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[2+2]-cycloadditions in organic photochemistry - the origin

EPA IS ON FACEBOOK

PHOTOCHEMICAL AND PHOTOBIOLOGICAL SCIENCES

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Past President and PPS matters

New Information Technologies
President’s Letter

Dear Colleagues,

The International Year of Light and Light-based technologies in 2015 (IYL2015) was a success with many interesting and imaginative activities aimed at highlighting the relevant role of light in our daily lives as a messenger, trigger and tool. These activities reached all the levels of our society and were also oriented towards making us aware that photochemistry, photophysics and light-based technology are research areas that remain to be exploited for future sustainable development of society.

Recently, the 39th Session of the General UNESCO Conference proclaimed the International Day of Light as 16th May, 2018. This initiative is complementary to the IYL2015 and will continue with the work carried out so far, following on in the wake of the success achieved in the IYL2015. This is magnificent news for our Society. All outreach and educational activities highlighting the relevance of light from different research areas, with a special focus on students at all the educational levels and the public at large, will be most welcome.

I would also like to mention the upcoming 27th IUPAC International Symposium on Photochemistry to be held in Dublin from 8th to 13th July, 2018. These IUPAC symposia are among the most important scientific events for the international photochemical community in which a good number of researchers from all over the world participate and will cover a broad range of scientific topics, all of them aimed at promoting knowledge for sustainable development and improvement in health, both of which have an impact on our lives beyond compare.

We expected that by now our new website would be operative, but unfortunately we are having some problems and the present webpage is not up-to-date; we will continue our efforts on this front.

The calls for the nominations for the EPA Prize for the Best PhD Thesis in Photochemistry during the previous two calendar years, and the Porter Medal, in cooperation with our Inter-American and
Asian/Oceanian photochemistry association counterparts, I-APS and APA, are open. The next EPA-PPS Prize for the most highly cited paper published in PPS, during the previous two calendar years, the EPA Prize for the Best PhD Thesis and the Porter Medal, will be awarded at the 27th IUPAC International Symposium on Photochemistry in Dublin (8th-13th July 2018).

Julia Pérez-Prieto
OBITUARY

Ugo Mazzucato

1929 - 2017
Remembering

Ugo Mazzucato
1929 - 2017

The members of the Photochemistry group of Perugia with profound sadness communicate that the beloved Professor Ugo Mazzucato, exceptional researcher and teacher for his great passion and scientific rigor, passed away on October, 15, 2017.

Born in Padua in 1929, Ugo Mazzucato married Gianna Favaro, also a chemist, and had two children: Lucia and Andrea. He received a degree in chemistry from the University of Padua in 1955. He was lecturer in physical chemistry and related subjects at the Universities of Padua, L’Aquila and Perugia. In Perugia, he has been full professor
of physical chemistry since 1969 and the Director of the Chemistry Department of the Science Faculty in the 1986-1992. After his retirement in November 2004 he continued to attend the Chemistry Department of the University of Perugia as Emeritus Professor, following some research lines and helping students in the thesis work.

He held important positions such as member of the Board of Governors of the University of Perugia. He worked in chemical education as part of commissions of the Italian Chemical Society (SCI) and of the National Research Council (CNR) for reforming the degree programs in the scientific field.

He was one of the founding members of the European Photochemistry Association, the Italian Group of Photochemistry, the national divisions of Physical Chemistry and Chemical Education, and the regional section of the Italian Chemical Society. He was a member of the editorial boards of the Gazzetta Chimica Italiana, EPA-Newsletter, the Journal of Photochemistry and Photobiology, A and C, and the Journal of Photoenergy.

Member of the Scientific Councils of the Center of Photochemistry of the CNR of Ferrara (1973-87), of the Laboratory of Photochemistry and High Energy Radiation (FRAE) of the CNR of Bologna (1969-2001, from 1978 to 2001 as President) and of the Center of Physical Chemical Studies on the Light Material Interaction of the CNR of Bari (1998-2001, as President).

He was part of the organizing committees of various international congresses of Scientific Photography and Photochemistry, he organized Schools, he was invited at various conferences in Italy and abroad in the fields of photochemistry, photophysics and scientific photography.

In the first part of his career he spent brief periods at the Universities of Sheffield (working under G. Porter), Orsay (S. Leach), and Moscow (L. A. Tumerman) to learn about photophysical and photochemical techniques. He has authored more than 220 scientific papers on kinetics, spectroscopy, acid-base and charge-transfer equilibria, photographic science, chemical education and, primarily,
on photochemistry. His main research interest was focused on the processes of rotation around double bonds (cis-trans photoisomerization) and single bonds (ground-state rotamerism) in stilbene-like compounds and their heteroanalogues and on their bimolecular processes with energy, electron and proton donors or acceptors.

His main hobbies were stamp collection, mountain hiking and wine tasting.
The Inter-American Photochemical Society

Gerald (Jerry) Meyer  
President, I-APS

The Inter-American Photochemical Society (I-APS) was born on August 12, 1975 at the 8th International Conference on Photochemistry in Edmonton Alberta. Many in attendance had long considered the merits of a photochemical society for America. After considerable and constructive discussions, an enthusiastic unanimous vote created I-APS at this location in northern Canada. Otto Strausz was given the authority to form an ad hoc committee whose names are listed in Table 1. Within four years the I-APS committee was determined entirely by election and was set in the mode of the highly successful European Photochemical Society. In 1976, a logo with the map of the Americas and an hv for inter-American photochemistry was introduced that closely resembles the I-APS symbol used today.

Table 1. 1975 Founding I-APS Committee
President: Otto Strausz, University of Alberta  
Vice-President: George Hammond, UC Santa Cruz  
Secretary: Paul de Mayo, University of Western Ontario  
Treasurer: Jack Williams, Eastman Kodak Co.
Advisory Board Members:
Presently, the Inter-American Photochemical Society has more than 600 members in academia, industry, and government throughout North and South America. Great emphasis is placed on engaging new scientists and students into the excitement of photochemistry to facilitate professional training and contact development. The Society maintains an active website (www.i-aps.org), holds annual meetings, and sponsor awards for outstanding contributions to the photochemical sciences. The current elected I-APS Committee is given in Table 2. In the following paragraphs, we highlight conferences and awards that may be of particular interest to photochemists from Europe.

Table 2. 2017 I-APS Committee
President: Gerald J. Meyer, University of North Carolina-Chapel Hill
        Vice-President: James K. McCusker, Michigan State University
        Secretary: Paul Jones, Wake Forest University
        Treasurer: Jayaraman Sivaguru, Bowling Green State University
        Advisory Board Members:
            Clemens Burda, Case Western Reserve University
            Belinda Heyne, University of Calgary
            Carolina Aliaga, University of Santiago Chile
            Sherri McFarland, University of North Carolina-Greensboro
            Jeffrey J. Rack, University of New Mexico
            Kirk Schanze University of Texas-San Antonio
            Ian Stanton, Edinburgh Instruments

While I-APS originated in Northern Canada, today’s annual meetings always occur in locations where photons are plentiful and the air is warm. In recent times, this has been the Gulf Coast of Florida with every 5th year being held in South America. This January marks the
27th I-APS Conference that will take place at the Lido Beach Resort in Sarasota FL, January 2-5 2018. These same dates and the same venue have already been reserved for the 28th Conference in 2019. This “Winter Conference,” as we often refer to it, is typically held right after New Year’s and consists of three days of scientific presentations, two evening poster sessions, and a banquet. Most all aspects of photochemistry are discussed that include fluorescent probes, quantum dots, light harvesting, excited states, polymers, catalysis, fuel production, medicinal chemistry, and new techniques. I-APS Award winners also give invited presentations. Lively evening poster sessions give students and new scientists the opportunity toingle and discuss photochemistry in a friendly and nurturing environment. The posters are left in place for the meeting entirety which provides an opportunity to visit them for additional discussions at any time during the Conference. Group runs and volley ball games on the beach as well as swimming or kayaking in the Gulf of Mexico are common activities.

Figure 1. Lido Beach Resort in Sarasota Florida site of the I-APS Winter Conferences.
The 2016 I-APS Conference was held in Santiago and represented the first time our Conference was held in Chile. The two previous South America Conferences have taken place in Mendoza Argentina (2011) and Salvador Brazil (2006). The South American site for the 2021 Conference has not yet been determined.

The Inter-American Photochemical Society sponsors six different annual awards for outstanding contributions by members to the photochemical sciences. These include the: 1) I-APS Award in Photochemistry, established in 1988 to recognize achievements made during the past ten years; 2) the I-APS Young Investigator Award, established in 2002 to recognize photo scientific contributions to members who have held an independent research position for no more than five years; 3) Gerhard Closs Student Award, for Ph.D. students whose thesis work advances photochemistry; 4) Gerhard Closs Post-Doctoral Award, for postdoctoral associates whose research advances photochemistry; 5) G. Cilento Award for scientists and students from Central or South America who are aged 35 or younger; and 6) I-APS Fellowship, which recognizes outstanding lifetime achievements in photochemistry and/or service to the Society. A list of the 2016 recipients is given in Table 3.

Figure 2. M. Jazmin Silvero, with mentor Tito Scaiano, receiving the G. Cilento Award from Jerry Meyer.
In addition, I-APS sponsors two biennial Awards: The George S. Hammond Award and The Nicholas J. Turro Award. The Hammond award is given for lifelong achievement and contributions to the photochemical sciences and is given in years that alternate with the Porter Medal. The Awards has been endowed by former students, colleagues, and associates of Professor Hammond and is administered by I-APS, but the Awardee need not be a member of I-APS. Former Porter Medalists and I-APS Awards winners are eligible. This Award was initiated in 2013 and recipients thus far are Nicholas Turro (2013), Josef Michl (2015), and David Whitten (2017).

Table 3. 2016 I-APS Award Winners

<table>
<thead>
<tr>
<th>Award</th>
<th>Winner</th>
</tr>
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<tbody>
<tr>
<td>I-APS Award in Photochemistry</td>
<td>Russell Schmehl, Tulane University</td>
</tr>
<tr>
<td>I-APS Award Young Investigator Award</td>
<td>Amanda Morris, Virginia Technical Institute</td>
</tr>
<tr>
<td>Gerhard Closs Student Award</td>
<td>Brian DiMarco, UNC-Chapel Hill</td>
</tr>
<tr>
<td>G. Cilento Award</td>
<td>M. Jazmin Silvero, National University of Cordoba</td>
</tr>
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The Nicholas J. Turro Award was established in 2017 and recognizes innovative contributions in photochemical sciences that transformed thinking or led to meaningful development of the field. Awardees will have made sustained scientific contributions with demonstrated successful mentoring of the next generation of photochemists over a period of at least twenty years. The Turro Award has also been endowed by former students, colleagues, and associates of Professor Turro and is administered by I-APS, but the Awardee need not be a member of I-APS. The Turro Award will be given in alternate years with the George S. Hammond Award and we look forward to hearing of the first recipient at our 27th I-APS Conference this January.

In closing, the Inter-American Photochemical Society continues to promote the photochemical sciences at annual conferences and through recognition of key scientific advances. From our creation in 1975, the European Photochemical Association has been an inspiration to us. We welcome and encourage your participation in all our future endeavors.
Moving Toward NIR Absorption and Emission with BODIPY Dyes in Two-Steps

Shawn Swavey,

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Boradiaza-s-indacene, more commonly known as BODIPY, represents a class of dyes based on coordination of BF2 to meso-linked pyrroles or dipyrrins. These dyes have been known for many decades but due to advances in, for example, phototherapeutics and dye sensitized solar cells (DSSCs) a growing interest in these dyes has emerged. Coordination of BF2 serves to align and extend the \( \pi \)-system of the dipyrrin thereby giving intense absorption and emission in the visible region of the spectrum with quantum efficiencies approaching unity. A typical BODIPY dye (Fig. 1) for example has peak absorption at 515 nm with an extinction coefficient in the 100's of thousands.

Regardless of their application it has been of paramount importance to shift the absorption of these BODIPY dyes into the NIR. Replacing the methine bridge carbon with nitrogen (azo-BODIPY) affords a bathochromic shift of nearly 100 nm; however, this
seemingly simple substitution can be synthetically problematic. Bathochromic shifts have been observed for BODIPY dyes substituted at the $\alpha$ or $\beta$ positions with either organic substituents or heavy atoms (i.e. iodine or bromine). However, the greatest bathochromic shifts (absorptions of 700-760 nm) have been observed for BODIPY dyes by fusing aromatic rings to the pyrrole units. Typically this process requires multiple synthetic steps with expensive catalysts and environmentally unfriendly organic solvents.

**Scheme 1.** Examples of BODIPY dyes synthesized by this route.

We have recently developed a new streamlined synthetic route toward dipyrromethenes requiring little to no organic solvents and no acid catalysts nor oxidizing agents. We have taken advantage of T.D.
Lash’s extensive work on π-extended pyrroles\(^6\) reacting them with a variety of aromatic aldehydes by simply mixing the reactants and heating in a water bath. Reactions of the crude dipyromethenes with boron trifluoride has resulted in the successful synthesis of a number of new BODIPY dyes. A small sample of the dyes made by this procedure is illustrated in Scheme 1.

![Absorption spectra](image)

**Figure 2.** Absorption spectra of isoquinol based BODIPY (green), naphthyl based BODIPY (red), and fluoranthro based BODIPY (blue).

As with most BODIPY dyes the dyes in Scheme 1 demonstrate intense absorption and emission in the visible region of the spectrum with quantum efficiencies near unity. We have observed that the absorption energy is dependent more on the pyrrole conjugation and less dependent on the aromatic aldehyde used in the reaction. Due to the extended π-system of the pyrroles these BODIPY dyes display lower energy absorption and emission spectra compared to traditional dyes using pyrrole. For instance absorption spectra of the isoquinopyrrole based BODIPY dyes display intense absorption at ca. 580 nm (green Fig. 2), the naphthyl based dyes absorb at ca. 600 nm.
nm (red Fig. 2), and the more highly conjugated fluoranthro BODIPY dyes absorb at ca. 650 nm (blue Fig. 2).^5

Typically quantum efficiencies decrease as the absorption moves to longer wavelengths; however, in these examples even the fluoranthro based dyes, which absorb at the longest wavelengths for this set of dyes, have near unit efficiencies. Our focus is on exploring more conjugated pyrroles to see if we can push the absorption and emission into the NIR region of the spectrum.

Applications

Our laboratory has been focused on the application of BODIPY dyes for photodynamic therapy (PDT) and more recently in developing light absorbers for dye sensitized solar cells (DSSCs).

\[
\text{Ru}_2-1: R_1 = \text{OH}; R_2 = \text{OCH}_3 \\
\text{Ru}_2-2: R_1 = \text{F}; R_2 = \text{H} \\
\text{Ru}_2-3: R_1 = R_2 = \text{H}
\]

Scheme 2. New bis-Ru(II)-BODIPY complexes.

In PDT developing a photosensitizer capable of light absorption within the PDT window (600-850 nm), for maximum tissue penetration, along with efficient energy conversion from the singlet excited state to the triplet state, to generate reactive oxygen species, is highly sought. Although examples of BODIPY dyes as PDT agents
have been presented they are limited by the fact that many of these dyes do not absorb light within the PDT window and due to their relatively short excited state lifetimes have low triplet oxygen to singlet oxygen conversion. In addition since most of the dyes are organic in nature they do not have the water solubility necessary for biological applications. By using the isoquinol based BODIPY dyes (Scheme 1) we have been able to coordinate ruthenium polypyriddyl complexes to the exposed nitrogen atoms. The result is a shift of the absorption to lower energy (within the PDT window) and added water solubility due to the cationic charge, Scheme 2.

In addition, by coordinating ruthenium(II) polypyridyl complexes directly to the BODIPY core these complexes have enhanced singlet to triplet conversion. Our studies indicate that all three complexes are highly efficient at generating singlet oxygen.

We are hopeful that this new synthetic route will allow us to generate libraries of BODIPY and Metal-BODIPY dyes with far reaching applications.

References


SPECIAL REPORTS ON SYNTHETIC ORGANIC PHOTOCHEMISTRY

The Thematic Issue has its focus on the use of light to achieve photochemical transformations from different angles of view. This includes chemical, mechanistic as well as technical aspects. The use of light as a green tool, especially when using visible light, has gained elevated attention during the last years. These trends are reflected for example in the contributions about photoinduced catalysis (groups of Prof. König, Prof. von Wangelin, Universität Regensburg, Germany). The large bandwidth of excited-state processes that can be employed for synthetic organic photochemistry includes hydrogen transfer, energy transfer, and electron transfer, as exemplified with some selected systems from the group of Prof. Griesbeck (Universität Köln, Germany). The use of intramolecular Photo-Dehydro-Diels-Alder reactions for obtaining cyclophanes is shown in the contribution by the group of Prof. Wessig (Universität Potsdam, Germany). Along the same line of using photochemistry to arrive at cyclized products are the efforts of the groups of Prof. Hoffmann (Université de Reims Champagne-Ardenne, France) and Prof. Kramer (Millsaps College, Jackson, USA). The usefulness of light in the manipulation/rearrangements of heterocyclic skeletons is demonstrated by the group of Prof. D'Auria (Università della Basilicata, Potenza, Italy). The technical advance in photochemistry is also discussed, covering for example microreactors and solar photochemistry for the synthesis of bioactive products, fragrances, etc.; see contributions by the groups of Prof. Oelgemöller (James Cook University, Townsville, Australia) and Prof. Loubière (Université de Toulouse, France). Although far from being complete, this Thematic Issue clearly showcases the renaissance that the field of organic photochemistry is living these days.

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A Simple Four-Step Synthesis of (1,7)Naphthalenophanes via Intramolecular Photo-Dehydro-Diels-Alder (IMPDDA) reaction

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Macrocycles and strained molecules, e.g. cyclophanes are of special scientific interest illustrated by their diverse properties and applications in several areas of chemistry.1 Scientifically relevant and naturally occurring cyclophanes often contain an arylnaphthalene core unit. If both aromatic units are bridged via a linker (in the most cases aliphatic) at their non-adjacent positions these structures are called naphthalenophanes.2 This particular compound class can be characterized by its ring strain, which depends strongly on the type and length of the used linker. Unfortunately, only less synthetic methods are known, where the corresponding aromatic core is build up during the course of the reaction. Other synthetic strategies are often hampered by unsatisfactory reaction methodology.3 One way to overcome those aforementioned problems, is the use of cycloaddition reactions towards the formation of differently substituted naphthalenophanes. Throughout the years, a relatively similar but mechanistically different type of Diels-Alder reaction, namely the so-called Dehydro-Diels-Alder (DDA) reaction4 became prominent and we proved its synthetic versatility and applicability in several synthetic examples in our lab, e.g. for the preparation of biaryls5, naphthylpyridines6 and variably bridged naphthalenophanes.7

Generally, DDA reactions can be triggered by different stimuli involving heat, transition metals and microwaves, respectively. Our approach makes use of a photochemical variant, which we termed the Photo-Dehydro-Diels-Alder (PDDA) reaction.8 We found in our cases, performing PDDA reactions intramolecularly (IMPDDA) is more efficient resulting in higher yields and lower reaction times.9 Based on these findings, our objective was based upon preparation and systematic investigation of hitherto unknown (1,7)naphthalenophanes.10
Our synthetic starting point was a simple four-step sequence starting from commercially available $p$-iodo arenes resulting in photoactive $p$-substituted aryl yrones (1). Upon irradiation ($\lambda_{exc} > 300$ nm, pyrex, mercury arc lamp, batch reactor) in dichloromethane we smoothly isolated the corresponding photo products (2) in good yields ranging from 33 – 74% (11 examples) depending on the length of the linker. We assume biradical (BR) and cycloallene (CA) intermediates being predominantly involved in the photocyclization step. (Fig. 1)

![Diagram of the reaction](image)

**Figure 1.** Exclusive Formation of (1,7)Naphthalenophanes 2 by IMPDDA reaction.

In order to calculate ring strain ($E_{STR}$) and other ring strain indicators (deformation angle of the phenyl ring) we used isodesmic reactions. With this tool in hand, it could be shown that
(1,7)naphthalenophanes can be highly ($E_{STR} = 13.2 - 25.4$ kcal/mol) and moderately strained ($E_{STR} = 1.0 - 6.0$ kcal/mol). Strain energies above 20 kcal/mol are synthetically not accessible by IMPDDA reaction, whereas all other strained (1,7)naphthalenophanes can be isolated. Quantum chemical calculations (B3LYP / 6-31G*) revealed a typical ground-state depending molecular geometry via dipole-dipole interactions of the corresponding chromophores (acyl groups) responsible for this high photochemical reactivity and selectivity in comparison to afore-investigated $o$- and $m$- aryl ynone systems. It should be outlined, that this is one of the most efficient PDDA systems investigated so far.

Furthermore, $^1$H NMR spectra showcased a typical electronic behavior caused by the bending of the phenyl ring (originally bending depends on the length of the ester linker), which stands nearly perpendicular to the naphthalene core. If protons from naphthalene core (blue) and the methyl group (red) are located inside the anisotropic cone of the phenyl ring chemical shifts are decreased (upfield shift), while protons outside this cone are shifted downfield (Fig. 2).

![Figure 2](image-url)  
**Figure 2.** NMR effects depending on increasing ring strain showing protons of naphthalene (blue) and methyl group (red) inside or outside the anisotropy cone (green)

This effect is maximized between highly ($n = 0, m = 3$) and moderately strained ($n = 2, m = 2$) cases, which reaches a value of $\Delta\delta = 0.7$ ppm.
Future research efforts will lay in the expansion of the substrate scope of IMPDDA reaction and the elucidation of the reaction mechanism during the photochemical key step using short-time spectroscopy tools.

References.
Gas, Liquid & Light – Photochemical Reactions of Three-Phase Systems

Michael Neumeier, Patrick Bayer, and Axel Jacobi von Wangelin*
Department of Chemistry, University of Regensburg, 93040 Regensburg, Germany

Photochemistry and photoredox catalysis have emerged as a powerful tools for the selective syntheses of complex molecules with the help of visible light.\(^1\) Besides the use of green solvents, non-toxic catalysts and light as one of the most sustainable sources of activation energy for a reaction, the fixation and utilization of unreactive exhaust gases (like CO, CO\(_2\), SO\(_2\), or NO\(_x\)) is a current objective in modern organic reaction developments. Our group has recently reported photochemical protocols that utilize visible light, technical gases, and liquid substrates. While the “mixing” of reaction components of organic reactions usually involves two distinct entities or phases (e.g. liquid-light or liquid-gas) due to the limitations of common flask chemistry, we have specifically addressed reactions between gases, liquids, and visible light. High dispersion in such “three-phase problems” has been ensured by using special reaction setups such as microreactors, gastight vessels, or a high-pressure photoreactors (Fig. 1).

![Figure 1. Combinations of gas, liquid, and light in special reaction setups.](image)

**Photooxygenation.** As reactions of organic molecules with molecular oxygen in its ground state often show poor selectivity,
protocols applying singlet oxygen for selective syntheses are well established. In contrast to commonly employed open-flask batch reactions, we have designed and built a modular photo-flow microreactor for “triphasic” reactions between oxygen, a liquid phase, and visible light.\(^2\) To demonstrate the benefits of this reactor, we investigated the oxidation of annelated cyclohexenes with singlet oxygen generated via photo-sensitization of atmospheric oxygen with methylene blue (MB) under visible light irradiation (Scheme 1).\(^2\) The enhanced mixing of the reagent, efficient temperature control, and the short residence times of a few minutes enabled highly selective Schenck-ene reactions of the cyclohexenes with high regio- and stereocontrol. The high reactivity of such cyclohexenes was rationalized on the basis of ground-state conformational analysis by NMR and DFT, which revealed the presence of accessible H atoms in the axial positions of boat conformers.

![Scheme 1](image)

**Scheme 1.** Selective oxidation and conformational analysis of cyclohexenes.

**Photoredox Catalysis.** In contrast to photochemical reactions of singlet oxygen which undergoes formal two-electron reactions with donors such as activated alkenes, visible light-driven chemistry featuring one-electron redox steps is another important possibility to fix exhaust gases such as CO or SO\(_2\) for the synthesis of complex molecules. Arenediazonium salts are a widely applied class of electrophiles in photoredox catalysis due to their ready availability...
from anilines, storability (as crystalline salts), and redox properties. The single-electron reduction of arenediazonium salts is a highly exergonic process at a reduction potential of around 0 V (vs. SCE) and with the extrusion of the stable dinitrogen as gas.⁴ Significant efforts have been reported toward the development of organic reaction methods that exploit the generation of aryl radicals from arenediazonium salts and involve subsequent radical trapping processes with π-donors such as (hetero)arenes, alkenes, alkynes, etc.⁵ We have recently expanded the scope of such aromatic functionalization reactions to gaseous σ-donors. In 2015, we successfully developed a photocatalytic strategy for the fixation of carbon monoxide in aromatic esters.⁶ A specially designed stainless steel photoreactor that allows the use of gas pressures up to 100 bars with simultaneous irradiation from the bottom of the reactor through a Quartz glass window. Under mild conditions (50 bar CO, alcohol as solvent, room temperature, green LED’s, few hours) arenediazonium salts were selectively converted to various benzoate derivatives (Scheme 2). Several electron-donating as well as electron-withdrawing groups were tolerated as substituents on the diazonium salts. Furthermore, different alcohols could be used; even tert-butanol was compatible with the reaction and afforded products that were not accessible via classical Pd- or Ni-catalyzed carbonylation reactions.⁷ Eosin Y was employed as inexpensive, metal-free photosensitizer. Detailed mechanistic investigations supported the notion of a photoredox catalysis mechanism via aryl and aroyl radical intermediates.

Very recently, we have demonstrated a conceptually related sulfonylation protocol. Instead of using technical SO₂, the in situ generation of the gaseous reagent from a 1:1 mixture of simple sulfonyl chloride and water was implemented into the photo-reaction.⁸ This strategy avoided the need for sophisticated equipment and ensured that the reaction could proceed in standard gas-tight snap vials. Various arenesulfonyl chlorides were prepared by this method in the presence of tris(2,2′-bipyridine)- ruthenium(II)dichloride, [Ru(bpy)₃]Cl₂, and green light irradiation. The reaction exhibited mild reaction conditions, high functional group tolerance, and perfect regiocontrol (Scheme 2).⁹ The photostability of the products under the reaction conditions are remarkable, even more so when considering the employment of
arenesulfonyl chlorides as starting material in several photoredox processes.\textsuperscript{10} We demonstrated the combination of the \textit{in situ} formation of arenediazonium salts with the in situ formation of SO\textsubscript{2}, and the photoredox catalysis. A one-pot procedure starting from anthranilamide completed a three-step synthesis of the commercial sweetener saccharin in quantitative yield. The mechanism of this reaction was corroborated by radical trapping experiments and DFT calculations.

\begin{center}
\includegraphics[width=\textwidth]{scheme2.png}
\end{center}

\textbf{Scheme 2.} Photoredox-catalyzed carbonylation and sulfonylation.

\textbf{References.}
\begin{enumerate}
\end{enumerate}


Applied and Green Photochemical Synthesis at James Cook University in Townsville, Australia

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The Group – The activities of the Applied and Green Photochemistry group of Associate Professor Michael Oelgemöller at James Cook University (JCU) range from the development of photochemical synthesis tools to the solar production of chemicals, photo-stability testing and photochemical degradation of organic and microbial pollutants. The group occupies modern and state-of-the-art laboratory facilities in The Science Place (Fig. 1) at JCU’s campus in Townsville, Australia.

Figure 1. The Science Place at JCU in Townsville, Australia.

Photochemical synthesis of bioactive compounds – The neglect of organic photochemistry by the industrial R&D community has left a diverse structural pool of possible new lead structures almost completely unexplored. The group at JCU has developed a series of useful photochemical transformations, which are applied to the synthesis of known and novel bioactive compounds. In particular,
the photodecarboxylative (PDC) addition to phthalimides – developed together with Professor Axel Griesbeck at the University of Cologne, Germany – has been utilized for the synthesis of alkyl- or arylmethylidene isoindolinones I and II (Scheme 1). An alternative approach deals with photochemical macrocyclizations to identify new candidates for molecular recognition, encapsulation or sensing, and to synthesize novel γ- or β-turn peptidomimetics. An additional research area deals with the synthesis of biologically active acylated naphthoquinones III and their corresponding naphtho-hydroquinone derivatives utilizing the metal-free Photo-Friedel-Crafts acylation.

Scheme 1. Generic target structures for photochemical synthesis.

Figure 2. Vertical falling-film (University of Cologne, Germany) and horizontal loop reactor (JCU, Australia).

Photochemical scale-up – Photochemical procedures are typically developed in the laboratory using small-scale chamber or immersion
well reactors (<1 L). Reaction scale-up for photochemical production is commonly restricted due to light penetration and mixing limitations, which has also hindered the acceptance of organic photochemistry in industrial R&D. The JCU team is investigating different approaches for multi-gram preparative photochemistry using vertical falling-film or horizontal tube loop-reactors (Fig. 2).

The falling-film design, developed at the University of Cologne in Germany, creates a thin layer of reaction mixture that passes the irradiated area vertically. Contact times are short and light penetration is highly effective. Likewise, the group has adopted a horizontal tube reactor for synthetic applications. The reactor creates a strong vortex flow with short residence times and excellent mixing of the reaction medium. Both reactors were successfully applied to photodecarboxylation reactions. Products were obtained under mild conditions, in high purities and on up to 50 g scales (<7 L) within hours.

Solar production of commodity chemicals – This research area investigates the large-scale, solar synthesis of fragrances (IV & V), pharmaceutical building blocks (VI & VII) and antimalarial compounds (VIII & IX) through dye-sensitized photooxygenation reactions (Scheme 2). Many starting materials are furthermore available from biomass, in particular agricultural waste material, thus reducing the dependency on fossil fuel derived chemicals.

Scheme 2. Target compounds for solar production.

Using a 2 m² CPC reactor (Fig. 3), the group at JCU has realized the semi-technical syntheses of commodity chemicals of specific interest to the agricultural industry in tropical Northern Australia. In collaboration with the German Aerospace Centre (DLR) in Cologne, Germany, the team has furthermore used concentrated sunlight for
solar manufacturing on kilogram-scales.

**Figure 3.** Solar CPC reactor at JCU (Australia) and PROPHIS plant at DLR (Germany).

Continuous-flow photochemistry – (Micro)flow photochemistry successfully combines the small dimensions of microreactors with continuous flow operation. The JCU team has pioneered this emerging technology and has constructed several novel flow reactors. These advanced devices are subsequently implemented in preparative photochemistry (Fig. 4). Bundling of microcapillaries furthermore allowed for rapid, resource- and space-efficient reaction optimization, scale-up and parallel synthesis. Likewise, the group has realized oneflow multistep reactions that combine photochemical and thermal reaction steps utilizing the advanced UV-150 module of Vapourtec Ltd (UK).

**Figure 4.** Continuous-flow photoreactors and Vapourtec’s UV-150 module.
Conclusion – The Applied and Green Photochemistry group at JCU is covering the entire spectrum of Synthetic Organic Photochemistry. The team is applying simple and efficient photochemical key-steps in the synthesis of biologically active compounds. In addition, the group is realizing solar manufacturing processes of valuable commodity chemicals. Likewise, the team is developing demonstration-scale and continuous-flow photoreactors for applications in organic synthesis.

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LED-driven Spiral-shaped Microreactor as a Tool to Investigate Sensitized Photooxygenations

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Organic photochemistry is a key synthesis pathway in sustainable chemistry,¹,² for example in the search for new compounds, for applications in medicine or agriculture, as well as in many other fields (e.g. material and environmental sciences). A variety of the fundamental principles of Green Chemistry³ are addressed by photochemistry: (i) multi step syntheses of complex molecules are shortened and simplified (often, a high molecular complexity is generated in one step from simple precursors); (ii) a large panel of novel compound families (e.g. strained rings) becomes accessible or more easily accessible; and (iii) in many reactions, the photon acts as a “traceless reagent” and no chemical catalysts (acid, base, metal, etc.) or activating groups are needed. Among the large portfolio of photochemical transformations, sensitized photooxygenations involving singlet oxygen are particularly attractive (e.g. photooxygenations of terpenes or the synthesis of the antimalarial drug artemisinin).⁴ Paradoxically, they have not found widespread implementations in the chemical industry, mainly due to the currently available technology based on outdated batch reactors (large dilution with poor light penetration) equipped with energy-demanding mercury lamps (intensive cooling, limited lifetime). Continuous-flow microstructured technologies have emerged as alternatives to batch processing and their suitability for photochemical reactions has been recently demonstrated.⁵ The combination of these devices with LED light sources additionally offers promising solutions for improving light penetration and controlling of light, thus enabling energy-savings while at the same time increasing yields and selectivity.⁶
In keeping with this context, we have designed and built a LED-driven spiral-shaped continuous-flow microreactor in Toulouse (France) specifically devoted to flow photochemical investigations. Its design aims at (i) studying how and why the operating conditions (irradiation, hydrodynamics conditions, initial concentration of reagents etc.) can affect a reaction’s yield and selectivity; (ii) acquiring data to establish a kinetic model based on mechanistic considerations; (iii) providing a tool for defining a methodology for smart scale-up. This device has been successfully used to investigate a monophasic photochemical reaction (photochromic system) requiring UV radiations. In an extension to this earlier work, the design of the continuous-flow microreactor has been extended to enable the study of heterogeneous sensitised photooxygenations.

![Figure 1. LED-driven spiral-shaped continuous-flow microreactor for investigating sensitized photooxygenations.](image)

Figure 1. LED-driven spiral-shaped continuous-flow microreactor for investigating sensitized photooxygenations.

The spiral-shaped microreactor consists of a tube (FEP material) inserted inside a channel carved into a flat aluminium plate and wound into a spiral geometry (Fig. 1). The use of tubing offers several advantages: low cost, easy replacement (‘disposable’ microreactor), controlled irradiation time (equal to the residence time), transparency to UV and visible light and flexibility in volume. Different diameters of tubing can be used, typically ranging from around a hundred µm to several mm and the length of the tubing can also be modulated from a few cm and up to 10 m. Thanks to its spiral geometry, the developed device is also flat and compact (160 × 160 mm²), allowing for homogeneous irradiation over the whole
tubing surface. This microreactor is now illuminated by a purpose-built visible-LED array (Fig. 1), made by the Led Engineering Development® company (Montauban, France), instead of the original UV-LED array. Compared to standard white LEDs, this advanced array consists of almost 1800 individual LEDs of ten different types, enabling an almost flat spectrum over the entire visible domain. The novel light-source additionally offers the possibility to select a specific spectral domain (e.g. 400-500 nm, 450-600 nm, 550-700 nm etc.) by means of an equalizer and an interface with Labview® software. Whatever the spectral domain selected, the photon flux emitted by the LED array can be modulated from a few mW.cm⁻² to 50 mW.cm⁻². The distance between the LED array and the spiral-shaped microreactor plate is chosen carefully to ensure an uniform illumination of the microreactor surface.

For implementing sensitized photooxygenations, the microreactor is fed through two inlets: the reaction solution containing the solvent, the starting material and the sensitizer (injected by a high-pressure syringe pump) and the gas phase containing oxygen (either pure oxygen or air). The latter is injected inside the microreactor tubing in a T-junction and regulated with a mass flow controller (Fig. 1). Following this approach, a segmented gas-liquid flow (called Taylor flow) is generated, which is characterised by a series of regular elongated bubbles separated by liquid slugs. In this flow pattern, the liquid surrounding the gas bubbles has two distinct regions: a recirculating region in the liquid slug between two consecutive bubbles and a liquid film region close to the wall. When compared to conventional gas-liquid reactors, such as bubble columns, higher interfacial areas (more than 1000 m².m⁻³) and intensified gas-liquid mass transfer (multiplied by 100-1000) are obtained, while at the same time generating regular and segmented gas-liquid flow. The spatial distribution of both phases (i.e. bubble length and liquid slug length) can be simply modified by changing the liquid flow rate and/or the gas flow rate.

To illustrate the potentiality of this LED-driven microreactor, the sensitized photooxygenation of alpha-terpinene was chosen as a benchmark reaction (Fig. 2a). The major product, ascaridole, is generated via [4+2] cycloaddition of singlet oxygen with the diene, with para-cymene being a minor by-product. The reaction is carried
out in ethanol as a green solvent. Rose Bengal is used as sensitizer because of its industrial importance and solubility in alcoholic solution, while air is used as reagent gas. Gas chromatography is routinely implemented to determine the amounts of ascaridole, alpha-terpinene and by-products, while NMR spectroscopy is used to identify the components in the reaction media. The diameter of the chosen tubing was equal to 1 mm and its exposed length was 5 m. Different initial concentrations of alpha-terpinene and Rose Bengal and various gas and liquid flow rates were subsequently studied, as well as different photon fluxes emitted by the LED-array (power, spectral domain). Exemplary results are shown in Fig. 2b. Full conversion is reached within a residence time of 40 seconds and the desired ascaridole is obtained as the sole product. Another key parameter to take into account is the bubble lengths, as it controls the stoichiometric conditions imposed (molar flux of oxygen vs. molar flux of alpha-terpinene) and enables mixing between the reactants and the transfer of oxygen from the gas bubbles to the liquid phase.

![Figure 2](image-url)

**Figure 2.** (a) Sensitized photooxygenation of alpha-terpinene as a benchmark reaction, (b) Conversion versus residence time profile.

All these findings illustrate that the developed LED-driven continuous-flow microreactor is a well-adapted tool for producing milligram quantities of a product of interest in minutes and that is can be used for quick data acquisition. A large range of operating parameters can likewise be screened under controlled conditions and by decoupling the effects of different parameters. This is a key feature to optimize the operating conditions and more generally to define the best strategy for smart scale-up.
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Photochemical Synthesis and Reaction Mechanisms at Millsaps College in Jackson, MS, USA

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The Group – Millsaps College is a purely undergraduate institution. The research activities of the group of Wolfgang Kramer are thus embedded in educational as well as collaborative programs, providing the best research education and network to undergraduate students. The projects range from synthetic applications of imide photochemistry, photochemical production of invasive, reactive intermediates and fluorescence sensors to solar photochemistry.

Synthetic Photochemistry of Imides – The phthalimide chromophore has been used extensively in synthetic photochemistry.¹ The photodecarboxylative cyclization (PDC),² developed in the lab of Prof. Axel Griesbeck, gives access to a variety of heterocyclic compounds and even allows for stereochemical control of the triplet radical reaction.³ Our group is exploring the potential of other imides for PDC applications. Following this strategy, the photodecarboxylative key step gives easy access to a variety of structurally interesting compounds. The current focus of the group are the naphthalimides as well as pyromellitic diimide.

Reactive Intermediates – N-substituted aromatic heterocycles containing a photoactivatable N-O bond can be homolytically cleaved upon excitation.⁴ The transient products can be used to induce damage in biomolecules and thus have potential applications in photoinduced cell death. The optimization of the photoreaction is achieved by modification of the corresponding photochemical precursor. Our current strategies aim to improve ground state
association with biomolecules and chromophore absorption in the visible region.

**Fluorescence Sensors** – The fluorescence of imides is strongly dependent on substituent effects and is used in several applications to quantitatively determine pH, ion concentration as well as oxidative strength of the solution. Subsequently, our group is currently developing novel imide-derived fluorescence sensors.

**Solar Photochemistry** – Students interested in pre-engineering are encouraged to design solar photoreactors that are used to produce chemicals on demonstration scales. The group has so far produced two solar reactors and has started the large-scale, solar synthesis of fragrances and other target chemicals through dye-sensitized photooxygenation reactions.

**Conclusion** – The Photochemistry group at Millsaps College is using synthetic and mechanistic photochemistry to prepare students for graduate and professional schools. The research projects range from imide photochemistry to solar photooxygenations.

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Photoredox Catalysis for Organic Synthesis

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Photoredox catalysis has evolved over the last years into a broadly applied tool in organic synthesis. The technique now moves from the academic laboratories into applications in the pharmaceutical industry, as the mild reaction conditions and exceptional easy access to highly reactive intermediates are advantageous. We, and many other groups, have contributed to the development of three areas, which we briefly describe here.

1. The photooxidation of inorganic anions
Inorganic anions, such as chloride, nitrate or sulfonate, are stable and react as nucleophiles in synthesis. However, highly reactive electrophiles are required and the stable ions typically do not react with arenes or alkenes. A one electron oxidation converts the anion into a radical and such inorganic radicals are highly reactive and undergo hydrogen atom abstraction or addition to alkenes at room temperature. The oxidation is induced by an oxidative photoredox catalyst and visible light. We used organic dyes, such as the Fukuzumi dye, an acridinium dye, or eosin, and air as the terminal oxidant. While nitrate radicals, which are obtained from the oxidation of nitrate anions, proved to be too reactive for selective organic synthesis and gave significant destruction of substrate molecules, sulfinate radicals, generated from the oxidation of sulfinate salts, react clean and selectively with activated alkenes (Fig. 1).1,2

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Figure 1. Photocatalytic synthesis of vinylsulfones by oxidation of sulfinate salts. R = aryl, heteroaryl, alkyl, cycloalkyl.
2. Sensitized electron transfer
On drawback of many visible light photoredox catalyses is their poor quantum yield. Only photo-initiated radical chain reaction proceed fast and with high quantum yields, while reactions that require excitation for each substrate conversion typically have quantum yields of less than 1% reflecting in reaction times of many hours or even days. One way to increase the efficiency of such processes is the combination of energy and electron transfer. Based on previous work by Goetz et al. we used ruthenium(trisbipyridine) as triplet sensitizer for redox active hydrocarbons, such as pyrene. An electron donor in the reaction mixture then converts pyrene into its radical anion, which is used to mediate e.g. the activation of aryl halides for cross coupling. By combining the energy- and the electron transfer step, the quantum yield of the cross coupling increases to 12%. The reaction time decreases from 16 to 2 h. The detailed mechanism of the reaction is still under investigation and discussed.

3. Carbon dioxide activation by dual photo-nickel catalysis
Combining metal- and photo-catalysis has enabled very useful synthetic transformations, such as cross couplings, C-N arylation reactions and many others. A challenge is the utilization of carbon dioxide in synthesis, due to the low chemical reactivity. We have developed a reaction, which combines the nickel-catalyzed activation of aryl- or alkyl-bromides with visible light photoredox activation using an organic dye to couple organic substrates with carbon dioxide. The method provides good yields for a variety of halides, proceeds at room temperature with blue light irradiation and uses potassium carbonate under ambient carbon dioxide pressure as carbon source.

\[
\text{R-Br} + \text{K}_2\text{CO}_3 \text{ (1.0 equiv.)} \quad \text{4CzIPN (1 mol%)} \quad \text{NiBr}_2\text{glyme (10 mol%)} \quad \text{Neocuproine (20 mol%)} \\
\text{Hantzsch ester (2 equiv.),} \quad \text{4 A MS (50 mg),} \quad \text{CO}_2 \text{ (balloon), DMF} \\
\text{blue LEDs, 24h, r.t.} \quad \text{2M HCl} \quad \text{R-COOH}
\]

**Figure 2.** Dual photocatalytic carboxylation of aryl- and alkyl-bromides with carbon dioxide. R = aryl, heteroaryl, alkyl, cycloalkyl.
References.
Photochemically Induced Hydrogen Transfer in Radical Cyclizations

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Photochemical excitation of organic molecules considerable modify their chemical properties. Consequently, compound families become available which are difficultly or not accessible using more conventional methods of organic synthesis. These reactions are therefore particularly interesting for being applied to the search of new biologically active compounds. Many photochemical reactions are performed respecting the requirements of sustainable chemistry. In particular photocycloadditions permit formation of C-C bonds without activation with chemical reagents which often reduce the formation of side products and waste. In this case, the photon is considered as a traceless reagent.

Some photochemically induced radical reactions involving a hydrogen atom transfer step also belong to this category. Intramolecular reactions of various chromophores have been studied in which a hydrogen is transferred form a donor moiety to a photochemically (most frequently triplet) excited state. Many transformations have been carried out with ketones. A typical example is shown in Scheme 1. Electronical excitation of the aromatic α-ketoester 1 to the \(^3\pi\pi^*\) state leads to hydrogen transfer from the glycine derived side chain the oxygen of keto group and the diradical intermediate 2 is generated. Radical combination leads to the final products 3a,b. Recently, the stereoselectivity of such reactions has been controlled using templating by ions or hydrogen bonds. The carbonyl function can be replaced by an α,β-unsaturated carbonyl or carboxyl function as hydrogen acceptor. 2,3-Unsaturated butyrolactone derivatives such as 4 may be electronically excited either by direct light absorption or be sensitization (Scheme 1). Due to increased spin density in the β position of ππ* triplet state 5, hydrogen is transferred from the acetale function of the side chain into this position leading to the diradical intermediate 6. Radical
combination leads to the final products 7. Thus, a C-C bond is
generated in the α position of an α,β-unsaturated carboxylic
compound. The regioselectivity of this reaction highly depends on
how the hydrogen atom transfer (HAT) from the donor moiety to
the electronically excited moiety occurs. Both particles, the electron
and the proton can be transferred simultaneously, or the electron is
transferred first and the proton follows. Both mechanisms most
frequently take place in these reactions and the impact of them on
the stereo and regioselectivity has been intensively discussed.10 Thus,
a two-step process in which the electron is transferred first (12),
would lead to an addition in the β position would take place (Scheme
2). After proton transfer to the basic site of the radical anion moiety
(13) and radical combination, a C-C bond would be formed in the β
position. However, the resulting product 14 is not observed. Indeed,
acetate functions such as in compound 4 are very difficultly oxidized.
This two-step process of hydrogen transfer has been discussed in the
case of tertiary amines as efficient electron and hydrogen donor
substrates.11

Scheme 1. Hydrogen transfer to an electronically excited species in a
one-step process.
Scheme 2. Hypothetical process for hydrogen transfer in a two-step process.

Imines such as 8 react in a similar way (Scheme 1). Upon irradiation, a hydrogen atom is transferred from the acetale moiety to the electronically excited imine function and the diradical intermediate 9 is formed.\(^\text{12}\) After cyclization, the spirocyclic compound 10 is obtained. This compound is not stable and is easily transformed into 11 by thermal elimination of carbon dioxide. Similar reactions have been carried out with aromatic imines derived from anthranilic acid.\(^\text{13}\) Many other chromophores undergo similar reactions which were applied to organic synthesis. Phthalimides were intensively investigated in this context.\(^\text{14}\) Such photochemically induced hydrogen transfer processes have also been discussed in connection with proton coupled electron transfer (PCET), in particular for photoredox catalytic reactions.\(^\text{15}\)

It should be pointed out that in these reactions C-H activation and C-C bond formation occurs selectively without participation of a chemical reagent or even a catalyst.\(^\text{16}\)

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Photoinduced Energy-, Electron-, and Hydrogen Transfer Reactions for Initiating Organic Syntheses

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Progress in organic photochemistry - a tool for the design and synthesis of new molecules - comes in waves. This is mainly due to the periodically changing activities of the synthetic chemists community in the field of radical chemistry and/or photochemistry. And this is possibly also correlated with the existence of the right human translators, i.e chemists that recognize the connections between the existing synthetic tools, especially in the catalysis field, and the demands for new structure motifs. David MacMillan, a leader in the fields of asymmetric synthesis and organocatalysis has recently recognized these new opportunities and published new concepts in the field of photoredox catalysis (the SOMO catalysis). These reports and others initiated a flood of studies in C-C and C-X coupling chemistry. These processes are driven by oxidative or reductive quenching of electronically excited catalysts like organic dyes, transitions metal complexes or semiconductor particles.

The basic underlying principle behind this prospering area is that especially designed catalysts can operate as unusually strong oxidants and reductants, respectively, and harvest electrons or holes from sacrificial donor or acceptor molecules. When clever combined, the synthetic reaction cycle combines forward electron transfer with the catalyst-reforming back electron transfer. The perfect photoredox catalysis needs no sacrificial components because the substrate and reagent(s) serve as donor/acceptor pairs. In reality, sacrificial components are often required such as donors, acceptors, acid and bases or electron-transfer mediators that allow faster electron/hole separation.

Three examples of photocatalysis are shown in Figure 1: the C-C coupling between ketones or aldehydes with cyclic acetals or ethers catalysed by organic dyes, semiconductor particles or titanium
complexes (Fig. 1). In this case, proton transfer follows the primary electron transfer; likewise the reaction can be directly initiated also by hydrogen transfer \((ET & HT)\).  

In the second example, a photoredox reaction cycle \((ET)\) generates an azidyl radical from oxidation of azide anions and terminates the reaction by reduction of an intermediary peroxy radical. The hydroperoxides 2 are useful precursors to 1,2-amino alcohols. A third process is also catalytic in the dye (rose Bengal) but initiated by energy transfer \((eT)\) to generate singlet excited oxygen \((1^\text{O}_2)\) as the reactive species. The ene reaction of \(1^\text{O}_2\) with allylic alcohols leads to \(\beta\)-hydroxy hydroperoxides 3, precursors to pharmaceutically active 1,2,4-trioxanes.

**Figure 1.** Photocatalytic oxygenation routes: initiated by hydrogen transfer, energy transfer and electron transfer.

We have recently developed a series of useful applications of singlet oxygen chemistry for the synthesis of oxyfunctionalized target molecules with cyclic peroxide functions (1,2-dioxanes, 1,2,4-trioxanes). The structural design of these targets follows the well-known and intensively studied role model artemisinin, a structurally
complex tetracyclic sesquiterpene lactone with an endoperoxide substructure that can be isolated from the leaves of *artemisia annua*. Due to its very high antimalarial activities, artemisinin, its derivatives, and numerous analogs have become important as antimalarial drugs against multidrug-resistant forms of *plasmodium falciparum*. Other activities of these peroxide structures are relevant for chemotherapeutic cancer treatment where these compounds serve as inhibitors of tumor-cell produced detoxification enzymes. Singlet oxygen again plays the crucial role as highly reactive photoexcited reagent that is able to generate an endoperoxide in the backbone of the semisynthetic artesunate 4 (Fig. 2).

![Figure 2. Photocatalytic singlet oxygenation for natural peroxide – synthetic peroxide dyad synthesis for pharmaceutical applications.](image)

**References.**


New Photoisomerizations of 1,2,4-Oxadiazoles

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Some years ago we started an ambitious project devoted to develop a unifying approach to the photochemical isomerization of pentaatomic heterocyclic compounds. The philosophy of this approach can be summarized assuming that, if the first excited state of a molecule is populated, this molecule can convert into the corresponding triplet state or into the corresponding Dewar isomer.

The efficiency of these processes will depend on energetic factor. If the Dewar isomer is formed, an isomeric product is obtained. If the triplet state is formed, cleavage of the X-Cα bond can occur to give ring opening products, decomposition products, or ring contraction products. However, if the radical formed after the X-Cα cleavage shows a higher energy than the triplet state, the triplet state will not be able to give the biradical with high efficiency, and then it will be quenched in radiative and not radiative processes. In this case, the Dewar isomer could be responsible for the isomerization reaction,

Scheme 1
but the isomerized products will probably be produced in very low quantum yields (Scheme 1). After these preliminary work, several applications of this approach to the photochemical isomerization of furan, thiophene, thiazole, pyrazole, and 1,2,4-oxadiazoles have been reported.\(^2\)

1,2,4-Oxadiazole derivatives can undergo a thermal isomerization known as Boulton-Katritzky rearrangement (Scheme 2).\(^3\) The rearrangement can occur in presence of acid and base catalysts as well as in the absence of catalyst.

![Scheme 2](image)

In this case, a proposed transition state for the reaction showed a partial charge transfer between the attacking nitrogen atom and the oxygen atom of the oxadiazole ring (Figure 1).\(^4\) The driving force of this thermal rearrangement is the transformation of the heterocyclic compound in another one characterized by a higher aromaticity.\(^5\)

![Figure 1](image)

**Figure 1.** The structure proposed for the transition state of the uncatalyzed path of the Boulton Katritzky rearrangement is depicted in the instance of the hydrazone of 3-formyl-1,2,4-oxadiazole.

In our previous research activity in this field, we found that the irradiation of 1,2,4-oxadiazole derivatives 1 allowed the formation of \(2H\)-1,2,3-triazoles 2 (Scheme 3).\(^6\) The reaction probably occurred through the first excited singlet state in a conrotatory \(6\pi\) electrocyclic process involving the interaction between LSOMO and LUMO.
This new process represents a new way to induce a photochemical isomerization of pentaatomic heterocyclic compounds. In order to investigate the synthetic potentiality of this new process, the possible use of metallic catalysts has been investigated. Recently, we described that the irradiation of 1 with visible light in the presence of Ru(bpy)$_2$Cl$_2$ allowed the formation of new 2H,1,2,4-triazole derivatives 3 (Scheme 4).

The photochemical isomerization of 1,2,4-oxadiazole derivatives to 1,2,4-triazoles has been studied at DFT/B3LYP/LanL2DZ level of theory. The reaction occurred in the presence of Ru(bpy)$_2$Cl$_2$. The irradiation of the Ru complex allowed the substitution of chlorine with the substrate. The irradiation at 760 nm of this new complex allowed an electron transfer process that favors the transfer of a
hydrogen atom from the hydrazonic NH group to the N atom in four position in the 1,2,4-oxadiazole ring. The resulting radical cation cyclized to give, through a Dewar isomer structure, to a reaction product.

References.
[2+2]-cycloadditions in organic photochemistry - the origin

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The photochemical [2+2]-cycloadditions represent one of the more studied reaction in the history of organic photochemistry. The first compound studied was thymoquinone. Lallemand reported in 1857 the instability under the light of this compound. He was able to isolate the reaction product but he could not determine the structure of the product. In 1877 Liebermann rediscovered the reaction determining the dimeric nature of the product (Scheme 1). However, he did not formulate a structure for this compound.

\[
\text{Scheme 1. Photochemical dimerization of thymoquinone.}
\]

In order to have the structure of the reaction product we need to expect several years. Only at the half of the forties of the last century a hypothesis on the structure of the product was made, and this hypothesis was then confirmed by spectroscopic data and by the X-ray analysis of the product.

In 1967 the irradiation in methanol gave a different behavior showing the presence of rearrangement products (Scheme 2).
Scheme 2. Photochemical behavior of thymoquinone in methanol.

This was the first example of the capability of α,β-unsaturated carbonyl compounds to give dimeric products when irradiated. A particular case was that of the dimerization of cinnamic acid derivatives.

There are several natural or biological active compounds that are dimers of cinnamic acid. α– and β-truxilines 1 and 2 are alkaloids found in *Erythroxylum coca* and in *Erythroxylum novogranatense*; they are potent cardiac toxins (Fig. 1).\(^7\)

Compound 3 is an antidepolarizing curare type agent able to induce tachycardia blocking the muscarinic receptors of the heart (Fig. 1). The dimers of p-cumaric and ferulic acids were found in the cellular membranes of graminaceae and are involved in the expression of the resistance of these structures. Compound 4 has been isolated in *Verbesina caracasana* and showed hypotensive properties (Fig. 1). Finally, compound 5 has been identified in Caribbean sponges *Agelas sceptrum* and *Agelas conifera*, showing antimicrobial and antibacterial activity.

The study of the photochemical behavior of cinnamic acid started at the end of XIX century when Libermann found that a cinnamic acid derivative, cinnamidinonemalonic acid 6 (Fig. 2), was unstable under the action of light. The colored solid material discolored under irradiation.\(^8\) He wrote: “the yellow color of cinnamidinonemalonic acid as well as of cinnamidycyanacrylic acid does not change in the dark (…). All the compounds, especially the first one that is of a more intense color, are in solid state very sensitive to sunlight. Their surface will soon dull. When larger quantities of cinnamidinonemalonic acid were placed under a glass bell in direct sunlight in summer, after 2-3 weeks the acid could be obtained in almost white form.”
Figure 1. Natural compounds dimers of cinnamic acid.
Liebermann also found that the irradiation of a benzenic solution of furylacrylic acid did not show the same behavior but that the irradiation induced trans-cis isomerization of the double bond.\textsuperscript{9}

In 1902, Riiber found that the irradiation of 6 allowed the formation of the corresponding dimer 7 (Scheme 3).\textsuperscript{10} The reaction product was identified by conversion in the corresponding truxilic acid.

In the same year Kohler reported similar results.\textsuperscript{11} Always in 1902 Riiber reported that solid cinnamic acid under irradiation was converted into truxilic acid.\textsuperscript{12} In particular we wrote: “It was evenly distributed, by means of a dumbbell motif, the acid in the form of fine and dry powder on a glass, in the amount of 1.5 g of acid per square decimeter. The powder was then carefully covered with a glossy sheet of paper; put in a wooden frame and exposed to the sun. After three and a half weeks, during which the frame was lightly exposed for 50 hours in the sun (causing very variable time), the acid was examined.”

Few years later Marussia Bakunin in Naple found similar reactions. The first experiments described by Bakunin are relative to the irradiation to the sun light of 2-phenyl-4-nitroindone in the solid state. Anticipating the work performed by Stobbe on cimmanic acid,
she found that this compound gave a single reaction product. “The best conditions are achieved when the substance is exposed to the sun in thin layer in the open containers; under these conditions not in months, but in a few hours in the warm months of July or August you have the almost complete transformation.

The transformation is made evident by the color change of the phenyl nitroindone, which from characteristic red becomes slightly yellowish white. (...) Crystallized from chloroform or benzene in which is very little soluble, the separation of the micaceous needles is cooled. It is difficult to clarify the melting point determined with the compressed nitrogen thermometers, it is noted that at melting temperature this body tends to decompose, and therefore with slow heating the substance decomposes without melting slowly carbonizing, with a rapid heating of the decomposing streams around 320- 325°.”

The photochemical dimerization of the reagent could furnish four different isomers (Scheme 4). On the contrary, Bakunin found that, performing the reaction in the solid state, the reaction was high stereoselective one. She was not able to determine the structure of the product; she thinks that the product was a dimer, but she did not have certain evidence confirming the hypothesis. Furthermore, she did not have way of determining the relative stereochemistry of the substituents.

Scheme 4. 2-phenyl-4-nitroindone dimerization. Possible stereoisomeric dimers.
Several years later, Remo de Fazi also, a coworker di Paternò, in some preliminair notes, showed that \( \alpha \)-methyl-\( \beta \)-phenylindone, irradiated with a UV lamp, gave two dimers (Scheme 5).

\[
\begin{align*}
\text{Scheme 5. Photochemistry of indones.}
\end{align*}
\]

The dimers were obtained in very different yields (56% and 8%).

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