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7. Strategies for the synthesis of enantiopure compounds focused on organocatalysis

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Abstract. The preparation of enantiomerically pure compounds (EPC) is a continuous social demand due to the clinical advantages that enantiopure drugs offer over the racemic forms. Here, the best well-established synthetic strategies to access to single-enantiomer compounds are briefly described and compared. In particular, the enantioselective catalysis is introduced paying special attention to the organocatalysis, an emerging and fruitful area in the EPC-synthesis. Of particular interest is the use of small organic molecules as catalysts in cascade reactions. Organocascade reactions involve the formation of several chemical bonds and often generate stereogenic centers with excellent stereoselectivity. Such one-pot reactions avoid time-consuming and costly step-by-step processes and are environmentally friendly as they occur in the absence of metals. Additionally, the chemical waste of the organocatytic cascade reactions is drastically reduced since the intermediates are not isolated and purified.

Introduction

In the pharmaceutical field, stereochemistry is placed in an extremely relevant position. The tridimensional structure of a compound is very important when interacting with a chiral medium as the human body, the

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biological effect directly depending on the stereochemistry of the exogenous compound and the receptor. Thus, a single-enantiomer drug can be pharmacologically interesting whereas its mirror image can be inactive or display a different desirable or non-desirable activity. Therefore, the administration of enantiopure drugs brings benefits in terms of improved efficacy, more predictable pharmacokinetics and reduced toxicity [1]. These advantages forced pharmaceutical companies [2] and health authorities [3] to place stereochemically pure substances in a privileged position. Consequently, it is not strange that 7 out of the top 10 most selling-drugs worldwide in 2010 are commercialized as enantiopure forms. Among them, the top three positions are for Nexium® (esomeprazole), Lipitor® (atorvastatin), and Plavix® (clopidogrel), with a whole invoicing of 15 billion dollars [4].

The large demand of enantiopure products has broken out the progress of the *asymmetric synthesis*, considered in the last years as one of the most important areas of research in both industry and academia. Nowadays, the number of synthetic methods available for the preparation of chiral molecules has permitted to efficiently gain access to a myriad of enantiomerically pure compounds.

1. Strategies for the elaboration of enantiopure compounds

In 1980 Prof. Seebach [5] introduced the term "*EPC-synthesis*" (synthesis of enantiomerically pure compounds) to include all the processes for the preparation of chiral enantiopure compounds. The three main synthetic approaches in EPC-synthesis are listed below (Fig. 1) [6]:

- *Resolution of racemates.*
- Synthetic transformations from an enantiomerically pure starting compound. In the particular case of an easily available natural compound it is called synthesis from the *chiral pool*.
- *Stereoselective reactions* that involve an enantiopure reagent as a source of chirality, in stoichiometric (auxiliary) or catalytic amounts, which is not included in the final product.

Next, the three main strategies to obtain enantiopure compounds are outlined.

The first optical resolution of a racemic mixture was performed by Prof. Pasteur in 1848, who was able to manually separate the two kinds of hemihedral crystals of racemic tartaric acid salts [7]. This fact represented the discovery of the molecular chirality and of the spontaneous resolution [8]. In

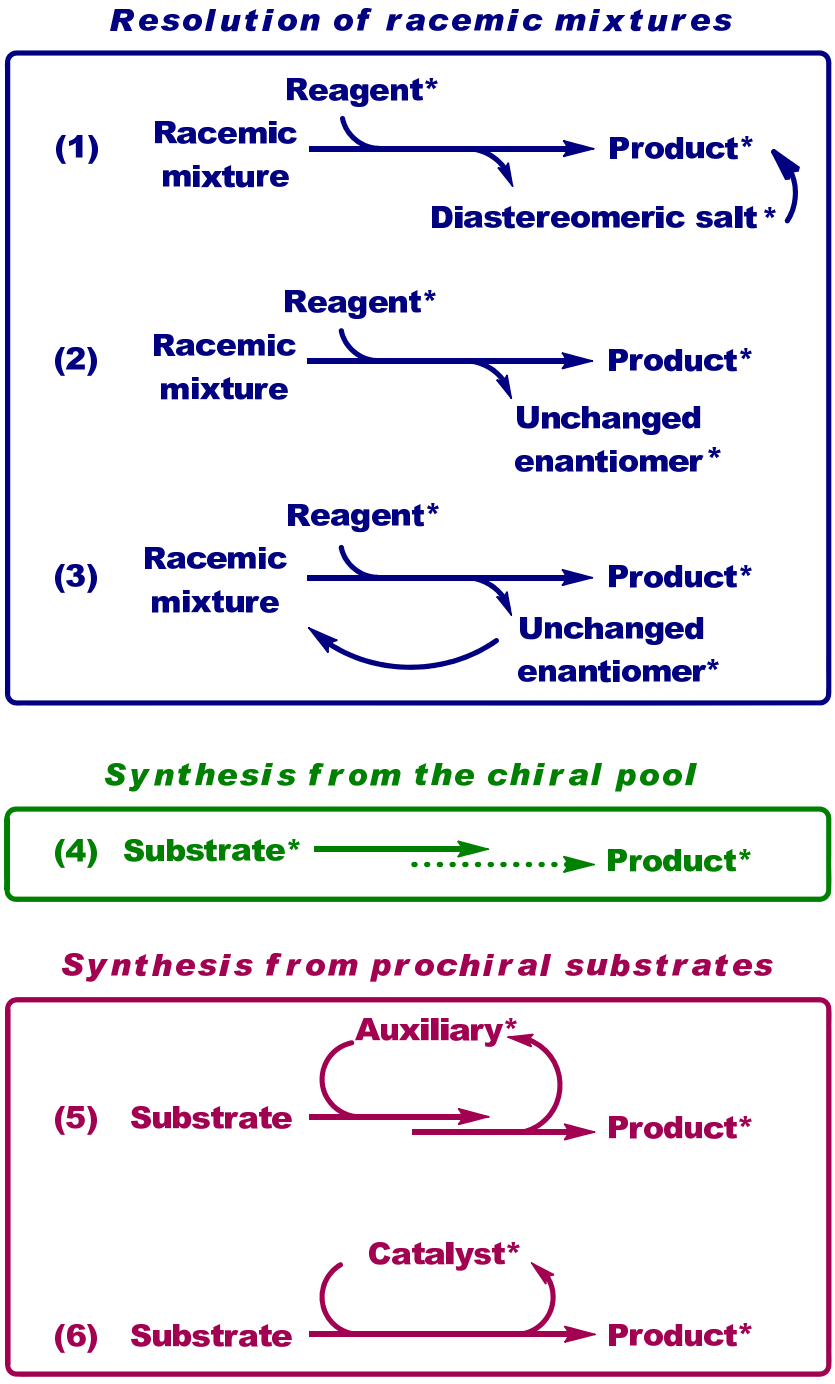

Figure 1. Strategies for the synthesis of enantiopure compounds.

spite of the simplicity of this separation technique it is limited to conglomerates, since both enantiomers of the substance deposit in equal quantities as enantiomorphous crystals [9]. It is worthy of note that only between 5 to 10% of the total chiral organic solids reveals as conglomerates. Notably, the vast majority of resolutions involve the conversion of a racemate, by treatment with an enantiomer of a chiral substance, into

diastereomeric salts (Eq.1, Fig. 1). The different solubility properties of the diastereomeric salts allow the separation of both products and the subsequent treatment with a base or an acid give access to both enantiomers.

Apart from the aforementioned resolution process based on physical properties like solubility, there are other resolution processes as the *kinetic resolution*. The kinetic resolution relies on the unequal reaction rates of the enantiomers with a chiral nonracemic reagent (Eq. 2, Fig. 1). In that case, the reaction rates should be different enough to recover the less reactive or non-reactive enantiomer. The maximum theoretical yield for a kinetic resolution is 50% for each enantiomer and one of them is chemically modified. Of particular interest is the *dynamic kinetic resolution* that permits the total conversion of a racemic mixture into a single enantiopure product (Eq. 3, Fig. 1). This strategy involves a standard kinetic resolution and an *in situ* racemization process of the less reactive enantiomer (unchanged enantiomer), which must be a labile chiral substrate for the easy conversion into the racemic mixture again [10].

In the *chiral pool* synthesis the chiral source is a natural enantiopure compound that will remain included in the structure of the final product (Eq. 4, Fig. 1). This methodology is therefore more useful when the desired final product and the chiral compound used are structurally similar. The chiral pool arsenal is integrated by carbohydrates, amino acids, hydroxy acids and terpenes.

The *stereoselective synthesis* from prochiral substrates is a potent tool that allows the preparation of a broad variety of enantiopure compounds. This methodology involves chemical reactions that introduce one or more elements of chirality in a substrate molecule producing stereoisomeric products (enantio- or diastereoisomers) in unequal amounts [11]. A chiral auxiliary or a catalyst is responsible for the asymmetric induction.

The use of auxiliaries is based on the temporarily incorporation of a chiral moiety in a prochiral substrate (Eq. 5, Fig. 1) generating new elements of chirality selectively. The process involves: 1) the introduction of the auxiliary; 2) high diastereoselectivity in the process of generation of the new elements of chirality, 3) separation of the formed diastereoisomers and finally 4) recovery of the chiral auxiliary. As chiral auxiliaries are required in stoichiometric quantities, their preparation has to be easy and inexpensive.

Nowadays, different well-known chiral auxiliaries allow to selectively perform a great number of reactions [12]. Among them the Evans' oxazolidinones [13] or the Oppolzer's sultames [14] constitute robust examples. Remarkably, the use of chiral amino alcohols pioneered by A. I. Meyers [15], and extended for other research groups [16], played an important role as chiral auxiliary strategy and nitrogen source for the efficient synthesis of alkaloids and nitrogen-containing bioactive compounds.

Chiral auxiliaries become very popular 30 years ago due to their efficiency in the generation of stereoselectivity, affording 100% pure enantiomers after the separation of the diastereoisomers. However, the need for using stoichiometric quantities of the chiral auxiliary and the disadvantage of requiring two additional synthetic steps, introduction and removal of the auxiliary, prompted synthetic chemists to divert their attention to the asymmetric or enantioselective catalysis.

In the *enantioselective catalysis* the chiral information is transferred by an enantiopure catalyst, which means that substoichiometric quantities of a chiral molecule activate the substrate in a reversible manner to accelerate the reaction (Eq. 6, Fig. 1). As the interaction between the catalyst and the substrate is reversible the catalyst is not consumed during the process and can be introduced in a new catalytic cycle. The atom economy of the process is optimal, minimizing the waste generated [17]. An additional advantage of this methodology is the multiplication of the chirality [18], since stoichiometric quantities of enantioenriched product are obtained from substoichiometric quantities of catalyst.

In contrast to the use of chiral auxiliaries that affords enantiopure compounds through diasteromeric intermediates, asymmetric catalysis furnishes directly enantiomers from prochiral compounds allowing the preparation of a broad variety of chiral compounds with high enantiomeric excess.

A relevant datum of the importance of asymmetric catalysis in Chemistry is that Profs. W. S. Knowles, R. Noyori and K. B. Sharpless were awarded with the Nobel Prize in 2001 due to their research on the field (Fig. 2).

Enantioselective catalysis can be divided in three main areas, biocatalysis, organometallic catalysis and organocatalysis, depending on the nature of the chiral catalysts employed.

In the *biocatalysis* an enzyme is responsible for the acceleration of the process [19]. Due to their complex tridimensional structure of *L*-amino acids, the biocatalysts are involved in highly chemo-, regio-, diastereo- and enantioselective processes. Moreover, these reactions are carried out under mild conditions to avoid side products and the processes are environmentally harmless.

The *organometallic catalysis* is responsible for the most part of the enantioselective catalysis published in the last years [20]. The success of this area is mostly due to the particular affinity of metals to complex with functional groups and to the structurally well defined metal-organic ligand complexes which is translated into an efficient asymmetric induction.

An important contribution in the field dates from the seventies when Prof. W. S. Knowles and co-workers [21] demonstrated that complexes of rhodium and phosphine ligands with C_2 symmetry catalysed the addition of

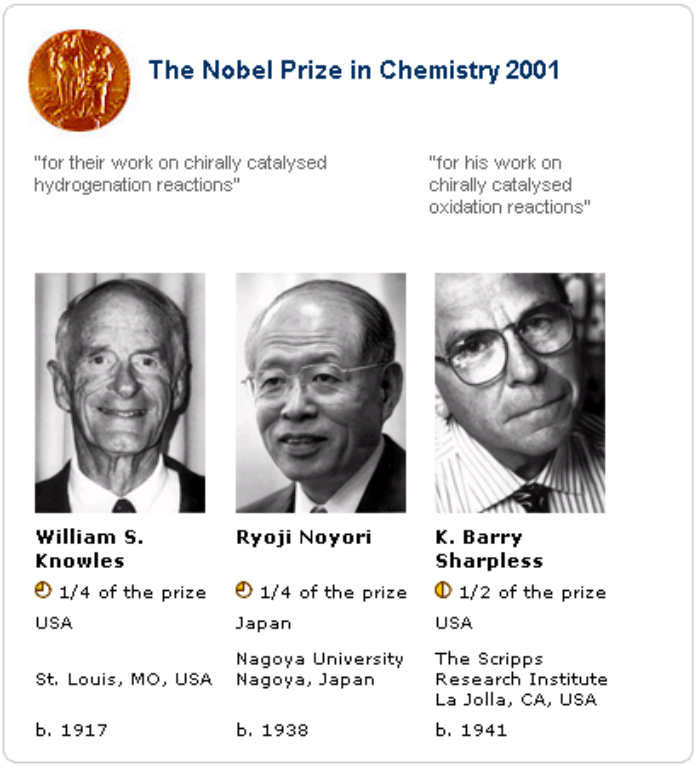

Figure 2. Nobel Prize in Chemistry (2001) shared by W. S. Knowles, R. Noyori and K. B. Sharpless. (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/)

hydrogen to one of the faces of a prochiral olefin to generate a stereogenic C-H center with high enantioselectivity (Fig. 3). Apart from giving a boost to the development of ligands with a C_2 symmetry axis, the main application of this reaction was the industrial preparation of *L*-dopa [22].

Nowadays, the organometallic catalysis enjoys an elevate grade of development including participation in a great variety of oxidations, reductions, insertions to σ bonds, activations of π bonds and reactions catalysed by Lewis acids. In spite of this advantage, some organometallic complexes are expensive, demanding on strict reaction conditions, and metals are toxic which is negative from both the environment and the contamination of the final product point of view.

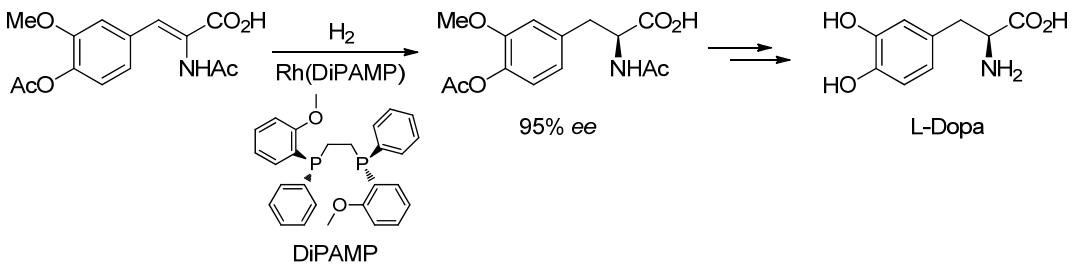

Figure 3. Enantioselective hydrogenation catalysed by rhodium-DiPAMP complex.

Environmental and health regulations gave strong support to cleaner and non-toxic chemical processes avoiding the use of toxic reagents. Chemical companies consider that get rid of transition metals in catalytic reactions is highly desirable. In fact Nature, our source of inspiration, does not use metals for the most part of biocatalytic processes. In this sense, the efforts made for the scientific community to get synthetic sequences free of metals have driven to the configuration of a new area within the enantioselective synthesis: the *organocatalysis*.

The organocatalysis is defined as the acceleration of chemical reactions by small organic molecules in the absence of metals [23]. Although the organocatalysis is a field that has been incredibly developed in the last decade, the use of organic molecules to catalise chemical reactions has been known for more than a century [24]. In 1896, Emil Knoevenagel used a secondary amine (piperidine) to accelerate the condensations that received his name (Fig. 4) [25].

The first example of an asymmetric organocatalysis was described by Mackwald in 1904 using the brucine alkaloid in a decarboxylation process [26]. In 1912, Bredig and Fiske described the asymmetric addition of HCN to benzaldehyde catalysed by cinchona alkaloids [27]. However, those examples occurred with a low enantiomeric excess, below 10%. Later on, in 1960 Pracejus published the organocatalytic methanolysis of a ketene with higher enantioselectivity levels (76% *ee*) [28]. In the seventies a remarkable hit in the organocatalysis was achieved when the first asymmetric aldolization (Hajos-Parrish-Eder-Sauer-Wiechert reaction) catalysed by *L*-proline was described (Fig. 5) [29].

In the following decades (1980-2000), two new fields in the catalysis with organic molecules started with the publication of the two first examples in the phase transfer catalysis [30] and the activation through hydrogen-bonding interactions [31].

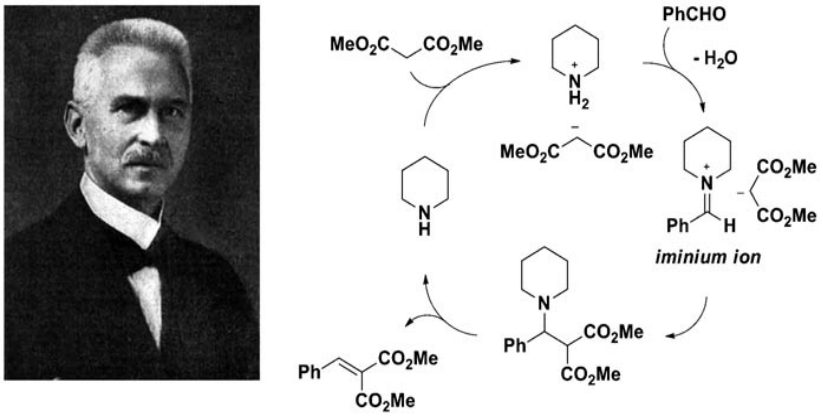

Figure 4. Prof. Emil Knoevenagel (1865-1921). Piperidine catalysed the reaction of diethyl malonate with benzaldehyde.

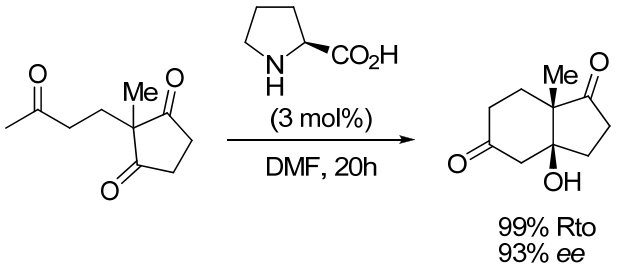

Figure 5. Hajos-Parrish-Eder-Sauer-Wiechert reaction.

In 2000, a study carried out by List, Lerner and Barbas III demonstrated the ability of small molecules to catalyse reactions that until then were promoted by bigger organic molecules or enzymes through similar mechanisms [32]. The same year, MacMillan and co-workers developed the first highly enantioselective organocatalytic Diels-Alder reaction catalysed by a secondary chiral amine, an imidazolidinone [33].

This new application and the conceptualization of the word "organocatalysis" by MacMillan, represented the revival of the secondary amines and other organic molecules as catalysts. The strong support of the scientific community to this field was due to the numerous advantages that the small molecules represent for catalysis. Some of them are listed below:

- The organocatalysts usually are non-sensitive to the humidity and the atmospheric oxygen. This stability makes catalysts easy to handle because it is not necessary the use of dry boxes, inert atmosphere or anhydrous solvents, improving the reproducibility of the results.
- Nature provides enantiopure compounds that can be used directly as organocatalysts. Thus, these molecules are easily available in considerable quantities and in both enantiomeric series.
- The organocatalysts are low or non-toxic substances, respectful with the environment. Moreover, they can be easily isolated from the reaction mixtures avoiding the contamination of the final product. It is noteworthy that the most part of the organocatalytic reactions are performed in high concentration or in the absence of solvent minimizing the expenses of solvent and the formation of additional residues. These properties increase the level of safety and reduce the cost of research either in the academic or industrial areas.

Nowadays, the organocatalysis is a potent synthetic tool situated in a privileged position between the two main catalytic strategies (the bio and metal catalysis) and complements them.

The interest in catalysis with organic molecules is indicated in the increasing number of publications related to this subject in the last decade. The number of publications containing the concept of "organocatalysis" rose steadily from 2000 to 2007 (Fig. 6) rising to 821 publications in the year 2010. Prior to 2000 the number of articles containing the indicated keyword was almost negligible.

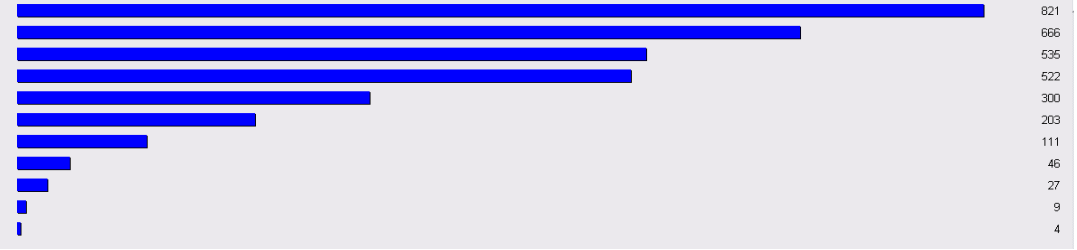

Figure 6. Number of publications including the term "organocatalysis" in the title or in the abstract from the year 2000 (4) to 2010 (821) in the SciFinder Scholar (2007) database.

This tremendous advance in the organocatalysis has given access to a great number of enantiomerically pure compounds with an added value from the biological and structural point of view including drugs and natural complex products [34].

The development of novel activation methods is responsible for the rapid and continuous progress on the organocatalytic area gaining applicability to wide organic reactions. In a first level, the different activation methods can be classified taking into account if the reversible interaction between the catalyst and the substrate is non covalent (1) or covalent (2). The former is also divided depending on the implication of ionic pairs or hydrogen bonds. The latter is classified into *N*-heterocycles carbene catalysis or amine catalysis, also known as *aminocatalysis*. The reactive species that is formed when the catalyst interacts with the substrate determines the kind of aminocatalysis involved. Next, this classification is underlined and the different headings are briefly described.

1. Non covalent interactions:
    a. Formation of ionic pairs:
        i. Phase transfer catalysis
        ii. Brønsted base catalysis
    b. Formation of hydrogen bonds
2. Covalent interactions:
    a. Catalysis with *N*-heterocyclic carbenes
    b. Catalysis with amines (via iminium ion, enamine, dienamine, radical cation or ammonium ion)

The enantioselective phase transfer catalysis (PTC) (1.a.i) is performed in a heterogeneous medium and uses quaternary ammonium salts to facilitate the migration of the reagent from one phase to the other. The asymmetric induction is based in the formation of a chiral ionic pair soluble in the organic phase that is where the stereoselective reaction occurs. The most used ammonium salts are the cinchona alkaloids derivatives and binaphthylamine derivatives [35]. The Brønsted base catalysis (1.a.ii) [36] is based on the use of a chiral base able to deprotonate a (pro)nucleophile (chiral ionic pair) increasing the reactivity in front of eletrophiles. The most employed Brønsted bases as chiral catalysts are the cinchona alkaloids and derivatives, due to their availability and their catalytic and inductive efficiency. This family of compounds is found in Nature as two pseudoenantiomeric forms (Fig. 7) and each of them furnishes one of the two possible enantiomers of the reaction product.

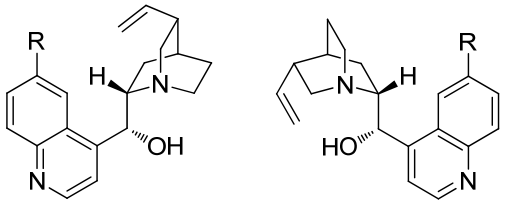

Figure 7. Pseudoenantiomeric cinchona alkaloids.

Cinchona alkaloids have been considered as one of the most privileged chiral inductors in organic synthesis [37]. Different structural features of cinchona alkaloids are responsible for the efficient activation and transmission of the chiral information to the substrate [38]: 1) the presence of a basic nitrogen atom included in a bulky quinuclidine nucleus and a secondary alcohol that can activate the substrate establishing hydrogen-bonding interactions; and 2) the presence of a quinoline ring that can adopt different conformations in the reaction media acting as a "molecular wall" for the preferential approach of the reagent. When the basic nitrogen of the quinuclidine activates the (pro)nucleophile and the hydroxyl group interacts with the electrophile through hydrogen-bonding interactions, cinchona alkaloids are considered to be bifunctional catalysts as a double simultaneous activation occurs in the process [39].

The formation of hydrogen bonds is very important in biological systems and in metabolic terms such interaction between enzymes and substrates means the acceleration of a wide variety of reactions. This biological strategy of activation is mimicked by different catalysts (1.b) [40]. Among them,

phosphoric acids and thioureas stand out due to their efficiency in the formation of highly organized transition states, a very important factor for the discrimination of the enantiotopic faces of a substrate.

In the catalysis through covalent interactions between a catalyst and a substrate is highlighted the use of *N*-heterocyclic carbenes (2.a) [41] and the catalysis using amines (2.b) [42]. The aminocatalysis is based on the use of amines as catalysts and represents an important part of the organocatalysis. There are different activation modes in aminocatalysis that allow to establish a classification depending on the reactive species that is generated in the interaction between the substrate and the catalyst.

In the iminium ion catalysis [43] the reactive species is an iminium salt formed by the reversible reaction between a primary or secondary amine (catalyst) and a carbonyl compound (substrate). Thus, a lowering in the energetic potential of the lowest unoccupied molecular orbital (LUMO) is observed facilitating the reaction with nucleophiles. The Knoevenagel condensation and the Michael addition are two examples of reaction in which this activation strategy has been successfully applied. When the substrate is an α,β-unsaturated ketone or aldehyde, the iminium ion catalysis favors the β-functionalization of the carbonyl compound (Fig. 8).

The catalysis via enamine [44] involves the generation of an enamine that results from the tautomerization of an iminium ion intermediate. In that case, a primary or secondary amine activates the substrate increasing the energetic potential of the highest occupied molecular orbital (HOMO). The HOMO-raising activation facilitates the reactivity of the α-carbonyl position with electrophiles. This strategy has been frequently used in aldol and Mannich reactions (Fig. 9).

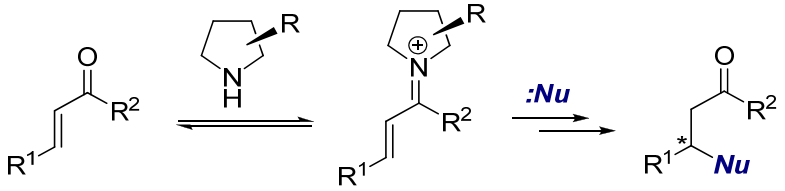

Figure 8. Activation via iminium ion (*Nu* = nucleophile).

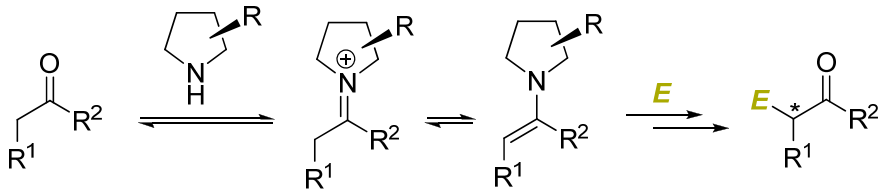

Figure 9. Activation via enamine (*E* = electrophile).

The catalysis via dienamine, introduced in 2006 by Jørgensen and co-workers [45], can be considered as a kind of catalysis via enamine and it has been used for the functionalization of the γ position of α,β-unsaturated aldehydes with electrophiles.

In the last years, a new class of catalysis via radical cation has been developed [46]. In this case, SOMO (single electron occupied molecular orbital) activation is produced allowing the introduction of different substituents in the α carbonyl position. This new methodology has expanded the field of organocatalysis merging aminocatalysis with radical chemistry.

Finally, the catalysis via ammonium ion implies tertiary amines [47] as catalysts. The formation of ammonium enolates [48] typically with cinchona alkaloids, and the formation of acyl-ammonium with DMAP analogues [49] are representative examples.

The transmission of the chiral information from the catalyst to the final product must be very efficient in order to achieve stereoselective chemical processes. In the particular case of the aminocatalysis, the stereoelectronic properties of the catalyst (amine) are responsible for the asymmetric induction. Thus, the stereocontrol of a reaction can be determined by steric factors, electronic factors or a combination of both. Chiral catalysts bearing bulky groups can prevent an arbitrary approach of the reagent to the substrate forcing an oriented bond formation that avoids the steric hindrance. In an opposite way but complementary, catalysts with hydrogen-bond donating groups can establish interactions of electronic affinity with hydrogen-bond accepting groups present in the reagent, thus facilitating the reaction between the two reacting partners in a well-defined manner.

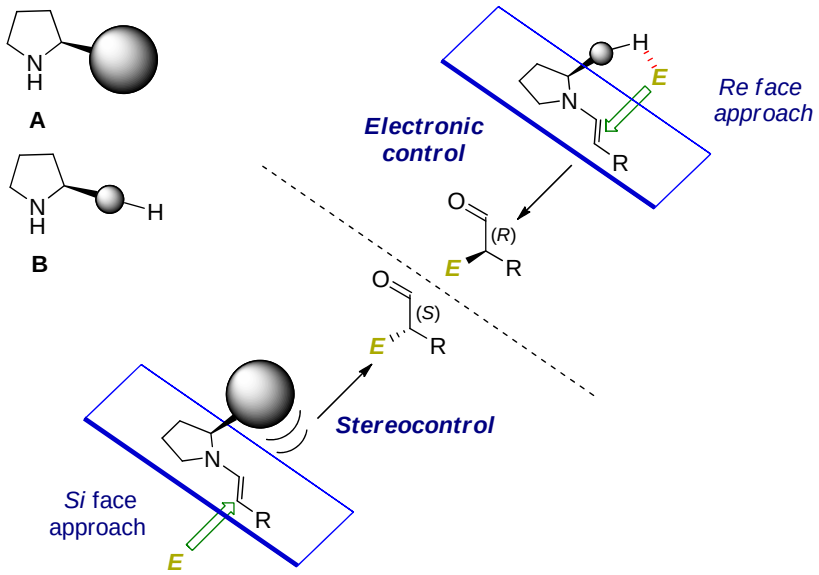

Figure 10. Stereoelectronic control of the reaction by the catalyst.

Figure 10 depicts how different substituted chiral pirrolidines (**A** and **B**) can orientate and control the addition of aldehydes to electrophiles through an enamine like intermediate. The presence of bulky substituents in the organocatalyst (**A**) can shield the enamine *Re* face forcing the electrophile to a *Si* face approach. However, the use of pirrolidines with hydrogen-bond donor groups (**B**) would facilitate the approach of the electrophile preferentially for *Re* face of the enamine. Thus, both strategies would drive to opposite enantiomers.

2. Cascade reactions

Evolution provided living organisms with biosynthetic processes that convert efficiently simple molecules into complex molecular systems. One of the key features of the biosynthetic routes in Nature is the achievement of cascade reactions. As an example, the pharmacologically and structurally very interesting diterpene taxol is proposed to be biosynthetically prepared in just five steps involving few enzymes [50] (Fig. 11). However, the most efficient synthesis of taxol achieved in the laboratory by Wender´s group involved 37 steps from verbenone with 0.44% overall yield [51].

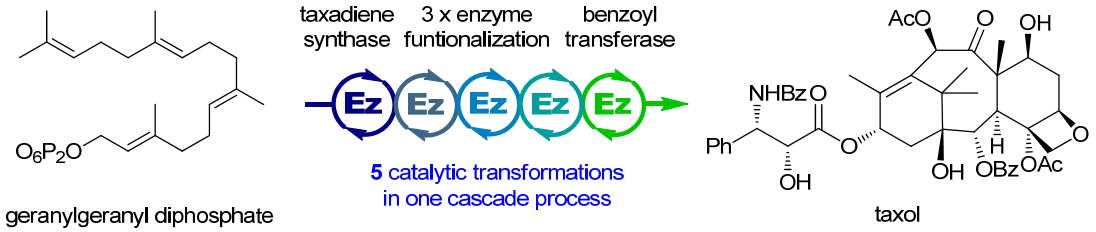

Figure 11. Proposed biosynthesis of taxol.

In the laboratory, the preparation of complex chiral molecules requires several synthetic steps and involves the isolation and purification of intermediates. This operational strategy prevents, in most cases, a low-cost fast access to enough quantities of interesting natural products and bioactive compounds for the benefit of the community.

The attempts to mimic Nature for avoiding these limitations led to the development of new *one-pot* strategies. The one-pot reactions are carried out in a simple vessel allowing the formation of various chemical bonds and stereogenic centers without the isolation or purification of intermediates. Thus, the efficiency of the synthesis increases since the number of synthetic steps is reduced. As a consequence, there is a minimum consumption of chemicals and a minimization of waste, reducing environmental contamination. Therefore, chemical companies concerned about economic

and ecological profitability are really interested in one-pot reactions. Merck Research Laboratories described an impressive synthetic sequence for the preparation of the anti-migraine drug telcagepant (Fig. 12) [52]. A symbiosis between one-pot reactions and organocatalysis using Jørgensen's catalyst is the key feature of a brilliant synthesis with the isolation of only three intermediates and without chromatographic purification. This example illustrates the preparation on an industrial scale drug by an environmentally friendly process with the high quality standards that the pharmaceutical production demands.

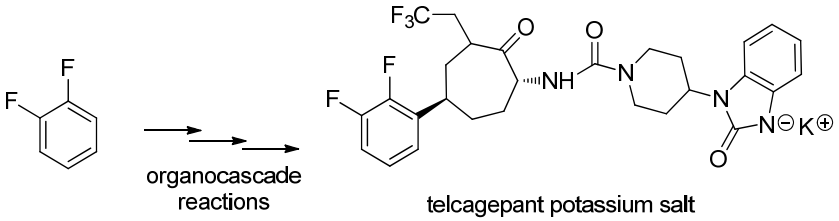

Figure 12. Synthesis of telcagepant potassium salt from 1,2-difluorobenzene by Merck Research Laboratories.

Recently, different terms to describe one-pot processes have been considered. Tietze [53] described a *domino* reaction as the process involving two or more sequential bond-forming transformations which take place under the same reaction conditions. In a *tandem* process the transformations occur simultaneously sometimes using two or more different catalytic processes [54]. However, the term *cascade* reaction is used to include the above mentioned one-pot reactions [55].

The advantages and continuous development of this bio-inspired strategy has converted cascade reactions in a useful tool for the rapid access to molecular complexity [56].

The combination of enantioselective catalysis, one of the most efficient methods in EPC-synthesis, with cascade reactions is one of the most powerful approaches for the preparation of chiral complex molecules, and it is known as *organocascades* or *organocatalytic cascades* (Fig. 13) [57].

The organocatalytic approach in cascade reactions frequently involves only one catalyst that usually interacts with carbonyl substrates. The organocascades are based on the easy tautomeric iminium ion-enamine conversion and the different reactivity of the resulting tautomers to furnish consecutive reactions. The catalysis via iminium ion allows the addition of nucleophiles in the β-position of α,β-unsaturated carbonyl compounds. This addition generates an enamine-like intermediate that can react with the electrophiles present in the reaction media (Fig. 14).

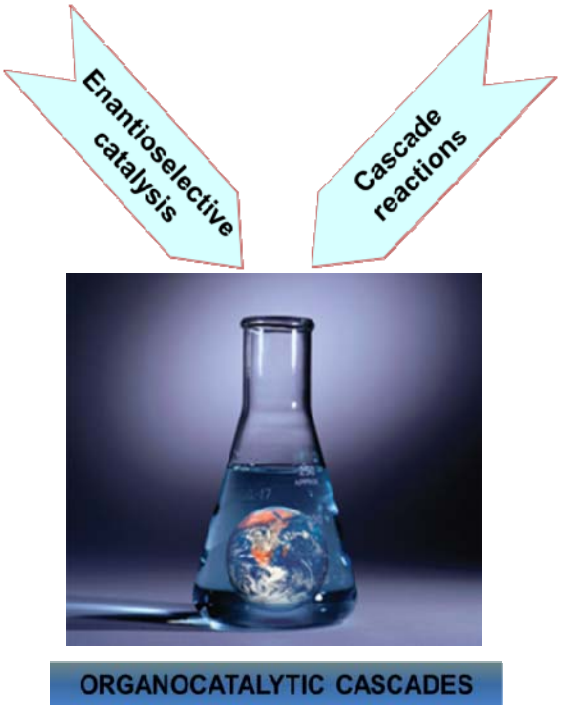

Figure 13. Organocatalytic cascades.

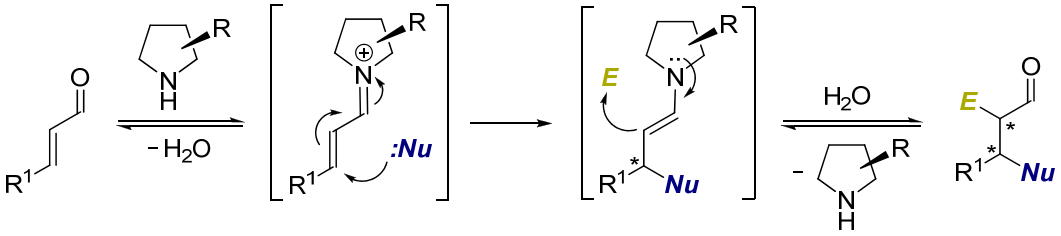

Figure 14. Domino reaction via activation iminium ion-enamine.

The combination of sequential activations via iminium ion-enamine has provided numerous organocatalytic cascade syntheses of enantiomerically pure molecules. It is noteworthy the triple cascade reaction via activation enamine-iminium-enamine reported by Enders and co-workers for the synthesis of pentasubstituted cyclohexanones (Fig. 15) [58].

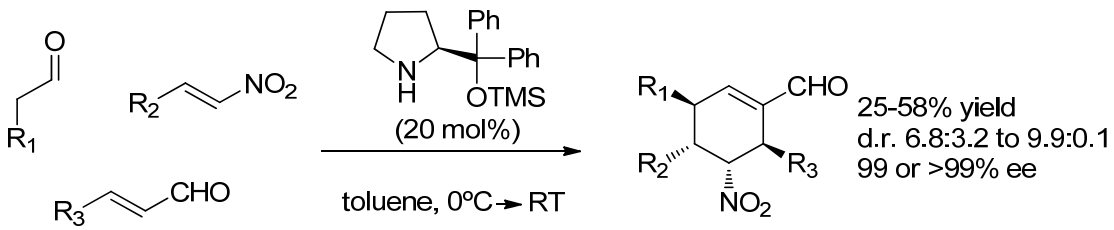

Figure 15. Synthesis of pentasubstituted cyclohexanones by Enders *et al*.

3. Cooperative catalysis

The structural diversity present in the biosynthetic molecules is due to the combination of catalytic cascades that involve different enzymes, which activate different substrates. For the success of this catalytic combination, it is essential the capability of different enzymes to coexist in the same media without undesirable interactions. Moreover, some reactions need the participation of coenzymes and metallic cofactors as further substrate activators. For this reason, the efficient combination of organocatalysts with other catalysts, which are able to activate different functional groups, is highly desirable to increase the molecular diversity of the synthetic products. *Cooperative catalysis* between organic and metal catalysts has evolved rapidly in recent years and its improvement offers to the synthesis of enantiomerically pure compounds levels of reactivity, selectivity and diversity that are very difficult to get using other methodologies [59].

Remarkably, this innovative strategy not only promotes single reactions but also enables multiple transformations in a one-pot process for the generation of previously unattainable compounds.

4. Conclusion

Therefore, the design and development of new catalytic strategies is a continuing challenge at the forefront of synthetic chemistry. Stereoselective organocatalytic reactions have proved to be a powerful tool for the synthesis of enantiomerically pure molecules. In addition, catalytic cascade sequences allow the minimization of time, cost, effort and waste of synthetic processes, thus becoming ideal biomimetic approaches to gain molecular complexity efficiently and ecologically.

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