Electronic Supplementary Information

Visible-Light Photoredox Catalysis using a Macromolecular Ruthenium Complex: Reactivity and Recovery by Size-Exclusion Nanofiltration in Continuous Flow

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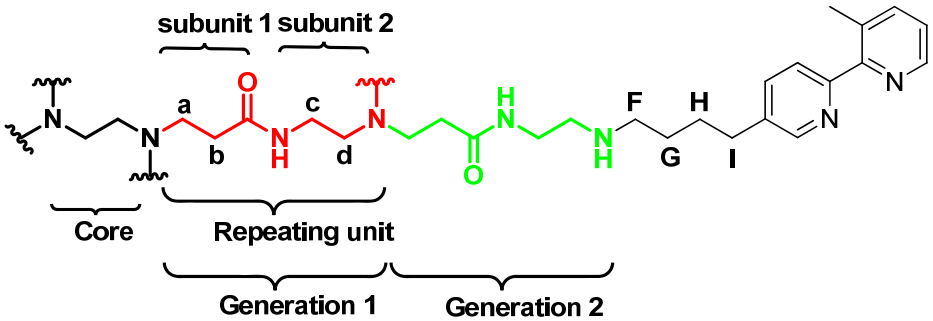
Contents:

General remarks. ^{1}H-NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 mm) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. GC/MS (FOCUS-GC/DSQ II MS, ThermoFisher) monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m×0.250 mm×0.025 μm). After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL min^{-1} in constant-flow mode. Flash chromatography purifications were carried out on an automated flash chromatography system using cartridges packed with KP-SIL, 60 Å (32-63 μm particle size) for 4-(3-formylpropyl)-4'-methyl-2,2'-bipyridine. MALDI-TOF Mass Spectrometry was performed on a Micromass TofSpec 2E Time-of-Flight Mass Spectrometer equipped with a nitrogen laser (337 nm wavelength, operated at a frequency of 5 Hz). ICP-MS analyses were carried out in an Agilent 7700x inductively coupled plasma mass spectrometer. Solid samples were dissolved in HCl/HNO_3 7:3 and subjected to microwave-assisted acid digestion in an MLS UltraClave IV instrument. The temperature was ramped up to 200 °C and kept at this temperature for 30 min. Liquid samples were directly analyzed after appropriate dilution.

4-(3-Formylpropyl)-4'-methyl-2,2'-bipyridine[1] and the ruthenium derivative[2,3] $Ru(bipy)_2(Me_2bipy)(PF_6)_2$ were synthesized as previously reported. The dendrimers were synthesized following previous methodologies.[4;5] All other chemicals were obtained from standard commercial vendors and were used without any further purification. Proof of purity and identity was obtained by ^{1}H NMR, ^{13}C NMR and MS spectroscopy.

Experimental procedures and characterization data



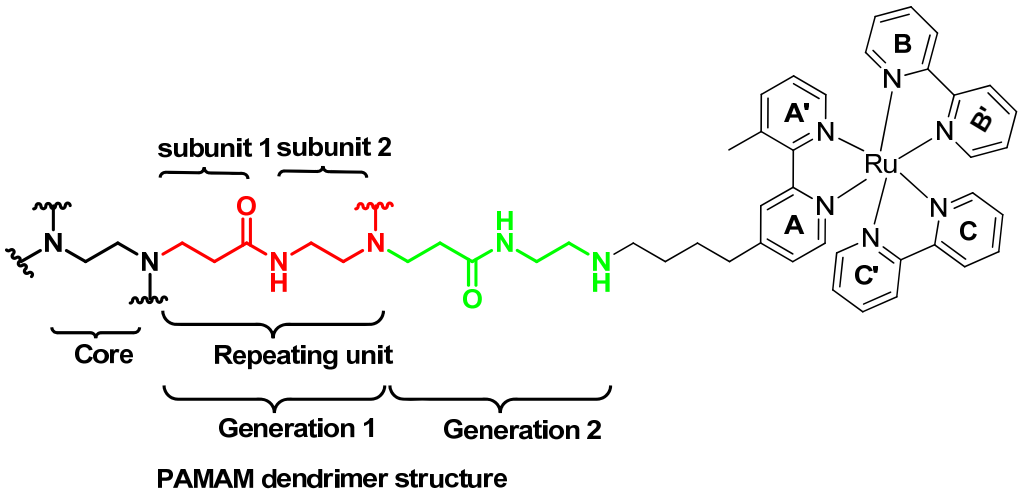
PAMAM dendrimer structure

Synthesis of G2-PAMAM(4,4'-^{n}BuMe-bipy)$_{16}$. Under inert atmosphere, 4-(3-formylpropyl)-4'-methyl-2,2'-bipyridine (596 mg, 2.48 mmol) was dissolved in 10 mL of anhydrous THF. The solution was degassed for 10 min. A commercially available 2nd generation amino-terminated PAMAM dendrimer solution (20% wt in methanol) was slowly added (2.55 mL, 0.124 mmol). The reaction turned yellowish and it was stirred for 18 h. No precipitate was observed. Once the imine synthesis has been performed, sodium borohydride was added (200 mg, 5 mmol). Hydrogen gas evolution was observed and the reaction mixture stirred overnight. Then, the solution was concentrated under vacuum until 4 mL volume and 25 mL of diethyl ether were added resulting in product precipitation. The solid was filtered and redissolved in methanol.

The purification of the bypiridine-dendrimer was done through nanofiltration in methanol with a size-exclusion membrane (NF080105, Solsep BV, The Netherlands) installed in a modified liquid-liquid separator system (Zaiput). The concentration of the dendrimer was 30 mg/mL (400 mg in 15 mL). The filtration was performed at 12.5 bar and a flow rate of 0.2 mL/min. We obtained 58% of the volume in the filtrate. The purification process was monitored by TLC (alumina plates, eluent: ACN/Water/NH_4NO_3 sat. solution 20/4/1). After the nanofiltration, the retentate solution was evaporated in vacuo leading to a white solid (398 mg, yield: 46.9%).

^{1}H NMR (300 MHz, CD_3OD), δ(ppm): 8.4 (32H, bs, bipy), 8.02 (32H, bs, bipy), 7.2 (32H, bs, bipy), 3.2 (56H, bs, PAMAM c signal), 2.7 (98H, bs, PAMAM a signal + I), 2.5 (32H, bs, PAMAM d signal), 2.3 (104H, PAMAM b signal + C*H*$_3$bipy), 1.9 (32H, bs, F), 1.5-1.7 (32H, bs, G-H signal).

MALDI-TOF:[G2-PAMAM(bipy)$_{16}$+Na$^+$]: 6863.3 Da; [G2-PAMAM(bipy)$_{15}$+Na$^+$]: 6638.4 Da; [G2-PAMAM(bipy)$_{14}$+Na$^+$]: 6413.3 Da. A distribution of peaks separated by 225 Da [-(CH$_2$)$_4$-bipy] units is observed. This distribution is centered at 6413 Da that corresponds to [G2-PAMAM(bipy)$_{14}$+Na$^+$].



Synthesis of G2-PAMAM[Ru(*n*BuMe-bipy)(bipy)$_2$(PF$_6$)$_2$]$_{16}$. G2-PAMAM(4,4'-^{n}BuMe-bipy)$_{16}$ (241 mg, 35.2 μmol) was dissolved in ethanol, 96% (10 mL). Then, Ru(bipy)$_3$Cl$_2$·2H$_2$O (366 mg, 704 μmol) was added. The solution was covered with aluminum foil, degassed with Ar and refluxed for 8 h. The reaction progress was followed by TLC (alumina plates, eluent: ACN/Water/NH_4NO_3 sat. solution 20/4/1). Once the reaction was completed, the solution was diluted till 20 mL and the crude was filtered as described in Figure S5. The solution was filtered at 12.2 bar and a flow rate of 0.2 mL/min. The membrane incorporated in the liquid-liquid separator (Zaiput) system was NF080105 (Solsep, BV). Then the product was evaporated in vacuo. This leads to the G2-PAMAM[Ru(^{n}BuMe-bipy)(bipy)$_2$(Cl)$_2$]$_{16}$ intermediate as a black solid.

Then, the intermediate was dissolved in ethanol (1.2 mL) leading to a black/red solution and ammonium hexafluorophosphate (1.0 g, 93.8 eq) was added. The mixture was stirred for 2 h at room temperature. The solid was filtered and washed with 5 mL of water. The product was dissolved again in acetone (5 mL) and filtered again but with a different nanomembrane (Ultracel, Millipore MWCO: 1000 Da or EXP-133-LP, Solsep, BV). It was filtered at 19 bar and a flow rate of 0.2 mL/min. The final solution was evaporated in vacuo leading to a red solid (452 mg, yield: 71%).

^{1}H NMR (300 MHz, acetone-d$_6$), δ(ppm): 8.74 (64H, bs, 3/3' bipy B/C rings), 8.61 (32H, bs, bipy A rings), 8.51 (16H, bs, NH), 8.14 (64H, bs, 4/4' bipy B/C rings), (64H, bs, 6/6' bipy B/C rings), 7.79 (32H, bs, 6/6' bipy A rings), 7.53 (64H, bs, 5/5' bipy A rings), 7.35 (32H, bs, 5/5' bipy A rings), 7.20 (16H, bs, NH), aliphatic PAMAM signals are very broad to distinguish any signal with exception of C*H*$_3$bipy that shows up at 2.55 ppm.

General procedure for the Appel reaction under continuous flow conditions (cf. Table 1). 2 mL of a solution containing the substrate **6** (0.4 mmol), 2 equiv of CBr_4, and the ruthenium catalyst (0.65 mol% of Ru centers) in the corresponding solvent (cf. Table 1) were introduced into the flow photoreactor (Vapourtec UV150, FEP tubing, 1.0 mm id, 10 mL volume) using a sample loop with a flow rate of 250 μL min^{-1} and irradiated with blue LEDs (450 nm) (see Figure S5 for details). The backpressure regulator was set at 3.0 bar. After a residence time of 40 min aliquots of the reaction mixture (200 μL) were collected from the reactor output, diluted to 10 mL with methanol, and analyzed by GC-MS or HPLC.

General procedure for the photochemical reduction reaction under continuous flow conditions (cf. Table 2). 2 mL of a solution containing the substrate **8** or **9** (0.4 mmol), 10 equiv of formic acid, 10 equiv of diisopropylethylamine (DIPEA) and the corresponding Ru catalyst (0.6-1.0 mol% in Ru centers) (Table 2) in acetonitrile were introduced into the flow photoreactor (Vapourtec UV150, FEP tubing, 1.0 mm id, 10 mL volume) using a sample loop with a flow rate of 500 μL min^{-1} and irradiated

with blue LEDs (450 nm) (see Figure S5 for details). The backpressure regulator was set at 3.0 bar. After a residence time of 20 min aliquots of the reaction mixture (200 μL) were collected from the reactor output, diluted to 10 mL with methanol, and analyzed by HPLC (215 nm).

In the case of the use of hydrazine hydrate as reducing agent, a 0.05 M solution of 4-chlorophenylazide was used, and 10 equiv of hydrazine hydrate replaces the mixture formic acid/DIPEA. The solvent was methanol.

General procedure for catalyst recovery under continuous flow conditions. The crude reaction mixture collected from the photoreactor output was diluted to 10 mL with the corresponding solvent (DMF for the Appel reaction and acetonitrile or methanol for the photochemical reduction of chalcone-*α,β*-epoxide or 4-chlorophenylazide). The setup consisted of a commercial liquid-liquid separator (Zaiput) in which a size-exclusion membrane (see Table below) was installed. The solutions were pumped using syringe pumps (Syrris). The system was pressurized to 20 bar in the case of the Appel reaction and 12.5-13 bar for the rest of the photochemical reductions. Before the introduction of the solution, the membranes are equilibrated with clean solvent during 1 hour. The crude mixture was then pumped with a flow rate of 250 μL min^{-1}. The filtration was performed for ca. 3 h. The retentate solution was weighted and fresh reagents for a new reaction cycle were added.

Reaction	Substrate	Solvent	Membrane	Pressure	Flow rate μL min^{-1}
Appel reaction	1-nonanol	DMF	Exp-133-LP	18.5-20	250
Reduction	chalcone-*α,β*-epoxide	ACN	NF080105	12.5-13	250
Reduction	4-chlorophenylazide	ACN or MeOH	NF080105	12.5-13	250

Kaiser test experiment for the bipyridine dendrimer

Figure S1. Kaiser test experiments. (Left) control experiment; (center) sample of bipyridine dendrimer; (right) pristine 2nd generation PAMAM dendrimer.

This test is a qualitative analysis to determine the amount of free primary amino groups, based on the reaction of ninhydrin with primary amines, which gives a characteristic dark blue color corresponding to an adduct whose concentration is calculated by means of UV-Vis spectroscopy.
The amount of moles of primary amines[6] per gram of dendrimer will be determined by the following procedure:
Three solutions were prepared separately.

1. 10 g of phenol dissolved in 20 mL of ethanol
2. 2 mL of KCN 1 mM (aqueous solution) dissolved in 98 mL of pyridine
3. 1.0 g of ninhydrine dissolved in 20 mL of ethanol.

A known mass amount of sample was carefully measured (8.2 mg of bipyridine dendrimer and 2.8 mg for the G2-PAMAM dendrimer)**.** A blank solution without dendrimer was prepared and treated separately in the same way. The solutions were carefully added to a haemolysis test tube in the following order: 75 μl of solution 1, 100 μl of solution 2 and 75 μl of solution 3. The test tube was incubated in a heating block at 100°C for 7 minutes and then removed and 4.8 mL of 60% ethanol was immediately added for a final volume of 5 mL. The tube was then mixed to render the violet color.

A 1 cm UV/Vis cuvette was filled with blank solution to zero the spectrophotometer at 570 nm. The absorbance of each sample was read at 570 nm. The calculation of amine loading is made using equation 1.

Dilution= 50 mL for bipyridine dendrimer and 500 mL for pristine 2nd generation PAMAM dendrimer and Extinction coefficient = 15000 $M^{-1}cm^{-1}$.

$$\mu mol_{amine\ group}/g_{dendrimer} = \frac{[Abs_{sample} - Abs_{blank}] \times dilution\ (ml) \times 10^6 \times 1(cm)}{Extinction\ coefficient \times sample\ mass\ (mg)}$$

Equation 1. PAMAM dendrimer loading calculation.

With this equation, the following values were obtained:

Bipyridine dendrimer = 42.5 $\mu mol_{amine\ group}/g_{dendrimer}$ and 2nd generation PAMAM dendrimer = 4355 $\mu mol_{amine\ group}/g_{dendrimer}$. Taking into account that a dendrimer has on average 16 free primary amine groups, this results in bipyridine dendrimer means that it is 0.86% free primary amino groups while 88% of free primary amines react in the Kaiser test.

Figure S2. The purification of the bypyridine-dendrimer was done through nanofiltration in methanol with the size-exclusion membrane (NF080105, Solsep BV, The Netherlands) installed in a commercial liquid-liquid separator system (Zaiput). Left vial: filtered solution; right vial: retentate solution. The concentration of the dendrimer was 30 mg/mL (400 mg in 15 mL). The filtration was performed at 12.5 bar and a flow rate of 0.2 mL/min. We obtained 58% of the volume in the filtrate.

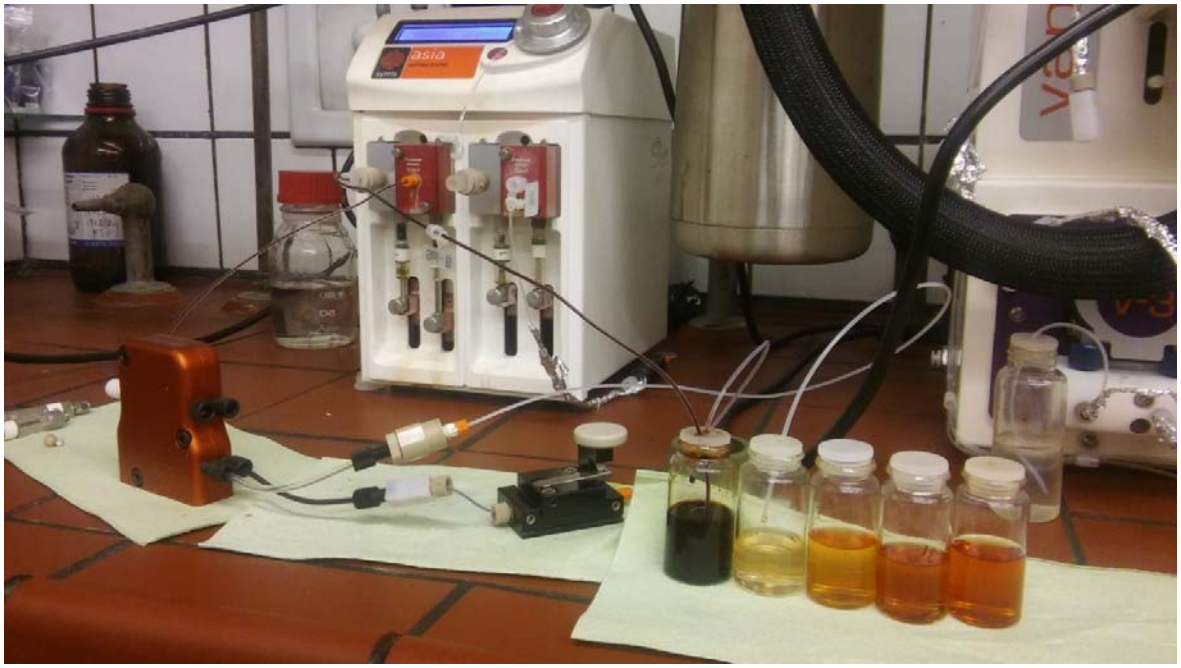
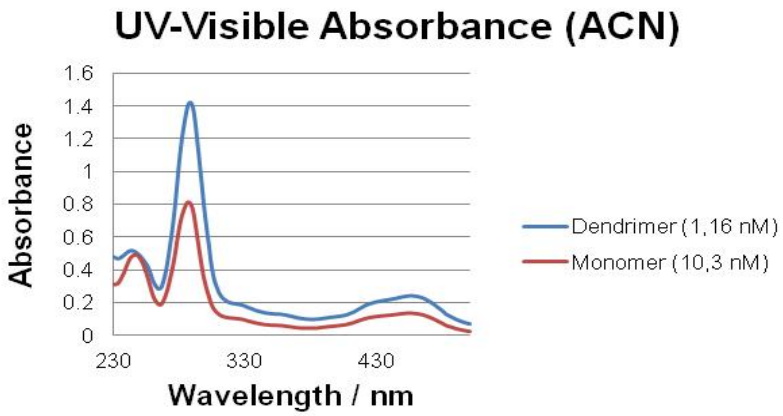


Figure S3. Off-line filtration of the Ru dendrimer with chloride anions in ethanol. Additions of fresh solvent were periodically introduced to efficiently purify the sample. The concentration of the dendrimer is 12 mg/mL (240 mg in 20 mL of ethanol). The solution was filtered at 12.2 bar and a flow rate of 0.2 mL/min. The membrane incorporated in the liquid-liquid separator (Zaiput) system was NF080105 (Solsep, BV). After 2-3 h, 4-5 mL of fresh solvent is introduced in the retentate solution and filtered again.

Ru content analysis by UV-Visible Spectroscopy and ICP-MS



Technique	Average Ru atoms/dendrimer
UV-Visible Spectroscopy	15.4
ICP-MS	14.7

Figure S4. (up) UV-Visible spectroscopy measurements of the Ru dendrimer G2-PAMAM[Ru(^{n}BuMe-bipy)(bipy)$_2$(PF$_6$)$_2$]$_{16}$ and Ru(bipy)$_2$(Me$_2$bipy)(PF$_6$)$_2$ with the aforementioned concentrations in HPLC-grade acetonitrile; (down) Table with the results corresponding to UV-Vis and ICP-MS measurements.

A calibration curve was performed for the monomers and dendrimers. The absorptivity coefficient values (ε, L/(mol·cm) were compared with those reported in the literature.

Sample	ε,L/(mol·cm)$_{exp}$	ε,L/(mol·cm)$_{lit}$	Ref.
Ru(bipy)$_3$Cl$_2$	13293	15600	4
Ru(bipy)$_2$(Me$_2$bipy)(PF$_6$)$_2$	13462	17000 20000 14600	2 3 6
G2-PAMAM[Ru(^{n}BuMe-bipy)(bipy)$_2$(PF$_6$)$_2$]$_{16}$	207523		
G2-PAMAM[Ru(CO(CH$_2$)$_3$bipy)(bipy)$_2$(PF$_6$)$_2$]$_{16}$		174000 283749	4 5

To determine the number of Ru atoms per dendrimer, we divided the absorptivity coefficient of our dendrimer G2-PAMAM[Ru(^{n}BuMe-bipy)(bipy)$_2$(PF$_6$)$_2$]$_{16}$ by the corresponding value of the monomer Ru(bipy)$_2$(Me$_2$bipy)(PF$_6$)$_2$ resulting in 15.4 atoms.

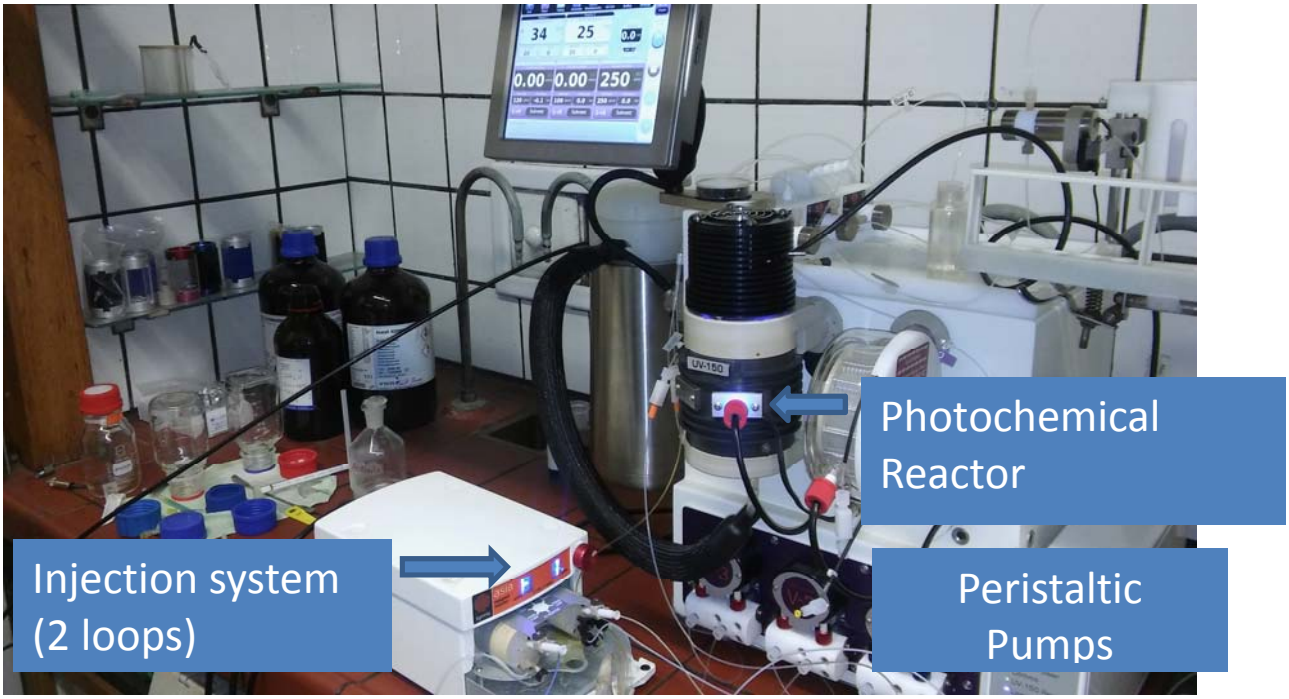


Figure S5. The photochemical reactions were studied using a Vapourtec Easy MedChem instrument with a photochemical reactor equipped with a 452 nm blue LED.

Figure S6. Visual inspection of the size-exclusion membrane; (up) pristine size-exclusion membrane; (down) size-exclusion membrane after a single Appel reaction run using 1-nonanol as substrate. The dendrimer catalyst has been partially retained on the membrane surface, possible due to the low solubility of the macromolecular catalyst in the organic solvents employed.

References

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