SYMPOSIUM
on caged compounds

BOOK OF ABSTRACTS

Prague, Czech Republic

June 16-20, 2024

Symposium on Caged Compounds

The Symposium on Caged Compounds 2024 is organized by the Institute of Organic Chemistry and Biochemistry (IOCB) of the Czech Academy of Sciences, Prague, Czech Republic and RECETOX, Faculty of Science, Masaryk University, Brno, Czech Republic.

The symposium takes place from June 16 to 20, 2024 at IOCB Prague, Flemingovo nám. 2, 160 00, Prague 6, Czech Republic.

URL: https://slanina.group.uochb.cz/en/symposium

Local organising committee

Tomáš Slanina, IOCB Prague, Academy of Sciences, Prague, Czech Republic
Petr Klán, RECETOX, Faculty of Science, Masaryk University, Brno, Czech Republic

Main Partners

Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
RECETOX, Masaryk University
IOCB Tech, Czech Academy of Sciences

SYMPOSIUM
on caged compounds

Foreword by the Organizers

Dear colleagues,

The Symposium on Caged Compounds will bring together researchers who develop and use different kinds of photoactivatable systems to present the state-of-the-art and perspectives of their use. It informally follows on the previous “Caged Compounds” meetings organized by Prof. Manabu Abe in 2018 and 2020.

We hope that a relatively small size of this meeting will allow for interesting and fruitful discussions. The general aim of this meeting is to focus on connecting basic research in the field of photoactivatable prodrugs with photopharmacological approaches and applications of drug delivery.

We look forward to an exciting line-up of speakers from around the world.

Tomáš Slanina & Petr Klán

Tomáš Slanina

Institute of Organic Chemistry and Biochemistry, Prague

Petr Klán

RECETOX
Faculty of Science
Masaryk University, Brno

Conference Program

DAY 1

Time	June 16	**Sunday**	Speaker
9:00			
9:30			
10:00			
10:30			
11:00			
11:30			
12:00			
12:30			
13:00			
13:30			
14:00			
14:30			
15:00		registration	
15:30			
16:00			
16:30			
17:15	chair:	welcoming speeches	**Slanina, Klán**
17:30	Slanina	lecture	**Heckel**
18:00		lecture	**Bochet**
18:30		dinner	
19:00			
19:30			
20:00			
20:30			
21:00			

DAY 2

Time	June 17	**Monday**	Speaker	
9:00	chair:	lecture	**Jullien**	
9:30	Weinstain	lecture	**Ma**	
10:00		lecture	**Šolomek**	
10:30		coffee break		
11:00		lecture	**Abe**	
11:30		lecture	**Nakagawa**	
12:00		lunch		
12:30				
13:00				
13:30	chair:	lecture	**Specht**	
14:00	Ellis-Davies	lecture	**Blanchard-Desce**	
14:30		lecture	**Šebej**	
15:00		lecture	**Wang P.**	
15:30		coffee break		
16:00		lecture	**Winter**	
16:30		lecture	**Gudmundsdottir**	
17:00		lecture	**Popik**	
17:30				
18:00		dinner		
18:30				
19:00				
19:30	chair:	short lectures	**Schulte**	**Mondal**
20:00	Lawrence	short lectures	**Okoročenkova**	**Poryvai**
20:30		short lectures	**Glotz**	**Bednářová**
21:00				

DAY 3

Time	June 18	**Tuesday**	Speaker
9:00	chair:	lecture	**Weinstain**
9:30	Winter	lecture	**Phillips**
10:00		lecture	**Wachtveitl**
10:30		coffee break	
11:00		lecture	**Basaric**
11:30		lecture	**Bojtár**
12:00		lunch	
12:30			
13:00			
13:30			
14:00			
14:30		Prague tour	
15:00			
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18:00			
18:30			
19:00		Gala dinner	
19:30			
20:00			
20:30			
21:00			

DAY 4

Time	June 19	**Wednesday**	Speaker	
9:00	chair:	lecture	**Ellis-Davies**	
9:30	Jullien	lecture	**Berreau**	
10:00		lecture	**Slanina**	
10:30		coffee break		
11:00		lecture	**Štacko**	
11:30		lecture	**Simeth**	
12:00		lunch		
12:30				
13:00				
13:30	chair:	lecture	**Lawrence**	
14:00	Abe	lecture	**Schnermann**	
14:30		lecture	**Wang W.**	
15:00		lecture	**Szymanski**	
15:30		coffee break		
16:00		lecture	**Beharry**	
16:30		lecture	**Furuta**	
17:00		lecture	**Kele**	
17:30				
18:00		dinner		
18:30				
19:00				
19:30	Moderator:	panel discussion	Winter	Jullien
20:00	Klán	panel discussion	Ellis-Davies	Szymanski
20:30		panel discussion	Rádl	Lawrence
21:00		concluding remarks		

lectures:	30 min (25+5)
short lecture:	15 min (12+3)
posters:	PhD students

posters:	Aydogan	Copko	Jézéquel
	Khan	Lopez-Miranda	Solanke
	Svěrák	Vivien	Wohlrábová

Click the speaker's name to navigate to the respective abstract.

Crucial Roles of Leaving Group and Open-shell Cation in Photoreaction of (Coumarin-4-yl)methyl Esters

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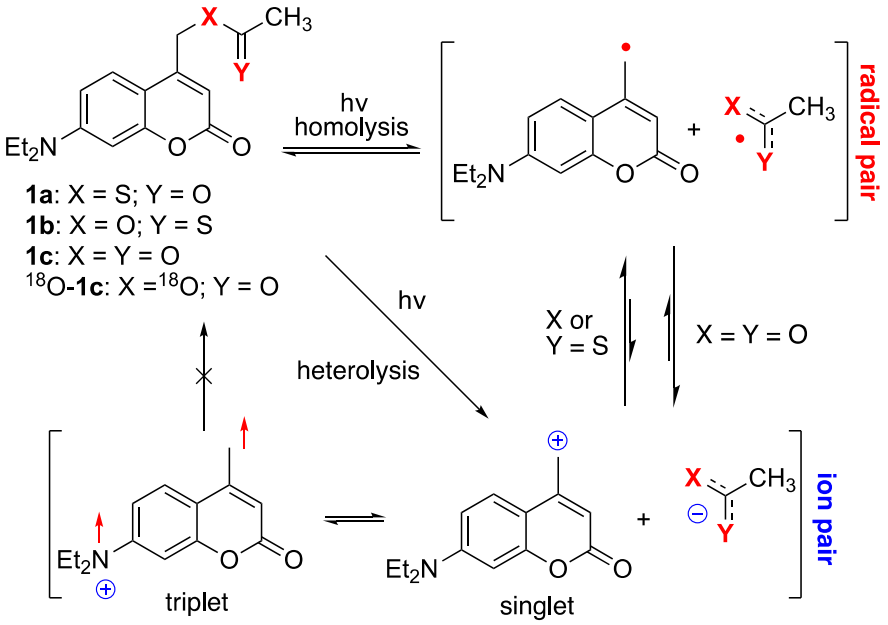
Photoreactions of (coumarin-4-yl)methyl compounds have been extensively studied in many fields of chemistry, including organic synthesis and photoinduced drug delivery systems. The identification of the reaction intermediates involved in the photoreactions is crucial not only for the elucidation of the reaction mechanism but also for the application of the photoreaction. In this study, the photoreactions of 7-diethylamino(coumarin-4-yl)methyl thioester **1a** (–$SC(O)CH_3$), thionoester **1b** (–$OC(S)CH_3$), and ester **1c** (–$OC(O)CH_3$) were investigated to understand the intermediary species and their chemical behavior. While a radical pair (i.e., 7-diethylamino(coumarin-4-yl)methyl radical and $CH_3C(O)S^{\bullet}$) plays an important role in the photoreaction of **1a** and **1b**, an ion pair (i.e., 7-diethylamino(coumarin-4-yl)methyl cation, and $CH_3CO_2^-$) was the key in the photoreaction of **1c**. ^{18}O-isotope-labeling of **1c** revealed a negligible recombination process within the ion pair. These unprecedented observations were rationalized by the open-shell character of the 7-diethylamino(coumarin-4-yl)methyl cation, whose formation was confirmed through product analysis and transient absorption spectroscopy.



Back to Conference Program

Strategies for improving the two-photon absorption properties of a photocage

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Photocages are powerful tools for spatiotemporal control of biological activity. However, many photocages are only efficiently activated by ultraviolet or visible light which is harmful for biological tissue. Thus, there is a high demand for near infrared and/or two-photon activatable photocages. Many well-established photocages exhibit inherently limited two-photon absorption (2PA) capabilities, but there are different approaches to push these limitations. One common approach is to use structural modifications such as π-extension or the addition of push-pull groups[1]. However, these modifications can lead to a significant drop in uncaging efficiency due to the introduction of additional deactivation pathways. Another strategy is to utilize fluorophores in the design of new photocages, as they often have inherently good 2PA properties. This approach offers the additional advantage of exploiting the extended excited state lifetimes typically associated with fluorophores, thereby minimizing faster decay channels[2]. So far, this strategy is not so straight forward and requires a careful assessment of the structural features and a perfect positioning of the leaving group for an adequate uncaging efficiency. The last strategy discussed is based on a modular approach, where the excitation and uncaging process are separated onto two molecular units[3]. The excitation unit works as a two-photon antenna which transfers the excitation energy to the uncaging unit. This approach offers the possibility to presumably maintain the uncaging efficiency of the photocage, while further improving its 2-photon properties. These methodologies will be examplified on different BODIPY photocages with the purpose to overcome the poor 2-photon activity of the basic BODIPY chromophore.

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BODIPY Photocages Cleavable at Boron

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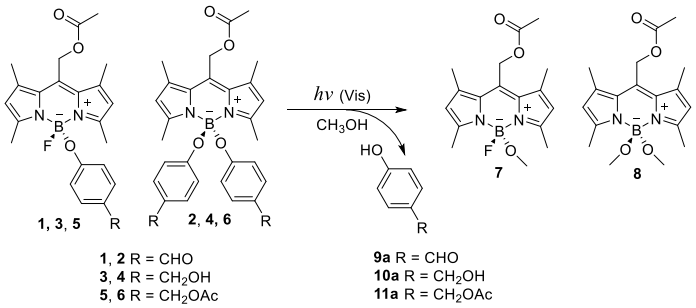
Photocleavable protective groups known as photocages are useful tools in biology,[1] that gained importance owing to the development of photocleavable chromophores absorbing visible light.[2] Among different photocages, BODIPY derivatives are particularly useful in organic synthesis and biology since they can release different functional groups from the *meso*-methylene position.[3]

Based on the known BODIPY photocages that release alcohols,[4] we designed a series of BODIPY compounds with a phenolic substituent at the *meso*-methylene position that were anticipated to be self-immolative and induce formation of quinone methides (QMs).[5] The research was initiated due to biological activity of QMs and the need to design new line of phototherapeutics that absorb visible light and do not base their action on production of singlet oxygen. However, we found out an unexpected photoreaction on boron atom of the BODIPY. That prompted us to investigate the photochemical cleavage reaction mechanism in detail by spectroscopic and computational methods. We found out that the photocleavage of the C-B bond in methanolic solution is followed by a rapid proton coupled electron transfer. Furthermore, we showed the scope of the BODIPY photocage to release different phenols substituted with electron withdrawing or donating groups (Scheme 1).



Scheme 1. Photocleavage at the BODIPY boron.

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Quinone Allides as Dynamic Photocages

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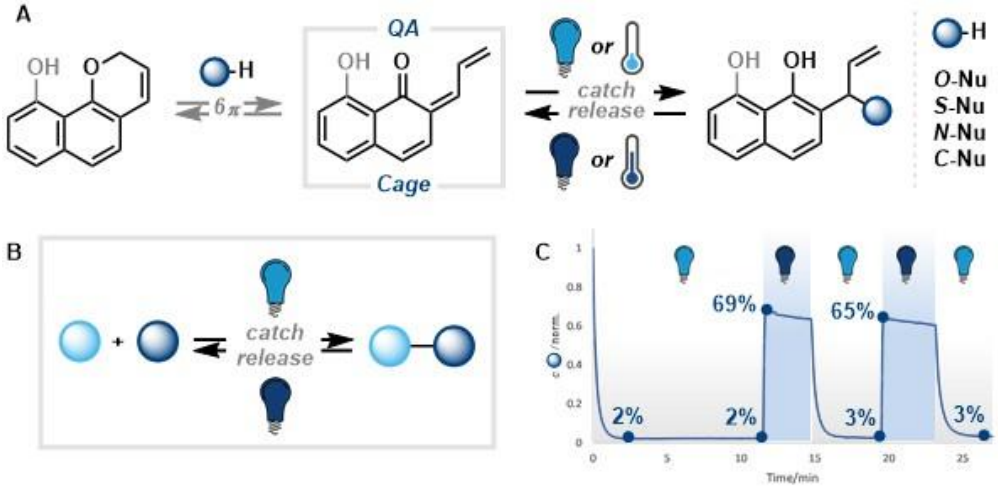
Quinone allides[1] (QA, Scheme A) are highly reactive species that can be generated *in situ* from *2H*-chromenes through photochemical electrocyclic ring opening or prepared in stable form if they possess additional stabilization. The dipolar nature of QA renders their utility as Michael acceptors, forming adducts with presented nucleophiles which, can be controllably liberated upon irradiation while restoring the original state of the system. This process is accompanied by a significant spectral change making QAs potential candidates for novel "dynamic" photocages.[2]

This system, based on the *de novo* strategy relying on reversible covalent bond formation ("*catch and release*", Scheme B), is envisioned to find applications across various scientific fields including materials chemistry, for development of new photoresponsive polymers; catalysis, for the discovery of photoactivated catalysts; (photo)pharmacology, as a method for *in vivo* drug activation; and molecular biology, as a novel system for reversible photolabeling of biomolecules.

In this study, we present the generation of QAs and their reactivity with various nucleophiles, including alcohols, thiols, amines, and carbon-nucleophiles. We discuss the structure-reactivity relationship of both starting materials (QA and nucleophile) and the products and document the reversible catch-and-release process (Scheme C).



Acknowledgements: Czech Science Foundation (22-20319S) and IOCB Fellowship.

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Photoactivatable β-Lapachone for Anticancer Therapy

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Pancreatic ductal adenocarcinoma (PDAC) has one of the shortest survivals among cancer patients. Most patients with PDAC have an unresectable tumor which leads to a 5-year survival rate of ~5%. β-Lapachone is a small molecule, natural product, exhibiting a wide variety of pharmacological properties. Most notably, β-lapachone was found to have potent anti-cancer activity for treating a variety of cancers including pancreatic cancer. Its anticancer activity is dependent on the intratumoural activity of the enzyme, NAD(P)H quinone oxidoreductase 1 (NQO1), which mediates a two-electron reduction of β-lapachone to a hydroquinone which spontaneously oxidizes back to the parent structure, completing a futile redox cycle that, in the process, produces cytotoxic reactive oxygen species (ROS) that kill cancer cells.

Despite its therapeutic promise, the clinical evaluation of β-lapachone has been limited by its poor water solubility, short in vivo half-life due to rapid metabolism ($\tau_{½}$ = 20 min), and narrow therapeutic window due to the generation of methemoglobinemia (i.e., oxidized hemoglobin which cannot deliver oxygen to tissues) as a side effect.

We developed a photoactivatable prodrug of β-lapachone. In contrast with native β-lapachone, our prodrug remained intact in a human whole blood assay ($\tau_{½}$ > 2 h), did not induce methemoglobinemia, and displayed no toxicity in pancreatic cancer cells in the dark (IC_{50} > 10 μM). Under violet light activation (420 nm), active β-lapachone is released within minutes, recovering its biological activity against the enzyme NQO1, causing production of ROS and inducing cytotoxicity with similar potency to native β-lapachone. Our photoactive β-lapachone was intravenously injected in established pancreatic tumour mouse models containing a surgically implanted transparent window to deliver the 420 nm light directly to the tumor. Under light conditions, we observed tumour shrinkage over days, in contrast to non-irradiated mice. Moreover, no shrinkage was observed with native β-lapachone under the same conditions. Overall, this presentation will highlight the potential of using photo-caging as a strategy to improve the anticancer activity of β-lapachone.

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CO Delivery Using Extended Flavonols

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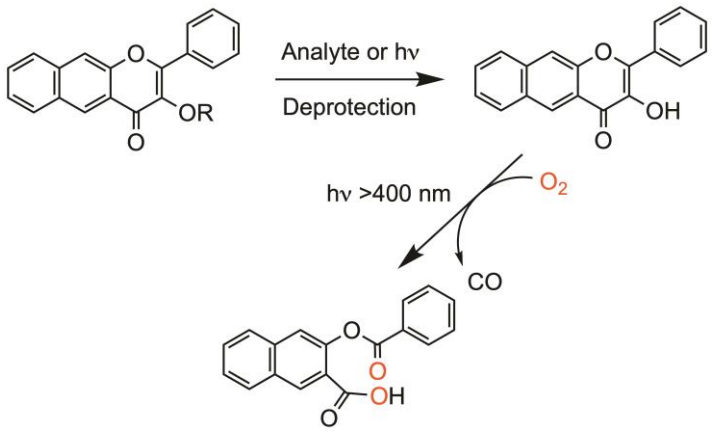
Carbon monoxide (CO) is a signalling molecule in humans. Its role in producing various effects including anti-inflammatory, antiapoptotic, antihypertensive, vasodialation, and cytoprotective outcomes remains to be fully defined.[1] Delivery of controlled amounts of CO is also known to produce antibacterial and anticancer effects.[2] Because of their potential for biomedical applications, molecules that can deliver a localized, controlled amount of CO are of current interest.

π-Extended flavonols were developed to enable CO delivery using a visible light triggered approach.[3] Caged versions of these molecules enable analyte sensing prior to CO release (Scheme 1). Fluorescence trackability is a key feature of these caged CO delivery vehicles, as the protected and deprotected forms have distinct fluorescence properties. In the research to be presented, new examples of caged π-extended flavonols will be discussed along with applications in producing anti-inflammatory effects.



Scheme 1: Caged π-extended flavonols for analyte sensing and visible light-triggered CO release.

Acknowledgements: The Berreau lab thanks the National Institutes of Health (R15GM124596) for funding.

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Engineering of Two-Photon Molecular Cages: Tandem versus Multimeric Systems

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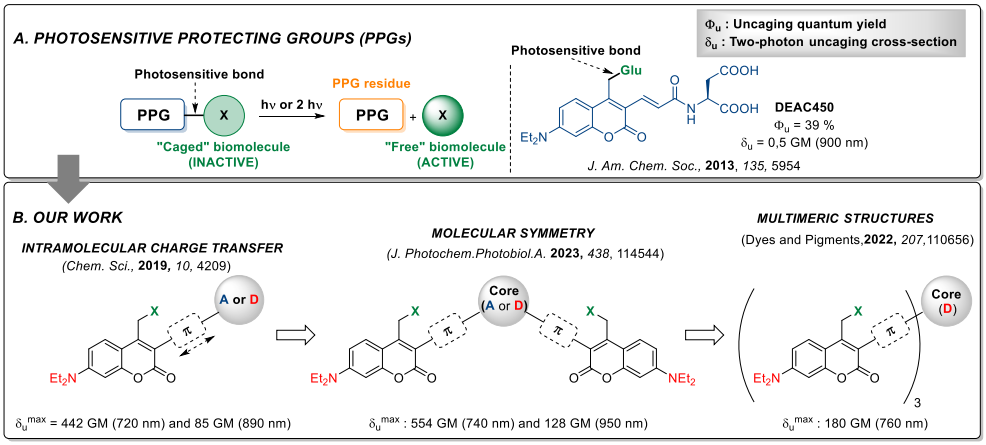
Molecular cages are organic molecules that are able to link biomolecules of interest and to impede their biological activity. This link can be cleaved by suitable light irradiation, releasing the caged biomolecule and restoring its biological activity.[1] One of the key issues for biological applications resides in their ability to use photons to trigger and spatially control drug delivery to a specific target, i.e. their uncaging efficiency (respectively ε_u and δ_u for one- and two-photon (2P) excitation). In that respect, 2PE in the biological spectral windows offers many advantages.[2] Yet, a major limitation has to be circumvented if real applications for in vivo biology or in the medical field are pursued, i.e., *the use of light irradiation conditions compatible with tissues*. With that aim in view, we have implemented molecular engineering routes towards tailor-made cages having suitable 2P uncaging efficiency (i.e., δ_u). We have investigated two main routes: (i) the design of tandem systems that take advantage of the use of 2P antennae[3], (ii) the design of polarized extended coumarinyl cages[4a] and (iii) multimeric coumarinyl cages of various symmetry.[4b-c] As a result, new PPGs showing unprecedented 2PU efficiency (typically higher than 100 GM) in the NIR1 region (i.e. 700-1000 nm) have been obtained:



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PPGs as tools for studying photochemical reactions

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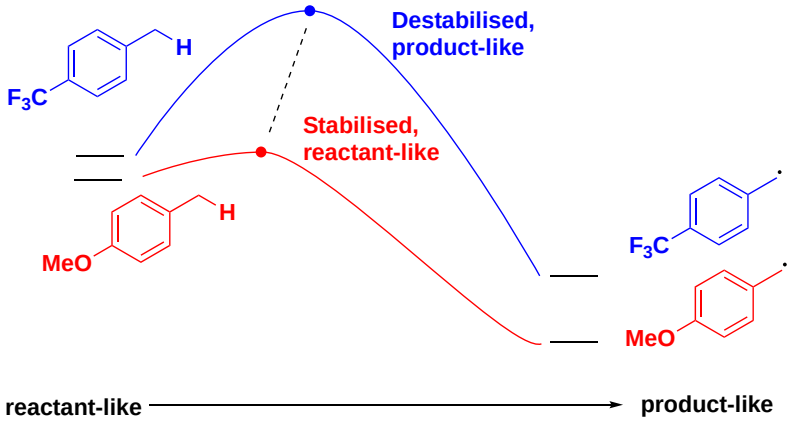
Half a century after the first reports on photolabile protecting groups (PPGs), the considerable efforts invested in improving their properties led to the availability of extremely valuable features, such as high quantum yield, operating wavelengths in the near infrared and high two-photon absorption cross sections.

The benefit of this large body of work is not limited to those features, and the general understanding of photochemical reactions is now much higher than it was in the 1960's. Concepts such as Vibrationally Promoted Electronic Resonance (VIPER) or Conical Intersections (CI) are now routinely used. Likewise for instrumentation: time-resolved spectroscopy down to the femtosecond time scale and free electrons lasers are not anymore reserved for dedicated physics departments.

Our group, together with others, took part to this collective study of PPGs.[1] However, we wondered whether we could use the accumulated data and models to go beyond the simple improvement of existing groups, and tried to figure out whether tools that are useful for ground state reactions can also be used for photochemical reactions, such as linear free energy relationships or even the Hammond Postulate. In this contribution, we will show our journey from the photolysis of *ortho*-nitrobenzylic derivatives to the attempt to confirm (or not) whether the Hammond Postulate is also valid for photochemical reactions, through the rather naïve eyes of synthetic organic chemists.[2]



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The missing chromophore: converting rhodamine dyes to photocages

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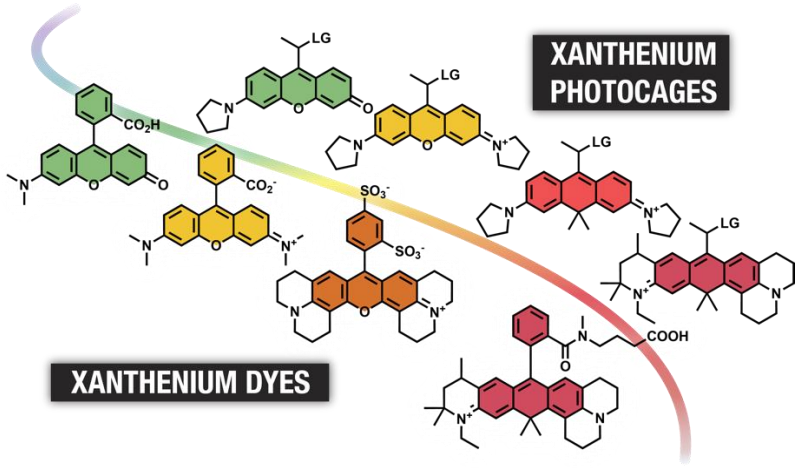
Visible light activatable photocages often feature chromophores from fluorescent dyes, however, xantheniums and related chromophores are not established caging groups. As rhodamines are among the most popular fluorescent dyes, their lack from the photocage palette is striking. Our aim was to fill this void of chromophores as caging groups and take advantage of their widely tunable optical properties, high absorption, water solubility and easy derivatization. Transforming the xanthenium scaffold to photocages could have a substantial impact on the phototherapeutic landscape[1] as well as provide new tools for light-assisted manipulations.

It turned out that there was a good reason behind their absence, however, with careful, seemingly minor modifications, we were able to synthesize and use these photocages in a photopharmacologically relevant biological system.[2] The challenges from their early development up to their optimized synthesis and advanced applications will be presented and the future research directions based on these novel chemical tools will be discussed in detail.



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Multiplicity-Driven Photochromism Controls Three-State Fulgimide Photoswitches

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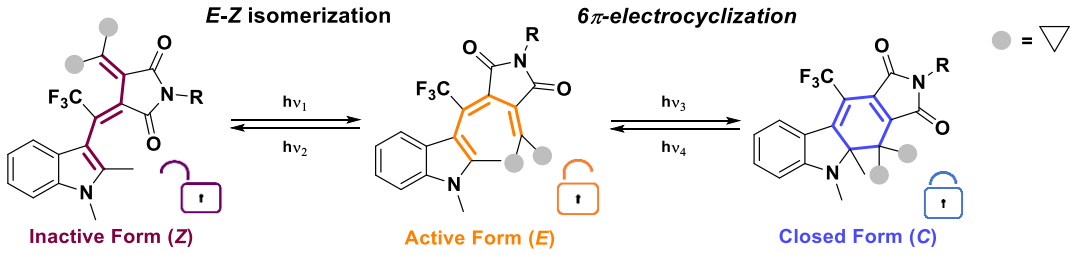
Photochromic organic motifs are being increasingly utilized in diverse applications, like optically active smart materials, catalysis, or photopharmacology.[1] Among the various photochromic motifs, fulgides have garnered significant attention due to their high thermal stability and fatigue resistance.[2] However, interest in fulgides has gradually declined, primarily due to their complex three-state photoswitching mechanism. The main photochromic process in fulgides, 6π-electrocyclization, is often limited by competing light-induced ***E-Z*** isomerization of the central double bond. The competing pathway can be partly mitigated by incorporating specific substituents; however, this adjustment can compromise the overall utility.[2]

Rather than inhibiting the ***E-Z*** isomerization, we focused on achieving control over this secondary photochromic motif to expand our toolkit for developing photosensitive systems and materials. We addressed this challenge by optimizing and meticulously controlling the conditions of photoinduced isomerization. This allows us to achieve nearly quantitative control over both the large structural changes induced by ***E-Z*** isomerization and the distinct colour changes induced by electrocyclization.[3] This unique monochromophoric three-state photoswitching system may rekindle interest in the development and application of fulgide photoswitches. Further, we aim to employ this system in the field of photopharmacology, an area where fulgide-based photoswitches have largely been overlooked.



Scheme 1: Three-state photoswitching between fulgimide isomers.

This work was supported by grant the Ministry of Education, Youth and Sports of the Czech Republic, LTAIN19166.

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Photopharmacology in vitro and in vivo.

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Caged compounds were invented by Jack Kaplan and colleagues in 1978. Kaplan's idea was to use photosensitive protecting groups to control the concentration of biological signaling molecules such as ATP and ionized calcium. Subsequently, caged compounds were developed by physiologists such David Tentham (caged IP3), George Hess (caged neurotransmitters), Henry Lester (caged cyclic nucleotides), Roger Tsien (caged nitric oxide and calcium), etc. using the ortho-nitrobenzyl PPG created by John Barltrop in 1966. Extending this technique to non-natural products was inevitable. However, in contrast to Kaplan's caged compounds, compelling biological investigations using such probes are lacking. To be explicit: what advantage does phasic pharmacology, when tonic pharmacology is so useful? I will present new data showing that drug uncaging in freely moving mice can evoke dopamine transients in the brain reward region (the nucleus accumbens) that mimic natural stimuli of this brain circuit. However, whether caged drugs will be very useful, only time will tell.

Design, synthesis and potential use of gene-directed caged compounds

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We have studied the design and synthesis of caged compounds with coumarin chromophores to manipulate cellular chemistry with high spatiotemporal resolution[1]. This research introduces a novel locked photocaging group that activates selectively in the presence of a specific non-endogenous enzyme (“key” enzyme), such as *E. coli* β-Gal. Our findings are crucial as they suggest that such "locked" caged compounds, like Gal-Bhc caged compounds, can be engineered to target specific cells and tissues marked genetically with the requisite enzyme[2]. This approach could serve as a viable alternative to optogenetic techniques.

The potential benefits of using gene-directed caged compounds over optogenetics include: (1) the rapid release of the compound, occurring from nanoseconds to milliseconds; (2) the ability to convert caged compounds into gene-directed caged compounds, which can cage both naturally occurring signaling molecules and synthetic selective inhibitors, activators, and ligands of target proteins; (3) engineered cells only become photosensitive when these caged compounds are introduced; (4) there is no need for genetic modifications when using an inherently expressed enzyme as the key enzyme; and (5) the low molecular weight of gene-directed caged compounds allows them to be cleared after a certain period, permitting subsequent use of another caged compound in the same engineered cells.

Acknowledgements

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Hunt for Dark States: The Photophysics and Photochemistry of Heptamethine Cyanine Dyes

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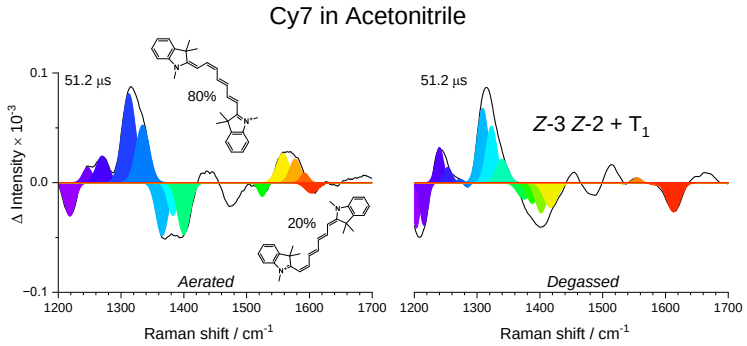
Heptamethine cyanines (Cy7) are near-infrared (NIR) fluorophores essential for modern bioimaging. Photoisomerization is one of the predominant nonradiative deactivation pathways of the Cy7 excited singlet state. This process produces Cy7 photoisomers with one or multiple carbon-carbon double bonds in the Z-configuration. The formation of these photoisomers contributes to the so-called blinking of Cy7 fluorescence; accordingly, they are referred to as dark states. Furthermore, the formation of the Cy7 triplet state also contributes to the blinking of Cy7 fluorescence. The photoisomerization and triplet formation processes have been extensively studied using picosecond transient absorption spectroscopy.[1] However, a large overlap between the transient absorption spectra of the triplet state and all possible mono-Z-photoisomers prevents a more profound elucidation. In this study, we investigated the photoisomerization of a Cy7 derivative in acetonitrile using femtosecond stimulated Raman spectroscopy (FSRS). Two photoisomers were identified based on the FSRS Raman shifts and comparison with the calculated Raman spectra. Their relative ratio was established to be 80% Z-3 *vs*. 20% Z-2. Additionally, the triplet state can clearly be identified and distinguished in FSRS based on the substantially different Raman shifts.



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Photoinitiated Release of Benzoic Acids from Solid-State Benzoyl Peroxide Derivatives

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We have developed photoprotecting groups that are crystalline, and upon exposure to light release their protected molecules into the gas phase. Although photoinitiated release of small gas molecules like nitrogen and carbon dioxide can be achieved from crystals,1,2 it is more challenging to release bigger molecules from crystals, due to the close packing of the photoprotecting group into the crystal lattice. Herein, we present how irradiation of crystalline benzoyl peroxide derivatives can be used to initiate the photorelease of benzoic acid derivatives. We will present the detailed mechanism for the photorelease as determined by solid state laser flash photolysis, theoretical calculations, and matrix isolation. In addition, we will present how the crystal packing arrangement and intermolecular forces affect the feasibility of the photorelease of benzoic acid derivatives

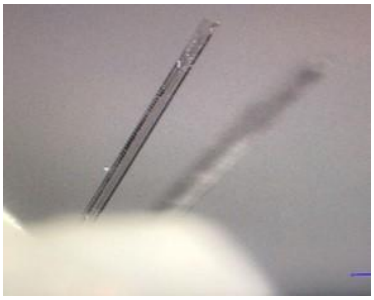

Figure 1. Photoinduced formation of benzoic acid crystals on benzoyl peroxide crystals

Acknowledgements: We are grateful for generous support from the National Science Foundation

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The worst photoswitches ever

Larita Luma,[1] Judith Pursteiner,[1] Nikolai Grebenovsky,[1] Carolin Feid,[2] Jan Gerrit Löffler,[2] Tobias Fischer,[3] Josef Wachtveitl,[3] Jens Bredenbeck,[2] Alexander Heckel[1]

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The regulation of nucleic acid activity with light is a worthwhile goal as it allows constructing clever experiments in which questions can be addressed with spatiotemporal resolution. While photoswitching of DNA hybridization is about 25 years old, there are still not too many approaches in which this has been realized and there is still room for improvement. In our search for new solutions, we encountered a system with surprisingly disappointing performance. The presentation will show how the story of this failure took unexpected turns and where we stand so far.

3-Hydroxyflavothiones Derivatives as Photoactivatable Carbon Monoxide Releasing Molecules (PhotoCORMs)

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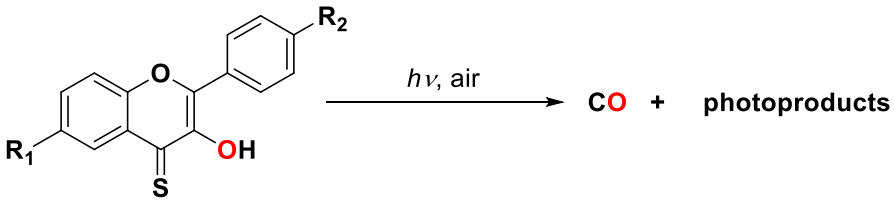
Carbon monoxide (CO) is a gas toxic to a wide variety of living organisms. At a low dose, it has promising therapeutic properties, including cytoprotective and anti-inflammatory effects.[1]

CO delivery to the target tissue can be achieved by various means (enzymatic cleavage, ligand exchange, etc.); light-activated CO-releasing molecules (photoCORMs) are of interest due to the high temporal and spatial precision of the CO release. While 3-hydroxyflavone derivatives as photoCORMs are well established, their sulfur analogs, 3-hydroxyflavothione derivatives, have rarely been studied[2], although the thione group is known to be photochemically very active.[3]

We show that 3-hydroxyflavothiones exhibit substantial bathochromic shifts of their absorption maxima and enhanced photosensitivity, although they provide lower yields of CO formation than their oxygenated analogs. Mechanistic aspects of this reaction will be presented.



R_1 = H, Br
R_2 = H, OMe, NMe_2

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Bioorthogonal modulation of photoresponsivity and vice versa

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Photoresponsive materials offer excellent spatiotemporal control over biological processes and the emerging phototherapeutic methods are expected to have significant effects on targeted therapies. Recent examples show that combination of photoactivatable approaches with bioorthogonal chemistry enhances the precision of targeted phototherapies and profound implications are anticipated particularly in the treatment of non-operable tumors. The extra level of on-target selectivity and improved spatial/temporal control considerably intensified related bioorthogonally assisted phototherapy research.[1]

We made several efforts toward the more efficient control of photoresponsivity using bioorthogonal reactions as triggers. The knowledge we gained upon the development of bioorthogonally activatable simple fluorogenic probes[2] and more complex red-emitting fluorogenic scaffolds[3] was applied to gain control over the photoresponsivity of photolabile protecting groups (photocages) paving the way for the highly precise activation of drugs in response to a specific ligation reaction and light illumination sequence.[4] Such release of payloads by a bioorthogonal reaction and light illumination follows a conditional AND-logic. We also envisioned that similar spatiotemporal precision is achieved by reversing the sequence of inputs and achieve light activatable bioorthogonal platforms that can be applied to trigger the release of chemically disabled payloads.

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Phototruncation of Heptamethine Cyanines

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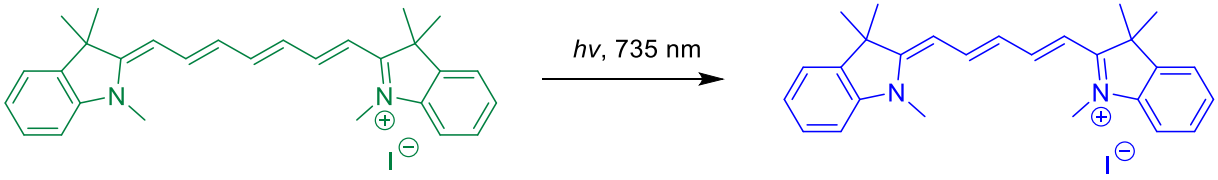
Cyanines are among the most popular chromophores utilized in single-molecule fluorescence and super-resolution microscopy.[1] The facile tailoring of absorption and emission properties of cyanines at the molecular level makes them ideal for target-specific labelling. Upon irradiation, heptamethine cyanines in aerated solutions typically undergo photobleaching to give non-emissive products, and under specific conditions, they give dyes with hypsochromically-shifted absorption maxima.[2] These derivatives were characterized as products of a two-carbon truncation (phototruncation) of the polymethine chain, namely pentamethine cyanine (Scheme 1). Our primary aim was to increase the yield of this phototruncation reaction.[3] We found that phototruncation can be enhanced and is highly affected by oxygen, pH, solvent, different reagents, and substituents on the polymethine chain. We will provide a detailed mechanistic analysis of phototruncation in this presentation.



Scheme 1

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Light-Triggered Drug Release from Cell-Conveyed Phototherapeutics

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Light-responsive therapeutics offer the promise of targeted therapy, whose benefits include (a) prolonged action at the target site, (b) reduced dosage due to enhanced therapeutic efficiency, (c) reduced systemic concentration as a consequence of direct action on target, (d) reduced adverse effects as a result of selective enhancement, (e) and localized delivery of multiple agents resulting in targeted combination therapy. Although photo-activatable pro-drugs have received considerable attention, these species are dependent upon short wavelengths (<450 nm) for activation. However, maximal tissue penetrance by light occurs within the "optical window of tissue" (650 – 900 nm), well beyond the wavelength range of most photo-cleavable functional groups. We've developed a technology that (a) uses light within the optical window to control drug delivery, (b) provides the means to assign distinct wavelengths to the photo-delivery of different drugs, (c) employs circulating lipid bilayer-containing carriers (e.g., RBCs, liposomes) as the drug transporters, and (d) is applicable to therapeutic agents that range in size from small molecules to proteins.[1] The design and biomedical applications of this technology will be discussed.

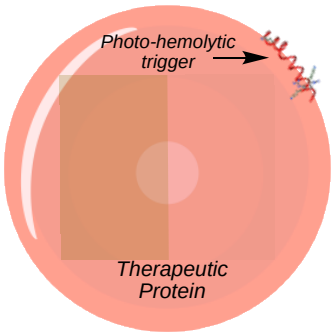

Figure: Cell conveyed therapeutic proteins are functionally and physically caged and subsequently photo-released.

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Red-Shifted Photoactivatable β-Lapachone Prodrugs

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β-lapachone is a small molecule quinone natural product that has potent anti cancer activity for pancreatic, prostate, breast, and lung. We found that β-lapachone when modified with a photolabile protecting group (i.e., 7-diethylaminocoumarin), improved its stability in blood and reduces methemoglobinemia formation. Irradiation using 420 nm light can then release active β-lapachone to effectively kill cancer cells. Although promising as a photo-therapeutic, a drawback with this construct is the short wavelength of light needed to trigger photo-uncaging which will suffer from poor tissue penetration in vivo.

My goal is to synthesize longer wavelength absorbing photoactivatable β lapachones. In this presentation, I will describe the use of thioxocoumarin and the use of halogenated (i.e., iodinated and brominated) 7-diethylaminocoumarins. Though these photocages have modest red-shifts (e.g., 420 nm – 490 nm), we found that in addition to uncaging, irradiation produces reactive oxygen species which may lead to improvements to β-lapachone efficacy in cancer cells. In parallel, we are also exploring the use of BODIPY-based photocages such as WinterGreen (515 nm) and a red-light absorbing BODIPY (640 nm) for their ability to mask β-lapachone activity until photo released.2,3 Overall, the red-shifted photoactivatable β-lapachone's described here may lead to higher β-lapachone efficacy in vivo compared to our original construct.

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Fluorescence to Measure Light Intensity

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Quantitative measurement of light intensity is required in many fields of biology, chemistry, engineering, and physics. The available protocols necessitate specific equipment and expertise, which often revealed limiting when it came to transfer our developments in optogenetics[1] and fluorescence imaging[2] to end-users. Hence, we recently exploited fluorescence for retrieving the light intensity even in the depth of samples, with spatial distribution information, over wide ranges of wavelengths and intensities, and in a quick, inexpensive, and simple manner.[3] Our protocol relies on analyzing the time evolution of the fluorescence signal from actinometers when constant light is applied. This protocol has been applied to quantitatively characterize the spatial distribution of light of various imaging systems, and to calibrate illumination of commercially available instruments and light sources.

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Reaction Mechanism Studies on Selected Photocaged Compounds

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Photochemical reaction mechanism study of organic molecules is an inter-discipline between physical organic chemistry and chemical kinetics. The mechanism study has important application requirements as the reactive intermediates might be toxic and lead to the side reaction. As well, understanding the mechanism is key to regulate and control the reactions, and design the molecules. Due to the complexity of the excited state reactions, and the low concentrations and fast decay time of the reactive intermediates, it is a big challenge to gain the chemical structures of the intermediates and unravel the photochemical reaction mechanisms. To solve this problem, we developed time-resolved resonance Raman spectroscopic technique, and with the help of time-resolved absorption/emission spectroscopies and theory calculations. In this meeting, I will report our recent reaction mechanism studies on photocaged compounds.

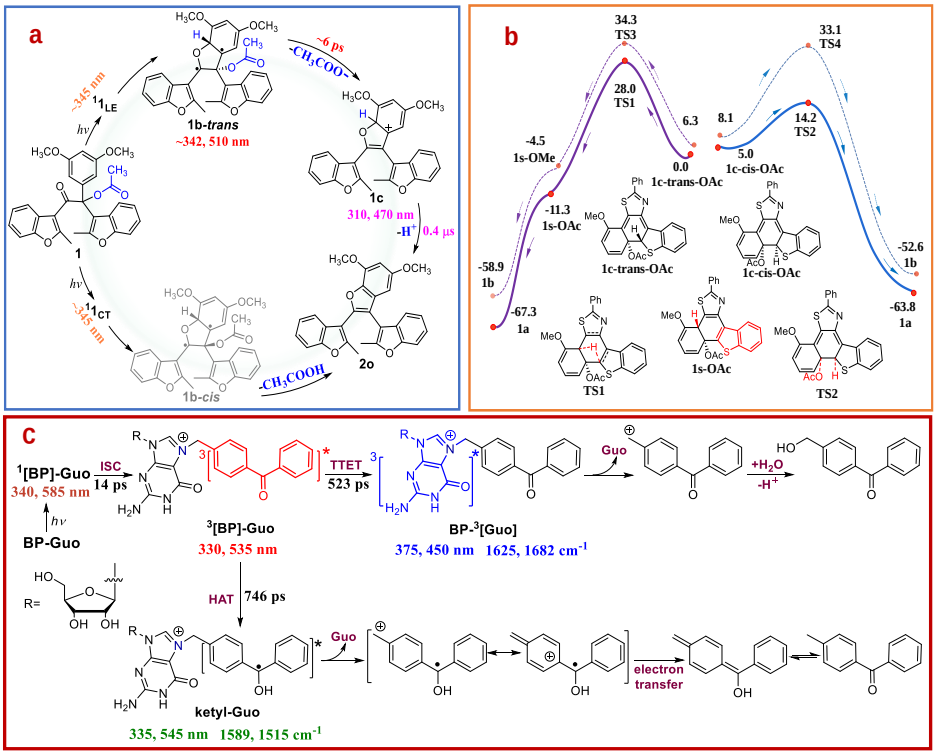

Fig. 1 The proposed reaction mechanisms of selected photocaged compounds.

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Wavelength Selective Xanthene-Based Monochromophoric Photo-removable Protecting Groups for Tuning Soft Matter Materials Properties

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Photocontrolled deprotection of specific functional groups has garnered significant interest over the past two decades.[1, 2] Notably, the selective deprotection of distinct groups based on wavelength has emerged as a prominent focus in recent research.[3] The achievement of this objective has primarily involved the utilization of linker-based bichromophoric systems and diverse cocktail mixtures of photoresponsive protecting groups (PRPGs), each responsive to varying wavelengths of light.[4, 5] Herein, we presented the first wavelength selective monochromophoric system based on a hydroxanthene moiety, enabling the wavelength selective release of two distinct functionalities under 450 nm blue light and 600 nm red light, respectively. The mechanism of the wavelength selective photodegradation was thoroughly investigated by ^{1}H NMR, UV-Vis, and Fluorescence spectroscopy, suggesting a proton-coupled electron transfer mechanism in the first photorelease step and electron transfer-based arylmethyl type of photorelease in the second step. The utility of the xanthene-based wavelength-selective PRPGs were demonstrated in the multi-step degradation of microparticles and dual-color tuning of polymer chain architecture, thus opening an avenue to design advanced photoreactive wavelength-controlled systems for applications in soft matter materials.

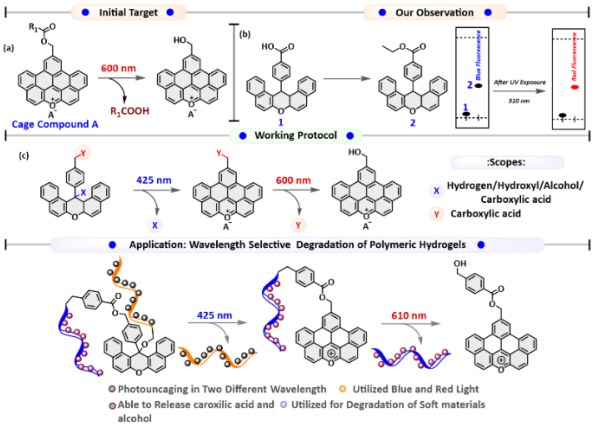

Figure 1: (a) Prior design on xanthylium-based NIR-active photoremovable protecting group; (b) observed change (blue to red fluorescence) in the TLC plate (after UV-exposure) during the synthesis of compound 2; (c) Working protocol and scope of xanthene-based wave-length selective PRPG; (c) Application: Xanthene-based wavelength selective PRPG of the release of two soft materials by blue light and red light irradiation.

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Spatiotemporal control of NO release with caged NOs and their biological application

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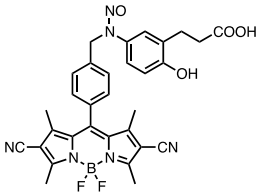
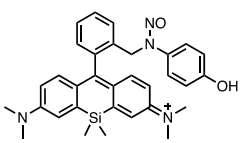
Nitric oxide (NO) is an important mediator involved in the biological processes, such as vasodilation, neuromodulation, and biodefence, while it is relatively unstable under ambient conditions and not easy to handle for biological experiments. Chemical NO releasers are practical tools to overcome such difficulties, and many NO releasers have been developed so far. Among them, Caged NOs, or photocontrollable NO releasers, would be useful experimental tools for biology of NO, with which, NO release can be controlled by photoirradiation with spatiotemporal resolution.

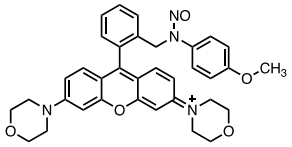
We have been studied on caged NOs and related caged compounds, and developed a series of caged NOs employing an intramolecular photoinduced electron transfer (PeT) for NO release. In those compounds, two components, a dye moiety for light harvesting and a *N*-nitrosoaminoaryl moiety for NO release. Our first caged NO, NOBL-1 [1a], can be uncaged with a light around 500 nm (blue light), in which the BODIPY moiety was incorporated as a dye moiety. Its *N*-nitrosoaminophenol moiety is oxidized by intramolecular PeT with the photo-excited BODIPY moiety, and the resulted unstable radical immediate spontaneously decomposes to the stable quinonimine group with concomitantly releasing NO. Based on this mechanism, we explored dye moieties and found that caged NOs bearing various dyes also work with appropriate wavelength lights. Our recent one, NORD1 [1b], was found to be activated by red light (650 nm) and applicable for local vasodilation *in vivo*. Another one, NO-Rosa6 [1c] employing *N*-nitrosoaminoanisol as a NO releasing moiety, can release NO depending on both light and ascorbic acid. This strategy is considered to be widely applicable for developing a variety of caged NOs, including those useful for in vivo experimental and potential therapeutics.



NOBL-1



NORD1



NO-Rosa6

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Chain-Shortening of Heptamethine Cyanine Dyes

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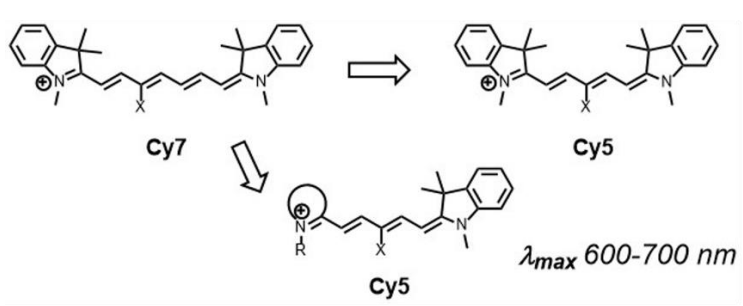
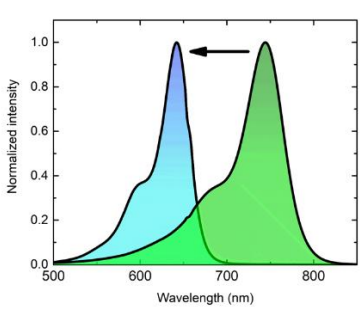
Cyanine dyes are a class of organic fluorophores containing conjugated polymethine chains. Heptamethine (Cy7) and pentamethine cyanine (Cy5) dyes fluorescent in the near-infrared region have emerged as a promising tool for cancer imaging and targeted therapy[1a]. Changing the structures and thus physicochemical properties of cyanine derivatives have attracted great interest in biology and medicine.[1b,c] Synthetic strategies toward the modification of cyanines generally rely on an early-stage introduction of various functional groups into the heterocyclic terminal groups or the heptamethine chain.[2] In contrast, a chain-shortening (truncation) reaction has been a scarcely described phenomenon. Here, we present a study of the truncation of Cy7 to Cy5 via homogeneous, acid-base-catalyzed nucleophilic exchange reactions. The study provides a critical insight into the reactivity of the polyene chains of cyanines and offers new approaches to the synthesis of *meso*-substituted symmetrical and unsymmetrical Cy5 from Cy7 derivatives with desired photophysical properties.





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Photochemical and Time-resolved Spectroscopic Studies of Blebbistatin and Potential for Photorelease of Caged Compounds

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We previously showed that blebbistatin had potential as a two-photon near infrared photoprotective group (2PA-NIR-PPG) to release hydroxyl radicals.[1] In addition, blebbistatin was demonstrated to be cell-membrane permeable and biocompatible.[2,] These results indicated that blebbistatin derivatives might serve as a promising novel platform for releasing molecules of interest under two-photon activation for biological applications.[2,3]

In this talk, blebbistatin derivatives with various electronic characteristic leaving groups were synthesized and studied. The photocleavage mechanism(s) and the effects of the leaving group properties were elucidated using photoproduct analysis, hydroxyl radicals detection and femtosecond transient absorption spectroscopy. This work found that more substantial electron-withdrawing leaving groups facilitate heterolysis of the C-O bond that leads to a cationic intermediate and corresponding fragment. Weaker electron-withdrawing leaving groups were found to give a higher proportion of homolysis of the C-O bond, accompanied by the production of some hydroxyl radical. These results suggest that blebbistatin-derived PPGs have potential to deliver an anti-cancer drug and hydroxyl radicals at the same time which may lead to more efficient photochemotherapy. This work provides new fundamental insights into the photocleavage of blebbistatin derivatives and may help in the development of novel 2PA-NIR-PPGs for various kinds of applications in the future.[3,4]

Acknowledgements

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En Route to Photo-Glycosylation: Light-induced S_N1 and S_N2 Reactions

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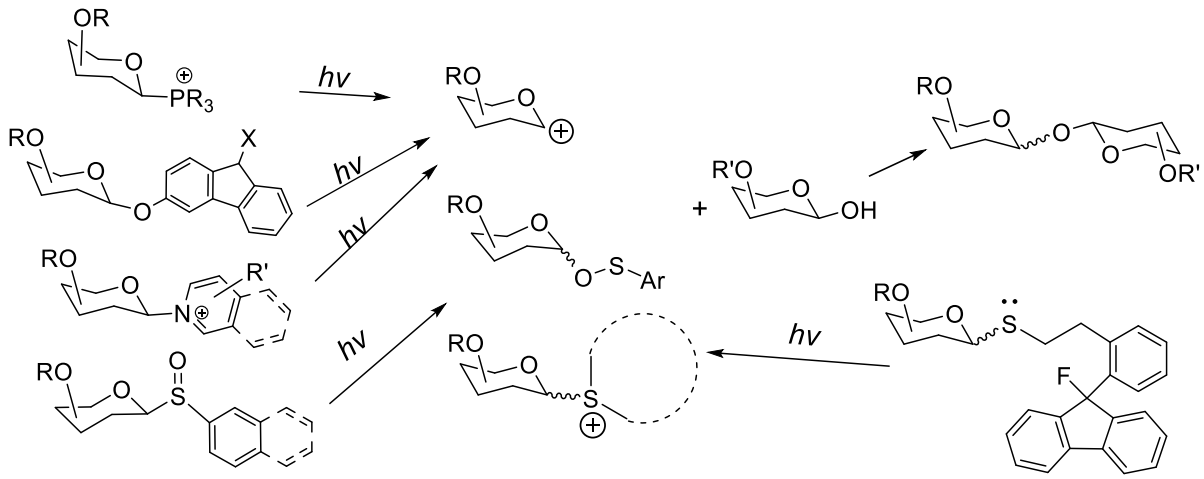
The absolute majority of photo-labile protecting groups release nucleophilic substrate (e.g., alcohol, carboxylic acid, amine, etc.) upon irradiation. The development of photo-glycosylation procedure requires an efficient method for the photochemical generation of electrophilic glycosyl donors. Two novel strategies for the photochemical induction of nucleophilic substitution will be presented. The first, i.e., photo-S_N1, relies on the photo-heterolysis of the bond between anomeric carbon and the "onium" heteroatom (N or P) with the generation of oxocarbenium ion (Scheme below). The alternative photo-S_N2 approach employs light-induced rearrangements to activate the leaving group. The latter strategy allows for the control of the reactivity-selectivity properties of the glycosyl donor. In addition, we explore concurrent generation of fluoride ion as a potential activator of glycosyl acceptor. The exploration of the scope of these photoreactions, as well as their potential utility for the photo-glycosylation will be discussed.



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Radical reactivity of BODIPY-based photocages as a key to "catch and release" process

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Photocages[1] are highly desirable compounds due to their potential applications in drug delivery systems. BODIPY-based photocages are promising candidates as the reactivity of the BODIPY scaffold enables a wide range of its modification.[2,3]

It has been previously shown that the photorelease of carboxylate from related BODIPY systems is a photoinduced S_N1 reaction. We have utilized this knowledge to release signalling lipids from π-extended BODIPYs.[4] Detailed mechanistic studies performed on these derivatives revealed possible parallel homolytic cargo cleavage.

Therefore, in the current study, we develop BODIPY-based systems, where a BODIPY-Cargo bond cleavage is a homolytic process, that enables a photoinduced release of organic radical species. Moreover, we also present applications of this reactivity mode in polymerization.

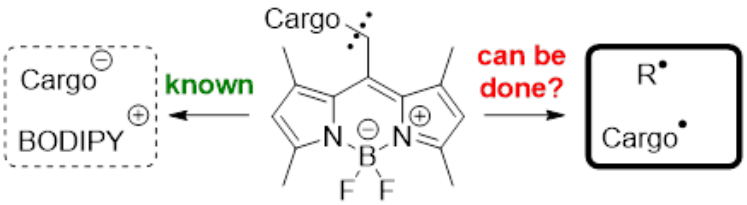

Figure: Radical reactivity of BODIPY-based photocages

Acknowledgements: This work was supported by the SNSF Swiss Postdoctoral Fellowship (217233).

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Harnessing Cyanine Reactivity for Imaging and Drug Delivery

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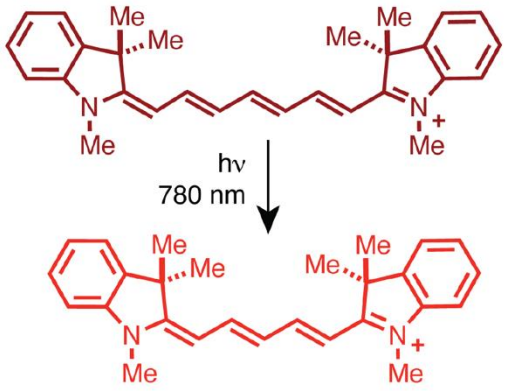
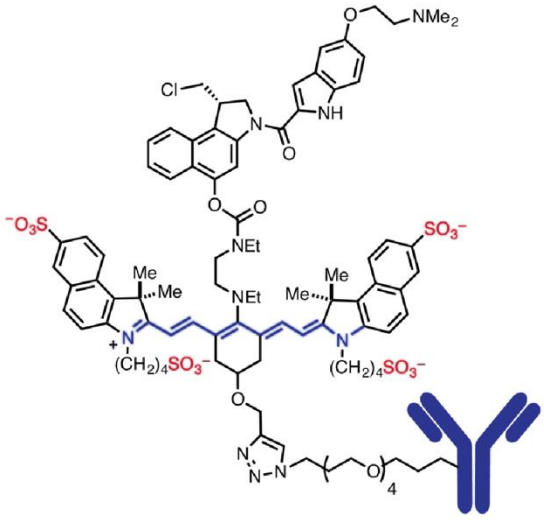
Tissue penetrant near-IR wavelengths can enable applications in complex settings, however developing molecules in this range remains a substantial challenge. We study and then use the chemistry of cyanine fluorophores to develop new long-wavelength optical tools for imaging and drug delivery. In the context of imaging, we recently defined a novel photochemical transformation with applications in microscopy and cell tracking. The light-promoted conversion of cyanines to blue-shifted emissive products had been observed in various contexts. However, both the underlying mechanism and the species involved in this photoconversion reaction have remained elusive. We found that irradiation of heptamethine cyanines provides pentamethine cyanines, which, in turn, are photoconverted to trimethine cyanines. We carried significant efforts to define the mechanism, scope, and utility of this two-carbon phototruncation reaction. In the context of drug delivery, we developed a single photon uncaging reaction initiated by light in the 690 to 780 nm range using readily synthesized C4'-dialkylamine-substituted heptamethine cyanines. Small molecule release occurs through a reaction sequence comprising regioselective photooxidative C-C cleavage and then hydrolysis of the C4'-amine. We developed an antibody-based approach that releases derivatives of the potent anti-cancer agent duocarmycin. Studies in animal models illustrate that the constructs can be imaged *in vivo* prior to uncaging, are well tolerated, and display promising efficacy. Details regarding the development of the uncaging reaction, ongoing mechanistic and optimization studies, and long-term goals will be described.

Cyanine Phototruncation



Cyanine Photocage



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Understanding and Engineering the Quantum Yield of Coumarin Photocleavable Protecting Groups

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Two parameters that fundamentally characterize photocleavable protecting groups (PPGs) are: 1) their ability to absorb a photon of a certain energy (wavelength) and 2) their ability to subsequently convert the absorbed energy into release of a payload, the efficiency of which is captured in the uncaging quantum yield (QY). Recently, we introduced a novel strategy to boost the QY of PPG uncaging, which relies on delocalization and hyperconjugation of the cation formed transiently in this process.[1] We illustrated the effectiveness of our strategy in improving the QY, achieving an up to 35-fold improvement in QY as compared to traditional coumarin PPGs. Also, we showed the general applicability of this strategy through applying it to PPGs bearing different payloads and to different classes of heterolytic PPGs.[1]

Furthermore, through the comparison of two heterolytic PPGs with slightly different uncaging mechanisms, we discovered that the fate of the contact ion pair (CIP) intermediate is crucial in determining the PPGs' photochemical properties.[2] A PPG with an unusual type of CIP escape mechanism displayed quantum yields that were robust and unaltered by payload size and solvent polarity, in stark contrast to the QYs of a PPG that displayed the usual type of CIP escape.

We performed DFT-calculations of the excited state energy barriers, that revealed a tight correlation between the height of one of these barriers and the uncaging QY, revealing that this particular barrier plays a crucial role in determining this QY. Furthermore, using the DFT-calculated energy barriers we were able to predict the uncaging QY of a newly designed PPG with particularly high accuracy.[2] Overall, this research furthers the understanding of the crucial factors that influence the uncaging QY of PPGs and provides a blueprint for the development of superior PPGs with robust QYs independent of payload topology and solvent polarity.

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Opto-Bioorganic Tools to Interrogate and Image Biology

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In recent years, light has been employed as an external stimulus to photocontrol diverse processes in various fields ranging from material science to biology. This approach relies on the use of small, light-responsive molecules that undergo a structural change upon irradiation, generating different functional states from a single molecule. By attaching suitable substituents to such photoresponsive compounds, these molecules can be embedded in a system of choice to link their structural change to a change in the system's properties. On the other hand, the sterical and electronic characteristics of the substituents influence the photophysical and photochemical properties of the core. This mutual interaction needs to be finely balanced and studied in detail to rationally design probes and tools to study and modulate biological systems.[1-2]

Here, we show different strategies to employ light-responsive building blocks to interact with and control biomacromolecules focusing on the 3D-structure of peptides and their supramolecular interaction. In this context, we will highlight how varying the substituents on different light-sensitive molecules allows us to tune several of their properties, such as their UV-Vis absorption profile and photoconversion quantum yield. We will demonstrate how these properties can be employed in various model systems.[3-5]

Eventually, we envision that deriving such design principles for an increasing number of light-responsive tools will pave the way to individually addressing a single photoresponsive molecule in a complex biologically relevant ensemble and thus, to the precise regulation of the biological machinery.

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Towards Multimodal Photochemistry

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The multiplicity of excited states is an important factor influencing the photophysical and photochemical properties of organic molecules and photocatalytic systems. While the differences between excited singlet and triplet states' behaviour have been understood merely on a phenomenological basis, the rational design of multiplicity-controlled photochemical processes based on spin-spin interactions offers an unprecedented possibility of redirecting photoreactivity on demand.

In this contribution, we show various strategies of multiplicity-induced control over photoactivation, related to photoswitching and photocleavage of covalent bonds. Various strategies for controlling intersystem crossing rate and the resultant multiplicity of the photochemically active excited state will be presented and demonstrated on BODIPY-based photocages[1,2] and fulgide photoswitches.[3] In addition, the dual character of excited states and photochemically formed reactive intermediates will be discussed.

Overall, these examples will be used to demonstrate the possibilities of photoactivatable compound development where the observed reactivity can be modulated or redirected by the multiplicity of the active state.

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Development of Photoactivable Herbicides

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Herbicides are vital in modern agriculture and global food security but have seen limited innovation in the past 40 years, leading to decreased efficacy and environmental concerns. Resistance, akin to antibiotics, emerges over time. Public awareness of environmental impacts has led to regulatory restrictions in developed countries. These challenges highlight the need for herbicide innovation to sustain food security. Controlled release of chemicals, popular in medical and biotech fields, remains underexplored in plant science.[1a]

Our concept is that photoactivatable herbicides (PAHs) will be applied in the field during dusk, allowing for many hours of abruption by the plant and biodistribution, and upon sunrise, they will be activated inside the plant, leading to its death (**Figure 1, *left***). We hypothesize that the generation of a high concentration of an active herbicide *in planta* in a very short time window would increase its efficacy compared to regular herbicides (**Figure 1, *right***). We expect that this strategy will allow us to reduce the amount of herbicide applied in the field, leading to reduced environmental impact.

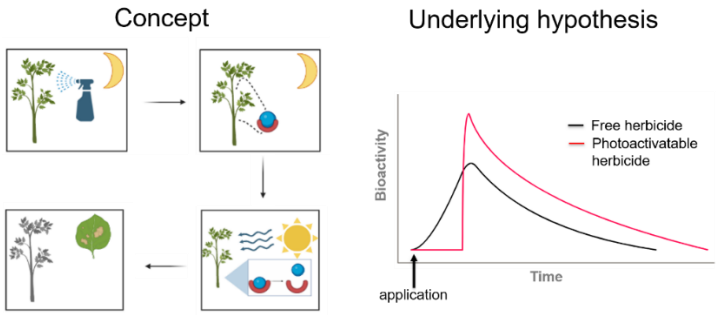

Figure 1. Schematic representation of the project concept and underlying hypothesis.

Although photo-protecting groups (PPG) are similar in the desired concept and function, each requires a different synthetic approach. A PPG designed to protect one type of functional group is not necessarily compatible with others. In this work, alcohols were protected with *o*-nitronenzyl (NB) derivatives while carboxylic acids were protected with a 4-methoxy-7-nitroindolinyl (MNI) group.[1]

Our results show that bromoxynil has potential but suffers from poor penetration and that bifenox-MNI performed poorly. Conversely, synthetic auxin-MNI conjugates were found to be much more effective than their free counterparts.[1a] This study shows the potential of PAHs to become agriculturally relevant. Further studies of the controlled release of herbicides need to be completed, and more experiments, mainly on soil and large-scale experiments in the fields are required to understand the full potential of those systems.

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Photoremovable protecting groups: From caged compounds to photoactivatable nanoparticles

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The use of photolabile protecting groups (PPGs) has been growing in emphasis for decades, and they nowadays enable cutting-edge results in numerous fields ranging from organic synthesis to biology.[1] PPGs are chemical entities that can be conjugated to a biological effector to hide its biological activity, forming a stable so called “caged compound”. This conjugate can be simply cleaved by light and therefore, the functionality of the biological effector is restored with the formation of a PPG by-product. The use of UV irradiation (normally within power density between 10^{-1} and 10^{-3} W.cm^{-2}) to manipulate the functions of biomolecules or mediate on-demand drug release in living systems *via* effective photoactivation with very high spatial and temporal control is well-developed and reviewed technique.[1] During the last two decades, the challenge was to overcome the difficulty that only high energy light (i.e. UV, the one damaging biological tissues) can induce photochemical reactions. One strategy to lower phototoxicity within the domain of one-photon excitation process is based on tailoring the caging groups with extended π-conjugation and introducing heteroatoms and functional groups in the ring system. Therefore, blue light-sensitive photoremovable groups have been reported.[3] This later strategies enable new biomedical applications in particular for the treatment of proliferative retinopathy and the development of blue light sensitive caged small gene inducers[3] will be presented in this context.

For more general biomedical applications the development of Red to NIR sensitive systems is highly sought after. In this context, we will also present our recent development emissive upconversion nanoparticles systems using the TTA-UC strategy[4] (for Red or NIR to blue light upconversion). And we will present how we have been able to further functionalize those nanoparticles with blue light-sensitive photocleavable linkers in order to trigger drugs releases using Red to NIR light *in vivo*.

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Light in a Heartbeat: Bond Scission by a Single Photon above 800 nm

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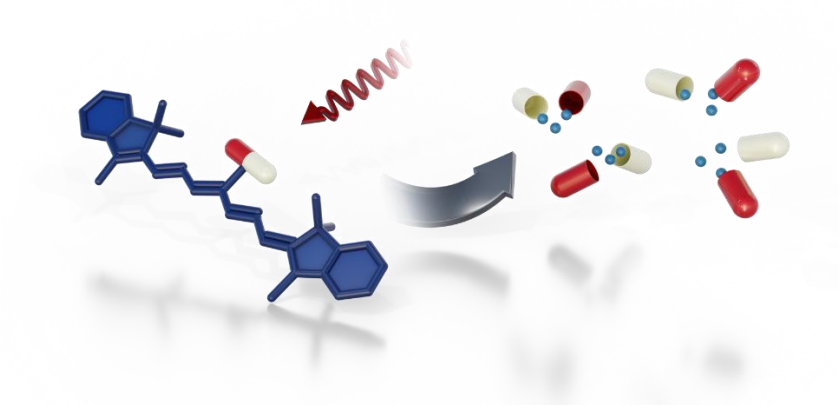
Photocages enable us to elicit control over the activity of molecules using light as a non-invasive and biocompatible stimulus. Yet efficient uncaging in the near-infrared (NIR) window required for their translation to photoactivated therapies remains far from being an accomplished task. Here I will showcase the birth of photocages based on cyanine scaffold.[1] These photocages can be functionalized with carboxylate alcohol, phenol, amine, and thiol payloads, including complex drug molecules, which are released in water upon irradiation with NIR light up to 820 nm.[2] Displaying unique chameleon-like behavior, they operate via two uncaging mechanisms – photooxidation and direct bond scission.[3] To highlight their potential in biology and medicine, I will demonstrate that they deliver payloads which are otherwise not uptaken by live cells, or regulate the beating rates of human cardiomyocytes at nanomolar concentrations. Finally, I will showcase how structural modifications boost their uncaging efficacies by up to two orders of magnitude.



Dedicated to our friend, professor Petr Klán, on the occasion of his sixtieth birthday.

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3-Hydroxyflavone Derivatives as Efficient PhotoCORMs

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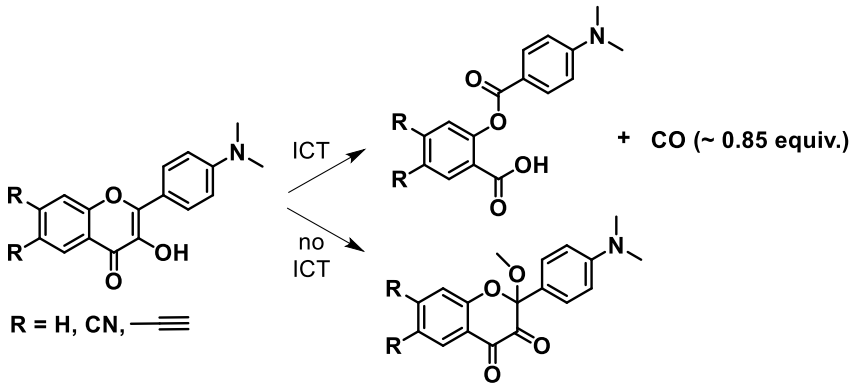
Recognition of carbon monoxide (CO) as a potential anti-tumorous agent[1] promoted the development of various systems for its targeted delivery. Photoactivable CO releasing molecules (photoCORMs) providing excellent control over the release emerged as an auspicious approach towards delivering carbon monoxide. Flavonols, offering biocompatibility as natural compounds, became promising photoCORMs. Flavonol derivatives with a π-extended aromatic system showed an efficient CO release,[2] and the mechanism of their photodecarbonylation has been described.[3] However, 3-hydroxyflavon and its simple derivatives do not absorb at wavelengths long enough to penetrate human tissues and do not produce CO in high yields.

This study presents several newly synthesized 4'-dimethylaminoflavonol derivatives exhibiting internal charge transfer in their excited state (ESICT). Substitution with one or two electron-withdrawing groups (EWGs) modified their photophysical properties and photochemical behavior. All EWGs provided a red-shift of the absorption maxima over 500 nm. Furthermore, most of these derivatives efficiently produced up to 0.85 equivalents of CO and exhibited high photorelease cross-section values, making them promising photoCORMs. 3,4-Flavandione derivatives were identified as side products competing with CO extrusion, whose formation is suppressed in derivatives possessing an ESICT state.



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Towards imaging-guided pharmacotherapy

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Molecular photomedicine holds the promise for precise treatments that avoid systemic adverse effects and development of drug resistance. This promise is supported by current medical imaging modalities that can reveal the nature and location of malignancies, such as cancer and infections. At the same time, biomedical engineering has recently created methods to deliver light deep into the human body. The photo-medicine puzzle is currently missing its final piece – the way of translating light into therapy. To address this challenge, drugs could be introduced whose activity could be reversibly or irreversibly turned on with light. The aim of this presentation is to present our recent results on design[1] and evaluation[2] of light-activated bioactive molecules and highlight the synergies between medical imaging and photopharmacology, enabled through photo-responsive optical and magnetic resonance imaging agents.[3]

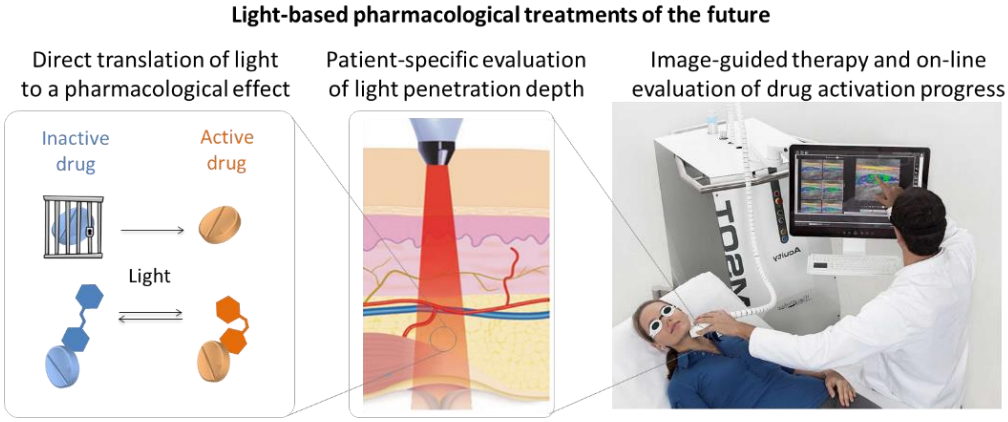

Figure. Synergy of Photopharmacology and medical imaging

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Are Known Xanthene Dyes Excited States Fates Helpful in Search of Cages for Compounds?

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Small molecule dyes with a chromophore based on xanthene tricyclic core are routinely used in different chemical and biological applications, including human medicine. Although they are typically very stable, our investigations of the photochemistry of some of the most common ones, fluorescein, eosin Y, and rose bengal, to our genuine surprise, revealed liberation of carbon monoxide in 40–80% chemical yields upon extensive irradiation with visible light in aqueous solutions during their concomitant multistep degradation processes.[1] Additionally, a few low-mass secondary photoproducts, such as phthalic and formic acids, were identified (Fig. 1a). This surprising reactivity substantially expanded the previously known applications of xanthenes as cage for good leaving groups like acyls attached on the central ring B (Fig. 1b).[2]

Both approaches have their pros and cons and even though there are now known structure-properties relationships useful in design of xanthene fluorophores with tailored properties,[3] at the moment it does not seem so for their role as cages.

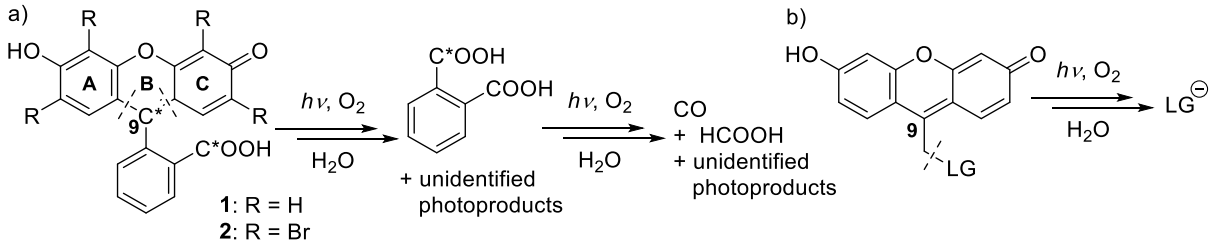

Figure 1. a) Multistep visible light induced photochemical degradation of xanthenes in aerated protic environment; b) Xanthene-9-ylmethyl as a protecting group.

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Giving the Green Light to Photochemical Uncaging in High Vacuum

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The isolation of biomolecules in a high vacuum enables experiments on fragile species in the absence of a perturbing environment.[1] Yet, many molecular properties are influenced by local electric fields created by charges of molecules in molecular beams in the gas phase. For example, the charge state of peptides and proteins determines not only their mass-to-charge ratio, but also plays a decisive role in their gas-phase structure,[2] including protein–protein[3] and protein–ligand complexes.[4] For some applications, such as in quantum metrology, a full neutralization of complex macromolecular ions in the gas phase is necessary.[5] Until now, there has been no robust and reliable method to accomplish such a task.[6]

In my talk, I will discuss how to gain control over the number of charges on a biopolymer by photochemical uncaging. I will present the design and modelling of photoactive molecular tags based on BODIPY to label peptides and proteins and I will discuss their photochemical validation in solution and in the gas phase. The redesigned photocage can be selectively cleaved off in high vacuum at a well-defined time and without the need for any external charge-transferring agents by absorption of a single or two green photons, a benign wavelength compatible with various biomolecular entities, such as oligonucleotides or oligosaccharides. In addition, I will show how the developed design strategy to repurpose the well-known BODIPY photocage to operate in the gas phase allows to study and improve other state-of-the-art photocages by computational means.

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Development of new self-immolative linkers for efficient photo-uncaging of photocleavable protecting groups

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Photocleavable protecting groups (PPGs) have received a lot of interest for their capacity to release a desired biological payload upon irradiation with light, giving incredible spatio-temporal control over the bioactivity of molecules. To this extent, development of PPGs has been focused on reaching higher molar absorptivity at longer irradiation wavelengths for deeper tissue penetration. However, another crucial parameter for the uncaging process is its uncaging quantum yield (QY).

Recently, our group introduced a new way to increase the QY through stabilization of the CIP intermediate.[1] This method relies on stabilization of the positive carbocation through hyperconjugation and delocalization. Here, we evaluate a set of different self-immolative linkers with low pK_a to stabilize the anionic part of the CIP.[2] This approach allows pharmacologically relevant functional groups like alcohols or amines to be caged and released with improved QY, while releasing the original payload after the photochemical process.

Caged compounds bearing novel linkers like sulfite, oxalate and oxamate esters have been synthesized and their photochemical properties have been studied. When compared to their traditional carbonate and carbamate counterparts they offered superior photochemical properties. The sulfite ester linker was particularly studied for the caging and release of alcohols. This new linker exhibited a 5-fold increase in QY, better solubility and stability in water compared to the carbonate counterpart. Concurrent releases of SO_2 gas was also observed, which could be of interest for synergy pharmacotherapy.

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2D-Photocages: Expanding Functionalities by Combination of Single Photoresponsive Elements

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The control of molecular processes by light has attracted considerable interest in different application fields such as optical data storage and super-resolution microscopy, but requires versatile modes of implementation. In particular, combination of different functionalities in photochromic molecular dyads widen the application range. This approach uses well-characterized molecular units, but in turn geometric and electronic properties need to be tuned for optimized photoresponse. Several dyad model systems with diverse target functionalities were examined using femtosecond time resolved spectroscopic techniques. Depending on the connectivity and the type of linker between the individual units, underlying photophysical principles like energy transfer[1], electronic conjugation[2] or vibrational coherences[3] are photomodulated.

Specifically, for next generation photocages, constructs with ultrafast and efficient energy transfer in one- and two-photon sensitized dyads offer a perspective for photolabile protecting groups with improved functionalities.[4,5]

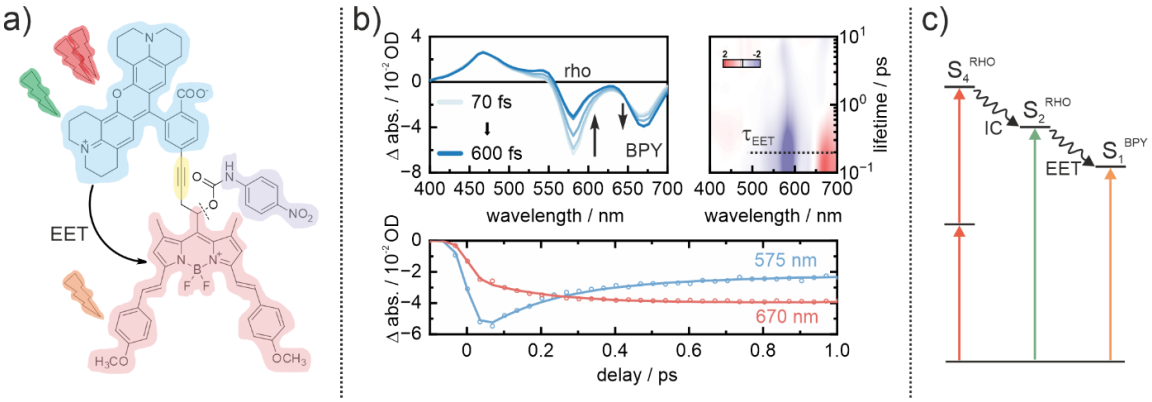

Figure 1. a) Sensitized system: PPG (BODIPY, red) - sensitizer (rhodamine, blue) - LG (*p*-nitroaniline, purple) . b) Time-resolved data of this dyad after rhodamine photoexcitation. The EET from rhodamine to BODIPY occurs within the first 300 fs. c) Corresponding energetic pathways depending on the excitation energies used.

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Application of benzylic bond breaking facilitated by the excited state meta effect

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A substituted benzene ring can serve as one of the simplest UV-chromophores capable of directly cleaving covalent bonds. The excited state *meta* effect (ESME) indicates that transmission of electron density from a meta-situated electron donor substituent in the first singlet excited state can facilitate benzylic C-O bond cleavage. Leveraging ESME, we have developed a series of structurally simple photolabile protecting groups (PPGs) designed to release carbonyl, hydroxyl, diol, carboxyl, and amino groups.[1-3] These PPGs are easily prepared and installed, and their removal can be achieved under ambient conditions, in various solvents or solvent-free environments. These PPGs have been explored for a broad range of applications, such as protecting in organic synthesis, liberation of biologically important molecules in aqueous or solid phases, polymer photocleavage, regulated hydrogel formation, and surface patterning.[3]

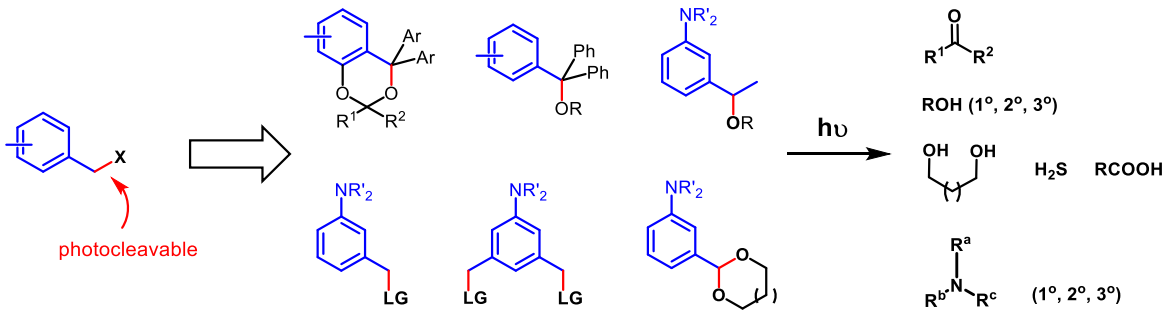

Figure 1. Structurally simple chromophore for benzylic bond cleavage.

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Photocleavage-based Photoresponsive Drug Delivery

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Light-sensitive drug delivery systems have been engineered to offer enhanced control and spatio-temporal resolution, which can enhance drug effectiveness and minimize unintended drug release. Photoremovable protecting groups are light-sensitive components that undergo irreversible photocleavage reactions when exposed to light. These groups can be covalently bonded to a molecule of interest, allowing its structure and function to be controlled by light. In this talk, I will discuss our recent research efforts centered on creating simple photoresponsive drug delivery systems employing photoremovable protecting groups, specifically targeting cancer and eye disease treatment. Furthermore, I will outline the approaches we have developed to address the challenge of limited light penetration within the body. By investigating these innovations and resolutions, we aim to expand the potential of photoresponsive nanomedicines and enhance their overall effectiveness in treating a broad spectrum of medical conditions.

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From chromophores to photoremovable protecting groups – development and potential applications

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Photoremovable protecting groups (PPGs, photocages) represent one of the main contemporary implementations of photochemistry in diverse fields of research and practical applications. Upon irradiation at a specific wavelength, the PPGs are tracelessly removed, allowing for non-invasive spatio-temporal control over the release of molecules with a high degree of chemoselectivity in complex chemical and biological environments.[1,2]

In recent years, we, and others, introduced and utilized meso-methyl BODIPY as a visible-light activatable PPG with tunable spectroscopic, chemical and biological properties for diverse applications in synthetic chemistry, biology and medicine.[3]

We now show that porphyrin, a highly abundant chromophore, can be repurposed as a PPG by introducing a similar meso-methyl motif.[4] Moreover, we show that meso-methyl porphyrin is a prototype hybrid-class PPG that unites traditionally exclusive elements of organic and metal-complex PPGs within a single structure. We demonstrate that the porphyrin scaffold allows for extensive modularity four sites of leaving group release via functional separation of the metal-binding chromophore. The insertion of metal ions can be used to tune their spectroscopic and photochemical properties. Our approach as applied herein could facilitate access to a hitherto untapped chemical space of potential PPG scaffolds and utilizations in combined photodynamic and chemotherapy.

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BODIPY Photocaging with Visible to Short-Wave IR Light

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This talk describes our work to develop chemical protecting groups that can be cleaved using visible light, particularly with light wavelengths in the biological window where light penetration into tissue is maximal to allow photorelease in living systems. This talk describes our work to develop a theoretical framework to understand photorelease reactions, leading towards the development of a family of BODIPY-derived photocages that release substrates with visible light. Preliminary developments to achieve absorptions in the near-infrared and (via two-photon activatable compounds) short-wave infrared will also be discussed.

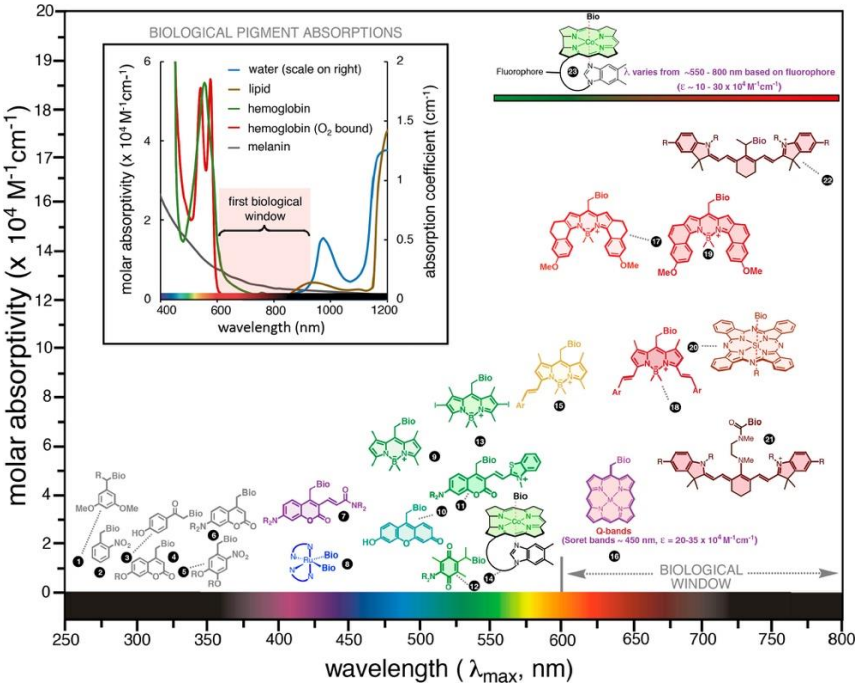

Figure 1. Absorption properties of select photocages. Inset: Absorption properties of common biological pigments showing the location of the first mammalian biological window (hemoglobin and melanin use scale on left).

References

1 Shrestha, P.†, Kand, D. † († denotes equal authorship), Weinstain,* and Winter, A.H.* "meso-Methyl BODIPY Photocages: Mechanisms, Photochemical Properties, and Applications." *J. Am. Chem. Soc.* **2023** 145 (32), 17497-17514 DOI: 10.1021/jacs.3c01682

A Novel Reactivity of BODIPY Disulfides as Effective Way for Thiol Labelling

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Thiols are important functional groups that are often used for labelling of biologically relevant molecules thanks to their higher reactivity compared to e.g., O- or N-nucleophiles. The labelling of free thiols is a crucial tool for understanding the function of thiols in redox homeostasis. Thiols can be also concealed in disulfide bonds in proteins and are particularly necessary for protein folding.[1]

Common methods often benefit from the reactivity of thiols with haloalkyl derivatives or maleimides which often suffer from the unwanted side reactions. More selective reactions are provided by so called mentahethiosulfonates (MTS) which are known for their pure and fast reactivity with thiols. Unfortunately, disulfides formed during this reaction can be readily reduced back to thiols.[2]

In our laboratory we explored a new reactivity of disulfides directly attached into meso-position of BODIPY efficiently providing thioethers after the irradiation by visible light. Thioethers are more stable than disulfides and do not undergo unwanted reduction. This method enhances MTS-based labelling chemistry by improving product stability without compromising selectivity.

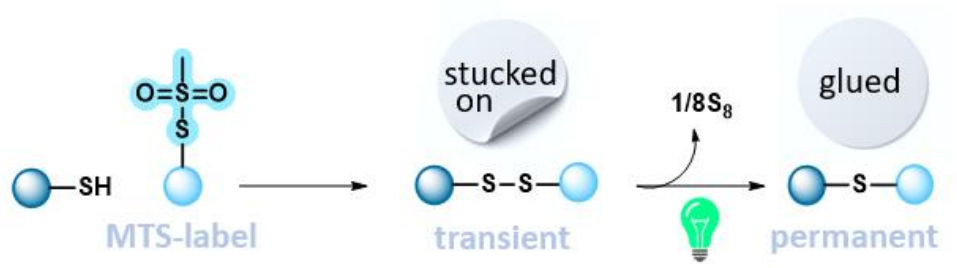

Figure 1. General scheme of the thiol labelling using improved MTS chemistry.

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2. Introduction to Thiol Modification and Detection—Section 2.1 - CZ. https://www.thermofisher.com/uk/en/home/references/molecular-probes-the-handbook/thiol-reactive-probes/introduction-to-thiol-modification-and-detection.html (accessed **2024-01-22**).