Electronic Supplementary Material (ESI) for Catalysis Science & Technology.

Electronic Supplementary Information

Substrate substitution effects in the Fries rearrangement of aryl esters over zeolite catalysts

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Method S1 Preparation of the reference solid acids. Several ZrO_2-supported solid acid catalysts were synthesised as reference samples. To prepare ZrO_2, an aqueous solution of ammonia (25 wt.%, Acros Organics) was added dropwise into a stirred (500 rpm) aqueous solution of $ZrOCl_2$ (0.2 M 99.9%, Alfa Aesar) at 23°C until reaching a pH of 10. The mixture was aged for 1 h with continuous stirring, then the solids were filtered off, washed with deionised water until the pH returned to neutral, dried at 110°C for 15 h to yield $Zr(OH)_4$, and calcined at 550°C (5°C min^{-1}, 3 h). The B_2O_3/ZrO_2,[1] WO_3/ZrO_2,[2] and ZrO_2-supported heteropoly acid catalyst (HPA/ZrO_2)[3] with 10 wt.% nominal loading of B_2O_3, WO_3, and HPA were synthesised by impregnation methods following reported procedures. **Fig. S1** presents the XRD patterns of the all the catalysts, which confirmed the characteristic diffractions for the as-expected zeolites, high dispersion of ZrO_2-supported solid acids, and the amorphous nature of MCM-41.

Method S2 Synthesis of the substrates and product reference compounds.

a) General. All reactions were performed under an argon atmosphere in pre-dried glass equipment. Room temperature was 20-24°C. Reagents and chemicals not mentioned separately were purchased from Merck, Sigma-Aldrich, Fluka, or Acros and used without further purification, unless otherwise noted. The reactions were monitored by thin layer chromatography (TLC) using glass plates coated with silica gel 60 F254, 0.25 mm thickness (Merck); spots were visualised by UV (254 and 366 nm) and spraying with cerium ammonium heptamolybdate solution (25 g $(NH_4)_6Mo_7O_{24}$, 10 g $Ce(SO_4)_4$, 100 cm^3 conc. H_2SO_4, 900 cm^3 H_2O) and subsequent heating with a blow-dryer. Flash column chromatography for product purification was performed using silica gel (particle size 0.040-0.063 mm or 0.020-0.040 mm) with max. 0.2 bar argon over-pressure. ^1H and ^{13}C NMR spectra were recorded at 27°C in $CDCl_3$ on a Bruker Avance III 300 FT-NMR spectrometer operated at 300.1 MHz (^1H) and 75.5 MHz (^{13}C). Chemical shifts (δ) are reported in parts per million (ppm) using the residual solvent resonance ($CDCl_3$: 7.26 ppm for ^1H, and 77.0 ppm for ^{13}C NMR) or 0.00 ppm for tetramethylsilane as the internal standard. If not stated differently, purities of compounds given are weight% values determined by ^1H NMR quantitative measurements performed with *p*-nitrotoluene or 1,4-dimethoxybenzene as internal standards. IR spectra were measured on a Perkin Elmer Frontier FT-IR spectrometer using the ATR sampling method in the range of 4000–650 cm^{-1}. UV-VIS spectra were performed on a Varian Cary 50 spectrometer using a 1 cm quartz cuvette; spectra were recorded between 200 and 800 nm. HPLC-analyses were performed on an Agilent 1100 instrument at 23°C with an Aquasil C18 column (150 × 3.0 mm, 3 µm film thickness), detection wavelength 210 nm; solvent A: CH_3CN:H_2O:phosphate buffer (17.01 g KH_2PO_4 + 14.41 g H_3PO_4 85% adjusted to pH 1.8 and filled to a volume of 250 cm^3 with H_2O) 100:710:10 (vol.), solvent B: CH_3CN:H_2O:phosphate buffer of 720:230:10 (vol.), gradient (start 80%A:20%B; 13 min 0% A, 100% B; 20 min 0% A, 100% B, stop; equilibration 10 min 80%A:20%B); concentration of analytes *ca.* 0.5 mg/cm^3 (solvent 1,4-dioxane); injection volume 2×10^{-3} cm^3; in the presence of easily oxidizable compounds (*e.g.*, hydroquinones) addition of 40 mg ascorbic acid per liter of dioxane. HPLC-MS-Analyses were obtained using a HP-MSD 1200 device with a YMC Pro C4 column (150 × 3.0 mm, 3 µm film thickness) at 123°C; solvent A: H_2O/ CH_3CN/ $MeSO_3H$, solvent B: H_2O, solvent C CH_3CN; gradient start to 5 min 10:85:5, 20 min 10:0:90, 60 min 2:0:98, post equilibration 40 min 10:85:5 (vol.). MSD mode ES positive, capillary voltage 3500 V, fragmentator 100 V, mass range 100-1000 amu; concentration of analytes *ca.* 10 mg/cm^3 (solvent MeOH:*tert*-butyl methyl ether 1:1), or 5-10 mg/ 10 cm^3 1,4-dioxane; injection volume

2×10^{-3} cm^3; in the presence of easily oxidizable compounds (*e.g.*, hydroquinones) addition of 40 mg ascorbic acid per liter of dioxane. GC-MS analyses for structure elucidation were conducted on an Agilent GC 6890N, 5973 MSD series system, equipped with a Gerstel MPS2 autosampler. The mass spectra were obtained by electron ionization (EI, 70 eV); for separation, a HP-5MS (fused silica, 30 m × 0.25 mm, film thickness 0.25 µm) from Agilent J&W was used; flow 21.57 psi He at constant pressure, split ratio 1:25, oven temp. 70°C (0 min) → 315°C (15 min), injector temp. 300°C, injection volume 1×10^{-3} $cm^3$of a solution of 5-10 mg of analyte in 1 cm^3 EtOAc; samples were analyzed neat or after derivatization with bis(trimethylsilyl)trifluoroacetamide (BSTFA) and trimethylsilyl chloride in pyridine. High-resolution GC-MS analyses were performed on a JEOL AccuTOF-GCv 4G MSD coupled to an Agilent 7890B GC with split/splitless-injector and equipped with a PAL COMBI-xt autosampler. The mass spectra were obtained by electron ionisation (EI) field ionization (FI). The determination of the molecular formula was calculated by MassCenter Software. Microanalyses have been performed by Solvias AG Analytics in Kaiseraugst (CH).

b) Synthesis of aryl acetates, hydroxyacetophenones and other products of Fries rearrangement reactions. If not stated differently, commercially available di- and trimethylphenols were esterified under basic conditions with Ac_2O and NEt_3, or AcCl and NEt_3, or Ac_2O and pyridine, or AcCl and pyridine in CH_2Cl_2, see e.g. references[4-6] The aryl acetates obtained were converted with BF_3 complexes in HOAc or in 1,2-dichloroethane (DCE) or with $AlCl_3$ to the corresponding hydroxyacetophenones according to published procedures.[4,7-10] For details see data given below at the corresponding compounds. Additional side products obtained were phenols, hydroquinones, quinones and chromanones.[11-15]

Method S3 Assessment of the accessibility of zeolite micropores for distinct substrates. The molecular diameters estimated based on the computed Connolly surfaces of representative substrates and zeolites of distinct framework type (MFI, BEA, and FAU) were analysed using the Schrödinger Software Suite 2019-3 (Maestro 12.1, MarcoModel 12.5).[16-19] The structures of the aromatic esters were optimised with force field OPLS3e, and minimal energy conformers chosen for visualisation. The crystal information files of the zeolites were sourced from the international zeolite database (http://www.iza-structure.org/databases/) and subsequently periodic structures were generated using the Mercury 2.3 (CCDC) or Schrodinger's Maestro 12.1 software. Molecular surfaces for both the molecules and zeolites were generated and displayed with Schrodinger's Maestro 12.1 (implemented as approximation of the Connolly surface). Aryl acetates were overlaid onto the zeolite structure without any energy optimisations.

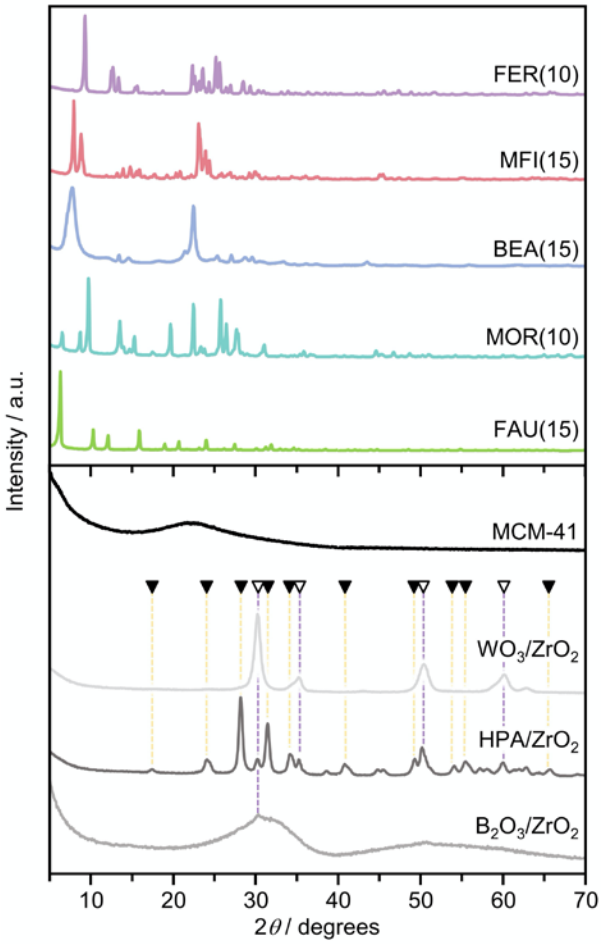


Fig. S1 X-ray diffraction patterns of the solid acids. Characteristic diffraction lines are observed for all the zeolitic materials. ZrO_2-supported catalysts only display some features of the monoclinic JCPDS 07-2209, solid triangles) and tetragonal phases (JCPDS 05-9166, open triangles) of the support, suggesting the high dispersion of the active components.

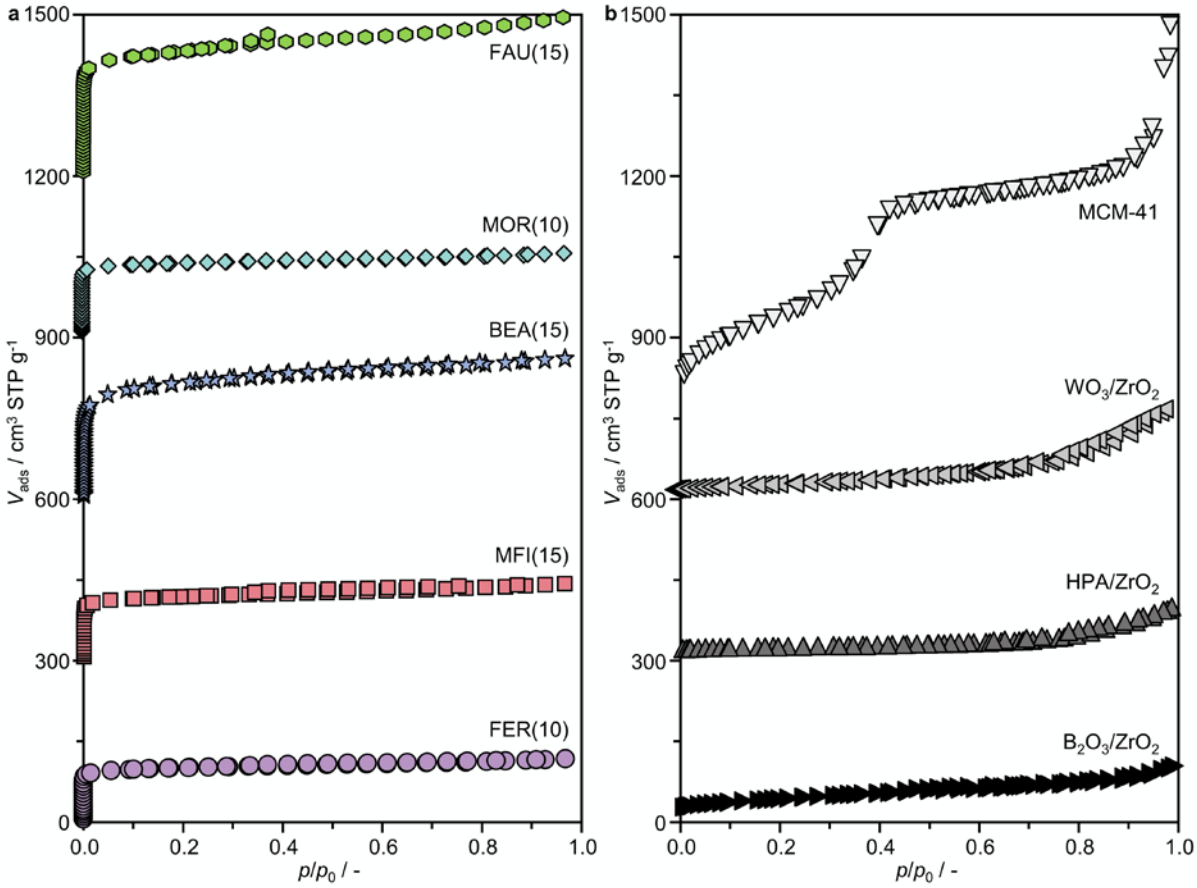


Fig. S2 Sorption isotherms of **a**) zeolites (Ar at 87 K) and **b**) other (N_2 at 77 K) solid acids. The isotherms were offset by 300 cm^3 STP g^{-1} for improved visualisation.

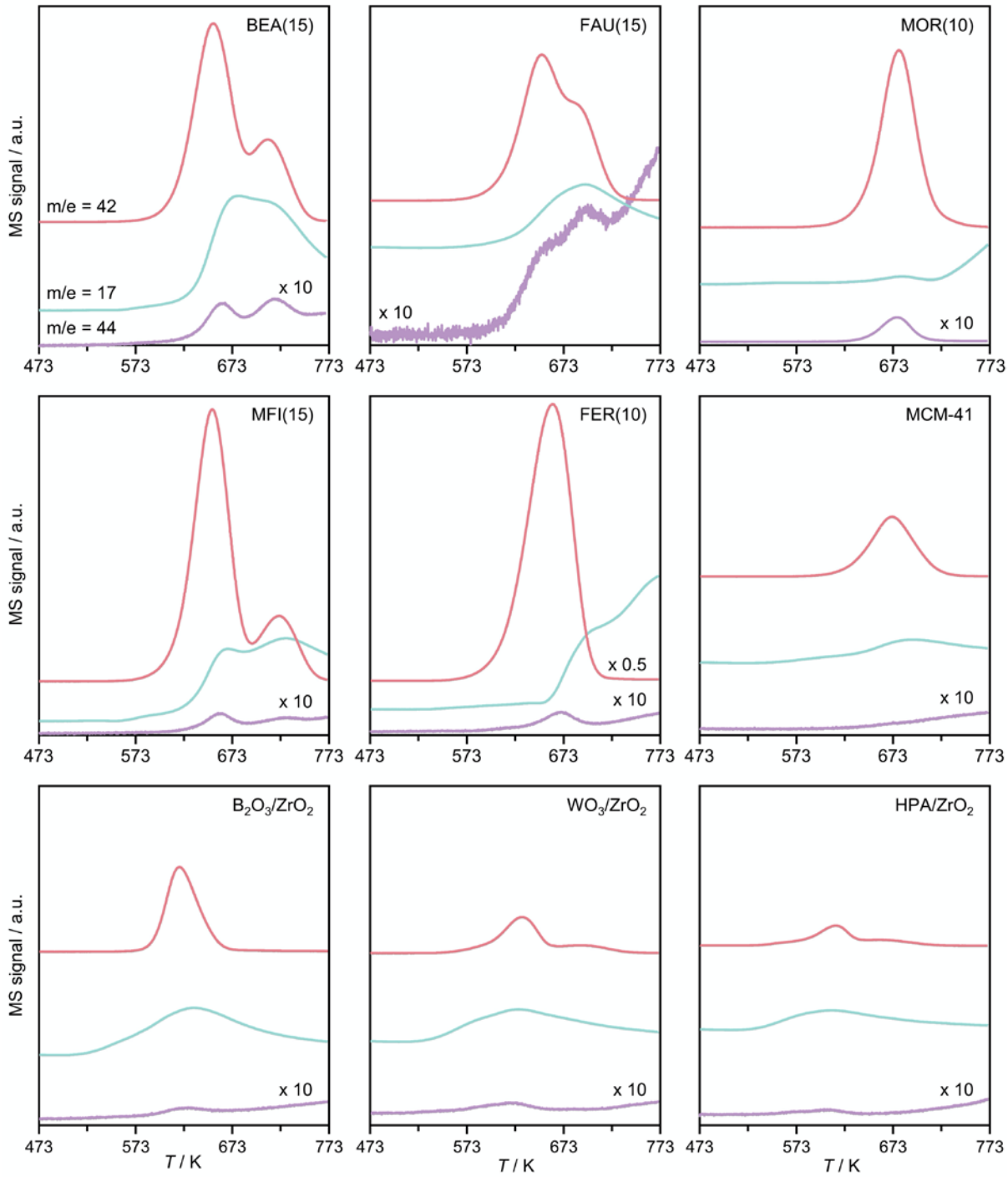


Fig. S3 Evolved products detected by mass spectrometry during the temperature-programmed surface reaction of *n*-propylamine on selected solid acids: *m*/*e* = 17 (ammonia), *m*/*e* = 42 (propene) and *m*/*e* = 44 (propane).

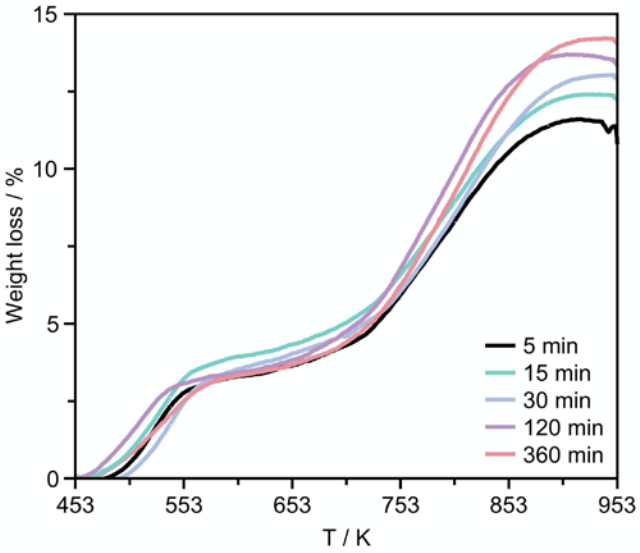


Fig. S4 Weight loss determined by thermogravimetric analysis of BEA(15) after use in the Fries rearrangement of *p*-tolyl acetate for different times. Conditions: 2.5 mmol *p*-TA, 340 mg catalyst, 10 cm^3 solvent, $T = 423$ K, $t = 6$ h.

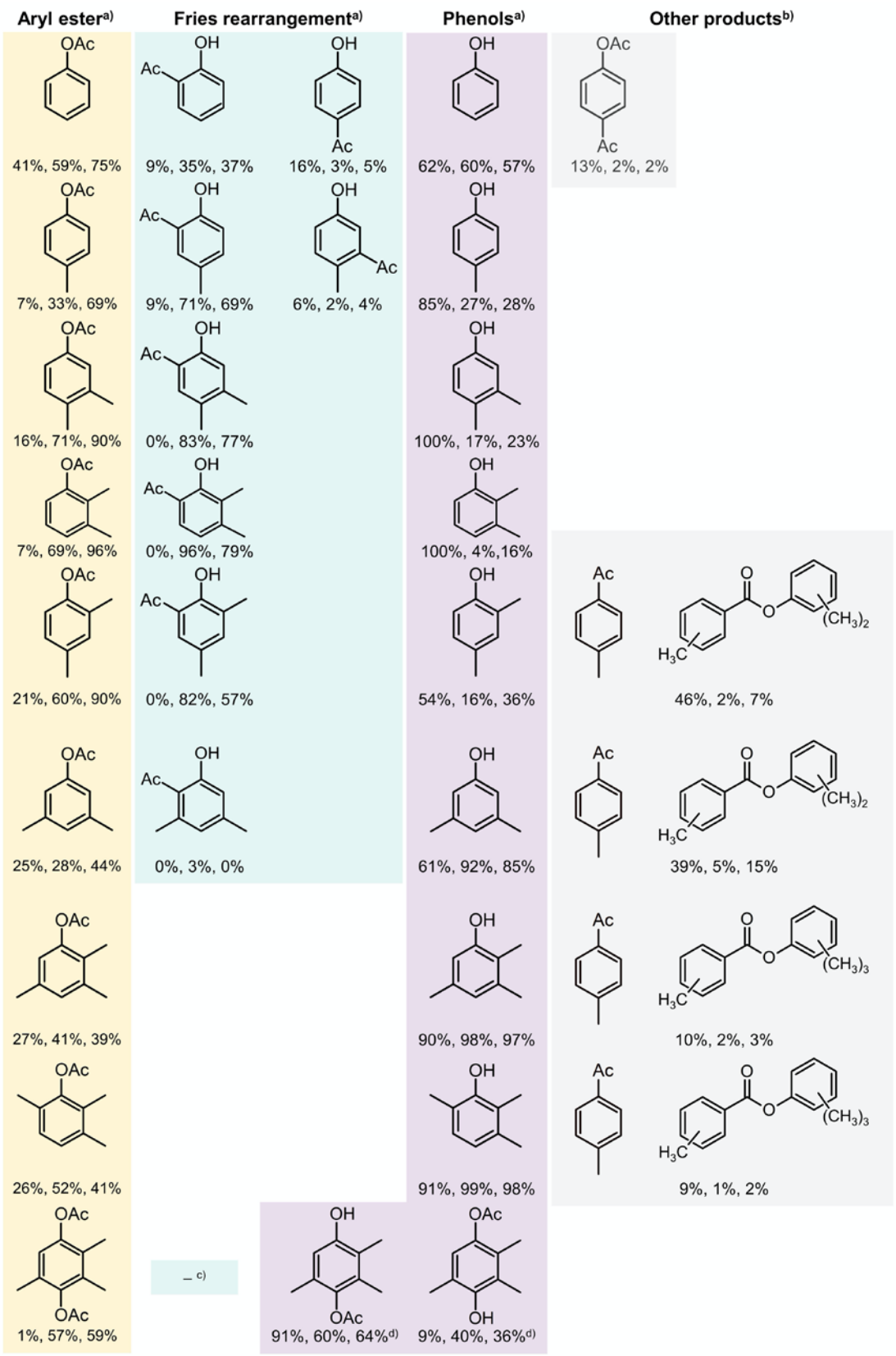
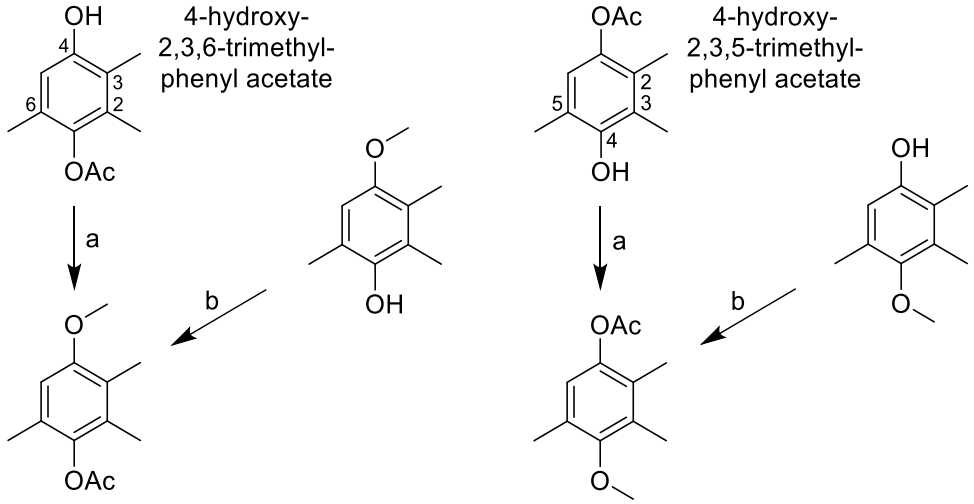


Fig. S5 Breakdown of the respective conversion of aryl ester and selectivity patterns to Fries rearrangement, phenols, and other products observed over MFI(15), FAU(15), and BEA(15) in the reactions reported in **Fig. 9a**. Conditions: 2.5 mmol substrate, 340 mg catalyst, toluene 10 cm^3, $T = 423$ K, $t = 6$ h.[a)] Numbers given are conversions of aryl esters (yellow), and selectivity of Fries rearrangement products (green) and phenols (pink),

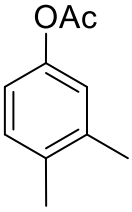
determined by quantitative HPLC analyses. [b)] Structures of other products (grey) were only tentatively assigned based on GC-MS data; numbers given correspond to the associated GC area% (calculated from the total ion current) obtained from the crude reaction mixtures. [c)] The formation of products from Fries rearrangement or other side products described in literature from transformations applying conventional Lewis acids ($AlCl_3$, BF_3) could be excluded by comparison experiments in homogeneous phase and with reference compounds (hydroquinones, quinones and chromanones) synthesized according to published procedures[4,7,10,11] and providing identical spectral data not reported here. [d)] For determination of the selectivity, the ratio between the two monoacetate derivatives of trimethylhydroquinone was determined by ^{1}H-NMR spectroscopy (H_{arom}); direct quantification in crude reaction mixtures was not possible due to the virtually identical retention times of the regioisomers in all GC and HPLC systems used. In order to assure the structural assignments, additional derivatization (dimethyl sulfate, 50% aq. KOH, 1,2-dimethoxyethane, room temp.) was performed providing the corresponding methyl ether derivatives, which were independently synthesized from the TMHQ monomethyl ethers according to **Scheme S1**.

Data S1. Analysis of products.



Scheme S1 Derivatization reactions for determination of the selectivity of formation of 4-hydroxy-2,3,6-trimethylphenyl acetate *versus* 4-hydroxy-2,3,5-trimethylphenyl acetate. a) $(H_3CO)_2SO_2$, 50% aq. KOH, 1,2-dimethoxyethane, room temp.; b) Ac_2O, pyridine, CH_2Cl_2, room temperature; for details see text below.

3,4-dimethylphenyl acetate



Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Prepared from the corresponding phenol by acetylation with Ac_2O (1.4 equiv.), NEt_3 (3.0 equiv.), 4-dimethylaminopyridine (2 mol%) in CH_2Cl_2 (conc. 10%), room temp. to 40°C, cooling with an ice bath to 23°C, 1 h; yellowish liquid, purity 99.5%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.11 (1 H_{arom}, d, J = 8.1 Hz), 6.85 (1 H_{arom}, d, J = 2.3 Hz), 6.80 (1 H_{arom}, dd, J = 8.1, 2.5 Hz), 2.28 (s, 3 H), 2.24 (s, 3 H), 2.23 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.8, 148.6, 137.9, 134.2, 130.3, 122.5, 118.6, 21.1, 19.9, 19.2.

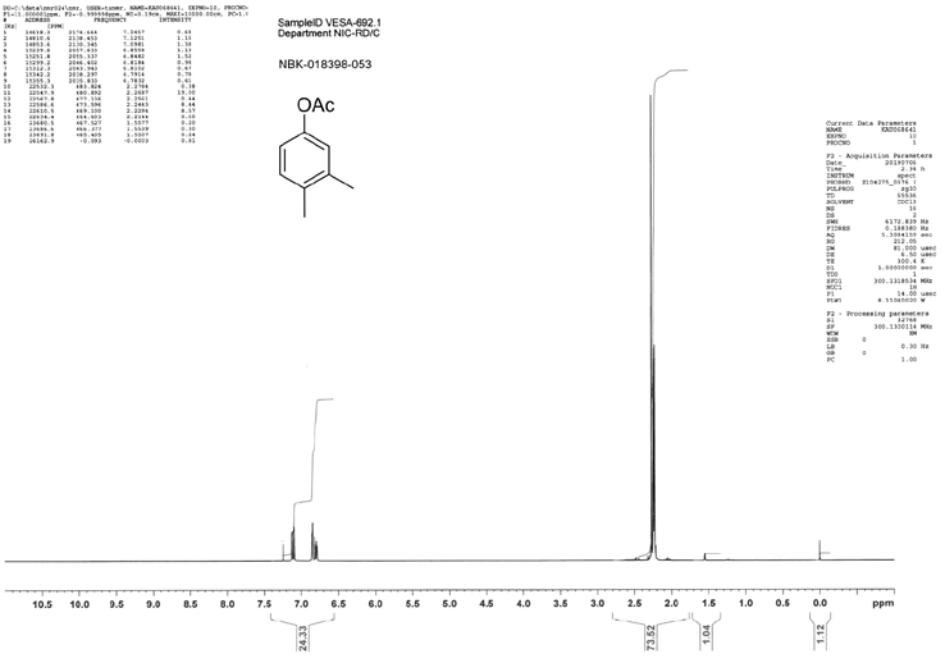


Fig. S6 ^{1}H NMR spectra of 3,4-dimethylphenyl acetate.

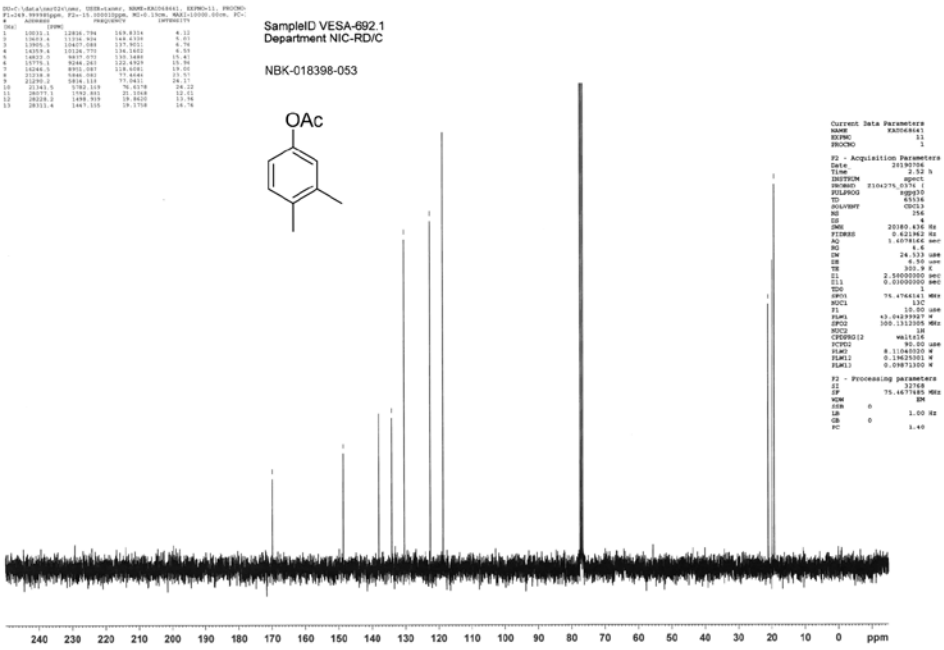
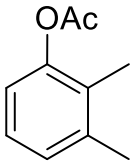


Fig. S7 ^{13}C NMR spectra of 3,4-dimethylphenyl acetate.

2,3-dimethylphenyl acetate



Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Prepared from the corresponding phenol by acetylation with Ac_2O (1.4 equiv.), NEt_3 (3.0 equiv.), 4-dimethylaminopyridine (2 mol%) in CH_2Cl_2 (conc. 10%), 23-40°C, 1 h; reddish liquid, purity 97.3%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 7.02-7.12 (m, 2 H_{arom}), 6.83-6.86 (m, 1 H_{arom}), 2.32 (s, 3 H), 2.29 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ(ppm) = 169.5, 149.3, 138.5, 128.7, 127.6, 126.1, 119.5, 20.8, 20.1, 12.4.

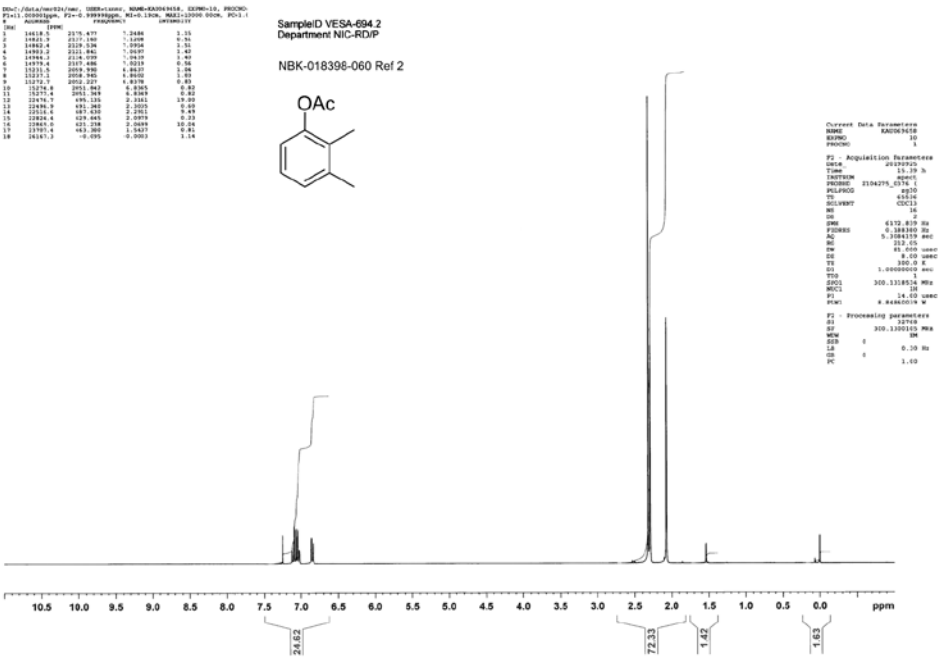


Fig. S8 ^{1}H NMR spectra of 2,3-dimethylphenyl acetate.

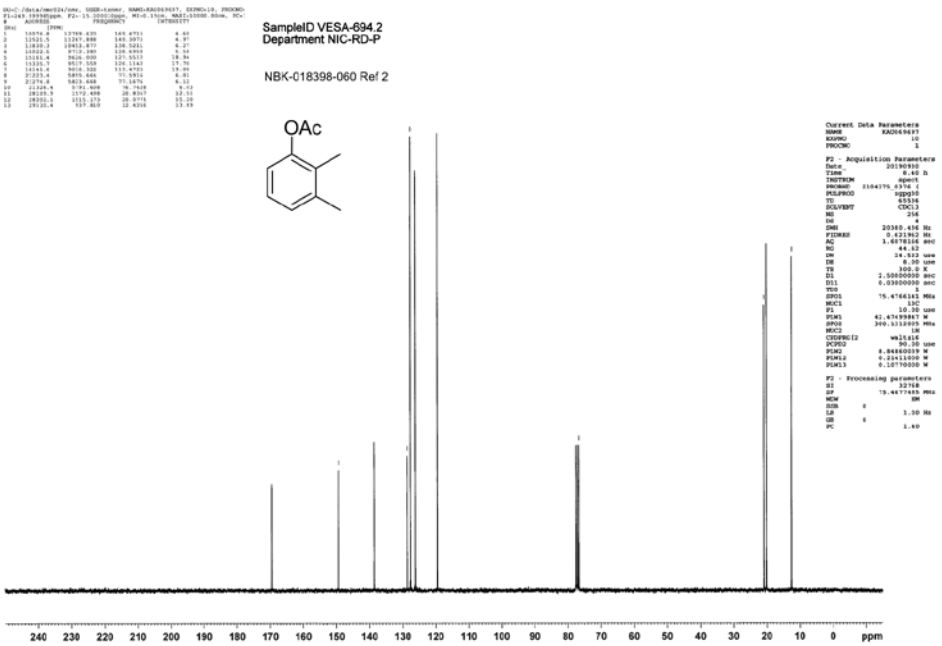
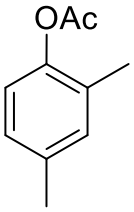


Fig. S9 ^{13}C NMR spectra of 2,3-dimethylphenyl acetate.

2,4-dimethylphenyl acetate



Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Prepared from the corresponding phenol by acetylation with Ac_2O (1.4 equiv.), NEt_3 (3.0 equiv.), 4-dimethylaminopyridine (2 mol%) in CH_2Cl_2 (conc. 10%), room temp. to 40°C (cooling with an ice bath), 1 h; colourless liquid, purity 95.7%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.97-7.03 (m, 2 H_{arom}), 6.87 (d, 1 H_{arom}, J = 8.1 Hz), 2.30 (s, 6 H), 2.14 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.5, 147.1, 135.6, 131.8, 129.6, 127.5, 121.5, 20.8, 16.1.

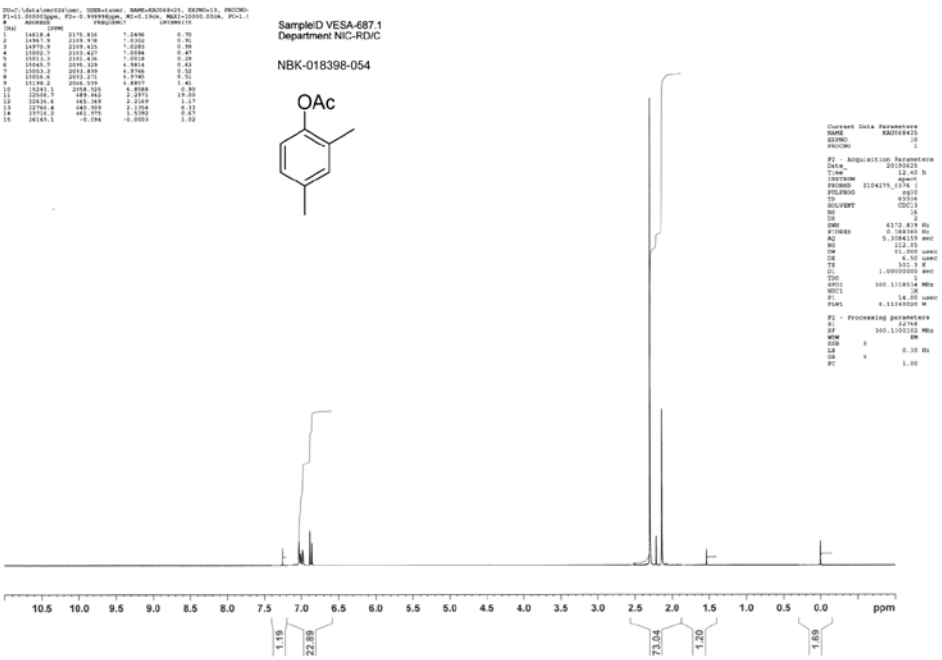


Fig. S10 ^{1}H NMR spectra of 2,4-dimethylphenyl acetate.

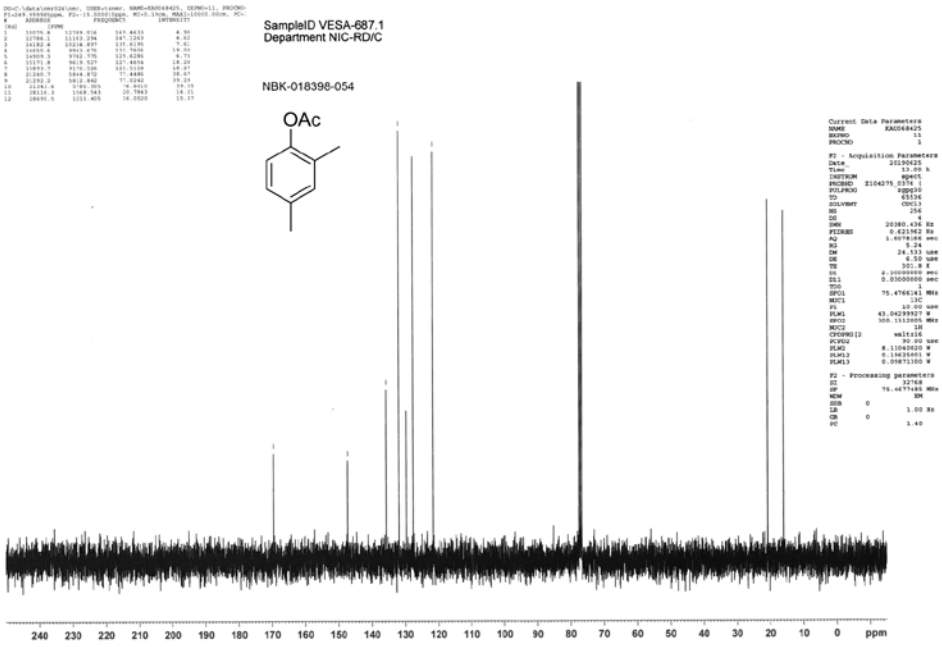
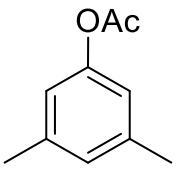


Fig. S11 ^{13}C NMR spectra of 2,4-dimethylphenyl acetate.

3,5-dimethylphenyl acetate



Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Prepared from the corresponding phenol by acetylation with Ac_2O (1.4 equiv.), NEt_3 (3.0 equiv.), 4-dimethylaminopyridine (2 mol%) in CH_2Cl_2, 23-31°C, 1 h; slightly yellowish liquid, purity 97.1%. For NMR data cf. a literature procedure.[5]

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.85-6.86 (m, 1 H_{arom}), 6.69 (br.s, 2 H_{arom}), 2.31 (s, 3 H), 2.30 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.7, 150.6, 139.3, 127.6, 119.2, 21.2, 21.1.

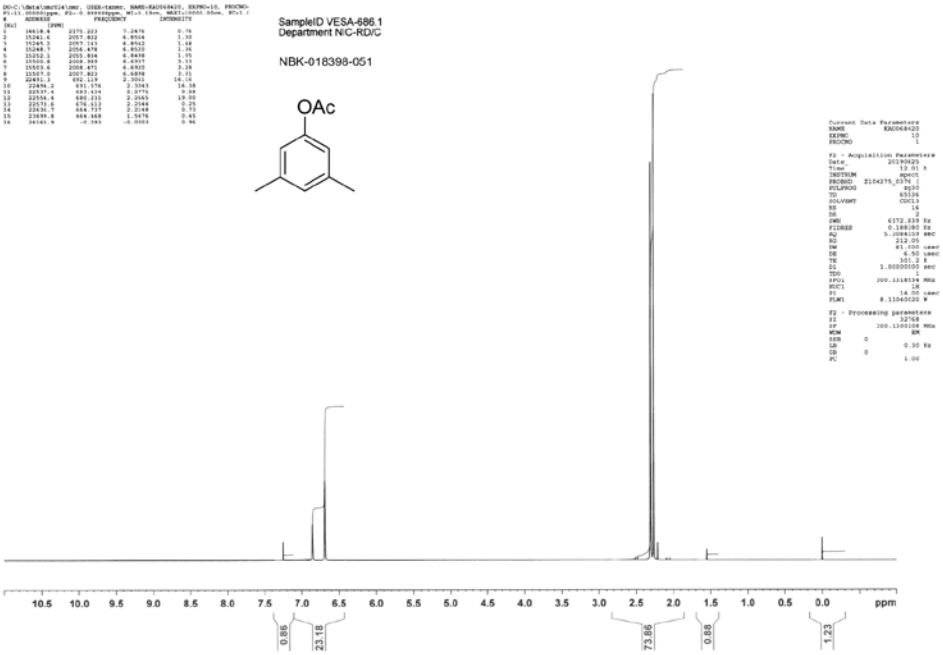


Fig. S12 ^{1}H NMR spectra of 3,5-dimethylphenyl acetate.

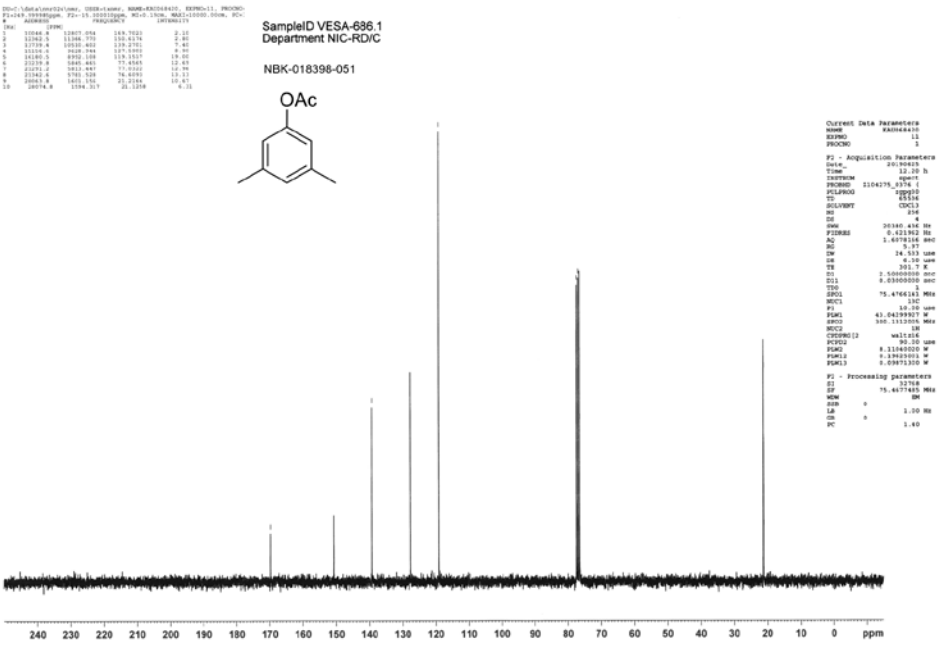
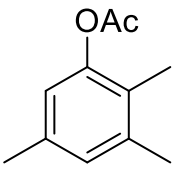


Fig. S13 ^{13}C NMR spectra of 3,5-dimethylphenyl acetate.

2,3,5-trimethylphenyl acetate



Chemical formula: $C_{11}H_{14}O_2$, Molecular weight: 178.2 g mol^{-1}

Prepared from the corresponding phenol by acetylation with Ac_2O (1.4 equiv.), NEt_3 (3.0 equiv.), 4-dimethylaminopyridine (2 mol%) in CH_2Cl_2, room temp. to 40°C, 2 h; purity 99.5%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.86 (br.s, 1 H_{arom}), 6.67 (br.s, 1 H_{arom}), 2.30 (s, 3 H), 2.27 (s, 3 H), 2.25 (s, 3 H), 2.02 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.6, 149.1, 138.1, 135.9, 128.5, 125.4, 119.9, 20.9, 20.8, 20.0, 12.1.

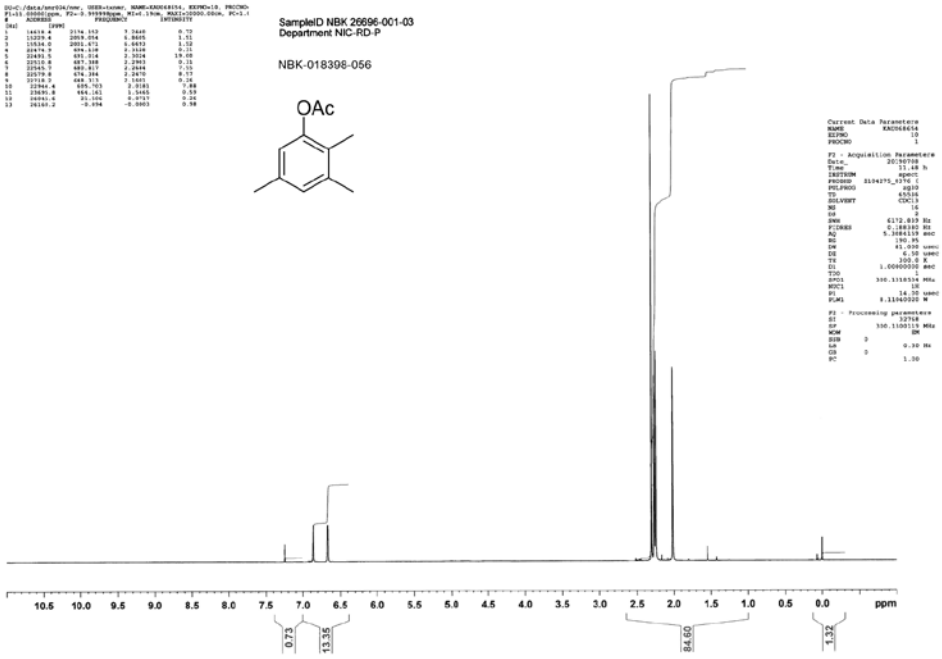


Fig. S14 ^{1}H NMR spectra of 2,3,5-trimethylphenyl acetate.

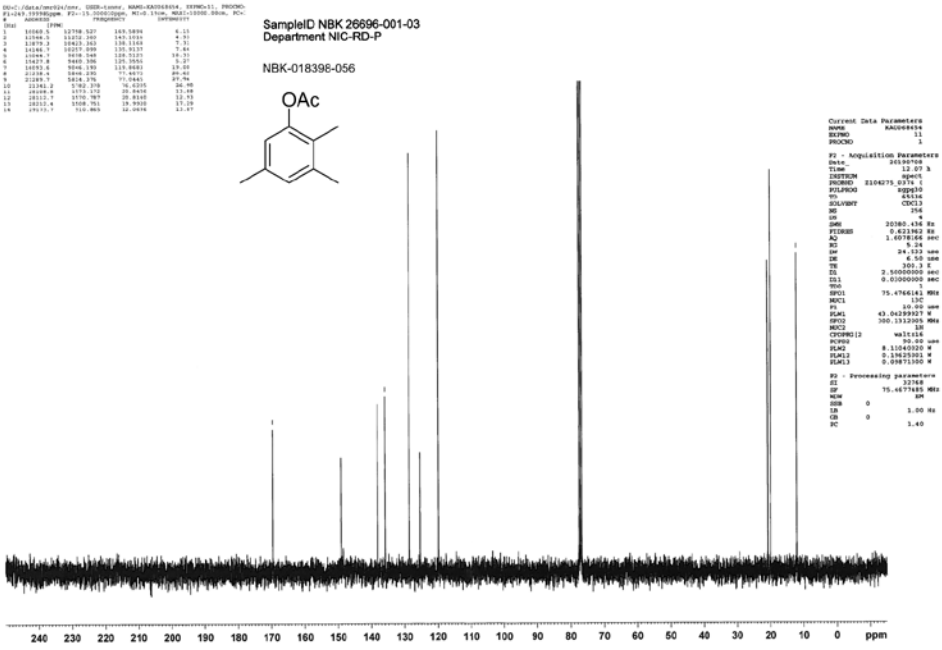
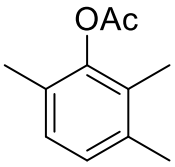


Fig. S15 ^{13}C NMR spectra of 2,3,5-trimethylphenyl acetate.

2,3,6-trimethylphenyl acetate



Chemical formula: $C_{11}H_{14}O_2$, Molecular weight: 178.2 g mol^{-1}

Prepared from the corresponding phenol by acetylation with Ac_2O (1.4 equiv.), NEt_3 (3.0 equiv.), 4-dimethylaminopyridine (2 mol%) in CH_2Cl_2, 23-31°C, 1.5 h; colourless liquid, purity 99.5%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.95 (br.s, 2 H_{arom}), 2.34 (s, 3 H), 2.25 (s, 3 H), 2.12 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.0, 135.6, 128.5, 127.6, 127.3, 20.5, 19.8, 16.3, 12.6.

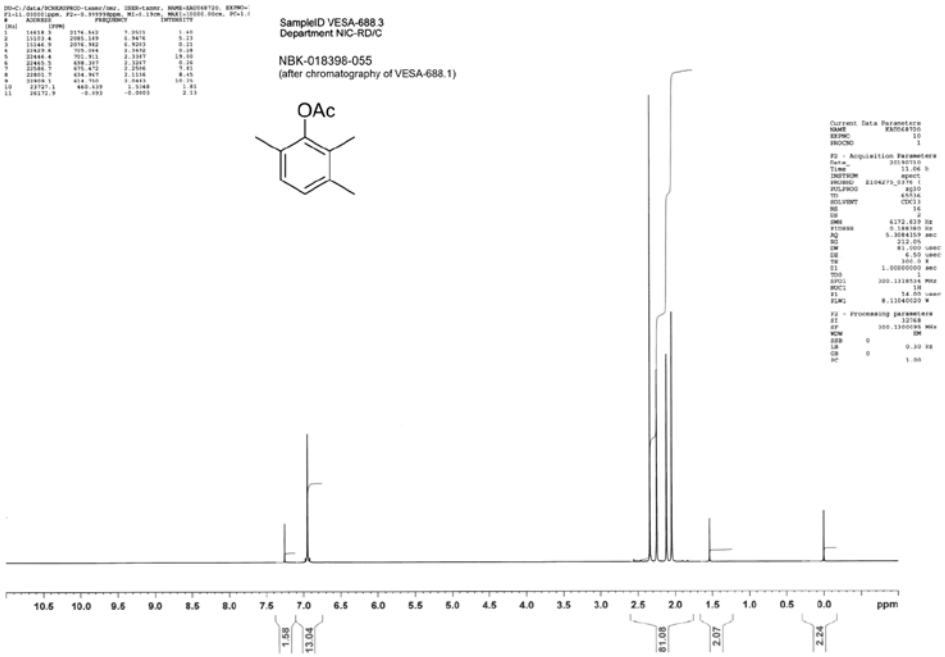


Fig. S16 ^{1}H NMR spectra of 2,3,6-trimethylphenyl acetate.

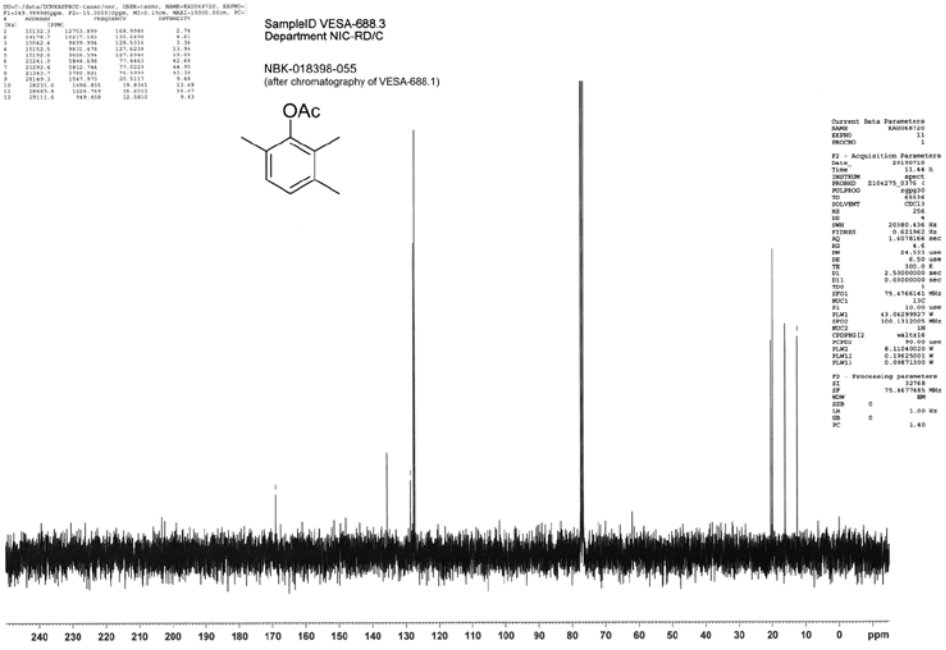
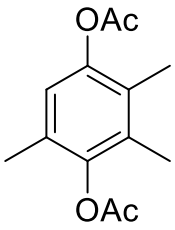


Fig. S17 ^{13}C NMR spectra of 2,3,6-trimethylphenyl acetate.

2,3,5-trimethylhydroquinone diacetate



Chemical formula: $C_{13}H_{16}O_4$, Molecular weight: 236.3 g mol^{-1}

Prepared by acetylation of trimethylhydroquinone[4,8] or from ketoisophorone.[20] Purity 99.7% (quant. HPLC, Aquasil method).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.75 (br.s, H_{arom}), 2.33 (s, $COCH_3$), 2.30 (s, $COCH_3$), 2.11 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H).

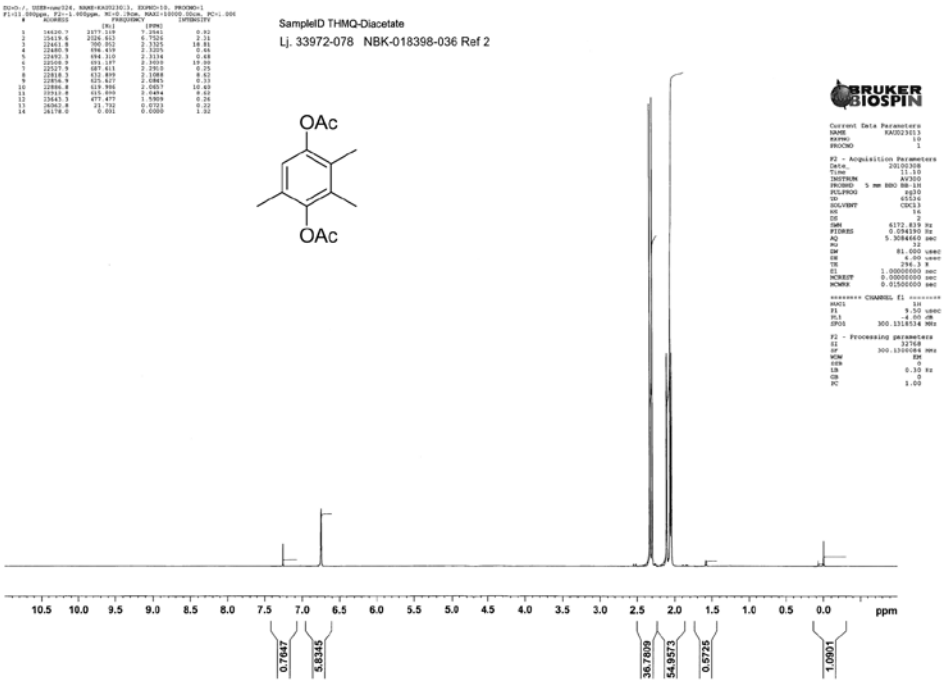
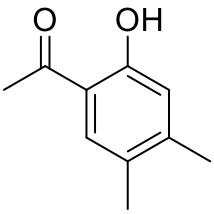


Fig. S18 ^{1}H NMR spectra of 2,3,5-trimethylhydroquinone diacetate.

2-hydroxy-4,5-dimethylacetophenone

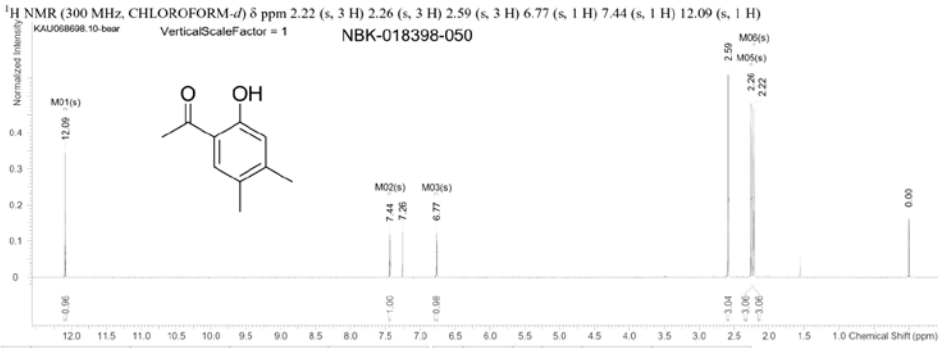


Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Purchased from TCI Tokyo Chemical Industry Co. Ltd; purity >98.0% (GC, CoA 9 July 2019).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 12.09 (s, OH), 7.44 (br.s, H_{arom}), 6.77 (br.s, H_{arom}), 2.59 (s, 3 H), 2.26 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 203.8, 160.7, 147.0, 130.8, 127.2, 118.9, 117.7, 26.5, 20.5, 18.9.



No.	(ppm)	Value	Absolute Value	Non-Negative Value
1	[12.07 .. 12.11]	0.962	4.206e+7	0.962
2	[7.42 .. 7.46]	1.000	4.371e+7	1.000
3	[6.75 .. 6.79]	0.981	4.286e+7	0.981
4	[2.57 .. 2.60]	3.041	1.329e+8	3.041
5	[2.24 .. 2.28]	3.060	1.337e+8	3.060
6	[2.20 .. 2.24]	3.063	1.339e+8	3.063

No.	Shift1 (ppm)	H's	Type	Multiplet1	(ppm)
1	2.22	3	s	M06	[2.20 .. 2.24]
2	2.26	3	s	M05	[2.24 .. 2.28]
3	2.59	3	s	M04	[2.57 .. 2.60]
4	6.77	1	s	M03	[6.75 .. 6.79]
5	7.44	1	s	M02	[7.42 .. 7.46]
6	12.09	1	s	M01	[12.07 .. 12.11]

Fig. S19 ^{1}H NMR spectra of 2-hydroxy-4,5-dimethylacetophenone.

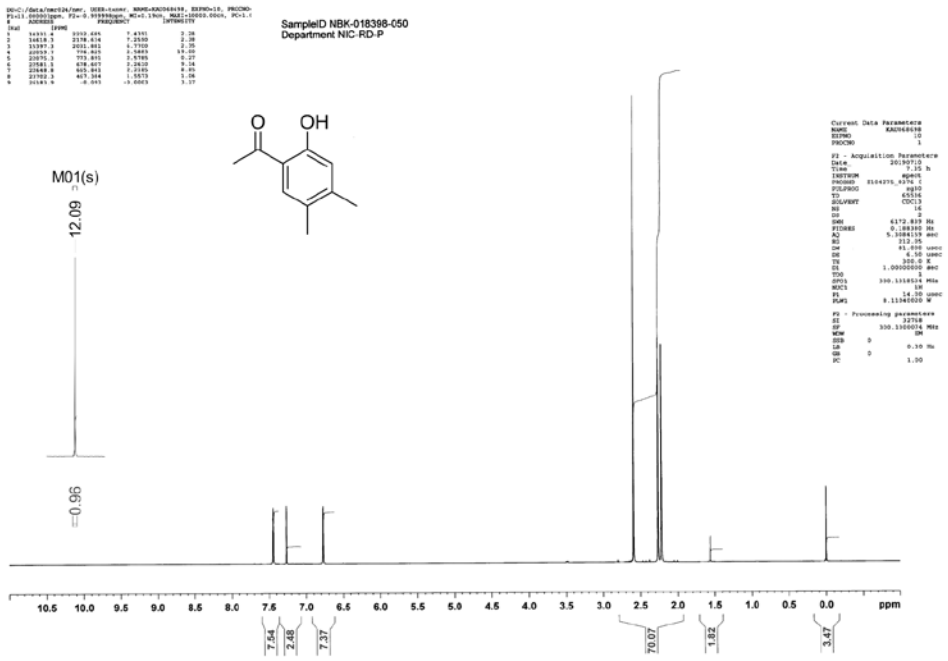


Fig. S20 [1]H NMR spectra of 2-hydroxy-4,5-dimethylacetophenone.

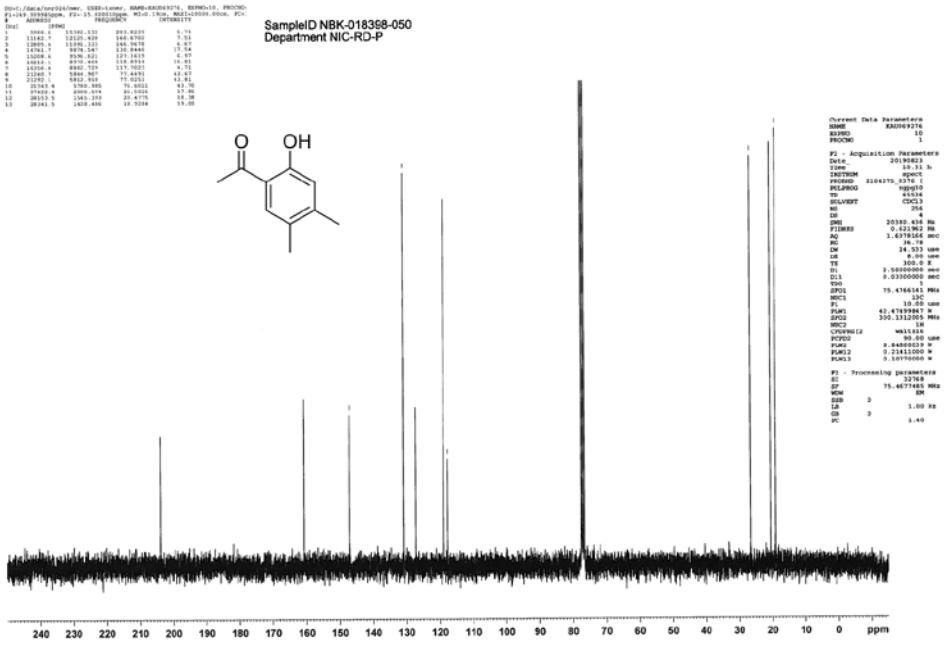
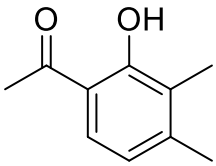


Fig. S21 [13]C NMR spectra of 2-hydroxy-4,5-dimethylacetophenone.

2-hydroxy-3,4-dimethylacetophenone



Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Synthesized by Fries rearrangement of 2,3-dimethylphenyl acetate with BF_3-HOAc complex in 1,2-dichloroethanre, reflux, 3 h;[9] slightly yellow, pleasant smelling oil, purity 98.7%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 12.68 (s, OH), 7.48 (AB, 1 H_{arom}, J = 8.2 Hz), 6.70 (AB, 1 H_{arom}, J = 8.3 Hz), 2.60 (s, 3 H), 2.31 (s, 3 H), 2.17 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 204.2, 160.7, 146.1, 127.5, 125.4, 120.4, 117.2, 26.5, 20.7, 10.9.

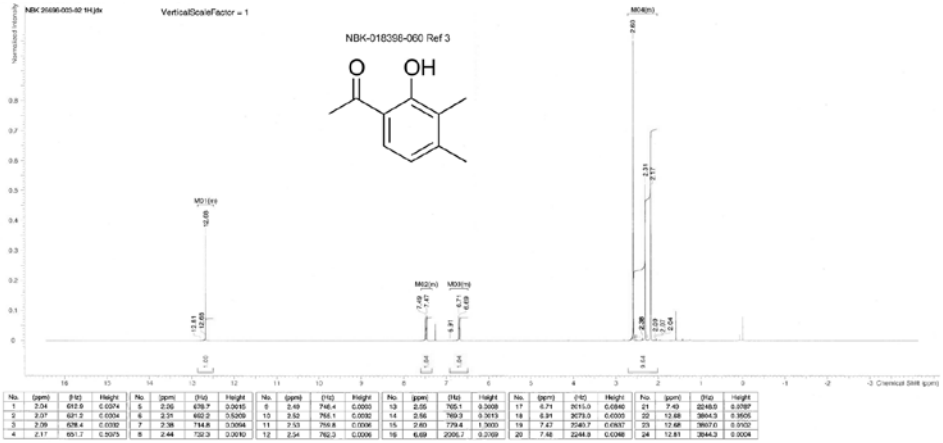


Fig. S22 ^{1}H NMR spectra of 2-hydroxy-3,4-dimethylacetophenone.

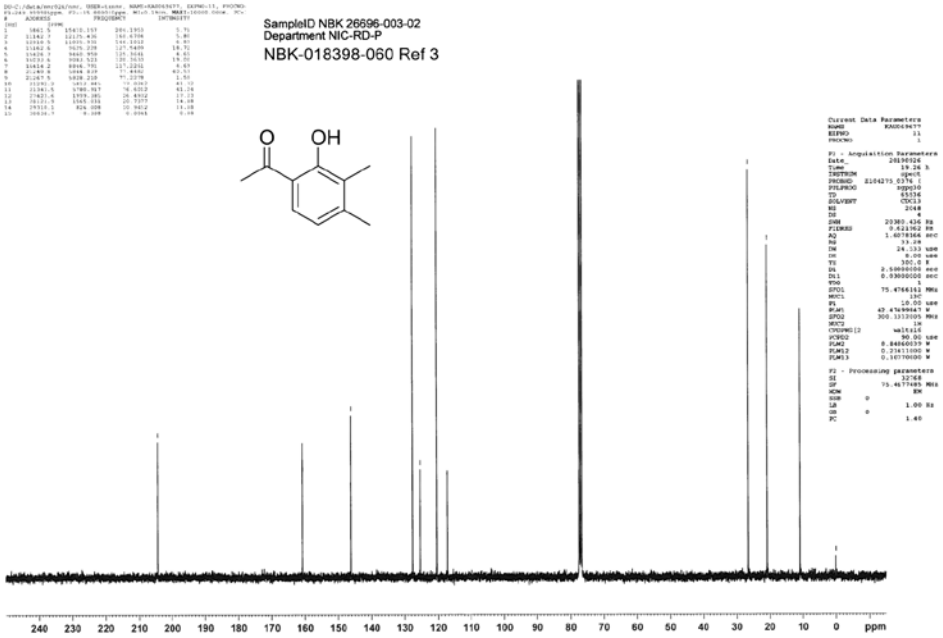
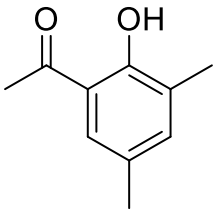


Fig. S23 ^{13}C NMR spectra of 2-hydroxy-3,4-dimethylacetophenone.

2-hydroxy-3,5-dimethylacetophenone



Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Purchased from TCI Tokyo Chemical Industry Co. Ltd; purity >98.0% (given by TCI).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 12.40 (s, OH), 7.36 (m_c, A<u>B</u>, 1 H_{arom}), 7.17 (m_c, <u>A</u>B), 2.61 (s, 3 H), 2.28 (s, 3 H), 2.23 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 204.6, 158.8, 138.4, 127.9, 127.1, 118.7, 26.7, 20.5, 15.4.

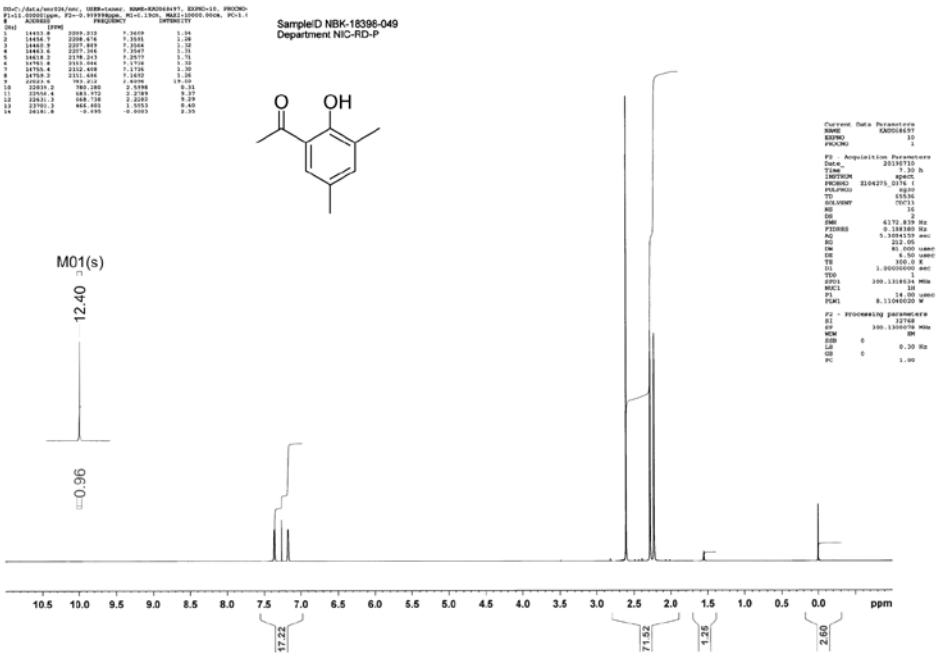


Fig. S24 ^{1}H NMR spectra of 2-hydroxy-3,5-dimethylacetophenone.

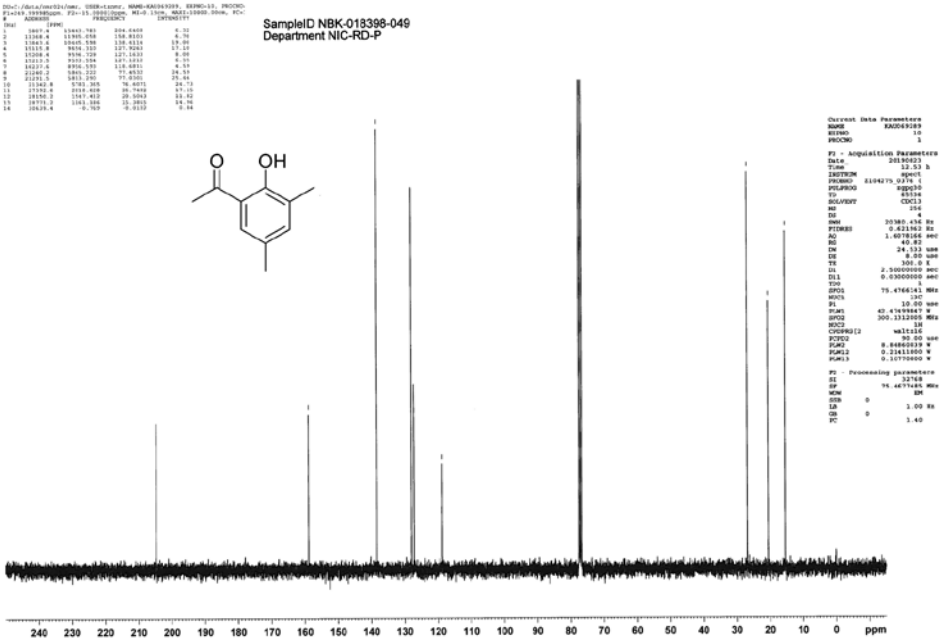
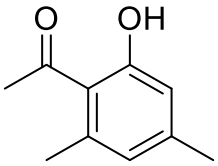


Fig. S25 ^{13}C NMR spectra of 2-hydroxy-3,5-dimethylacetophenone.

2-hydroxy-4,6-dimethylacetophenone



Chemical formula: $C_{10}H_{12}O_2$, Molecular weight: 164.2 g mol^{-1}

Synthesized by Fries rearrangement of 3,5-trimethylphenyl acetate with 2.5 equiv. $AlCl_3$ in nitromethane (addition at 0 to 5°C), then 50°C, 15 h;[5] for preparation with 1 equiv. $AlCl_3$ at 120-150°C see ref.[21]; yellow solid, purity 96.2%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 12.63 (s, OH), 6.64 (m_c, 1 H_{arom}), 6.53 (m_c, 1 H_{arom}), 2.63 (s, 3 H), 2.55 (s, 3 H), 2.26 (s, 3 H).[22,23]

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 205.4, 163.5, 146.1, 139.4, 124.5, 119.1, 116.7, 33.2, 24.6, 21.5.

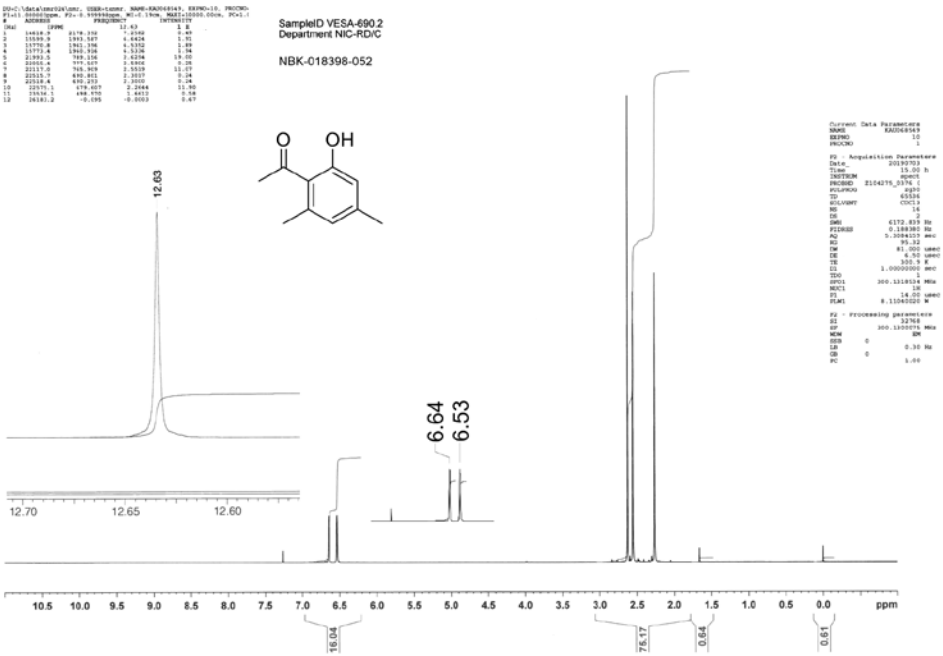


Fig. S26 ^{1}H NMR spectra of 2-hydroxy-4,6-dimethylacetophenone.

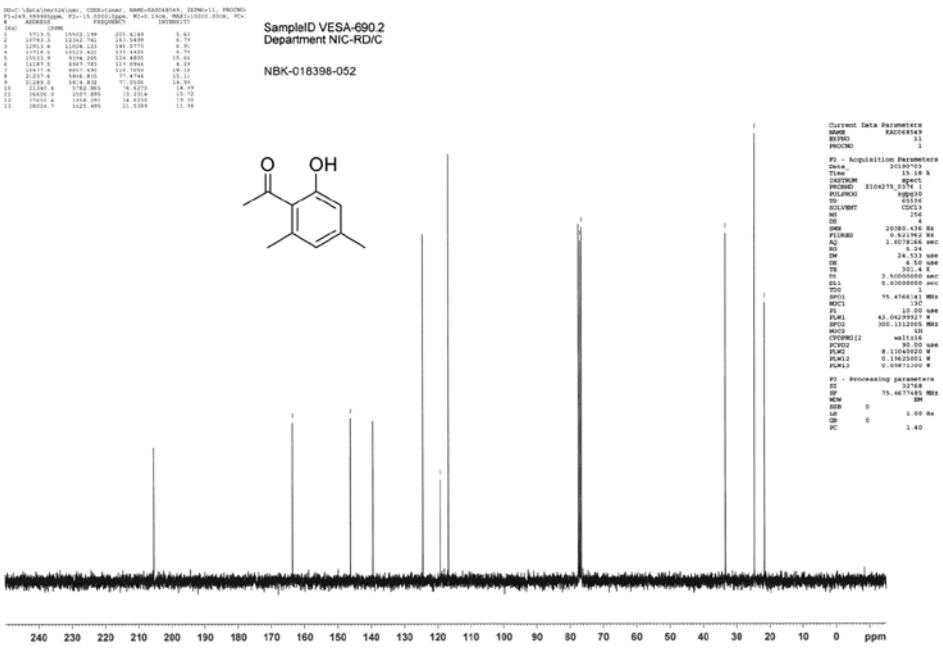
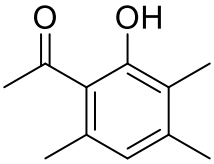


Fig. S27 ^{13}C NMR spectra of 2-hydroxy-4,6-dimethylacetophenone.

2-hydroxy-3,4,6-trimethylacetophenone



Chemical formula: $C_{11}H_{14}O_2$, Molecular weight: 178.2 g mol^{-1}

Synthesized from 2,3,5-trimethylphenyl acetate with BF_3-HOAc complex in 1,2-dichloroethane, reflux, 3 h,[9] yellow solid, m.p. 46.2-47.1°C (lit.[21] 46°C), purity 98.0%. It has be noted that physical data (m.p. 32-34°C and NMR) of a compound prepared by using $AlCl_3$ as a reagent reported by Bertrand *et al.*[24] are not in agreement with our values: After having confirmed the structure by 2D NMR experiments we assume that the data set reported[24] belongs to the isomerized product 2-hydroxy-3,4,5-trimethylacetophenone (m.p. 42°C) as described by Baddeley[21] when using >2 equiv. $AlCl_3$.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 13.08 (s, OH), 6.54 (s, 1 H_{arom}), 2.64 (s, 3 H), 2.54 (s, 3 H), 2.25 (s, 3 H), 2.13 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 205.8, 161.6, 144.2, 136.0, 124.6, 123.2, 118.7, 33.3, 24.6, 20.4, 11.2.

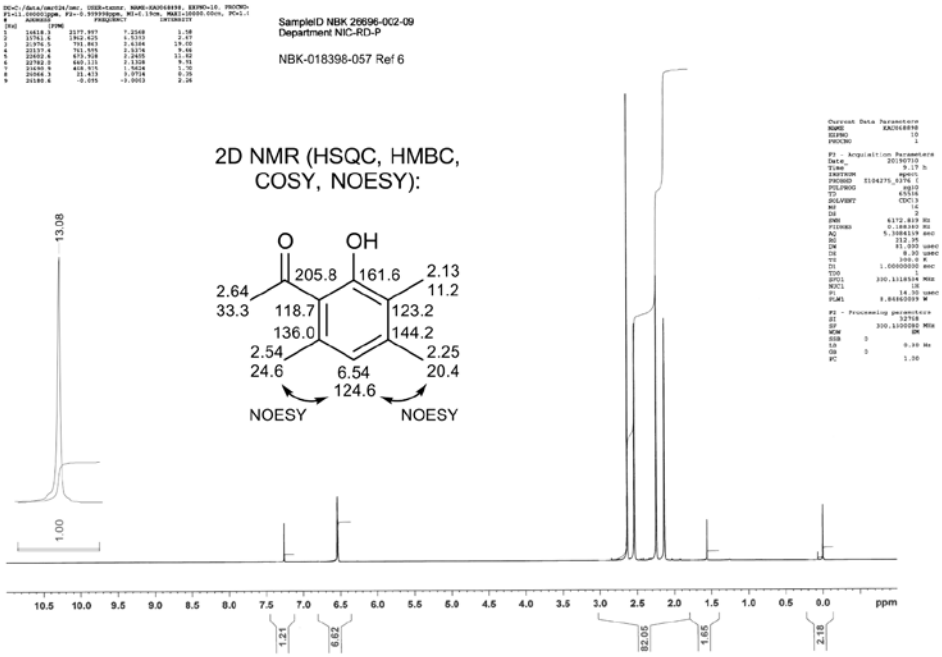


Fig. S28 ^{1}H NMR spectra and assignments by 2D NMR measurement of 2-hydroxy-3,4,6-trimethylacetophenone.

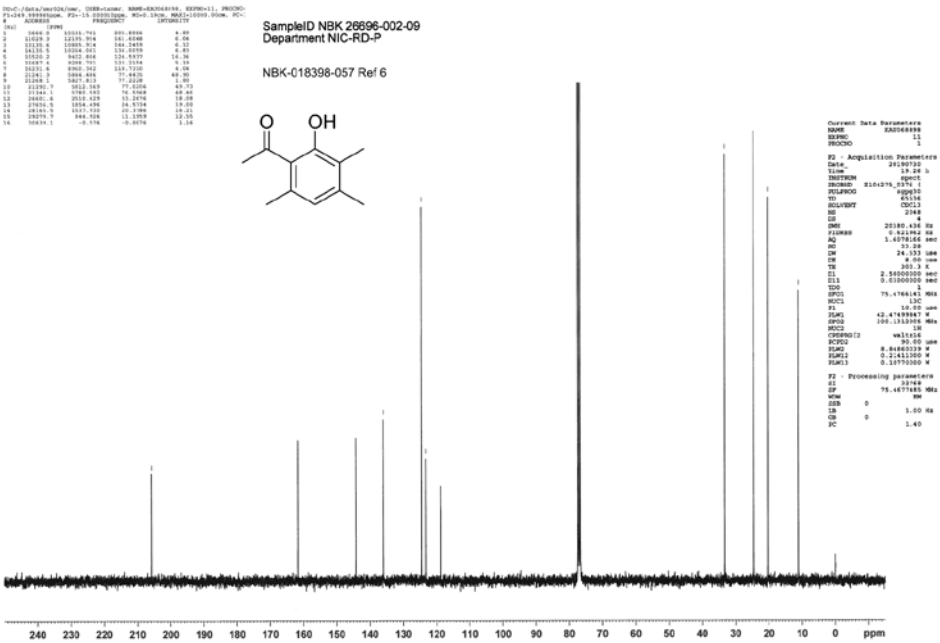
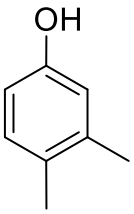


Fig. S29 ^{13}C NMR spectra of 2-hydroxy-3,4,6-trimethylacetophenone.

3,4-dimethylphenol



Chemical formula: $C_8H_{10}O$, Molecular weight: 122.2 g mol^{-1}

Purchased from Acros, purity >98.5% (GC).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.97 (1 H_{arom}, d, J = 8.1 Hz), 6.63 (1 H_{arom}, d, J = 2.6 Hz), 6.57 (1 H_{arom}, dd, J = 8.1, 2.7 Hz), 4.75 (s, OH), 2.20 (s, 3 H), 2.17 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 153.4, 138.0, 130.5, 128.7, 116.6, 112.4, 19.9, 18.8.

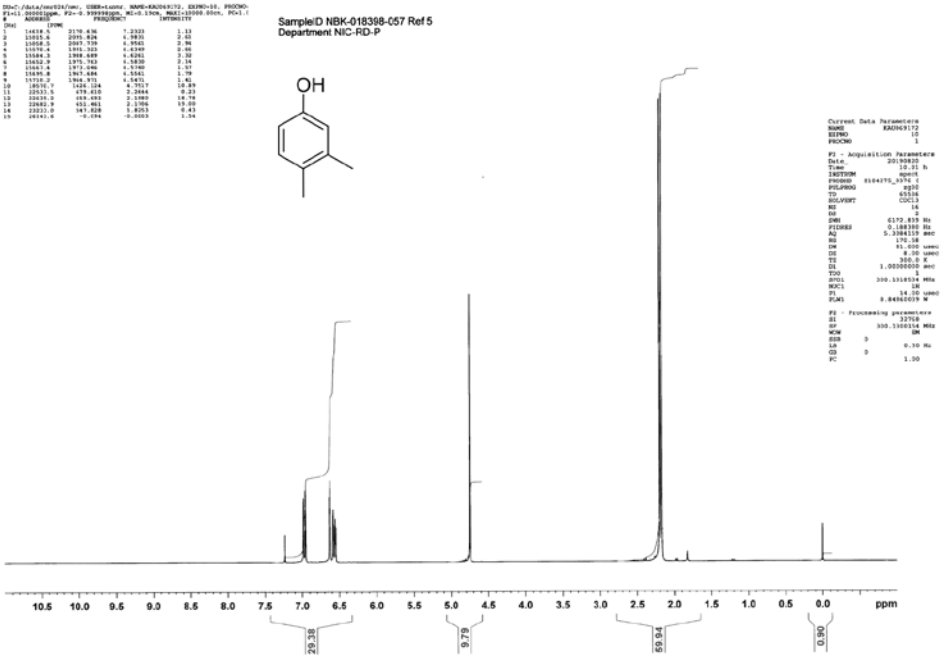


Fig. S30 ^{1}H NMR spectra of 3,4-dimethylphenol.

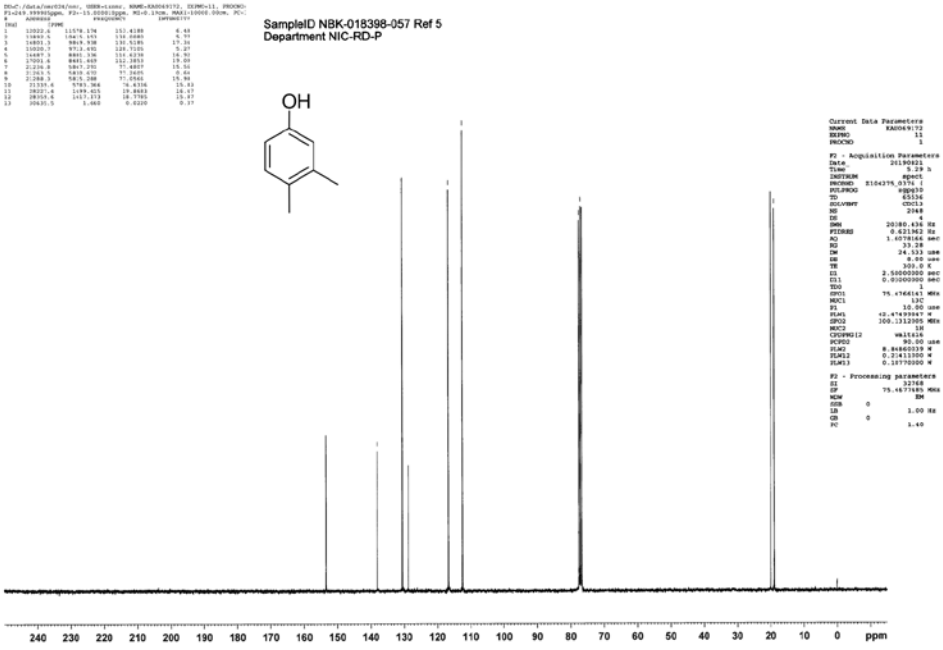
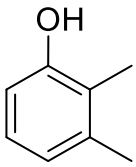


Fig. S31 ^{13}C NMR spectra of 3,4-dimethylphenol.

2,3-dimethylphenol



Chemical formula: $C_8H_{10}O$, Molecular weight: 122.2 g mol^{-1}

Purchased from Fluka, purity 99.5% (CoA).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.94 ("t", 1 H_{arom}, J = 7.7, 7.8 Hz), 6.74 (d, 1 H_{arom}, J = 7.5 Hz), 6.60 (d, 1 H_{arom}, J = 8.0 Hz), 4.87 (br.s, OH), 2.25 (s, 3 H), 2.14 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 153.5, 138.4, 126.1, 122.6, 122.5, 112.7, 20.1, 11.5.

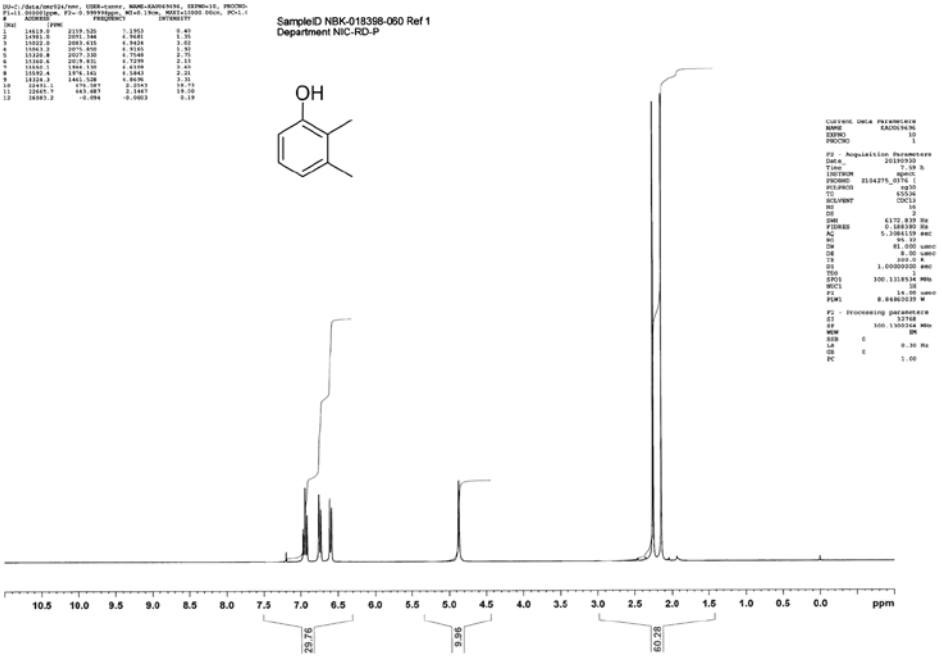


Fig. S32 ^{1}H NMR spectra of 2,3-dimethylphenol.

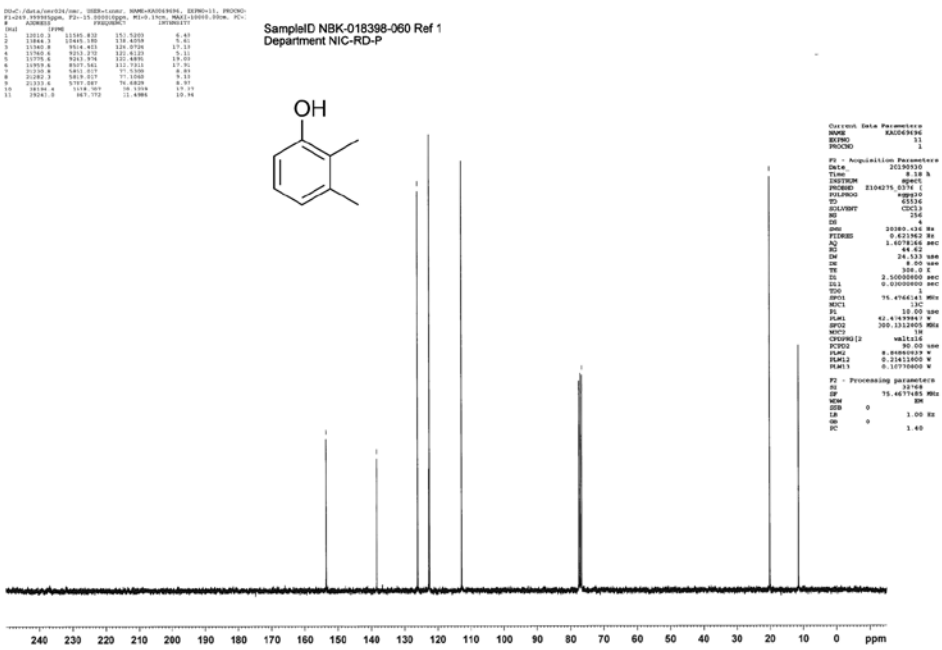
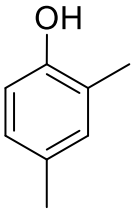


Fig. S33 ^{13}C NMR spectra of 2,3-dimethylphenol.

2,4-dimethylphenol



Chemical formula: $C_8H_{10}O$, Molecular weight: 122.2 g mol^{-1}

Purchased from Aldrich, purity >97.5% (GC, area).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.92 (s, 1 H_{arom}), 6.85-6.89 (m, 1 H_{arom}, J = 8.0, ca. 1.5 Hz), 6.66 (d, 1 H_{arom}, J = 8.0 Hz), 4.52 (s, OH), 2.24 (s, 3 H), 2.21 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 151.5, 131.6, 129.9, 127.4 ,123.4, 114.7, 20.4, 15.7.

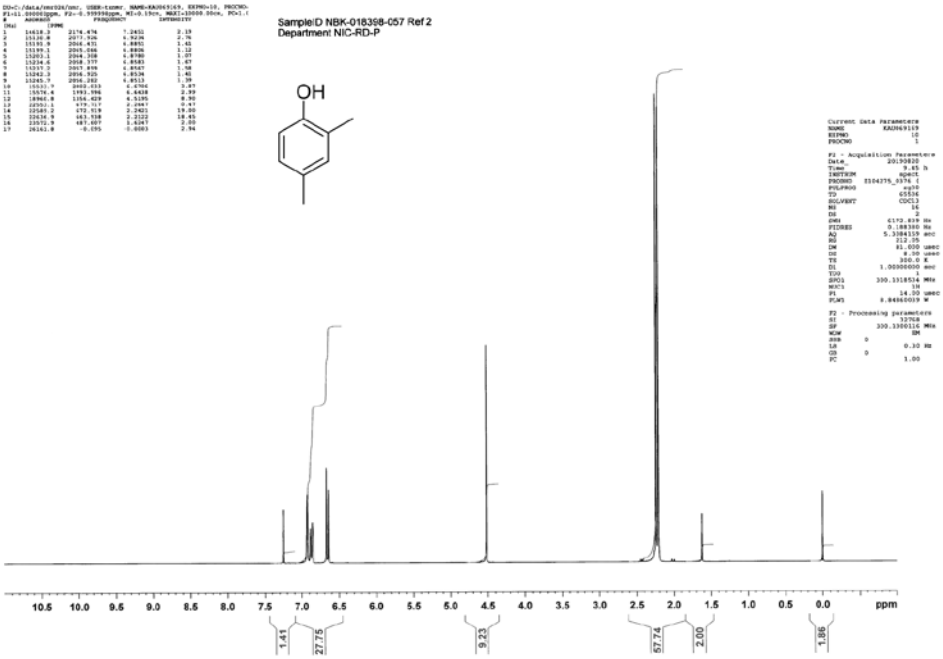


Fig. S34 ^{1}H NMR spectra of 2,4-dimethylphenol.

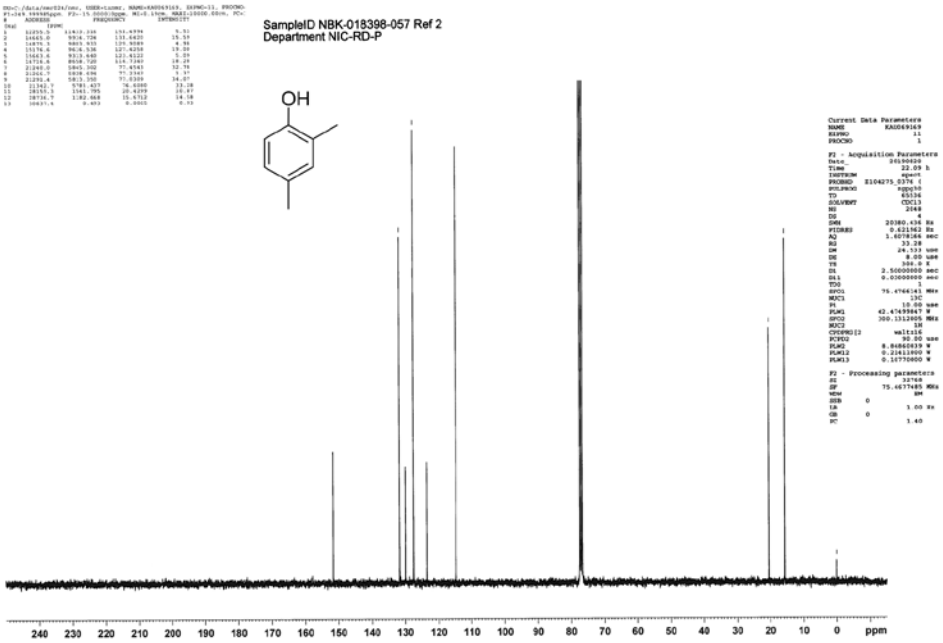
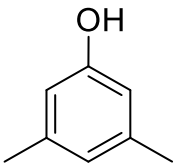


Fig. S35 ^{13}C NMR spectra of 2,4-dimethylphenol.

3,5-dimethylphenol



Chemical formula: $C_8H_{10}O$, Molecular weight: 122.2 g mol^{-1}

Purchased from Fluka, purity >98% (GC).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.58 (br.s, 1 H_{arom}), 6.46 (br.s, 2 H_{arom}), 4.60 (s, OH), 2.26 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 155.4, 139.6, 122.6, 113.0, 21.2.

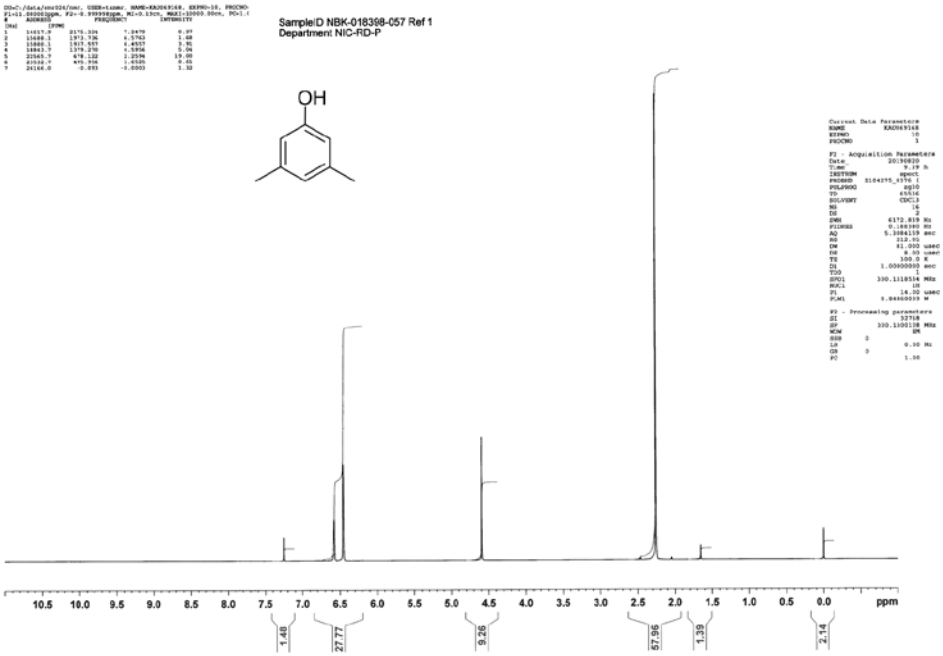


Fig. S36 ^{1}H NMR spectra of 3,5-dimethylphenol.

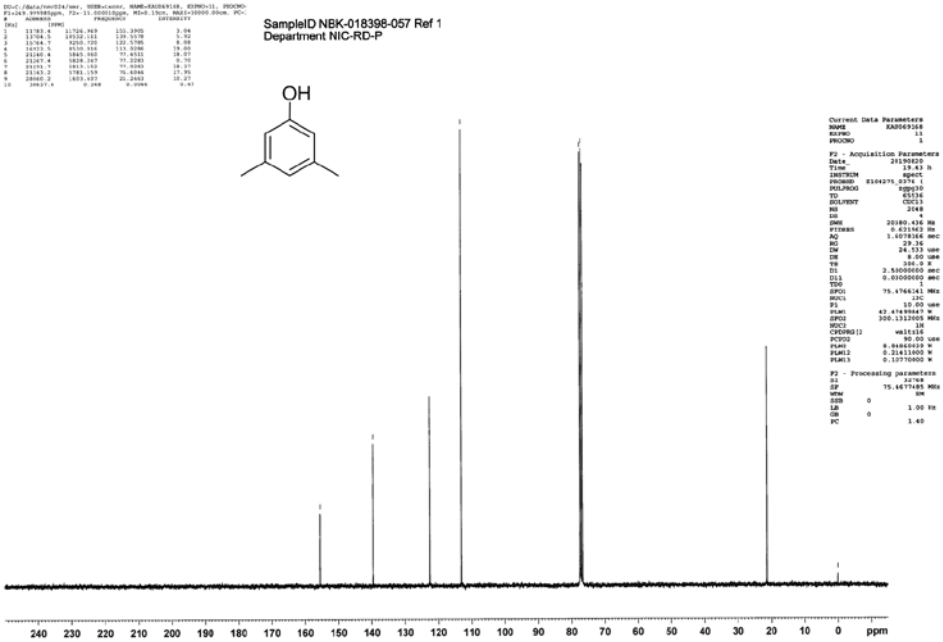
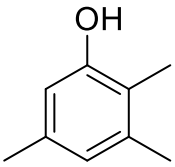


Fig. S37 ^{13}C NMR spectra of 3,5-dimethylphenol.

2,3,5-trimethylphenol



Chemical formula: $C_9H_{12}O$, Molecular weight: 136.2 g mol^{-1}

Purchased from Aldrich.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.58 (br.s, 1 H_{arom}), 6.45 (br.s, 1 H_{arom}), 4.57 (s, OH), 2.23 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 153.4, 138.0, 135.9, 123.3, 119.2, 113.4, 20.9, 20.0, 11.1.

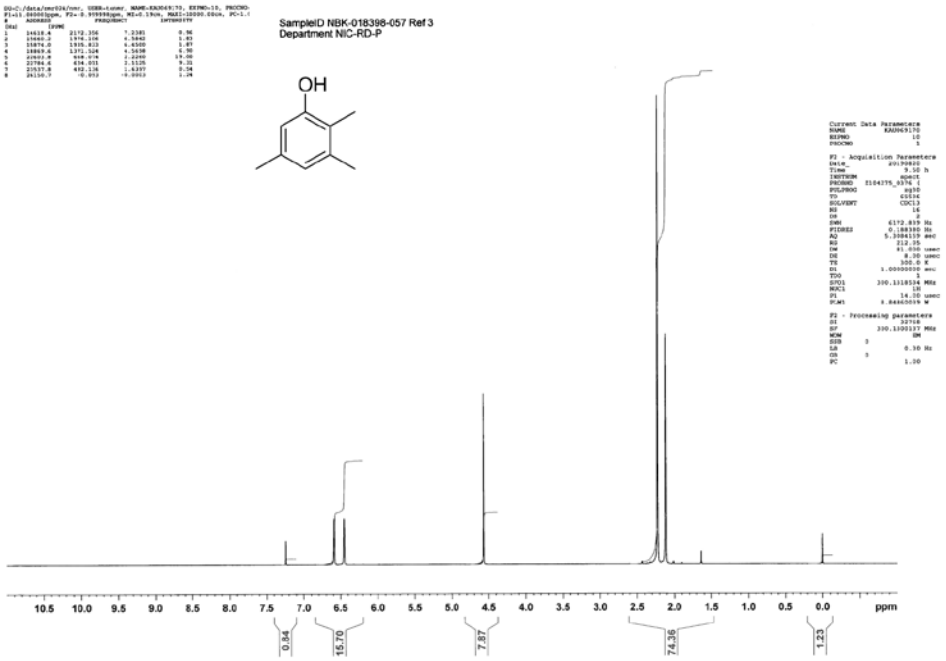


Fig. S38 ^{1}H NMR spectra of 2,3,5-trimethylphenol.

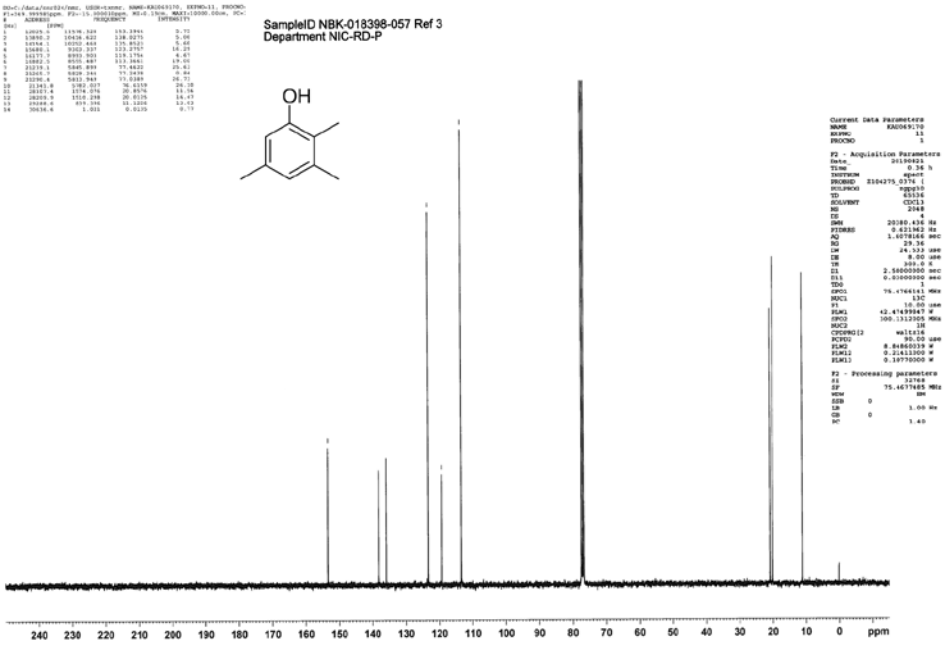
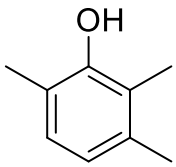


Fig. S39 ^{13}C NMR spectra of 2,3,5-trimethylphenol.

2,3,6-trimethylphenol



Chemical formula: $C_9H_{12}O$, Molecular weight: 136.2 g mol^{-1}

Purchased from Fluka.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.86 (AB, 1 H_{arom}, J = 7.6 Hz), 6.66 (AB, 1 H_{arom}, J = 7.6 Hz), 4.57 (s, OH), 2.24 (s, 3 H), 2.21 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 151.9, 135.6, 127.4, 121.8, 121.7, 120.2, 20.0, 15.8, 11.7.

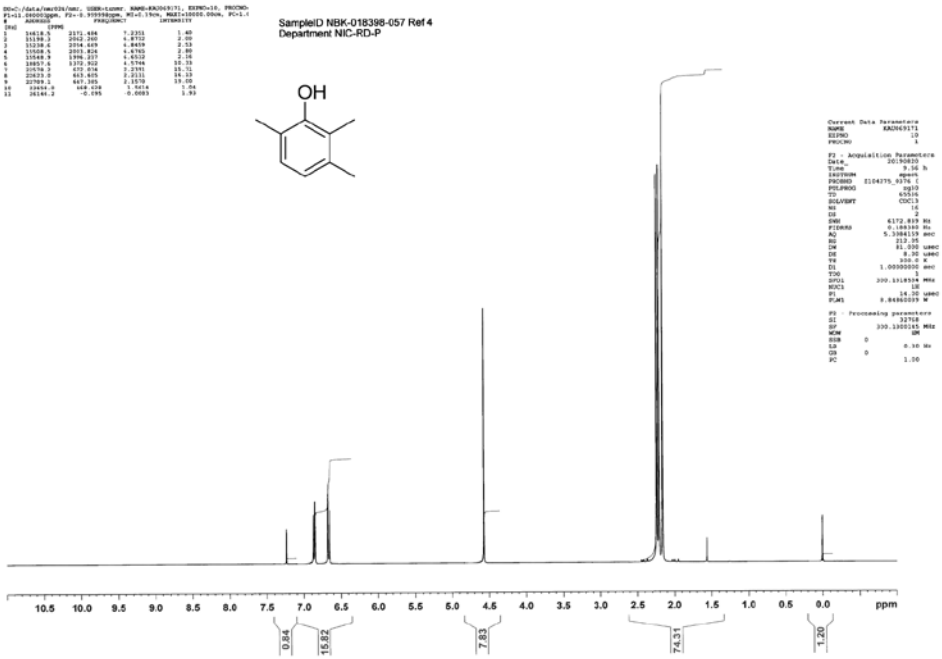


Fig. S40 ^{1}H NMR spectra of 2,3,6-trimethylphenol.

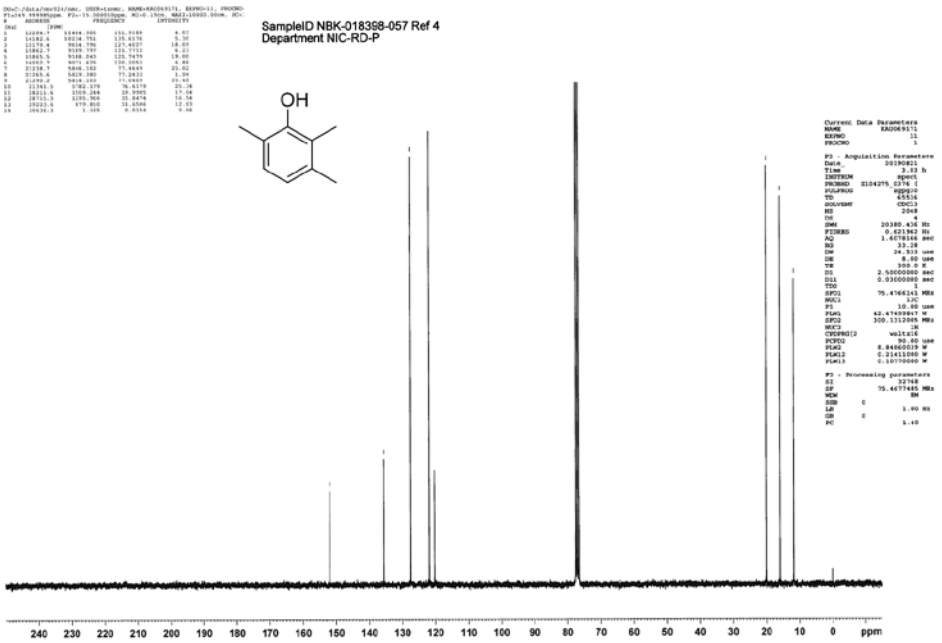
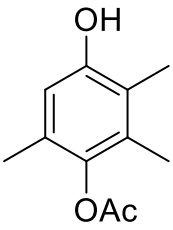


Fig. S41 ^{13}C NMR spectra of 2,3,6-trimethylphenol.

4-hydroxy-2,3,6-trimethylphenyl acetate



Chemical formula: $C_{11}H_{14}O_3$, Molecular weight: 194.2 g mol^{-1}

Synthesized from 2,3,5-trimethylhydroquinone diacetate (obtained *via* the ketoisophorone route[20]) by regioselective mono-saponification with NaOH; a sample from a kilolab batch (F. Hoffmann-La Roche, Basel) was used; white powder, m.p. 106.6°C, 100.0 wt% (HPLC Aquasil method), 99.9% (GC, area). For enzymatic mono-saponification see ref.[15]

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.46 (s, 1 H_{arom}), 4.70 (s, OH), 2.33 (s, $COCH_3$), 2.11 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 170.2, 151.3, 141.4, 129.5, 127.3, 121.5, 114.6, 20.6, 16.2, 13.0, 11.8.

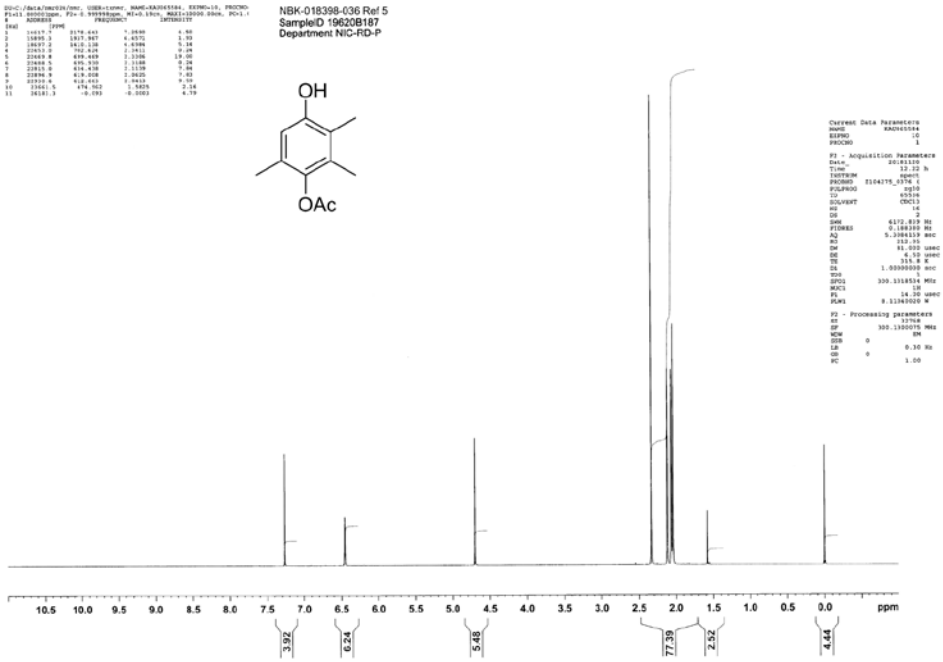


Fig. S42 ^{1}H NMR spectra of 4-hydroxy-2,3,6-trimethylphenyl acetate.

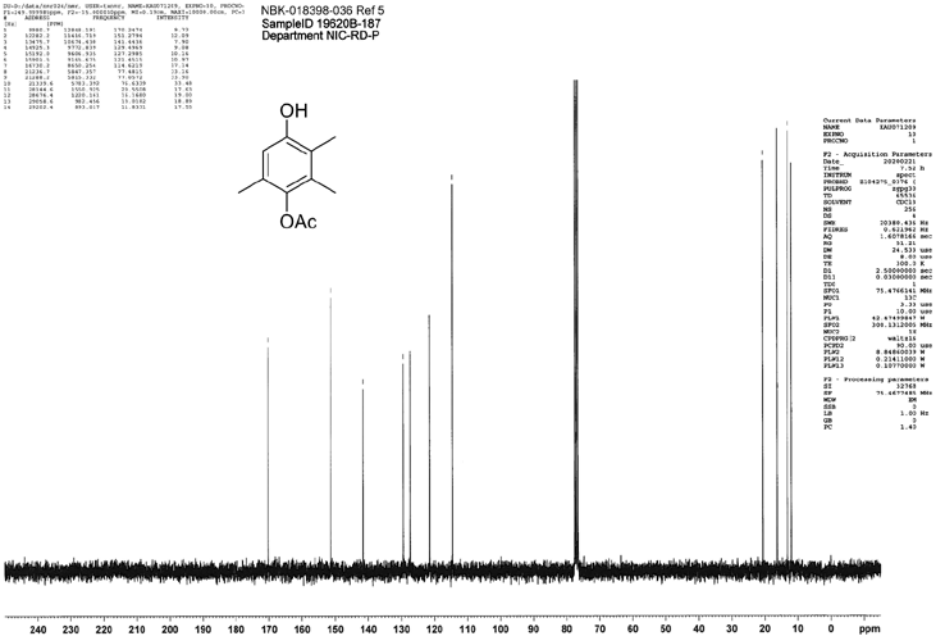
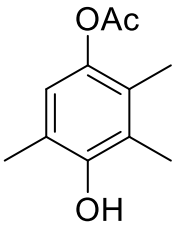


Fig. S43 ^{13}C NMR spectra of 4-hydroxy-2,3,6-trimethylphenyl acetate.

4-hydroxy-2,3,5-trimethylphenyl acetate



Chemical formula: $C_{11}H_{14}O_3$, Molecular weight: 194.2 g mol^{-1}

Synthesized from 2,3,5-trimethylhydroquinone with HOAc/ Ac_2O, reflux, 4.5 h, according to a literature procedure.[12] After chromatographic purification (*n*-heptane/EtOAc 95:5→70:30) white solid, purity 94.7% (GC, area) containing 1.1% TMHQ-diacetate.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.65 (s, 1 H_{arom}), 4.52 (br.s, OH), 2.30 (s, 3 H), 2.20 (s, 3 H), 2.17 (s, 3 H), 2.04 (s, 3 H). Remark: δ-Values for CH_3-resonances[12] are different from our data.

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 170.0, 149.8, 142.3, 127.1, 123.3, 121.0, 120.7, 20.8, 15.9, 12.8, 12.3.

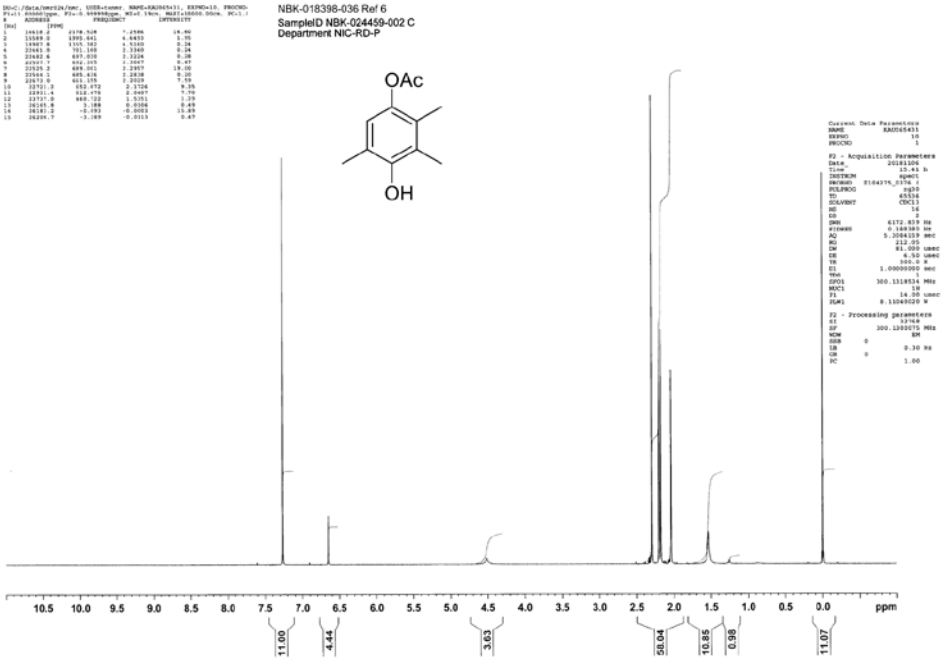


Fig. S44 ^{1}H NMR spectra of 4-hydroxy-2,3,5-trimethylphenyl acetate.

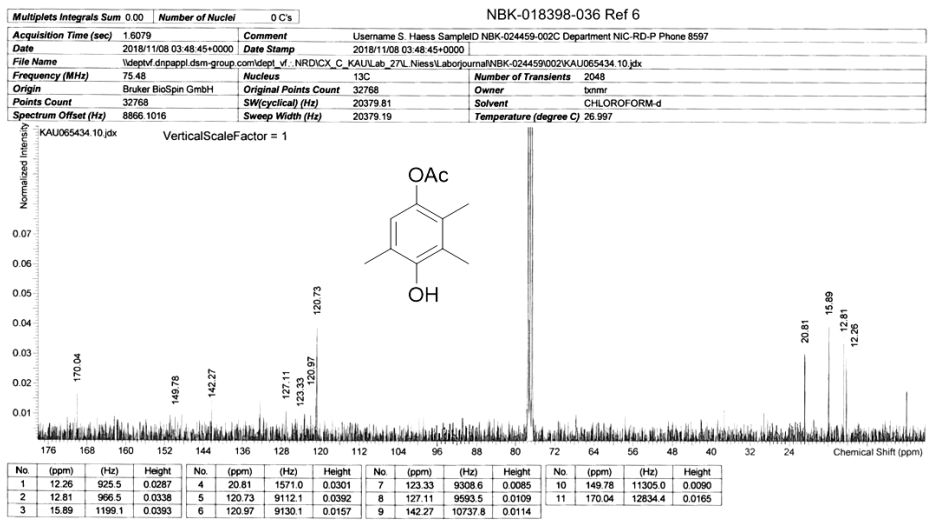
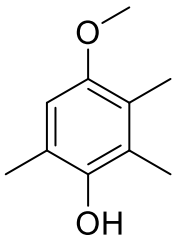


Fig. S45 ^{13}C NMR spectra of 4-hydroxy-2,3,5-trimethylphenyl acetate.

4-methoxy-2,3,6-trimethylphenol



Chemical formula: $C_{10}H_{14}O_2$, Molecular weight: 166.2 g mol^{-1}

Sample kindly provided by Dr. A. Weyland, DSM Nutitional Products, Sisseln (CH), synthesized by treatment of 2,3,5-trimethylhydroquinone with MeOH/ H_2SO_4 according to a literature procedure.[13] Light pink crystals, m.p. 100.3°C. For NMR data see ref.[14]

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.52 (s, 1 H, H5), 4.24 (br.s, OH), 3.76 (s, 3 H, 4-OMe), 2.23 (s, 3 H, H6'), 2.17 (s, 3 H, H2'), 2.13 (s, 3 H, H3').

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 151.3, 145.9, 123.8, 123.6, 120.0, 110.9, 56.3 (4-OMe), 16.2, 12.2, 11.9.

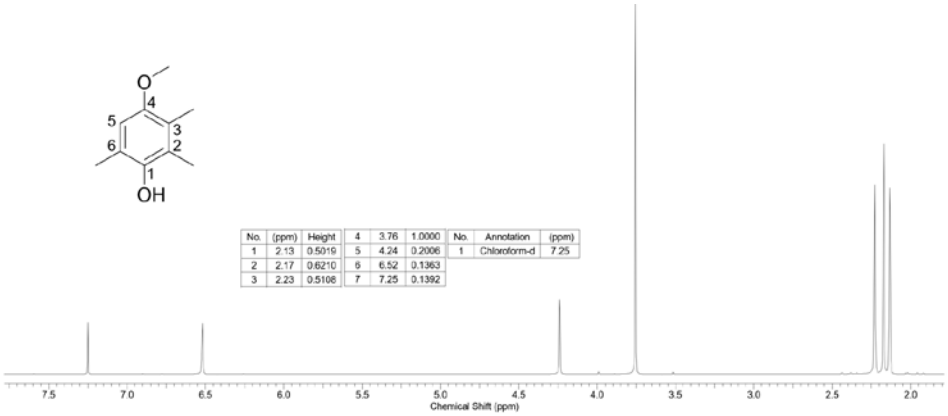


Fig. S46 ^{1}H NMR spectra of 4-methoxy-2,3,6-trimethylphenol.

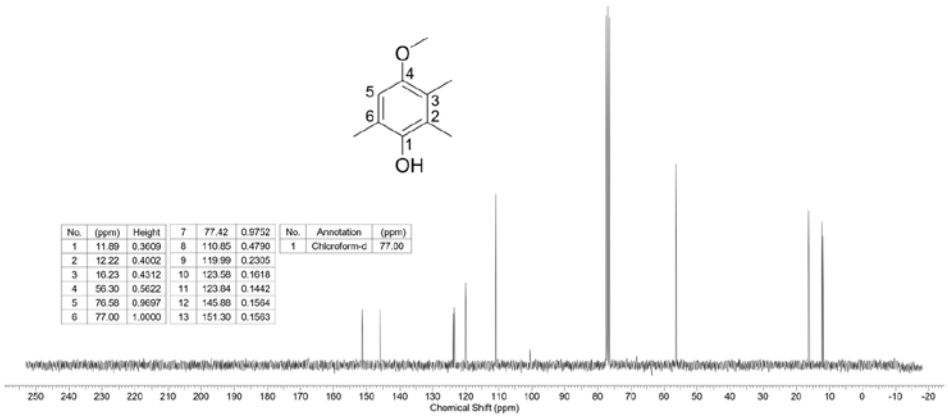
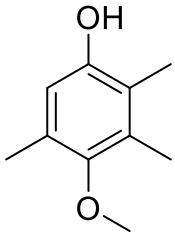


Fig. S47 ^{13}C NMR spectra of 4-methoxy-2,3,6-trimethylphenol.

4-methoxy-2,3,5-trimethylphenol



Chemical formula: $C_{10}H_{14}O_2$, Molecular weight: 166.2 g mol^{-1}

Synthesized from 4-hydroxy-2,3,6-trimethylphenyl acetate according to an unpublished reaction sequence of Dr. R. Schmid, F. Hoffmann-La Roche, Basel (1. Dihydropyran/ H^+, 2. Ester hydrolysis with base, 3. *O*-methylation, 4. Acidic hydrolysis); colourless crystals. For an alternative preparation method and NMR data see ref.[6]

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.44 (s, 1 H, H6), 4.75 (br.s, OH), 3.65 (s, 3 H, 4-OMe), 2.21 (s, 3 H, H5'), 2.20 (s, 3 H, H3'), 2.12 (s, 3 H, H2').

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 150.5, 149.4, 130.6, 128.3, 121.0, 114.4, 60.2, 15.9, 12.7, 11.9.

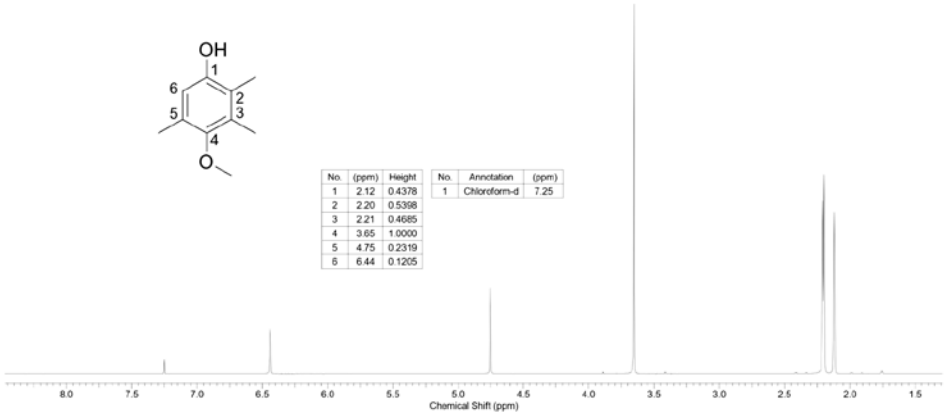


Fig. S48 ^{1}H NMR spectra of 4-methoxy-2,3,5-trimethylphenol.

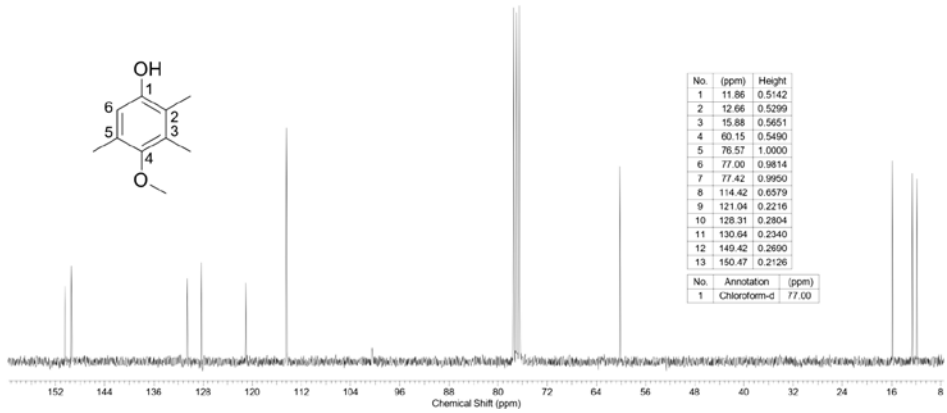
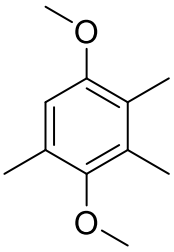


Fig. S49 ^{13}C NMR spectra of 4-methoxy-2,3,5-trimethylphenol.

1,4-dimethoxy-2,3,5-trimethylbenzene



Chemical formula: $C_{11}H_{16}O_2$, Molecular weight: 180.1 g mol^{-1}

Synthesized from 2,3,5-trimethylhydroquinone by *O*-methylation; colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.53 (s, 1 H, H6), 3.77 (s, 3 H, 1-OMe), 3.65 (s, 3 H, 4-OMe), 2.27 (s, 3 H, H5'), 2.20 (s, 3 H, H3'), 2.11 (s, 3 H; H2').

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 153.5 (1), 150.6 (4), 130.6 (3), 127.7 (5), 123.8 (2), 110.4 (6), 60.2 (4-OMe), 55.8 (1-OMe), 16.3 (5'), 12.7 (3'), 11.9 (2').

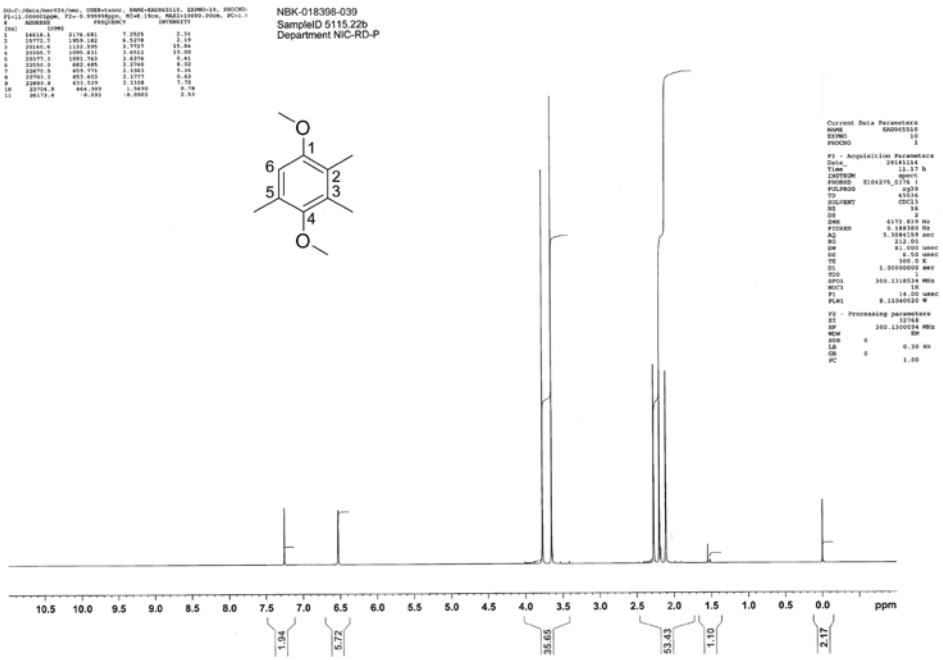


Fig. S50 ^{1}H NMR spectra of 1,4-dimethoxy-2,3,5-trimethylbenzene.

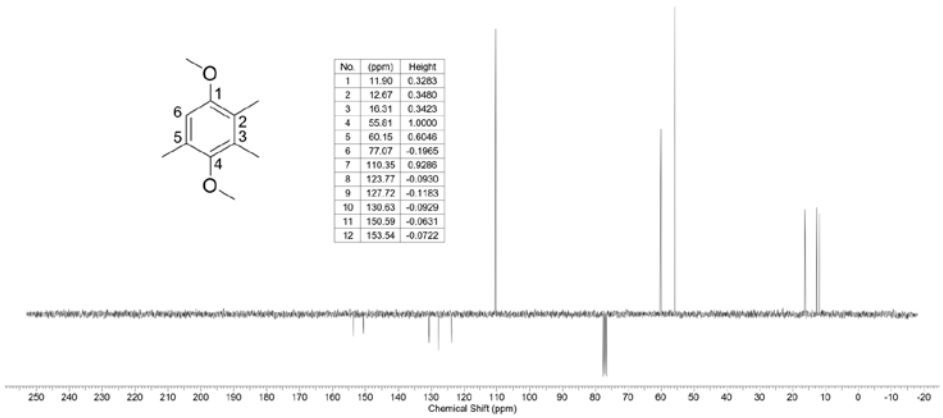
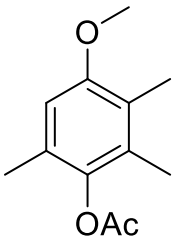


Fig. S51 ^{13}C NMR spectra of 1,4-dimethoxy-2,3,5-trimethylbenzene.

4-methoxy-2,3,6-trimethylphenyl acetate



Chemical formula: $C_{12}H_{16}O_3$, Molecular weight: 208.3 g mol^{-1}

Synthesized from 4-hydroxy-2,3,6-trimethylphenyl acetate by treatment with dimethyl sulfate (5 mol-equiv.) and 50% aq. KOH in 1,2-dimethoxyethane, room temp., 1 h.[25] 1,4-Dimethoxy-2,3,5-trimethyl-benzene is formed as a by-product; TLC (n-heptane/ EtOAc 9:1, SiO_2): R_f starting phenol 0.08, methoxy-acetate product 0.21, dimethyl ether 0.43. After chromatographic purification slightly yellow oil which crystallized upon standing for several weeks at room temp.: pale yellowish solid, m.p. 32.2°C, purity 96.9%, contains 1.2% trimethylquinone acording to GC.

^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 6.56 (s, 1 H_{arom}), 3.78 (s, 3 H), 2.32 (s, 3 H), 2.12 (s, 6 H), 2.05 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ(ppm) = 169.5, 155.1, 141.6, 129.6, 127.1, 123.8, 110.1, 55.7, 20.5, 16.6, 13.0, 11.9.

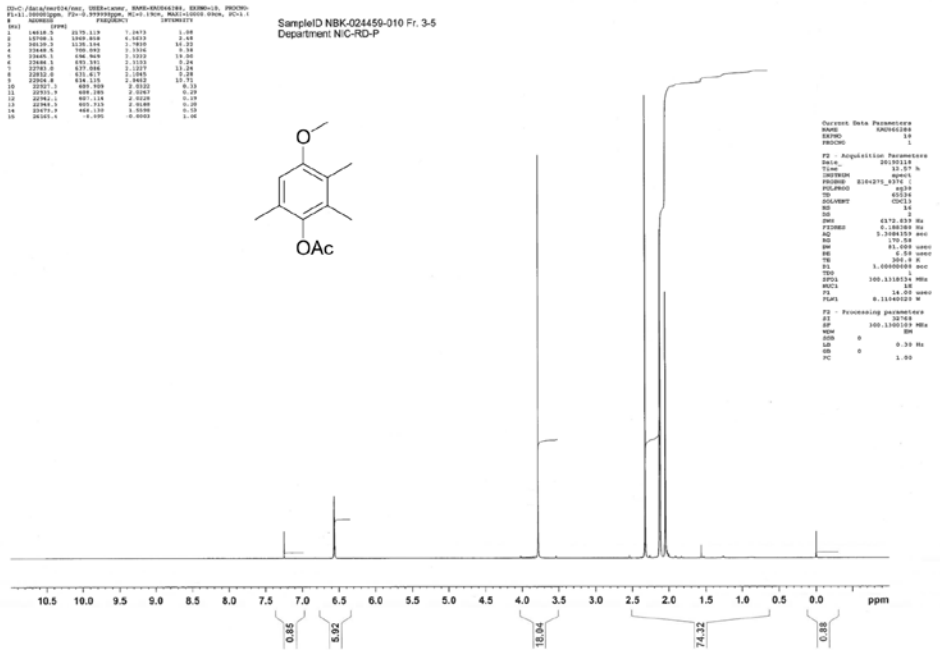


Fig. S52 ^{1}H NMR spectra of 4-methoxy-2,3,6-trimethylphenyl acetate.

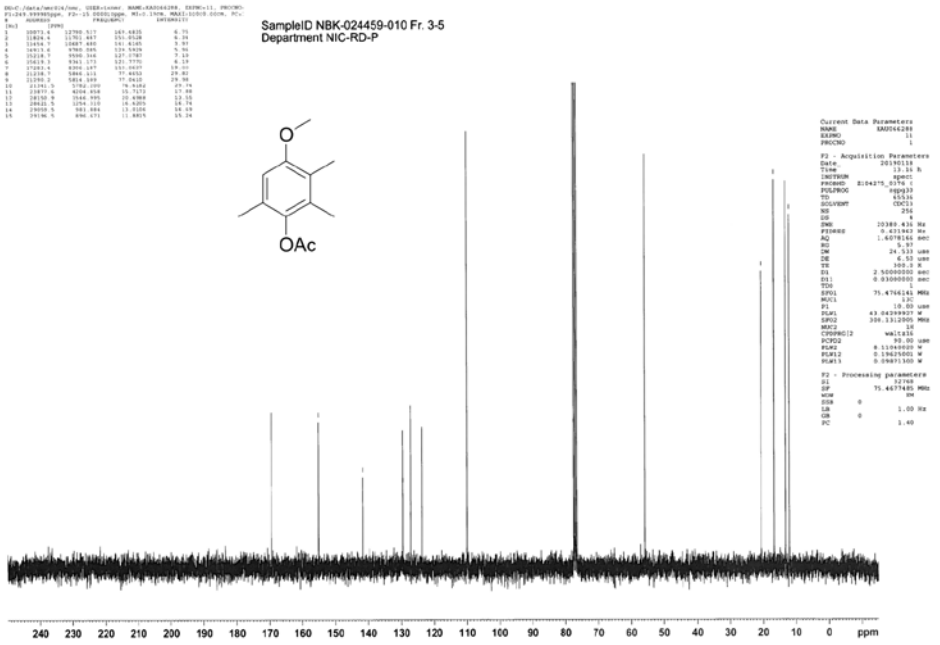


Fig. S53 ^{13}C NMR spectra of 4-methoxy-2,3,6-trimethylphenyl acetate.

MS: *m*/*z* = 208 (M•+, 15%), 166 (M•+-Ac, 100), 151 (M•+-Ac -CH_3, 87).

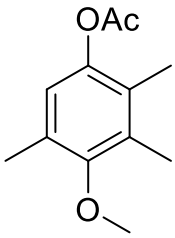
HR-MS: Calcd. for $^{12}C_{12}{}^{1}H_{16}{}^{16}O_3$: 208.10994, Found 208.11028, mass difference 0.33 mDa (1.60 ppm).

IR: 2932, 1755 (C=O), 1466, 1369, 1190, 1121, 1078, 898, 835 cm^{-1}.

UV: $\lambda_{max}(\varepsilon)$ = 275 nm (1890), 280 nm (1950), 284 nm (1910).

Anal. $C_{12}H_{16}O_3$ (208.26): calcd. C 69.21, H 7.74, O 23.05, found C 69.08, H 7.80.

4-methoxy-2,3,5-trimethylphenyl acetate



Chemical formula: $C_{12}H_{16}O_3$, Molecular weight: 208.3 g mol^{-1}

Prepared by acetylation of 4-methoxy-2,3,5-trimethylphenol with Ac_2O/ pyridine/ cat. 4-dimethylaminopyridine, room temp., 1 h. After column chromatography colourless oil, purity 98.8%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.68 (s, 1 H_{arom}), 3.68 (s, 3 H), 2.30 (s, 3 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 2.02 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 169.7, 154.6, 144.9, 131.0, 128.9, 127.3, 121.2, 59.94, 20.8, 16.0, 12.8, 12.8.

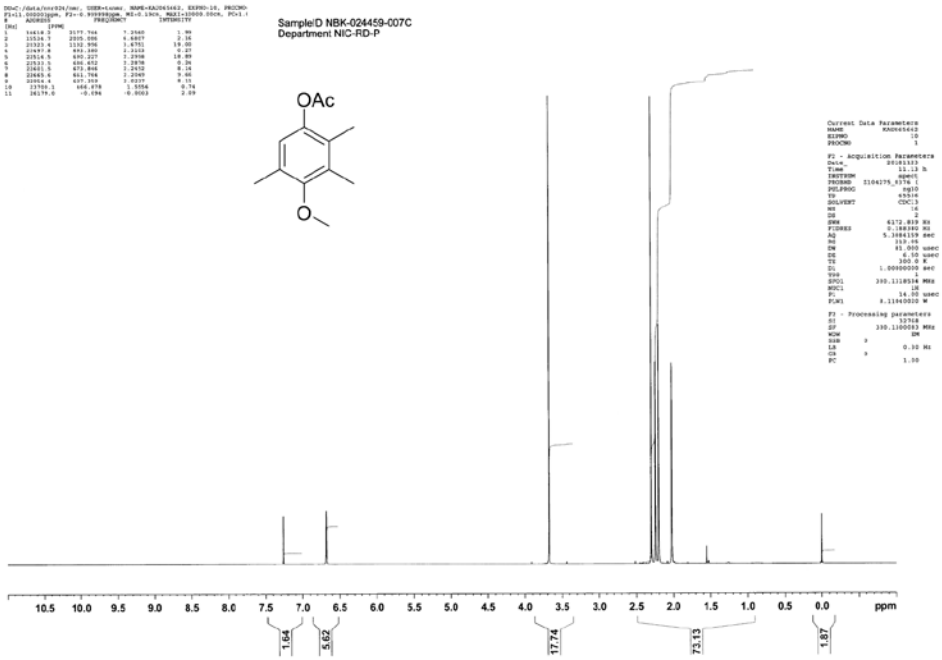


Fig. S54 ^{1}H NMR spectra of 4-methoxy-2,3,5-trimethylphenyl acetate.

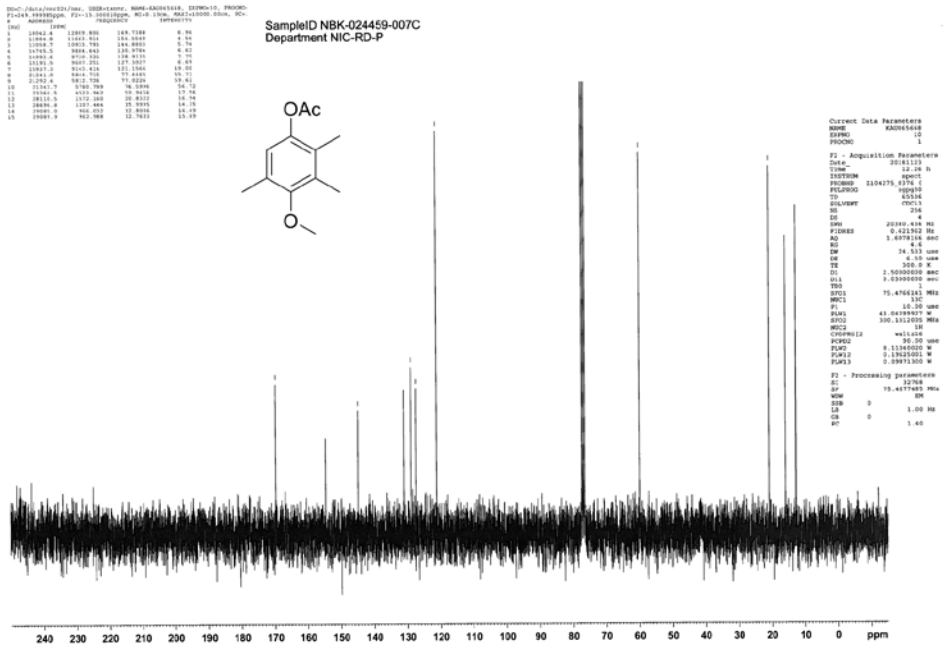


Fig. S55 ^{13}C NMR spectra of 4-methoxy-2,3,5-trimethylphenyl acetate.

Supplementary references

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