Enantioselective Vinylogous Organocascade Reactions

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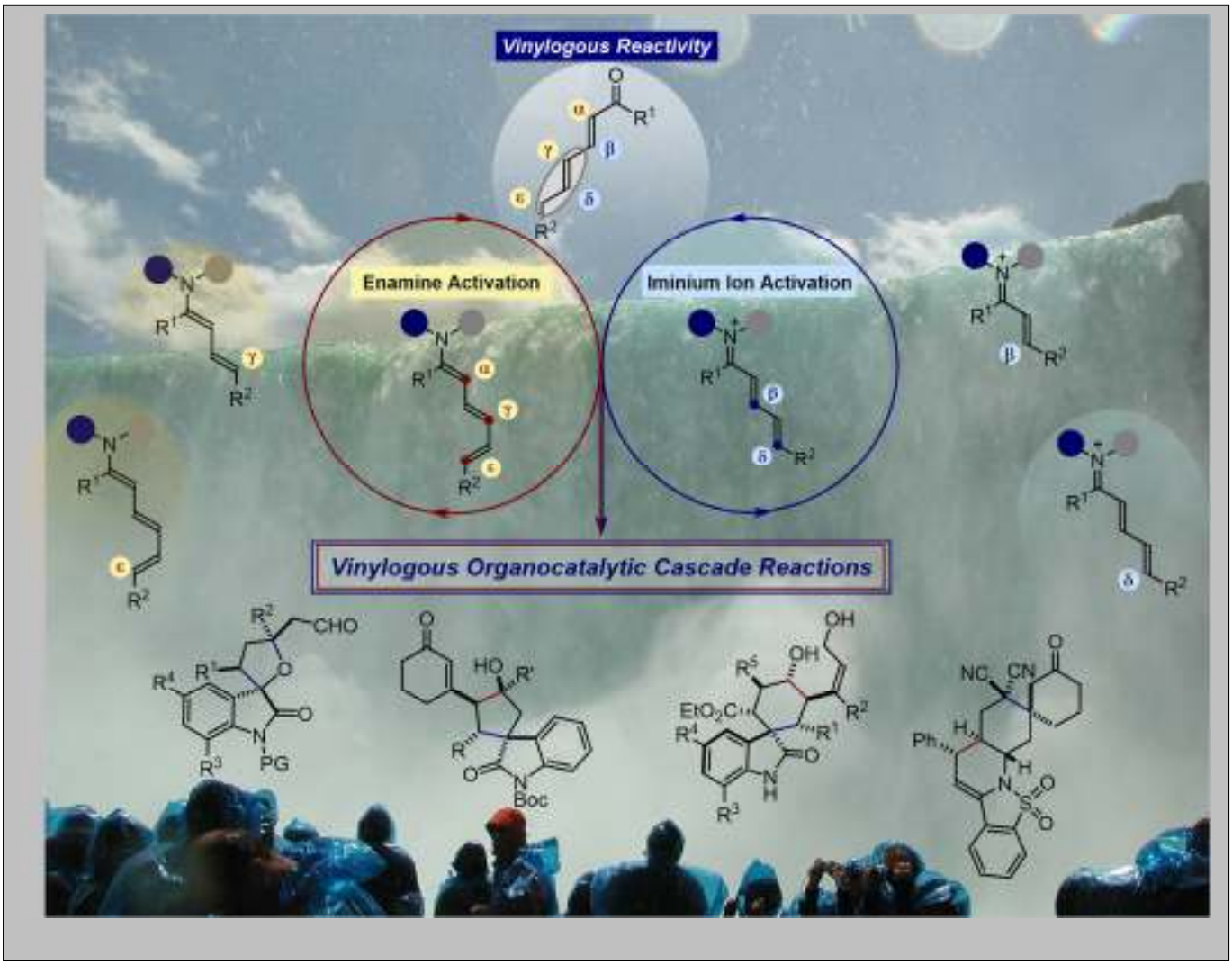

Abstract

Cascade reactions are powerful tools for rapidly assembling complex molecular architectures from readily available starting materials in a single synthetic operation. Their marriage with asymmetric organocatalysis has led to the development of novel techniques, which are now recognized as reliable strategies for the one-pot enantioselective synthesis of stereochemically dense molecules. In recent years, even more complex synthetic challenges have been addressed by applying the principle of vinylogy to the realm of organocascade catalysis. The key to success of vinylogous organocascade reactions is the unique ability of the chiral organocatalyst to transfer reactivity to a distal position without losing control on the stereo-determining events. This approach has greatly expanded the synthetic horizons of the field by providing the possibility of forging multiple stereocenters in remote positions from the catalyst's point of action with high selectivity while simultaneously constructing multiple new bonds. This article critically describes the developments achieved in the field of enantioselective vinylogous organocascade reactions, charting the ideas, the conceptual advances, and the milestone reactions that have been essential for reaching highly practical levels of synthetic efficiency.

1. Introduction

Cascade reactions are powerful tools for rapidly achieving molecular complexity since multiple chemical bonds are formed in a single synthetic operation.[1] They fall in the broader definition of domino processes,[2] where sequences of chemical transformations take place under the same reaction conditions (*i.e.* a single solvent, workup procedure, and purification step is required). Thus, all the reagents and catalysts are added at (or nearly at) the outset of the process to undergo a chemical transformation whose product becomes the substrate for the next step, whose product again becomes the substrate for the next step, and so on, until a product stable to the reaction conditions is reached. Cascade reactions pose an intellectually stimulating problem, since they require careful consideration of the compatibility of the transiently formed intermediates and the substrates, which should not undergo alternative irreversible reactions to form by-products. Thus, achieving a high degree of chemoselectivity represents the greatest obstacle in the design of cascade reactions.[3] But success results in a big payoff, since cascade reactions reduce time-consuming and expensive protection/deprotection and isolation procedures of intermediates. In addition, this experimentally simple strategy offers the potential for rapidly increasing structural and stereochemical complexity. In a single synthetic step, it converts simple starting materials into complex molecular systems containing multiple stereocenters. Even more appealing is the development of enantioselective catalytic cascade reactions.[4] By combining multiple asymmetric, catalytic transformations in a domino sequence, chemists can impart increased enantiomeric excess to the final product when compared to the corresponding discrete transformations.[5] This requires a chiral catalyst that can effectively drive, in a stereocontrolled fashion, consecutive catalytic reactions using different modes of substrate activation.

Given the above, it is easy to understand why the many synthetic benefits of cascade reactions have attracted the interest of asymmetric organocatalysis[6] researchers. The stability, versatility, and compatibility with distinct functional groups make simple chiral organic catalysts perfectly suited for engineering effective asymmetric catalytic methods. The recent marriage with asymmetric organocatalysis has led to the emerging field of organocatalytic cascade reactions[7], which has provided a way of achieving stereochemical and molecular complexity from readily available starting materials. The synthetic potential of this bio-inspired approach has been validated by recent applications to the total synthesis of natural products.[8] Within this context, a key role was played by chiral primary and secondary amines, which exploit fundamental and well-established mechanistic patterns, mainly using the chemistry of simple enamine[9] and iminium ion intermediates[10], to asymmetrically functionalize carbonyl compounds.[11] Chiral amines were quickly recognized as ideal for catalyzing highly efficient cascade processes. This is mainly because of the ability of a single chiral amine to integrate orthogonal activation modes of carbonyl compounds into more elaborate reaction sequences, thus enabling the concomitant construction of two consecutive carbon-carbon bonds in one simple synthetic operation (Figure 1a).

To fully harness the synthetic power of organocascade catalysis, it was crucial to identify the iminium ion-enamine activation sequence as an enabling approach to highly efficient domino reactions (Figure 1b).[12] The strategy is based on the 1,4-addition of a nucleophile (*Nu*) to α,β-unsaturated aldehydes or ketones and subsequent α functionalization of the resulting saturated carbonyl with an electrophile (*El*). In this well-defined sequence, the chiral amine plays an active role in both steps. Initially it lowers the lowest unoccupied molecular orbitals (LUMO-lowering activation)[13] of chiral iminium ions, thus facilitating the 1,4-addition of a general nucleophile (*Nu*), while in the second event it exerts an energy-raising effect on the highest occupied molecular orbital (HOMO-raising activation) of the enamine intermediate, promoting the addition to an electrophilic compound (*El*). The strategy has been extensively applied by the synthetic community to access α- and β-functionalized carbonyl chiral building blocks.[7,12]

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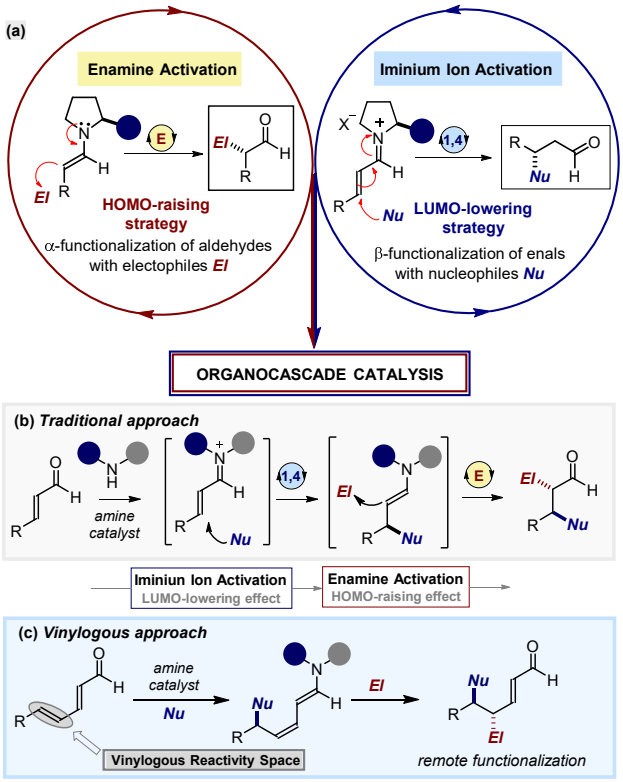


Figure 1. (a) Combining enamine and iminium ion activations. (b) The established iminium ion-enamine activation strategy for designing organocascade reactions. (c) Transferring the technique into a vinylogous reactivity pattern to forge multiple stereocenters remote from the catalyst's point of action; El: electrophile, Nu: nucleophile; E: Enamine activation; 1,4: iminium ion-mediated 1,4-addition.

Recently, the potential of organocascade catalysis has been further expanded to target more daunting synthetic objectives. Key to bringing this chemistry to the next level of efficiency and sophistication was the inclusion of *vinylogous reactivity*[14] as a new design principle for developing unprecedented asymmetric organocatalytic domino reactions. This has facilitated the rapid synthesis of complex chiral molecules while selectively forging multiple stereocenters at distant positions from the catalyst's point of action (Figure 1c).[15]

Central to pursuing this goal is the ability of chiral amine catalysts to propagate the electronic effects inherent to aminocatalytic reactivity modes (*i.e.* the HOMO-raising and the LUMO-lowering activating effects) through the conjugated π-system of poly-unsaturated carbonyls while transmitting the stereochemical information at distant positions. The fruitful combination of asymmetric aminocatalysis with the principle of vinylogy has expanded the chemists' ability to functionalize a carbonyl compound at distant positions such as the γ-,δ-, and ε-carbon atoms (Figure 2).[16]

On the one hand, the propagation of the HOMO-raising electronic effect (inherent to enamine activation) through the conjugated π-system of poly-unsaturated carbonyls has been used to induce vinylogous nucleophilicity in extended enamines. Dienamine (E^2)[17] and trienamine activations (E^3)[18] have accounted for the direct, stereoselective, and site-selective functionalization of unsaturated carbonyls at the γ and ε positions, respectively. On the other hand, the successful combination of the LUMO-lowering effect (inherent to iminium ion activation) with the vinylogy principle accounts for the direct and stereoselective functionalization with nucleophiles of unmodified carbonyl compounds at the remote δ-position (vinylogous iminium ion activation (1,6)).[19]

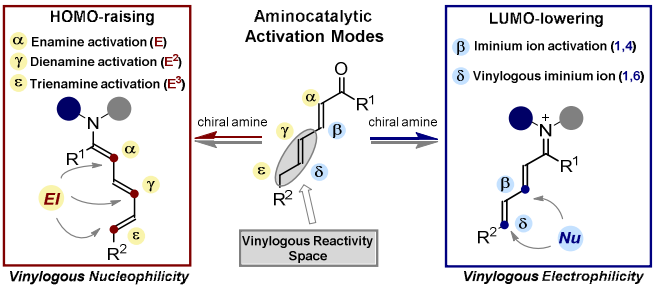


Figure 2. Established activation modes in aminocatalysis and the possibility of inducing vinylogous nucleophilicity and electrophilicity; the reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center; El: electrophile, Nu: nucleophile.

In this article, we discuss the many opportunities provided by the vinylogous aminocatalytic activation modes for the design of novel enantioselective organocascade reactions. The discussion is organized based on the nature of the initial vinylogous activation mode, which triggers the whole cascade sequence. After the condensation of polyunsaturated carbonyl compounds with a chiral amine catalyst, the HOMO-raising activation strategy brings about the formation of nucleophilic dienamine and trienamine intermediates, which can start a domino sequence upon reacting with an electrophile (E^2 or E^3-initated cascade, respectively). The LUMO-lowering activation, instead, would provide the electrophilic vinylogous iminium ion that can initiate a cascade by reacting with a nucleophile (1,6-initated cascade). We have decided to include enantioselective vinylogous cycloaddition reactions only when evidence supporting a stepwise mechanism was provided in the original studies.

2. HOMO-Raising Activation-Initiated Vinylogous Cascade Reactions

2.1 Sequential Dienamine-Iminium Ion Cascade Pathway

The propagation of the HOMO-raising electronic effect through a conjugated π-system of a poly-unsaturated carbonyl compound (dienamine catalysis, E^2) has found extensive use in vinylogous cascade reactions. Upon the condensation of a chiral aminocatalyst with an α,β-unsaturated carbonyl substrate, the transiently generated dienamine can attack a suitable electrophile to construct a new bond while leading to an electrophilic iminium ion (Figure 3). If an additional nucleophilic handle is present in the original substrate, a second intramolecular bond forming event can occur by means of an iminium ion-mediated conjugate addition (1,4). This dienamine-iminium ion cascade sequence (E^2-1,4) allows functionalization of a carbonyl compound at the γ- and β-position and it requires the intervention of the aminocatalyst in both bond forming steps .

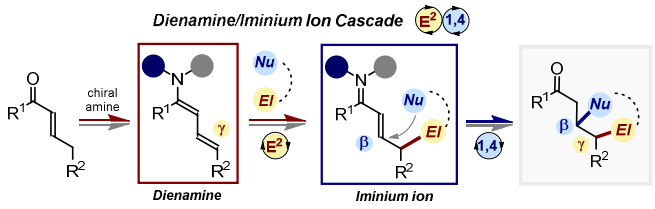
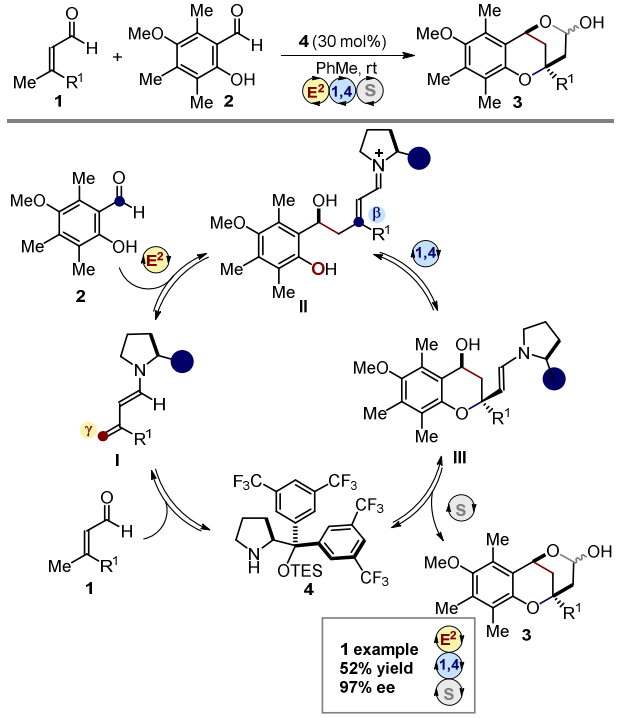


Figure 3. Dienamine (E^2) / iminium ion (1,4) cascade sequence; the blue and grey circles represent the chiral scaffolds of the aminocatalyst.

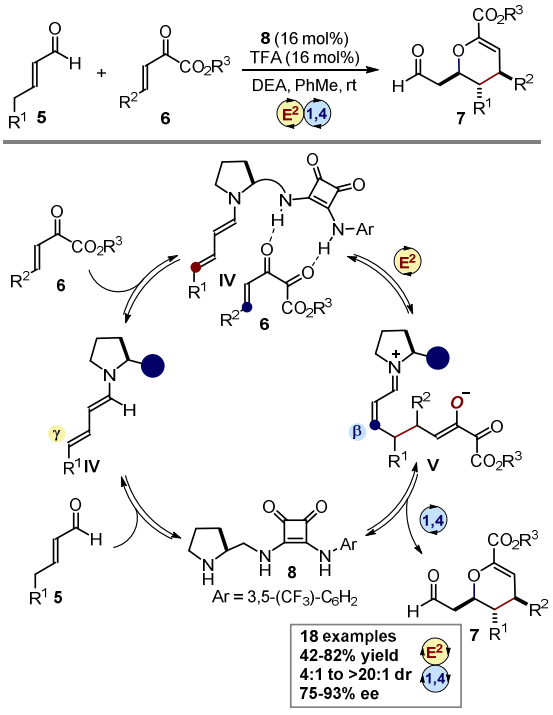
The first dienamine-iminium ion activation strategy (E^2-1,4 sequence) was reported by Woggon and co-workers in 2008 in the total synthesis of α-tocopherol (Scheme 1), one of the most significant members of the vitamin E family.[20] The process constructed the core of α-tocopherol through a three-step cascade, two of which were catalyzed by the chiral silyl prolinol aminocatalyst **4** (TES: triethylsilane).



Scheme 1. The first example of a dienamine/iminium ion cascade; E^2: dienamine; 1,4: iminium ion; S: spontaneous step. The blue circle represents the chiral scaffolds of the aminocatalyst **4**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

The reaction was triggered by the vinylogous aldol reaction between the terminal dienamine **I**, formed upon catalyst condensation with the β-methyl substituted enal **1**, and the salicyaldehyde derivative **2**. The resulting iminium ion intermediate **II** was then attacked by the phenolic oxygen in an *oxa*-Michael fashion to form a six-membered ring in **III**. Finally, following hydrolysis of the aminocatalyst, a third bond-forming step, namely a spontaneous (*S*) intramolecular acetalization, led to the formation of **3** with high stereofidelity, an advanced intermediate en route toward the synthesis of α-tocopherol. Following this preliminary report, Woggon and others have since utilized this vinylogous triple cascade process to synthesize an array of related natural products.[21]

The dienamine–iminium ion cascade pathway has also served for the rapid construction of six-membered rings (Scheme 2). Jørgensen and co-workers reported that the reaction of enals **5** with β,γ-unsaturated-α-ketoester **6**, proceeding through a vinylogous 1,4-addition/*oxa*-Michael sequence, provided dihydropyran derivatives **7** in good yields (42-82%) and enantioselectivities (75-92% ee).[22] Crucial for the successful development of the chemistry was the design of a bifunctional secondary amine-thiourea catalyst that combined hydrogen (H)-bond directing activation of the electrophile with the dienamine activation of enals to ensure high levels of enantio- and regio-selectivity. The bifunctional catalyst **8** was designed to facilitate the simultaneous activation of both α-ketoester **6** and enal **5** while positioning them in an advantageous three-dimensional assembly to ensure control over the trajectory of the approaching electrophile. This secured high levels of stereoinduction in the addition of the dienamine **IV** to the conjugate acceptor **6**. The resulting intermediate **V**, which featured both an iminium ion and an enolate functionality, eventually underwent a ring closure through an *oxa*-Michael reaction to furnish dihydropyrans **7**. Although this reaction can be considered as an inverse-electron-demand Diels-Alder reaction, theoretical calculations supported a stepwise process as the more likely pathway.[22]

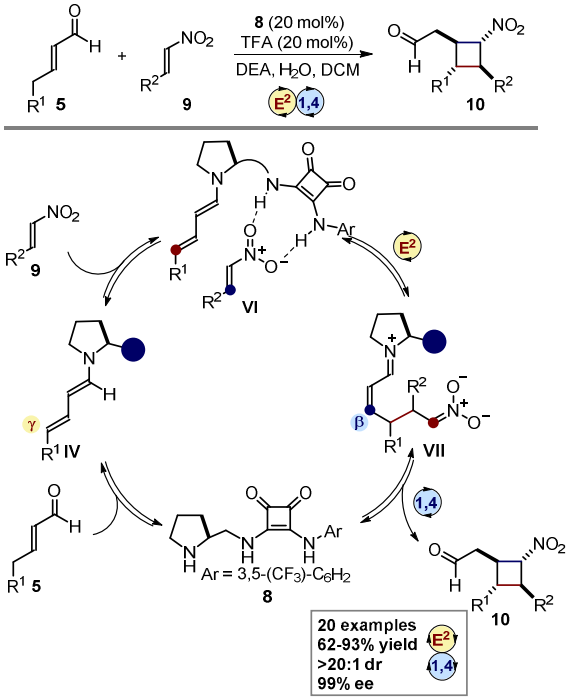


Scheme 2. Synthesis of dihydropyrans **7** through a E^2-1,4 cascade reaction facilitated by the bifunctional catalyst **8**. E^2: dienamine; 1,4: iminium ion; the blue circle in **IV** and **V** represents the chiral scaffolds of catalyst **8**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center. DEA: diethylamine; TFA: trifluroacetic acid.

As for the atom connectivity, the E^2-1,4 cascade sequence requires the enal substrate to act as a two carbon partner, with both new carbon-carbon bonds being formed in a 1,2-relationship.

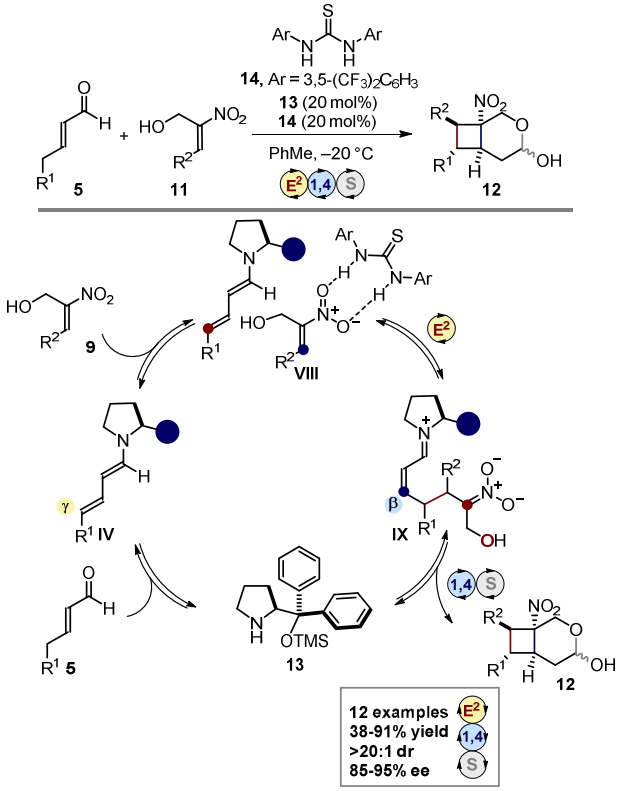
This means that, as seen in the previously discussed works (Schemes 1 and 2), the use of the four-atom partners **2** and **6** brings about the formation of six-membered ring products **3** and **7**, respectively, through a formal [4+2] reaction. However, cyclic products of different ring size can be prepared by purposely modulating the reacting partners. For example, a E^2-1,4 cascade strategy to form a four-membered ring through a formal [2+2] reaction can be envisaged when using a two carbon partner, such as nitroolefins **9** (Scheme 3). These compounds can act similarly to α,β-unsaturated carbonyl compounds **6**, but the enolate emerging from the dienamine-triggered Michael addition is unlikely to act as oxygen-centered nucleophile. Independently and concurrently, the group of Jørgensen[23] and Vicario[24] developed vinylogous E^2-1,4 cascade sequences that utilized nitroolefins to facilitate the formation of enantioenriched cyclobutanes.

In analogy to the cascade depicted in Scheme 2, Jørgensen used the bifunctional secondary amine-thiourea catalyst **8** to activate the nitroolefins **9** while ensuring a close proximity with the dienamine **IV** (Scheme 3).[23] The simultaneous activation of the two reacting partners secured a high stereofidelity in the first bond forming step (dienamine-driven conjugate addition) leading to the iminium ion intermediate **VII**. The nascent carbon-centered nucleophile then underwent an iminium ion-mediated conjugate addition to form cyclobutane **10** in good yields (62-93%) and perfect stereoselectivities (single diastereoisomer and 99% ee or greater).



Scheme 3. E^2-1,4 cascade reaction: use of a two-carbon electrophile **9** to access cyclobutanes **10** by means of a vinylogous formal [2+2] reaction. E^2: dienamine; 1,4: iminium ion; the blue circle represents the chiral scaffold of catalyst **8**. DEA: diethylamine; TFA: trifluroacetic acid.

A related but different approach was reported by Vicario and co-workers,[24] who used two distinct organocatalysts to mimic the action of the bifunctional catalyst **8**. Specifically, while the secondary amine **13** served to activate enal **5** through dienamine catalysis, the achiral thiourea catalyst **14** activated the nitroolefin **11** through H-bonding catalysis (Scheme 4). Although intermediate **VIII** does not feature the same level of three-dimensional organization achieved by a bifunctional catalyst, impressive levels of regio- and stereo-selectivity (85-95% ee) were achieved. Following the attack of the dienamine **IV** on the activated nitroolefin in **VIII**, the iminium ion intermediate **IX** is formed, which then drives the conjugate addition of the enolate in an intramolecular fashion. Finally, the hydrolysis of the aminocatalyst **13** (TMS: trimethylsilyl), and a spontaneous acetalization (*S*), furnishes the bicyclic product **12**.



Scheme 4. E^2-1,4 cascade reaction: synthesis of enantioenriched cyclobutanes using two distinct organocatalysts. E^2: dienamine; 1,4: iminium ion; S: spontaneous step; the blue circle represents the chiral scaffold of catalyst **13**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

2.2 Sequential Dienamine-Enamine Cascade Pathway

Vinylogous cascade reactions are not limited to functionalizing α,β-unsaturated aldehydes in a 1,2-fashion. Unusual functionalizations in a 1,3-relationship, namely at the α- and γ-position, have also been achieved. This strategy relies on a dual HOMO-raising activation pathway which combines a dienamine/enamine sequence (E^2-E, Figure 4). First, after condensation of a chiral aminocatalyst with an unsaturated carbonyl substrate, the resultant dienamine attacks an electrophile to form a transient iminium ion (not shown). However, γ-deprotonation returns a nucleophilic dienamine which can trap a second electrophile at the α-position. This E^2-E cascade reaction allows the functionalization of a carbonyl substrate at the

γ- and α- positions and relies on the aminocatalyst for both bond forming steps.

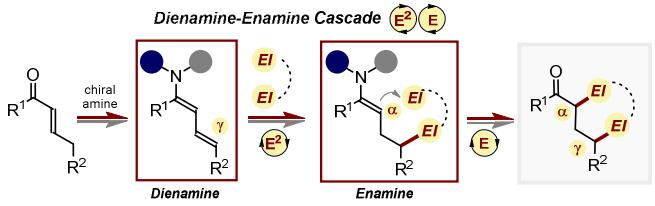
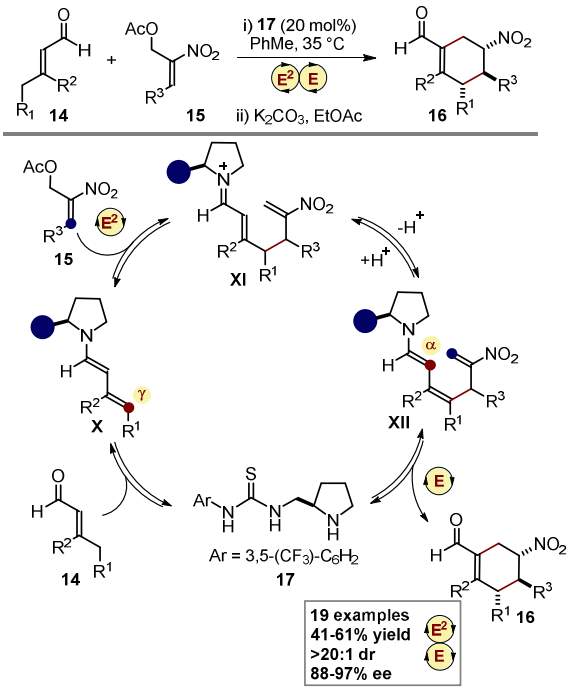


Figure 4. Dienamine (E^2) / enamine (E) cascade sequence; the blue and grey circles represent the chiral scaffolds of the aminocatalyst.

The main issue to address when designing this cascade is that the reaction partner, reacting with the dienamine, should feature two distinct electrophilic sites. Thus, it is essential to discriminate between them to ensure high levels of regioselectivity. Recently the first E^2-E cascade has been realized using enal **14** and a 2-acetoxymethyl nitroolefin **15** (Scheme 5).[25]



Scheme 5. Functionalization of the α- and γ- position of enals **14** through a dienamine (E^2) / enamine (E) cascade sequence. E^2: dienamine; E: enamine; the blue circle represents the chiral scaffold of the bifunctional catalyst **17**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

The substrate **15** avoids the issue of regioselectivity since the second electrophilic position is revealed only once the initial dienamine-triggered reaction has happened. Indeed, the first conjugate addition of the dienamine **X** to **15**, proceeding through an S_N2' pathway, efficiently generates the required second electron-poor alkene moiety in **XI** through the elimination of acetic acid. Deprotonation to form **XII** favours the subsequent enamine-mediated intramolecular conjugate addition (α-functionalization) to furnish the cyclohexene structures **16** in good yields (41-61%) and high enantiomeric excess (88-97% ee). The generally poor diastereomeric ratio of the process (about 2:1 dr) is ascribable to the low stereoselectivity of the protonation step in **XII**, which sets the stereocenter bearing the R^1 substituent. However, it was found that treating the products **16** with K_2CO_3 readily epimerized the stereocenter to exclusively afford the *trans*-adduct.

2.3. Sequential Dienamine-Spontaneous Cyclization Cascade Pathway

An alternative strategy to developing vinylogous cascade reactions is based on the use of a chiral aminocatalyst to only facilitate the formation of the first new bond, while a second spontaneous bond-forming step sequentially occurs (Figure 5). After condensation of an aminocatalyst with an unsaturated carbonyl substrate, the resultant dienamine attacks an electrophile (which can then reveal a nucleophilic moiety) to form the iminium ion intermediate. However, rather than an additional bond forming step at this point, hydrolysis of the catalysts creates a tethered carbonyl intermediate, which can then undergo a range of different spontaneous, non-catalyzed ring closing reactions to complete the cascade sequence (E^2-S). Although this strategy does not involve the chiral aminocatalyst for both bond-forming steps, the stereochemical information encoded during the first dienamine step ensures high stereofidelity in the second spontaneous reaction, leading to products with high levels of stereocontrol. This approach lacks the complementary activation seen in the E^2-1,4 and E^2-E cascades but it is still a powerful synthetic tool for the construction of multiple bonds in one step.

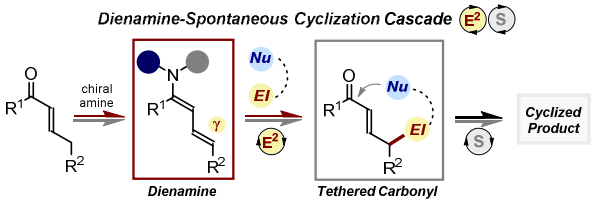
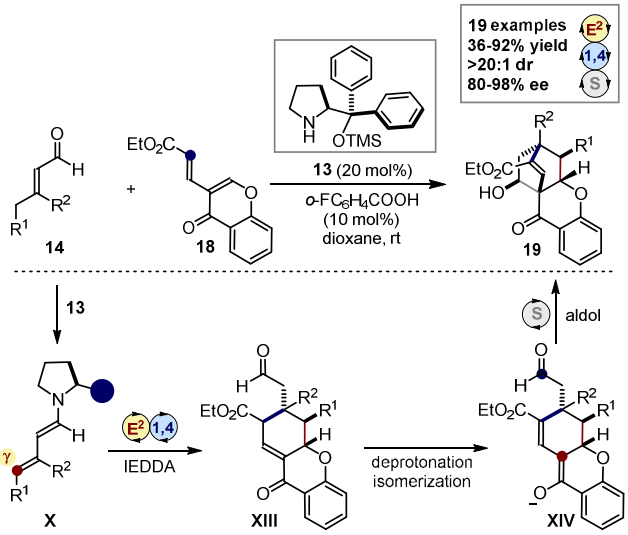


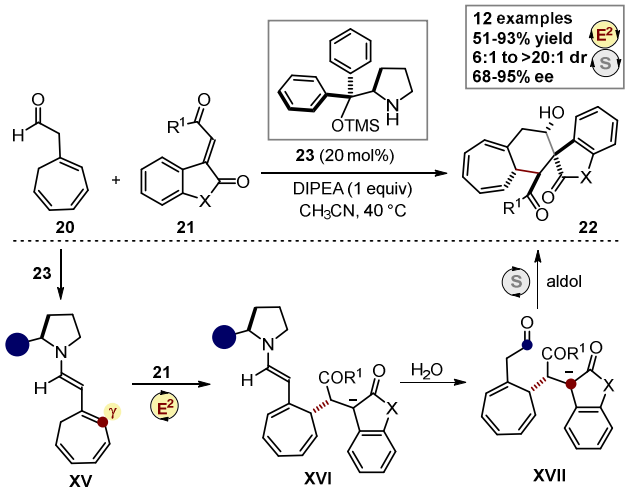
Figure 5. Dienamine(E^2)/spontaneous (S) non-catalyzed cyclization cascade pathway; the blue and grey circles represent the chiral scaffolds of the aminocatalyst.

Given the presence of an aldehydic moiety in the products of aminocatalytic vinylogous cascades, the most commonly reported spontaneous step is an intramolecular aldol reaction. The first vinylogous cascade of this type involved the reaction of the enal **14** with a diene **18** to form tetracyclic skeletons **19** (Scheme 6).[26] The mechanism is proposed to proceed as follows: the dienamine **X** participates in an inverse electron demand Diels-Alder reaction with **18** (this step can also be envisaged as a E^2-1,4 reaction sequence). After hydrolysis of the chiral aminocatalyst **13**, isomerization and deprotonation of the newly formed intermediate **XIII** generates the enolate **XIV**, which undergoes an intramolecular aldol reaction to form product **19** in high yields (36-92%) and enantiomeric excess (80-98% ee).



Scheme 6. Dienamine-spontaneous cyclization (E^2-S) cascade sequence for the construction of tetracyclic products. The non-catalyzed step is an intramolecular aldol reaction; E^2: dienamine; 1,4: iminium ion; S: spontaneous step. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

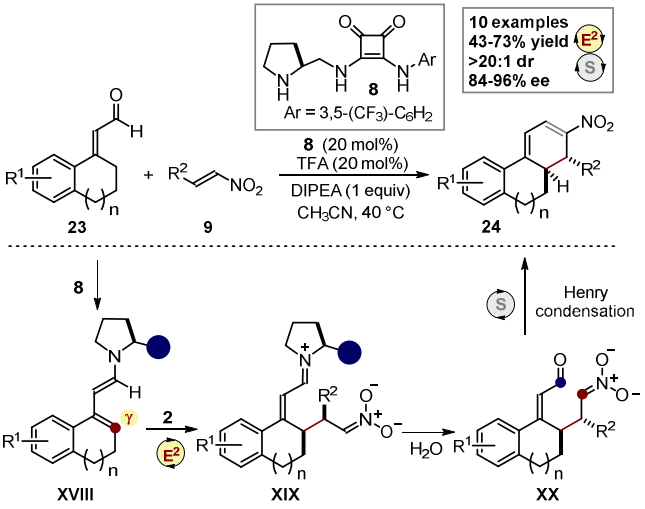
The strategy of employing an aldol condensation in a E^2-S cascade sequence was also used in conjunction with tetraenamine intermediates **XV** formed upon condensation of the aminocatalyst **23** with enal **20** (Scheme 7).[27] Although these species have the potential to react at very remote positions, they were found to selectively react at the γ-position. The reaction of **XV** with electrophilic 3-olefinic oxindoles **21** led to the formation of spirocyclic products **22** through a E^2-S vinylogous cascade.



Scheme 7. Dienamine-spontaneous cyclization (E^2-S) cascade sequence to form spirocyclic products. The non-catalyzed step is an intramolecular aldol reaction; E^2: dienamine; S: spontaneous step. The blue circle represents the chiral scaffolds of the aminocatalyst. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center. DIPEA: N,N-diisopropylethylamine.

Mechanistically, the nucleophilic tetraenamine **XV** attacks the Michael acceptor **21**. After hydrolysis of the aminocatalyst, the intermediate **XVII**, which contains both an aldehyde and an enolate, experiences an intramolecular aldol pathway to give **22** in good yields (51-93%), diastereomeric (86:14 to >20:1), and enantiomeric excess (68-95% ee).

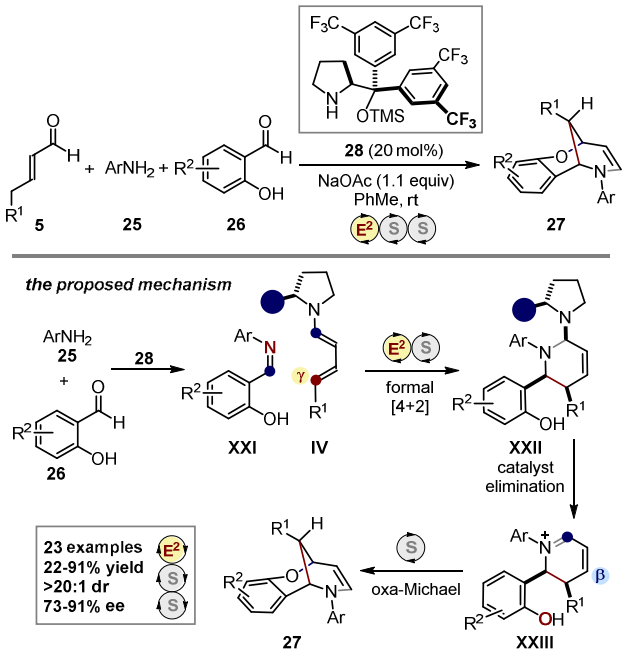
E^2-S cascade reactions often feature very similar intermediates to E^2-1,4 cascade sequences. The reasons why a reaction proceeds through a E^2-S pathway instead can be subtle, and often ascribable to differences in the substrate´s electronic and steric characteristics. For example, the cascade sequence illustrated in Scheme 8 appears, at first glance, very similar to the cascade illustrated in Scheme 3: it is indeed a reaction between an enal (**23** or **5**) and nitroolefin **9** in the presence of the bifunctional amine-thiourea catalyst **8**.[28] However, it the case of Scheme 3 the reaction proceeds through a E^2-1,4 cascade sequence to form the formal [2+2] cyclobutane product **10** while in Scheme 8 the reaction proceeds through a E^2-S cascade affording the six-membered ring **24**. This divergent pathway can be attributed to the nature of the cyclic intermediate **XIX**. After nucleophilic attack of dienamine **XVIII** to nitroolefin **9**, the β-position of the cyclic iminium ion **XIX** is not sufficiently electrophilic to permit the conjugate addition of the α-nitro anion, due to the steric hindrance of the β,β-disubstitution pattern. This, along with the conformational constraints enforced by the cyclic structure of **XIX**, channels the process through a different pathway. Following hydrolysis of catalyst **8**, the α-nitro anion undergoes a spontaneous Henry condensation, forming product **24** in moderate yields (43-73%) and good enantiomeric excess (84-96% ee).



Scheme 8. Dienamine-spontaneous cyclization (E^2-S) cascade between enal **23** and nitroolefin **9**. The non-catalyzed step is an intramolecular Henry condensation; E^2: dienamine; S: spontaneous step. The blue circle represents the chiral scaffolds of the aminocatalyst. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center. DIPEA: N,N-diisopropylethylamine.; TFA: trifluroacetic acid.

E^2-S cascade reactions can also be utilized to rapidly construct structurally complex molecules through multiple bond forming events. This strategy served for the synthesis of bridged benzoxazocines **27** by means of a one-pot vinylogous cascade reaction (Scheme 9).[29] A multicomponent reaction between an aniline **25**, a salicylaldehyde **26**, and an enal **5** resulted in the formation of four new bonds and featured an unique γ,δ,*ipso*-

functionalization of enal **5**. The reaction is proposed to proceed as follows: condensation of aniline **25** and salicylaldehyde **26** forms the aromatic imine **XXI**, while condensation of the chiral aminocatalyst **28** and enal **5** forms the dienamine **IV**. These two intermediates undergo a stepwise Mannich-initiated formal *aza*-[4+2] cyclization to form the cyclic six-membered intermediate **XXII**. Elimination of the aminocatalyst **28** renders the achiral iminium ion **XXIII**. Last, an *oxa*-Michael reaction furnishes the product **27** in good yield (22-91%) and enantioselectivities (73-91% ee, Scheme 9).



Scheme 9. The formation of structurally complex benzoxazocines **27** through a E^2-S-S reaction sequence. The non-catalyzed step is an intramolecular *oxa*-Michael reaction; E^2: dienamine; S: spontaneous step. The blue circle represents the chiral scaffolds of the aminocatalyst. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

2.4. Extending the HOMO-Raising Activation Strategy Beyond the γ-Position

Condensation of an aminocatalysts with an α,β,γ,δ-unsaturated aldehyde forms a trienamine intermediate which can extend the HOMO-raising activation further into the vinylogous reactivity space, well beyond the γ position. Trienamines feature similar reactivity profiles as the related enamine and dienamines and can facilitate functionalization at ε carbon atom.[16a] Although the field of vinylogous cascade reactions using trienamine catalysis is far less developed than the corresponding dienamine field, some examples have been reported. These cascade sequences are based upon the trienamine/iminium ion (E^3-1,4) pathway illustrated in Figure 6.

The earliest example of a E^3-1,4 cascade sequence was detailed in 2013[30] with the trienamine-catalyzed *aza*-Diels-Alder process between the interrupted 2,5-dienones **28** and α,β-unsaturated imines **29** in the presence of the cinchona-based primary amine catalyst **31**[31] (Scheme 10).

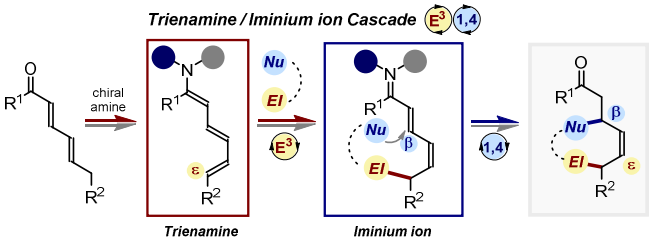
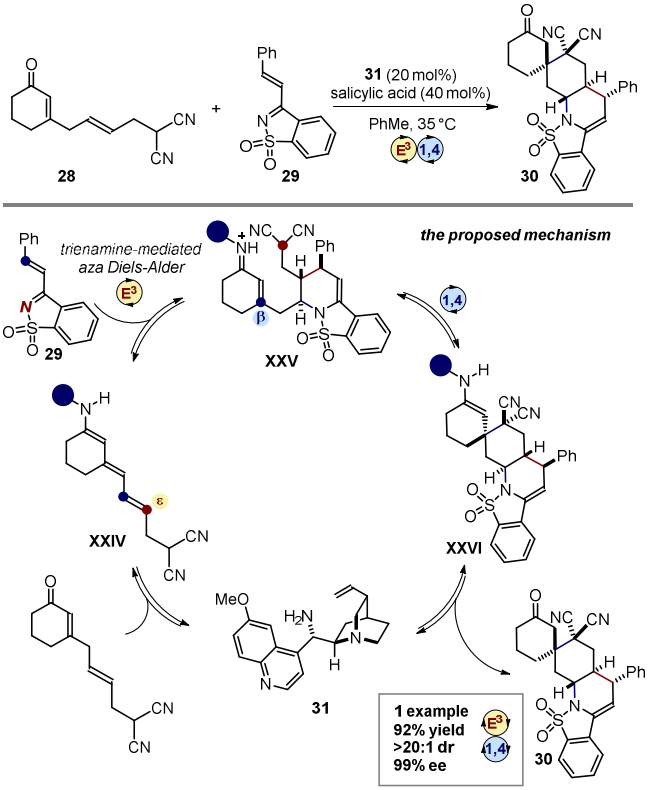


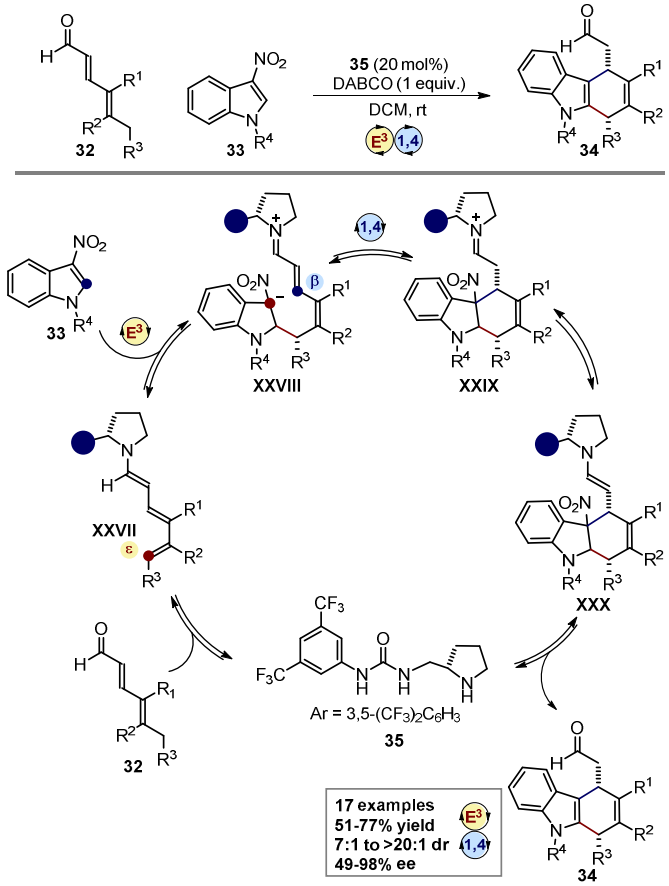
Figure 6. Trienamine (E^3) / iminium ion (1,4) cascade sequence; initial HOMO-raising activation event at the ε-position, followed by a complementary LUMO-lowering event. The blue and grey circles represent the chiral scaffolds of the aminocatalyst.

It was found that tethering a Michael donor to the interrupted dienone **28** resulted in a E^3-1,4 cascade sequence to generate spirocycle **30** in 92% yield, 99% ee, and as a single diastereomer. The trienamine intermediate **XXIV** was formed through condensation of the cinchona-based primary amine catalyst **31** with skipped dienone **28** and this intermediate served as diene for an inverse electron-demand *aza*-Diels-Alder with imine **29** to form the intermediate **XXV** (this step, if stepwise, can also be seen as a E^3-1,6 sequence). Deprotonation of the acidic proton in the malononitrile moiety resulted in an iminium ion-mediated addition to form the intermediate **XXVI**, which after catalyst hydrolysis afforded the product **30**.[30]



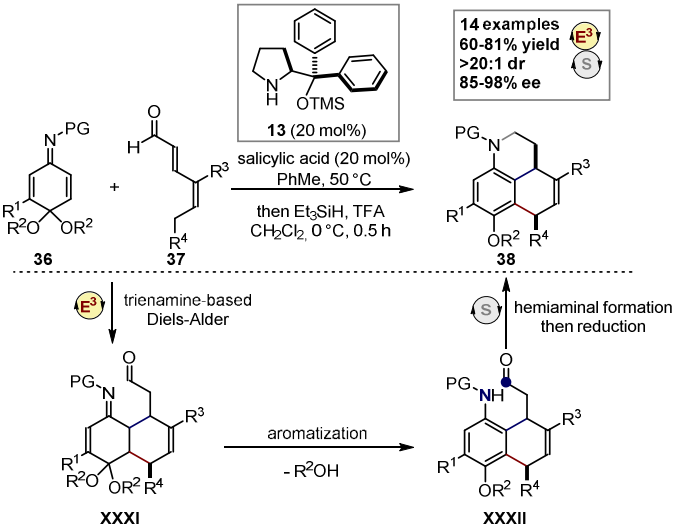
Scheme 10. The first trienamine-initiated vinylogous cascade reaction: E^3-1,4 reaction sequence; E^3: trienamine; 1,4: iminium ion. The blue circle represents the chiral scaffold of the cinchona-based primary amine catalyst **31**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

Very recently, the E^3-1,4 cascade strategy has been utilized in the formal [4+2] reaction between a nitroindole **33** and an α,β,γ,δ-unsaturated aldehyde **32** catalyzed by a bifunctional catalyst **35** to furnish the tricyclic products **34** (Scheme 11).[32] The condensation of the aminocatalyst **35** with enal **32** leads to the formation of the trienamine **XXVII**, while simultaneously the urea moiety within **35** activates the nitroolefin **33** through H-bonding interaction. This double activation manifold promotes the trienamine-driven conjugate addition to form the iminium ion **XXVIII**. The resultant α-nitro anion attacks the electrophilic iminium ion to form the intermediate **XXIX**. Finally, elimination of the nitro group and rearomatization of the indole nucleus leads to the formation of the product **34** in good yields (51-77%) and enantioselectivities (49-98% ee).



Scheme 11. The formation of cyclic products **34** through E^3-1,4 cascade reaction. E^3: trienamine; 1,4: iminium ion. The blue circle represents the chiral scaffold of the bifunctional amine-thiourea catalyst. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

It has also been possible to develop a trienamine-initiated vinylogous cascade reaction of the E^3-S type. The use of the chiral secondary amine catalyst **13** triggered the formation of tricyclic benzo[*de*]quinolone products **38** from quinone imine ketals **36** and 2,4-dienals **37** through a E^3-S pathway in good yields (60-81%) and enantiomeric excess (85-98% ee, Scheme 12).[33] The cascade sequence is initiated by the condensation of catalyst **13** with enal **37** to form a reactive trienamine which then participates in a Diels-Alder reaction to furnish the [4+2] adduct **XXXI**. Aromatization of this intermediate through elimination of an alcohol forms the quinolone core **XXXII**, which undergoes a final spontaneous cyclization. The resulting hemi-acetal (not shown in Scheme 12) is reduced *in situ* to aid isolation of the product **38**.



Scheme 12. E^3-S cascade sequence to generate quinolones; E^3: trienamine; S: spontaneous step. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

3. Vinylogous Iminium Ion-Initiated Cascade Reactions

In 2012, our research group became interested in the possibility of transmitting the LUMO-lowering activating effect, inherent to iminium ion catalysis (1,4), through the conjugated π-system of polyunsaturated carbonyl compounds, in order to realize a direct nucleophilic 1,6-addition. The difficulty of this goal becomes apparent when considering that the larger π-orbital LUMO coefficient and the more positive Mulliken atomic charge of extended iminium ions reside at the β carbon atom, thus explaining the intrinsic preference for a nucleophilic 1,4-addition manifold.[19b] The requirement for the chiral catalyst to forge a remote stereocenter with high fidelity while inducing exclusive δ-site selectivity in the 1,6-addition manifold further complicates matters. We have found, however, that when a cinchona-based primary amine catalyst condenses with β-substituted cyclic dienones, it determines the formation of an extended iminium ion intermediate (Figure 7), with an enhanced electrophilic character at the δ-carbon atom. The resulting vinylogous iminium ion activation (1,6) was used to develop an asymmetric organocatalytic 1,6-addition of alkyl thiols to cyclic α,β,γ,δ-unsaturated dienones **39** proceeding with high stereocontrol and δ-site selectivity.[19a] Crucial for success was *i*) the unique ability of a cinchona amine of type **40** to stereochemically bias intermediary cyclic species thus ensuring highly predictable reaction outcomes along with *ii*) the inherent steric bias of the β-substituent in **39**, which provided a useful steric element for securing δ-site selectivity by suppressing the competing 1,4-addition manifold. The development of the vinylogous iminium ion

activation provided new opportunities for the design of novel cascade reactions.

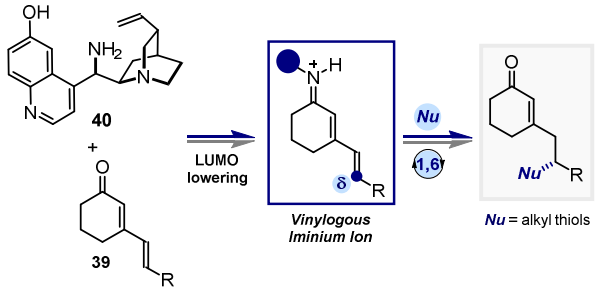


Figure 7. Asymmetric 1,6-additions to cyclic dienones **39** mediated by vinylogous iminium ion activation (1,6). The blue circle represents the chiral scaffold of the cinchona-based primary amine catalyst.

3.1 Sequential Vinylogous Iminium Ion/Dienamine Cascade Pathway

The identification of the vinylogous iminium ion activation allowed the design of more complex cascade reactions upon combination with other aminocatalytic activation modes. For example, the condensation of the chiral aminocatalyst generates an extended iminium ion which can facilitate a nucleophilic attack at the δ position (1,6). After this addition, a nucleophilic dienamine intermediate is transiently formed. If an electrophilic position is present in the original substrate, a second intramolecular bond forming event can occur under dienamine activation (E^2, Figure 8). The vinylogous iminium ion-dienamine (1,6-E^2) cascade accounts for the functionalization of a α,β,γ,δ-unsaturated carbonyl compound at the δ- and γ-position while relying on the chiral aminocatalyst for both bond forming steps.

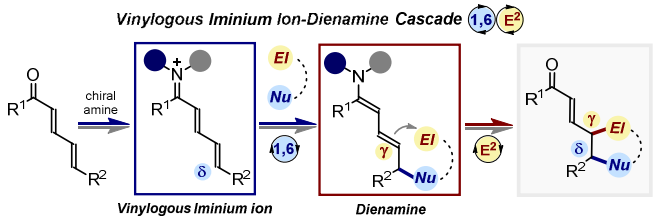
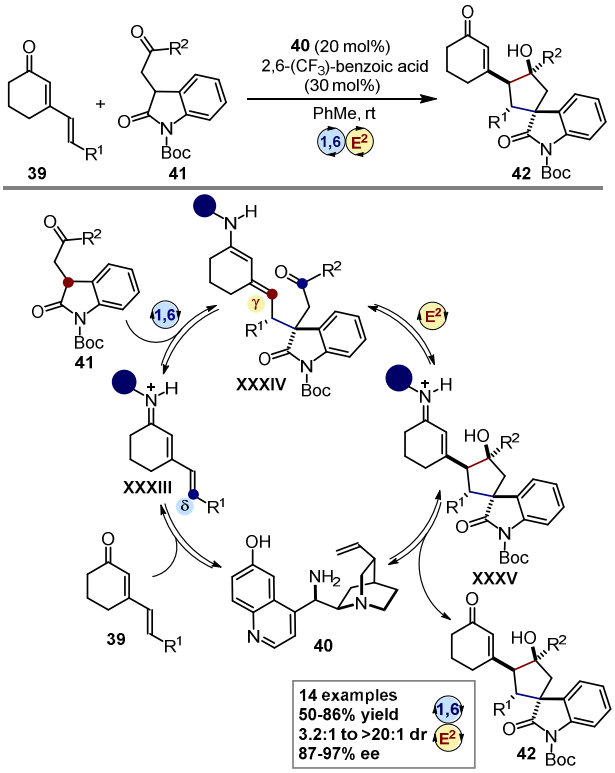


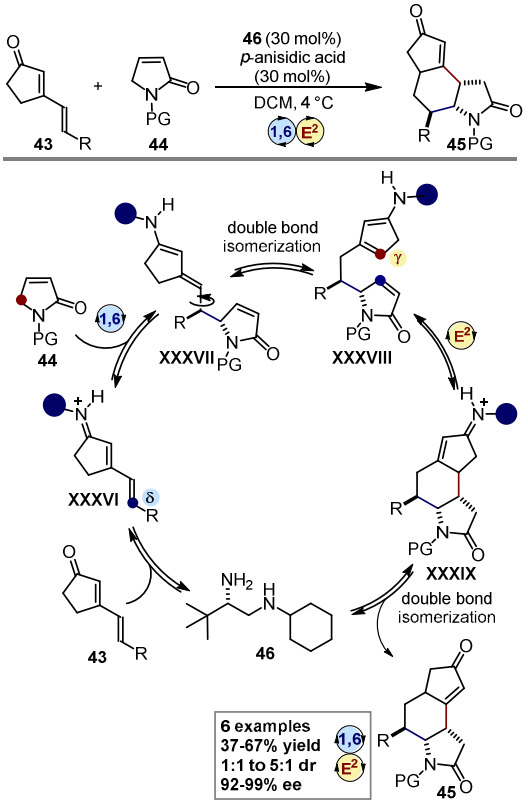
Figure 8. Vinylogous iminium ion (1,6)/dienamine (E^2) cascade pathway; the blue and grey circles represent the chiral scaffolds of the aminocatalyst.

The first example of 1,6-E^2 cascade capitalized upon the already discussed ability of the cinchona-based primary amine catalyst of type **40** to condense with β-substituted cyclic dienones **39** while controlling the geometry of the reactive cyclic iminium ion intermediate **XXXIII**. We recognized that a well-suited substrate, characterized by a dichotomous reactivity profile, was crucial to realizing a cascade process. On the basis of the inspiring studies by Carlos Barbas III,[34] the 3-substituted oxindole **41** seemed well-tailored to first act as a carbon-centered nucleophile and then to develop, after the δ-site 1,6-addition, an electrophilic behavior (Scheme 13). The pendant carbonyl moiety within the transiently generated nucleophilic dienamine intermediate **XXXIV** did drive an intramolecular aldol reaction, resulting in a fast cyclization. The product of the vinylogous cascade reaction, which is based on a δ-addition/aldolization sequence, is a complex spirocyclopentane oxindole **42** bearing four contiguous stereocenters and a preserved α,β-unsaturated carbonyl system.[35]



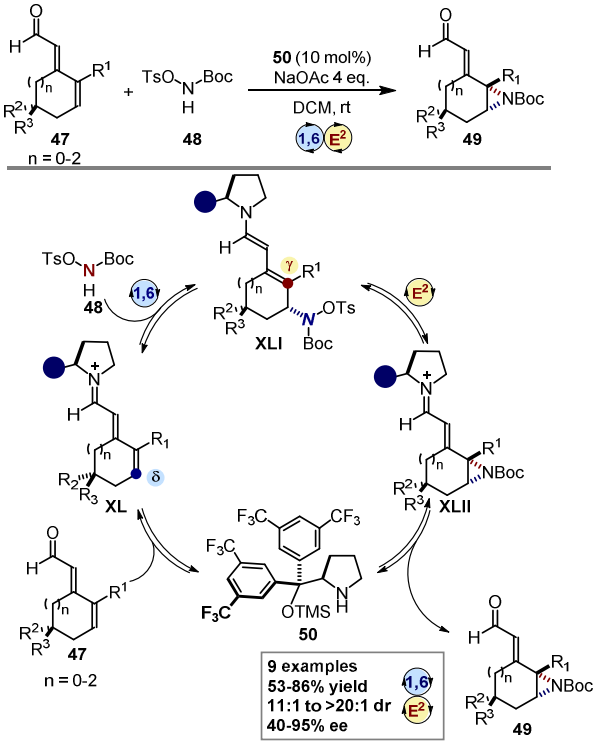
Scheme 13. The first report of a 1,6-E^2 cascade sequence; 1,6: vinylogous iminium ion; E^2: dienamine. The blue circle represents the chiral scaffold of the cinchona-based primary amine catalyst. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

Building upon this precedent, Dixon, Ye and co-workers developed, in 2015, a vinylogous organocascade reaction employing five-membered cyclic dienones **43** and *N*-protected pyrrolinones **44**.[36] The process, promoted by the chiral primary amine catalyst **46**, furnished enantioenriched tricyclic γ-lactams **45** in moderate chemical yields (37-67%) and diastereocontrol and a high level of enantiocontrol (92-99% ee, Scheme 14). A non-trivial reaction mechanism was proposed: After the vinylogous iminium ion formation and the subsequent 1,6-addition reaction, an isomerization of the transient dienamine intermediate **XXXVII** takes place driven by the formation of the corresponding iminium ion intermediate (not shown). The newly formed internal dienamine **XXXVIII** is now well positioned to undergo an intramolecular Michael addition forming the second carbon-carbon bond. Migration of the C-C double bond in **XXXIX** to the other side of the carbonyl group (ascribable to an isomerization via the dienamine of cyclopentenone presumably driven by the thermodynamic stability of the product) furnished, after hydrolysis and liberation of the catalyst, the final tricyclic product **45**.



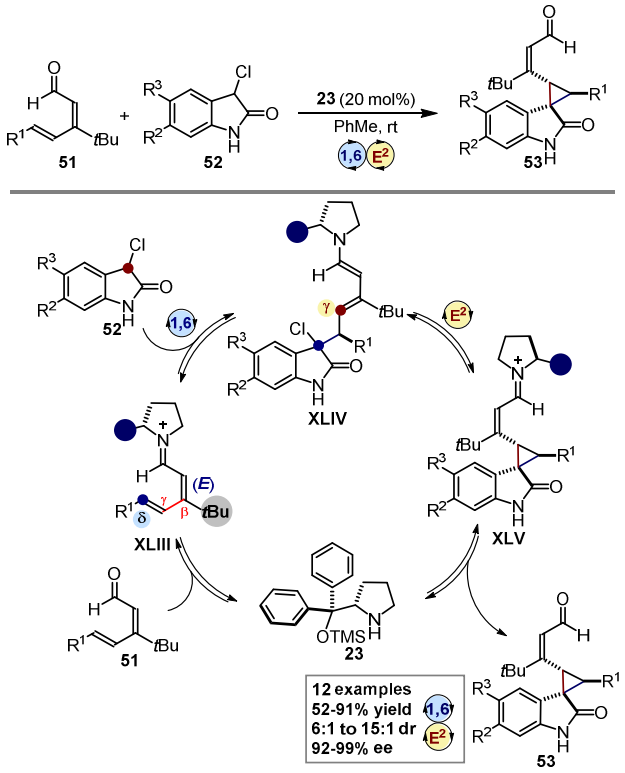
Scheme 14. Synthesis of tricyclic products **45** through a 1,6-E^2 cascade reaction; 1,6: vinylogous iminium ion; E^2: dienamine. The blue circle represents the chiral scaffold of the aminocatalyst **46**. PG: protecting group. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

The concept of vinylogous organocascade reaction based on 1,6-addition/dienamine chemistry was then successfully extended from cyclic enone to cyclic enals. In 2013, Jørgensen and co-workers reported an enantioselective remote aziridination reaction, based on the 1,6-E^2 sequence.[37] Extended cyclic 2,4-dienals of type **47** formed the vinylogous iminium ion *in situ* which later underwent 1,6-addition from the nitrogen-centered nucleophile **48**, resulting in the formation of the dienamine **XLI**. An intramolecular S_N2 process, facilitated by the leaving group (TsO-), led to the aziridinated iminium ion **XLII**. Hydrolysis of **XLII** afforded the desired aziridine **49** in good yields, excellent diastereoselectivity, and moderate to excellent enantiocotrol (40-95% ee).



Scheme 15. Remote aziridination of cyclic enals by means of a 1,6-E^2 cascade reaction; 1,6: vinylogous iminium ion; E^2: dienamine. The blue circle represents the chiral scaffold of the aminocatalyst **50**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

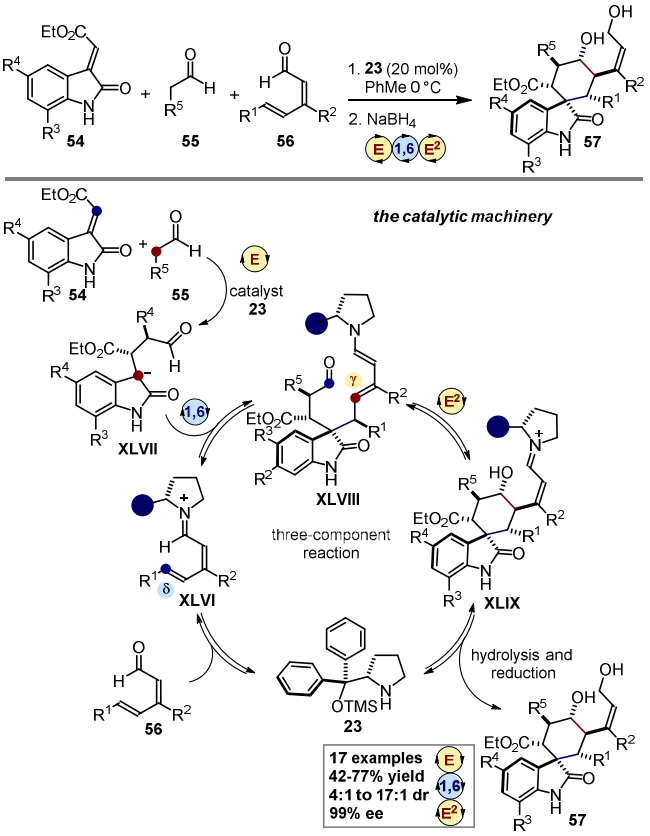
Although the 1,6-E^2 sequence demonstrated its usefulness for the implementation of vinylogous cascade strategies, as highlighted in Schemes 13-15, the synthetic potential of the approach was limited by the need for a cyclic substrate. Clearly, the use of a *linear* α,β,γ,δ-unsaturated carbonyl compound would provide a tool for designing more flexible and synthetically relevant vinylogous cascade reactions. However, the successful realization of this plan was far from easy since controlling the site and stereo-selectivity in the initial 1,6-addition reactions of linear substrates poses more than a conundrum. As a matter of fact, it is easier for a chiral amine catalyst to stereochemically bias the geometry of a cyclic vinylogous iminium ion intermediate than a linear counterpart. Such geometrical control is generally essential for securing selectivity. We found, though, that the presence of a steering group at the β-position of linear 2,4-dienals accounted for a perfect δ-site selective 1,6-addition reaction. This was critical to the design of a 1,6-E^2 process proceeding by way of an aminocatalyzed 1,6-addition/vinylogous S_N2 sequence (Scheme 16). The notion that a suitable reaction partner for the cascade requires the ability of the substrate of acting as both a nucleophile and an electrophile suggested 3-chlorooxindole **52** as a potential substrate. The resulting cascade provided a straightforward access to a range of chiral cyclopropane spiro-oxindoles **53**.[38]



Scheme 16. Synthesis of cyclopropane spiro-oxindoles **53** by means of a 1,6-E^2 cascade reaction with linear dienals; 1,6: vinylogous iminium ion; E^2: dienamine. The blue circle represents the chiral scaffold of the aminocatalyst **23**. The grey circle in **XLIII** highlights the importance of the *tert*-butyl moiety as a steering group.

The reaction relies on the activation of the extended dienal **51** by means of vinylogous iminium ion formation **XLIII**. The presence of a bulky *tert*-butyl substituent at the β-position was essential to secure high levels of both regio- and stereoselectivity. Specifically, the *tert*-butyl group, serving as a steering group, directed the nucleophilic attack of **52** to the less congested δ-carbon while controlling the molecular topology of the extended iminium ion **XLIII**. NMR spectroscopic studies indicated that the dominant ground-state conformer in solution has an *E*,*E*,*E* topology, with the same configuration for the three double bonds in **XLIII**. The steric prominence of the *tert*-butyl group makes it a topologically dominant element that can enforce an uncommon *s*-cis conformation around the single C(β)-C(γ) bond (highlighted in red in **XLIII**, Scheme 16). Collectively, these features contribute to a highly preorganized, configurationally stable, transient intermediate **XLIII**, which was crucial to reaction development. Indeed, the chiral fragment within the catalyst **23** was positioned close enough to the reactive δ-carbon to determine an effective shielding of the *Re* face of the extended iminium ion **XLIII**, leaving the opposite *Si* face available for the approach of the 2-chlorooxindole **52**. The resulting dienamine intermediate **XLIV** then underwent an intramolecular nucleophilic substitution affording, after hydrolysis, the cyclopropane spiro-oxindole **53** in good yields and high levels of stereocontrol.

The next step in further expanding the versatility of vinylogous iminium ion-initiated cascades was to overcome the need for carefully designed substrates. Indeed, the first step of the previously developed 1,6-E^2 sequences all required the generation of a multifunctional intermediate able to successively undergo an *intramolecular* process. The possibility of using *linear* polyunsaturated carbonyl compounds, though, provided a more flexible tool for designing more complicated cascade reactions based on *intermolecular* and stereoselective bond-forming events. Specifically, a three-component domino process proceeding by way of an aminocatalyzed Michael addition/1,6-addition/vinylogous aldolization sequence, which combines two intermolecular and one intramolecular bond-forming event, was developed. The triple vinylogous organocascade yielded valuable spiro-oxindolic cyclohexane derivatives **57** with six stereogenic centers and very high control over the stereochemistry (from 4:1 to 17:1 dr, 99% ee, Scheme 17).[39,40]



Scheme 17. The vinylogous triple cascade proceeds by way of an enamine (E)/vinylogous iminium ion (1,6)/dienamine activation (E^2) sequence; E: enamine; 1,6: vinylogous iminium ion; E^2: dienamine. The blue circle represents the chiral scaffold of the aminocatalyst **23**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

The triple cascade process is based on complicated catalytic machinery, which is largely based on vinylogous reactivity. An enamine-catalyzed Michael addition of the aldehyde **55** to the alkylidine oxindole acceptor **54** leads to the transient formation of the nucleophilic intermediate **XLVII**. The nucleophile can then engage in the γ-site selective *intermolecular* 1,6-addition, upon vinylogous iminium ion activation of the β-substituted 2,4-dienal

56, to forge the spiro-stereocenter. The transient formation of a nucleophilic dienamine **XLVII** drives an intramolecular vinylogous aldolization to provide the final cyclohexane product **57**.

3.2 Sequential Vinylogous Iminium Ion/Iminium Ion Cascade Pathway

Vinylogous iminium ion-initiated vinylogous cascade processes are not limited to the functionalization of α,β,γ,δ-unsaturated carbonyl compounds at the adjacent δ and γ carbon atoms. Stereoselective functionalization of the δ- and β-carbons can also be accomplished when using a dual LUMO-lowering activation sequence, specifically a vinylogous iminium ion /iminium ion pathway (1,6/1,4 cascade, Figure 9). After condensation of the carbonyl compound with a chiral aminocatalyst, the resultant vinylogous iminium ion is intercepted by a nucleophile affording, in analogy to the precedent 1,6-E^2 sequence, a dienamine intermediate. At this point, protonation of the dienamine results in the formation of an iminium ion intermediate that can trap a second nucleophilic species. If the original substrate features a second nucleophilic site, an additional bond formation follows under the control of the chiral catalyst. This vinylogous iminium ion/iminium ion (1,6-1,4) cascade reaction allows functionalization of a carbonyl at the δ- and β- positions and relies on the chiral aminocatalyst for both bond forming steps.

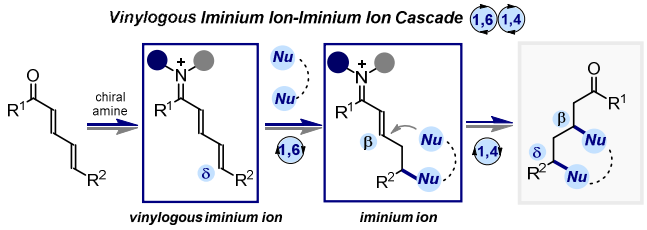
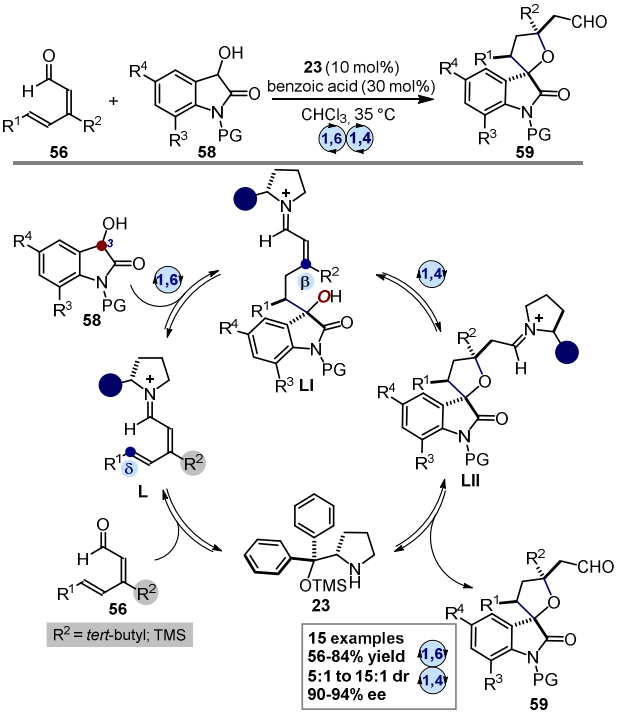


Figure 9. Vinylogous iminium ion (1,6)/iminium ion (1,4) cascade pathway; the blue and grey circles represent the chiral scaffolds of the aminocatalyst.

When planning a vinylogous iminium ion-initiated cascade reaction of a linear polyunsaturated carbonyl compound, the main difficulty is that the chiral catalyst must forge a remote stereocenter with high fidelity while inducing exclusive δ-site selectivity in the initial 1,6-addition. This is strictly dependent on the ability of controlling the molecular topology of the acyclic intermediate, so as to ensure highly predictable reaction outcomes. As discussed in the precedent section, the use of the linear 2,4-dienals **56**, bearing a *tert*-butyl steering group at the β position, ensured molecular preorganization of the catalytically active vinylogous iminium ion intermediate (Scheme 18). The presence of such steric control element resulted in only the conformationally stable *E*,*E*,*E* iminium ion isomer **L** forming, and this turned out to be key for achieving high selectivity. The use of 3-hydroxyoxindoles **58**, which is characterized by a bidentate nucleophilic profile (both the C3 carbon and the oxygen atom are nucleophilic sites), allowed the realization of a 1,6/1,4 cascade with enals **56**.[41] This process, which is based on a highly regio- and stereoselective 1,6-addition/*oxa*-Michael sequence, directly afforded tetrahydrofuran spirooxindole derivatives **59**. Mechanistically, the reaction proceeds through the formation of the *E*,*E* iminium ion isomer **L**, which drives a selective 1,6-addition of the nucleophilic carbon within **58** to form the iminium ion intermediate **LI**. Then, the hydroxyl group participates in an intramolecular *oxa*-Michael process leading to the final spirocyclic adduct **59**.

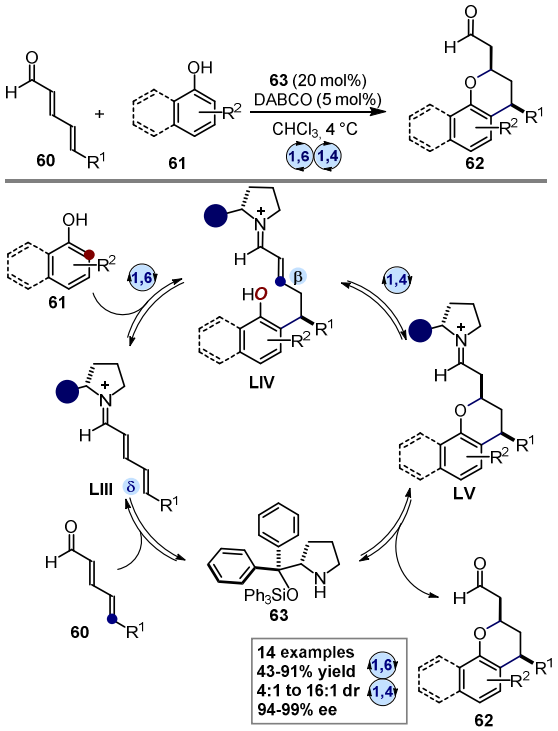


Scheme 18. Synthesis of tetrahydrofuranyl spirooxindoles **59** by means of a 1,6-1,4 cascade reaction with linear dienals; 1,6: vinylogous iminium ion; 1,4: iminium ion. The blue circle represents the chiral scaffold of the aminocatalyst **23**. The grey circle in **L** highlights the importance of the bulky R^2 substituent as a conformational anchor; TMS: trimethylsilyl; PG: protecting group. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

Remarkably, the presence at the β position of the dienal substrate **56** of a trimethylsilyl group, characterized by a similar Charton steric parameter[42] of a *tert*-butyl moiety, directed the process exclusively toward a 1,6-addition manifold while preserving the high enantioselectivity. This result further highlights how strongly the steric profile of the β-substituent in **56** is connected with an effective control over the molecular topology of the vinylogous iminium ion intermediate. Synthetically, it is worth noting that the trimethylsilyl group could be eventually removed upon protiodesilylation under basic conditions, which makes the trimethyl silyl moiety a traceless directing group to achieve δ-site selectivity, providing a formal 1,6-addition of geometrically unbiased, linear dienals.

Recently, Jørgensen and coworkers reported that different types of naphthols **61** were suitable substrates for the 1,6-1,4 vinylogous cascade process with linear, completely unbiased enals **60** (Scheme 19).[43] Mechanistically, a Friedel–Crafts 1,6-addition reaction of hydroxyarenes to a vinylogous iminium ion intermediate **LIII** and subsequent *oxa*-Michael addition to the iminium ion **LIV** formed in the first step led to chromans **62** with high stereofidelity. Importantly, no substituents on the 2,4-dienal **60** are required to ensure complete remote selectivity in the first step. Computational studies suggested that the δ-site selectivity

is driven by thermodynamic control of the Friedel–Crafts reaction step.



Scheme 19. 1,6-1,4 cascade reaction with linear, completely unbiased dienals; 1,6: vinylogous iminium ion; 1,4: iminium ion. The blue circle represents the chiral scaffold of the aminocatalyst **63**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

4. N-Heterocyclic Carbene-mediated Vinylogous Cascade Processes

Aminocatalysis is not the only successful organocatalytic approach for designing vinylogous cascade reactions. N-heterocyclic carbenes (NHC)[44] have also been used as viable catalytic intermediates for these transformations. Evidence for the existence of carbenes dates back to the late 19th century,[44a] and then they have been used extensively as organocatalysts to functionalize carbonyl compounds at the α- and β-positions. The activation modes that permit such reactivity can also be extended into the vinylogous reactivity space to facilitate remote transformations, including stepwise cascade processes.

Three strategies have been reported to facilitate NHC-catalyzed vinylogous cascade processes (Figure 10). The first two are related and proceed through a common activated ester intermediate. This intermediate can be formed either through the addition of an NHC to an enal and the subsequent oxidation of the Breslow intermediate (Strategy 1) or through the addition of an NHC to an α,β-unsaturated ester to directly access the activated ester intermediate (Strategy 2). This strategy results in the activation of the remote γ-carbon which, in the presence of a base, undergoes deprotonation to afford a vinylogous enolate. A third conceptually different strategy has also been reported, which requires enals that feature a leaving group at the γ-position. Following the addition of the NHC, intramolecular elimination from the Breslow intermediate generates the crucial vinylogous enolate species (Strategy 3 in Figure 11).

Once the vinylogous enolate has been formed, it can undergo a vinylogous nucleophilic attack to an electrophile. If this electrophile is tethered to a masked nucleophile, a cascade reaction occurs where the nucleophilic moiety utilizes the intrinsic nature of the NHC as a leaving group to attack the carbonyl moiety and undergo a cyclization (En^2-S) (Figure 11). These En^2-S cascade reactions rely on the NHC catalyst for both new bond forming steps and, although a cycloaddition pathway cannot be excluded for these types of transformations, the current understanding is that they are more likely to proceed through a cascade process.[45]

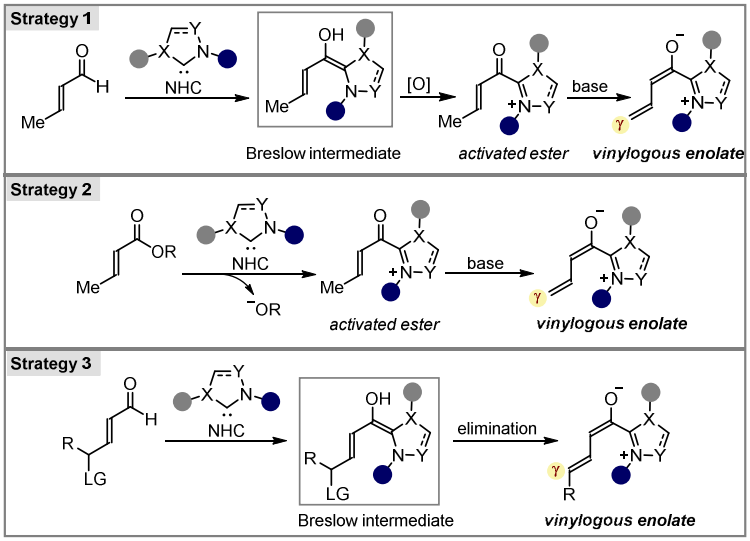


Figure 10. The different strategies utilized to form vinylogous enolates using NHC catalysis; the blue and grey circles represent the chiral scaffold of the NHC catalyst.

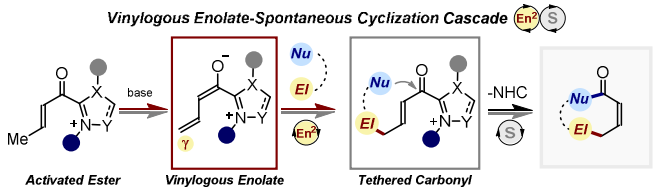
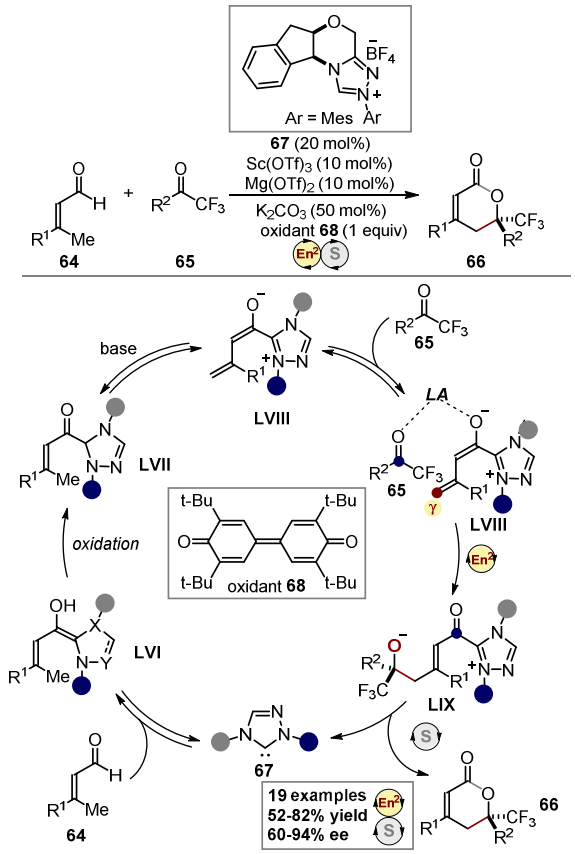


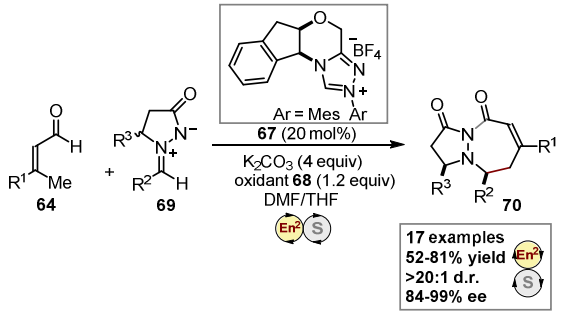
Figure 11. Vinylogous enolate (En^2)/spontaneous (S) cyclization cascade pathway; the initial organocatalytic event is followed by a spontaneous *ipso*-cyclization. The blue and grey circles represent the chiral scaffolds of the NHC catalyst.

The first reported use of NHC-catalysis to develop a En^2-S vinylogous cascade reaction was based on Strategy 1 to activate the γ-carbon. This work, shown in Scheme 20, featured the formation of lactones **66** from enals **64** and electron-deficient ketones **65**.[46] In the mechanistic proposal, the addition of the NHC **67** to enal **64** forms the Breslow intermediate **LVI** that, upon oxidation from **68**, generates intermediate **LVII**. Deprotonation of **LVII** affords the vinylogous enolate **LVIII** which undergoes a Lewis acid-mediated vinylogous addition to the ketone **65**. After this addition, the resulting anionic intermediate **LIX** undergoes a spontaneous intramolecular cyclization to form the lactone product **66** in good yields (52-82%) and enantioselectivities (60-94% ee).



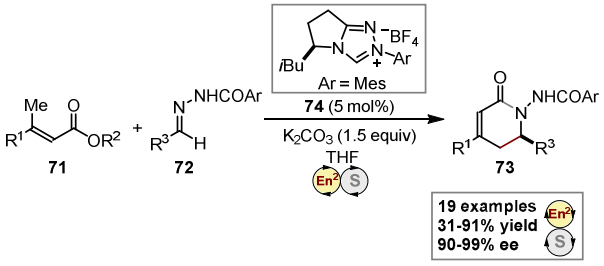
Scheme 20. The first reported use of NHC catalysis to develop a vinylogous cascade; En^2/S cyclization pathway. En^2: vinylogous enolate, S: spontaneous cyclization. The blue and grey circles represent the chiral scaffolds of the NHC catalyst **67**. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: magenta stands for a nucleophilic position, blue for an electrophilic center.

Strategy 1 was also used for the formation of bicycle **70** through a formal [3+4] cycloaddition between enal **64** and azomethine **69** in the presence of NHC **67** and the oxidant **68** (Scheme 21).[47] The mechanism is believed to proceed similarly to the one illustrated in Scheme 20: the vinylogous enolate **LVIII**, upon nucleophilic addition to imine **69**, forms the [3+4] adduct **70** after spontaneous intramolecular lactamization in good yields (51-81%) and enantioselectivities (84-99% ee)



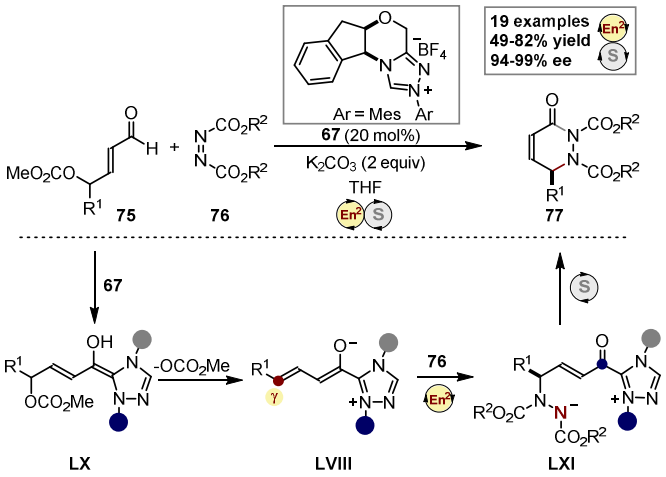
Scheme 21. The formation of the formal [4+3] product **70** through a En^2-S cascade sequence; En^2/S cyclization pathway; En^2: vinylogous enolate, S: spontaneous cyclization.

The use of Strategy 2 to form the vinylogous enolate (Figure 10) has also served for the implementation of a En^2-S cascade sequence. Direct addition of NHC **74** to the α,β-unsaturated ester **71** generates the intermediate without the need for an oxidation step. Besides the different activation strategy to access the key vinylogous enolate intermediate, the reaction proceeds in a similar fashion as discussed in Scheme 20: vinyl enolate **LVIII** attacks the hydrazine **72** and then a spontaneous cyclization delivered the lactam product **73** in good yields (31-91%) and enantiomeric excess (90-99% ee).[48]



Scheme 22. NHC-mediated En^2-S cascade sequence; En^2: vinylogous enolate, S: spontaneous cyclization. Formation of the vinylogous enolate achieved via Strategy 2 in Figure 10.

Recently, the vinylogous enolate-generation Strategy 3 (Figure 10) was also applied to realize an En^2-S cascade sequence. Using the enal **75**, which bears a suitable carbonate leaving group at the γ position, it was possible to generate the intermediate **LVIII** after elimination of the leaving group following formation of the Breslow intermediate **LX**. Nucleophilic addition of **LVIII** to di-*tert*-butyl azodicarboxylate **76** and subsequent lactamization gave product **77** in good yields (49-82%) and enantiomeric excess (94-99% ee, Scheme 23).[49]



Scheme 23. NHC-mediated En^2-S cascade sequence; En^2: vinylogous enolate, S: spontaneous cyclization. Formation of the vinylogous enolate achieved via Strategy 3 in Figure 10.

5. Summary and Outlook

The intense investigations into organocatalytic cascade reactions have led to the development of highly innovative techniques, which now provide reliable and versatile tools for modern asymmetric synthesis. Recently, the combination of organocatalysis and the principle of vinylogy has opened up new avenues for reaction design, further expanding the synthetic potential of cascade processes. Vinylogous cascade strategies provide effective means to build stereochemically dense, complex molecules from readily available substrates and using simple producers while forging stereogenic centers remote from the catalyst's point of action. Further interesting development along these lines are foreseen in the near future.[50]

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Paolo Melchiorre was born in 1973 in Camerino (Italy). He earned his M.Sc. degree (1999) and then his PhD in Chemistry (2003) from Bologna University under the supervision of A. Umani-Ronchi and P. G. Cozzi. After a research period with K. A. Jørgensen at Center for Catalysis, Århus University (Denmark), he joined the research group of G. Bartoli at Bologna University, where he became Assistant Professor in 2007. In 2009, Paolo moved to Tarragona (Spain) as an ICREA Research Professor and an ICIQ Senior Group Leader. His current scientific interests lie on the discovery and mechanistic elucidation of new enantioselective organocatalytic and photochemical processes.

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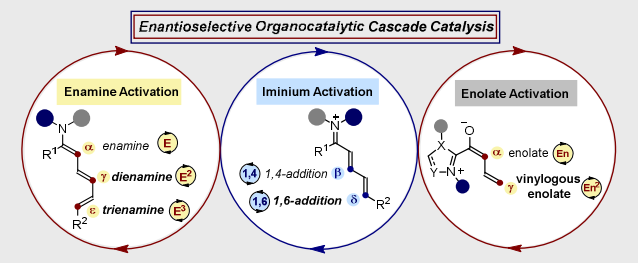

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Enantioselective Vinylogous Organocascade Reactions

This article critically describes the developments achieved in the field of enantioselective vinylogous organocascade reactions, charting the conceptual advances, and the milestone reactions that have been essential for reaching highly practical levels of synthetic efficiency.