Elisabetta Massolo* and Maurizio Benaglia

Stereoselective organocascades: from fundamentals to recent developments

Abstract: Reaction sequences where more bonds are sequentially formed (cascade reactions) may be started either by a stoichiometric or by a catalytic reagent, and proceed in an enantio- diastereo- or non-stereo- selective manner. A wide variety of such strategies has been developed, including both stoichiometric and catalytic ones.

Within the widely developed cascade reactions field, this chapter is not meant to be omni-comprehensive, but to offer an as much as possible complete overview on organocatalytic stereoselective methods. We embrace the more general definitions by Tietze and Denmark, considering as *cascade reactions* all those one-pot processes that involve two or more bond formations, where each subsequent step is enabled by a structural change caused by the previous one. We will include both two- and multi-component reactions where one or more organocatalysts may be responsible either for all or just some of the occurring transformations. Organocascades will be reported according to the number of involved catalytic cycles.

In the following paragraphs, only cascade reactions that are stereoselective by means of a chiral catalyst will be considered. It will be shown that multiple possibilities, relying on different catalysis modes, are available to achieve the same reaction sequence.

Keywords: domino reactions, organocascade, stereoselectivity, organocatalysis, synthetic methodologies

Notes: 1. TS are drawn to clearly shown the activation mechanism involved in the transformation, but conformational details related to the stereochemical outcome are neglected.

2. In the reaction mechanisms schemes, only those parts of the catalysts' structures that are involved in the catalytic steps are drawn

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1 Introduction

Over 150 years of research made Chemistry progress to a point where no synthetic wish can stay unfulfilled. Strategies are available to reach high level of structural and stereochemical complexity, so that every desired target, including natural isolates, would finally be achieved. The ultimate challenge of synthesis, now, is "to be able to provide large quantities of complex natural products with a minimum amount of labor and material expense" [1] and *sustainability* has progressively become a central topic. Efforts are now devoted to the development of methods to be environmentally conscious and resource-effective, aiming to save raw materials, energy and time and to minimize waste.

It clearly appears that the number of steps is a preeminent factor in defining the feasibility of a synthesis route, as it influences the (man)power and material input, the cost and the environmental impact. Thus, *step* [2] and *pot economy* [3] represent significant leading principles to be considered when elaborating a new synthetic strategy. In this context, stop-and-go sequences are progressively outcompeted by methods where multiple transformations are combined into one synthetic operation. For their effective implementation the key issue to be addressed is the compatibility of substrates and conditions across the different occurring steps. Inspired by Nature, although not so efficient and sophisticated yet, these approaches enable indeed a rapid increase in molecular complexity, improving operational simplicity and making processes more feasible from both an economic and ecological standpoint [4].

Reaction sequences where more bonds are sequentially formed may get started either by a stoichiometric or by a catalytic reagent and proceed in an enatio- diastereo- or nonstereo-selective manner. A wide variety of such strategies has been developed, including both stoichiometric and catalytic ones and, simultaneously, a plethora of definitions aiming to classify those emerged.

1.1 Taxonomy

In Tietze's work, *domino catalysis* is defined as "a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts and in which subsequent reactions result as a consequence of the functionality in the previous step" [5] and Faber added that "each individual reaction belong tightly together and are rather difficult to perform in a stepwise fashion" [6]. Additionally, Fogg stated that "the transformations must be effected by a single catalytic mechanism" [7] and Chapman and Frost completed the definition expressing that "a catalyst must be integral to both of the bond-forming transformations" [8]. Previous to these specification, Denmark integrated Tietze's work defining *tandem cascade reactions*, wherein each subsequent stage can occur by virtue of the structural change brought about by the previous step under the

same reaction conditions, *tandem consecutive reactions*, wherein the first reaction is necessary but not sufficient for the tandem process, so external reagents or changes in reaction conditions are also required, and *tandem sequential reactions*, wherein the second stage requires the addition of another reagent [9].

The term domino was thus placed side by side to the term *cascade*. When employed alone, this term is meant to indicate a transformation where a single catalyst is responsible for subsequently building new bonds; however, additional features may accompany *cascade*, making the term suitable to different situations including even those where more than one catalytic species is employed. In fact, MacMillan and Walji introduced three other denominations: *iterative cascade catalysis*, i.e. cascade catalysis involving one catalyst and one iterative reaction type, *cascade catalysis based on multiple reaction types*, i.e. cascade catalysis involving one catalyst but multiple reaction types and *cycle-specific cascade catalysis*, i.e. cascade catalysis involving multiple catalysts and multiple reaction types [10].

These partially overlap to Fogg's definition of *tandem catalysis*, involving more than one catalytic cycle and including the cases of *orthogonal catalysis*, where more catalysts are required, and of *assisted tandem* and *auto-tandem catalysis*, where a chemical trigger is or not needed to transform the catalyst or to cause a change in mechanism, respectively [6].

In 2005 Bazan group specified the concept of *concurrent tandem catalysis* (CTC), which involves the cooperative action of two or more catalytic cycles in a single reactor, and classified generic CTC cycles according to the number of unique catalytic cycles and the manner in which the products from each cycle are distributed in subsequent reactions [11]. When a set of starting materials A reacts with catalyst I to produce intermediate B and then, upon the addition of C but still under the action of I, the final product P forms, the cycle below is designated $(A_IB)(BC_IP)$. When, instead, a second catalyst (II) is added together with C to react with B toward P, the cycle is indicated ad $(A_IB)(BC_{II}P)$. The generic term $(A_IB)(B_{II}C)..(S_{nIn}P)$ refers to a situation where S*n* is the nth substrate and I*n* is the nth catalyst.

While being highly specific, these classification approaches lack in giving the direct macroscopic distinction between *organomulticatalysis* and *organocascade*, the difference lying in the number of catalysts, more or one, respectively, employed. This was adopted in 2014 by Volla et al. who, reviewing this field, pointed out double, triple and even quadruple cascades [12].

A further specification within *organomulticatalysis* was given by Wende and Schreiner. The situation represented by the case $(A_IB)..(S_{In}P)$, in which the intermediate generated from one catalytic cycle is the substrate for the subsequent one promoted by a different catalyst or by an independent catalytic moiety on the same catalyst, is precisely defined as *multicatalysis*. This strategy was also translated in the design of *multicatalysts*, i.e. a catalyst equipped with an appropriate spacers [13]. Going back to the origin of this rather articulated taxonomy system, it is possible to notice that multicatalysis can be considered a kind of subgroup of domino reactions as defined by Tieze.

In 2012, Allen and McMillan made clear the difference between *double activation catalysis*, where two different catalysts activate the same starting material, and *synergistic catalysis*, where two different catalyst act on two different reaction partners [14].

Shifting the attention from the number of catalytic species to the number of substrates, it is possible to identify single-component, two-component, and multicomponent transformations. *Multicomponent* reactions are defined as domino reactions involving at least three substrates and, according to Ramon and Yus, "these should be clearly differentiated from other one-pot processes [..] that involve the reaction between two reagents to yield an intermediate which is captured by the successive addition of a new reagent" [15].

A tetra-coordinated [a,b,c,d] system was very recently introduced by Indu and Kaliappan, applicable to multistep reactions independently from the number of components and even transferable to sequences occurring in different reaction vessels. In this nomenclature (a) indicates the number of pots, (b) the number of reactions taking place in one-pot, (c) the number of rings formed in one-pot and (d) the number of bonds formed in the same one-pot sequence [16].

A different systematic description and classification of one-pot reactions was introduced by Jorgensen group in 2011 [17]. Considering that this kind of transformations have the ultimate goal of reducing time demand and waste production and have a evident link to industrial processes, the author proposed not to focus on the involved activation modes, but on the number of "manual operations", which is easily counted and may provide an indication of the complexity of the overall reaction and the required manual effort. This system relies on three parameters: type, indicating the position of the enantiodifferentiating manual operation; order, indicating total number of manual operations that are defined as "interruptions of the cascade by the addition of reagents or the removal of the solvent"; fingerprint, indicating the number of C-C (m) and C-X (n) bonds formed and abbreviate as mCnX. In particular, the authors proposed three types underlying the different "chemical purposes" on the basis of which the position of the stereoselective step is chosen. Specifically, in Type A reactions (with asymmetric catalysis as the first manual operation) rapid assembly of structurally diverse chiral frameworks, subsequently modified by in situ modification may lead to highly complex target molecules; in this case, the main concerns are racemization and decomposition of the assembled chiral framework. Instead, Type C strategies (with asymmetric catalysis at the end of the sequence), are performed to avoid handling of delicate starting materials, reaching the stereoselective step as last one; in this case, success is threatened by contaminants somehow hampering the late-stage reaction. In the paper, a flowchart is offered to make the assignment easier.

$$Z = \sqrt[b]{\frac{Y}{100}} \times 100 \qquad Y_{PMO} = \sqrt[nmo]{\frac{Y}{100}} \times 100 \qquad P_f = nmo - 1 - n(INI) + x$$

The remarkable analysis work carried out in the last twenty years offered a deep insight in to the area of one-pot transformation, even though sometimes directness

and univocity have been sacrificed. Herein, we will use domino, cascade and tandem as synonymous terms without aiming to a strict categorization but to illustrate the main concepts and logics on which the field is based and develops.

1.2 Reaction sequences

Within the widely developed cascade reactions field [12], this Chapter is not meant to be omni-comprehensive but to offer an as much as possible complete overview on organocatalytic stereoselective methods. We embrace the more general definitions by Tietze and Denmark, considering as *cascade reactions* all those one-pot processes that involve two or more bond formations where each subsequent step is enabled by a structural change caused by the previous one. We will include both two- and multi-component reactions where one or more organocatalysts, which may be mono- or multifunctional, may be responsible either for all or just some of the occurring transformations.

Organocascades will be reported according to the number of involved catalytic cycles. Here below, a synopsis illustrating the main classes of organocatalysts and the activation modes through which they operate. The employed catalysts often feature more than one functionality participating in the activation mechanisms.

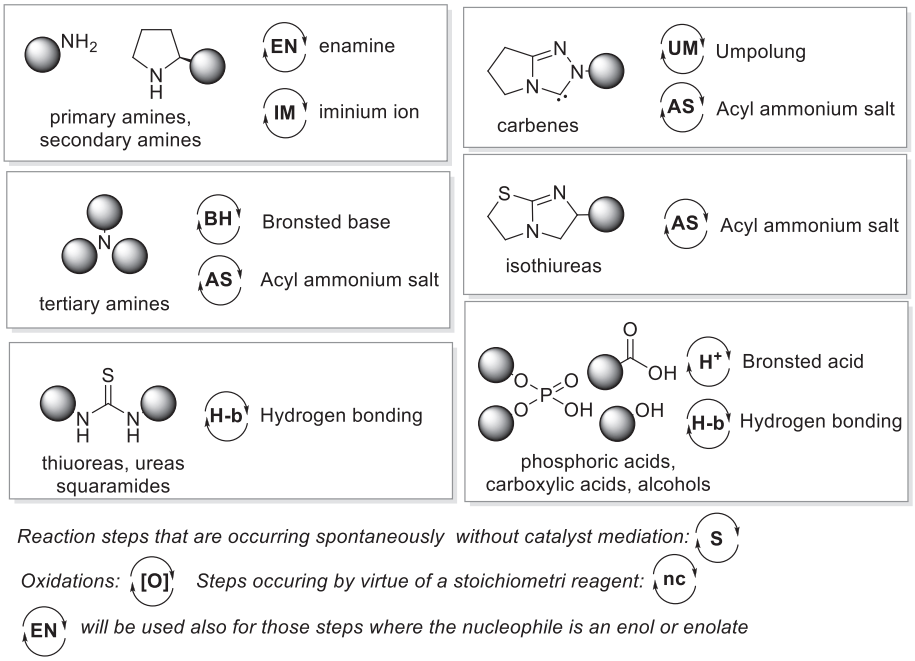
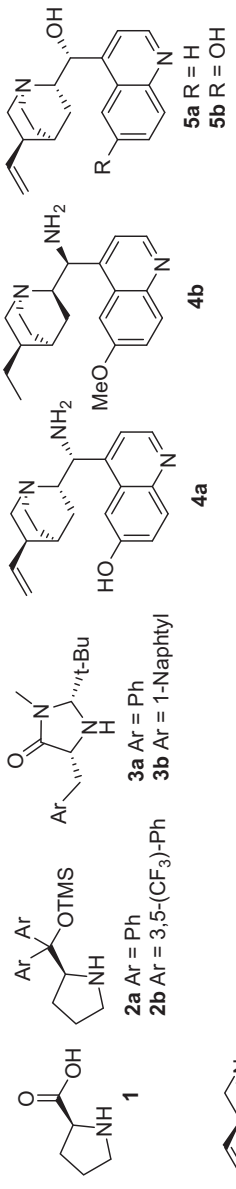


Figure 1: Main classes of organocatalysts and their activation modes.


1
2a Ar = Ph
2b Ar = 3,5-(CF3)-Ph
3a Ar = Ph
3b Ar = 1-Naphtyl
4a
4b
5a R = H
5b R = OH
6
7
8a
8b
9a Ar = 3,5-(CF3)-Ph
9b R = H, Ar = 3,5-(CF3)-Ph
9c R = OMe, Ar = 3,5-(CF3)-Ph
10 Ar = 1-Naphtyl
11a Ar = 9-Phenanthryl
11b Ar = octahydro-1,4:5,8-diethanoanthracene

As for the substrates of domino reactions, they typically need to fulfil structural requirements that become stricter as the number of sequential steps increases, as the proper functional groups are to be in key positions to allow the desired bond forming events.

In the following paragraphs, only cascade reactions that are stereoselective by means of a chiral catalyst will be reported. Organocascades will be classified according to the reaction types they are constituted by a grouped based on the reaction type that starts the sequence. It will be shown that multiple possibilities, relying on different catalysis mode, are available to achieve the same reaction sequence.

2 Double cascade sequences

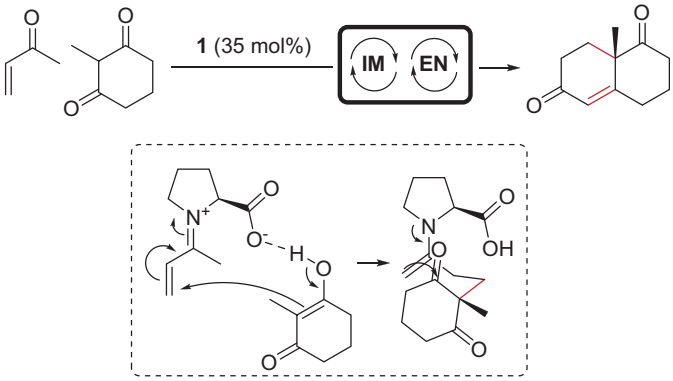
For the concept of cascade to be realized, at least two consecutive transformations need to take place. The simplest sequences that can be implemented are thus double cascades, arising from the combination of different activation modes. A wide variety of these two-steps tandem processes have been developed, relying either on one or more mono- or bifunctional catalysts.

2.1 Michael-type reaction initiated sequences

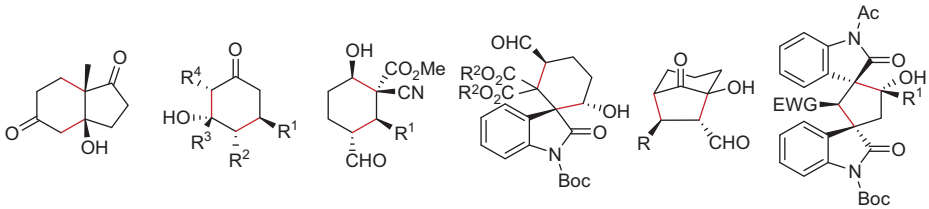
The most of cascade sequences gets started by a 1,4-addition event, generating a nucleophilic intermediate that may undergo different fates. Selected cases will be illustrated to highlight the main synthetic concepts.

The field of stereoselective organocatalyzed domino reactions [18] was opened by Barbas et al. The group demonstrated the ability of Ab38C2 to accomplish the Michael addition/aldol condensation sequence proceeding via amine catalysis exerted by a lysine residue [19]. Shortly after the disclosure of this antibody promoted Robinson annulation, the authors reported secondary amines as catalysts for the Michael/Aldol sequence. In particular, with methyl vinyl ketone (MVK) and 2-methylcyclohexane-1,3-dione, proline afforded the cyclized product in 49% yield and 76% enantiomeric excess (ee) [20]. According to the proposed mechanism, both reaction partners are simultaneously activated: the LUMO lowering of the electrophile is achieved by condensation with the amine function leading to a chiral iminium ion; the presence of a carboxylate group on the catalyst – and, thus, on this active intermediate – allows coordination of the nucleophilic diketone in its enolate form. After the conjugate addition takes place, the resulting enamine intermediate acts as the nucleophile in the intramolecular aldol via a Zimmerman – Traxler-type transition state, proposed by Houk et al. [21].

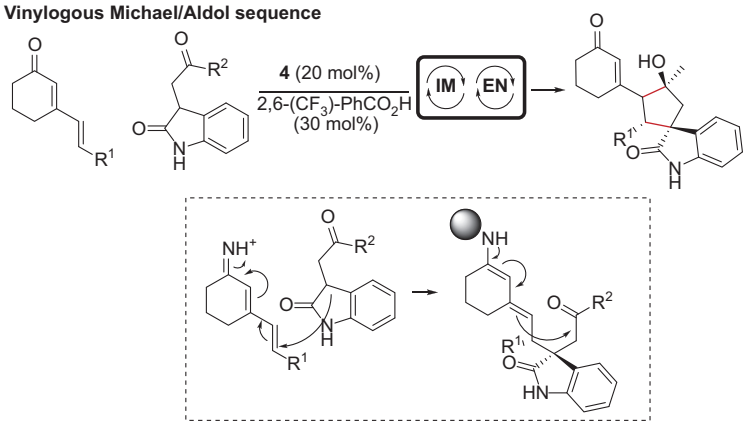
Michael/Aldol sequence



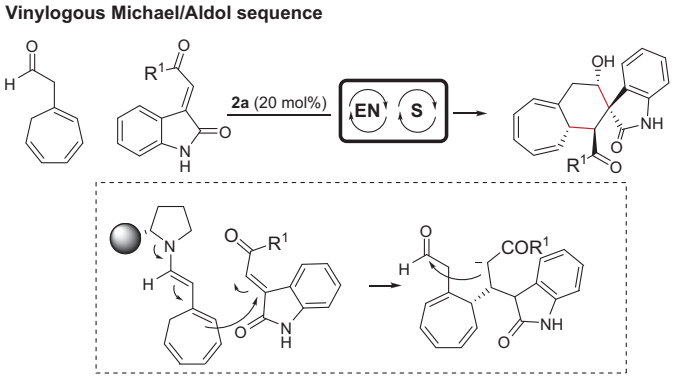
Over the years, several contributions were published where domino sequences led to Wieland – Miescher ketone analogues and to a wide variety of mono-, bi- and spirocyclic derivatives. Few examples are reported here below to illustrate the variety of structures achieved by this method.



Vinylgous versions of this cascade have been reported as well, setting remote stereocenters. Key to the success of this strategy is the identification of well suited substrates, characterized by the needed substitution pattern [22]. The first example was published by Tian and Melchiorre employing dienones and 3-substituted oxindoles. After a primary amine promoted 1,6-addition, the resulting dienamine attacks the ketone substituent on the indole core. Interestingly, the whole sequence is dragged by the final aldol step, which provides the thermodynamic advantage needed to overcome the intrinsic low efficiency of the γ-addition. In fact, no reaction occurs employing oxindoles lacking the carbonyl group that allows the intramolecular aldol. Spirocyclopentanes bearing four contiguous stereocenters and the unaltered α,β-unsaturated carbonyl system form in good yield an ee >96% [23].

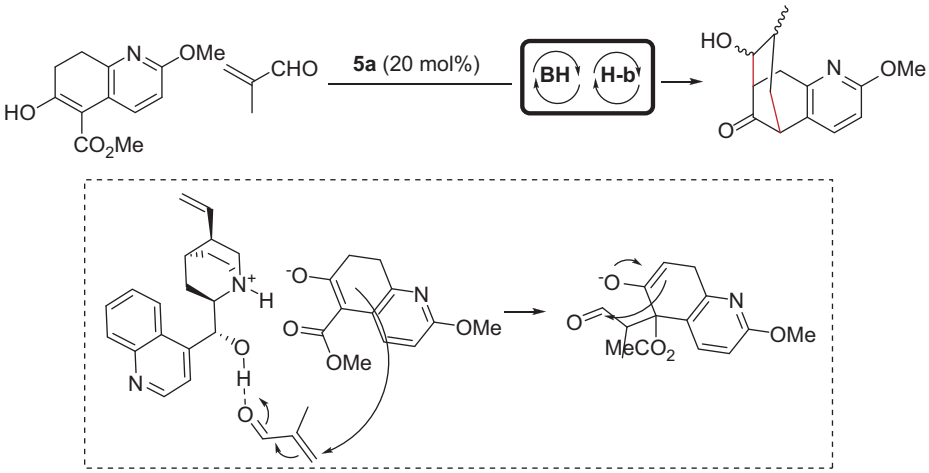


Domino reactions proceeding through the same sequence where, instead, the aminocatalyst is involved in the activation of the nucleophile, are also known. These consist in dienamine conjugate additions followed by a spontaneous cyclization event. The Jørgensen group reported the preparation of highly functionalized tricyclic cores from 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde and 3-olefinic oxindoles. Condensation between the aldehyde and the TMS-protected prolinol catalyst leads to a trienamine species; this reacts at its δ-position in a conjugate addition affording an anionic intermediate. No such 1,4-addition occurs when 2-cycloheptylideneacetaldehyde, that features one less unsaturation and thus can be activated only as the corresponding dienamine: on the other hand, when a stoichiometric amount of prolinol is used, it ends up trapped in the final product. This evidence attests the need for a trienamine system for the catalyst turnover. The intramolecular aldol reaction takes place in a high diastereostereoselective way after the catalyst is released via iminium ion hydrolysis. Indeed, products are typically obtained in >95:5 diastereomeric ratio (d) and ee higher than 90% [24].



Robinson-type annulations have also been afforded by exploiting activation modes other than those provided by aminocatalysis. In 1998, Terashima et al. employed (-)-cinchonidine as both a Brønsted base and a hydrogen bonding donor for the preparation of an intermediate toward (–)-huperzine A, a natural product that features biological activity. Although results were modest in terms of enantioselectivity and yield, this represent the first synthetically practical way to access this tricyclic core [25].

Michael/Aldol sequence

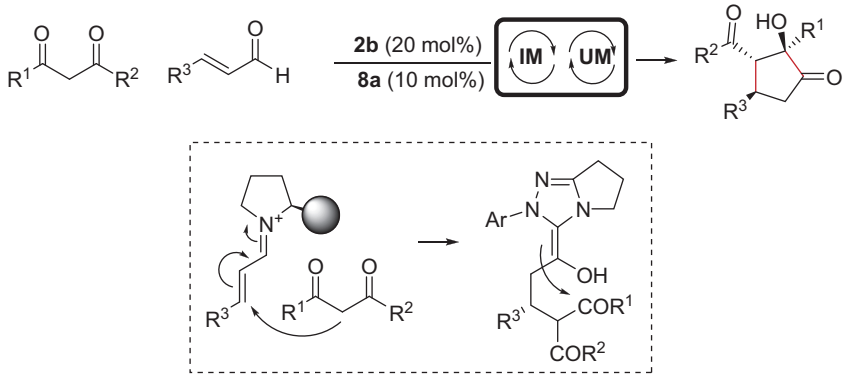


As a variant of the Michael/Aldol sequence, the Jørgensen group showed that the ring-closing event could occur via a Morita – Baylis – Hillman reaction. Here, after generating the iminium ion to promote the nucleophilic attack by a Nazarov reagent, the prolinol catalyst is hydrolysed. At this stage, the released prolinol acts as a nucleophilic catalyst via conjugate addition on the intermediate and thus starts the second catalytic cycle. This was the first example of an enantioselective Morita–Baylis–Hillman reaction catalyzed by a secondary amine. The proposed mechanism was supported by the isolation of the Michael addition product and control experiments revealed the stereoselectivity of the cyclization step to be substrate controlled. Products were obtained in good yields and ees generally higher than 90% and they were subjected to subsequent synthetic transformations [26].

Attack on a carbonyl function, following a 1,4-addition, may also be performed by a Breslow intermediate in a Michael/benzoin sequence. Lathrop and Rovis combined a prolinol ether and a triazolium salt in the presence of an additional base to prepare α-hydroxy-cyclopentanones from α,β-unsaturated aldehydes and either diketones or β-keto-esters. Within the fairly wide reaction scope, only two out of the four possible product diastereomers were observed. In this domino, the enal was first activated as an iminium ion undergoing a Michael reaction; the aldehyde intermediate is

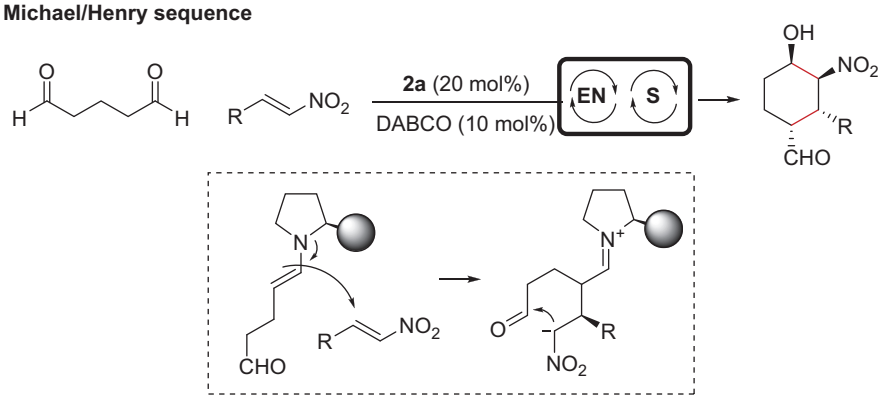
then attacked by the carbene, thus causing its unpolung: the originally carbonyl carbon thus becomes nucleophilic and responsible for the ring closing 1,2-adddition. group The authors demonstrated that trapping the aldehyde in the Breslow intermediate avoids the prolinol-mediated retro-Michael to occur, thus ensuring the high ee of the final product (80%< ee <97%) [27].

Michael/Benzoin sequence

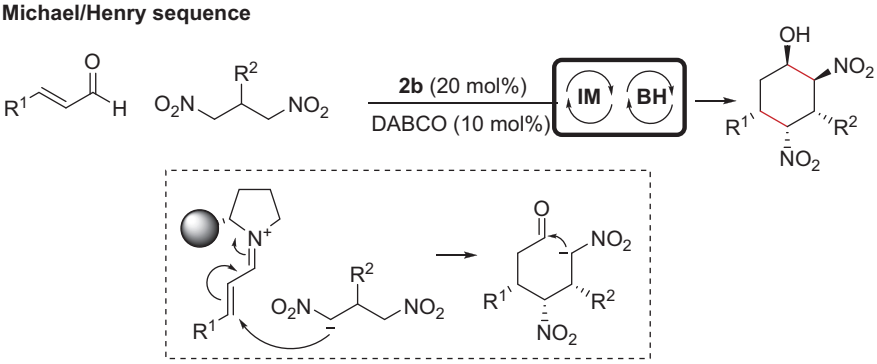


Also for Michael/Henry sequences, most methods rely on amine catalysts that may start the cascade activating either the nucleophile or the electrophile. In an example by the Hayashi group, the enamine of pentane-1,5-dial and a prolinol derivative react with nitrostyrene and the so generated nitronate intermediate attacks the remaining carbonyl group to afford cyclic structures with four contiguous stereogenic centers in ees mainly higher than 98% [28]. On the other hand, in the approach by Jørgensen et al., the same catalyst is employed for enal activation as iminium ion, while the nitroalkane partner deprotonation is performed by an achiral base [29].

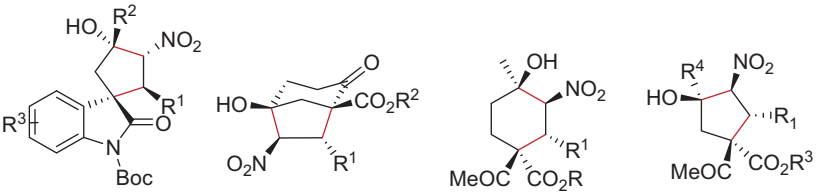
Michael/Henry sequence



Michael/Henry sequence

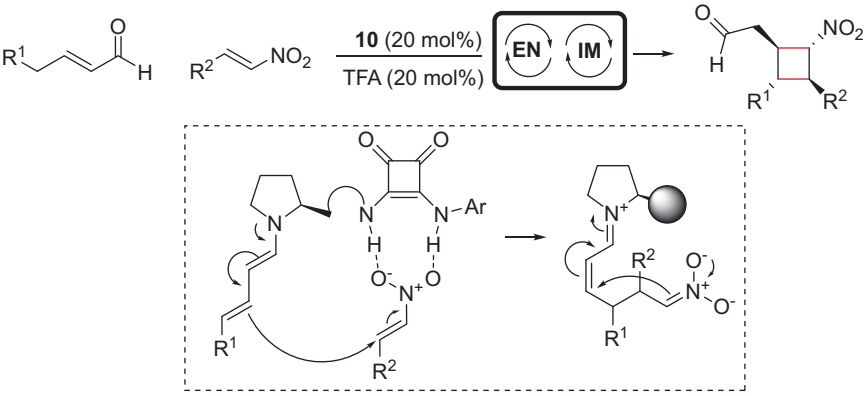


Dicarbonyl compounds and nitroalkenes have often been combined in the presence of a bifunctional catalyst; two different activation mechanisms are possible. Various bicyclic products have been obtained with very high selectivity [30–32].



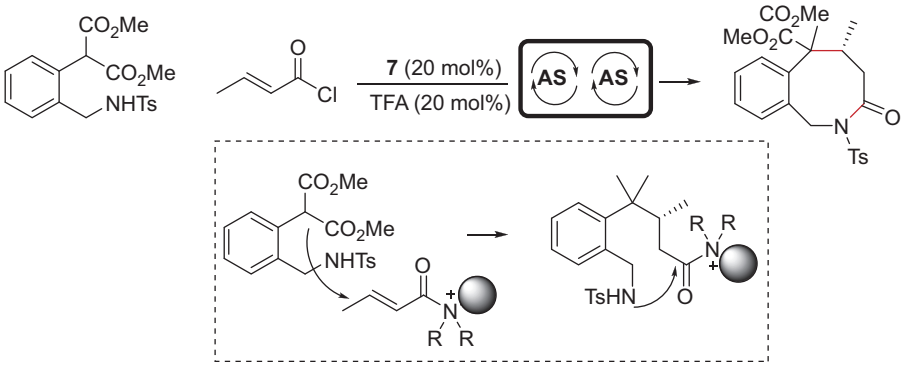
Again, vinilogous versions are available. In a work by Jørgensen, a bifunctional secondary amine-squaramide catalyst turns the enal into the active dienamine via condensation while increases the nitroolefin electrophilicity via hydrogen bonding [33]. In an analogous transformation, Vicario et al. used instead two distinct organocatalysts [34].

Michael/Henry sequence



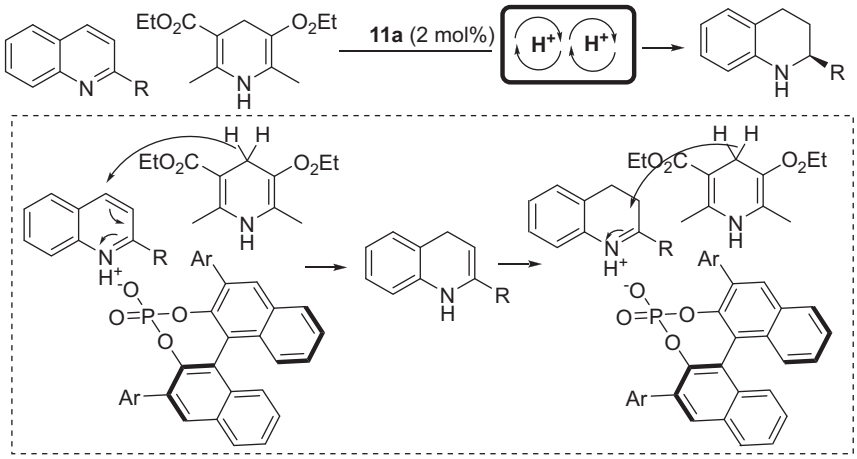
Michael/lactamization cascades have also been developed. The Romo group reported unsaturated acyl ammonium salts as the active γ-electrophiles generated from an acyl chloride and a chiral tertiary amine catalyst in the presence of a Brønsted base. N-protected benzylamines functionalized with an *ortho*-malonate pendant were chosen as substrates to achieve benzazepinones, bezo-fused lactams of pharmaceutical interest. The malonate function was used as nucleophile for the conjugate addition, followed by intramolecular amide bond formation that lead to the targeted eight-membered lactams in good yields and er higher than 97:3 [35]. In a contribution by Jin and co-authors, homobenzotetramisole was employed as nucleophilic catalyst for a lactamization leading to dihydrothiopyranone derivatives from indoline-2-thiones and α,β-unsaturated anhydrides [36].

Michael/Lactamization sequence



Extending the idea to the use of the hydride anion as nucleophile, the transfer hydrogenation of pyridines and quinolones promoted by Brønsted acids may be seen as a 1,4/1,2-addition sequence. Reported by Rueping et al. [37], it allows the preparation of the corresponding tetrahydroetherocycles with higher chemoselectivity with respect to metal catalysed transfer hydrogenation and a broad scope. According to the author's hypothesis, the cascade is initiated by formation of the quinoline substrate to the corresponding iminium ion. This protonated intermediate will hydride transfer; the generated enamine intermediate will be subjected to a further reduction via the same protonation/hydride attack sequence. This strategy allow accessing tetrahydrquinolines typically in higher than 90% yield and ee often close to 99% and was applied to the synthesis of biologically active alkaloids [38].

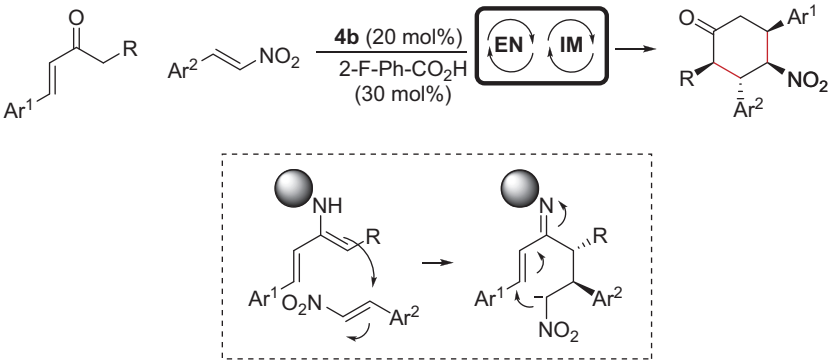
Michael/Mannich sequence



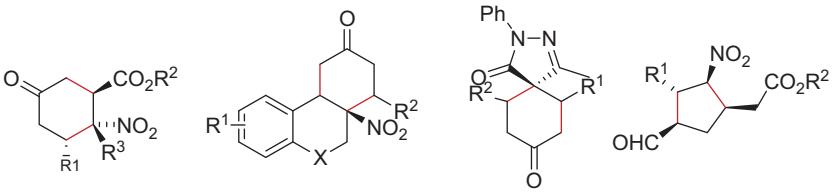
Michael/Michael sequences are also well established, implemented by means of different activation modes [39].

Using primary amine catalysts, dienamines derived from enones proved effective nucleophiles toward different unsaturated acceptors. A representative example was published by the Melchiorre group: a primary amine promoted the formation of cyclohexanones with up to four contiguous stereogenic center in good yield, complete diastereoselectivity and enantioselection higher than 94%, starting from enones and nitrostyrenes, *trans*-α-cyanocinnamate and maleimides. The transformation is proposed as a stepwise sequence that, oppositely to what observed in the analogous secondary amine promoted Diels-Alder reaction, gives access to the *endo* product. Reactivity suppression by polar reaction media and isolation of the first conjugate addition intermediate strongly support the double-Michael mechanicistic hypothesis [40].

Michael/Michael sequence

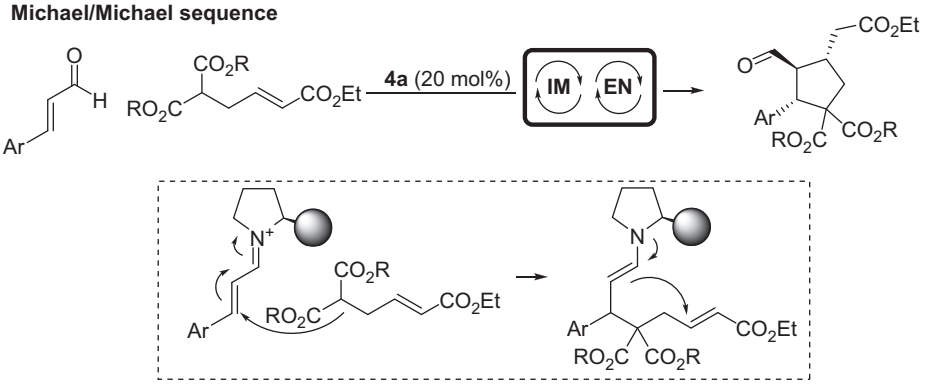


The same cascade, catalysed either by primary or secondary amines, successfully lead to a variety of cyclic structures with typically excellent stereocontrol [41– 44].

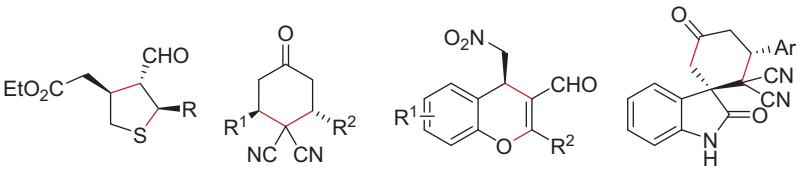


The opposite activation sequence, namely the iminium/enamine cascade, has been even more widely applied. One of the first report was published by the Wang group [45], consisting in the synthesis of densely functionalized cyclopentanes from enals and unsaturated esters bearing a malonate moiety at the γ-position. This activate methylene was the nucleophile attacking the iminium ion generated by condensation between a prolinol derivative catalyst and the aldehyde; this conjugate addition resulted in an intermediate chiral enamine responsible for the subsequent intramolecular Michael addition, affording the five membered products in 85–95% yield, 9:1–20:1 dr a and 94–99% ee.

Michael/Michael sequence



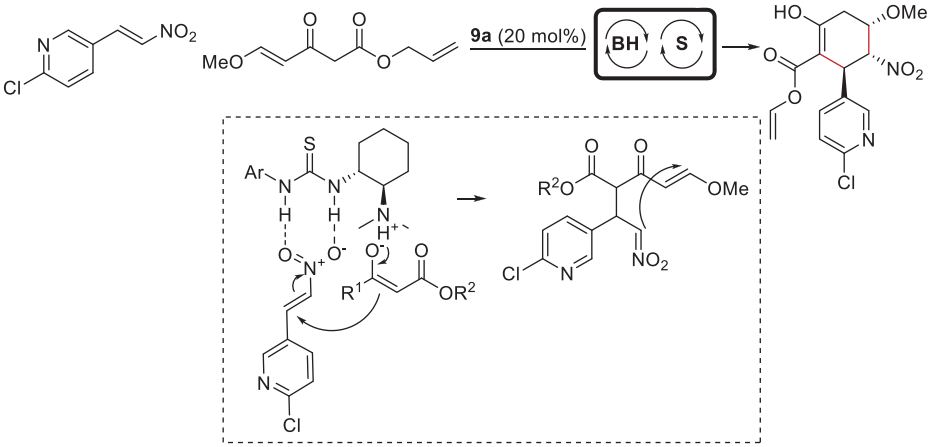
Application of this strategy, based on substrate activation by different primary and secondary amines successfully afforded several cyclic compounds, including heterocycles and spiro-derivatives.



A different approach relies on noncovalent catalysis, as showcased by a work from the Takemoto group and pursued by several other authors. The use of bifunctional

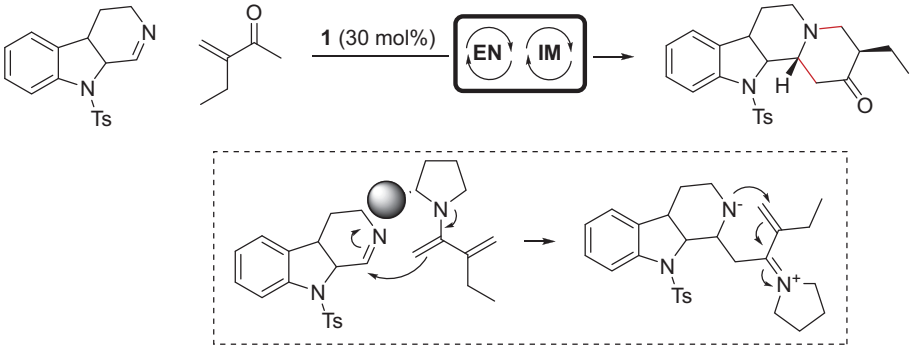
catalysts allows in fact deprotonation of methylene nucleophiles and simultaneous activation of the electrophilic counterpart. While the simple diaminocyclohexane derived thiourea allowed only modest ees [46], more hindered catalysts offering more hydrogen bonding sites ensured higher enantioselectivity [47].

Michael/Michael sequence

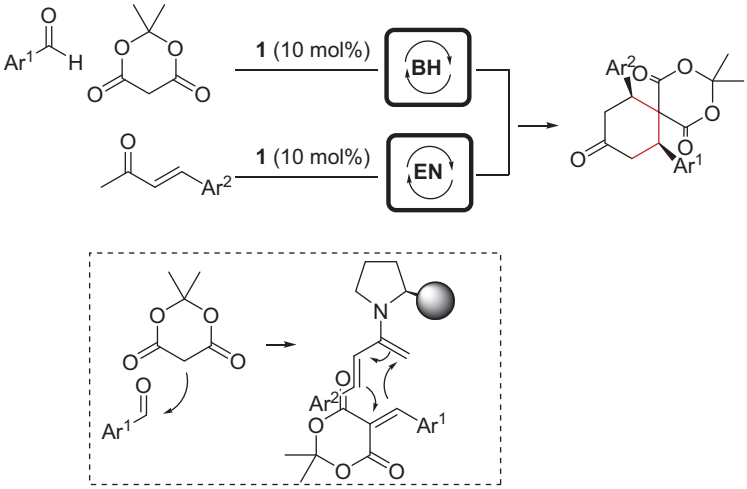


2.2 1,2-Additions initiated sequences

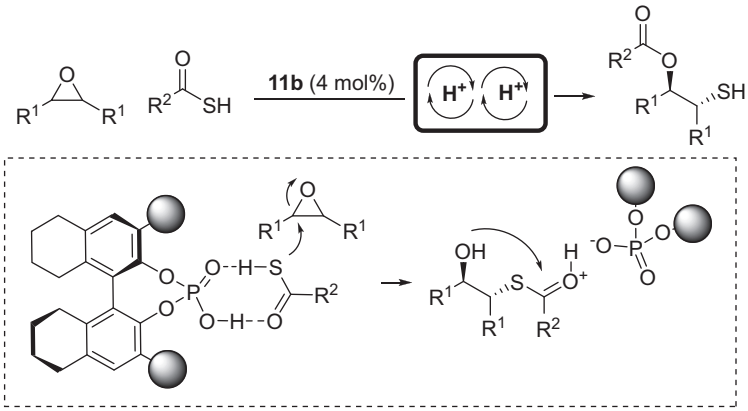
Cascades initiated by 1,2-additions have also been developed. When the domino is started by an aldol or a Mannich reaction, the first nucleophilic event is accomplished by α,β-unsaturated carbonyl species, which may be activated as enamines or dienamines. The intermediate iminium ion will then undergo conjugate addition with consequent carbon-carbon or carbon-heteratom bond formation. This strategy was applied by the Itoh group to access in 85% yield and almost complete stereocontrol a key intermediate en route to *ent*-dihydrocorynantheol, an archetypal indole alkaloid exhibiting antiparasitic, antiviral or analgesic activities. As for the proposed mechanism in this specific case, the enone substrate is catalytically turned into the corresponding dienamine, nucleophilic at its C2 position to attack the endocyclic imine. The resulting iminium ion is instead attacked by the amine function.



A convergent method was developed by Ramachary et al., who looked at it as at an asymmetric three-component Diels–Alder (ATCDA). Here, the amino acid catalyst, namely proline, is responsible for the formation of both reaction partners of the subsequent Diels-Alder step. In fact, the dienophile is represented by the alkylidene Meldrum's acid, generated by proline-promoted Knowenagel reaction, and the diene by the dienamine deriving from condensation between proline and the enal. Different pyrrolidine-like secondary amines were tested and the best results in terms of yield (up to 85%) and ee (up to 91%) was obtained with amino acids [48].



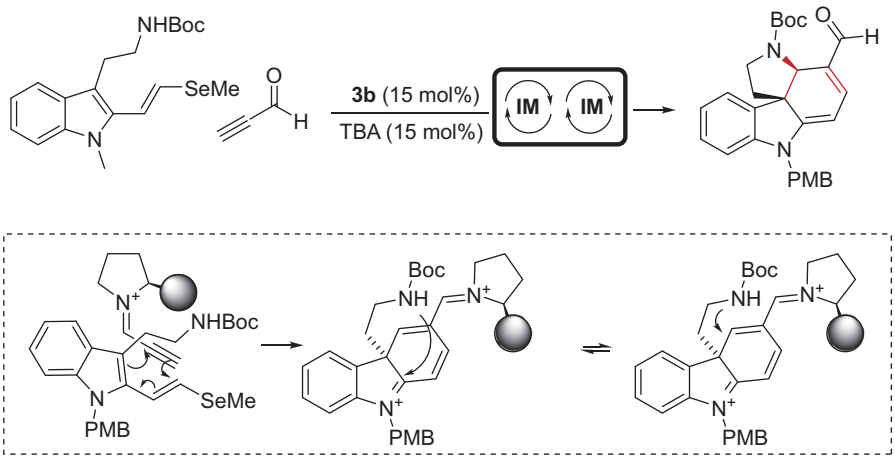
Exploiting Brønsted acid catalysis by chiral phosphoric acids, List et al. developed a stereoselective synthesis of β-hydroxythiols in yields generally higher than 80%. As supported by NMR analysis, the reaction proceeds through the formation of a dimeric complex between the phosphoric acid and thiobenzoic acid. In analogy to what has been found for self-assembled complexes between phosphoric acid catalysts and carboxylic acids, the observed dimer shows an increase in both the nucleophilicity of the thiocarboxylic acid and in the acidity of the complex. Indeed, epoxide ring opening occurs by the thiol group with enantioselectivity affording higher that 95:5 er. Mildly pushing reaction conditions allows the rate determining acyl transfer, thus realizing a tandem process [49].



2.3 Diels-Alder-type reaction initiated sequences

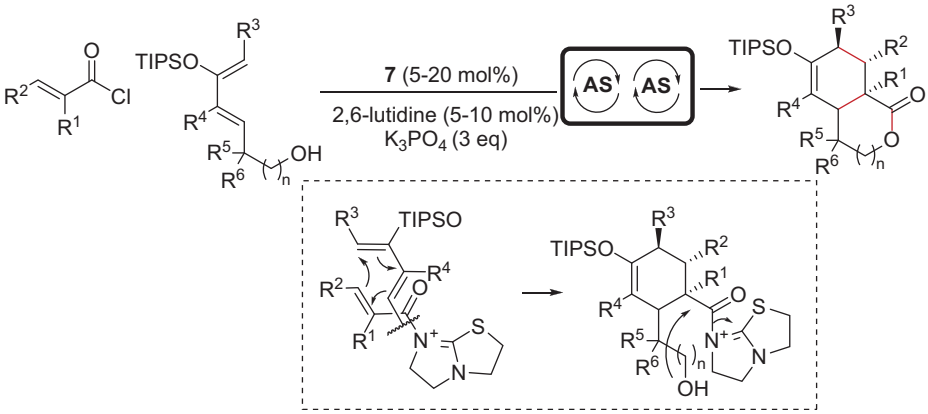
Domino sequences can also be started by Diels-Alder reactions, known to be intrinsically highly efficient transformations especially in their stereoselective versions that allow to rapidly generate enantioenriched heterocycles and carbocycles featuring complex architectures and dense functionalization.

The McMillan group developed a Diels-Alder/Mannich reaction cascade between an ad-hoc prepared indole derivative and propynal, promoted by an imidazolidinone catalyst. According to the working hypothesis, the unsaturated aldehyde was activated as an iminium ion and underwent a [4 + 2] cycloaddition. In the so formed tricyclic intermediate, an enamine-iminium ion tautomerization involving the PMB protected heterocyclic nitrogen, allowed then to unmask the electrophilic function, which is thus intramolecularly attacked by the *N*-Boc amine. Optimization of the catalysts/co-catalyst system allowed obtaining, in no less than 80% yield, ees higher than 94% for this tetracyclic core that is only five steps away from Minfiensine, an isolation product from *Strychnos minfiensis* [50].



Shortly after, the same group developed a closely related Diels-Alder/Michael addition sequence exploiting the same catalytic system and starting from the same aldehyde and an analogous indole derivative, where the sulfide pendant is replaced by a selenide one. After the cycloaddition step, elimination occurs giving access to a conjugated intermediate that could potentially undergo both a 1,2- and a 1,4-addition step. Likely, a series of equilibria take place and, differently from what is observed in the previous case, the non-bridged tetracyclic intermediate is the one that evolves toward the product [51].

As alternative dienophiles, α,β–unsaturated acylammonium salts have been employed by the Romo group in a Diels-Alder/lactonization sequence. Employing chiral isothioureas catalysts, the authors developed the first enantioselective organocatalytic Diels-Alder reaction involving in situ activated α,β-unsaturated acid chlorides. With a Danishefsky diene derivative featuring a hydroxyl pendant, the reaction is postulated to proceed via the formation of a chiral ammonium salt upon condensation between a tertiary amine and the acyl chloride, [4 + 2]-cyclization and final lactonization. To suppress the direct participation of acyl chlorides in the cyclization step, their slow addition to the reaction mixture proved effective: avoiding a large excess of this reaction partner, the relative concentration between the acyl chloride itself and its catalytically generated chiral derivative was such to enable the stereoselective pathway to compete with the background one. An additional Brønsted base is needed and revealed influencing the *endo/exo* selectivity, even though no rationalization was yet proposed. Working under optimized conditions, bicyclic products were obtained in good yields (between 46 and 99%) and excellent ee (between 91 and 99%). Using a racemic diene, stereodivergent resolution was observed leading to separable tricyclic γ-lactones. The method was extended to in situ activated carboxylic acids, and applied on gram scale as well [52].



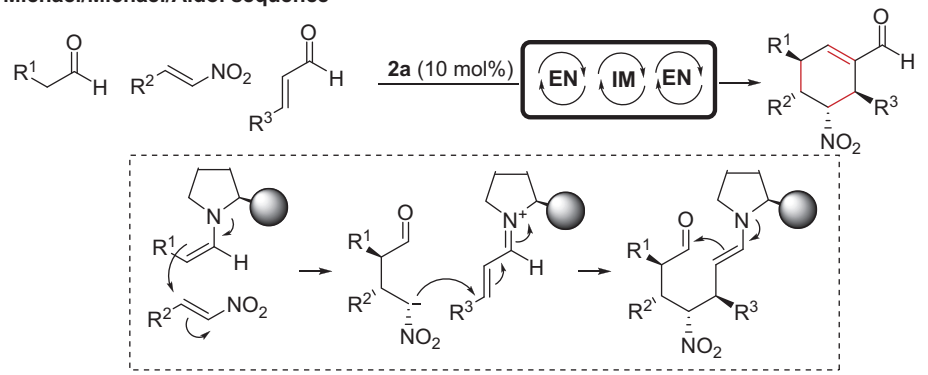
3 Triple cascade sequences

Evolution within the field lead to methods where more than two events were concatenated.

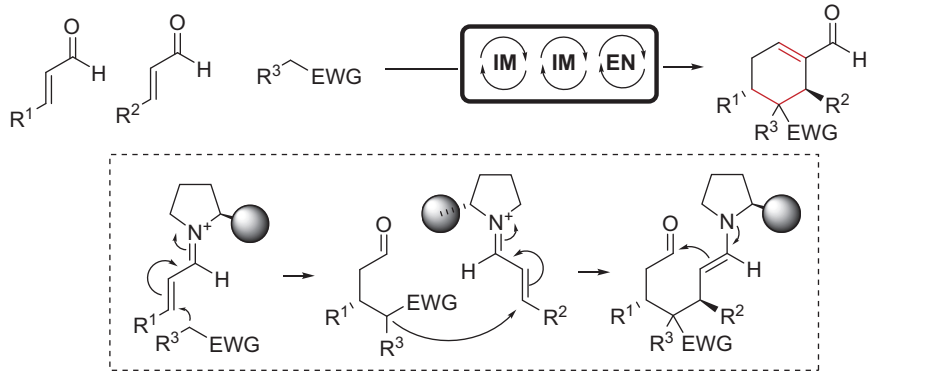
3.1 Michael-type reaction initiated sequences

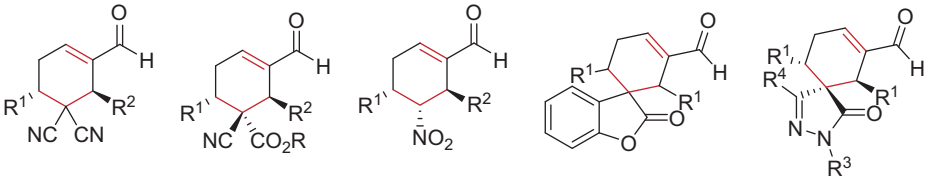
In the contribution by the Enders group, three components were combined in the presence of a single organocatalyst leading to a cyclohexene with four stereogenic centers with high selectivity [53]. The secondary amine catalyst gave aldehyde activation via enamine formation; difference in reactivity between the two Michael acceptors allowed the 1,4-addition to be selective for the nitroalkene over the enal. The enal underwent condensation with the prolinol catalyst performing the typical iminium ion/enamine sequence. Only two out of the eight possible diastereoisomers were observed, the major one being enantiopure. The same kind of reactivity was exploited by Melchiorre et al. to obtain analogous cyclic derivatives featuring a quaternary stereocenter [54].

Michael/Michael/Aldol sequence

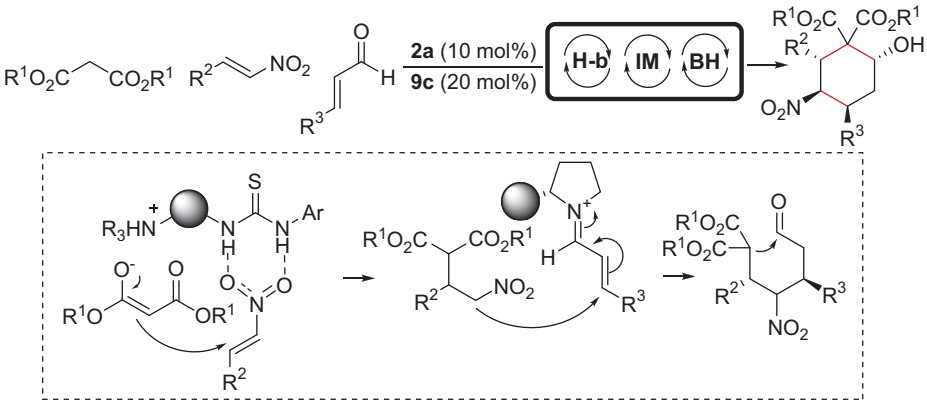


Aminocatalysis has been also applied to develop diverse iminium ion/iminium ion/enamine tandem reactions [55], giving access to highly functionalized cyclic products in good yield and enantioselectivity typically higher than 95%.

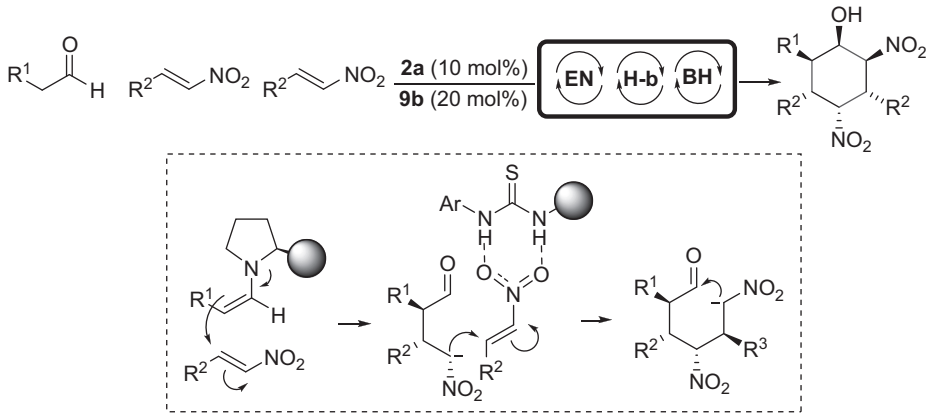




The Michael/Michael/Aldol sequence was also achieved relying on Brønsted base catalysis by a bifunctional thiourea for the first step, followed by iminium ion activation. In this example by Dixon et al., diesters are used as activated methylene nucleophiles attacking the nitrostyrene derivative in a stereoselective way thanks to simultaneous coordination of the two reaction partners to the Brønsted base/hydrogen bonding catalyst. The α,β-unsaturated aldehyde condenses with the prolinol to undergo the second 1,4-addition and subsequent Aldol condensation [56]. This procedure led to a mixture of two diastereoisomers, the major of which in >98% ees.

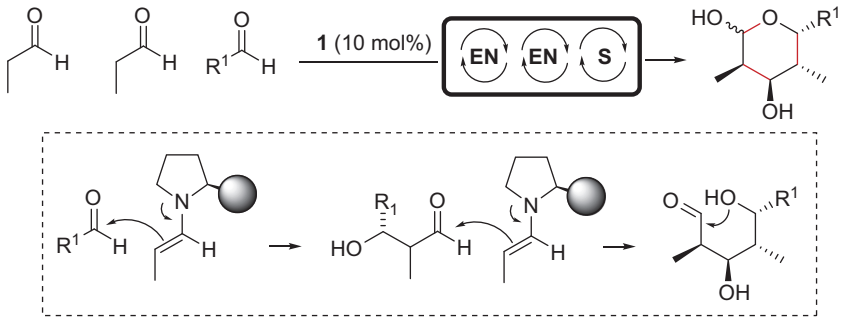


Replacing the ring-closing Aldol step with a Henry reaction, the group of Wang prepared cyclohexanols featuring six stereogenic centers with good diastereoselection and excellent enantiocontrol (ees >99%). Two catalysts, namely a thiourea bifunctional one and a secondary amine, were employed and proved to act independently. Despite relying on the same catalysts combination, this reaction proceeds though a different activation sequence with respect to that reported by the Dixon group. Indeed, the protected prolinol provides the formation of the chiral nucleophile, spontaneously undergoing addition to the first equivalent of nitroalkene; this hypothesis was supported by the sole formation of this first addition intermediate when carrying out the reaction without the thiourea catalyst. For the second Michael reaction, instead, hydrogen bonding activation of the electrophile is needed. The final base- promoted Henry step proceeded immediately, as in fact no acyclic product was ever isolated [57].

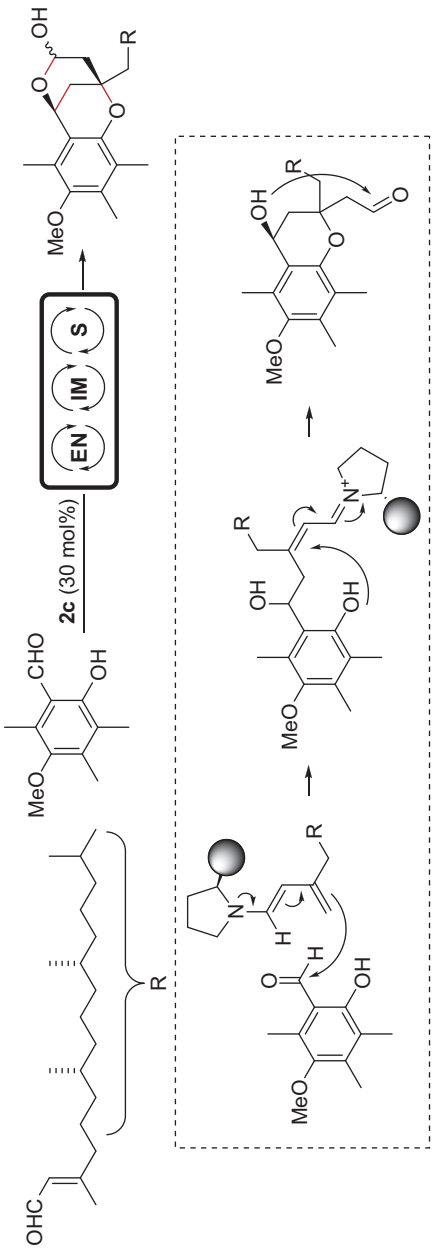


3.2 1,2-Additions initiated sequences

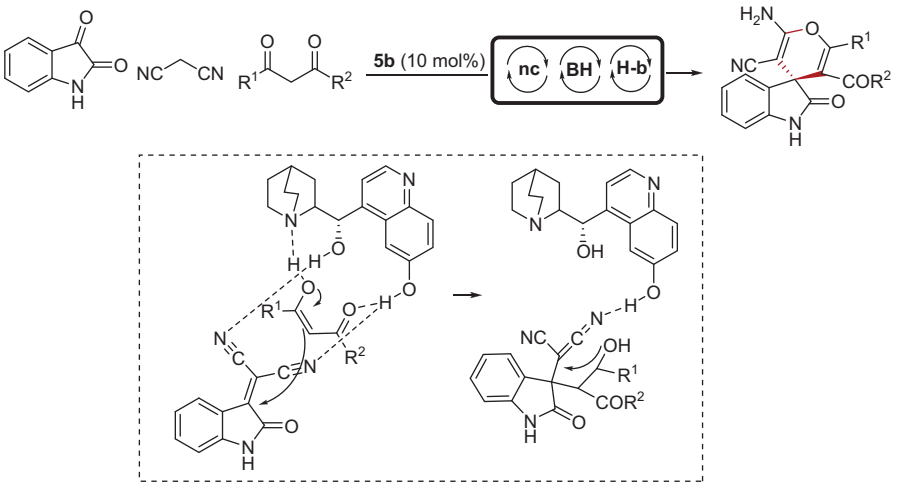
One of the first examples was reported by Còrdova et al., in continuation with their previous work on the proline-catalyzed assembly of three acetaldehyde molecules providing (+)-5-hydroxy-(2E)-hexenal [58]. A proline-promoted Aldol/Aldol/acetalization sequence led to trimeric lactols with four stereogenic centers. These pyranoses were isolated as 1:2 mixtures of α/β anomers upon slow addition of two equivantes of propionaldehyde to acceptor aldehydes in up to 53% yield and 33% ee [59].



Exploiting the enamine/iminium ion activation cascade, the Woggon group got access to the lactol deriving from the condensation between phytenal and an *ortho*-hydroxybenzaldehyde in 58% yield and 97% ee. This intermediate, generated upon an Aldol/Michael/acetalization domino process, is a key intermediate in the total synthesis of α-tocopherol [60].


OHC
R
MeO
CHO
OH
2c (30 mol%)
EN
IM
S
MeO
OH
O
O
R
N
H
H
O
OH
MeO
R
OH
OH
MeO
N+
R
OH
O
O
MeO

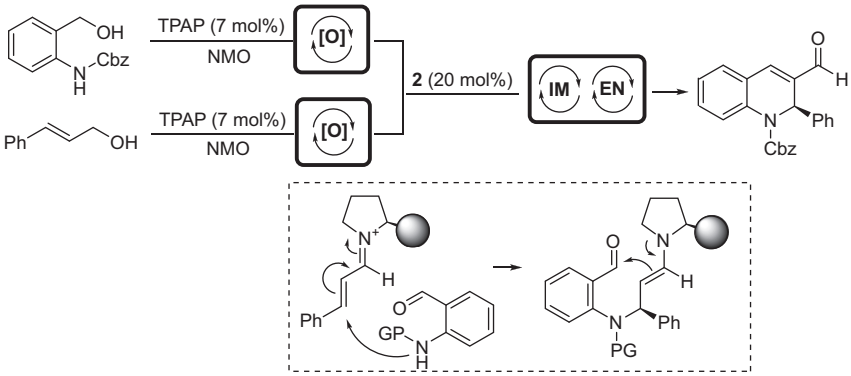
To build a longer-than-two-steps cascades, Knoevenagel reactions can be exploited as first transformation to allow a subsequent Michael addition, which is known to turn a β-acceptor into an α-donor intermediate able to react on its turn. An application of this strategy was reported by the Yuan group and consisted in a three component reaction between differently *N*-protected isatins, malonitrile and diketones or β-ketoesters mediated by cupreine, a cinchona alkaloid [61]. According to the proposed mechanism, the reaction proceeds via condensation between the 2,3-dioxoindoline and malonitrile leading an α,β-unsaturated intermediate. The subsequent conjugate addition is promoted by the bifunctional catalyst: its tertiary amine function deprotonates the 1,3-dione and stays associated with it being its counteranion while engaging in hydrogen bonding with the electrophile reaction partner. The final cyclization affords the desired spiro[4 H-pyran-3,3′-oxindoles]. Under optimized conditions, this Knoevenagel/Michael/cyclization sequence proceeds with yields typically higher than 90% and ee up to 97% [62–64].



3.3 Miscellaneous

Rueping et al. reported a convergent catalysis approach, where two oxidative cycles lead to the in situ generation of an aldehyde and an enal derivative starting from an allylic alcohol and a 2-amino benzyl alcohol. A prolinol catalyst allowed their subsequent activation for an aza-Michael initiated iminium ion-enamine sequence leading to the desired 1,2-dihydroquinolines in 40–80% yield and ee often up to 99%. The relevance of this strategy does not lie only in the originality of the cascade design, but also in its formally enabling aminocatalysis on primary alcohol, more desirable substrates than the corresponding carbonyl compounds [65].

oxidation/aza-Michael/Aldol sequences



4 Quadruple cascade sequences

The need for methods giving access to complex skeletons in a single step, avoiding lengthy and time-consuming paths, prompt to reach a further level of sophistication in designing domino events. Indeed, transformations involving four sequential reactions have been implemented. These elaborate dominos acquire a higher synthetic impact when heading to articulated molecular structures. The employed starting materials need to feature proper functionalities in the key positions, and this translates in different levels of substrates customization, ranging from the simple introduction of aromatic substituents to the preparation of tailor made derivatives.

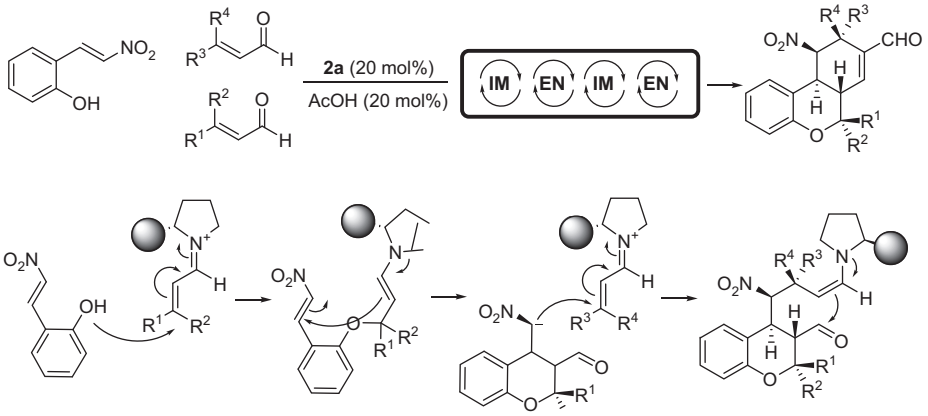
4.1 Michael-type reaction initiated sequences

Coherently with what observed in shorter sequences, also in the context of quadruple ones the most start with a Michael-type addition, where the nucleohpìile is either a carbon, and oxygen or a nitrogen center.

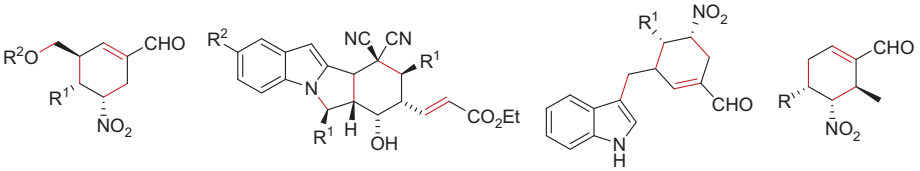
Again, exploiting the iminium/enamine activation sequence allowed preparing cyclic structure with multiple stereocenters combining simple enals, nitroalkenes and aldehydes. The Hong and Gong groups simultaneously reported an oxa-Michael initiated quadruple reaction. In both cases, the electrophile is represented by an enal activated as chiral iminium ion. Selectivity for the iminium ion over the nitroalkene as an electrophile is explained by the hard nature of the oxygen nucleophile. In a three component reaction, Hong demonstrated that two different enals can be simultaneously employed and still have the formation of a single product thanks to a steric hindrance-based selectivity [66]. Gong developed instead a four component reaction where the same unsaturated aldehyde is incorporated twice in

the final product [67]. In both cases, pretty good yields (about 50%) where accompanied by complete enantioselection.

Oxa-Michael/Michael/Michael/Aldol Condensation Sequence

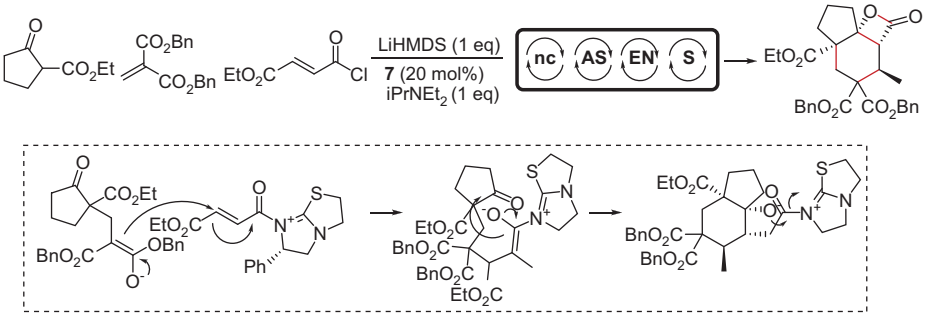


An aza-Michael initiated sequence as well as all carbon-carbon bond forming sequences were reported by the Enders group [68–70].



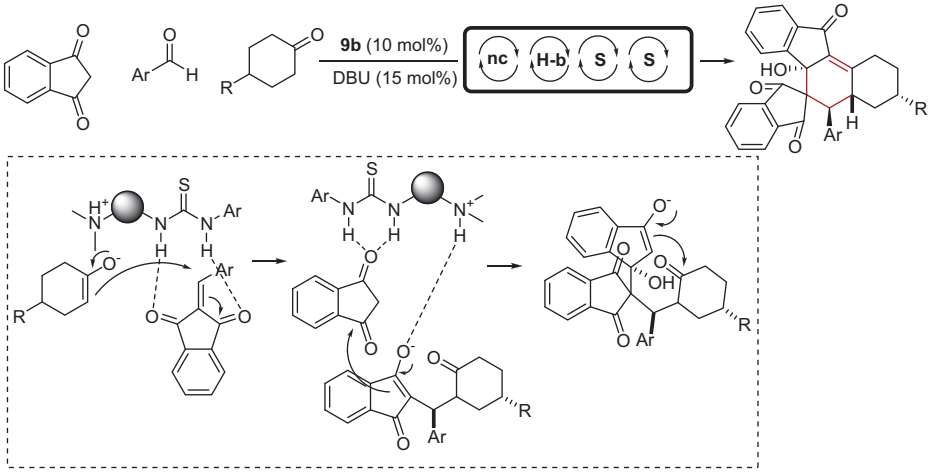
Besides aminocatalysis, involving enamine and iminium ion activation by primary and secondary amines, Lewis base catalysis by tertiary amines has also been exploited within quadruple cascades, although not being responsible for all the steps. In fact, the Romo group developed a Michael/Michael/aldol/β-lactonization to form highly functionalized bi- and tricyclic β-lactones where the only the last three steps are indeed born by the chiral isothiourea catalysts, while the first conjugate addition occurs by means of a stoichiometric base. The initial racemic Michael adduct undergoes kinetic resolution in the subsequent 1,4-addition on the chiral acyl ammonium salt, generated in situ by condensation between the tertiary amine and the acyl chloride. The proposed mechanism involves intermediate species existing in rig conformations due to noncovalent interactions, including a mo – s*s donation that keeps the acyl ammonium in an s-cis geometry and Lithium bidentate chelation of the amide enolate. As the resolution process was not made effectively dynamic, yields rarely exceeded 50%; however, almost complete diastereoselection and er between 82:18 and 97.5:2.5 were obtained [71].

Michael/Michael/Aldol/β–lactonization sequence



4.2 1,2-Additions initiated sequences

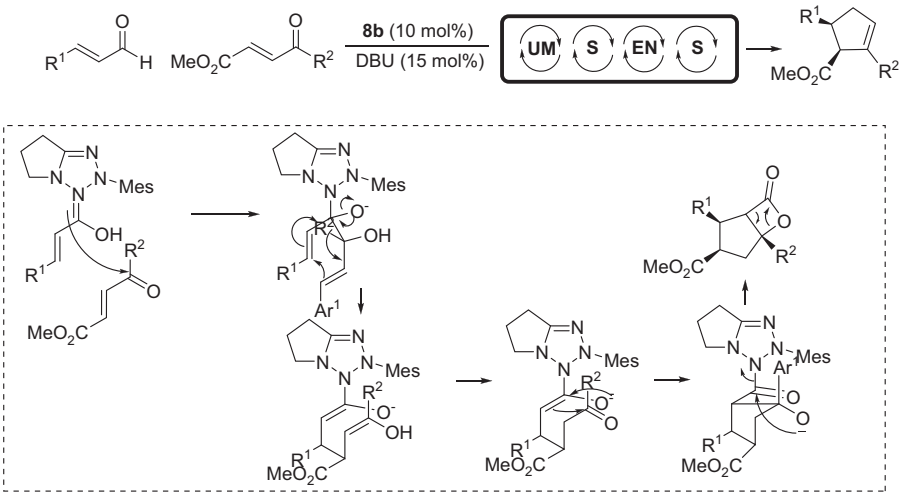
A Knoevenagel reaction initiated sequence was reported by Chang et al. Starting from simple commercially available compounds, this three component quadruple reaction gave access to spirocyclic products in good yield (about 70%) and excellent dr (often higher than 19:1) and ee (between 85 and 98%). After the addition/elimination of the dione on benzaldehye. the quinine-derived thiourea catalyst acts both as a hydrogen bond donor and Brønsted base to promote and stereochemically control the subsequent steps via noncovalent interactions with both the reaction partners [72].



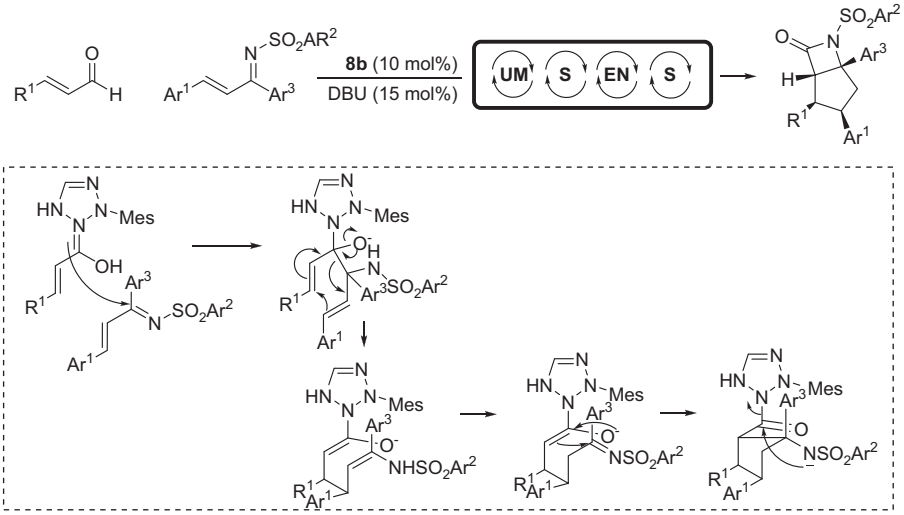
Maybe less exploited but still well established as a powerful enantioselective transformation, the benzoin reaction has also been applied as first step in cascades. The Bode group has been active in studying N-heterocyclic carbene as chiral catalysts and in this context developed a highly enantioselective *cis*-cyclopentene-

forming annulation via intermolecular benzoin condensation-oxy-Cope rearrangement followed by an intramolecular Aldol reaction. In particular, the authors found that the use of a triazolium salt in the presence of a strong base allowed a cross-benzoin between enals and 4-oxoenones, giving rise to an intermediate that spontaneously undergoes a sigmatropic rearrangement. These couples reactions led to a species featuring both an enolate and an enol: as the latter tautomerizes, its attacked in a ring-closing 1,2-addition followed by lactonization and decarboxylaton. The products were obtained in good yields (ranging from 50 t 93%) and almost complete diastereo- and enantioselection. The stereochemical outcome was justified considering the electrophile was mainly living in an *s-cis* conformation and the oxy-Cope step proceeded via a boat TS.

Cross-benzoin/oxy-Cope/Aldol/decarboxylation sequence



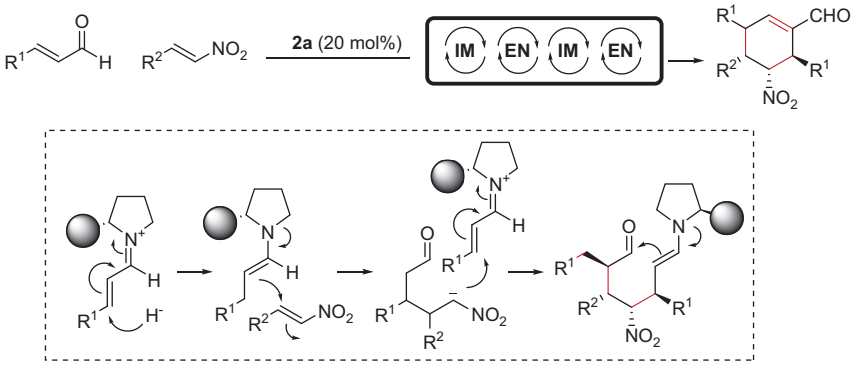
Within his studies on NHC-promoted reactions, Bode et al. also developed a four step cascade started by a cross-benzoin/oxy-Cope reaction between enals and chalcone-derived imines. A substoichiometric achiral base turned the triazolium precatalyst into the active carbene able to condense with the aldehyde and generate the Breslow intermediate. Concertedly, 1,2-addition to the imine and oxy-Cope rearrangement led to an enolate species, which was the nucleophile for the subsequent Mannich reaction; nitrogen attack onto the carbonyl allowed the released of the catalyst and formation of ring fused β-lactams in 60–80% yield and 88–99% ee. These outstanding results were obtained thanks to a careful tuning of reaction conditions, especially in the choice of the precatalyst/base combination, as the desired transformation has to outcompete the highly probable enal dimerization and aza-Diels-Alder reaction [73].



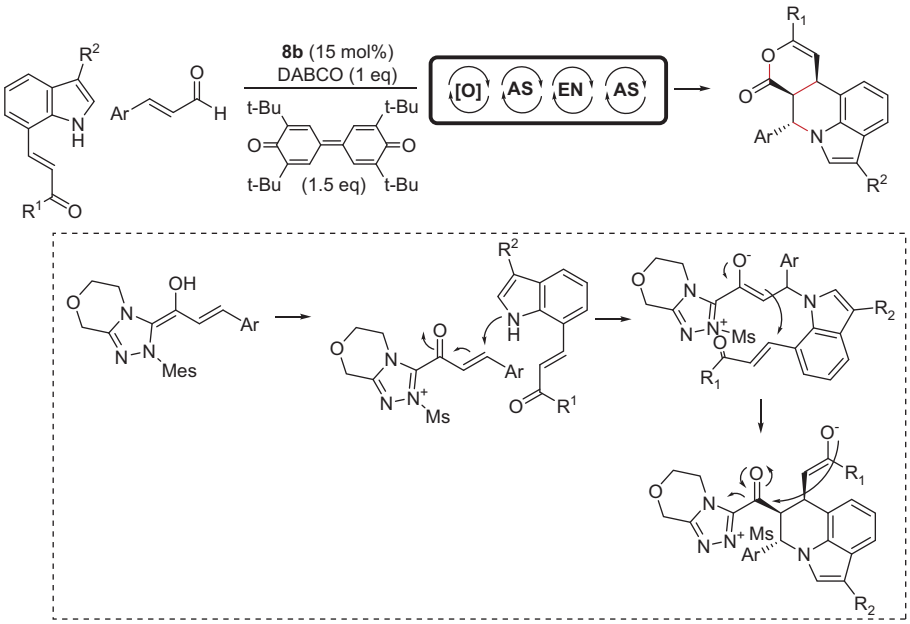
4.3 Miscellaneous

Reduction by Hantzsch ester was also exploited as the initial step of the hydrogenation/Michael/Michael/Aldol condensation sequence reported by Rueping et al. In this work, selective transfer hydrogenation of enals over nitroalkenes was achieved by the substrate activation as iminium ion. Hydride donation thus led to an enamine intermediate undergoing addition to the nitrostyrene derivative. Using an excess of the unsaturated aldehyde allowed a further 1,4-addition and a ring-closing crotonic step. The full four-step sequence occurred in about 50% yield and ee typically higher than 99% [74].

Hydrogenation/Michael/Michael/Aldol reaction sequence



Oxidation was instead a key step in the synthesis of δ-lactone reported by the Bijou group. In this work, the Breslow intermediated formed by condensation between the NHC catalyst and an enal is turned into the corresponding chiral α,β-unsaturated acyl azolium by the bisquinone oxidant. The so formed intermediate undergoes an aza-Michael attack by a tailor made indole, featuring an enone group at the 7-position; this pendant becomes the protagonist of the subsequent intramolecular conjugate addition and lactonization. The tetracyclic products were obtained in yield typically higher than 80%, complete diastereoselectivity (dr >20:1) and excellent enantioselection (er >90:10) [75].



5 Conclusions and outlook

Besides being valuable from a synthetic standpoint, developing a cascade sequence is of great conceptual interest, as it demands to intensively exploit every reaction, engaging transient intermediates and making bond forming those steps that would otherwise have represented the quenching event.

As we have just shown, organocascades are meant to enable effective synthesis of structurally and stereochemically complex compounds. Even if tailor made substrates are often required, especially for long sequences and/or to obtain densely decorated products, their preparation is made worthy by the specificity of the connectivity achieved; (poli)cyclic compounds featuring several stereogenic centers are

often prepared. For their efficacy organocascades find application as key steps in the synthesis natural products [76], including bioactive ones [77].

Abbreviations

PMB = -*ortho*-methoxybenzene
Boc = tert-butyloxycarbonyl
Ts = tosyl
Ms = mesyl
TFA = trifluoroacetic acid
TBA = tribromoacetic acid
ee = enantiomeric excess
er = enantiomeric ratio
dr = diastereoisomeric ratio
TMS = tetramethylsilyl
TPAP = tetrapropylammonium perruthenate
NMO = *N*-methylmorpholine N-oxide
TS = transition state

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