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Grand challenges in chemical biology from the perspective of organic chemical synthesis

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Introduction

Living systems perform chemical transformations under conditions and with precision that synthetic chemistry cannot reach. As such, the field has increasingly moved toward bioinspired and bio-integrated strategies, including biocatalysis, chemoenzymatic cascades, metabolic engineering, and bio-orthogonal chemistry, each of which still relies heavily on chemical biology. This is a rapidly evolving discipline that uses molecular tools and principles to study and manipulate biological systems. At the heart of this field lies organic chemical synthesis, which provides fundamental capabilities for constructing and modifying molecules that can probe, modulate, or mimic biological functions.

Organic synthesis gives access to small molecules, natural product analogues, molecular probes, modified biomacromolecules, bioconjugation, and non-natural building blocks that may be not accessed by biosynthetic or enzymatic methods alone. It also provides the structural precision necessary for mechanistic studies and therapeutic development.

However, designing synthetic routes compatible with biological systems poses distinctive challenges: mild conditions, aqueous environments, functional group tolerance, and demands for stereoselectivity, scalability, and environmental sustainability. In this perspective of the grand Challenges series, we discuss the major challenges and emerging opportunities that define chemical biology through the lens of organic synthesis.

Challenges at the interface between chemical biology and organic synthesis

Synthetic methods are being developed or adapted to meet biological requirements, and to intersect with biological machinery to unlock new directions in therapeutic design, molecular imaging, and sustainable production of complex molecules. Recent literature especially underscores the urgency of these challenges (Reisenbauer et al., 2024; Petrovskii et al., 2024; Moody and Kilpatrick, 2018) and reveals gaps in methodology and implementation.

Libraries of chemically-diverse, small organic molecules furnished by synthetic organic chemistry are widely used to investigate biological systems by acting as tools to manipulate biological targets like receptors or enzymes. They can be used to understand function, phenotypic effects, identify pathways, and monitor processes at a molecular, cellular, or whole-body level. In the quest for bioactive compounds, diversity-oriented synthesis is capable of creating molecular entities starting from simple building blocks, and represents

an efficient strategy to significantly broaden the chemical space explored by DNA-encoded libraries (Lenci et al., 2021). This classic approach still presents challenges. One limitation of small molecules is their frequent lack of specificity for a single target protein. This can lead also to unexpected (dose-dependent) toxicity. Another challenge is that there is an inherent trade-off between the level of throughput and data quality in large-scale data collection.

Biocatalysis is the process of using biological catalysts, primarily enzymes or whole cells, to promote chemical reactions. Natural enzymes catalyse reactions with high selectivity under mild, environmentally benign conditions. However, extending enzyme utility to non-natural substrates and reactions such as C–H activation, or oxidative coupling, remains challenging. Mimicking these transformations with synthetic catalysts, including organocatalysts or artificial metalloenzymes, also presents obstacles in terms of selectivity, scalability, and compatibility with the principles of Green Chemistry. Nevertheless, enzymes can be manipulated by side-chains derivatization or by introduction of non-canonical residues, to perform difficult or previously impossible reactions (Giri et al., 2021). Advances include biocatalytic amide bond formation, use of hydrolases and ATP-dependent enzymes in nonaqueous systems, and integration of enzymes into multi-step synthetic cascades (Reisenbauer et al., 2024; Kroutil et al., 2021). Frances Arnold received the 2018 Nobel Prize in Chemistry for her work in directed evolution of enzymes. This technique uses the principles of evolution, i.e., random gene mutation and natural selection, to engineered enzymes and improve their performances (Arnold and Volkov, 1999). This gave access to new biocatalysts, new products and processes for pharmaceuticals, renewable fuels, and more sustainable industrial applications.

Biomimetic reactions are chemical reactions that mimic the processes and strategies found in nature, e.g., those catalyzed by enzymes. These processes are designed to imitate biological systems to create more efficient and selective synthetic pathways for chemical transformations. This approach involves studying how nature achieves specific reactions or synthesizes complex molecules and then applying those principles in organic synthesis. Biomimetic catalysts aim at reproducing active site features while maintaining robustness and recyclability. These efforts align with Green Chemistry goals (Anastas and Warner, 1998), especially solvent safety, atom economy, and waste minimization, but require continued innovation in catalyst design and process integration. Challenges in designing biomimetic reactions range from technical difficulties, like controlling stereoselectivity and achieving high yields, scalability issues for industrial production, and the use of expensive or environmentally hazardous reagents, to complexity in translating natural systems into laboratory protocols.

The biomimetic synthesis of natural products employs principles from biomimicry, applying inspiration from biogenetic processes to design synthetic strategies that mimic biosynthetic processes. Natural products are a rich source of complex bioactive structures (Seshadri et al., 2025). Genome mining, pathway refactoring, and heterologous expression offer routes to rediscover and produce natural products. This includes peptides with site-specific modifications, functional proteins, oligonucleotides (e.g., siRNA, mRNA), glycoproteins, lipids, and synthetic biopolymers. One major challenge in transforming natural products into viable medicines is the difficulty in acquiring adequate amounts of the original compounds and their structural variants to support further research, let alone large-scale manufacturing. Additionally, natural products are finite, and their consistent availability is threatened by resource depletion and environmental variability. To address these challenges, researchers in both academia and industry have long pursued synthetic strategies to ensure a reliable and sustainable supply of these valuable compounds.

Hence, organic synthesis remains essential for functional diversification and analog generation beyond the scope of biosynthesis. As a consequence, the field of organic chemistry has recently witnessed a rapid rise in the use of chemoenzymatic strategies for the synthesis of complex molecules. The chemoenzymatic approach combines enzymatic and chemical steps in a complementary fashion, installing complexity via enzymes, then elaborating via synthesis, or *vice versa*. Chemical steps allows for the possibility to generate analogues with modified scaffolds.

In the last two decades, there has been an increased interest in photobiocatalytic strategies for organic synthesis, i.e., enzymatic processes that utilize electronically excited states accessed through photoexcitation (Emmanuel et al., 2023). This hybrid strategy demands careful coordination of solvents, protective groups, and reaction conditions. Combining chemical synthetic steps with enzyme catalysis can improve access to medicinally relevant natural products. However, enzymes only catalyze a small subset of organic transformations and designing novel non-natural transformations using biological systems remains non-trivial. Challenges include pathway optimization, enzyme engineering, and coupling biosynthetic routes with chemical transformations to produce novel compounds (Renata, 2025; Li et al., 2020).

Bioorthogonal chemistry refers to chemical reactions that can occur within a living organism without interfering with its natural biochemical processes. Within the field of bioorthogonal reactions, click reactions are defined according to a set of stringent criteria, which include modularity, wideness in scope, high yield, stereospecificity, and the generation of inoffensive by-products. Bioorthogonal chemistry and in particular click chemistry consent selective reactions in biological systems, critical for *in vivo* imaging, drug delivery, and prodrug activation (Delplace, 2024). This relevance has been acknowledged in 2022, when C. R. Bertozzi, M. Meldal and K. B. Sharpless received the Nobel Prize in Chemistry for their studies. Organic synthesis is central to designing reagents with fast kinetics, minimal toxicity, and functional group tolerance under physiological conditions. Recent developments in tetrazine ligations, strained alkynes, and light-activated or redox-triggered reactions reflect progress.

The biggest challenge is represented by translation from model systems to living organisms and in particular to humans for clinic applications (de Roode et al., 2025). Performing a reaction in a chemical laboratory is clearly different from delivering a reaction in a living patient. High reactivity of a biorthogonal system is therefore crucial to obtain sufficient reaction yields at medically relevant concentrations within the available reaction time. Also, for reagents with a too limited stability or circulation time, reaction rate of the reagents must be rapid enough to consent to elicit the desired effect. To achieve maximum reaction yields *in vivo*, a

reaction must reach full conversion within the available time. The time required for a reaction to be completed is determined by the reaction rate and the concentration of the reagents, and this depends on pharmacokinetic properties of both reagents, which dictate the *in vivo* behavior in terms of absorption, distribution, metabolism, and excretion. Closely linked to available reaction time, the stability of the reactants is another relevant factor when considering the *in vivo* application of bioorthogonal chemistry. Another factor influencing the success of a bioorthogonal reaction *in vivo* is the bioavailability of the reaction components, i.e., the degree at which the components are able to access the circulation and reach the target area in the body of a patient unencumbered. All these factors influencing the applicability of biorthogonal chemistry *in vivo* are closely dependent on a drug's chemical structure, hence, all translating into challenges for synthetic organic chemistry.

Synthetic organic chemistry offers opportunities to design and construct precise three-dimensional structures with tailored functionalities that address critical needs in biochemistry (Wang et al., 2020). Metal-organic frameworks (MOFs), composed of metal ions coordinated to organic ligands, exemplify this potential by providing highly ordered, porous architectures that can be finely tuned for applications such as drug delivery, bioimaging, and biosensing (Abánades Lázaro, 2024). Not surprisingly, the Nobel Prize in Chemistry 2025 was awarded to S. Kitagawa, R. Robson and O. M. Yaghi for the development of MOFs. Their modularity allows incorporation of functional groups and active sites, enabling highly specific interactions within biological environments. However, despite their promise, significant challenges remain. The stability of these organic-inorganic scaffolds under physiological conditions can be limited, often compromising their integrity and performance *in vivo*. Achieving biocompatibility and minimizing toxicity require careful ligand and metal selection, while maintaining precise control over framework assembly at the nanoscale is technically demanding. Furthermore, scalable and reproducible synthetic methods remain a hurdle for translating these materials from laboratory curiosities to practical biomedical tools.

Conclusion

Organic chemical synthesis lies at the core of chemical biology, not merely as a supporting tool but as a primary engine of molecular innovation. From designing enzyme-compatible substrates to constructing non-natural molecules that interrogate or modulate biological systems, synthetic chemistry continues to shape the questions and capabilities of biological research. Several *in vivo* applications of hybrid biologic-synthetic processes have been reported in recent years. Although to date very few have been clinically approved, ample preclinical studies have been performed, and some of these concepts are already in clinical trials. Many of the grand challenges in health, sustainability, and industrial innovation cannot be solved without innovations in synthetic methodology.

To further strengthen the impact of chemical biology from a synthetic perspective, future efforts must prioritize: scalable, green synthetic routes that minimize waste and use renewable inputs, including non-precious metal catalysts, solvent-friendly conditions, or solvent-free transformations; deeper integration of chemical and enzymatic steps, including multi-step cascades and hybrid radical/enzyme processes; rapid and selective reactions for *in vivo* use, especially those suitable for therapeutic or diagnostic applications, which require probe stability, fast kinetics, and low toxicity; engineering enzymes and metabolic pathways that cooperate with chemical transformations, including tailoring for non-natural substrata or unnatural cofactors; machine learning and computational tools to guide synthetic planning, reaction design, and outcome prediction in biologically relevant settings.

By facing these challenges, organic synthesis will not only continue to support but expand the horizons of biological chemistry, contributing decisively to scientific discovery, human health, and sustainable innovation.

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