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Organocatalytic Michael and Friedel – Crafts reactions in enantioselective synthesis of biologically active compounds †

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Abstract. Recent applications of organocatalytic Michael and Friedel – Crafts reactions in enantioselective synthesis of biologically active compounds: natural products, pharmaceutical agents and plant protection agents are reviewed. The key mechanisms of stereoinduction, types of organocatalysts and reagents used in these reactions are considered. The material is classified according to the type of newly formed bonds incorporating the asymmetric carbon atom, and the information for the most numerous C – C coupling reactions is systematized according to the natures of the electrophile and the nucleophile. The bibliography includes 433 references.

I. Introduction

Most of organic compounds that play a key role in living systems (amino acids, proteins, carbohydrates, hormones, nucleic acids, *etc*.) contain asymmetric carbon atoms. The chirality in living nature is of essential sense: it considerably increases the accuracy of transfer of biological information, as the receptor molecules, which themselves have chiral centres, recognize only one enantiomer of the substrate.[1 – 5] As a consequence, two enantiomers of a chiral compound (including a natural one), which have the same chemical properties in an achiral environment, behave as two different compounds when in contact with chiral receptors *in vivo*. As applied to pharmacology and medicine, this means that out of two optical isomers of a pharmaceutical drug, only one exhibits, most often, high biological activity, whereas the second one is at best less active, while at worst it may be harmful for the organism (Fig. 1).[6] According to the guidelines governing the development of new chiral drugs enacted in 1992 in the USA [see *FDA's Policy Statement for the Development of New Stereoisomeric Drugs. Chirality*, **4**, 338 (1992)] and in 1993 in the EU,[7] each new drug can be produced as a racemate only provided that it was proved that neither of the enantiomers exhibits undesirable side effects.

Currently, the major part of enantiomerically pure drugs are isolated from plants or synthesized artificially using natural compounds as sources of chiral fragments.[6, 8] However, a more rational way of synthesis is asymmetric catalysis, which allows transforming achiral compounds into chiral products using a small amount of a chiral catalyst. In nature, these catalysts are represented by enzymes. In organic chemistry, the notion 'asymmetric catalysis' was usually associated with the catalysis by metal complexes with chiral ligands;[9, 10] however, relatively recently chemists realized the enormous potential opened up by use of metal-free low-molecular-mass chiral organic compounds composed of only C, H, O, N, P or S atoms as the catalysts. This type of asymmetric catalysis vigorously developing in the last decade was called organocatalysis.[11 – 13] In view of the similarity of the mechanisms of catalytic action of some types of organocatalysts and enzymes, organocatalysts are considered as artificial analogues (models) of biocatalysts, in particular, aldolases, decarboxylases and some other.[14 – 16] In addition, metal-free organocatalysts attract pharmacologists by the fact that they rule out the risk of drug contamination by metals (which are often toxic).[17, 18]

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† Dedicated to Academician O M Nefedov on the occasion of his 80th birthday.

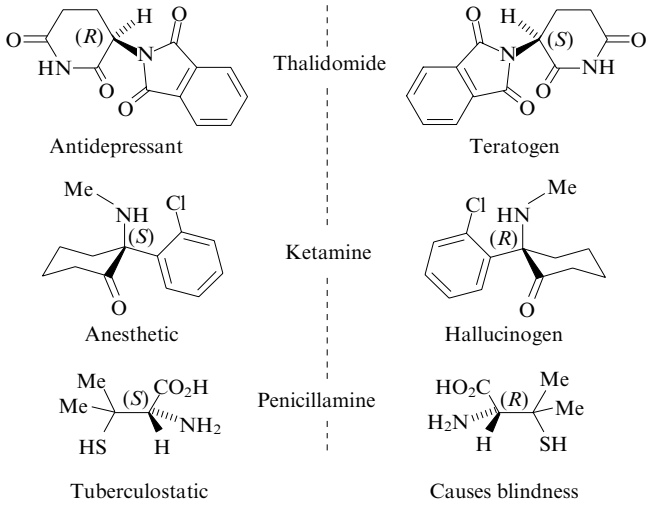


Figure 1. Various biological activities of enantiomers.

Impressive results were achieved, in particular, by the use of organocatalysts in the addition of nucleophiles to electron-deficient alkenes (Michael and Friedel–Crafts reactions), which is among the most effective methods for the formation of carbon–carbon and carbon–heteroatom bonds in organic compounds.[12,19–22] The trend of development of asymmetric organocatalysis as a whole and as applied to the addition reactions to electron-deficient alkenes is illustrated by the number of publications, which has increased by a large factor during the last decade (Fig. 2).

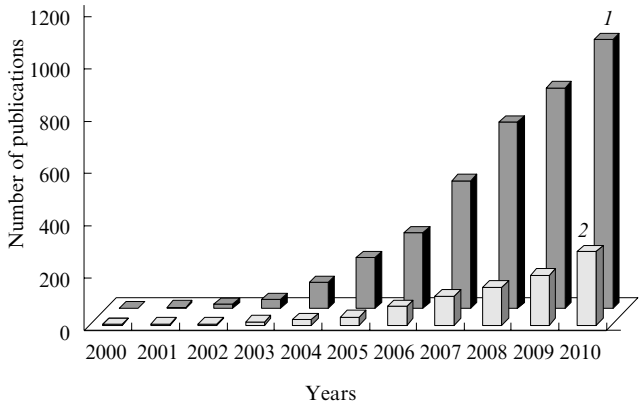


Figure 2. Growth of the number of publications on the asymmetric organocatalysis (*1*) and asymmetric organocatalytic Michael and Friedel–Crafts reactions (*2*).

The conduction of the Michael reactions and related Friedel–Crafts reactions involving activated arenes in the presence of chiral organocatalysts markedly extended the scope of enantioselective preparation of analogues of natural products and biologically active compounds. It became possible to increase the yield and/or the enantiomeric excess of the products and to synthesize some compounds that cannot be prepared using metal complex catalysis. Certain aspects of application of the organocatalytic Michael reaction in the synthesis of natural compounds were recently reviewed.[17,18,23] However, in these reviews, the information is classified according to the reaction mechanisms. This structure, which is justified from the standpoint of classical chemistry, is not very convenient for the specialists engaged in the synthesis of natural compounds and biologically active compounds, because it is rather difficult to find information about the known methods of synthesis of the desired compound and/or structural fragments it contains.

This review, which covers data on the synthesis of chiral pharmaceutical drugs and natural compounds that are of interest for pharmacology based on the Michael reaction in the presence of organocatalysts published before February 2011, differs from the earlier reviews by more extensive coverage of the published data and by the fact that these data were systematized for the first time according to the type of the formed bond (C–C, C–N, C–O, *etc.*) giving rise to the asymmetric carbon atom and also, for most numerous C–C-coupling reactions, according to the nature of the electrophile and nucleophile. As a rule, we do not give the detailed chart of the preparation of the target biologically active compounds, reader's attention being mainly drawn to the key, catalytic, step of the multistep synthesis which determines the configuration of the chiral centre (chiral centres). In order to restrict the size of the review, we excluded a considerable portion of information concerning the domino reactions containing an asymmetric 1,4-conjugated addition step and also concerning the use of the Michael reaction in the synthesis of compounds with no proven biological activity.

The description of the main body of information is preceded by brief analysis of the key types of organocatalysts used in asymmetric Michael reactions, description of the ways the starting compounds are activated by the catalysts and the stereodifferentiation mechanisms involved.

II. Organocatalysts for asymmetric Michael and Friedel–Crafts reactions

From the energy standpoint, the chiral organic catalysts used in the asymmetric 1,4-conjugated addition can be divided into three groups (Fig. 3). The catalysts of the first group (Fig. 3 *a*) activate one of the reactants (either nucleophile or electrophile) through weak (< 30 kJ mol^{-1}) but fairly efficient interactions, resulting in the formation of ion pairs **a** or hydrogen-bonded associates **b** or **c**.[24–26] The catalysts of the second group (Fig. 3 *b*) interact with carbonyl compounds to form enamine ($\mathbf{d}_{en}$)[12] or iminium ($\mathbf{d}_{im}$)[27] intermediates through covalent bonds having much greater energy (usually > 150 kJ mol^{-1}). As a consequence, the frontier orbital energies of the reactants (HOMO of the nucleophile and/or LUMO of the electrophile) change so as to decrease the activation barrier of the reactions in which they take part. The catalysts of the third group (Fig. 3 *c*) activate both reactants by forming hydrogen bonds (associate **e**) or both covalent and hydrogen bonds (complex **f**) with them (bifunctional catalysis).[28,29]

Stereoinduction is caused by a combination of valence, hydrogen, ionic, $\pi-\pi$, van der Waals, *etc.* interactions with the substrates, specific for each type of catalysts, which ensure the three-point fixation of reactants needed for enantiomeric differentiation. Organocatalysts $\mathbf{a}_1-\mathbf{a}_3$ containing the tetraalkylammonium cations form, with

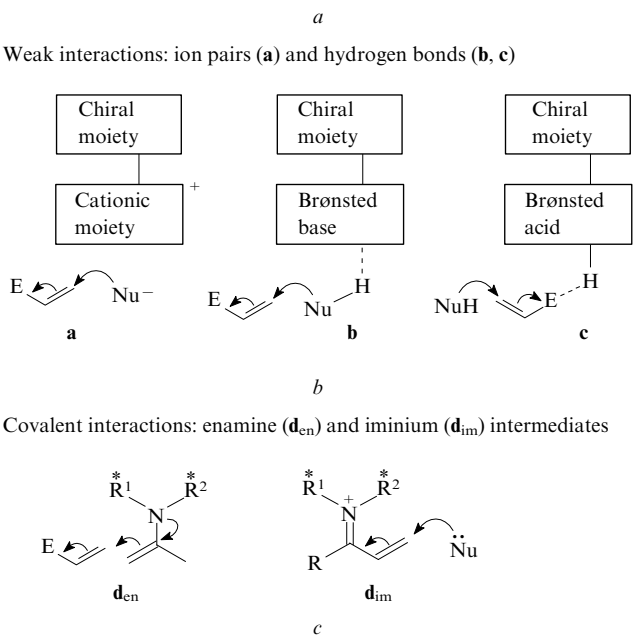


Figure 3. Ways of organocatalytic activation of reactants; (*a*–*c*) are three types of organocatalysts (see the text); E is electrophile, Nu is nucleophile, the asterisk marks chiral groups.

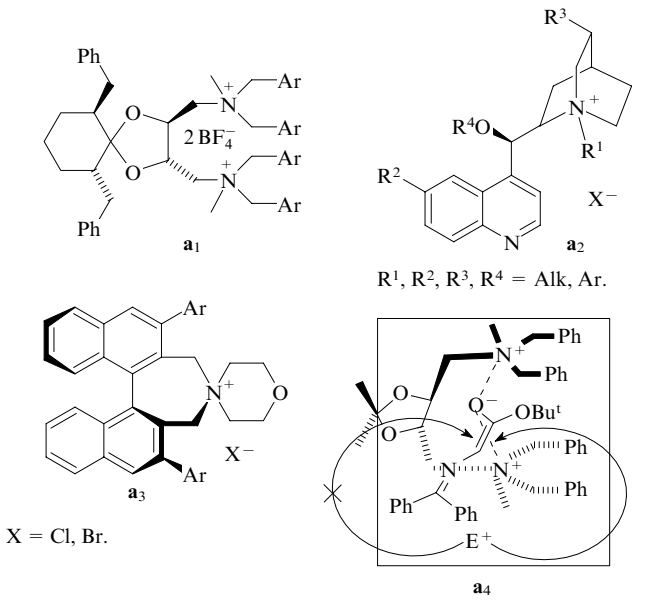


Figure 4. Catalysts activating reagents forming ion pairs ($\mathbf{a}_1$–$\mathbf{a}_3$) and typical example of this type of stereoinduction ($\mathbf{a}_4$).

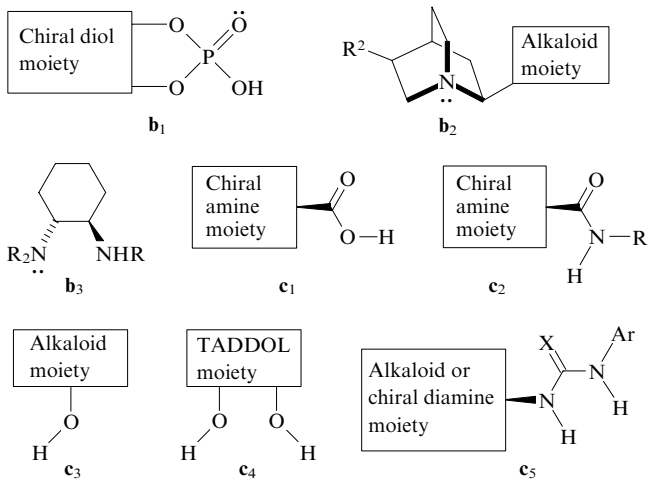


Figure 5. Types of organocatalysts participating in hydrogen bonding processes with reactants as H-acceptors (**b**) and H-donors (**c**).

C-nucleophiles, chiral contact ion pairs (Fig. 4).[30–33] These catalysts perform several functions during the reaction: they activate the carbanion through ion–ion interaction, deliver it to the reaction zone (phase transfer catalysis) and create the spatial organization of the transition state that enables effective reaction between the nucleophile and the electrophile, using only one of the two non-equivalent lobes of the orbital involved in the reaction (complex $\mathbf{a}_4$).[32]

The hydrogen bonds between the catalyst and the reactants play an exceptionally important role in the asymmetric organocatalysis,[34–36] the catalyst being able to function as proton acceptor and/or donor (Fig. 5). In the reactions considered, protons are usually accept by organocatalysts of type $\mathbf{b}_1$ based on phosphoric acid esters with chiral diols[37] or by tertiary amine derivatives $\mathbf{b}_2$ (Refs 38, 39) and $\mathbf{b}_3$.[40] Proton donors are usually derivatives of chiral amino acids (most often, α-amino acids) $\mathbf{c}_1$,[41,42] their amides $\mathbf{c}_2$,[43] hydroxyl-containing alkaloids of the quinuclidine type $\mathbf{c}_3$,[44] TADDOL derivatives (TADDOL is α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) $\mathbf{c}_4$,[45] chiral compounds $\mathbf{c}_5$ containing thiourea or (more rarely) urea group,[34,40,46,47] and some other catalysts. This classification is rather arbitrary: phosphates $\mathbf{b}_1$[37] and amino acid derivatives $\mathbf{c}_1$ and $\mathbf{c}_2$, which are amphoteric, behave as Brønsted bases and/or acids depending on the conditions.[35]

Organocatalysts containing a primary or secondary amino group at the chiral carbon atom and a bulky substituent (substituents) in the α position to this atom (α-amino acids,[12,22,27,42] prolinol[48] and imidazolidin-4-one[49] derivatives and other chiral amines) form enamines[12,22,50] or iminium cations[19,22,27,51] with the carbonyl compounds involved in the reaction (Fig. 6, compounds $\mathbf{d}_1$–$\mathbf{d}_5$). This gives chiral transition states of types $\mathbf{d}_6$[50,52–54] or $\mathbf{d}_7$,[51,55] $\mathbf{d}_8$[51,56] in which the bulky catalyst moiety makes the most remote trajectory of attack of the second reactant (electrophile in the case of enamine or nucleophile in the case of the iminium cation) energetically favourable.

The majority of the most efficient modern organocatalysts are bifunctional compounds.[34,40,46,57–60] One func-

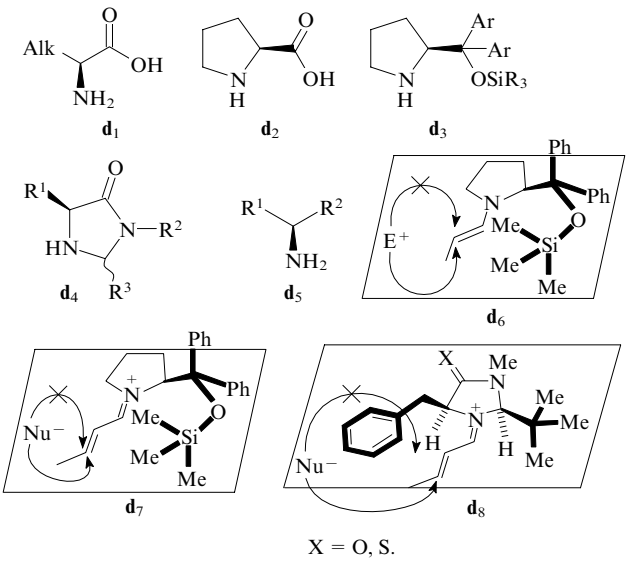


Figure 6. Types of organocatalysts activating the reactants through the formation of enamines and iminium cations and the relevant stereoinduction patterns.

tional group activates the first reactant and the other activates the second reactant using weak interactions (**e**) or a combination of strong and weak interactions (**f**) (see Fig. 3). This, fairly efficient way of activation not only considerably reduces the energy of the transition state of the reaction but also serves as an important stereodifferentiating factor promoting the formation of the required architecture of the activated complex and, hence, bringing about high stereo- and enantioselectivity characteristics of the reactions (for self-association in organocatalysis, see, for example, Refs 47 and 61).

The BINOL-derived hydrogen phosphates (BINOL is 1,1′-binaphthyl-2,2′-diol) (associate $\mathbf{e}_1$)[37,62] and alkaloid- (associates $\mathbf{e}_2$ and $\mathbf{e}_3$)[28,39,59] and tertiary amine-based organocatalysts (associates $\mathbf{e}_4-\mathbf{e}_5$),[34,38–40,46,47] in particular those containing thiourea or (more rarely) urea group (associates $\mathbf{e}_4$ and $\mathbf{e}_5$) belong to the bifunctional catalysts that use weak interactions (Fig. 7). The BINOL phosphates form hydrogen bonds with the reactants one of which is Brønsted acid and the other of which is Brønsted base; their spatial proximity in associate $\mathbf{e}_1$ and the structure of the binaphthyl fragment provide the stereochemical outcome of the reaction.[37,62] A number of the quinuclidine deruved catalysts contain a hydroxy group which is capable of hydrogen-bonding to the basic fragment of the substrate and the bridgehead nitrogen atom activating the nucleophile.[44,63] In the associate $\mathbf{e}_2$ thus formed, the nucleophile attacks the Michael acceptor mainly from the side of the tertiary nitrogen atom of the catalyst, as otherwise it is impossible to attain the simultaneous activation of both the substrate and the reagent.[44,63–65] An important role in the stereodiscrimination may be played by the quinoline moiety of the alkaloid. In some cases, for example, in associate $\mathbf{e}_3$, it is associated with the aryl ring of the Michael acceptor through $\pi-\pi$ interactions and blocks one of the possible sites of the nucleophilic attack.[66] The chiral thiourea 1,2-diaminocyclohexane derivatives (Takemoto catalysts) are widely used in the Michael reactions involving nitro compounds and some other compounds containing π-donor functional groups. The thiourea moiety of these catalysts activates the substrate (Michael donor or acceptor) by hydrogen bonding to its oxygen-containing group, while the amino group in position 2 of the cyclohexane ring fixes the second component by lending the electron pair to the electrophile (associate $\mathbf{e}_4$) or by accepting a proton from the nucleophile (associate $\mathbf{e}_5$), which determines the transition state geometry and the energetically favourable stereodirection of the reaction.[67–72]

The type **f** bifunctional catalysts, which activate the reactants by a combination of weak and strong interactions, are represented by chiral derivatives of prolinamide,[73] pyrrolidine (for example, pyrrolidin-2-yltetrazole[74]) and some other compounds (Fig. 8, compounds $\mathbf{f}_1-\mathbf{f}_3$). These catalysts, like type **d** catalysts, activate the carbonyl-containing reagent by forming with it an enamine or iminium cation involving the pyrrolidine nitrogen atom. Simultane-

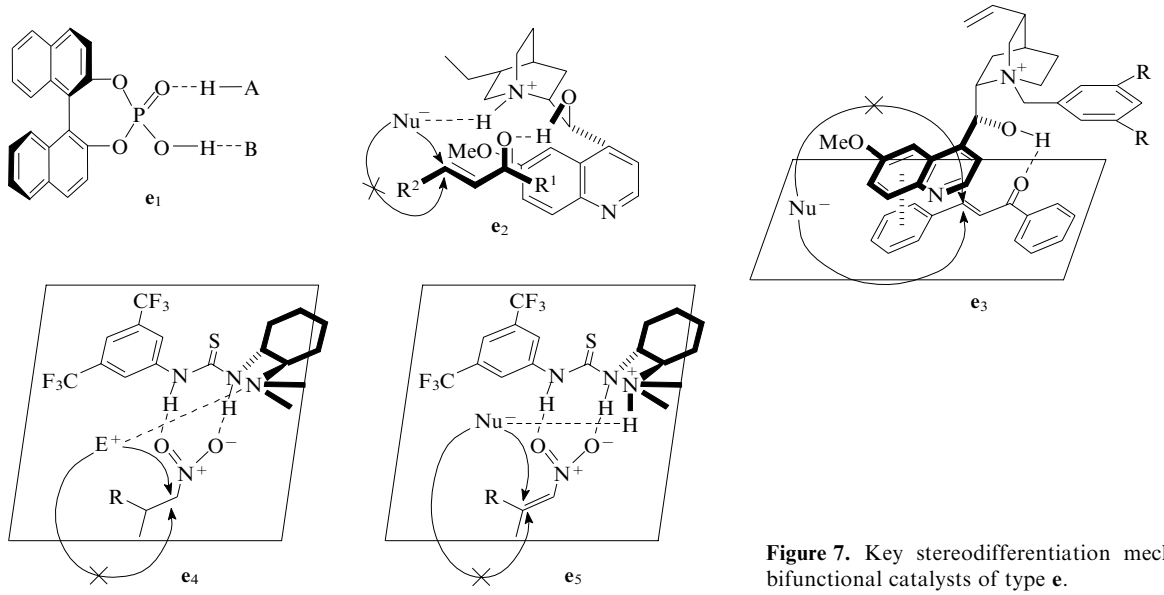


Figure 7. Key stereodifferentiation mechanisms with bifunctional catalysts of type **e**.

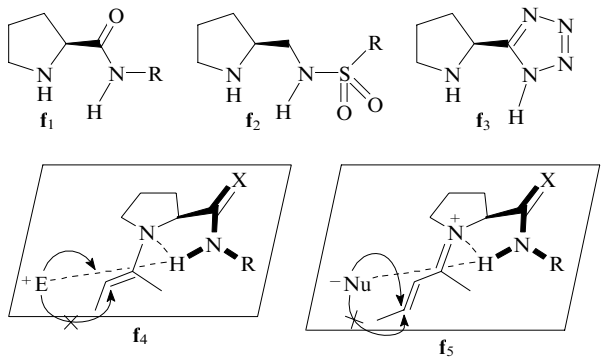
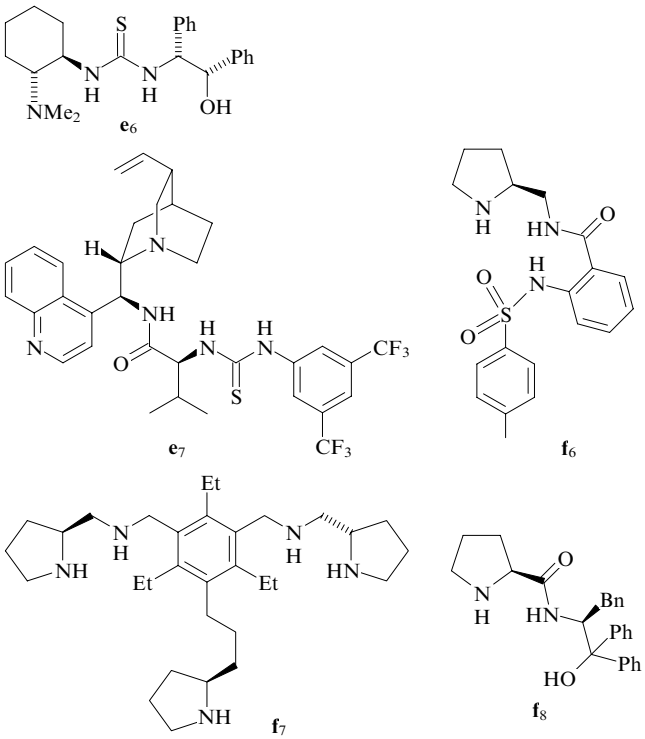


Figure 8. Examples of organocatalysts activating the reactants by combination of weak and strong interactions and the relevant stereoinduction patterns.

ously they fix in space the second reactant (see Fig. 8, electrophile in associate $\mathbf{f}_4$ or nucleophile in associate $\mathbf{f}_5$) by being hydrogen bonded to the 2-substituent in the pyrrolidine ring and thus provide the stereochemical outcome of the reaction.

In recent years, multifunctional catalysts that perform more complex reactant activation pathways have been obtained. Examples of such catalysts are compounds $\mathbf{e}_6$, $\mathbf{e}_7$ capable of multicentre hydrogen bonding to the reactants [75,76] and compounds $\mathbf{f}_6$–$\mathbf{f}_8$, which form activated complexes with the reactants involving covalent (enamine) and several hydrogen bonds.[77–79] The use of these catalysts makes it possible in some cases (not always) to increase the rates and enantioselectivity of the reactions they catalyze as compared with the structurally simpler catalysts considered above.

Particular examples of reactions using type **a**–**f** catalysts are presented in Sections III and IV of the review with references to the relevant Figures in Section II.



III. Asymmetric formation of carbon–carbon bonds

A majority of asymmetric 1,4-conjugated addition reactions in the presence of organocatalysts, including those used in the key steps of the synthesis of chiral biologically active compounds, are reactions of activated alkenes with C-nucleophiles giving rise to a carbon–carbon bond where one or both carbon atoms are chiral. These reactions can be conveniently classified into sections according to the types of electrophiles (α,β-unsaturated aldehydes, α,β-unsaturated ketones, α-nitroalkenes and alkenes activated by other electron-withdrawing substituents), as the catalysts used to perform these reactions and the ways of organocatalytic activation are as a rule different. Thus the Michael reactions involving α,β-enals are usually carried out in the presence of *O*-trialkyl(aryl)-α,α-diarylprolinols [48] and imidazolidin-4-ones, the reactions of α,β-enones are best catalyzed by *O*-methyl-α,α-diphenylprolinol,[54] proline [80] and its derivatives,[81] and the additions of C-nucleophiles to other electron-deficient alkenes are often performed with catalysts containing a thiourea moiety.[34,46,47,58] Within each Section, the material is arranged according to the type of atoms bonded to the active carbon atom of the nucleophile in the sequence: carbon, nitrogen, oxygen, sulfur. In some cases, the same biologically active compounds can be synthesized by different routes; therefore, whenever necessary we will refer the reader to other Sections of this review to compare the efficiency of the methods.

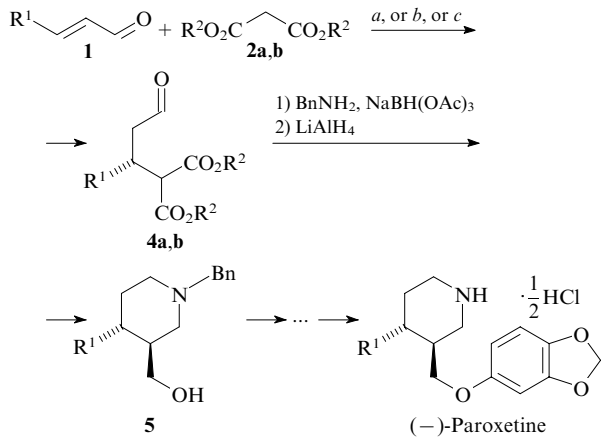
1. Reactions of C-nucleophiles with α,β-unsaturated aldehydes

The asymmetric 1,4-conjugated addition of C-nucleophiles to α,β-enals in the presence of organocatalysts is widely used for the formation of a chiral centre in β and/or γ positions to the aldehyde group. The mechanism of the asymmetric catalysis of these reactions usually includes reversible addition of the catalyst to the aldehyde group of the enal to give highly electrophilic iminium cation (see Fig. 6, transition states $\mathbf{d}_7$ and $\mathbf{d}_8$), which then reacts with the nucleophile. This reaction is possible for α,β-enals of the aliphatic and aromatic (heteroaromatic) series and for a broad range of C-nucleophiles, including various carbon acids, enol ethers (Mukaiyama–Michael reaction), electron-donating arenes and heterocycles (Friedel–Crafts reaction). Then, the aldehyde group in the addition products can be selectively converted to other functional and pharmacophore groups with retention of the chiral centre (centres).

a. Reactions of α,β-enals with malonic and acetoacetic acid derivatives

The antidepressant drug paroxetine,[82–84] one of the most efficient serotonin reuptake inhibitors, was first obtained by the organocatalytic route in 2006 by the Jørgensen group [85] as the product of a six-step synthesis. The key chiral centre of the molecule was formed *via* the Michael reaction between 4-fluorocinnamic aldehyde (**1**) and dibenzyl malonate (**2a**) in the presence of organocatalyst (*S*)-**3**. The resulting Michael adduct **4a** was successively treated with $BnNH_2$, $NaBH(OAc)_3$ and $LiAlH_4$ to give piperidine **5** (yield 60%, 2 steps), which was then (in 3 steps) converted to the desired (−)-paroxetine (Scheme 1,

Scheme 1



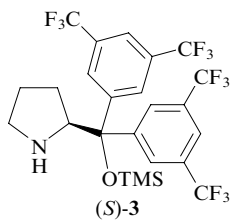
R^1 = 4-FC_6H_4; R^2 = Bn (**a**), Me (**b**).

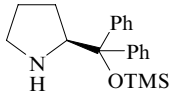
Conditions	Catalyst	Additives, solvent, temperature	Time /h	Yield (%)	*ee* (%)	Ref.
a	(*S*)-**3** (10 mol.%)	no additives, EtOH, 0 °C	96	72	86	85
b	(*S*)-**6** (1 mol.%)	AcOH (20 mol.%), H_2O, 0 °C → rt [a]	14	67	96	86
c	(3*R*,5*S*)-**7a** (10 mol.%)	no additives, EtOH, 5 °C	24	94	96	87

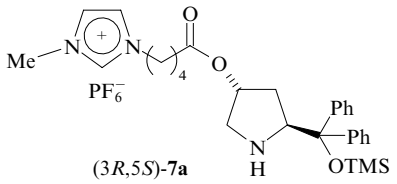
[a] Here and below rt is room temperature.

conditions *a*). The authors noted that the proposed synthetic route (6 steps) is much shorter than the routes described previously (usually 12–14 steps).

Later, several modifications of the asymmetric synthesis of paroxetine were proposed,[88] in partucular, organocatalytic ones.[86,87,89–92] In 2008, Ma *et al.*[86] found that *O*-trimethylsilyldiphenylprolinol (*S*)-**6** is a more efficient catalyst for the asymmetric step. In the presence of this catalyst, dimethyl malonate (**2b**) added to 4-fluorocinnamaldehyde (**1**) in water to give adduct **4b** in a 67% yield and 96% *ee* (see Scheme 1, conditions *b*). In 2009, prolinol (3*R*,5*S*)-**7** modified by the imidazolium cation was used for the first time in the reaction of dialkyl malonates **2a**,**b** with cinnamaldehyde derivatives;[87] this resulted in high yields and high enantiomeric excess of the key intermediates **4a**,**b**, which were retained when the same catalyst sample was used three times (see Scheme 1, conditions *c*). This reaction is one of the few examples of practical use of recoverable organocatalysts published to date.


(*S*)-**3**

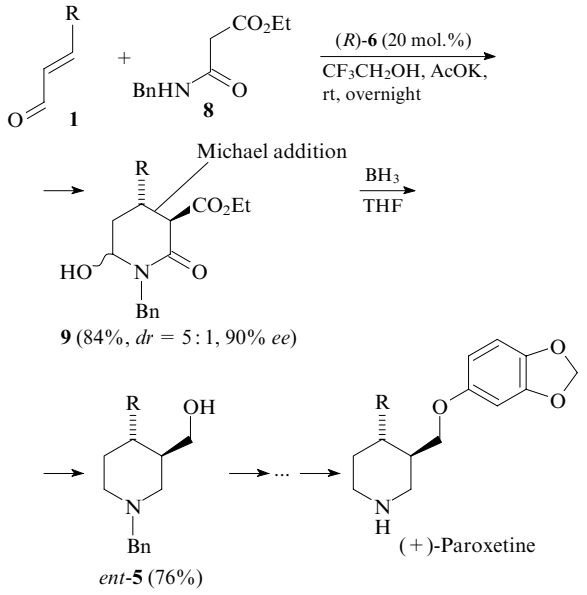

(*S*)-**6**


(3*R*,5*S*)-**7a**

TMS = $SiMe_3$.

In 2009, the Rios' group[90] made the preparation of paroxetine easier by synthesizing its (+)-enantiomer using malonic amidoester **8** instead of dialkyl malonate **2**. Compound **8** was made to react with 4-fluorocinnamaldehyde (**1**) in the presence of catalyst (*R*)-**6** having the *R*-configuration of the pyrrolidine C(2) atom. As a result, cyclic adduct **9** was obtained in one experimental step; on treatment with borane in THF, this compound was easily converted to piperidine derivative *ent*-**5**; this can be transformed to (+)-paroxetine by usual methods (Scheme 2). As we found out from the authors, there are misprints in the paper cited[90] [(−)-paroxetine instead of (+)-paroxetine, the rotation angle of compound **5** is indicated to be −23.4° instead of +23.4°], which, however, do not cast doubt on the obtained results.‡

Scheme 2



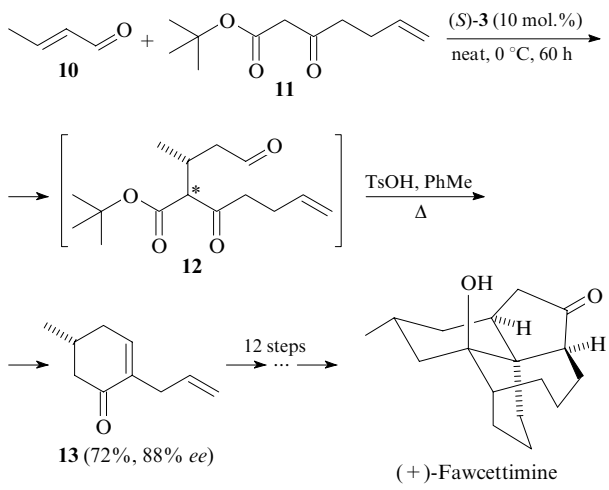
R = 4-FC_6H_4.

Organocatalysts based on *O*-trimethylsilyl-α,α-diarylprolinol derivatives also proved efficient in the syntheses of other natural compounds comprising the step of addition of C-nucleophiles to α,β-enals. In 2007, Toste and coworkers[93] applied catalyst (*S*)-**3** in the asymmetric Michael reaction between the crotonaldehyde (**10**) and β-keto ester **11** in the stereodetermining step of synthesis of (+)-fawcettimine, a representative of the *Lycopodium* alkaloids.[94,95] The adduct **12** thus obtained was cyclized without isolation by treatment with TsOH in toluene to give (*R*)-2-allyl-

‡ An alternative approach to the synthesis of (−)-paroxetine from dimethyl malonate (**2b**) and 4-fluoronitrostyrene is described in Section III.3 (Scheme 30).

5-methylcyclohex-2-enone (**13**), which was then converted to the target compound (12 steps) (Scheme 3).§

Scheme 3



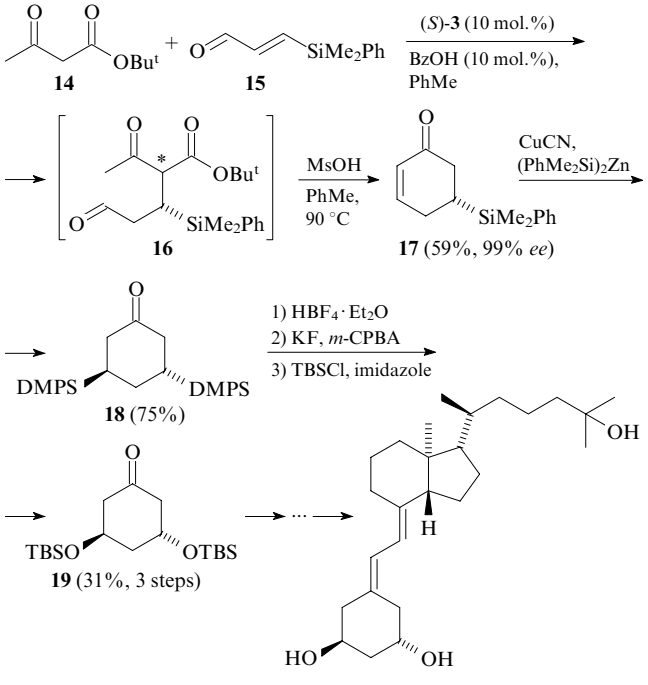
10 **11** **12** **13** (72%, 88% *ee*) (+)-Fawcettimine

In 2008, Jørgensen and co-workers[96] discovered that in the presence of compound (*S*)-**3**, the reaction with C-nucleophiles can proceed with acrolein derivatives containing a dialkylarylsilyl group (in the β position to the aldehyde group), which can be subsequently replaced by an OH group. The addition of *tert*-butyl acetoacetate (**14**) to β-silylacrolein **15** gave product **16**, which was converted without isolation to silylcyclohexenone **17** *via* MsOH-catalyzed intramolecular aldol condensation. A series of transformations of cyclohexenone **17** involving the intermediate ketone **18** produced compound **19**, an intermediate for the synthesis of the optical antipode of 19-*nor*-1α,25-dihydroxyvitamin D_3 (Scheme 4).[97,98]

As shown above, the Michael reactions involving α,β-unsaturated aldehydes catalyzed by compounds **3** and **6** effectively produce a chiral centre in the β position to the aldehyde group[99–101] or two stereocentres in the β and γ positions to it, although the selectivity of formation of the second centre can be low. This is not crucially important in those cases where the chirality of the γ-carbon atom is lost during the subsequent transformations of the product, *e.g.*, decarboalkoxylation (see Schemes 3 and 4). However, in some cases, the creation of a chiral centre in the γ position to the aldehyde group is the target task that requires special solutions.[102] Thus Deng and co-workers[103] applied the asymmetric reaction of β-keto ester **20** with acrolein (**21**) as the key step of the total synthesis of the alkaloid (+)-tanikolide produced by the sea cyanobacteria *Lyngbya majuscula* and having antifungal activity.[104] It was necessary to form the quaternary stereocentre in the γ position to the aldehyde group. The use of quinidine derivative **23** as the organocatalyst made it possible to solve this problem and to synthesize the addition product **22** with exceptionally high (> 99%) enantioselectivity.

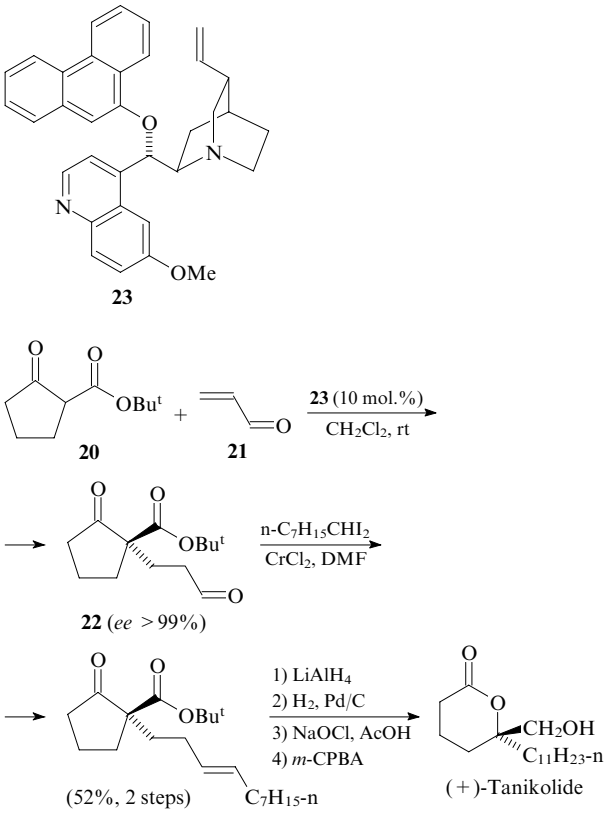
§ The organocatalytic synthesis of another representative of this alkaloid family, lycopodine, is described in Section III.2 (Scheme 22).

Scheme 4



14 **15** **16** **17** (59%, 99% *ee*) **18** (75%) **19** (31%, 3 steps) *ent*-19-nor-1α,25-Dihydroxyvitamin D_2

DMPS = $SiMe_2Ph$, TBS = $SiMe_2Bu^t$,
m-CPBA is *m*-chloroperoxybenzoic acid.



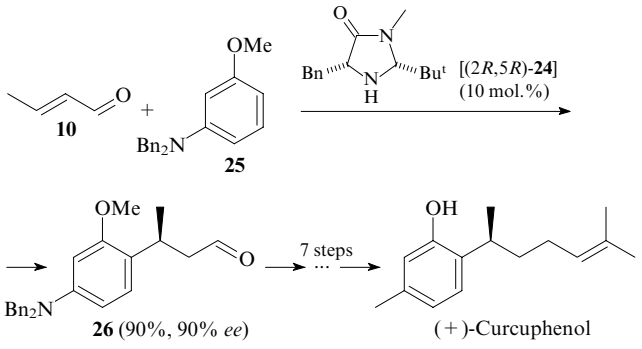
23 **20** **21** **22** (*ee* > 99%) (52%, 2 steps) (+)-Tanikolide

b. Reactions of α,β-enals with aromatic (heteroaromatic) compounds

The reactions of acrolein (**21**) and its derivatives with electron-donating carbo- and heteroaromatic compounds (Friedel–Crafts reaction) can also be formally classified as

1,4-conjugated addition in which electron-rich aromatic or heteroaromatic fragments act as C-nucleophiles. Chiral imidazolidin-4-one-derived catalysts developed by MacMillan [105] exhibit high activity and enantioselectivity through activation of α,β-enals by reversible formation of iminium ions (see Fig. 6, transition state $\mathbf{d}_8$).

Using this type of catalyst, Kim *et al.*[106] were able to introduce enantioselectively an aryl moiety into the β position of crotonaldehyde (**10**) in the key step of the synthesis of (+)-curcuphenol, a sesquiterpene, isolated from the sea sponges *Didiscus flavus* and *Epipolasis* and exhibiting antifungal, antitumour and antimalarial activities.[107, 108] In the presence of chiral imidazolidin-4-one (2*R*,5*R*)-**24**, *N*,*N*-dibenzyl-*m*-anisidine (**25**) adds to crotonaldehyde (**10**) to give adduct **26** in a 90% yield and 90% *ee*; then this adduct was converted to the target product without using chiral reagents or catalysts.

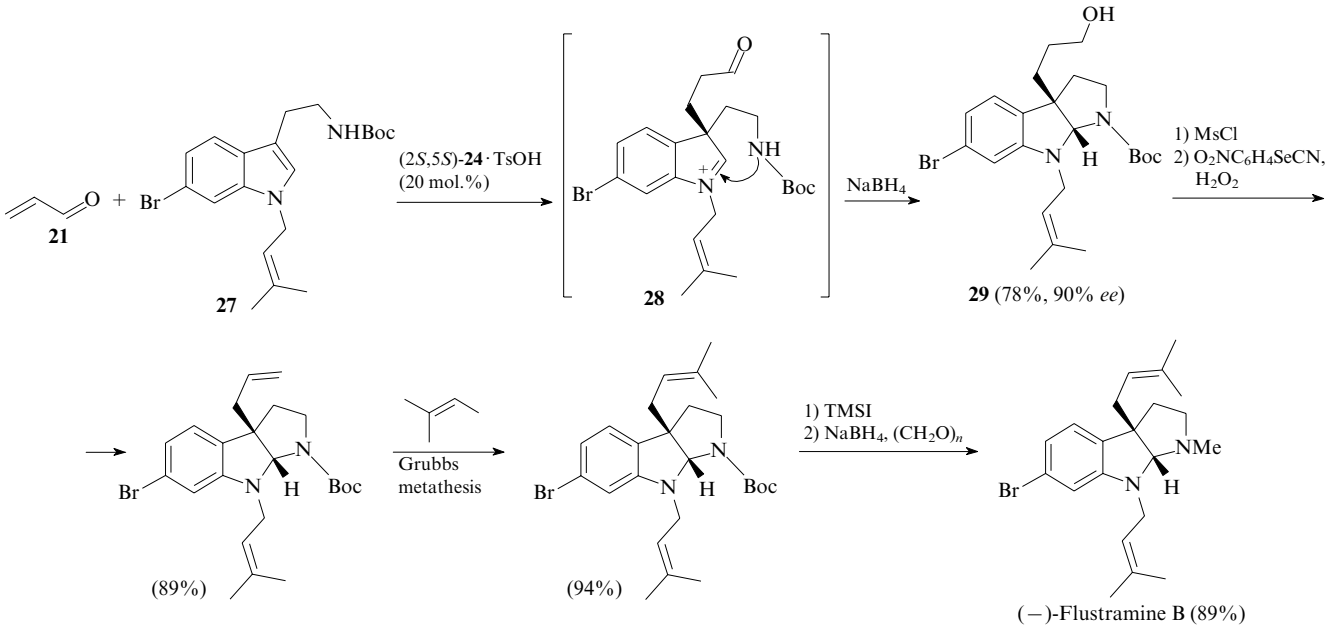


The use of chiral imidazolidin-4-ones as organocatalysts in the Friedel–Crafts reactions with participation of indole and pyrrole derivatives provided enantioselective synthesis of a number of biologically active compounds containing these heterocycles. In 2004 MacMillan and co-workers [109] used the reaction of the tryptamine derivative **27** with acrolein (**21**) catalyzed by enantiomer (2*S*,5*S*)-**24** in the stereoselective step of synthesis of the alkaloid (−)-flustramine B, a representative of the alkaloid family isolated from the bryozoa *Flustra foliacea* L.,[110–112] an effective potassium channel blocker,[113] a skeletal and smooth muscle relaxant.[114] On treatment with sodium borohydride, the addition product **28** was converted to tricyclic product **29** (with rather high enantiomeric excess), which is then converted to the target product (Scheme 5).

Recently, Hanessian *et al.*[115] used this approach to prepare chiral pyrrolidine derivatives containing an indole fragment in position 3. Bromoindole **30** effectively reacts with enal **31** in the presence of the salt of catalyst (2*R*,5*R*)-**24** to give addition product **32** in a nearly quantitative yield and 88% *ee*. Then adduct **32** is subjected to a transformation sequence comprising reduction of the aldehyde group with sodium borohydride to the hydroxymethyl group, mesylation of the latter on treatment with the MsCl–Et_3N system, deprotection and cyclization of compound **33** to be converted to pyrrolidin-3-ylindole derivative **34** (88% *ee*), a precursor of amidine **35**. Compound **35**, a highly active inhibitor of neuronal NO synthase and serotonin 5-HT1B/1D receptors, has been prepared previously as a racemate. The developed asymmetric synthesis is promising, as it may provide chiral drugs for the therapy of migraine (Scheme 6).[116]

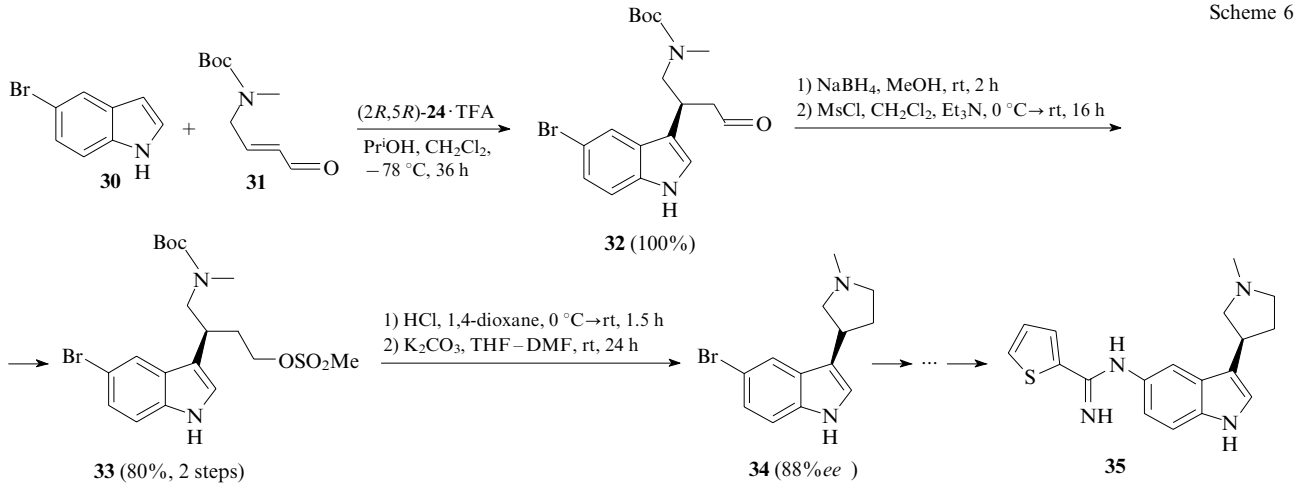
The asymmetric addition of pyrrole and indole derivatives to α,β-enals in the presence of MacMillan organocatalysts was used to prepare a number of other drug candidates that are currently at various stages of preclinical and clinical trials, in particular, the cyclooxygenase-2 inhibitor,[117] the serotonin reuptake inhibitor BMS-594726,[118] the alkaloids (−)-rhazinal, (−)-rhazinilam, (−)-leuconolam and (+)-epileuconolam.[119] The organocatalytic steps of their syntheses were similar to the syntheses described

Scheme 5



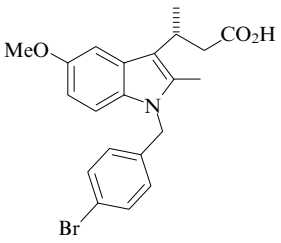
Boc is *tert*-butyloxycarbonyl.

Scheme 6

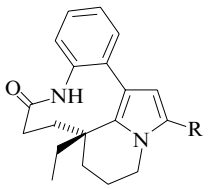


TFA is trifluoroacetic acid.

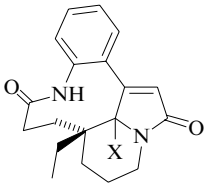
above (see Schemes 5 and 6); therefore, we are not going to consider them in detail.



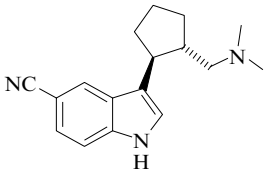
Cyclooxygenase-2 inhibitor



(−)-Rhazinal (R = CHO);
(−)-rhazinilam (R = H)



(−)-Leuconolam (X = β-OH);
(+)-epileuconolam (X = α-OH)



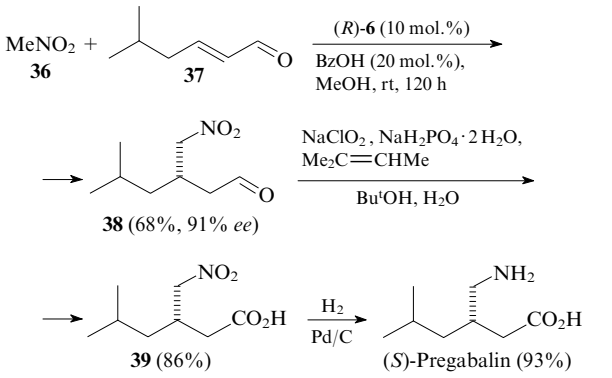
BMS-594726

c. Reactions of α,β-enals with nitroalkanes

A considerable group of asymmetric reactions of α,β-enals with C-nucleophiles in the presence of chiral organocatalysts is formed by reactions with nitroalkanes giving γ-nitroaldehydes, which are immediate precursors of the lipophilic analogues [120–122] of γ-aminobutyric acid (GABA), an important neuromediator [123, 124] of the mammalian central nervous system, and some other types of pharmaceutical drugs. *O*-Trimethylsilylprolinol derivatives proved useful as the catalysts of these reactions.

In 2007, Hayashi and co-workers [99] reported the first organocatalytic synthesis of the *S*-enantiomer of the anticonvulsant pregabalin [122] used to treat epilepsy and neuropathic pain.¶ The synthesis of the drug included the asymmetric reaction of nitromethane (**36**) with α,β-enal **37** in the presence of catalyst (*R*)-**6**, giving rise to Michael adduct **38**, which was subsequently converted to pregabalin *via* γ-nitro acid **39** (Scheme 7). Previously, fairly toxic catalysts based on aluminium [128] or gadolinium [129] complexes or metal cyanides [128, 129] were used for the enantioselective pregabalin synthesis; therefore, the proposed approach is preferred from the 'green chemistry' standpoint.[130]

Scheme 7

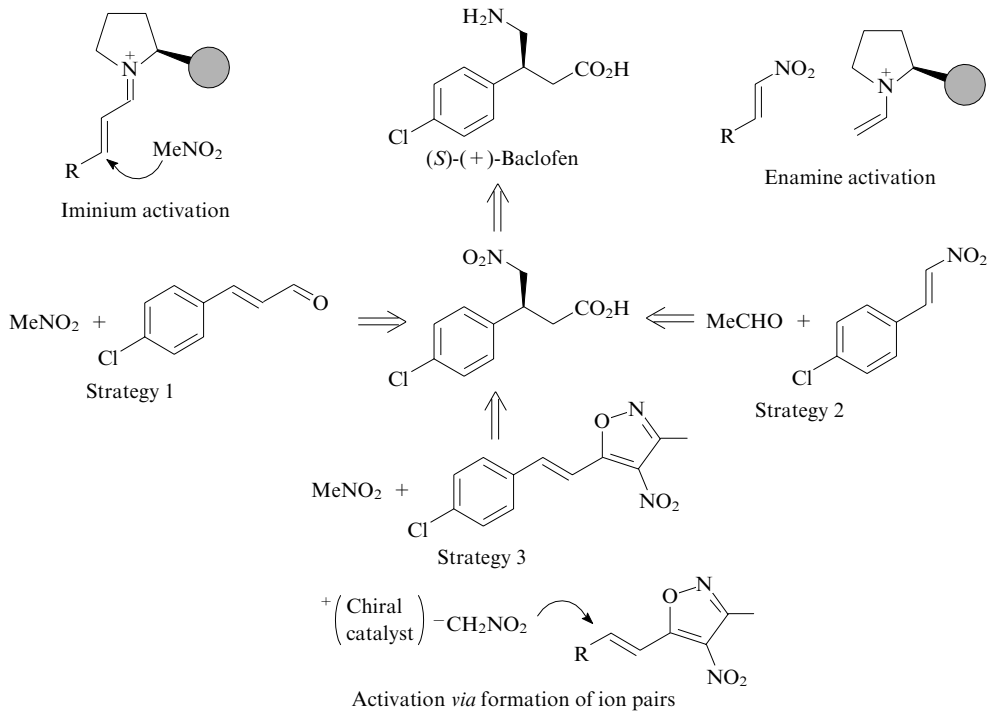


The organocatalytic Michael reaction proved to be an efficient method for the synthesis of the chiral drug baclofen,[131–134] which is a potent $GABA_B$-receptor agonist. Although baclofen is currently used as a racemate, it is known that the *R*-enantiomer has a higher biological activity.[135] Recently, a number of organocatalytic approaches to the enantioselective synthesis of *S*- or *R*-enantiomer of baclofen have been developed (Scheme 8). They use various types of electrophiles and activation modes, including iminium [55, 99–101, 136] and enamine [137, 138] activation (see Fig. 6), the formation of chiral ion pairs (see Fig. 4) [139, 140] and some other organocatalytic approaches,[92] which demonstrate the power of modern organocatalysis.

In 2007, Palomo *et al.*[55] synthesized the key intermediate for the preparation of (*S*)-(+)-baclofen *via* asymmetric addition of nitromethane (**36**) to enal **40**. The reaction was carried out in water in the presence of prolinol (*S*)-**41** containing hydrophobic long-chain alkyl groups. Under these conditions, γ-nitroaldehyde **42** was obtained in a moderate yield (69%) but with high *ee* (95%) (Scheme 9, conditions *a*). Compound **42** was easily converted to baclofen *via* γ-nitro acid **43**. Attempts were made to optimize the process using other solvents, catalysts and additions of acids or bases (see Scheme 9, conditions

¶ Other organocatalytic syntheses of pregabalin [92, 125–127] are described in Section III.3 (Schemes 28 and 29).

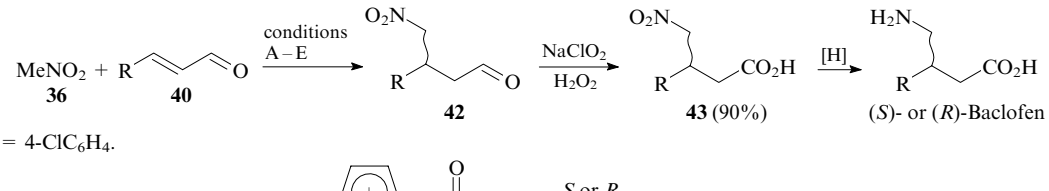
Scheme 8



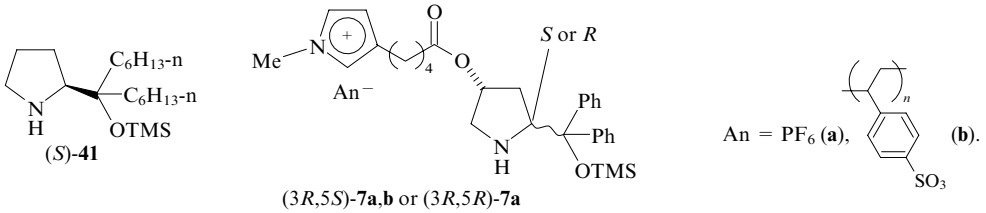
b—*e*).[99–101,136] The highest enantioselectivity (97%) was attained by Chinese researchers,[101] who carried out the reaction in ethanol in the presence of diphenylprolinol (*S*)-**6**–benzoic acid system (see Scheme 9, conditions *d*). Catalysts (3*R*,5*S*)-**7a** or (3*R*,5*R*)-**7a** (An = PF_6)[136] and (3*R*,5*S*)-**7b** (An is sulfated polystyrene)[141] containing imidazolium cation 'built-in' into the molecule that we developed for this reaction deserve attention from the practical standpoint. Using these catalysts, it is possible to prepare both enantiomers of the chiral compound, while the catalysts can be recovered and reused (more than 10 times under argon [142]), although the reaction enantioselectivity achieved in this case (90%) was somewhat lower than in the presence of compounds **6** and **41** (Scheme 9, conditions *e*). The asymmetric reactions in the presence of organocatalysts modified by ionic groups were recently reviewed.[143–145]

The deep understanding of the mechanisms of organocatalytic reactions allowed Hayashi *et al.*[146] to develop an elegant method for the preparation of γ-nitroaldehydes **42** from alkanals **44** and nitromethane (**36**) in the presence of an oxidant, 2,3-dichloro-5,6-dicyanoquinone (DDQ), which ensured generation of an electron-deficient alkene in the reaction mixture (Scheme 10). This reaction is a four-step one-pot process that includes the formation of enamines **45** from alkanals **44** and catalyst (*S*)-**6**, their oxidation induced by DDQ, the formation of iminium cations **46** and addition

Scheme 9

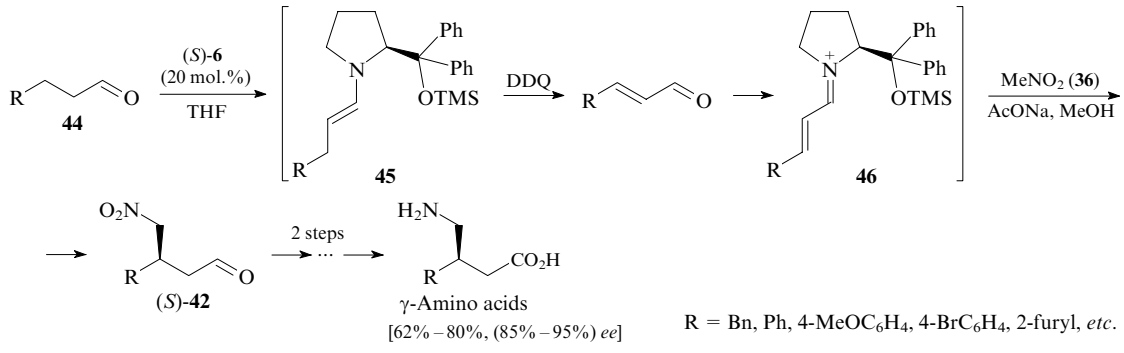


R = 4-ClC_6H_4.



Conditions	Catalyst	Additives [amount (mol.%)]	Solvent	Temperature	Time /h	Yield (%)	*ee* (%)	Ref.
a	(*S*)-**41** (5 mol.%)	BzOH (5)	H_2O	rt	16	69	95 (*S*)	55
b	(*R*)-**6** (2 mol.%)	AcOLi (10)	CH_2Cl_2–MeOH	rt	84	61	95 (*R*)	100
c	(*S*)-**6** (10 mol.%)	BzOH (20)	MeOH	rt	17	83	94 (*S*)	99
d	(*S*)-**6** (20 mol.%)	BzOH (20)	EtOH	0 °C	15	75	97 (*S*)	101
e	(3*R*,5*S*)-**7a,b** or (3*R*,5*R*)-**7a** (10 mol.%)	no additives	MeOH	rt	24	91	90–91 (*S* or *R*)	136

Scheme 10



of nitromethane (**36**) to cations **46** in the presence of sodium acetate to recover catalyst (*S*)-**6**. The γ-nitroaldehydes **42** thus obtained can be converted to γ-amino acids, in particular, to (*S*)-(+)-baclofen and its analogues.†

The asymmetric reactions of nitromethane (**36**) with cinnamaldehyde and its derivatives in the presence of prolinol-type organocatalysts were successfully used in the key steps of synthesis of other practically valuable GABA analogues, including the antidepressant drug phenibut [136] and type IV phosphodiesterase inhibitor rolipram [55, 136] (Fig. 9). The asymmetric synthesis of these GABA analogues is fairly valuable, as only one enantiomer has clear-cut biological properties, while the other is less active [see also (*S*)-pregabalin,[148] (*R*)-baclofen,[135] (*R*)-phenibut [149] and (*R*)-rolipram [150]].

Xu *et al.*[151] proposed an organocatalytic approach to the preparation of the drug telcagepant,[152–154] which is under clinical trial as a remedy against migraine (Scheme 11). The key stereocentre of the molecule was formed in the reaction of nitromethane (**36**) with 2,3-difluorocinnamaldehyde (**47**) in the presence of compound (*S*)-**6**, resulting in chiral Michael adduct **48** in 73% yield and 95% *ee*. Then nitroaldehyde **48** was subjected to pyrrolidine-catalyzed Doebner–Knoevenagel reaction to be

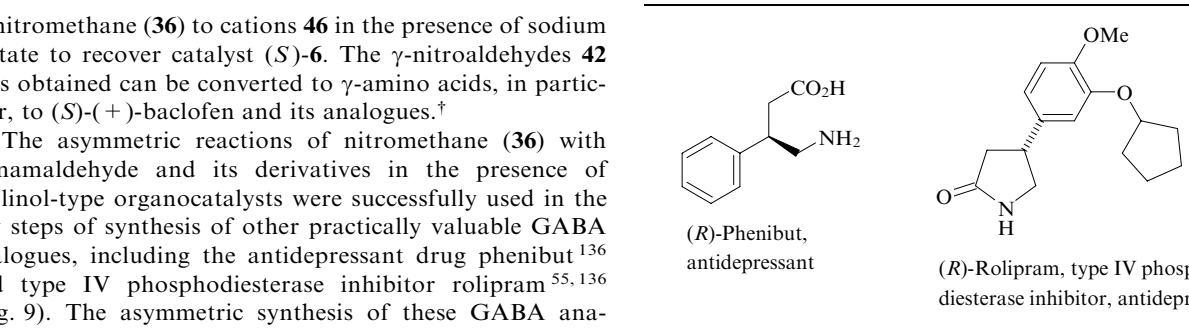
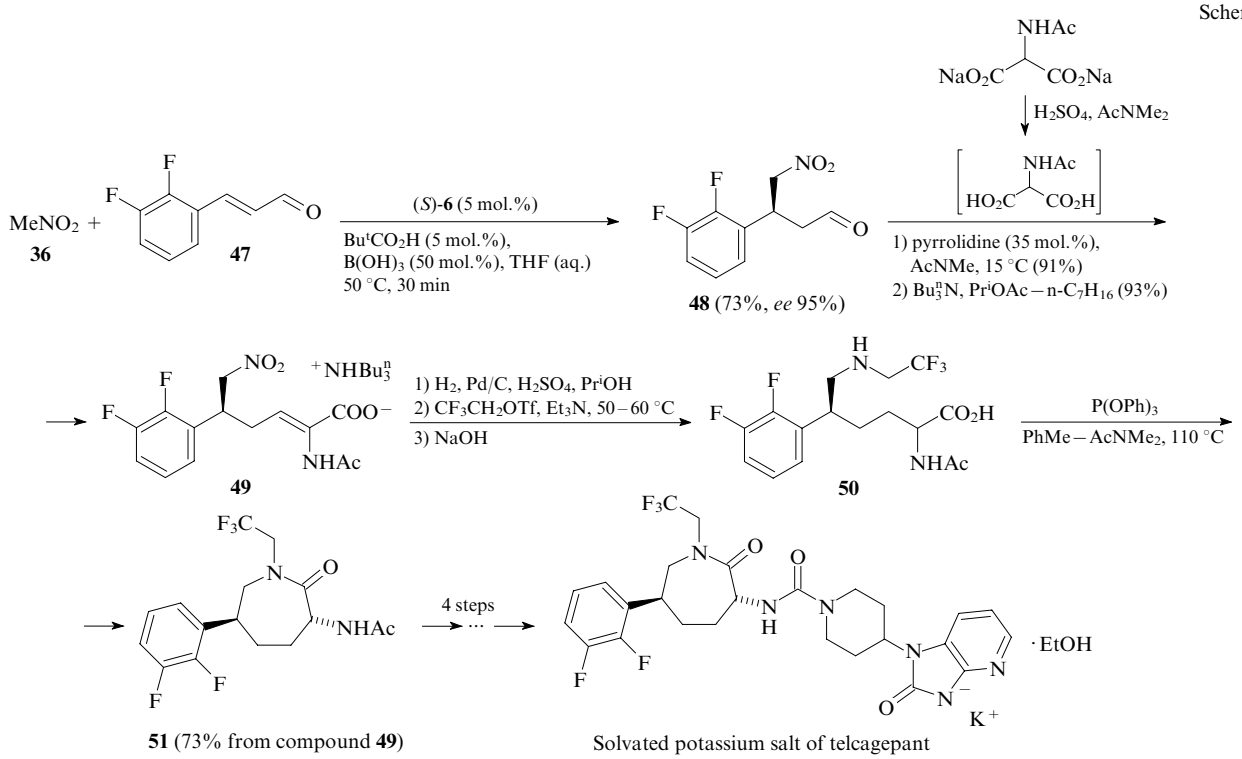


Figure 9. Pharmaceutical drugs (*R*)-phenibut and (*R*)-rolipram obtained by organocatalytic routes.

Scheme 11



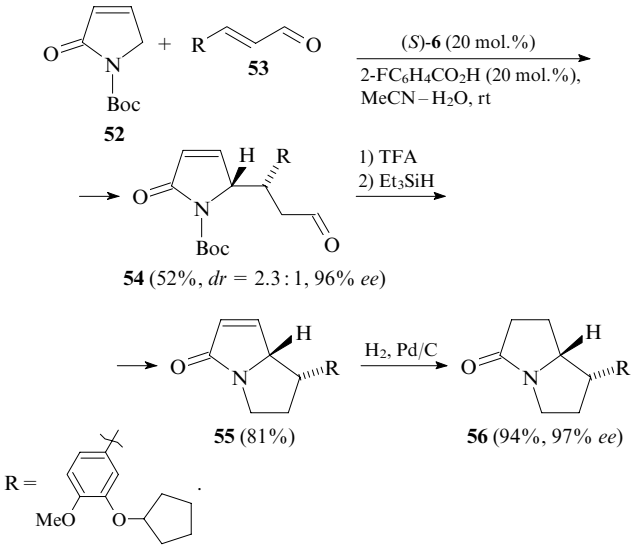
† Other methods for the synthesis of baclofen in the presence of organocatalysts include reactions of acetaldehyde [137, 138] (Scheme 23) or diethyl malonate (**2c**) with β-nitro-4-chlorostyrene [147] (Scheme 27) and addition of nitromethane (**36**) to chalcone [139] (Scheme 19) or 4-nitro-5-styrylisoxazole [140] (Scheme 34).

converted to enamine **49**, which was in turn transformed to compound **50** and then to azepinone **51**, which represents the chiral moiety of the telcagepant molecule (see Scheme 11).

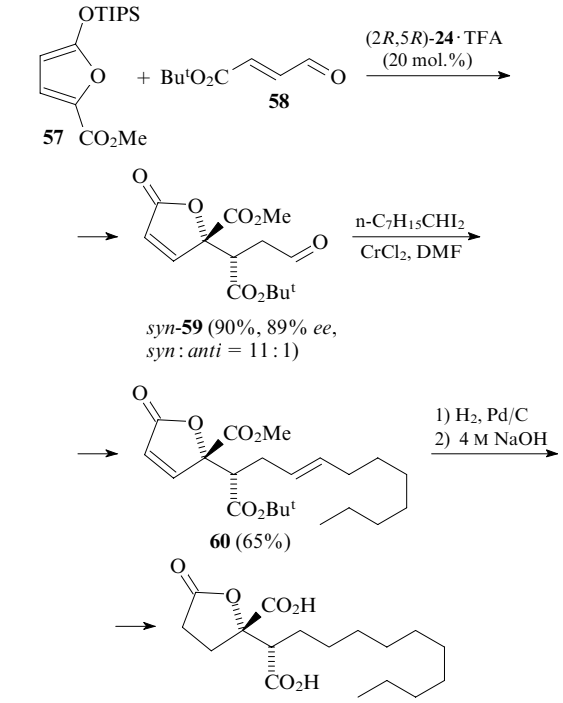
d. Reactions of α,β-enals with 2-hydroxypyrrole, 2-hydroxyfuran (Mukaiyama – Michael reaction) and 2-furylboronic acid derivatives

When *O*-trimethylsilyl-α,α-diarylprolinols and imidazolidinones are used as catalysts, N-protected 2-hydroxypyrroles (pyrrolin-2-ones) and silicic esters of 2-hydroxyfurans react with α,β-enals (Mukaiyama – Michael reaction) to form the bond between the C(5) atom of the heterocycle and the C(3) atom of the enal, and one of these or both (in the case of 3-substituted acrolein derivatives) become chiral.

Chen and co-workers [155] found that *N*-*tert*-butyloxycarbonyl-1-hydroxypyrrole **52** reacts with substituted cinnamaldehyde **53** in the presence of the (*S*)-**6** – *o*-fluorobenzoic acid system as the catalyst to give addition product **54** in moderate yield and diastereoselectivity (the formation of a chiral centre in the γ position to the aldehyde group is a challenge, see also Section III.1.a), but the enantiomeric excess of the desired diastereomer was fairly high (96%). Upon the reaction sequence including deprotection, cyclization and dehydroxylation, adduct **54** was converted to bicyclic amine **55**, which is the immediate precursor of compound **56**, adenosine monophosphate-dependent phosphodiesterase IV inhibitor.[156, 157]

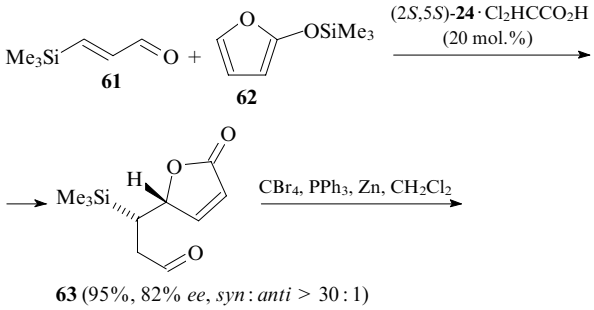


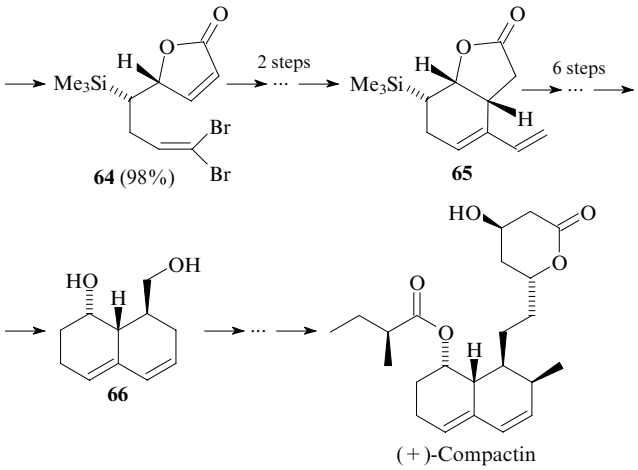
Of considerable interest are the asymmetric Mukaiyama – Michael reactions in which protected 2-hydroxyfurans act as the Michael donors. These reactions, which can be considered to a certain extent as Friedel – Crafts reactions, proceed efficiently in the presence of chiral imidazolidin-4-ones (for the use of MacMillan catalysts in Friedel – Crafts reactions involving pyrrole and indole derivatives, see also Section III.1.b), resulting in five-membered lactones (butenolides) the structural fragment of which is an integral part of many natural compounds. In 2003, MacMillan and co-workers [158] used the organocatalytic Mukaiyama – Michael reaction of furan **57** with α,β-unsaturated aldehyde **58** in the synthesis of spiculisporic acid isolated from cultures of the fungi *Penicillium spiculisporum* L. and P [159] and used to extract heavy metal cations.[160] In the presence of imidazolidinone (2*R*,5*R*)-**24**, this reaction affords butenolide *syn*-**59**, which was converted to spiculisporic acid *via* a sequence of Takai olefination (compound **60**), catalytic hydrogenation of C=C bonds and hydrolysis of ester groups. Note that after the replacement of the bulky *tert*-butyl group in compound **58** by the methyl group, the reaction with the same catalyst affords butenolide *anti*-**59** with high diastereo- and enantioselectivity (*syn* : *anti* = 1 : 22, 97% *ee*), which opens up the way to 5-epispiculisporic acid.



TIPS = $SiPr^i_3$.

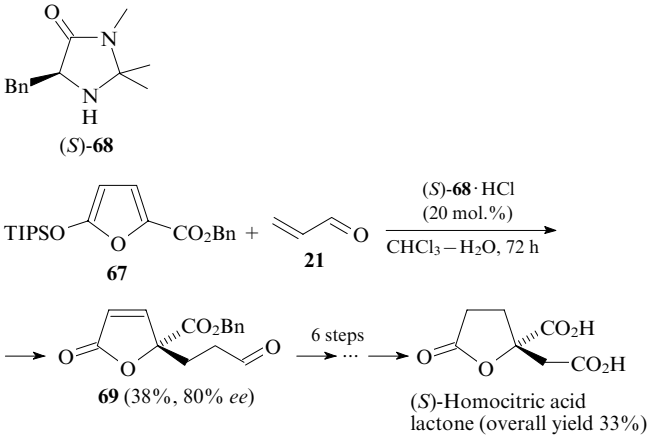
In 2006, Robichaud and Tremblay [161] used a similar approach to prepare (+)-compactin,[162 – 166] an HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme-A reductase) inhibitor. The reaction of 3-trimethylsilylacrolein (**61**) with 2-silyloxyfuran **62** in the presence of imidazolidinone (2*S*,5*S*)-**24** gave addition product **63**. Note that the presence of the TMS group in acceptor **61** is favourable for the increase in the reaction enantioselectivity; the enantiomeric excess of the adduct of furan **62** with unsubstituted acrolein (**21**) obtained under the same conditions was only 33%. The Corey – Fuchs olefination of butenolide **63** yielded dibromoalkene **64**, which was converted to bicyclic lactone **65** and then (in 6 steps) to compound **66**,[167] containing two annelated cyclohexene rings, which is the precursor of (+)-compactin. It is noteworthy that the lactone moiety of





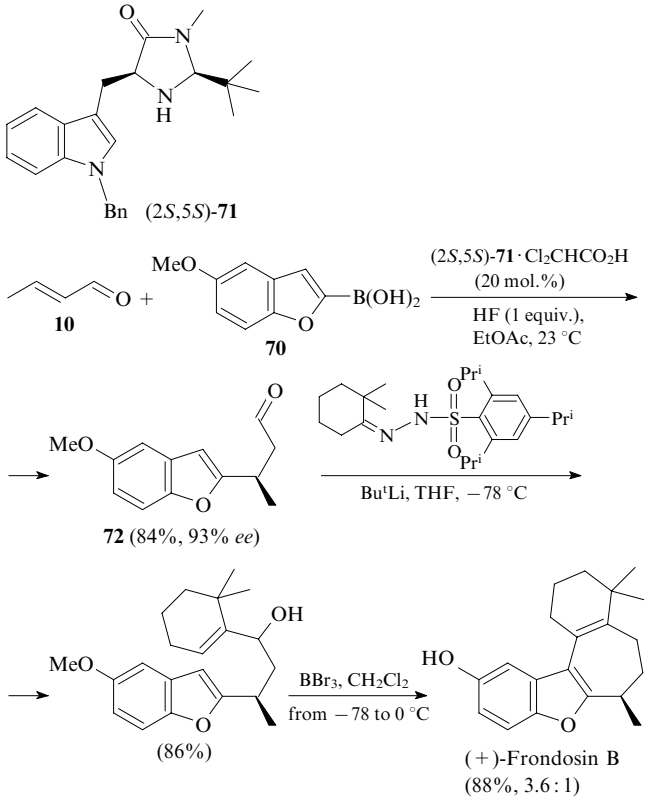
compactin can also be formed by another organocatalytic process, namely, (*S*)-proline-catalyzed aminoxylation.[168]

Recently, Pansare *et al.*[169] developed a method for the synthesis of (*S*)-homocitric acid lactone comprising the organocatalytic Mukaiyama–Michael reaction. Silyloxyfuran **67** was added to acrolein (**21**) in the presence of imidazolidinone (*S*)-**68** to give adduct **69**, which was converted in 6 steps to the target product in an overall yield of 33%.



Probably, by using the developed method and applying catalyst (*R*)-**68**, it would be possible to obtain (*R*)-homocitric acid, which is involved in L-lysine biosynthesis, is present in some yeasts and fungi[170] and is a component of the nitrogenase Fe–Mo cofactor.[171]

MacMillan and co-workers[172] found that the $B(OH)_2$ group can serve as a regiospecific activator of furan derivatives in organocatalytic reactions with α,β-unsaturated aldehydes. They proposed an original approach to the synthesis of (+)-frondosin B, a sesquiterpene isolated from the sea sponge *Dysidea frondosa* and exhibiting anti-inflammatory and antitumour activities;[173–178] the stereocentre of the sesquiterpene molecule was formed in the reaction of benzofuran-derived boronic acid **70** with crotonaldehyde (**10**) in the presence of imidazolidinone (2*S*,5*S*)-**71**. This reaction, first discovered by the authors, efficiently proceeds in the presence of acidic co-catalyst (dichloroacetic acid) and equimolar HF additive to give adduct **72**. The cyclic system of the natural sesquiterpene is introduced in two steps, the overall yield of (+)-frondosin B based on compounds **10** and **70** being 50% (a frondosin isomer with a different double bond position is formed as a minor product). This method considerably surpasses the known methods for (+)-frondosin B synthesis as regards simplicity and efficiency (Danishefsky,[179] 2001: 17 steps, yield 1%; Trauner,[180,181] 2002: 20 steps, 7%; Ovaska,[182] 2009: 10 steps, 13%) and is an excellent illustration of the enormous synthetic potential of organocatalysis.



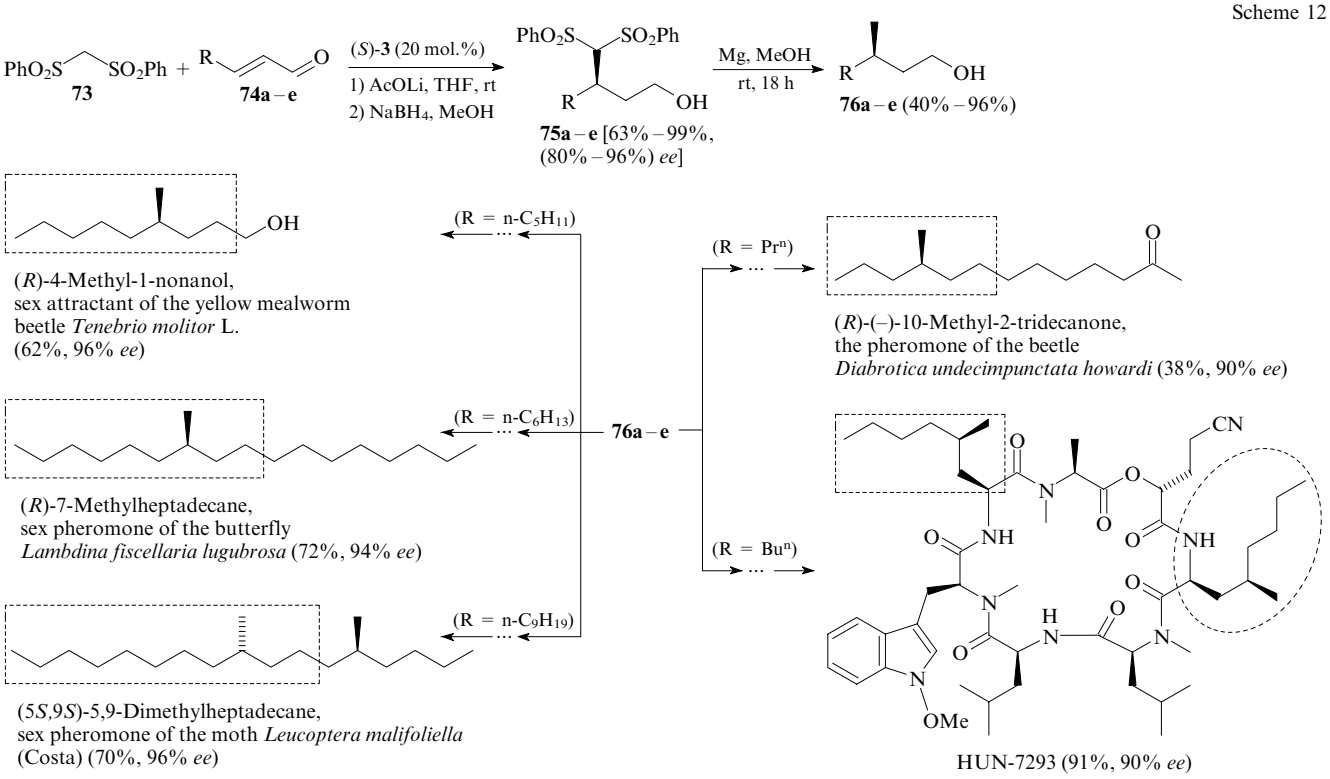
e. Reactions of α,β-enals with disulfonylmethanes

Disulfonylmethanes are among the most important nucleophiles for the asymmetric Michael reactions; they are used to introduce a disulfonylmethyl group, which is a synthetic equivalent of a methyl group, into the β position to the aldehyde group.[183] These reactions are usually performed in the presence of *O*-trimethylsilyl-α,α-diarylprolinols, the most versatile catalysts for reactions of α,β-enals with methylene-active compounds. Compounds in which a chiral carbon atom is bonded to a methyl group are widespted in nature (isoprenoids, terpenes) and are important building blocks for the preparation of chiral biologically active products.

Alemán and co-workers[184] used asymmetric addition of di(phenylsulfonyl)methane (**73**) to aliphatic α,β-enals **74a–e** catalyzed by compound (*S*)-**3** and subsequent reduction of the resulting chiral adducts with sodium borohydride *in situ* to prepare optically active 3-[di(phenylsulfonyl)methyl]-substituted alkanols **75** (Scheme 12).‡ Products **75a–e** were obtained in high yield and enantioselectivity. The di(phenylsulfonyl)methyl group in compounds **75** is readily converted to the methyl group on treatment with magnesium in methanol. 3-Methyl-substituted alcohols **76a–e**

‡ The dashed lines in Scheme 12 encompass fragments of the target molecules formed in the organocatalytic step of the synthetic sequence.

Scheme 12

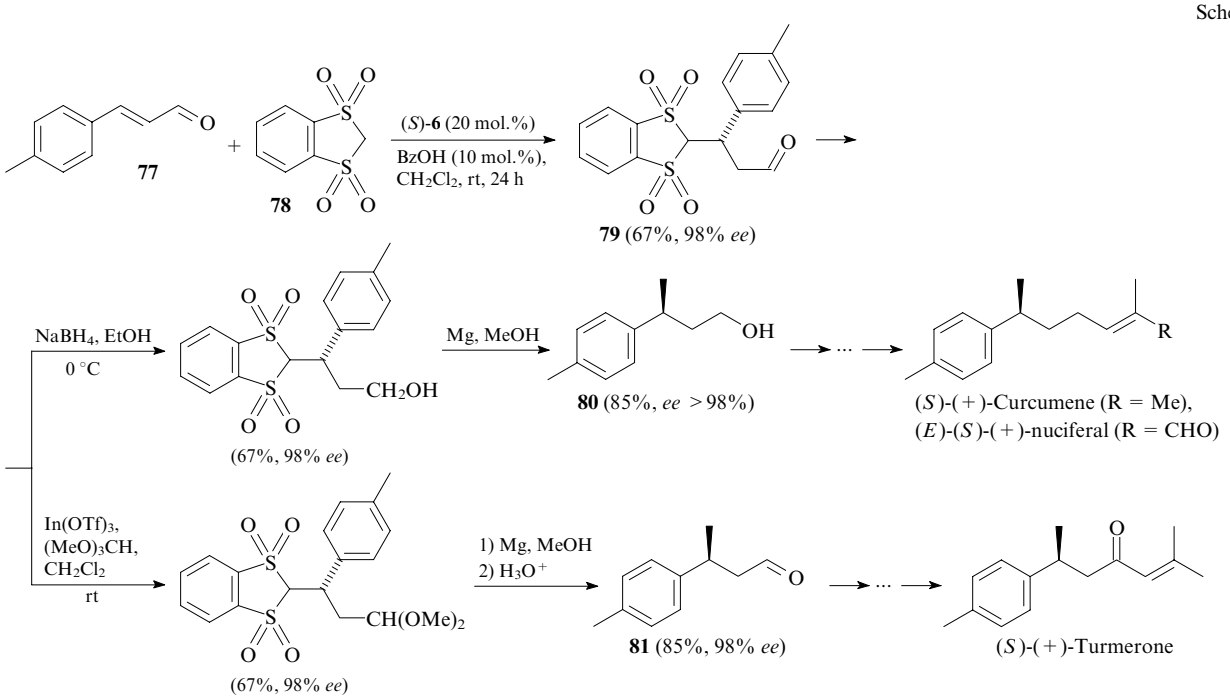


R = Pr^n (**a**), Bu^n (**b**), n-C_5H_{11} (**c**), n-C_6H_{13} (**d**), n-C_9H_{19} (**e**).

obtained in this way are valuable intermediates in the synthesis of chiral biologically active products. For instance, compound **76a** is used to obtain the beetle *Diabrotica undecimpunctata howardi* pheromone,[185] compound **76b** is used in the synthesis of the antiinflammatory agent HUN-7293 [186] and some pheromones,[187] alcohol **76c** is a precursor of the sex attractant of the yellow mealworm beetle *Tenebrio molitor* L.,[188] products **76d**,**e** are used to prepare pheromones of the butterfly *Lambdina fiscellaria lugubrosa*,[189] the red flour beetle *Tribolium castaneum*,[190] some other pheromones,[191] and lipids [192] present in sea algae (see Scheme 12).

Palomo and co-workers [193] demonstrated that aromatic α,β-unsaturated aldehydes are also able to add methylene-bis(sulfones) under catalysis by compound (*S*)-**6**, which can be utilized in the synthesis of some sesquiterpenes,[194–197] in

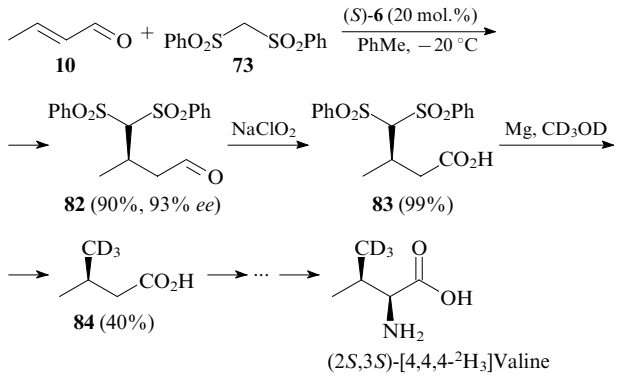
Scheme 13



particular of (*S*)-(+)-curcumene, (*E*)-(*S*)-(+)-nuciferal and (*S*)-(+)-turmerone. The reaction of α,β-unsaturated aldehyde **77** with bis-sulfone **78** in the presence of catalyst (*S*)-**6** furnished Michael adduct **79**. Then compound **79** was subjected to reduction (acetalization) and desulfurization to give 3-aryl-substituted derivatives of butanol **80** and butanal **81**, which were converted to the target sesquiterpenes by known methods with retention of the chiral centre (Scheme 13).

The ease of desulfurization of the chiral products of addition of methylenebis(sulfones) to α,β-enals makes the organocatalytic method suitable for the preparation of ^{2}H- and ^{13}C-labelled α-amino acids to be used in the studies of the metabolism of natural compounds.[198] In 2009, Moyano, Rios and co-workers[199] proposed an efficient method for the synthesis of (2*S*,3*S*)-[4,4,4-$^{2}H_3$]valine from product **82** of the asymmetric addition of di(phenylsulfonyl)methane (**73**) to crotonaldehyde (**10**) in the presence of (*S*)-**6**. The method included oxidation of the aldehyde group in sulfone **82** on treatment with $NaClO_2$ and desulfurization of the carboxylic acid **83** thus formed on treatment with magnesium in CD_3OD to give [4,4,4-$^{2}H_3$]isopentanoic acid **84** (Scheme 14). By using different enantiomers of catalyst **6**, it is possible to synthesize both enantiomers of compound **84**, which is an intermediate for the preparation of deuterated valine (organocatalytic α-amination[200,201]); this method differs from the known nine-step synthesis of (2*S*,3*S*)-[4,4,4-$^{2}H_3$]valine[202] as it includes fewer steps, provides higher product yields and does not require the use of expensive deuterated reagents.

Scheme 14



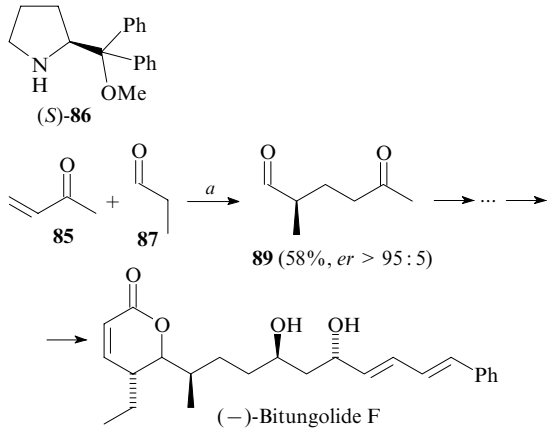
2. Reactions of C-nucleophiles with α,β-unsaturated ketones

The asymmetric 1,4-conjugated addition of C-nucleophiles to α,β-unsaturated ketones is an effective method for the construction of a number of chiral structural fragments, which are often encountered in natural compounds and chiral biologically active substances or are used in the key steps of their synthesis. These include fragments of chiral 1,5-dicarbonyl (carboxyl) compounds, the cyclohexane, cyclohexene and pyrrolidine rings, and so on. Linear and cyclic α,β-unsaturated ketones can be involved in organocatalytic Michael reactions. The reactions of linear and cyclic substrates are considered separately, as they differ by the catalysts used and the mechanisms of reactant activation.

a. Addition of C-nucleophiles to acyclic α,β-enones

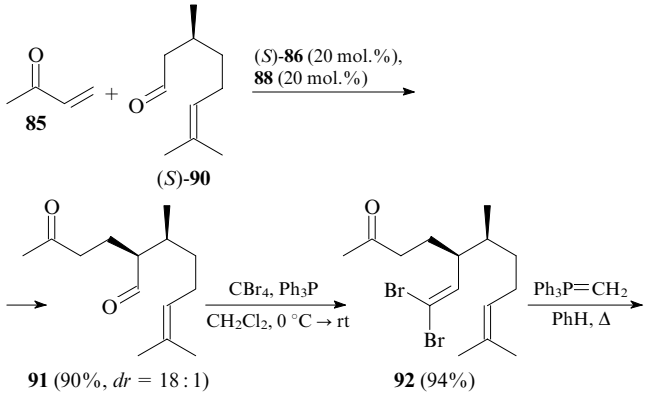
In 2005, Gellman and Chi[54] demonstrated for the first time that aldehydes stereoselectively add to methyl vinyl ketone (**85**) in the presence of *O*-methyldiphenylprolinol [(*S*)-**86**] to give chiral 1,5-dicarbonyl compounds. In the authors' opinion, in this process, the catalyst activates the donor component [for example, propanal (**87**)] by enamine formation (see Fig. 6). A positive effect on the reactions is also exerted by addition of pyrocatechol derivative **88**, which activates α,β-enone **85** through hydrogen bonding with the carbonyl oxygen atom. The methyl ether (*S*)-**86** proved to be a much more active catalyst of this reaction than diarylprolinol trimethylsilyl ethers used in the reactions of C-nucleophiles with enals, for example, compounds (*S*)-**3** or (*S*)-**6** (see Section III.1).

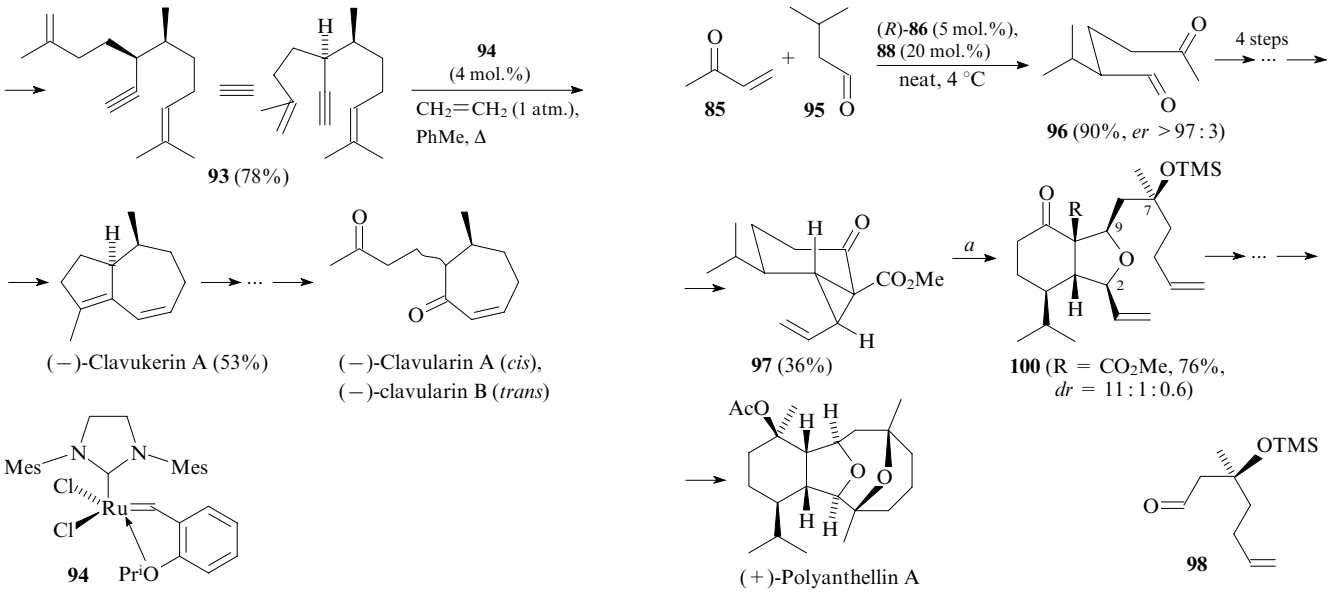
This approach was used by other researchers for enantioselective preparation of natural compounds *via* the formation of chiral 1,5-dicarbonyl compounds. Thus Arseniyadis, Cossy and co-workers[203] prepared 2-methyl-5-oxohexanal **89** in a satisfactory yield with fairly high enantioselectivity by the (*S*)-**86**-catalyzed reaction of methyl vinyl ketone (**85**) with propanal (**87**) in the presence of catechol **88** (20 mol.%) under neat conditions. Michael adduct **89** was then converted to the phosphatase inhibitor (−)-bitungolide F in 8 steps in an overall yield of 20% without the use of chiral reagents or catalysts.



(*a*) (*S*)-**86** (5 mol.%), 3,4-$(HO)_2C_6H_3CO_2Et$ (**88**) (20 mol.%), 5 °C.

Metz and co-workers[204] used a similar approach to prepare the sesquiterpenes (−)-clavukerin A and (−)-isoclavukerin A, which had been isolated earlier from the marine soft coral *Clavularia koellikeri*.[205–208] The Michael reaction between (*S*)-citronellal [(*S*)-**90**] and methyl vinyl ketone (**85**) in the presence of the prolinol ether (*S*)-**86**–diol **88** system was the stereodetermining step of the synthesis.





Under the proposed conditions, this stereoselectively gave keto aldehyde **91**, the desired diastereomer with *syn*-arrangement of the methyl and oxobutyl groups being the predominant product. The chemoselective dibromoolefination of the aldehyde group in adduct **91** and subsequent treatment of dibromide **92** with excess methylene(triphenyl)phosphorane produced dienine **93**. The synthesis of (−)-clavukerin A was completed by metathesis of dienine **93** with ethylene in the presence of ruthenium catalyst **94**. (−)-Clavukerin A can be transformed to natural cycloheptenones, (−)-clavularin A [209] and (−)-clavularin B,[207] by known methods.

When (*R*)-citronellal [(*R*)-**90**] is introduced in this sequence of transformations, diastereomeric (−)-isoclavukerin A is formed.

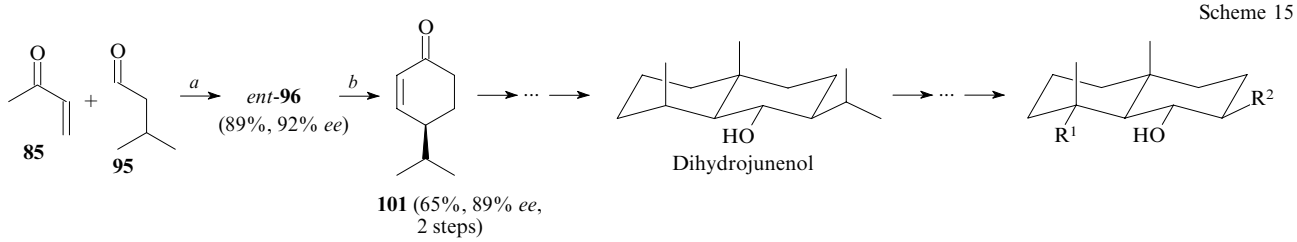
The prolinol (*R*)-**86**–diol **88** system was found to be also efficient in the asymmetric reaction of methyl vinyl ketone (**85**) with isovaleraldehyde (**95**),[210] which is the key step of the synthesis of the metabolite (+)-polyanthellin A, isolated from *Gorgonian octocorals* and exhibiting antimalarial activity.[211, 212] The Michael adduct **96** formed in a 90% yield was converted in 4 steps to bicyclo[4.1.0]heptanone **97**. The diastereoselective [3 + 2]-cycloaddition of bicyclic ketone **97** containing a strained cyclopropane moiety, to β-silyloxyaldehyde **98** in the presence of Lewis acid **99** resulted in tetrahydrofuran **100**, which was converted to the target product (apart from the major isomer **100**, its 7-epimer and the isomer with *trans*-oriented 2- and 9-substituents were formed).

(*a*) **98**, (4-Me-2,6-$Bu^t_2C_6H_2O)_2AlMe$ (**99**, 15 mol.%), $HNTf_2$ (10 mol.%), CH_2Cl_2, −30 °C.

The organocatalytic method for the synthesis of 1,5-dicarbonyl compounds proposed by Gellman and co-workers [213] proved to be exceptionally useful for the preparation of cyclohexenone derivatives containing a chiral carbon atom in the γ position to the carbonyl group. Compounds of this type are precursors for a representative series of sesquiterpenes (about 1000 compounds), which exhibit fungicidal, antibacterial and antitumour activities. Baran and co-workers [214, 215] converted Michael adduct *ent*-**96**, formed in the *O*-methyldiphenylprolinol [(*S*)-**86**]-catalyzed asymmetric reaction of methyl vinyl ketone (**85**) with isovaleraldehyde (**95**), without isolation, to cryptone **101** by means of base-induced intramolecular aldol condensation. Cyclohexenone **101** served as the starting compound in the synthesis of dihydrojunenol, the simplest sesquiterpene in the series of eudesmane terpenes, which in turn was used to prepare other terpenes of this series including 4-epiajanol, dihydroxyeudesmane, pygmol and eudesmanetetraol (Scheme 15).

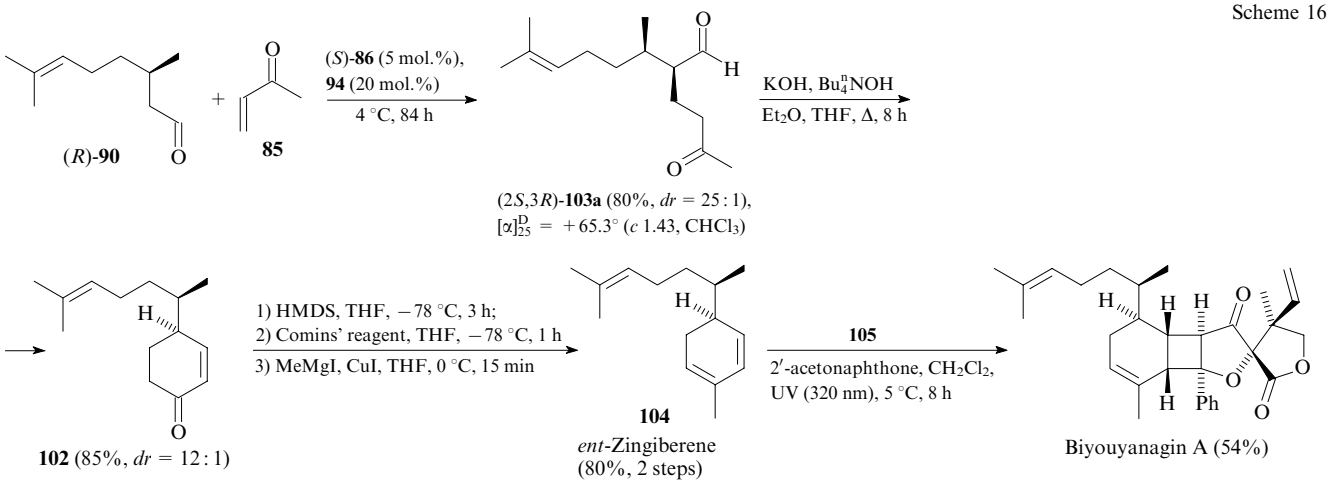
The organocatalytic step giving chiral cyclohexenone **102** is also included in the total synthesis of biyouyanagin A, a complex polycyclic compound incorporating sesquiterpene, cyclobutane and spirolactone moieties, performed by Nicolaou *et al.*[216] This compound occurs in the leaves of *Hypericum chinese* L. var. *salicifolium* used in traditional Japanese medicine. In addition, it can inhibit HIV replication in H9-lymphocytes.[217] The intermediate (*S*)-4-[(*R*)-6-

Scheme 15



(*a*) (*S*)-**86** (5 mol.%), **88** (20 mol.%), neat, 4 °C, 36 h; (*b*) LiOH, PriOH, rt, 24 h; 4-epiajanol (R^1 = OH, R^2 = Pri); pygmol (R^1 = OH, R^2 = CMe_2OH); dihydroxyeudesmane (R^1 = H, R^2 = CMe_2OH); eudesmanetetraol (R^1 = OH, R^2 = $CMe(OH)CH_2OH$).

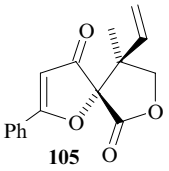
Scheme 16



HMDS is hexamethyldisilazane.

methylhept-5-en-2-yl]cyclohex-2-enone (**102**) containing a chiral isoprenoid moiety in position 4 of the carbocycle was prepared in a 68% overall yield and a 86% diastereomeric excess by the reaction sequence including addition of (*R*)-citronellal (*R*)-**90** to enone **85** in the presence of the prolinol (*S*)-**86**–diol **88** catalytic system followed by potassium hydroxide-induced intramolecular crotonic condensation *in situ* of the resulting Michael adduct (2*S*,3*R*)-**103a** (Scheme 16).

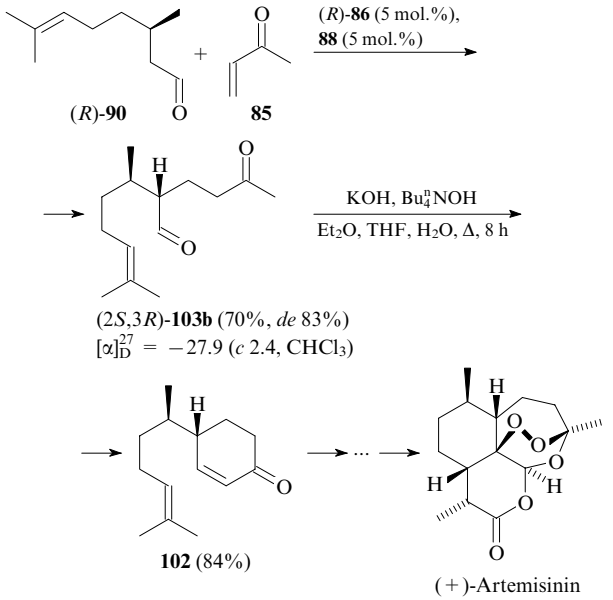
Terpenoid **102** was then converted to biyouyanagin A *via* the sequence of reactions comprising methylation with the Grignard reagent and photochemical [2 + 2]-cycloaddition of the resulting cyclohexadiene derivative **104** to spiro compound **105** (yield 54%).



105

It is of interest that intermediate **104** is the antipode of the natural terpene zingiberene.[218–221]

In 2010, Yadav *et al.*[222] synthesized, based on the results obtained by Nicolaou,[216] the sesquiterpene lactone (+)-artemisinin, which has 7 stereocentres and *endo*-peroxide group. This compound is present in medicinal herbs growing in China,[223] and it exhibits antimalarial activity.[224–226] The key organocatalytic step of the synthesis was also 1,4-addition of (*R*)-citronellal (*R*)-**90** to methyl vinyl ketone (**85**); however, in this case, the reaction was carried out in the presence of the catalyst antipode (*R*)-**86**. Since the syntheses of Nicolaou[216] and Yadav[222] were catalyzed by the antipodes of compound **86**, the products (2*S*,3*R*)-**103a** and (2*S*,3*R*)-**103b** should also have different absolute configurations of the arising stereocentre. However, both authors ascribed the same (2*S*,3*R*)-configuration to the corresponding addition products **103a** and **103b**. The Nicolaou's results are well correlated with the data of Gellman and Chi,[54] who demonstrated that the addition products of aldehydes to methyl vinyl ketone (**85**) in the presence of catalyst (*S*)-**86** have 2*S*-configuration. However, the researchers[222] were able to convert product **103b** to the target (+)-artemisinin (7 steps) and to confirm its structure by X-ray diffraction. It is obvious that additional studies are needed to determine the structure of products **103**.



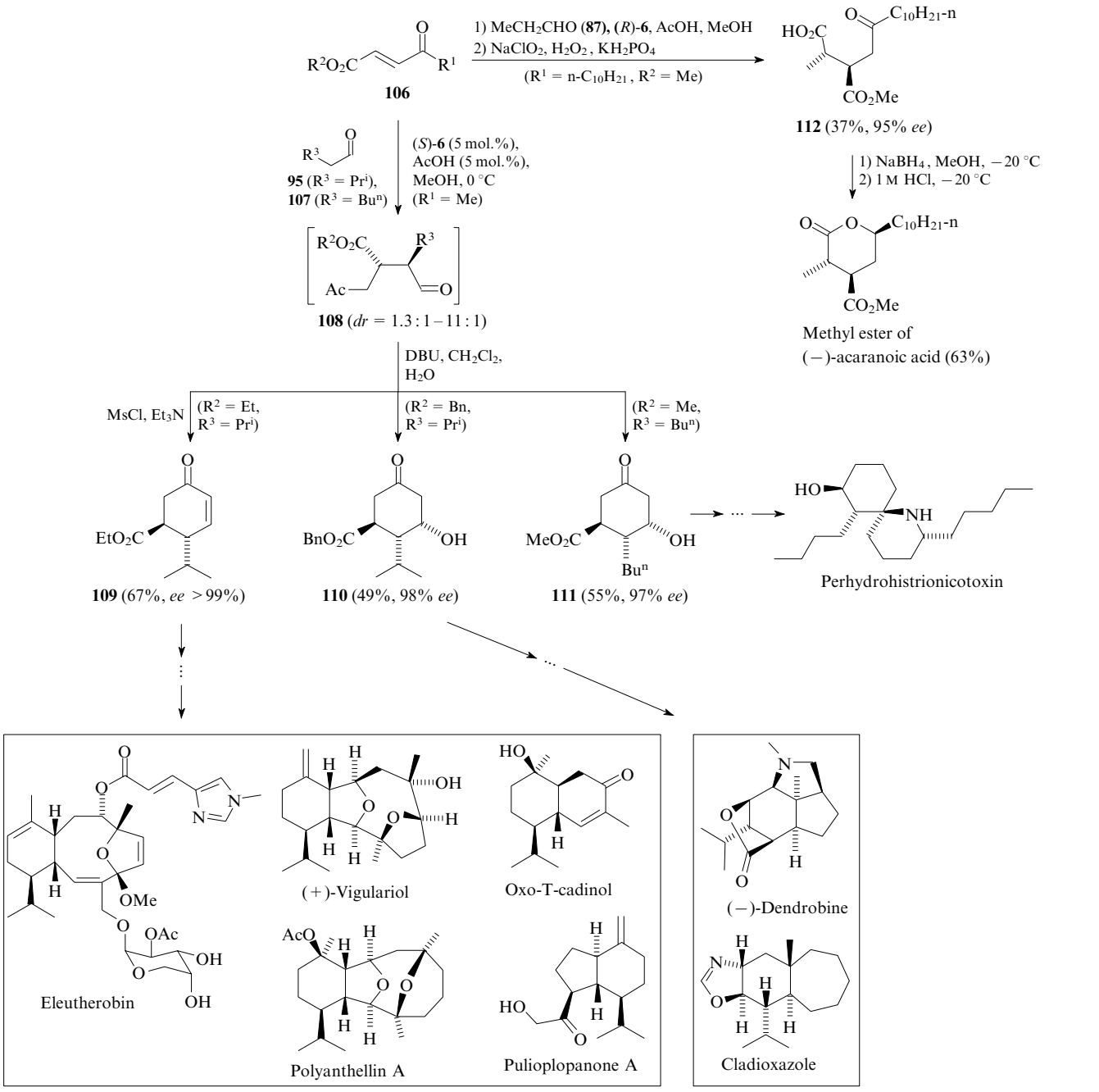
Ma and co-workers[227] markedly extended the scope of the organocatalytic reaction of aldehydes with α,β-unsaturated ketones as an efficient tool in the synthesis of natural compounds by demonstrating that this reaction can be performed for α,β-unsaturated γ-keto esters **106**. The authors found that aldehydes (in particular, compounds **95** and **107**) activated by prolinol ether (*S*)-**6** add to keto esters **106** to give chiral intermediates **108** containing two carbonyl and one ester groups [45%–74%, *dr* = 1.3 : 1–11 : 1, (93%–99%) *ee*]. Unlike the above-considered reactions of aldehydes with methyl vinyl ketone (**85**), the reactions involving keto esters **106** are catalyzed by sterically hindered prolinol diphenyltrimethylsilyl ether **6**, apparently, due to the higher activity of the acceptor containing an ester group. Adducts **108** were subjected without isolation to intramolecular aldolization induced by base (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) to furnish functionally substituted cyclohexene **109** or cyclohexane **110** and **111** derivatives, valuable chiral building blocks for the synthesis of a series of natural compounds and pharmaceutical drugs,

formed with high stereoselectivity (Scheme 17). For example, enone **109** can be converted to diterpenes contained in sea corals, namely, eleutherobin (from the soft coral *Eleutherobia* sp.),[228–231] (+)-vigulariol (from the octocoral *Vigularia juncea*)[232,233] and polyanthellin A (from the Indian soft coral *Cladiella krempfi*),[211,234] calcium channel blocker oxo-T-cadinol[235,236] and the sesquiterpenoid pulioplopanone A,[237] which have cytotoxic properties, and some immunomodulators that stimulate proliferation of T- and B-lymphocytes.[238] Compound **110** is an intermediate for the preparation of the alkaloid dendrobine,[239] which exhibits antipyretic action, and the sesquiterpene cladioxazole isolated from the soft coral *Cladiella*;[240] compound **111** can be used to prepare the alkaloid perhydrohistrionicotoxin.[241]

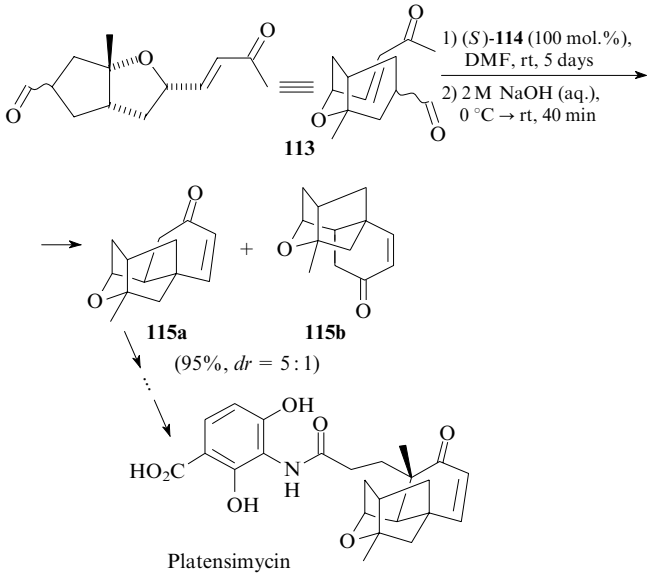
One more promising application of γ-keto esters **106** in the synthesis of natural compounds is their transformation to ketodicarboxylic acid derivatives. Thus the asymmetric addition of propanal (**87**) to enone **106** (R^1 = n-$C_{10}H_{21}$, R^2 = Me) catalyzed by compound (*R*)-**6** and the subsequent selective oxidation of the aldehyde group in the Michael adduct by $NaClO_2$ gave ketodicarboxylic ester **112**.[227] Compound **112** was then converted by conventional keto group reduction and lactonization reactions to the methyl ester of (−)-acaranoic acid, a natural δ-lactone present in the lichen *Acarospora chlorophana*[242] (see Scheme 17).

The above reactions of addition of aldehydes containing no substituents in the α position to the aldehyde group to methyl vinyl ketone (**85**) in the presence of prolinol ether **86**

Scheme 17

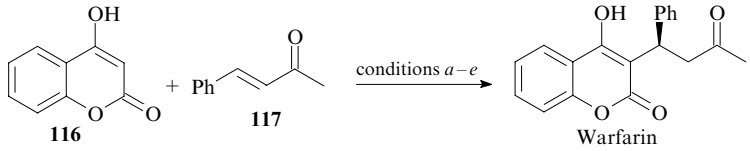


or **6** include catalyst activation of the donor aldehyde through the formation of active enamine intermediate (see Section II, Fig. 6, $\mathbf{d}_6$). However, this type of activation appears to be less efficient in the case of sterically more hindered nucleophiles due to destabilizing interaction with bulky aryl groups of the catalyst. This problem was solved by using other, less sterically crowded catalysts (proline, proline amides, imidazolidine derivatives, primary chiral amines and so on). For example, Yamamoto and co-workers[243] found that bicyclic α,β-unsaturated keto aldehyde **113** undergoes (*S*)-proline (*S*)-**114**-promoted intramolecular Michael reaction to give an adduct, which can be subjected without isolation to base-induced intramolecular crotonic condensation to be stereoselectively converted to a mixture of tetracyclic epimers **115a**,**b** in 5 : 1 ratio. Since the starting compound **113** already contains 4 stereocentres, in this case, only diastereoselectivity of reactions can be considered, the stereoinduction performed by the chiral catalyst being superimposed onto the stereodiscriminating influence of the stereocentres present in the molecule, resulting in a change in the diastereomer ratio. Unfortunately, the Michael reaction proceeds efficiently only when an equimolar amount of catalyst (*S*)-**114** is used. The tetracyclic cage of epimer **115a** is a part of the natural antibiotic platensimycin,[244] which is a metabolite of the bacteria *Streptomyces platensis* and can block enzymes responsible for the biosynthesis of fatty acids in the cells of gram-positive bacteria.[245–247]



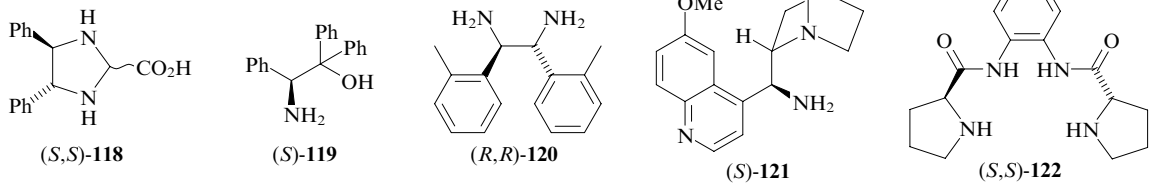
The drug warfarin is a representative of effective up-to-date blood thinners, which being a vitamin K antagonist, inhibits the epoxide reductase dependent on it and thus retards the protein synthesis that results in blood coagulation. This drug having a relatively simple structure is still produced and used as a racemate, although it is known that *S*-enantiomer is 2–5 times more active than *R*-enantiomer.[248] The organocatalytic synthesis of wafrarin enantiomers [(80%–82%) *ee*] was first accomplished by Jørgensen's group[249] in 2003 by the Michael reaction of 4-hydroxycoumarin (**116**) with enone **117** in the presence of chiral imidazolidine (*S*,*S*)-**118** or (*R*,*R*)-**118**. However, the activity of catalysts **118** was moderate: 130–150 h were required for the reaction to complete (Scheme 18, conditions *a* and *a*′). Hansen and co-workers[250] carried out this reaction in the presence of amino alcohol (*S*)-**119** (see Scheme 18, conditions *b*), which allowed the reaction time to be considerably reduced, although at the expense of some decrease in the product yield. Chin and co-workers[251] attained the best results when chiral 1,2-diamine (*R*,*R*)-**120** is used as the catalyst: the yield of wafrarin is 99% and the enantioselectivity is 92% (see Scheme 18, conditions *c*). Chen and co-

Scheme 18



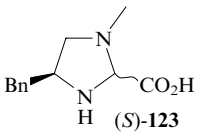
Conditions	Catalyst [amount (mol.%)]	Additive (amount)	Solvent, temperature	Time /h	Yield (%)	Configuration, *ee* (%)	Ref.
a	(*S*,*S*)-**118** (10)	–	THF, rt	130	90	(*S*), 80 (>99)[a]	249
a′	(*R*,*R*)-**118** (10)	–	CH_2Cl_2, rt	150	96	(*R*), 82 (>99)[a]	249
b	(*S*)-**119** (20)	AcOH (1 equiv.)	THF, rt	24	76	(*S*), 81	250
c	(*R*,*R*)-**120** (10)	AcOH (10 equiv.)	THF, rt	24	99	(*R*), 92	251
d	(*S*)-**121** (20)	TFA (40 mol.%)	CH_2Cl_2, rt	12	90	(*S*), 92	252
e	(2*R*,2′*R*)-**122** (20)	succinic acid (10 mol.%)	$Bu^nOH + H_2O$ (50 μl), 40 °C	12	99	(*R*), 83 (>99)[a]	253
e′	(2*S*,2′*S*)-**122** (20)	the same	the same	12	99	(*S*), 83 (>99)[a]	253

[a] The value in parenthrses is *ee* after recrystallization



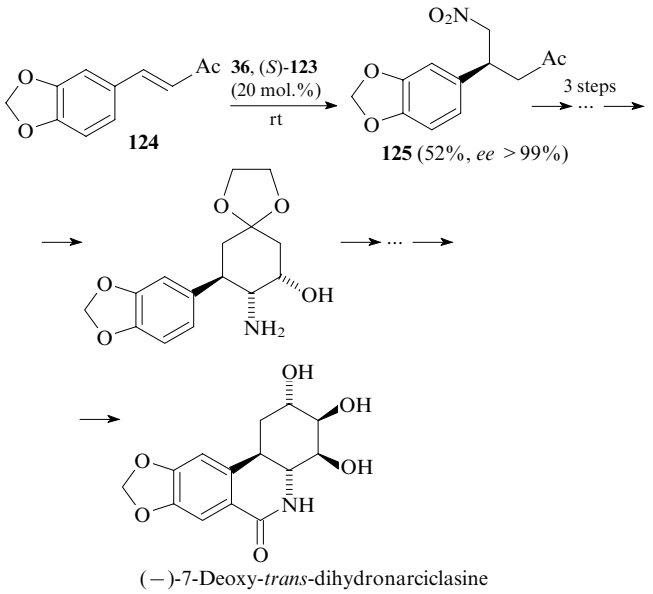
workers [252] were able to reduce the reaction time to 12 h by performing it in the presence of quinuclidine derivative **121** (20 mol.%) (see Scheme 18, conditions *d*). According to Feng and co-workers,[253] 1,2-bis[(*S*)-prolinamido]benzene [(2*S*,2′*S*)-**122**] and the antipode (2*R*,2′*R*)-**122** were efficient catalysts: the enantiomeric excess of the obtained raw wafrarin was fairly high (83%) despite the elevated reaction temperature (40 °C) and increased to 99% after recrystallization (see Scheme 18, conditions *e* and *e*′).

The organocatalytic reactions with α,β-enones can be carried out for the carbon acids in which the nucleophilic centre is bonded to nitrogen or sulfur atoms. Thus under catalysis by imidazolidine-2-carboxylic acid (*S*)-**123**



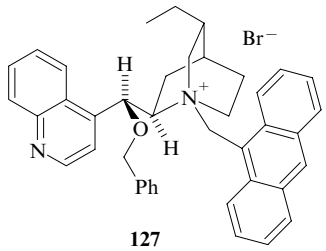
(*S*)-**123**

arylideneacetone **124** adds nitromethane (**36**) giving rise to γ-nitroketone **125** in moderate yield (52%) but with very high enantioselectivity (> 99%).[254] Adduct **125** is a valuable intermediate for the preparation of (−)-7-deoxy-*trans*-dihydronarciclasine, an alkaloid isolated from the *Narcissus* bulbs, which inhibits the synthesis of some proteins and has an antitumour action.[255]



(−)-7-Deoxy-*trans*-dihydronarciclasine

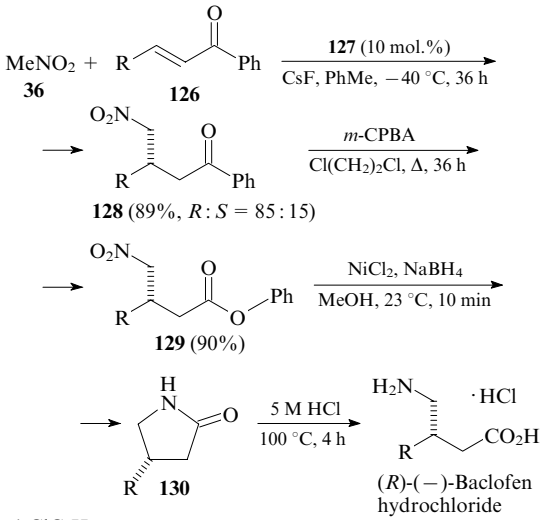
Corey and Zhang [139] found out that the reaction of α,β-enone **126** with nitromethane (**36**) can be carried out in the presence of chiral phase transfer catalyst **127**,



127

which apparently forms a chiral ion pair with the nucleophile (see Section II, Fig. 4). The addition of thus activated nitromethane (**36**) to α,β-enone **126** (R = 4-ClC$_6$H$_4$) resulted in the Michael adduct **128** [yield 89%, *er* (*R* : *S*) = 85 : 15]. The enantiomeric excess for product **128** was increased to 95% by recrystallizing it from an n-hexane – ethyl acetate mixture. The Baeyer – Villiger oxidation of nitroketone **128** gave nitro ester **129**, which was converted to (*R*)-baclofen hydrochloride by reduction and hydrolysis of the resulting lactam **130** (Scheme 19). (Other approaches to the synthesis of baclofen enantiomers are shown in Schemes 9, 10, 23, 27 and 34.)

Scheme 19

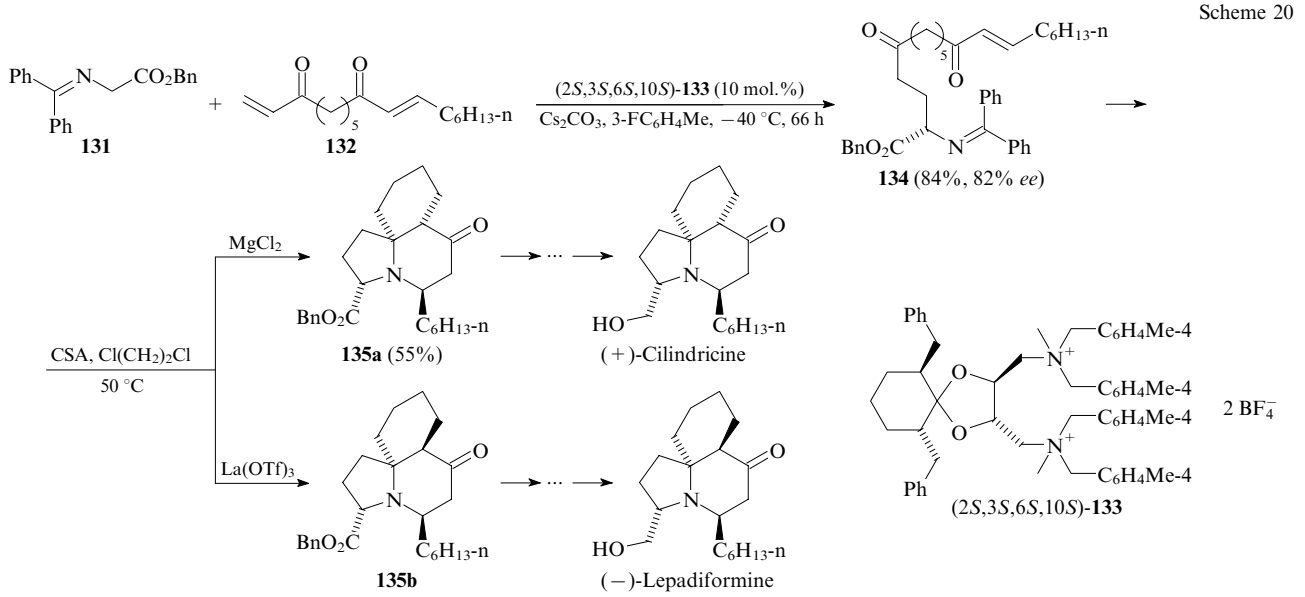


R = 4-ClC$_6$H$_4$.

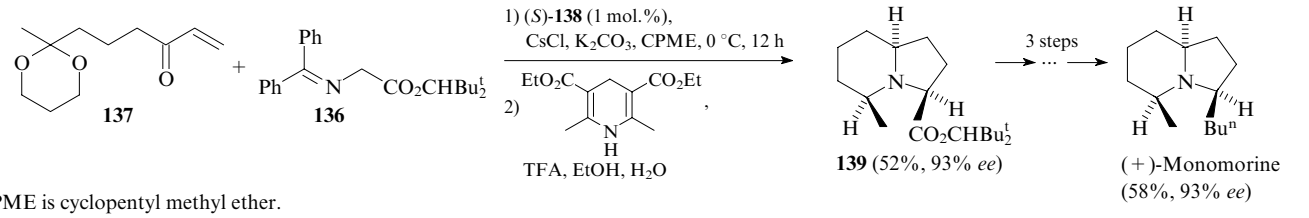
The Schiff's bases obtained from glycine and diphenyl ketone can act as nucleophiles in the reactions with α,β-enones. These compounds are rather weak carbon acids; therefore, reactions with their participation are carried out in the presence of strong inorganic bases (metal carbonates), which promote deprotonation. These reactions are important, as they provide proline derivatives (in particular, annelated ones) and some natural alkaloids. Shibasaki and co-workers [256] used this approach to prepare (+)-cilindricine C, an alkaloid isolated from sea ascidia *Clavelina cylindrica*,[257–259] which suppresses the growth of some types of yeast [260, 261] and tumours.[262] The stereodiscriminating step of the synthesis was the addition of glycine derivative **131** to the terminal double bond of diketodiene **132** in the presence of Cs_2CO_3 and chiral bis(tetraalkylammonium) tetrafluoroborate **133** (10 mol.%). The polycyclic structural fragment of (+)-cylindricine was then formed *via* elegant cyclization of the chiral Michael adduct **134** to tricyclic compound **135a** under the action of camphor-10-sulfonic acid (CSA) in dichloroethane (Scheme 20). It is of interest that in the presence of La(OTf)$_3$, another diastereomer, compound **135b**, which is the precursor of the alkaloid (−)-lepadiformine, was formed predominantly.[263]

In 2009, Maruoka and co-workers [31] developed the enantioselective synthesis of (+)-monomorine, the pheromone of the worker ant *Monomorium pharaonis*.[264] The synthesis includes the step of asymmetric conjugated addition of glycine derivative **136** to enone **137** containing a peripheral protected carbonyl group needed for the subse-

Scheme 20

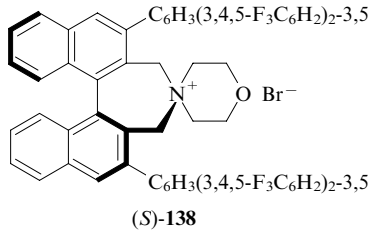


Scheme 21



CPME is cyclopentyl methyl ether.

quent transformations. The reaction was induced by K_2CO_3 in the presence of chiral phase transfer catalyst (*S*)-**138**;

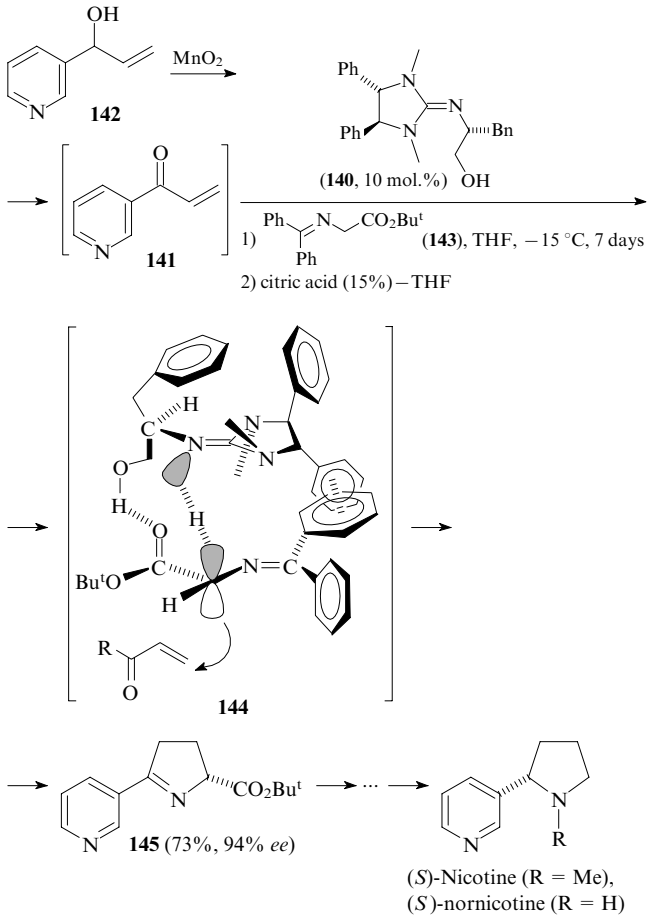


(*S*)-**138**

and the resulting Michael adduct was treated in the same reactor without isolation with the Hantzsch ester and CF_3CO_2H to give octahydroindolizine **139** containing a structural fragment of the target pheromone (Scheme 21).

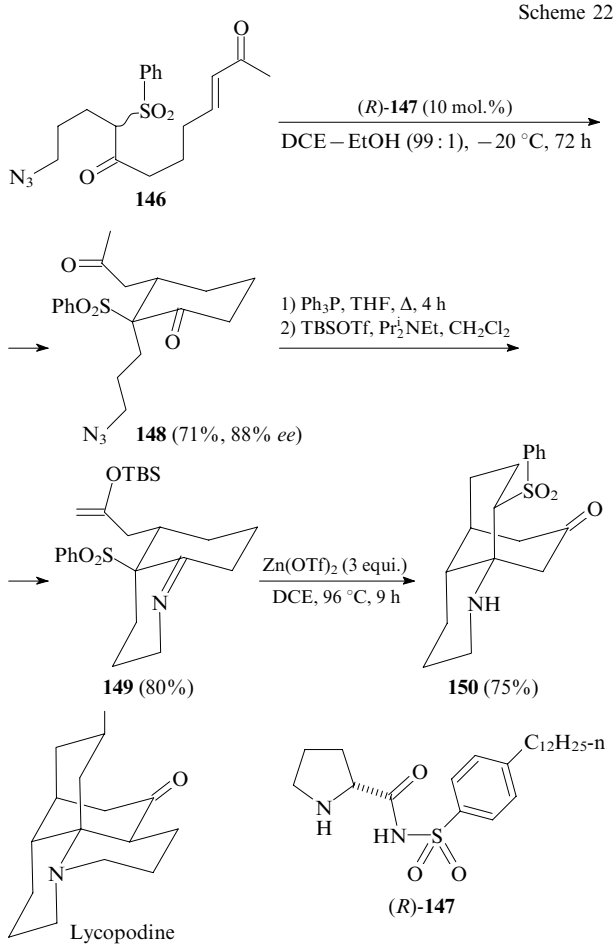
Recently, Ishikava and co-workers[265] successfully applied chiral organocatalyst **140** containing a guanidine fragment in the reaction of pyridyl vinyl ketone **141** (prepared *in situ* by oxidation of alcohol **142**) with diphenyl iminoacetate **143**. In this case, compound **140** functioned simultaneously as a deprotonating agent and a chiral inductor, stereodiscrimination being due to hydrogen bonding between the hydroxy group of the catalyst and the ester group of nucleophile **143** (see associate **144**). The resulting Michael adduct was subjected, without isolation, to intramolecular cyclization to chiral pyrrolinylpyridine **145** by treatment with citric acid in THF. Compound **145** is the direct precursor of (*S*)-nicotine and (*S*)-nornicotine, important chemical nervous system mediators.[266]

The carbon acid in which the nucleophilic centre is activated by an electron-withdrawing sulfone group can also add to α,β-enones in the presence of some organo-



catalysts; the highest selectivity was provided by proline sulfonamides. Carter and Yang [267] found that α,β-enone **146** undergoes intramolecular asymmetric Michael reaction catalyzed by sulfonimide (*R*)-**147** (containing the long-chain alkyl group for improving the solubility) to give cyclization product **148** (after recrystallization, *ee* was 95%). Compound **148** was converted to the silyl ether of bicyclic enol **149** *via* the sequence of Staudinger amination and enolization. Cyclization of product **149** induced by $Zn(OTf)_2$ accompanied by 1,3-migration of the sulfonyl group yielded tricyclic compound **150** containing a structural fragment of lycopodine, a *Lycopodium* alkaloid inhibiting cholinesterase, which has antipyretic [268] and nootropic action (Scheme 22).[94]

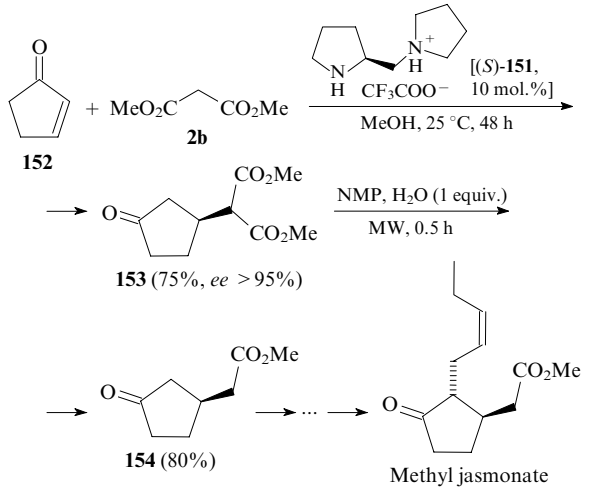
Scheme 22



DCE is dichloroethane.

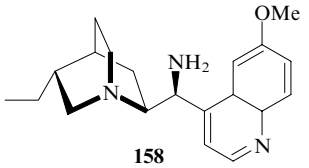
b. Addition of C-nucleophiles to cyclic α,β-enones

As noted above, a number of natural and biologically active compounds contain cyclohexane or cyclopentane moiety. A convenient method for the introduction of stereocentres into such moieties is the asymmetric addition of nucleophiles to cyclic α,β-enones giving rise to a chiral centre in the β position to the carbonyl group. The asymmetric Michael reactions involving cyclic α,β-enones are catalyzed by pyrrolidine derivatives and some other chiral amines able to form iminium cations with enones (see Section II, Fig. 6). Mase *et al.*[269] showed that trifluoroacetate of the pyrrolidine derivative (*S*)-**151** catalyzes the addition of dimethyl malonate (**2b**) to cyclopentenone (**152**), resulting in ketone **153** (yield 75%, *ee* > 95%). Partial hydrolysis and decarboxylation of adduct **153** under microwave irradiation (MW) gives a high yield of cyclopentanone derivative **154**, which is a valuable intermediate in the synthesis of methyl jasmonate [270, 271] used for plant protection.[272]

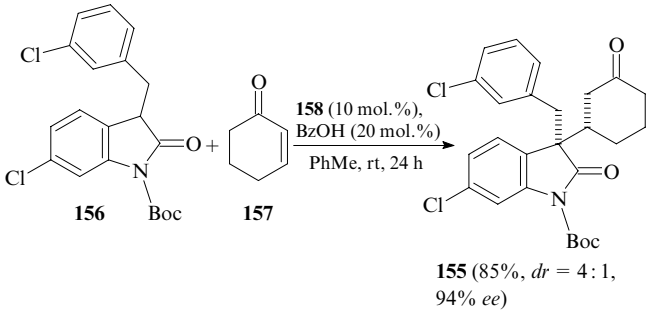


NMP is *N*-methylpyrrolidin-2-one.

In 2010, Melchiorre and co-workers [273] applied the method they developed for asymmetric conjugated addition of oxindoles to cyclic enones to prepare compound **155**, which was patented in 2006 by Hoffmann-La Roche as an antitumour agent.[274] The reaction of oxindole **156** with cyclohexenone (**157**) was catalyzed most efficiently by 9-amino(9-deoxy)dihydroepiquinine **158**;

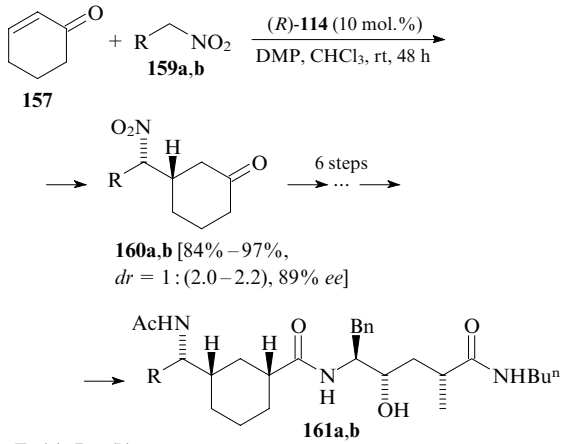


in the presence of this catalyst, product **155** was obtained in a 85% yield, the optical purity of the major *syn*-diastereomer reaching 94%.



In 2010, Hanessian *et al.*[275] carried out the reaction of cyclohexenone (**157**) with nitroalkanes catalyzed by (*R*)-proline (*R*)-**114** to prepare chiral carbocyclic δ-amino acids, which are analogues of inhibitors of some enzymes. Since proline has a substantially lower basicity than catalysts (*S*)-**151** and **158**, this reaction was performed in the presence of deprotonating agent (*trans*-2,5-dimethylpiperazine, DMP), which converts nitroalkanes **159a**,**b** to nitro-

nate anions. Under these conditions, the reaction occurs with relatively low diastereoselectivity; however, the enantiomeric excess of minor diastereomers **160a**,**b**, which are in this case the target compounds, was fairly high (89%). After chromatographic isolation, these diastereomers were converted to dipeptides **161a**,**b**, which inhibit the beta-secretase (BACE1, BACE2) and catepsin D enzymes.



R = Et (**a**), Pr^n (**b**).

3. Reactions C-nucleophiles with α-nitroalkenes

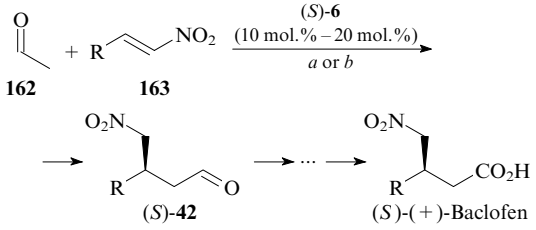
The asymmetric addition of C-nucleophiles (carbonyl compounds, malonic and acetoacetic acid derivatives and so on) to α-nitroalkenes is widely used for the synthesis of chiral nitro compounds.[276] Despite their relatively high toxicity, C-nitro compounds [277,278] are used in medicine (7-nitroindazole, nitrazepam, armin, furacilin) [279] and agriculture (nitropeptin, prolan).[280,281] In addition, the nitro group can be converted to other functional, in particular, pharmacophore groups (amino, hydroxy, keto, carboxy and nitrile oxide groups) or replaced by hydrogen.[282,283] Thus, chiral adducts of α-nitroalkenes with carbonyl compounds are converted to enantiomerically enriched β,γ-substituted pyrrolidines, *i.e.*, heterocyclic compounds having a broad spectrum of biological activities. This method considerably supplements the above-considered method for the preparation of pyrrolidine derivatives from glycine Schiff's bases and α,β-enones (see Section III.2.a). A number of other practically valuable chiral carbo- and heterocyclic compounds can be prepared from the products of asymmetric reactions of α-nitroalkenes with malonic, acetoacetic acid or indole derivatives.

In the reactions of α-nitroalkenes with C-nucleophiles, the catalyst activates the nucleophile (carbonyl compound) by giving enamine intermediates with it (for catalysis by chiral amines, see Section II, Fig. 6) and/or dictates the geometry of the transition state by forming hydrogen bonds with the nitroalkene (for catalysis by urea or thiourea derivatives, see Section II, Fig. 7).[34]

a. Reactions of α-nitroalkenes with aldehydes and ketones

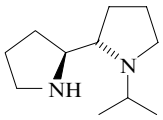
Above (see Scheme 8) we considered methods for the synthesis of the drug baclofen (GABA receptor agonist) that included the asymmetric reaction of nitromethane (**36**) with 4-chlorocinnamaldehyde (**40**) catalyzed by pyrrolidine derivatives [55,121,132–133] (iminium catalysis, see Scheme 9) and the reaction of nitromethane (**36**) with α,β-enone **126** catalyzed by the alkaloid salt **127** [137] (phase transfer catalysis, see Scheme 19). An alternative approach to the synthesis of (*S*)-(+)-baclofen which is based on prolinol (*S*)-**6**-catalyzed reaction of acetaldehyde (**162**) with 4-chloro-β-nitrostyrene (**163**) and includes enamine activation of the carbonyl component was proposed independently by groups of List [137] and Hayashi [138] (Scheme 23). An advantage of this method is the ready accessibility of the reactants; however, the yield (58%–75%) and enantiomeric purity (92% *ee*) of adduct **42** obtained in this way were somewhat lower than those in the reaction of nitromethane (**36**) with 4-chlorocinnamaldehyde (**40**) [61%–91% and (90%–97%) *ee*]; this may be attributed to small size of the acetaldehyde molecule, which makes stereodifferentiation less efficient, and to its partial oligomerization under the conditions used.

Scheme 23



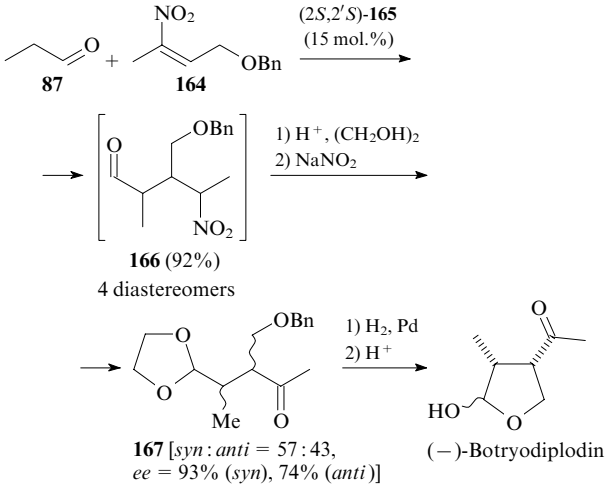
R = 4-ClC_6H_4; (*a*) MeCN, 0 °C, 62–93 h; yield 58%, *er* = 96:4;[137] (*b*) 1,4-dioxane, rt, 36 h; yield 75%, 92% *ee*.[138]

The reactions of α-nitroalkenes with other aliphatic aldehydes are usually more chemoselective. Alexakis and co-workers [284,285] added propanal (**87**) to nitroalkene **164** in the presence of bis-pyrrolidine (2*S*,2′*S*)-**165**

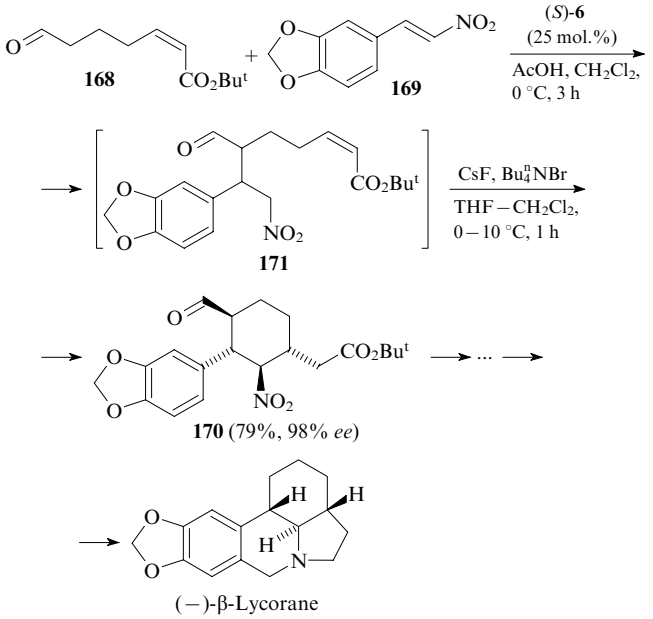


(2*S*,2′*S*)-**165**

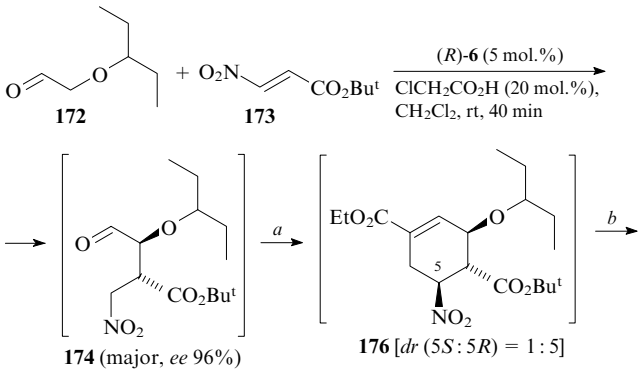
to give the Michael adduct **166** as a mixture of four diastereomers in a 92% total yield. Using acetalization and the Nef reaction, nitro compound **166** was converted to ketone **167**; the number of diastereomers decreased to two and the *ee* value for *syn*-diastereomer was 93%. Hydrogenation and deprotection of the latter product afforded natural antibiotic (−)-botryodiplodin, which was isolated from the mold fungus *Botryodiplodia theobromae* and exhibited a broad spectrum of biological activities.[286–292]

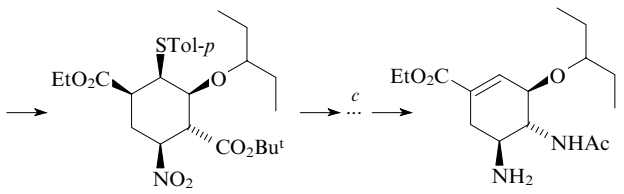


Hong *et al.*[293] used the organocatalytic reaction of the α,β-unsaturated aldehydo ester **168** with nitrostyrene derivative **169** for the enantioselective synthesis of compound **170**, the key intermediate in the synthesis of (−)-β-lycorane, an unusual tetracyclic alkaloid active against tumour cells.[294] In this case, the best results were obtained with prolinol (*S*)-**6** as the catalyst. Adduct **171** was introduced, without isolation, into the second, this time intramolecular, Michael reaction by treatment with the base (CsF) in the presence of phase transfer catalyst (Bu^n_4NBr). The nitronate anion generated *in situ* served as the nucleophile in this reaction and cyclization product **170** formed almost stereospecifically (98% *ee*).



In 2009, Hayashi and co-workers[295] developed a method for the synthesis of the medicinal drug oseltamivir (tamiflu), a neuramidase inhibitor used for the combat against the bird flu virus H5N1.[296] The method was based on prolinol (*R*)-**6**-catalyzed asymmetric addition of glycolaldehyde ether **172** to β-nitroacrylate **173**. The chiral addition product **174**, which formed in a quantitative yield and with very high enantioselectivity, was introduced without isolation into the reaction with vinylphosphonate **175** in the presence of a base (Cs_2CO_3). This brought about a Michael and Horner–Wadsworth–Emmons domino reaction sequence to give cyclohexene derivative **176**. Compound **176** was formed as a mixture of 5*R*- and 5*S*-diastereomers in which the desired 5*S*-diastereomer was a

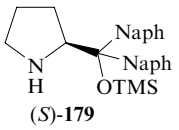




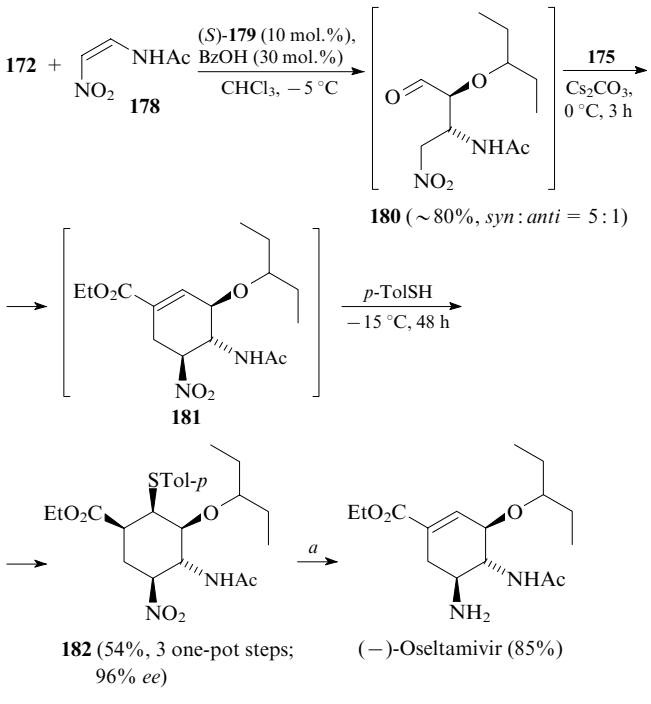
(*a*) 1) $(EtO)_2P(O)C(=CH_2)CO_2Et$ (**175**), Cs_2CO_3, 0 °C, 3 h; 2) EtOH, rt, 15 min; (*b*) *p*-TolSH, EtOH, −15 °C, 36 h; (*c*) 2 one-pot reactions (6 steps).

minor component. The problem was solved owing to the fact that treatment of cyclohexene **176** with *p*-toluenethiol in the presence of Cs_2CO_3 induced C(5)-epimerization, giving rise to the desired configuration of the Michael adduct **177**. Compound **177** was converted to the target drug (−)-oseltamivir in several steps in an overall yield of 82%.

Yet another, shorter (5 steps, 2 synthetic operations) route to oseltamivir was proposed recently by Ma and coworkers.[297] To eliminate the transformation of the ester group into the acylamino group at the final steps of the sequence, they used nitroenamine **178** instead of β-nitroacrylate **173** in the reaction with glycolaldehyde ether **172** and carried out the Michael reaction in the presence of prolinol ether (*S*)-**179**,



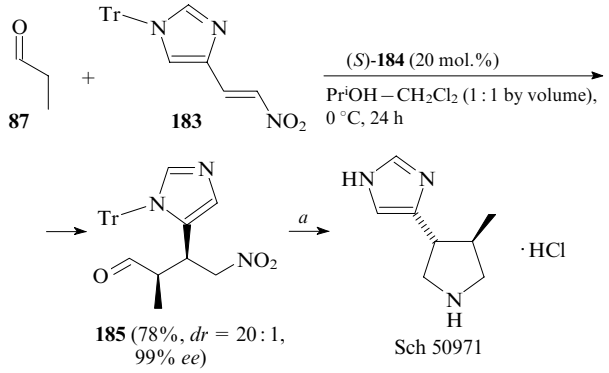
which has configuration at the C(2) chiral centre of the pyrrolidine ring different from that in catalyst (*R*)-**6**. Consequently, adduct **180** in which the desired 2*R*,3*S*-isomer predominated was obtained in ∼80% yield with fairly high



(*a*) 1) TMSCl, Zn, EtOH; 2) K_2CO_3, EtOH.

syn-diastereoselectivity. Product **180** was converted successively, without isolation, to nitrocyclohexene **181** and nitrocyclohexane **182** derivatives by a scheme similar to Hayashi's scheme;[295] the overall yield of compound **182** (3 steps) was 54% and the enantiomeric excess was 96%. The synthesis of oseltamivir was completed by one-pot (yield 85%) reduction of the nitro group by the Zn–TMSCl system and elimination of the arylthio group on treatment with K_2CO_3. The authors believe that owing to its efficiency, this method has good prospects for practical application.

Chiral γ-nitrocarbonyl compounds formed in the asymmetric addition reactions of aldehydes and ketones to α-nitroalkenes are valuable building blocks for the preparation of enantiomerically enriched derivatives of pyrrolidine, which is a part of many biologically active compounds. In 2006, Chinese researchers[298] reported the synthesis of 4-[(3*R*,4*R*)-4-methylpyrrolidin-3-yl]-1*H*-imidazole hydrochloride (product Sch 50971), a potent agonist of histamine H_3 receptors, which is under trials as a remedy for treating obesity, Alzheimer's disease and attention deficit hyperactivity disorder.[299–302] The key reaction was the asymmetric addition of propanal (**87**) to nitroalkene **183** in the presence of 2-(*S*)-[(*N*-trifluoromethylsulfonyl)aminomethyl]pyrrolidine (*S*)-**184**, resulting in the desired Michael adduct **185** with exceptionally high *syn*-diastereo- and enantioselectivities. Compound **185** was converted to the target product Sch 50971 by catalytic hydrogenation and deprotection of the imidazole ring.

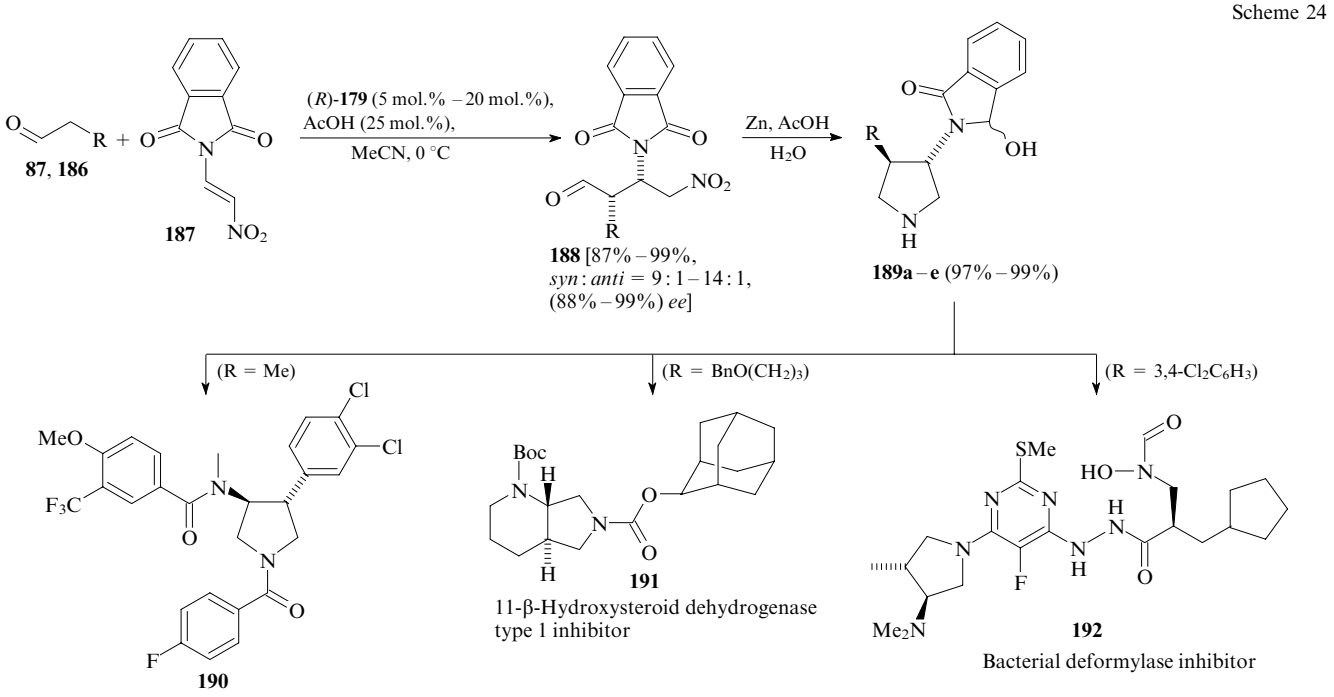


Tr = CPh_3; (*a*) 1) H_2, $Pd(OH)_2$ (20%), MeOH, 3 atm, rt, 96 h (yield 65%); 2) TFA (95%), 3 h (yield 91%).

3-Aminopyrrolidine derivatives are popular target compounds in the search for new pharmaceutical drugs. In 2010, Ma and coworkers[297] proposed an approach to the synthesis of these chiral biologically active compounds based on dinaphthylprolinol (*R*)-**179**-catalyzed asymmetric addition of aliphatic and aromatic aldehydes **87** and **186** to 1-nitro-2-(phthalimido)ethene **187** (synthetic equivalent of 1-amino-2-nitroethene). This gave chiral β-phthalimido-γ-nitroaldehydes **188** with high *syn*-diastereo- (*dr* = 9 : 1–14 : 1) and enantioselectivity [(88%–99%) *ee*] (Scheme 24). Nitroaldehydes **188** were then reduced with the Zn–AcOH system to 3-aminopyrrolidine derivatives **189a–e**, which are intermediates for the preparation of important natural receptor antagonists and enzyme inhibitors. For example, compound **189a** can be a precursor of the neurokinin-2 receptor (NK2) antagonist **190**;[303] compound **189b** is used to prepare 11-β-hydroxysteroid dehydrogenase inhibitor **191**,[304] and compound **189c** serves for the synthesis of bacterial deformylase inhibitor **192**.[305] Furthermore, pyrrolidine derivatives **189d,e** can serve as building blocks for the synthesis of drugs for treating schizophrenia symptoms (NK1/NK3 receptor antagonists).[306]

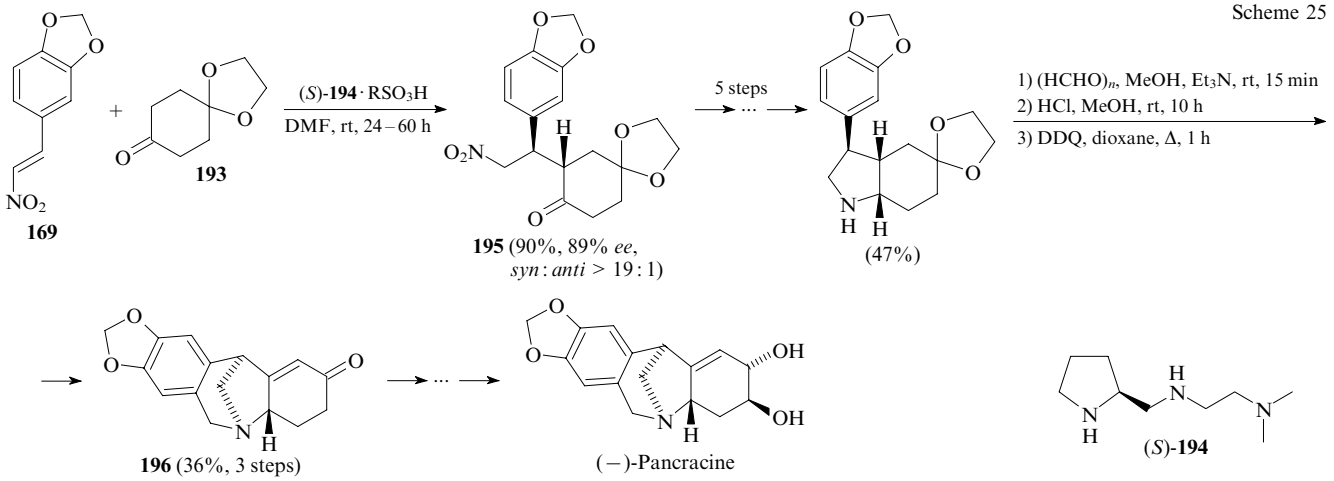
Recently, Pansare *et al.*[307] utilized the asymmetric Michael reaction in the total synthesis of the montanine alkaloid (−)-pancracine.[308, 309] A specific feature of this reaction is that ketone **193** was used as the nucleophile and

Scheme 24



For **189**: R = Me (**a**), $BnO(CH_2)_3$ (**b**), 3,4-$Cl_2C_6H_3$ (**c**), 4-ClC_6H_4 (**d**), 4-F-C_6H_4 (**e**).

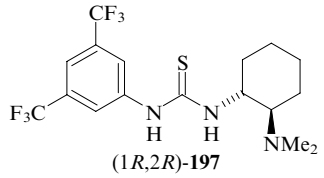
Scheme 25



highly basic diamino pyrrolidine derivative (*S*)-**194** was used as the organocatalyst. Under proposed conditions, ketone **193** added to nitroalkene **169** to give Michael adduct **195** in a good yield and with high diastereo- and enantioselectivities. Using a reaction sequence consisting of reduction, two cyclizations, ketal deprotection and dehydrogenation, nitroketone **195** was converted to compound **196** containing the (−)-pancracine polycyclic cage (Scheme 25).

b. Reactions of α-nitroalkenes with malonic and acetoacetic acid derivatives

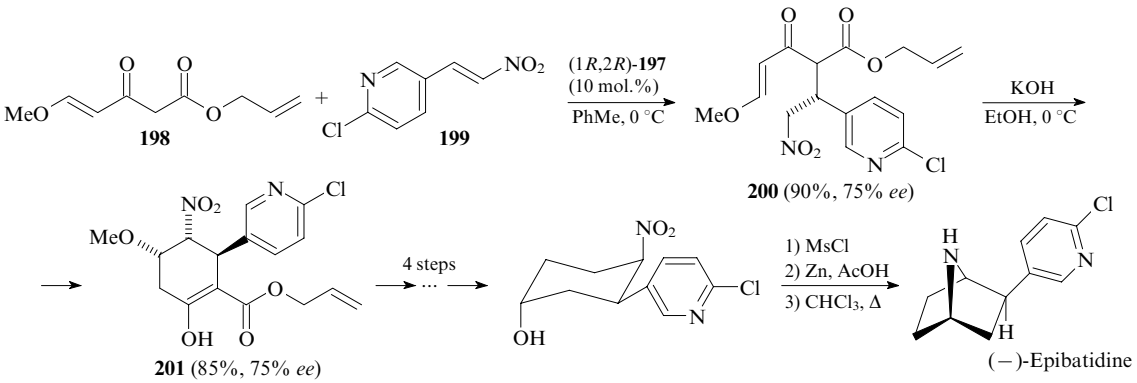
Malonic and acetoacetic acid derivatives (usually esters) are applicable as C-nucleophiles in the reactions with α-nitroalkenes. As a rule, these nucleophiles do not form enamines with chiral amines; therefore, the reactions are performed in the presence of so-called bifunctional catalysts, which, on the one hand, activate the electrophile (α-nitroalkene) by hydrogen bonding and, on the other hand, promote deprotonation of the nucleophile by means of the basic amino group (see Section II, Fig. 7, associate $\mathbf{e}_5$). An example are organocatalysts developed by Takemoto and co-workers,[147] containing a chiral amine (diamine) fragment and an urea (thiourea) group in one molecule, in particular, compound (1*R*,2*R*)-**197**. In the presence of chiral thiourea (1*R*,2*R*)-**197**, β-keto ester **198** added to nitroalkene **199** to give the Michael adduct **200**. The latter was converted to densely substituted cyclohexene **201** through the intramolecular Michael reaction. This product is a precursor[310] of (−)-epibatidine[311] (7 steps), an alkaloid having analgesic and paralytic properties and binding to nicotine- and muscarine-type acetylcholine receptors (Scheme 26).



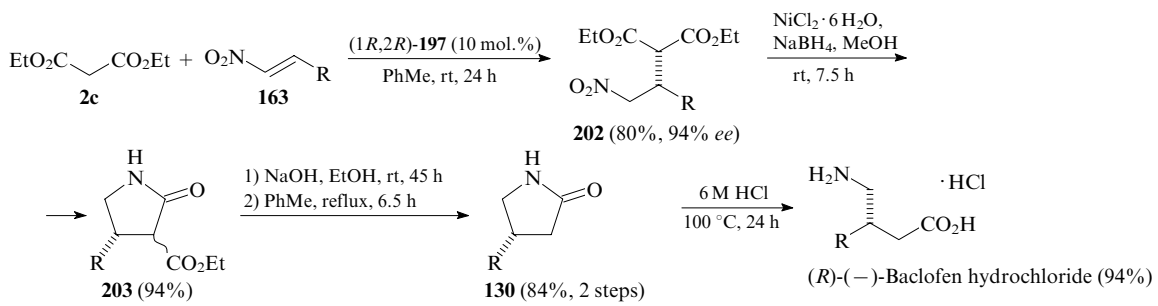
Catalyst (1*R*,2*R*)-**197** developed by Takemoto[147] also proved to be efficient in the synthesis of enantiomers of the drug baclofen mentioned above (see Schemes 9, 10, 19 and 23), which is used to treat central nervous system diseases. In the presence of this catalyst, diethyl malonate (**2c**) added to nitroalkene **163** to give adduct **202**. However, unlike nitroaldehyde **42**, which is obtained by alternative Scheme 9, adduct **202** was readily crystallized from an n-hexane–ethyl acetate mixture, which increased *ee* to >99%. The reduction of the nitro group in adduct **202**, which was accompanied by spontaneous cyclization, gave lactam **203**; upon decarboxylation and hydrolysis of the amide bond in the resulting pyrrolidinone, compound **130** was converted to (*R*)-(−)-baclofen hydrochloride (yield 59% over 5 steps, *ee* >99%) (Scheme 27).

Recently, Li and co-workers[125] used a similar approach to prepare the (*S*)-enantiomer of the anticonvulsant pregabalin. Unlike the synthesis of this drug by prolinol (*R*)-**6**-catalyzed reaction of nitromethane (**36**) with α,β-enal **37** (see Section III.1, Scheme 7),[99] in this case, the asymmetric reaction of diethyl malonate (**2c**) with α-nitroalkene **204** catalyzed by compound (1*R*,2*R*)-**197** was the stereodetermining step of the process (Scheme 28); the yield and *ee* of chiral adduct **205** were comparable with these values obtained in the work considered above.[99] Adduct **205** was

Scheme 26



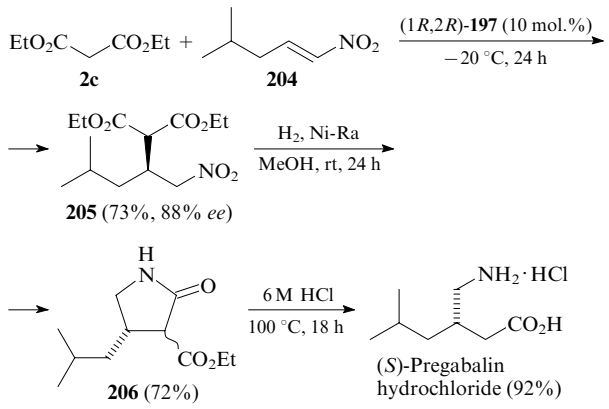
Scheme 27



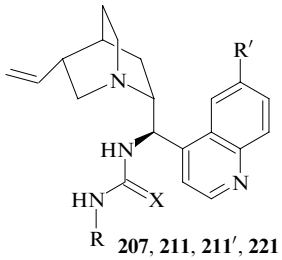
R = 4-ClC_6H_4.

converted to the target compound *via* reductive amidation in the presence of Raney nickel (Ni-Ra) and hydrolysis of pyrrolidone **206** accompanied by decarbonylation.

Scheme 28



Quinine derivatives containing thiourea groups are effective catalysts for the reactions of carbon acids with α-nitroalkenes; these catalysts induce chirality by forming hydrogen bonds with nitroalkene being simultaneously coordinated to the hydrogen atom of the carbon acid by the basic nitrogen atom (see Section II, Fig. 7, associate $\mathbf{e}_5$). Koskinen and coworkers [126] employed bifunctional catalyst **207** to synthesize (*S*)-pregabalin *via* the reaction of nitroalkene **204** with Meldrum's acid (**208**).



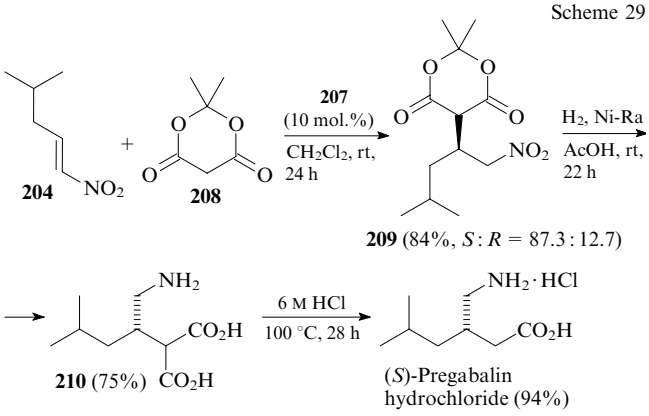
207, **211**, **211′**, **221**

R = CPh_3, R′ = OMe, X = S (**207**);
R = 3,5-$(CF_3)_2C_6H_3$, R′ = H:
X = S (**211**), O (**221**);
R = 3,5-$(CF_3)_2C_6H_3$, R′ = OMe,
X = S (**211′**).

Adduct **209** (75% *ee*) was reduced to aminodicarboxylic acid **210**, which was partially decarboxylated to give the desired (*S*)-pregabalin hydrochloride (Scheme 29).

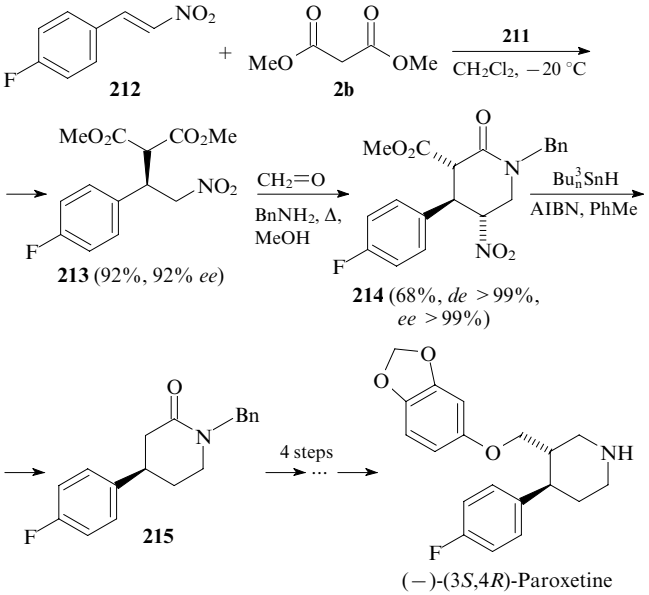
Alkaloid **211** with similar structure and catalysis mode was used as the organocatalyst to prepare the antidepressant (−)-(3*S*,4*R*)-paroxetine and the phosphodiesterase inhibitor (*R*)-rolipram [89] (see also Section III.1, Schemes 1, 2 and Fig. 9). In the presence of thiourea **211**, carbon acid **2b** reacts with 4-fluoro-β-nitrostyrene (**212**) to give Michael adduct **213** (after recrystallization from an Et_2O–petroleum ether mixture, the yield was 78% and *ee* was >99%), which

Scheme 29



was converted to piperidinone **214** by the Mannich reaction and then to compound **215** containing the key structural fragment of (−)-paroxetine by denitration and decarboxylation reactions (Scheme 30). The synthetic route comprising a similar organocatalytic step gave also (*R*)-rolipram [89] with extremely high *ee* value (>99%).

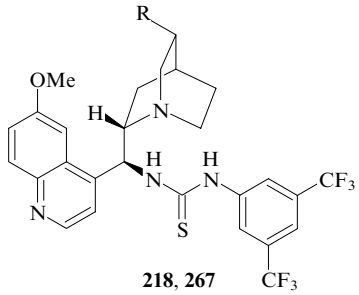
Scheme 30



AIBN is azobis(isobutyronitrile).

γ-Butyrolactone derivatives play an important role in the living nature. These small chiral molecules perform the signalling function [312] in some enzymatic reactions, in particular, in the preparation of secondary metabolites of the bacteria *Streptomyces*, which are used as antibio-

tics.[313] In 2008, Jørgensen and co-workers[314] developed an enantioselective method for the synthesis of compounds containing a γ-butyrolactone moiety based on the asymmetric Michael reaction of carbon acid **216** with nitroalkene **217**. Quinine-derived thiourea **218** proved to be the most efficient catalyst for this reaction.



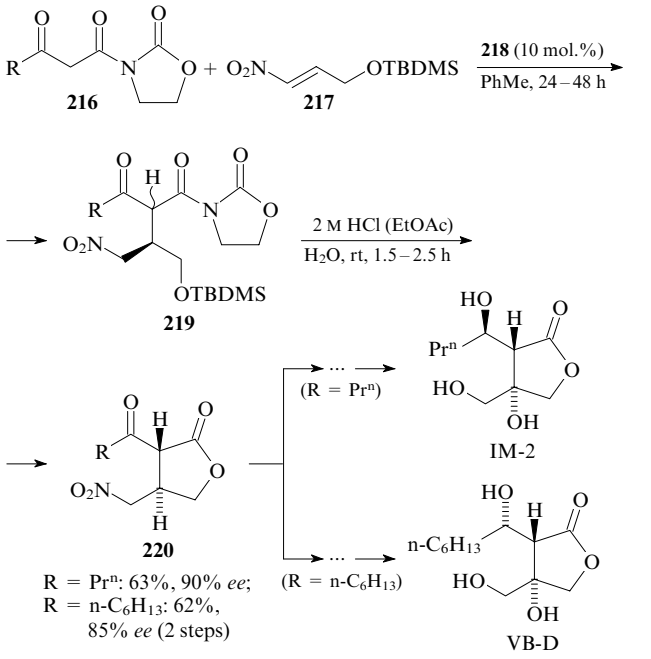
218, **267**

R = CH_2=CH (**218**), Et (**267**).

Adducts **219** were obtained as a mixture of diastereomers (*dr* = 3 : 1 – 4 : 1); however, the products of their lactonization **220** were isolated as single diastereomers having 85% *ee* – 90% *ee*. Using trivial transformations of functional groups, lactones **220** were converted to known regulators VB-D and IM-2 of antibiotic biosynthesis (Scheme 31).

In 2009, Dixon and co-workers[315] applied alkaloid **221** with a similar structure, in this case, modified by an urea fragment, in the total synthesis of (−)-nakadomarin A, an alkaloid isolated from the sea sponges *Amphimedon* sp., which grow in the coastal water of Okinawa (Japan). This alkaloid suppresses the development of the mouse lymphoma L1210 cells, inhibits the cyclin-dependent kinase-4 and exhibits antimicrobial activity against some fungi and gram-positive bacteria.[316, 317] In the presence of catalyst **221**, the chiral polycyclic carbon acid **222** stereoselectively added to nitroalkene **223** to give Michael adduct **224** in a moderate yield as a diastereomer mixture (∼10 : 1). Compound **224** was converted to the target alkaloid over 5 synthetic steps, which occur with retention of the configuration of stereocentres (Scheme 32).

Scheme 31

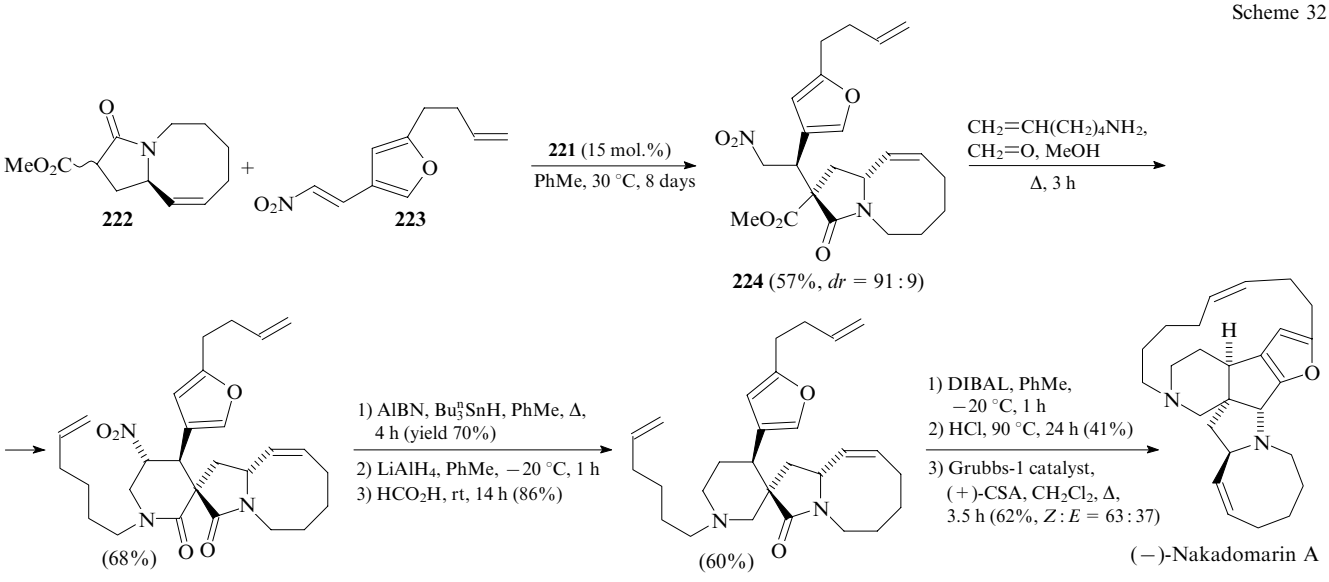


TBDMS = $SiBu^tMe_2$.

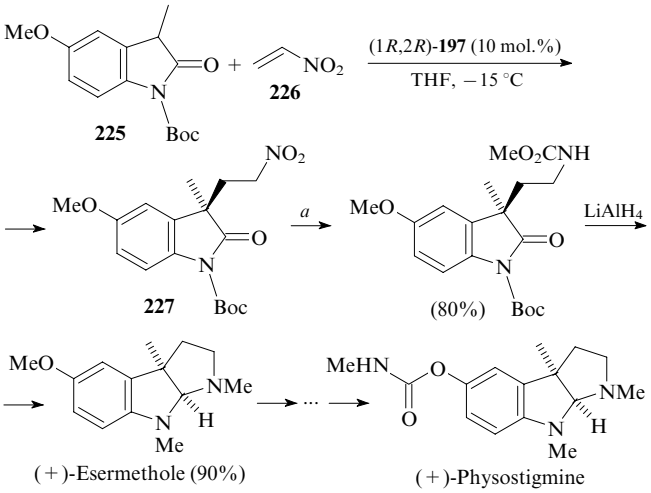
c. Reactions of α-nitroalkenes with indole derivatives

Derivatives of indole, a heterocycle present in a number of pharmaceutical drugs and natural alkaloids, can function as nucleophiles in the reactions with α-nitroalkenes. These reactions are catalyzed by chiral thioureas and phosphates, which activate the nitroalkene by hydrogen bonding. Barbas III and co-workers[318] demonstrated that in the presence of thiourea derivative (1*R*,2*R*)-**197**, N-protected 3-methyl-2-oxoindole **225** reacts with nitroethylene **226** to give Michael adduct **227**, having a quaternary stereocentre C(3) and difficult to access by other methods, with a very high enantioselectivity (96%). Using trivial reduction, cyclization and modification of the methoxy group in the aromatic ring, compound **227** was converted to alkaloids (+)-esermethole and (+)-physostigmine in high yields.

Scheme 32

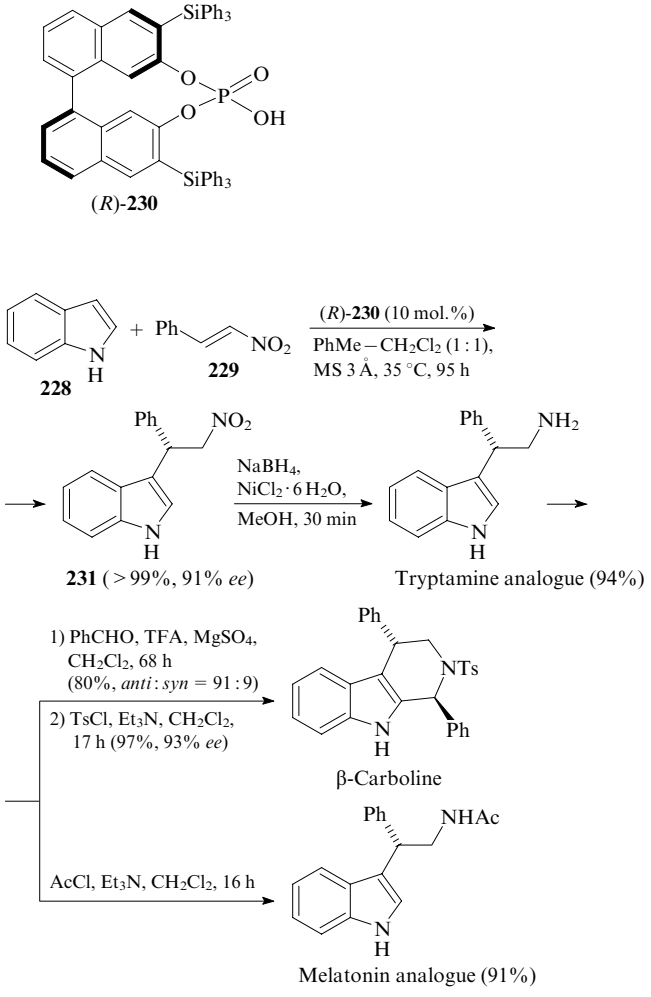


DIBAL is diisobutylaluminium hydride.



(*a*) 1) Ni-Ra; 2) $ClCO_2Me$, Hünig base.

Direct enantioselective Friedel–Crafts alkylation of indole (**228**) with β-nitrostyrene (**229**) (and its derivatives substituted in the ring) was used by Akiyama and co-workers [319] to synthesize analogues of tryptamine [320] and melatonin [321] (natural amines that play an important role in the living organisms) and β-carbolines.[322] This reaction was found to efficiently proceed in the presence of chiral phosphoric acid ester (*R*)-**230**



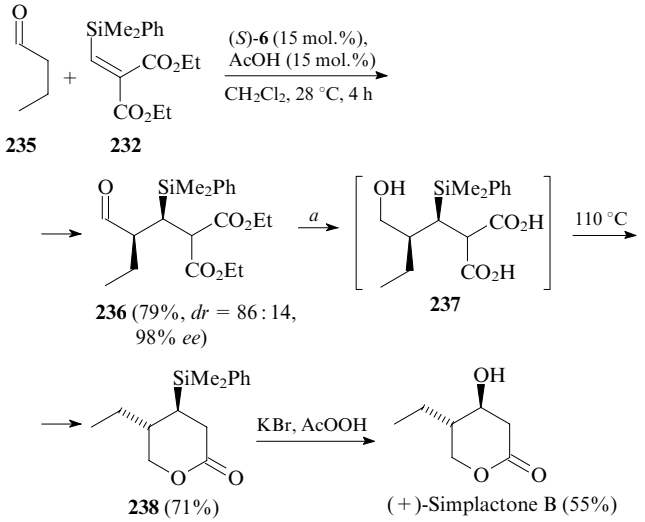
and molecular sieves (MS 3 Å), resulting in alkylated product **231** (*ee* 91%).

According to the authors, the role of the molecular sieves is to dry the solvent, thus providing anhydrous conditions optimal for this reaction. Note that in the presence of organocatalysts containing a bis(sulfonamide) [323] or thiourea moiety,[324] indole derivatives reacted with α-nitroalkenes much less selectively.

Currently, methods of organocatalytic addition of other C-nucleophiles (oxazolones,[325] alkylidenemalononitriles [70, 326, 327]) to α-nitroalkenes have been developed; they can be useful for the preparation of chiral biologically active compounds (α,α-disubstituted α-amino acids, 1-tetralones, *etc.*).

4. Reactions of C-nucleophiles with other electron-deficient alkenes

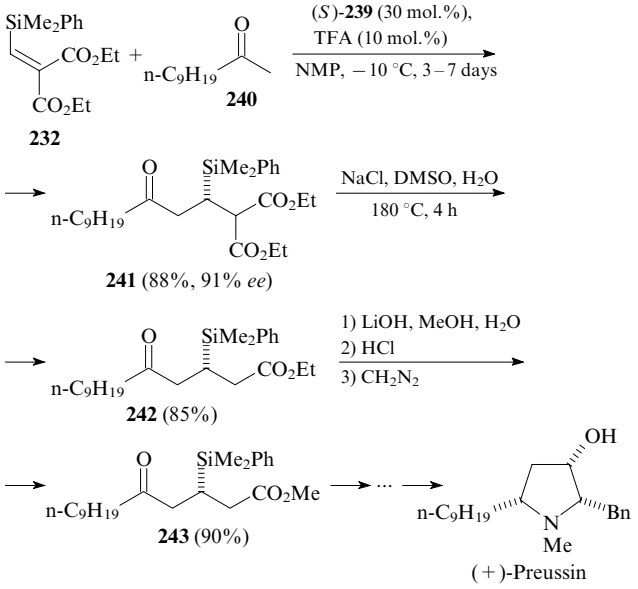
Several examples of organocatalytic asymmetric reactions of C-nucleophiles with other electron-deficient alkenes are known, in particular, with diethyl 2-[(dimethyl(phenyl)silyl)methylene]malonate (**232**), 1-chloro-1-cyanoethene (**233**), 1,1-bis(phenylsulfonyl)ethene (**234**), 4-nitro-5-styrylisoxazole and α,β-unsaturated *N*-acylpyrrole. Chowdhury and Ghosh [328] developed a method for the synthesis of (+)-simplactone B, which is the antipode of the corresponding natural compound.[329] The key step of the synthesis is the asymmetric addition of butanal (**235**) to silylmethylidenemalonate **232** in the presence of prolinol (*S*)-**6**. This reaction, which includes enamine activation of the donor aldehyde, furnishes chiral adduct **236** in 79% yield and with fairly high *syn*-diastereo- and enantioselectivities. Using the one-pot sequence of reduction and hydrolysis, product **236** was converted to dicarboxylic acid **237**, which eliminated the carboxy group on heating being cyclized to lactone **238**. The Fleming–Tamao oxidation of the latter completed the total synthesis of (+)-simplactone B.



(*a*) 1) $NaCNBH_3$, THF; 2) LiOH, MeOH, H_2O.

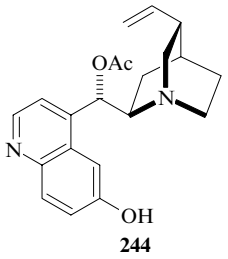
The same authors [330] found that in the presence of pyrrolidino(pyrrolidin-2-yl)methane (*S*)-**239** [deprotonated analogue of catalyst (*S*)-**151**], which is a stronger nucleophile than prolinol (*S*)-**6**, methyl ketones can also react with alkene **232**, the reaction occurring regioselectively at the ketone methyl group. Using this method, undecan-2-one (**240**) was converted fairly enantioselectively to adduct **241**,

which was then transformed to monoethyl ester **242** and then to keto ester **243**, an intermediate for the preparation of a pyrrolidine alkaloid, (+)-preussin,[331,332] having antifungal properties.



Interesting opportunities for the enantioselective preparation of natural alkaloids are opened by asymmetric addition reactions of C-nucleophiles to 1-chloro-1-cyanoethene (**233**). The chlorine atom present in the resulting adduct can then be replaced by the azide group, which serves as the source of nitrogen for construction of the desired heterocycle. These reactions are carried out in the presence of bifunctional organocatalysts that contain a tertiary amino group, which forms, after ionization of C-nucleophile, a chiral ion pair with its conjugate base, and a hydroxy or thiourea group, which enantioselectively fixes the alkene in the transition state by means of hydrogen bonding with the cyano group (see also Section II, Fig. 7).

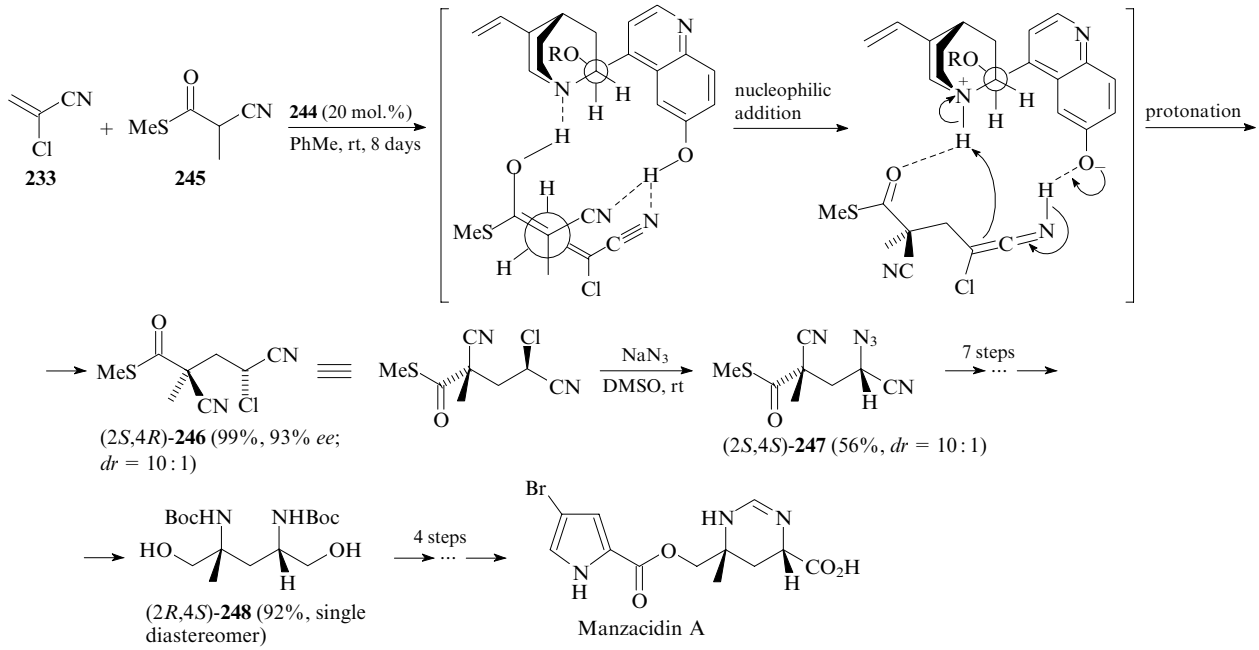
In 2006, Deng and co-workers [333] used for the first time quinidine derivative **244**

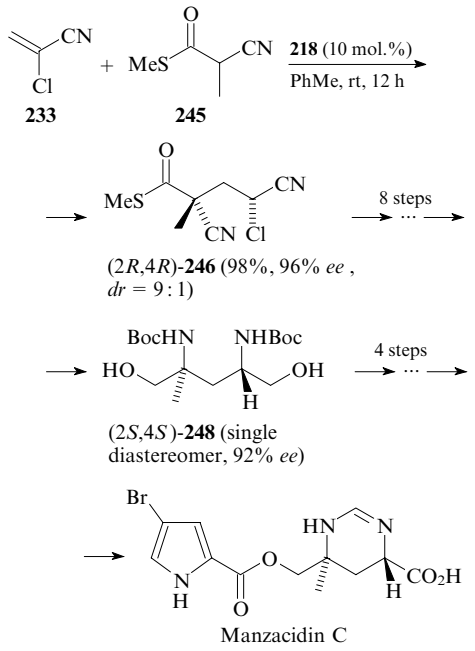


to catalyze the reaction of carbon acid **245** with 1-chloro-1-cyanoethene (**233**) for one-step formation of two stereocentres separated by a methylene group, one centre containing a tertiary and the other containing a quaternary carbon atom. The corresponding Michael adduct (2*S*,4*R*)-**246** was prepared in a quantitative yield and with high diastereo- and enantioselectivities. A multistep sequence of reactions that included nucleophilic substitution of the azide group for the chlorine atom [compound (2*S*,4*S*)-**247**] and transformation of the nitrile and thioester groups [compound (2*R*,4*S*)-**248**] produced the target alkaloid (−)-manzacidin A (Ref. 334) with retention of the chiral centres formed in the organocatalytic step (Scheme 33).

A year later the same group of researchers [64] carried out the reaction between compounds **233** and **245** in the presence of quinine derivative **218** modified with a thiourea group and having configuration of one of the chiral centres different from that of compound **244**. This gave Michael adduct (2*R*,4*R*)-**246** with the opposite configuration of the quaternary carbon atom, which was converted to the alkaloid (−)-manzacidin C, a diastereomer of manzacidin A obtained previously.

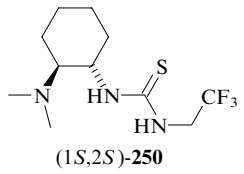
Scheme 33



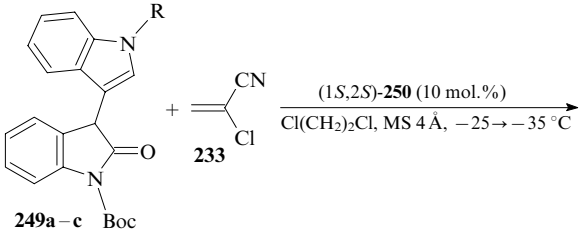


This proves the applicability of organocatalysis for targeted stereoselective formation of polynuclear building blocks for preparing natural alkaloids containing tertiary and quaternary carbon atoms with different configurations in positions 1 and 3 of the carbon chain.

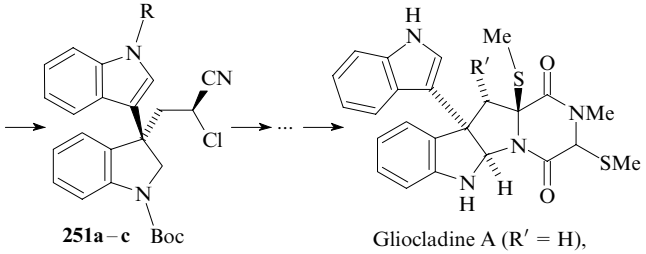
Recently, Luo and co-workers [335] found that the asymmetric Michael reaction of 1-chloro-1-cyanoethene (**233**) with 3-substituted 2-oxindoles **249** can be efficiently catalyzed by bifunctional derivative of *trans*-1,2-diaminocyclohexane (1*S*,2*S*)-**250** containing a thiourea fragment.



According to this method and using 3-(3-indolyl)oxindoles **249a–c** as nucleophiles, they were able to synthesize



R = H (**a**), Bn (**b**), Boc (**c**).

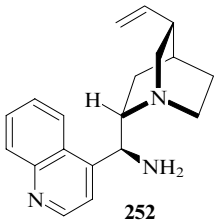


(**a**: 56%, *dr* = 2 : 1, 74% *ee*; **b**: 61%, *dr* = 5 : 1, 81% *ee* ; **c**: 70%, *dr* = 7 : 1, 91% *ee*)

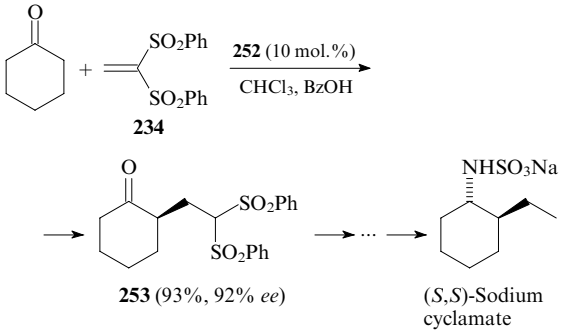
Gliocladine A (R′ = H), gliocladine B (R′ = OH)

adducts **251a–c** with fairly good diastereo- and enantioselectivities, the structural fragment of these adducts being a part of a number of natural compounds, in particular, alkaloids gliocladines A and B.[336, 337]

A promising approach to the synthesis of chiral biologically active compounds is the sequence of reactions comprising asymmetric addition of C-nucleophiles to 1,1-bis(phenylsulfonyl)ethene (**234**) and desulfurization of the resulting adducts (on treatment with Mg in MeOH). This is suitable for enantioselective introduction of an ethyl group into a nucleophile (carbonyl compound, enol salt, nitroalkane). In 2008, Lu and co-workers [338] employed the asymmetric Michael reaction in the stereodetermining step of the synthesis of sodium cyclamate, an important intermediate used to produce artificial sugar substitutes.[339] The reaction of cyclohexane with 1,1-bis(phenylsulfonyl)ethene (**234**) in the presence of catalyst **252** containing primary amino group (enamine catalysis, see Section II, Fig. 6)

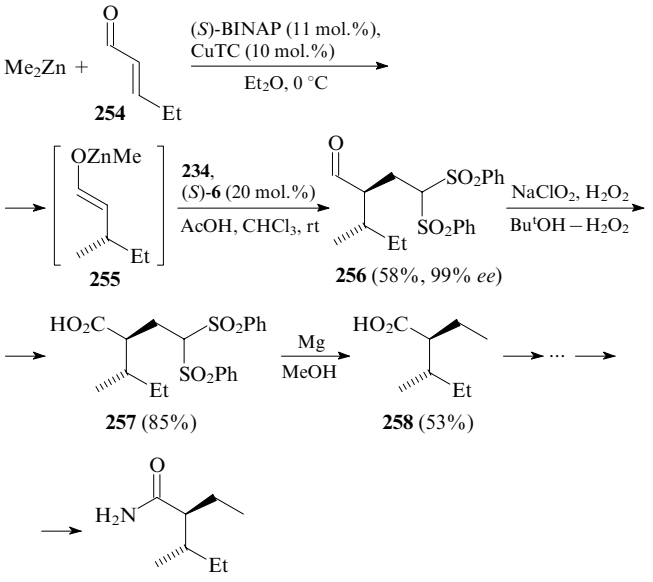


gave enantioselectively a high yield of bis-sulfone **253**, which was converted to the desired sodium cyclamate *via* a series of simple transformations not accompanied by racemization of the stereocentre.



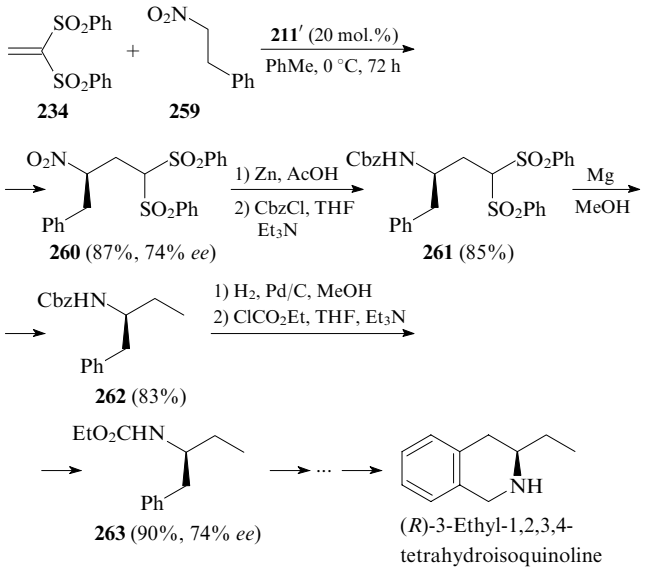
Aldehyde enolates can be involved in the asymmetric addition to 1,1-bis(phenylsulfonyl)ethene (**234**). Quintard and Alexakis [340] developed a highly enantioselective one-pot reaction sequence including 1,4-addition of dimethylzinc to α,β-enal **254** in the presence of copper complex with 2,2′-bis(diphenylphosphino)-1,1-binaphthyl (BINAP) and enantioselective *in situ* addition of the resulting enolate **255** to 1,1-bis(phenylsulfonyl)ethene (**234**) in the presence of prolinol (*S*)-**6**. This gave Michael adduct **256** with relatively high diastereoselectivity (*dr* = 83 : 17) and very high enantiomeric purity. The developed approach was used to obtain (2*S*,3*S*)-2-ethyl-3-methylvaleramide, one of the stereoisomers of the mild sedative hypnotic drug valnoctamide,[341, 342] which is under preclinical trials as a mixture of four stereoisomers having different therapeutic action.[343] To prepare the target product, aldehyde **256** was oxidized to acid **257** and the $PhSO_2$ groups were removed by treatment with magnesium in methanol. (2*S*,3*S*)-2-Ethyl-3-methylvaleric acid (**258**) thus formed was converted to valnoctamide by a known method.[341] The efficiency of the proposed

approach was indicated by the preparation of (2*S*,3*S*)-valnoctamide from enal **256** in four experimental steps, whereas the known synthetic route to the racemic product includes eight steps.



TC is thiophene-2-carboxylate.

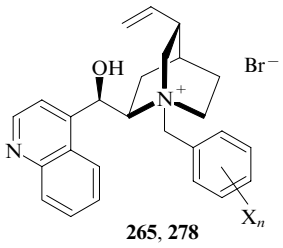
Nitroalkanes can be used as C-nucleophiles in the asymmetric Michael reactions with 1,1-bis(phenylsulfonyl)ethene (**234**), which opens up direct route to the synthesis of chiral α-alkylamines. This reaction occurs most efficiently when catalyzed by alkaloid derivatives containing a thiourea group, which not only deprotonate the nitroalkane but also determine the geometry of the activated complex through hydrogen bonding with the nitro group oxygen atoms. Zhu and Lu[344] developed a synthesis of (*R*)-3-ethyl-1,2,3,4-tetrahydroisoquinoline, the phenylethanolamine *N*-methyltransferase inhibitor,[345] the key step of the synthesis being asymmetric addition of (2-nitroethyl)benzene (**259**) to bis(sulfonyl)ethene (**234**) in the presence of alkaloid-type bifunctional catalyst **211′**. The *ee* value of Michael adduct **260** was relatively low, this value was retained in the



Cbz is benzyloxycarbonyl.

subsequent steps of the multistep synthesis (*via* intermediates **261** and **262**) of ethyl (*S*)-1-phenylbutan-2-ylcarbamate **263**, which is the direct precursor of the target compound.[345]

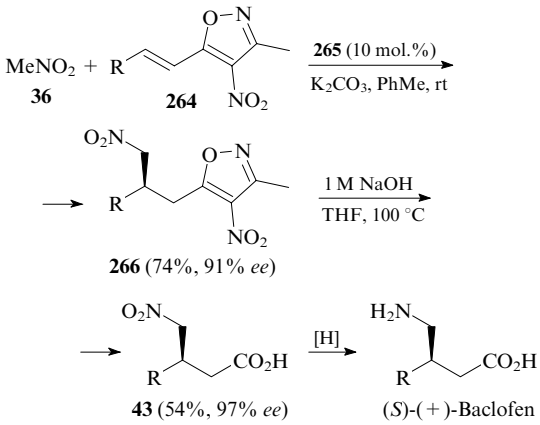
Recently Adamo and co-workers[140] proposed an original approach to the synthesis of a chiral GABA analogue, baclofen, which included the asymmetric addition of nitromethane (**36**) to 4-nitro-5-styrylisoxazole **264** in the presence of chiral phase transfer catalyst **265**.



X_n = 3,5-$(CF_3)_2$ (**265**), 4-CF_3 (**278**).

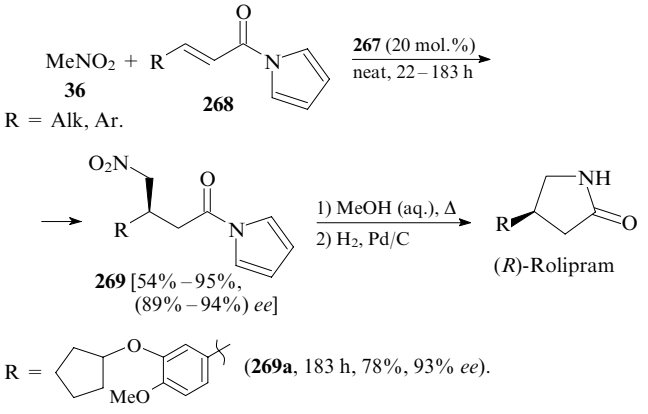
The reaction affords Michael adduct **266** in a 74% yield and with a 91% enantioselectivity (other approaches to the synthesis of baclofen are shown in Schemes 9, 10, 19, 23 and 27). According to the authors, nitromethane is activated in this case *via* the formation of a chiral ion pair with the catalyst. The subsequent alkaline hydrolysis of isoxazole **266** affords nitro acid **43**, which is transformed to baclofen by nitro group reduction (Scheme 34). However, as regards the product yields and the accessibility of the starting alkene, this method is inferior to the alternative methods of baclofen synthesis.

Scheme 34

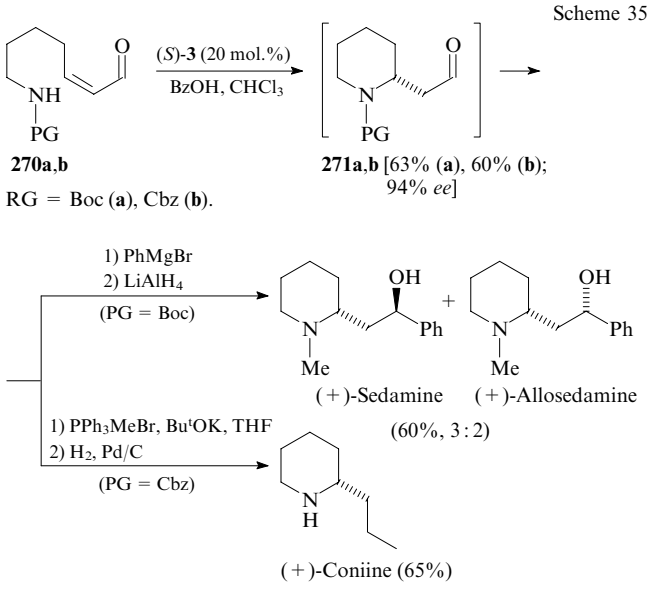


R = 4-ClC_6H_4.

Methodically, the Adamo approach resembles the synthesis of γ-nitro acid derivatives (see also the synthesis of γ-nitro acid derivatives in Schemes 7–11, 23 and 27–32) proposed by Vakulya *et al.*[346] in 2008. In the presence of alkaloid **267** (analogue of compound **218** with ethyl instead of the vinyl group), nitromethane (**36**) reacts with α,β-unsaturated *N*-acylpyrroles **268** to give Michael adducts **269** in a 54%–95% yield and a 89%–94% enantioselectivity. The authors successfully used this method to prepare the antidepressant (*R*)-rolipram. The key intermediate **269a** was formed in a 78% yield and 93% *ee* and was readily (in 2 experimentally simple steps) converted to the target compound. However, the method requires long-term keeping of reactants (up to 183 h) and in this respect it is inferior to the alternative organocatalytic methods for the synthesis of this drug.



Scheme 35



IV. Asymmetric formation of carbon–heteroatom bonds

The asymmetric Michael reactions open up broad opportunities for the enantioselective preparation of organic compounds in which the chiral carbon atom is connected to the heteroatom. Direct and effective approaches to their synthesis are intra- and intermolecular reactions of electron-deficient alkenes with N-, O-, S- and P-nucleophiles in the presence of chiral organocatalysts. The most efficient catalysts of these reactions are trimethylsilyl ethers α,α-diarylprolinol and quinine (quinidine) or other chiral amine derivatives, in particular, those modified by a thiourea (urea) moiety. In some cases, heteronucleophiles undergo the Michael reactions catalyzed by Brønsted acids (chiral diol, *e.g.*, BINOL-derived phosphates) (see Section II).

1. Reactions of N-nucleophiles with electron-deficient alkenes

The reactions of electron-deficient alkenes with N-nucleophiles in the presence of organocatalysts are used to obtain chiral β-amino acids, β-lactams, alkaloid derivatives and other chiral heterocycles.[347] Further, the N-nucleophile (amine, hydroxylamine, nitrogen heterocycle) and activated alkene (most often, α,β-unsaturated aldehyde) can occur in the same molecule (intramolecular reactions) or in two different molecules (intermolecular reactions).

a. Intramolecular reactions

α,β-Unsaturated aminoaldehydes in which the amino group and the aldehyde group are separated by a chain of five or six carbon atoms are convenient synthons for the construction of the pyrrolidine or piperidine ring, respectively, present in some natural alkaloids.[348] In an asymmetric intramolecular Michael reaction, a stereocentre is formed in the α position to the heteroatom.

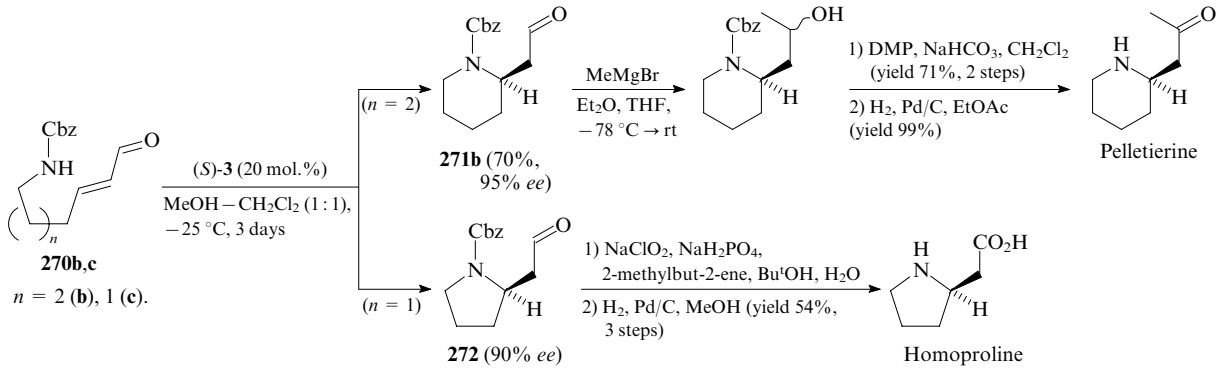
In 2007, Fustero *et al.*[349] used the prolinol (*S*)-**3**-catalyzed intramolecular cyclization of compounds **270a**,**b** containing a protected amino group to prepare some alkaloids of the piperidine series. This reaction, which proceeded *via* iminium activation of the reactant aldehyde group by the catalyst (see Section II, Fig. 6), resulted in (2-piperidyl)acetaldehyde derivatives **271a**,**b** in a moderate yield but with a high enantioselectivity. Treatment of aldehyde **271a** with phenylmagnesium bromide gives rise to diastereomeric secondary alcohols (in 3 : 2 ratio), which were separated by chromatography and reduced with lithium aluminium hydride to the alkaloids (+)-sedamine and (+)-allosedamine. Aldehyde **271b** was converted to the alkaloid (+)-coniine by a sequence the Wittig and catalytic hydrogenation reactions (Scheme 35).

Carter and co-workers[350] used (*R*)-1-benzyloxycarbonyl-2-(formylmethyl)piperidine (**271b**) and (*R*)-1-benzyloxycarbonyl-2-(formylmethyl)pyrrolidine (**272**) obtained by prolinol (*S*)-**3**-catalyzed intramolecular Michael reaction for the synthesis of the alkaloid pelletierine (isolated by Tanret[351,352] in 1878) and β-amino acid homoproline, respectively.[353,354] In this case, too, the synthetic route to the target compounds was rather simple and based on the trivial Grignard or oxidation reactions of the corresponding chiral Michael adducts **271b** and **272**. It is noteworthy that the amino acid homoproline synthesized in this way can itself act as the organocatalyst for some asymmetric reactions[355,356] (Scheme 36).

Hong and co-workers[357] applied the organocatalytic aza-Michael reaction in 2011 for the stereoselective synthesis of 2,6-disubstituted piperidines. Using chiral 4-{2-[(*R*)-2-(tosylamino)propyl]-1,3-dithian-2-yl}but-2-enal (**273**) as the starting compound and by carrying out reactions in the presence of catalyst (*S*)-**6** or (*R*)-**6**, they were able to synthesize cyclization products having both *cis*- and *trans*-arrangement of the substituents in the piperidine ring. With catalysis by prolinol (*S*)-**6** *cis*-diastereomer (8*S*,10*R*)-**274** was formed with a very high stereoselectivity (*cis* : *trans* = 15 : 1). The stereoselectivity of reactions catalyzed by prolinol (*R*)-**6** was somewhat lower [for compound (8*R*,10*R*)-**274**, *trans* : *cis* = 2 : 1–4 : 1]. Compounds (8*S*,10*R*)-**274** and (8*R*,10*R*)-**274** were then subjected to the reaction sequence comprising Horner–Emmons olefination, heterocyclization and deprotection to remove the dithiane group being thus converted to the alkaloids (−)-epimyrtine and (+)-myrtine present in *Vaccinium Myrtillus* (Scheme 37).[358,359]

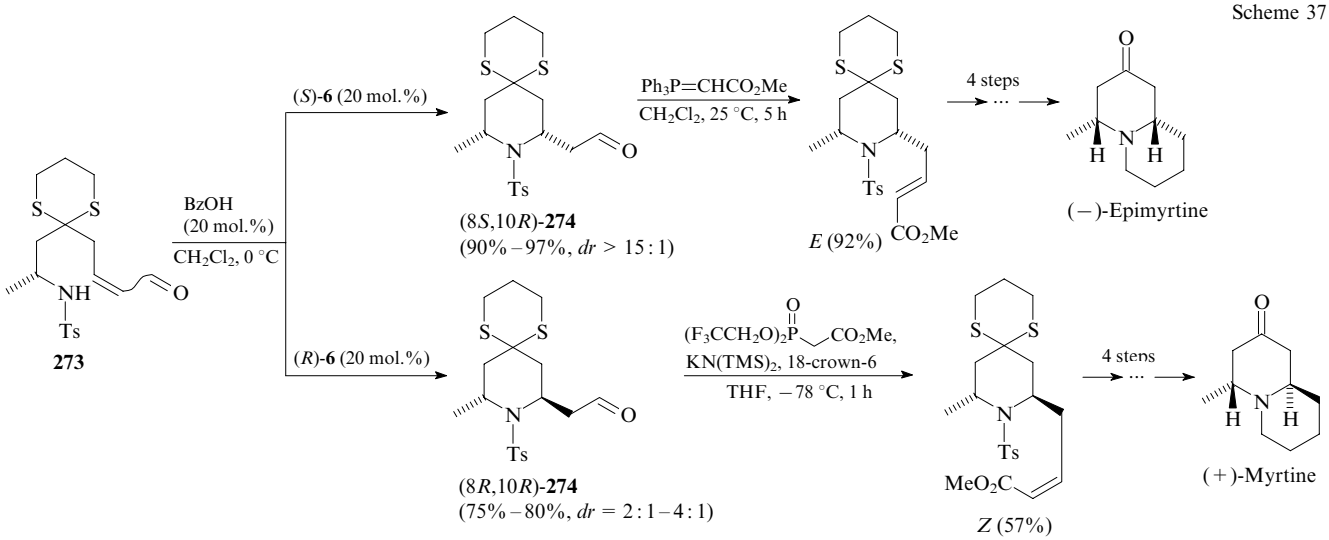
Fustero and co-workers[360] found that intramolecular asymmetric Michael reaction is suitable for preparing pyrrolidine and piperidine derivatives annelated to an aromatic ring. The structural fragment of benzoannelated nitrogen-containing heterocycles is often encountered in natural compounds. The intramolecular cyclization of aniline derivative **275** in the presence of catalyst (*S*)-**3** produced tetrahy-

Scheme 36

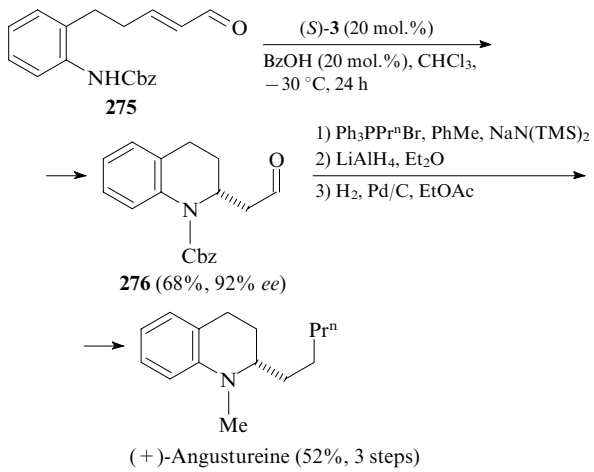


DMP is 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

Scheme 37

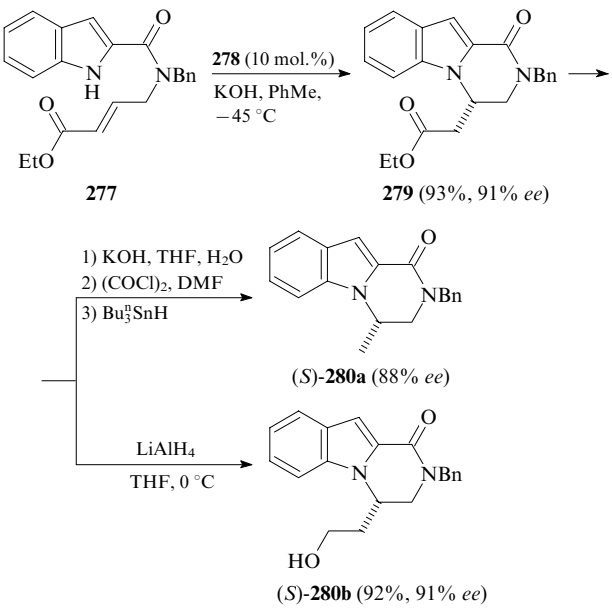


droquinoline **276**, which was converted to the alkaloid (+)-angustureine *via* the Wittig olefination and reduction.



Biologically active compounds can be synthesized by asymmetric intramolecular Michael-type aza-cyclization of compounds in which the alkene moiety is bonded to an ester group and has weaker acceptor properties than the C=C bond in α,β-enals. The iminium activation of such reactants by chiral Lewis bases is usually inefficient; therefore a catalyst of a different type was used in this case. Umani-Ronchi and co-workers [361] found that treatment of indole-2-carboxamide **277** containing an γ-aminocrotonate moiety in the amide part of the molecule with a base (KOH) in toluene in the presence of chiral phase transfer catalyst, namely, (*p*-trifluoromethylbenzyl)cinchondinium bromide (**278**), an analogue of catalyst **265** affords 3,4-dihydropyrazino-[1,2-*a*]indol-1(2*H*)-one derivative **279** in a high yield and with high enantioselectivity (Scheme 38). The good stereochemical outcome of the reaction was attributed to the

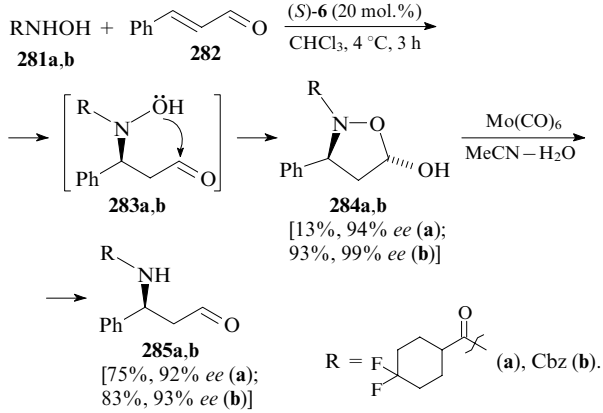
Scheme 38



formation of contact ion pair between the indolate anion and chiral cinchondinium cation **278** in which one of the two possible directions of alkene approach to N-nucleophile is effectively blocked (see Section II, Fig. 4). The synthetic potential of the proposed method was confirmed by decarboethoxylation and reduction of compound **279** to heterocycles (*S*)-**280a**,**b** without considerable racemization of the stereocentre. Note that compounds containing a dihydropyrazino[1,2-*a*]indol-1(2*H*)-one structural fragment exhibit antifungal and antihistaminic activities, some being able to specifically inhibit serotonin receptors.[362–365]

b. Intermolecular reactions

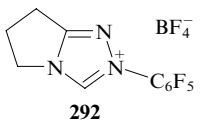
In the presence of organocatalysts, it is possible to carry out intermolecular asymmetric reactions of N-nucleophiles with electron-deficient alkenes to synthesize the intermediates for the preparation of β-amino acid derivatives and chiral compounds with a nitrogen heterocycle in the β position to the carbon atom of the aldehyde group (or a group to which it was then converted). In 2010, Córdova and co-workers[366] proposed methods for the synthesis of chiral medicinal drug maraviroc (UR-427857), a potent antagonist of the CCR5 receptors playing an important role in the mechanism of HIV penetration into the body cells.[367, 368] The methods are based on the asymmetric addition of hydroxylamine derivatives **281a**,**b** to cinnamaldehyde (**282**) in the presence of



diarylprolinol (*S*)-**6**. As noted above, catalyst (*S*)-**3** activates α,β-enals by forming iminium cations with them (see Section II, Fig. 6). The Michael adducts **283a**,**b** thus formed cyclize spontaneously under the reaction conditions to 5-hydroxyisoxazolidines **284a**,**b**; the yield and the enantiomeric purity were much higher for **284b** obtained from hydroxylamine **281b** than for **284a** synthesized from the *N*-hydroxyamide of 4,4-difluorocyclohexanecarboxyl acid (**281a**). Heterocycles **284a**,**b** were converted to β-aminoaldehydes **285a**,**b** on treatment with $Mo(CO)_6$, the reactions being accompanied by some decrease in the enantiomeric purity of the products.

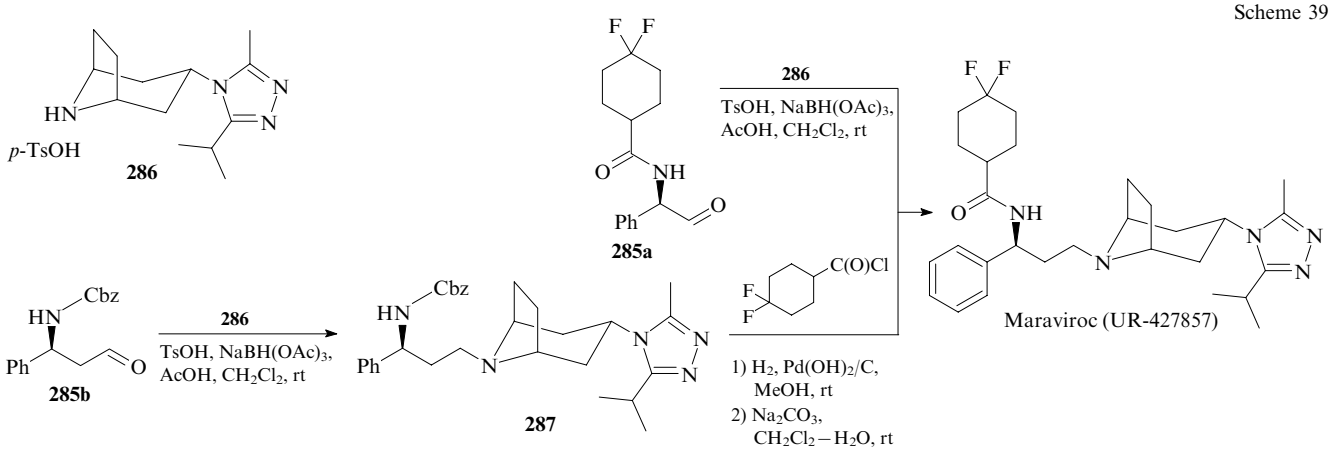
The final steps of the maraviroc synthesis included reductive amination of aldehyde **285a** with amine **286** in the presence of $NaBH(OAc)_3$ or, in the case of aldehyde **285b**, the sequence of reductive amination followed by deprotection and amidation of the resulting amino compound **287** with 4,4-difluorocyclohexanecarboxylate chloride (Scheme 39).

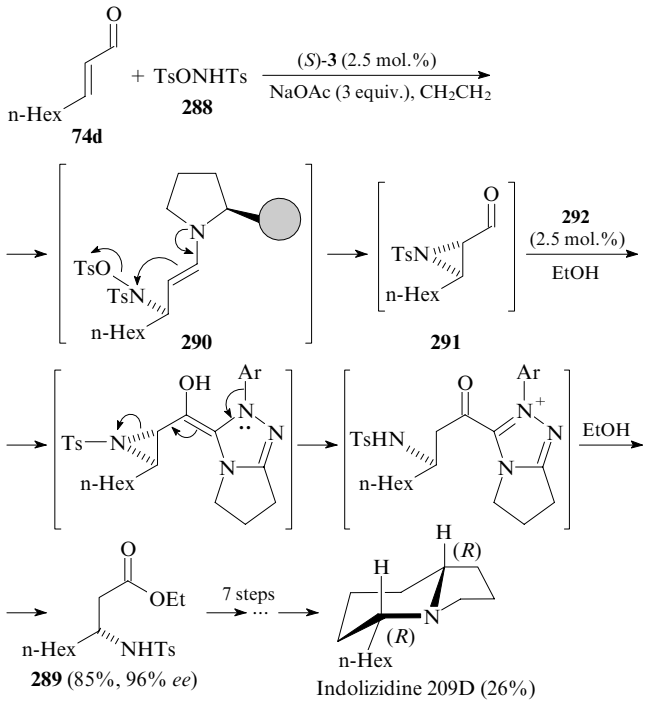
In 2010, Jørgensen and co-workers[369] developed an effective method for the synthesis of chiral β-amino esters from α,β-unsaturated aldehydes and *O*,*N*-bis(*p*-toluenesulfonyl)hydroxylamine (**288**) and applied it to prepare (*R*)-3-aminononanoic acid derivative (**289**), the key intermediate in the total synthesis of the alkaloid indolizidine 209D. The method comprises two steps, which are successively carried out in the same reactor in the presence of different organocatalysts. The first step, catalyzed by diarylprolinol (*S*)-**3**, is the asymmetric addition of hydroxylamine **288** to *trans*-non-2-enal (**74d**) and spontaneous elimination of the tosyloxy group from the Michael adduct **290** to give chiral aziridine derivative **291**. The second step is the redox intramolecular opening of the aziridine ring in compound **291**, which is carried out in the presence of the N-heterocyclic carbene obtained *in situ* from the 1,2,4-triazolium salt (**292**)



under the action of the base present in the system (NaOAc). As a result, a high yield of (*R*)-3-aminononanoate **289** was obtained enantioselectively; this product could be converted to the target alkaloid indolizidine 209D by known methods.[370]

Scheme 39

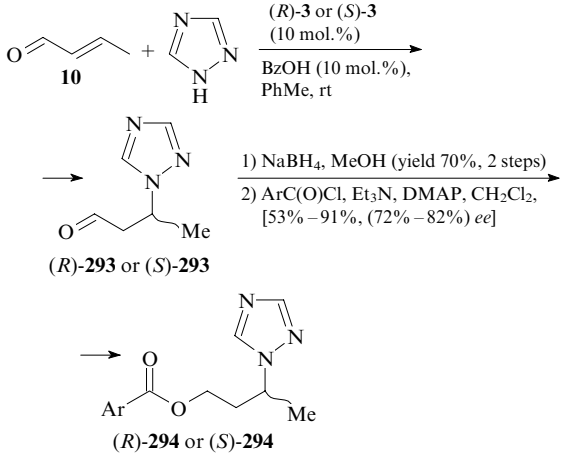




n-Hex = n-C_6H_{13}; ⬤ = $C(C_6H_3(CF_3)_2\text{-}3,5)_2OTMS$; Ar = C_6F_5,

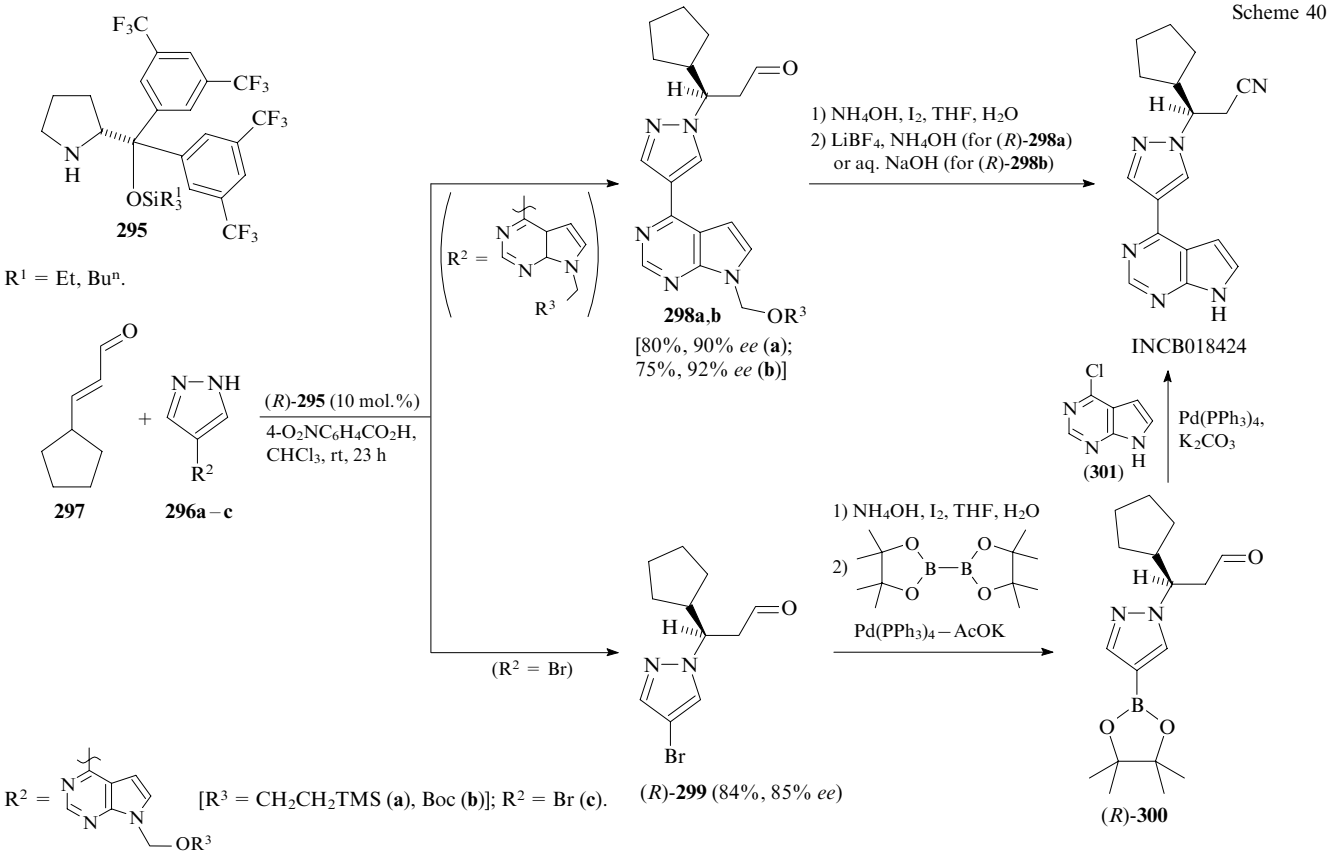
Advantages of the proposed method include the ready accessibility of the starting compounds, low catalyst loads (2.5 mol.%) and the simplicity of the experimental procedure, which does not require the use of inert atmosphere or anhydrous conditions.

Nitrogen heterocycles are suitable as N-nucleophiles in the intermolecular asymmetric Michael reactions. In 2009, Xiao and co-workers [371] found that 1,2,4-triazole reacts with crotonaldehyde (**10**) in the presence of α,α-diarylprolinol silyl ether (*R*)-**3** or (*S*)-**3** and benzoic acid to give the corresponding enantiomers of 3-(1,2,4-triazol-1(1*H*)-yl)butanal (*R*)-**293** or (*S*)-**293**. By the reduction (with $NaBH_4$) and acylation, these products were converted to triazole derivatives (*R*)-**294** or (*S*)-**294** with rather high *ee* (72% – 82%). The practical value of this method is demonstrated by the fact that some of the obtained compounds **294** exhibit strong binding interactions with the cytochrome-P450-dependent lanosterol 14a-demethylase (CYP51), which can be used to develop effective and environmentally safe fungicides.[372]



DMAP is 4-dimethylaminopyridine; Ar = Ph, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, *etc*.

Scheme 40



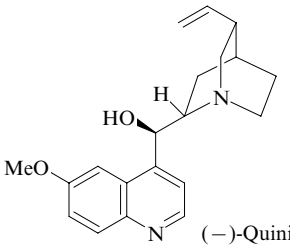
Recently, Lin *et al.*[373] demonstrated that pyrazole derivatives are capable of reacting with α,β-enals in the presence of prolinol silyl ethers. This reaction opened up the way to organocatalytic synthesis of the chiral drug INCB018424 containing a pyrazole ring in the molecule. The compound INCB018424 is a potent inhibitor of tyrosine kinases, which function as signalling molecules that regulate the functions of cytokines, growth factor and some other systems; currently, this drug is under clinical trials[374–377] as a remedy against myeloproliferative disorders[378] and rheumatoid arthritis.[379] Two approaches to the synthesis of the target compound were proposed. One includes the use of (*R*)-α,α-diarylprolinol trialkylsilyl ether (*R*)-**295** to catalyze the asymmetric addition of 4-(pyrazol-4(1*H*)-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine derivatives **296a**,**b** to (*E*)-3-(cyclopentyl)acrylaldehyde (**297**), the subsequent oxidative amination and deprotection of the resulting Michael adducts (*R*)-**298a**,**b** (Scheme 40). The second approach implies the use of 4-bromopyrazole (**296c**) as the nucleophile and the subsequent introduction of the pyrrolo[2,3-*d*]pyrimidine fragment into the chiral adduct (*R*)-**299** by means of cross-coupling reaction of compound **300** with heterocycle **301**. In both cases, the enantioselectivity of the key organocatalytic step, which forms the stereocentre in the α position to the pyrazole ring, and the yields of the Michael adducts were fairly high and the reaction rates markedly increased upon the addition of 4-nitrobenzoic acid.

2. Reactions of O-nucleophiles with electron-deficient alkenes

Addition of O-nucleophiles to electron-deficient alkenes where the double bond is activated by the carbonyl or nitro group is used for the synthesis of oxygen-containing heterocycles, β-hydroxycarbonyl compounds, β-diols and β-amino alcohols; these structural fragments are parts of some natural compounds and synthetic pharmaceutical drugs.[380] In this case, the Michael reaction is an alternative to the asymmetric aldol reaction, which is widely used for the preparation of compounds containing β-hydroxycarbonyl group, in particular, using organocatalysts.[16] Examples of intra- and intermolecular organocatalytic Michael reactions involving O-nucleophiles are known.

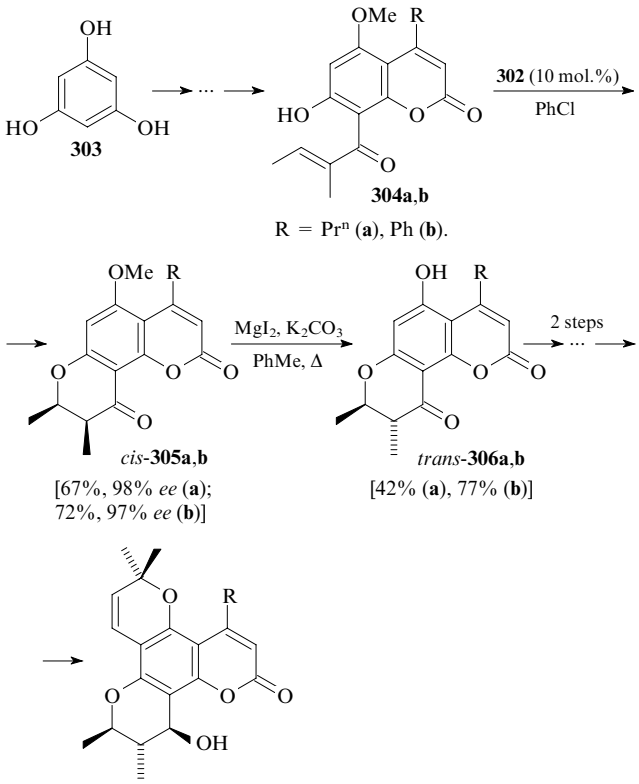
a. Intramolecular reactions

The intramolecular version of the oxa-Michael reaction is used to prepare polycyclic compounds with five- and six-membered oxygen-containing heterocycles, in particular those possessing biological activities. Ishikawa and co-workers [381] found that in the presence of (−)-quinine (**302**)



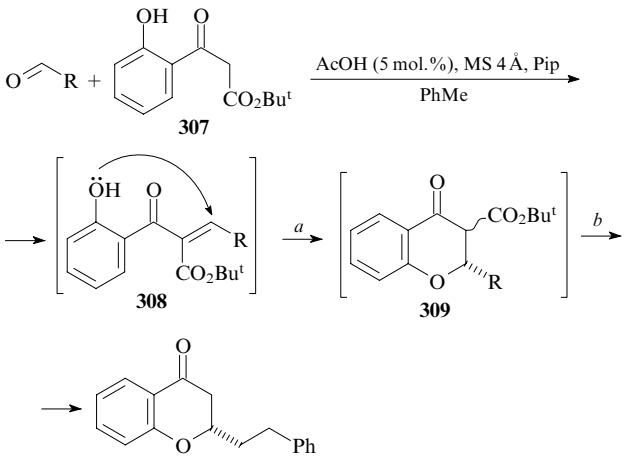
(−)-Quinine (**302**)

the 4-substituted 7-hydroxy-5-methoxy-8-tigloylcouomarins **304a**,**b** obtained from phloroglucinol **303** undergo the intramolecular Michael cyclization to give the corresponding 2,3-dimethyl-4-chromanone derivatives *cis*-**305a**,**b** with very high enantiomeric purity. The authors proposed an elegant solution to the problem of deprotection, removing the 5-methoxy group from the products (treatment with $MgI_2-K_2CO_3$) with simultaneous isomerization to *trans*-isomers *trans*-**306a**,**b**, which are the direct precursors of natural coumarins (+)-calanolide A and (+)-inophyllum B. These natural compounds isolated in 1992 from *Calophyllum lanigerum* var. *Austrocoriaceum* (Guttiferae)[382, 383] are active HIV-1 reverse transcriptase inhibitors and are studied in the USA as drugs for AIDS therapy. The method proposed for their synthesis is based on readily accessible starting compound (phloroglucinol) and is suitable for enantioselective preparation of these compounds in amounts needed for clinical trials.



Flavanone and chromanone moieties are present in some other natural compounds exhibiting useful types of biological activity,[384–387] in particular, antitumour and antiinflammatory activities. Some of these are studied as selective modulators of estrogen receptors.[388, 389] Scheidt and co-workers[390] developed an enantioselective method for the synthesis of compounds of this series, which included a sequence of Knoevenagel reaction of *tert*-butyl 3-(2-hydroxyphenyl)-3-oxopropanoate (**307**) with aldehydes (aliphatic or aromatic), asymmetric cyclization of enones **308** and decarboxylation *in situ* of the resulting keto esters **309**; the Knoevenagel and Michael reactions can be carried out separately or (which is more convenient) in one pot. The best catalytic properties were found for the bifunctional catalyst **218** containing alkaloid and thiourea moieties; in the presence of this catalyst, enantiomerically enriched flavanones and chromanones were synthesized in high yield and enantioselectivity. Using this method, the authors were able to obtain the natural compound 2-(2-phenyl-

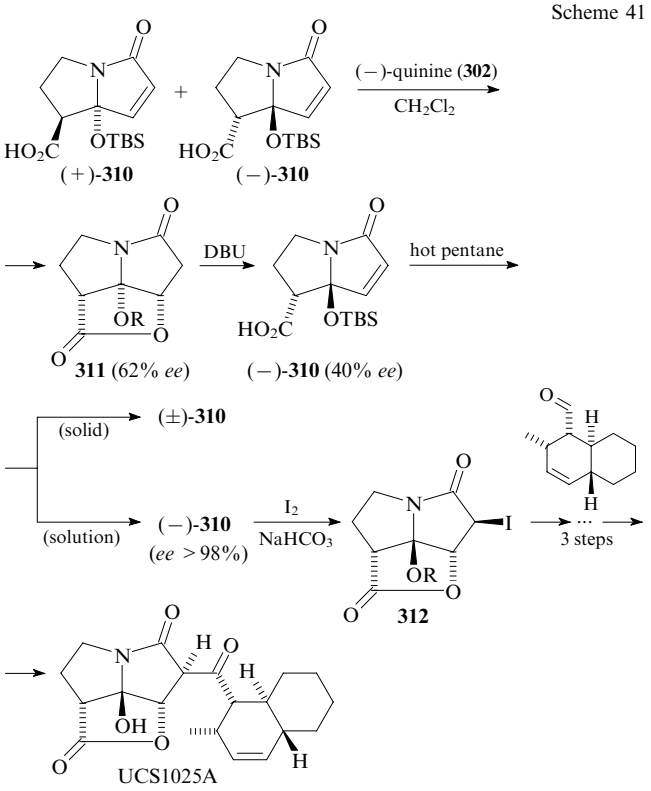
ethyl)chromanone (flindersiachromanone)[391] in one experimental step in a 77% yield and 80% *ee*.



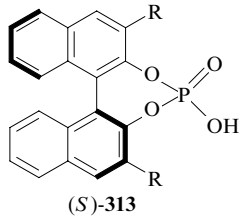
(*a*) **218** (20 mol.%), PhMe, −20 °C → rt; (*b*) *p*-TsOH, 80 °C (R = CH_2Bn); R = Alk, Ar; Pip is piperidine.

Christmann and co-workers[392] applied quinine-catalyzed asymmetric oxa-Michael reaction for kinetic resolution of the racemic tetrahydropyrrolizine (±)-**310** (Scheme 41). This reaction where the carboxyl oxygen atom of compound **310** serves as the nucleophile is apparently the first example of enantioselective addition of a carboxylic acid to a Michael acceptor in the presence of organocatalyst. It was found that under the proposed conditions, enantiomer (−)-**310** cyclizes much faster than the antipode (+)-**310** giving rise to enantiomerically enriched lactone **311**. Under the action of DBU, the obtained lactone **311** was again converted, now to enantiomerically enriched acid (−)-**310** (40% *ee*). The optical purity of the product was markedly increased by treatment with hot pentane; enantiomer (−)-**310** passed to the solution almost entirely, whereas racemate (±)-**310** remained as the precipitate. Compound (−)-**312** obtained in this way (*ee* > 98%) was converted to telomerase UCS1025A inhibitor[393–395] in 4 steps by the Danishefsky method.[396]

Scheme 41



In 2010, Chinese researchers[397] proposed a method for desymmetrization of 4-hydroxyalkyl-substituted cyclohexadienones by intramolecular oxa-Michael reaction catalyzed by (*S*)-BINOL-derived phosphates. This reaction gave chiral bicyclic compounds containing dioxane or tetrahydrofuran moieties. The developed method was applied for enantioselective synthesis of cleroindicins C, D and F — natural compounds isolated from the plant *Clerodendum indicum*, which is used in China to treat malaria and rheumatism.[398,399] The key step of this synthesis is the catalysis by acid (*S*)-**313** [analogue of catalyst (*R*)-**230**]

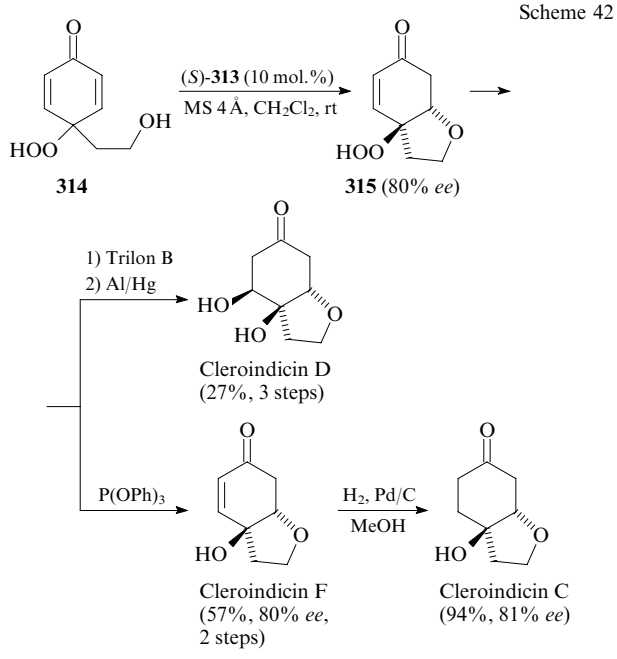


R = 2,6-Pr^i_2-4-$Bu^tC_6H_2$.

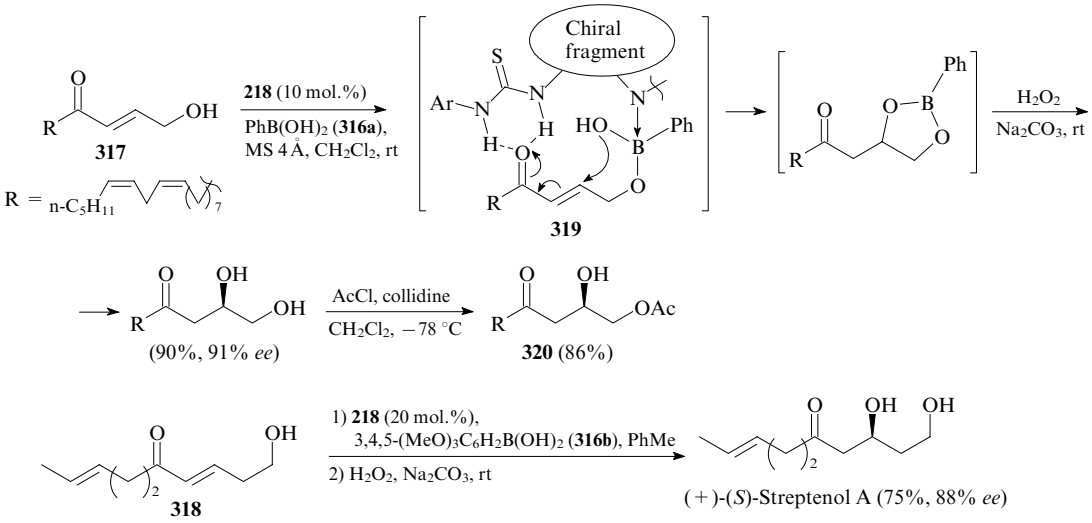
of the intramolecular cyclization of readily accessible hydroxy peroxide **314**, resulting in the tetrahydrobenzofuranone derivative **315** with rather high enantioselectivity (Scheme 42). Compound **315** was then converted to cleroindicin D *via* epoxidation (phase transfer catalysis) and reduction with aluminium amalgam in a 27% overall yield (3 steps). By using $P(OPh)_3$ as the reducing agent, peroxide **315** was converted to cleroindicin F the catalytic hydrogenation of which afforded cleroindicin C.

In 2008, Li, Murugan and Falck[400] developed an effective method for the synthesis of chiral β,γ- and β,δ-dihydroxy ketones widely used for preparing natural compounds.[401–408] The method is based on enantioselective

Scheme 42



Scheme 43



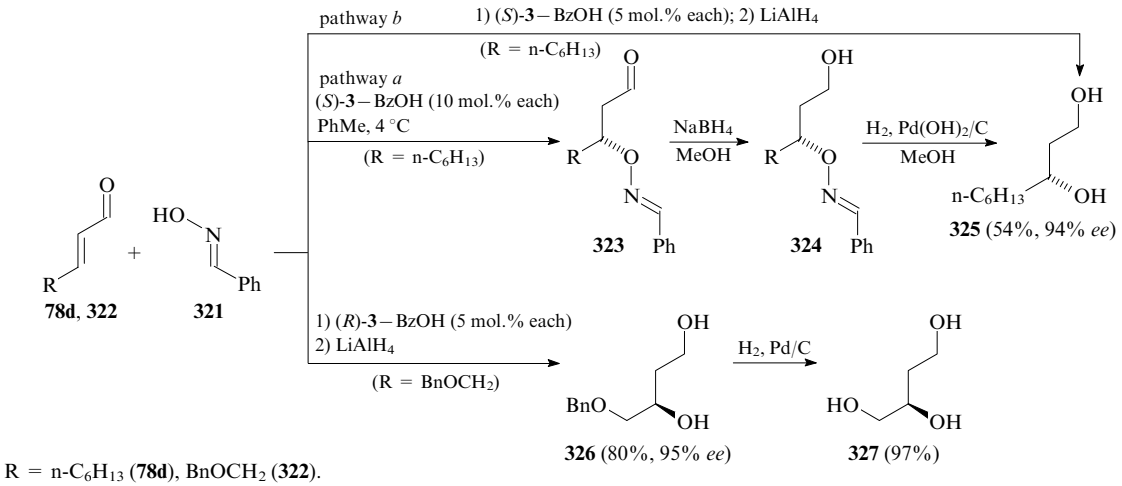
reaction of arylboronic acid **316a**,**b** with γ- (**317**) or δ-hydroxy-α,β-enones **318**. Formally, this reaction is intermolecular; however, its organocatalytic step determining the absolute configuration of the products is intramolecular nucleophilic addition of the hydroxy group of the half-ester of boronic acid formed *in situ* to the activated multiple bond of α,β-enone **319**. The nucleophilic and electrophilic components of the molecule are concertedly activated by the same bifunctional catalyst **218** containing alkaloid and thiourea moieties connected to each other. The authors applied the developed method for the total synthesis of acetate **320**, a compound isolated from alligator pear and having strong fungicidal and hepatoprotective properties,[409] and (+)-(*S*)-streptenol A produced by *Streptomyces luteogriseus*, which exhibits immunostimilating properties and can inhibit the biosynthesis of cholesterol and proliferation of tumour cells (Scheme 43).[410]

b. Intermolecular reactions

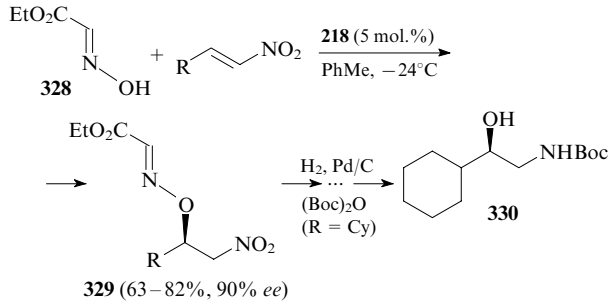
In 2007, Jørgensen and co-workers[411] proposed a method for preparing biologically important polyfunctional alcohols with the stereocentre at the internal hydroxy group. The method is based on conjugated 1,4-addition of aldoximes **321** to α,β-unsaturated aldehydes **78d** and **322** in the presence of diarylprolinol ether (*S*)-**3**. Michael adducts **323** were converted to β-diols by reduction of the aldehyde group with $NaBH_4$ and catalytic hydrogenation of the resulting hydroxy ethers **324** [$Pd(OH)_2$/C] (Scheme 44, pathway *a*). It was found that using $LiAlH_4$ as the reducing and deprotecting agent, it is possible to combine these steps into a single cascade process and perform it in the same reactor as the organocatalytic step (see Scheme 44, pathway *b*).[412] β-Diol **325**, the major component of endogenous sex pheromone of the melon fly *Bactrocera cucurbitae*,[413] and triol benzyl ether **326** (which was converted to known glycerol kinase substrate **327** by catalytic debenzylation) were enantioselectively prepared in this way.[414] In the latter case, to obtain product **327** with the desired absolute configuration of the stereocentre, the Michael reaction was carried out in the presence of enantiomeric catalyst (*R*)-**3** (see Scheme 44).

The same group of researchers found that ethyl glyoxylate oxime **328** reacts with aliphatic α-nitroalkenes in the presence of quinine-derived thiourea **218** to give the corresponding Michael adducts **329** in high yield and with high enantioselectivity.[415] Among the obtained adducts, of particular interest is compound **329** [R = Cy (cyclohexyl)], as the product of its reduction, amino alcohol **330**, exhibits adrenomimetic properties.[416]

Scheme 44



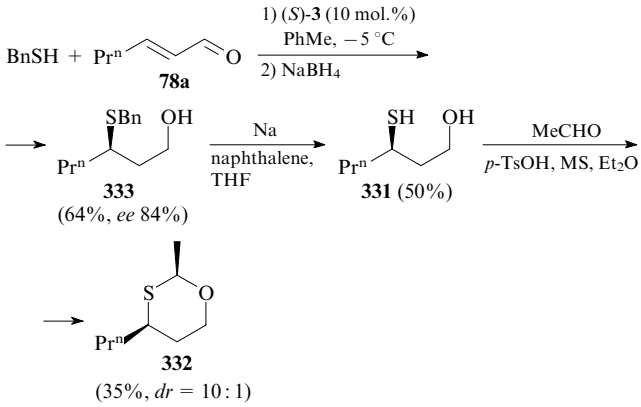
R = n-C_6H_{13} (**78d**), $BnOCH_2$ (**322**).



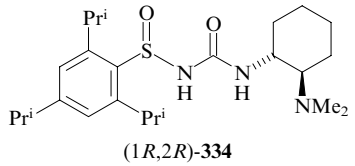
R = Alk.

3. Reactions of other heteronucleophiles with electron-deficient alkenes

Several asymmetric addition reactions of nucleophiles containing other heteroatoms to activated alkenes have been described;[417,418] however, examples of their use for the preparation of natural compounds and biologically active products are few and far between. In 2009, Rosini and co-workers[419] described the enantioselective organocatalytic synthesis of (*R*)-3-mercaptohexan-1-ol (**331**)[420] and *cis*-2(*S*)-methyl-4(*R*)-propyl-1,3-oxathiane (**332**),[421–423] sulfur-containing volatile components of the passion fruit. The key step of this method is the asymmetric addition of phenylmethanethiol to *trans*-hex-2-enal (**78a**) in the presence of catalyst (*S*)-**3**. The resulting Michael adduct was reduced without isolation with sodium borohydride to enantiomerically enriched alcohol **333** (84% *ee*), which was converted *via* debenzylation and thioacetalization to target compounds **331** and **332** having rather high enantio- and diastereomeric purity.

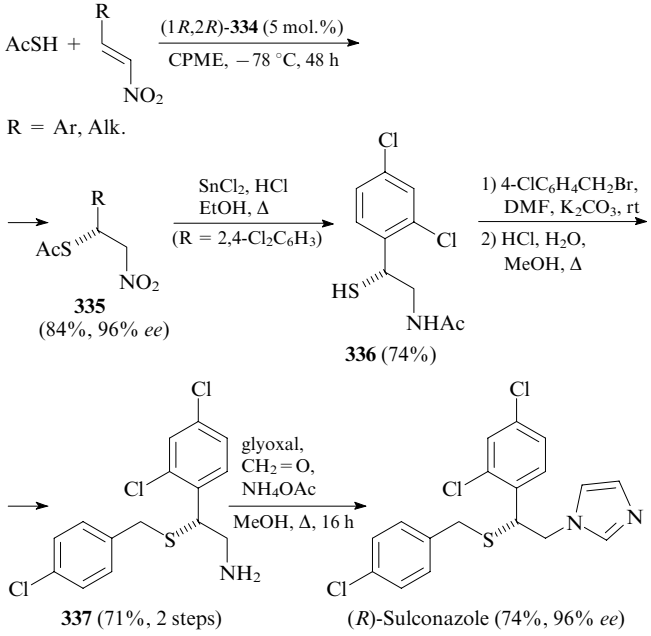


Yet another sulfur-containing pharmacophoric group is the β-aminothiol fragment, which is present, in particular, in the antibiotics penicillamine and penicillin, vitamin H (biotin) and the fungicide sulconazole.[424,425] Ellman and co-workers[426] found that asymmetric addition of thioacetic acid to α-nitroalkenes is an effective approach to the synthesis of chiral β-aminothiol derivatives. *N*-Sulfinylurea derivative (1*R*,2*R*)-**334**



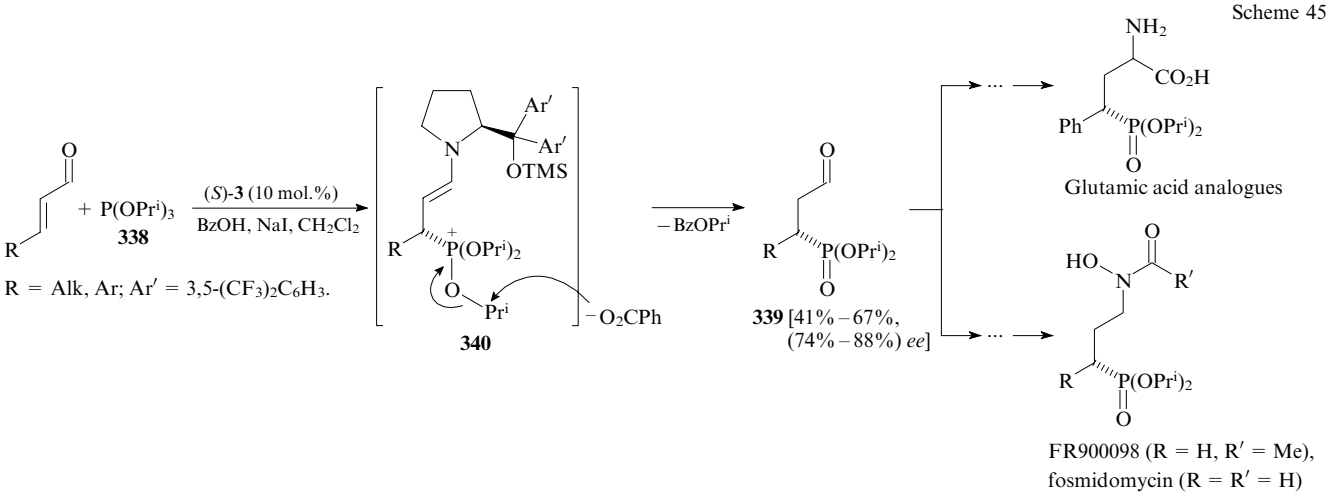
(1*R*,2*R*)-**334**

proved to be the most active and selective organocatalyst of this reaction; this compound belongs to the recently developed original type of catalysts in which the chiral sulfinyl group participates itself in the stereodifferentiation and simultaneously substantially increases the hydrogen bonding acidity of the urea group.[427] In the presence of catalyst (1*R*,2*R*)-**334**, the Michael reaction can be carried out at −78 °C to synthesize a broad range of β-nitroethanethiol derivatives **335**, the enantiomeric excess of the products reaching 96%. The synthetic potential of the method was demonstrated by the enantioselective synthesis of (*R*)-sulconazole from the Michael adduct **335** (R = 2,4-$Cl_2C_6H_3$) in 4 steps comprising reduction of the nitro group to the acetylamino group, alkylation of thiol **336** with four-chlorobenzyl bromide, deacylation and transformation of the amino group in compound **337** into the imidazole ring by means of a four-component reaction with glyoxal, formaldehyde and ammonium acetate. All these reactions proceeded with high yields and were not accompanied by racemization of the stereocentre formed in the organocatalytic step.



In 2007, Jørgensen and co-workers[428] developed the first organocatalytic phosphonylation of α,β-unsaturated aldehydes induced by phosphoric acid ester **338**. In the presence of the (*S*)-**3**–BzOH–NaI catalytic system, aldehydes are converted to β-phosphonate aldehydes **339** in moderate yields and rather good enantioselectivity (Scheme 45). The presence of benzoic acid and NaI is needed for S_N2-dealkylation of the phosphite group in intermediate **340** and oxidation of P^{III} to P^{V}. The synthesized compounds are intermediates for the preparation of fosmidomycin analogues and some other phosphonylated compounds (for example, compound FR9000098) exhibiting antimalarial activity.[429–433]

Scheme 45



V. Conclusion

The extensive opportunities opened up by the application of the asymmetric organic catalysis in the enantioselective formation of carbon–carbon and carbon–heteroatom bonds in organic compounds are demonstrated considering 1,4-conjugated addition reactions of nucleophiles to electron-deficient alkenes. Using chiral organocatalysts, it is possible to convert readily accessible alkenes to practically valuable products, precursors of natural compounds and chiral pharmaceutical drugs, in one step under simple experimental conditions that do not require introduction or removal of auxiliary chiral groups. Organocatalysts perfectly supplement metal complex catalysts, as they are able to perform reactions in which the latter are not always effective (in some cases, the opposite is true) and rule out the stage of product purification from traces of heavy metals, which are undesirable in pharmaceutical drugs.

However, the practical use of organocatalysts for the synthesis of natural compounds otherwise difficult to obtain and for drug manufacture still requires solution of some problems. The most efficient catalysts known to date have rather complex structure and, hence, high cost; moreover, they are to be used in considerable amounts (normally, 10 mol.%–20 mol.%). It is obvious that the search for new catalysts and development of immobilized forms of known catalysts suitable for regeneration and reuse are needed. There are almost no data on continuous processes of pharmaceutical drug manufacture in the presence of organocatalysts.

Nevertheless, the intensity and diversity of the studies that are currently in progress leave no doubts that the scope of application of asymmetric organocatalysis in organic synthesis will be considerably extended in the coming years. It is likely that it would be used also in industrial production processes of enantiomerically pure pharmaceutical drugs.

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