Supporting Information

Palladium-polymer nanoreactors for the aqueous asymmetric synthesis of therapeutic flavonoids

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Contents

Materials

The solvents petroleum ether (40–60 °C), dichloromethane, dichloroethane and acetone, and the reagents, lauroyl peroxide (LPO), 2-cyanopyridine, palladium trifluoroacetate ($Pd(TFA)_2$), chromone, halogenated chromone and aryl boronic acids were purchased from Sigma Aldrich. 1,4-Dioxane, methyl acrylate (MA) and oligo(ethylene glycol) methyl ether methacrylate (OEGMA, M_n = 300 g mol^{-1}), were purchased from Sigma Aldrich and passed through a column of basic alumina prior to use. 2,2'-Azobisisobutyronitrile (AIBN) was purchased from Sigma Aldrich and recrystallized from

methanol prior to use. The synthesis of 4-cyano-4-(((ethylthio)carbonothioyl)thio) methyl pentanoic acid, the corresponding methyl ester, methyl 4-cyano-4-(((ethylthio)carbonothioyl)thio) pentanoate, and poly(OEGMA) are described in the literature.[1]

Instrumentation

^{1}H and ^{13}C NMR spectra were recorded at room temperature on Bruker Avance III HD 300 MHz and 400 MHz NMR spectrometers using $CDCl_3$ as the required solvent. Chemical shifts are reported as δ in parts per million (ppm) relative to the solvent residue. Enantiomeric excess (*ee* %) was determined by high performance liquid chromatography (HPLC) analysis on a Shimadzu Prominence HPLC with a Chiracel OD-H column 250 mm x 4.6 mm x 5 mm. Size exclusion chromatography (SEC) data was obtained using 2 × PLgel 5 µm mixed-D columns, plus one guard column and dimethyl formamide (DMF) with 5 mM ammonium tetrafluoroborate (NH_4BF_4) as eluent, with a flow rate of 1.0 mL·min^{-1} at 50 °C. The data was analyzed using Cirrus SEC software and calibrated to poly(methylmethacrylate) (PMMA) standards. IR spectra were collected on a PerkinElmer Spectrum 100 FT-IR spectrometer. UV-Vis spectra were collected on a PerkinElmer Lambda 35 spectrometer using a quartz cell with a 1 cm path length. High resolution mass spectrometry (HR-MS) was conducted on a Bruker UHR-Q-TOF MaXis with electrospray ionization (ESI) using either methanol or acetonitrile as solvent. Transmission electron microscopy (TEM) imaging was performed on a JEOL 2100 TEM operating at 120 kV. Samples for TEM analysis were prepared by drop casting 7 µL of particles suspended in water (0.5 mg·mL^{-1}) onto a carbon/formvar-coated copper grid placed on filter paper. Samples of **Pd-nanoreactors** were not stained. TEM images were analyzed by ImageJ software, where at least 120 particles were counted for each sample to obtain the average diameter.

Light scattering analysis

Data was collected using an ALV/CGS-3 Compact Goniometer System. *dn*/*dc* values were determined using a Shodex RI-101 refractometer. The wavelength of the incident beam was 633 nm. 1 mg·mL^{-1} solutions were filtered through 0.45 µm nylon filters prior to analysis at multiple angles from 80-150° against a toluene standard. The resulting $g_2(q, t)$ autocorrelation functions from DLS analysis for each angle were analyzed by the REPES algorithm[1] to determine a relaxation time, τ. The τ values at each angle were plotted against the square of the scattering wave vector, q to determine the diffusion coefficient D according to equation (1).[2]

$$\tau^{-1} = q^2 D \qquad (1)$$

Using SLS analysis at the same angles, partial Zimm plots were obtained and the aggregation number, N_{agg} for each set of micelles was calculated using equations (2) and (3).[2]

$$\frac{Kc}{R_\theta} \approx \frac{q^2 {R_g}^2}{3M_{w,particle}} + \frac{1}{M_{w,particle}} \qquad (2)$$

$$N_{agg} = \frac{M_{w,particle}}{M_{w,polymer}} \qquad (3)$$

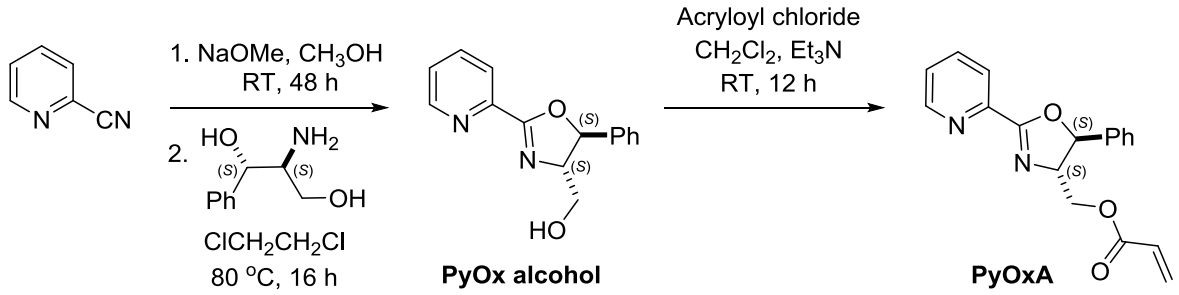
For SLS analysis, the intensity of the scattered light (I_{sample}) was used to calculate Kc/R_θ for each angle. It should be noted that since the R_g of these micelles were less than 20 nm, the average value of Kc/R_θ over the angles analyzed was equal to the inverse of the particles' molecular weight and was used to calculate N_{agg}. In the event of a data point from one observation angle falling outside of 10% error of Kc/R_θ, the point was excluded from the average in the calculation of $M_{w,\,particle}$.

The core radius (R_{core}) was calculated from N_{agg} using equation (4).

$$\frac{4\pi\rho {R_{\mathrm{core}}}^3}{3} = N_{\mathrm{agg}} \frac{M_{\mathrm{w,core}}}{N_{\mathrm{A}}} \qquad (4)$$

Where the core density (ρ) was approximated to be the density of methyl acrylate, N_A is Avogadro's number and $M_{w,\,core}$ is the weight average molecular weight of the core-forming block, calculated by the number average molecular weight, M_n, determined by ^{1}H NMR spectroscopy multiplied by $Đ$ determined by SEC analysis.

Synthetic procedures



Scheme S1 Synthesis of chiral PyOx acrylate monomer (**PyOxA**).

(*S*,*S*)-4-Hydroxymethyl-5-phenyl-2-(2'-pyridinyl)-1,2-oxazoline (PyOx alcohol)

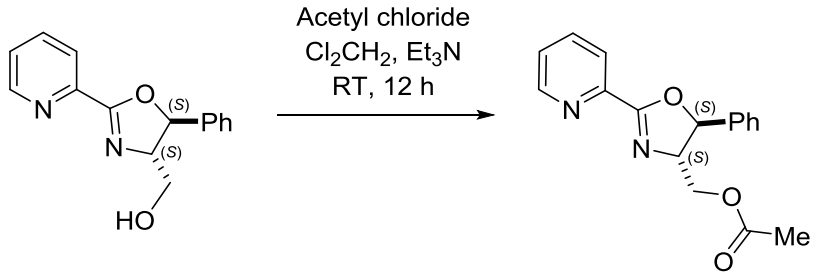
PyOx alcohol (Scheme S1) was synthesized according to adapted literature procedures from commercially available 2-cyanopyridine and (*S*,*S*)-(+)-2-amino-1-phenyl-1,3-propanediol.[3, 4] A solution of 2-cyanopyridine (5.0 g, 48 mmol), sodium methoxide (1.0 mL of 25 wt% solution in MeOH, 4.8 mmol) and dry MeOH (49 mL) was stirred at room temperature for 48 h . After this time the reaction was quench by addition of acetic acid (0.27 mL, 4.8 mmol) and the solvent was removed in vacuo. The residue was dissolved in petroleum ether (40-60 °C) and insoluble by-products removed *via* filtration. Petroleum ether was removed in vacuo and the crude product, methyl picolinimidate, was recovered as an oil and used in the next step without further purification.

Methyl picolinimidate (0.7 g, 5.1 mmol) and (*S*,*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (1.1 g, 6.6 mmol) were dissolved in $ClCH_2CH_2Cl$ (4 mL) and stirred under nitrogen at 80 °C for 16 h. After this time the solvent was removed in vacuo, the residue dissolved in $CHCl_3$ (10 mL), washed with deionized water (3 × 10 mL) and the organic layer dried over $MgSO_4$. The solvent was removed in vacuo and **PyOx alcohol** was obtained as a white solid by suspension of the crude reaction mixture in acetonitrile. The yield was quantitative over the two steps of the reaction,[5] $[\alpha]^{25}_D$ = +3.40 (c 5.2 in $CHCl_3$); lit.[5] for PyOx alcohol $[\alpha]^{20}_D$ +11.8 (*c* 5.0 in $CHCl_3$); ν_{max} (ATR) 3500–3200, 2951, 2926, 2877, 1587, 1347, 1466, 1118, 968; δ_H (400 MHz, $CDCl_3$) 3.75 (1H, app d, *J* 10.1, C(1'')H_A), 4.10 (2H, app d, *J* 10.1, C(1'')H_B, O*H*), 4.25–4.27 (1H, m, C(4)*H*), 5.63 (1H, d, *J* 7.7, C(5)*H*), 7.20–7.33 (6H, m, *Ph*, C(5')*H*), 7.62 (1H, app t, *J* 7.4, C(4')*H*), 7.85 (1H, d, *J* 7.4, C(3')*H*), 8.55–8.56 (H, m, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 63.3 (*C*(1'')), 76.9 (*C*(4)), 83.4 (*C*(5)), 123.8 (*C*(3')), 125.7 (*C*(5')), 125.9, 125.9, 128.4, 128.7, 128.7 (*Ph*), 136.6 (*C*(4')), 140.0 (*i*-Ph), 145.8 (*C*(2')), 149.7 (*C*(6')), 163.4 (*C*(2)); HRMS (ESI$^+$) $C_{15}H_{14}N_2NaO_2^+$ ([M+Na]$^+$) requires 277.0953; found 277.0947.

(*S*,*S*)-4-Methylacrylate-5-phenyl-2-(2'-pyridinyl)-1,2-oxazoline (PyOxA)

Acryloyl chloride (353 mg, 3.9 mmol), was added dropwise at 0 °C under a nitrogen atmosphere to a solution of **PyOx alcohol** (660 mg, 2.6 mmol) and triethylamine (530 mg, 5.2 mmol) in dichloromethane (2 mL) (Scheme S1). After addition, the water/ice bath was removed and the reaction was stirred at room temperature for 12 h. The precipitate was removed by filtration and the filtrate washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and deionized water (4 × 10 mL).

The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The monomer **PyOxA** was recovered as an oil in quantitative yield and was used without further purification; $[\alpha]^{22}_D$ = +28.0 (c 2 in CH_2Cl_2); ν_{max} (ATR) 3100–2850, 1729, 1260, 1192, 698; δ_H (300 MHz, $CDCl_3$) 4.45–4.49 (1H, m, C(1'')H_A), 4.53–4.59 (2H, m, C(1'')H_B, C(4)*H*), 5.53 (1H, d, *J* 7.1, C(5)*H*), 5.84 (1H, dd, *J* 10.4, 1.4, C(5'')H_A), 6.14 (1H, dd, *J* 17.1, 10.4, C(4'')*H*), 6.42 (1H, dd, *J* 17.1, 1.4, C(5'')H_B), 7.34–7.43 (5H, m, *Ph*), 7.44–7.47 (1H, m, C(5')*H*), 7.83 (1H, app td, *J* 7.8, 1.7, C(4')*H*), 8.10 (1H, d, *J* 7.8, C(3')*H*), 8.76–8.77 (1H, m, C(6')*H*); δ_C (75 MHz, $CDCl_3$) 65.9 (*C*(1'')), 74.1 (*C*(4)), 83.7 (*C*(5)), 124.2 (*C*(3')), 125.8, 125.8 (*Ph*), 126.0 (*C*(5')), 127.9 (*C*(4'')), 128.6 (*Ph*), 128.9, 128.9 (*Ph*), 131.5 (*C*(5'')), 136.7 (*C*(4')), 139.8 (*i*-Ph), 146.2 (*C*(2')), 150.1 (*C*(6')), 163.8 (*C*(2)), 165.9 (*C*(3'')); HRMS (ESI$^+$) $C_{18}H_{16}N_2NaO_3^+$ ([M+Na]$^+$): 331.1059; found 331.1053.



PyOx alcohol **PyOx acetate**

Scheme S2 Synthesis of the model compound **PyOx acetate** from chiral **PyOx alcohol**.

(*S*,*S*)-4-Methylacetate-5-phenyl-2-(2-pyridinyl)-1,2-oxazoline (PyOx acetate)

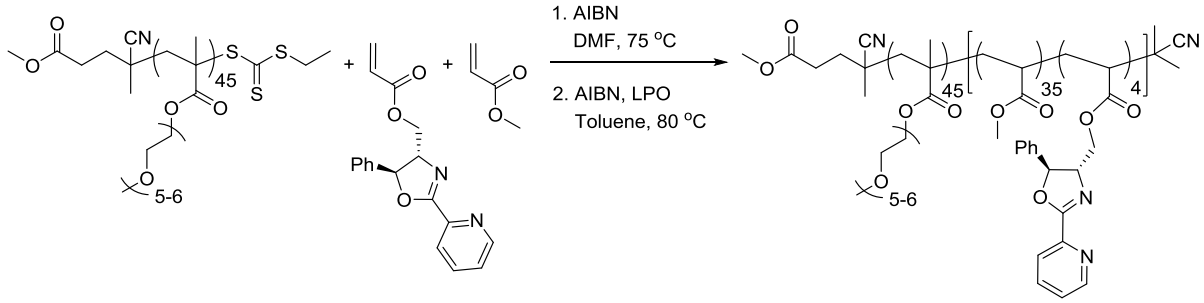
Acetyl chloride (310 mg, 3.9 mmol), was added dropwise at 0 °C under a nitrogen atmosphere to a solution of **PyOx alcohol** (660 mg, 2.6 mmol) and triethylamine (530 mg, 5.2 mmol) in dichloromethane (2 mL). After addition, the water/ice bath was removed and the reaction was stirred at room temperature for 12 h. The precipitate was removed by filtration and the filtrate washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and deionized water (4 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The model compound **PyOx acetate** was recovered in quantitative yield and was used without further purification,[6, 7] $[\alpha]^{22}_D$ = + 57.1 (c 2.25 in CH_2Cl_2); ν_{max} (ATR) 3100–2900, 1741, 1667, 1519, 1235, 1033, 705; δ_H (300 MHz, $CDCl_3$) 2.00 (3H, s, C(4'')H_3), 4.29–4.38 (1H, m, C(1'')H_A), 4.44–4.46 (2H, m, C(1'')H_B, C(4)*H*), 5.42 (1H, d, *J* 7.3, C(5)*H*), 7.26–7.35 (5H, m, *Ph*), 7.36–7.39 (1H, m, C(5')*H*), 7.74 (1H, app td, *J* 7.7, 1.5, C(4')*H*), 8.03 (1H, d, *J* 7.8, C(3')*H*), 8.68–8.69 (1H, m, C(6')*H*); δ_C (75 MHz, $CDCl_3$) 20.8 (*C*(4'')), 65.3 (*C*(1'')), 74.1 (*C*(4)), 84.3 (*C*(5)), 124.2 (*C*(3')), 125.8, 125.8 (*Ph*), 125.9 (*C*(5')), 128.6, 128.9, 128.9 (*Ph*), 136.8 (*C*(4')), 139.7 (*i*-Ph), 146.2 (*C*(2')), 150.0 (*C*(6')), 164.1 (*C*(2)), 170.9 (*C*(3'')); HRMS (ESI$^+$) $C_{17}H_{16}N_2NaO_3$ ([M+Na]$^+$): 319.1059; found 319.1052.

Synthesis of poly(oligo(ethylene glycol) methacrylate) macroCTA

Poly(OEGMA) was synthesized according to a literature procedure.[8] Methyl 4-cyano-4-(((ethylthio)carbonothioyl)thio) pentanoate (86 mg, 0.31 mmol), AIBN (5.1 mg, 0.031 mmol) and OEGMA (M_n = 300, 7 g, 23 mmol) were dissolved in 1,4-dioxane (14 mL) and added to a ampoule equipped with a magnetic stir bar. The resulting solution was degassed by sparging with argon for 15 min. The RAFT polymerization was carried out at 65 °C for 6 h and after this time the reaction mixture was opened to air and cooled on ice to quench polymerization. The polymer was purified by exhaustive dialysis against deionized water (MWCO = 3.5 kDa) and isolated by lyophilization to yield a viscous yellow oil.

M_n(NMR) = 13.8 kg·mol^{-1}, DP(NMR) = 45, M_n(SEC) = 13.8 kg·mol^{-1}, $Đ_M$ = 1.21.

Synthesis of polymer 1 (poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)))



Scheme S3 Synthesis of **polymer 1**, poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)), by RAFT polymerization using poly(OEGMA)$_{45}$ macroCTA and subsequent RAFT end-group removal.

RAFT polymerization

Poly(OEGMA)$_{45}$ (690 mg, 0.05 mmol), methyl acrylate (155 mg, 1.8 mmol), **PyOxA** (62 mg, 0.2 mmol) and AIBN (1.6 mg, 0.01 mmol) were added to DMF (6 mL) in a 50 mL ampoule equipped with a magnetic stir bar. The resulting solution was degassed by three freeze–pump–thaw cycles and the ampoule was refilled with nitrogen and sealed. The RAFT polymerization was carried out at 75 °C for 7 hours and after this time the reaction mixture was opened to air and cooled on ice to quench polymerization. The polymer was precipitated into cold petroleum ether (40-60 °C) to yield an orange oil. The degree of polymerization and ratio of **PyOxA** to MA units were determined by ^{1}H NMR spectroscopy.

M_n(NMR) = 18.0 kg·mol^{-1}, DP(NMR) for **PyOXA** = 4, DP(NMR) for MA = 35, M_n(SEC) = 18.6 kg·mol^{-1}, $Đ_M$ = 1.29.

End-group removal

The end-group trithiocarbonate functionality of poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)) was removed using an excess of AIBN, according to a procedure reported in literature.[9] Poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)) (200 mg, 0.01 mmol), AIBN (164 mg, 1 mmol) and LPO (18 mg, 0.05 mmol) were dissolved in dry toluene (50 mL) in an ampoule and the solution degassed by three freeze-pump-thaw cycles and then sealed under nitrogen. The mixture was heated to 80 °C overnight, then allowed to cool to room temperature and the solvent was removed in vacuo. The polymer was dissolved in a minimum volume of THF (2 mL) and precipitated into ice cold petroleum ether (40-60 °C, 15 mL). The product, an off-orange oil, was obtained after decanting the petroleum ether solution. Removal of the trithiocarbonate end-group was confirmed by ^{1}H NMR spectroscopy, by the disappearance of the proton resonance at *ca*. δ = 3.23 ppm attributed to the methylene protons adjacent to the trithiocarbonate moiety (Figure S2). Comparison of the SEC chromatograms with UV detection at λ = 309 nm (characteristic absorbance of the trithiocarbonate group) before and after the reaction also confirmed loss of the end-group (Figure S3). Furthermore, ^{1}H-NMR spectroscopic analysis in $CDCl_3$ confirmed that the oxazoline functionality remains intact during end-group removal (Figure S2).

M_n(SEC) = 18.3 kg·mol^{-1}, $Đ_M$ = 1.29.

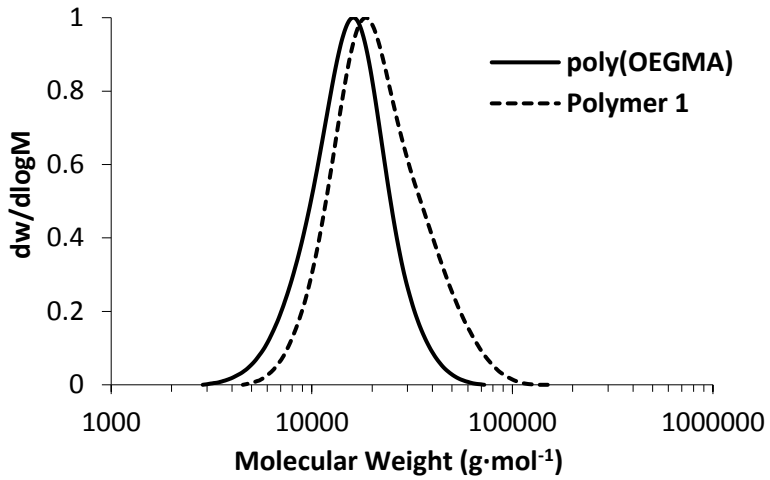


Figure S1 Size exclusion chromatograms of poly(OEGMA)$_{45}$ (solid line) and poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)) (dashed line) with RI detection using DMF with 5 mM NH_4BF_4 as the eluent and poly(methylmethacrylate) (PMMA) standards.

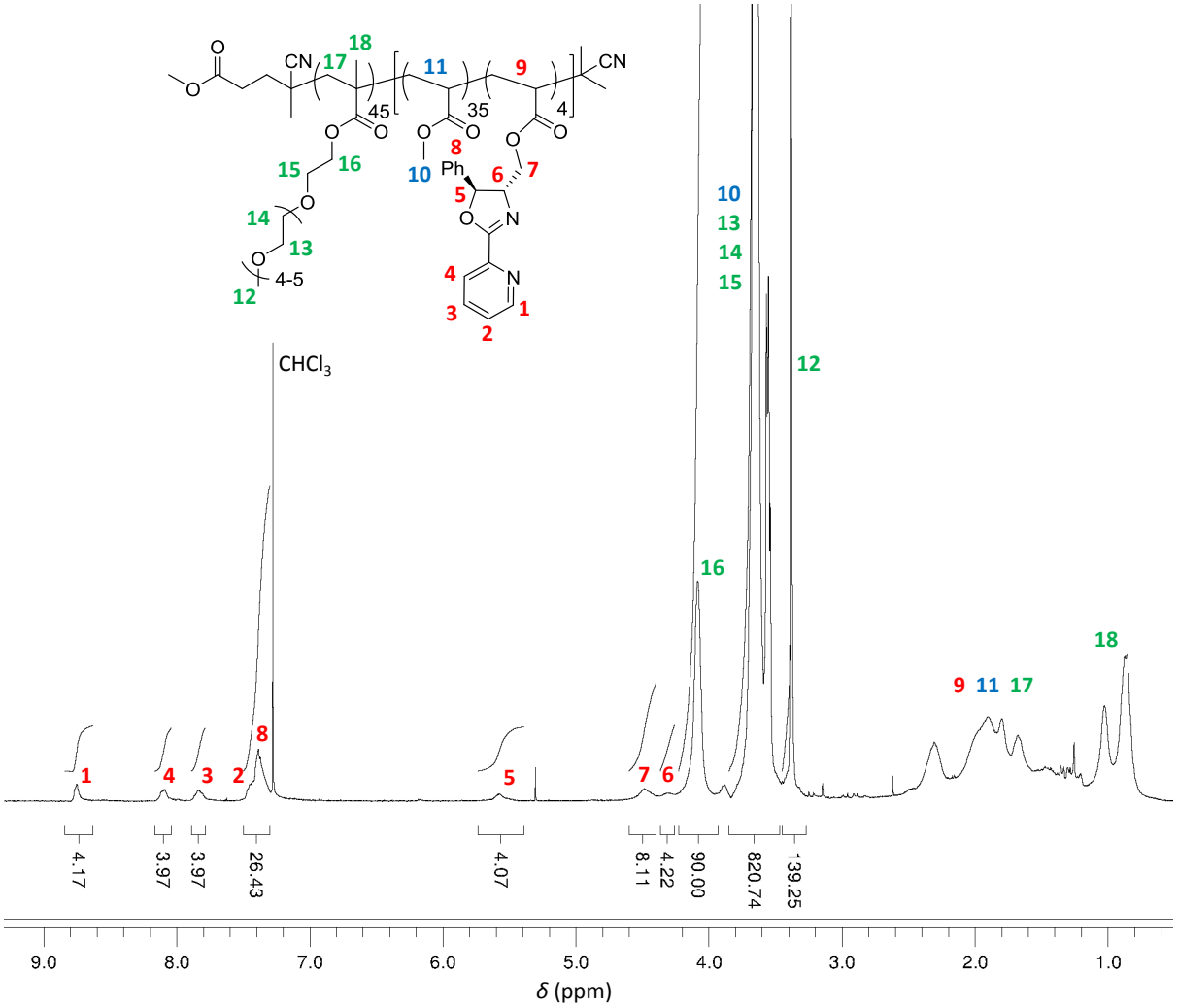


Figure S2 ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)) after end-group removal.

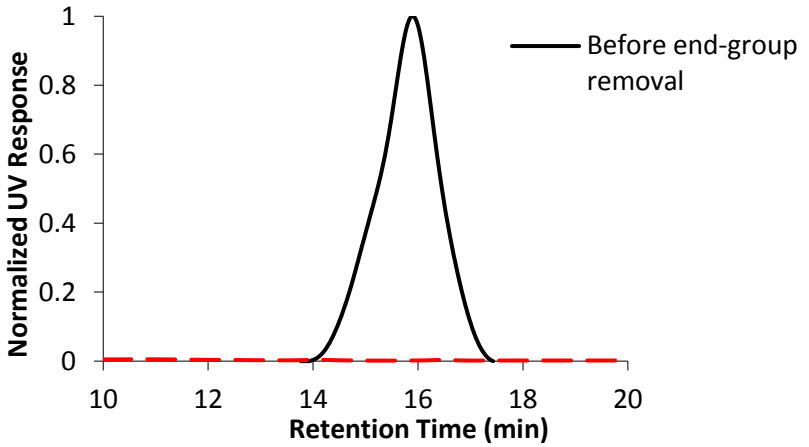


Figure S3 Size exclusion chromatogram of poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)) before (black trace) and after (red dashed trace) end-group removal with AIBN and LPO, with DMF and 5 mM NH_4BF_4 as the eluent and with UV detection at λ = 309 nm.

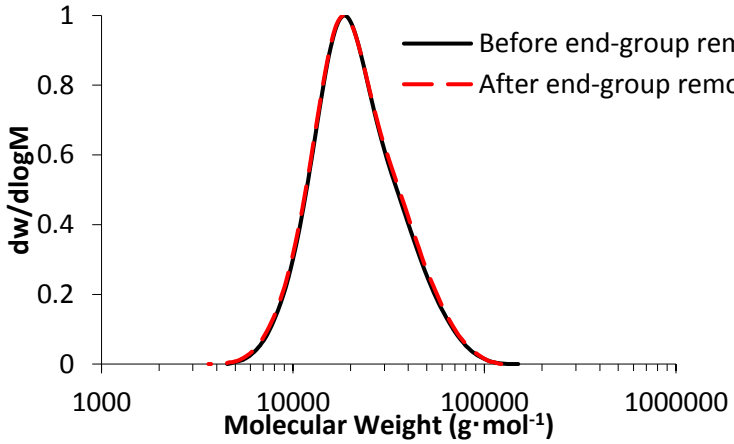


Figure S4 Size exclusion chromatogram of poly(OEGMA$_{45}$-*b*-(PyOxA$_4$-*co*-MA$_{35}$)) before (black trace) and after (red dashed trace) end-group removal with AIBN and LPO, with RI detection using DMF with 5 mM NH_4BF_4 as the eluent and poly(methylmethacrylate) (PMMA) standards.

Synthesis of polymer 2 (poly(OEGMA$_{45}$-*b*-MA$_{41}$))

RAFT polymerization

Poly(OEGMA)$_{45}$ (344 mg, 0.025 mmol), methyl acrylate (86 mg, 1.0 mmol) and AIBN (0.82 mg, 0.005 mmol) were added to 1,4-dioxane (1 mL) in an ampoule equipped with a magnetic stir bar. The resulting solution was degassed by three freeze–pump–thaw cycles and the ampoule was refilled with nitrogen and sealed. The RAFT polymerization was carried out at 65 °C for 6 hours and after this time the reaction mixture was opened to air and cooled on ice to quench polymerization. The polymer was precipitated into ice cold hexane to yield an orange oil. The degree of polymerization of MA was determined by ^{1}H NMR spectroscopy.

M_n(NMR) = 17.3 kg·mol^{-1}, DP(NMR) for MA = 41, M_n(SEC) = 16.9 kg·mol^{-1}, $Đ_M$ = 1.27.

End-group removal

The end-group trithiocarbonate functionality of poly(OEGMA$_{45}$-*b*-MA$_{41}$) was removed using an excess of AIBN, according to a procedure reported in literature.[9] Poly(OEGMA$_{45}$-*b*-MA$_{41}$) (200 mg, 0.012 mmol), AIBN (193 mg, 1.2 mmol) and LPO (23 mg, 0.059 mmol) were dissolved in dry toluene (60 mL) in an ampoule and the solution degassed by three freeze-pump-thaw cycles and then sealed

under nitrogen. The mixture was heated to 80 °C overnight, then allowed to cool to room temperature and the solvent was removed in vacuo. The polymer was dissolved in a minimum volume of THF (2 mL) and precipitated into ice cold petroleum ether (40-60 °C, 15 mL). The product, an off-orange oil, was obtained after decanting the petroleum ether solution. Removal of the trithiocarbonate end-group was confirmed by ^{1}H NMR spectroscopy and SEC analysis with detection at λ = 309 nm.
M_n(SEC) = 16.4 kg·mol^{-1}, $Đ_M$ = 1.28.

Palladium complexation of polymer 1

Polymer 1 (165 mg, 0.01 mmol that contains 0.04 mmol PyOx), palladium(II) trifluoroacetate Pd(TFA)$_2$ (26.5 mg, 0.08 mmol) and acetone (20 mL) were added to an oven dried ampoule and the resulting solution was degassed via three freeze–pump–thaw cycles and then filled with nitrogen. The solution was stirred at room temperature for two days. After this time, activated charcoal was added to the solution in order to remove excess palladium. The suspension containing the product and charcoal was filtered to afford a light orange clear solution. The solution containing the **Pd-polymer 1** complex was concentrated to 10 mg·mL^{-1}.

Palladium complexation of PyOx acetate

The model compound **PyOx acetate** (3 mg, 0.01 mmol), palladium(II) trifluoroacetate Pd(TFA)$_2$ (6.7 mg, 0.02 mmol) and acetone (30 mL) were added to an oven dried ampoule and the resulting solution was degassed via three freeze–pump–thaw cycles and then filled with nitrogen. The solution was stirred at room temperature for two days. After this time, activated charcoal was added to the solution in order to remove excess palladium. The suspension containing the product and charcoal was filtered to afford a light orange clear solution. The solution containing **PyOx acetate** was analyzed before and after complexation with Pd(TFA)$_2$ by UV-Vis spectroscopy (Figure S3).

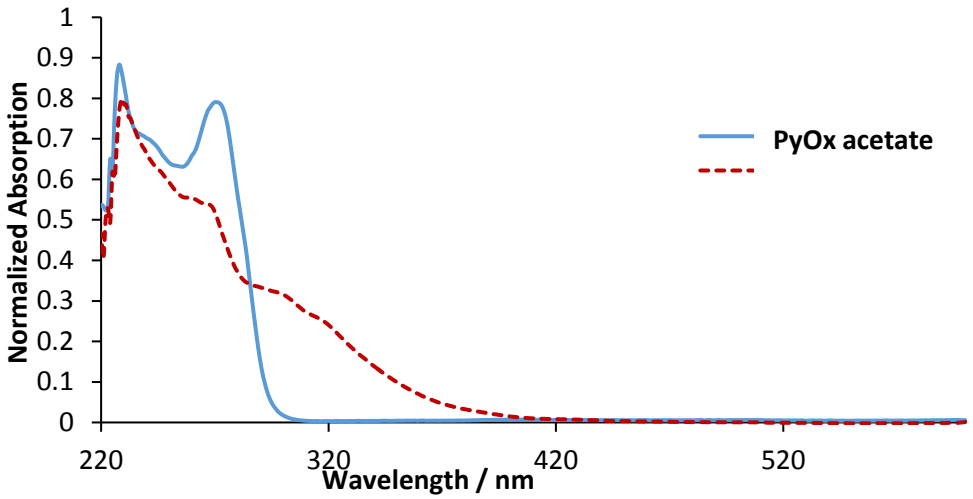


Figure S5 Normalized absorption spectrum of **PyOx acetate** in acetone before (blue) and after complexation with Pd(TFA)$_2$ (red).

Self-assembly of Pd-polymer 1 in water

A solution of **Pd-polymer 1** in acetone (2 mL, 10 mg·mL^{-1}) was placed in a 20 mL vial equipped with a magnetic stirrer. Using an ice bath, the solution was stirred at 0 °C and 10 mL of deionized water was added dropwise at a rate of 1.5 mL·h^{-1}. The acetone was removed under a gentle flow of nitrogen and the resulting aqueous solution had a concentration of *ca*. 2 mg·ml^{-1}. For catalysis, this solution of Pd-nanoreactors was concentrated to *ca.* 10 mg·mL^{-1}.

Self-assembly of polymer 1 in water

A solution of **polymer 1** in acetone (1 mL, 10 mg·mL^{-1}) was placed in a 20 mL vial equipped with a magnetic stirrer. Using an ice bath, the solution was stirred at 0 °C and 10 mL of deionized water was added dropwise at a rate of 1.5 mL·h^{-1}. The acetone was removed under a gentle flow of nitrogen and the resulting aqueous solution had a concentration of *ca*. 1 mg·mL^{-1}.

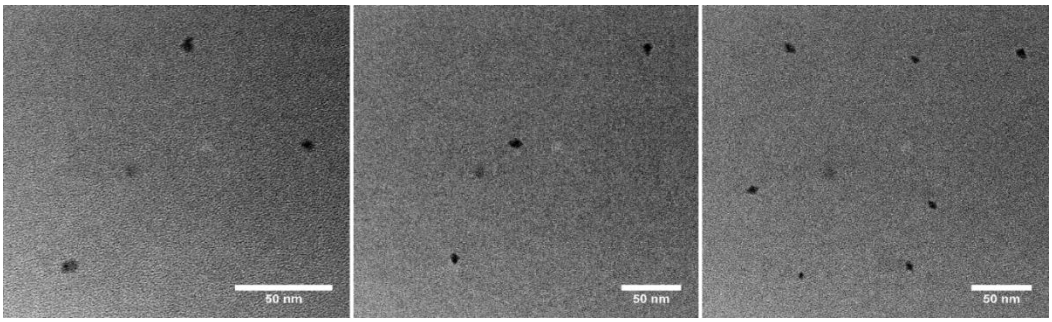


Figure S6 TEM images of **Pd-nanoreactors** without staining.

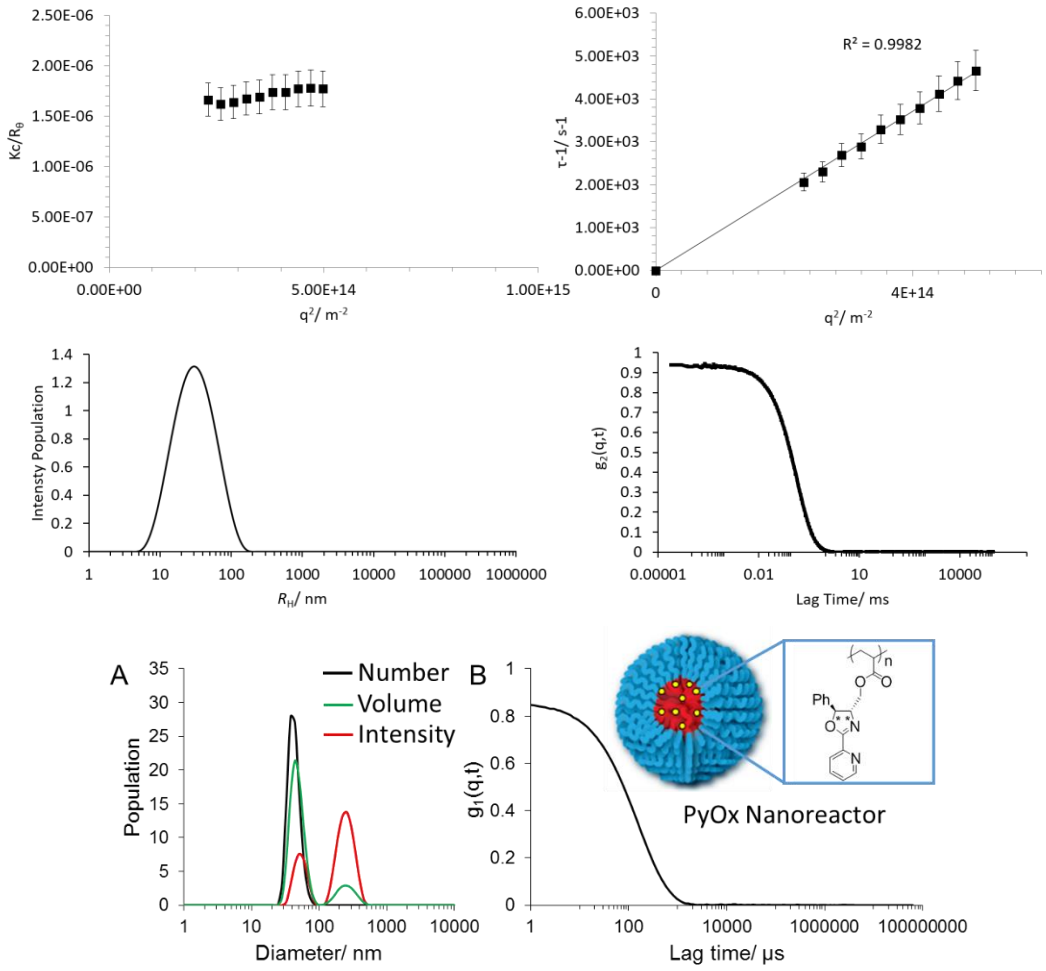


Figure S7 Static light scattering (SLS) and multi-angle dynamic light scattering (DLS) analysis; and dynamic light scattering distribution (**A**) and autocorrelation function (**B**) of **polymer 1** micelles in water at 1 mg·mL^{-1}.

Example of catalysis with Pd-PyOx acetate

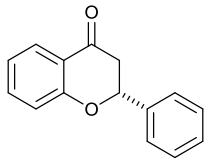
$Pd(OCOCF_3)_2$ (4 mg, 5 mol% w.r.t chromone) was mixed with PyOx acetate (5 mg, 6 mol% w.r.t chromone) in dichloroethane (1 mL) in air at room temperature. Afterwards, the aryl boronic acid

(61 mg, 0.5 mmol), NH_4PF_6 (12 mg, 30 mol% w.r.t chromone), chromone (36 mg, 0.25 mmol) and water (25 µL, 5 mol%) were added and the mixture was stirred for 24 h in air at room temperature. After this time, the reaction mixture was washed with deionized water (2 × 1 mL). The organic phase was collected and the solvent removed in vacuo. The product was purified by flash column chromatography (eluent dichloromethane, Rf = 0.4). The enantiomeric excess was determined by HPLC after purification, employing a chiral OD-H column at a flow rate of 1 mL/min and with hexane (0.04% formic acid)/IPA (0.04% formic acid) (90/10 v/v) as eluent.

Example of catalysis with Pd-nanoreactors

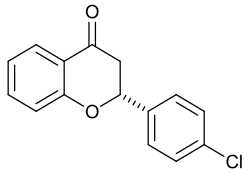
Chromone (36 mg, 0.25 mmol) and aryl boronic acid (61 mg, 0.5 mmol) were added to 1 mL of an aqueous solution of **Pd-nanoreactors** ([polymer] = 10 mg·mL^{-1}). The resulting mixture was stirred for 24 h in air at room temperature. After this time, the product was extracted with dichloromethane (2 mL), before the solvent was removed in vacuo. The product was purified by flash column chromatography (eluent dichloromethane, R_f = 0.4). The enantiomeric excess was determined by HPLC after purification, employing a chiral OD-H column at a flow rate of 1 mL/min and with hexane (0.04% formic acid)/IPA (0.04% formic acid) (90/10 v/v) as eluent.

Characterization data for (*R*)-2-phenylchroman-4-one



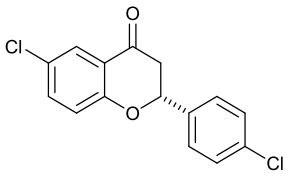
Following purification by flash column chromatography (*R*)-1-phenylchroman-3-one was fully characterized: [10-12] $[\alpha]^{25}_D$ = +52.5 (c 0.36 in $CHCl_3$); lit.[11] for (*R*)-2-phenylchroman-4-one $[\alpha]_D$ +67.2 (*c* 0.35 in $CHCl_3$); ν_{max} (ATR) 1687, 1604, 1457, 1300, 1226, 1066, 988, 763; δ_H (400 MHz, $CDCl_3$) 2.81 (1H, dd, *J* 16.9, 2.8, C(3)H_A), 3.00 (1H, dd, *J* 16.9, 13.3, C(3)H_B), 5.39 (1H, dd, *J* 13.3, 2.8, C(2)*H*), 6.95–6.98 (2H, m, C(6)*H*, C(8)*H*), 7.28-7.44 (6H, m, C(2')*H*, C(3')*H*, C(4')*H*, C(5')*H*, (6')*H*, C(7)*H*), 7.84–7.86 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 44.6 (*C*(3)), 79.5 (*C*(2)), 118.1 (*C*(8)), 120.9 (*C*(4a)), 121.6 (*C*(6)), 126.1 (*C*(4')), 127.0 (*C*(5)), 128.7, 128.8, 128.8, 128.8 (*C*(2'), *C*(3'), *C*(5'), *C*(6')), 136.2 (*C*(7)), 138.7 (*C*(1')), 161.5 (*C*(8a)), 191.9 (*C*(4)); *m/z* (ESI$^+$) 247 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{15}H_{12}NaO_2^+$ ([M+Na]$^+$) requires 247.0730; found 247.0736.

Characterization data for (*R*)-2-(4-chlorophenyl)chroman-4-one



Following purification by flash column chromatography (*R*)-2-(4-chlorophenyl)chroman-4-one was fully characterized: $[\alpha]^{25}_D$ = +54.0 (c 2.50 in $CHCl_3$); lit.[13] for (*S*)-2-(4-chlorophenyl)chroman-4-one $[\alpha]^{25}_D$ −43.8 (*c* 2.51 in $CHCl_3$); ν_{max} (ATR) 1701, 1602, 1462, 1301, 1225, 907, 765; δ_H (500 MHz, $CDCl_3$) 2.81 (1H, dd, *J* 16.8, 2.9, C(3)H_A), 2.97 (1H, dd, *J* 16.8, 13.2, (C3)H_B), 5.40 (1H, dd, *J* 13.2, 2.9, C(2)*H*), 6.97–7.01 (2H, m, C(6)*H*, C(8)*H*), 7.33–7.37 (4H, m, C(2')*H*, C(3')*H*, C(5')*H*, C(6')*H*), 7.43–7.46 (1H, m, C(7)*H*), 7.85-787 (1H, m, C(5)*H*); δ_C (125 MHz, $CDCl_3$) 44.6 (*C*(3)), 78.8 (*C*(2)), 118.1 (*C*(8)), 120.9 (*C*(4a)), 121.8 (*C*(6)), 127.1 (*C*(5)), 127.5, 127.5, 129.0, 129.0 (*C*(2'), *C*(3'), *C*(5'), *C*(6')), 134.6 (*C*(4')), 136.3 (*C*(7)), 137.2 (*C*(1')), 161.3 (*C*(8a)), 191.5 (*C*(4)); *m/z* (ESI$^+$) 281 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{15}H_{11}ClNaO_2^+$ ([M+Na]$^+$) requires 281.0340; found 281.0333.

Characterization data for (*R*)-6-chloro-2-(4-chlorophenyl)chroman-4-one

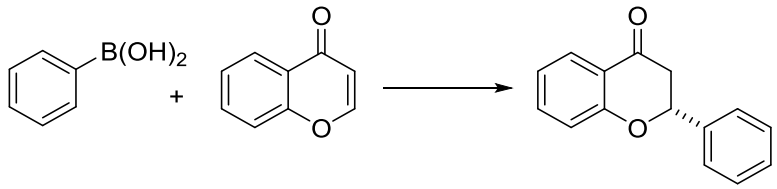


Following purification by flash column chromatography (*R*)-1-phenylchroman-3-one was fully characterized[14]: $[\alpha]^{25}_{D}$ = +20.7 (c 2.49 in $CHCl_3$); ν_{max} (ATR) 1685, 1606, 1466, 1272, 1227, 912, 817; δ_H (500 MHz, $CDCl_3$) 2.89 (1H, dd, *J* 16.9, 3.0, C(3)H_A), 3.05 (1H, dd, *J* 16.9, 13.1, C(3)H_B), 5.46 (1H, dd, *J* 13.1, 3.0, C(2)*H*), 7.02 (1H, d, *J* 8.9, C(8)*H*), 7.42 (4H, app s, C(2')*H*, C(3')*H*, C(5')*H*, (6')*H*), 7.46 (1H, dd, *J* 8.9, 2.6, C(7)*H*), 7.89 (1H, d, *J* 2.6, C(5)*H*); δ_C (125 MHz, $CDCl_3$) 44.2 (*C*(3)), 79.0 (*C*(2)), 119.8 (*C*(8)), 121.6 (*C*(4a)), 126.4 (*C*(5)), 127.4 (*C*(6)), 127.5, 127.5, 129.1, 129.1 (*C*(2'), *C*(3'), *C*(5'), *C*(6')), 134.8 (*C*(4')), 136.1 (*C*(7)), 136.7 (*C*(1')), 159.7 (*C*(8a)), 190.3 (*C*(4)); *m/z* (ESI^+) 315 ($[M+Na]^+$); HRMS (ESI^+) $C_{15}H_{10}Cl_2NaO_2^+$ ($[M+Na]^+$) requires 314.9950; found 314.9948.

Example of catalysis control experiment

Chromone (36 mg, 0.25 mmol) and aryl boronic acid (61 mg, 0.5 mmol) were added to 1 mL of an aqueous solution of **polymer 1** ([polymer] = 10 mg·mL^{-1}). The resulting mixture was stirred for 24 h in air at room temperature. After this time, the product was extracted with dichloromethane (2 mL), before the solvent was removed in vacuo. The crude product was analyzed by ^{1}H NMR spectroscopic and HPLC analysis in order to assess formation of the product.

Table S1 Control experiments for catalysis with uncomplexed **polymer 1**, non-PyOx containing **polymer 2** and in the absence of PyOx and polymer.[a]



Entry	Water (ml)	NH_4PF_6 (mol %)	catalyst	$Pd(TFA)_2$ (mol%)	yield (%)	*ee*[b] (%)
1	1	–	**Polymer 1**	–	–	–
2	1	30	**Polymer 1**	–	–	–
3	1	–	**Polymer 2**	–	–	–
4	1	30	**Polymer 2**	–	–	–
5	1	--	**Polymer 2**	0.5	–	–
6	1	30	**Polymer 2**	0.5	–	–
7	0.025	--	**–**	5	–	–
8	0.025	30	**–**	5	–	–

[a] Reactions of chromone (0.25 mmol) with phenyl boronic acid (0.5 mmol) in air at room temperature for 24 h; [b] *ee* determined by HPLC.

NMR Spectra

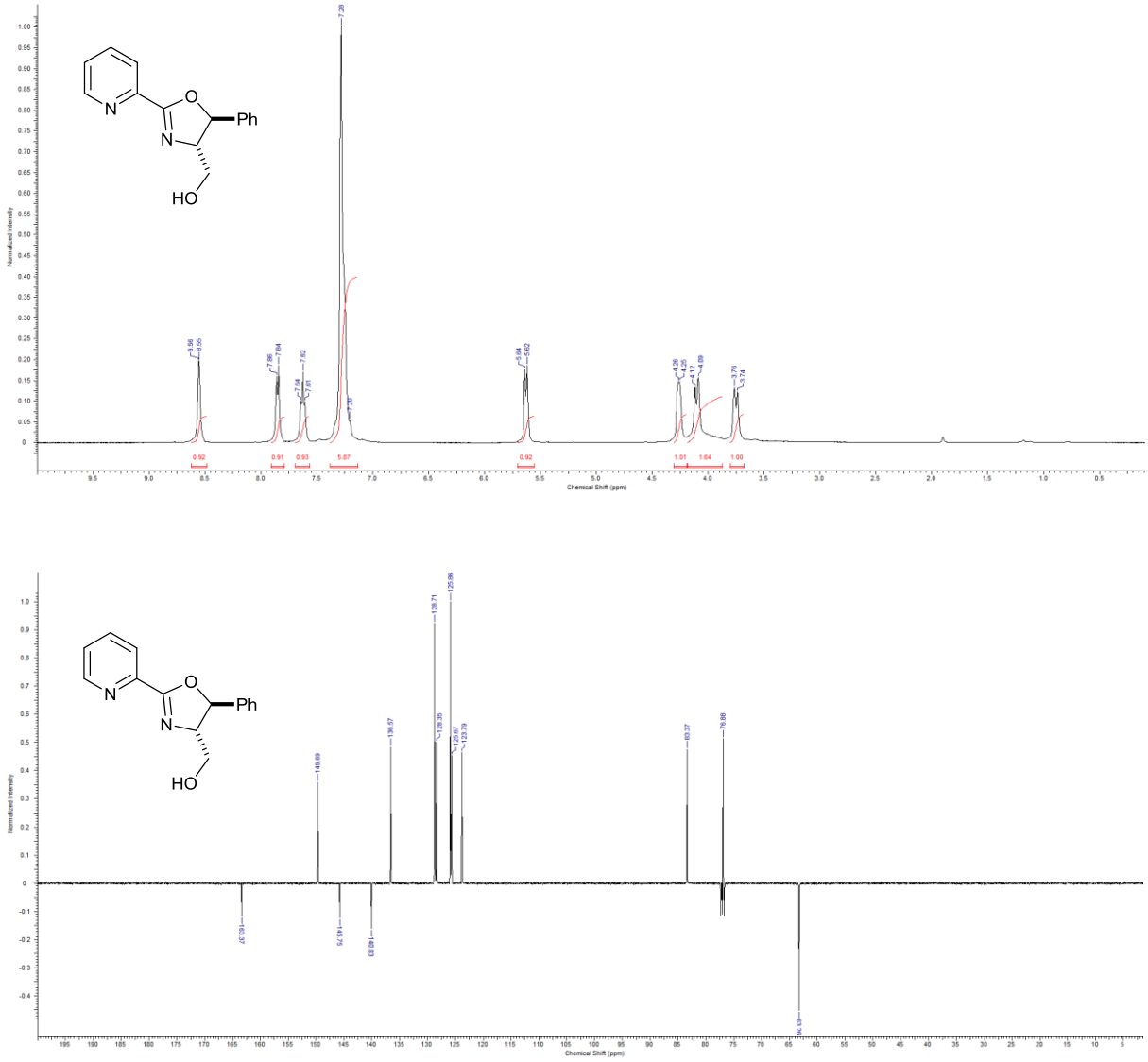


Figure S8 ^{1}H NMR (400 MHz, top) and ^{13}C NMR (100 MHz, bottom) spectra of **PyOx alcohol** in $CDCl_3$.

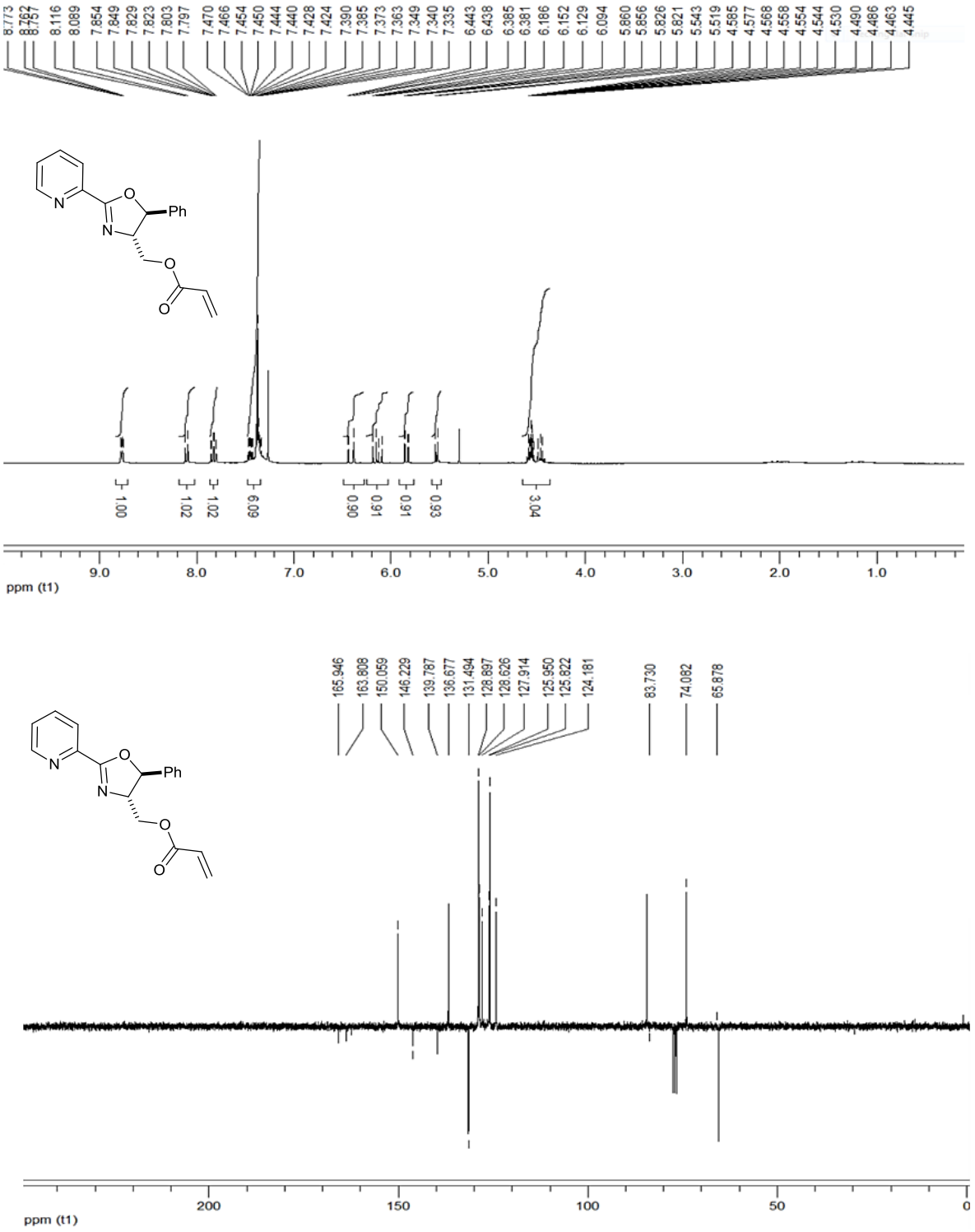


Figure S9 ^{1}H NMR (300 MHz, top) and ^{13}C NMR (75 MHz, bottom) spectra of **PyOxA** in $CDCl_3$.

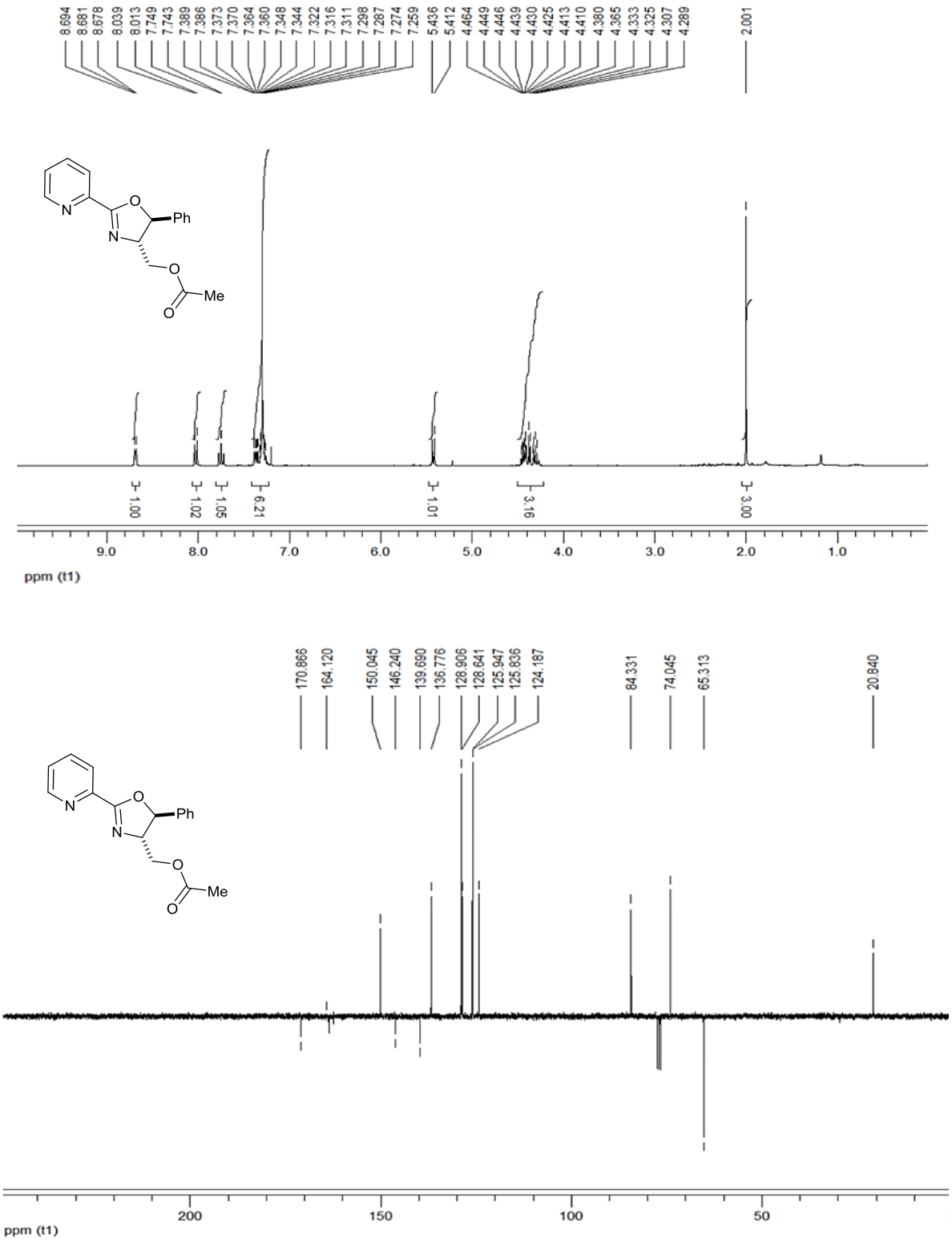


Figure S10 ^{1}H NMR (300 MHz, top) and ^{13}C NMR (75 MHz, bottom) spectra of **PyOx acetate** in $CDCl_3$.

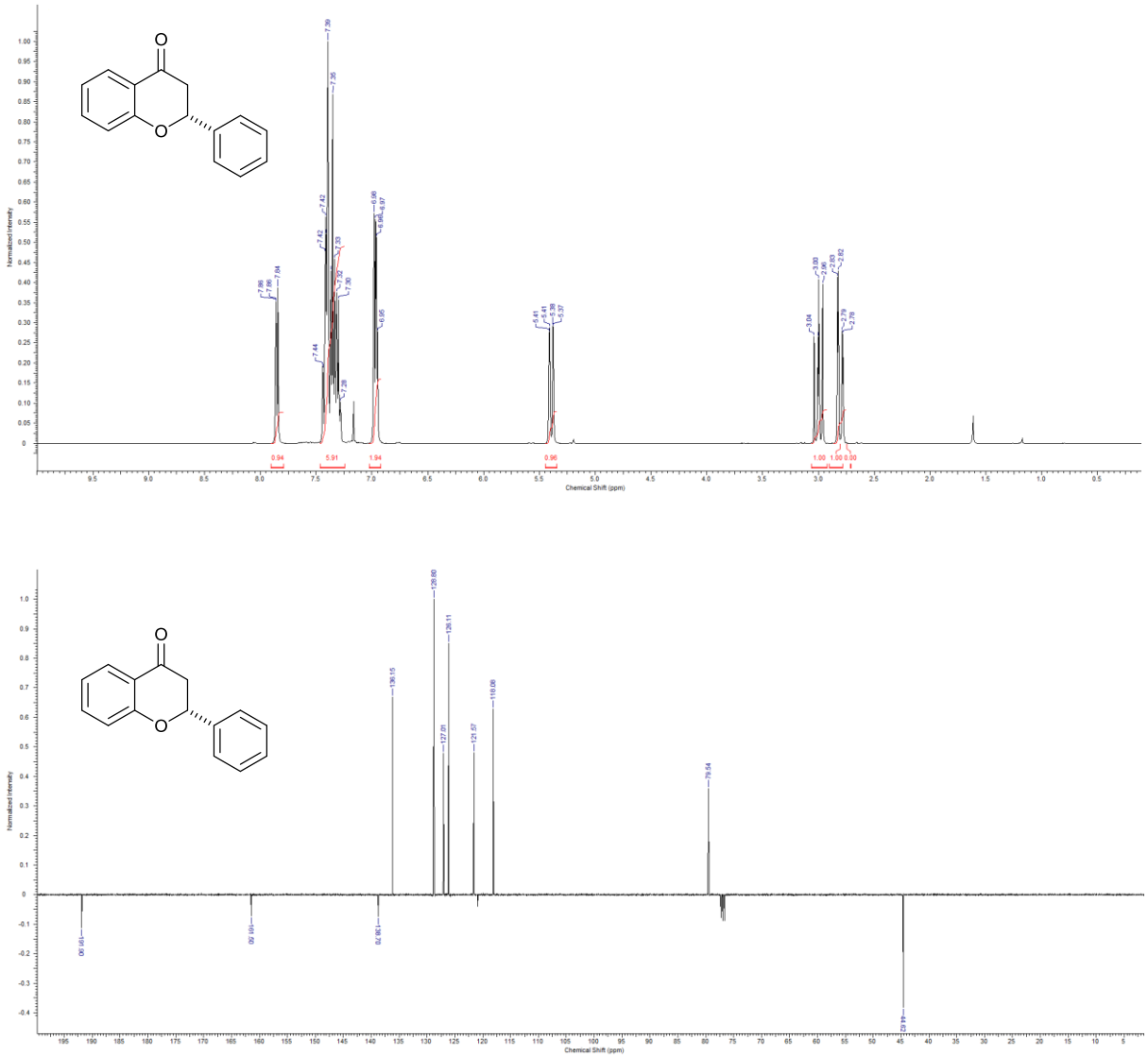


Figure S11 ^{1}H NMR (400 MHz, top) and ^{13}C NMR (100 MHz, bottom) spectra of **(*R*)-2-phenylchroman-4-one** in $CDCl_3$.

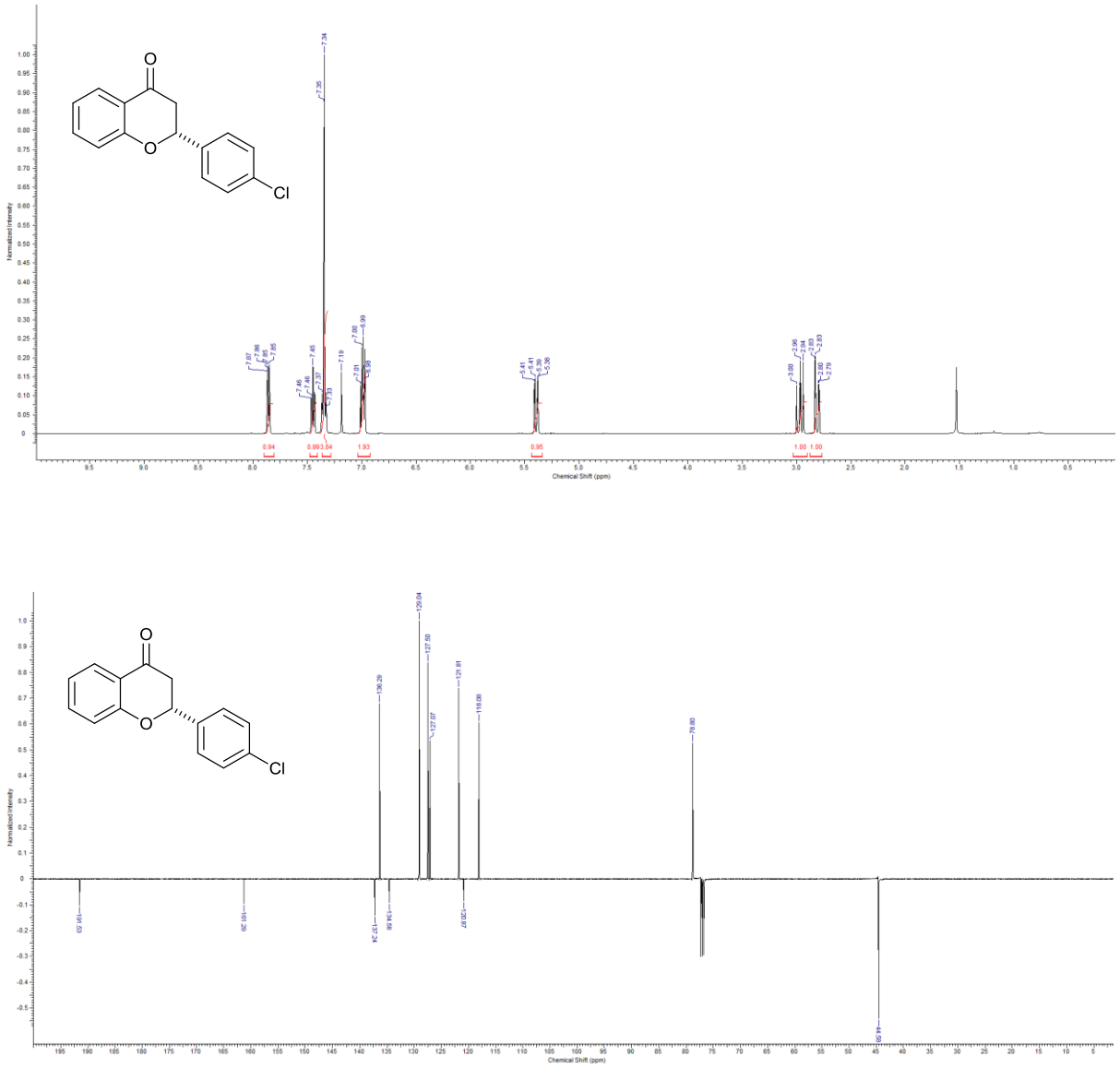


Figure S12 ^{1}H NMR (400 MHz, top) and ^{13}C NMR (100 MHz, bottom) spectra of **(*R*)-2-(4-chlorophenyl)chroman-4-one** in $CDCl_3$.

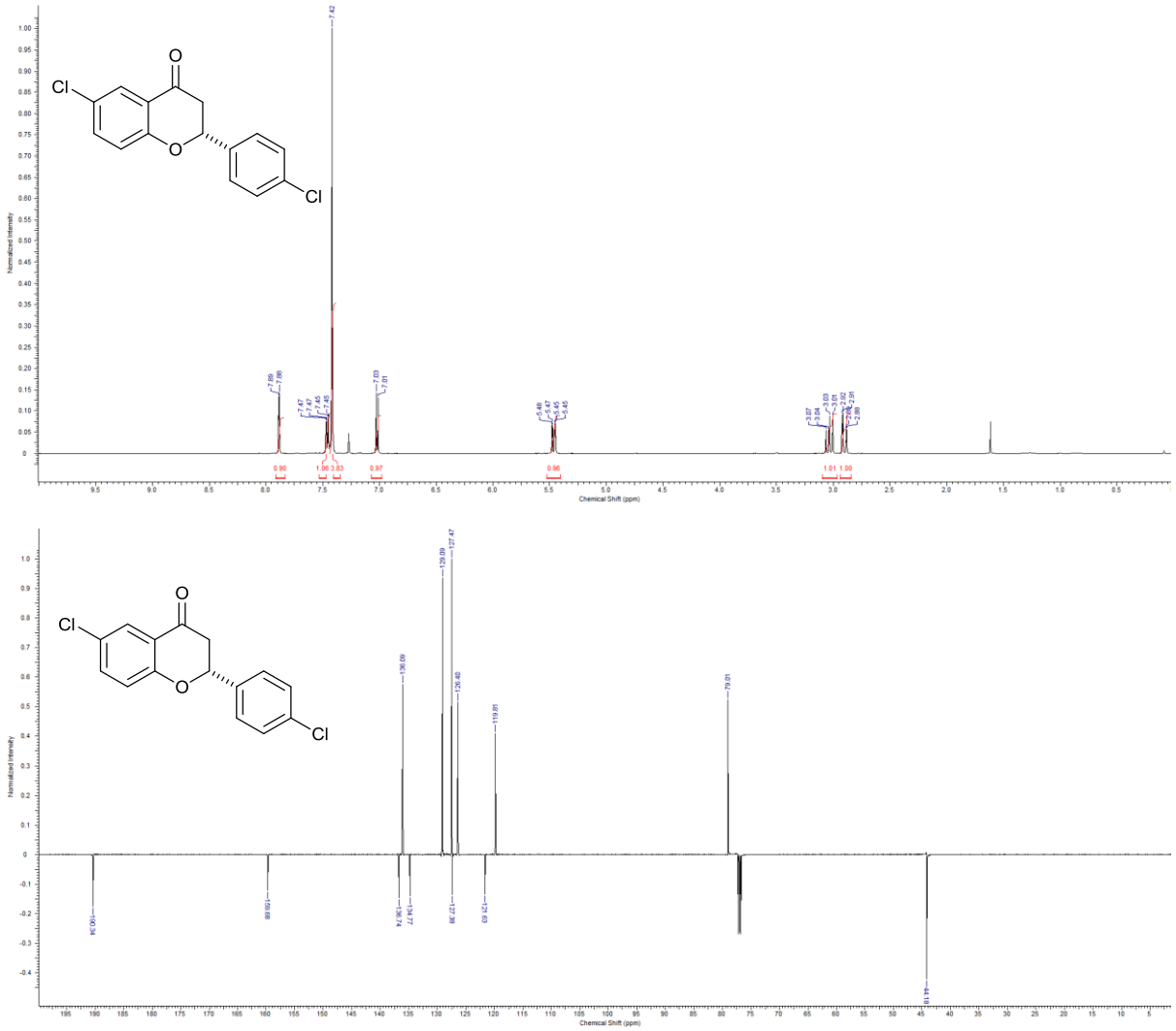
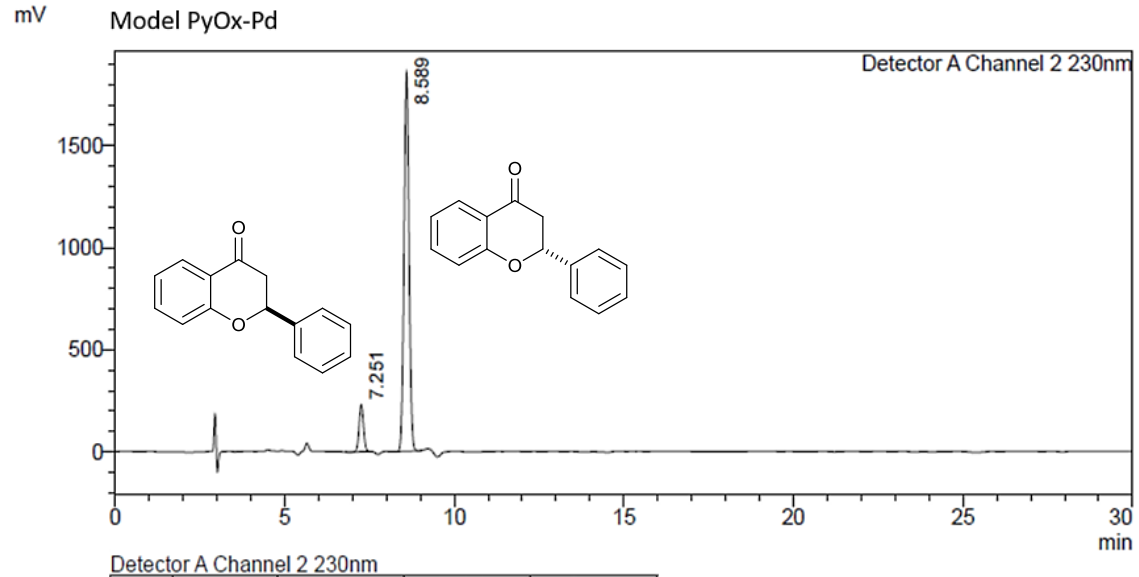


Figure S13 ^{1}H NMR (500 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra of **(*R*)-6-chloro-2-(4-chlorophenyl)chroman-4-one** in $CDCl_3$.

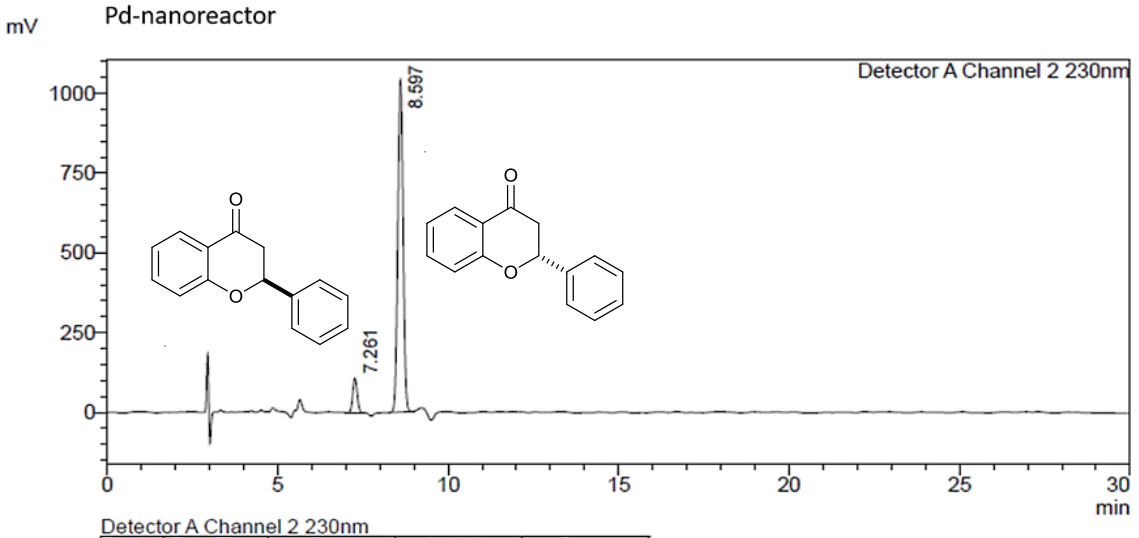
HPLC Chromatograms

The following conditions were used for the HPLC method: a Chiralcel OD-H column; mobile phase composition at 90:10 v/v hexane (0.04% v/v formic acid)/isopropanol (0.04% v/v formic acid); flow rate at 1.0 mL/min; column temperature held at 30 °C; length of method fixed at 30 min; detection wavelength at 230 nm.



Detector A Channel 2 230nm

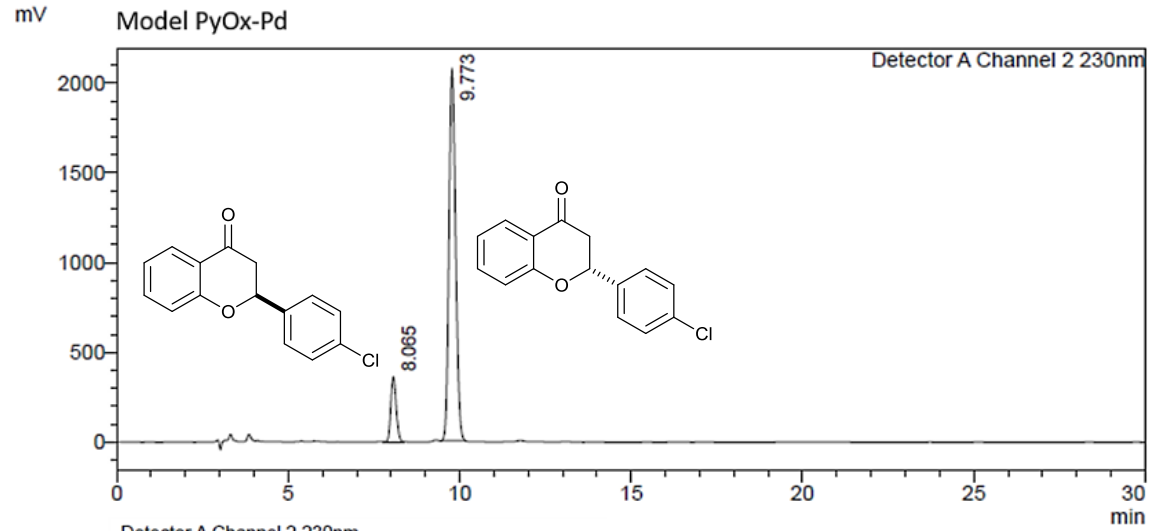
Peak#	Ret. Time	Area	Height	Conc.
1	7.251	2111636	230760	9.943
2	8.589	19125994	1851739	90.057
Total		21237629	2082500	



Detector A Channel 2 230nm

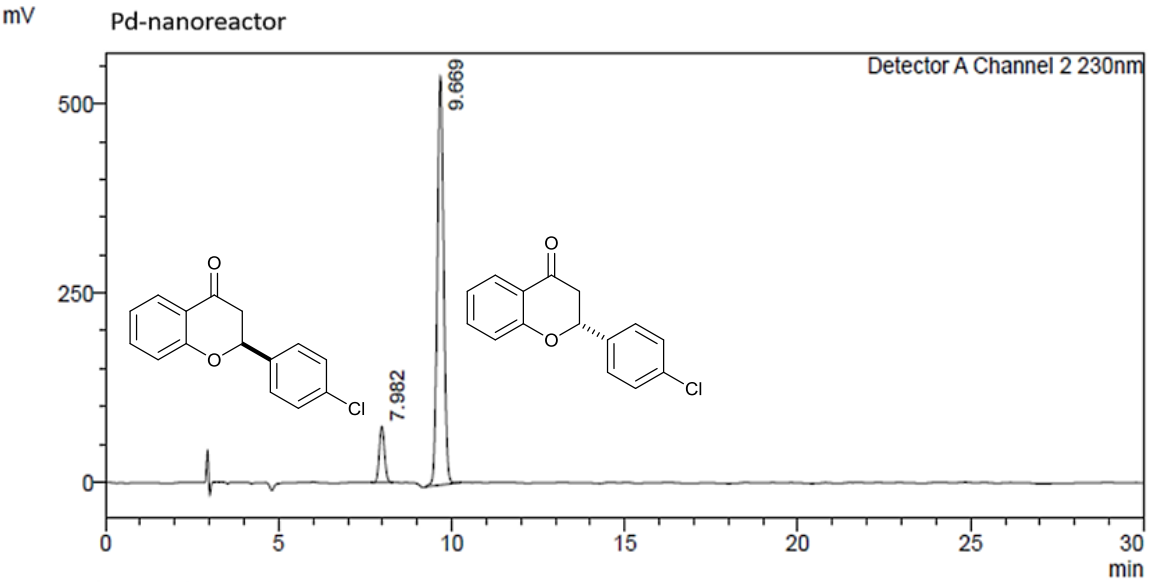
Peak#	Ret. Time	Area	Height	Conc.
1	7.261	969524	107530	8.021
2	8.597	11117288	1040278	91.979
Total		12086812	1147808	

Figure S14 HPLC chromatogram of (*R*)-2-phenylchroman-4-one obtained by asymmetric catalysis using (top) the **Pd-PyOx acetate** catalyst (bottom) the **Pd-nanoreactor**.[10]



Detector A Channel 2 230nm

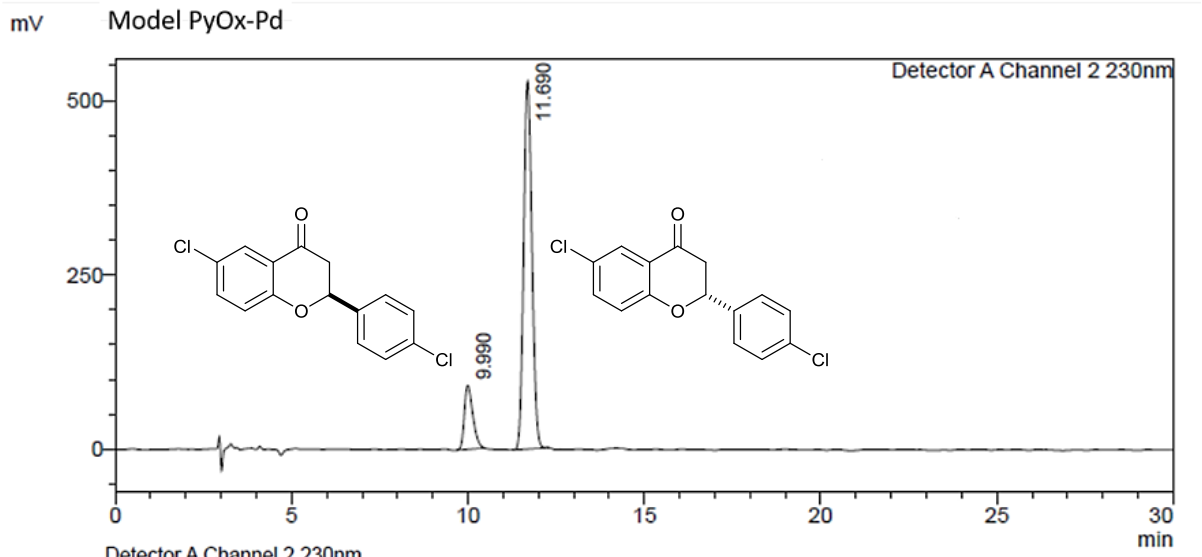
Peak#	Ret. Time	Area	Height	Conc.
1	8.065	3799099	360200	11.911
2	9.773	28097410	2063014	88.089
Total		31896509	2423215	



Detector A Channel 2 230nm

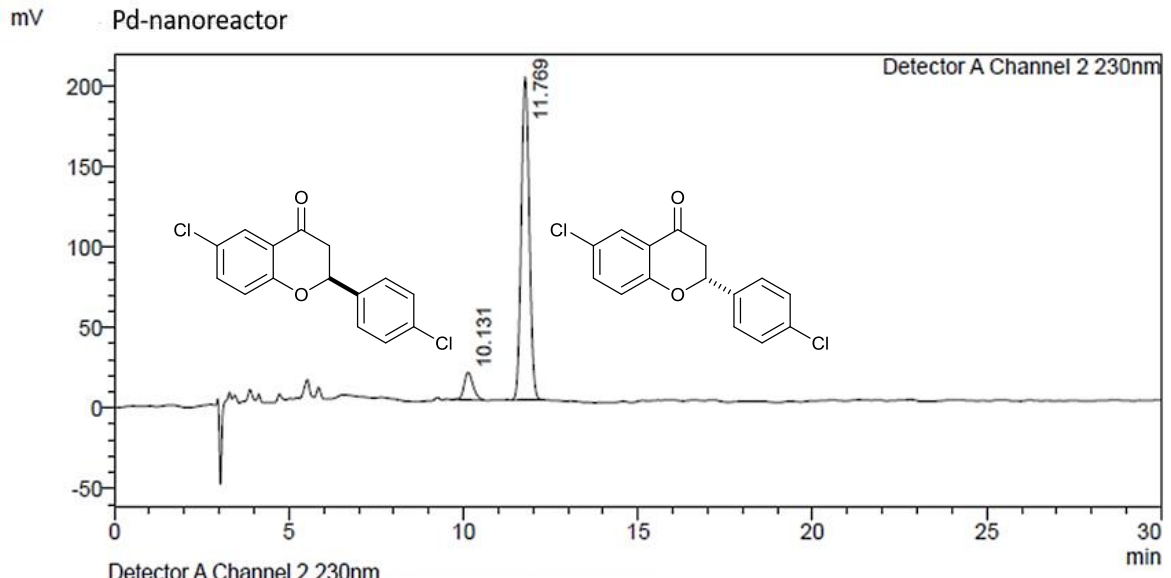
Peak#	Ret. Time	Area	Height	Conc.
1	7.982	767787	73682	10.034
2	9.669	6883804	538261	89.966
Total		7651591	611943	

Figure S15 HPLC chromatogram of (*R*)-2-(4-chlorophenyl)chroman-4-one obtained by asymmetric catalysis using (top) the **Pd-PyOx acetate** catalyst and (bottom) the **Pd-nanoreactor**.



Detector A Channel 2 230nm

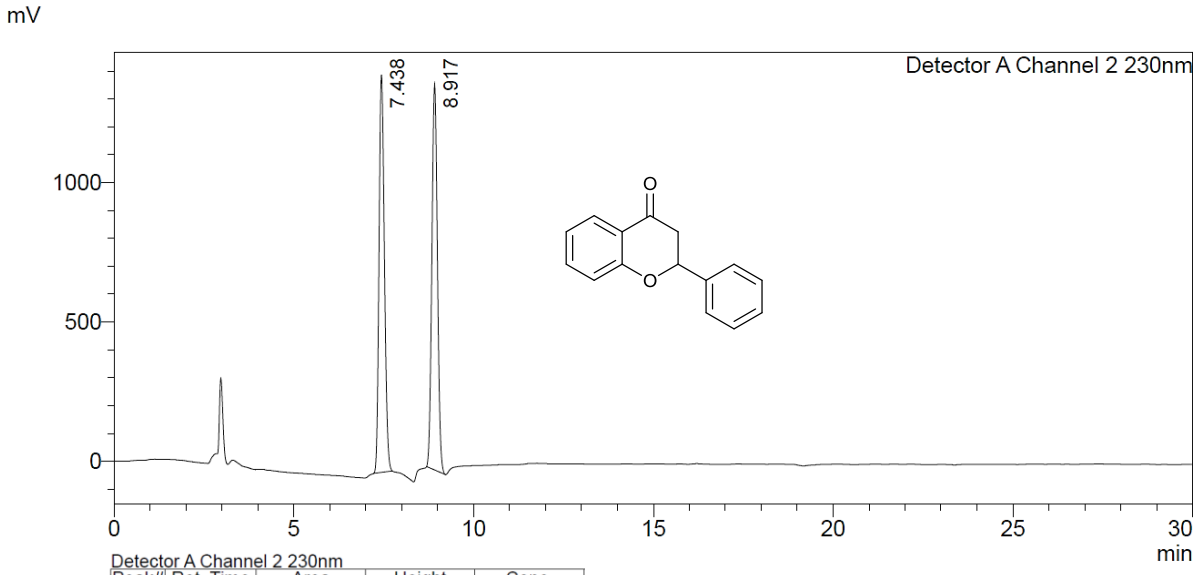
Peak#	Ret. Time	Area	Height	Conc.
1	9.990	1547790	91441	15.089
2	11.690	8710011	527233	84.911
Total		10257802	618674	



Detector A Channel 2 230nm

Peak#	Ret. Time	Area	Height	Conc.
1	10.131	301299	16992	8.556
2	11.769	3220095	200122	91.444
Total		3521394	217115	

Figure S16 HPLC chromatogram of (*R*)-6-chloro-2-(4-chlorophenyl)chroman-4-one obtained by asymmetric catalysis using (top) the **Pd-PyOx acetate** catalyst and (bottom) the **Pd-nanoreactor**.



Detector A Channel 2 230nm

Peak#	Ret. Time	Area	Height	Conc.
1	7.438	14910966	1425629	49.958
2	8.917	14936310	1385028	50.042
Total		29847276	2810657	

Figure S17 HPLC chromatogram of (*RS*)-2-phenylchroman-4-one.

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