Cascade reactions for syntheses of heterocycles

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Abstract
Cascade reactions are useful method for the construction of polycyclic skeletons, which are important cores for biological activities. A variety of cascade reactions, carried out under multiple reaction conditions, such as pericyclic, polar, radical, and transition metal catalyzed reaction conditions, have been investigated. Novel methodologies, developed by us, and their applications are discussed.

Keywords: Cascade reaction, polar reaction, radical reaction, transition metal catalyzed reaction, polycyclic compounds, biologically active compounds

Contents

Introduction

When various functional groups exist on polycyclic skeleton, the three dimensional relationship of functional groups would be restricted and a specific biological activity would be expected due to the rigid conformation (Figure 1). Therefore, the development of efficient method for the construction of polycyclic ring systems would be highly desired particularly in the field of medicinal chemistry. Cascade reactions[1–6] forming a number of bonds by one operation are

useful for the creation of polycyclic compounds. Many stereogenic centers would be created at the same time. Reduction of reaction steps leads to saving reagents, energy and reduction of wastes. Therefore, cascade reaction is important from the economical point view and from the green chemistry. In this context, we have been studying cascade reactions carrying out under various reaction conditions, such as pericyclic, polar reaction, radical reaction, and transition metal catalyzed conditions. Recent progress relating to heterocycles would be accounted.

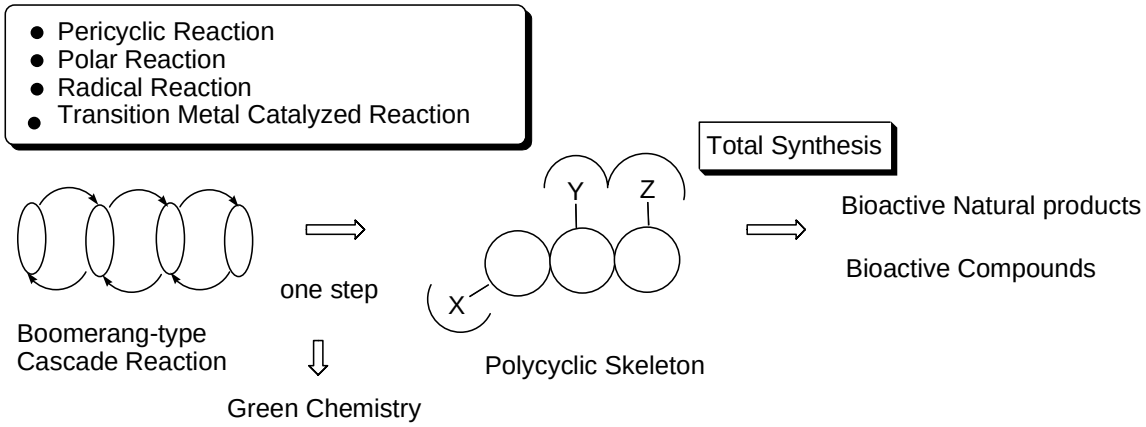
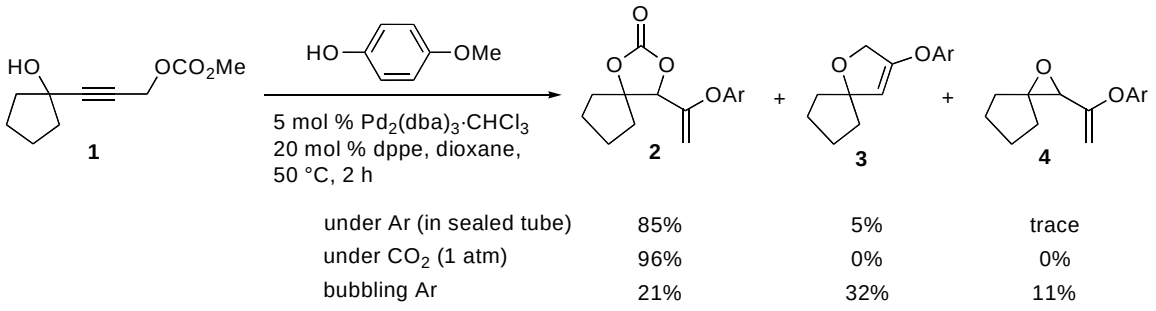


Figure 1

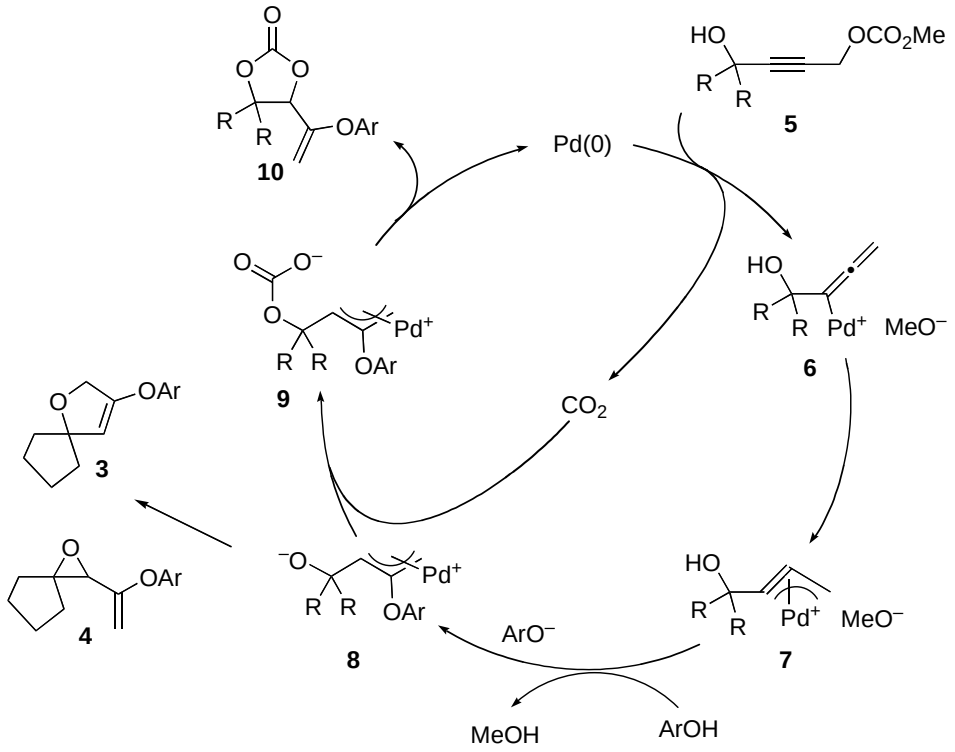
1. Cascade reaction under transition metal catalyzed conditions

Several cascade reactions of cyclobutanols forming cyclpentane derivatives have been performed by palladium or ruthenium catalyst[7] and a novel cascade reaction forming cyclic carbonates has been also devised (Scheme 1). When the propargylic carbonate **1** was treated with *p*-methoxyphenol in the presence of catalytic amount of zero valence of palladium catalyst under Ar atmosphere, the cyclic carbonate **2** was obtained together with the dihydrofuran **3** and the epoxide **4**. The reaction, carried out under CO_2 atmosphere, gave the cyclic carbonate **2** in a quantitative yield. On the other hand, bubbling with Ar during the reaction to remove CO_2 resulted in the increased formation of the dihydrofuran **3** and the epoxide **4**.[8]



Scheme 1

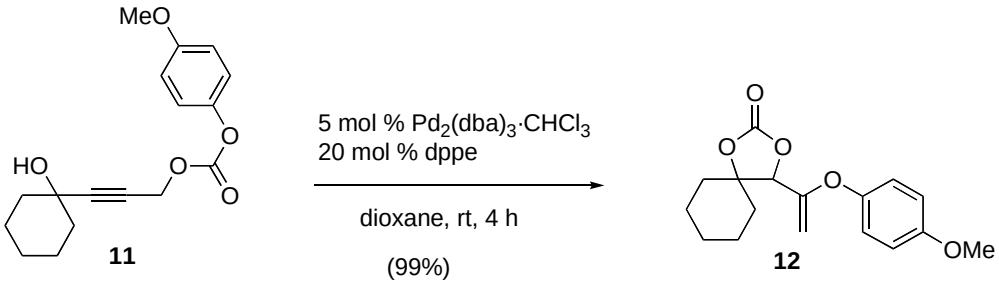
On the basis of the above observations, a possible mechanism for the transformation is considered as shown in Scheme 2. Reaction of the propalgylic carbonate **5** with palldium catalyst would afford CO_2 and the allenylpalladium **6**, which equilibriums with the π-propargylpalladium **7**. Attack of the phenol to **7** yields the π-allylpalladium complex **8**, which could trap CO_2 to provide the cyclic carbonate **10** via **9** and zero valence palladium. The dihydrofuran **3** and the epoxide **4** must be directly formed from the π-allylpalladium complex.[8]



Scheme 2

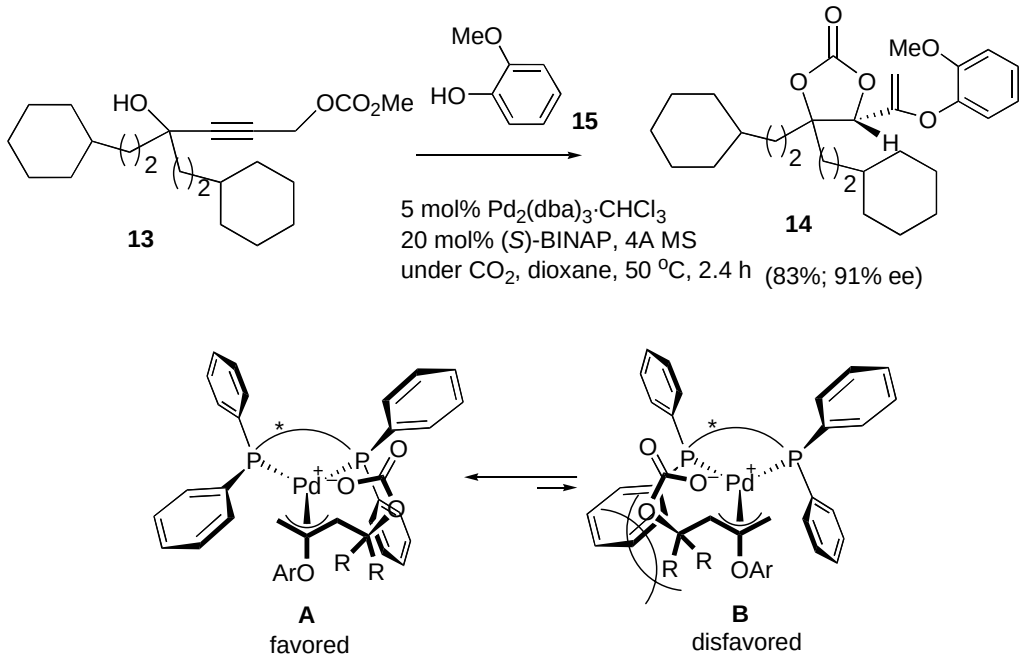
Various cyclic carbonates were prepared in good yields by this procedure. It was noteworthy that when the phenyl carbonate **11** was used as a substrate, the cyclic carbonate **12**

was quantitatively obtained in the absence of the phenol (Scheme 3). The reaction must be performed via splitting into three components followed by their recombination without any loss of atoms.[8]



Scheme 3

Catalytic asymmetric synthesis was easily applied to the above CO_2 fixation reaction.[9] Thus, a highly optically active product **14** was produced from the symmetrical compound **13** in the presence of a catalytic amount of a chiral ligand (Scheme 4). The preferred formation of one enantiomer could be explained by the favorable transition state **A** over **B**. The chirality transfer reaction was also studied.[10]



Scheme 4

2. **Cascade reaction under radical conditions**

In addition to our cascade reactions under radical conditions,[11] a novel strategy for the synthesis of heterocyclic spiro compounds has been worked out. Treatment of the piperidin-2-one derivative **16** with Bu_3SnH in the presence of AIBN in hot benzene caused the radical translocation followed by radical cyclization to give the aza-spiro compounds **17** and **18**. The diasterelselectivity of the one product **17** was improved, when *tert*.-butyl ester was used (Scheme 5). The same transformation was also carried out under electroreductive reaction conditions, the environmentally friendly methodology. The preferred formation of **17** could be explained by the transition states of the radical intermediates. The major product **17** was converted into the diol **19**, a possible synthetic intermediate of pinnaic acid and halichlorine.[12]

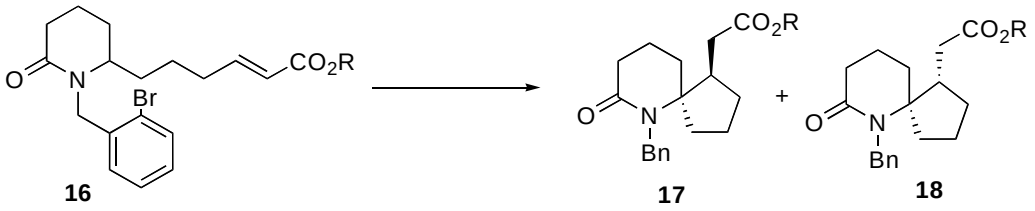
3. Cascade reaction under polar conditions

3.1 Double Michael reaction

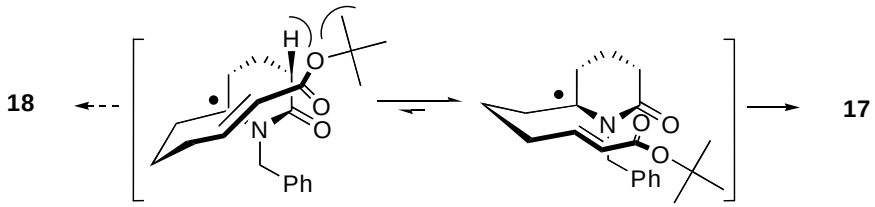
Bicyclo[2.2.2]octane skeleton is a framework of several natural products. We encountered a difficulty for stereoselective synthesis of the corresponding polycyclic systems using the intramolecular Diels–Alder reaction.[13] The problem was solved by the intramolecular double Michael reaction, carried out by the treatment with $LiN(TMS)_2$.[14]

As a typical example of the application of this methodology, a synthetic plan of atisine is shown in Scheme 6.[15] Since synthesis of racemic atisine had been carried out by several workers, the asymmetric synthesis was designed. The synthetic intermediate **20** could be stereoselectivly obtained by the intramolecular double Michael reaction of the enone **21**. We envisaged that the substrate **21** of the key reaction could be prepared as an optically active form from the symmetrical compound **22**, derived from **23**.

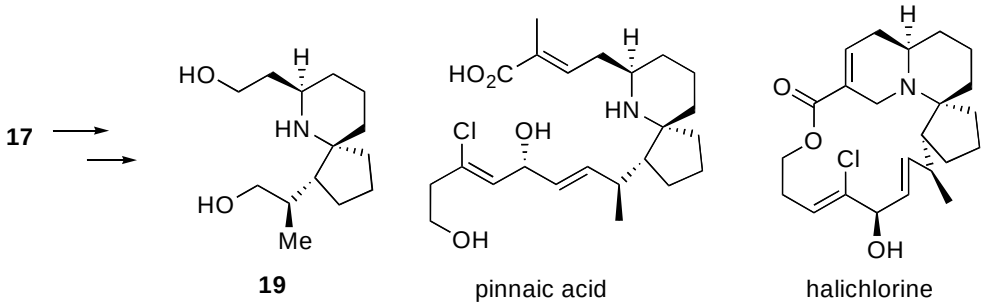
The diol **25**, obtained via **24** from **23**, was subjected to lipase-catalyzed transesterification in neat vinyl acetate to afford the acetate **26** in an optically pure form (Scheme 7).[16] The absolute configuration was determined by X-ray analysis of the corresponding camphorsulfonyl derivative.



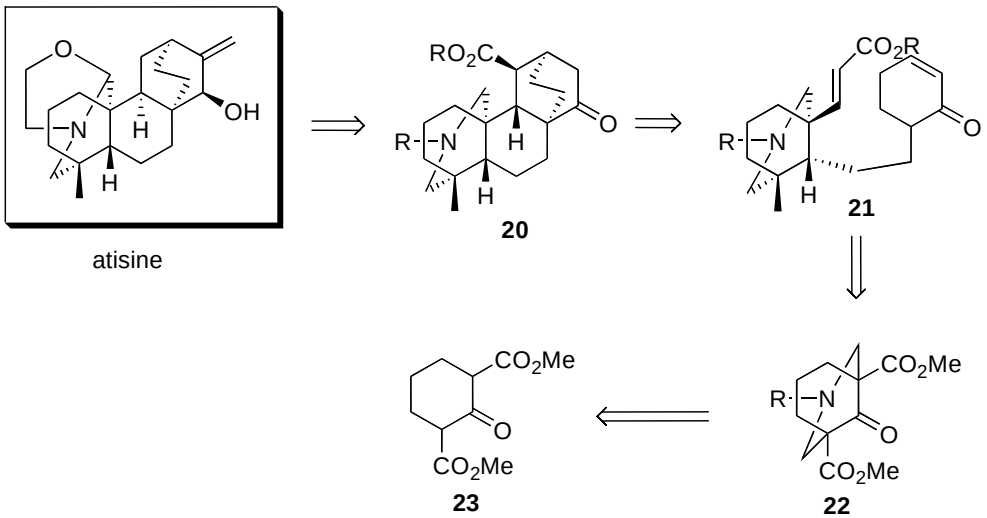
R = Me	Bu_3SnH, AIBN, benzene, heat	88% (7 : 2)
R = ^{t}Bu	Bu_3SnH, AIBN, benzene, heat	78% (10 : 1))
R = ^{t}Bu	$Ni(cyclam)(ClO_4)_2$, NH_4ClO_4, DMF, –1.5 V, rt	62% (10 : 1))



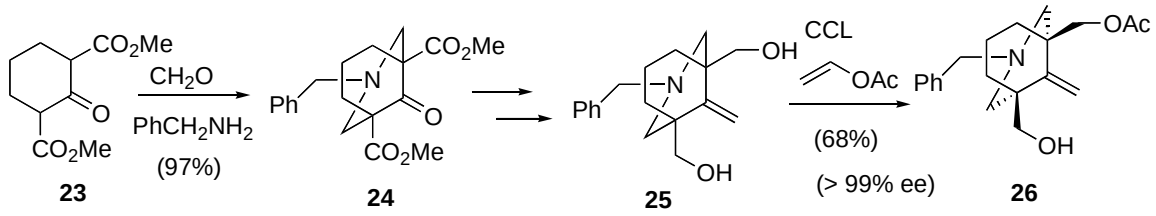
unfavorable TS favorable TS



Scheme 5

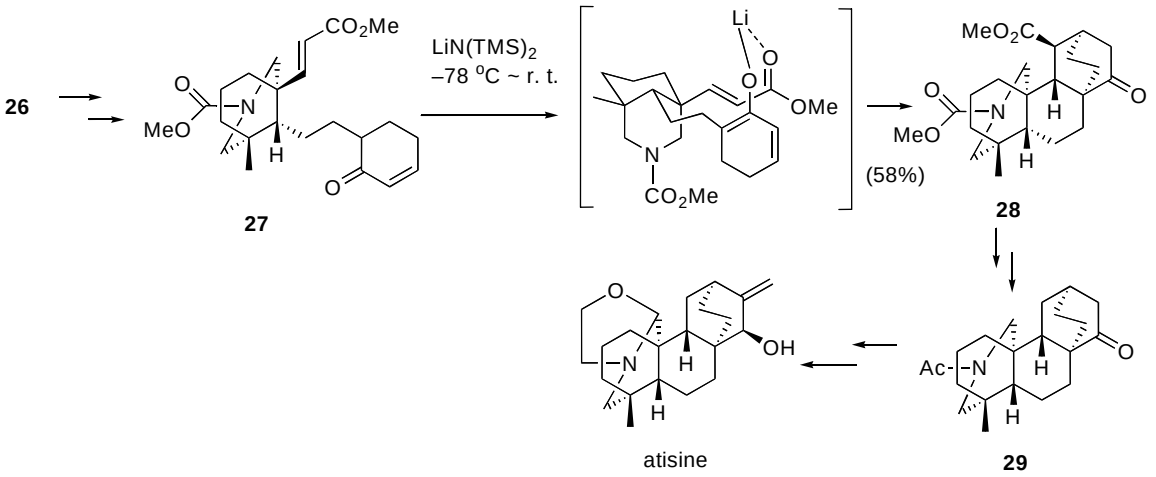


Scheme 6



Scheme 7

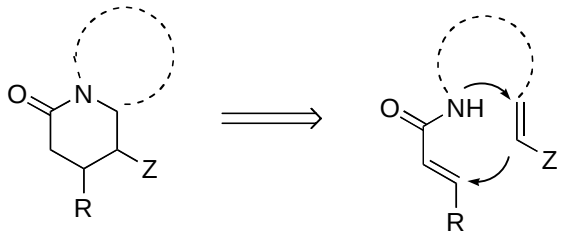
The chiral acetate **26** was transformed to the enone **27**, which was treated with $LiN(TMS)_2$ to provide the desired penta cyclic compound **28** as a single diastereoisomer. The product **28** was then converted into **29**, which had been correlated with atisine. Thus, asymmetric synthesis of atisine has been accomplished in a highly stereoselective manner (Scheme 8).[15]



Scheme 8

3.2 Aza double Michael reaction

The success of the above double Michael reaction promoted us to investigate extensions of the strategy for the synthesis of heterocyclic compounds. We planned the construction of piperidin-2-ones **30** by reactions of α,β–unsaturated amides with α,β–unsaturated carbonyl groups as shown in Scheme 9.

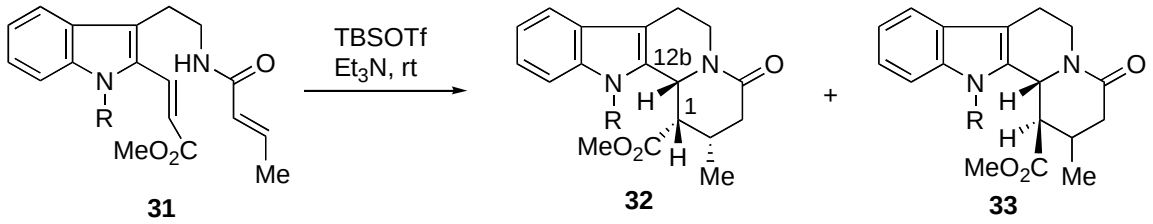


30

Scheme 9

The desired intramolecular cascade reaction was successfully performed under several reaction conditions, such as heating with a mixture of TMSCl, Et_3N and $ZnCl_2$,[17] treatment with TBSOTf in the presence of Et_3N,[18] treatment with TMSI in the presence of $(TMS)_2NH$,[19] and treatment with Bu_2BOTf in the presence of $(TMS)_2NH$.[19]

For example, treatment of **31** with TBSOTf in the presence of Et_3N at room temperature gave two diastereoisomers, **32** and **33**. When the *N*-tosylate was used as a substrate, the diastereoselective formation of **32** was improved (Scheme 10).[18b] Formation of **32** having *syn* hydrogens at the 1 and 12b positions would support a stepwise mechanism for the transformation. It was observed that the rate of reaction was enhanced by the use of dichloroethane in stead of dichloromethane as a solvent.



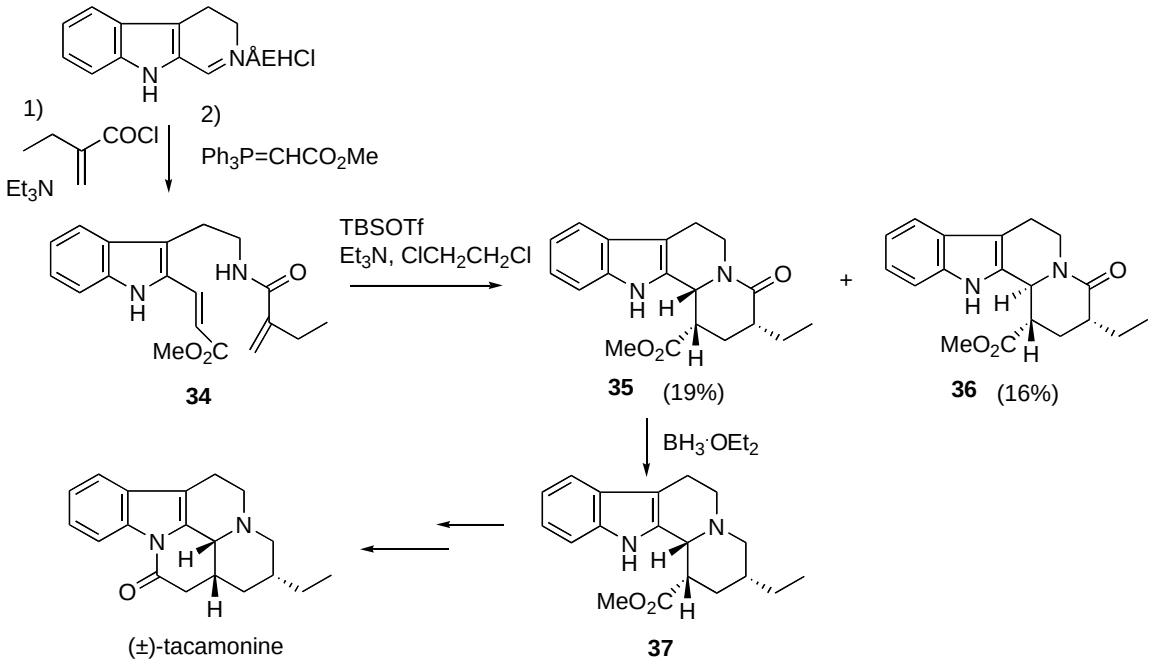
31 **32** **33**

R = H	(60%)	60	:	40
R = Ts	(94%)	83	:	17

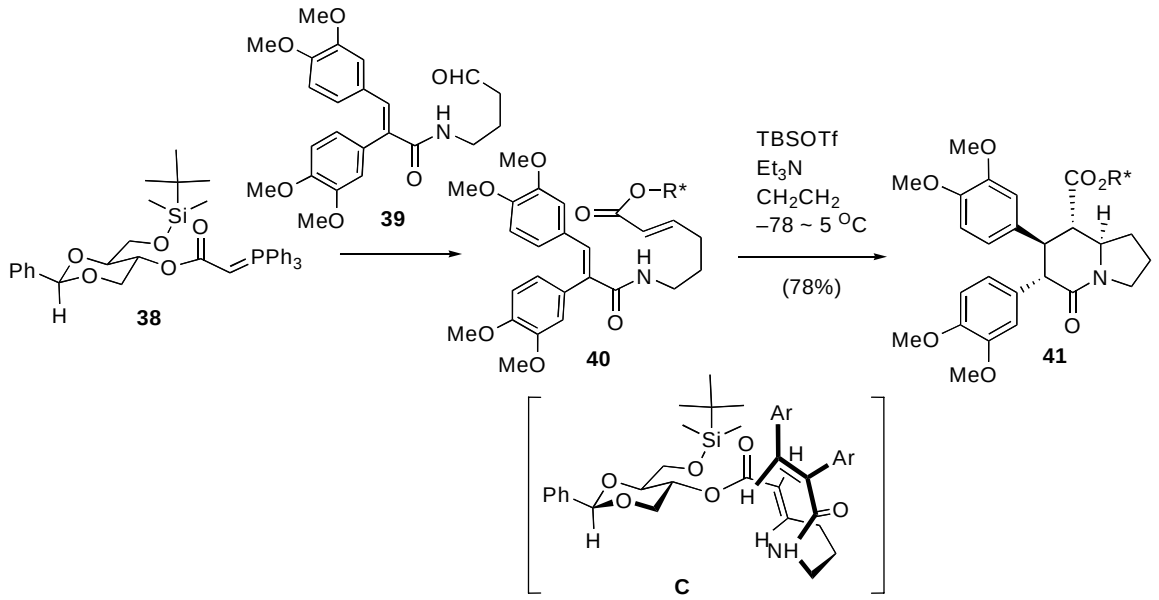
Scheme 10

The method was applied to the synthesis of tacamonine, isolated from *Tabernaemontana eglandulosa*. The substrate **34** of the key reaction was prepared in two steps from the dihydro-β-carboline hydrochloride (Scheme 11). Treatment of **34** with TBSOTf and Et_3N in dichloroethane provided two diastereoisomers **35** and **36**. The product **35** was reduced with borane to give the amine **37**, which had been transformed into tacamonine by Lounasmaa.[20] Thus, a short synthesis of the racemate of tacamonine was accomplished.[21] It is observed by using our synthetic sample that IC_{50} of (±)-tacamonine against M2 receptor is 0.9 μg/ml.

The naturally occurring enantiomer of tylophorine was synthesized by the diastereofacially controlled intramolecular aza double Michael reaction. Prior to our work, optically active tylophorine was synthesized starting with amino acids.[22] So, the naturally occurring (*R*)-enantiomer had not been chemically prepared. We designed an asymmetric synthesis of tylophorine possessing the desired absolute configuration by the cascade reaction, whose stereochemistry would be controlled by a chiral auxiliary.



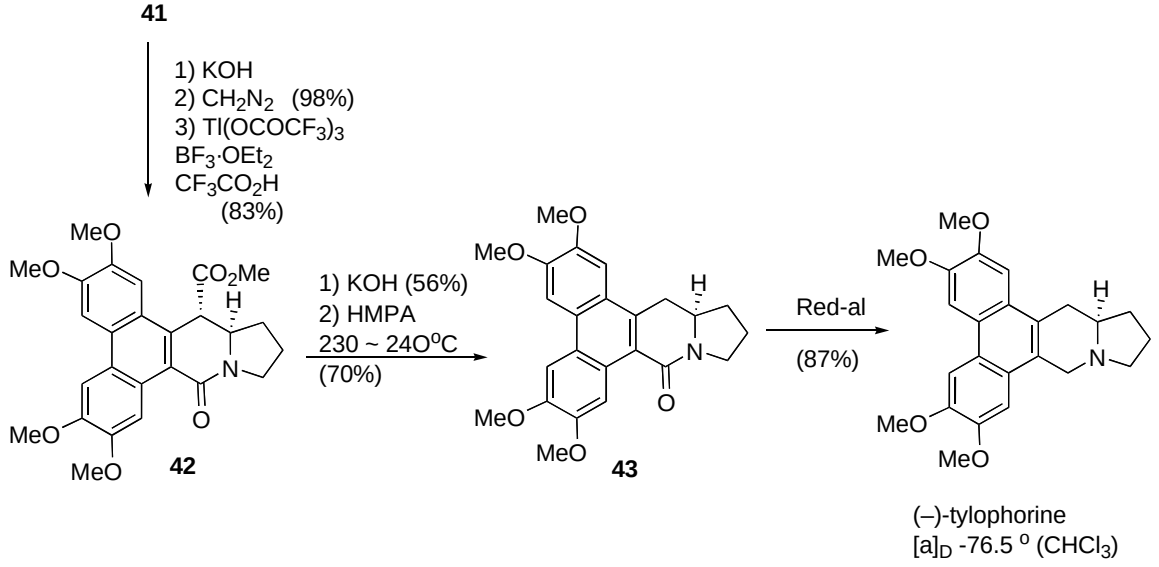
Scheme 11



Scheme 12

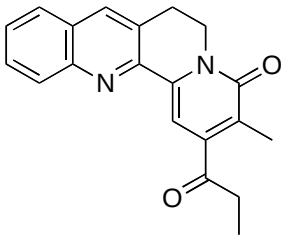
A novel chiral auxiliary was prepared from glucose and converted to the phosphorane **38**, which was reacted with the aldehyde **39** to afford the α,β-unsaturated ester **40**. Treatment of **40** with TBSOTf in the presence of Et_3N furnished the indolizidine **41** as a single diastereisomer.

The presence of Lewis acid such as TBSOTf would force the α,β-unsaturated ester part as a *s-trans* form and the α,β-unsaturated amide part would approach from the less hindered *si-re* face (Scheme 12). Thus, the desired compound having the (*R*)-configuration at the angular position could be preferentially formed via the transition state **C**. The result was confirmed by the transformation of the product **41** into the natural product (Scheme 13).[23]



Scheme 13

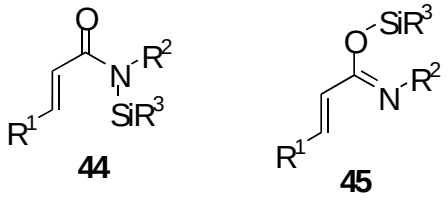
After conversion of **41** to the corresponding methyl ester, phenanthroindolizidine **42** was constructed by the oxidative aryl coupling. Removal of the ester function via the carboxylic acid, followed by reduction with red-al, produced (–)-tylophorine, whose first chiral synthesis was thus effectively achieved.



mappicine ketone

Recently, Greene and co-workers synthesized mappicine ketone having anti herpes virus activity by the application of this strategy.[24]

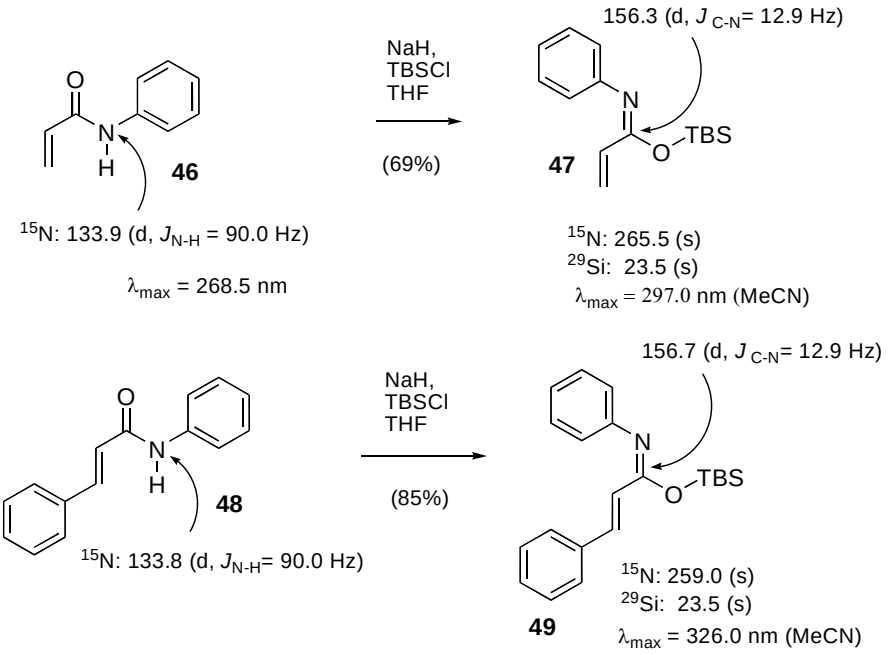
Although the stepwise mechanism was supported by the formation of the two diastereomers **32** and **35** from the (*E*)-α,β-unsaturated ester **31**, the solution of mechanism of the cascade reaction is an attractive problem. For this purpose, the structures of products, formed by the reaction of α,β-unsaturated amide with the silylating agents, were studied, since two possibilities, the *N*-silyl amide **44** and *O*-silyl imidate (1-aza-2-siloxydiene) **45**, are expected (Figure 2).



44 **45**

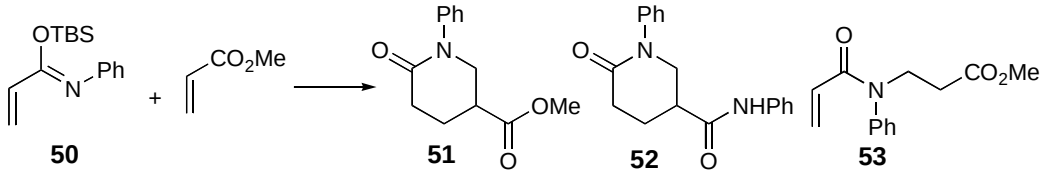
Figure 2

Treatment of α,β-unsaturated amides with TBSOTf and Et_3N did not afford pure products. But, pure compounds were obtained by treatment with TBSCl and NaH. The structures of products **47** and **49**, produced from **46** and **48**, respectively, were determined as the 1-aza 2-siloxydienes on the basis of ^{15}N and ^{29}Si NMR as well as UV spectroscopies as shown in Scheme 14.[25]



Scheme 14

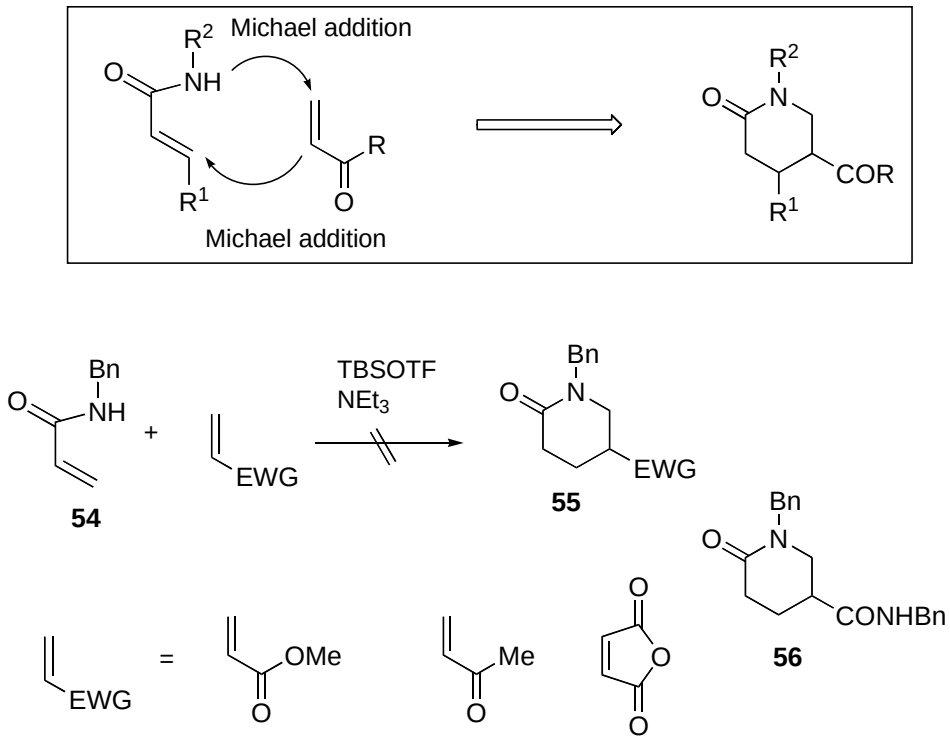
The formed 1-aza-2-siloxydiene **50** was reacted with methyl acrylate in the presence of Lewis acids (Scheme 15). The desired piperidin-2-one derivative **51** was obtained by treatment with TBSOTf or $FeCl_3$. Dimer **52**, derived from **50,** was obtained in a significant amount. The formation of the unsaturated amide **53** would indicate the stepwise mechanism.[25]



TBSOTf, dichloroethane	48%	0%	3%
TBSOTf, neat	47%	10%	0%
$FeCl_3$, dichloroethane	38%	21%	trace

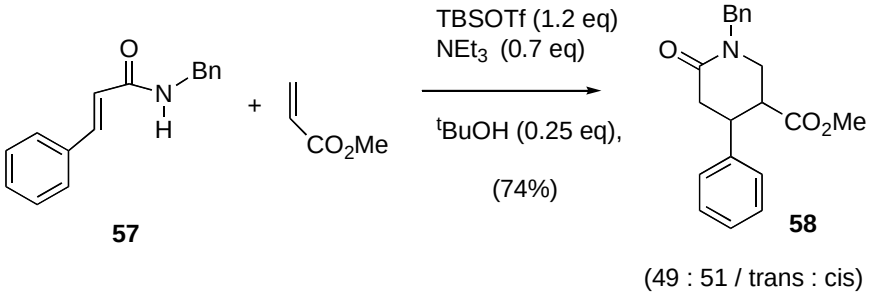
Scheme 15

We next investigated the intermolecular cascade reaction between α,β-unsaturated amide and α,β-unsaturated carbonyl compounds (Scheme 16). However, reaction of the acryloyl amide **54** with α,β-unsaturated carbonyl compounds in the presence of TBSOTf and Et_3N resulted in the formation of the dimmer **56** of **54**. No formation of the desired compound **55** was observed.



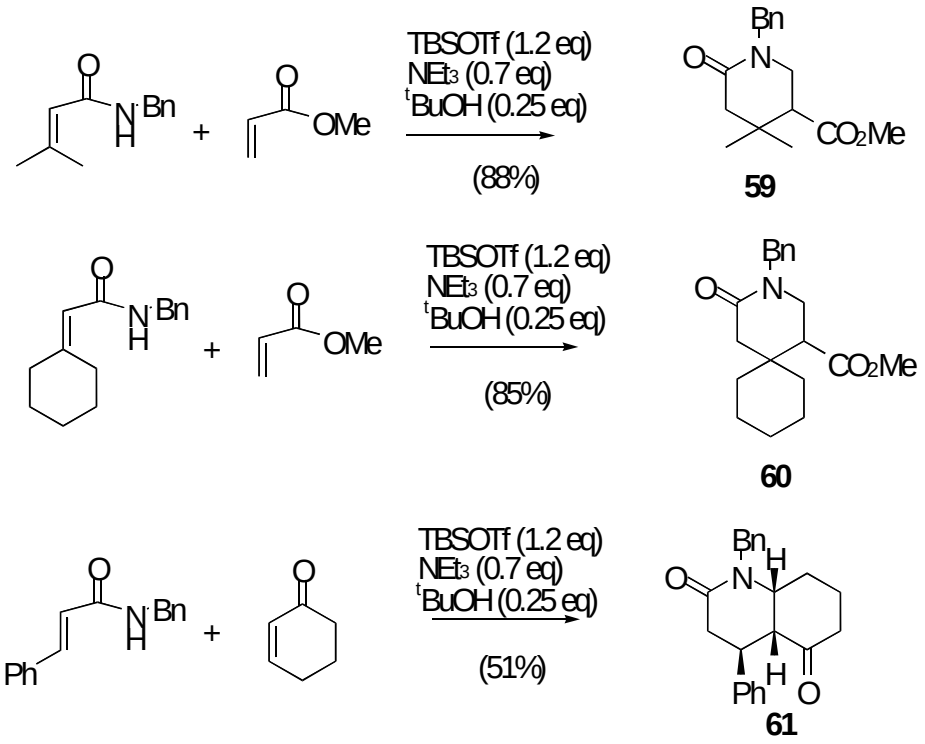
Scheme 16

It was suggested on the consideration of the high yield formation of the previous products **32** and **33** that the presence of a substituent at the β-position of the α,β-unsaturated amide would be preferable for the cross process. The desired compound **58** was actually obtained from **57**. It was further established that the use of excess TBSOTf and the presence of a catalytic amount of *t*-BuOH are required for the production of the desired compound in a good yields (Scheme 17).[26]

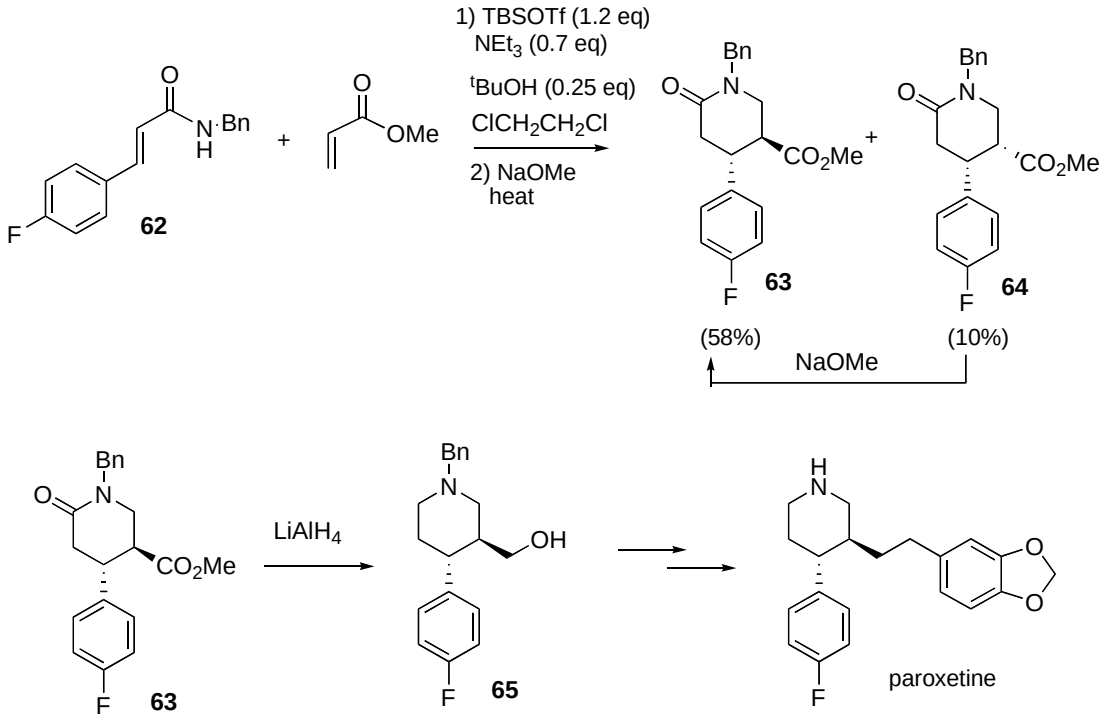


Scheme 17

Various piperidin-2-one derivatives **59** – **61** were synthesized by the combination of α,β–unsaturated amides and α,β–unsaturated carbonyl compounds (Scheme 18).



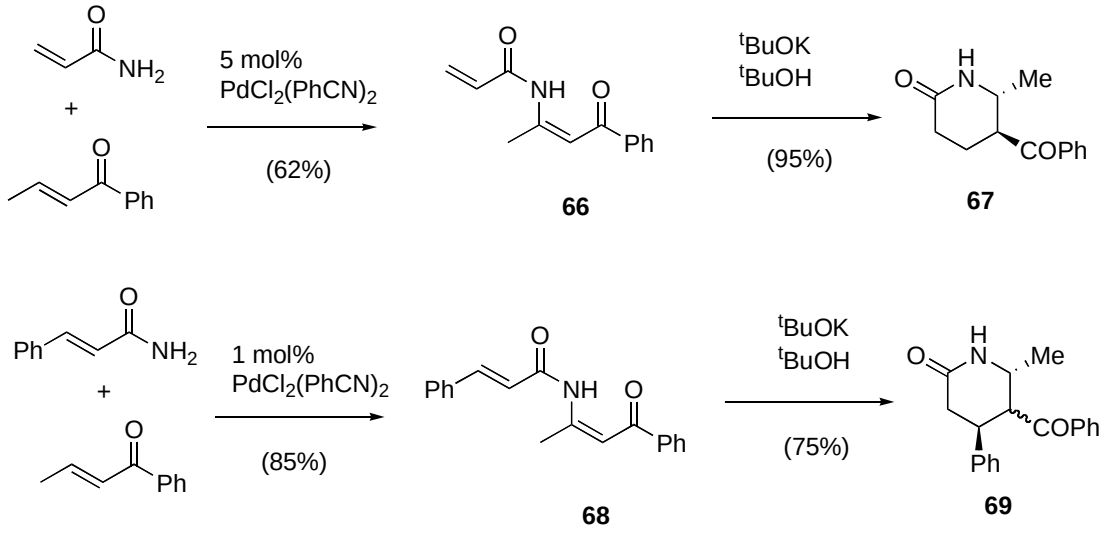
Scheme 18



Scheme 19

The methodology was applied to the synthesis of paroxetine, a selective serotonin reuptake inhibitor (SSRI). Treatment of the mixture of the amide **62** and methyl acrylate with TBSOTf in the presence of Et_3N and *t*-BuOH provided two stereoisomers **63** and **64**. The minor *cis* isomer **64** could be epimerized to **63** by treatment with NaOMe. The *trans* isomer **63** was reduced with $LiAlH_4$ to afford the piperidine **65**, which had been correlated with paroxetine. Thus, the important antidepressant was prepared in short steps (Scheme 19).[26]

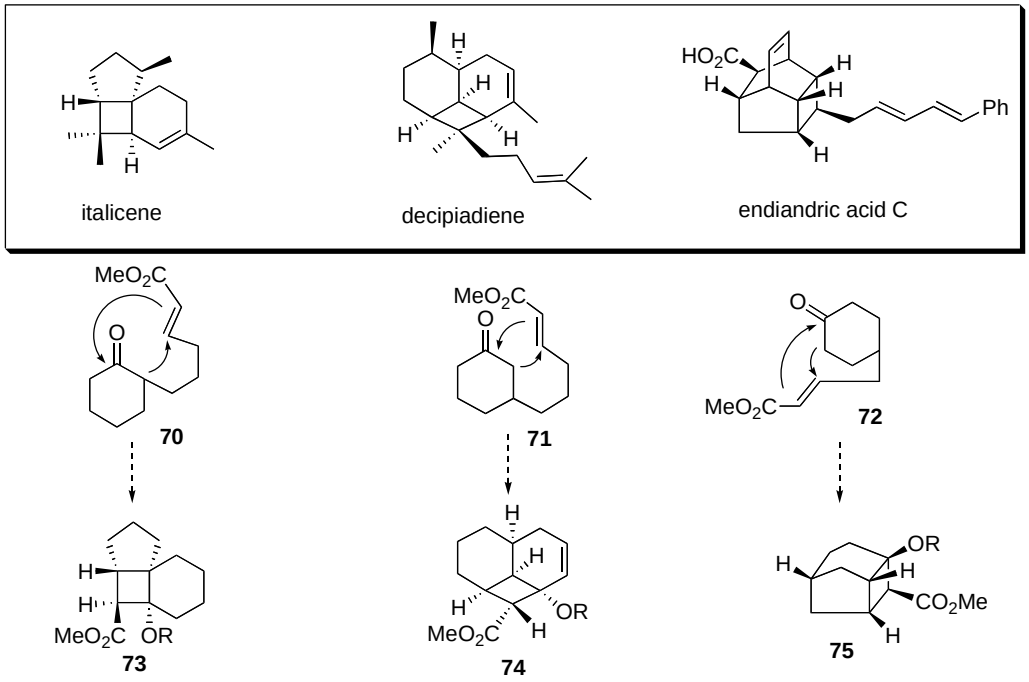
We further searched the catalytic reaction conditions for the intermolecular aza double Michael reaction. The ideal reaction conditions have not yet been established, the synthesis of piperidin-2-ones from α,β-unsaturated amides and α,β-unsaturated carbonyl compounds was performed in two steps. Thus, a catalytic amount of $Pd(PhCN)_2Cl_2$ promoted the conjugate addition reaction of amides with enones to afford β-amideketones **66** and **68**, which were then cyclized by a basic treatment to provide piperidin-2-ones **67** and **69**.[27]



Scheme 20

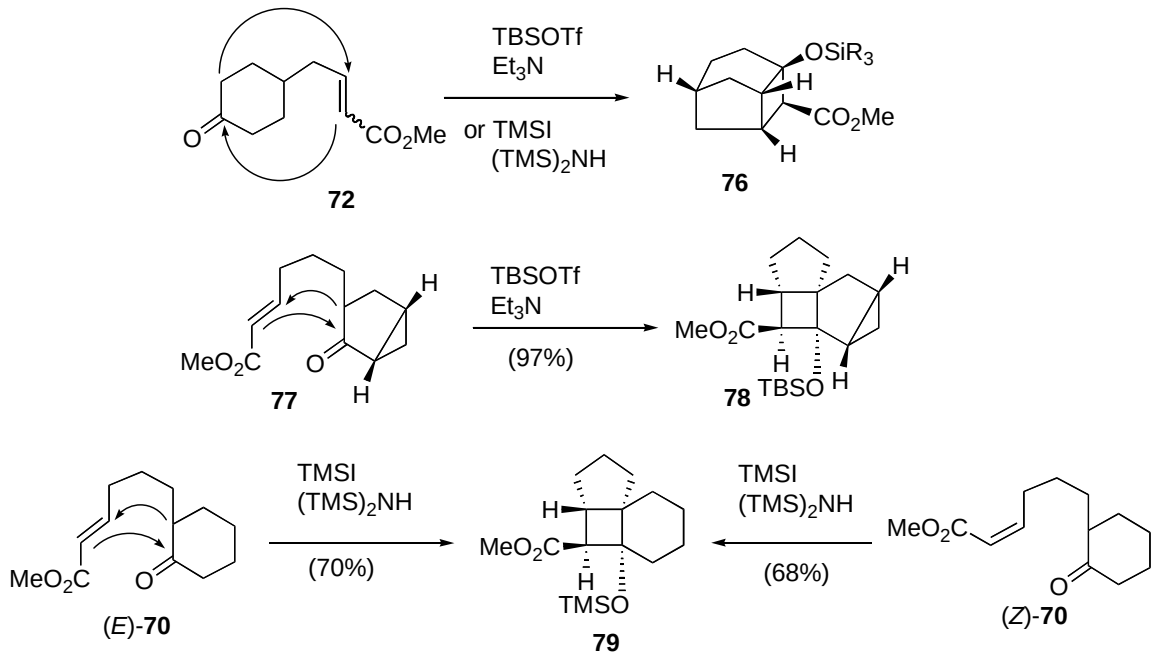
3.3 Michael–Aldol reaction

Four-membered ring systems are important structural units frequently found in biologically important compounds. Among the synthetic methods available for the synthesis of cyclobutanes, [2+2] cycloaddition is the most commonly used. As an extension of our study of the double Michael reaction, we envisaged the formation of polycyclic ring systems fused to a cyclobutane by the sequential Michael and aldol reactions. Namely, the cascade reactions of α-substituted **70**, β-substituted **71**, and γ-substituted cyclohexanones **72** would provide tricyclic compounds **73**, **74**, and 75, which are the frameworks of italicene, decipiadiene, and endiandric acid C, respectively (Scheme 21).



Scheme 21

The intramolecular Michael-aldol reaction could be performed under various reaction conditions, such as treatment with TBSOTf and Et_3N,[28] treatment with TMSI and $(TMS)_2NH$,[29] and treatment with Bu_2BOTf and $(TMS)_2NH$.[30]

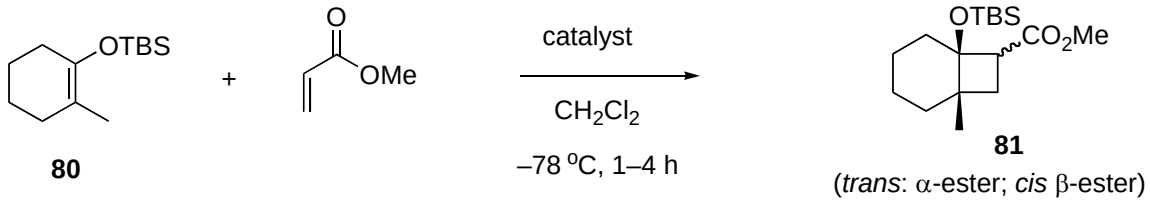


Scheme 22

Thus, treatment of the symmetrical ketone **72** with TBSOTf in the presence of Et_3N or TMSI in the presence of $(TMS)_2NH$ gave **76** in a good yields (Scheme 22). Both (*E*)- and (*Z*)-unsaturated esters of **72** produced the same compound **76**. The tetracyclic compound **78** was obtained in a quantitative yield from **77**. For the cascade reaction of **70** having two types of hydrogens, the thermodynamically controlled reaction conditions, TMSI-$(TMS)_2NH$, was demanded. The same product **79** was provided from both (*E*)- and (*Z*)-**70**. Therefore, the stepwise mechanism was clearly supported for the cascade process.

Asymmetric synthesis of the cascade reaction was further studied in the presence of chiral amines.[31]

Although the intermolecular Michael-aldol reaction between ketones and α,β-unsaturated carbonyl compounds has not yet been carried out, it has been made clear that four-membered carbocyclic compounds could be prepared by the reaction of the silyl enol ethers with α,β-unsaturated carbonyl compounds in the presence of catalytic amount of Lewis acids (Scheme 23).[32-34]



80 **81** (*trans*: α-ester; *cis* β-ester)

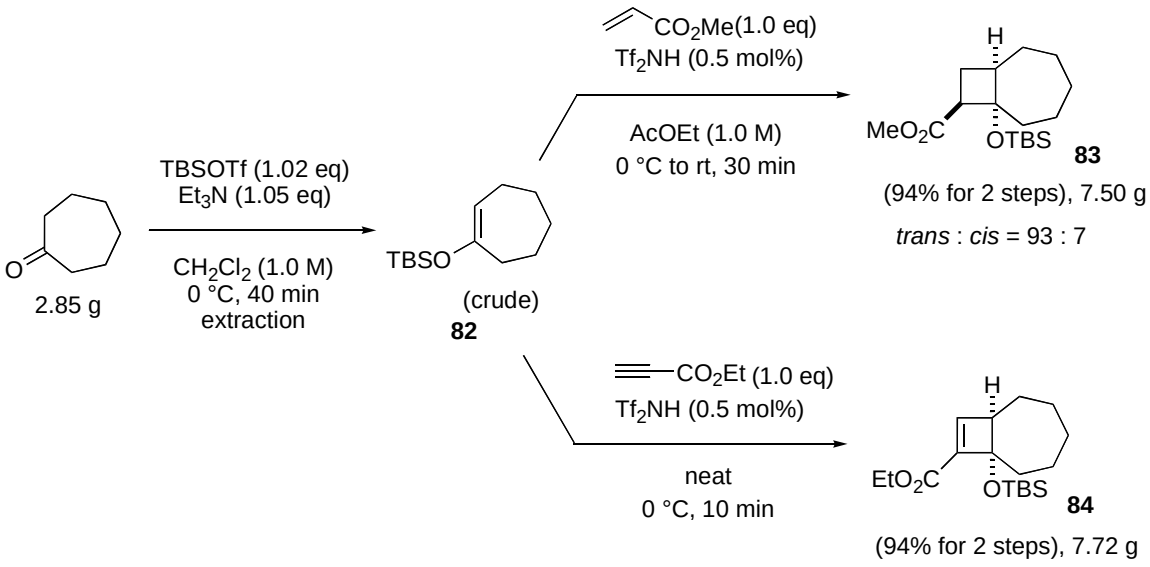
$EtAlCl_2$	(20 mol%)	79% (95 : 5)
Tf_2NH	(1.0 mol%)	92% (100 : trace)
Tf_2NH	(0.1 mol%)	98% (100 : trace)
Tf_2NTBS	(1.0 mol%)	99% (9 : 1)

Scheme 23

The best result was obtained when the reaction was carried out in the presence of Tf_2NH. Use of the equivalent mole of Tf_2NH gave no production of **81** and the bicyclic compounds **81** was provided in a quantitative yield by using a catalytic amount of Tf_2NTBS. The results indicate that the actual reagent must be Tf_2NTBS, which would be formed by the reaction of the silyl enol ether **80** with Tf_2NH.[35]

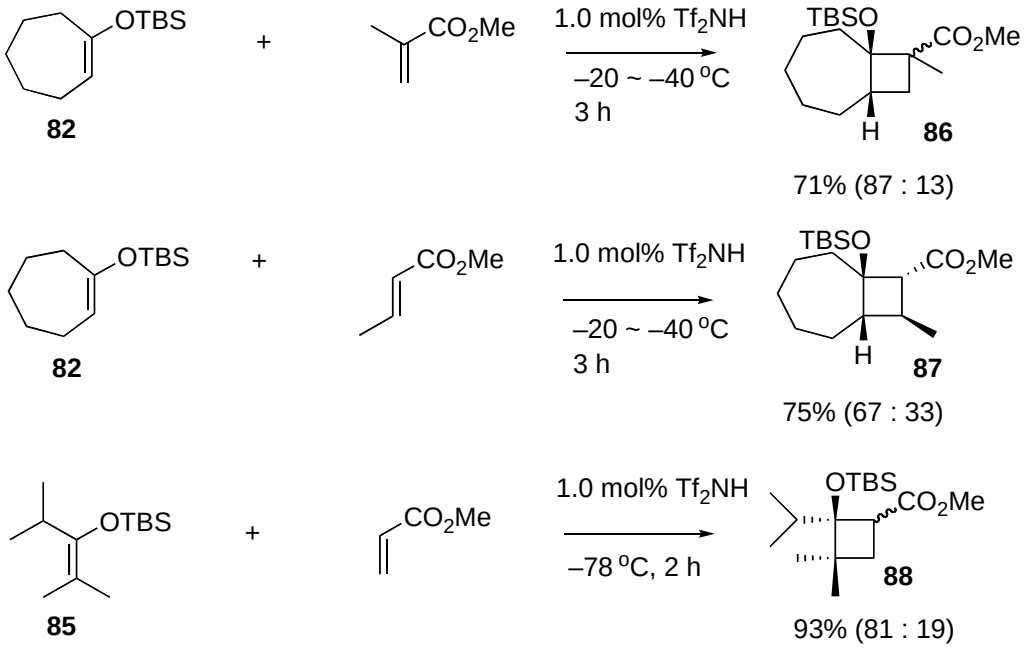
The above procedure is a practical method for the preparation of cyclobutane and cyclobutene derivatives. Examples of gram scale productions are shown in Scheme 24. Thus, the

bicyclic cyclobutane **83** and the bicyclic cyclobutene **84** were synthesized in excellent yields from cycloheptanone via **82** in two steps under mild reaction conditions.[34]



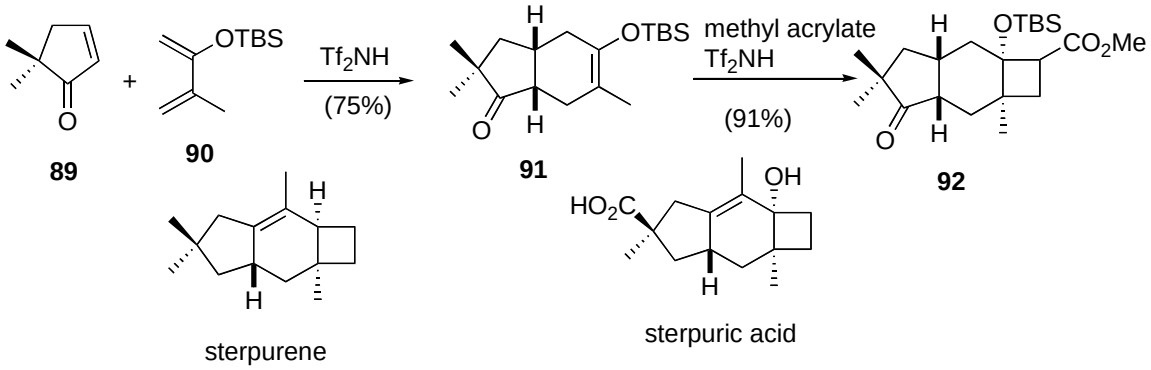
Scheme 24

Various cyclobutane derivatives **86** – **88** were prepared from **82** and **85** by the similar reactions as shown in Scheme 25.



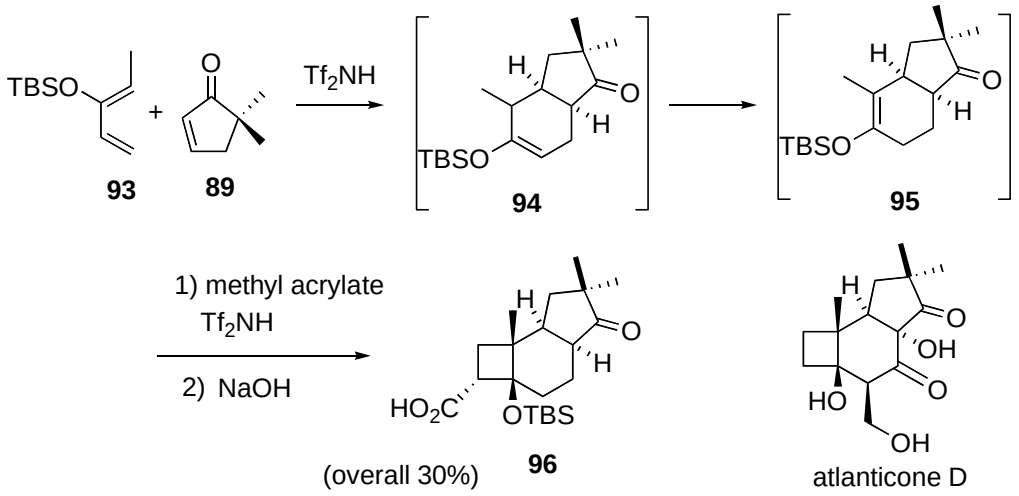
Scheme 25

Tf_2NH is a good catalyst for Diels–Alder reaction. Thus, bicyclic compound **91** was obtained by the cycloaddition of the enone **89** with diene **90**, catalyzed by Tf_2NH and then reacted with methyl acrylate in the presence of Tf_2NH to afford the tricyclic compound **92** as a mixture of diastereoisomers. The tricyclic structure is a skeleton of sterpurene type sesquiterpenes (Scheme 26)



Scheme 26

On the other hand, the cycloadduct **94** from the diene **93** and the enone **89** was easily isomerized to **95** under the reaction conditions. Subsequent reaction of the resulting **95** with methyl acrylate in one pot, followed by hydrolysis of the ester group, provided the tricyclic compound **96** in 30% overall yield as a crystalline compound (Scheme 27). The structure of the product **96** is a framework of protoilludanes (e.g. atlanticone D).

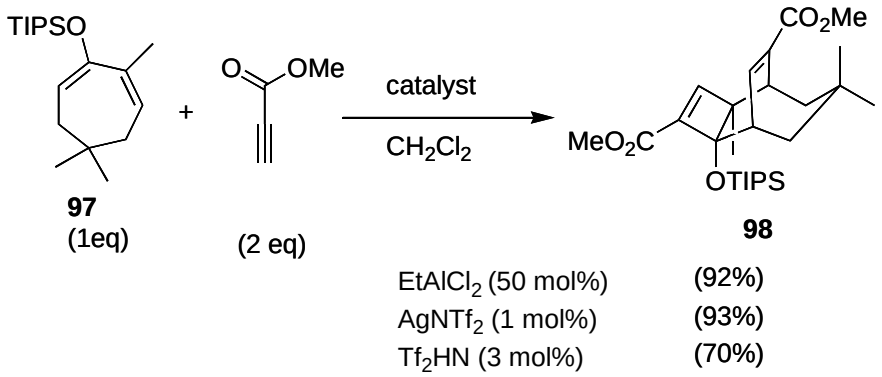


Scheme 27

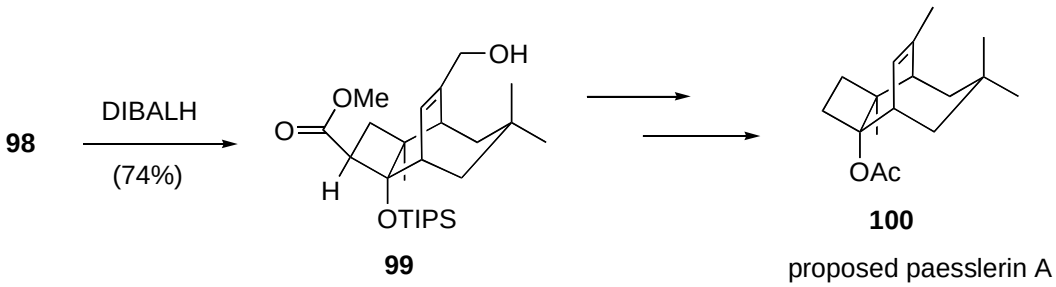
On the basis of the above observations, we devised three components cascade reaction. Namely, the formation of the tricyclic compound **98** was achieved by the reaction of one equiv.

of the diene **97** and two equiv. of methyl propiolate. The cascade reaction was conducted by three different Lewis acid as shown in Scheme 28.

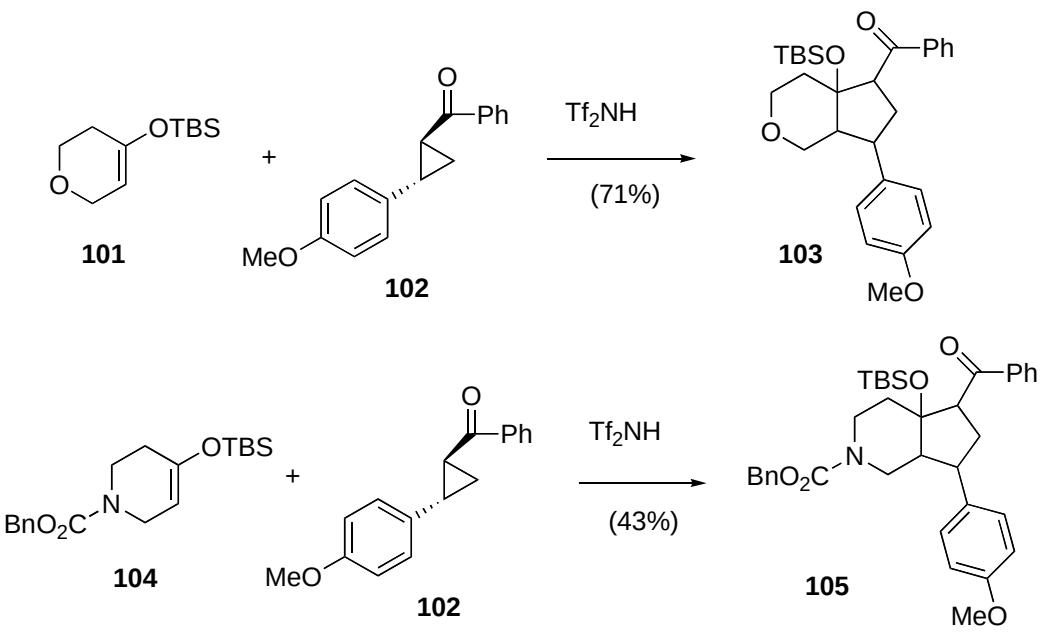
Reduction of the product **98** with DIBALH provided the unexpected alcohol **99**, which was then transformed into paesslerin A **100** (Scheme 29), isolated from the soft coral *Alcyonium paessleri*.[36] The racemate of the natural product **100** was totally synthesized in 34% overall yield in 8 steps from a known compound. However, the spectral data of the synthetic compound were not consistent with the reported ones for the natural product. The structure of the synthetic compound was verified by X-ray analysis. The result clearly indicates that a revision of the structure of natural paesslerin A is required.[33]



Scheme 28



Scheme 29



Scheme 30

It has been further demonstrated that Tf_2NH is useful reagent for the Diels–Alder reaction of imines as dienophiles and the [2+2]–cycloaddition of allylsilane with α,β-unsaturated esters. Additionally, the construction of the five-membered skeleton was performed in the presence of Tf_2NH (Scheme 30). Thus, bicyclic compounds **103** and **105** were obtained as diastereoisomeric mixtures by treatment of the silyl enol ethers **101** and **104** with the cyclopropyl ketone **102** under the same reaction conditions as above.

The usefulness of cascade reactions for syntheses of polycyclic compounds has been demonstrated. These methodologies could be applied for the efficient preparation of various pharmacologically active compounds.

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