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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 synthons 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 **1** 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.

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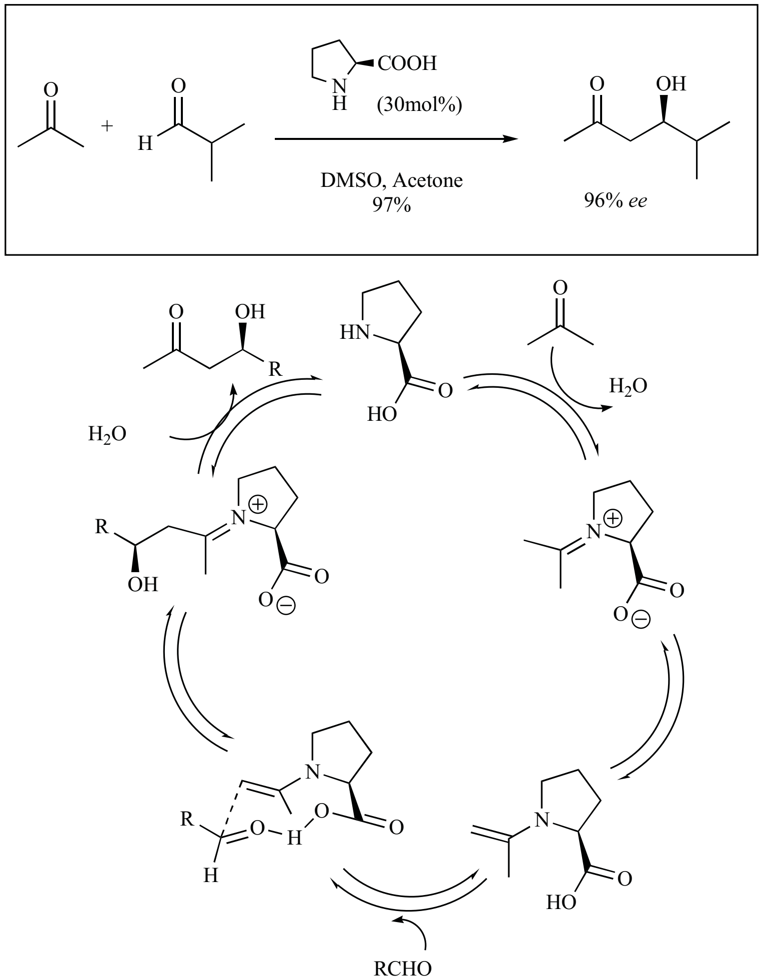


Scheme 1. Example of a proline-catalyzed aldol reaction proceeding *via* an enamine mechanism [1].

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*-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.

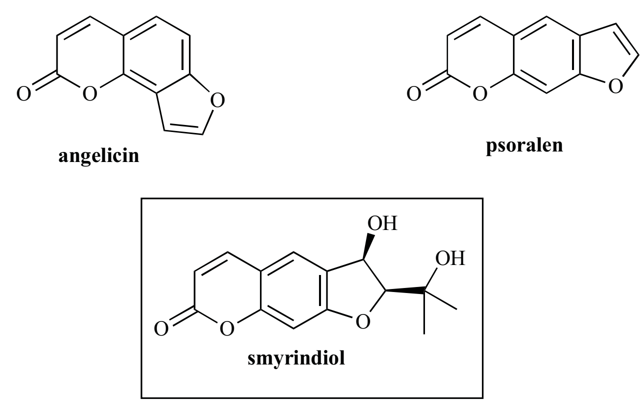
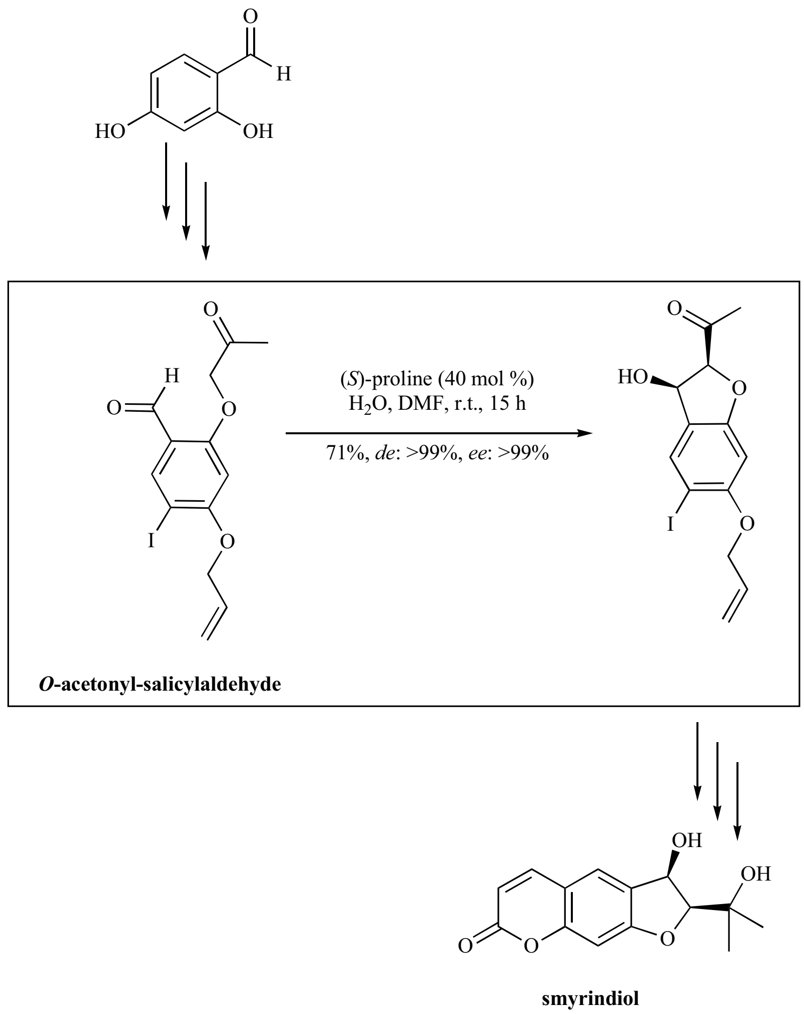


Fig. (1). Structure of naturally occurring furocoumarins [27].

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 2. Synthetic route to smyrindiol [27].

organocatalyzed total synthesis of smyrindiol was achieved using (*S*)-proline to catalyze a 5-*enolexo* 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 to 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 diastereo- and enantiomeric excesses (*de* ≥95%, *ee* ≥99%).

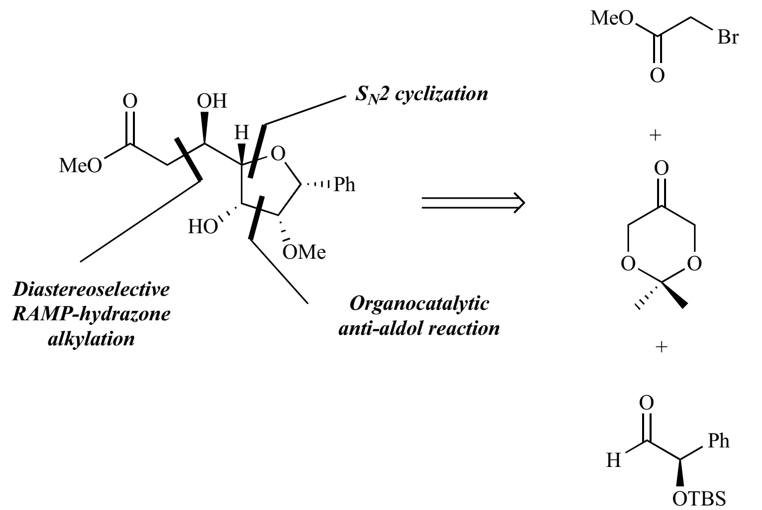
Florence and Wlochal used an organocatalytic aldol reaction as the first step in the synthetic sequence to palmerolide C, a polyketide-derived macrolide from the antarctic tunicate *Synoicum adereanum*, which shows remarkable activity towards the UACC-62 human melanoma cell line (IC_{50} = 110 nm), [31] (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.

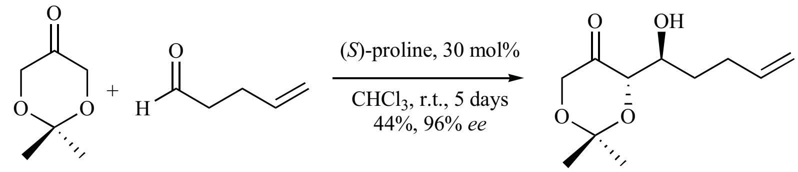
The diastereo- and enantioselective syntheses of 3-acetyl-4-hydroxyisochroman-1-ones (structural feature found in several natural products) *via* an intramolecular *trans*-selective aldol reaction were described by Enders and coworkers, employing proline-type organocatalysts [34].

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**).

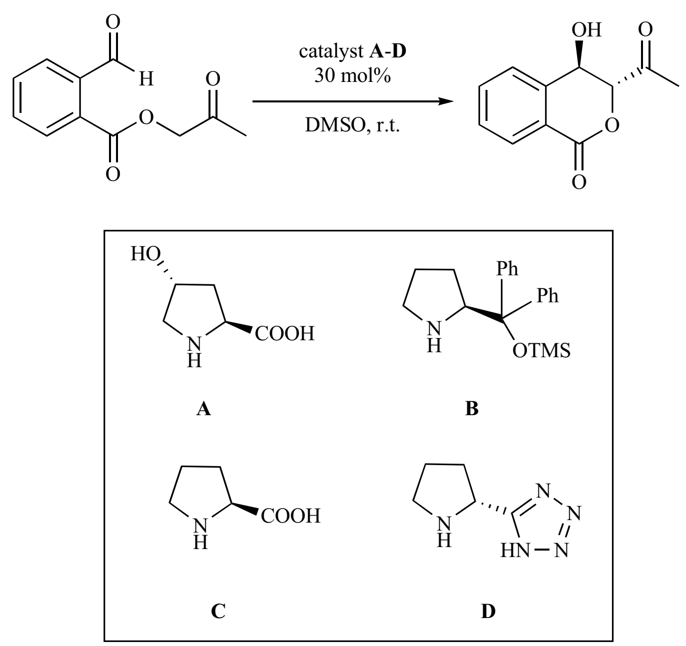
Catalysts **A** and **B** did not give significant conversions, while (*S*)-proline (**C**) afforded the desired isochromanone



Scheme 3. Retrosynthetic analysis for 4-*epi*-methoxy-gonioheptolide A [30].



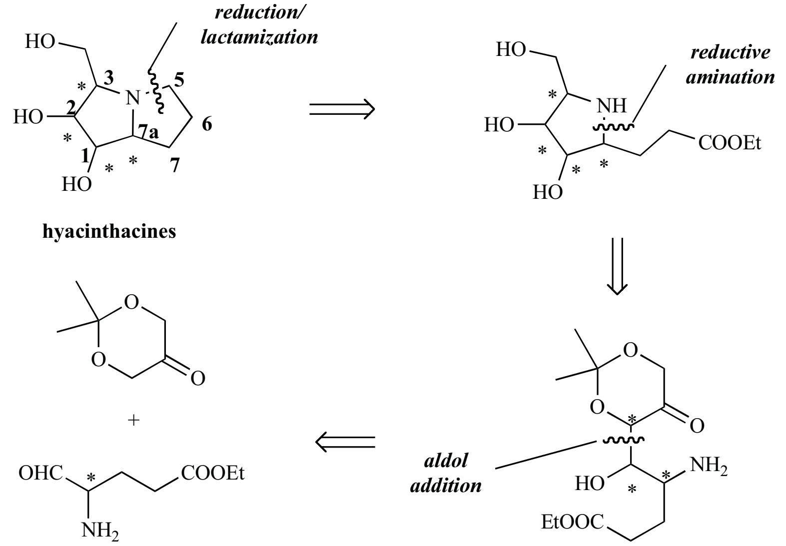
Scheme 4. (*S*)-Proline-catalyzed first step in the synthetic route to the proposed structure of palmerolide C [31].



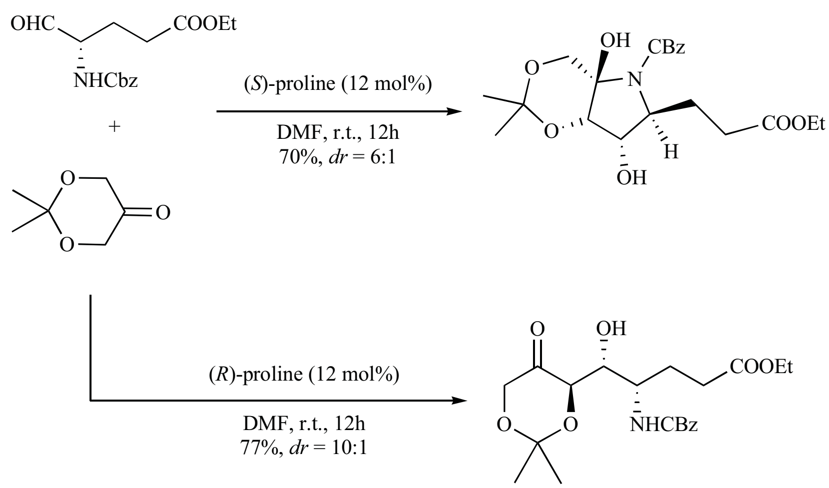
Scheme 5. Catalyst screening for the organocatalytic isochroman-1-one synthesis [34].

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)-1*H*-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 hyacinthacines 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-



Scheme 6. Retrosynthetic analysis of hyacinthacines [35].



Scheme 7. (*R*)-and (*S*)-proline-catalyzed aldol reaction, first step in the synthetic route to hyacinthacines [35].

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 sterochemical outcome of this key step in both, the matched and mismatched cases.

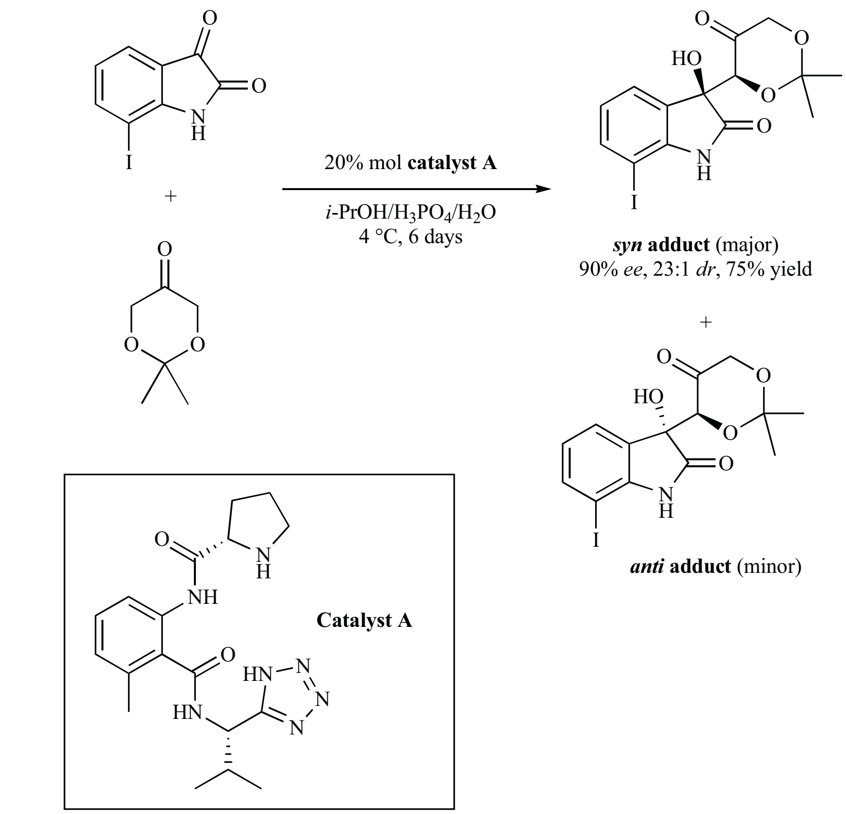
The preparation of *ent*-2-*epi*-hyacinthacine A_2 started with the (*S*)-proline-catalyzed aldol addition of dioxanone to the adequate *N*-carbobenzyloxy-protected aldehyde yielded the aldol adduct (the product adopted the cyclic hemiaminal form) as the major product, along with a minor amount of its 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 A_1, 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].

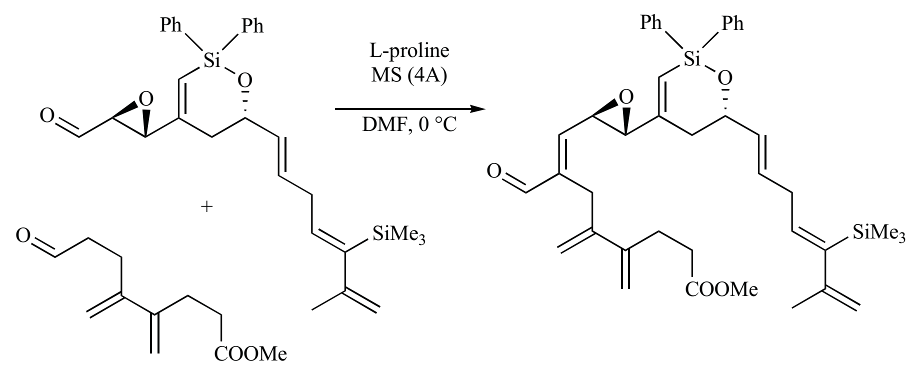
A L-proline-mediated direct cross-aldol condensation of two advanced aldehyde-intermediates was utilized by Volchkov and Lee for the construction of an α,β-unsaturated epoxyaldehyde, a key compound in route to (-)-amphidinolide V (Scheme **9**) [38].

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).

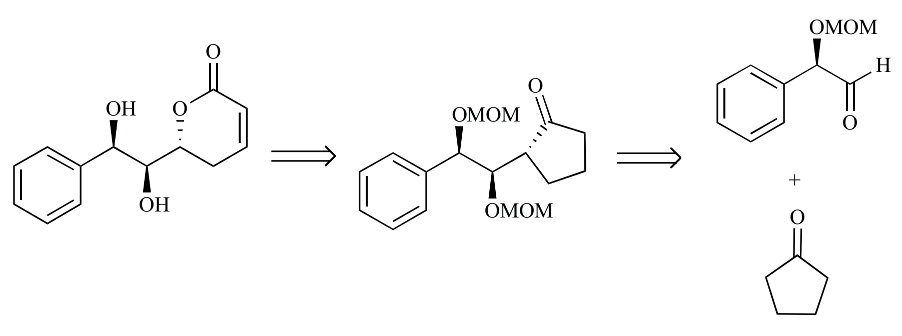
Phansavath and colleagues reported a convergent stereoselective synthesis of one isomer of the C44-C65 fragment of mirabalin, in which the first step is the organocatalytic cross-aldol reaction of isobutyraldehyde and propanal, carried out at 4°C during 48 hours, and using L-proline as catalyst [39].



Scheme 8. Organocatalytic aldol reaction of 7-iodoisatin and 2,2-dimethyl-1,3-dioxan-5-one [36].



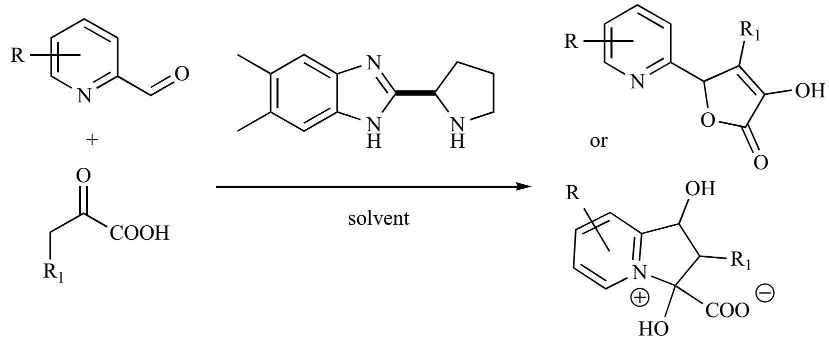
Scheme 9. Organocatalytic cross aldol reaction for the synthesis of a key intermediate in the route to (-)-amphidinolide V [38].



Scheme 10. Retrosynthetic analysis for 7-*epi*-goniodiol [40].

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



Scheme 11. Organocatalyzed reactions between pyridine carbaldehyde derivatives and α-ketoacids [41].

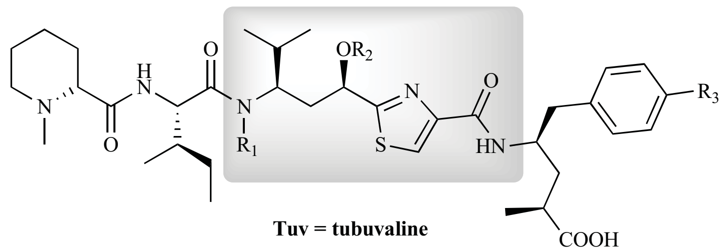


Fig. (2). General structure of tubulysins, a family of tetrapeptides with potent anti-cancer activity [44].

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 foccused on the organocatalyzed aldol reaction between pyridine-2-carbaldehyde derivatives and various α-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 tubavaline (Tuv) core of tubusylins 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.

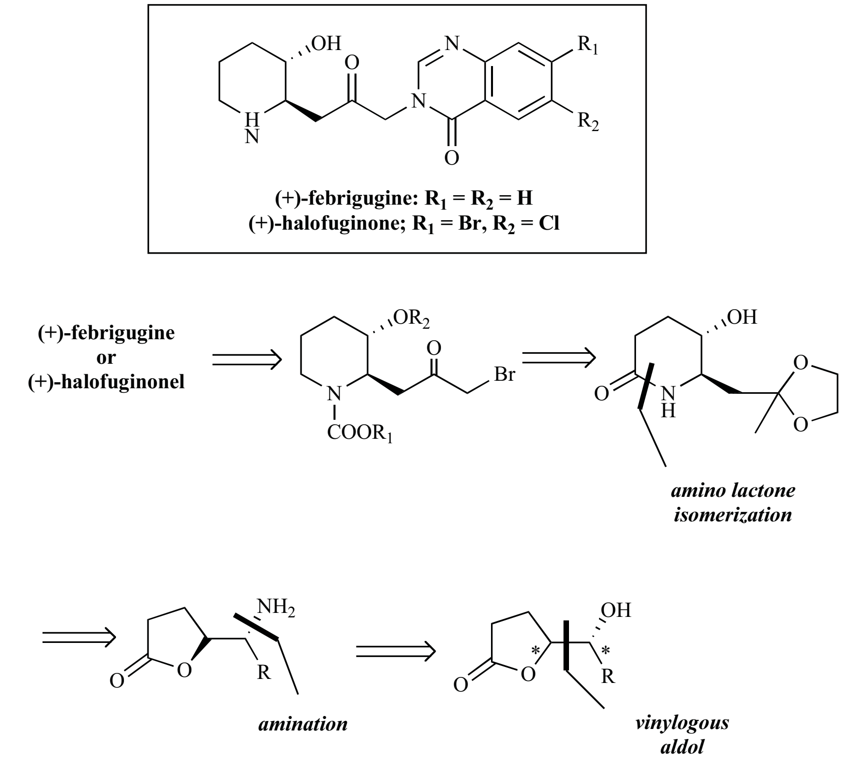
Pansare and colleagues described the enantioselective organocatalytic direct vinylogous aldol reaction of γ-crotonolactone and a suitable aldehyde, for the synthesis of a functionalized γ-butenolide [45]. These aldol product was stereoselectively converted into 5-aminoalkyl butyrolactone, which isomerized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

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

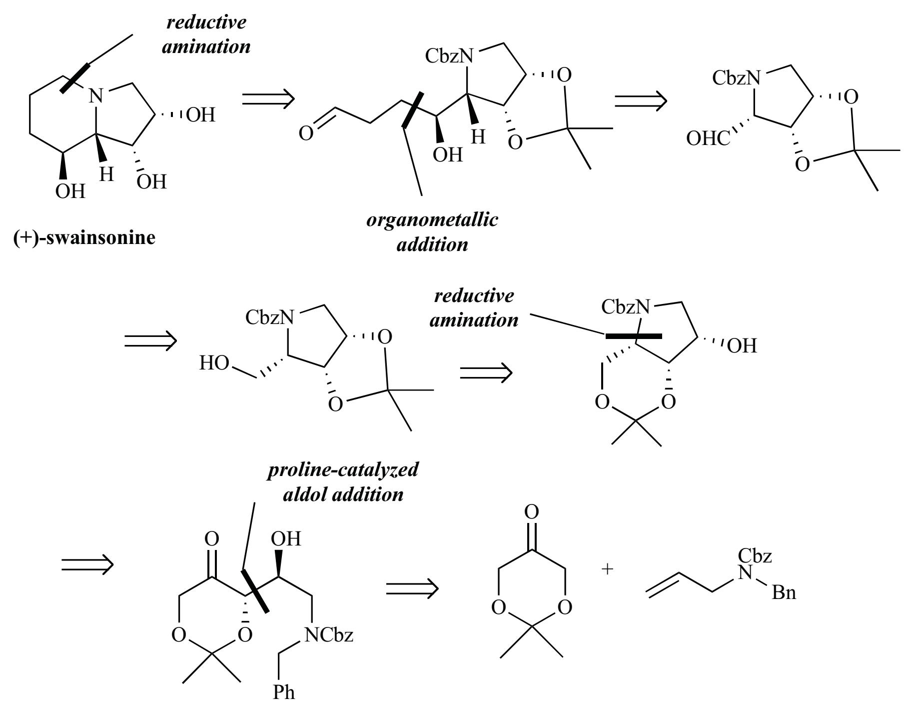
The enantioselective synthesis of (+)-swainsonine was carried out by Saicic and co-workers, achieving the final purpose in 9 steps with 24% overall yield [50]. The key feature of the synthesis was the combination of an organocatalyzed aldolization and a reductive amination, allowing for a rapid construction 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 indanone 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-diacylbencenes to construct highly funcionalized 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 (+)-febrifugine and (+)-halofuginome [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 overal yield of 68%, and > 99% *ee* starting from really inexpensive material.

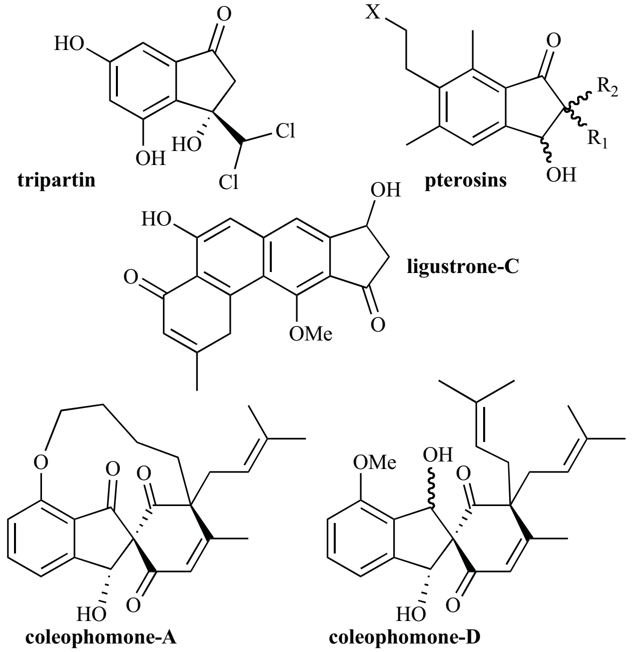
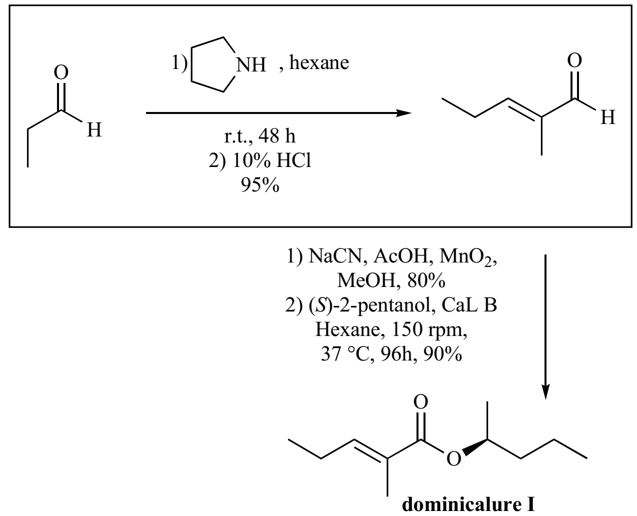


Fig. (3). Selected examples of natural products bearing a 3-hydroxyindanone core [55].

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.

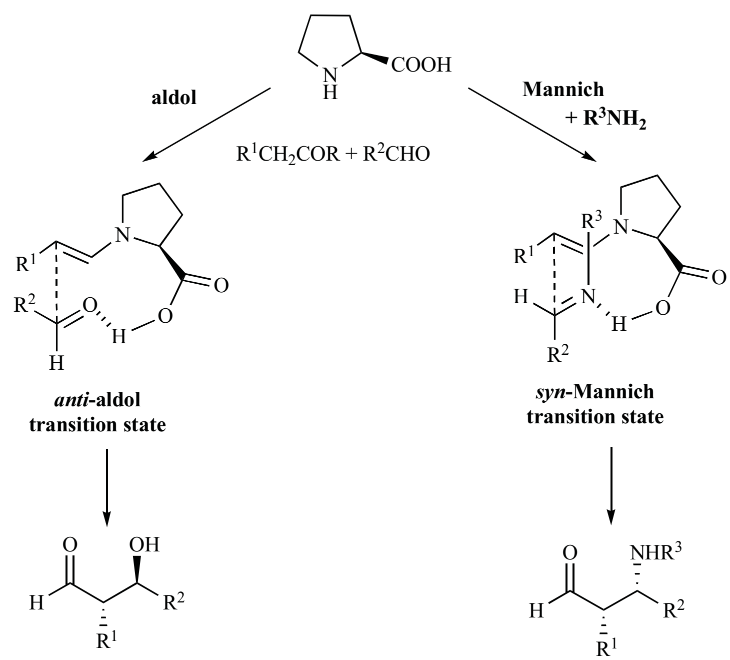
Scheme **15** shows the transition state for the aldol and Mannich reaction using proline as catalyst [15]. As it can be seen, the presumed configurations of (*E*)-enamine and (*E*)-imine give rise to the preferred *anti*- and *syn*-products respectively, *via* chair-like, hydrogen-bonded transition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



Scheme 14. Pyrrolidine-catalyzed self-aldol condensation of propanal, as key step in route to dominicalure I [56].

A good example of the usefulness and synthetic potential of this kind of reactions was described by Keley *et al*. It consisted on the development of an asymmetric organocatalytic Mannich cyclization for the synthesis of the bicyclic skeleton of izidine (pyrrolizidine, indolizidine and quinolizidine) alkaloids, and its use as key strategy in the total synthesis of (-)-epilupinine, (-)-tashiromine and (-)-trachelanthamidine (Fig. **4**) [60].

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.



Scheme 15. Comparison of the proposed transition states for aldol and Mannich reactions [15].

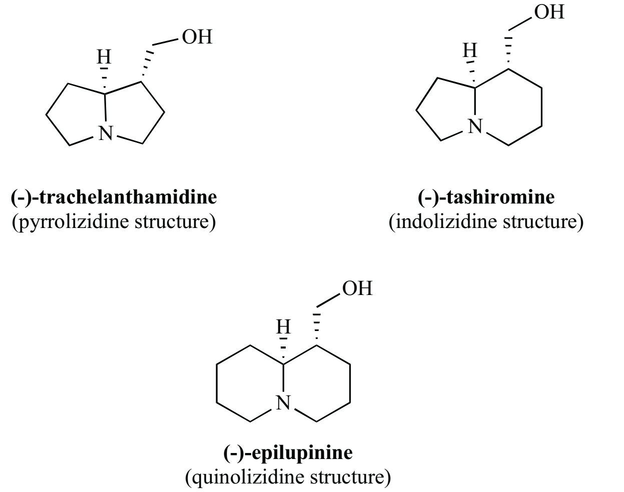


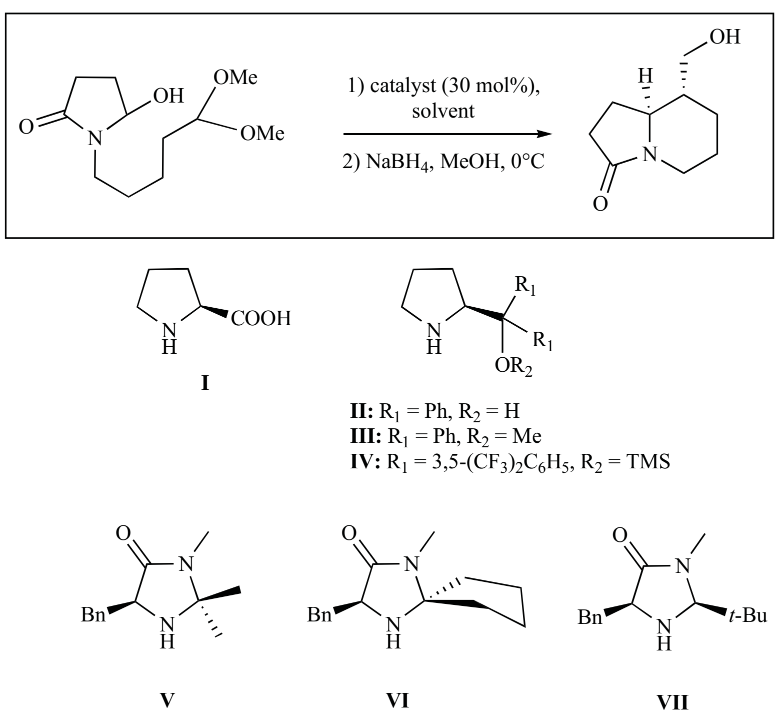
Fig. (4). Structures of izidine alkaloids (-)-epilupinine, (-)-tashiromine and (-)-trachelanthamidine [60].

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 izidinone 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.

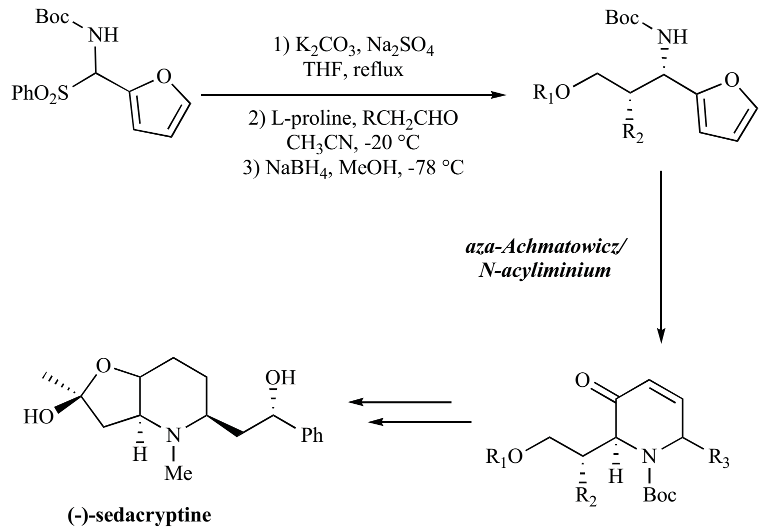
Rutjes and colleagues synthesized enantiomerically pure 2,6-disubstituted piperidinones from furfural, involving an organocatalyzed Mannich reaction as one of the initial steps. The overall synthetic approach allowed the preparation of (-)-sedacryptine and one of its epimers (Scheme **17**) [61]. Despite 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-Achmotowicz 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 β-amino aldehydes. The resulting crude Mannich products were directly *in situ* reduced resulting in the expected γ-amino alcohols. Aliphatic, allylic and aromatic substituents were prepared with reasonable yields and excellent selectivities according to this methodology.

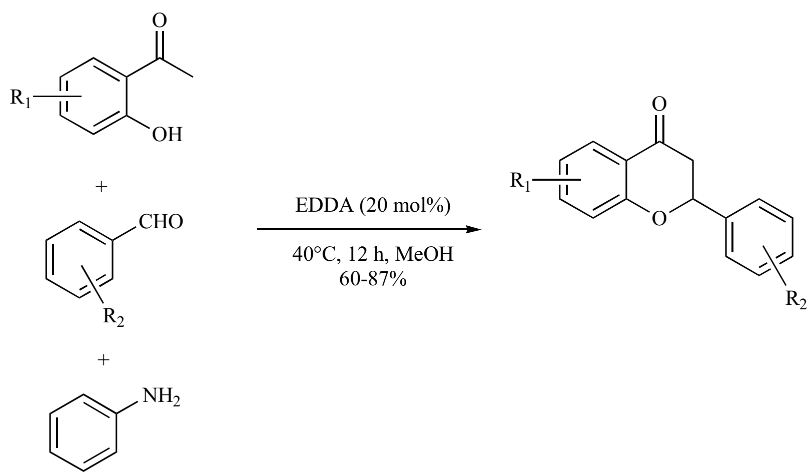
Lee and co-workers described the synthesis of biologically interesting flavanone derivatives, through an ethylenediamine diacetate (EDDA)-catalyzed Mannich reaction from 2-hydroxyacetophenone derivatives, aromatic aldehydes and aniline (Scheme **18**).



Scheme 16. Optimization of the enantioselective organocatalyzed cyclization for the synthesis of indolizidine derivatives [60].



Scheme 17. Enantioselective synthesis of (-)-sedacryptine, through an organocatalytic asymmetric Mannich reaction as one of the key initial steps [61].



Scheme 18. EDDA-organocatalyzed synthesis of flavanone derivatives [62].

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.

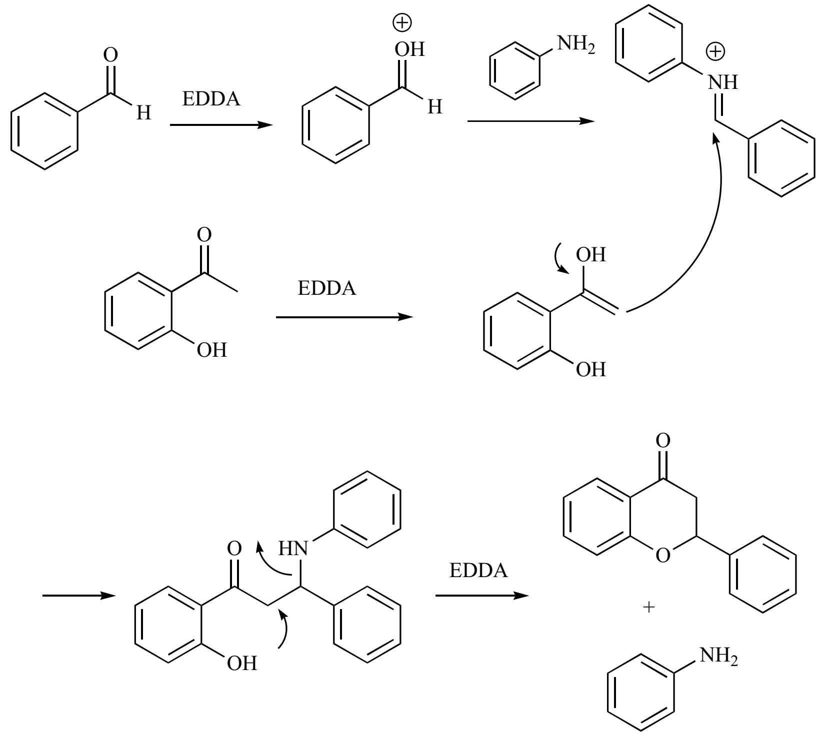
The mechanism of the reaction was analyzed on the model reaction involving benzaldehyde, and was explained according to Scheme **19**. The carbonyl group of benzaldehyde could be protonated by EDDA, enabling the formation of an iminium ion as intermediate. The enol form, generated from 2-hydroxyacetophenone 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.

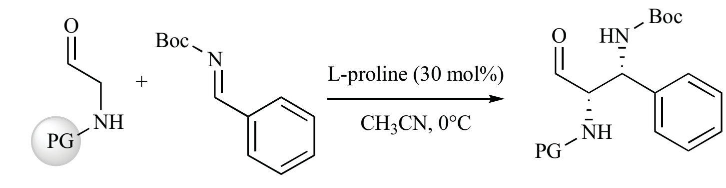
A stereocontrolled synthesis of vicinal diamines from protected α-aminoacetaldehydes through amine-catalyzed Mannich reactions was reported by Maruoka *et al.* [63]. The reaction was carried out with benzoyloxycarbonyl (Bz)- and *tert*-butoxycarbonyl (Boc)-protected aminoacetaldehydes and *N*-Boc-protected 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 α-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 binaphtyl-amine-catalyst.

The proline-catalyzed addition of various aliphatic aldehydes to sterically hindered 2-arylsubstituted 3*H*-indol-3-ones by Rueping and colleagues, afforded 2,2-disubstituted 2,3-dihydro-1*H*-indol-3-one derivatives with high enantioselectivities [64]. The described highly enantioselective proce-



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].

dure allowed to the preparation of a chiral derivative, (*S*)-2-(2-bromophenyl)-2.3-dihydro-2-(2-hydroxyethyl)-1*H*-indol-3-one, which can be used as advanced intermediate in the synthetic route to the natural product hinckdentine 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

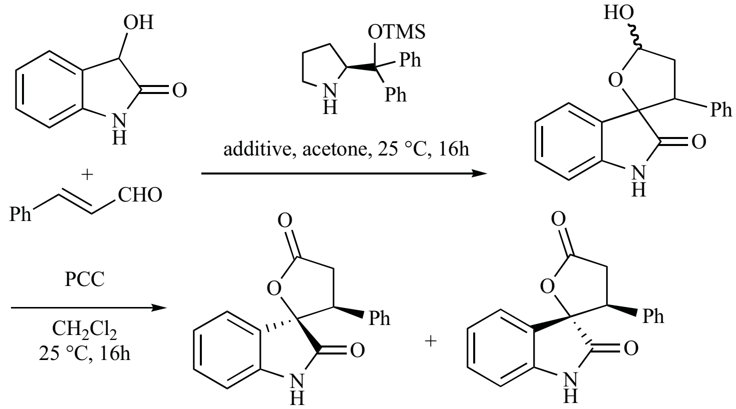
In addition to Aldol and Mannich-type reactions, secondary amines also react with α,β-unsaturated aldehydes, giving the corresponding enamine or iminium intermediates, which can undergo 1,4-additions [15, 66].

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].

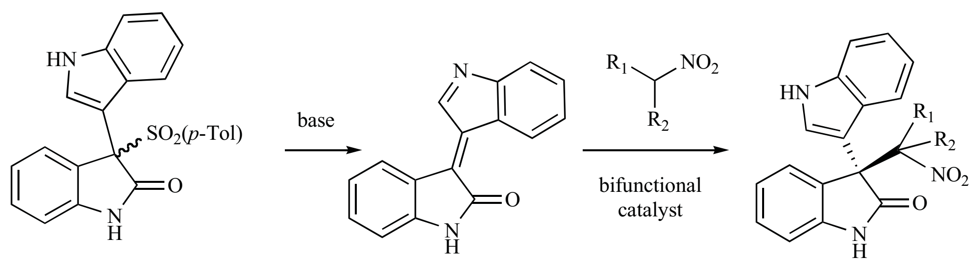
Melchiorre and Bergonzini described an efficient enantioselective synthetic strategy to access 3-substituted 3-hydroxyoxindole derivatives, usual framework of many biologically active compounds and natural products, which possess an oxindole core with a hydroxyl-bearing tetrasubstituted stereogenic center 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 γ-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-hydroxindole 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 oxindolylideneindolenines 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



Scheme 21. Conjugated addition of oxindoles and cinnamaldehyde in route to 3-substituted 3-hydroxindoles [68].



Scheme 22. Organocatalytic reaction of nitromethane and 3-(1*H*-indol-3-yl)-3-tosylindolin-2-one [69].

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-(1*H*-indol-3-yl)-3-tosylindolin-2-one in the presence of K_3PO_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-oxyndoles 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*.

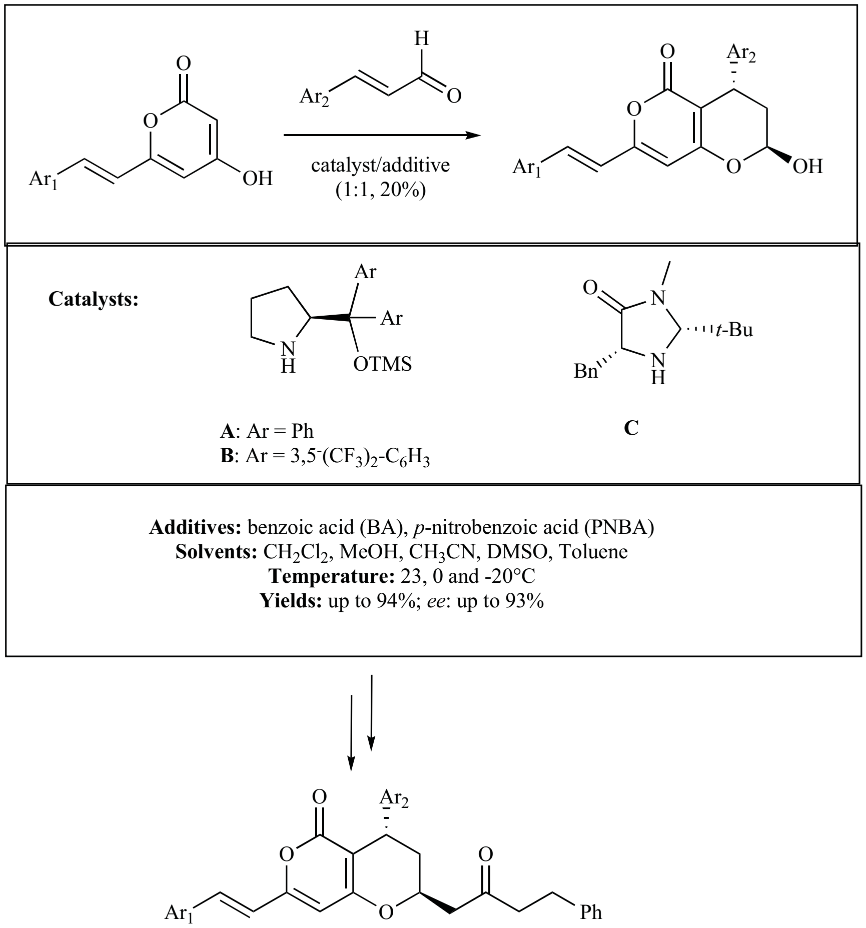
Hayashi, [71] Jørgensen [72] and MacMillan's [73] catalysts were screened for the preparation of Katsumadain A, a naturally occurring influenza virus neuraminidase (NA) inhibitor, through an enantioselective 1,4-conjugated addition of styryl-2-pyranone to cinnamaldehyde as a key step, and followed by 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-donatin 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_2Cl_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].

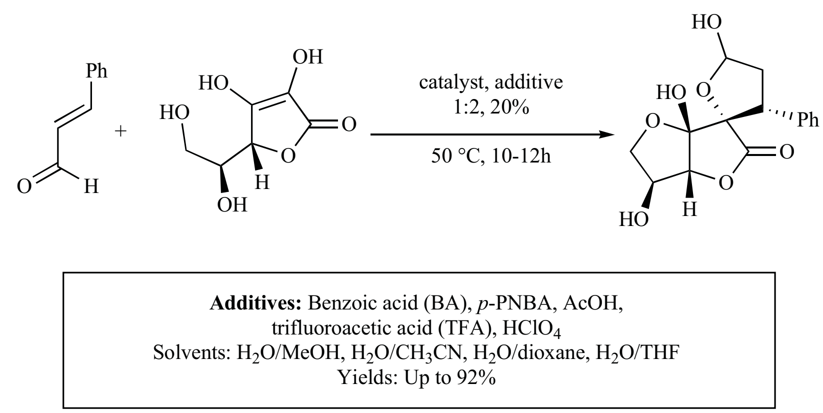
The optimal conditions proved to be when using MacMillan's catalyst, benzoic acid as additive and H_2O/MeOH as solvent, yielding the desired compound as a single isomer in 92% yield. The scope of the reaction was expanded to cinammaldehyde-derivatives comprising either electron-withdrawing or electron-donating substituents in the aromatic ring.

Also (*S*)-diphenylprolinol trimethylsilyl ether was used for the synthesis of optically pure 2-alkyl-3-(1*H*-indol-3-yl)-



Ar = Ph: katsumadain A

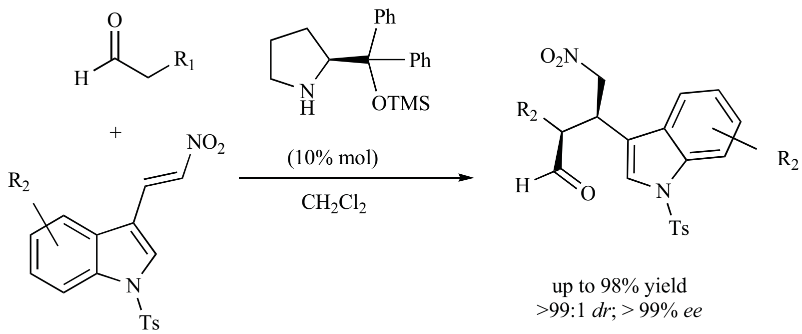
Scheme 23. Screening of reaction conditions for the organocatalytic 1,4-conjugate addition/hemiketalization of styryl-2-pyranone with α,β-unsaturated aldehydes [74].



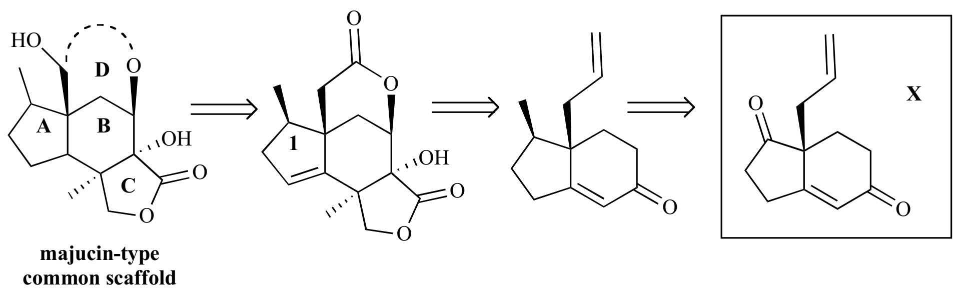
Scheme 24. Screening of conditions for the organocatalytic 1,4-addition of ascorbic acid to cinnamaldehyde [75].

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 indolylnitroalkenes was developed, providing the desired optically pure *syn* 2-alkyl-3-(1*H*-indol-3-yl)-4-nitrobutanal derivatives in up to 98% yield, and with ≥99:1 *dr* and >99% *ee* (Scheme **25**).

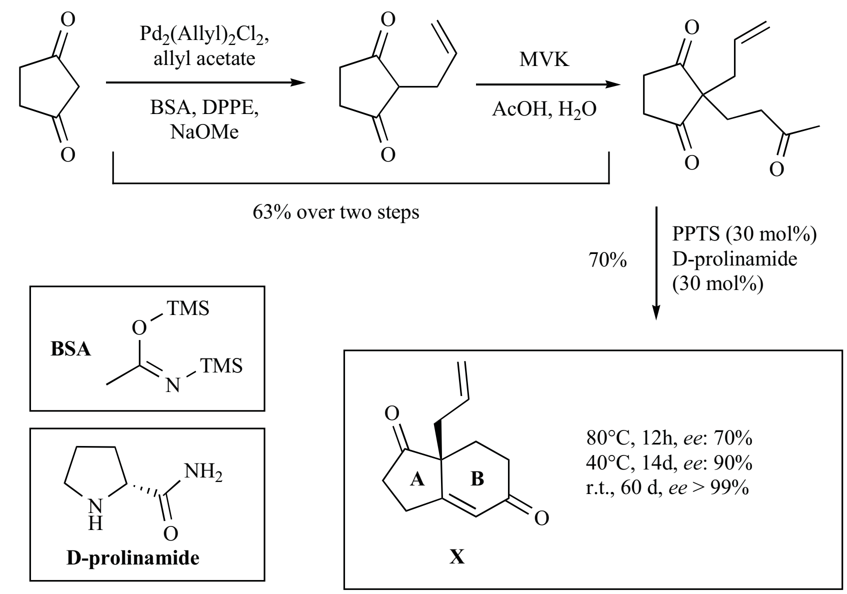
Peptides of the type Pro-Pro-Xaa (Xaa = acidic amino-acid) were also tested as catalysts for the conjugated addition of aldehydes to α,β-disubstituted nitroolefins, with the aim to provide symmetrically γ-nitroaldehydes with three consecutive stereogenic centers [77]. These synthons are key intermediates 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-



Scheme 25. Organocatalyzed Michael addition of aliphatic aldehydes to indolylnitroalkenes, 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].



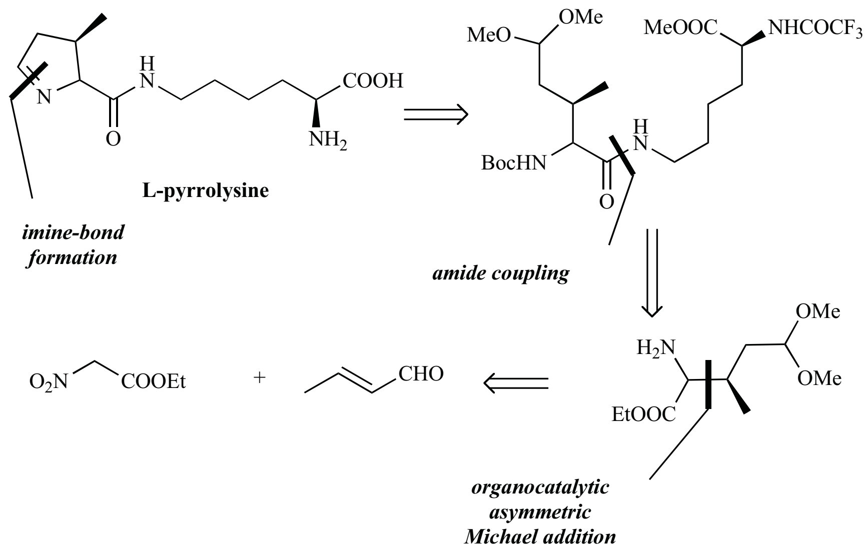
Scheme 27. Organocatalyzed asymmetric Robinson annulation leading to an enantioenriched bicyclic intermediate **X** [79]. DPPE: 1,2-*Bis*(diphenylphosphino)ethane. BSA: *Bis*(trimethylsilyl)acetamide.

hydes 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 (2*R*)-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 acces to the enantiomerically enriched bicyclic motif **X** from commercially available cyclopentane-1,3-dione (Scheme **27**).



Scheme 28. Retrosynthetic analysis of L-pyrrolysine [80].

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 22[nd] 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 enantioselectivities, 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.

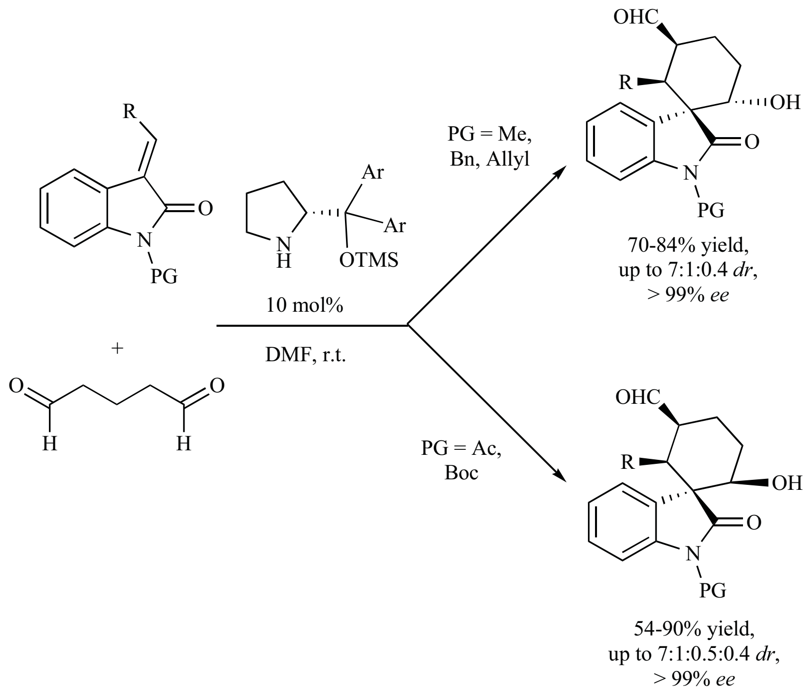
Chiral primary and secondary amine catalysts have been extensively used to activate carbonyl groups, participating in various enamine- and iminium-mediated processes. This makes them ideal for sequential addition of nucleophiles and electrophiles in a cascade manner, easily accessing products with multiple stereocenters [67, 83]. Particularly, complex molecules such as spirooxindoles -structural motifs which are very important building blocks for preparations of bioactive compounds, natural products and pharmaceuticals- have been prepared with high enantioselectivities, using pyrrolidine 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 Michel/aldol sequence in the presence of the pyrrolidine-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.

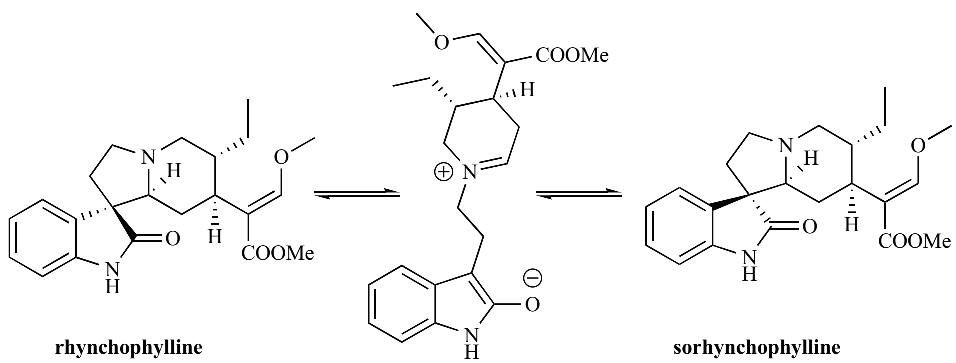
Wang and colleagues reported the synthesis of spirocyclohexaneoxindoles through domino Michael-Aldol reactions between isatin derived alkenes and also pentane-1,5-dial in the presence of Jørgensen-Hayashi catalyst [85]. As result, a series of multistereogenic and functionalized spirocyclohexaneoxindoles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



Scheme 29. Organocatalyzed Michael/Aldol cascade reaction between methyleneoxindoles and pentane-1,5-dial, for the preparation of spirocyclohexane oxindoles [84]. PG: Protecting group.



Scheme 30. Isomerization of secoyohimbane alkaloids [86].

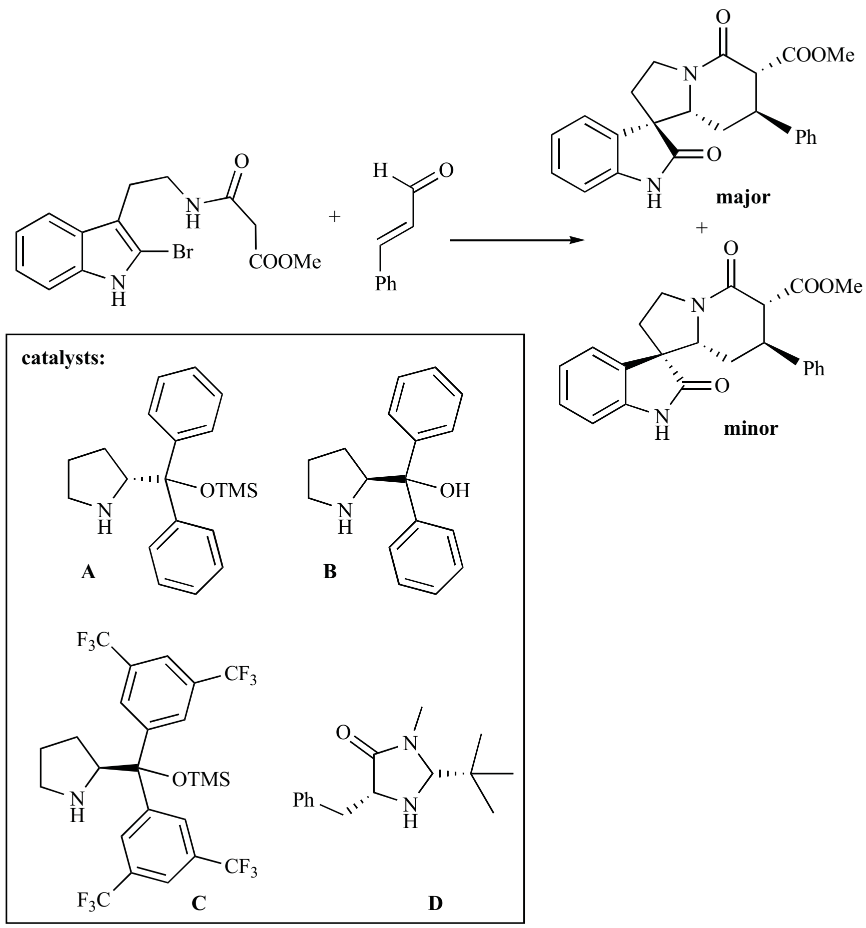
excess, diastereoselectivity and yield were obtained with 100 mol% of organocatalysts **A**, caesium acetate as additive and methanol as solvent (Scheme **31**).

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, β-elimination and conjugated addition sequence [93]. The key cascade step was conducted in $CHCl_3$ 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**).

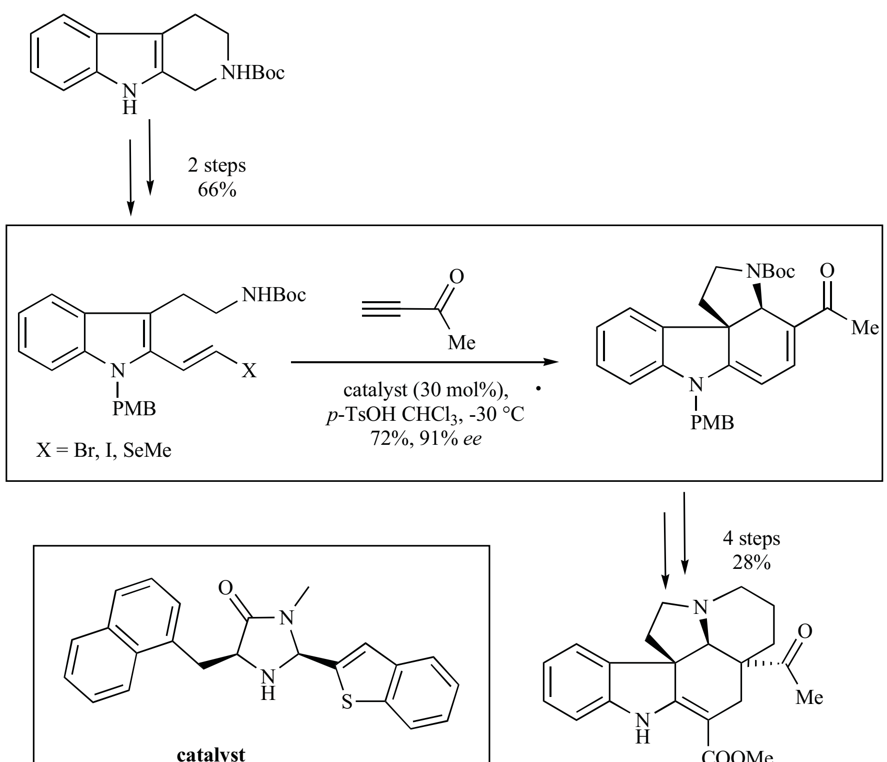
Chiral indane frameworks, were also a goal for Han *et al.*, who described the stereoselective three-step organocatalytic cascade to yield synthetically important oxa-spirocyclic indanone scaffolds [94]. The first step in the synthetic sequence was a tertiary amine-catalyzed Morita-Baylis-Hillman (MBH) 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 acetylization 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 (-)-cermizine 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

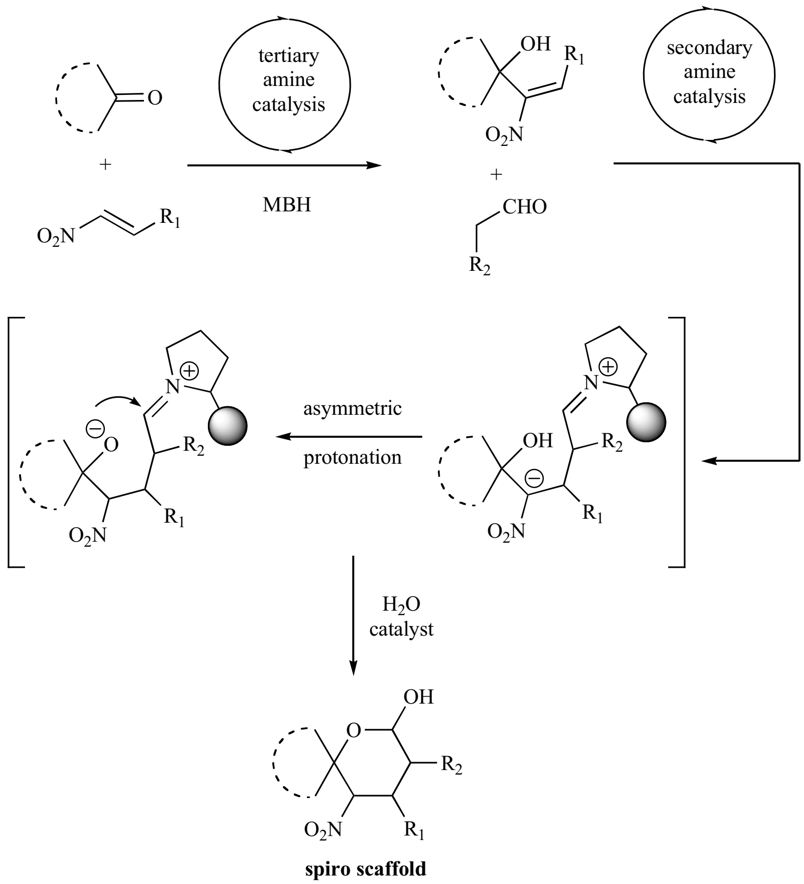


Scheme 31. Key step in route to secoyohimbane alkaloids [86].

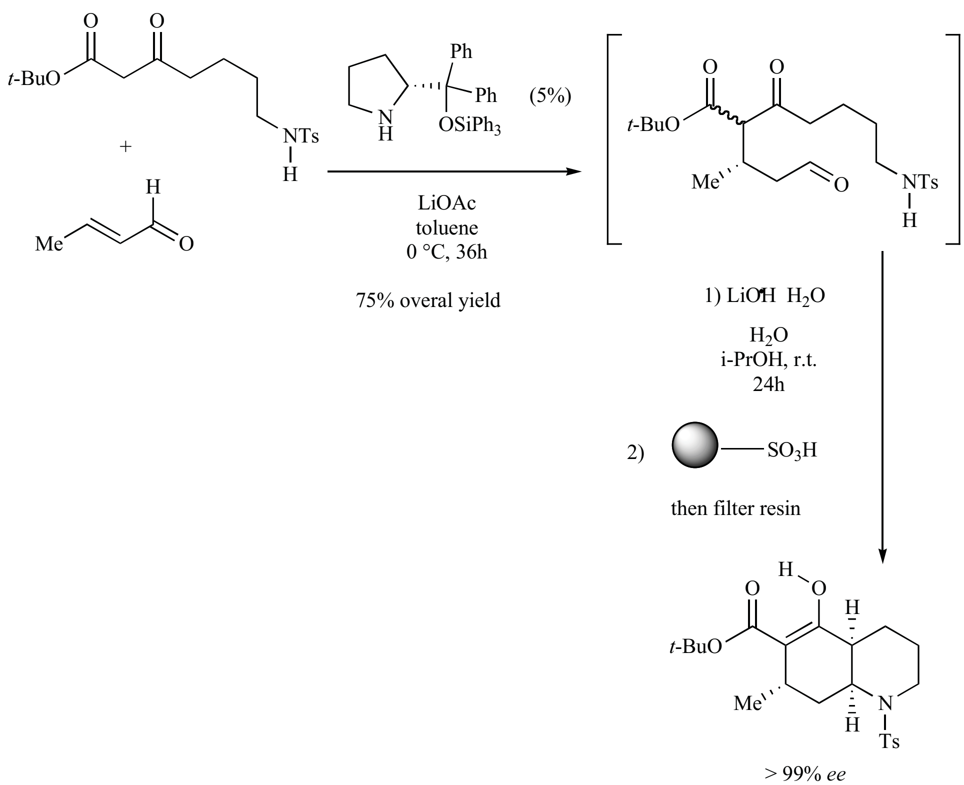


(-)-minovincine

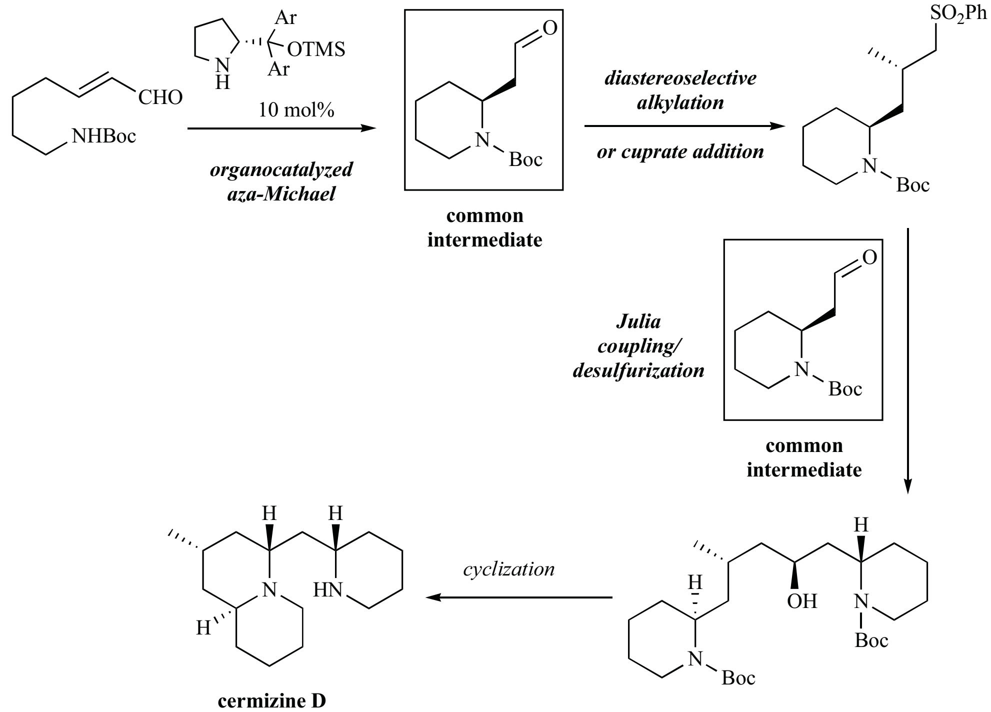
Scheme 32. Key organocatalytic cascade in the synthetic route to (-)-minovincine [93].



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].



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

treatment of the intermediate with LiOH/*i*-PrOH and water, the tandem aldol condensation/aza-Michael reaction gave the corresponding *cis*-decahydroquinoline (Scheme **34**).

With a similar approach, the same group designed a concise synthesis of the Lycopodium alkaloid lycoposerramine Z [96]. The key step in the synthetic strategy is a one-pot organocatalyzed Michael reaction followed by a domino Robinson annulation/intramolecular aza-Michael reaction promoted by LiOH, leading to the desired enantiopure *cis*-decahydroquinolines. *Cis*-5-oxodecahydroquinolines were also synthesized in a diastereoselective manner [97]. Three stereocenters were generated in a one-pot reaction, which also involves a lithium hydroxide-promoted Robinson annulation/intramolecular aza-Michael domino process from an achiral acyclic tosylamine-tethered β-ketoester. The development and scope of the reaction was envisaged by DFT-based mechanistic studies, enabling the rationalization of the diastereodivergent course of the aza-cyclization.

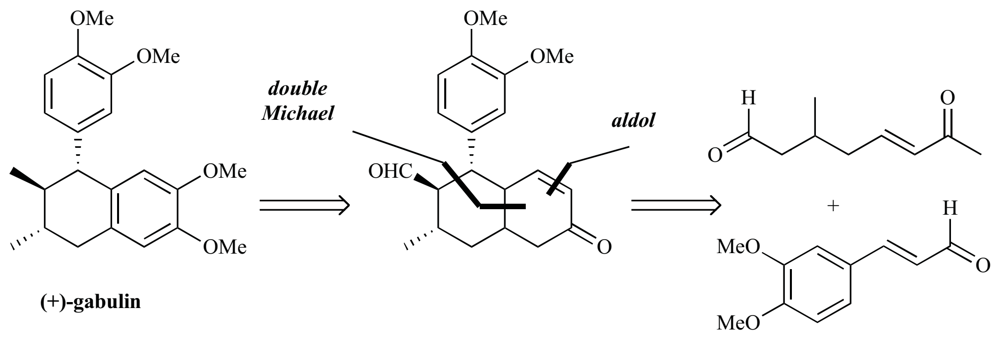
Rueping *et al*. developed a convergent catalytic approach for the asymmetric synthesis of dihydroquinolines [98]. The designed procedure involved a tandem metal-catalyzed and organocatalytic sequence. The combined cascade consisted in two oxidations, an aza-Michael addition and an aldol condensation, providing 1,2-dihydroquinolines in an enantioselective fashion.

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].

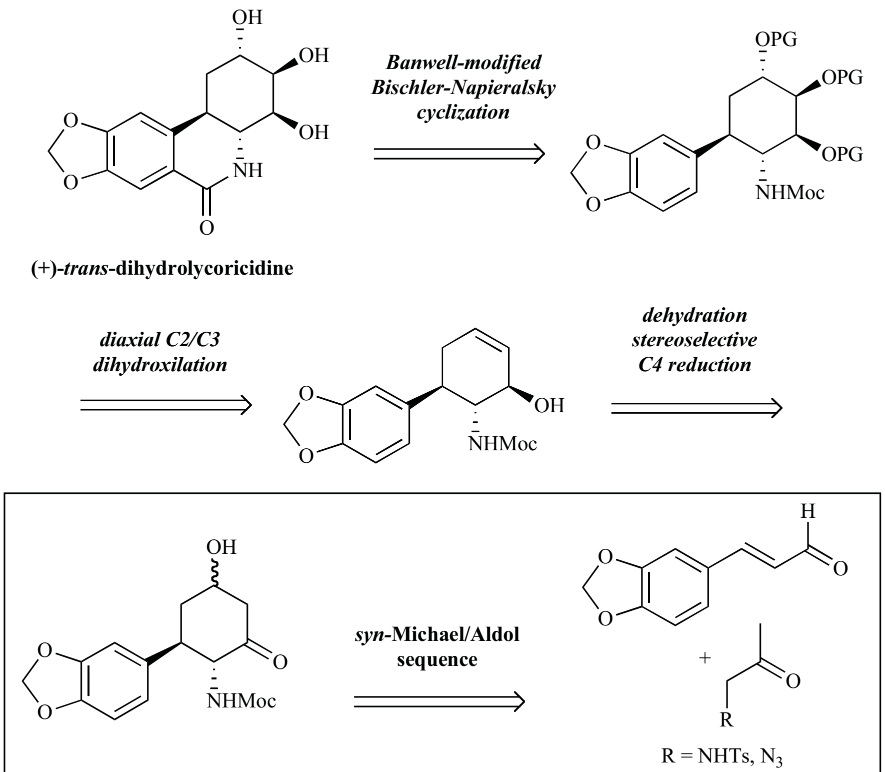
(+)-Galbulin has a tetrahydronaphthalene carbon skeleton, prevalent in many lignans, a class of secondary metabolites widely found in plants, and derived biosynthetically from the oxidative dimerization of two cinnamic acid units. Its concise enantioselective synthesis was developed by Hong *et al*., 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**.

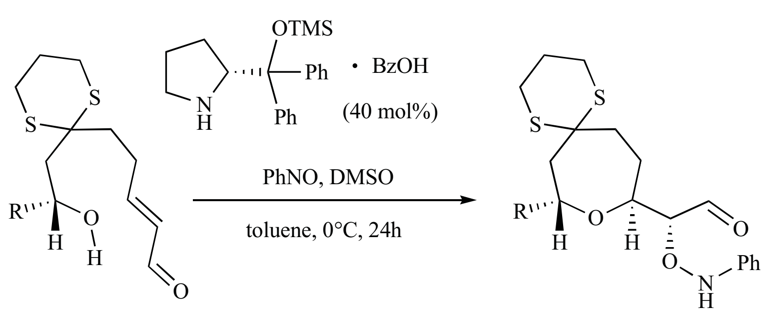
Another structural motif found in a wide range of natural products is the oxepane ring. They are challenging synthetic targets due to enthalpic and entropic barriers. Hong and coworkers developed an organocatalytic oxaconjugate addition reactions promoted by *gem*-disubstituent (Thorpe-Ingold) effect, 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].



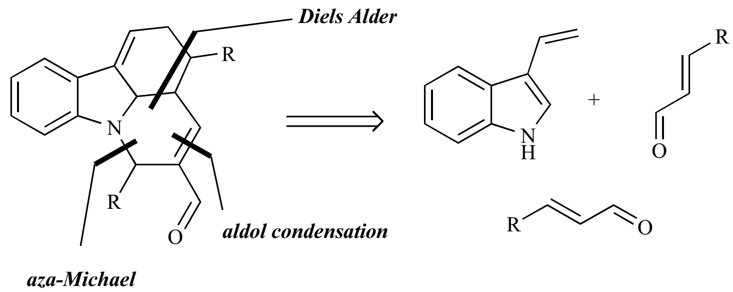
Scheme 37. Retrosynthetic analysis of (+)-*trans*-dihydrolycoricidine [102]. PG = Protecting group, Moc = methoxycarbonlamino, Ts = *p*-toluensulfonyl.



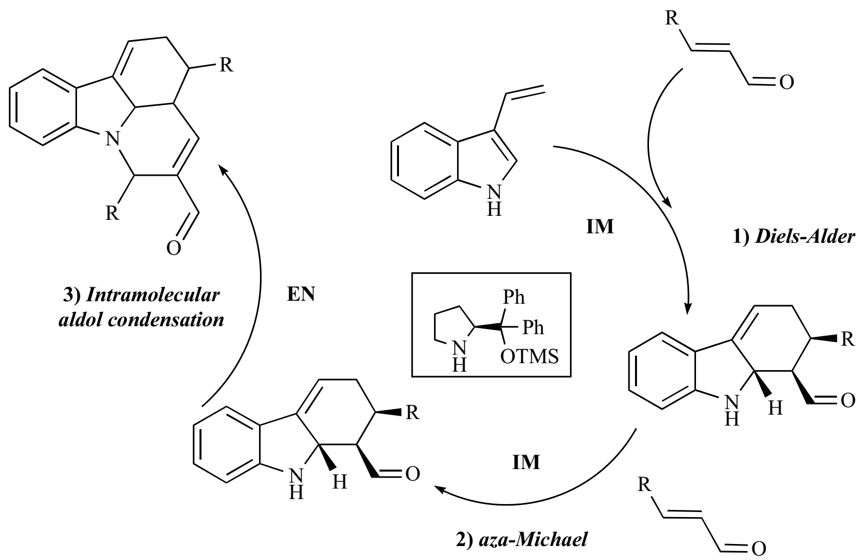
Scheme 38. Organocatalytic oxa-conjugate addition: synthesis of α,α'-*trans*-oxepanes [103].

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 cynnamaldehyde in dichloromethane at room temperature, and using 20 mol% of (*S*)-TMS-diphenylprolinol as catalyist. After 24 hs, the corresponding pyridocarbazole derivative was obtained as a single di-



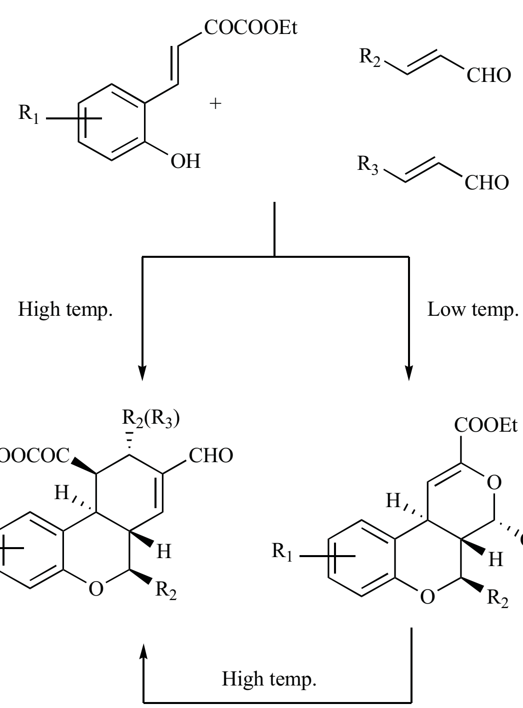
Scheme 39. Retrosynthetic analysis of the asymetric synthesis of tetracyclic pyridocarbazole derivatives using an organocatalytic triple domino reaction [104].



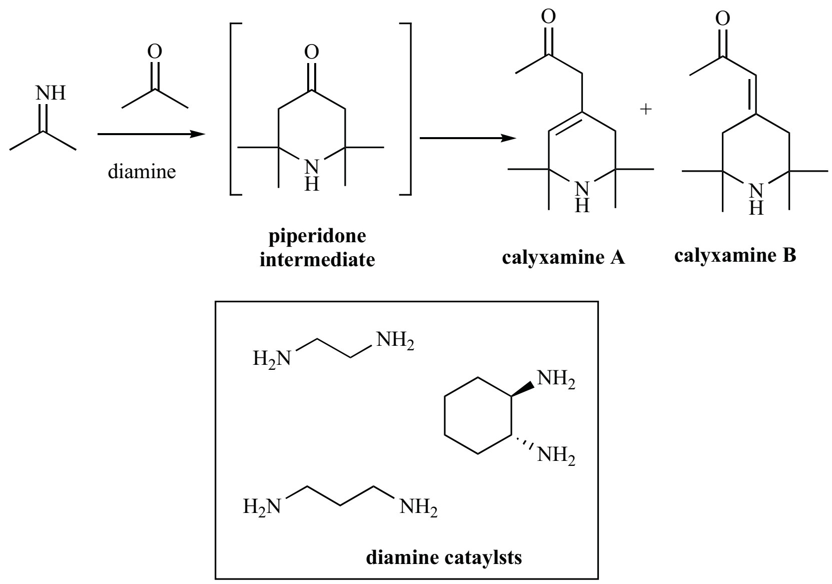
Scheme 40. Proposed mechanism for the Diels-Alder/aza-Michael/Aldol condensation organocatalytic cascade reaction. IM: iminium activation; EN: enamine activation [104].

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 trycyclic 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 diastereo- (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 acces 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**).



Scheme 41. Synthesis of two type of tricyclic chroman derivatives by adjusting both reactant ratio and reaction temperature [105].



Scheme 42. Two-step organocatalytic synthesis of calyxamine A and B [106].

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_4Cl 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 fre 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*-benzyloxycarbonyl)hydroxylamine. The synthetic sequence started from cyclopentene-2-carbaldehyde, and used diphenylprolinol 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.

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ABBREVIATIONS

AcOH = Acetic acid
Ar = Aromatic
Bz = Benzyl
BzOH = Benzyl alcohol
Cbz = Carboxybenzyl
de = Diastereomeric excess
DMF = Dimethylformamide
DMSO = Dimethylsulfoxide
Dr = Diastereomeric ratio
ee = Enantiomeric excess
Et = Ethyl
i-Pr = Isopropyl
Me = Methyl
MOM = Methoxymethylacetal
MVK = Methylvinylketone
PG = Protecting group
Ph = Phenyl
PPTS = Pyridinium *p*-toluensulfonate
p-TsOH = *p*-Toluensulfonic acid
R.T. = Room temperature
RAMP = (*R*)-1-amino-2-methoxymethylpyrrolidine

TBS = *t*-Butyldimethylsilil

THF = Tetrahydrofurane

TMS = Trimethylsilil

REFERENCES

[1] *Asymmetric Organocatalysis in Natural Product Syntheses in* Progress in the Chemistry of Organic Natural Products Waser, M., Ed.; Springer-Verlag: Wien, **2012**; Vol. 96.

[2] Shoji, M.; Hayashi, Y. In: *Modern Tools for the Synthesis of Complex Bioactive Molecules*; Cossy, J., Arseniyadis, S., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ., **2012**.

[3] Eder, U.; Sauer, G.; Wiechert, R. New type of asymmetric cyclization to optically active steroid CD partial structures. *Angew. Chem. Int. Ed*., **1971**, *10* (7), 496-497.

[4] Hajos, Z.G.; Parrish, D.R. Asymmetric synthesis of bicyclic intermediates of natural product chemistry. *J. Org. Chem*., **1974**, *39* (12), 1615-1621.

[5] Hajos, Z.G.; Parrish, D.R. Asymmetric synthesis of optically active polycyclic organic compounds; german patent; DE 2102623; 1971.

[6] List, B.; Lerner, R.A.; Barbas III, C.F. Proline-catalyzed direct asymmetric aldol reactions. *J. Am. Chem. Soc*., **2000**, *122* (10), 2395-2396.

[7] Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. New strategies for organic catalysis: the first highly enantioselective organocatalytic Diels−Alder reaction. *J. Am. Chem. Soc*., **2000**, *122* (17), 4243-4244.

[8] Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis - From Biomimetic Concepts to Applications in Asymmetric Synthesis*; 1st ed.; Wiley-VCH, **2005**.

[9] Enders, D.; Jaeger, K.E. *Asymmetric Synthesis with Chemical and Biological Methods* In: Eds.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, **2007**.

[10] Guillena, G.; Mahrwald, R. In: *Modern Methods in Stereoselective Aldol Reactions*; Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: **2013**, p 155-268.

[11] Dalko, P.I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures* In: Ed.; WILEY-VCH Verlag GmbH & Co. KGaA,: Weinheim, **2007**.

[12] Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. Asymmetric enamine catalysis. *Chem. Rev*., **2007**, *107* (12), 5471-5569.

[13] Gualandi, A.; Mengozzi, L.; Wilson, C.M.; Cozzi, P.G. Synergy, compatibility, and innovation: merging Lewis acids with stereoselective enamine catalysis. *Chem. Asian J*., **2014**, *9* (4), 984-995.

[14] Mlynarski, J.; Gut, B. Organocatalytic synthesis of carbohydrates. *Chem. Soc. Rev*., **2012**, *41*, 587-596.

[15] Marson, C.M. Multicomponent and sequential organocatalytic reactions: diversity with atom-economy and enantiocontrol. *Chem. Soc. Rev.* **2012**, *41*, 7712-7722.

[16] Giacalone, F.; Gruttaduría, M.; Agrigento, P.; Noto, R. Low-loading asymmetric organocatalysis. *Chem. Soc. Rev*., **2012**, *41*, 2406-2447.

[17] Dalpozzo, R.; Bartoli, G.; Bencivenni, G. Recent advances in organocatalytic methods for the synthesis of disubstituted 2- and 3-indolinones. *Chem. Soc. Rev*., **2012**, *41*, 7247-7290.

[18] Brière, J.F.; Oudeyer, S.; Dalla, V.; Levacher, V. Recent advances in cooperative ion pairing in asymmetric organocatalysis. *Chem. Soc. Rev*., **2012**, *41*, 1696-1797.

[19] Wende, R.C.; Schreiner, P.R. Evolution of asymmetric organocatalysis: multi- and retrocatalysis. *Green Chem*., **2012**, *14*, 1821-1849.

[20] Pellissier, H. Recent developments in asymmetric organocatalytic domino reactions. *Adv. Synth. Catal*., **2012**, *354* (2-3), 237-294.

[21] Kumar, P.; Dwivedi, N. Proline catalyzed α-aminoxylation reaction in the synthesis of biologically active compounds. *Acc. Chem. Res*., **2012**, *46* (2), 289-299.

[22] Russo, A.; De Fusco, C.; Lattanzi, A. Enantioselective organocatalytic [small alpha]-heterofunctionalization of active methines. *RSC Adv*., **2012**, *2* (2), 385-397.

[23] Abbasov, M.E.; Romo, D. The ever-expanding role of asymmetric covalent organocatalysis in scalable, natural product synthesis. *Nat. Prod. Rep*., **2014**, *31* (10), 1318-1327.

[24] Trost, B.M.; Brindle, C.S. The direct catalytic asymmetric aldol reaction. *Chem. Soc. Rev*., **2010**, *39*, 1600-1632.

[25] Dzhafarov, Z.R.; Kuliev, Z.A.; Vdovin, A.D.; Kuliev, A.A.; Malikov, V.M.; Ismailov, N.M. Coumarins of *Smyrniopsis aucheri*. *Chem. nat. Compd*., **1992**, *28* (1), 27-31.

[26] Vilegas, W.; Pozetti, G.L.; Harumi, J.; Vilegas, Y. Coumarins from *Brosimum gaudichaudii*. *J. Nat. Prod*., **1993**, *56* (3), 416-417.

[27] Enders, D.; Fronert, J.; Bisschops, T.; Boeck, F. Asymmetric total synthesis of smyrindiol employing an organocatalytic aldol key step. *Beilstein J. Org. Chem*., **2012**, *8*, 1112-1117.

[28] Hlubucek, J.R.; Robertson, A.V. (+)-(5S)-δ-Lactone of 5-hydroxy-7-phenylhepta-2,6-dienoic acid, a natural product from *Cryptocarya caloneura* (Scheff.) Kostermans. *Aust. J. Chem*., **1967**, *20* (10), 2199-2206.

[29] Wiart, C. Goniothalamus species: A source of drugs for the treatment of cancers and bacterial infections. *Evid. Based Med*., **2007**, *4* (3), 299-311.

[30] Enders, D.; David, S.; Deckers, K.; Greb, A.; Raabe, G. Asymmetric synthesis of gonioheptolide A analogues *via* an organocatalytic aldol reaction as the key step. *Synthesis,* **2012**, *44* (22), 3483-3484.

[31] Florence, G.J.; Wlochal, J. Synthesis of the originally proposed structure of palmerolide C. *Chem. Eur. J*., **2012**, *18* (45), 14250-14254.

[32] Enders, D.; Grondal, C. Direct organocatalytic *de novo* synthesis of carbohydrates. *Angew. Chem. Int. Ed*., **2005**, *44* (8), 1210-1212.

[33] Grondal, C.; Enders, D. Direct asymmetric organocatalytic de novo synthesis of carbohydrates. *Tetrahedron,* **2006**, *62* (2-3), 329-337.

[34] Fronert, J.; Bisschops, T.; Cassens-Sasse, E.; Atodiresei, I.; Enders, D. Asymmetric organocatalytic synthesis of *trans*-3,4-disubstituted isochromanones *via* an intramolecular aldol reaction. *Synthesis,* **2013**, *45* (12), 1708-1712.

[35] Marjanovic, J.; Divjakovic, V.; Matovic, R.; Ferjancic, Z.; Saicic, R.N. Double asymmetric induction in organocatalyzed aldol reactions: total synthesis of (+)-2-*epi*-hyacinthacine A_2 and (-)-3-*epi*-hyacinthacine A_1. *Eur. J. Org. Chem.* **2013**, *25*, 5555-5560.

[36] Pearson, A.J.; Panda, S.; Bunge, S.D. Synthesis of a potential intermediate for TMC-95A *via* an organocatalyzed aldol reaction. *J. Org. Chem*., **2013**, *78* (19), 9921-9928.

[37] Koguchi, Y.; Kohno, J.; Nishio, M.; Takahashi, K.; Okuda, T.; Ohnuki, T.; Komatsubara, S. TMC-95A, B, C, and D, novel proteasome inhibitors produced by Apiospora montagnei Sacc. TC 1093. Taxonomy, production, isolation, and biological activities. *J. Antibiot*., **2000**, *53* (2), 105-109.

[38] Volchkov, I.; Lee, D. Asymmetric total synthesis of (−)-amphidinolide V through effective combinations of catalytic transformations. *J. Am. Chem. Soc*., **2013**, *135* (14), 5324-5327.

[39] Echeverria, P.G.; Prévost, S.; Cornil, J.; Férard, C.; Reymond, S.; Guérinot, A.; Cossy, J.; Ratovelomanana-Vidal, V.; Phansavath, P. Synthetic strategy toward the C44-C65 fragment of mirabalin. *Org. Lett*., **2014**, *16* (9), 2390-2393.

[40] Veena, B.; Sharma, G.V.M. Synthesis of 7-*epi*-goniodiol by proline-catalyzed diastereoselective direct aldol reaction. *Synlett*., **2014**, *25* (9), 1283-1286.

[41] Liautard, V.; Jardel, D.; Davies, C.; Berlande, M.; Buffeteau, T.; Cavagnat, D.; Robert, F.; Vincent, J.M.; Landais, Y. Organocatalyzed aldol reaction between pyridine-2-carbaldehydes and α-ketoacids: a straightforward route towards indolizidines and iIsotetronic acids. *Chem. Eur. J*., **2013**, *19* (43), 14532-14539.

[42] Stork, G.; Rychnovsky, S.D. Iterative butenolide construction of polypropionate chains. *J. Am. Chem. Soc*., **1987**, *109* (5), 1564-1565.

[43] Sasse, F.; Steinmetz, H.; Heil, J.; Höfle, G.; Reichenbach, H. Tubulysins, new cytostatic peptides from myxobacteria acting on microtubuli. Production, isolation, physico-chemical and biological properties. *J. Antibiot*., **2000**, *53* (9), 879-885.

[44] Paladhi, S.; Das, J.; Samanta, M.; Dash, J. Asymmetric aldol reaction of thiazole-carbaldehydes: regio- and stereoselective synthesis of tubuvalin analogues. *Adv. Synth. Catal*., **2014**, *356* (16), 3370-3376.

[45] Pansare, S.V.; Paul, E.K. Synthesis of (+)-febrifugine and a formal synthesis of (+)-halofuginone employing an organocatalytic direct vinylogous aldol reaction. *Synthesis,* **2013**, *45* (13), 1863-1869.

[46] Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael reaction of malonates to nitroolefins catalyzed by bifunctional organocatalysts. *J. Am. Chem. Soc*., **2003**, *125* (42), 12672-12673.

[47] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. Enantio- and diastereoselective Michael reaction of 1,3-dicarbonyl com-

pounds to nitroolefins catalyzed by a bifunctional thiourea. *J. Am. Chem. Soc*., **2005**, *127* (1), 119-125.

[48] Konishi, H.; Lam, T.Y.; Malerich, J.P.; Rawal, V.H. Enantioselective α-amination of 1,3-dicarbonyl compounds using squaramide derivatives as hydrogen bonding catalysts. *Org. Lett*., **2010**, *12* (9), 2028-2031.

[49] Zhu, Y.; Malerich, J.P.; Rawal, V.H. Squaramide-catalyzed enantioselective Michael addition of diphenyl phosphite to nitroalkenes. *Angew. Chem. Int. Ed*., **2010**, *49* (1), 153-156.

[50] Trajkovic, M.; Balanac, V.; Ferjancic, Z.; Saicic, R.N. Total synthesis of (+)-swainsonine and (+)-8-*epi*-swainsonine. *RSC Adv*., **2014**, *4*, 53722-53724.

[51] Nagle, D.G.; Zhou, Y.D.; Park, P.U.; Paul, V.J.; Rajbhandari, I.; Duncan, C.J.G.; Pasco, D.S. A new indanone from the marine cyanobacterium *Lyngbya majuscula* that inhibits hypoxia-induced activation of the VEGF promoter in Hep3B cells. *J. Nat. Prod*., **2000**, *63* (10), 1431-1433.

[52] Snyder, S.A.; Zografos, A.L.; Lin, Y. Total synthesis of resveratrol-based natural products: A chemoselective solution. *Angew. Chem. Int. Ed*., **2007**, *46* (43), 8186-8191.

[53] Okpekon, T.; Millot, M.; Champy, P.; Gleye, C.; Yolou, S.; Bories, C.; Loiseau, P.A.L.; A., L.; Hocquemiller, R. A novel 1-indanone isolated from *Uvaria afzelii* roots. *Nat. Prod. Res*., **2009**, *23* (10), 909-915.

[54] Kim, S.H.; Kwon, S.H.; Pard, A.H.; Lee, J.K.; Bang, H.S.; Nam, S.J.; Kwon, H.C.; Sin, J.; Oh, D.C. Tripartin, a histone demethylase inhibitor from a bacterium associated with a dung beetle larva. *Org. Lett*., **2013**, *15* (8), 1834-1837.

[55] Chanda, T.; Chowdhyry, S.; Anand, N.; Koley, D.; Gupta, A.; Singh, M.S. Synthesis of 3-hydroxyindanones *via* potassium salt of amino acid catalyzed regioselective intramolecular aldolization of orthodiacylbenzenes. *Tetrahedron Lett*., **2015**, *56* (8), 981-985.

[56] Dibello, E.; Seoane, G.; Gamenara, D. Green and catalytic synthesis of dominicalure I, major component of the aggregation pheromone of *Rhyzpertha dominica* (Fabricius) (Coleoptera: Bostrichidae). *Synth. Commun*., **2015**, *45* (8), 975-981.

[57] Corey, E.J.; Gilman, N.W.; Ganem, B.E. New methods for the oxidation of aldehydes to carboxylic acids and esters. *J. Am. Chem. Soc*., **1968**, *90* (20), 5616-5617.

[58] List, B. The direct catalytic asymmetric three-component Mannich reaction. *J. Am. Chem. Soc*., **2000**, *122* (38), 9336-9337.

[59] List, B.; Pojarliev, P.; Biller, W.T.; Martin, H.J. The proline-catalyzed direct asymmetric three-component mannich reaction: scope, optimization, and application to the highly enantioselective synthesis of 1,2-amino alcohols. *J. Am. Chem. Soc*., **2002**, *124* (5), 827-833.

[60] Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A.A.; Kant, R. Organocatalytic asymmetric Mannich cyclization of hydroxylactams with acetals: total syntheses of (−)-epilupinine, (−)-tashiromine, and (−)-trachelanthamidine. *Angew. Chem. Int. Ed*., **2014**, *53* (48), 13196-13200.

[61] van der Pijl, F.; Harmel, R.K.; Richelle, G.J.J.; Janssen, P.; van Delft, F.L.; Rutjes, F.P.J.T. Organocatalytic entry into 2,6-disubstituted aza-Achmatowicz piperidinones: application to (−)-sedacryptine and its epimer. *Org. Lett*., **2014**, *16* (7), 2038-2041.

[62] Vuppalapati, S.V.N.; Xia, L.; Edayadulla, N.; Lee, Y.R. Mild and efficient one-pot synthesis of diverse flavanone derivatives *via* an organocatalyzed Mannich-type reaction. *Synthesis,* **2014**, *46* (4), 465-474.

[63] Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. Stereocontrolled synthesis of vicinal diamines by organocatalytic asymmetric Mannich reaction of *N*-protected aminoacetaldehydes: formal synthesis of (−)-agelastatin A. *J. Am. Chem. Soc*., **2012**, *134* (17), 7516-7520.

[64] Rueping, M.; Rasappan, R.; Raja, S. Asymmetric proline-catalyzed addition of aldehydes to 3*H*-Indol-3-ones: Enantioselective synthesis of 2,3-dihydro-1*H*-indol-3-ones with quaternary stereogenic centers. *Helv. Chim. Acta,* **2012**, *95* (11), 2296-2303.

[65] Yuen, T.Y.; Eaton, S.E.; Woods, T.M.; Furkert, D.P.; Choi, K.W.; Brimble, M.A. A Maillard approach to 2-formylpyrroles: Synthesis of magnolamide, lobechine and funebral. *Eur. J. Org. Chem*., **2014**, *7*, 1431-1437.

[66] Li, Y.; Li, X.; Cheng, J.P. Catalytic asymmetric synthesis of chiral benzofuranones. *Adv. Synth. Catal*., **2014**, *356* (6), 1172-1198.

[67] Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C.F. Organocatalytic asymmetric assembly reactions: synthesis of spirooxindoles *via* organocascade strategies. *ACS Catal*., **2014**, *4* (3), 743-762.

[68] Bergonzini, G.; Melchiorre, P. Dioxindole in asymmetric catalytic synthesis: routes to enantioenriched 3-substituted 3-hydroxyoxindoles and the preparation of maremycin A. *Angew. Chem. Int. Ed*., **2012**, *51* (4), 971-974.

[69] Huang, J.Z.; Wu, X.; Gong, L.Z. Enantioselective organocatalytic addition of nitroalkanes to oxindolylideneindolenines for the construction of chiral 3,3-disubstituted oxindoles. *Adv. Synth. Catal*., **2013**, *355* (13), 2531-2537.

[70] Cui, B.D.; You, Y.; Zhao, J.Q.; Zuo, J.; Wu, Z.J.; Xu, X.Y.; Zhang, X.M.; Yuan, W.C. 3-Pyrrolyl-oxindoles as efficient nucleophiles for organocatalytic asymmetric synthesis of structurally diverse 3,3′-disubstituted oxindole derivatives *Chem. Commun*., **2015**, *51*, 757-760.

[71] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. Diphenylprolinol silyl ethers as efficient organocatalysts for the asymmetric Michael reaction of aldehydes and nitroalkenes *Angew. Chem. Int. Ed*., **2005**, *44* (27), 4212-4215.

[72] Marigo, M.; Wabnitz, T.C.; Fielenbach, D.; Jorgensen, K.A. Enantioselective organocatalyzed α sulfenylation of aldehydes. *Angew. Chem. Int. Ed*., **2005**, *44* (5), 794-797.

[73] Austin, J.F.; MacMillan, D.W.C. Enantioselective organocatalytic indole alkylations. Design of a new and highly effective chiral amine for iminium catalysis. *J. Am. Chem. Soc*., **2002**, *124* (7), 1172-1173.

[74] Wang, Y.; Bao, R.; Huang, S.; Tang, Y. Bioinspired total synthesis of katsumadain A by organocatalytic enantioselective 1,4-conjugate addition. *Beilstein J. Org. Chem*., **2013**, *9*, 1601-1606.

[75] Wang, Z.; Zhao, K.; Fu, J.; Zhang, J.; Yin, W.; Tang, Y. Organocatalytic 1,4-conjugate addition of ascorbic acid to α,β-unsaturated aldehydes: bio-inspired total syntheses of leucodrin, leudrin and proposed structure of dilaspirolactone. *Org. Biomol. Chem*., **2013**, *11*, 2093-2097.

[76] Chen, J.; Geng, Z.C.; Li, H.Y.; Huang, X.F.; Pan, F.F.; Wang, X.W. Organocatalytic asymmetric Michael addition of aliphatic aldehydes to indolylnitroalkenes: Access to contiguous stereogenic tryptamine precursors. *J. Org. Chem*., **2013**, *78* (6), 2362-2372.

[77] Duschmalé, J.; Wennemers, H. Adapting to substrate challenges: Peptides as catalysts for conjugate addition reactions of aldehydes to α,β-disubstituted nitroolefins. *Chem. Eur. J*., **2012**, *18* (4), 1111-1120.

[78] Urabe, D.; Inoue, M. Total syntheses of sesquiterpenes from Illicium species. *Tetrahedron,* **2009**, *65* (32), 6271-6289.

[79] Trzoss, L.; Xu, J.; Lacoske, M.H.; Theodorakis, E.A. Synthesis of the tetracyclic core of *Illicium* sesquiterpenes using an organocatalyzed asymmetric Robinson annulation. *Beilstein J. Org. Chem.* **2013**, *9*, 1135-1140.

[80] Han, M.Y.; Wang, H.Z.; An, W.K.; Jia, J.Y.; Ma, B.C.; Zhang, Y.; Wang, W. A concise synthesis of L-pyrrolysine. *Chem. Eur. J.* **2013**, *19* (25), 8078-8081.

[81] Hao, B.; Gong, W.; Ferguson, T.K.; James, C.M.; Krzycki, J.A.; Chan, M.K. A new UAG-encoded residue in the structure of a methanogen methyltransferase. *Science,* **2002**, *296* (5572), 1462-1466.

[82] Han, M.Y.; Zhang, Y.; Wang, H.Z.; An, W.K.; Ma, B.C.; Zhang, Y.; Wang, W. Organocatalytic Michael addition of nitro esters to α,β-unsaturated aldehydes: Towards the enantioselective synthesis of *trans*-3-substituted proline derivatives. *Adv. Synth. Catal*., **2012**, *354* (14-15), 2635-2640.

[83] Jensen, K.L.; Dickmeiss, G.; Jiang, H.; Albrecht, K.; Jorgensen, K.A. The diarylprolinol silyl ether system: A general organocatalyst. *Acc. Chem. Res*., **2012**, *45* (2), 248-264.

[84] Ghosh, A.K.; Zhou, B. Enantioselective synthesis of spiro[cyclohexane-1,3′-indolin]-2′-ones containing multiple stereocenters *via* organocatalytic Michael/aldol cascade reactions. *Tetrahedron Lett*., **2013**, *54* (19), 2311-2314.

[85] Huang, X.F.; Liu, Z.M.; Geng, Z.C.; Zhang, S.Y.; Wang, Y.; Wang, X.W. Enantioselective construction of multifunctionalized spirocyclohexaneoxindoles through organocatalytic Michael-aldol cyclization of isatin derived alkenes with linear dialdehydes. *Org. Biomol. Chem*., **2012**, *10* (44), 8794-8799.

[86] Antonchick, A.P.; López-Tosco, S.; Parga, J.; Sievers, S.; Schürmann, M.; Preut, H.; Höing, S.; Schöler, H.R.; Sterneckert, J.; Rauh, D.; Waldmann, H. Highly enantioselective catalytic synthe-

sis of neurite growth-promoting secoyohimbanes. *Chem. Biol.* **2013**, *20* (4), 500-509.

[87] Shellard, E.J.; Lala, P.K. The alkaloids of *Mitragyna rubrostipulata* (Schum.) Havil. *Planta Med*., **1978**, *33*, 63-69.

[88] Shellard, E.J.; Phillipson, J.D.; Gupta, D. The *Mitragyna* species of Asia. XV. The alkaloids from the bark of *Mitragyna parvifolia* (Roxb.) Korth and a possible biogenetic route for the oxindole alkaloids. *Planta Med*., **1969**, *17*, 146-164.

[89] Phillipson, J.D.; Hemingway, S.R. Indole and oxindole alkaloids from *Uncaria bernaysia*. *Phytochemistry*, **1973**, *12*, 1481-1487.

[90] Phillipson, J.D.; Hemingway, S.R. Oxindole alkaloids from *Uncaria macrophylla*. *Phytochemistry.* **1973**, *12*, 2795-2798.

[91] Seaton, J.C.; Nair, M.D.; Edwards, O.E.; Marion, L. The structure and stereoisomerism of three mitragyna alkaloids. *Can. J. Chem*., **1960**, *38*, 1035-1042.

[92] Wenkert, E.; Udelhofen, J.H.; Bhattacharyya, N.K. 3-Hydroxymethyleneoxindole and its derivatives. *J. Am. Chem. Soc*., **1959**, *81*, 3763-3768.

[93] Laforteza, B.N.; Pickworth, M.; MacMillan, D.W.C. Enantioselective total synthesis of (−)-minovincine in nine chemical steps: an approach to ketone activation in cascade catalysis. *Angew. Chem. Int. Ed*., **2013**, *125* (43), 11479-11482.

[94] Li, X.; Yang, L.; Peng, C.; Xie, X.; Leng, H.J.; Wang, B.; Tang, Z.W.; He, G.; Ouyang, L.; Huang, W.; Han, B. Organocatalytic tandem Morita-Baylis-Hillman-Michael reaction for asymmetric synthesis of a drug-like oxa-spirocyclic indanone scaffold. *Chem. Commun*., **2013**, *49* (77), 8692-8694.

[95] Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. A gram-scale route to phlegmarine alkaloids: rapid total synthesis of (-)-cermizine B. *Chem. Commun*., **2014**, *50* (54), 7099-7102.

[96] Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *cis*-Decahydroquinolines *via* asymmetric organocatalysis: Application to the total synthesis of lycoposerramine Z. *Org. Lett*., **2013**, *15* (2), 326-329.

[97] Bradshaw, B.; Luque-Corredera, C.; Saborit, G.; Cativiela, C.; Dorel, R.; Bo, C.; Bonjoch, J. Synthetic and DFT studies towards a unified approach to phlegmarine alkaloids: Aza-Michael intramolecular processes leading to 5-oxodecahydroquinolines. *Chem. Eur. J*., **2013**, *19* (41), 13881-13892.

[98] Rueping, M.; Dufour, J.; Bui, L. Convergent catalysis: asymmetric synthesis of dihydroquinolines using a combined metal catalysis and organocatalysis approach. *ACS Catal*., **2014**, *4* (3), 1021-1025.

[99] Veerasamy, N.; Carlson, E.C.; Carter, R.G. Expedient enantioselective synthesis of cermizine D. *Org. Lett*., **2012**, *14* (6), 1596-1599.

[100] Veerasamy, N.; Carlson, E.C.; Collett, N.D.; Saha, M.; Carter, R.G. Enantioselective approach to quinolizidines: Total synthesis of cermizine D and formal syntheses of senepodine G and cermizine C. *J. Org. Chem*., **2013**, *78* (10), 4779-4800.

[101] Hong, B.; Hsu, C.S.; Lee, G.H. Enantioselective total synthesis of (+)-galbulin *via* organocatalytic domino Michael-Michael-aldol condensation. *Chem. Commun*., **2012**, *48* (18), 2385-2387.

[102] McNulty, J.; Zepeda-Velázquez, C. Enantioselective organocatalytic Michael/aldol sequence: anticancer natural product (+)-*trans*-dihydrolycoricidine. *Angew. Chem. Int. Ed*., **2014**, *53* (32), 8450-8454.

[103] Lanier, M.L.; Kasper, A.C.; Kim, H.; Hong, J. Synthesis of α,α′-*trans*-oxepanes through an organocatalytic oxa-conjugate addition reaction. *Org. Lett*., **2014**, *16* (9), 2406-2409.

[104] Enders, D.; Joie, D.; Deckers, K. Organocatalytic asymmetric synthesis of tetracyclic pyridocarbazole derivatives by using a Diels-Alder/aza-Michael/aldol condensation domino reaction. *Chem. Eur. J*., **2013**, *19* (33), 10818-10821.

[105] Geng, Z.C.; Zhang, S.Y.; Li, N.K.; Li, N.; Chen, J.; Li, H.Y.; Wang, X.W. Organocatalytic diversity-oriented asymmetric synthesis of tricyclic chroman derivatives. *J. Org. Chem*., **2014**, *79* (22), 10772-10785.

[106] Meza León, R.L.; Dávila García, A.; Sartillo Piscil, F.; Quintero, L.; Sosa Rivadeneyra, M.; Cruz Gregorio, S. Two-step synthesis and biological evaluation of calyxamines A and B. *Tetrahedron Lett*., **2013**, *54* (50), 6852-6854.

[107] Pou, A.; Moyano, A. Stereoselective organocatalytic approach to α,β-disubstituted-β-amino acids: A short enantioselective synthesis of cispentacin. *Eur. J. Org. Chem*., **2013**, *15*, 3103-3111.

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