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Perspective

Horizons in Asymmetric Organocatalysis: *En Route* to the Sustainability and New Applications

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Abstract: Nowadays, the development of new enantioselective processes is highly relevant in chemistry due to the relevance of chiral compounds in biomedicine (mainly drugs) and in other fields, such as agrochemistry, animal feed, and flavorings. Among them, organocatalytic methods have become an efficient and sustainable alternative since List and MacMillan pioneering contributions were published in 2000. These works established the term asymmetric organocatalysis to label this area of research, which has grown exponentially over the last two decades. Since then, the scientific community has attended to the discovery of a plethora of organic reactions and transformations carried out with excellent results in terms of both reactivity and enantioselectivity. Looking back to earlier times, we can find in the literature a few examples where small organic molecules and some natural products could act as effective catalysts. However, with the birth of this type of catalysis, new chemical architectures based on amines, thioureas, squaramides, cinchona alkaloids, quaternary ammonium salts, carbenes, guanidines and phosphoric acids, among many others, have been developed. These organocatalysts have provided a broad range of activation modes that allow privileged interactions between catalysts and substrates for the preparation of compounds with high added value in an enantioselective way. Here, we briefly cover the history of this chemistry, from our point of view, including our beginnings, how the field has evolved during these years of research, and the road ahead.

Keywords: chirality; enantioselective; green chemistry; organocatalysis; sustainability

Citation: Ardevines, S.; Marqués-López, E.; Herrera, R.P. Horizons in Asymmetric Organocatalysis: *En Route* to the Sustainability and New Applications. *Catalysts* **2022**, *12*, 101. https://doi.org/10.3390/catal12010101

Academic Editors: Tatiana G. Chulkova and Evgeny Bulatov

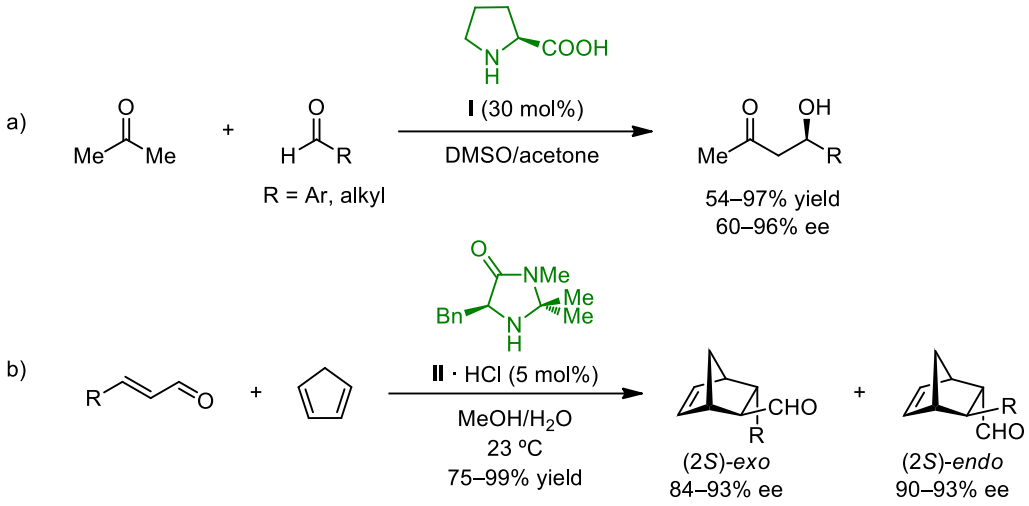
Received: 24 December 2021
Accepted: 13 January 2022
Published: 16 January 2022

1. Introduction

More than twenty years ago, a new Big Bang occurred in organic chemistry [1]. In 2000, we witnessed the conceptualization of a new field, asymmetric organocatalysis, even though the first asymmetric organocatalytic reaction appeared in 1904 [2], when this discipline had not yet emerged. It was only at the beginning of the 21st century with the parallel publications of List [3] and MacMillan [4], when a stream of work focused on this amazing area of research was triggered (Scheme 1). In fact, these researchers have recently been awarded the 2021 Nobel Prize in Chemistry, as the maximum recognition for their contribution to the progress of this field.

However, we cannot forget pivotal achievements before those above-mentioned. Hence, regarding non-asymmetric organocatalysis, Kelly [5], Jorgensen [6,7], and Curran [8] are relevant authors, as well as Jacobsen [9] for the use of chiral thioureas as catalysts (Figure 1). They all became a source of inspiration for one of the greatest subareas within this field: activation by hydrogen bond interactions. Even earlier, other researchers, e.g., Bredig and Fiske [10,11], Pracejus [12,13], and Wynberg [14], employed Cinchona derivatives as catalysts, contributing to the subsequent launch of a parcel in asymmetric catalysis centered on the use of alkaloids as chiral catalytic bases. Moreover, the singular chemistry

of *N*-heterocyclic carbenes [15], the activation using chiral phase transfer catalysts [16] or chiral guanidines [17], have been known for a long time. More recently, the use of phosphoric acids [18,19] to promote interesting processes has also efficiently contributed to the expansion of this field.



Scheme 1. Pioneering processes reported by (**a**) List [3] and (**b**) MacMillan [4].

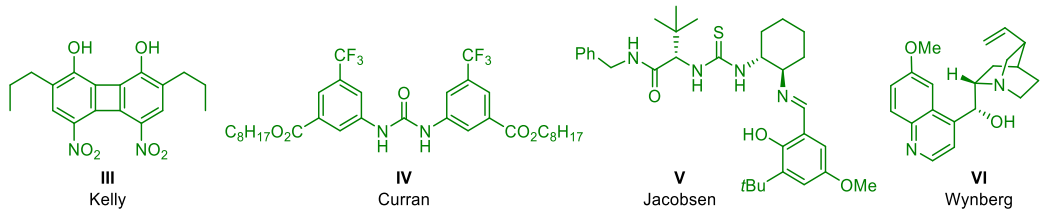


Figure 1. Crucial organocatalytic structures reported previously to 2000.

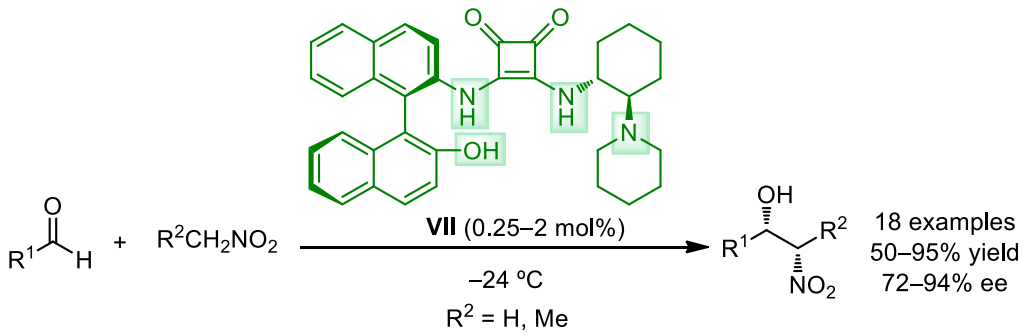
Nowadays, the term asymmetric organocatalysis covers a wide range of organic processes and methodologies, providing efficient and environmentally friendly access to enantiomerically pure compounds, including many drugs and bioactive natural products.

The origin of our research group can be traced to Professor Ricci's group (Bologna, Italy), where we took our first steps in this burgeoning field. In 2003, when this discipline was still in its infancy and talk about asymmetric organocatalysis was barely common, as almost nobody knew this field, we explored the first approach to the Friedel–Crafts-type reaction (a well-known metal-catalyzed process) using simple thioureas as organic catalysts [20]. Looking back, we remember a funny anecdote. "Are you sure that you do not have any metal atom in the reaction medium?". This was the question that a professor asked us in front of our poster at a congress in Ischia (Italy, 2004). Nowadays, no one would doubt this aspect.

Certainly, at the beginning, using organic molecules to promote and activate reactions was nearly a dogma of faith, maybe because the hegemony of metals was so great that it was hard to think that simpler structures could unseat this supremacy. Although there is still a long way to go, we are humbly proud to note that today many organocatalytic processes are at the level of those previously developed with metal catalysts, and in some cases, the achievements of metal catalysis have even been surpassed [21,22]. Nevertheless, the great success of this novel field does not imply the disappearance of the previously existing ones, i.e., metal and biocatalysis, which can be considered complementary and completely necessary for the progress and evolution of modern chemistry. In fact, the combination of organocatalysis and metal- or bio-catalysis for diversity-oriented synthesis is expected to broaden the scope of synthesis much more by allowing genuinely new drugs

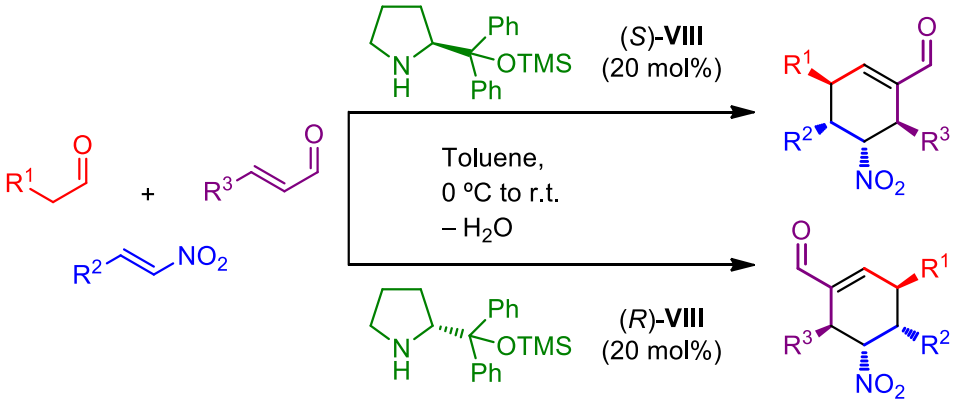
to be discovered. This approach is innovative and requires the integration of very different disciplines within common scientific efforts.

Many research groups have devoted their efforts to overcome these initial fears and during all these years, very interesting strategies have been developed. While at the beginning there was still a great deal to be done and maybe the first investigations were focused on more basic and known reactions, step-by-step, asymmetric organocatalysis has made its way into the field of catalysis, reaching a remarkable level of complexity in terms of both new reactions and more active catalysts. In this field, the authors' imagination to design increasingly complex molecules has perhaps even outweighed the lower reactivity of the organocatalysts. In our case, we moved from structurally simple thioureas [23] to the discovery of the first demonstrated trifunctional squaramide catalyst supported with computational calculations [24,25]. This species exhibited an unusually high activity compared to other organocatalysts without impairing the enantioselectivity of the chemical process, since a catalyst loading of only 0.25 mol% is required *versus* 5–20 mol% usually employed (Scheme 2) [26].



Scheme 2. Henry reaction catalyzed by trifunctional organocatalysts **VII**.

The tremendous grade of complexity accomplished in the new molecular structures obtained by means of organocatalytic reactions during this time is also noteworthy. Without belittling Nature, many authors have been able to obtain numerous new stereogenic centers following a cascade of stereoselective reactions, as biomimetic of tandem reactions that take place during the biosynthesis of complex natural products [27], with incredible enantiocontrol (up to >99% ee) (Scheme 3) [28].



Scheme 3. Multicomponent triple cascade organocatalytic reaction giving rise to four stereocenters.

Taking advantage of the capacity of many organocatalysts, as a singular property of these molecules, to promote several different types of reactions through diverse activation modes, during these two decades, new modes of activation have also been discovered or potentially developed mainly in this field. Hence, bifunctional [29], trifunctional [30], dual [31,32], synergistic [33,34], SOMO (singly occupied molecular orbital) [35,36], and photoredox catalysis [37], among others, have been discovered and tuned. In addition, different sources of energy, such as light [38], microwave [39], ultrasounds [40,41], mechanochemical [42,43], and electrochemical [44,45], have been employed, in all cases looking for greener protocols motivated by the increasing concern over sustainable chemistry. Moreover, the use of different reaction media, such as ionic liquids [46,47], deep eutectic solvents [48,49], water [50,51], more sustainable solvents [52], solvent-free processes [53], and even immobilized catalysts [54,55], have been exciting topics of research, with the main objective of using step-by-step greener conditions [56–58]. We cannot forget challenging strategies that have acquired incredible notoriety in this field in order to achieve these common goals, preventing waste, energy, time, or even motivated by economic reasons, as multicomponent [59–61], one-pot [62–64], cascade, or tandem reactions [65–69]. Nowadays, the protocols developed 15–20 years ago can be revisited to support the 'eco-design' of molecules, providing products of high molecular complexity while ensuring sustainability as much as possible.

2. Discussion

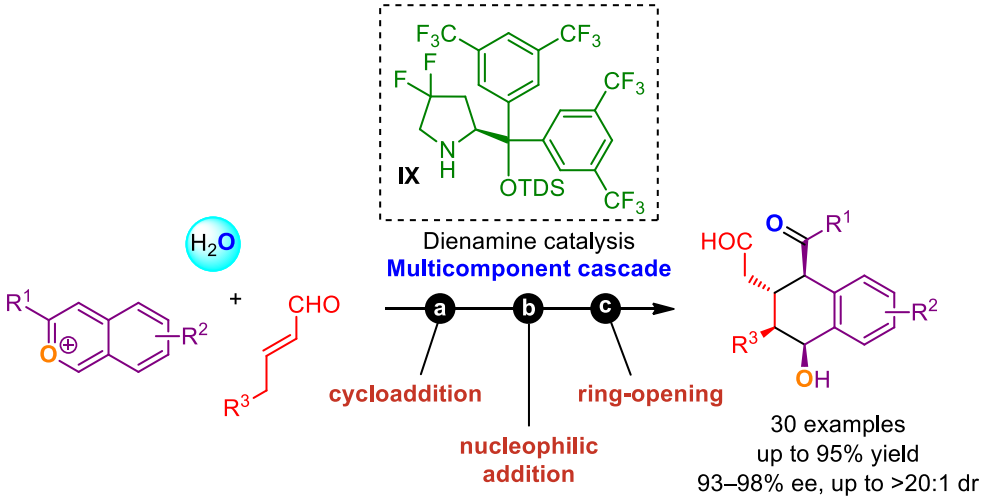
If we should choose three different aspects mentioned above among all, we would like to highlight the growing importance of developing new multicomponent reactions, the continuous search for new applications in this field, and the possibility of reaching a remarkable level of complexity in the catalytic structures.

2.1. Organocatalytic Asymmetric Multicomponent Reactions

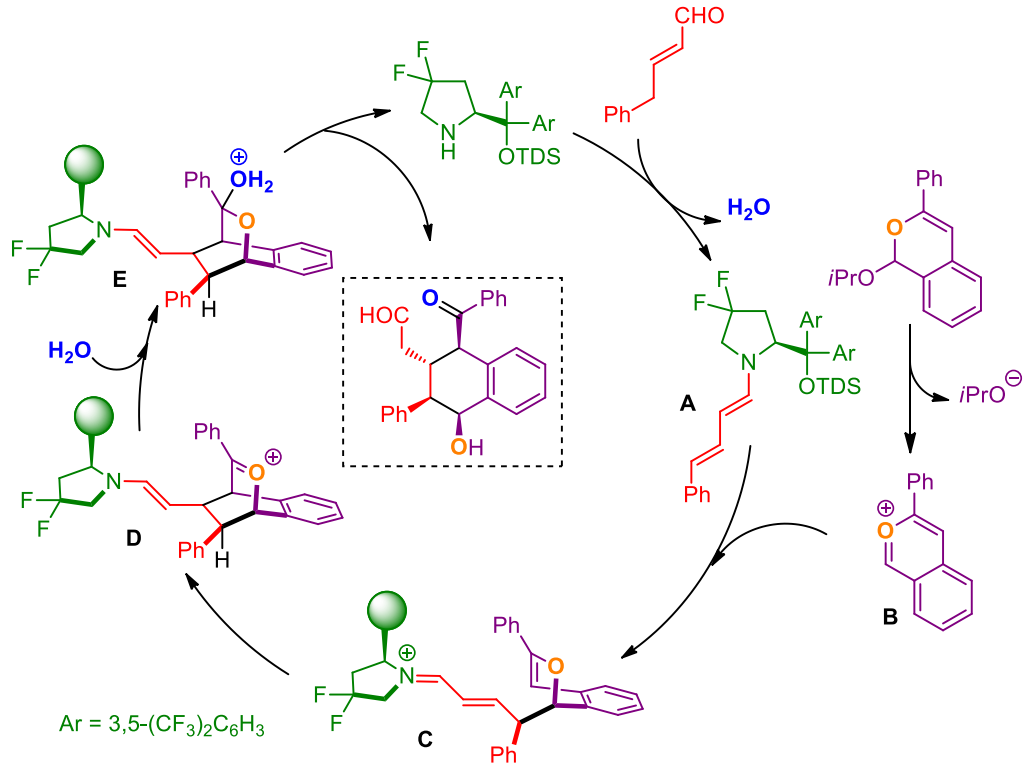
In the pursuit of developing more efficient and sustainable protocols for synthesis, multicomponent (MCRs) or one-pot reactions should be regarded as the suitable option. In such processes, the time-consuming isolation and purification of synthetic intermediates disappear and, in general, the energy, solvents, manipulations, and therefore costs are reduced, compared to classical stepwise methods. These processes also emulate Nature where metabolic pathways occurring in living cells involve an elegant orchestration of a series of biocatalytic steps into an exquisite multi-catalytic cascade, without the need for the separation of intermediates. Since the renascence of the organocatalytic field, many improvements have been made in the progress of organocatalyzed asymmetric MCRs and one-pot reactions using overall chiral secondary amines [70,71], and less explored with hydrogen bond-based catalysts [72]. These spectacular synthetic strategies serve as powerful tools for the efficient construction of complex molecular architectures, and generally these are based on biomimetic principles.

We would like to comment on a pivotal recent example, since sometimes it is difficult to separate a multicomponent reaction from a cascade process, and the complexity of both processes together can be of extraordinary elegance [73]. Recently, Jørgensen and co-workers reported an amazing example of an organocatalytic multicomponent cascade process via dienamine catalysis, involving at the same time a cycloaddition, a nucleophilic addition, and a ring-opening reaction between uncommon isobenzopyrylium precursors, α,β-unsaturated aldehydes, and H_2O [74]. The process was successfully developed to prepare chiral tetrahydronaphthols containing four contiguous stereocenters in good to high yield (up to 95%), high diastereoselectivity (up to >20:1), and excellent enantioselectivity (93−98% ee) (Scheme 4).

On the basis of additional experimental results and computational calculations, the authors proposed a sophisticated multicomponent cascade mechanism supporting the final products obtained (Scheme 5).



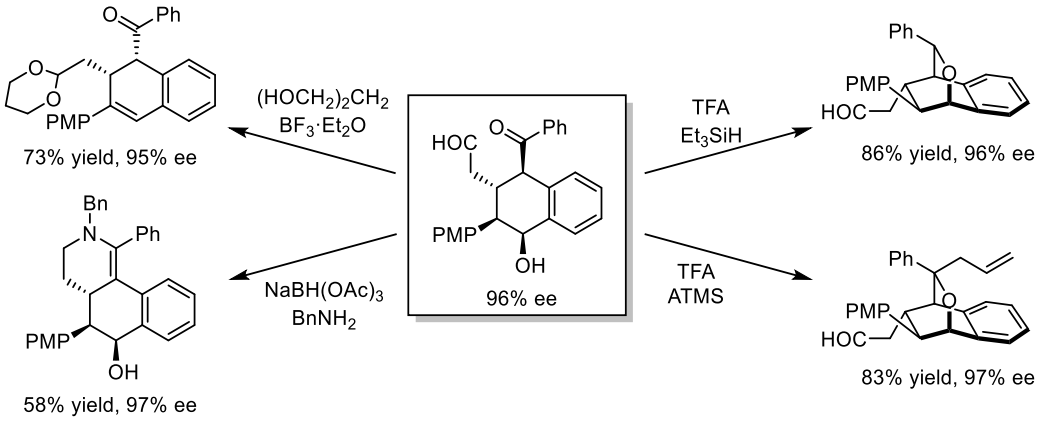
Scheme 4. Asymmetric multicomponent cascade process for the synthesis of tetrahydronaphthols.



Scheme 5. Mechanistic proposal to explain the multicomponent cascade process.

First, the catalytic cycle would start with the formation of the dienamine intermedia **A** by condensation of the catalyst and the aldehyde. The isobenzopyrylium ion intermediate **B** would be generated in a concomitant process by the release of the ion isopropoxide from the starting reagent. Then, **B** would be attacked at the carbonyl position by the γ-carbon of dienamine **A**, giving rise to intermediate **C**. An ensuing ring-closure would generate intermediate **D**. The addition of a molecule of water at the carbonyl group would afford intermediate **E**. Finally, a C-O bond scission, hydrolysis, and proton transfer render final products and release the molecule of catalyst to start the cycle again.

The importance of the final products of this catalytic process was also demonstrated by generating subsequent interesting scaffolds (Scheme 6).



Scheme 6. Synthesis of derivates of interest related with API (active pharmaceutical ingredients) and natural products.

2.2. New Organocatalytic Applications

The interest of the pharmaceutical and agrochemical industries in chiral products has prompted the intensive search for more efficient methods of asymmetric synthesis [75]. The chiral drug industry has become a rapidly growing segment of the drug market and represents close to one-third of all drug sales worldwide [76]. This has been driven by the increased regulatory control of the enantiomeric composition of drug candidates and the potential of enantiomerically pure drugs to provide improvements over the previously available racemates. On the base of this continuous searching for interesting new applications in different areas of knowledge, it is no longer strange to find an organocatalytic protocol, for instance, as part of a total synthesis of a natural product [77,78], or in the synthesis of biologically active compounds [79–81] (Figure 2). In fact, during these two decades, asymmetric organocatalysis has evolved as a powerful synthetic tool for the preparation of chiral building blocks with a wide range of applications in medicinal chemistry and drug discovery [82].

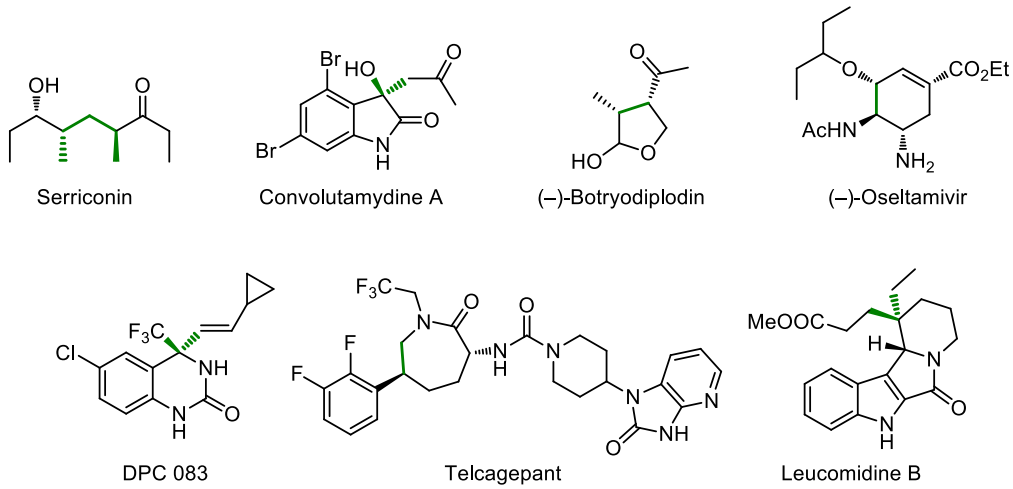


Figure 2. Selected biologically active compounds synthesized using organocatalytic key steps: Serriconin [83], Convolutamydine A [84], (–)-Botryodiplodin [85], (–)-Oseltamivir [86], DPC 083 [87], Telcagepant [88] and Leucomidine B [89]. The bond formed during the organocatalytic step is highlighted in green.

Regarding this chapter, Peng, Li and co-workers have reported an incredible a crucial work comprehensively covering all the applications of asymmetric organocatalysis in medicinal chemistry since the early 2000s [90]. Returning to our chemistry, we have also de-

veloped some active compounds using organocatalysis as a key step in their synthesis, such as antimicrobial β-nitrohidrazydes [91,92], Warfarin and derivatives [93], iridodials [94,95], or the key intermediate to the analgesic Funapide [96] (Figure 3).

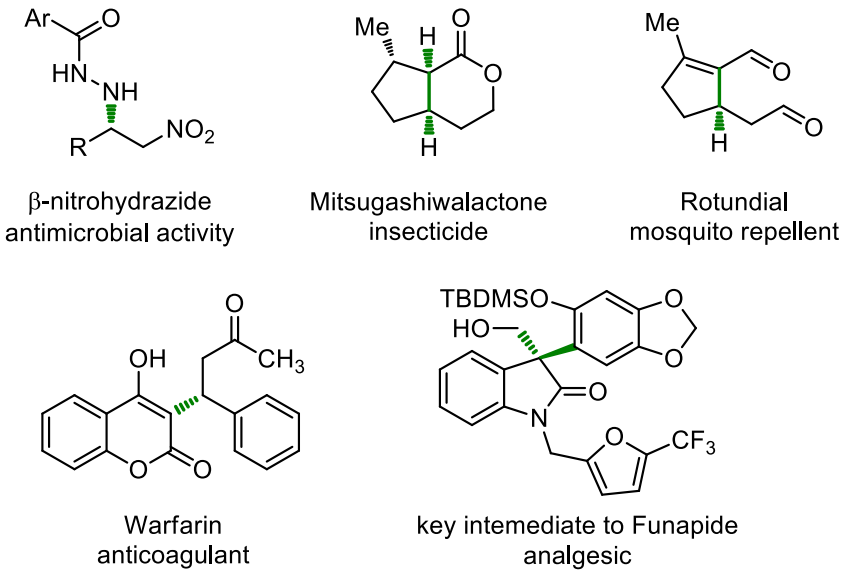


Figure 3. Biologically active compounds synthesized by our group using organocatalytic approaches. The bond formed during the organocatalytic step is highlighted in green.

More recently, we have become interested in the preparation and evaluation of potential anticancer drugs, as cancer is one of the leading causes of death in the world. Hence, while working on the development of organocatalytic methodologies, we became aware of the features of the final products, as well as the interesting properties that the organocatalysts themselves could exhibit beyond their catalytic activity, since most of them are structural cores present in Nature, as (thio)ureas and cinchonas. For this reason, we have started to explore the antitumor properties of some organocatalysts such as squaramides [97,98], as well as the *in vitro* and *in vivo* activity of 1,4-dihydropyridine derivatives synthesized following an organocatalytic protocol as potential anticancer drugs [99] (Figure 4).

2.3. Increasingly Complex Catalytic Structures

Although organocatalysis has experienced great progress in the field of homogeneous catalysis, where rate and enantioselectivity together define the catalytic proficiency, the organocatalysts still require much more improvement to emulate the achievements with metal or enzyme catalysts. In this sense, the general catalyst loading is still in the range of 5–20 mol% and only in some cases this has been lower. Therefore, the catalytic activity and turnover number of metal catalysts or an enzyme are extremely high in comparison with an organocatalyst. These problems increase when at lower temperature the reaction rate decreases and a greater amount of organocatalyst is necessary to compare its activity with the same reaction at room temperature. Although organocatalysts have often been proposed as "artificial enzymes" or small enzyme mimics [100], there are still many differences and a long way to go to reach them. Among other factors, they are still inferior to natural enzymes in terms of catalytic activity and turnover [101]. One strategy to overcome this inconvenience has been to develop more acidic organocatalysts [102]. Another strategy has been to design plausible bifunctional organocatalysts [103–105] following the prevalence of multifunctional catalysis in enzyme catalysis. In this sense, the bifunctionality has served as the inspiration for many synthetic catalytic systems, such as chiral thioureas/ureas, cinchona alkaloids, chiral phosphoric acids, or chiral proline derivatives, which retain the simultaneous activation of nucleophile and electrophile. Interestingly, and more recently, the term trifunctional has acquired more importance [106,107]. Generally, this family

of molecules is expected to activate the process by their three different functionalities, achieving optimal cooperativity and increasing the activity of the catalytic species. Some of these pioneering structures that are believed to act in a trifunctional manner are described in the Figure 5. In all these cases, the authors based their tentative proposal only on experimental results, but in any case, with additional computational calculations supporting a real trifunctional role of the catalysts or not.

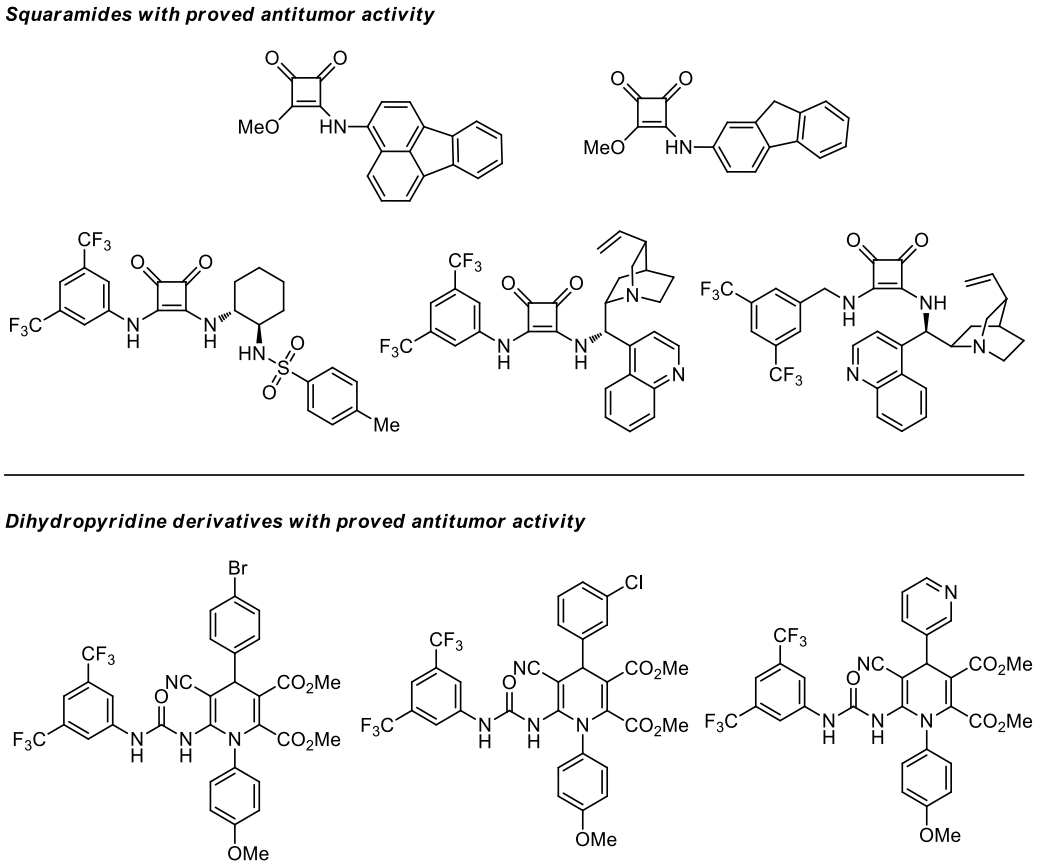


Figure 4. Antitumor squaramides and 1,4-dihydropyriridines synthesized by our group.

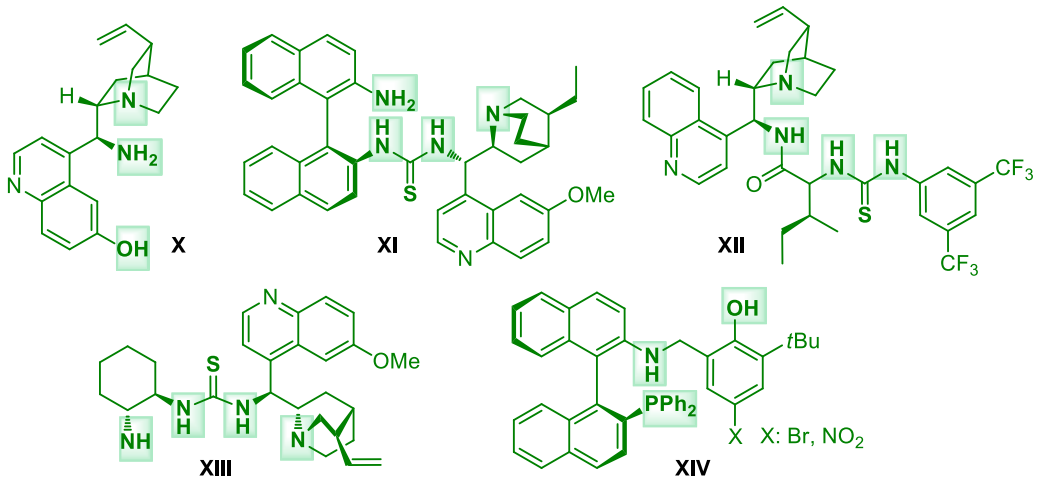


Figure 5. Catalytic structures proposed as trifunctional organocatalysts: **X** [30], **XI** [108], **XII** [109], **XIII** [110] and **XIV** [111].

It is important to remark that only in our developed example [24–26] did additional computational calculations support the trifunctional mode of action demonstrated by the catalysts. Therefore, we think that there is still room in this field to improve and to discover new real trifunctional catalysts, and even tretrafunctional ones.

3. Conclusions

We are convinced that even after the award of the Nobel Prize this year, there is still a long way to go in searching for new milestones in this field. Undoubtedly, new challenges with all the aforementioned characteristics and new sustainable aspects converging in the processes (sustainable methodology, solvent, energy source, structural complexity, and final application) will emerge in the near future. This opinion article is also a small tribute to the efforts and pivotal contributions made by all authors in this appealing field. Indeed, we apologize we cannot name every author involved, as we would desire, and whose seminal and crucial work has also contributed to the development of this broad area of research. We hope that researchers, encouraged by interesting applications [112], will invest efforts in order to expand the scope of this kind of catalysis, because these goals will also be crucial for the evolution of the pharmaceutical industry, among other sectors.

Author Contributions: Writing—original draft preparation, all authors; writing—review and editing, all authors; visualization, E.M.-L. and R.P.H.; supervision E.M.-L. and R.P.H.; project administration, E.M.-L. and R.P.H.; funding acquisition, E.M.-L. and R.P.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Agencia Estatal de Investigación (AEI), project PID2020-117455GB-I00/AEI/10.13039/501100011033; and Gobierno de Aragón-Fondo Social Europeo (Research Group E07_20R).

Acknowledgments: S.A. thanks the DGA (Aragon Government) for a predoctoral fellowship.

Conflicts of Interest: The authors declare no conflict of interest.

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