Organocatalysis in the Synthesis of Natural Products: Recent Developments in Aldol and Mannich Reactions, and 1,4-Conjugated Additions

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Abstract: The use of organocatalysis has simplified and increased the potential of synthetic approaches to natural products. Different aspects, regarding applications and even perspectives of iminium- or enamine-catalysis have been studied in this increasingly developing area during the past decades. Addressing those features, this article aims to give an overview through selected examples, focusing on discussing academic insights of a variety of key reactions such as aldol and Mannich reactions, and 1,4-conjugated additions, as well as applications to the synthesis of natural products, in the period 2012 to date.

Keywords: 1,4-conjugated addition, aldol reaction, asymmetric synthesis, enamine-activation, mannich reaction, natural products, organocatalysis.

1. INTRODUCTION

The identification, isolation and synthesis of novel biologically active natural products represent a major goal in organic chemistry. However, some potentially useful natural compounds cannot be easily isolated in adequate quantities, so the development of synthetic routes to them is of paramount importance. Over the history, the aim of organic chemists has been the synthesis of complex molecules mimicking the elegance and efficiency of biosynthetic pathways in Nature. Due to the complex stereochemistry, high functionalization and structural diversity of many natural products, asymmetric synthesis has been an important tool for their preparation, since it allows to stereoselectively introduce stereogenic centers [1]. Among the available stereoselective strategies catalytic methods are considered appealing approaches, since the use of stoichiometric amounts of expensive chiral reagents can be avoided. Besides enzymes and transition metals, the use of small organic molecules, named organocatalysts, has proven to possess an enormous potential for the catalysis of stereoselective reactions. The introduction of organocatalytic methodologies in synthetic routes to natural products, allows to achieve more efficient, economical and environmentally benign procedures, considering their tolerance to moisture and oxygen atmospheres, compatibility with mild reaction conditions, and absence or very low toxicity [2]. The use of small organic molecules as catalysts for the preparation of chiral synths was described independently for the first time by Eder and by Hajos [3-5]. Nevertheless, only in the 2000s, from the contribution of List, Lerner and Barbas III [6], and the seminal work of McMillan et al. [7] the high potential of this methodology was rediscovered and originated an intense study of its synthetic possibilities [1, 2, 8-12].

In those early works of the decade of 2000, two main activation mechanisms were described for organocatalytic processes: enamine catalysis [6] and iminium catalysis [7]. While in the latter a chiral imidazolium salt is used to activate α,β-unsaturated aldehydes by the reversible formation of an iminium ion, enamine-catalysis uses aminoacids (or derivatives) and proceeds via an enamine intermediate. Scheme I shows that when the organocatalytic reaction goes through this pathway, the catalyst plays two functions. First, the nucleophile is activated via enamine formation, and then, activation and coordination of the electrophile via the carboxylic acid leads to the formation of a defined transition state, which explains the high selectivity of the reaction [1, 13]. As this approach can be viewed as reducing the function and activation mechanism of Type I aldolases to small organic molecules, it can be stated beyond doubt that it represents a powerful method for the stereoselective α-functionalization of aldehydes and ketones, not having to face the substrate limitation characteristic for enzyme catalysts [14].

In 2012, many excellent reviews regarding different aspects, applications, and perspectives of iminium- or enamine-catalysis in the synthesis of natural products made valuable contributions to the knowledge in this increasingly developing area [14-22]. Recently, Abbasov and Romo briefly highlighted significant examples of iminium and enamine catalysis in the synthesis of natural products [23]. Herein, a detailed account of recent developments in the organocatalyzed synthesis of natural products will be presented, focusing Mannich reactions, aldol and 1,4-conjugated additions- covering the period 2012-to date.
1.1. Aldol Reactions

The asymmetric aldol reaction is an outstanding method for the enantioselective carbon-carbon bond formation. The development of organocatalytic methods to perform these reactions, gave them an additional improvement regarding atom economy and milder and greener aspects [24]. Many organocatalytic aldol reaction protocols have been developed and included in synthetic routes to natural products. Some relevant contributions are highlighted in this section.

In 2012 Enders and co-workers described for the first time an organocatalytic asymmetric synthesis of smyrindiol [(+)-(2'S,3'R)-3-hydroxymarmesin, isolated from roots of *Smyrniopsis aucheri* [25] and *Brosimum gaudichaudii* [26]] by using (S)-proline as catalyst, through an intramolecular aldol reaction as key step [27]. This natural furocoumarin was synthesized from commercially available 2,4-dihydroxybenzaldehyde in 15 steps, with excellent stereoselectivity \(de = 99\%, \; ee = 99\%\). Naturally occurring furocoumarins, a group of compounds structurally derived from psoralen or angelicin (Fig. 1), are found in plants of the Apiaceae and Rutaceae families, and are used in the treatment of skin diseases such as vitiligo and psoriasis. In addition, they show vasodilatory, antifungal and antibacterial activities. The total synthesis of smyrindiol was carried from 2,4-dihydroxybenzaldehyde as starting material, from which the substrate for the aldol reaction \((O\text{-acetonyl-salicylaldehyde})\) was prepared in five steps with an overall yield of 34\% (Scheme 2), in multigram scale without the need of purification steps. The aldol key step in the designed synthetic sequence, was carried out using (S)-proline as catalyst, and yielded the expected product in 71\% yield, as a single stereoisomer.

The following nine steps of the synthetic route were easily carried out with an overall yield of 27\%. In summary, an efficient and completely stereoselective asymmetric

![Scheme 1. Example of a proline-catalyzed aldol reaction proceeding via an enamine mechanism [1].](image-url)
organocatalyzed total synthesis of smyrindiol was achieved using (S)-proline to catalyze a 5-enol-endo aldol reaction as the key step. The target compound was obtained in 15 steps with an overall yield of 6.3%, using mild conditions and short reaction times in all steps.

In the same year, an efficient asymmetric synthesis of the potential antitumor agent (-)-gonioheptolide A derivatives was described by the same group. The target compound 4-epi-methoxy-gonioheptolide A and analogues belong to a group of secondary metabolites isolated from plants of the annonaceae family, genus goniothalamus, [28] called styryl-lactones. These compounds, which characteristic feature is the presence of mono- or bicyclic highly oxygenated tetrahydrofuran ring systems, show cytotoxic, pesticidal and antitumor activity [29]. The first step in the designed synthetic sequence was a (S)-proline-catalyzed aldol reaction, followed by a RAMP hydrazone-α-alkylation and a diastereoselective reduction with zinc borohydride, allowing the establishment of the required five stereocenters in the molecule. The retrosynthetic analysis of the target compound is shown in Scheme 3. As final result, 4-epi-methoxy-gonioheptolide A was obtained in ten steps with 15% overall yield and excellent diastere- and enantiomeric excesses (de ≥95%, ee ≥99%).

Florence and Wlochal used an organocatalytic aldol reaction as the first step in the synthetic sequence to palmerolide C, a polyketide-derived macrolide from the antarctic tunicate Synoicum adereanum, which shows remarkable activity towards the UACC-62 human melanoma cell line (IC₅₀ = 110 nm), [31] (Scheme 4).

The synthesis of the first subunit in the designed synthetic route began with an Enders’ proline-catalyzed aldol reaction of suitably substituted dioxanone and aldehyde, to establish the anti-configuration in the newly formed stereocenters [32, 33]. The reaction with 30 mol% (S)-proline in chloroform over five days provided the anti-aldol in 44% yield with 96% enantiomeric excess.

The diastereo- and enantioselective syntheses of 3-acetyl-4-hydroxyisochroman-1-ones (structural feature found in several natural products) via an intramolecular trans-selective aldol reaction were described by Enders and co-workers, employing proline-type organocatalysts [34].

A series of pyrrolidine-derived catalysts was evaluated for the preparation of an isochroman-1-one, carrying out the reactions at room temperature in 1.0 M DMSO (Scheme 5).

Catalysts A and B did not give significant conversions, while (S)-proline (C) afforded the desired isochromanone
within 23 hours in 67% yield, good enantioselectivity (84% ee) and excellent diastereoselectivity (> 95% de). The more acidic catalyst D, (R)-5-(pyrrolidin-2-yl)-1H-tetrazole, gave the final compound in reduced time (5 hours) with a slightly increased yield (71%), the same diastereoselectivity and better enantioselectivity (99% ee). The scope of the reaction was studied with several 2-oxopropyl 2-formylbenzoate derivatives, finding a robust procedure that allowed a broad range of substituents on the aromatic ring.

The stereodivergent synthesis of two hyacinthacine analogues relying on an organocatalyzed aldol addition was carried out with dioxanone and an α-N-carbobenzyloxy-substituted chiral aldehyde, promoted by both (R)- and (S)-proline (Scheme 6) [35]. A retrosynthetic analysis of hyacinthaines on the basis of the organocatalyzed aldol addition as a key step is given in Scheme 5. It shows that the stereogenic centers at C1 and C2 should be created in an aldol reaction, which was the first step in the synthetic sequence. The reac-
tion proceeded in good yields and diastereomeric ratios, which may be due to the use of an acyclic chiral aldehyde as acceptor, allowing reagent control of the stereochemical outcome of this key step in both, the matched and mismatched cases.

The preparation of ent-2-epi-hyacinthacine A2 started with the (S)-proline-catalyzed aldol addition of dioxanone to the adequate N-carbobenzyloxy-protected aldehyde yielded the aldol adduct (the product adopted the cyclic hemiaminal form) as the major product, along with a minor amount of its diastereomers (70%; diastereomeric ratio (dr) = 6:1). The mixture was easily separated by column chromatography. In turn, for the synthesis of ent-3-epi-hyacinthacine A1, the aldol reaction was catalyzed by (R)-proline, affording aldol adduct in 77% yield with 10:1 dr. The higher yield and stereoselectivity may indicate that this is the matched case (Scheme 7).

Pearson and colleagues described the enantioselective aldol reaction of 7-iodoisatin and 2,2-dimethyl-1,3-dioxan-5-one, using a N-prolinylanthranilamide-based pseudopeptide as catalyst (catalyst A, Scheme 8) [36]. The aldol adduct was obtained with 75% yield, 90% ee in 23:1 diastereomeric ratio, and used for the construction of a potential intermediate of the natural product TMC-95A, a powerful reversible proteasome inhibitor [37].

A l-proline-mediated direct cross-aldol condensation of two advanced aldehyde-intermediates was utilized by Volchkov and Lee for the construction of an α,β-unsaturated epoxyaldehyde, a key compound in route to (-)-amphidinolide V (Scheme 9) [38].

The reaction was conducted in the presence of 4 Å molecular sieves (MS) with increased loading of L-proline in DMF as solvent and at 0°C. These conditions dramatically increased the ratio between cross-condensation and cross-aldol products, obtaining a sole product in 66% yield (E/Z = 12.5:1).

Phansavath and colleagues reported a convergent stereo-selective synthesis of one isomer of the C44-C65 fragment of mirabalin, in which the first step is the organocatalytic cross-aldol reaction of isobutyraldehyde and propanal, carried out at 4°C during 48 hours, and using L-proline as catalyst [39].
Veena and Sharma worked on an organocatalytic approach for the total synthesis of 7-epi-goniodiol, and developed a strategy that involves a L-proline-catalyzed diastereoselective aldol reaction and a Baeyer-Villiger oxidation as key steps for the construction of the chiral lactone [40]. The retrosynthetic analysis of 7-epi-goniodiol is shown in Scheme 10.

The synthetic route starts with the oxidation of (R)-phenylethane-1,2-diol giving the corresponding aldehyde
which was subjected to a L-proline-catalyzed diastereoselective direct aldol reaction with cyclopentanone. This key step was conducted at room temperature for 12 hours, affording a diastereomeric mixture in a 88:12 ratio in 82% yield. The major diastereomer is the one shown in Scheme 10.

Landais and colleagues, focussed their interest in naturally occurring isotetronic acids, which exhibit relevant biological properties [41]. These simple motifs, are also found in more complex compounds, such as erythronolide A [42]. Their studies focussed on the organocatalyzed aldol reaction between pyridine-2-carbaldehyde derivatives and various \( \alpha \)-ketoacids (Scheme 11).

Depending on the nature of the substituents on the pyridine skeleton, the reactions provided the expected isotetronic acid, and, surprisingly, their corresponding pyridinium salt. Further functionalization of the pyridinium salt, provided access to valuable building blocks in enantiomerically pure form, including indolizidines, aldol products and butyrolactones.

Tubulysins are cytostatic peptides isolated from myxobacteria *Archangium gephyra* and *Angiococcus disciformis*, and act on microtubulin production (Fig. 2) [43]. A direct flexible approach to the tubuvaline (Tuv) core of tubulins was established by Dash and co-workers, employing a reductive amination of precursors of tubuvaline (pre-Tuv) [44]. The analogues of the pre-Tuv were achieved using a proline-catalyzed direct asymmetric aldol reaction of substituted thiazole-carbaldehydes with acetone. The first organocatalytic enantioselective approach to precursors of pre-Tuv was presented, employing a prolineamide catalyzed aldol reaction of thiazole-carbaldehyde with methyl isopropyl ketone in water, obtaining excellent yields and regio- and enantioselectivities.

Pansare and colleagues described the enantioselective organocatalytic direct vinylogous aldol reaction of \( \gamma \)-crotonolactone and a suitable aldehyde, for the synthesis of a functionalized \( \gamma \)-butenolide [45]. These aldol product was stereoselectively converted into 5-aminoalkyl butyrolactone, which isomerized to the key 2,3-disubstituted piperidinone, a common intermediate to \((+)-febrifugine and \((+)-halofuginone (Scheme 12).

The initial vinylogous aldol reaction was conducted using cyclohexanediamine, stilbenediamine and cinchonidine derived thioureas [46, 47] and stilbenediamine derived squaraines [48, 49]. Through the designed organocatalytic sequence, \((+)-febrifutine was obtained in 14 steps with 6.8% overall yield.

The enantioselective synthesis of \((+)-swainsonine was carried out by Saicic and co-workers, achieving the final purpose in 9 steps with 24% overall yield [50]. The key feature of the synthesis was the combination of an organocatalyzed aldolization and a reductive amination, allowing for a rapid construction of highly functionalized heterocyclic system. Employing a similar approach, also \((+)-8-epi-swainsonine was synthesized in 7 steps and 28% overall yield. The retrosynthetic analysis for \((+)-swainsonine is shown in Scheme 13.

Chiral indane frameworks, such as indane subunits, being widely distributed in biologically active natural products, are also desirable targets in organic synthesis [51-54]. Singh described organocatalytic intramolecular aldolization of ortho-diaxylbenzenes to construct highly functionalized 3-hydroxyindanones [55]. In this transformation, a high trans-selectivity was achieved by the use of metal salts of aminoacids. The method allowed the access to the strained spirocyclic 3-hydroxyindanones related to a number of natural product frameworks. Fig. (3) shows the structure of some selected natural products bearing a 3-hydroxyindanone core.

Finally, our group designed the synthesis of Dominicalure I, the major component of the aggregation pheromone...
Scheme 12. Retrosynthetic analysis of (+)-febrigugine and (+)-halofuginonel [45].

Scheme 13. Retrosynthetic analysis for (+)-swainsonine [50].

of Rhyzopertha dominica (Fabricius) (Coleoptera: Bostrichidae) using a pyrrolidine-catalyzed self aldol condensation of propanal as the key step (Scheme 14) [56].

The organocatalytic reaction was carried out in hexane at room temperature during 48 hours, and then a 10% solution of HCl was added, yielding the condensation product in 95% for both steps. Together with an esterification under Corey’s conditions [57] and enzymatic transesterification with (S)-2-pentanol, the three steps constituted the concise sequence through which the target pheromone was prepared with an overall yield of 68%, and > 99% ee starting from really inexpensive material.
1.2. Mannich Reactions

The first report of an organocatalytic enantioselective Mannich reaction was stated by List in 2000 [58]. Proline was used as catalyst and acetone or hydroxyacetone as the Mannich donor, affording predominantly the syn-product.

Scheme 15 shows the transition state for the aldol and Mannich reaction using proline as catalyst [15]. As it can be seen, the presumed configurations of (E)-enamine and (E)-imine give rise to the preferred anti- and syn-products respectively, via chair-like, hydrogen-bonded transition states [59].

A set of pyrrolidine- and imidazolidinone-based organocatalysts was evaluated using a suitable starting material for the preparation of quinolizidine derivatives (Scheme 16). The pyrrolidine-based catalysts I-IV did not lead to the desired cyclization. However, using catalyst V-HCl the reaction took place in 74% yield, displaying a 12:1 trans/cis diastereomeric ratio and 46% ee for trans-isomer.
Once the optimal reaction conditions were established, the authors also investigated the scope and generality of this cyclization, finding that the yields of the six-membered ring-closed products were obtained in good to very good yields (63-88%). Additionally, dialkylsubstituted substrates and sterically hindered cyclopentyl and cyclohexyl acetals afforded the desired products in good yields and ee values up to 97%. The process was also found useful for five- and seven-membered rings and provided the corresponding izidine derivatives in very good yields and ee values (up to 87%). Finally, the total synthesis of representative natural products with indolizidine, quinolizidine and pyrrolizidine alkaloids structures such as (-)-tashiromine (6 steps, 43% overall yield, \(dr = 4:1\), \(ee = 92\%\)), (-)-epilupinine (7 steps, 38% overall yield, \(dr = 10:1\), \(ee = 88\%\)) and (-)-trachelanthamidine (6 steps, 52% overall yield, \(dr = 7:1\), \(ee = 74\%\)) respectively were also achieved through this method.

Rutjes and colleagues synthesized enantiomerically pure 2,6-disubstituted piperidinones from furfural, involving an organocatalyzed Mannich reaction as one of the initial steps. The overall synthetic approach allowed the preparation of (-)-sedacryptine and one of its epimers (Scheme 17) [61]. Despite existing methods for the synthesis of such considered privileged structural motif in Nature, that is the 3-hydroxypiperidine scaffold, catalytic methodologies for the asymmetric synthesis of these structures could give access to new substitution patterns.

Proline-catalyzed Mannich reaction was chosen to prepare the needed enantiopure aminoalkyl furans from a furfural derivative. Thus \(N\)-Boc (N-tert-butyloxycarbonyl)-protected amines, substrates for the aza-Achmatowicz reaction that follows in the designed synthetic sequence, were prepared via the organocatalytic Mannich reaction. The protocol involves basic conditions, under which the sulfone was eliminated to give the corresponding crude imine, which was directly treated with L-proline (20 mol%) and an aldehyde to give the corresponding \(\beta\)-amino aldehydes. The resulting crude Mannich products were directly in situ reduced resulting in the expected \(\gamma\)-amino alcohols. Aliphatic, allylic and aromatic substituents were prepared with reasonable yields and excellent selectivities according to this methodology.

Lee and co-workers described the synthesis of biologically interesting flavanone derivatives, through an ethylenediamine diacetate (EDDA)-catalyzed Mannich reaction from 2-hydroxyacetophenone derivatives, aromatic aldehydes and aniline (Scheme 18).
The scope of the reaction was studied using different substituents on the 2-hydroxyacetophenone nucleus, bearing either electron-donating or electron-withdrawing groups on the aromatic ring.

The mechanism of the reaction was analyzed on the model reaction involving benzaldehyde, and was explained according to Scheme 19. The carbonyl group of benzaldehyde could be protonated by EDDA, enabling the formation of an iminium ion as intermediate. The enol form, generated from 2-hydroxyacetophenone in the presence of EDDA, could attack such iminium ion giving an intermediate, which could undergo cycloaddition and give the final flavanone via an intramolecular $S_N2$ reaction.

It is important to notice that, when aniline was not used, the reaction did not proceed, suggesting that a pathway via a direct aldol reaction and further 1,4-Michael-type cycloaddition to give the final product is not taking place.

A stereocontrolled synthesis of vicinal diamines from protected $\alpha$-aminoacetaldehydes through amine-catalyzed Mannich reactions was reported by Maruoka et al. [63]. The reaction was carried out with benzoyloxy carbonyl (Bz)- and tert-butoxy carbonyl (Boc)-protected aminoacetaldehydes and N-Boe-protected imine derived from benzaldehyde, using 30 mol% of l-proline in acetonitrile at 0°C (Scheme 20).

Favored by the presence of the protecting groups, the reaction proceeded enantioselectively giving the syn-Mannich product. The results, clearly outstanding from an academic point of view, suggested that the protecting groups in the aldehyde are sufficient to suppress undesired side reactions (formation of anti-vicinal diamines) caused by the nucleophilic character of the $\alpha$-Nitrogen. Then, a variety of amines and solvents were evaluated, giving in all cases good yields and excellent stereoselectivities. The authors also attempted the preparation of the corresponding anti-products, which was successfully achieved by substituting l-proline by a chiral binaphthyl-amine-catalyst.

The proline-catalyzed addition of various aliphatic aldehydes to sterically hindered 2-arylsubstituted 3H-indol-3-ones by Rueping and colleagues, afforded 2,2-disubstituted 2,3-dihydro-1H-indol-3-one derivatives with high enantioselectivities [64]. The described highly enantioselective proce-
dure allowed to the preparation of a chiral derivative, (S)-2-(2-bromophenyl)-2,3-dihydro-2-(2-hydroxyethyl)-1H-indol-3-one, which can be used as advanced intermediate in the synthetic route to the natural product hinckedentine A.

A proline-catalyzed Mannich reaction was also part of the synthetic sequence designed by Brimble and colleagues for the preparation of the natural 2-formylpyrrole derivatives magnolamide, lobechine and funebral [65].

1.3. Conjugated Additions

In addition to Aldol and Mannich-type reactions, secondary amines also react with α,β-unsaturated aldehydes, giving the corresponding enamine or iminium intermediates, which can undergo 1,4-additions [15, 66].

Particularly, organocatalysis has led to significant progress in the asymmetric synthesis of stereochemically complex molecules, such as spirooxindoles, which are found in many natural products and biologically active molecules [67].

Melchiorre and Bergonzini described an efficient enantioselective synthetic strategy to access 3-substituted 3-hydroxyoxindole derivatives, usual framework of many biologically active compounds and natural products, which possess an oxindole core with a hydroxyl-bearing tetrasubstituted stereogenic center at C-3 [68]. The reaction was first studied as shown in Scheme 21, using basic additives, a proline-derivative as catalyst, and model substrates such as cinnamaldehyde and the given dioxindole.

The addition was followed by a fast hemiacetalization, which led to a mixture of the two anomers. Direct oxidation of the crude with pyridine chlorochromate (PCC) gave the corresponding spirooxindole /butyrolactones with high optical purity. The reactions were performed on a 0.05 mmol scale using 1.2 eq. of the aldehyde. All reactions afforded poor diastereomeric ratios. The following step in the research process was the study of the scope of aldehydes and dioxindoles. Showing an ample range of substrates, the reaction proved to be suitable for accessing to enantioenriched 3-substituted 3-hydroxyindole derivatives.

Oxindole derivatives were used by Gong et al. as building blocks for the synthesis of natural products [69]. The enantioselective organocatalytic addition of nitroalkanes to oxindolyldieneindolinenines in the presence of bifunctional organocatalysts provided an efficient method for the preparation of 3,3-disubstituted oxindole derivatives. High yields and excellent enantioselectivities were achieved, and the

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**Scheme 19.** Proposed mechanism for the flavanone formation through an EDDA-catalyzed Mannich reaction [62].

**Scheme 20.** Stereocontrolled preparation of vicinal diamines through L-proline-catalyzed Mannich-type reaction [63].
transformation could be used in the synthesis of the key intermediate for a formal total synthesis of (+)-gliocladin C (Scheme 22).

A variety of structurally related chiral bifunctional organocatalysts were first investigated in the reaction between nitromethane and the 3-(1H-indol-3-yl)-3-tosylindolin-2-one in the presence of K$_3$PO$_4$ as an inorganic base in dichloromethane. Bifunctional urea-based organocatalysts proved to be highly enantioselective.

The reaction conditions were optimized and used in the substitution reaction of nitroalkanes with a variety of substituted 3-(arylsulfonylalkyl)oxindoles. Either indole or oxindole moieties substituted with electron-donating or electron-withdrawing substituents afforded the desired products in good to excellent yields (79-86%) and enantioselectivities (89-98%).

A range of 3-pyrrolyl-3-3'-disubstituted oxindoles were also obtained via the reaction of 3-pyrrolyl-oxindoles with nitroalkenes, through an organocatalytic procedure [70]. The usefulness of the protocol was demonstrated by the conversion of the corresponding Michael adducts into other functionalized 3,3'-disubstituted oxindoles, as well as into a pyrrolidinoindoline derivative which has a core structure similar to natural products such as CPC-1, (-)-physostigmine, (-)-pseudophrynaminol, etc.

Hayashi, [71] Jørgensen [72] and MacMillan’s [73] catalysts were screened for the preparation of Katsumadain A, a naturally occurring influenza virus neuraminidase (NA) inhibitor, through an enantioselective 1,4-conjugated addition of styryl-2-pyranone to cinnamaldehyde as a key step, and followed by a tandem Horner-Wadsworth-Emmons (HWE)/Oxa-Michael addition [74]. An ample study of reaction conditions was carried out for the organocatalytic 1,4-conjugate addition/hemiketalization of styryl-2-pyranone with α,β-unsaturated aldehydes, regarding substrate scope, catalyst, additive, solvent and temperature (Scheme 23).

Regarding the substrate scope, while the styryl-2-propanone remained unchanged, a variety of cynamaldehyde derivatives bearing either electron-withdrawing groups (4-Cl, 4-CF$_3$ and 4-NO$_2$) or electron-donating groups (4-MeO, 3,5-MeO) or the phenyl ring proved to be suitable substrates, affording the corresponding products in good yields and enantioselectivities. With using cynamaldehyde as Michael acceptor, best results were achieved using catalyst A, benzoic acid as additive and CH$_2$Cl$_2$ as solvent, yielding the Katsumadain A core in 78% yield and 91% ee. The next step then was the proposed tandem HWE/oxa-Michael addition, which gave Katsumadain A as a single diastereomer in 52% yield.

The same catalysts [71-73] were used for the 1,4-conjugated addition of ascorbic acid to also various α,β-unsaturated aldehydes, and further hemiacetalization/hemiketalization provided a rapid access to 5-5-5 spirodilactone cores with five continuous stereogenic centers, of a family of ascorbylated natural products (Scheme 24) [75].

The optimal conditions proved to be when using Mac-Millan’s catalyst, benzoic acid as additive and H$_2$O/MeOH as solvent, yielding the desired compound as a single isomer in 92% yield. The scope of the reaction was expanded to cinnamaldehyde-derivatives comprising either electron-withdrawing or electron-donating substituents in the aromatic ring.

Also (S)-diphenylprolinol trimethylsilyl ether was used for the synthesis of optically pure 2-alkyl-3-(1H-indol-3-yl)-
Organocatalysis in the Synthesis of Natural Products

Catalysts:

A: Ar = Ph
B: Ar = 3,5-(CF3)2-C6H3

Additives: benzoic acid (BA), p-nitrobenzoic acid (PNBA)
Solvents: CH2Cl2, MeOH, CH3CN, DMSO, Toluene
Temperature: 23, 0 and -20°C
Yields: up to 94%; ee: up to 93%

Scheme 23. Screening of reaction conditions for the organocatalytic 1,4-conjugate addition/hemiketalization of styryl-2-pyranone with α,β-unsaturated aldehydes [74].

4-nitrobutanals, one type of tryptamine precursors which are of great interest for pharmaceutical and biological research [76]. In this work, the Michael addition of aliphatic aldehydes to indolynitroalkenes was developed, providing the desired optically pure syn 2-alkyl-3-(1H-indol-3-yl)-4-nitrobutanal derivatives in up to 98% yield, and with ≥99:1 dr and >99% ee (Scheme 25).

Peptides of the type Pro-Pro-Xaa (Xaa = acidic amino-acid) were also tested as catalysts for the conjugated addition of aldehydes to α,β-disubstituted nitroolefins, with the aim to provide symmetrically γ-nitroaldehydes with three consecutive stereogenic centers [77]. These synths are key intermediates for the synthesis of chiral pyrrolidines, fully substituted γ-butyrolactams and γ-aminoacids, frequently found in natural products. The research led to the identification of H-Pro-Pro-D-Gln-OH and H-Pro-Pro Asn-OH as excellent stereoselective catalysts for this transformation. The use of 5 mol% of these peptides, and different combinations of alde-
hydrazides and α,β-disubstituted nitroolefins, provided the corresponding γ-nitroaldehydes in good yields and diastereoselectivities, as well as excellent enantioselectivities.

An enantioselective synthesis of the core framework of neurotrophic *Illicium* majucin-type sesquiterpenes [78] was described by Theodorakis and colleagues [79]. The synthetic sequence was based on the organocatalytic asymmetric Robinson annulation, providing an efficient approach for a diversity-oriented synthesis of *Illicium* natural products, which holds remarkable therapeutic potential for neurodegenerative diseases.

Majucin-type *Illicium* sesquiterpenes, such as majucin, jiadifenolide, jiadifenin, jiadifenoxolane A and (2R)-hydroxynorneomajucin share a caged tetracyclic scaffold, representing a major synthetic challenge. A retrosynthetic analysis of the core framework of these molecules is shown in Scheme 26.

The enantioselectivity of these molecules is introduced by an organocatalyzed asymmetric Robinson annulation that allows access to the enantiomerically enriched bicyclic motif X from commercially available cyclopentane-1,3-dione (Scheme 27).

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**Scheme 25.** Organocatalyzed Michael addition of aliphatic aldehydes to indolyl nitroalkenes, as key synthetic scheme to tryptamine precursors [76].

**Scheme 26.** Retrosynthetic analysis of majucin-type common scaffold, from a bicyclic motif as key intermediate [79].

**Scheme 27.** Organocatalyzed asymmetric Robinson annulation leading to an enantioenriched bicyclic intermediate X [79]. DPPE: 1,2-Bis(diphenylphosphino)ethylene. BSA: Bis(trimethylsilyl)acetamide.
One of the key features in the synthesis of L-pyrrolysine by Wang et al. is an organocatalytic Michael addition of ethyl nitroacetate to crononaldehyde (Scheme 28) [80]. L-pyrrolysine is the 22nd genetically encoded amino acid, which was first identified in 2002 in the crystal structure of Methanosarcina barkeri monomethylamine methyltransferase [81].

The group used same synthetic strategy was used for the preparation of trans-3-substituted proline derivatives, which are common scaffolds for the synthesis of a variety of natural products, such as domoic acid, (-)-α-kainic acid, among others [82]. The synthetic targets were obtained with diastereoselectivities in the range of $dr > 20:1$, and excellent enantiomeric selectivities, up to 97% ee.

### 1.4. Cascade Reactions

According to the above examples, proline-derived catalysts act through enamine-based pathways in Aldol or Mannich reactions, and additionally react with α,β-unsaturated aldehydes giving the corresponding iminium intermediates, that can undergo 1,4-additions [15]. This dual aspect of proline derivatives-mediated catalysis leads directly to multicomponent or cascade (domino) reactions, since from them, both nucleophilic enamines and electrophilic iminium species can be formed in one pot or successively.

Chiral primary and secondary amine catalysts have been extensively used to activate carbonyl groups, participating in various enamine- and iminium-mediated processes. This makes them ideal for sequential addition of nucleophiles and electrophiles in a cascade manner, easily accessing products with multiple stereocenters [67, 83]. Particularly, complex molecules such as spiropyrrolidines -structural motifs which are very important building blocks for preparations of bioactive compounds, natural products and pharmaceuticals- have been prepared with high enantioselectivities, using pyrroolidine derivatives as catalysts [67]. As example, Ghosh and Zhou reported the synthesis of substituted spirocyclohexane oxindoles through the reaction between methyleneoxindole-derivatives and pentane-1,5-dial (Scheme 29) [84].

The formation of the oxindole derivatives proceeded through a Michael/aldol sequence in the presence of the pyrroolidine-derived Jørgensen-Hayashi catalyst, to afford products with multiple stereocenters in high yields and excellent enantioselectivities. This work emphasizes that, when N-protecting groups on the oxindole were modified from an electron-withdrawing group to an electron-donating one, the absolute configuration on the hydroxyl center also changed, indicating that these N-protecting groups have a critical effect on the stereochemistry of the aldol ring closure.

Wang and colleagues reported the synthesis of spirocyclohexaneoxindoles through domino Michael-Aldol reactions between isatin derived alkenes and also pentane-1,5-dial in the presence of Jørgensen-Hayashi catalyst [85]. As result, a series of multistereogenic and functionalized spirocyclohexaneoxindoles were obtained in good yields, moderate diastereoselectivities and excellent enantioselectivities.

The spirocyclic secoyohimbane alkaloid rhynchophylline is the major component of the extracts of Uncaria species, a plant used in Chinese traditional medicine for the treatment of disorders of the central nervous system. Based on the structure of rhynchophylline, Waldmann and colleagues developed an enantioselective organocatalyzed synthetic method which gave access to the tetracyclic secoyohimbane scaffold. The quaternary and the three tertiary stereogenic centers were achieved in a one-pot multistep reaction sequence [86]. Rhynchophylline and its isomer isorhynchophylline, embody the secoyohimbane scaffold [87-90]. Its key structural feature is a complex spiro ring fusion at the position three of the oxindole core, and the position one of an octahydroindolizine. They occur as pairs of interconvertible isomers due to isomerization at the spiro center through Mannich/retro-Mannich reactions (Scheme 30) [91, 92].

The key step in the proposed synthetic route was an asymmetric domino Michael-Mannich reaction of an oxindole derivative and an α,β-unsaturated aldehyde. The optimization of the reaction conditions was conducted with a model nucleophile and aldehyde using different organocatalysts, solvents and additives. Best results regarding enantiomeric...
excess, diastereoselectivity and yield were obtained with 100 mol% of organocatalysts A, caesium acetate as additive and methanol as solvent (Scheme 31).

Another related motif, spiroindoline frameworks, are a common structural feature found among a number of high-profile natural products such as those derived from Aspidosperma, Kopsia and Catharanthus genre. In 2013, MacMillan and co-workers detailed the first enantioselective total synthesis of (-)-minovincine in nine steps, using an organocatalytic cascade which incorporates an enantioselective Diels-Alder cycloaddition, /notdef.g0006-elimination and conjugated addition sequence [93]. The key cascade step was conducted in CHCl3 at -30°C with an imidazolidinone-derived MacMillan catalyst in 30 mol%, and the sequence of reactions yielded 72% to give the product in 91% ee (Scheme 32).

Chiral indane frameworks, were also a goal for Han et al., who described the stereoselective three-step organocatalytic cascade to yield synthetically important oxa-spiro cyclic indanone scaffolds [94]. The first step in the synthetic sequence was a tertiary amine-catalyzed Morita-Baylis-Hillman (MBH) reaction of a conjugated nitroalkene with an activated ketone (Scheme 33).

The resulting tertiary alcohol then participates directly in the second catalytic cycle by serving as the receptor in an asymmetric Michael reaction with an enamine-activated aldehyde. Finally, the asymmetric protonation of Michael adduct forms a zwitterion, whose subsequent hydrolysis and acetylation provides the desired spirohemiacetal.

The preparation of enantiopure cis-decahydroquinolines is an important goal for the group of Bradshaw and Bonjoch. A gram-scale organocatalytic route to phlegmarine alkaloids, and the total synthesis of the cis-phlegmarine-type alkaloid (-)-cemnizine B were developed [95]. The overall process was divided into three sets of tandem reactions, which were subsequently fused into a single sequence. The first one-pot operation began with a β-ketoester which underwent an organocatalyzed Michael reaction in the presence of 5% of a modified Hayashi catalyst. After removal of the solvent and
Scheme 31. Key step in route to secoyohimbane alkaloids [86].

Scheme 32. Key organocatalytic cascade in the synthetic route to (-)-minovincine [93].
Scheme 33. Asymmetric assembly of ketones, disubstituted olefins and aldehydes into chiral oxa-spiro derivatives via organocatalyzed cascade reactions [94].

Scheme 34. Organocatalyzed tandem Michael/aldol cyclization/aza-Michael reaction [95].
Organocatalysis in the Synthesis of Natural Products

Scheme 35. Schematic synthetic approach to cermizine D [99].

An organocatalytic aza-Michael reaction was also included as key step in the synthetic route to cermizine D [99]. The developed strategy exploits the use of a common intermediate to access over 85% of the carbon backbone. The overall synthetic procedure include the above mentioned organocatalyzed aza-Michael addition, a diastereoselective alkylation with (R)-iodomethyl phenyl sulfide, a conjugated addition to a vinyl sulfone species and a sulfone coupling/desulfurization sequence to join the two major subunits (Scheme 35). The same strategy was later employed in the formal synthesis of senepodine G and cermizine C [100].

(+)-Galbulin has a tetrahydronaphthalene carbon skeleton, prevalent in many lignans, a class of secondary metabolites widely found in plants, and derived biosynthetically from the oxidative dimerization of two cinnamic acid units. Its concise enantioselective synthesis was developed by Hong et al., which was achieved through an organocatalytic domino Michael-Michael-Aldol condensation using Jørgensen-Hayashi catalyst, and finally an organocatalytic kinetic resolution as key steps [101]. The retrosynthetic analysis for (+)-galbulin is shown in Scheme 36.

A total synthesis of the anticancer natural product (+)-trans-dihydrolycoricidine was reported by McNulty, from α-azidoacetone and cinnamaldehyde precursors [102]. The key step includes an asymmetric organocatalytic sequence proceeding by a regiospecific proline-catalyzed syn-Michael addition followed by an intramolecular aldol reaction. The sequence results in the formation of an advanced intermediate, containing three stereogenic centers, which was converted in eight steps in the final product. The retrosynthetic analysis of (+)-trans-dihydrolycoricidine is shown in Scheme 37.

Another structural motif found in a wide range of natural products is the oxepane ring. They are challenging synthetic targets due to enthalpic and entropic barriers. Hong and coworkers developed an organocatalytic oxaconjugate addition reactions promoted by gem-disubstituent (Thorpe-Ingold) effect, which provided α,α'-trans-oxepanes [103]. The authors demonstrated the potential of an organocatalytic tandem oxa-conjugate addition/α-oxidation, through the rapid generation of molecular complexity (Scheme 38). The designed procedure could provide powerful tools for the synthesis of natural products that contain highly functionalized oxepanes.
Scheme 36. Retrosynthetic analysis for (+)-galbulin [101].

Scheme 37. Retrosynthetic analysis of (+)-trans-dihydrolycoricidine [102]. PG = Protecting group, Moc = methoxycarboxylamino, Ts = p-toluensulfonyl.

Scheme 38. Organocatalytic oxa-conjugate addition: synthesis of α,α’-trans-oxepanes [103].

The development of a catalytic asymmetric three-component triple cascade of 3-vinylindoles with α,β-unsaturated aldehydes, following by an iminium-iminium-enamine activation sequence, was accomplished by Enders et al. (Scheme 39) [104]. The reaction was at first carried out with a mixture of 3-vinylindole and cinnamaldehyde in dichloromethane at room temperature, and using 20 mol% of (S)-TMS-diphenylprolinol as catalyst. After 24 hs, the corresponding pyridocarbazole derivative was obtained as a single di-
astereoisomer. The scope of the reaction was studied regarding the catalyst used, solvent, and 3-vinylindole and aldehyde derivatives. The proposed mechanistic sequence for the tandem Diels-Alder, aza-Michael and aldol condensation is shown in Scheme 40.

The same pyrrolidine-derived organocatalyst was used by Wang and co-workers in the tandem oxo-Michael-IED/HAD (IED/HAD: Inverse electron demand hetero Diels-Alder) and oxo-Michael-IED/HAD-Michael-IED/HAD-Michael-Aldol condensations of (E)-hydroxyaryl-2-oxobut-3-enoate derivatives with enals [105]. Two tricyclic chroman derivatives found in many different natural products were respectively obtained by optimizing the reactant ratio and reaction temperature in good yields (up to 96%) with good diastereoselectivities (up to 30:1) and excellent enantioselectivities (up to 99% ee). The chemical versatility of (E)-2-oxo-3-butenoates was exploited in the designed tandem reactions with cinnamaldehyde derivatives. The reaction initiates through iminium catalysis by the secondary amine, and a subsequent cyclization, leading to access to the chroman skeleton. The authors found that two types of chiral tricyclic chroman derivatives could be obtained through organocatalytic domino oxo-Michael-IED/HAD and oxo-Michael IED/HAD-Michael-Aldol condensations by controlling reaction conditions (Scheme 41).
Also primary amines were used as catalysts in a two-step synthesis of naturally occurring alkaloids calyxamines A and B, in a tandem Mannich-Aldol reaction under solvent free conditions (Scheme 42) [106].

The starting imine was prepared through the condensation of NH_2Cl with acetone, and the piperidone intermediate was obtained from a Mannich condensation with another equivalent of acetone. The following step, was its aldol condensation with acetone as well. The two condensations were carried out in a two-step sequential process under solvent free conditions, and both catalyzed by diamines.

The biologically active natural product cispentacin was synthesized through a concise and efficient route, in a 93-98% overall yield in three steps, and good enantioselectivity (up to 96% ee) [107]. For designing the synthetic strategy, α-branched α,β-unsaturated aldehydes were tested in the organocatalytic tandem Michael addition/cyclization with N-benzoxycarbonylhydroxylamine. The synthetic sequence started from cyclopentene-2-carbaldehyde, and used dihydroxylpoinol trymethylsilyl ether as chiral catalyst. The reaction yield was found to depend on the substitution pattern of the aldehydes, and cis- and trans-isomers were obtained. Nevertheless, the reaction proceeded efficiently when using 2-ethylcrotonaldehyde, obtaining the desired product with a 98% ee.

CONCLUSION

In this article, we have addressed the importance of organocatalytic processes as part of synthetic routes to natural products. Key reactions such as aldol and Mannich reactions, and 1,4-conjugated additions, either as concrete steps or being part of cascade reactions were exposed through selected examples, covering the period from 2012 to date.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.
TMS = Trimethylsilyl
THF = Tetrahydrofuran
TBS = Butyldimethylsilil

REFERENCES


[37] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. Enan-tio- and diastereoselective Michael reaction of 1,3-dicarboxyl com-


Dibello et al.


