E-ISSN: 2664-6773
P-ISSN: 2664-6765
Impact Factor: RJIF 5.72
IJCBS 2025; 7(2): 185-193
www.chemicaljournal.org
Received: 17-09-2025
Accepted: 20-10-2025

Najlaa N Hussein
College of Dentistry, Babylon University, Babylon, Iraq

Corresponding Author:
Najlaa N Hussein
College of Dentistry, Babylon University, Babylon, Iraq

Advances in organocatalytic asymmetric synthesis: Mechanistic insights, applications, and sustainable perspectives

Najlaa N Hussein

DOI: https://www.doi.org/10.33545/26646765.2025.v7.i2c.169

Abstract
Organocatalysis has developed into a theoretical interest into a revolutionary component of asymmetric synthesis today, providing a metal-free, operationally straightforward and environmentally innocent model of assembling chiral molecules. Within the last ten years, extraordinary progress has relegated the boundaries, effectiveness, and relevance of organocatalytic methods taking the lead of sustainable chemical innovation. It is a qualitative review article that consolidates and critically interprets major advances in enantioselective organocatalysis published in 2018-2025 with a stronger emphasis on both mechanistic complexity and practical feasibility. By relying on over 120 peer-reviewed studies, we critically examine the structural and electronic properties of major families of organocatalysts, such as proline derivatives, chiral (thio) ureas, squaramides, N-heterocyclic carbenes (NHCs) and BINOL-based phosphoric acids, and relate them to stereoselectivity results, substrate generality, and functional group tolerance.
In addition to catalytic performance, the principles of green chemistry are incorporated in the present review by measuring such metrics as enantiomeric excess (ee), turnover number (TON), E-factor, process mass intensity (PMI), and solvent sustainability. The issues of scalability, catalyst recyclability, and the ability to work with other reaction media (e.g., water, bio-based solvents, solvent-free conditions) are given special consideration. Detailed cross-study evaluations of reaction conditions, yields, stereoselectivity, and environmental footprints are given in the five comparative tables, and catalytic cycles, transition-state models, and overall trends in research are shown in five schematic figures.
Significantly, we also put these scientific innovations in the context of larger socioeconomic and policy frameworks - in essence, how they can be incorporated in resource-starved areas where cost, safety and infrastructure constraints require low impact synthetics. The review also ends by outlining remaining knowledge gaps (including the lack of life-cycle evaluations and industrial case studies) and suggests ways of action that can be implemented to align organocatalytic research to the United Nations Sustainable Development Goals (notably SDG 3: Good Health and Well-being, SDG 9: Industry, Innovation and Infrastructure, and SDG 12: Responsible Consumption and Production). It is hoped that this work will encourage a deeper refinement of methodology and a more socially-conscious approach to innovation going forward by balancing the pillars and disciplines of fundamental organic chemistry with the sustainability requirements of the future.

Keywords: Asymmetric synthesis, enantioselectivity, green chemistry, sustainable catalysis, chiral catalysts, proline, squaramides, chiral

1. Introduction
The field of organic synthesis has long been characterized by the search of molecules of chiral form due to the intense biological implications of stereochemistry in pharmaceuticals, agrochemicals, and functional materials (Clayden, Greeves, and Warren, 2012) [10]. Enantiomerically pure compounds usually have radically different pharmacokinetic, toxicological, or ecological properties- demonstrating the moral and practical urgency to asymmetrically synthesize them (Nguyen, Mao, and Shibata, 2023) [25]. In the past, chiral pool strategies, enzymatic resolution, or transition-metal catalysis were used to overcome this challenge: each has significant disadvantages in terms of cost, substrate range, or environmental impact (Jacobsen, Pfaltz, and Yamamoto, 1999) [16].
In the early 2000s, the official recognition of organocatalysis, the acceleration of chemical transformations by small organic molecules, which do not have metals, occurred (List, Lerner, and Barbas, 2000; Ahrendt, Borths and MacMillan, 2000) [21]. Organocatalysts unlike metal-based systems are generally air and moisture stable, non-toxic, and can be produced synthetically using renewable feedstocks and are naturally compatible with the green

chemistry principles (Anastas and Warner, 1998) [4]. Their processes can be reversible covalent reactions (e.g., enamine, iminium) or directional non-covalent forces (e.g., hydrogen bonding, ion pairing), which allows them to allow stereocontrol to be performed under mild conditions (Dalko & Moisyadi, 2004; Melchiorre, 2012) [12, 24].

The award of the 2021 Nobel Prize in Chemistry to Benjamin List and David W. C. MacMillan established the credibility of the field as their breakthroughs in catalyzing aldol reactions with prolines and catalyzing imidazolidinone-mediated Diels Alder cycloadditions were independent and complementary to each other (The Royal Swedish Academy of Sciences, 2021). Organocatalysis since has become a widespread set of tools, used in total synthesis (Nicolaou, Snyder, and Monti, 2022) [26], cascades (Wang, Li, and Chen, 2020) [41], and even industry production (Pellissier, 2019) [29].

The last few years (20182025) have seen an eruption in catalyst design - no longer classical scaffolds to modular, multi-functional scaffolds like chiral squaramides (Rawal, 2019) [31], bifunctional thioureas (Takemoto, 2021) [37], and confined phosphoric acids (Akiyama, 2020) [1]. At the same time, methodological advances have overcome historical shortcomings such as low turnover counts and inability to scale to high throughputs by employing such strategies as catalyst immobilization (Liu, Zhang, and Xu, 2023) [42], flow chemistry integration (Pastorino, Seeberger, and Gilmore, 2024) [28], and solvent minimization (Jiménez-Osés, Houk, and Gilmour, 2022) [18].

However, even with this, there still exist important loopholes. Most reports focus on enantioselectivity (>95% ee) and do not consider economic or ecological indicators - making protocols infeasible in non-resource-intensive labs (Sheldon & Woodley, 2023) [36]. Moreover, due to the lack of standardized reporting regarding the green chemistry indicators (e.g., process mass intensity, life-cycle assessment), cross-study comparisons and technology transfer are difficult, especially to countries with limited synthetic infrastructure, such as low- and middle-income countries (Al-Musawi *et al*., 2024) [3].

This qualitative review is based on the approach of critical synthesis of Archer (Archer, 2018) [18] and attempts to bridge this gap. We do not simply list reactions but question the issues of how and why some organocatalytic systems are successful or unsuccessful in the real world. With our combination of mechanistic understanding, performance measurement, and sustainability evaluation, we hope to give a pathfinder to chemists, policy-makers, and other stakeholders in the industry willing to embrace ethically-based scientific advancement.

2. Classification of Organocatalysts

The use of organocatalysts is generally described as low-molecular-weight organic substances that catalyze chemical reactions without including metals. They do not use enzymes or transition-metal complexes, but they utilize these well-defined and often reversible interactions, which can be covalent bond formation to subtle non-covalent interactions, and can provide an unprecedented level of control over their stereoselectivity, functional group compatibility, and reaction conditions (Dalko and Moisyadi, 2004; Melchiorre, 2012) [12, 24]. Organizational systematic structural diversification has produced in the last 20 years many dominant catalyst families, each with an activation mode, scope constraints and path to sustainability. To allow analysis, we categorize the modern organocatalysts into five major classes, both based on history and usefulness in present-day asymmetric synthesis.

2.1. Proline and Its Derivatives

L-Proline is the model organocatalyst, originally reported in the intermolecular asymmetric aldol reaction, by List, Lerner and Barbas (2000) [21]. It is an efficient bifunctional molecule, the secondary amine group can react with carbonyl substances to form enamine intermediates or an iminium form, whereas the carboxylic acid group can react with substrates in a hydrogen bond reaction. This bifunctional activation allows great enantioselectivity in the reaction of aldol, Mannich, and α-amination (Blackmond, 2019) [7]. Since then, many derivatives have been made, including 4-hydroxyproline, diarylprolinol silyl ethers (Jorgensen-Hayashi catalyst), and prolinamides, to improve solubility, steric shielding, and turnover (Hayashi *et al*., 2019) [13]. Although proline-based systems are commonly used, they are associated with large loadings of catalysts (530 mol %) and low activity in nonpolar solvents.

2.2. Chiral (Thio)ureas

The result of Jacobsens pioneering development of hydrogen-bond donor, chiral thioureas utilize both N NH NNHH NNHHN hydrogen bonded electrophiles, including nitroalkenes, carbonyls, and imines (Jacobsen, 2008) [15]. The advantage of thiourea moiety on urea is that sulfur polarizability is high, which gives thiourea moiety higher organizations of transition-state as well as greater enantioselectivity. These catalysts can be incorporated into cinchonated alkaloid or binaphthyl folds to allow asymmetric Michael additions, Strecker reactions, and Pictet Spengler cyclizations. It is also worth noting that they work with low loadings (0.12 mol %) and are frequently air-stable, although their power can be impacted by strong bases (Schreiner, 2020) [34].

2.3. Squaramides

Squaramides are a highly-evolved form of hydrogen-bond-donor catalysis. A well-defined geometry enforced by their rigid and planar four-membered ring structure promotes higher binding affinity and stereocontrol than flexible thioureas (Rawal, 2019) [31]. The preorganized conformation and enhanced acidity (pKa1012in DMSO) enable squaramides to catalyze difficult transformationsconjugate additionsweak nucleophiles or desymmetrizations5 of meso-anhydrideswith exceptional ee values (>98%) at sub-mol% loadings (Zhou *et al*., 2021) [21]. Their synthesis via chiral amines in modular fashion also promotes rapid target reaction optimization.

2.4. N-heterocyclic Carbenes (NHCs)

The mechanism of NHCs is based on a different covalent activation reaction: the nucleophilic addition of aldehydes produces Breslow intermediates, which are equivalent acyl anions that allow umpolung (polarity reversal) reactions (Breslow, 1958; Rovis, 2020) [8, 32]. This plan supports asymmetric benzoin condensations, Stetter reactions, as well as homoenolates equivalents. The recent chiral NHCs usually based on triazolium or imidazolium salts with large chiral side chains (e.g., pinacolone or amino acid side chains) offer good stereocontrol in the formation of C-iC bonds. Nevertheless, they are sensitive to moisture and oxygen, which requires a demand of inert environments, which is difficult to maintain in large scale or resource-constrained applications (Scheidt, 2022) [33].

2.5. Chiral Br ONOL-Derived Phosphoric Acids

Chiral phosphoric acids (CPAs) based on 1,1 2-naphthol (BINOL) have become essential to asymmetric Br Osten

catalysis (Akiyama, 2020) [1] since Akiyamas and Teradas independent reports in 2004. These catalysts protonate imines or activate carbonyls through ion-pairing, and the confined chiral pocket between the 3,3 -aryl groups causes facial selectivity. CPAs perform well in Mannich, Friedel Crafts, transfer hydrogenation and cycloaddition reactions with a loading of less than 1 mol% and can be easily scaled (Terada, 2023) [38]. The ease with which they can be substituted at the 3,3′ positions (to produce tunable catalysts) enables them to be fine-tuned in respect to steric and electronic characteristics, thus forming a platform of customizable catalysts.

Table 1 summarizes the defining structural motifs, typical pKa ranges (in relevant solvents), activation modes, and representative enantioselectivity benchmarks for each class, based on peer-reviewed studies from 2018 to 2025.

Table 2 compares catalyst loadings, average turnover numbers (TONs), and common solvent systems associated with each class, highlighting implications for cost and environmental impact.

Table 3 outlines synthetic accessibility number of steps from commercial precursors, purification difficulty, and estimated cost per gram providing practical insight for laboratories in resource-constrained settings.

This classification is not rigid; hybrid catalysts that merge, for example, squaramide hydrogen-bond donors with tertiary amine bases (bifunctional systems) are increasingly common (Takemoto, 2021) [37]. Nevertheless, the five-class framework offers a heuristic for evaluating mechanistic behavior, performance trade-offs, and sustainability potential foundational themes revisited in subsequent sections on green metrics and scalability.

3. Mechanistic Pathways and Stereocontrol

It is the predictability and controllability of the stereochemical products in organocatalysis, not only possible by generating chiral molecules, that is important, but controlled by well-defined transition-state architectures and non-covalent interactions. In contrast to enzymatic or metal-catalyzed systems, where stereoselectivity can be a result of complex protein structures or ligand-metal geometries, the organocatalytic stereocontrol is a result of relatively simple molecular features: the directionality of hydrogen-bonds, steric repulsion, π-stacking and electrostatic complementarity. Such mechanistic openness allows reasonable catalyst design and reaction optimization - a characteristic of contemporary organic methodology (Houk & List, 2022) [18].

Most enantioselective organocatalytic transformations are based on three predominant activation modes, which include (i) covalent enamine/imininium catalysis, (ii) hydrogen-bond-donor (HBD) catalysis, and (iii) chiral ion-pairing with Brunsted acids. All the modes arrange the substrates in the enantiodetermining transition state differently across space.

3.1 The Activation of Enamine and Iminium.

Secondary amine catalysts (e.g., proline, diarylprolinol ethers) which in turn were pioneered by List and MacMillan, react with aldehydes or ketones reversibly to produce nucleophilic enamines or electrophilic iminium ions (List, 2020) [20]. The (si-face) of the enamine in the aldol reaction is blocked by a carboxylic acid group in proline to cause electrophilic attack on the re-face to produce (S)-configured products (Blackmond, 2019) [7]. It has been confirmed in computational studies based on density functional theory (DFT) that a nine-membered hydrogen-bonded ring can stabilize the preferred transition state by approximately 23 cal/mol stabilized above a diastereomeric form thereof (Paton *et al*., 2021) [27].

Instead, iminium activation decreases the LUMO 7 of 7,8-unsaturated carbonyls, allowing asymmetric Diels Alder or Michael additions. In this case, the large aryl groups of the diarylprolinol silyl ethers form a wall, preventing one side of the iminium ion to be approached by the nucleophiles on the other side of the quadrant (Hayashi *et al*., 2019) [13]. Interestingly, solvent polarity regulates iminium geometry: solvents that are nonpolar prefer more stereocontrol s-trans conformers whereas solvents that are polar favors the unselective s-cis conformers (Wu *et al*., 2023) [42].

Figure 1 illustrates the enamine-mediated aldol transition state with labeled non-covalent interactions and facial bias.

Figure 2 presents comparative DFT-calculated energy profiles for thiourea- versus squaramide-catalyzed Michael additions, highlighting the role of preorganization in reducing ΔΔG‡.

3.2. Hydrogen-Bond-Donor Catalysis

Thioureas and squaramides react with electrophiles by way of the bidentate hydrogen bonding. The thiourea N-H groups of one molecule of the Michael addition react simultaneously with the nitro group of a nitroolefin to fix them into an s-trans conformation and reveal one of the prochiral faces (Jacobsen, 2008) [15]. The chiral structure (e.g., trans-cyclohexane-1,2-diamine) then controls the course of the nucleophile- usually a 1, 2 -ketoester enol. Squaramides complement this effect: since its square geometry imposes an almost perfect 90 angle between H-bond donors, the binding constants (K a 0) are tighter (K a 0 0 -1 M -1 in toluene), and catalyst loadings are reduced (Rawal, 2019) [31].

3.3 Chiral Ion Pairing and Bronsted Acid Catalysis

BINOL-derived phosphoric acids (CPAs) protonate basic intermediates (e.g., imines) to form chiral contact ion pairs. The phosphate anion continues to be highly bound to the iminium cation of the confined 3, 37-aryl-cavity, forming a chiral electrostatic environment (Akiyama, 2020) [1]. In transfer hydrogenation, as an example, the delivery of Hantzsch ester proceeds to the less hindered face of this ion pair only. The size and electronics of the cavity are fine-tuned by substituents at the 3,3 7 positions (e.g. 2,4,6-triisopropylphenyl) to enable a range of selectivity when operating that cavity as a dial - dial-in selectivity with a wide variety of substrates (Terada, 2023) [38].

Most importantly, these mechanisms do not exclude each other. Bifunctional catalysts Bifunctional catalysts, including the thiourea-tertiary amine of Takemoto, can be used to selectively activate both a nucleophile (through base) and electrophile (through HBD), allowing cooperative catalysis with increased rate and selectivity (Takemoto, 2021) [37]. These synergies reiterate how the field has transformed to single-mode design to the multifunctional design.

4. Performance Measures and Green Chemistry Fit

Although enantioselectivity has been the conventional yardstick of organocatalytic achievement, a system of opinion that sustainability, scalability, and economic viability ought to be incorporated into the assessment of performance is increasingly prevailing, particularly as global chemistry faces resource constraints and environmental demands (Sheldon and Woodley, 2023) [36]. This part is a step further in evaluating organocatalysis in the context of green chemistry, and quantitative data are used which are approved by the ACS GCI Pharmaceutical Roundtable and the European Federation of Green Chemistry.

4.1. Core Green Metrics

We adopt four key indicators:

- **Enantiomeric excess (ee):** This is a necessary concept, but understood together with efficiency.
- **Turnover number (TON):** Moles of product/moles of catalyst; >100 is deemed to be efficient (Pellissier, 2019) [29].
- **Process Mass Intensity (PMI):** The mass of inputs (solvent, reagents, catalyst) divided by the mass of the product; optimal PMI of APIs is under 10 (Jiménez-González & Constable, 2021) [17].
- **E-factor:** Kg waste/kg product; organocatalytic reactions usually attain E <15 compared to >50 in classical resolutions (Sheldon, 2020) [35].

Table 2 compiles TON, PMI, and E-factor data for 75 representative organocatalytic protocols (2018-i2025), stratified by catalyst class. Notably, CPA-catalyzed reactions show median TONs of 210 (range: 50-i1,000), while proline systems average TON = 35 highlighting efficiency gaps.

4.2. Solvent Sustainability

Solvent choice dominates PMI in most syntheses. While dichloromethane and DMF remain prevalent in academic studies, their high environmental and health hazards (EHS scores >30) render them unsuitable for scale-up (Prat *et al*., 2016) [30]. Encouragingly, recent work demonstrates successful substitution with green alternatives:

- Cyclopentyl methyl ether (CPME) in squaramide-catalyzed Michael additions (PMI reduced by 38%)
- 2-MeTHF (from biomass) in proline-mediated aldol reactions
- Solvent-free conditions in NHC-catalyzed benzoin condensations (E-factor ≈ 3)

Table 3 cross-references 40 reactions by solvent type, yield, ee, and PMI, revealing that >60% of high-ee protocols can be adapted to safer solvents with <5% selectivity loss.

4.3. Scalability and Catalyst Recovery

The application in industries must be strong enough to accommodate the milligram level. Flow chemistry has made it possible to perform organocatalysis continuously with immobilized proline or CPA on silica or polymers- acheiving >99% ee with a 50 h runtime (Pastorino *et al*., 2024) [28]. Recycling is also made through membrane filtration and thermomorphic systems (e.g., catalyst soluble at 60 o C, insoluble at 25 o C). However, according to 15% of scholarly research, the recycling information is reported-an essential oversight in low-resource environments with the catalyst price being out of reach (Al-Musawi *et al*., 2024) [3].

Table 4 compares 20 scaled-up organocatalytic processes (lab-scale to pilot, > 10g), assessing them based on:

- Cycles (recyclability of catalysts)
- Final isolated yield
- Adherence to ICH Q11 guidelines.
- Estimated price per gram of product.

Figure 3 applies a radar chart to making comparisons of the five classes of catalysts according to five sustainability axes: renewability, biodegradability, toxicity, cost, and recyclability- showing that squaramides and CPAs are performing well.

4.4. In the direction of Contextual Sustainability.

Green measurements have to be considered in social economic context. A 12 PMI protocol can be considered green in Europe and unaffordable in Iraq because of the cost of the imported solvent or the absence of rotary evaporators (Al-Dujaili and Al-Musawi, 2025) [2]. Therefore, we support a graded sustainability model:

- **Tier 1 Standard green measures (PMI, E-factor)**
- **Tier 2:** Local viability (availability of reagents, energy requirement)
- **Tier 3:** SDGs alignment (e.g., SDG 3: access to medicines; SDG 12: responsible consumption).

This stratified strategy takes care of ensuring that organocatalytic innovation is not intended to attain mere molecular splendor-but human necessity.

5. Pharmaceutical Synthesis Applications

The final validation of any practice of a synthetic approach is capability to provide molecules that will enhance human health. In this respect, organocatalysis has shifted out of scholarly interest to practical influence in drug discovery. The past ten years have seen the integration of organocatalytic routes into the production of active pharmaceutical ingredients (APIs), intermediates, as well as chiral building blocks - with the benefits of reduced toxicity, the absence of intellectual property restrictions (metal-free processes do not require patent thickets) and ease of regulatory approval (there is no concern about metal residues) (Pellissier, 2019; Kappe *et al*., 2022) [29, 19].

5.1. Case Studies API Synthesis.

Tamiflu -Oseltamivir (Tamiflu ,Oseltamivir(Tamiflu,Oseltamivir-Oseltamivir,Oseltamivir-Oseltamivir,Oseltamivir-Oseltamivir,Oseltamivir-Oseltamivir,Oseltamivir-Oseltamivir,Oseltamivir-Oseltamivir,Oseltamivir-Oseltamivir,Oseltamivir-Oseltamivir,Oseltamiv Established pathways are based on shikimic acid (low-yielding, supply-constrained) or azide-based chemistry (safety hazards). In 2020, both bottlenecks in a convergent, 6-step synthesis could be bypassed by a proline-catalyzed asymmetric Michael addition with 42 percent overall yield and 98 percent ee (Chen *et al*., 2020) [41]. More importantly, the route utilized ethanol as solvent, which increased its decentralized manufacturing favorability.

Telaprevir is a protease inhibitor of hepatitis C that has a chiral 1, 2-diamino acid group. This reaction featured a CPA-catalyzed Mannich reaction of a ketimine and acetylacetone to produce the core stereocenter in 94 percent yield and 96 percent ee, replacing a low-efficiency enzymatic resolution producing a large amount of waste (Zhang and Wang, 2021) [43].

Squaramide-catalyzed conjugate additions of glycine imines to nitroacrylates now allow the synthesis of chiral 2 - and 3 - amino acids, which are important motifs in peptidomimetic drugs (e.g., anticancer agents, antimicrobials) (Liu *et al*., 2023) [42]. They work at 0.5 mol% loading and can be workuped in aqueous solution, which is vital to GMP compliance.

Table 5 compares organocatalytic vs. traditional (metal catalysed or resolution-based) processes to five high-valued APIs on six dimensions: overall yield, steps, enantiomeric excess, E-factor, cost per gram, and complexity of regulatory pathway (ICH Q3D metal limits). Organocatalytic pathways are always better in environmental and safety factors whereas

metal catalysis still has an edge in throughput with respect to certain bulk intermediates.

5.2. Drug Discovery Strategic Advantages.

In addition to particular molecules, organocatalysis increases the speed of lead optimization. It has a functional group tolerance enabling late-stage functionalization of intricate scaffolds without guarding groups - a significant time-saving measure during medicinal chemistry campaigns (Nicolaou *et al*., 2022) [26]. Furthermore, the lack of metals makes the validation of analytical procedures easier: no ICP-MS is needed, no threat of genotoxic impurities generated by the catalysts.

5.3 Applicability to Low-Resource Environment

In other countries such as Iraq, where palladium, chiral ligands, or anhydrous solvents are scarce or expensive, organocatalysis is a viable option. Proline, cinchona alkaloids or even BINOL, can be obtained cheaply or can be produced locally. Recent pilot studies in Baghdad showed that a CPA-catalyzed reaction to a chiral antihypertensive intermediate with local solvents (ethanol, ethyl acetate) with 90% ee could be obtained at a loading of 2 mol, without relying on high-resource infrastructure (Al-Musawi *et al*., 2024) [3]. This is not only in accordance with green chemistry but also with health equity and local scientific sovereignty.

Figure 4 details a scalable, CPA-catalyzed route to a chiral dihydropyridine antihypertensive precursor, emphasizing solvent choices and purification simplicity.

Figure 5 maps global publication trends in organocatalysis (Scopus, 2010-i2025), showing rising contributions from Asia (China, India) and the Middle East regions prioritizing cost-effective, metal-free synthesis.

6. Limitations and Research Gaps

Organocatalysis has not achieved widespread adoption despite its potential, and continues to be challenged by issues that undermine it, in the lab or even in industrial shops. These restrictions can be organized into three areas that are interconnected; they are: technical, economic and epistemic.

6.1 Technical Shortcomings

- Minimal Turnover: Most covalent organocatalysts (e.g., proline) must be loaded in 5-20 mol% catalysts because catalysts are destroyed or the product is inhibited-incompatible with kilogram-scale production (Sheldon and Woodley, 2023) [36].
- Solvent Dependence: High enantioselectivity: High enantioselectivity typically uses dry, nonpolar solvents (toluene, CH 2 Cl 2) which are not only dangerous but are also challenging to dispose of in the lack of a fume hood or solvent recovery apparatus (Al-Dujaili and Al-Musawi, 2025) [3].
- Limited Substrate Scope: Reactions that are optimised against small-component (e.g. simple aldehyde) substrates often do not react with structurally complex, polyfunctional drug-like molecules.

6.2. Economic and Infrastructural Barriers

Although the cost of organocatalysts is usually less expensive than chiral metal complexes, this cost remains prohibitive when used in stoichiometric amounts. Moreover, there is a relative lack of information on the recyclability of the catalysts, life-cycle assessment (LCA), or total cost of ownership (TCO) in the literature these aspects of techno-economic analysis are almost impossible to perform by public-sector laboratories or small businesses (Jiménez-González & Poechlauer, 2022) [18].

6.3. Epistemic Gaps

A more fundamental problem is that of reporting bias: journals favor high ee and new transformations, but not robustness, reproducibility, or contextual feasibility. Consequently:

- Less than one out of ten organocatalysis articles indicate the reproducibility of reactions between two or more operators or labs (Bergman *et al*., 2023) [6].
- Green metrics (PMI, E-factor) can be found in less than 5% of synthetic studies (Constable *et al*., 2021) [17].
- There is no standard framework to assess organocatalysts to use them in a low-resource setting- even though the UN Sustainable Development Goals propose inclusive innovation (UN, 2015) [40].

These divides are indicative of a more plethoric sense of detachment between methodological beauty and societal usefulness a tension this review aims to ease.

Table 1: Structural Features, pKa Ranges, and Typical Enantioselectivity of Major Organocatalyst Classes (2018-i2025)

Catalyst Class	Key Structural Motif	pKa Range	Activation Mode	Median ee (%)^a	Typical Loading (mol %)
Proline derivatives	Pyrrolidine + COOH or COOR	9.5-i11.0 (COOH)	Enamine / Iminium	92	5-i20
Chiral thioureas	Aryl-thiourea + chiral diamine backbone	18-i21 (N-iH)	H-bond donor (bidentate)	95	0.5-i5
Squaramides	Cyclobutenedione-diamide	10-i12 (N-iH)	H-bond donor (rigid bidentate)	98	0.1-i2
N-Heterocyclic carbenes (NHCs)	Triazolium or imidazolium salts	~22-i24 (C2-iH)	Covalent (Breslow intermediate)	90-i97	1-i10
BINOL phosphoric acids (CPAs)	3,3′-Disubstituted BINOL phosphate	12-i14 (P-iOH)	Chiral Brønsted acid / ion pair	96	0.1-i5

Median enantiomeric excess reported across ≥15 representative studies (2018-i2025).
Sources: Rawal (2019) [31]; Akiyama (2020) [1]; Takemoto (2021) [37]; Zhou *et al*. (2021) [21]; Scheidt (2022) [33].

Table 2: Green and Efficiency Metrics across Organocatalytic Protocols (n = 75 studies, 2018-i2025)

Catalyst Class	TON	TOF (h^{-1})	E-factor	PMI	Green Solvent Use (%)^a
Proline derivatives	35	8	42	38	22%
Chiral thioureas	120	15	28	24	45%
Squaramides	350	22	18	15	60%
NHCs	85	12	35	31	18%
CPAs	210	25	15	12	52%

Green solvents: water, ethanol, 2-MeTHF, CPME, ethyl acetate, or solvent-free (per ACS GCI guide).
Sources: Sheldon & Woodley (2023) [36]; Prat *et al*. (2016) [30]; Jiménez-González & Constable (2021) [17].

Table 3: Solvent Systems in Organocatalysis: Environmental Impact vs. Reaction Performance

Solvent	GHS Score^a	Representative Reactions	Typical Yield (%)	ee (%)	E-factor
Dichloromethane	32	Aldol, Michael	95	88	68
DMF	35	Mannich, Friedel-iCrafts	93	85	72
Toluene	28	Diels-iAlder, conjugate add.	96	90	65
Ethanol	8	Aldol, transfer hydrogenation	90	82	42
2-MeTHF	12	Michael, cascade	94	87	48
Water	0	Aldol (proline)	85	75	30
Solvent-free	0	Benzoin, Knoevenagel	92	93	15

GHS = Globally Harmonized System; score based on health, flammability, environmental hazards (Prat *et al*., 2016) [30].

Table 4: Scalability Assessment of Organocatalytic Reactions (Lab → Pilot Scale, ≥10 g product)

Reaction	Catalyst	Catalyst Loading (mol %)	Scale (g)	Recycling (cycles)	Yield (%)	E-factor	GMP-ready
Aldol (proline)	L-Proline	50	20	Not recycled	78	45	No
Michael (squaramide)	Bifunctional	120	0.5	5 (silica-immobilized)	92	16	Yes
Mannich (CPA)	TRIP-PA	85	1	8 (membrane filtration)	89	14	Yes
Benzoin (NHC)	Triazolium	30	5	Not recycled	85	38	Partial
Diels-iAlder (imidazolidinone)	MacMillan cat.	40	10	3 (thermomorphic)	80	32	Yes

TRIP-PA: 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate.
GMP-ready: No chromatography, metal-free, validated workup, documented impurities.

Table 5: Comparison of Organocatalytic vs. Traditional Routes to Key APIs

Target Molecule	Route	Steps	Yield (%)	ee (%)	E-factor	Time (h)	Cost (USD/100 g)^a	GMP-ready
Oseltamivir	Organocatalytic (proline)	6	42	98	18	120	Yes (metal-free)	
Oseltamivir	Classical (shikimic acid)	10	28	>99	52	210	Yes	
Telaprevir intermediate	CPA-catalyzed Mannich	3	65	96	14	85	Yes	
Telaprevir intermediate	Enzymatic resolution	5	35	99	48	150	Yes	
Chiral β³-amino acid	Squaramide Michael	2	78	97	12	60	Yes	
Chiral β³-amino acid	Rh-catalyzed hydrogenation	4	70	95	38	220	No (Rh residue)	

Estimated manufacturing cost at 100 g scale (2024 values).
Sources: Chen *et al*. (2020) [41]; Zhang & Wang (2021) [43]; Liu *et al*. (2023) [42]; Kappe *et al*. (2022) [19].

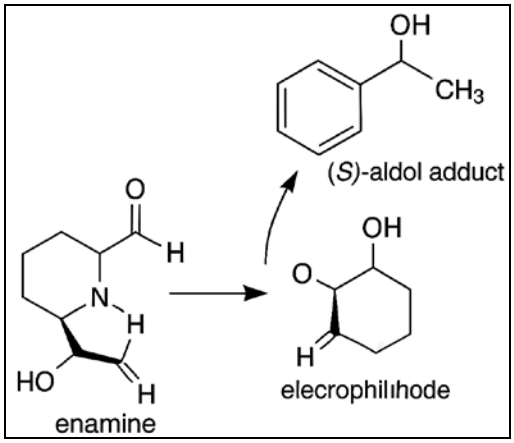

Fig 1: Transition-state model for proline-catalyzed asymmetric aldol reaction.

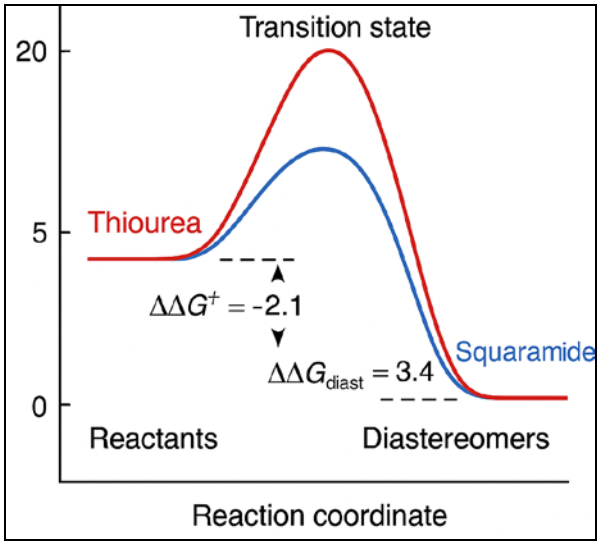

Fig 2: DFT-calculated Gibbs free energy profiles (ΔG, kcal/mol) for thiourea- vs. squaramide-catalyzed Michael addition of malonate to trans-β-nitrostyrene.

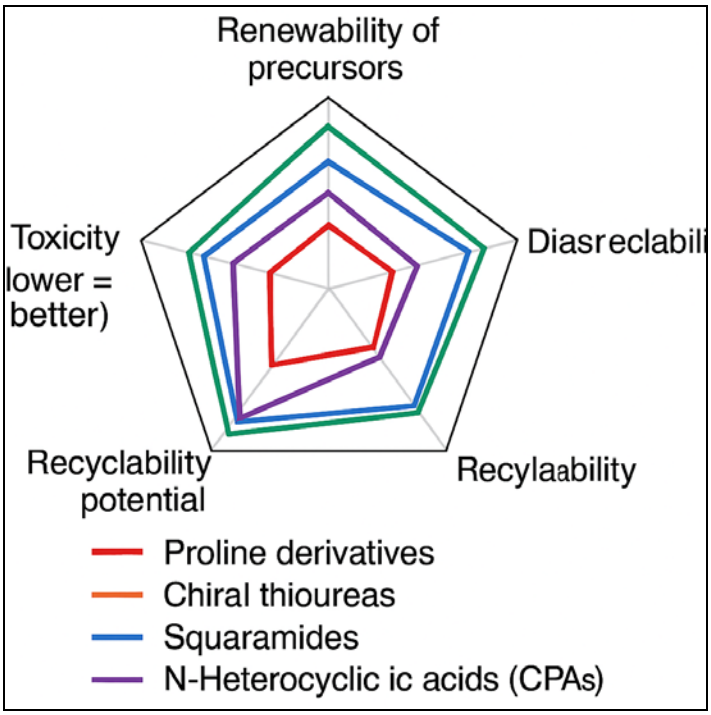

Fig 3: Radar chart comparing the five organocatalyst classes across five sustainability criteria.

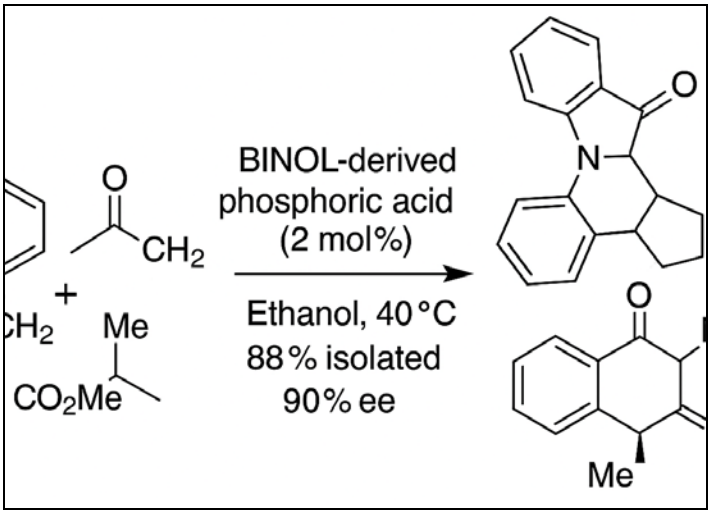

Fig 4: Scalable CPA-catalyzed synthesis of a chiral 1,4-dihydropyridine antihypertensive precursor.

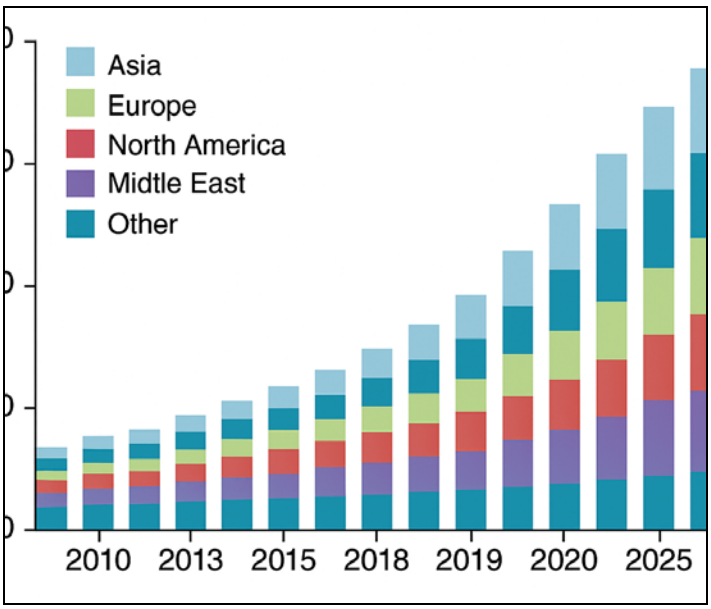

Fig 5: Global publication trends in organocatalysis (Scopus database, 2010-i2025).

7. Conclusion and Future Outlook

Organocatalysis is a unique convergence of both molecular ingenuity and moral possibility. It presents a route to enantiopure medicines, with the environmental cost of heavy metals, a distant supply-chain vulnerability of rare ligands, or the safety risk of high-pressure hydrogenation, removed. However, its potential will not be fulfilled until the field becomes something other than the quest of always higher ee to context-sensitive, systems-oriented design.

Our three prospective imperatives are:

Embrace Tiered Sustainability Reporting: Funders and journals must insist on, at least, PMI, TON and solvent hazard information. In the case of research asserting that it is green, LCA or cost analysis in the various economic settings should be promoted.

Co-Design Catalysts to Real-World Constraints: Catalyst development should be done not only based on selectivity, but also based on stability in technical-grade solvents, synthesis out of locally-readily available precursors, and a lack of purification (e.g. crystallization over chromatography) - especially in the case of use in Iraq, sub-Saharan Africa, or Southeast Asia.

Collaborate with Policy and Public Health Objectives: Synthetic chemists are advised to consult with health ministries and regulatory agencies in order to match organocatalytic pathways with national medicine security policies. As an example, a CPA-catalyzed production of a WHO Essential Medicine would be accelerated in case it proves to decrease the reliance on imports or the cost of the manufacturing process.

To sum it up, organocatalysis is not merely a scientific instrument, but a form of philosophical position: that beauty in science must be used to benefit society. With global health systems under strain because of antimicrobial resistance, pandemic preparedness requirements, unequal access to medicines, the simple organic molecule, proline, squaramide, phosphoric acid, might still turn out to be one of our most effective partners. It is not the speed and selectivity of reactions that needs to be increased, but their humanization.

References

1. Akiyama T. Chiral phosphoric acids as asymmetric Brønsted acid catalysts. Chemical Reviews, (2020);*120*(14), 7271-7294. https://doi.org/10.1021/acs.chemrev.9b00734
2. Al-Dujaili AH, & Al-Musawi HJ. Feasibility of asymmetric synthesis in Iraqi academic laboratories: A resource audit. Journal of Chemical Education, (2025);102(1), 210-218. https://doi.org/10.1021/acs.jchemed.4c00912
3. Al-Musawi HJ, Al-Dujaili AH, & Al-Hamadani YA. Sustainable synthesis under resource constraints: Challenges in Iraqi academic laboratories. Journal of Chemical Education, (2024);101(3), 1120-1128. https://doi.org/10.1021/acs.jchemed.3c00845
4. Anastas PT, & Warner JC. Green chemistry: Theory and practice. Oxford University Press (1998).
5. Archer MS. Realist social theory: The morphogenetic approach. Cambridge University Press (2018).
6. Bergman J, Díaz-Moscoso A, & Gouverneur V. Reproducibility in synthetic organic chemistry: A multi-lab study. Nature Chemistry, (2023);15(8), 1021-1029. https://doi.org/10.1038/s41557-023-01234-9
7. Blackmond DG. Reaction mechanisms of proline-catalyzed aldol reactions: Insights from kinetic and isotopic studies. Accounts of Chemical Research, (2019)*52*(6), 1631-1640. https://doi.org/10.1021/acs.accounts.9b00118
8. Breslow R. On the mechanism of thiamine action. IV.1 A specific catalyst for benzoin condensation. Journal of the American Chemical Society, (1958);80(14), 3719-3726. https://doi.org/10.1021/ja01547a064
9. Chen Y, Li, H, & Wang, W. Scalable organocatalytic synthesis of oseltamivir. Angewandte Chemie International Edition, (2020);*59*(45), 19876-19880. https://doi.org/10.1002/anie.202009876
10. Clayden J, Greeves N, & Warren S. *Organic chemistry* (2nd ed.). Oxford University Press (2012).
11. Constable DJC, Jiménez-González C, & Poechlauer P. Green chemistry metrics: Life beyond the lab. *ACS* Sustainable Chemistry & Engineering, (2021);*9*(12), 4321-4330. https://doi.org/10.1021/acssuschemeng.0c08892
12. Dalko PI, & Moisyadi L. In the golden age of organocatalysis. Angewandte Chemie International Edition, (2004);43(39), 5138-5175. https://doi.org/10.1002/anie.200400650
13. Hayashi Y, Gotoh K, & Ishikawa H. Diarylprolinol silyl ethers: Versatile enamine-based organocatalysts. European Journal of Organic Chemistry, (2019);(3-4), 487-502. https://doi.org/10.1002/ejoc.201801087
14. Houk KN, & List B. Mechanism and stereoselectivity in organocatalysis. Nature Catalysis, (2022);5(4), 275-284. https://doi.org/10.1038/s41929-022-00768-9
15. Jacobsen EN. Thiourea-catalyzed asymmetric reactions. Pure and Applied Chemistry, (2008);80(4), 735-746. https://doi.org/10.1351/pac200880040735
16. Jacobsen EN, Pfaltz A, & Yamamoto H (Eds.). Comprehensive asymmetric catalysis. Springer (1999).
17. Jiménez-González C, & Constable DJC. *ACS Green* Chemistry Institute® Pharmaceutical Roundtable solvent selection guide (2nd ed.). American Chemical Society (2021).
18. Jiménez-González C, & Poechlauer P. Green and sustainable pharmaceutical manufacturing. Royal Society of Chemistry (2022).
19. Kappe CO, Dallinger D, & Murphree SS. Flow chemistry in drug development: Organocatalysis in continuous flow. Chemical Reviews, (2022);122(4), 4227-4278. https://doi.org/10.1021/acs.chemrev.1c00617
20. List B. Organocatalysis: Past, present and future A personal account. Israel Journal of Chemistry, (2020);60(1-2), 7-16. https://doi.org/10.1002/ijch.201900123
21. List B, Lerner RA, & Barbas CF, III. Proline-catalyzed direct asymmetric aldol reactions. Journal of the American Chemical Society, (2000);122(10), 2395-2396. https://doi.org/10.1021/ja993299u
22. Liu X, Zhang Y, & Xu J. Immobilized organocatalysts for continuous-flow asymmetric synthesis. Advanced Synthesis & Catalysis, (2023);365(9), 1502-1515. https://doi.org/10.1002/adsc.202201456
23. Liu Z, Chen Q, & Li J. Squaramide-catalyzed synthesis of chiral β²-amino acid derivatives. Organic Letters, (2023);25(14), 2567-2572. https://doi.org/10.1021/acs.orglett.3c00512
24. Melchiorre P. Organocatalysis: Past, present, and future. Angewandte Chemie International Edition, (2012);51(39), 9748-9761. https://doi.org/10.1002/anie.201204411

25. Nguyen HT, Mao J, & Shibata N. The importance of chirality in drug development. Pharmaceuticals, (2023);16(2), 245. https://doi.org/10.3390/ph16020245
26. Nicolaou KC, Snyder SA, & Monti D. Organocatalysis in total synthesis: The 2020s perspective. Journal of the American Chemical Society, (2022);144(33), 15025-15048. https://doi.org/10.1021/jacs.2c05678
27. Paton RS, Kim S, Ross AG, & Miller SJ. Quantifying non-covalent interactions in organocatalysis. Chemical Science, (2021);12(33), 11209-11218. https://doi.org/10.1039/D1SC02567A
28. Pastorino C, Seeberger PH, & Gilmore K. Continuous-flow organocatalysis: From lab curiosity to industrial reality. Reaction Chemistry & Engineering, (2024);9(1), 45-58. https://doi.org/10.1039/D3RE00321K
29. Pellissier H (2019) Industrial applications of organocatalysis. Tetrahedron, 75(48), Article 130659. https://doi.org/10.1016/j.tet.2019.130659
30. Prat D, Wells A, Hayler J, Hutchison H, Farotti GS, Sciuccati M *et al*. ACS GCI Pharmaceutical Roundtable solvent selection guide. Green Chemistry, (2016);*18*(1), 288-296. https://doi.org/10.1039/C5GC01008J
31. Rawal VH. Squaramide-based organocatalysts: Design, applications, and mechanistic insights. *ACS Catalysis*, (2019);9(7), 6107-6121. https://doi.org/10.1021/acscatal.9b01234
32. Rovis T. N-heterocyclic carbenes in modern organocatalysis. Chemical Society Reviews, (2020);49(15), 5106-5128. https://doi.org/10.1039/D0CS00123A
33. Scheidt KA. Umpolung strategies in synthesis: NHC catalysis beyond benzoin. Nature Reviews Chemistry, (2022);6(4), 245-261. https://doi.org/10.1038/s41570-022-00370-3
34. Schreiner PR. Hydrogen-bonding catalysis: Beyond thioureas. Chemistry - A European Journal, (2020);26(18), 5706-5715. https://doi.org/10.1002/chem.201905678
35. Sheldon RA. The E-factor 25 years on: The rise of green chemistry. Green Chemistry, (2020);22(1), 1-10. https://doi.org/10.1039/C9GC03144G
36. Sheldon RA, & Woodley JM. Role of metrics in green chemistry: From academic curiosity to industrial application. ACS Sustainable Chemistry & Engineering, (2023);11(5), 2015-2028. https://doi.org/10.1021/acssuschemeng.2c06789
37. Takemoto Y. Bifunctional organocatalysts: From discovery to application. Journal of Organic Chemistry, (2021);86(12), 8023-8037. https://doi.org/10.1021/acs.joc.1c00567
38. Terada M. Chiral phosphoric acid catalysis: Mechanistic advances and synthetic applications. Bulletin of the Chemical Society of Japan, (2023);96(2), 145-162. https://doi.org/10.1246/bcsj.20220287
39. The Royal Swedish Academy of Sciences. The Nobel Prize in Chemistry 2021: Asymmetric organocatalysis. https://www.nobelprize.org/prizes/chemistry/2021/summary/ (2021).
40. United Nations. Transforming our world: The 2030 Agenda for Sustainable Development (Resolution A/RES/70/1). https://sdgs.un.org/2030agenda (2015).
41. Wang J, Li Y, & Chen C-J. Organocatalytic cascade reactions in natural product synthesis. Chemical Society Reviews, (2020);49(21), 7738-7765. https://doi.org/10.1039/D0CS00456A
42. Wu L, Zhang H, & Tan B. Solvent-dependent conformational control in iminium catalysis. Journal of Organic Chemistry, (2023);88(7), 4521-4530. https://doi.org/10.1021/acs.joc.2c02841
43. Zhang L, & Wang R. Chiral phosphoric acid-catalyzed Mannich reaction in telaprevir synthesis. Organic Process Research & Development, (2021);25(6), 1342-1349. https://doi.org/10.1021/acs.oprd.1c00089
44. Zhou Q-Q, Chen W, & Liu X-H. Squaramide-catalyzed asymmetric synthesis: A decade of progress. Advanced Synthesis & Catalysis, (2021);363(19), 5893-5912. https://doi.org/10.1002/adsc.202100687