Electronic Supplementary Information (ESI)

Site-selective binding of terpenoids within a confined space of metal–macrocycle framework: Substrate-specific promotion or inhibition of cyclization reactions

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1. Materials and methods

Metal–macrocycle framework (MMF) and macrocyclic ligand **L** were prepared according to our procedure.[1] MMF crystals were washed with acetonitrile before used for guest incorporation. MMF immobilizing *p*-toluenesulfonic acid (*p*-TsOH) in the pores, *p*-TsOH@MMF, was prepared according to our previous report.[2] $CDCl_3$ was passed through basic Al_2O_3 before use to remove a trace of DCl. Milli-Q water was used for the examination of reactions. Only reaction products that could be directly compared to standard samples in ^{1}H NMR spectra were assigned in this study. For instance, *cis*/*trans*-*p*-menthane-3,8-diols, (+/–)-limonene and terpinolene, were identified by matching their ^{1}H NMR resonances to the commercially available samples, and (+)-isopulegol and (–)-neo-isopulegol were identified by matching their ^{1}H NMR resonances to literature data[3,4] and the ^{1}H NMR resonances of commercially available isopulegol (a mixture of isomers). All terpenoid substrates, standard samples for product assignment, solvents, organic and inorganic reagents are commercially available, and were used without further purification. Note that commercially available farnesol was a mixture of *E*/*Z*-isomers and was used without separation.

The catalytic equivalents of MMF and *p*-TsOH@MMF were calculated based on their chemical compositions estimated previously. As the chemical composition of almost dried MMF (one unit space) is $(C_{42}H_{42}N_6Cl_6Pd_3)_4\cdot(CH_3CN)_{2.0}\cdot(H_2O)_{36}$ (Mw = 5381.84),[1] the molecular weight of one corner pocket is 2690.92 g/mol (two corner pockets/unit space). Similarly, as the chemical composition of *p*-TsOH@MMF was previously estimated to be $(C_{42}H_{42}N_6Cl_6Pd_3)_4\cdot(p\text{-}TsOH)_{1.5}\cdot(CHCl_3)_8\cdot(H_2O)_{20}$ (Mw = 6224.8),[2] the molecular weight of one acid species in *p*-TsOH@MMF is 4149.9 g/mol (1.5 molecules/unit space).

Single-crystal XRD analyses were performed using a an XtaLAB P200 system diffractometer with CuKα radiation, and the obtained data were analyzed using an Olex2 software package[5] except for refinement, which was performed using SHELXL-2018/3 program suite.[6] Several restraints were applied to MMF and guest molecules in all the crystal structures. Hydrogen atoms were placed at the calculated positions and refined using a riding model. The occupancies of guest molecules were refined based on electron densities using free variables in the SHELXL-2018/3 program. X-ray structures were displayed using a Mercury program or a PyMOL program. Electron density maps were generated using a ShelXle program.[7] NMR spectroscopic measurements were performed using a Bruker AVANCE 500 spectrometer. ^{1}H NMR spectra are calibrated as below: $Si(CH_3)_4$ = 0 ppm in $CDCl_3$, CHD_2CN = 1.94 ppm in CD_3CN. FT-IR spectra were recorded on a JASCO FT/IR-4200 spectrometer using a ZnSe attenuated total reflection (ATR) method.

2. Crystal structures of (*S*)-citronellal@MMF

Uptake of (*S*)-citronellal in water

Procedure for guest uptake: MMF crystals were soaked in an aqueous emulsion of (*S*)-citronellal (76.6 μmol/960 μL) for 16 h at 20 °C, and one of the crystals was picked up and immediately mixed with paratone oil to measure single-crystal XRD.

Crystal data for $(Pd_3LCl_6)_2 \cdot ((S)\text{-citronellal})_{0.75} \cdot (H_2O)_{2.63}$: $C_{91.52}H_{97.53}Cl_{12}N_{12}O_{3.38}Pd_6$, F_w = 2483.39, crystal dimensions 0.557 × 0.282 × 0.126 mm^3, monoclinic, space group $P2_1$, a = 14.20620(10), b = 52.5096(4), c = 19.64140(10) Å, β = 91.6630(10)°, V = 14645.56(17) Å^3, Z = 4, ρ_{calcd} = 1.126 g cm^{-3}, μ = 8.125 mm^{-1}, T = 93 K, λ(CuKα) = 1.54187 Å, $2\theta_{max}$ = 136.49°, 155701/53000 reflections collected/unique (R_{int} = 0.0632), R_1 = 0.0792 ($I > 2\sigma(I)$), wR_2 = 0.2379 (for all data), GOF = 1.013, largest diff. peak and hole 3.712/–2.435 eÅ^{-3}, Flack parameter = 0.144(12). CCDC deposit number 2076031. Several restraints were applied to MMF and guest molecules to avoid collapse of the structure during the least-squares refinement. The structure was refined as an inversion twin.

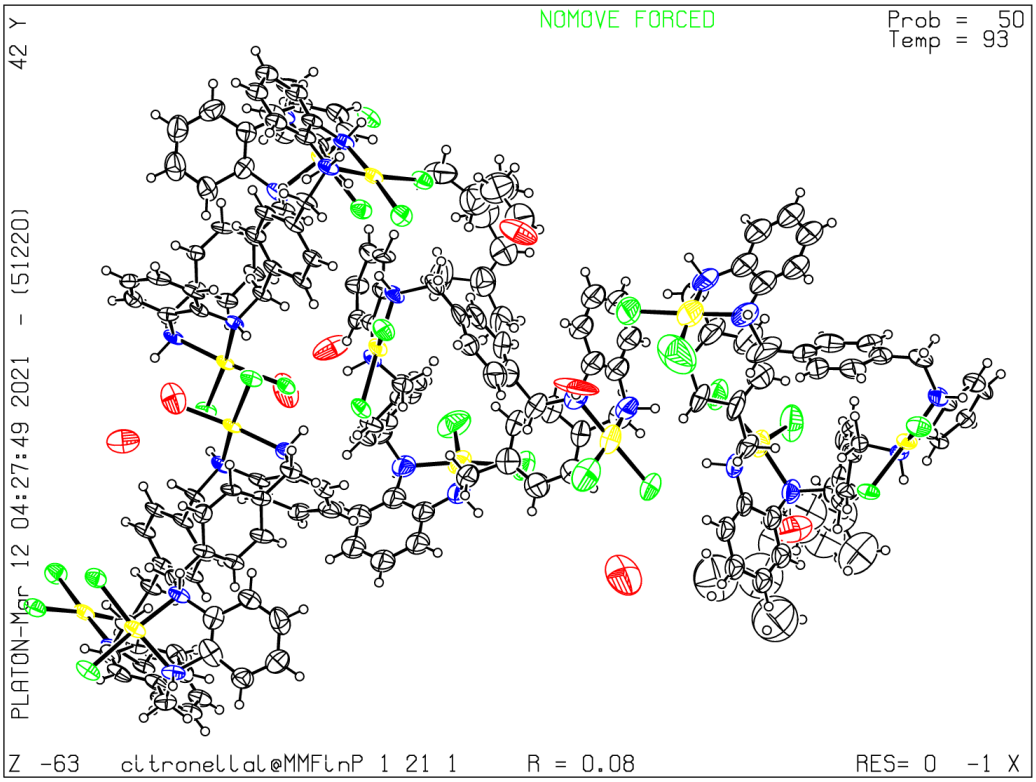


Fig. S1 ORTEP drawing of (*S*)-citronellal@MMF (water) at the 50% probability level. Color: C black, N blue, O red, Cl green and Pd yellow.

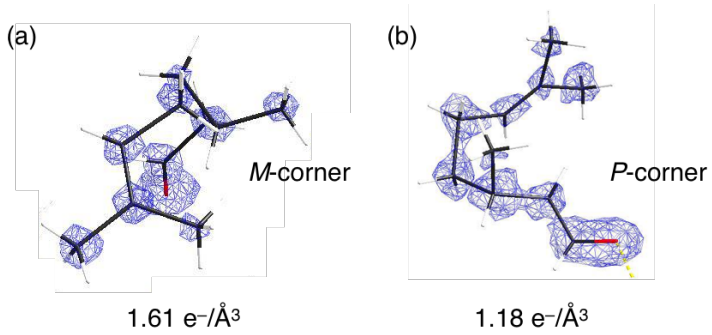


Fig. S2 Electron density maps of (*S*)-citronellal on (a) the (*M*)-corner (contour level: 1.61 $e^{-}/Å^3$) and (b) the (*P*)-corner pockets (contour level: 1.18 $e^{-}/Å^3$).

Procedure for FT-IR: MMF crystals were soaked in an aqueous emulsion of (*S*)-citronellal (1.39 mmol/500 μL) for 16 h at 20 °C, and then collected by filtration to measure ATR-IR. An aqueous emulsion of (*S*)-citronellal and MMF soaked in H_2O were also subject to ATR-IR measurement.

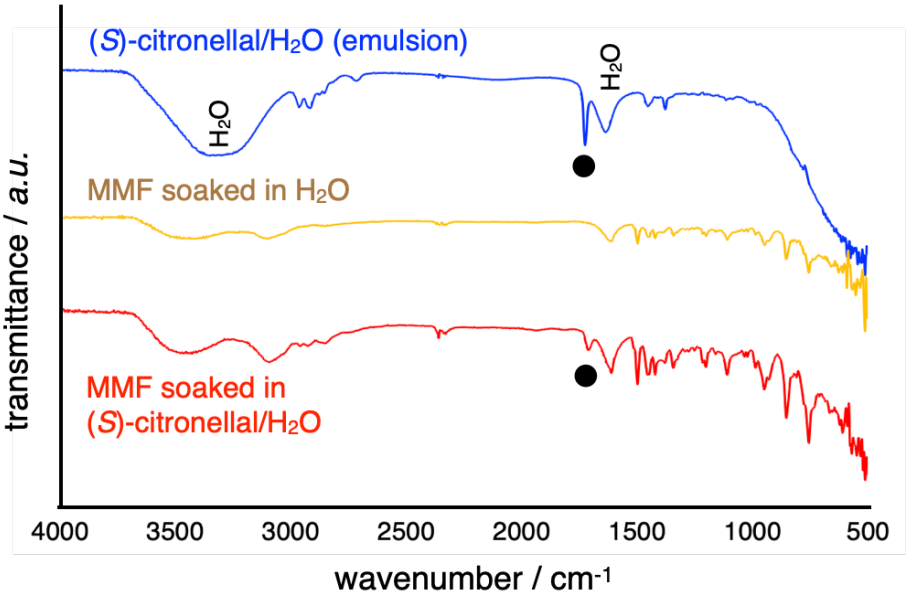


Fig. S3 FT-IR spectra of an aqueous emulsion of (*S*)-citronellal, MMF soaked in H_2O and MMF soaked in an aqueous emulsion of (*S*)-citronellal (ATR, neat, 20 °C). The black circles indicate the C=O stretching bands of (*S*)-citronellal.

<u>Uptake of (*S*)-citronellal in chloroform</u>

Procedure for guest uptake: MMF crystals were soaked in CH_2Cl_2 (1 mL) for 1 h at room temperature, and then soaked again in a chloroform solution of (*S*)-citronellal (100 μmol, 0.2 mL, 0.5 M) for 24 h at room temperature. One of the crystals was picked up and immediately mixed with paratone oil to measure single-crystal XRD.

Crystal data for $(Pd_3LCl_6)_2 \cdot ((S)\text{-citronellal})_{0.35} \cdot (H_2O)_2$: $C_{87.41}H_{89.64}Cl_{12}N_{12}O_{2.34}Pd_6$, F_w = 2409.54,

crystal dimensions 0.199 × 0.154 × 0.095 mm^3, monoclinic, space group $P2_1$, a = 19.3108(2), b = 52.2420(5), c = 14.25460(10) Å, β = 92.3910(10)°, V = 14368.0(2) Å^3, Z = 4, ρ_{calcd} = 1.114 g cm^{-3}, μ = 8.262 mm^{-1}, T = 93 K, λ(CuKα) = 1.54187 Å, $2\theta_{max}$ = 147.07°, 146415/55235 reflections collected/unique (R_{int} = 0.0632), R_1 = 0.0929 ($I > 2\sigma(I)$), wR_2 = 0.2924 (for all data), GOF = 1.093, largest diff. peak and hole 3.188/–2.320 eÅ^{-3}, Flack parameter = 0.183(15). CCDC deposit number 2076032. Several restraints were applied to MMF and guest molecules to avoid collapse of the structure during the least-squares refinement. The structure was refined as an inversion twin.

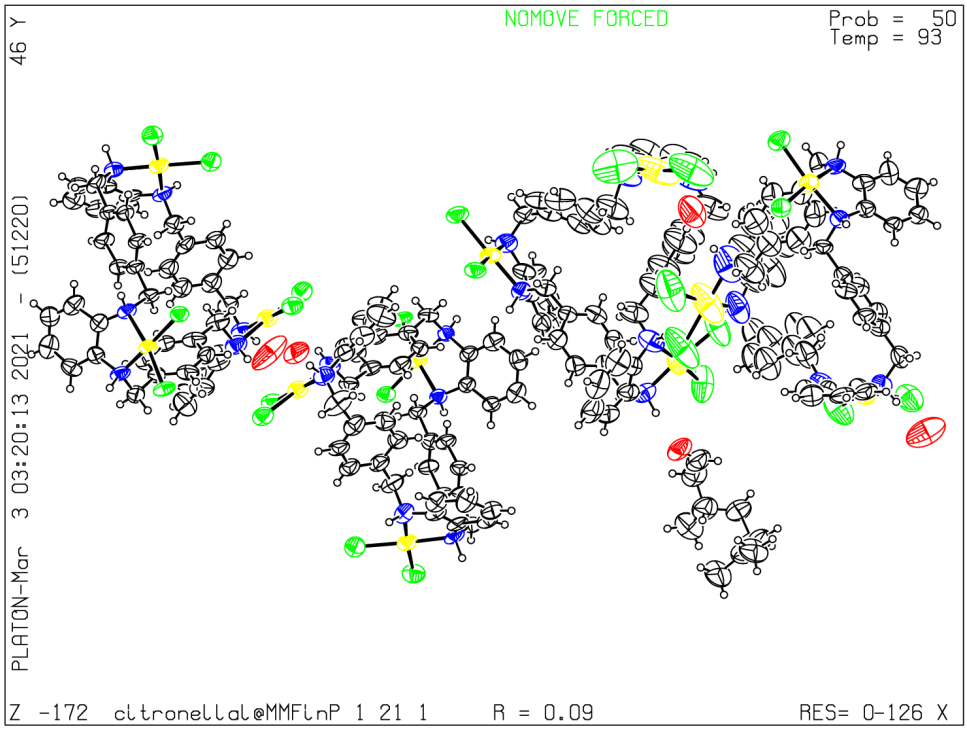


Fig. S4 ORTEP drawing of (*S*)-citronellal@MMF ($CHCl_3$) at the 50% probability level. Color: C black, N blue, O red, Cl green, and Pd yellow.

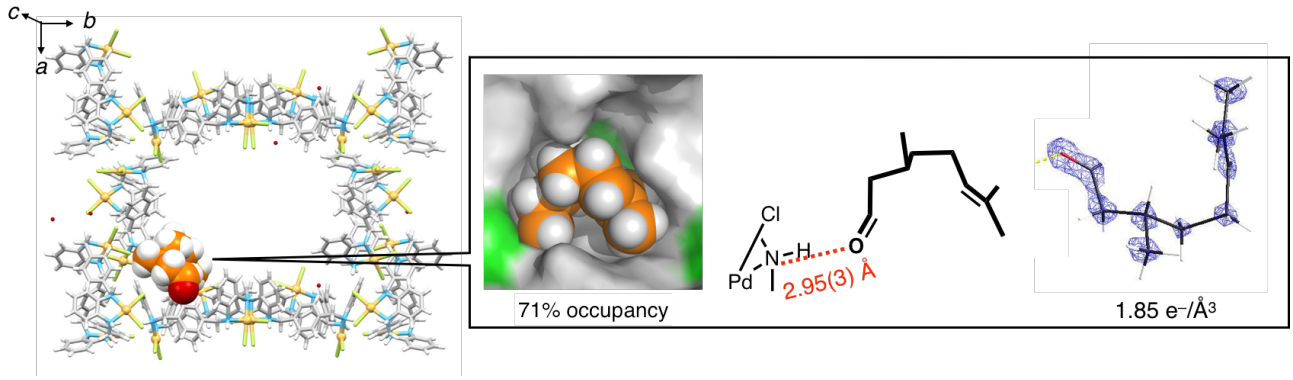


Fig. S5 Crystal structure of (*S*)-citronellal@MMF prepared by soaking in a chloroform solution, the binding structure, hydrogen bonding pattern and electron density map of (*S*)-citronellal in the (*M*)-corner pocket.

3. Reactions of (*S*)-citronellal in the presence of MMF

Reactions of (*S*)-citronellal with or without MMF crystals in water

Procedure for the reaction in water: MMF crystals (2.59 mg, 0.96 μmol of corner pockets, 1.2 mol%) were soaked in an aqueous emulsion of (*S*)-citronellal (83.1 μmol/1.0 mL) in a micro-tube and heated at 45 °C for 24 h. The resulting products were extracted with 600 μL of $CDCl_3$ and examined by ^1H NMR (500 MHz, $CDCl_3$, 300 K).

Also, as a control experiment, an aqueous emulsion of (*S*)-citronellal without MMF was heated and examined in the same way.

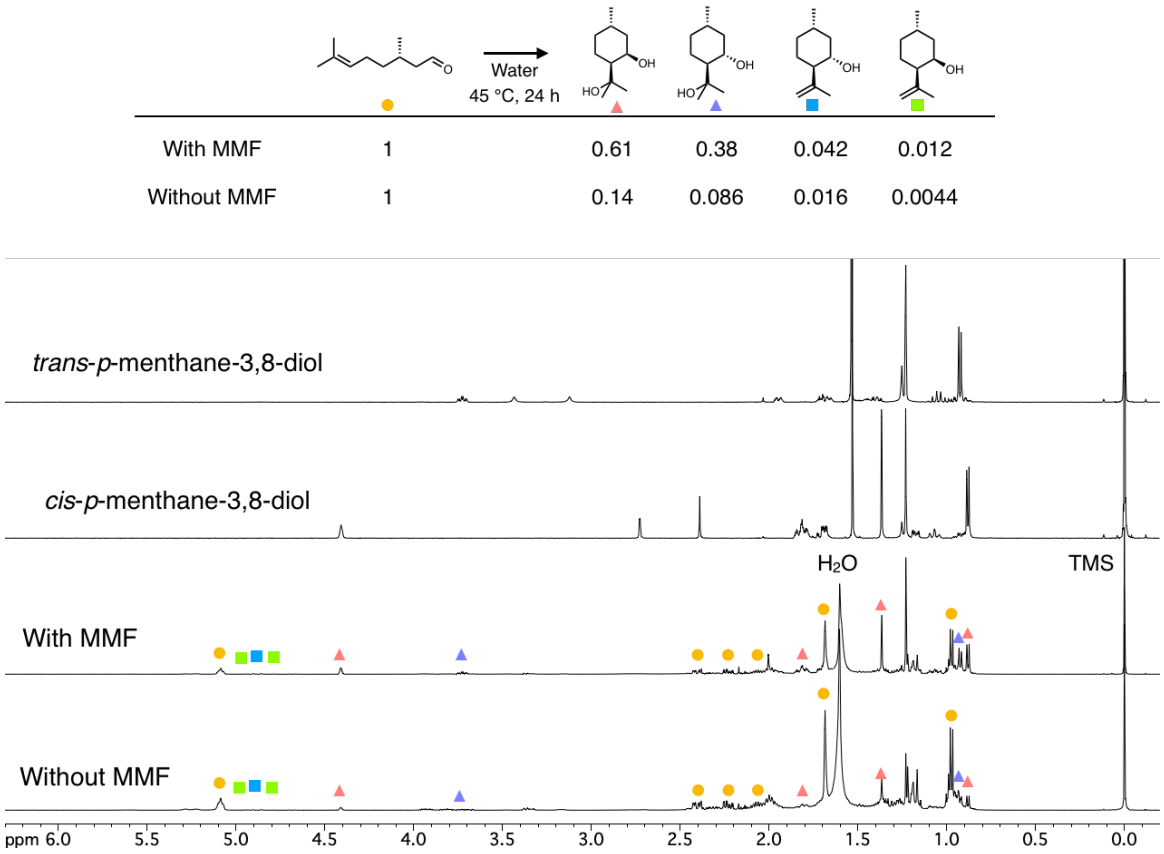
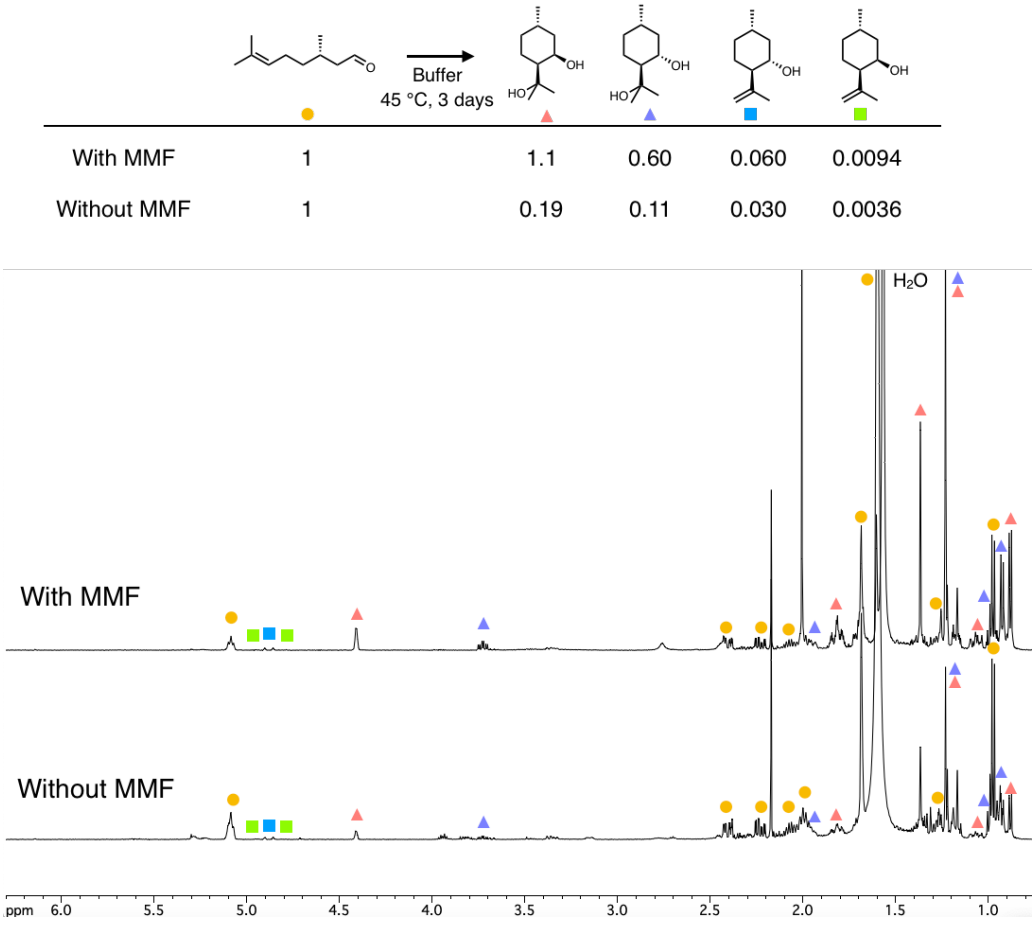


Fig. S6 The molar ratio of each compound after the reactions and ^1H NMR spectra (500 MHz, $CDCl_3$, 300 K) for *cis*- and *trans*-*p*-menthane-3,8-diols, and $CDCl_3$ extracts from the reaction of (*S*)-citronellal with or without MMF in water at 45 °C for 24 h.

Procedure for the reaction in a phosphate buffer solution: MMF crystals (3.53 mg, 1.31 μmol of corner pockets, 2.4 mol%) were soaked in a 0.10 M phosphate buffer solution (pH = 5.9) containing (*S*)-citronellal (55.4 μmol/1.0 mL) as an emulsion in a micro-tube and heated at 45 °C with stirring for 3 days. The resulting products were extracted with 600 μL of $CDCl_3$ and examined by ^1H NMR (500 MHz, $CDCl_3$, 300 K).

Also, as a control experiment, a phosphate buffer emulsion of (*S*)-citronellal without MMF was heated and examined in the same way.



With MMF	1	1.1	0.60	0.060	0.0094
Without MMF	1	0.19	0.11	0.030	0.0036

Fig. S7 The molar ratio of each compound after the reactions and ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for $CDCl_3$ extracts from the reaction of (*S*)-citronellal with or without MMF in a phosphate buffer (pH = 5.9) at 45 °C for 3 days.

Procedure for a competition experiment with (–)-α-pinene as an inhibitor: MMF crystals were soaked in neat (–)-α-pinene in a micro-tube at room temperature for 2 days. Then, neat (–)-α-pinene was replaced with an aqueous emulsion of (*S*)-citronellal (78.0 μmol/1.0 mL) and kept at 0 °C for 3 days. The resulting products were extracted with 600 μL of $CDCl_3$ and examined by ^{1}H NMR (500 MHz, $CDCl_3$, 300 K).

Also, as a control experiment, an aqueous emulsion of (*S*)-citronellal with as-synthesized MMF was allowed to stand at 0 °C and examined in the same way.

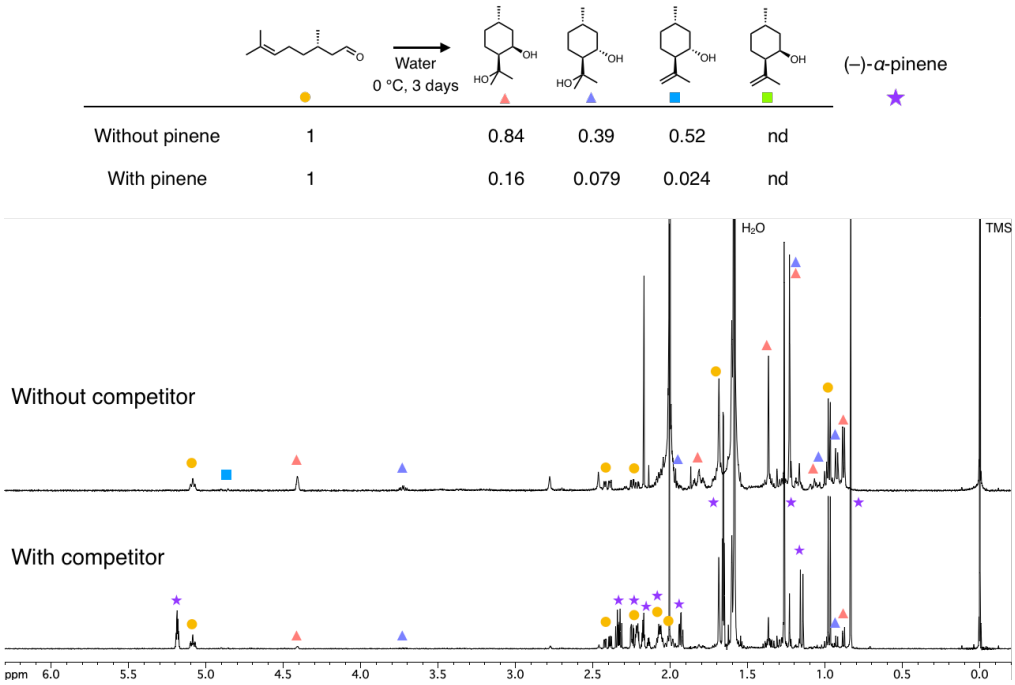


Fig. S8 The molar ratio of each compound after the reactions and ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for $CDCl_3$ extracts from the reaction of (*S*)-citronellal with or without (–)-α-pinene as a competitor within MMF in water at 0 °C for 3 days.

Reactions of (*S*)-citronellal with or without MMF crystals in chloroform

Procedure for the reaction in $CDCl_3$: MMF crystals (ca. 0.5 mg, 0.2 μmol of corner pockets, 2 mol%) and a $CDCl_3$ solution of (*S*)-citronellal (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement. As a controlled experiment, a $CDCl_3$ solution of (*S*)-citronellal without MMF was also put under identical conditions, and then analyzed in the same way.

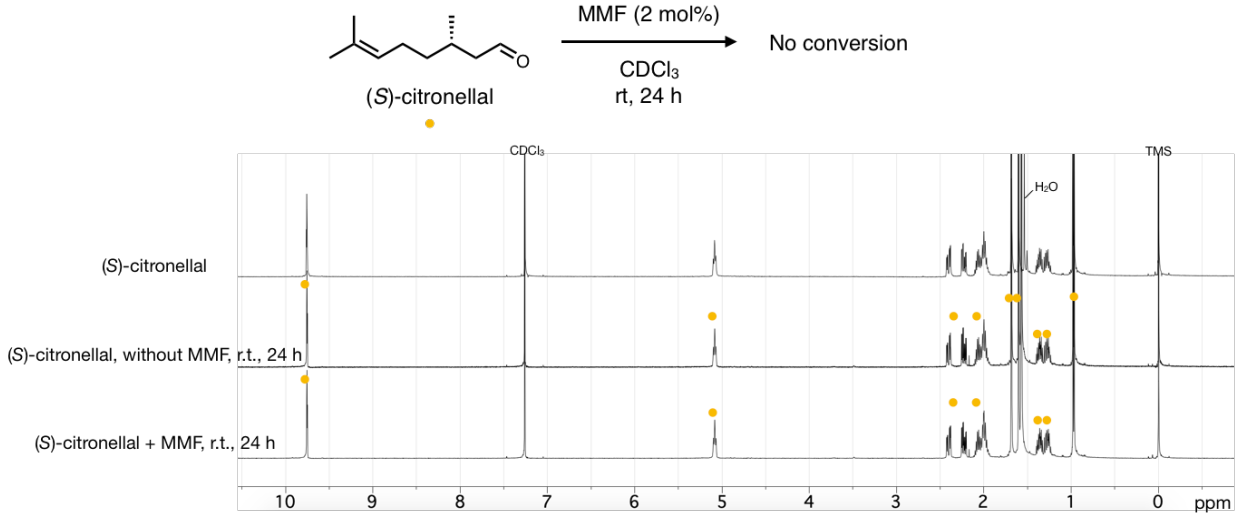


Fig. S9 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, (*S*)-citronellal in $CDCl_3$ without MMF crystals, and the reaction mixture of (*S*)-citronellal and MMF in $CDCl_3$ after 24 h.

4. Crystal structures of nerol@MMF, geraniol@MMF and farnesol@MMF

Uptake of nerol in chloroform

Procedure for guest uptake: MMF crystals were soaked in a chloroform solution of nerol (100 μmol, 0.2 mL, 0.5 M) for 24 h at room temperature, and one of the crystals was picked up and immediately mixed with paratone oil to measure single-crystal XRD.

Crystal data for $(Pd_3LCl_6)_2 \cdot (nerol)_{1.16} \cdot (H_2O)_{3.35} \cdot (CHCl_3)_{0.39}$: $C_{94.09}H_{98.85}Cl_{13.16}N_{12}O_{4.50}Pd_6$, F_w = 2574.76, crystal dimensions 0.21 × 0.172 × 0.102 mm^3, monoclinic, space group $P2_1/c$, a = 19.5440(2), b = 51.9646(5), c = 14.20810(10) Å, β = 92.0600(10)°, V = 14420.4(2) Å^3, Z = 4, ρ_{calcd} = 1.186 g cm^{-3}, μ = 8.469 mm^{-1}, T = 93 K, λ(CuKα) = 1.54187 Å, $2\theta_{max}$ = 147.28°, 178339/28631 reflections collected/unique (R_{int} = 0.0589), R_1 = 0.1129 ($I > 2\sigma(I)$), wR_2 = 0.2901 (for all data), GOF = 1.154, largest diff. peak and hole 4.663/–2.459 eÅ^{-3}. CCDC deposit number 2076033. Several restraints were applied to MMF and guest molecules to avoid collapse of the structure during the least-squares refinement.

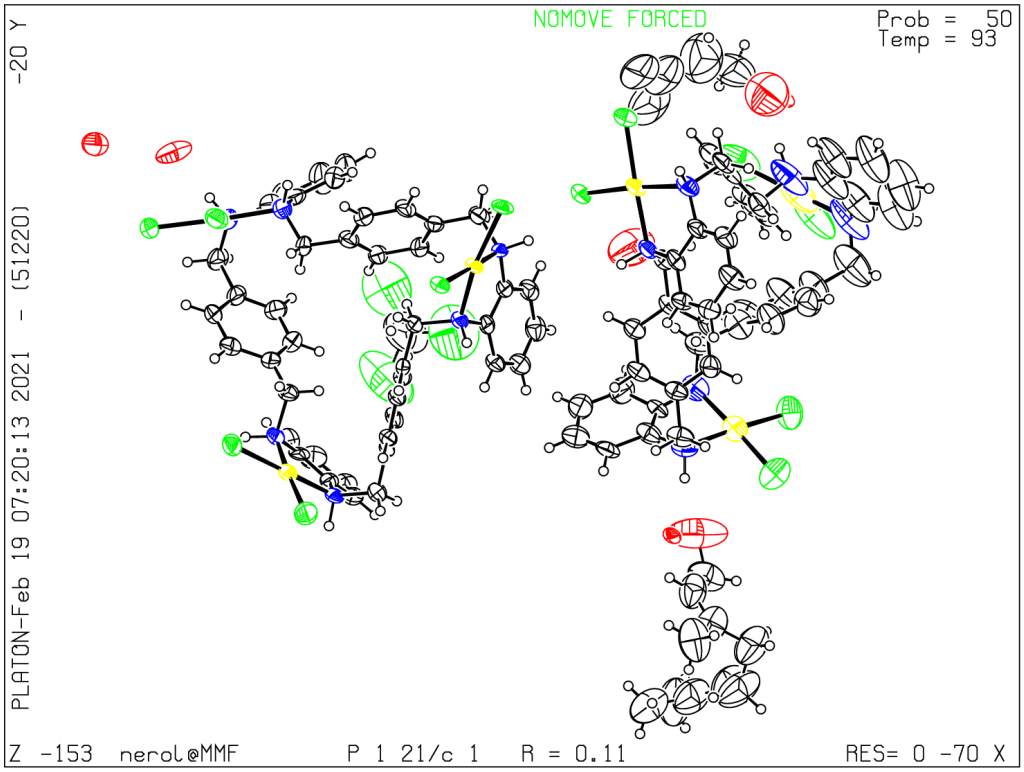


Fig. S10 ORTEP drawing of nerol@MMF at the 50% probability level. Color: C black, N blue, O red, Cl green and Pd yellow.

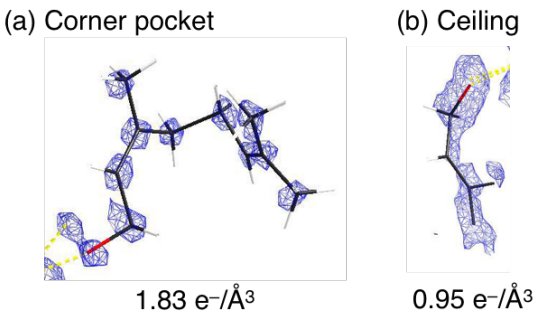


Fig. S11 Electron density maps of nerol on (a) the corner pocket (contour level: 1.83 $e^{-}/Å^3$) and (b) the ceiling (contour level: 0.95 $e^{-}/Å^3$).

Uptake of geraniol in chloroform

Procedure for guest uptake: MMF crystals were soaked in a chloroform solution of geraniol (100 μmol, 0.2 mL, 0.5 M) for 24 h at room temperature, and one of the crystals was picked up and immediately mixed with paratone oil to measure single-crystal XRD.

Crystal data for $Pd_3LCl_6 \cdot (geraniol)_{0.61} \cdot (H_2O)_{1.28}$: $C_{48.10}H_{52.37}Cl_6N_6O_{1.89}Pd_3$, F_w = 1276.72, crystal dimensions 0.104 × 0.088 × 0.067 mm^3, monoclinic, space group $P2_1/c$, a = 19.6098(3), b = 51.8539(8), c = 14.21020(10) Å, β = 91.7540(10)°, V = 14442.8(3) $Å^3$, Z = 8, ρ_{calcd} = 1.174 g cm^{-3}, μ = 8.254 mm^{-1}, T = 93 K, λ(CuKα) = 1.54187 Å, $2\theta_{max}$ = 147.29°, 68503/27850 reflections collected/unique (R_{int} = 0.0526), R_1 = 0.0789 ($I > 2\sigma(I)$), wR_2 = 0.2532 (for all data), GOF = 1.040, largest diff. peak and hole 1.858/–2.124 $eÅ^{-3}$. CCDC deposit number 2076034. Several restraints were applied to MMF and guest molecules to avoid collapse of the structure during the least-squares refinement.

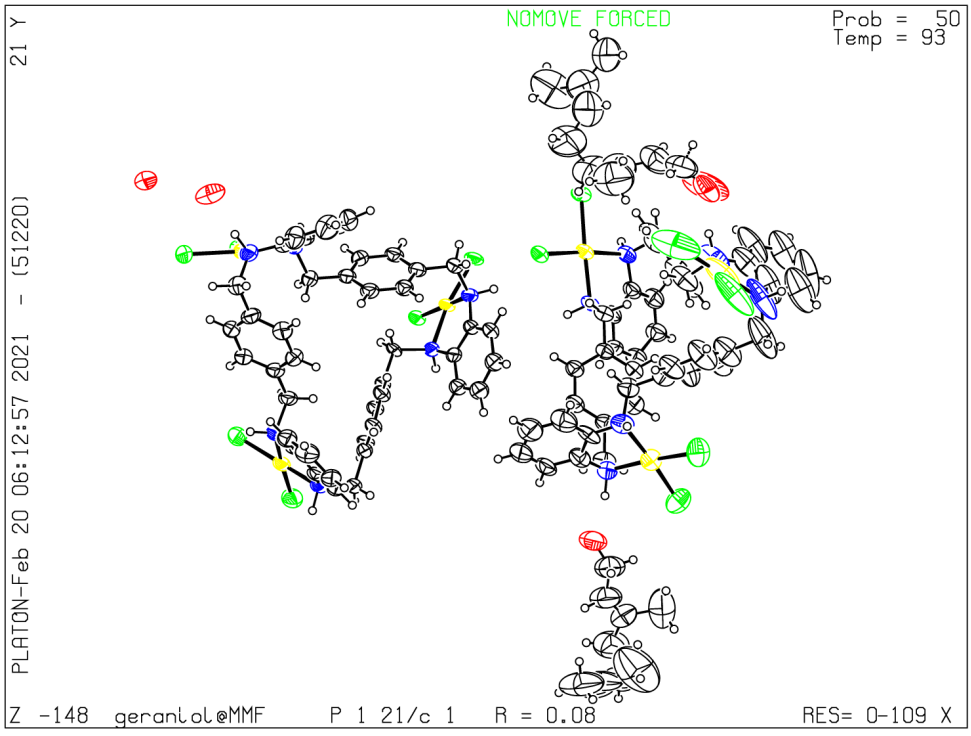


Fig. S12 ORTEP drawing of geraniol@MMF at the 50% probability level. Color: C black, N blue, O red, Cl green and Pd yellow.

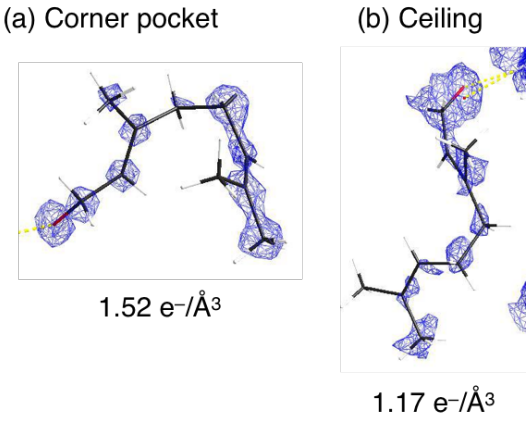


Fig. S13 Electron density maps of geraniol on (a) the corner pocket (contour level: 1.52 $e^{-}/Å^{3}$) and (b) the ceiling (contour level: 1.17 $e^{-}/Å^{3}$).

Uptake of farnesol in chloroform

Procedure for guest uptake: MMF crystals were soaked in a chloroform solution of farnesol (100 μmol, 0.2 mL, 0.5 M) for 24 h at room temperature, and one of the crystals was picked up and immediately mixed with paratone oil to measure single-crystal XRD.

Crystal data for $Pd_3LCl_6 \cdot (farnesol)_{0.79} \cdot (H_2O)_{1.14}$: $C_{48.56}H_{52.22}Cl_6N_6O_{1.79}Pd_3$, F_w = 1280.48, crystal dimensions 0.147 × 0.094 × 0.077 mm^3, monoclinic, space group $P2_1/c$, a = 19.5907(2), b = 52.0744(8), c = 14.2304(2) Å, β = 91.7300(10)°, V = 14510.9(3) $Å^3$, Z = 8, ρ_{calcd} = 1.172 g cm^{-3}, μ = 8.216 mm^{-1}, T = 93 K, λ(CuKα) = 1.54187 Å, $2\theta_{max}$ = 147.37°, 75019/27949 reflections collected/unique (R_{int} = 0.0551), R_1 = 0.0870 ($I > 2\sigma(I)$), wR_2 = 0.2636 (for all data), GOF = 1.016, largest diff. peak and hole 2.850/–1.901 $eÅ^{-3}$. CCDC deposit number 2076035. Several restraints were applied to MMF and guest molecules to avoid collapse of the structure during the least-squares refinement.

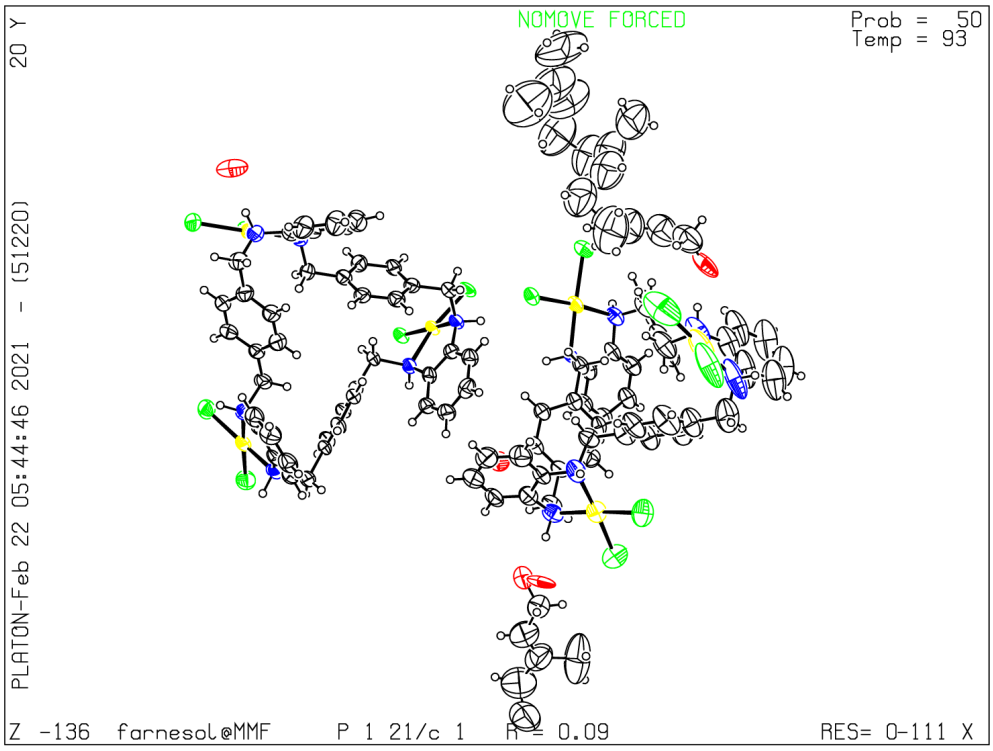


Fig. S14 ORTEP drawing of farnesol@MMF at the 50% probability level. Color: C black, N blue, O red, Cl green and Pd yellow.

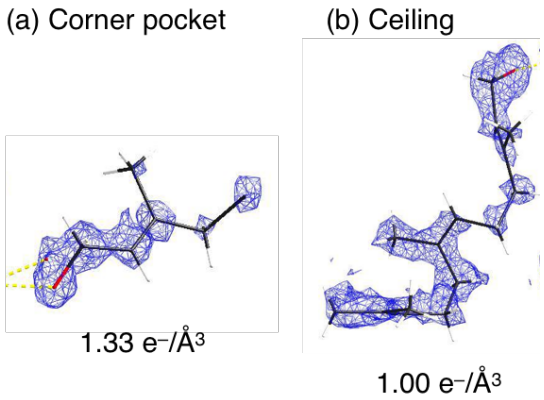


Fig. S15 Electron density maps of farnesol on (a) the corner pocket (contour level: 1.33 $e^{-}/Å^{3}$) and (b) the ceiling (contour level: 1.00 $e^{-}/Å^{3}$).

5. Reactions of nerol, geraniol and farnesol in the presence of MMF

Reactions of nerol with MMF crystals

Procedure for the reaction in water: MMF crystals (ca. 0.5 mg, 0.2 μmol of corner pockets, 2 mol%) and an aqueous emulsion of nerol (10 μmol/1.0 mL) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, extracted with $CDCl_3$ (1.0 mL), then analyzed by ^1H NMR measurement.

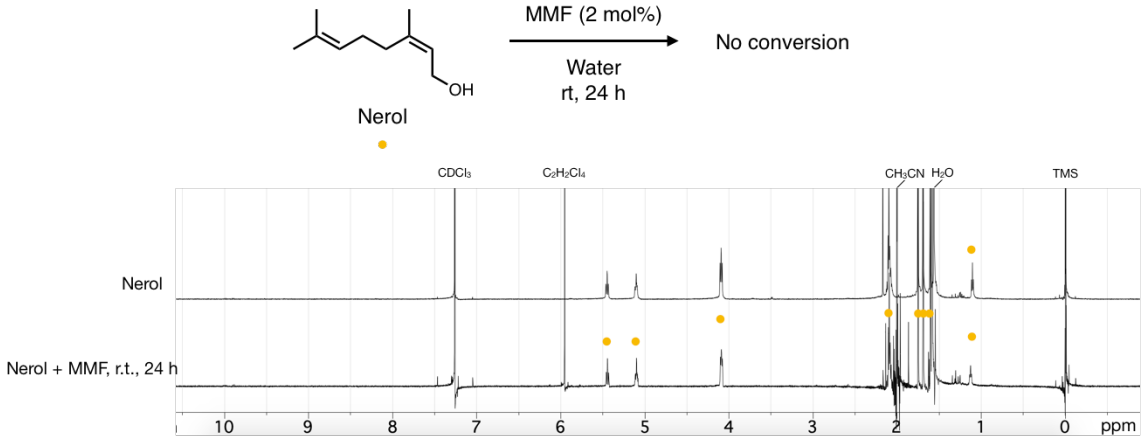


Fig. S16 ^1H NMR spectra (500 MHz, $CDCl_3$, 300 K) for nerol and a $CDCl_3$ extract from the reaction mixture of nerol and MMF in water after 24 h.

Procedure for the reaction in $CDCl_3$: MMF crystals (ca. 0.5 mg, 0.2 μmol of corner pockets, 2 mol%) and a $CDCl_3$ solution of nerol (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^1H NMR measurement.

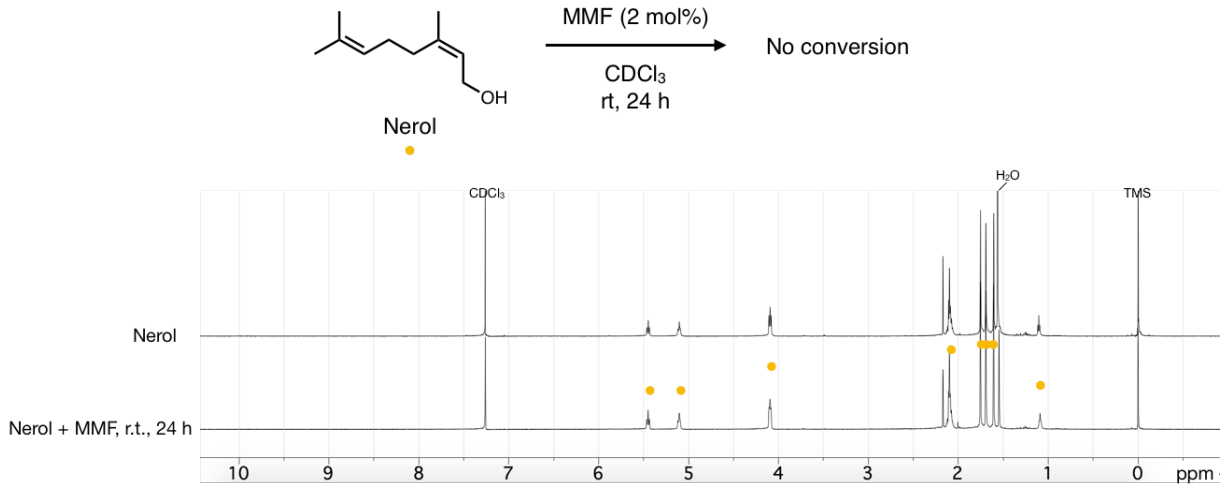


Fig. S17 ^1H NMR spectra (500 MHz, $CDCl_3$, 300 K) for nerol and the reaction mixture of nerol and MMF in $CDCl_3$ after 24 h.

Procedure for the reaction in CD_3CN: MMF crystals (ca. 0.5 mg, 0.2 μmol of corner pockets, 2 mol%) and a CD_3CN solution of nerol (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement.

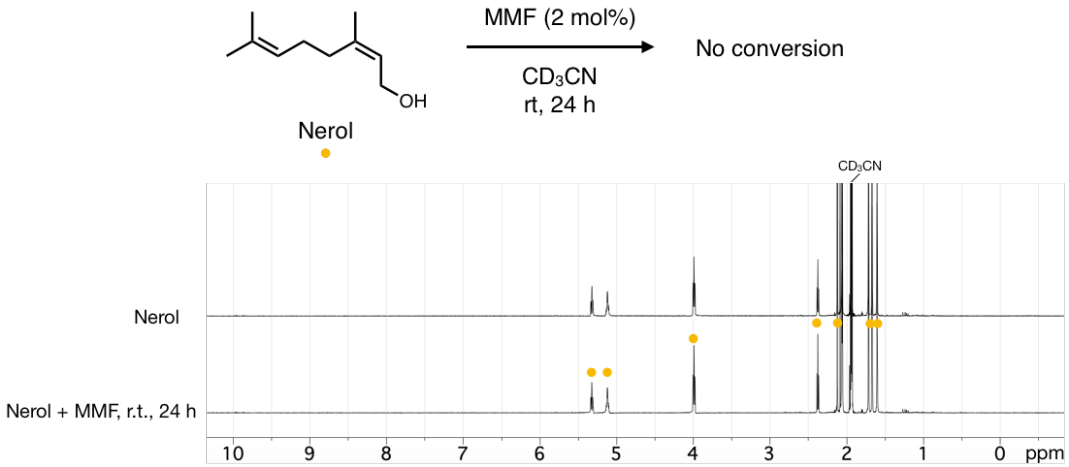


Fig. S18 ^{1}H NMR spectra (500 MHz, CD_3CN, 300 K) for nerol and the reaction mixture of nerol and MMF in CD_3CN after 24 h.

Reactions of geraniol with MMF crystals

Procedure for the reaction in $CDCl_3$: MMF crystals (ca. 0.5 mg, 0.2 μmol of corner pockets, 2 mol%) and a $CDCl_3$ solution of geraniol (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement.

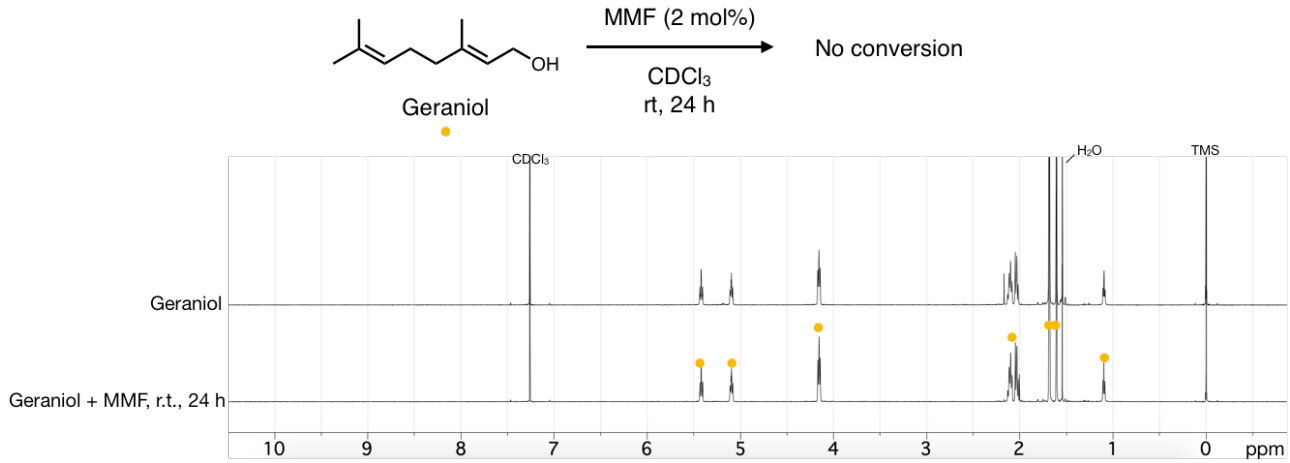


Fig. S19 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for geraniol and the reaction mixture of geraniol and MMF in $CDCl_3$ after 24 h.

Reactions of farnesol with MMF crystals

Procedure for the reaction in $CDCl_3$: MMF crystals (ca. 0.5 mg, 0.2 μmol of corner pockets, 2 mol%) and a $CDCl_3$ solution of farnesol (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This

heterogeneous mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement.

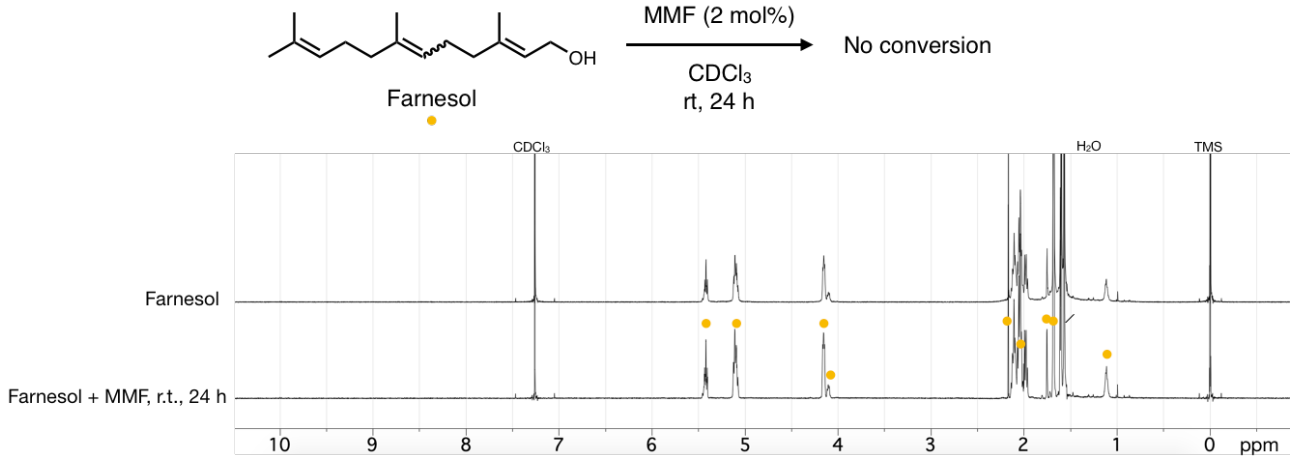


Fig. S20 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for farnesol and the reaction mixture of farnesol and MMF in $CDCl_3$ after 24 h.

6. Reactions of terpenoids with *p*-TsOH@MMF

Reactions of (*S*)-citronellal with *p*-TsOH@MMF or *p*-TsOH·H_2O in chloroform

Procedure for the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF, 1 mol%) and a $CDCl_3$ solution of (*S*)-citronellal (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane. Treating (*S*)-citronellal with *p*-TsOH@MMF resulted in 98% conversion of (*S*)-citronellal to (+)-isopulegol and (–)-neo-isopulegol, which were obtained in 97% total yield (product selectivity: 57% (+)-isopulegol, 40% (–)-neo-isopulegol).

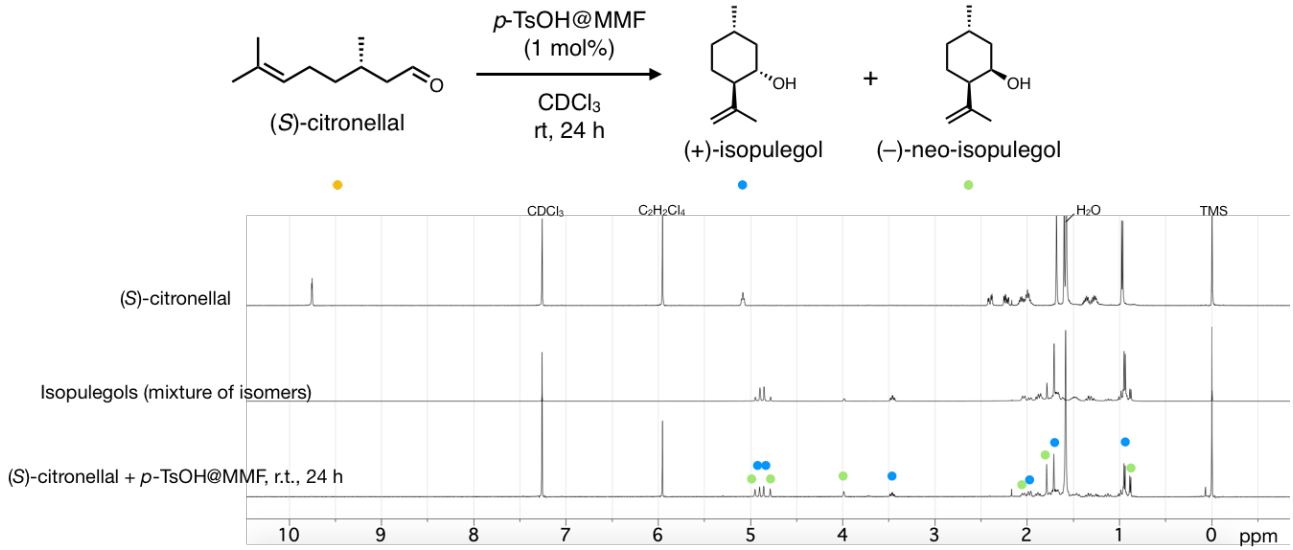


Fig. S21 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, isopulegols, and the reaction mixture of (*S*)-citronellal and *p*-TsOH@MMF in $CDCl_3$ after 24 h.

Confirmation of the heterogeneous character of the p-TsOH@MMF catalyst: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF, 1 mol%) and a $CDCl_3$ solution of (*S*)-citronellal (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature. After 2 h, ^{1}H NMR measurement revealed that 20% of (*S*)-citronellal was converted to (+)-isopulegol and (–)-neo-isopulegol.

Then, a half of the supernatant was taken out by a syringe and filtrated with a membrane filter unit. The supernatant and the remaining suspension were separately put under identical conditions. After 24 h, ^{1}H NMR measurement revealed that the conversion of the supernatant hardly increased (21%), while the conversion of the suspension reached 94%.

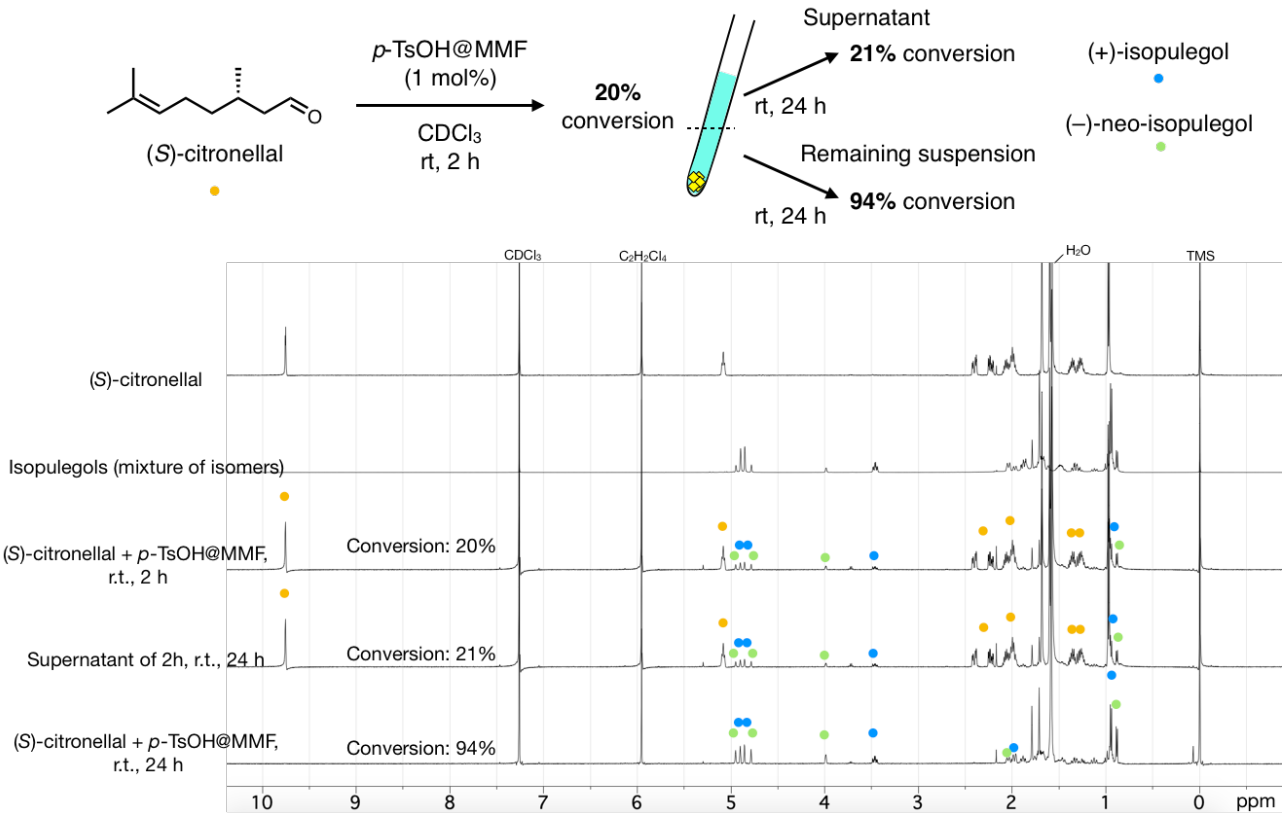
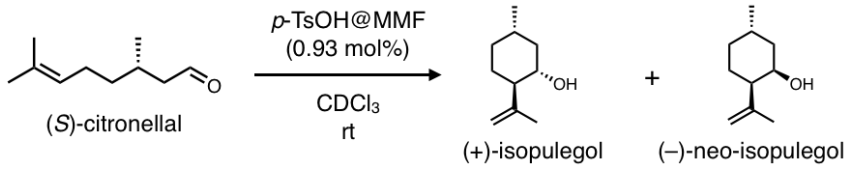


Fig. S22 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, isopulegols, the reaction mixture of (*S*)-citronellal and *p*-TsOH@MMF after 2 h, the supernatant of the 2 h-reaction after 24 h, and the remaining suspension of the 2 h-reaction after 24 h.

Kinetic analysis of the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (1.15 mg, 0.28 μmol of *p*-TsOH in MMF, 0.93 mol%) and a $CDCl_3$ solution of (*S*)-citronellal (30 mM, 1.0 mL, 30 μmol) were added to NMR tubes. These heterogeneous mixtures were shaken with a shaker at room temperature and monitored by ^{1}H NMR measurement. The obtained data were analyzed based on the following first-order reaction, and the experimental data were well consistent with the theoretical lines. The turnover frequency was calculated based on the mole number of *p*-TsOH in *p*-TsOH@MMF crystals.



$$\ln[C] = \ln C_0 - kt$$

[(*S*)-citronellal]	Solvent	Temperature	*p*-TsOH@MMF	k/h^{-1}	Turnover frequency/h^{-1}
30 mM	$CDCl_3$	r.t.	0.93 mol%	0.1278	14

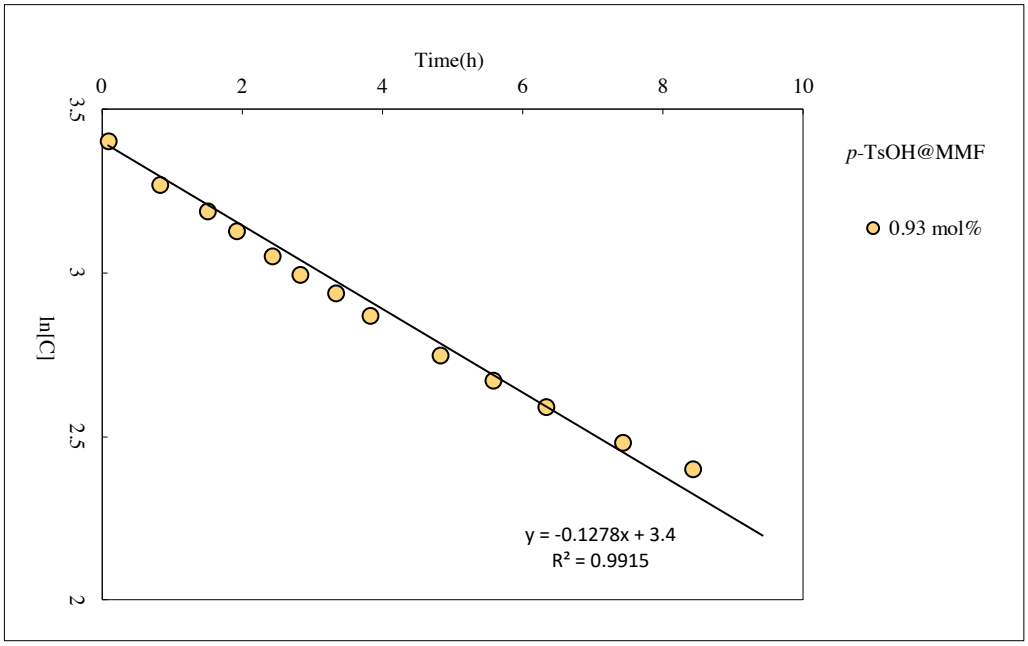


Fig. S23 Plots for ln[C] versus time for the reaction of (*S*)-citronellal and *p*-TsOH@MMF. [C] stands for the concentration of (*S*)-citronellal in the reaction mixture.

Procedure for the reaction with p-TsOH·H₂O: A $CDCl_3$ solution of *p*-TsOH·H_2O (1 mM, 0.1 mL, 0.1 μmol, 1 mol%) and a $CDCl_3$ solution of (*S*)-citronellal (11 mM, 0.9 mL, 9.9 μmol) were added to an NMR tube. This mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane. Treating (*S*)-citronellal with *p*-TsOH·H_2O resulted in 99% conversion of (*S*)-citronellal to (+)-isopulegol and (–)-neo-isopulegol, which were obtained in 97% total yield (product selectivity: 55% (+)-isopulegol, 42% (–)-neo-isopulegol).

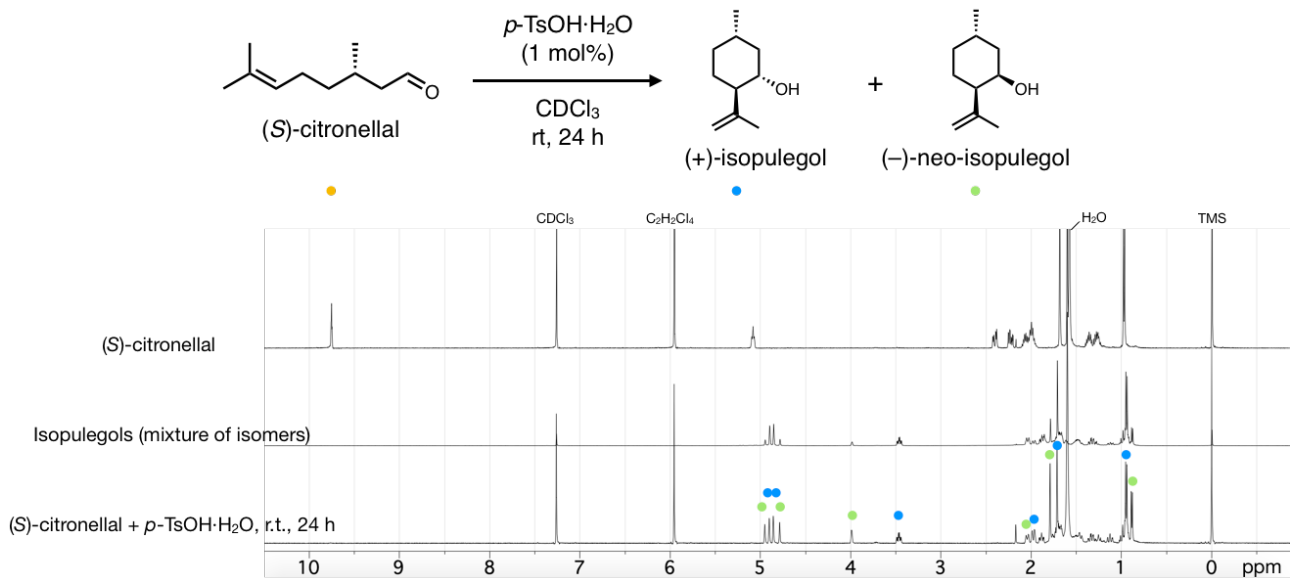
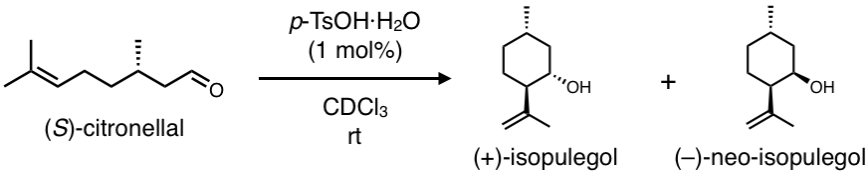


Fig. S24 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, isopulegols and the reaction mixture of (*S*)-citronellal and *p*-TsOH·H_2O in $CDCl_3$ after 24 h.

Kinetic analysis of the reaction with p-TsOH·H₂O: A $CDCl_3$ solution of *p*-TsOH·H_2O (3 mM, 0.1 mL, 0.3 μmol, 1 mol%) and a $CDCl_3$ solution of (*S*)-citronellal (33 mM, 0.9 mL, 29.7 μmol) were added to an NMR tube. This mixture was shaken with a shaker at room temperature and monitored by ^{1}H NMR measurement. The obtained data were analyzed based on the following first-order reaction, and the experimental data were well consistent with the theoretical lines. The turnover frequency was calculated based on the mole number of *p*-TsOH in the homogeneous mixture.



$$\ln[C] = \ln C_0 - kt$$

[(*S*)-citronellal]	Solvent	Temperature	*p*-TsOH·H_2O	k/h^{-1}	Turnover frequency/h^{-1}
30 mM	$CDCl_3$	r.t.	1 mol%	0.2696	27

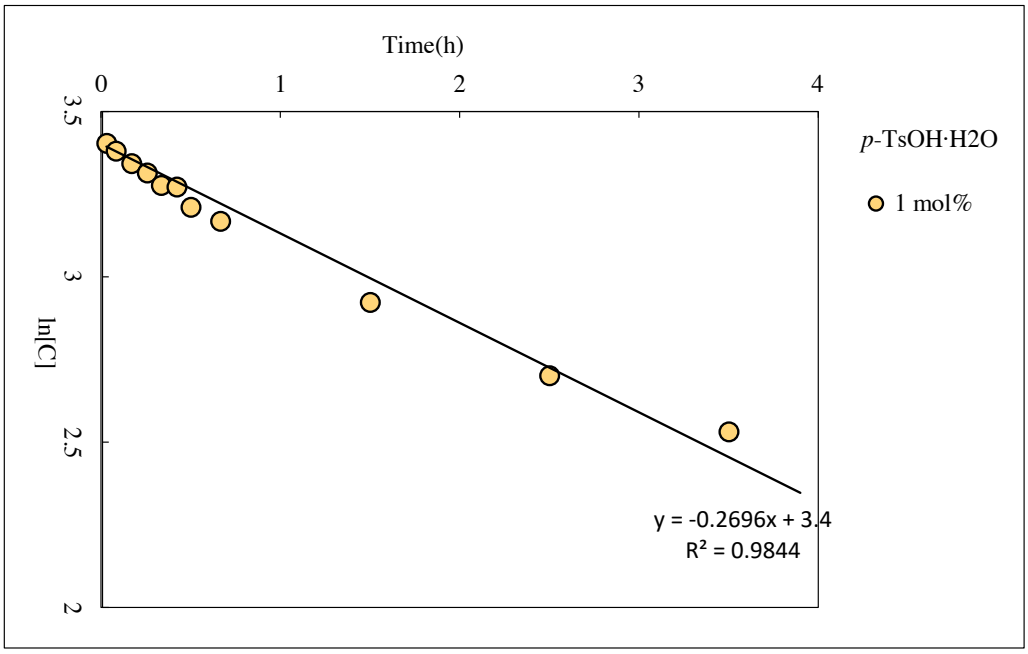


Fig. S25 Plots for ln[C] versus time for the reaction of (*S*)-citronellal and *p*-TsOH·H_2O. [C] stands for the concentration of (*S*)-citronellal in the reaction mixture.

Reactions of nerol with *p*-TsOH@MMF or *p*-TsOH·H_2O in chloroform

Procedure for the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF, 1 mol%) and a $CDCl_3$ solution of nerol (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at 50 °C for 24 h, then analyzed by ^{1}H NMR measurement.

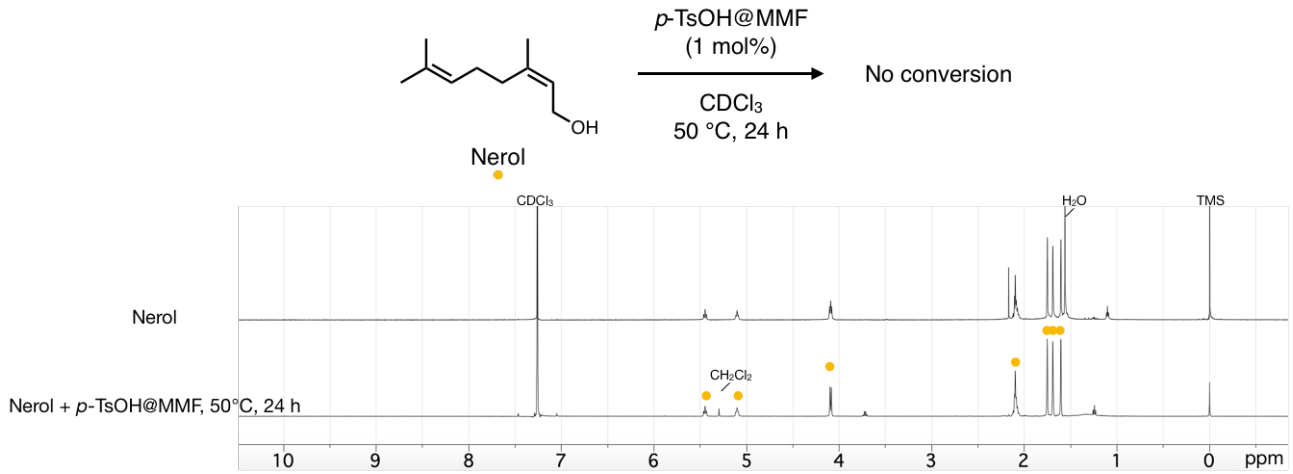


Fig. S26 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for nerol and the reaction mixture of nerol and *p*-TsOH@MMF in $CDCl_3$ after 24 h at 50 °C.

Procedure for the reaction with p-TsOH·H₂O: A $CHCl_3$ solution of *p*-TsOH·H_2O (3 mM, 0.1 mL, 0.3 μmol, 1 mol%) and a $CDCl_3$ solution of nerol (33 mM, 0.9 mL, 29.7 μmol) were added to an NMR tube. This mixture was shaken with a shaker at 50 °C for 24 h, and then analyzed by ^{1}H NMR measurement. The conversion ratio of nerol and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane. Treating nerol with *p*-TsOH·H_2O resulted in 97% conversion of nerol, and (+/–)-limonene and terpinolene were obtained in 75% total yield (product selectivity: 58% (+/–)-limonene, 17% terpinolene).

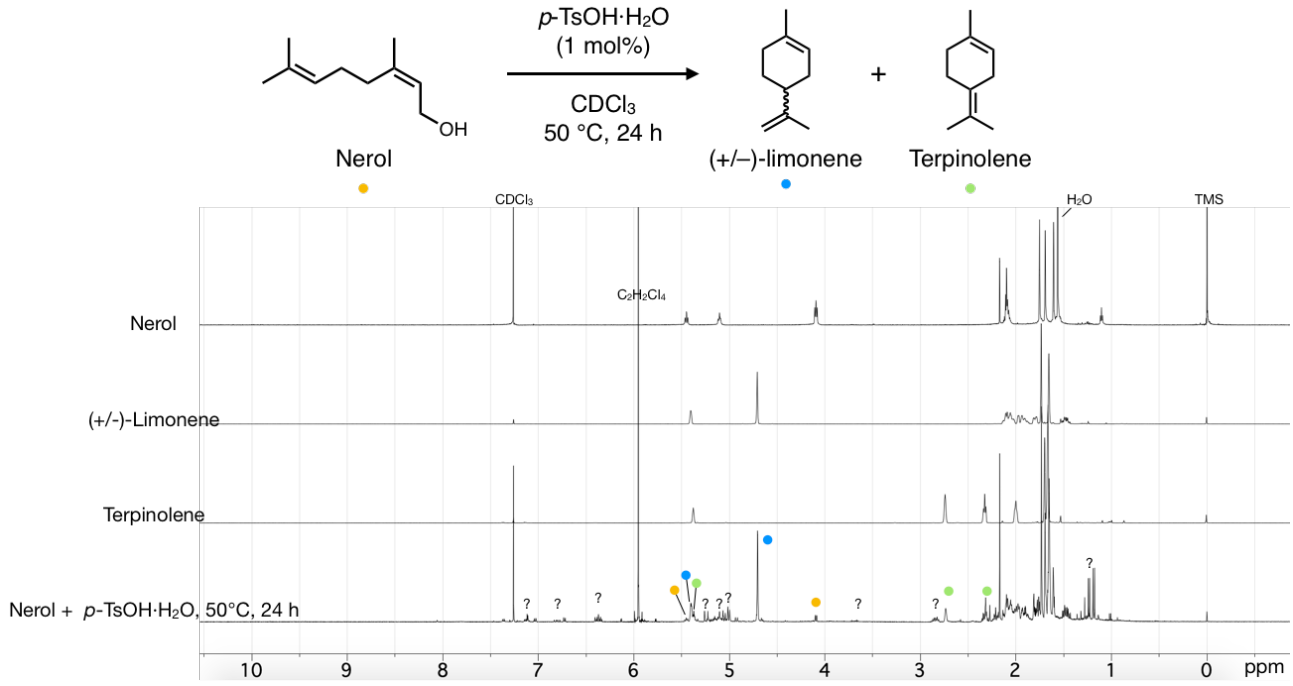


Fig. S27 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for nerol, (+/–)-limonene, terpinolene and the reaction mixture of nerol and *p*-TsOH·H_2O in $CDCl_3$ after 24 h at 50 °C.

Reactions of geraniol with *p*-TsOH@MMF or *p*-TsOH·H_2O in chloroform

Procedure for the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF, 1 mol%) and a $CDCl_3$ solution of geraniol (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at 50 °C for 24 h, and then analyzed by ^1H NMR measurement.

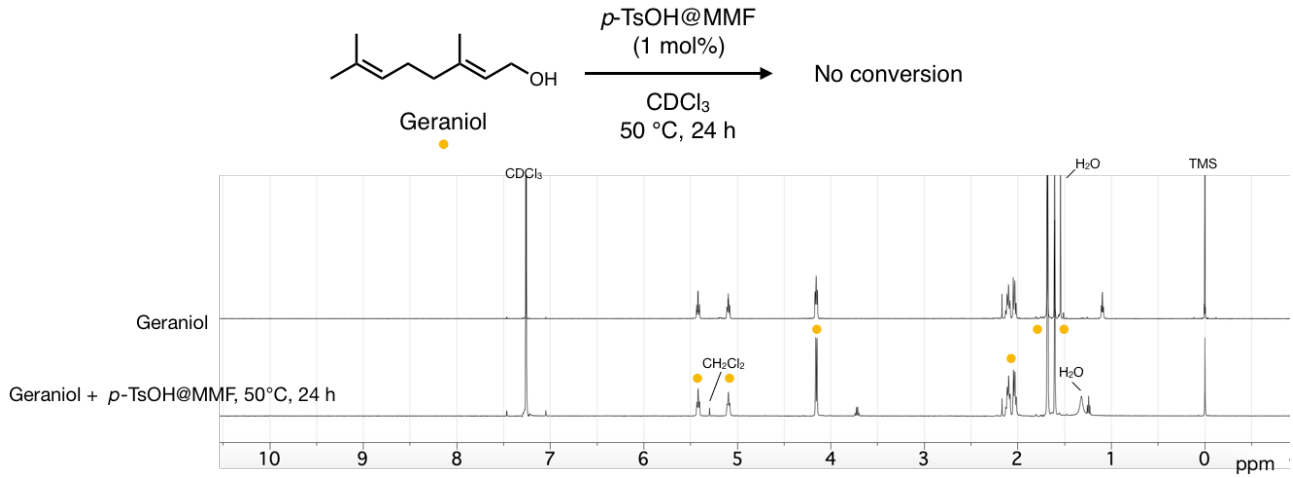


Fig. S28 ^1H NMR spectra (500 MHz, $CDCl_3$, 300 K) for geraniol and the reaction mixture of geraniol and *p*-TsOH@MMF in $CDCl_3$ after 24 h at 50 °C.

Procedure for the reaction with p-TsOH·H_2O: A $CHCl_3$ solution of *p*-TsOH·H_2O (3 mM, 0.1 mL, 0.3 μmol, 1 mol%) and a $CDCl_3$ solution of geraniol (33 mM, 0.9 mL, 29.7 μmol) were added to an NMR tube. This mixture was shaken with a shaker at 50 °C for 24 h, and then analyzed by ^1H NMR measurement. The conversion ratio of geraniol and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane. Treating geraniol with *p*-TsOH·H_2O resulted in 87% conversion of geraniol, and (+/–)-limonene and terpinolene were obtained in 40% total yield (product selectivity: 32% (+/–)-limonene, 8% terpinolene).

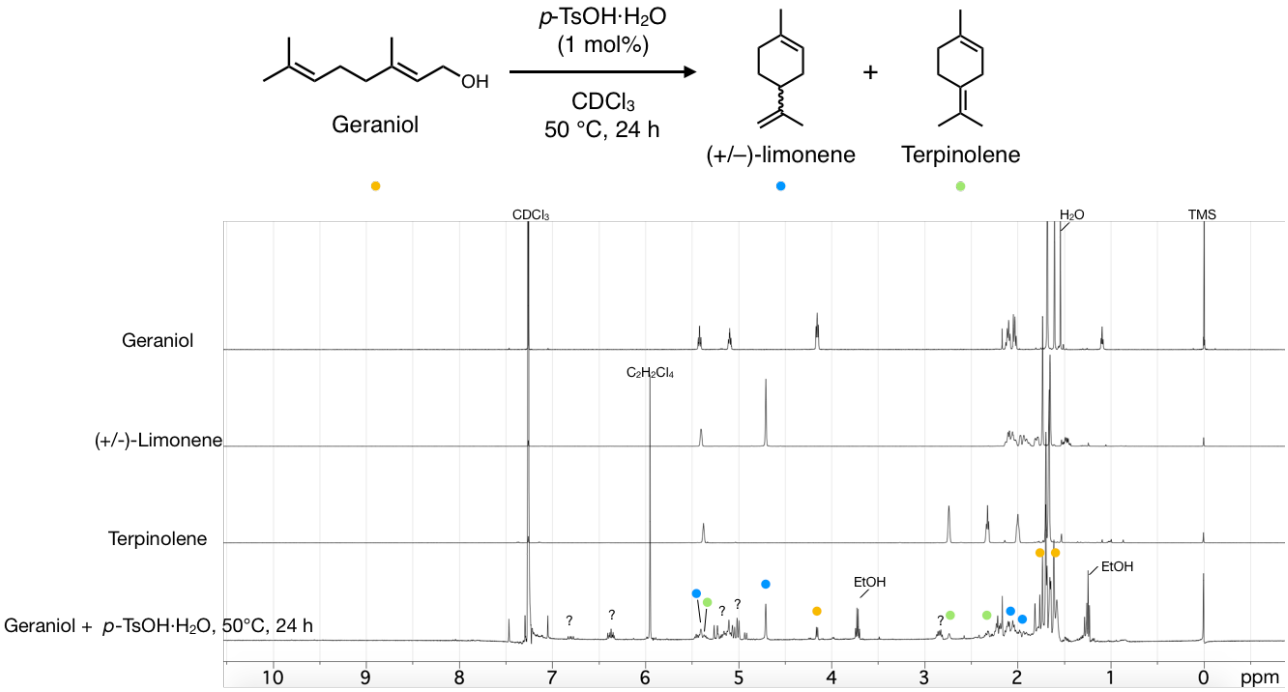


Fig. S29 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for geraniol, (+/–)-limonene, terpinolene and the reaction mixture of geraniol and *p*-TsOH·H_2O in $CDCl_3$ after 24 h at 50 °C.

Reactions of farnesol with *p*-TsOH@MMF or *p*-TsOH·H_2O in chloroform

Procedure for the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF, 1 mol%) and a $CDCl_3$ solution of farnesol (10 mM, 1.0 mL, 10 μmol) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at 50 °C for 24 h, and then analyzed by ^{1}H NMR measurement.

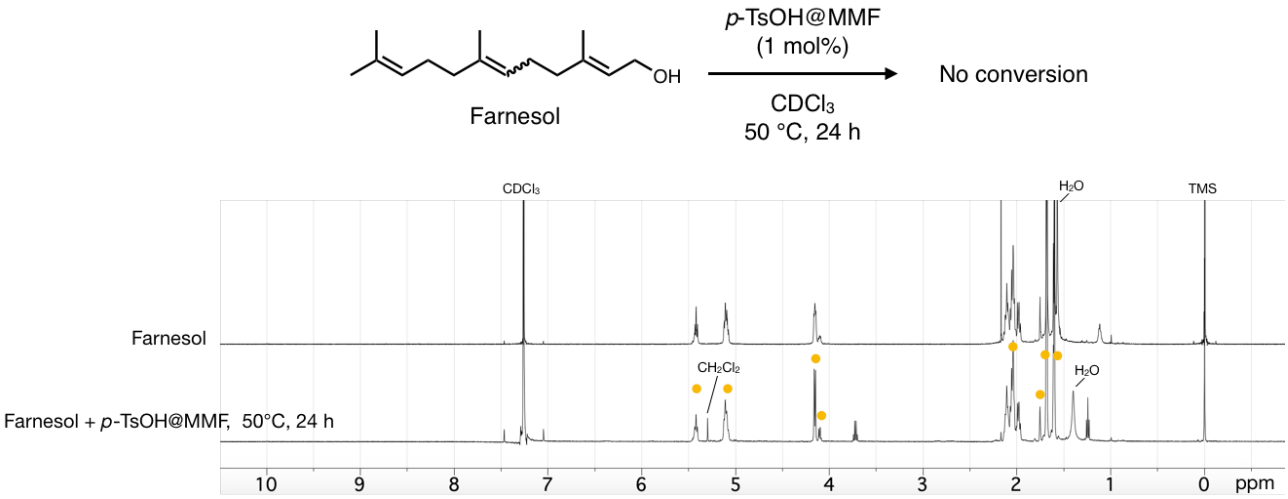


Fig. S30 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for farnesol and the reaction mixture of farnesol and *p*-TsOH@MMF in $CDCl_3$ after 24 h at 50 °C.

Procedure for the reaction with p-TsOH·H₂O: A $CHCl_3$ solution of *p*-TsOH·H_2O (3 mM, 0.1 mL, 0.3 μmol, 1 mol%) and a $CDCl_3$ solution of farnesol (33 mM, 0.9 mL, 29.7 μmol) were added to an NMR tube. This mixture was shaken with a shaker at 50 °C for 24 h, and then analyzed by ^{1}H NMR measurement. Treating farnesol with *p*-TsOH·H_2O resulted in 66% conversion of farnesol to a complicated mixture of products.

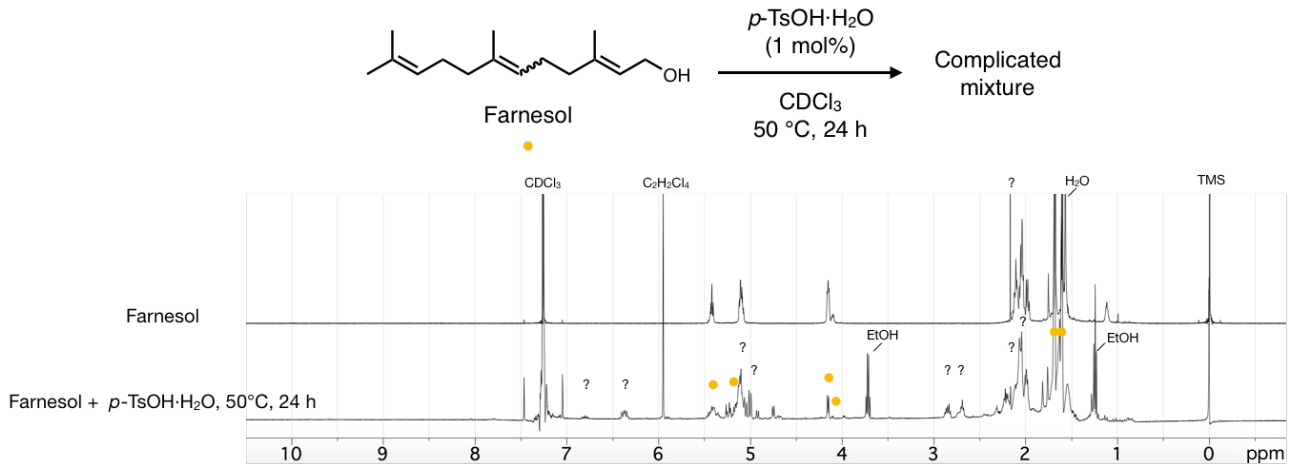


Fig. S31 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for farnesol and the reaction mixture of farnesol and *p*-TsOH·H_2O in $CDCl_3$ after 24 h at 50 °C.

7. Competitive reactions of terpenoids with *p*-TsOH@MMF

Reactions of (*S*)-citronellal and geraniol with *p*-TsOH@MMF or *p*-TsOH·H_2O in chloroform

Procedure for the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF) and a mixed $CDCl_3$ solution of (*S*)-citronellal and geraniol (1.0 mL; (*S*)-citronellal: 30 mM, 30 μmol; geraniol: 30 mM, 30 μmol, 100 mol%) (or 1.0 mL; (*S*)-citronellal: 30 mM, 30 μmol; geraniol: 100 mM, 100 μmol, 333 mol%) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, then analyzed by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane.

Treating (*S*)-citronellal and 100 mol% geraniol with *p*-TsOH@MMF resulted in 42% conversion of (*S*)-citronellal and < 1% conversion of geraniol. Treating (*S*)-citronellal and 333 mol% geraniol with *p*-TsOH@MMF resulted in 3% conversion of (*S*)-citronellal and < 1% conversion of geraniol.

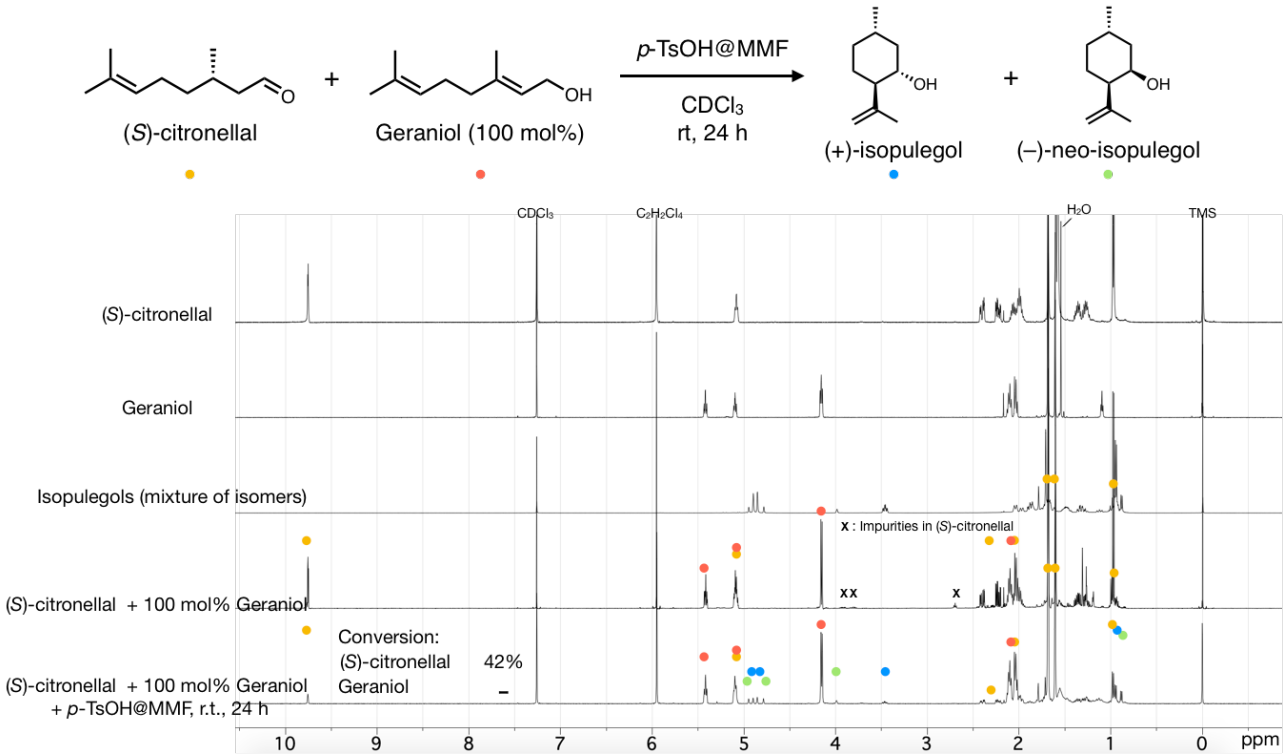


Fig. S32 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, geraniol, isopulegols, the mixture of (*S*)-citronellal and 100 mol% geraniol, and the mixture with *p*-TsOH@MMF in $CDCl_3$ after 24 h at room temperature.

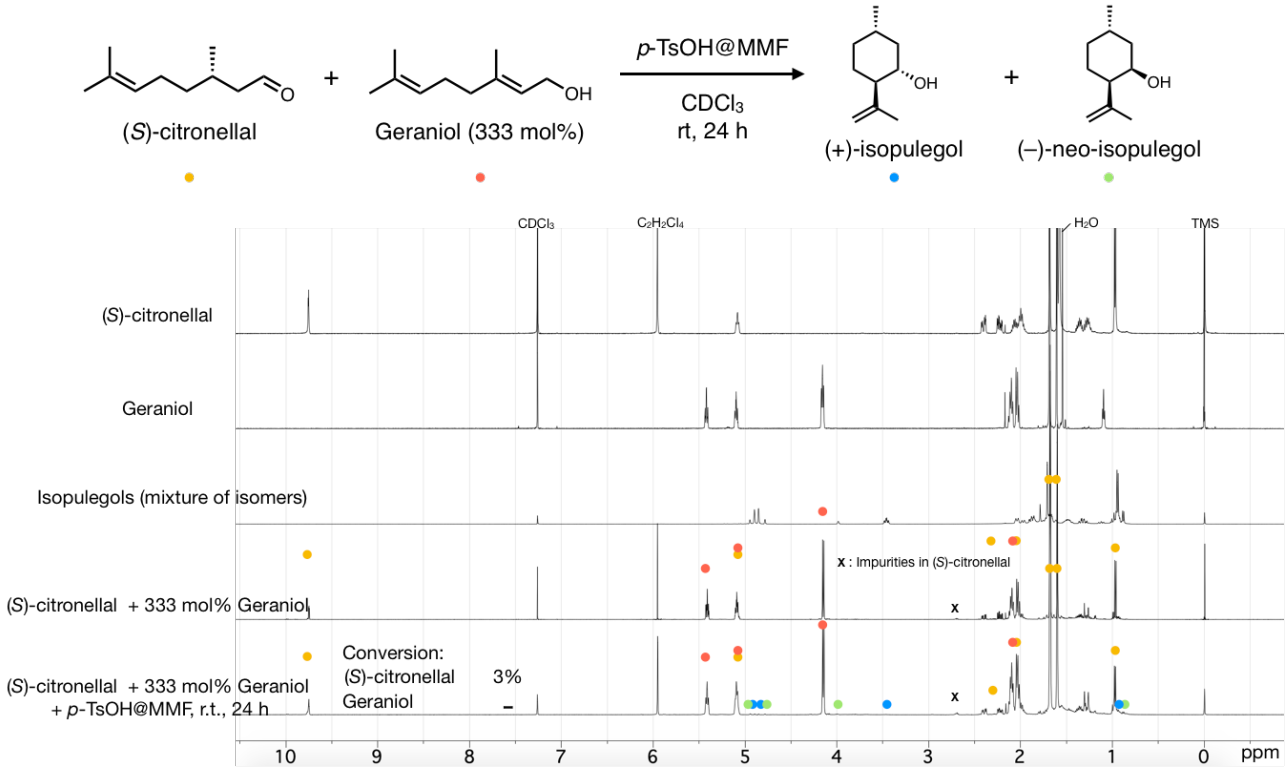


Fig. S33 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, geraniol, isopulegols, the mixture of (*S*)-citronellal and 333 mol% geraniol, and the mixture with *p*-TsOH@MMF in $CDCl_3$ after 24 h at room temperature.

Procedure for the reaction with p-TsOH·H₂O: A $CHCl_3$ solution of *p*-TsOH·H_2O (3 mM, 0.1 mL, 0.3 μmol) and a $CDCl_3$ solution of (*S*)-citronellal and geraniol (0.9 mL; (*S*)-citronellal: 33 mM, 29.7 μmol; geraniol: 33 mM, 29.7 μmol, 100 mol%) (or 0.9 mL; (*S*)-citronellal: 33 mM, 29.7 μmol; geraniol: 110 mM, 99 μmol, 333 mol%) were added to an NMR tube. This mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal and geraniol, and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane.

Treating (*S*)-citronellal and 100 mol% geraniol with *p*-TsOH·H_2O resulted in 99% conversion of (*S*)-citronellal and 91% conversion of geraniol. Treating (*S*)-citronellal and 333 mol% geraniol with *p*-TsOH·H_2O resulted in 99% conversion of (*S*)-citronellal and 56% conversion of geraniol.

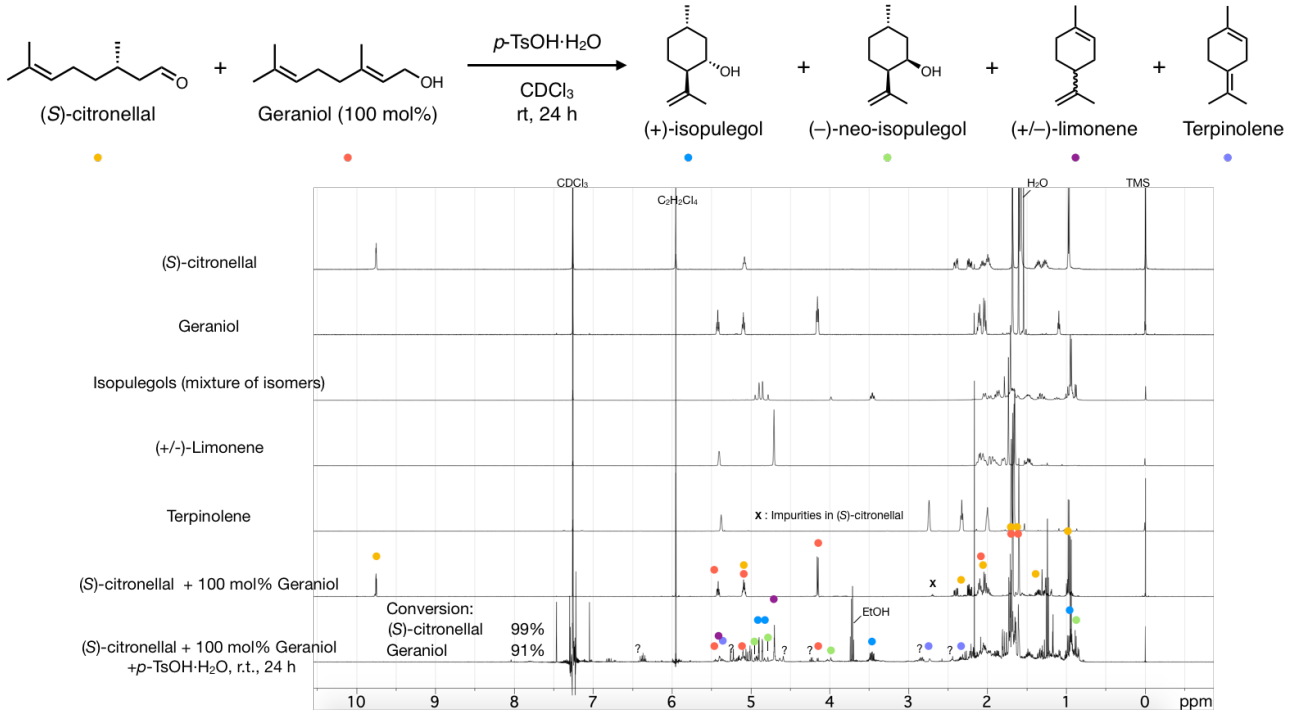


Fig. S34 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, geraniol, isopulegols, (+/–)-limonene, terpinolene, the mixture of (*S*)-citronellal and 100 mol% geraniol, and the mixture with *p*-TsOH·H_2O in $CDCl_3$ after 24 h at room temperature.

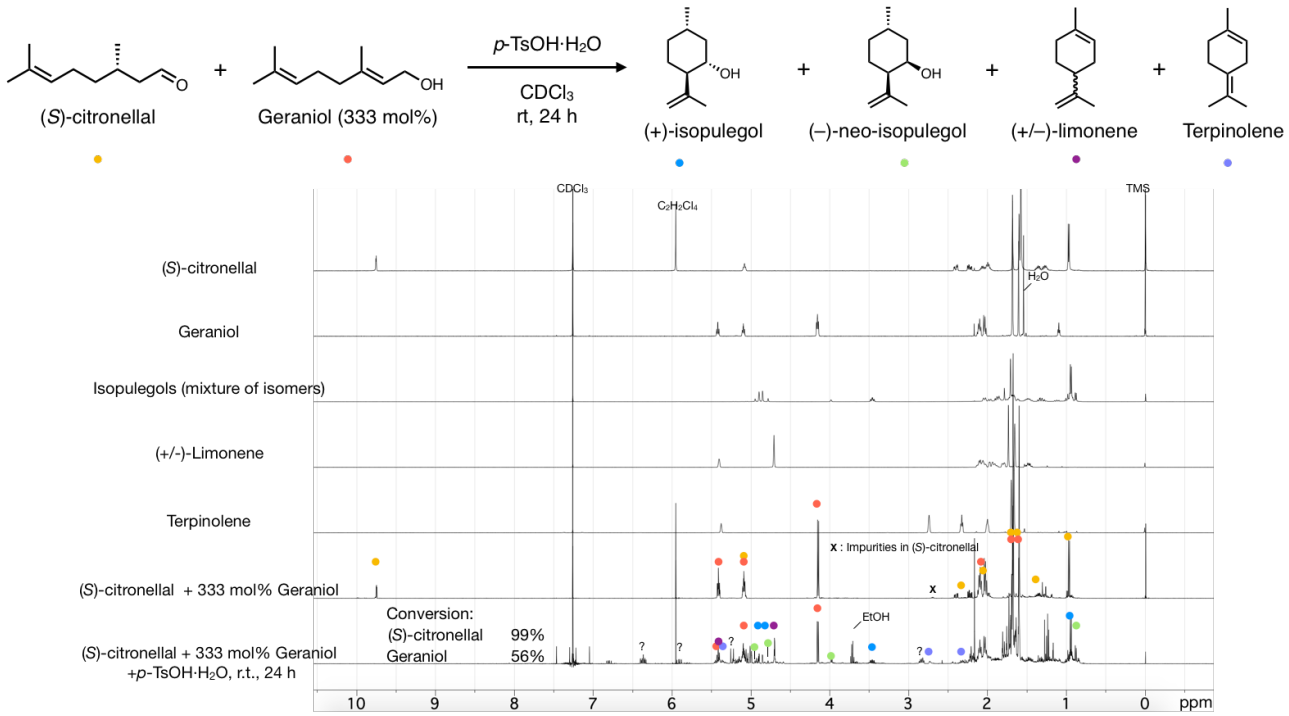


Fig. S35 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, geraniol, isopulegols, (+/–)-limonene, terpinolene, the mixture of (*S*)-citronellal and 333 mol% geraniol, and the mixture with *p*-TsOH·H_2O in $CDCl_3$ after 24 h at room temperature.

Reactions of (*S*)-citronellal and farnesol with *p*-TsOH@MMF or *p*-TsOH·H_2O in chloroform

Procedure for the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF) and a $CDCl_3$ solution of (*S*)-citronellal and farnesol (1.0 mL; (*S*)-citronellal: 30 mM, 30 μmol; farnesol: 30 mM, 30 μmol, 100 mol%) (or 1.0 mL; (*S*)-citronellal: 30 mM, 30 μmol; farnesol: 100 mM, 100 μmol, 333 mol%) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, then analyzed by ^1H NMR measurement. The conversion ratio of (*S*)-citronellal and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane.

Treating (*S*)-citronellal and 100 mol% farnesol with *p*-TsOH@MMF resulted in 41% conversion of (*S*)-citronellal and < 1% conversion of farnesol. Treating (*S*)-citronellal and 333 mol% farnesol with *p*-TsOH@MMF resulted in <1% conversion of (*S*)-citronellal and < 1% conversion of farnesol.

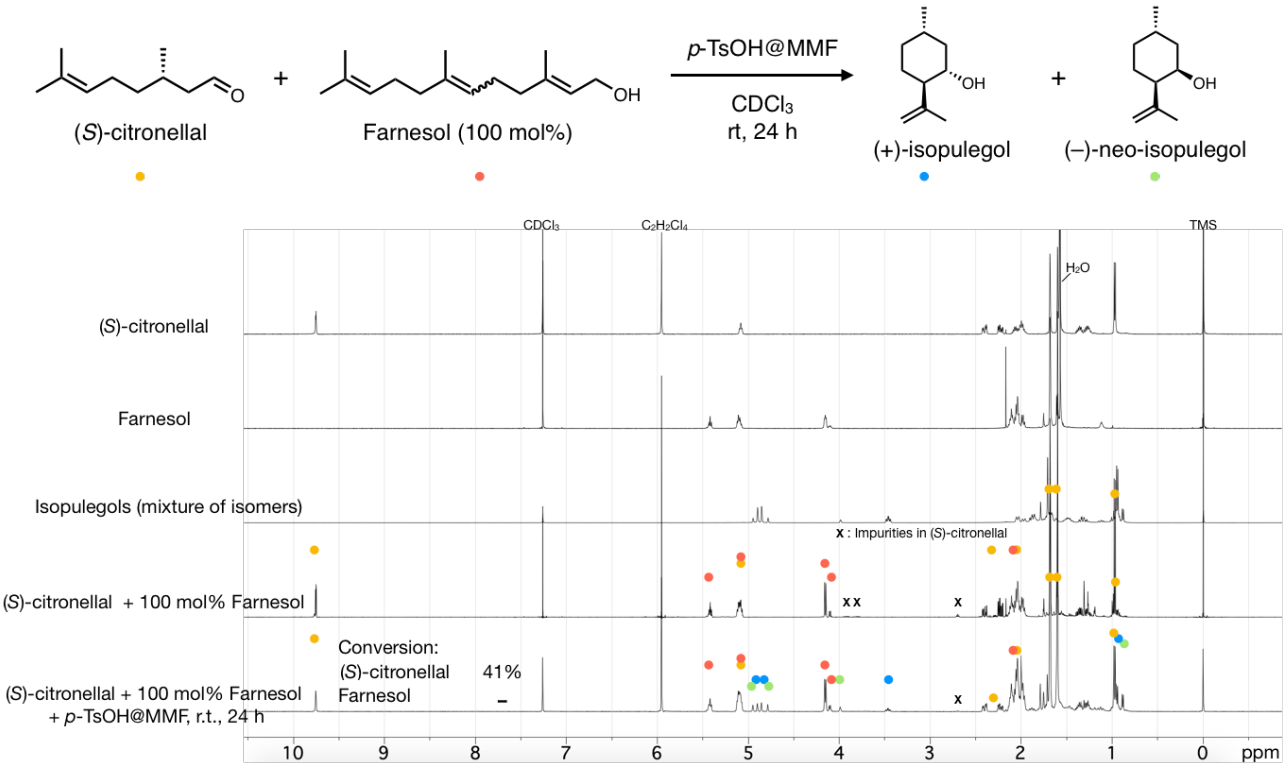


Fig. S36 ^1H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, farnesol, isopulegols, the mixture of (*S*)-citronellal and 100 mol% farnesol, and the mixture with *p*-TsOH@MMF in $CDCl_3$ after 24 h at room temperature.

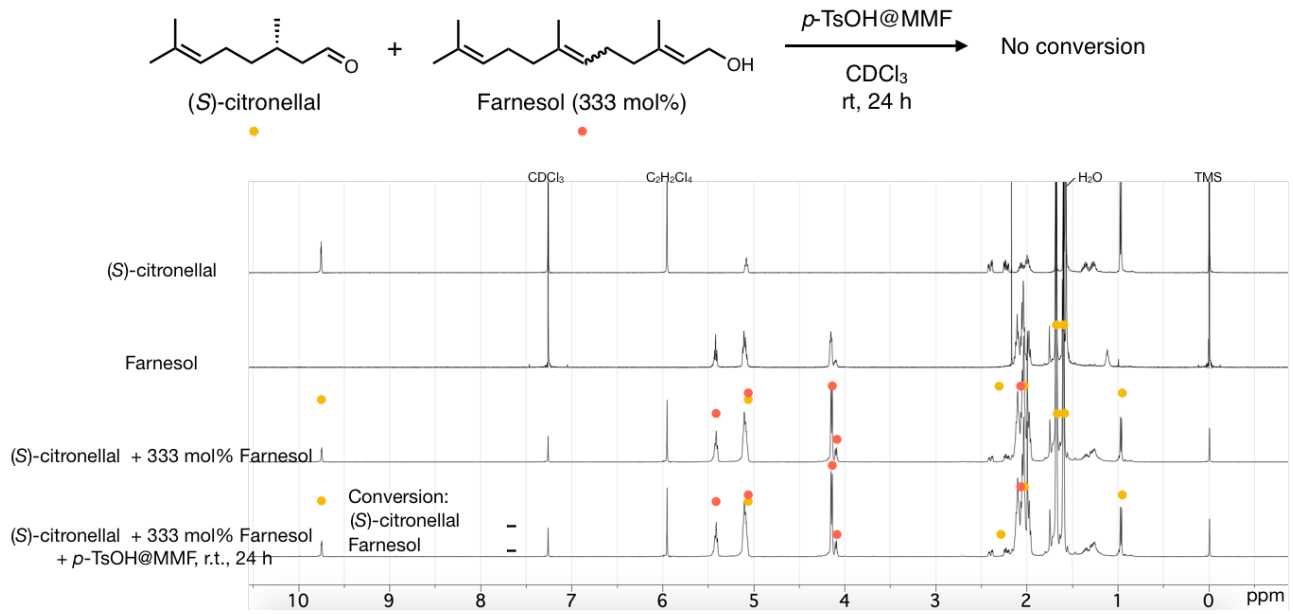


Fig. S37 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, farnesol, the mixture of (*S*)-citronellal and 333 mol% farnesol and the mixture with *p*-TsOH@MMF in $CDCl_3$ after 24 h at room temperature.

Procedure for the reaction with p-TsOH·H₂O: A $CHCl_3$ solution of *p*-TsOH·H_2O (3 mM, 0.1 mL, 0.3 μmol) and a $CDCl_3$ solution of (*S*)-citronellal and farnesol (0.9 mL; (*S*)-citronellal: 33 mM, 29.7 μmol; farnesol: 33 mM, 29.7 μmol, 100 mol%) (or 0.9 mL; (*S*)-citronellal: 33 mM, 29.7 μmol; farnesol: 110 mM, 99 μmol, 333 mol%) were added to an NMR tube. This mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal and farnesol, and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane.

Treating (*S*)-citronellal and 100 mol% farnesol with *p*-TsOH·H_2O resulted in 100% conversion of (*S*)-citronellal and 92% conversion of farnesol. Treating (*S*)-citronellal and 333 mol% farnesol with *p*-TsOH·H_2O resulted in 100% conversion of (*S*)-citronellal and 39% conversion of farnesol.

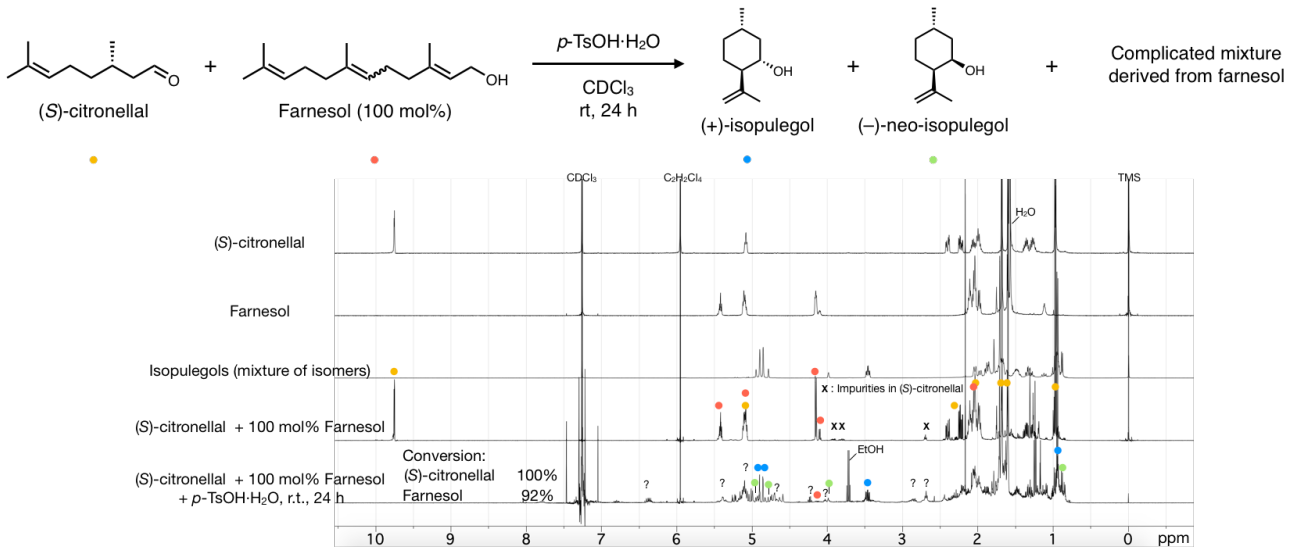


Fig. S38 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, farnesol, isopulegols, the mixture of (*S*)-citronellal and 100 mol% farnesol, and the mixture with *p*-TsOH·H_2O in $CDCl_3$ after 24 h at room temperature.

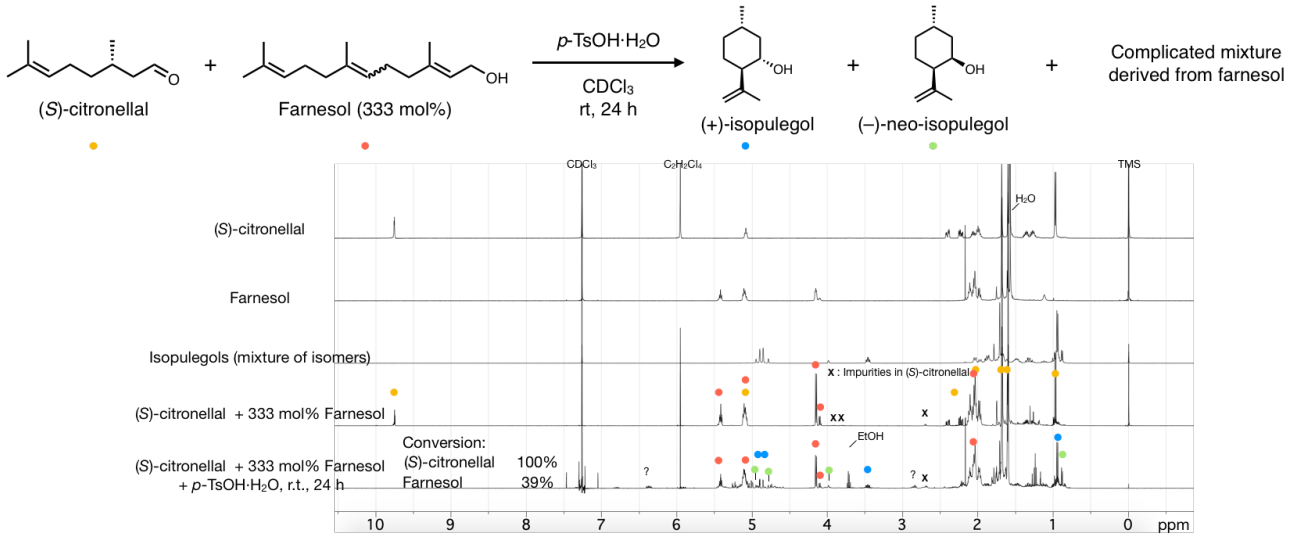


Fig. S39 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, farnesol, isopulegols, the mixture of (*S*)-citronellal and 333 mol% farnesol, and the mixture with *p*-TsOH·H_2O in $CDCl_3$ after 24 h at room temperature.

<u>Reactions of (*S*)-citronellal and nerol with *p*-TsOH@MMF or *p*-TsOH·H_2O in chloroform</u>

Procedure for the reaction with p-TsOH@MMF: Fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of p-TsOH in MMF) and a mixed $CDCl_3$ solution of (*S*)-citronellal and nerol (1.0 mL; (*S*)-citronellal: 30 mM, 30 μmol; nerol: 30 mM, 30 μmol, 100 mol%) (or 1.0 mL; (*S*)-citronellal: 30 mM, 30 μmol; nerol: 1 mM, 1 μmol, 3 mol%) were added to an NMR tube. This heterogeneous mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal and the yield of main products were assessed against an internal

standard of 1,1,2,2-tetrachloroethane.

Treating (*S*)-citronellal and 100 mol% nerol with *p*-TsOH@MMF resulted in < 1% conversion of (*S*)-citronellal and < 1% conversion nerol. Treating (*S*)-citronellal and 3 mol% nerol with *p*-TsOH@MMF resulted in 38% conversion of (*S*)-citronellal.

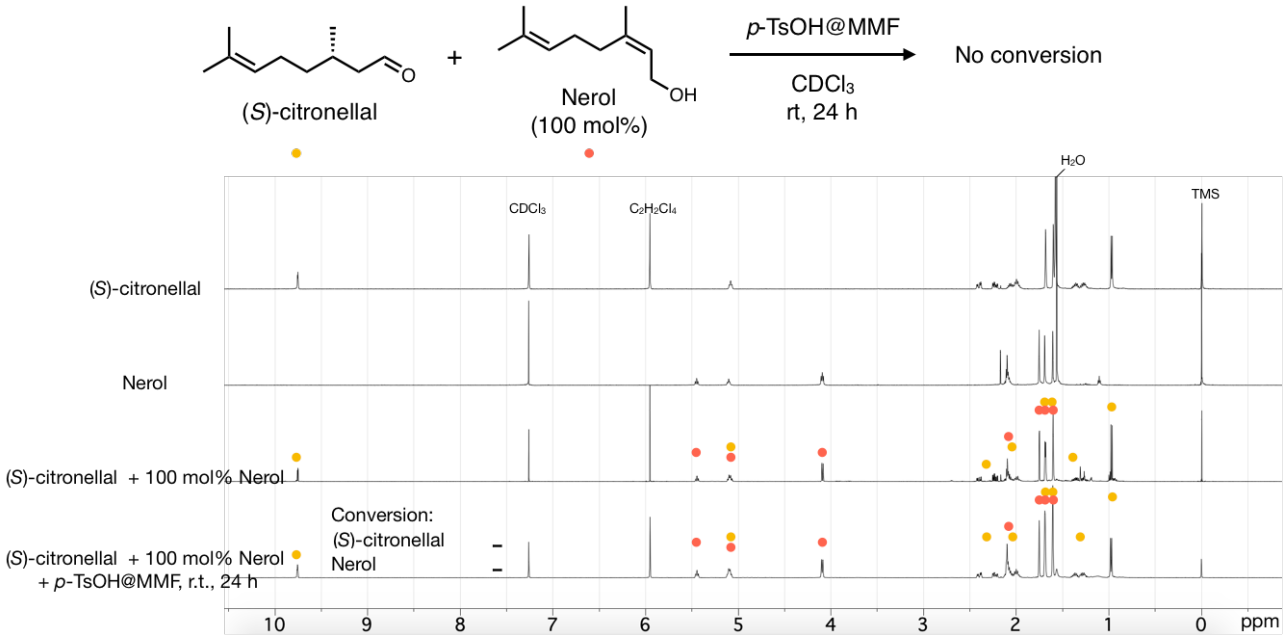


Fig. S40 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, nerol, the mixture of (*S*)-citronellal and 100 mol% nerol, and the mixture with *p*-TsOH@MMF in $CDCl_3$ after 24 h at room temperature.

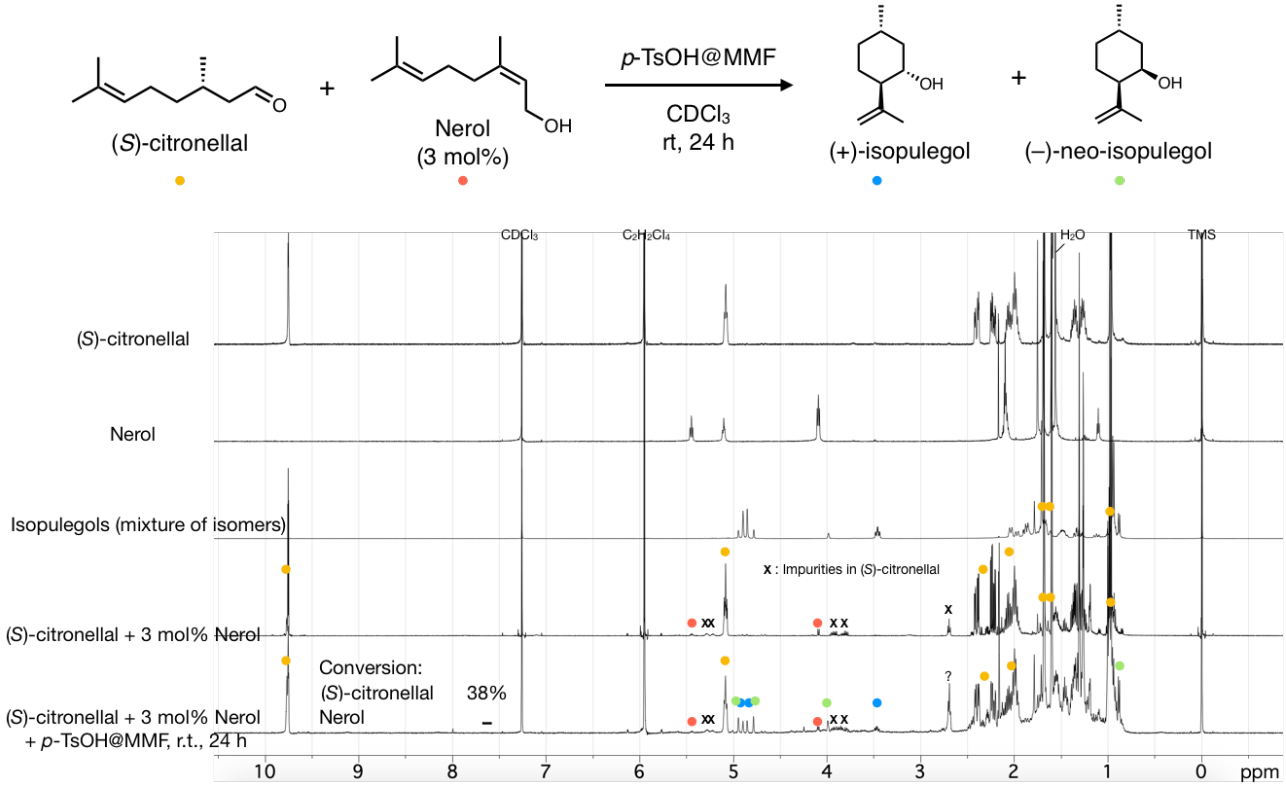


Fig. S41 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, nerol, isopulegols, the

mixture of (*S*)-citronellal and 3 mol% nerol, and the mixture with *p*-TsOH@MMF in $CDCl_3$ after 24 h at room temperature.

Addition of nerol into the reaction mixture of (S)-citronellal and p-TsOH@MMF after 8.5 h: Two reaction mixtures were prepared by adding fresh crystals of *p*-TsOH@MMF (ca. 0.5 mg, 0.1 μmol of *p*-TsOH in MMF, 0.3 mol%) and $CDCl_3$ solutions of (*S*)-citronellal (30 mM, 1.0 mL, 30 μmol) to two NMR tubes. Both mixtures were shaken with a shaker at room temperature and monitored by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal was assessed against an internal standard of 1,1,2,2-tetrachloroethane. After 8.5 h, nerol (30 μmol, 100 mol%) was added to one of the reaction mixtures. ^{1}H NMR measurements revealed that the reaction of (*S*)-citronellal with *p*-TsOH@MMF was notably inhibited by adding 100 mol% of nerol.

Procedure for the reaction with p-TsOH·H₂O: A $CHCl_3$ solution of *p*-TsOH·H_2O (3 mM, 0.1 mL, 0.3 μmol) and a $CDCl_3$ solution of (*S*)-citronellal and nerol (0.9 mL; (*S*)-citronellal: 33 mM, 29.7 μmol; nerol: 33 mM, 29.7 μmol, 100 mol%) (or 0.9 mL; (*S*)-citronellal: 33 mM, 29.7 μmol; nerol: 1.1 mM, 1 μmol, 3 mol%) were added to an NMR tube. This mixture was shaken with a shaker at room temperature for 24 h, and then analyzed by ^{1}H NMR measurement. The conversion ratio of (*S*)-citronellal and nerol, and the yield of main products were assessed against an internal standard of 1,1,2,2-tetrachloroethane.

Treating (*S*)-citronellal and 100 mol% nerol with *p*-TsOH·H_2O resulted in 99% conversion of (*S*)-citronellal and 89% conversion of nerol. Treating (*S*)-citronellal and 3 mol% nerol with *p*-TsOH·H_2O resulted in 98% conversion of (*S*)-citronellal.

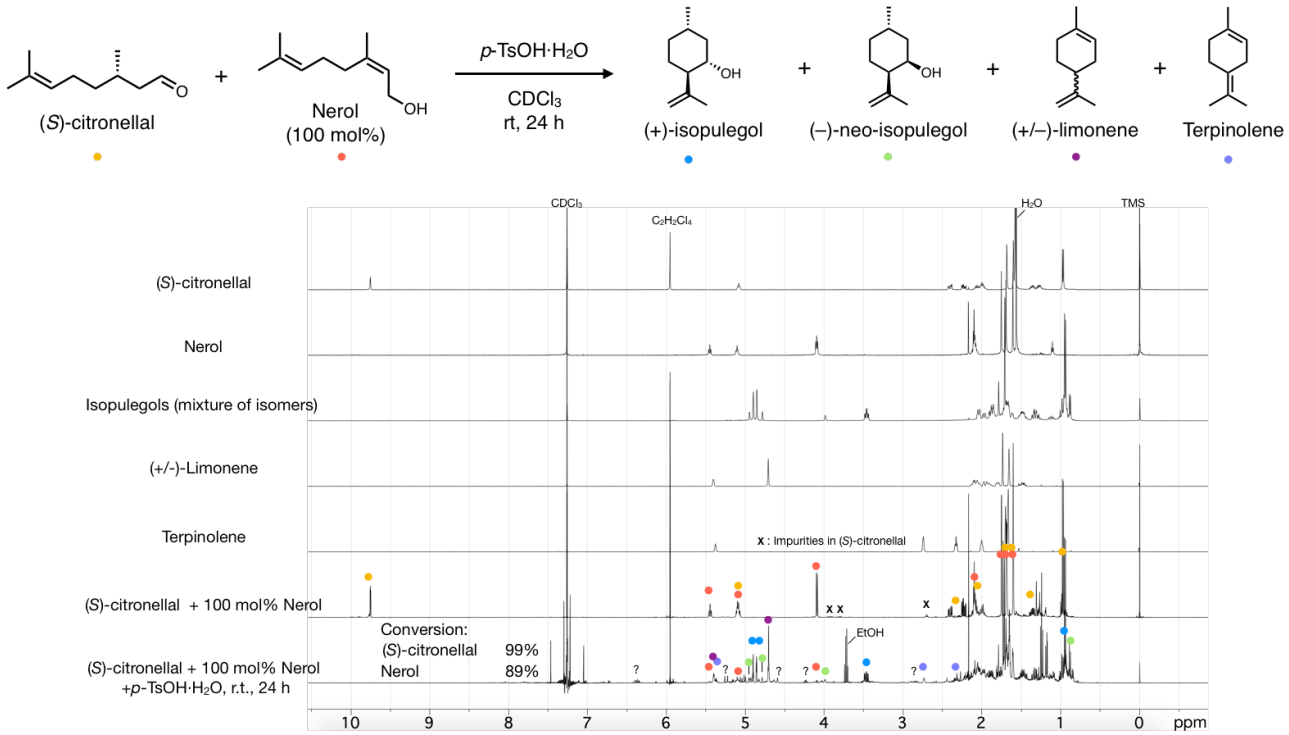


Fig. S42 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, nerol, isopulegols, (+/–)-limonene, terpinolene, the mixture of (*S*)-citronellal and 100 mol% nerol, and the mixture with *p*-TsOH·H_2O in $CDCl_3$ after 24 h at room temperature.

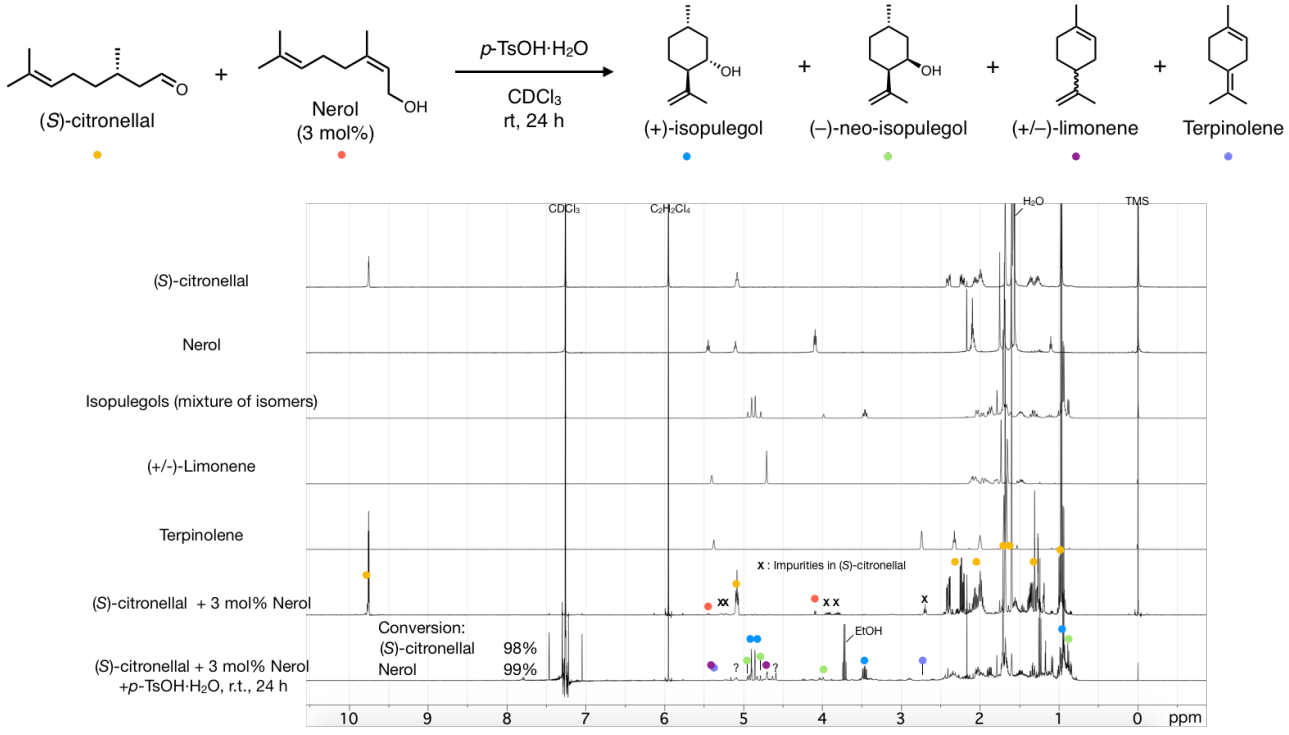


Fig. S43 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 300 K) for (*S*)-citronellal, nerol, isopulegols, (+/–)-limonene, terpinolene, the mixture of (*S*)-citronellal and 3 mol% nerol, and the mixture with *p*-TsOH·H_2O in $CDCl_3$ after 24 h at room temperature.

8. References

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