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Organocatalytic conjugate addition in stereoselective synthesis

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Quintard, Adrien; Alexakis, Alexandre

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ORGANOCATALYTIC CONJUGATE ADDITION IN STEREOSELECTIVE SYNTHESIS
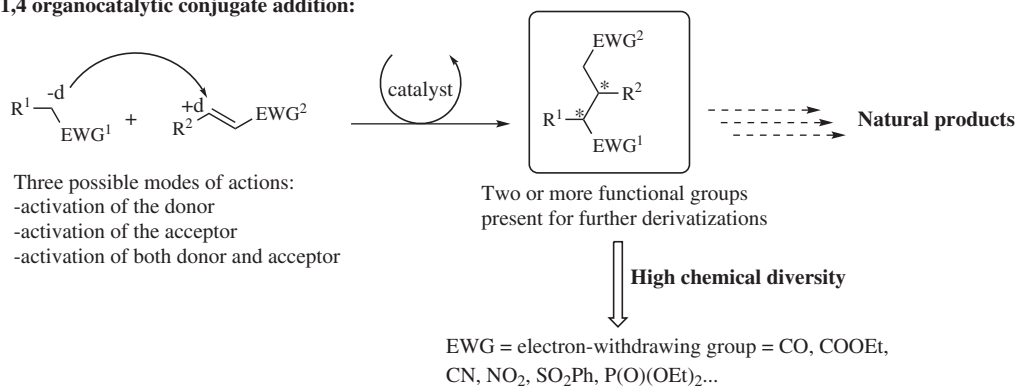
Adrien Quintard and Alexandre Alexakis

11.1. ORGANOCATALYTIC CONJUGATE ADDITION

Conjugate addition is a privileged method in organic synthesis allowing the formation of new C−C bonds, molecules that can serve as valuable synthons for total synthesis.[1–4] It is highly attractive thanks to the presence of at least one functional group on the Michael partners, a group that can be easily derivatized. In this field, organocatalyzed reactions have recently changed the way of thinking about synthetic approaches, notably, as soon as carbonyl groups are involved.[5–9] As a result, numerous applications of organocatalytic Michael additions in natural product synthesis have emerged in the last few years.

The reasons for such an explosion of the organocatalytic applications in synthesis can be found in the new reactivities (and thus new synthetic disconnections) discovered that are often complementary to the one used in organometallic chemistry. An emphasis must also be placed on another major aspect: the practicability of the methodologies. Taking into account the requirements for the industrial application of an academic reaction (functional group/H_2O tolerance, simple procedures, no extreme temperatures, etc.), these methodologies are candidates of choice to fulfill the ideal goal of maximized reaction efficiency.[10] Furthermore, because of the mild reaction conditions, the reactions are most of the time easily scalable and highly predictable, notably, for aminocatalysis. High functional group tolerance is observed, rendering it attractive for late-stage synthesis.

There can be several activation principles in organocatalytic Michael additions. The catalyst is appropriately activating either the nucleophile or the electrophile, or it can in some cases activate both donor and acceptor (bifunctional catalysis) (Scheme 11.1). A quick glance at the general scheme rapidly reveals one main advantage of organocatalyzed Michael additions. Given the fact that both the Michael donor and the acceptor need activation by electron-withdrawing groups, the obtained molecules usually contain at minimum two or more functional groups present for further derivatization (Scheme 11.1).

These activating groups can be diverse such as carbonyls, nitros, cyanos, esters, sulfones, and so on. This need of functionalized molecules is at the same time a great advantage and a limitation of organocatalytic Michael additions. Indeed, the great number of functionalized groups present on the final compound of an organocatalytic Michael addition is highly attractive in view of further derivatization and construction of complex molecules. On the other hand, for the synthesis of less elaborated synthons (e.g., simple alkyl chain and C−H group), the numerous functional groups need to be simplified (or removed) after the key step to obtain the desired molecule. This has a major drawback in cost (redox efficiency, waste, and step economy)[11–13] but clearly renders organocatalysis complementary to "classic organometallic chemistry" where a simple alkyl chain can be easily introduced on poorly functionalized substrates. As a result, organocatalysis is powerful and is often applied to construct relatively elaborated building blocks in few steps from easily available starting materials, building blocks that were impossible to prepare without organocatalysis. This is

1,4 organocatalytic conjugate addition:

Three possible modes of actions:
-activation of the donor
-activation of the acceptor
-activation of both donor and acceptor

Two or more functional groups
present for further derivatizations

High chemical diversity

EWG = electron-withdrawing group = CO, COOEt,
CN, NO_2, SO_2Ph, $P(O)(OEt)_2$...

SCHEME 11.1. Organocatalytic Michael addition.

notably the case of the carbonyl group (only one methodology presented here does not contain any carbonyl function on either the donor or the acceptor).

11.2. MODES OF ACTIVATIONS

During the last decade, thousands of different reactions have been developed using different concepts based on either covalent or noncovalent interactions (Scheme 11.2).
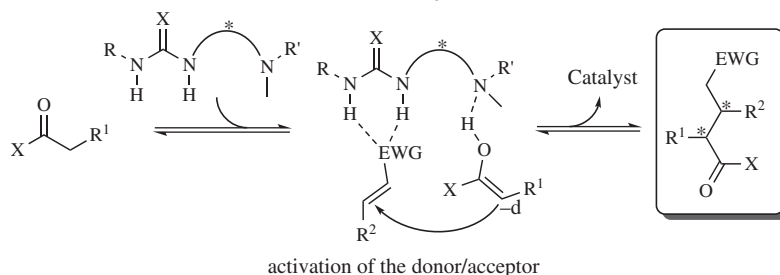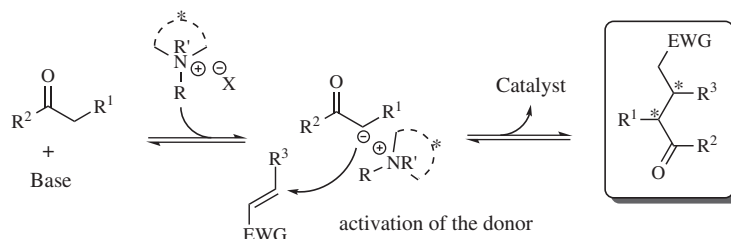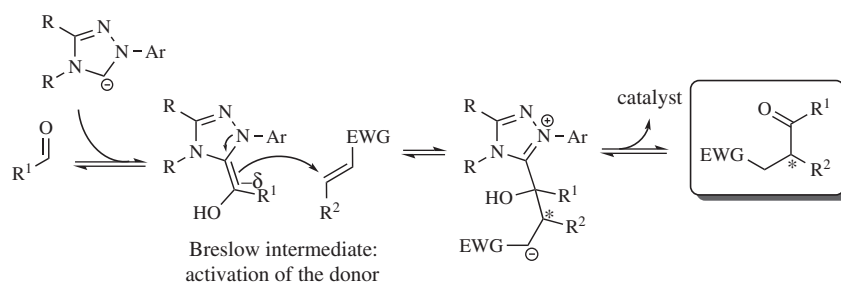
1. **Iminium catalysis** consists in the addition of primary or secondary amines to an α,β-unsaturated carbonyl (Scheme 11.2, eq 1).[14] The transient iminium ion has its lowest unoccupied molecular orbital (LUMO) lowered, activating the substrate toward the attack of a nucleophile and creating the new stereocenter. Liberation of the catalyst furnishes the enantioenriched Michael adduct.

2. **Enamine catalysis** is based on the ability of primary or secondary amines to displace the equilibrium of a carbonyl compound to the more reactive enamine (Scheme 11.2, eq 2).[15] The subsequent enamine has its highest occupied molecular orbital (HOMO) increased, facilitating the attack on a suitable Michael acceptor.

3. **Hydrogen bonding** is one of the key interactions in living organisms. Applying this principle to catalysis by using chiral thioureas or phosphoric acids, a different type of electrophiles could be activated toward an asymmetric nucleophilic attack.[16–18] **Brønsted bases** such as tertiary amines are known to activate carbonyl nucleophiles by deprotonation resulting in chiral ion pairs.[19] These two modes of action can be used separately or combined together in a **bifunctional activation** mode, resulting in extremely well-defined and reactive transition states (Scheme 11.2, eq 3).[20,21] Another mechanistic hypothesis for this dual activation involves enol formation by activation by the thiourea and electrophile activation by H-bond formation.[22]

4. The oldest conceptualized organocatalytic mode of action is **phase-transfer catalysis (PTC)**.[23,24] It consists in the creation of a chiral environment thanks to a chiral cation salt, in the proximity of a deprotonated carbonyl (Scheme 11.2, eq 4). This transient chiral anion can react in an enantioselective addition to appropriate electrophiles and notably Michael acceptors.

5. The organocatalysis using **N-heterocyclic carbenes** (NHC) is by far less studied than other areas of organocatalysis despite its inherent interest, notably, by applying aldehydes in an umpolung manner (Scheme 11.2, eq 5). Indeed, the NHC can attack aldehydes forming the Breslow intermediate, which can then perform a nucleophilic attack on an appropriate electrophile.[25]

In addition, the unique ability of organocatalysis to combine multiple modes of activation in cascade reactions is another great advantage, allowing for an increase in the molecular complexity that can be obtained in a limited number of operations.

The field of organocatalyzed Michael addition has rapidly evolved to reach its maturity as exemplified by the number of applications of the most classic reactions in total synthesis. It is not surprising that the methodologies first developed with enantioselectivities in a practical range and with broad scope were the first ones widely accepted and used by the synthetic community. The best examples are the addition of aldehydes to methyl vinyl ketone, iminium nucleophilic carbon addition to enals, or phase-transfer–catalyzed addition to vinyl ketones.

1) Iminium catalysis:

activation of the acceptor

2) Enamine catalysis:

activation of the donor
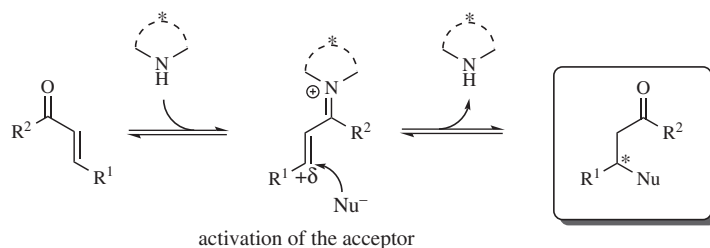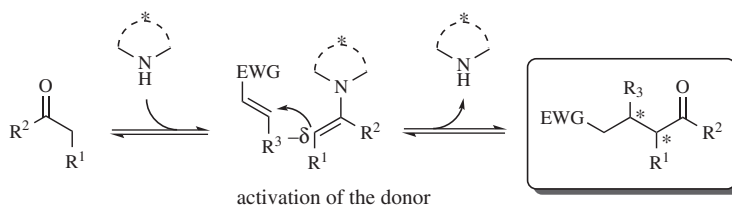
3) Brønsted bases/acids or bifunctional catalysis:

activation of the donor/acceptor

4) Phase-transfer catalysis:

activation of the donor

5) N-Heterocyclic carbenes catalysis (NHC):

Breslow intermediate:
activation of the donor

SCHEME 11.2. Organocatalytic modes of actions.

11.3. EXPERIMENTAL ASPECTS

As mentioned, from a practical point of view, most organo-catalytic reactions can be performed using simple experimental conditions, commercially or easily available catalysts obtained enantiomerically pure from natural sources (amino acids and cinchona alkaloids). As a result, these reactions can be run by first-year graduate students. Indeed, no Schlenk technique or anhydrous solvents are needed thanks to the high H_2O/O_2 tolerance of the reactions, and

the order of addition often has a poor impact on the reaction efficiency. A small difficulty may arise in some particular cases from the isolation of the final compound, notably, because of the excess of either the Michael donor or the acceptor present in the mixture. If one of these compounds is not sufficiently volatile or eliminated by aqueous workup, then column chromatography might be required to afford the pure Michael adduct. Furthermore, the excess reagent can in some cases self-condense (cross aldol, for example), rendering this purification trickier. In addition, decreasing the excess of reactant becomes a priority as soon as expensive reactants are used. It is obvious that extensive optimization of reaction conditions tends to reduce these side reactions and the required excess of reagent facilitating the overall experience.

This chapter deals with organocatalytic C−C bond conjugate addition in the synthesis of various biologically active molecules covering until the beginning of 2011. Focus will be done on the enantioselective key steps and on their particular interest in constructing the final backbone of the target molecule. The chapter is organized by activation type (enamine, iminium, and PTC), and examples of total synthesis are given for each of these activations modes.
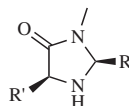
11.4. IMINIUM CATALYSIS

Iminium catalysis is one of the most powerful methods for the introduction of a nucleophile in β-position of an α,β-unsaturated carbonyl. Various nucleophiles can be entered such as N, O, C, aryl, and heteroaryl nucleophiles in usually high levels of stereoselectivity. To obtain these high enantioselectivities, two catalysts have seemed to be more general as soon as aldehydes are involved. Diaryl-prolinol silyl ethers and MacMillan imidazolidinones have found applications in numerous processes (Scheme 11.3).[26,27] These catalysts are
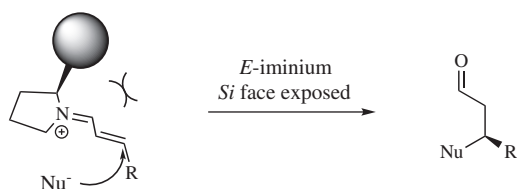
General catalysts:
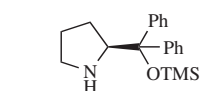
Diaryl prolinol silyl ethers   MacMillan imidazolidinones

SCHEME 11.3. Origin of the stereoselectivity in iminium catalysis.

commercially available, being an attractive future for the synthetic applications by the organic synthesis community. Most of the time, stereoselectivity is governed by pure steric factors with one single face of the transient E-iminium ion exposed. In the addition to enones, the recent development of primary amine catalysts notably derived from cinchona alkaloids have led to the best results.[28,29]

To exemplify most clearly the discovered methodologies, research groups first focused on applying iminium reactions for the synthesis of relatively small natural products before it really entered the synthetic community with more complex ones.

In 2002, Austin and MacMillan reported on the Michael addition of indoles to α,β-unsaturated aldehydes catalyzed by imidazolidinone (S)-3.[30] This strategy was applied in a concise two-step synthesis of indole 4, a cyclooxygenase-2 inhibitor, even though a relatively modest 87% ee was obtained (Scheme 11.4). The same strategy was applied in 2005 by the group of King et al. for the synthesis of another bioactive molecule: BMS-594726, a selective serotonin reuptake inhibitor. This potential drug could be synthesized on a 20-g scale, highlighting the efficiency of the iminium step on larger scale operations.[31]

The Jørgensen et al. synthesis of warfarin, an anticoagulant, is another example of short drug synthesis (Scheme 11.5).[32] Indeed, the enantioenriched product could be obtained directly by a single-step procedure. The 1,3-dicarbonyl compound 6, a powerful nucleophile, reacted without any need of extra additive on commercially available enone 7 activated by iminium formation with 8 and yielding warfarin in excellent 90% yield and a promising 80% ee. This synthesis further exemplifies the power of iminium catalysis for the fast synthesis of small drugs.

Hayashi et al. took advantage of the propensity of diphenyl prolinol silyl ether 12 to catalyze the addition of nitromethane to enals in high enantioselectivities (typical >99% ee) to design a short three-step synthesis of two pharmaceuticals: baclofen and pregabalin (Scheme 11.6, eq 1).[33] A simple transformation of the Michael adducts by oxidation-reduction sequence led to commercial drugs in high enantiopurity. Using the same methodology, Palomo et al. disclosed the addition of nitromethane for the two-pot synthesis of Rolipram (Sigma-Aldrich, St. Louis, MO), another commercial drug (Scheme 11.6, eq 2).[34] A slight modification of the catalyst structure allowed for an improvement of the enantiocontrol together with the application of water as solvent.

Paroxetine is another serotonin reuptake inhibitor used to treat depression and panic disorders. The group led by Jørgensen reported on a concise four-step synthesis of this drug containing a piperidine unit (Scheme 11.7). Crucial stereogenic center construction was achieved via malonate addition to the activated α,β-unsaturated aldehyde 18 in
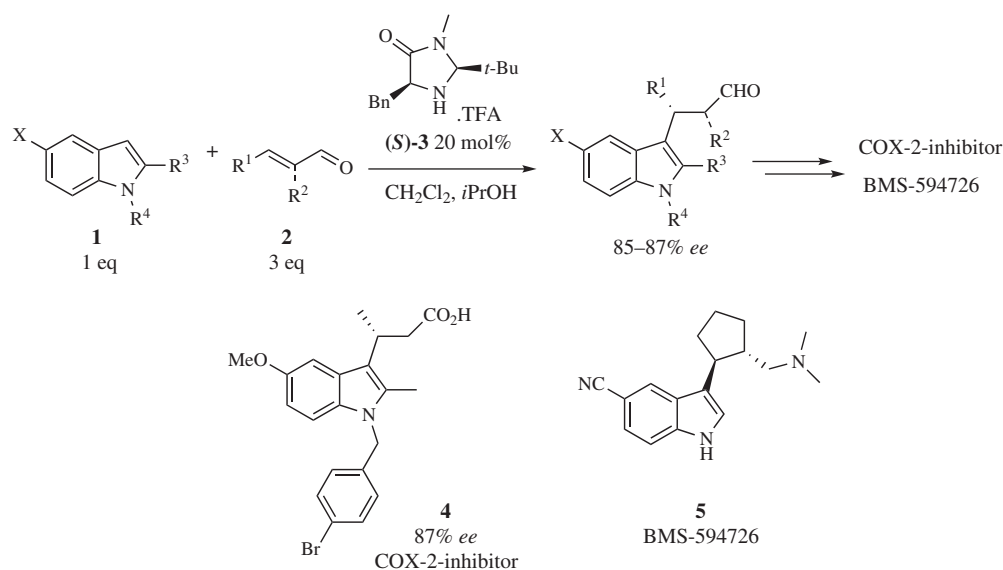
SCHEME 11.4. Indole alkylation for the synthesis of potential drugs.

86% *ee*. The aldehyde could be easily transformed by reductive amination and subsequent lactonization of the corresponding ester.

γ-Butenolides are highly potent functional groups present in many natural compounds. In 2003, MacMillan et al. disclosed the attractive addition of silyloxyfuran to enals leading to γ-butenolides in typical high enantioselectivities (Scheme 11.8).[35] The catalyst controlled the two contiguous stereocenters, leading to the desired *syn* diastereoisomer. This strategy was applied to the four-step synthesis of spiculisporic acid, a commercial biosurfactant.

Besides the applications for small drug synthesis, iminium catalysis has found applications in the synthesis of much more complexes molecules.

The Mukaiyama-Michael reaction was further applied by Robichaud et al. at Merck (Whitehouse Station, NJ) for the synthesis of compactin, an 3-hydroxy-3-methyl-glutaryl-coenzyme A inhibitor (Scheme 11.9).[36] The organocatalytic reaction created two of the four stereocenters in 82% *ee* and

perfect diastereoselectivity ($>30:1 \, dr$). In addition, the iminium catalysis step could be conducted on 5.82 g without compromising the reaction efficiency and using only a slight excess of Michael donor.

In the organocatalytic synthesis of complex structures, MacMillan et al. were one of the pioneers with the 2004 synthesis of flustramine (Scheme 11.10).[37] Flustramine is an alkaloid isolated from *Flusta foliacea* containing the challenging bridged quaternary stereocenter in position 3. MacMillan et al. hypothesized that an appropriate indole would react on iminium-activated acrolein. Using their homemade imidazolidinone catalyst (*S*)-**3**, stereocontrol of the challenging quaternary stereocenter was achieved in a good 90% *ee*. The transient iminium intermediate **34** instantaneously cyclized to furnish the Flustramine backbone. The only limitation of such a process is the extreme temperature required for good reaction efficiency ($-84°C$).

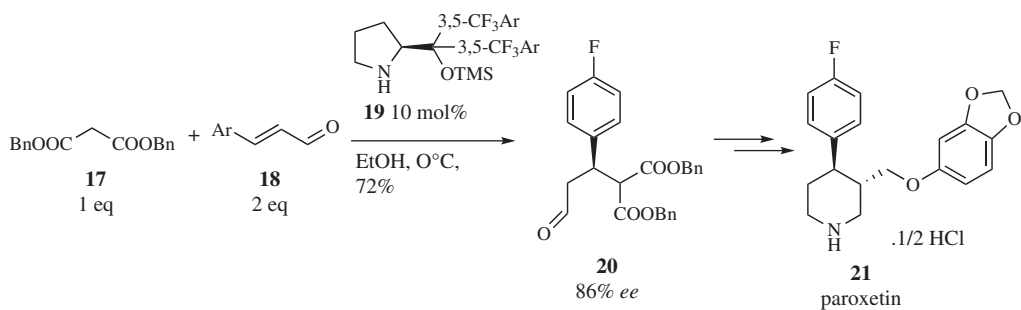The Toste group applied the Robinson annulation of **35** to crotonaldehyde catalyzed by **19** for their synthetic route
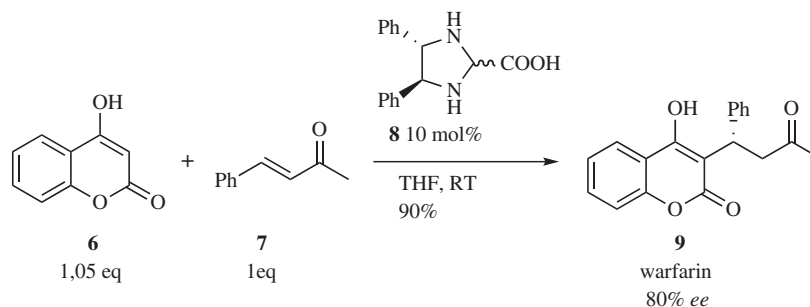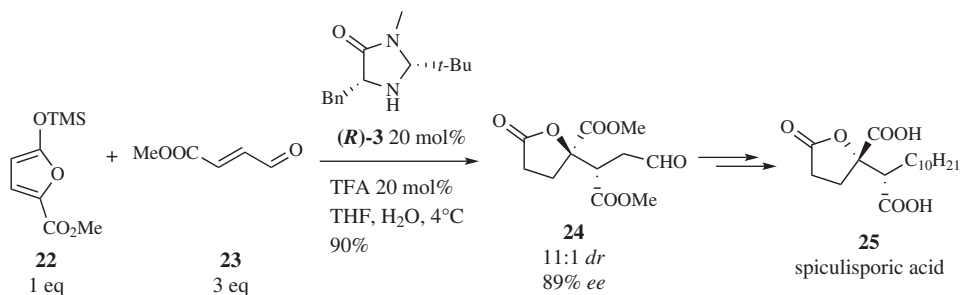

SCHEME 11.5. Jørgensen et al.'s synthesis of warfarin.
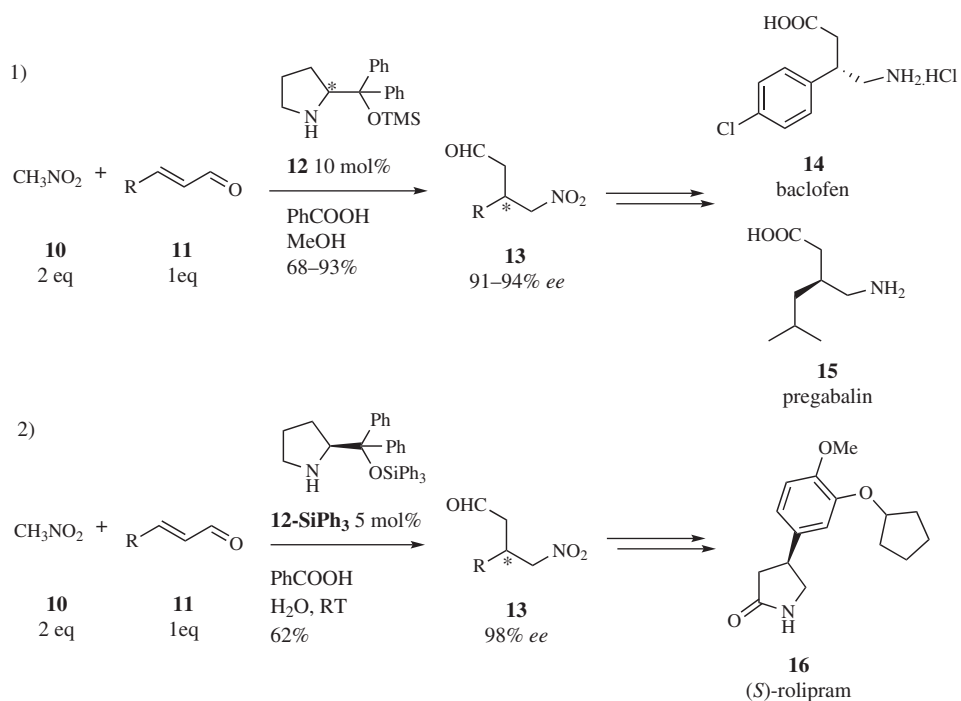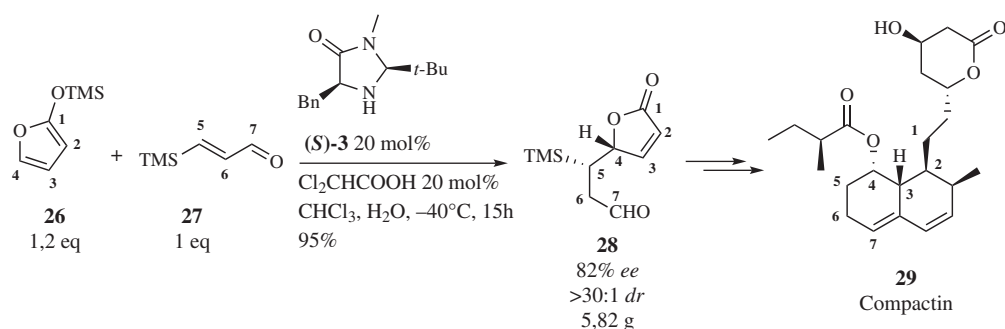
SCHEME 11.6. Synthesis of commercial drugs by iminium-catalyzed nitromethane addition.

SCHEME 11.7. Jørgensen et al.'s four-step synthesis of paroxetin.

SCHEME 11.8. MacMillan et al. synthesis of spiculisporic acid.

SCHEME 11.9. Mukaiyama-Michael route to compactin.
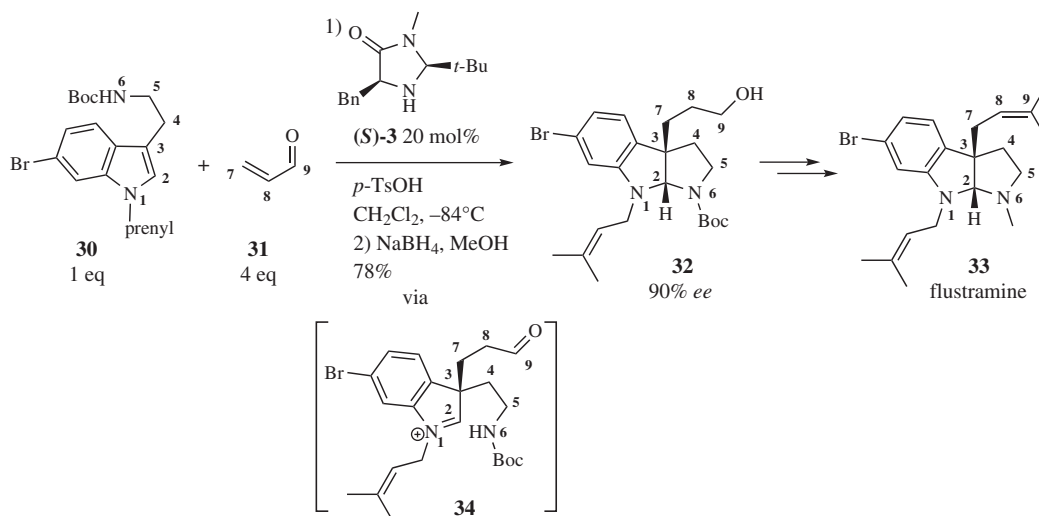
SCHEME 11.10. MacMillan et al. synthesis of flustramine.

to fawcettimine, a *Lycopodium* alkaloid (Scheme 11.11).[38] The addition of ketoester **35** followed by *in situ* aldolization-elimination constructed the chiral cyclohexenone intermediate **36** in 88% *ee*. It is worth mentioning that the single stereogenic center of the cyclohexenone **36** introduced by this organocatalytic step can control all the other stereocenters with high diastereocontrol. This robust Michael

methodology could be performed on a 10-g scale, which is key for the complex synthesis completion.

More recently, Lee and MacMillan developed the addition of heteroaryl boronic acids to α,β-unsaturated aldehyde by what was called a Friedel-Crafts–type reaction.[39] Applying this methodology, the straightforward synthesis of frondosin, a potential treatment against inflammatory
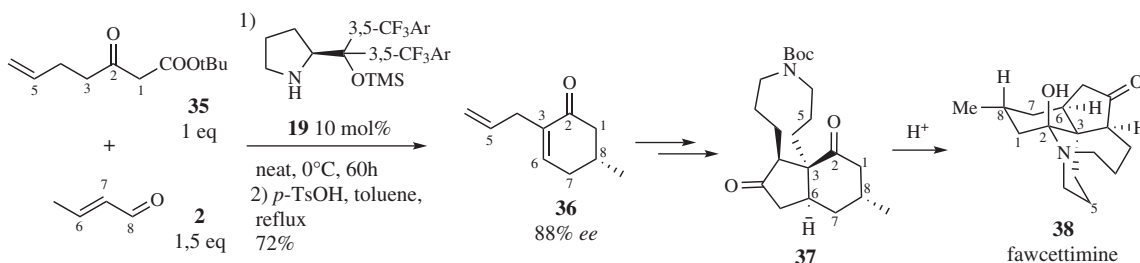
SCHEME 11.11. Toste et al. synthesis of fawcettimine *via* Robinson annulation.
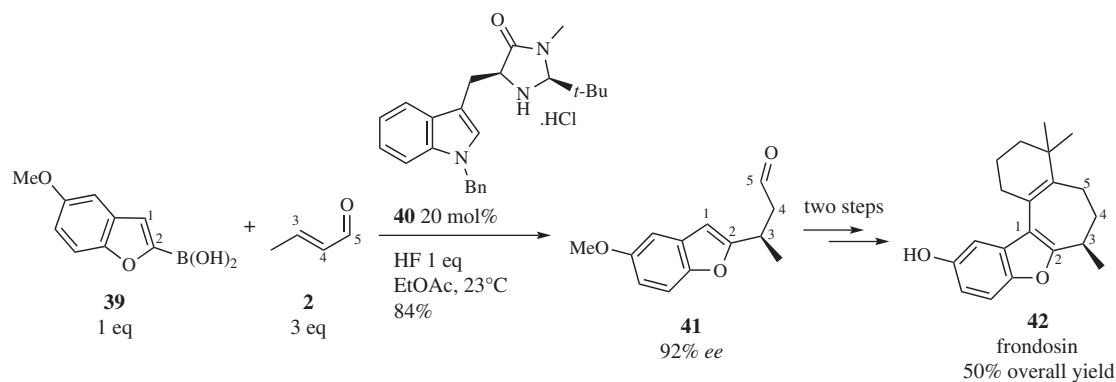
SCHEME 11.12. Friedel-Crafts addition for the concise synthesis of frondosin.

diseases, could be achieved (Scheme 11.12).[40] Starting from commercially available boronic acid and α,β-unsaturated aldehyde, the Friedel-Crafts reaction furnished the desired 1,4-adduct in 93% *ee*. The only critical issue with this process is the use of hydrofluoric acid, which considerably limits its application. Two-step derivatization gave the expected frondosin in an overall 50% yield for the three-step total synthesis; this process is by far the most efficient synthesis to date.

Despite the construction of relatively simple key building blocks, the total synthesis community recently began applying iminium reactions to increasingly elaborated systems. Again, the MacMillan group pioneered this field with the synthesis of diazonamide A, a potential anticancer agent (Scheme 11.13).[41] This last example demonstrates the exceptional power of iminium catalysis for constructing complex natural products and especially its high compatibility/tolerance with numerous functional groups. Indeed, the key C−C bond constructing the reaction was applied on an impressive structurally complex molecule at the late stage of the total synthesis. It is remarkable that the starting molecule for the planned Michael addition contains numerous
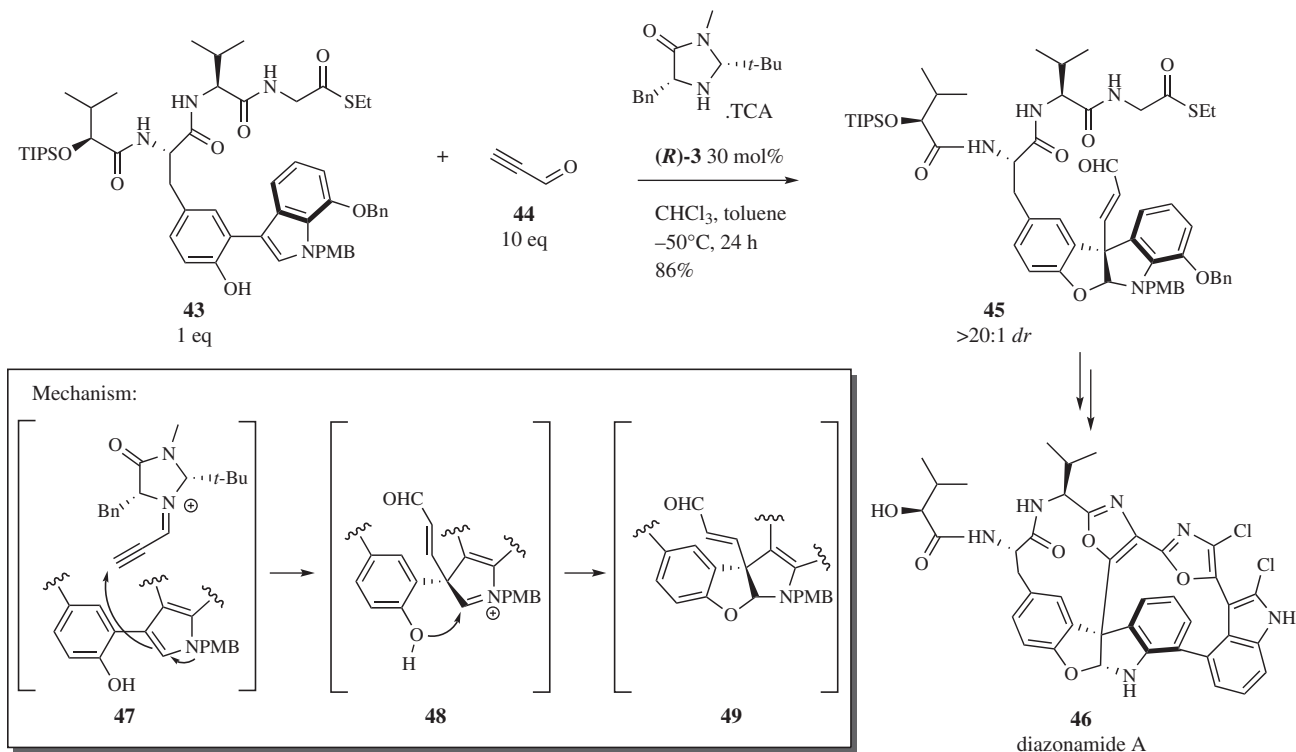
SCHEME 11.13. Iminium catalysis on elaborated substrate for the synthesis of diazonamide A.
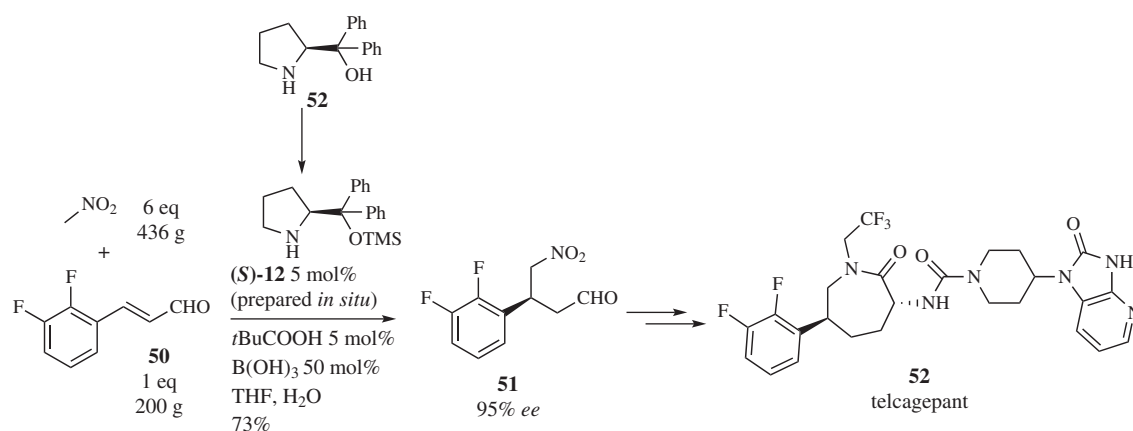
SCHEME 11.14. Large-scale synthesis of Telcagepant.

functionalities such as amide, thioester, and alcohol. Activated by the imidazolidinone catalyst, propynal could undergo the attack of the indole leading to the iminium **48**. This intermediate undergoes the cyclization by phenol nucleophilic attack. At a low temperature ($-50°C$) and using a ternary solvent mixture, a good $20:1\, dr$ was obtained for this highly challenging generation of a quaternary stereogenic center. It is important to notice that using a racemic catalyst, only $1:1\, dr$ was obtained indicating the need for a chiral catalyst control for such reaction.

On a totally different aspect, the synthesis of Telcagepant by a group at Merck demonstrated the potential of iminium catalysis on large-scale reactions (Scheme 11.14).[42] Telcagepant is a Calcitonin gene-related peptide (CGRP) receptor antagonist with potential as a treatment for migraines. The key step in the large-scale synthesis of Telcagepant is the asymmetric addition of nitromethane to enal **50**. Extensive optimization of the reaction conditions allowed for the discovery of a "cocktail" of weak acids (t-BuCOOH, $B(OH)_3$) that allowed for obtaining **51** in good 73% yield using only 5 mol% of catalyst (S)-**12**. In a typical procedure, the different catalysts and the nitromethane are added to the aldehyde solution (nonanhydrous conditions) and stirred at room temperature. Simple acid-base treatment furnishes the Michael adduct in sufficient purity and excellent 95% ee.

Synthesis of 51[42]: A concentrated solution of aldehyde **50** (1.189 mol assay, 200 g of **50**) was diluted with tetrahydrofuran (THF) to a volume of 2.8 L. H_2O (400 mL), pivalic acid (6.08 g, 0.0594 mol), boric acid (36.78 g, 0.594 mol), tetramethylsilane (TMS)-prolinol (S)-**12** (19.36-g assay, 0.0594 mol, 250-mL solution in THF/methyl $tert$-butyl ether [MTBE]), and nitromethane (436 g, 7.143 mol) were added at an ambient temperature. The resulting homogeneous solution was stirred at an ambient temperature for 30 hours (>94% conversion). The reaction solution was cooled to 2–7°C and quenched by addition of i-PrOAc (2 L), 15% aq NaCl (600 mL), and 1-N HCl (200 mL). The organic layer was

washed with 6% $NaHCO_3$ in 5% aq NaCl (1 L) and 15% aq NaCl (600 mL × 2). The organic phase was azeotropically dried and solvent switched to i-PrOAc while maintaining the internal temperature at <15°C. The final solution (~2 L, 10 wt of **51**) was directly used in the subsequent step or could be stored at 5°C; 73–75% assay yield of **51**; 95% ee.

(Reprinted with permission from Reference 42. Copyright 2010, American Chemical Society.)

Noteworthy, the catalyst could be prepared on a 12.47-kg scale by an extraordinarily simple procedure: Slow addition of trimethylsilyl chloride (TMSCl) to a slurry of the diphenyl prolinol and imidazole in THF leads to the protected catalyst. A simple quench by MTBE addition and 15% NaCl washing directly gives the catalyst.

This large-scale synthesis highlights the extraordinary potential of organocatalysis for industrial-scale drug preparation. More examples of such large-scale applications should be discovered in the next few years.

11.5. ENAMINE CATALYSIS

The enamine-catalyzed Michael addition has recently been introduced as a method of choice as soon as a new stereocenter needs to be created α- to a carbonyl. Rarely has a research area been investigated so heavily in such a short period of time (4–5 years), leading to powerful catalytic systems notably in the addition to nitroolefins. Varying the Michael donor and acceptor, a wide array of structurally diverse and complex molecules can be obtained. In these methodologies, protected diaryl prolinol silyl ether, developed simultaneously by research groups led by Hayashi and Jørgensen, were found as the most powerful catalysts thanks to a high predictability in both reactivity and stereoselectivity, as soon as aldehydes are used. Indeed, the classic Seebach transition state taking into account the single

SCHEME 11.15. Origin of the stereoselectivity in enamine catalysis.

steric hindrance of the bulky substituents of the catalysts was found to be remarkably general (Scheme 11.15).[43,44] In contrast, the catalysts applied in the addition of ketones have by far less broad applicability, and more investigations are still needed to afford the same levels of predictability as for aldehydes.

In most enamine processes, the stereointegrity of the α-carbonyl stereocenters can be preserved because most of the products are kinetically stable in the presence of enamine catalysts.

As stated in section 11.1, it is not surprising that the addition of aldehydes to methyl vinyl ketone, one of the first practical Michael additions leading to valuable 1,5-di-carbonyl compounds in a simple and efficient way, was the first widely applied by the synthetic community (Scheme 11.16).[45–48] Using commercially available catalyst **55**, above 90% *ee* could be obtained for this valuable synthon using particularly simple procedures. In a typical manner, the methyl vinyl ketone just needed to be added to a 0°C solution of the aldehyde with the catalyst and acidic co-catalyst present. The resulting neat solution was stirred

at 0–5°C for 24–36 hours before being directly purified by silica gel chromatography furnishing directly the Michael adduct. Interestingly, the reactions could be run on up to 74.8 mmol without any decrease in efficiency.

The obtained products could serve as crucial synthons for complex molecule synthesis by derivatization of both carbonyl moieties. This behavior was highlighted in the remarkable syntheses of polyanthelin, dihydrojunenol, or biyouyanagin A. Notably, the treatment of the 1,4 adduct under basic conditions (KOH) affords directly the corresponding chiral cyclohexenone by aldol condensation-elimination (Scheme 11.17).

More recently, the Kotsuki group expanded this reaction to the generation of quaternary stereocenters. Primary amine catalyst **62** was required to limit the steric strain obtained during the transition state and to favor the formation of the congested quaternary stereocenter. This process was applied to the synthesis of sporochnol A, a fish deterrent previously synthesized in a racemic form by a three-step procedure (Scheme 11.17).[49] Despite the relatively lengthy completion of the synthesis, this approach is highly interesting because high enantioselectivities are obtained by the use of catalysts available on kilograms scale.

By taking advantage of the insertion of an ester γ- to the vinyl ketone, the Ma group reported on the synthesis of acaranoic acid, a δ-lactone isolated from *Acarospora chlorophana* (Scheme 11.18).[50] The addition of this extra electron-withdrawing group was inserted at the same time as the required carbonyl skeleton of the final molecule (obtained with the appropriate stereoselectivity) but also allowed for an impressive increase in reactivity.

SCHEME 11.16. Michael addition to methyl vinyl ketones in total synthesis.

SCHEME 11.17. Addition to methyl vinyl ketone in the synthesis of sporochnol A.


SCHEME 11.18. Ma et al. synthesis of acaranoic acid.

The overstudied addition of carbonyls to nitroolefins represents a marvelous example of the rapid progress obtained in organocatalysis. The organocatalytic community has focused on this reaction optimizing the methodologies and leading to highly practical catalytic systems.

In 2003, the Alexakis group was the first to demonstrate the power of this methodology in the synthesis of botryodiplodin, a molecule with potential antibiotic properties isolated from *Botryodiplodia theobromae* (Scheme 11.19).[51] They took advantage of the **70** catalyzed addition of the highly reactive propionaldehyde to the trisubstituted nitroolefin **69**, to construct the carbonyl backbone of the natural product. The relatively long reaction time and poor diastereoselectivity is a result of the known difficulty of reacting trisubstituted nitroolefins in Michael additions. Taking advantage of the Nef reaction, the nitro was converted into a ketone showing the potential of nitroolefins as umpolung

synthons in retrosynthetic analysis. The mixture of two diastereosiomers could be separated after aldehyde protection to furnish, after several transformations, the cyclized botryodiplodin in 92% *ee*.

In a classic approach, several groups applied the Michael addition of aldehydes to nitroolefins to synthesize small natural products containing an amine and, notably, pyrrolidine rings. Indeed, reduction of the nitro group to the corresponding amine and subsequent reductive amination converts the obtained 1,4 adduct into the crucial pyrrolidine structure, a motif present in a wide variety of pharmaceuticals. Wang et al. and the Ma group[52] both applied the addition of commercial aldehydes to functionalized nitroolefins and subsequent cyclization to form highly attractive optically active pyrrolidine rings such as **77** (Scheme 11.20).[53] More importantly, the insertion of an ester on the nitroolefin increasing the electrophilicity of the Michael acceptor **79**
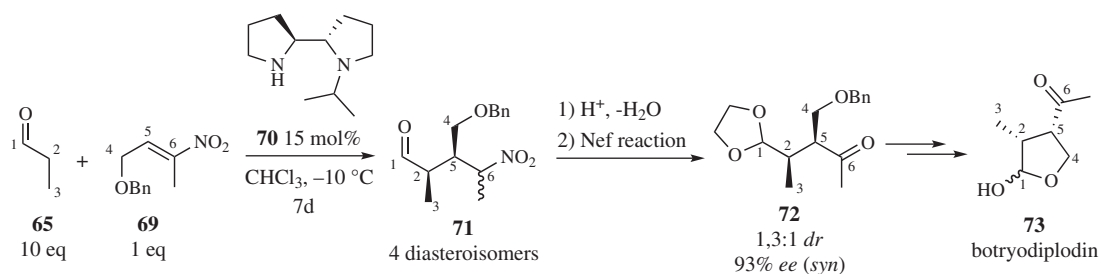
SCHEME 11.19. Addition to trisubstituted nitroolefin and the synthesis of botryodiplodin.
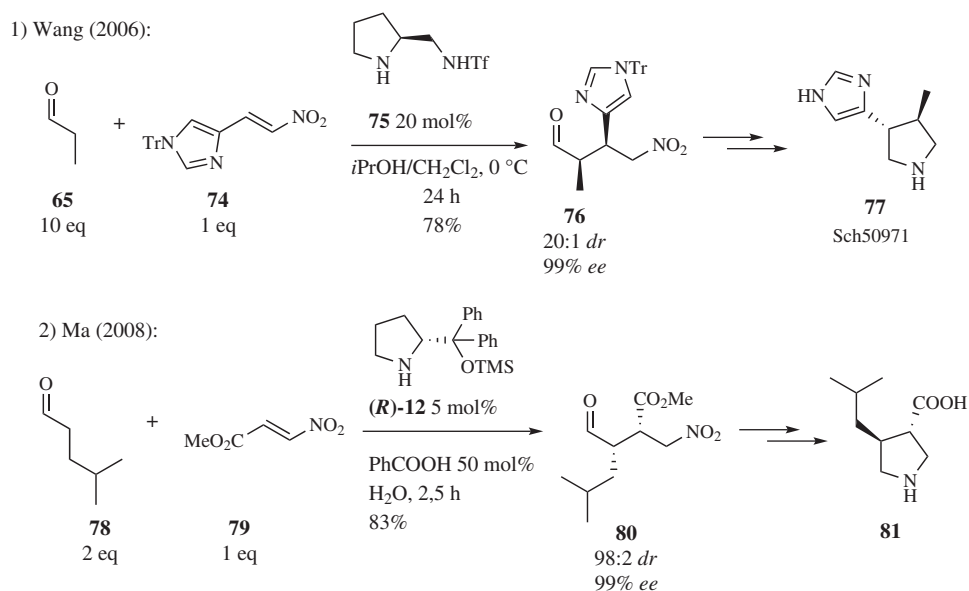
SCHEME 11.20. Addition to nitroolefins in the synthesis of various pyrrolidines.

allowed for water to be applied as solvent and to decrease to only 2 equivalents the excess of aldehyde and to 5 mol% the amount of catalyst (eq 2).

As for iminium catalysis, the enamine Michael addition was shown to have a great potential for the fast construction of simple drugs. The group led Benjamin List reported on the highly challenging addition of acetaldehyde to nitroolefins for the synthesis of three different small bioactive natural products (Scheme 11.21).[54] The Michael adducts **83** obtained using commercial catalyst in 88% to 94% *ee* and containing both aldehyde and nitro functionality could be transformed by a classic one- to three-step transformation

(oxidation-reduction) to different drugs. Baclofen is a GABA$_B$ receptor antagonist, pregabalin an anticonvulsant, and rolipram an antidepressant.

On more complex natural product synthesis, Pansare and co-workers exploited the well-studied addition of cyclohexanone to nitroolefin to introduce the requisite functionalities of pancranine (Scheme 11.22).[55] As mentioned, the diaryl prolinol silyl ethers, general catalysts for aldehyde, do not work in the case of ketones because of the steric constraint of the requisite transition state. A good 89% *ee* and >19 : 1 *dr* was obtained using catalyst **89**. Interestingly, the final construction of the complex
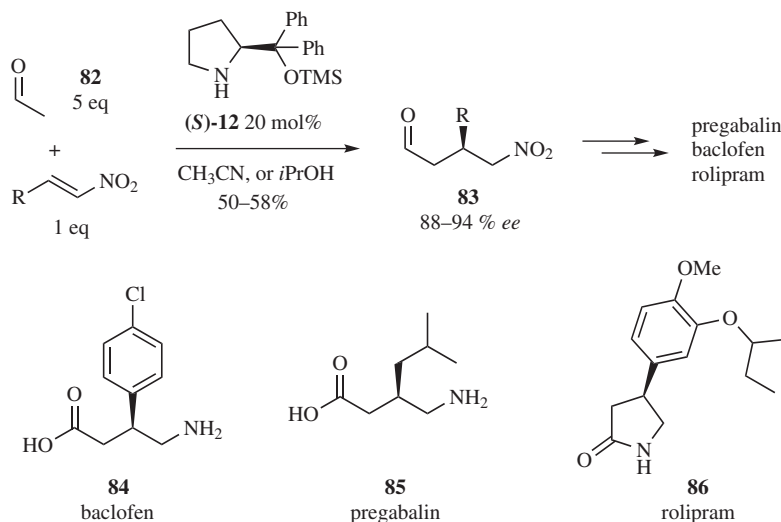
SCHEME 11.21. Michael addition of acetaldehyde for the construction of small drugs.
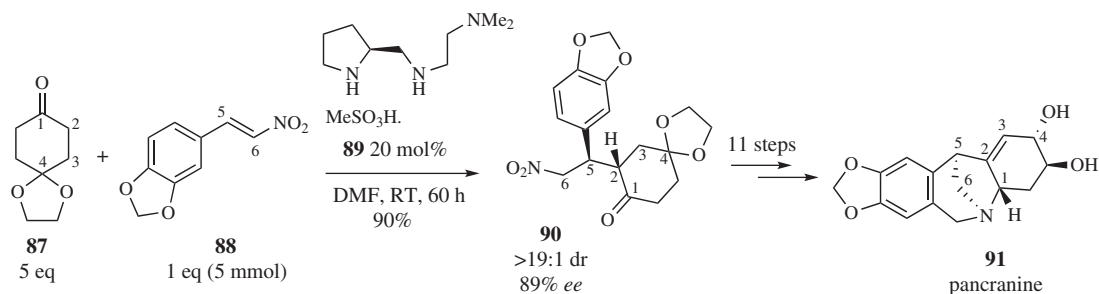
SCHEME 11.22. Pansare et al. synthesis of pancranine.
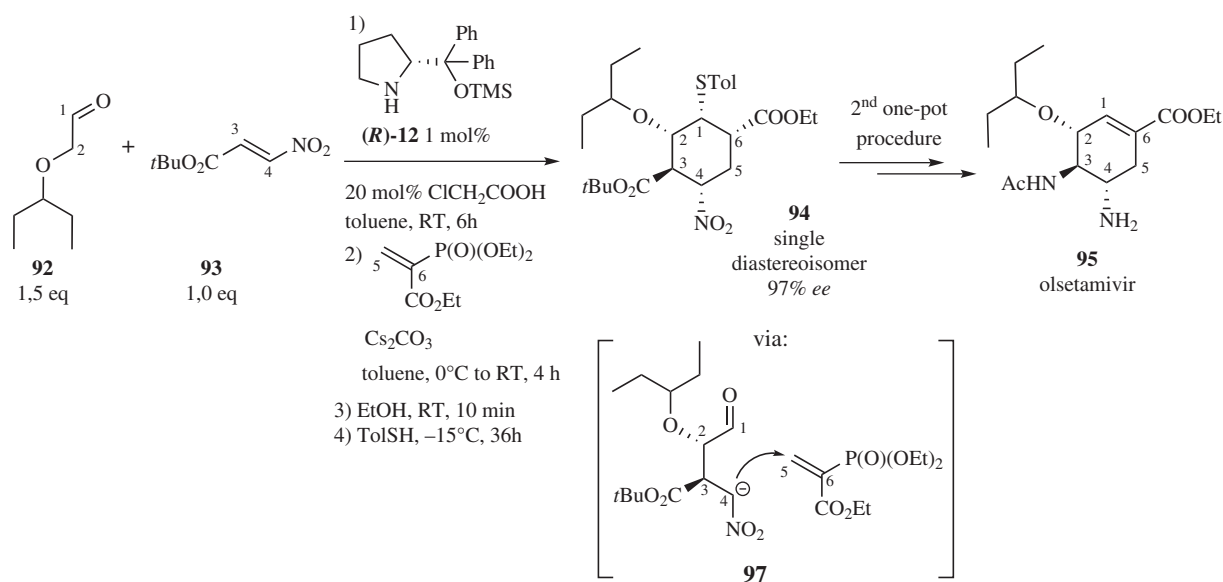
**SCHEME 11.23.** Hayashi et al.'s approach to the synthesis of olsetamivir.

backbone of pancranine could be achieved in 11 steps from this advanced precursor.

By far the most accomplished synthesis applying nitro-olefins as Michael acceptors is the Hayashi et al. synthesis of the well-known anti-influenza virus drug olsetamivir, a drug commercialized under the name of Tamiflu (Genentech, South San Francisco, CA) (Scheme 11.23).[56,57] This synthesis is impressive in terms of both practicability and chemical efficiency. It takes advantage of the addition of aldehyde **92** to the vinyl nitroester **93**. Extensive optimization of the process has allowed for the use of only 1 mol% of catalyst. *In situ* treatment with Cs_2CO_3 addition of the vinyl-phosphonate, subsequent one-pot cyclization-isomerization, and final 1,4 thiol addition led to the six-membered ring precursor **94** containing five contiguous stereocenters.

This highly complex precursor is purified at this stage before being engaged in a second one-pot procedure leading to Tamiflu as a single diastereoisomer and >97% *ee*. Further optimizations have allowed for avoiding the need

for silica gel chromatography by taking advantage of acid-base treatment. It must be pointed out that this sequence allowed for the synthesis of 1.49 g of olsetamivir in conditions suitable for industrial scaleup. In 2011, Hayashi et al. expanded this approach to the one-pot synthesis of DPP4 inhibitor ABT-341 (**96**) (Figure 11.1).[58]

It is worth mentioning that the group led by Dawei Ma also brought an impressive improvement to this system by
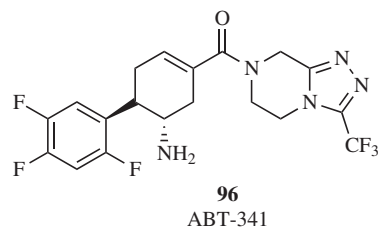
FIGURE 11.1. ABT-341 (**96**), a DPP4 inhibitor.
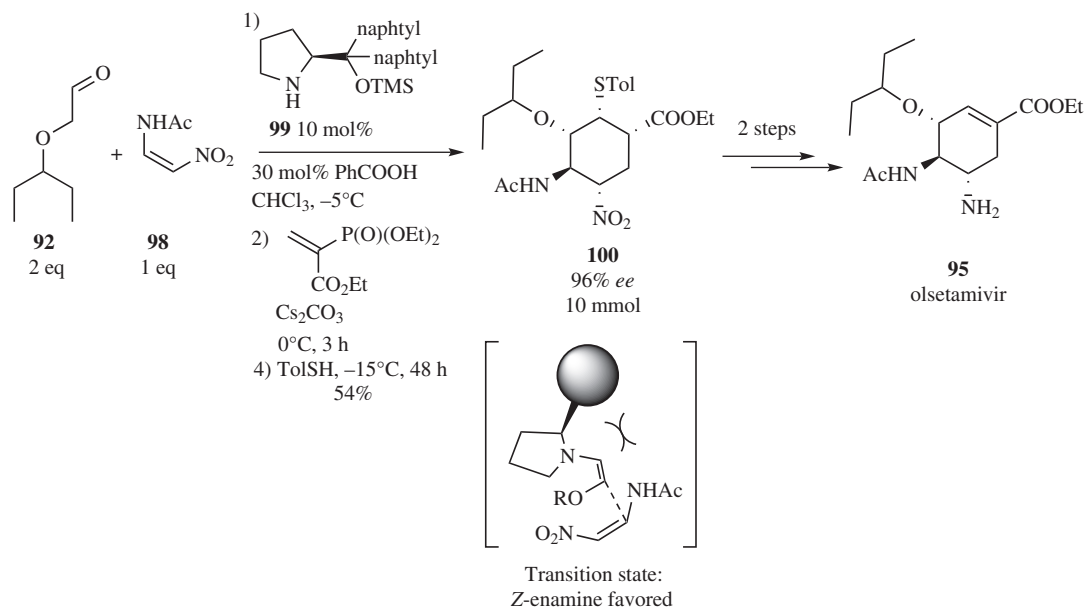
**SCHEME 11.24.** Ma et al.'s improvement of the olsetamivir synthesis.

directly incorporating the amine on the nitroolefin of substrate **98** (Scheme 11.24).[59] This amine incorporation avoids the required ester conversion to the amine in Hayashi et al.'s synthesis and considerably shortens the sequence. The Z-nitroolefin **98** is stabilized by H-bonding favoring the formation of the expected isomer by an uncommon Z-enamine transition state.

In 2005, Mangion and MacMillan reported on the smart synthesis of two closely related natural compounds: littoralisone isolated from *Verbena littoralis* and brasoside (Scheme 11.25).[60] These two syntheses were crucial for the expansion of organocatalysis because they highlighted the extraordinary potential of several organocatalytic methodologies. The key point for the synthesis of these molecules was the development of an intramolecular Michael addition. Using L-proline as catalyst, the substrate reacted under kinetic catalyst control to furnish the desired

diastereoisomer in 91% isolated yield. This advanced intermediate containing five stereocenters could be converted in seven additional steps into the complex littoralisone.
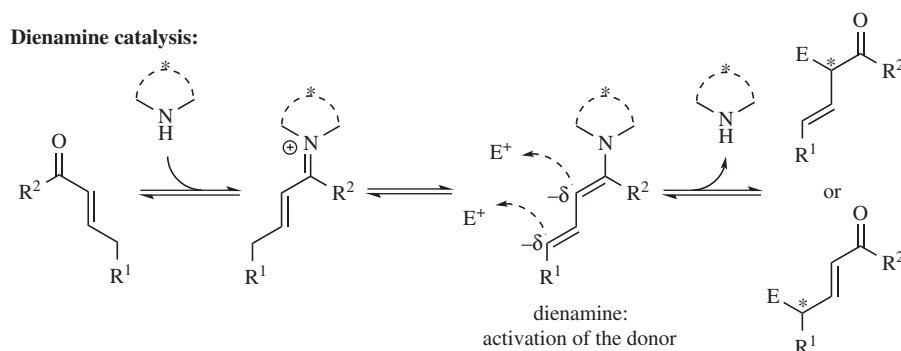
11.6. DIENAMINE CATALYSIS

Dienamine is a recent extension of the enamine concept to extended donors by using the principle of vinylogy. By extension of the enamine to conjugated dienamine starting from alkyl substituted enals or enones, it allows for the functionalization of α,β-unsaturated carbonyls in α- or γ-position using various electrophiles (Scheme 11.26). This potential of amine catalysts to promote extended functionalization is highly interesting, but because of its relative infancy, few synthetic applications of such activation have been reported to date.
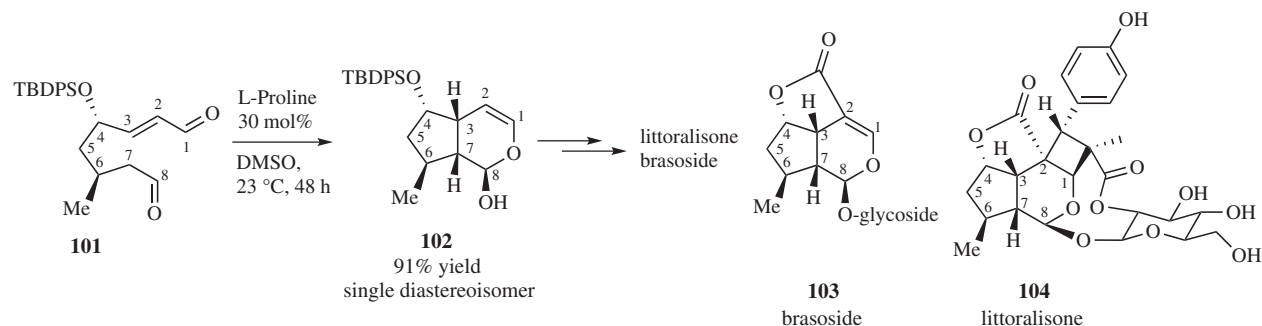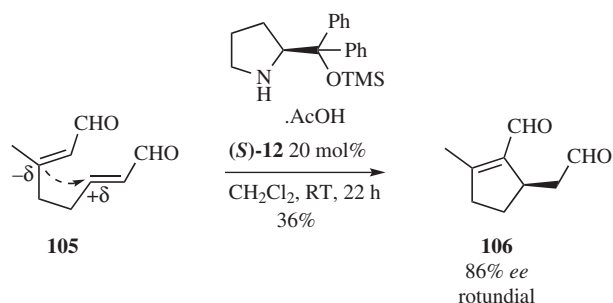

SCHEME 11.25. Mangion and MacMillan's approach to brasoside and littoralisone.

Dienamine catalysis:

SCHEME 11.26. Principle of dienamine catalysis.

SCHEME 11.27. Christmann et al.'s dienamine synthesis of rotundial.

The group led by Christmann exploited this property for the synthesis of rotundial, a mosquito repellent isolated from *Vitex rotundifolia* (Scheme 11.27).[61] Using catalyst **12**, the dienamine was formed on the most hindered enal. Intramolecular addition of the dienamine to the enal and subsequent isomerization of the double bond to the more stable conjugated one affords rotundial in a relatively modest 36% yield and 86% *ee*.

Hong et al.'s preparation of palitantin, a natural product with potential antibiotic and antifungal activity, is another application of dienamine catalysis to natural product synthesis (Scheme 11.28).[62] L-Proline was able to self-condense two **107** units forming the six-member ring **108** containing

two contiguous stereocenters in 95% *ee*. The reaction proceeds *via* dienamine 1,4 addition on the enal and subsequent aldolization. This is one of the rare examples with littoralisone synthesis where L-proline reacts as an efficient catalyst in Michael addition. In this methodology, the 50 mol% of L-proline required is not a limiting issue thanks to the availability of this natural amino acid.

## 11.7. CASCADE REACTIONS IN THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

One main advantage of aminocatalysts is their ability to promote several activation modes (iminium-enamine) or their high compatibility with other systems allowing for their applications in cascades reactions.

In this very active field, Michrowska and List applied the combination of iminium-catalyzed 1,4 hydride addition and subsequent intramolecular 1,4 Michael addition for the one-pot synthesis of ricciocarpin, a molluscicidal natural product isolated from the liverwort *Ricciocarpos natans* (Scheme 11.29).[63] This cascade reaction could be initiated by the single imidazolidinone (*R*)-**3** that catalyzed both iminium hydride addition and Michael addition. Treatment of the Michael adduct with Sm(O*i*-Pr)$_3$ induced the epimerization of the aldehyde carbon center to the more thermodynamically stable *trans* ring junction and subsequent Tishchenko reaction (redox process between the aldehyde
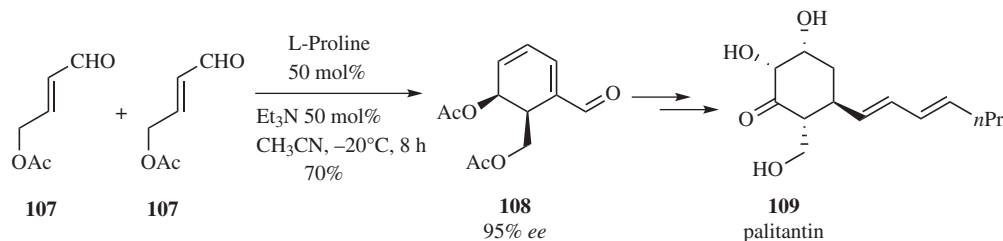
SCHEME 11.28. Dienamine catalysis synthesis of palitantin.
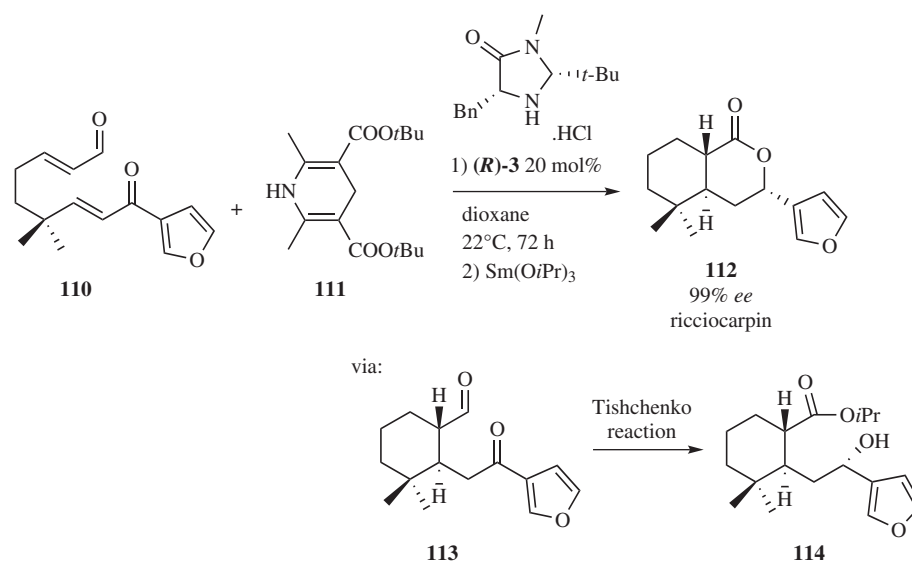
**SCHEME 11.29.** Michrowska and List's cascade synthesis of ricciocarpin.

and the ketone). Final lactonization affords the expected ricciocarpin.

Quintard and Alexakis developed the combination of copper and enamine catalysis for the synthesis of the most active isomer of valnoctamide, which is a commercial mild tranquilizer (Scheme 11.30).[64] Combining in one pot the copper-catalyzed asymmetric 1,4-addition of dimethylzinc to the α,β-unsaturated aldehyde **115** and subsequent enamine trapping using vinyl sulfone **117** led to the advanced precursor with the appropriate carbon skeleton. The enantioselectivity was determined after conversion into the acid. Further sulfone removal afforded the valnoctamide precursor in a perfect 99% ee. The main practical advantage of this one-pot methodology is to avoid the isolation of the volatile intermediate, facilitating the process and increasing the overall yield.
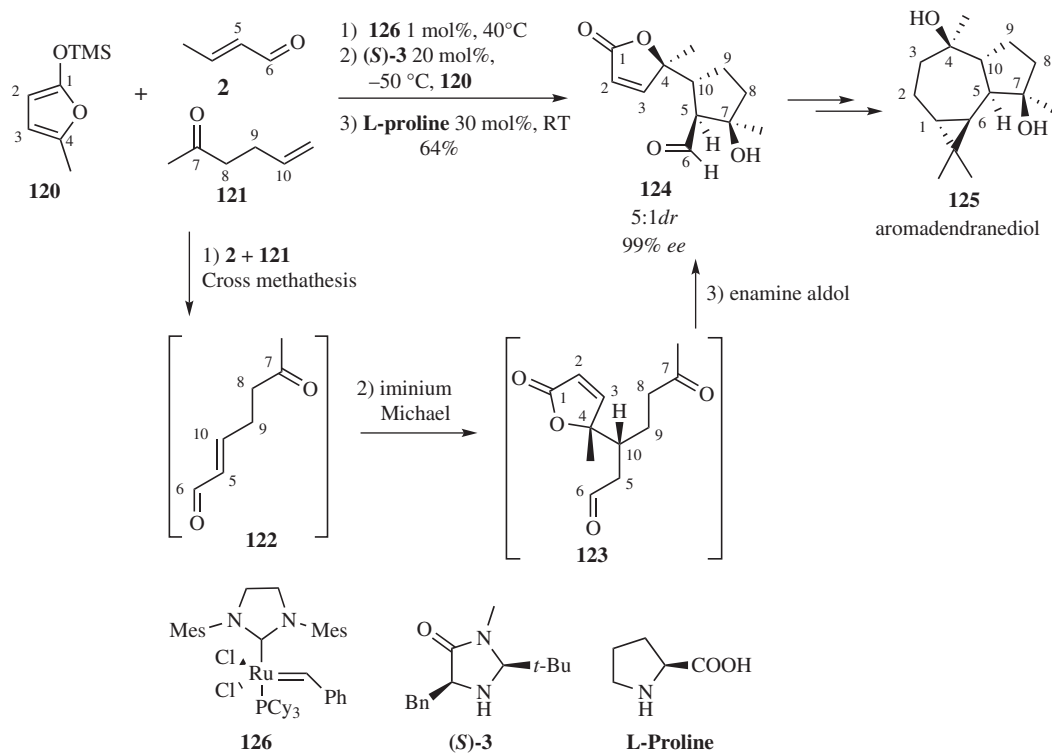
The synthesis of aromadendranediol by MacMillan and co-workers represents another example of the extraordinary compatibility and selectivity of aminocatalytic reactions

(Scheme 11.31).[65] Indeed, in their synthesis of this attractive sesquiterpene isolated from both marine coral *Sinularia mayi* and Amazonian tree *Xylopia brasiliensis*, three different catalytic systems were combined in one pot without decreasing the overall efficiency of the reactions. The catalytic sequence is initiated by cross-metathesis between **2** and **121**. Subsequent addition of **120** and (S)-**3** in the same vessel allows for the asymmetric Michael addition, and further addition of L-proline induces the final intramolecular Michael addition. The efficiency of the sequence is demonstrated by the high stereoselectivity obtained (5 : 1 dr, 99% ee) in the construction of this complex skeleton from readily available starting materials.

Hong and co-workers entirely exploited the ability of amine catalysts to promote cascade reactions by different mechanisms. They applied a one-pot oxa Michael-Michael-Michael-aldol reaction for the synthesis of conicol, a marine terpenoid isolated from *Aplidium conicum* (Scheme 11.32).[66] Using diphenyl prolinol silyl ether **12**,
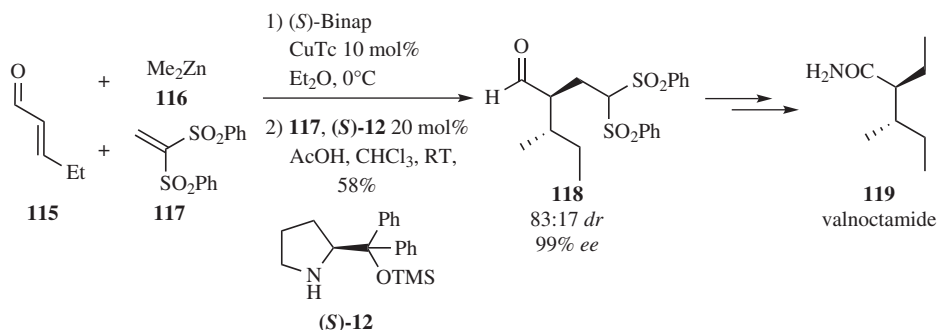
SCHEME 11.30. Quintard and Alexakis's one-pot approach for the synthesis of valnoctamide.

**SCHEME 11.31.** MacMillan et al.'s cascade synthesis of aromadendranediol.
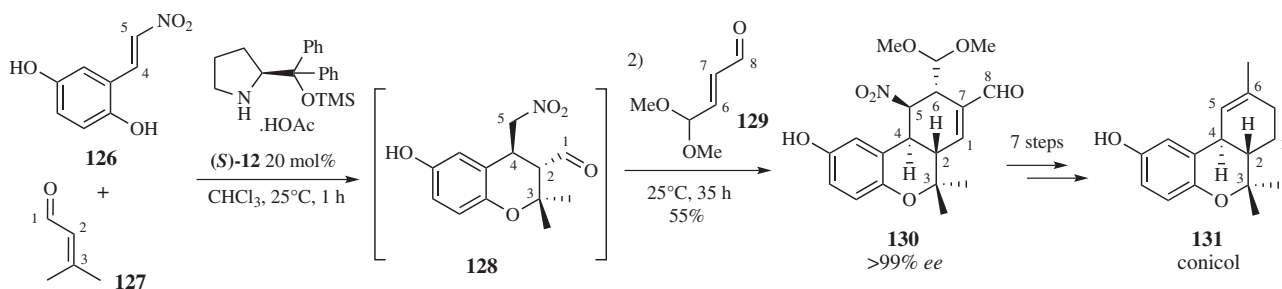
SCHEME 11.32. Hong et al.'s organocascade synthesis of conicol.

α,β-unsaturated aldehyde **127** was activated *via* iminium formation toward an intermolecular oxa-Michael addition of phenol **126**. Subsequent enamine intramolecular addition on the nitroolefin creates the adequate *trans*-relationship at the ring junction of the natural product. At this stage, **129** is directly added to the mixture promoting the second iminium-catalyzed addition of the nitroalkane to **129**, and intramolecular aldol addition-elimination finishes creating the two new rings of the natural product. In this cascade process, four new bonds and four contiguous stereocenters are created in 99% *ee*. This one-pot installation of the three-member ring backbone of conicol clearly demonstrates the efficiency of the amino-catalyzed cascade reaction. Unfortunately, it also indicates the problem of

functional group removal in organocatalyzed Michael addition discussed in the Introduction of this chapter. Indeed, whereas all the prerequisite backbone is installed in one pot, seven steps are needed to remove the different functional groups present on this advanced synthon and to furnish the carbocycle of conicol.

11.8. BIFUNCTIONAL BRØNSTED BASE/ACID CATALYSIS

Organocatalysis is powerful in the sense that several activation modes can be combined in a single catalyst. This is notably the case for Brønsted base and acid catalysts. They
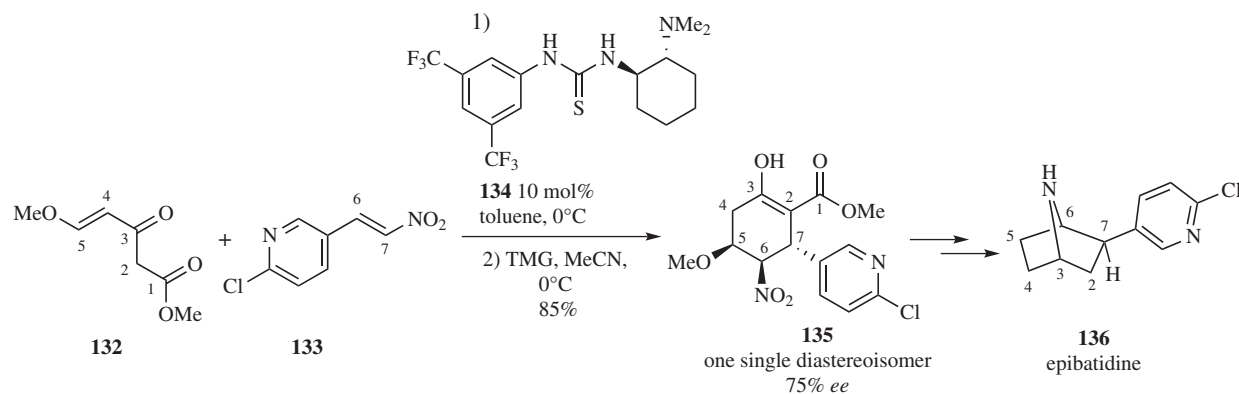
SCHEME 11.33. Addition of keto-ester to nitroolefin toward the synthesis of epibatidine.

are often combined in a single molecule, strongly rigidifying the system and thus enhancing the overall efficiency (reactivity and stereoselectivity). Different catalytic systems have been used applying this dual activation concept. Noteworthy, in contrast to many aminocatalytic processes, the required excess of Michael donor or acceptor necessary in this type of activation can often be reduced, being a great practical advantage.

As for enamine catalysis, the addition to nitroolefins has been extensively studied using this activation principle. This is a result of the high reactivity and versatility of the nitro group. This property was applied by Takemoto et al. in the total synthesis of epibatidine, an alkaloid isolated from the frog *Epibatidores tricolor* (Scheme 11.33). The addition of the keto-ester **132** to nitroolefin **133** catalyzed by bifunctional commercially available catalyst **134** furnishes intermediate Michael adduct.[67] The addition of additional base (tetramethylguanidine) promotes the intramolecular Michael addition-cyclization between positions 7 and 5 creating the six-member ring **135** in 75% *ee*.

The synthesis of esermethole, a precursor of physostigmine, a calabar alkaloid, reported by Barbas III et al. is another example of the addition to nitroolefin catalyzed by a bifunctional catalyst (Scheme 11.34).[68] The key step

consisted in the addition of oxindole **137** to nitroethylene, a substrate prompt to decomposition by polymerization. Performing the reaction in THF at −15°C, again using commercially available **134**, good 65% yield and 96% *ee* of the Michael adduct could be obtained. Transformation of the nitro into amine and subsequent cyclization afforded esermethole.

More recently, the group led by Dixon extended the addition of keto-esters to nitroolefins to the synthesis of the complex nakadomarin A, another marine alkaloid (Scheme 11.35).[69] This example of catalysis on a highly elaborated system further demonstrates the power of this methodology. A combination of the two elaborated fragments **141** and **142**, catalyst **143**, another bifunctional catalyst easily available from cinchona alkaloid, constructed the key fragment **144**. Even though the reaction time is relatively long (8 days), the compound is obtained in a high 91 : 9 *dr*. At this stage, three of the four stereocenters of nakadomarin and the three-ring backbone are created, and just five more steps are needed for the completion of the synthesis. Only a slight excess of Michael donor was required in the key reaction, but because of the long synthesis sequence required for its preparation, this represents a serious limitation to the process. At another time, the experimental procedure required
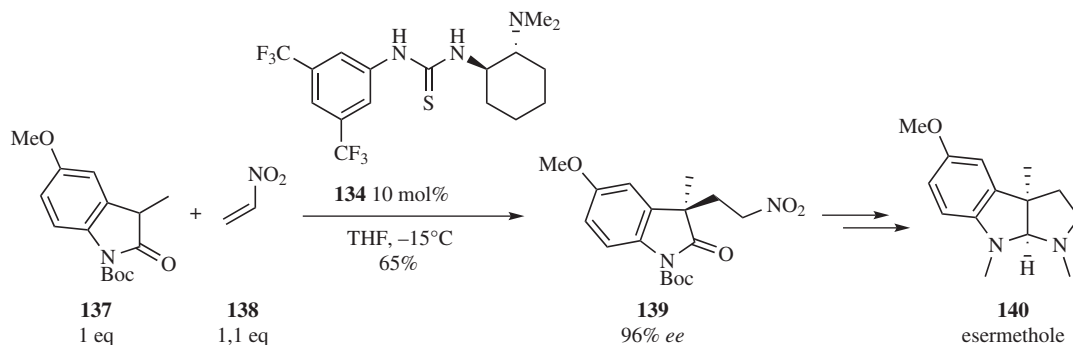
SCHEME 11.34. Barbas et al.'s synthesis of esermethole.
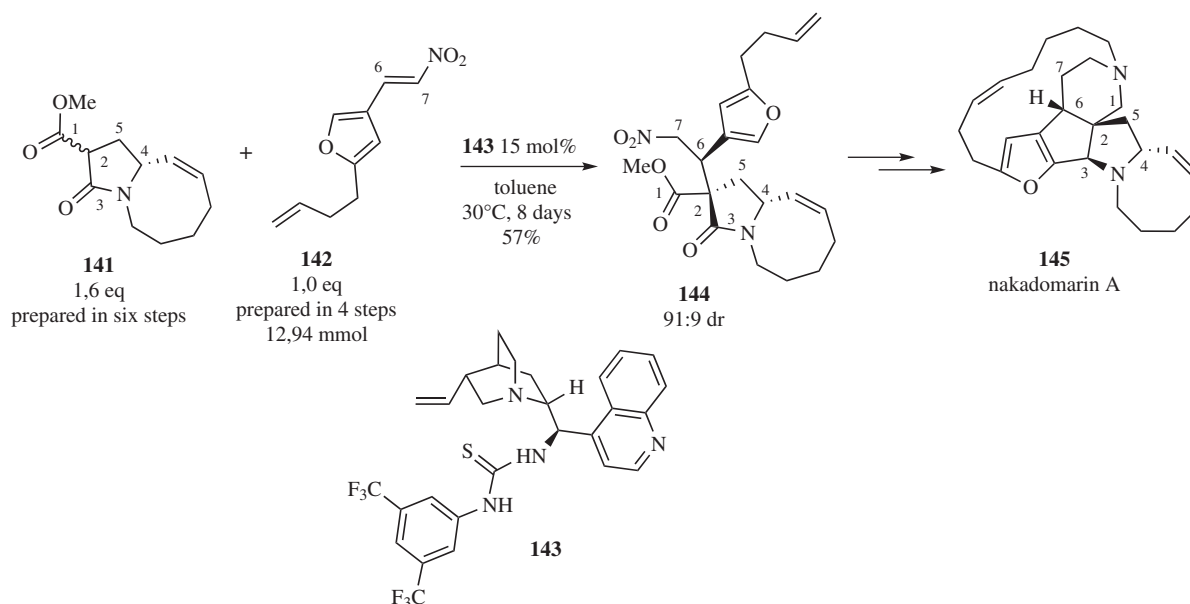
SCHEME 11.35. Dixon group approach to nakadomarin A.

for this key organocatalytic transformations is simplified at a maximum on a relatively large scale.

Synthesis of 144[69]: A solution of **142** (12.94 mmol, 2.5 g), **141** (1.6 equiv, 20.6 mmol, 4.566 g), and **143** (0.15 equiv, 19.4 mmol, 1.061 g) in toluene (39 mL) was stirred at 30°C with exclusion of light. After 8 days, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether: diethyl ether 2 : 1 to 1 : 1) yielding the title compound **144** as a chromatographically inseparable mixture of diastereoisomers (3.05 g, 57%, 91 : 9 *dr*). The *dr* can easily be increased to >99 : 1 by simple recrystallization in ether.

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The Michael donor/acceptor and the catalyst were mixed in toluene, and the resulting solution was stirred at 30°C for

8 days. Solvent evaporation and column chromatography yielded directly the complex synthon **144**.

In 2008, Jørgensen et al. reported on the Michael addition to functionalized nitroolefins for the synthesis of γ-butyrolactone autoregulators, secondary metabolites of the *Streptomyces* species (Scheme 11.36).[70] The key stereogenic center of this family of butyrolactone was achieved *via* the cinchona derivative **148** catalyzed addition of suitable carbonyl donor containing an oxazolidinone such as **146**. This moiety can easily be converted into the lactone by *O*-silyl deprotection-cyclization, affording the *trans*-ring junction. The appropriate stereoselectivity on the alcohol stereogenic center is obtained *via* asymmetric transfer hydrogenation.

In another application of interesting Michael acceptors, Zhu and Lu reported on the addition of nitroalkanes to vinyl
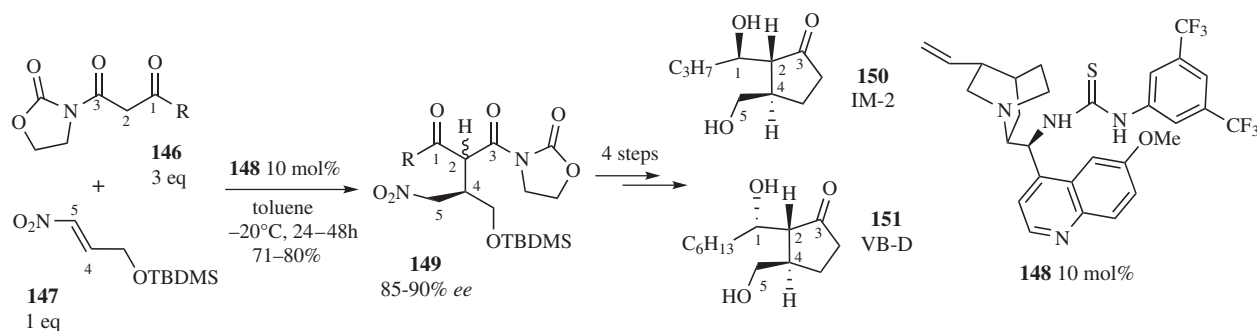
SCHEME 11.36. Addition to functionalized nitroalkene in the synthesis of small bioactive γ-butyrolactone.
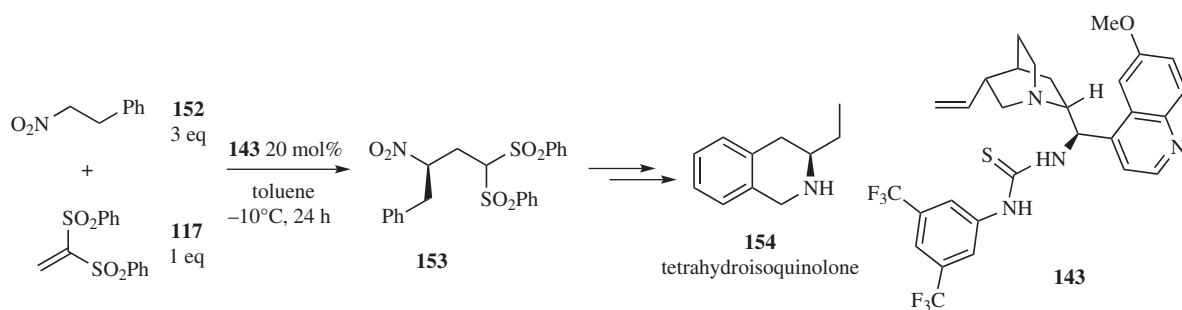
SCHEME 11.37. Nitroalkane addition to 1,1′-vinyl sulfone.
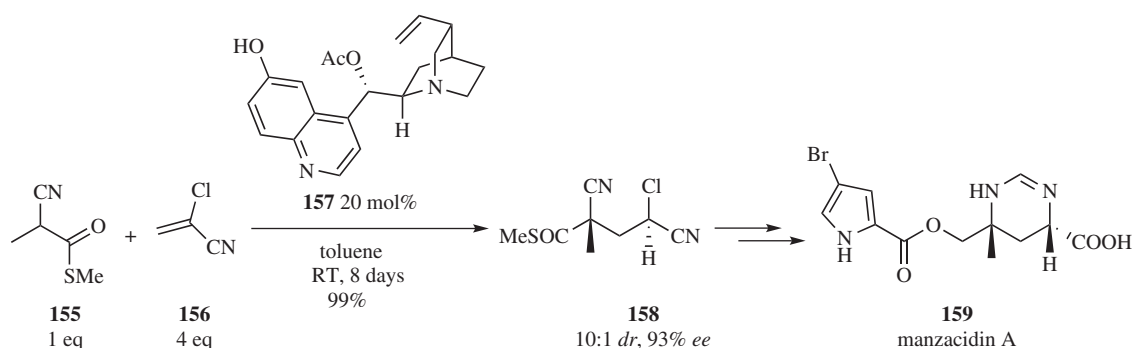
SCHEME 11.38. Deng group synthesis of manzacidin A.

sulfone (Scheme 11.37).[71] Using the highly electrophilic bis-vinyl sulfone **117**, nitroalkane **152** was sufficiently activated to perform the conjugate addition creating the single stereocenter of 1,2,3,4-tetrahydroisoquinoline, an inhibitor of phenylethanolamine *N*-methyltransferase. Removal of the two sulfones under reductive conditions gave the corresponding naked alkyl chain of the bioactive compound.

Manzacidin A is an alkaloid isolated from the Okinawan sponge *Hymeniacidin* sp (Scheme 11.38). The group led by Deng applied the conjugate addition of cyclic cyano-ketone to **156**, a particular Michael acceptor containing a chlorine.[72] Applying cinchona derivative **157**, compound **158** containing four different functional groups was obtained in a good 10 : 1 *dr* and 93% *ee*. Despite the generation of a quaternary stereocenter, the most interesting is the control of the nonadjacent chlorine stereocenter. Because the quaternary stereocenter does not control this particular position, the stereoselectivity is controlled by asymmetric protonation of the transient anion by the cinchona alkaloid. This highlights the potential of this easily available catalyst to govern two different enantiodetermining steps: the Michael addition and the asymmetric protonation, even though a relatively long reaction time was required (8 days).

The Deng group also applied this type of cinchona-based catalyst to the synthesis of tanikolide, a metabolite with antifungal activity of the marine cyanobacterium *Lyngbya*

majuscula (Scheme 11.39).[73] Activation of the keto-ester by the tertiary amine and addition to acrolein creates the new C−C bond controlling the challenging tetra-substituted carbon center of tanikolide with a perfect 99% *ee*. Only 2.5 equivalents of inexpensive acrolein were needed in the reaction despite the well-known tendency of acrolein to polymerize. In addition, compound **162** could be used directly in the next step after simple filtration on a plug of silica.

11.9. PHASE-TRANSFER CATALYSIS

Phase-transfer catalysis was for a long time one of the single organocatalytic fields that had been fully studied and conceptualized, notably, in the late 1990s. This has allowed synthetic chemists to assimilate it more completely and to perform a wide variety of synthetic applications, some of them applying Michael additions. A great advantage of these methodologies is the obvious absence of anhydrous conditions and the high functional group tolerance.

This was exemplified by the early report (1990) by Nerinckx and Vandewalle on the synthesis of podocarp-8(14)-en-13-one, a key precursor of several diterpenes (Scheme 11.40).[74] Deprotonation of **164** in the presence of the phase-transfer catalyst **166**, again a catalyst derived from
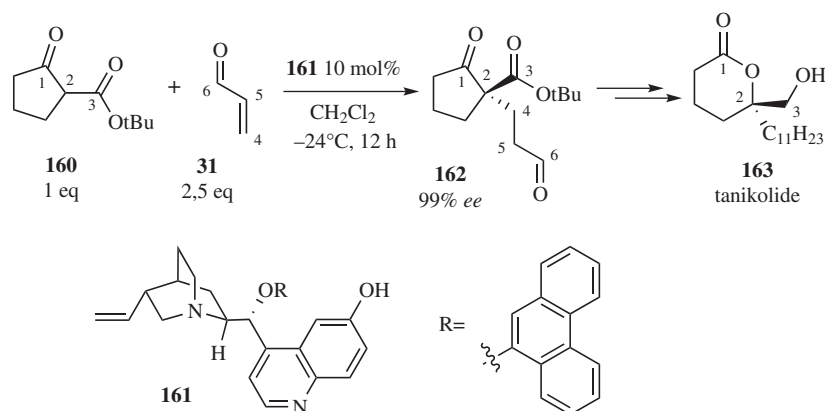
SCHEME 11.39. Keto-ester addition to acrolein for the synthesis of tanikolide.
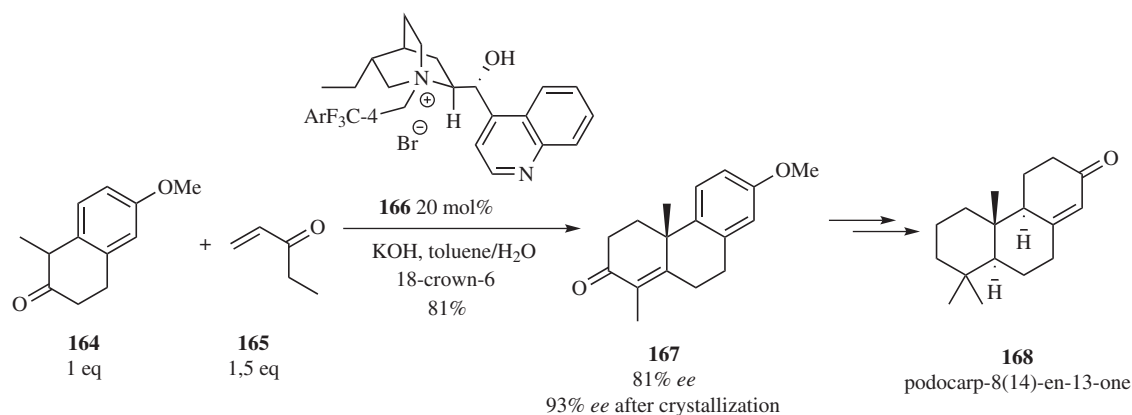
SCHEME 11.40. Early example of PTC in natural product synthesis.

cinchona alkaloid, created a chiral information on the enolate allowing for the asymmetric addition to enone. The result of this Robinson annulation is the formation of tricyclic **167** in 81% *ee*. Simple crystallization of the minor enantiomer in a mixture of hexane/ethyl acetate increased the enantioselectivity of the Michael adduct to 93% *ee*.

Shishido and co-workers extended the same strategy to the synthesis of triptoquinone A in 1994 (Scheme 11.41).[75] Triptoquinone A is an active molecule with potential as treatment for rheumatoid arthritis. Applying the same conditions to the complex ketone **169**, annelated product **170** could be produced on a gram scale in
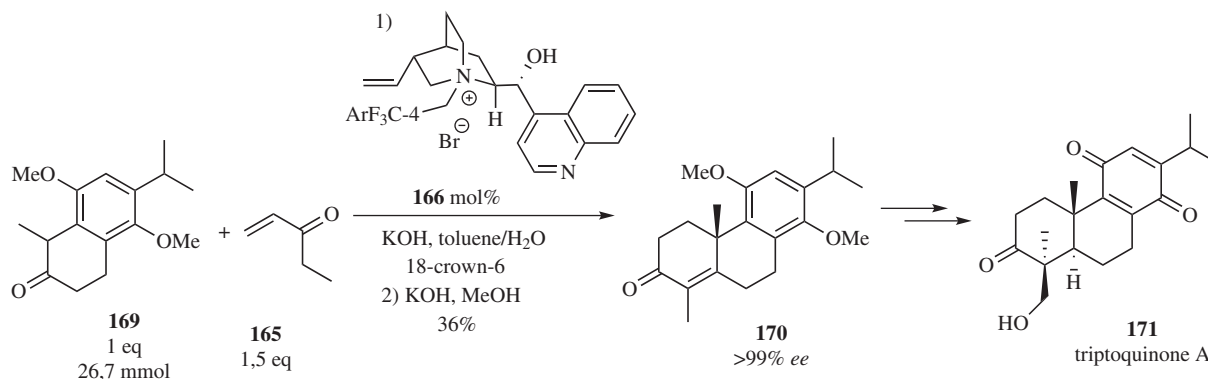
SCHEME 11.41. Annulation strategy toward the synthesis of triptoquinone A.
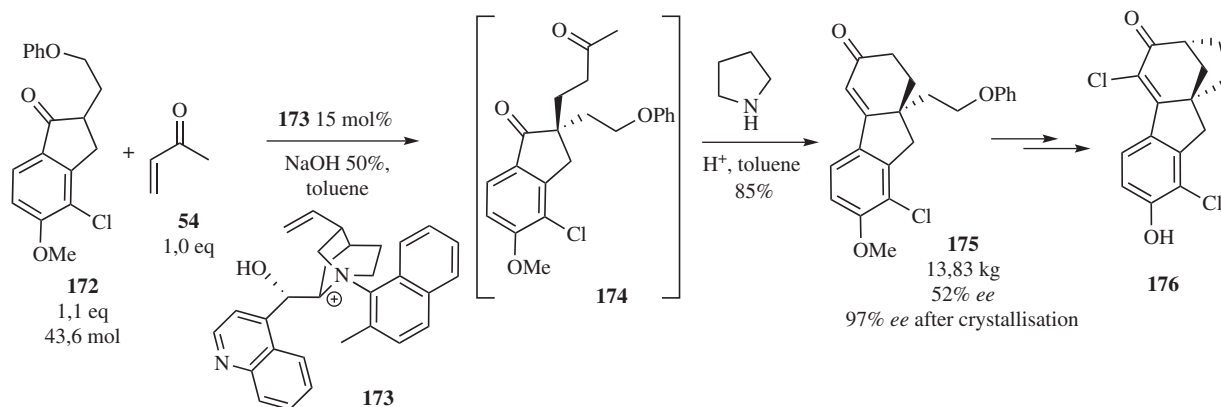
SCHEME 11.42. Kilogram-scale synthesis of 476.

virtually perfect enantioselectivity (>99% ee). The single limitation to this process is the relatively modest yield of cyclized product (20% yield) that could be increased to 36% by cyclizing the remaining Michael adduct thanks to additional base.

The robustness of this Robinson annulation was exploited by chemists at Merck for the kilogram synthesis of an estrogen receptor β-selective agonist **176**, a potential drug candidate (Scheme 11.42).[76] A key feature for the development of this molecule was the discovery of a synthetic route amenable to scaleup. It was found that applying phase-transfer–catalyzed-Robinson annulation to **172**, a molecule containing two ethers and one chloride, the annelated product was obtained on a 13.83-kg scale (85% yield), even though the enantioselectivity remained low (52% ee). After acidic workup, the diketone could be cyclized by using pyrrolidine to give the enone **175** directly. The relative moderate enantiocontrol was not a problem because it could be easily increased to 97% ee by simple crystallization from isopropyl acetate (47% yield of crystallization).

Synthesis of 175[76]: **173** (3.38 kg, 6.56 mol) and indanone **172** (13.8 kg, 43.6 mol) were slurried in toluene (208.9 kg). Sodium hydroxide (50%, 51.5 kg) was then charged, and the batch was aged for 14 hours at 20–25°C. A solution of methyl vinyl ketone **54** (2.75 kg, 39.2 mol) in toluene (26.4 kg) was added at 20°C over 30 minutes at $T < 27$°C. After 15 minutes of aging, a further charge of methyl vinyl ketone **54** (366 g, 5.2 mol) in toluene (3.0 kg) was then made such that high-performance liquid chromatography assay indicated <0.5% unconverted indanone. Water (67.0 kg) was added over 40 minutes such that $T < 30$°C. After allowing the batch to settle, around 90% by weight of the lower aqueous layer was cut. The remaining batch was filtered and washed through with additional toluene (2 × 12.5 kg). The batch was settled, and the remaining aqueous was cut away. The toluene layer was washed successively with 2-M HCl containing MeOH (5.76 kg) followed by water (87.3 kg). The batch was distilled at 45°C to a volume of 167 L and held overnight. AcOH (2.62 kg,

43.6 mol) and pyrrolidine (3.11 kg, 43.6 mol) were then added, and the batch was aged at 85°C for 4 hours. Water (130.9 kg) was charged at 85°C, and the batch was mixed for 10 minutes prior to settling. The lower aqueous was cut away, and the organic was washed with more water (130.9 kg). The aqueous was cut, and the organics were distilled to a volume of 57 L at 45°C. On cooling to 39°C, the batch crystallized, and after formation of a seedbed, heptane (58.5 kg) was added over 20 minutes. After aging a minimum of 1 hour, filtration, washing with heptane (14.9 kg), and drying *in vacuo* at 45°C for 16 hours, afforded 13.83 kg of **175** as a tan solid in 85% yield with 52% ee.

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The addition of diester **178** to cyclic enone was applied by Plaquevent et al. in the synthesis of methyl dihydrojasmonate, a natural ketone with olfactory properties isolated from *Jasminum grandiforum* L (Scheme 11.43).[77] Despite the relatively moderate 80% ee and large excess of dimethyl malonate required (30 equiv), the rapidity of the synthesis (two steps to the natural product) and the simple reaction conditions remained attractive for scaleup.

The addition of other deprotonated nucleophiles to vinyl ketone was further expanded recently to the synthesis of much more complex molecules. In 2006, the group led by Shibasaki reported on the concise synthesis of cylindricine C, a spirocyclic molecule with numerous biological properties isolated from *Clavelina cylindrical* (Scheme 11.44).[78] Glycine Schiff base **182** was found to react efficiently with enone **183**. Catalyst **184** was the most effective for this transformation giving a good 82% ee at −40°C. Noteworthy, the process tolerated numerous functional groups such as the more substituted enone that was kept untouched. Remarkably, compound **185** could be transformed into the tricyclic backbone **186** of cylindricine C by a tandem cyclization in acidic conditions.

Finally, phase-transfer catalysis was also applied in the synthesis of small building blocks such as amino acids by
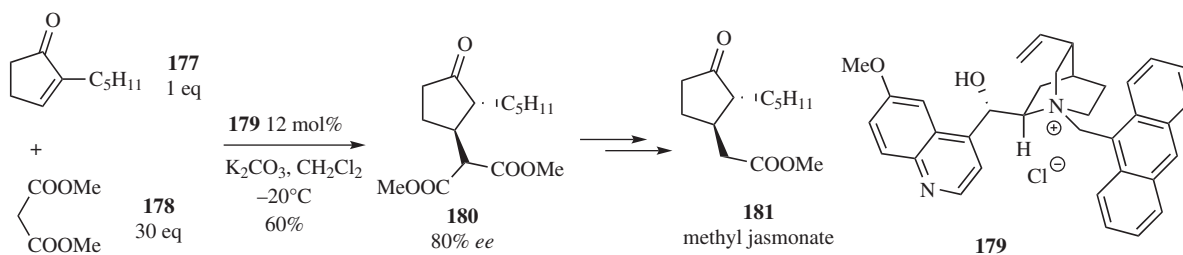
SCHEME 11.43. Plaquevent et al.'s synthesis of methyl jasmonate.
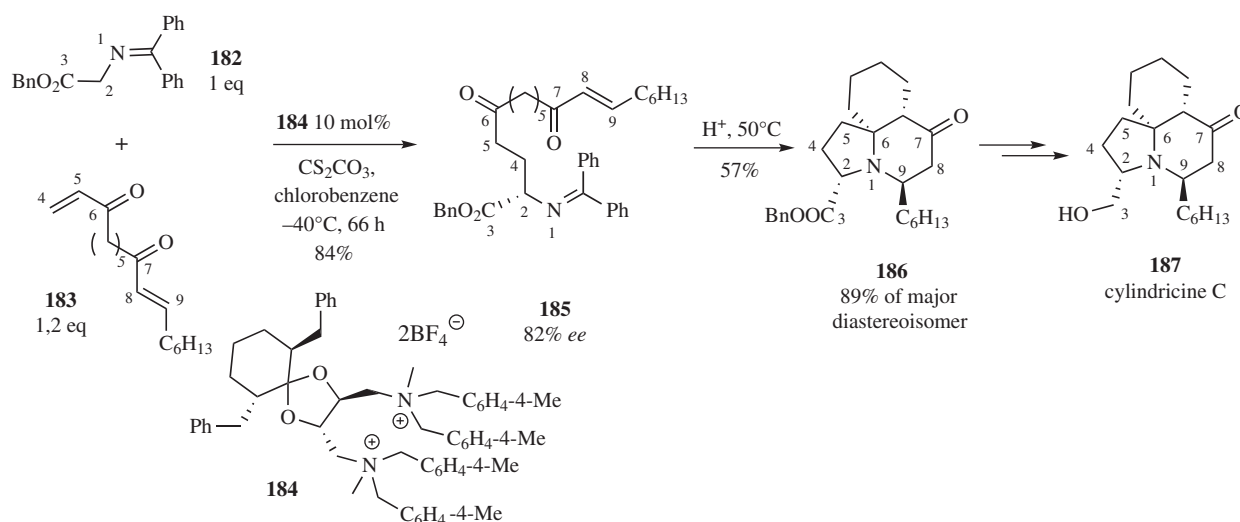
SCHEME 11.44. Shibasaki et al.'s synthesis of cylindricine C.

varying the Michael donor/acceptor combination (Scheme 11.45). The addition of Schiff base to vinyl cyanide furnished the key precursor of ornithine in 91% *ee*.[79] Remarkably, the stereogenic center did not racemize under the reaction conditions, despite the high acidity of the proton of the chiral center.

Another type of phase-transfer catalyst based on binaphtyl quaternary ammonium salt such as **194** could be used in the creation of amino acid bearing a tetrasubstituted stereocenter.[80] Up to 97% *ee* could be obtained for the generation of glutamic acid analog **196**, an excitatory neurotransmitter.

## 11.10. *N*-HETEREOCYCLIC CARBENES CATALYSIS

The organocatalysis using NHC is by far less studied than the other organocatalytic areas despite its inherent interest, notably, in applying aldehydes in an umpolung manner. This fact is reflected in the poor number of catalysts able

to give high enantioselectivities in these reactions. Thanks to the increasing interest of different research groups on the subject, this current limitation should be overcome in the future.

One of the pioneering applications of *N*-heterocyclic carbene (NHC) organocatalysts in the view of synthesizing natural products is the application by Orellana and Rovis of a Stetter reaction to construct the spirocyclic core of the antibiotic FD-838 (Scheme 11.46).[81] Applying the triazole NHC precursor and activating the catalyst with 20 mol% of potassium 1,1,1,3,3,3-hexamethyldisilazide [potassium bis (trimethylsilyl)amide] (KHMDS), compound **197** underwent the Stetter reaction in a perfect 99% *ee*. This simplified skeleton of the bioactive molecule was one of the first examples applying the great power of NHC catalysis toward natural product synthesis.

Synthesis of 199[81]**:** To a cooled 0°C solution of triazolium precatalyst **198** (20 mol%, 16 mg, 0.034 mg) in 2-mL toluene under positive argon pressure is added, dropwise *via* a cannula, a freshly prepared, cooled 0°C solution of KHMDS
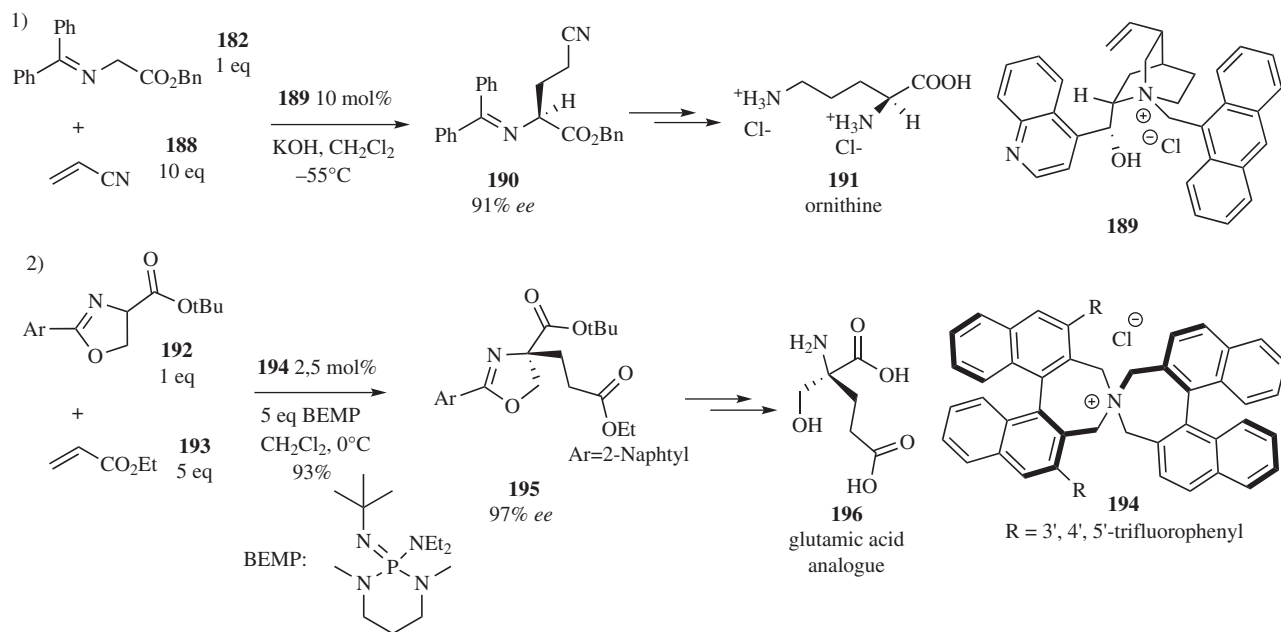
SCHEME 11.45. PTC synthesis of enantioenriched amino acids.
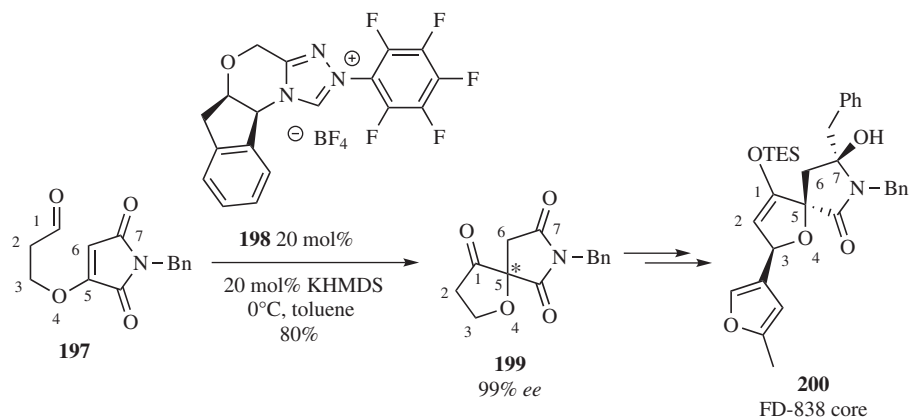
SCHEME 11.46. Orellana and Rovis's pioneering approach toward the synthesis of the FD-838 core structure.

(20 mol%, 220 μL of a 0.016-M solution) in toluene. After this mixture has been stirred for 10 minutes, a cooled 0°C solution of **197** (45 mg, 0.17 mmol) in toluene was added *via* cannula. The consumption of aldehyde **197** was monitored by TLC. After completion, the mixture was filtered through a pad of silica gel to remove the solids and eluted with ethyl acetate. The collected fractions were concentrated *in vacuo*, and the resulting oil was purified by flash chromatography using 1 : 1 hexanes/EtOAc to yield **199** (36 mg, 0.27 mmol, 80% yield).

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More recently, the group led by Glorius reported on an intermolecular Stetter reaction for the synthesis of FCE28833, a kynurenine 3-hydroxylase inhibitor (Scheme 11.47).[82] Applying a triazole from the same family as **198**, the key precursor could be obtained in 94% *ee* and transformed in one step into FCE28833. In contrast to classic Stetter reactions, the origin of the stereoselectivity is much more complex. Indeed, the 1,4 addition leads to a chiral transient alcohol. This transient alcohol can stereoselectively transfer its hydrogen to the transient enolate, creating the amino-ester stereogenic center.
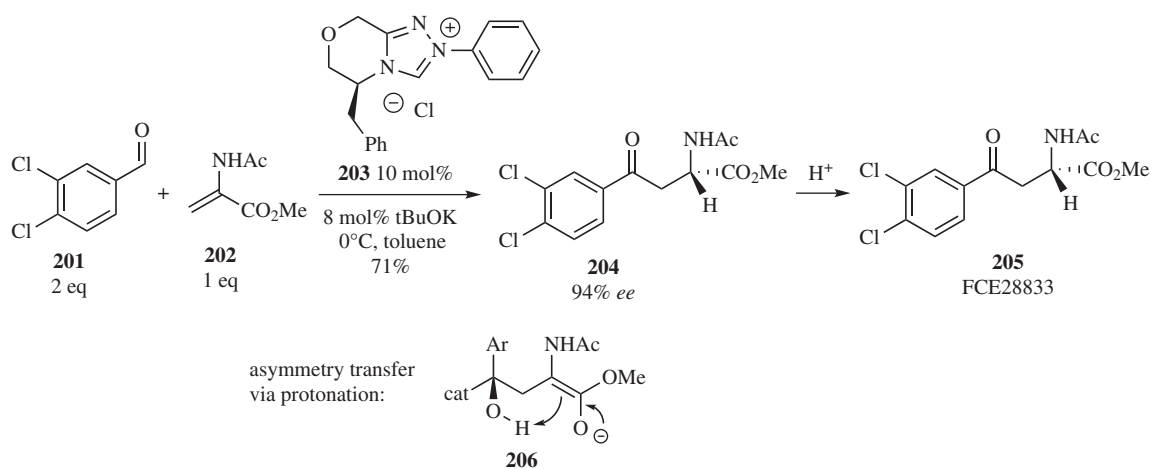
SCHEME 11.47. Glorius et al.'s synthesis of FCE28833.

11.11. CONCLUSION

In conclusion, organocatalyzed Michael additions have recently proven their great potential in total synthesis, and they have been allowed to enter the synthetic community. The impressive diversity of possible structures obtained applying these strategies is a result of the wide variety of possible electron-withdrawing groups present on both Michael donors and acceptors. Thanks to the multiple possibilities of constructing highly functionalized molecules offered, the newly developed methodologies have found applications from the construction of simple drugs to highly complex natural products.

Preliminary applications on a large scale are highly promising, and it seems obvious that these types of reactions should readily find their place in industry in the next few years. To finish demonstrating the utility of the developed methodologies, more examples applying organocatalytic Michael additions at the late stage of a long sequence of total synthesis should be discovered. We are confident that an increasing number of such applications will be discovered and that these processes will definitely enter the toolbox of organic synthesis leading to new innovative synthetic disconnections.

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