

Supporting Information for:

Scalable and robust photochemical flow process towards small spherical gold nanoparticles

Pauline Bianchi^a, Guillaume Petit^a and Jean-Christophe M. Monbaliu^{a,*}

*Center for Integrated Technology and Organic Synthesis, MolSys Research Unit, University of Liège, B-4000 Liège (Sart Tilman), Belgium

Table of contents

1. Reaction setups	3
1.1. Batch preliminary trials	3
1.2. Mesofluidic modules	3
1.2.1. Lab scale mesofluidic photoreactor setup	3
1.2.2. Pilot scale mesofluidic photoreactor setup	4
1.2.3. Production scale mesofluidic photoreactor setup	4
1.3. Detailed setups.....	6
1.3.1. Batch trials	6
1.3.2. Lab scale mesofluidic photoreactor setup	6
1.3.3. Pilot scale mesofluidic photoreactor setup	7
1.3.4. Production scale mesofluidic photoreactor setup	7
2. Additional experimental details	8
2.1 Chemicals	8
2.2 Preparation of the Feed solutions A & B.....	9
2.2.1 Feed solution A (HAuCl ₄).....	9
2.2.2 Feed solution B (LAP/citrate)	9
2.3 Startup and shutdown procedures.....	9
2.3.1 Startup procedure.....	9
2.3.2 Shutdown procedure	10
2.4 Removing of gold coating.....	10
3. Additional experimental results	12
3.1. Preliminary optimization with various Norrish Type I & II photosensitizers	12
3.2. Identification of the most suitable stabilizer.....	14
3.3. Estimation of the impact of 2,4,6-trimethylbenzoic acid as a stabilizing agent.....	15

3.4.	Identification of suitable conditions for avoiding gold coating.....	15
3.4.1.	Biphasic conditions	16
3.4.2.	Hydrophobic coating.....	16
3.5.	Control experiments.....	17
3.6.	Control of the pH.....	18
3.6.1.	Stabilization of the pH.....	18
3.6.2.	Impact of the pH on the population of anionic citrate	19
3.6.3.	Stability of the gold and LAP /citrate solutions in phosphate buffer.....	19
3.6.4.	Effect of the irradiation wavelength on the synthesis of Au NPs.....	20
3.7.	Characterization	20
3.7.1.	Color.....	20
3.7.2.	UV spectroscopy	21
3.8.	Comparison with I-2959	24
3.9.	Fine tuning of the conditions and reproducibility tests in the Corning® Advanced-Flow™ G3 Photo Reactor.....	25
4.	References.....	27

1. Reaction setups

1.1. Batch preliminary trials

A graduated cylinder was filled with the solution containing the gold precursor (HAuCl_4) and the photoinitiator (PI). The cylinder was surrounded by 4 LED pillars, equipped with 3 LEDs each (365 nm, UV LED Gen 2 Emitter, Led Engin) connected in series. The power supply (Tenma 72-8695A) delivered an intensity of 0.6 A and a voltage of 21.1 V. The solution in the cylinder was maintained under agitation with a magnetic stirrer (IKA RCT basic).

1.2. Mesofluidic modules

1.2.1. Lab scale mesofluidic photoreactor setup

1.2.1.1. Pumps

The aqueous HAuCl_4 feed was injected with a Corning dosing line (FLOM dual-piston metal-free pump) and the aqueous sodium citrate and **LAP** feed was handled with a ThalesNano microHPLC pump.

1.2.1.2. Reactor setup

The continuous flow synthesis of Au NPs in a lab scale was studied in a Corning® Advanced-Flow™ Lab Photo Reactor (one fluidic module of 2.5 mL internal volume of effective irradiation integrated with a double layer heat exchanger and sandwiched between two LEDs panels with 2*20 LEDs at each wavelength) operated between 25 °C and 60 °C under irradiation at 365, 385 and 405 nm.

1.2.1.3. Thermoregulatory devices

Thermoregulation of the reaction path was carried out with a Huber Ministat thermostat (THERM 180 thermofluid). The LED panels were maintained at 15 °C with a Huber Minichiller 280 chiller (water/ethylene glycol).

1.2.1.4. In line monitoring of outlet flow

Absorbance was recorded on an AvaSpec-ULS2048XL EV spectrometer (Ultra low Stray light Fiber optic Spectrometer, 75 mm AvaBench, 2048 large 500 μm pixel back-thinned CCD detector). The light source was an AvaLight-DH-S light source (Deuterium-Halogen light source, 190-2500 nm, incl. TTL shutter). The samples were analyzed in a Hellma Analytics flow cell (10 mm light path) held in an Avantes CUV-ALL/UV/VIS cuvette sample holder (10x10 mm). The link between the source, the holder and the analyzer was ensured by Avantes FCB-UVIR400 fiber optic cables (Bifurcated cable 2x400 μm , 2 or 1 m length, SMA terminations).

1.2.2. Pilot scale mesofluidic photoreactor setup

1.2.2.1. Pumps

A Corning dosing line equipped with a HNP micro gear pump was used for the delivery of the solution containing **LAP** and sodium citrate while the handling of the gold feed was carried out by a metal-free four pistons Car-May pump.

1.2.2.2. Reactor setup

The scalability of the Au NPs synthesis was tested in a Corning® Advanced-Flow™ G1 Photo Reactor (5 fluidic modules of 8 mL internal volume connected in series; each fluidic module is integrated with a double layer heat exchanger and sandwiched by two LEDs panels with 2*30 LEDs at each wavelength) operated between 25 and 60 °C under irradiation at 375, 395 and 405 nm.

1.2.2.3. Thermoregulatory devices

The temperature of the reaction path was regulated with a LAUDA Integral XT 280 thermostat (THERM 180 thermofluid), whereas the LED panels were maintained at 10 °C with a LAUDA Proline RP845 (THERM 180 thermofluid).

1.2.2.4. Off line analysis

Absorbance was recorded on an AvaSpec-ULS2048XL EV spectrometer (Ultra low Stray light Fiber optic Spectrometer, 75 mm AvaBench, 2048 large 500 µm pixel back-thinned CCD detector). The light source was an AvaLight-DH-S light source (Deuterium-Halogen light source, 190-2500 nm, incl. TTL shutter). The samples were analyzed in PMMA cells inside an Avantes CUV-ALL/UV/VIS cuvette sample holder (10x10 mm). The link between the source, the holder and the analyzer was ensured by Avantes FCB-UVIR400 fiber optic cables (Bifurcated cable 2x400 µm, 2 or 1 m length, SMA terminations).

1.2.3. Production scale mesofluidic photoreactor setup

1.2.3.1. Pumps

A Corning dosing line (HNP micro gear pump) was used for the delivery of the solution containing **LAP** and sodium citrate while the handling of the gold feed was carried out by a metal-free four pistons Car-May pump.

1.2.3.2. Reactor setup

The production scale mesofluidic reactor used for the continuous flow synthesis of Au NPs is a Corning® Advanced-Flow™ G3 Photo Reactor (one fluidic module of 50 mL internal volume integrated with a double layer heat exchanger and sandwiched by two LED panels with 2*192 405 nm LEDs).

1.2.3.3. Thermoregulatory devices

Thermoregulation of the reaction path was carried out with a HUBER Unistat P505, whereas the LED panels were maintained at 10 °C with a LAUDA Proline RP845 (THERM 180 thermofluid).

1.2.3.4. Off line analysis

Absorbance was recorded on an Agilent Cary 60 UV-Vis spectrometer. Measurements were performed from 1000 nm to 350 nm in PMMA cells.

1.3. Detailed setups

1.3.1. Batch trials

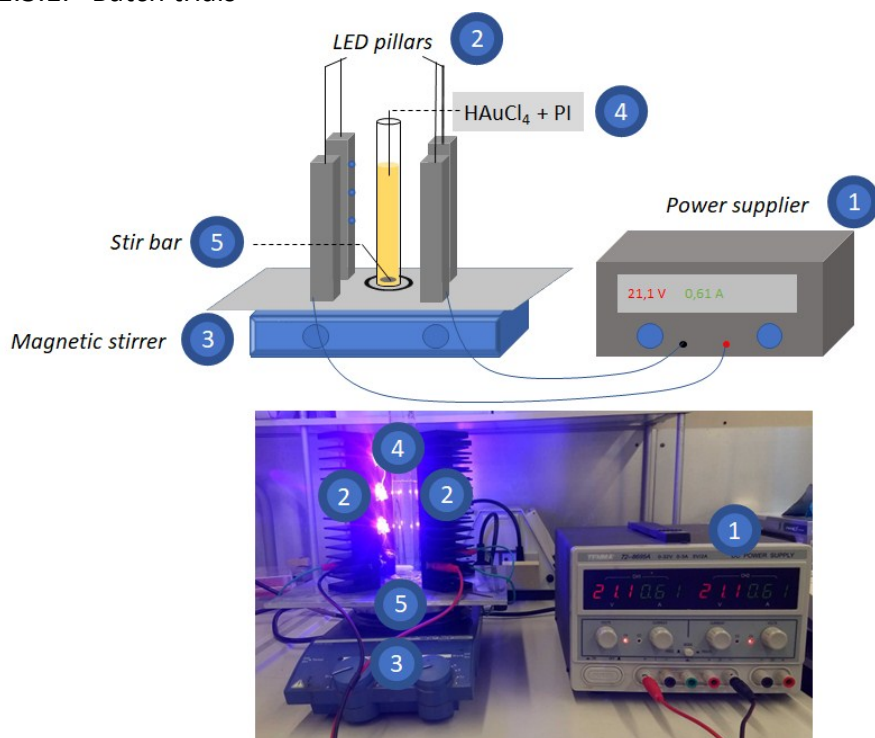


Figure S1. Photograph of the batch setup for the preliminary screening of photoinitiators

1.3.2. Lab scale mesofluidic photoreactor setup

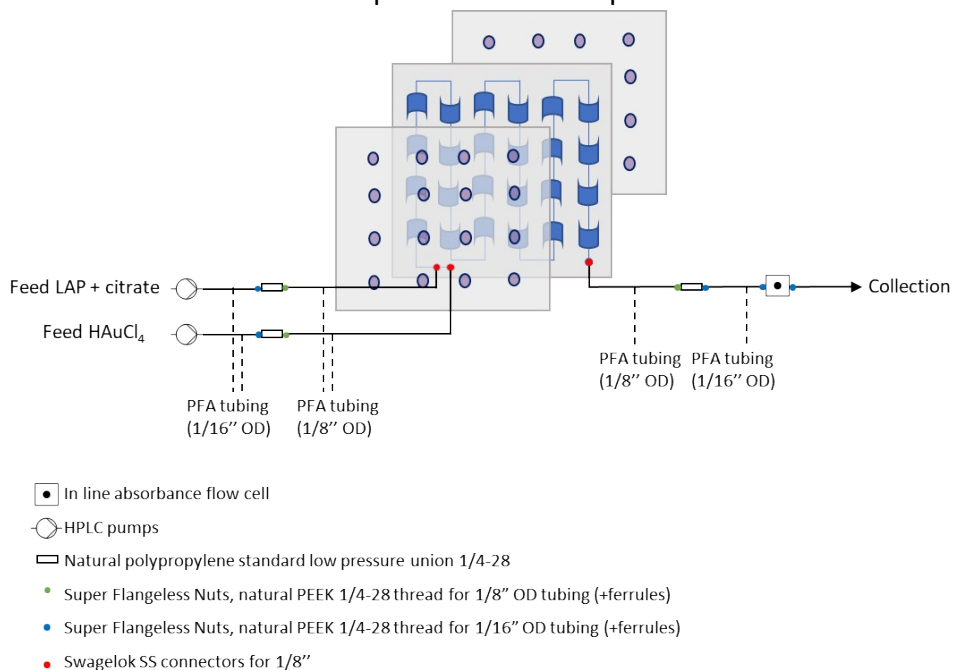


Figure S2. Simplified flow chart for the lab scale mesofluidic photoreactor setup

1.3.3. Pilot scale mesofluidic photoreactor setup

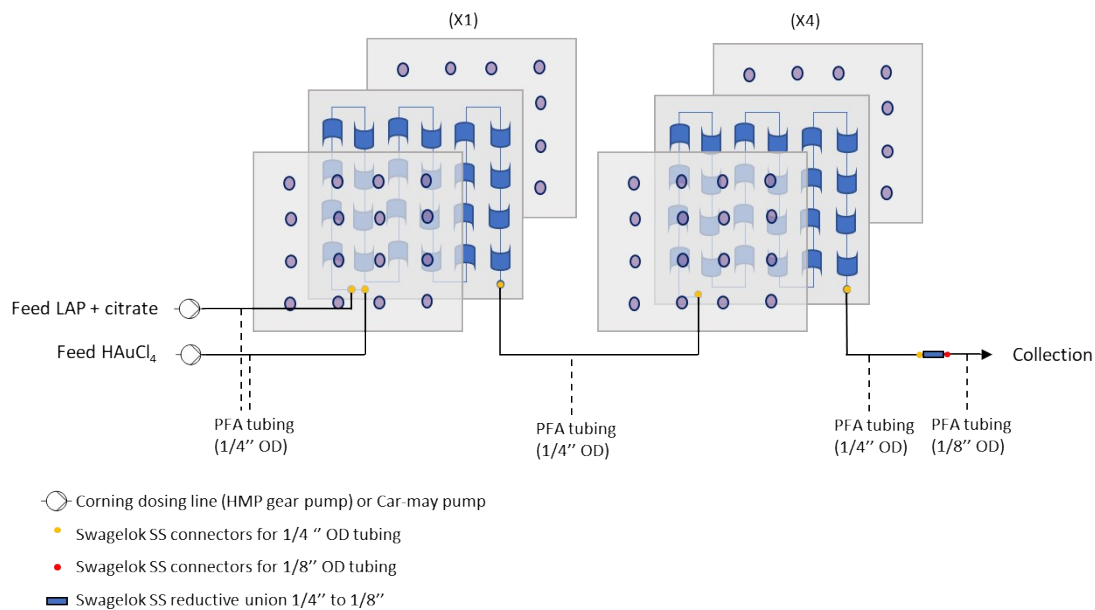


Figure S3. Simplified flow chart for the pilot scale mesofluidic photoreactor setup

1.3.4. Production scale mesofluidic photoreactor setup

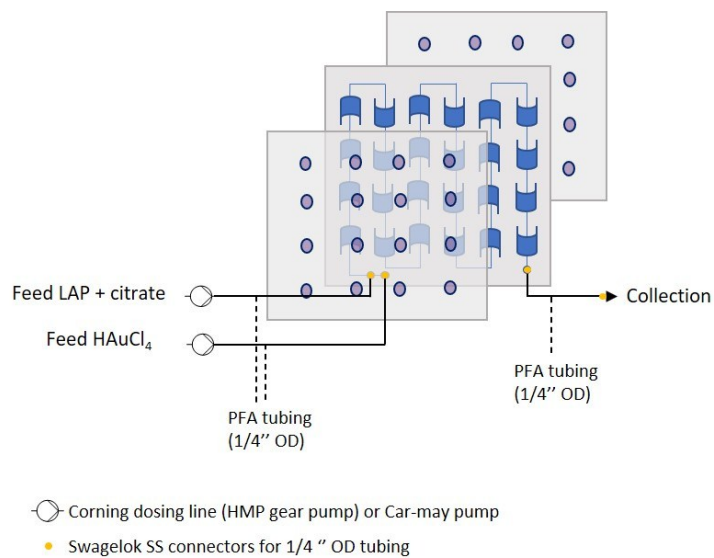


Figure S4. Simplified flow chart for the production scale mesofluidic photoreactor setup

2. Additional experimental details

2.1 Chemicals

Chemicals, purity, CAS numbers and suppliers are provided in Table S1.

Table S1. Solvents, chemicals and suppliers

Chemicals	Purity (%)	CAS number	Supplier
Gold(III) chloride trihydrate	≥99.9%	16961-25-4	Merck (Sigma Aldrich)
Potassium hydroxide, pellets	85.9%	1310-58-3	VWR
Di-sodium hydrogen phosphate anhydrous	≥99.9%	13472-35-0	Merck (Sigma Aldrich)
Water HiPerSolv CHROMANORM®			VWR
Sodium citrate dihydrate	≥99%	6132-04-3	Merck (Sigma Aldrich)
Lithium phenyl-2,4,6-trimethylbenzoyl-phosphinate (LAP)	≥95%	85073-19-4	Merck (Sigma Aldrich)
2-Hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (I-2959)	>98%	106797-53-9	TCI
2-Hydroxy-2-methylpropiophenone	97%	7473-98-5	Merck (Sigma Aldrich)
Diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide	>98.0%	75980-60-8	TCI
Benzophenone	>99%	119-61-9	TCI
4,4'-Dimethoxybenzophenone	>99%	90-96-0	TCI
4,4'-Bis(diethylamino)benzophenone	≥99%	90-93-7	Merck (Sigma Aldrich)
9-Fluorenone	≥99%	486-25-9	Acros
Thioxanthone	>98.0%	492-22-8	TCI
2-Isopropylthioxanthone	>98.0%	5495-84-1	TCI
2-Chlorothioxanthone	>98.0%	86-39-5	TCI
2,4-Diethylthioxanthone	98%	82799-44-8	Merck (Sigma Aldrich)

2,4,6-Trimethylbenzoic acid	99%	480-63-7	Merck (Sigma Aldrich)
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2.2 Preparation of the Feed solutions A & B

2.2.1 Feed solution A (HAuCl₄)

HAuCl₄ must preferably be weighted quickly under an inert atmosphere (Ar). The desired amount of HAuCl₄ (0.66 mM) was dissolved in phosphate buffer (1.98 mM, pH = 7.2) in a volumetric flask. The pH of the corresponding solution was next adjusted to 7 with 3 volume% of KOH 0.1 M upon filling of the flask with 80% of the buffer (the remaining volume is then filled with phosphate buffer). It is strongly advised to check the pH before each run and to adjust its value accordingly.

2.2.2 Feed solution B (**LAP**/citrate)

LAP must be preferably handled in the dark. The desired amount of **LAP** (1.98 mM) was dissolved in phosphate buffer (1.98 mM, pH = 7.2) under sonication and then transferred to a volumetric flask. The desired amount of sodium citrate dihydrate (1.98 mM) was dissolved in phosphate buffer (1.98 mM, pH = 7.2) and transferred to the same volumetric flask, which was next filled with phosphate buffer.

2.3 Startup and shutdown procedures

The following procedures apply to the preparation of Au NPs in the lab, pilot and production scale mesofluidic photoreactor setups and are intended to avoid gold coating.

2.3.1 Startup procedure

- Turn on the thermostats. Set point for the reactor: 40 °C; set point for the LEDs: 10 °C. Wait at least 10 min for thermal stabilization.
- Fill the reactor with aqueous phosphate buffer.
- Set the pump handling the solution containing **LAP** and citrate (Feed solution B) to 6.25 mL min⁻¹ (AFR Lab Photo) or 100 mL min⁻¹ (AFR G1 Photo) or 125 mL min⁻¹ (AFR G3 Photo) and fill the reactor. It is critical to start the pump with Feed solution B beforehand.
- Set the pump handling the aqueous gold solution (Feed solution A) to 6.25 mL min⁻¹ (Lab Photo) or 100 mL min⁻¹ (G1 Photo) or 125 mL min⁻¹ (G3 Photo).
- Switch on the LEDs with the main control panel at 405 nm with 75% (Lab Photo) or 100% (G1 Photo or G3 Photo) of intensity.

Figure S5 shows that it is crucial to wait 1.5 times the residence time to be at steady state before collecting NPs samples.

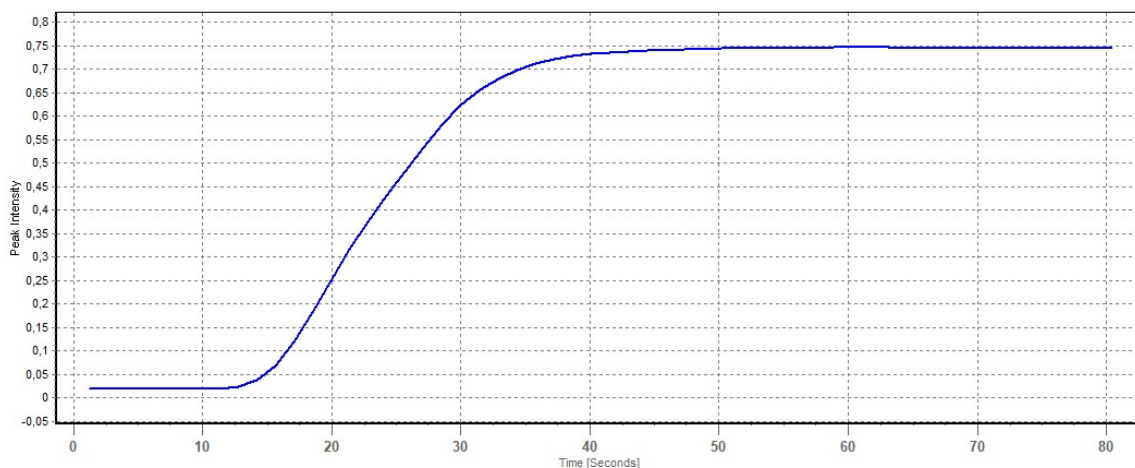


Figure S5. Peak intensity of Au NPs (520 nm) versus time ($t = 0$ is the time when the light is on). The residence time is 20 s.

2.3.2 Shutdown procedure

- Turn off the LEDs.
- Stop feeding the reactor with Feed solution A and flush the reactor with Feed solution B.
- Turn off the thermostats.
- Flush thoroughly the reactor with aqueous phosphate buffer for 10 residence times, and then flush the reactor with water for 10 residence times.

2.4 Removing of gold coating

If the instructions in section 2.3 are carefully executed, gold coating should not appear even for prolonged operations.

The standard procedure for removing gold coating relies on *aqua regia*.

CAUTION: *aqua regia* is a strong oxidizer and is extremely corrosive. It should be used under a fume hood and with the appropriate PPEs.



- Flush the reactor according to section 2.3.2
- Flush the reactive path of the reactor with air
- Prepare a volume of *aqua regia* corresponding to 1.5 x the internal volume of the reactor. *Aqua regia* is prepared by mixing 3 volumes of hydrochloric acid and 1 volume of nitric acid. It can also be prepared *in situ* with metal-free pumps.

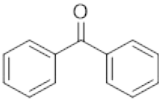
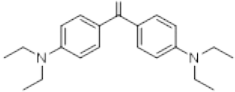
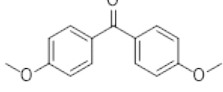
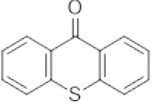
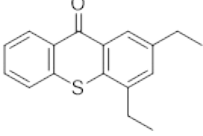
- Fill the reactor with *aqua regia* and leave it for about 2 min.
- Flush carefully the reactive path of the reactor with air; collect all reactor effluents and disposed them according to the EH&S guidelines for strong acid wastes.
- Flush thoroughly the reactor with aqueous phosphate buffer for 10 residence times, and then flush the reactor with water for 10 residence times.
- Check the pH of the effluent; repeat the previous operation if necessary.

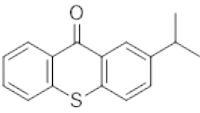
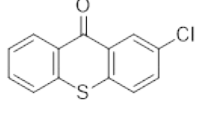
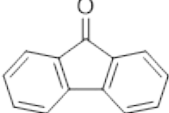
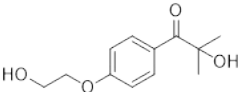
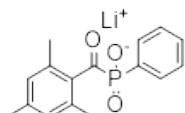
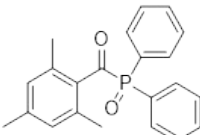
3. Additional experimental results

3.1. Preliminary optimization with various Norrish Type I & II photosensitizers

The samples were loaded in a 25 mL flask and were irradiated over 10 min with 365 nm LEDs (12 LEDs, U = 28,14 V and A = 0.60 A). Offline UV spectra were recorded after 5 and 10 min. The results are presented in Table S2. Size evaluation was made by comparison with data proposed by Sigma Aldrich^{S1}, which are in good agreement with different correlations calculated^{S2,3}.

Table S2. Preliminary screening of photoinitiators

PI	λ_{\max} (nm)	Type	Coinitiator	Solubility	Color (10 min)	Size evaluation (10 min)	NPs morphology (10 min)
<i>Benzophenone</i> ^{S4} 	343	II	Acetone	Partially soluble	/	/	Nanorods
<i>4,4'-Bis(diethylamino)benzophenone</i> ^{S5} 	365	II	Isopropanol (water : co-initiator = 50:50)	Partially soluble	Yellow-brown	Extremely large: >>100 nm	Probably sphere
			Acetone (water : co-initiator = 50:50)	Partially soluble	Yellow-brown	Extremely large: >>100 nm	Probably sphere
			Isopropanol (water : co-initiator = 50:50 & 20:80)	Partially soluble	Pink/Purple (50:50)	Middle: ± 50 nm (50:50)	Sphere (50:50)
<i>4,4'-Dimethoxybenzophenone</i> ^{S6} 	345	II			Purple (20:80)	Large: >100nm (20:80)	
			Acetone (water : co-initiator = 50:50 & 20:80)	Soluble (only for water : co-initiator = 20:80)	Purple (50:50)	Large: ± 70 nm (50:50)	Nanorod (50:50)
					Blue (20:80)	Very large: >>100 nm (20:80)	
<i>Thioxanthone</i> ^{S7} 	380	II	Isopropanol (water : co-initiator = 50:50)	Partially soluble	/	Large (± 90 nm)	Sphere
			Acetone (water : co-initiator = 50:50)	Partially soluble	/	/	Nanorod
<i>2,4-Diethylthioxanthone</i> 	N.A.	II	Isopropanol (water : co-initiator = 50:50)	Insoluble	/	/	/
			Acetone (water : co-initiator = 50:50)	Partially soluble	Blue	Very large (>100 nm)	Sphere

<p><i>2-Isopropylthioxanthone</i>⁵⁷</p> 	386	II	<p>Isopropanol (water : co-initiator = 20:80)</p> <p>Acetone (water : co-initiator = 20:80)</p>	<p>Partially soluble</p> <p>Soluble</p>	<p>Pink</p> <p>Transparent but pink on the beaker walls</p>	<p>/</p> <p>(no signal because NPs on the walls)</p>	<p>Nanorod</p> <p>/</p>
<p><i>2-Chlorothioxanthone</i>⁵⁷</p> 	388	II	<p>Isopropanol (water : co-initiator = 20:80)</p> <p>Acetone (water : co-initiator = 20:80)</p>	<p>Partially soluble</p> <p>Soluble</p>	<p>Purple</p> <p>Pink /purple</p>	<p>/</p> <p>Large (± 70 nm)</p>	<p>Nanorod</p> <p>Sphere</p>
<p><i>Fluorenone</i>⁵⁸</p> 	397	II	<p>Isopropanol (water : co-initiator = 50:50)</p>	<p>Insoluble</p>	<p>/</p>	<p>/</p>	<p>/</p>
<p><i>2-Hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (I-2959)</i>⁵⁹</p> 	274	I	<p>Acetone (water : co-initiator = 50:50)</p>	<p>Partially soluble</p>	<p>Pink</p>	<p>Large (± 70 nm)</p>	<p>Sphere</p>
<p><i>Lithium phenyl-2,4,6-trimethylbenzoylphosphinite (LAP)</i>⁵¹⁰</p> 	375	I	<p>/</p>	<p>Soluble</p>	<p>Red/purple</p>	<p>Large</p>	<p>Sphere</p>
<p><i>Diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide</i>⁵¹¹</p> 	368, 382, 397	I	<p>/</p>	<p>Insoluble</p>	<p>/</p>	<p>/</p>	<p>/</p>

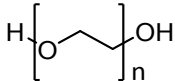
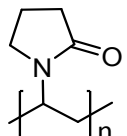
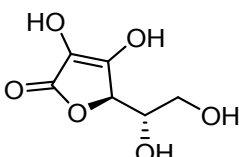
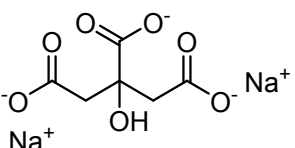
3.2. Identification of the most suitable stabilizer

Different stabilizers were tested to stabilize Au NPs. Five different experiments were carried out to evaluate their binding strength under different conditions (Table S3) using the Corning® Advanced-Flow™ Lab Photo Reactor. The results are presented in Table S4 and are representative for the five conditions tested. Citrate appeared as the most promising stabilizer because it binds to gold but not too strongly, enabling stability as well as relatively fast NPs nucleation and growth.

Table S3. Experimental conditions to evaluate the efficiency of different stabilizers

	Wavelength (nm)	Temperature (°C)	Light intensity (%)	Feed gold (mL min ⁻¹)	Feed LAP + stabilizer (mL min ⁻¹)	Residence time (s)
1	405	25	50	1.25	1.25	60
2	405	25	50	2.5	2.5	30
3	405	25	50	5	5	15
4	405	25	80	2.5	2.5	30
5	405	25	80	5	5	15

Table S4. Preliminary screening of stabilizers

Stabilizer	Interaction with Au	Repulsions	Solution color	Type of NPs	Stability
<p><i>Polyethylene glycol (PEG)</i>^{S12} (300 g/mol)</p> 	Lone pair of oxygen	Steric	Red	NPs	Not stable
<p><i>Polyvinylpyrrolidone (PVP)</i>^{S13} (10 000 g/mol)</p> 	Lone pair of nitrogen or oxygen	Steric	Orange	Ultrasmall NPs	Stable
<p><i>Ascorbic acid</i>^{S14}</p> 	Lone pair of oxygen	Electrostatic	Red	NPs	Not stable
<p><i>Sodium citrate</i>^{S15}</p> 	Lone pair of oxygen	Electrostatic	Red	NPs	Stable

3.3. Estimation of the impact of 2,4,6-trimethylbenzoic acid as a stabilizing agent

This section aims to estimate whether the 2,4,6-trimethylbenzoic acid (**TMBA**), the product obtained subsequently to the homolytic cleavage of **LAP**, can play a role as a stabilizing agent of the gold nanoparticles. To do so, a solution of HAuCl_4 (0.66 mM) in phosphate buffer (1.98 mM) was engaged in a reaction with a feed containing **LAP** (1.98 mM) and **TMBA** (1.98 mM) in a Corning® Advanced-Flow™ Lab Photo Reactor. The reaction was performed at 40 °C under LED irradiation (405 nm). The results are shown in Figure S6.

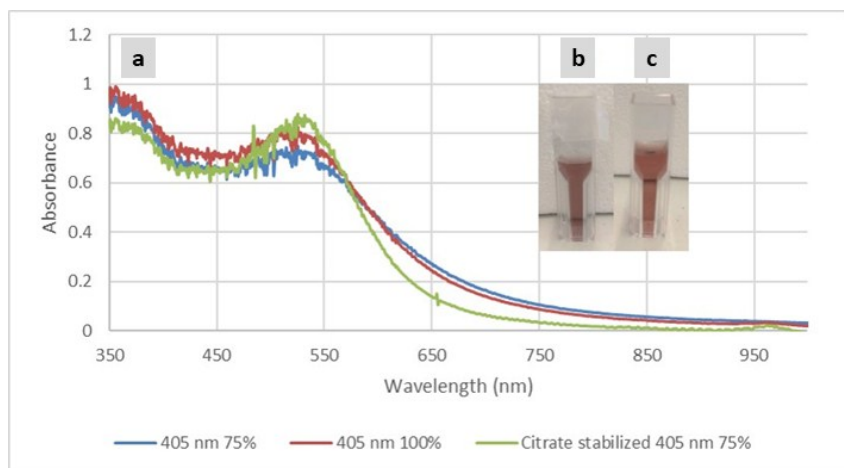


Figure S6. Estimation of **TMBA** as stabilizing agent compared with citrate capped AuNPs. (a) Impact of light intensity; (b) picture of 405 nm 75%; (c) picture of 405 nm 100%

These results show that **TMBA** can play a role as a stabilizing agent during the synthesis of gold NPs. However, the size distribution is wider with **TMBA** than with citrate.

3.4. Identification of suitable conditions for avoiding gold coating

Figures S7 shows the characteristic gold coating obtained upon irradiation at 405 nm of an aqueous mixture of **LAP**/citrate and chloroauric acid at pilot and production scales.

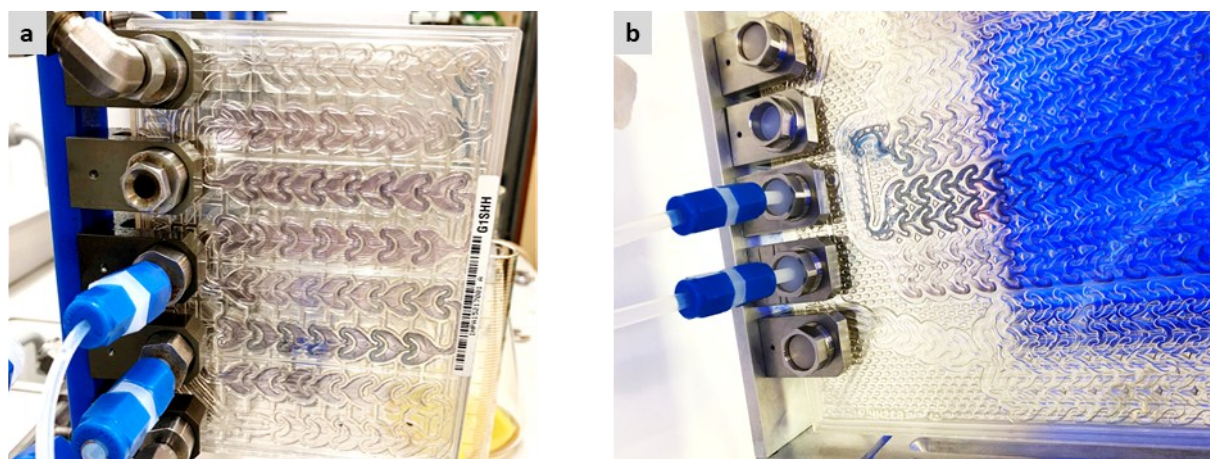


Figure S7. Pink/purple gold coating along the channels surface in (a) G1 Photo Reactor, (b) G3 Photo Reactor.

3.4.1. Biphasic conditions

Heptane was selected as an immiscible carrier in a Corning® Advanced-Flow™ Lab Photo Reactor. Different ratios between the organic and aqueous phases were tested for a fixed total flow rate. Samples were collected and analyzed (Figure S8). The presence of a gold coating was checked after each experiment. Gold coating was observed for low heptane/water ratios. Increasing the proportion of the organic hydrophobic phase (for a constant total flow rate) reduced the size and the amount of NPs formed. For similar irradiation times within the reactor, a larger proportion of the hydrophobic phase reduces the quantity of photoexcited PI formed because it locally dilutes the amount of PI present at a precise position in the reactor. Therefore, the amount of radicals able to reduce Au⁺³ decreases and smaller and fewer NPs are thus produced.

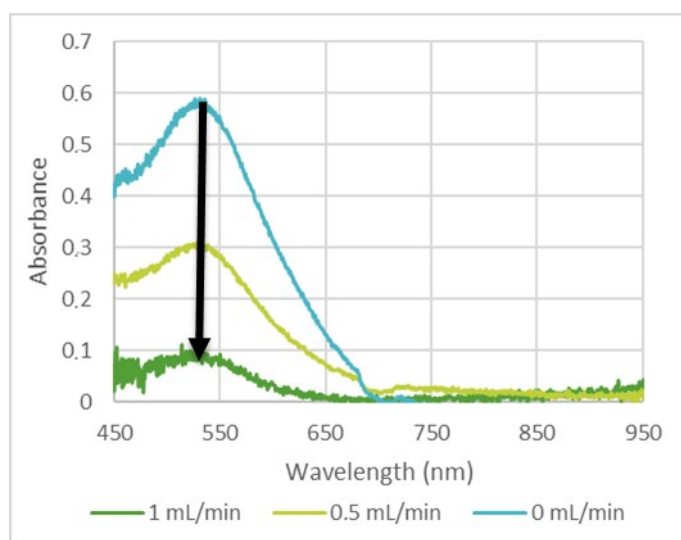


Figure S8. Au NPs obtained after 30 s of residence time (total flow rate = 5 mL min⁻¹) with different flow rates of n-heptane.

3.4.2. Hydrophobic coating

Sigmacote® was utilized for the tentative silanization of the inner glass surface of the Corning® Advanced-Flow™ Lab Photo Reactor. The silanization was carried out following a conventional protocol. Despite the hydrophobic coating, the photochemical preparation of Au NPs led to a yellow coating, characteristic of bulk gold (see manuscript, Figure 5b).

3.5. Control experiments

Different control tests were carried out in the Corning® Advanced-Flow™ Lab Photo Reactor to identify any interferences between the additives for the reduction of HAuCl_4 towards Au NPs. The results are shown in Table S5 and Figure S9.

Table S5. Control experiments for the continuous flow synthesis of Au NPs with **LAP** (Temperature = 25 °C - Residence time = 30 s).

	Irradiation (365 nm, 50%)	Observations
<i>HAuCl₄ + sodium citrate dihydrate</i>	NO	Transparent solution - No NPs formed
<i>HAuCl₄ + sodium citrate dihydrate</i>	YES	Transparent solution - No NPs formed
<i>HAuCl₄ + sodium citrate dihydrate + LAP</i>	NO	Transparent solution - No NPs formed
<i>HAuCl₄ + sodium citrate dihydrate + LAP</i>	YES	Red solution – NPs formed
<i>HAuCl₄</i>	NO	Transparent solution - No NPs formed
<i>HAuCl₄</i>	YES	Transparent solution - No NPs formed

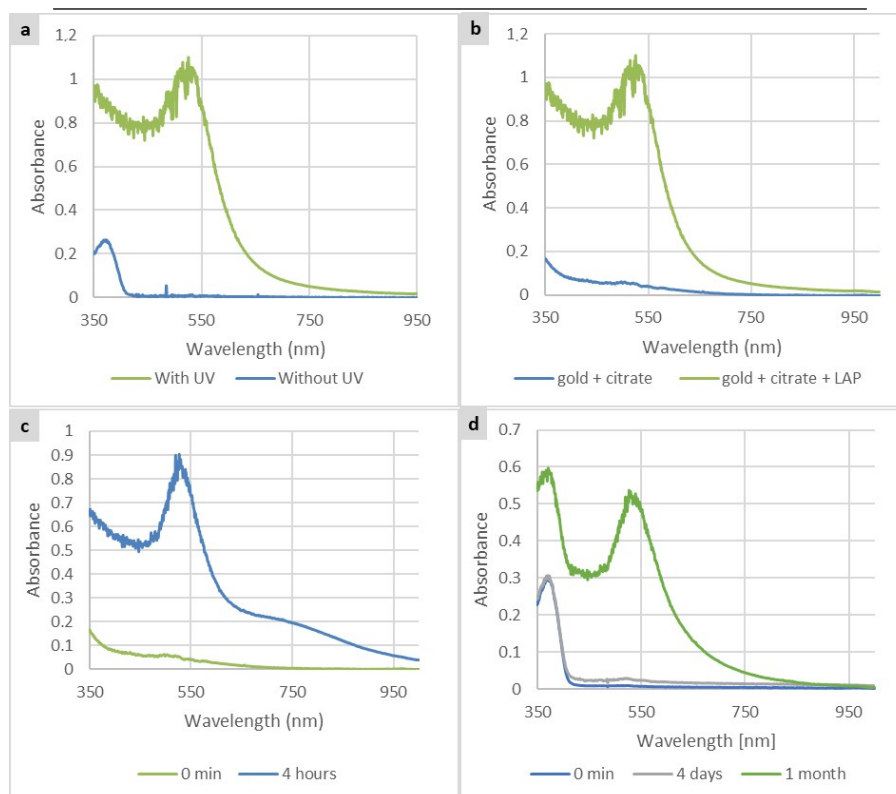


Figure S9. Control experiments for the continuous flow synthesis of Au NPs with **LAP**. (a) Impact of the irradiation on the synthesis of Au NPs with **LAP** and citrate; (b) Effect of **LAP** on the synthesis of Au NPs (light on); (c) Aging of Au NPs obtained with citrate upon irradiation; (d) Aging of Au NPs obtained with **LAP** and citrate but without irradiation.

It can be concluded from Table S5 and Figure S9 that both light and **LAP** are required to generate gold NPs. The direct chemical reduction and the photochemical reduction of chloroauric acid both citrate-promoted are much slower than the photochemical reduction triggered by **LAP**. Under these conditions, **LAP** is the only reducer and citrate acts as the stabilizer.

Even in the occurrence where no NPs are detected in the reactor effluent, it appeared clearly that the irradiation of the solution containing chloroauric acid and citrate (in the absence of **LAP**) enhanced gold reduction. Indeed, NPs were obtained after a few hours for samples irradiated for 30 s in the reaction (Figure S9c) instead of a few days (Figure S9d). It is therefore crucial that the reaction promoted by **LAP** is completed within the reactor in order to avoid any additional reductions by citrates, and a degradation of the quality of Au NPs in the collection flask.

3.6. Control of the pH

3.6.1. Stabilization of the pH

Different control tests were carried out in the Corning® Advanced-Flow™ Lab Photo Reactor to identify suitable conditions to stabilize the pH upon reaction (Table S6).

Table S6. Stabilization of the pH for the preparation Au NPs

Strategy	Target pH	Results
<i>Adjust pH of the gold solution as well as of LAP and citrate with KOH 0.1 M</i>	Variable (7 to 10)	Gold solution not stable over time, decrease of pH (8.44 → 7.25 after 1 h) Difficulties to reach the target pH because a very small deviation from the pH of LAP leads to large differences of pH after mixing the two solutions.
<i>Adjust the pH of the solution of LAP and citrate with KOH 0.1 M to 10.82</i>	7	The required quantity of OH ⁻ to neutralize HAuCl ₄ into AuCl ₄ ⁻ is much larger than that for adjusting pH.
<i>In situ neutralization of the gold feed (1.32 mM because of dilution x2) with a feed of KOH (1.32 mM and 132 mM)</i>	7	pH is too low at the output of the reactor: 5.5
Working in a phosphate buffer 1.98 mM	7	Stable over time

Figure S10 shows that hydroxide ions are consumed during complexation with Au³⁺ overtime, explaining the drastic pH drop for the chloroauric acid solution. The various complexed species, AuCl₄⁻, AuCl₃OH⁻, AuCl₂(OH)₂⁻, AuCl(OH)₃⁻, Au(OH)₄⁻ are predominantly found at pH 3.3, 6.2, 7.1, 8.1 and 12.9 respectively. Their reactivity decreases when the number of hydroxide ligands increases.

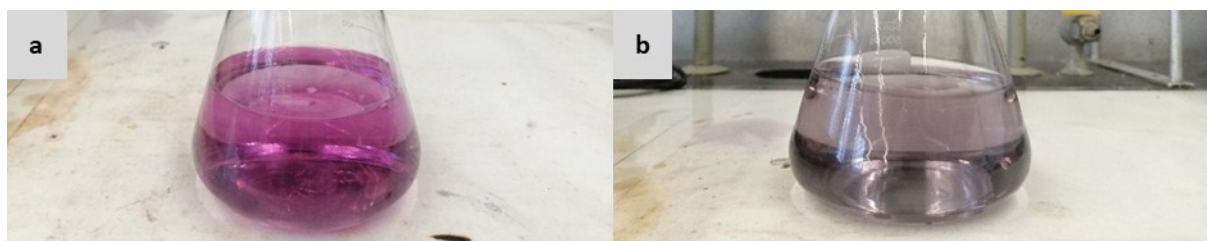


Figure S10. (a) fresh solution of HAuCl_4 0.66 mM, KOH 0.1 M and a few drops of phenolphthalein – pH = 8 (b) solution of HAuCl_4 0.66 mM, KOH 0.1 M and a few drops of phenolphthalein after 4 h of aging – pH = 6.

3.6.2. Impact of the pH on the population of anionic citrate

From the preliminary tests (see section 3.6.1), it appeared that the most suitable pH to photogenerate Au NPs is ~ 7 . Indeed, at this pH, citrate is predominantly fully deprotonated (80%, Figure S11), which is critical for ensuring an efficient stabilization of Au NPs^{S16} and for preventing the gold coating on the inner wall of the reactor.

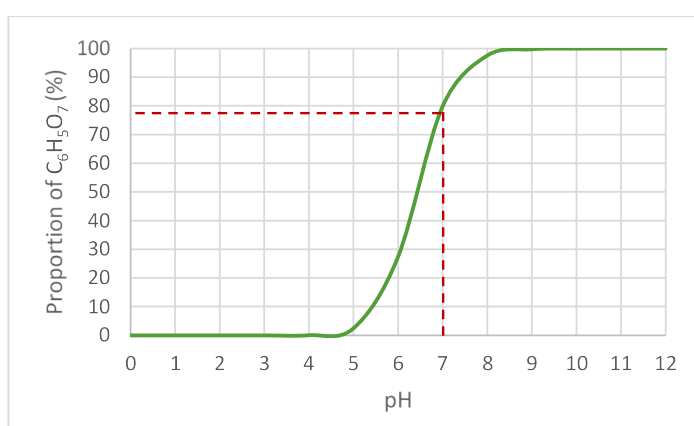


Figure S11. Speciation of fully deprotonated citrate

3.6.3. Stability of the gold and LAP/citrate solutions in phosphate buffer

The two solutions were stable (Figure S12) as long as they were protected from light.

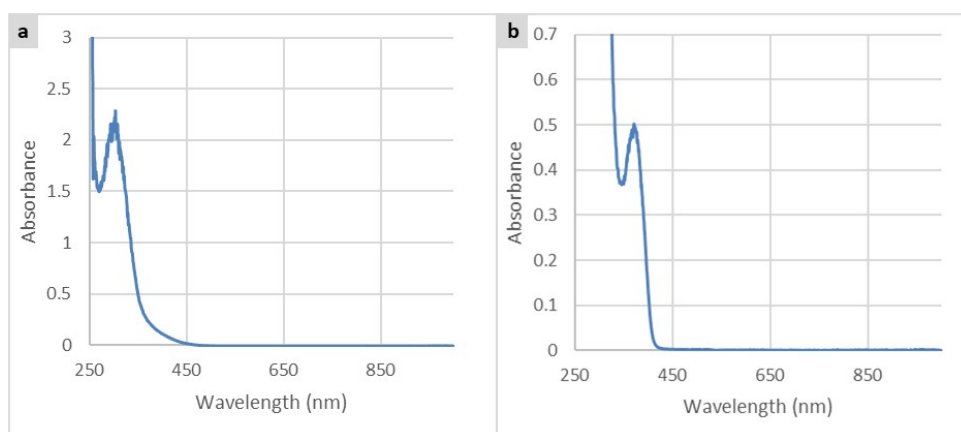


Figure S12. UV spectra of gold solution (a) and LAP (b) in phosphate buffer (1.98 mM)

3.6.4. Effect of the irradiation wavelength on the synthesis of Au NPs

Different control tests were carried out in the Corning® Advanced-Flow™ Lab Photo Reactor using a 0.66 mM solution of HAuCl_4 in phosphate buffer (1.98 mM) and a solution of **LAP**/citrate (both 1.98 mM) in phosphate buffer (1.98 mM). Since the absorption of **LAP** depends on the incident wavelength, it is important to check the impact of the wavelength on the Au NPs synthesis (Figure S13). The maximum absorption of **LAP** is at 375 nm. Therefore, an irradiation at 365 and 385 nm is much more efficient than at 405 nm. Despite that working at 405 nm gives a smaller concentration of larger NPs, it also enables a more precise tuning of the experimental parameters. Indeed, the LSRP of Au NPs does not vary a lot when the light is set at 365 or 385 nm. Therefore, decision was made to consider the irradiation at 405 nm for the rest of the experiments.

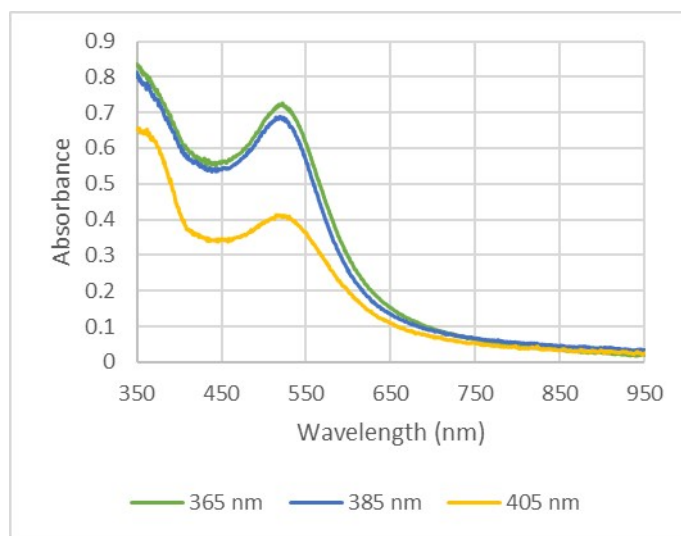


Figure S13. Impact of the light wavelength on the preparation of Au NPs

3.7. Characterization

3.7.1. Color

Figure S14 shows the effect of residence time on the particle size. The red color is typical of spherical Au NPs. The NPs size increases with the residence time since the solutions become increasingly darker.

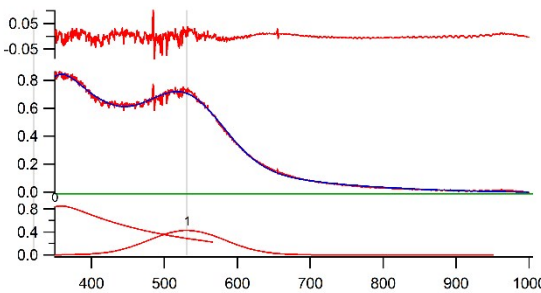


Figure S14. Impact of the residence time on the preparation of Au NPs

3.7.2. UV spectroscopy

3.7.2.1. Software treatment of the UV spectra obtained

The data from the UV spectra were treated with Igor®. The peak wavelength corresponds to the location of the Gaussian peak.

<p>Y data wave: [0, 1125] X data wave: root:Wavelength Chi square: 0.17224 Total fitted points: 1126 Multi-peak fit version 2.22 Total Peak Area = 229.67 +/- 0.49686</p>	<p>BaselineType: Constant $y_0 = -0.012174 \quad +/- \quad 0.0013059$</p> 
<p>Peak 0 Type: ExpModGauss</p> <p>Location = 358.38 Height = 0.85483 Area = 173.83 +/- 0.016118 FWHM = 157.2 Gauss Loc = 321.21 +/- 2.76 Gauss Height = 2.9279 +/- 0.18117 Gauss FWHM = 55.774 +/- 4.3461 Exp Tau = 147.34 +/- 1.4278</p> <p>Fit function parameters</p> <p>GaussX0 = 321.21 +/- 2.76 GaussWidth = 23.685 +/- 1.8456 Height = 2.9279 +/- 0.18117 ExpTau = 147.34 +/- 1.4278</p>	<p>Peak 1 Type: Gauss</p> <p>Location = 530.97 +/- 0.20129 Height = 0.42985 +/- 0.0021371 Area = 55.842 +/- 0.49659 FWHM = 122.04 +/- 0.6859</p> <p>Fit function parameters</p> <p>Location = 530.97 +/- 0.20129 Width = 73.293 +/- 0.41192 Height = 0.42985 +/- 0.0021371</p>

3.7.2.2. Typical UV spectrum

A typical spectrum of the NPs formed in this work is shown in Figure S15.

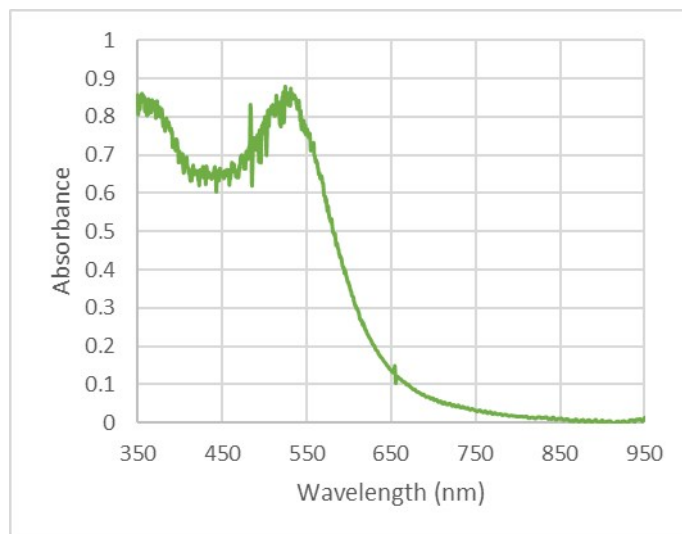


Figure S15. Typical UV spectrum of Au NPs obtained during this work. Conditions: HAuCl_4 = 0.66 mM; **LAP** = 1.98 mM; citrate = 1.98 mM; Flow rates = 6.25 mL min^{-1} ; Residence time = 12 s; $T = 40 \text{ }^\circ\text{C}$; $\text{pH} = 7$; Wavelength = 405 nm (75%).

3.7.2.3. Transmission Electron Microscopy

The samples were prepared by deposition of a drop of Au NP aqueous colloidal solution onto carbon-coated copper grids (SPI), followed by drying at room temperature, with no other additional treatments. Figure S16 shows spherical Au NPs with a mean size of 5.24 nm, and a size distribution of 0.59 nm.

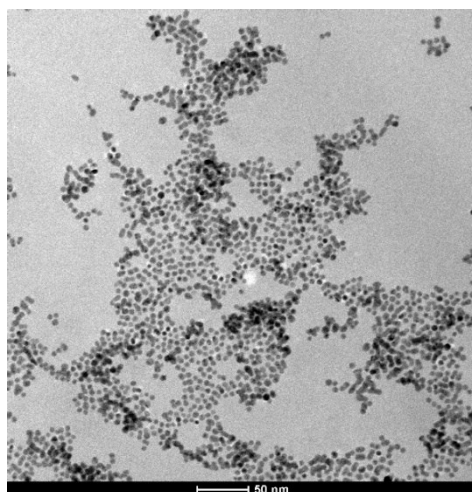


Figure S16. Typical TEM spectrum of a representative sample of Au NPs. Conditions: HAuCl_4 = 0.66 mM; **LAP** = 1.98 mM; citrate = 1.98 mM; Flow rates = 6.25 mL min^{-1} ; Residence time = 12 s; $T = 40 \text{ }^\circ\text{C}$; $\text{pH} = 7$; Wavelength = 405 nm (75%).

There is a non-negligible difference between sizes predicted from UV spectroscopy and those calculated from TEM images. This difference is likely related to the anisotropy of some Au NPs, which could lead to a red-shift of the maximum wavelength of the LSPR.

3.7.2.4. Nuclear magnetic resonance

Samples were prepared by increasing the pH of samples to 11 with NaOH 1 M, adding acetone (1 eq. to water) until precipitation occurred; then the solutions were centrifuged 15 min at 5000 rpm and filtrated to recover the Au NPs. NMR samples were then prepared by suspending the Au NPs in D₂O. Samples were analyzed by ¹H NMR and ³¹P NMR (not shown) to determine the nature of ligands capping the Au NPs. Figure S17 shows the different spectra obtained. Since the peaks relative to **LAP** are absent in the spectrum of Au NPs, one can conclude that the fragments formed during the Norrish Type I cleavage do not contribute to the stabilization of Au NPs. However, the NMR data indicate that several equivalents of citrate act as ligands. This is confirmed by the presence of the two CH₂ of citrate on the ¹H NMR spectrum of Au NPs. Citrate in phosphate buffer is characterized by two doublets coupled at 2.55 and 2.45 ppm (AB system: $J = 15.1$ Hz). When it is bound to Au NPs, the peaks are shifted to 2.65 and 2.15 ppm^{S17,18}. The absence of phosphorous ligands derived from **LAP** was also confirmed by the absence of relevant peaks in the corresponding ³¹P NMR spectrum.

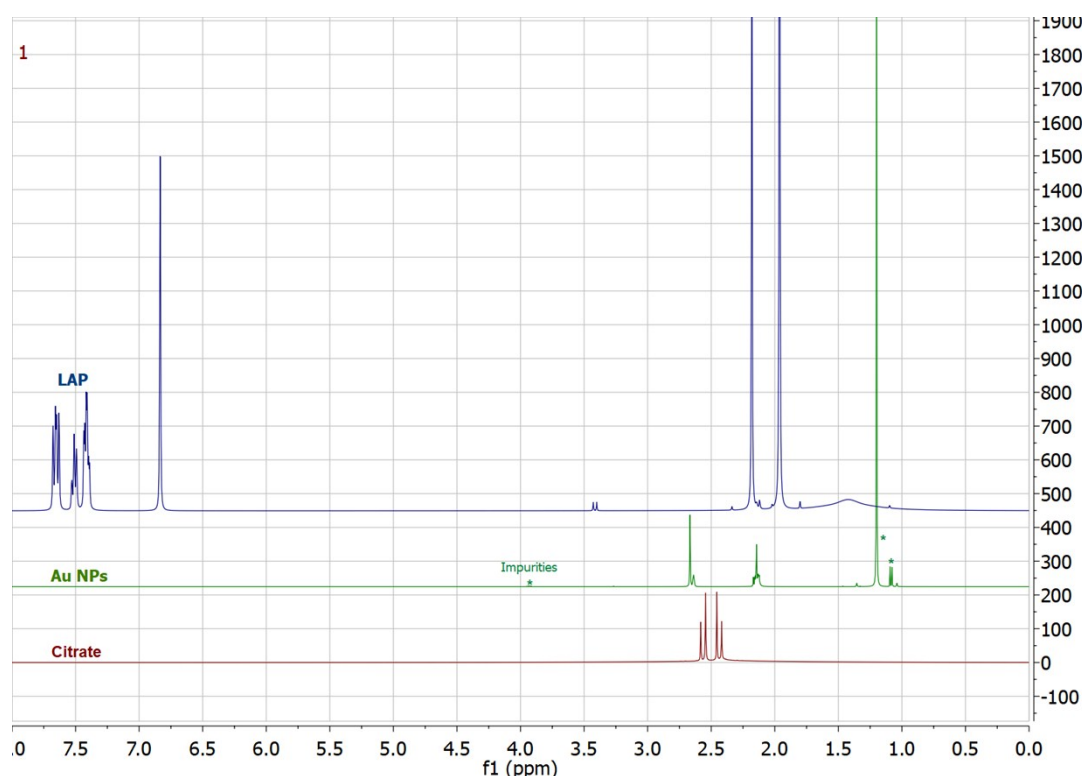


Figure S17. Characterization of Au NP ligands by ¹H NMR (400 MHz, D₂O). Blue: **LAP** (1.98 mM) in phosphate buffer (1.98 mM, pH 7). Green: Au NPs in phosphate buffer (1.98 mM, pH 7). Red: sodium citrate (1.98 mM) in phosphate buffer (1.98 mM, pH 7).

3.8. Comparison with I-2959

Trials for the continuous flow photochemical synthesis of Au NPs with **I-2959** and without gold deposits were made for further comparisons with **LAP**. Citrate was not strong enough to stabilize Au NPs and prevent gold deposits. Therefore, 3-mercaptopropionic acid (3-MPA) was selected as a new ligand since sulfur binds more strongly to gold than oxygen. Its concentration was adjusted to afford an efficient stabilization without affecting too much the kinetics related to the NPs formation. Moreover, the pH of the reaction mixture had to be increased since thiolate anions are only obtained in significant amounts when the pH is high enough ($pK_a = 10.3$). The concentration of **I-2959** was also increased to 2.5 mM instead of 1.98 mM to enhance the formation of Au NPs. In the same way, the temperature was also increased to 30 °C instead of 25 °C for **LAP**, as well as residence time. Since **I-2959** has a maximum absorption at 274 nm, it does not absorb at 405 nm. The irradiation was therefore performed at 365 nm. Despite all these changes with a view of improving the reaction efficiency, results obtained with **I-2959** were much less convincing than those obtained with **LAP** (Figure S18).

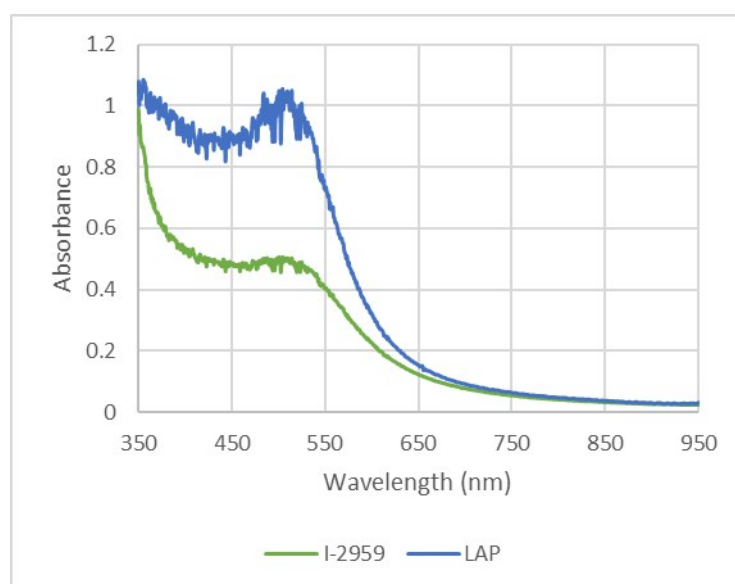
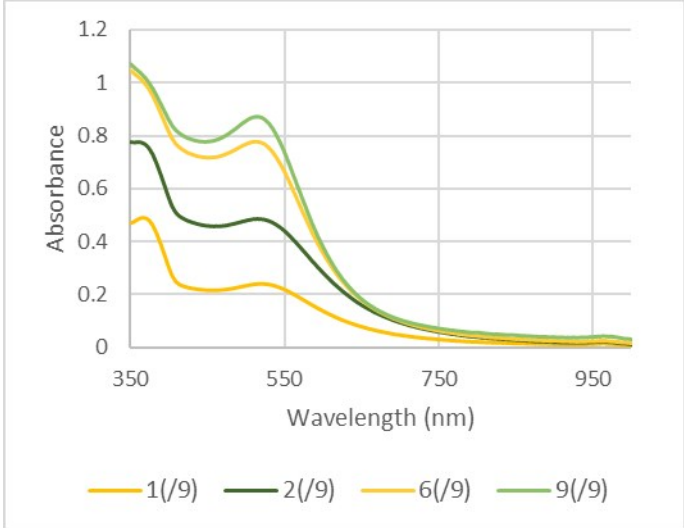
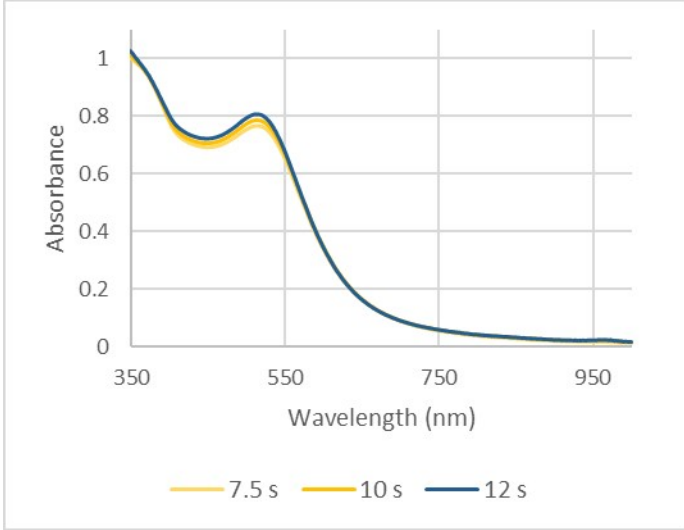


Figure S18. Comparison between **I-2959** and **LAP** for the continuous flow synthesis of gold NPs. Conditions for **I-2959**: $\text{HAuCl}_4 = 0.66 \text{ mM}$; **I-2959** = 2.5 mM; 3-MPA = 0.198 mM; Flow rates = 0.36 mL min^{-1} ; Residence time = 3.5 min; $T = 30 \text{ }^\circ\text{C}$; $\text{pH} = 9$; Wavelength = 365 nm (100%). Conditions for **LAP**: $\text{HAuCl}_4 = 0.66 \text{ mM}$; **LAP** = 1.98 mM; citrate = 1.98 mM; Flow rate = 5 mL min^{-1} ; Residence time = 15 s; $T = 25 \text{ }^\circ\text{C}$; $\text{pH} = 7$; Wavelength = 365 nm (100%).

3.9. Fine tuning of the conditions and reproducibility tests in the Corning® Advanced-Flow™ G3 Photo Reactor

Table S7. Tuning of the conditions for the Au NPs photochemical synthesis with a G3 Photo reactor.

Parameter	Results
Light intensity	
Residence time	

Video S1 illustrates the short residence times which are achieved for this photogeneration of Au NPs under continuous flow conditions. Only 8 s are required to collect approximately 40 mL of Au NPs when the total flow rate is fixed at 300 mL min⁻¹ (10 s of residence time).



Au NPs at production scale.mp4

Video S1. Au NPs obtained at a production scale under optimized conditions and with a residence time of 10 s.

The robustness of this protocol was tested by performing two different runs operated with the same experimental conditions for both the pilot and the industrial scale reactors. Results from Figure S19 show that similar LSPR profiles are obtained, which proves the reproducibility at different scales.

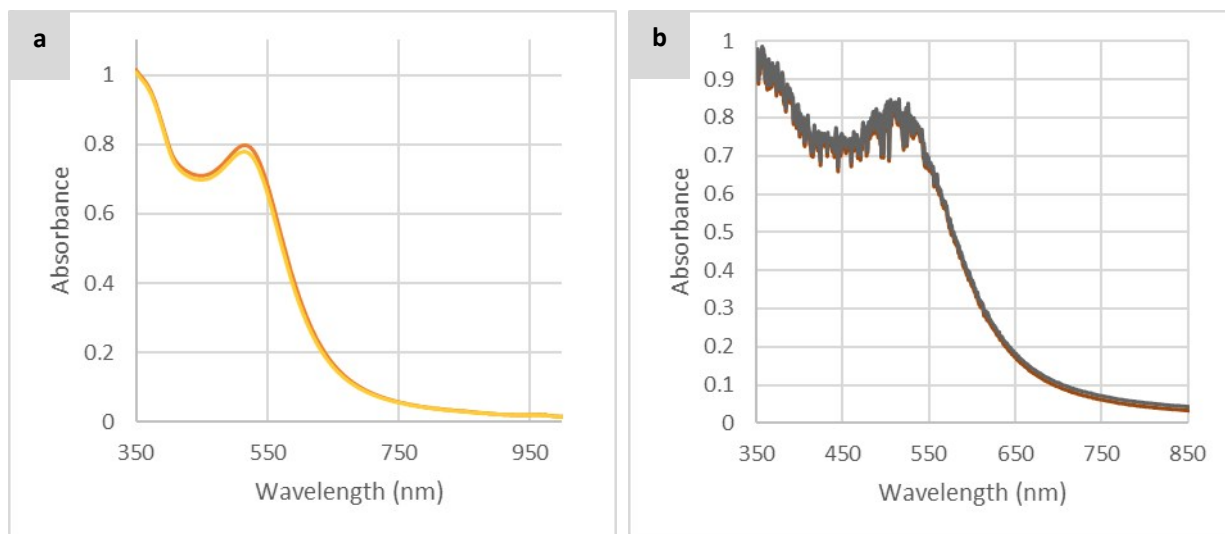


Figure S19. Reproducibility tests with two different runs (a) G3 Photo Reactor (Conditions: $\text{HAuCl}_4 = 0.66 \text{ mM}$; **LAP** = 1.98 mM; citrate = 1.98 mM; Flow rates = 150 mL min^{-1} ; Residence time = 10 s; $T = 40 \text{ }^\circ\text{C}$; $\text{pH} = 7$; Wavelength = 405 nm (100%)), (b) G1 Photo Reactor. Conditions for **LAP**: $\text{HAuCl}_4 = 0.66 \text{ mM}$; **LAP** = 1.98 mM; citrate = 1.98 mM; Flow rate = 100 mL min^{-1} ; Residence time = 12 s; $T = 40 \text{ }^\circ\text{C}$; $\text{pH} = 7$; Wavelength = 405 nm (100%).

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