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PALLADIUM(II)-CATALYZED CYCLIZATION *VIA N*-ALKYLATION OF AN ALLYL ALCOHOL WITH AN URETHANE AND ITS APPLICATION TO THE SYNTHESES OF NATURAL PRODUCTS

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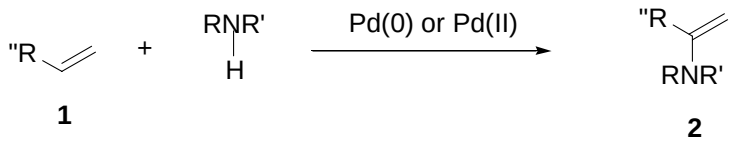
Abstract –Stereoselective amino-palladation of alkenylamines is one of the most important approaches for the stereoselective construction of *N*-hetero-alicycles, which form the skeletons of several biologically active natural products and related compounds. We reviewed our work with the utility of palladium(II)-catalyzed cyclization via *N*-alkylation of an allyl alcohol with a urethane. The syntheses of natural products by using Pd(II)-catalyzed cyclization were also reviewed.

INTRODUCTION

Among the vast number of biologically active natural products, the alkaloids, which have often complex structures containing multiple chiral centers, show considerable potential as drug candidates. Some, such as morphine and quinine, are already in clinical use. Alkaloids are interesting synthetic targets not only because of their potential medical applications, but also because of their structural complexity in many cases. Stereoselective amino-cycloaddition of alkenylamines is one of the most important approaches for the stereoselective construction of *N*-hetero-alicycles, which form the skeletons of several biologically active natural products and related compounds. Many syntheses along this line have been reported, including palladium chemistry.[1] In palladium chemistry, amino-palladation is one of interesting and exciting topics.[2] As we know, three relevant termination mechanisms have been proposed for amino-palladation. One mechanism, amino-palladation-β-elimination, produces a enamine (**2**) (Figure 1).[2, 3]



1 **2**

Figure 1

The second mechanism, amino-palladation via π-allyl palladium complex, gives allylamines (**4**) and (**5**).[2, 4] The π-allyl-palladium chemistry have many books and reviews.[1] The allylic esters (**3**) are used as the substrate (Figure 2).

3 **4** **5**

Figure 2

The last mechanism, amino-palladation-hydroxy elimination, gives allylamines (**4**) and (**5**) as same as these of second mechanism (Figure 3).[5] The Pd(II) species are not reduced, and thus the catalyst can re-cycle without reoxidation. Sometimes allylethers are used in stead of allyl alcohol (**6**).

6 **4** **5**

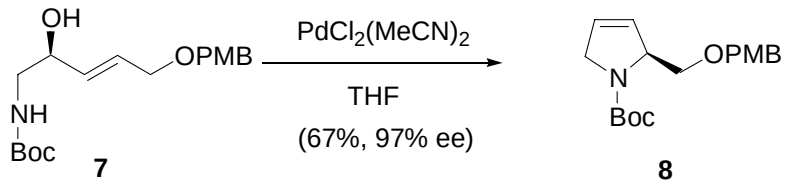
Figure 3

In this review, we should focus the amino-palladation-hydroxy elimination sequence in the sight of total synthesis of natural products. Especially, in the application to the synthesis, scope and limitation of this methodology and stereoselectivity were discussed.

SYNTHESIS OF PYRROLIDINE ALKALOID

Synthesis of (-)-bulgecinine (11)[7]

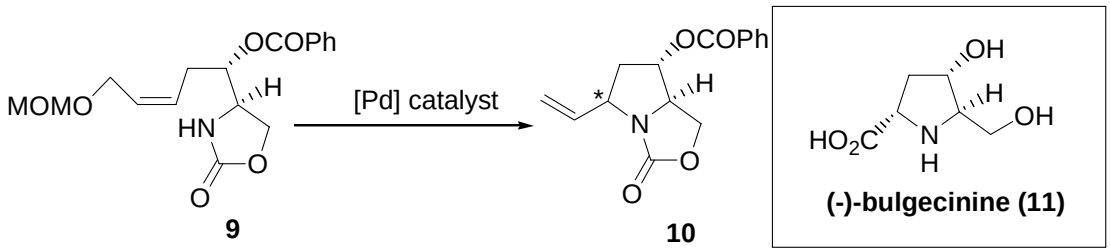
In 1992, Saito group reported the synthesis of the dihydropyrrol using Pd(II)-catalyzed cyclization. The cyclization of the allyl alcohol (**7**) was effected with palladium catalyst in THF to afford the dihydropyrrol derivative (**8**) in 67% yield with 97% ee (Figure 4).[6]



7 **8**

Figure 4

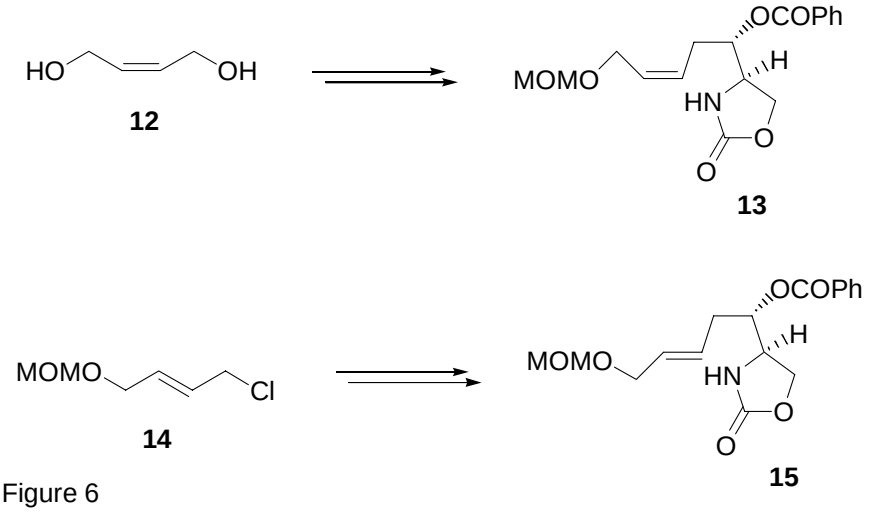
On the other hand, we examined the construction of the pyrrolidine using Pd(II)-catalyzed cyclization of the urethane and its application to the synthesis of natural products, such as (-)-bulgecinine (**11**) in 1992, independently. (-)-Bulgecinine (**11**) is one of the constituted amino acid of the novel glycopeptides bulgecins, which are potent β-lactam synergists found in the culture broth of *Pseudomonas acidophila* and of *Pseudomonas mesoacidophila*.[8, 9] We have focused our attention to the asymmetric construction of an oxazolidinone (**10**) which were expected to be an important intermediate on the synthesis of (-)-bulgecinine (**11**) (Figure 5).



9 **10**

Figure 5

The substrate (**13**) was synthesized from (*Z*)-2-butene-1, 4-diol (**12**) via Sharpless asymmetric epoxidation by 7 steps. In order to examine the effect of the double bond geometry on the stereochemical outcome of this cyclization, **15**, the *E*-isomer of **13**, was also prepared from 2-butyne-1, 4-diol derivative (**14**) by the similar method to the synthesis of **13** (Figure 6).



12 **13** **14** **15**

Figure 6

The intramolecular cyclization of **13** was effected by treatment with bis(acetonitrile)palladium(II) chloride (30 mol%) in THF to give an oxazolidinone (**16**) in 85% yield (96% ee) as a single diastereoisomer. The palladium(II)-catalyzed cyclization of the isomer **15** resulted in the formation of the same product **16** in 85% yield (Figure 7).

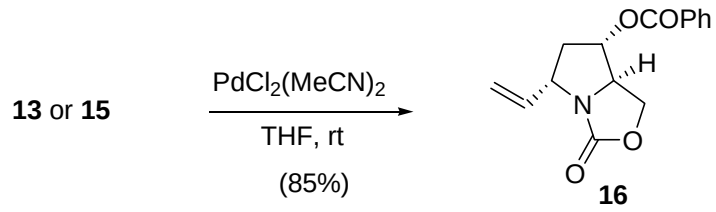


Figure 7

The reaction mechanism may be shown in Figure 8. The oxa-π-alkene palladium complex would be produced by coordination of the Pd catalyst with C-C double bond of allyl alcohol and alcohol moiety. The stereoselective formation of **16** could be explained by assuming the transition state **A** or **B**. The transition state **A** would be disadvantageous, because of steric repulsion between the amide moiety and oxa- π-alkene palladium complex (Figure 8). The geometry of double bond was not affected to the diastereoselectivity.

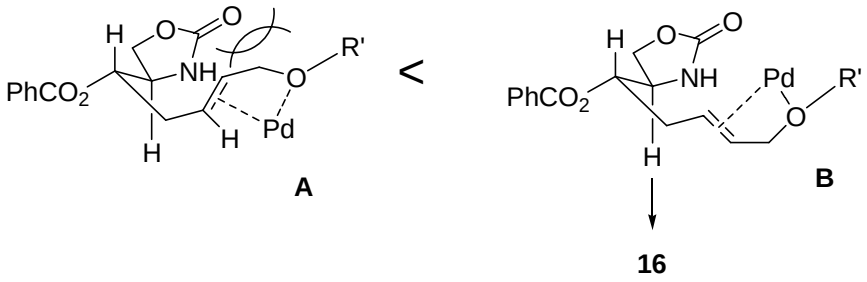


Figure 8

The oxazolidinone (**16**) thus obtained is a useful precursor for the preparation of the nitrogen-containing natural products, and its versatility was demonstrated by its transformation into (-)-bulgecinine (**11**) (Figure 9). The deprotection of **16** followed by benzylation gave a benzyl ether (**17**). The cleavage of the oxazolidinone ring in **17** was effected by the treatment with 1 N KOH to give a pyrrolidine derivative, which was subjected to sequential *N*-benzyloxy carbonylation and *O*-benzoylation to afford the pyrrolidine (**18**). Finally, the conversion of **18** to **11** was achieved in four steps[10] (ozonolysis, oxidation of the resulting aldehyde with $KMnO_4$, debenzylation, and acid hydrolysis of the carbamate and benzoate moiety). The physical data for the synthetic product (**11**) were in accordance with those reported for natural (-)-bulgecinine.

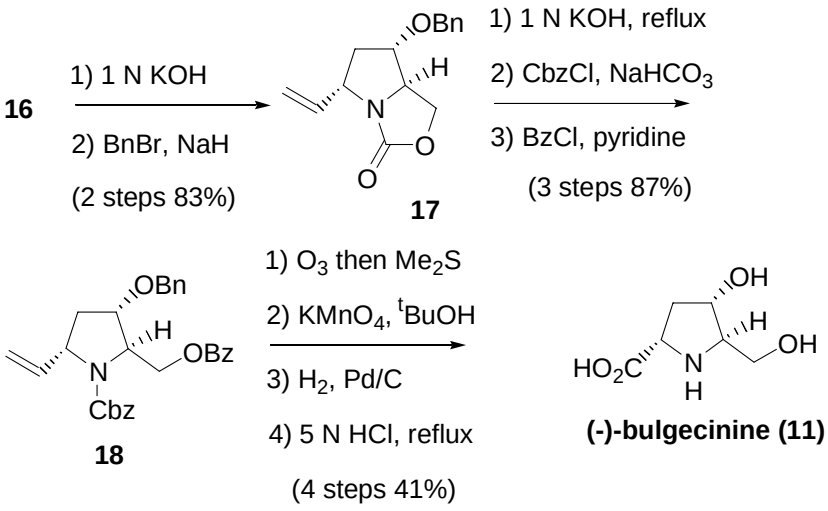


Figure 9

SYNTHESIS OF PIPERIDINE ALKALOID

Synthesis of (+)-prosopinine (21)[11]

In 1997, we tried on the asymmetric construction of bicyclic oxazolidinone derivatives (**20**), which provide a path to piperidine alkaloids[12] (Figure 10). Prosopinine (**21**), which was isolated from the leaves of the African mimosa *Prosopis africana* Taub,[13] is one of the piperidine alkaloids and has anesthetic, analgesic and antibiotic activities.[14]

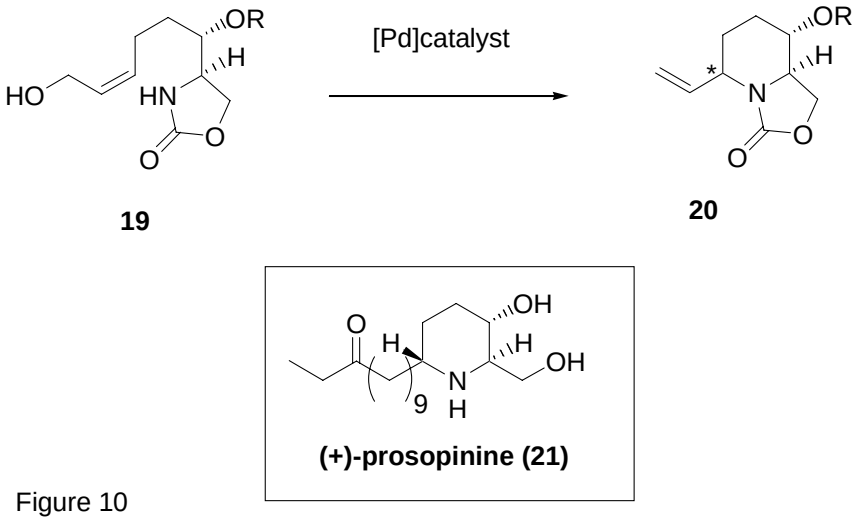


Figure 10

We prepared the chiral allyl alcohol (**19**) as the substrate for Pd(II)-catalyzed cyclization from 3-methoxymethoxypropyne by 9 steps. The intramolecular cyclization of **19** was achieved by treatment with bis(acetonitrile)palladium(II) chloride (20 mol%) [$PdCl_2(MeCN)_2$] in THF at room temperature to give a bicyclic oxazolidinone (**22**) in 75% yield as a single diastreoisomer (Figure 11).[15] The structure of

22 was confirmed by the spectral data and by an NOE experiment that indicated that the proton at the 1-position and the vinyl group at the 5-position are in a *cis* relation.

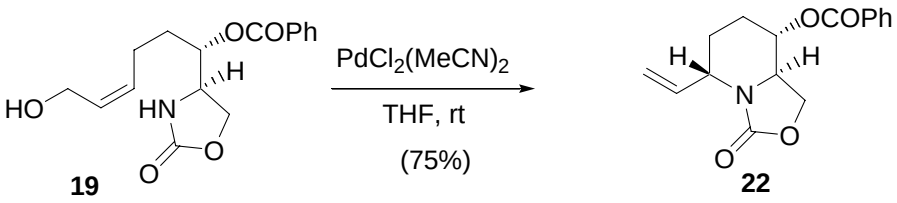


Figure 11

This high stereoselectivity of the palladium(II)-catalyzed cyclization can be explained by assuming the involvement of a transition state **A**, which minimizes steric repulsion between the oxa-π-alkene palladium complex and the oxazolidinone ring (Figure 12). The initial formation of an oxa-π-alkene palladium intermediate **A**, followed by backside *N*-nucleophilic attack upon the remote Pd-coordinated alkene, usually results in palladium-hydroxy elimination to give the trans-2,6-disubstituted piperidine system (**22**) stereoselectively.

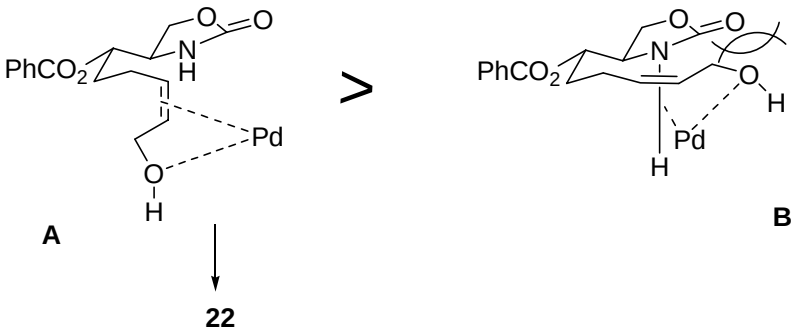


Figure 12

The resulting oxazolidinone (**22**) is an useful chiral building blocks for the preparation of the piperidine alkaloids and that versatility was demonstrated by the transformations into (+)-prosopinine (**21**). Debenzoylation and benzylation of **22** followed by ozonolysis gave the aldehyde, which was subjected to Wittig reaction and hydrolysis of the acetate moiety to give the alcohol (**23**) in 22% overall yield (Figure 13). After Swern oxidation of **23**, Grignard reaction with EtMgBr in THF and oxidation of the resulting alcohol with PCC gave the ketone, which was converted to the ketal (**24**). Finally, the conversion of the ketal (**24**) to (**21**) was achieved in three steps: debenzylation and hydrogenation of the olefin moiety, cleavage of the oxazolidinone ring, and deketalization. The physical data for the synthetic product (**21**), including the specific rotation, were identical to those reported for natural (+)-prosopinine.[16]

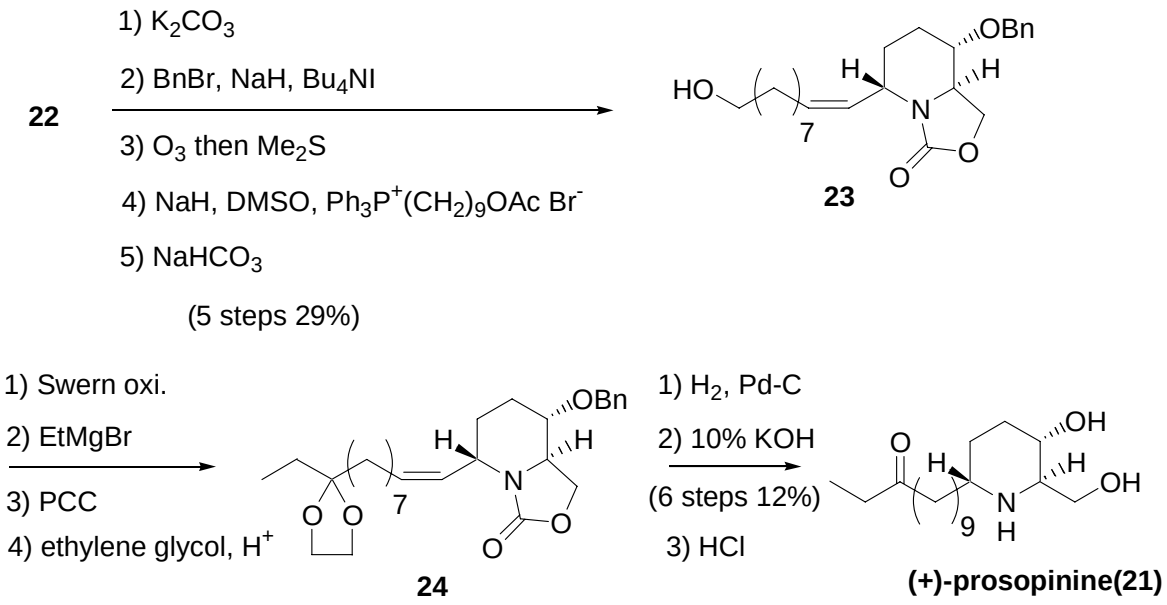


Figure 13

Synthesis of (+)-coniine (27)[17]

We examined the Pd(II)-catalyzed cyclization of the chiral allyl alcohol (**25**) to discuss the reaction mechanisms and chiral transfer (Figure 14).

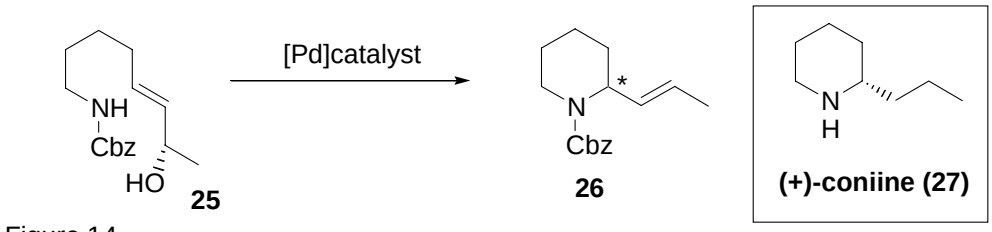


Figure 14

The chiral alcohol (-)-(**25**) was easily prepared via enzymatic resolution from 5-amino-1-pentanol by 5 steps. The palladium-catalyzed cyclization of the optically active urethane (-)-(**25**) (98% ee) gave the piperidine (**28**) in 89% yield. In these reactions, highly efficient intramolecular chirality transfer was achieved. The absolute configuration of **28** was established by its conversion into (+)-coniine (**27**). The catalytic hydrogenation and deprotection of **28** over $Pd(OH)_2$ under hydrogen, followed by treatment with HCl gas in Et_2O, afforded (+)-coniine (**27**) hydrochloride[18,19] in 98% yield (99% ee) of 2 steps (Figure 15).

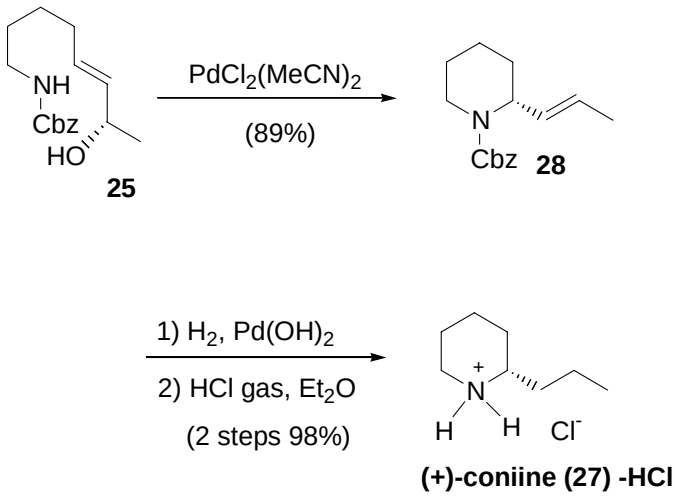


Figure 15

Synthesis of (-)-hydroxysedamine (31) and (-)-pseudoconhydrine (32) [20]

In 1997, we had interest of 1, 4-asymmetric induction in Pd(II)-catalyzed cyclization. So we examined the stereocontrolled construction of 2-functionalized 5-hydroxypiperidine (**30**) by a palladium(II)-catalyzed intramolecular cyclization and the synthesis of (-)-hydroxysedamine (**31**) and (-)-pseudoconhydrine (**32**), which are one of the hemlock alkaloids (Figure 16).

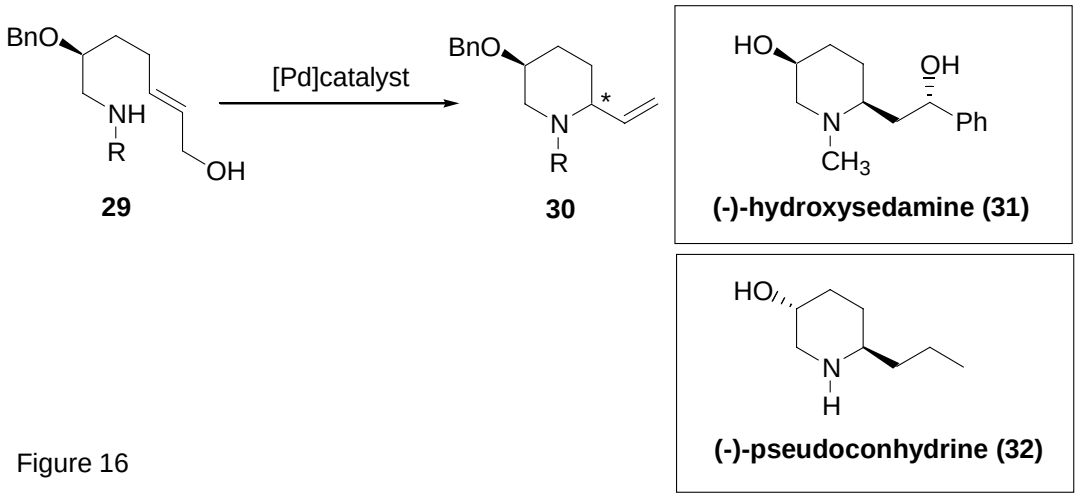
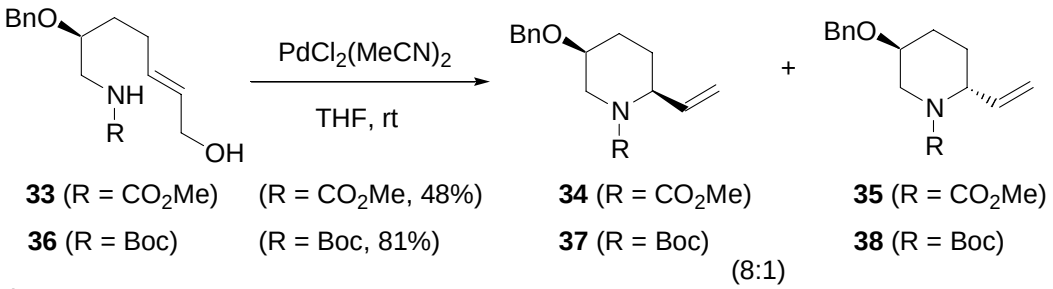


Figure 16

The substrates (**33**) and (**36**) for Palladium(II)-catalyzed cyclization was prepared in straightforward fashion from (*R*)-*O*-*t*-butyldimethylsilyl glycidol by 12 steps. The intramolecular cyclization of **33** was effected by treatment with bis(acetonitrile)palladium(II) chloride (30 mol%) [$PdCl_2(MeCN)_2$] in THF to give a separatable mixture consisting predominantly of the piperidine (**34**) and its stereoisomer (**35**) in a ratio of 8:1. And the Pd(II)-catalyzed cyclization of **36** gave the mixture of **37** and **38** in the ratio of 8:1 in 81% yield (Figure 17). The stereoselective formation of **34** could be explained by assuming the transition state **A** or **B** (Figure 18). The transition state **B**, which leads to **35**, would be disadvantageous because of steric repulsion between the carbamate moiety and oxa-π-alkene palladium complex.

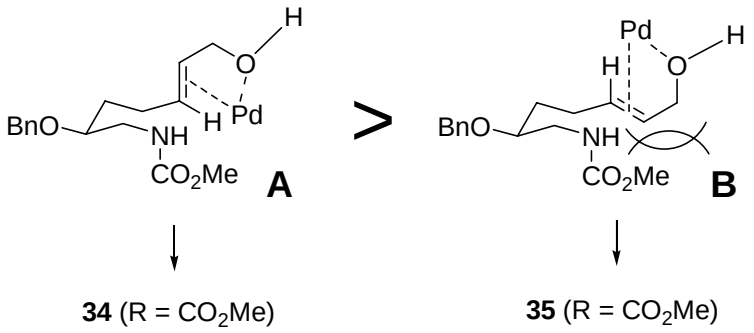


33 (R = CO_2Me) (R = CO_2Me, 48%) **34** (R = CO_2Me) **35** (R = CO_2Me)

36 (R = Boc) (R = Boc, 81%) **37** (R = Boc) **38** (R = Boc)

(8:1)

Figure 17



34 (R = CO_2Me) **35** (R = CO_2Me)

Figure 18

We examined the conversion of **34** to (-)-hydroxysedamine (**31**) (Figure 19). Ozonolysis of **34** followed by Wittig reaction with (methoxy)methyl-triphenylphosphonium chloride and subsequent hydrolysis with perchloric acid to give **39** in 36% yield of 3 steps. The aldehyde group of **39** was treated by PhMgBr, followed by oxidation with PCC to provide the ketone (**40**) in 42% yield of 2 steps. The protection of **40** by ethylene glycol, hydrogenation with Pd-C and deprotection with perchloric acid gave the alcohol (**41**) in 53% yield of 3 steps. The physical data for the synthetic product (**41**) were in accordance with those reported for the synthesis of natural (-)-hydroxysedamine (**31**).[21, 22]

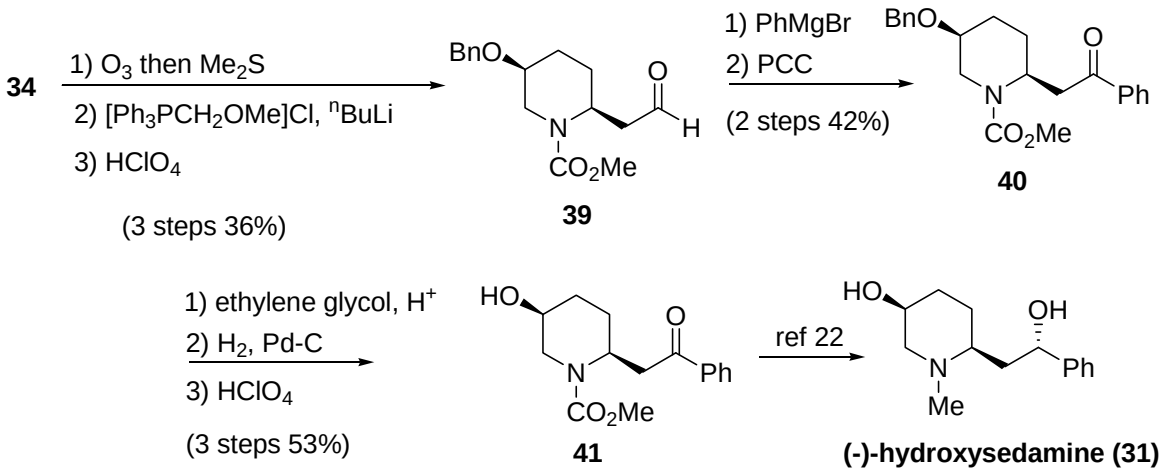


Figure 19

Next we examined the conversion of a mixture of **37** and **38** to (-)-epi-pseudoconhydrine (**44**) and (+)-pseudoconhydrine (**45**) (Figure 20). Ozonolysis of a mixture of **37** and **38** followed by Wittig reaction using ethyltriphenylphosphonium bromide and subsequent catalytic hydrogenation on Pd-C gave **42** and **43** in 42% and 6% yield, which were easily separated by silica gel column chromatography. The carbamate group of **42** and **43** was removed by treatment with CF_3CO_2H (TFA) to provide **44** and **45**, respectively. The physical data for the synthetic product (**45**) were in accordance with those reported for (+)-pseudoconhydrine.[23] The compound (**42**) was also converted to (-)-pseudoconhydrine (**32**) (Figure 20). The inversion of the alcohol moiety of **42** under Mitsunobu conditions followed by deprotection of the resulting benzoate with K_2CO_3 in MeOH gave **46**, which was treated with TFA to furnish (-)-pseudoconhydrine (**32**).[23]

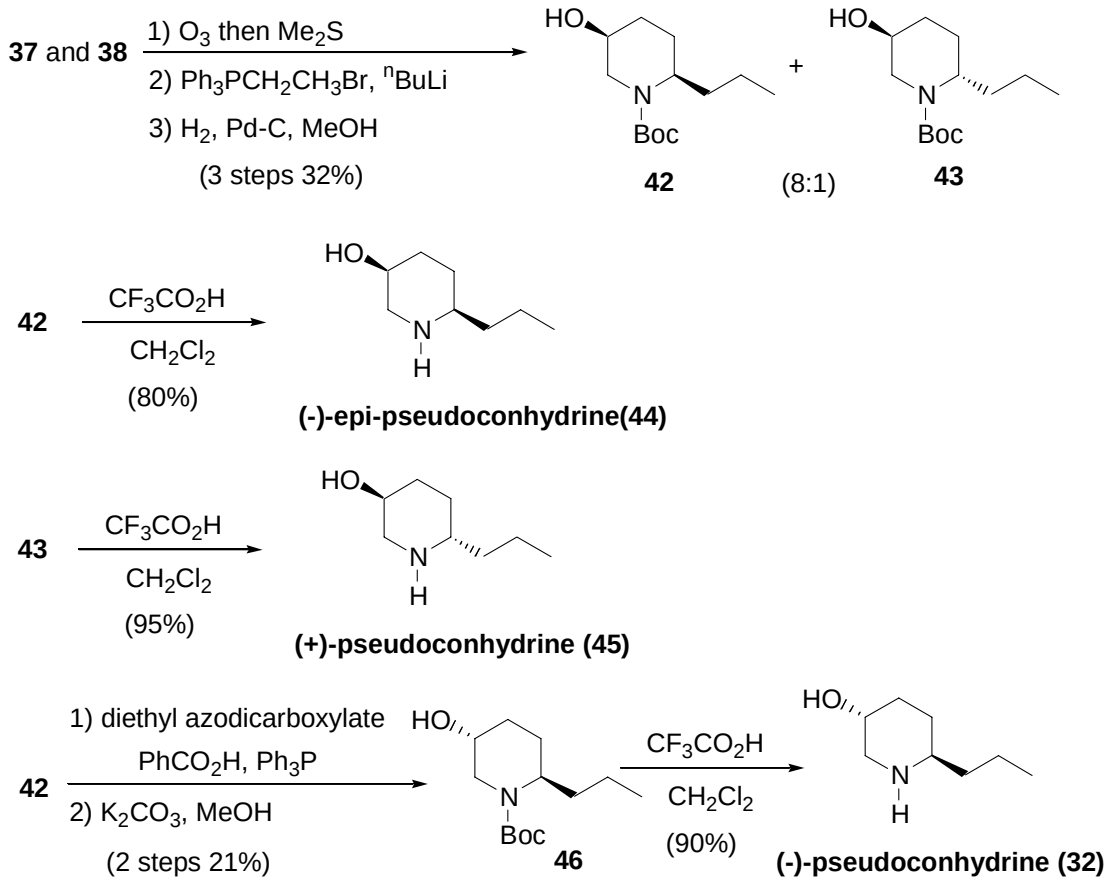


Figure 20

Synthesis of SS20846A (49)[24]

In 1999, we had interest of 1, 3-asymmetric induction in Pd(II)-catalyzed cyclization and focused on a novel stereoselective synthesis of SS20846A (**49**) via the intramolecular cyclization of the corresponding urethane (**47**) using palladium(II) catalyst (Figure 21). SS20846A (**49**) is a biologically active piperidine

alkaloid isolated from *Streptomyces* sp. S20846.[25,26] It is also a biosynthetic intermediate of streptazolin.[27]

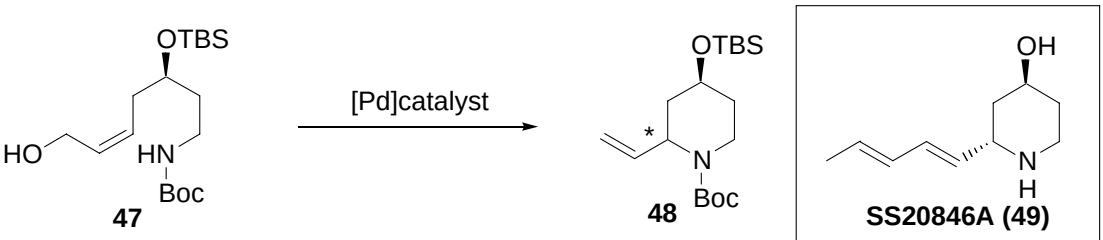


Figure 21

The precursor (**47**) for palladium(II)-catalyzed cyclization was prepared from (*S*)-glycidol by 11 steps. Pd(II)-catalyzed cyclization of **47** was performed as follows (Figure 22). The intramolecular cyclization of **47** was effected by treatment with bis(acetonitrile)palladium(II) chloride (10 mol%) [$PdCl_2(MeCN)_2$] in THF to give a separatable mixture of *trans*- **50** and *cis*- **50** (89% yield) in a ratio of 85:15. Next, the conversion of **50** to SS20846A (**49**) was examined in the following way (Figure 23). The alcohol (**51**) was prepared from **50** in 4 steps (dihydroxylation of olefin (OsO_4, NMO; 89% yield), oxidative cleavage ($NaIO_4$, CH_2Cl_2; 87% yield), Horner-Emmons-Wittig reaction, and reduction (DIBAL, THF; 96% yield)). Swern oxidation of **51** followed by Wittig reaction, desilylation, olefin isomerization, and deprotection

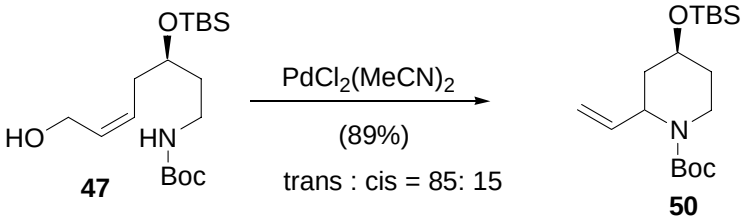


Figure 22

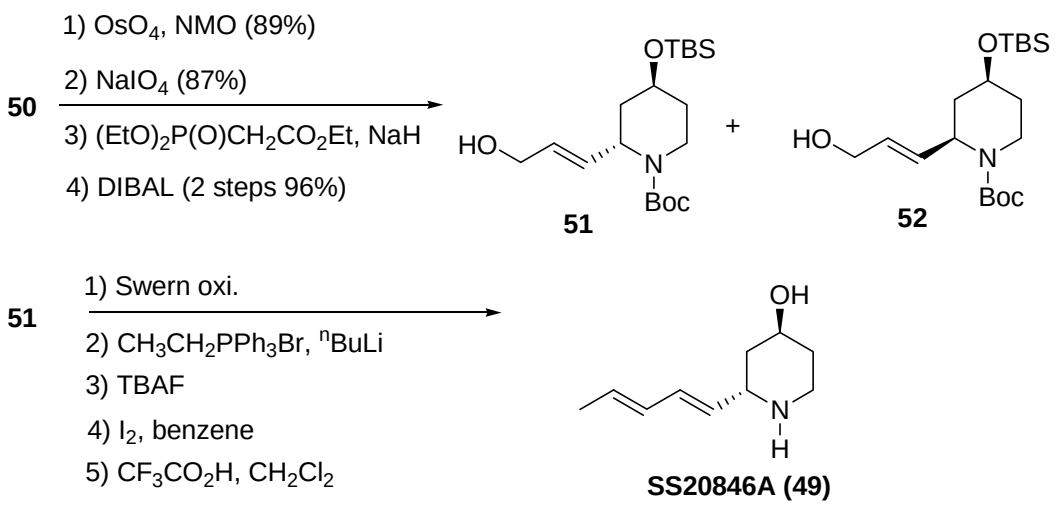


Figure 23

gave SS20846A (**49**) in 22% overall yield. The physical data for the synthetic product (**49**) were in accordance with those reported for SS20846A (Figure 23).[25]

A possible explanation for the stereoselective formation of *trans*- **50** is shown as follows (Figure 24). If the transition states are assumed to be **A** and **B**, the transition state **B**, which leads to *cis*- **50**, would be disfavored because of steric repulsion between the carbamate moiety and the palladium complex.

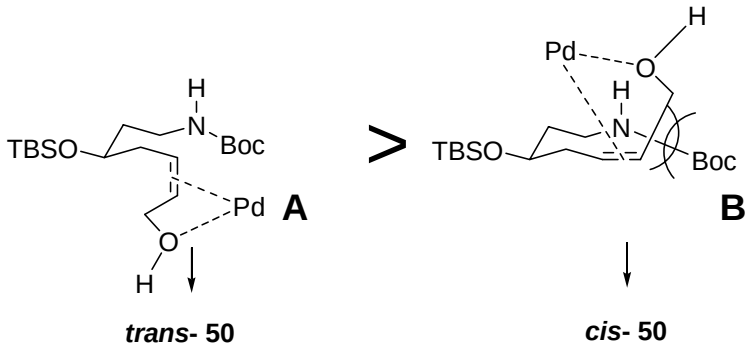


Figure 24

Synthesis of 1-deoxymannojirimycin (56)[28]

In 2000, we decided to investigate the synthesis of azasugar such as 1- deoxymannojirimycin (**56**) via intramolecular Pd(II)-catalyzed cyclization of **54** (Figure 25). Carbohydrates play an important role in many *in vivo* biological phenomena. Recently many azasugars were found to be efficient inhibitors of the carbohydrate hydrogenase and transferase.[29] In these azasugars, 1-deoxymannojirimycin (**56**)[30] isolated from *Lonshocarpus sericeus* by Fellows in 1979, showed significant biological activity as an inhibitor of α-L-fucosidase, α-D-mannnosidase and α-D-glucosidase.[31, 32]

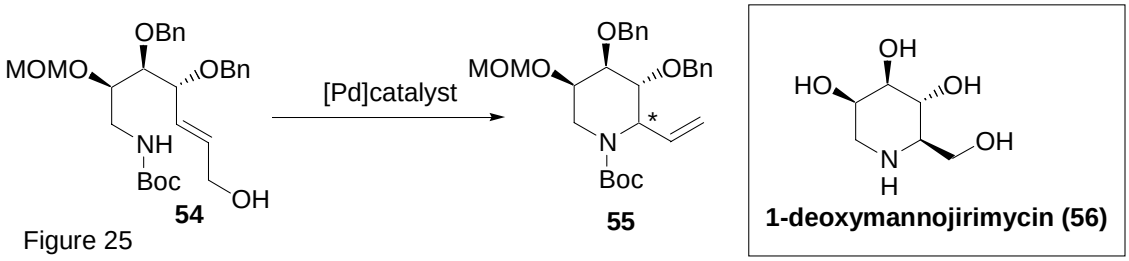


Figure 25

The allyl alcohol (**54**) was prepared from D-mannitol by 15 steps. The allyl alcohol (**54**) was treated with 15 mol % $PdCl_2(MeCN)_2$ in THF at room temperature to give the cyclized mixture (**57**) and (**58**) in 86% yield, the ratio of which was >26:1 (Figure 26). The structure of the major product (**57**) was confirmed by its spectral data. The stereoselective formation of **57** could be explained by assuming the cyclization proceed via transition state **A**. Transition state **B**, which leads to **58**, would be disadvantageous because

of steric repulsion between the Boc group and the oxa-π-alkene- palladium complex (Figure 26).

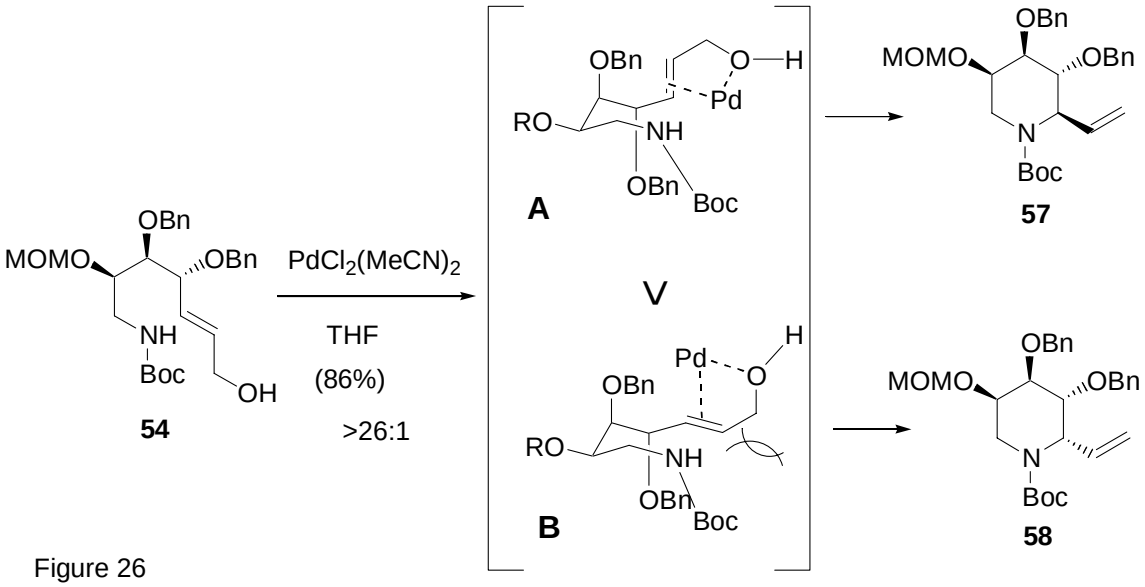


Figure 26

Conversion of **57** to 1-deoxymannojirimycin was effected by the three-step sequence shown in Figure 27. Ozonolysis of **57** and reductive workup ($NaBH_4$) gave the alcohol (**59**) in 92% yield. Removal of the benzyl group and the *N*-*t*-butoxy carbonyl group (Boc) in **59** (TFA, CH_2Cl_2; H_2, Pd-C, EtOH) provided 1-deoxymannojirimycin (**56**), whose structure was established by comparison of its NMR data with that of the natural compound.[30-32]

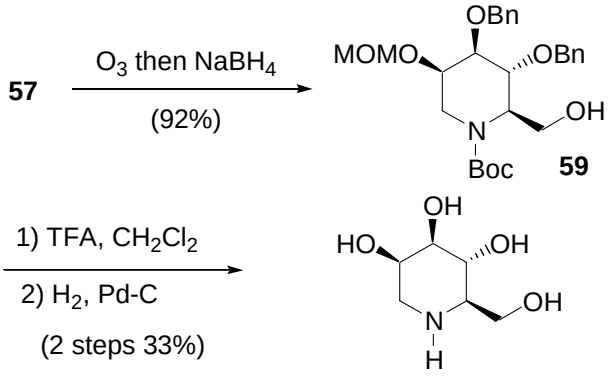


Figure 27

Synthesis of (-)-cassine (62)[33]

(-)-Cassine (**62**) was isolated from the leaves of *Cassia excelsa*, which has antimicrobial activity against *Staphylococcus aureus*.[35] Its structure was determined by Highet in 1963 and its absolute configuration was determined by Rice in 1966.[34, 36] In 2003, Makabe group attained the total synthesis of (-)-cassine (**62**) by using Pd(II)-catalyzed cyclization of **60** (Figure 28).

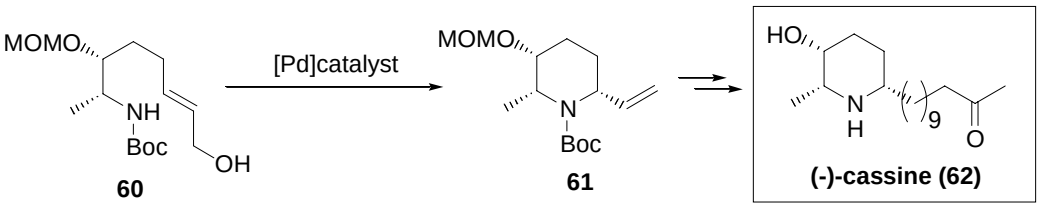


Figure 28

The cyclization of allyl alcohol (**60**), which prepared from 1,5-hexadiyne, was effected with $PdCl_2$ in THF to give the mixture (**61**) and (**63**) in 69% yield. The ratio of this diastereoselectivity for **61** and **63** was >49:1 (Figure 29). The stereoselective formation of **61** could be explained by assuming the transition state **A**. The transition state **B** would be disadvantageous, because of steric repulsion between the carbamate moiety and oxa-π-alkene- palladium complex (Figure 29).

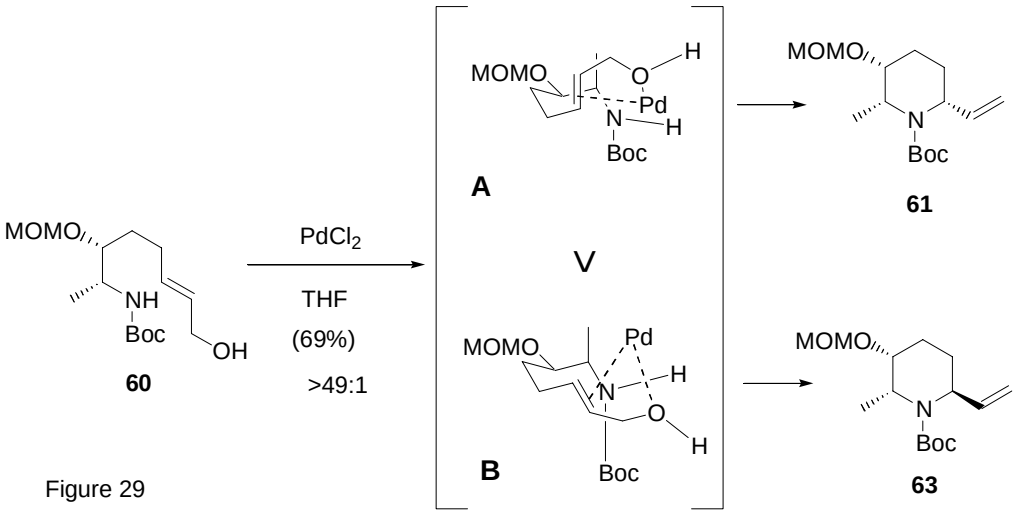


Figure 29

And then hydroboration of cyclized compound (**61**) gave the alcohol, which was followed by oxidation with PCC and Wittig carbon elongation reaction to afford **64** in 64% yield (Figure 30). The last task was Wacker oxidation, hydrogenation and deprotection. The synthetic product (**62**) was in good agreement with the reported values.[34, 36]

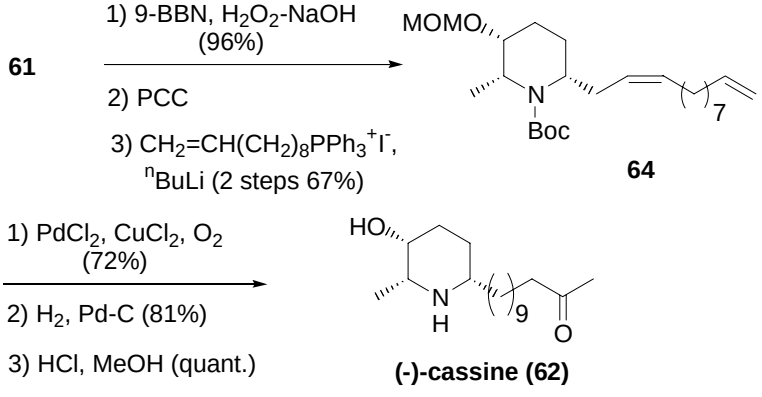


Figure 30

Synthesis of fagomine (67)[37]

Fagomine (**67**) is a piperidine alkaloid isolated from buckwheat seeds (*Fagopyrum esculentum*) (*Polygonaceae*) and more recently from *Xanthocericis zambesiaca*, which is found in dry forests in southern Africa.[38-40] Fagomine exhibits inhibitory activity towards mammalian α-glucosidase and β-galactosidase.[39] In 2007, we examined an asymmetric synthesis of fagomine (**67**) via Sharpless asymmetric dihydroxylation and Pd(II)-catalyzed cyclization (Figure 31).

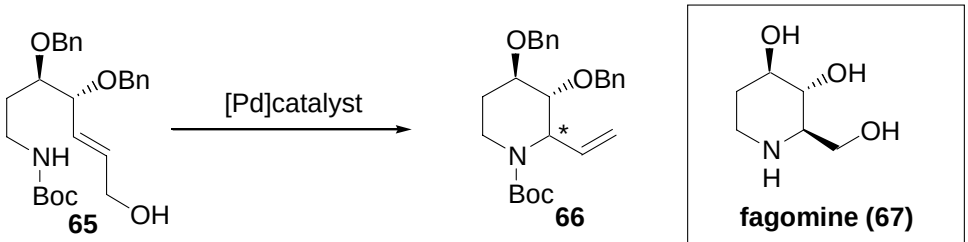


Figure 31

The substrate (**65**) for the Pd(II)-catalyzed cyclization was prepared from 3-(*t*-butoxylcarbonylamino) propanol by 10 steps. The allyl alcohol (**65**) was treated with $PdCl_2(MeCN)_2$ in THF at room temperature to give the cyclic compound (**68**) as a single isomer in 90% yield (Figure 32). Next, we examined the transformation from **68** into fagomine (**67**). Ozonolysis of **68** followed by reductive work-up with $NaBH_4$ provided the alcohol (**69**). Deprotection of the Boc group of **69** under acidic conditions and removal of the benzyl groups by hydrogenation provided fagomine (**67**). The spectral data of synthetic product (**67**) were in agreement with reported data.[39]

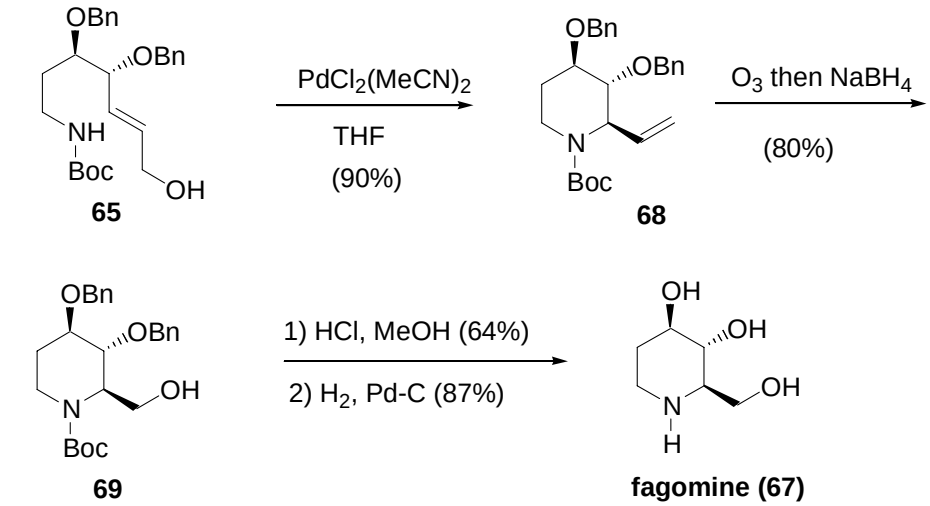


Figure 32

The reaction mechanism may be shown in Figure 33. The stereoselective formation of **68** could be explained by assuming the transition state **A**. The transition state **B** would be disadvantageous, because of steric repulsion between the carbamate moiety and oxa-π-alkene-palladium complex (Figure 33).

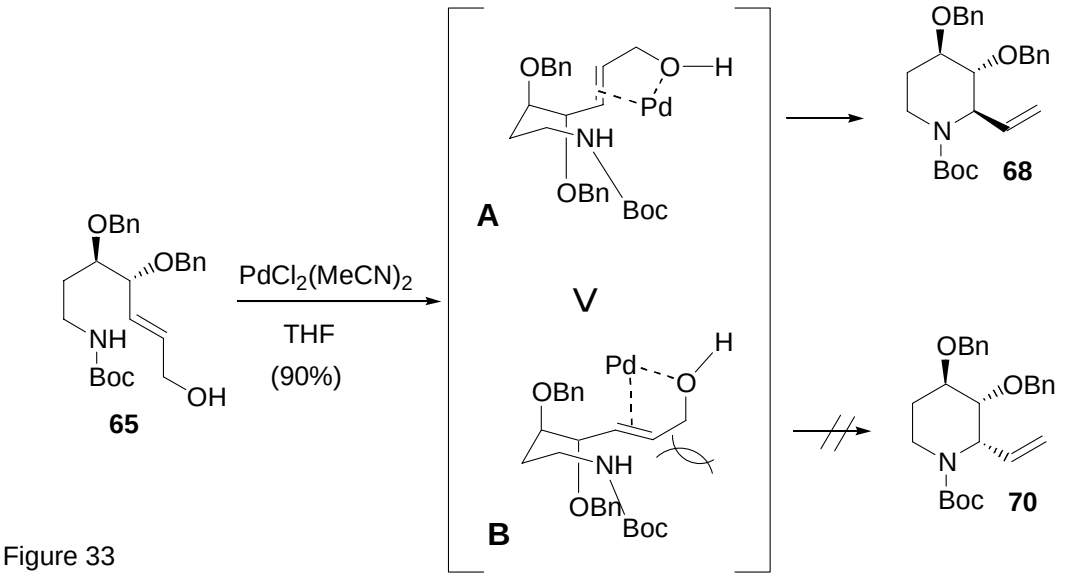
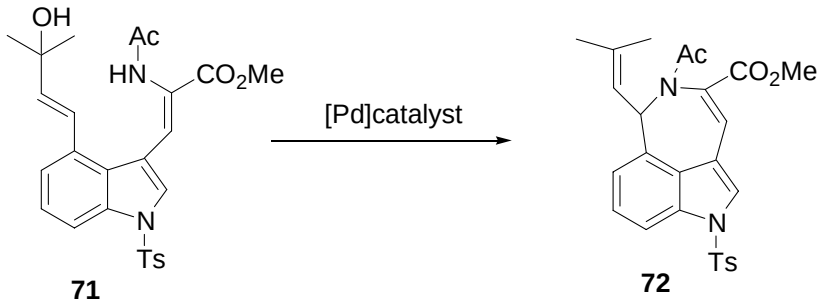


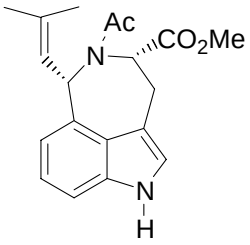
Figure 33

SYNTHESIS OF ERGOT ALKALOID

Synthesis of *N*-acetyl methyl ester of clavicipitic acid (73)[41]

Clavicipitic acid is an ergot alkaloid isolated from SD58 and *Claviceps fusiformis*.[42] Clavicipitic acid was isolated as mixture of *cis* and *trans* diastereoisomers. In 1987, Hegedus group reported the total synthesis of *N*-acetyl methyl ester of clavicipitic acid (**73**) via Pd(II)-catalyzed cyclization of **71**, which is a useful tool in the synthesis of ergot alkaloids (Figure 34).





***N*-acetyl methyl ester of clavicipitic acid (73)**

Figure 34

The allyl alcohol (**71**), which was prepared from 2-bromo-6-nitrotoluene, was treated with $PdCl_2(MeCN)_2$ in CH_3CN at room temperature to give the cyclic compound (**72**) in 95% yield (Figure 35). By photochemical reduction with $NaBH_4$ under Na_2CO_3, the cyclized product (**72**) was converted to target compound (**73**) in 61% yield.

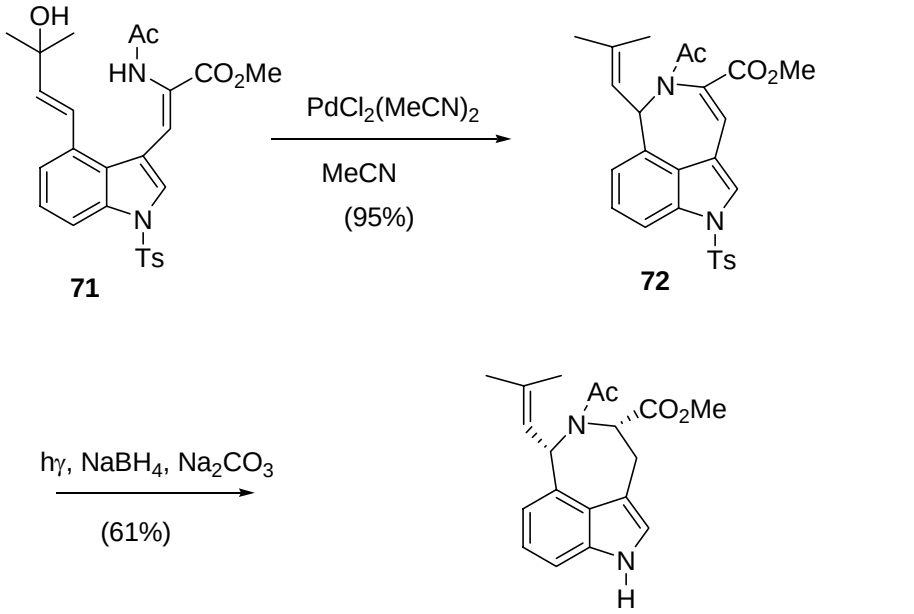


Figure 35

Recently, Hyeung-geun group attained the total synthesis of (-)-*cis*-clavicipitic acid by using Pd(II)-catalyzed cyclization as a key step.[44]

CONCLUSION

We found that the Pd(II)-catalyzed cyclization of urethane gives the stereoselective formation of *N*-hetero alicycles, and done the several syntheses of natural products. In addition, the mechanistic aspect has been proposed and investigated so that the scope and stereoselectivity of this reaction can be revealed.

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15. In stead of allylalcohol (**19**), allyl chloride (**74**) derivative was treated with $AgOCOCF_3$ to give the diastereoisomer (**75**) in 61% yield.

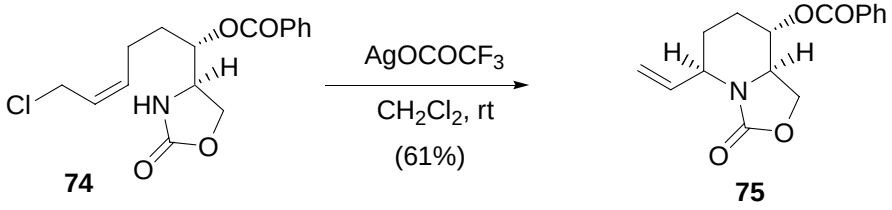

Figure 36

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