AMINE-CATALYZED CASCADE REACTIONS

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1.1 INTRODUCTION

Chiral amine-mediated organocatalytic cascade reactions have become a benchmark in contemporary organic synthesis, as witnessed by a number of cascade processes developed in the past decade [1]. The great success is attributed to two unique interconvertible activation modes, enamine [2] and iminium activations [3]. Enamine catalysis has been widely applied to the \( \alpha \)-functionalizations of aldehydes and ketones. Mechanistically, dehydration between a chiral amine and the carbonyl of an aldehyde or ketone generates an intermediate, 2, which undergoes an enantioselective \( \alpha \)-substitution or nucleophilic addition reaction to produce respective iminium intermediate 3 or 5 (Scheme 1.1). Hydrolysis affords the products and, meanwhile, releases the chiral amine catalyst.

![Scheme 1.1 Enamine-catalyzed nucleophilic substitution (a) and addition (b) reactions.](image)
Correspondingly, iminium catalysis involves nucleophilic addition to the β-position of an iminium species 8 derived from an α,β-unsaturated aldehyde or ketone 7 with an amine catalyst (Scheme 1.2).

1.2 ENAMINE-ACTIVATED CASCADE REACTIONS

We define the cascade reactions initiated by enamine catalysis in the initial step as an enamine-activated mode, although an iminium mode might be involved in the following steps. In this regard, several catalytic cascade sequences, including enamine–enamine, enamine–iminium, and enamine cyclization, are discussed here.

1.2.1 Enamine–Enamine Cascades

1.2.1.1 Design of Enamine–Enamine Cascades Three possible active sites (e.g., carbonyl group, nucleophilic α- and Y-positions) of enamine catalysis product 4 or 6 (Figure 1.1) can be further functionalized via a second enamine process in a cascade manner. Taking advantage of the electrophilic carbonyl in 4 and 6, intermolecular enamine–enamine (Scheme 1.3a) and enamine–enamine cyclization (Scheme 1.3b) cascades could be possible. In addition, the α-position of the same (Scheme 1.3c) or different (Scheme 1.3d, e.g., Robinson annulation) carbonyl group can be subjected to a second enamine process.

1.2.1.2 Examples of Enamine–Enamine and Enamine–Enamine Cyclization Cascades Inspired by a 2-deoxyribose-5-phosphate aldolase (DERA)–catalyzed double-aldol sequence using only acetaldehyde to afford cyclized trimer 23
(a) Intermolecular enamine–enamine catalysis

(b) Intermolecular enamine–enamine catalysis and cyclization

(c) Double-enamine catalysis at the same site

(d) Robinson annulation

**Scheme 1.3** Design of enamine–enamine cascade catalysis.
SCHEME 1.4  Aldolase- and proline-catalyzed self-aldolization of acetaldehyde.

(Scheme 1.4) [4], Códova et al. conducted L-proline-catalyzed direct asymmetric self-aldolization of acetaldehyde, furnishing a triketide 24, instead of trimer 23, with 90% ee and 10% yield for the first time [5].

The mechanism proposed suggested that an enamine was involved in an Re-facial attack of the carbonyl group of acetaldehyde (Scheme 1.5). After the carbon–carbon bond-forming step, the resulting reactive iminium ion, instead of being hydrolyzed, underwent a Mannich type of condensation [6] to give 24.

Although the formation of hemiacetal 23 from acetaldehyde did not result from the use of L-proline, trimeric aldol product 25 was obtained in 12% isolated yield with propionaldehyde [7]. Slow addition of propionaldehyde to the reaction produced 25 in a significantly improved yield (53%) as a 1:8 mixture of diastereomers (Scheme 1.6). Subsequent oxidation of the product enabled the synthesis of lactone 26 with modest enantioselectivity (47% ee).

Reactions involving nonequivalent aldehydes were also examined. When 2 equiv of propionaldehyde was added slowly over 24 h to acceptor aldehydes such as isobutyraldehyde or isovaleraldehyde, lactones were formed as single diastereomers in moderate yields (20 to 30%) and poor ee (12%). Improved ee (25%) was observed when the reaction was conducted in an ionic liquid [8].

It was problematic to obtain high enantioselectivity when these consecutive aldol reactions were conducted within a single catalytic system. Two-step synthesis of
similar products was developed. In 2004, Northrup and MacMillan reported an
elegant synthesis of hexoses based on a proline-catalyzed dimerization of protected
α-oxyaldehydes, followed by a tandem Mukaiyama aldol cyclization catalyzed by a
Lewis acid (Scheme 1.7) [9]. The products were obtained in modest to good yields,
with high diastereoselectivity (10 : 1 to 19 : 1) and enantioselectivity (95 to 99%).

To improve the efficiency and selectivity of the tandem aldol process, Córdova’s
group also isolated the β-hydroxyaldol intermediate from the first aldol transformation
prior to the second aldol reaction. The pure intermediate was subjected to the
second aldol reaction with a different catalyst (Scheme 1.8). The two-step synthetic
protocol made it possible to investigate both (L)- and (D)-catalysts in stereocontrol.
The synthesis of hexoses proceeded with excellent chemo-, diastereo-, and
enantioselectivity. In all cases except one, the corresponding hexoses were isolated
as single diastereomers with >99% ee [10].

1.2.1.3 Enamine–Enamine in Three-Component Cascades As part of a continuing
effort, Chowdari et al. reported L-proline-catalyzed direct asymmetric assembly
reactions involving three different components—aldehydes, ketones, and azodicarbox-
ylic acid esters—to provide optically active functionalized β-amino alcohols in an
enzyme-like fashion. These are the first examples of using both aldehydes and ketones
as donors in one pot (Scheme 1.9) [11].
1.2.1.4 Enamine-Activated Double α-Functionalization

Enders et al. reported an organocatalytic domino Michael addition/alkylation reaction between aliphatic aldehydes and (E)-5-iodo-1-nitropent-1-ene 33 involving enamine–enamine activation (Scheme 1.10) [12]. This process is highly stereoselective and leads to the γ-nitro aldehydes, which contain an all-carbon-substituted quaternary stereogenic center.

Moreover, enamine catalytic in situ sequences of acetaldehyde with two electrophiles can be envisioned (Scheme 1.11). The first successful realization of this concept with a proline-catalyzed double Mannich reaction of acetaldehyde with N-Boc-imines 36 was developed to give pseudo-C₂-symmetric β,β'-diaminoaldehydes 37 with extremely high stereoselectivities (>99:1 dr, >99% ee) [13]. A similar approach with ketones was also realized [14].

1.2.1.5 Robinson Annulations

A silica gel–absorbed amino acid salt (39)–catalyzed asymmetric intramolecular Robinson annulation reaction with 38 was developed (Scheme 1.12). A tricyclic ring structure 40 was obtained in 84% yield and up to 97% ee [15]. Intermolecular Robinson annulations with structurally diverse aldehydes and unsaturated ketones were also developed [16].
1.2.2 Enamine–Iminium Cascades

1.2.2.1 Design of Enamine–Iminium Cascades  Similar to an enamine–enamine activation sequence, a subsequent iminium process is possible on 6 and 41 (Figure 1.2).

A special but significant case of 6 is that of the \(\alpha,\beta\)-unsaturated ketones 41 (R is a vinyl group). An intramolecular attack on the \(\alpha,\beta\)-unsaturated carbonyl group of 41 by nucleophilic Y can be envisioned in an iminium activation process (Scheme 1.13a). The formation of 42 through an enamine–iminium sequence can also be viewed as a Diels–Alder reaction between intermediate 43 and the electrophile (Scheme 1.13b).

In principle, simple intermediate 6 can undergo a similar intramolecular iminium process with an electrophilic carbonyl group. However, the resulting four-membered ring is too small to be formed from the attack of carbonyl by nucleophilic Y. Prolongation of electrophile 44 is necessary (Scheme 1.14). Nucleophilic 1,2-addition to the iminium ion 45 resulting from the first enamine catalysis furnishes 46, which is then hydrolyzed to afford 47 (Scheme 1.14a). The overall reaction sequence can also be considered to be a \([4+2]\) reaction between activated dienophiles 2 and 44 (Scheme 1.14b).

1.2.2.2 Examples of \([4+2]\) Reactions with Enamine-Activated Dienes  It is well known that Diels–Alder reactions can usually be regarded as double Michael
reactions, although concerted mechanisms are always proposed for these reactions. Thus, the enamine–iminium activation sequence has been used in [4 + 2] cycloaddition reactions.

In addition to the consecutive aldol reactions of aldehydes, Barbas’s group also reported enamine-activated Diels–Alder reactions (or double Michael reactions) between α,β-unsaturated ketones and nitroolefin (Scheme 1.15) for the first time in 2002 [17]. In contrast to MacMillan’s iminium catalysis for Diels–Alder reactions, wherein α,β-unsaturated carbonyl compounds were activated as dienophiles in a LUMO-lowering strategy based on iminium formation [3], an alternative strategy involving the in situ generation of 2-amino-1,3-dienes from α,β-unsaturated ketones.

(a) Double-addition reactions via enamine–iminium cascade

(b) [4 + 2] Reactions with HOMO-raising dienes

SCHEME 1.13 Design of an enamine–iminium cascade with enones.

(a) Double-addition reactions via enamine–iminium cascade

(b) [4 + 2] Reactions with activated dienophiles

SCHEME 1.14 Design of an enamine–iminium sequence based on 6 and 44.
was developed in a HOMO-raising fashion. Either (S)-1-(2-pyrrolidinylmethyl)-pyrrolidine or L-proline catalyzed the in situ formation of 2-amino-1,3-dienes 53 to provide cyclohexanone derivatives 51 and 52 in good yield (up to 87%) in one step with modest enantioselectivity (up to 38% ee).

On another occasion, Barbas’s group developed the first organocatalytic diastereospecific and enantioselective direct asymmetric domino Knoevenagel/Diels–Alder reactions that produce highly substituted spiro[5,5]undecane-1,5,9-triones 57 from commercially available 54, aldehydes 55, and 2,2-dimethyl-1,3-dioxane-4,6-dione 56 (Scheme 1.16) [18]. Among the catalysts screened, 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) proved to be the optimal catalyst with respect to yield, and provided 57 in 88% yield and 86% ee. Up to 93% yield and 99% ee were observed when the reaction was extended to other substrates. It is noteworthy that the product 57 was accompanied by a trace amount of the unexpected symmetric spirocyclic ketone 58.

![Scheme 1.15](image1.jpg)

**SCHEME 1.15** Enamine-activated dienes for Diels–Alder reactions.

![Scheme 1.16](image2.jpg)

**SCHEME 1.16** Amino acid–catalyzed asymmetric three-component Diels–Alder reaction.
The mechanism proposed is summarized in Scheme 1.17. Knoevenagel reaction between aldehyde 55 and 2,2-dimethyl-1,3-dioxane-4,6-dione 56 will provide the dienophile for subsequent Diels–Alder reaction with the reactive diene produced from 54. Then the intermediate 60 was hydrolyzed to produce the product desired and to release the catalyst. The asymmetric domino three-component Knoevenagel/Diels–Alder addition reaction promoted by the primary amine catalyst 9-amino-9-deoxy-epi-quinine was also reported. Various pharmacological multisubstituted spiro[5,5]undecane-1,5,9-triones were obtained in moderate to good yields (up to 81%) with excellent diastereoselectivities (up to 99:1 dr) and enantioselectivities (up to 97% ee) [19]. The enamine-mediated Diels–Alder reactions of α,β-unsaturated ketones were also extended to nitroalkenes [20] and 3-olefinic oxindoles [21].

Inspired by the unexpected formation of symmetric 58, Ramachary and Barbas extended the synthesis of polysubstituted spirotriones to more complex systems through an aldol/Knoevenagel/Diels–Alder reaction sequence in one pot (Scheme 1.18) [22]. The Diels–Alder product desired was obtained as a single diastereomer in moderate yield accompanied by some by-products.
The formation of these by-products could be avoided by changing acetone to Wittig reagent 61. It was found that Diels–Alder product 62 could be obtained in 99% yield as a single diastereomer (Scheme 1.19).

Use of proline-catalyzed five-component cascade olefination/Diels–Alder/epimerization/olefination/hydrogenation reactions of enones, aryl aldehydes, alkyl cyanoacetates, and Hantzsch ester to furnish highly substituted 66 in a highly diaste-reoselective fashion (99% de) with excellent yields (70 to 75%) was also reported (Scheme 1.20) [23].

The possible reaction mechanism for a cascade olefination–hydrogenation reaction is illustrated in Scheme 1.21. First, the reaction of proline with cis-isomer 67 generates the iminium cation 68, which reacts with electrophile 64 via a Mannich-type reaction to generate Mannich product 69. A retro-Mannich or base-induced elimination reaction of amine 69 would furnish active olefin 70. The subsequent hydrogen-transfer reaction is dependent on the electronic nature of the in situ–generated conjugated system or, more precisely, the HOMO–LUMO gap of reactants 65 and 70.

The strategy was extended to a tandem o-nitroso aldol–Michael reaction with cyclic α,β-unsaturated ketones to produce enantiopure nitroso Diels–Alder adducts 74 in moderate yields (Scheme 1.22) [24].

Similarly, the first direct catalytic enantioselective aza-Diels–Alder reaction was also accomplished with excellent stereoselectivity (94 to 99% ee) (Scheme 1.23) [25].
1.2.2.3 Inverse-Electron-Demand [4+2] Reactions with Enamine-Activated Dienophiles

In contrast to the Barbas group’s ingenious design of Diels–Alder reactions using enamine-activated dienes, Jørgensen envisioned that chiral enamines could act as electron-rich dienophiles and undergo an enantioselective inverse-electron-demand hetero-Diels–Alder reaction (Scheme 1.24) [26].
the mechanism proposed involved in situ generation of a chiral enamine 81 from a chiral pyrrolidine 78 and the aldehyde 76 (Scheme 1.25), followed by a stereoselective hetero-Diels–Alder reaction with enone 77 to give aminal 82. The presence of silica facilitates the hydrolysis step in the catalytic cycle.

**SCHEME 1.24** Organocatalytic hetero-Diels–Alder reaction.

Inverse-electron-demand hetero-Diels–Alder reaction of enolizable aldehydes with \( \alpha,\beta \)-unsaturated ketophosphonates [27], \( \alpha \)-quinones [28], \( \alpha \)-keto-\( \alpha,\beta \)-unsaturated esters [29], \( \alpha,\beta \)-unsaturated trifluoromethyl ketones [30], and \( \alpha \)-benzoquinone diimide [31] was also reported.

Encouraged by Jørgensen’s inverse-electron-demand hetero-Diels–Alder reaction of aldehydes and \( \alpha,\beta \)-unsaturated \( \alpha \)-keto esters, Han, He, and others envisaged that an unprecedented asymmetric aza-Diels–Alder reaction of \( N \)-sulfonyl-1-aza-1,3-butadienes and aldehydes might be developed by employing a similar strategy. They found that the process proceeded with a chiral secondary amine, 34 (Scheme 1.26) [32]. Excellent enantioselectivities (up to 99% ee) were observed for a broad spectrum of substrates under mild conditions.

Inspired by dienamine catalysis in inverting the inherent reactivity of \( \alpha,\beta \)-unsaturated aldehydes, which acted as nucleophiles for direct enantioselective \( \gamma \)-amination with
diethyl azodicarboxylate [33], Han et al. extended inverse-electron-demand aza-Diels–Alder reaction of electron-deficient N-sulfonyl-1-aza-1,3-butadienes to α,β-unsaturated aldehydes to construct chiral piperidine derivatives bearing several functional groups in a straightforward manner (Scheme 1.27) [34]. Moderate to good yields (66 to 95%), good diastereoselectivities ($E/Z = 8:1$), and excellent enantioselectivities (97 to 99% ee) were observed for this system.

The asymmetric inverse-electron-demand aza-Diels–Alder reaction of $N$-Ts-1-aza-1,3-butadienes derived from 3-argiocarbonylcoumarins and acetaldehyde has also been developed using chiral aminocatalysis, giving tricyclic chroman-2-one derivatives in high enantioselectivities (up to 95% ee) [35].

Although the diversity of asymmetric inverse-electron-demand hetero-Diels–Alder reactions has been well established, examples of all-carbon-based catalytic asymmetric versions have rarely been reported, and all fall into the LUMO-lowering strategy. Based on previous applications of dienamine catalysis in asymmetric inverse-electron-demand hetero-Diels–Alder reactions, Li et al. extended this strategy to all-carbon-based asymmetric inverse-electron-demand Diels–Alder reactions (Scheme 1.28) [36]. The products of cyclohexene derivatives with substantial substitution diversity of electron-deficient dienes and crotonaldehyde were obtained with high diastereo- and enantioselectivities (up to 99% ee, dr up to 95:5).

Synthesis of dicyano-2-methylene-but-3-enoates as novel dienes for all-carbon-based asymmetric inverse-electron-demand Diels–Alder reactions with aldehydes was also developed [37].

Based on the success of dienamine catalysis in inverse-electron-demand Diels–Alder reactions, Jia et al. explored the possibility of applying the HOMO-activation mode to poly-conjugated enals, such as 2,4-dienals, to form a reactive trienamine
intermediate [38]. It was demonstrated that the merger of optically active secondary amines and polyenals generates reactive trienamine intermediates, which readily participate in Diels–Alder reactions with different classes of dienophiles with excellent stereocontrol [39] (Scheme 1.29). Reaction with 3-olefinic oxindoles leads to spirocyclic oxidoles \( \text{89} \) in high yields and with enantioselectivities in the range of 94 to 98% ee and good yields (47 to 99%). The beauty of this activation strategy lies in the perfect chirality relay over a distance of up to eight bonds.

1.2.2.4 Enamine–Iminium–Enamine Cascades The enamine-activated process followed by an intermolecular iminium-mediated process will undergo a new enamine activation step to afford multisubstituted cyclohexanes via an enamine–iminium–enamine sequence. In this way, multicomponent reaction could be designed to produce complex structures from simple reactants.

The asymmetric organocatalytic triple cascade reaction for the synthesis of tetrasubstituted cyclohexene carbaldehydes developed by Enders et al. (Scheme 1.30) [40] is a milestone of organocatalytic cascade reactions. This three-component domino reaction proceeds by way of a catalyzed Michael–Michael–aldol condensation sequence affording products in good to moderate yields (25 to 58%). Notably, four stereogenic centers are formed with high diastereoselectivity and complete enantioselectivity.

This catalytic cascade is a three-component reaction comprising a linear aldehyde, a nitroalkene, an \( \alpha,\beta \)-unsaturated aldehyde, and a simple chiral secondary amine. The catalyst mediates the Michael addition of the linear aldehyde to the nitroalkene via enamine catalysis in the first step. Then the catalyst is liberated by hydrolysis to form the iminium ion of the \( \alpha,\beta \)-unsaturated aldehyde to accomplish the conjugate addition
with the nitroalkane 91. Subsequently, further enamine activation of the intermediate proposed, 92, leads to the intramolecular aldol condensation adduct 93 (Scheme 1.31).

It is well known that nitroalkenes are among the most reactive Michael acceptors, explaining the chemoselectivity of the first step of the catalytic cycle. Therefore, the enamine of the linear aldehyde reacts much faster with the nitroalkene than with the \( \alpha,\beta \)-unsaturated aldehyde. Once the Michael adduct 91 is formed, the following steps are so quick that the intermediates 92 and 93 could not be detected by gas chromatographic measurements. The final product, 90, also an \( \alpha,\beta \)-unsaturated aldehyde, is highly sterically hindered for further Michael addition compared to the enal.

Extension of this chemistry by alternation of the substrates [41] was conducted soon after. Using a variety of Michael acceptors, in addition to nitroalkenes, cyanoacrylates [42], N-Boc-protected olefinic oxindole [43], or changing \( \alpha,\beta \)-unsaturated aldehyde to

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**SCHEME 1.30** Organocatalytic three-component cascade involving an enamine–iminium–enamine cycle.
a diethyl vinylphosphonate derivative [44], multisubstituted structurally diverse cyclo-
hexene carbaldehydes with several stereogenic centers were efficiently synthesized.

Enders et al. also developed an efficient one-pot procedure that provided direct entry
to diastereo- and enantiomerically pure (≥99% de, ee) polyfunctionalized tricyclic frame-
works 95 [45] (Scheme 1.32). The organocatalytic triple cascade, followed by a Diels–
Alder sequence, leads to decahydroacenaphthylene and decahydrophenalene cores.

SCHEME 1.32 One-pot procedure for the synthesis of tricyclic carbaldehydes.

An organocatalytic triple cascade reaction, followed by an intramolecular
sulfa-Michael addition to produce bicyclic rings with six consecutive stereocenters,
was also realized [46].

In an effort to develop new cascade reactions, Zhang et al. envisioned that a linear alde-
hyde can also be generated in situ via an extra iminium catalysis from an \( \alpha,\beta \)-unsaturated
aldehyde prior to the triple cascade reaction. Therefore, there would be a possibility of
extending the triple cascade reactions to four-component cascade reactions. Based on
this design, a four-component quadruple cascade reaction through iminium–enamine–
iminium–enamine sequential activation initiated by oxa-Michael addition of alcohol to
acrolein in moderate yield (about 50%), excellent diastereoselectivities (>20:1), and
excellent enantioselectivities (>99% ee) was accomplished (Scheme 1.33) [47].

SCHEME 1.33 Four-component cascade reactions through iminium–enamine–iminium–
enamine sequential activation.

A similar organocatalytic quadruple domino Friedel–Crafts/Michael/Michael/
aldol condensation reaction initiated by Friedel–Crafts reaction of indole to acrolein
was also developed by Enders et al. [48], as well as a microwave-assisted quadruple
cascade organocatalytic Michael/Henry condensation/Michael/aldol condensation
employing acetaldehyde and nitroalkenes as substrates [49].
1.2.3 Enamine Catalysis Cyclization

In addition to the enamine–enamine and enamine–iminium catalytic sequences, it was found that the resulting intermediate 6 can also initiate cyclization reactions in the subsequent step via a substrate-control mode.

1.2.3.1 Design of Enamine-Cyclization Cascade Reactions  The nucleophilic Y in intermediate 6 can react with other electrophiles intermolecularly (Scheme 1.34a) or intramolecularly (Scheme 1.34b) as well as with the iminium ion. Moreover, the carbonyl group of 6 can also undergo intramolecular aldol reaction with nucleophilic X (Scheme 1.34c). These nucleophilic addition reactions after enamine catalysis induce cyclization reactions to produce versatile five- or six-membered ring structures.

(a) Enamine–intermolecular addition cascade

(b) Enamine–intramolecular addition cascade

(c) Enamine–intramolecular aldol cascade

SCHEME 1.34  Design of an enamine cyclization cascade.

1.2.3.2 Enamine-Intermolecular Addition Cascades  It was suggested that the intermediate γ-nitroaldehyde 91 in Scheme 1.31 might react with an aldehyde via an oxo-Henry sequence, and subsequent hemiacetalization would provide tetrahydropyran derivatives. Uehara et al. [50] and Iskikawa et al. [51] realized this hypothesis independently through a four-component reaction in one pot to furnish highly substituted tetrahydropyran derivatives 102 with excellent diastereo- and enantioselectivity (up to 98:2 dr and 99% ee) (Scheme 1.35). These two methods are complementary because anti-Michael products were synthesized using catalyst 101 [50], while syn-Michael products were obtained with diphenylprolinol silyl ether catalyst 34 [51].

A similar strategy was used in the synthesis of piperidine derivatives when the γ-nitroaldehydes 91 were reacted with an imine through a Henry reaction followed by intramolecular hemiaminalization (Scheme 1.36). An efficient asymmetrical
four-component one-pot synthesis of highly substituted piperidines as a single diastereomer with excellent enantioselectivity (93 to 99% ee) could be realized, as well as a Lewis acid–mediated allylation reaction to give 103 [52]. Extension of the linear aldehydes to ketone in this system was reported soon after [53].

1.2.3.3 Enamine-Intramolecular Addition Cascades Hayashi et al. envisioned that an enamine generated from one carbonyl of pentane-1,5-dial with catalyst 34 reacted with a nitroalkene in a Michael addition, followed by an intramolecular Henry reaction with the other aldehyde, would provide substituted nitrocyclohexancarbaldehyde 104 (Scheme 1.37) [54].

A similar strategy was extended to the reaction of pentane-1,5-dial with aldehydes [55a], imine [55b], and alkylidene malonate [55c]. It also proved feasible to replace pentane-1,5-dial with alkenal 105 [56] or 2-(5-oxopentylidene) malonates [57] for α-aminoxylation/aza-Michael reactions based on a similar strategy. The α-aminoxylation of alkenal 105 with nitrosobenzene
and subsequent intramolecular conjugate attack of the in situ–generated amine on electrophilic nitroolefin afforded functionalized tetrahydro-1,2-oxazines 106 in good yield and with excellent stereoselectivity (>99 : 1 dr, about 99% ee) (Scheme 1.38).

1.2.3.4 Enamine-Intramolecular Aldol Cascades Jørgensen developed the first highly asymmetric direct α-arylation of aldehydes using quinones as the aromatic partner, leading to optically active α-arylated aldehydes 108 in good yields with excellent ee (92 to 99%) and dr values (Scheme 1.39) [58].

Other acetalizations or ketalizations in an enamine-initiated cascade process were also reported [59].

1.3 IMINUM-INITIATED CASCADE REACTIONS

The cascade reactions induced by iminium catalysis in the first step are defined as iminium-activated cascade reactions, although almost all of the iminium-initiated cascade reactions are followed by an enamine-mediated process in the subsequent step. Considerable effort has been directed to construction of diverse cyclic structures via the iminium–enamine catalytic sequence.

1.3.1 Design of Iminium–Enamine Cascade Reactions

Three-component reactions can be designed by incorporating suitable nucleophiles and electrophiles into iminium-activated systems (Scheme 1.40a). Furthermore, cyclic structures can be constructed if these nucleophiles and electrophiles can be incorporated into the same molecule as 111 (Scheme 1.40b). In fact, [2+1], [3+2], sequential [4+2], and Diels–Alder reactions have been developed, depending on the distance between nucleophilic and electrophilic positions of 111 to furnish diverse cyclic structures.
1.3.2 Iminium-Activated Diels–Alder Reactions

In an analog to Lewis acid catalysis, Northrup and MacMillan introduced the first organocatalytic asymmetric Diels–Alder reaction between diverse dienes and \( \alpha,\beta \)-unsaturated aldehydes catalyzed by 115 (Scheme 1.41), which proceeded with excellent enantioselectivity despite low diastereoselectivity [60].

It was proposed that condensation of aldehyde with 115 would lead to the formation of an iminium ion 116 (Scheme 1.42). The activated dienophile reacted with a diene to lead to iminium ion 117. Upon hydrolysis, the enantioenriched cycloaddition product was produced while releasing the chiral amine catalyst.

MacMillan’s group advanced the iminium activation strategy to intramolecular Diels–Alder reactions with good diastereoselectivity (up to 20:1) and enantioselectivity [61]. The strategy was applied in the total synthesis of (+)-hapalindole Q [62]. A novel binaphthyl-based diamine was utilized to catalyze Diels–Alder reaction of \( \alpha,\beta \)-unsaturated aldehydes with unprecedented high \( \text{exo} \) selectivity [63]. It was reported that the same reaction was also catalyzed by diphenylprolinol silyl ether and an acid as cocatalyst [64]. However, with the same reactants and the same catalyst, an ene reaction took place instead without an acid additive. Diels–Alder reactions of 2-vinylindoles and \( \alpha,\beta \)-unsaturated aldehydes were also developed [65].
Northrup and MacMillan extended the iminium-mediated Diels–Alder reactions to $\alpha,\beta$-unsaturated ketones using a new chiral amine catalyst (Scheme 1.43) [66]. They found that cycloadDITION of $\alpha,\beta$-unsaturated ketones was unsuccessful with the chiral amine salts previously identified as excellent catalysts for enal activation. In contrast, the 2-(5-methylfuranyl)-derived imidazolidinone 118 afforded good levels of enantiofacial discrimination while maintaining high reaction efficiency (89% yield, 25:1 endo/exo, 90% ee).

The chiral primary amine catalyst 121 proved to be highly effective for the asymmetric Diels–Alder reaction of simple enones with 2-pyrone 120 to furnish chiral bicyclic structures (Scheme 1.44) [67].
and cyclohexadiene with \(\alpha\)-(p-methoxybenzoyloxy)acroleins \(124\) furnished the adducts \(126\) with moderate diastereoselectivities and high enantioselectivities (up to 92%). Relative low enantioselectivity (up to 83% ee, 20 mol% of catalyst loading) was observed for the reaction of cyclopentadiene.

A diammonium salt of chiral 1,1′-binaphthyl-2,2′-diamine and trifluoromethanesulfonimide (Tf, Nh) (5 mol% loading) showed excellent catalytic activity and enantioselectivity (88% yield with 92% \textit{exo} and 91% ee) toward the Diels–Alder reaction of \(\alpha\)-acyloxyacroleins with cyclic dienes [69]. Extension of Diels–Alder reactions to \(\alpha\)-branched aldehydes was also reported [70].

### 1.3.3 Iminium-Activated Sequential [4+2] Reactions

In addition to conventional Diels–Alder reactions, consecutive [4+2] reactions have been subjected to extensive investigation through the iminium–enamine catalytic sequence. Wang, Rios, and others simultaneously described enantioselective cascade sulfa-, oxa-, and aza-Michael/aldol/dehydration reactions promoted by chiral secondary amines. An initial strategy for a one-pot synthesis of chiral thiocromenes with good to high enantioselectivities was reported (Schemes 1.46 and 1.47) [71].

![Scheme 1.45](image)

\[\text{Diels–Alder reaction with } \alpha\text{-substituted acroleins.}\]

In the process, activation of \(\alpha,\beta\)-unsaturated aldehydes by a chiral organocatalyst produces iminiums which trigger a Michael–aldol cascade process to afford intermediates which undergo spontaneous dehydration to give \(\alpha,\beta\)-unsaturated aldehydes \(129\).
The extension of this strategy to 2-mercaptobenzaldehyde and α,β-unsaturated ketones [72], 2-mercaptoacetophenones [73], salicylaldehydes [74], 2-amino benzaldehydes [75], 2-(nitromethyl)benzaldehyde [76], and 2-((E)-2-nitrovinyl)phenol [77] has been disclosed.

In contrast to the slow reaction of 2-((E)-2-nitrovinyl)phenol and enals [77], a highly efficient iminium–allenamine cascade was developed when enals were replaced with alkynals (Scheme 1.48) [78]. The process serves as a feasible one-pot approach to synthetically and biologically significant chiral 4'H-chromenes in high yields (92 to 98%) with excellent enantioselectivities (98 to 99%). It was found that cascade reactions between alkynals and ethyl 2-(2-hydroxyphenyl)-2-oxoacetates [79], salicyl N-tosylimine [80], and salicylaldehyde [81] also proved to be feasible.

Carlone et al. assumed that reactants bearing 1,4-nucleophilic–electrophilic sites for sequential [4+2] reactions of enals could be possible (Scheme 1.49) [82]. The overall [3+2+1] reaction was thus achieved with 2 equiv enals and 1 equiv malononitrile to afford cyclohex-1-ene-carbaldehyde derivatives 134 in good to high yields and a nearly enantiopure diastereomer. Other nucleophilic carbon-initiated sequential [4+2] reactions of α,β-unsaturated aldehydes were also accomplished [83].

1.3.4 Iminium-Activated [3+2] Reactions

In addition to the LUMO-lowering activated enantioselective Diels–Alder reactions of enals, MacMillan’s group revealed that this catalytic strategy was also amenable to [3+2] cycloadditions between nitrones and α,β-unsaturated aldehydes to provide isoxazolidines in high yields, moderate diastereoselectivity, and moderate enantioselectivity.
AmInE-CATAlyZED CASCADE REACtIONs (Scheme 1.50) [84]. Improved diastereoselectivity was achieved when a triflate salt of diphenyl-S-prolinol and trimethylsilyl triflate was used to catalyze this reaction [85]. Highly chemo- and enantioselective organocatalytic three-component reaction of enals with in situ–generated nitrones from N-arylhydroxylamines and aldehydes was also reported [86].

Inspired by the MacMillan group’s LUMO-lowering strategy in cycloaddition reactions, Vicario et al. developed a chiral prolinol 139–promoted enantioselective [3 + 2] cycloaddition reaction between α,β-unsaturated aldehydes and azomethine ylides 138. The reaction proceeded via exclusive regioselectively and with very high diastereo- and enantioselectivity to furnish highly functionalized polysubstituted pyrrolidines 140 in good yields (Scheme 1.51) [87].

A stereoselective [3 + 2] dipolar cycloaddition of azomethine imines 141 with α,β-unsaturated aldehydes catalyzed by α,α-diarylprolinol salts was also reported by Chen et al. [88]. More important, they extended the strategy to cyclic enones by employing a Cinchona alkaloid–derived bifunctional primary amine catalyst 142 (Scheme 1.52) [89]. The synergistic hydrogen-bonding interaction of the catalyst and 1,3-dipoles 141 plays a critical role in high enantiocontrol (dr > 99:1, up to 95% ee).

SCHEME 1.50  Dipolar [3+2] cycloadditions between nitrones and enals.

SCHEME 1.51  Organocatalytic [3+2] cycloaddition of azomethine ylides.

SCHEME 1.52  1,3-Dipolar cycloaddition of azomethine imines to cyclic enones.
1.3.5 Iminium-Activated Sequential [3+2] Reactions

In a continuation of enantioselective cascade sulfa-, oxa-, and aza-Michael/aldol/dehydration cascade reactions, Wang et al. envisioned that the employment of a nucleophilic carbon atom for the initial Michael addition could enable the generation of two new C—C bonds in sequential [3+2] reactions.

Development of such a catalytic cascade process requires a stable and electron-rich carbon species as a nucleophile, which should be compatible with electrophilic aldehyde functionality in one of the chemical entities 144 (Scheme 1.53) [90]. Undesired reaction of 144 with the catalyst to produce an iminium or enamine could significantly complicate the cascade process. Potentially, the iminium 144a could undergo reversible intramolecular cyclopropanation and thus slow down the desired cascade process. Moreover, the enamine 144b could participate in the Michael reaction with iminium 144c.

These problems could be minimized by the use of bulky and readily enolizable malonates and a sterically hindered organocatalyst such as 145. Accordingly, substrate 144, bearing a nucleophilic malonate and an electrophilic aldehyde group, was utilized for the cascade Michael–aldol condensation process (Scheme 1.54) [90]. The process is catalyzed efficiently by readily available (S)-diphenylprolinol triethylsilyl ether 145 to give synthetically useful, highly functionalized chiral cyclopentenes.

Rueping et al. developed a sequential [3+2] cascade reaction between 1,2-cyclohexadione 147 and enals through a Michael–aldol sequence to furnish the bicyclic

![Scheme 1.53](image)

Possible undesired reactions.

![Scheme 1.54](image)

Cascade Michael–aldol reactions with malonate aldehyde.
compound 148 in good yields and with excellent enantioselectivities (90 to 98% ee) (Scheme 1.55) [91].

With regard to the reaction mechanism of the asymmetric domino Michael–aldol reaction, it was proposed that the diphenylprolinol ether 34 formed the intermediate iminium ion 147a from α,β-unsaturated aldehyde (Scheme 1.56). 1,4-Addition then occurred with the tautomeric structure of 1,2-cyclohexadione, resulting in the Michael adduct 147b, an activated enamine that subsequently underwent an intramolecular aldol reaction.

A thia-Michael/aldol cascade [92] of α,β-unsaturated aldehydes with 3-mercapto α-carbonyl esters or 1,4-dithiane-2,5-diol and aza-Michael/aldol reactions of α,β-unsaturated aldehydes with indole-2-carbaldehydes or pyrroles [93] was also developed.

An interesting sequential [3+2] reaction between a dihydroxyacetone dimer and α,β-unsaturated aldehydes, which leads to the enantioselective formation of hexahydrofuro[3,4-c]furanes 150 in excellent yields and diastereo- and enantioselectivities, was also illustrated through an oxo-Michael/aldol/hemiacetalization sequence (Scheme 1.57) [94].

A plausible mechanistic proposal for this transformation is described (Scheme 1.58). The reaction started with the conjugate addition of 149 to the enal under iminium activation, and then the intermediate enamine 149a would undergo an intramolecular
IMINNIUM-INITIATED CASCADE REACTIONS

SCHEME 1.57  One-step synthesis of hexahydrofuro[3,4-c]furanes.

SCHEME 1.58  Possible pathway for the synthesis of hexahydrofuro[3,4-c]furanes.

The aldol reaction, delivering the final adducts 150 after releasing the catalyst upon hydrolysis and a final internal hemiacetal-formation step.

Furthermore, change of the aldehyde group of 144 to α,β-unsaturated esters 151 as the electrophile led to a new cascade double-conjugate addition process (Scheme 1.59) [95]. Significantly, the cascade process afforded a product with the formation of three stereogenic centers in one pot. The [3 + 2] transformation enables the facile assembly of tetrasubstituted highly functionalized cyclopentanes from simple achiral molecules with high levels of enanto- and diastereoccontrol in a single operation.


SCHEME 1.59  Double Michael addition reactions with malonate α,β-unsaturated esters.
aldehydes with a \textit{trans}-\textit{\(\gamma\)}-N-protected \(\alpha,\beta\)-unsaturated ester, and a nitro-Michael/ Michael sequence [98] of \(\alpha,\beta\)-unsaturated aldehydes with 5-nitropentenoate esters was also developed. Moreover, a chiral amine–catalyzed domino Michael/\(\alpha\)-alkylation reaction that provides access to cyclopentanones was also reported [99].

1.3.6 \textbf{Iminium-Activated [2+1] Reactions}

Having established the capacity of chiral amines to catalyze asymmetric [4+2] and [3+2] reactions of unsaturated aldehydes, researchers sought to extend this olefin-activation platform to [2+1] reactions to produce three-membered rings. Amazing organocatalytic [2+1] reactions, including cyclopropanation, epoxidation, and aziridination, were developed.

1.3.6.1 \textbf{Iminium-Activated Cyclopropanations}  Kunz and MacMillan developed a highly efficient protocol for the construction of enantioenriched cyclopropanes using stabilized ylides with dihydroindole catalysts (Scheme 1.60) [100]. 2-Carboxylic acid dihydroindole 154 might function as a directed electrostatic activation (DEA) cyclopropanation catalyst. Iminium 156 and the ylide 153 engaged in electrostatic association via their pendant carboxylate and thionium substituents. The zwitterion 156 would predominately populate the \((Z)\)-iminium isomer to minimize van der Waals interactions between the substrate olefin and the aryl hydrogen. As a result, the carboxylate group on the catalyst framework would direct ylide addition selectively to the \(Re\)-face of the activated olefin, thereby ensuring enantiocontrol and facilitating carbon–carbon bond formation.

\[
\begin{align*}
\text{R} &= \text{CHO} \\
\begin{array}{c}
153 \\
154 \\
155 \\
156
\end{array}
\end{align*}
\]

\textbf{SCHEME 1.60}  Organocatalytic ylide cyclopropanation.

A second-generation catalyst in which the carboxylic acid of (S)-(–)-indole-2-carboxylic acid was replaced by tetrazolic acid was used to improve enantioselectivity as a consequence of increased steric bulk while retaining important structural functionality associated with the proposed directed electrostatic activation mode [101]. Combination of the iminium catalysis with arsonium ylides also provided access to cyclopropanes with high enantioselectivity [102].
In contrast to the use of the specific type of ylides, the employment of readily available alkyl halides for a catalytic Michael-alkylation reaction with α,β-unsaturated aldehydes to produce cyclopropanes is an extremely challenging task. The high tendency toward N-alkylation of the secondary amino group of the catalyst with alkyl halides leads to poisoning the catalyst. However, by careful design of the substrates and optimization of the reaction conditions, it was demonstrated that the use of bromomalonates or 2-bromo-3-keto esters reacting with α,β-unsaturated aldehydes and chiral diphenylprolinol TMS ether as promoter in the presence of 2,6-lutidine as an acid scavenger enabled the cascade Michael-alkylation process to proceed efficiently (Scheme 1.61) [103]. The tandem reactions afford chiral cyclopropanes with high levels of enantio (90 to 98% ee)- and diastereoselectivities (≥30:1 dr) and in high yields without intoxicating the catalyst.

Scheme 1.61 Domino Michael alkylation for cyclopropanation.

Scheme 1.62 Mechanism for a Michael-alkylation cascade.

In view of the issues associated with the tendency of N-alkylation, side reactions, and diastereoselectivity, it was envisioned that utilization of bromomalonates 157 would kill two birds with one stone (Scheme 1.62). The favorable enol form 157a renders Br to be a poor leaving group as a result of p–π conjugation with the sp2-hybridized carbon and thus overcomes the problem of possible N-alkylation with an amine catalyst, whereas serving as a nucleophile, it makes possible participation in the conjugate addition of an activated α,β-unsaturated aldehyde by an amine catalyst through an
iminium. On the other hand, once the nucleophilic enamine 157b is produced, it undergoes a second catalytic cycle alkylation reaction. The resulting tertiary bromide from the Michael addition process cannot form an enol form, which should readily undergo an intramolecular α-alkylation reaction to produce a cyclopropane.

Nitrocyclopropanation of enones [104] and enals [105] with 2-bromonitromethane was also reported.

1.3.6.2 Iminium-Activated Epoxidations  Similar to ylides 153 and bromomalonates 157, it was proposed that hydrogen peroxide could also be used as an amphiphilic reactant for [2+1] reactions of α,β-unsaturated aldehydes to furnish epoxidation products. Inspired by this hypothesis, Jørgensen’s group developed an organocatalytic asymmetric epoxidation system of α,β-unsaturated aldehydes with H₂O₂ as the oxidant (Scheme 1.63) [106]. The reactions take place under mild conditions in good to high yields and enantio- and diastereoselectivities.

In the reaction pathway, the iminium ion formed from corresponding α,β-unsaturated aldehyde with the chiral amine is subject to nucleophilic attack by the peroxide, leading to an enamine intermediate (Scheme 1.64). Formation of the epoxide then takes place by attack of the nucleophilic enamine carbon atom on the electrophilic peroxygen atom.
Despite the excellent results of epoxidation of simple $\alpha,\beta$-unsaturated aldehydes, a general method for the epoxidation of $\alpha$-branched $\alpha,\beta$-unsaturated aldehydes was challenging. After several years, the process was realized by the combination of a chiral primary Cinchona-based amine and a chiral phosphoric acid as cocatalysts, making it possible to achieve high efficiency (Scheme 1.65) [107]. It is believed that chiral phosphoric acid provides additional enantiodiscrimination in both steps as a chiral counterion in 160a and as a Brønsted acid in 160b. This is supported by the match or mismatch observed when the phosphoric acids ($R$)-TRIP and ($S$)-TRIP were used in parallel studies.

Logically, the organocatalytic epoxidation reactions were extended to $\alpha,\beta$-unsaturated ketones using $\alpha,\alpha$-diphenyl-l-prolinol 139 as a bifunctional organocatalyst and tert-butyl hydroperoxide (TBHP) as an oxidant to furnish the epoxides 160 in good yields with up to 80% ee (Scheme 1.66) [108].

A novel reaction pathway was proposed for the prolinol-mediated epoxidation of enones (Scheme 1.67). Catalyst 139 activates the TBHP by deprotonation to generate more nucleophilic tert-butyl hydroperoxide anion and the corresponding ammonium cation 161, which constitute a tight ion pair in hexane. The hydroxyl group of the diarylmethanol moiety of 139 appears to activate the enone by hydrogen bonding to the carbonyl group. The polar-electrostatic interactions of the three partners provide an organizational template that correctly positions the enone for conjugate addition.
of the tert-butyl hydroperoxide anion. The hydrogen-bond-stabilized enolate then attacks the O—O bond intramolecularly, giving rise to epoxide ring closure and elimination of the tert-butoxy anion.

It was found that 4-substituted α,α-diarylprolinol 162 catalyzed the asymmetric epoxidation of α,β-enones to give the corresponding chiral epoxides in good yields and high enantioselectivities (up to 96%) under mild reaction conditions (Scheme 1.68) [109]. The extension of epoxidation to cyclic α,β-unsaturated ketones with chiral primary salts was reported by Wang et al. in good yields and excellent enantioselectivities (up to 99%) [110].

1.3.6.3 Iminium-Activated Aziridinations

The aziridinations of α,β-unsaturated aldehydes can also be carried out through an iminium–enamine sequence if a nitrogen-atom source acts as a nucleophile and at a later stage becomes electrophilic. After extensive screening of catalysts and various suitable nitrogen-atom sources for asymmetric aziridination, Vesely et al. found that acylated hydroxycarbamates 163 had the right properties to promote product formation (Scheme 1.69) [111]. The reaction was efficiently catalyzed by a simple chiral catalyst 34 and gave the corresponding 2-formylaziridines in good to high yields with dr 4 : 1 to 19 : 1 and 84 to 99% ee. Aziridination of α-branched α,β-unsaturated aldehydes was also developed [112].
It is proposed that efficient shielding of the Si-face of the chiral iminium intermediate by the bulky aryl groups of the catalyst leads to a stereoselective Re-facial nucleophilic conjugate attack on the electrophilic β-carbon by the amino group of 163 (Scheme 1.70). Then the chiral enamine intermediate generated performs a 3-exo-tet nucleophilic attack on the now electrophilic nitrogen atom, and acetic acid is released. The intramolecular ring closure pushes the equilibrium in the forward direction and makes this step irreversible.

Aziridinations of α,β-unsaturated ketones triggered by chiral primary amine salts via iminium catalysis were reported soon after (Scheme 1.71) [113]. The reduced steric constraint of primary amines offers the unique possibility of catalyzing processes between sterically demanding partners, overcoming the inherent difficulty of chiral secondary amine catalysis. The reaction affords valuable N-Cbz- as well as N-Boc-protected aziridines 167 with almost complete diastereocontrol and very high enantioselectivity (up to 99% ee).

### 1.3.7 Iminium-Activated Multicomponent Reactions

As illustrated in Scheme 1.40, in addition to the amphiphilic reactants bearing nucleophilic and electrophilic sites, compatible separated nucleophiles and electrophiles can also be employed in iminium-activated cascades in multicomponent reactions.
Marigo et al. developed a multicomponent domino–conjugated nucleophilic thiol addition–electrophilic amination reaction that gave access to 1,2-aminothiol derivatives with >99% ee in a one-pot process using 128 as a catalyst (Scheme 1.72) [114]. The soft sulfur nucleophile 168 first reacted with the iminium ion intermediate, followed by addition of the enamine intermediate to the azodicarboxylates 169. In situ reduction and cyclization resulted in the formation of highly functionalized oxazolidinones 170 in nearly enantiopure form.

It was possible to incorporate amphiphilic components in one substrate in the organocatalytic domino reactions of enals. This concept was implemented in highly enantioselective aminosulfenylation of α,β-unsaturated aldehydes with amphiphilic N-benzylsulfanyl imide 171 that furnished valuable β-amino-α-mercaptoaldehydes 172 and 173 in high yields with 93 to 99+% ee (Scheme 1.73) [115].
An organocascade aminofluorination reaction of $\alpha,\beta$-unsaturated aldehydes with 174 and NFSI ($N$-fluorobenzenesulfonimide) as an electrophilic fluorination agent was developed to produce chiral $\alpha$-fluoro-$\beta$-amino aldehydes using catalyst 34 (Scheme 1.74) [116]. Up to 85% yield, 98 : 2 dr, and 99% ee of the reduced alcohols 175 were achieved.

Quintard and Alexakis developed a double Michael addition reaction of enals, taking advantage of the high reactivity of vinyl sulfone–initiated nucleophilic addition of benzaldoxime, triazole, Angelica lactone, benzyl mercaptan, and 174. The powerful organocascade allows for the rapid construction of highly attractive synthons in high enantioselectivities (typically, 99% ee) [117].

**SCHEME 1.74** Organocatalytic aminofluorination reactions.

### 1.3.8 Iminium-Activated [3+3] Reactions

In addition to the cyclization reactions above via the widely applied iminium–enamine sequence, in which diverse amphiphilic substrates bearing nucleophilic and electrophilic groups are added simultaneously to $\alpha,\beta$-enals, [3+3] reactions can also be conducted by employing reactants bearing 1,3-nucleophilic sites in the iminium-mediated reactions of $\alpha,\beta$-enals to furnish six-membered rings (Scheme 1.75). Reactants bearing 1,3-nucleophilic sites, such as enamines, enols, and 1,3-nucleophilic carbon species, have been used in iminium-activated [3+3] reactions. Furthermore, five-membered rings have also been synthesized through a similar approach with reactants bearing 1,2-nucleophilic sites, such as N-protected hydroxylamines [118].

**SCHEME 1.75** Design of iminium-activated [3+3] reactions.

#### 1.3.8.1 Iminium-Activ ted All-Carbon-Centered [3+3] Reactions

The first highly enantioselective organocatalytic [3+3] reaction through Michael–Darzens condensation giving highly functionalized complex epoxyclohexanone derivatives with up to four chiral centers was developed by Marigo et al. with excellent diastereo- and enantioselectivities (Scheme 1.76) [119]. The one-pot organocatalytic domino reactions between $\gamma$-chboro-$\beta$-keto esters 176 and $\alpha,\beta$-unsaturated aldehydes occurred with catalyst 128 and AcONa as additive. The product was then
converted into the optically active epoxy cyclohexanone 177 in the presence of K$_2$CO$_3$.

The mechanism proposed for the transformations is illustrated in Scheme 1.77. The β-keto ester 176 approaches the planar iminium ion from the Re-face due to steric hindrance of the bulky substituents at the chiral substituent in the pyrrolidine ring of catalyst 128. Hydrolysis of the enamine intermediate leads to the formation of Michael adducts 178 in a 1:1 diastereomeric mixture. The role of AcONa is therefore to promote the aldol reaction and the consequent consumption of the optically active product 179. Finally, the stronger base (K$_2$CO$_3$) deprotonates the alcohol and enables the intramolecular S$_{N}$2 reaction, which leads to one-pot formation of the highly functionalized products 177.

Similar [3+3] reactions of α,β-unsaturated aldehydes initiated by iminium-mediated Michael addition, followed by aldol [120], Knoevenagel [121], or Wittig [122] reactions to generate 2-cyclohexenones, were also developed.

It is noteworthy that the 2-cyclohexenones generated from [3+3] reactions are suitable substrates for another [3+3] reaction. As shown in Scheme 1.78, double [3+3] reactions of α,β-unsaturated aldehydes with 2 equiv of 180 selectively form

\[
\text{SCHEME 1.76 Organocatalyzed one-pot Michael–aldol–S$_{N}$2 cascade.}
\]

\[
\text{SCHEME 1.77 Mechanism proposed for a one-pot Michael– aldol–S$_{N}$2 cascade.}
\]
four new carbon–carbon bonds, provide six new stereocenters, and thus 1 of 64 possible stereoisomers with excellent diastereo- and enantioselectivity is created (up to >99:1 dr and 96% ee) [123].

What’s more, the addition of nitroalkanes to α,β-unsaturated aldehydes followed by an intramolecular Henry reaction which led to the formation of highly substituted cyclohexanols with control over five contiguous stereocenters was illustrated (Scheme 1.79) [124]. This novel domino reaction catalyzed by diarylprolinol silyl ether 128 proceeded in moderate to good yields with high diastereo- and enantioselectivity.

Interestingly, [3 + 3] reaction of α,β-unsaturated aldehydes with 185 bearing single nucleophilic site also proved to be feasible through a Michael–Morita–Baylis–Hillman sequence catalyzed by a chiral secondary amine (Scheme 1.80) [125]. The reaction proceeds in high enantio- and diastereoselectivity for a wide range of α,β-unsaturated aldehydes and β-keto esters.

A two amine-catalyzed cycle mechanism for the formation of the products 186 was proposed (Scheme 1.81). First, catalyst 34 activates the α,β-unsaturated aldehyde, thereby forming an iminium intermediate which undergoes Michael addition.
1.3.8.2 Iminium-Activated Hetero-[3+3] Reactions

Stable enol and enamine bearing 1,3-nucleophilic sites have also been utilized to develop oxo- or aza-[3+3] reactions of α,β-unsaturated aldehydes. A chiral secondary amine-catalyzed enantioselective [3+3] cyclization cascade, resulting in biologically interesting quinones, was conducted from hydroxynaphthoquinone and α,β-unsaturated aldehydes (Scheme 1.82) [126]. Both aliphatic and aromatic α,β-unsaturated aldehydes can be employed to provide 1,4-pyranonaphthoquinones 190 in good yields and with excellent enantioselectivities (90 to 99% ee). A similar strategy was extended to 4-hydroxycoumarin and 4-hydroxy-6-methyl-2-pyrone by the same group [127].

SCHEME 1.81 Mechanism proposed for the Michael–Morita–Baylis–Hillman cascade.

SCHEME 1.82 Enantioselective synthesis of 1,4-naphthoquinones.
With regard to the mechanism, it was assumed that the reaction of diphenylprolinol ether 128 with $\alpha,\beta$-unsaturated aldehyde resulted in an intermediary iminium ion (Scheme 1.83). Subsequent 1,4-addition of 2-hydroxy-1,4-naphthoquinone 189 to iminium ion followed by isomerization gives rise to the adduct 191. After hydrolysis, acetylation yields the desired 1,4-naphthoquinones 190 with regeneration of the catalyst.

**SCHEME 1.83**  Mechanism for the synthesis of 1,4-naphthoquinones.

The equilibrium between 1,3-diones and the corresponding enol form renders it a suitable reactant for [3+3] reactions of $\alpha,\beta$-unsaturated aldehydes [128]. The Michael–Morita–Baylis–Hillman reaction between $\alpha,\beta$-unsaturated aldehydes and 5-substituted Nazarov reagent (Scheme 1.81) was inhibited because of the steric effect. However, oxo-[3+3] cyclization proceeded in good yields and high enantioselectivities in this system [129].

The highly enantioselective organocatalytic aza-[3+3] reaction of $\alpha,\beta$-unsaturated aldehydes and enamide was reported by Hayashi’s and Wang’s groups respectively, via a mechanism similar to that shown in Scheme 1.83. Piperidine derivatives were generated efficiently in high yields and enantioselectivities despite low diastereoselectivities (Scheme 1.84) [130]. Later, it was found that simple amide and urea were also nucleophilic enough for the [3+3] reactions of $\alpha,\beta$-unsaturated aldehydes [131].

**SCHEME 1.84**  Catalytic asymmetric formal aza-[3+3] cycloaddition reaction.
1.3.9 Other Iminium-Activated Cascade Reactions

It is observed that 1,5-hydride transfer can be accelerated by iminium activation. Therefore, it is speculated that cinnamaldehyde derivatives 194 represent ideal acceptors that are susceptible to activation by secondary amine catalysts capable of forming an iminium ion (Scheme 1.85) [132]. The resulting iminium ion activation is expected to increase hydride transfer to alkene. The subsequent ring-closure reaction mediated by enamine catalysis furnishes ring-fused tetrahydroquinoline derivatives in moderate yields and high levels of enantioselectivity.

![Scheme 1.85](image)

**SCHEME 1.85** Catalytic enantioselective hydride-transferring closure.

Other iminium-activated cascade reactions, including [4+3] cycloaddition, Robinson annulations, and reductive Michael cyclization, were also developed to furnish useful synthons [133].

1.4 CYCLE-SPECIFIC CATALYSIS CASCADES

Inspired by the capacity of discrete transform-specific enzymes to coexist in the same reaction medium without unfavorable consequences, Huang et al. hypothesized that the conceptual blueprints of biosynthesis might be translated into a laboratory cascade catalysis sequence through a combination of chiral amine catalysts [134]. Cycle-specific catalysis, in which cycle-specific catalysts are employed discretely in iminium and enamine steps, is thus established, although a single imidazolidinone catalyst enables both activation cycles. The benefits of cycle-specific catalysis, including modular control of an enforced sense of enantio- and diastereoinduction, can be achieved via judicious selection of the chiral amine enantiomer involved in each catalytic cycle. Induction in the enamine addition step arising from catalyst control (as opposed to substrate control) is essential to ensure high levels of diastereoselectivity for the overall process, regardless of the stereogenicity forged in the first iminium step. Improved diastereoselectivities were observed in hydrofluorination of α,β-unsaturated aldehydes using cycle-specific catalysts (the combination A or B) compared with that of the single chiral amine 196–mediated process (Scheme 1.86).
As revealed in Scheme 1.86, the hydrofluorinated product 198 was obtained with 99% ee and 3:1 syn/anti in the presence of catalyst 196. However, implementation of catalyst combination A made possible the formal addition of HF to a trisubstituted enal with 16:1 anti selectivity (99% ee). Remarkably, the syn-HF addition product could be accessed with 9:1 selectivity and in 99% ee simply by changing the enantiomeric series of either amine employed in this catalyst combination (catalyst combination B).

Transfer hydrogenation followed by alkylation of α,β-unsaturated aldehydes mediated by a combination of cycle-specific catalysts of 115 and ent-115 was also developed [135]. It is believed that monofunctional imidazolidinones are optimal for iminium catalysis but without the necessary structural features to participate in bifunctional enamine catalysis (e.g., activation of electrophiles via electrostatic interaction). Conversely, proline has proved to be an enamine catalyst for which bifunctional activation is a standard mode of operation across a variety of transformation types, yet it is generally ineffective as an iminium catalyst with enals or enones. Therefore, a combination of imidazolidinone and proline may provide a dual-catalyst system that could fully satisfy the chemoselectivity requirements for cycle-specific catalysis [136].

The ingenious design proved to be feasible in diverse enantioselective transformations, including olefin hydroamination (Scheme 1.87), hydrooxidation, aminooxidation, reductive Mannich, arylamination, alkylamination, and diamination, to furnish the corresponding products in good yields with high 99% ee. Moreover, impressively, syn- or anti-selective diastereomers 199 were obtained selectively by choosing different enantiomer of proline in conjunction with imidazolidinone catalysts.

What’s more, Chi et al. envisioned that proper site isolation with star polymers could enable the combination of otherwise incompatible catalysts for sophisticated asymmetric cascade reactions (Scheme 1.88) [137]. Noninterpenetrating star polymer
catalysts were designed to combine iminium, enamine, and hydrogen-bond catalysts in one pot for imidazolidinone-mediated nucleophilic addition of N-methyl indole to 2-hexenal, followed by pyrrolidine-catalyzed Michael addition of \textbf{204} to methyl vinyl ketone to afford the product in 89% yield with 100:8 dr and 99% ee. It was shown that none of the three catalysts and cocatalysts, nor any of their combinations, could mediate both reaction steps.

Star polymers 200 and 202 cannot penetrate each other’s core and therefore are expected to maintain their catalytic integrity. On the other hand, small-molecule reagents and catalysts can freely diffuse to the core of the star polymers. MacMillan’s imidazolidinone can diffuse to the core of the acid star polymer 200 to form the desired salt 201, which is an optimal iminium catalyst. Electrostatic attraction should retain 199 within the core of 200 during catalysis. The presence of strong acid p-TSA (alone or paired with imidazolidinone 199) diminishes the ability of 202 to effect iminium catalysis. Additionally, a hydrogen-bond donor catalyst 203...
added to the one-pot reaction is expected to activate the relatively nonreactive Michael acceptor (methyl vinyl ketone) in the enamine catalysis cycle. It also demonstrates that the proper combination of catalyst chirality allows straightforward access individually to all possible stereoisomers of the cascade products.

Interestingly, a polarity-directed cascade reaction in which two catalysts were involved, with each catalyst mediating an individual reaction step in either the aqueous or organic phase, was also developed by Fréchet’s group [138].

In addition to iminium-initiated cascade reactions, two of the steps in enamine-activated cascade reactions can also be enforced by cycle-specific catalysis. It is well known that diphenylprolinol silyl ether catalyst 34 is optimal for diverse enamine-mediated transformations to furnish products with high enantioselectivities. However, similar to imidazolidinone catalysts, it proved to be less effective or ineffective for bifunctional enamine catalysis. Cycle-specific catalysis via an aza-Michael/Mannich sequence by combining 34 and either enantiomer of proline was thus developed to generate 206 in about 60% yields with excellent diastereo- and enantioselectivities (Scheme 1.89) [139].

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\text{Scheme 1.89 Aza-Michael/Mannich cascade by cycle-specific catalysis.}
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The combination of diphenylprolinol silyl ether catalyst 34 with a primary amine catalyst was used to promote the double α-functionalization of aldehydes [140]. A combination of enamine or iminium catalysis with N-heterocyclic carbene catalysis [141] and hydrogen-bonding catalysis [142] was also developed.

1.5 OTHER STRATEGIES

Chiral amine catalysts have also been used in cascade reactions mediated by SOMO catalysis [143] and Lewis base catalysis [144]. MacMillan’s group developed a powerful cascade reaction moderated by SOMO catalysis. The radical cation, generated from an enamine in condensation of imidazolidinone catalyst 208 with aldehyde 207 and subsequent oxidation by Cu\(^{2+}\) oxidant, was expected to engage in a series of 6-endo-trig radical cyclizations terminated by a suitable arene to give a cyclohexadienyl radical. After a second oxidation, rearomatization, and liberation of the catalyst, the requisite 209 would be generated (Scheme 1.90).
1.6 SUMMARY AND OUTLOOK

Beyond the organic chemists’ initial imagination, two unique interconvertible enamine and iminium activation modes have produced a number of unprecedented powerful cascade processes in the formation of diverse complex structures with high efficiency and excellent stereoselectivities. This not only expands the scope of amino catalysis significantly, but more important, affords new and efficient synthetic methods in organic synthesis. It is expected that new cascade reactions with activation modes will continue to be developed to meet the synthetic demand.

We are delighted that beyond the original domain of organocatalysis, powerful cycle-specific catalyses, in which cycle-specific catalysts are employed discretely in iminium and enamine steps, have been established as effective strategies to achieve new organic transformations. Furthermore, chiral amino catalysts have been employed in cascade reactions mediated by new SOMO catalysis. However, the scope of the cascade reactions mediated by cycle-specific and SOMO catalysis is still limited. More important, further efforts also need to be made in larger-scale synthesis and possible applications in the total synthesis of natural products. Among existing problems, it is also realized that, for example, in general, high catalyst loadings are required for effective transformations. Therefore, the development of new and more efficient catalysts and new activation modes to overcome the obstacles is a fundamentally important but challenging task for organic chemists.

REFERENCES


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