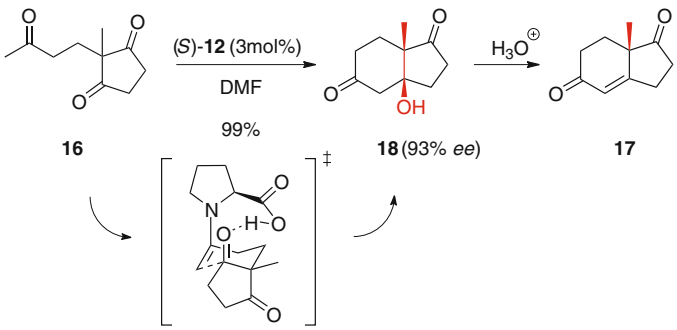
2 Enamine Catalysis

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*).



Scheme 5 *Hajos-Parrish-Eder-Sauer-Wiechert* synthesis

M. Waser, *Asymmetric Organocatalysis in Natural Product Syntheses*,
Progress in the Chemistry of Organic Natural Products 96,
DOI 10.1007/978-3-7091-1163-5_2, © Springer-Verlag Wien 2012

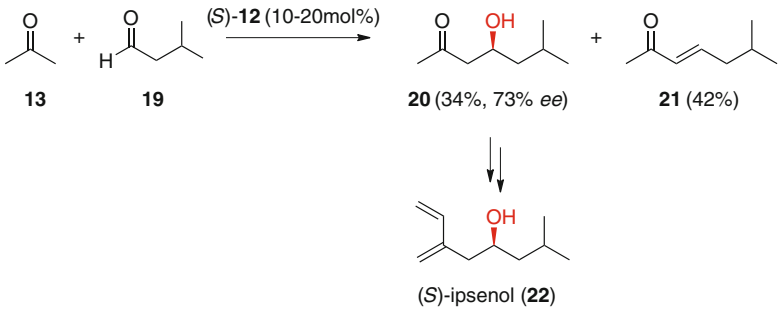
Presently, enamine catalysis, meaning the utilization of carbonyl groups by catalyzing their reactions with primary or secondary amines *via* enamine derivatives, plays a fundamental role in organic synthesis (*5*, *6*, *8*, *9*, *35*, *36*). As enamine catalysis can be viewed as reducing the function 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.

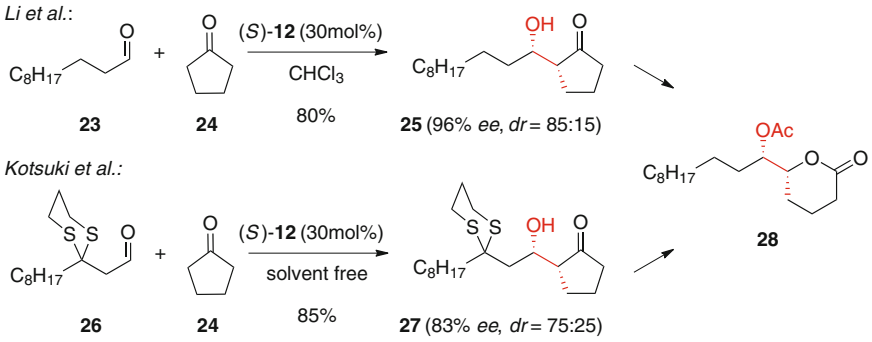
2.1.1 Ketone Donors in Intermolecular Aldol Reactions

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).



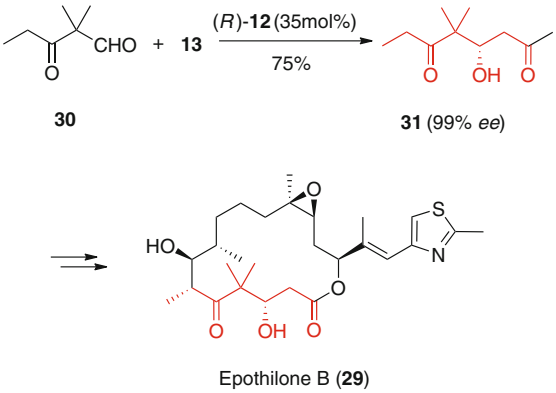
Scheme 6 (*S*)-Proline (**12**)-catalyzed formation of a key intermediate in the synthesis of (*S*)-ipsenol (**22**)

A methodologically similar approach was successfully utilized independently for the synthesis of the oviposition attractant pheromone of the female *Culex* mosquito (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**28**), by *Kotsuki et al.* (*45*) and *Li 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 7 Two approaches for the synthesis of (-)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**28**) (*45*, *46*)

The amine-catalyzed aldol reaction between ketone donors and α-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.



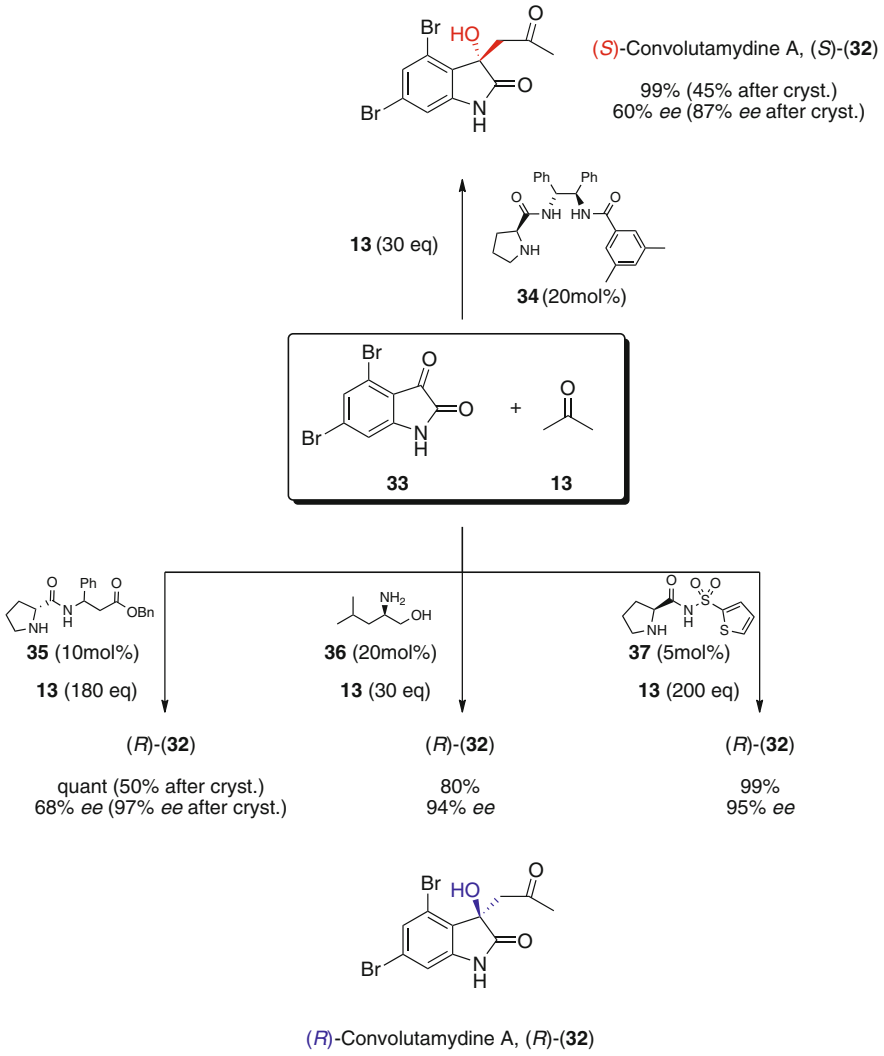
Scheme 8 (*R*)-Proline (**12**)-catalyzed aldol reaction in the synthesis of the southern part of epothilone B (**29**)

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.

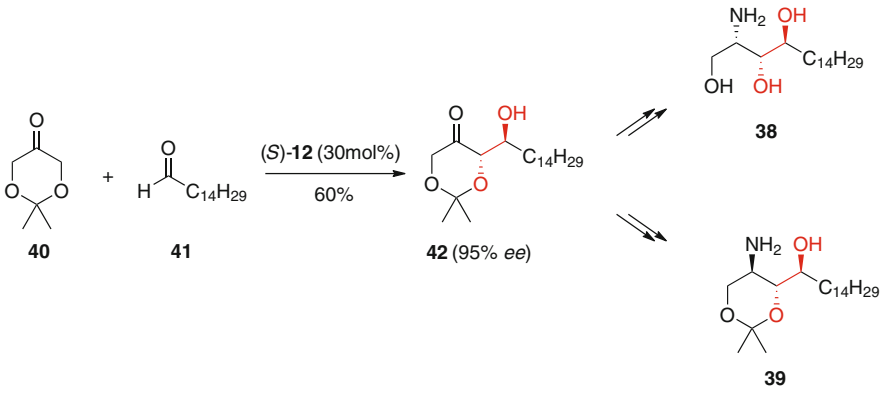
Synthesis of the (*R*)-enantiomer of **32** was first accomplished by *Tomasini et al*. (*51*) using the proline amide catalyst **35**, resulting in an *ee* of 68% and excellent yield. In this case, **35** was superior when compared to the parent compound **12**, which displayed a poor enantioselectivity of less than 55% *ee* only (*51*).



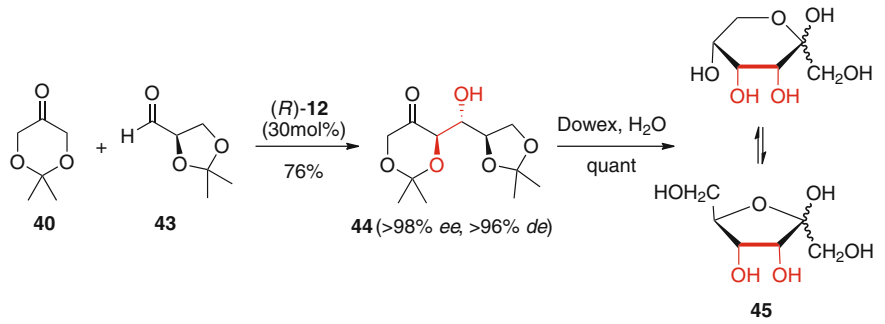
Scheme 9 Syntheses of (*R*)- and (*S*)-convolutamydine A (**32**)

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*-heteroarylsulfonylprolinamide 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



Scheme 10 Organocatalytic access to a key fragment in the synthesis of D-*arabino*-phytosphingosine (**38**) and protected L-*ribo*-phytosphingosine (**39**)

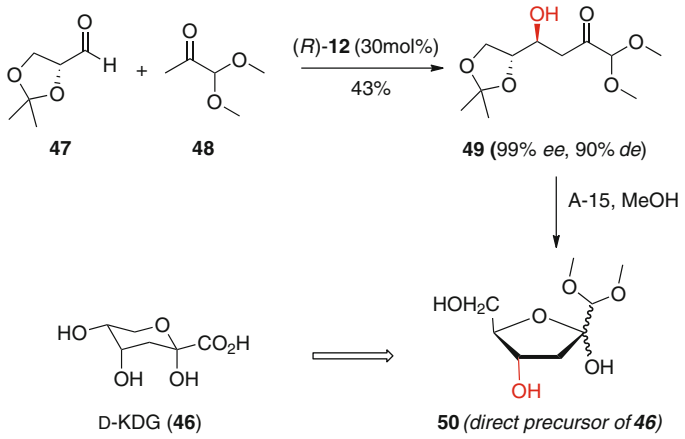


Scheme 11 *Enders*' carbohydrate synthesis (*57*)

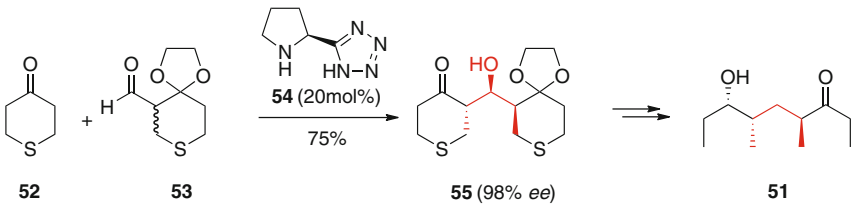
successfully for the syntheses of carbohydrates and phytosphingosines, as demonstrated by *Enders et al.* (*57*, *58*). The short and flexible syntheses of D-*arabino*-phytosphingosine (**38**) and protected L-*ribo*-phytosphingosine (**39**) represent impressive examples for the successful application 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 D-psicose **44** in 76% with excellent dia- and enantioselectivity. Deprotection of **44** gave D-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



Scheme 12 Organocatalytic entry to a direct precursor of D-KDG (**46**)

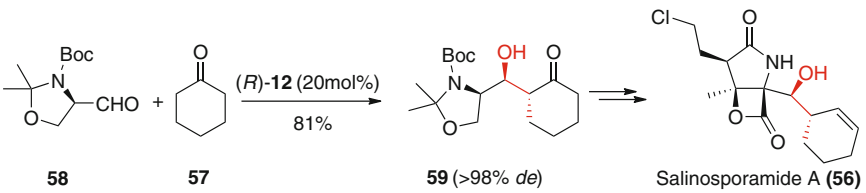


Scheme 13 Assembly of the tetrapropionate unit **55**, a key fragment in the synthesis of serricornin (**51**) (*62*)

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 (*61*) (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 α-chiral aldehyde was carried out with high selectivity.

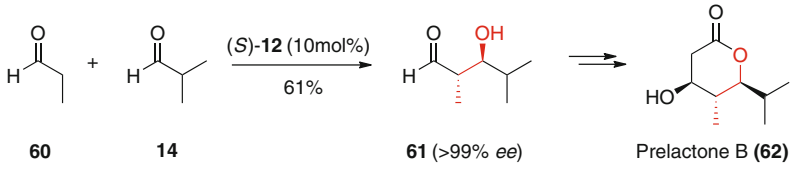


Scheme 14 Proline-catalyzed aldol reaction in the synthesis of salinosporamide A (**56**)

Reaction between cyclohexanone (**57**) and the α-chiral aldehyde **58** furnished the aldol product **59** in good yield and excellent diastereoselectivity (*67*, *68*) (Scheme 14).

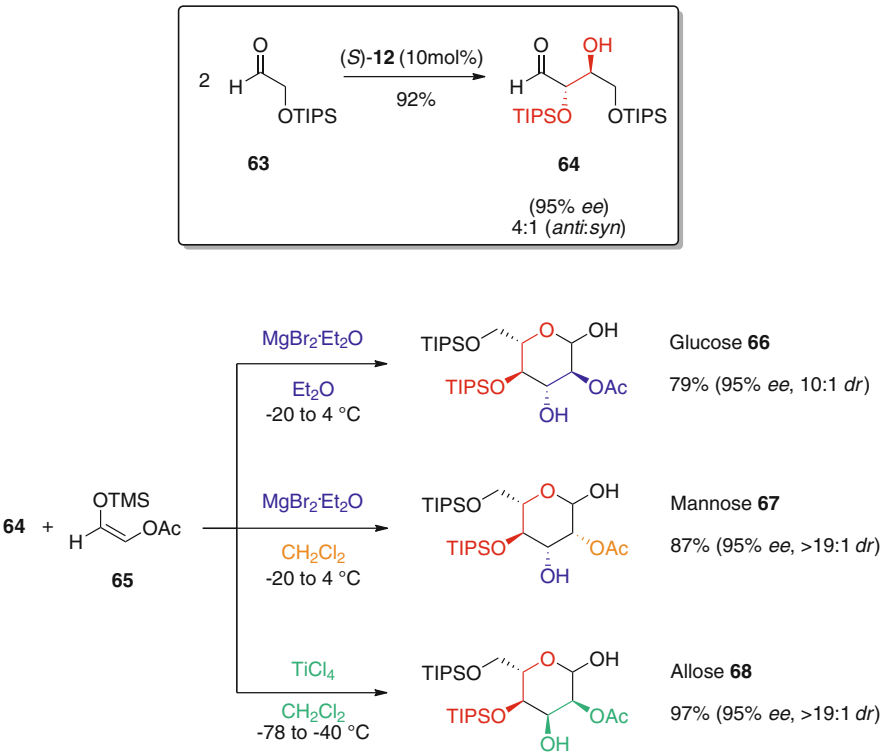
2.1.2 Aldehyde Donors in Intermolecular Aldol Reactions

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).



Scheme 15 Organocatalytic key transformation in the synthesis of prelactone B (**62**)

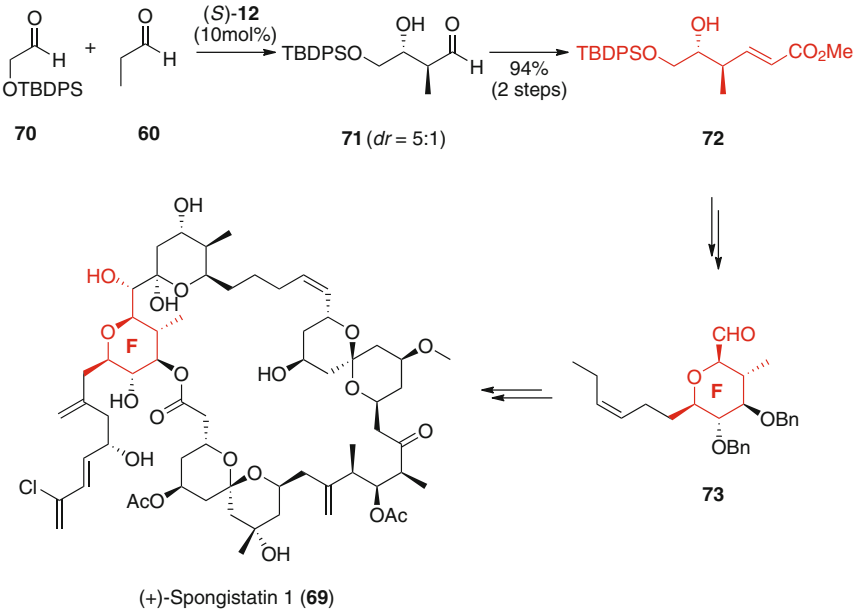
In 2004, the group of *MacMillan* published a report, which can now be regarded as one of the milestones in (organo-) catalysis. By carrying out an organocatalytic aldol reaction first, followed by a metal-catalyzed one, a two-step carbohydrate synthesis starting from simple starting materials could be achieved (*71*, *72*). The key organocatalytic step was a (*S*)-**12** catalyzed enantio- and diastereoselective dimerization of α-oxyaldehyde **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



Scheme 16 *MacMillan's* two-step carbohydrate synthesis (*71*)

carbohydrates. It is worth noting that selective access to either protected glucose **66**, protected mannose **67**, or protected allose **68** can be accomplished by proper choice of the *Lewis* acid and the solvent (Scheme 16).

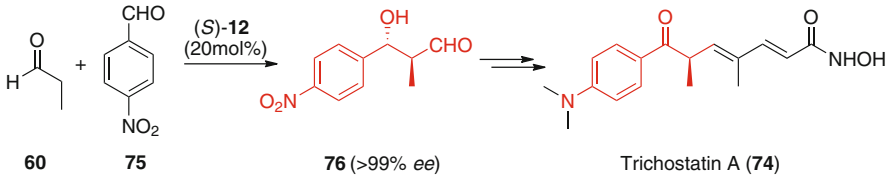
The spongistatin natural products (*e.g.* (+)-spongistatin 1 (**69**)) belong to some of the most potent antimitotic growth inhibitory substances discovered to date (*73–75*). However, their extremely low natural abundance (according to *Pettit* only 13.8 mg of (+)-spongistatin 1 (**69**) can be isolated 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 **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 **70** and propanal (**60**), in accordance with the procedure published by *MacMillan* (Scheme 16). Crude **71** was then submitted directly to an olefination reaction to give the key



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

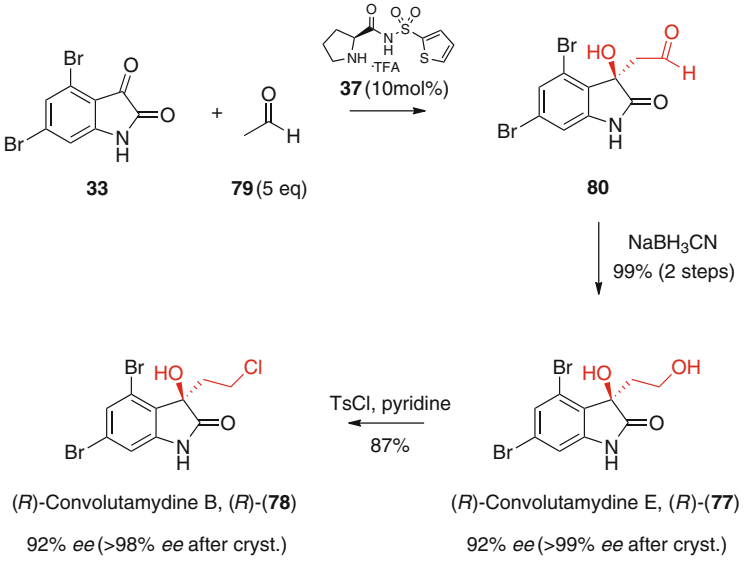
intermediate **72**, which was used to synthesize the F-ring synthon **73**. Notably, the eight-step synthesis towards **73** proceeded with an impressive overall yield of 50%, which was significantly better than other approaches investigated in parallel by *Smith III et al*. Final assembly of the different 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*).



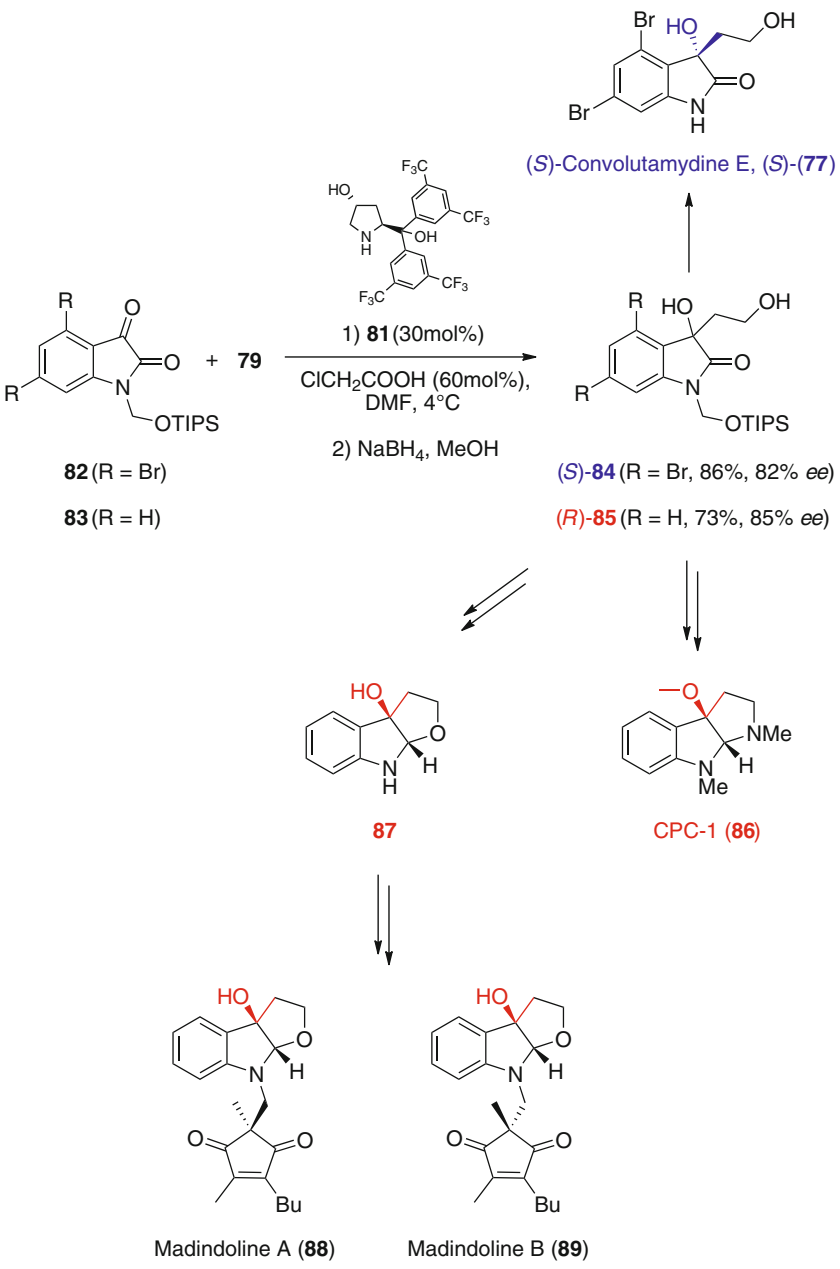
Scheme 18 Synthesis of trichostatin A (**74**)

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*)-convolutamydine 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 $NaBH_3CN$-mediated reduction to obtain (*R*)-convolutamydine E (**77**) in excellent yield and enantioselectivity. Chlorination of **77** then gave (*R*)-convolutamydine B (**78**) (Scheme 19) (*80*, *81*).



Scheme 19 *Nakamura's* syntheses of (*R*)-convolutamydine E (**77**) and B (**78**)

Synthesis of the unnatural (*S*)-convolutamydine E (**77**) was reported by *Hayashi et al.* using the diarylprolinol catalyst **81** (*82*). In contrast to other convolutamydine 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*)-convolutamydine 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).

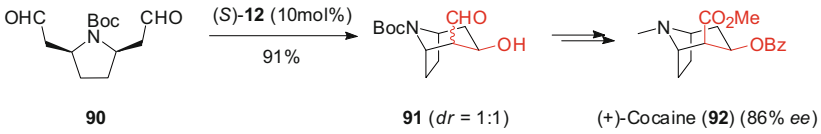


Scheme 20 Syntheses of (*S*)-convolutamydine E (**77**), CPC-1 (**86**), and a fragment (**87**) for the synthesis of madindolines A (**88**) and B (**89**)

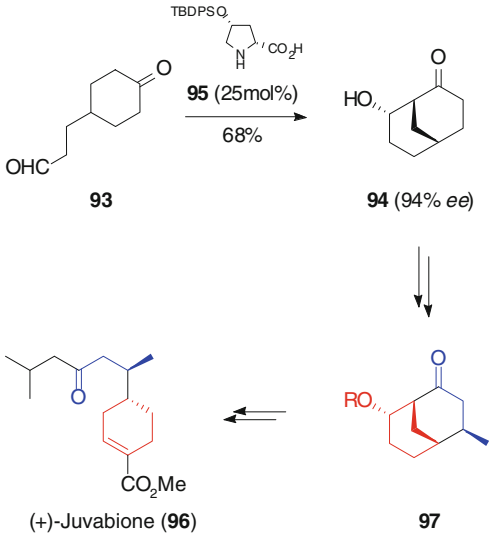
2.1.3 *Intramolecular Aldol Reactions*

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).

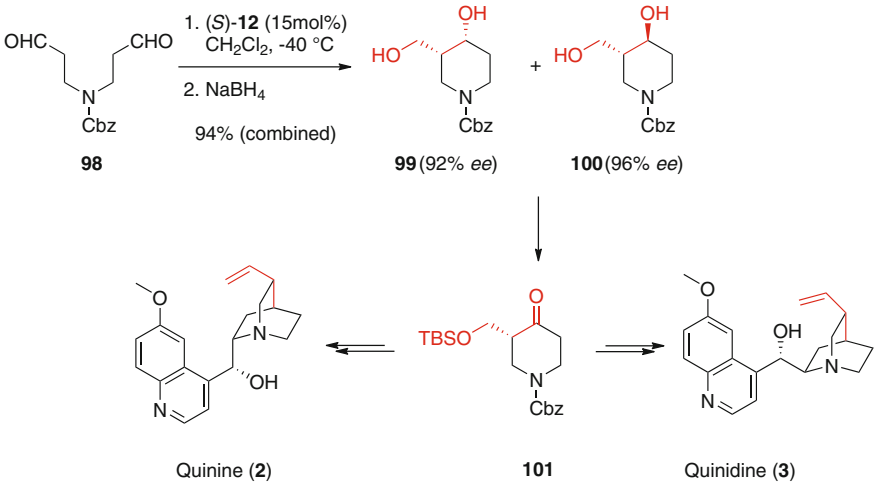
Iwabuchi et al. developed an intramolecular desymmetrization approach for the conversion of the cyclohexanone **93** into the bicyclic **94** using the silylated hydroxyproline **95** as an enamine-catalyst (*87*). Using 25 mol% of **95**, the product **94** was obtained in good yield and excellent stereoselectivity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



Scheme 21 Organocatalytic desymmetrization approach towards (+)-cocaine (**92**)



Scheme 22 Enamine-catalyzed synthesis of **94**, a key fragment in the synthesis of (+)-juvabione (**96**)



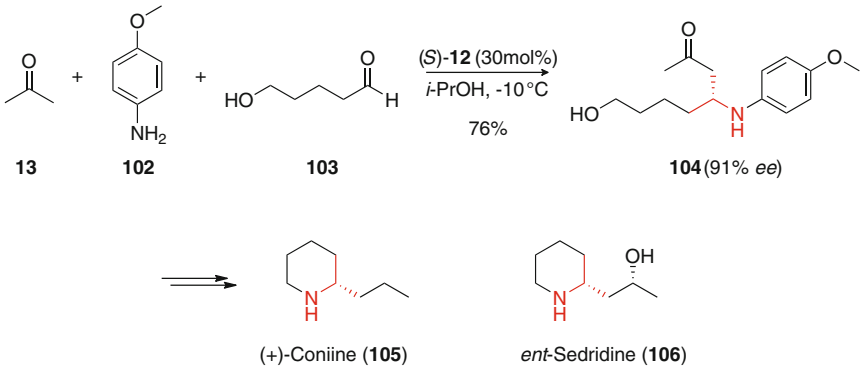
Scheme 23 Enamine-catalyzed introduction of one stereogenic center of quinine (**2**) and quinidine (**3**)

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 $NaBH_4$ to obtain the diastereomers **99** and **100** in good yield and enantioselectivity ($dr = 1{:}2$). 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

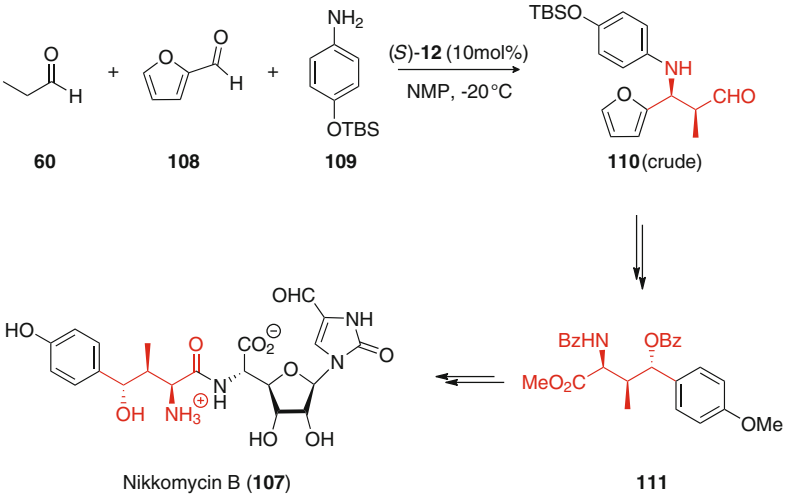
The *Mannich* reaction represents a useful extension of aldol-type approaches for the stereoselective formation of C–C bonds with concomitant introduction of O- and N-functionality. In this reaction two carbonyl compounds and an amine react to form β-amino-carbonyl compounds. Besides indirect variants 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



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

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

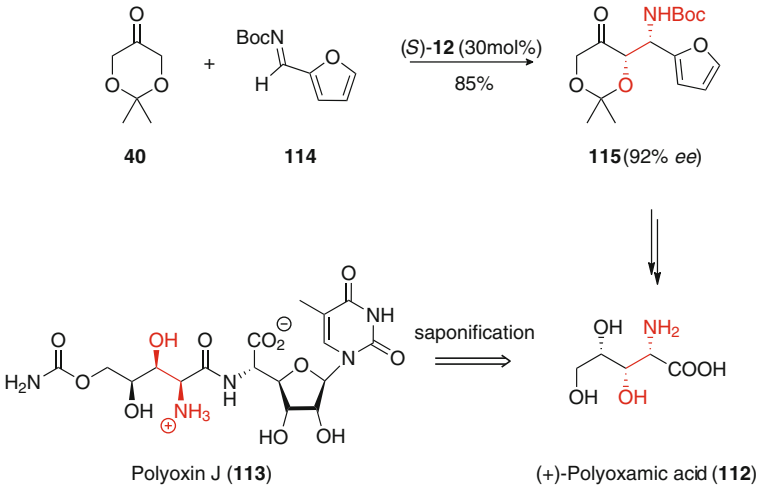


Scheme 25 Formal total synthesis of nikkomycin B (**107**)

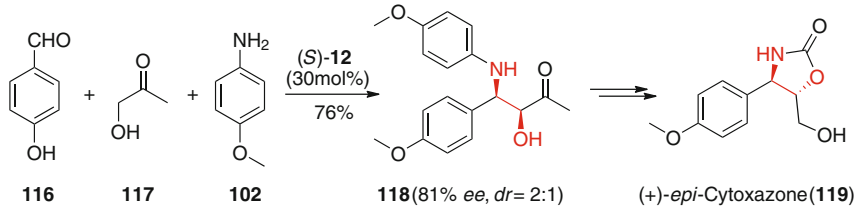
10 mol% (*S*)-**12** to give the unstable chiral β-amino aldehyde **110** in high enantiopurity (determined later on in the sequence to be > 92%). Crude **110** was directly converted further representing a formal total synthesis of **107** (*96*).

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 cacoi* 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*).

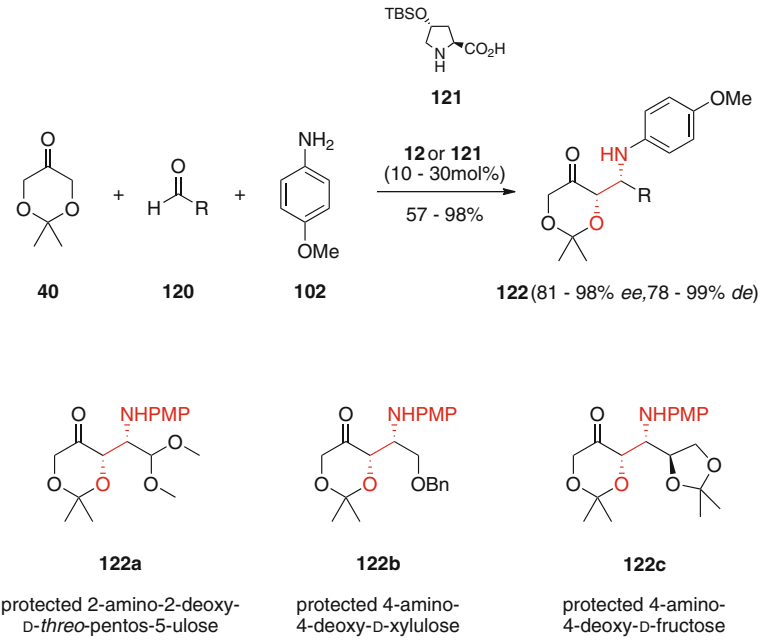
A three-component *Mannich* reaction between *p*-methoxybenzaldehyde (**116**), hydroxyacetone (**117**), and **102** was used successfully to build up the two consecutive stereogenic centers of **118**, an intermediate in the synthesis of (+)-*epi*-cytoxazone (**119**), as shown by *Sudalai et al.*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



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



Scheme 27 *Mannich* reaction in the synthesis of (+)-*epi*-cytoxazone (**119**)



Scheme 28 Enamine-catalyzed three-component direct *Mannich* reaction for the syntheses of protected amino sugars

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,

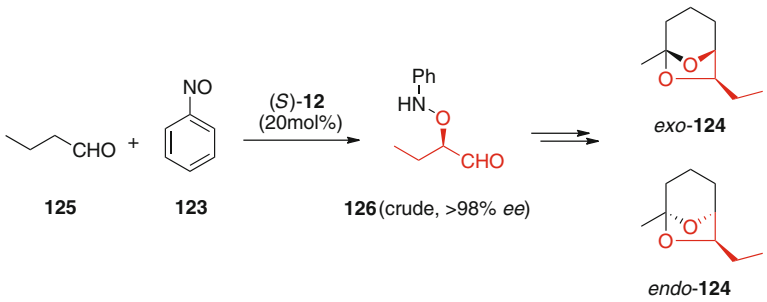
α-halogenation approaches have attracted considerable interest over the last few years (*36*). However, whereas stereoselective α-amination and α-oxygenation strategies have been used in several natural product and natural product analogue syntheses, enamine-catalyzed α-halogenations, especially α-fluorinations, 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

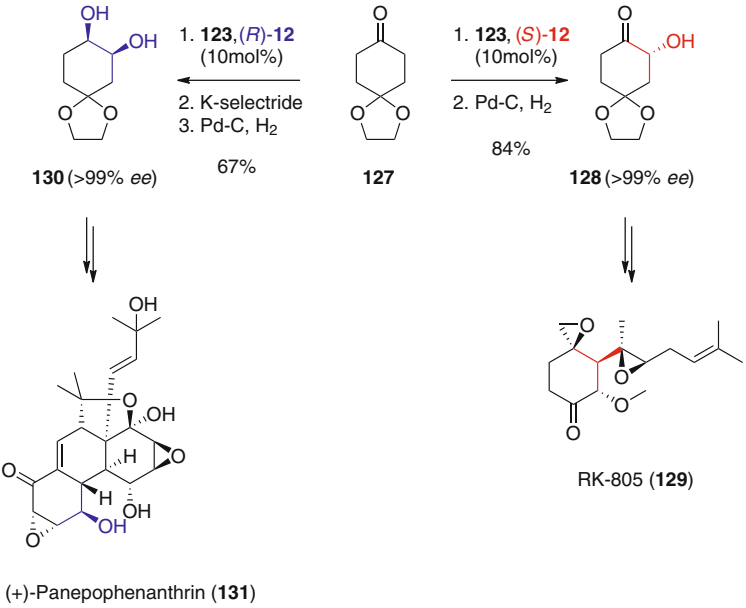
One of the requirements for such reactions is the availability of suitable electrophilic reagents for the introduction of heteroatoms. Nitrosobenzene (**123**) is normally the reagent of choice for the α-oxygenation of carbonyl groups, giving α-anilinooxy carbonyl compounds as the primary products. The 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*).

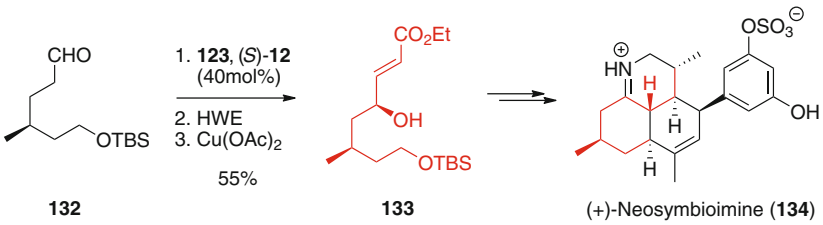
Hayashi et al. used (*R*)- or (*S*)-proline as catalysts to hydroxylate the cyclohexanone **127** selectively to get either the intermediate **128** (upon hydrogenolysis of the N—O bond of the primary reaction product), which was converted further to the natural anti-angiogenesis agent RK-805 (**129**) 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



Scheme 29 Proline (**12**)-catalyzed α-oxygenation in the synthesis of (+)-*exo*- and (−)-*endo*-brevicomin (**124**)



Scheme 30 Proline (**12**)-catalyzed α-hydroxylation for the synthesis of RK-805 (**129**) and (+)-panepophenanthrin (**131**)

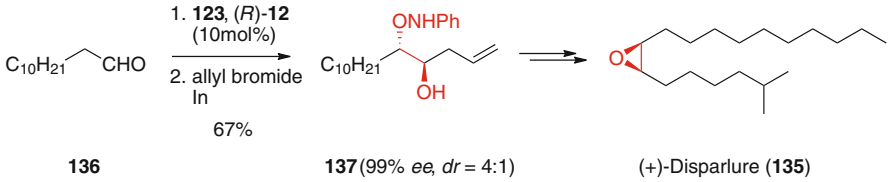


Scheme 31 Total synthesis of neosymbioimine (**134**)

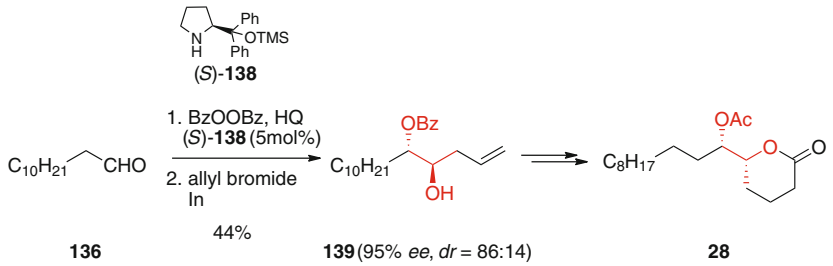
inhibitor of the ubiquitin-activating enzyme (E1) that plays an important role in activating the ubiquitin-proteasome pathway (*114*).

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



Scheme 32 Total synthesis of (+)-disparlure (**135**)



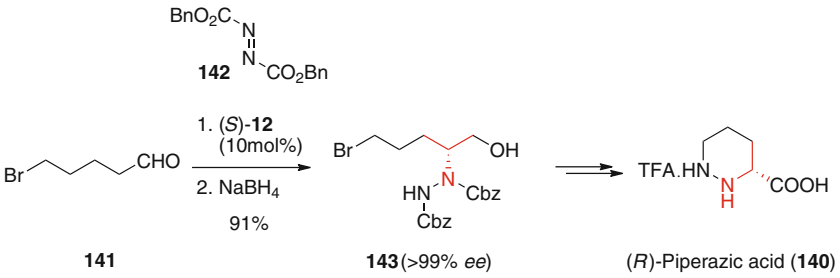
Scheme 33 Enamine-catalyzed α-oxygenation in the synthesis of (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**28**)

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 α-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 α-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 allyation gave the benzoyl-protected **139** in moderate yield and good selectivity. Intermediate **139** could then be further transformed to give (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**28**) (Scheme 33).

2.3.2 α-Amination

The direct stereoselective introduction of a nitrogen functionality in the α-position of a carbonyl group is of high interest as it leads to valuable compounds like



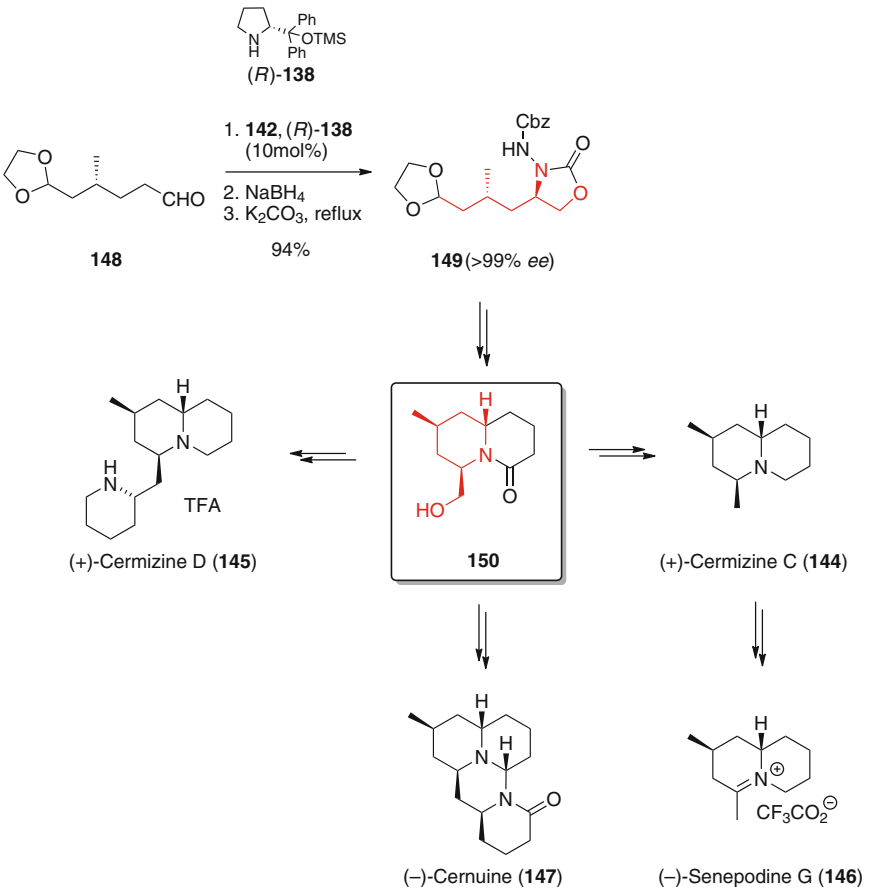
Scheme 34 Asymmetric α-nitrogen-functionalization in the synthesis of (*R*)-piperazic acid (**140**)

α-amino acids, α-amino aldehydes, and β-amino alcohols, and it also gives access to several intermediates in complex natural product syntheses (*123–127*). The first direct catalytic α-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 α-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 μg/cm^3), **144** did not show cytotoxicity at 10 μg/cm^3. In contrast to the relatively recent discovery of **144–146**, the structurally related cernuane-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 cernuane- 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 α-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 *a*-functionalizations have also been used very often in combined organocatalytic approaches, *e.g.*



Scheme 35 Asymmetric α-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**)

accompanied with conjugate additions or other organocatalytic transformations. Some examples, therefore, will be covered in a later section (see Sect. 2.6).

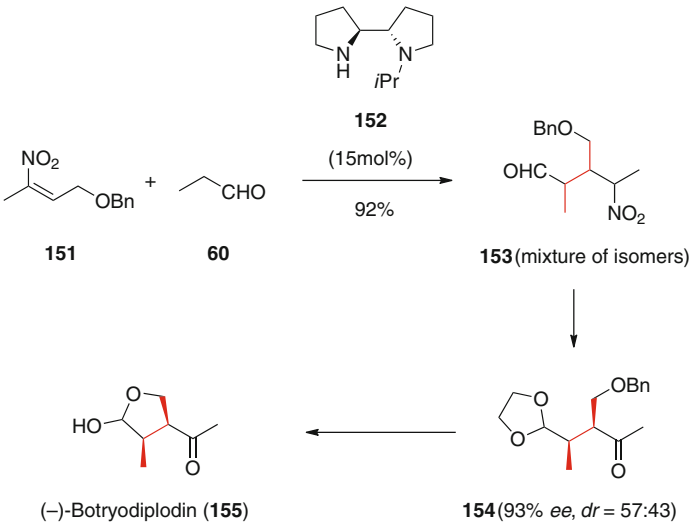
2.4 Conjugate Additions

Conjugate additions of enamines to α,β-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 α-heterofunctionalizations. These combined examples will be described in more detail in Sect. 2.6.

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.

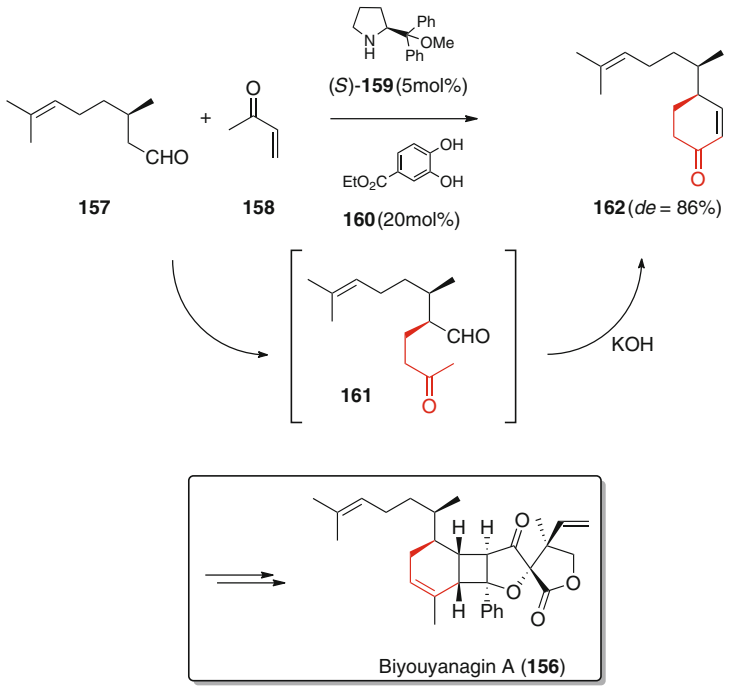
Interesting examples for conjugate additions mediated by chiral amines have been described by *Alexakis et al.* (Scheme 36), who used the nitroalkene **151** as a *Michael* acceptor in organocatalytic enamine-catalyzed conjugate addition reactions (*149*, *150*, *153*). *Michael* reaction of **151** 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



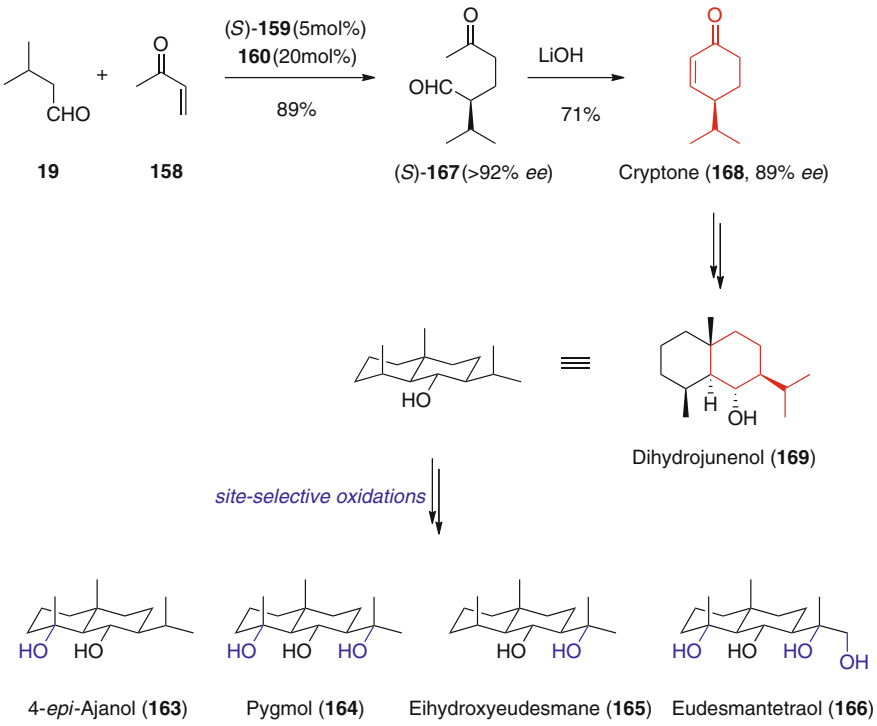
Scheme 36 Asymmetric conjugate addition to nitroalkene **151** in the synthesis of (−)-botryodiplodin (**155**)

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*).



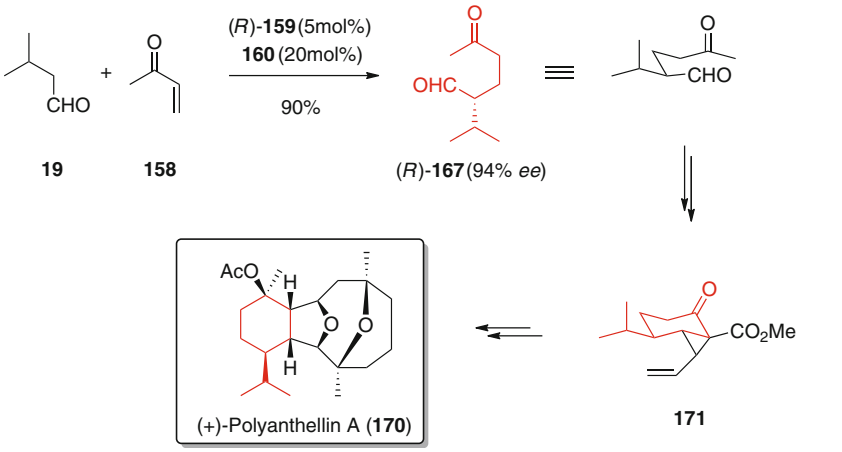
Scheme 37 Early stage enamine-catalyzed *Michael* addition in *Nicolaou's* total synthesis of biyouyanagin A (**156**)



Scheme 38 Enamine-catalyzed *Michael* addition for the synthesis of the eudesmane terpene precursor **168**

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

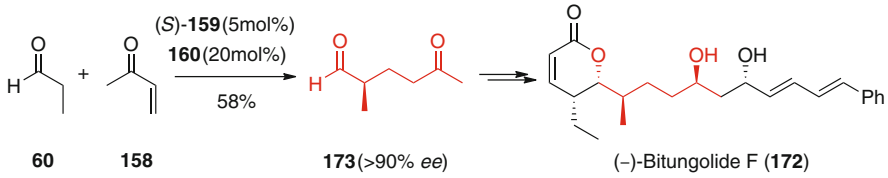


Scheme 39 Enamine-catalyzed *Michael* addition in the synthesis of (+)-polyanthellin A (**170**)

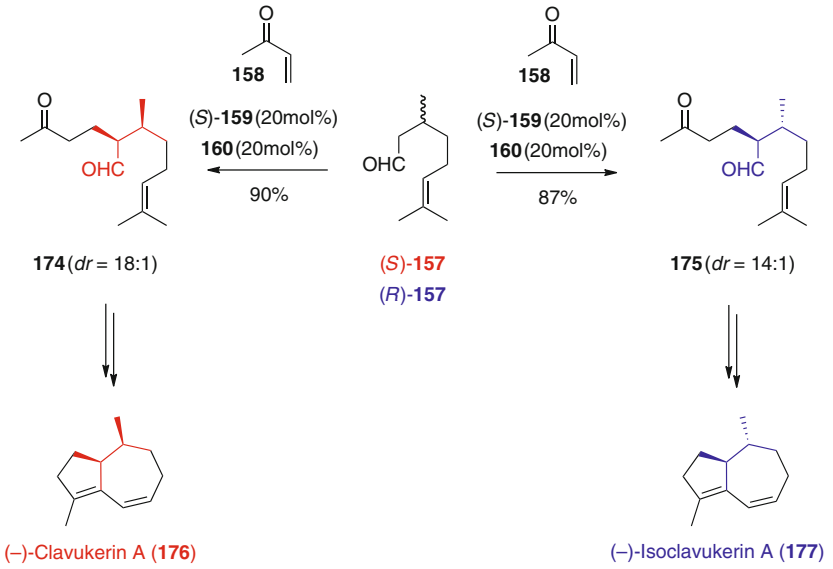
isovaleraldehyde (**19**) and enone **158**. In this case, the (*R*)-configured **167** could be obtained in excellent yield and enantioselectivity. In contrast to the previous examples, no intramolecular aldol condensation was carried out but **167** was used to synthesize the bicyclic compound **171**, 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-specifity 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*).



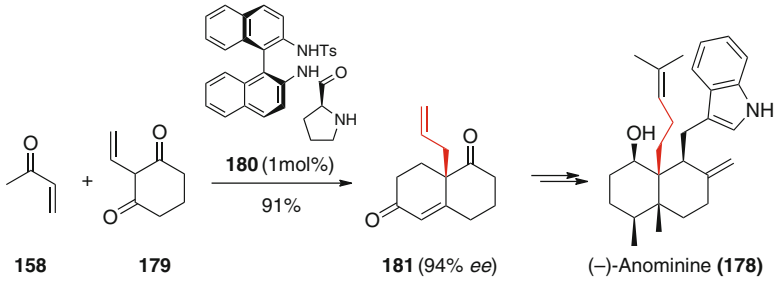
Scheme 40 Enamine-catalyzed *Michael* addition in the synthesis of (−)-bitungolide F (**172**)



Scheme 41 *Michael* addition in the syntheses of (−)-clavukerin A (**176**) and (−)-isoclavukerin A (**177**)

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

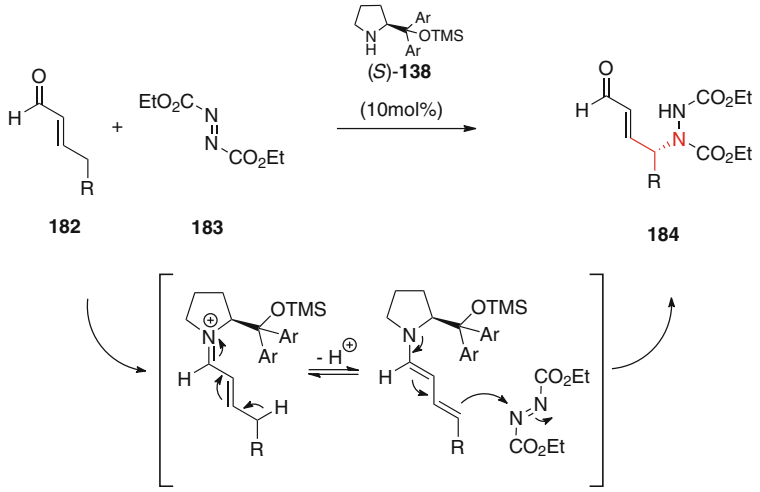


Scheme 42 Enamine-catalyzed *Robinson* annulation in the synthesis of (−)-anominine (**178**)

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*).

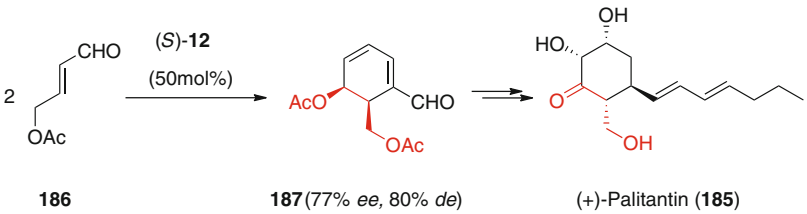
2.5 Dienamine Catalysis

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 (vinylogy), 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 *Jørgensen's* dienamine-catalyzed γ-functionalization protocol (*166*)

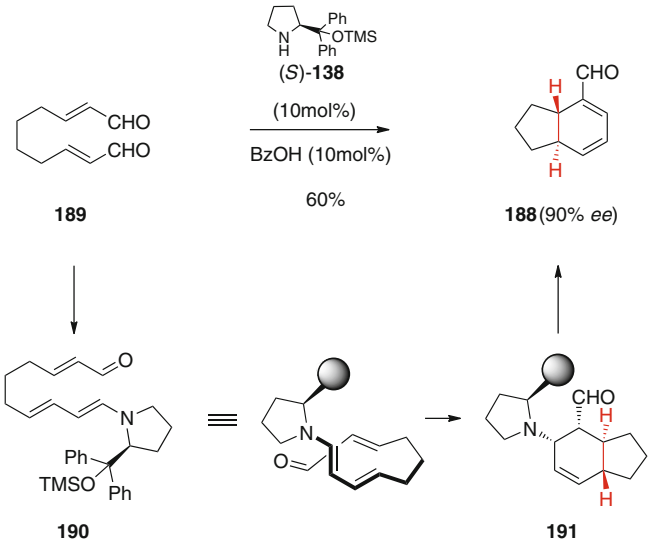
One of the first applications of dienamine catalysis in natural product synthesis was reported by *Hong* and co-workers, who described an efficient organocatalytic synthesis of (+)-palitantin (**185**) (*167*). Palitantin is a highly oxygenated polyketide-derived fungal metabolite isolated from *Penicillium 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



Scheme 44 Dienamine-catalyzed approach in the synthesis of (+)-palitantin (**185**)

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.

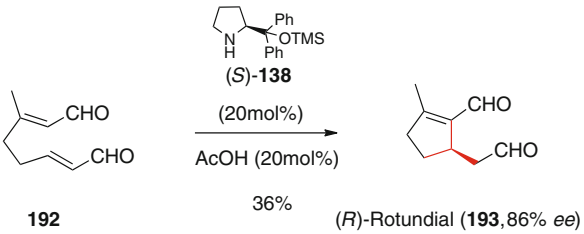
Over the last few years the *Christmann* group has reported some interesting approaches towards the synthesis of mono- and bicyclic skeletons based on dienamine catalysis (*172*, *173*). As an example, (Scheme 45) compound (±)-**188**, a pungent constituent of black cardamom (*174*), was synthesized 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 enantioselectivity through a formal [4 + 2] cycloaddition catalyzed by **138** in the presence



Scheme 45 Dienamine-catalyzed synthesis of bicyclic scaffolds according to *Christmann et al.*

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).

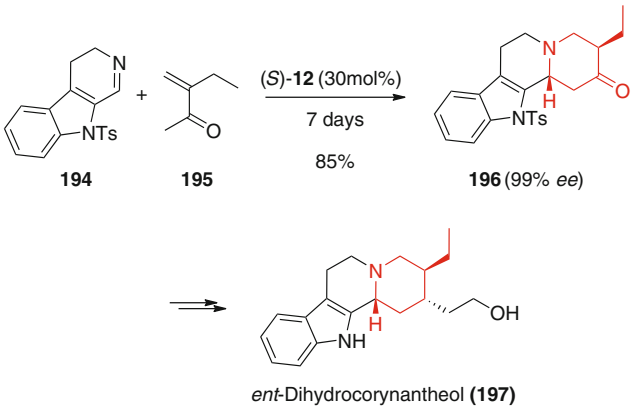


Scheme 46 Dienamine-catalyzed synthesis of (*R*)-rotundial (**193**)

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.

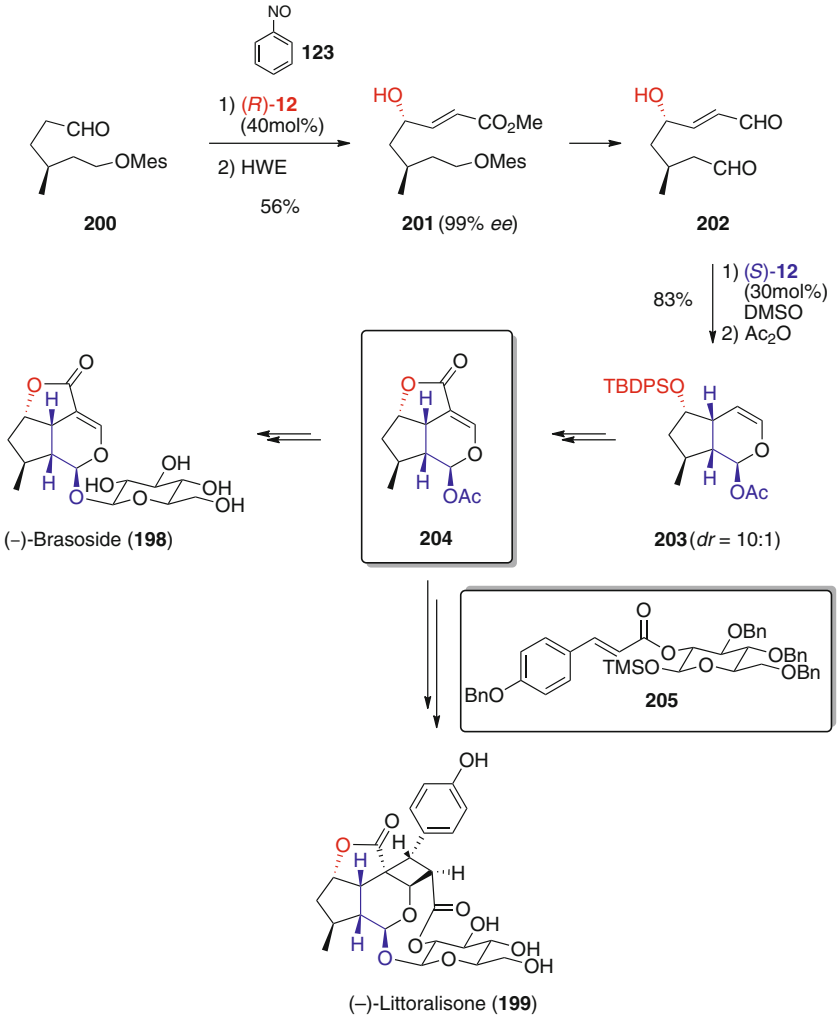
One of the first examples of an enamine-catalyzed cascade reaction for the synthesis of a complex alkaloid was reported by *Itoh et al.* (*179*). Reaction of the dihydrocarboline **194** with enone **195** in the presence of (*S*)-**12** (7 days) gave the tetracycle **196** as a single diastereomer and 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 Enamine-catalyzed *Mannich-Michael* addition in the synthesis of *ent*-dihydrocorynantheol (**197**)

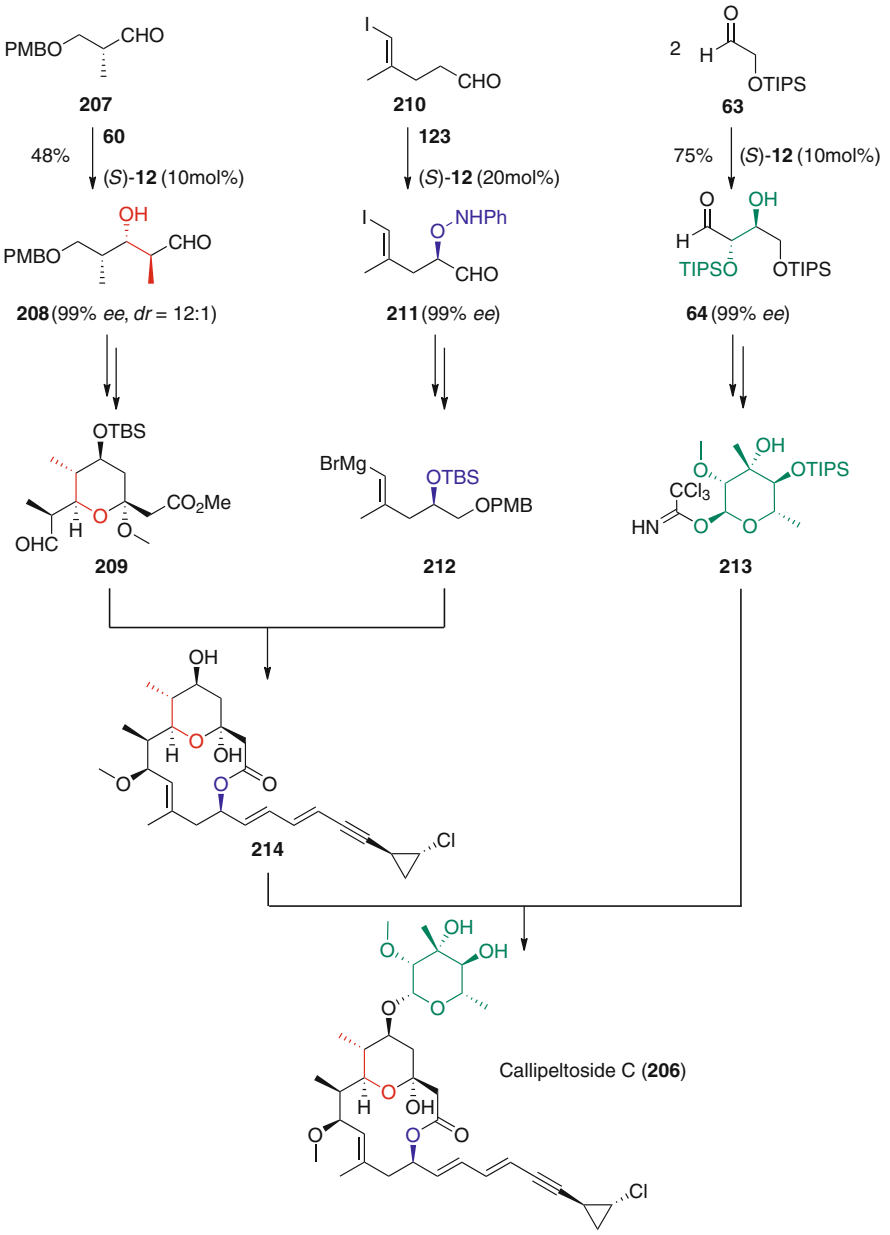
Scheme 47, use of (*R*)-**12** as a catalyst in the first step should therefore give access to the natural product dihydrocorynantheol, a compound isolated from *Aspidosperma marcgravianum* showing activity against *Gram*-positive bacteria (*180*).

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 (−)-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 $CHCl_3$ 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*).



Scheme 48 *MacMillan's* enamine catalysis-based total syntheses of (−)-brasoside (**198**) and (−)-littoralisone (**199**)

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

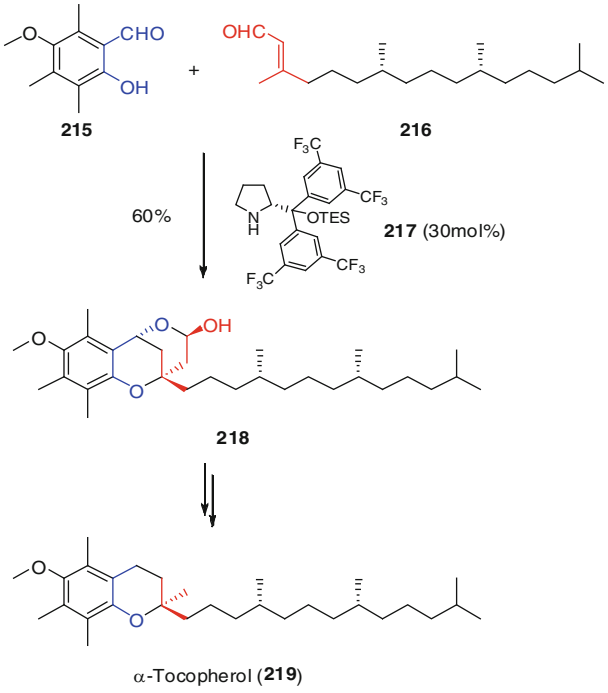


Scheme 49 Total synthesis and structural revision of callipeltoside C (**206**)

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



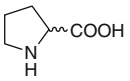
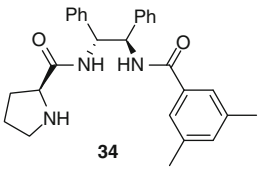
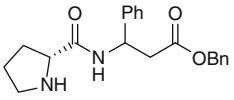
Scheme 50 Dienamine-catalyzed aldol-oxa-*Michael* domino reaction in the synthesis of α-tocopherol (**219**)

(**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

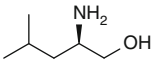
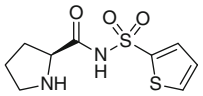
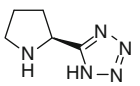
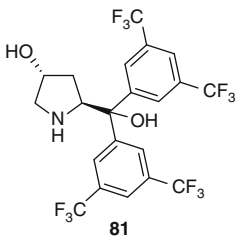
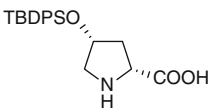
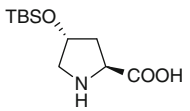
Although enamine catalysis has only been attracting the attention of a broader audience for approximately the last 10 years, this activation mode has (together with iminium catalysis) contributed to possibly the most significant recent progress in the field of asymmetric organocatalysis. This methodology 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

Catalyst	Product	References
 **12**	(*S*)-Ipsenol (**22**)	(*44*)
	(−)-6-Acetoxyhexadecanolide (**28**)	(*45*, *46*)
	Epothilone B (**29**)	(*47*)
	D-*arabino*-Phytosphingosine (**38**)	(*58*)
	L-*ribo*-Phytosphingosine (**39**)	(*58*)
	D-Psicose (**45**)	(*57*)
	D-KDG (**46**)	(*60*)
	Salinosporamide A (**56**)	(*68*)
	Prelactone B (**62**)	(*70*)
	O-Protected Hexoses (**66**, **67**, **68**)	(*71*)
	(+)-Spongistatin 1 (**69**)	(*78*)
	Trichostatin A (**74**)	(*79*)
	(+)-Cocaine (**92**)	(*86*)
	Quinine (**2**)	(*91*)
	Quinidine (**3**)	(*91*)
	(+)-Coniine (**105**)	(*94*, *95*)
	ent-Sedridine (**106**)	(*94*, *95*)
	Nikkomycin B (**107**)	(*96*)
	(+)-Polyoxamic acid (**112**)	(*97*)
	(+)-*epi*-Cytoxazone (**119**)	(*99*)
	Protected amino sugars (**122**)	(*101*)
	Brevicomin (**124**)	(*111*)
	RK-805 (**129**)	(*112*)
	(+)-Panepophenanthrin (**131**)	(*113*)
	Neosymbioimine (**134**)	(*116*)
	Disparlure (**135**)	(*120*)
	Piperazic acid (**140**)	(*128*)
	(+)-Palitantin (**185**)	(*167*)
	ent-Dihydrocorynantheol (**197**)	(*179*)
	(−)-Brasoside (**198**)	(*115*)
	(−)-Littoralisone (**199**)	(*115*)
	Callipeltoside C (**206**)	(*184*)
 **34**	(*S*)-Convolutamydine A (**32**)	(*52*)
 **35**	(*R*)-Convolutamydine A (**32**)	(*51*)

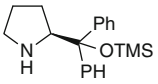
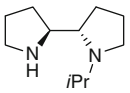
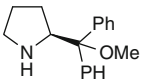
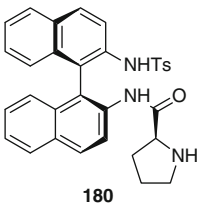
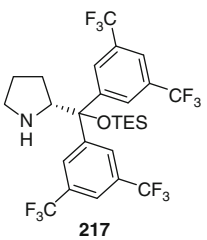
(continued)

Table 1 (continued)

Catalyst	Product	References
 **36**	(*R*)-Convolutamydine A (**32**)	(*53*)
 **37**	(*R*)-Convolutamydine A (**32**) (*R*)-Convolutamydine E (**77**) (*R*)-Convolutamydine B (**78**)	(*54*) (*80*, *81*) (*80*, *81*)
 **54**	Serricornin (**51**)	(*62*)
 **81**	(*S*)-Convolutamydine E (**77**) CPC-1 (**86**) Madindoline A (**88**), B (**89**)	(*82*) (*83*) (*84*)
 **95**	(+)-Juvabione (**96**)	(*89*)
 **121**	Protected amino sugars (**122**)	(*101*)

(continued)

Table 1 (continued)

Catalyst	Product	References
 **138**	(−)-6-Acetoxyhexadecanolide (**28**)	(*121*)
	Cermizine C (**144**)	(*138*, *139*)
	Cermizine D (**145**)	(*138*, *139*)
	Senepodine G (**146**)	(*138*, *139*)
	Cernuine (**147**)	(*138*, *139*)
	(*R*)-Rotundial (**193**)	(*173*)
 **152**	(−)-Botryodiplodin (**155**)	(*153*)
 **159**	Biyouyanagin A (**156**)	(*155*)
	Eudesmane terpenes (**163–166**)	(*158*)
	(+)-Polyanthellin A (**170**)	(*160*)
	(−)-Bitungolide F (**172**)	(*161*)
	(−)-Clavukerin A (**176**)	(*162*)
	(−)-Isoclavukerin A (**177**)	(*162*)
 **180**	Anominine (**178**)	(*164*)
 **217**	α-Tocopherol (**219**)	(*187*)

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