PhotoReAct Project:
A Textbook of Scientific Results

Project acronym: PhotoReAct

Project full title: ‘Photocatalysis as a tool for synthetic organic chemistry’ — ‘PhotoReAct’

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TABLE OF CONTENTS

Abstract

The PhotoReAct project (“Photocatalysis as a Tool for Synthetic Organic Chemistry”, Grant Agreement No. 956324) is a major European research initiative that has transformed the landscape of sustainable synthesis by harnessing light as a clean, controllable, and renewable energy source. This textbook presents the core scientific achievements of the consortium’s fifteen Early-Stage Researchers (ESRs), whose collective efforts bridge the gap between academic innovation and industrial implementation in photocatalysis.

Over the course of the project, PhotoReAct successfully demonstrated that visible light, an abundant and renewable energy source, can power highly selective and efficient chemical transformations that rival or surpass conventional thermochemical methods. At its core, PhotoReAct established a comprehensive framework for translating photochemical processes from academic discovery to industrial application.

The consortium designed new families of photocatalysts ranging from thermally activated delayed fluorescence (TADF) and multi-resonant organic systems to earth-abundant transition-metal and chiral organophotocatalysts. These catalysts are capable of mediating single-electron transfer (SET) and energy transfer (EnT) reactions with exceptional efficiency under visible light. They enabled diverse bond-forming transformations including C–C, C–N, C–Si, and C–O couplings, as well as contra-thermodynamic alkene isomerizations and radical-mediated processes.

Methodological breakthroughs included the development of dual catalytic platforms that combine photoredox and nickel catalysis, enantioselective transformations using chiral organophotocatalysts, and the visible-light-driven generation of high-energy intermediates such as singlet nitrenes and carbon-centered radicals. Beyond catalyst development, PhotoReAct delivered technological innovations that make photochemistry scalable and industry-ready. The integration of continuous-flow photoreactors, sustainable dual-catalytic systems, and machine learning-based automation through the RoboChem platform has accelerated reaction optimization, enhanced reproducibility, and enabled rapid scale-up from laboratory to production scale.

Collectively, these advances directly address the chemical industry’s need for greener, safer, and more energy-efficient synthetic tools. Spanning from fundamental mechanistic insight to practical industrial application, the achievements of PhotoReAct, including solar-compatible photoreactors, visible-light activation strategies, and data-driven automation, have redefined the boundaries of modern photocatalysis. By uniting molecular design, process technology, and digital innovation, PhotoReAct positions light-driven chemistry as a cornerstone of the European Green Deal and a foundation for the next generation of sustainable chemical manufacturing.

List of contributors

Name	Organisation	Role
Lea Hämmerling	USTAN	Early-Stage Researcher, editor
Aminata Mariko	JM/USTAN	Early-Stage Researcher, editor
Sultan Çetin	UniBo	Early-Stage Researcher, editor
Silvia Dell'Uomo	ULEI	Early-Stage Researcher, editor
Joseph Milton	ICHO PAS	Early-Stage Researcher, editor
Debora Belmonte	UZH	Early-Stage Researcher, editor
Raquel Sánchez Bento	UoM	Early-Stage Researcher, editor
Matteo Leone	CNRS	Early-Stage Researcher, editor
Adrián Luguera Ruiz	UNIPV	Early-Stage Researcher, editor
Byeongseok Kweon	WWU	Early-Stage Researcher, editor
Stefano Bonciolini	UvA	Early-Stage Researcher, editor
Pauline Tenblad	UvA	Early-Stage Researcher, editor
Damiano Diprima	ES/UvA	Early-Stage Researcher, editor
Matteo Gasparetto	X-Chem/UvA	Early-Stage Researcher, editor
Brenda Pijper	J&J	Early-Stage Researcher, editor
Meike Berkhout	UvA	Project manager, editor
Prof. Cristina Nevado	UZH	PI, Dissemination Director and internal review
Prof. Timothy Noël	UvA	PI, Project Coordinator and internal review

Introduction

The PhotoReAct project kicked off in 2021 with a vision to transform the chemical industry by using alternative energy sources to cut down on fossil fuel reliance and overall energy consumption. By utilizing light energy as a reactant, PhotoReAct aimed to boost the efficiency and precision of key chemical processes, producing fine chemicals, pharmaceuticals, agrochemicals, and other specialty chemicals. This initiative is set to transform the European chemicals industry, making it more energy-efficient and technologically advanced, significantly reducing its fossil fuel dependency and driving innovative solutions.

From the start, the goal of PhotoReAct has been to greatly advance the applicability and scalability of photocatalytic processes. This has involved designing innovative photocatalysts, developing new photocatalytic methodologies, and implementing cutting-edge technological solutions that support automation and scalability for immediate industrial use. And as the PhotoReAct project wraps up, the results and expertise will be shared widely, enabling other research organizations and industries to benefit from the work of our Early-Stage Researchers (ESRs).

According to the Description of Action (DoA) of the project, the current key research questions include rational photocatalyst design (WP2), new synthetic strategies for creating agrochemicals, fine chemicals, and pharmaceuticals (WP3), scaling up processes (WP4), using solar energy (WP4), and implementing these processes in drug discovery programs (WP5). These challenges have been tackled by the ESRs within PhotoReAct, and their progress is paved the way for new scientific opportunities and applications of photocatalysis. This textbook will highlight the most important results obtained by the ESRs during the PhotoReAct project and how these results contribute to the project's goals.

Main body of report

PhotoReAct addressing the Societal and Technological Challenges

Since its start, the PhotoReAct project has aimed to address key challenges facing the European Chemical Industry. Our network sought to achieve significant advancements in photocatalysis, tackling various societal and technological issues relevant to the European Union and the market. Below, we will highlight each of these challenges and how the PhotoReAct network has successfully addressed them.

Societal Challenge 1: Alternative energy sources for chemical processes in industry

The chemicals industry is still reliant on the use of thermochemical activation pathways, which requires the use of fossil fuels to generate the required energy. Despite access to an essentially infinite amount of solar energy, this energy source has seen only limited use in the chemicals industry. The PhotoReAct program aims to overcome the chemical and technological barriers, which prevents the market penetration of photocatalysis.

The PhotoReAct program has successfully demonstrated that visible light, an abundant and sustainable energy source, can drive complex chemical processes with efficiency, selectivity, and scalability. The program's outcomes provide both the fundamental understanding and the technological tools necessary to accelerate the industrial adoption of photocatalysis as a viable alternative to fossil fuel-driven thermochemical processes.

By systematically addressing:

- Catalyst development (organic, metal-free, and chiral).
- Methodological innovations (novel reactions and activation pathways).
- Technological integration (automation and continuous flow).

PhotoReAct has bridged the gap between academic discovery and practical application, positioning photocatalysis as a competitive solution for sustainable chemical manufacturing.

Societal Challenge 2: Reduction of chemical waste

The use of toxic solvents, stoichiometric amounts of reagents, including toxic radical initiating reagents, the often-limited selectivity, as well as the inefficiency of chemical processes on an industrial scale lead to the production of significant amounts of waste. Development of new and improved photocatalytic transformations as delineated in this proposal will address the production of chemical waste. Moreover, the development of new photocatalysts based on sustainable materials in combination with continuous-flow reactors (e.g. micro- and milli-reactors), together with (a) optimization of the radiation and mass transport phenomena in these reactors and (b) input from mechanistic studies on photocatalytic transformations, will further improve the efficiency of the photochemical processes for industrial applications.

The PhotoReAct program has successfully addressed key contributors to chemical waste in synthesis:

- Replacing stoichiometric reagents with efficient, catalytic alternatives.
- Eliminating toxic radical initiators and reducing hazardous solvent use.
- Increasing selectivity to minimize by-products and purification steps.
- Implementing continuous-flow technologies to optimize reagent use, energy input, and waste streams.

By coupling fundamental catalyst design with process innovation (e.g. RoboChem, flow reactors), PhotoReAct has laid the foundation for industrial-scale chemical processes that are significantly more sustainable and resource-efficient.

These advancements directly contribute to greener chemical manufacturing, aligning with both the original objectives of Societal Challenge 2 and the broader goals of the EU Green Deal and sustainable industrial practices.

Societal Challenges 3: Fast and reliable access to life-saving molecules

In the modern fine-chemical, pharmaceutical and agrochemical industries, a fast and facile implementation of chemical processes from laboratory to industrial scale is crucial. Fast but accurate data acquisition in automated flow platforms is essential in the early development phases to facilitate this transition. The PhotoReAct network will focus on the design and implementation of such standardized models. In addition, the development of scalable photocatalyzed processes will be established allowing to bring the methodology to an industrial scale.

The PhotoReAct program has profoundly contributed to the acceleration of chemical process development, ensuring that innovative, photochemically driven routes to complex, bioactive molecules can be rapidly designed, optimized, and scaled.

Through the combined advances in:

- Automated flow chemistry platforms (RoboChem).
- Scalable photocatalytic methodologies.
- High-throughput synthesis compatible with drug discovery timelines.
- Continuous-flow process intensification.

PhotoReAct has established practical, efficient pathways that can significantly shorten the timeline from initial reaction discovery to industrial application, directly supporting the goal of providing fast and reliable access to life-saving molecules.

These contributions position photocatalysis as a serious contender in the industrial toolset for pharmaceutical and fine chemical manufacturing, with demonstrated potential for rapid response to emerging healthcare needs.

Technological Challenge 1: Suitable, visible light photo activation of organic molecules

Many molecules can only be directly activated through use of UV irradiation as they only absorb in that part of the electromagnetic spectrum. In the past decade, photocatalysis has offered the potential to use visible light as an energy source to initiate chemical transformations. New and improved photocatalytic transformations and catalysts will be developed in the PhotoReAct network. Important in the development stages will be the synthetic application (as identified by the industry partners, e.g. specific steps in the preparation of pharmaceuticals or agrochemicals) and the compatibility with the reactor design.

The PhotoReAct network has:

- Provided safe, scalable, and visible-light-driven alternatives to traditionally UV-dependent transformations.

- Delivered new photocatalysts and methodologies that broaden the chemical space accessible under visible light.
- Integrated these innovations with reactor designs and continuous-flow systems to ensure real-world applicability.

By focusing on reactions of high synthetic value, particularly those relevant to pharmaceutical and agrochemical manufacturing, PhotoReAct has directly contributed to overcoming a key bottleneck in the field: the transition from UV to visible light activation without sacrificing reactivity or selectivity.
These achievements not only improve process safety, scalability, and sustainability but also enable broader industrial adoption of photocatalytic technologies.

Technological Challenge 2: Scalability of photochemistry
One of the major issues encountered in traditional photochemistry is the distribution of photons with increasing reactor dimensions. The attenuation effect of photon transport (Beer-Lambert law) prevents efficient scaling to what is required in the industry. In the PhotoReAct network, continuous-flow reactors with small characteristic dimensions will be used to ensure scalability from a laboratory scale to pilot scale and finally to small production scale.

The PhotoReAct network has systematically addressed one of the core technical challenges in industrial photochemistry by:

- Developing flow-compatible photocatalytic reactions.
- Utilizing continuous-flow reactors with efficient photon transport.
- Integrating automation and rapid process optimization (RoboChem).

The network has provided robust, scalable solutions that facilitate the industrial adoption of photochemical processes. These achievements ensure that photochemistry can move beyond laboratory-scale curiosity to a practical, industrially viable methodology capable of producing life-saving molecules, fine chemicals, and agrochemicals at relevant scales.

Technological Challenge 3: Use of green and sustainable solar irradiation
The use of solar energy as an infinite source of green and clean energy is essential to reduce the chemicals industry carbon footprint. Within PhotoReAct, we will actively promote alternative light sources, i.e. (i) the irradiation with energy-efficient LEDs, which are driven by sustainable electricity and (ii) the use of solar light directly via so-called LSC-based photoreactors.

The PhotoReAct network has demonstrated a practical pathway for implementing green, sustainable irradiation sources in photocatalytic processes by:

- Transitioning from energy-intensive UV sources to visible-light-driven, LED-compatible processes.
- Promoting and enabling direct solar utilization via LSC-based reactor designs.
- Prioritizing sustainability in both the catalyst design and reactor engineering stages.

These efforts directly support the chemical industry's move toward decarbonization and lower energy footprints, and position photocatalysis as an energy-efficient, sustainable tool for fine chemical, pharmaceutical, and agrochemical production.

The PhotoReAct project has successfully addressed critical societal and technological challenges facing the European chemical industry by advancing photocatalysis as a sustainable, scalable, and industrially relevant technology. By harnessing visible light as an alternative energy source, the network demonstrated efficient and selective chemical transformations that replace fossil fuel–driven thermochemical methods. Through the development of novel catalysts, methodologies, and continuous-flow technologies, PhotoReAct significantly reduced chemical waste, minimized the use of toxic reagents and solvents, and improved reaction selectivity. Its integration of automation and high-throughput platforms, such as RoboChem, has accelerated the design and optimization of photochemical processes, enabling faster access to life-saving pharmaceuticals and fine chemicals. The project also delivered key technological breakthroughs, including the transition from UV to visible-light activation, the development of scalable flow photoreactors, and the implementation of sustainable light sources such as LEDs and solar-powered LSC systems. Collectively, these achievements bridge the gap between academic innovation and industrial application, positioning photocatalysis as a cornerstone of the green transition in chemical manufacturing and aligning closely with the objectives of the EU Green Deal.

The following projects were undertaken by the individual students; for more comprehensive information, we refer to their individual publications.

1. **ESR 1** has shown that DET to substrates with triplet energies as high as 3.0 eV is feasible with DiICztBu4 and DiICzMes4, both of which catalyze the sigmatropic shift of (S)-verbenone, yielding the product in around 38% yield. This finding highlights the ability of DiICztBu4 and DiICzMes4 to efficiently catalyze energy transfer reactions even with substrates that have very high triplet energies. This demonstrates the exceptional triplet energy activation capability of these emitters, outcompeting many known photocatalysts and showing significant potential for diverse and challenging photocatalytic applications. This finding underscores the breakthrough in developing highly efficient DET photocatalysts and their broad applicability in synthetic chemistry.

2. The main result of **ESR 2** her research was the photocatalytic borylation of aryl halide catalysed by Cu(MAC)(β-Cb). This reaction was compared to several other literature copper catalysts, none of which catalysed the reaction. This was a major result, because it underscores a significant breakthrough in photoreduction chemistry. The successful catalytic borylation of aryl halides by Cu(MAC*)(β-Cb) not only demonstrates the exceptional photoreducing power of these complexes but also distinguishes them from other copper catalysts that failed in similar conditions. This result highlights the unique capability of the Cu(MAC*)(β-Cb) complex and sets a new standard in photocatalytic processes, potentially leading to novel applications and advancements in synthetic chemistry.

3. The work undertaken by **ESR 3** substantially advances the field by proving the effectiveness of donor–acceptor TADF (thermally activated delayed fluorescence) chromophores as photocatalysts. It provides crucial mechanistic insights into photoredox reactions and identifies key factors that impact photocatalytic performance. This research sets the stage for the development of more efficient and sustainable organic catalysts. It has wide-ranging implications for the future of photocatalysis, enhancing the understanding and application of TADF chromophores in various chemical transformations.

4. **ESR 4**'s research concentrated on the strategic design and creation of widely applicable, purely organic photocatalysts. These novel photocatalysts are envisioned as more sustainable and environmentally friendly alternatives to traditional organometallic-based photocatalysts. This addresses a crucial need for sustainable and environmentally friendly photocatalytic solutions in the field of synthetic chemistry.

By developing purely organic photocatalysts through strategic structural modifications of cyanoarene-based TADF systems and expanding the donor–acceptor design principle, ESR 4 her work provides innovative, versatile, and efficient alternatives to traditional organometallic-based photocatalysts. This advancement not only enhances the structural versatility and adaptability of these photocatalysts for diverse applications but also promotes a more sustainable approach, significantly impacting future photocatalytic processes and environmental considerations in chemistry.

5. **ESR 5** his research involved the development of a novel strategy towards utilising blue light absorbing diazo compound in an aqueous medium, namely with a DTAC micellar solution. This finding is significant as it introduces a significant advancement in the photochemical cyclopropanation of diazo compounds in water. This insight and methodology pave the way for more efficient and sustainable aqueous photochemical processes, representing a significant breakthrough in the field.

6. **ESR 6** her research successfully developed a nickel- and photoredox dual-catalyzed asymmetric carbosilylation of alkenes. Following extensive optimization, efficient conditions were established for stereoselective C–C and C–Si bond formation. The methodology demonstrated robustness and synthetic utility across a broad range of aryl bromides, acrylates, and acrylamides. To distinguish from previous protocols, the scope was expanded to include Group 14 elements, requiring re-optimization with germane reagents in place of silanes. These refined conditions allowed investigation of both silanes and germanes, highlighting the catalytic system's versatility and enhancing synthetic divergence. These findings underscore the project's success and the established methodology's broad applicability and versatility.

7. The research of **ESR 7** has led to the development of a powerful and conceptually novel platform for the generation and synthetic application of singlet aryl nitrenes from nitroarenes. This development fundamentally redefines the role of nitroarenes in organic chemistry. Historically, aryl nitrenes were constrained by hazardous precursors and high-energy activation, limiting their practical use. This research overcomes those barriers by enabling the generation of singlet aryl nitrenes under mild, azide-free conditions using visible-light excitation. This breakthrough opens up new synthetic possibilities for generating complex nitrogen heterocycles and bicyclic pyrrolidines, which are important in medicinal chemistry. It marks a significant shift in synthetic strategies, leveraging photochemistry to transform traditionally challenging intermediates into versatile tools for molecule construction.

8. Achieving enantioselective photocatalyzed transformations has been a rare and highly sought-after goal in photocatalysis. To address this challenge, **ESR 8** focused his efforts on developing a new class of visible-light-sensitive chiral organocatalysts. This finding is pivotal because it addresses the significant challenge of achieving asymmetric photocatalyzed reactions, which is crucial for advancing sustainable catalytic processes. The development of visible-light-sensitive chiral organocatalysts, especially those featuring a BINOL-derived Chiral Phosphoric Acid backbone with various photosensitizers, represents a groundbreaking step in the field. The successful demonstration of enantioselective activity, leading to efficient synthesis of fully substituted 1,2-diamines with excellent enantioselectivities, highlights the transformative potential of these catalysts for complex molecule construction in pharmaceuticals and beyond.

9. **ESR 9** discovered that 2-substituted-1,3-oxaxolidines were suitable as easily oxidizable compounds for the photorelease of carbon-based radicals. It introduces 2-substituted-1,3-oxaxolidines and 2-

substituted-1,3-imidazolidines as highly effective radical precursors for photoredox reactions. These compounds are easily oxidizable, allowing for the generation of (substituted) alkyl radicals under mild, metal-free conditions. This discovery addresses the urgent need for novel, neutral, easily prepared, and highly reactive radical sources, significantly advancing eco-sustainable tin-free radical chemistry. The resulting radicals facilitate the formation of C(sp3)–C(sp3) bonds, which are crucial in synthetic organic chemistry and drug discovery processes.

10. In order to address the challenge of accessing Z-isomers of alkenes and vinyl nucleophiles and electrophiles, which are valuable precursors in stereospecific cross-coupling reactions, **ESR 10** and the research group that he works in, have developed a general platform for the isomerization of activated alkenes through selective energy transfer catalysis, with an emphasis on achieving precise structural control over their geometry. This introduces a transformative approach to the challenging task of isomerizing alkenes into their Z-isomers, significantly expanding the accessible chemical space for drug discovery. The ability to control the geometry of alkenes through selective energy transfer catalysis opens up new avenues for synthesizing stereospecific compounds, which are crucial in pharmaceuticals and other chemical applications. The development of this platform is foundational, providing a versatile and efficient method that can be broadly applied to various substrates, including complex organic molecules. This breakthrough holds substantial implications for the future of synthetic chemistry and medicinal chemistry, facilitating the construction of structurally precise and functionally diverse compounds.

11. In the work of **ESR 11**, a practical methodology to enable the modular and regioselective allylation of C(sp3)−H bonds was performed. it introduces a groundbreaking method for the allylation of C(sp3)−H bonds using a synergistic merger of photocatalytic Hydrogen Atom Transfer (HAT) and Horner-Wadsworth-Emmons (HWE) olefination in a continuous flow protocol. This finding lays a robust groundwork for future advancements, integrates innovative methodologies, ensures broad applicability and scalability, and significantly impacts automation, making it the keystone to subsequent developments and broader adoption in the chemical industry.

12. The work that **ESR 12** on the development and validation of the RoboChem Platform. RoboChem revolutionizes the field by integrating automation, machine learning, and flow chemistry into a closed-loop reaction optimization system. The validation of the platform across diverse photocatalytic transformations, achieving results that match or outperform existing protocols, highlights its efficacy and potential for wide-ranging application. Published in *Science* and receiving substantial attention (over 19,000 downloads and more than 100 citations), this innovation underscores the platform's transformative impact on data-driven chemical discovery and methodology development.

13. One of the most significant findings of **ESR 13**'s research is the development of a light-mediated aerobic oxidation method, as documented in patent WO2024165619. This innovative methodology enables the selective and scalable oxygenation of heteroatoms using fundamental elements like air, water, and light. This approach showcases the substantial potential to reduce the environmental footprint and economic costs associated with industrially relevant chemical processes. Its importance lies in the ability to leverage renewable resources in chemical transformations, aligning with green chemistry principles and advancing sustainable practices in the industry. Implementing this method on a larger scale could revolutionize industrial workflows, offering more eco-friendly and cost-effective alternatives to traditional oxidative processes and setting a new standard for environmental

responsibility in chemical manufacturing.

14. **ESR 14** successfully reoptimized the amidine arylation protocol for off-DNA applications. He established a high-yielding nickel/photoredox-catalyzed method that demonstrated excellent substrate compatibility, tolerating a wide range of aryl halides and amidines. This marks a significant advancement in synthetic methodology beyond the initial constraints of DNA-tagged applications. The reoptimization led to a versatile and high-yielding nickel/photoredox-catalyzed process with broad substrate compatibility, including late-stage functionalization of complex molecules. This breakthrough not only showcases synthetic utility and efficiency but also extends the applicability of the method, providing robust tools for complex molecule construction, crucial for various applications in organic chemistry and medicinal chemistry.

15. The work of **ESR 15** has significantly enhanced the automated toolbox for medicinal chemists. By introducing methodologies for aryl halides, tertiary amides, and Giese acceptors, it broadens the range of medicinal chemistry scaffolds. The ART method has been evolved into a multivectorial approach, integrating assembly line-like synthesis applicable to small molecule drug discovery, PROTACs, and fragment-based drug discovery. All methods are fully automated, offering medicinal chemists advanced tools to expand chemical space and accelerate drug discovery through high-throughput and extensive library synthesis.

Besides the important findings above, in the following chapters we will outline the most important results that the PhotoReAct ESRs have obtained during their PhD trajectory and what these results mean for the field.

ESR 1 – Lea Hämmerling (USTAN)

At the end of the PhD studies at USTAN in the group of Prof. Eli Zysman-Colman, April 2025, ESR 1 has published a manuscript (Hämmerling & Zysman-Colman, 2024[1]) describing a class of B/N containing multi-resonant thermally activated delayed fluorescence (MR-TADF) emitters in their application as photocatalysts (PCs) in a range of literature example reactions. In this project, the ESR obtained highly photoreducing PCs with excited-state oxidation potentials, E_{ox}*, of up to -1.98 eV for ***t*DABNA**, which is comparable to the literature PC **Ph-PTZ** with E_{ox}* = -2.10 eV. This photoreducing strength has been demonstrated in a dehalogenation reaction of aryl halides. Furthermore, the class of B/N PCs showed versatility by also being active in a photocatalysed atom transfer radical addition (ATRA) reaction, a pinacol coupling and an energy transfer reaction. In all reactions, the B/N PCs could compete or outcompete literature-known PCs.

In a second project ESR 1 has investigated four DiICz emitters, **DiICztBu$_4$**, **DiICzMes$_4$**, **DiICztBuCz$_4$** and **DiICztBuDPA$_4$**, as fast and efficient DET photocatalysts in five different energy transfer reactions, highlighting their ability to activate high triplet energy substrates, outcompeting literature reference PCs. Photophysical studies have shown that there was scant solvent dependency on the T_1 state energies of these four MR-TADF PCs, unlike D-A TADF PCs like **4CzIPN**. The study of energy transfer reactions has shown a dependency of the sensitivity to oxygen quenching, which can act as a competitive triplet quencher of the excited PC, as a function of the nature of the PEnT reaction. Reactions that proceed sufficiently rapidly with these PCs show little-to-no oxygen dependency on the final yield, which is a benefit of these compounds as photocatalysts. This suggests that the quenching of the excited state by O_2 is not competitive with the DET kinetics to the substrate. ESR 1 has shown that DET to substrates with triplet energies as high as 3.0 eV is feasible with **DiICztBu$_4$** and **DiICzMes$_4$**, both of which catalyze the sigmatropic shift of (*S*)-verbenone, yielding the product in around 38% yield.

In a third study, ESR 1 has started to investigate three B/O containing MR-TADF emitters as PCs, **DOBNA**, **2c** and **2d**, for a range of reactions, given their high reported triplet state in literature while showing low-energy UV to visible light absorption (E_T = 2.97 eV for **DOBNA**/**2a** in Hirai et al., (2015)[2]). This would give access to triplet sensitizers for substrates having high triplet energy with the use of visible light as the excitation source. In preliminary results, ESR 1 has shown that the three PCs can act as photooxidants, photoreductants and energy transfer catalysts. The sigmatropic shift of (*S*)-verbenone with E_T = 3.0 eV, yielded the product in a 67% yield for **2d**.

ESR 1 conducted a secondment at the University of Wisconsin, Madison in the research group of Prof. Tehshik Yoon in April 2024 till May 2024, studying the effect of ligand design in photoactive scandium complexes. This collaboration is leading to a manuscript which is currently written up. The ESR took part and helped to organize the summer school in May 2024 in St Andrews. The ESR presented her research in the DiICz project at the final PhotoReAct conference in December 2024 in Amsterdam. The ESR handed in her PhD thesis titled 'Evaluation of Multi-Resonant Thermally Activated Delayed Fluorescence Emitters as Photocatalysts'[3] and successfully defended this work on the 8th of April 2025. The ESR will graduate from the University of St Andrews on the 3rd of July with a PhD following her work as part of the PhotoReAct ITN.

ESR 2 – Aminata Mariko (JM/USTAN)

At the end of her PhD studies at Johnson Matthey, March 2025, ESR 2 has made significant progress on several projects and is on the verge concluding them. The first project was the use of CMA complexes as photocatalysts. In this project, the ESR obtained highly photoreducing PCs with excited-state oxidation potentials, E_{ox}*, of up to -2.32 eV for **Cu(MAC*)(β-Cb)**. This photoreducing power was demonstrated in the dehalogenation of aryl halides, reducing substrates with reduction potentials as low as –2.72 V vs. SCE. The main result was the photocatalytic borylation of aryl halide catalysed by **Cu(MAC*)(β-Cb)**. This reaction was compared to several other literature copper catalysts, none of which catalysed the reaction. This was a major result. Furthermore, the high triplet energy of these complexes was exploited, and several energy transfer reactions were tested: the *E/Z* isomerisation of E-stilbene, the cycloaddition of norbornadiene to quadricyclane, the [2+2] photodimerisation of *trans*-chalcone, and the intermolecular [2+2] cycloaddition of electron-deficient alkenes. In all reactions, the CMA complex matched or outperformed literature-reported photocatalysts. Further mechanistic studies are being carried out in collaboration with an academic partner.

The second project was the scale-up of the synthesis of **Cu(MAC*)Cz**. We optimised the synthetic route for eight **Cu(MAC*)(Amide)** complexes and reported the first gram-scale synthesis of **Cu(MAC*)Cz** using a simpler, more sustainable, and cost-efficient process. The scale-up reactions were performed in 2 L and 5 L industrial reactors. However, a shortage of 3-chloropivaloyl chloride, one of the main reagents, arose from European suppliers due to new regulations. This necessitated a reassessment of the entire synthetic route to one of the key intermediates, which is currently ongoing.

ESR 2 conducted a secondment at the University of Amsterdam in the research group of Prof. Timothy Noël from September to December 2024. Two projects were undertaken. The first investigated a Minisci-type reaction using CMA complexes as photocatalysts. The second project, carried out in collaboration with ESR 11 Stefano Bonciolini, studied the synthesis and application of N-vinylpyridinium salts. Both projects did not yield conclusive results, but new project ideas emerged from the experimental work and will be considered for future students.

ESR 2 conducted a secondment at J&J in Toledo, Spain, under the supervision of Dr. Jesús Alcázar. The project studied **(Metal)(MAC*)(Amide)** complexes in several oxidative quenching reactions using an automated flow system. The first challenge was optimising conditions to obtain soluble reagents for the flow system. Several reactions screened were successful, including the α-amino C–H arylation and the photoredox-catalysed deoxyfluorination of activated alcohols. Further screening has been conducted using a smaller flow system, and a manuscript is being written.

The ESR took part in and helped to organise the summer school in May 2024 in St Andrews. She presented her research at the Johnson Matthey Academic Conference in April 2024 and at the Johnson Matthey Science Conference in June 2024. She also presented a poster at the BOSS XVIII Conference in July 2024 in Liège, where she was awarded a poster prize. Finally, ESR 2 presented at the final PhotoReAct conference in December 2024 in Amsterdam.

ESR 3 – Sultan Çetin (UniBo)

The research conducted by ESR 3 makes a significant contribution to the field by demonstrating the viability of donor–acceptor TADF (thermally activated delayed fluorescence) chromophores as photocatalysts. It provides mechanistic insights into photoredox reactions and highlights key factors influencing photocatalytic performance. This work paves the way for the development of more efficient and sustainable organic catalysts.

Mechanistic Study of pDTCz-DPmS

A thorough investigation of the photocatalytic mechanism of the TADF emitter **pDTCz-DPmS**, developed by the Zysman-Colman group, in a C–C bond-forming reaction revealed that multiple mechanisms may be involved. Understanding these pathways is crucial for optimizing the efficiency of such photocatalytic systems.

Photoconversion of 3DPAFIPN

A carbazole-1,3-dicarbonitrile derivative was obtained through the photoconversion of 3DPAFIPN, a well-known cyanoarene-based PC. This product exhibited TADF properties and was successfully employed in photoredox catalysis with a Co(II) species in collaboration with the Cozzi group. This study reveals that photodegradation products of conventional PCs can possess useful photophysical properties and retain or even enhance catalytic functionality. Traditionally seen as a limitation, photodegradation is reframed as a synthetic opportunity, enriching the design space for novel TADF emitters. These findings contribute to the understanding of PC stability and could inspire new materials for photoredox applications.

Role of Radical Anions in Photoredox Catalysis

Investigations into the radical anion of the commonly used TADF emitter 4CzIPN addressed longstanding misconceptions regarding its photophysical properties and its formation and degradation. The study demonstrated that $4CzIPN^{\bullet-}$ is a highly transient species that rapidly converts into substitution products, raising doubts about its role in the ConPET (consecutive photoinduced electron transfer) mechanism. The findings suggest that alternative species, such as these substitution products or solvated electrons, may be the actual photoreductants in such systems. Further research conducted by group members supported this idea, showing that longer-lived solvated electrons are generated upon excitation of 4CzIPN in acetonitrile. It is proposed that these solvated electrons are primarily responsible for the exceptional reducing power observed in such photocatalytic systems.

Design of Novel Thioether-Linked TADF Chromophores

Thioether-based donors, though less common in TADF molecules, are gaining attention due to their strong electron-donating capacity and conformational flexibility. A novel class of donor–acceptor chromophores was developed using dicyanoarene cores and sulfur-linked donor groups such as carbazole (Cz) and diphenylamine (DPA), including brominated derivatives. These compounds exhibited strong charge-transfer character, TADF, visible light absorption, phosphorescence, and photocatalytic activity. This work demonstrates how structural modifications, like thioether incorporation, can significantly enhance photophysical properties and broaden the functional utility of organic PCs.

In a broader extent, this research supports the advancement of sustainable chemistry by exploring metal-free organic photocatalysts that harness visible light to drive chemical transformations. The development of efficient, tunable chromophores and understanding photocatalytic process is critical for the continued success of photocatalytic methodologies. Overall, the study makes a compelling case for the use of TADF chromophores in photocatalysis, offering both fundamental insights and practical strategies for optimization.

ESR 4 – Silvia Dell'Uomo (ULEI)

The research activities of ESR4 focused on the rational design and development of broadly applicable, purely organic photocatalysts, conceived as potentially more sustainable and environmentally benign alternatives to conventional photocatalysts based on organometallic complexes. Leveraging the group's established expertise in the strategic structural modification of cyanoarene-based thermally activated delayed fluorescence (TADF) photocatalysts, the donor–acceptor (D–A) design principle was successfully expanded to a wider variety of molecular frameworks. This approach enabled the exploration of novel scaffolds with tailored photophysical and redox properties suitable for diverse photocatalytic applications.

Synthesis, photophysical and electrochemical characterisation of new scaffolds.
Novel photocatalysts, named **PIns** and **InIs**, were synthesized *via* a straightforward two-step procedure with satisfactory yields. The synthesized photocatalysts differ in the strategic placement of electron-withdrawing (EWG) and electron-donating groups (EDG), located in proximity to the HOMO and LUMO.

This rational design enables systematic structural modifications aiming at tuning the photophysical and electrochemical properties of the corresponding core systems. It could be experimentally demonstrated, then also confirmed by TDA calculation, that these compounds behave as powerful, novel D–A systems, thereby allowing, through only two synthetic steps, the creation of a modular set of photocatalysts adaptable to various functional requirements and well-endowed for diverse photocatalytic transformations.

Photocatalytic activity
The synthesized photocatalysts were subjected to a broad set of different test reactions to assess their photocatalytic performance. The results demonstrated that these compounds exhibit excellent activity in both oxidative and reductive quenching pathways. This efficiency is attributed to the tunability of their redox potentials, enabled by the facile introduction of various functional groups onto the core structure. Consequently, they serve as effective photocatalysts in single-electron transfer (SET) processes.

Their capability to – alternatively – mediate energy transfer (EnT) was also evaluated, also providing highly promising results. Furthermore, dual catalytic approaches involving EnT and nickel catalysis were explored, showing outcomes consistent with those reported in the literature.

These findings position the developed systems as competitive alternatives to established photocatalysts, offering the advantages of an effortless, straightforward synthetic route and enhanced structural versatility.

It is to be noted that as one of the late recruited ESRs, ESR 4 is currently in the process of completing her research. Her findings are not yet been published yet, but will be published in more detail in the near future.

ESR 5 – Joseph Milton (ICHO PAS)

The most important results of ESR 5 are collected in three publications, namely:

1. Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies, by Milton et al. (2024)[4].
2. TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines, by Leone et al. (2024)[5].
3. Photochemical Functionalization of 4-Diazoisoquinoline-1,3(2H,4H)-diones and Their 1-Sulfoxide Analogues, by Milton and Gryko (2025)[6].

Publication 1 involves the development of a novel strategy towards utilising blue light absorbing diazo compound in an aqueous medium, namely with a DTAC micellar solution. Organic reagents typically do not dissolve well in water, but the addition of a surfactant enables the generation of a micellar solution which can then dissolve the hydrophobic compounds. We used this knowledge to enable the photochemical cyclopropanation of diazo compounds in water, which has not been achieved previously. We found an important linear trend where, when the length of the alkyl chain attached to the ester substituent was increased, the yield increased too, leading us to use dodecyl esters for the highest yields. Computational calculations (COSMO-RS) revealed that these longer alkyl chains contributed towards the construction of the micelle, and thus we hypothesised that larger micelles are formed, which enabled more styrene molecules to enter the micelle, thus increasing the chance of a successful collision with the styrene and carbene instead of decomposition. ESR 5 also showed that this reaction is viable when generating diazo compounds in situ by treating hydrazones with a small excess of triethylamine.

Publication 2, in collaboration with Dr. Géraldine Masson, Dr. Luc Neuville, and Dr. Matteo Leone (ESR 8) at CNRS, focusses on a diastereoselective hydrogen atom transfer (HAT) reaction with an inexpensive tungsten-based catalyst, TBADT. This work will be outlined in the greater detail in ESR 8 report, but ESR 5 contributed several examples to the substrate scope and subsequent analysis for such products was performed.

Publication 3 concerns the behaviour of 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones under direct blue light irradiation. Whilst 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones have been investigated under various metal-catalysis. We found that the diazo compounds in question underwent efficient O-H, S-H and C-H insertion reactions with fluorinated alcohols, thiols and aromatic compounds, respectively. A small series of novel 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides were also synthesised that underwent similar O-H and S-H insertions under violet LED irradiation.

ESR 6 – Debora Belmonte (UZH)

The project initially focused on the development of a nickel- and photoredox dual-catalyzed asymmetric carbosilylation of alkenes, aiming to establish a new strategy for stereoselective C–C and C–Si bond formation under mild conditions. Following extensive optimization of the reaction parameters, including catalyst loading, light source, ligand selection, and solvent system, suitable conditions were identified that enabled the efficient execution of the target transformation.

With these optimized conditions in hand, subsequent investigations were directed toward evaluating the substrate scope of this novel transformation. The methodology proved to be applicable to a broad range of aryl bromides, acrylates, and acrylamides, demonstrating its robustness and synthetic utility. These results underlined the potential of the protocol in enabling modular and stereocontrolled difunctionalization of alkenes. To further enhance the synthetic divergence of the methodology and distinguish it from previously reported protocols (Yuan et al., 2025)[7], the scope was expanded to include additional Group 14 elements. In particular, the focus shifted toward incorporating germane reagents as radical precursors in place of silanes. This required re-optimization of the reaction conditions.

These newly refined conditions allowed for a broader investigation of both silanes and germanes, highlighting the versatility of the catalytic system. To complete the second phase (carbogermylation of alkenes) of this research, further work remains to be conducted. This includes the synthesis and evaluation of additional complex substrates, particularly those bearing heterocyclic motifs and diverse Michael acceptors, as well as studies on post-functionalization of the products and detailed mechanistic investigations, including control experiments. These efforts are essential to consolidate the scope and limitations of the method and to gain deeper insight into the reaction pathway. At the same time, manuscript preparation for publication of this first project is underway. In parallel, initial investigations have been initiated on the original proposal for the site-selective functionalization of peptide substrates at inert C(sp^3)–H bonds via water-compatible photoredox catalysis.

Preliminary experiments involving the synthesis of water compatible photocatalysts to evaluate them later on in this transformation have been conducted. This second project will be pursued in earnest upon the successful completion of the current asymmetric alkene group 14 hetero-difunctionalization study.

It is to be noted that ESR 6 is currently still working on her research project. This is due to the fact that ESR 6 was one of the late recruited ESRs. Therefore, outcome of the second project cannot be recorded as of this moment.

ESR 7 – Raquel Sánchez Bento (UoM)

The research of ESR 7 has led to the development of a powerful and conceptually novel platform for the generation and synthetic application of singlet aryl nitrenes from nitroarenes. Historically, the synthetic use of aryl nitrenes has been severely constrained by the hazardous nature of azide precursors and the need for high-energy activation conditions. These limitations rendered aryl nitrenes largely academic curiosities rather than practical intermediates for synthesis. Through two complementary studies, published in *Nature Chemistry* (Sánchez-Bento et al., 2024)[8] and *Chem* (Sánchez-Bento et al., 2023)[9], we have systematically addressed these challenges and redefined the role of nitroarenes in organic chemistry.

In the *Nature Chemistry* study, we showed that visible-light excitation of electron-deficient nitroarenes enables access to singlet aryl nitrenes under mild, azide-free conditions. These intermediates undergo controlled ring-expansion to generate azepanes—medium-sized nitrogen heterocycles that are structurally complex, synthetically challenging, and of growing relevance in medicinal chemistry. The key innovation lies in the ability to preserve and translate the benzenoid substitution pattern of the starting material onto the azepane scaffold. This direct substitution-pattern retention eliminates the need for multistep manipulations typically required to install heteroatoms into ring-expanded frameworks. Furthermore, the method exhibits a broad functional group tolerance, allowing for late-stage modification and scaffold diversification—an essential feature for applications in drug development and chemical biology.

Building on this foundation, our *Chem* paper expands the conceptual reach of this chemistry by demonstrating a complementary, divergent transformation: the ring-contraction of nitroarenes to yield densely functionalized bicyclic pyrrolidines. These structures are equally valuable as pharmacophores but have remained synthetically inaccessible through conventional methods. In this work, we uncovered how subtle electronic and structural tuning of the nitroarene substrate, along with judicious choice of photochemical conditions, allows selective access to either ring-expanded or ring-contracted products from the same class of starting materials. This level of reactivity control, achieved without altering the core molecular framework, highlights the strategic advantage of engaging aryl nitrenes as transient, high-energy intermediates in synthesis.

Together, these two studies form a coherent and impactful body of work that opens entirely new avenues for nitrogen insertion chemistry. They demonstrate that nitroarenes, typically regarded as inert or terminal functionalities, can serve as photochemical precursors to highly reactive nitrenes, enabling direct C–N bond formation and scaffold rearrangement in a single operational step. Beyond the fundamental novelty, this platform offers medicinal chemists new synthetic entry points into underexplored chemical space, with control over regioselectivity, substitution pattern, and ring topology. It also underscores a broader conceptual shift: by leveraging photochemistry, it is possible to convert historically challenging or dangerous intermediates into versatile, programmable tools for complex molecule construction.

This body of work therefore represents more than just the development of two useful synthetic methods; it establishes a new strategic logic for the transformation of simple arenes into diverse, complex nitrogen-containing frameworks. It also affirms the value of visible-light activation in controlling high-energy reactive species, providing a foundation for future work in photochemical reactivity and heterocycle synthesis.

ESR 8 – Matteo Leone (CNRS)

Visible light, known for being an abundant and economical energy source, has recently become crucial in advancing sustainable catalytic chemical processes. Among the various synthetic applications developed so far, achieving photocatalyzed reactions in an asymmetric fashion remains a considerable challenge. In this specific context, our focus extended beyond the creation of new sustainable and efficient light-mediated methodologies especially dedicating the work to pioneering innovative asymmetric processes.

Photocatalyzed processes involving acid-derived redox-active esters (RAEs) has been successful in an array of reaction. Combining this radical source with aldehyde derived sulfonyl hydrazones, employing Eosin Y as an organophotocatalyst under visible light irradiation followed by a deamination step allowed to developing a metal-free C(sp3)−C(sp3) cross-coupling platform. Its synthetic utility applicable to C1 homologation of carboxylic acids was demonstrated, providing an alternative to the traditional Arndt-Eistert reaction. Notably, the method is compatible with late-stage functionalization of peptides on solid-phase, simplifying the modification of intricate peptides without the need for time demanding de novo synthesis (Bonciolini et al., 2024)[10].

To devise new challenging asymmetric photocatalyzed processes, we decided to explore readily available chiral auxiliaries based strategies:

- As such, building on chiral sulfinyl-imines and by utilizing readily available non-prefunctionalized radical precursors and TBADT as a photocatalyst to generate radicals through direct hydrogen atom transfer (HAT), we developed a method enabling the synthesis of diverse chiral amines with high yields and excellent diastereoselectivities under mild conditions. This approach proves to be effective for accessing a varied range of both natural and synthetic α-amino acids relevant to pharmaceuticals products (Leone et al., 2024)[11].
- The radical Truce–Smiles rearrangement is a straightforward strategy for incorporating aryl groups into organic molecules for which asymmetric processes remains rare. By employing a readily available and non-expensive chiral auxiliary, we developed the second to date asymmetric Truce–Smiles rearrangement approach: highly efficient asymmetric photocatalytic acyl and alkyl radical Truce–Smiles rearrangement of α-substituted acrylamides using tetrabutylammonium decatungstate (TBADT) as a hydrogen atom–transfer photocatalyst, along with C−H containing precursors lead to rearranged products exhibiting excellent diastereoselectivities. Mechanistic studies allowed understanding the transformation in which density functional theory (DFT) calculations provided insights into the stereochemistry-determining step *(*Ma et al., 2024)[12].

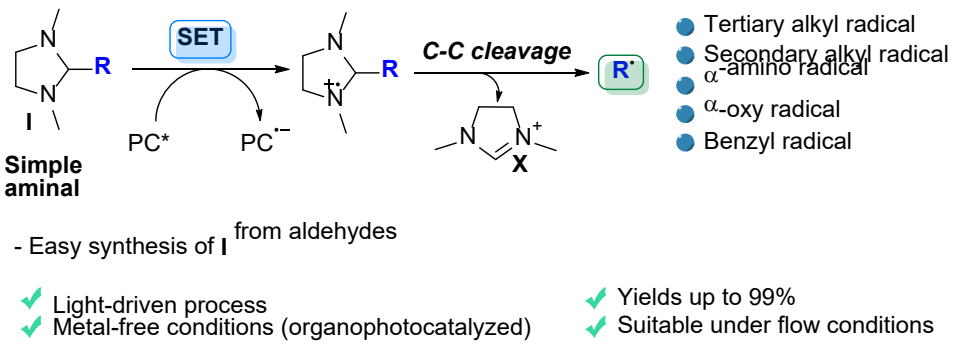
Enantioselective photocatalyzed transformations remain rare and is still a golden goal in photocatalysis. To contribute to this field, we dedicated our work to building a novel category of visible-light-sensitive chiral organocatalysts. These catalysts feature a covalently linked backbone of BINOL-derived Chiral Phosphoric Acids (CPAs) with various photosensitizers, such as aryl ketones and phenothiazine. Several CPAs were synthesized and their photophysical and electrochemical properties investigated. Enantioselective activity of the ketone-based chiral photocatalysts was demonstrated when applied in an enantioselective multicomponent tandem process, enabling the efficient synthesis of fully substituted 1,2-diamines with excellent enantioselectivities (Lyu et al., 2021)[13].

ESR 9 – Adrián Luguera Ruiz (UNIPV)

With the renaissance of the photocatalytic processes, radical chemistry emerged as a powerful tool in organic synthesis. This has paved the way to a more eco-sustainable tin-free radical chemistry. In fact, a lot of radical precursors were designed to liberate an alkyl (or a related) radical upon a single electron transfer reaction with a photoredox catalyst. The strategy is based on the fragmentation of the species formed upon oxidation/reduction of the radical precursor. An ideal radical source should be easily reducible or oxidizable. There is an urgent need to develop new neutral easily prepared and highly reactive radical precursors.

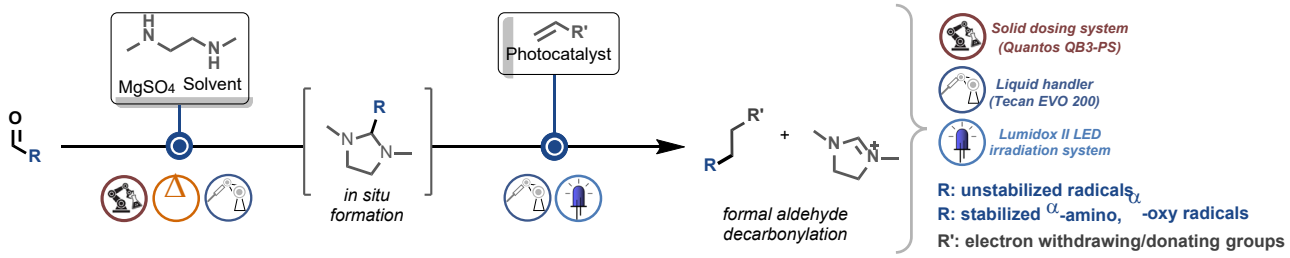
In the first part of the project, we discovered that 2-substituted-1,3-oxaxolidines were suitable for this purpose[14]. In the frame of developing easily oxidizable compounds for the photorelease of carbon-based radicals, we now described the use of 2-substituted-1,3-imidazolidines (**I**, Scheme **1**). These compounds (Eox ca. 1 V vs. SCE) were used to generate (substituted) alkyl radicals under photoredox conditions. The radicals smoothly added to electron-poor C-C bonds for the forging of $C(sp^3)$–$C(sp^3)$ bonds under metal-free conditions. Acridinium salts and even 4-CzIPN were used as photocatalysts[15].

Scheme 1



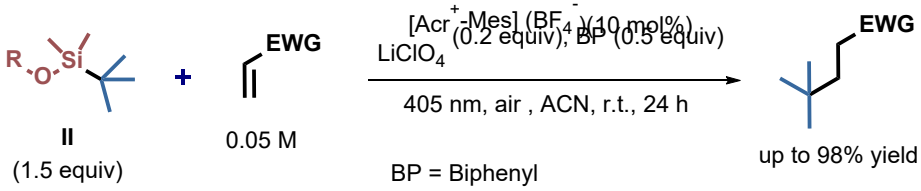
These heterocycles were then used (in cooperation with J&J) for the discovering of new drug candidates thanks to the facilities and the synthetic tools to accelerate drug discovery processes present. Accordingly, a fully automated strategy for the addition of Csp^3 enriched building blocks onto olefins via Giese addition to forge Csp^3-Csp^3 bonds was devised. The developed fully automated protocol allowed the *in-situ* conversion of aldehydes (non-redox-active species) to electroactive imidazolidines and their use as precursors of C-centered radicals under photoredox catalyzed conditions for the synthesis of building blocks and bioactive compound libraries (Scheme **2**)[16].

Scheme 2



We then shifted to consider the silyl ethers of phenols (**II**, Eox > 1.7 V vs. SCE) as neutral carbon (silicon) centered radical precursors. The organophotocatalyzed oxidation (by the Fukuzumi catalyst) of these ethers caused the cleavage of a C-Si (or a Si- Si) bond for the release of the desired radical for the forging of $C(sp^3)$-$C(sp^3)$ (or $C(sp^3)$-Si) bonds (Scheme **3**)[17].

Scheme 3



ESR 10 – Byeongseok Kweon (WWU)

The research of ESR 10 focuses on contra-thermodynamic alkene isomerization via selective energy transfer catalysis. Alkenes, as well as vinyl nucleophiles and electrophiles, serve as valuable precursors in stereospecific cross-coupling reactions. However, accessing the corresponding Z-isomers remains challenging due to the contra-thermodynamic or thermo-neutral nature of these processes, which limits the scope of accessible chemical space in drug discovery. To address this, our group has developed a general platform for the isomerization of activated alkenes through selective energy transfer catalysis, with an emphasis on achieving precise structural control over their geometry. Building on this foundation, my research aims to expand the methodology and demonstrate its synthetic utility across a broader range of substrates. In particular, I have applied this platform to investigate both geometric and positional isomerizations using vinyl boronate compounds.

The first project focuses on the geometric isomerization of alkenyl fluorides, which are widely used as bio-isosteres of amide bonds. This study merges the concept of vinyl boronates with the unique properties of alkenyl fluorides. Alkenyl fluorides have emerged as effective amide bond isosteres, as the polar C(sp^2)–F bond closely mimics both the steric and electronic features of native amides. However, realizing endergonic isomerization in Ψ[CF=CH]-based systems remains a significant challenge. To address this, I envisioned that fluorinated β-boryl acrylates could serve as attractive substrates for the development of an operationally simple isomerization strategy via selective energy transfer catalysis. I have thus established a catalytic platform that enables the efficient geometric isomerization of these fluorinated β-borylacrylate linchpins using an inexpensive photosensitizer, achieving high selectivity (up to *E/Z* 98:2 within 1 hour). Owing to the ambiphilic nature of the resulting products, facile derivatization at both molecular termini was demonstrated, including in the context of target-oriented synthesis (Wienhold et al., 2023)[18].

The second project builds upon our earlier work with C3 vinyl boronates by extending the concept to the geometric isomerization of borylated C5 building blocks. 1,3-Dienes are prevalent structural motifs in bioactive small molecules, where their two-dimensional stereochemical information often plays a critical role at the structure–function interface. In this context, I introduced 1,3-borylated dienes as substrates to enable selective alkene isomerization at specific positions within the polyene scaffold. Using selective energy transfer catalysis, I achieved a highly regio- and stereoselective isomerization of β-boryl-substituted 1,3-dienes, reaching *E*:*Z* ratios of up to 99:1. The synthetic utility of this transformation was further demonstrated through its application in stereospecific [4+2] and [2+2] cycloaddition reactions, furnishing complex cyclic structures bearing up to four contiguous stereocenters. Furthermore, the downstream functionalization of individual isomers via cross-coupling reactions showcased the potential of this strategy for the precise synthesis of geometrically defined polyenes (Kweon et al., 2024)[19].

As a follow-up and ongoing study, ESR 10 is currently investigating the deconjugative isomerization of borylated 1,3-dienes. By employing short-wavelength light, this transformation extends beyond simple geometric isomerization to achieve positional alkene isomerization, disrupting the original conjugated system and enabling access to thermodynamically unfavorable deconjugated products. Inspired by the photoisomerization process of vitamin D, this transformation proceeds via a radical cascade mechanism and accommodates a broad range of substrates. The synthetic utility of the resulting deconjugated dienes is currently being explored through various downstream applications.

ESR 11 – Stefano Bonciolini (UvA)

In the **first year**, a practical methodology to enable the modular and regioselective allylation of C(sp3)−H bonds was performed. This method involves a synergistic merger of a photocatalytic Hydrogen Atom Transfer (HAT) and an ensuing Horner-Wadsworth-Emmons (HWE) olefination in a telescoped flow protocol. The synthetic platform stands out for its modularity and simplicity, enabling the rapid synthesis of diverse and complex di- and tri-substituted olefins from readily available and inexpensive starting materials, such as C(sp3)−H bonds and aldehydes. The two-step telescoped process in continuous flow should facilitate a rapid transition from academic to industrial settings, with minimal reoptimization required for scale-up and smooth integration into automatic platform for library synthesis. To improve the relevance of this methodology, future endeavors should focus on developing more efficient photocatalytic system to reduce the excess of C−H donors. Furthermore, while the stereochemical outcome is largely substrate dependent, the use of photosensitizers could provide a solution for the selective isomerization of the alkene geometry.

In the **second year**, a straightforward and practical protocol to forge C(sp3)–C(sp3) bonds from easily accessible N-sulfonyl hydrazones and C(sp3)–H donors was presented. This cross-electrophile coupling is based on a two-step synthetic strategy, comprising a photocatalytic HAT step and a subsequent fragmentation reaction of the hydrazide intermediate. The discovery of the 4-trifluoromethylphenylsulfonyl group was pivotal to enhance the reactivity during the light-induce step and to ensure a smooth decomposition of the hydrazide derivative in a one-pot fashion. Additionally, the use of glyoxylate-derived sulfonyl hydrazones enabled the formal α-alkylation of esters with nucleophilic carbon radicals, a transformation not previously reported in literature. The synthetic utility of this protocol was demonstrated through the preparation of medicinally-relevant scaffolds, such as homobenzylic ethers, aryl ethyl amines, and β-amino acids. However, the methodology is mainly limited to the coupling of activated α-C–H bonds and aromatic aldehydes. This method is mechanistically different from traditional metal-mediated cross coupling processes, enabling the construction of similar C(sp3)–C(sp3) fragments directly from the well-defined properties of imine derivatives. Given this metal-free paradigm, we anticipate that this reaction, along with future developments, will have significant value for both academic and industrial researchers.

In the **third year**, a further application of aldehyde-derived sulfonyl hydrazones as deoxygenative alkylating reagents was presented. Herein, a visible light-mediated metal-free cross-electrophile coupling of carboxylic acid-derived redox-active esters with aldehyde sulfonyl hydrazones, yields the desired C(sp3)–C(sp3) bond via subsequent fragmentation. The synthetic utility was highlighted by the preparation of a variety of cross-coupled products, as well as the late-stage functionalization (LSF) of peptides on solid-phase. Furthermore, the bench-stable glyoxylate-derived sulfonyl hydrazone was employed for the C1 homologation of primary, secondary and tertiary carboxylic acids, offering a safer alternative to the traditional Arndt–Eistert reaction, which relies on the hazardous and explosive diazomethane. Despite its widespread use, the generation and handling of gaseous diazomethane raises significant safety concerns in both small- and large-scale reactions. Given the general importance of strategic carbon chain elongation of carboxylic acids in medicinal chemistry, our C1 homologation strategy is distinguished by its practicability, functional group tolerance and scalability.

In the **fourth (final) year**, considering our efforts on the development of new strategies for the deoxygenative functionalization of carbonyl derivatives, we targeted secondary amides as abundant precursors for the synthesis of α-substituted secondary amines. This method involves a triflic anhydride mediated deoxygenative semi-reduction of secondary amides, leading to the formation of reactive iminium ions, followed by a photochemical radical alkylation with alkyl iodides. Compared to existing methodologies that rely on organometallic reagents, this approach demonstrates broader functional group tolerance and has been

successfully applied to the late-stage modification of drug-like molecules. Notably, process optimization has enhanced efficiency and enabled scalability up to 10 mmol for both α-substituted secondary and tertiary amines, particularly through the implementation of continuous-flow technology. Given the abundance of amide drug candidates and extensive libraries of custom-made carboxylic acids, this method offers significant advantages over traditional routes, where iminium ions are typically prepared from the condensation of amines with often sensitive aldehydes. Future endeavors should aim to generate the desired iminium ions directly from mixing carboxylic acids and primary amines, without prior isolation of the secondary amides. This advancement would offer important advantages in the context of high-throughput experimentation (HTE) and automation.

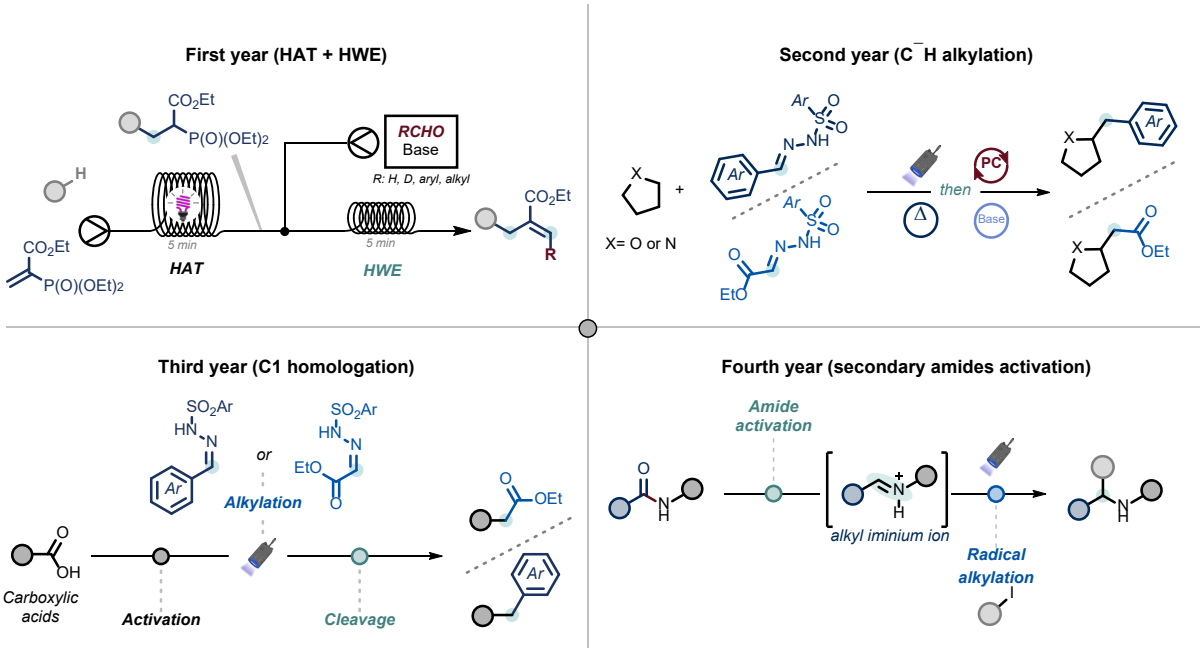


Figure 1. Summary of the main projects executed.

ESR 12 – Pauline Tenblad (UvA)

The PhD research of ESR 12 has led to several key innovations in data-driven chemical discovery through the integration of automation, machine learning, and flow chemistry. The most significant contributions are outlined below:

1. **Development and Validation of the RoboChem Platform**

   RoboChem, a modular and fully automated flow chemistry platform, was designed to perform closed-loop reaction optimization by combining Bayesian optimization algorithms, inline benchtop NMR analysis, and a custom-built photocatalytic reactor. The platform was validated across a diverse set of photocatalytic transformations. In all tested cases, RoboChem matched or outperformed reported literature protocols. These findings were published in *Science* (Slattery et al., 2024)[20], with the work receiving substantial attention—over 19,000 downloads and more than 100 citations to date.

2. **Machine Learning-Guided High-Throughput Screening for C(sp^3)–C(sp^3) Bond Formation**

   A Random Forest-based strategy was developed to guide a high-throughput screening campaign focused on discovering new C(sp^3)–C(sp^3) bond-forming reactions. A plate population methodology was implemented to balance exploration of novel chemical space with exploitation of model-predicted reactivity. This approach enabled efficient identification of new reactivity patterns and facilitated the construction of a chemically diverse dataset that includes both successful and non-productive reactions, enhancing its utility for future machine learning applications.

3. **Standardized Dataset Construction and Predictive Modeling of Reaction Outcomes**

   A curated, high-quality dataset was compiled from RoboChem experiments, incorporating structured reaction inputs, product yields, and metadata such as light intensity, residence time, and categorical variables including solvent and catalyst identity. This dataset was used to train machine learning models to predict reaction outcomes. The results demonstrate strong predictive performance for known substrates and conditions. However, generalization to entirely new substrate combinations remains limited, highlighting the need for broader and more diverse data. Despite this, the current models have proven useful for guiding experimental decision-making and prioritization.

Together, these contributions demonstrate the potential of data-driven automation to advance chemical discovery and methodology development.

ESR 13 – Damiano Diprima (ES/UvA)

ESR 13 started his PhD research at EcoSynth where he focused on the development of new photochemical methods exploiting flow chemistry to handle complex mixtures involving solids and gas. As part of this work, an article and a patent have been published in the *Beilstein Journal of Organic Chemistry*:

Patent: Light mediated aerobic oxidation method: WO2024165619
Publication: Selective and scalable oxygenation of heteroatoms using the elements of nature: air, water, and light (Diprima et al., 2023)[21].

The newly developed light-mediated aerobic oxidation methodology has the potential to substantially decrease the environmental impact and cost of some industrially relevant procedures. This finding emphasizes significant environmental and economic benefits, suggesting that if adopted at an industrial scale, it could lead to more sustainable and cost-effective processes, making a substantial impact on various industries. This highlights the broader applicability and importance of ESR 13's work in driving eco-friendly innovations in chemical processing.

Additionally, ESR 13 collaborated with PhotoReAct associated partner CreaFlow to improve and extend the COSTA technology platform, leading to the development of the GALI reactor. This device simplifies gas-liquid reactor setups and facilitates flow chemistry adoption in regulated industries by delivering gas continuously along the channel, improving efficiency and scalability, which is vital for industrial applications.

In March 2024, ESR 13 moved to the UvA to continue his research in the group of Prof. Timothy Noël, focusing on deoxygenative photochemical methodologies. His work led to the production of two articles, enabling streamlined synthesis of substituted amines and modular synthesis of substituted lactams. These methodologies provide straightforward and broadly applicable solutions to access previously difficult-to-achieve moieties, with significant implications for synthetic organic chemistry. ESR 13 published the following two articles:

1. Deoxygenative photochemical alkylation of secondary amides enables a streamlined synthesis of substituted amines, by Pulcinella et al. (2025)[22].

2. Modular synthesis of substituted lactams via deoxygenative photochemical alkylation-cyclization cascade of secondary amides in flow, by Diprima et al. (2025)[23].

Additionally, a review about the use of solids in flow reactors is being finalized, highlighting the potential to overcome one of the main limitations of these platforms. Historically, solid handling has been a significant challenge in continuous flow reactors. The review aims to showcase solutions to this problem, expanding the applicability and benefits of flow manufacturing to a broader range of chemistries. This insight is crucial for advancing flow chemistry and enhancing its practical utility in various chemical processes. ESR 13 is finalizing the following review:

3. The Achilles Heel of Flow Chemistry: Solids Handling in Heterogeneous Continuous-Flow Reactors, by Diprima, Anwar and Noël (2025, *In press*)[24].

ESR 14 – Matteo Gasparetto (X-Chem/UvA)

ESR 14 focused on exploiting photochemistry for improving the field of DNA-Encoded Libraries (DELs). Firstly, he developed a 3 to 5 steps synthetic protocol for the straightforward preparation of α-aryl-α-amino acids, very useful building blocks for DELs and combinatorial chemistry approaches. This protocol has been shown to be applicable to different types of heteroaryl halides leading to the production of substrates that were finally validated for on-DNA applications (Figure **2**). This work was published in the *Beilstein Journal of Organic Chemistry* in 2024[25].

Starting from the end of September 2022, ESR 14 moved to the X-Chem site in Waltham (MA) for his first secondment. During the three months he spent there, the ESR improved his skills in on-DNA organic chemistry, and then he focused on the development of a new photocatalyzed C-N coupling for DNA-tagged compounds[26]. He developed an innovative method for a photocatalyzed amidine arylation on-DNA using a dual catalytic approach. Up to 70% yield was achieved during proof of concept. Further work on the optimization and exploration of the scope of the reaction revealed that the methodology could not meet the criteria of generality required for combinatorial chemistry approaches (Figure **3**). For this reason, this project was not published even though it served as a base for further applications off-DNA.

Building on the insights gained, ESR 14 successfully reoptimized the amidine arylation protocol for off-DNA applications. He established a high-yielding nickel/photoredox-catalyzed method that demonstrated excellent substrate compatibility, tolerating a wide range of aryl halides and amidines. The reaction conditions also proved effective in late-stage functionalization of complex molecules, highlighting the method's synthetic utility (Figure **4**).

In March 2024, ESR 14 began his second secondment at the University of Bologna, working in the group of Prof. Paola Ceroni. There, he collaborated on mechanistic investigations of the newly developed protocol. These studies revealed the key role of an in situ generated triazine co-catalyst, which was critical for enhancing reaction rates, enabling milder conditions, and—importantly—broadening the substrate scope to include sulfonamides and primary amines. The results of this comprehensive work have been compiled into a manuscript, now available as a preprint on *ChemRxiv*, with journal submission currently in progress[27].

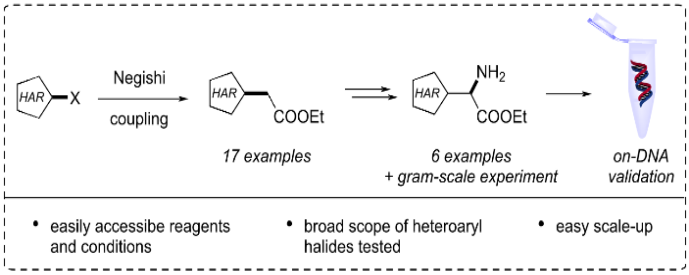


Figure 2. Graphical abstract of the unnatural amino acids project.

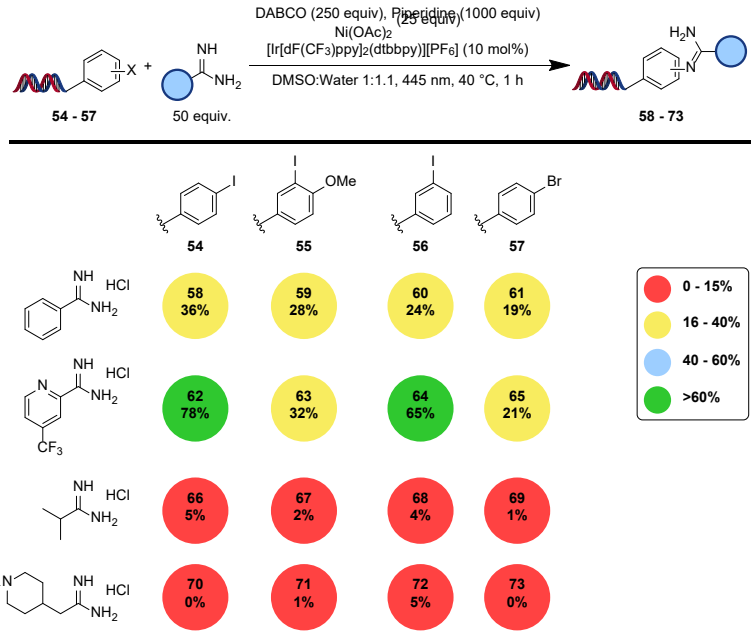


Figure 3. Summary of the scope for the on-DNA amidine arylation protocol with reaction scheme and conditions.

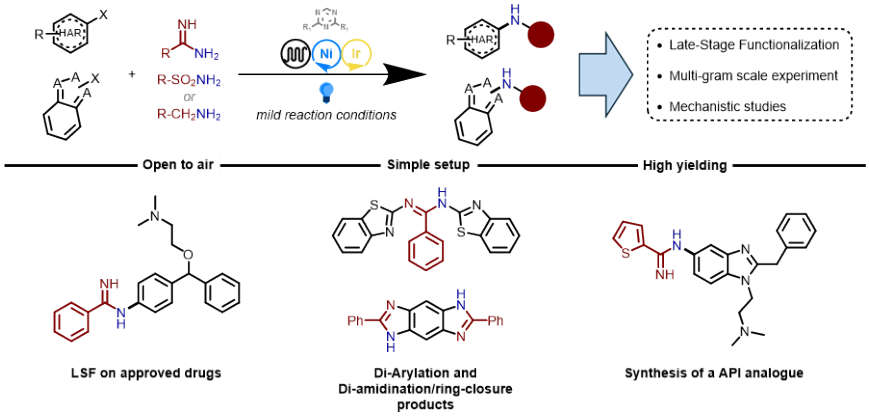


Figure 4. Graphical abstract for the small molecule amidine arylation project.

ESR 15 – Brenda Pijper (J&J)

The work of ESR 15 during these 3 years has clearly boosted the part of automation in flow photochemistry with new methodologies and approaches that have been applied on different Drug discovery programs.

When she joined the group in September 2021 she helped us to complete the work on automated Negishi reaction that was fairly advanced within the team and harmonized the data for creating a high quality supporting information for publication. This was really helpful to complete the manuscript finally published (Abdiaj et al., 2023)[28]. On her side this part of the work supported her integration within the team and her introduction in flow chemistry space.

Once this part was finished, she also continued the work that we started in collaboration with UCLM where we validated the mild reduction of a tertiary amide bond followed by a nucleophilic attack with organozinc reagents. This method utilizes the abundant amide bond in drug discovery to create C(sp^3)-C(sp^3) bonds, opening new chemical space. The reduction of the amide with the Vaska complex and tetramethyldisiloxane (TMDS) generates a hemiaminal, which reacts with organozinc reagents to make libraries. Initial validation performed at UCLM combined batch and flow methods, but proved to be unsuccessful for lactams, the most relevant compounds as their synthesis is less straightforward. She studied the kinetics and stability of the initial reduction so that the data obtained allowed the translation of this transformation to flow. In this way the intermediate could be generated and reacted *in situ* with the corresponding nucleophile to allow the formation of the final product. Moreover, this allowed us to fully automate the protocol and build up combinatorial libraries based on this chemistry. This has added quite a lot of value to our Drug Discovery programs, as it has been used in several of them as well as for the preparation of key intermediates. Results from this work were published in *Organic Letters* (Pijper et al., 2024a)[29].

Following on C(sp^3)-C(sp^3) bond formation, she enabled large library synthesis through XAT in an automated fashion. It was her first full project. The methodology was adapted from batch to flow by modifying the solvent system to DMF:ACN:H2O (9:1:1) and reducing the concentration (0.1 to 0.05 M), facilitating continuous flow library synthesis. This adaption allowed the introduction of sp^3-rich fragments in a combinatorial manner, with the method providing scalable, highly reproducible, and applicable for late-stage functionalization of drug-like molecules, including amino acids. This methodology is so mild that has been applied to modify complex molecules such as peptides. The results were published in *ChemCatChem* (Pijper, Abdiaj and Leonori, 2023)[30].

Addressing the reproducibility challenges in photochemistry for high-throughput chemistry was crucial for advancing the application of these methodologies in early drug discovery. For this purpose she focused her efforts on evaluating and building a robust HTE platform for flow photochemistry. Using the Amino-Radical-Transfer (ART) reaction, chosen for its resilience to oxygen and moisture, she developed a plate to plate approach in flow that allowed us to perform up to 96 reactions with excellent reproducibility. This integration allowed the execution of High-Throughput experimentation (HTE) plates, covering catalyst screening to condition optimization. Within four plates, the reaction was fully optimized with a 10-minute residence time. These optimized conditions facilitated a 24-library synthesis and a 96-combinatorial library comprising 8 drug-like scaffolds and 12 bpins. HTE in flow has been used for other chemistries within our Medicinal Chemistry programs and the result were published in *JACS Au* (Pijper et al., 2024b)[31].

Her last contribution was enabling multivectorial exploration library synthesis by combining multiple components in-line, like a production assembly line. This approach aims to explore all possible combinations simultaneously, rather than one vector at a time, to map the chemical space comprehensively. To achieve this,

the ASIA system of Syrris, which features multiple injection ports and allows for multiple slugs in-line, was employed. The system was validated using robust chemistry, including amide coupling with LiHMDS and Negishi coupling. Following this validation, the optimization of the carrier solvent (DMF), and cross-contamination studies, a 48-compound combinatorial library was synthesized as proof-of-concept, combining four anilines, four (hetero)aryl bromides, and three organozinc reagents. To expand the exploration of the chemical space even further, the ASIA photoreactor was integrated into the system. This allowed for the implementation the ART chemistry with free amino bpins, which was then telescoped with six different chemistries. This integration of photoredox catalysis with more traditional chemistries facilitated extensive chemical space exploration without requiring any changes to the setup. This approach is not only valuable for the rapid exploration of the SAR but also holds significant potential for linker strategies in PROTAC synthesis or fragment-based drug discovery. For this final contribution she continued with initial experiments performed in the team, led the writing of the supporting information and co-wrote the paper with the PI. For this reason she was considered as co-corresponding author of the article *Chem Catalysis* (Pijper et al., 2024c)[32]. This a really novel approach that will open new avenues in flow chemistry.

In summary, ESR 15 her work has significantly enhanced the automated toolbox for medicinal chemists. It presents methodologies for aryl halides, tertiary amides, and Giese acceptors, diversifying the available handles for medicinal chemistry scaffolds. The ART method was expanded to a multivectorial approach, combining assembly line-like synthesis, applicable to small molecule drug discovery, PROTAC, and fragment-based drug discovery. All methods were fully automated, providing medicinal chemists with tools to expand the chemical space and accelerate drug discovery through high-throughput and large library synthesis.

Conclusions

The PhotoReAct project has successfully addressed critical societal and technological challenges facing the European chemical industry by advancing photocatalysis as a sustainable, scalable, and industrially relevant technology. By harnessing visible light as an alternative energy source, the network has demonstrated efficient and selective chemical transformations that replace fossil fuel–driven thermochemical methods. Through the development of novel catalysts, methodologies, and continuous-flow technologies, PhotoReAct significantly reduced chemical waste, minimized the use of toxic reagents and solvents, and improved reaction selectivity.

The integration of automation and high-throughput platforms, such as RoboChem, has accelerated the design and optimization of photochemical processes, enabling faster access to life-saving pharmaceuticals and fine chemicals. The project also delivered key technological breakthroughs, including the transition from UV to visible-light activation, the development of scalable flow photoreactors, and the implementation of sustainable light sources such as LEDs and solar-powered LSC systems.

Collectively, these achievements bridge the gap between academic innovation and industrial application, positioning photocatalysis as a cornerstone of the green transition in chemical manufacturing and aligning closely with the objectives of the EU Green Deal. Through the extensive efforts of the Early-Stage Researchers, PhotoReAct has provided a robust scientific and technological foundation for the next generation of sustainable synthesis. Their collaborative work across academia and industry has not only produced significant scientific outcomes but also cultivated a new generation of experts equipped to drive the European chemical sector toward a greener and more innovative future.

Looking ahead, continued integration of photochemical technologies with digital automation, AI-driven optimization, and renewable energy sources will further expand the industrial reach of photocatalysis. These directions represent the next frontier for sustainable process chemistry and ensure that the impact of PhotoReAct will continue to shape the development of greener and more efficient manufacturing processes across Europe and beyond.

Glossary

ART	Amino-Radical-Transfer
ATRA	Atom Transfer Radical Addition
BINOL	1,1'-bi-2-naphthol
B/N	Boron-nitrogen
CMA	Carbene Metal Amide
CONPET	Consecutive Photoinduced Electron Transfer
COSMO-RS	Conductor-like Screening Model for Real Solvents
CPA	Chiral Phosphoric Acids
Cz	Carbazole
D-A	Donor-Acceptor
DET	Dexter Energy Transfer
DELs	DNA-Encoded Libraries
DFT	Density Functional Theory
DMF	*N*,*N*-Dimethylformamide
DNA	Deoxyribonucleic acid
DoA	Description of the Action
DPA	Diphenylamine
DTAC	dodecyltrimethylammonium Chloride
EDG	Electron Donating Group
EnT	Energy Transfer
ESR	Early-Stage Researcher
eV	Electron volt
EWG	Electron-Withdrawing Groups
HAT	Hydrogen Atom Transfer

HOMO	Highest Occupied Molecular Orbital
HTE	High-throughput experimentation
HWE	Horner-Wadsworth-Emmons
InIs	Indolizino[3,4,5-*ab*]Isoindole
ITN	Innovative Training Networks
LED	Light Emitting Diode
LSC	Luminescent Solar Concentrator
LSF	Late-stage functionalization
LUMO	Lowest Unoccupied Molecular Orbital
MR-TADF	Multi-resonant Thermally Activated Delayed Fluorescence
PC	Photocatalyst
PenT	Photoinduced energy Transfer
PIns	Pyrrolo[2,1,5-*cd*]Indolizines
PROTAC	proteolysis-targeting chimera
RAEs	Redox-active esters
SCE	Saturated Calomel Electrode
SET	Single Electron Transfer
TADF	Thermally Activated Delayed Fluorescence
TBADT	Tetrabutylammonium decatungstate
TMDS	tetramethyldisiloxane
UV	Ultraviolet
WP	Work package
XAT	Halogen atom transfer

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