TOTAL SYNTHESIS OF STRYCHNINE

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Abstract — Strychnine is one of the most famous and complex natural products in its size. Woodward succeeded in the total synthesis of (-)-strychnine in 1954, but there were no other reports of the total synthesis of strychnine for about 40 years. In 1992, Magnus succeeded in the total synthesis of (-)-strychnine and then due to the dramatic progress of synthetic organic chemistry and organometallic chemistry, many researchers tried to synthesize (±)- and (-)-strychnine by their original methods. We developed a novel synthetic method of a chiral cyclohexenyl amine derivative having an aryl group at the 2-posotion by palladium catalyst for the synthesis of (-)-mesembrine. Furthemore, (+)-crinamine, (-)-haemanthidine, and (+)-pretazettine could be synthesized by the same procedure. Modifying this method, the total synthesis of (-)-strychnine was achieved. The chiral cyclohexenyl amine derivative having the sylyloxymethyl group at the 2-position was synthesized using the palladium catalyst. From this comopound, construction of the ABE-rings of (-)-strychnine was carried out. The C-ring was constructed using palladium-catalyzed allylic oxidation. The G-ring and then the F-ring were constructed by intramolecular Heck reaction. All cyclizations for synthesis of (+)-isostrychnine were performed using palladium catalysts. (+)-Isostrychnine was converted into (-)-strychnine by the known method. The progress of the synthesis of a chiral cyclohexenyl amine derivative having the substituent at the 2-position was described.

CONTENTS

1. INTRODUCTION

(-)-Strychnine, which was first isolated in 1818 from the seeds and bark of *Strychnos nux vomica* by Pelletier and Caventous,[1] is one of the most famous and complex natural products in its size. It has seven rings and six asymmetric centers in the molecule. Woodward succeeded in the total synthesis of (-)-strychnine in 1954,[2] but there were no other reports on the total synthesis of strychnine for about 40 years. However, recently, due to the dramatic progress of synthetic organic chemistry and organometallic chemistry, the total synthesis of strychnine was achieved by several groups.[3] The numbering system and ring laveling used throughout this review is shown in Figure 1.[4]
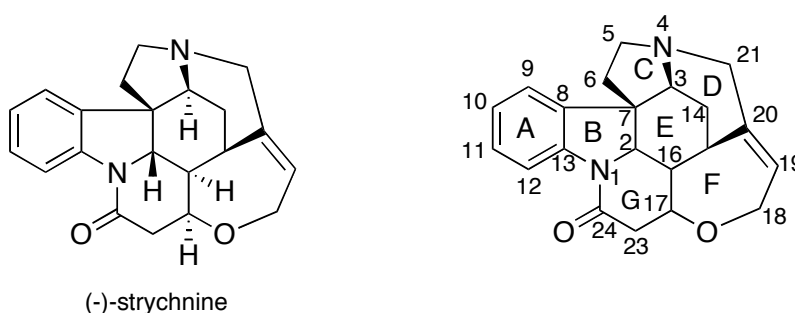

(-)-strychnine

Figure 1. Structure of Strychnine and Its Numbering and Ring Labeling

In 1992, Magnus succeeded in the total synthesis using a relay compound obtained from (-)-strychnine.[5] Overman prepared the starting material by an enzymatic desymmetrization and succeeded in the first asymmetric total synthesis of (-)- and (+)-strychnine in 1993.[6] Kuehne[7] succeeded in the total synthesis of (-)-strychnine from a chiral pool, L-tryptophane, and Bosch[7] used diastereoselective reductive double amination for the synthesis of perhydroindolone derivative as an intermediate. Following these reports,

several groups succeeded in the total synthesis of (-)- or (±)-strychnine.[3] Rawal's synthetic process is particularly remarkable, although it is a racemic form.[8] Very recently, Vollhardt succeeded in the total synthesis of (±)-strychnine using an ingenious cobalt-catalyzed [2+2+2]cycloaddition as a key step.[9] However, there has been no report on total synthesis of (-)-strychnine from enantiomerically pure compound obtained by a transition metal-catalyzed asymmetric synthesis. In 2002, we have succeeded in the total synthesis of (-)-strychnine.[10] For the chiral starting material, 2-substituted cyclohexenylamine derivative prepared by palladium catalyzed asymmetric allylic substitution was used. In 2004, Shibasaki succeeded in the total synthesis of (-)-strychnine from the chiral starting material prepared by his asymmetric Michael reaction.[11] In this review, the progress for development of palladium catalyzed asymmetric allylic substitution developed by our group and the total syntheses of some natural products using this method are reported.

2. EARLIER TOTAL SYNTHESES OF STRYCHNINE (~2000)

An exquisite review of the total synthesis of strychnine was reported by Bonjoch and Sole in 2000.[3c] Thus, in this chapter, only the first total synthesis of (-)-strychnine reported by Woodward[2] and Rawal's total synthesis[8] of (±)-strychnine are shown. The first total synthesis of (-)-strychnine by Woodward in 1954 is a memorial affair in the field of synthetic organic chemistry. In the Rawal's total synthesis of strychnine, which was achieved by two researchers, we can find the progression of synthetic organic chemistry using the transition metal complex.

The brilliant total synthesis of strychnine by Woodward is shown in Schemes 1 and 2. He started from an indole derivative (**1**), prepared by Fischer indole synthesis, which was converted into a tryptamine derivative (**2**). Condensation of **2** with ethyl glyoxylate followed by treatment with TsCl gave the spiro compound (**3**), which was treated with NaBH$_4$ followed by acetylation to give the compound (**4**). The next pyridone formation is the most impressive process for the synthesis of strychnine. When the compound (**4**) was treated with ozone in aqueous acetic acid, the veratryl group was selectively cleaved between the two methoxy groups to give the muconic ester (**5**), which was heated in methanolic hydrogen chloride to afford the pyridone (**6**). To construct of E-ring, Dieckman condensation was carried out to give **8**, whose keto-carbonyl group was removed via the thienol ether (**9**) and then hydrolysis of the ester

group afforded **10** with the more stable equatorial orientation for the carboxyl group (Scheme 1).
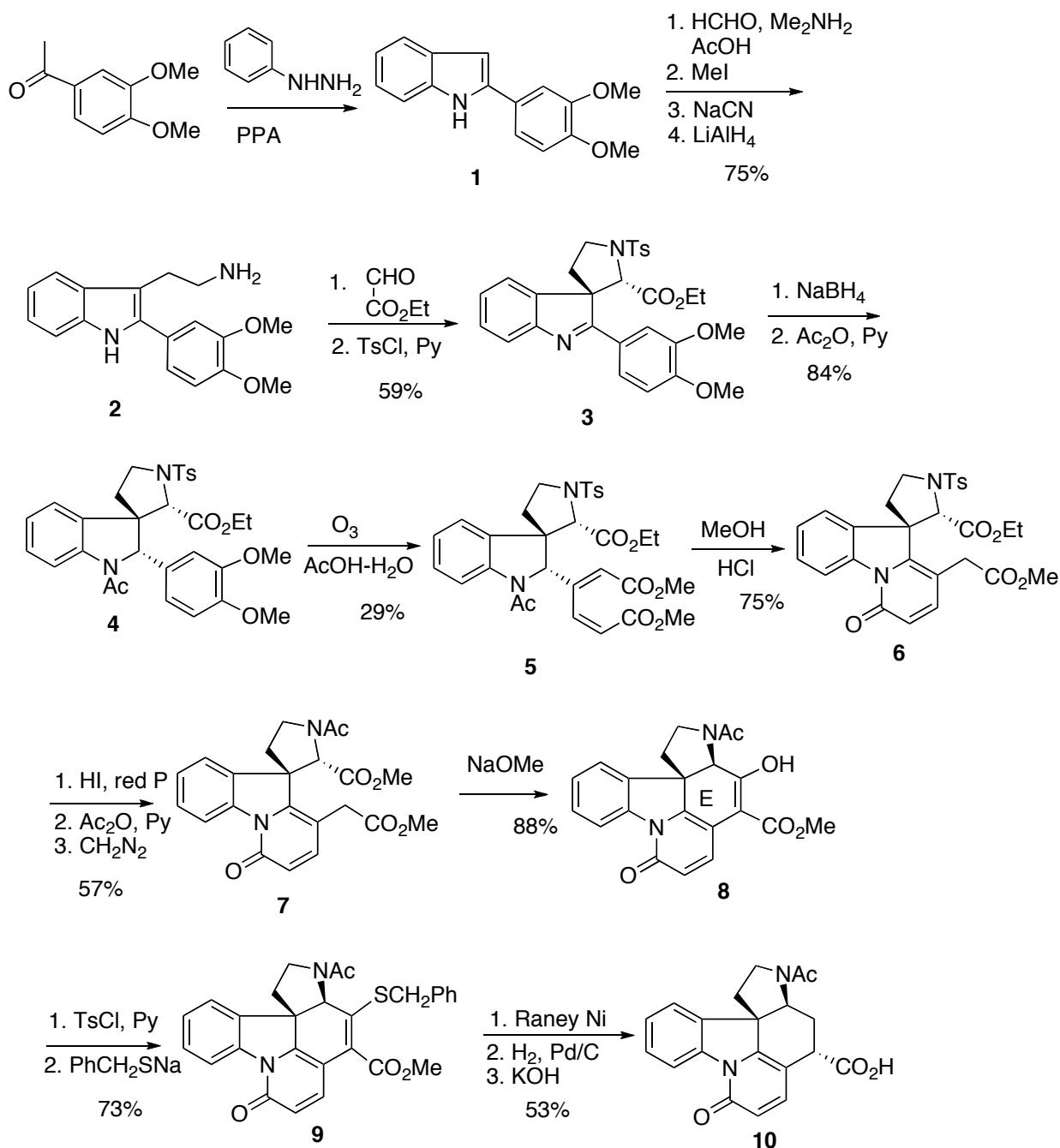
Scheme 1. Synthesis of Pentacyclic Compound

Acetylation of **10** gave **13**. This reaction involves the initial formation of a mixed anhydride (**11**), which undergoes conversion to a methyl ketone under the reaction condition by evolution of carbon dioxide followed by acetylation. Treatment of **13** with aqueous hydrochloric acid in acetic acid gave the methyl ketone (**14**), with the more stable equatrial orientation for the acetyl group. Oxidation of **14** with SeO$_2$ in ethanol gave **16** via the keto-aldehyde (**15**). Reaction of **16** with sodium acetylide followed by

hydrogenation with Lindlar catalyst gave an allylic alcohol (**17**). Treatment of **17** with LiAlH$_4$ gave amine (**18**), whose pyridone ring was reduced to the desired dihydro level. Acid treatment of **18** gave isostrychnine. Finally, isostrychnine was treated with potassium hydroxide in ethanol to give strychnine (Scheme 2).
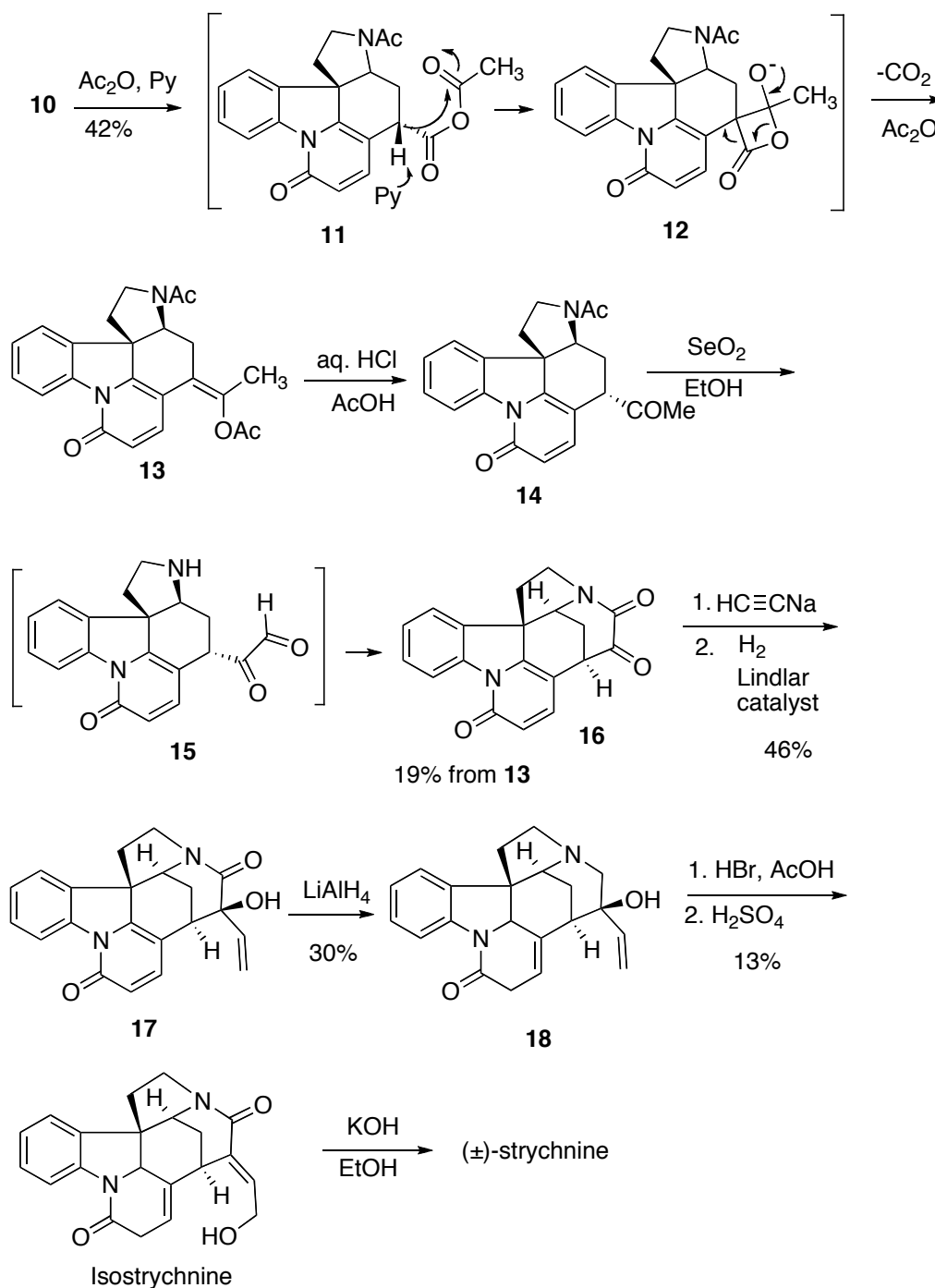
Scheme 2. Woodward's Total Synthesis of (±)-Strychnine

Rawal's total synthesis is notable for the conciseness, short steps (15 steps) and high overall yield (10%).[8] They prepared ABCE-rings by intramolecular Diels-Alder reaction. The most unique point of their

synthesis is the use of the palladium catalyst for the construction of the D-ring and this procedure affected the later total synthesis of strychnine. They prepared a pyrroline (**20**) from 2-nitrobenzylcyanide as shown in Scheme 3.

Scheme 3. Synthesis of Pyrroline **20**.
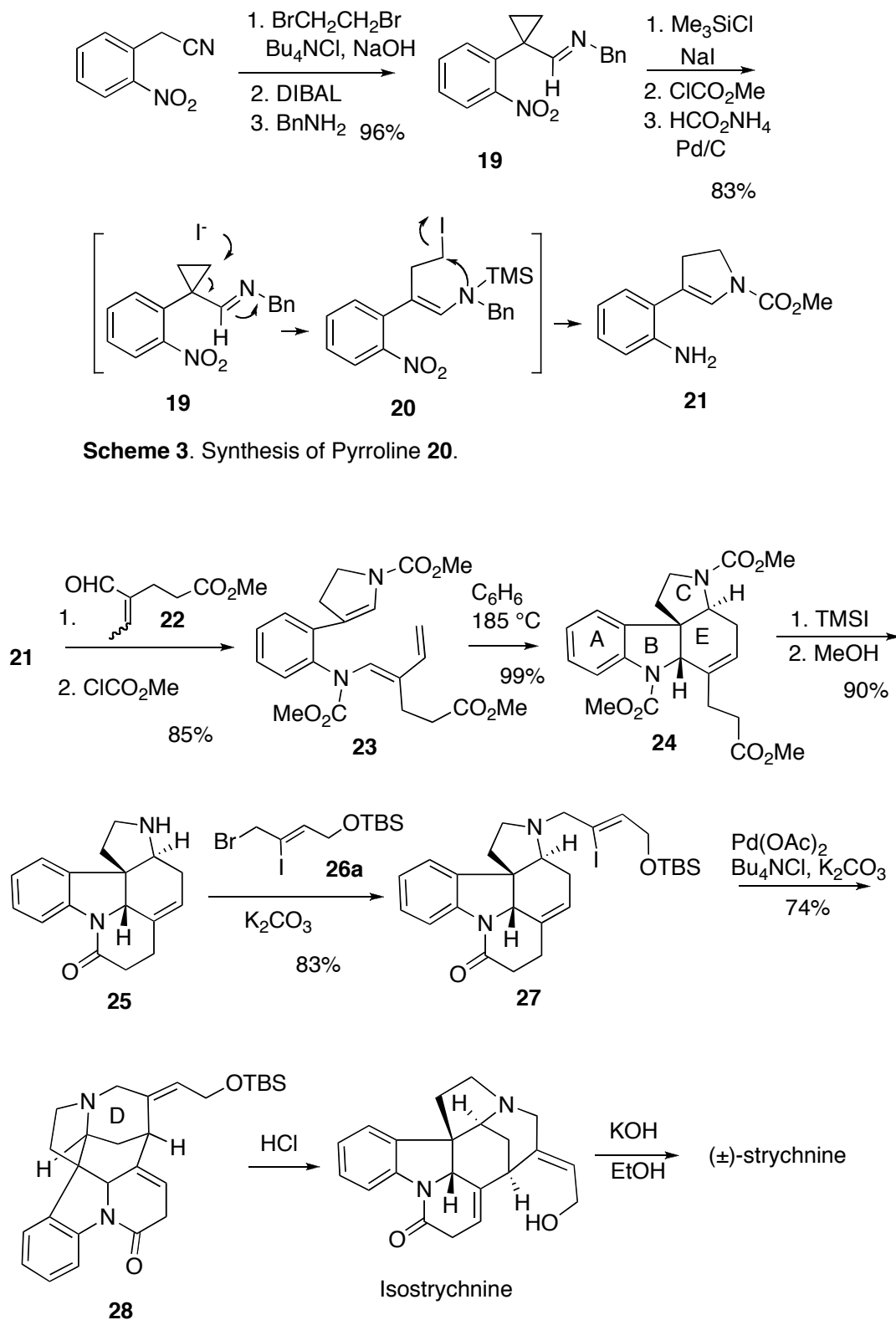
Scheme 4. Rawal's Total Synthesis of (±)-Strychnine

Condensation of **21** with **22** followed by treatment with methyl chloroformate afforded a triene (**23**).

Intramolecular Diels-Alder reaction of **23** smoothly proceeded to give the tetracyclic compound **24** in

high yield. Deprotection of the methoxycarbonyl group on nitrogen gave the compound (**25**), whose

amino group was alkylated with **26a** to give **27**. To construct D-ring, intramolecular Heck reaction[12] of **27**

was carried out in the presence of the palladium catalyst and the hexacyclic compound (**28**) was obtained

in good yield. Acid treatment of **28** gave isostrychnine. Thus, the total synthesis of (±)-strychnine was

achieved (Scheme 4).

3. RECENT TOTAL SYNTHESIS OF STRYCHNINE (2000~)

After 2000, six groups succeeded in the total synthesis of strychnine. Vollhardt succeeded in the total

synthesis of (±)-strychnine using cobart-mediated [2+2+2]cycloaddition reaction in 2000.[9] Then our

group,[10] Bodwell,[13] Shibasaki,[11] Fukuyama,[14] and Padwa[15] reported the total synthesis of strychnine. All

approaches aimed at the synthesis of isostrychnine or the Wieland-Gumlich aldehyde as the final target

molecule because they have already led to strychnine.[16]
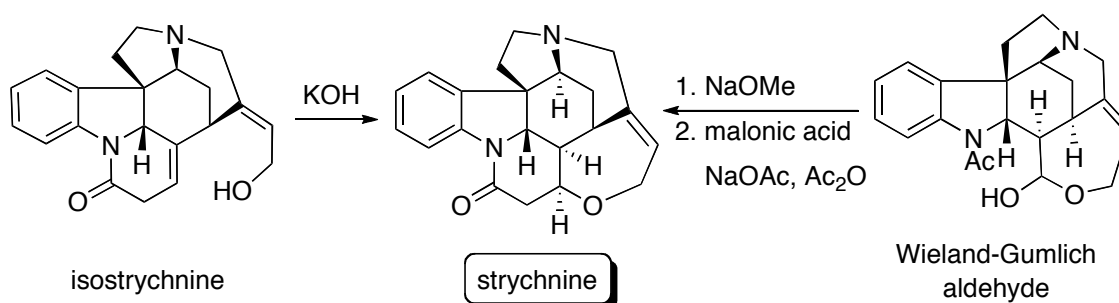
Scheme 5. Route to Synthesis of Strychnine

In 2000, Vollhardt reported a short, a highly convergent total synthesis of strychnine using

cobalt-mediated [2+2+2]cycloaddition.[9] He had already reported the cycloaddition of three unsaturated

functionalities using cobalt complex. The reaction proceeded with a high degree of chemo-, regio-, and

stereoselectivity and a number of aromatic heterocycles is included as the unsaturated functionalily. The

indole nucleus is also active in these cyclizations to provide a polycyclic ring system. For example,

tetracyclic compound (**29**) was synthesized by [2+2+2]cycloaddition of N-acetyl indole and octa-1,7diyne
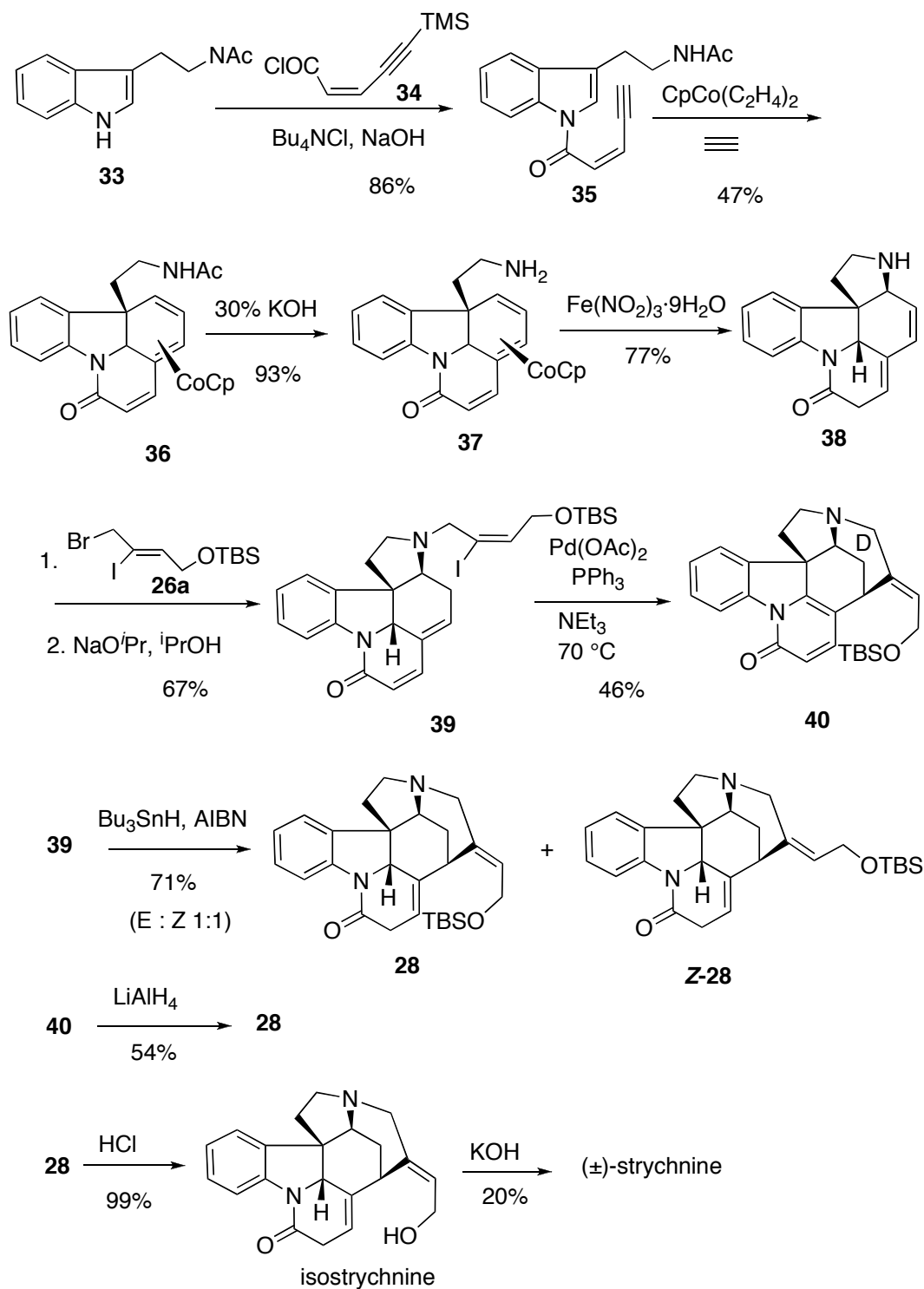
(Scheme 6).
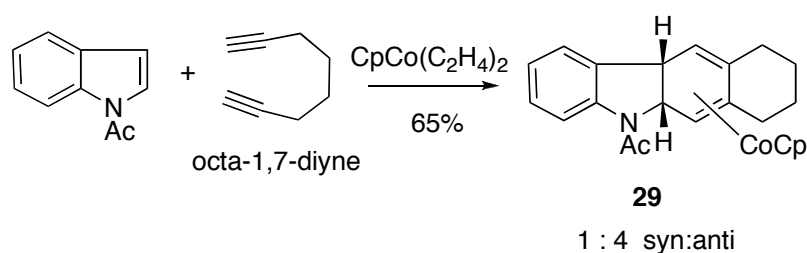
Scheme 6. Cobalt Mediated [2 + 2 + 2]Cycloaddition

His retrosynthetic analysis of strychnine is shown in Scheme 7. The feature of his synthesis is that the E and G rings are constructed from an indole derivative (**31**) and an alkyne (**32**) by his original method.
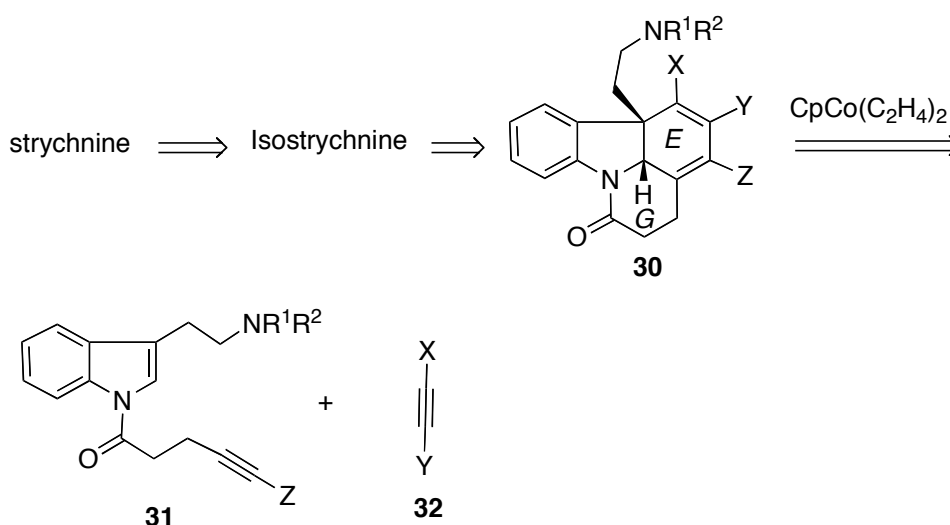
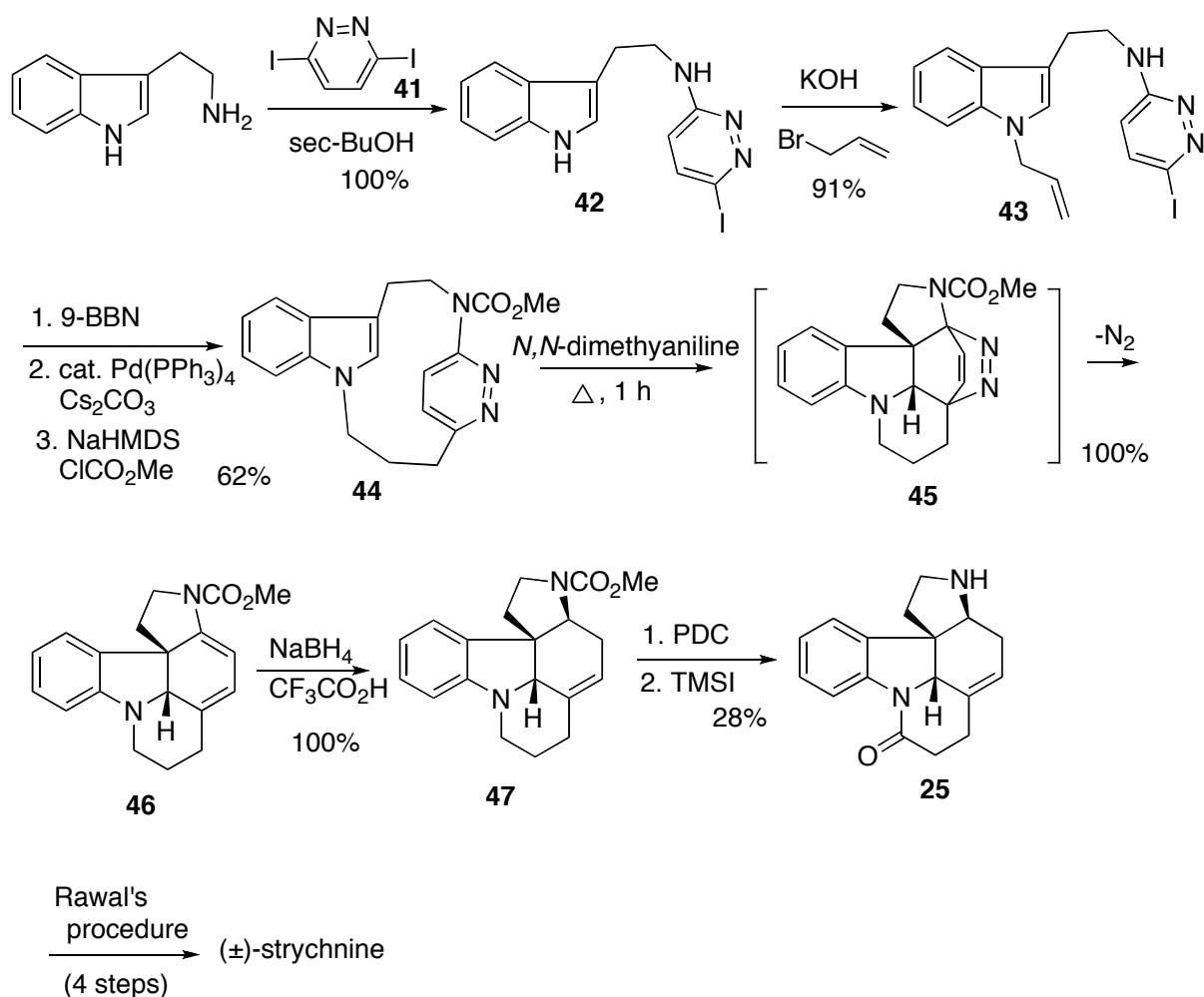**Scheme 7**. Retrosynthetic Analysis of Strychnine by Vollhardt

[2+2+2]Cycloaddition reaction of **35**, which was prepared from N-acetyl tryptamine (**33**) and an ene-yne (**34**), with acetylene using $CpCo(C_2H_4)_2$ at 0 °C smoothly proceeded to give the tetracyclic compound (**36**) in 47% yield. Pyrrolidine ring closure occurred by deacetylation followed by demetalation with iron (III) to give the pentacycle (**38**) in high yield. To construct D-ring, they examined Rawal's procedure[8] and radical cyclization. Alkylation of amine nitrogen of **38** with **26a** followed by base-catalyzed isomerization of the diene unit into conjugation with the amide carbonyl afforded the vinyl iodide (**39**). Palladium catalyzed Heck reaction of **39** in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 gave the hexacyclic compound (**40**). On the other hand, reaction of compound (**39**) with Bu_3SnH and AIBN afforded the desired hexacyclic silyl ethers (**28**) and (**Z-28**) in 71% yield as a 1 : 1 mixture. Treatment of **40** with $LiAlH_4$ gave the same compound (**28**). Deprotection of the silyl group of **28** followed by treatment with KOH gave (±)-strychnine.

Scheme 8. Vollhardt's Total Synthesis of Strychnine.

Bodwell reported a concise formal total synthesis of (±)-strychnine using a transannular inverse electron demand Diels-Alder reaction of a [3](1,3)indolo[3](3,6)pyridazinophane.[13] The reaction of tryptamine and 3,6-diiodopyridazine gave **42**. *N*-Allylation of the indole moiety yielded **43**, which was subjected to a sequential hydroboration/intramolecular B-alkyl Suzuki-Miyaura cross coupling reaction to give

cyclophane. Protection of the secondary amine afforded **44**, which was heated in *N,N*-dimethylaniline to induce the pentacyclic compound (**46**) by expulsion of N$_2$ from **45** in quantitative yield. Reduction of (±)-**46** with NaBH$_4$/CF$_3$CO$_2$H occurred with complete chemo- and stereoselectivity to afford **47**. Oxidation of the tertiary amine with PDC followed by deprotection gave an amide (**25**), which is an intermediate for the synthesis of strychnine by Rawal.[8] Thus the formal total synthesis of (±)-strychnine was established (Scheme 9).

Scheme 9. Bodwell's Total Synthesis of (±)-Strychnine

Shibasaki *et al.*,[11] succeeded in the synthesis of (-)-strychnine from chiral **51** prepared by their highly practical asymmetric Michael reaction. Their retrosynthetic analysis is shown in Scheme 10. To utilize **51** effectively in the synthesis, cyclohexene ring of **51** is used as E-ring and construction of B- and D-rings is carried out from **51**. The spirocenter C7 is constructed in the last stage by intramolecular alkylation (Scheme 10).
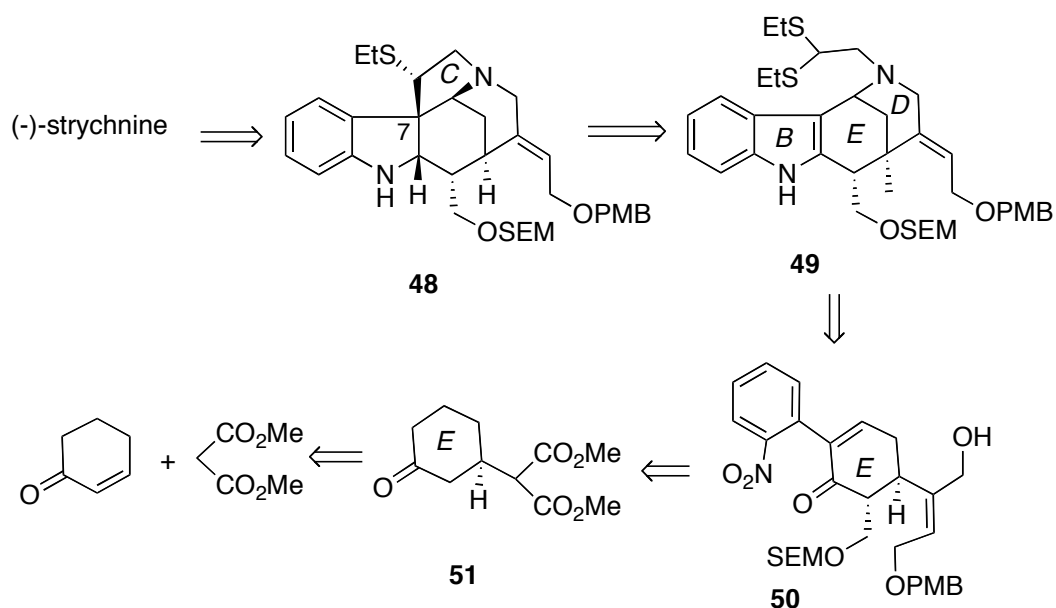
Scheme 10. Retrosynthetic Analysis of (-)-Strychnine by Shibasaki
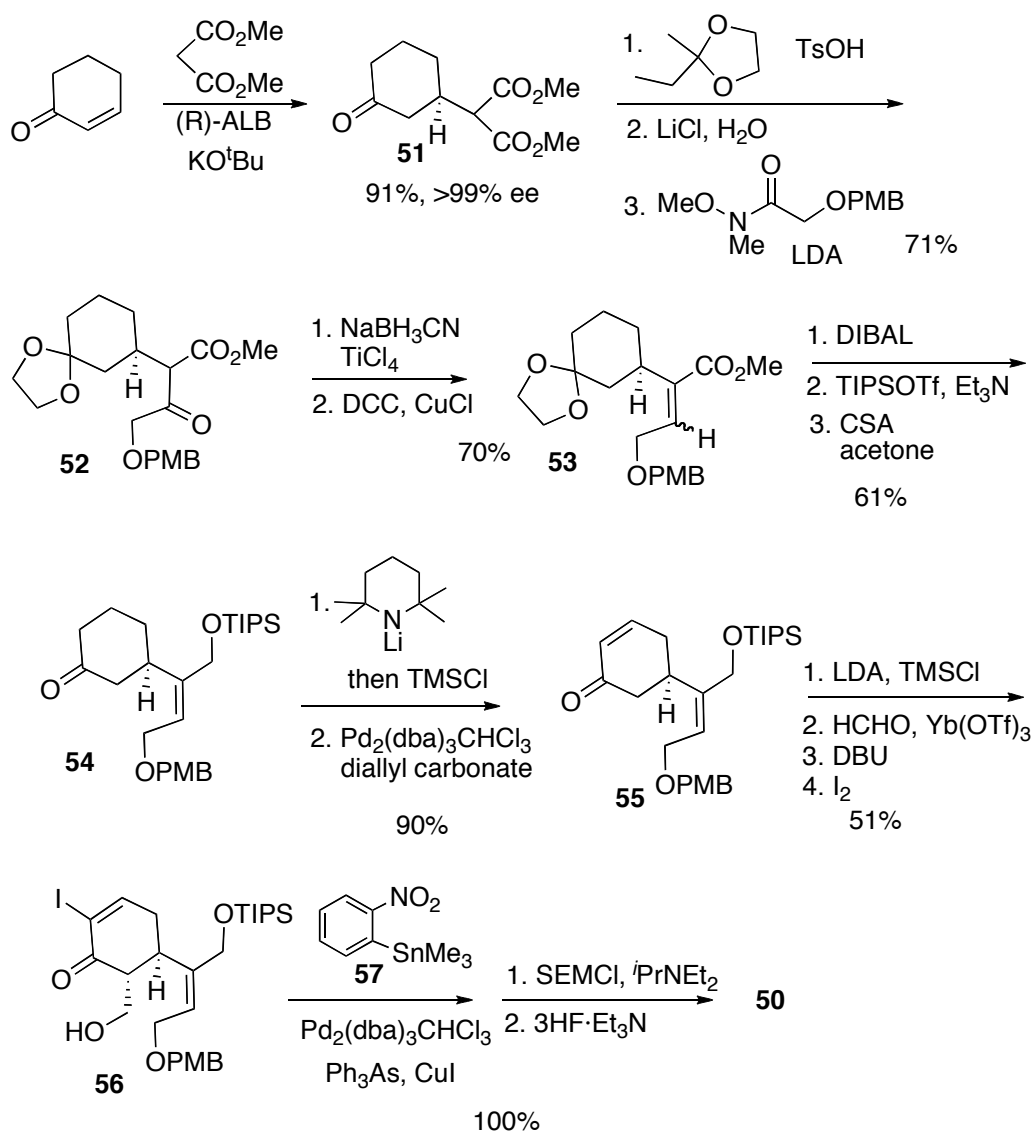
Scheme 11. Shibasaki's Total Synthesis of (-)-Strychnine - Synthesis of Key Compound **50**.

Only 0.1 mol% of (*R*)-AlLibis-(binaphtoxide) (ALB) completed the Michael reaction[17] to give **51** (> 99% ee). Then **51** was converted into **56** via several steps as shown in Scheme 11. Palladium catalyzed coupling reaction of **56** with ortho-stannylated nitrobenzene (**57**) smoothly proceeded, and then protection of the hydroxyl group and deprotection of the silyl group gave the key intermediate (**50**).

After introduction of the amine moiety, the crude product was treated with Zn in MeOH-aqueous NH₄Cl to produce **49** via **59**.   For the construction of C-ring, **49** was treated with DMTSF to afford **60**, which was converted into **61**. Desulfurization followed by oxidation with SO₃-pyridine and then deprotection of the silyl group gave Wieland-Gumlich aldehyde, which was converted into (-)-strychnine (Scheme 12).
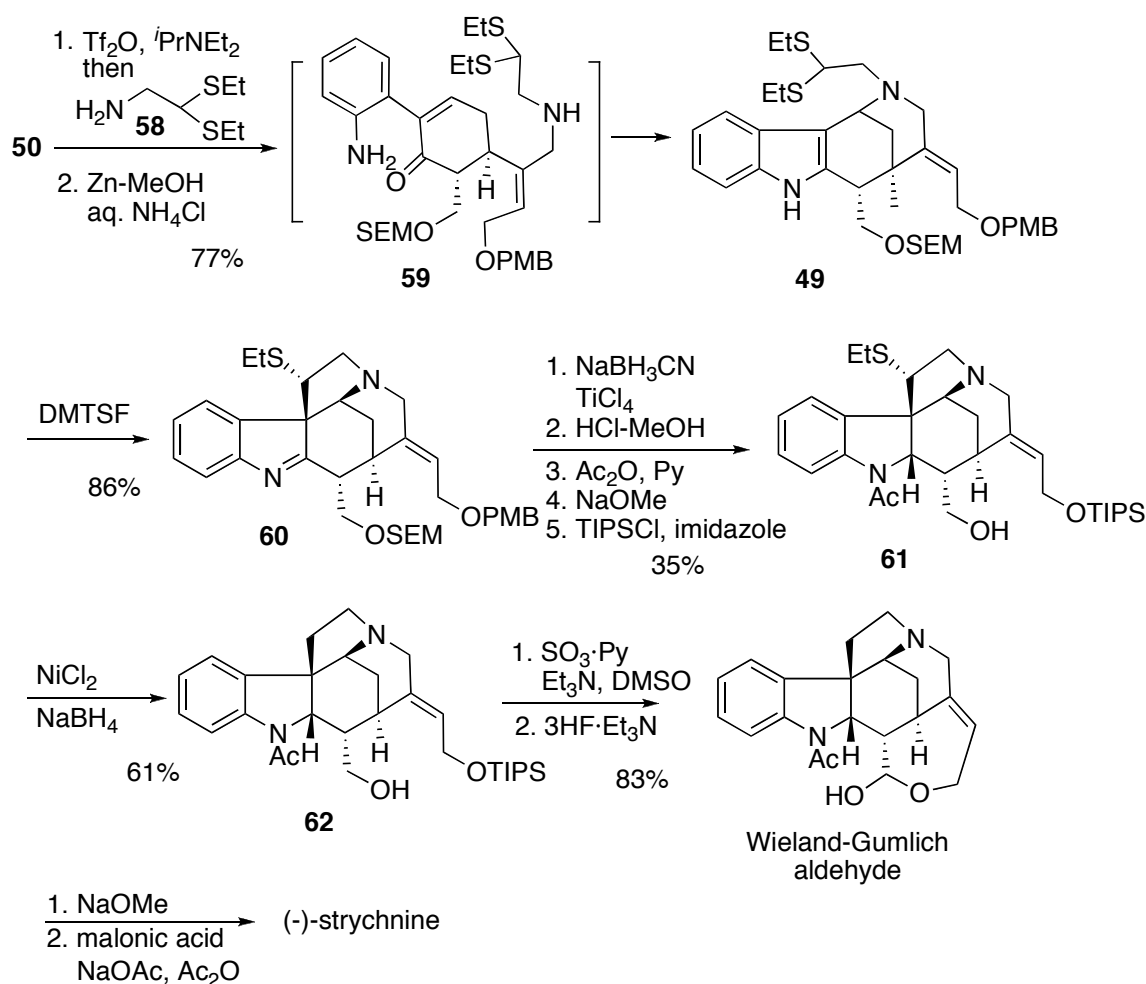
Scheme 12. Shibasaki's Total Synthesis of (-)-Strychnine

Fukuyama succeeded in total synthesis of (-)-strychnine in 2004.[14] His retrosynthetic analysis is shown in Scheme 13. Construction of the nine-membered ring is performed by his 2-nitrobenzenesulfonamide (NsNH₂) strategy.[18] To secure the geometry of the trisubstituted olefin, they planned to cleave the

cyclohexene ring at the C3-18 bond of **64** to generate the two side chains. The precursor (**64**) should be obtained by palladium-catalyzed coupling reaction of **65** and **66**.
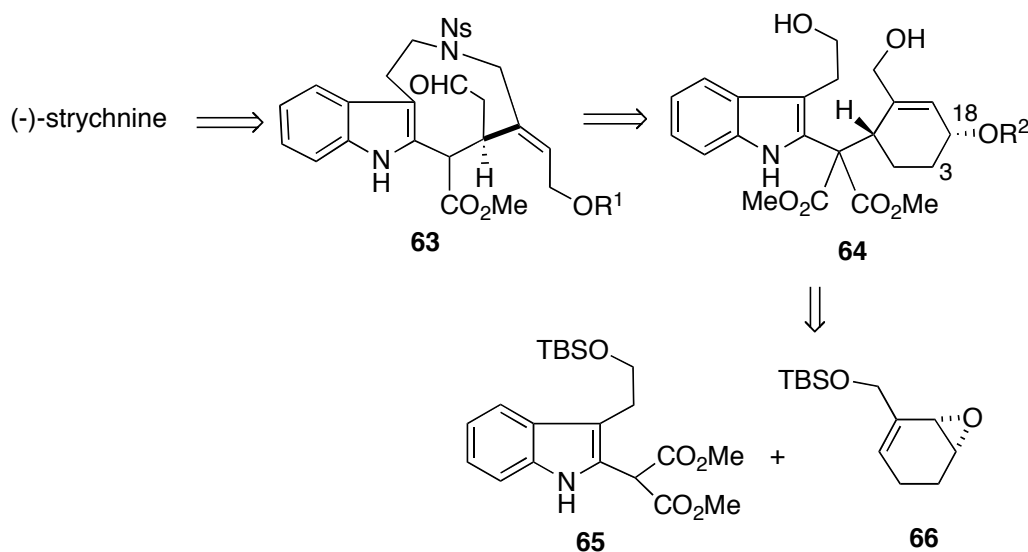
Scheme 13. Retrosynthetic Analysis of (-)-Strychnine

The starting cyclohexadiene (**67**) was converted into **68**, which was subjected to an enzymatic resolution with lipase AYS to provide the desired bromohydrin acetate (**69**) with high ee. From **69**, the desired epoxide (**66**) was obtained (Scheme 14).
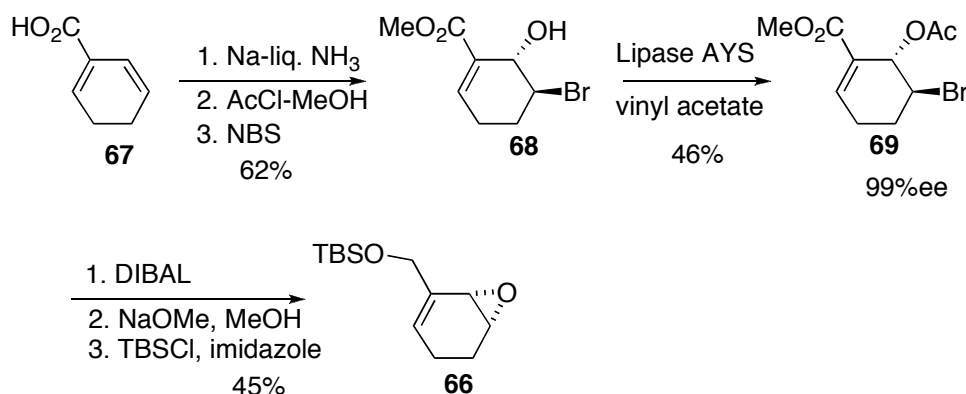
Scheme 14. Synthesis of **66**.

The palladium-catalyzed coupling reaction of **65** and **66** was carried out in the presence of Pd$_2$(dba)$_3$ and P(2-furyl)$_3$ in toluene to afford **70** in high yield with complete control of regio- and stereochemistry. Then coupling product (**70**) was converted into the diol (**71**), which was treated with NsNH$_2$ via double N-alkylation to form the nine-membered ring compound (**72**). Epimerization of C16, and then deprotection followed by oxidation gave **73**, which was converted into **74**. Oxidative cleavage of the

α-hydroxy ketone (**74**) with Pb(OAc)$_4$ was performed to afford an aldehyde (**75**). Removal of the nosyl group followed by treatment with TFA and Me$_2$S induced a transannular cyclization to give the pentacyclic compound (**77**), which is an intermediate of the Kuehne's total synthesis of strychnine.[7a] Thus, **77** was converted into (-)-strychnine via the Wieland-Gumlich aldehyde **13** (Scheme 15).
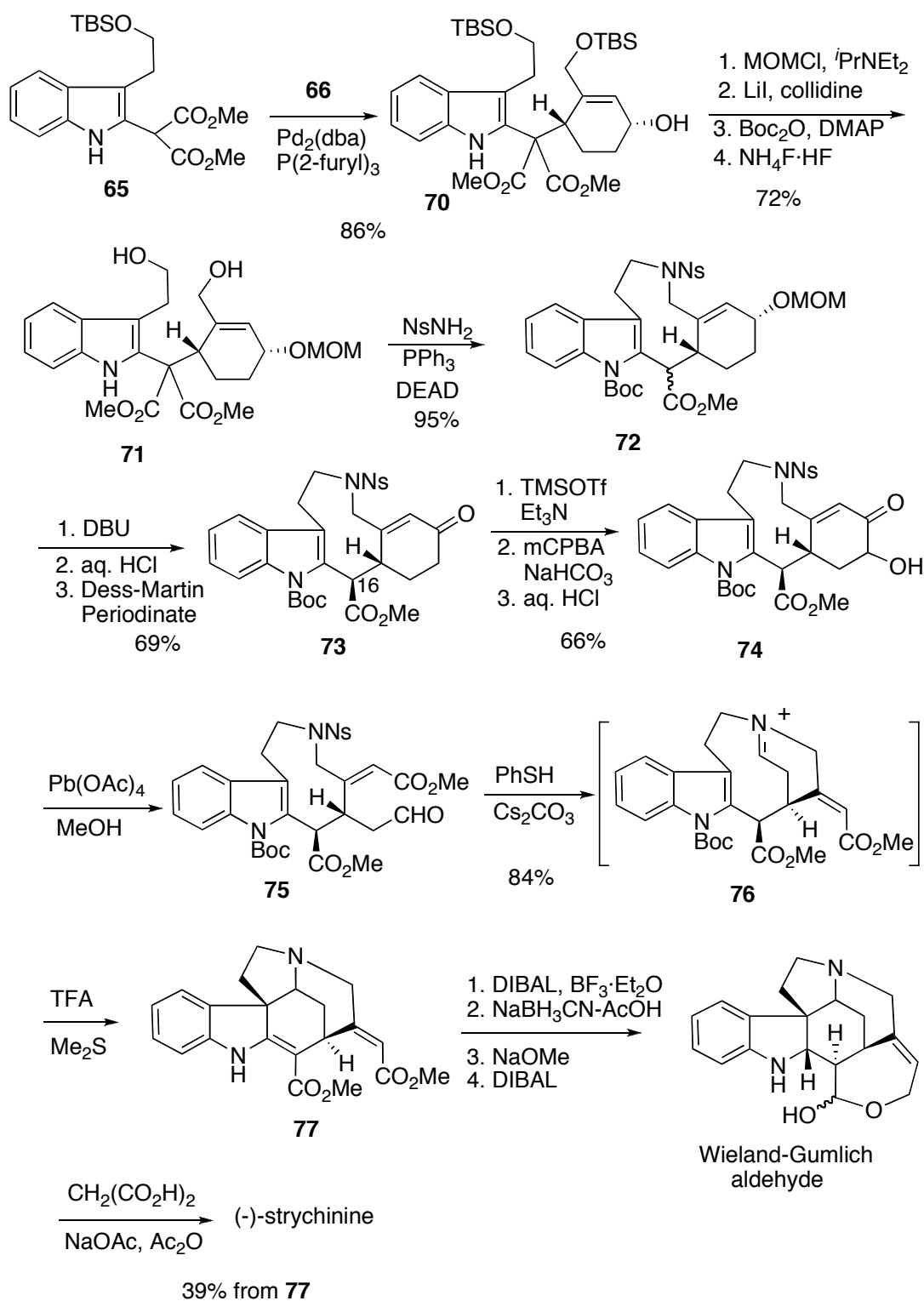
Scheme 15. Fukuyama's Total Synthesis of (-)-Strychnine

In 2007, Padwa reported the total synthesis of (±)-strychnine.[15] Their retrosynthetic analysis is shown in Scheme 16. The feature of his synthesis is an intramolecular [4 +2]cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran (**81**) for the construction of the ABCE rings. Furthermore, they used intramolecular palladium catalyzed coupling reaction of vinyl iodide and α-position of the carbonyl group of **79**.
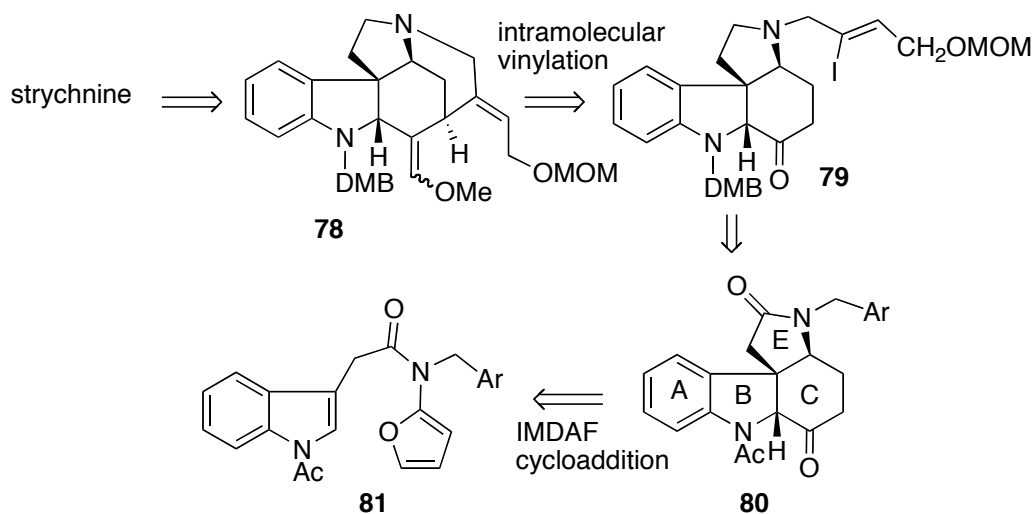
Scheme 16. Retrosynthetic Analysis of (±)-Strychnine

Heating the compound (**81**), prepared from **82** and **83**, at 150 °C (toluene) in a microwave reactor for 30 min in the presence of catalytic amount of MgI_2 afforded the desired aza-tetracycle (**86**) via **84** and then **85** in 95% yield, which was converted into **88**. Alkylation of **88** with **26b** followed by protection of the amino group and then oxidation afforded the desired compound (**79**). For the construction of D-ring, palladium catalyzed cyclization was carried out to give the pentacyclic compound (**90**), which was converted into an enol ether (**78**). Acid hydrolysis of **78** gave Wieland-Gumlich aldehyde. From this compound total synthesis of (±)-strychnine was achieved (Scheme 17).
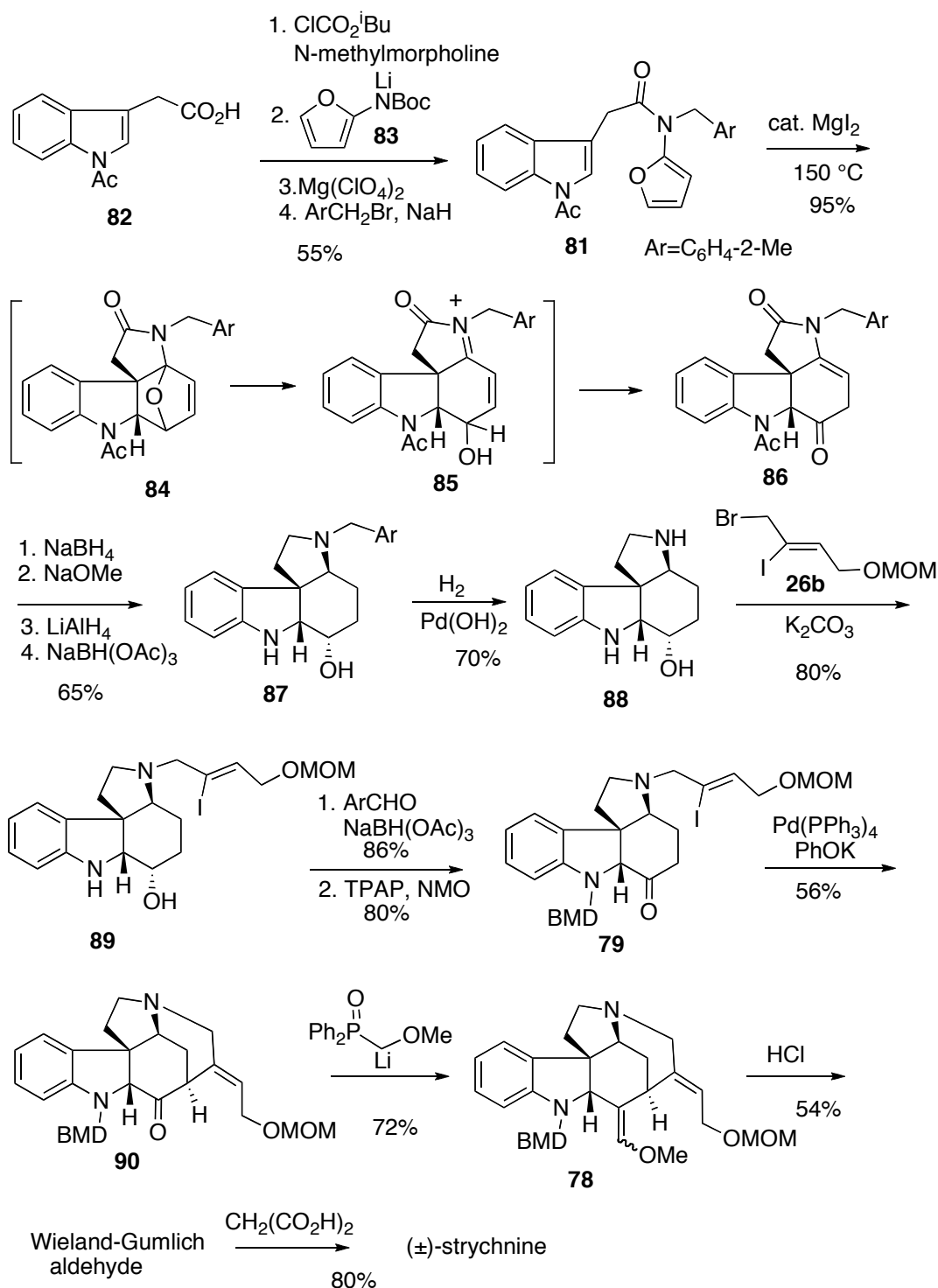
Scheme 17. Padwa's Total Synthesis of (±)-Strychnine

4. TOTAL SYNTHESIS OF (-)-STRYCHNINE BY OUR GROUP

4-1. BACKGROUND ON THE SYNTHESIS OF (-)-STRYCHNINE

Zirconium-mediated cyclization is useful method for the synthesis of fused cyclic compounds. We developed this reaction for the synthesis of fused heterocyclic compounds.[19] The cyclohexene derivative

(**91**), prepared from (-)-carvone, was treated with Cp$_2$ZrBu$_2$ to give a zirconacycle (**92**), whose solution was stirred under an atmosphere of carbon monoxide to give **93**. From this compound (**93**), (-)-dendrobine could be synthesized (Scheme 18). [19]
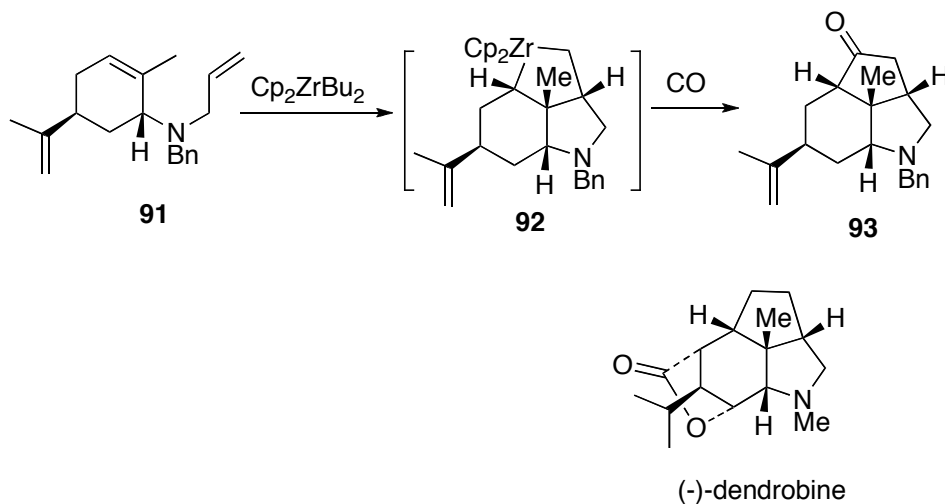
Scheme 18. Synthesis of (-)-Dendrobine Using Zirconium-Promoted Cyclization

When the cyclohexenylamine derivative (**94**) having an aryl group at the 2-position was treated with Cp$_2$ZrBu$_2$ and a solution of **95** was stirred under O$_2$, the indoline derivative (**96**) having the aryl group at the 8-poistion was synthesized, and the total syntheses of mesembrane and mesembrine were achieved from this compound. As the next problem, how to obtain a chiral **94** for the synthesis of (-)-mesembrane and (-)-mesembrine was considered. Thus, a novel synthesis of a chiral cyclohexenylamine derivative (**94**) having the aryl group at the 2-position was planed (Scheme 19).

X=H$_2$ mesembrane
X=O   mesembrine
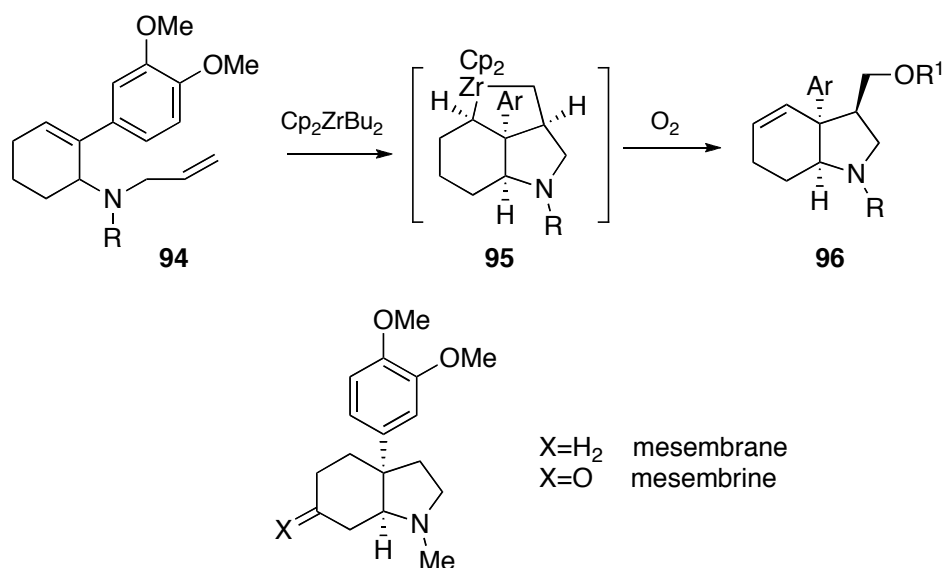
Scheme 19. Synthesis of (±)-Mesembrane and (±)-Mesembrine

There are many alkaloids that have an aromatic ring connected to a cyclohexane ring. Even in the case of indole alkaloids, these ring systems are found in the molecule. Thus, various indole alkaloids could be synthesized from a chiral cyclohexenylamine derivative having substituent at the 2-position. In this chapter, the progress of the syntheses of chiral indole alkaloids was described.

4-1-1. DEVELOPMENT OF NOVEL SYNTHETIC PROCEDURE OF CHIRAL CYCLOHEXENYLAMINE DERIVATIVE HAVING THE SUBSTITUENT AT 2-POSITION

Palladium-catalyzed alkylation or amination of the compound (**97**) should give compound (**99**) *via* a π-allylpalladium complex (**98**).   If a chiral ligand is used for this reaction, an optically active **99** or ent-**99** should be formed from the racemic **97** (Scheme 20).
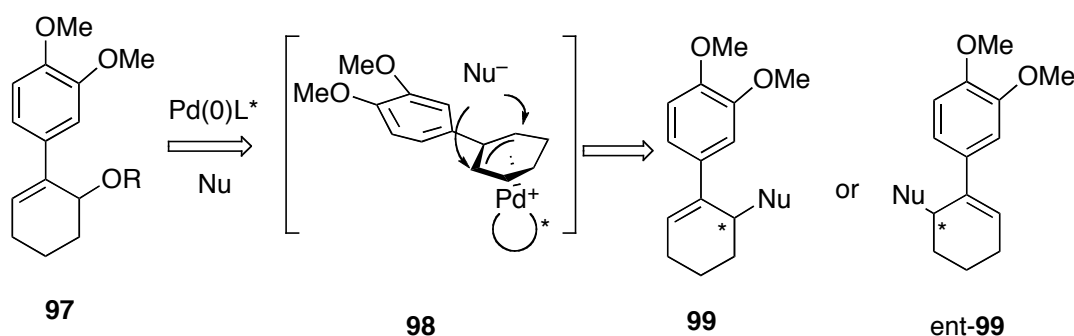
Scheme 20. Asymmetric Synthesis of 2-Arylcyclohexen Derivatives.

When a DMSO solution of an allyl carbonate (**97a**) and an N-tosylallylamine was warmed in the presence of Pd$_2$(dba)$_3$·CHCl$_3$ (2.8 mol%) and dppb (5.6 mol%) as a ligand at 50 °C for 13 h, the desired tosylamide (**100**) was obtained in 36% yield (Table 1, run 1).   The same reaction was carried out in the presence of (*S*)-BINAP[20] or (+)-**101**[21] as a chiral ligand, but the reaction rate was lower and good results were not obtained (runs 2 and 3).   However, when the reaction was carried out in the presence of palladium catalyst and (*S*)-BINAPO,[22] the reaction proceeded smoothly at room temperature for 3 h to produce **100** in 51% yield with 70% ee (run 4). With regard to the solvent, non-polar solvent gave good results (runs 4-9). When the reaction was carried out in THF at room temperature for 19 h, the chiral diene (**100**) was produced in 80% yield with 86% ee (run 9), which was recrystallized from MeOH to give **100** with 99% ee (79% recovery).

Table 1 Reaction of **97a** with *N*-tosylallylamide under various conditions[a]
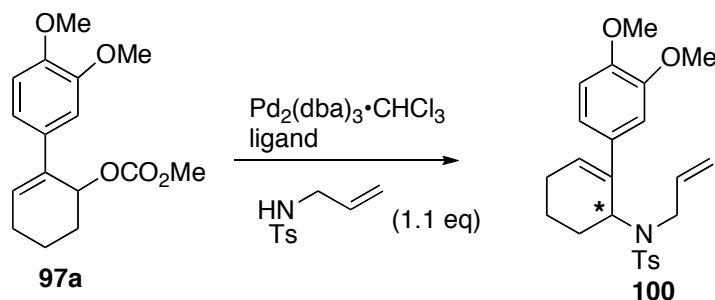
run	ligand	solvent	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	dppb	DMSO	50 °C	13	36	—
2	(*S*)-BINAP	DMSO	70 °C	50	12[c]	9
3	(+)-**103**	THF	50 °C	98	0	—
4	(*S*)-BINAPO	DMSO	rt	3	51	70
5	(*S*)-BINAPO	DMF	rt	3	70	71
6	(*S*)-BINAPO	toluene	rt	31	76	80
7	(*S*)-BINAPO	CH₃CN	rt	4	68	66
8	(*S*)-BINAPO	CH₂Cl₂	rt	2	75	73
9	(*S*)-BINAPO	THF	rt	19	80	86

a) All reactions were carried out in the presence of N-tosyl allylamine (1.1 eq.), Pd$_2$(dba)$_3$•CHCl$_3$ (2.8 mol%), and ligand (5.6 mol%). b) The ees were determined by HPLC analysis. (DAICEL CHIRALCEL OJ, hexane/^{i}PrOH=9/1). c) The starting material was recovered in 89% yield.
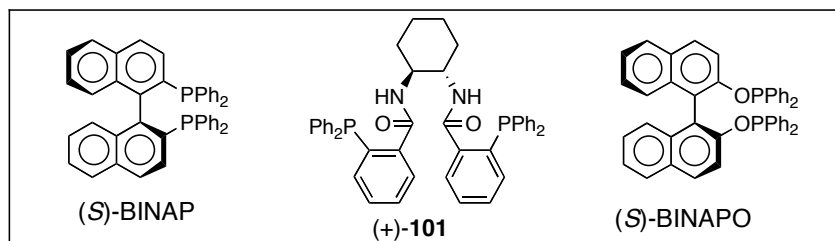
Thus, the development of the novel synthetic method of the chiral cyclohexenylamine derivative having the substituent at the 2-position could be achieved. From the compound (**100**), (-)-mesembrane and (-)-mesembrine were synthesized.[23]

4-1-2. ASYMMETRIC TOTAL SYNTHESES OF (+)-CRINAMINE, (-)-HAEMANTHIDINE, AND (+)-PRETAZETTINE

Subseqently, the asymmetric total syntheses of the crinane-type alkaloid, (+)-crinamine,[24] (-)-haemanthidine, and (+)-pretazettine[25] were planned using our method.
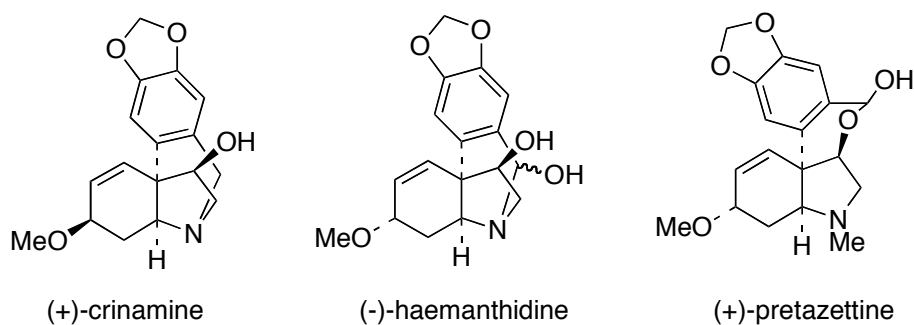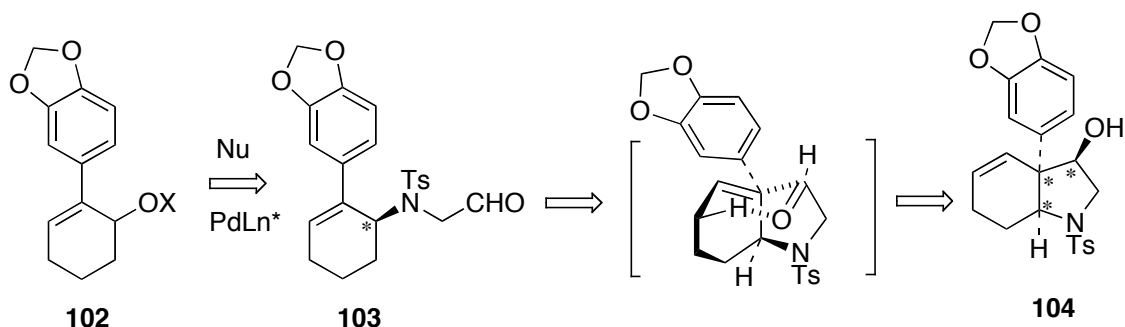
Figure 2. Crinane Alkaloids

If an aldehyde ((S)-**103**) is obtained from **102** using this asymmetric allylic substitution, the intramolecular carbonyl-ene reaction[26] of **103** would construct the quaternary carbon center of **104** in a stereoselective manner.   From this compound (**104**), the target alkaloids would be synthesized in an optically pure form in short steps (Scheme 21).

Scheme 21. Our Plan for the Synthesis of Crinane Alkaloids

Initially, the cyclohexenylamine derivative (**106**) was synthesized from the allyl alcohol (**102**) and the tosylamide (**105**).   When a THF solution of **102a** (1 equiv), **105** (1.1 equiv), Pd$_2$(dba)$_3$·CHCl$_3$ (2.5 mol%), and (S)-BINAPO (5.0 mol%) was stirred at room temperature for 18 h, the desired cyclohexenylamine derivative (**106**) was obtained in 68% yield with 60% ee as a crystalline product (Table 2, run 1).   The ee of **106** was slightly raised when the reaction was carried out at a low temperature, although the reaction time was longer and the yield is moderate (run 2).   Then the leaving group was changed to phosphonate. At a low temperature, the desired product (**106**) was obtained in 80% yield with 74% ee (run 4).   As a solvent, THF was the most suitable (runs 4-6), and the use of (S)-BINAP as the ligand gave **106** with a high ee, although the yield was moderate (run 7). When the compound (**106**) with 74% ee was recrystalyzed from MeOH, the racemic **106** was obtained as colorless crystals, and the concentration of the mother liquor gave the oily (-)-**106** with 99% ee.

Table 2. Reaction of **106** with **107** in the presence of palladium catalyst.[a]
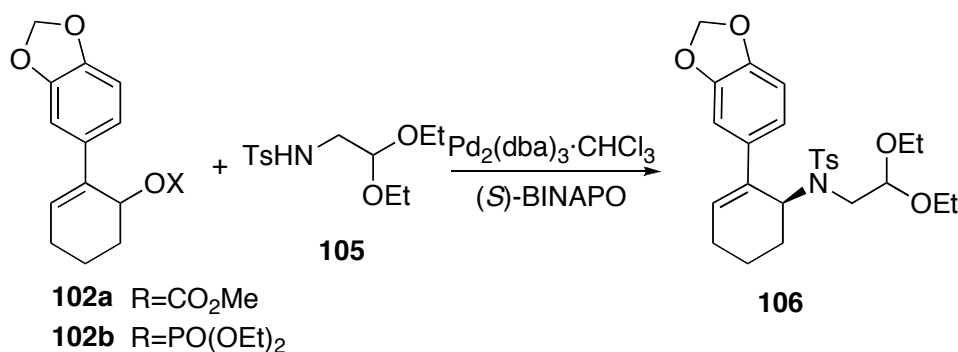
| run	substrate	solv.	temp (°C)	time (h)	yield (%)[b]	ee (%)
1	**102a**	THF	rt	18	68	60
2	**102a**	THF	0	106	31 (38)	68
3	**102b**	THF	0	4	73	69
4	**102b**	THF	-20	48	80	74
5	**102b**	DMF	-20	91	65	67
6	**102b**	EtCN	-20	310	48 (21)	68
7 [c]	**102b**	THF	rt	160	43 (28)	75

a) 2.5 mol % of Pd$_2$(dba)$_3$•CHCl$_3$ and 5.0 mol% of (*S*)-BINAPO were used. In the case of **102b**, NaH was added. b)The number in parenthesis shows the yield of recovered starting material. c) (*S*)-BINAP was used as a ligand.

Deacetalization of **106** (99% ee) with FeCl$_3$•SiO$_2$ gave the aldehyde (**103**) in high yield.   As expected, when a toluene solution of **103** was heated at 230-240 °C in the presence of 4Å molecular sieves for several hours, the desired hexahydroindole (**104**) was obtained in 58% yield (72% conversion) as a sole product.   The NOE experiment with acetylated compound (**107**) indicates that the ring junction of the 5,6 membered ring is *cis* and that the acetoxy group is *trans* to the aryl group.   The stereochemistry of this compound is consistent with that of the target alkaloids.   Allylic oxidation of **107** with SeO$_2$ gave the alcohol (**108**) in a highly stereoselective manner as the sole product because SeO$_2$ approached the olefin from the face opposite of the large phenyl group.   The reaction of Ms$_2$O with **108** in the presence of NEt$_3$ followed by treatment with MeOH, gave **109a** as the main product (β : α, 6.0 : 1).   Detosylation of **109a** followed by methylenation and deacetylation smoothly proceeded to give (+)-crinamine.   Thus, the asymmetric total synthesis of (+)-crinamine was achieved in 9 steps from **102b** in 20% overall yield, and this establishes the absolute confuguration of C-3 in (-)-**106** to be *S* (Scheme 22).
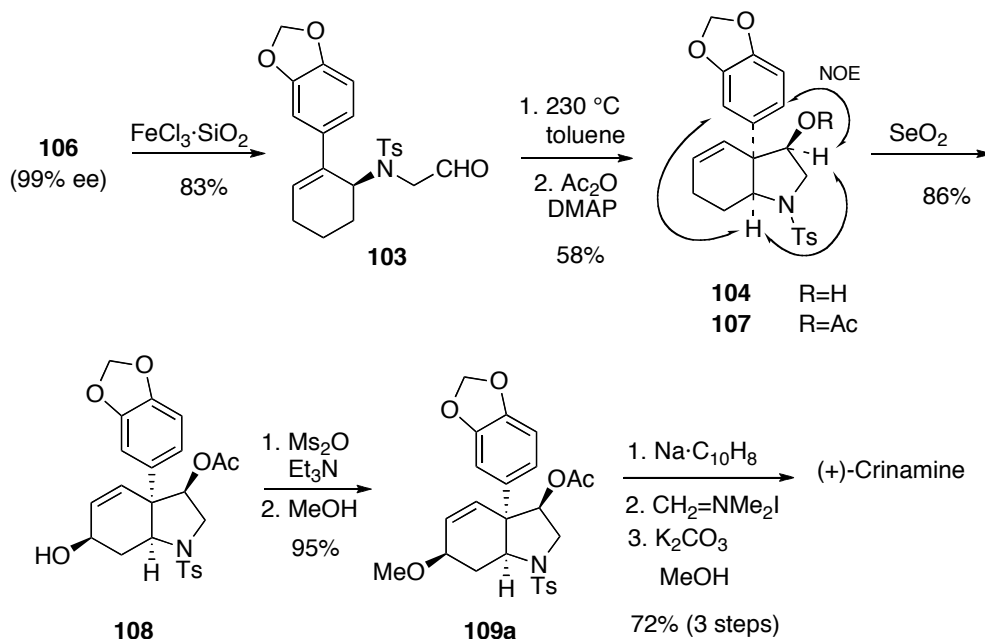
Scheme 22. Syntehsis of (+)-Crinamine

Treatment of **108** with HC(OMe)$_3$ in the presence of Montmorillonite K-10 gave **109b** in high yield (α : β, 4.0 : 1).   Detosylation of **109b** followed by formylation, gave the compound (**110**).   Treatment of **110** with POCl$_3$ followed by deacetylation gave (-)-haemanthidine, which could be converted into (+)-pretazettine by a known method. Thus, the total syntheses of (-)-crinamine, (-)-haemanthidine and (+)-pretazettine were achieved (Scheme 23).[27]
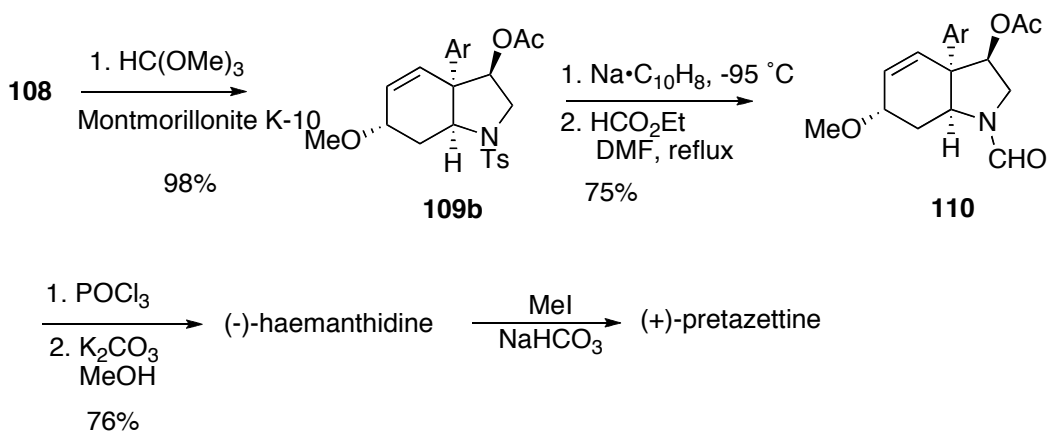
Scheme 23. Synthesis of (-)-Haemanthidine and (+)-Pretazettine

4-1-3.   REACTION MECHANISM FOR ASYMMETRIC ALLYLIC SUBSTITUTION

During the course of our study on the total synthesis of (+)-crinamine, (–)-haemanthidine, and (+)-pretazettine, when (±)-**97a** was reacted with **105** in the presence of Pd$_2$(dba)$_3$·CHCl$_3$ and (S)-BINAPO, the desired product (S)-**111** with 83% ee was obtained in 73% yield.   We were very surprised to find that

the recovered starting material (*R*)-**97a** showed 60% ee in 12% yield.   This means that kinetic resolution would occur upon the formation of (π-allyl)palladium complex (Scheme 24).   The fact that kinetic resolution occurred on palladium-catalyzed enantioselective allylic alkylation was found by Prof. Hayashi, and recently a few group reported in regard to this phenomenon.[28]
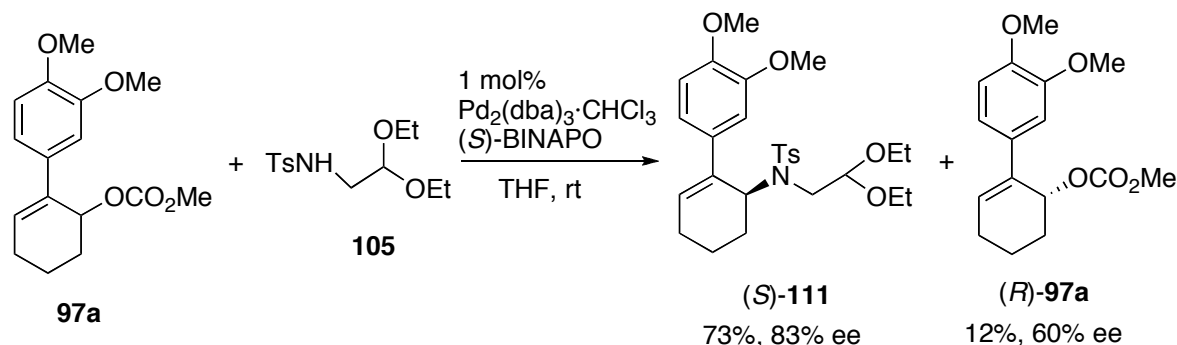
**Scheme 24**. Kinetic Resolution on Palladium-Catalyzed Allylic Substitution

To confirm this, the same reaction was carried out at 0 °C and the time courses of the ees of the product (*S*)-**111** and the starting material (**97a**) were monitored by HPLC.   The results are shown in Table 3. Apparently, kinetic resolution was also shown in this reaction; that is, after 3 h, the ee of the product (*S*)-**111** was 86%, while the ee of the recovered starting material (*R*)-**97a** was 30% ee.   Although the same ee of (*S*)-**111** was obtained in each time, the ee of the recovered starting material (*R*)-**97a** gradually increased, and after 165 h, (*R*)-**97a** with 93% ee was obtained in 14% yield along with (*S*)-**111** with 88% ee in 60% yield (Figure 3).

Table 3. Kinetic resolution of **97a**

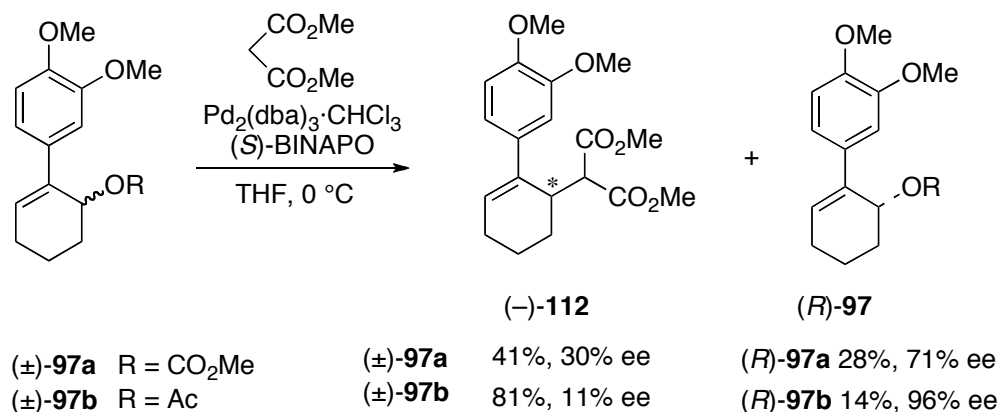| run	time (h)	(*S*)-**111** (% ee)	(*R*)-**97a** (% ee)
1	3	86	30
2	6	87	46
3	19	88	65
4	47	88	78
5	75	88	79
6	120	88	91
7	165	88	93

The reaction was carried out using 5 mol % of Pd$_2$(dba)$_3$·CHCl$_3$and 5 mol% of (*S*)-BINAPO in THF at 0 °C.

**Figure 3**. The ees of (*S*)-**111** and **97a** on each time.
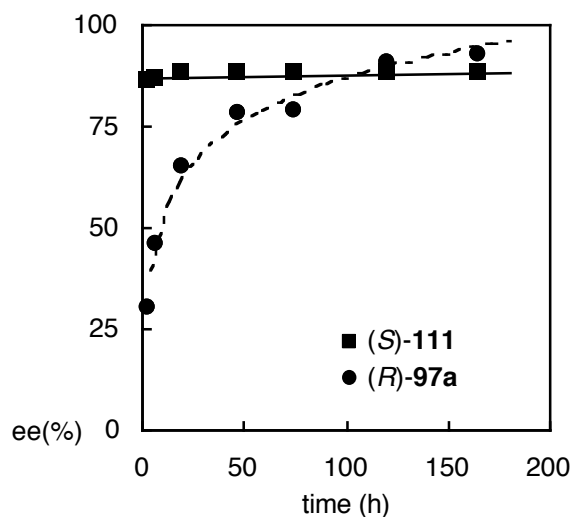
On the other hand, when the reaction of (±)-**97a** with dimethyl malonate was carried out in the presence

of a palladium catalyst and (S)-BINAPO, (–)-**112** was obtained in 41% yield but the ee was only 30%.

However, the recovered starting material (R)-**97a** showed 71% ee.   When the same reaction was carried

out using (±)-**97b** as the substrate in the presence of NaH, the ee of the recovered starting material was

96%, but the ee of (-)-**112** was only 11% (Scheme 25).[29]

| (±)-**97a** R = CO₂Me | (±)-**97a** | 41%, 30% ee | (R)-**97a** 28%, 71% ee |
| (±)-**97b** R = Ac | (±)-**97b** | 81%, 11% ee | (R)-**97b** 14%, 96% ee |

Scheme 25. Reaction of **97** with Methyl Malonate

These results indicate that there are two independent pathways in the asymmetric synthesis of (S)-**97**: that

is, kinetic resolution and asymmetric substitution.   If the reaction rate of (S)-**I** with Pd(0) having

(S)-BINAPO is faster than that of (R)-**I** with Pd(0) having (S)-BINAPO, kinetic resolution would occur

and (R)-**I** would remain unchanged.   In this process, (R)-**I** also can react with Pd(0) having (S)-BINAPO

to produce the same π-allylpalladium complex.   The intermediary (π-allyl)palladium complex **II** reacts

with nucleophile enantioselectively to give (S)-**III**.   Thus, both (S)- and (R)-**I** can be converted into

(S)-**III**.   If the starting material is recovered, (R)-**I** with a high ee can be obtained (Scheme 26).[29]
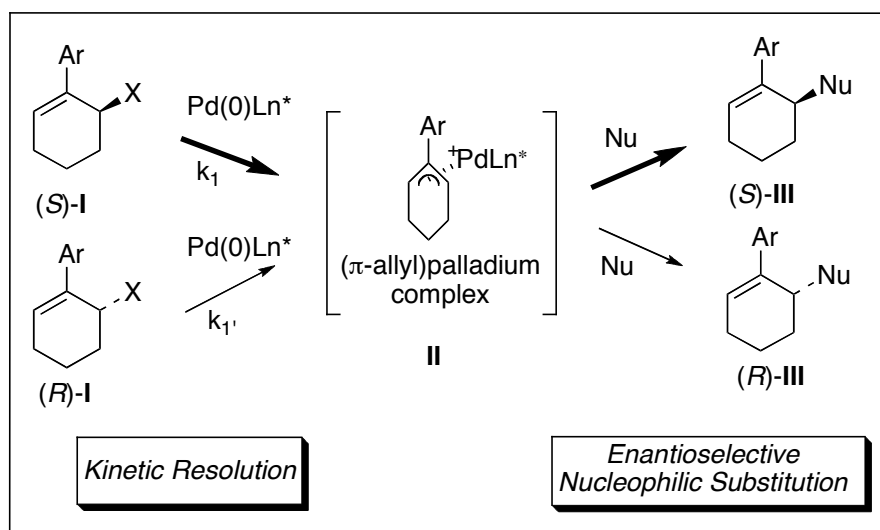
Scheme 26. Reaction Pathways

4-2. TOTAL SYNTHESIS OF (-)-TUBIFOLINE

We next turned our attention the total syntheses of strychnine and tubifoline.[30] These alkaloids could be synthesized from the tetracyclic ketone (**114**), which should be an important intermediate for the synthesis of various indole alkaloids as the chiral forms. The compound (**114**) would be obtained from **115**, which would be obtained from **116** by a Heck reaction. If the cyclohexenol derivative (**117**) having the functional group at the 2-position is reacted with an *o*-haloaniline derivative (**118**) in the presence of Pd(0) with a chiral ligand, the cyclohexenyl amine derivative (**116**) should be obtained as a chiral form (Scheme 27).
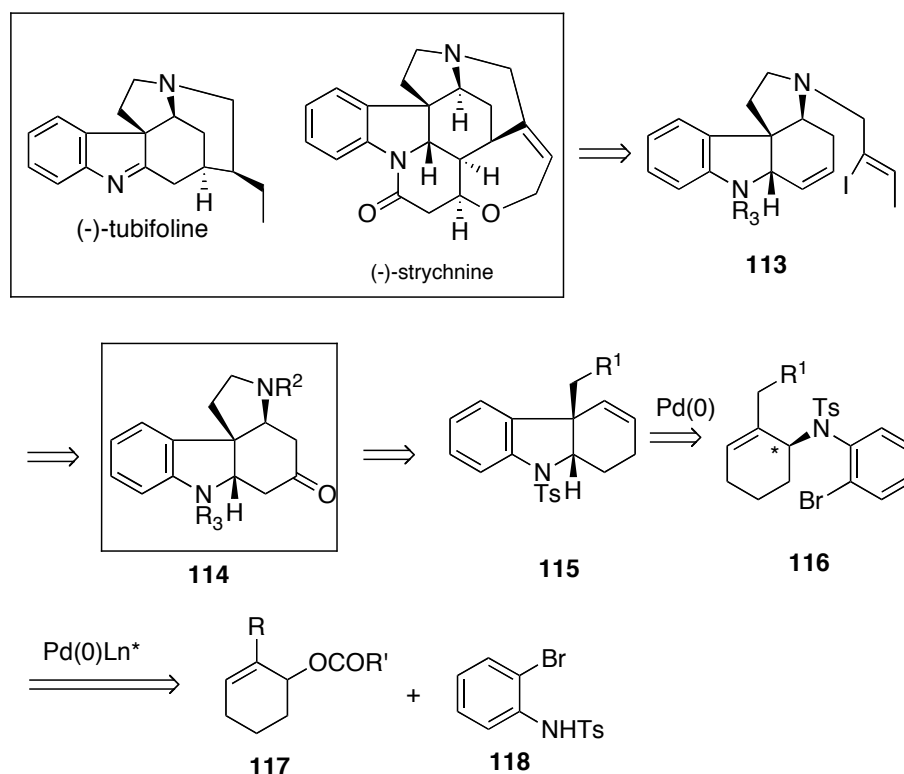
Scheme 27. Our Plan for the Synthesis of Strychnos Alkaloids

To construct an indole skeleton, an *o*-haloaniline derivatives (**118**) were used as a nucleophile. When the reaction of **117a** and the *N*-tosylaniline (**118b**) was carried out in the presence of Pd$_2$(dba)$_3$·CHCl$_3$ and (*S*)-BINAPO, the cyclohexenylamine derivative (**116b**) was obtained in 85% yield (Table 4, run 1). The reaction of **117**a with the *N*-tosyl-*o*-bromoaniline (**118a**) gave a desired compound (**116a**) with 80% ee in 78% yield. To enhance the reactivity of the leaving group, a vinyl carbonate (**117b**) was used, and the reaction was carried out at 0 °C to give **116a** with 84% ee in 75% yield (run 3). The lower reaction temperature did not affect the ee of **116a** (run 4).

Table 4. Reaction of **117** with aniline Derivative **118**
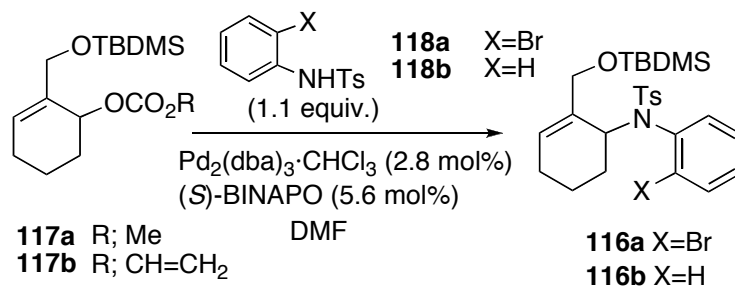
run	117	118, X	temp (°C)	time (h)	116	yield (%)	ee (%)
1	**117a**	H	rt	3	**116b**	85	76
2	**117a**	Br	rt	7	**116a**	78	80
3	**117b**	Br	0	21	**116a**	75	84
4	**117b**	Br	-20	168	**116a**	67	83

Deprotection of **116a** with 4N HCl followed by treatment with PBr$_3$ and then NaCN in DMSO gave a nitrile (**119**) in good yield.   Palladium-catalyzed Heck reaction of **119** proceeded smoothly to give **120** in high yield.   The results of an NOE experiment of **120** indicated that the ring junction of the fused 5,6-membered ring is cis.   The compound (**120**) was recrystallized from EtOH to give the optically pure **120** ([α]$_D$ -46.7°, 99% ee, 73% recovery).   Treatment of **120** with LiAlH$_4$ followed by protection of the primary amine with Boc$_2$O afforded the compound (**121**).   To construct the E-ring, cyclization of **121** was carried out using Pd(II).   When an acetic acid solution of **121** was stirred in the presence of 10 mol% of Pd(OAc)$_2$, 40 mol% of benzoquinone and 2 equiv of MnO$_2$ at 50 °C for 15 min, the compound (**122**) was obtained in 77% yield.   Probably, the double bond of **121** coordinates to Pd(II) to form **123** and then amide nitrogen attacks olefin to give the palladium complex (**124**).   Then β-hydrogen elimination from **124** occurs to give **122**.   Conversion of olefin into ketone was carried out.   Based on the results of a modeling study, it was thought that the C-15 position is less hindered than the C-14 position.   Thus, it was expected that the hydroxyl group would be introduced at the C-15 position by hydroboration.   Hydroboration of **122** using BH$_3$·THF followed by treatment with H$_2$O$_2$ in aq.   NaOH gave the alcohols (**125**) and (**125'**) in 49% and 51% yields, respectively.   The use of a large hydroboration reagent, 9-BBN, afforded the desired alcohols (**125**) as a major product and an elevated temperature gave the alcohol (**125**) in 80% yield.   Swern oxidation of **125** was carried out to give the desired tetracyclic ketone (**126**) in high yield.   Thus, the synthesis of the tetracyclic ketone (**126**) from

the cyclohexenol derivative (**117b**) was achieved (Scheme 28).
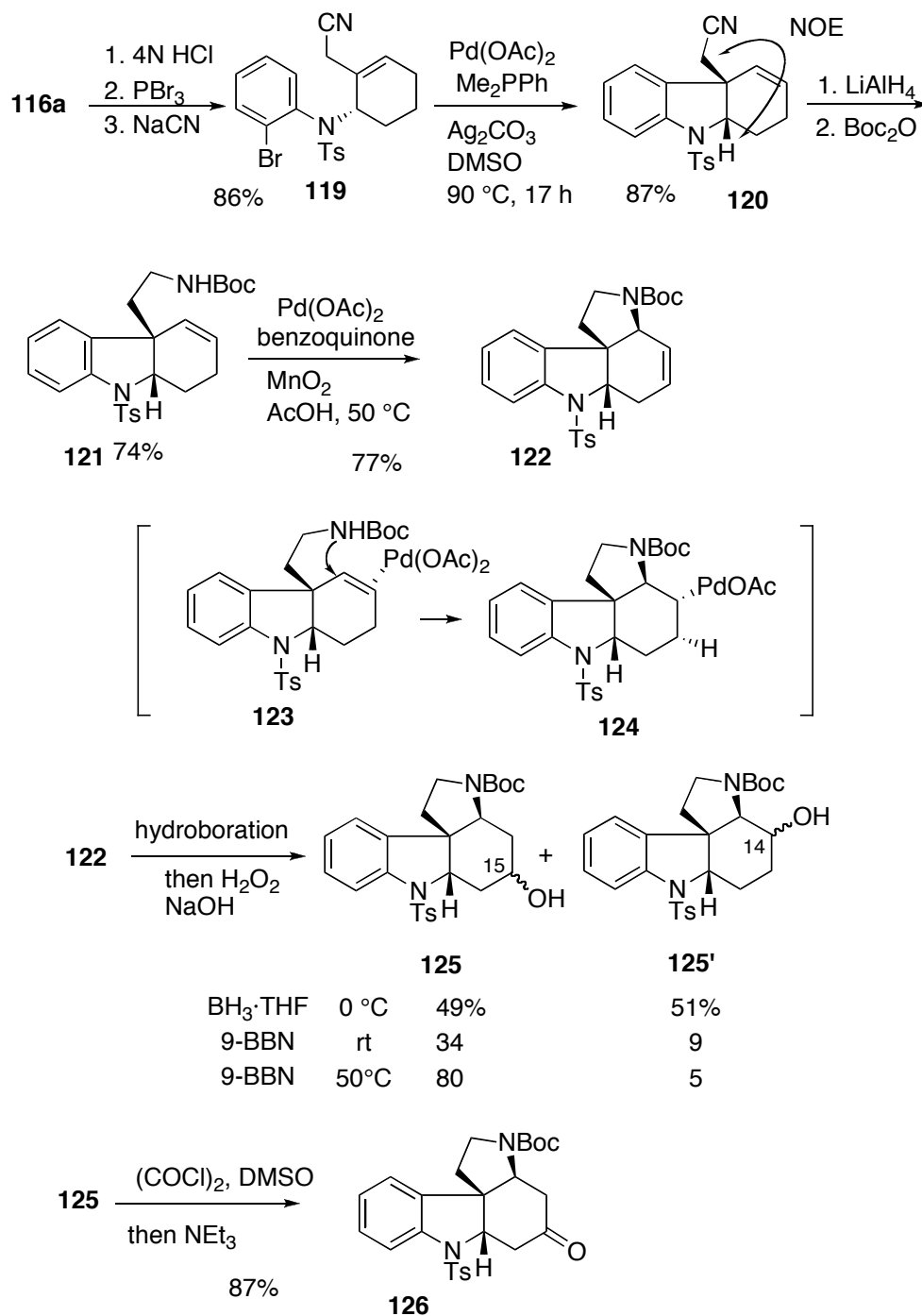
Scheme 28. Synthesis of Tetracyclic Ketone **126**

Subsequently, the synthesis of tusbifoline[31] was examined.   Treatment of **126** with LDA followed by the addition of PhNTf$_2$ at –78 °C afforded the enol triflates (**127**) and (**128**) in 8% and 14% yields, respectively.   The base was changed to potassium hexamethyldisilazamide (KHMDS) and the reaction was carried out at –78 °C to give **127** and **128** in 35% yield (ratio of 3 to 2).   Since **127** was considered

to be the thermodynamic product, the reaction was carried out at –35 °C to afford the desired compound (**127**) as a sole product in 64% yield.   Treatment of the enol triflate (**127**) with HCO_2H in the presence of $Pd(OAc)_2$ and PPh_3[32] gave the desired the olefin (**129**) in quantitative yield.   Deprotection of the tosyl group of **129** with sodium naphthalenide followed by treatment with CF_3CO_2H gave diamine. Monoalkylation with **130** in the presence of K_2CO_3 gave **131** in 49% yield from **129**.   An intramolecular Heck reaction using a palladium catalyst gave a (-)-dehydrotubifoline in 59% yield.   Hydrogenation of (-)-dehydrotubifoline with PtO_2 in EtOH was carried out to give (-)-tubifoline (Scheme 29).
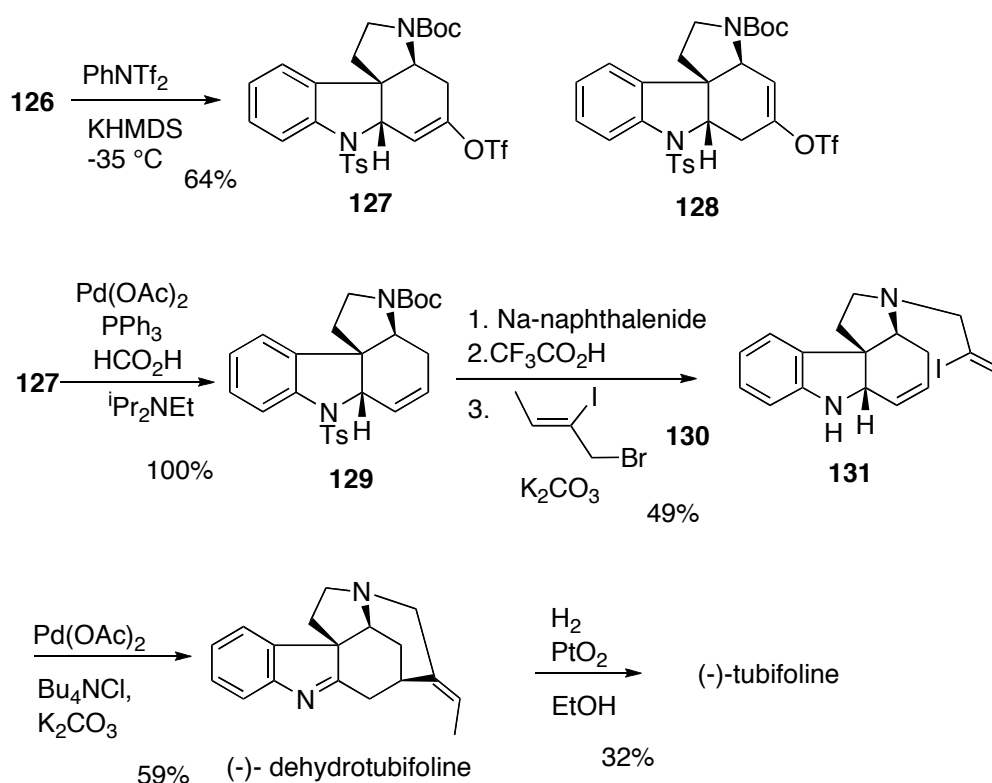
Scheme 29. Synthesis of (-)-Tubifoline.

The results indicated that the absolute configuration of **116a** obtained by asymmetric allylic substitution was *S*.   Thus, we succeeded in the total syntheses of (-)-dehydrotubifoline and (-)-tubifolin from the cyclohexenylamine derivative (**116a**), which was synthesized by palladium-catalyzed asymmetric allylic substitution by 16 steps.   All of the steps for the ring constructions were achieved using palladium catalysts.[10,33]

4-3. TOTAL SYNTHESIS OF (-)-STRYCHNINE

The next target molecule is (-)-strychnine, which should be synthesized from the tetracyclic ketone (**126**).

Our retrosynthetic analysis of (-)-strychnine is shown in Scheme 30. Since the construction of the ABCE-rings of strychnine have been already achieved as a tetracyclic ketone, construction of the G-ring is required for the synthesis of (-)-strychnine. Two pathways should be considered. One is the introduction of an alkyl or an acyl group at the α-position of the carbonyl group of **126** and the formation of a carbon-nitrogen bond for construction of the G-ring. The other is the introduction of an acyl group on nitrogen to form **135** and then construction of the G-ring (Scheme 30).
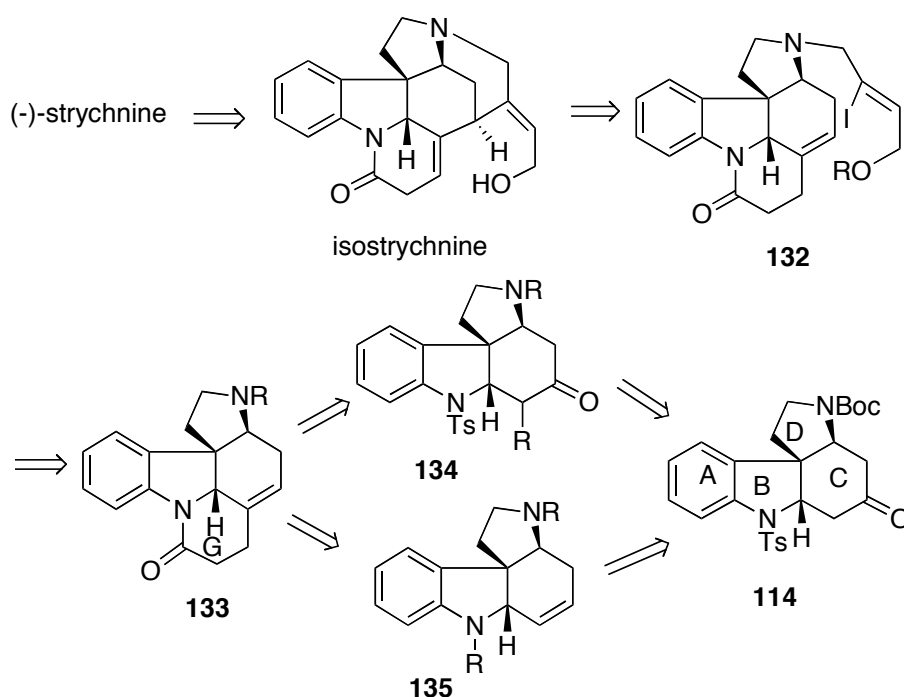
Scheme 30. Retrosynthetic Analysis of (-)-Strychnine

At first, we chose the former reaction pathway to construct **133** by introduction of an acyl group at the α-position of the carbonyl group in **114**. However, many attempts to introduce an acyl group to the α-position of the keto-carbonyl group of **114** were fruitless due to steric hindrance of the large protecting group on aniline nitrogen. Thus, construction of the G-ring by the Heck reaction was tried. Detosylation of **129** followed by treatment with 3-bromoacryloyl chloride in the presence of K$_2$CO$_3$ gave **137**, which was treated with 10 mol% of Pd(OAc)$_2$ and 20 mol% of PPh$_3$ in the presence of ^{i}Pr$_2$NEt in DMSO at 80 °C for 1.5 h to give the pentacyclic compound (**138**) in 46% yield. Isomerization of the double bond of **138** by NaO^{i}Pr in ^{i}PrOH followed by deprotection of the Boc group and then alkylation with **26a** afforded the compound (**39**), which is an intermediate for the synthesis of (±)-strychnine reported by Vollhardt (See Scheme 8). Treatment of **39** with Pd(OAc)$_2$, Bu$_4$NCl and K$_2$CO$_3$ in DMF

afforded hexacyclic compound (**40**), which was treated with LiAlH$_4$ followed by deprotection of the silyl group to give (+)-isostrychnine. (+)-Isostrychnine was converted into (-)-strychnine by treatment with KOH in EtOH by the known method (Scheme 31).
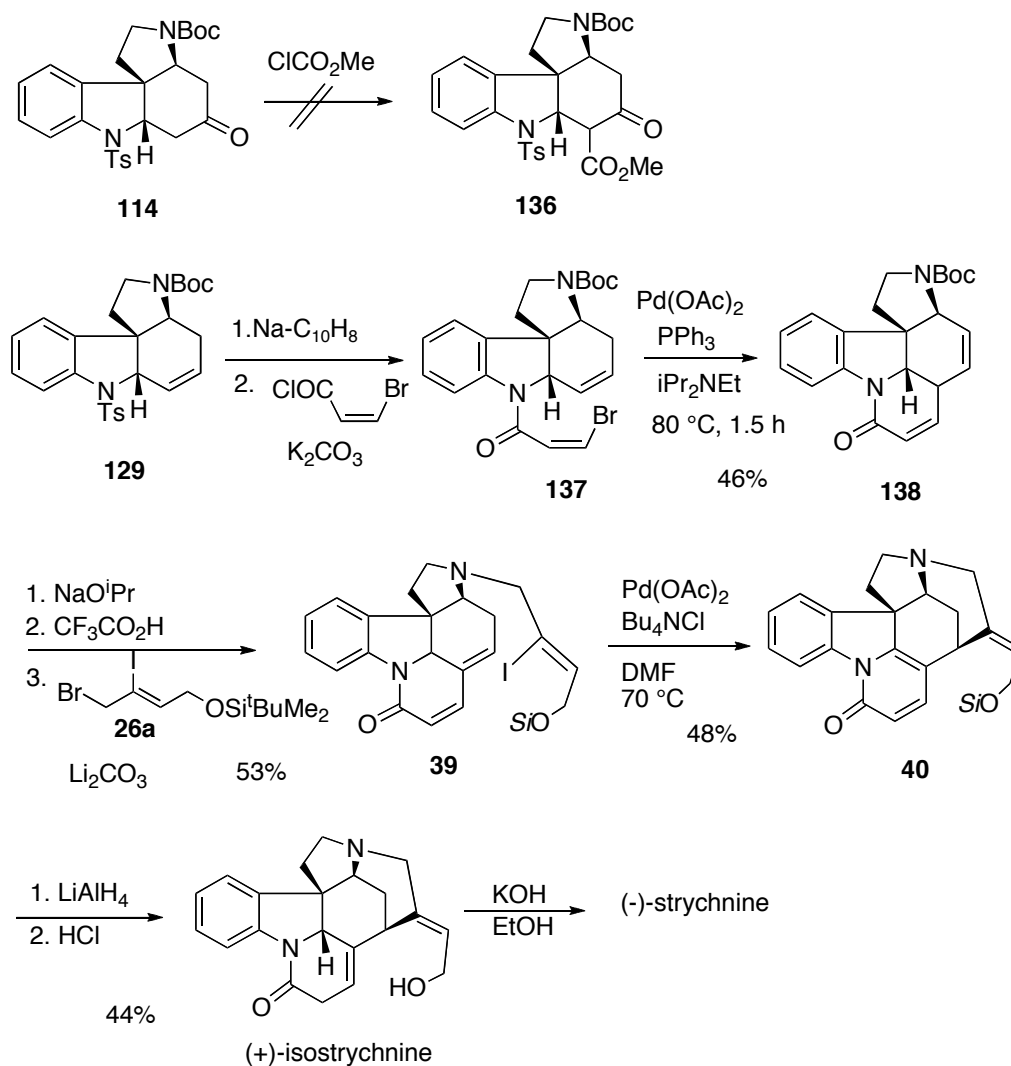
Scheme 31. Total Synthesis of (-)-Strychnine.

Thus, the total synthesis of (-)-strychnine was achieved by 22 steps from **117b**.[10]

In the total synthesis of (-)-strychnine, the starting cyclohexenylamine derivative (**116a**) was synthesized from **117b** by palladium-catalyzed allylic substitution, and all cyclizations for synthesis of (+)-isostrychnine were performed using a palladium catalyst. The compound (**116a**), obtained from the cyclohexenol derivatives (**117b**) and (**118a**) by palladium catalyst, was converted into **121** by palladium catalyzed Heck reaction and it has the ABE-ring system. The C-ring was constructed from the compound (**121**) using palladium-catalyzed allylic oxidation. The G-ring was formed by

palladium-catalyzed cyclization of **137**. The D-ring was constructed by Heck reaction of **39**. From **39**, (-)-strychnine was synthesized. The total synthesis of (-)-strychnine was achieved by 22 steps from **117b** (Scheme 32).
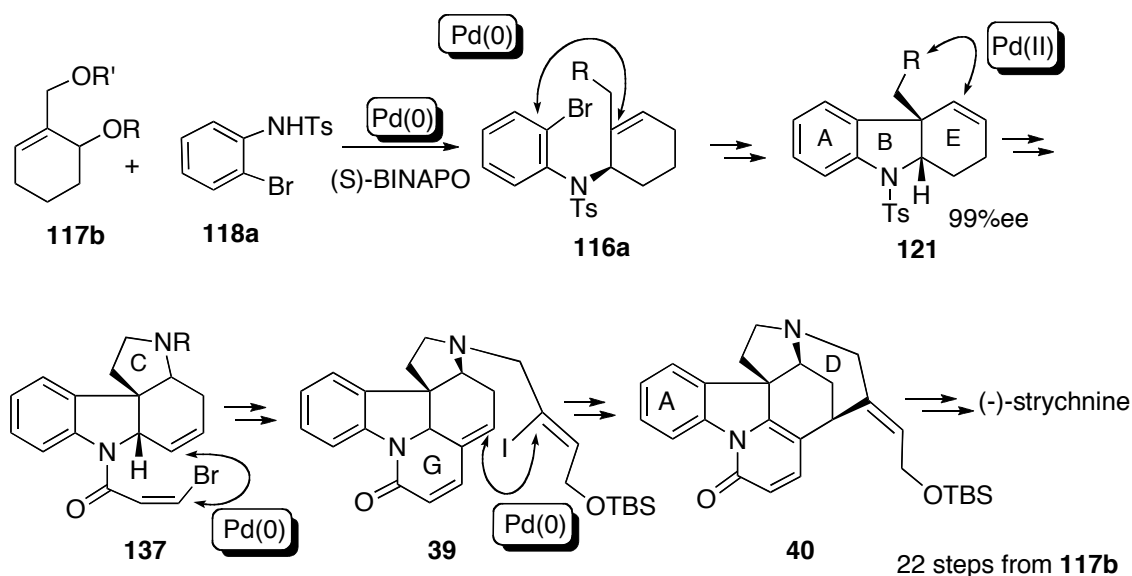
Scheme 32. Summary of Total Synthesis of (±)-Strychnine

The fact that all rings of (-)-tubifoline, (+)-isostrychnine and (-)-strychnine were constructed using a palladium catalyst indicates the importance of a palladium catalyst in modern synthetic organic chemistry.

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