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Organocatalytic total synthesis of bioactive compounds based on one-pot methodologies

Hélène Pellissier

Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France

h.pellissier@univ-amu.fr

Abstract: The combination of one-pot methodologies to asymmetric organocatalysis allow a green and direct access to many types of complex highly functionalized chiral products, including important key intermediates in total syntheses of important bioactive compounds. A series of chiral organocatalysts have already been successfully applied to such syntheses. This chapter collects major developments in the total synthesis of biologically active products based on the use of enantioselective organocatalytic domino/tandem reactions as key steps. It is divided into two parts dealing successively with reactions based on the use of proline-derived catalysts and other organocatalysts.

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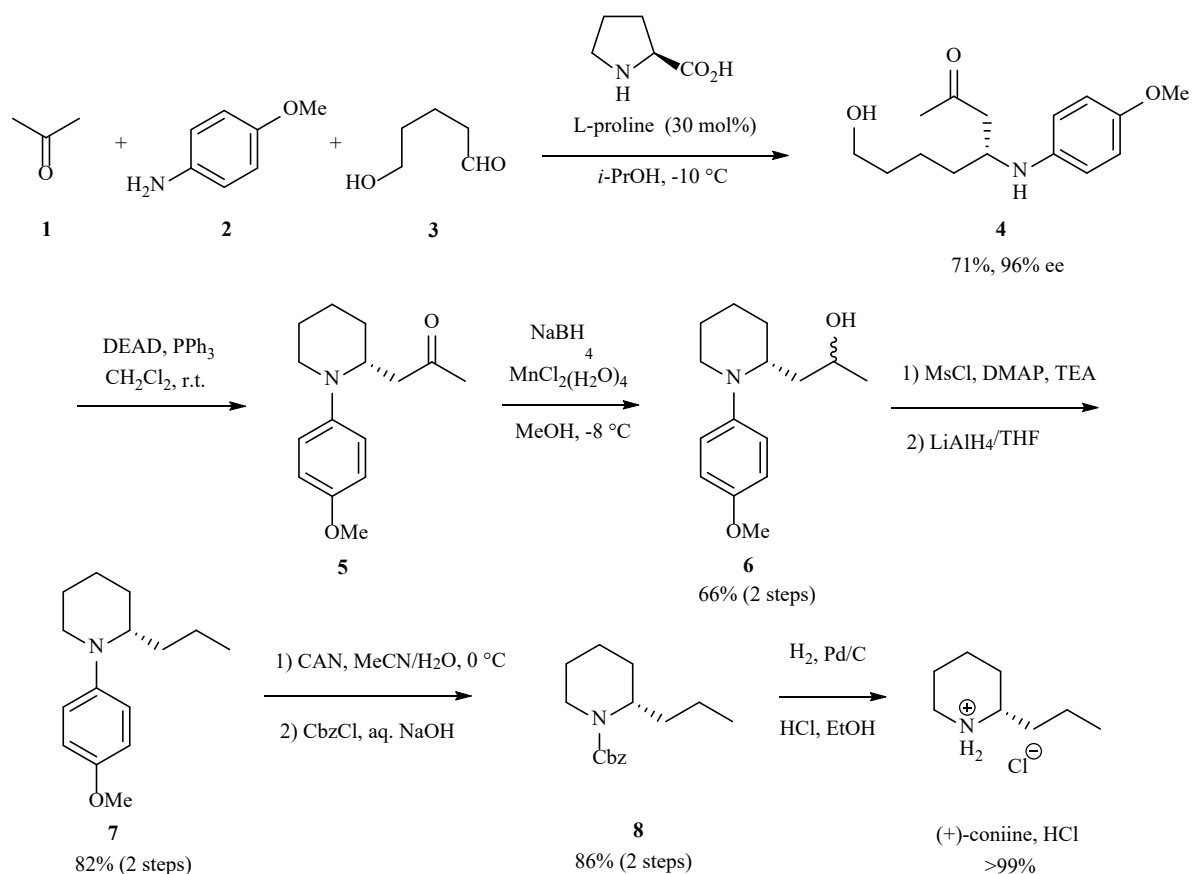
1 Introduction

By avoiding costly purification of intermediates and protection/deprotection steps, one-pot synthetic procedures, such as domino and tandem processes [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17], constitute a challenge in total synthesis. These powerful reactions allow a direct and economic route to sophisticated and highly functionalized molecules starting from simple materials. Thanks to the advent of asymmetric catalysis, a number of asymmetric catalytic versions of these economic methodologies have been employed as key steps in the synthesis of many bioactive products [18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]. In contrast with metal catalysts [35,36,37,38,39,40,41,42,43,44,45] which are often toxic, cost, moisture sensitive, green organocatalysts present the advantages to be cheaper, robust, non-toxic, more stable, readily available, and inert towards moisture and oxygen [46,47,48,49,50,51,52,53,54,55,56]. Moreover, organocatalytic processes are particularly adapted for the total synthesis of drugs related to the absence of metal contamination. Consequently, various types of chiral

organocatalysts have been applied to the total synthesis of many biologically important products, spanning from common proline-derived secondary amines to cinchona alkaloids, phosphoric acids, and imidazolidinones among others. This chapter collects the major developments in the total synthesis of important bioactive products based on the use of asymmetric organocatalytic domino and tandem processes. It is decomposed into two sections, focussing successively with total syntheses employing proline-derived catalysts and other organocatalysts.

2 Proline-derived catalysts

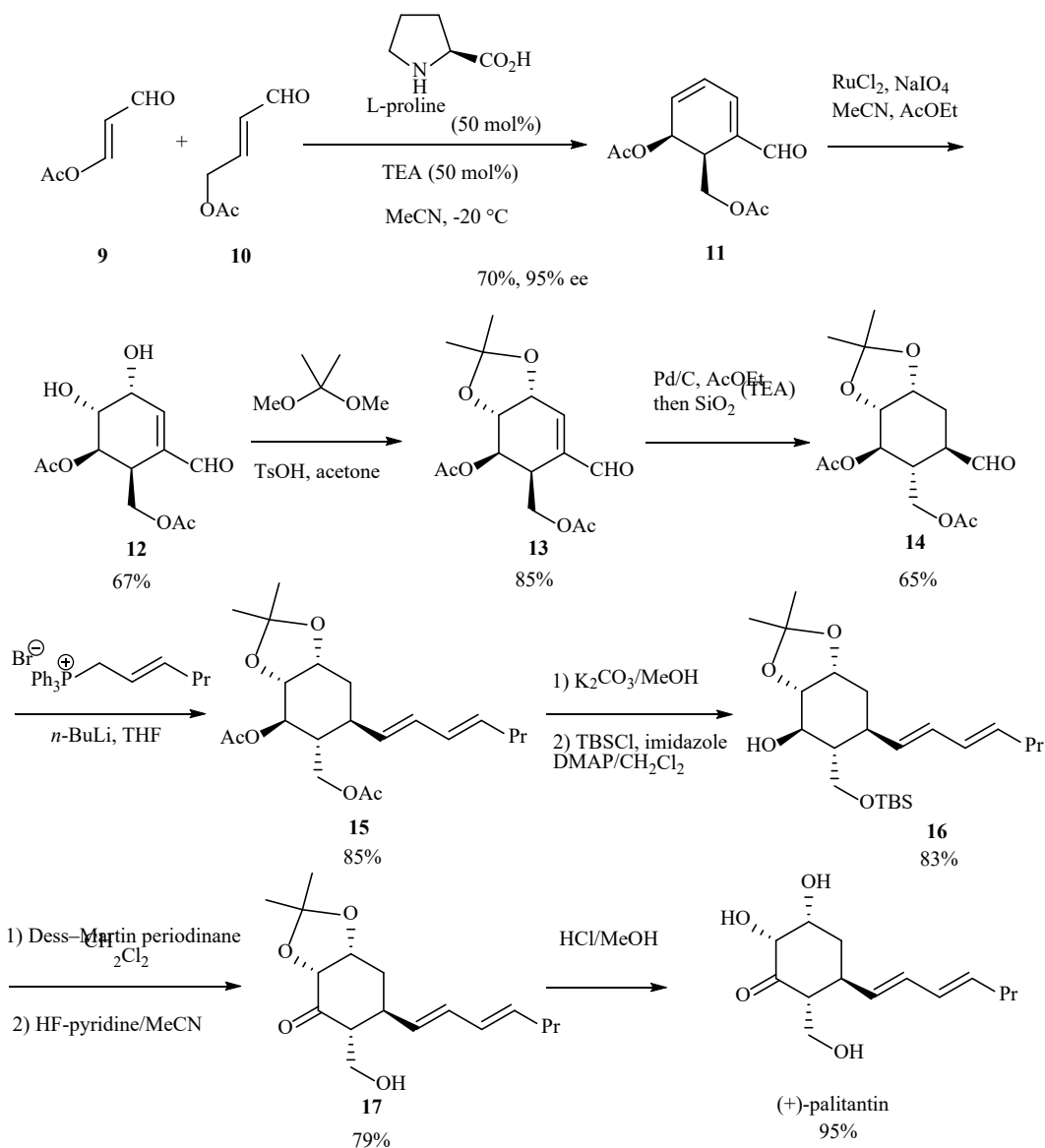
Proline-derived organocatalysts are among the most employed organocatalysts [57,58]. An early example of using this type of organocatalysts in total synthesis of bioactive products was reported in 2006 by Itoh et al. (Scheme 1) [59]. It dealt with the synthesis of alkaloid (+)-coniine, which is a neuro-muscular blocking agent inducing respiratory paralysis. The strategy of the synthesis was based on an asymmetric three-component Mannich reaction organocatalyzed by L-proline. Indeed, the reaction between acetone **1**, *p*-anisidine **2** and 5-hydroxypentanal **3** led to the corresponding chiral Mannich product **4** in both high enantioselectivity (91% ee) and yield (76%). The conversion of this key product into desired (+)-coniine was achieved through seven steps, beginning with its cyclization into piperidine **5** through Mitsunobu reaction followed by reduction of the latter with NaBH₄ to give **6** in 66% yield (2 steps). Subsequently, intermediate **6** was mesylated and then reduced with LiAlH₄ to give **7** in 82% yield (2 steps). Then, CAN oxidation of **7** followed by Cbz protection led to product **8** in 86% yield (2 steps). A final catalytic hydrogenation of **8** afforded (+)-coniine hydrochloride in quantitative yield.



Scheme 1. Synthesis of (+)-coniine.

Later in 2007, a total synthesis of natural product (+)-palitantin, exhibiting anti-HIV, antibiotic, and antifungal activities, was disclosed by Hong et al. [60]. The key step of the synthesis consisted in an enantioselective L-proline-catalyzed Robinson annulation between α,β -unsaturated aldehydes **9** and **10**, which afforded almost enantiopure (95% ee) cyclohexadiene carbaldehyde **11** in good yield (70%) (Scheme 2). This key intermediate was converted into expected (+)-palitantin through nine supplementary steps, beginning with its dihydroxylation into diol **12** achieved with 67% yield. Diol **12** was then protected into acetonide **13** with 85% yield, and then hydrogenation yielded aldehyde **14** in 65% yield. Wittig reaction of the latter with (2*E*)-hexenyl triphenylphosphonium bromide led to diene **15** in 85% yield. Further hydrolysis of **15** followed by protection provided alcohol **16** in 83% yield. Subsequent oxidation of **16** by Dess–Martin periodinane, followed by deprotection of

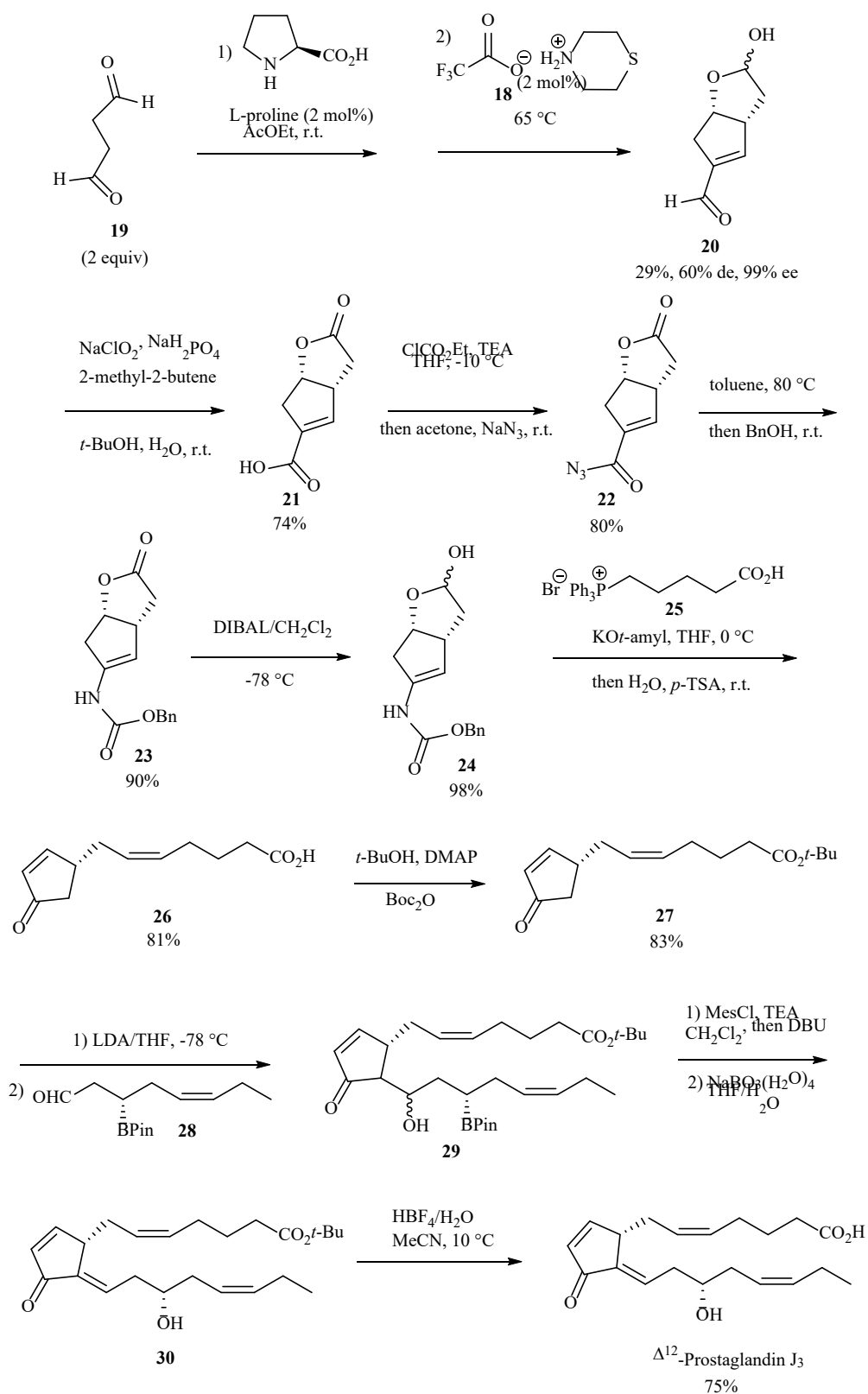
the TBS ether provided acetonide **17** with 79% yield. Finally, deprotection of acetonide **17** afforded (+)-palitantin in 95% yield.



Scheme 2. Synthesis of (+)-palitantin.

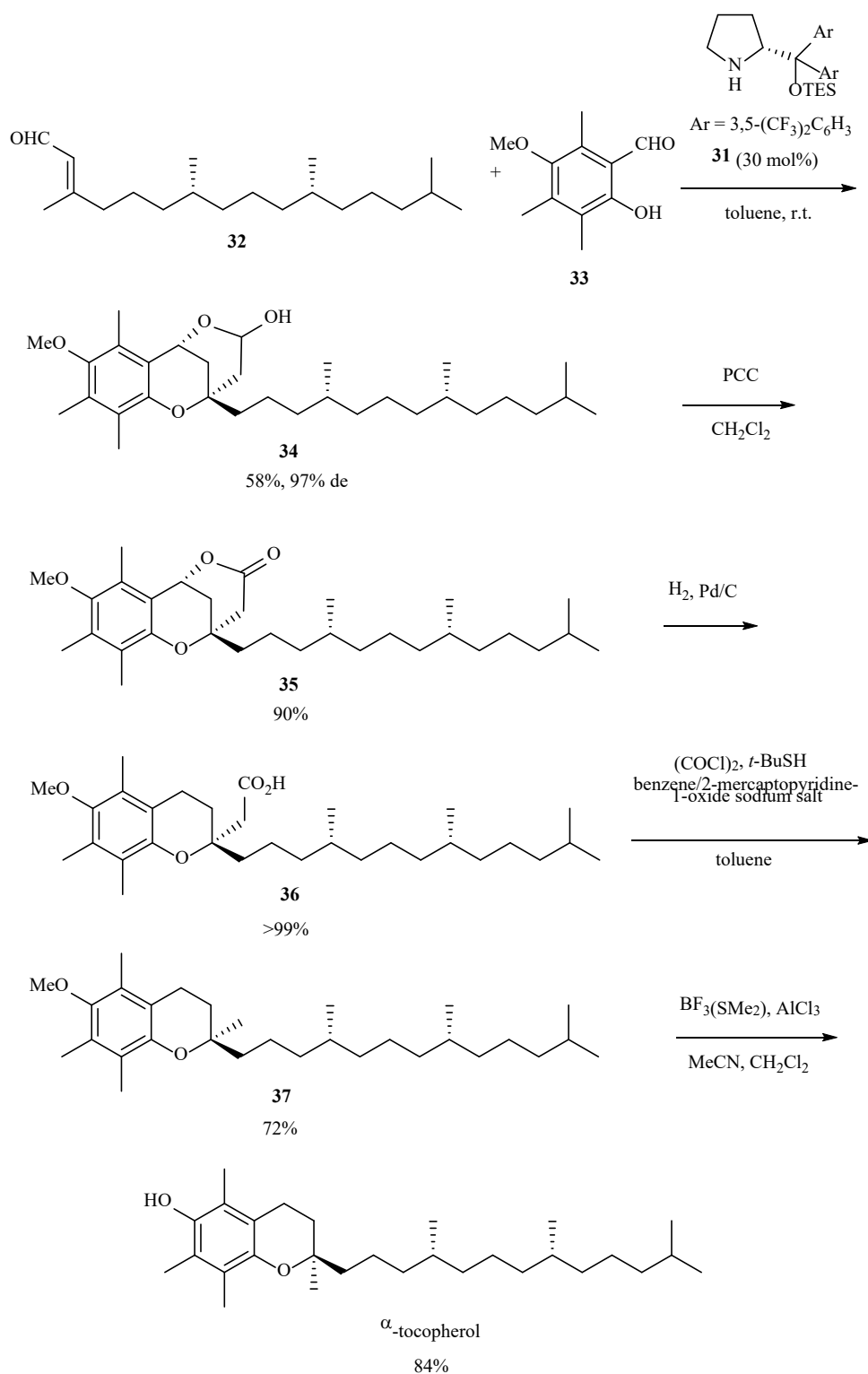
In 2018, an enantioselective tandem double aldol reaction catalyzed by simple L-proline and achiral thiomorpholinium trifluoroacetate **18** was developed by Aggarwal et al. as key step in a total synthesis of Δ^{12} -prostaglandin J₃ exhibiting anti-leukemic properties [61]. This one-pot two-step aldol dimerization of succinaldehyde **19** led to the corresponding chiral bicyclic enal

intermediate **20** in 29% yield, 60% de and 99% ee (Scheme 3). This product was converted through ten supplementary steps into Δ^{12} -prostaglandin J₃. The sequence began with the oxidation of the aldehyde group in **20** into carboxylic acid **21** with 74% yield. Then, the latter was converted into acyl azide **22** in 80% yield. Heating **22** in toluene effected a Curtius rearrangement leading to an isocyanate, which was trapped with benzyl alcohol to give carbamate **23** in 90% yield. The latter was then reduced to hemiacetal **24** in the presence of DIBAL with 98% yield. Then, Wittig reaction of **24** with phosphonium salt **25** provided the corresponding enamide which was not isolated but directly hydrolyzed and then dehydrated to afford enone **26** in 81% yield. The latter was further converted into *t*-butyl ester **27** in 83% yield. This product subsequently underwent aldol condensation with β -boryl aldehyde **28** to give alcohol **29** 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 exclusively the corresponding *E*-configured elimination product. The resulting boronic ester was oxidized into secondary alcohol **30** using NaBO₃(H₂O)₄ in 23% overall yield (3 steps). Finally, treatment of **30** with HBF₄ yielded expected Δ^{12} -prostaglandin J₃ in good yield (75%).



Scheme 3. Synthesis of Δ^{12} -prostaglandin J₃.

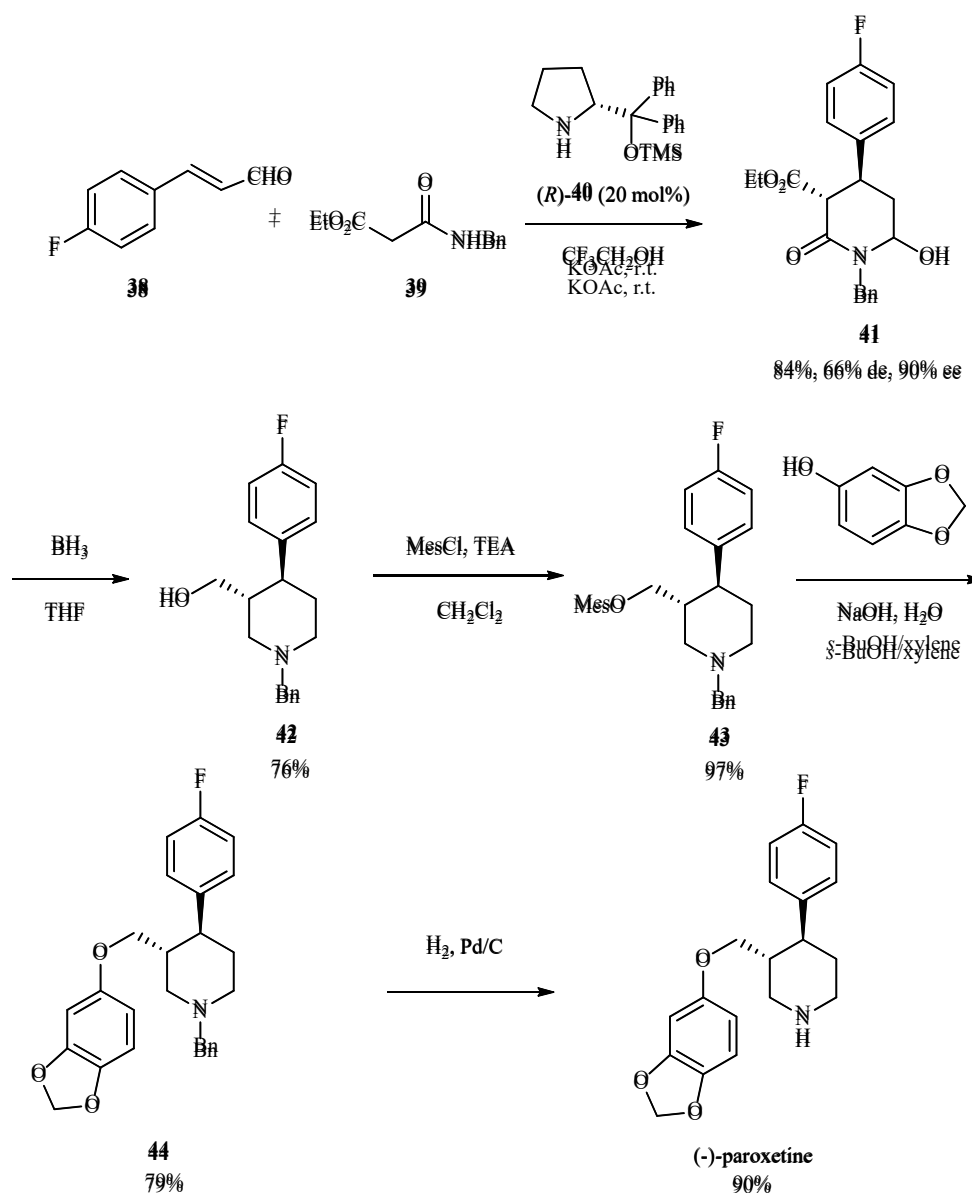
However, proline-derived catalysts have assumed higher and higher importance and are often named “Jorgensen-Hayashi” catalysts. In 2008, a synthesis of the most important member of the vitamin E family, namely α -tocopherol, was developed by Woggon et al. on the basis of an enantioselective domino aldol/oxa-Michael reaction (Scheme 4) [62]. Proline-derived amine catalyst **31** was employed to promote this reaction between α,β -unsaturated aldehyde **32** and aldehyde **33**, which led with moderate yield (58%) to chiral tricyclic hemiaminal **34** as almost single diastereomer (97% de). This key product could be transformed into desired α -tocopherol in only four steps. The first one consisted in its oxidation with PCC into lactone **35** achieved with 90% yield. Then, this benzylic lactone was quantitatively hydrogenated into carboxylic acid **36**, which was further submitted to a Barton decarboxylation procedure to give α -tocopherol ether **37** in 72% yield and 94% de. Final cleavage of the methyl ether of **37** by treatment with $\text{BF}_3(\text{SMe}_2)/\text{AlCl}_3$ yielded expected α -tocopherol with 84% yield.



Scheme 4. Synthesis of α -tocopherol.

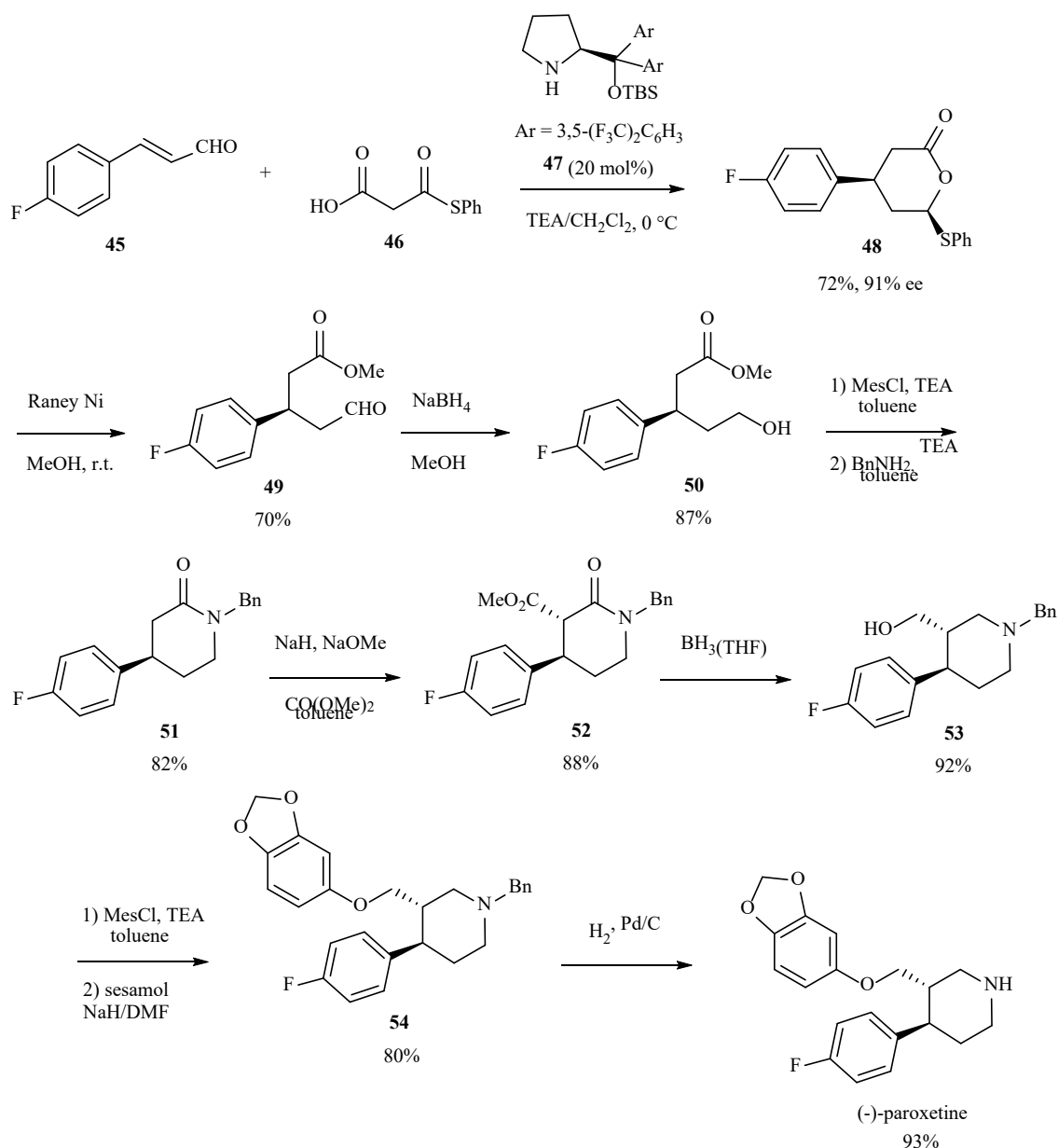
In 2009, Rios et al. described a highly enantioselective synthesis of piperidines through domino Michael/cyclization reaction of α,β -unsaturated aldehydes **38** with amidomalonates

39 catalyzed by chiral proline-derived amine (*R*)-**40** [63]. Among these products, chiral piperidine **41**, obtained with 84% yield, 66% de and 90% ee, was used as key intermediate in a synthesis of (-)-paroxetine which is a selective serotonin reuptake inhibitor drug. As shown in Scheme 5, domino product **41** was further converted into primary alcohol **42** with 76% yield by treatment with BH₃. After subsequent protection of the latter into the corresponding mesylate **43** achieved with 97% yield, etherification with sesamol led to product **44** with 79% yield. A final deprotection of the *N*-benzyl group in **44** through hydrogenation afforded expected (-)-paroxetine in 90% yield.



Scheme 5. Synthesis of (-)-paroxetine.

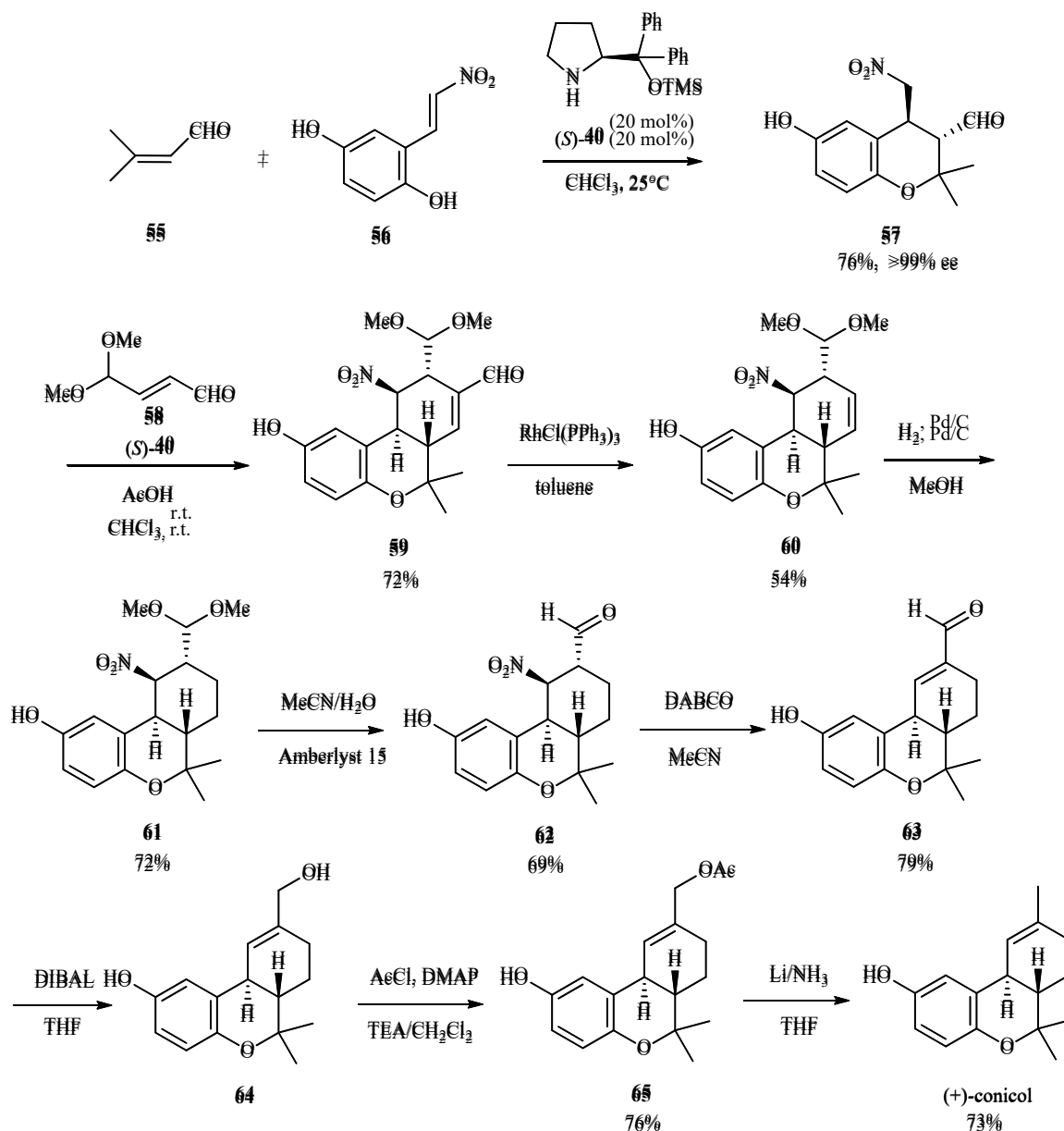
Later in 2014, Wang and Sun described another synthesis of (-)-paroxetine the key step of which was another asymmetric domino Michael/cyclization sequence [64]. This occurred with 72% yield and 91% ee between α,β -unsaturated aldehyde **45** and malonic half-thioester **46** in the presence of catalyst **47** (Scheme 6). The formed chiral lactone **48** could be further converted in nine supplementary steps into (-)-paroxetine. Firstly, lactone **48** was submitted to nickel-catalyzed ring-opening reaction to give aldehyde **49** in 70% yield. A subsequent reduction of **49** afforded the corresponding chiral primary alcohol **50** in 87% yield. According to previously described works [65], alcohol **50** was mesylated and then submitted to reaction with benzylamine to give the corresponding lactame **51** in 82% yield. A subsequent carboxymethylation gave **52** in 88% yield, which was further reduced into primary alcohol **53** in 92% yield. Then, mesylation followed by reaction with sesamol afforded ether **54** in 80% yield. The latter was finally hydrogenated with 93% yield into expected (-)-paroxetine. This second total synthesis of (-)-paroxetine presents the disadvantage in comparison with that described in Scheme 5 to be longer with 10 steps instead of 5 steps for the former.



Scheme 6. Another synthesis of (-)-paroxetine.

In 2010, Hong et al. developed the first total synthesis of natural and biologically active product (+)-conicol (Scheme 6) [66]. The synthesis involved an enantioselective domino oxa-Michael/Michael reaction of 3-methylbut-2-enal **55** with (*E*)-2-(2-nitrovinyl)-benzene-1,4-diol **56** catalyzed by L-proline-derived secondary amine (*S*)-**40**, which afforded the corresponding enantiopure cycloadduct **57** in good yield (76%). This compound was further implicated in a domino Michael/aldol sequence catalyzed by the same organocatalyst through

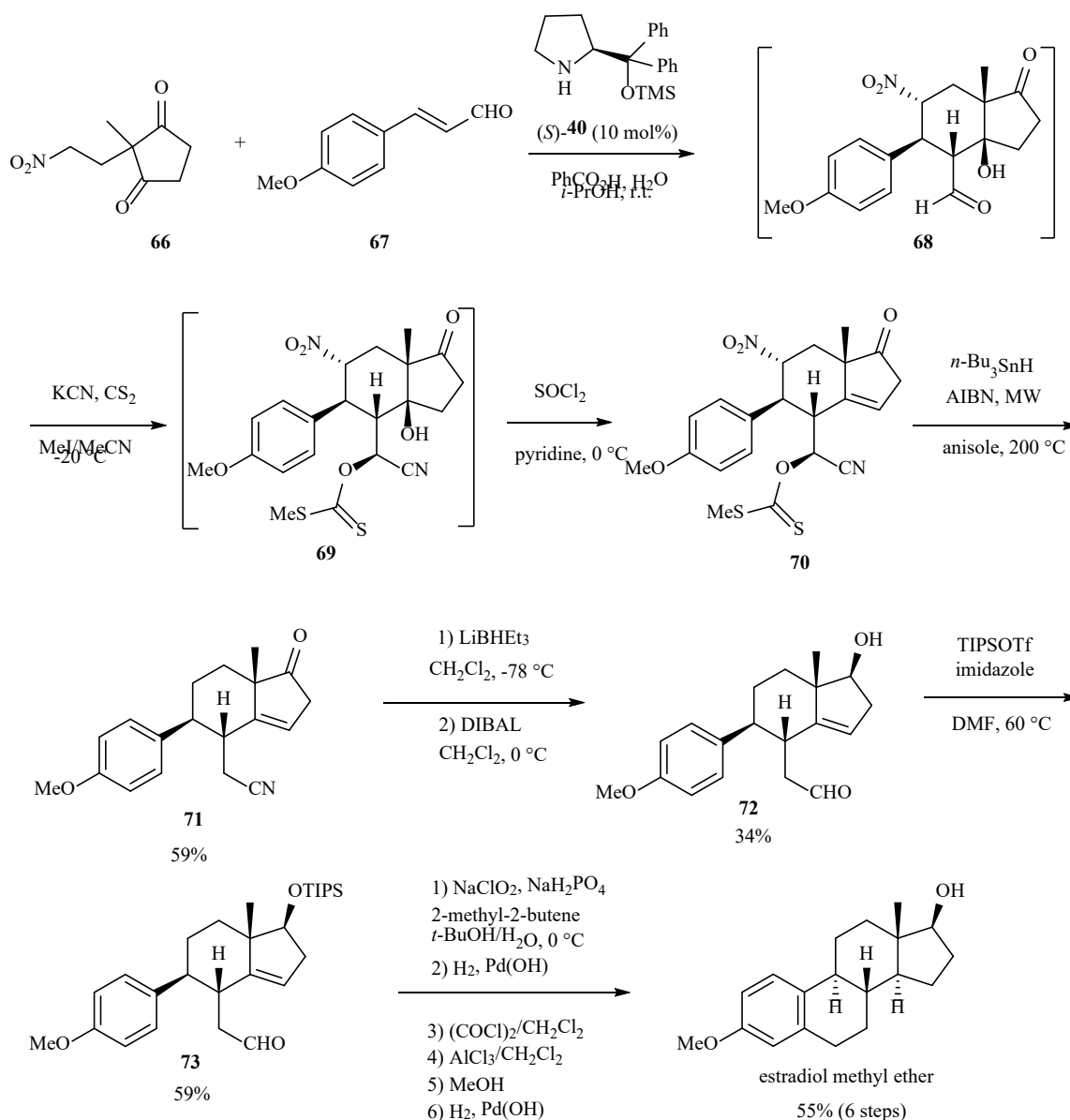
reaction with crotonaldehyde **58**, leading to chiral hexahydro-6*H*-benzo[*c*]chromene **59** in good yield (72%). The latter was submitted to decarbonylation in the presence of Wilkinson catalyst to give alkene **60** in moderate yield (54%). Then, hydrogenation of **60** provided **61** in 72% yield. Hydrolysis of the dimethoxymethyl group in **61** gave product **62** in 69% yield. A subsequent denitration elimination of **62** performed with DABCO led to **63** in 79% yield. Reduction of **63** with DIBAL afforded primary alcohol **64** in 73% yield. A further acetylation of **64** yielded acetate **65** in 76% yield, which finally underwent lithium reduction to provide expected (+)-conicol with 73% yield.



Scheme 7. Synthesis of (+)-conicol.

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 a proline-derived organocatalyst [67]. Indeed, the first step of the sequence consisted in an enantioselective domino Michael/aldol reaction of nitroalkane **66** with α,β -unsaturated aldehyde **67** catalyzed by chiral amine (S)-**40** to give the corresponding enantiopure bicyclic product **68**. This highly functionalized bicyclo[4.3.0]nonane was not isolated but directly

submitted to stereoselective addition of KCN to the carbonyl group of the aldehyde, and then generation of xanthate ester **69**. Again, the latter was not isolated but directly dehydrated upon further addition of SOCl₂ in the presence of pyridine to provide enantiopure cyclopentene **70** in 78% yield (3 steps). Subsequently, treatment of **70** with HSnBu₃ in the presence of AIBN resulted in the hydrogenolysis of both the nitro and the xanthate ester groups to give intermediate **71** in 59% yield. Then, the ketone moiety in **71** was submitted to diastereoselective reduction in the presence of LiBHET₃ to give the corresponding chiral alcohol. The latter was not isolated but directly treated with DIBAL which resulted in the conversion of the nitrile group into a formyl moiety. The formed hydroxy aldehyde **72** was obtained in 34% yield for the two-step one-pot reaction. The next step was the protection of **72** into the corresponding silyl ether **73** with 59% yield. The latter was then submitted to a one-pot cascade of six reactions detailed in Scheme 8, involving successively a Kraus–Pinnick oxidation, an 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 consisted finally in only five one-pot reactions 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% [68].

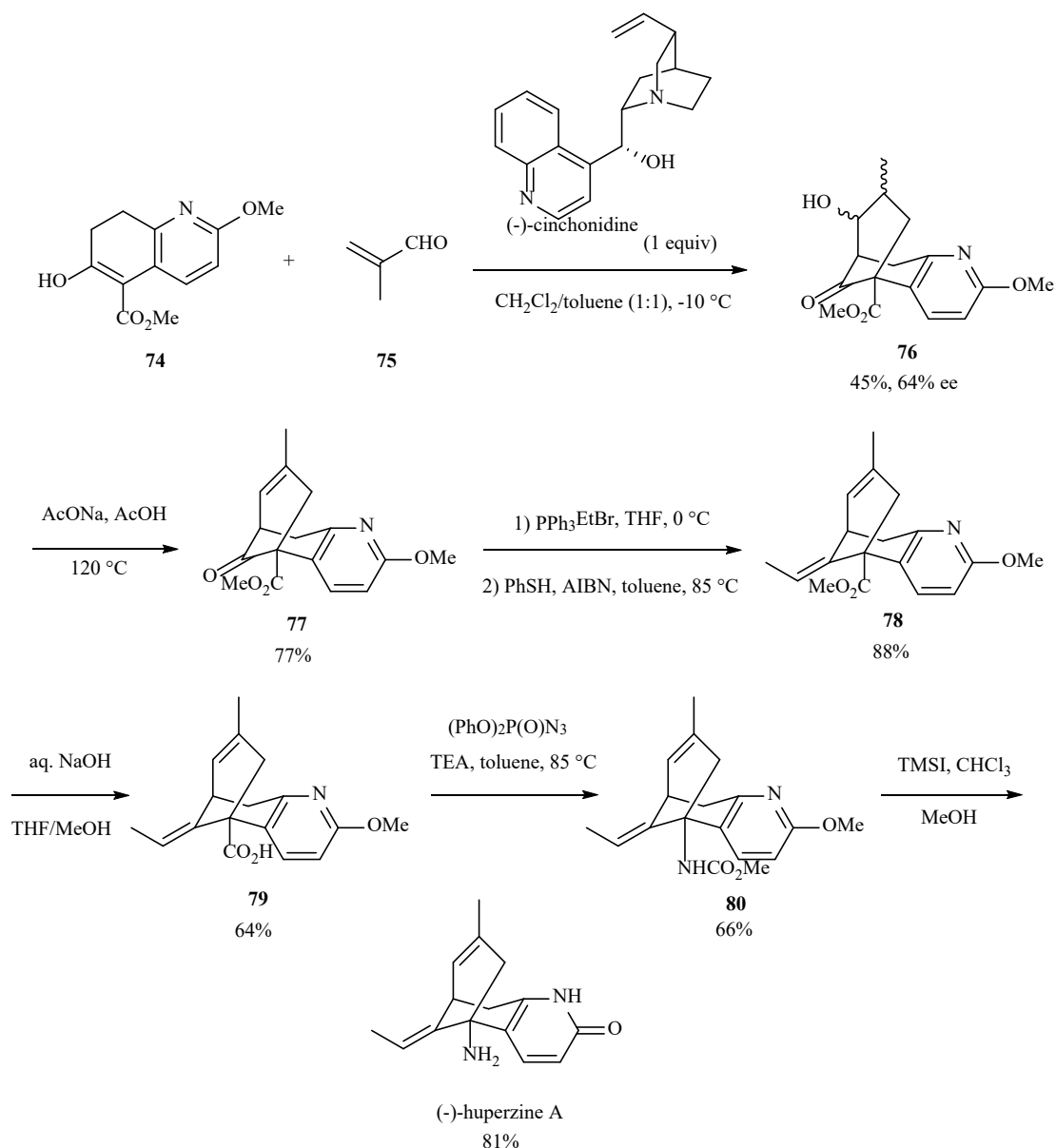


Scheme 8. Synthesis of estradiol methyl ether.

3 Other organocatalysts

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 [69]. As shown in Scheme 9, the key step of this short synthesis consisted in an enantioselective domino Michael/aldol reaction between β -keto ester **74** and methacrolein **75** organocatalyzed

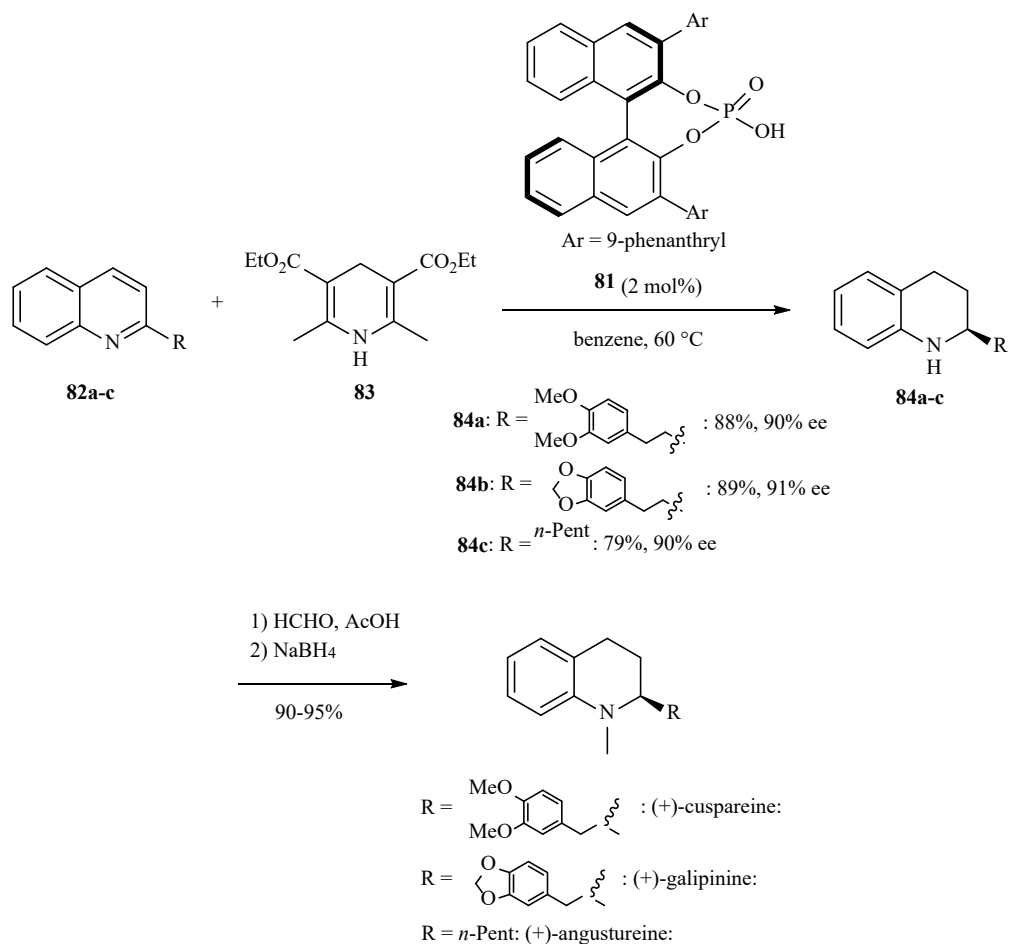
by (-)-cinchonidine, leading to chiral key tricyclic product **76** in both moderate yield (45%) and enantioselectivity (64% ee). The latter was further converted through six supplementary steps detailed in Scheme 1 into expected (-)-huperzine A. In a first step, domino product **76** was submitted to dehydration in the presence of acetic acid to give product **77** in 77% yield. The second and third steps consisted in a Wittig reaction of **77** with ethylenetriphenylphosphorane followed by isomerization of the ethylidene moiety to afford (*E*)-configured ethylenic product **78** in 88% yield (2 steps). A subsequent alkaline hydrolysis of this product led to the corresponding carboxylic acid **79** in 64% yield. Then, a modified Curtius rearrangement of the latter gave amide **80** in 66% yield, which was finally submitted to deprotection in the presence of TMSI to provide expected (-)-huperzine A in 81% yield.



Scheme 9. Synthesis of (-)-huperzine A.

Later in 2006, chiral phosphoric acid **81**, 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 [70]. Indeed, Brønsted acid **81** was found to catalyze highly enantioselectively the cascade transfer hydrogenation of 2-substituted quinolines **82a-c** with Hantzsch ester **83**. As shown in Scheme 10, this one-pot double-transfer hydrogenation afforded the corresponding chiral tetrahydroquinolines **84a-c** in both high yields (79-89%)

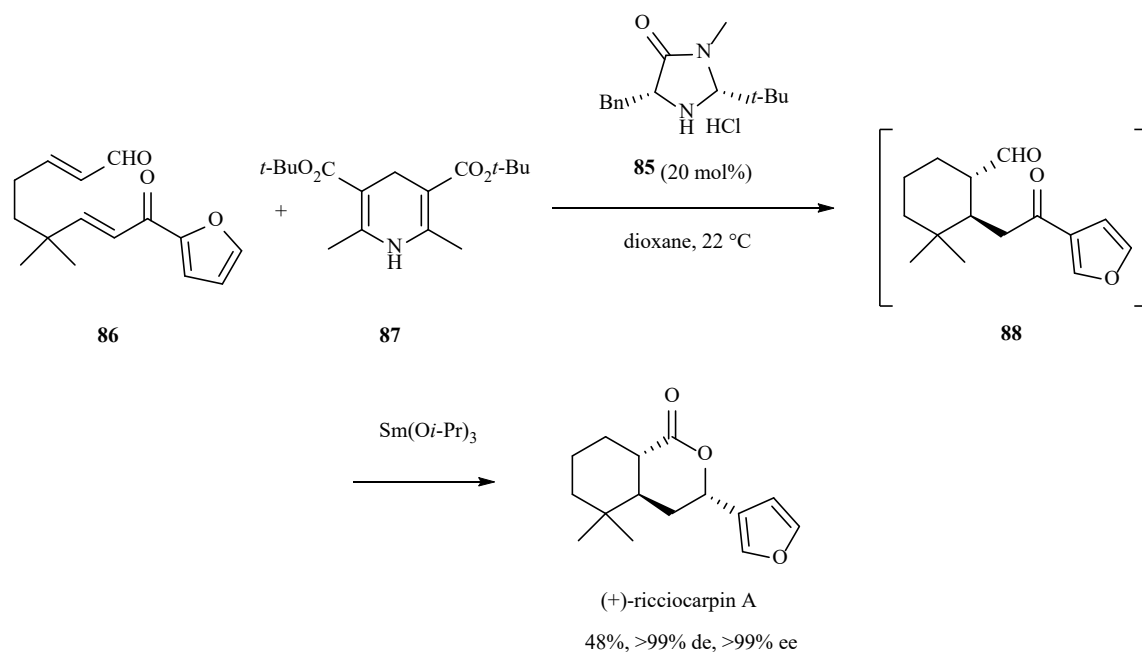
and enantioselectivities (90-91% ee). The latter were further *N*-methylated to give expected (+)-cuspareine, (+)-galipinine and (+)-angustureine in excellent yields (90-95%).



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

In 2009, List and Michrowska employed a chiral imidazolidinone catalyst, such as **85**, to promote enantioselective domino conjugate reduction/Michael cyclization reaction between aldehyde **86** and Hantzsch ester **87** [71]. This reaction allowed the synthesis of chiral ketoaldehyde **88** to be achieved. The latter was not isolated, but directly submitted to Sm(Oi-Pr)₃, undergoing isomerization followed by a highly diastereoselective Tishchenko reaction, which yielded ricciocarpin A, an anti schistosomiasis agent. Remarkably, this natural product

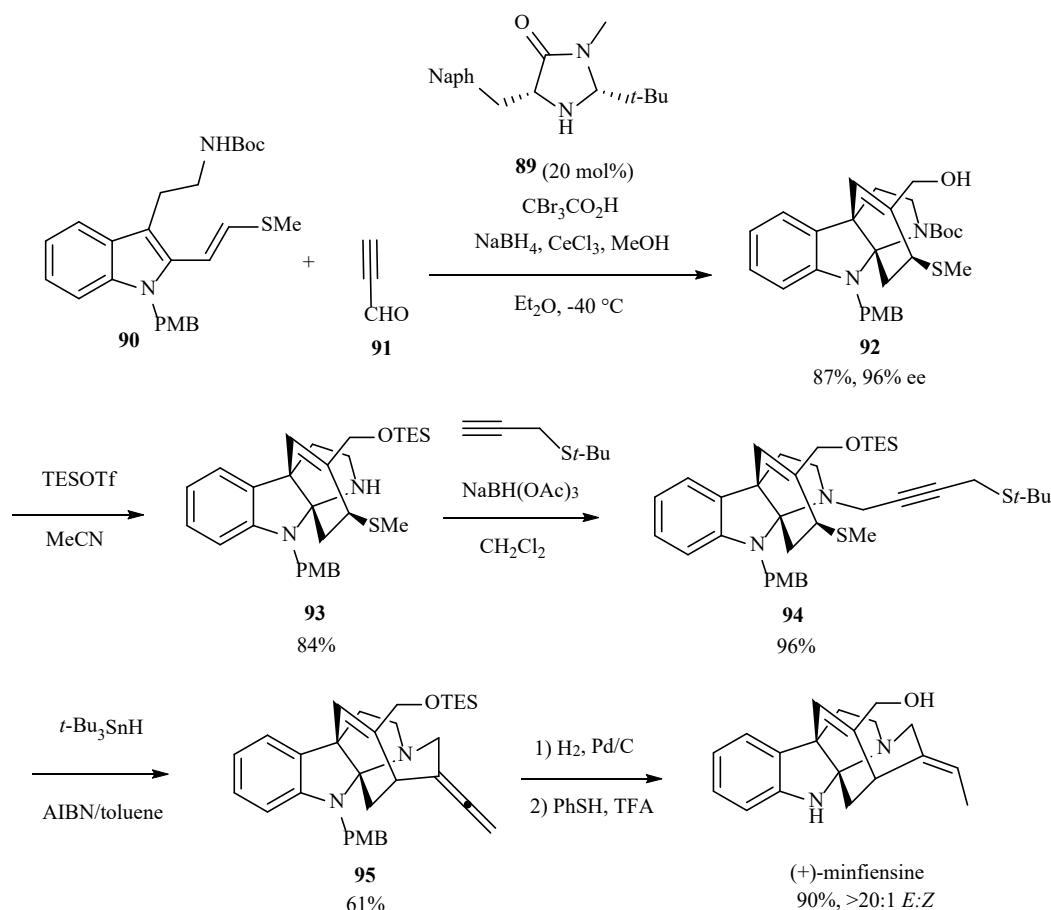
was obtained as a single diastereo- (>99% de) and enantiomer (>99% ee) in 48% yield (Scheme 11). This synthesis of ricciocarpin A represented the shortest reported so far.



Scheme 11. Synthesis of ricciocarpin A.

The indole skeleton is widely expanded in medicinal chemistry [72,73]. The same year, MacMillan et al. reported a total synthesis of natural and biologically active (-)-minfiensine the key step of which was an highly enantioselective organocatalytic domino Diels–Alder/amine cyclization reaction building the central tetracyclic pyrroloindoline framework of (-)-minfiensine (Scheme 12) [74]. Indeed, the reaction of 2-vinylindole **90** with propynal **91** organocatalyzed by chiral imidazolidinone **89** led to the corresponding chiral tetracyclic pyrroloindoline **92** in both high yield (87%) and enantioselectivity (96% ee). This carbamate was further converted through only five steps into (-)-minfiensine. The first step consisted in the treatment of **92** by TESOTf to provide silyl ether **93** in 84% yield. A reductive amination of this secondary amine **93** with butynal *t*-butyl sulfide was performed in the presence of $\text{NaBH}(\text{OAc})_3$ to give intermediate **94** in 96% yield. The latter was further

submitted to a radical cyclization, affording allene **95** with 61% yield. Hydrogenation of this allene followed by deprotection in the presence of TFA led to final (-)-minfiensine in both high yield (90%) and *E/Z* diastereoselectivity (>20:1).



Scheme 12. Synthesis of (-)-minfiensine.

4 Conclusion

This chapter collects major developments in the use of enantioselective organocatalytic domino/tandem processes for the total synthesis of bioactive products. It demonstrates that a wide 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 most employed organocatalysts employed in these syntheses are proline-derived secondary amines which have allowed 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 types of chiral organocatalysts, such as chiral 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 also gave success 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 organocatalytic asymmetric domino and tandem methodologies were undoubtedly applied as key economic steps in the total synthesis of other bioactive products in the near future.

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