

Soxhlet-dialysis: a method to recover soluble polymer supported catalysts

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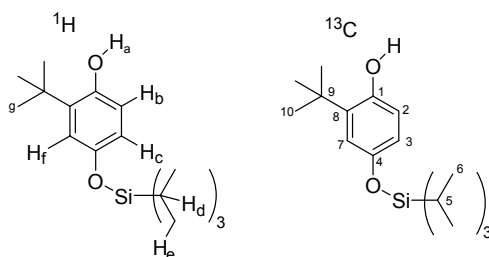
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Supporting Information

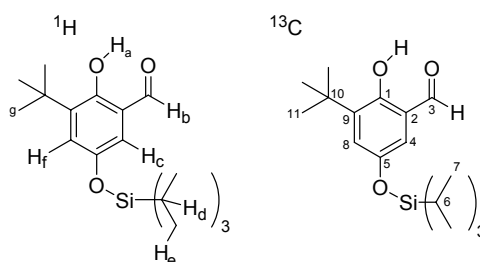
All reagents were purchased from Acros and Aldrich and used without further purification. Dichloromethane (CH_2Cl_2) was dried over 3 Å molecular sieves, distilled and stored under inert atmosphere. Purification was performed by flash chromatography using ICN Flash Silica Gel, 230-400 mesh. Reported yields for the synthesis of the catalysts refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^1H NMR, ^{13}C NMR and FT-IR. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were reported in ppm downfield from tetramethylsilane as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; br, broad; and m, multiplet. The coupling constants, J , are reported in Hertz (Hz). FT-IR spectra of a KBr pellet were carried out on a MIDAC M-2000 FT-IR using GRAMS/32 software. Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski. Regenerated cellulose Spectra/Por® Biotech dialysis membranes (MWCO: 3500 Da) were purchased from Spectrum Laboratories. UV-vis spectroscopic analysis was carried out on a Shimadzu® UV-240 1PC spectrophotometer using UV-Probe software. Enantiomeric excesses were

determined by GC using a Hewlett-Packard 6850 gas chromatograph on a Cyclosil-BTM capillary column purchased from J&W Scientific, Folsom, CA. In all cases, baseline separation of enantiomers was observed. All gas chromatography (GC) operating conditions were set as follows: Carrier gas: H₂. Detector: temperature, 300 °C; flow, 40 mL/min. Inlet: temperature, 300 °C, 10.31 psi; 44.6 mL/min. The column was calibrated with a racemic mixture of the product cyanohydrin trimethylsilyl ether.

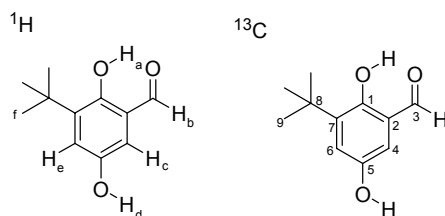
2-tert-Butyl-4-triisopropylsiloxyphenol: To a solution of tert-butylhydroquinone (2.50 g, 15.1 mmol) in dichloromethane (100 mL) was added imidazole (1.33 g, 19.6 mmol) and N,N-dimethylaminopyridine (DMAP) (0.93 g, 7.6 mmol). To this solution was added triisopropyl chloride (3.48 g, 18.1 mmol) in 8 mL of dichloromethane in a dropwise manner and the mixture was then stirred for 15 h at RT. The mixture was then filtered and the solution was concentrated under vacuum. The resultant residue was purified by flash column chromatography on silica gel (1:4 EtOAc/hexanes) to yield the product as a clear liquid (4.39 g, 91% yield): ¹H NMR (300 MHz, CDCl₃) δ 6.82 (d, J = 2.8 Hz, 1 H; H_c), 6.59 (d, J = 2.8 Hz, 1H; H_f), 6.52 (d, J = 8.29 Hz, 1H; H_b), 4.50 (s, 1 H; H_a), 1.38 (s, 9 H; H_g), 1.28-1.25 (m, 3 H; H_d), 1.10-1.08 (d, 18 H; H_e); ¹³C NMR (300 MHz, CDCl₃) δ 149.5 (C₄), 148.1 (C₁), 137 (C₈), 118.8 (C₃), 117.2 (C₇), 116.8 (C₂), 34.5 (C₁₀), 29.5 (C₉), 17.9 (C₆), 12.6 (C₅). Anal. Calcd. For C₁₉H₃₄O₂Si: C, 70.81; H, 10.56; Found C, 70.22; H, 10.78.



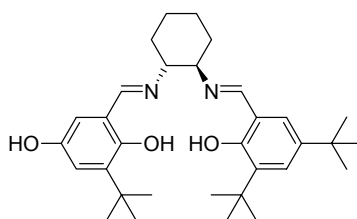
3-tert-Butyl-2-hydroxy-5-triisopropylbenzaldehyde: A three-necked round-bottom flask equipped with an addition funnel, reflux condenser and a magnetic stir-bar was connected to a nitrogen inlet and was charged with 2,6-lutidine (3.12 mL, 26.8 mmol), 4-tert-butylphenol (7.19 g, 22.3 mmol), SnCl₄ (0.79 mL, 6.70 mmol) and toluene (200 mL). The resulting yellow heterogeneous mixture was stirred at RT under nitrogen for 10 min. followed by the addition of paraformaldehyde (2.68 g, 89.3 mmol). The mixture was heated under reflux at 90 °C for 6 h and the reaction progress was monitored by TLC. The reaction mixture was allowed to cool to RT and water (200 mL) and diethyl ether (200 mL) was added. The resulting emulsion was filtered through a pad of Celite and the layers were separated. The organic layer was washed with water (x1), brine (x1), and dried over anhydrous Na₂SO₄, and then concentrated. The crude product was purified by flash column chromatography on silica gel (1:9 EtOAc/hexanes) to afford the title compound as a pale yellow oil (5.04 g, 65% yield): ¹H NMR (300 MHz, CDCl₃) δ = 11.40 (s, 1 H; H_b), 9.70 (s, 1 H; H_a), 7.14 (d, J = 3.0 Hz, 1 H; H_c), 6.85 (d, J = 3.0 Hz, 1 H; H_f), 1.39 (s, 9 H; H_g), 1.28-1.24 (m, 3 H; H_d), 1.11 (d, J = 6.8 Hz, 18 H; H_e); ¹³C NMR (300 MHz, CDCl₃) δ = 197.1 (C₃), 156.2 (C₅), 148.4 (C₁), 139.9 (C₉), 127.9 (C₂), 120.6 (C₄), 120.3 (C₈), 35.3 (C₁₁), 29.5 (C₁₀), 18.3 (C₇), 12.9 (C₆). Anal. Calcd. For C₂₀H₃₄O₃Si: C, 68.57; H, 9.71; Found: C, 68.51; H, 9.99.



3-tert-Butyl- 2, 5-dihydroxybenzaldehyde: Tetrabutylammonium fluoride (a 1.0 M solution in THF, 7.03 mL, 7.03 mmol) was added dropwise to a solution of 3-tert-Butyl-2-hydroxy-5-triisopropylbenzaldehyde (2.05 g, 5.86 mmol) in 15 mL of THF at RT and the mixture was allowed to stir for 3 h. The reaction mixture was then poured into 50 mL of water and extracted (50 mL x 2), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (1:4, diethyl ether/hexanes) to give 0.9 g (80% yield) of the product as a yellow crystalline solid: Mp. 181-183 °C; ¹H NMR (300 MHz, CDCl₃) δ = 11.39 (s, 1 H; H_b), 9.79 (s, 1 H; H_a), 7.10 (d, J = 3.0 Hz, 1 H; H_c), 6.83 (d, J = 3.0 Hz, 1 H; H_e), 4.60 (s, 1 H; H_d), 1.40 (s, 9 H; H_f); ¹³C NMR (300 MHz, CDCl₃) δ = 196.5 (C₃), 153.1 (C₅), 149.6 (C₇), 138.4 (C₁), 122.9 (C₂), 115.4 (C₄), 101.8 (C₆), 34.4 (C₈), 28.8 (C₉). Anal. Calcd. For C₁₁H₁₄O₃: C, 68.02; H, 7.27; Found: C, 67.90; H, 7.22.

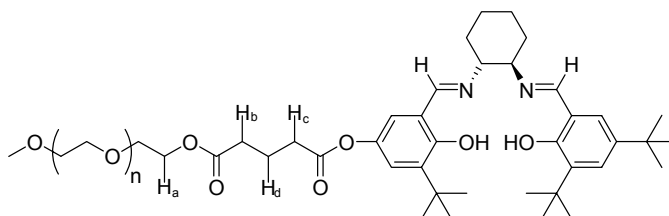


Unsymmetrical salen ligand¹: To a solution of 3, 5-di-tert-butylsalicylaldehyde (1.72 g, 7.53 mmol), and 3-tert-Butyl- 2,5-dihydroxybenzaldehyde (0.48 g, 2.45 mmol) in CH₂Cl₂ (15 mL) was added R-1,2-diaminocyclohexane (0.56 g, 4.89 mmol). The reaction mixture was allowed to stir at RT for 15 h, after which it was concentrated in vacuo to yield a yellow foam. This crude product (mixture of salens) was purified by column chromatography on silica gel (gradient elution: 1:20 to 1:1, diethyl ether/hexanes) to give 2 (0.68 g, 55% yield) as a yellow foam. IR (KBr pellet) 3316 (br), 2954, 2864, 1630, 1598, 1465, 1440 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 8.28 (s, 1 H, -N=C-H), 8.18 (s, 1 H, -N=C-H), 7.31 (d, J = 2.4 Hz, 1 H, H_{Ar}), 6.96 (d, J = 2.4 Hz, 1 H, H_{Ar}), 6.80 (d, J = 3.2 Hz, 1 H, H_{Ar}), 6.45 (d, J = 3.2 Hz, 1 H, H_{Ar}), 3.33-3.29 (m, 2 H), 2.0-1.45 (m, 8 H, H_{cyclohexyl}), 1.41 (s, 9 H), 1.38 (s, 9 H), 1.23 (s, 9 H); ¹³C NMR (300 MHz, CDCl₃) δ = 165.4, 164.5, 157.6, 154.0, 146.2, 139.5, 138.1, 135.9, 126.4, 117.8, 117.4, 117.3, 114.1, 71.9, 34.5, 34.4, 33.6, 32.7, 31.2, 30.9, 28.9, 28.7, 23.8. Anal. Calcd for C₃₂H₄₆N₂O₃: C, 75.89; H, 9.71; N, 5.53 Found: C, 75.70; H, 9.25; N, 5.34; HRMS (EI) calcd m/z 506.3508 (C₃₂H₄₆N₂O₃), found 506.3517.



(2) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147-4154.

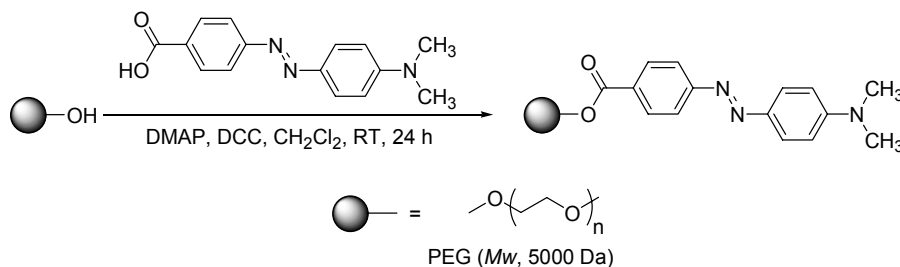
PEG-supported salen ligand ²: To a solution of MeO-PEG₅₀₀₀ (2.60 g, 0.52 mmol), the unsymmetrical salen 3 (0.65 g, 1.04 mmol), and DMAP (0.03 g, 0.26 mmol) in CH₂Cl₂ (20 mL), was added dicyclohexylcarbodiimide (DCC) (0.23 g, 1.10 mmol). The reaction mixture was stirred at RT for 24 h and the urea by-product was removed by filtering through a pad of Celite. The filtrate was then concentrated to 5 mL and then added dropwise into 200 mL of cold stirring diethyl ether. The yellow solid precipitate was filtered off, and dried under vacuum (2.25 g, 77% yield): IR (KBr pellet) 3330, 2890 (b), 1756, 1737, 1630, 1461, 1349 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 8.27 (s(br), 1 H, -N=C-H), 8.20 (s(br), 1 H, -N=C-H), 7.31 (d, 1 H, H_{Ar}), 6.95 (s(br), 1 H, H_{Ar}), 6.88 (d, 1 H, H_{Ar}), 6.73 (s(br), 1 H, H_{Ar}), 4.20 (t, 2H, H_a), 3.34 (s, 3 H, CH₃-O-PEG-), 2.54 (t, J = 7.3 Hz, 2H, H_c), 2.42 (t, J = 7.3 Hz, 2H_b), 2.10-1.50 (m, 10 H, H_d, H_{cyclohexyl}), 1.36 (s, 9 H, H_{t-Bu}), 1.34 (s, 9 H, H_{t-Bu}), 1.19 (s, 9 H, H_{t-Bu}).



PEG-supported *p*-methyl-red. To a solution of *p*-methyl-red (0.79 g, 2.97 mmol) in CH₂Cl₂ (50 mL), was added DCC (0.64 g, 3.11 mmol), DMAP (0.09 g, 0.74 mmol) and MeO-PEG₅₀₀₀ (7.42 g, 1.48 mmol), and the solution was allowed to stir at RT. After 24 h, the reaction mixture was concentrated to 5 mL and added dropwise into 250 mL of cold stirring diethyl ether. The precipitate was collected by vacuum filtration and dried under

(1) Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929-6934.

vacuum to give the PEG-dye (7.14 g, 1.36 mmol) : IR (KBr pellet) 2890 (b), 1685, 1602, 1520, 1467, 1360, 1242 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ = 8.36-7.49 (m, 8 H, H_{Ar}), 4.32 (t, 2H), 3.34 (s, 3 H, $\text{CH}_3\text{-O-PEG-}$), 3.14 (s, 6 H, $\text{-N-(CH}_3)_2$).



General procedure for the asymmetric addition of TMSCN to benzaldehyde The polymer supported salen ligand (0.1 g, 0.018 mmol), dichloromethane (10 mL) and a magnetic stir bar, are placed into a 25 mL round-bottomed flask. Titanium tetrachloride (3.4 mg, 0.018 mmol) was then added and the solution was allowed to stir at RT for 1 h. Next, benzaldehyde (1.9g, 18 mmol) and TMSCN (1.8 g, 18 mmol) were added to the reaction mixture which was left to stir at RT for 24 h. The product trimethylsilyl cyanide ether was obtained from complete conversion of the starting materials (3.7 g, >99% yield), and in 86% ee by chiral GC. ^1H NMR (300 MHz, CDCl_3) δ = 7.50-7.31 (m, 5 H, H_{Ar}), 5.43 (s, 1 H, -OH), 0.15 (s, 9 H, $\text{-O-Si-(CH}_3)_3$).

Procedure for Soxhlet Dialysis recovery of 1. On completion of the reaction, the solution was concentrated in vacuo to 5 mL. A 4 cm length of the dialysis tubing (flat width, 16/22 mm; diameter, 10 mm; vol./length, 1.5 mL/cm) was washed with distilled water, and one end tied shut. The reaction solution and a magnetic stir bar were transferred into the dialysis tubing and the open end of the tubing was tied with a string.

The Soxhlet Dialysis apparatus was set up as depicted in the picture below. The dialysis bag was washed with CH_2Cl_2 and placed in the soxhlet chamber. Next, CH_2Cl_2 was poured into the soxhlet chamber (25 mL) and the three-necked recovery flask (100 mL) (dodecane was added to the solvent in the recovery flask as an internal standard for GC analysis) and it was placed in an oil bath and heated to 60 °C. The soxhlet chamber was periodically replaced with fresh CH_2Cl_2 from the reflux every 20 min. The solution in the recovery flask was sampled over 38 h, and a recovery of 97% was achieved.



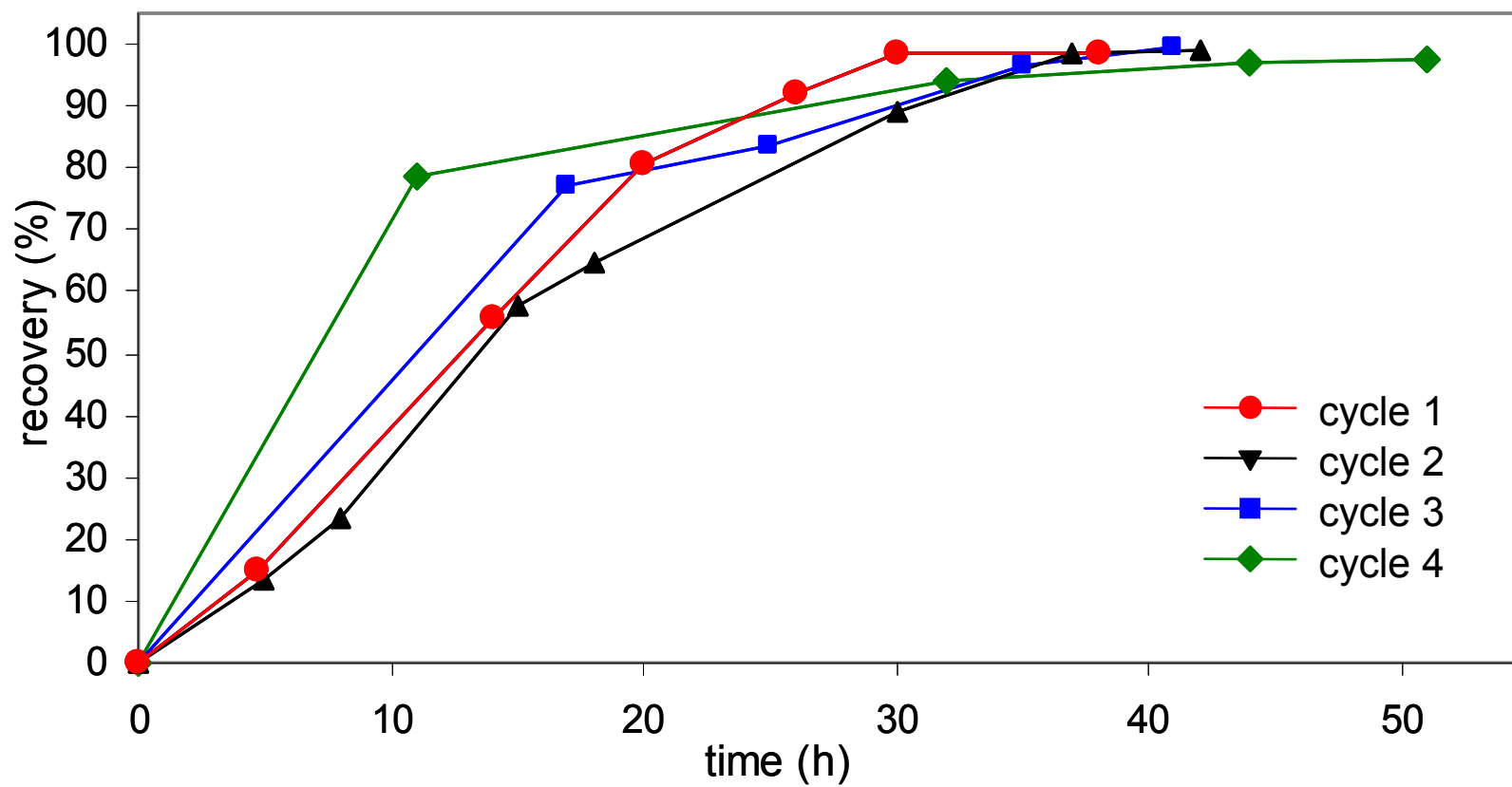
After each cycle, the contents of the dialysis bag was poured into a 25 mL round bottomed-flask and fresh substrates (benzaldehyde and TMCN) were added. The reaction was then carried out with stirring at RT for 24 h until complete conversion of benzaldehyde was observed by GC. This reaction solution was then subjected to another Soxhlet Dialysis cycle. The PEG-supported chiral Ti-salen catalysts could thus be recycled up to five times (average recovery = 98%) with no loss in selectivity and reactivity.

Soxhlet Dialysis of PEG-dye: UV-vis experiments. A solution of the PEG-dye in CH_2Cl_2 (10 mL of a 10 mM solution, 0.1 mmol) and a magnetic stir bar, were placed in a 3.5 kDa dialysis bag. To the soxhlet chamber and three-necked recovery flask was placed 25 mL and 50 mL of CH_2Cl_2 respectively. Soxhlet Dialysis was carried out under similar conditions as mentioned previously. Samples of the dialysate were taken periodically

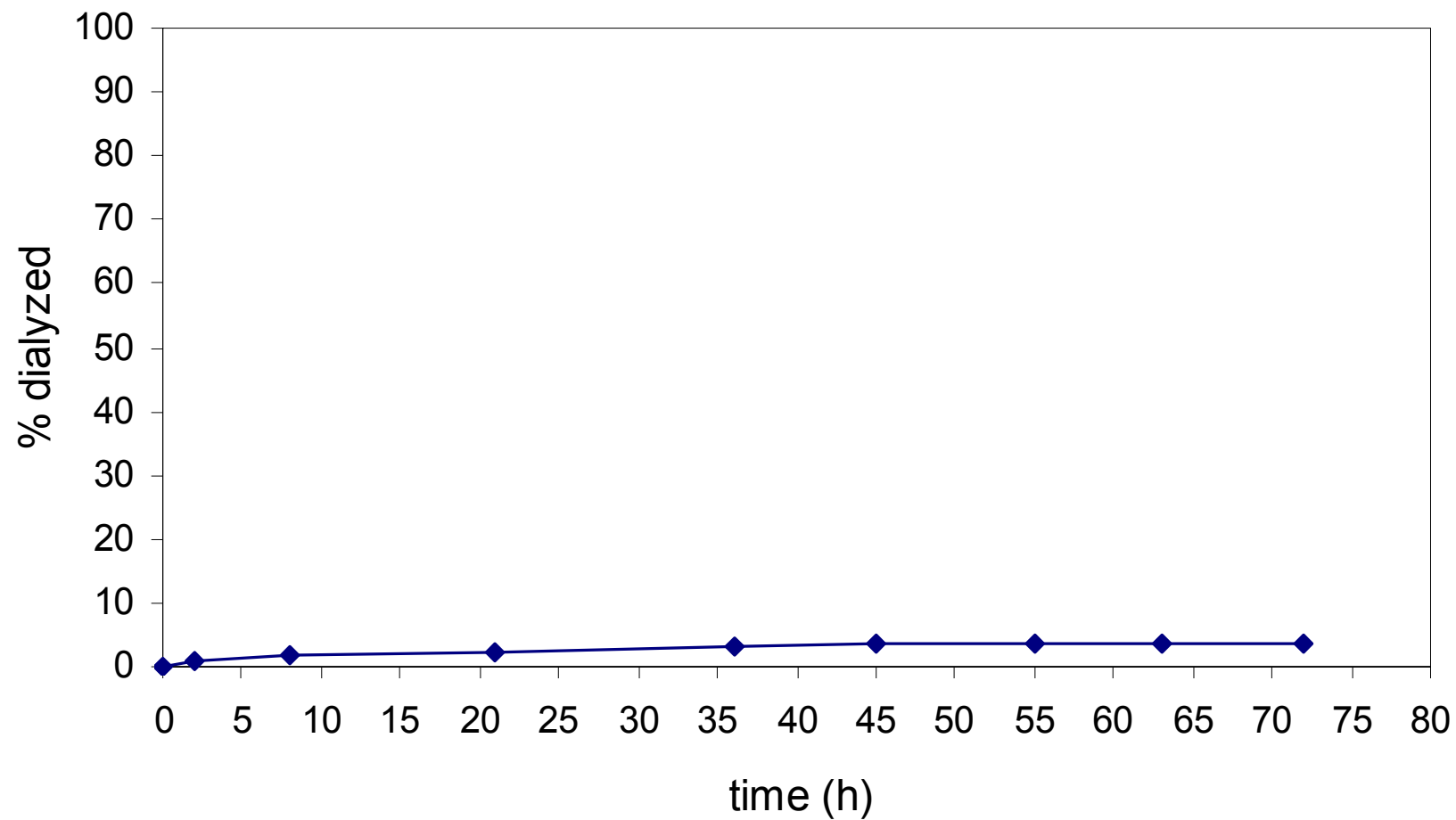
from the recovery flask immediately after reflux from the solvent in the soxhlet back into the recovery flask. The samples were analyzed by UV-vis spectroscopy and their absorbance at λ_{\max} were recorded. The molar concentration of the PEG-dye in the samples was thus calculated using the Beer-Lambert's Law. $A = (\epsilon)(c)(l)$; where A = absorbance, ϵ = molar absorptivity, c = molar concentration and l = path length (1 cm). The A at λ_{\max} of a standard solution of the PEG-dye was recorded and this was used to determine ϵ (1.23×10^4) and ultimately c of each sample. The results are reported in the table below:

time (h)	A at λ_{\max}	c (mM)	% dialyzed ^a
0	0	0	0
2	0.133	0.011	0.8
8	0.323	0.026	1.9
19	0.401	0.033	2.5
25	0.503	0.041	3.1
33	0.588	0.048	3.6
48	0.618	0.05	3.7
62	0.628	0.051	3.8
72	0.63	0.051	3.8

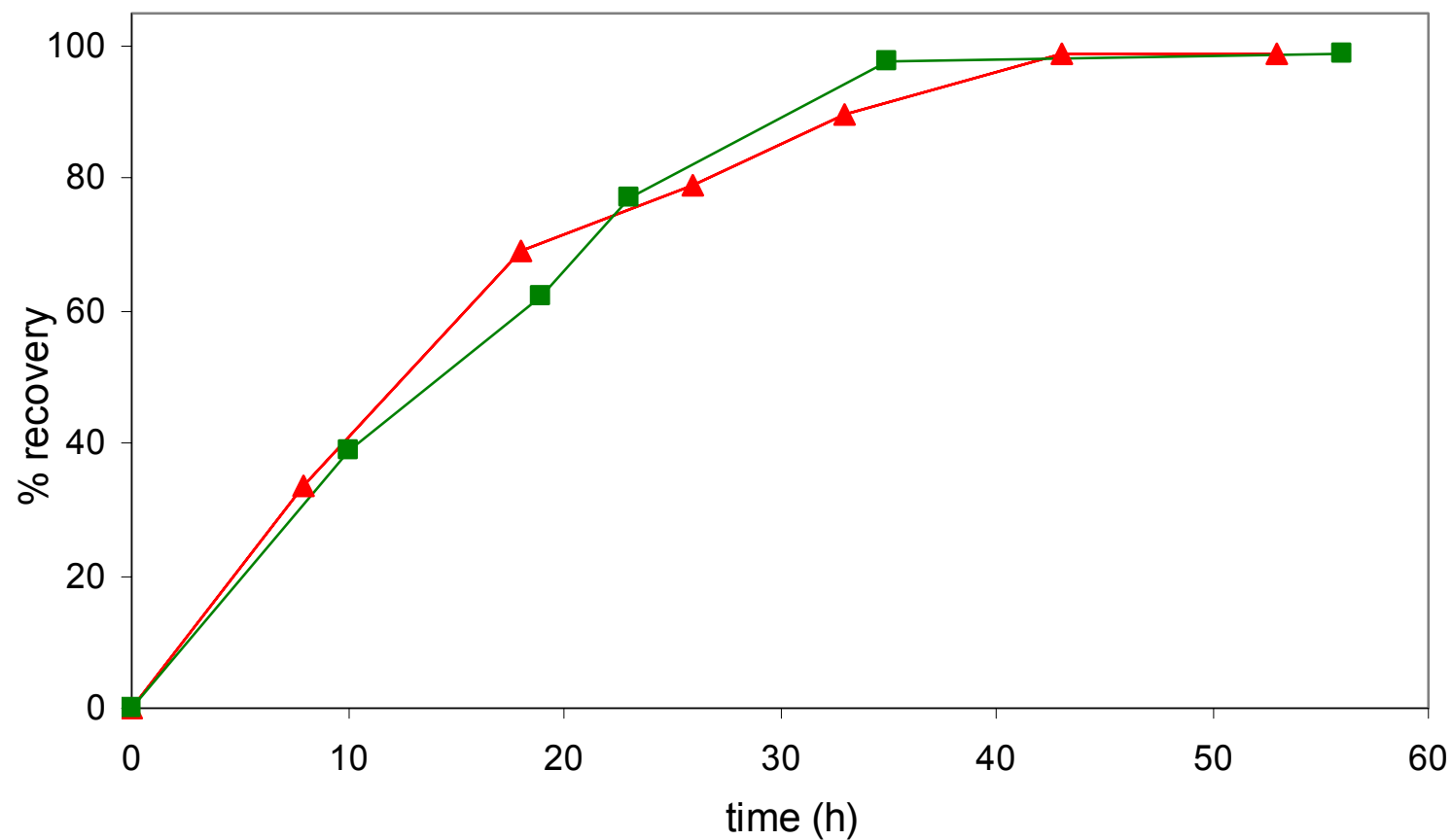
^aThe theoretical maximum concentration of the PEG-dye possible in the recovery flask is 1.33 mM (0.1 mmol of PEG-dye in 75 mL of CH₂Cl₂). Hence the % dialyzed out can be computed as; $\{c / (1.33 \text{ mM}) \times 100\}$



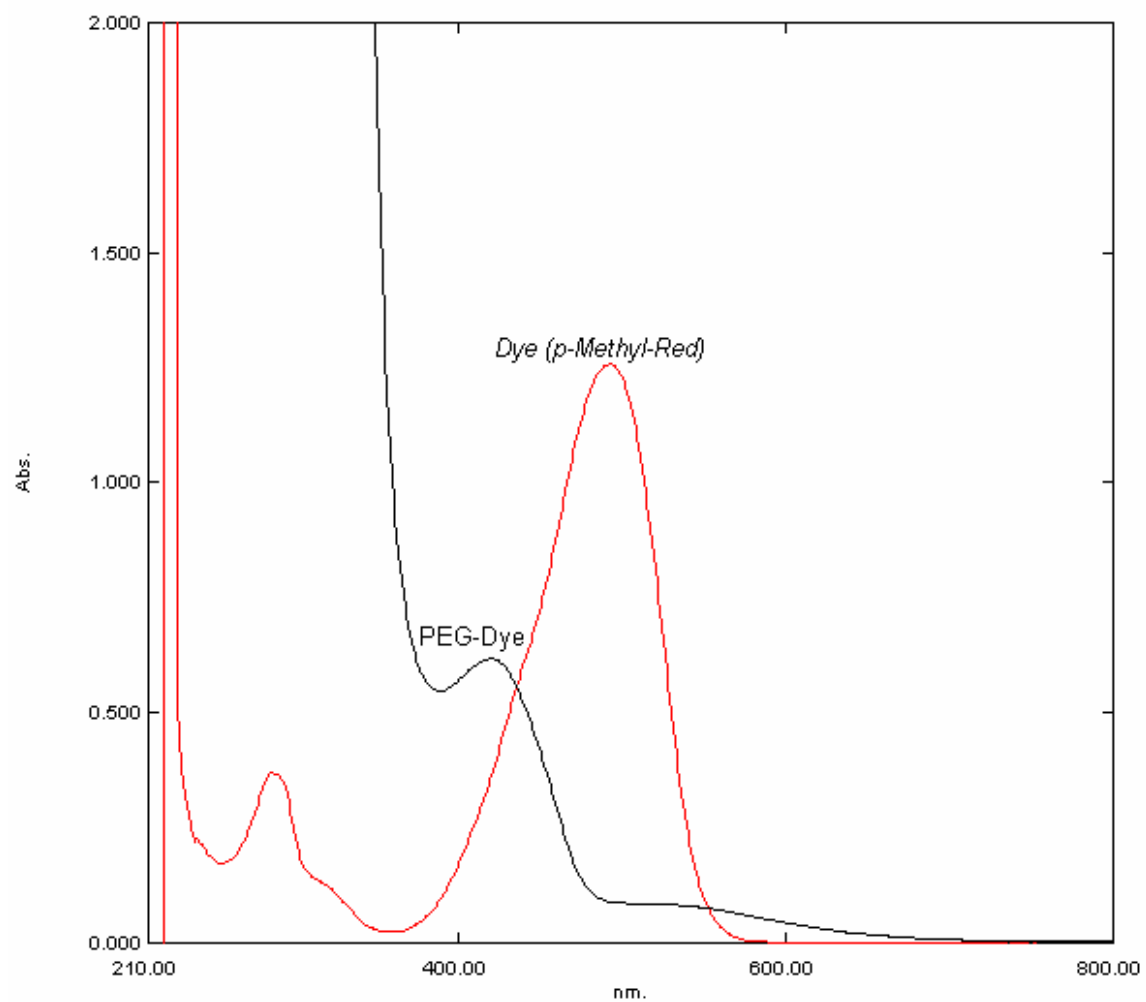
Soxhlet Dialysis for the recovery of **1**: average recovery = 98%



Soxhlet Dialysis of PEG-dye: 3% dialyzed, 97% retained.



Change in the rate of Soxhlet Dialysis by changing the capacity of the soxhlet chamber: —▲— = 50 mL soxhlet chamber; —■— = 100 mL soxhlet chamber.



UV-vis spectra of PEG-dye and *p*-Methyl-Red dye.