DOI: 10.1002/ejoc.200700032

Organocatalytic Synthesis of Drugs and Bioactive Natural Products

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Keywords: Total synthesis / Natural products / Organocatalysis / Medicinal chemistry / Asymmetric synthesis

Catalytic reactions are a key element in the design of sustainable chemical processes. As witnessed in the field of transition metal-catalysed processes, only those reactions that are reliable over a broad substrate range and tolerant toward a multitude of functional groups have found their way into the repertoire of preparative chemists. Natural product synthesis provides a good benchmark for the maturity of a new synthetic method and in this microreview we discuss the scope and limitations of organocatalytic reactions in the synthesis of biologically important molecules.
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1. Introduction

The synthesis of molecules that exert measurable effects on living systems has always fascinated chemists. Over the years, a powerful repertoire of synthetic methods that allows for the synthesis of even the most complex molecular entities has emerged. With the continuing exploration of the human proteome, the development (i.e., synthesis) of small molecules that modulate protein function has become increasingly appealing. Highly selective ligands usually possess a certain degree of complexity, so it has therefore been a constant challenge to develop new synthetic methodology that provides more efficient access to natural and unnatural compounds of biological interest. At the end of the last century it seemed that transition metal-catalysed transformations were destined to have the most impact on this challenge,[1] but two publications on metal-free catalysis in 2000 undoubtedly called this into question. List, Lerner and Barbas showed that the simple amino acid proline (**3**) catalysed enantioselective cross-aldol reactions between acetone (**1**) and different aldehydes (Scheme 1, Equation 1),[2] while MacMillan, Ahrendt and Borths demonstrated that chiral imidazolidinium salts (**7**) were able to activate α,β-unsaturated aldehydes for asymmetric Diels–Alder reactions (Equation 2).[3] In both studies small organic catalysts offered a simple solution to extremely recalcitrant synthetic problems.

The term "organic catalysts" was introduced by Ostwald (1900), in order to distinguish small organic molecules as catalytic principles from enzymes or inorganic catalysts.[4] In the following years, Marckwald[5] and Bredig[6] used alkaloids in the desymmetrization of prochiral substrates. An

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Mathias Christmann was born in Peine, Lower Saxony, Germany, in 1972. He studied chemistry in Braunschweig (1993–1998) and Hannover (1998–2001) and obtained his Ph.D. under the guidance of Markus Kalesse with a total synthesis of ratjadone. After a postdoctoral appointment with Craig J. Forsyth at the University of Minnesota in Minneapolis (2001–2002) he moved back to pursue an independent academic career in Germany. In 2003 he joined the RWTH Aachen as a Liebig-Fellow associated with Dieter Enders. Together with Stefan Bräse he has edited "Asymmetric Synthesis – The Essentials". His research interests include organocatalysis and natural products synthesis.

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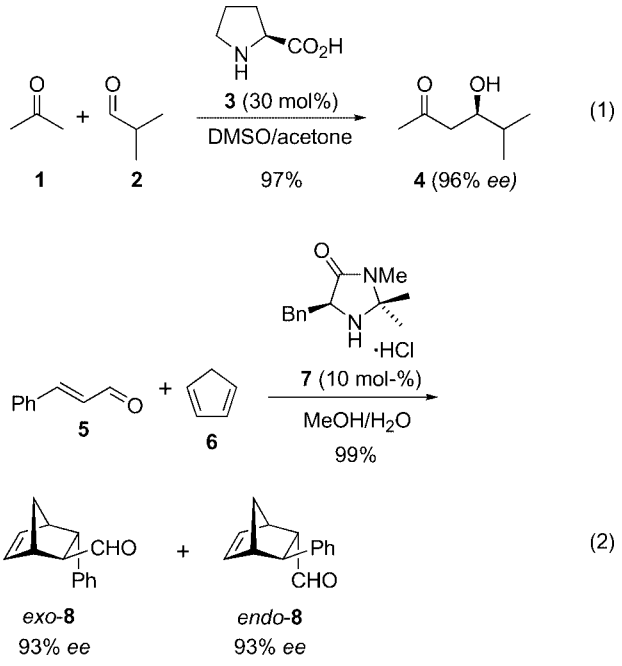


Scheme 1. Key reactions for the renaissance of organocatalysis.

early treatise on "organic catalysis", with a reaction mechanism, kinetics and catalyst optimization with amine-catalysed decarboxylations, was published by Langenbeck (1932).[7] Nowadays, MacMillan's neologism "organocatalysis" has become the catchword for this field of research.[8] Figure 1 illustrates the increase in publications containing the words "organocatalysis", "organocatalytic" or "organocatalyst" from 2000 to 2006.[9]

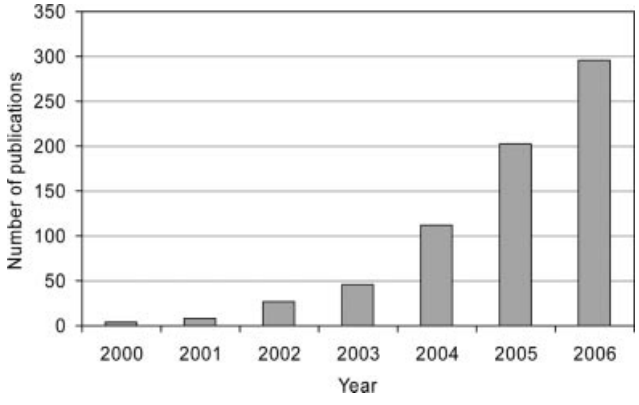


Figure 1. Publications on organocatalysis (SciFinder®).

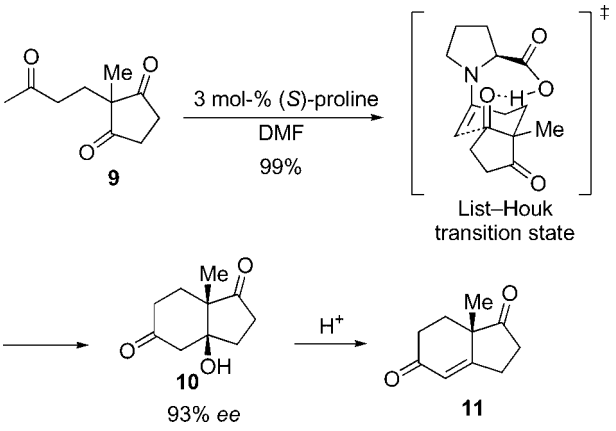
This review gives the reader an overview of recent applications of organocatalytic reactions in the synthesis of natural products and active pharmaceutical ingredients (APIs) published within this timeframe (2000–2006). The synthesis of sugars[10] and amino acids[11] is not covered as it has been highlighted elsewhere. It is the authors' aim to inspire the readers to use organocatalysis in their own setting. For the benefit of broader coverage, only the organocatalytic key steps for every synthesis are given. When appropriate, further transformations are provided. In order to limit the scope of this review somehow, we have not included work that has provided drug-like or natural product-like structures[12] or catalytic processes that use metals or metal salts in the catalytic step.[13]

2. Enamine Catalysis

2.1 Aldol Reactions

Intramolecular Aldolization

In 1971, Hajos and Parrish at Hoffmann-La Roche[14] and Eder, Sauer and Wiechert at Schering[15] independently reported a proline-catalysed intramolecular aldol reaction of triketone **9**. Under optimized conditions in a polar aprotic solvent and in the presence of 3 mol-% of catalyst, Hajos and Parrish obtained **10** in 99% yield and with 93% *ee* (Scheme 2). Acid-catalysed dehydration concluded the synthesis of ketone **11**, an important intermediate in the total synthesis of steroids. The Wieland–Miescher ketone[16] can be obtained similarly, albeit with lower enantiomeric excess. Related cyclizations have proven to be extremely useful in the synthesis of many natural products.[17] It is interesting to note that Hajos and Parrish regarded this reaction as "a simplified model of a biological system in which (*S*)-proline plays the role of an enzyme". The mechanism of this reaction has been the subject of heated discussion[18] and the transition state in Scheme 2 summarizes the work of List and Houk.[19]



Scheme 2. Synthesis of the Hajos–Parrish ketone (**11**).

From the perspective of the starting material, this process can formally be considered a 6-*enolendo* cyclization, with the enamine C–C double bond constituting part of the newly formed carbocycle. In 2003, List described the first intramolecular *enolexo* aldolization (Scheme 3, Equation 3).[20] This process is particularly attractive for the desymmetrization of *meso* compounds,[21] as demonstrated in a concise synthesis of (+)-cocaine by Pearson and Mans (Equation 4).[22] The tropane skeleton **15**, suitable for further elaboration into cocaine, was obtained in 91% yield as a mixture of epimers by treatment of the *meso*-dialdehyde **14** in the presence of 10 mol-% of (*S*)-proline.

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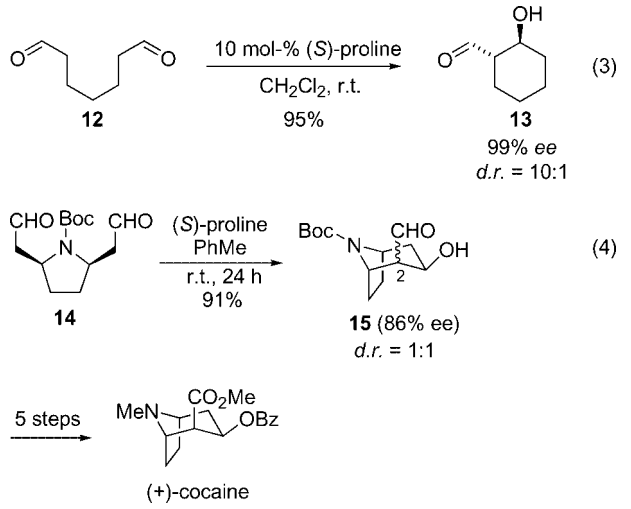


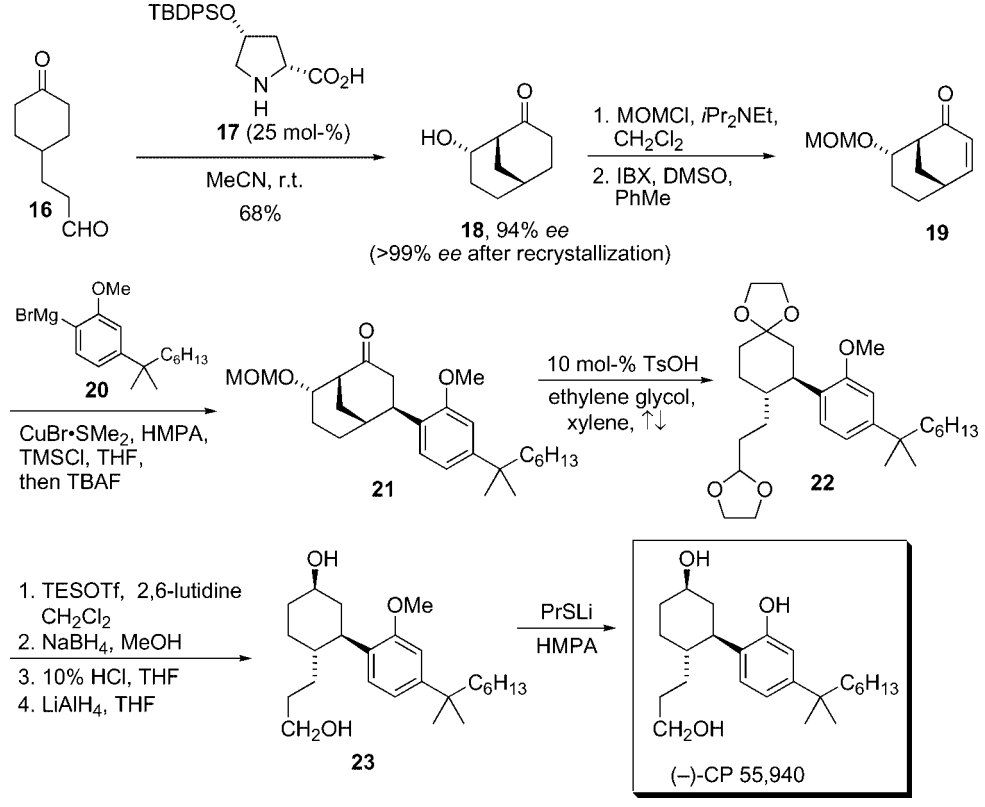
Scheme 3. *Enolexo* aldolizations. Application to the synthesis of (+)-cocaine.

Iwabuchi has developed an intramolecular aldolization-based desymmetrization of σ-symmetric 4-substituted cyclohexanones (Scheme 4). With 25 mol-% of the silylated hydroxyproline **17** as catalyst, the desired bicyclic product **18** was obtained in 68% yield and with 94% *ee*, which was increased to >99% *ee* after recrystallization.[23] This material was used in a synthesis of the cannabinoid receptor agonist (–)-CP 55940.[24] Protection of the hydroxy group was followed by dehydrogenation with IBX to provide the unsaturated ketone **19**, while a cuprate addition of a suitable aromatic moiety (**20**) furnished the carbon skeleton of the target compound. In the last transformation, the bicycle served as steric control element. Subsequent reopening in a retro-aldol reaction with concomitant acetalization of the two carbonyl functions afforded the bis-acetal **22**, and sequential deprotection/reduction of the two acetals and cleavage of the methyl ether gave (–)-CP 55940 in five further steps.

Through the use of a methyl cuprate addition similar to that in the previous synthesis and an exchange of protecting groups (MOM → TES), compound **24** was obtained in three steps from **19** (Scheme 5). After a Norrish-I-type fragmentation to give aldehyde **25**, eight further steps were required to finish an enantioselective synthesis of (+)-juvabione.[25]

Ketone–Aldehyde Coupling

Additions of ketones to aldehydes under enamine catalysis conditions often compete with the self-aldolization of the aldehyde component. Unless non-enolizable or α-substituted aldehydes are employed, excess of ketone or slow addition of the aldehyde acceptor minimizes aldehyde dimerization. In addition, the formation of condensation products **27** can significantly reduce overall yields (Scheme 6). However, operationally simple access to enantiomerically enriched intermediates **28** from readily available starting materials **1** and **26** makes this approach highly attractive for the synthesis of biologically active compounds. In a short synthesis of the bark beetle pheromone (*S*)-ipsenol,[26] List et al. converted **28** into the enol triflate **29**, which was in



Scheme 4. Synthesis of (–)-CP 55940.

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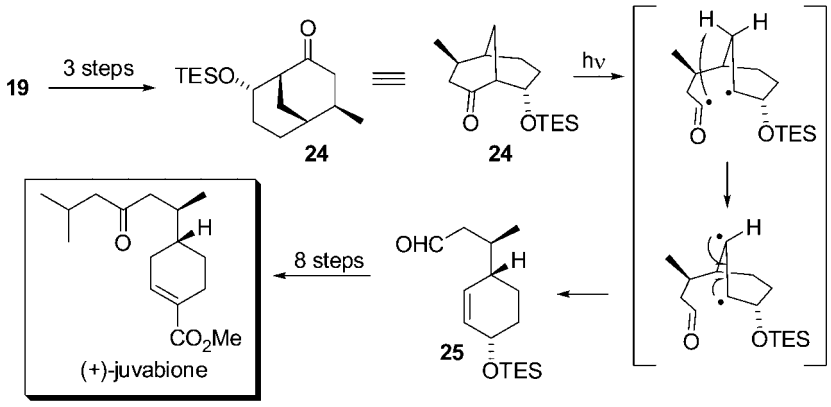
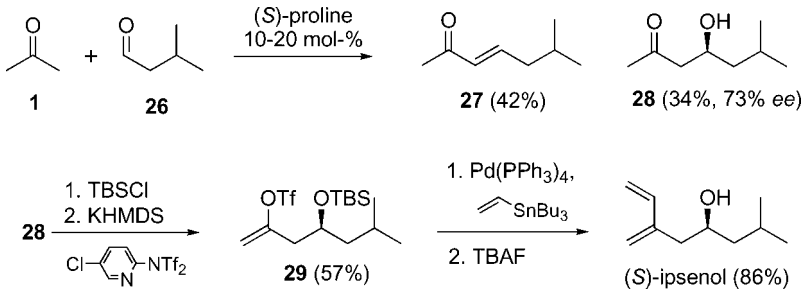


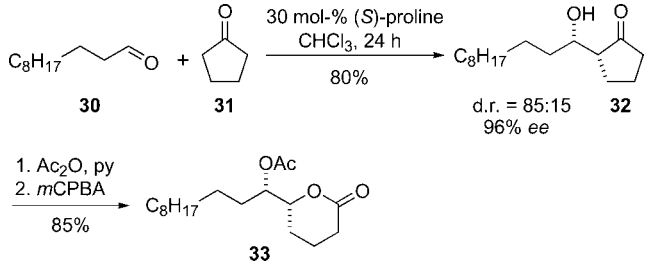
Scheme 5. Synthesis of (+)-juvabione.



Scheme 6. Synthesis of (*S*)-ipsenol.

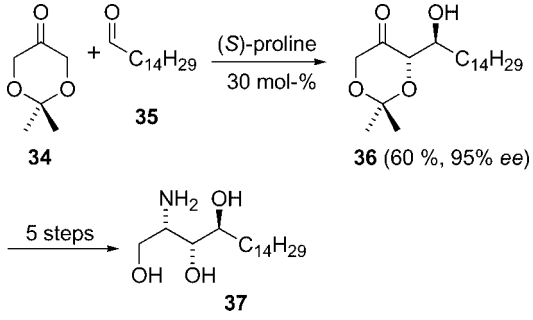
turn subjected to a Stille coupling. Removal of the silyl ether afforded the natural product in good yield.

Li[27] and Kotsuki[28] independently reported efficient syntheses of (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**33**), an oviposition attractant pheromone of the female *Culex* mosquito. In the Li approach, a proline-catalysed aldol reaction is used to connect undecenal (**30**) and cyclopentanone (**31**) to afford the desired isomer **32** in 80% yield with good selectivity (*dr* = 85:15, 96% *ee*). Acetylation of the hydroxy group was followed by a Baeyer–Villiger ring-expansion to give the δ-lactone **33** in 85% yield (Scheme 7).



Scheme 7. Synthesis of (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**33**).

Enders et al. used their trademark dioxanone **34**[29] as a three-carbon building block for the synthesis of sphingosines (Scheme 8). The carbon framework was assembled in a proline-catalysed aldol reaction, which was followed by a series of functional group manipulations to afford D-*arabino*-phytosphingosine (**37**).[30]



Scheme 8. Synthesis of D-*arabino*-phytosphingosine.

Ward has devised a thiopyranone-based route to polypropionates, in which **38** is used as a more reactive synthetic equivalent of pentan-3-one. In an application of their methodology, a short enantioselective synthesis of serricornin was developed (Scheme 9).[31] In the presence of 20 mol-% of the proline tetrazole **40**,[32] the aldol reaction between **38** and **39** proceeded smoothly to give the desired product **41**. Gratifyingly, a concomitant dynamic kinetic resolution of racemic **39** was also observed under these conditions. In six further steps, including a Barton deoxygenation and a desulfurization, serricornin was obtained and characterized as its acetate derivative.

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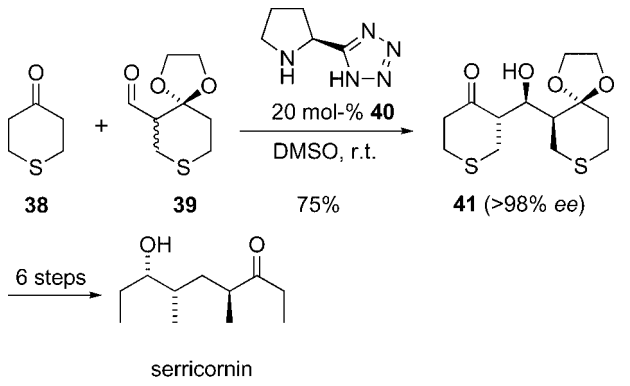


Scheme 9. Synthesis of serricornin.

The following examples illustrate the use of organocatalysis in the synthesis of fragments of epothilone (C1–C6) and apratoxin A (C35–C40, Figure 2).

As can be seen above, ketone-aldehyde couplings with unbranched aldehydes can be problematic. However, α-disubstituted aldehydes usually give very high enantioselectivities. Avery and Zheng[33] obtained **43** in good yield and *ee* from a proline-catalysed aldol reaction between acetone and ketoaldehyde **42** (Scheme 10). Since the transformation of the methyl ketone **43** into the desired carboxylic acid **46** by means of a haloform reaction failed, a detour was inevitable, and so a regioselective intramolecular aldolization was followed by TBS protection of the hydroxy group. Finally, oxidative cleavage of cyclohexenone **45** afforded the ketoacid **46**.

Like the Sharpless asymmetric olefin oxidations, organocatalysis has extended the "synthetic chiral pool"[34] (i.e., enantiopure material obtained from achiral bulk chemicals). Hydroxy ketone **47** is readily available in >99% *ee* from acetone and pivaldehyde. Not surprisingly, two groups identified **47** as starting material for their synthesis of apratoxin (Scheme 11).[35] In Doi's and Takahashi's approach, the hydroxy group was protected and the keto group was transformed into the allylic acetate **48**. This material was subjected to a Pd^{II}-catalysed allylic isomerization to afford **49**, and three additional steps furnished aldehyde **52** (R = PMB). Ma et al. used the acetone aldol reaction as a substitute for an asymmetric allylation of pivaldehyde (**47**→**50**). An additional eight steps gave the C35–C40 aldehyde **52** (R = Ac) of apratoxin A.

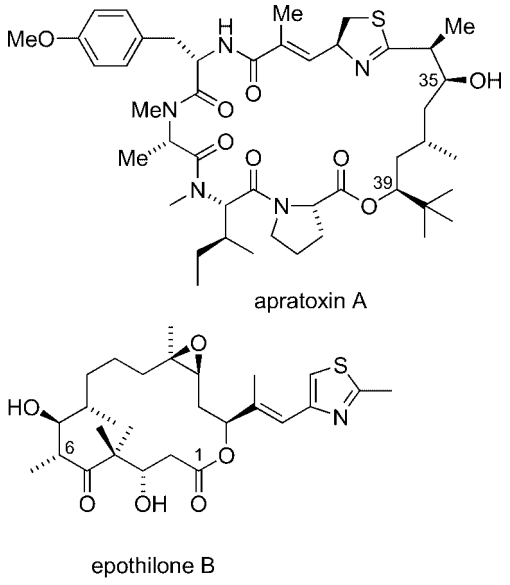
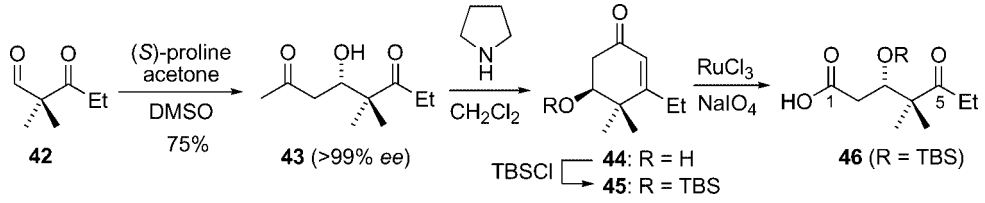
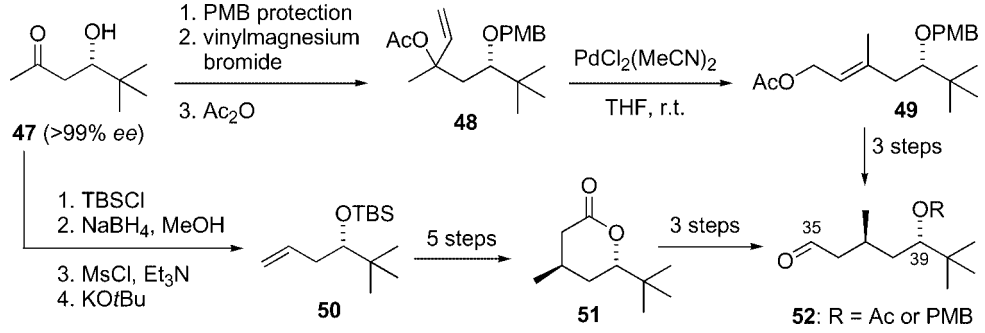


Figure 2. Apratoxin A and epothilone B.

The examples above illustrate the synthetic potential of ketone-aldehyde couplings, but also reveal the problems associated with the manipulation of the keto group, when in fact an acetate aldol reaction was the required transformation.



Scheme 10. Synthesis of the C1–C6 ketoacid of epothilone.



Scheme 11. Synthesis of the C35–C40 fragment of apratoxin A.

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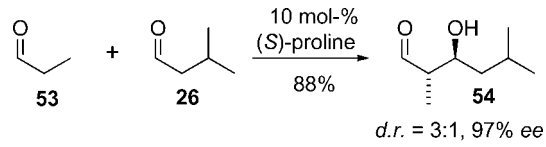
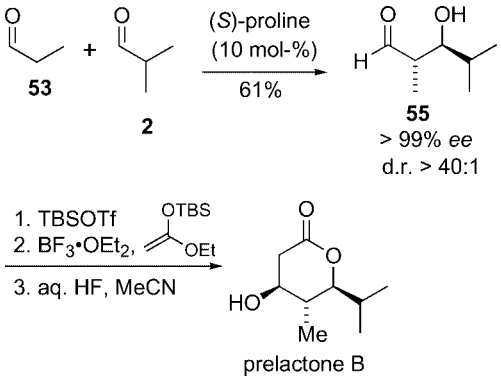
Aldehyde–Aldehyde Coupling

In 2002, MacMillan reported the first organocatalytic direct cross-aldol reaction of aldehydes (Scheme 12).[36] In the presence of 10 mol-% of (*S*)-proline, the aldol adduct **54** of propionaldehyde (**53**) and isovaleraldehyde (**26**) was obtained in 88% yield and with 97% *ee* as a 3:1 mixture of diastereomers.



Scheme 12. Cross-aldol reaction of aldehydes.

Pihko[37] applied this methodology to a remarkably short synthesis of prelactone B. Under carefully controlled conditions, propionaldehyde was added to a solution of a catalytic amount of proline and isobutyraldehyde (**2**, Scheme 13). The cross aldol product **55** was obtained in >99% *ee* and a *dr* > 40:1 in favour of the desired *anti* isomer. Protection of the hydroxy group was followed by a Mukaiyama aldol reaction, affording the Felkin product as the only observed isomer. Upon removal of the protecting group, cyclization occurred smoothly to give prelactone B.

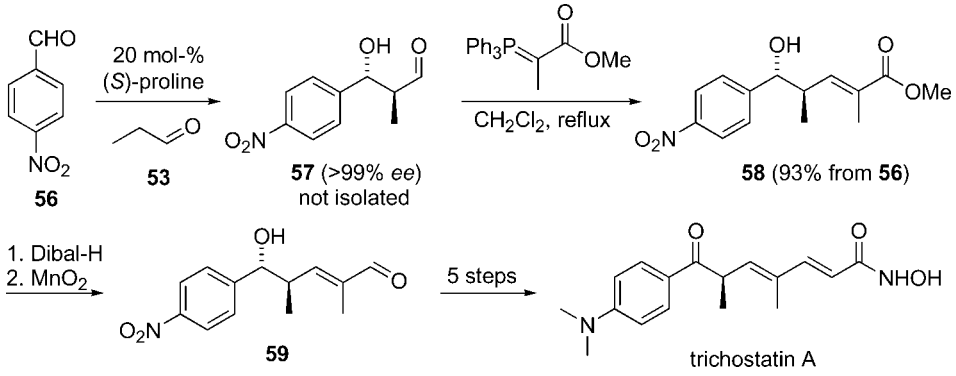


Scheme 13. Synthesis of prelactone B.

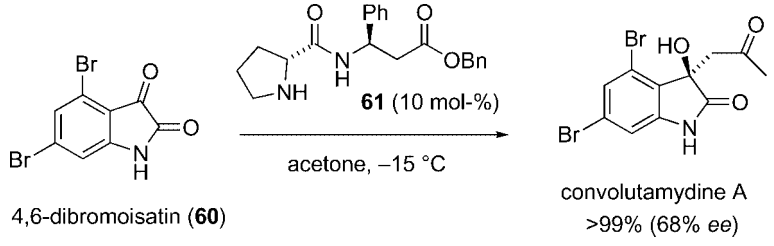
Duan and Wang[38] anticipated that the stereocenter in the histone deacetylase inhibitor trichostatin A should be attainable through an aldehyde-aldehyde coupling. As shown in Scheme 14, a proline-catalysed aldol reaction between *p*-nitrobenzaldehyde (**56**) and propionaldehyde (**53**) produced the *anti*-aldol product **57** with excellent selectivity (*dr* = 16:1, >99% *ee*). Because of its instability towards chromatography, **57** was used directly in a subsequent Wittig reaction to give **58** in 93% yield from **56**. Reduction of the ester to the allylic alcohol and selective oxidation of the allylic over the benzylic position afforded **59**, which was taken forward to trichostatin A.

Ketone–Ketone Coupling

Aldol couplings between two ketones are rather difficult, owing to their lower reactivity as acceptors. Garden and Tomasini[39] recently achieved the first synthesis of convolutamydine A through an enantioselective addition of acetone to dibromoisatin (**60**). In the presence of 10 mol-% of the prolinamide catalyst **61**, convolutamydine A was obtained in excellent yield and with 68% *ee*. A recrystallization increased the *ee* to 97% (Scheme 15).



Scheme 14. Synthesis of trichostatin A.



Scheme 15. Synthesis of convolutamydine A.

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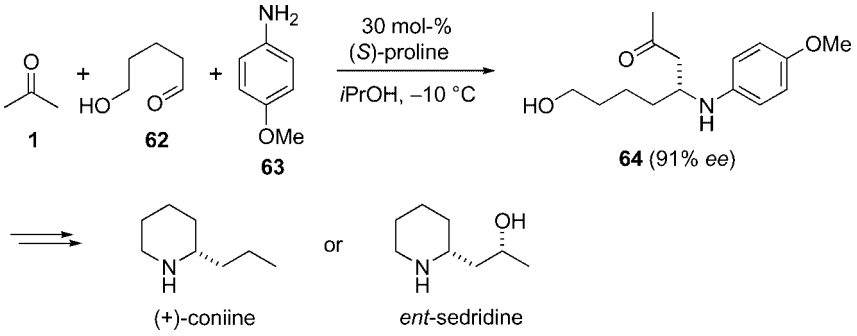
2.2 Mannich Reactions

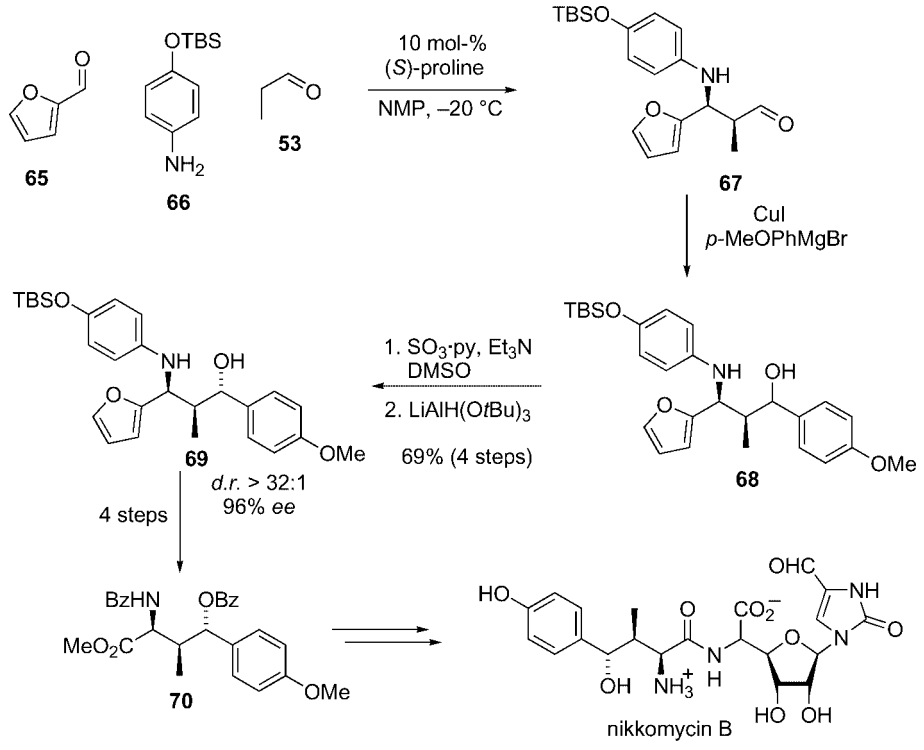
The Mannich reaction is an efficient tool for the enantioselective formation of C–C bonds with concomitant introduction of *N*- and *O*-heterofunctionality. Since these features are present in many active pharmaceutical ingredients (APIs), organocatalysis has impacted their synthesis. Shortly after the proline-catalysed aldol reaction, the first example of a direct organocatalytic Mannich reaction was published.[40] With proline as the catalyst, the *anti* products are usually formed as the major adducts. Barbas and Maruoka have recently devised catalysts that favour the *syn* products, rendering this reaction stereodivergent.[41] *p*-Anisidine is usually used for the in situ imine formation and as *N*-protecting group but its removal requires strongly oxidizing conditions that are incompatible with many substrates. Boc-imines have been found to be a viable alternative,[42] but they are limited to aromatic aldehydes and they cannot be formed in situ.

Coniine is a popular target among *N*-heterocyclic natural products. Very recently, Itoh et al. have developed a new synthesis of this natural product through a proline-catalysed Mannich reaction (Scheme 16).[43] From intermediate **64**, *ent*-sedridine and (+)-coniine were obtained in six and eight steps, respectively.

Hayashi et al. have used a three-component Mannich reaction for an enantioselective synthesis of the amino acid moiety of nikkomycin B (Scheme 17).[44] In the key step, 4-(*tert*-butyldimethylsilyloxy)aniline (**66**) and furfural (**65**) were used to form an imine, which readily reacted with the enamine formed from (*S*)-proline and propionaldehyde (**53**). The resulting amino aldehyde **67** was directly arylated to give **68** in high yield but with low diastereoselectivity, and an oxidation/reduction sequence afforded the desired diastereomer **69** in high purity. The furan (as a surrogate for a carboxylic acid) was converted into the methyl ester **70** in four steps. Cleavage of the benzoate (K_2CO_3, MeOH)



Scheme 16. Synthesis of (+)-coniine and *ent*-sedridine.



Scheme 17. Formal synthesis of nikkomycin B.

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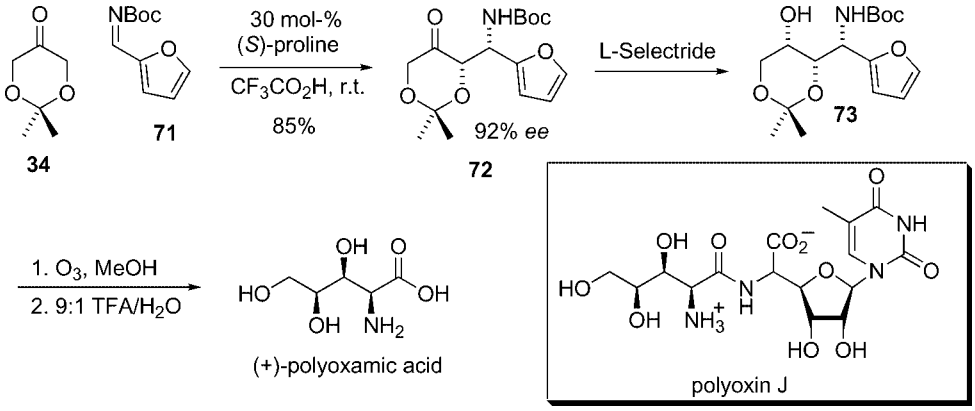
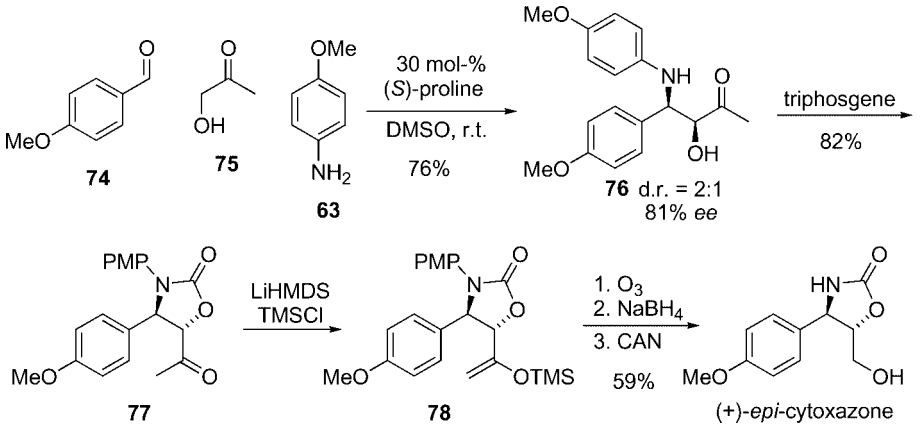
resulted in the formation of a γ-lactone (not depicted), concluding a formal synthesis of nikkomycin B.

Using a similar approach, Enders' group has synthesized (+)-polyoxamic acid, which is part of the polyoxins (Scheme 18).[45] In this instance, the preformed Boc-imine of furfural (**71**) was used. A Mannich reaction with dioxanone **34** proceeded smoothly to give the amino ketone **72** in 85% yield and with 92% *ee*, while a diastereoselective reduction with L-Selectride (**72**→**73**) was followed by the oxidative degradation of the furan moiety. Finally, concomitant removal of the Boc protecting group and the acetal with trifluoroacetic acid yielded (+)-polyoxamic acid. It should be noted that pre-formed Boc-imines of aromatic aldehydes offer advantages over *N*-aryl-protecting groups because of their facile removal under acidic instead of oxidative conditions.

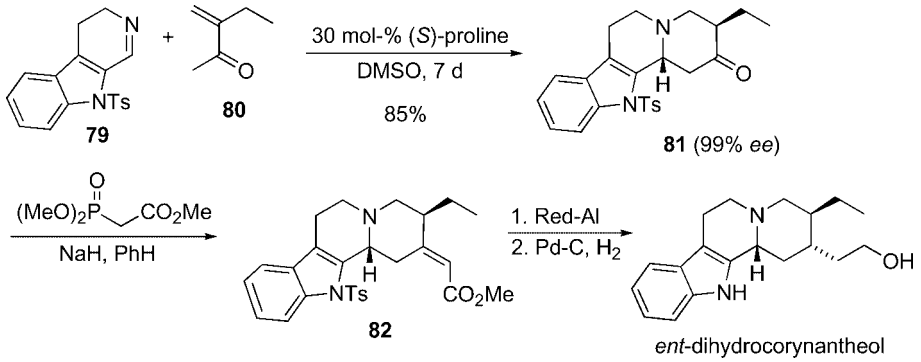
Sudalai et al. have described a synthesis of (+)-*epi*-cytoxazone (Scheme 19).[46] To this end, *p*-methoxybenzaldehyde (**74**) was treated with hydroxyacetone (**75**) and *p*-anisidine (**63**). The Mannich products were obtained as a separable 2:1 mixture of diastereomers, and the major *syn* isomer **76** (81% *ee*) was cyclized to the corresponding oxazol-



Scheme 18. Synthesis of (+)-polyoxamic acid.



Scheme 19. Synthesis of (+)-*epi*-cytoxazone.



Scheme 20. Synthesis of *ent*-dihydrocorynantheol.

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idinone **77** with triphosgene. The ketone was then converted into the silyl enol ether **78**, which was transformed easily into (+)-*epi*-cytoxazone.

Mannich–Michael (Hetero-Diels–Alder) Reaction

Itoh developed a proline-catalysed addition of 3-ethylbut-3-en-2-one (**80**) to dihydrocarboline **79**, which afforded the tetracyclic core of *ent*-dihydrocorynantheol as a single diastereomer in 85% yield and with 99% *ee* (Scheme 20). The reaction mechanism has not been elucidated but it probably proceeds through a Mannich–Michael addition rather than a hetero-Diels–Alder pathway. Ketone **81** was subjected to a Horner–Wadsworth–Emmons reaction, which was followed by a reduction of the ester group. A diastereoselective hydrogenation and concomitant hydrogenolysis of the tosyl group gave *ent*-dihydrocorynantheol.[47]

2.3 α-Heterofunctionalizations

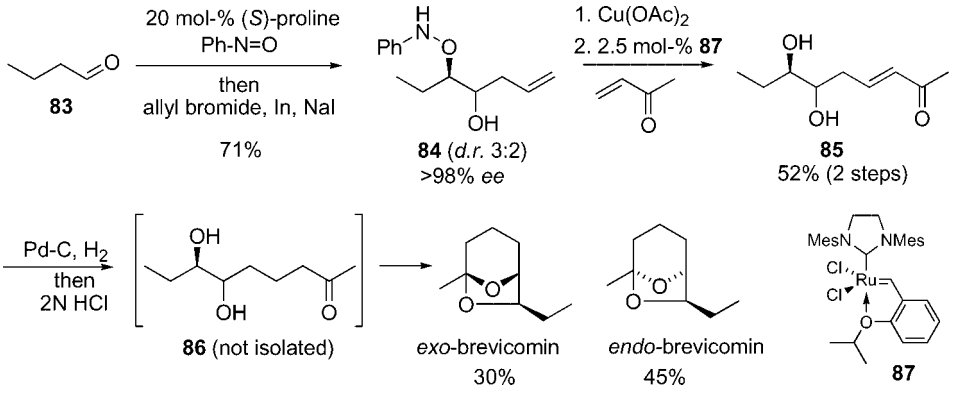
After the successful demonstration of the concept of enamine catalysis in the aldol and Mannich reactions, it became clear that results from stoichiometric enamine and hydrazone chemistry were very helpful for the design of other organocatalytic processes. On the other hand, reagents developed through mild electrophilic introduction of *N*- and *O*-heteroatoms proved highly useful in organocatalysis.[48]

The bark beetle pheromones (+)-*exo*- and (–)-*endo*-brevicomin have been classical targets for demonstrating the state of the art in asymmetric synthesis. The following synthesis by Kim et al. (Scheme 21) is an elegant example in which organic and transition metal catalysis complement each other.[49] The crude reaction mixture obtained from an asymmetric α-hydroxylation of butyraldehyde (**83**) was directly subjected to an indium-mediated allylation. Whereas the enantioselectivity was excellent (>98% *ee*), the diastereoselectivity was only moderate (*dr* 3:2). Cleavage of the N–O bond proceeded uneventfully to give the corresponding diol in 65% yield, and a cross-metathesis reaction with methyl vinyl ketone in the presence of catalyst **87** afforded **85** in 80% yield. The α,β-unsaturated double bond was hydrogenated with palladium on carbon, and treatment of the crude reaction mixture with HCl (2 N) triggered ketalization to give (–)-*endo*- and (+)-*exo*-brevicomin as a 3:2 mixture.

α-Hydroxylation represents yet another useful reaction for the extension of the synthetic chiral pool. As shown in Scheme 22, the proline-catalysed addition of nitrosobenzene to the cyclohexanone **88** was followed by a reductive cleavage of the N–O bond, to give **89** in 84% yield and with >99% *ee*. If the hydrogenolysis step was preceded by a diastereoselective reduction, diol **90** was obtained in 67% yield. The alcohols **89** and **90** are valuable starting materials for the synthesis of oxygenated cyclohexane derivatives: Hayashi et al. used **90** for the synthesis of (+)-panepophenanthrin[50] and **89** for the synthesis of RK-805 and similar natural products such as fumagillol and ovalicin.[51]

Since the early days of organocatalysis, Barbas' group has been at the forefront of applying organocatalytic reactions to the synthesis of biologically active molecules. Enantioselective α-amination is particularly useful in this context and the syntheses of the following targets from the area of medicinal chemistry are illustrative.

In the first example, an efficient synthesis of the cell adhesion inhibitor BIRT-377 was developed (Scheme 23).[52] A classical strategy for the generation of quaternary stereocenters is Seebach's alkylation of amino acid-derived oxazolidinones (self-regeneration of stereocenters). Whereas alkylations are still somewhat problematic in organocatalysis,[53] azodicarboxylates have proven to be good electrophiles even for the generation of quaternary stereocenters. With 30 mol-% of (*S*)-proline as the catalyst and azodicarboxylate **93**, hydrazino aldehyde **94** was obtained in 90% yield after 5 days, albeit with a disappointing 44% *ee*. With the proline-derived tetrazole **40**, however, the reaction proceeded much more rapidly (3 h), to give the required product in 95% yield and with 80% *ee*. A single recrystallization improved the *ee* to >99%. Oxidation of the aldehyde to the carboxylic acid was followed by the formation of the methyl ester. A two-step reduction of the N–N bond afforded the Cbz-protected amino acid methyl ester **95**, which was converted into BIRT-377 in three further steps.



Scheme 21. Synthesis of (+)-*exo*- and (–)-*endo*-brevicomin.

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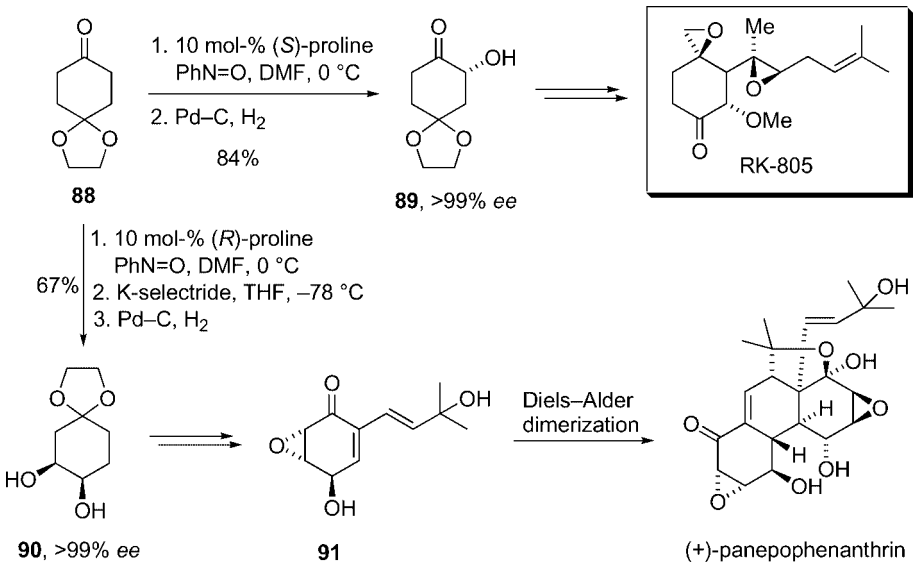
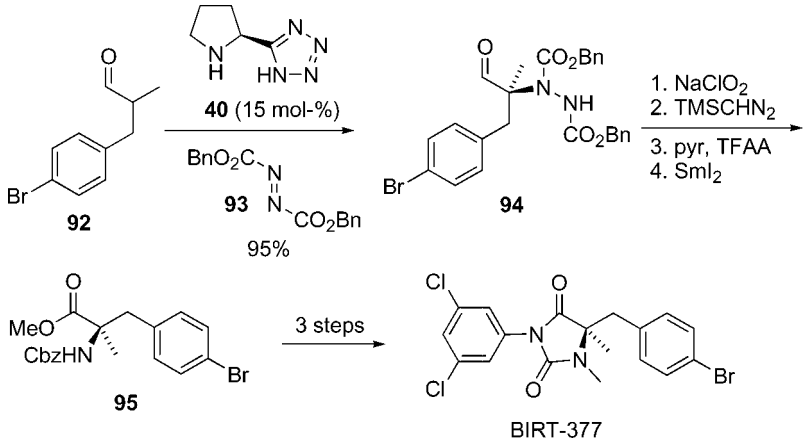
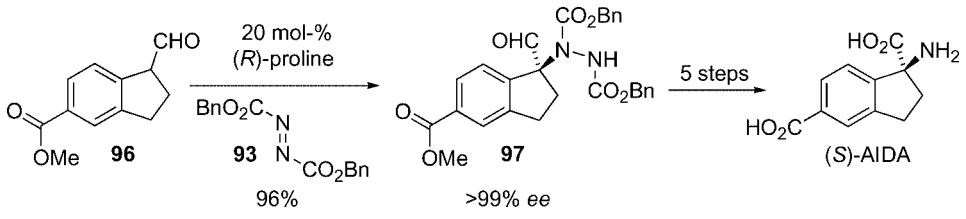


Scheme 22. Synthesis of RK-805 and (+)-panepophenanthrin.



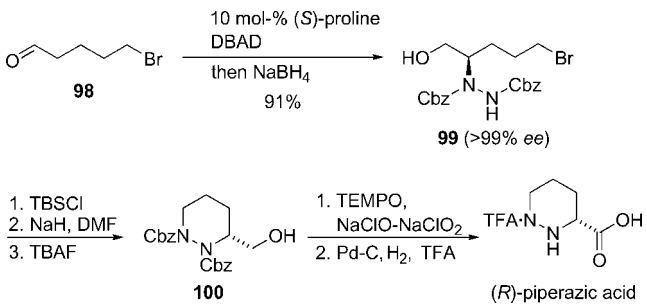
Scheme 23. Synthesis of BIRT-377.



Scheme 24. Synthesis of (*S*)-AIDA.

Another application was the synthesis of the metabotropic glutamate receptor ligands (*S*)-APICA and (*S*)-AIDA (Scheme 24).[54] A proline-catalysed amination of the indane carboxyaldehyde **96** with dibenzyl azodicarboxylate (DBAD, **93**) afforded the corresponding α-hydrazinoaldehyde **97** in excellent yield and with >99% *ee*. This material was then converted into (*S*)-AIDA by oxidation of the aldehyde and N–N bond cleavage.

The cyclic α-hydrazinocarboxylic acids (*R*)- and (*S*)-piperazic acid are found in several bioactive cyclodepsipeptides. Hamada et al. have devised an efficient synthesis



Scheme 25. Synthesis of (*R*)-piperazic acid.

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starting from 5-bromovaleraldehyde (**98**).[55] The α-hydrazination proceeded uneventfully to give alcohol **99** after reduction with $NaBH_4$ in 91% yield and with >99% *ee*. TBS protection of the hydroxy group was followed by an intramolecular displacement of the bromide. After a few oxidation and deprotection steps, (*R*)-piperazic acid was obtained as its TFA salt (Scheme 25).

2.4 Conjugate Additions

Michael additions are important transformations, especially in the synthesis of polyketide natural products, and organocatalytic versions of this reaction have recently been developed.[56] The following syntheses of brasoside and littoralisone show the potential of enamine catalysis in a complex target setting.[57] The reader is encouraged to take a brief look at the target structures before proceeding. It is hard not to appreciate the creativity in MacMillan's and Mangion's synthetic strategy, which utilizes organocatalytic reactions heavily. As discussed in the previous section, α-aminoxylation is a very efficient process for the introduction of heterofunctionality. The MacMillan group used a one-pot procedure consisting of α-aminoxylation, Horner–Wadsworth–Emmons reaction and N–O bond methanolysis to give **102** in a 56% yield (Scheme 26). After conversion into the dialdehyde **103**, the stage was now set for the crucial intramolecular Michael addition. Prolonged treatment of **103** with (*S*)-proline in chloroform as the solvent afforded the thermodynamic product – a cyclopentane with the two aldehyde-bearing side chains in a *trans* orientation. Alternatively, the use of DMSO as the solvent yielded the desired kinetic *cis* product. In situ acetylation afforded **104** in 83% yield. This material was elaborated into **105** by a series of standard transformations. A two-step glycosidation finally concluded a 13-step synthesis of brasoside.

Alternatively, **105** can be converted into (–)-littoralisone by glycosylation with an appropriately differentiated glucose (also available through organocatalytic reactions), and this was followed by a light-induced [2+2] photocycloaddition (Scheme 27).

Alexakis and co-workers[58] used the nitroalkene **107** as a synthetic equivalent of the non-existent electrophile **108** (Figure 3).

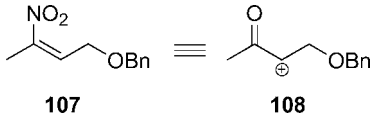
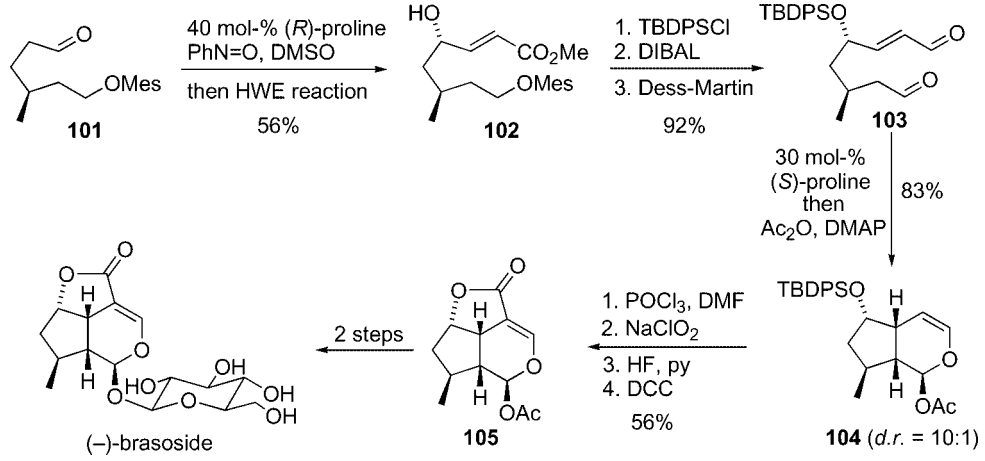
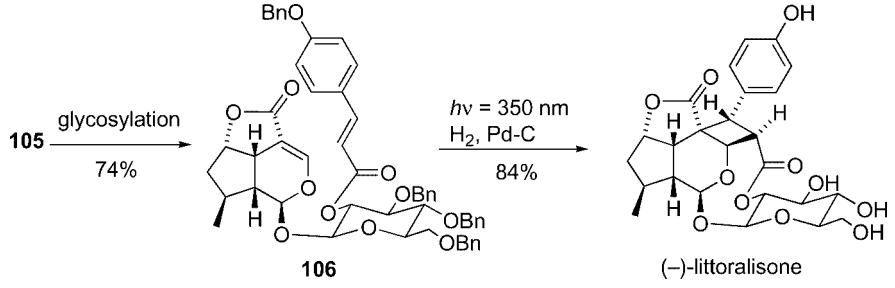


Figure 3. Masked cation.

With 15 mol-% of **109** as the catalyst and propionaldehyde as the nucleophile, a Michael reaction provided **110** as a mixture of four diastereomers in 92% yield (Scheme 28). After protection of the aldehyde functionality, the nitro group was converted into a keto group in a Nef reaction,



Scheme 26. Synthesis of (–)-brasoside.



Scheme 27. Synthesis of (–)-littoralisone.

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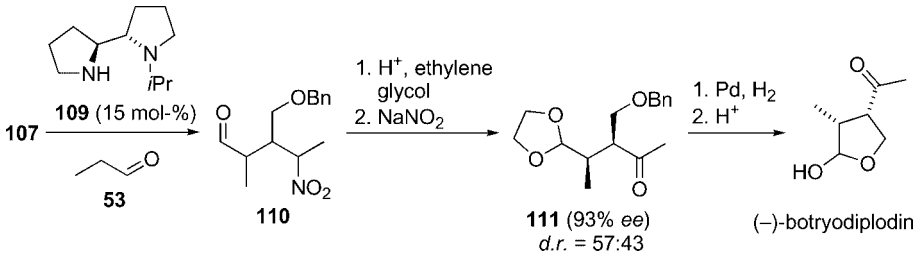
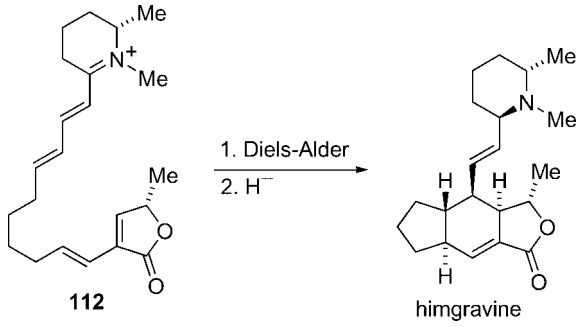


Scheme 28. Synthesis of (–)-botryodiplodin.

which also reduced the number of stereoisomers present. The two remaining diastereomers were separated by flash chromatography, and the major isomer, *syn*-**111** (93% *ee*), was taken on to give (–)-botryodiplodin in two further steps.

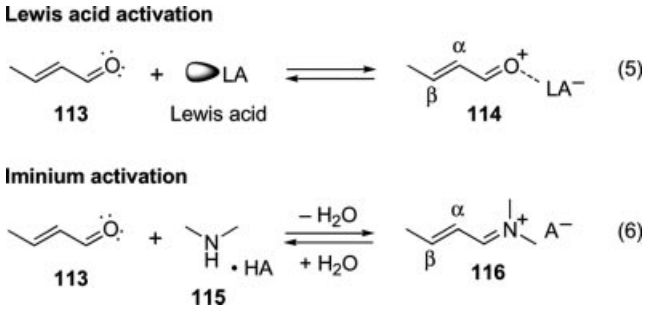
3. Iminium Catalysis

The iminium activation of conjugated enones has been postulated to play a pivotal role in the biogenesis of some natural products. Baldwin proposed an "iminium ion-accelerated Diels–Alder" reaction as the key step in the biogenesis of himgravine (Scheme 29).[59] The origin of this activation had been ascribed much earlier to an inductive effect and the mesomeric stabilization of the iminium group.[60]



Scheme 29. Proposed biosynthesis of himgravine.

In 2000, MacMillan defined a generalized catalysis concept for the activation of α,β-unsaturated carbonyl compounds **113** with an external secondary amine catalyst **115**. As illustrated in Scheme 30, **113** can be activated by the *reversible* formation of an iminium ion **116** with an external amine catalyst (Equation 6). As in Lewis acid activation (Equation 5), the LUMO is lowered, but unlike in such instances, the chiral information resides closer to the olefin when a chiral secondary amine is employed. A proof of concept was first demonstrated for intermolecular Diels–Alder reactions and later extended to 1,3-dipolar cycloaddition reactions and (conjugate) additions of nucleophiles to the β-carbon.



Scheme 30. Activation of carbonyl compounds.

It becomes clear that the use of chiral secondary amines as the catalyst would be the most obvious choice for discrimination between the enantiotopic faces of the olefin (Scheme 30, Equation 6). However, from experience with chiral Lewis acids (Equation 5) it also seems conceivable that chiral counterions (A^-) could make additions enantioselective. Figure 4 shows the two conceptionally different catalyst systems.

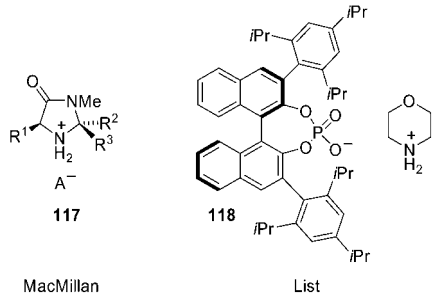


Figure 4. Catalysts for iminium catalysis.

3.1 Conjugate Additions

Conjugate Reductions

Once the catalytic principles of enamine and iminium catalysis had been established, some asymmetric reactions could be predicted before they had actually been performed. Nevertheless, many were surprised when the iminium-catalysed reduction of olefins with Hantzsch dihydropyridines as the hydride source was reported independently by the groups of List and MacMillan.[61] The two

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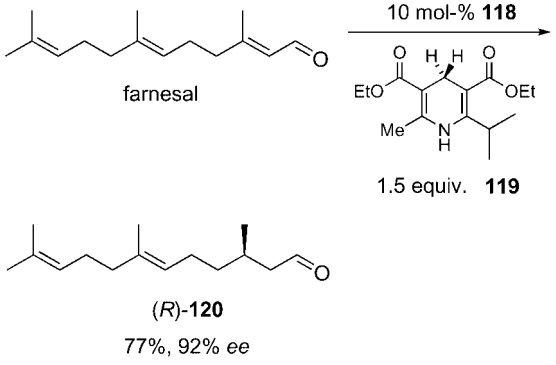
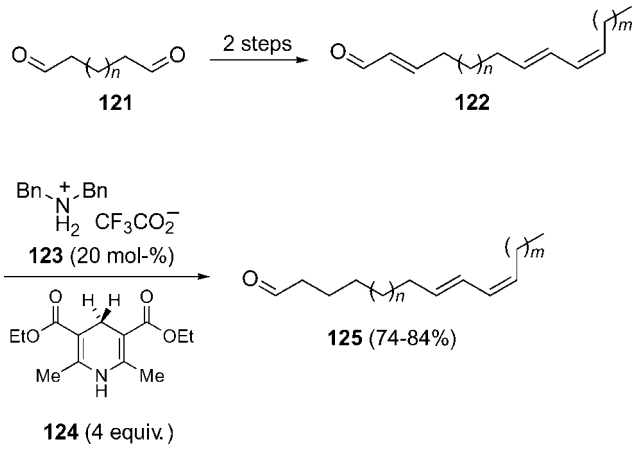
following examples illustrate the application of organocatalytic reductions in the synthesis of pheromones.

List et al. used their asymmetric counteranion-directed catalysis (ACDC) in an enantioselective synthesis of the bee pheromone (*R*)-**120**. Conjugate reduction of farnesal with **118** as the catalyst and Hantzsch ester **119** as the hydride source afforded the desired aldehyde **120** with a 92% *ee* (Scheme 31).[62]



Scheme 31. Enantioselective synthesis of the bee pheromone (*R*)-**120**.

Christmann et al. have developed a bidirectional, organocatalytic synthesis of a series of lepidopteran sex pheromones (Scheme 32).[63] The synthesis started from simple dialdehydes **121**, which were homologated on both ends and then desymmetrized by two consecutive Wittig reactions to give the trienals **122**. A position-selective organocatalytic reduction afforded the desired pheromones **125**.

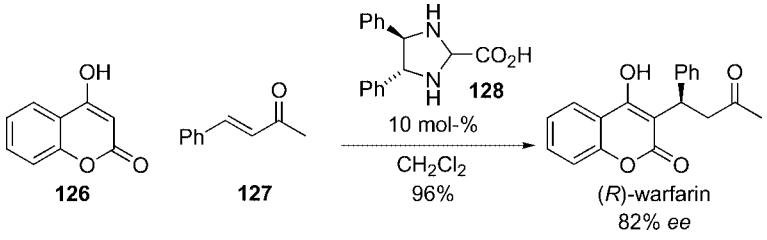


Scheme 32. Synthesis of lepidopteran sex pheromones.

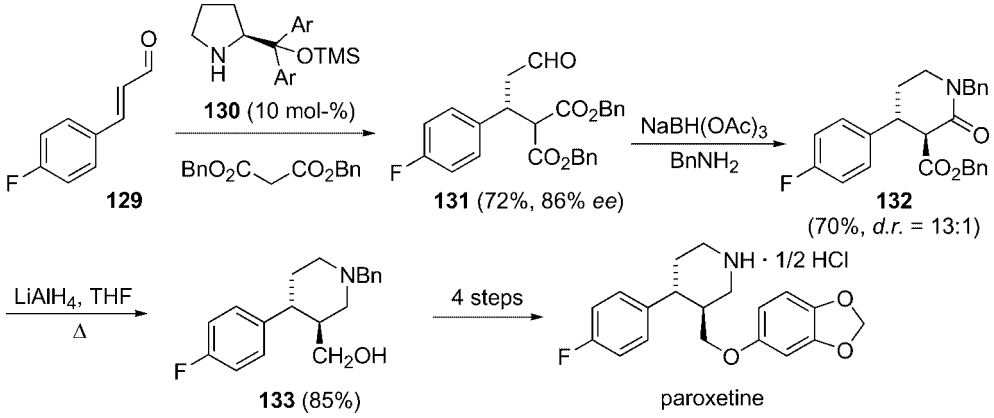
Addition of 1,3-Dicarbonyl Compounds

Warfarin (coumadin) is a commonly used anticoagulant. Jørgensen's group has developed an efficient and scalable enantioselective synthesis using an amine-catalysed conjugate addition.[64] As depicted in Scheme 33, in the presence of 10 mol-% of imidazolidine catalyst **128**, hydroxycoumarin **126** smoothly added to benzylideneacetone **127** in excellent yield and with good enantioselectivity. The enantiomeric excess of warfarin could be raised from 82% to >99.9% by a single recrystallization.

Paroxetine is the most prominent member of a class of serotonin reuptake inhibitors, which are used to treat depression, and an efficient route to this scaffold is desirable



Scheme 33. Enantioselective synthesis of warfarin.



Scheme 34. Formal synthesis of (–)-paroxetine [Ar = 3,5-bis(CF_3)Ph].

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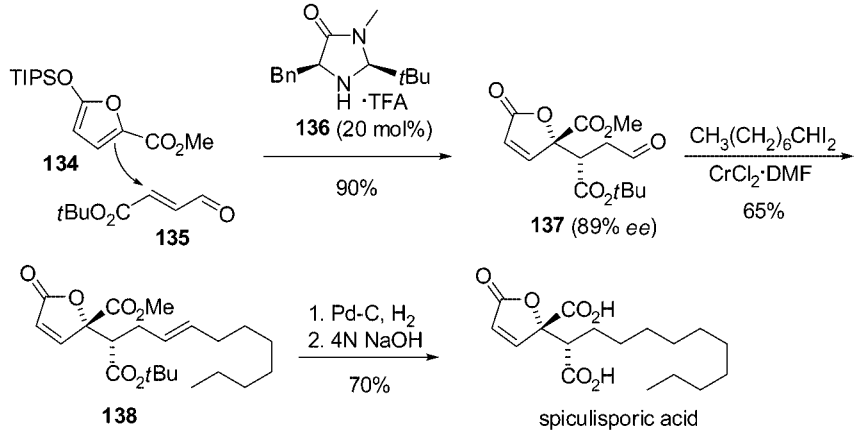
for further SAR-studies. To this end, Jørgensen et al. have developed an organocatalytic addition of malonates to substituted cinnamaldehydes (Scheme 34).[65] In the presence of 10 mol-% of the proline-derived catalyst **130**, the Michael adduct **131** was obtained in 72% yield and with 86% *ee*. This material was subjected to a diastereoselective reductive amination/cyclization, which was followed by a reduction with $LiAlH_4$ to give the known piperidine alcohol intermediate **133**.

Mukaiyama–Michael Reactions

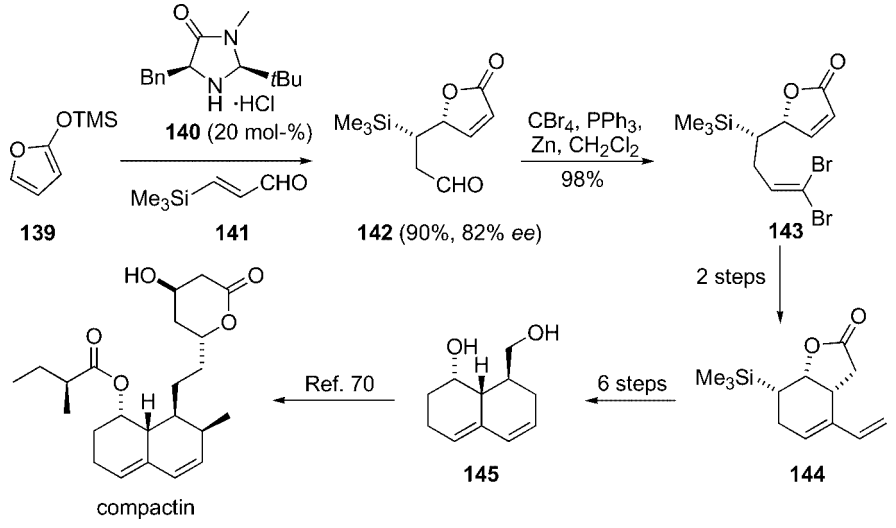
We have seen that iminium organocatalysis has proven to be competitive with or even superior to Lewis acid-catalysed processes. In some instances, however, complementary reactivity is observed, which in has turn enabled the development of new synthetic strategies for total synthesis.

While Lewis acids catalyse 1,2-additions of silyloxy furans to α,β-unsaturated aldehydes, iminium catalysis promotes the 1,4-addition. Both reactions provide the important butenolide architecture. MacMillan has developed an organocatalytic Mukaiyama–Michael reaction and has used it in a short synthesis of spiculisporic acid.[66] As shown in Scheme 35, the 1,4-addition of furan **134** to aldehyde **135** afforded the desired butenolide **137** in 90% yield and with 89% *ee*. The side chain was attached by use of a Takai-type reaction. Selective hydrogenation of the exocyclic olefin and hydrolysis of the esters concluded the synthesis of this natural product.

The discovery of compactin as an inhibitor of HMG-CoA reductase resulted in the development of the statins as a new class of cholesterol-reducing drugs. Robichaud and Tremblay have devised an unusual approach to the decalin core (Scheme 36).[67] In their strategy, the furan **139** – a dienolate equivalent – was added to the silylated acrolein derivative **141**. Acrolein itself exhibited only moderate selectivity (33% *ee*) in this Mukaiyama–Michael reaction. In the presence of 20 mol-% of MacMillan's catalyst **140**, the product **142** was obtained in 90% yield and with 82% *ee*, while a Corey–Fuchs reaction[68] smoothly afforded the dibromide **143**. This material was subjected to a radical cyclization and the vinyl group was attached



Scheme 35. Synthesis of spiculisporic acid.



Scheme 36. Formal synthesis of (+)-compactin.

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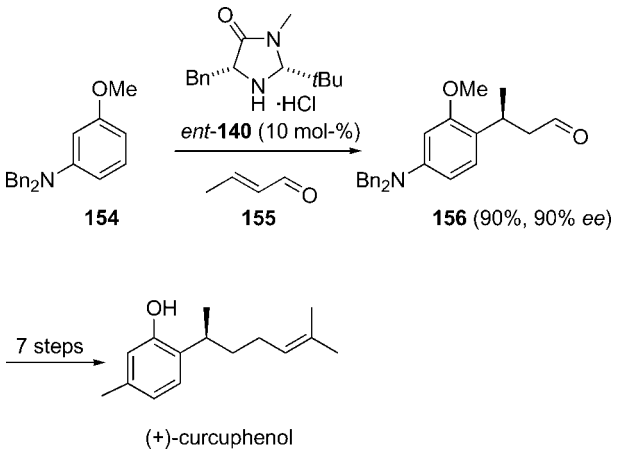
by Stille chemistry. In six further steps, **144** was converted into **145**,[69] which at this stage constitutes a formal synthesis[70] of compactin.

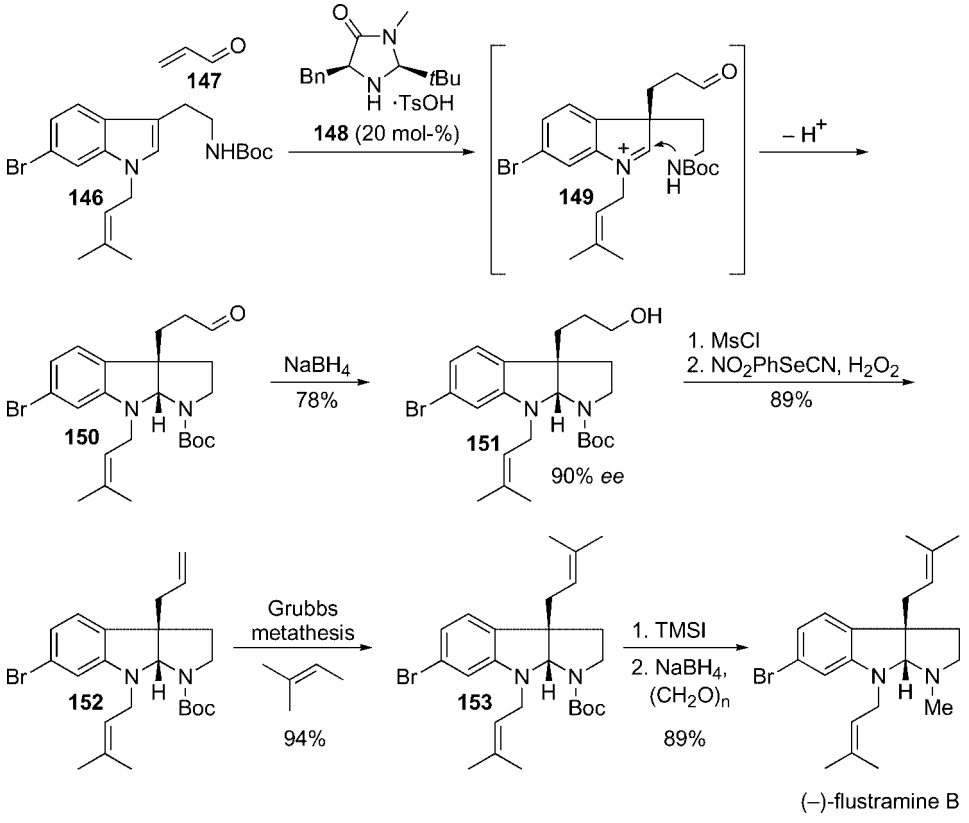
Friedel–Crafts Reactions

MacMillan's group also developed iminium catalysis into a powerful method for enantioselective Friedel–Crafts alkylations, which works exceptionally well for heteroaromatic substrates but also for anilines (vide infra). In a synthesis of the alkaloid flustramine B, a novel addition-cyclization cascade provided access to the pyrroloindoline core. As shown in Scheme 37, the 6-bromotryptamine derivative **146** was treated with acrolein (**147**) in the presence of catalyst **148**. The adjacent Boc-amino group readily intercepted the intermediate indolium ion **149** to give **150**, which was directly reduced with $NaBH_4$. Elimination of the hydroxy group (**151**→**152**) was followed by a cross-metathesis reaction (**152**→**153**), and removal of the Boc protecting group and a reductive methylation concluded this elegant synthesis of (–)-flustramine B.[71] Not surprisingly, enantioselective indole alkylations quickly found their way into the synthesis of drug candidates, such as a COX-2 inhibitor[72] and the selective serotonin reuptake inhibitor BMS-594726.[73] The Banwell group also used this class of Friedel–Crafts reactions in their syntheses of the alkaloids (–)-rhazinal,[74] (–)-rhazinilam, (–)-leuconolam and (+)-*epi*-leuconolam and tashiromine.[75]

Kim et al. employed a Friedel–Crafts alkylation of *N*,*N*-dibenzyl-3-anisidine (**154**) as the key step in a synthesis of (+)-curcuphenol (Scheme 38).[76] In the presence of 10 mol-% of MacMillan's catalyst *ent*-**140**, a regio- and stereoselective (90% *ee*) addition of **154** to crotonaldehyde (**155**) afforded **156** in a 90% yield. Because of the necessity for modifications at all functional groups, a few further steps were required to conclude this synthesis.



Scheme 38. Synthesis of (+)-curcuphenol.



Scheme 37. Synthesis of (–)-flustramine B.

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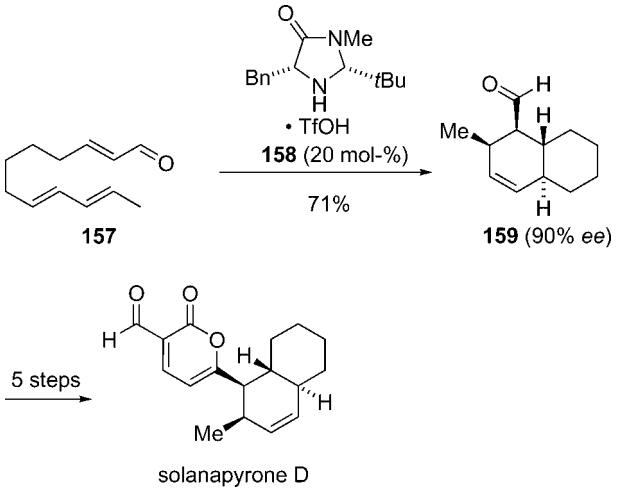
3.2 Pericyclic Reactions

Intramolecular Diels–Alder Reactions

MacMillan et al. investigated intramolecular Diels–Alder (IMDA) reactions of several trienals and applied his methodology to a short enantioselective synthesis of solanapyrone D.[77] As depicted in Scheme 39, treatment of **157** with 20 mol-% of catalyst **158** gave the decalin **159** in 71% yield and with 90% *ee*.[78] The aldehyde **159** was converted to solanapyrone D in a further five steps. Using a similar approach, Koskinen synthesized the bicyclo[4.3.0]nonane core of amaminols A and B.[79]



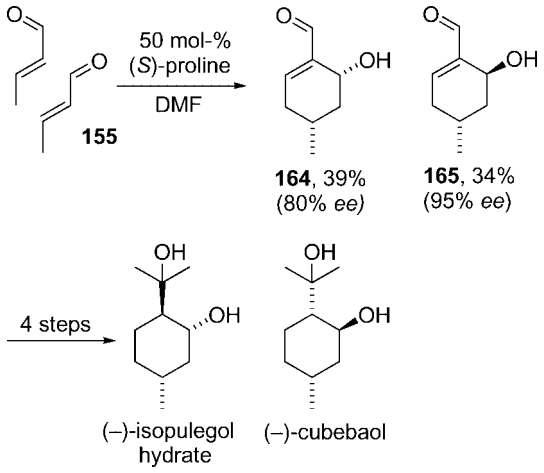
Scheme 39. Synthesis of solanapyrone D.

Intermolecular Diels–Alder Reactions

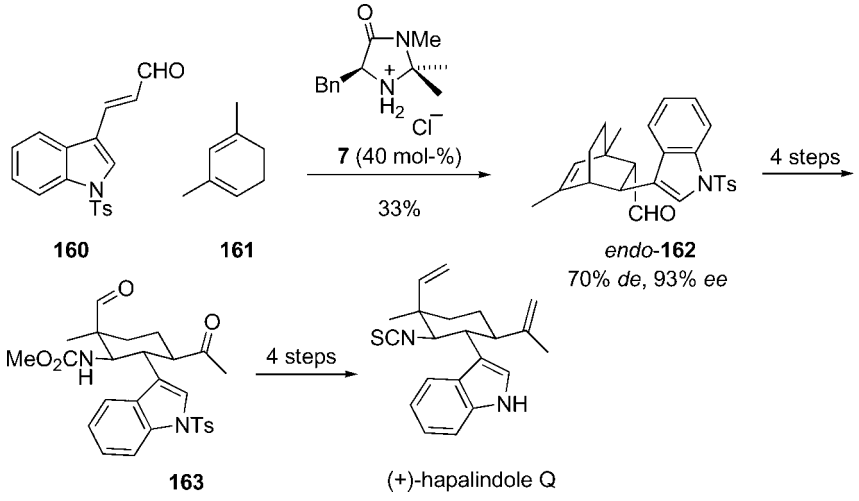
One of the first applications of MacMillan's organocatalyst was in Kerr's insightful synthesis of (+)-hapalindole Q (Scheme 40),[80] the key step in this synthesis being an intermolecular Diels–Alder reaction between **160** and **161**. Because the catalyst loading was higher than the actual yield, the reaction has been dubbed *organomediated*, but Kerr was also able to show that the reaction was catalytic in **7**, albeit with lower selectivity. In turn, the formyl group was oxidized and rearranged in a Curtius reaction. Cleavage of the olefinic double bond afford dicarbonyl compound **163**, which was subsequently converted into hapalindole Q.

3.3 [3+3] Cycloadditions

Hong et al. have developed a formal [3+3] cycloaddition of α,β-unsaturated aldehydes (Scheme 41).[81] This process, which can also be regarded as the addition of a vinylogous enolate to a Michael acceptor, appears to involve both iminium and enamine activation. The dimerization of crotonaldehyde (**155**) affords the diastereomeric cyclohexene carboxyaldehydes **164** and **165**. After separation, the individual isomers were converted into (–)-isopulegol hydrate and (–)-cubebaol, respectively. Very recently, Hong used a similar trimerization of acrolein for the total synthesis of montiporyne F.[82]



Scheme 41. Synthesis of (–)-isopulegol hydrate and (–)-cubebaol.



Scheme 40. Synthesis of (+)-hapalindole Q.

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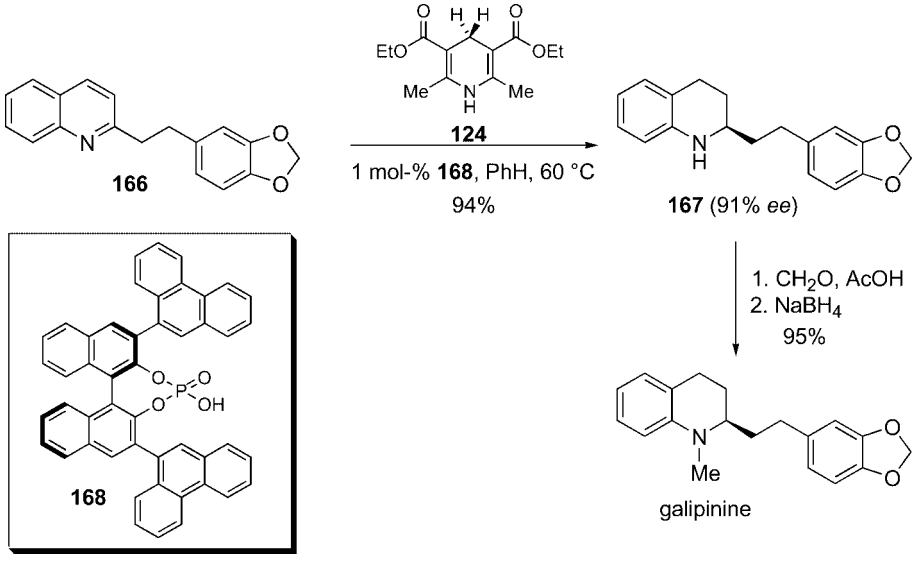
4. Brønsted Acid and Hydrogen Bond Catalysis

4.1 Phosphates

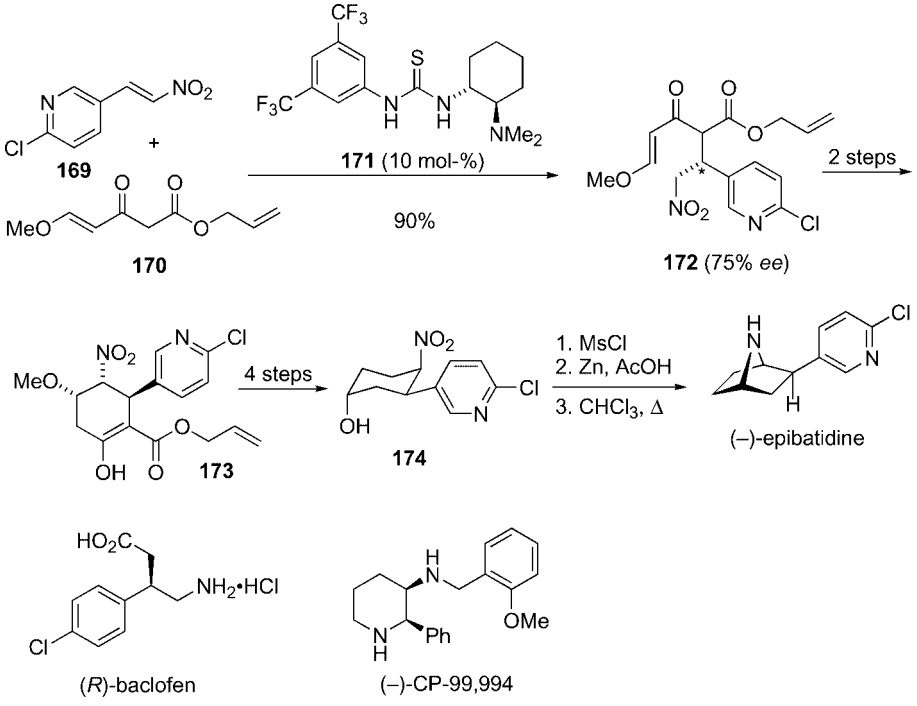
Rueping[83] developed an organocatalytic transfer hydrogenation cascade of 2-substituted quinolines, which was applied to the synthesis of some plant alkaloids. Through the use of 1 mol-% of binaphtholphosphate catalyst **168**,[84] a stepwise hydride transfer from the Hantzsch ester (**124**) to quinoline **166** afforded the corresponding tetrahydroquinoline **167** in excellent yields and enantioselectivities (Scheme 42). A reductive *N*-methylation concluded a concise synthesis of (+)-galipinine.[85]

4.2 Thioureas

Takemoto's group has made important contributions to the application of chiral thioureas[86] in asymmetric catalysis. In the example shown in Scheme 43, a conjugate addition of the β-keto ester **170** to the nitroalkene **169** afforded the desired product **172** in 90% yield and with 75% *ee*. This material can be cyclized to the highly functionalized cyclohexene **173**. Contrary to common belief, "highly functionalized" is not always an advantage – especially in natural product synthesis, when abundant functionality has to be removed at the price of additional steps. In this synthesis, **173** was converted into epibatidine in



Scheme 42. Synthesis of (+)-galipinine.



Scheme 43. Synthesis of (–)-epibatidine.

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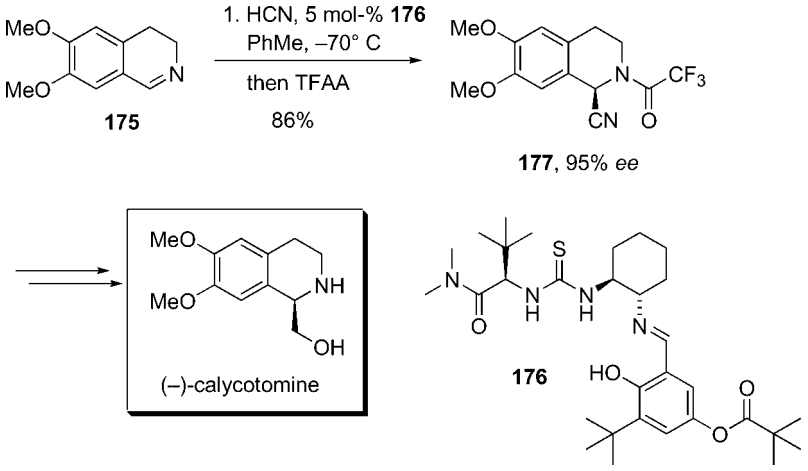


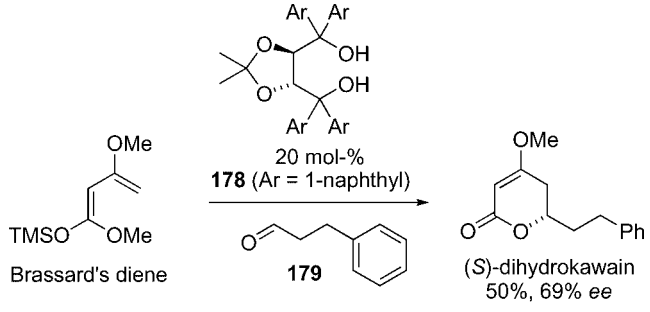
Scheme 44. Synthesis of (–)-calycotomine.

seven further steps.[87] Other applications of Takemoto's catalyst include the syntheses of (*R*)-(–)-baclofen[88] and (–)-CP-99 994.[89]

Itoh et al. examined the asymmetric Strecker reaction for the synthesis of three tetrahydroisoquinoline alkaloids.[90] A screening of suitable catalysts revealed Jacobsen's thiourea **176** to be most efficient; in the presence of 5 mol-% of catalyst **176**, the desired product **177** was isolated in 86% yield and with 95% *ee* (Scheme 44). Hydrolysis of the cyano group and a series of high-yielding standard transformations afforded (–)-calycotomine and the related natural products (–)-salsolidine and (–)-carnegine.

4.3 Diols

The Lewis acid-catalysed hetero-Diels–Alder reaction is a powerful method for the asymmetric synthesis of *N*- and *O*-heterocycles. Ding et al. used a TADDOL-type[91] hydrogen-bonding catalyst **178**, application of which as a Brønsted acid was pioneered by Rawal.[92] In a single step, dihydrokawain was assembled from Brassard's diene and 3-phenylpropanal (**179**), albeit in moderate yield and enantioselectivity (Scheme 45).[93]



Scheme 45. Synthesis of (*S*)-dihydrokawain.

5. Brønsted and Lewis Base Catalysis

Tertiary amines and phosphanes are powerful nucleophilic catalysts for a variety of useful synthetic applications. The most prominent member is probably 4-(dimethylamino)pyridine (4-DMAP), and efforts to develop chiral versions of this and other nucleophilic catalysts are ongoing.[94] In nature's catalyst toolbox for chemists, the cinchona alkaloids offer outstanding properties. Apart from their application as nucleophilic catalysts, these compounds have been widely used as chiral bases and as scaffolds for chiral ligands. Currently, covalent combinations with other catalyst motifs have been showing promising results.

5.1 Cinchona Alkaloids and Derivatives

In their seminal 1981 publication, Hiemstra and Wynberg[95] reported a thorough investigation of the cinchona alkaloid-catalysed addition of thiols to α,β-unsaturated enones. Since that time, there have been different applications of this methodology with significantly improved catalysts. This concept has also been extended to oxygen nucleophiles. In some cases very high enantioselectivities can be obtained, as demonstrated in a total synthesis of calanolide by Ishikawa et al. (Scheme 46).[96] In the presence of 10 mol-% of quinine, **181** was obtained in 67% yield and with 98% *ee*, along with 21% of the diastereomer. This material was taken forward to give calanolide, a potential inhibitor of HIV-reverse transcriptase.

The Christmann group has used quinine for the kinetic resolution of a racemic pyrrolizidine (Scheme 47). When **182** was treated with quinine, an unprecedented enantioselective oxa-Michael lactonization occurred, to afford the enantiomerically enriched lactone **183**. The enantiomeric excess of the remaining carboxylic acid **182** was further enriched to >98% *ee* by simple trituration,[97] and an iodolactonization afforded **184**, suitable for couplings with aldehydes.

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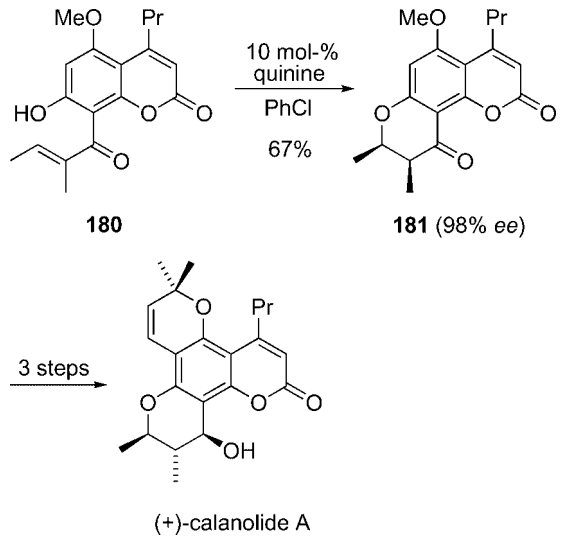
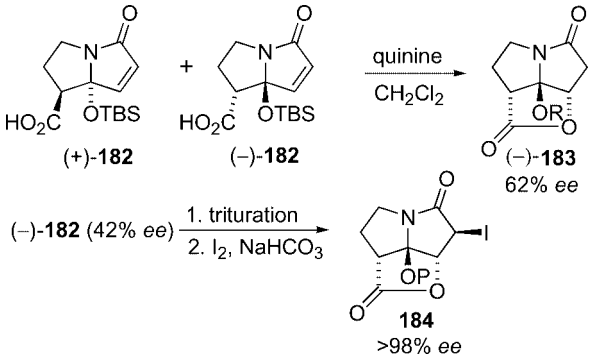
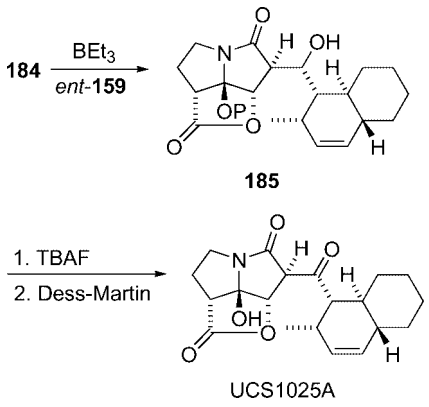


Scheme 46. Synthesis of (+)-calanolide.



Scheme 47. Kinetic resolution of (±)-**182**.

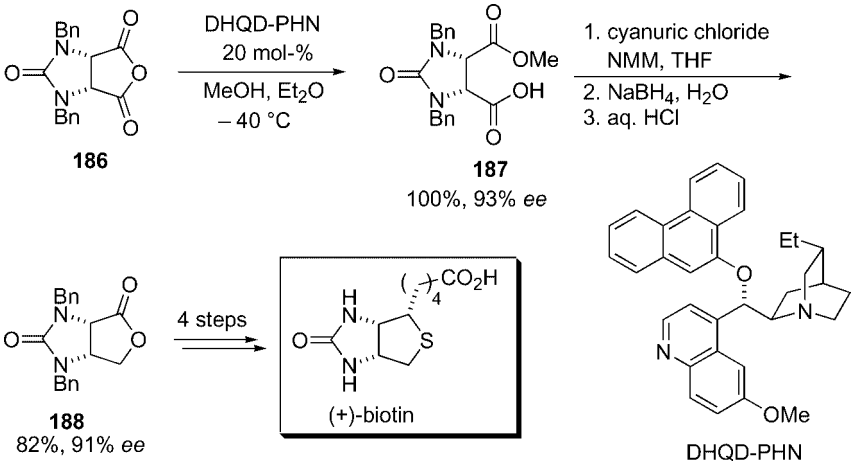
Iodofuropyrrolizidine **184**, as well as the enantiomer of the previously shown decalin (*ent*-**159**), were intermediates in Danishefsky's synthesis of the telomerase inhibitor UCS1025A (Scheme 48). As shown below, **184** and *ent*-**159** were joined in a BEt_3-mediated coupling. Removal of the TBS protecting group (TBAF) and oxidation (Dess–Martin periodinane) completed Danishefsky's elegant synthesis[98] of UCS1025A, which nicely combines two fragments accessible by organocatalysis.



Scheme 48. Synthesis of UCS1025A (P = TBS).

Deng et al. have established commercially available cinchona alkaloid-derived ligands[99] as powerful organocatalysts.[100] In the example shown in Scheme 49, the desymmetrization of *meso*-anhydride **186** commenced a formal synthesis of (+)-biotin.[101] In the presence of 20 mol-% of DHQD-PHN the hemiester **187** was obtained in quantitative yield and with 93% *ee*. As the borane reduction suffered from racemization of the substrate, a modified protocol afforded lactone **188** – an intermediate in the Goldberg–Sternbach synthesis of (+)-biotin.

Another area of application of cinchona alkaloid catalysis is the conjugate addition of dicarbonyl compounds to α,β-unsaturated carbonyl compounds. In 1998, Tereshima used cinchonidine in an approach to huperzine A.[102] More recently, Deng has developed a synthesis of tanikolide (Scheme 50).[103] In this instance, QD-PHN was the catalyst of choice. The conjugate addition of the β-keto ester **189** to acrolein (>99% *ee*) was followed by the introduction of the side chain through a Takai-type reaction (**190** → **191**). In four further steps (+)-tanikolide was obtained in 41% overall yield.



Scheme 49. Formal synthesis of (+)-biotin.

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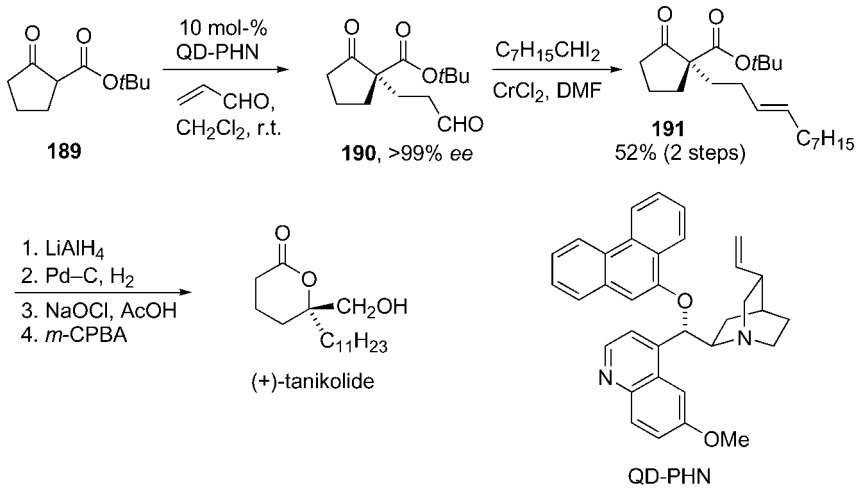
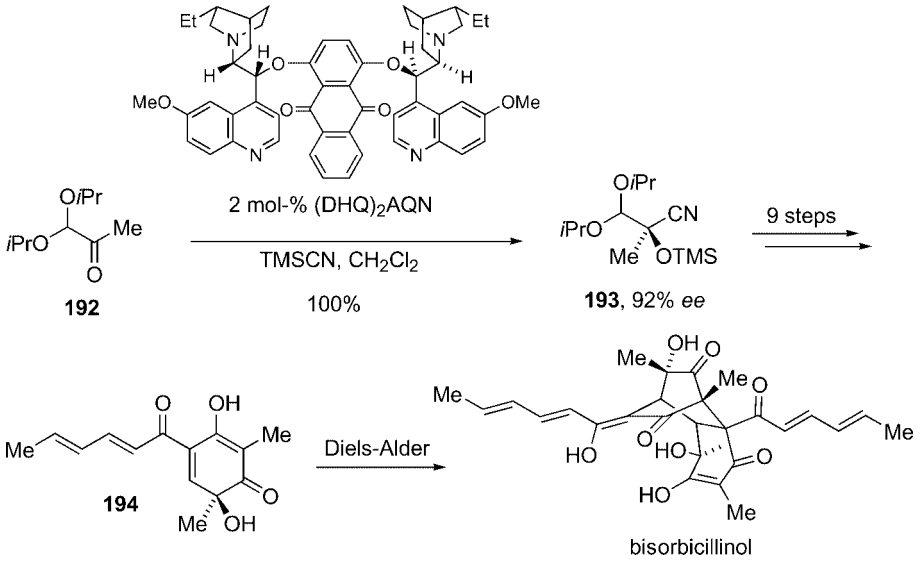
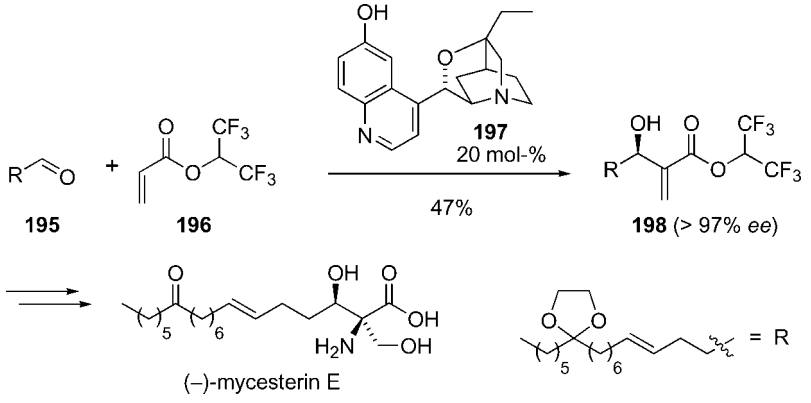


Scheme 50. Synthesis of (+)-tanikolide.



Scheme 51. Synthesis of bisorbicillinol.



Scheme 52. Synthesis of (–)-mycesterin E.

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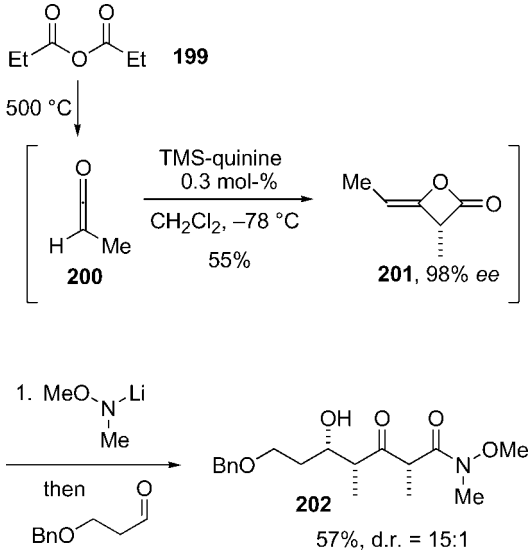
The bisorbicillinoids are a structurally complex family of natural products originating from a Diels–Alder dimerization of a monocyclic precursor. The monomer **194**, bearing a single quaternary stereocenter, has been approached by the Deng group through the use of an enantioselective cyanosilylation as the key step (Scheme 51). Only 2 mol-% of $(DHQ)_2AQN$ as the catalyst were necessary to afford **193** smoothly in quantitative yield and with 92% *ee*.[104] This material was taken forward to complete an elegant and enantioselective synthesis of bisorbicillinol.[105]

Hatekeyama et al. have developed a highly enantioselective Morita–Baylis–Hillman reaction[106] of aldehyde **195** and the activated acrylate **196** in the presence of the quinidine-derived catalyst **197**.[107] The addition product **198** was then taken forward in a diastereoselective fashion to give mycesterin E in 11 steps overall from **195** (Scheme 52).[108]

Chiral ketene dimers are valuable spring-loaded starting materials for the synthesis of polyketides. Treatment of methyl ketene **200**[109] with TMS-quinine afforded the dimer **201** in good yield and excellent enantiomeric excess (Scheme 53). The strained ring was opened with a lithiated amine to give a lithium enolate, which was in turn trapped by an aldehyde. The Calter group has employed this compound (**202**) and related building blocks in partial and total syntheses of polyketides such as pamamycin,[110] aplyronine,[111] siphonarienal[112] and siphonarienedione.[113]



Scheme 53. Dimerization of ketenes and conversion to polyketide building blocks.

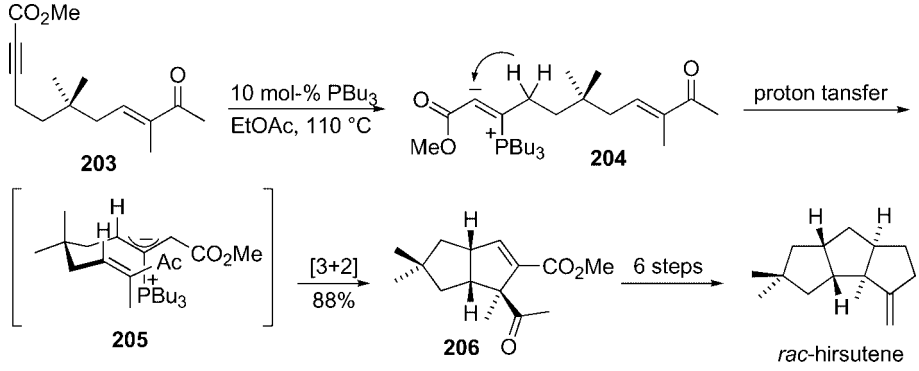
5.2 Phosphanes

Intramolecular cycloadditions represent a valuable strategy for the synthesis of polycyclic frameworks. Krische et al. used a phosphane-catalysed [3+2] cycloaddition[114] for their approach to the triquinane natural product hirsutene (Scheme 54).[115] The reaction is believed to proceed by a stepwise mechanism. Addition of tributylphosphane to alkyne **203** is followed by an intramolecular proton transfer to give **205**, which readily participates in an intramolecular [3+2] cycloaddition to afford **206**. In six further steps, **206** was converted to racemic hirsutene, thereby constituting one of the quickest syntheses to date.

6. Asymmetric Oxidations

Catalytic asymmetric oxidations have traditionally been dominated by transition metal-catalysed processes, the Sharpless–Katsuki reaction[116] having proven very reliable in enantioselective epoxidations of allylic alcohols. In recent years a number of metal-free oxidation processes, such as the Shi[117] and the Juliá–Colonna epoxidation,[118] have been discovered. The enantioselective synthesis of non-activated olefins is still a daunting task in asymmetric catalysis.[119] Shi has developed the fructose-derived ketone **208** as an efficient catalyst for these transformations. As a selected example, Corey and Xiong have used **208** in a remarkably selective oxidation of the tetraene **207** to give the tetraepoxide **209** in 66% yield and with over 80% diastereomeric purity.[120] In three further steps **209** was cyclized to give the oxasqualenoid natural product glabrescol (Scheme 55).[121]

Jørgensen's group has developed an asymmetric epoxidation of α,β-unsaturated aldehydes with the aid of iminium activation.[122] In the presence of 10 mol-% of the proline-



Scheme 54. Synthesis of hirsutene.

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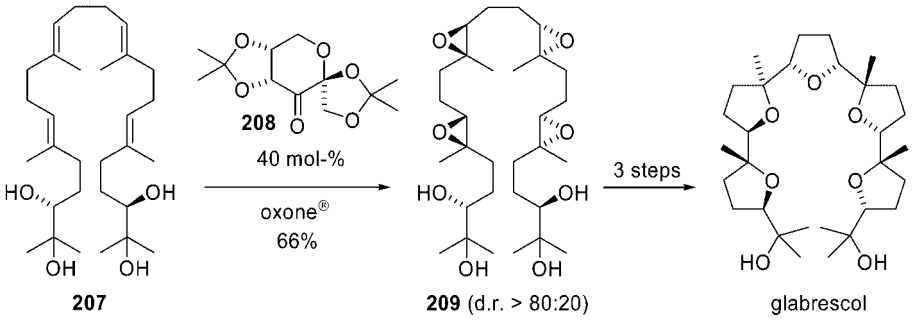
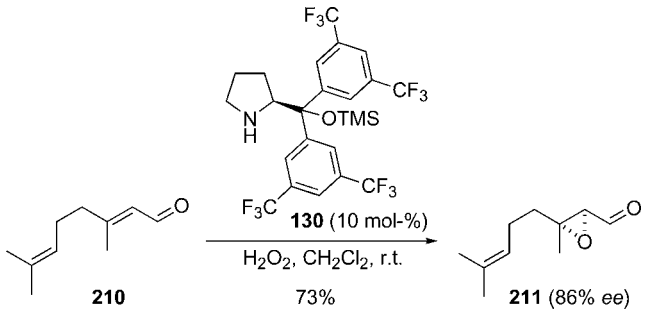


Scheme 55. Synthesis of glabrescol.

derived catalyst **130** and hydrogen peroxide as the stoichiometric oxidant, citral (**210**) was oxidized to give **211**, a sex pheromone of an acaric mite, in a respectable 73% yield and with 86% *ee* (Scheme 56).



Scheme 56. Synthesis of a mite pheromone.

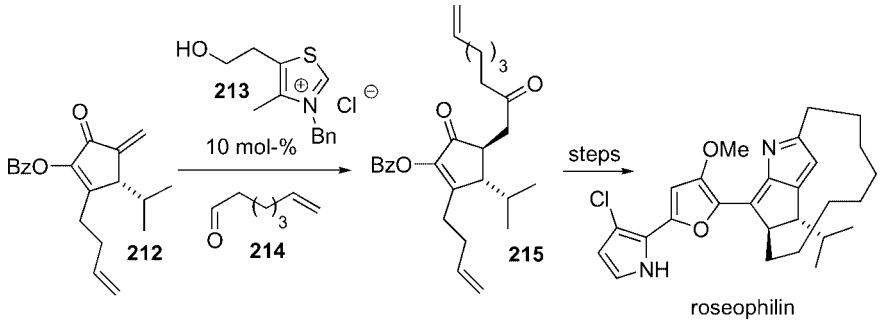
7. Carbene Catalysis

Carbene-catalysed processes are currently enjoying a renaissance.[123] Tius et al. have employed thiazolium chloride **213** as a carbene precursor in a diastereoselective intermolecular Stetter reaction[124] between **212** and **214** as a key step in their elegant synthesis of roseophilin (Scheme 57).[125] A ring-closing metathesis reaction served to join the unsaturated side chains and the 1,4-dicarbonyl functionality in **215** acted as a precursor for the central pyrrole unit of the natural product.[126]

8. Outlook

Our motivation in writing this review was to let organocatalysis sink into the mindset of other synthetic chemists in industry and academia. It is, however, mandatory to cultivate an awareness of the advisability not just of advertising the tremendous potential of a given reaction but also of critically discussing its limitations in substrate scope. Nothing is more frustrating than a failed reaction on a related substrate.

We have shown organocatalysis to be an enabling technology for the efficient synthesis of several biologically relevant molecules. Many reactions can be catalysed today, although a number of tough challenges remain. When the organocatalytic steps fit nicely into the overall synthetic concept, very short syntheses are possible. However, the need for excision of carbon atoms and removal of functional groups can result in rather lengthy syntheses. Organocatalysis has clearly demystified the aldehyde oxidation state and allows intermediates to be taken forward without repeated oxidations and reductions.



Scheme 57. Tius' synthesis of roseophilin.

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In a number of C–C bond-forming reactions, unparalleled enantioselectivities are observed. This can be attributed in part to the catalyst, covalently bound to one of the reactants. The selectivities are sometimes complementary to metal-catalysed reactions, which adds a new page to the book of useful transformations.

Another point that should not be underestimated is the attractiveness of the operational simplicity of organocatalytic reactions: rigorous exclusion of oxygen or moisture is not usually required. In fact, most organocatalytic reactions are tolerant of water and air and can be carried out in a temperature window that is compatible with industrial process chemistry. An issue that has to be addressed in the future is the catalyst loading, although encouraging results have been recently achieved with Brønsted acids.[127]

If a catalyst is not commercially available and its synthesis requires several synthetic steps it is unlikely to be used in total synthesis. Facile access to proline derivatives and the modular character of MacMillan's catalyst (amino acid plus carbonyl compound) should increasingly result in hand-crafted catalysts for a required transformation. In addition, additives such as organic acids[128] have been shown to have dramatic influences on the reaction outcome, although their role is still poorly understood at present.

Finally, we would like to note that organocatalytic reactions seem to be exceptionally amenable to sequential transformations[129] and cascade processes,[130] which should allow for the rapid assembly of complex molecular frameworks in the future.

Acknowledgments

We thank the Fonds der Chemischen Industrie for a Liebig fellowship (M. C.), the Deutsche Forschungsgemeinschaft for funding (SPP1179 Organokatalyse) and Prof. Dieter Enders for his encouragement and support. We are grateful to Dr. Arun A. Narine, Florian Boeck, Dr. Ingo Schiffers, and Dr. Michael J. McLaughlin for proof-reading the manuscript. Finally, we thank the referees for their valuable advice.

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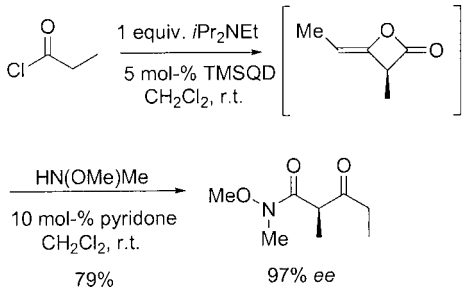

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Received: January 16, 2007
Published Online: April 25, 2007

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