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A Novel Approaches On Catalytic Asymetric Synthesis

ANUSURI S CHANDRAVATI

Head of the department of Chemistry, VSM COLLEGE(A)

RAMACHANDRAPURAM, ANDHRA PRADESH.

Abstract :

Asymmetric catalysis stands at the forefront of modern chemistry, serving as a cornerstone for the efficient creation of enantiopure chiral molecules characterized by their high selectivity. In this review, we delve into the realm of asymmetric catalytic reactions, which spans various methodologies, each contributing to the broader landscape of the enantioselective synthesis of chiral molecules. Transition metals play a central role as catalysts for a wide range of transformations with chiral ligands such as phosphines, N-heterocyclic carbenes (NHCs), etc., facilitating the formation of chiral C-C and C-X bonds, enabling precise control over stereochemistry. Enantioselective photocatalytic reactions leverage the power of light as a driving force for the synthesis of chiral molecules. Asymmetric electrocatalysis has emerged as a sustainable approach, being both atom-efficient and environmentally friendly, while offering a versatile toolkit for enantioselective reductions and oxidations. Biocatalysis relies on nature's most efficient catalysts, i.e., enzymes, to provide exquisite selectivity, as well as a high tolerance for diverse functional groups under mild conditions. Thus, enzymatic optical resolution, kinetic resolution and dynamic kinetic resolution have revolutionized the production of enantiopure compounds. Enantioselective organocatalysis uses metal-free organocatalysts, consisting of modular chiral phosphorus, sulfur and nitrogen components, facilitating remarkably efficient and diverse enantioselective transformations. Additionally, unlocking traditionally unreactive C-H bonds through selective functionalization has expanded the arsenal of catalytic asymmetric synthesis, enabling the efficient and atom-economical construction of enantiopure chiral molecules. Incorporating flow chemistry into asymmetric catalysis has been transformative, as continuous flow systems provide precise control over reaction conditions, enhancing the efficiency and facilitating optimization. Researchers are increasingly adopting hybrid approaches that combine multiple strategies synergistically to tackle complex synthetic challenges. This convergence holds great promise, propelling the field of asymmetric catalysis forward and facilitating the

efficient construction of complex molecules in enantiopure form. As these methodologies evolve and complement one another, they push the boundaries of what can be accomplished in catalytic asymmetric synthesis, leading to the discovery of novel, highly selective transformations which may lead to groundbreaking applications across various industries

KEYWORDS asymmetric catalytic synthesis, asymmetric organocatalysis, asymmetric photocatalysis, asymmetric electrocatalysis, biocatalysis, C-H activation, flow chemistry

1 Introduction

One of the fundamental challenges in organic synthesis is the creation of molecules with specific chirality. The synthesis of enantiopure compounds remains a significant focus in pharmaceutical research, due to the fact that each enantiomer may well have distinct metabolic and toxicological characteristics and only specific enantiomer possesses desirable pharmacological properties, while the other enantiomer may cause undesirable side effects. Thus, the use of racemic compounds as pharmaceutical drugs may impose serious risks (Ceramella et al., 2022). The production of enantiomerically pure drugs is often timeconsuming, costly, and environmentally deleterious (Meggers, 2015). The use of chiral auxiliaries or enantiomerically pure starting materials from natural sources is costly in general and inefficient. Therefore, the development of highly efficient methods and processes in catalytic asymmetric synthesis has profound significance in the pharmaceutical industry, which needs to develop efficacious and safe chiral drugs with high target specificity (Betz et al., 2023).

In 2022, a book, “Catalytic Asymmetric Synthesis, fourth Edition” edited by Akiyama and Ojima, was published, which provided a comprehensive overview of the advances in the field between 2010 to early 2020 (Akiyama and Ojima, 2022). Since the advancement in this field of research is continuous, very fast and highly robust, numerous publications emerged since early 2020. Accordingly, the purpose of this review article is to focus on the most significant advances in catalytic asymmetric synthesis in the last 5 years (2018–2023) in specific areas, i.e., organocatalysis, photocatalysis, electrochemical catalysis, biocatalytic transformations, and applications of these catalytic processes in continuous flow system

This review also intends to showcase how different chiral catalysts can be synergistically used in addressing complex synthetic challenges (Emmanuel et al., 2023; Malakar et al., 2023). The development of these protocols has been spearheading the development of sophisticated, but cost-friendly and environmentally benign processes in catalytic asymmetric synthesis (Guo et al., 2022; Nagib, 2022; Wang et al., 2023). Judicious combination of various chiral catalysts and catalytic asymmetric processes would substantially expand chemist’s toolbox for the design and synthesis of target molecules with chiral centers bearing required absolute configurations

Where a drug's efficacy and safety hinges on its purity and stereochemical integrity, continuous flow processes can provide precise control over the quality of products (Tsubogo et al., 2015). There has been a substantial advancement in continuous flow processes since Kobayashi and coworkers demonstrated the potential of these systems in practical catalytic asymmetric synthesis in 2013 (Tsubogo et al., 2013). This area of research involves chemistry, chemical engineering and computer science, aiming at rendering chemical manufacturing processes more efficient, safe and eco-friendly (Plutschack et al., 2017).

Catalytic asymmetric synthesis appears to have a bright future not only for the productions of pharmaceuticals, diagnostics and materials, but also for the advancement of chemical sciences through new discoveries and innovative applications (Yamamoto and Ishihara, 2008; Reyes et al., 2022).

2 Asymmetric organocatalysis

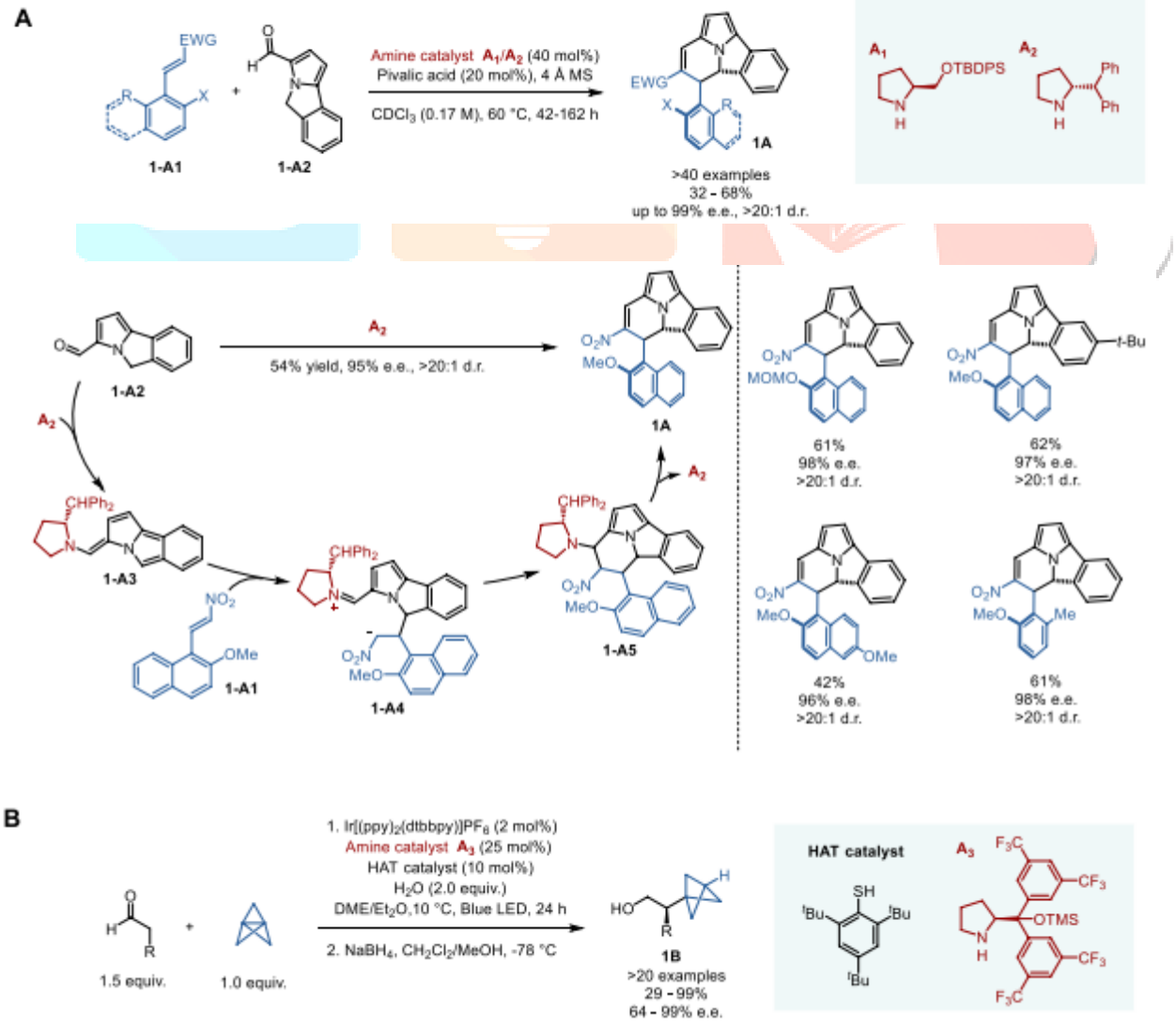
2.1 Enamine/iminium catalysis

Enamine species are prevalent in literature as a key intermediate for a diverse array of asymmetric organocatalytic transformations. In 2000, List, Lerner, and Barbas reported their proline-catalyzed intermolecular aldol condensation with an enamine species as a key intermediate (Bahmanyar and Houk, 2001; Sakthivel et al., 2001; Mukherjee et al., 2007) and in the same year MacMillan reported a Diels–Alder cyclization catalyzed by a chiral imidazolidinone via an iminium ion intermediate (Sakthivel et al., 2001; Erkkilä et al., 2007; Mukherjee et al., 2007). Since initial discoveries in 1970s (Hajos ZGP and Parrish, 1974), proline-derived organocatalysts have been indispensable tools in asymmetric catalytic transformations with some advantages associated with their usage, e.g., reactions proceed under mild and aerobic conditions, wherein moisture is tolerated. In 2021, the Nobel Prize in Chemistry was awarded jointly to Benjamin List and David MacMillan, highlighting the importance of asymmetric enamine/ iminium organocatalysis as a versatile and environmentally benign chemical process, effective for complex organic transformations in laboratories and industry (Mukergee, 2021).

In 2022, Jørgensen and coworkers succeeded in synthesizing atropoisomeric cyclizine cores with a conformationally stable C (sp2)-C (sp3) stereogenic axis for the first time, via enantioselective cyclization (Bertuzzi et al., 2022). This reaction took place between 5H-benzo [a]pyrrolizine-3-carbaldehydes and nitroolefins, α,βunsaturated ketoesters or α,β-unsaturated aldehydes, and represents the first example of highly enantioselective synthesis of cyclazine cores. For the reaction of 1-A1 with 1-A2, a modified amine catalyst A2 was found to be optimal, which gave cyclizine 1A in 54% yield and 95% e. e. As 1A shows, the condensation of aldehyde 1-A2 with organocatalyst A2, produces enamine 1-A3, followed by C-C bond formation with nitroolefin 1-A1 to afford 1-A4. Then, 1-A4 cyclizes to give 1-A5, and the subsequent elimination of organocatalyst A2 yields 1A. This reaction tolerated a diverse scope of aldehydes, nitroolefins

with different O-protecting groups, and naphthalene substitutions, giving the corresponding cyclizine products 1A in 32–68% yields with 92–99% e. e. and 10:1~>20:1 d. r.

In 2021, Anderson and coworkers reported a multi-catalytic strategy, incorporating organo-, photo- and hydrogen atom transfer (HAT) catalysis to synthesize α-chiral bicyclo [1.1.1]pentanes (BCPs) 1B, which are important bioisosteres for 1,4-disubstituted arenes, alkynes, and tert-butyl groups (1B) (Wong et al., 2021). The three catalytic cycles operate in unison without side reactions. During the optimization of reaction conditions, it was confirmed that iridium photocatalyst, Jørgensen-Hayashi's catalyst A3 and HAT catalyst were essential to obtain BCPs in 29–99% yield and 64–98% e. e. This multicatalyst process is applicable to the asymmetric synthesis of various αchiral BCPs bearing various functional groups at the α-position. For example, α-chiral BCP aldehydes were further derived into carboxylic acids, secondary amines, secondary alcohols, and homologated to alkynes without erosion of enantiomeric purity.



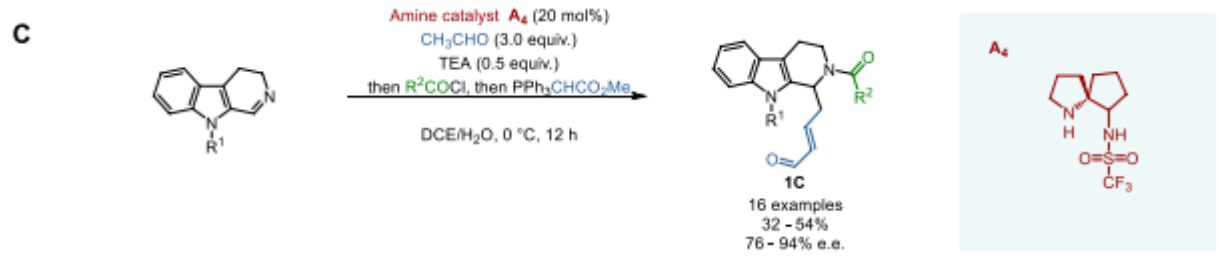
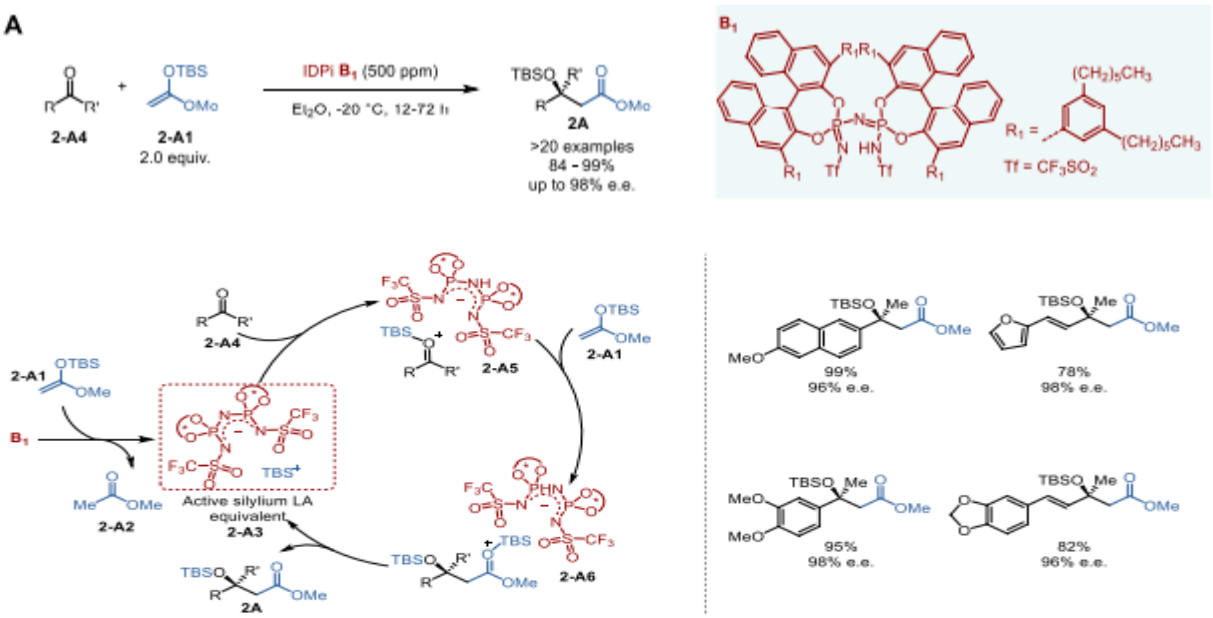


FIGURE 1 Asymmetric enamine-iminium catalysis (A–C).

2.2 Asymmetric Brønsted acid catalysis

Chiral Brønsted acid catalysts have been playing an important role in various asymmetric transformations since early 2000s (Yamamoto and Ishihara, 2008). Chiral Brønstead acids are tunable by varying the pKa, steric environment and mode of activation to produce effective catalysts for different asymmetric transformations (Akiyama and Ojima, 2022). Among a variety of chiral Brønsted acid catalysts, chiral phosphoric acids (CPAs) have been extensively studied and developed as one of the most versatile chiral catalysts. CPA is a bifunctional catalyst that functions as a Brønsted acid, as well as a Brønsted base, to form a hydrogen bonding network, involving a nucleophile and electrophile to promote asymmetric transformations (Faisca Phillips and Pombeiro, 2023). In 2004, Akiyama and Terada reported successful application of CPAs to enantioselective Mannich-type reactions, achieving high yields and excellent enatioselectivity (Akiyama et al., 2004; Uraguchi and Terada, 2004). Chiral Brønsted acids were also designed for asymmetric counter-anion directed catalysis (ACDC), as demonstrated by the works of List, wherein chiral imidodiphosphorimidates (IDPis) were successfully used as catalysts in a variety of asymmetric transformations (Schreyer et al., 2019)



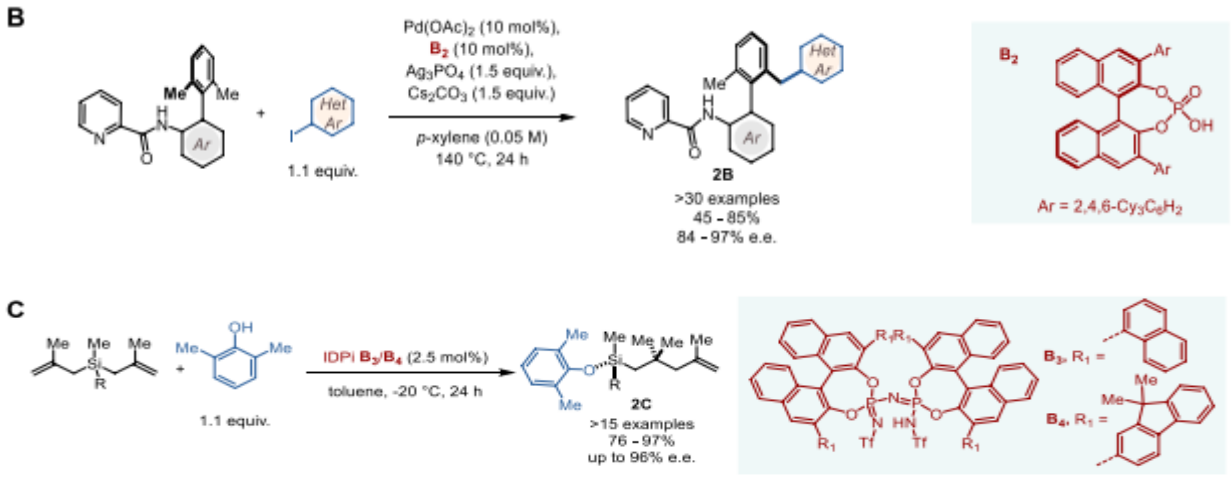


FIGURE 2 Chiral Brønsted acid catalyzed asymmetric reactions (A–C).

2.3 Asymmetric Brønsted base and hydrogen-donor catalysis

In a manner similar to that of proline-derived organocatalysts, chiral Brønsted bases function as catalyst for a variety of asymmetric transformations under mild conditions. Chiral Brønsted bases typically consist of chiral amine moieties as essential components by design. This asymmetric catalysis involves rather complex hydrogen-bonding networks among the substrate, chiral catalyst and nucleophile. This multi-component process also requires a delicate balance between the basicity of the catalyst and the acidity of the nucleophile. Since a variety of chiral Brønsted bases can be rationally designed, a large number of chiral catalysts have been invented and developed (Denmark and Beutner, 2008; Ishikawa et al., 2017), which are impossible to cover comprehensively. Accordingly, only a few selected examples, including hydrogen-donor catalysis are discussed here

2.4 Asymmetric N-heterocyclic carbene catalysis

In 2022, Chi and coworkers reported the enantioselective sulfonylation of 2-(substituted acryloyl)benzaldehydes catalyzed by chiral NHC species generated from triazolium pre-catalyst D1 to give the corresponding sulfonylethylideneisobenzofuranones 4A in 20–95% yield and 87–98% e.e. (4A) (Deng et al., 2022). Since chiral sulfones are unique functional groups found in pharmaceuticals and natural products, this process may provide an efficient access to biologically active sulfone-containing compounds. In this NHC catalysis, sulfonyl chloride functions as both an oxidant and a nucleophile via its reduced form. The chiral NHC species generated from pre-catalyst D1 reacts with the aldehyde moiety to initiate the activation of sulfonyl chloride, generating a sulfinate species that undergoes Michael addition to a remote enone moiety stereoselectively, triggering the cascade cyclization to give the product 4A and regenerate the chiral NHC catalyst. Mechanistic studies, including DFT calculations, suggest the involvement of an unprecedented Breslow intermediate and a novel mode of oxidation

Although successful chiral NHC catalyzed asymmetric reactions typically involve aldehydes, enals and esters as substrates, the reactions involving amides are still challenging. Nevertheless, in 2022, Huang and coworkers reported a successful protocol for the enantioselective desymmetrization of 4-substituted and 4,4- disubstituted N-Cbz-glutarimides (4-B1) with alcohols under mild conditions in the presence of triazolium pre-catalyst D2 (4B) (Hu et al., 2022). This process includes the enantioselective cleavage of the imide C-N bond by chiral NHC species generated from D2, followed by ester formation with an alcohol to give the corresponding glutarate-N-Cbz-amide 4B. A structurally diverse 3-substituted and 3,3-disubstituted glutarate-NCbz-amides 4B were synthesized by this process in 40–97% yield and 46–98% e. e. Furthermore, this process was successfully applied to the synthesis of the key intermediates of (R)-Baclofen (skeletal muscular relaxant) in 74% yield and 91% e. e., and (R)-Rolipram (antidepressant) in 50% yield and 95% e. e.

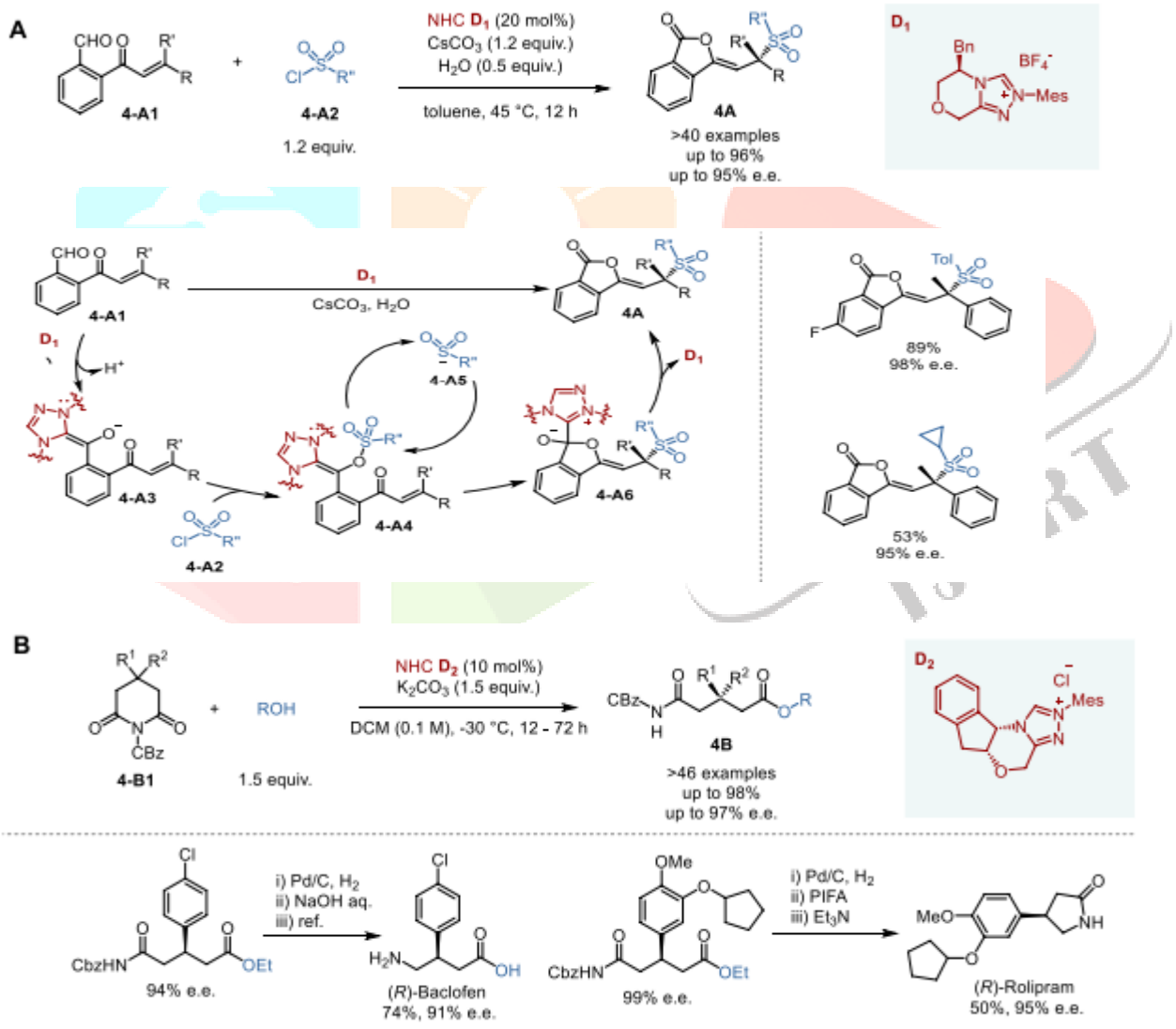


FIGURE 3 Chiral NHC catalyzed asymmetric synthesis (A,B).

2.5 Hypervalent iodine catalysts in asymmetric synthesis

In 2018, Jacobsen and coworkers reported the synthesis of syn-βfluoroaziridines 5A through diastereo- and enantioselective fluorination-aziridination of N-tosyl-3-arylprop-2-enylamines (5- A1) with mCPBA (stoichiometric oxidant) and HF-pyridine (nucleophilic fluoride source) promoted by chiral aryl iodide catalyst E1, which generates hypervalent iodine species (5A) (Mennie et al., 2018). A variety of allylamines 5-A1 bearing substituted aryl and fused hetero-bicyclic aryl groups were employed as substrates in this reaction to give the corresponding fluoroaziridines 5A in 44–93% yield and 61–97% e. e. with perfect diastereoselectivity. Since the catalyst-controlled diastereoselectivity in this process is extremely high, the fluorination of chiral 1-substituted N-tosyl-3- arylprop-2-enylamines afforded the corresponding 1,3-difluoro-2- amines bearing three contiguous stereocenters with very high diastereoselectivity (>20:1). This process was also successfully applied to the fluoroamination of N-tosyl-3-nitrophenylpent-4- ylamine to give the corresponding anti-β-fluoropyrrolidine in 82% yield with 86% e. e. and >20:1 d. r. Furthermore, variants of this process were applied to allyl benzyl ether, allyl carbamate and allyl acetate to give the corresponding 1,2-oxyfluorinated products in 64–77% yield and 92–94% e.e.

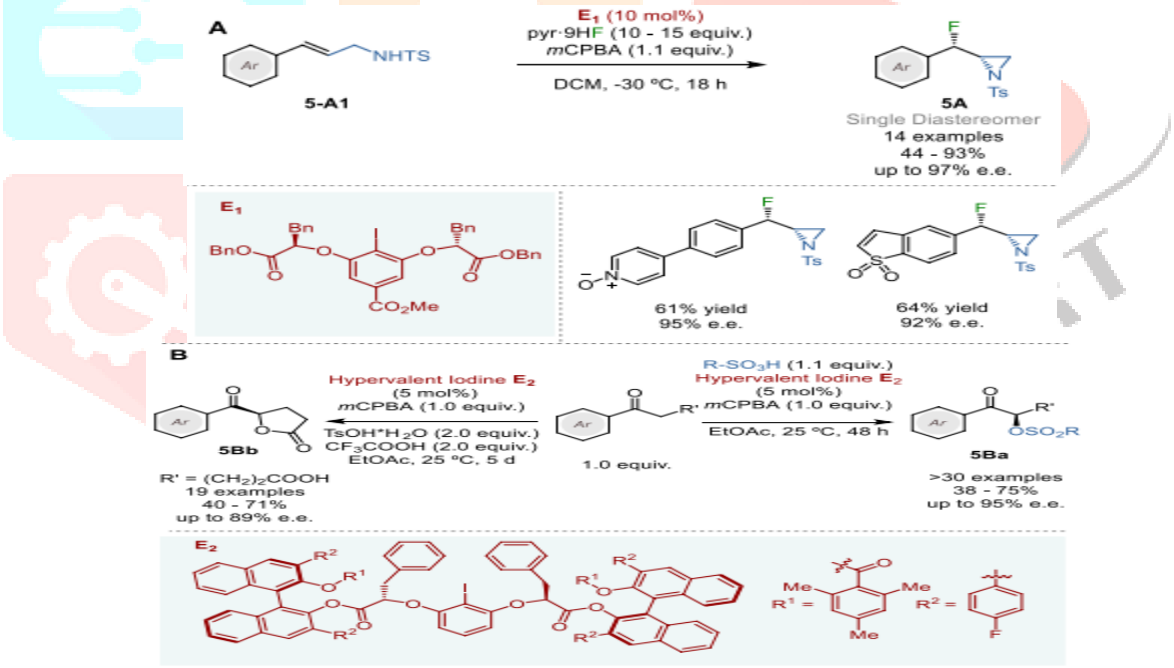


FIGURE 4 Hypervalent iodine catalyzed asymmetric transformations (A,B)

3 Asymmetric visible-light photoredox catalysis

Visible-light photoredox catalysis represents a fundamental departure from traditional methods of activating chemical reactions. Visible light, which is abundant and non-destructive, is an ideal energy source for these processes. The process involves a catalyst that absorbs visible light, triggering an electron transition from HOMO to LUMO (Li et al., 2020). Then, the excited catalyst species thus formed can undergo intersystem crossing to reach a triplet excited state (T1), which is more stable than the singlet excited state (S1). This approach offers several appealing and complementary advantages over conventional ground-state catalysis. It facilitates the generation of reactive radical species under mild reaction conditions, thereby enabling unique transformations that can rapidly generate molecular complexity and the late-stage functionalization of intricate molecules (Albini and Fagnoni, 2004; Prier et al., 2013; Schultz and Yoon, 2014). Establishing enantioselective photoredox-catalyzed processes is challenging in organic synthesis, given that intermediate radicals are highly reactive and reactions involving these species have low energy barriers (Shaw et al., 2016). This eventually leads to side reactions that are not enantioselective. Even with these problems, new ways of controlling the stereochemistry in photoredox processes have emerged in the last 10 years, facilitating the efficient synthesis of chiral molecules (Yoon, 2016; Saha, 2020; Yao et al., 2022).

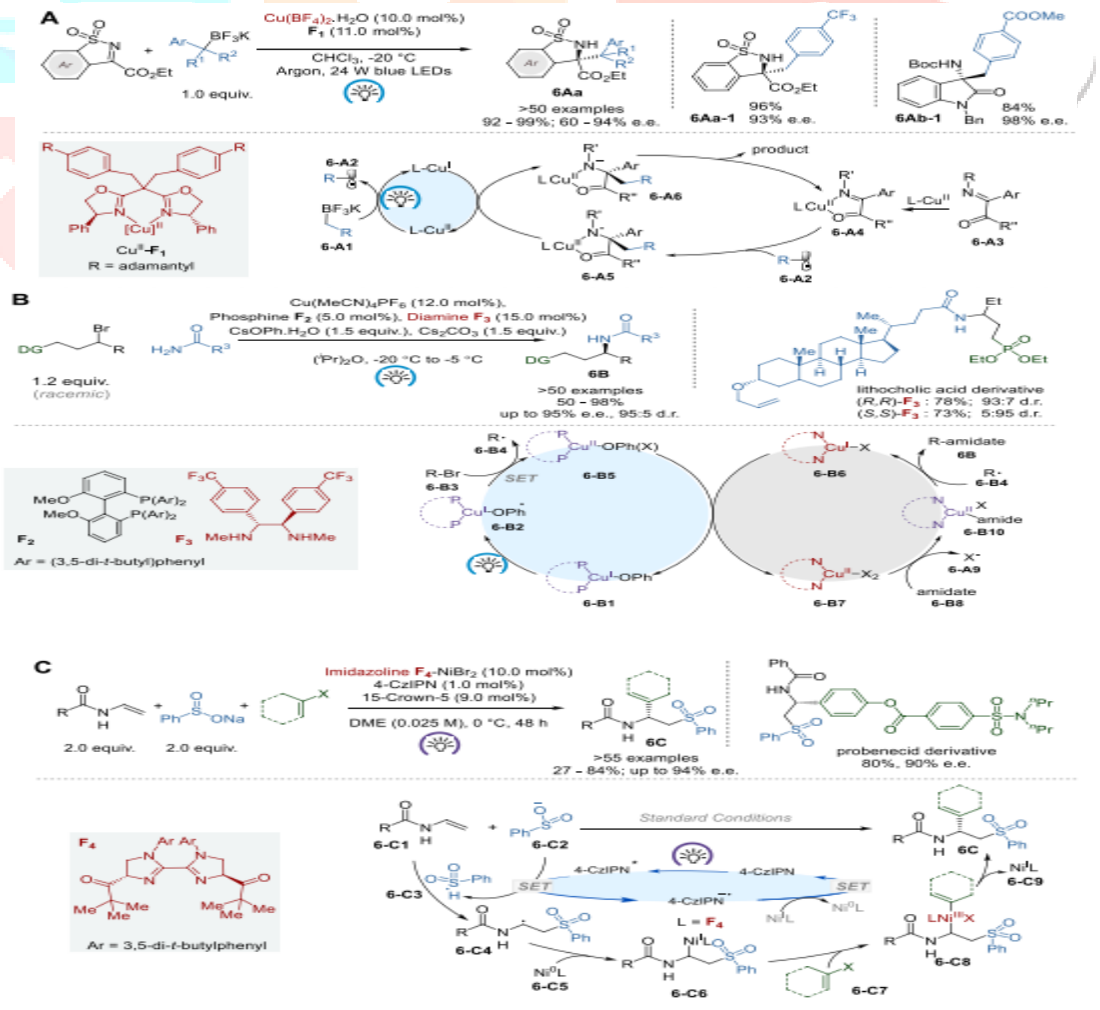


FIGURE 5 Metallaphotoredox asymmetric catalysis (A–C).

3.1 Asymmetric metallaphotoredox catalysis

In 2018, Gong and coworkers reported an enantioselective lightinduced alkylation of N-sulfonylimines with benzyl trifluoroborates catalyzed by copper (II)-bisoxazoline complexes (CuII-BOX), which was generated in situ from Cu(BF4)2 and BOX ligands (6A) (Li et al., 2018). The CuII-BOX complexes (e.g., CuII-F1) act as chiral photoredox bifunctional catalysts in this process to give various chiral N-sulfonylamines 6Aa with tetrasubstituted carbon stereocenters in 92–99% yield and 60–94% e. e. This reaction was also successfully applied to the asymmetric alkylation of isatinderived ketimines to afford the corresponding 3-N-t-Boc-amino-3- alkyloxindoles 6Ab in 69–84% yield and 96–98% e.e.

3.2 Asymmetric photoredox organocatalysis

The advancement of asymmetric photoredox catalysis has gained utmost recognition in recent years (Shaw et al., 2016). Asymmetric organocatalysis, including enamine, iminium-ion, Brønsted acid/base, and N-heterocyclic carbene catalysis, has been used to induce chirality transfer in photocatalytic reactions (Yoon, 2016; Zou et al., 2018). In general, asymmetric photoredox catalysis needs a second activation mode to facilitate asymmetric induction, due to the absence of general methods to control the stereochemistry of radical ion species (Nicewicz and MacMillan, 2008; Proctor et al., 2018; Huan et al., 2021; Sherbrook et al., 2021). However, in 2023, List and coworkers reported a single-catalyst solution for enantioselective [2 + 2] cross-cycloaddition of styrenes using a chiral organic salt G1 with confined imidodiphosphorimidate (IDPi) counteranions as the catalyst (7A) (Das et al., 2023). A broad range of mono/di-substituted styrenes with different electronic properties were employed in the reaction with trans-anethole derivatives to give the corresponding chiral cyclobutanes 7A in 31–91% yield and 76–96% e.e., wherein various functionalities, including alcohol, silyl ether, aldehyde, ester, and terminal olefin, were well tolerated. Mechanistic investigations suggest that the first step in the catalytic cycle, generating cation radical intermediate complexed to G1 (7-A4), determines the enantioselectivity, and the second step, forming the cyclobutane cation radical complexed to G1 (7-A5), determines the diastereoselectivity, resulting in thermodynamically and kinetically favored C-C bond formation between two benzylic sites in a trans-configuration. Finally, single electron transfer from the counter anion radical of G1* to the cyclobutane cation radical gives product 7A,

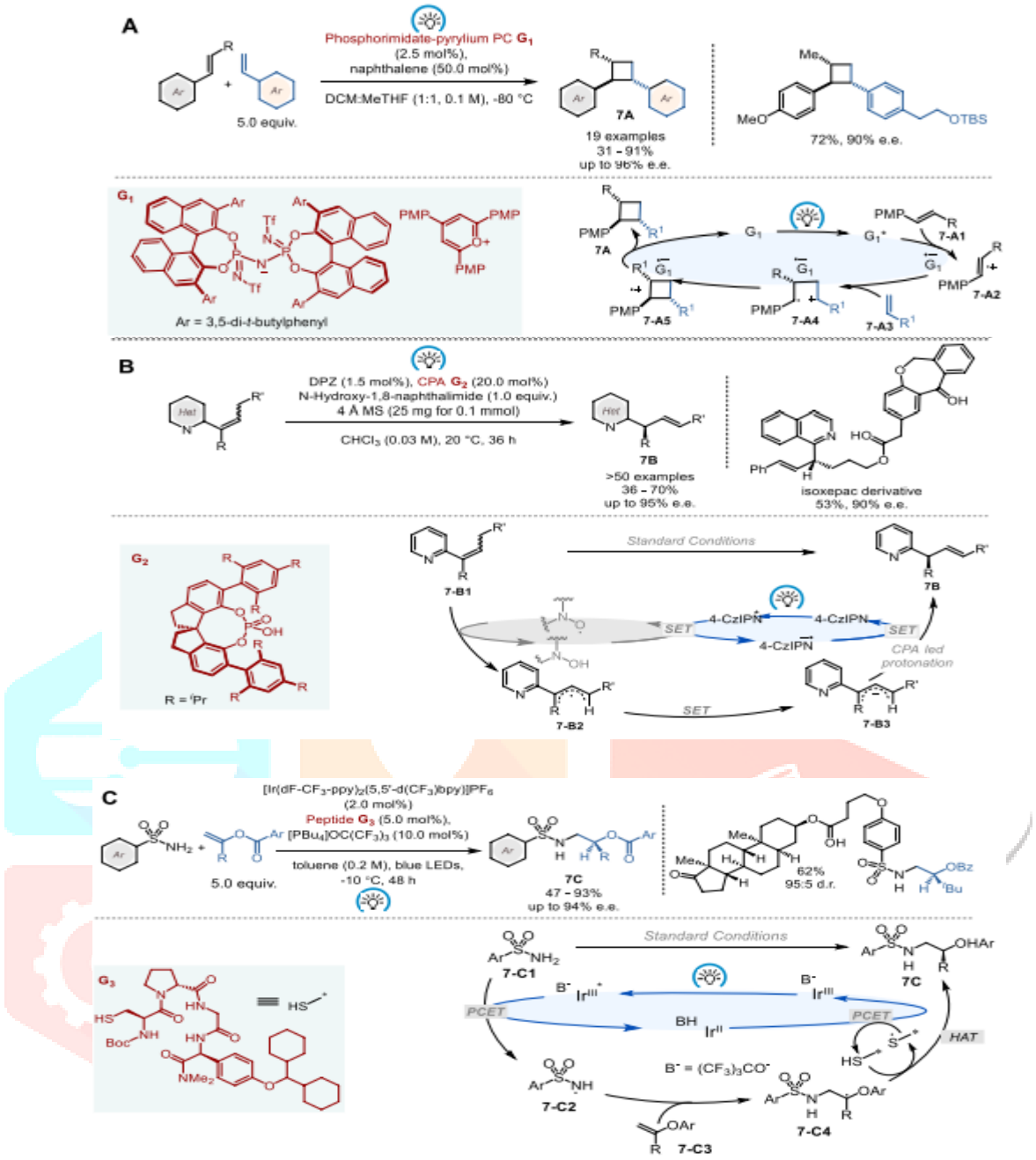


FIGURE 6 Photoredox organocatalysis for asymmetric synthesis (A–C)

4 Asymmetric electrochemical catalysis

The coupling of electrochemistry with chiral transition metal catalysis or organocatalysis has been recognized as a powerful strategy for asymmetric electrochemical catalysis, leveraging precise control over redox processes to drive enantioselective reactions. Electrosynthesis uses electricity instead of chemical reagents to transform organic molecules, which involves oxidation at the anode and reduction at the cathode in a conductive medium and is executed at either constant current or potential. Electrosynthesis can be carried out in a cell with or without a membrane, separating the anodic and cathodic spaces. The electrochemical transformations can be conducted directly at the electrode or indirectly using a redox mediator in the solution,

and the latter can enhance efficiency and selectivity under milder conditions. Thus, catalytic asymmetric electrosynthesis can be realized by the combination of a chiral catalysts and a redox mediator (Yan et al., 2017; Shah and Ngai, 2022). This approach is more economically feasible and versatile than the use of specialized chiral electrodes, electrolytes, solvents or pre-modified chiral substrates (Arnaboldi et al., 2018). Moreover, electrochemical synthesis can be effectively combined with various asymmetric catalyst systems, such as transition metalcatalysts and organocatalysts, as well as photochemical and bioelectrochemical asymmetric synthesis (Kärkäs, 2018; Kingston et al., 2019; Zhu et al., 2021).

4.1 Asymmetric electrochemical organocatalysis

In 2021, Mei and coworkers reported an electrochemical asymmetric coupling of secondary acyclic amines 8-A1 with ketones 8-A2 via Shono-type oxidation for the formation of amino acid derivatives 8A (8A) (Wang et al., 2021). In this process, an N-oxyl radical TEMPO was used as the redox mediator for anodic oxidation, which enables selective oxidation of N-arylglycinate substrates, but not α-substituted products 8A by exploiting a slight potential difference between the two. The use of TEMPO provided better functional group tolerance, as compared to the use of stoichiometric additives such as metals, electrolytes, and oxidants. For the substrate scope of this process, a variety of N-anisylglycinate derivatives, as well as cyclohexanone, cycloheptanone, tetrahydro-4-pyranone and tetrahydro-4- thiopyranone were employed to give the corresponding N-aryl-αcycloalkylglycinates in 33–80% yield with diastereoselectivity up to >99:1 d.r. and enantioselectivity up to 99% e.e.

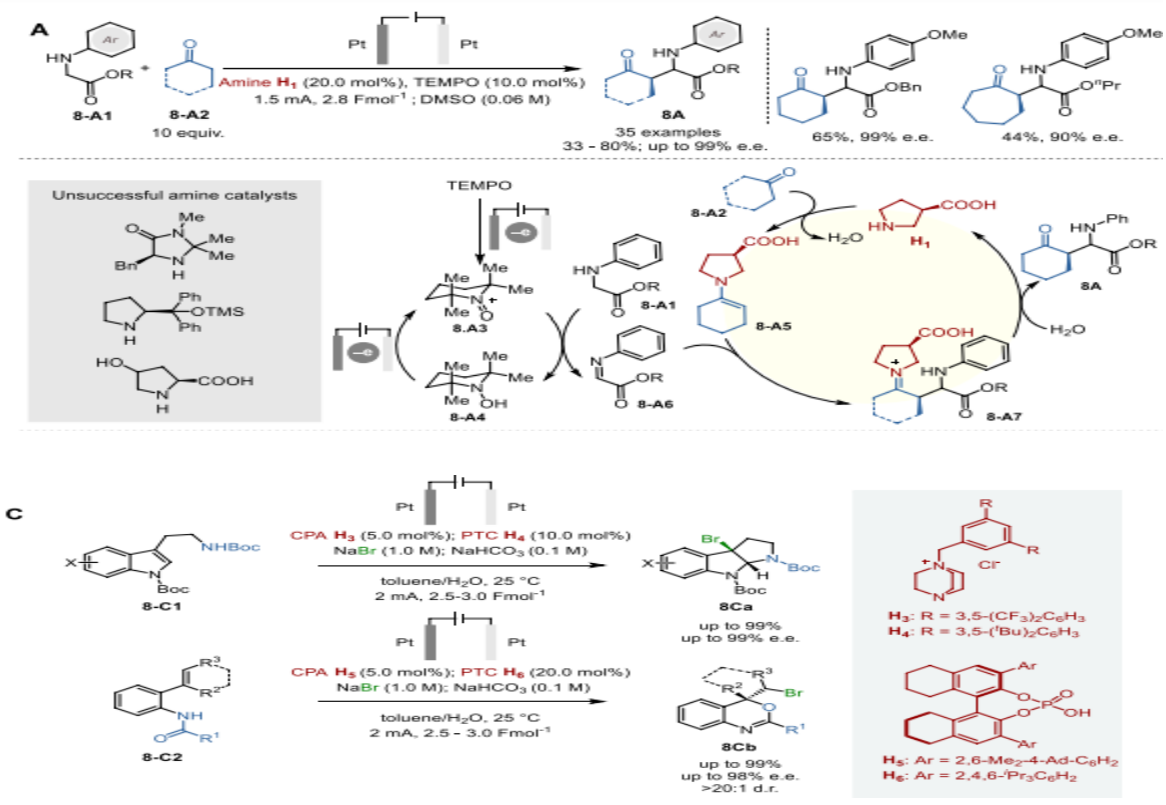


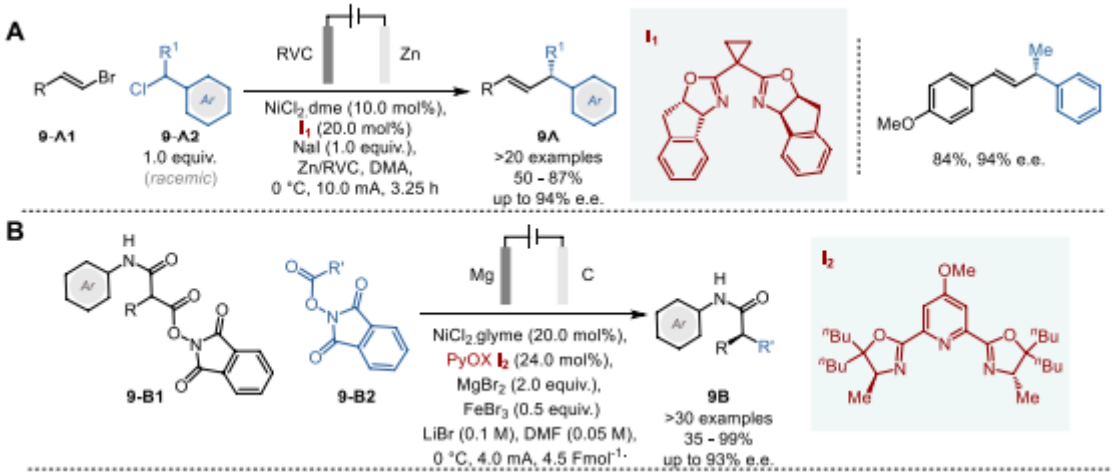
FIGURE 7 Eelectrochemical organocatalysis for asymmetric synthesis (A–C)

4.2 Asymmetric metallaelectrocatalysis

Asymmetric metallaelectrocatalysis is another successful combination of transition-metal catalyzed asymmetric synthesis with electrochemistry, which has proven to be highly effective, as evidenced by its growing use in organic synthesis (Chakraborty et al., 2021). Although the use of heterogenous metal reductants such as Mn0 and Zn0 is a common practice to generate and maintain the active catalyst species in transition-metal catalyzed processes, it is associated with some major issues, such as variability in activity due to different sources, batches, storage conditions, stirring conditions, production of excess waste, etc. Thus, more environmentally friendly and efficient alternative to heterogenous metal reductants is desirable

4.3 Asymmetric photoelectrochemical catalysis

Molecular photoelectrocatalysis has been under rapid development, allowing access to a broad range of redox potentials, enabling oxidative transformations with mild electrode potentials (Barham and König, 2020; Wu et al., 2022). Asymmetric photoelectrochemical catalysis (PEAC) combines photoredox catalysis with asymmetric electrocatalysis to facilitate enantioselective reactions without the need for external chemical oxidants



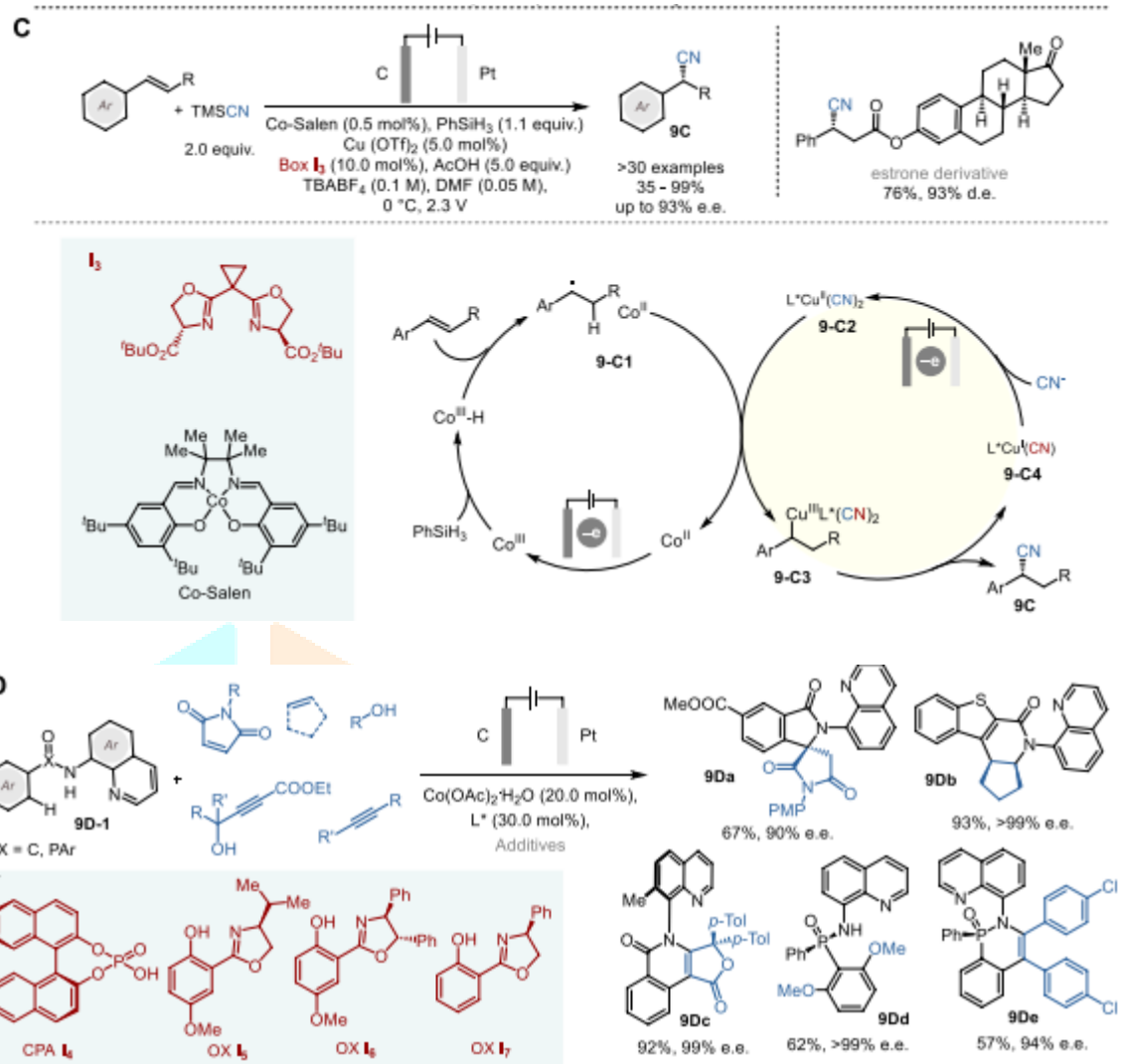


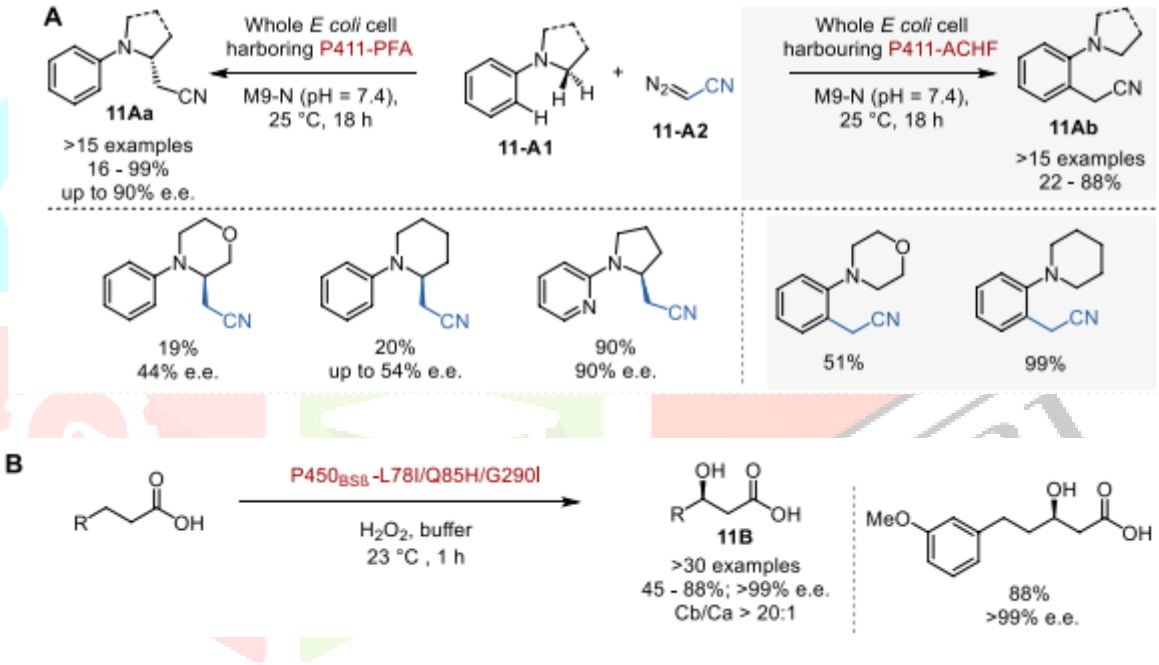
FIGURE 8 Metallaelectrocatalytic asymmetric synthesis (A–D).

5 Asymmetric biocatalysis

By leveraging the inherent selectivity and efficiency of enzymes and other biological catalysts, biocatalytic asymmetric reactions offer a powerful tool for sustainable and efficient chemical synthesis (Hauer, 2020). In recent years, significant advances have been made in the evolution of biocatalysis (Bornscheuer et al., 2012; Bell et al., 2021). The exploration of biocatalysts underwent a transformative transition from the extraction of compounds from natural sources to the sophisticated approach of gene mining, facilitated by bioinformatics (Yi et al., 2021). Enzymes are highly efficient as they possess a directing group, which controls selectivity, and a catalytic domain in one molecule. Moreover, an enzyme can be combined with other enzymes in a single process, augmenting their adaptability and effectiveness. Broadly, three distinct approaches have been pursued to enhance enantioselective reactions: (i) the generation of whole-cell biocatalysts by crafting designer organisms, (ii) the refinement of existing enzymes with inherent enantioselectivity for a specific process, and (iii) the evolution of novel enantioselective biocatalysts, starting from non-selective wild-type enzymes (Jaeger and Eggert, 2004).

5.1 Asymmetric enzymatic biocatalysis

In 2023, Arnold and coworkers reported the selective αcyanocarbene insertion into α-aminoalkyl C (sp3)-H bonds of N,N-dialkylaniline congeners 11-A1 via cytochrome P450 enzymes from Bacillus megaterium through minimal protein modifications to give enantioenriched αcyanomethylamines 11Aa in 16–99% yield with up to 90% e. e. (11A) (Zhang et al., 2023b). Following comprehensive crystallographic structural analysis, P411-PFA and P411-ACHF were selected as two distinct cyanomethylases. Fluoroalkylase P411-PFA effectively introduces a cyanomethyl group into the αaminoalkyl C (sp3)-H bond of 11-A1 with notable chemo-, regio-, and enantioselectivity. In sharp contrast, P411-ACHF catalyzes an alkylation of the ortho-C (sp2)-H bonds of 11-A1. This approach represents a significant advancement in the field of biocatalysis, demonstrating the enzyme's ability to perform highly selective and efficient chemical transformations that are challenging to achieve through chemical catalysis



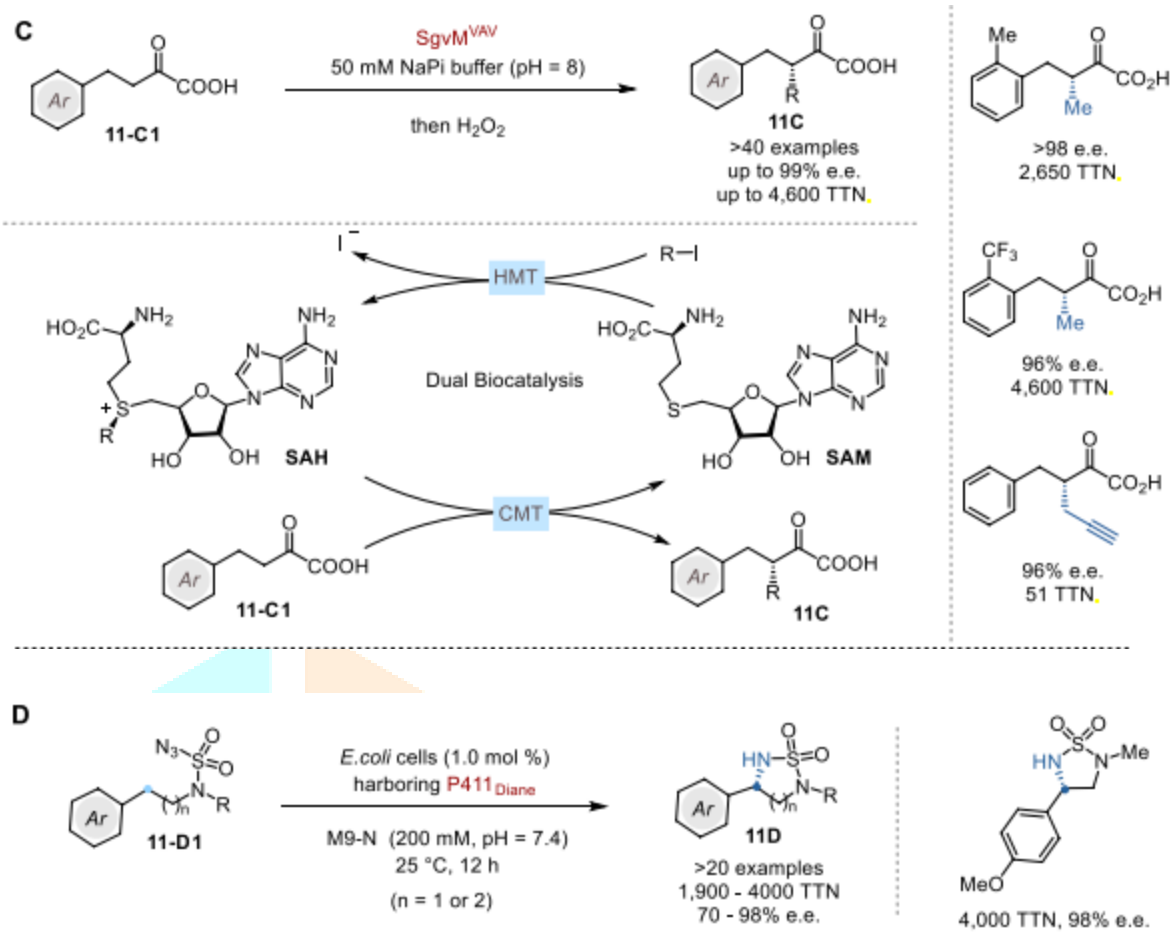


FIGURE 9 Asymmetric enzymatic biocatalysis (A–D).

5.2 Asymmetric photoredox enzymatic biocatalysis

Nature is the best example to showcase how enzymes like fatty acid photodecarboxylase, DNA photolyase, etc., use light to facilitate biologically essential transformations (Schmermund et al., 2019). Asymmetric photoredox enzymatic biocatalysis has recently emerged as an innovative and highly promising synthetic methodology (Schmermund et al., 2019; Emmanuel et al., 2023). Merging biocatalysis with photocatalysis enables selective, lightdriven transformations that offer novel reactivity, high selectivity, and better yields under environmentally benign conditions (Emmanuel et al., 2023).

6 Asymmetric catalysis in continuous flow system

Continuous flow reactions and processes have been continuously developed, which encompass a diverse chemical transformations. The advancement in the engineering of continuous flow reactors and precise control of reaction conditions will lead to more productive and energy-efficient systems. While continuous flow processes are not always a replacement for batch processes, there are many advantages that flow chemistry can offer, including safe handling of gaseous reagents, high-pressure reactions, better mixing and heat transfer for very rapid exothermic reactions, and full-automation for higher efficiency (Plutschack et al., 2017). Flow chemistry has attracted much attention from chemists and engineers both in academia and industry, since the

continuous flow systems can produce a large quantity of fine chemicals and commodity chemicals through continuous operation. As the research on continuous flow reactions has progressed (Ingham et al., 2015), naturally the applications of the continuous flow system to catalytic asymmetric transformations have attracted substantial interest among synthetic chemistry communities in the last decade, and significant advances have been made (Pastre et al., 2013).

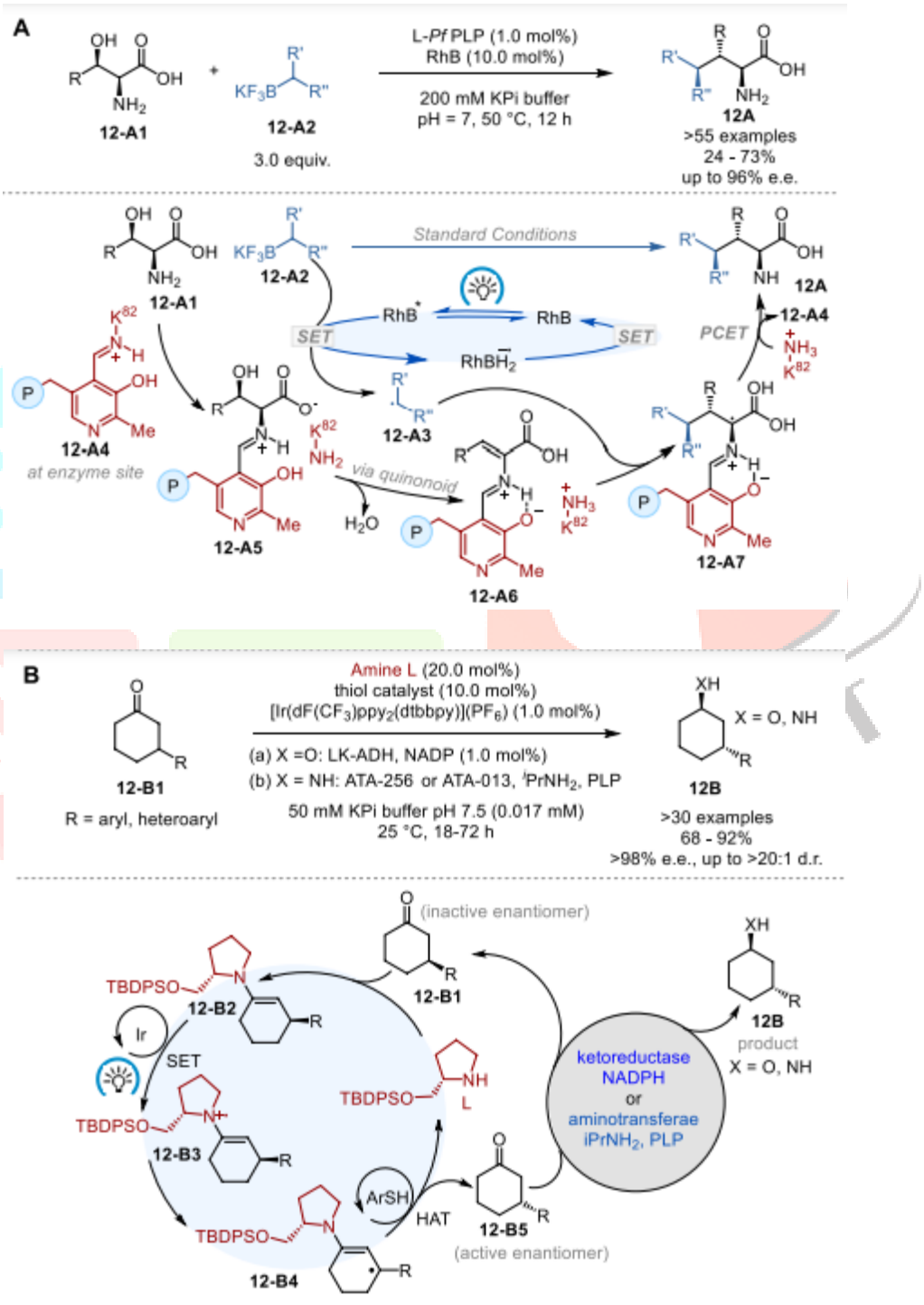


FIGURE 10 Asymmetric photoredox enzymatic biocatalysis (A,B).

7 Conclusion and future perspective

Development of catalytic asymmetric reactions continues to be an important research topic in organic chemistry, partly because it will contribute significantly to the pharmaceutical sciences and production of therapeutic drugs. The ideal catalytic reactions would proceed in 100% yield with complete chemoselectivity, regioselectivity, and stereoselectivity. From the standpoint of green chemistry, highly efficient (i.e., high turnover number) and safe reagents are desirable. We have highlighted the most significant works on the catalytic asymmetric reactions from 2018 to 2023 in this review article, which clearly shows that significant advances have been made in this field in the last 5 years. In addition to metal catalysis and biocatalysis, organocatalysis has also proven to be a valuable tool for the construction of optically active compounds as evidenced by the Nobel Prize in Chemistry awarded jointly to Benjamin List and David MacMillan in 2021. Recently, electrocatalysis and photoredox catalysis have emerged as powerful tools for the development of new and valuable transformations for construction of organic molecules in enantiomerically pure form.

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