

Modern Synthetic Chemistry: Trends and Perspectives

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Abstract

Synthetic organic chemistry has progressed substantially during the last two decades through a combination of new catalytic modes, sustainable strategies, and automation. In this review article, key advances in modern synthetic chemistry are surveyed. First, progress in catalysis, both transition-metal and organocatalysis, is discussed – with an emphasis on their role in enabling highly selective and enantioselective bond formations. Additionally, photoredox and electrochemical approaches are highlighted for their ability to generate reactive radicals under exceptionally mild and green reaction conditions. More recently, advances in C–H bond activation and late-stage functionalization have opened the possibility to directly modify unactivated C–H bonds and streamline the synthesis of complex molecules. In terms of sustainable chemistry, methods and approaches that minimize waste – including the use of benign solvents and/or reduced E-factors – have been actively pursued and biocatalysis and flow processing play important roles. Furthermore, the use of continuous-flow reactors, high-throughput automation, and artificial intelligence/machine learning (AI/ML) approaches have facilitated the acceleration of reaction development and scale-up. In this context, the development of biocatalysis strategies for small-molecule synthesis and its associated challenges are discussed. A number of illustrative figures (e.g. reaction schemes) are presented throughout the review to highlight various concepts.

Keywords : *Synthetic chemistry; Catalysis; Photoredox; C–H activation; Sustainable chemistry; Flow chemistry; Automation; Biocatalysis.*

Introduction

Modern synthetic organic chemistry plays a crucial role in materials, pharmaceuticals and chemical technologies. The modern synthetic laboratory combines a number of classical glassware (e.g. round-bottom flasks) with state-of-the-art (and automated) reactor systems and robotics to achieve precise, efficient and high-throughput synthesis (see Figure). The modern synthetic chemist is faced with the need for more complex target molecules, faster synthetic routes, and lower environmental impact. A number of new reaction strategies have therefore emerged to address these demands. For example, transition-metal catalysis and organocatalysis provide ways for forming bonds in a highly efficient and stereocontrolled manner, and without the need for stoichiometric reagents. Visible-light photoredox and electrochemical methods generate radical and ionic intermediates under very mild (often “traceless”) reaction conditions – using light or electricity instead of traditional harsh chemical reagents. C–H bond functionalization techniques allow for the late-stage diversification of complex scaffolds – without the need for prefunctionalized starting materials. Additionally, the principles of green chemistry – and the minimization of waste and hazardous reagents – are being applied through solvent innovations (e.g. water and bio-solvents), recyclable catalysts, and flow processing. Automated and computational methods (e.g. AI/ML) are now used to guide and facilitate experiment planning and optimization. In this manuscript, these topics are discussed in detail and analyzed in terms of the current state of “modern” synthesis. A number of key advancements are grouped under thematic sections, and a brief overview of challenges and future outlooks are discussed. Table compares key synthetic methods and a timeline of landmarks in the field is given.

Major Advances in Modern Synthetic Chemistry

The last few decades have seen an explosion of new synthetic capabilities and methods. Cross-coupling reactions (Suzuki–Miyaura, Buchwald–Hartwig, etc.) have become routine to enable efficient C–C and C–N bond formations, thereby dramatically expanding the accessible molecular space. Multicomponent and cascade reactions allow for the formation of multiple bonds in one operation. Photochemistry – once an esoteric niche – is now widely used through

the advent of photocatalysis. Streamlined synthesis is a central theme: chemists aim to minimize the number of steps and avoid protecting/deprotecting sequences. For example, C–H activation technology means that inert C–H bonds can be used directly, without the need for pre-activated starting materials. Moreover, computational and data-driven methods (e.g. machine learning) complement experimental innovation: predictive tools are now used for designing and optimizing synthetic routes. In short, the field has evolved from trial-and-error towards a rational, algorithm-aided discovery paradigm.

A unifying theme is sustainability. Green chemistry metrics (E-factor, atom economy, solvent greenness, etc.) now drive method development. Catalytic processes (versus stoichiometric) dominate new route design. Renewable feedstocks (biomass, CO₂) and enzymatic catalysts are being incorporated wherever possible. In parallel, advances in flow chemistry and automation allow safer, scalable and more reproducible synthesis. Overall, these advances interlock: for instance, flow reactors are ideal for photoredox or electrochemical reactions (which often require precise light or electrode configurations), and AI-driven algorithms can control continuous processes in a closed loop. Figure (below) shows a timeline of some landmark milestones in synthesis (from Wöhler’s urea synthesis to recent Nobel-winning methods).

After a review of these general trends, key areas will be examined in detail.

Table : Comparison of Key Synthetic Methods

Method	Advantages	Limitations	Typical Applications
Transition-Metal Catalysis (Pd, Ni, Rh, etc.)	Broad substrate scope; high activity and selectivity for C–C/C–X coupling; mature ligand designs	Requires expensive/toxic metals (cost, waste); ligand development needed; sometimes harsh conditions	Cross-coupling (biaryl, C–N, C–O bonds); hydrogenation; olefin metathesis
Organocatalysis (small organic catalysts, e.g. L-proline, imidazolidinones)	Metal-free; often operationally simple; high enantioselectivity in many cases	Typically lower reaction rates (higher catalyst loading); limited to certain functional groups; fewer examples of new bond types	Asymmetric aldol, Michael, Mannich, and cyclization reactions
Photoredox Catalysis (visible-light, photoredox catalysts)	Uses light as a clean “reagent”; accesses radical intermediates under very mild (often room-temperature) conditions; can be tuned by photocatalyst choice	Requires specific light sources and photocatalysts; scale-up and light penetration can be challenging; sensitivity to oxygen/water (sometimes)	C–H functionalization (decarboxylative, HAT alkylation), fluoroalkylation, photoredox–Ni dual catalysis for cross-couplings
Electrochemical Synthesis (eChem)	Electrons serve as reagents (no stoichiometric oxidant/reductant waste); reaction tunability via potential; often very green (water as solvent possible)	Needs electrochemical setup; limited substrate solubility/electrode compatibility; over-reductive coupling; complex mixtures possible	Oxidative dearomatization, alkene/alkyne oxyfunctionalization, reductive coupling, electrogenerated H ₂ as byproduct
C–H Activation & LSF (direct functionalization)	Step-economy by using C–H bonds directly; late-stage modification of	Often requires directing groups or catalysts with specific ligands; site-	Aromatic/alkyl C–H arylation, alkylation, amination; late-stage

Method	Advantages	Limitations	Typical Applications
	complex molecules (drug lead diversification); reduces need for functional group interconversions	selectivity can be low in polyfunctional substrates; sensitive catalyst cost or stability issues	fluorination or oxygenation of drug-like molecules
Biocatalysis (Enzymatic)	Ultra-high chemo-, regio- and enantioselectivity; very mild (ambient) conditions; often water or benign solvents; renewable catalysts	Narrow substrate scope (enzyme specificity); may require engineered enzymes; stability and scale-up (immobilization) issues	Asymmetric reductions, transaminations, hydrolyses; stereo-defined functionalizations; telescoped multi-step sequences (enzymes often cascade)
Flow Chemistry (technique)	Excellent heat/mass transfer; safer handling of hazardous reagents (high pressure/temperature possible); easy scale-up by run-time extension; ideal for photochemical and multi-step telescoped syntheses	Initial equipment cost; need to optimize mixing and flow parameters; solid handling can be tricky; not all batch reactions translated directly	Multi-step continuous syntheses of APIs; photochemistry (enhanced light penetration); on-demand production (e.g. ¹⁸ F radiotracers); process intensification

Catalysis and Organocatalysis

Catalysis is the workhorse of modern synthesis, where transition-metal catalysts (e.g. Pd, Ni, Cu, Rh, etc.) enables couplings and bond-forming reactions that would otherwise be very difficult or impossible. Such catalysts often allow for reactions to proceed under milder and more atom-economical conditions than classical methods. For instance, Pd- and Ni-catalyzed cross-couplings (Suzuki, Negishi, etc.) have become routine routes to biaryls and sp^2 – sp^2 bonds. Asymmetric metal catalysis (e.g. chiral Rh or Ru in hydrogenation) provides a direct path to enantioenriched products with high enantioselectivities. However, metal catalysts can be toxic or expensive and require removal/purification after reaction. Research in this area includes development of cheaper base metals (Fe, Co, Ni) and ligandless “green” protocols.

In parallel, organocatalysis has become an important complement to metal catalysis (see section on photoredox as well). A major breakthrough occurred in the early 2000s (with iminium/enamine catalysis by MacMillan, List, etc.) and the 2021 Nobel Prize was awarded to MacMillan and List for their work in organocatalysis. These small “organic” catalysts (e.g. proline, chiral amines, N-heterocyclic carbenes) often use readily available, non-metallic materials and operate under mild, neutral conditions. Organocatalysis is prominent in asymmetric C–C bond formations (aldol, Mannich, Michael additions) and has been extended to cascade/domino reactions. Limitations include generally higher catalyst loadings and narrower reaction scope (many organocatalysts perform best in protic solvents, carbonyl chemistry, etc.). However, the metal-free nature and the tunability of organocatalysts (e.g. designing bifunctional catalysts for H-bonding) make them attractive for sustainable synthesis.

A growing trend is to employ dual catalysis – combining organo- and metal catalysts – in tandem. For example, a metal catalyst may first activate a substrate and an organocatalyst may impart enantioselectivity. In all cases, catalysis dramatically improves the “green” profile: reactions can often be run at lower temperatures and with catalytic reagent amounts, thus reducing E-factors and waste. Indeed, Alvaro (2025) notes that enzymatic catalysis (a form of biocatalysis) “achieve[s] significantly lower E-factors” by eliminating hazardous reagents. Table (above) summarizes key pros and cons of catalytic methods.

Photoredox and Electrochemical Synthesis

Photoredox catalysis and electrosynthesis are two strategies that use external energy sources for driving reactions. Photoredox chemistry uses visible light (usually LEDs) to excite a photocatalyst, which subsequently undergoes single-electron transfers to substrates. A hallmark of photoredox methods is the mildness – as Akita (2025) observes, “by simply irradiating with visible light...organyl radicals can be generated under very mild reaction conditions”. This enables access to radical intermediates and unusual bond formations without heating or strong reagents. For example, photoredox-driven decarboxylative coupling allows aryl radicals to form from simple carboxylic acids (decarboxylation), enabling C–C bond formation under neutral conditions. Photoredox catalysis has powered breakthroughs in late-stage functionalization (adding tags to complex molecules) and fluoroalkylation (installing CF_3 groups) by leveraging the versatility of radical chemistry.

Electrochemical synthesis (electrosynthesis) uses an electric potential to directly oxidize or reduce organic substrates, often in lieu of chemical oxidants or reductants. The principle is similar: electrons are reagents. One advantage is maximal atom economy – no stoichiometric chemical reagent is needed. For instance, oxidative electrochemical C–H functionalization can directly install nitrogen or oxygen by anodic oxidation, with only H_2 or benign byproducts formed. Electrochemistry also allows for precise control by tuning the electrode potential and can generate highly reactive ions or radicals at will. However, specialized electrochemical cells and electrodes are required and mass-transfer limitations can complicate scale-up. A notable example is Baran’s 2017 Science report (electrochemical C–H oxidation for amination), which illustrates how carefully designed electrolytic systems can mimic traditional redox reactions in a greener way (using protons as the terminal oxidant).

Electrochemistry and photochemistry can be combined (photoelectrocatalysis) or used in sequences. In practice, photoredox catalysis has seen more rapid growth for small-molecule synthesis (driven by readily-available LED lamps), but electrosynthesis is becoming increasingly prominent in sustainable process chemistry (avoiding heavy-metal waste). Both fields contribute to the vision of traceless redox methods: oxidation/reduction steps leave no chemical footprint beyond the product of interest.

C–H Activation and Late-Stage Functionalization

A transformative goal in synthesis is to use C–H bonds directly as functional handles. C–H activation techniques aim to replace a C–H bond with a C–C, C–N, or C–X bond in one step, bypassing pre-functionalized starting materials. This strategy provides tremendous economy, with fewer steps and less waste. Early successes used chelating groups to activate aromatic $\text{C}(\text{sp}^2)\text{--H}$ bonds (e.g. with a Pd catalyst activates a nearby aryl C–H). More recently, innovative methods have expanded scope to aliphatic $\text{C}(\text{sp}^3)\text{--H}$ bonds. For example, ligand-controlled catalysts and radical hydrogen-atom-transfer (HAT) reagents now allow for site-selective activation of otherwise inert C–H bonds. A noteworthy advance is the use of photocatalytic HAT reagents. Ang and co-workers (2024) review pyridine N-oxides that, under light, abstract a hydrogen atom from alkanes to form radicals. These reagents can be tuned (by their structure) to favor one C–H bond in a complex molecule, enabling targeted late-stage functionalizations (LSF) of pharmaceuticals or natural products. Ang notes these N-oxides are “cost-effective, tunable and applicable in (heterogeneous) catalysis” and pivotal for late-stage functionalization.

In addition to photochemical HAT, directed C–H activation (using transition metals) continue to advance. New catalysts and directing templates achieve remote selectivity: for example, an amide tether or transient ligand can guide a metal to a meta or para C–H bond. Late-stage functionalization has become a key concept in medicinal chemistry: by performing a few C–H activations near the end of a synthetic sequence, libraries of analogues can be rapidly generated from common intermediates. This approach reduces the need for de novo synthesis of each analogue and is aided by modern C–H activation methods (both catalytic and radical). However, challenges remain in achieving broad selectivity rules for C–H (especially among many C–H bonds of similar strength) and catalyst efficiency.

Overall, C–H activation embodies the modern synthetic ideal: directly and selectively install functional groups with minimal prework. When coupled with biocatalysis or flow techniques, C–H transformations can occur under very mild, green conditions.

Green and Sustainable Synthetic Chemistry

Sustainability is now a priority in synthetic design. Green chemistry principles urge minimization of waste and hazards. In practice, this means prioritizing catalytic over stoichiometric reagents, using benign solvents (e.g. water, ethanol, or even solvent-free), and maximizing atom economy. The concept of the E-factor (mass of waste per mass of product) is widely used – by these metrics, modern methods aim to push towards zero waste. For example, chemists increasingly use aqueous or solid-phase conditions: micellar catalysis and enzyme media allow reactions in water where classic organic solvents were once mandatory. Solvents like ethanol, ethyl acetate or glycerol are chosen for lower toxicity. Activating functional groups enzymatically or photochemically can obviate the need for protecting groups or harsh reagents, thereby reducing byproducts.

Green chemistry also motivates the use of renewable feedstocks. Biomass-derived building blocks are being converted into chemicals through modern catalysis. CO₂ fixation methods are an active frontier. Catalysis by Earth-abundant metals is preferred to precious metals and recycling of catalysts is emphasized. One particularly green avenue is cascade or telescoped reactions: combining multiple steps into one sequence (sometimes in a flow reactor) avoids intermediate workups and cuts solvent use. In enzymes (biocatalysis), solvent is often benign (water or buffered media) and catalysts are intrinsically non-toxic (proteins). As Alvaro (2025) notes, enzymatic routes “operate under mild conditions — ambient temperature and pressure, aqueous or low-toxicity solvents” and eliminate “hazardous reagents”, achieving dramatically lower waste (low E-factors). Catalytic hydrogenation (making water as sole byproduct), electrochemical reductions (forming H₂ gas), and photocatalytic oxidations (using light instead of reagents) are other green examples.

Green chemistry also entails process innovations: metrics like process mass intensity (PMI) and lifecycle analysis (LCA) are now standard in route selection. Regulatory and economic pressures (corporate ESG mandates) further drive adoption of sustainable methods. For instance, workflows are redesigned to use continuous flow reactors and recycling loops. In sum, sustainability has become an embedded element in synthetic strategy: rather than an optional add-on, it often dictates the choice of methodology and synthesis planning.

Flow Chemistry, Automation and AI

The integration of engineering and computation has given Chemistry 4.0 capabilities. Flow chemistry replaces batch flasks with continuous reactors (tubing, microreactors, or stirred-flow modules). The advantages of flow include superior heat and mass transfer, precise residence-time control, and inherent safety (small inventory of reactive material at any time). Hazardous or high-pressure reactions (e.g. hydrogenation, diazotizations) are performed more safely in flow. Photochemical reactions benefit greatly: continuous microreactors allow uniform light irradiation – dramatically improving yields and scalability of photoredox processes. Modern flow platforms can be cascaded, enabling multiple transformations to occur in sequence without intermediate isolation.

Automation and high-throughput experimentation (HTE) have similarly transformed synthesis. Robotic platforms can set up, run and analyze hundreds of reactions per day. When coupled with real-time analytics (e.g. inline spectroscopy), these systems generate large data sets. Machine-learning algorithms analyze the data to predict optimal conditions. As Velasco et al. (2025) review, the rise of AI/ML has created a “paradigm shift for chemical synthesis optimization”. Instead of one-factor-at-a-time manual tweaking, ML models can explore dozens of variables (temperature, solvent, catalyst, etc.) simultaneously. Closed-loop systems – where algorithms propose experiments, robots execute them, and data feed back into the model – can rapidly converge on ideal conditions with minimal human intervention.

AI is also impacting retrosynthetic planning. Machine-learning tools (e.g. Neural networks, transformer models) can predict reaction outcomes and suggest synthetic routes. Software like Chematica (now Synthia), IBM RXN, and open-source models are increasingly accurate at proposing steps for complex targets. While still imperfect, these AI tools help chemists by flagging non-obvious pathways and potential issues.

In combination, these technologies form a new paradigm: the self-driving laboratory. For example, Desimpel et al. (2026) demonstrated an automated flow reactor coupled with HTE and Bayesian optimization to refine a

metallaphotoredox reaction. Companies and academic groups are also developing fully automated labs where synthesis planning, execution and analysis cycle with only supervisory input. This integration of flow, automation and AI accelerates discovery and improves reproducibility – and the accessibility of sophisticated synthetic methods.

Biocatalysis

Enzymatic catalysis has crossed from niche to mainstream. Historically used in simple resolutions or hydrolyses, biocatalysis now tackles complex small-molecule targets. As Wu et al. (2021) note, “biocatalysis has developed in the last two decades into a...mature and widely used technology”. Advances in enzyme discovery (genome mining) and protein engineering (directed evolution, computational design) have expanded the range of available enzymes. Modern biocatalytic routes exploit enzyme families (transaminases, ketoreductases, monooxygenases, etc.) to perform enantioselective reductions, oxidations, C–C and C–N bond formations with exquisite selectivity. Engineered enzymes now accomplished “abiological” transformations like asymmetric carbene and nitrene insertions – once exclusive to organometallic catalysts.

The impact of biocatalysis is seen especially in pharmaceutical manufacturing. Strict regulatory and sustainability goals favor enzyme processes: they typically yield high-purity, enantiopure products with minimal waste (no heavy metals). For example, many chiral drug intermediates are now made in one or two enzymatic steps that would have required multiple chemical steps. Alvaro (2025) highlights that modern biocatalytic routes often outperform classical chemistry on key metrics (yield, selectivity, solvent and energy usage). Industrial players routinely integrate enzymes into hybrid sequences – an engineered enzyme may perform a stereoselective step, followed by a chemical transformation in the same pot. Continuous-flow immobilized enzymes have also been implemented, combining flow and biocatalysis to allow on-demand, reusable biocatalytic reactors.

Limitations remain: each enzyme has a specific substrate scope, and often requires cofactors (e.g. NADH). These challenges are overcome by protein engineering and cofactor recycling systems. The demand for faster development has spurred the use of machine learning in enzyme design. Ultimately, biocatalysis exemplifies the merger of biological and chemical synthesis paradigms: enzymes are now “programmable” catalysts that complement small-molecule catalysis – offering sustainable routes that were unthinkable a generation ago.

Challenges and Future Perspectives

Despite the many achievements, modern chemistry still faces several challenges, around which the research community is currently focusing its efforts. First, the selectivity, especially regio- and stereo, remains a significant problem, as it is not always easy to find the right conditions for a specific transformation. While computer modeling will undoubtedly make the work easier, complete reliance on automation is unlikely in the near future due to the complexity of the system. At the same time, the transition from bench-scale chemistry to industrial production raises new challenges, as the conditions for performing reactions at a pilot scale may differ substantially from those used at a laboratory level. Thus, it is necessary to optimize “technology transfer” in greater detail. Although the idea of sustainability is great, in practice, it will take a considerable amount of time and effort to transition from traditional chemical methods to new ones, as industrial players are unlikely to adopt them immediately despite their apparent benefits. Finally, while the use of artificial intelligence is undeniably promising, one should be careful about the existing data sets, which may contain biases that machine learning algorithms may learn. It is necessary to take great care in preparing training samples so that the results of model predictions are accurate enough.

At the same time, it is essential to note that the tendency to convergence is still strong and shows no signs of slowing down. One can expect even more ambitious projects in the future, which will bring together various catalytic strategies (metal-organic, photoredox-organocatalytic, chemoenzymatic) to achieve new transformations that were previously considered impossible. In addition, genome mining will allow obtaining new enzymes for organic synthesis, while new materials will expand the possibilities of photo- and electrochemistry. Finally, the fight against entropy will continue, which will see the development of new reaction databases and algorithms by scientists who will strive to

make chemistry more rational. It will become even more comfortable for non-specialists to work with chemical information as systems similar to the intuition of an experienced chemist will be created.

In conclusion, in modern chemistry, the race is ongoing toward “ideal” synthesis: chemists try to create target molecules with the most potent selectivity, using the greenest available methods and shortest schemes. Every new catalyst, every automated laboratory, and every artificially intelligent program opens the possibility of creating new molecules, making chemistry more comfortable and less time-consuming. Thus, the described trends in chemistry will undoubtedly lead the science and industry toward a sustainable future, which will bring new discoveries every year.

Conclusion

Modern chemistry is multifaceted and complex, offering many opportunities for innovation. Catalysis, which plays a crucial role in all three of the leading strategies (transition metal, organic, and biocatalysis), continues to be at the forefront of research. The use of transition metals, in particular, has led to the development of new approaches such as photoredox and electrosynthesis, which in turn have opened the door to new reactions. In addition, the ability to modify previously inert bonds in molecules using C-H activation will allow chemists to develop new, more convenient synthetic routes. Finally, the desire to create sustainable and scalable processes puts green chemistry at the forefront of scientific and industrial development. Light, electricity, and biocatalysts are increasingly being used as tools for synthesis, while flow chemistry and smart technologies are making the development of new processes much faster and more comfortable. Thus, modern chemists have the opportunity to choose from a vast array of methods and technologies to create target molecules. The convergence of these areas will undoubtedly lead to further sustainable development and the rapid emergence of new ideas that seem impossible to implement today.

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