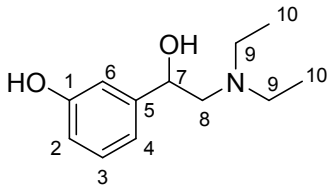
Reaction conditions adapted from literature.[14] Acetaldehyde (0.23 mL, 4 mmol, 4 equiv.) was added to a solution of norfenefrine (153 mg, 1 mmol, 1 equiv.) in EtOH (10 mL), and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to 0 °C in an ice bath before the slow addition of $NaBH_4$ (158.8 mg, 4.2 mmol, 4.2 equiv.), and stirred at 0°C for 1 hour. The reaction was quenched with water, and the reaction mixture was concentrated under reduced pressure before being dissolved in DCM. The organics were washed with sat. $NaHCO_3$ (60 mL), and the aqueous layer was extracted with a mixture of 3:1

DCM: isopropanol (5×60 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Methanol: dichloromethane: aq. NH_3 = 10: 90: 1) to afford a colourless oil (98 mg, 54%). δ_H (500 MHz, MeOD) 1.18 (3H, t, J = 7.2 Hz, H_{10}), 2.71-2.90 (4H, m, $H_{8,9}$), 4.74 (1H, dd, J = 5.4, 7.7 Hz, H_7), 6.67-6.72 (1H, m, ArH), 6.79-6.90 (2H, m, ArH), 7.16 (1H, t, J = 8.0 Hz, ArH); δ_C (126 MHz, MeOD) 13.8 (C_{10}), 44.4 (C_9), 57.0 (C_8), 72.4 (C_7), 113.8, 115.7, 118.0, 130.5 (ArH), 145.6 (C_5), 158.8 (C_1). *The spectroscopic properties of this compound were similar to those of* etilefrine. *HCl.* [15]

Method 2: Ethylation

Reaction conditions adoapted from literature.[12] Ethyl triflate (190 ml, 1.5 mmol, 1.5 equiv.) was added to a solution of norfenefrine (153 mg, 1 mmol, 1 equiv.) in HFIP (1 mL) under stirring at room temperature. After 1 h, the reaction mixture was quenched by an aq. sol. of HCl (2 mol dm^{-3}, 1 mL) and the reaction mixture was concentrated under reduced pressure. Dodecane was used as internal standard for an NMR yield in deuterated methanol (79%).

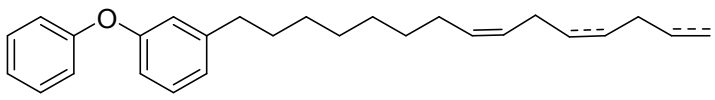
3-(2-(diethylamino)-1-hydroxyethyl)phenol, 23



Reaction conditions adapted from literature.[14] **23** was obtained as a side product during the synthesis of 3-(2-(ethylamino)-1-hydroxyethyl)phenol (etilefrine) by reductive amination. The crude product was purified by flash column chromatography (methanol: dichloromethane: aq. NH_3 = 10: 90: 1) to a colourless oil (73 mg, 35%). δ_H (500 MHz, MeOD) 1.08 (6H, t, J = 7.2 Hz, H_{10}), 2.59-2.78 (6H, m, $H_{8,9}$), 4.68 (1H, dd, J = 4.1, 8.7 Hz, H_7), 6.66-6.70 (1H, m, ArH), 6.79-6.85 (2H, m, ArH), 7.14 (1H, t, J = 8.0 Hz, ArH); δ_C (126 MHz, MeOD) 11.6 (C_{10}), 48.4 (C_9), 62.2 (C_8), 71.9 (C_7), 113.9, 115.3, 118.2, 130.4 (ArH), 146.3 (C_5), 158.6 (C_1).

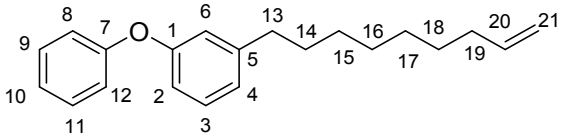
2.2.7 Synthesis of Fenoprofen

O-Phenyl Cardanol, 24



Anhydrous dimethyl sulfoxide (10 mL) was added into a microwave vial containing cardanol (3.03 g, 10 mmol, 1 equiv.) and bromobenzene (2.1 mL, 20 mmol, 2 equiv.). The solution was stirred for 5 minutes before introducing anhydrous potassium *tert*-butoxide (2.8 g, 25 mmol, 2.5 equiv.) portionwise. The microwave vial was sealed, and the reaction mixture was heated to 100°C for 8 hours. The reaction mixture was then added to water (50 mL) and extracted with DCM (4 × 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product as a brown oil. The crude material was purified by flash column chromatography (20% DCM / Hexane) to afford the desired product as a yellow oil (3.1 g, 82% yield). δ_H (500 MHz, $CDCl_3$) 0.83-0.94 (4H, m, CH_3/CH_2), 1.10-1.38 (15.9 H, m, CH_2), 1.57-1.64 (2H, m, CH_2), 1.98-2.06 (3.8H, m, CH_2), 2.53-2.62 (1.9H, m, CH_2), 5.29-5.40 (1.4H, m, CH), 6.79-6.84 (1H, m, Ar-H), 6.84-6.87 (1H, m, CH), 6.91-6.95 (1H, m, CH), 6.99-7.04 (2.7H, m, ArH), 7.06-7.13 (1.7H, m, ArH), 7.18-7.25 (1.4H, m, ArH), 7.30-7.37 (3.5H, m, ArH); δ_C (126 MHz, $CDCl_3$) 14.3, 22.8, 27.3, 27.4, 29.1, 29.4, 29.5, 29.6, 29.9, 31.5, 31.9, 36.0, 116.3, 118.8, 119.0, 119.2, 123.1, 123.3, 123.6, 129.5, 129.8, 129.9, 130.0, 130.1, 145.2, 157.2, 157.6. The uneven integral numbers in the proton NMR arise because O-phenyl cardanol is a mixture of saturated, mono-ene, di-ene and tri-ene compounds. HRMS: (EI+) Mono-ene: Found: [M]+ 378.2921, $C_{27}H_{38}O$ requires 378.2923; Tri-ene: Found: [M]+ 374.2595, $C_{27}H_{34}O$ requires 374.2610; Saturated: Found: [M]+ 380.3071, $C_{27}H_{40}O$ requires 380.3079;

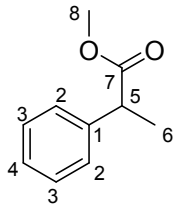
1-(Non-8-en-1-yl)-3-phenoxybenzene, 26



Reaction conditions adapted from literature.[5] In the glove box, Hoveyda-Grubbs 1st generation catalyst (3.0 mg, 5 μmol, 0.5 mol%) was weighed into a 30 mL microwave vial fitted with a stirrer bar. The microwave vial was sealed and removed from the glove box. Under a flow of Ar, degassed O-phenyl cardanol (0.38 g, 1 mmol, 1 equiv.) and anhydrous DCM (3 mL) were introduced into the microwave vial by syringes. The microwave vial was introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (10 bar). The reaction mixture was stirred at room temperature for 16 hours before being concentrated under reduced pressure.

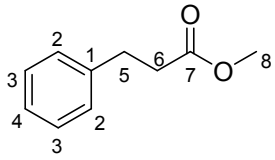
The product was obtained as a colourless oil (0.284 g, 97% yield) after purification by flash column chromatography (1% acetone/ pentane). δ_H (500 MHz, $CDCl_3$) 1.28-1.41 (8H, m, H_{15-18}), 1.61-1.71 (2H, m, H_{14}), 2.05-2.15 (2H, m, H_{19}), 2.63 (2H, t, J = 7.8 Hz, H_{13}), 4.95-5.08 (2H, m, H_{21}), 5.80-5.92 (1H, m, H_{20}), 6.85-6.89 (1H, m, ArH), 6.90-6.92 (1H, m, ArH), 6.96-6.99 (1H, m, ArH), 7.04-7.08 (2H, m, ArH), 7.12-7.16 (1H, m, ArH), 7.26-7.30 (1H, m, ArH), 7.35-7.40 (2H, m, ArH); δ_C (126 MHz, $CDCl_3$) 29.0, 29.1, 29.3, 29.4 (C_{15-18}), 31.3 (C_{14}), 33.9 (C_{19}), 35.9 (C_{13}), 114.2, 116.2, 118.8, 119.1, 123.0, 123.5, 129.5, 129.7, 139.2, 145.1, 157.1, 157.5 ($C_{1,7}$). HRMS: (ASAP+) Found: [M+H]+ 295.2061, $C_{21}H_{27}O$ requires 295.2062.

Methyl 2-phenylpropanoate



Reaction conditions adapted from literature.[2] In the glovebox, [$Pd(dba)_2$] (2.9 mg, 5 μmol, 0.5 mol%), bis(ditertiarybutyl-phosphinomethyl)benzene (DTBPMB) (7.9 mg, 20 μmol, 2 mol%), *rac*-BNPA (26 mg, 75 μmol, 7.5 mol%) were weighed and added into a 10 mL microwave vial. The microwave vial was sealed and removed from the glovebox. Under a flow of Ar, anhydrous DCM (0.75 mL), distilled MeOH (0.25 mL), and styrene (115 μL, 1.0 mmol, 1 equiv.) were added into the microwave vial. The vial was then introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with CO gas (~5 bar), and charged with CO (5 bar). The reaction mixture was stirred at room temperature for 24 hours. The b : l ration was determined by GC-FID (91 : 9). The yield was determined by GC-FID with dodecane as internal standard (93% yield). The crude product was purified by flash column chromatography (5% ethyl acetate/ cyclohexane), the regioisomeric compounds were obtained as a colourless oil (0.15 g, 92% yield). δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, J = 7.2 Hz, H_6), 3.69 (3H, s, H_8), 3.77 (1H, q, J = 7.2 Hz, H_5), 7.29-7.39 (5H, m, H_{1-4}); δ_C (101 MHz, $CDCl_3$) 18.7 (C_6), 45.5 (C_5), 52.1 (C_8), 127.2, 127.6, 128.7 (C_{2-4}), 140.6 (C_1), 175.1 (C_7).

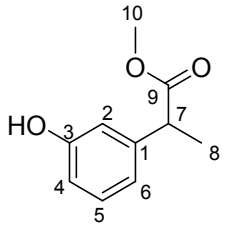
Minor signals for linear regioisomer:



δ_H (400 MHz, $CDCl_3$) 2.68 (2H, dd, J = 7.2, 8.5 Hz, H_6), 3.00 (2H, t, J = 7.8 Hz, H_5), 3.71 (3H, s, H_8), aromatic region was not assigned because of the overlap; δ_C (101 MHz, $CDCl_3$) 31.0 (C_5), 35.8 (C_6), 51.7 (C_8), 126.4, 128.3, 128.6 ($C_{2\text{-}4}$), 140.5 (C_1), 173.4 (C_7).

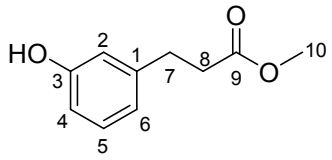
The spectroscopic properties of this compound were consistent with literature data.[2]

methyl 2-(3-hydroxyphenyl)propanoate



Reaction conditions adapted from literature.[2] In the glovebox, [$Pd(dba)_2$] (2.9 mg, 5 μmol, 0.5 mol%), bis(ditertiarybutyl-phosphinomethyl)benzene (DTBPMB) (7.9 mg, 20 μmol, 2 mol%), *rac*-BNPA (26 mg, 75 μmol, 7.5 mol%) were weighed and added into a 10 mL microwave vial. The microwave vial was sealed and removed from the glovebox. Under a flow of Ar, anhydrous DCM (0.75 mL), distilled MeOH (0.25 mL), and 3-vinylphenol in anhydrous DCM (1 mL, 1.0 mmol, 1 equiv., 1 M stock solution) were added into the microwave vial. The vial was then introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with CO gas (~5 bar), and charged with CO (5 bar). The reaction mixture was stirred at room temperature for 24 hours. The b : l ratio was determined by GC-FID (91 : 9). The crude product was purified by flash column chromatography (20% ethyl acetate/ petroleum ether), the regioisomeric compounds were obtained as a colourless oil (0.16 g, 89% yield of both branched and linear products in 91 : 9 ratio). δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, J = 7.2 Hz, H_8), 3.67 (3H, s, H_{10}), 3.69 (1H, q, J = 7.2 Hz, H_7), 6.48 (1H, br s, OH), 6.74-6.78 (1H, m, H_6), 6.81-6.86 (2H, m, $H_{2,4}$), 7.14-7.21 (1H, m, H_5); δ_C (101 MHz, $CDCl_3$) 18.5 (C_8), 45.4 (C_7), 52.5 (C_{10}), 114.4, 114.5 ($C_{2,4}$), 119.8 (C_6), 130.0 (C_5), 142.0 (C_1), 156.3 (C_3), 175.9 (C_9).

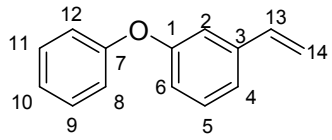
Minor signals for linear regioisomer:



δ_H (400 MHz, $CDCl_3$) 2.63 (2H, dd, J = 7.2, 8.4 Hz, H_8), 2.89 (2H, t, J = 7.8 Hz, H_7), 3.68 (3H, s, H_{10}), 3.69 (1H, q, J = 7.2 Hz, H_7), 6.28 (1H, br s, OH), aromatic region was not assigned because of the overlap; δ_C (101 MHz, $CDCl_3$) 30.9 (C_7), 35.7 (C_8), 52.0 (C_{10}), 113.5, 115.4 ($C_{2,4}$), 120.5 (C_6), 129.8 (C_5), 142.2 (C_1), 156.0 (C_3), 174.2 (C_9).

The spectroscopic properties of these compounds were consistent with literature data.[16]

1-phenoxy-3-vinylbenzene, 25



Method 1: Metathesis of 3-(non-8-en-1-yl)phenol

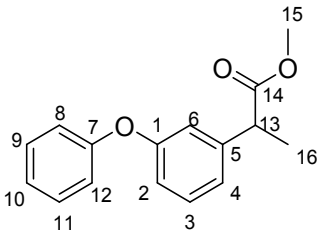
Reaction condition adapted from literature.[5] In the glove box, Bromo(tri-tert-butylphosphine)palladium(I) dimer (5 mg, 6.5 μmol, 1.3 mol%) and **M1** (6.6 mg, 10 μmol, 2 mol%) were weighed into a 10 mL microwave vial fitted with a stirrer bar. 1-(Non-8-en-1-yl)-3-phenoxybenzene (147 mg, 0.5 mmol) in anhydrous THF (2 mL) was also added into the microwave vial. The microwave vial was sealed, removed from the glove box, and introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (5 bar). The reaction mixture was stirred at 50 °C for 16 hours. After cooling to -78 °C, the pressure was slowly released. The reaction mixture was filtered through a plug of silica gel and the solvent was removed under reduced pressure. Under inert atmosphere, **M1** (6.6 mg, 10 μmol, 2 mol%), crude product and anhydrous THF (2 mL) were added into a microwave vial with two needles in an autoclave, the autoclave was purged and charged with ethylene gas again (5 bar). The reaction mixture was stirred at 50 °C for another 16 hours. Purification by flash column chromatography (20% ethyl acetate/ petroleum ether) afforded the product as a colourless oil (79 mg, 80% yield).

Method 2: Wittig reaction

Reaction conditions adapted from literature.[7] A Schlenk flask was charged with methyltriphenylphosphonium bromide (10.71 g, 30 mmol, 2 equiv.) and anhydrous THF (150 mL, 0.2 mol dm^{-3}). The suspension was cooled to 0 ˚C and n-BuLi (12 mL, 30 mmol, 2.5 M in hexanes, 2 equiv.) was added dropwise. The yellow solution was then stirred for 2 h at 0 °C. Afterwards, 3-phenoxybenzaldehyde (2.6 mL, 15 mmol, 1 equiv) in anhydrous THF (12 mL, 1.25 M) was added dropwise. After allowing the solution to warm to room temperature, it was stirred for a further 16 hours. The solvent was evaporated under reduced pressure to afford the crude product, which was then purified by flash column chromatography (20% ethyl acetate/ petroleum ether) to afford the desired 1-phenoxy-3-vinylbenzene as a colourless oil. (1.7 g, 58% yield).

δ_H (400 MHz, $CDCl_3$) 5.27 (1H, dd, J = 0.8, 10.9 Hz, $H_{14\ cis\ to\ 13}$), 5.73 (1H, dd, J = 0.8, 17.6 Hz, $H_{14\ trans\ to\ 13}$), 6.69 (1H, dd, J = 10.9, 17.6 Hz, H_{13}), 6.92 (1H, ddd, J = 1.0, 2.5, 8.1 Hz, H_2), 6.99-7.06 (2H, m, ArH), 7.08-7.20 (3H, m, ArH), 7.27-7.41 (3H, m, ArH); δ_C (101 MHz, $CDCl_3$) 114.8 (C_{14}), 116.6, 118.4, 119.0, 121.5, 123.4, 129.8 129.9 (ArC), 136.4 (C_{13}), 139.6 (C_3), 157.3, 157.6 ($C_{1,\ 7}$). *The spectroscopic properties of these compounds were consistent with literature data*.[17]

methyl 2-(3-phenoxyphenyl)propanoate, 28



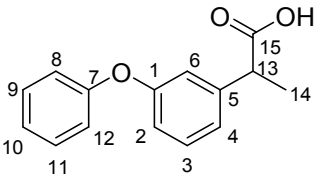
Reaction conditions adapted from literature.[2] In the glovebox, [Pd(dba)$_2$] (2.9 mg, 5 μmol, 0.5 mol%), bis(ditertiarybutyl-phosphinomethyl)benzene (DTBPMB) (7.9 mg, 20 μmol, 2 mol%), *rac*-BNPA (26 mg, 75 μmol, 7.5 mol%) were weighed and added into a 10 mL microwave vial. The microwave vial was sealed and removed from the glovebox. Under a flow of Ar, anhydrous DCM (0.75 mL), distilled MeOH (0.25 mL), and 1-phenoxy-3-vinylbenzene (0.196 g, 1.0 mmol, 1 equiv.) were added into the microwave vial. The vial was then introduced into a pre-purged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with CO gas (~5 bar), and charged with CO (5 bar). The reaction mixture was stirred at room temperature for 24 hours. The b : l ratio was determined by GC-FID (89 : 11). The crude

product was purified by flash column chromatography (10% ethyl acetate in petroleum ether) and the regioisomeric compounds were obtained as a colourless oil (0.24 g, 94% yield in total, 82% branched, 12% linear product by isolation and NMR analysis of the mixture). δ_H (500 MHz, $CDCl_3$) 1.49 (3H, d, J = 7.2 Hz, H_{16}), 3.67 (3H, s, H_{15}), 3.70 (1H, q, J = 7.2 Hz, H_{13}), 6.86-6.89 (1H, m, ArH), 6.97-7.05 (4H, m, ArH), 7.09-7.13 (1H, m, ArH), 7.27 (1H, t, J = 7.9 Hz, ArH), 7.32-7.37 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 18.6 (C_{16}), 45.4 (C_{13}), 52.3 (C_{15}), 117.4, 118.2, 119.1, 122.4, 123.5, 129.9, 130.0 (ArC), 142.6 (C_5), 157.1, 157.5 ($C_{1,7}$), 174.8 (C_{14}). *The spectroscopic properties of this compound were consistent with literature data*.[18]

[redacted]

The reaction procedure was adapted from literature.[19] Lithium chloride (4.8 mg, 0.11 mmol), *para*-toluenesulfonic acid monohydrate (20.9 mg, 1.1 mmol) and [$PdCl_2$((R)-xylyl-phanephos)] (4.84 mg, 0.0055 mmol) were weighed into a microwave vial equipped with a magnetic stirrer bar. The vial was sealed and flushed with Ar for 30 min. 3-Vinylphenol (66 mg, 0.55 mmol) was dissolved in degassed methanol (0.75 mL) which was transferred into the microwave vial. The microwave vial was pierced with two needles and quickly placed in to an autoclave. The autoclave was sealed, purged three times with CO and then pressurized to 30 bar. The autoclave was then placed in an oil bath at 40 °C for 17 h. Afterwards, the autoclave was cooled to room temperature, the pressure was slowly released into a well-ventilated fume cupboard. The conversion (43.6%) and the branch: linear selectivity of the product (69 %) was analysed by GC-FID with dodecane as internal standard. The enantiomeric excess was obtained by using chiral HPLC (88 % e.e., OD-H column, 99:1 hexane /Isopropanol), 1 mL/min, t_R[+]-S=12.51 min, t_R[-]-R= 13 min).

2-(3-phenoxyphenyl)propanoic acid; Fenoprofen, 5



Methyl 2-(3-phenoxyphenyl)propanoate (50 mg, 0.2 mmol, 1 equiv.) was introduced into a round bottomed flask. Dioxane (5 mL), distilled water (5 mL), and hydrochloric acid (36% in water, 2 drops) were added and the mixture was heated under relux overnight until TLC indicated the full consumption of the ester. After cooling, dilute HCl (1M) was added to the

reaction mixture to a pH of 1, which was then extracted 3 times with DCM (20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% ethyl acetate/ petroleum ether) to a colourless oil (43 mg, 91%). δ_H (500 MHz, $CDCl_3$) 1.51 (3H, d, J = 7.2 Hz, H_{14}), 3.72 (1H, q, J = 7.2 Hz, H_{13}), 6.87-6.91 (1H, m, ArH), 7.00-7.04 (3H, m, ArH), 7.05-7.08 (1H, m, ArH), 7.09-7.14 (1H, m, ArH), 7.29 (1H, t, J = 7.9 Hz, ArH), 7.32-7.36 (2H, m, ArH); δ_C (126 MHz, $CDCl_3$) 18.2 (C_{14}), 45.3 (C_{13}), 117.6, 118.4, 119.1, 122.5, 123.5, 129.9, 130.0 (ArC), 141.8 (C_5), 157.0, 157.6 ($C_{1,7}$), 180.4 (C_{15}). *The spectroscopic properties of this compound were consistent with literature data*.[20]

2. Atom Economy and E Factors

2.1 Atom economy[21,22]

Atom economy for the processes described in this paper and representative process derived from the literature were obtained by calculating:

$$100 * M_r \text{ (desired product)} / M_r \text{ (all starting materials)}$$

In addition, since the two of the side products in the formation of 3-non-8-enylphenol from cardanol (1-octene and 1,4-cycohexadiene) and the side product from the formation of 2-vinylphenol (propene) are valuable and easily separable, we have calculated an atom economy based on all valuable products. Both of these Atom economy values are included in Table 4 of the main paper. Overall atom economies for the drug syntheses and for their literature comparators were obtained either by considering all starting materials together or as the product of the atom economies for each individual step.

Since cardanol is a mixture of compounds, all having the same basic structure but with 0, 1, 2 or 3 double bonds in the C_{15} chain and since the metathesis of 3-pendeca-8, 11, 14-trienlyphenol to 3-non-8-enylphenol and 1,4-cyclohexadiene does not require ethene, we have taken the composition and ethene requirement of each compound in the mixture into account when calculating the atom economy.

2.2 E Factor[23,24]

E factors were calculated by assuming all useful and easily separable products should not be considered as waste using the formula:

$$\text{E Factor} = \text{total mass of waste/total mass of useful products}$$

The same considerations about ethene usage and the non-homogeneity of cardanol described in Section 2.1 also apply to the E factor calculations. In addition, it was assumed, when calculating the E factor for the formation of 2-vinylphenol from 9-non-8-enylphenol, that the major side products were 3-propenylphenol and 1-butene, as discussed in a previous publication.[5]

3. NMR spectra of pure samples

3.1. Cashew nut shell liquid, anacardic acids and cardanols

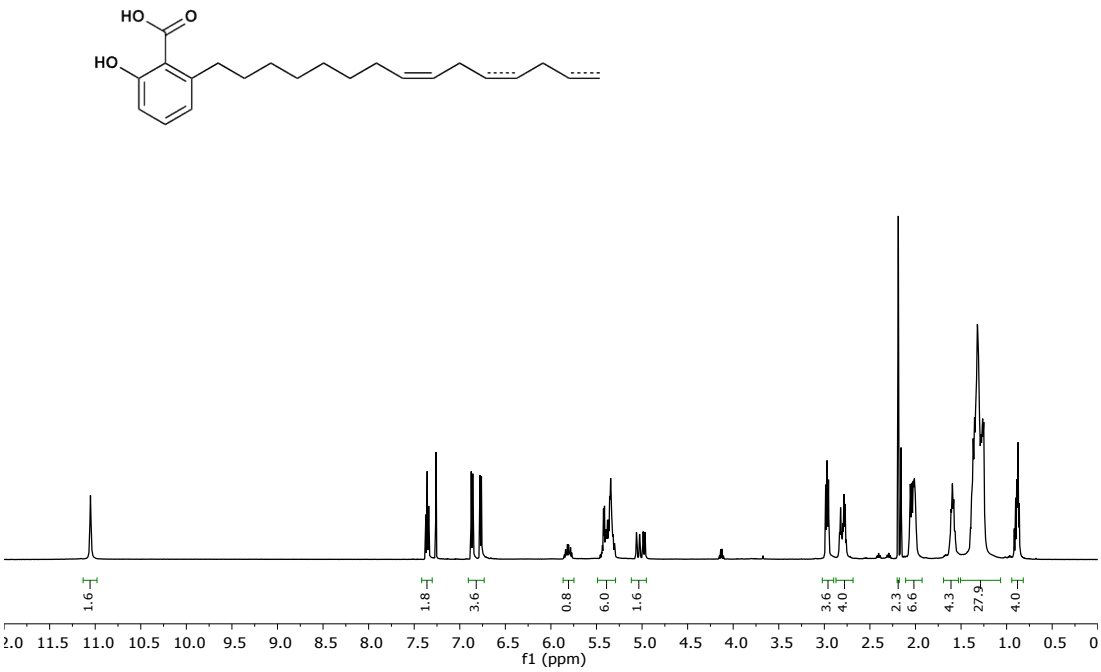


Figure S2. ^{1}H NMR (500 MHz, $CDCl_3$) of anacardic acid.

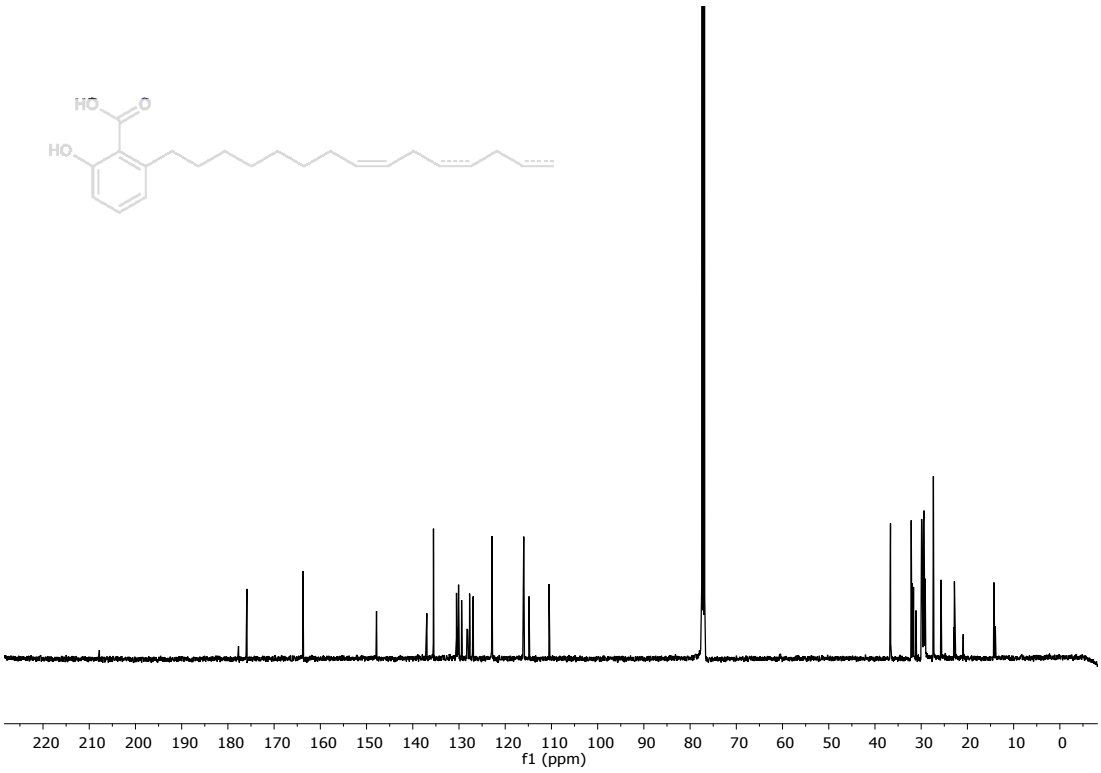


Figure S3. ^{13}C NMR (126 MHz, $CDCl_3$) of anacardic acid.

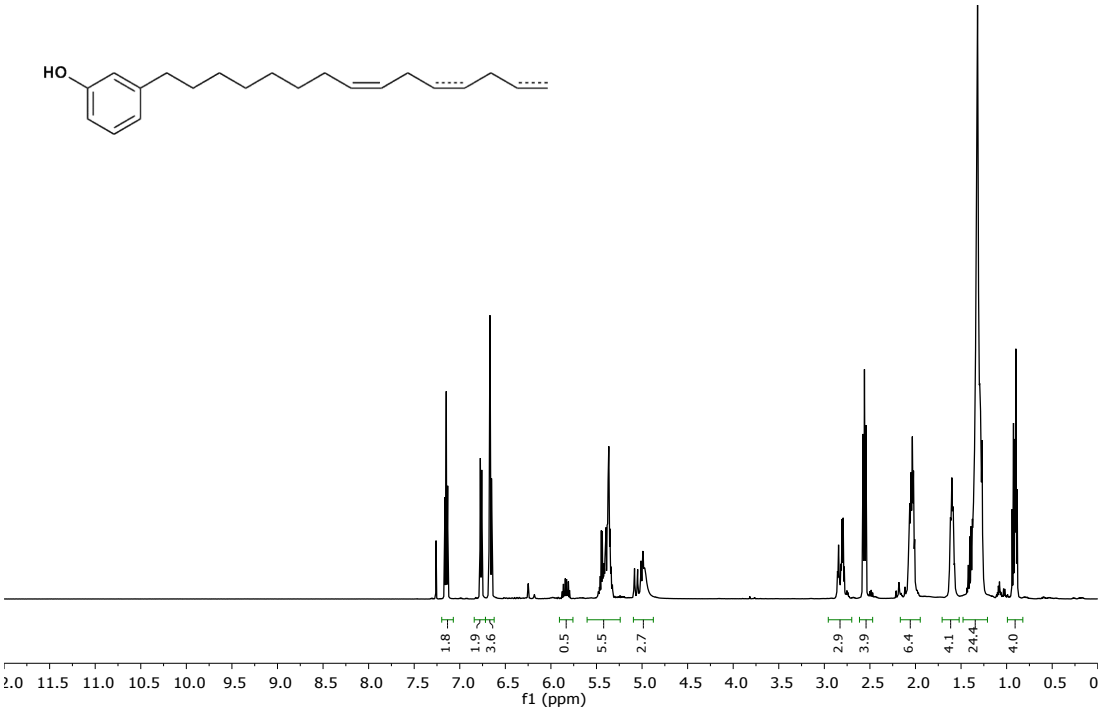


Figure S4. ^{1}H NMR (500 MHz, $CDCl_3$) of cardanol.

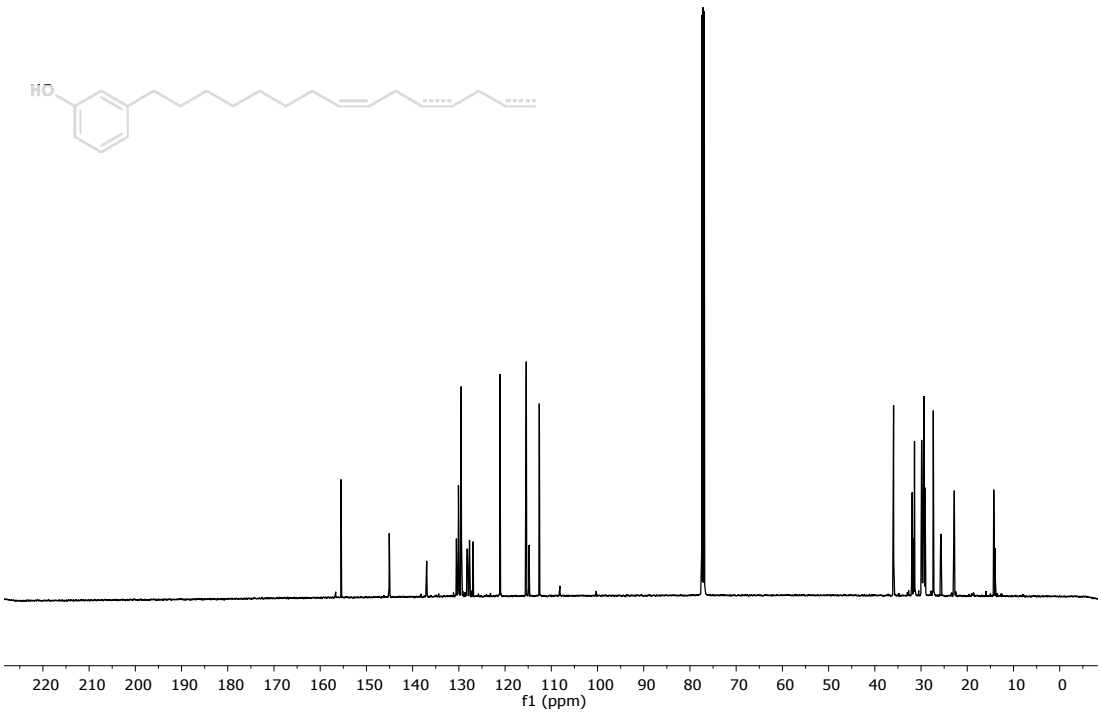


Figure S5. ^{13}C NMR (126 MHz, $CDCl_3$) of cardanol.

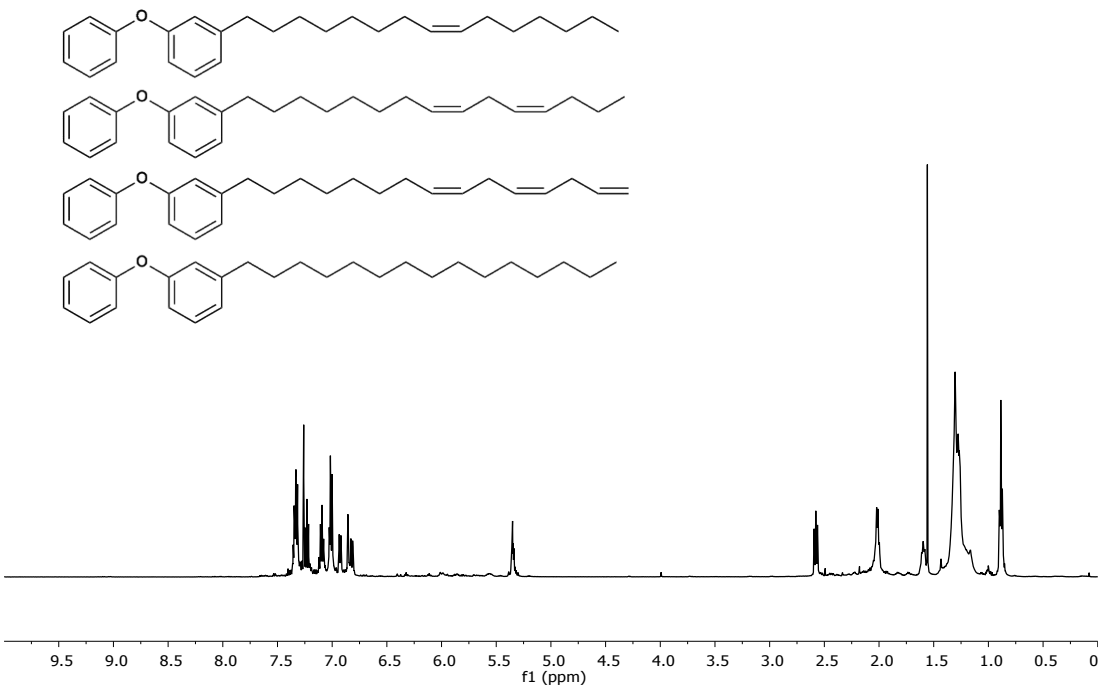


Figure S6. ^{1}H NMR (500 MHz, $CDCl_3$) of 3-(pentadec-8-en-1-yl)phenol (O-Phenyl cardanol).

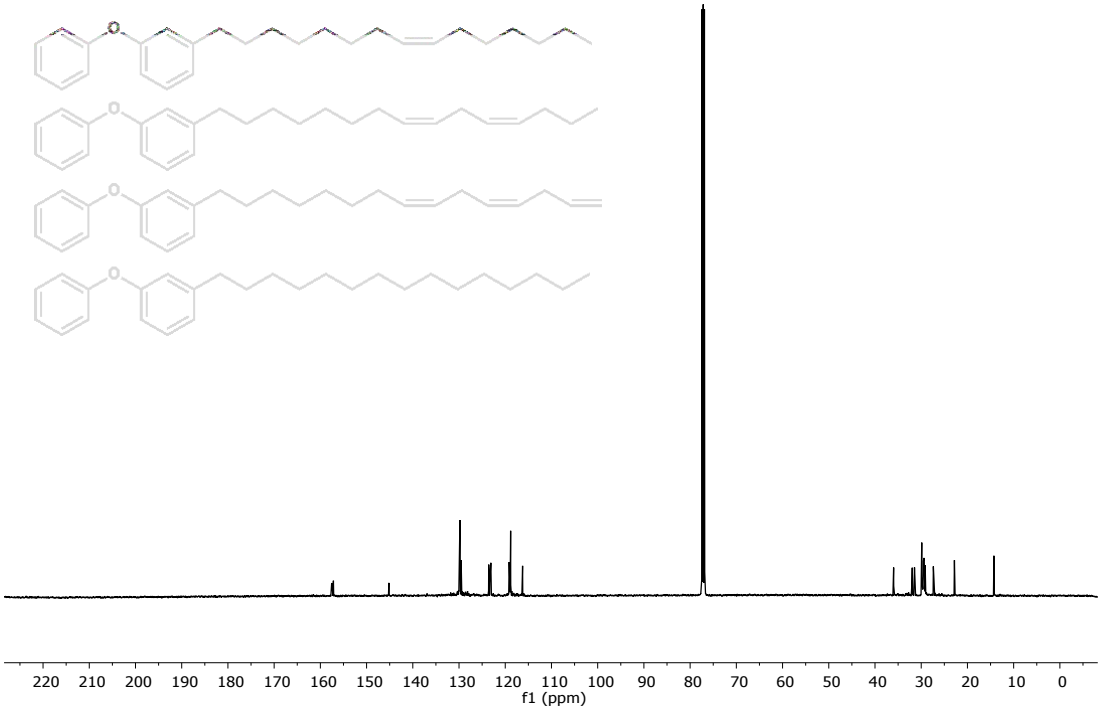


Figure S7. ^{13}C NMR (126 MHz, $CDCl_3$) of 3-(pentadec-8-en-1-yl)phenol (O-Phenyl cardanol).

3.2. Synthesis styrene type materials from cashew nut shell liquid, anacardic acid, and cardanol

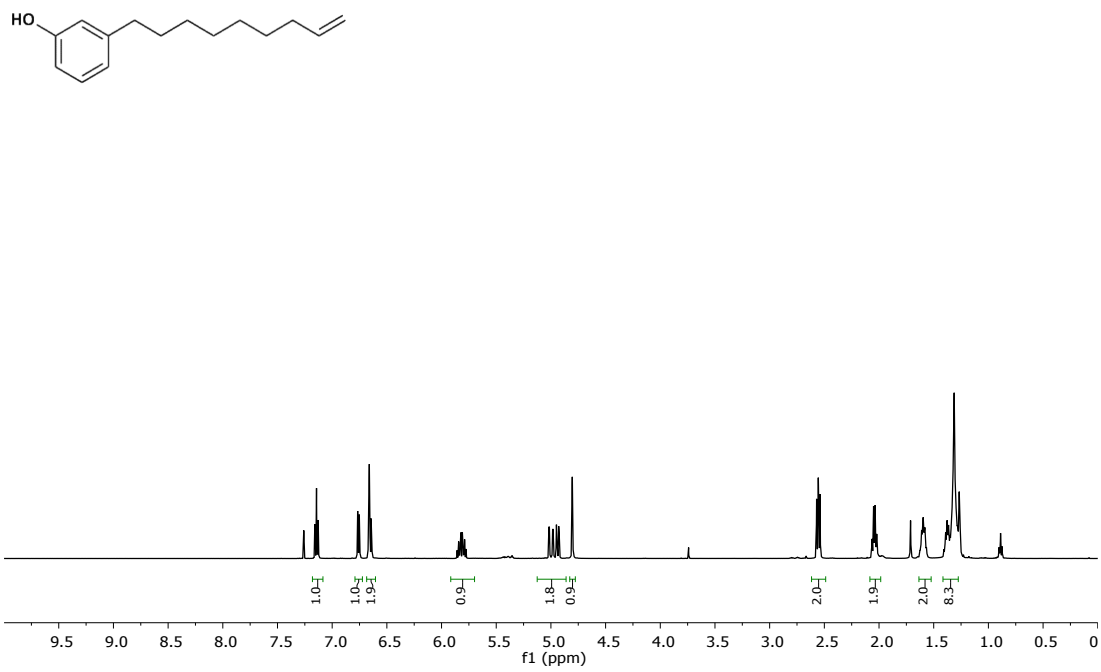


Figure S8. ^{1}H NMR (500 MHz, $CDCl_3$) of 3-(non-8-en-1-yl)phenol.

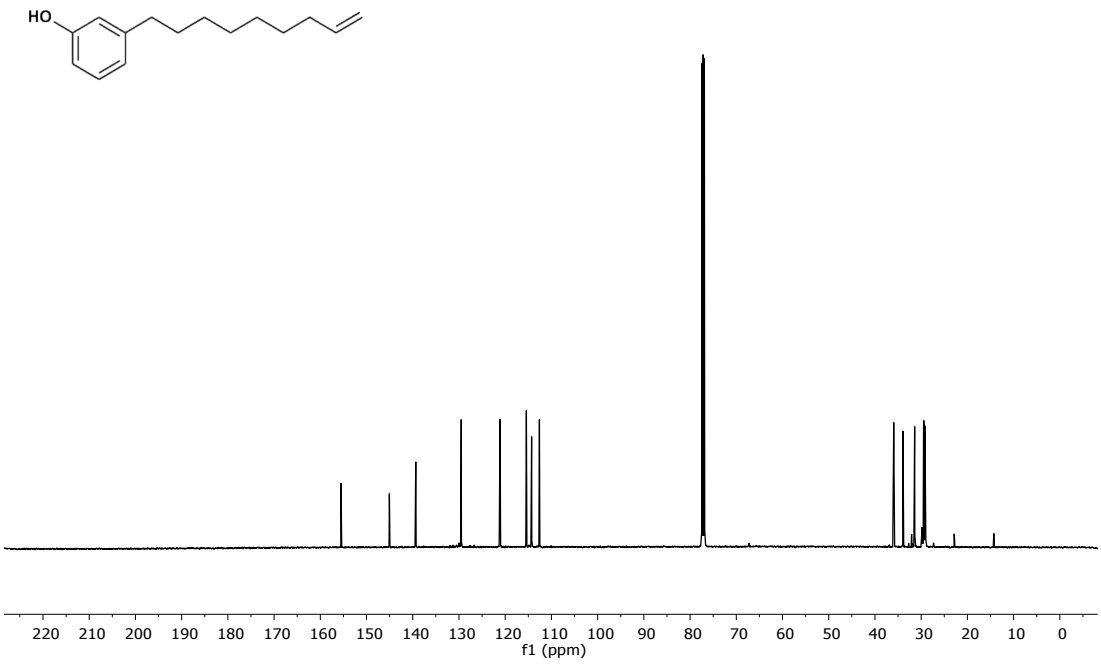


Figure S9. ^{13}C NMR (126 MHz, $CDCl_3$) of 3-(non-8-en-1-yl)phenol.

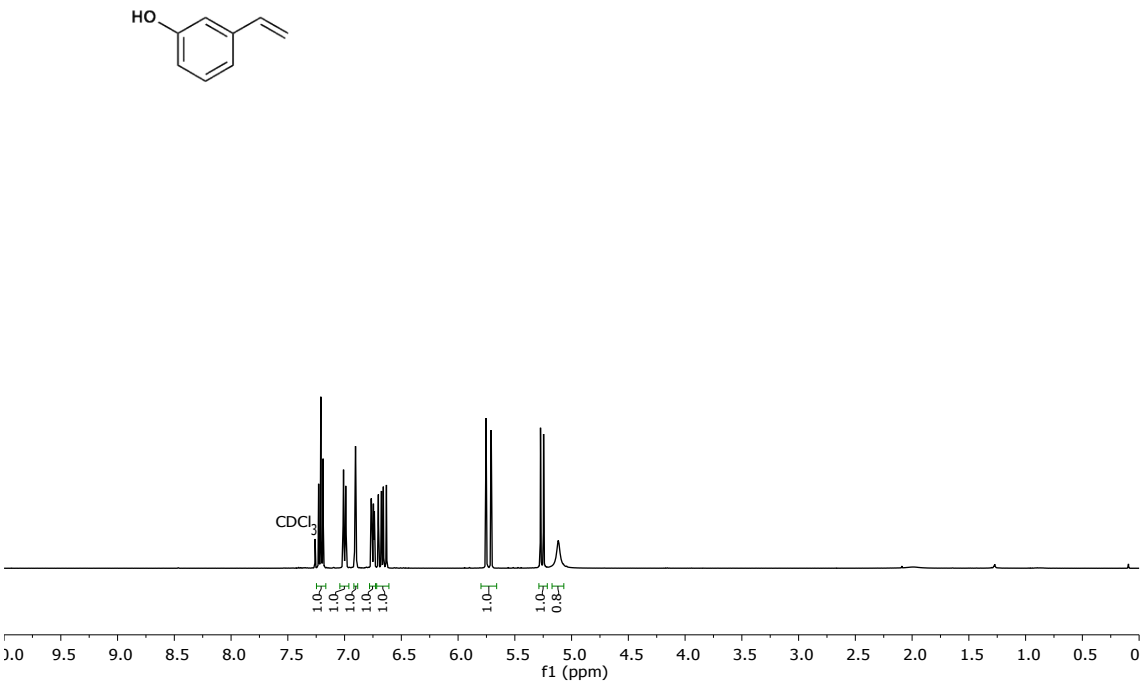


Figure S10. ^{1}H NMR (400 MHz, $CDCl_3$) of 3-vinyl phenol.

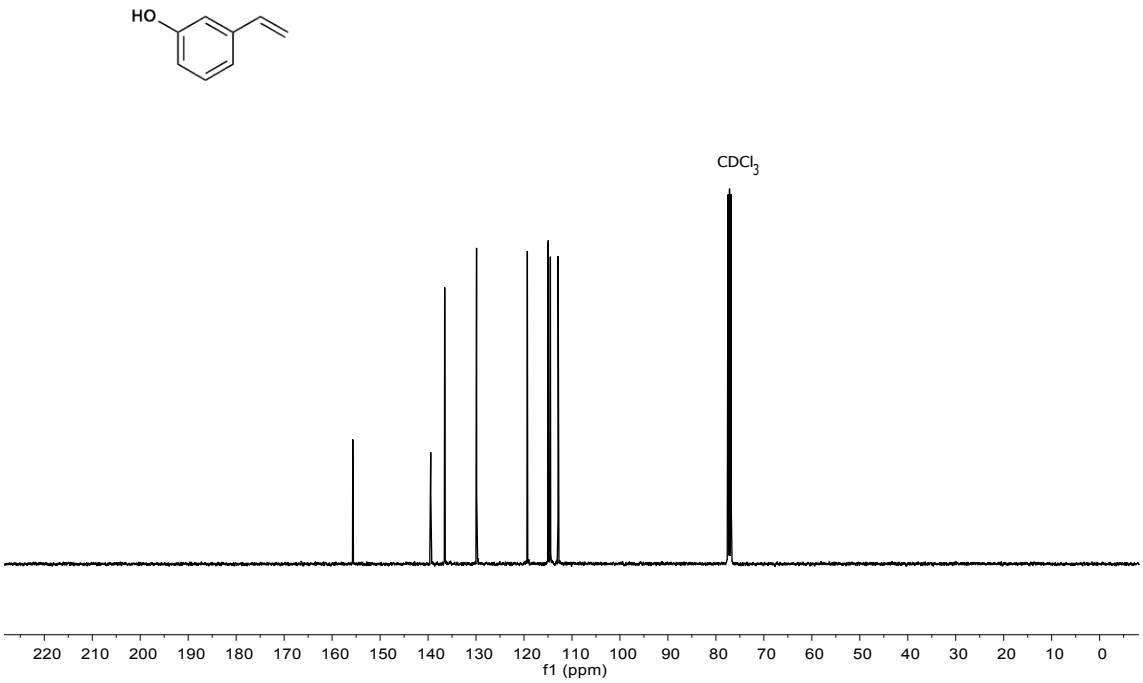


Figure S11. ^{13}C NMR (101 MHz, $CDCl_3$) of 3-vinyl phenol.

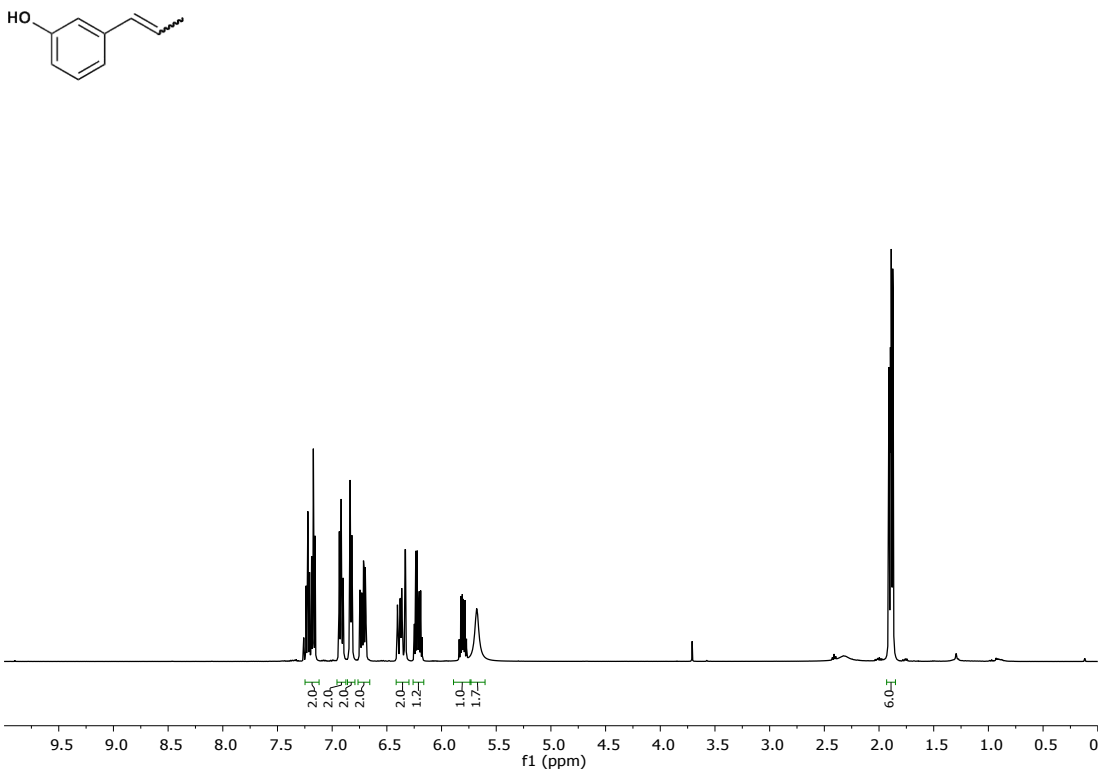


Figure S12. ^{1}H NMR (500 MHz, $CDCl_3$) of 3-(prop-1-en-1-yl)phenol.

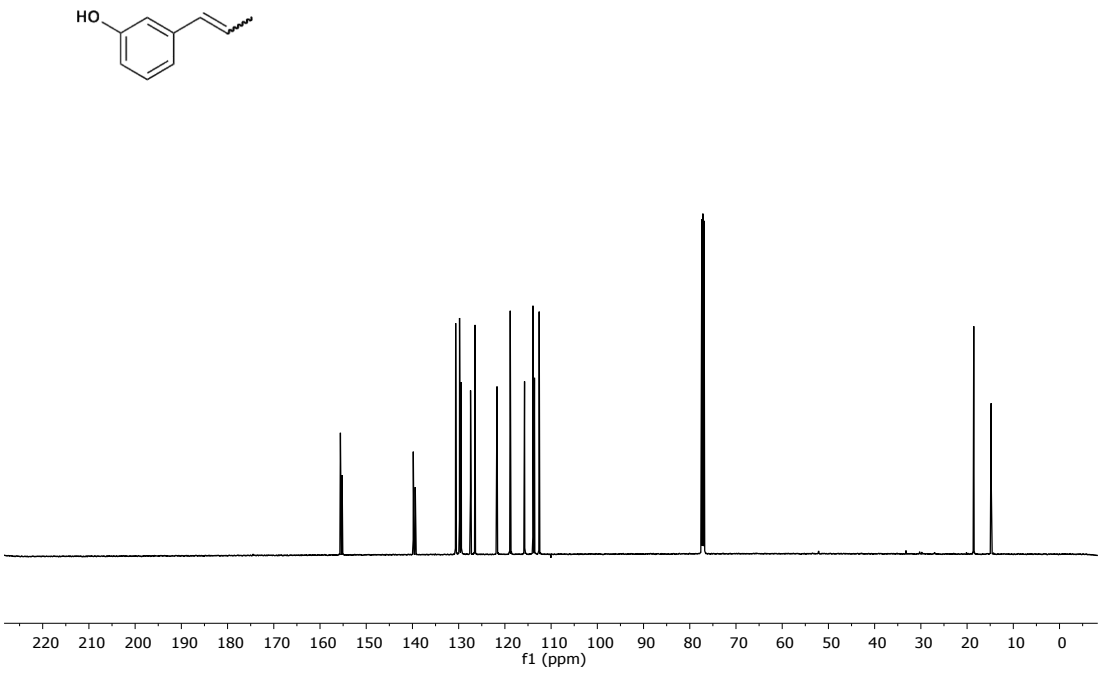


Figure S13. ^{13}C NMR (126 MHz, $CDCl_3$) of 3-(prop-1-en-1-yl)phenol.

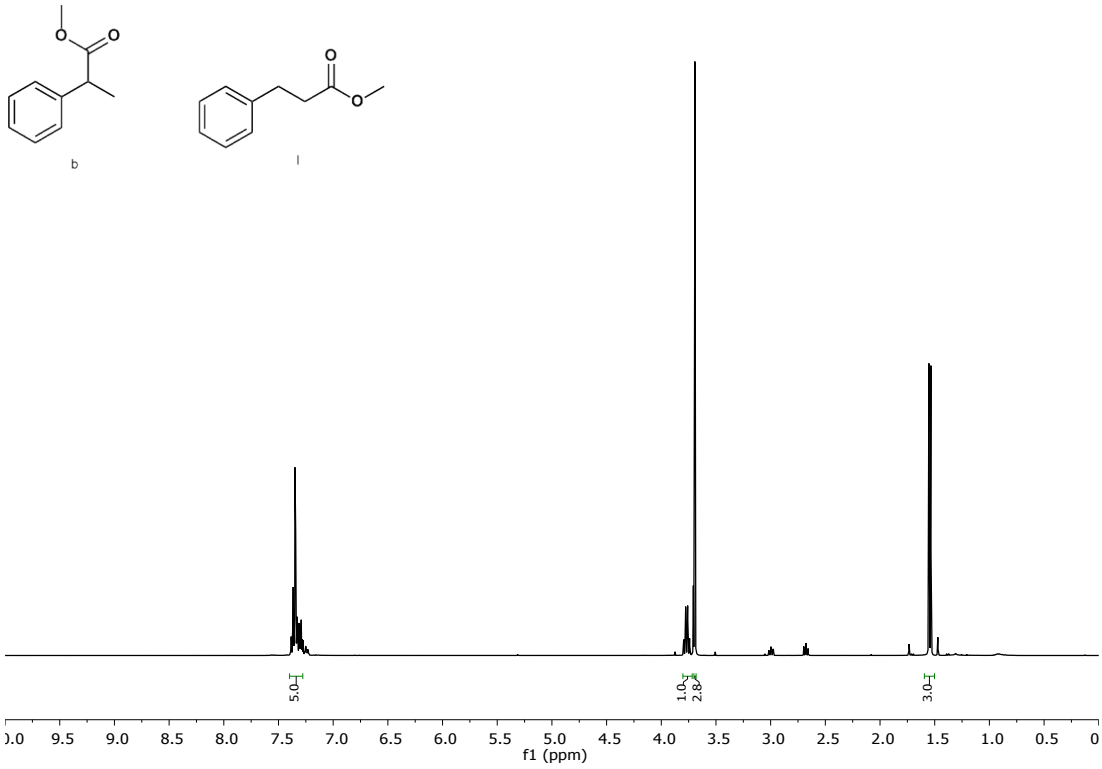


Figure S14. ^{1}H NMR (400 MHz, $CDCl_3$) of methyl 2-phenylpropanoate with methyl 3-phenylpropanoate as side product.

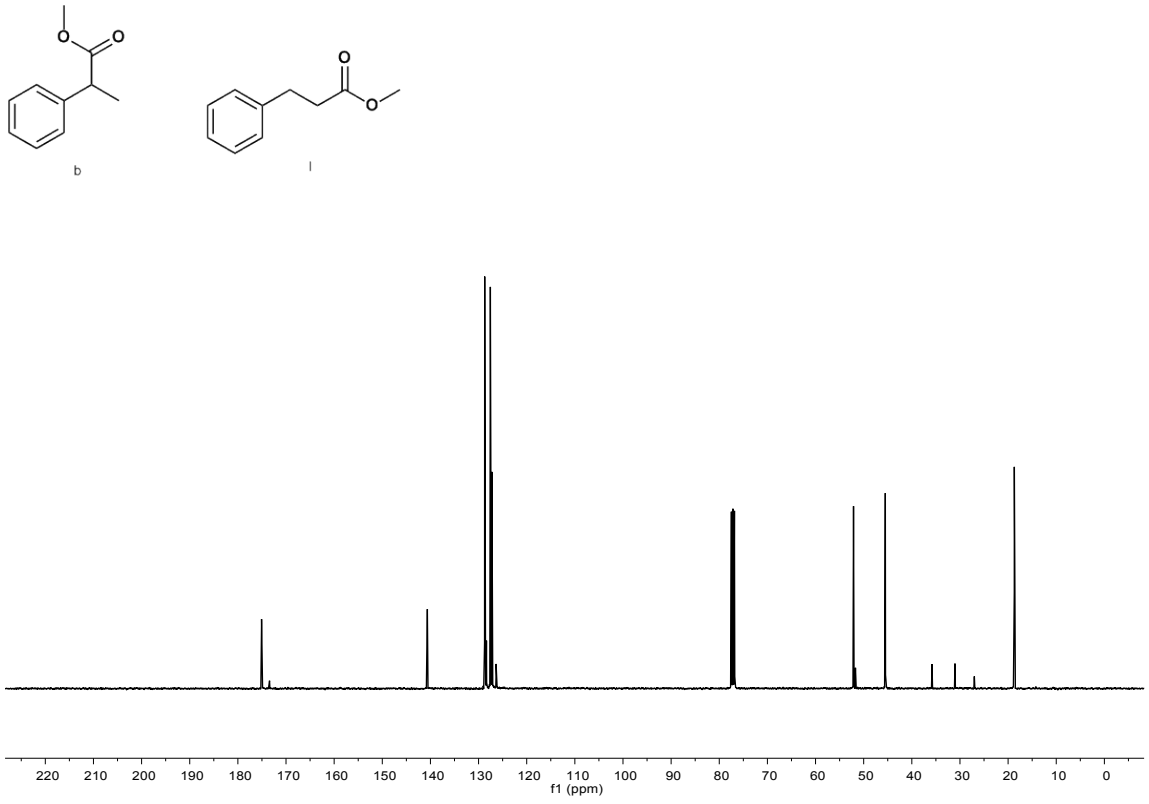


Figure S15. ^{13}C NMR (101 MHz, $CDCl_3$) of methyl 2-phenylpropanoate with methyl 3-phenylpropanoate as side product.

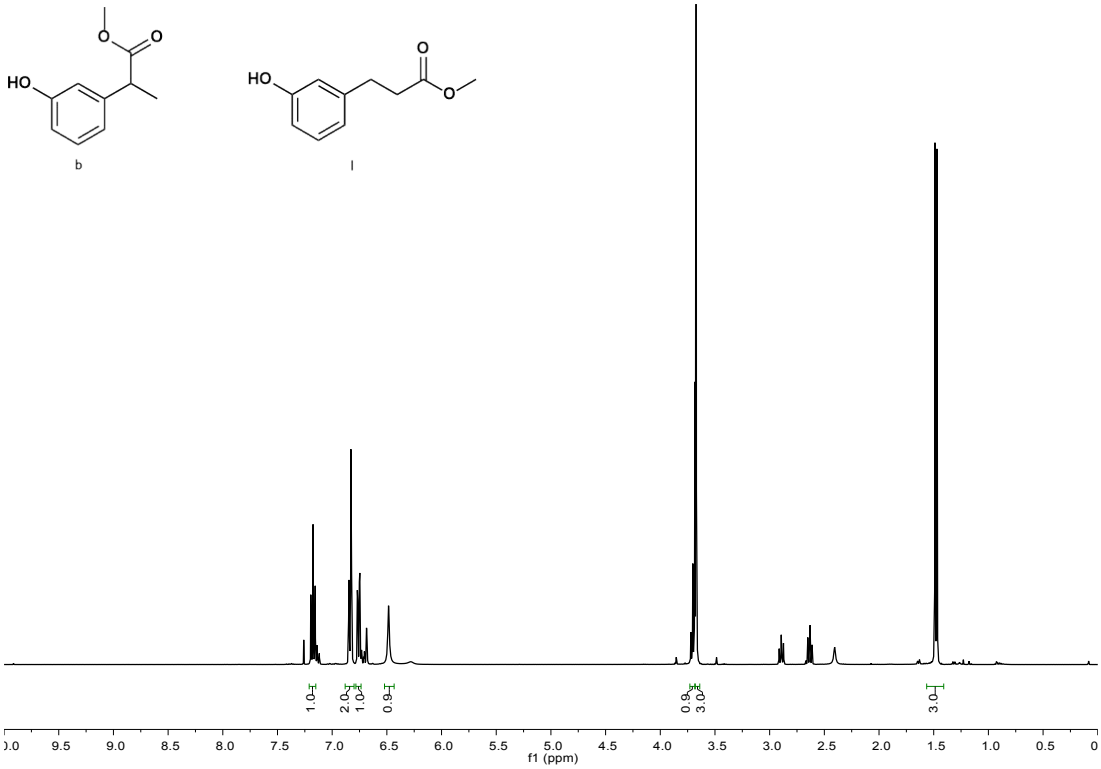


Figure S16. ^{1}H NMR (400 MHz, $CDCl_3$) of methyl 2-(3-hydroxyphenyl)propanoate with methyl 3-(3-hydroxyphenyl)propanoate as side product.

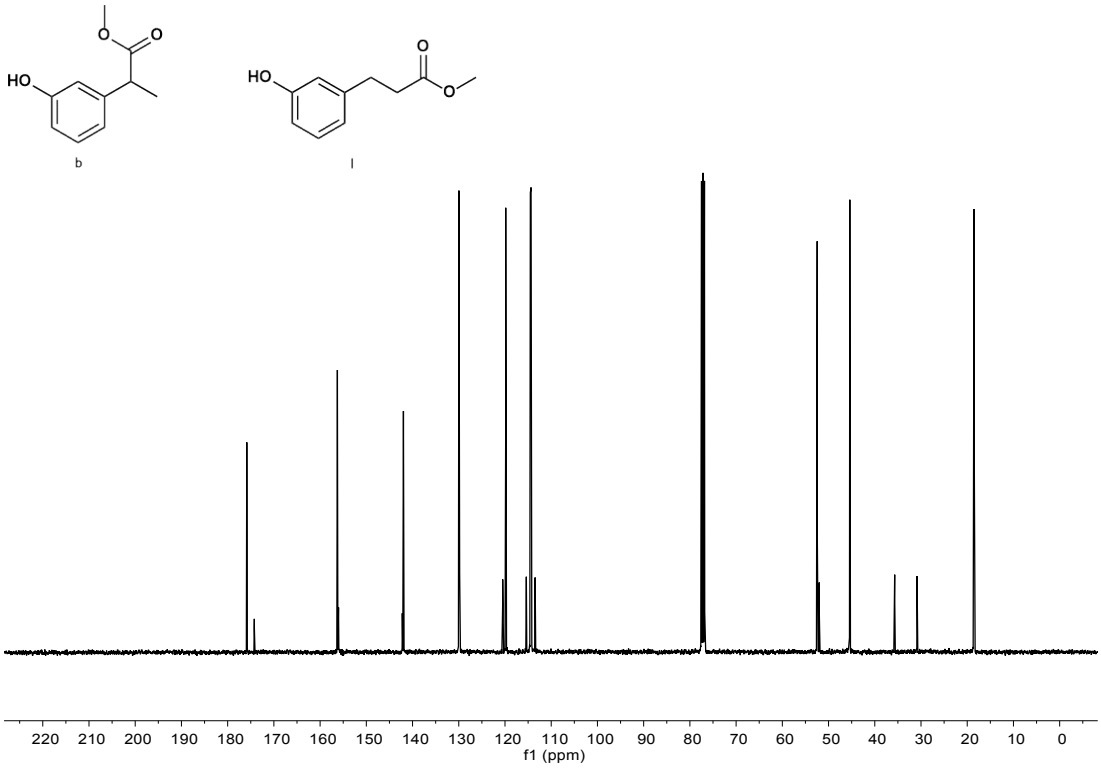
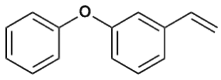


Figure S17. ^{13}C NMR (101 MHz, $CDCl_3$) of methyl 2-(3-hydroxyphenyl)propanoate with methyl 3-(3-hydroxyphenyl)propanoate as side product.



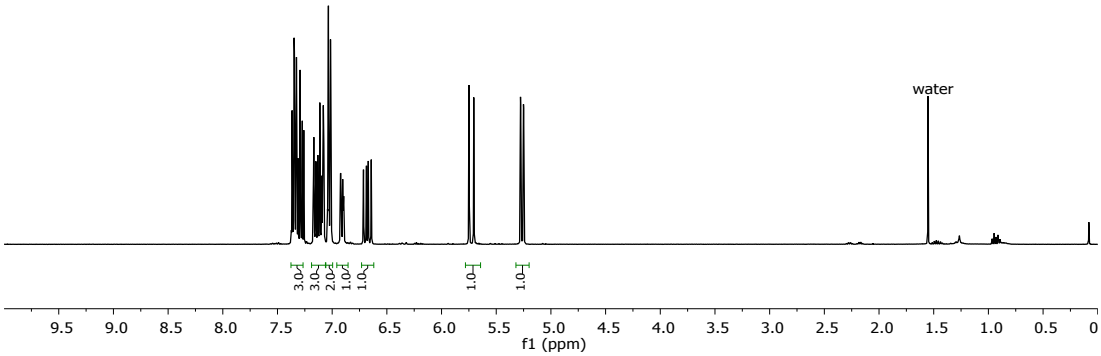
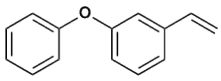


Figure S18. ^{1}H NMR (400 MHz, $CDCl_3$) of 1-phenoxy-3-vinylbenzene.



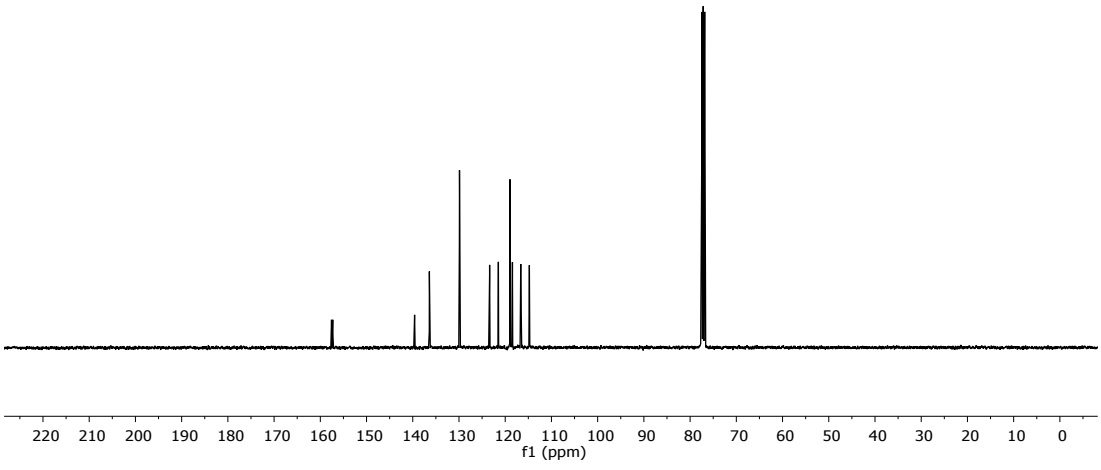


Figure S19. ^{13}C NMR (101 MHz, $CDCl_3$) of 1-phenoxy-3-vinylbenzene.

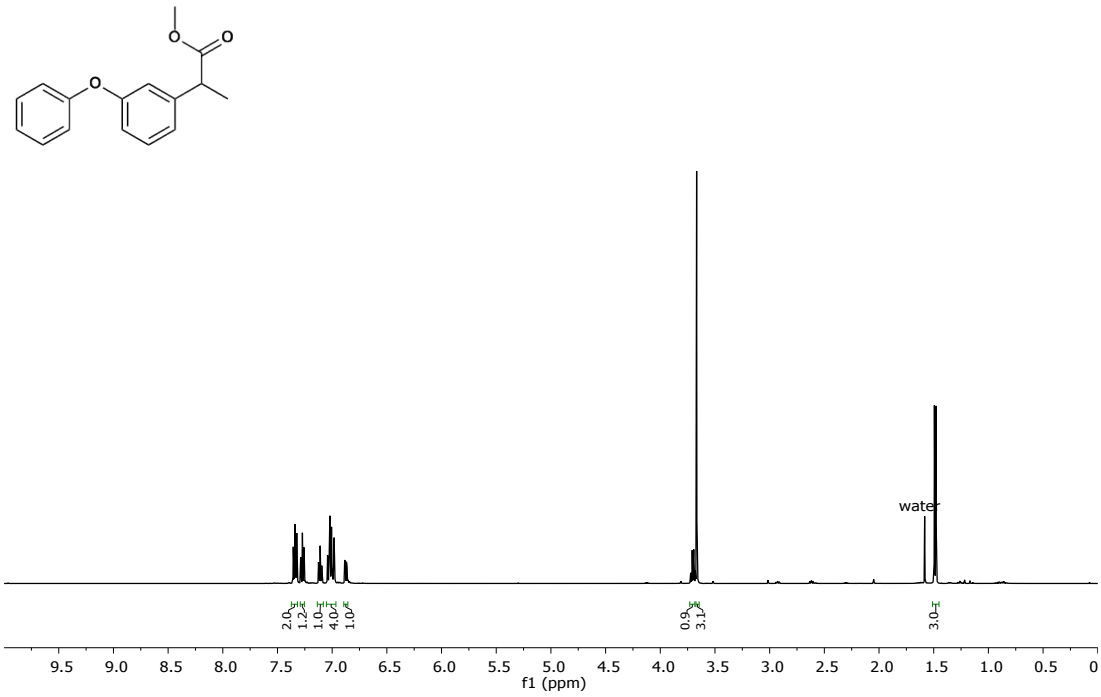


Figure S20. ^{1}H NMR (500 MHz, $CDCl_3$) of methyl 2-(3-phenoxyphenyl)propanoate.

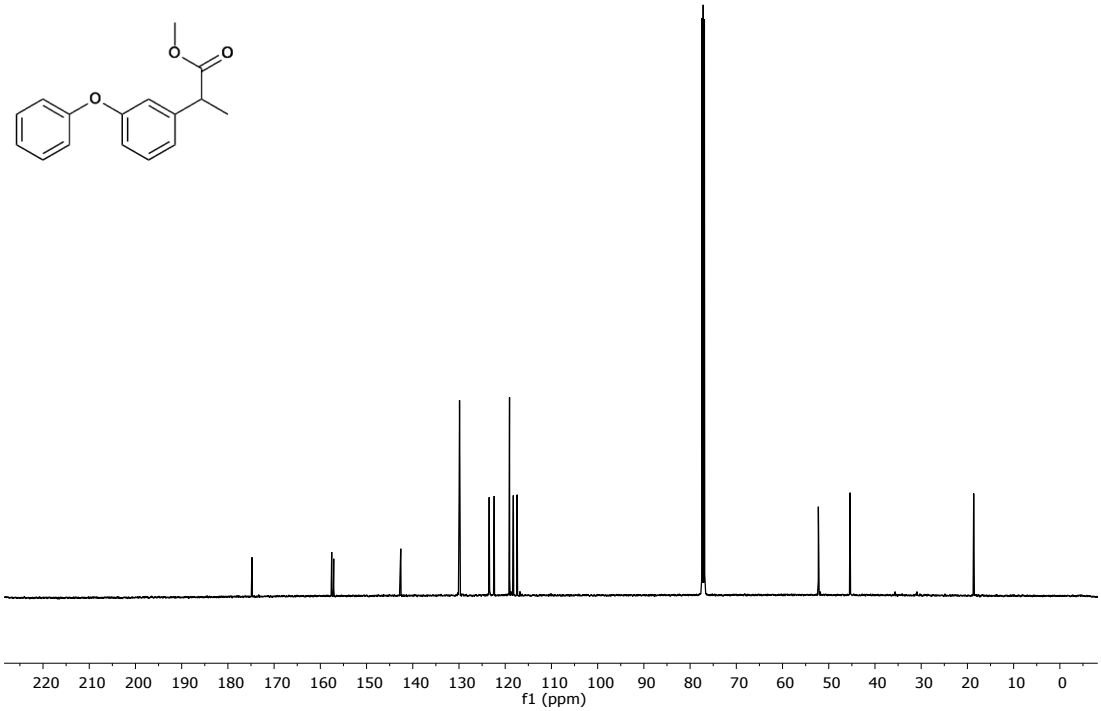


Figure S21. ^{13}C NMR (126 MHz, $CDCl_3$) of methyl 2-(3-phenoxyphenyl)propanoate.

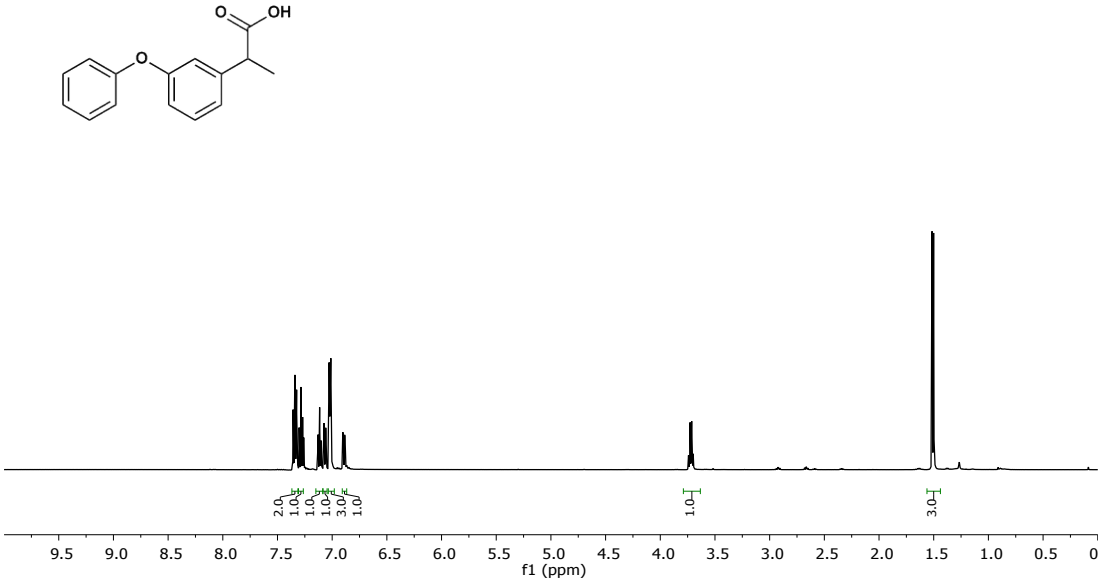


Figure S22. ^{1}H NMR (500 MHz, $CDCl_3$) of 2-(3-phenoxyphenyl)propanoic acid (fenoprofen).

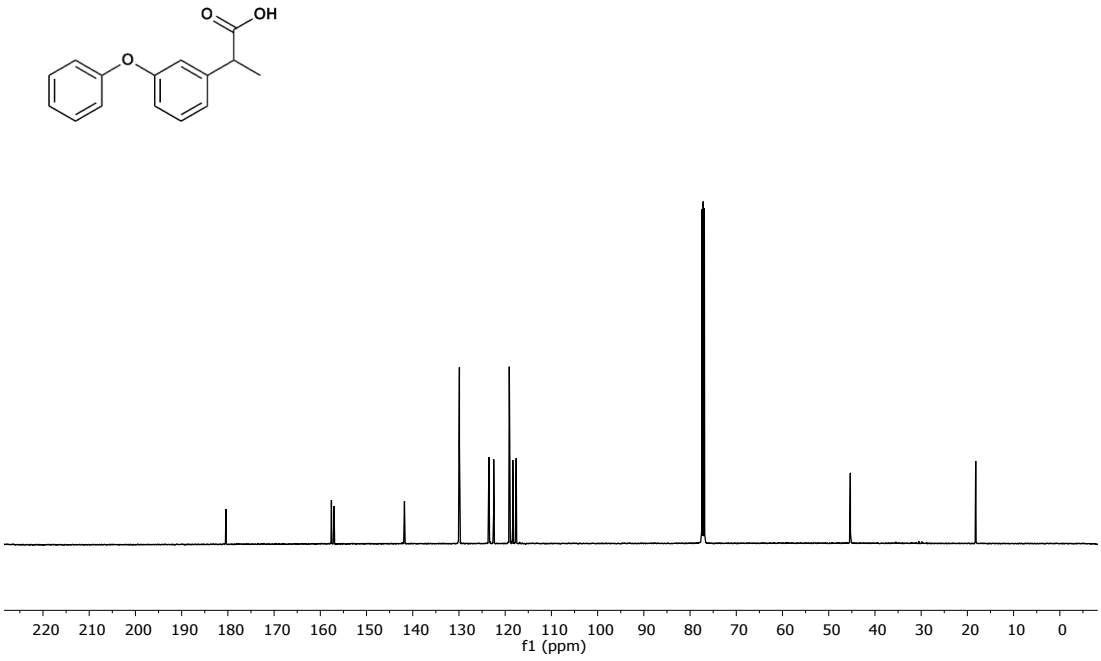


Figure S23. ^{13}C NMR (126 MHz, $CDCl_3$) of 2-(3-phenoxyphenyl)propanoic acid (fenoprofen).

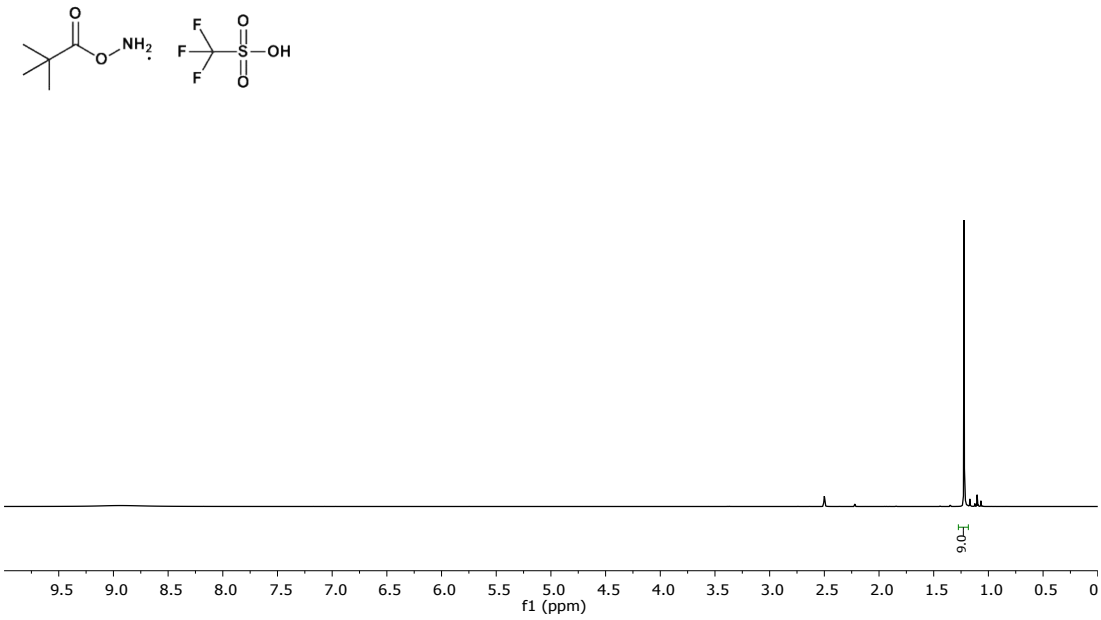


Figure S24. ^{1}H NMR (500 MHz, d_6-DMSO) of O-pivaloylhydroxyamine triflic acid.

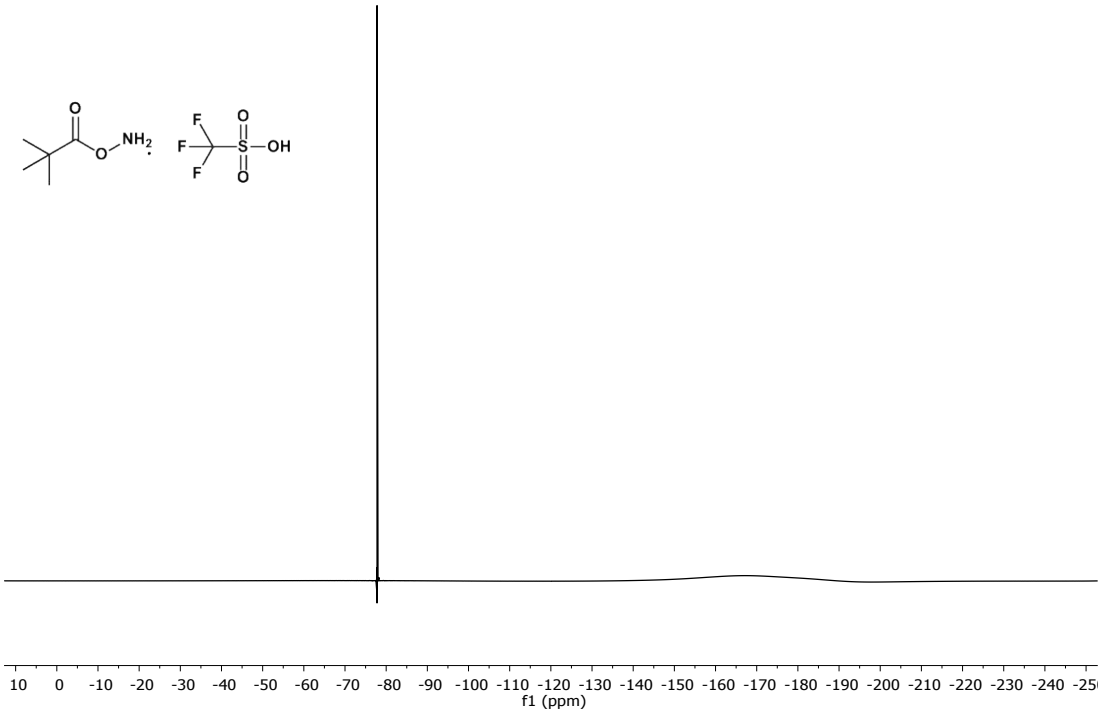


Figure S25. ^{19}F NMR (471 MHz, d_6-DMSO) of O-pivaloylhydroxyamine triflic acid.

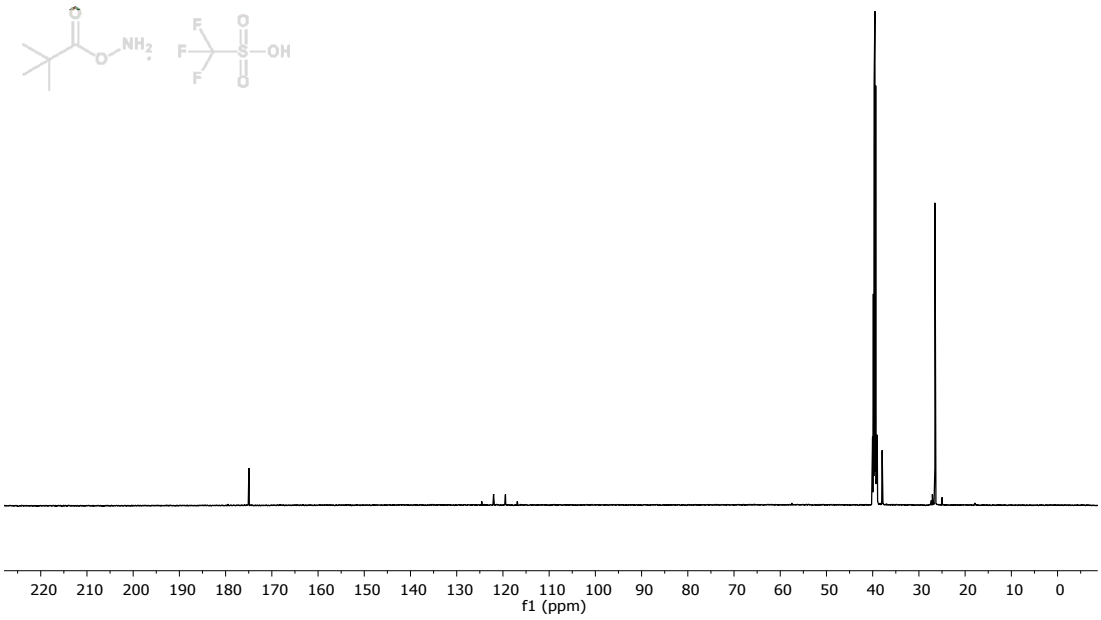


Figure S26. ^{13}C NMR (126 MHz, d_6-DMSO) of O-pivaloylhydroxyamine triflic acid.

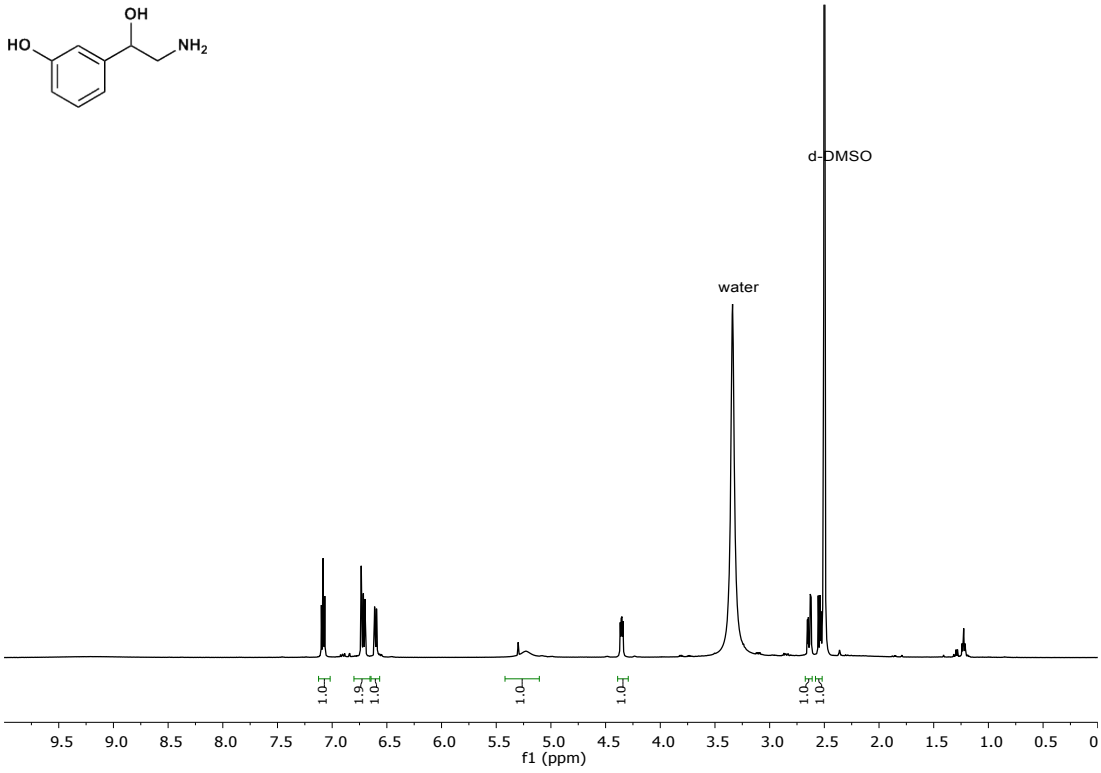


Figure S27. ^{1}H NMR (500 MHz, d_6-DMSO) of 3-(2-amino-1-hydroxyethyl)phenol.

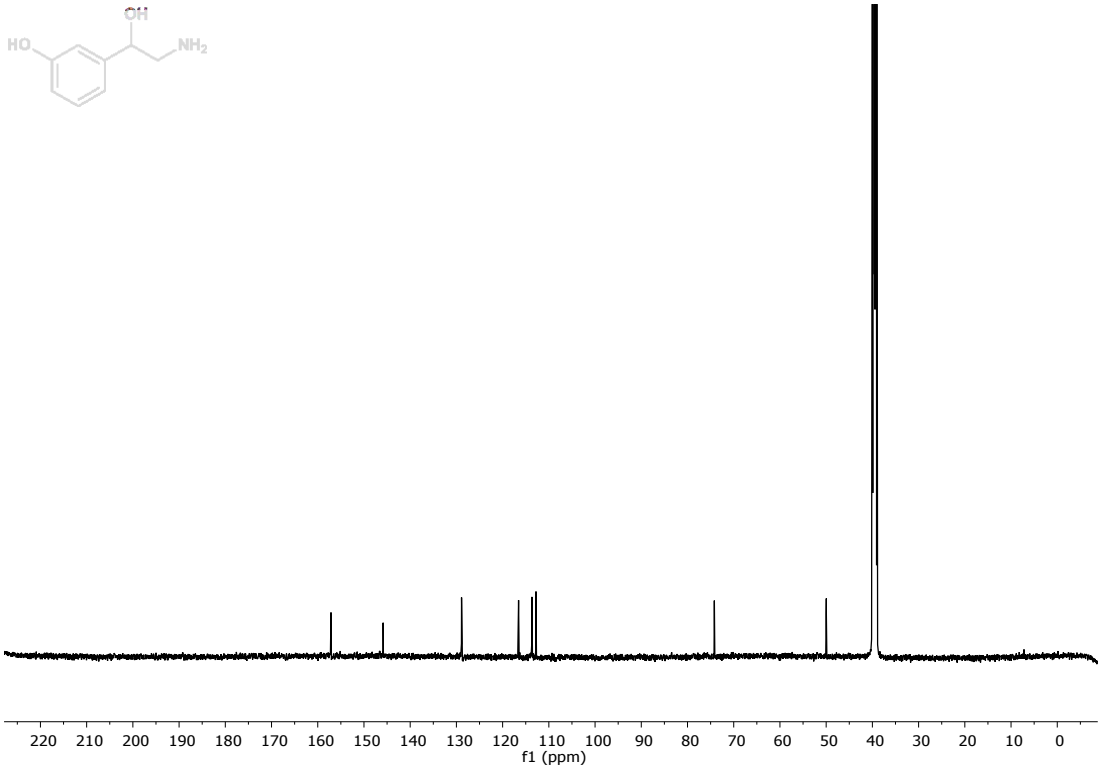


Figure S28. ^{13}C NMR (126 MHz, d_6-DMSO) of 3-(2-amino-1-hydroxyethyl)phenol.

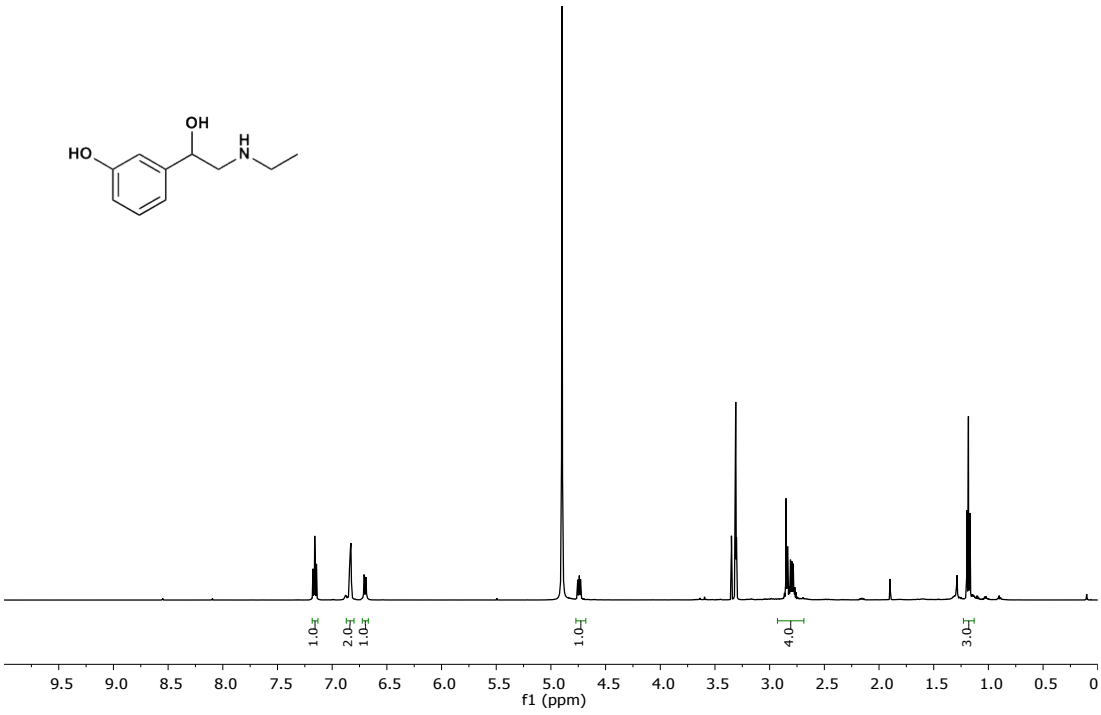


Figure S29. ^{1}H NMR (500 MHz, MeOD) of 3-(2-(ethylamino)-1-hydroxyethyl)phenol.

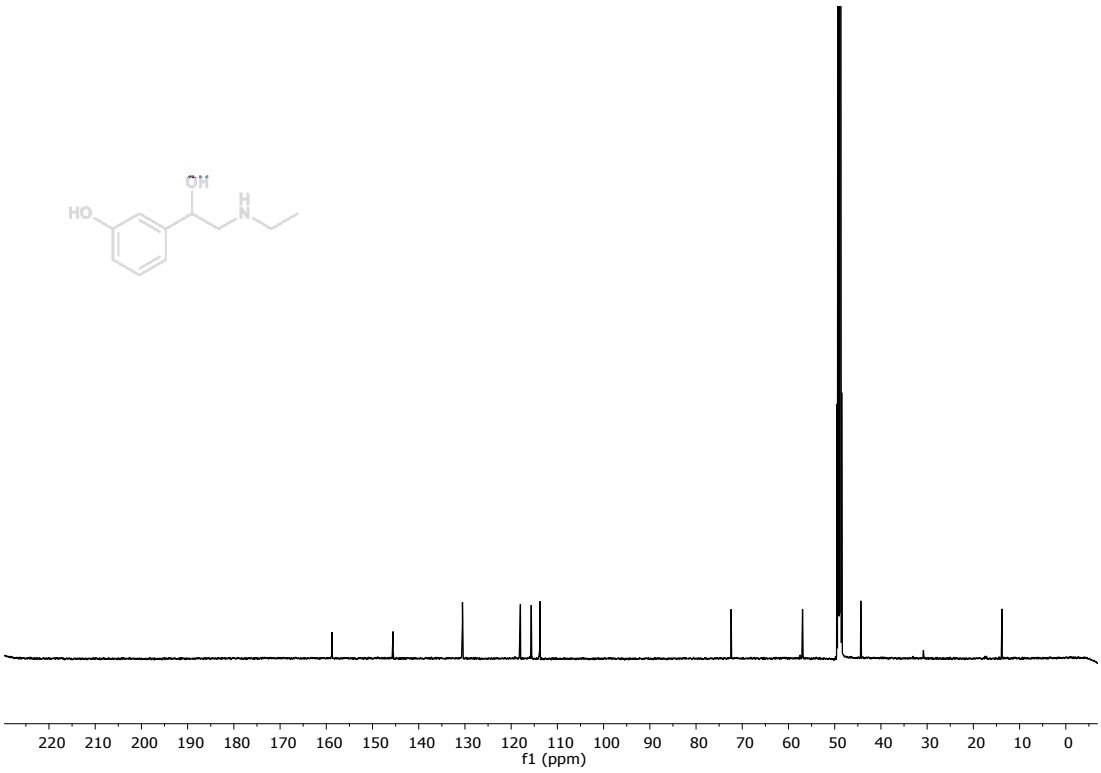


Figure S30. ^{13}C NMR (126 MHz, MeOD) of 3-(2-(ethylamino)-1-hydroxyethyl)phenol.

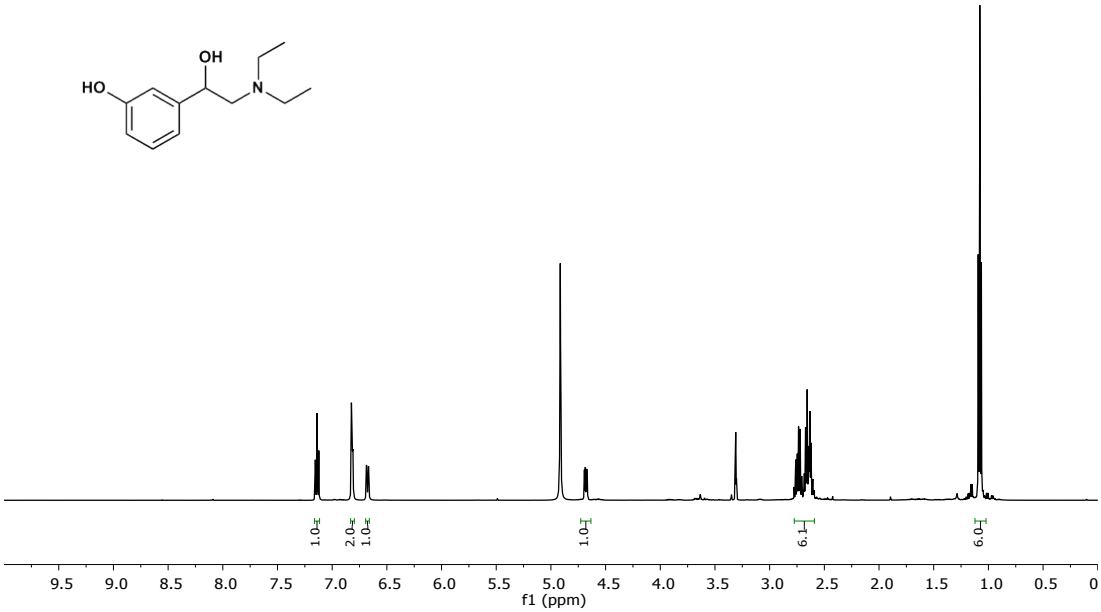


Figure S31. ^{1}H NMR (500 MHz, MeOD) of 3-(2-(diethylamino)-1-hydroxyethyl)phenol.

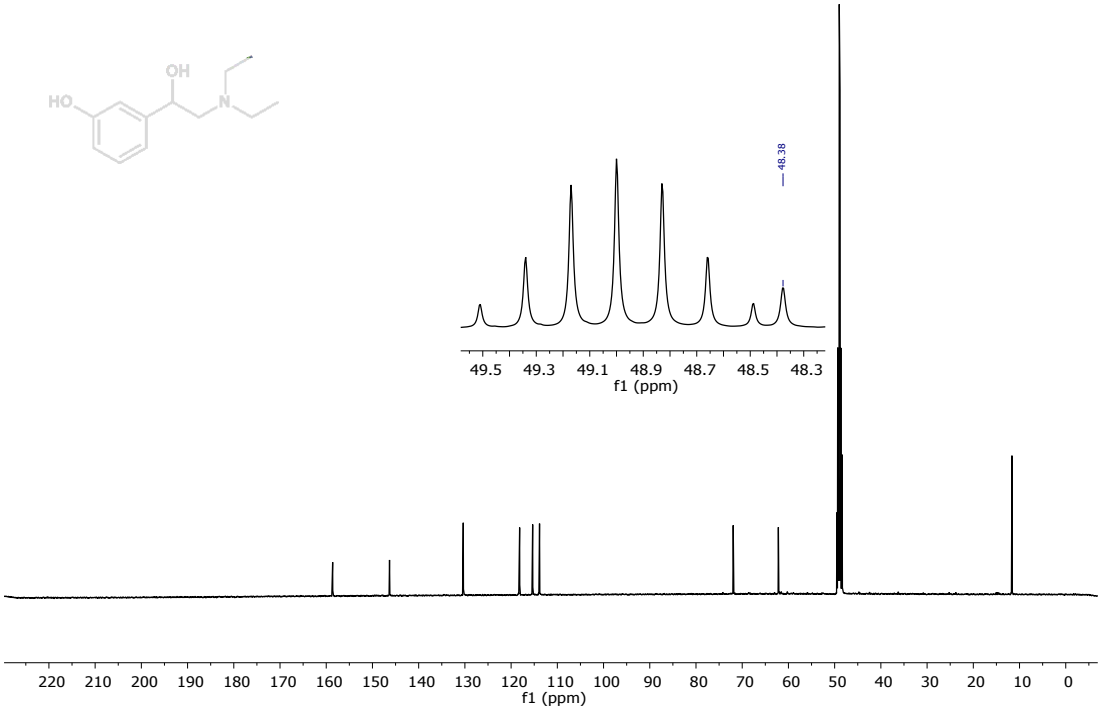
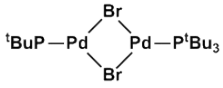


Figure S32. ^{13}C NMR (126 MHz, MeOD) of 3-(2-(diethylamino)-1-hydroxyethyl)phenol.



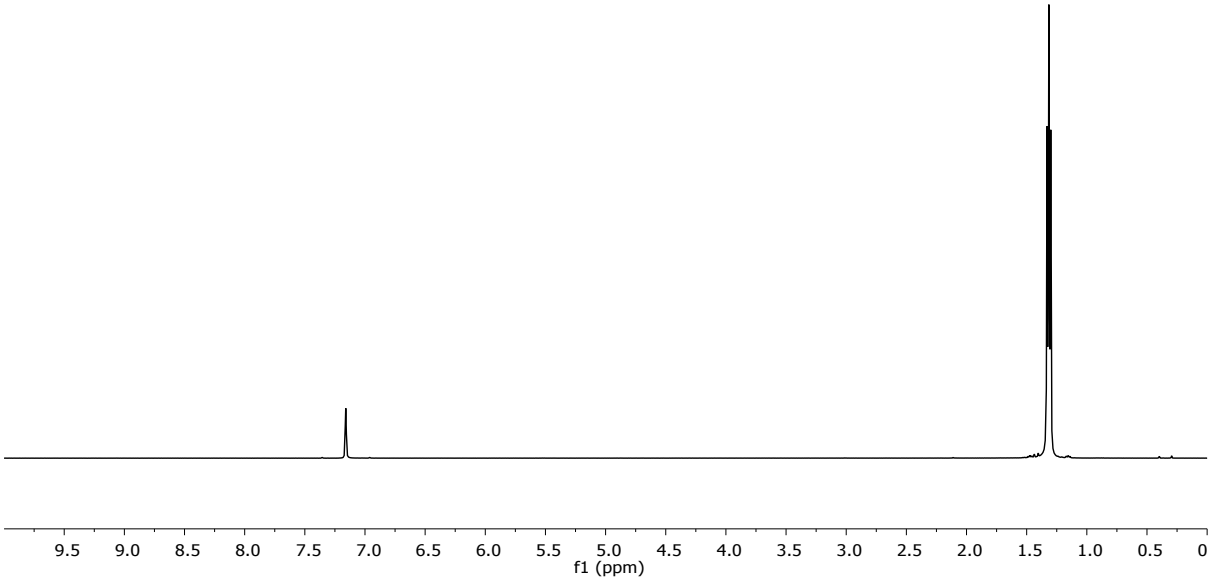


Figure S33. ^{1}H NMR (400 MHz, C_6D_6) of Di-μ-bromobis(tri-tert-butylphosphine)dipalladium(I).

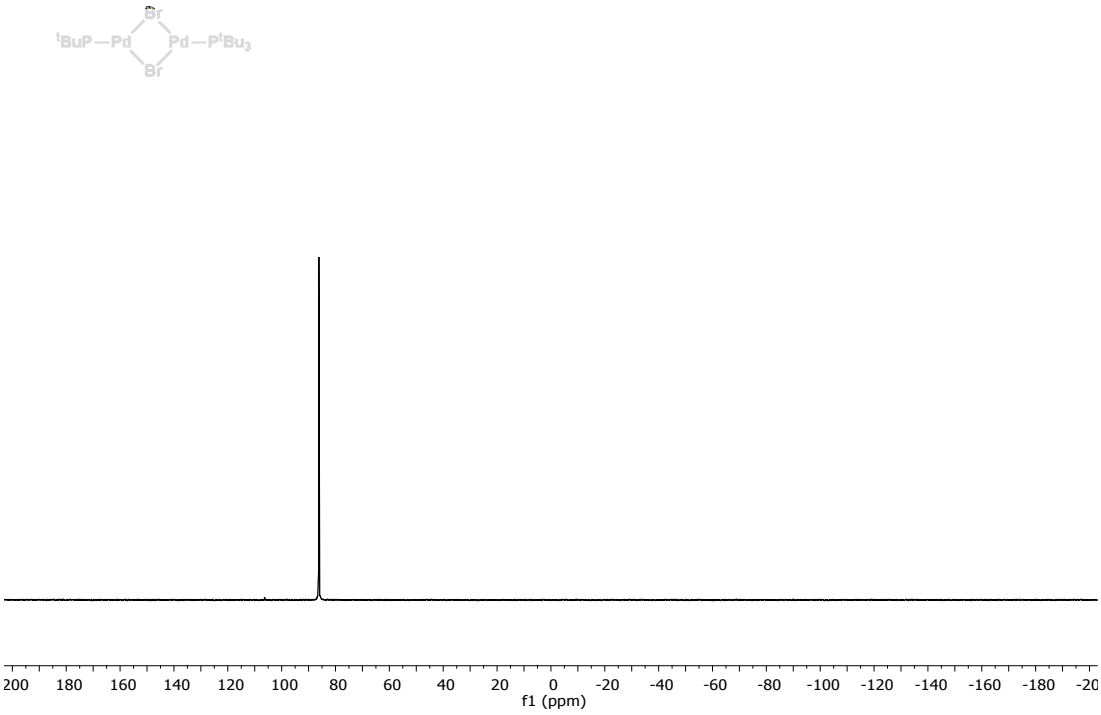


Figure S34. ^{31}P NMR (162 MHz, C_6D_6) of Di-μ-bromobis(tri-tert-butylphosphine)dipalladium(I).

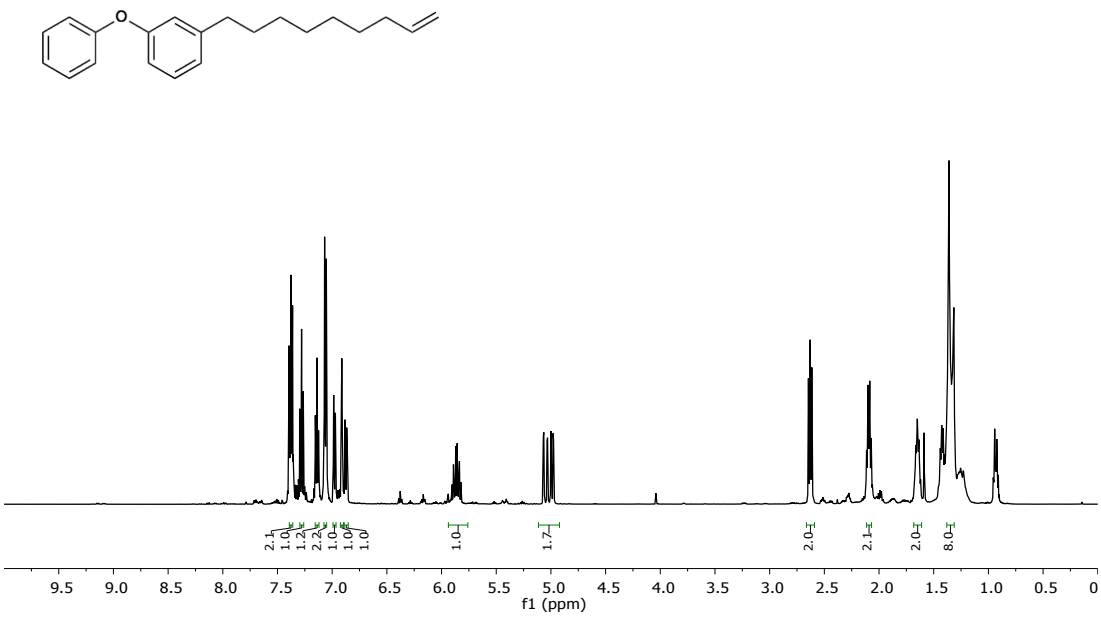


Figure S35. ^{1}H NMR (500 MHz, $CDCl_3$) of 1-(non-8-en-1-yl)-3-phenoxybenzene.

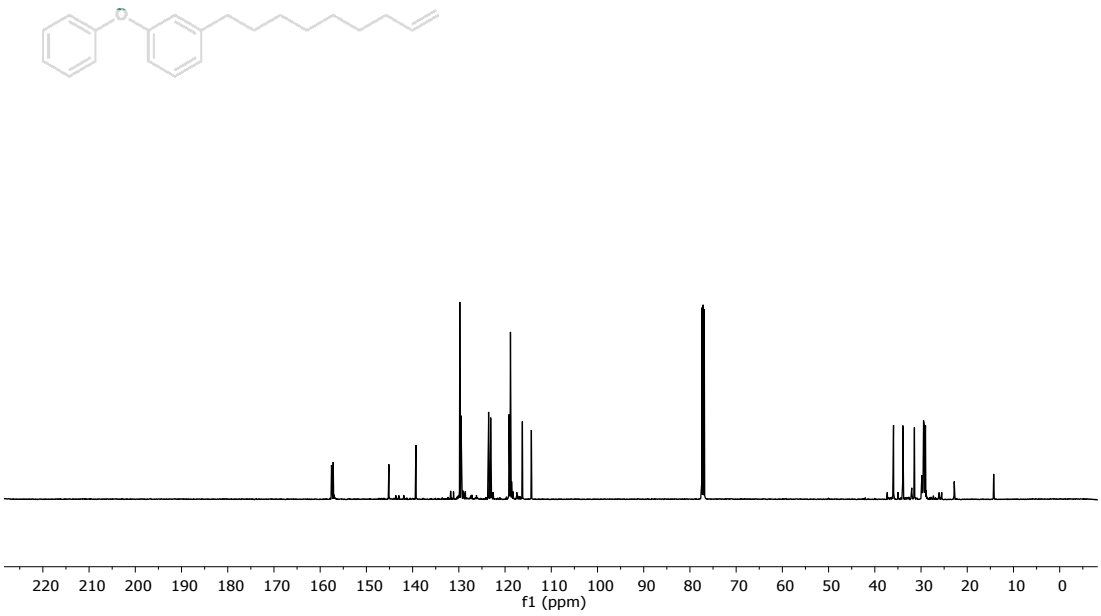


Figure S36. ^{13}C NMR (126 MHz, $CDCl_3$) of 1-(non-8-en-1-yl)-3-phenoxybenzene.

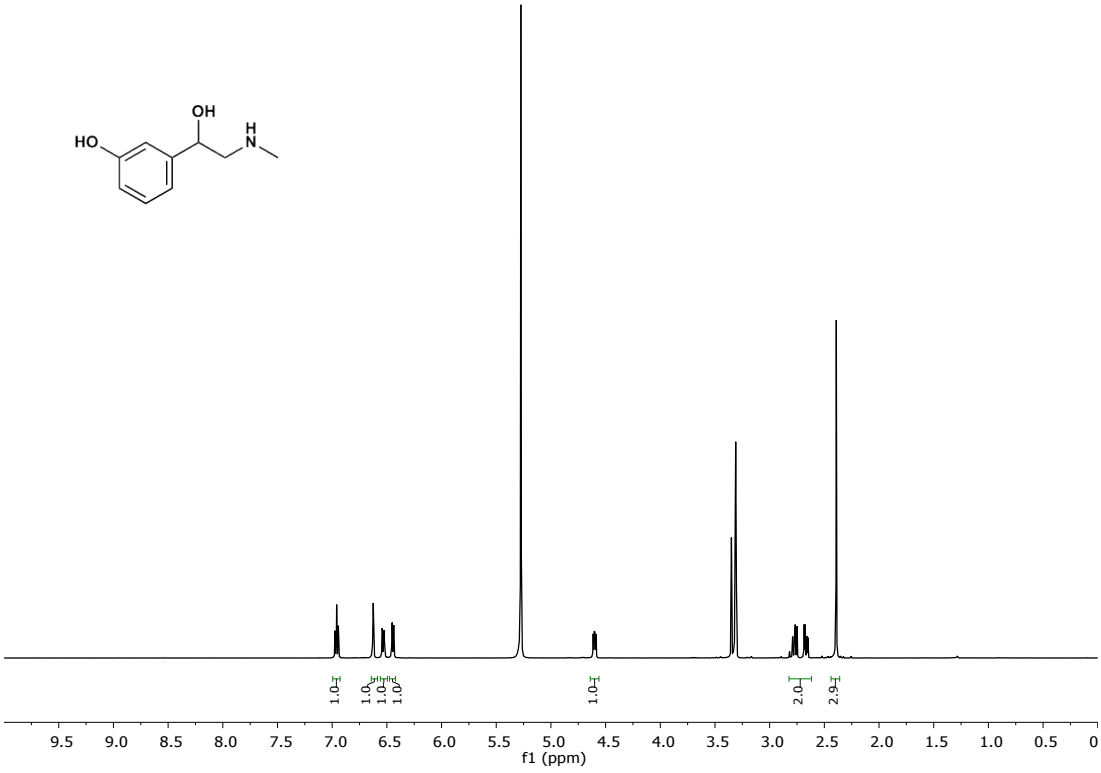


Figure S37. ^{1}H NMR (500 MHz, MeOD) of *rac*-phenylephrine.

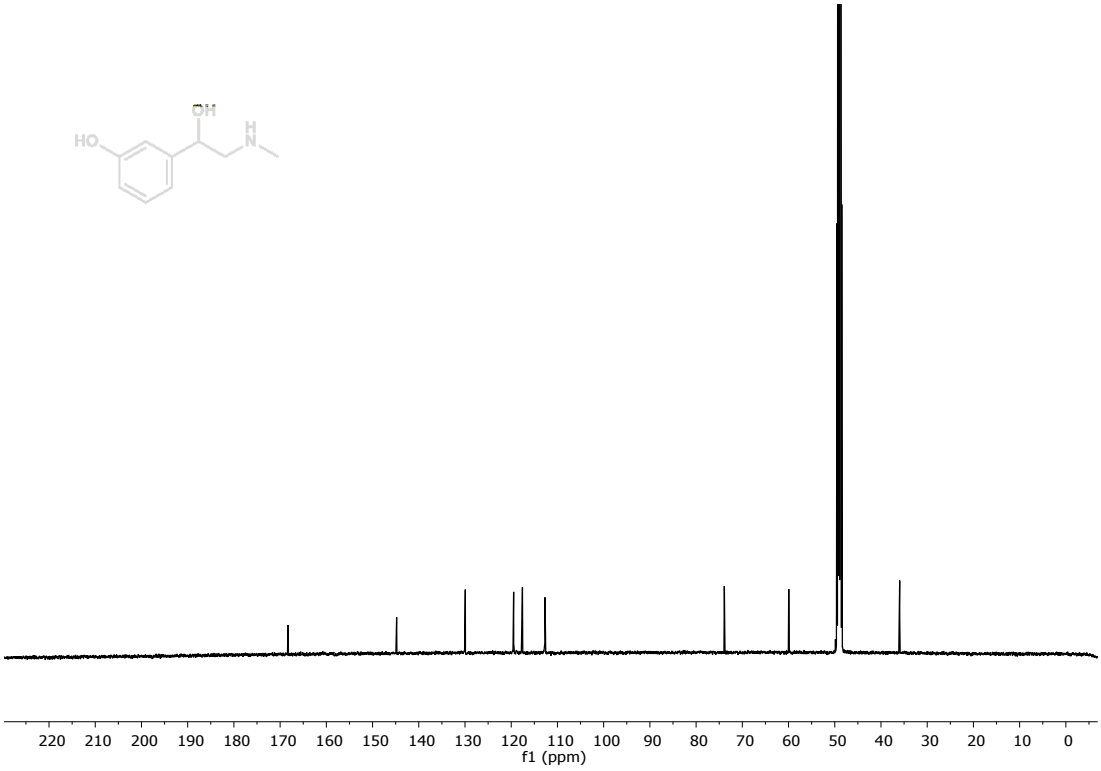


Figure S38. ^{13}C NMR (126 MHz, MeOD) of *rac*-phenylephrine.

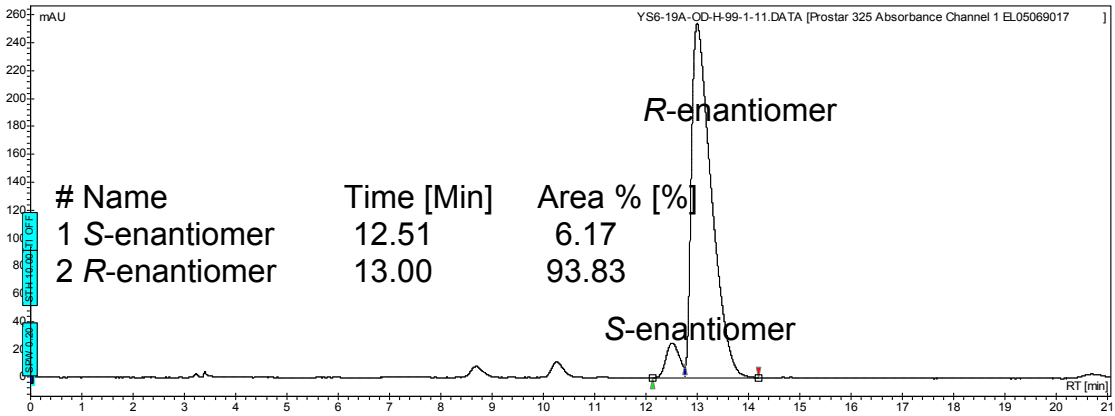


Figure S39. Chiral HPLC spectrum for the enantioselective synthesis of fenoprofen.

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