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Conhydrine: An Account of Isolation, Biological Perspectives and Synthesis

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Abstract: Conhydrine is a naturally occurring 2-substituted piperidine alkaloid from the plant *Conium maculatum L* that exists in four different forms and is known for its high toxicity. This article focuses on the synthesis of conhydrine as its medicinal applications are limited due to its high toxicity. The various asymmetric methods developed for the synthesis of conhydrine are classified based on the methodology: the chiral pool method, the chiral auixiliary method, and asymmetric catalysis. A brief overview of the complete synthetic coverage of conhydrine (1948–2014) in different isomeric forms is given.

Key words: conhydrine, organocatalysis, enantioselective, synthesis, piperidine alkaloid

1 Introduction

1,2-Amino alcohols are ubiquitous among various natural products and they have attracted considerable synthetic interest due to their interesting medicinal and pharmacological applications.[1,2] Many of these compounds are cyclic pyrrolidine and piperidine ring structures with a 1-hydroxyalkyl side chain at the 2-position, and these have wide medicinal relevance for the treatment of various diseases.[3] The piperidine nucleus with a hydroxylated side chain has special synthetic interest due to its anti-HIV, antiviral, and antitumor activity.[2,4] Moreover, these molecules are basically small organic compounds that have facile synthetic approaches and, hence, they are highly beneficial from industrial and practical points of view. Most of these appendages are derived from easily available starting materials, and various unnatural analogues of such entities have been synthesized and in clinical trials in recent years. The design and synthesis of such natural and unnatural components has been a formidable challenge for chemists due to difficulties in isolation, global scarcity, and high pharmacological demand.

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Conhydrine is one such alkaloid comprising of a simple piperidine unit tethered to 1-hydroxyalkyl side chain that finds special synthetic interest due to its unique biological properties and vicinal chiral hydroxy and amino functionalities.

2 Isolation and Biological Perspectives

Conhydrine is a piperidine alkaloid from the hemlock family first isolated by Wertheim from the leaves and

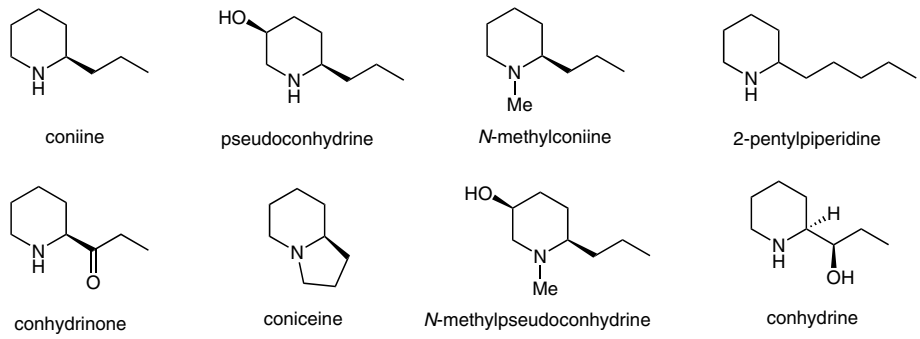


Figure 1 Alkaloids isolated from *Conium maculatum L*

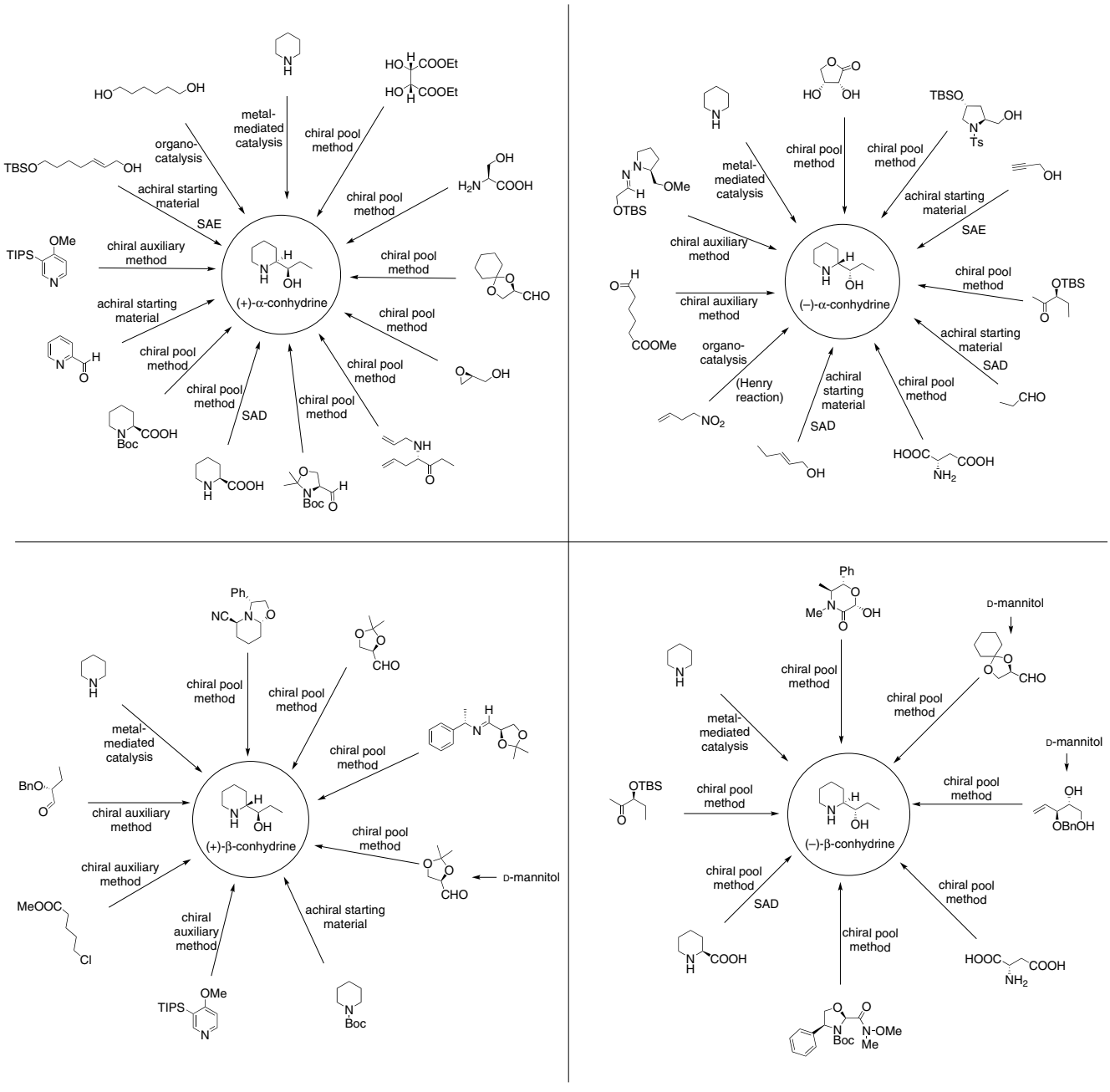


Figure 2 The different methods of chiral induction for conhydrine

seeds of plant *Conium maculatum L* in 1856;[5] its structure was elucidated in 1933.[6] *Conium maculatum L* is a highly poisonous hemlock that belongs to the family of Apiaceae, which is widespread throughout the world, including Australia, New Zealand, North America, and different parts of Asia. In ancient Greece, an extract of hemlock was used for the execution of criminals; the Greek philosopher Socrates was condemned to death in 399 BC and drank hemlock. The seeds of *Conium maculatum* are rich in alkaloids and different piperidine-based alkaloids have been isolated and identified (Figure 1).[7] Among them coniine and γ-coniceine are the most abundant and they are hemlocks chronic and acute toxicity is attributed to them. The consumption of this plant affects the central nervous system (CNS), causes depression, paralysis, hyperventilation, coma, and even death.[7]

Clinical studies show that the presence of an aliphatic side chain in the 2-position consisting of at least three carbons is responsible for the enhanced toxicity of these alkaloids. These alkaloids have been screened for various other biological applications, but their medicinal application is limited due to closeness of their therapeutic and poisonous values. However, hemlock has found useful medical applications in homeopathic medicine with the name conium, and it is best utilized for the treatment of various diseases including breast cancer.[8]

3 Synthesis

The present article reviews the synthesis of conhydrine by various synthetic approaches. It covers all the synthetic methods to conhydrine from the first synthesis in 1948 to recent synthesis in 2014. Figure 2 describes the various chiral approaches using different starting material for the synthesis of conhydrine in all the four different isomeric forms. Accordingly the review is broadly organized according to the asymmetric method of synthesis: chiral pool methods, starting from achiral materials, using chiral auxiliary mediated synthesis, and using the catalysis approach (organo and metal catalysis).

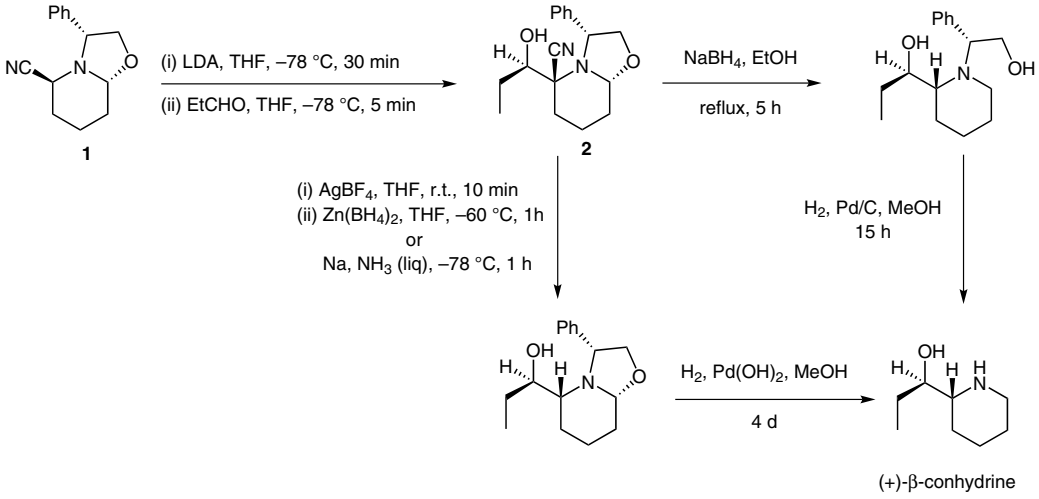
3.1 Chiral Pool Methods

This method mainly involves multistep synthesis using amino acids and sugar-derived compounds like mannitol as the starting chiral pool material. After the first synthesis of racemic conhydrine by Galinovsky and Mulley using the high pressure hydrogenation of a pyridine derivative,[9] its synthesis remained untouched for a period of 37 years. Husson and co-workers undertook the first enantiospecific synthesis of (+)-β-conhydrine by illustrating the potential application of chiral synthon **1** (Scheme 1).[10]

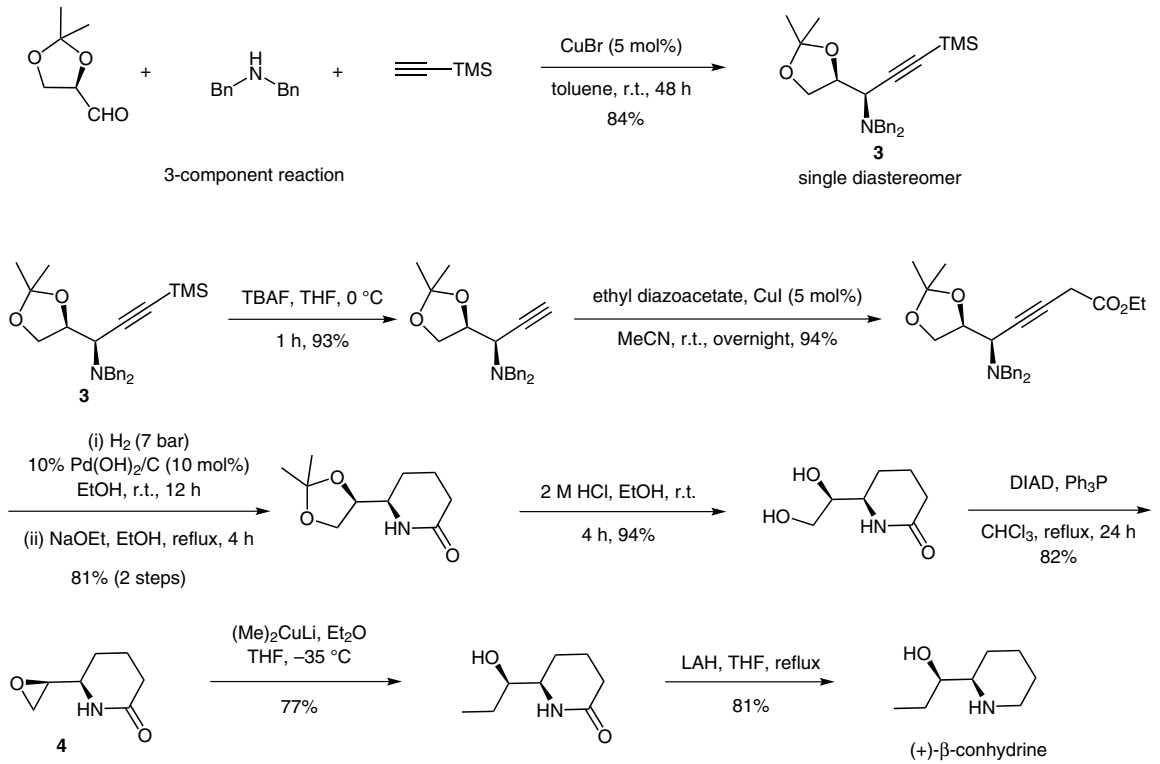
The generation of the anion next to the nitrogen atom followed by alkylation using propionaldehyde delivered the single isomer **2**. Subsequent complete reduction of intermediate **2** produced (+)-β-conhydrine.

The copper-catalyzed three-component reaction of alkyne–dibenzylamine–α-oxyaldehyde permit the construction of α-oxyamines with very high diastereoselectivity. The methodology was initially used by Haung et al. for the construction of *syn*-α-oxyamines[11] and further extended to the synthesis of 1,2-amino alcohol (+)-β-conhydrine by Talukdar and co-workers (Scheme 2).[12] The diastereomer **3**, synthesized by the reaction of the corresponding alkyne, dibenzylamine, and aldehyde using a copper(I) bromide catalyzed one-pot reaction, was further transformed into epoxide **4** using classical synthetic steps. The regio- and stereoselective opening of epoxide **4** using the Gilman reagent lithium dimethylcuprate, followed by subsequent lithium aluminum hydride (LAH) reduction gave (+)-β-conhydrine.

An interesting serendipitous reduction of aliphatic and aromatic carbonyls using cyclopentylmagnesium bromide was observed together with the Grignard addition product by Chattopadhyay and co-workers.[13] However, cyclopentylmagnesium bromide followed normal Grignard addition in the presence of 10 mol% zinc(II) chloride. This

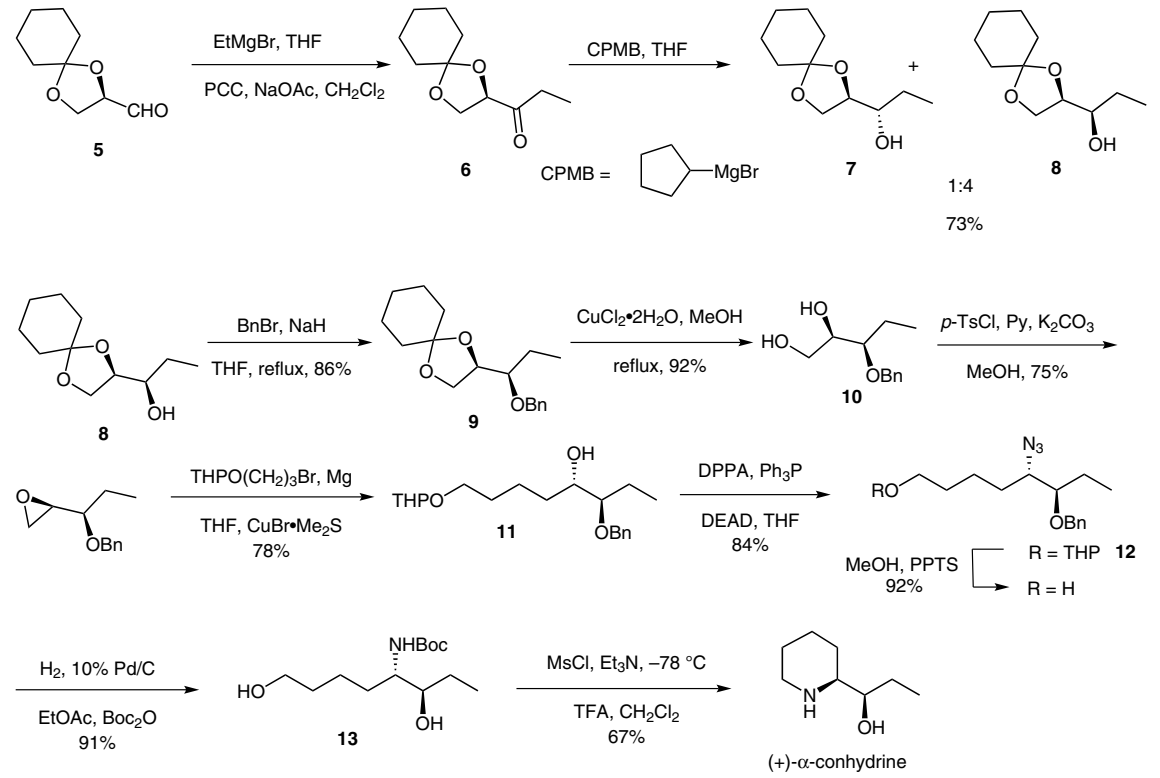


Scheme 1



Scheme 2

interesting behavior of cyclopentylmagnesium bromide was utilized for the synthesis of (+)-α-conhydrine (Scheme 3). To this end, the aldehyde **5**, derived from glyceraldehyde, was converted into ketone **6** and then reacted with cyclopentylmagnesium bromide to give a mixture of secondary alcohols **7** and **8**. The desired alcohol **8**



Scheme 3

was separated and converted into benzyl ether **9** which on deprotection gave the diol **10**. The epoxidation of the diol followed by Grignard reaction with the reagent prepared from $THPO(CH_2)_3Br$ afforded **11**, which on reaction with diphenylphosphoryl azide (DPPA) under Mitsunobu condition produced the azide **12**. The removal of THP and subsequent reduction of azide followed by Boc protection delivered **13**. The mesylation of the terminal hydroxy group and subsequent deprotection of the Boc group afforded (+)-α-conhydrine.

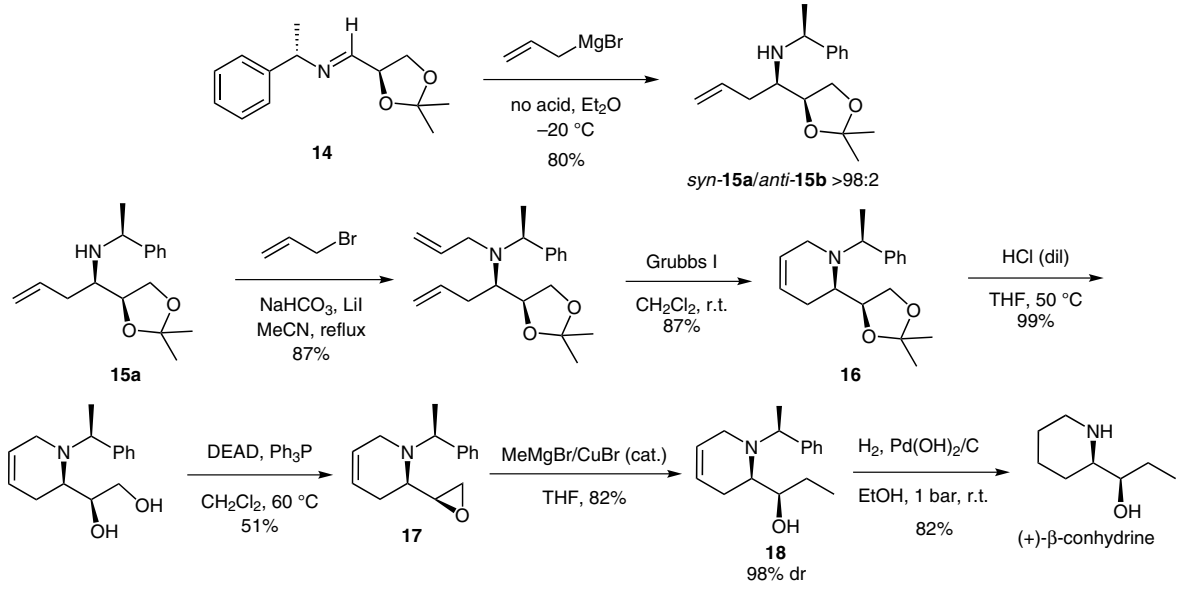
A switch in regioselective opening of a chiral epoxide by changing the organometallic reagent was observed by Gálvez and co-workers (Scheme 4).[14] The imine **14**, synthesized from D-glyceraldehyde, was subjected to diastereoselective addition of allylmagnesium bromide resulting the homoallyl amine **15**. The various acid additives added during the Grignard reaction had an excellent effect in controlling the diastereoselectivity resulting in *syn* and *trans* isomers in different ratios. However, the required *syn* selectivity was achieved without the addition of an acid in 80% yield. The desired *syn* isomer **15a** was subjected to allylation followed by ring-closing metathesis (RCM) resulting in the cyclic product **16**. The subsequent hydrolysis of the acetonide using HCl and epoxidation under Mitsunobu conditions afforded compound **17**. Opening the epoxide **17** using MeMgBr from the less substituted side was achieved in the presence of catalytic copper(I) bromide. Compound **18** was further subjected to hydrogenation to furnish (+)-β-conhydrine.

The stereoselective synthesis of (+)-β-conhydrine was achieved using D-mannitol as a starting chiral source (Scheme 5).[15,16] The protected glyceraldehyde was converted into alcohol **19** by treatment with allyl bromide and zinc under Barbier reaction condition. The alcohol group was then converted into the azide which on subsequent lithium aluminum hydride reduction followed by Boc protection gave compound **20**. The acetal group was hydrolyzed and the resultant diol was subjected to monotosylation under Martinelli conditions;[17] the monotosyl compound on treatment with potassium carbonate afforded the epoxide **21**. Further classical synthetic transformations involving the Grignard reaction, RCM, hydrogenation, and deprotection gave (+)-β-conhydrine.

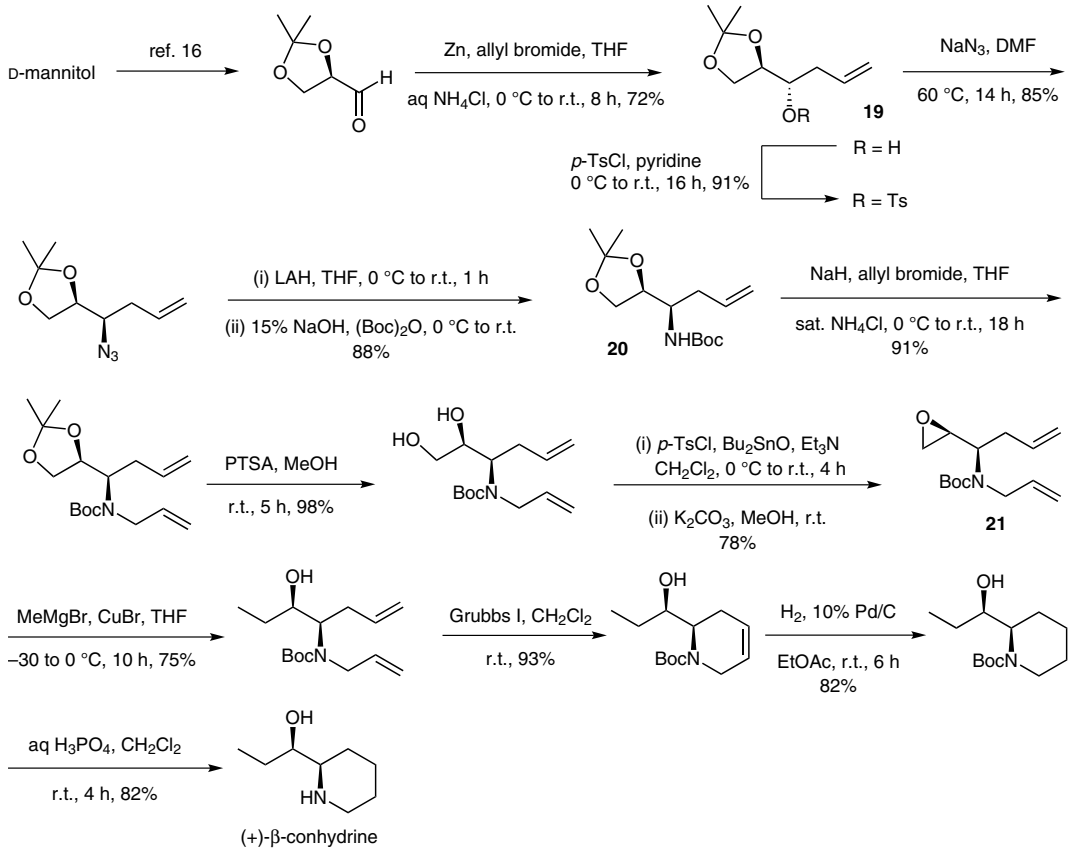
Fadnavis and Venkatiah successfully achieved the stereoselective synthesis of (–)-β-conhydrine, starting from D-mannitol (Scheme 6).[18] Aldehyde **22**, derived from mannitol,[19] was subjected to Grignard reaction to give **23** diastereoselectively. The alcohol **23** was converted into key requisite imine **24** using classical synthetic steps. The Grignard addition of allylmagnesium bromide across the imine bond gave **25** with very high diastereoselectivity. The formation of the *syn* diastereomer was consistent with Cram's chelation model. The imine was then sequentially converted into (–)-β-conhydrine.

Kamal and Vangala achieved the synthesis of (–)-β-conhydrine using D-mannitol as a chiral pool substrate (Scheme 7).[20] The alkene **26**, obtained according to the reported method,[21] was converted into epoxide **27**. The regioselective opening of the epoxide by alkyne **28** followed by reduction, tosylation, and azidation gave **29**. Further tosylation of the primary alcohol **30** followed by azide reduction gave the desired natural product.

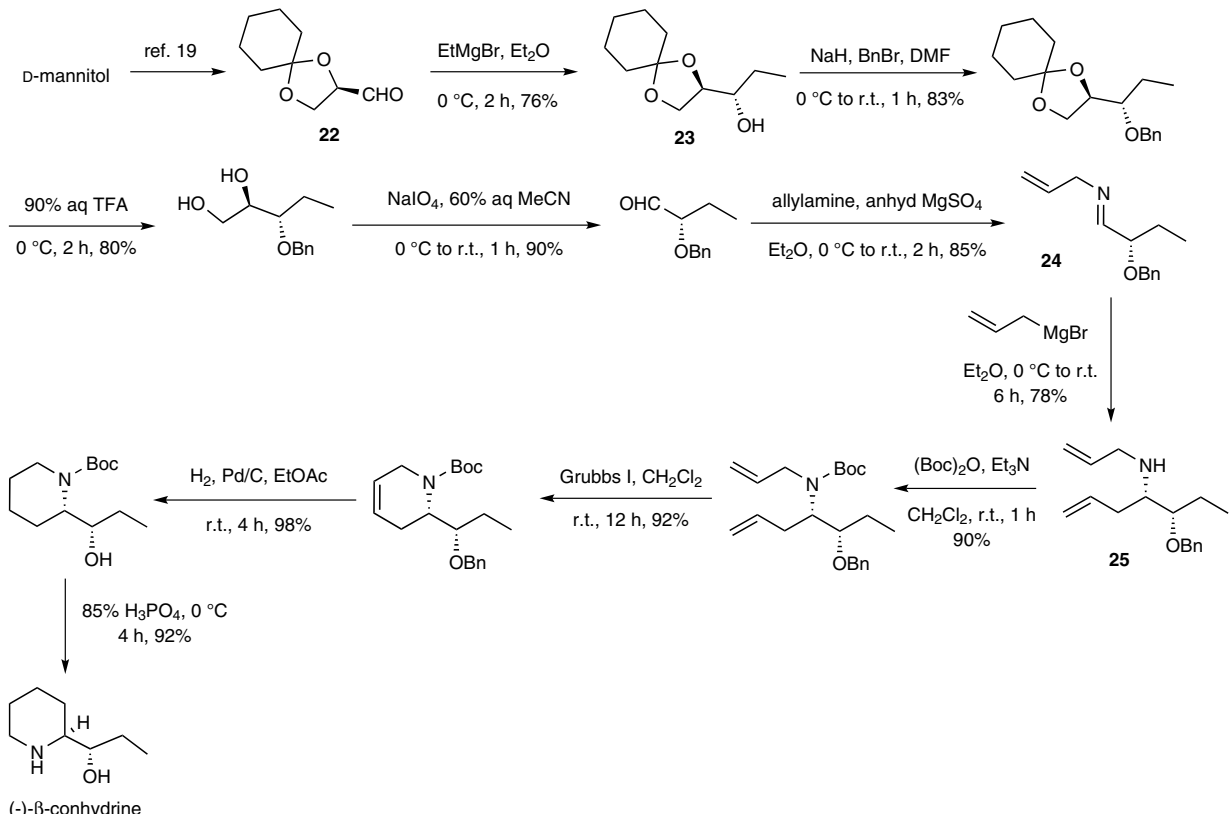
Ham and co-workers synthesized (+)-α-conhydrine utilizing the existing stereocenter of L-serine (Scheme 8).[22] Thus L-serine was converted into carbamate ester **31** by previously reported procedures,[23] Grignard reaction of the amide of **31** afforded the ketone **32**. The reduction of the ketone followed by benzylation of the hydroxy group gave **33**. Subsequent deprotection, oxidation, and Wittig olefination produced the allylamine **34**, which on treatment with homoallyl bromide followed by ring-closing



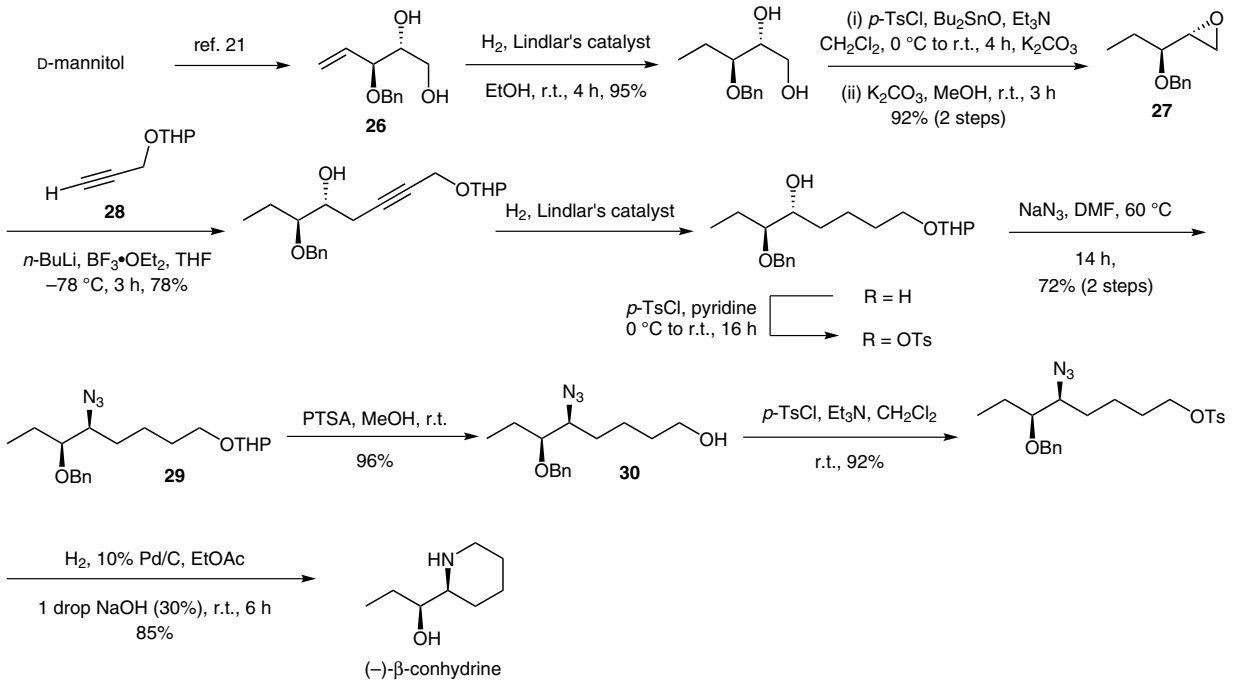
Scheme 4



Scheme 5



Scheme 6

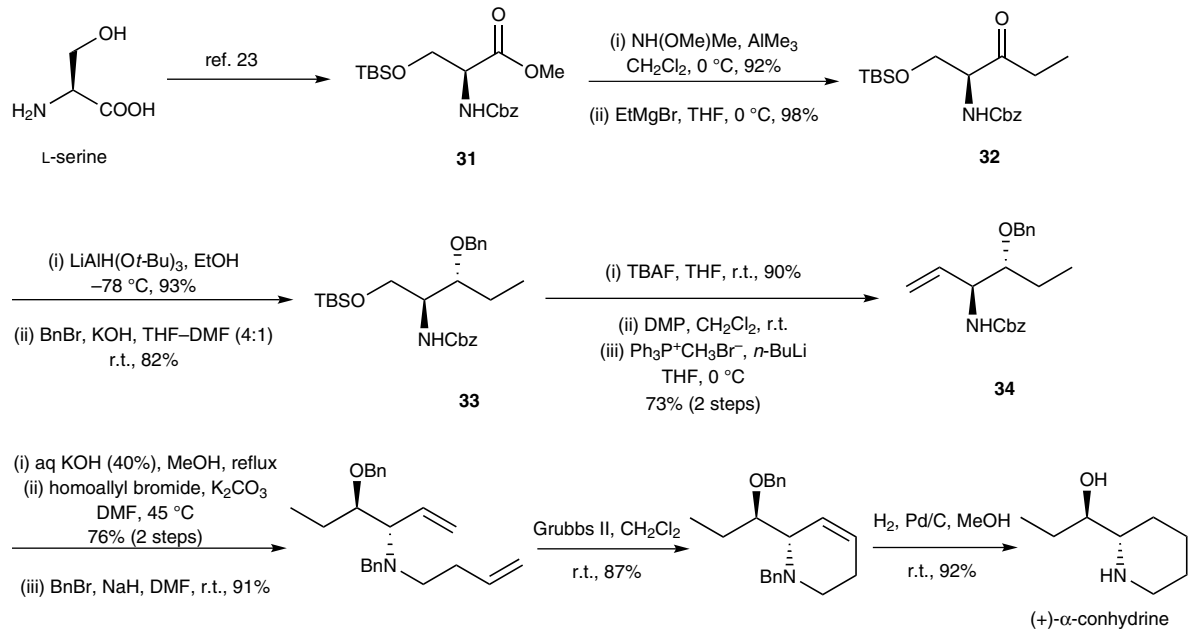


Scheme 7

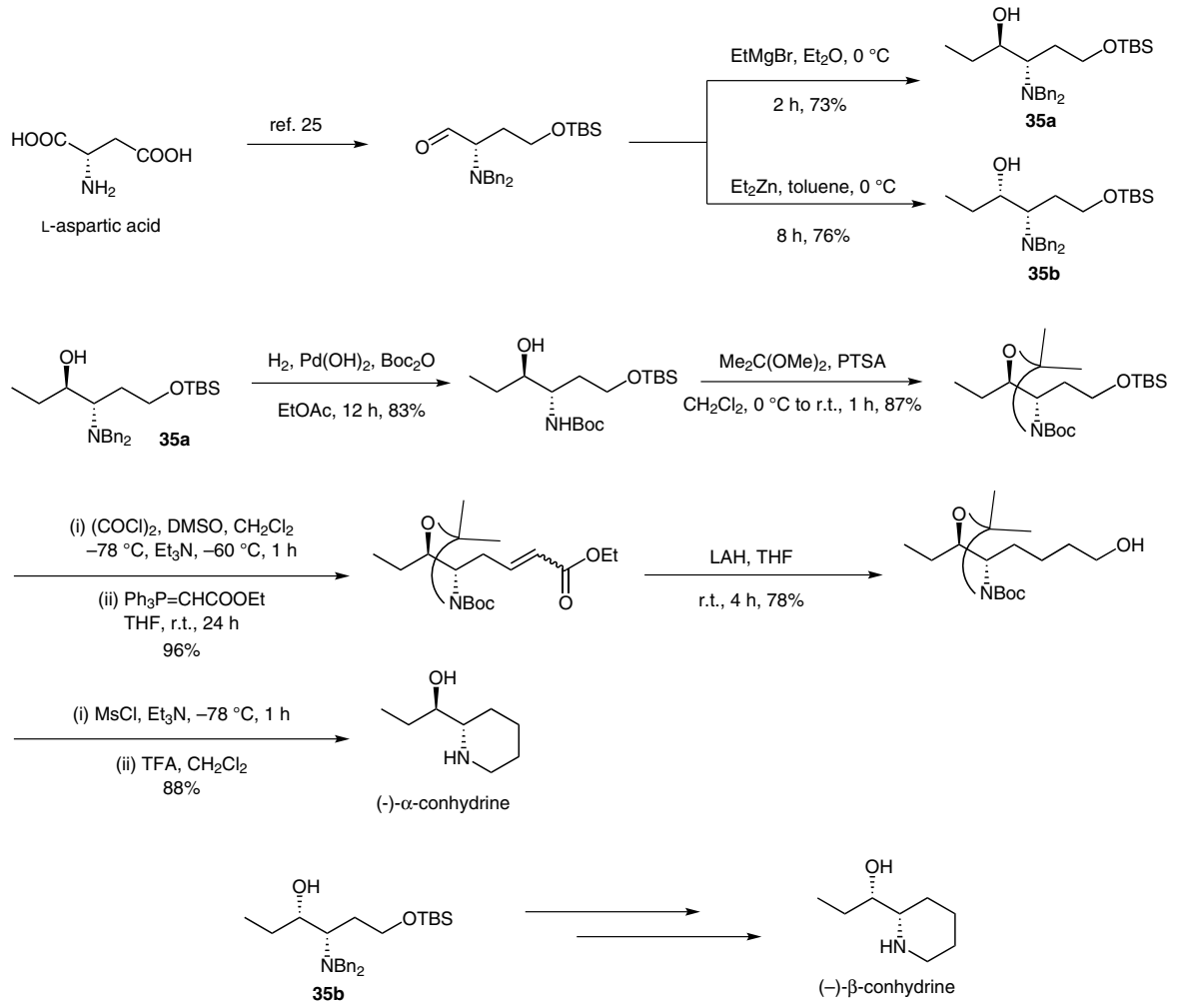
metathesis and hydrogenation furnished (+)-α-conhydrine.

Kumar and Pandey successfully used L-aspartic acid as the starting material in the synthesis of conhydrine (Scheme 9).[24] The commercially available L-aspartic acid was transformed[25] diastereoselectively to *anti* and *syn* alcohols **35a** and **35b** by chelation controlled addition of organometallic reagents. The isomers **35a** and **35b** were then separately converted into (–)-α-conhydrine and (–)-β-conhydrine, respectively, via classical synthetic sequences.

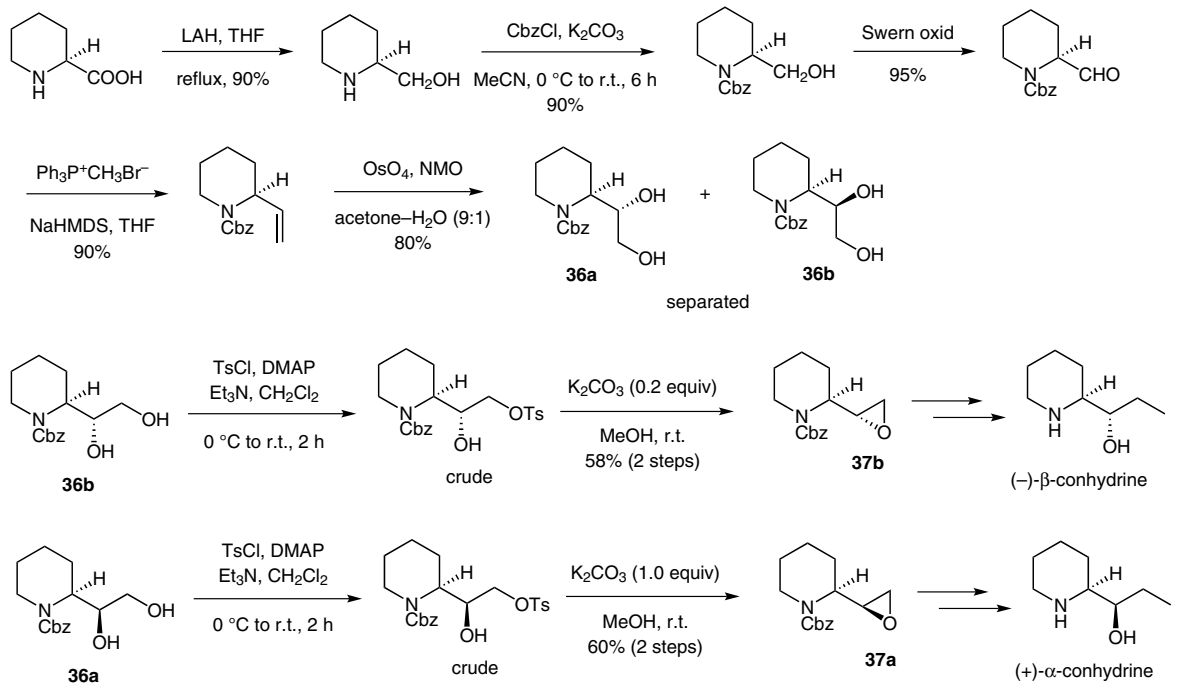
The formal synthesis of (–)-β-conhydrine and (+)-α-conhydrine was accomplished in our laboratory using pipecolinic acid as the chiral source via Wittig and Sharpless asymmetric dihydroxylation (SAD) as the key steps (Scheme 10).[26] The diols **36a** and **36b**, synthesized from pipecolinic acid, were further converted into the corresponding epoxides **37a** and **37b**, respectively, to complete the formal synthesis of (+)-α-conhydrine and (–)-β-



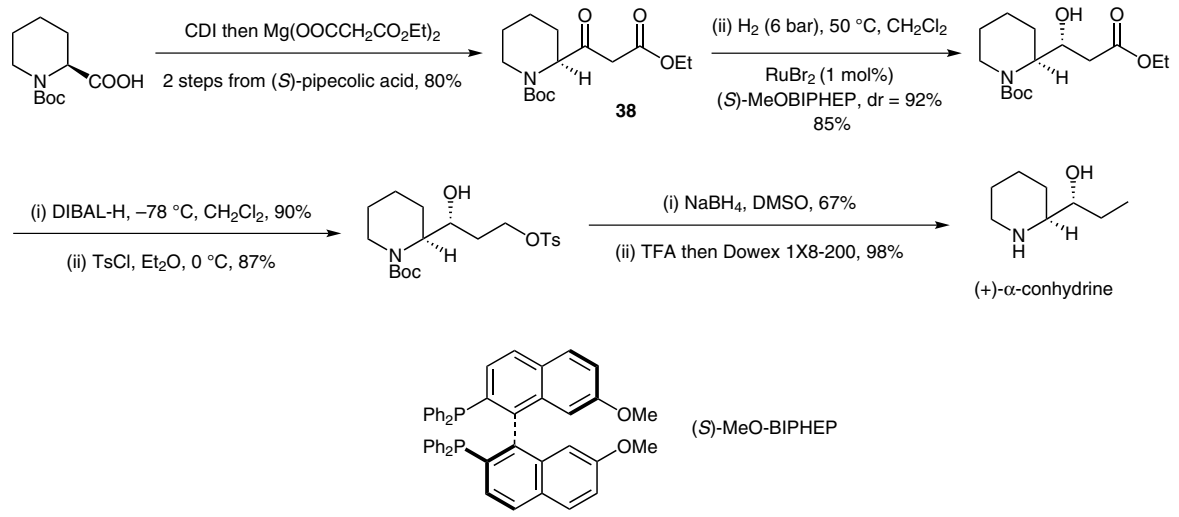
Scheme 8



Scheme 9



Scheme 10



Scheme 11

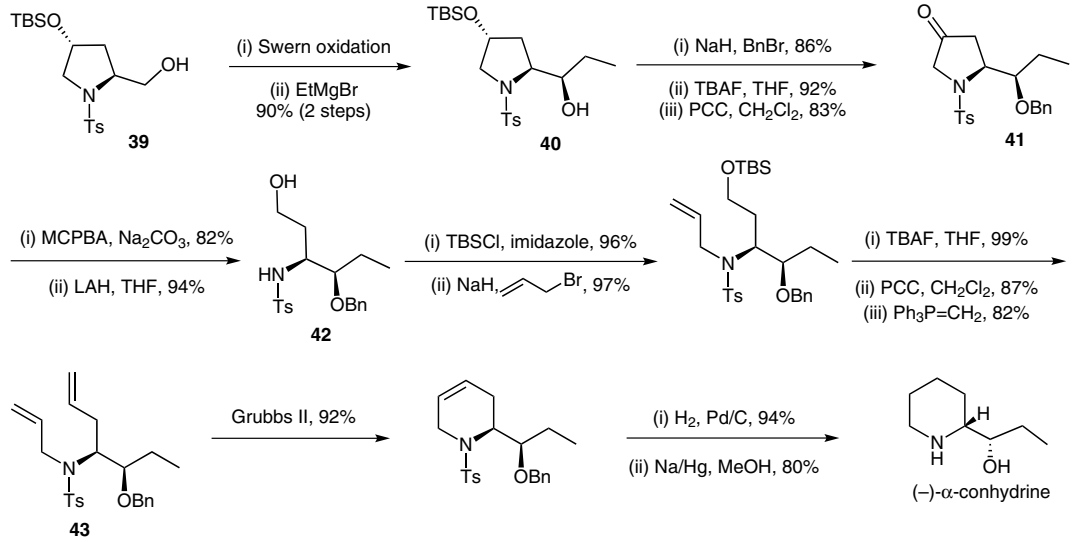
conhydrine according to Mayano and co-workers (discussed under Scheme 23).

The ruthenium-catalyzed asymmetric hydrogenation of keto esters was utilized by Guerreiro et al. for the synthesis of hydroxylated indolizidine and pyrrolizidine alkaloids using BIPHEP catalysts (Scheme 11).[27] The methodology was successfully extended to the synthesis of (+)-α-conhydrine by employing asymmetric hydrogenation of the keto ester **38**; successive reduction of the ester group completed the synthesis of the natural product.

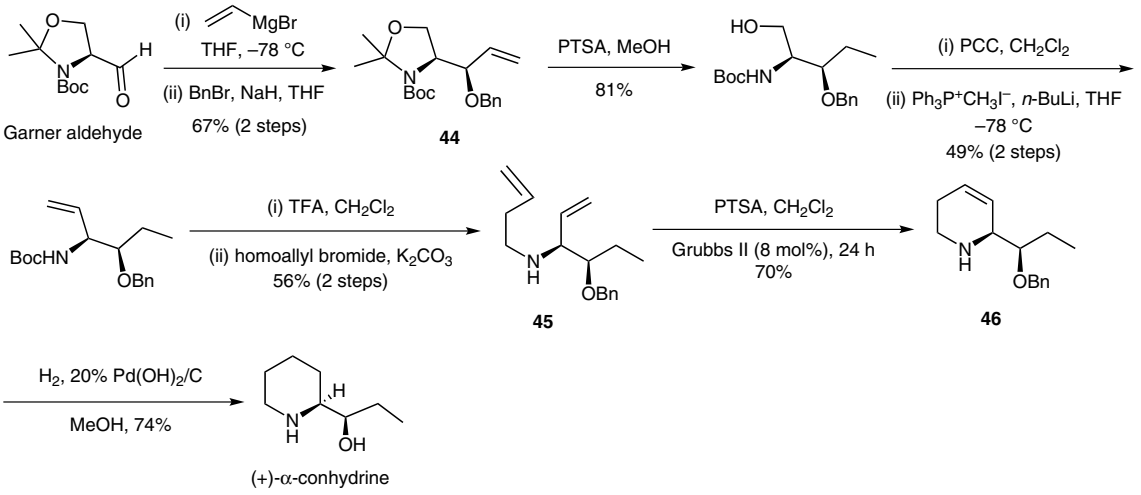
The synthesis of (–)-α-conhydrine was achieved using 4-hydroxyproline as the starting chiral source (Scheme 12).[28] Compound **39**, prepared from 4-hydroxyproline, was subjected to oxidation followed by Grignard reaction with ethyl magnesium bromide to give **40**. Compound **40** was subsequently converted into keto compound **41**, which on regiospecific ring expansion using MCPBA and sodium carbonate followed by lithium aluminum hydride reduction gave exclusively **42**. Compound **42** was transformed into key diene **43** and this on RCM followed by hydrogenation and deprotection of the tosyl group furnished (–)-α-conhydrine.

The serine-derived aldehyde, popularly known as 'Garner aldehyde' is routinely utilized in the synthesis of natural products. Srivatsava et al. have successfully utilized this aldehyde for the synthesis of (+)-α-conhydrine (Scheme 13).[29] The Grignard product **44** was transformed into the diene **45** and then subjected to RCM using the Grubbs 2nd generation catalyst. The olefin **46** obtained was hydrogenated to give the target natural product.

The diastereoselective reduction of a carbonyl group next to heterocyclic system in *N*-Boc-2-acyloxazolidines was well demonstrated by Couty and co-workers (Scheme 14).[30] Compound **47**, obtained by diastereoselective reduction of the carbonyl group, was further subjected to cyclization to deliver carbamate **48**. Treatment of **48** with



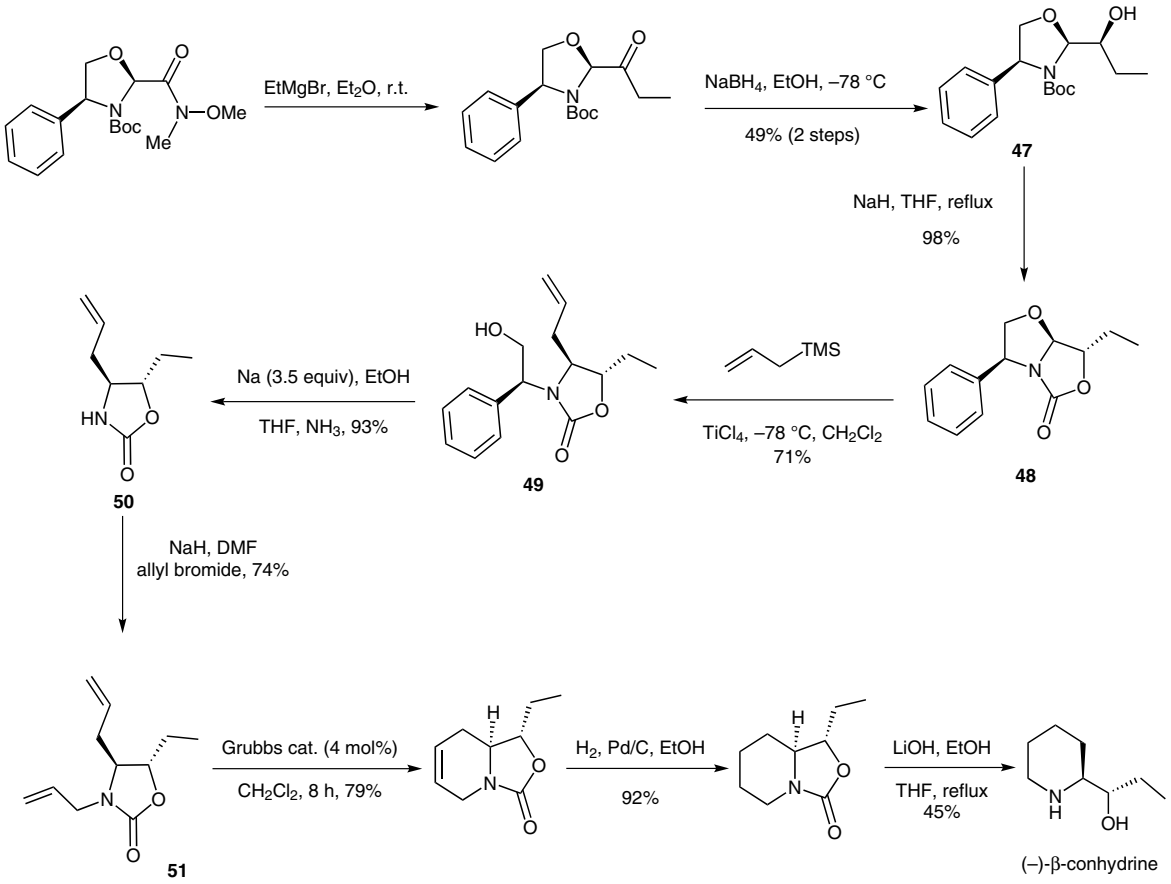
Scheme 12



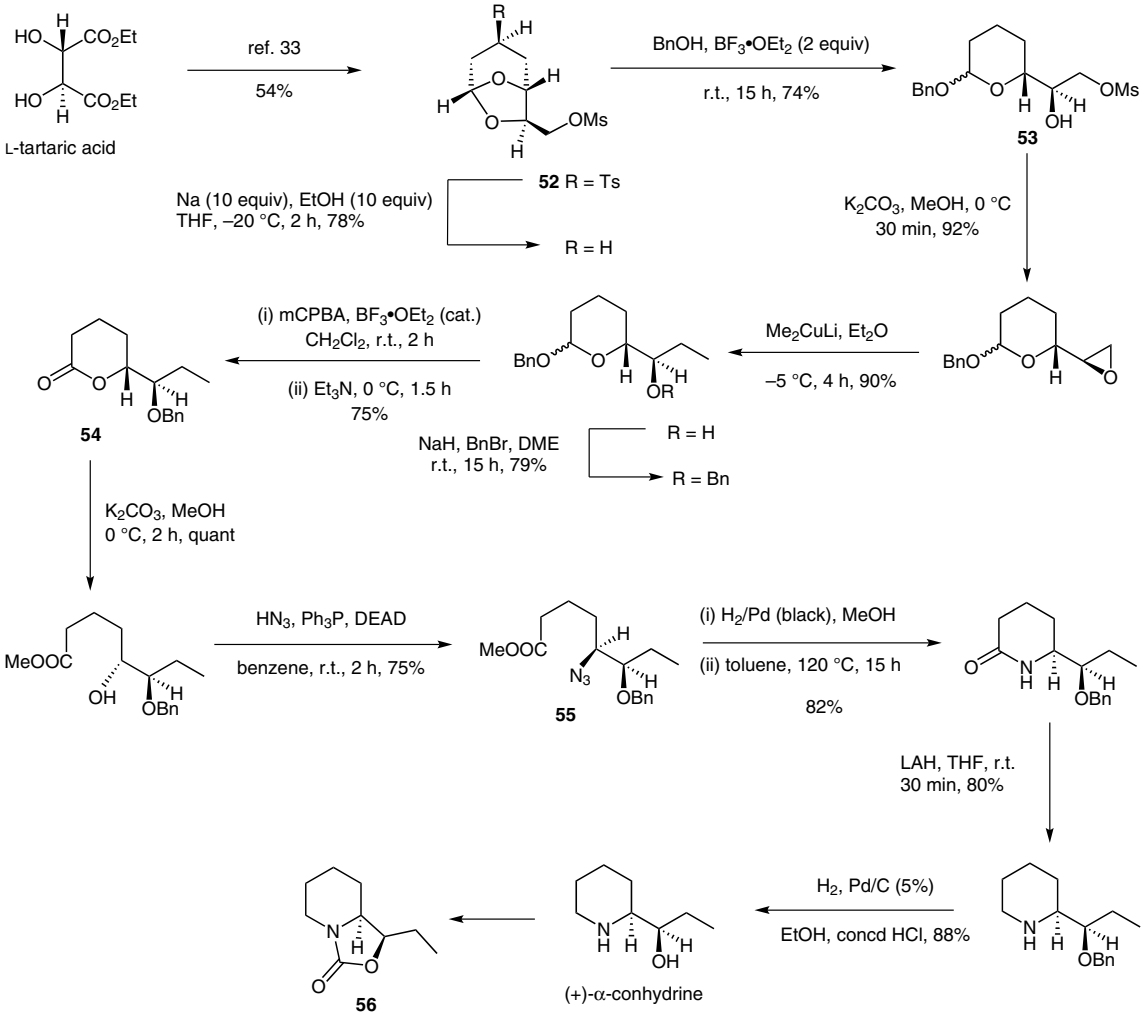
Scheme 13

allyltrimethylsilane in the presence of titanium(IV) chloride gave the alcohol **49**, which on subsequent deprotection of the aryl group produced the alkene **50**. The diene **51**, prepared by alkylation of **50**, was subjected to RCM followed by hydrogenation and hydrolysis to complete the synthesis of (–)-β-conhydrine.

The first enantiospecific synthesis of (+)-α-conhydrine was achieved by Masaki et al. using tartaric acid as the starting chiral source (Scheme 15).[31] The cyclic tosyl derivative **52** was prepared from tartaric acid using a previously reported method.[32] Desulfurization followed by subsequent opening of the cyclic scaffold using benzyl alcohol afforded the benzyl ether **53**. The epoxide obtained by treatment of **53** with methanolic potassium carbonate was opened using lithium dimethylcuprate, the Gilman reagent, and further oxidized to the six-membered lactone



Scheme 14



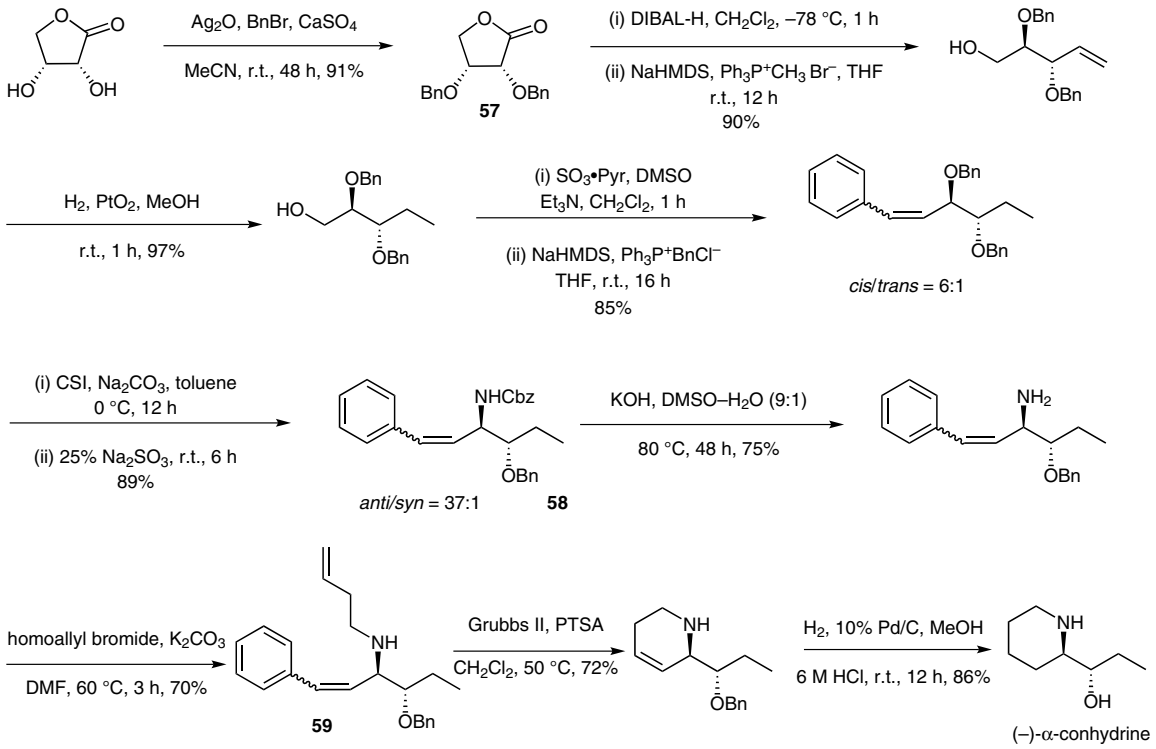
Scheme 15

54 using MCPBA. The methanolysis of lactone **54** followed by subsequent azidation with concomitant inversion of the chiral center gave compound **55**. Further cyclization and reduction afforded (+)-α-conhydrine whose structure was confirmed by converting it into the known compound **56**.

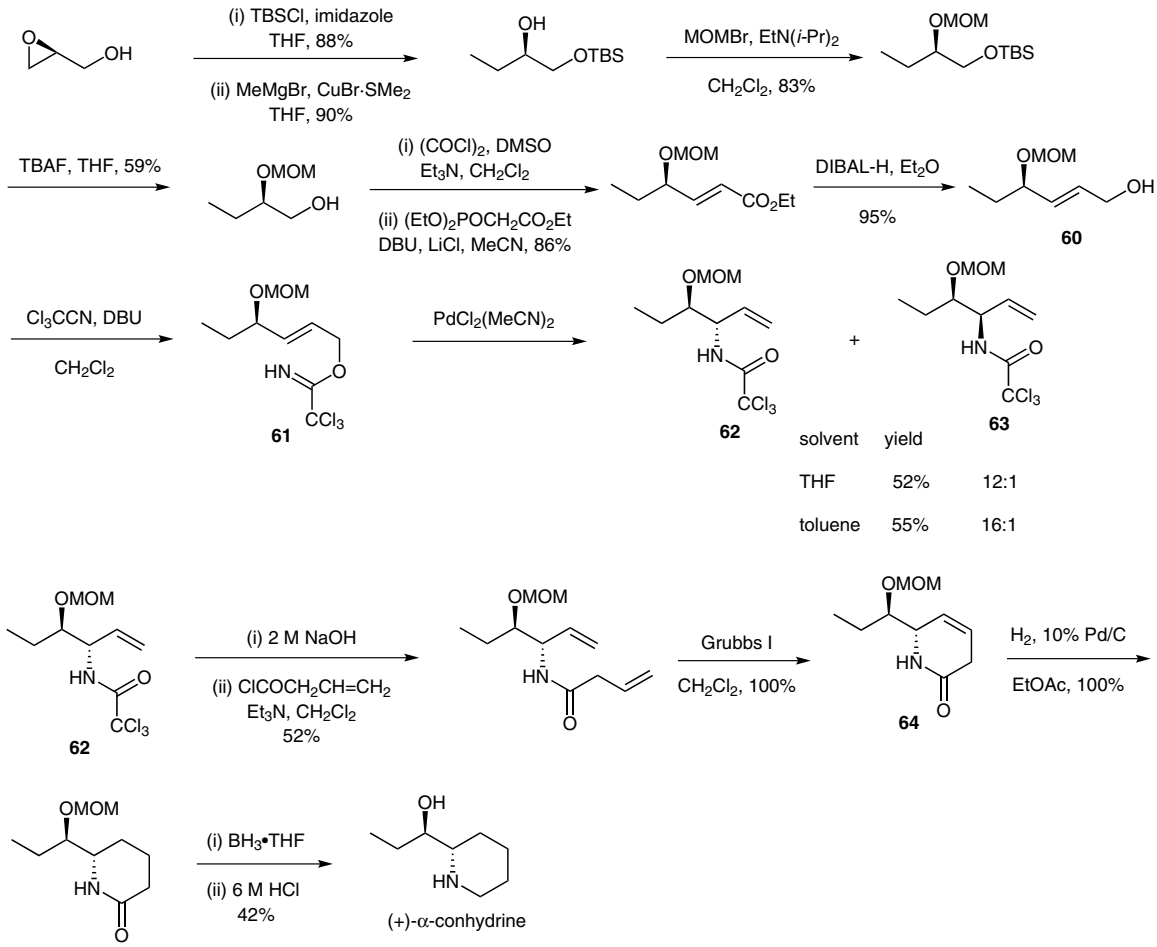
D-Erythronolactone, with two existing chiral centers served as an efficient chiral source for the synthesis of (–)-α-conhydrine (Scheme 16).[33] The dibenzylic ether compound **57** was converted into the desired 1,2-amino alcohol **58** using a previously developed chlorosulfonyl isocyanate (CSI) reaction.[34] Deprotection of the carbamate followed by reaction with homoallyl bromide afforded the diene **59**. RCM of **59** followed by subsequent reduction and hydrogenolysis resulted in the target natural product.

Sutherland and Jamieson synthesized (+)-α-conhydrine via ether-directed aza-Claisen rearrangement (Scheme 17).[35] The requisite allyl alcohol **60** was synthesized starting from (*S*)-glycidol. Treatment of alcohol **60** with Cl_3CCN in the presence of DBU afforded the allylic trichloroacetimidate **61** that on further reaction with $PdCl_2(MeCN)_2$ underwent aza-Claisen rearrangement with Pd complexation with both the oxygen atoms to give **62** and **63** with excellent diastereoselectivity. The required isomer **62** was separated and converted into the diene which on subsequent RCM afforded the key piperidine ring **64** in quantitative yield. Further hydrogenation, amide reduction, and MOM deprotection produced (+)-α-conhydrine.

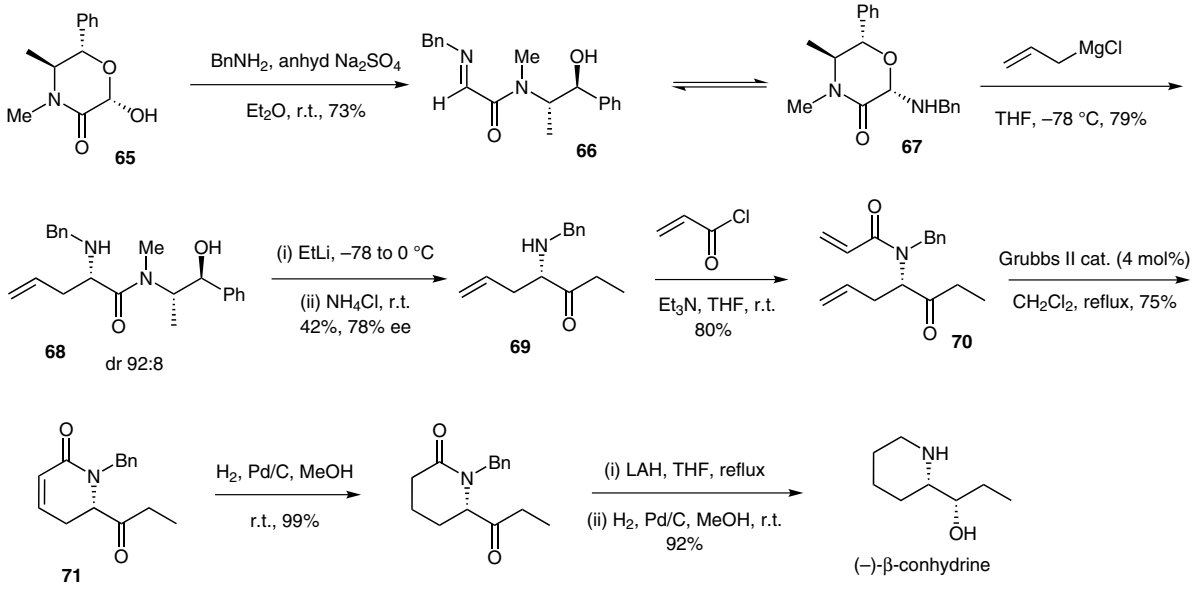
Vicario and co-workers approached the synthesis of (–)-β-conhydrine and (+)-α-conhydrine using commercially available (+)-(*S*,*S*)-pseudoephedrine **65** as the starting material (Scheme 18).[36] The amino alcohol **65** was condensed with benzylamine to give imine **66** which exists in equilibrium with the cyclized form **67**. Grignard addition of allylmagnesium chloride across the imine occurred with excellent chemo- and diastereoselectively to give the amino amide **68** that on treatment with ethyllithium afforded the enantioenriched amino ketone **69**. This amino ketone **69** was then transformed into diene **70** and subjected to RCM to afford the cyclic compound **71** that on reduction followed by hydrogenation gave (–)-β-conhydrine, but with reduced optical activity compared to



Scheme 16



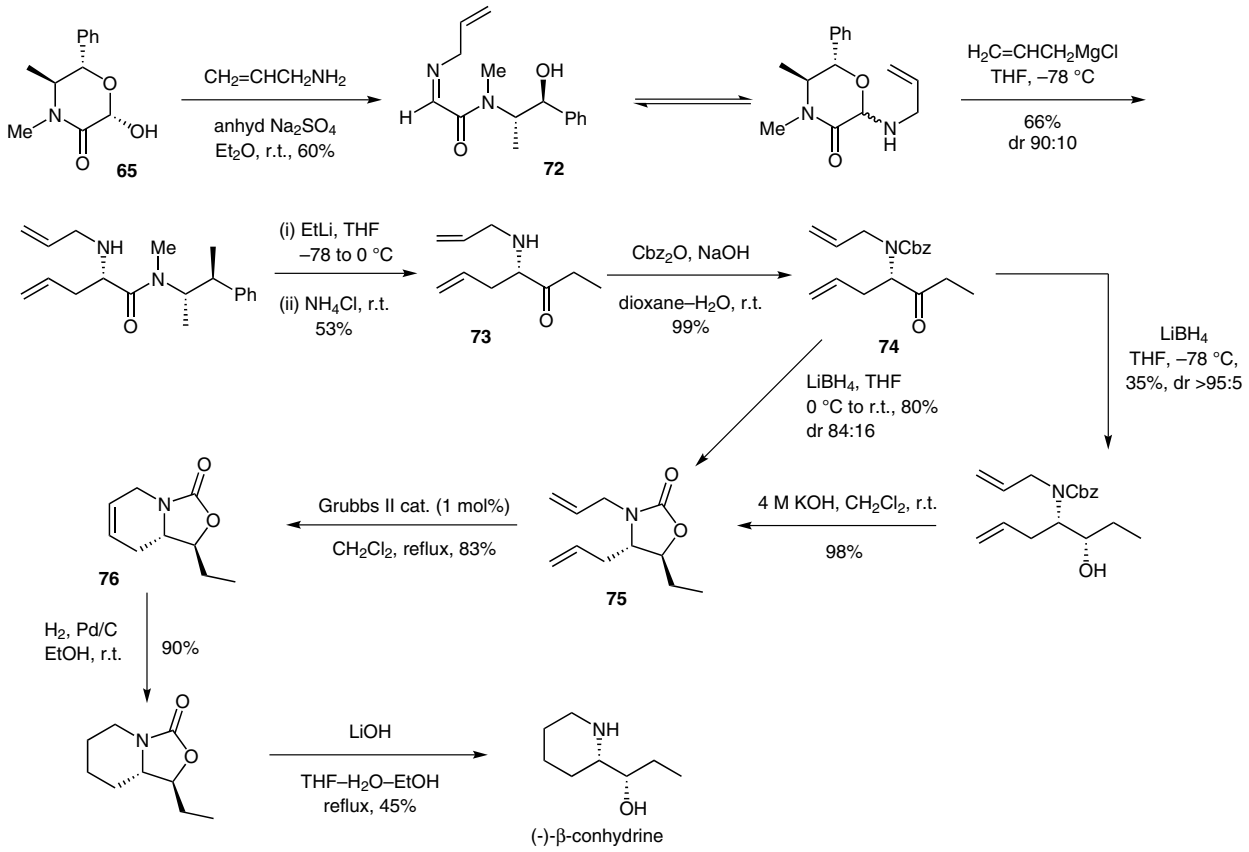
Scheme 17



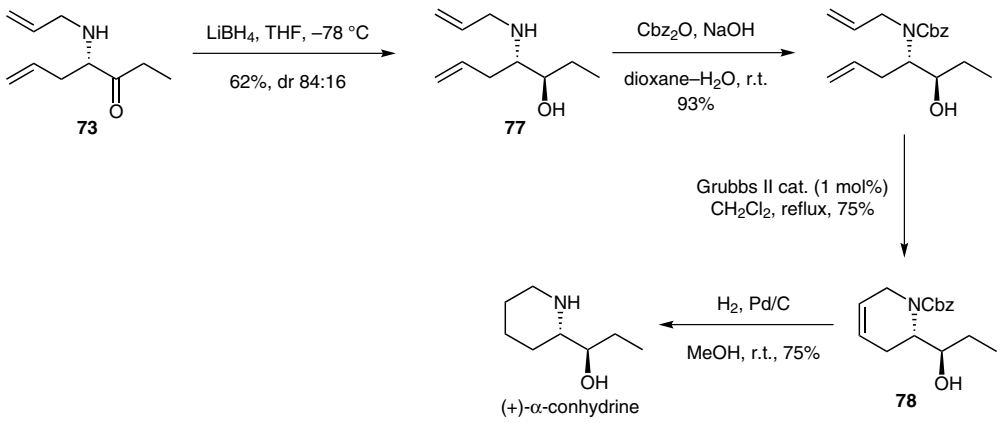
Scheme 18

a natural sample. The authors speculated that racemization occurred at the RCM stage due to prolonged heating of the amide **70**. In order to circumvent this, a convenient modified strategy was proposed by synthesizing a benzyl carbamate to execute the RCM reaction rather than involvement of amide.

The modified strategy involved the formation of imine **72**, starting from **65**, which was sequentially transformed to benzyl carbamate **74** (Scheme 19). The reduction of the ketone group favored the formation of cyclic product **75** which when subjected to RCM resulted in the formation of the bicyclic compound **76**. Further, hydrogenation fol-



Scheme 19



Scheme 20

lowed by hydrolysis of the carbamate produced (–)-β-conhydrine with excellent enantiomeric excess.

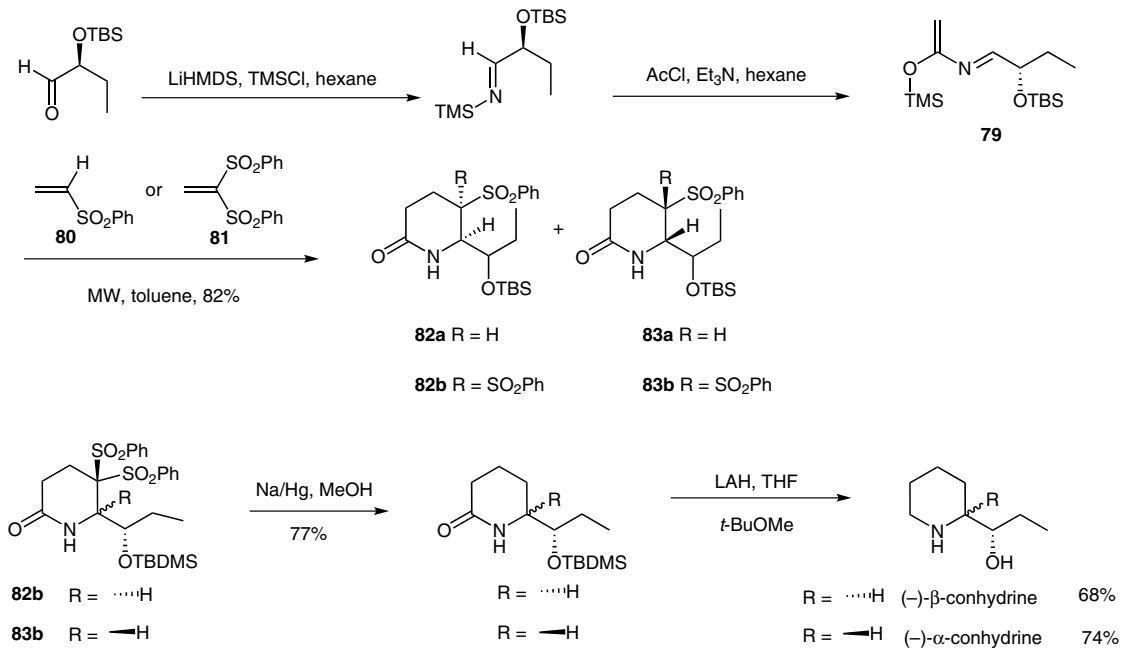
For the synthesis of (+)-α-conhydrine, the strategy was slightly modified (Scheme 20). The amine **73** was directly reduced with excess lilthium borohydride to give preferentially **77**. Compound **77** was converted into the corresponding carbamate and further subjected to RCM to afford **78**. The exposure of **78** to H_2 over Pd/C completed the synthesis of (+)-α-conhydrine.

Panunzio and co-workers successfully synthesized (–)-β- and (–)-α-conhydrine using microwave-assisted hetero-Diels–Alder reaction (Scheme 21).[37] The optically active *N*-vinyl imine **79** on reaction with dienophilic vinyl sulfones **80** or **81** under microwave conditions produced **82** and **83** in almost equal proportions and they were separated by flash chromatography. The stereochemistry of **82** and **83** were confirmed by the synthesis of (–)-β-conhydrine and (–)-α-conhydrine.

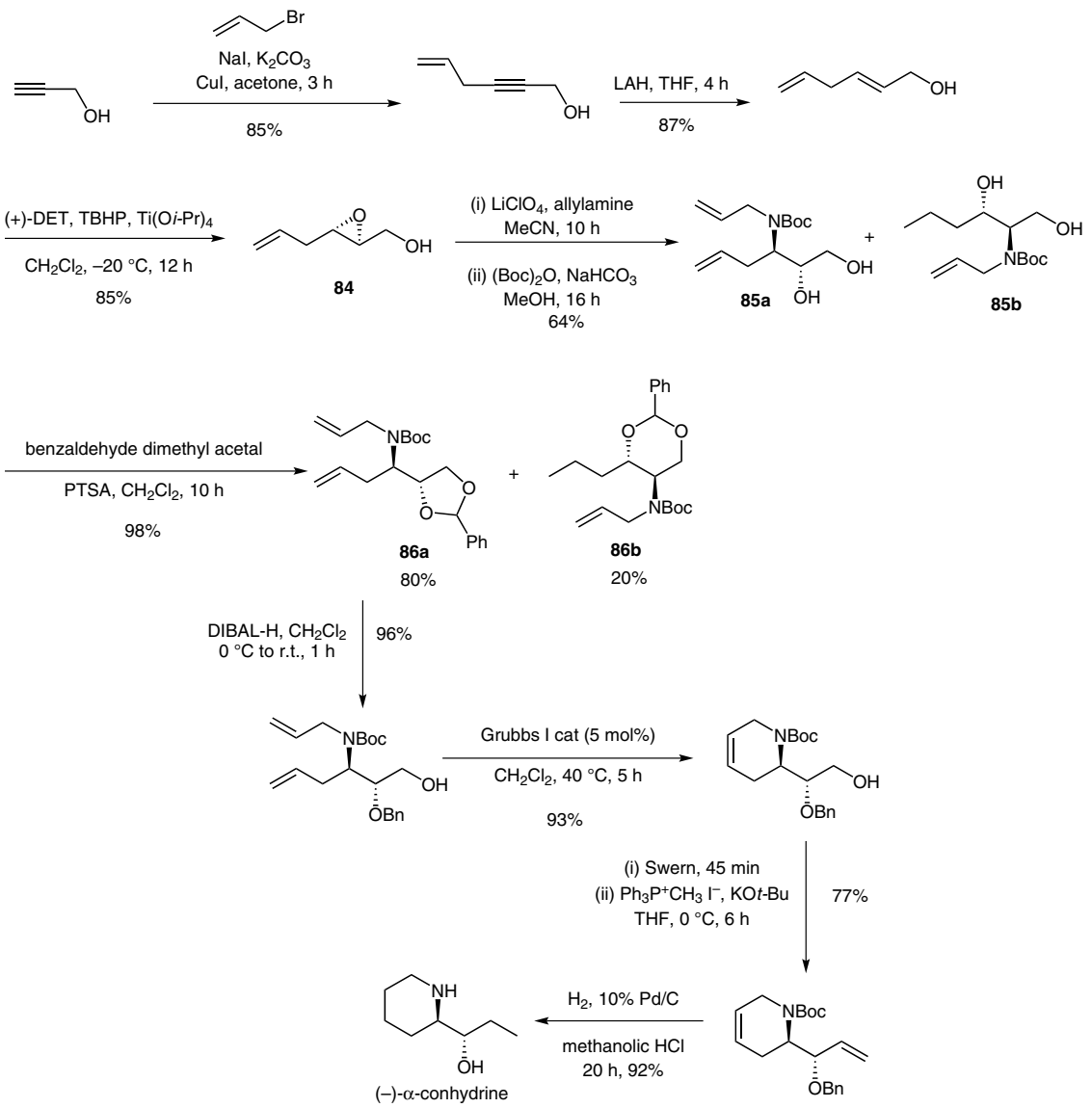
3.2 From Achiral Starting Material

The synthesis of conhydrine using various achiral starting material involves mainly Sharpless asymmetric dihydroxylation (SAD) or Sharpless asymmetric epoxidation (SAE) as the key step to introduce chirality into the synthetic intermediates. In addition to this, Wittig reaction, Grignard reaction, RCM, regioselective epoxide opening, and cyclization are other key methods employed in the synthetic sequences.

Fadnavis and co-workers achieved the asymmetric synthesis of (–)-α-conhydrine starting from propargyl alcohol. The chirality of the molecule was introduced using Sharpless asymmetric epoxidation as the key step (Scheme 22).[38] The chiral epoxide **84** thus obtained was subjected to regioselective opening using allylamine under Chini's conditions followed by Boc protection to give an inseparable mixture of diols **85a** and **85b**. The extent of



Scheme 21



Scheme 22

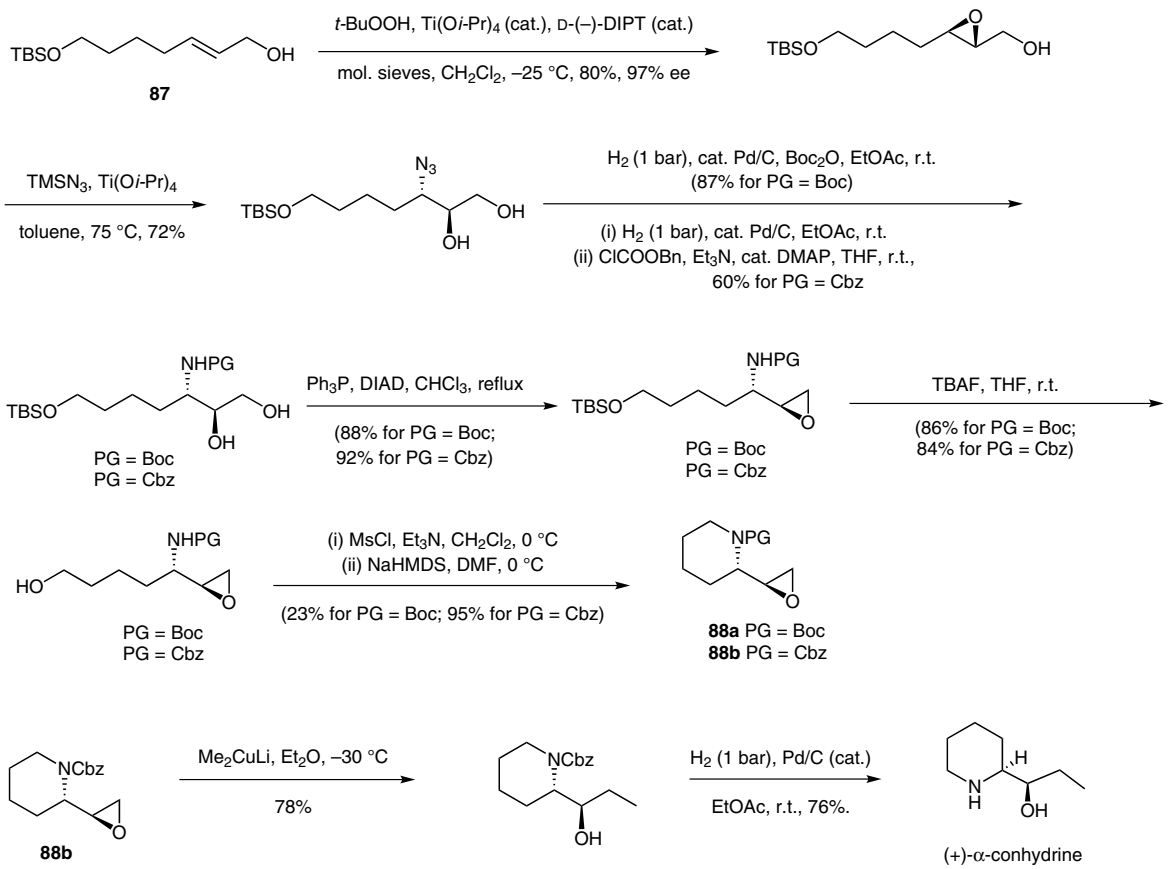
regioselectivity in the epoxide opening was determined by the direct conversion of the diol mixture of **85a** and **85b** into the corresponding separable acetals **86a** and **86b** (8:2), respectively. The requisite five-membered **86a** was separated and further transformed sequentially into (–)-α-conhydrine.

Moyano and co-workers reported the synthesis of (+)-α-conhydrine using Sharpless asymmetric epoxidation (Scheme 23).[39] The key oxirane **88** was synthesized starting from **87** following classical synthetic steps. The regioselective opening of epoxide **88b** using lithium dimethylcuprate followed by hydrogenolysis of the Cbz protection furnished the natural product.

Kumar and Kandula approached the synthesis of (–)-α-conhydrine by two different synthetic routes using Sharpless asymmetric dihydroxylation, regioselective opening of a cyclic sulfate, and Wittig olefination as key steps.[40] The first method involves the synthesis of aldehyde **89** starting from propionaldehyde following key synthetic steps (Scheme 24). The aldehyde **89** was then subjected to Wittig olefination to afford the olefin **90**. The subsequent hydrogenation, cyclization, and Boc deprotection resulted in the natural product.

In order to improve the yield and efficiency of the synthesis in the Wittig step, an alternate method was demonstrated (Scheme 25). Commercially available (*E*)-pent-2-enol was converted into the triol and subsequently protected to give acetal **91**. It was then converted into azide **92** with inversion of configuration and transformed into olefinic compound **93** using classical synthetic methods. The synthesis of (–)-α-conhydrine was then completed as previously.

Itoh and co-workers achieved the asymmetric synthesis of (+)-α-conhydrine using enzymatic resolution of pyridine-derived alcohol **94** obtained by Grignard reaction of com-



Scheme 23

mercially available pyridine-2-carbaldehyde (Scheme 26).[41]

A short and efficient synthesis of (+)-β-conhydrine was achieved via catalytic dynamic resolution of *N*-Boc-piperidine with the help of chiral ligand **95** and TMEDA (Scheme 27).[42]

3.3 Chiral Auxiliary Mediated Synthesis

Conhydrine isomers are also synthesized by the chiral auxiliary method.

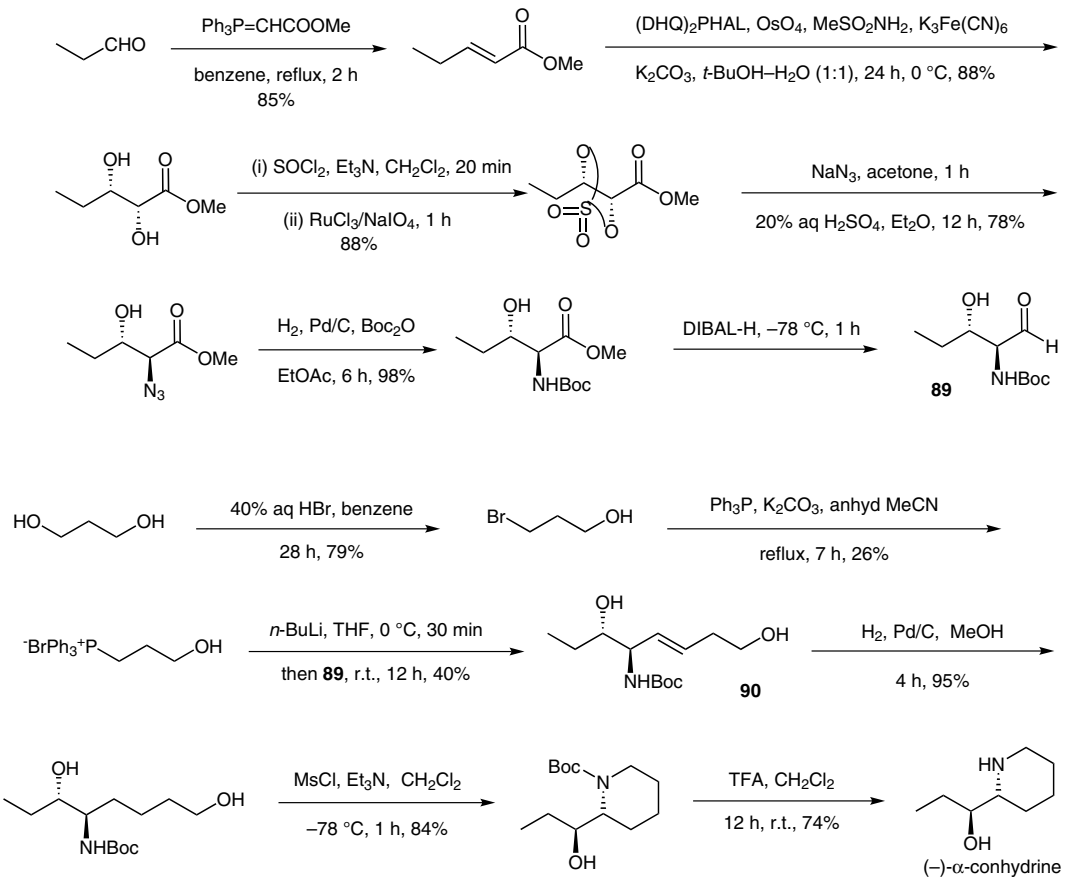
The synthesis of (+)-β-conhydrine and (+)-α-conhydrine was achieved using regio- and stereoselective construction of the O–C bond using an iodocyclocarbamation reaction (Scheme 28).[43] The pyridine derivative **96** on N-carbamation using chiral auxiliary (+)-TCC[44] followed by subsequent Grignard addition afforded **97** with 91% dr. Compound **97** was transformed into **98** by a one-pot process upon deprotection of the triisopropylsilyl group and removal of the chiral auxiliary. The intermediate **98** was then subsequently transformed into triflate **99** and subjected to the iodocyclocarbamation reaction to give the bicyclic product **100a**. Further catalytic hydrogenation and carbamate hydrolysis furnished (+)-β-conhydrine.

For the synthesis of (+)-α-conhydrine, the corresponding enantiomer **100b** was synthesized using chiral auxiliary (–)-TCC following a similar synthetic procedure (Scheme 29). The required inversion of the O–C bond was achieved via olefination followed by hydrogenation. Subsequent hydrolysis of the carbamate group afforded the desired natural product.

Chemla and co-workers successfully synthesized (–)-α-conhydrine in just seven steps with an overall yield of 41% (Scheme 30).[45] The key diastereoselective addition of **102** to imine **101** was executed via zinc-chelated stereocontrol to produce *trans* isomer **103** exclusively. Compound **103** on removal of the chiral auxiliary group and treatment with a base underwent cyclization to produce amide **104**. Deprotection of the TMS group, hydrogenation, and subsequent reduction of the amide and MOM deprotection afforded (–)-α-conhydrine.

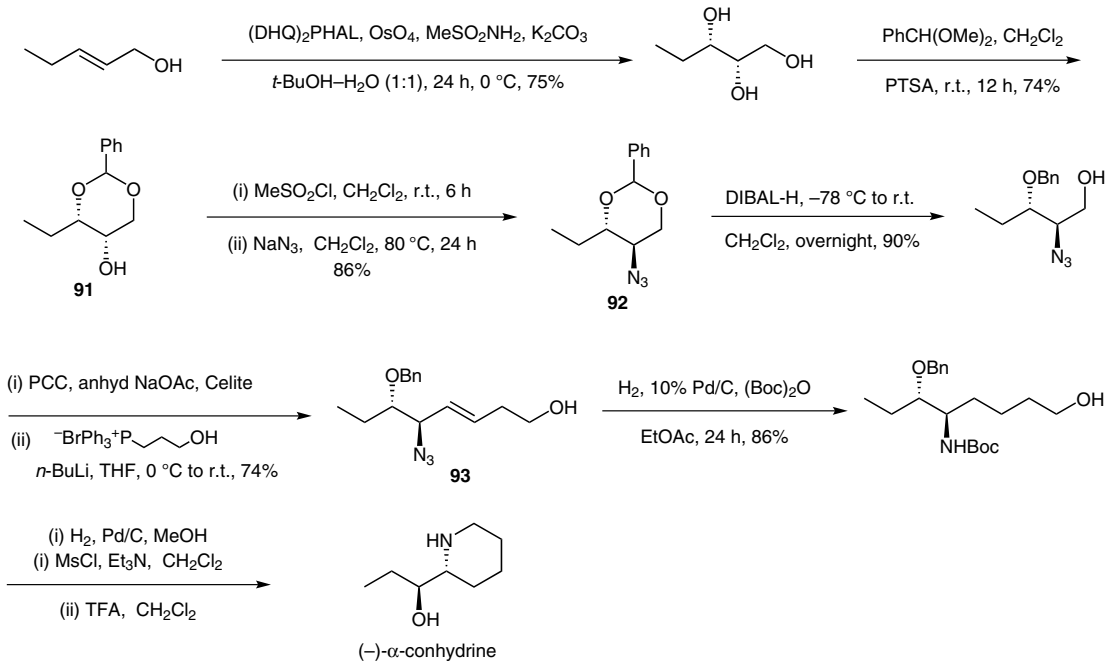
In continuation of research work on the synthesis of 1,2-amino alcohols, Chemla's group achieved the synthesis of (+)-β-conhydrine by carrying out the diastereoselective addition of lithium 3-(methoxymethoxy)allenylcuprates to enantiopure chiral *N*-*tert*-butylsulfinilimines in *cis* fashion (Scheme 31).[46,47] Thus the reaction of **105** with **106** afforded the required *syn*-β-aminopropargylic ether **107**. The base-induced cyclization, hydrogenation, and subsequent deprotection of the chiral auxiliary group gave (+)-β-conhydrine.

The first and notable synthesis of (–)-α-conhydrine was performed by Enders and co-workers using SAMP [(*S*)-1-amino-2-(methoxymethyl)pyrrolidine] as an efficient chi-

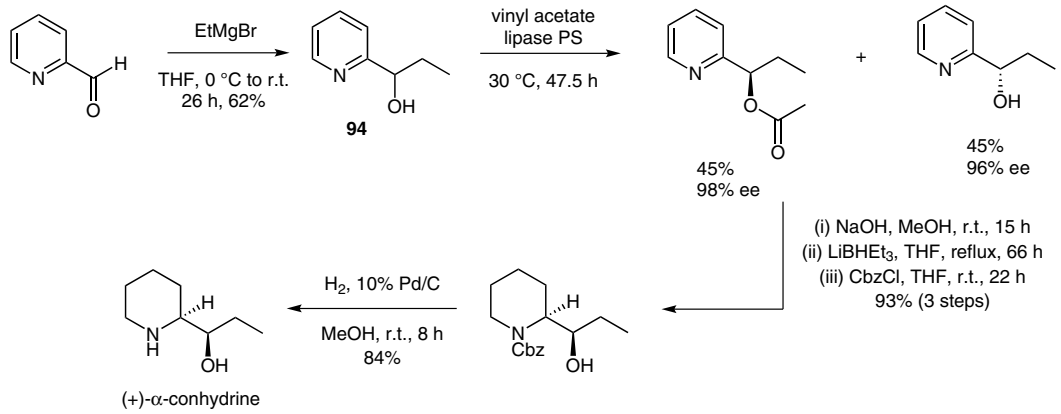


Scheme 24

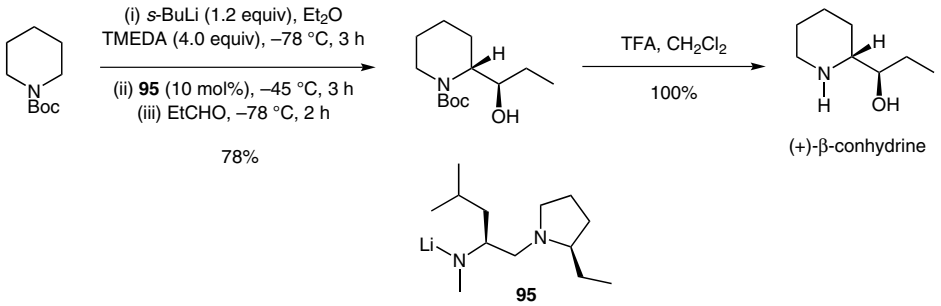
ral auxiliary (Scheme 32).[48] The hydrazone **108** on treatment with LDA followed by trapping with ethyl iodide gave **109** with 89% dr. Highly diastereoselective addition of the corresponding organolithium to the imine bond was achieved to afford **110** in 88% yield. The reduction of the N–N bond using $BH_3 \cdot THF$ followed by subsequent treat-



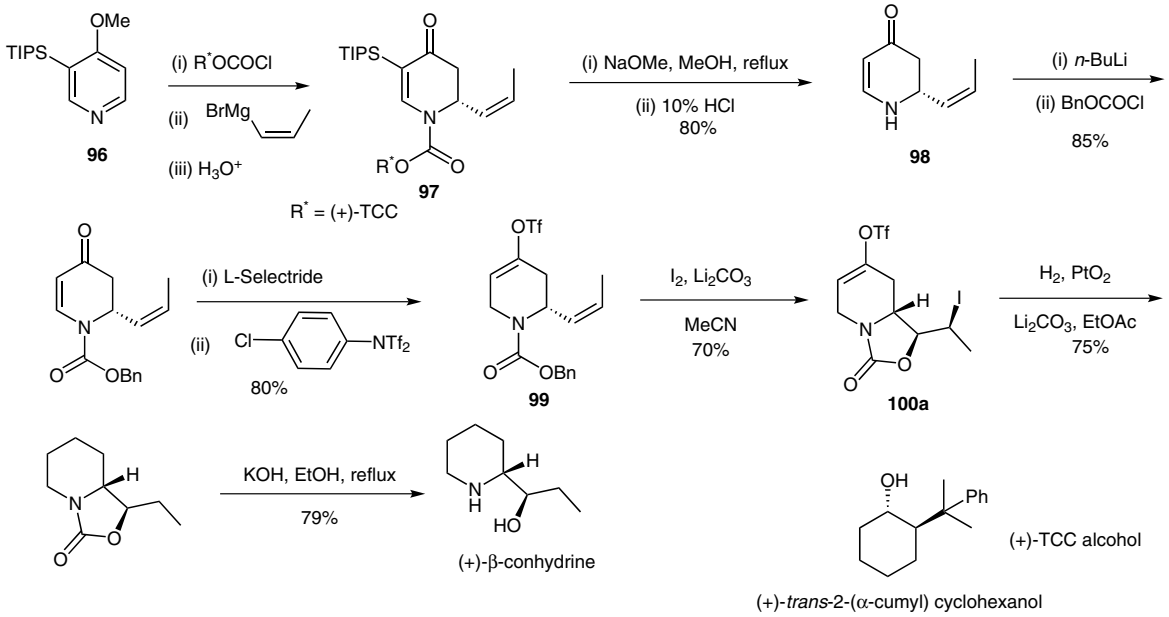
Scheme 25



Scheme 26



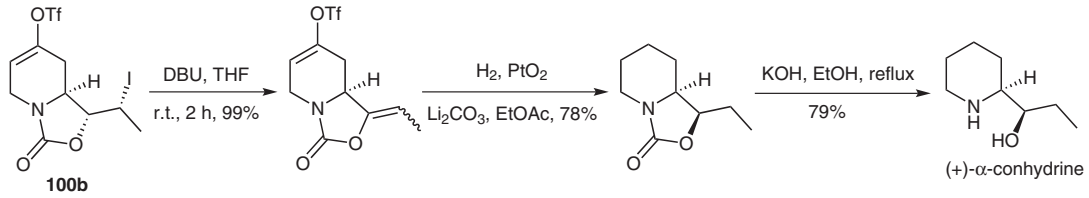
Scheme 27



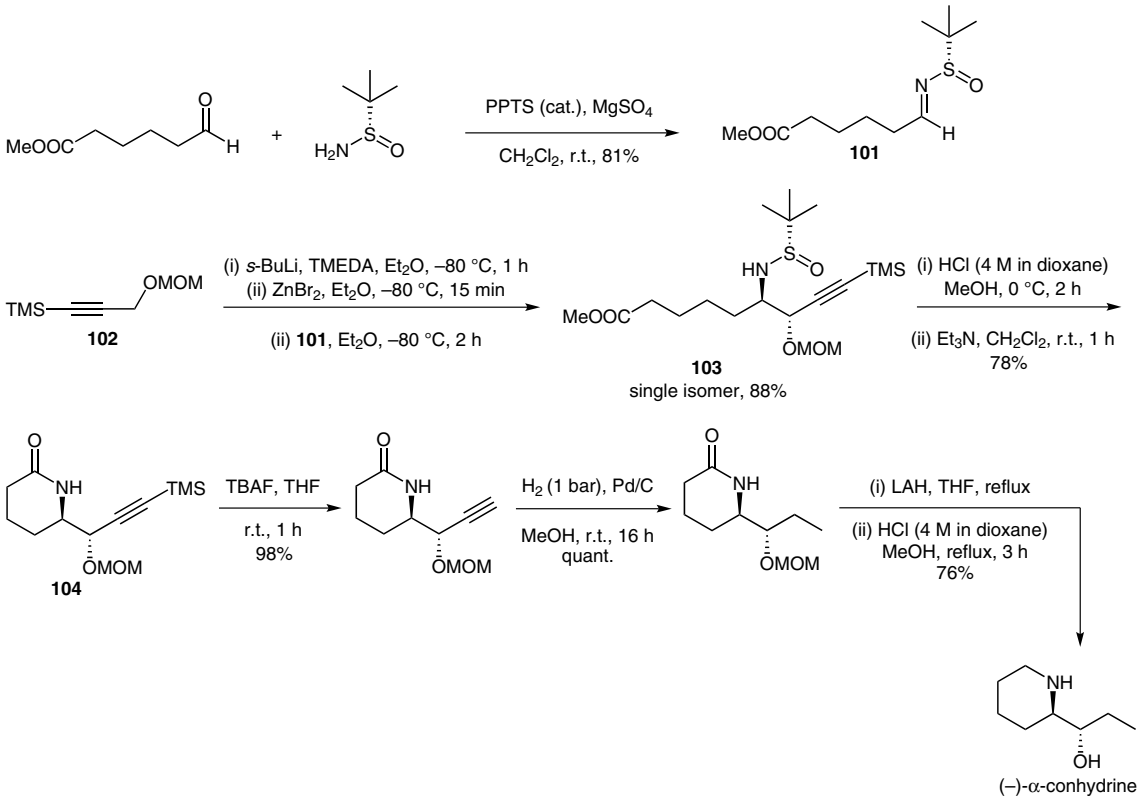
Scheme 28

ment with HCl gave the cyclic imine which was reduced in situ using $NaBH_4$ to give (–)-α-conhydrine.

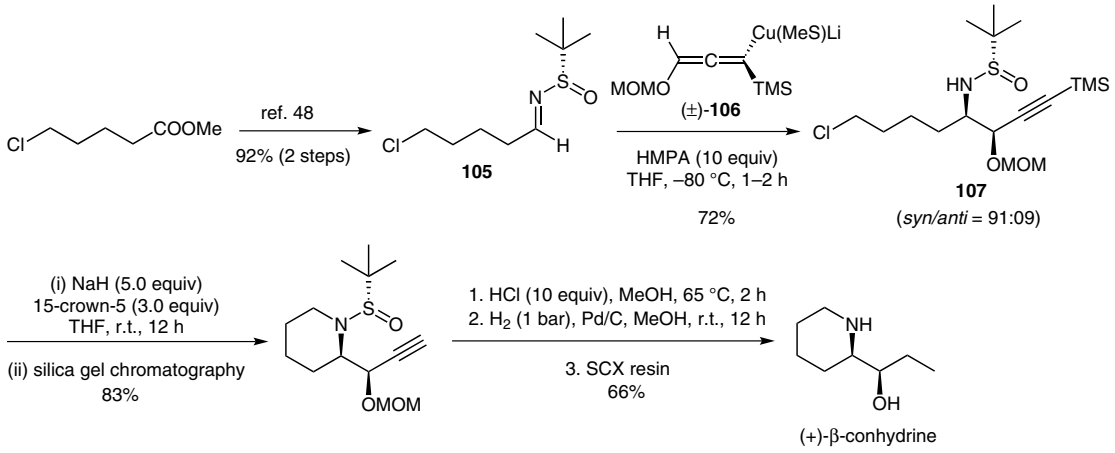
The simple mixing of SAMP **111** with chiral enantiopure benzyloxy aldehyde **112** delivered the hydrazone **113** which on sequential treatment with allyllithium and acryloyl chloride gave the desired diene **114** diastereoselectively. Diene **114** was subjected to RCM using Grubbs' 1st generation catalyst to produce a mixture of **115** and **116** both of which were eventually transformed into (+)-β-conhydrine (Scheme 33).[49]



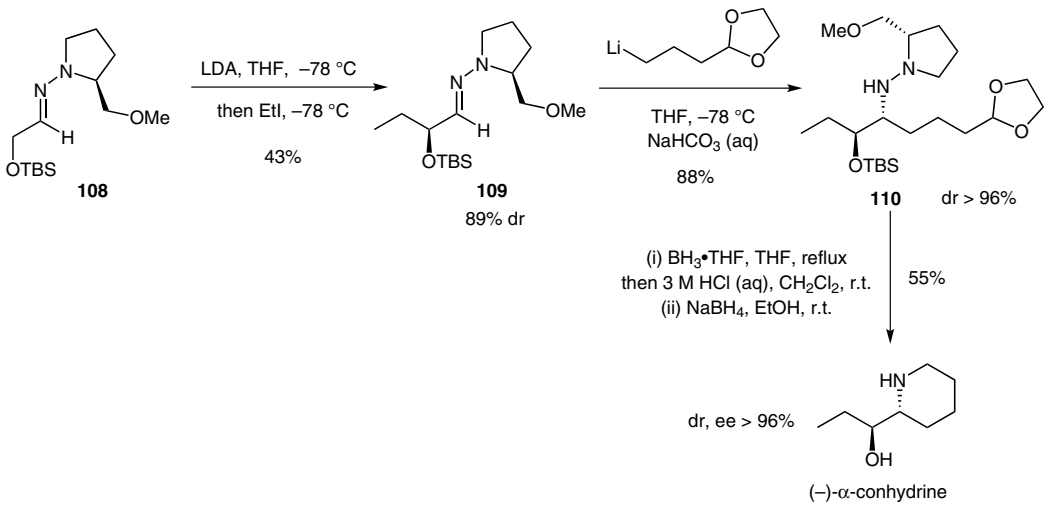
Scheme 29



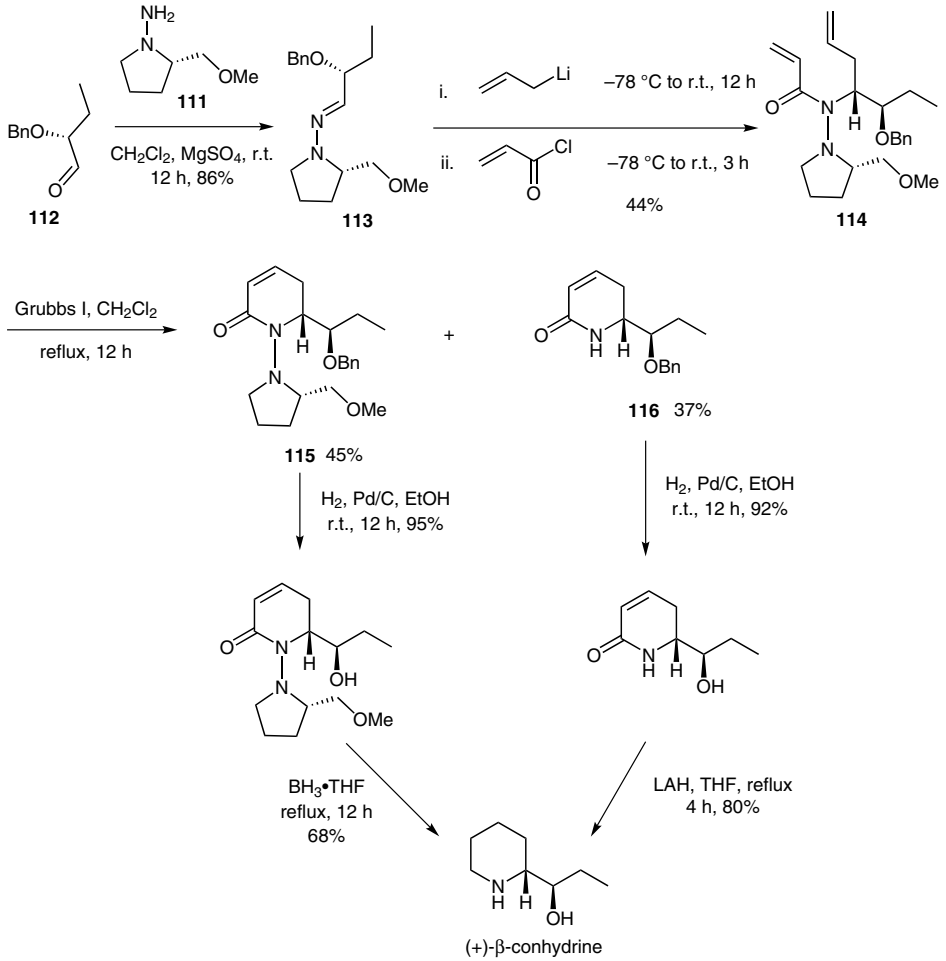
Scheme 30



Scheme 31



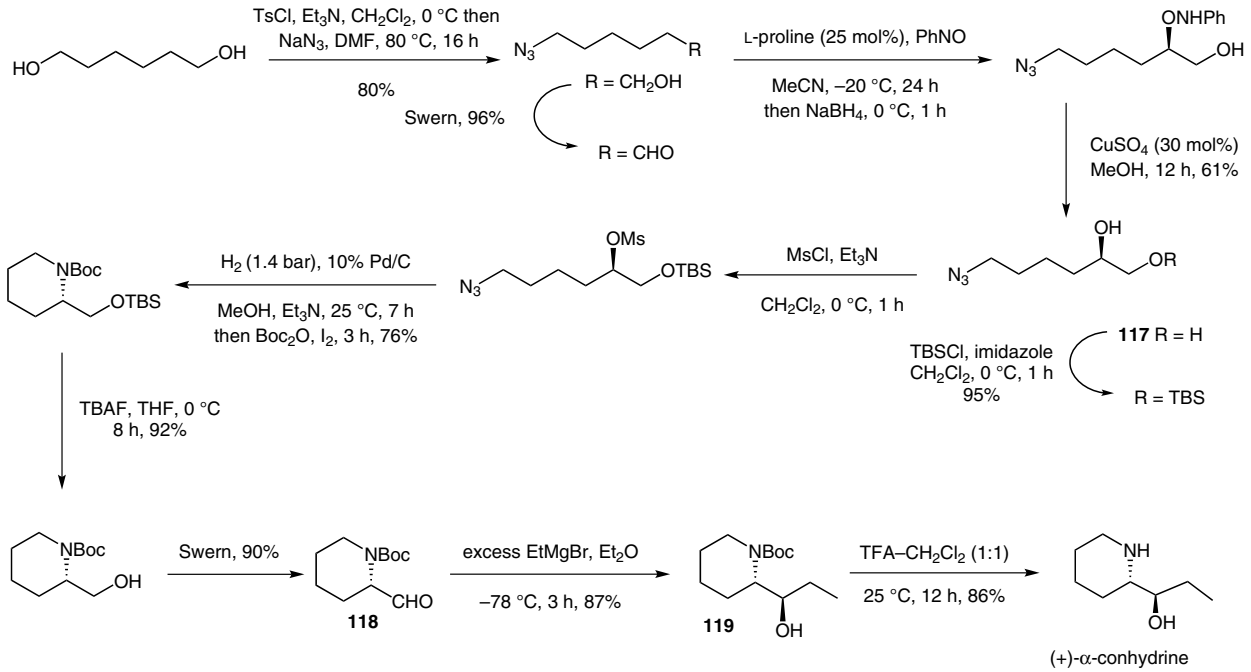
Scheme 32



Scheme 33

3.4 Catalysis Approach (Organo and Metal Catalysis)

The synthesis of conhydrine is also accomplished using organo or metal catalysis. The strategies start with some achiral materials and utilize proline, BINOL, and ruthenium-based metal catalysts to induce the chirality in the molecules.

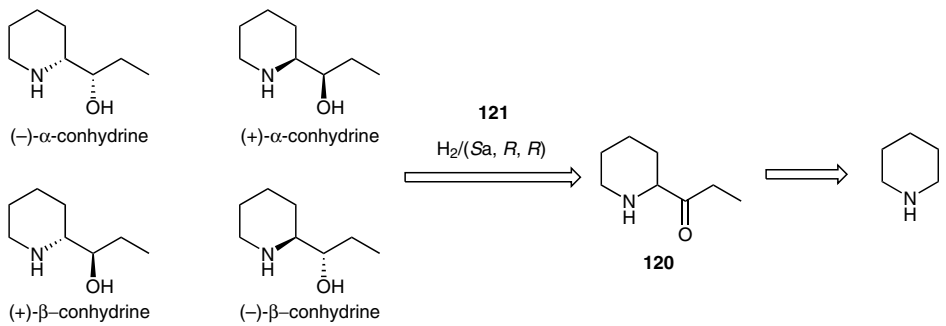


Scheme 34

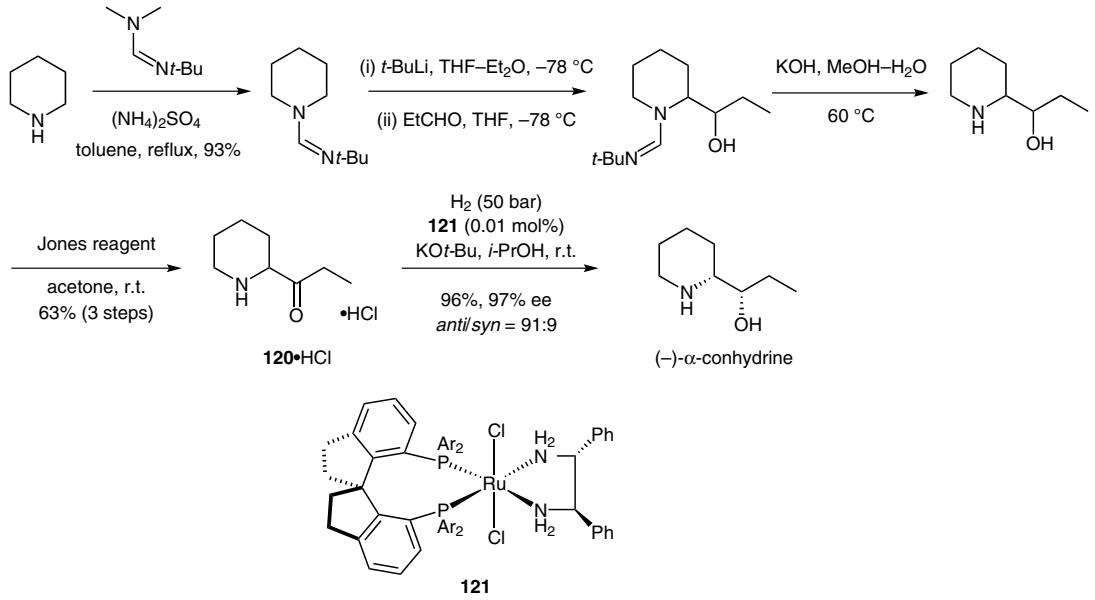
Sudalai and Shaikh successfully applied L-proline-catalyzed aminoxylation for the synthesis of (+)-α-conhydrine (Scheme 34).[50] Thus the starting material, hexane-1,6-diol, was sequentially transformed into the corresponding aldehyde and subjected to aminoxylation followed by reduction in situ to give **117** enantioselectively. It was then transformed into cyclic aldehyde **118** by classical synthetic routes which upon addition of Grignard reagent ethylmagnesium bromide afforded the alcohol **119** as a single diastereomer. The Boc deprotection of **119** using TFA gave the desired product.

Zhou and co-workers achieved the dynamic kinetic resolution of α-amino ketones to amino alcohols via ruthenium-catalyzed catalytic hydrogenation.[51] The methodology was successfully applied to the synthesis of all isomers of conhydrine (Scheme 35). Commercially available piperidine was converted into ketone **120** which was subjected to asymmetric hydrogenation in the presence of ruthenium-based catalyst **121** to give (–)-α-conhydrine with 97% ee (Scheme 36). The formation of the desired product was also favored with very high diastereoselectivity. The conversion of α-conhydrine into β-conhydrine was accomplished by employing the inversion of the chiral center using cyclic sulfate methodology (Scheme 37).

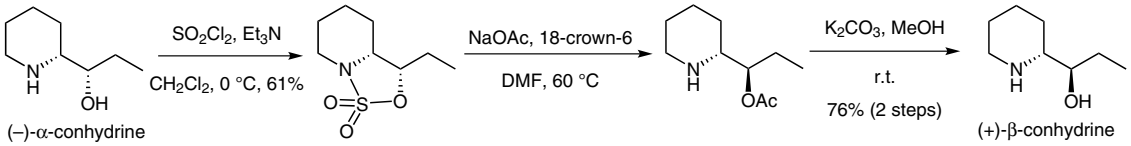
The synthesis of (–)-α-conhydrine was achieved by Barua and co-workers using the one-pot reduction of a nitro compound to give an amino alcohol which was converted into the carbamate (Scheme 38).[52] The requisite chiral nitro alcohol **122** was prepared by asymmetric Henry addition of 4-nitrobut-1-ene with propionaldehyde using La-(*R*)-BINOL. The one-pot reduction and protection of the amino compound in the presence of Zn/NH_4Cl and $(Boc)_2O$ afforded the alcohol **123**. The subsequent conversion of this alcohol into its acetate followed by N-allylation and RCM gave **124**. The reduction of double bond followed by Boc deprotection afforded (–)-α-conhydrine.



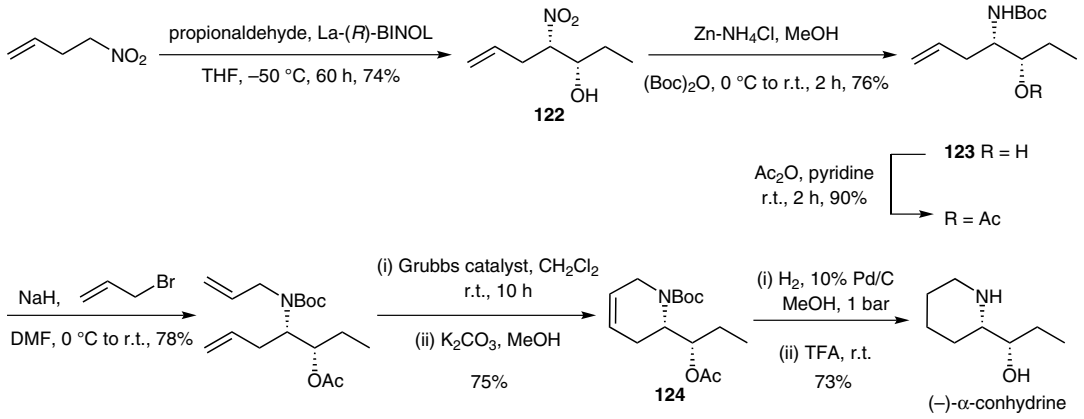
Scheme 35



Scheme 36



Scheme 37



Scheme 38

4 Conclusion and Outlook

This article comprehensively summarizes various synthetic approaches to conhydrine a 1,2-amino alcohol; its therapeutical value is limited due to its toxicity. However, conhydrine and several such entities are in clinical trials in recent years in order to explore novel pharmaceutical outcomes and drug applications. The review also emphasizes several synthetic protocols developed specially for its synthesis that have room for further improvement. Overall, this article provides a collection of the entire literature on conhydrine (1948–2014), which will aid chemists specifically working in this area.

Acknowledgment

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