The Promise and Pitfalls of Photocatalysis for Organic Synthesis

Timothy Noël[a] and Eli Zysman-Colman[b*]*

[a] Flow Chemistry Group, Van ’t Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, Science Park 904, 1098 XH, Amsterdam, The Netherlands. E-mail: t.noel@uva.nl

[b]Organic Semiconductor Centre, EaStCHEM School of Chemistry, University of St Andrews, St Andrews, UK, KY16 9ST. E-mail: eli.zysman-colman@st-andrews.ac.uk;

Abstract

Progress in photocatalysis for organic synthesis over the last 15 years has been undeniably rapid. The number of transformations enabled by visible light has exploded as have new reactor technologies and the availability of structurally diverse photocatalysts. This perspective takes stock of the advances made and highlights the benefits of employing photocatalysis towards the synthesis of compounds, but also identifies critical challenges to be overcome as photocatalysis enters a new era of ever widening adoption.

Introduction

The history of synthetic organic chemistry coincides largely with the development of more effective medical treatments. Progress in synthesis, and especially advances in retrosynthetic analysis, cross coupling methodologies, stereoselective catalysis, have enabled medicinal chemists to speedily examine structure-activity relationships and to prepare chiral drugs in an enantiopure fashion. However, despite these important advances, synthesis remains the most time-consuming step within the development of new drugs. Hence, new activation modes that enable faster and more effective syntheses continue to be of great interest and their arrival will surely spur future drug discovery programs.

In the past two decades, photocatalysis has been hailed as a transformative synthetic tool by researchers in both academia and industry. While photochemistry and the use of photocatalysts are actually not new,[1] the combination of more powerful light sources with improved reactor technology, and the development of a myriad of powerful photocatalytic methods and photocatalysts has enabled photocatalysis to become a relevant synthetic tool across many sectors, including in early drug discovery and the large-scale production of chemicals.

However, despite the promising and expanding future for photocatalysis, some challenges and pitfalls remain. In this perspective, we aim to provide a concise overview of these exciting aspects and the often-overlooked challenges associated with photocatalytic transformations. When these aspects are considered, we believe that photocatalysis is poised to transform even more substantially the practice of synthesis.

Promise

Exploring novel chemical space by accessing unique mechanistic pathways

Innovations in synthetic methodology determine the scope and diversity of our portfolio of pharmaceuticals, agrochemicals, materials and other fine chemicals. However, overreliance on specific synthetic modes has led to bias in the synthesis of these organic molecules. For example, cross-coupling chemistry resulted in the generation of large numbers of drug structures with high levels of desaturation and sp^2-sp^2 linkages.[2,3] Hence, the development of new molecule activation modes is paramount to the expansion of the accessible chemical space, to access previously elusive molecules and to reduce the attrition rate in drug discovery.

Modern visible light photocatalysis has been transformative, allowing synthetic chemists to update their molecular toolbox and enabling activation of previously inert bonds in organic molecules. In photoredox catalysis, transition metal-based organometallic complexes, organic dyes or semiconductors absorb photons to reach an electronic excited state. This excited state species can subsequently engage in electron transfer with organic molecules (redox chemistry), leading to a wealth of new reactivities, and thus opportunities, in organic synthesis.[4] Alternatively, C–H bonds can be readily cleaved chemoselectively using either hydrogen atom transfer (HAT)[5] or proton coupled electron transfer (PCET) photocatalysis.[6]

In addition, photocatalysis can be seamlessly blended with other catalytic modes, enabling transformations only possible when both catalysts are working in concert with each other. For instance, unique enantioselective transformations have been realized through the combination of photocatalysis and organocatalysis or enzyme catalysis.[7,8] Also, distinctive cross-coupling of challenging sp^2-sp^3 and sp^3-sp^3 bonds are possible by merging photocatalysis with transition metal catalysis (also termed metallaphotocatalysis).[9]

Owing to the mild reaction conditions (photoexcitation in the visible regime at room temperature), photocatalysis displays a high functional group tolerance and chemoselectivity, making it compatible with the functionalization of complex molecules, such as proteins[10] and active pharmaceutical ingredients.[11] Such late-stage functionalization provides opportunities to accelerate the creation of drug libraries, the optimization of ADME profiles (i.e., absorption, distribution, metabolism, and excretion of drugs within an organism) and the elucidation of structure-activity relationships (SAR).[12]

Tuning photocatalysis by rational catalyst design

Modification of the structure of the photocatalyst permits a fine-tuning of its reduction/oxidation potentials, its excited state lifetime and energy, and its solubility.[13] Highly reducing and/or oxidizing species can be obtained by two consecutive photon absorptions[14] or by merging photocatalysis with electrochemistry.[15] Despite near-infrared (NIR) energy being generally unsuitable for photocatalytic applications, using upconversion strategies photoexcitation at these wavelengths can lead to productive reactivity in organic synthesis.[16]

While homogeneous photocatalysts have been used frequently, their recuperation and reuse after the reaction have been cumbersome, and are mostly ignored, requiring additional purification steps to remove the photocatalyst from the target compound. Indeed, minute amounts of toxic noble metals will fall afoul of the strict purity standards in place in the pharmaceutical industry. However, recovery is possible by immobilizing them on a heterogenous support or by using nanofiltration.[17] Alternatively, heterogeneous photocatalysts can be used, such as metal oxide semiconductors[18] or graphitic carbon nitrides.[19] Through surface modification and doping, these photocatalysts can be tuned to absorb visible light. Moreover, due to their heterogeneous nature and high stability against photodegradation, these heterogeneous photocatalysts can be easily and repeatedly recycled, making the overall photocatalytic process more sustainable and economical.

Greener and safer processes

Most photochemical processes adhere to the principles of green chemistry[20] and engineering.[21] Indeed, the use of light to activate organic molecules enables synthetic processes to be carried out at room temperature, effectively eliminating the need for harsh reaction conditions, elevated temperatures, and/or the addition of activation agents, such as redox reagents, acids/bases. While most organic molecules can only reach an electronic excited state by UV irradiation, photocatalysis enables the harvesting and productive use of lower energy photons (e.g., UV-A, visible light and even near infrared).[22] Under such photocatalytic reaction conditions, except for the photocatalyst, most reagents are transparent at these wavelengths, minimizing the risk of light-induced by-product formation. These simplifications of the reactions conditions also result in a higher functional group tolerance and minimizes the need for complicated downstream purifications or functional group protection.[23] Moreover, reaction rates are directly dependent on the supply of photons and thus tuning the light intensity provides a unique opportunity to initiate, accelerate or even stop chemical transformations promptly in case of an emergency.[24]

Driven by the need to address ecological emergencies, visible light photocatalysis can also provide opportunities to harvest solar energy, as a free, inexhaustible and non-polluting source of photons.[25] Recently, dedicated reactors have been developed that display an increased solar light harvesting capacity, enabling efficient solar-powered photochemistry[26,27] and providing even energy-neutral plants.[28]

Mature technology enables reproducible and scalable processes

In the past century, photocatalysis was rarely implemented in industrial synthetic processes.[29] The main reasons were the high cost associated with the generation of photons and the poor scalability of photochemical transformations due to a rapid decline in light intensity inside the reactor, rendering the photocatalysis inefficient at scale. However, in recent years, the required technology has evolved rapidly to address these issues, enabling the integration of photochemical steps in the synthetic routes to prepare pharmaceuticals, agrochemicals and other fine chemicals.[30]

Light-emitting diodes are now available across the entire UV-A, visible light and NIR spectrum, with long lifetimes, high photon intensities and high energy efficiencies, reducing the overall photon cost. These light sources can be easily combined with various reactor types (e.g., batch or flow reactors) and they emit over a narrow wavelength regime, matching the requirements of the selected photocatalyst, and providing excellent photochemoselectivity.

In addition, advanced reactor technology based on continuous-flow principles has been developed, which provides small dimensions (e.g., narrow capillaries) to tackle issues associated with the light intensity attenuation as a result of the Beer Lambert law.[31] Indeed, such small continuous-flow reactors in combination with high intensity light sources provide a vehicle for the accelerated efficiency and rates of photochemical reactions, facilitating the scale up in both laboratory and industrial settings.[32] Photochemical microreactors also provide a solution for the handling of challenging reactions conditions, opening up opportunities to safely and reliably handle gaseous or hazardous reagents.[33]

More recently, high-throughput experimentation technology has been developed, which enables experimentalists to execute a large number of photocatalytic experiments in an automated fashion[34,35] and which can be combined with inline analytical technology.[36-38] Furthermore, repetitive tasks relevant for mechanistic studies, such as fluorescence quenching analysis,[39] can be readily automated, resulting in higher accuracy and reproducibility of the obtained kinetic data.

Pitfalls

The value of synthetic photocatalysis to mediate the reaction of a wide range of substrates into a panoply of products is evident by the large volume of papers that have been published over the past decade or so. However, the full potential of photocatalysis is constrained by the inconsistent reporting of protocols and conditions used within the synthetic photocatalysis community. This leads to challenges in making cross-comparisons of reaction efficiency and efficacy from one laboratory to another, generating difficulties in reproducibility, a core tenant of science. By contrast, the solar cell community has adopted clear standards that are broadly followed in both academia and industry.[40,41] It has been argued that a similar philosophy should be adopted with evaluating the performance of LED technology.[42] Here we outline pitfalls and propose guidelines that we believe will not only enhance the science of photocatalysis but also catalyse the next advances in the field.

Reaction setup

It is frequently the case that there exists an insufficient description of the photoreactor setup to permit reproduction of the published experimental results.[43] A central reactant in any photocatalysis reaction is the photon.[44] The rate of the reaction and the stability of the reagents are dependent on the energy of the photons being absorbed and on the intensity of the photons incident on the reaction vessel. The capacity to control and accurately measure the excitation energy and the incident photon flux on the reaction vessel is central to reaction reproducibility. Indeed, it would be advisable to interrogate the reaction efficiency as a function of photon flux, including control reactions in the absence of a photocatalyst. Thus, a detailed description of both the excitation source (excitation energy, intensity) and the photoreactor (dimensions and configuration of the photoreactor) are key, in addition to a description of the reaction vessel dimensions and scale of the reaction in terms of solvent volume and concentration of reactants; what is often provided in the literature is not sufficiently detailed to describe an accurate description of the optical power. The importance of a sufficiently detailed description of the excitation source was recently documented by Edwards and co-workers.[24]

As batch-to-batch inconsistency in spectral output of the light source can occur, it is important that actinometry of a reaction with a known quantum yield be used as a tool to characterize the light source and calculate the number of photons absorbed. As light intensity decreases with the distance from the light source, it is important to ascertain with precision the distance between the light source and reaction vessel. Many modern photoreactors permit running parallel reactions in batch. Thus, it is important to obtain statistics on reaction yield as a function of the position of the vessel within these photoreactors.[45] Temperature control is likewise important, both from a point of view of limiting/ruling out thermochemical reactions and in temperature-dependent spectral variation of the excitation source. Thus, we would advocate *in situ* monitoring of the temperature in the reaction vessel and the use of heat transfer elements such as cooling fans or metallic heat sinks to mitigate this issue. Documentation of the internal temperature of the reaction vessel both during photocatalysis experiments and control experiments in the absence of illumination would help to standardize reaction outcomes. Many companies have made efforts to standardize their photochemistry platforms[34,46,47] and we would advocate that academia rapidly follow suit.

Reaction scale-up

Photochemical reactions at large scale must take into particular consideration the path length of the light through the reaction vessel, the concentration of photocatalyst and any other reactants that can absorb incident light and the molar absorptivity coefficients of absorption bands that overlap with the spectrum of the excitation source. The Beer-Lambert law[22] dictates the extent to which the excitation light can penetrate the solution. Indeed, the photochemistry only really occurs within ca. 2 mm from the vessel wall.[48] The main solution to mitigate against the attenuation of the light intensity because of absorption by the photocatalyst is to minimize the path length by running photochemical reactions in flow.[49] To ensure reproducibility of photochemical reactions in flow it is necessary to have a clear handle on residence and reactions times, area of the reactor that is illuminated, and to be cognizant of whether the reaction remains homogeneous or becomes heterogeneous.

Accurate optoelectronic characterization of the photocatalyst

In order to be able to optimize reaction conditions and to standardize reaction protocols it is vital to understand the key photophysical parameters of the photocatalyst that govern photochemical reactions.[50] Redox potentials, which are frequently measured by cyclic voltammetry, and optical gaps, a measure of the electronic energy of the excited state, which most accurately is determined by the intersection point of the normalized absorption and emission spectra, define the thermodynamic driving force of photochemical reactions in terms of the excited state redox potentials. However, these thermodynamic parameters are normally ascertained in solvents that are different from those used in the reaction. This is problematic considering that redox potentials, and especially optical gaps, can be solvent dependent, particularly if the excited state of the photocatalyst is charge transfer in nature.[51] Thus, we would advocate that the choice of solvent be standardized across both measurement and reaction conditions.

It is important to note that upon absorption of light the photocatalyst is in its singlet excited state; however, this does not necessarily reflect population of excited states encountered prior to electron, energy or atom transfer photochemical reactions. It may be that intersystem crossing is a competitive or even dominant process with photochemical processes.[52] For instance, if the photocatalyst is essentially always in its triplet excited state as intersystem crossing occurs on the picosecond time scale, which is the case for Ru(II) and Ir(III) photocatalysts, then the exclusion of oxygen must be considered as oxygen is an efficient triplet quencher; note too that oxygen can also quench singlet excited states and so may not be benign even if the photocatalyst were a fluorescent compound. The excited state must be sufficiently long-lived to allow for formation of bimolecular encounter complexes between the substrate and the photocatalyst, which is under diffusion control. Thus, excited state lifetimes of greater than a few nanoseconds are required; it is not necessary to have long-lived excited states on the order of microseconds for photochemistry to occur, as is often erroneously advanced in the literature. As mentioned above, temperature control is important, this due to the temperature dependence of both radiative and non-radiative processes. For instance, operating photochemical reactions using $[Ru(bpy)_3]^{2+}$ at even modestly elevated reaction temperatures can lead to off-cycle thermal population of metal-centred states and rapid quenching of the excited state. An accurate determination of the absorption spectrum is also necessary, particularly as the rate of the photochemical reaction is proportional to the number of photons absorbed by the photocatalyst, which is governed by the molar absorptivity coefficient of the absorption band that overlaps with the excitation source. We would strongly advocate that the synthetic photochemistry community embrace the accurate determination of these photophysical parameters.

Proposed mechanisms not grounded in experimental evidence

Too frequently in the synthetic photochemical literature, mechanisms are proposed with little to no experimental evidence provided. When mechanisms are indeed advanced, these are largely based on attempted correlations of reaction yield to thermodynamics parameters through an assessment of relative redox potentials, according to the Rehm-Weller theory. This strategy ignores reaction kinetics, especially when multiple photochemical processes are thermodynamically allowed. Indeed, the rate of the reaction is a function of the light absorbed by the photocatalyst, which is a function of the molar absorptivity, while the efficiency of the reaction depends on the concentration of the species that reacts with the photocatalyst in its excited state.[44] In order to accurately compare the performance of different photocatalysts it is essential that experimental conditions be consistent, both in terms of accounting for the incident photon flux but also in terms of the concentration of substrate and the absorbance of the photocatalyst. Thus, we would advocate that photocatalyst loading experiments be integrated within the experiment design.

Stern-Volmer quenching studies provide insight into the relative quenching rates of the photocatalyst by other solute molecules in the reaction solution. While such an analysis can be quite informative, it presumes that the rate-determining step of the reaction involves initial deactivation of the photocatalyst by the quencher. A more wholistic mechanistic picture would require knowledge of the identity of intermediates, their photophysical properties and the relative kinetics of different PET, PEnT and other radiative and non-radiative pathways.[53] This is typically only possible using a combination of spectroscopic and computational studies,[54-58] including an analysis of bond dissociation energies.

A valuable quantifier of a photochemical reaction is the quatum yield, which depends on the excited state lifetime of the photocatalyst, the rate of the electron-transfer reaction between the excited state of the photocatalyst and the quenching substrate, and its concentration. Typically, a quantum yield much less than 1 indicates a reaction that is based on a nonradical chain propagation.[59] However, care must be taken here as well in terms of the interpretation of this value as the quantum yield may not be governed only by the kinetics of the reaction but can be influenced by both scattering and parasitic absorption of other species in solution.[60] Judicious assessment of all these data and parameters can then be used to improve reaction yield and shorten reaction times. Finally, it is essential to verify whether the photocatalyst is photochemically stable, including under the reaction conditions or may also act as a competitive reactant, thereby altering its reactivity and acting as a parasitic trap for substrate.[61]

Caveats concerning using reaction yield

Too frequently, a reaction yield (isolated or determined using NMR spectroscopy) is quoted at some arbitrary time. The reader is left to infer whether the reaction has gone to completion. Further, it may be that the product is itself photoactive and is implicated in subsequent photochemistry, potentially leading to its consumption.[62] Thus, without information relating to reaction kinetics it is not advisable to correlate reaction yield with the thermodynamic properties of the photocatalyst. Such information can be obtained readily by dynamically monitoring the evolution of the reaction by NMR spectroscopy under photoexcitation conditions,[63] provided there is no significant pressure build up and no requirement for aerobic conditions as these conditions are incompatible with the closed reaction system that typically exists in the NMR tube.

Conclusions

The modern era of photocatalysis has resulted in myriad novel transformations and has become a powerful synthetic methodology. As the field matures and the equipment becomes more standardized and readily available, site-to-site reproducibility will increase and the accessible chemical space will expand. More in-depth mechanistic investigations are required to elucidate more clearly reaction mechanisms. Too often, mechanisms are advanced without sufficient experimental evidence. It is important to understand more completely the reactivity of the excited states of the photocatalyst and substrates and the interplay between the two if further advances are to be made in terms of new activation modes and synergies in cooperative-mode catalysis. The future is bright for photocatalysis, and we anticipate that photocatalysis will become part of the common lexicon of reactions in the 21st century just as transition metal catalysis has revolutionized synthetic advances in the last century.

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Declaration of Interests

The authors declare no competing interests.

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