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Asymmetric Organocatalytic Tandem/Domino Reactions to Access Bioactive Products

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Abstract: Tandem and domino reactions constitute economic methodologies to prepare complex molecules starting from simple materials. Especially, combining these powerful procedures to asymmetric catalysis allows direct access to many elaborated chiral products, including important key intermediates in total syntheses of important biologically active compounds. A range of various types of chiral organocatalysts have already been successfully applied to such syntheses. This review presents major developments in the total synthesis of bioactive products based on the use of enantioselective organocatalytic domino/tandem reactions as key steps. It is divided into three parts, dealing successively with syntheses based on organocatalytic asymmetric Michael-initiated domino reactions as key steps; aldol-initiated domino/tandem reactions and other domino reactions.

Keywords: Total synthesis, bioactive products, enantioselective domino/tandem reactions, organocatalysis, asymmetric catalysis, chirality.

1. INTRODUCTION

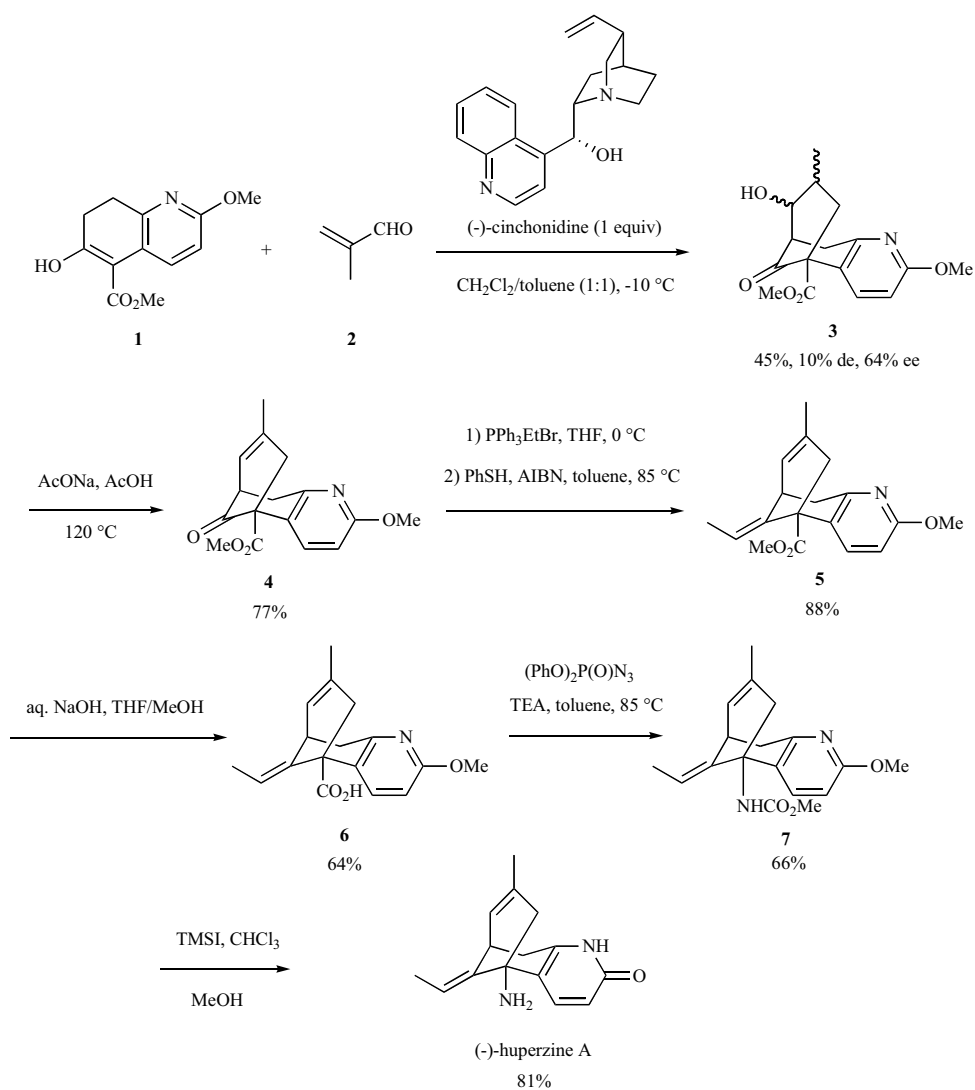
By avoiding costly purification of intermediates and protection/deprotection steps, one-pot synthetic procedures, such as domino and tandem processes [1], constitute a challenge in total synthesis. These powerful reactions allow easy and direct access to elaborated molecules starting from simple materials. Especially, a number of asymmetric organocatalytic versions of these economic methodologies have been employed as key steps in the synthesis of many bioactive products [2]. Indeed, organocatalytic processes are particularly adapted for the total synthesis of drugs related to the absence of metal contamination. By means of the impressive advent of asymmetric catalysis, many types of chiral green organocatalysts have been successfully used in such syntheses, spanning from common proline-derived secondary amines to cinchona alkaloids, phosphoric acids, and imidazolidinones, among others. Remarkably, very high enantioselectivities are commonly observed in these single processes. This review aims to summarize the major developments in the total synthesis of important bioactive products based on the use of asymmetric organocatalytic domino and tandem procedures. It is divided into three parts, dealing successively with syntheses based on organocatalytic asymmetric Michael-initiated domino reactions as key steps; aldol-initiated domino/tandem reactions and other domino reactions.

2. MICHAEL-INITIATED DOMINO REACTIONS AS KEY STEPS

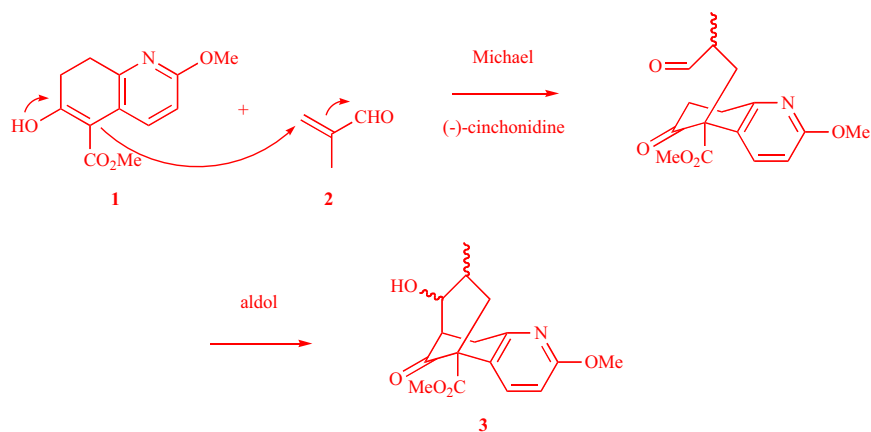
In comparison with metal catalysts [3] presenting drawbacks such as toxicity, cost, moisture sensitivity, and recoverability, organocatalysts have the serious advantages to be cheaper, robust, non-toxic, more stable, readily available, and inert towards moisture

and oxygen [4]. So far, various types of chiral organocatalysts have been applied to the total synthesis of a range of biologically important products, spanning from common proline-derived secondary amines to cinchona alkaloids, phosphoric acids, and imidazolidinones, among others. For example, in 1998, Terashima *et al.* applied for the first time the concept of organocatalysis to the total synthesis of a drug, namely (-)-huperzine A, which is a naturally occurring potent reversible acetylcholinesterase inhibitor agent employed for the treatment of Alzheimer's disease [5]. Indeed, the key step of this short synthesis consisted an enantioselective domino Michael/aldol reaction between β -keto ester **1** and methacrolein **2** organocatalyzed by (-)-cinchonidine, leading to chiral key tricyclic product **3** as a mixture of three diastereomers (10:7:1) in 45% yield and 64% ee (Scheme 1). The latter was further converted through six supplementary steps (detailed in Scheme 1) into expected (-)-huperzine A. In the first step, domino product **3** was undergone dehydration in the presence of acetic acid to give product **4** in 77% yield. The second and third steps consisted of a Wittig reaction of **4** with ethylidene triphenylphosphorane followed by isomerization of the ethylidene moiety to afford (*E*)-configured ethylenic product **5** in 88% yield (2 steps). Subsequent alkaline hydrolysis of this product led to the corresponding carboxylic acid **6** in 64% yield. Then, a modified Curtius rearrangement of the latter gave amide **7** in 66% yield, which was finally deprotected in the presence of TMSI to provide expected (-)-huperzine A in 81% yield.

In 2007, total synthesis of a natural product (+)-palitantin, exhibiting anti-HIV, antibiotic, and antifungal activities, was disclosed by Hong *et al.* [6]. It was based on an enantioselective domino Michael/aldol reaction of two equivalents of α,β -unsaturated aldehydes **8** catalyzed by L-proline, which afforded chiral cyclohexadiene carbaldehyde **9** in 70% yield and 95% ee (Scheme 2). This key intermediate was converted into expected (+)-palitantin through nine supplementary steps, beginning with its dihydroxylation into diol **10** achieved with 67% yield. Diol **10** was then pro-



mechanism for domino Michael/aldol reaction:

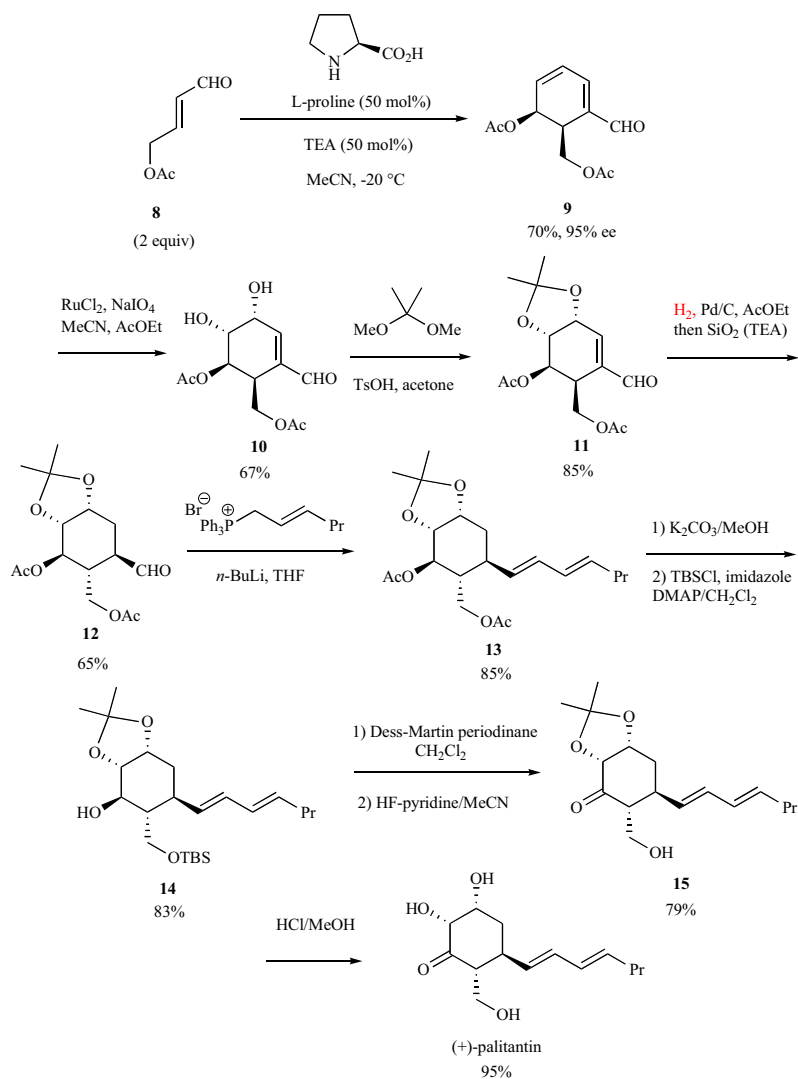


Scheme 1. Synthesis of (-)-huperzine A.

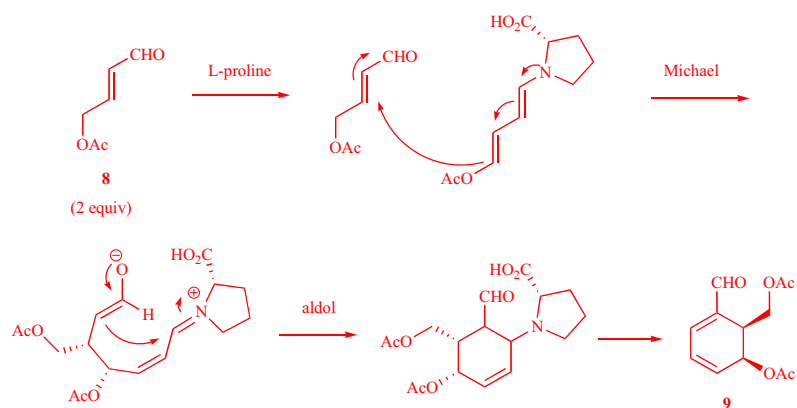
ected into acetonide **11** with 85% yield, and then hydrogenation yielded aldehyde **12** in 65% yield. Wittig reaction of the latter with (*2E*)-hexenyl triphenylphosphonium bromide led to diene **13** in 85% yield. Further hydrolysis of **13** followed by the protection provided alcohol **27** in 83% yield. Subsequent oxidation of **14** by Dess–Martin periodinane, followed by deprotection of the TBS

ether, provided acetonide **15** with 79% yield. Finally, deprotection of acetonide **15** afforded (+)-palitantin in 95% yield.

In 2009, Rios *et al.* described a highly enantioselective synthesis of piperidines through domino Michael/cyclization reaction of α,β -unsaturated aldehydes **16** with amidomalonates **17** catalyzed by



mechanism for domino Michael/aldol reaction:

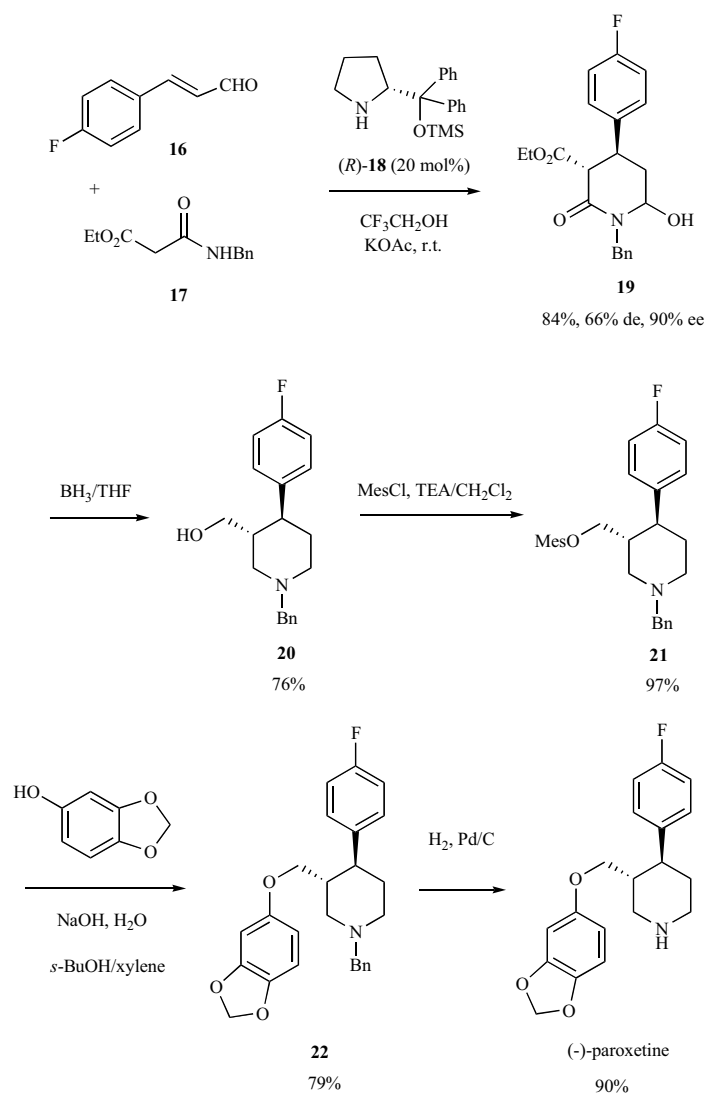


Scheme 2. Synthesis of (+)-palitantin.

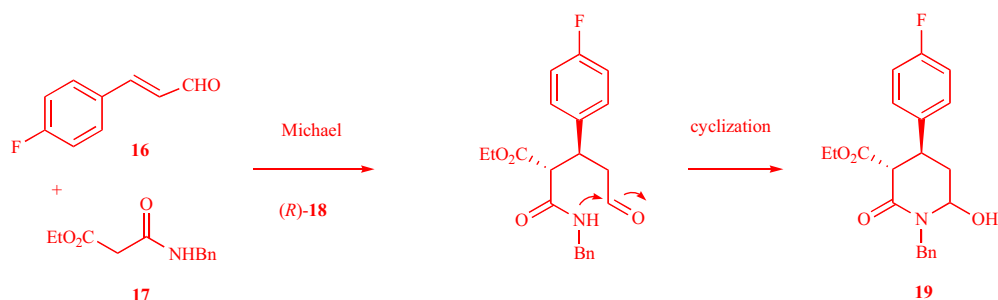
chiral proline-derived amine (*R*)-**18** [7]. Among these products, chiral piperidine **19**, obtained with 84% yield, 66% de, and 90% ee, was used as a key intermediate in a synthesis of (-)-paroxetine which is a selective serotonin reuptake inhibitor drug. As shown in Scheme 3, domino product **19** was further converted into primary alcohol **20** with 76% yield by treatment with BH_3 . After subsequent

protection of the latter into the corresponding mesylate **21** achieved with 97% yield, etherification with sesamol led to product **22** with 79% yield. Final deprotection of the *N*-benzyl group in **22** through hydrogenation afforded expected (-)-paroxetine in 90% yield.

In 2009, List and Michrowska employed another chiral imidazolidinone catalyst, such as **23**, to promote enantioselective domino



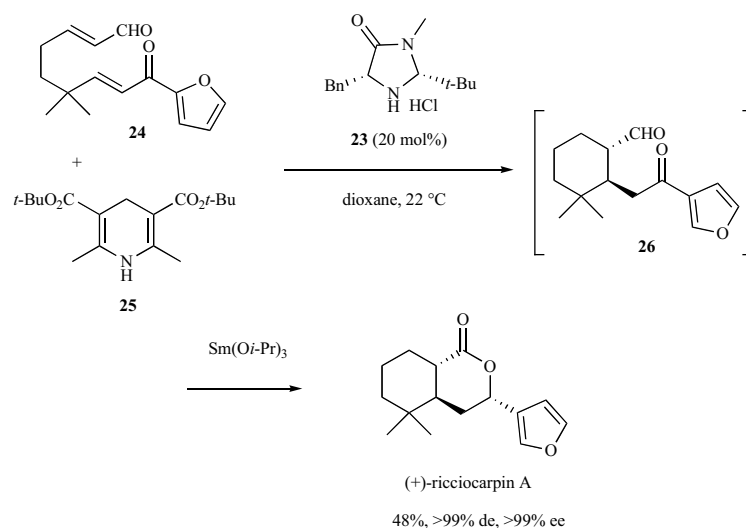
mechanism for domino Michael/cyclization reaction:



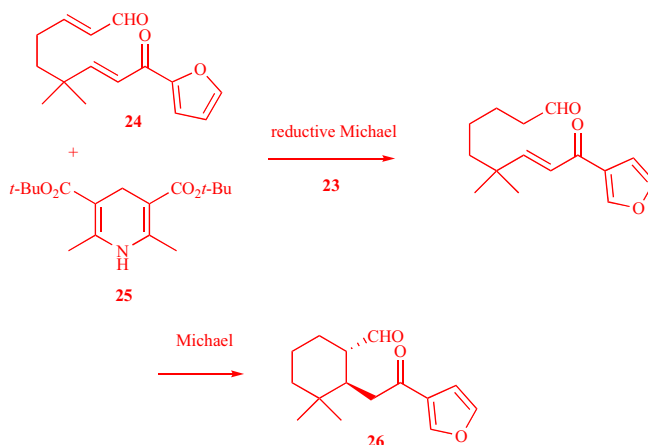
Scheme 3. Synthesis of (-)-paroxetine.

reductive Michael/Michael cyclization reaction between aldehyde **24** and Hantzsch ester **25** [8]. This reaction allowed the synthesis of chiral ketoaldehyde **26** to be achieved. The latter was not isolated but directly submitted to $\text{Sm}(\text{O}i\text{-Pr})_3$, undergoing isomerization followed by a highly diastereoselective Tishchenko reaction, which yielded ricciocarpin A, an anti schistosomiasis agent. Remarkably, this natural product was obtained as a single diastereo- (>99% de) and enantiomer (>99% ee) in 48% yield (Scheme 4). This synthesis of ricciocarpin A is the shortest reported so far.

In 2010, the first total synthesis of a natural and biologically active product (+)-conicol was reported by Hong *et al.* [9]. The key step of this synthesis consisted in an enantioselective domino oxa-Michael/Michael reaction of 3-methylbut-2-enal **27** with (*E*)-2-(2-nitrovinyl)-benzene-1,4-diol **28** upon catalysis with *L*-proline-derived secondary amine (*S*)-**18**, affording the corresponding enantiopure cycloadduct **29** in 76% yield (Scheme 5). This intermediate was further implicated in a domino Michael/aldol sequence catalyzed by the same organocatalyst through reaction with crotonalde-



mechanism for domino reductive Michael/ Michael reaction:



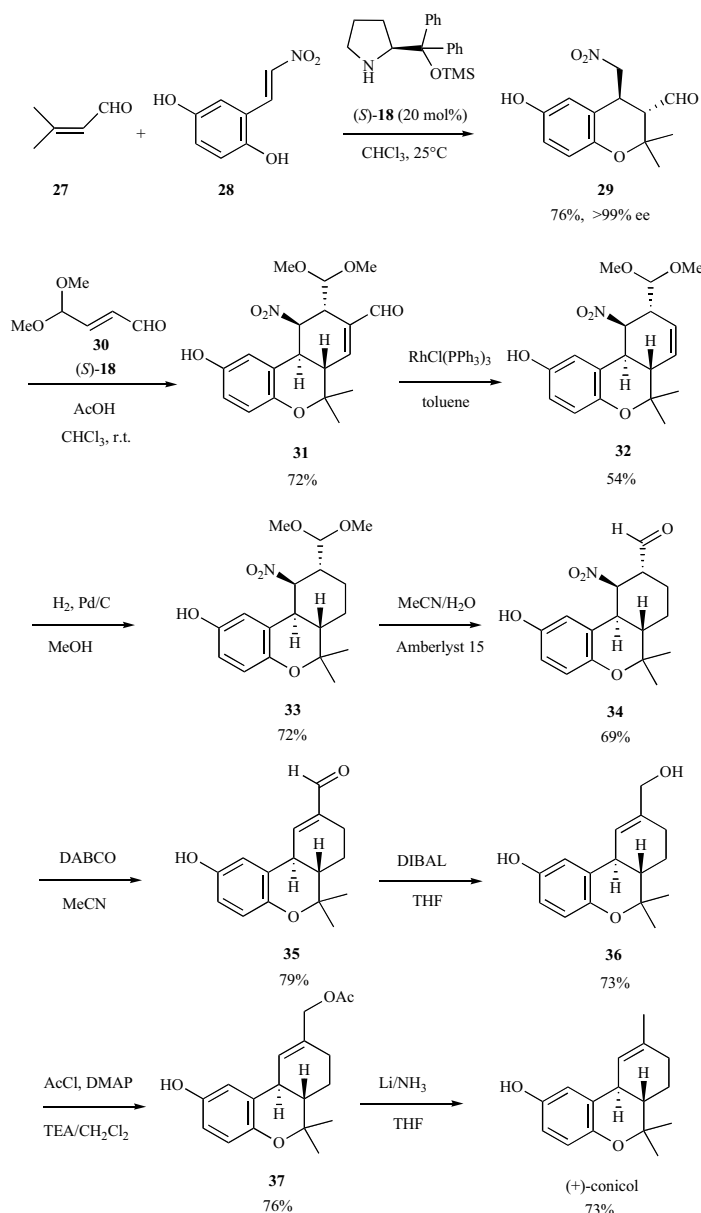
Scheme 4. Synthesis of riccioarpin A.

hyde **30**, leading to chiral hexahydro-6*H*-benzo[*c*]chromene **31** in 72% yield. The latter was submitted to decarbonylation in the presence of Wilkinson catalyst to give alkene **59** in 54% yield. Then, hydrogenation of **32** provided **33** in 72% yield. Hydrolysis of the dimethoxymethyl group in **33** gave product **34** in 69% yield. A subsequent denitration elimination of **34** performed with DABCO led to **35** in 79% yield. Reduction of **35** with DIBAL afforded primary alcohol **36** in 73% yield. Further acetylation of **36** yielded acetate **37** in 76% yield, which finally underwent lithium reduction to provide expected (+)-conicol with 73% yield.

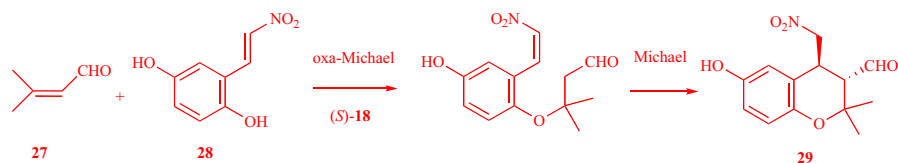
The antidepressant drug (-)-paroxetine was also synthesized in 2014 by Wang and Sun based on another organocatalytic asymmetric domino sequence [10]. This occurred with 72% yield and 91% ee between α,β -unsaturated aldehyde **38** and malonic half-thioester **39** in the presence of L-proline-derived amine catalyst **40** through successive Michael addition, cyclization, and nucleophilic addition (Scheme 6). The formed chiral lactone **41** could be further converted into (-)-paroxetine in nine supplementary steps. Firstly, lactone **41** was submitted to nickel-catalyzed ring-opening reaction to give aldehyde **42** in 70% yield. A subsequent reduction of **42** afforded the corresponding chiral primary alcohol **43** in 87% yield. According to previously described works [11], alcohol **43** was me-

sylated and then undergone a reaction with benzylamine to give the corresponding lactame **44** in 82% yield. A subsequent carboxymethylation gave **45** in 88% yield, which was further reduced into primary alcohol **46** in 92% yield. Then, mesylation followed by reaction with sesamol afforded ether **47** in 80% yield. The latter was finally hydrogenated with 93% yield into expected (-)-paroxetine.

In order to propose a novel route to estrogenic hormone estradiol, Hayashi *et al.* developed in 2017 an asymmetric total synthesis of estradiol methyl ether based on the use of an organocatalyst [12]. Indeed, the first step of the sequence consisted of an enantioselective domino Michael/aldol reaction of nitroalkane **48** with α,β -unsaturated aldehyde **49** catalyzed by chiral amine (*S*)-**18** to give the corresponding enantiopure bicyclic product **50**. This highly functionalized bicyclo[4.3.0]nonane was not isolated but directly submitted to stereoselective addition of KCN to the aldehyde moiety, followed by the formation of the xanthate ester **51**. Again, the latter was not isolated but directly dehydrated upon further addition of SOCl_2 in the presence of pyridine to provide enantiopure cyclopentene **52** in 78% yield (3 steps). Then, reductive removal of both the nitro group and the xanthate ester moiety in **52** was accomplished simultaneously by treatment with HSnBu_3 in the pres-



mechanism for domino oxa-Michael/Michael reaction:



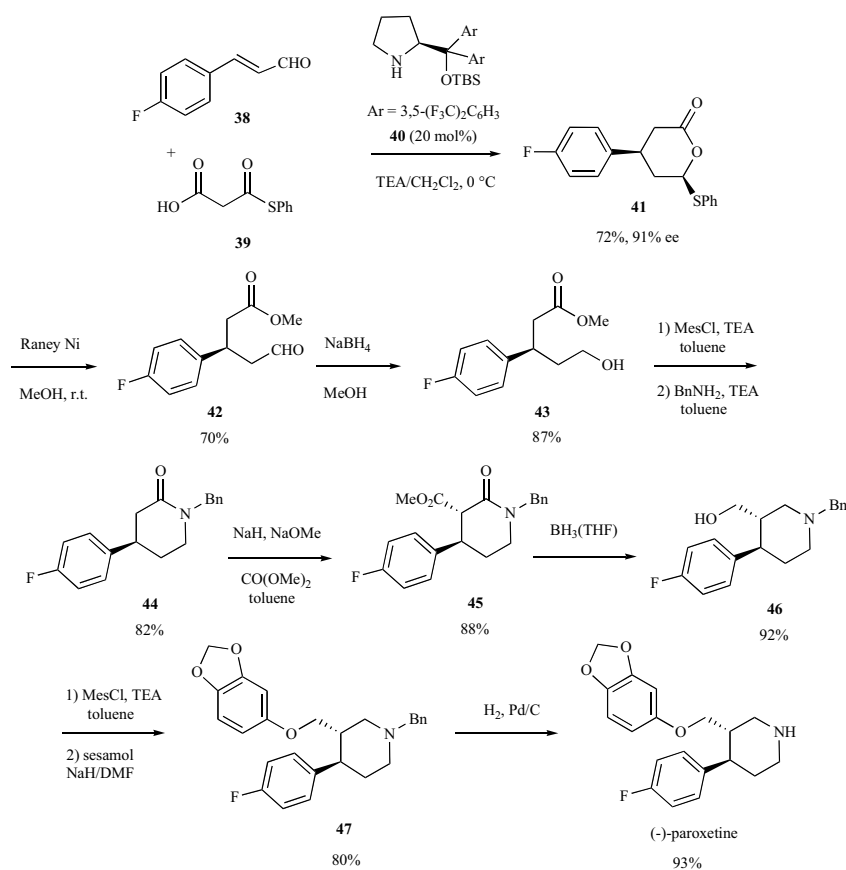
Scheme 5. Domino oxa-Michael/Michael reaction of 3-methylbut-2-enal with (*E*)-2-(2-nitrovinyl)-benzene-1,4-diol as key-step of synthesis of (+)-conicol.

ence of AIBN to afford intermediate **53** in 59% yield. Subsequently, diastereoselective reduction of the ketone moiety in **53** and conversion of the nitrile group into a formyl moiety were conducted in a single pot by successive treatment with LiBHET_3 and DIBAL to give hydroxy aldehyde **54** in 34% yield. The next step was the protection of **54** into the corresponding silyl ether **55** with a 59% yield. The latter was then submitted to a series of six reactions (detailed in Scheme 7) conducted in a single vessel, involving successively a Kraus–Pinnick oxidation, hydrogenation, an acyl chloride formation, a Friedel–Crafts acylation, a TIPS deprotection, and a reduction of benzyl ketone moiety to afford final enantiopure estradiol

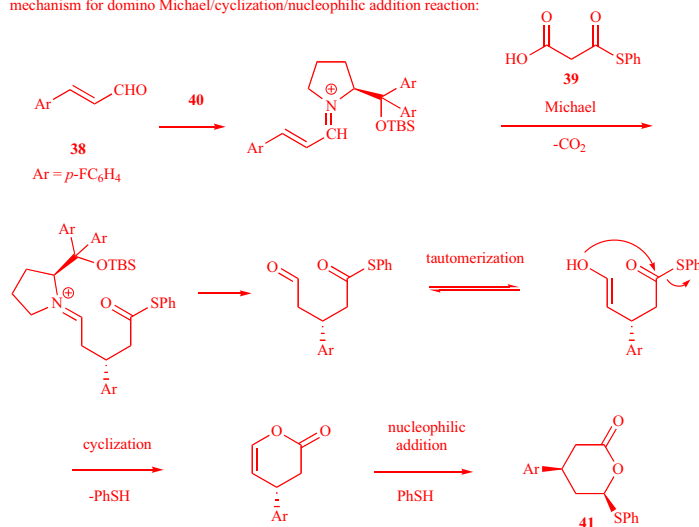
methyl ether in 55% overall yield (6 steps). It must be noted that this total synthesis employed a total of only five reaction vessels to be accomplished along with as low as four purification procedures. Later in 2018, the same authors improved this synthesis, increasing the overall yield from 5% to 6.8% [13].

3. ALDOL-INITIATED DOMINO/TANDEM REACTIONS AS KEY STEPS

In 2008, a synthesis of the most important member of the vitamin E family, namely α -tocopherol, was developed by Woggon *et al.*, including an enantioselective organocatalyzed domino al-



mechanism for domino Michael/cyclization/nucleophilic addition reaction:

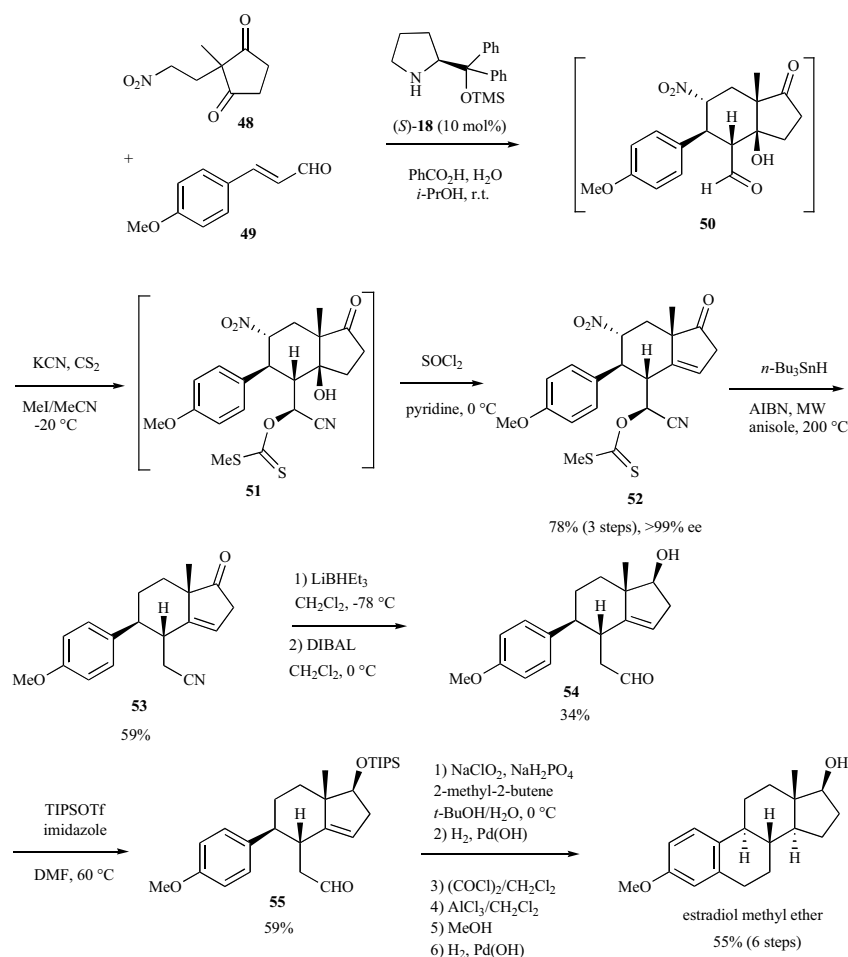


Scheme 6. Synthesis of (-)-paroxetine.

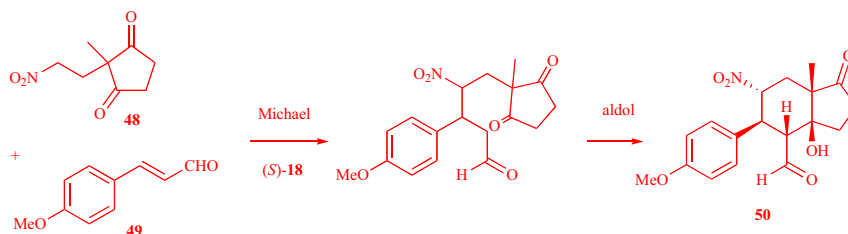
dol/oxa-Michael/hemiacetalization reaction (Scheme 8) [14]. Proline-derived amine catalyst **56** was employed to promote this reaction between α,β -unsaturated aldehyde **57** and salicylic acid **58**, which led to a 58% yield of chiral tricyclic hemiaminal **59** as almost single diastereomer (97% de). This key product could be transformed into desired α -tocopherol in only four steps. The first one consisted of its oxidation with PCC into lactone **60** achieved with 90% yield. Then, this benzylic lactone was quantitatively hydrogenated into carboxylic acid **61**, which was further submitted to a Barton decarboxylation procedure to give α -tocopherol ether

62 in 72% yield and 94% de. Final cleavage of the methyl ether of **62** by treatment with $\text{BF}_3(\text{SMe}_2)/\text{AlCl}_3$ yielded expected α -tocopherol with 84% yield.

In 2018, an enantioselective tandem double aldol reaction catalyzed by simple L-proline and achiral thiomorpholinium trifluoroacetate **63** was developed by Aggarwal *et al.* as a key step in a total synthesis of Δ^{12} -prostaglandin J₃ exhibiting anti-leukemic properties [15]. This one-pot two-step aldol dimerization of succinaldehyde **64** followed by hemiacetalization and dehydration led to the corresponding chiral bicyclic enal intermediate **65** in 29% yield,



mechanism for domino Michael/aldol reaction:



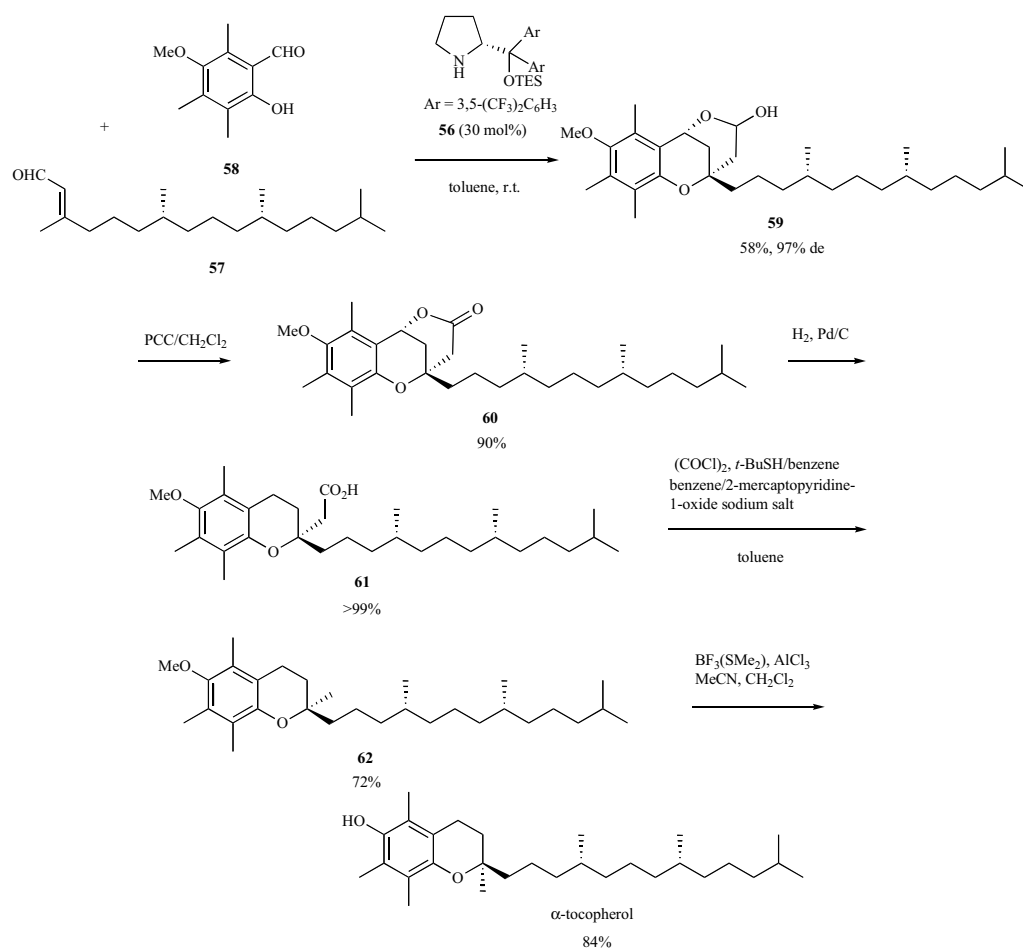
Scheme 7. Synthesis of estradiol methyl ether.

60% de, and 99% ee (Scheme 9). The synthetic utility of this product was demonstrated in its conversion through ten supplementary steps into Δ^{12} -prostaglandin J₃. The sequence began with the oxidation of the aldehyde group in **65** into carboxylic acid **66** with a 74% yield. Then, the latter was converted into acyl azide **67** in 80% yield. Heating **67** in toluene affected a Curtius rearrangement leading to an isocyanate, which was trapped with benzyl alcohol to give carbamate **68** in 90% yield. The latter was then reduced to hemiacetal **69** in the presence of DIBAL with a 98% yield. Then, Wittig reaction of **69** with phosphonium salt **70** provided the corresponding enamide, which was not isolated but directly hydrolyzed and then dehydrated to afford enone **71** in 81% yield. The latter was further converted into *t*-butyl ester **72** in 83% yield. This product subsequently underwent aldol condensation with β -boryl aldehyde **73** to give alcohol **74** as a mixture of epimers. The latter was treated

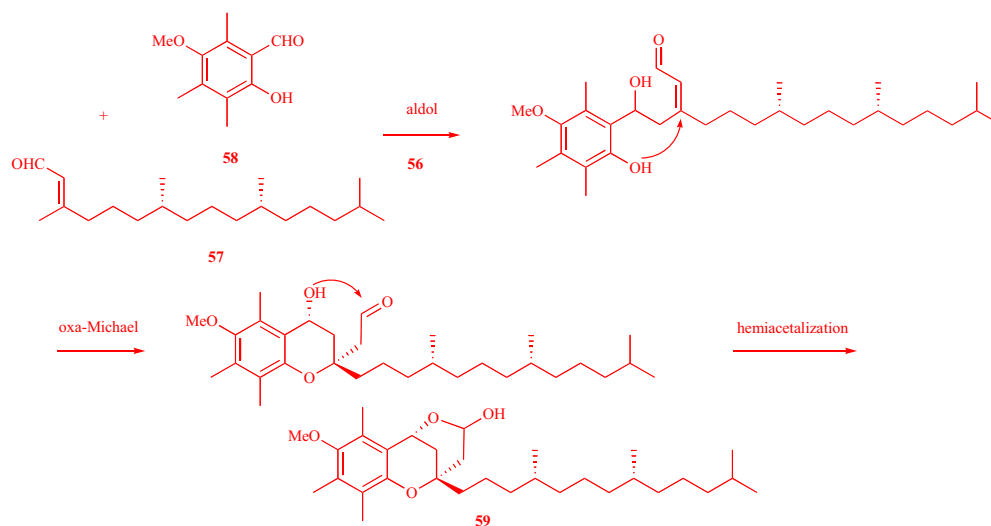
with MesCl and TEA to afford the corresponding mesylate, which underwent elimination in the presence of DBU to produce the corresponding *E*-configured elimination product exclusively. The resulting boronic ester was oxidized into secondary alcohol **75** using NaBO₃(H₂O)₄ in 23% overall yield (3 steps). Finally, treatment of **75** with HBF₄ yielded an expected Δ^{12} -prostaglandin J₃ in 75% yield.

4. OTHER DOMINO REACTIONS AS KEY STEPS

Later in 2006, chiral phosphoric acid **76** was applied by Rueping *et al.* to promote the key step of the synthesis of three bioactive tetrahydroquinoline alkaloids, such as (+)-cuspareine, (+)-galipinine, and (+)-angustureine [16]. Indeed, Brønsted acid **76** was found to catalyze highly enantioselectively, the double transfer hydrogenation of 2-substituted quinolines **77a-c** with Hantzsch



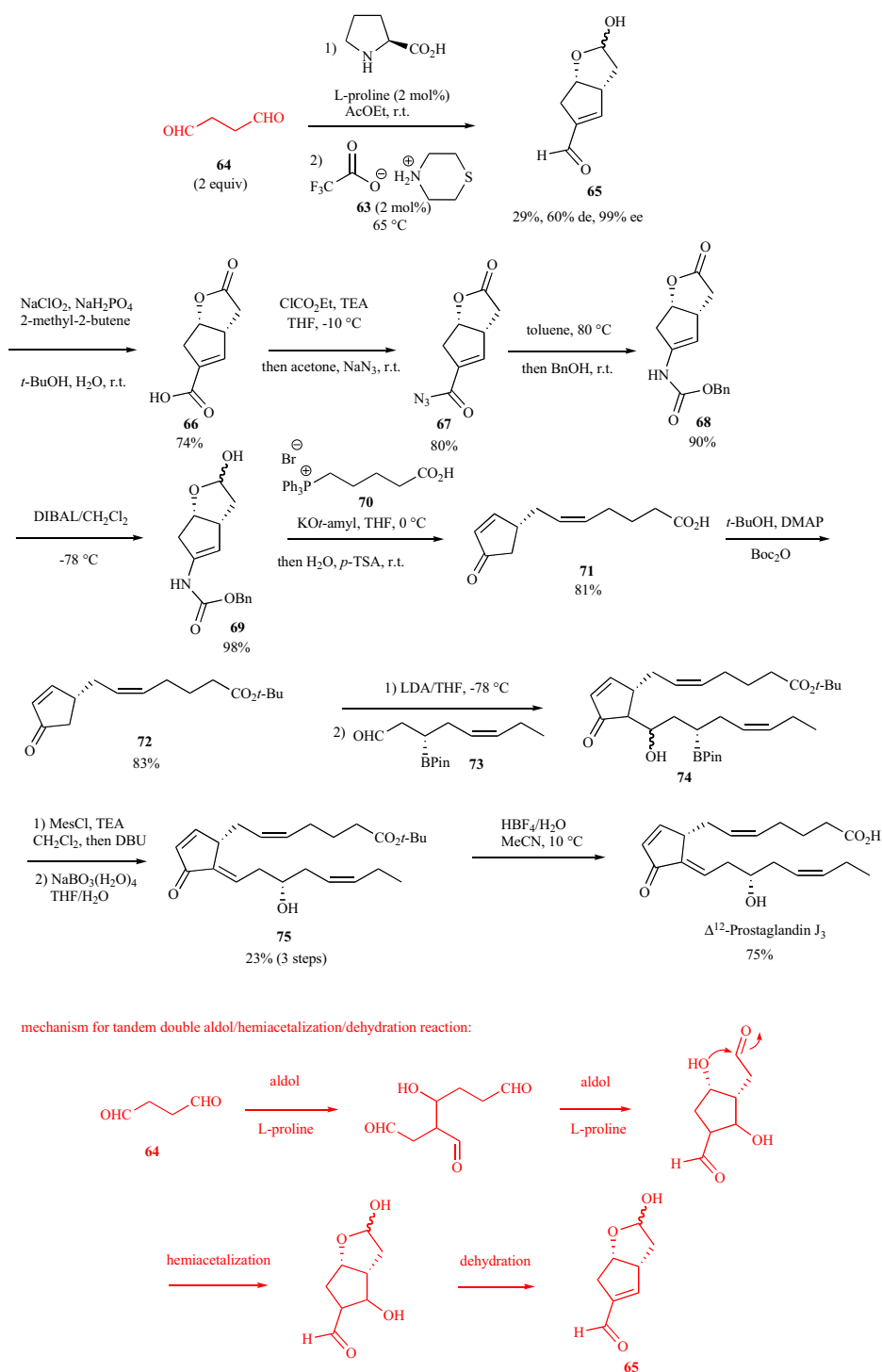
mechanism for domino aldol/oxa-Michael/hemiacetalization reaction:



Scheme 8. Synthesis of α -tocopherol.

ester **78**. As shown in Scheme 10, this one-pot double-transfer hydrogenation afforded the corresponding chiral tetrahydroquinolines **79a-c** in both high yields (79-89%) and enantioselectivities (90-91% ee). The latter were further *N*-methylated to give expected (+)-cuspareine, (+)-galipinine, and (+)-angustureine in excellent yields (90-95%).

In 2006, Itoh *et al.* reported synthesis of the highly toxic alkaloid (+)-coniine, which is known to induce curare-type paralysis [17]. The synthesis included an asymmetric three-component Mannich reaction organocatalyzed by L-proline. It involved acetone **80**, *p*-anisidine **81**, and 5-hydroxypentanal **82** as substrates, leading to chiral Mannich product **83** in 76% yield and 91% ee (Scheme 11). The conversion of this key product into desired (+)-coniine was

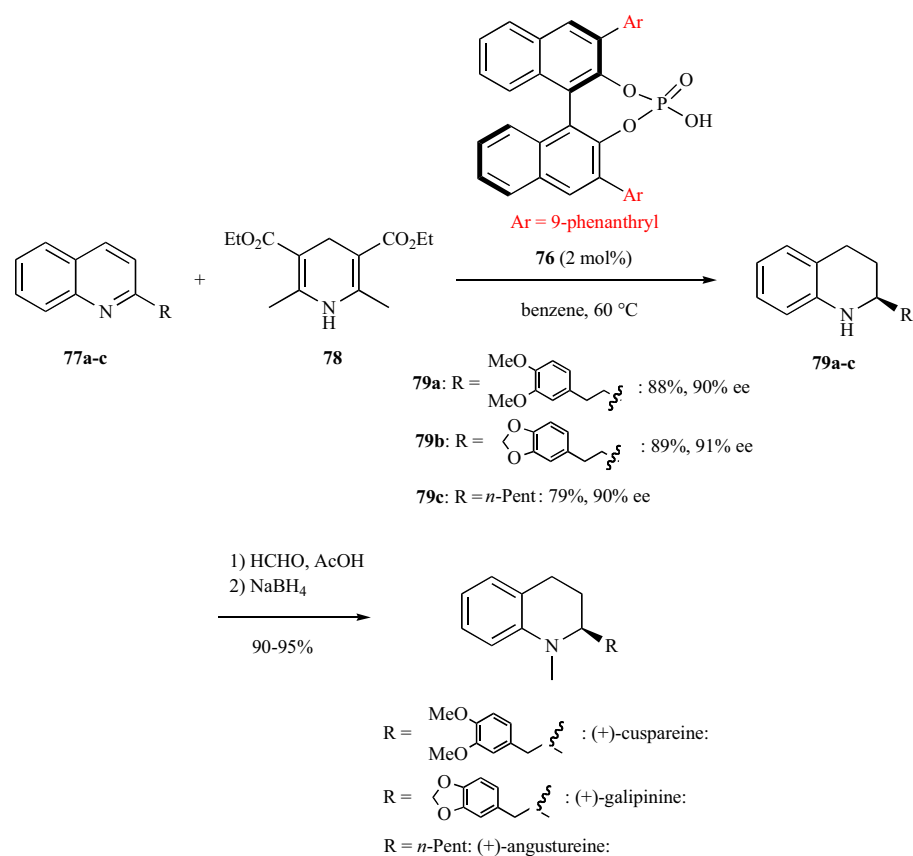


Scheme 9. Synthesis of Δ^{12} -prostaglandin J_3 .

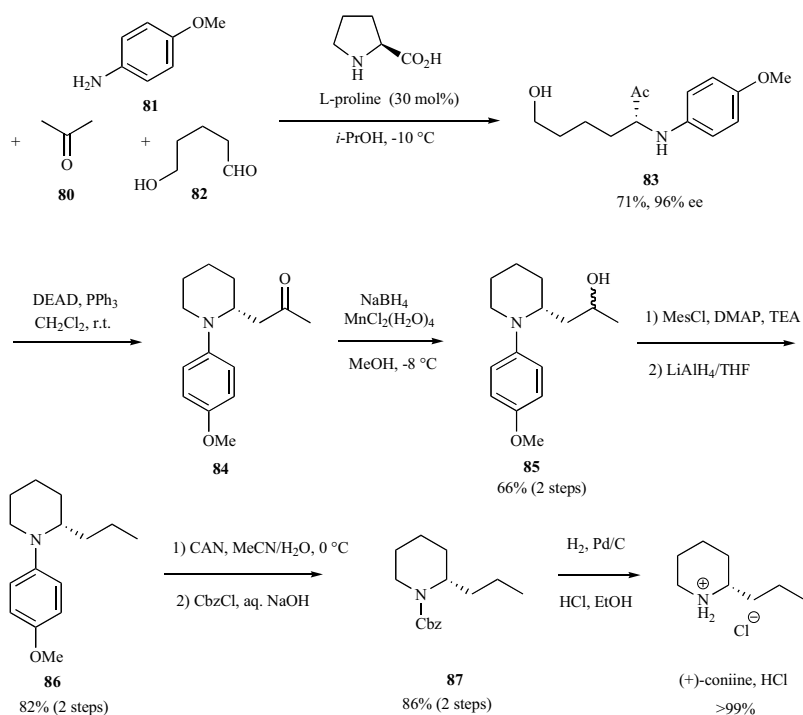
achieved through seven steps, beginning with its cyclization into piperidine **84** through Mitsunobu reaction followed by reduction of the latter with NaBH_4 to give **85** in 66% yield (2 steps). Subsequently, intermediate **85** was mesylated and then reduced with LiAlH_4 to give **86** in 82% yield (2 steps). Then, CAN oxidation of **86** followed by Cbz protection led to product **87** in 86% yield (2 steps). Finally, catalytic hydrogenation of **87** afforded (+)-coniine hydrochloride in quantitative yield.

The indole skeleton is widely expanded in medicinal chemistry [18]. In 2009, MacMillan *et al.* reported total synthesis of natural

and biologically active (-)-minfiensine, the key step of which was a highly enantioselective organocatalytic domino Diels–Alder/amine cyclization reaction building the central tetracyclic pyrroloindole framework of (-)-minfiensine [19]. As illustrated in Scheme 12, in the presence of chiral imidazolidinone catalyst **88**, 2-vinylindole **89** reacted with propynal **90** to give the corresponding chiral tetracyclic pyrroloindole **91** in 87% yield and 96% ee. This carbamate was further converted through only five steps into (-)-minfiensine. The first step consisted of the treatment of **91** by TESOTf to provide silyl ether **92** in 84% yield. Reductive amination of this second



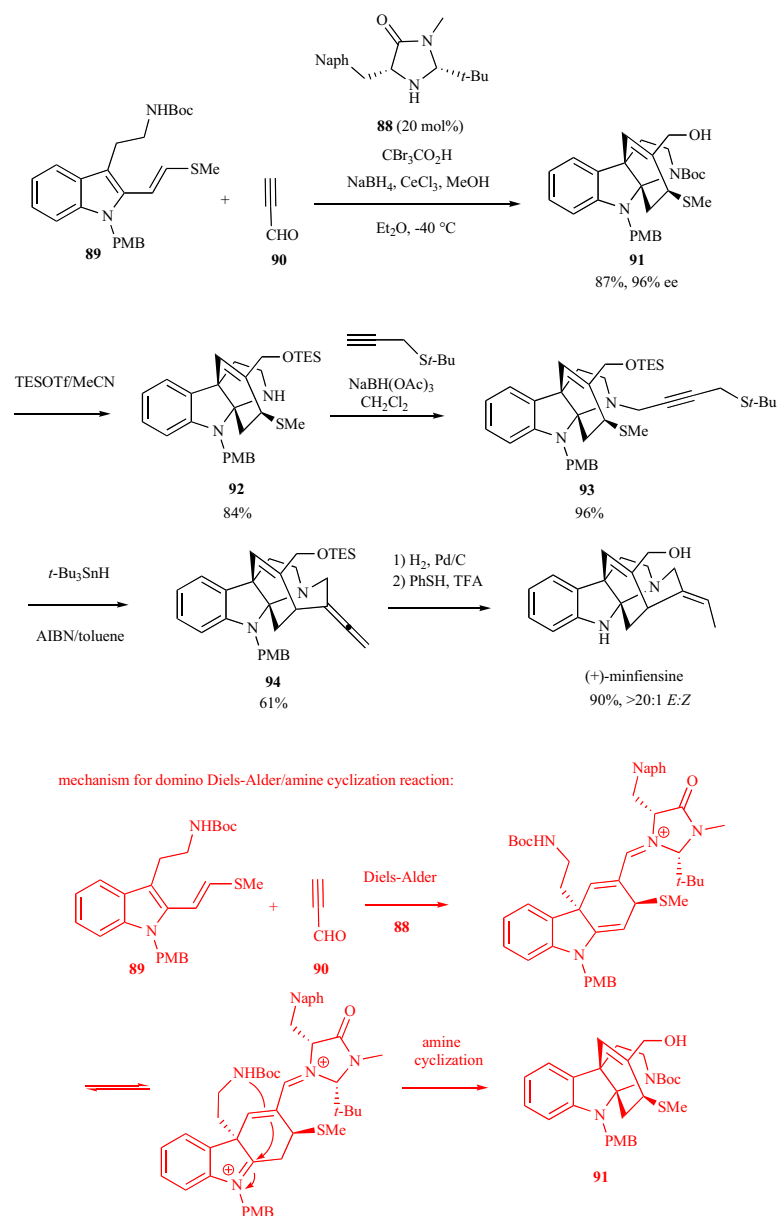
Scheme 10. Synthesis of (+)-cuspareine, (+)-galipinine, and (+)-angustureine.



Scheme 11. Synthesis of (+)-coniine.

dary amine **92** with butynal *t*-butyl sulfide was performed in the presence of NaBH(OAc)₃ to give intermediate **93** in 96% yield. The latter was further undergone to a radical cyclization, affording al-

lene **94** with a 61% yield. Hydrogenation of this allene followed by deprotection in the presence of TFA led to final (-)-minfiensine in 90% yield and >20:1 *E/Z* diastereoselectivity.



Scheme 12. Synthesis of (-)-minfiensine.

CONCLUSION

This review collects major advances in the total synthesis of bioactive products using enantioselective organocatalytic domino/tandem processes as key steps. It demonstrates that a variety of one-pot asymmetric reactions catalyzed by chiral green organocatalysts have already allowed a diversity of biologically important products and drugs to be economically synthesized. The diversity of these single vessel reactions reflects that of the catalysts employed to promote them. Indeed, various chiral organocatalysts have already been successfully applied to the total synthesis of pharmaceutical and bioactive products. The most employed are proline-derived secondary amines which allow the syntheses of products as different as (+)-conicol with >99% ee, (+)-coniine with 91% ee, (+)-paroxetine with 91% ee, estradiol methyl ether with >99% ee, Δ^{12} -prostaglandin J₃ with 99% ee, (+)-palitantin with 95% ee, and α -tocopherol with 97% de. Other chiral amine catalysts, such as imidazolidinones, have been used in the key steps of total syntheses of (+)-minfiensine with 96% ee, and (+)-ricciocarpin A with >99%

ee. Chiral phosphoric acids were successfully applied in the total syntheses of (+)-cuspareine, (+)-galipinine, and (+)-angustureine with 91% ee, while cinchona alkaloids were employed to promote the key steps in the synthesis of (-)-huperzine A with 64% ee. In accordance with the huge advent of asymmetric catalysis, more and more organocatalyzed asymmetric domino and tandem methodologies will undoubtedly be applied as economic key steps in the total synthesis of other bioactive products in the near future.

LIST OF ABBREVIATIONS

AIBN	=	Azobisisobutyronitrile
Ar	=	Aryl
Bn	=	Benzyl
Boc	=	<i>tert</i> -butoxycarbonyl
CAN	=	Ceric ammonium nitrate
Cbz	=	Benzyloxycarbonyl
DABCO	=	1,4-diazabicyclo[2.2.2]octane

DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
de	=	Diastereomeric excess
DEAD	=	Diethyl azodicarboxylate
DIBAL		
(DIBAL-H)	=	Diisobutylaluminium hydride
DMAP	=	4-(dimethylamino)pyridine
DMF	=	<i>N,N</i> -dimethylformamide
ee	=	Enantiomeric excess
HIV	=	Human immunodeficiency virus
LDA	=	Lithium diisopropylamide
Mes	=	Mesyl
Naph	=	Naphthyl
PCC	=	Pyridinium chlorochromate
Pent	=	Pentyl
Pin	=	Pinacolato
PMB	=	<i>para</i> -methoxybenzyl
<i>p</i> -TSA	=	<i>p</i> -toluenesulfonic acid
r.t.	=	Room temperature
TBS	=	<i>tert</i> -butyldimethylsilyl
TEA	=	Triethylamine
TES	=	Triethylsilyl
Tf	=	Trifluoromethanesulfonyl
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
TIPS	=	Triisopropylsilyl
TMS	=	Trimethylsilyl
Tol	=	Tolyl
Ts	=	4-toluenesulfonyl (tosyl)

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- (b) Tietze, L.F.; Beifuss, U. Sequential transformations in organic chemistry: a synthetic strategy with a future. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 131-163. <http://dx.doi.org/10.1002/anie.199301313>
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