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AMINE-CATALYZED CASCADE REACTIONS

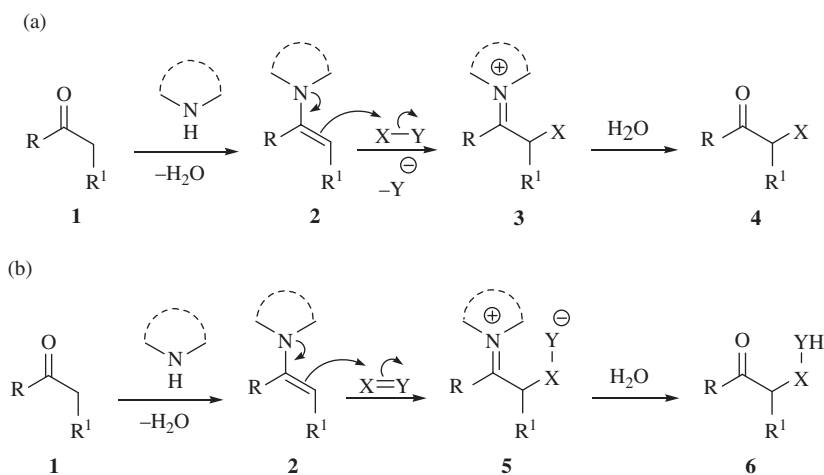
AIGUO SONG AND WEI WANG

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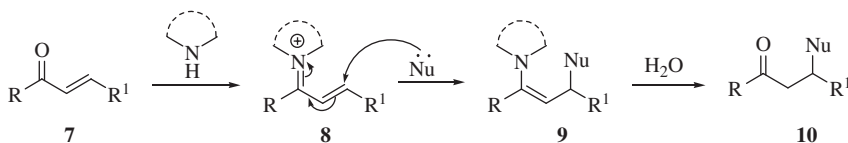
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1.1 INTRODUCTION

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 α -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 α -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.



SCHEME 1.2 Iminium catalysis.

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 γ -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.

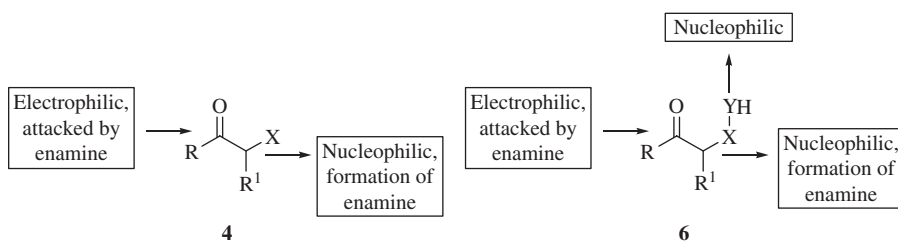
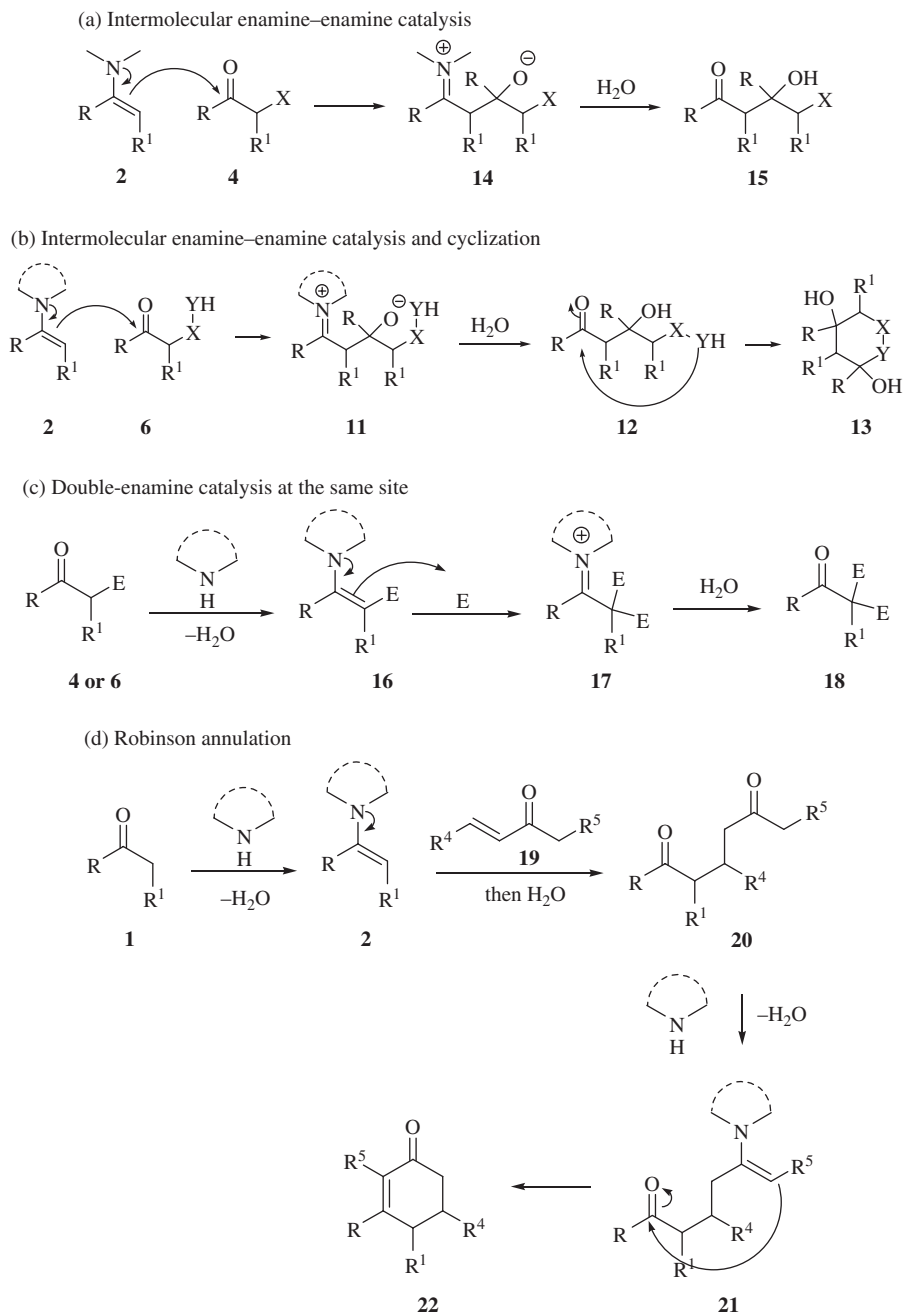
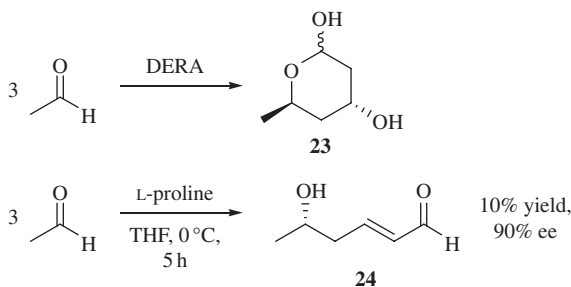


FIGURE 1.1 Possible sites of enamine catalysis products for a second enamine-activated process.

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**



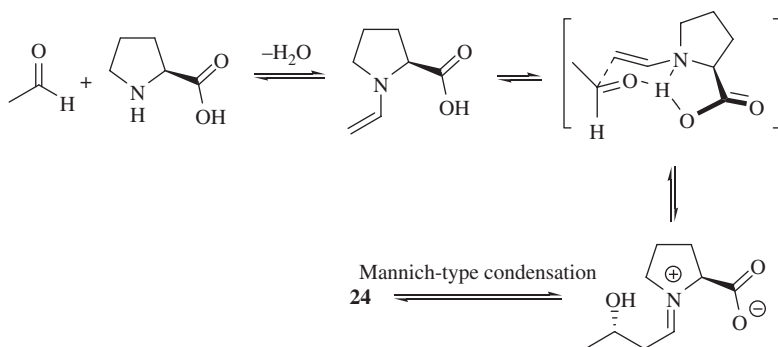
SCHEME 1.3 Design of enamine–enamine cascade catalysis.



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**.

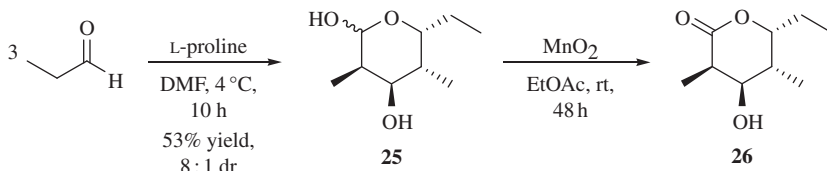


SCHEME 1.5 Mechanism proposed for proline-catalyzed self-aldolization of acetaldehyde.

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).

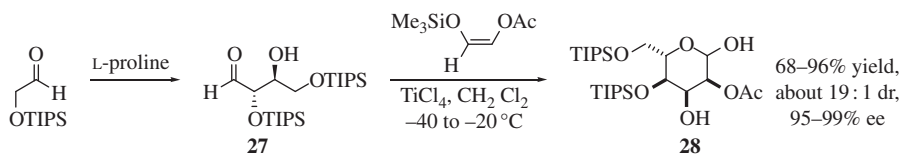
Reactions involving nonequivalent aldehydes were also examined. When 2 equiv of propionaldehyde was added slowly over 24 h to acceptor aldehydes such as isobutyraldehyde or isovaleraldehyde, lactones were formed as single diastereomers in moderate yields (20 to 30%) and poor ee (12%). Improved ee (25%)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



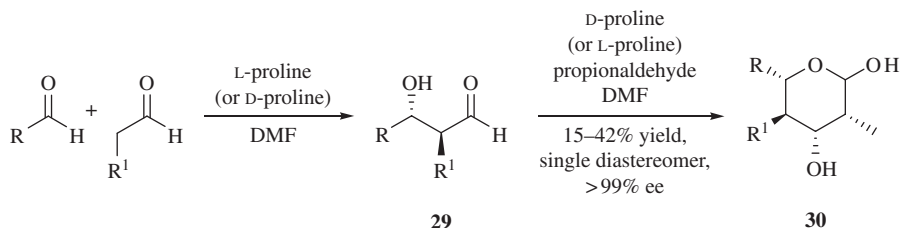
SCHEME 1.6 Proline-catalyzed assembly of propionaldehyde and conversion to lactone.

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%).



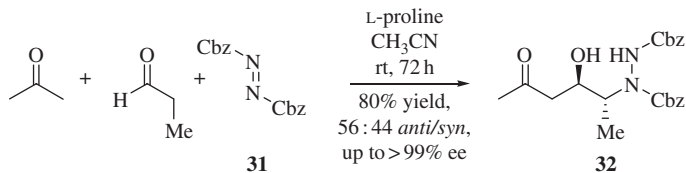
SCHEME 1.7 Two-step synthesis of hexoses with organo- and Lewis acid catalysis.

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].



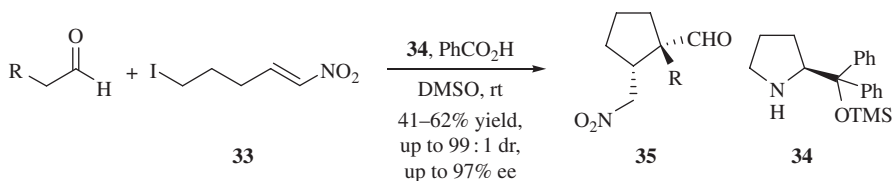
SCHEME 1.8 Two-step direct proline-catalyzed enantioselective synthesis of hexoses.

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 azodicarboxylic 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].



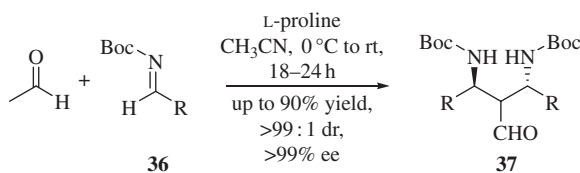
SCHEME 1.9 Proline-catalyzed three-component reaction.

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.



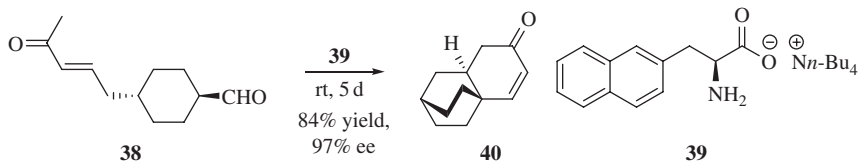
SCHEME 1.10 Organocatalytic domino reaction of aldehydes and (*E*)-5-iodo-1-nitropent-1-ene.

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- C_2 -symmetric β,β' -diaminoaldehydes **37** with extremely high stereoselectivities (>99:1 dr, >99% ee) [13]. A similar approach with ketones was also realized [14].



SCHEME 1.11 Double Mannich reactions of acetaldehyde.

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].



SCHEME 1.12 Amino acid salt-catalyzed intramolecular Robinson annulation.

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).

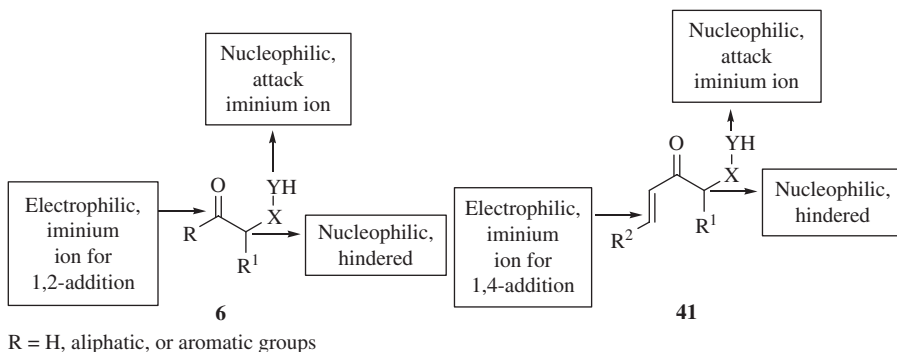


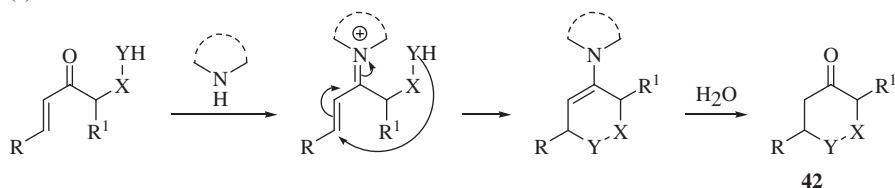
FIGURE 1.2 Design of enamine–iminium cascade catalysis.

A special but significant case of **6** is that of the α,β -unsaturated ketones **41** (R is a vinyl group). An intramolecular attack on the α,β -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).

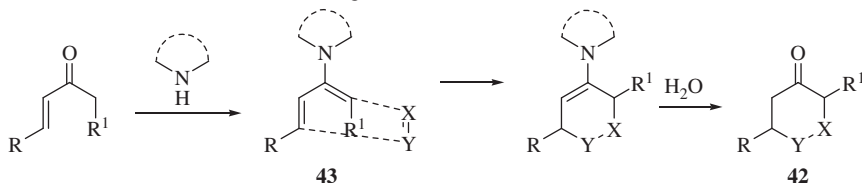
In principle, simple intermediate **6** can undergo a similar intramolecular iminium process with an electrophilic carbonyl group. However, the resulting four-membered ring is too small to be formed from the attack of carbonyl by nucleophilic Y. Prolongation of electrophile **44** is necessary (Scheme 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

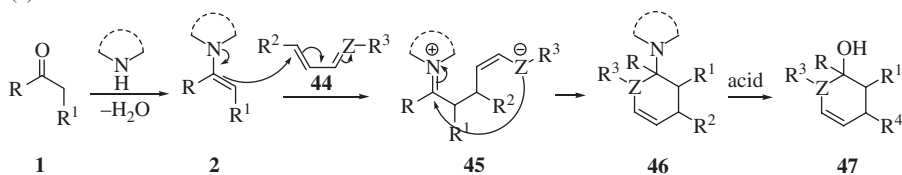
(a) Double-addition reactions via enamine–iminium



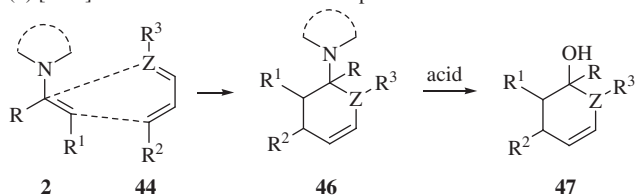
(b) [4+2] Reactions with HOMO-raising dienes

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

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

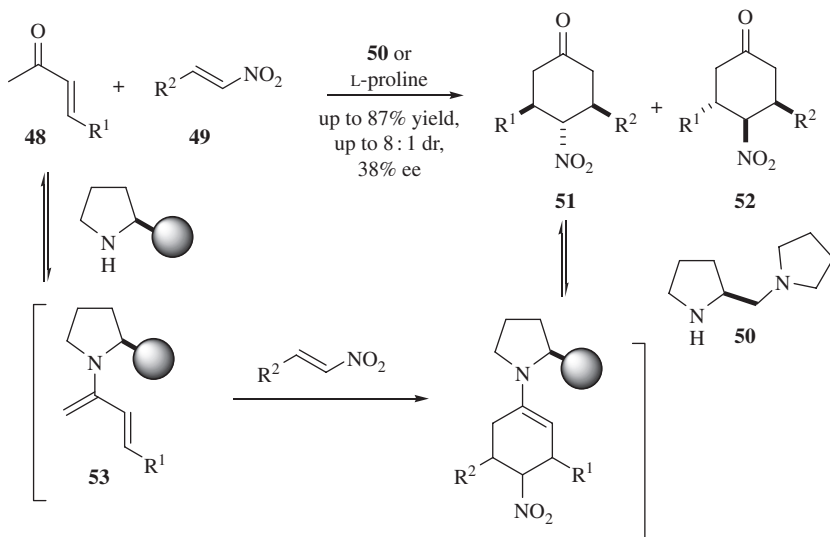


(b) [4+2] Reactions with activated dienophiles

**SCHEME 1.14** Design of an enamine–iminium sequence based on **6** and **44**.

reactions, although concerted mechanisms are always proposed for these reactions. Thus, the enamine–iminium activation sequence has been used in [4+2] cycloaddition reactions.

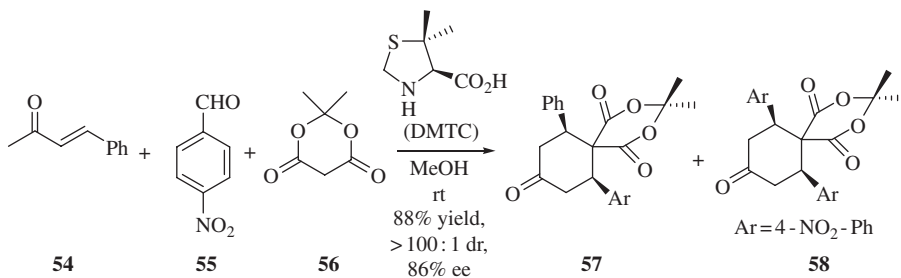
In addition to the consecutive aldol reactions of aldehydes, Barbas's group also reported enamine-activated Diels–Alder reactions (or double Michael reactions) between α,β -unsaturated ketones and nitroolefin (Scheme 1.15) for the first time in 2002 [17]. In contrast to MacMillan's iminium catalysis 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



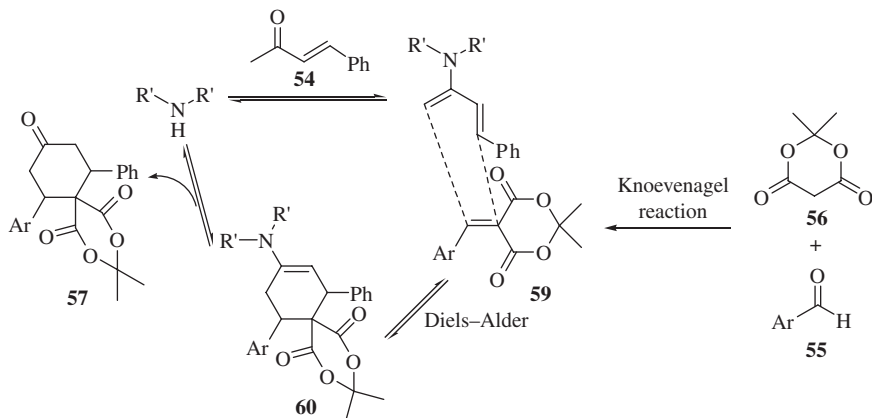
SCHEME 1.15 Enamine-activated dienes for Diels–Alder reactions.

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 1.16 Amino acid-catalyzed asymmetric three-component Diels–Alder reaction.

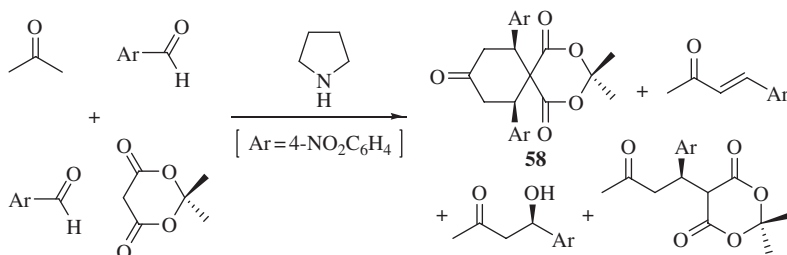


SCHEME 1.17 Mechanism of a secondary amine-catalyzed asymmetric three-component Diels–Alder reaction.

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.

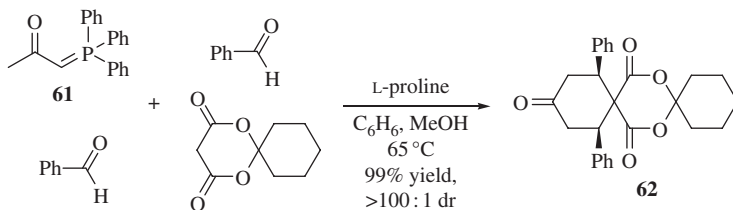
The asymmetric domino three-component Knoevenagel/Diels–Alder addition reaction promoted by the primary amine catalyst 9-amino-9-deoxy-*epi*-quinine was also reported. Various pharmacological multisubstituted spiro[5,5]undecane-1,5,9-triones were obtained in moderate to good yields (up to 81%) with excellent diastereo- (>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.



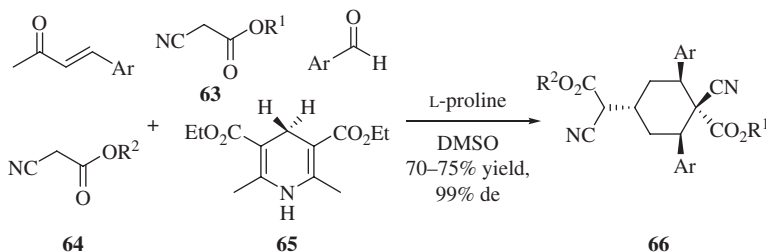
SCHEME 1.18 Pyrrolidine-catalyzed stereospecific multicomponent aldol/Knoevenagel/Diels–Alder reaction.

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).



SCHEME 1.19 Wittig/Knoevenagel/Diels–Alder reaction.

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 diastereoselective fashion (99% de) with excellent yields (70 to 75%) was also reported (Scheme 1.20) [23].

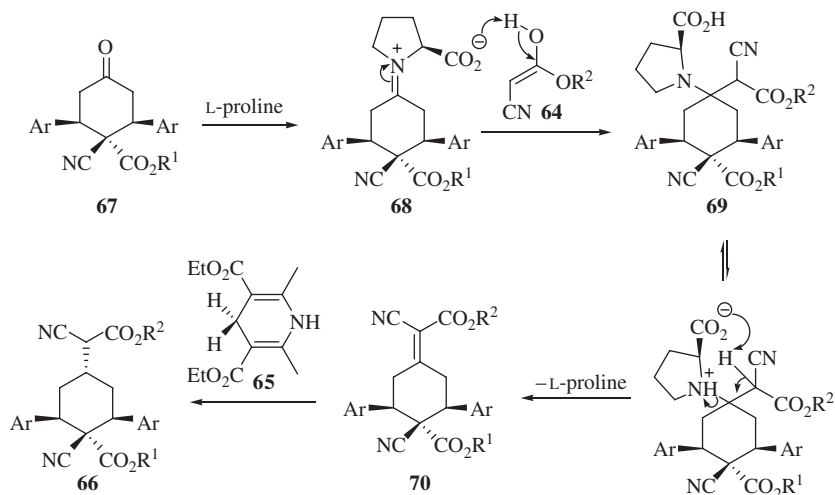


SCHEME 1.20 Cascade olefination/Diels–Alder/epimerization/olefination/hydrogenation reactions.

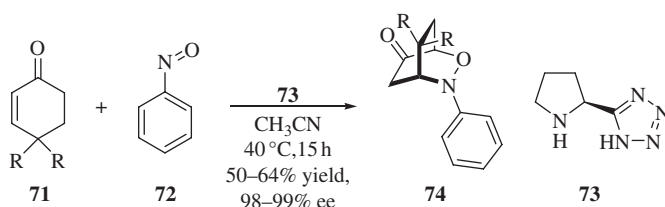
The possible reaction mechanism for a cascade olefination–hydrogenation reaction is illustrated in Scheme 1.21. First, the reaction of proline with *cis*-isomer **67** generates the iminium cation **68**, which reacts with electrophile **64** via a Mannich-type reaction to generate Mannich product **69**. 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].

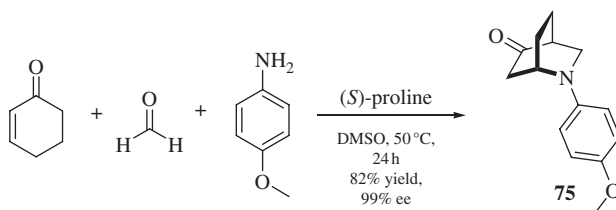
Similarly, the first direct catalytic enantioselective aza-Diels–Alder reaction was also accomplished with excellent stereoselectivity (94 to 99% ee) (Scheme 1.23) [25].



SCHEME 1.21 Mechanism proposed for proline-catalyzed olefination–hydrogenation reactions.

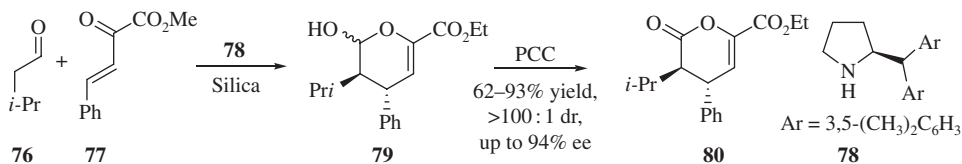


SCHEME 1.22 *o*-Nitroso aldol–Michael reactions.



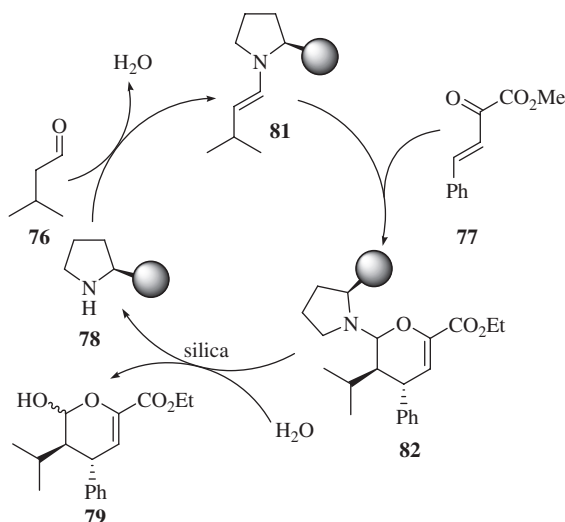
SCHEME 1.23 Amine-catalyzed direct enantioselective aza-Diels–Alder reaction.

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].



SCHEME 1.24 Organocatalytic hetero-Diels–Alder reaction.

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 amination **82**. The presence of silica facilitates the hydrolysis step in the catalytic cycle.

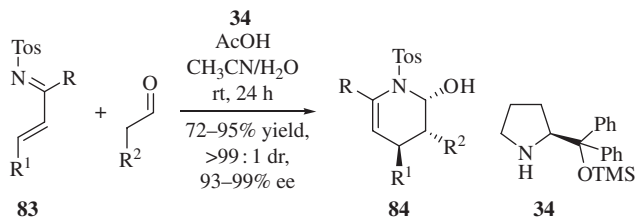


SCHEME 1.25 Catalytic cycle for an organocatalytic hetero-Diels–Alder reaction.

Inverse-electron-demand hetero-Diels–Alder reaction of enolizable aldehydes with α,β -unsaturated ketophosphonates [27], *o*-quinones [28], α -keto- α,β -unsaturated esters [29], α,β -unsaturated trifluoromethyl ketones [30], and *o*-benzoquinone diimide [31] was also reported.

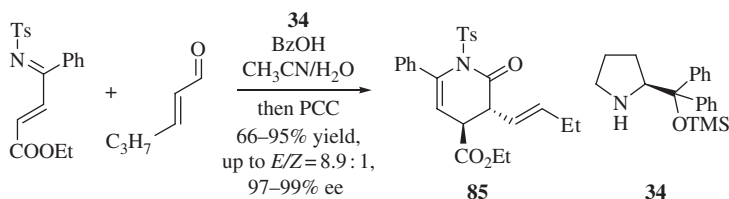
Encouraged by Jørgensen's inverse-electron-demand hetero-Diels–Alder reaction of aldehydes and α,β -unsaturated α -keto esters, Han, He, and others envisaged that an unprecedented asymmetric aza-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes and aldehydes might be developed by employing a 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 α,β -unsaturated aldehydes, which acted as nucleophiles for direct enantioselective γ -amination with



SCHEME 1.26 Aza-Diels–Alder reaction with aldehydes by dienamine catalysis.

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.



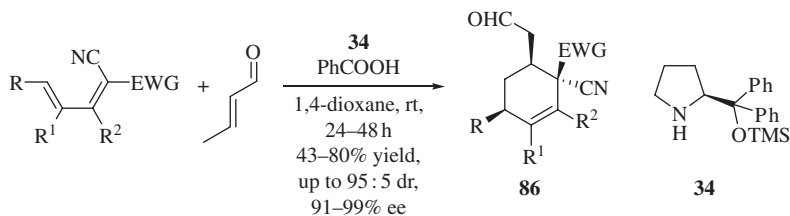
SCHEME 1.27 Aza-Diels–Alder reaction with enals by dienamine catalysis.

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).

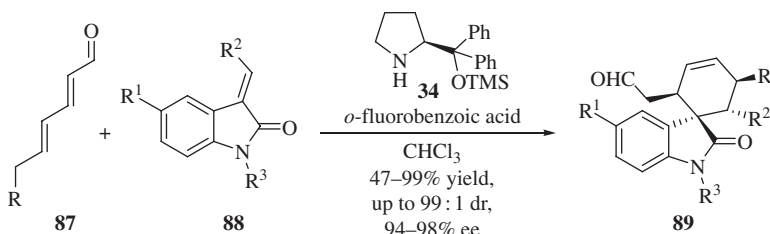
Synthesis of dicyano-2-methylene-but-3-enoates as novel dienes for all-carbon-based asymmetric inverse-electron-demand Diels–Alder reactions with aldehydes was also developed [37].

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



SCHEME 1.28 Diels–Alder reaction by dienamine catalysis.

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 oxindoles **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.

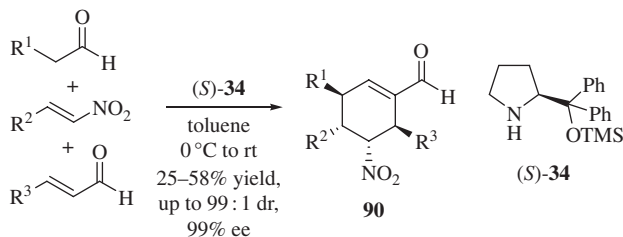


SCHEME 1.29 Organocatalyzed Diels–Alder reactions with 3-olefinic oxindoles involving trienamine catalysis.

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.

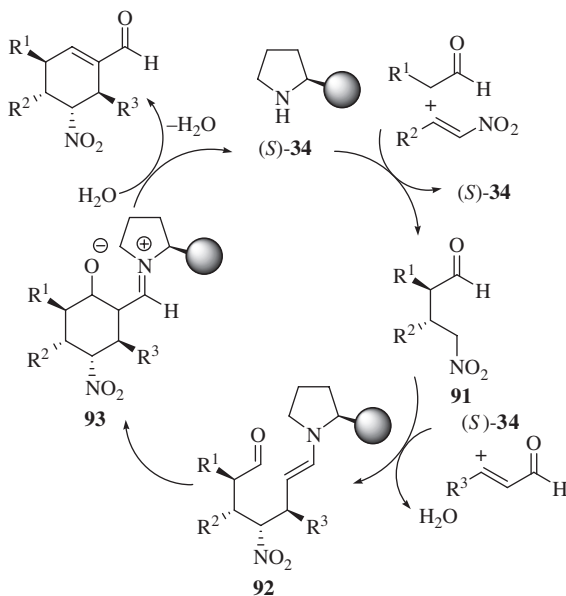
The asymmetric organocatalytic triple cascade reaction for the synthesis of tetrasubstituted cyclohexene carbaldehydes developed by Enders et al. (Scheme 1.30) [40] is a milestone of organocatalytic cascade reactions. This three-component domino reaction proceeds by way of a catalyzed Michael–Michael–aldol 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 α,β -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 α,β -unsaturated aldehyde to accomplish the conjugate addition



SCHEME 1.30 Organocatalytic three-component cascade involving an enamine–iminium–enamine cycle.

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 α,β -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 α,β -unsaturated aldehyde, is highly sterically hindered for further Michael addition compared to the enal.

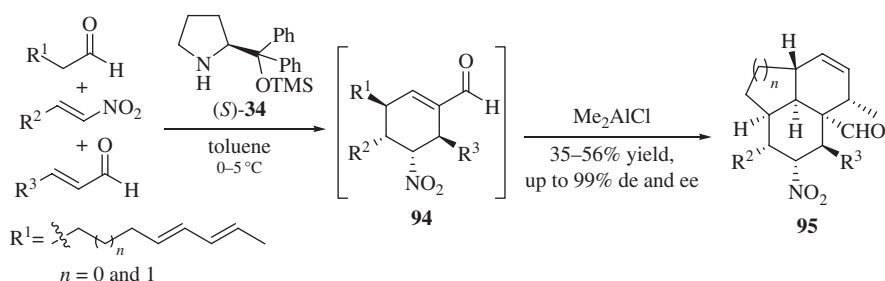


SCHEME 1.31 Catalytic cycle proposed for the triple cascade.

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 α,β -unsaturated aldehyde to

a diethyl vinylphosphonate derivative [44], multisubstituted structurally diverse cyclohexene carbaldehydes with several stereogenic centers were efficiently synthesized.

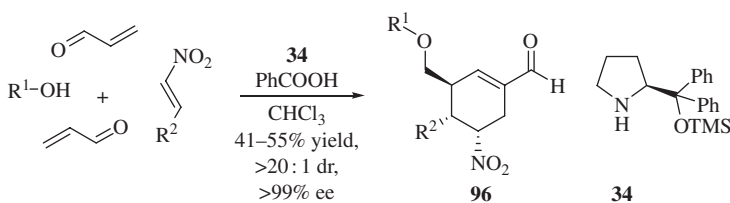
Enders et al. also developed an efficient one-pot procedure that provided direct entry to diastereo- and enantiomerically pure ($\geq 99\%$ de, ee) polyfunctionalized tricyclic frameworks **95** [45] (Scheme 1.32). The organocatalytic triple cascade, followed by a Diels–Alder sequence, leads to decahydroacenaphthylene 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 aldehyde can also be generated in situ via an extra iminium catalysis from an α,β -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].



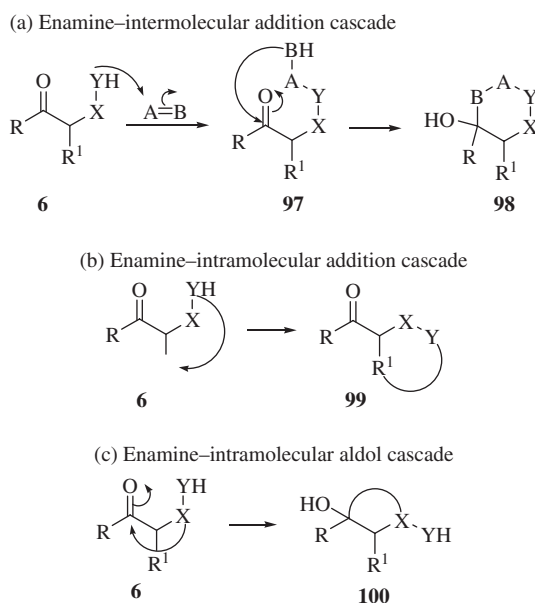
SCHEME 1.33 Four-component cascade reactions through iminium–enamine–iminium–enamine sequential activation.

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.

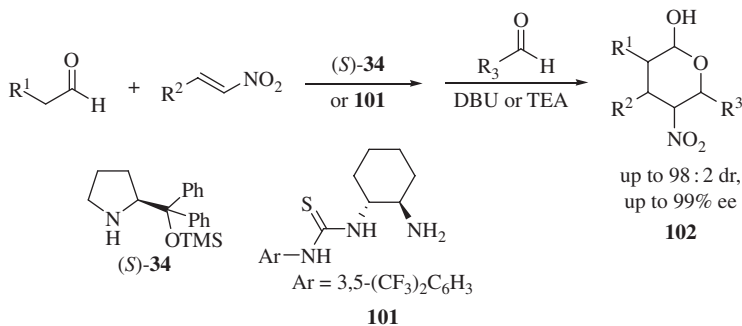
1.2.3.1 Design of Enamine-Cyclization Cascade Reactions The nucleophilic Y in intermediate **6** can react with other electrophiles intermolecularly (Scheme 1.34a) or intramolecularly (Scheme 1.34b) as well as with the iminium ion. Moreover, the carbonyl group of **6** can also undergo intramolecular 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.



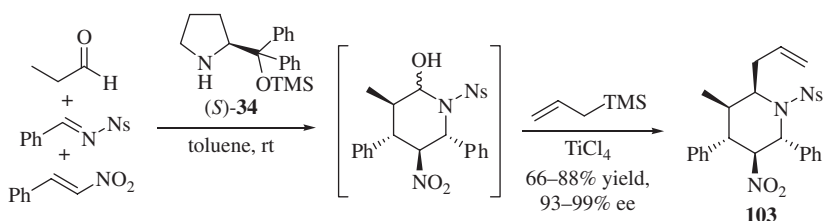
SCHEME 1.34 Design of an enamine cyclization cascade.

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



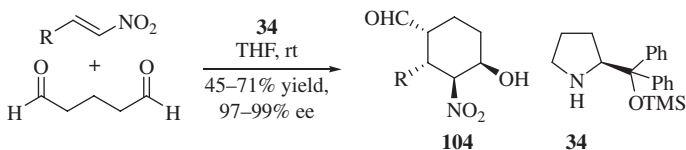
SCHEME 1.35 One-pot synthesis of tetrahydropyrans.



SCHEME 1.36 One-pot synthesis of chiral piperidine derivatives.

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].

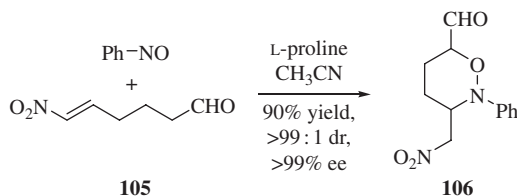
1.2.3.3 Enamine-Intramolecular Addition Cascades Hayashi et al. envisioned that an enamine generated from one carbonyl of pentane-1,5-dial with catalyst **34** reacted with a nitroalkene in a Michael addition, followed by an intramolecular Henry reaction with the other aldehyde, would provide substituted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



SCHEME 1.37 Catalytic asymmetric Michael-Henry cascade.

A similar strategy was extended to the reaction of pentane-1,5-dial with aldehydes [55a], imine [55b], and alkylidene malonate [55c].

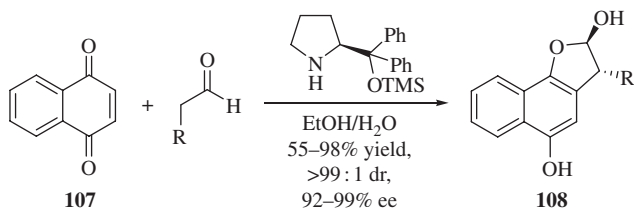
It also proved feasible to replace pentane-1,5-dial with alkenal **105** [56] or 2-(5-oxopentylidene) malonates [57] for α -aminoxylation/aza-Michael reactions based on a similar strategy. The α -aminoxylation of alkenal **105** with nitrosobenzene



SCHEME 1.38 Synthesis of functionalized tetrahydon-1,2-oxazines.

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].



SCHEME 1.39 Organocatalytic α -arylation of aldehydes.

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

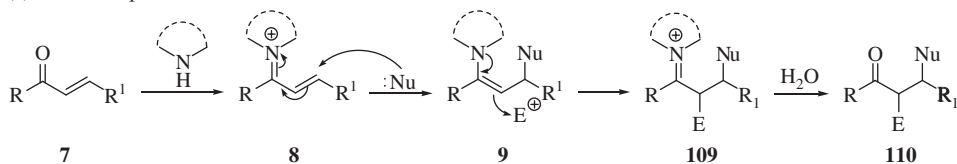
1.3 IMINIUM-INITIATED CASCADE REACTIONS

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.

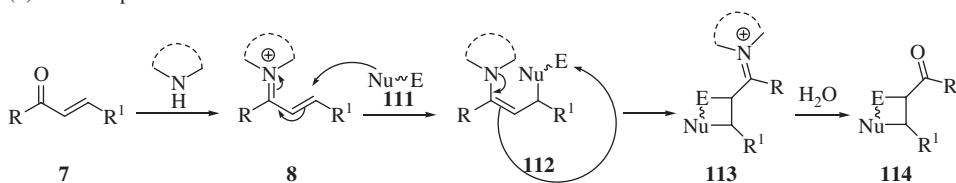
1.3.1 Design of Iminium–Enamine Cascade Reactions

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.

(a) Three-component iminium–enamine cascade reactions



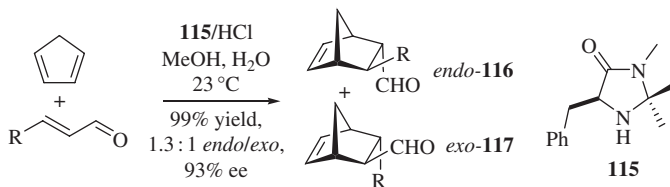
(b) Two-component iminium–enamine cascade reactions



SCHEME 1.40 Iminium–enamine cascade catalysis.

1.3.2 Iminium-Activated Diels–Alder Reactions

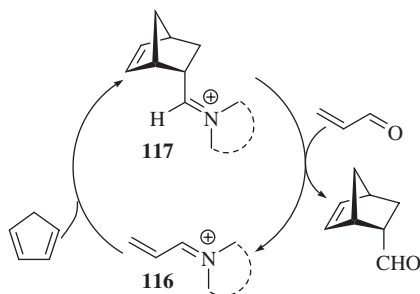
In an analog to Lewis acid catalysis, Northrup and MacMillan introduced the first organocatalytic asymmetric Diels–Alder reaction between diverse dienes and α,β -unsaturated aldehydes catalyzed by **115** (Scheme 1.41), which proceeded with excellent enantioselectivity despite low diastereoselectivity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



SCHEME 1.41 Organocatalytic Diels–Alder reactions.

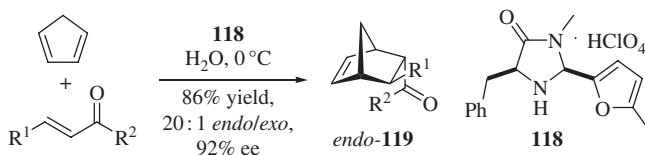
It was proposed that condensation of aldehyde with **115** would lead to the formation of an iminium ion **116** (Scheme 1.42). The activated dienophile reacted with a diene to lead to iminium ion **117**. Upon hydrolysis, the enantioenriched cycloaddition product was produced while releasing the chiral 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 α,β -unsaturated aldehydes with unprecedented high *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 α,β -unsaturated aldehydes were also developed [65].



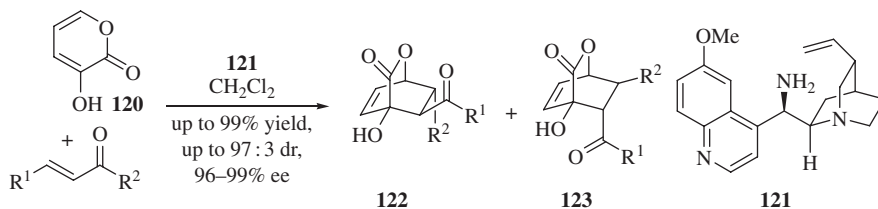
SCHEME 1.42 Mechanism proposed for organocatalyzed Diels–Alder reactions.

Northrup and MacMillan extended the iminium-mediated Diels–Alder reactions to α,β -unsaturated ketones using a new chiral amine catalyst (Scheme 1.43) [66]. They found that cycloaddition of α,β -unsaturated ketones was unsuccessful with the chiral amine salts previously identified as excellent catalysts for enal activation. In contrast, the 2-(5-methylfuryl)-derived imidazolidinone **118** afforded good levels of enantiofacial discrimination while maintaining high reaction efficiency (89% yield, 25:1 *endo/exo*, 90% ee).



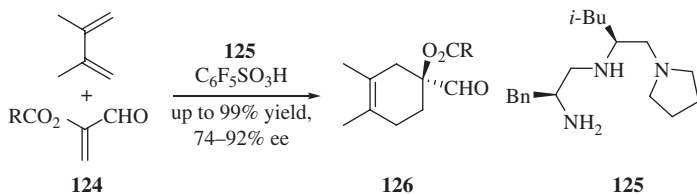
SCHEME 1.43 Diels–Alder reaction of enones with cyclopentadiene.

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].



SCHEME 1.44 Diels–Alder reaction of enones with 2-pyrone.

It was difficult to activate α -branched aldehydes such as acroleins with secondary amines because of the steric effect of poor generation of the corresponding iminium ions. An enantioselective Diels–Alder reaction with α -substituted acroleins **124** was realized by a primary amine organocatalyst **125** (Scheme 1.45) [68]. Acyclic dienes



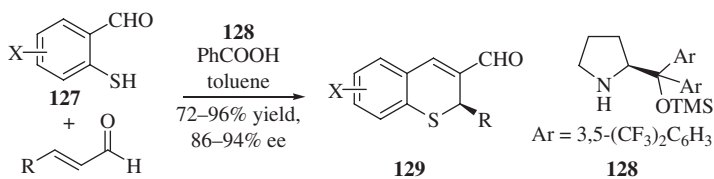
SCHEME 1.45 Diels–Alder reaction with α -substituted acroleins.

and cyclohexadiene with α -(*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.

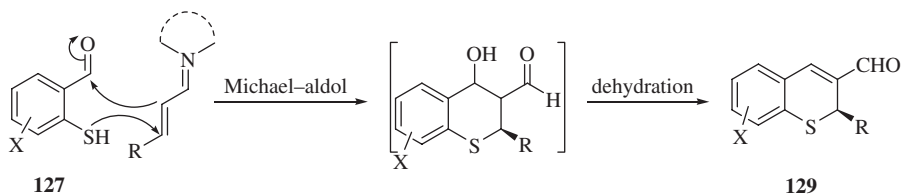
A diammonium salt of chiral 1,1'-binaphthyl-2,2'-diamine and trifluoromethanesulfonimide (Tf_2NH) (5 mol% loading) showed excellent catalytic activity and enantioselectivity (88% yield with 92% *exo* and 91% ee) toward the Diels–Alder reaction of α -acyloxyacroleins with cyclic dienes [69]. Extension of Diels–Alder reactions to α -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 thiochromenes with good to high enantioselectivities was reported (Schemes 1.46 and 1.47) [71].



SCHEME 1.46 Cascade Michael–aldol condensation reactions.

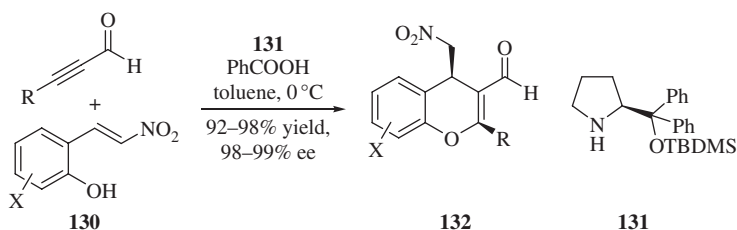


SCHEME 1.47 Pathway of cascade Michael–aldol condensation reactions.

In the process, activation of α,β -unsaturated aldehydes by a chiral organocatalyst produces iminiums which trigger a Michael–aldol cascade process to afford intermediates which undergo spontaneous dehydration to give α,β -unsaturated aldehydes **129**.

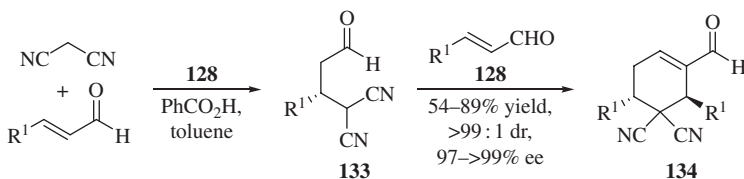
The extension of this strategy to 2-mercaptobenzaldehyde and α,β -unsaturated ketones [72], 2-mercaptoacetophenones [73], salicylaldehydes [74], 2-amino benzaldehydes [75], 2-(nitromethyl)benzaldehyde [76], and 2-((*E*)-2-nitrovinyl)phenol [77] has been disclosed.

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.



SCHEME 1.48 Enantioselective oxa-Michael/Michael cascade reactions with alkynals.

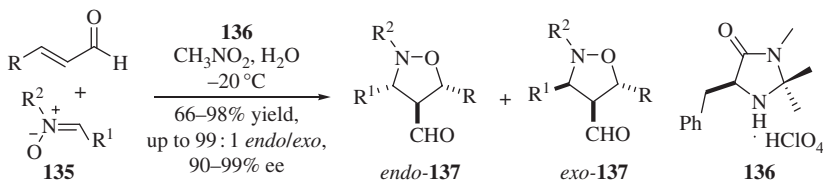
Carlone et al. assumed that reactants bearing 1,4-nucleophilic–electrophilic sites for sequential [4+2] reactions of enals could be possible (Scheme 1.49) [82]. The overall [3+2+1] reaction was thus achieved with 2 equiv enals and 1 equiv malononitrile to afford cyclohex-1-ene-carbaldehyde derivatives **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].



SCHEME 1.49 Cascade reaction of enals with malononitrile.

1.3.4 Iminium-Activated [3+2] Reactions

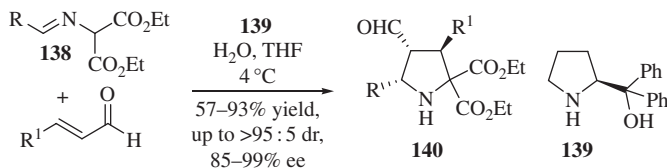
In addition to the LUMO-lowering activated enantioselective Diels–Alder reactions of enals, MacMillan’s group revealed that this catalytic strategy was also amenable to [3+2] cycloadditions between nitrones and α,β -unsaturated aldehydes to provide isoxazolidines in high yields, moderate diastereoselectivity, and moderate enantioselectivity



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

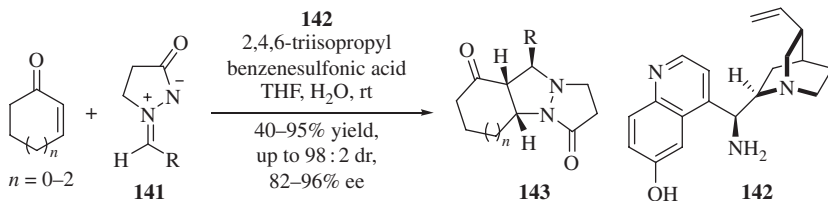
(Scheme 1.50) [84]. Improved diastereoselectivity was achieved when a triflate salt of diphenyl-*S*-prolinol and trimethylsilyl triflate was used to catalyze this reaction [85]. Highly chemo- and enantioselective organocatalytic three-component reaction of enals with in situ-generated nitrones from *N*-arylhydroxylamines 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 regioselectivity and with very high diastereo- and enantioselectivity to furnish highly functionalized polysubstituted pyrrolidines **140** in good yields (Scheme 1.51) [87].



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

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).

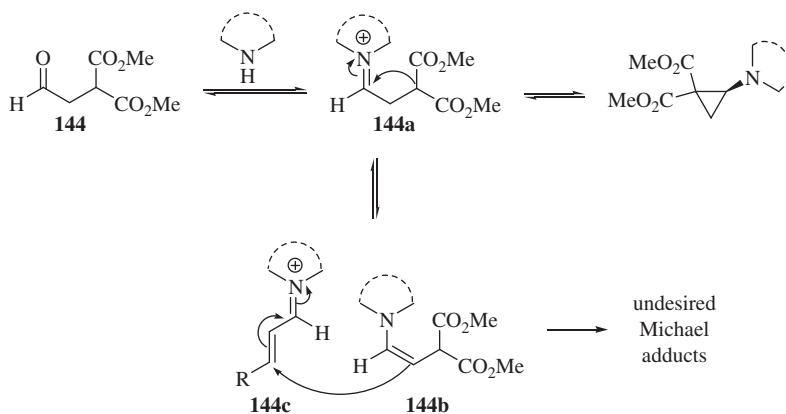


SCHEME 1.52 1,3-Dipolar cycloaddition of azomethine imines to cyclic enones.

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.

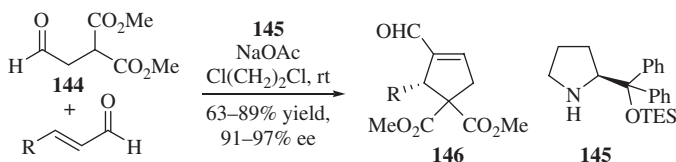
Development of such a catalytic cascade process requires a stable and electron-rich carbon species as a nucleophile, which should be compatible with electrophilic aldehyde functionality in one of the chemical entities **144** (Scheme 1.53) [90]. Undesired reaction of **144** with the catalyst to produce 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**.



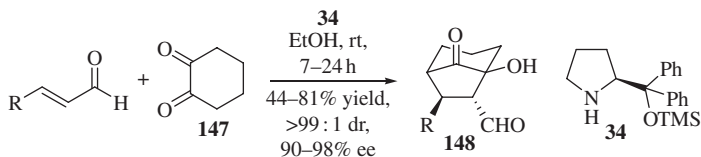
SCHEME 1.53 Possible undesired reactions.

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



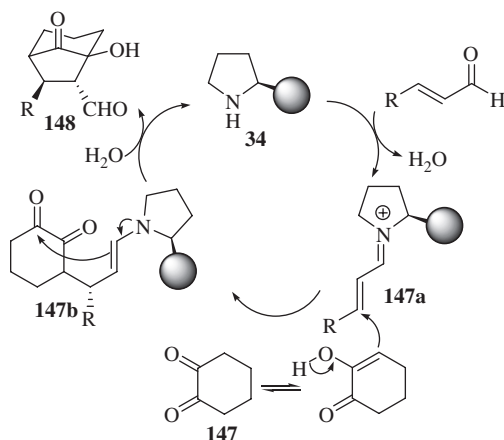
SCHEME 1.54 Cascade Michael–aldol reactions with malonate aldehyde.



SCHEME 1.55 Cascade Michael–aldol reactions with 1,2-cyclohexadione.

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.



SCHEME 1.56 Catalytic cycle proposed for cascade Michael–aldol reactions with 1,2-cyclohexadione.

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].

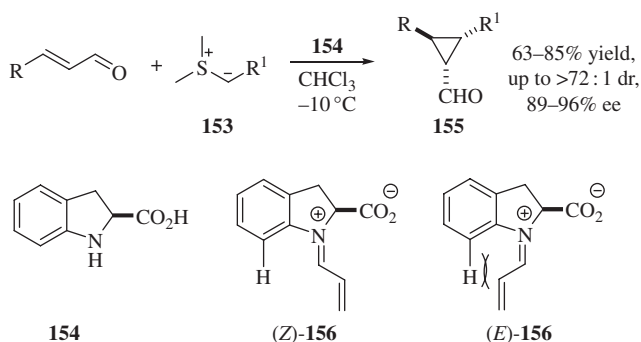
A plausible mechanistic proposal for this transformation is described (Scheme 1.58). The reaction started with the conjugate addition of **149** to the enal under iminium activation, and then the intermediate enamine **149a** would undergo an intramolecular

aldehydes with a *trans*- γ -N-protected α,β -unsaturated ester, and a nitro-Michael/Michael sequence [98] of α,β -unsaturated aldehydes with 5-nitropentenoate esters was also developed. Moreover, a chiral amine-catalyzed domino Michael/ α -alkylation reaction that provides access to cyclopentanones was also reported [99].

1.3.6 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.

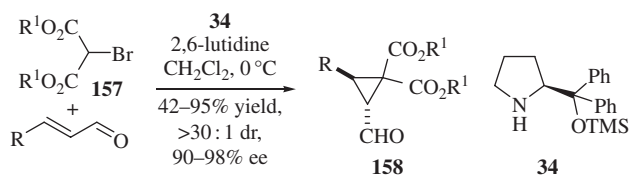
1.3.6.1 Iminium-Activated Cyclopropanations Kunz and MacMillan developed a highly efficient protocol for the construction of enantioenriched cyclopropanes using stabilized ylides with dihydroindole catalysts (Scheme 1.60) [100]. 2-Carboxylic acid dihydroindole **154** might function as a directed electrostatic activation (DEA) cyclopropanation catalyst. Iminium **156** and the ylide **153** engaged in electrostatic association via their pendant carboxylate and thionium substituents. The zwitterionic **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.



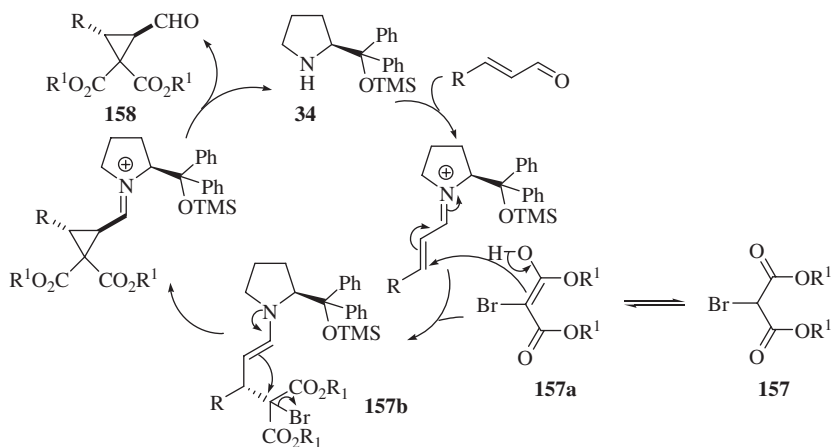
SCHEME 1.60 Organocatalytic ylide cyclopropanation.

A second-generation catalyst in which the carboxylic acid of (*S*)-(-)-indoline-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 ($\geq 30:1$ dr) and in high yields without intoxicating the catalyst.



SCHEME 1.61 Domino Michael alkylation for cyclopropanation.



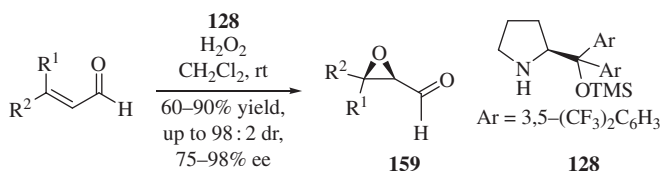
SCHEME 1.62 Mechanism for a Michael-alkylation cascade.

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.

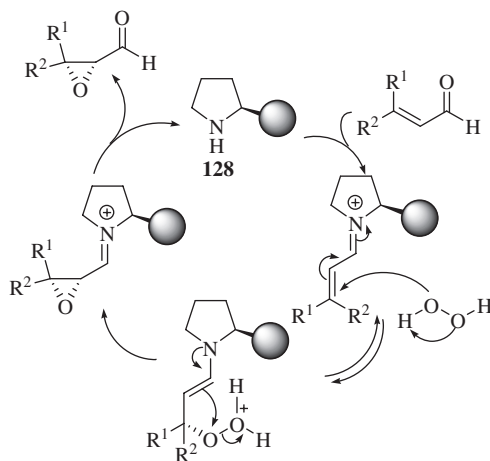
Nitrocyclopropanation of enones [104] and enals [105] with 2-bromonitromethane was also reported.

1.3.6.2 Iminium-Activated Epoxidations Similar to ylide **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 H_2O_2 as the oxidant (Scheme 1.63) [106]. The reactions take place under mild conditions in good to high yields and enantio- and diastereoselectivities.



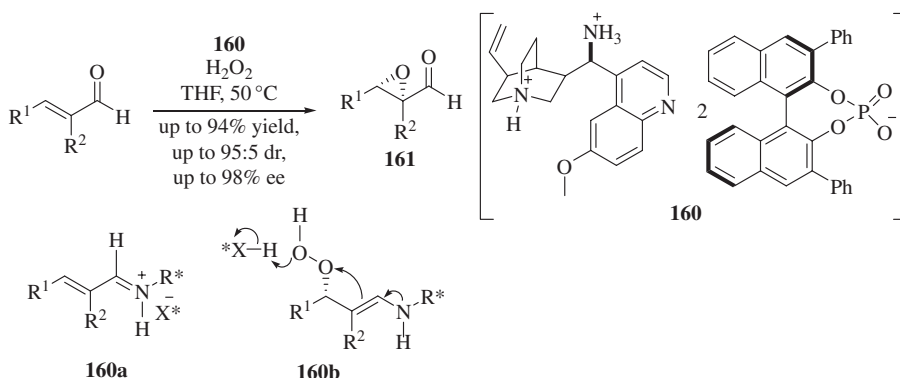
SCHEME 1.63 Organocatalytic epoxidation of enals with hydrogen peroxide.

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 peroxy oxygen atom.



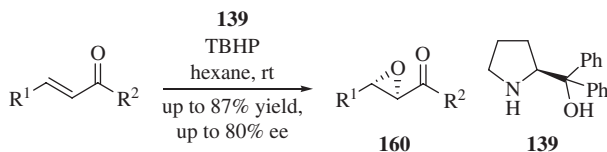
SCHEME 1.64 Mechanism of organocatalytic epoxidation.

Despite the excellent results of epoxidation of simple α,β -unsaturated aldehydes, a general method for the epoxidation of α -branched α,β -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.



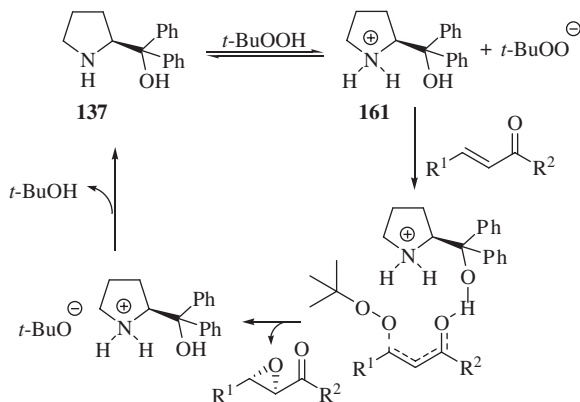
SCHEME 1.65 Epoxidation of α,β -disubstituted enals.

Logically, the organocatalytic epoxidation reactions were extended to α,β -unsaturated ketones using α,α -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].



SCHEME 1.66 α,α -Diphenyl-*L*-prolinol-catalyzed epoxidation of enones.

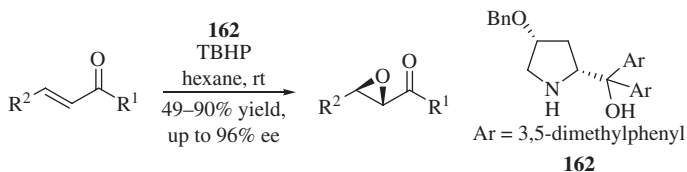
A novel reaction pathway was proposed for the prolinol-mediated epoxidation of enones (Scheme 1.67). Catalyst **139** activates the TBHP by deprotonation to generate more nucleophilic *tert*-butyl hydroperoxide anion and the corresponding ammonium cation **161**, which constitute a tight ion pair in hexane. The hydroxyl group of the diaryl-methanol 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



SCHEME 1.67 Catalytic cycle proposed for epoxidation of enones.

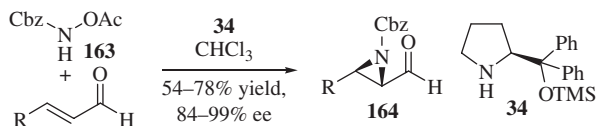
of the *tert*-butyl hydroperoxide anion. The hydrogen-bond-stabilized enolate then attacks the O—O bond intramolecularly, giving rise to epoxide ring closure and elimination of the *tert*-butoxy anion.

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].



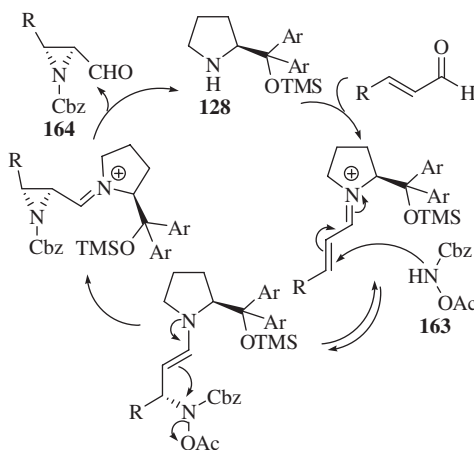
SCHEME 1.68 4-Substituted α,α -diarylprolinol-catalyzed epoxidation of enones.

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].



SCHEME 1.69 Enantioselective organocatalytic aziridination of enals.

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.

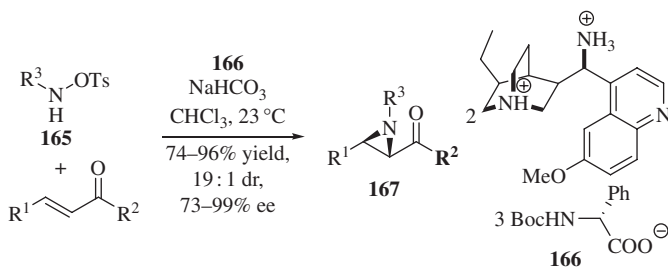


SCHEME 1.70 Mechanism proposed for aziridination.

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).

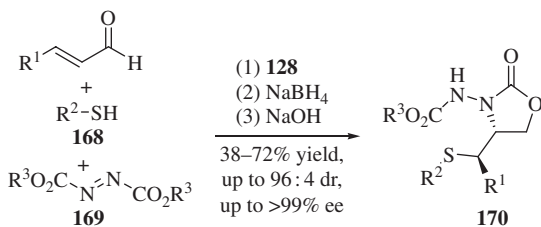
1.3.7 Iminium-Activated Multicomponent Reactions

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.



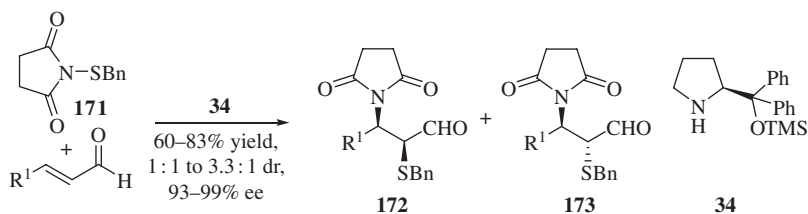
SCHEME 1.71 Enantioselective aziridination of enones.

Marigo et al. developed a multicomponent domino–conjugated nucleophilic thiol addition–electrophilic amination reaction that gave access to 1,2-aminothiols 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.



SCHEME 1.72 Thiol addition–amination–reduction–cyclization reaction.

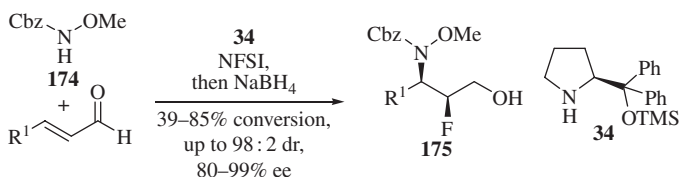
It was possible to incorporate amphiphilic components in one substrate in the organocatalytic domino reactions of enals. This concept was implemented in highly enantioselective aminosulfenylation of α,β -unsaturated aldehydes with amphiphilic *N*-benzylsulfanyl imide **171** that furnished valuable β -amino- α -mercaptoaldehydes **172** and **173** in high yields with 93 to 99+% ee (Scheme 1.73) [115].



SCHEME 1.73 Catalytic asymmetric aminosulfenylation of enals.

An organocascade aminofluorination reaction of α,β -unsaturated aldehydes with **174** and NFSI (*N*-fluorobenzenesulfonimide) as an electrophilic fluorination agent was developed to produce chiral α -fluoro- β -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.

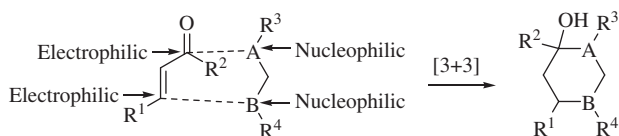
Quintard and Alexakis developed a double Michael addition reaction of enals, taking advantage of the high reactivity of vinyl sulfone-initiated nucleophilic addition of benzaldoxime, triazole, *Angelica* lactone, benzyl mercaptan, and **174**. The powerful organocascade allows for the rapid construction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



SCHEME 1.74 Organocatalytic aminofluorination reactions.

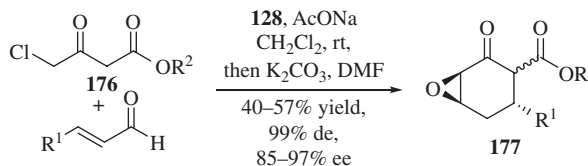
1.3.8 Iminium-Activated [3+3] Reactions

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 α,β -enals, [3+3] reactions can also be conducted by employing reactants bearing 1,3-nucleophilic sites in the iminium-mediated reactions of α,β -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.

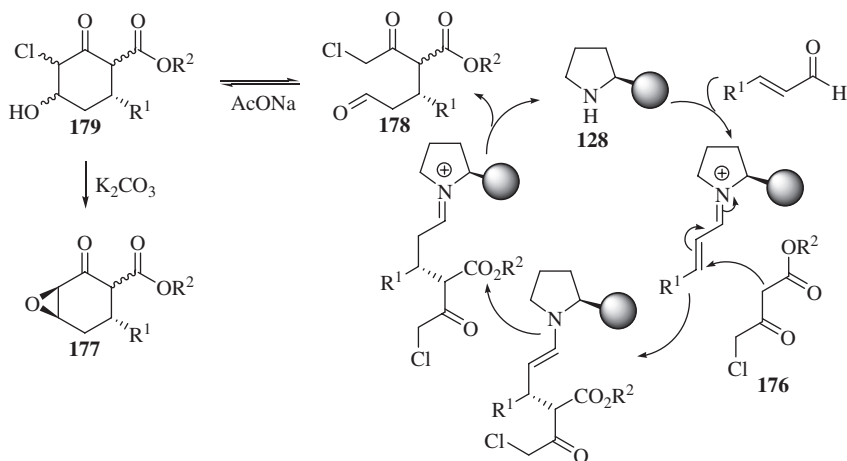
1.3.8.1 Iminium-Activated All-Carbon-Centered [3+3] Reactions The first highly enantioselective organocatalytic [3+3] reaction through Michael–Darzens condensation giving highly functionalized complex epoxy-cyclohexanone derivatives with up to four chiral centers was developed by Marigo et al. with excellent diastereo- and enantioselectivities (Scheme 1.76) [119]. The one-pot organocatalytic domino reactions between γ -chloro- β -keto esters **176** and α,β -unsaturated aldehydes occurred with catalyst **128** and AcONa as additive. The product was then



SCHEME 1.76 Organocatalyzed one-pot Michael–aldol–S_N2 cascade.

converted into the optically active epoxy cyclohexanone **177** in the presence of K₂CO₃.

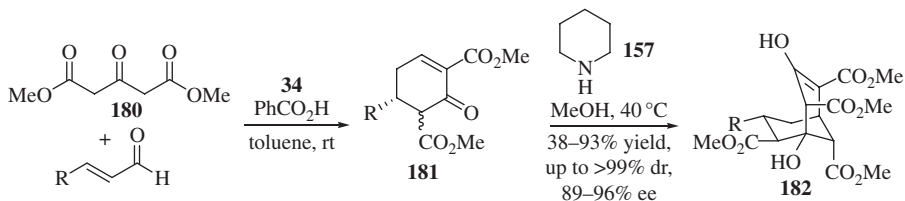
The mechanism proposed for the transformations is illustrated in Scheme 1.77. The β-keto ester **176** approaches the planar iminium ion from the *Re*-face due to steric hindrance of the bulky substituents at the chiral substituent in the pyrrolidine ring of catalyst **128**. Hydrolysis of the enamine 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 (K₂CO₃) deprotonates the alcohol and enables the intramolecular S_N2 reaction, which leads to one-pot formation of the highly functionalized products **177**.



SCHEME 1.77 Mechanism proposed for a one-pot Michael–aldol–S_N2 cascade.

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.

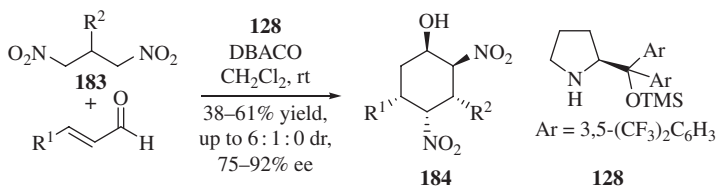
It is noteworthy that the 2-cyclohexenones generated from [3+3] reactions are suitable substrates for another [3+3] reaction. As shown in Scheme 1.78, double [3+3] reactions of α,β-unsaturated aldehydes with 2 equiv of **180** selectively form



SCHEME 1.78 Double [3+3] reactions.

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].

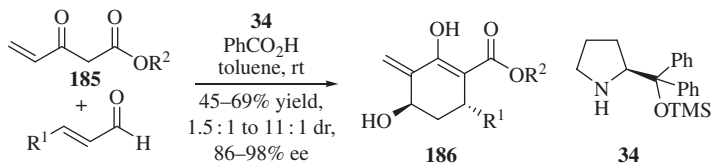
What's more, the addition of nitroalkanes to α,β -unsaturated aldehydes followed by an intramolecular Henry reaction which led to the formation of highly substituted cyclohexanols with control over five contiguous stereocenters was illustrated (Scheme 1.79) [124]. This novel domino reaction catalyzed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



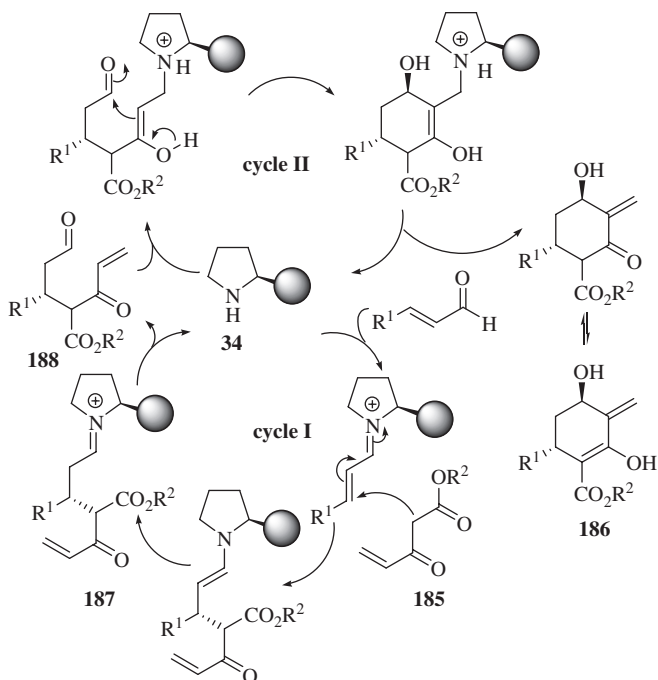
SCHEME 1.79 Organocatalyzed asymmetric nitro-Michael/Henry cascade.

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



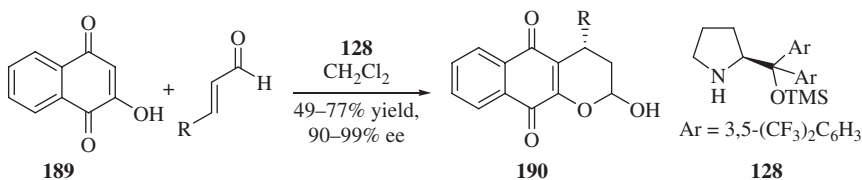
SCHEME 1.80 Organocatalytic Michael–Morita–Baylis–Hillman cascade.



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

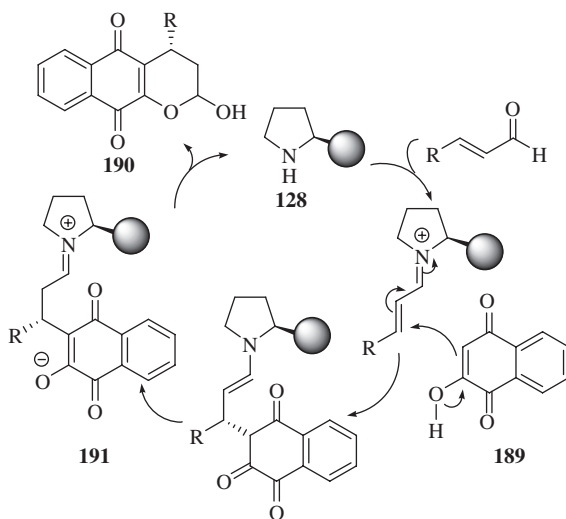
with a Nazarov reagent **185** (cycle I). Then, hydrolysis of the intermediate **187** leads to intermediate **188** and recovery of the catalyst. In the second cycle (cycle II), it is suggested that **34**, now acting as a nucleophilic catalyst for activation of the double bond, is involved in the intramolecular Morita–Baylis–Hillman reaction of **188**.

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 1.82 Enantioselective synthesis of 1,4-naphthoquinones.

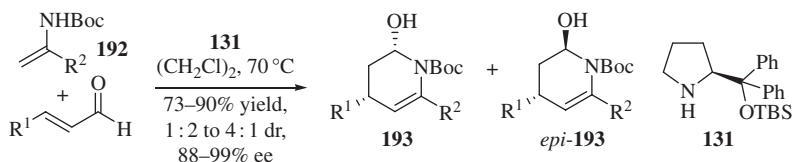
With regard to the mechanism, it was assumed that the reaction of diphenylprolinol ether **128** with α,β -unsaturated aldehyde resulted in an intermediary iminium ion (Scheme 1.83). Subsequent 1,4-addition of 2-hydroxy-1,4-naphthoquinone **189** to iminium ion followed by isomerization gives rise to 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 α,β -unsaturated aldehydes [128]. The Michael–Morita–Baylis–Hillman reaction between α,β -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].

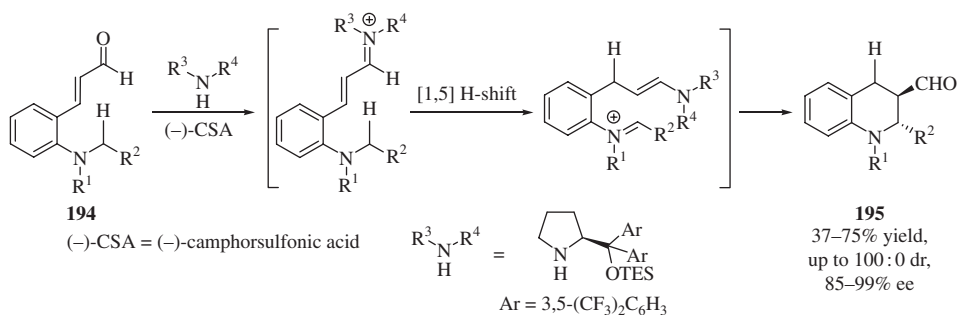
The highly enantioselective organocatalytic aza-[3+3] reaction of α,β -unsaturated aldehydes and enamide was reported by Hayashi's and Wang's groups respectively, via a mechanism similar to that shown in Scheme 1.83. Piperidine derivatives were generated efficiently in high yields and enantioselectivities 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 α,β -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.

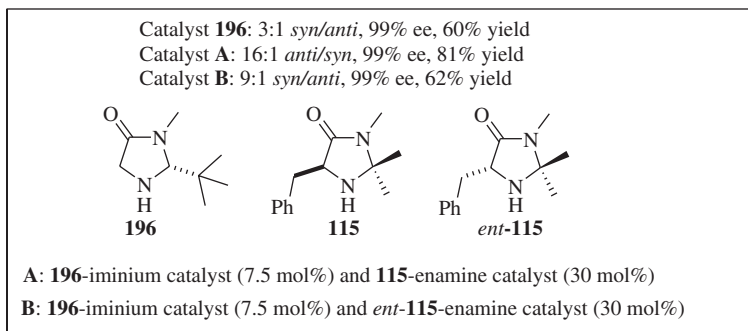
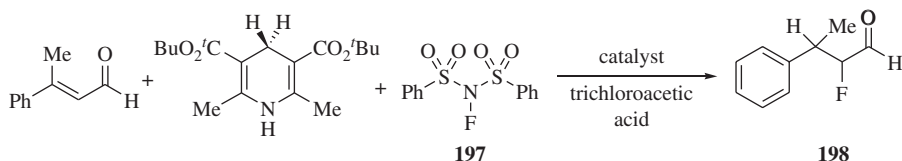


SCHEME 1.85 Catalytic enantioselective hydride-transferring closure.

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 diastereoselection, 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).



SCHEME 1.86 Organocatalyzed hydrofluorination reactions by cycle cascade catalysis.

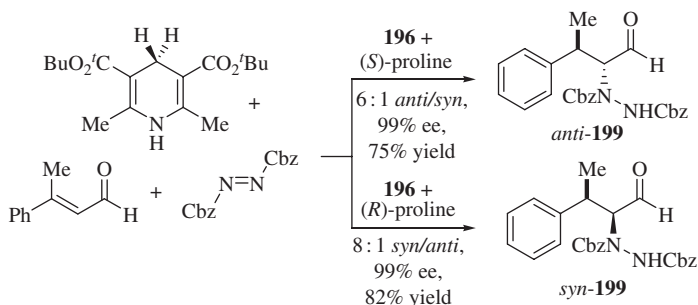
As revealed in Scheme 1.86, the hydrofluorinated product **198** was obtained with 99% ee and 3:1 *syn/anti* in the presence of catalyst **196**. However, implementation of catalyst combination **A** made possible the formal addition of HF to a trisubstituted enal with 16:1 *anti* selectivity (99% ee). 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*-**196** was also developed [135].

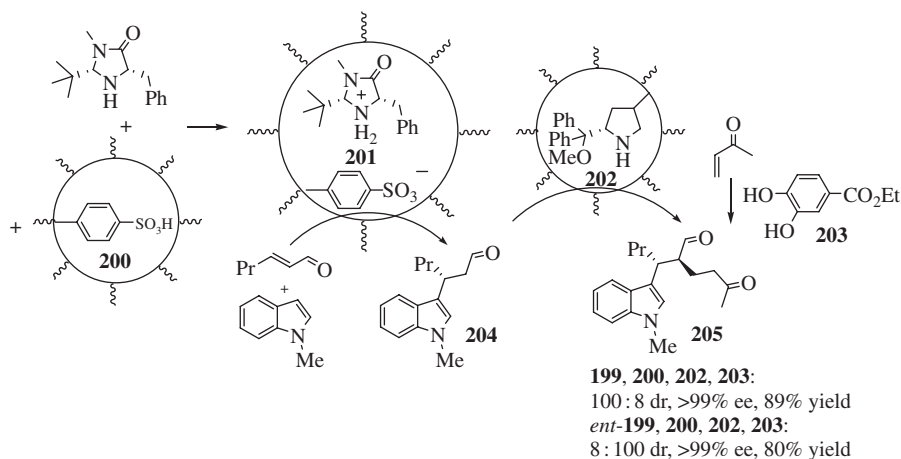
It is believed that monofunctional imidazolidinones are optimal for iminium catalysis but without the necessary structural features to participate in bifunctional enamine catalysis (e.g., activation of electrophiles via electrostatic interaction). Conversely, proline has proved to be an enamine catalyst 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



SCHEME 1.87 Organocatalytic hydroamination reactions.



SCHEME 1.88 Noninterpenetrating star polymer for one-pot cascade catalysis.

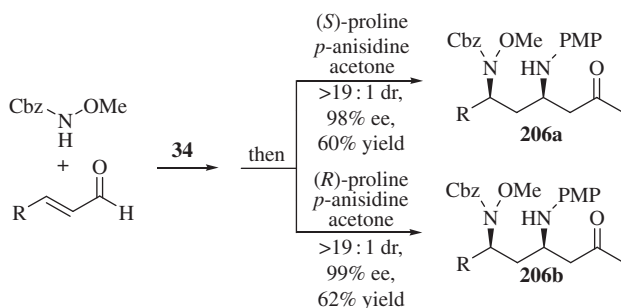
catalysts were designed to combine iminium, enamine, and hydrogen-bond catalysts in one pot for imidazolidinone-mediated nucleophilic addition of *N*-methyl indole to 2-hexenal, followed by pyrrolidine-catalyzed Michael addition of **204** to methyl vinyl ketone to afford the product in 89% yield with 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].

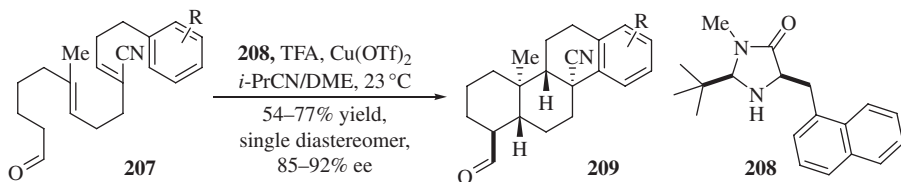


SCHEME 1.89 Aza-Michael/Mannich cascade by cycle-specific catalysis.

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).



SCHEME 1.90 Enantioselective SOMO-catalyzed cyclization.

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.

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