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Evolution of design approaches in asymmetric organocatalysis over the last decade

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ABSTRACT

This perspective intends to cover the vast field of asymmetric organocatalysis and its evolution during the last ten years. This work has evaluated the corresponding timeline of the progression of the field concerning the main synthetic approaches as well as the ground-breaking synergetic approach between experimental and computational methods. With the combination of an evolutionary trend and the expansion of computing technology, further advancements in the field of asymmetric organocatalysis are undeniable.

1. Introduction

Asymmetric synthesis has become a dominant field in organic chemistry, mainly, due to pharmaceutical and societal necessities. Such reactions are facilitated by molecules called chiral catalysts, which play the role of steering the reaction towards enantiomeric excess and high yield. Organocatalysis is a branch of catalysis that is a robust, environmentally, and economically sustainable leading standard for modern-day asymmetric catalysis, in alignment with the current industrial demands regarding environmental degradation [1]. The application of small organic molecules for catalysis requires mild reaction conditions and facile catalyst substrate separation processes, offering solutions to limitations associated with the respective metal-based catalysts [2–5]. Despite such merits, the growth of organocatalysis was stagnant in its early years, leaving a vacancy in its research and chemists sceptical of its ability to be a worthwhile candidate. The first organocatalytic study dates to 1860 [6], when cyanogen was converted to oxamide in the presence of aqueous acetaldehyde. However, regardless of such early exposure to organocatalysts, its ability to encourage enantioselectivity was only detected in 1912 [7,8] in the addition of hydrogen cyanide to benzaldehyde in the presence of a chiral cinchona alkaloid catalyst. The momentum rapidly changed following the pivotal publication by Hajos and Parrish in 1974 [9] on the first proline catalysed asymmetric aldol reaction; the Hajos-Parrish-Eder-Sauer-Wiechert reaction. Each decade following the work by Hajos and Parrish presented its unique set of attributes and accomplishments within organic synthesis, leaving a set of hopeful starting points for decades to come. Between 1970 and 2000, there was an abundance of interest and development of asymmetric organocatalytic concepts, namely phase-transfer catalysis (PTC) [10,11], Brønsted acid catalysis [12], tertiary amine catalysis [13] and phosphine catalysis [14].

The early 2000s were primarily governed by the influential and persistent work performed by List [15–17] and MacMillan [18–22]. Their work was focused on enamine and iminium ion-based organocatalysis [23,24], while also advocating the field's novelty and potential by exhibiting that organocatalysts are not only versatile but could potentially fill many existing gaps in organic chemistry. Theoretical concepts submerged into organic studies throughout the 2000s [25–28] and provided clarification for ambiguous experimental results, thus the process of catalyst investigation/design began to shift from trial and error to a more rational approach. The first ever theoretical application to asymmetric organocatalysis was in 2004 by Cheong et al.; [29] a mechanistic study on the archetypal Hajos-Parrish reaction. As a result, the plethora of unanswered questions related to the perplexing reaction from the 1970s were addressed allowing the fog of doubt and criticism surrounding asymmetric organocatalysis to clear.

Herein, we present a perspective article featuring some of the synthetic milestones of this decade we believe played an evolutionary role in asymmetric organocatalysis (Fig. 1). The direction of sustainable catalytic development has also been strongly highlighted in this perspective by emphasising the application and evolution of quantum mechanics and machine learning this decade, navigating the field towards a more efficient rational design approach.

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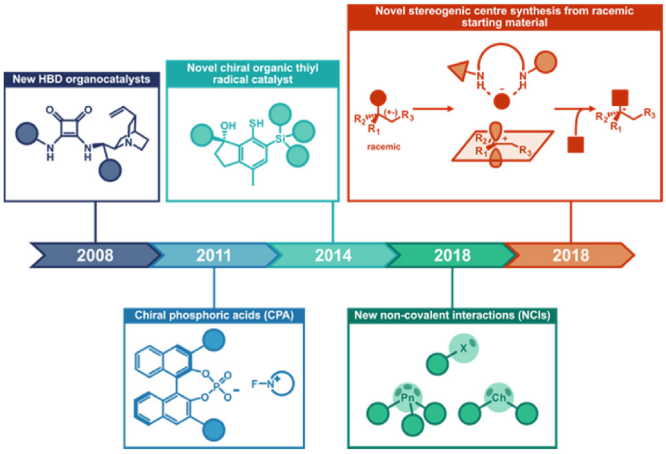

Fig. 1. The synthetic milestones of this decade.

2. Synthetic milestones

Organocatalysis has continued to undergo a gradual yet dynamic expansion in the realm of organic synthesis. Its prevalent application in classical and contemporary synthetic chemistry [30–33] has maintained its lively *tempo* into the present decade.

In previous decades phase transfer catalysis (PTC) primarily relied on the cinchona alkaloid scaffold (Fig. 2a) [34], despite such scaffolds presenting plausible merits, they also exhibited limitations such as strenuous catalytic modifications. These limitations established a promising starting point for Maruoka et al. [35] in the development of spiro-quaternary ammonium salts PTC (Fig. 2b). The unique scaffold was found to be catalytically rewarding as well as vigorous under mild phase transfer conditions [36]. However, within this decade, alternative catalytic strategies are beginning to emerge. For instance, chiral phosphoric acids (CPA) [37–42] were incorporated within PTC on account of their efficiency and tremendous structural versatility (Fig. 2c). At the beginning of the decade, Toste & co-workers [43] proposed a fascinating alternative to the traditional use of chiral cation salts for PTC. An asymmetric electrophilic fluorination reaction was facilitated using a chiral phosphate catalyst through an innovative anionic chiral phase-transfer approach. A chiral fluorinating reagent was generated through ion exchange, permitting the synthesis of an invaluable carbon-fluorine stereocenter. Prior to this study, limited catalytic systems retained both reactivity and stereoselectivity in the challenging carbon-fluorine bond formation reaction. Research in previous decades regarding chiral anionic catalysts for PTC was constrained, but over the years organic chemists have taken an interest in the budding yet promising synthetic strategy. Consequently, it has been propagated to other chemical synthesis processes this decade [44–47], even acquiring the title as one of the contemporary methods for the synthesis of carbon-fluorine quaternary stereogenic centres [48].

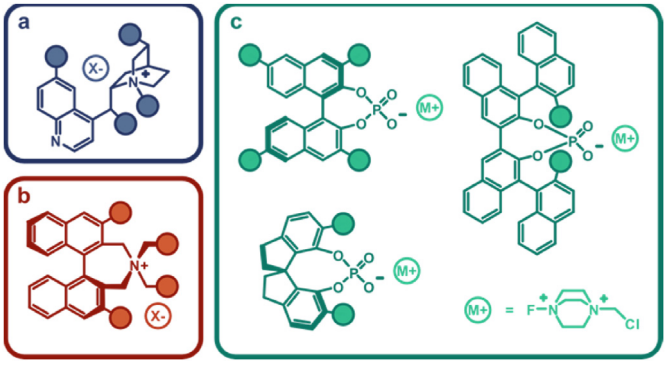

Fig. 2. (a) Chiral cinchona alkaloid-based scaffold (b) Spiro-quaternary ammonium salts-based scaffold (c) Varied chiral backbones of CPA used within anionic PTC.

A novel acid-base chiral organic thiyl radical catalyst was designed by Hashimoto et al. in 2014 (Fig. 1) [49]. Despite being seldom investigated in past decades, the newly designed chiral radical catalyst proved to be extremely diastereo- and enantioselective in the *C*–C bond forming radical cyclization reaction. Its novelty is accentuated by its conceptually distinct reaction mode in which chiral information is conveyed by the closed-shell intermediate upon radical reaction with the corresponding substrates. The publication of this work created optimistic starting points for research circulating photochemical and electrochemical methods within organocatalysis [50–52], and will potentially continue to inspire for decades to come.

Hydrogen bond (HB) mediated asymmetric organocatalysis continues to prosper throughout this decade. The captivating topic has been extensively explored since its pivotal role in organic synthetic reactions at the dawn of the millennium. Hydrogen bond donor (HBD) organocatalysts based on the thiourea motif were dominant in the early 2000s [53], but in the late 2000s, squaramide-based organocatalysts began to gain acknowledgment earning the scaffold popularity. It was the critical work by Rawal [54] that ignited interest in the overlooked squaramide motif as a forcible HBD organocatalysts, consequently setting the pace for further developments on such a catalytic scaffold. Subsequently Jacobsen discovered an effective catalytic strategy for asymmetric reactions involving cationic intermediates [55]. The logistics of the new strategy consisted of an interaction between silyl triflate and squaramide, giving rise to a reactive, enantioselective, yet stable Lewis acid complex. By cooperative effect the complex was found to be highly efficient in controlling the production of ionic intermediates at low temperatures. Considering this strategy, Jacobsen went on to further develop an enantioconvergent and novel catalytic SN1 reaction in 2018 (Fig. 1) [56]. The pioneering collaborative effect between the HBD squaramide and strong Lewis acid TMSOTf accommodated the synthesis of a tertiary carbocation intermediates with substantial influence over the enantioselectivity of the reaction at low temperatures. The strategy presented in this study has notable potential to be applied in the future synthesis of structurally paramount congested stereogenic centres from racemic starting material. The considerable success of HBD as organocatalysts has gradually cultivated interest in other non-covalent interactions as promising activation modes, such as σ hole [57]. Consisting of halogen bonds (XB), chalcogen bonds (ChB), and pnictogen bonds (PnB), the family of σ holes is still in its infancy, currently being assessed via experimental and theoretical means [58,59]. Despite such interactions being conceptually new within catalysis, they surpass HB in directionality and rigidity [60]. Recent studies have shown their ability to stabilise nucleophilic intermediates and transition states, hence establishing a promising starting point for decades to come [61].

3. Design approaches

While experimental studies were the mainstay of catalyst design in the early stages [62], over time computational methods have increasingly become a popular approach within asymmetric organocatalysis in this decade; predominantly utilised as a tool to validate experimental findings and to elucidate mechanistic pathways. Obtaining a meaningful correlation between experimental and theoretical approximations allowed chemists to gain insightful information and thus producing logical explanations for aspects that facilitate reactions. Furthermore, the rapid progression in computing capacities has made computational methods a more desirable approach, exhibiting cost-effectiveness for investigating mechanistic pathways in chemical systems with high accuracy [63]. It has been established that the continuous incorporation of theoretical investigations into experimental studies has generated the possibility of doing something novel and, additionally, resulted in the resolution of limitations in certain areas of research. Where previous

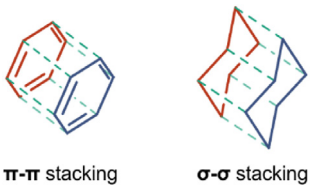

Fig. 3. The non-covalent interactions prevalent in asymmetric organocatalysis; π-π stacking (left) between two benzene molecules and σ-σ stacking (right) between two non-conjugated cyclohexane molecules.

experimental studies were limited to conjugated systems that involved π-π stacking interactions in the intermolecular charge transport, Feng et al. [64] recently demonstrated an alternative charge transport pathway between two non-conjugated molecules supported through theoretical calculations. The group showed that σ-σ stacking interaction energies between two non-conjugated cyclohexane molecules is equally as significant as π-π stacking between two benzene molecules (Fig. 3). This discovery within non-covalent interactions may have previously set back experimentalists, but now opens an opportunity to elevate the ongoing research in asymmetric organocatalytic reactions in which these non-covalent interactions play a pivotal role in the stereochemical outcome [65], considering that studying the interactions in silico have been proven to produce invaluable insight towards stereoselectivity.

Since the development of experimental routes within the field and the further use of computational methods as a complementary aspect, within this decade, there has also been a rapid growth in the incorporation of data-driven statistical approaches towards catalyst design. Data-driven approaches offer many benefits and highly complement pre-existing quantum mechanical methods towards mechanistic studies and catalyst design. While DFT calculations have been applied extensively for mechanistic investigations despite advancements in computing accuracy, there are still challenges that need to be overcome. Mainly, the exploration of the potential energy surface (PES) [66], as a precise simulation of the chemical process involved, is required for an in-depth study and although quantum methods offer reasonable accuracy with economical running times, it is time-demanding and computationally expensive. Automatization methods allow to overcome these challenges with machine learning techniques and are quickly becoming known as a powerful platform within asymmetric organocatalysis. The reason for this is due to the high probability of producing faster results via high-throughput experimentation with screening libraries of catalysts rather than a comprehensive quantum mechanical analysis alone [67]. Additionally, this approach does not require in-depth knowledge, making it an excellent method for exploring homogenous catalysis. Furthermore, machine learning techniques provide an advantageous path in the evolution of organocatalysis towards a more sustainable and greener chemistry which is prevalent in contemporary research [68].

Machine learning (ML), a data-driven statistical method that implements artificial intelligence, focuses on developing computer algorithms that enhance and facilitate learning from raw data [69,70]. They rely on chemical databases within organocatalysis, which provides chemical knowledge to develop an accurate and generalisable ML model, and molecular descriptors, which translate chemical structures into digital language. ML algorithms can be divided into three different categories: reinforcement learning, unsupervised learning, and supervised learning. The reinforced learning model rewards positive stimuli and punishes undesirable ones based on reward feedback [71,72]. In unsupervised machine learning, a model analyses and clusters unlabelled datasets [73]. The supervised machine learning method trains algorithms based on labelled datasets to predict an output based on inputs and outputs [74]. While the utilisation of ML techniques is still relatively new, they have made great progress within the field having been successfully applied in the preparation of synthesis, in the prediction of reaction conditions, reaction performance and outcomes within a chemical reaction, and in the optimisations of reaction performance [75].

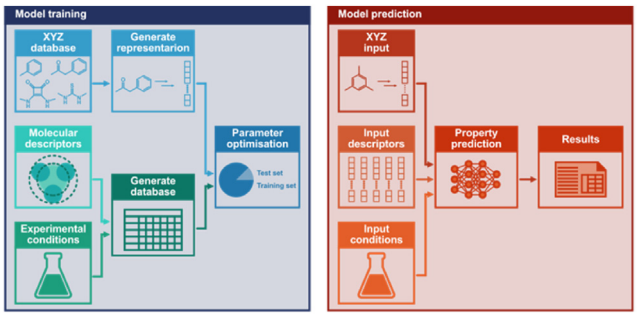

Fig. 4. General workflow of machine learning.

In a recent review presented by our group [25], ML is highlighted within organocatalytic design to accurately predict an optimal catalyst by recognising patterns in large data sets using robust molecular descriptors, in contrast with the classical quantum approach. The general workflow (Fig. 4) to train a ML model follows a similar procedure in most cases and differs in the types of data that can be fed to the model. For instance, varying molecular or physical properties and/or experimental conditions. For example, molecular descriptors designed specifically for asymmetric catalysis have been seen to establish a compilation of calculations for a comprehensive library of compounds based on steric and electronic properties. This was applied by Zahrt and co-workers [76] to train machine learning methods to make accurate prediction models over a wide range of selectivity spaces. ML models have been implemented by Li et al. [77] to quantitatively predict stereoselectivity of CPA – catalysed addition of protic nucleophiles to imines. The group developed a composite machine learning model, which combined models such as LASSO, regression tree, random forest, and boosting tree models, learning from pre-existing stereoselective reactions to accurately predict the activation energy. This model allows the exploration of interactions and the selection of the most relevant features for accurate predictions and has provided the basis for further exploration of other stereoselective reactions with synthetic value and mechanistic interest. Similarly, Gallarati and co-workers developed an improved atomistic machine learning model to predict the stereoselectivity of Lewis base-catalysed propargylation reactions [78]. This was achieved by using dissimilarity plots to rationally design a reaction-based approach accurately characterising the enantio-determining transition state energy. Additionally, ML models have also been performed by Kondo et al. [79] to explore and predict optimal flow reaction conditions through the screening of multiple parameters. As the application of a micro-mixing flow system which suppressed side reactions was found to result in an improved chemical yield, the group proceeded to optimise reaction conditions in a flow system for the enantioselective organocatalyzed Rauhut–Currier and [3 + 2] annulation sequence. The temperature and flow rate were screened using a programming library for Gaussian process regression to achieve an ML estimation of the optimal flow reaction conditions which were subsequently confirmed through experimentation with excellent results.

The synergy between experimental, quantum mechanical methods and data-driven approaches, is quickly becoming a powerful platform in catalyst design within asymmetric catalysis, with machine learning techniques expected to be a pivotal design approach. Despite still being novel with many under-explored research opportunities, ML models have proven to be highly advantageous in reproducing accurate predictions in a satisfactory time frame while maintaining the green aspect.

4. Future developments and challenges within the field

It is clear that ML models have appeared as a revolutionary and successful practice to approach chemical enigma, and therefore, they are regularly suited into chemistry research workflows. The integration of

different programs and techniques into ML models as well as implementing and analysing several descriptors have had an enormous impact within organic chemistry - reactivity- and more recently, within the asymmetric catalysis domain. However, there remain challenges mainly related to predictability, interpretability, and generalizability of those recently developed models. A prime example, demonstrated by Lee et al. [80], concluded that while ML models depend on recognisable patterns to make predictions from the training data, they do not necessarily correlate with actual underlying chemical reactivity, leading to incorrect predictions through learning bias. In addition, the authors have also proven what has been called, a prominent 'Scaffold bias', which exists in the published literature on reaction prediction resulting in the overstatement in the generalisation of the models. Nevertheless, as previously discussed, ML will inevitably develop and further advance within this field in the future to overcome such challenges.

The development of new methods that incorporate ML techniques is a constant progression. One of these methods includes data-driven automation laboratories, a relatively new and innovative approach towards obtaining high-quality experimental data, recently been developed, incorporating a robotic synthesis engine 'Chemspeed' to automatise a whole synthetic workflow using robots and machine learning in parallel, iteratively improving the ML model by adding new data (Fig. 5) [81]. The self-driven lab uses a highly flexible and versatile software package, 'ChemOs' [82], which orchestrates experiment scheduling and selects future experiments using feedback from previous experiments through ML. In addition to providing highly reproducible results by eliminating human error, these systems provide higher throughput, collecting large amounts of quantitative data in comparison to ML models alone. The development of such systems can potentially expedite molecular discovery significantly by enabling systematic optimisations, increasing efficiency, and decreasing the consumption of materials. However, they present their own limitations. These automated labs struggle with aspects associated with integrating human cognitive processes; encountering unexpected or difficult-to-predict results, assuming the absence of gaps in knowledge or that all constraints are known and the identification of unknown or unexpected products and side products, and motor functions within ML models where manufacturers design their software without self-driving laboratories in mind. While the applications of these autonomous systems are currently limited to organometallic chemistry; they present vast potentials of its applications within the field of asymmetric organocatalysis [83]. In combination with growing synthetic advancements within the field, such as continuous flow systems (Fig. 6) [84–86],

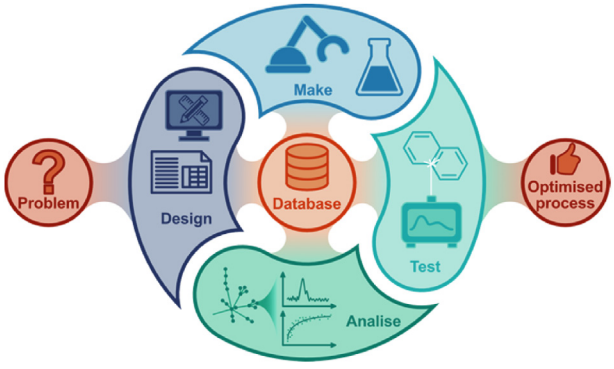

Fig. 5. Schematic representation of the autonomous laboratories.

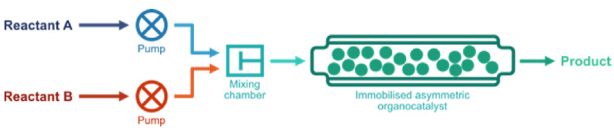

Fig. 6. General procedure of continuous flow systems.

potentially opening the possibility of applying automatic labs to organic asymmetric catalysis in the near future and, therefore, unequivocally accelerating automated asymmetric synthesis, resulting in a huge point of interest within asymmetric organocatalysis in the coming years.

5. Concluding thoughts

Since the initial division of the term organocatalysis in the 1990s, the field has evolved and continues to evolve tremendously [87]. We have highlighted the novel catalytic strategies of this decade that we think establish a promising foundation for the development and design of future robust asymmetric organocatalytic scaffolds. It is evident that asymmetric organocatalysis was well received and flourished within academia, however, the equivalent progression pace has not been integrated into industrial applications. Nonetheless, an industrial revelation is gradually becoming an obtainable aspiration for the future as there has been inspiring work carried out this decade investigating the sustainable recyclability and stability aspects of immobilised organocatalysts [88]. In addition, we have discussed how design approaches have evolved over the recent years. From experimental screening alone to the integration of computational methods, highly emphasising the importance of data-driven approaches. Shown to be a powerful tool to predict molecular properties and catalytic reactions, especially yields and selectivities, the success of ML models is strongly dependent on the quality and quantity of the available databases and on the choice of molecular descriptors. It is highly evident that as time progresses, machine learning will no doubt become a prominent and essential tool for designing better catalysts and optimising reactions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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