# PHOTOCATALYSIS AT THE FRONTIERS OF SYNTHESIS AND BIOLOGY

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Over the last half century, advances in catalysis have reshaped organic synthesis. New activation modes in transition-metal catalysis, organocatalysis and biocatalysis have revealed unprecedented levels of selectivity and efficiency, enabling chemists to access complex molecular architectures with a precision once reserved for nature. Within this trajectory, photoredox catalysis has emerged as a transformative addition [1]. Harnessing visible light to generate open-shell intermediates under mild conditions, it provides reactivity that is often intractable through classical polar or organometallic chemistry. Early studies established the power of single-electron transfer to access radicals with control; subsequent advances in hydrogen-atom transfer [2] and energy transfer [3] opened site-selective C–H functionalisation and new polar-inaccessible transformations. Merging photoredox with other platforms—organic photocatalysts [4], transition metals [5,6] or enzymes [7]—has created dual and synergistic catalysis with growing sophistication, while the rise of enantioselective photocatalysis shows that fleeting radicals can be channelled into precise stereochemical outcomes [8].

The scope of photoredox has also expanded towards biology. Its ability to operate under biocompatible conditions and to manipulate reactive intermediates with temporal precision enables selective editing of biomolecules [9,10]. Such developments reframe photocatalysis as more than a means to construct small molecules: it is also a tool for probing and reprogramming biological systems. Together these advances highlight the complementarity of catalytic strategies. Transition-metal catalysis provides strong-bond activation, organocatalysis unlocks polar reactivity and enzymes remain benchmarks of efficiency. Photoredox adds a new dimension, merging seamlessly with these platforms to expand the synthetic toolbox. Synthesis has thus moved from a craft of molecular construction to an engine for discovery across chemistry, medicine and materials science.

**Our research: inventing new photocatalytic reactivity concepts for the synthesis of complex organic molecules.**

My research program is founded on exploiting the power of reaction design, rooted in deep mechanistic insight and catalytic innovation to drive problem-solving and field-defining discovery in synthetic organic chemistry. At its core is a philosophy that combines bold conceptual thinking with creative chemical invention and seeks to unlock

entirely new reactivity paradigms that shift synthetic logic, expand molecular complexity and inspire transformative applications across chemical and biological domains. My group is focused on inventing ways to build organic molecules by rethinking how carbon–carbon and carbon–heteroatom bonds can be formed, using catalysts to impart novel reactivity. While the scope of our broader research extends to many different aspects of catalyst controlled reactivity, our work in photoredox catalysis is captured across three research themes.

*Solving the alkylamine synthesis problem*. While alkylamines are among the most ubiquitous and valuable functional groups in chemistry, their synthesis is often considered a solved problem. However, classical approaches like reductive amination frequently fail to deliver the modularity and complexity required in many applications. As demand for C($sp^3$)-rich molecules has grown, our group introduced distinct reactivity paradigms through light-driven multicomponent strategies that built alkylamines directly from simple feedstocks. The key intellectual shift lay in reimagining iminium ions, not as polar electrophiles but as linchpins for radical pathways (Fig. A). In the first advance, our work showed that transiently generated iminiums could undergo photocatalytic one-electron reduction to give α-amino radicals, expanding to reactivity once thought inaccessible due to high reduction potentials. It merged a range of alkylamine-types, carbonyls and alkenes in a photocatalytic reaction to deliver complex secondary and tertiary alkylamines in a single step. A carefully designed photocatalytic system reduced the alkyl-iminium—usually out of reach common photocatalysts—forming a structurally and functionally unbiased 'all-alkyl' α-amino radical that added to alkenes, giving linear, branched and spirocyclic products without the need for pre-activation or protecting groups [11]. This strategy has substantially expanded the chemical space accessible through the alkylamine scaffold.

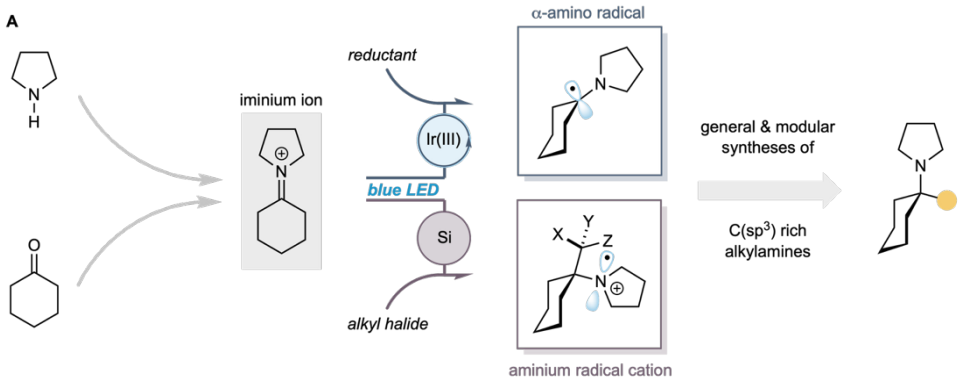


Fig. A. Recasting the reactivity of iminium ions through photochemistry: radical linchpins for a general and modular alkylamine syntheses.

In another innovation, we solved the challenge of direct alkylative amination of carbonyls. Conventional reductive amination, while a powerful amine synthesis strategy, is fundamentally restricted by the need hydride addition to an imine, which limits

structural diversity. Organometallic additions to alkyl-iminium ions fail to deliver a practical higher-order reductive amination process. By developing a light-induced, metal-free radical chain reaction, alkyl radicals—generated from halides using a silane and visible light initiation—add directly to iminiums to form complex amines of all types. Radical addition to unactivated alkyl-iminiums had long been thought intractable due to a lack of stabilization of the radical adduct. Critically, the silane traps the aminium radical cation intermediate after alkyl addition to the iminium ion, kinetically driving the reaction to product. The modular carbonyl alkylative amination method builds a vast range of structurally diverse alkylamine-types and establishes general frameworks for alkylamine synthesis with exceptional breadth and adaptability [12].

*Anion-gated dual catalysis for alkene difunctionalization*. An early research area for our group had merged copper's redox flexibility with the latent aryl-donating power of diaryliodonium salts to unlock access to high-energy aryl intermediates. Distinct from classical palladium-methods, this copper-catalysed arylation platform established novel approaches to hydrocarbon functionalization through catalytically generated aryl electrophiles and led to a suite of versatile transformations that dramatically streamlined the synthesis of complex molecules [13]. Evolving this platform, our group recast copper-catalysed arylation through a radical lens. We introduced a visible-light mediated dual-catalysis system for aryl-azidation of alkenes to construct β-aryl ethylamines, privileged pharmaceutical motifs that are elusive to palladium-based synthesis (Fig. B). The design used two copper catalysts: one channelling diaryliodonium salts into aryl radicals—rather than an aryl electrophile—via photoredox catalysis, mediating addition to an alkene; the other effected azide transfer to the incipient alkyl radical. Redox events were uniquely orchestrated by the azide, introducing a powerful new logic for modular radical cascades.

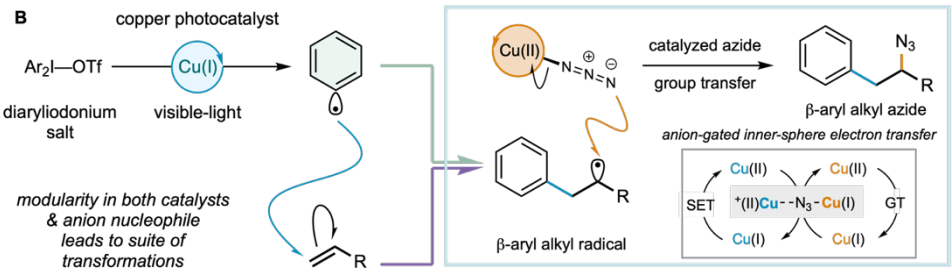


Fig B. Anion-gated dual catalysis: a new activation mode for programmable radical cascades.

It marked a shift in alkene functionalization chemistry as each bond-formation is programmed by a different catalyst, introducing exceptional modularity that accessed a suite of transformations with broad substrate scope and functional diversity. This strategy has been widely adopted, inspiring a field centred on programmable radical cascades. Subsequent studies expanded this "anion-gating" concept beyond azide. Halide ions were shown to play analogous roles, enabling chloro-arylation and related di-functionalisations through precise control of radical capture and group transfer. Key to the success of these ideas was the capacity to interchange the two catalysts, enabling a highly modular and versatile system. Together, these contributions established anion-gated dual catalysis as a

general design principle: simple counterions, once considered spectators, can serve as programmable switches that unify radical photochemistry with the selectivity of transition-metal catalysis [14].

*Structural Editing at the Chemistry–Biology Interface.* Our group has also extended the reach of innovative reaction design principles beyond small-molecule synthesis to address challenges in biomacromolecule functionalization [15]. New chemical tools for precision editing of biomolecules are essential for understanding and manipulating their function and underpin advances in therapeutics, diagnostics and synthetic biology. Applying the principles of catalyst control and mechanistic precision that underpinned our small molecule programs, we have pioneered several transformative methods for selective biomolecule editing in a range of settings. For example, with Professor Balasubramanian, we developed a method to selectively label 6-methyladenosine (m6A), a biologically important epigenetic modification in RNA and DNA [16]. Despite its central role in cellular biology, chemical tools for m6A detection were limited. A distinctive photocatalytic C–H functionalisation strategy was able to target the uniquely reactive N6-methyl group of m6A by abstracting a single hydrogen atom from the N-methyl group in m6A, generating an α-amino radical directly on the nucleobase (Fig. C). An inventive design of the photocatalytic cycle co-released a spin-trapping reagent that intercepted this radical, enabling covalent bioorthogonal labelling. The method is highly selective, distinguishing m6A from canonical bases and the resulting tagged nucleobase can be enriched and analysed, offering a chemical means to study modified nucleic acids. The method underscores the translational potential of photoredox catalysis and has helped launch a growing field at the intersection of chemistry, epigenetics and biology.

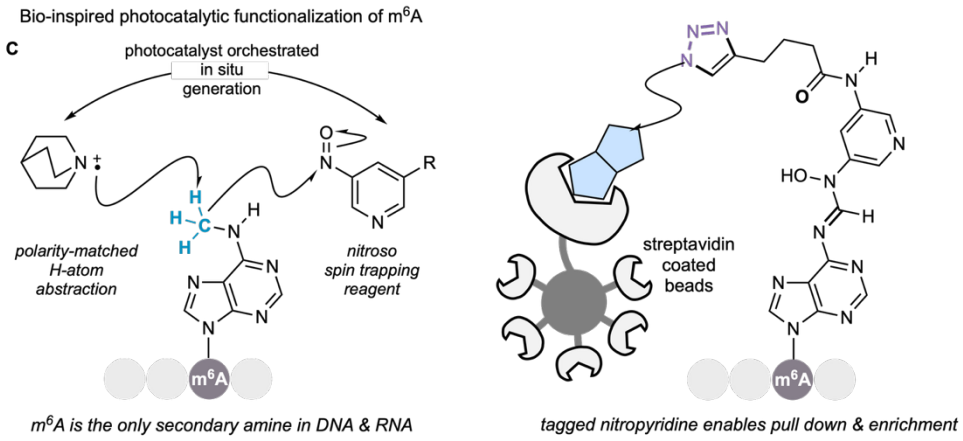


Fig C. Photocatalytic labelling of m6A in DNA & RNA

**Outlook: photocatalysis as an enabler for synthesis-driven biology.**

An exciting frontier for photoredox catalysis and catalyst-controlled reactivity lies at the interface with biology, where new chemistry could transform how we interrogate and

manipulate living systems. The opportunity is not only to adapt existing reactions for biocompatible settings, but to create a genuinely synthesis-driven chemical biology, in which entirely new fields of search are opened by reactivity that nature itself does not provide.

A particularly powerful direction is the selective modification of nucleic acids. Current approaches to genetic editing rely heavily on enzymatic machinery; the prospect of programmable, small-molecule catalysis that could achieve site- or sequence-selective transformations on DNA and RNA is profoundly enabling. Such chemistry could underpin new ways of controlling gene expression, epigenetic state or RNA folding, and might one day deliver synthetic analogues of CRISPR-like precision, but through catalytic reactivity rather than biological editing complexes. In parallel, the development of biomacromolecule editing strategies—capable of remodelling proteins, polysaccharides, or even complex cellular assemblies—would provide tools to reprogramme biological function directly, with the versatility and tunability that only synthetic chemistry can bring.

Achieving this vision will demand a new level of catalyst control in complex systems: reactions that can distinguish between nearly identical functional groups in a crowded macromolecular landscape, operate in aqueous and cellular environments, and be regulated with exquisite spatial and temporal precision. Photoredox catalysis, with its responsiveness to light and its ability to generate open-shell intermediates under mild conditions, offers a natural foundation for such advances. Looking ahead, the bold challenge is not merely to build molecules more efficiently, but to develop catalytic strategies that allow chemists to write new rules for biology itself, forging a future where synthesis is a driver of discovery in medicine, genetics, and beyond.

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## References

1. M. H. Shaw, J. Twilton, D. W. C. MacMillan. *J. Org. Chem*. **81**, 6898 (2016).
2. L. Capaldo, D. Ravelli, M. Fagnoni. *Chem. Rev*. **122**, 1875 (2022).
3. S. Dutta, J. E. Erchinger, F. Streith-Kalthoff, R. Kleinmans, F. Glorius. *Chem. Soc. Rev*. **53**, 1068 (2024).
4. A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, *et. al*. *Chem. Rev*. **122**, 1485 (2022).
5. J. Twilton, C. C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan. *Nat. Rev. Chem*. **1**, 0052, (2017).

6. N. A. Romero, D. A. Nicewicz. *Chem. Rev*. **116**, 10075 (2016).
7. M. A. Emmanuel, S. G. Bender, C. Bilodeau, J. M. Carceller, J. S. DeHovitz, *et. at. Chem. Rev*. **123**, 5459 (2023).
8. S. Mondal, F. Dumur, D. Gigmes, M. P. Sibi, M. P. Bertrand, M. Nechab. *Chem. Rev*. **122**, 5842 (2022).
9. M. Lechner, M. Nappi, P. J. Denemy, S. Folliet, J. C. K. Chu, *et. al. Chem. Rev*. **122**, 1752 (2022).
10. S. D. Knutson, B. F. Buksh, S. W. Huth, D. C. Morgan, D. W. C. MacMillan. *Cell. Chem. Bio*. **31**, 1145 (2024).
11. A. D. Trowbridge, D. Reich, M. J. Gaunt. *Nature* **561**, 522 (2018).
12. R. Kumar, N. J. Floden, W. G. Whitehurst, M. J. Gaunt. *Nature* **581**, 415 (2020).
13. R. J. Phipps. M. J. Gaunt. *Science* **323**, 1593 (2009).
14. A. Bunescu, Y. Abdelhamid, M. J. Gaunt. *Nature* **598**, 597 (2021).
15. M. C. Grocott, M. J. Gaunt. *Nature* **643**, 130 (2025).
16. M. Nappi, A. Hofer, S. Balasubramanian, M. J. Gaunt. *J. Am. Chem. Soc*. **142**, 21484 (2020).

**Keywords**

Photocatalysis; radical reactivity; alkylamines; iminium ion; α-amino radical; dual catalysis; alkene difunctionalization; inner-sphere electron transfer; epigenetics; nucleic acids.