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RESEARCH ARTICLE

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A new era for organic synthesis—highlights of the recent progress

Abstract The major progress in organic synthesis since 2005 is briefly surveyed in two parts. The first part deals with some of the most impressive advances in the synthetic methodology, which includes: (1) metal-mediated synthetic reactions, with an emphasis on the olefin metathesis and gold-mediated reactions; (2) free radical-based organic synthesis; (3) synthetic transformations performed in a "one-pot" manner involving either tandem reactions or multi-component reactions; (4) asymmetric reactions catalyzed by metal and organo-catalysts. The major advances in total synthesis of some complex natural products with significant biological activities are presented in the second part, with detailed illustrations of ten selected molecules, including dragmacidin F, abyssomicin C, 11-acetoxy-4-deoxyasbestinin D, pentacycloanammoxic acid, UCS1025A, (−)-merrilactone A, nigellamine A_2, (+)-saxitoxin, and Tamiflu (an artificially designed natural product-like molecule). An array of complicated structures of the natural products synthesized over the last two years is also listed to serve as a convenient lead to the original literature for the prospective interested readers.

Keywords organic synthesis, metal-mediated synthetic reaction, free radical reaction, "in one pot" reaction, asymmetric reaction, total synthesis of natural products

Chemistry is a central science and synthesis holds a central place in chemistry. In the field of organic chemistry, synthesis has been an ever-advancing area at the far front, full of striking developments and cutting-edge innovations. In collaboration with other experts in the field, we have made several efforts [1–7] to introduce the state-of-the-art achievements over the last decade to the readers in China, with the most recent collection entitled "Progress in Modern Organic Synthesis" [8] published in 2005.

From the last compilation, which covered the most important advances in organic synthesis around the world from mid 1990 through late 2004, it can be readily sensed that organic synthesis has been experiencing a period of rapid development and has adopted a new look since the turn of the century. What pleases us even more is that new reports of very interesting syntheses still keep pouring in, especially in the sub-area of multi-step total synthesis of natural products and other complicated molecules. The ever-increasing complexity of the target molecules and the constantly climbing level of elegance of the synthetic strategy unmistakably signal a new wave of advancements in organic synthesis. It should be noted that conferment of the Nobel Prize in chemistry on the pioneers of olefin metathesis in 2005 had also a boosting effect on the flourishing of organic synthesis.

Deeply impressed by the tremendous advances in organic synthesis in the last two years, we believed that the time was mature for another survey. However, soon after we started working on this survey, we realized that the space limitation of a paper like this does not allow for a complete coverage of all the fantastic works published since 2004. This forced us to make a painful compromise: to restrict the type of work to only synthetic methodologies and total synthesis of natural products, and the reference source to only those papers of most distinct novelty published in two top chemistry journals—the *J Am Chem Soc* and the *Angew Chem Int*. It is hoped that the examples selected in the present review would make it easier for the readers to appreciate the beauty of the original contributions from those leading chemists and to gain enlightenment as well as inspiration for the readers' own studies. Possible coverage of the work from our colleagues in mainland China in our next survey is also greatly anticipated.

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1 Some new advances in organic synthetic methodology

Organic reactions are of central importance to organic synthetic methodology and underlie all types of organic syntheses. Traditionally, organic reactions are divided into two major types: (1) formation of carbon-carbon bonds as well as cleavage and (2) functional groups transformations. However, as described above, the present survey is intended to cover only the newest advancements in the field, only those hot-spots (in our opinion) including organic synthetic reactions mediated by metals or radicals, multi-step reactions fulfilled in "one-flask", and asymmetric synthetic reactions are discussed below.

1.1 Metal-mediated synthetic reactions

Since the 1980s, most of the newly discovered synthetic reactions have been mediated by metals, with transition metals (especially palladium) catalyzed carbon-carbon bond formation as a particularly striking example. The potential and influence of the metal-mediated reactions are further manifested by the broad application of Pd-catalyzed reactions [9] in the synthesis of natural products and complex molecules. Currently, the olefin metathesis and the reactions mediated by gold are probably the ones that receive most attention of the chemical community.

1.1.1 Olefin metathesis reaction

For some years, organic chemists had been expecting that those pioneers of olefin metathesis would eventually win the Nobel Prize. The prediction came true in 2005 when the Nobel Prize in chemistry went to Chauvin et al. [10–12], rewarding them with what they really deserved.

It perhaps should be noted that the English word for our Chinese term (pronounced as *Xi Ting Fu Fen Jie Fan Ying*) is *metathesis*, which originates from Greek and means "transposition". As the existing Chinese translation has been adopted broadly in mainland China, we chose to keep it (in the Chinese original of the present survey) as is although some alternative translations appear to be more pertinent. (Currently, the committee of terminology of organic chemistry suggests the Chinese term (pronounced as *Xi Ting Huan Wei Fan Ying*) for "olefin metathesis")

Olefin metathesis is one of the fastest developing organic reactions over the last decade, with remarkable improvements made in the catalyst (or initiator), the reaction conditions, and the scope. The major developments during the last two years are primarily in its application in the synthesis of unusual molecules and asymmetric synthesis. Many interesting cases have appeared in the literature. Here are a few selected examples.

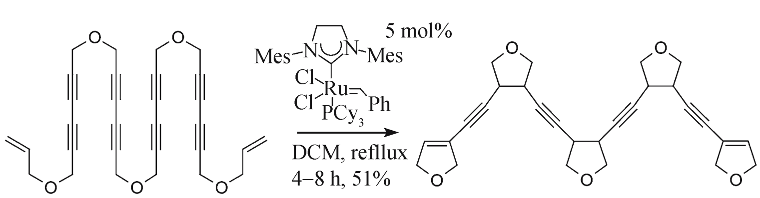
Lee et al. reported a one-step construction of enediynes and oligoenynes [13] using a uniquely controlled metallotropic [1,3]-shift followed by an enyne ring-closing metathesis (RCM) mediated by the Grubbs catalyst. Below is one of the examples (Scheme 1-1):

Recently, more and more attention has been paid to the exploration of metathesis, especially in the context of RCM, in the construction of aromatic compounds. Donohoe et al. made a thorough survey on the progress [14] of this aspect. The primary routes to aromatic compounds through the RCM process are ring closure followed by an allylic oxidation or elimination of a leaving group, and direct RCM or RCM combined with tautomerization to form aromatic compounds [15]. This approach has been successfully employed by Yoshida and Imimoto in the construction of a series of substituted phenol derivatives. (Scheme 1-2)

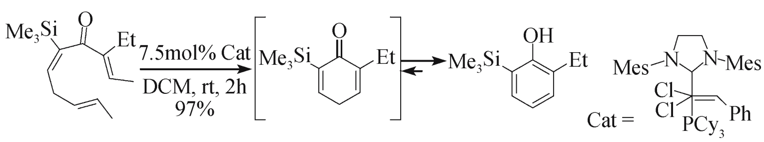
Collins et al. [16] developed a novel approach to the synthesis of helicenes on the basis of RCM, which represent successful examples in this field with bright application prospects. (Scheme 1-3)

In their enantioselective studies, Schrock et al. achieved asymmetric ring-closing metathesis (ARCM) of some nitrogen-containing alkenes in 85% to $>98\%$ ee [17] using their chiral Mo-based chiral catalyst (Scheme 1-4).

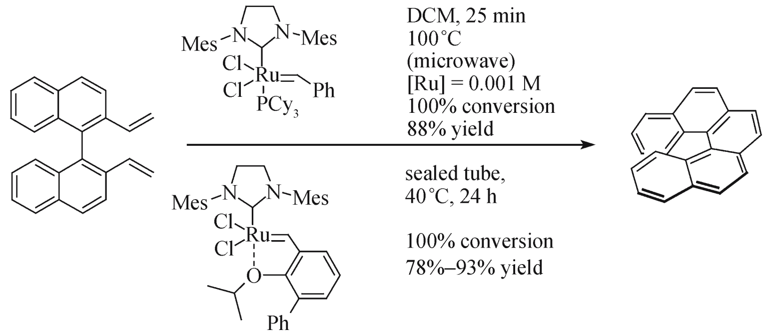
Blechert et al. [18] studied diastereoselective ring-rearrangement metathesis (RRM) of some symmetrical cycloalkenes with a stereocenter in the side chain. After the RRM reaction, the stereocenter originally in the side chain was converted into part of the newly formed rings. The reaction occurred with certain diastereoselectivity (Scheme 1-5). The ring accessible from this methodology also includes 2,5-substituted dihydropyrans, dihydropyrroles,



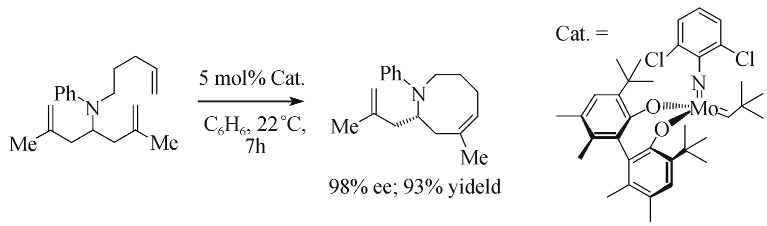
Scheme 1-1



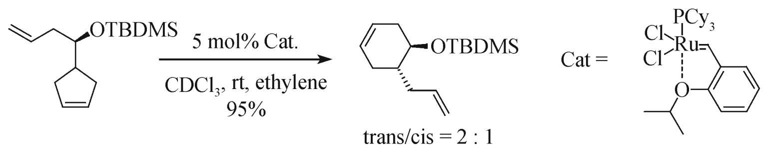
Scheme 1-2



Scheme 1-3



Scheme 1-4



Scheme 1-5

and dihydropyridines. The method may also be applied in the synthesis of certain natural products.

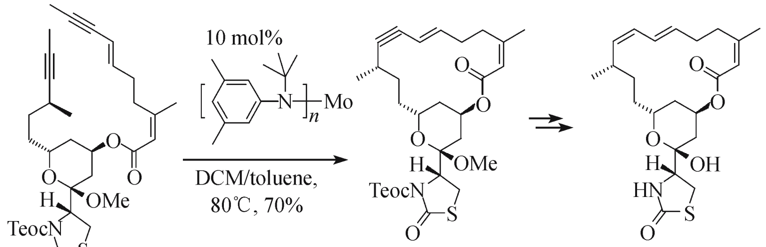
Olefin metathesis in its broadest sense also includes metathesis of alkynes. In recent years, tremendous efforts have been made in improving the catalyst and the reaction conditions, which lead to significant expending in the scope of the reaction and broad application in the total synthesis of natural products. It is no exaggeration that metathesis has become a key reaction in total synthesis, which was recently reviewed by Nicolaou et al. [19] and Perez-Castells et al. [20], respectively.

On the other hand, the unique structures of natural products also prompt further exploration and development of new conditions as well as procedures for olefin metathesis. For instance, (Scheme 1-6) the feature of a conjugated diene in a macrocycle in the structure of marine natural product latrunculin A promoted appearance of a novel approach [21] on the basis of the ring-closing alkyne metathesis (RCAM) without affecting the adjacent olefin.

The information about reactivity and selectivity of relay olefin metathesis in the presence of multi-double/triple bonds [22], olefin metathesis controlled by a template [23], and the catalysts for alkene as well as alkyne metathesis [24] are all well documented now.

1.1.2 Gold-mediated organic synthetic reactions

As previously noted [8], gold-catalyzed reactions only appeared in recent years. The developments in this area around 2004 have been briefly reviewed by Hashmi et al. [25]. In 2006, Ma et al. [26] also wrote a highlight about gold-mediated cyclization of enynes. A few more interesting



LatrunculinA

Scheme 1-6

works along this line published in the last two years are given below.

Using supported nano gold catalysts, Corma et al. [27] recently achieved chemoselective hydrogenation of nitro compounds in the presence of cyano, olefinic, and carbonyl groups. The yields were much higher than those using Pt or Pd catalysts (Scheme 1-7).

Echavarren et al. [28] utilized Au(I) complexes as the catalyst to realize a tandem cyclization-intramolecular Prins reaction of enyne-ketone substrates with high selectivity and moderate yields (Scheme 1-8).

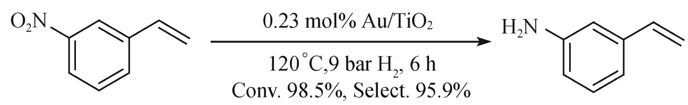
Gold (I) can also catalyze the conversion of certain ene-ynes into cyclopentenones [29] as shown in Scheme 1-9, with a broad scope of substrates and good prospects in asymmetric synthesis.

Gagosz et al. [30] recently disclosed that the substrates similar to those in Scheme 1-9 could undergo isomerization in the presence of gold (I), leading to bicyclo[3.1.0] type compounds with a corner acetoxy group. Such compounds can readily rearrange into α,β-unsaturated cyclohexenones. (Scheme 1-10) Gold (III), Pt (II), and Ag (II) cannot mediate such reactions.

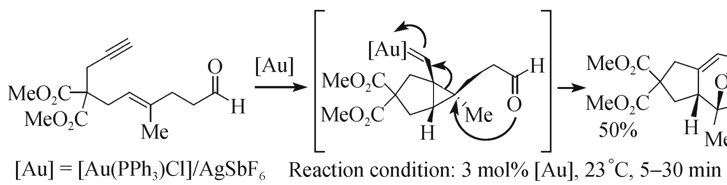
Propargyl vinyl ethers can be converted into dihydropyrans via a tandem Claisen rearrangement and 6-endo-trig ring-closure (Scheme 1-11) in the presence of gold (I) in good yields [31].

Another interesting observation is that phenols or carboxylic acids can be added to carbon-carbon double bonds (Scheme 1-12) in the presence of gold (I) [32]. The addition obeys the Markovnikov rule.

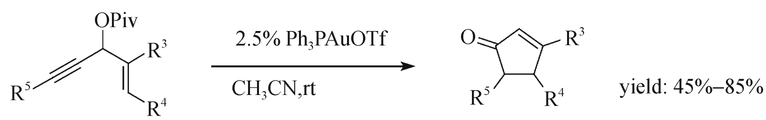
Propargylic acetate can be transformed into *α*-alkylidene-*β*-diketones (Scheme 1-13) via an Au (III) catalyzed acyl migration [33]. Acrylates were found to be even better than acetates.



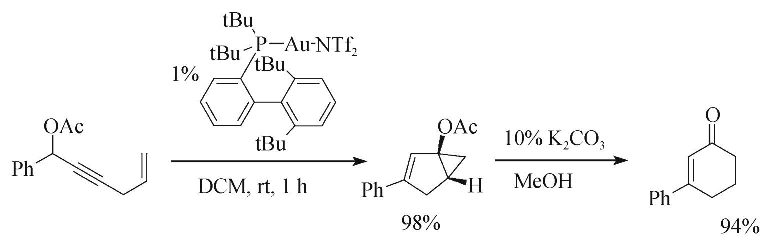
Scheme 1-7



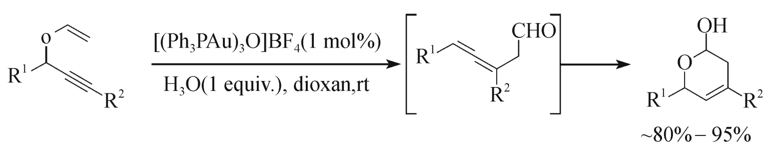
Scheme 1-8



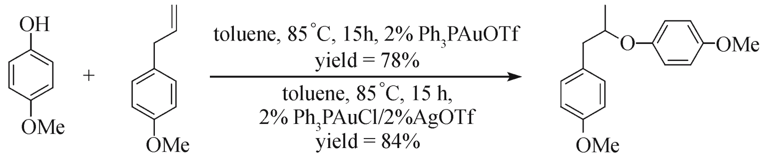
Scheme 1-9



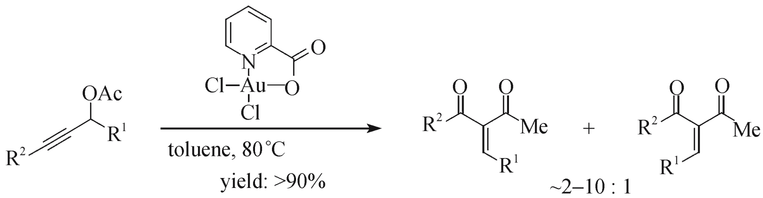
Scheme 1-10



Scheme 1-11



Scheme 1-12



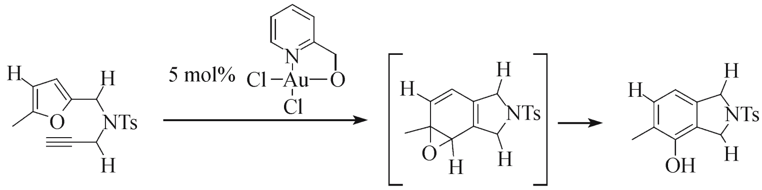
Scheme 1-13

Furan-alkynes shown in Scheme 1-14 can be converted into corresponding benzene-fused heterocycles in the presence of a gold catalyst [34] via an epoxy intermediate. The yields were higher than those catalyzed by other transition metals.

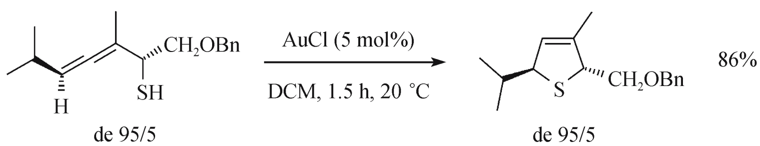
In 2006, Morita and Krause [35] reported the first gold-catalyzed C-S bond formation (Scheme 1-15).

Synthesis of benzothiophenes (Scheme 1-16) represents another advantage of gold catalysis. Traditional palladium catalysts failed to promote the reactions due to poisoning problem [36].

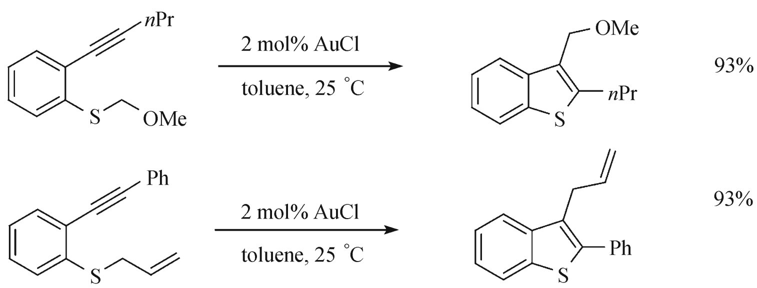
Campagne et al. [37] reported that gold (III) could catalyze direct substitution of propargylic alcohol by carbon, oxygen, or sulfur nucleophiles (Scheme 1-17). Pd (II) and Pt (II) failed



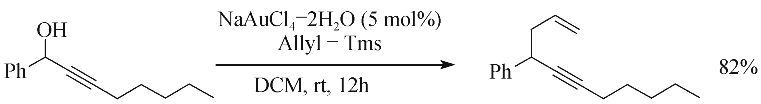
Scheme 1-14



Scheme 1-15



Scheme 1-16



Scheme 1-17

to catalyze these reactions under the otherwise identical conditions.

1.1.3 Others

Although Suzuki coupling has been the most commonly employed method for preparing biaryls for several decades, new improvements still keep coming. One of the recent developments is the decarboxylative coupling of aryl carboxylic acids with aryl bromides in the presence of a catalytic amount of palladium catalyst and an excess of copper salt [38]. Two sets of examples (Scheme 1-18) are given here. Starting from *o*-nitrobenzoic acid, the yield is $>80\%$ (even quantitative in some extreme cases). Such reactions have good scaling up prospects and hence may be applied to the synthesis of Boscalid (one of the BSAF agrochemicals).

There are a great many other examples that are also very interesting, such as those involving catalysis by Pd [39−44], Rh [45−47], Co [48], Ni [49], Cu [50−52], rare earth elements [53], and Te [54]. However, due to the length limit, they are not included here.

1.2 Radical-mediated synthetic reactions

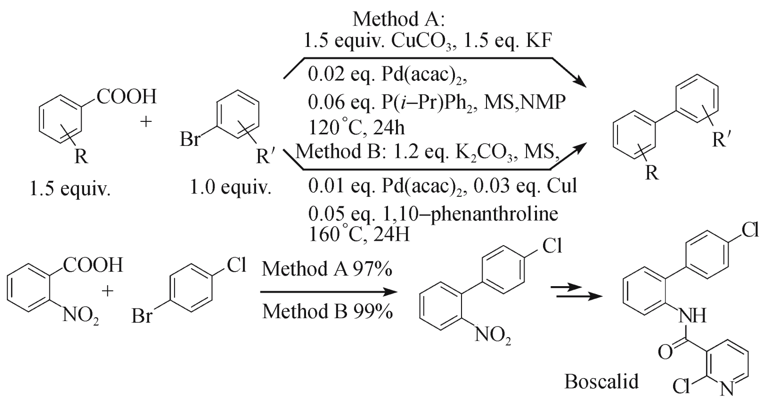
The reactions (especially cyclizations) mediated by radicals have been surveyed by Li in a book published in 2005 [8]. As a hot spot in organic synthesis, radical-mediated reactions are still full of striking new advances. The developments in the recent two years are mainly on the selectivity for different substrates under different conditions and the elimination of the involvement of the highly toxic tin-containing reagents.

Application of radical chemistry has led to successful *C*-glycosylations, with apparent selectivity in some cases [55]. (Scheme 1-19)

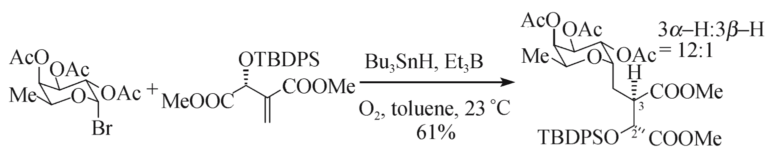
On the basis of their previous work on enone radial reaction with amines leading to lactams, Ryu et al. [56] designed a new cascade reaction consisting of a terminal alkyne radical triggered carbonylation followed by an addition of amine leading to α-methylene amides (Scheme 1-20). The reaction worked out nicely. However, substantial quantities of Bu_3SnH were required.

In their collaboration, Kim et al. [57] explored radical mediated carbonylation in the absence of any tin-containing radical initiator. After many tries, they finally succeeded in synthesizing thiol esters of aliphatic acids containing one more carbon atom with alkyl allyl sulfones as a starting material and phenyl benzenethiosulfonate as the radical trapping reagent (Scheme 1-21).

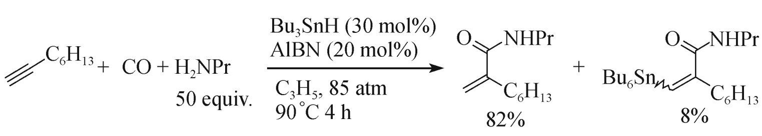
Recently Kim et al. [58] also reported a facile radical alkylation of bis(silyloxy)enamine derived from nitroalkanes, which led to carbonyl compounds after hydrolysis with the yields up to 80%. The transformation could also be achieved under tin-free conditions (Scheme 1-22).



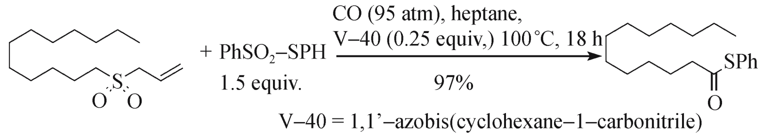
Scheme 1-18



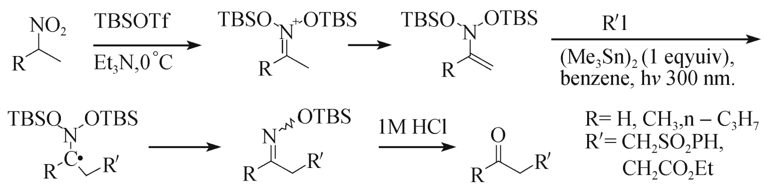
Scheme 1-19



Scheme 1-20



Scheme 1-21



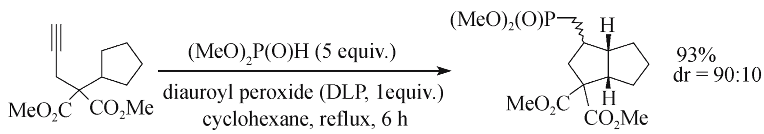
Scheme 1-22

Renaud et al. [59] studied radical cyclizations by exploiting hydrogen abstraction of dimethyl phosphite. With dilauroyl peroxide as the initiator, five-member rings could be readily constructed with good yields and selectivity. (Scheme 1-23) The procedure is also applicable to the synthesis of monocyclic, fused bicyclic, and spiro compounds.

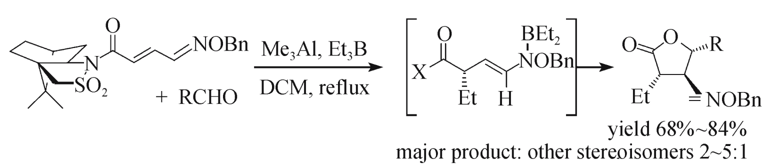
It is quite common nowadays that a radical reaction is incorporated into a reaction cascade, even an asymmetric one. One of such examples is shown in Scheme 1-24. The cascade started with the addition of an ethyl radical generated from triethylboron to the acyl substrate. The resulting enamine intermediate then underwent an aldol reaction with the aldehyde catalyzed by Me_3Al. Finally, a cyclization occurred with concurrent elimination of the chiral auxiliary [60]. The overall reaction showed some stereoselectivity and the major products had an all-trans configuration.

Another example is the Lewis acid mediated radical cyclization in the presence of a chiral auxiliary [61]. Starting from the phenylseleno substrate via a phenylselenyl transfer, a new ring with three chiral centers was constructed, which could eventually lead to the formation of two new rings containing four chiral centers. The reaction is exemplified by Scheme 1-25, where the monocyclic product was formed in 70%−80% yields, representing a successful case in catalytic radical cyclization although the quantity of the chiral ligand required appeared a little too large.

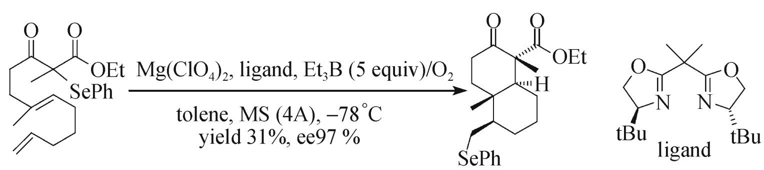
The radicals generated from xanthates are frequently utilized in organic synthesis. We utilized such radicals to construct a key intermediate for our synthesis of natural product clavulactone [62−64]. However, the reaction was set back by the involvement of organo tin species. Recently, Zard et al. [65] reported that organo boron could also initiate radical



Scheme 1-23



Scheme 1-24



Scheme 1-25

reactions and had been successfully applied to ring opening of a vinyl ethylene epoxide (Scheme 1-26).

1.3 Several steps of reactions in one flask

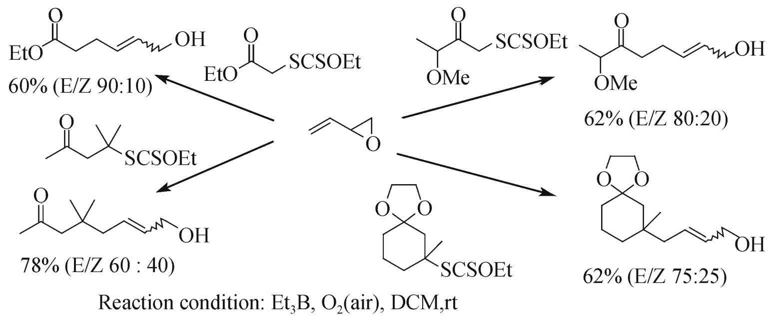
In a monograph [8] published in 2005, we mentioned particularly that "completing several steps of reactions in one flask" appeared to be a major trend in organic synthetic methodology. Such an approach may start from relatively simple, readily available compounds directly obtaining structurally more complex ones without involving separation of the intermediates and thus are economical and environment-benign. In that monograph, the advances along this line were presented under the title of "multi-component reactions" (Chapter 5) and "Tandem reactions" (Chapter 6). The last two years has witnessed a plethora of papers on "completing several steps of reactions in one flask", confirming it is indeed one of the hot spots in synthetic methodology studies. Here are a few of the recent examples for "tandem reactions" and "multi-component reactions".

1.3.1 Tandem reactions

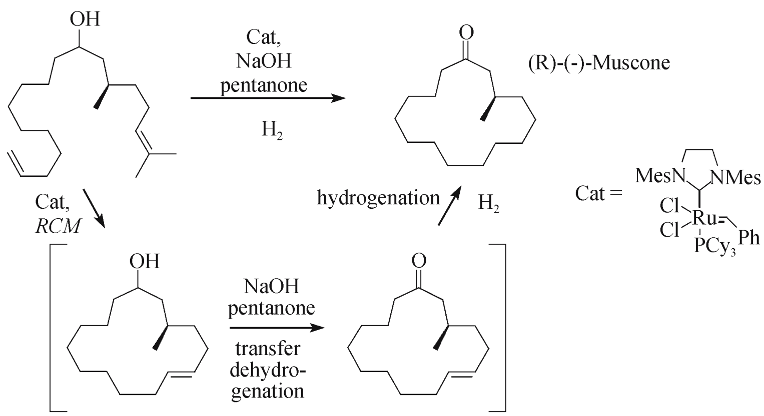
One of the reactions that have been most frequently mentioned in chemistry papers over the last two years is olefin metathesis. Understandably, such reaction is also encountered in tandem (or sequential) reactions. Tandem CM-CM reactions are already mentioned in the preceding section. Olefin metathesis is also employed in the synthesis of novel cyclic siloxanes [66] via sequential CM-RCM reactions.

What is even more interesting is that after olefin metathesis the catalyst could be utilized to catalyze another reaction in the same flask. Such tandem reactions have been vividly referred to as "Killing two birds with one stone". A piece of pioneering work of this type, where tandem reactions were applied to the synthesis of muscone, was completed by Grubbs et al. [67] in 2001 (Scheme 1-27).

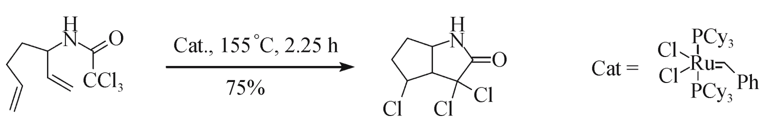
In 2005, Snapper et al. [68] developed a ruthenium-catalyzed ring-closing metathesis/Kharasch addition cascade reaction (Scheme 1-28).



Scheme 1-26



Scheme 1-27



Scheme 1-28

In 2006, Snapper et al. [69] reported the tandem RCM-cyclopropanation (Scheme 1-29).

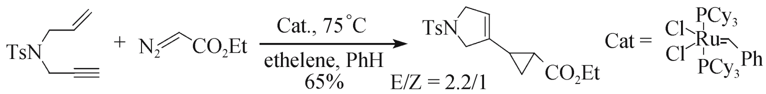
Using the same Grubbs catalyst, Blechert et al. [70] achieved tandem RCM-dihydroxylation, which is also an example of "one-flask" reactions (Scheme 1-30). However, after completion of the first step, the solvent must be removed. A new solvent was then added, followed by $NaIO_4$ and $YbCl_3 \cdot 6H_2O$. The overall yield was very good.

Apart from olefin metathesis, other reactions are also frequently found their applications in tandem reactions. One such example [71] is the Rh catalyzed $[2+2+2+1]$ reaction in the presence of CO (Scheme 1-31).

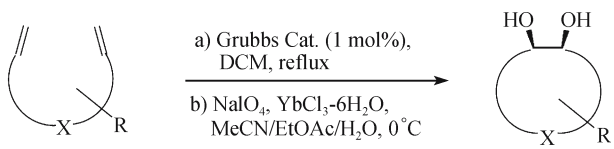
Pd-catalyzed intermolecular alkylation followed by an intramolecular aryl annulation [72] is another example (Scheme 1-32).

In 2006, Kamijo and Dudley [73] designed a smart and broadly applicable sequential reaction consisting of nucleophilic addition and 1,3-fragmentation (Scheme 1-33).

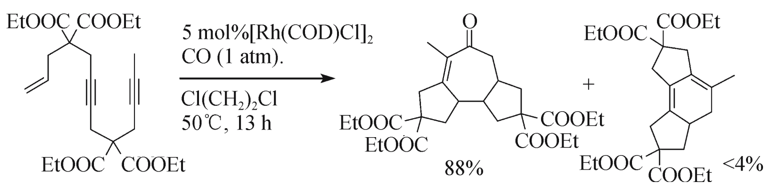
Another type of "one-flask" reactions, which are different from "killing two birds with one stone", is such that two catalysts are used to catalyze two sequential different reactions. Although strictly speaking such reactions are not tandem reactions, under properly chosen conditions, they may lead to excellent results due to avoidance of intermediate separations. Using such a strategy, Trost et al. [74] utilized first a Ru then a Pd catalyst to synthesize N- and O-containing heterocycles (Scheme 1-34). In the second step, a chiral ligand was employed, which led to products of fairly good enantiomeric excess.



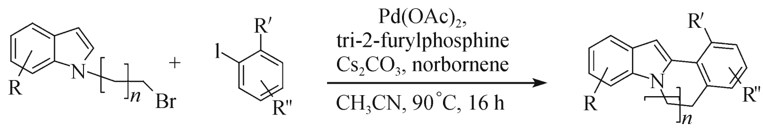
Scheme 1-29



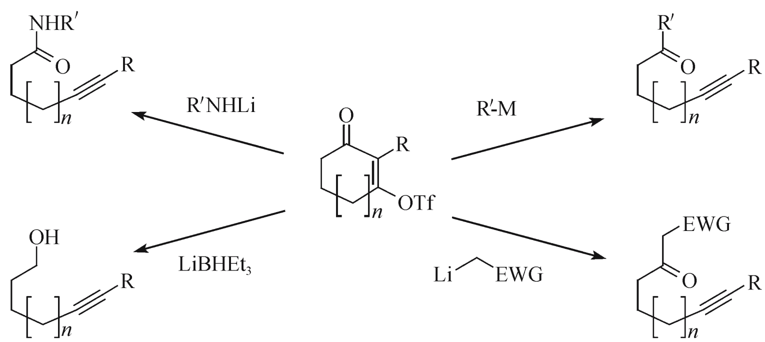
Scheme 1-30



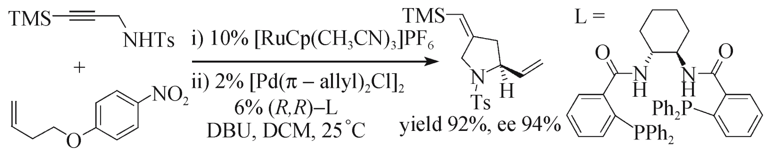
Scheme 1-31



Scheme 1-32



Scheme 1-33



Scheme 1-34

Also performed in a one-flask manner, Yamamoto et al. [75] realized Cu-catalyzed Mannich reaction and an Ir-catalyzed Diels-Alder reaction in the same flask (Scheme 1-35).

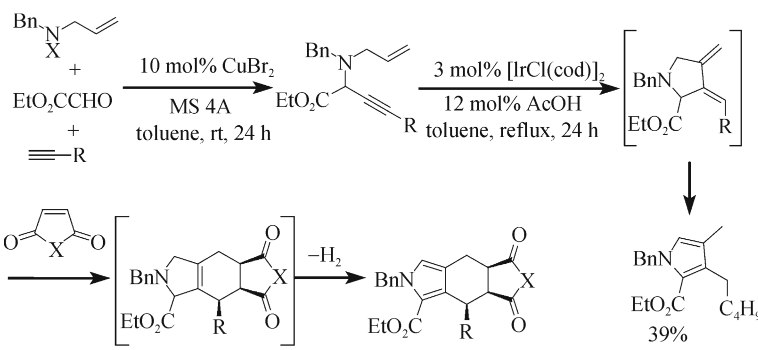
A number of other reports have also appeared in the last two years, including the molybdenum carbonyl mediated tandem allenic Pauson-Khand reaction [76] in the presence of CO- the highly enantio- and diastereoselective one-pot synthesis [77] of acyclic epoxy alcohols and allylic epoxy alcohols, the domino ring-opening/rearrangement reaction [78] of 2,3-epoxy-1-alcohols and PIFA(phenyliodine(III) bis(trifluoroacetate)), the tandem [4 + 2]/1,3-dipolar [3 + 2] cycloaddition of oxadiazoles [79] that allowed direct access to the pentacyclic aspidosperma skeleton in a reaction cascade forming four new C—C bonds and three new rings, and a catalytic asymmetric three-component 1,4-addition/aldol reaction in the enantioselective synthesis [80] of the spirocyclic moiety of Vannusal A. All these will not be detailed here due to space limitation.

1.3.2 Multi-component reactions

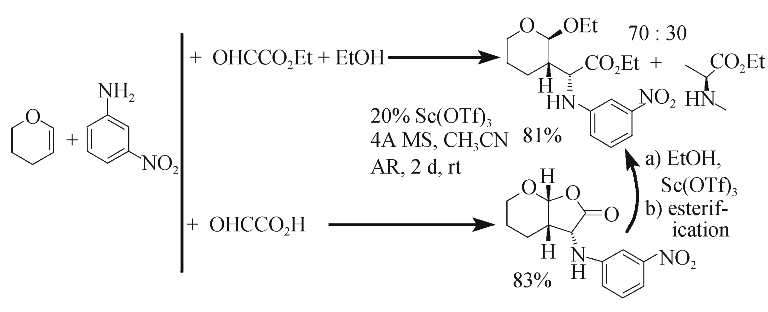
As already mentioned above, multi-component reactions have been receiving more and more attention from the world community of organic synthesis since the 1950s−1960s. From the 1990s up to the early years of this century, multi-component reactions already entered a prosperous period. Many reactions, especially those catalyzed by metals, have been employed in multi-component reactions. Facilitated by the advantages of green chemistry such as high efficiency and good atom-economy, tremendous amounts of reports on multi-component reactions have appeared in many organic chemistry journals. Some outstanding works were even published in general chemistry journals. This type of reactions has been applied to the synthesis of N- and O-containing heterocycles, open-chain compounds as well as precursors for natural and natural-like products.

$Sc(OTf)_3$ catalyzed three-component reaction of a cyclic enol ether, an arylamine, and ethyl glyoxylate led to α-amino lactones [81]. (Scheme 1-36) Similar four-component reactions of cyclic enol ethers, arylamines, ethyl glyoxylate, and alcohols gave the lactone ring-opening products. The aryl amines with electron-donating groups might lead to further cyclization, giving benzene fuse N-containing heterocycles (Scheme 1-37).

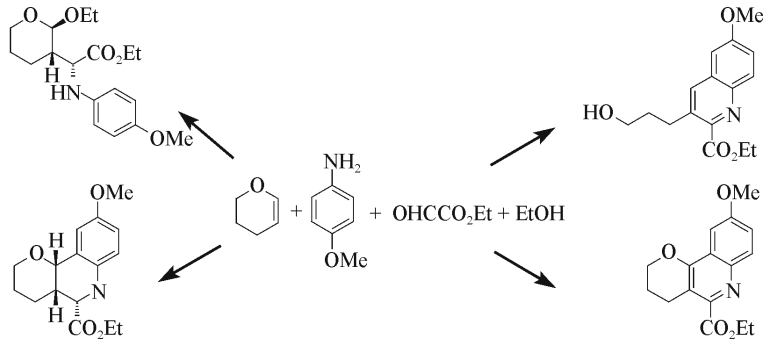
Using Pd-catalyzed four-component (iodoarene, alkyne, CO, and amidinium salt) reaction may lead to pyrimidines in "one-step" [82]. This method has also been applied to the synthesis of meridianins (Scheme 1-38).



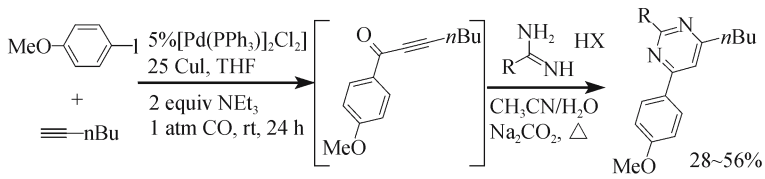
Scheme 1-35



Scheme 1-36



Scheme 1-37



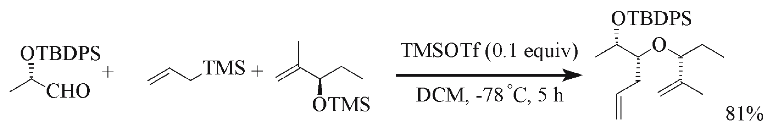
Scheme 1-38

Marko et al. [83] reported an improved Sakurai-MCR reaction, i.e., the three-component reaction between Lewis acid catalyzed carbonyl compounds (ketones, aldehydes, actetals, orthoesters, and ortholactones), allylsilanes, and alcohols (Scheme 1-39). The reaction is highly enantio-selective and the products are very suitable substrates for metathesis with good prospects in the synthesis of natural products.

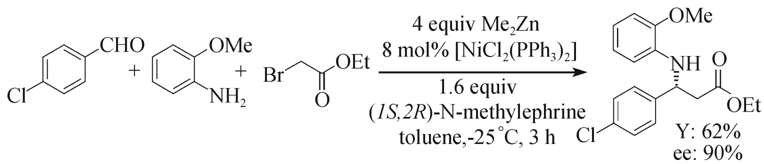
Cozzi and Rivalta [84] elaborated enamine Reformatsky reaction into an enantioselective three-component reaction, providing a new approach to β-amino acids (Scheme 1-40).

Rh catalyzed three-component reaction is another tool for the synthesis of β-amino acids (but with an α-hydroxyl group) [85]. The yield and diastereomeric selectivity of this reaction is rather good. It has been applied to the synthesis of the racemic side chain of taxol (Scheme 1-41).

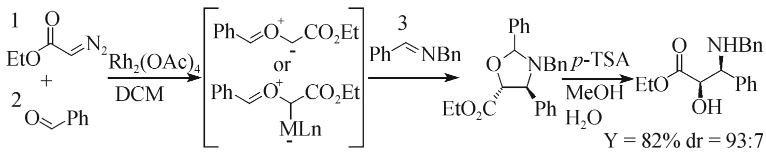
In the presence of a proper Pd catalyst allenylboronate, secondary amine, and iodoarene may undergo a three-component reaction leading to vinylboronates [86], which may further react with a fourth component in the same flask to give allylic amines (Scheme 1-42). The four-component reaction has been successfully applied [86] to the synthesis



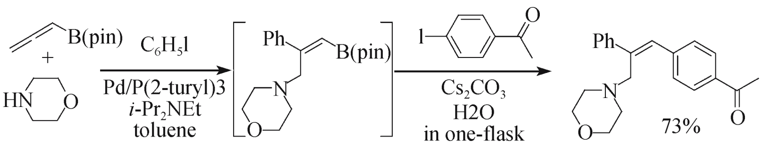
Scheme 1-39



Scheme 1-40



Scheme 1-41



Scheme 1-42

of rolipram, a selective inhibitor of phosphodiesterase-4 (Scheme 1-43).

1.4 Asymmetric reactions

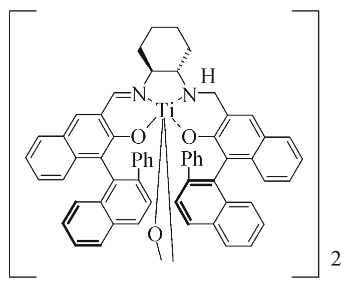
Synthesis of chiral pure compounds is one of the fields that have been receiving more and more attention since 1970s−1980s in organic synthesis. Besides resolution, chiral pure compounds can be gained by chemical transformation including diastereoselective reactions forming new chiral centers, starting from available chiral pure natural products (carbohydrates, terpenes). This involves the synthetic design and strategy, which we have mentioned on the basis of our own works in our newly published brochure [87] and will not be dealt with here. Another way to obtain the chiral pure compounds is asymmetric synthesis (substrate induced and stoichiometric chiral reagent mediated asymmetric organic synthesis and chiral-catalyst catalyzed catalytic asymmetric organic synthesis). The latter received more attention recently and developed rapidly. We will introduce here the metal catalyzed asymmetric reaction and organocatalyst catalyzed asymmetric reaction.

1.4.1 Metal-catalyzed asymmetric reactions

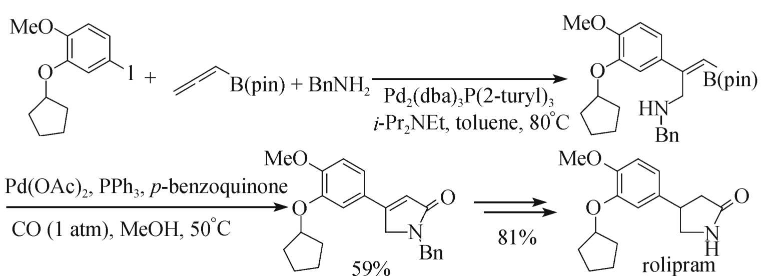
New reports of the metal-catalyzed asymmetric reaction on the reaction category, metal-involved, and the chiral ligands, have come forth these days. Below are the examples in the recent two years that we picked out to illustrate the situation.

Recently, a number of examples of asymmetric Streker synthesis of amino acid have been reported. More recently Shibasaki et al. [88] explored the Strecker reaction of ketoimines in the presence of chiral ligands and a rare earth metal. A Gd-complex prepared in situ could catalyze this reaction efficiently, and afforded high ee. Accordingly, the separated single crystal of Gd-complex could also catalyze this reaction, while the reaction proceeded slowly to give slight lower ee product, and configuration of the major product was just the opposite of that formed by the in-situ active species (Scheme 1-44). This finding is instructive for the further understanding of asymmetric Streker reaction.

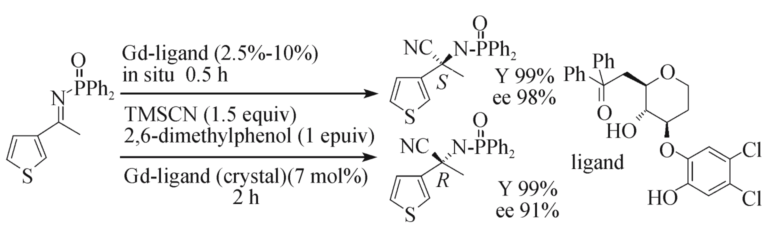
The state of the art in asymmetric epoxidation with aqueous hydrogen peroxide as the oxidant was represented by using [Ti(salalen)] and [Ti(salan)] complexes as the catalyst. For the first time, asymmetric catalyzed epoxidation for a terminal olefin had been demonstrated. This is a breakthrouth in this area [89]. Below is one of the catalysts.



[(μ-O)$_2$Ti(salalen)]



Scheme 1-43



Scheme 1-44

Asymmetric hydrogenation and synthesis of α-amino acid are classical and continually-developing projects in asymmetrical synthesis. Using the concept of combinatorial chemistry, Ding et al. developed new simpler monodentate phosphoramidite ligands for rhodium-catalyzed enantioselective hydrogenation. Below are two of the examples (Scheme 1-45). The rhodium-catalyzed asymmetric hydrogenation of imino-ester and terminal imine gave a product with high ee [90].

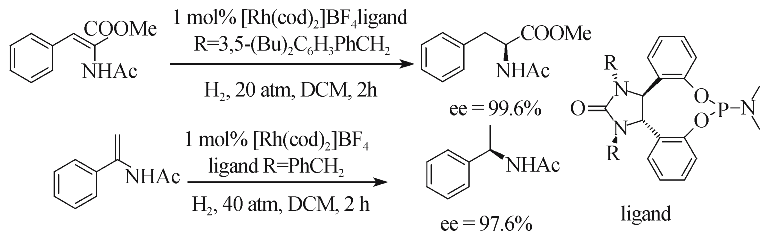
Zhang et al. reported the Rh-catalyzed asymmetric hydrogenation of α-aryl imino esters using (*S*,*S*,*R*,*R*)-tangphos as the ligand, giving an efficient enantioselective synthesis of aryl glycine derivative, with almost 100% yield and enantioselectivity [91] (Scheme 1-46).

Just before the above report, Zhang et al. had reported the asymmetric hydrogenation of *β*-secondary-amino ketone with the similar rhodium-catalyst, while yield and enantioselectivity were all over 90% (Scheme 1-47). This method could be of great interest in chiral drug synthesis [92].

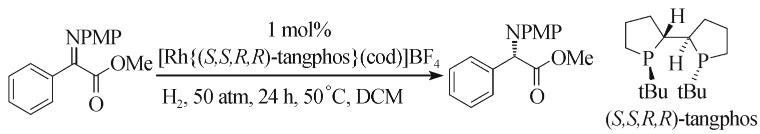
Shibasaki et al. [93] reported an asymmetric alkynylation of aldehydes catalyzed by an In (III)/BINOL complex. This reaction could be expanded to both aromatic and aliphatic aldehydes, and also showed rather strong positive nonlinear effects (Scheme 1-48). This is a breakthrough in this kind of well-investigated asymmetric reactions.

Trost et al. reported a direct catalytic asymmetric Mannich-type reaction via a dinuclear zinc catalyst toward the synthesis of either *anti*- or *syn*-*α*-hydroxy-*β*-amino ketone with high ee, starting from α-hydroxy ketone and Dpp-protected imine [94] (Scheme 1-49).

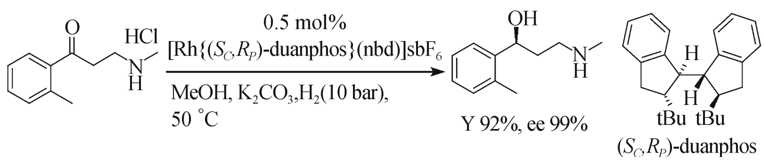
Shibasaki et al. reported a direct catalytic asymmetric Mannich-type reaction of *N*-(2-hydroxyacetyl)-pyrrole as an



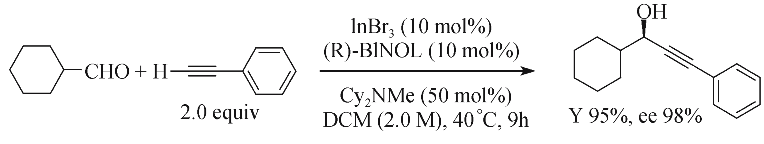
Scheme 1-45



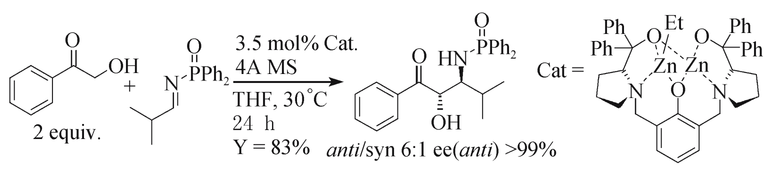
Scheme 1-46



Scheme 1-47



Scheme 1-48



Scheme 1-49

ester-equivalent donor. The result turned out to be good but with longer reaction time and the N-Ts group could not be easily removed [95] (Scheme 1-50).

Asymmetric Diels-Alder reaction is always one of the spectacular fields. Mikami et al. reported the asymmetric synergy between chiral dienes and diphosphines in cationic Rh(I)-catalyzed intramolecular [4 + 2] cycloaddition (Scheme 1-51). This is an interesting report. Referring to its application as a methodology, it is bound to have a great limitation [96].

Pu and Qin [97] reported the highly enantioselective addition of diphenylzinc to aliphatic and aromatic aldehydes catalyzed by a readily available *S*-H_8-binol derivative. The aliphatic aldehyde substrate gave the product of *R*-configuration. As to the aromatic aldehyde, it turned out to be an *S*-configuration (Scheme 1-52). Later, Nelson and Wang [98] reported the asymmetric addition of diethyl zinc to α,β-unsaturated aldehyde in the presence of (−)-MIB to give an enantioenriched product, which could be used for further Claisen rearrangement.

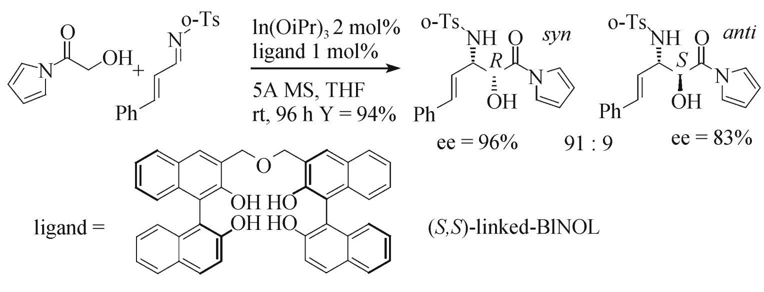
Selective C—H functionalization is always one of the most interesting fields in organic synthesis. Enantioselective functionalization is the direction that intrigues more attention. Recently, Davies [99] summarized the recent advance in catalytic enantioselective intermolecular C—H functionalization using dirhodium complex.

Another direction in catalytic asymmetric reaction is the reaction carried out on the complex structure-related substrates. Trost and Frederiksen [100] reported the synthesis of 3-allyl-3-aryl oxindoles through palladium-catalyzed asymmetric allylic allylation (AAA) of prochiral nucleophile, with good to excellent enantioselectivity in the generation of sterically congested quaternary stereocenter.

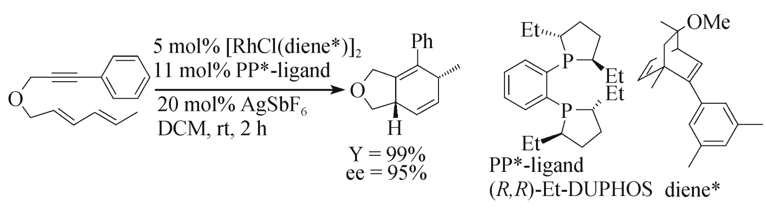
From the above examples, it can be seen that the metals involved in the catalytic asymmetric reactions are those of the main group, rare earth group, and transition group. The reaction types involved are multifarious. Basically, the types of the chiral ligands are essentially the same as those developed in previous years. Because asymmetric reactions are sensitive to the structure of the substrates, many protocols so far reported are only applicable to a particular class of substrates. Therefore, more specific methodologies are needed for realize different specific transformations. On the other hand, the appearance of the widely applicable metal catalyzed asymmetric reactions is also anticipated.

1.4.2 Organocatalyst catalyzed asymmetric synthesis

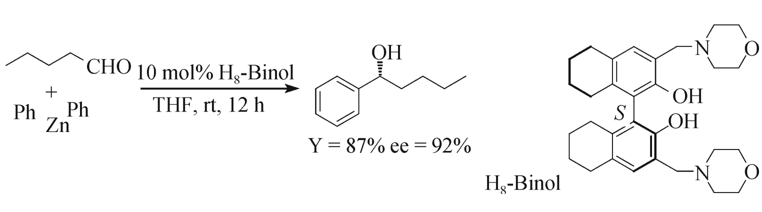
Just as we mentioned in our monograph [8] last year, the widespread-applications of small molecule organocatalysis are the most outstanding development in asymmetric catalysis reaction; a golden age for organocatalysis has come. The development of organocatalysis has been astonishing in the last two years. In the two leading chemistry journals, articles on organic catalysis appear frequently, sometimes even with more than one paper in an issue.



Scheme 1-50



Scheme 1-51



Scheme 1-52

The organocatalysts have been extended from the proline and its derivatives or analogs to chiral ureas, thioureas, cinchona alkaloids and derivatives as well as other organic Brϕnsted acid. The types of the catalyzed asymmetric reactions have also been developed from aldol reaction to a range of other reactions. Below, we will introduce the progress in these two years by some examples according to the type of organocatalysts.

1.4.2.1 Proline-catalyzed asymmetric reaction

People have paid great attention to the control of four chiral centers formed in a three-step cascade and three-component reaction, affording the chiral-pure cyclohexene derivative using proline derivative as catalysts [101] (Scheme 1-53).

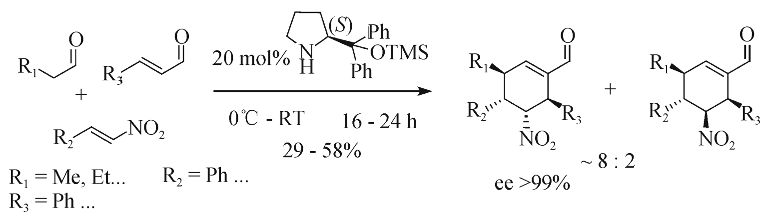
Chi and Gellman [102] have reported enantioselective organocatalytic aminomethylation of aldehyde using the same proline derivative as catalyst. The *β*-amino alcohol generated via the Mannich-type reaction could be converted in a straightforward manner to a corresponding *β*-amino acid (Scheme 1-54).

Nitrogen-containing carbohydrate derivatives were obtained with very good stereoselectivity from dihydroxyacetone through L-proline catalyzed Mannich-type reactions [103] (Scheme 1-55). It was possible to improve the existing protocol (shorter reaction times, less catalyst) by using 2,2,2-trifluoroethanol as solvent and microwave-assisted procedure. Because of their application prospects the asymmetric Mannich-type reactions have been mentioned in many publications. The situation with metal-catalyzed asymmetric reactions is the same over the last two years. A simple survey in 2006 may serve as a reference [104].

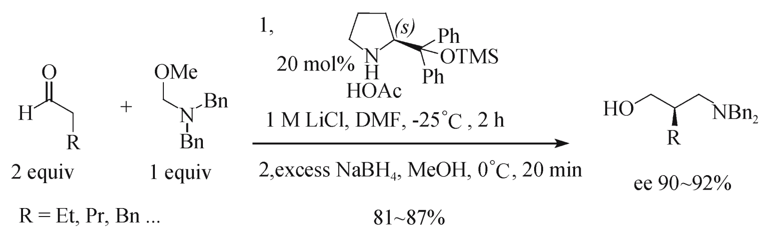
(*S*)-Proline-catalyzed aldol reaction of the DHA equivalent with 2,3-*O*-(isopropylidene)-D-glyceraldehyde generates the rare ketosugar D-psicose. This work is of great significance and deserves to be mentioned here again [105]. Later, Cordova et al. [106] reported a two-step direct catalytic synthetic protocol including direct amino acid catalyzed asymmetric synthesis of polyketide sugars. Kazmaier et al. have also highlighted the progress on the aminoacids-type organocatalysts in carbohydrate synthesis [107].

One novel proline-type catalyst is combined hydroxyproline and fatty acid, which show it as a surfactant and could catalyze the cross-aldol reaction of aldehydes with high diastereo- and enantioselective in the aqueous solution [108] (Scheme 1-56).

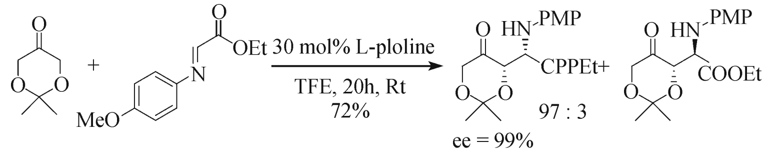
The success of proline-catalyzed aldol reactions ensured its growing application in natural product synthesis. Below is an example of intramolecular conjugated addition of aldehyde to unsaturated aldehyde (Scheme 1-57). It can be used in the total synthesis of brasoside and littoralisone [109].



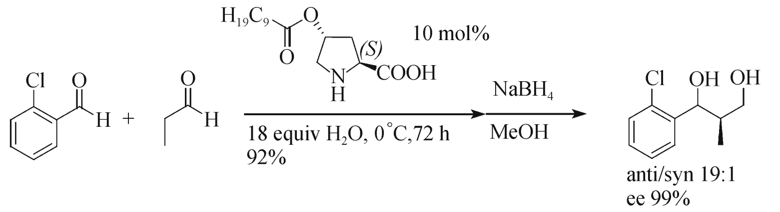
Scheme 1-53



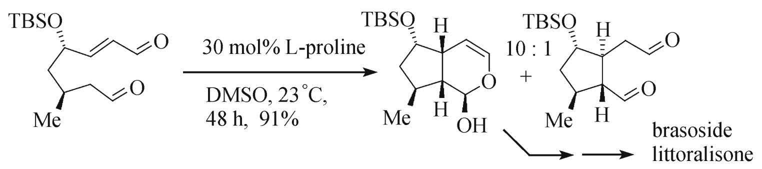
Scheme 1-54



Scheme 1-55



Scheme 1-56



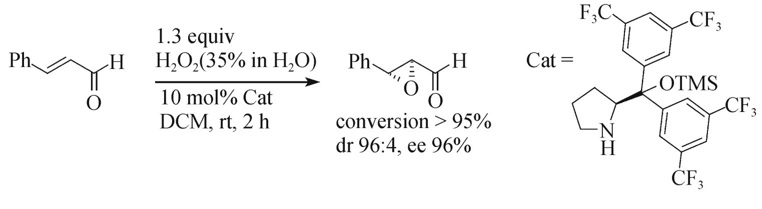
Scheme 1-57

Besides the organocatalyst catalyzed aldol-type catalytic reaction, Jørgensen reported in 2005 the asymmetric epoxidation of *α,β*-unsaturated aldehyde with hydrogen peroxide, which has great significance both in academic and industrial fields [110] (Scheme 1-58).

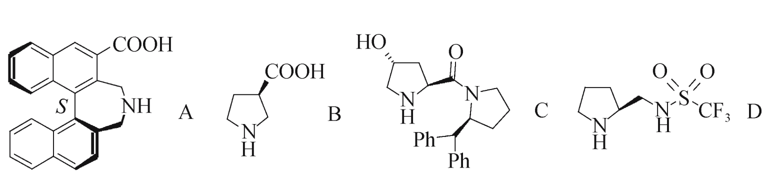
There are a number of research works on the proline-type organocatalysts, for example: Jørgensen et al. reported the organocatalytic diastereo- and enantioselective annulation reactions in the construction of optically active 1,2-dihydroisoquinoline and 1,2-dihydrophthalazine derivatives [111]; Maruoka et al. reported the design of an axially chiral amino acid with a binaphthyl backbone as an organocatalyst (Structure A) for a direct asymmetric aldol reaction [112]; Jørgensen et al. reported organocatalytic conjugate addition of malonates to *α,β*-unsaturated aldehydes and finished the asymmetric formal synthesis of (–)-paraxetine [113]; Zhao et al. reported organocatalytic enantioselective synthesis of α-hydroxy phosphonates via a proline-catalyzed asymmetric cross aldol reaction of activated ketones [114]; proline derivatives were reported to be involved into the organocatalytic direct Michael reaction of ketones and aldehydes with nitroalkenes [115,116]; Barbas, III explored 3-pyrrolidinecarboxylic acid (Structure B) for direct catalytic asymmetric Mannich-type reaction of unmodified ketone with *anti*-selectivity [117]; Palomo reported highly efficient asymmetric Michael addition of aldehyde to nitroalkene catalyzed by *trans*-4-hydroxyprolylamide (Structure C), with 4-hydroxy group involved in the reaction transition state [118]; Wang and Wang [119] reported the directly, highly enantioselective Michael addition of aldehyde to nitro styrene catalyzed with pyrrolidine sulfonamide (Structure D).

1.4.2.2 Cinchona alkaloids catalyzed asymmetric reactions

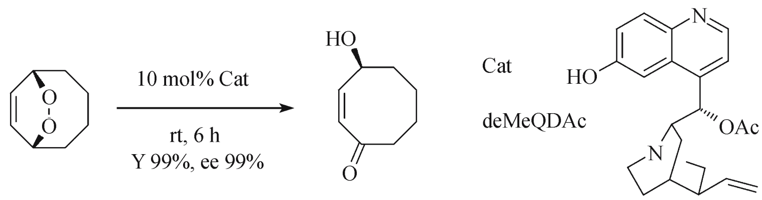
Cinchona alkaloids have many applications as ligand involved in metal-catalyzed asymmetric reactions. After some modifications, they themselves could also be good catalysts of asymmetrical reaction. Some interesting developments have been reported, such as enantioselective synthesis of *γ*-hydroxy cycloalkenones by chiral quinidine base-catalyzed Kornblum DeLaMare desymmetric rearrangement of symmetric 1,4-epoxy-cycloalk-2-ene (Scheme 1-59). This was the first report on this facet, but it was applicable only to 7,8-membered ring [120].



Scheme 1-58



Structures A−D



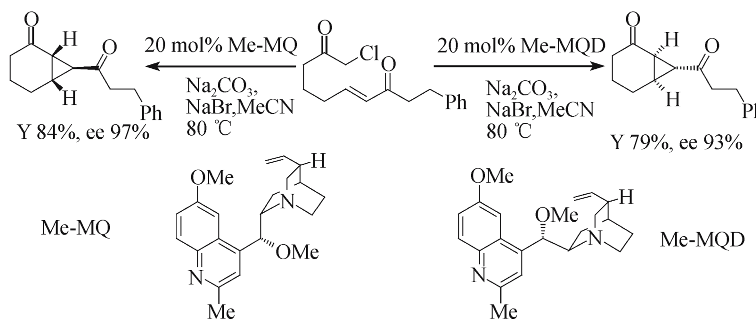
Scheme 1-59

Gaunt et al. reported enantioselective catalytic intramolecular cyclopropanation using modified cinchona alkaloid organocatalyst with good yield and enantioselectivity. It is noteworthy that the quinine catalyst and the quinidine catalyst gave the enantiomer with opposite configuration [121] (Scheme 1-60).

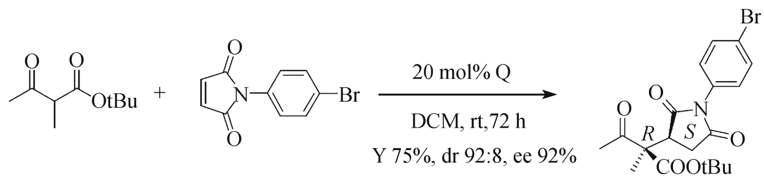
Melchiorre reported the organocatalytic asymmetric conjugate addition of 1,3-dicarbonyl compounds to maleimide catalyzed by quinine and quinidine themselves with good enantioselectivity and diastereoselectivity. Quinine and quinidine afforded the products as a pair of enantiomers respectively [122] (Scheme 1-61). Prakash et al. reported a highly enantioselective organocatalytic Friedel-Crafts hydroxyalkylation of indole with ethyl trifluoropyruvate catalyzed by cinchona alkaloids [123]. Jørgensen et al. [124] reported direct organocatalytic and highly enantio- and diastereoselective Mannich reactions of α-substituted α-cyanoacetates catalyzed by $(DHQD)_2PYR$, which was once the ligand in metal catalysis.

Wang et al. reported organocatalytic enantioselective conjugate additions to enone, catalyzed by a cinchona alkaloid-derived thiourea organocatalyst, but with longer reaction times [125] (Scheme 1-62).

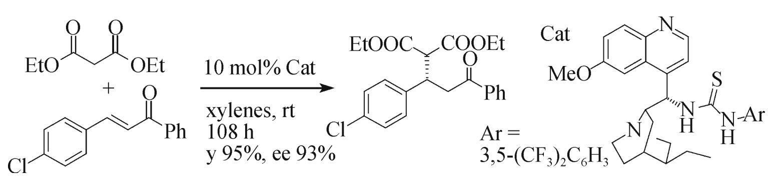
Another way is to prepare chiral quaternary ammonium salt, which could be used in organocatalysis, from cinchona alkaloids. Palomo et al. reported catalytic enantioselective aza-Henry reaction with broad substrate scope [126] (Scheme 1-63). Jørgensen et al. reported organocatalytic enantioselective nucleophilic vinylic substitution through an addition-elimination (Ad_N-E) mechanism [127] (Scheme 1-64).



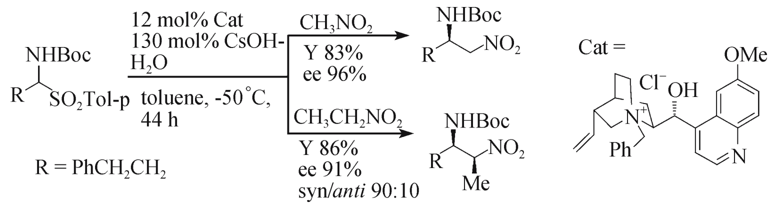
Scheme 1-60



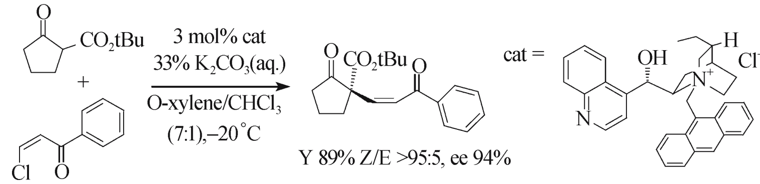
Scheme 1-61



Scheme 1-62



Scheme 1-63



Scheme 1-64

1.4.2.3 Chiral ureas and thioureas catalyzed asymmetric reactions

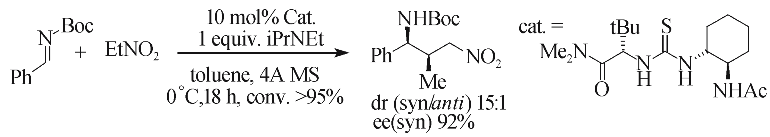
Jacobsen et al. had identified a family of chiral urea and thiourea catalysts that catalyzed a variety of enantioselective reactions with imines, including hydrocyanation, Mannich, hydrophosphonylation, and acyl-Pictet-Spengler reactions. In 2005, Jacobsen developed highly enantioselective thiourea-catalyzed nitro-Mannich reactions (aza-Henry reaction) using the novel chiral thioureas that he had synthesized [128] (Scheme 1-65). Jacobsen et al. then reported a chiral primary amine thiourea catalyst for the highly enantioselective direct conjugate addition of α,α-disubstituted aldehyde to nitroalkene [129] (Scheme 1-66).

Another laboratory, also reported an organocatalytic approach to enantiomerically pure β-amino acids using this kind of catalysts to realize the kinetic resolution of oxazinones [130] (Scheme 1-67).

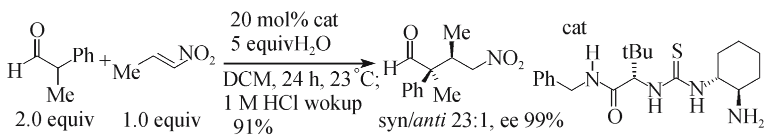
Ricci et al. reported catalytic enantioselective Friedel-Crafts alkylation of indoles with nitroalkene by using a simple thiourea organocatalyst [131].

1.4.2.4 Chiral phosphoric Brønsted acids catalyzed asymmetric reaction

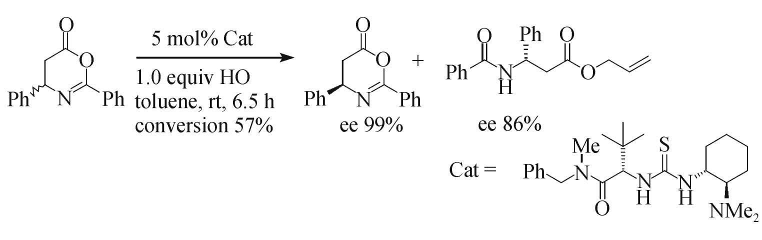
In 2004, the research groups of Akiyama and Terada independently reported the development of a new class of chiral phosphoric Brønsted acid catalysts (Structures A and B)



Scheme 1-65



Scheme 1-66



Scheme1-67

derived from binaphthol. In 2006, a survey [132] was reported on the application of these novel catalysts in asymmetric Mannich-type reaction and asymmetric reductive-amination reaction of imino-compounds. New reports on the chiral phosphoric Brønsted acid catalyst in asymmetric reaction came forth thereafter. Rueping et al. reported a highly enantioselective Brønsted acid catalyst (Structure C) for the Strecker reaction [133] (Scheme 1-68).

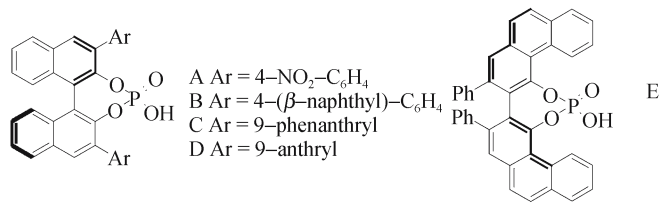
Terada et al. [134] reported the application of these organocatalysts for an enantioselective aza-ene-type reaction. Akiyama et al. [135] reported chiral Brønsted acid (Structure D) catalyzed inverse electron-demanded aza Diels-Alder reaction (Scheme 1-69). Just before this report, they also reported a chiral Brønsted acid catalyzed normal electron-demanded enantioselective aza-Diels-Alder reaction of Brassard's diene with imines [136].

Rueping et al. [137] reported a highly enantioselective Brønsted acid (Structure C) catalyzed cascade reaction, realizing organocatalytic transfer hydrogenation of quinolines and their application in the synthesis of alkaloids (Scheme 1-70).

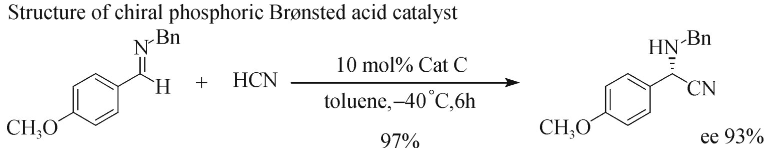
1.4.2.5 Other organocatalytic asymmetric reaction

Besides the above-mentioned types of organocatalysts, there are still many other metal-free chiral catalysts. Schaus et al. reported the first example of a highly enantioselective asymmetric allylboration of ketones using chiral bromo-substituted BINOL catalysts and allyldiisopropoxyborane [138] (Scheme 1-71).

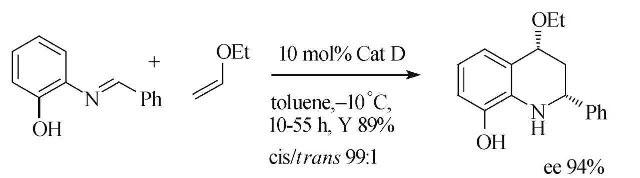
Rawal et al. [139] reported highly diastereo- and enantioselective Mukaiyama Aldol reactions catalyzed by organocatalyst with good selectivity and yield. The employed catalysts were simple diols of the taddol family, which were highly effective catalysts for enantioselective reactions. This kind of catalysts was unsuccessful in the above-mentioned work (Scheme 1-72).



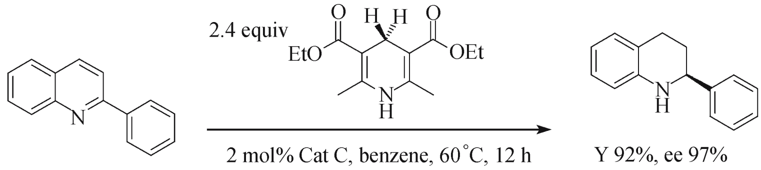
Structure of chiral phosphoric Brønsted acid catalyst



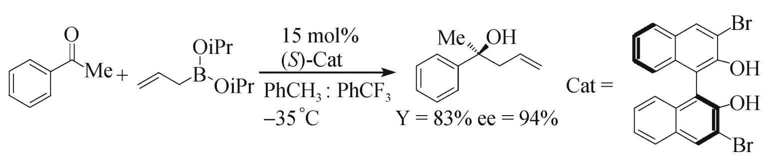
Scheme 1-68



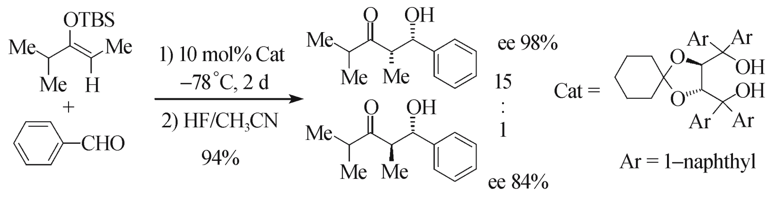
Scheme 1-69



Scheme 1-70



Scheme 1-71



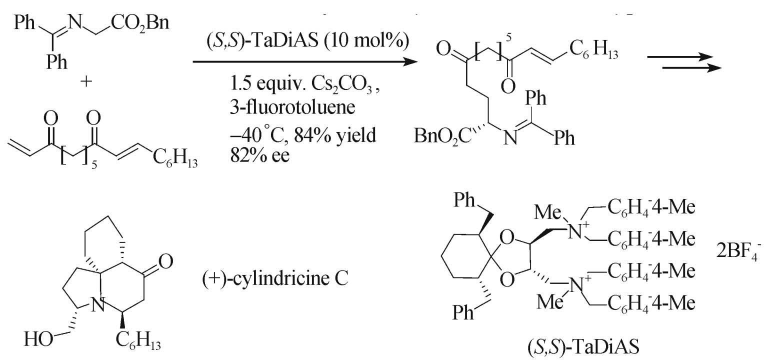
Scheme 1-72

Shibasaki et al. [140] developed a two-center phase-transfer organocatalyst (TaDiAS; tartrate-derived diammonium salt) that efficiently catalyzed Michael reactions and Mannich-type reactions of the glycine Schiff base. Also, Shibasaki reported a short synthesis of (+)-cylindricine C by using a catalytic asymmetric Michael reaction with this two-center organocatalyst (Scheme 1-73). Before, they had applied this organocatalyst in the Mannich-type reaction of a glycine Schiff base, but with very low ee [141].

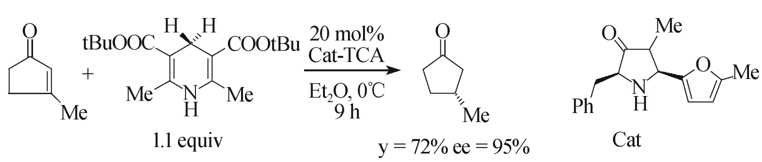
It was mentioned earlier that a phosphoric catalyst could take part in the hydrogen-transfer asymmetric hydrogenation on quinoline compounds. MacMillan et al. developed the first organocatalytic transfer hydrogenation of cyclic enones catalyzed by chiral tetrapyrrolidones [142] (Scheme 1-74).

In the context of his studies on the selective synthesis of natural products with α-keto tertiary alcohols, such as eucomol, Suzuki et al. [143] reported the viability of benzoin cyclizations of ketoaldehydes with triazolium catalysts, thus affording the desired structure under mild conditions (Scheme 1-75). Christmann has highlighted the development of asymmetric Stetter reactions between aldehydes and conjugated ketones with such kind of organocatalyts and with similar selectivity. This reaction showed a good application prospect in the asymmetric synthesis of natural products [144].

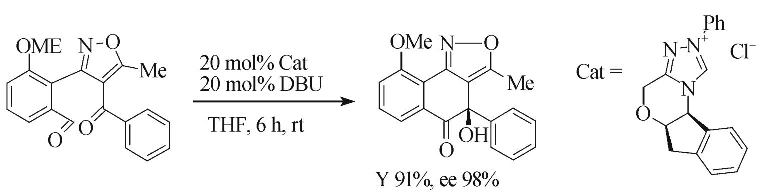
From the above examples, we can see that organocatalysis is now at its flourishing stage with continuous introductions of new organocatalysts. It is also difficult to classify them, such as the chiral quaternary ammonium salt of two



Scheme 1-73



Scheme 1-74



Scheme 1-75

binaphthyl, which may catalyze the asymmetric alkylation [145] of diaryloxazolidin-2,4-diones. In addition, more and more organocatalytic reactions come forth. In general, it really deserves to pay more attention to the organocatalysis within the field of contemporary organic synthesis.

2 Progress in total synthesis of complex natural products

Total synthesis of complex natural products is one of the most traditional and most challenging areas of organic synthetic chemistry. This type of work often involves a range of different reactions and usually takes some ten or even several-dozen steps of transformations to complete. For these reasons, total synthesis has become an ideal stage for chemists to demonstrate their intelligence, knowledge, courage, stamina, and skill.

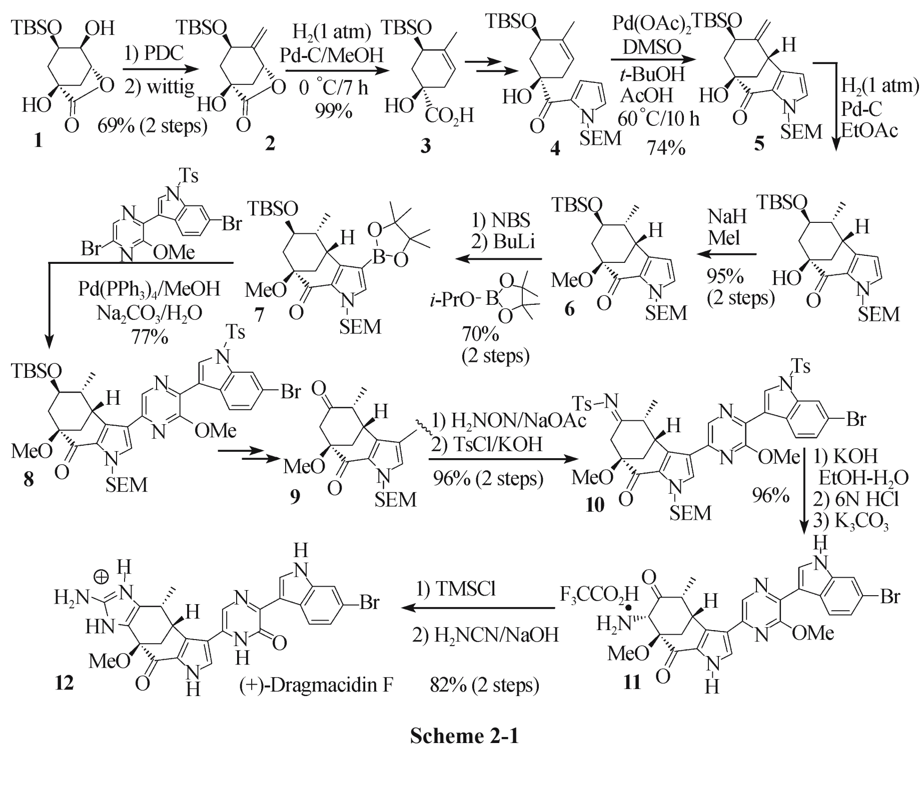
The brilliant total syntheses published in the top chemistry journals over the last two years are huge in number. Because of the length limitation of this paper, we can only give a few examples here that do not require excessive space to present.

2.1 The synthesis of Dragmacidin F

Dragmacidin F, an antiviral bromoindole alkaloid possessing *in vitro* activity against HSV-1 (EC_{50} = 95.9 μM) and HIV-1 (EC_{50} = 0.91 μM), was isolated from the ethanol extracts of the Mediterranean sponge *Halicortex* sp. by Ricco et al. [146]. This compound was synthesized for the first time in 2004 by Stoltz et al. [147]. (Scheme 2-1) Their synthesis used (−)-quinic acid as the starting material. Following literature procedures through a lactonization and selective silylation, the starting material was converted to the bicyclic lactone **1**. An oxidation followed by a Wittig reaction converted **1** into alkene **2**. Then they developed a previously unknown yet very simple way of opening the lactone ring with simultaneous double bond migration leading to acid **3**. The acid was transformed to Weinreb amide over two steps. The latter was treated with an N-protected lithiopyrrole to yield **4**.

Treatment of **4** with $Pd(OAc)_2$ led to coupling between the pyrrole and the alkene moieties, giving the desired bicyclic structure. Finally, through substrate-induced asymmetric hydrogenation, the last stereogenic center in the target molecule was established.

The other two heterocyclic moieties were introduced in one go, contributing to the rather high degree of convergence for the whole synthesis. The Susuki coupling of **7** leading to **8** occurred in a highly regioselective way with only the bromide on the pyrazine ring reacted. Introduction of an amino group at the α-position of the ketone carbonyl group is also one of the great merits of this work. The authors attempted a range of conventional methods to introduce the amino group but all ended in failure. Finally, they achieved the goal in excellent yield by using the Neber rearrangement, which was almost forgotten nowadays and has never been employed in the synthesis of complex molecules up to now.



Scheme 2-1

2.2 The synthesis of Abyssomicin C

Abyssomicin C was isolated from a sediment sample collected *ca.* 300 m beneath the surface of the Sea of Japan. This compound has a unique structure and is able to inhibit Gram-positive bacteria including the pathogenic *Staphylococcus aureus* strains, which is resistant to methicillin and vancomycin, through blocking of the conversion of chorismate to *para*-aminobenzoic acid (*p*ABA). As this conversion is quite common in microbes but not present in humans, abyssomicin C is a good lead for novel antibacterial agents.

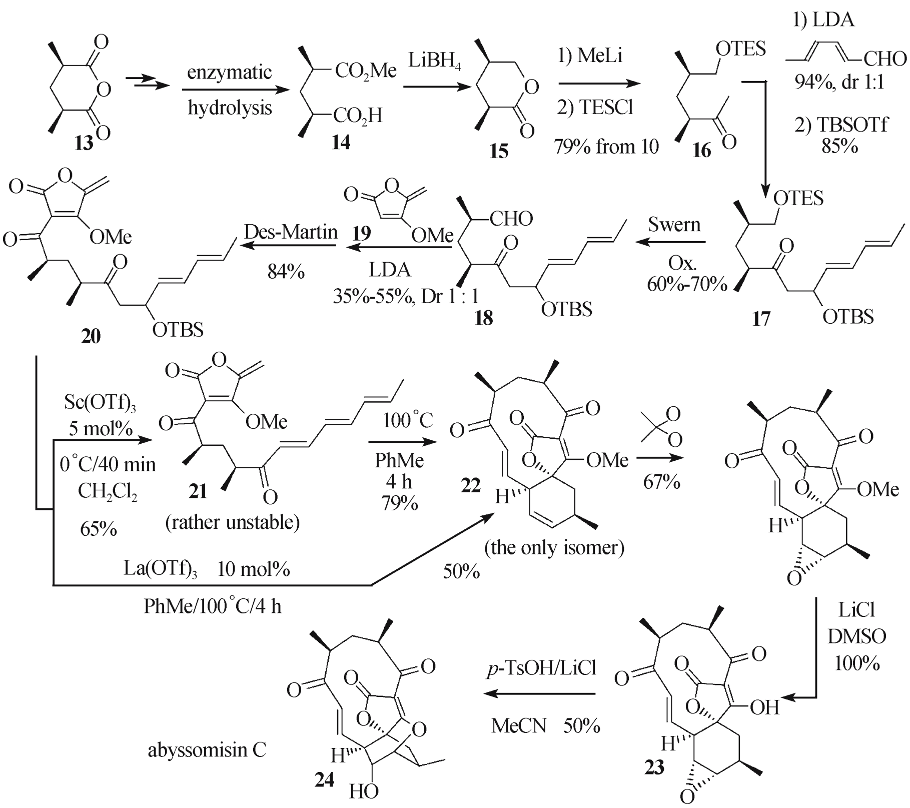
On the basis of their analysis of the structure, Sorensen et al. [148] reasoned that a Diels-Alder macrocyclization step was probably involved in the biosynthesis of abyssomicin C and therefore designed a synthetic plan accordingly (Scheme 2-2). The precursor of the Diels-Alder reaction in their synthesis was not so apparent as in many other literature cases, with a number of potential side reaction pathways co-existing. Besides, as later proven by experiments, the presence of many conjugated C-C double bonds in the structure made the molecule very unstable. Because of this unfavorable feature and the fact that the key step of the whole synthesis to be explored was at a very late stage of the synthesis, the stake for their plan was rather high. Their eventual realization of the plan and observation of no side products in the Diels-Alder reaction impressively manifests the authors' courage, knowledge, and skills, providing an invaluable piece of reference for the newcomers.

Shortly after publication of Sorensen's work, Nicolaou and Harrison [149] reported another enantioselective total synthesis of Abyssomicin C together with atropabyssomicin C (Scheme 2-3). In this synthesis, Diels-Alder reaction also played a key role, with conjugated amide **25** as the starting material.

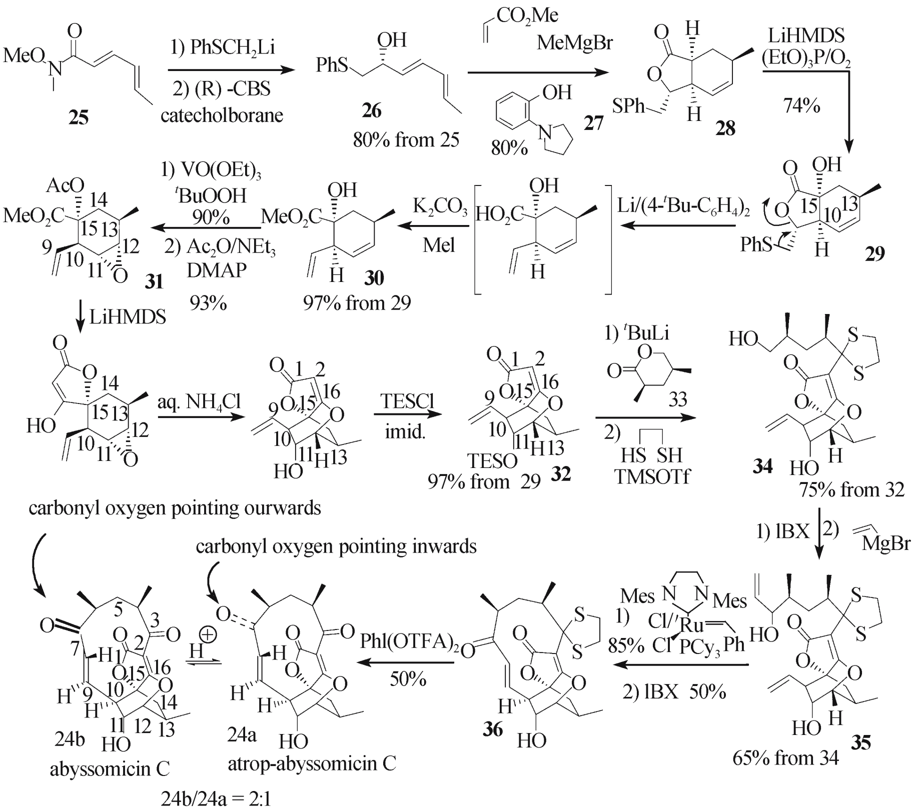
Treatment of **25** with $PhSCH_2Li$ led to a ketone carbonyl, which on Corey-Bakshi-Shibata (CBS) reduction became a chiral hydroxyl group of (*R*)-configuration and thus created the origin of the chirality needed in the induction of all other stereogenic centers in the target molecule with well-defined absolute configurations.

In the subsequent templated Diels-Alder reaction, they stereospecifically established three new stereogenic centers at C-10, C-13, and C-15. The prototype of this reaction was originally reported by Ward and Abaee [150] in 2000, with a less satisfactory selectivity. Nicolaou and Harrison utilized a different ligand (**27**) and obtained the desired **28** as the only product in 80% yield.

The hydroxyl group at C-15 was introduced stereospecifically by treatment of **28** with LiHMDS followed by $(EtO)_3P/O_2$ and thus finished the construction of all the three stereogenic centers at C-10, C-13, and C-15. Treatment of **29** with radical anion reagent led to the elimination of a thiophenol with concurrent opening of the lactone ring. The intermediate carboxylate was intercepted with MeI to afford ester **30**, converting the C-9 stereogenic center into a terminal alkene for the RCM at a later stage of the synthesis.



Scheme 2-2



Scheme 2-3

The stereogenic centers at C-11 and C-12 were established through a substrate chirality-induced asymmetric epoxidation. Following Sharpless' advice, here Nicolaou and Harrison utilized $VO(OEt)_3$, which was much less commonly used than $VO(acac)_2$, and thus obtained a much better yield.

Introduction of C-1 and C-2 is also worth mentioning—they were not introduced through direct bonding between C-2 and C-16. Instead, the two-carbon unit was incorporated into the substrate through forming an ester to the hydroxyl group at C-15. Formation of the bond between C-2 and C-16 thus became a much favored intramolecular process. More importantly, the subsequent enolization and epoxide-opening also could be fulfilled in a one-flask manner and hence greatly improved the efficiency of the synthesis.

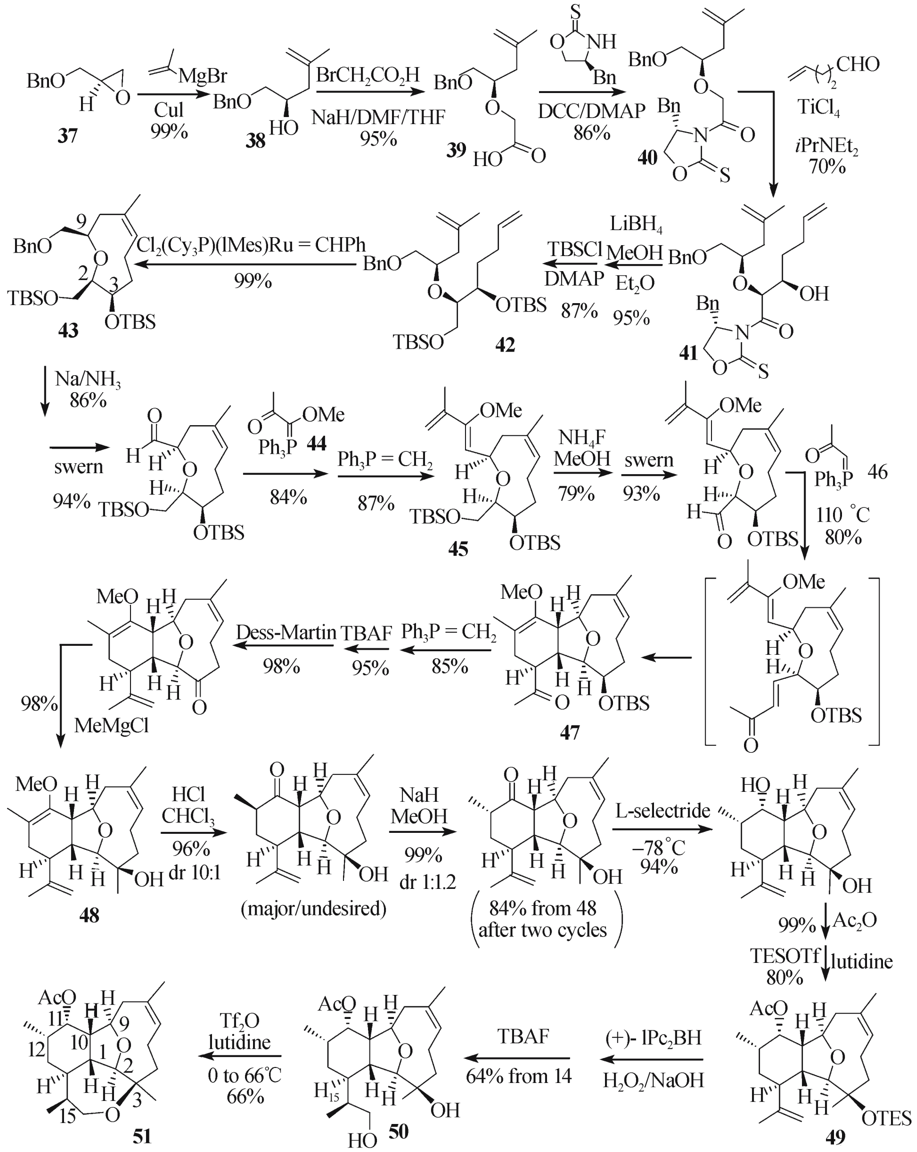
Installation of the C-3 to C-7 fragment was achieved through an addition reaction of the C-2 carbanion of **32** to lactone **33**. Note that formation of a carbanion at such a position by deprotonation with *t*-BuLi is not a common practice in organic synthesis.

The remaining steps are relatively conventional. However, the eventual obtaining of atro-abyssomicin A, a conformational isomer of abyssomicin C, deserves to be mentioned. The spectroscopic data for this compound are rather similar but not identical to those reported for the natural abyssomicin C. Nicolaou and Harrison did not let go the delicate difference. Through X-ray crystallography, they finally established that the compound is a conformer of the natural product. They also noticed that two conformers are interchangeable under acidic conditions (in the NMR sample solution in $CDCl_3$/24 h), a phenomenon that was overlooked by Sorensen et al. [148]. Very interestingly, the bioactivity of atro-abyssomicin C turned out to be even better than that of abyssomicin C.

2.3 Marine natural product 11-Acetoxy-4-deoxyasbestinin

Crimmins and Ellis [151] completed the first total synthesis of the marine natural product, 11-acetoxy-4-deoxyasbestinin D (**51**) and thus established the absolute configurations of this family of compounds (Scheme 2-4). One of the distinct features of the Crimmins synthesis is the elegant use of the stereogenic centers in the macro-cyclic ether ring to control the stereochemistry of the intramolecular Diels-Alder reaction, highly efficiently completing the construction of the molecular framework. Formation of the macro-cycle was achieved using the now broadly employed RCM reaction.

The three stereogenic centers in the macro-cyclic ether ring were derived from chiral epoxide **39** and asymmetric aldolization, respectively. Although the chirality (which was lost due to oxidation into a ketone) at C-3 did not appear in the final product, it played an important role in the control of the stereochemistry of the key Diels-Alder reaction.



Scheme 2-4

Apart from the elegantly-designed synthetic plan, a number of steps of transformations in this work are also noteworthy: for instance, selective removal of the TBS (t-butyldimethylsilyl hydroxy) protecting group on the primary hydroxyl group without touching that on the C-3, inverting the wrong configuration at C-12 into the desired one, and establishment of the stereogenic center at C-15. The final conversion of the two hydroxyl groups into a cyclic ether under mild conditions is also very interesting.

2.4 The synthesis of pentacycloanammoxic acid

Pentacycloanammoxic acid **61** is found in the principal lipid components of a compartment membrane of the anaerobic microbe *Candidatus Brocadia anammoxidans*, which utilizes nitrite ion and ammonia as energy sources. This compound has a very unusual ladder-like structure.

Following their synthesis of racemic **61** in 2004 [152], Mascitti and Corey [153] recently completed an enantio-selective total synthesis. The synthesis started from a photo-induced [2 + 2] cycloaddition of cyclobutene to cyclopentenone. The resulting cyclopentanone was then converted into the corresponding α-diazo species, which on irradiation with light rearranged into a compound with three four-membered rings linearly fused to each other giving the first "step" of the "ladder".

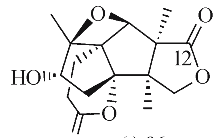
Decarboxylative bromination of the resulting acid **54** under the Barton's conditions, followed by elimination of HBr, led to cyclobutene **55**. As this compound is prochiral, lack of control of the absolute configurations over the preceding steps of reactions does not have any adverse effects on the rest of the synthesis. However, construction of the next "step" of the "ladder" requires enantio-control at the subsequent [2 + 2] addition. To achieve this, the authors utilized an optically active silyl-substituted cyclopentenone **56** to influence the stereochemical course of the cycloaddition with the chiral silyl functionality and obtained the optically active adduct **58** as expected. With **58** in hand, the target compound 61 was readily obtained after a few more routing transformations and repetition of the sequence for converting the cyclopentanone moiety into the cyclobutane carboxylic acid (Scheme 2-5).

2.5 The synthesis of UCS1025A

UCS1025A was isolated from the fermentation broth of the *Acremonium sp.* KY4917 fungus. It has been shown to possess antiproliferative activity against human cancer cell lines by inhibition of the telomerase enzyme. The first total synthesis (Scheme 2-6) of this compound was reported in 2006 by Lambert and Danishefsky [154]. The whole synthesis is extremely concise, with the critical retrosynthetic disconnection done right in the middle of the molecule between the two apparent fragments (one of the fragments was synthesized using McMillian et al.'s method [155]).

What is particularly noteworthy of this total synthesis is the final connection of the two major fragments. Those authors first attempted the traditional carbanion approach, i. e., to use an analogue of **66** with a carbanion at the carbon that carries the iodine atom to attack the aldehyde, to bond the two fragments together. Unfortunately, all such efforts under a variety of conditions ended in failure. However, despite all the frustration and depression they eventually found an elegant way to achieve the planned goal in such excellent yield by just putting an iodine at the α-position of that cyclopentanone and using BEt_3 to initiate the reaction.

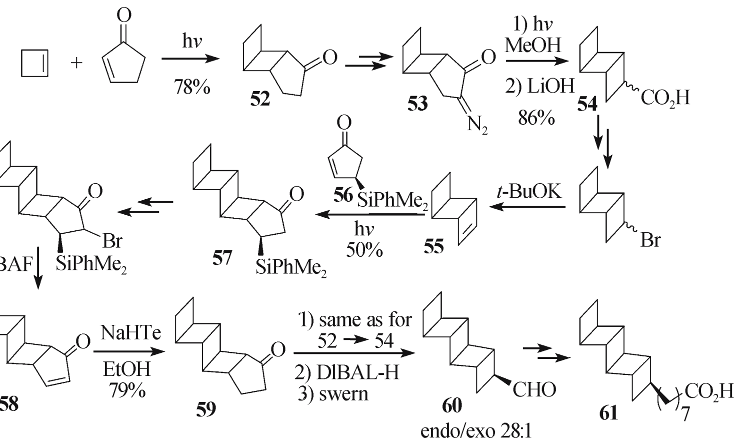
2.6 The synthesis of (−)-Merrilactone A [156]



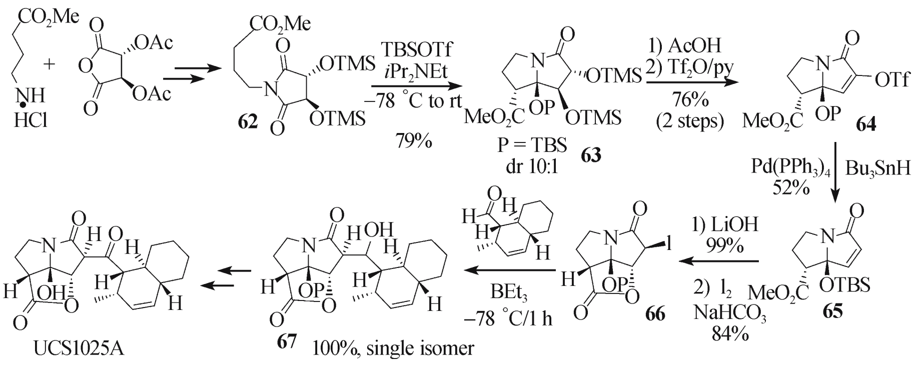
(-)-96

(-)-Merrilactone A

(−)-Merrilactone A is a sesquiterpenoid isolated from *Illicium merrillianum* in 2000 by Fukuyama and co-workers [157,158].



Scheme 2-5



Scheme 2-6

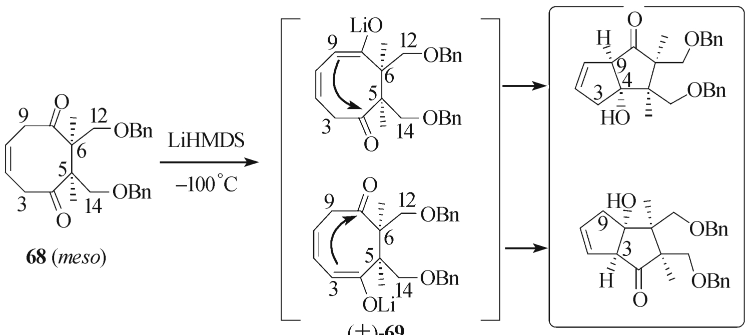
This compound has been shown to possess nueroprotective and neuritogenic activity in cultures of fetal rat cortical neurons and is therefore expected to be a therapeutic agent for the neurodegeneration associated with Alzheimer's and Parkinson's diseases.

Inoue et al. [159] recently disclosed an asymmetric total synthesis of (−)-merrilactone. In their previous work [160], Inoue and coworkers already demonstrated that the core structure of the two *cis*-fused five-membered rings could be constructed from the eight-membered precursor **68** (meso) via an intramolecular aldolization (Scheme 2-7). On the basis of this result, they envisioned that replacement of one of the two benzyl groups in **68** with a sterically more bulky protecting group would lead to differentiation in the deprotonation at positions 3 and 9. If the deprotonation occurred mainly at position 9, an enantioselective aldolization might lead to the aldol of desired absolute configuration.

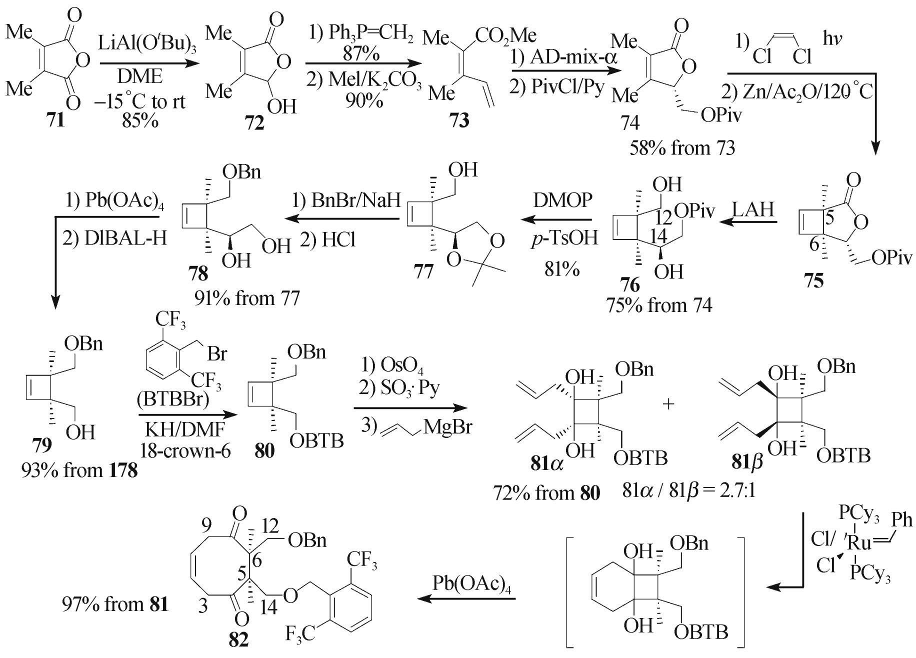
Starting with anhydride **71** (Scheme 2-8) via three steps of reactions, they obtained compound **73**. Then they utilized a Sharpless asymmetric dihydroxylation to introduce the first stereogenic center, from which another two stereogenic centers at positions 5 and 6 were induced.

A key task in their strategy, i.e., the differentiation of the two hydroxyl groups, was readily realized by exploiting the difference between the functionalities at the two positions. With a benzyl group on one hydroxyl group and a 2,6-bistrifluoromethylbenzyl (BTB) on another, the cyclobutene **80** was first transformed into the corresponding diketone and eventually to the key intermediate **82** after chain extension, RCM reaction, and cleavage of vicinal diol.

Next, they attempted the asymmetric deprotonation under a series of conditions, which led to the discovery that NaHMDS was an even better base than the LiHMDS in the



Scheme 2-7



Scheme 2-8

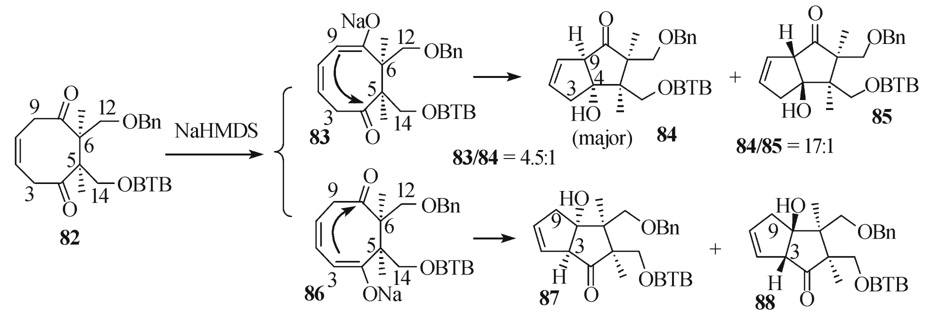
original recipe (Scheme 2-9). Under such conditions, the desired product **84** could be obtained in maximal yield.

Starting from **84** via another 11 steps of reactions, the end product (−)-**96** was finally obtained (Scheme 2-10).

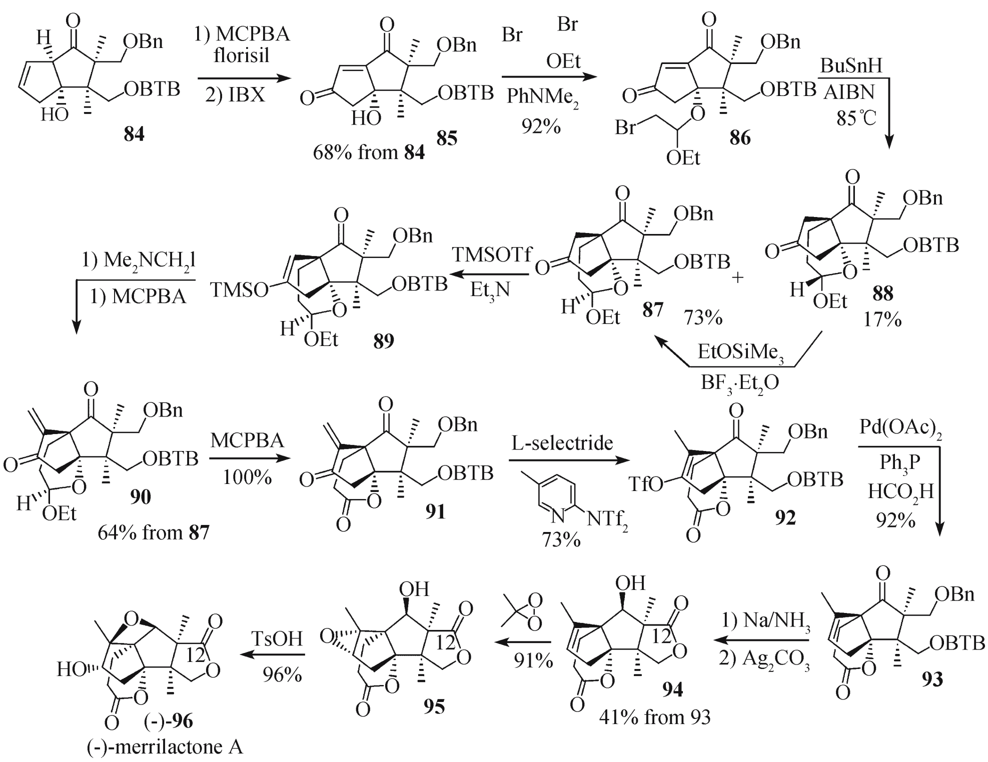
2.7 Enantioselective total synthesis of nigellamine A_2 [161]

Nigellamine A_2, isolated from *Nigella sativa* (black cumin) by Yoshikawa and co-workers [162,163], is a dolabellane type diterpine possessing potent lipid metabolism-promoting activity. Using a novel ring-closure strategy developed in their previous studies as the key step, Ready et al. [161] completed a total synthesis of Nigellamine A_2. The ring-closure intermediate **99**, which contained a conjugated diene, a malonic ester, and an allylic leaving group (isobutyric ester) as required by their ring-closure strategy, underwent an intramolecular S_N2 process on treatment with a Pd catalyst in the presence of a chiral ligand (*S*)-**100** (Scheme 2-11), leading to the five-membered ring with concurrent formation of the first stereogenic center in 95% ee. Then, they utilized an iodolactonization controlled by the substrate chirality to establish the second stereogenic center with a dr of 10:1.

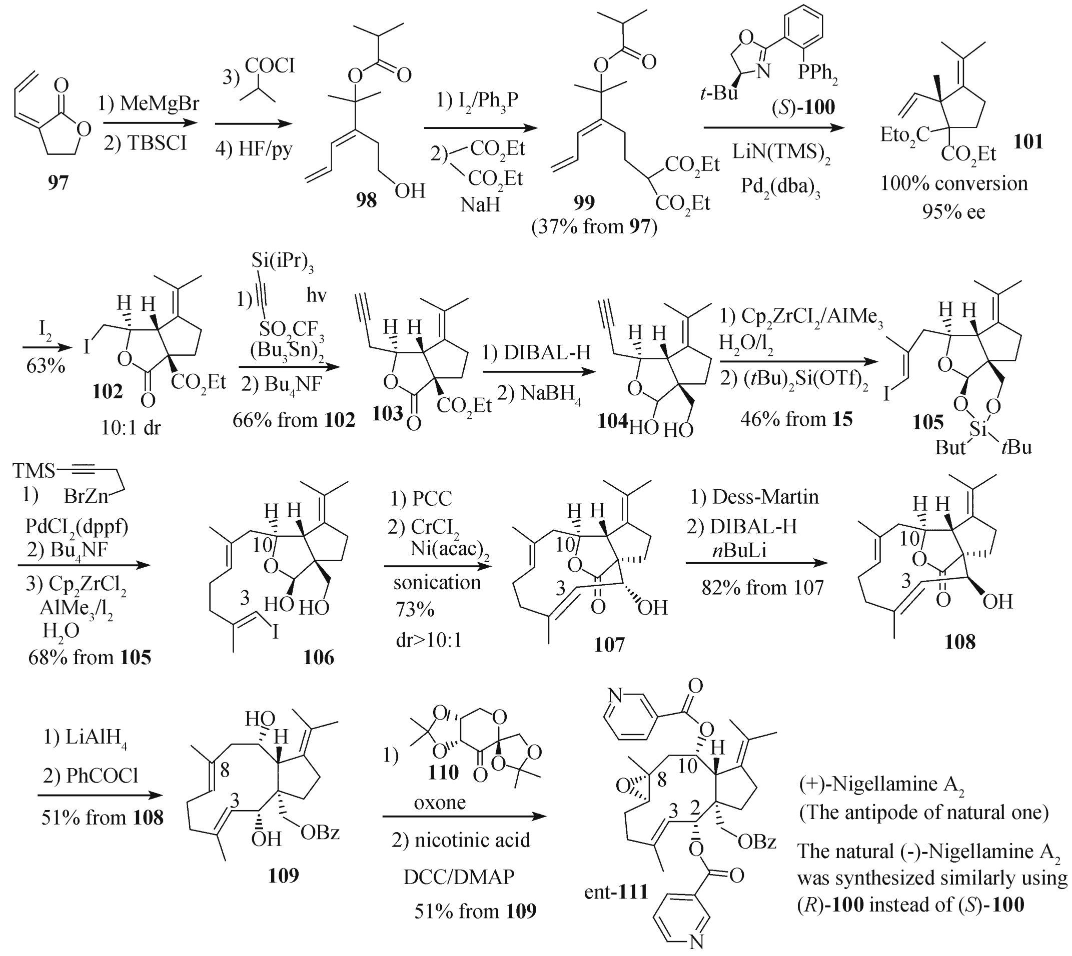
The side chain was introduced in a stepwise way, starting with incorporation of an acetylene moiety. Because of the presence of ester functionalities, conventional acetylide anion methods all failed here. The desired transformation was finally achieved using a very interesting radical reaction. The



Scheme 2-9



Scheme 2-10



Scheme 2-11

methyliodonation of the terminal alkyne was also noteworthy. Under conventional anhydrous conditions, the methyl did not add to the alkyne, but the lactol. Introduction of one equivalent of water to the reaction system, however, led to the desired product.

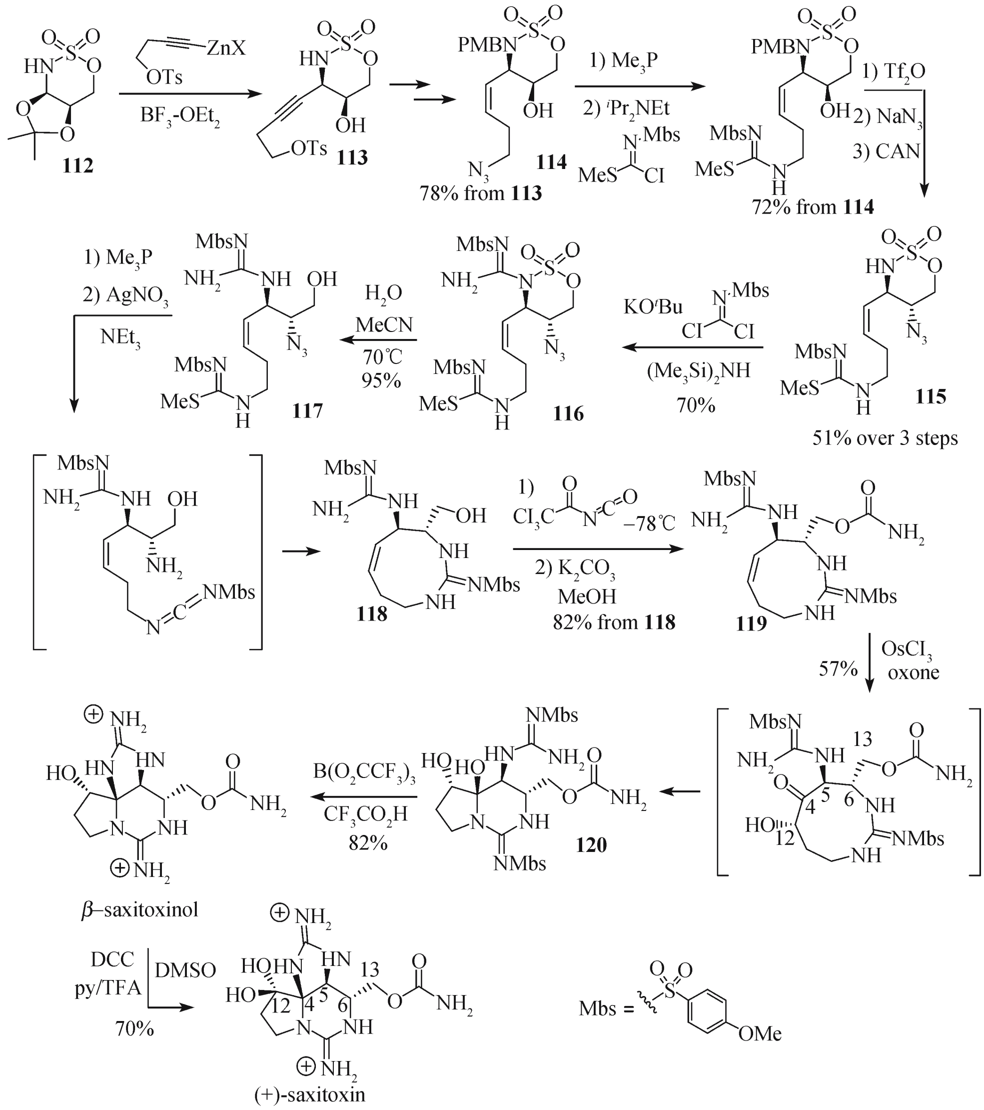
Construction of the macro-ring was fulfilled under the Nozaki-Hiyama-kishi (NHK) conditions, selectively yielding **107** with a dr of $>10:1$ and a hydroxyl group of incorrect configuration at the C-2. To invert the stereochemistry, the authors oxidized (Dess-Martin) the alcohol into a ketone and then tried to reduce the carbonyl to an alcohol of correct configuration. They noticed that using $NaBH_4/CeCl_3$, $Li(O^tBu)_3AlH$, or CBS reduction all led to the starting **107** rather than the expected **108**, while L-Selectride resulted in mainly 1,4-reduction. Eventually, the problem was solved by an "ate" reagent formed from DIBAL-H and *n*-BuLi.

The intermediate **108** was then converted into triene **109** via two steps of conventional transformation. Selective epoxidation of one of the three C-C double bonds relied entirely on the delicate difference of steric crowding between these three bonds. Initially, the authors attempted MCPBA and found that all the three double bonds reacted rapidly. Finally, the problem was ideally solved by using the method developed by Shi and co-workers.

2.8 The synthesis of (+)-saxitoxi [164]

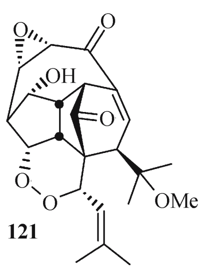
(+)-Saxitoxin (STX) is a highly potent paralytic agent. Although at first sight its molecular size and complexity does not look as striking as other poisons associated with the red tides, its synthesis is definitely a great challenge. The unassuming nine-carbon framework carries as many as seven nitrogen atoms, with six of them as parts of the two guanidyl groups. These features unavoidably lead to very high polarity/water solubility and thus add tremendous additional difficulties to the synthesis.

Fleming and Du Bois recently disclosed a very concise synthesis of (+)-saxitoxin (Scheme 2-12). Along with the total synthesis, they also developed a series of new methodologies and strategies, providing a good reference for the synthesis of other related target molecules. For instance, they introduced a novel reagent MeS(Cl)C = NMbs for facile



Scheme 2-12

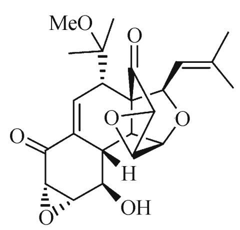
introduction of guanidyl groups. Utilization of $Cl_2C = NMbs$/ $(Me_3Si)_2NH$ to install the first guanidyl group and activate the cyclic sulfate for the subsequent hydrolytic cleavage of the heterocycle is also noteworthy. The distinct merits of this work also include construction of the 5-6-5 fused ring system from a nine-membered ring and use of Mbs as protecting groups for guanidyl groups, which dramatically reduce the polarity and water solubility of the guanidyl groups and greatly facilitate the detection of the molecules due to Mbs' UV-chromophore nature.



121

(original structure)

hexacyclinol



(revised structure)

2.9 The synthesis of hexacyclinol

Hexacyclinol (**121**) was isolated by Gräfe et al. [165] and co-workers from the basidiospores collected from *Panus rudis* growing on dead betula woods in Siberia. In 2006, La Clair [166] reported a total synthesis of this compound with himself as the sole author, although the assistance of five unidentified technicians was acknowledged. The whole synthesis took a lot of work, involving many interesting reactions. Some of them even looked rather brilliant. However, neither experimental details nor characterization data for most of the intermediates were provided in the supporting information section. La Clair's synthesis invoked many critiques and commentaries soon after its publication.

By calculating the ^{13}C NMR chemical shifts, Rychnovsky [167] concluded that the original structure for hexacyclinol must be wrong and proposed another structure (the revised structure), which was soon confirmed by a total synthesis performed by Porco et al. [168]. Because the latter synthesis was accompanied by detailed experimental procedures and complete spectroscopic data that survived scrutiny of others and were in full agreement with those reported for the natural product, the structure of hexacyclinol was finally established as proposed by Rychnovsky. As for whether La Clair really completed the synthesis as he claimed in that communication, further investigation still remains to be done. No matter what the final conclusion will be, the event has caused broad concerns in the chemical community since the early 2006.

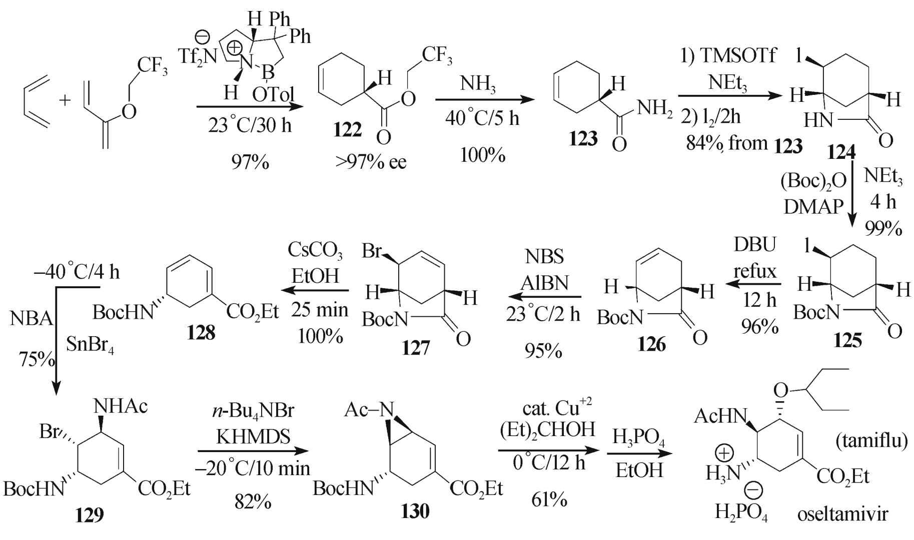
2.10 The synthesis of Tamiflu

Tamiflu (Oseltamivir) is one of the NA inhibitors discovered in the late 1990s and was marketed as an anti-influenza agent by Hoffmann-La Roche Ltd. in 1999. Shortly afterwards, it was found to be effective also for treating avian influenza. Originally, this compound was synthesized from natural Shikimic acid or Quinic acid. At the beginning of 2006, urged by the serious threat of bird flu at that time, two new (total) syntheses [169,170] appeared timely, revealing the great concern of the synthetic community about the public needs. Below we shall look into these two syntheses, which were developed independently by American and Japanese chemists, respectively.

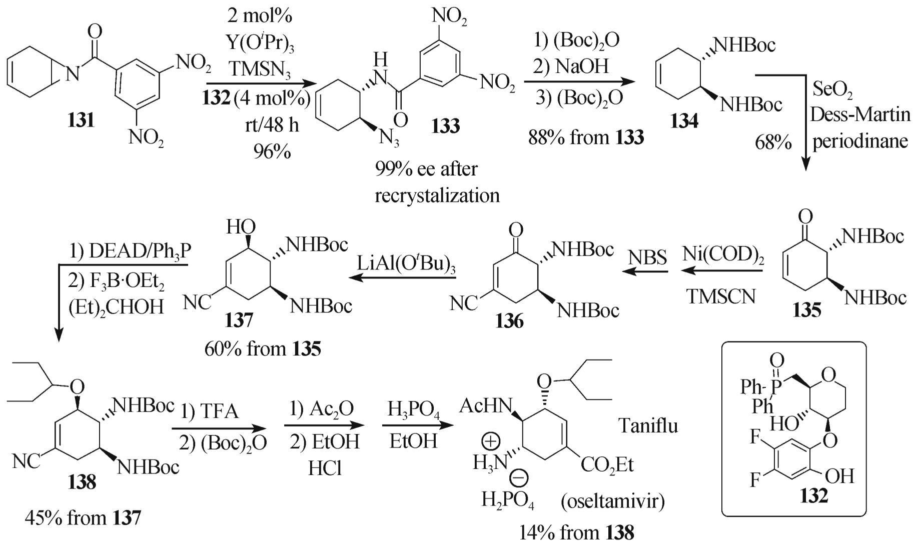
Corey's synthesis (Scheme 2-13) [169] emerged with construction of an optically active six-membered ring bearing a stereogenic center using a chiral catalyst mediated asymmetric Diels-Alder reaction. Then, through an iodolactamization, another two stereogenic centers were readily created with high stereoselectivity. The first three stereogenic centers were later very nicely elaborated into those three in the target molecule in a stereoselective way over several steps of ingenious transformations, completing the whole synthesis of Tamiflu.

The Kanai-Shibasaki [170] group reported another synthesis of Tamiflu at the same time (Scheme 2-14). Their approach featured use of a catalytic asymmetric ring-opening of *meso*-aziridines with $TMSN_3$ to obtain the optically active *trans*-diamino-cyclohexane **134**. However, the overall excellence of that route was counterbalanced by the relatively lengthy route and the moderate yields for the subsequent steps.

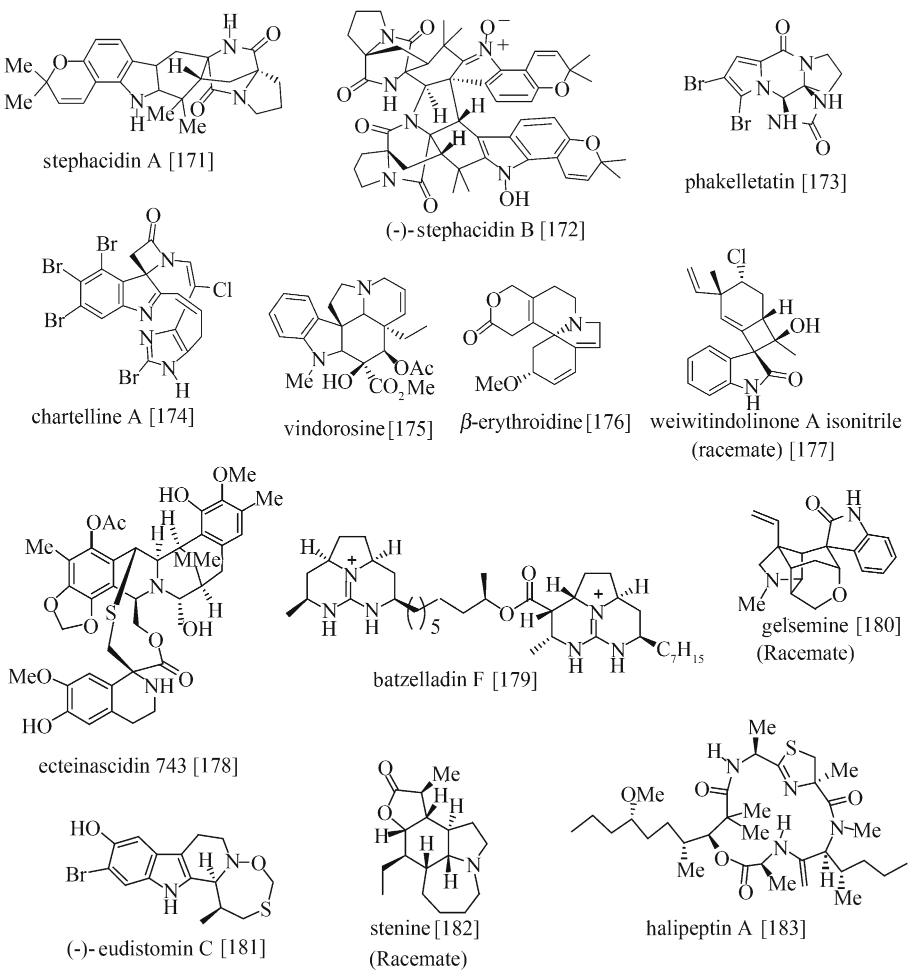
As mentioned above, because of the length restriction of this paper, it is impossible to pack all the brilliant total syntheses published in the past two years into the present review. To partially make up for this, we provide here a list of other total syntheses. Those who are particularly interested in total synthesis can use it as a quick guide to the original publications: Stephacidin A [171], Stephacidin B [172], Phakellstatin [173], Chartelline A [174], Vindorosine [175], *β*-Erythroidine [176], Ecteinascidin 743 [177], Weiwitindolinone A isonitrile [178], Batzelladin F [179], Gelsemine (racemate) [180], Stenine (racemate) [181], (−)-Eudistomin C [182], Halipeptin A [183−184], Amythiamicin D [185], Thiostrepton [186], Isocomplestatin [187], Colombiasin A and elisapterosin B [188], (+)-Leucascandrolide [189], Spongistatin [190], Azaspiracid-2/3 [191−194], Spinosyns A and D [195], Apoptolidinone [196], RK-397 [197], Brevetoxin B [198], Tetracycline [199], Littoralisone [200], Garsubellin A [201], (+)-Absinthin [202], Machaeriol D [203], Mycalamide A [204], Haterumalide NA/oocydin A [205], Kendomycin [206], and OSW-1 [207] (and analogues).

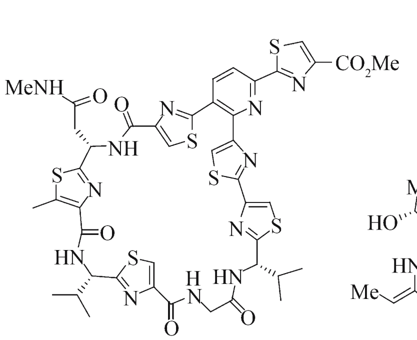


Scheme 2-13

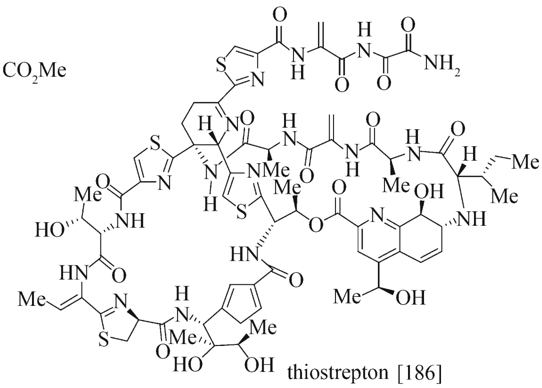

131
2 mol% Y(O^iPr)3 TMSN3 132 (4 mol%) rt/48 h 96%
133
99% ee after recrystalization
1) (Boc)2O 2) NaOH 3) (Boc)2O
88% from 133
134
SeO2 Dess-Martin periodinane
68%
135
Ni(COD)2 TMSCN
NBS
136
LiAl(O^tBu)3
137
60% from 135
1) DEAD/Ph3P 2) F3B·OEt2 (Et)2CHOH
138
45% from 137
1) TFA 2) (Boc)2O
1) Ac2O 2) EtOH HCl
H3PO4 EtOH
Taniflu
(oseltamivir)
14% from 138
132

Scheme 2-14

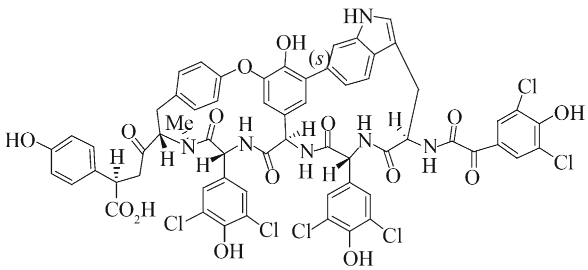

stephacidin A [171]
(-)-stephacidin B [172]
phakelletatin [173]
chartelline A [174]
vindorosine [175]
β-erythroidine [176]
weiwitindolinone A isonitrile (racemate) [177]
ecteinascidin 743 [178]
batzelladin F [179]
gelsemine [180] (Racemate)
(-)-eudistomin C [181]
stenine [182] (Racemate)
halipeptin A [183]



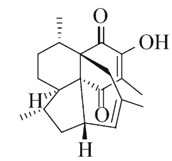
amythiamicin D [185]



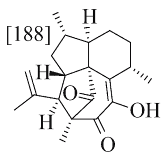
thiostrepton [186]



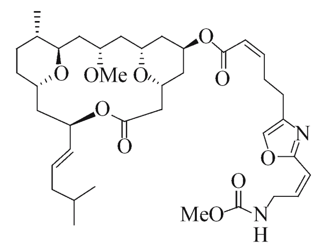
Isocomplestatin [187]



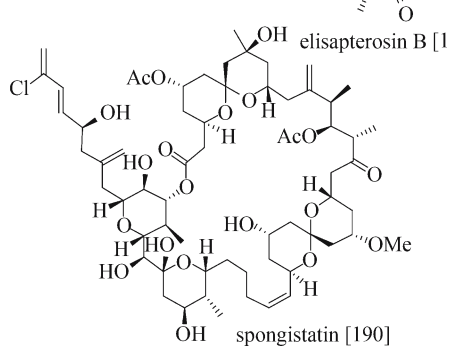
colombiasin A [188]



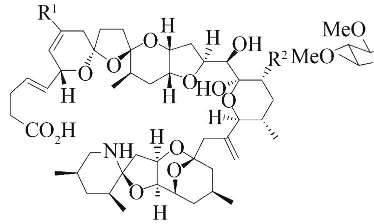
elisapterosin B [188]



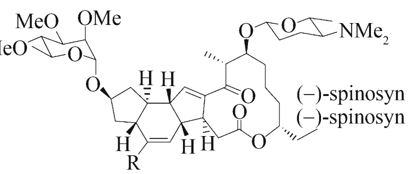
(+)-leucascandrolide [189]



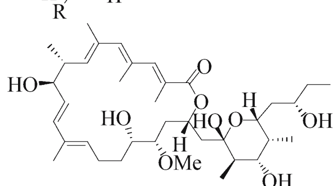
spongistatin [190]



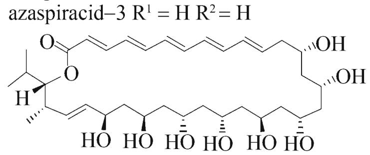
azaspiracid–1 R^1 = H R^2 – Me [190–194]
azaspiracid–2 R^1 = R^2 = Me
azaspiracid–3 R^1 = H R^2 = H



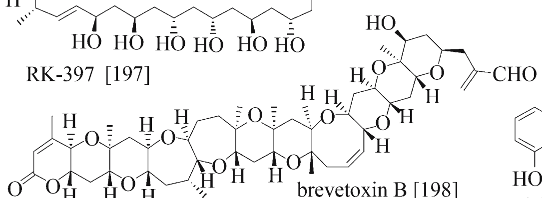
(–)-spinosyn A R = H [195]
(–)-spinosyn D R = Me



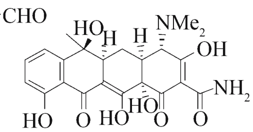
apoptolidinone [196]



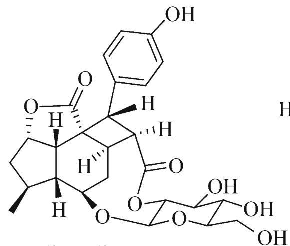
RK-397 [197]

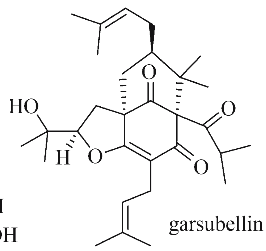


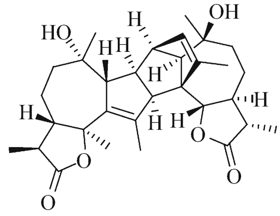
brevetoxin B [198]

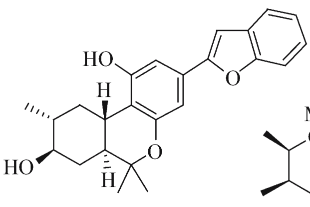


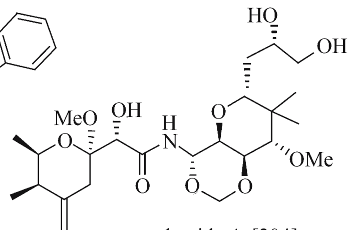
(–)-tetracycline [199]

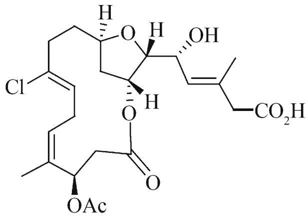

littoralisone [200]

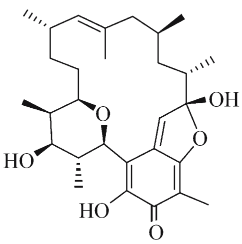

garsubellin A [201]

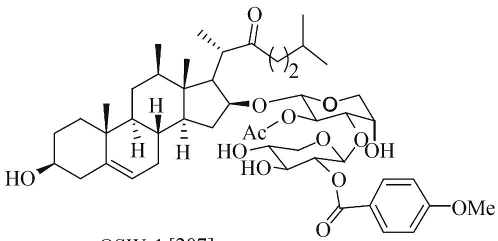

(+)-absinthin [202]


machaeriol D [203]


mycalamide A [204]


haterumalide NA [205]


kendomycin [206]


OSW-1 [207]

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