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The Prospect of Photochemical Reactions in Confined Gel Media

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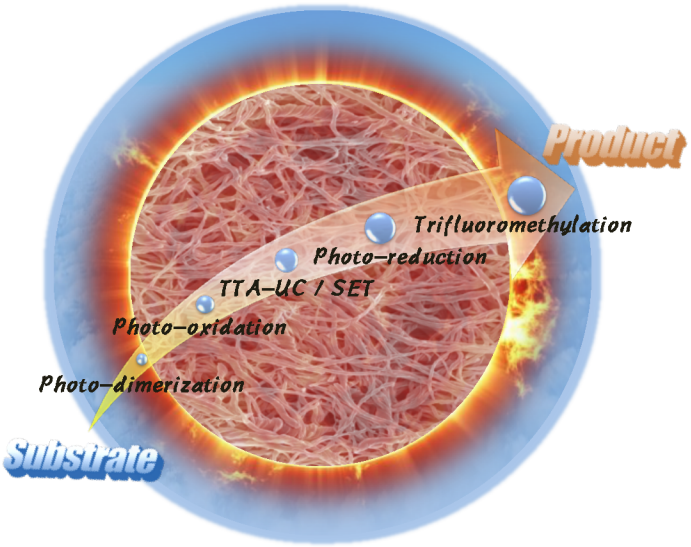
CONSPECTUS

Nature is capable *per se* to control kinetics, conversion and selectivity of biochemical processes by means of confined reaction environments such as enzyme pockets, bilayer membranes, micelles, vesicles, cells or bioorganic frameworks. The main reason for this fact is the optimal molecular alignment and restricted motion of reactant molecules compared to those found in bulk solution. Under this inspiration, a number of synthetic photonanoreactors based on supramolecular self-assembled systems have been developed during the last decades, including mesoporous inorganic materials, microemulsions, micelles, vesicles, lipid bilayers foams, polyelectrolyte nanoparticles, etc. In a broader sense, nanoreactors technology constitutes nowadays a promising tool to enhance organic synthesis under sustainable reaction conditions. In general, nanoreactors change the essential properties of the molecules within them, thus affecting their chemical reactivity. Among the nanoreactor-like systems described in the literature to facilitate photochemical processes, the more recent use of viscoelastic supramolecular gels, typically made of low-molecular-weight (LMW) compounds self-assembled through non-covalent interactions, as compartmentalized reaction media is particularly appealing due to the versatility of these materials in terms of fabrication, properties and processability. Furthermore, the high specific surface areas found in supramolecular gels, their stimuli-responsive reversibility, good diffusion properties -enhancing the interactions between reactants and the

three dimensional (3D) porous network-, functional tuneability and blocking effect of external oxygen, are some of the most important features that can benefit photoinduced processes carried out in confined gel media. Not surprisingly, the efficiency of photochemical processes inside gel media is largely dependent on the type of reaction, characteristics of the gel network, solvent nature, reactants properties and reaction conditions. Thus, the main focus of this report is to provide a concise overview of the most relevant examples reported by us and others in order to illustrate the main advantages associated to the emerging use of gel-based materials as non-conventional reaction media to facilitate and control photochemical reactions. In particular, photodimerization, triplet-triplet annihilation upconversion (TTA-UC) coupled to single electron transfer (SET), photooxidation, photoreduction and trifluorometylation reactions will be illustrated during the discussion. These examples suggest that gel-based media can provide a versatile platform for the discovery of new reaction pathways and facilitate the way that photochemical reactions are traditionally carried out in academia and industry in terms of reaction conditions and required infrastructure. In addition, the use of physical or chemical gels as reaction systems may also accelerate high-throughput screening of photocatalysts. Overall, a judicious choice of gelators, reactants, solvent and reaction conditions for the assembly of these gelators is crucial for controlling conversion, kinetics and selectivity of intragel photo-induced processes.



INTRODUCTION

Over millions years of evolution, nature has optimized confined and compartmentalized environments such as cell organelles to carry out sophisticated chemical reactions with a precise control of kinetics and selectivity. This has inspired research groups all over the world to develop artificial nanoreactors based on hierarchical self-assembly of low-molecular-weight (LMW) molecules through non-covalent interactions (e.g. hydrogen-bonding, van der Waals, charge-transfer, dipolar, π-π stacking).[1,2] In this context, photochemistry is a major beneficiary of reactivity in confined spaces, including for example mesoporous inorganic materials,[3] microemulsions,[4] micelles,[5,6,7] vesicles,[8] lipid bilayers[9] foams,[10] polyelectrolyte nanoparticles[11] and gels.[12,13] In general, the proper confinement of reactants in these media improve photochemical processes by enhancing key properties such as light absorption and the lifetime of redox intermediates.[14,15]

Among the above-mentioned non-conventional reaction media, supramolecular gels[16] are typically made of LMW compounds (i.e. gelators) self-assembled through non-covalent interactions. The solid-like appearance and mechanical properties of these materials result from the immobilization of the liquid (major component) into the interstices of a self-assembled solid matrix (minor component) due to surface tension and capillary forces. The generation of the 3D-network linked thorough numerous junction points derives from an effective entanglement of 1D-strands of gelator molecules, usually of nm diameters and mm lengths, which can increase the viscosity of the medium by factors up to 10^{10}. In contrast to most covalently crosslinked polymer gels, supramolecular gels usually display reversible *gel*-to-*sol* phase transitions, which can be triggered by a variety of external stimuli responses (e.g. irradiation, temperature, pH, ionic strength). This feature constitutes an important asset for the recycling of the gel media. At this point, it is important to realize that aerobic environments do not compromise the high efficiency of biochemical processes that occur in nature involving different reactive intermediates. In this sense, molecular compartmentalization overcome potential deactivation pathways while enhancing the desired chemical route. Thus, supramolecular gels displaying high specific surface areas, stimuli-responsive reversibility, good diffusion properties and functional tuneability, have recently been identified with a remarkable prospective to mimic compartmentalization of complex natural systems to perform photochemical reactions that are

otherwise more difficult to do. Furthermore, the viscoelastic nature of gel-based materials may also help to reduce overconcentration and overheating effects compared to more rigid systems.

Herein, we wish to provide a brief insight into the potential advantages of carrying out photochemical processes in gels as confining and non-conventional reaction media. Photopolymerization/photo-induced gelation processes[17] and other catalytic reactions (i.e. without using light irradiation) inside gel media are out of the scope of this contribution.[18]

PHOTODIMERIZATION

Motivated by the desire of gaining control on product selectivity, the well-established photodimerization of acenaphthylene (ACN) has been studied in different nanoreactor systems such as nanocapsule, micellar media, polymeric systems, zeolites, clay environments or liquid crystalline systems.[19,20] Maitra *et al.* showed for the first time that ACN photodimerization (Figure 1) in supramolecular hydrogels made of LMW bile acids as reaction media took place with higher selectivity than in homogeneous solution.[21] Specifically, this group reported photodimer ratios *syn*:*anti* (**2**:**3**) 3-10 times higher than the ratio in aqueous or micellar solutions [e.g. sodium dodecyl sulfate (SDS), cetyltrimethylammonium bromide (CTAB), etc.]. Furthermore, when this reaction was further investigated by using different gelators (Figure 1, gelators **4**-**7**), the *syn*/*anti* dimer ratios were found to be largely dependent on the hydrogel rheological properties. Thus, the gels with highest rigidity also showed the highest product selectivity, following the order **6** > **5** > **7** > **4**.

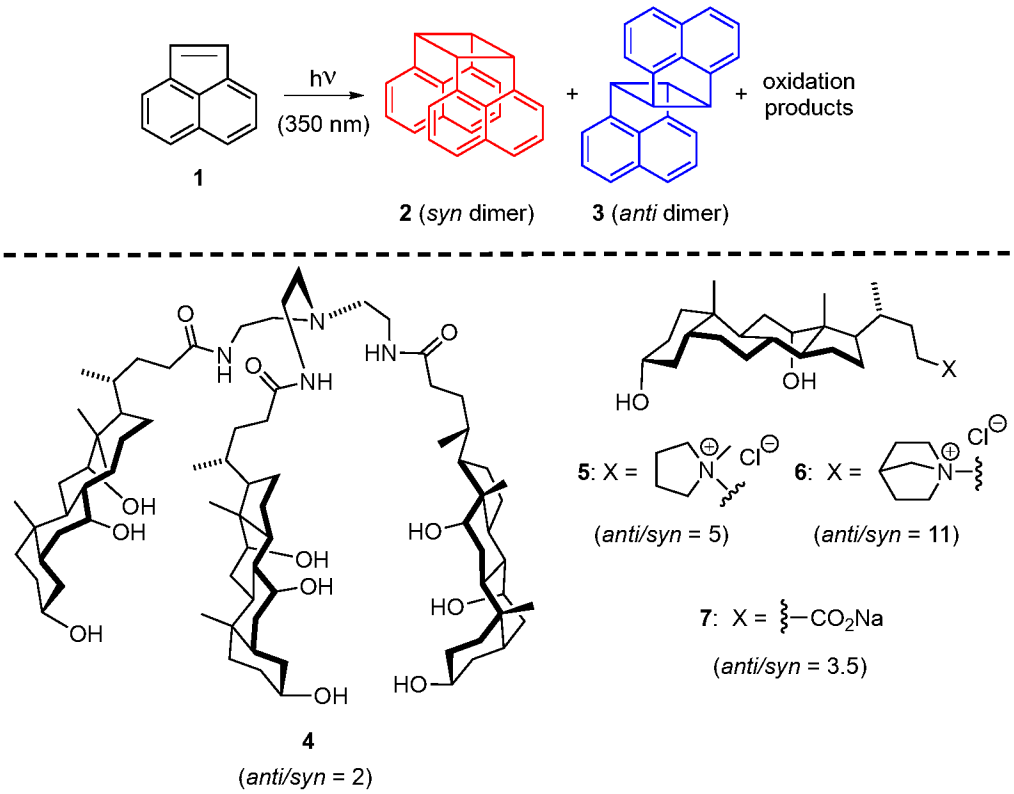


Figure 1. Photodimerization reaction of acenaphthylene (**1**) (*top*) carried out in supramolecular hydrogels made of different LMW gelators **4-7** (*bottom*). *Anti*/*syn* dimer ratios obtained with each gelator are given in brackets.

In 2009, Shinkai *et al.* studied the photodimerization of anthracene carboxylic acid inside a binary gelator based on 3,4,5-tris(*n*-dodecyloxy)benzoylamide substituted D-alanine (Figure 2).[22] Interestingly, the results revealed that only two products (*anti*- and *syn*- head-to-head) were obtained in the gel matrix, differing from the production of the four different [4 + 4] cyclodimers in cyclohexane solution. These early studies put in the spotlight the potential of gel networks to drastically influence the selectivity of photo-induced processes.

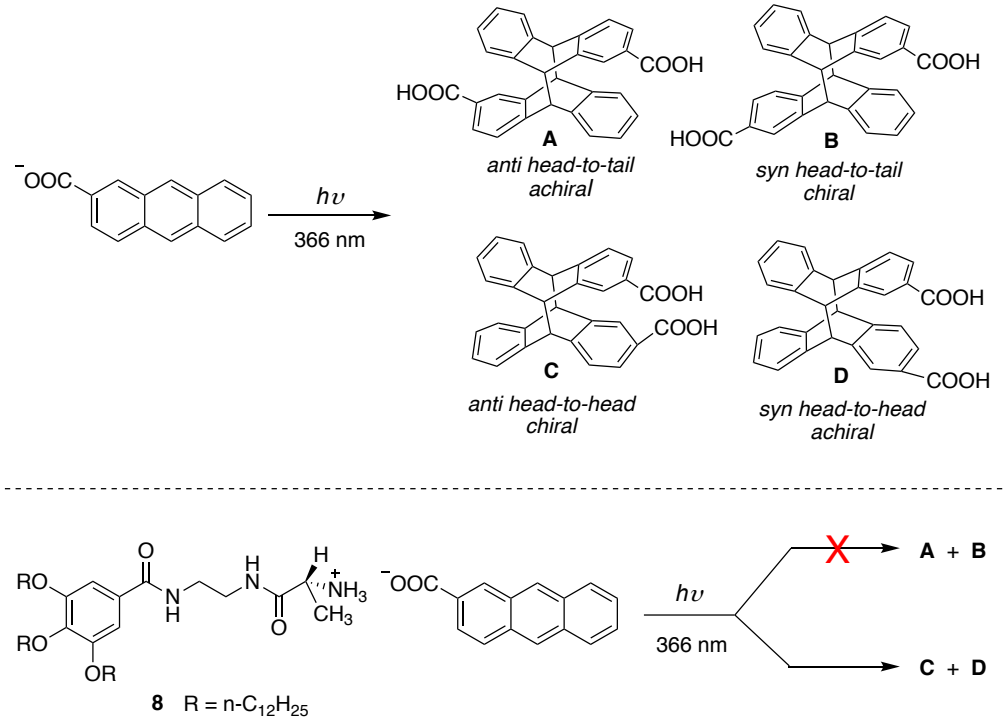


Figure 2. Schematic representation of [4 + 4] photocyclodimerization of 2-anthracenecarboxylic acid in the free state (*top*) and in the cyclohexane gel of binary system **8** (*bottom*) showing the products obtained in each case.

TRIPLET FUSION UPCONVERSION

Photon upconversion (UC) based on triplet-triplet annihilation (TTA) has attracted considerable interest during the last decade due to its low excitation power density demand (ambient sunlight) and readily tunable excitation/emission wavelengths. Indeed, it is also a safer, practically and economically more viable option than commercial UV sources. This technology, which has been successfully applied in different areas such as photocatalysis, photovoltaics, artificial photosynthesis, optics, etc., is capable of transforming visible into UV light involving a bimolecular system (i.e. a sensitizer or donor and an emitter or acceptor) and the connection of multistep photochemical pathways (Figure 3). Briefly, after the absorption of low-energy photons ($h\nu_1$), the triplet excited state (T_1) of the donor (sensitizer) is produced by intersystem crossing (ISC) from the singlet excited state (S_1). Subsequently, triplets of the acceptor (emitter) are populated by triplet-triplet energy transfer (TTET) from the triplets of the sensitizer (Dexter mechanism). When two acceptor molecules in their triplet states are capable of colliding during

their lifetimes, a higher singlet energy level is formed by TTA and, consequently, generates delayed upconverted fluorescence ($h\nu_2$).[23]

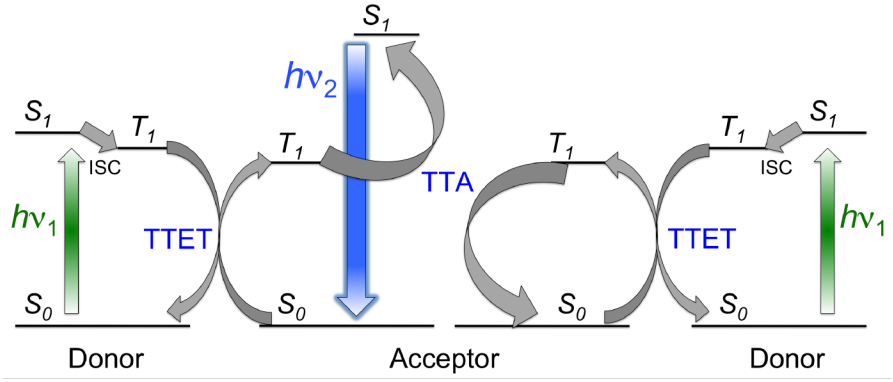


Figure 3. Simplified Jablonski diagram illustrating the mechanism of TTA-UC showing the main energy levels involved in the process (S = singlet, T = triplet). Reprinted with permission from ref. 13. Copyright 2015 Royal Society of Chemistry.

The most efficient TTA-UC processes are usually carried out in solution phase because they allow fast diffusion of excited molecules. However, one of the key requisites of TTA-UC in solution is the anaerobic conditions of the reaction medium due to efficient triplet quenching by oxygen. Therefore, proper sealing of the reaction vessel must be ensured for TTA-UC in solution.[24] In order to block oxygen diffusion, TTA-UC process has been applied under aerated conditions by using different solid polymers or viscous liquids as support material.[25,26,27] However, such solid polymer film or thick matrixes sometimes limit the diffusion of excited triplet molecules, requiring high-power incident photon source to maintain a certain concentration of excited triplet states. Therefore, development of new support materials that shows oxygen-blocking capability and simultaneously allows efficient TTA-UC of the incorporated donor/acceptor couple under low-power excitation appears to be a challenging task. In this context, employment of viscoelastic gel could fulfill the abovementioned criteria, opening a new research area to study the TTA-UC process for the different combinations of suitable donor and acceptor.

Simon *et al*. encapsulated Pd(II) mesoporphyrin IX and 9,10-diphenylanthracene (DPA) as UC chromophore pair into a DMF/DMSO based covalently crosslinked organogel prepared

from poly(vinyl alcohol) and hexamethylene diisocyanate (HMDI) (Figure 4).[28] The crosslinked organogel possessed good mechanical integrity, high molecular mobility, and high optical quality with a transmittance of above 95% in the visible range and additionally provided protection against triplet states quenching by oxygen. The UC quantum yield[29] increased from > 0.6 (under ambient conditions) to 14% (under oxygen-free conditions). Meanwhile, Schmidt *et al.* also reported TTA-UC in a supramolecular tetralin organogel made of 1,3:2,4-bis(3,4-dimethylbenzylidene) sorbitol (DMDBS) and containing palladium tetraphenylporfirin and DPA as UC pair.[30]

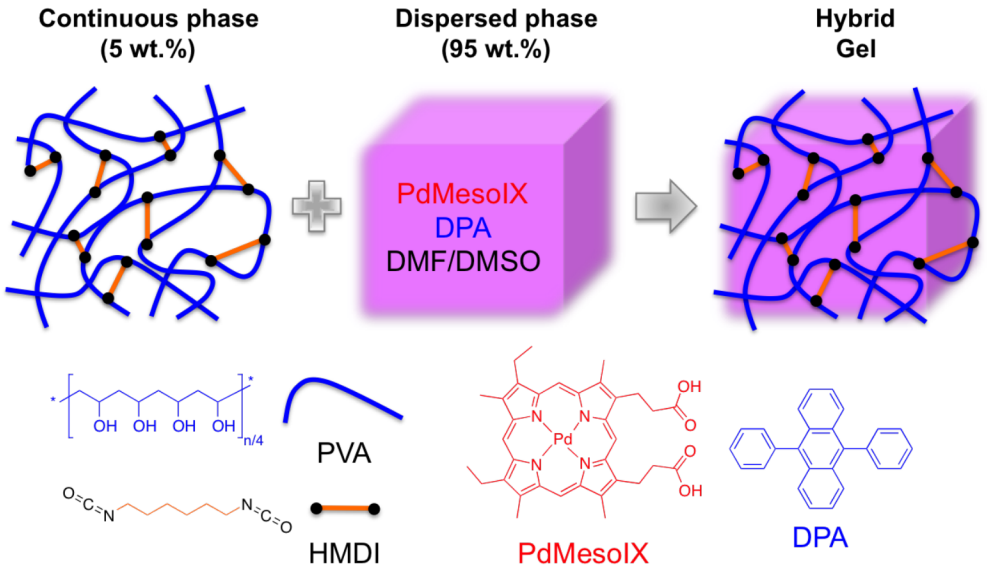


Figure 4. Graphic representation of the structure of the upconverting organogels studied and chemical structures of the constituents used. The photoactive material consists of a continous polymer network and a liquid organic phase in which the upconverting chromophores are dissolved. Adapted with permission from ref. 28. Copyright 2015 Royal Society of Chemistry.

In the same year, Kimizuka *et al.* developed a very efficient TTA-UC process in a supramolecular organogel system under aerobic conditions and low-power excitation.[31] *N,N'*-bis(octadecyl)-L-boc-glutamic diamide (LBG) was used as gel matrix, which can form a stable gel in a wide variety of polar and non-polar solvents due to the formation of hydrogen bond between the amide moieties and van der Waals interactions between the long aliphatic chains of

the gelator molecules (Figure 5A).[32] The well-known bimolecular system consisting of PtOEP (donor) and DPA (emitter) was chosen in this study as suitable TTA-UC pair.[29,33] Excitation of the PtOEP/DPA/LBG ternary gel system (air saturated state) with 532 green laser light caused an upconverted emission at 435 nm, which was similar to that of DPA fluorescence when directly excited with UV light (375 nm). A threshold excitation intensity of 1.48 mW cm^{-2} was observed under aerobic conditions, lower than the solar irradiance of 1.6 mW cm^{-2} at 532 ± 5 nm. Interestingly, the intensity of DPA upconverted emission remained almost unchanged even after exposure to air for 25 days. The upconversion quantum yield values under anaerobic and air-saturated conditions were found to be 2.7% and 1.5%, respectively. Enhancement of the acceptor concentration under air-saturated conditions gave rise to an increment in the upconversion quantum yield value to ca. 3.5%. An exceptionally high oxygen blocking efficiency of 78% was determined from the ratio between the measured lifetime of acceptor triplets for deaerated (228 ms) ternary gels and that for the air-saturated ternary gels. Additionally, the authors also showed that UC emission intensity gradually decreased and reached an almost constant value above the *gel*-to-*sol* transition. This fact was confirmed using the temperature-responsive nature of the fibrous gel network. The disruption of the network upon increasing the temperature caused the quenching of the excited triplet species due to dissolved oxygen. Furthermore, a few more combinations of UC pairs were introduced into the supramolecular gel nanofibers, which enabled some efficient near red-to-cyan, green-to-blue, IR-to-yellow and blue-to-UV wavelength conversions (Figure 5B). Importantly, measurements of the diffusion constant of DPA triplets at different temperatures, as well as studies in different solvents, confirmed a TTA mechanism based on the triplet energy migration (TEM) in the supramolecular organized molecular assembly. This concept involves the integration of donor molecules in the gel fibers (supported by electron microscopy data) with densely accumulated acceptor molecules, where the excitation of donor molecules is followed by donor-to-acceptor TTET, TEM through the acceptor arrays and TTA of excited acceptors. In other words, a proximate preorganization of donor-acceptor and acceptor-acceptor arrangements is crucial for favorable energy transfer processes and TEM in the absence of free molecular diffusion. Such synergistic integration of donor–acceptor pairs in nanofibrous aggregates has been identified as reminiscent of the biological photon-harvesting apparatuses where excitation light energy is effectively harvested and converted in the array of photosynthetic pigments embedded in the biomembranes.[31]

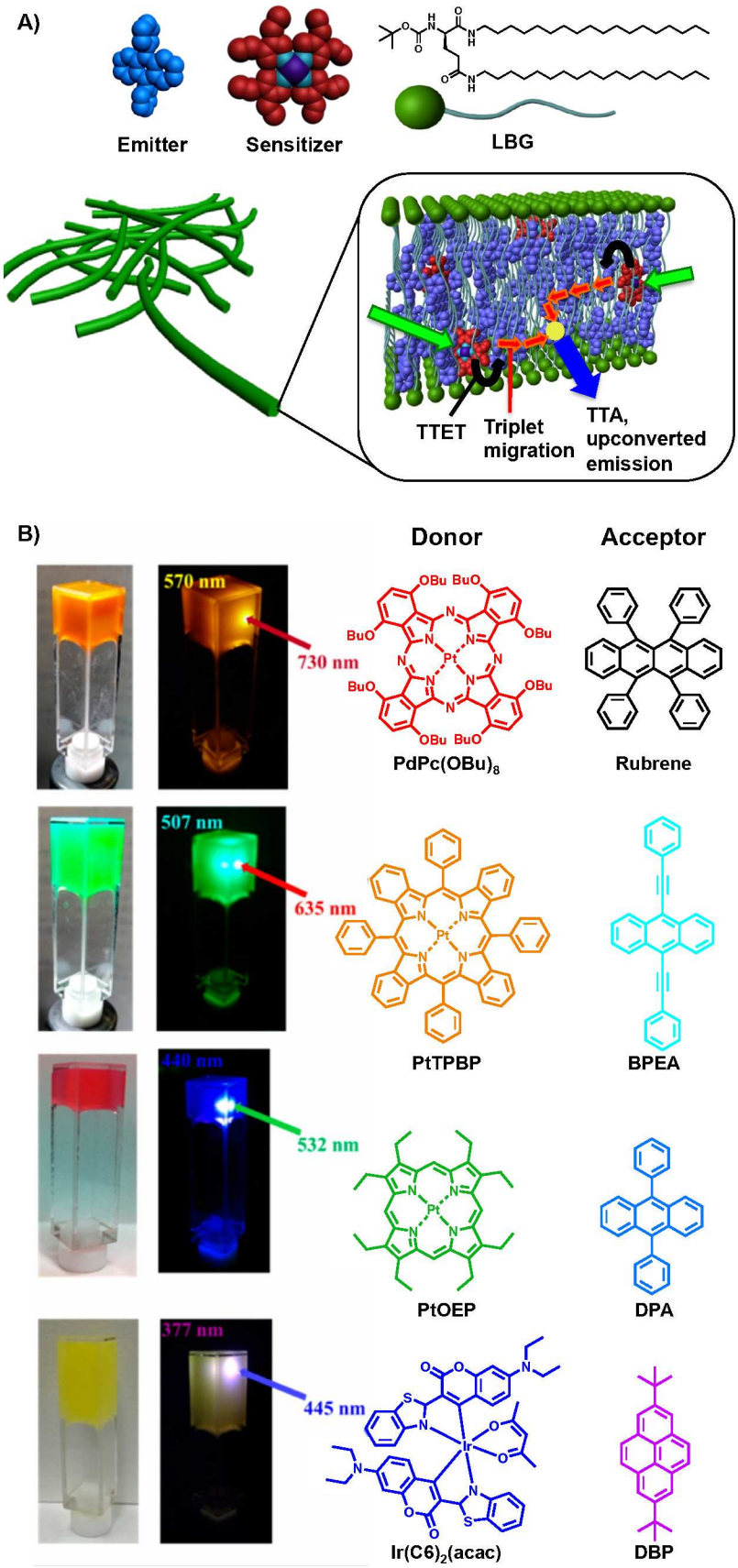

A)
Emitter
Sensitizer
LBG
TTET
Triplet migration
TTA, upconverted emission
B)
Donor
Acceptor
570 nm
730 nm
PdPc(OBu)8
Rubrene
507 nm
635 nm
PtTPBP
BPEA
440 nm
532 nm
PtOEP
DPA
377 nm
445 nm
Ir(C6)2(acac)
DBP

Figure 5. A) Schematic representation of the structural unit of the UC ternary gel system made of a donor-acceptor pair and a LMW gelator, and proposed TEM mechanism occurring inside the self-assembled gel fibers. B) Photographs of the UC co-gels in air-saturated DMF. Typical UC pairs were used to form ternary gels allowing efficient (*from top to bottom*) near IR-to-yellow, red-to-cyan, green-to-blue and blue-to-UV wavelength conversions. For all cases: [Donor] = 67 μM (except [PtOEP] = 33 μM); [acceptor] = 6.7 mM; [LBG] = 13.3 mM. Adapted with permission from ref. 31. Copyright 2015 American Chemical Society.

The same research group also designed a novel amphiphilic acceptor molecule (Figure 6), which contained a solvophobic multiple-amide-substituted 9,10-diphenylanthracene unit and solvophilic alkyl chains, both units attached *via* a L-glutamate linker. [34] The presence of amide bonds in the linker helped to promote crosslinking *via* hydrogen bonding among the networks and also introduced chirality for better molecular orientation and thermal stability. When this organogel was doped with PtOEP, an efficient TTA-UC with high UC quantum yield (30 ± 1%) was obtained under ambient conditions. Interestingly, no upconverted emission was observed from the frozen chloroform solution of DPA-PtOEP without the acceptor self-assembly at 77 K. This can be explained because molecular diffusion is restricted at frozen conditions, resulting in large intermolecular distance between chromophores and hence no energy migration and TTA takes place. Additionally, different important materials such as gels and solid films made of above-mentioned acceptor and donor were investigated as a TTA-UC system in the presence of air demonstrating the versatility of the current design.[34]

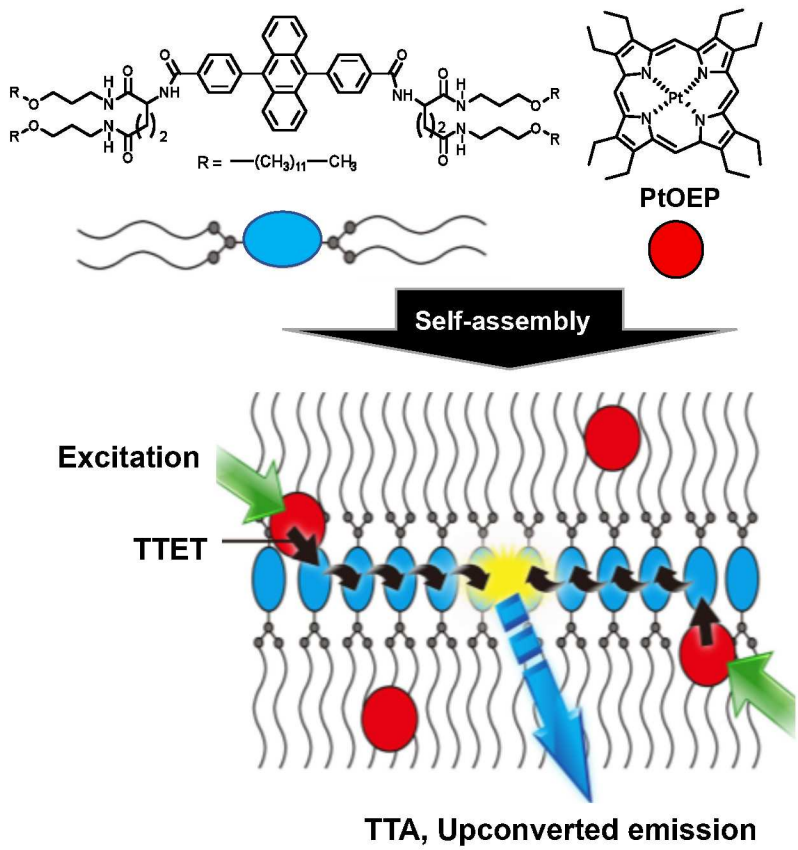


Figure 6. Schematic illustration of the basic self-assembly structure made of an amphiphilic acceptor molecule (*top-left*) in the presence of donor molecules (PtOEP), which bind to the self-assemblies by solvophobic interaction. Photoexcitation of donor molecules by green light induces donor-to-acceptor TTET, followed by TEM among the acceptor molecules, leading to efficient TTA and consequent upconverted blue emission. Adapted with permission from ref. 34. Copyright 2015 Nature Publishing Group.

Examples of TTA-UC in aqueous environments are scarce, essentially due to insolubility of chromophores and deactivation of excited triplets by dissolved oxygen molecules. In order to overcome these problems, Kimizuka *et al.* have very recently developed an air-stable photon upconverting hydrogel, which was formulated based on the concept of synergistic biopolymer-surfactant interactions.[35] The overall gel system consisted of gelatin, Triton X-100, sulfonated DPA (DPAS) as acceptor and PtOEP as a donor (Figure 7). They established that the non-polar surfactant domains constructed by definite organization of donor and acceptor chromophores, concomitantly shielded with dense gelatin hydrogen-bond networks prevented O_2 penetration in

the matrix. The UC efficiency was found to be 13.5%, which is to date the highest UC efficiency reported for air-saturated aqueous UC systems. Furthermore, the versatility of this strategy was demonstrated by studying the TTA-UC process in other biopolymers such as sodium alginate and agarose. Here, UC efficiencies were comparable to the gelatin based hydrogel. The use of biopolymer-based hydrogels as advanced light-harvesting systems opens some new potential applications in pharmaceutical, cosmetic, and detergent industries.

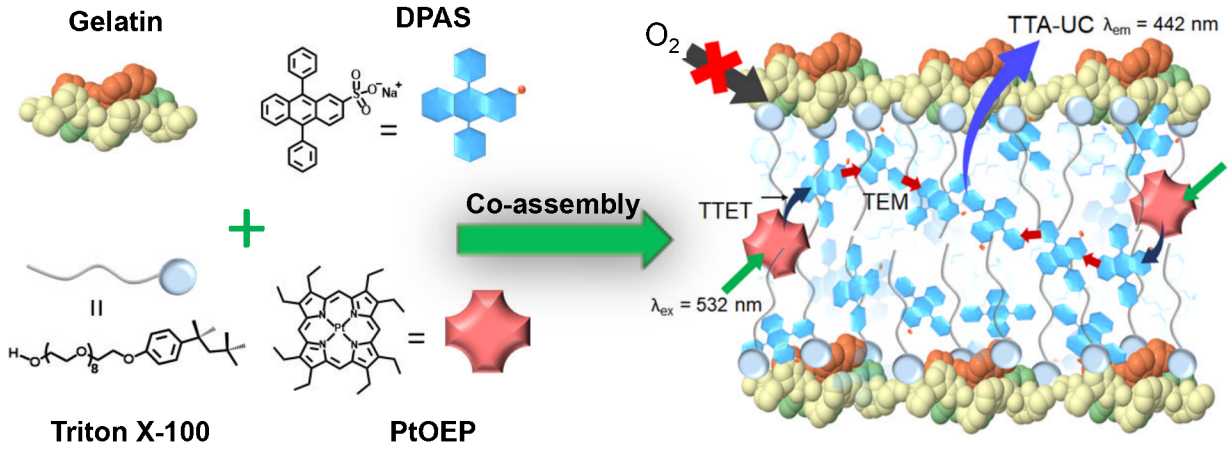


Figure 7. A schematic representation of G-TX-DPAS-PtOEP coassembly in photon upconverting hydrogel. Donor (PtOEP) and acceptor (DPAS) molecules are accumulated in the nonpolar domains of gelatin-TX100 hydrogel. The photoexcitation of donor is followed by a sequence of donor to-acceptor triplet−triplet energy transfer (TTET), triplet energy migration (TEM), triplet−triplet annihilation (TTA) among the acceptor molecules, and upconverted fluorescence from the acceptor excited singlet state. Adapted with permission from ref. 35. Copyright 2018 American Chemical Society.

PHOTOOXIDATION

In recent years, photooxidation processes inside nanoreactors such as micelles,[36] mesoporous molecular sieves,[37] oil-in-water emulsions,[38] among others, have attracted much attention due to the possibility of tailoring additional functionalities, organization and orientation of catalytic species, controllable molecular diffusion, large surface area to volume ratios, reduction of overheating/-concentration and the possibility of modeling and mimicking photoinduced processes in nature at the micron and submicron level.

Our research group studied for the first time the photooxidation of 1-(4-methoxyphenyl)ethanol catalyzed by riboflavin tetraacetate (RFT) under air using visible light inside different soft gel matrixes based on either LWM gelators or different biopolymers (Figure 8).[39] In this report, different approaches were adopted in order to achieve a tunable well-defined nanoreactor. In the first approach, the catalyst was physically immobilized into several bio-based polymers such as methylcellulose (**14**), κ-carrageenan (**15**), gelatin (**16**) and several LMW gelators (Figure 8, compounds **5**-**12**) to investigate their possible effects on both selectivity and reaction kinetics. Surprisingly, cyclohexane-based bis-amide based organogels made in CH_3CN afforded full conversion (100 %) within 60 min in absence of thiourea (proton transfer agent) in comparison with the solution phase where thiourea was needed to achieve 69 % conversion in 120 min. In addition, the kinetics of the photocatalytic process suggested a dependence between the mechanical properties of the matrix and the efficiency of the reaction. For example, gels with consisting of dense fibrillar networks and relatively high strength (confirmed from scanning electron microscopy (SEM) and rheological measurements) usually showed the lowest reaction rates. It is also worth mentioning that the chemical integrity and gelation propensity remained unchanged even after several cycles of reuse. In comparison to this approach, the reaction rates decreased significantly when other strategies were adopted to incorporate the photocatalyst into the gel network, for example using a gelator molecule with covalently tethered photocatalyst or employing a combination of photocatalyst and 6-methyl-1,3,5-triazine-2,4-diamine to form a highly fluorescent H-bonded gelator. Overall, the results derived from this study supported the existence of favorable interactions between gel fibers and substrates and/or catalyst.

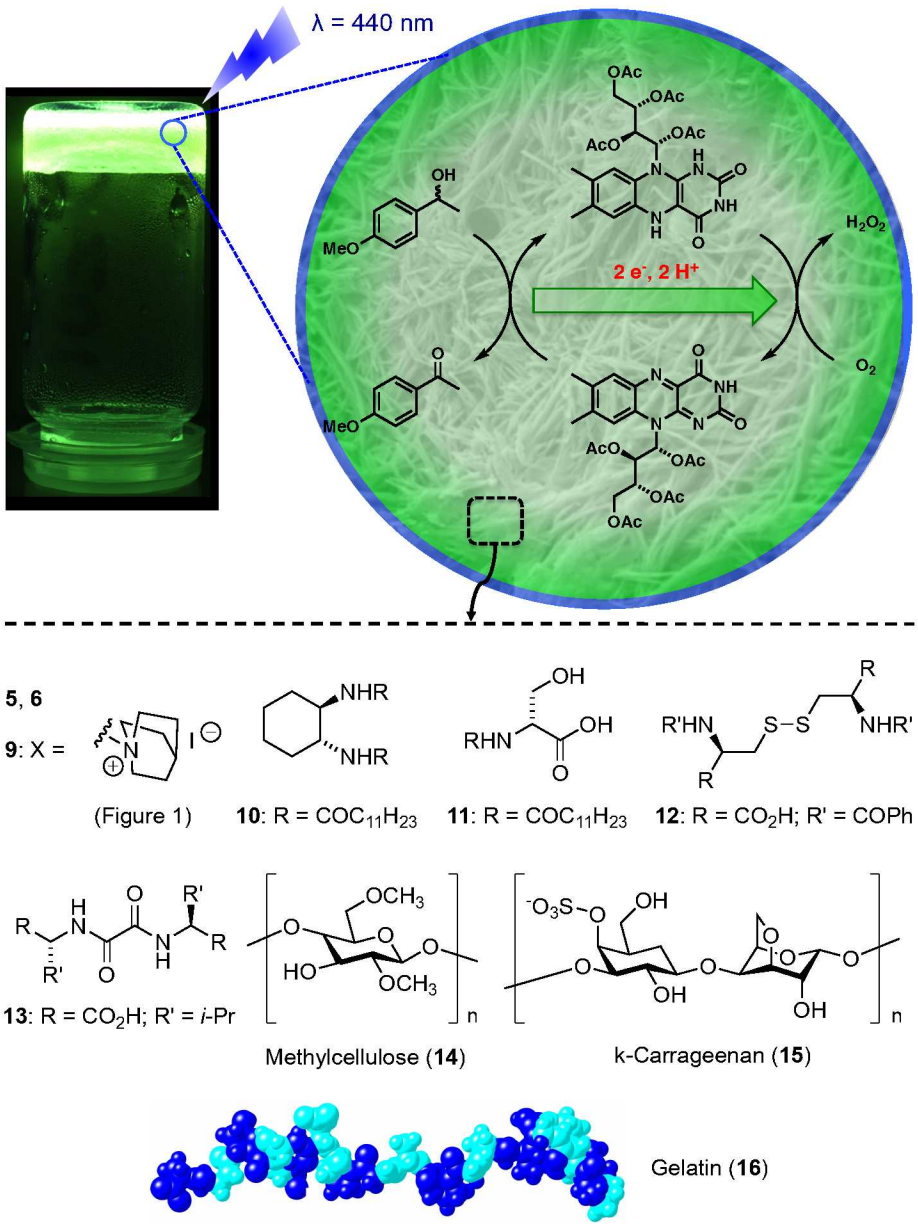


Figure 8. Illustration of riboflavin tetracetate-catalysed photooxidation of 1-(4-methoxymethyl)ethanol using blue visible light inside gel media (*top*) made of different types of gelators including low and high molecular weight compounds **5**,**6**, **9-16** (*bottom*). Adapted with permission from ref. 39. Copyright 2013 Royal Society of Chemistry.

PHOTOREDUCTION

The photoreduction of aryl halides under mild conditions involving visible light as energy source, room temperature, ambient pressure and air atmosphere is one of the most challenging tasks in photoredox catalysis. The bond dissociation energy of PhBr (BDE_{PhBr} = 3.6 eV) that is significantly higher than the maximum energy of a single visible photon (3.1 eV) together with high reduction potentials makes necessary the search for new activation methodologies. In this sense, TTA-UC has been found to be a suitable tool for activating stable aryl halides under mild conditions in solution.[40] Although hydrodebromination of aryl halides were successfully achieved, the general method experienced low photocatalyst stability and oxygen-free atmosphere was a crucial requirement. In order to overcome these limitations, we envisioned LMW organogels as suitable confining media for such photoreactions under milder conditions. Thus, we reported the first intragel photoreduction of aryl halides via a TTA mechanism. The gel network provided a stable microenvironment for the challenging multi-step process under aerobic conditions, room temperature and without additional additives. Specifically, intragel photoreductions of aryl halides in air were investigated using PtOEP (sensitizer)-DPA (emitter) pair in supramolecular gel networks made of *N*,*N'*-bis(octadecyl)-L-boc-glutamic diamide (**G-1**) or *N*,*N'*-((1*S*,2*S*)-cyclohexane-1,2-diyl)didodecanamide (**G-2**).[41] Photoreduction of 4-bromoacetophenone to acetophenone catalyzed by the TTA-UC system was achieved after 2 h laser irradiation at 532 nm, yielding 58.2% of the desired product and nearly quantitative mass balance (Figure 9A). Interestingly, the success of this approach was also perceptible to the naked eye. When the reaction was performed in aerated DMF, complete decolorization of the original pink solution was observed after irradiation due to decomposition of PtOEP by diffused molecular oxygen. On the contrary, there was no change in the pink color in gel phase, supporting the hypothesis of an efficient confinement effect of the gel network, preventing any quenching of the excited species by dissolved oxygen (Figure 9B). Importantly, the results obtained in aerobic gel phase were comparable to those obtained in solution under strict inert atmosphere. Furthermore, rheological measurements of the gel matrix before and after laser irradiation demonstrated also the preservation of the gel integrity in terms of thermal and mechanical properties.

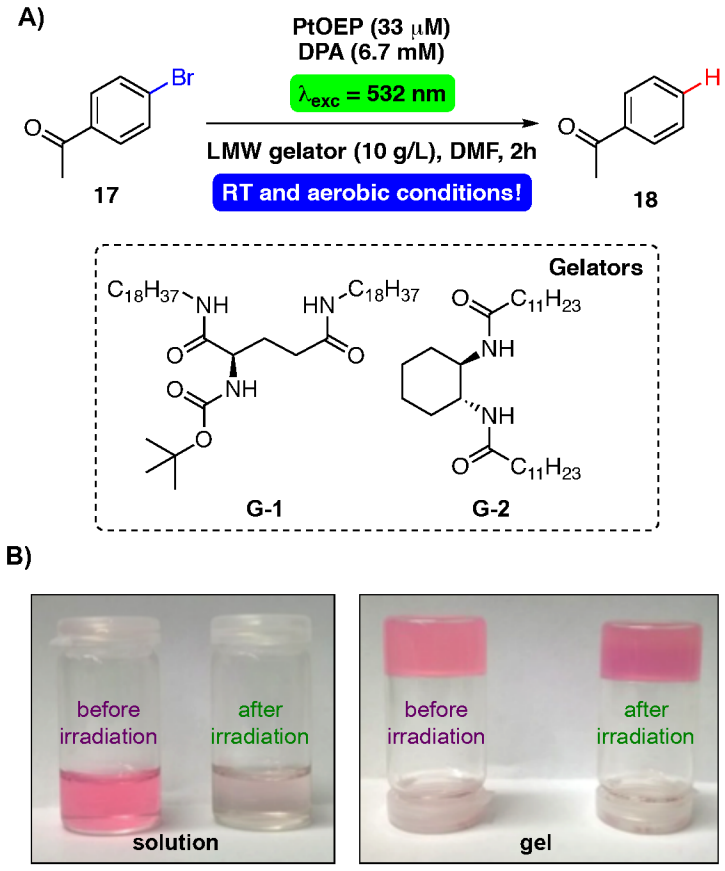


Figure 9. A) Scheme of photoreduction of 4-bromoacetophenone performed in gels made of LMW gelators **G-1** and **G-2**. B) Photographs of doped solutions before/after irradiation showing decolorization caused by degradation of PtOEP (*left*), and photographs of doped gel before/after irradiation (*right*). Adapted with permission from ref. 41. Copyright 2015 Royal Society of Chemistry.

A series of control experiments supported a reaction mechanism depicted in Figure 10. The intragel photoreduction of aryl halides takes place by successive TTA, single electron transfer (SET) and H-atom transfer (HAT) processes. The green-to-blue conversion begins with the selective irradiation at 532 nm of the sensitizer PtOEP. Then, after fast ISC the PtOEP triplet, ^{3}(PtOEP)*, is efficiently quenched by DPA through triplet-triplet energy transfer (TTET) to generate long-lived DPA triplets, ^{3}(DPA)*, and restoring PtOEP. Then, triplet energy migration (TEM) through the acceptor arrays in the supramolecular gel network induces the annihilation of ^{3}(DPA)* molecules affording the upconverting fluorescence ^{1}(DPA)*. These species then induce

SET to the electrophilic aryl halides, forming the unstable radical anions $ArX^{\bullet -}$, which in turn undergo fragmentation into the corresponding aryl radicals $Ar^{\bullet}$ and anions X^{-}. Finally, the product Ar-H is generated in a reduction reaction through rapid HAT from DMF. Oxidation of the resultant $DMF^{\bullet}$ radical occurs by an exergonic back-electron transfer (BET), regenerating DPA and leading highly electrophilic DMF^{+} species, which are further hydrolyzed into volatile products upon workup. Control experiments in non-proton donor solvents such as benzene showed no conversion of the starting material, thus discarding the possibility of $Ar^{\bullet}$ trapping by gelator molecules through N-H abstraction.

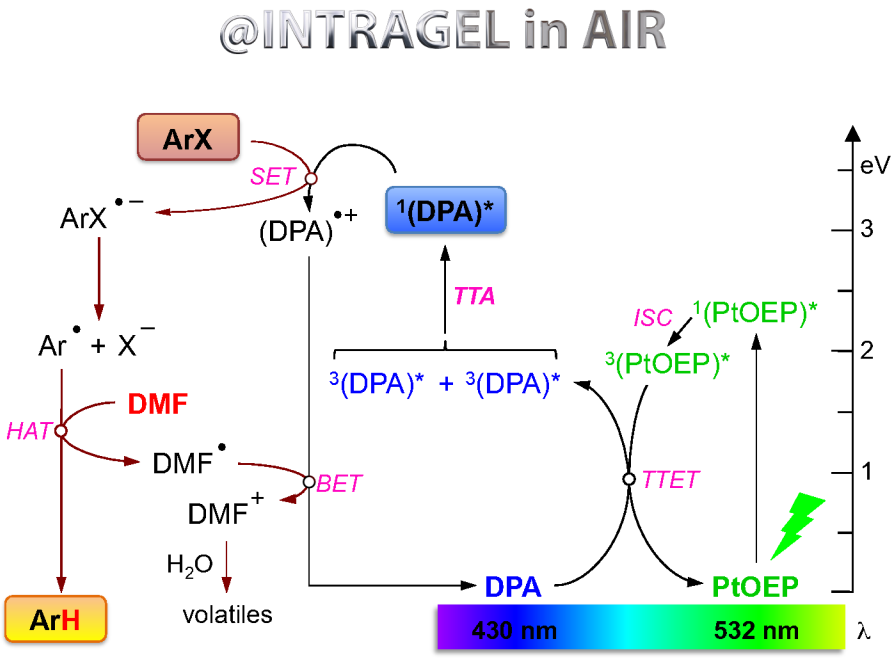


Figure 10. Plausible mechanism for visible light photoreduction of aryl halides at RT in air based on the combination of TTA-UC, SET and HAT processes inside the gel medium shown in Figure 9. Reprinted with permission from ref. 41. Copyright 2015 Royal Society of Chemistry.

Interestingly, all the foregoing learning can be applied to other challenged air-sensitive photo-redox catalytic reactions involving C-C bond formation. Very recently, our group has reported the proof of concept[42] achieving selective functionalization of aryl halides using rhodamine-6G (Rh-6G)[43] as a photocatalyst under aerobic conditions in gel media, affording the desired products in comparable results to those obtained under strict inert conditions. The reaction is based on the application of different colours of visible light, which allows tuning the

redox potential of Rh-6G. For example, the ground state of the Rh 6G radical anion (Rh-6G•−) formed upon photo-irradiation under green-light irradiation in the presence of an electron donor (e.g. DIPEA) has a reduction potential of -1.0 V vs. SCE. However, subsequent irradiation of Rh-6G•− with blue light generates the corresponding excited radical anion (Rh-6G•−*), which displays a reduction potential of -2.4 V vs. SCE. As molecular oxygen quenches very efficiently the excited states of the Rh-6G radical anions (Rh-6G•−*), an oxygen-free environment has been strictly required to carry out these reactions. We demonstrated that this practical limitation can be easily overcome replacing solution by a viscoelastic gel medium upon addition of a certain amount of LMW gelator into the reaction mixture.

Initially, the reaction was carried out by using 2-bromobenzonitrile (**1**) as test substrate, *N*-methylpyrrole (**25**) as trapping agent, Rh-6G as photocatalyst, *N,N'*-diisopropylethylamine (DIPEA) as electron donor, *N,N'*-bis(octadecyl)-L-Boc-glutamic diamide (**G-1**) as gelator, and DMSO as solvent (Figure 11). The reaction carried out in aerated DMSO solution at room temperature under blue LED irradiation resulted in very low yield (5%) of the desired coupling product. In sharp contrast, when the same reaction was carried out in presence of **G-1** gelator the yield of the reaction significantly increased to 53%. The yield of the reaction can be improved further by increasing the concentration of **G-1** (15 g/L), and the amount of DIPEA with respect to reactant molecule. The use of other LMW gelators such as (*S*,*S*)-dodecyl-3-[2(3-dodecyl-ureido)cyclohexyl]urea or *N,N'*-((1R,2R)-cyclohexane-1,2-diyl)didodecanamide, provided comparable results during the photoredox reductive arylation with slight differences in their final yields. Nevertheless, when 1,3:2,4-bis(3,4-dimethylbenzylidine)-sorbitol was used as a gelator, the formation of the reduction byproduct was totally suppressed. Detailed reaction kinetics data supported the effect of the gel network on the reaction rates. In addition, when 1,4-dibromo-2,5-difluorobenzene was irradiated with green light (λ_{Ex} = 530 ± 15 nm) in the presence of Rh-6G, DIPEA and *N*-methylpyrrole, only the corresponding monosubstituted product was formed. The monosubstituted derivative is the only product obtained since activation of the second bromide substituents is not possible by Rh-6G (reduction potential of Rh-6G ca. -1.0V vs. SCE), even with higher catalyst loading. In contrast, when the reaction was performed under blue light irradiation, the significant increase of the reduction potential of Rh-6G•−* enabled the formation of the disubstituted product in good yields (Figure 11C). Additionally, this light colour-guided photocatalytic arylation can also be performed in a sequential manner in aerated gel media

(Figure 11C). At first the substrate ethyl 2-bromo-(4-bromophenyl)acetate (**39**), which have two different carbon-halogen bonds (i.e., benzylic and aryl), lead to dehalogenation at the benzylic position upon irradiation with green light, affording the corresponding product **40** in modest yield. Subsequent activation of the aryl-bromide bond of product **40** under blue-light irradiation enabled the formation of the desired product **42** in good yield. In contrast to the observations made with the intragel TTA-UC process, comparative SEM images of undoped gels, gels loaded with the corresponding photocatalyst, and gels loaded with the photocatalyst and substrates, before and after irradiation, indicated that the incorporation of the substrates caused apparently a higher impact on the fibrillar morphology of the xerogel network than the photocatalysts alone. These results suggested that in this scenario there is not a spontaneous incorporation of the photocatalyst inside the gel fibers. It is worth mentioning that the separation of the gelator in these reactions is achieved by simple dilution-filtration and/or column chromatography.[42]

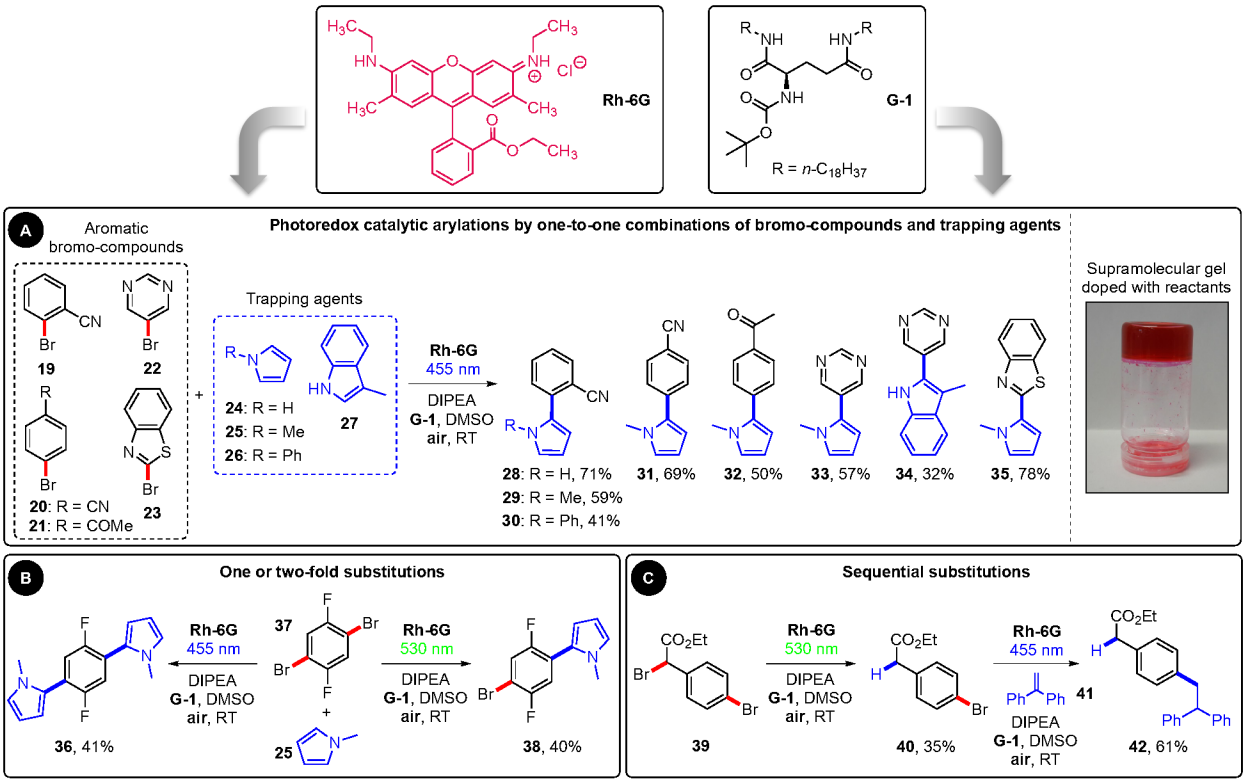


Figure 11. A) Substrate scope of intragel cross-coupling reactions between bromo compounds and trapping agents. Conditions: Bromo-compound **19-21** (0.1 mmol), trapping agent **24-27** (5-18 equiv), Rh-6G (15 mol%), DIPEA (2.2 equiv), **G-1** (15 g·L^{-1}), DMSO, air, RT, λ_{Ex} = 455

nm, reaction time: 24-96 h. Inset picture on the right: Typical appearance of a gel made of **G-1** in DMSO loaded with catalyst, substrate and DIPEA. B) Chromoselective one- or two-fold substitution reactions. C) Sequential substitution reactions. All yields correspond to isolated products. Adapted with permission from ref. 42. Copyright 2018 American Chemical Society.

TRIFLUROMETHYLATION

Fluorinated and trifluoromethylated compounds have become widespread and indispensable drugs in our modern society.[44] The incorporation of fluorine atoms into drug candidates has major effects on the physico-chemical and biological properties of the parent molecule. For instance, the inductive effects of the trifluoromethyl-group enhance bioavailability by reducing the basicity of neighboring amines.[45] In 2001, Macmillan *et al.* reported a photocatalytic method to carry out the trifluoromethylation of a broad range of arenes and heteroarenes. This strategy es based on the use of $Ru(phen)_3Cl_2$ as photocatalyst, which generates trifluoromethyl radicals ($\bullet CF_3$) *via* concomitant reduction of triflyl chloride (TfCl) upon light irradiation (λ_{Ex} = 455 ± 15 nm).[46] The proposed mechanism suggests the formation of a cyclo-hexadienyl radical from the corresponding arene, which generates a cyclohexadienyl cation upon oxidation. Finally, deprotonation of the cyclohexadienyl cation takes place in the presence of K_2HPO_4, leading to the formation of the targeted trifluoromethyl arene. As this method also requires a strict inert oxygen-free atmosphere, we recently optimized different gel formulations to carry out trifluoromethylation of arenes under aerobic conditions.[42] Specifically, a series of electron-rich 5-membered heteroarenes (**25, 43-46**) and also electron-deficient 6-membered heteroarenes (**50-52**) were transformed to the targeted products in the presence of **G-1** gelator (Figure 12) under aerated conditions in reasonable yields compared to those obtained in solution under an inert atmosphere. Furthermore, when the same reaction proceeded in solution in the presence of gelator **G-1** at a concentration marginally below the critical gelation concentration (CGC), the final obtained product yields were ~10−15% lower compared to the reaction carried out in gel phase at a concentration above the CGC. This makes sense if we consider that the oxygen-blocking efficiency is achieved with the gel network is fully developed (i.e. above the CGC). However, the product formation under these conditions supports the existence of intermolecular interactions within some domains of the gel network and/or a beneficial effect of the enhanced viscosity reducing the oxygen diffusion. The latter was also supported by the formation of the

reaction product in aerated frozen solution, albeit in ca. half yield compared to that observed in gel at room temperature. Apparently, even a non-fully meshed network may offer some interfaces to protect against oxygen deactivation compared to bulk solution. Interestingly, a series of detailed kinetic and spectroscopic studies under different conditions indicated that in this case the photocatalyst is not effectively shielded inside gel nanofibers from dissolved oxygen. Contrary to the observations made in TTA-based reactions, the results of this study indicated that the photocatalyst undergo oxygen quenching as it is dissolved in the solvent pools trapped in between the gel nanofibers. In this situation, and in contrast to free diffusion in solution, the oxygen initially trapped in the gel –which has been proven to be still reactive– should go through numerous entangled fibers to quench active species compartmentalized in other solvent pools. In addition, although local consumption of dissolved oxygen could potentially occur during photoirradiation, its effect has not been observed in phosphorescence decay curves. Moreover, the gel network slows down significantly the diffusion of external oxygen through the gel-air interface, thus preventing a fast deactivation of excited species generated after the initial photoexcitation of the catalyst.

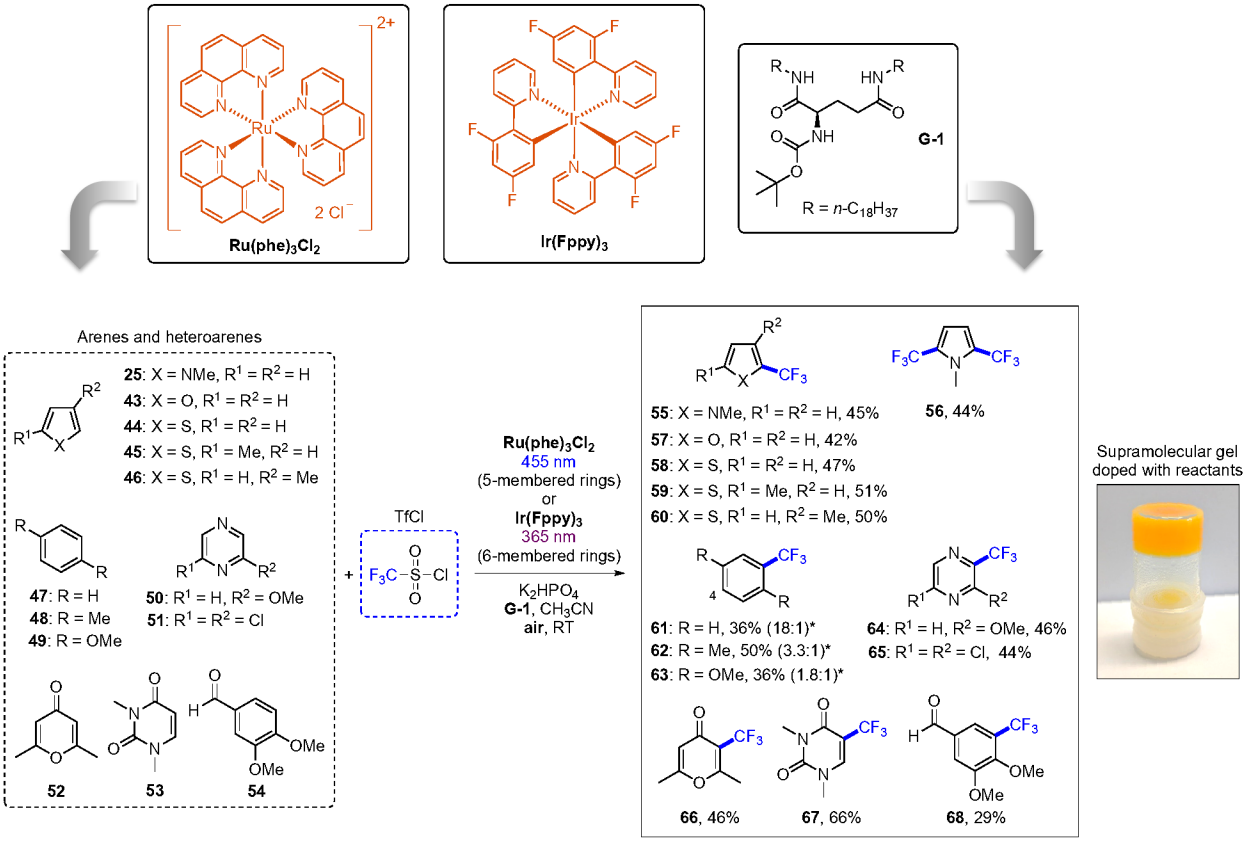


Figure 12. Substrate scope of intragel trifluoromethylation of 5- and 6-membered (hetero)arenes with TfCl. Conditions: (hetero)arene **25**, **43**–**54** (0.25 mmol), TfCl (2–4 equiv), photocatalyst ($Ru(phen)_3Cl_2$ (for 5-membered rings) or $Ir(Fppy)_3$ (for 6-membered rings) (catalyst loading: 1 mol% for 5-membered heteroarenes and 6-membered arenes; 2 mol% for 6-membered heteroarenes), K_2HPO_4 (3 equiv), **G-1** (10 $g{\cdot}L^{-1}$), 2.5 mL MeCN, air, RT, λ_{Ex} = 455 ± 15 nm (for ($Ru(phen)_3Cl_2$) or 365 nm ± 15 nm (for $Ir(Fppy)_3$), reaction time = 24–48 h. Picture on the right: Typical appearance of a gel made of **G-1** in MeCN loaded with $Ru(phen)_3Cl_2$/$Ir(Fppy)_3$, substrate, and K_2HPO_4. Reprinted with permission from ref. 42. Copyright 2018 American Chemical Society.

Recently, Li and co-workers described a metal-free strategy for trifluoromethylation of unactivated six-membered (hetero)arenes under UV or visible light irradiation.[47] In this method, sodium triflinate (CF_3SO_2Na, Langloies reagent) acts as a source of trifluoromethyl radicals ($\bullet CF_3$) and diacetyl as a radical initiator, also requiring an inert atmosphere. We have recently described our preliminary results regarding a similar trifluoromethylation reaction of unactivated six-membered (hetero)arenes reaction under aerobic conditions using supramolecular gels as confining media.[48] When the reaction was performed under inert atmosphere conditions with vigorous stirring the overall yield was 96% favoring the monosubstituted product (i.e. monosubstituted 79%, disubstituted: 17%, Figure 13). The overall yield decreased to only 37% when the reaction was carried out under aerobic conditions. However, when the same reaction was performed in gel matrix under aerobic conditions the overall yield increased to 85%. It is worth mentioning that the yields and selectivity of this process are governed by several variables such as use of different light sources, LMW gelators (**G1-G4**, Figure 13) and gelator concentration. For instance, a maximum amount of monosubstituted product **2** (93%) was obtained when the gelator **G-1** was used at a concentration of 25 g L^{-1}, and provided full conversion with a percentage ratio 2:3 > 13:1. This was ascribed to the faster rate of oxygen diffusion below the optimal gelator concentration leading to the quenching of excited state intermediates, which cause a decrease in the overall reaction yield. Similarly, above the optimal concentration of the gelator the diffusion of reactants molecules into the gel matrix were restricted due to the compact nature of the reaction media causing a decrease in the overall product yield.

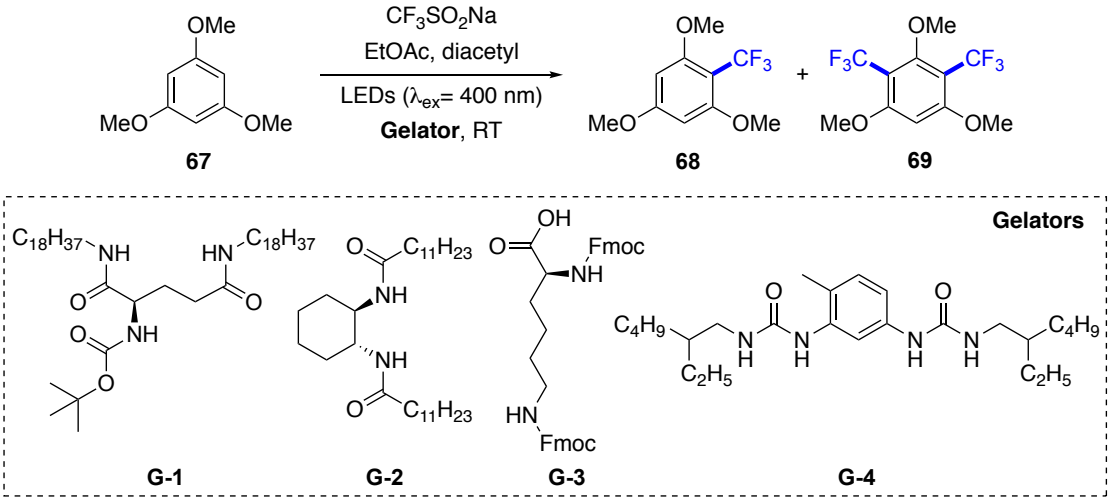


Figure 13. Model intragel photoinduced trifluoromethylation of 1,3,5-trimethoxy benzene **67** performed in gel media made using different LMW gelators (**G1-G4**).

CONCLUSION AND PERSPECTIVE

During the last few years, several groups have demonstrated the potential of gel networks as confining reaction media to perform photochemical processes under conditions milder than those required in homogeneous solution. Gel media has features that can be advantageous including, easy preparation and processability of the material, broad spectrum and rapid availability of gelator molecules, low gelator concentrations, large active surface areas and reversible stimuli-responsive nature, which is important for reutilization purposes. Apart from that, the photochemical reactions do not require any thermal trigger (that could lead to breakage of the gel matrix) to initiate reactions. In principle, confined spaces (e.g. solvent pools, inner part of the nanofibers) within the gel medium increase the local concentration of reactants and may positively influence the reaction outcome inside the soft nanoreactors through specific binding or interactions with gel fibers. Several photochemical reactions such as photo-dimerization, photo-oxidation, TTA-UC/SET-mediated photoreduction and trifluoromethylation reactions have been successfully carried out in gel media under aerobic conditions, affording the desired products in comparable yields to those obtained in homogeneous solution under rigorous inert conditions. Although this approach is just at its inception and additional fundamental studies are still required to establish the different kind of molecular interactions between reactants and gel

matrices, there is not doubt that non-conventional gel media can provide a versatile platform for the discovery of new reaction pathways and facilitate the way that photochemical reactions are traditionally carried out in academia and industry. The correct choice of gelators, reactants, solvent and conditions for the assembly of these gelators is essential for controlling conversion, kinetics and selectivity of intragel photo-induced reactions. In other words, fitting the reactant in a specific alignment in the solvent pool of the gel matrix and making a specific reaction pathway is a great and motivating challenge ahead for the scientific community. In addition, it is important to carry out studies that will allow meaningful comparisons with other confined systems. With remarkably similarities with the efficiency of biochemical reactions in confined spaces (e.g. cell) under aerobic conditions, viscoelastic gel media seems to be a promising candidate to facilitate important photochemical reactions under very mild conditions and accelerate high-throughput screening of photocatalysts.

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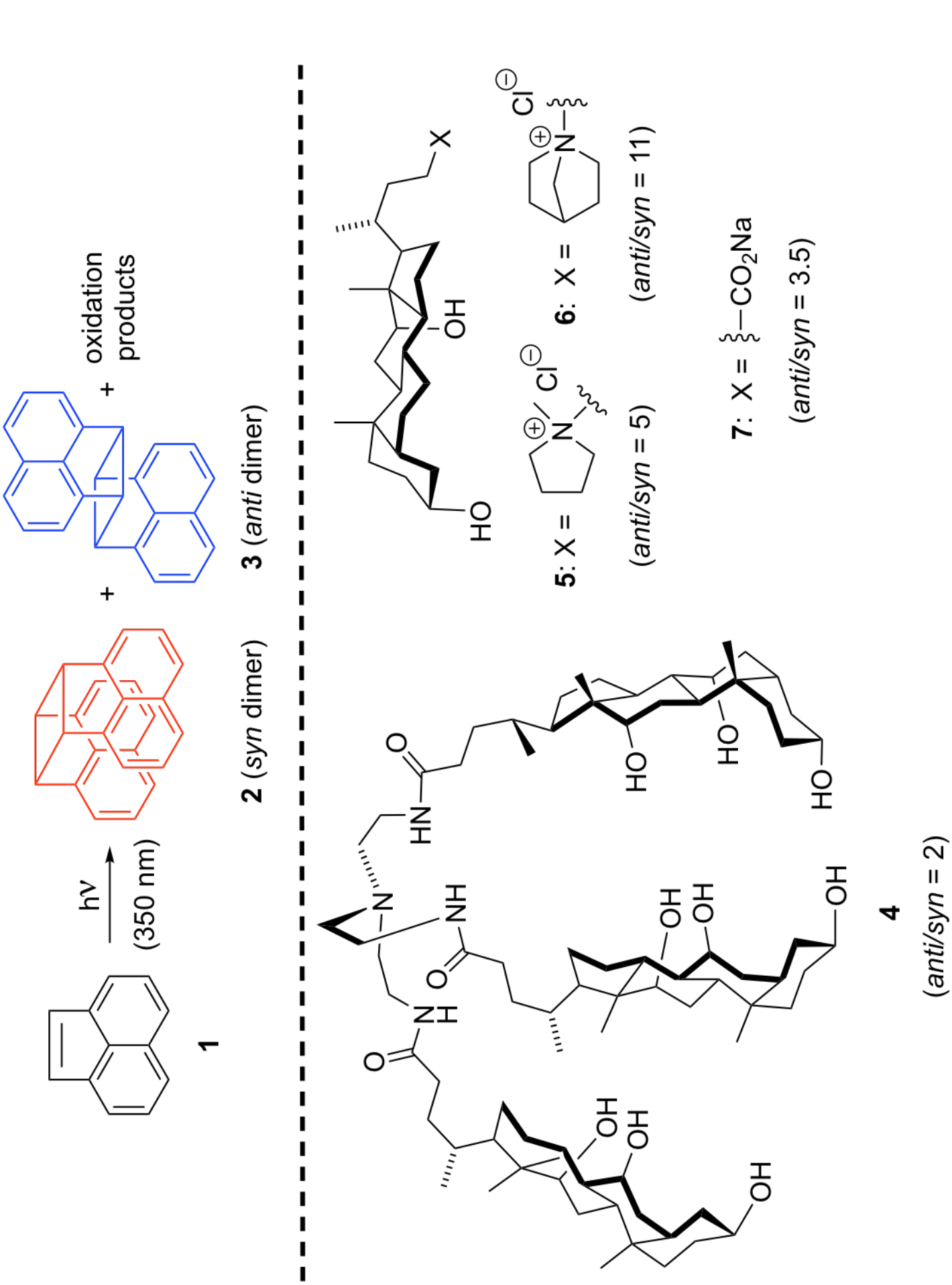
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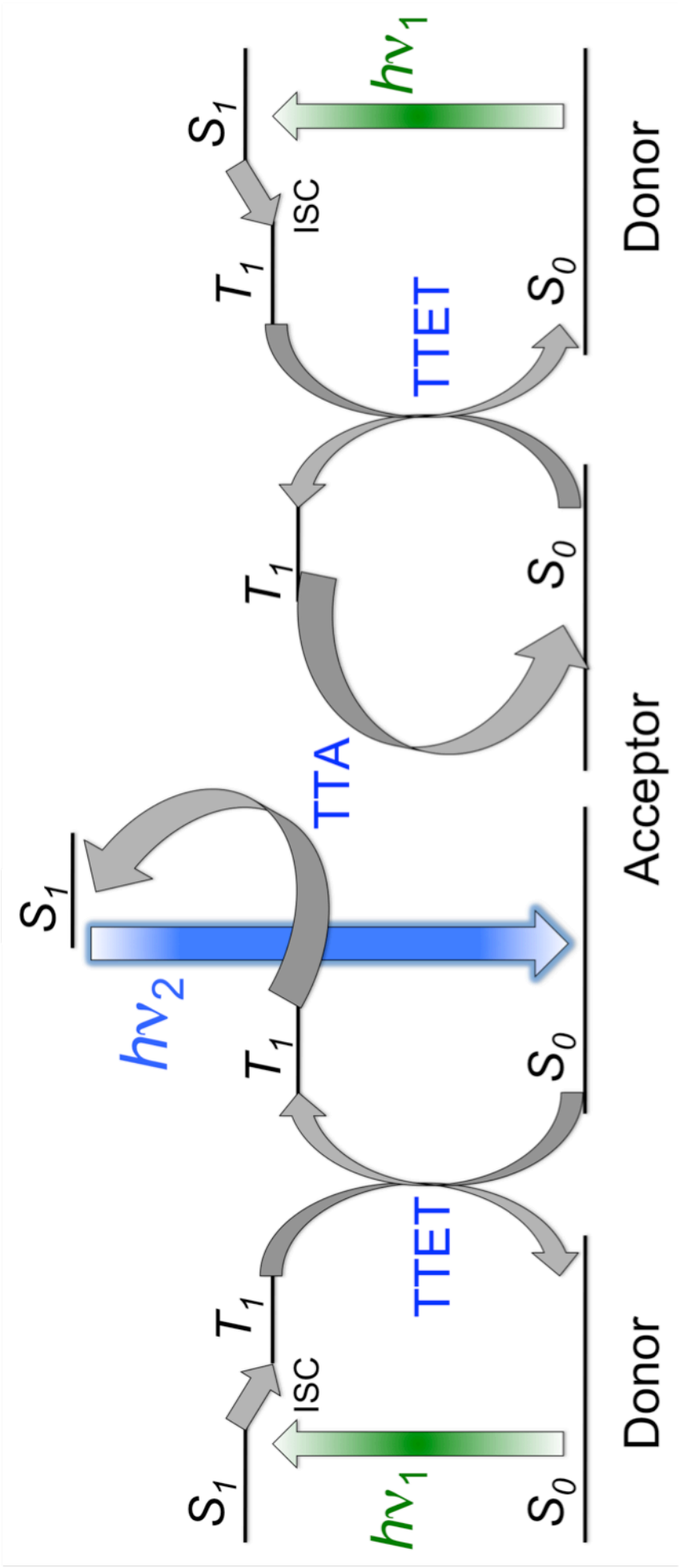
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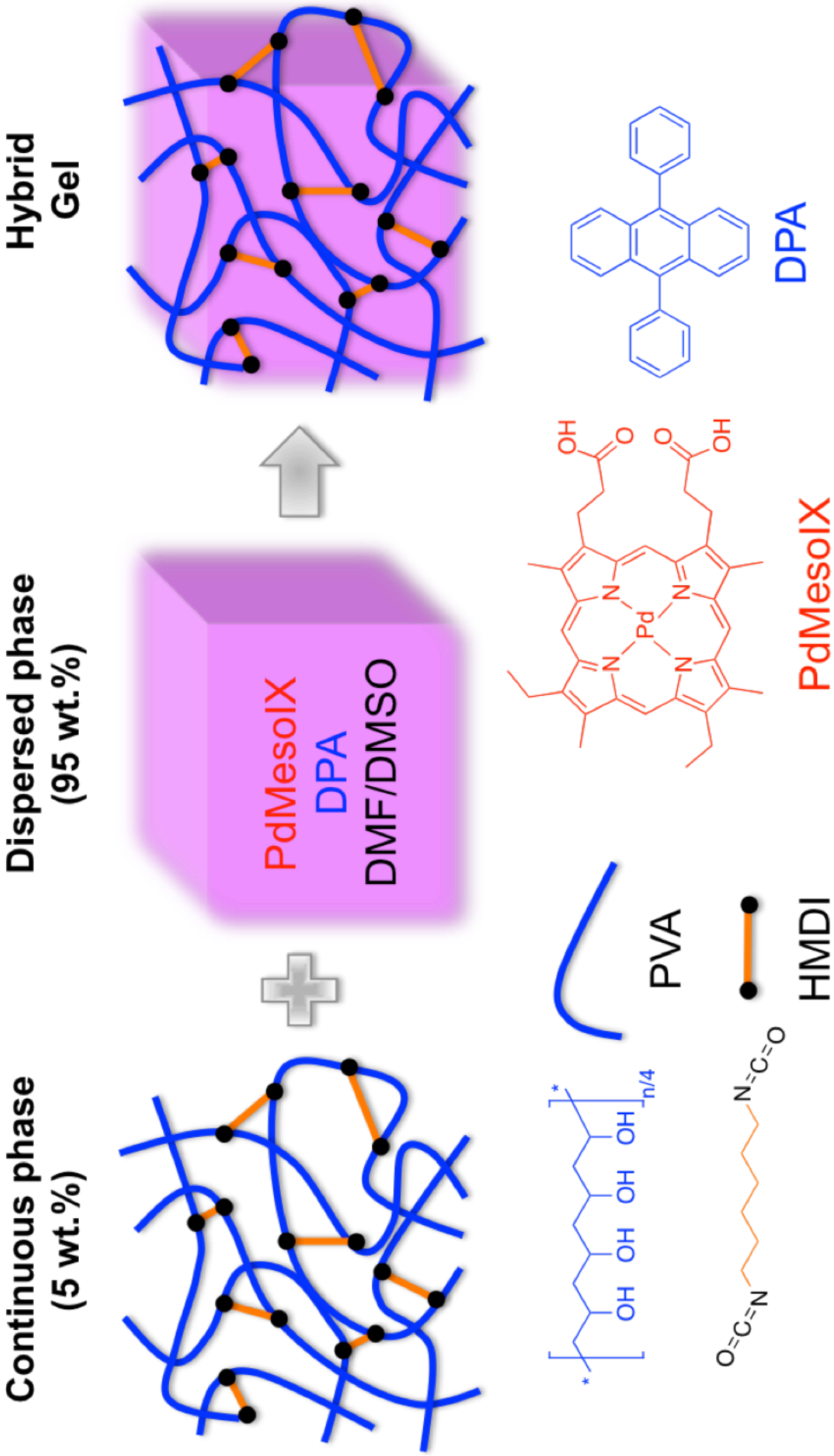
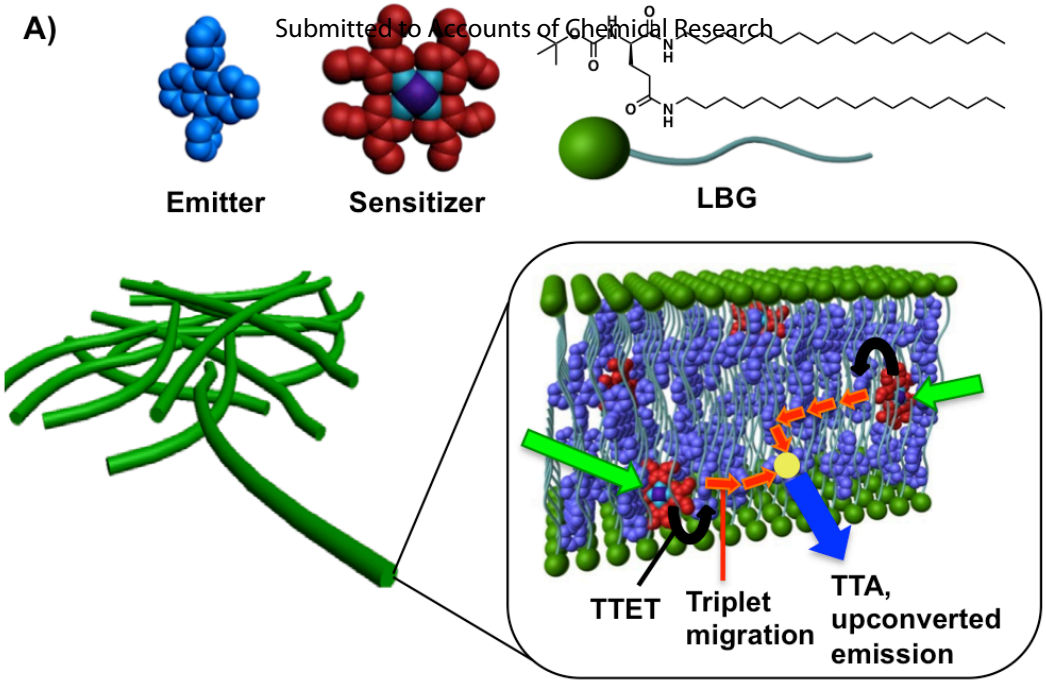
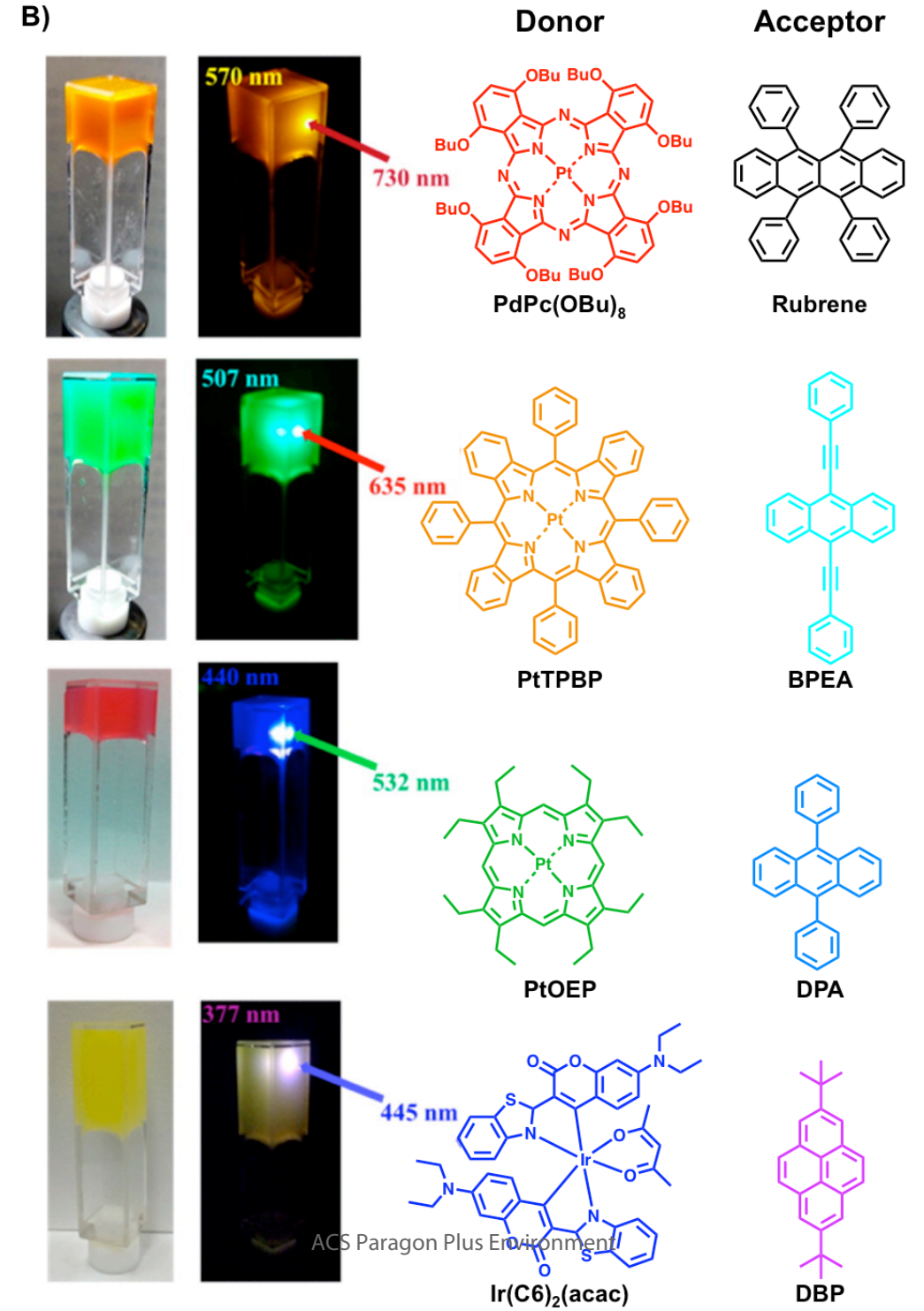
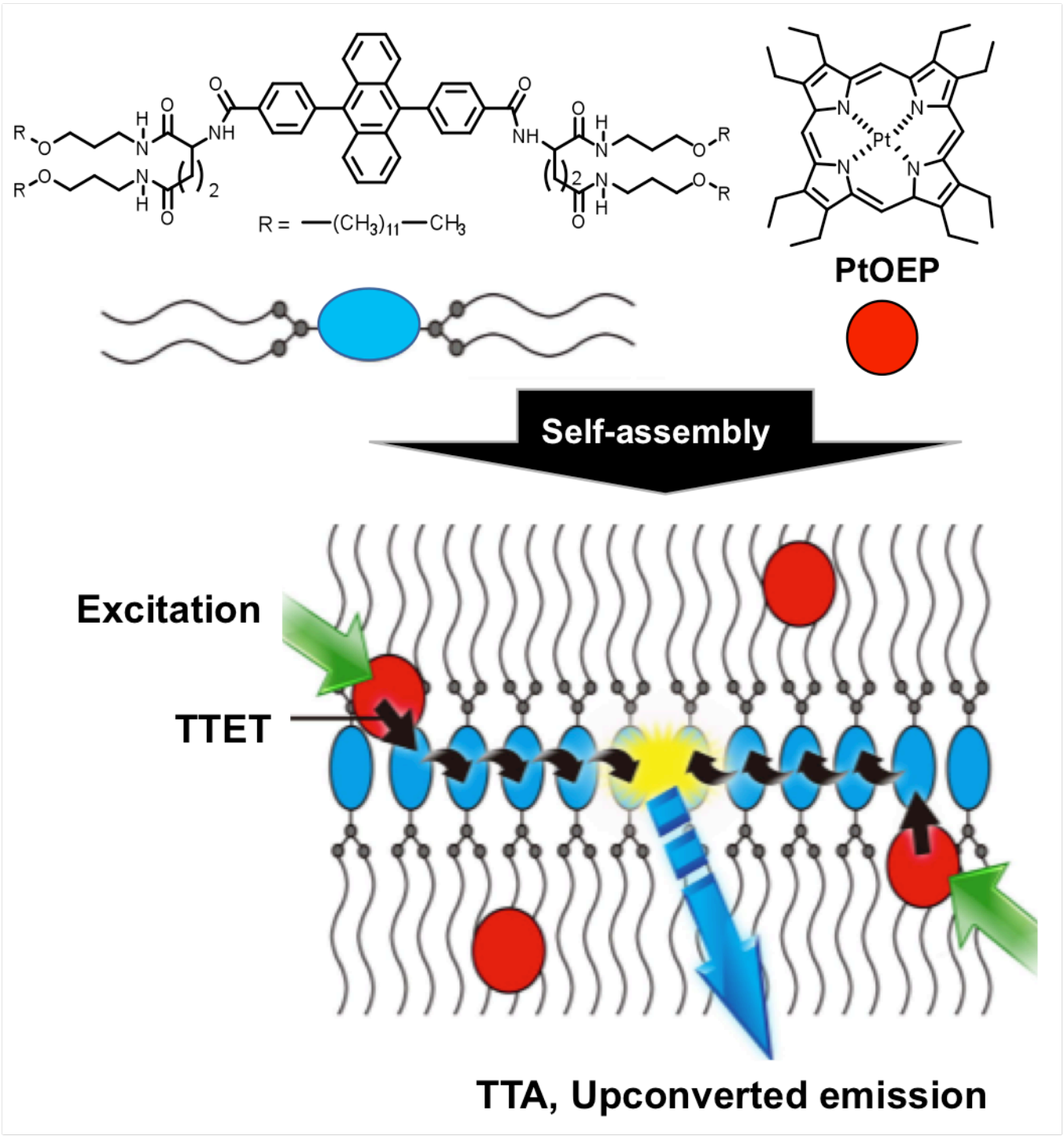
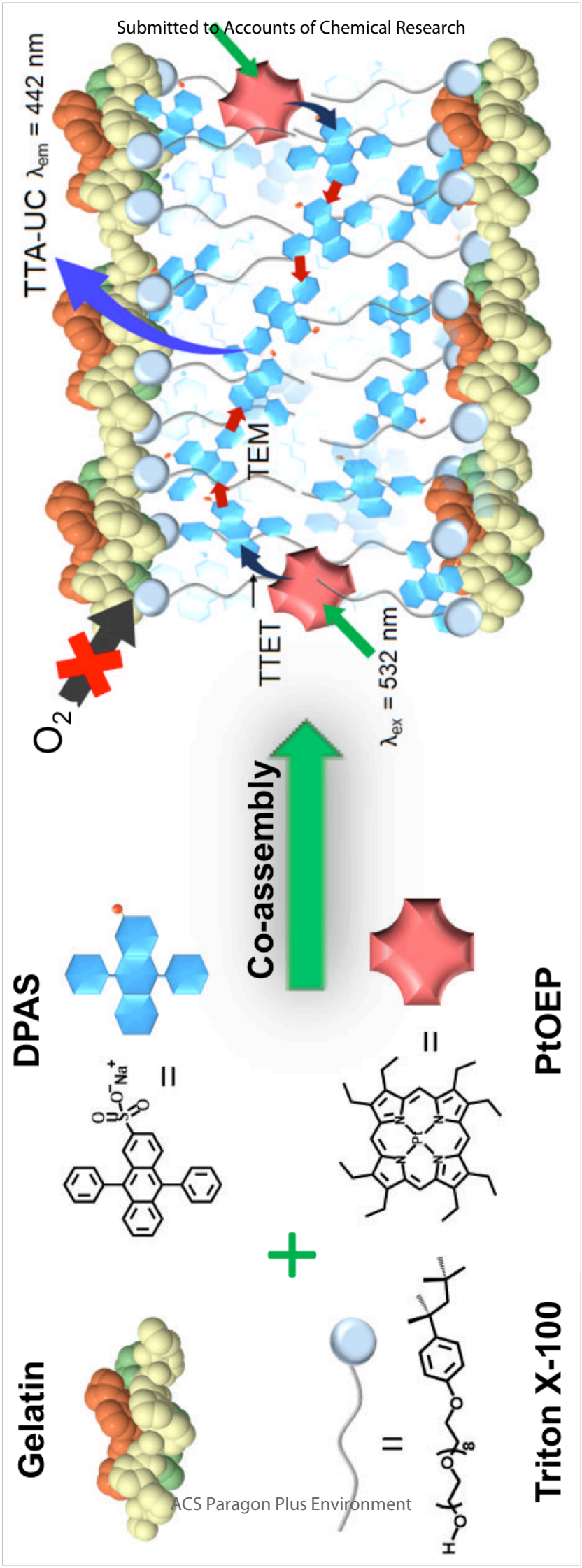
S_0
Donor

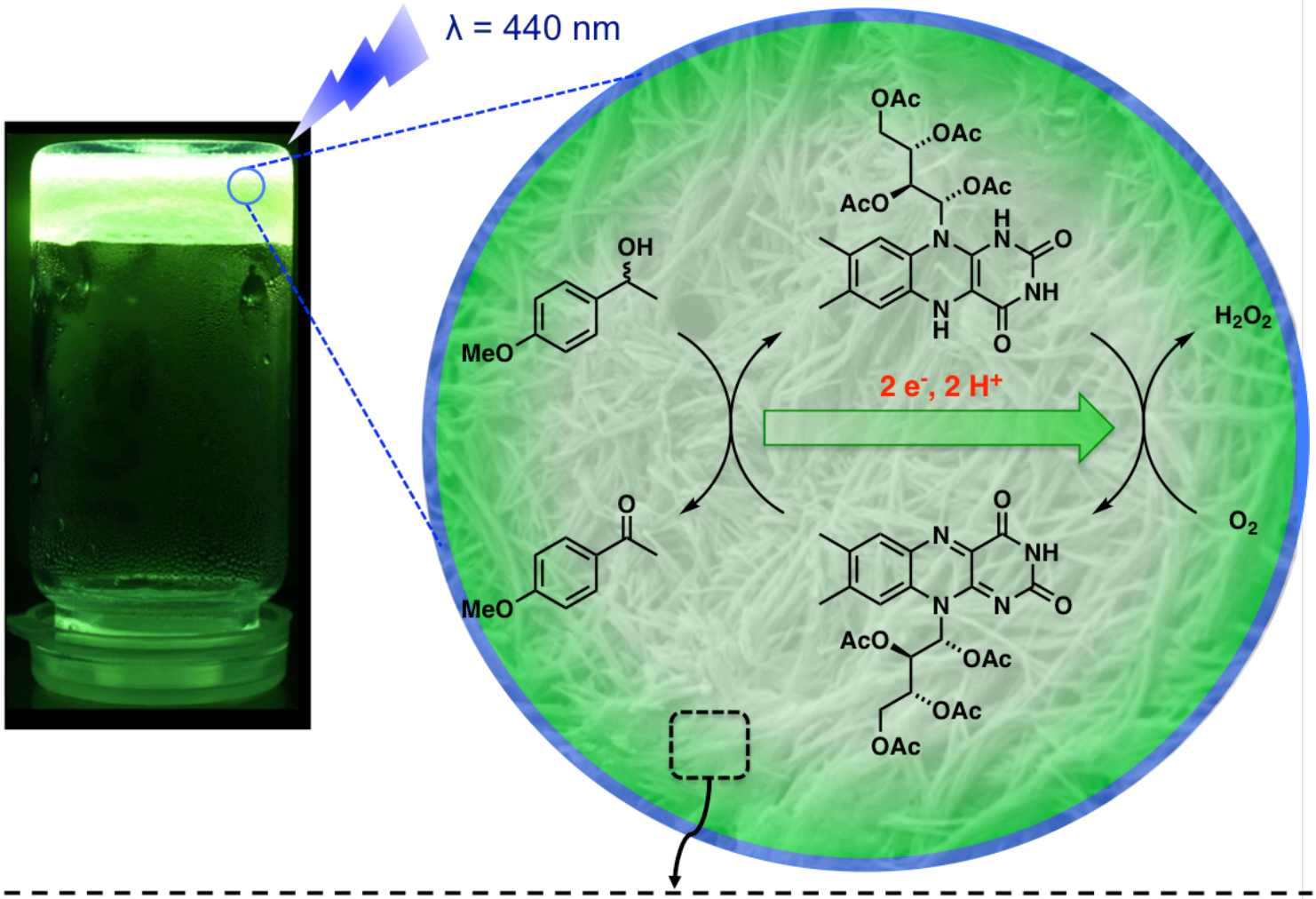

Hybrid Gel
Dispersed phase (95 wt.%)
PdMesoIX
DPA
DMF/DMSO
Continuous phase (5 wt.%)
DPA
PdMesoIX
PVA
HMDI






R = —(CH3)11—CH3
PtOEP
Self-assembly
Excitation
TTET
TTA, Upconverted emission

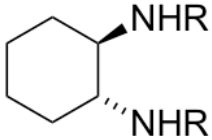

TTA-UC λ_{em} = 442 nm
TEM
TTET
λ_{ex} = 532 nm
O_2
Co-assembly
DPAS
PtOEP
Gelatin
Triton X-100



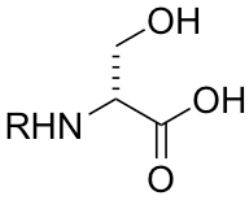
5, **6**

9: X =

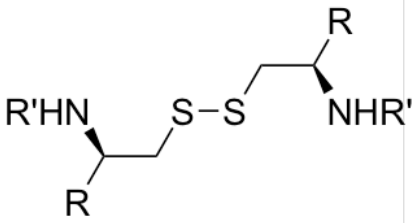
(Figure 1)



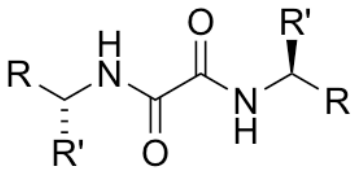
10: R = $COC_{11}H_{23}$



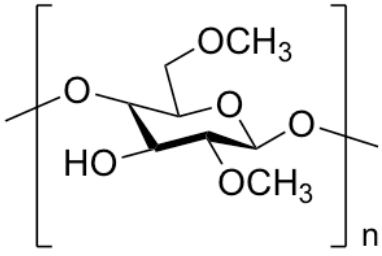
11: R = $COC_{11}H_{23}$



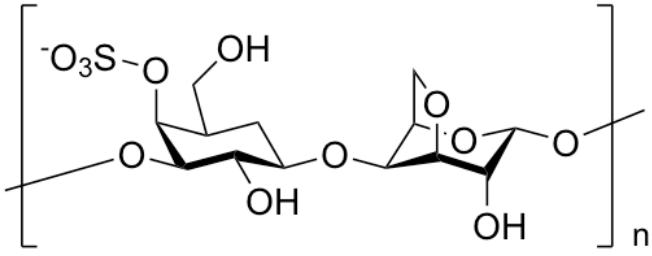
12: R = CO_2H; R' = COPh



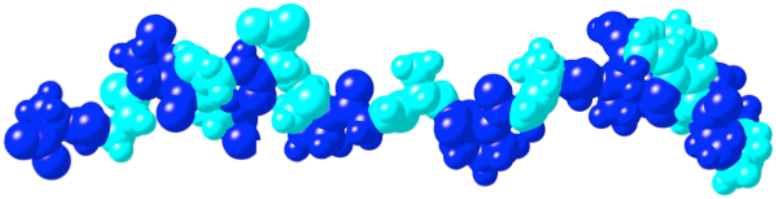
13: R = CO_2H; R' = *i*-Pr



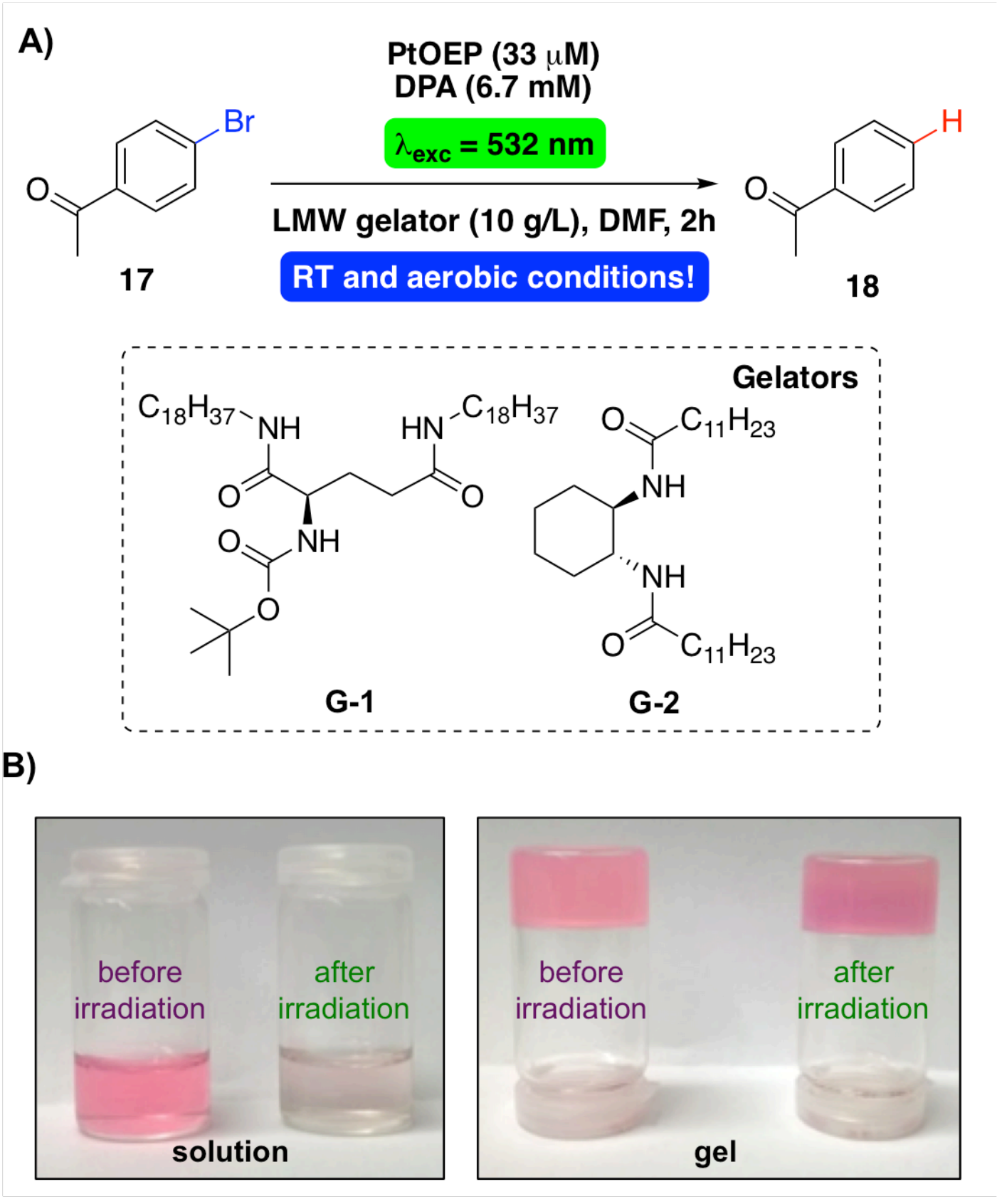
Methylcellulose (**14**)

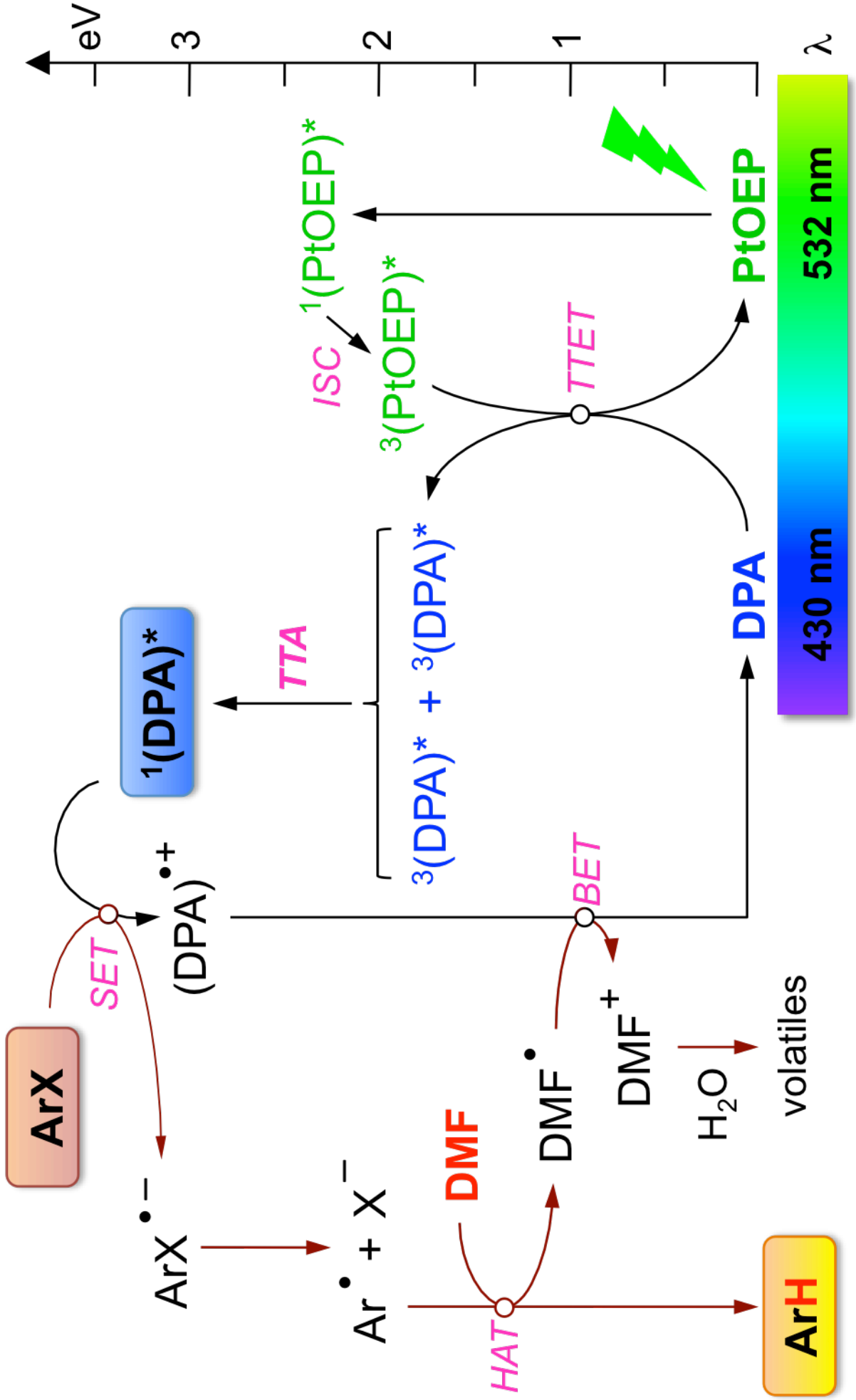


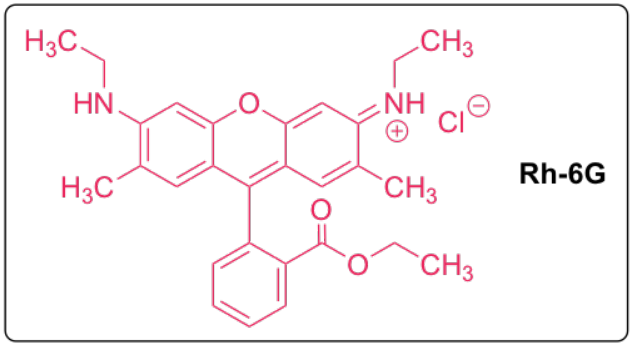
k-Carrageenan (**15**)

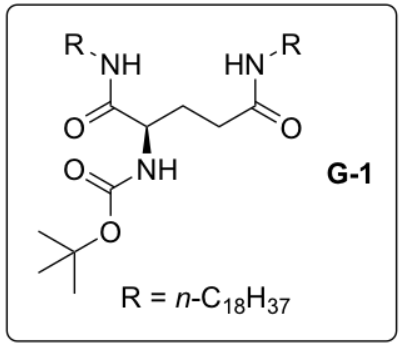


Gelatin (**16**)


A)
PtOEP (33 μM)
DPA (6.7 mM)
λexc = 532 nm
LMW gelator (10 g/L), DMF, 2h
RT and aerobic conditions!
Br
H
O
17
18
Gelators
C18H37
NH
HN
C18H37
O
NH
O
O
C11H23
NH
NH
G-1
G-2
B)
before irradiation
after irradiation
solution
before irradiation
after irradiation
gel


@INTRAGEL in AIR
eV
3
2
1
λ
532 nm
430 nm
PtOEP
DPA
ISC
1(PtOEP)*
3(PtOEP)*
TTET
TTA
1(DPA)*
3(DPA)* + 3(DPA)*
SET
(DPA)•+
BET
ArX
ArX•−
Ar• + X−
DMF
DMF•
DMF+
H2O
volatiles
HAT
ArH





A Photoredox catalytic arylations by one-to-one combinations of bromo-compounds and trapping agents

Aromatic bromo-compounds

19

22

20: R = CN
21: R = COMe

23

Trapping agents

24: R = H
25: R = Me
26: R = Ph

27

Rh-6G
455 nm
DIPEA
G-1, DMSO
air, RT

28: R = H, 71%
29: R = Me, 59%
30: R = Ph, 41%

31, 69%

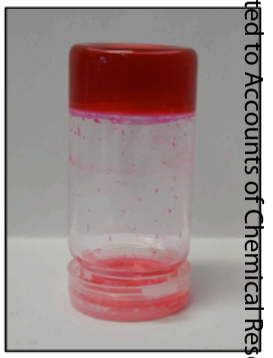
32, 50%

33, 57%

34, 32%

35, 78%

Supramolecular gel doped with reactants



B One or two-fold substitutions

36, 41%

Rh-6G
455 nm
DIPEA
G-1, DMSO
air, RT

37

25

Rh-6G
530 nm
DIPEA
G-1, DMSO
air, RT

38, 40%

C Sequential substitutions

39

Rh-6G
530 nm
DIPEA
G-1, DMSO
air, RT

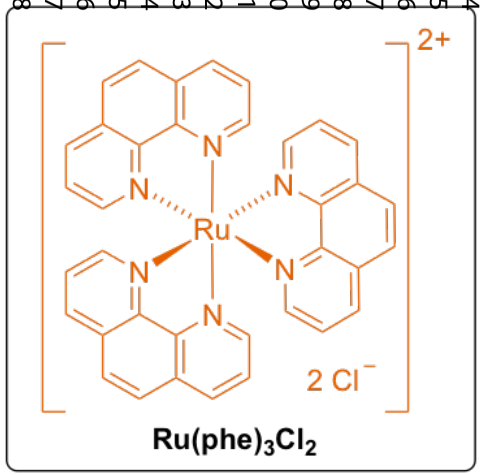
40, 35%

Rh-6G
455 nm

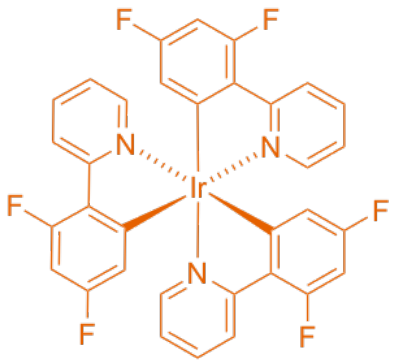
41

DIPEA
G-1, DMSO
air, RT

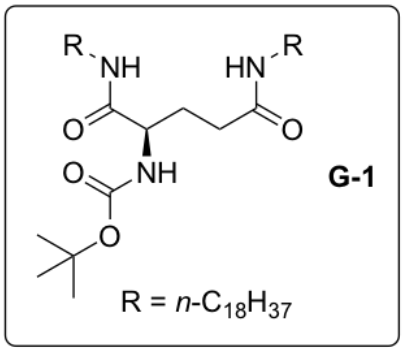
42, 61%



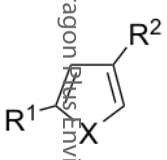
$Ru(phe)_3Cl_2$



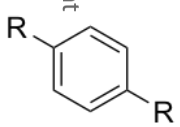
$Ir(Fppy)_3$



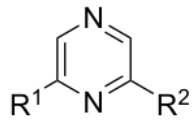
Arenes and heteroarenes



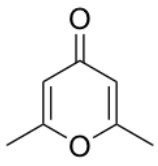
25: X = NMe, $R^1 = R^2 = H$
43: X = O, $R^1 = R^2 = H$
44: X = S, $R^1 = R^2 = H$
45: X = S, $R^1 = Me$, $R^2 = H$
46: X = S, $R^1 = H$, $R^2 = Me$



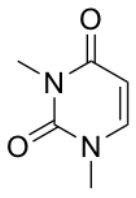
47: R = H
48: R = Me
49: R = OMe



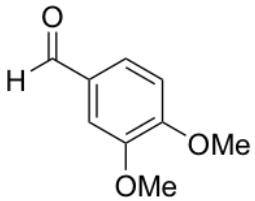
50: $R^1 = H$, $R^2 = OMe$
51: $R^1 = R^2 = Cl$



52

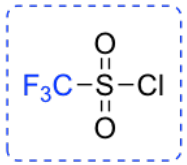


53



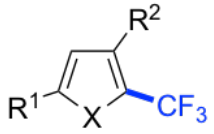
54

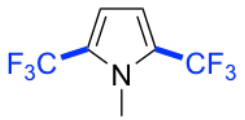
TfCl



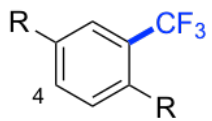
$Ru(phe)_3Cl_2$
455 nm
(5-membered rings)
or
$Ir(Fppy)_3$
365 nm
(6-membered rings)

K_2HPO_4
G-1, CH_3CN
air, RT

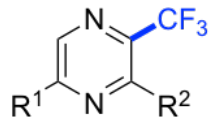




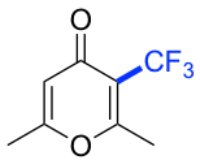
55: X = NMe, $R^1 = R^2 = H$, 45%
56, 44%
57: X = O, $R^1 = R^2 = H$, 42%
58: X = S, $R^1 = R^2 = H$, 47%
59: X = S, $R^1 = Me$, $R^2 = H$, 51%
60: X = S, $R^1 = H$, $R^2 = Me$, 50%



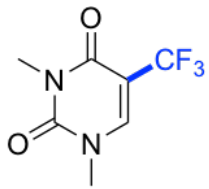
61: R = H, 36% (18:1)*
62: R = Me, 50% (3.3:1)*
63: R = OMe, 36% (1.8:1)*



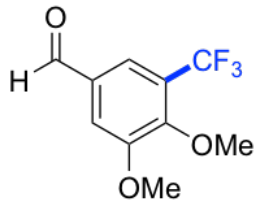
64: $R^1 = H$, $R^2 = OMe$, 46%
65: $R^1 = R^2 = Cl$, 44%



66, 46%

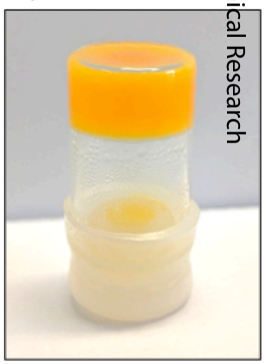


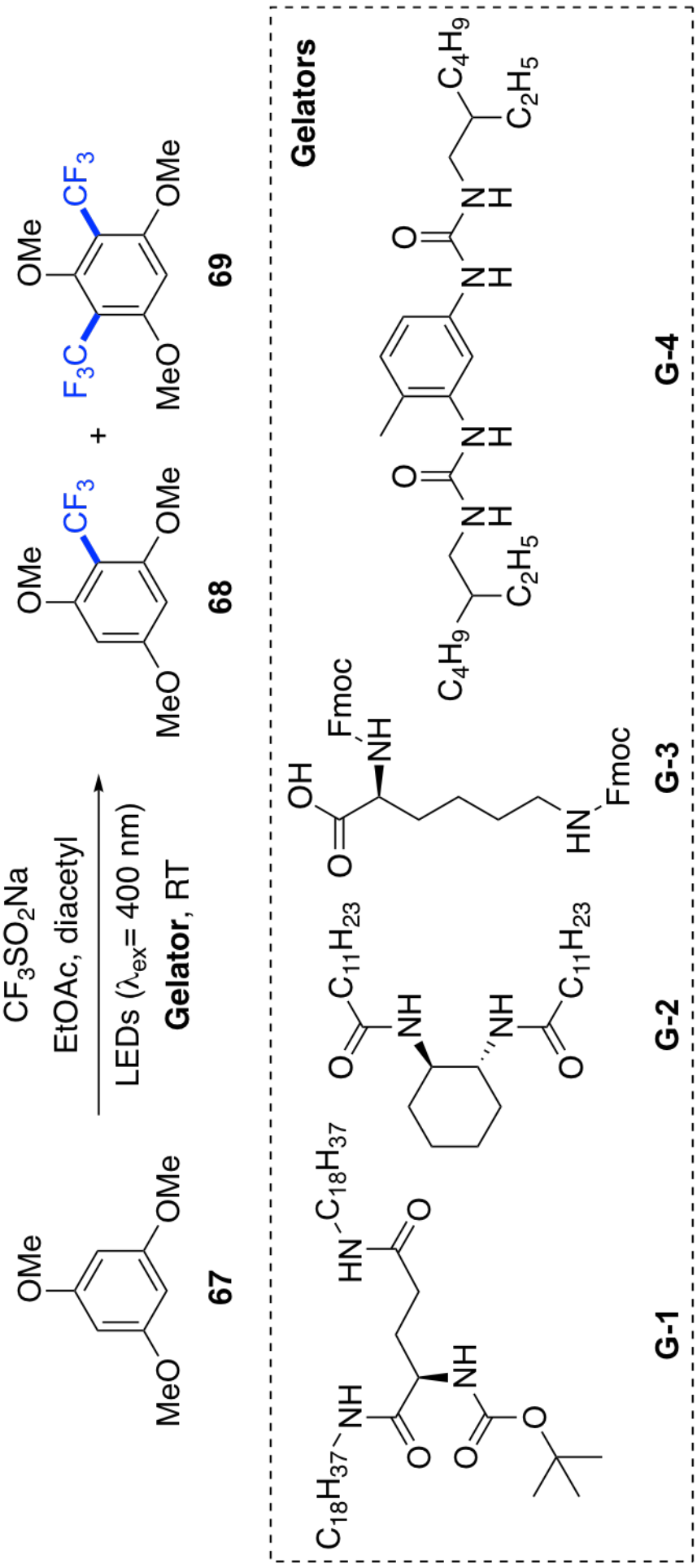
67, 66%

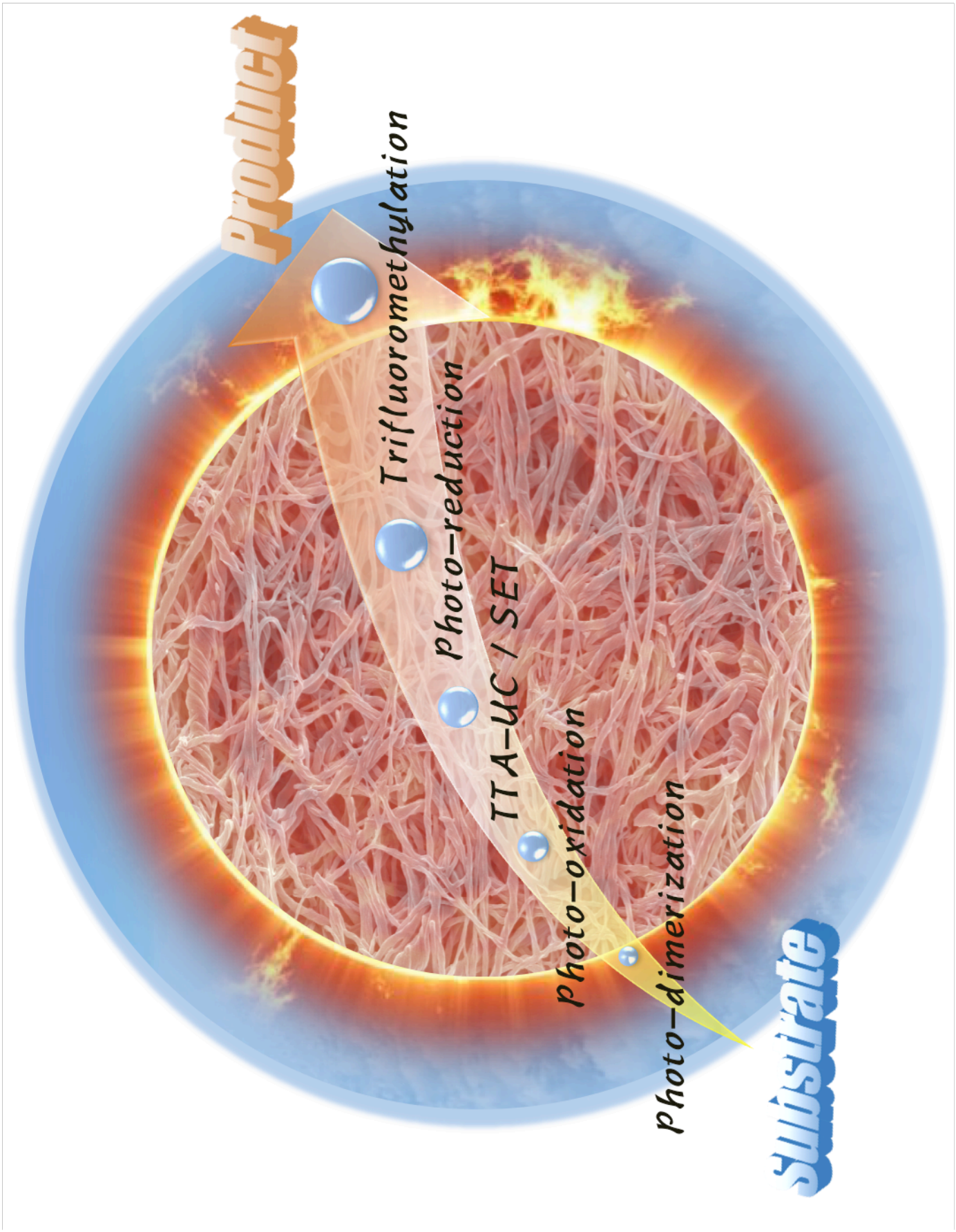


68, 29%

Supramolecular gel doped with reactants




CF3SO2Na
EtOAc, diacetyl
LEDs (λex= 400 nm)
Gelator, RT
OMe
MeO
67
CF3
F3C
69
68
Gelators
G-1
G-2
G-3
G-4
C18H37
C11H23
Fmoc
C4H9
C2H5


Product
Trifluoromethylation
Photo-reduction
TTA-UC / SET
Photo-oxidation
Photo-dimerization
Substrate