



Recent Advances in Organic Chemistry: Emerging Strategies in Molecular Design, Green Synthesis, and Therapeutic Applications

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Abstract:

Organic chemistry continues to evolve rapidly at the intersection of synthetic methodology, molecular design, and pharmaceutical application. Over the past two decades, the discipline has moved decisively away from stoichiometric, metal- and solvent-intensive transformations toward catalytic, atom-economical, and energy-efficient strategies capable of constructing complex molecular architectures with minimal environmental burden. In parallel, a small number of conceptually transformative design paradigms most notably click and bioorthogonal chemistry, and, more recently, targeted protein degradation using proteolysis-targeting chimeras (PROTACs) have reshaped how chemists approach the construction of bioactive molecules, shifting emphasis from occupying a binding site to engineering a desired biological outcome through selective covalent linkage or induced protein degradation. This review surveys these two convergent threads of modern organic chemistry: emerging strategies for green and sustainable synthesis, including metal-free and photoredox catalysis, C–H activation, and flow chemistry; and molecular design paradigms built on click and bioorthogonal reactions and targeted protein degradation technology. We examine how these methodologies have been translated into pharmaceutical and biomedical applications, from large-scale process synthesis of active pharmaceutical ingredients to click-chemistry-enabled construction of PROTAC degraders now advancing through clinical trials, and we critically assess the methodological, scale-up, and translational challenges that continue to constrain this field. We conclude that the convergence of sustainable synthetic methodology with rationally engineered molecular design represents the most productive current trajectory in organic chemistry, and that continued progress will depend on closing the gap between laboratory-scale innovation and robust, reproducible translation to process and clinical scale.

Keywords: organic chemistry; green chemistry; molecular design; click chemistry; bioorthogonal chemistry; PROTAC; photoredox catalysis; flow chemistry; therapeutic applications

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1. Introduction

Organic chemistry has, since its emergence as a distinct discipline in the nineteenth century, been defined by an evolving relationship between synthetic capability and application: the ability to construct a given molecule reliably, efficiently, and at scale has repeatedly determined which biologically active compounds could progress from laboratory curiosity to industrial or pharmaceutical reality. Numerous Nobel Prizes across more than a century of the field's history, from early work on carbohydrate and purine synthesis through to the 2021 prize for asymmetric organocatalysis and the 2022 prize for click and bioorthogonal chemistry, testify to the continued centrality of new synthetic methodology to the discipline's scientific standing⁸. Two broad and increasingly interconnected trends characterise the current state of the field. The first is a sustained shift toward green and sustainable synthesis, driven both by regulatory and environmental pressure on the chemical and pharmaceutical industries and by the recognition that catalytic, atom-economical methods are frequently also the most step-efficient and cost-effective routes to complex targets. The second is the emergence of new molecular design paradigms – most prominently click and bioorthogonal chemistry, and more recently targeted protein degradation technology – that have expanded the conceptual toolkit available to medicinal and synthetic chemists well beyond the classical framework of designing a small molecule to occupy an enzyme active site or receptor binding pocket.

These two trends are not independent. Many of the synthetic advances discussed in Section 2 (photoredox catalysis, C–H activation, and flow chemistry in particular) have been essential enablers of the molecular design strategies discussed in Section 3, since bioorthogonal reagents, PROTAC linkers, and other structurally demanding chemotypes frequently require exactly the kind of mild, selective, functional-group-tolerant transformations that green and sustainable methodology has been developed to provide. This review accordingly treats green synthesis and molecular design as complementary rather than separate strands of the same broader movement in modern organic chemistry, and traces their convergence through to concrete therapeutic applications in Section 4, before critically examining the field's remaining methodological and translational challenges in Section 5.

From a pharmaceutical industry perspective, this convergence has practical significance beyond its conceptual elegance. The synthetic route used to manufacture a drug candidate is not incidental to its development but frequently determines whether that candidate can be produced economically and reliably at the scale required for clinical trials and, eventually, commercial supply; a synthetically elegant laboratory route that cannot be translated to kilogram or tonne scale within acceptable cost and safety parameters will not reach patients regardless of the quality of the underlying biological hypothesis. The methodological advances surveyed in this review are therefore best understood not merely as academic contributions to synthetic methodology, but as infrastructure that determines which classes of molecule – including the structurally demanding heterobifunctional degraders and bioorthogonally functionalised conjugates discussed in Section 3 – can realistically be developed into medicines.

2. Green Synthesis: Principles and Emerging Strategies

2.1 Foundational Principles

Modern green chemistry rests on two foundational conceptual contributions from the final decade of the twentieth century. Trost's articulation of atom economy reframed synthetic efficiency in terms of the proportion of reactant atoms incorporated into the final product, providing chemists with a simple, quantitative criterion for comparing competing synthetic routes that complements the traditional metric of percentage yield. Shortly afterward, Anastas and Warner's twelve principles of green chemistry spanning waste prevention, atom economy, the use of safer solvents and auxiliaries, energy efficiency, and the design of degradable products, among others provided a systematic framework that has since become the standard reference point against which new synthetic methodology is evaluated for its sustainability credentials. Contemporary reviews of green chemistry in pharmaceutical synthesis continue to organise their analysis explicitly around these atom-economy and waste-reduction principles, applying them to the selection of eco-friendly solvents, catalytic strategies, and sustainable feedstocks in active pharmaceutical ingredient manufacture⁹.

These foundational frameworks have proven durable precisely because they provide criteria that can be applied prospectively, during route design, rather than only retrospectively once a synthesis has already been completed and its environmental footprint measured. A chemist evaluating competing synthetic routes to a given target can, in principle, estimate the atom economy of each candidate route from the balanced reaction equations alone, without needing to first execute the chemistry, allowing sustainability considerations to inform route selection from the earliest stages of synthetic planning rather than being addressed only as an afterthought once a route has already been optimised for yield and selectivity. This prospective applicability is a large part of why atom economy and the twelve principles of green chemistry remain the standard reference frameworks cited across the contemporary literature reviewed in this section, more than two and three decades respectively after their original articulation.

2.2 Metal-Free and Catalytic Strategies

A major recent thrust in green synthetic methodology has been the development of metal-free alternatives to classical transition-metal-catalysed transformations, motivated by concerns over the cost, toxicity, and limited natural abundance of many catalytic metals, as well as the difficulty of removing trace metal residues from pharmaceutical products to meet regulatory specification limits. A comprehensive 2025 review of transition-metal-free coupling methods highlights hypervalent-iodine-mediated and related metal-free coupling strategies that achieve high functional group tolerance while avoiding rare-metal catalysts, together with methods for recycling the aryl iodide by-products these reactions generate, directly addressing both the atom-economy and waste-minimisation principles discussed above³¹⁰. Complementary work has demonstrated metal-free oxidative coupling routes to pharmaceutically relevant heterocycles such as 2-aminobenzoxazoles, imidazoles, and pyrazoles, alongside the use of natural catalysts (including plant-derived extracts), microbial biotransformation, and bio-based solvents such as eucalyptol and ethyl lactate as environmentally benign alternatives to conventional organic solvents⁹. Microwave-assisted synthesis has been shown in several of these studies to further reduce reaction times and energy consumption relative to conventional thermal heating while maintaining or improving yield, illustrating how green methodology can

simultaneously advance sustainability and practical synthetic efficiency rather than requiring a trade-off between the two.

2.3 Photoredox Catalysis and C–H Activation

Photoredox catalysis, in which visible light is used to generate reactive radical intermediates under mild conditions, has become one of the most widely adopted green synthetic strategies of the past decade, particularly in combination with C–H activation methodology that allows direct functionalisation of otherwise unreactive carbon–hydrogen bonds without pre-installing a reactive handle. This combination substantially improves step economy relative to classical cross-coupling approaches that require pre-functionalised coupling partners, since C–H bonds are ubiquitous in organic molecules and their direct, selective functionalisation removes the need for additional synthetic steps to install and later remove directing or activating groups⁴. Dual photoredox/transition-metal catalytic systems have extended this approach further, enabling room-temperature C–H functionalisation reactions, including acylation and related transformations, that proceed efficiently in both conventional batch reactors and continuous flow systems, with flow conditions in several reported cases substantially accelerating reaction rates and improving yields relative to batch processing⁴. Photoredox catalysis has additionally proven valuable specifically in the synthesis of known pharmaceutically active compounds, both as a standalone methodology and in synergistic combination with nickel catalysis, and pioneering work applying continuous flow technology to scale photoredox transformations to preparative and process scale has begun to address one of the historical limitations of photochemical methods, namely the difficulty of efficiently delivering light to reaction mixtures at larger reactor volumes.

Mechanistically, photoredox catalysts function by absorbing visible light to reach an excited state capable of engaging in single-electron transfer with a substrate or co-catalyst, generating radical intermediates under conditions far milder than those required by classical thermal radical-generation methods such as peroxide decomposition or high-temperature homolysis. This mild radical generation is particularly valuable for late-stage functionalisation of complex, densely functionalised pharmaceutical intermediates, where the high temperatures or strongly oxidising or reducing conditions required by older radical methods would risk decomposing sensitive functional groups already present elsewhere in the molecule. Dual photoredox/nickel catalytic systems extend this mild-radical-generation capability further by coupling the photoredox-generated radical with a nickel-mediated cross-coupling step, enabling carbon–carbon and carbon–heteroatom bond formation under conditions that avoid both the strongly basic or acidic conditions of classical cross-coupling and the high temperatures of purely thermal radical chemistry.

2.4 Flow Chemistry and Process-Scale Translation

A comprehensive review of how photoredox catalysis, electrochemistry, C–H activation, reductive coupling, and flow chemistry have been translated from milligram-scale laboratory demonstrations to multi-hundred-gram and kilogram-scale production of active pharmaceutical ingredients and their intermediates documents both the strategic advantages these modern reaction classes offer for streamlining synthetic routes and the substantial chemical and engineering challenges including heat and mass transfer limitations, photon penetration depth,

and reactor design constraints that must be resolved before laboratory-scale innovations can be reliably reproduced at process scale³. This scale-up gap represents one of the central practical challenges discussed further in Section 5, and is a key reason why flow chemistry, which offers superior heat and mass transfer characteristics and more readily accommodates hazardous or highly reactive intermediates through small-volume continuous processing, has become an increasingly standard tool for translating green synthetic methodology from academic demonstration to industrial application.

Flow chemistry's advantages extend beyond heat and mass transfer to encompass improved process safety more generally: because only a small volume of reactive or hazardous intermediate is present in the reactor at any given moment, continuous flow processing substantially reduces the consequences of a reaction excursion relative to batch processing of the same overall reaction at the same production scale, an advantage of particular importance for the exothermic, potentially hazardous transformations including several of the metal-free oxidative coupling and photoredox radical reactions discussed elsewhere in this review that are increasingly central to sustainable pharmaceutical process chemistry. Flow platforms additionally facilitate direct in-line reaction monitoring and real-time process analytical technology integration, allowing reaction parameters to be adjusted dynamically in response to measured conversion or impurity formation rather than relying solely on offline sampling, further improving both the safety and the reproducibility of large-scale syntheses employing these modern reaction classes.

2.5 Biocatalysis and Enzymatic Synthesis

A further green synthetic strategy of growing importance is biocatalysis, in which engineered or naturally occurring enzymes are used to perform selective transformations under mild aqueous conditions that would otherwise require harsh reagents, extreme temperatures, or extensive protecting-group manipulation using classical chemical methods. Microbial biotransformation and whole-cell biocatalytic approaches have been applied directly within green organic synthesis reviews as complements to purely chemical metal-free methodology, illustrating how enzymatic and small-molecule catalytic strategies are increasingly combined within a single synthetic route rather than treated as competing paradigms⁹. The inherent stereoselectivity of enzymatic catalysis is particularly valuable for pharmaceutical synthesis, where a single incorrect stereocentre can render an otherwise identical molecule pharmacologically inactive or, in some documented historical cases, toxic, making biocatalytic methods an increasingly standard component of the green chemist's toolkit alongside the metal-free and photoredox strategies discussed above.

Table 1. Representative emerging strategies in green and sustainable organic synthesis

Strategy	Key mechanism / feature	Principal sustainability benefit
Metal-free coupling	Hypervalent-iodine-mediated and related transition-metal-free bond formation	Avoids rare/toxic metal catalysts; simplifies pharmaceutical purity specification

Strategy	Key mechanism / feature	Principal sustainability benefit
Photoredox catalysis	Visible-light-generated radical intermediates under mild conditions	Ambient temperature operation; reduced energy input
C–H activation	Direct functionalisation of unreactive C–H bonds	Improved step and atom economy; fewer protecting-group steps
Microwave-assisted synthesis	Dielectric heating for rapid, uniform reaction temperature control	Shorter reaction times; reduced energy consumption
Bio-based solvents/catalysts	Plant-derived extracts, microbial biotransformation, natural solvents (e.g., eucalyptol)	Reduced reliance on hazardous petrochemical solvents
Flow chemistry	Continuous processing in small-volume reactors	Superior heat/mass transfer; safer handling of reactive intermediates; scalability

3. Molecular Design Strategies in Modern Organic Chemistry

Alongside these advances in synthetic methodology, organic chemistry has undergone an equally significant conceptual shift in how molecules are designed to achieve a desired biological effect. Figure 1 summarises how the green synthetic strategies discussed in Section 2 converge with the molecular design paradigms discussed in this section to enable the therapeutic applications surveyed in Section 4.

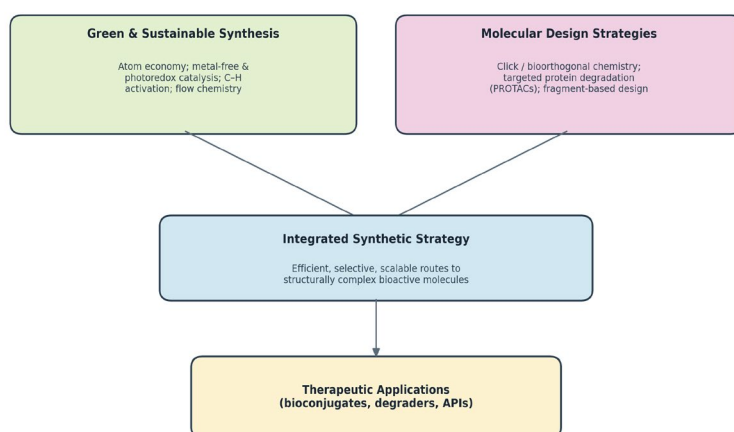


Figure 1. Convergence of green synthesis and molecular design strategies toward therapeutic applications.

3.1 Click and Bioorthogonal Chemistry

Click chemistry, formally defined in 2001 as a class of modular, high-yielding, stereospecific reactions with minimal by-product formation that proceed efficiently under simple reaction

conditions, established a design philosophy centred on reliability and selectivity rather than exhaustive optimisation of a single bespoke transformation for each target molecule¹. The copper-catalysed azide–alkyne cycloaddition rapidly became the paradigmatic click reaction, but its reliance on a copper catalyst limited its use in living systems owing to copper-associated cytotoxicity. This limitation was directly addressed by the development of strain-promoted azide–alkyne cycloaddition using cyclooctyne reagents, which proceeds efficiently under physiological conditions without any catalyst and enabled selective covalent modification of biomolecules on the surface of living cells with no apparent toxicity, establishing the field of bioorthogonal chemistry as a distinct extension of click chemistry principles into live-cell and, ultimately, live-animal settings². The transformative significance of this body of work was recognised by the 2022 Nobel Prize in Chemistry, awarded jointly for the development of click chemistry and bioorthogonal chemistry.

Beyond its original applications in bioconjugation and chemical biology imaging, click chemistry has become a core methodology in medicinal chemistry more broadly, described in a recent review as a “paintbrush” for drug design owing to the versatility with which click and bioorthogonal reactions can be layered onto virtually any synthetic scheme to introduce reporter tags, assemble combinatorial libraries, or covalently link two independently optimised molecular fragments⁷. This combinatorial, modular character is precisely what has made click chemistry so well suited to the construction of the heterobifunctional molecules discussed in Section 3.2.

The click chemistry toolkit itself has continued to expand well beyond the original copper-catalysed azide–alkyne cycloaddition and strain-promoted cyclooctyne variants, now encompassing inverse electron-demand Diels–Alder ligations between tetrazines and strained alkenes or alkynes, sulfur(VI) fluoride exchange chemistry, and photo-cross-linking methodologies that extend bioorthogonal labelling to include light-triggered spatial and temporal control over when and where a given covalent bond is formed. Each of these variants trades off reaction rate, biocompatibility, and functional-group tolerance somewhat differently, giving medicinal and chemical biology researchers a diversified portfolio of click reactions from which to select the variant best matched to a specific therapeutic or diagnostic application, rather than a single one-size-fits-all bioorthogonal reaction.

3.2 Targeted Protein Degradation: PROTACs

Proteolysis-targeting chimeras (PROTACs) represent a qualitatively different molecular design paradigm from classical occupancy-based small-molecule drug design. A PROTAC is a heterobifunctional molecule comprising a ligand for a protein of interest connected via a flexible linker to a ligand that recruits an E3 ubiquitin ligase; by simultaneously engaging both proteins, the PROTAC induces formation of a ternary complex that directs the target protein toward ubiquitination and subsequent proteasomal degradation, achieving pharmacological effect through target elimination rather than through sustained occupancy-dependent inhibition⁶. Because PROTACs must simultaneously present two independent binding pharmacophores connected through an appropriately spaced and oriented linker, they are considerably larger and structurally more complex than conventional small-molecule drugs, and their design and synthesis pose distinct challenges around linker length and geometry optimisation, physicochemical property management, and synthetic step count⁶.

Click chemistry has proven particularly well suited to addressing these PROTAC-specific synthetic challenges. Copper-catalysed azide–alkyne cycloaddition has been used to assemble PROTAC molecules directly from azide-functionalised target-protein ligands and alkyne-linked E3-ligase-recruiting ligands, including in miniaturised, high-throughput “direct-to-biology” formats that allow biological screening of crude click reaction products without intermediate purification, substantially accelerating early-stage PROTAC hit identification⁵. Bioorthogonal click reactions, including the tetrazine–trans-cyclooctene ligation pair prized for its exceptionally fast reaction kinetics, have additionally enabled “click-release” and chemically controlled PROTAC platforms in which the active degrader is assembled or activated selectively within target cells or tissues, improving selectivity for malignant over healthy tissue and thereby addressing a key safety limitation of constitutively active PROTAC molecules⁵.

PROTACs sit within a broader family of induced-proximity therapeutic modalities that has expanded considerably alongside them, including molecular glue degraders, which achieve a functionally similar outcome to PROTACs recruitment of an E3 ubiquitin ligase to a target protein through a single, typically much smaller molecule that stabilises a direct protein–protein interaction rather than bridging two independently drug-like binding pockets with a synthetic linker. Molecular glues avoid several of the physicochemical property liabilities associated with the large size of classical bivalent PROTACs, but their discovery has historically relied more heavily on serendipity than the modular, structure-guided design that click chemistry has enabled for bivalent PROTACs, and rational molecular glue design remains a comparatively less mature methodology than the PROTAC assembly strategies discussed above.

3.3 Toward Rational, Multi-Objective Molecular Design

Taken together, the click/bioorthogonal and PROTAC design paradigms illustrate a broader shift in organic and medicinal chemistry away from single-objective optimisation of binding affinity at one target and toward multi-objective molecular design that must simultaneously satisfy reactivity, selectivity, pharmacokinetic, and, in the case of PROTACs, ternary-complex geometry constraints. Methods reviews focused specifically on accelerating this style of PROTAC drug discovery emphasise the growing role of DNA-encoded library screening and related high-throughput approaches for optimising ternary complex formation, reflecting a broader trend across modern molecular design toward systematic, parallelised experimental strategies capable of navigating this expanded design space more efficiently than traditional one-compound-at-a-time medicinal chemistry iteration⁶.

3.4 Fragment-Based and Computationally Guided Design

A further molecular design strategy that has matured alongside click chemistry and targeted protein degradation is fragment-based drug design, in which screening begins from very small, low-molecular-weight chemical fragments that bind weakly but efficiently to a target, which are then elaborated, linked, or grown into larger, higher-affinity leads. This fragment-based philosophy shares conceptual common ground with PROTAC design in its emphasis on modular assembly of independently characterised molecular pieces, and the two approaches are increasingly used in combination, with fragment-based screening frequently used to

identify the initial target-protein-binding warhead that is subsequently elaborated into a full heterobifunctional degrader⁶. Computational methods, including molecular docking, molecular dynamics simulation, and increasingly machine-learning-based structure and property prediction, are now routinely integrated into this fragment-elaboration process to prioritise which fragment growth vectors and linker geometries are most likely to yield productive ternary complexes or high-affinity binders, reducing the number of physical analogues that must be synthesised and tested experimentally before a viable lead is identified.

4. Therapeutic Applications

4.1 Click Chemistry in Drug Discovery and Bioconjugation

Beyond its role in PROTAC assembly, click and bioorthogonal chemistry has found direct therapeutic application in antibody–drug conjugate construction, in situ combinatorial library screening for enzyme inhibitor discovery, and pretargeted radioimmunotherapy and imaging strategies that exploit the exceptionally fast, bioorthogonal tetrazine ligation to achieve high-contrast, low-background localisation of therapeutic or diagnostic payloads in vivo⁷. The reliability and functional-group tolerance that originally defined click chemistry as a synthetic methodology translate directly into therapeutic advantage in these applications, since bioconjugation reactions performed on complex, sensitive biomolecules such as antibodies must proceed with high selectivity and minimal side-product formation under mild, biologically compatible conditions.

A further, increasingly clinically relevant application of bioorthogonal chemistry is prodrug activation, in which a therapeutic payload is administered in an inactive, click-masked form and subsequently unmasked selectively at the target site through reaction with a second, orthogonally administered click partner. This click-release strategy allows the therapeutic payload to circulate systemically in an inert form, substantially reducing off-target toxicity relative to a constitutively active drug, before rapid bioorthogonal unmasking restores full activity locally at the intended site of action; this same design logic, discussed in Section 3.2 in the specific context of chemically controlled PROTAC platforms, is increasingly being generalised to small-molecule cytotoxics and other payload classes beyond targeted protein degraders.

4.2 PROTACs in the Clinic

Targeted protein degradation has progressed rapidly from a conceptual proof-of-principle to a clinically validated therapeutic modality, with a growing number of PROTAC molecules advancing through clinical trials across oncology and other therapeutic areas⁶. This clinical progress has been enabled directly by the synthetic and molecular design advances discussed in Sections 2 and 3: click-chemistry-based assembly methods have shortened PROTAC hit-to-lead timelines, while a growing methodological toolkit for optimising linker chemistry, ternary complex geometry, and E3 ligase selection has improved the pharmacokinetic and safety profile of clinical-stage degrader molecules relative to early first-generation PROTACs⁶.

4.3 Large-Scale Synthesis of Pharmaceutical Agents

The ultimate test of any new synthetic methodology's therapeutic relevance is whether it can be reliably scaled from milligram laboratory synthesis to the multi-kilogram or larger quantities required for clinical development and commercial manufacture. Documented examples of photoredox catalysis, electrochemical synthesis, C–H activation, and flow chemistry successfully applied at this process scale to produce active pharmaceutical ingredients and key intermediates demonstrate that these green and modern synthetic methods are not confined to academic proof-of-concept demonstrations, but are increasingly integrated into mainstream pharmaceutical process chemistry³. This translation from laboratory to process scale is itself a specialised sub-discipline requiring close collaboration between synthetic and process chemists, chemical engineers, and safety specialists, and represents one of the clearest illustrations of how the green synthesis and molecular design strands of this review converge in practice to deliver therapeutic agents to patients.

Beyond individual reaction-class case studies, the broader pattern documented across this process-chemistry literature is that the reaction classes most readily translated to large scale tend to be those offering the greatest inherent operational simplicity and functional-group tolerance characteristics that, notably, are also central to the original green chemistry principles discussed in Section 2.1 rather than those offering the highest laboratory-scale yield or the most conceptually novel mechanism. This observation reinforces a broader theme of this review: that sustainability-oriented design criteria and practical, scalable manufacturability are frequently aligned rather than competing objectives in modern pharmaceutical process chemistry, even though they are sometimes presented in the literature as separate or even conflicting priorities.

Table 2. Representative therapeutic and translational applications of the molecular design and synthetic strategies discussed in this review

Application area	Underlying methodology	Illustrative outcome / status	Ref.
Antibody–drug conjugates & bioconjugation	Click / bioorthogonal chemistry (CuAAC, SPAAC, tetrazine ligation)	Selective, high-yielding conjugation of payloads to biomolecules under physiological conditions	1,2,7
Targeted protein degradation	Heterobifunctional PROTAC design; click-chemistry-based assembly	Growing number of PROTAC degraders in oncology clinical trials	5,6
Pretargeted imaging/radiotherapy	Fast bioorthogonal tetrazine–TCO ligation	High-contrast, low-background in vivo targeting strategies	7
API process-scale synthesis	Photoredox catalysis, electrochemistry, C–H	Multi-hundred-gram to kilogram-scale production of	3

Application area	Underlying methodology	Illustrative outcome / status	Ref.
	activation, flow chemistry	pharmaceutical intermediates/APIs	
Metal-free heterocycle synthesis	Transition-metal-free oxidative coupling	Access to pharmaceutically relevant heterocycles with reduced metal-residue burden	9,10

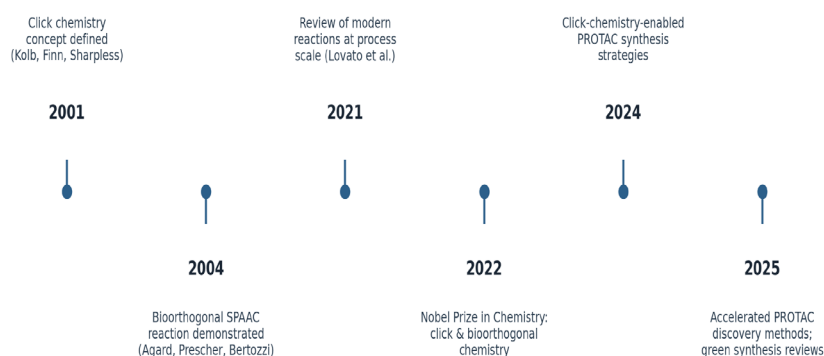


Figure 2. Timeline of key milestones in click/bioorthogonal chemistry and their translation toward pharmaceutical synthesis.

4.4 Illustrative Case Study: From Click Reaction to Clinical Degradation

The trajectory from the original definition of click chemistry in 2001 through to click-chemistry-enabled PROTAC assembly platforms reaching clinical evaluation two decades later provides a particularly clear illustration of how a foundational synthetic methodology advance can propagate through multiple intermediate stages to eventual therapeutic application. The initial 2001 definition of click chemistry criteria—modularity, wide scope, high yield, and simple reaction conditions—was motivated primarily by combinatorial chemistry and materials science applications rather than any specific therapeutic target¹. The subsequent development of copper-free, strain-promoted variants in 2004 specifically to enable use in living systems represented the critical translational step that made click chemistry compatible with biological and, eventually, therapeutic application². Only after this bioorthogonal extension, and after roughly two additional decades of parallel methodological development in targeted protein degradation, did the specific convergence of click chemistry with PROTAC assembly discussed in Section 3.2 emerge as a distinct, clinically relevant application area. This extended, multi-stage translational pathway, summarised in Figure 2, is typical of how foundational organic chemistry methodology advances generally propagate to therapeutic application, and offers a useful cautionary perspective on the timescales realistically required

for newly emerging synthetic strategies, including several of those surveyed in Section 2, to achieve comparable clinical impact.

5. Challenges and Limitations

Despite substantial progress across both the green synthesis and molecular design strands surveyed in this review, several methodological and translational challenges continue to constrain the field. These challenges cluster around three broad themes: the difficulty of reliably scaling laboratory-optimised methodology to process and manufacturing scale; the distinctive physicochemical and design challenges posed by the new, structurally complex molecular classes that click chemistry and targeted protein degradation have made accessible; and the regulatory and analytical infrastructure gap that these genuinely novel chemotypes have opened up relative to the well-established frameworks developed for classical small-molecule drugs.

A further, cross-cutting challenge is economic: many of the green synthetic strategies discussed in Section 2, particularly specialised photoredox catalysts, engineered biocatalysts, and continuous-flow reactor infrastructure, require significant capital investment and specialised technical expertise that may be more readily available to large pharmaceutical manufacturers than to smaller academic or generic-drug-focused organisations, raising the possibility that the sustainability benefits of these methods could be realised unevenly across the pharmaceutical industry unless supported by broader technology-transfer and training initiatives.

Table 3. Principal challenges in translating emerging organic chemistry strategies to therapeutic application

Challenge	Description	Illustrative consequence
Laboratory-to-process scale-up gap	Photoredox, electrochemical, and C–H activation methods face heat/mass transfer and photon-penetration limitations at larger reactor volumes	Promising laboratory-scale routes may require substantial re-engineering, or prove impractical, at manufacturing scale
PROTAC physicochemical properties	Heterobifunctional PROTACs are large, exceed classical drug-likeness rules, and often show poor oral bioavailability	Limits the therapeutic areas and administration routes accessible to first-generation degrader molecules
Linker and ternary-complex optimisation	PROTAC activity depends sensitively on linker length, rigidity, and resulting ternary complex geometry, which is difficult to predict a priori	Extensive empirical optimisation often required; limited generalisable design rules across target classes
Metal-free method scope limitations	Transition-metal-free coupling methods, while reducing metal burden, can have narrower	May not be directly substitutable for metal-catalysed steps in existing

Challenge	Description	Illustrative consequence
	substrate scope than established metal-catalysed methods	synthetic routes without re-optimisation
Bioorthogonal reagent stability and kinetics	Some bioorthogonal reagents (e.g., certain cyclooctynes) show limited in vivo stability or off-target reactivity at achievable concentrations	Constrains dosing and pharmacokinetic design of bioorthogonally assembled therapeutics
Regulatory and analytical complexity	Novel chemotypes (degraders, click-assembled conjugates) require new analytical and regulatory frameworks distinct from those developed for classical small molecules	Longer, more complex development and approval pathways for first-in-class agents

6. Future Directions

Several directions appear likely to shape the next phase of development in this field. First, continued integration of flow chemistry with photoredox, electrochemical, and C–H activation methodology is likely to remain the primary route by which laboratory-scale green synthetic innovations are translated to process scale, given flow chemistry's demonstrated advantages in heat/mass transfer and safe handling of reactive intermediates³. Second, further refinement of click-chemistry-based and high-throughput “direct-to-biology” PROTAC assembly and screening methods is likely to continue accelerating early-stage degrader discovery, potentially extending targeted protein degradation technology to a wider range of therapeutic targets and disease areas beyond its current concentration in oncology⁵. Third, continued mechanistic and structural studies of ternary complex formation should progressively improve the predictability of PROTAC linker design, reducing current reliance on largely empirical optimisation^{6,11}.

Fourth, expanding the substrate scope and functional group tolerance of metal-free coupling methodology, including through continued development of recyclable hypervalent-iodine and related reagent systems, will be important for these methods to more fully substitute for established metal-catalysed transformations across a broader range of pharmaceutical synthetic routes¹⁰. Finally, closer integration between synthetic methodology development and downstream regulatory and analytical science anticipating the characterisation and quality-control requirements of novel chemotypes such as degraders and bioorthogonally assembled conjugates earlier in the discovery process is likely to shorten the translational timeline from first synthetic demonstration to clinical application for the next generation of molecular design paradigms that will inevitably follow click chemistry and targeted protein degradation¹²⁻¹³.

Achieving these goals will also depend on continued investment in training synthetic organic chemists who are equally fluent in green process chemistry, structural biology, and pharmacokinetics, since the multi-objective design problems posed by PROTACs and related heterobifunctional molecules increasingly require synthetic chemists to reason jointly about

reactivity, physicochemical property space, and target biology rather than treating synthesis and biological evaluation as sequential, separately staffed activities. Academic organic chemistry curricula have historically emphasised synthetic methodology and total synthesis largely in isolation from pharmacology and process engineering; closing this training gap is likely to be as consequential for the field's continued translational productivity as any single new reaction or reagent class discussed in this review ¹⁴.

7. Conclusion

Organic chemistry's continued vitality as a discipline rests on the ongoing, mutually reinforcing development of synthetic methodology and molecular design strategy. Green and sustainable synthetic methods metal-free and photoredox catalysis, C–H activation, biocatalysis, and flow chemistry have made complex molecular targets accessible with substantially reduced environmental burden and, in many documented cases, at process scales sufficient for pharmaceutical manufacture. In parallel, click and bioorthogonal chemistry and targeted protein degradation technology have expanded the conceptual space of molecular design beyond classical occupancy-based small-molecule inhibition, enabling therapeutic strategies selective bioconjugation, pretargeted imaging, and induced protein degradation that were not accessible to earlier generations of medicinal chemistry. The clinical translation of PROTAC degraders and the process-scale application of modern green synthetic methods to active pharmaceutical ingredient manufacture demonstrate that this convergence of sustainable methodology and rational molecular design is already yielding real therapeutic impact, even as scale-up, physicochemical property, and regulatory challenges continue to constrain the pace of further translation. Continued progress will depend on treating synthetic methodology and molecular design not as separate subfields but as an integrated discipline, in which advances in one continually enable and are shaped by ambitions in the other.

As the field looks toward the next generation of synthetic and design paradigms beyond those surveyed in this review, the two-decade trajectory from the original definition of click chemistry to clinically advancing PROTAC degraders, traced in Section 4.4, offers an instructive benchmark against which to judge the pace of translation for emerging methodologies. Organic chemistry's demonstrated capacity to convert a fundamentally new synthetic or conceptual insight into genuine therapeutic impact, repeatedly and across multiple independent methodological traditions, remains the discipline's strongest argument for continued sustained investment in foundational synthetic methodology research, even where the eventual clinical application is not yet apparent at the time a new reaction or design principle is first reported.

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