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TOTAL SYNTHESES OF CONHYDRINES VIA RUTHENIUM-CATALYZED RING-CLOSING METATHESIS (RCM) REACTIONS

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Abstract – Conhydrines are extremely interesting target molecules in organic synthesis because of their unique structural motifs and potent bioactivities. The ring-closing metathesis (RCM) reaction has received considerable attention for a long time. In this review, we highlight 13 total syntheses of conhydrines by using RCM reaction as the key step from different research groups during the period 2000 to 2021.

CONTENTS

1. INTRODUCTION

Conhydrine, a piperidine alkaloid, extracted from the seeds and leaves of the poisonous plant *Conium maculatum* L. by Wertheim group[1] in 1856, is a potent glycosidase inhibitor, exhibits both antitumor and antiviral activities[2] (Figure 1). From a structural point of view, conhydrines have two vicinal stereogenic centers.[2] Owing to their prominent bioactive properties and unique structure motifs, a great deal of efforts has been devoted to the total syntheses of conhydrines.

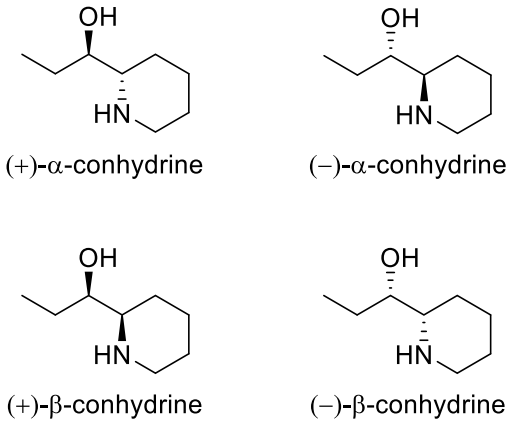


Figure1. Structures of conhydrine family

Ring-closing metathesis (RCM) reaction is an outstanding topic in organic synthesis. In this field, ruthenium–carbene catalysts have been developed for this reaction because of their functional group tolerance, readily available, insensitive to air, and easy to handle. As depicted in Figure 2, representative

ruthenium–carbene catalysts including Grubbs I, Grubbs II, Hoveyda–Grubbs I and Hoveyda–Grubbs II catalysts etc.[3–11] Grubbs I catalyst was first reported by Grubbs and co-workers,[12,13] and extensively used in the total synthesis of natural products. Since this pioneering report, well-defined ruthenium catalysts have been developed for RCM reactions and tremendously contributed to the total synthesis of natural products.[14–32] For example, Martin group reported[33] an elegant work on the Grubbs I catalyzed RCM reaction of highly functionalized diene to afford the key intermediate of eight membered ring, which can deliver natural product (+)-FR900482 in a few steps. In a recent example, Takemoto, Tsukano and co-workers completed the first asymmetric total synthesis of shagenes A and B by using RCM reaction of an enamide and Ir-catalyzed double-bond isomerization of an alkylidenecyclopropane as the key steps.[28]

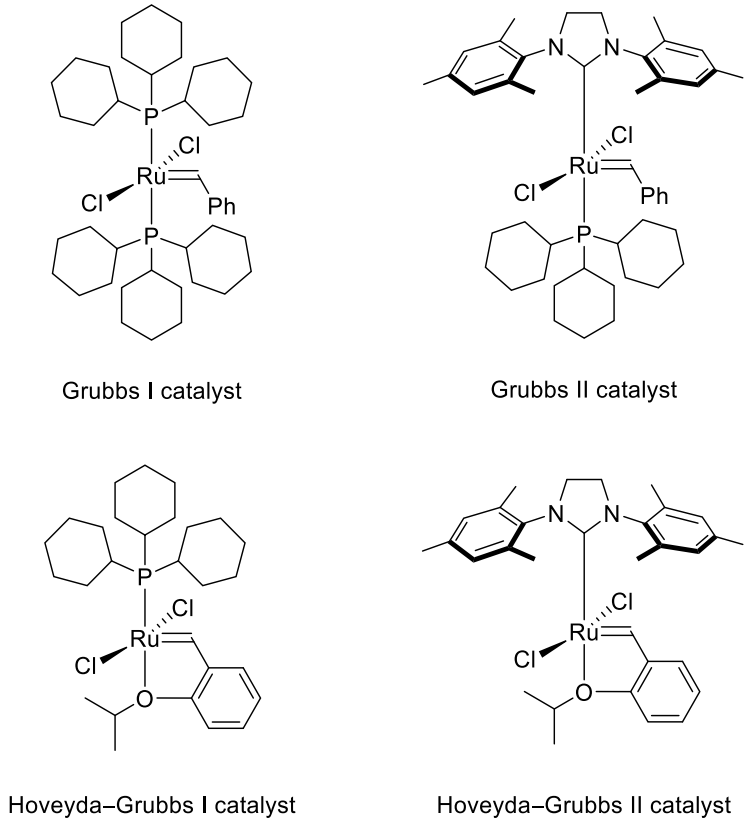


Figure 2. Representative ruthenium catalysts

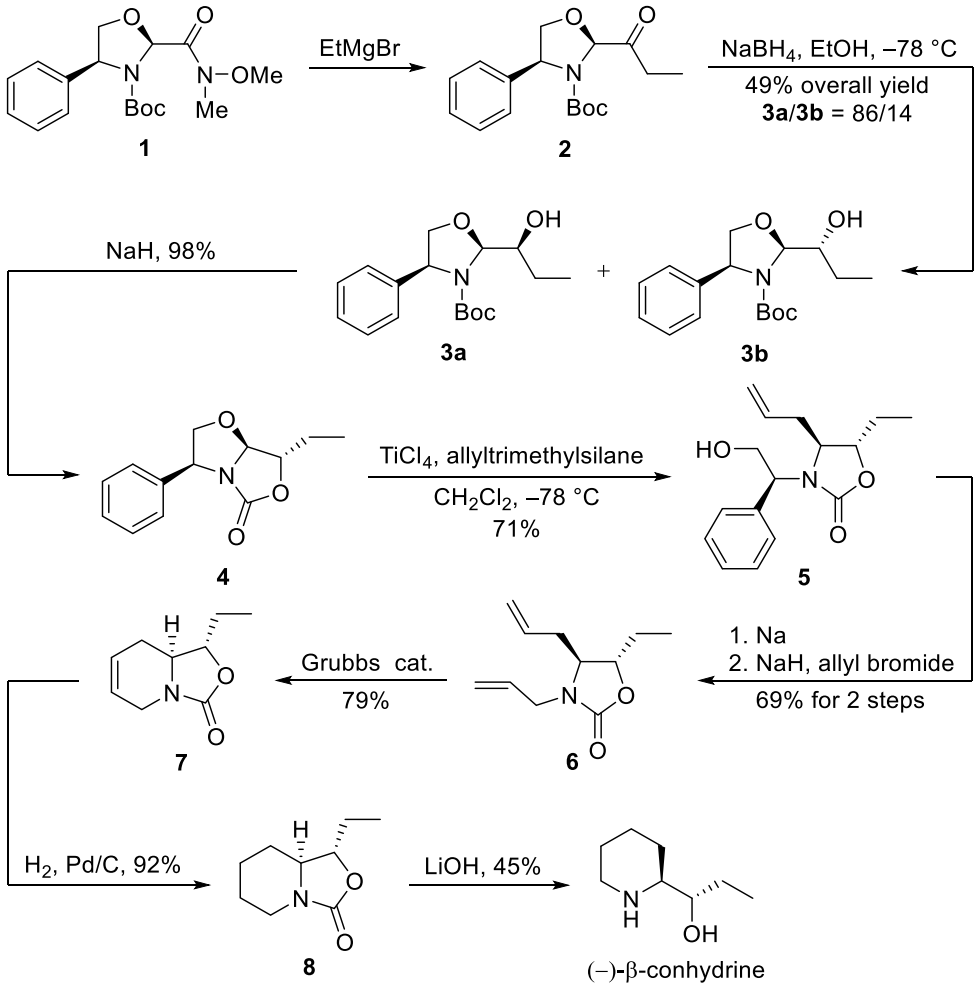
During the last few decades, RCM reaction has developed rapidly, and their applications in the total syntheses of conhydrines were also increasing. In the syntheses of conhydrines, the RCM reaction is one of the most efficient methods to construct the piperidine ring under mild reaction conditions (catalyst loadings can be as low as 1 mol% without loss of efficiency), with the generation of the double bond in the right position occurring simultaneously in a single step and excellent chemical yield (up to 100%), which was further used as a key intermediate in the syntheses of conhydrines. To the best of our

knowledge, review with regard to total syntheses of conhydrines on the basis of RCM reactions have not been published. Therefore, in this review, we will focus on recent advances in the syntheses of conhydrines based on the RCM strategy as the key step and covers the literature from 2000 to 2021.

2. Total synthesis of conhydrine via RCM reaction as the key steps

2-1. Total synthesis of (–)-β-conhydrine by Couty and co-workers – 2000

In 2000, Couty and co-workers described[34] the total synthesis of (–)-β-conhydrine, starting from Weinreb amide via RCM reaction as the key step (Scheme 1). Ethylation of Weinreb amide **1** with EtMgBr followed by diastereoselective reduction using $NaBH_4$ at –78 °C in EtOH afforded a mixture of **3a** and **3b**, which was converted to bicyclic compound **4** by using NaH.



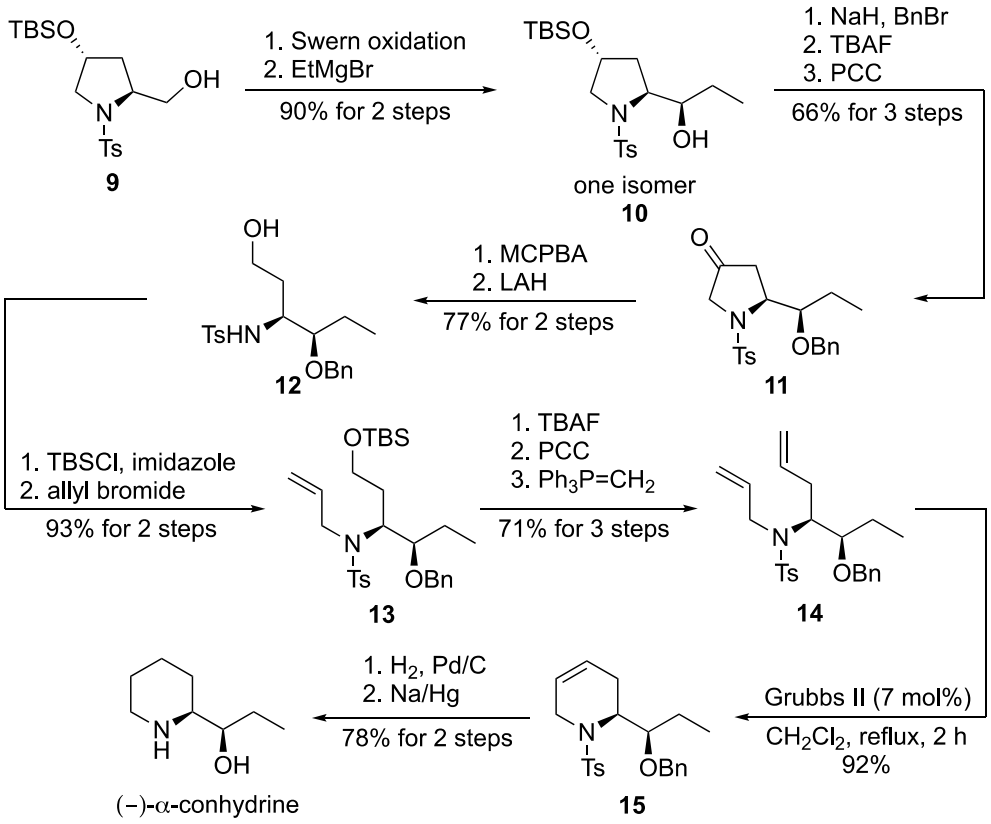
Scheme 1. Highlights of the total synthesis of (–)-β-conhydrine by Couty and co-workers

Next, diastereoselective allylation of **4** with allyltrimethylsilane and $TiCl_4$ via *N*-acyliminium chemistry[35] yielded allylated oxazolidinone **5** with 98% de, followed by reductive debenzylation of resulting

compound with Na provided oxazolidinone, which underwent alkylation process with NaH in the presence of allyl bromide to give **6** in 49% yield for three steps. Subsequent RCM reaction followed by catalytic hydrogenation afforded **7**, which could be converted to (–)-β-conhydrine via hydrolysis reaction with LiOH. Therefore, the (–)-β-conhydrine was synthesized in 9 steps with an overall yield of 8%.

2-2. Total synthesis of (–)-α-conhydrine by Chang and co-workers – 2006

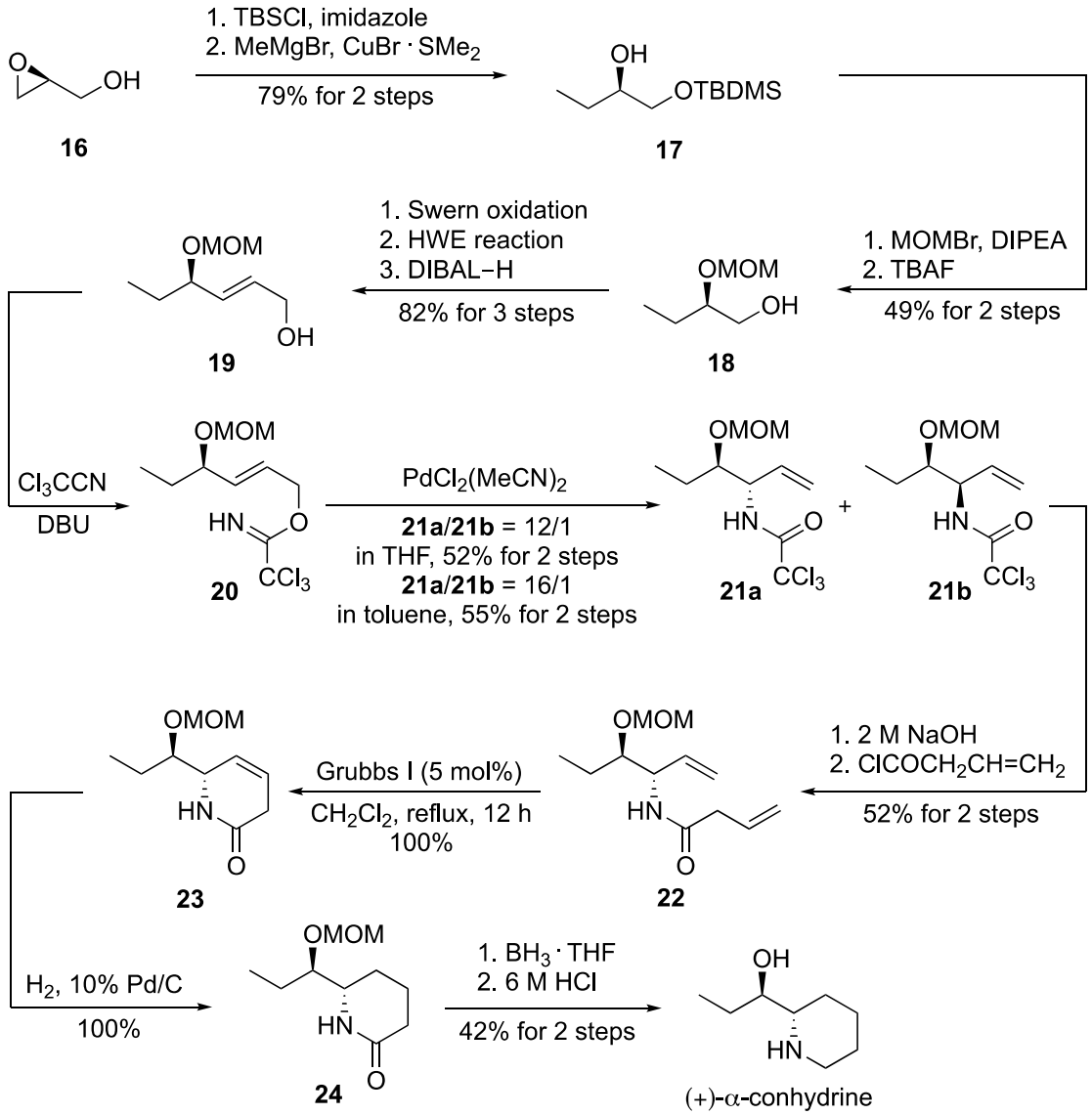
In 2006, Chang and co-workers reported[36] total synthesis of (–)-α-conhydrine via diastereoselective Grignard addition, regioselective Baeyer–Villiger reaction, and RCM reaction as the key steps (Scheme 2). Swern oxidation of compound **9** followed by treatment with EtMgBr afforded **10** as a one isomer in 90% yield over two steps, which was transformed to **11** in standard synthetic steps. Treatment of **11** with MCPBA followed by LAH-mediated reduction yielded **12** exclusively, which was converted to **13** over two steps including silylation of hydroxy group in **12**, and alkylation of secondary amine. Further manipulations including desilylation, oxidation and Wittig olefination furnished diene **14**, which underwent RCM reaction using Grubbs II (7 mol%) to afford expected piperidine ring **15**. Next, catalytic hydrogenation followed by desulfonation afforded (–)-α-conhydrine. Therefore, the synthesis of (–)-α-conhydrine was accomplished in 15 steps with an overall yield of 23%.



Scheme 2. Highlights of the total synthesis of (–)-α-conhydrine by Chang and co-workers

2-3. Total synthesis of (+)-α-conhydrine by Sutherland and Jamieson – 2007

In 2009, Sutherland and Jamieson realized[37] asymmetric synthesis of (+)-α-conhydrine using MOM-ether-directed aza-Claisen rearrangement and RCM as the key steps (Scheme 3). Reaction of **16** with TBSCl and imidazole followed by regioselective ring opening with a copper-catalyzed Grignard reaction[38] afforded **17** in 79% yield over two steps. Protection of hydroxy group in compound **17** with MOMBr in the presence of Hünig's base followed by removal of silyl-ether with TBAF yielded **18**.



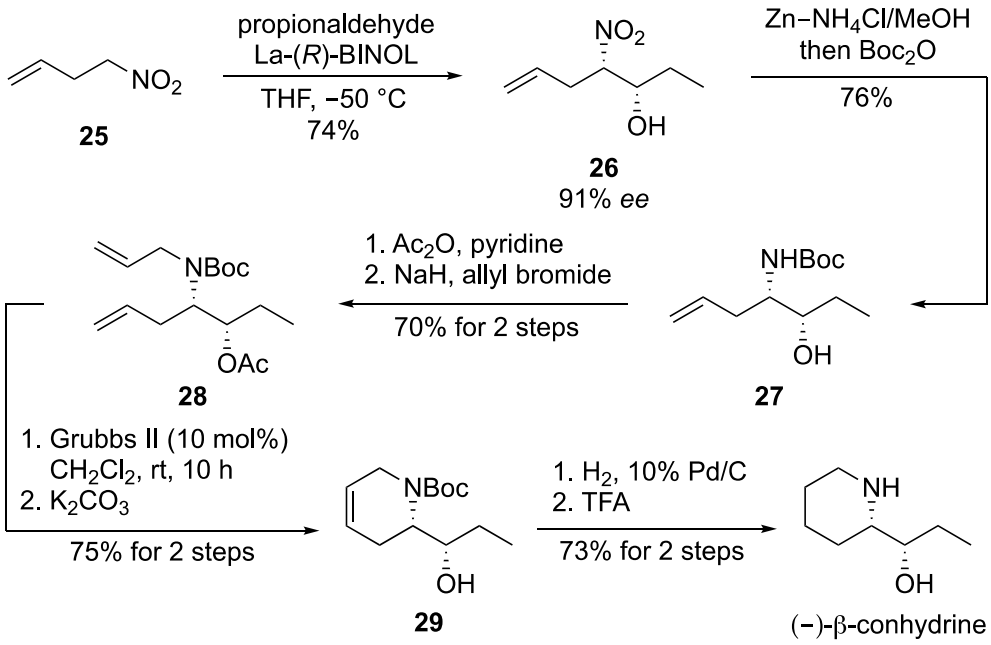
Scheme 3. Highlights of the total synthesis of (+)-α-conhydrine by Sutherland and Jamieson

Next, compound **18** was constructed via Swern oxidation/Horner–Wadsworth–Emmons (HWE) reaction in one-pot followed by reduction of *E*-*α,β*-unsaturated ester with DIBAL–H provided *E*-allylic alcohol **19** in excellent yield. Exposure of **19** to trichloroacetonitrile (Cl_3CCN) and DBU afforded trichloroacetimidate **20**. Next, the *erthyro*- and *threo*-allylic trichloroamides **21a** and **21b** were achieved

successfully from compound **19** in 52% overall yield with ratio of 12:1 through a palladium(II)-catalyzed MOM-ether-directed aza-Claisen rearrangement as the key steps. After the optimization of the reaction conditions under various solvents, they found that, when **20** in toluene using $PdCl_2(MeCN)_2$ (10 mol%) as the catalyst gave the **21a** and **21b** in 55% yield (2 steps) with an excellent 16:1 ratio. Having key intermediate **21a** in hand, (+)-α-conhydrine was accomplished as outlined in Scheme 3. Hydrolysis of **21a** with 2 M NaOH followed by acylation with 3-butenoyl chloride afforded **22**, which underwent RCM reaction using Grubbs I (5 mol%) to yield unsaturated *δ*-lactam **23**. Subsequent, a sequence of palladium catalyzed hydrogenation, reduction of the lactam with BH_3·THF followed by deprotection MOM group with 6 M HCl provided (+)-α-conhydrine in 42% yield for three steps. Therefore, (+)-α-conhydrine was obtained in 15 steps with an overall yield of 4%.

2-4. Total synthesis of (–)-β-conhydrine by Barua and co-workers – 2008

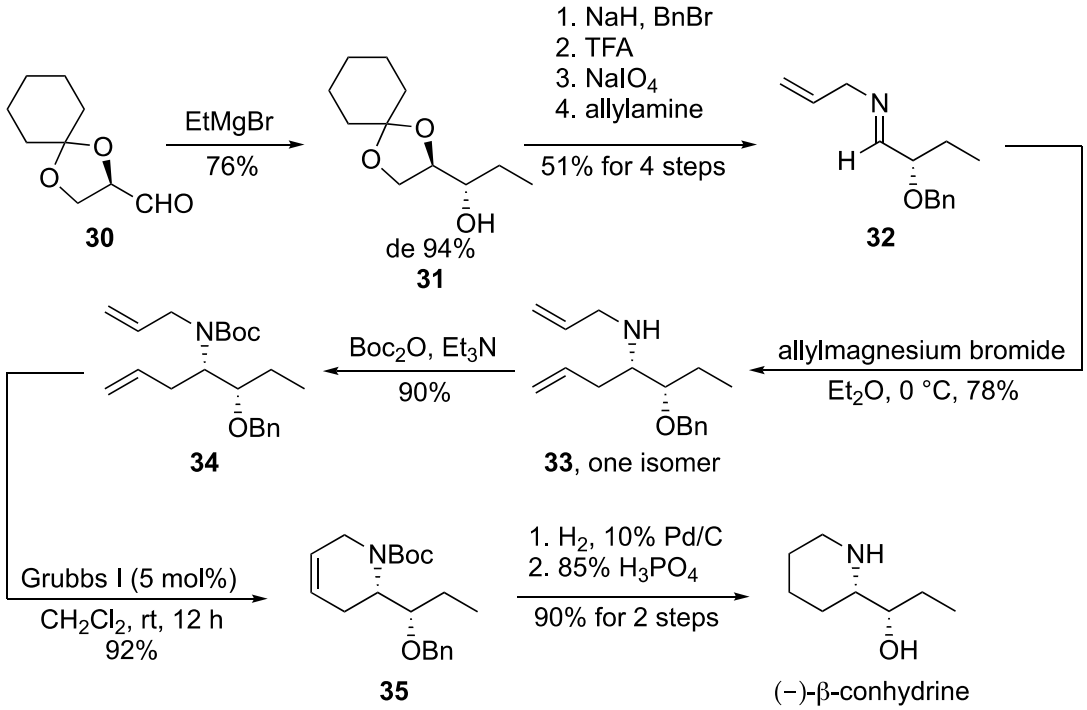
In 2008, Barua and co-workers disclosed[39] an efficient synthesis of (–)-β-conhydrine using RCM reaction as the key step (Scheme 4). Exposure of **25** to asymmetric Shibasaki's Henry reaction conditions with propionaldehyde in the presence of La-(*R*)-BINOL yielded **26**. Treatment of **26** with Zn/NH_4Cl followed by reacted with Boc_2O gave the **27** in one-pot operation. Protection of hydroxy group in **27** followed by *N*-allylation afforded **28**. Smoothly, compound **29** was generated from **28** under RCM reaction conditions using Grubbs II (10 mol%) followed by hydrolysis of acetyl group. Finally, hydrogenation and deprotection afforded (–)-β-conhydrine. Therefore, the (+)-α-conhydrine was accessed in 8 steps with an overall yield of 22%.



Scheme 4. Highlights of the total synthesis of (–)-β-conhydrine by Barua and co-workers

2-5. Total synthesis of (–)-β-conhydrine by Fadnavis and Venkataiah – 2009

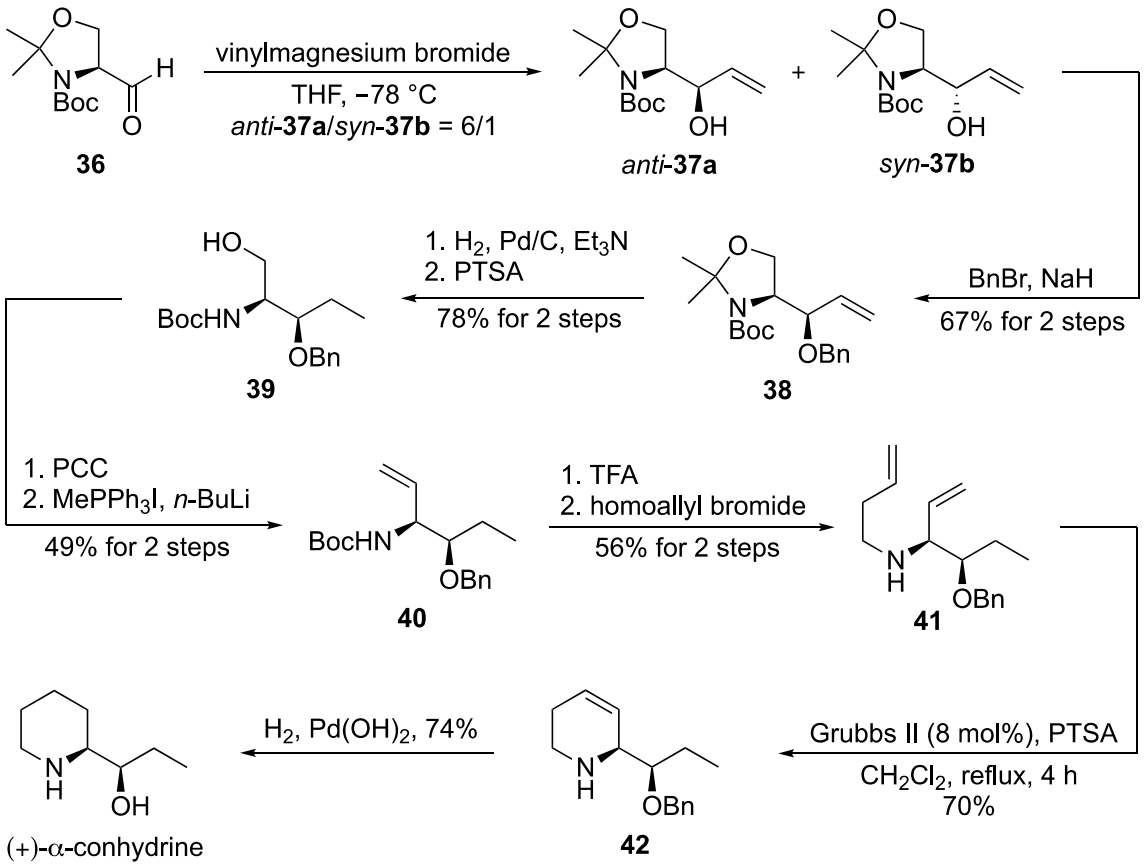
In 2009, Fadnavis and Venkataiah completed[40] asymmetric synthesis of (–)-β-conhydrine by using chelation-controlled diastereoselective Grignard reaction and RCM reaction as the key steps (Scheme 5). Grignard reaction of compound **30** with EtMgBr gave **31** (de 94%) diastereoselectively, which was converted to the allylimine **32** under classical operations over four steps. It should be pointed out that the stereochemical of **31** was explained on the basis of a Felkin-Anh control.[41] Next, chelation-controlled stereoselective Grignard reaction of **32** with allylmagnesium bromide afforded corresponding *syn* diallyl amine **33** as a single diastereomer, which treatment with Boc_2O provided dine **34**. Exposure of **34** to Grubbs I (5 mol%), RCM reaction proceeded smoothly to generate **35**, which further advanced to (–)-β-conhydrine via palladium catalyzed hydrogenation and phosphoric acid-mediated deprotection of Boc group. Therefore, the synthesis of (–)-β-conhydrine was achieved in 10 steps with an overall yield of 55%.



Scheme 5. Highlights of the total synthesis of (–)-β-conhydrine by Fadnavis and Venkataiah

2-6. Total synthesis of (+)-α-conhydrine by Panda and co-workers – 2009

In 2009, a short and enantioselective strategy for the total synthesis of (+)-α-conhydrine was developed by Panda and co-workers.[42] As depicted in Scheme 6, Diastereoselective nucleophilic addition of Garner aldehyde[43] **36** with vinylmagnesium bromide followed by benzylation of resulting alcohol with BnBr/NaH afforded major *anti* product **38**.

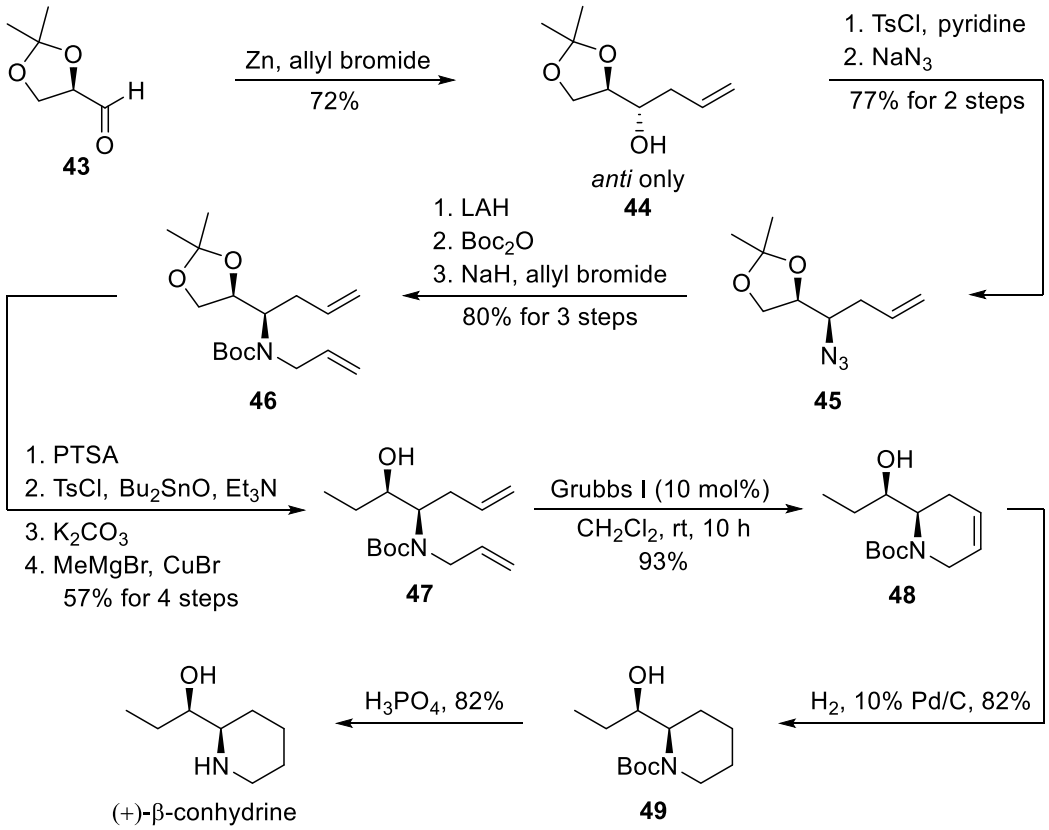


Scheme 6. Highlights of the total synthesis of (+)-α-conhydrine by Panda and co-workers

A sequence of catalytic hydrogenation of double bond in **38** with Pd/C in the presence of Et_3N, opening of acetonide with PTSA followed by oxidation and Wittig reaction gave **40**. Removal of Boc group in **40** followed by *N*-alkylation with homoallyl bromide furnished **41**. Next, acid mediated RCM reaction of **41** with Grubbs II (8 mol%) and PTSA gave **42**, which on treatment with $Pd(OH)_2$ under H_2 provided (+)-α-conhydrine in 74% yield. Therefore, (+)-α-conhydrine was prepared in 10 steps with an overall yield of 7%.

2-7. Total synthesis of (+)-β-conhydrine by Kamal and co-workers – 2009

In 2009, Kamal and co-workers demonstrated[44] total synthesis of (+)-β-conhydrine via azide nucleophilic substitution and RCM reaction as the key steps (Scheme 7). Treatment of **43** with Zn in the presence of allyl bromide afforded exclusively *anti*-alcohol **44**. Reaction of this alcohol with TsCl and pyridine gave tosylate, which was subjected to nucleophilic displacement using standard conditions to provide azide **45** in 77% yield for two steps. Reduction of azide group in **45** with LAH followed by protection of resulting primary amine with Boc_2O gave corresponding carbamate, which underwent allylation (allyl bromide/NaN/THF) to give **46**.



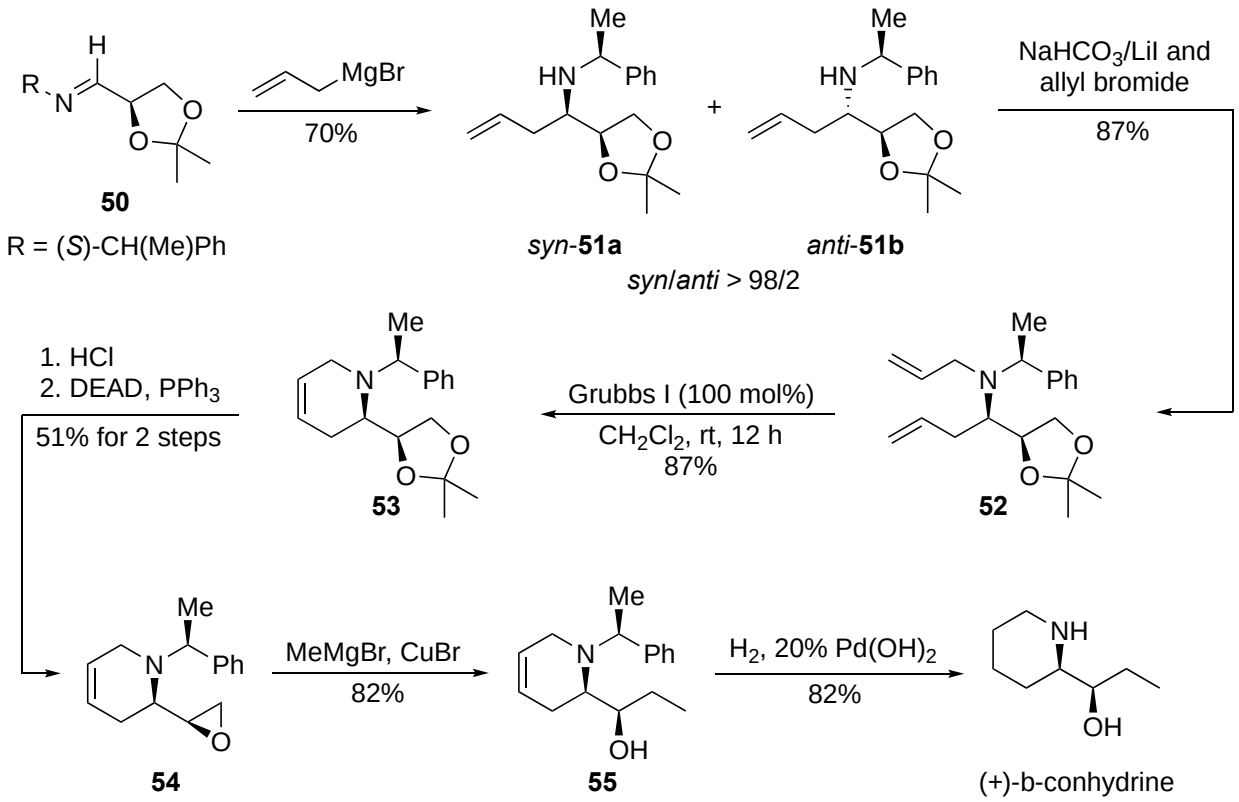
Scheme 7. Highlights of the total synthesis of (+)-β-conhydrine by Kamal and co-workers

Having the intermediate **46** in hand, a sequence of deprotection with PTSA, momotosylate formation with Martinelli conditions[45–47] (TsCl/Bu_2SnO/Et_3N), epoxidation with K_2CO_3 in MeOH followed by Grignard reaction with MeMgBr in the presence of CuBr furnished **47** in 57% overall yield. Treatment of **47** with Grubbs I (10 mol%) produced **48** in 93% yield. Further elaborations including catalytic hydrogenation followed by deprotection smoothly obtained (+)-β-conhydrine in 67% for two steps. Therefore, (+)-β-conhydrine was synthesized in 13 steps with an overall yield of 16%.

2-8. Total synthesis of (+)-β-conhydrine by Gálvez, Villegas and co-workers – 2011

In an elegant example, total synthesis of (+)-β-conhydrine was reported by Gálvez, Villegas and co-workers[48] via regioselective epoxide ring-opening followed by RCM reaction as the key steps (Scheme 8). The desired *syn* isomer **51a** was regioselectively constructed from starting compound **50** with allylmagnesium bromide in the absence of any acid additive. Treatment of **51** with allyl bromide in the presence of $NaHCO_3$ and LiI gave diene **52**, which underwent RCM reaction with Grubbs I (100 mol%) to yield **53**. Hydrolysis of this compound followed by epoxidation provided **54** in 51% yield for two steps. Exposure of **54** to MeMgBr in the presence of CuBr afforded **55**, which was then transformed to (+)-β-conhydrine through a palladium catalyzed hydrogenation with concomitant *N*-deprotection.

Therefore, the synthesis of (+)-β-conhydrine was accomplished in 7 steps with an overall yield of 18%.



Scheme 8. Highlights of the total synthesis of (+)-β-conhydrine by Gálvez, Villegas and co-workers

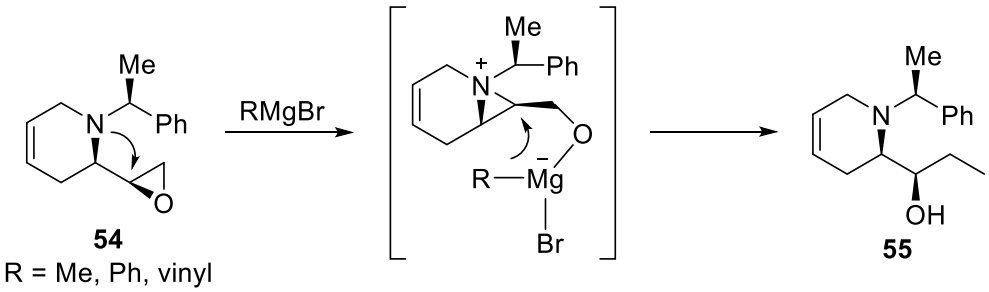
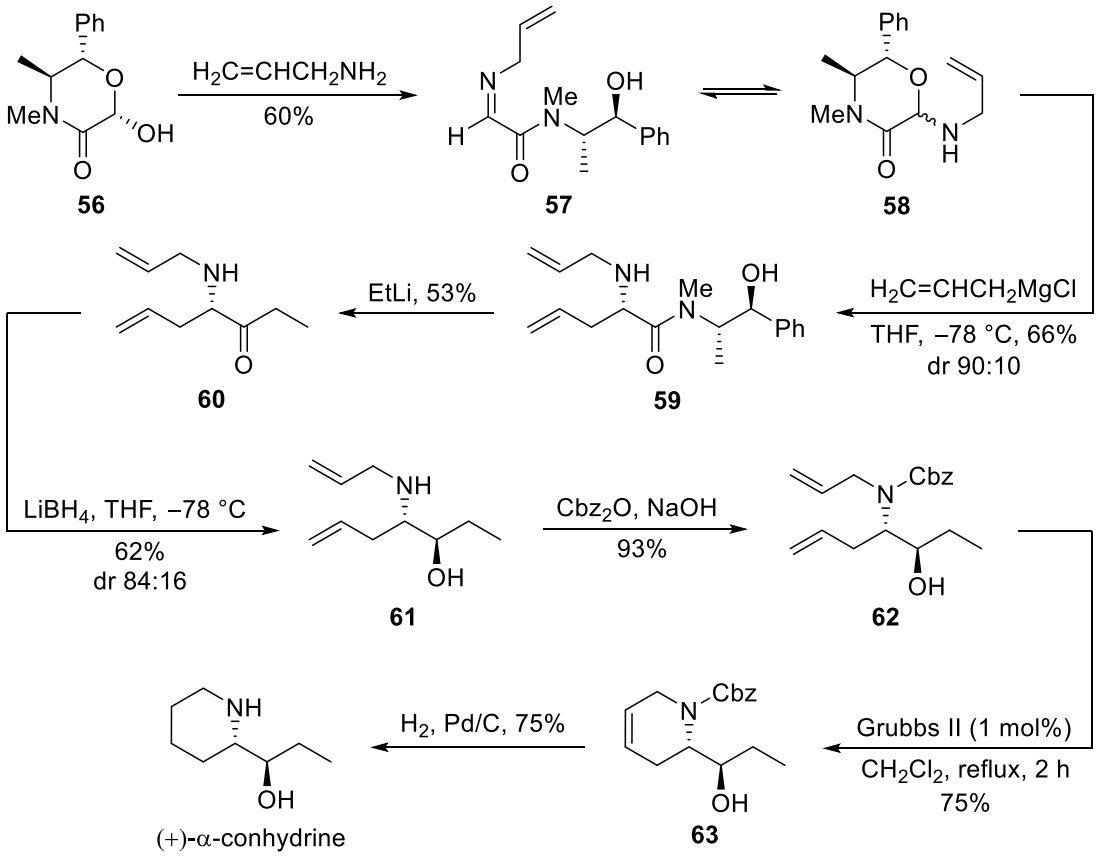


Figure 3. Reaction mechanism of epoxide ring-opening with organomagnesium reagents

As shown in Figure 3, reaction mechanism of **54** to **55** can be explained by the organomagnesium reagent coordinates the epoxide oxygen and nitrogen atom attacks at C–2 of the epoxide from the back side, forming the fairly stable aziridinium ion. Then, an intramolecular attack of the nucleophile on the C–2 of the aziridinium ion from the coordinated magnesium reagent from the back side to provide compounds **55** with neat retention of configuration.[48]

2-9. Total synthesis of (+)-α-conhydrine by Badía, Vicario and co-workers – 2011

In 2011, Badía, Vicario and co-workers accomplished[49] total synthesis of (+)-α-conhydrine by using chemo- and diastereoselective Grignard reaction including RCM reaction as the key steps (Scheme 9).



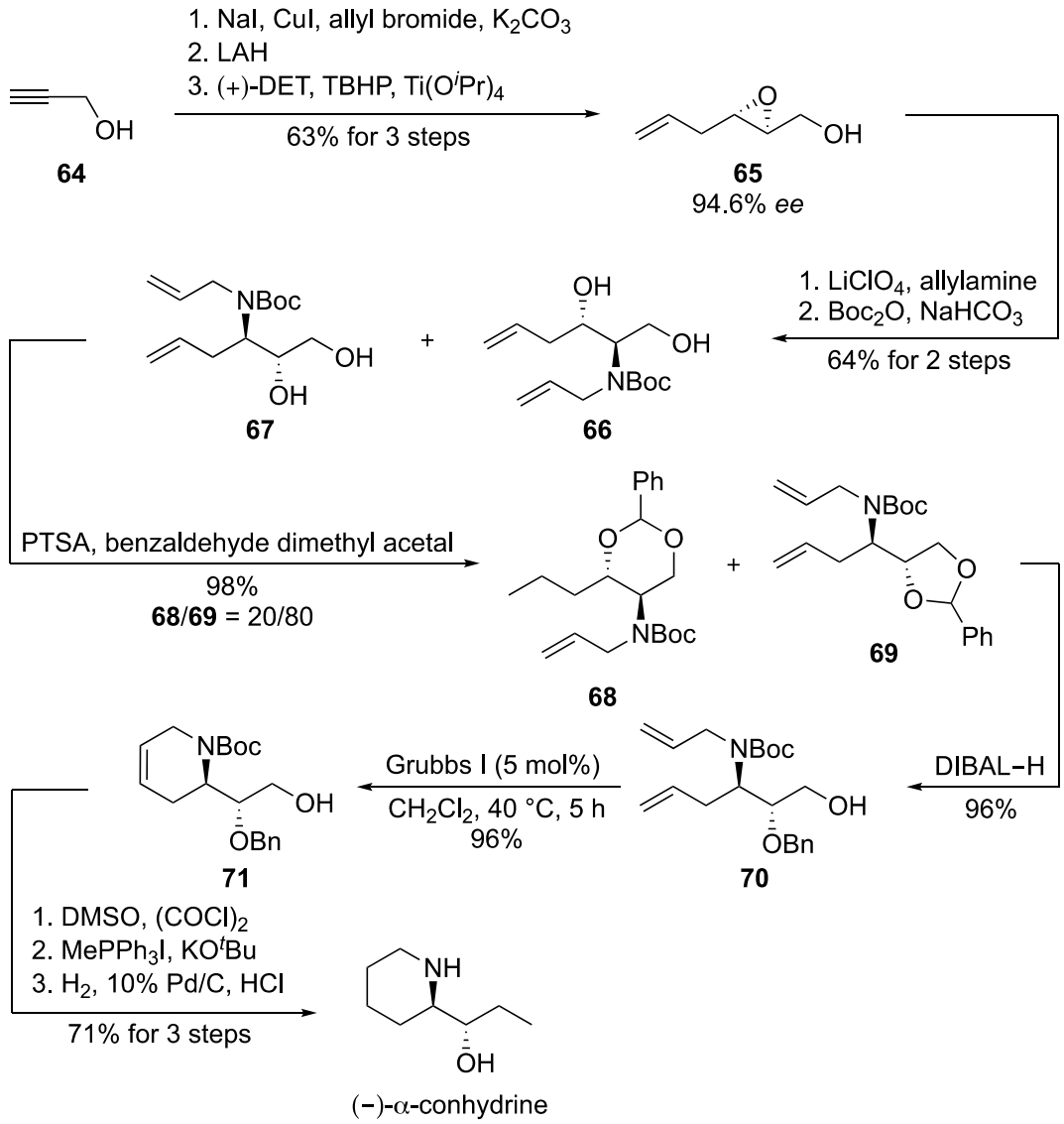
Scheme 9. Highlights of the total synthesis of (+)-α-conhydrine by Badía, Vicario and co-workers

Treatment of **56** with allylamine afforded **57**, which exists in equilibrium with the cyclized form **58**, followed by Grignard addition of equilibrating mixture of **57** and **58** gave desired α-amino amide **59**. Exposure of **59** to EtLi followed by treatment with excess $LiBH_4$ resulted **61**, which was readily transformed to **62**. RCM reaction of **62** with Grubbs II (1 mol%) gave **63**, which enabled the total synthesis of (+)-α-conhydrine. Therefore, (+)-α-conhydrine was obtained in 7 steps with an overall yield of 7%. In this study, using similar strategy they have also completed total synthesis of (–)-β-conhydrine.

2-10. Total synthesis of (–)-α-conhydrine by Fednavis and co-workers – 2011

In 2011, Fednavis and co-workers realized[50] total synthesis of (–)-α-conhydrine by using regioselective epoxide opening, stereoselective dihydroxylaton and RCM reaction as the key steps (Scheme 10). Treatment of **64** with allyl bromide in the presence of CuI, NaI and K_2CO_3 followed by reduction with LAH and Sharpless asymmetric epoxidation[51] with (+)-DET/TBHP/Ti(O*i*-Pr)$_4$ gave **65** in 94.6% ee.

Regioselective epoxide opening in **65** with $LiClO_4$/allylamine followed by treatment with Boc_2O afforded an inseparable mixture of allyl diols **66** and **67**.

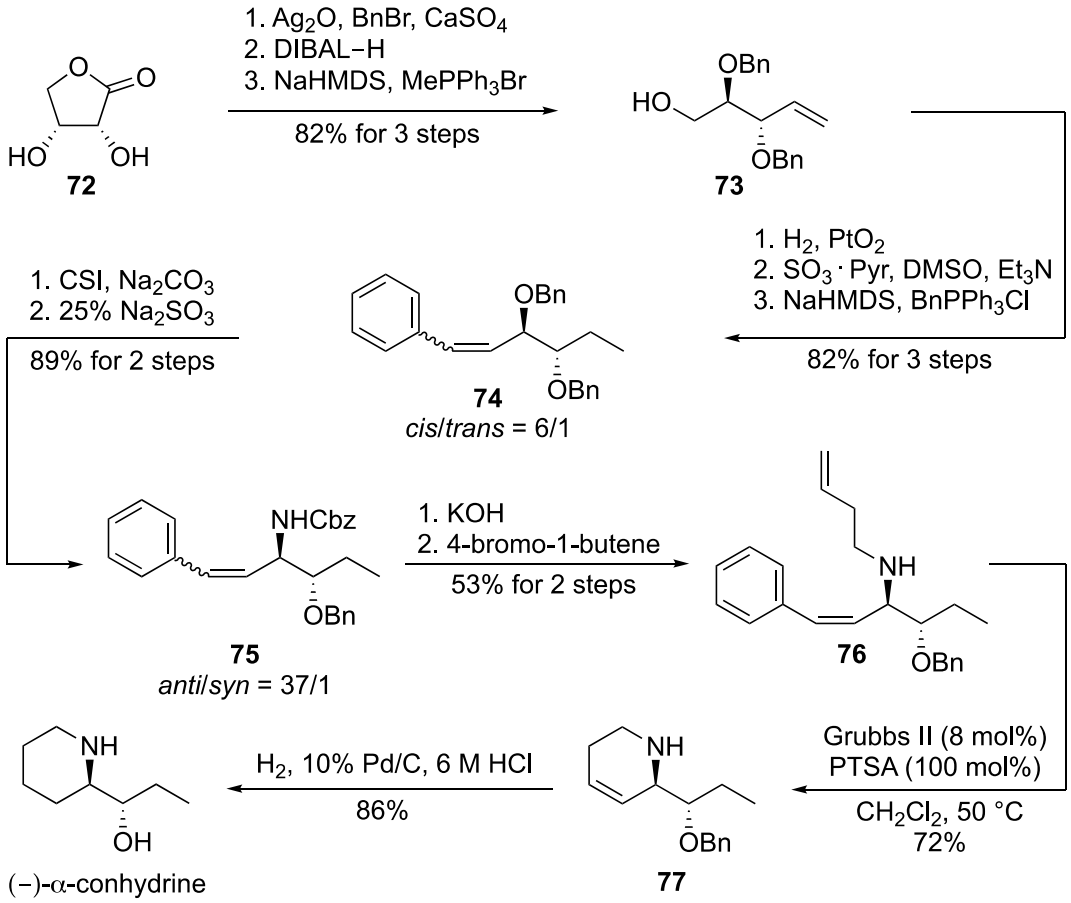


Scheme 10. Highlights of the total synthesis of (–)-α-conhydrine by Fednavis and co-workers

Exposure of the mixture to benzaldehyde dimethyl acetal gave **68** and **69** in an 20:80 ratio, which were easily isolated by column chromatography. Treatment **69** with DIBAL–H provided **70**. RCM reaction were carried out starting form **70** using Grubbs I (5 mol%) gave **71**, which underwent Swern oxidation followed by Wittig reaction and palladium catalyzed hydrogenation to yield (–)-α-conhydrine. Therefore, (–)-α-conhydrine was synthesized in 11 steps with 26% overall yield.

2-11. Total synthesis of (–)-α-conhydrine by Jung and co-workers – 2012

In 2012, Jung and co-workers disclosed[52] an elegant strategy for the synthesis of (–)-α-conhydrine using their previously developed regioselective and diastereoselective chlorosulfonyl isocyanate (CSI) reaction and RCM reaction as the key steps (Scheme 11). Treatment of **72** with Ag_2O and BnBr in the presence of $CaSO_4$ followed by partial reduction with DIABL–H, subsequent Wittig reaction of resulting lactol gave **73**. A sequence of chemoselective hydrogenation, oxidation and Wittig reaction provided cinnamylic dibenzyl ether **74** as a 6:1 mixture of *cis*/*trans* isomers in 85% yield.



Scheme 11. Highlights of the total synthesis of (–)-α-conhydrine by Jung and co-workers

Exposure of **74** to CSI reaction followed by desulfonylation afforded *anti*-1,2-amino alcohol **75** in 89% yield with excellent diastereoselectivity (*anti*/*syn* = 37/1, determined by ^{1}H NMR spectroscopy). From a mechanistical point of view, the diastereoselectivity of compound **75** can be explained by the neighboring group effect, whereby the orientation of the NHCbz group retains its original configuration through double inversion of configuration.[52,53] Hydrolysis of **75** followed by *N*-alkylation yielded **76**, which was subjected to RCM reaction using Grubbs II (8 mol%) and PTSA as an additive provided **77**. Finally, (–)-α-conhydrine was obtained through a palladium catalyzed hydrogenation. Therefore, the synthesis of

(–)-α-conhydrine was accomplished in 12 steps with 20% overall yield.

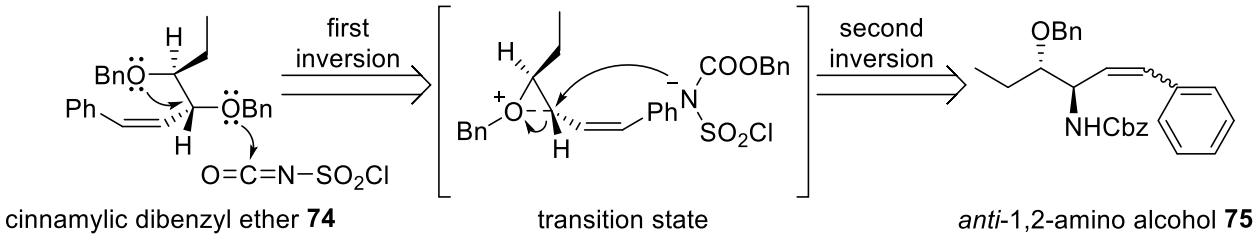
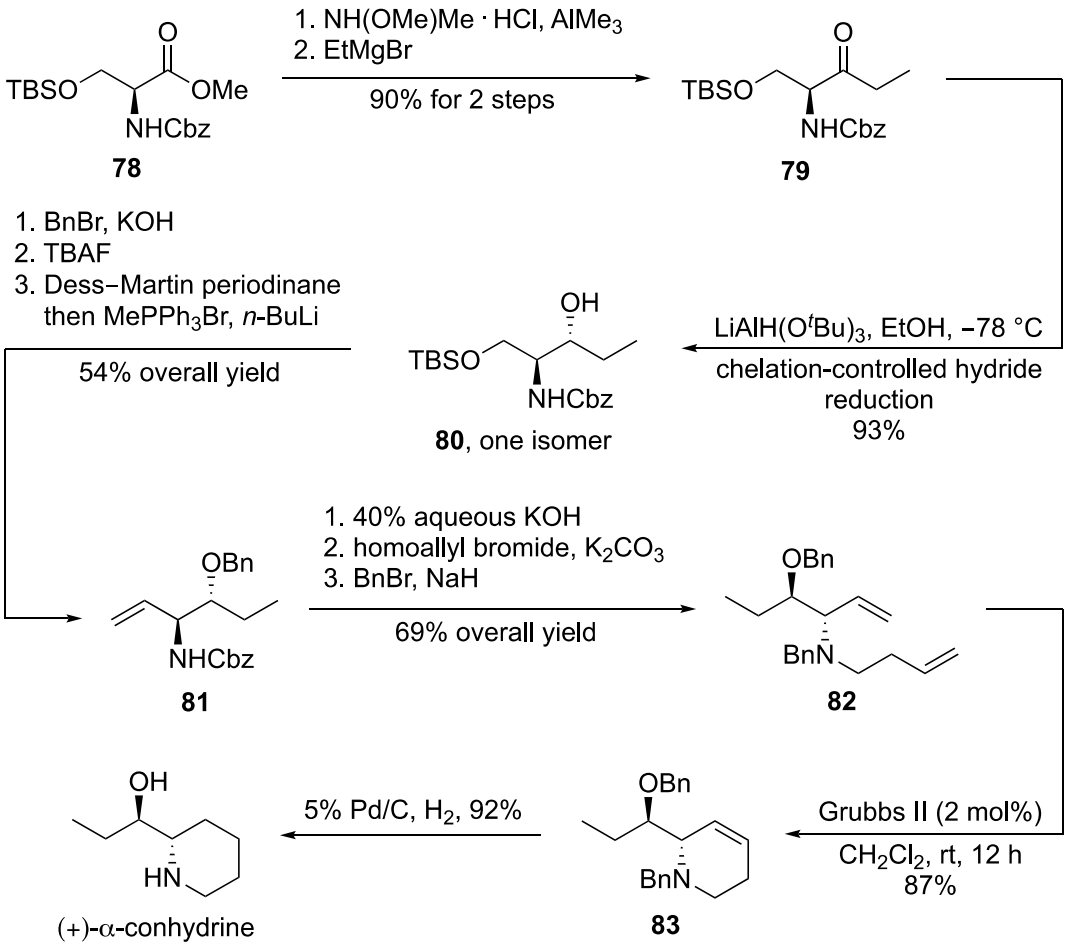


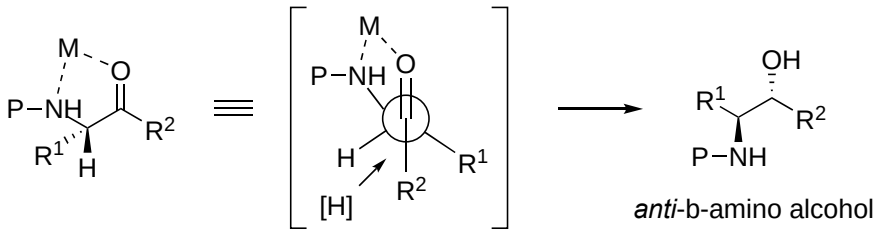
Figure 4. Reaction mechanism of cinnamylic dibenzyl ether **74** with chlorosulfonyl isocyanate

2-12. Total synthesis of (+)-α-conhydrine by Ham and co-workers – 2012

In 2012, our group accomplished[54] the total synthesis of (+)-α-conhydrine employing chelation-controlled hydride reduction followed by RCM reaction as the key chemical transformations (Scheme 12). As shown in Scheme 12, the key intermediate **80** was prepared from methyl ester **78** via Weinreb amide formation with MeO(Me)NH·HCl in the presence of $AlMe_3$ followed by Grignard reaction with EtMgBr and chelation-controlled hydride reduction of resulting amino ketone using $LiAlH(O^tBu)_3$ as the reducing agent[55,56] in EtOH at –78 °C afforded *anti*-β-amino alcohol **80** as a single isomer in 84% yield for three steps. As shown in Figure 5, the stereochemistry of this reaction mechanism can be explained by the chelation of the aluminum ion to both the carbonyl oxygen and the amine nitrogen, enforcing a *syn*-periplanar relationship between the amine and ketone groups and lead to the *anti*-β-diastereomer.[57–59] Having key compound **80** in hand, a sequence of benzylation, deprotection, Dess–Martin oxidation followed by Wittig reaction furnished **81** in a synthetically useful yield. Hydrolysis of Cbz group in compound **81** under basic conditions followed by *N*-alkylation with homoallyl bromide and subsequent benzylation of resulting diene using benzyl bromide in the presence of NaH gave **82** in 69% overall yield. Treatment of **82** with Grubbs II (2 mol%) smoothly yielded **83** in 87% yield. Finally, catalytic hydrogenation of **83**, the total synthesis of (+)-α-conhydrine was achieved in 92% isolated yield. Therefore, the (+)-α-conhydrine was accomplished in 11 steps with 25% overall yield.



Scheme 12. Highlights of the total synthesis of (+)-α-conhydrine by Ham and co-workers



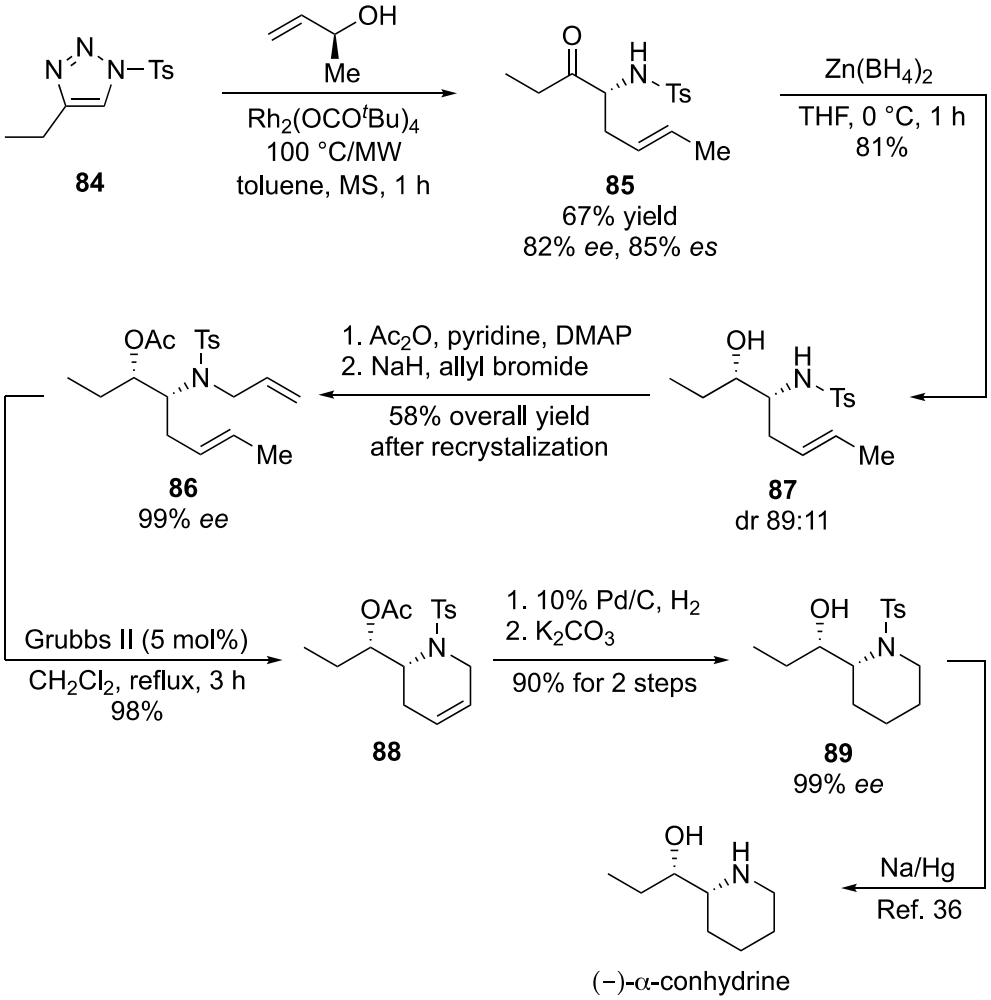
M = aluminum ion (from the reducing agent)
P = alkyl, H, protecting group
R^1 = aryl, alkyl, H
R^2 = aryl, alkyl, H

Figure 5. Chelation-controlled hydride reduction model

2-13. Total synthesis of (–)-α-conhydrine by Murakami, Miura and co-workers – 2017

Recently, Murakami, Miura and co-workers reported[60] concise formal synthesis of (–)-α-conhydrine by using rhodium(II)-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles with 2-alkenols followed by RCM reaction as the key steps (Scheme 13). Reaction of triazole **84** with (*S*)-but-3-en-2-ol in the presence of

$Rh_2(OCO^tBu)_4$ as the catalyst in toluene afforded ketone **85** in 67% yield with 82% ee. Exposure of **85** to $Zn(BH_4)_2$ followed by acetylation and *N*-allylation provided **87**. Treatment of **87** with Grubbs II (5 mol%) gave **88**, which underwent catalytic hydrogenation followed by removal of acetyl and tosyl group to give (−)-α-conhydrine.[36]



Scheme 13. Highlights of the formal synthesis of (−)-α-conhydrine by Murakami, Miura and co-workers

3. Conclusion

The RCM reaction has been recognized as a powerful strategy for the construction of a variety of carbocyclic and heterocycles because of its remarkable potential for a wide range of functional group tolerance, commercially available, stable to air, and easy handling. Since the pioneering report by Grubbs, ruthenium−carbene catalysts have been successfully employed to the total syntheses of natural products. In the syntheses of conhydrines, the RCM reaction is a very useful synthetic reaction, because it was conveniently constructing piperidine ring under mild reaction conditions in good to excellent chemical yields and catalyst even with low catalyst loadings (1 mol%), which was further used as a key intermediate in the synthesis of conhydrine. In a representative example, Sutherland and Jamieson

completed total synthesis of (+)-α-conhydine by using MOM-ether-directed aza-Claisen rearrangement and RCM reaction as the key steps (Scheme 3). In 2012, (−)-α-conhydrine has also been efficiently synthesized by Jung's group using their previously developed CSI methodology including RCM reaction as the key steps (Scheme 11). Very recently, we have described concise synthesis of (+)-α-conhydrine. Our strategy relies primary on stereoselective chelation-controlled hydride reduction followed by Grubbs II catalyzed RCM reaction as the key steps (Scheme 12). We do hope that the content in this review may assist further developments in the area of natural products and medicinal molecules.

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