In 1971, Eder, Sauer, and Wiechert at Schering (12) and Hajos and Parrish at Hoffmann-La Roche (13, 14) independently reported a proline-catalyzed intramolecular aldol reaction of the triketone 16 as the key step in the synthesis of the diketone 17, a highly important intermediate in steroid synthesis. Remarkably, Hajos and Parrish obtained the diketone 18 in excellent yield and enantioselectivity with only 3 mol% of catalyst (Scheme 5). Acid-mediated dehydration then furnished the targeted 17. The accepted transition state for this reaction is believed to include one proline molecule as elucidated by List and Houk (21, 34).

It is worth noting that, although Hajos and Parrish considered this reaction to be “a simplified model of a biological system in which (S)-proline plays the role of an enzyme”, which represented a unique and groundbreaking approach for the introduction of stereogenic centers, this methodology was not developed further for almost 30 years until List, Barbas, and Lerner published their breakthrough report on the intermolecular aldol reaction, as depicted in Scheme 4 (28).
Presently, enamine catalysis, meaning the utilization of carbonyl groups by catalyzing their reactions with primary or secondary amines via enamine derivatives, plays a fundamental role in organic synthesis (5, 6, 8, 9, 35, 36). As enamine catalysis can be viewed as reducing the function and activation mode of aldolase enzymes to small organic molecules, it can be stated beyond doubt that this methodology represents one of the most powerful methods for the stereoselective α-functionalization of aldehydes and ketones currently known (35, 36). The following sections of this chapter will be subdivided into different transformation types that can be achieved by enamine catalysis.

2.1 Aldol Reactions

Aldol and Mannich-type reactions were the first systematically investigated applications for enamine catalysis. Aldol reactions belong to the most commonly applied C–C bond-forming reactions (37, 38) allowing for the construction of chiral building blocks for the syntheses of a variety of structurally complex molecules. These reactions are very often carried out using a preformed enolate (indirect aldol reaction) in combination with a chiral catalyst or using covalently bond chiral auxiliaries (38–41). Very often asymmetrically catalyzed reactions are carried out in the presence of metal catalysts or chiral Lewis bases (41). Besides the indirect approach, the direct aldol reaction between two unmodified carbonyl compounds is of great interest as it avoids the formation and handling of an enolate equivalent (42, 43). The seminal publication of List, Barbas, and Lerner for the proline (12)-catalyzed aldol reaction in 2000 (28) set the starting point for a number of impressive applications of enamine-type direct aldol reactions in natural product syntheses.

2.1.1 Ketone Donors in Intermolecular Aldol Reactions

Reactions between ketone donors and aldehyde acceptors strongly depend on the nature of the aldehyde. While α-disubstituted aldehydes normally react easily, unbranched ones often undergo self-addition reactions. List et al. reported one of the first examples of a direct aldol addition of ketones to α-unbranched aldehydes en route to a natural product in 2001 (44). The operationally simple reaction between 13 and 19 in the presence of catalytic amounts of (S)-12 furnished the enantiomerically enriched β-hydroxy-ketone 20 in moderate yield. The reduced yield can be rationalized by the concomitant formation of the condensation product 21, which is one of the limiting factors in such reactions (besides the self reaction of α-unbranched aldehydes). Intermediate 20 can then be further converted to the bark beetle pheromone (S)-ipsenol (22) in two more steps (Scheme 6).
A methodologically similar approach was successfully utilized independently for the synthesis of the oviposition attractant pheromone of the female \textit{Culex} mosquito \((5R,6S)-6\text{-acetoxyhexadecanolide} \ (28)\), by Kotsuki \textit{et al.} \((45)\) and Li \textit{et al.} \((46)\). While the Li group carried out a direct aldol reaction between undecanal \((23)\) and cyclopentanone \((24)\) to obtain the desired isomer \(25\) in excellent enantio- and diastereoselectivity, the Kotsuki group introduced the stereogenic centers by a reaction between \(24\) and the dithiane \(26\) under solvent-free conditions (Scheme 7).

![Scheme 6](image)

\textbf{Scheme 6} \((S)\)-Proline \((12)\)-catalyzed formation of a key intermediate in the synthesis of \((S)\)-ipsenol \((22)\)

The amine-catalyzed aldol reaction between ketone donors and \(\alpha\)-disubstituted aldehydes normally proceeds much more easily and with excellent enantioselectivity, which was demonstrated impressively in the synthesis of the southern part of the highly cytotoxic potential anticancer drug epothilone B \((29)\) \((47, 48)\) by Avery and Zheng \((49)\) (Scheme 8). In this case \((R)\)-proline was the catalyst of choice to introduce the secondary alcohol group in high enantioselectivity early in the synthesis sequence.
This example demonstrates the strength and versatility of enamine-catalyzed aldol reactions between ketone donors and aldehydes for the synthesis of key natural product synthons in a very impressive way. Like other routinely used asymmetric organic transformations that are applied commonly in total synthesis, this type of reaction today belongs to the standard repertoire for the introduction of chiral alcohols by aldol-type reactions in natural product synthesis (50–54).

Although organocatalytic direct aldol reactions are very often carried out early in the synthesis of natural products, as shown in the case of epothilone B (29) (49) or in the synthesis of apratoxin A (50), there are also some excellent examples of late-stage enamine-catalyzed aldol reactions present in the literature (51–54). One good example refers to convolutamydine A (32), a naturally occurring potent inhibitor of HL-60 human promyelocytic leukemia cells (55, 56). Convolutamydine A (32) has been synthesized independently by several research groups (51–54) using a direct organocatalytic late-stage aldol reaction between acetone (13) and the dibromo-isatin 33. These reports are remarkable for two reasons: (a) direct aldol reactions between two ketones are normally more difficult to execute than those with aldehyde acceptors due to the lower electrophilicity of ketones, and (b) all these reports used different amine-catalysts to achieve the same targeted transformation (Scheme 9).

Xiao et al. (52) used the bifunctional chiral bisamide 34 to catalyze the reaction between 13 and 33 to give (S)-32 in a moderate enantiomeric excess of 60%. The enantiomeric excess (ee) could be enhanced significantly by a single crystallization (87%), albeit with a considerable decrease in yield. The enantioselectivity can be explained by the bifunctionality of catalyst 34 resulting in an enamine formation of the proline-nitrogen and acetone, accompanied with hydrogen bonds between the isatin carbonyl group and the two amide protons of the catalyst, leading to the correct orientation between electrophile and nucleophile.

Scheme 9 (R)-Proline (12)-catalyzed aldol reaction in the synthesis of the southern part of epothilone B (29)

Synthesis of the (R)-enantiomer of 32 was first accomplished by Tomasini et al. (51) using the proline amide catalyst 35, resulting in an ee of 68% and excellent yield. In this case, 35 was superior when compared to the parent compound 12, which displayed a poor enantioselectivity of less than 55% ee only (51).
Two high-yielding and highly enantioselective approaches were reported by Malkov et al. (53) and Nakamura et al. (54). Using D-leucinol (36) as the catalyst, Malkov and co-workers were able to obtain (R)-32 in high yield and excellent enantioselectivity. Again, the high face selectivity can be rationalized by the presence of the hydroxy group of 36, which is thought to coordinate the isatin keto group (53). Using only 5 mol% of the N-heteroaryl sulfonylprolinamide catalyst 37, Nakamura et al. were able to isolate (R)-32 quantitatively in almost enantiopure form (54) (Scheme 9).

The high versatility of proline-catalyzed aldol reactions with ketone donors for the selective introduction of adjacent stereogenic centers was also applied...
successfully for the syntheses of carbohydrates and phytosphingosines, as demonstrated by Enders et al. (57, 58). The short and flexible syntheses of \( \alpha \)-arabino-phytosphingosine (38) and protected \( \beta \)-ribo-phytosphingosine (39) represent impressive examples for the successful application of this methodology (58). Herein, the characteristic amino-triol units of the sphingoids were introduced using the dioxanone 40 (59) and carrying out a proline-catalyzed aldol reaction giving the key fragment 42 in excellent stereoselectivity and good yield. Further functional group manipulations gave access to 38 and 39 in an easy and highly efficient manner (Scheme 10).

Using the dioxanone 40 as a synthetic dihydroxyacetone phosphate analogue, Enders and Grondal were able to synthesize several selectively protected carbohydrates in a direct and highly stereoselective fashion (57). As an example, the reaction between 40 and the aldehyde 43 catalyzed by (R)-12 gave the acetonide-protected \( \alpha \)-psicose 44 in 76% with excellent dia- and enantioselectivity. Deprotection of 44 gave \( \alpha \)-psicose (45) quantitatively (Scheme 11).

Enders also applied a proline-catalyzed strategy to develop a direct biomimetically inspired route towards precursors of ulosonic and sialic acids (60) as demonstrated in
the synthesis of a precursor of 2-keto-3-deoxy-D-glucosonic acid (D-KDG, 46), a compound that takes part in the Entner-Doudoroff pathway in its phosphorylated form (Scheme 12).

Another impressive short-step synthesis using this type of methodology was reported by Ward et al. (62). In their synthesis of serricornin (51), a sex pheromone produced by the female cigarette beetle (Lasioderma serricorne), the key step was an enantioselective aldol reaction between racemic aldehyde 53 and ketone 52 catalyzed by the tetrazole-catalyst 54 (63–66). This furnished the targeted tetrapropionate skeleton, which could be further transformed to the natural product 51 in six steps (Scheme 13). Interestingly, a concomitant dynamic kinetic resolution (DKR) of 53 was observed also under these conditions. It is worth noting that the key transformation can be carried out also in a highly selective manner but in a slightly lower yield using (S)-12. However, in this case a larger excess of ketone 52 was necessary, which complicated work up and purification on a larger scale (62).

Total synthesis of the potential anticancer drug salinosporamide A (56) represents an example where a proline-catalyzed aldol reaction between an achiral ketone donor and an a-chiral aldehyde was carried out with high selectivity.
2.1.2 Aldehyde Donors in Intermolecular Aldol Reactions

The first direct enantio- and diastereoselective organocatalytic cross-aldol reaction between aldehydes was reported by MacMillan in 2002 (69). Soon afterwards, Pihko and co-workers used this strategy for the reaction between propionaldehyde (60) and isobutyraldehyde (14). Carrying out this reaction under carefully controlled conditions with 10 mol% (S)-12, the β-hydroxy-aldehyde 61 could be obtained in good yield (61%) and excellent enantio- and diastereoselectivity (>99% ee, dr > 40:1) (70). Intermediate 61 could then be transformed readily into prelactone B (62), a natural product isolated from the bafilomycin-producing Streptomyces griseus (Scheme 15).

In 2004, the group of MacMillan published a report, which can now be regarded as one of the milestones in (organo-) catalysis. By carrying out an organocatalytic aldol reaction first, followed by a metal-catalyzed one, a two-step carbohydrate synthesis starting from simple starting materials could be achieved (71, 72). The key organocatalytic step was a (S)-12 catalyzed enantio- and diastereoselective dimerization of α-oxoaldehyde 63 (72). The α,γ-oxy-protected product 64 proved to be inert to further enolization or enamine addition. However, a subsequent Lewis acid-mediated aldol reaction of 64 with 65 then gave access to O-protected hexose
carbohydrates. It is worth noting that selective access to either protected glucose $\text{66}$, protected mannose $\text{67}$, or protected allose $\text{68}$ can be accomplished by proper choice of the Lewis acid and the solvent (Scheme 16).

The spongistatin natural products (e.g. (+)-spongistatin 1 ($\text{69}$)) belong to some of the most potent antimitotic growth inhibitory substances discovered to date (73–75). However, their extremely low natural abundance (according to Pettit only 13.8 mg of (+)-spongistatin 1 ($\text{69}$) can be isolated from 400 kg of wet sponge (73)) fuels the demand for a synthesis approach to furnish sufficient amounts for further investigations. The group of Amos B. Smith III has for years been among the front-runners in the syntheses of complex natural products with a special focus on the development of scalable routes (76–78). Very recently, they reported an impressive gram-scale synthesis of $\text{69}$ involving an early step organocatalytic aldol reaction to synthesize the F-ring (78). Synthesis of the F-ring started with an anti-selective aldol reaction between the TBDPS-protected electrophile $\text{70}$ and propanal (60), in accordance with the procedure published by MacMillan (Scheme 16). Crude $\text{71}$ was then submitted directly to an olefination reaction to give the key...
intermediate 72, which was used to synthesize the F-ring synthon 73. Notably, the
eight-step synthesis towards 73 proceeded with an impressive overall yield of 50%,
which was significantly better than other approaches investigated in parallel by
Smith III et al. Final assembly of the different synthons then gave access to over 1 g
of (+)-spongistatin 1 (69) (Scheme 17)(78).

An aldehyde-aldehyde coupling was also the key transformation in the synthesis
of the histone deacetylase inhibitor trichostatin A (74), developed by Duan and Wang
(79). Reaction of p-nitrobenzaldehyde (75) and propionaldehyde (60) catalyzed by
(S)-12 gave the rather unstable enantiopure 76, which was used directly for the
subsequent steps towards trichostatin A (74). Notably, the chiral secondary alcohol
group is oxidized later on in the sequence. Similar to some of the examples already
depicted above, the organocatalytic introduction of the targeted stereogenic center is
carried out very early in the multi-step sequence (Scheme 18) (79).

Scheme 17  Organocatalysis in A.B. Smith III’s gram-scale synthesis of (+)-spongistatin 1 (69)

Scheme 18  Synthesis of trichostatin A (74)
Aldehyde donors were also employed successfully in the syntheses of convolutamydines E (77) and B (78) (80–82). The strategy was the same as depicted for the synthesis of (R)- and (S)-convolutamidine A (32) (Scheme 9), but using acetaldehyde (79) instead of acetone (13) as the nucleophile in the cross-aldol reaction with dibromo-isatin 33 (Scheme 19). Nakamura et al. utilized catalyst 37, followed by a NaBH₃CN-mediated reduction to obtain (R)-convolutamidine E (77) in excellent yield and enantioselectivity. Chlorination of 77 then gave (R)-convolutamidine B (78) (Scheme 19) (80, 81).

Synthesis of the unnatural (S)-convolutamidine E (77) was reported by Hayashi et al. using the diarylprolinol catalyst 81 (82). In contrast to other convolutamidine approaches, the N-protected isatins 82 and 83 were used, giving the aldol products 84 and 85 in good yield and ee. It is worth noting that in the case of 82 the (S)-configured 84 was obtained, whereas 83 gave the (R)-85 under the same conditions. This difference in stereoselectivity was rationalized by Hayashi et al. as being due to the large C-5-substituent (Br) in the case of 82, resulting in a different transition state than in the case of 83 with only a proton on C-5 (82). While 84 was easily converted to (S)-convolutamidine E (77), 85 could be used to synthesize either the alkaloid CPC-1 (86) (83), or to obtain 87, a key fragment in the synthesis of madindolines A (88) and B (89), two selective inhibitors of interleukin-6, isolated from Streptomyces nitrosporeus K93-0711 (84) (Scheme 20).
Scheme 20  Syntheses of (S)-convolutamydine E (77), CPC-1 (86), and a fragment (87) for the synthesis of madindolines A (88) and B (89)
2.1.3 Intramolecular Aldol Reactions

The *Hajos-Parrish-Eder-Sauer-Wiechert* synthesis (Scheme 5) was the first example of an intramolecular proline-catalyzed asymmetric aldol reaction. Systematically, this reaction can be described as a 6-enolendo cyclization. In 2003, *List et al.* described the first example of an intramolecular enolexo aldolization (85). This approach was then used by *Pearson* and *Mans* for the synthesis of (+)-cocaine 92, starting from the meso-dialdehyde 90 on treatment with (S)-12 (86). This desymmetrization process gave 91 as a mixture of epimers with good enantioselectivity. The tropane skeleton 91 could be further transformed into (+)-92 by conventional means (Scheme 21).

*Iwabuchi et al.* developed an intramolecular desymmetrization approach for the conversion of the cyclohexanone 93 into the bicyclic 94 using the silylated hydroxyproline 95 as an enamine-catalyst (87). Using 25 mol% of 95, the product 94 was obtained in good yield and excellent stereoselectivity and was employed

![Scheme 21 Organocatalytic desymmetrization approach towards (+)-coca (92)](image)

![Scheme 22 Enamine-catalyzed synthesis of 94, a key fragment in the synthesis of (+)-juvabione (96)](image)
later on as a synthon for the synthesis of natural and non-natural targets (88, 89). As an example of its usefulness as a starting material for complex natural compounds, Iwabuchi et al. developed an elegant synthesis of (+)-juvabione (96) (89), a natural sesquiterpene exhibiting insect juvenile hormone activity (90) (Scheme 22).

Very recently, an intramolecular cycloaldolization was employed successfully early in the synthesis of quinine (2) and quinidine (3) (91). Hatakeyama et al. used a (S)-12 catalyzed aldol reaction followed by in situ reduction of the aldol product with NaBH4 to obtain the diastereomers 99 and 100 in good yield and enantios-electivity (dr = 1:2). Followed by protection of the primary alcohol and oxidation of the secondary one, intermediate 101 with the desired configuration could easily be obtained. The intermediate 101 was then transformed into either 2 or the pseudoenantiomeric 3 by known methods (Scheme 23) (91).

2.2 Mannich Reactions

The Mannich reaction represents a useful extension of aldol-type approaches for the stereoselective formation of C–C bonds with concomitant introduction of O- and N-functionality. In this reaction two carbonyl compounds and an amine react to form β-amino-carbonyl compounds. Besides indirect variants using preformed enolates the use of unmodified nucleophiles (direct variant) has attracted considerable interest (92). Therefore, it is not surprising that the first example of a direct organocatalytic Mannich reaction was published only shortly (93) after the first proline-catalyzed aldol reaction (28). p-Anisidine (102) is commonly used for
in situ imine formation and as an N-protecting group. However, its removal under strongly oxidizing conditions sometimes leads to incompatibilities. Thus, other protecting groups like Boc-groups also were used successfully in Mannich-type approaches. Itoh et al. developed a proline-catalyzed approach towards the intermediate 104 in the synthesis of (+)-coniine (105) and ent-sedridine (106) by carrying out a three-component Mannich reaction between 13, 102, and the hydroxy-aldehyde 103 (Scheme 24) (94, 95).

Hayashi and co-workers used a similar strategy (Scheme 25) for the formal total synthesis of nikkomycin B (107) (96), a nucleoside peptide antibiotic isolated from the culture broth of Streptomyces tendae. In the key step, propionaldehyde (60), furfural (108), and the TBS-protected aniline 109 were reacted in the presence of

![Scheme 24](image1)

Scheme 24 Enamine-catalyzed three-component Mannich reaction in the syntheses of (+)-coniine (105) and ent-sedridine (106)

![Scheme 25](image2)

Scheme 25 Formal total synthesis of nikkomycin B (107)
10 mol% (S)-12 to give the unstable chiral β-amino aldehyde 110 in high enantiopurity (determined later on in the sequence to be > 92%). Crude 110 was directly converted further representing a formal total synthesis of 107 (96).

Besides three-component direct Mannich approaches, also the strategy of using preformed imines was applied successfully. For example, a preformed Boc-protected imine was used successfully by the Enders group in their synthesis of (+)-polyoxamic acid (112) (97). Polyoxamic acid is one of the saponification fragments of polyoxin J (113), an unusual peptidyl nucleosidic antibiotic isolated from the culture broths of *Streptomyces cacao var. asoensis* (98). The preformed Boc-imine of furfural (114) was reacted with the dioxanone (40) in the presence of (S)-12. The amino ketone 115 could be obtained in good yield and enantioselectivity and was easily transformed into (+)-polyoxamic acid (112) (Scheme 26) (97).

A three-component Mannich reaction between *p*-methoxybenzaldehyde (116), hydroxyacetone (117), and 102 was used successfully to build up the two consecutive stereogenic centers of 118, an intermediate in the synthesis of (+)-epi-cytotoxazone (119), as shown by Sudalai et al. (99) (Scheme 27). Cytotoxazone was isolated from *Streptomyces* sp. and is a potent inhibitor of the signaling

![Scheme 26](image)

**Scheme 26**  *Mannich* reaction in the synthesis of (+)-polyoxamic acid (112)

![Scheme 27](image)

**Scheme 27**  *Mannich* reaction in the synthesis of (+)-epi-cytotoxazone (119)
pathways of Th2 cells and therefore a potential chemotherapeutic agent in the field of immunotherapy (100).

By analogy to their elegant approach for the syntheses of carbohydrates (Scheme 11) (57) and phytosphingosines (Scheme 10) (58), Enders and co-workers used their dioxanone 40 (59) to synthesize a variety of protected amino sugars by a direct organocatalytic Mannich reaction (101). This approach is especially interesting as the syntheses of aminosugars are normally rather challenging including several protecting group manipulations, carbon-carbon bond formations and oxidation-reduction steps (102–104). In contrast, reacting 40 with different aldehydes 120 and the aniline 102 in the presence of either (R)- or (S)-proline (12) or the protected hydroxyproline (121) gave access to several protected amino pentoses and hexoses with high diversity in just one step (Scheme 28) (101).

2.3 α-Heterofunctionalizations

Introducing heteroatoms in the α-position of carbonyl groups in a direct approach is one of the types of transformations that have benefitted the most from recent progress in the field of enamine catalysis (105–109). Besides the development of suitable methods for the stereoselective introduction of O- and N-heteroatoms,
α-halogenation approaches have attracted considerable interest over the last few years (36). However, whereas stereoselective α-amination and α-oxygenation strategies have been used in several natural product and natural product analogue syntheses, enamine-catalyzed α-halogenations, especially α-fluorinations, were used mainly in the syntheses of non-natural products. Therefore, the main focus in this chapter will be on the introduction of N- and O-heteroatoms.

2.3.1 α-Hydroxylation

One of the requirements for such reactions is the availability of suitable electrophilic reagents for the introduction of heteroatoms. Nitrosobenzene (123) is normally the reagent of choice for the α-oxygenation of carbonyl groups, giving α-anilinooxy carbonyl compounds as the primary products. The use of 123 benefits from its high reactivity and the fact that the N-O bond easily can be cleaved (e.g. Cu (II)-salts) to give the corresponding chiral α-hydroxy carbonyl compounds (110).

An illustrative example for the strength of this methodology was reported by Kim et al. who used an enamine-catalyzed α-oxidation in the synthesis of the bark beetle pheromones (+)-exo- and (−)-endo-brevicomin (124) (111). The asymmetric proline-catalyzed α-hydroxylation of butyraldehyde (125) with 123 gave the crude anilinooxy compound 126 in excellent enantioselectivity (>98%). Compound 126 was used directly further to give (+)-exo- and (−)-endo-brevicomin (124) in just three more steps (Scheme 29) (111).

Hayashi et al. used (R)- or (S)-proline as catalysts to hydroxylate the cyclohexa-none 127 selectively to get either the intermediate 128 (upon hydrogenolysis of the N—O bond of the primary reaction product), which was converted further to the natural anti-angiogenesis agent RK-805 (129) and similar natural products such as fumagillol and ovalicin (112), or the intermediate 130. The latter could be transformed into (+)-panepophenanthrin (131) (113) (Scheme 30), a potent

\[ \text{CHO} + \text{NO} \xrightarrow{(S)-12 (20mol\%)} \text{Ph} \xrightarrow{\text{HN}} \text{CHO} \]

\[ 125 \quad 123 \quad 126 \text{(crude, >98\% ee)} \]

Scheme 29 Proline (12)-catalyzed α-oxygenation in the synthesis of (+)-exo- and (−)-endo-brevicomin (124)
inhibitor of the ubiquitin-activating enzyme (E1) that plays an important role in activating the ubiquitin-proteasome pathway (114).

Maier and Varseev recently applied MacMillan’s elegant one-pot three-step protocol (115) (1. α-hydroxylation, 2. Horner-Wadsworth-Emmons (HWE) olefination, 3. N—O cleavage) for the conversion of the (S)-citronellol-derived aldehyde 132 to γ-hydroxy-α,β-unsaturated ester 133 early in their 18-step first total synthesis of neosymbioimine (134) (116), a minor amphoteric metabolite of the symbiotic marine dinoflagellate Symbiodinium sp. (117) (Scheme 31).

The synthesis of disparlure (135) represents yet another fine example for the high potential of enamine-catalyzed α-functionalizations of aldehydes in the synthesis of natural products. The enantiomer (+)-135 is a sex pheromone of the female gypsy
moth, *Porthetria dispar* (118), whereas the \((/-)\)-enantiomer has been shown to antagonize this effect (119). *Kim* reported a proline-catalyzed approach towards both enantiomers (120). Thus, the aldehyde 136 was aminooxylated with 123 in the presence of catalytic amounts of \((R)\)-12 followed by direct allylation of the primary reaction product to give the homoallylic alcohol 137 in good yield, good diastereoselectivity and excellent enantioselectivity. Standard manipulations then gave \((+/-)\)-disparlure (135) in a total of six steps with 30% overall yield (Scheme 32). Using \((S)\)-12 as a catalyst for the \(\alpha\)-oxygenation gave access to \((/-)\)-135 in the same way.

As depicted in Scheme 7, the synthesis of the mosquito oviposition pheromone \((-)\)-6-acetoxy-5-hexadecanolide (28) via an intermolecular aldol reaction represents a powerful demonstration of the high potential of asymmetric enamine catalysis (45, 46). It is noteworthy that a methodologically different successful organocatalytic approach towards 28, based on an asymmetric \(\alpha\)-oxygenation, was reported recently (121). Reaction of aldehyde 136 with dibenzoyl peroxide (BzOOBz) and hydroquinone (HQ) (122) in the presence of the TMS-protected prolinol catalyst \((S)\)-138 followed by a direct allylation gave the benzoyl-protected 139 in moderate yield and good selectivity. Intermediate 139 could then be further transformed to give \((-)\)-(5\(R,6S\))-6-acetoxy-5-hexadecanolide (28) (Scheme 33).

### 2.3.2 \(\alpha\)-Amination

The direct stereoselective introduction of a nitrogen functionality in the \(\alpha\)-position of a carbonyl group is of high interest as it leads to valuable compounds like
\(\alpha\)-amino acids, \(\alpha\)-amino aldehydes, and \(\beta\)-amino alcohols, and it also gives access to several intermediates in complex natural product syntheses (123–127). The first direct catalytic \(\alpha\)-aminations of aldehydes were reported independently by Jørgensen et al. (123, 124) and List et al. (125), both using azodicarboxylates as electrophilic N-agents.

The cyclic \(\alpha\)-hydrazinocarboxylic acids (R)- and (S)-piperazic acid (140) are present in a variety of bioactive cyclodepsipeptides. Hamada et al. have developed a highly efficient synthesis of (R)-(140) by reacting 5-bromovaleraldehyde (141) with azodicarboxylate 142 in the presence of 10 mol% (S)-12 (128). The reaction product was directly treated with NaBH\(_4\) to give the alcohol 143 in excellent yield and enantioselectivity. The product 140 could then be obtained successfully after cyclization, oxidation, and Cbz-cleavage (Scheme 34).

Lycopodium alkaloids have always been attractive targets for synthesis-oriented organic chemists due to the combination of having unique polycyclic structures with promising biological activities (129–135). A few years ago, Kobayashi et al. isolated cermizine C (144), cermizine D (145), and senepodine G (146) together with other alkaloids from the club mosses Lycopodium cernuum and L. chinense (136). It is of interest to note that whereas 145 and 146 exhibited in vitro cytotoxicity against murine lymphoma L1210 cells (IC\(_{50}\) 7.5 and 7.8 \(\mu\)g/cm\(^3\)), 144 did not show cytotoxicity at 10 \(\mu\)g/cm\(^3\). In contrast to the relatively recent discovery of 144–146, the structurally related cermuane-type alkaloid cernuine (147) was isolated over 60 years ago by Marion and Manske (137). The Takayama group has for several years been at the forefront in the synthesis of cermuane- and quinolizidine-type alkaloids (138–142). Recently, they developed a divergent strategy for the syntheses of 144–147 starting from the (+)-citronellal-derived aldehyde 148 (138, 139). Organocatalytic \(\alpha\)-amination of 148 catalyzed by (R)-138 gave a rather labile amination product that was directly converted further to the stable oxazolidinone 149. Further modification then gave the key intermediate 150, which could be used to obtain cermizine C (144), cermizine D (145), and senepodine G (146), as well as cernuine (147) (Scheme 35).

It should be noted that stereoselective enamine-catalyzed \(\alpha\)-functionalizations have also been used very often in combined organocatalytic approaches, e.g.
accompanied with conjugate additions or other organocatalytic transformations. Some examples, therefore, will be covered in a later section (see Sect. 2.6).

2.4 Conjugate Additions

Conjugate additions of enamines to $\alpha,\beta$-unsaturated carbonyl or nitro compounds belong to the most commonly applied and useful organocatalytic C–C bond-forming reactions ($135$, $143–150$). As already mentioned above, enamine-catalyzed conjugate additions are often used in combination with $\alpha$-heterofunctionalizations. These combined examples will be described in more detail in Sect. 2.6.

**Scheme 35** Asymmetric $\alpha$-amination in the synthesis of the key fragment 150 for the syntheses of the alkaloids cermizine C (144), cermizine D (145), and senepodine G (146), and cernuine (147)
Besides the use of enamine-catalyzed Michael-type reactions in natural product syntheses, also its high potential for the syntheses of bioactive “designer drugs” has been demonstrated. As an example, Hayashi et al. developed an efficient, enantioselective total synthesis of the anti-influenza neuramidase inhibitor (-)-oseltamivir using an enamine-catalyzed Michael addition early in the sequence (151). This strategy was especially interesting, as it provided a novel, non-shikimic acid-based approach towards (−)-oseltamivir phosphate (Tamiflu®), one of the most prominent antiviral drugs that is currently on the market (152). As this impressive example is not part of a natural product total synthesis, no further details will be given in this review but the interested reader may be referred to the original literature (151).

Similar to aldol approaches, also organocatalytic conjugate addition reactions have been used mainly in the early steps of complex natural product syntheses to obtain useful chiral synthons in an easy and reliable fashion. Very recently, Carter et al. described the application of an intramolecular highly diastereoselective Michael addition of a chiral starting material catalyzed by an achiral amine for the total synthesis of lycopodine (129, 135). Accordingly, there is not only a high demand for enamine catalysis in the syntheses of chiral molecules using enantiopure chiral amines, but also the use of achiral amines for the diastereoselective transformation of chiral starting materials is highly appreciated.

Interesting examples for conjugate additions mediated by chiral amines have been described by Alexakis et al. (Scheme 36), who used the nitroalkene 151 as a Michael acceptor in organocatalytic enamine-catalyzed conjugate addition reactions (149, 150, 153). Michael reaction of 151 with propionaldehyde 60 in the presence of the diamine catalyst 152 (15 mol%) gave 153 as a mixture of four diastereomers in good yield. Subsequent aldehyde protection and conversion of the

\[
\begin{align*}
\text{NO}_2 & \text{OBn} + \text{CHO} \\
\text{151} & \text{60} \\
\text{152} & \text{153 (mixture of isomers)} \\
\end{align*}
\]

\[
\begin{align*}
\text{154 (93% ee, } dr = 57:43) \\
\end{align*}
\]

Scheme 36 Asymmetric conjugate addition to nitroalkene 151 in the synthesis of (−)-botryodiplodin (155)

\[
\begin{align*}
\text{HO} & \text{O} \\
\text{O} & \text{OBn} \\
\text{154 (93% ee, } dr = 57:43) \\
\end{align*}
\]
nitro group into a keto group resulted in 154 as a mixture of two diastereomers in good enantioselectivity. The major isomer was utilized successfully to synthesize (−)-botryodiplodin (155) (153), an antibiotic isolated from the plant pathogen Botryodiplodia theobromae, which causes many tropical fruit diseases including mango twig blight and mango stem rot (154).

Recently, the group of Nicolaou (155) reported a very elegant 12-step enantioselective synthesis of biyouyanagin A (156), an anti-HIV-active compound isolated from Hypericum chinense var. salicifolium, which is used as a common folk medicine in Japan (156). As already shown in several examples so far, organocatalysis was found to be rather fruitful early on in this synthesis, giving access to a key synthon in a highly stereoselective manner. The sequence started with a Michael addition of (R)-citronellal (157) to methyl vinyl ketone (158), catalyzed by 5 mol% of (S)-159 and 20 mol% of catechol 160, which is considered to function as a co-catalyst via hydrogen bond donation to the enone (157). The reaction was carried out as an organocatalytic cascade reaction, proceeding via the primary addition product 161, which was directly transformed further into the enone 162 by an intramolecular aldol condensation. Employing this strategy, 162 could be obtained in 68% yield and reasonable stereoselectivity ($de = 86\%$). Further manipulations then accomplished the total synthesis of biyouyanagin A (156) in a straightforward and effective way (Scheme 37) (155).

![Scheme 37](image-url)  
*Scheme 37* Early stage enamine-catalyzed Michael addition in Nicolaou’s total synthesis of biyouyanagin A (156)
A rather similar organocatalytic strategy was applied by Chen and Baran in the first steps of their syntheses of the eudesmane terpenes 163–166 (158). The eudesmane family of sesquiterpenoids contains over 1000 members with almost every conceivable oxidation pattern expressed (159). Despite their low molecular weight, the rigid skeletons of these natural products make them difficult targets for synthesis. Baran and Chen developed a scalable procedure towards these interesting compounds. By analogy to Nicolaou’s approach (Scheme 37), the sequence commenced with a Michael addition of isovaleraldehyde (19) to enone 158. The primary Michael product (S)-167 was directly cyclized to afford the natural product cryptone (168), which was then transformed into dihydrojunenol (169) on a multigram scale in seven steps. The substituted trans-decalin 169 then served as the substrate of choice for a variety of very impressive site-selective C-H functionalization reactions, which gave access to the four eudesmane terpenes 163–166 in good yields and excellent selectivities (Scheme 38) (158).

Finally, the high versatility of this Michael strategy was also shown in the total synthesis of the antimalarial agent (+)-polyanthellin A (170), which was described recently by Johnson et al. (160). The first step was similar to that depicted in Scheme 38, only using (R)-159 as a catalyst for the Michael reaction between

![Scheme 38](image-url)
isovaleraldehyde (19) and enone 158. In this case, the (R)-configured 167 could be obtained in excellent yield and enantioselectivity. In contrast to the previous examples, no intramolecular aldol condensation was carried out but 167 was used to synthesize the bicyclic compound 171, which served as one of two key building blocks for the final approach towards (+)-polyanthellin A (170) (Scheme 39) (160).

Once again it should be noted that the main purpose of this volume is to illustrate the high potential of organocatalysis and therefore the focus on the organocatalytic transformations in all these multi-step sequences. Very often these reactions have been carried out early in a sequence, giving access to chiral precursors and key intermediates in an elegant and easy fashion. Therefore, some of the most highly innovative transformations, which were applied later in the final steps, are not given in detail, as this is beyond the scope of this account.

Recently, the dual-specificity phosphatase inhibitor (−)-bitungolide F (172) was synthesized successfully by the Cossy group (161). The nine-step synthesis started with an organocatalytic Michael addition of aldehyde 60 to methyl vinyl ketone (158). The enantio-enriched 173 was then used to synthesize (−)-bitungolide F (172) in a straightforward manner and good yield (nine steps, 11% overall yield) (Scheme 40) (161).

### Scheme 39

Enamine-catalyzed Michael addition in the synthesis of (+)-polyanthellin A (170)

![Scheme 39](image)

### Scheme 40

Enamine-catalyzed Michael addition in the synthesis of (−)-bitungolide F (172)

![Scheme 40](image)
The group of Metz employed the proline-derived catalyst 159 in combination with co-catalyst 160 to catalyze additions of (R)- and (S)-citronellal (157) to 158 for the selective syntheses of the diastereomeric keto aldehydes 174 and 175. These intermediates could then be used to synthesize the marine sesquiterpenoids (−)-clavukerin A (176) (starting from (S)-157) and (−)-isoclavukerin A (177) (derived from (R)-157) (Scheme 41) (162).

Anominine (178) is an indole terpene (Scheme 42) isolated from the sclerotia of Aspergillus nomius by Gloer et al. (163). The natural (+)-178 exhibits potent activity against the widespread crop pest Heliothis zea in controlled feeding experiments. Very recently, the (−)-enantiomer was synthesized successfully by the group of Bonjoch for the first time (164). This impressive route commenced
with a stereoselective Robinson annulation between 158 and 179 catalyzed by only 1 mol% of the binaphthyl-derived catalyst 180 (165) to build up the Wieland-Miescher ketone 181. Compound 181 was then used successfully to achieve the first total synthesis of (−)-anominine (178) in several steps (164).

### 2.5 Dienamine Catalysis

The use of an amine catalyst for the activation of an α,β-unsaturated carbonyl group as a nucleophile represents a very useful extension of the concept of enamine activation. By transmission of the nucleophilic properties of an enamine to an adjacent olefin (vinyllogy), the dienamine can be considered to be a compound bearing two nucleophilic sites (the α- and the γ-position) and furthermore it can react as an electron-rich diene in [4 + 2] cycloadditions. This concept was introduced in 2006 by Jørgensen et al. who successfully applied it for the stereoselective γ-amination of α,β-unsaturated carbonyl compounds (166) (Scheme 43).

![Scheme 43](image)

**Scheme 43** Jørgensen’s dienamine-catalyzed γ-functionalization protocol (166)

One of the first applications of dienamine catalysis in natural product synthesis was reported by Hong and co-workers, who described an efficient organocatalytic synthesis of (+)-palitantin (185) (167). Palitantin is a highly oxygenated polyketide-derived fungal metabolite isolated from *Penicillium palitans* and *Penicillium frequentans* (168, 169) and some interesting synthesis strategies have been reported so far (167, 170, 171). Hong’s synthesis was based on an enantioselective formal [4 + 2] self-dimerization of the α,β-unsaturated aldehyde 186. The reaction proceeded well in the presence of a higher amount of (S)-12 (50 mol%) to give
the product 187 in reasonable selectivity. From a mechanistic point of view, the authors reasoned that the reaction more likely proceeded through a dienamine-catalyzed Michael reaction followed by an intramolecular Mannich-type addition rather than through a Diels-Alder reaction (167). Thus, and according to the mechanistic rationalization given by Hong et al., this type of transformation can also be considered to be a domino or cascade process. Compound 187 was then converted successfully into (+)-palitantin (185) (Scheme 44). Further examples of dienamine catalysis in combination with other transformations or involved in cascade reactions will be given in Sect. 2.6.

Over the last few years the Christmann group has reported some interesting approaches towards the synthesis of mono- and bicyclic skeletons based on dienamine catalysis (172, 173). As an example, (Scheme 45) compound (±)-188, a pungent constituent of black cardamom (174), was synthesized in a single transformation starting from the acyclic tethered α,β-unsaturated dialdehyde 189. The bicyclic product 188 could be obtained in reasonable yield and good enantioslectivity through a formal [4 + 2] cycloaddition catalyzed by 138 in the presence...
of small amounts of benzoic acid (BzOH). Mechanistically, this elegant transformation can be rationalized by the formation of the dienamine intermediate 190 first, which then undergoes a [4 + 2] cycloaddition to give 191 followed by a β-elimination to deliver the target compound 188 (172).

In 2009, the Christmann group reported the application of a dienamine intermediate for Rauhut-Currier-type reactions (173). In this case, the α-position of the dienamine acts as the nucleophile in an intramolecular cyclization reaction giving access to functionalized monocyclic compounds. The applicability of this strategy was illustrated in the synthesis of (R)-rotundial (193), a mosquito repellent from the leaves of Vitex rotundifolia (175). Hence, an organocatalytic Rauhut-Currier-type reaction of dialdehyde 192 catalyzed by 20 mol% (S)-138 gave (R)-rotundial (193) directly in good enantioselectivity, albeit in only a moderate yield (Scheme 46).

![Scheme 46](image)

Scheme 46  Dienamine-catalyzed synthesis of (R)-rotundial (193)

### 2.6 Combined Enamine-Catalyzed Approaches and Cascade Reactions

The examples depicted so far have made use primarily of single organocatalytic transformations conducted typically quite early in the multi-step sequences applied towards the syntheses of complex natural products. In contrast, more and more reports describing organocatalytic cascade reactions or combined approaches using different organocatalytic key transformations to achieve a complex synthesis have been reported over the last several years (30, 32, 176–178). In this chapter, the application of combined enamine-catalyzed approaches for the syntheses of natural products will be described. Examples using different activation modes (e.g. enamine and iminium activation) will be discussed later.

One of the first examples of an enamine-catalyzed cascade reaction for the synthesis of a complex alkaloid was reported by Itoh et al. (179). Reaction of the dihydrocarboline 194 with enone 195 in the presence of (S)-12 (7 days) gave the tetracycle 196 as a single diastereomer and in excellent enantiopurity (99%). This reaction can be described best as an enamine-catalyzed Mannich-Michael domino addition. Further manipulations then gave access to the indole alkaloid ent-dihydrocorynantheol (197) in an elegant and facile manner. As depicted in
Scheme 47, use of (R)-12 as a catalyst in the first step should therefore give access to the natural product dihydrocorynantheol, a compound isolated from Aspidosperma marcgravianum showing activity against Gram-positive bacteria (180).

The combined use of an asymmetric α-oxygenation of an aldehyde followed by an olefination reaction and an organocatalytic conjugate addition was found to be a very useful approach for the syntheses of the complex natural products brasoside (198) and littoralisone (199) (115) (Scheme 48). Littoralisone (199) was found to be the active constituent of extracts of Verbena littoralis for increased nerve growth factor (NGF)-induced neurite outgrowth in PC12D cells (181) and is presumed to be derived biochemically from brasoside (198) (182, 183). In 2005, MacMillan and Mangion reported the first total syntheses of 198 and 199 using three proline (12)-catalyzed transformations early in the synthesis. The cis-bicyclic skeleton was obtained successfully starting from the (−/C0)-citronellol-derived aldehyde 200. An asymmetric α-oxygenation catalyzed by (R)-12 followed by a Horner-Wadsworth-Emmons (HWE)-olefination gave 201 initially. Redox-state manipulations then gave the dialdehyde 202. This formyl-enal Michael acceptor was submitted further to a (S)-12-catalyzed intramolecular conjugate addition. The crucial part in this transformation was the choice of solvent. While CHCl₃ resulted in the formation of the trans-isomer, the use of DMSO gave the kinetic cis-product 203 in good yield and selectivity upon in situ O-acylation of the intermediate lactol. The iridoid 203 was then converted into the lactone 204 by standard methods. This key intermediate was used to accomplish the total syntheses of (−)-brasoside (198) and (−)-littoralisone (199) in a straightforward manner. Notably, the synthesis of 199 required the coupling partner 205 that was obtained easily using MacMillan’s two-step carbohydrate protocol (Scheme 16) (71). Coupling of 204 and 205 followed by an impressive light-induced [2 + 2] cycloaddition and deprotection sequence then gave (−)-littoralisone (199) (115).
Another excellent example from the MacMillan laboratory using enamine-catalyzed key-transformations to accomplish a complex total synthesis was the first total synthesis and structural revision of the cytotoxic marine macrolide callipeltoside C (206) (184). Callipeltosides A-C were isolated and characterized in 1996 and 1997 by Minale et al. They were found to be cytotoxic against the human bronchopulmonary NSCLC-N6 cell line (IC$_{50}$ values ranging from 11.3 to 30.0 µg/cm$^3$) (185, 186). MacMillan’s synthesis of 206 takes advantage of three highly selective organocatalytic key transformations to obtain the target in 20 steps and a very
Scheme 49  Total synthesis and structural revision of callipeltoside C (206)
satisfactory overall yield of 11% (184). The (S)-12-catalyzed aldol reaction between 60 and 207 gave 208 in high selectivity. The aldol product 208 was progressed towards the functionalized tetrahydropyran 209, a key intermediate in the overall assembly strategy. The second key fragment 212 was obtained after an enantioselective α-oxygenation of 210 to give 211 followed by standard transformations. The L-callipeltose-based third fragment 213 was synthesized successfully by the group’s trademark carbohydrate protocol (Scheme 16) (71). Coupling of fragments 209 and 212 followed by further transformations furnished the aglycone 214. Finally, the originally proposed structure of 206 suggested a glycosylation of 214 with the enantiomer of 213 (which was prepared in the same way as 213, but using (R)-12 as a catalyst). However, comparison of the spectroscopic data of the natural compound and the synthetic version revealed a significant difference. In contrast, coupling of 214 with 213 gave 206, as shown in Scheme 49, and in full spectroscopic data accordance of the synthetic compound with the naturally isolated product (184).

Accordingly, the total synthesis of callipeltoside C (206) not only showed the high potential of organocatalysis in complex natural product synthesis, but it also pointed out the advisability of proving initially proposed structures of natural compounds by total synthesis.

Woggon and co-workers reported recently (Scheme 50) a highly diastereoselective domino aldol-oxa-Michael reaction of salicylaldehyde 215 and phytenal

![Scheme 50 Dienamine-catalyzed aldol-oxa-Michael domino reaction in the synthesis of α-tocopherol (219)](image)
(216) in the presence of catalyst 217, giving the hemiacetal 218 (187). Formation of this product can be explained by an initial dienamine-catalyzed aldol reaction of 216 to 215, followed by an intramolecular oxa-Michael addition of the phenolic OH-group to the α,β-unsaturated iminium intermediate. Thus, from the mechanistic point of view, this domino reaction can be considered to make use of two different activation modes, namely, a dienamine activation first enabling the aldol reaction and an iminium activation then enabling the oxa-Michael addition (more distinct examples of iminium catalysis will be given in the next chapter). Finally, the thus obtained hemiacetal 218 then allowed the synthesis of α-tocopherol (219) in a direct and facile way (187).

2.7 Synopsis

Although enamine catalysis has only been attracting the attention of a broader audience for approximately the last 10 years, this activation mode has (together with iminium catalysis) contributed to possibly the most significant recent progress in the field of asymmetric organocatalysis. This methodology belongs to the most useful and broadly applicable current strategies to carry out a variety of different α-carbonyl reactions in a stereoselective fashion. As shown by previous examples, this methodology has quickly found its way into the toolbox of synthesis-oriented organic chemists. The following table gives a summary of enamine-catalyzed reactions presented in Section 2. (Table 1). As can be seen from this table, by far the most commonly employed catalyst included therein is proline (12).
Table 1  Enamine catalysis employed in complex natural product syntheses

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<td></td>
<td>(−)-6-Acetoxyhexadecanolide (28)</td>
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<td></td>
<td>Epothilone B (29)</td>
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<td>d-arabino-Phytosphingosine (38)</td>
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<tr>
<td></td>
<td>d-Psicose (45)</td>
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<td></td>
<td>d-KDG (46)</td>
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<td>Salinosporamide A (56)</td>
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<td>Prelactone B (62)</td>
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<td>O-Protected Hexoses (66, 67, 68)</td>
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### Table 1 (continued)

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Table 1 (continued)

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