Review

Development of a Novel Synthetic Method for Ring Construction Using Organometallic Complexes and Its Application to the Total Syntheses of Natural Products[1)]

Miwako MORI

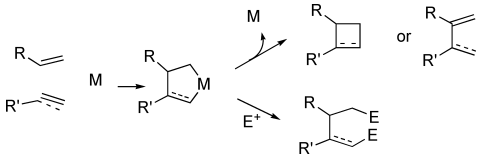
Health Sciences University of Hokkaido; Tobetsu, Hokkaido 061–0293, Japan.

Received December 2, 2004

Organometallic complexes are useful tools in synthetic organic chemistry. We investigated a novel synthetic method for ring construction using organometallic complexes and synthesized natural products and biologically active substances using these methods. Metalacycles formed from an early transition metal and diene, enyne, and diyne are stable under the reaction conditions and they are easily converted into compounds with functional groups by the addition of various agents. We have developed a novel synthetic method of heterocycles from enyne and diene using Cp_2ZrBu_2. The total syntheses of (−)-dendrobine, (±)-mecembrane, and (±)-mecembrine were achieved using this procedure. To synthesize these natural products as a chiral form, a novel palladium-catalyzed asymmetric allylic amination was developed, and chiral 2-arylcyclohexenylamine derivatives were synthesized. From these compounds, the total syntheses of (−)-mesembrane, (−)-mesembrine, (+)-crinamine, (−)-haemanthidine, and (+)-pretazetine were achieved. By further development of this procedure, a chiral 2-siloxymethylcyclohexenylamine derivative could be synthesized and the novel synthesis of indole derivatives was developed from this compound. From this indole derivative, (−)-tsubifoline and (−)-strychnine were synthesized.

Key words organometallic complex; palladium catalyst; natural product synthesis; strychnine; mesembrine; zirconocene

Organometallic complexes are useful tools in synthetic organic chemistry. In particular, they play an important role in carbon–carbon bond formation. A metalacycle, *i.e.*, a ring compound containing a transition metal, is a useful intermediate in synthetic organic chemistry. Oxidative cyclization of unsaturated hydrocarbons, such as alkene, alkyne, carbonyl compounds, or nitrile, using a low-valent transition metal is a useful reaction for synthesis of metalacycles. It is known that a metalacycle formed from a late transition metal and unsaturated hydrocarbons is not stable and is easily converted into the reductive elimination product or β-hydrogen elimination product (Eq. 1). Since the low-valent metal complex is regenerated in this reaction, the reaction proceeds with a catalytic amount of the transition metal. On the other hand, the metalacycle formed from an early transition metal and unsaturated hydrocarbons is fairly stable and can be converted into various compounds with functional groups by treatment with various agents (Eq. 2). Therefore a stoichiometric amount of the metal complex is required in this reaction.

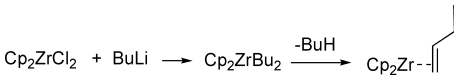


(1)

(2)

Negishi *et al.*[2)] and Nugent and Calabrese[3)] reported the syntheses of zirconacycles **2** from diene, enyne, and diyne **1** using zirconocene (Cp_2Zr). Hydrolysis of zirconacycle afforded the cyclized compound **3** (Chart 1).

Negishi *et al.* also found a synthetic method of dibutylzirconocene (Cp_2ZrBu_2) from zirconocenedichloride (Cp_2ZrCl_2) and butyl lithium, and dibutylzirconocene is easily converted into zirconocene coordinated by a butene ligand *in situ* at room temperature[4)] (Eq. 3).



(3)

This was a great discovery in zirconium chemistry because it is difficult to isolate zirconocene with no ligand. We were interested in those results and attempted to form carbon–carbon bonds between the unsaturated hydrocarbons, such as enyne and diene, using zirconocene.

Synthesis of Heterocycles Using Zirconium-Mediated Cyclization and Total Synthesis of (−)-Dendrobine

The zirconacycles **2** were easily synthesized *in situ* from Cp_2ZrCl_2 and diene, enyne, or diyne **1**. To a THF solution of Cp_2ZrCl_2 and unsaturated hydrocarbon **1** was added BuLi at −78 °C under argon gas, and the solution was stirred at room

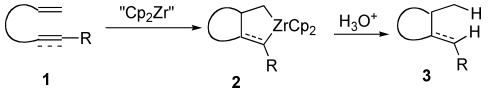


Chart 1. Formation of Zirconacycles from Unsaturated Hydrocarbons and Cp_2ZrBu_2

* To whom correspondence should be addressed. e-mail: mori@pharm.hokudai.ac.jp

© 2005 Pharmaceutical Society of Japan

temperature for 1 to 2 h to form zirconacycle **2**. We reacted enyne **1a** with dibutylzirconocene (Cp_2ZrBu_2), and bicyclic compound **3a** was obtained in high yield after hydrolysis. An intermediary zirconacycle should be tricyclic complex **2a**. Since the reaction proceeded in a highly stereoselective manner, the addition of iodine into the solution of **2a** gave iodinated compounds **5a** and **5b**. Interestingly, the atmosphere of a solution of **2a** was changed from argon to carbon monoxide, and the solution was stirred at room temperature to give tricyclic keto-aldehyde **4a** after hydrolysis. Furthermore, enyne **1b** was treated with Cp_2ZrBu_2 in a similar manner to give bicyclic compound **3b** in high yield. The atmosphere of intermediary zirconacycle **2b** was changed from argon to oxygen, and the solution was stirred at room temperature to give alcohol **6-D** after treatment with 10% DCl. Treatment of **2b** with carbon monoxide afforded tricyclic ketone **4b**.[5]

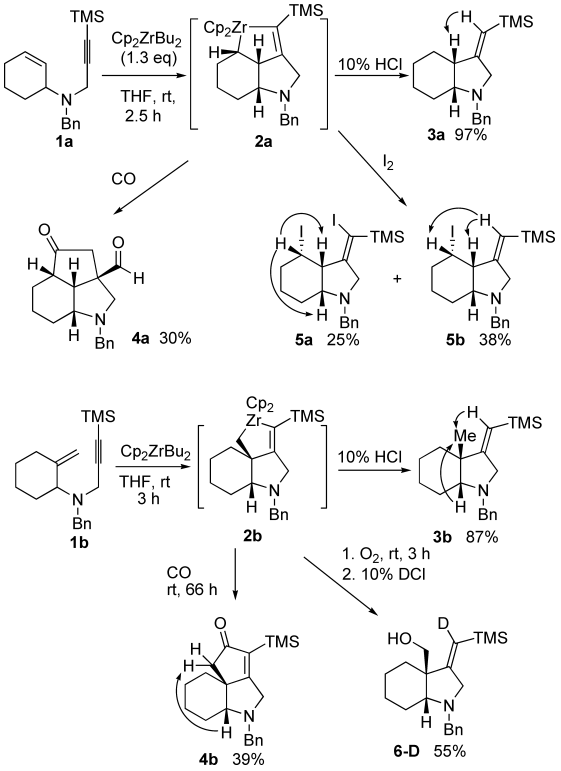


Chart 2. Synthesis of Bi- or Tricyclic Compounds Using Zirconium-Mediated Cyclization

The reaction of diene **7a** with Cp_2ZrBu_2 was carried out, and the perhydroindole derivative **9a** was obtained in high yield. Treatment of diene **7a** with Cp_2ZrBu_2 and then conversion of the atmosphere to carbon monoxide afforded tricyclic ketone **10a** in 94% yield.[6] The stereochemistry of **9a** and **10a** could not be determined at this stage.

Since tricyclic ketone **10a** was obtained from **7a** in a one-pot reaction in high yield, the total synthesis of (−)-dendrobine was planned. (−)-Dendrobine was first isolated from *Dendrobium nobile* lindle by Suzuki *et al.*[7] and Inubushi *et al.*[8] Total syntheses of (−)-dendrobine were achieved by several groups.[9,10] Our retrosynthetic analysis is shown in Chart 4. Kende *et al.* previously synthesized (−)-dendrobine from compound **11**.[10] This compound should be synthesized from tricyclic ketone **10b**, which would be obtained from diene **7b** using our zirconium-mediated cyclization. Although the stereochemistry of the 5,5-membered ring junction of the tricyclic ketone was not clear, we believed it to be *cis* on the basis of common sense.

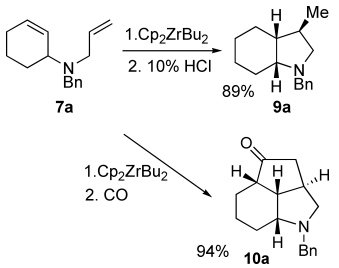


Chart 3. Reaction of Diene with Cp_2ZrBu_2

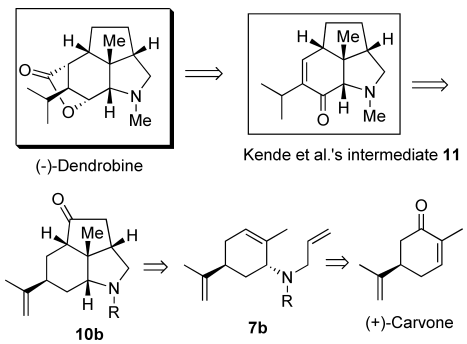


Chart 4. Retrosynthetic Analysis of (−)-Dendrobine

Dr. Miwako Mori was obtained her Ph. D. degree in 1971 (Supervisor, Professor Yoshio Ban) from Hokkaido University. She joined the Faculty of Pharmaceutical Sciences, Hokkaido University as an instructor in 1971, and was promoted to Associate Professor in 1987 and was promoted to Professor in 1992. In 2004, she was retired from Hokkaido University and is an emeritus professor of Hokkaido University from 2004. In 2005, she moved to Health Sciences University of Hokkaido.

Her research interest is in the area of organometallic chemistry toward synthetic organic chemistry, asymmetric synthesis, synthesis of heterocycles using molecular nitrogen and utilization of carbon dioxide.

She was awarded the Pharmaceutical Society of Japan Award for Young Scientist in 1980, Saruhashi Prize (Superior Women's Scientist) in 1991, Synthetic Organic Chemistry Award in 2001, the Akiyama foundation Award in 2001, and the Pharmaceutical Society of Japan Award in 2004.

Miwako Mori

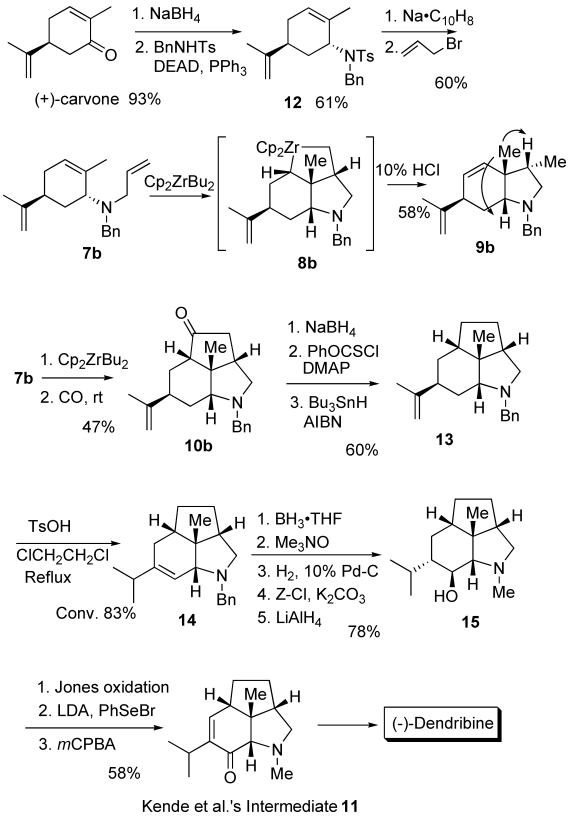


Chart 5. Formal Total Synthesis of (−)-Dendrobine

Treatment of (+)-carvone with $NaBH_4$ followed by the Mitsunobu reaction[11] gave the cyclohexenylamine derivative **12**. Detosylation of **12** followed by allylation afforded diene **7b** in high yield. Cyclization of diene **7b** with Cp_2ZrBu_2 followed by hydrolysis gave the perhydroindole derivative **9b** in 58% yield. The stereochemistry of the cyclized compound was determined to be **9b** in an NOE experiment, and this means that the stereochemistry of the intermediary zirconacycle should be **8b**. Treatment of **8b**, obtained from **7b** and Cp_2ZrBu_2, with carbon monoxide gave the tricyclic ketone **10b** in 47% yield. Deoxygenation of the keto-carbonyl group was carried out to give **13**, of which TsOH isomerized the double bond in dichloroethane to afford **14**. Hydroboration of **14** followed by conversion of the *N*-benzyl group into the *N*-methyl group gave **15**, which was converted into α,β-unsaturated ketone **11**. The spectral data and $[\alpha]_D$ value of this compound agreed with those of Kende *et al.*'s intermediate.[10] Thus we succeeded in the formal total synthesis of (−)-dendrobine using zirconium-mediated cyclization as a key step.[12,13]

In the reaction of diene **7a** with Cp_2ZrBu_2, the perhydroindole derivative **9a** was obtained. To determine the stereochemistry of **9a**, an *N*-benzyl group of **9a** was converted into a *N*-tosyl group and X-ray analysis of this crystallized compound was carried out. The stereochemistry of this compound was determined to be **9a′** (Fig. 1). Thus the stereochemistry of **9a** was confirmed. This means that the ring junction of the fused 5,5-membered ring of zirconacycle **8a** is *trans* and that of the tricyclic ketone **10a** should also be *trans*.

It was known that the ring junction of the 5,5-membered

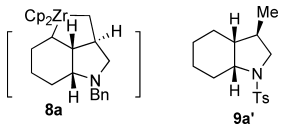


Fig. 1.

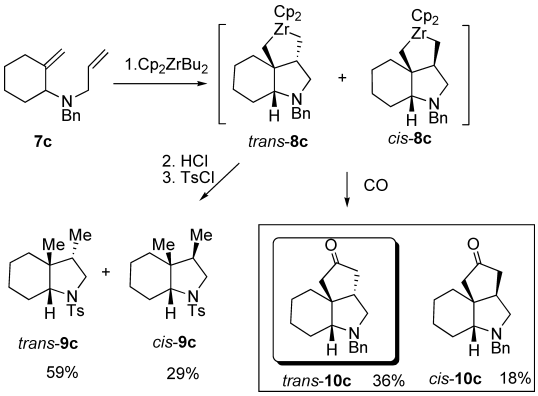


Chart 6. Synthesis of *trans*-5,5-Fused Bicyclic Compound

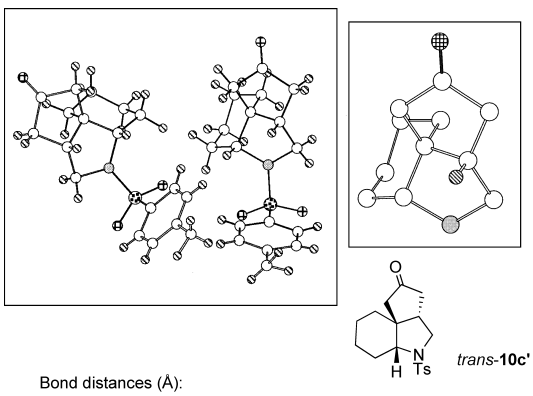


Fig. 2. X-Ray Crystallography of *trans*-**10c′**

ring is *cis* because of the steric factor. Thus we further investigated the stereochemistry of the ring junction of the fused 5,5-membered ring of the zirconacycle.[14] When diene **7c** was treated with Cp_2ZrBu_2 and then 10% HCl was added, the two perhydroindole derivatives *trans*-**9c** and *cis*-**9c** were obtained in a ratio of 2 to 1. Furthermore, treatment of the zirconacycles with carbon monoxide gave the two tricyclic ketones *trans*-**10c** and *cis*-**10c** in a ratio of 2 to 1. Since the *trans*-fused 5,5-membered ring compound is rare, conversion of *trans*-**10c** into *trans*-**10c′** was performed and X-ray analysis was carried out (Fig. 2).

It is clear that the ring junction of the fused 5,5-membered ring of zirconacycle *trans*-**10c′** is *trans*. This is the second example of the X-ray crystallography of a *trans*-fused 5,5-membered ring compound.[14]

Total Syntheses of (−)-Mesembrane and (−)-Mesembrine Using Zirconium-Mediated Cyclization

The ring junction of the fused 5,5-membered ring of the tricyclic ketone **10a** is *trans*, but that of **10b** is *cis*. The difference in starting dienes **7a** and **7b** is the reason for the methyl group at the 2-position of the cyclohexene ring of **7b**. Thus we further examined the reaction of **7d**, which has the phenyl group instead of the methyl group on the cyclohexene ring. When the reaction of **7d** with Cp_2ZrBu_2 was carried out and the solution was hydrolyzed with 10% HCl, the perhydroindole derivative **9d** was obtained in 26% yield. The stereochemistry of the product was determined to be **9d** in an NOE experiment. This means that the ring junction of the fused 5,5-membered ring of **8d** is *cis*. Presumably, the stereochemistry of the zirconacycle would be affected by the steric effect of the substituent of the olefin. To improve the yield of the desired cyclized product **9d**, the effect of the substituent on nitrogen was examined, and diene **7e** with a diphenylmethyl group on nitrogen afforded **9e** in 58% yield. This means that the larger substituent on nitrogen gave a good result.

Since the cyclization of **7e** with the diphenylmethyl group on the cyclohexene ring gave the perhydroindole derivative **9e** in good yield, the total syntheses of mesembrane and mesembrine were examined. Our retrosynthetic analysis is shown in Chart 8. Reaction of **7f** with Cp_2ZrBu_2 followed by treatment with oxygen would give alcohol **16**, which would lead to these natural products.

Zirconium-mediated cyclization of **7f** gave the perhydroindole derivative **9f** in 61% yield after hydrolysis. The NOE experiment of **9f** indicated that the ring junction of **9f** is *cis* and the methyl group is *trans* to the aryl group. The atmosphere of the resultant zirconacycle **8f** was changed to oxygen to give a small amount of alcohol **16**. To improve the yield of alcohol **16**, transmetalation of zirconacycle to a magnesium complex was carried out.

To the THF solution of intermediary zirconacycle **8f** was added MeMgBr, and then the atmosphere of argon was changed to oxygen to afford alcohol **16** in 63% yield after hydrolysis. Presumably, complex **17** would be formed from **8f** by treatment with MeMgBr and it reacts with oxygen to give **16**. After conversion of **16** into **18**, (±)-mesembrane was synthesized. On the other hand, allylic oxidation of **18** followed by deformylation of **19** was carried out to give **20**, which was led to (±)-mesembrine.[15] Thus we succeeded in the total syntheses of (±)-mesembrane and (±)-mesembrine using zirconium-mediated cyclization.

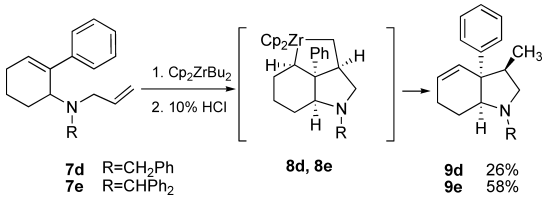


Chart 7. Reactions of Dienes **7d** and **7e** with Cp_2ZrBu_2

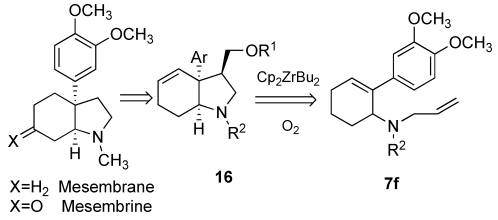


Chart 8. Retrosynthetic Analysis of Mesembrine

Development of Palladium-Catalyzed Asymmetric Allylic Amination

Although the total syntheses of (±)-mesembrane and (±)-mesembrine were achieved, they were not the optically active form because the starting diene **7f** is racemic. To obtain the chiral diene **7f**, the novel asymmetric synthesis of the cyclohexenylamine derivative using a palladium catalyst was examined. Our plan is shown in Chart 10. If the 2-arylcyclohexenol derivative **21** is treated with Pd(0), π-allylpalladium complex I should be formed. Since this is a meso type, a nucleophile should attack both sides of the cyclohexene ring to give the racemic cyclohexene derivative **22**. However, if a palladium catalyst has a chiral ligand, the intermedially π-allylpalladium complex I should be a chiral form. Thus the nucleophile might attack one side of the cyclohexene ring coordinated to the palladium metal to give the chiral cyclohexene derivative **22**.

When a THF solution of **21a** and allyl tosylamide **23a** was

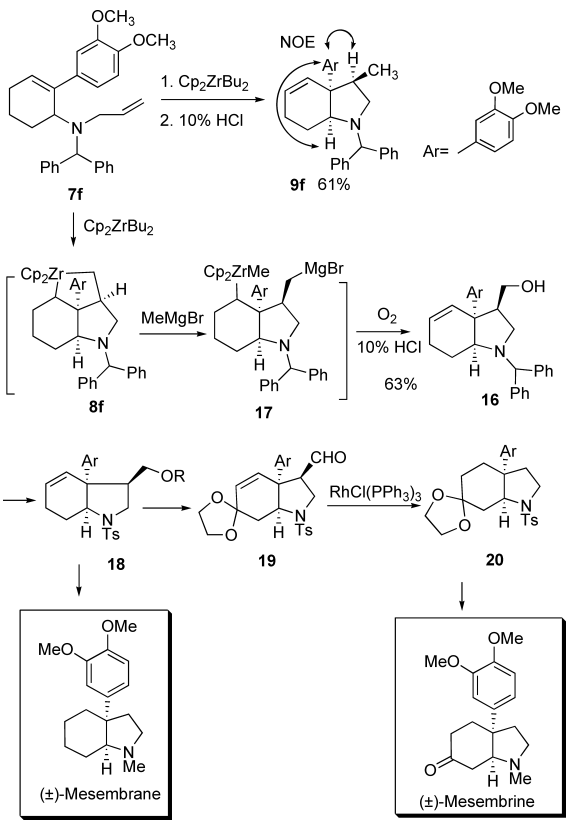


Chart 9. Total Syntheses of Mesembrine and Mesembrane

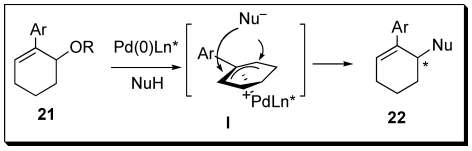
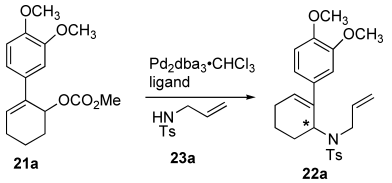


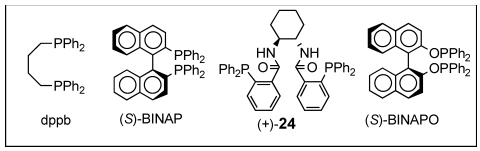
Chart 10. Plan for Palladium-Catalyzed Asymmetric Synthesis of the Cyclohexene Derivative

Table 1. Reactions of **21a** with **23a** under Various Conditions



Entry	Ligand	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	dppb	DMSO	50	13	36	—
2	(*S*)-BINAP	DMSO	60—75	50	12	9
3	(+)-**24**	THF	50	98	0[c]	—
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	CH_3CN	rt	4	68	66
8	(*S*)-BINAPO	CH_2Cl_2	rt	2	75	73
9	(*S*)-BINAPO	THF	rt	19	80	86
10	(*S*)-BINAPO	THF	0	216	53	87

a) All reactions were carried out in the presence of **23a** (1.1 eq), $Pd_2dba_3 \cdot CHCl_3$ (2.8 mol%), and (*S*)-BINAPO (5.6 mol%). *b*) The ee values were determined using HPLC analysis. (DAICEL CHIRALCEL OJ, hexane/^{i}PrOH=9/1). *c*) **21a** was recovered in 89% yield.



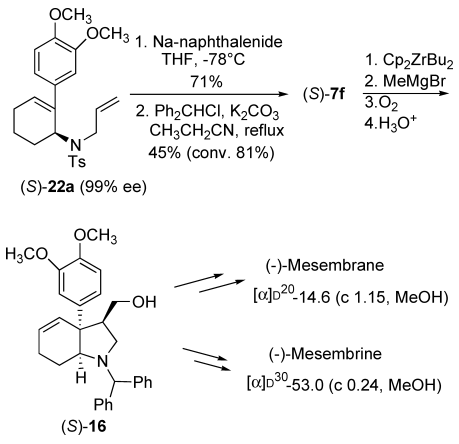


Chart 11. Total Syntheses of (−)-Mesembrane and (−)-Mesembrine

stirred in the presence of a catalytic amount of $Pd_2dba_3 \cdot CHCl_3$ and dppb, the reaction did not proceed. The reaction temperature was raised to 50 °C, but no product was obtained (Table 1, entry 1). The use of (*S*)-BINAP as a ligand afforded a small amount of the desired product **22a**, but the enantiomeric excess (ee) was only 9% (entry 2). Reaction of **21a** with **23a** using (+)-**24**[16] as a ligand did not proceed (entry 3). We were pleased to find that (*S*)-BINAPO[17] gave **22a** with 70% ee in 51% yield (entry 4). As a solvent, THF gave a good result, and **22a** with 86% ee was obtained in 80% yield (entry 9). The lower reaction temperature affected the yield of **22a** but did not affect the ee (entry 10).

Since the cyclohexenylamine derivative **22a** was obtained as a chiral form, the total syntheses of (−)-mesembrane and (−)-mesembrine were carried out. Recrystallization of (*S*)-**22a** with 84% ee from MeOH gave optically pure (*S*)-**22a**, which was converted into diene (*S*)-**7f**. Zirconium-mediated cyclization of (*S*)-**7f** was carried out to give (*S*)-**16**, and from this compound the total syntheses of (−)-mesembrane and (−)-mesembrine were achieved following the previously mentioned route.[15]

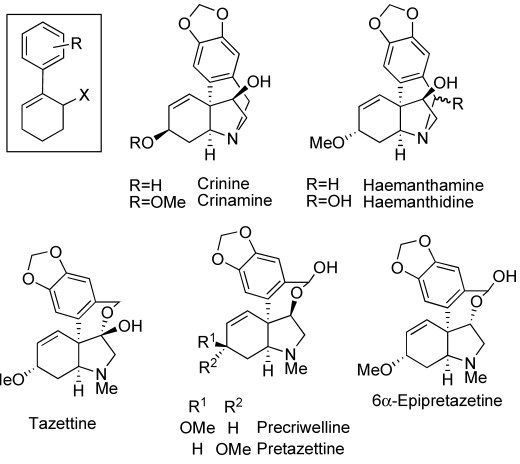


Fig. 3. Typical Crinine-Type Alkaloids

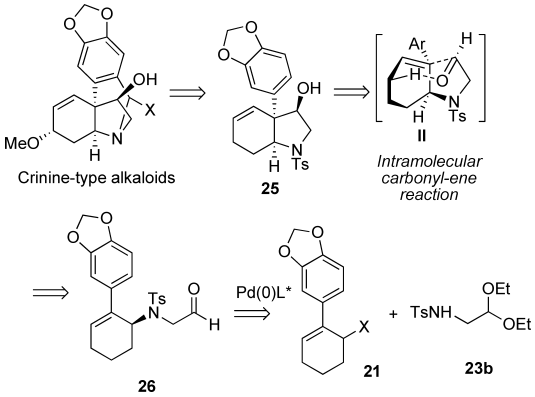


Chart 12. Retrosynthetic Analysis of Crinine-Type Alkaloids

Total Syntheses of (+)-Crinamine, (−)-Haemanthidine, and (+)-Pretazetine Using Palladium-Catalyzed Asymmetric Allylic Amination

Amaryllidaceae alkaloids constitute an important group of naturally occurring bases, and much interest has been shown in them due to the wide range of biological activities they exhibit.[18] Over 100 alkaloids have been isolated from members of the *Amaryllidaceae* family, and most of these compounds can be classified into eight skeletally homogeneous groups. Crinine-type alkaloids such as crinamine,[19] haemanthidine[20,21] and pretazettine[21,22] have a perhydroindole skeleton connected to an aromatic ring at the ring junction (Fig. 3).

We decided to synthesize (+)-crinamine because to the best of our knowledge, the asymmetric total synthesis of (+)-crinamine had not been reported. For the synthesis of (+)-crinamine, the starting cyclohexenylamine derivative **26** would be obtained by palladium-catalyzed asymmetric allylic amination of **21b**, followed by deacetalization. To shorten the process of the total synthesis, it was thought a carbonyl-ene reaction of **26** would be suitable for the synthesis of the perhydroindole derivative **25** instead of zirconium-mediated cy-

clization (Chart 12).

When a THF solution of **21a** and **23b** was stirred in the presence of 2.5 mol% of $Pd_2dba_3 \cdot CHCl_3$ and (*S*)-BINAPO at room temperature for 19 h, the desired **22b** with 84% ee was obtained in 87% yield (Table 2, entry 1). However, the reaction of **21b** with **23b** gave compound **22c** in 68% yield, and the ee was only 60% (entry 2). To improve the yield and ee of **22c**, the reaction was carried out under various conditions. When the reaction of phosphate **21c** with **23b** was carried out in the presence of $Pd_2dba_3 \cdot CHCl_3$ and (*S*)-BINAPO at −20 °C, **22c** with 74% ee was obtained in 80% yield after 48 h (entry 5). The use of (*S*)-BINAP gave the same ee, but the reaction rate decreased (entry 6).

Although phosphate is a good leaving group on palladium-catalyzed allylic substitution, we searched for another effective leaving group. The reaction of palladium-catalyzed allylic substitution proceeds *via* the formation of the π-allylpalladium complex. If alkyl allyl carbonate III is used for this reaction, complex IVa is formed from III and Pd(0), and it is converted into complex IVb by abstraction of a proton from a nucleophile. Thus the nucleophile can attack the π-allylpalladium complex in the absence of a base.

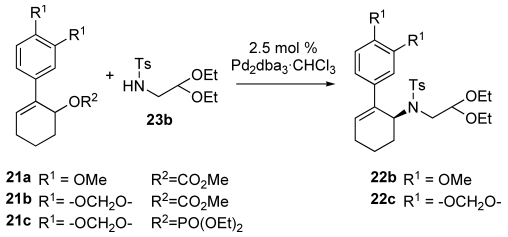
If vinyl carbonate IIIa is used for this reaction, oxo-π-allylpalladium complex IVa′ will be formed. It is thought that IVa′ is a base and would be stable.[23] Thus the reaction rate might be accelerated.

When a THF solution of methyl carbonate **21a** and tosylamide **23b** was stirred in the presence of $Pd_2dba_3 \cdot CHCl_3$ and (*S*)-BINAPO at 0 °C, the desired product **22b** with 88% ee was obtained in 30% yield after 330 h (Table 3, entry 1). However, in the case of allyl vinyl carbonate **21d**, surprisingly **22b** was obtained in 90% yield after only 2 h under the same reaction conditions and the same ee value was found (entry 2). Even at −20 °C, the reaction proceeded, and the desired product **22b** with 92% ee was obtained in 78% yield (entry 3). The reactivity of isopropenyl carbonate **21e** was slightly lower than that of vinyl carbonate **21d** because of the steric hindrance (entries 2, 4). A similar result was also obtained when vinyl carbonate **21f** was used for this reaction; the desired product **22c** with 74% ee was obtained in 82% yield after 53 h at −20 °C (entry 8).

These results indicate that the reaction rate for vinyl carbonate **21f** is almost the same as that of phosphate **21c** (Table 2, entry 5 and Table 3, entry 8).[24]

Recrystallization of **22c** from MeOH afforded crystallized racemic **22c**, but the oily compound in mother liquor was the optically pure form of **22c**. Deacetalization of optically pure

Table 2. Palladium-Catalyzed Asymmetric Amination



Entry	Substrate	Ligand	Temp. (°C)	Time (h)	Product	Yield (%)[a]	ee (%)
1	**21a**	(*S*)-BINAPO	rt	19	**22b**	87	84
2	**21b**	(*S*)-BINAPO	rt	18	**22c**	68	60
3	**21b**	(*S*)-BINAPO	0	106	**22c**	31	68
4	**21c**	(*S*)-BINAPO	0	4	**22c**	73	69
5	**21c**	(*S*)-BINAPO	−20	48	**22c**	80	74
6	**21c**	(*S*)-BINAP	0	160	**22c**	43	75

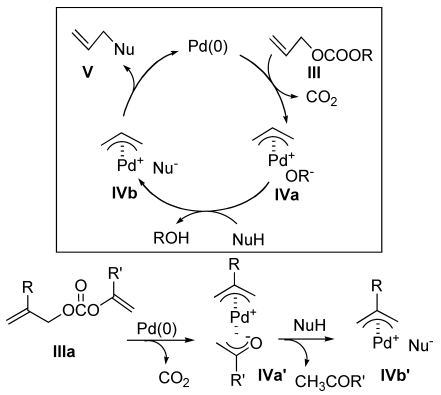
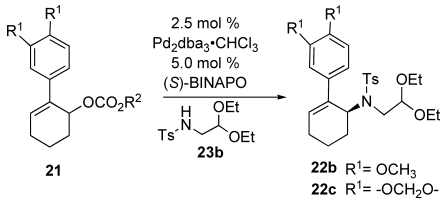


Chart 13. Plan for Use of Vinyl Carbonate as a Leaving Group

Table 3. Reaction of Vinyl Carbonate with **23b** in the Presence of Pd(0)



Entry	R^1	R^2	Substrate	Temp. (°C)	Time (h)	Product	Yield (%)	ee (%)
1	OMe	Me	**21a**	0	330	**22b**	30	88
2	OMe	CH=CH_2	**21d**	0	2	**22b**	90	88
3	OMe	CH=CH_2	**21d**	−20	116	**22b**	78	92
4	OMe	C(Me)=CH_2	**21e**	0	5	**22b**	67	88
5	OMe	C(Me)=CH_2	**21e**	−20	145	**22b**	50	91
6	–OCH_2O–	Me	**21b**	0	106	**22c**	31	68
7	–OCH_2O–	CH=CH_2	**21f**	0	2.5	**22c**	69	68
8	–OCH_2O–	CH=CH_2	**21f**	−20	53	**22c**	82	74
9	–OCH_2O–	C(Me)=CH_2	**21g**	−20	245	**22c**	39	74

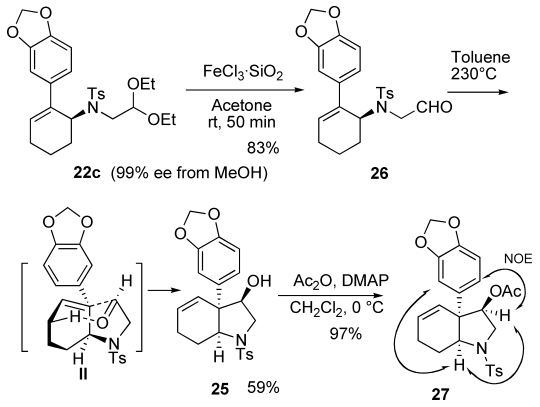


Chart 14. Carbonyl-Ene Reaction of **26**

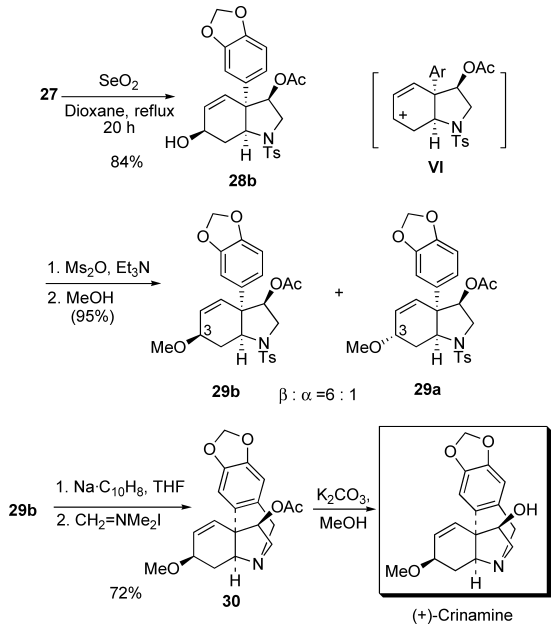


Chart 15. Total Synthesis of (+)-Crinamine

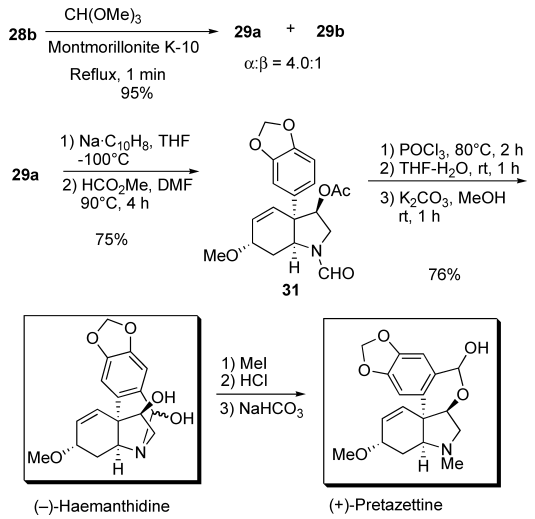


Chart 16. Total Syntheses of (−)-Haemanthidine and (+)-Pretazettine

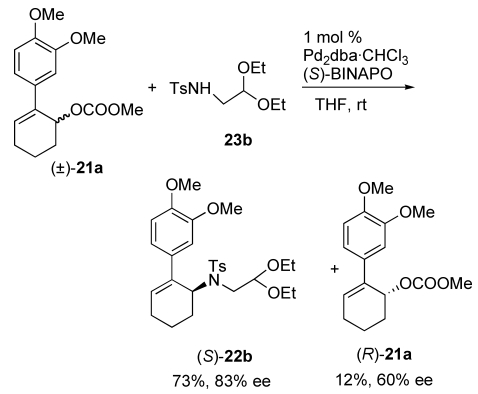


Chart 17. Ee Value of Recovered Strating Material on Asymmetric Substitution

22c afforded aldehyde **26** and the thermal carbonyl-ene reaction of **26** proceeded smoothly at 230 °C in the presence of molecular sieves 4 Å to give the perhydroindole derivative **25** in 59% yield. The stereochemistry of **25** was confirmed in an NOE experiment on acetylated compound **27**.

Allylic oxidation of **27** gave the β-hydroxylated compound **28b**, of which methylation did not give the methylated compound **29b**. Thus mesylation of **28b** was carried out, and to the solution of mesylated compound was added MeOH at 0 °C to give **29b** and **29a** in a ratio of 6 to 1. Presumably, the reaction proceeds *via* allylic cation VI. Detosylation of **29b** followed by methylenation and then deacetylation gave alcohol, of which the $[\alpha]_D$ value and spectral data agreed with those of (+)-crinamine reported in the literature.[19] Thus, we succeeded in the first asymmetric total synthesis of (+)-crinamine from the cyclohexenol derivative **21c** using the palladium-catalyzed asymmetric allylic amination and the carbonyl-ene reaction as the key steps. The overall yield was 19% *via* 10 steps from cyclohexenol derivative.[25,26]

Subsequently, (−)-haemanthidine and (+)-pretazetine were synthesized, which have 3-α-alkoxy groups. Thus **28b** was treated with methyl orthoformate in the presence of monmorilonite K-10 to give **29a** and **29b** in a ratio of 4 to 1. Detsosylation of **29a** followed by formylation with methyl formate gave **31**, which was treated with $POCl_3$, and then deacetylation was carried out to give (−)-haemanthidine. From this compound, (+)-pretazetine was synthesized[25,26] by the known method.[27]

Thus the total syntheses of (+)-crinamine, (−)-haemanthidine, and (+)-pretazettine could be achieved using palladium-catalyzed asymmetric allylic amination developed by our group.

When the reaction of racemic starting material **21a** with **23b** was carried out in the presence of Pd(0) and (*S*)-BINAPO, (*S*)-**22b** with 83% ee was obtained in 73% yield. Surprisingly, the recovered starting material **21a** had an ee of 60%.

To clarify the reason for the 60% ee, the yield and ee of the reaction of **21a** with **23b** were monitored using gas chromatography. The results are shown in Table 4 and Fig. 4. It is clear that the ee of **22b** is almost the same each time, but the ee value of the recovered starting material **21a** gradually increased with time. This indicates that kinetic resolution should occur in this reaction.

These results indicate that there are two independent pathways in the synthesis of (*S*)-**22b**: kinetic resolution and asymmetric substitution. If the reaction rate of (*S*)-**21a** with

Table 4. Ee Values of **22b** and Recovered **21a**

Time (h)	(*S*)-**22b** (% ee)	(*R*)-**21a** (% ee)
3	86	30
6	87	46
19	88	65
47	88	78
75	88	79
120	88	91
165	88	93

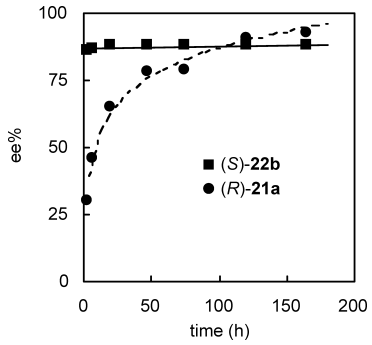


Fig. 4. Ee Values of **22b** and **21a**

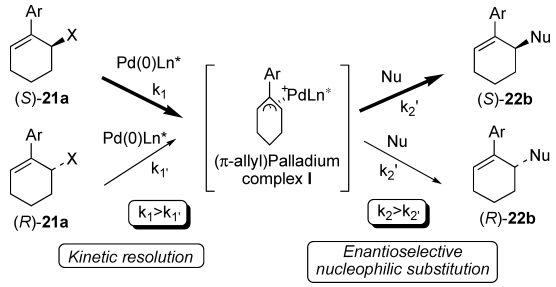


Chart 18. Reaction Pathways for Formation of (*S*)-**22b**

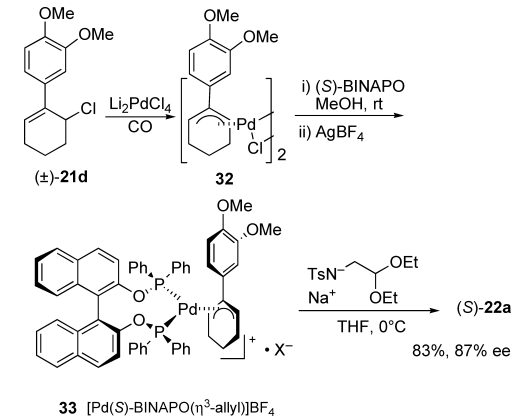


Chart 19. Synthesis of Palladium Complex

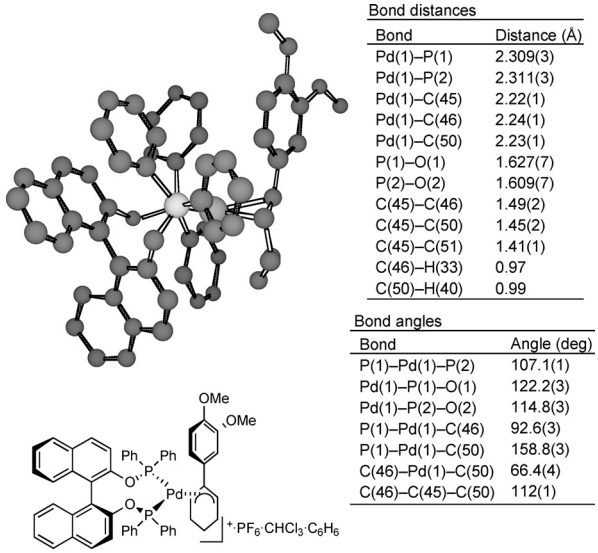


Fig. 5. X-Ray Crystallography of [Pd(*S*)-BINAPO(allyl)] Complex

Pd(0) having (*S*)-BINAPO is faster than that of (*R*)-**21a** with Pd(0) having (*S*)-BINAPO, π-allylpalladium complex I is formed from (*S*)-**21a**, and (*R*)-**21a** remains unchanged. Thus kinetic resolution would occur. Subsequently, (*R*)-**21a** also can react with Pd(0) having (*S*)-BINAPO to produce the same π-allylpalladium complex. Intermediary π-allylpalladium complex I formed from (*S*)- and (*R*)-**21a** reacts with a nucleophile enantioselectively to give (*S*)-**22b**. Thus both (*S*)- and (*R*)-**21a** can be converted into (*S*)-**22b**. If the starting material is recovered, (*R*)-**21a** with a high ee value can be obtained.

To examine the structure of the intermediary chiral π-allylpalladium complex, complex **33** was synthesized from complex **32** by ligand exchange. Reaction of a stoichiometric amount of **33** with **23b** was carried out in the presence of NaH in THF at 0 °C to give (*S*)-**22a** with 87% ee in 83% yield, and the ee value in this reaction is same as that obtained in a catalytic reaction. The results indicate that complex **33** can be considered to be an intermediate for this asymmetric reaction.

The results of X-ray crystallography of **33** are shown in Fig. 5.[28] Interestingly, the cyclohexenyl ring with the palladium metal appears to be in a chair form, and the ligand on the palladium metal is overlain on the cyclohexene ring. The nucleophile attacks from the back of the cyclohexene ring with the palladium metal. Thus it is difficult to explain the origin of the enantioselectivity from the X-ray crystallographic data.

Development of a Novel Synthetic Method for the Chiral Indole Derivative

Many alkaloids have an aromatic ring connected to a cyclohexane ring. Even in the case of indole alkaloids, these ring systems are found in the molecule (Fig. 6). These alkaloids can be synthesized from an 2-arylcyclohexene derivative.

If we expect to obtain an indole derivative in a chiral form using our palladium-catalyzed asymmetric allylic substitution, the reaction of **34** and Pd(0) with a chiral ligand should afford the indole derivative **35** in chiral form. However, since the functional group in **35** is only an olefin, it is difficult to synthesize indole alkaloids from **35**. Thus we considered an alternative procedure (Chart 20). If the cyclohexenol derivative **36** with a functional group at the 2-position is reacted with the *o*-halo aniline derivative **23c** in the presence of Pd(0) with a chiral ligand, we would obtain the cyclohexenylamine derivative **37**, which should give an indoline derivative **38** in chiral form after treatment with a palladium cata-

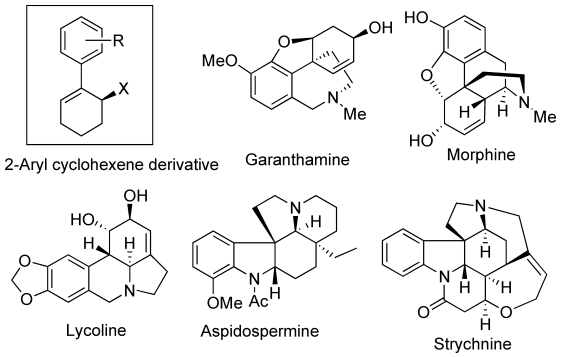


Fig. 6. Natural Products with the 2-Aryl Cyclohexane Moiety

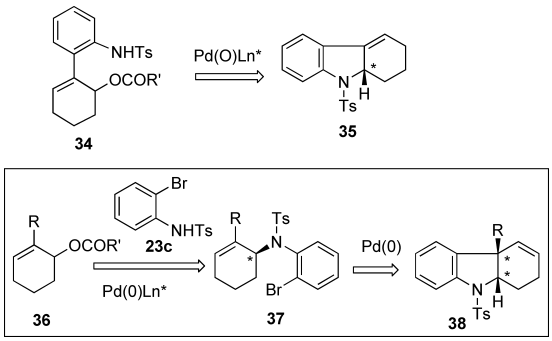
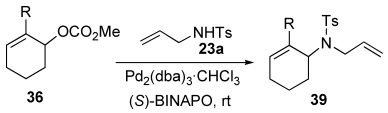


Chart 20. Plan for New Synthetic Method of an Indole Derivative

Table 5. Asymmetric Allylic Substitution



Entry	R		Solvent	Time (h)	Product	Yield (%)[a]	ee (%)[b]	**36** (%)
1	COOEt	**36a**	DMF	3	**39a**	40	5	—
2		**36b**	THF	24	—	—	—	84
3	CH_2OH	**36c**	DMF	13	—	—	—	29
4	CH_2OBn	**36d**	THF	28	**39d**	49	34	36
5	$CH_2OTBDMS$	**36e**	THF	100	**39e**	53	78	23
6	$CH_2OTBDMS$	**36e**	DMF	3.5	**39e**	70	77	—
7	CH_2OTES	**36f**	DMF	2	**39f**	66	71	—

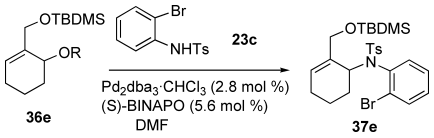
a) All reactions were carried out using $Pd_2(dba)_3 \cdot CHCl_3$ (2.6 mol%) and (*S*)-BINAPO at room temperature. *b*) Ee values were determined using HPLC (DAICEL CHIRACEL AD, hexane : iPrO=9 : 1) after debenzylation of **39d** or desilylation of **39e** and **39f**.

lyst.

First, 2-carboethoxycyclohexenol derivative **36a**[29] was chosen as a substrate. When a DMF solution of **36a** and allyl tosylamide **23a** was stirred in the presence of 2.6 mol% of $Pd_2(dba)_3 \cdot CHCl_3$ and 5.2 mol% of (*S*)-BINAPO at room temperature for 3 h, the cyclohexenylamine derivative **39a** was obtained in 40% yield, but the ee was only 5% (Table 5, entry 1). Compounds **36b** or **36c** with a ketal or a hydroxymethyl group as the functional group did not afford the desired products (entries 2, 3). In the case of the 2-benzyloxymethylcyclohexenol derivative **36d**, the desired compound **39d** was obtained in 49% yield and the ee was 34% (entry 4). Encouraged by this result, the *tert*-butyldimethylsilyloxymethyl group was chosen as the functional group, and the reaction was carried out under similar conditions in THF. After 100 h, the desired compound **39e** with 78% ee was obtained in 53% yield (entry 5). When the solvent was changed to DMF, the reaction time was surprisingly shortened to 3.5 h (entry 6). Another silyl group gave similar results (entry 7). Various solvents, such as CH_2Cl_2, DMSO, and CH_3CN, were examined in this reaction, and DMF gave the best result.

To construct an indole skeleton, the nucleophile was changed to the *o*-bromo aniline derivative **23c**. When the reaction of **36e** with **23c** was carried out in the presence of Pd(0) and (*S*)-BINAPO as a ligand, the desired compound **37e** with 80% ee was obtained in 78% yield after 7 h (Table 6, entry 1). In the case of vinyl carbonate **36eb**, the reaction

Table 6. Reaction of **36e** with the Aniline Derivative



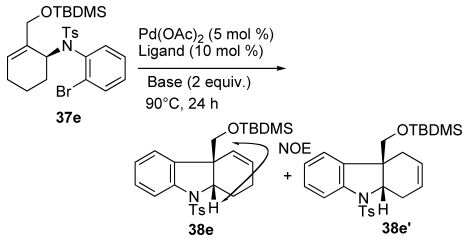
Entry	R		Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	CO_2Me	**36e**	rt	7	78	80
2	$CO_2CH_2{=}CH_2$	**36eb**	0	21	64	84
3	$CO_2CH_2{=}CH_2$	**36eb**	−20	168	67	83
4	$PO(OEt)_2$	**36ec**	0	36	80	84

a) All reactions were carried out using $Pd_2(dba)_3 \cdot CHCl_3$ (2.6 mol%) and (*S*)-BINAPO in THF. *b*) Ee values were determined using HPLC (DAICEL CHIRACEL OJ) after desilylation of **37e**.

proceeded at 0 °C and the desired compound **37e** with 84% ee was obtained in 64% yield (entry 2). The lower reaction temperature did not affect the ee value of **37e** (entry 3). In the case of phosphate **36ec**, the reaction rate slightly decreased compared with that of vinyl carbonate **36eb**, but **37e** with the same ee was obtained in high yield (entry 4).

Since the asymmetric synthesis of a cyclohexenylamine derivative was established, the construction of an indole skeleton was next examined using the Heck reaction.[30] When a DMF solution of **37e** was stirred in the presence of

Table 7. Synthesis of Indole Derivative



Entry	Ligand	Solvent	Base	**38e** (%)	**38e′** (%)	**37e** (%)
1	PPh_3	DMF	$^iPr_2NEt$	26	13	31
2	dppb	DMF	$^iPr_2NEt$	13	1	76
3	PPh_3	DMF	Ag_2CO_3	42	8	33
4	$PMePh_2$	DMF	Ag_2CO_3	52	13	29
5	PMe_2Ph	DMF	Ag_2CO_3	56	19	20
6	PMe_2Ph	C_3H_7CN	Ag_2CO_3	17	1	71
7	PMe_2Ph[a)]	DMSO	Ag_2CO_3	47	0	38

a) Reaction temp: 105 °C.

5 mol% of $Pd(OAc)_2$, 10 mol% of PPh_3, and $^iPr_2NEt$ (2 eq) as a base at 90 °C for 24 h, the desired indolines **38e** and **38e′** were obtained in 26% and 13% yields, respectively, along with **37e** in 31% yield (Table 7, entry 1). The use of a bidentate ligand did not give a good result (entry 2). When Ag_2CO_3[31)] was used as a base to prevent the formation of the olefin isomer **38e′**, the yield of the desired indoline **38e** increased to 42%, although **38e′** was formed in 8% yield (entry 3). Various ligands were examined, and PMe_2Ph gave good results (entry 5). The reaction rate decreased when DMSO was used as a solvent, but only **38a** was formed (entry 7). The results of an NOE experiment of **38e** indicated that the ring junction of **38e** is *cis*. Thus we succeeded in the novel enantioselective synthesis of indole derivative.

Total Synthesis of (−)-Tubifoline Using Palladium-Catalyzed Allylic Amination

Since the indole skeleton could be constructed as a chiral form, we attempted to synthesize indole alkaloids. As a target molecule for the synthesis of indole alkaloids, we focused on *Strychnos* alkaloids, (−)-dehydrotubifoline and (−)-tubifoline,[32)] which have been synthesized by several groups as racemic[33)] or chiral forms.[34)] (−)-Tubifoline can be obtained from dehydrotubifoline, which can be obtained from compound **40** using a palladium catalyst. Compound **40** is synthesized from the tetracyclic ketone **41**, which should be an important intermediate for the synthesis of indole alkaloids and is synthesized from compound **38** obtained by Heck reaction of **37**. This compound was previously obtained in a chiral form from **36**.

Desilylation of **37e** (84% ee) with 4 N HCl followed by treatment with PBr_3 and then NaCN in DMSO gave the nitrile **37f** in good yield. The palladium-catalyzed Heck reaction of **37f** proceeded smoothly under previously described reaction conditions to give **38f** in high yield. Treatment of **38f** with $LiAlH_4$ followed by protection of the primary amine with Boc_2O afforded compound **42**. Allylic oxidation of **42** was carried out using a catalytic amount of $Pd(OAc)_2$ in the presence of benzoquinone and MnO_2[35)] to afford tetracyclic compound **43** in 77% yield. The double bond of **42** probably coordinates with the palladium catalyst, and then amide nitrogen attacks olefin to give palladium complex VIII. Then β-hydrogen elimination from VIII occurs to give **43**. Hydroboration of **43** using $BH_3\cdot THF$ followed by treatment with H_2O_2 in aqueous NaOH gave alcohols **44** and **45** in 51% and 49% yields, respectively. The use of a large hydroboration reagent, 9-BBN, afforded the desired alcohol **44** in 80% yield as a major product. Swern oxidation of **44** gave the desired tetracyclic ketone **41a** in high yield.

Subsequently, the keto-carbonyl group of tetracyclic ketone **41a** was converted into olefin. Treatment of **41a** with LDA followed by the addition of $PhNTf_2$ at −78 °C afforded the enol triflates **46** and **47** in 8% and 14% yields, respectively (Table 8, entry 1). The base was changed to potassium hexamethyldisilazamide (KHMDS)[36)] and the reaction was carried out at −78 °C to give **46** and **47** in 21% and 14%

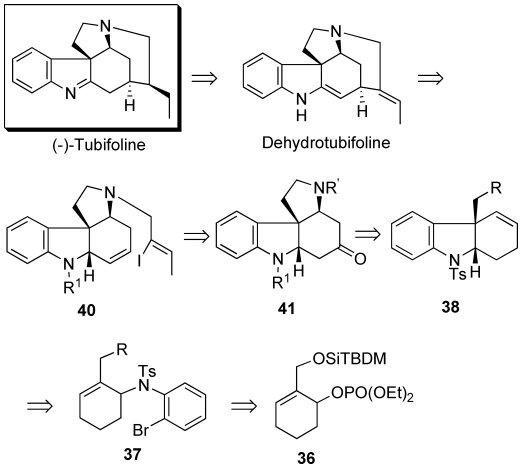


Chart 21. Retrosynthetic Analysis of (−)-Tubifoline

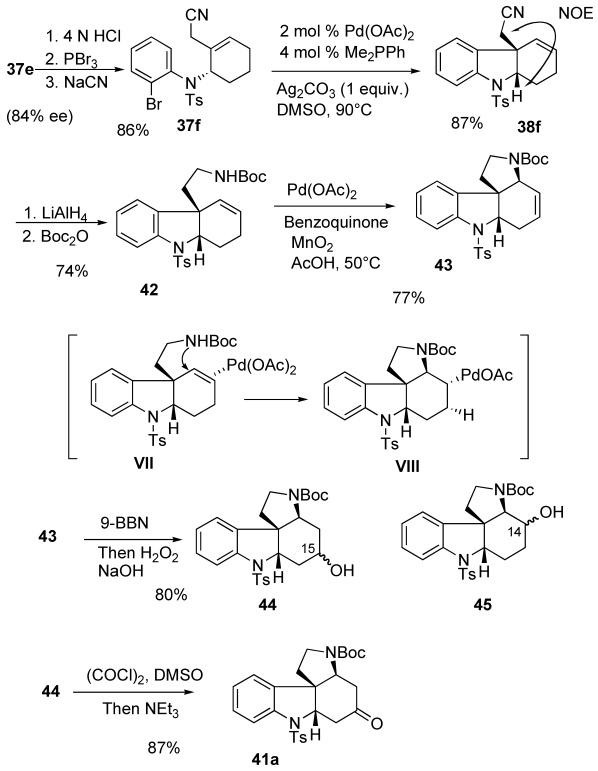
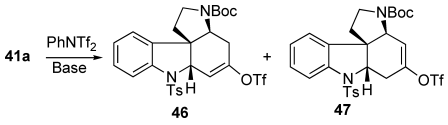


Chart 22. Synthesis of Tetracyclic Ketones

Table 8. Conversion of Ketone to Enol Triflate



Entry	Base	Temp. (°C)	**46** (%)	**47** (%)	**39a** (%)
1	LDA	−78	8	14	55
2	KHMDS	−78	21	14	24
3	KHMDS	−50	53	trace	11
4	KHMDS	−35	64	—	—

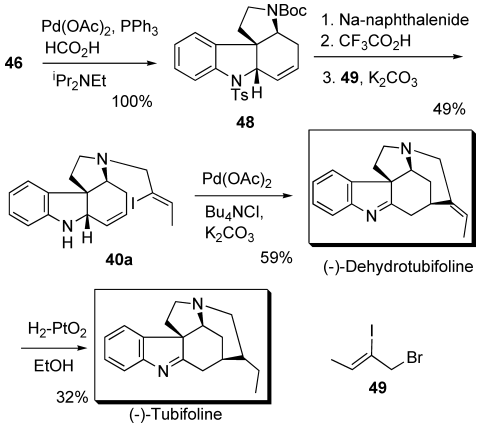


Chart 23. Total Synthesis of (−)-Tsubifoline

yields (entry 2). Since **46** was considered to be a thermodynamic product, the reaction temperature was raised to −35 °C, and desired compound **46** was obtained as a sole product in 64% yield (entry 4). Treatment of enol triflate **46** with HCO_2H in the presence of $Pd(OAc)_2$ and PPh_3[37] gave the desired olefin **48** in quantitative yield. Detosylation of **48** with sodium naphthalenide followed by treatment with CF_3CO_2H gave diamine, of which monoalkylation with **49**[38] in the presence of K_2CO_3 gave **40a** in 49% yield. An intramolecular Heck reaction[38,39] using a palladium catalyst gave pentacyclic compound in 59% yield, of which the ^1H- and ^{13}C-NMR spectra agreed with those of (−)-dehydrotubifoline reported in the literature.[40] However, the $[\alpha]_D$ value of (−)-dehydrotubifoline is not known. Thus hydrogenation of (−)-dehydrotubifoline with PtO_2 in EtOH was carried out. The $[\alpha]_D$ value {84% ee, $[\alpha]_D^{22}$ −311° (c=0.236, AcOEt)} and ^1H- and ^{13}C-NMR spectra of the hydrogenation product agreed with those of (−)-tubifoline reported in the literature.[41] Thus we succeeded in the total synthesis of (−)-dehydrotsubifoline and (−)-tubifoline using palladium-catalyzed asymmetric amination followed by Heck reaction as a key step.[42] It was interesting that all ring constructions of (−)-dehydrotubifoline were performed using the palladium catalyst.

Total Synthesis of (−)-Strychnine

(−)-Strychnine was isolated by Pelletier and Caventou in 1818 (Fig. 7),[43] and the structure was determined by Briggs and Robinson *et al.*[44] and Woodward and Brehm.[45] The first total synthesis of (−)-strychnine was achieved by Woodward *et al.* in 1954.[46] After that brilliant achievement, there were

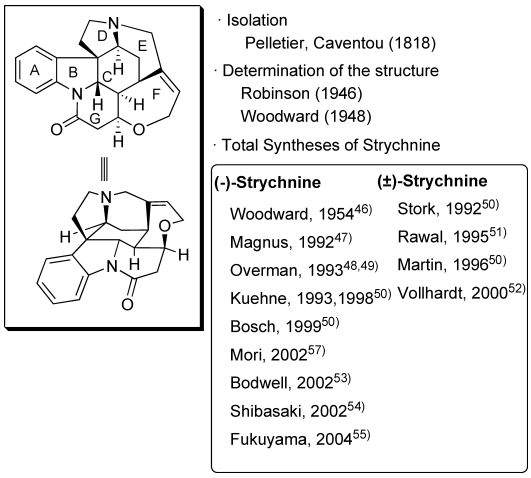


Fig. 7. Total Syntheses of Strychnine

no other reports on the total synthesis of strychnine for about 40 years. However, tremendous progress has been made recently in synthetic organic chemistry using organometallic complexes, and the total syntheses of complicated natural products have been achieved using novel procedures. In 1992, Magnus *et al.*[47] reported the total synthesis of (−)-strychnine, and Knight and Overman *et al.* succeeded in the first asymmetric total synthesis of (−)-[48] and (+)-strychnine[49] in 1993 and 1995, respectively. Following those reports, several groups succeeded in the total synthesis of (−)- or (±)-strychnine.[50] Rawal and Iwasa's synthetic process was particularly remarkable, although strychnine obtained in their process is a racemic form.[51] Eichberg and Vollhardt succeeded in the total synthesis of (±)-strychnine using an ingenious cobalt-catalyzed [2+2+2] cycloaddition as a key step.[52] In the past decade, many synthetic approaches to strychnine have been successful. Among them, five enantiospecific syntheses of (−)-strychnine have been reported. However, there has been no report on the total synthesis of (−)-strychnine from an enantiomerically pure compound obtained by a transition metal-catalyzed asymmetric synthesis. Very recently, three groups were succeeded in the total synthesis of (−)-strychnine.[53—55]

Since the total synthesis of (−)-tubifoline was achieved, we focused on synthesizing (−)-strychnine because tubifoline consists of five rings and these rings are among the seven rings of strychnine. In the total synthesis of (−)-strychnine, the tetracyclic ketone **41a** should be an important intermediate. Thus the most important point in the synthesis of (−)-strychnine is the construction of the G-ring. Two pathways should be considered. One is the introduction of an alkyl group at the α-position of the carbonyl group of **41a** to give **52**, and then the G-ring is constructed using carbon–nitrogen bond formation. The other is the introduction of an acyl group on nitrogen to form **53**, and then the G-ring is constructed.

We first chose the former reaction pathway to synthesize **51**. Conversion of the cyclohexenol derivative **36ec** into **38f** was carried out following a previous method. Compound **38f** (84% ee) was recrystallized from EtOH to give optically pure **38f** ($[\alpha]_D$ −46.7°, 99% ee, 73% recovery), which was converted into the tetracyclic ketone **41a** using the known method. Many attempts were made to introduce an acyl

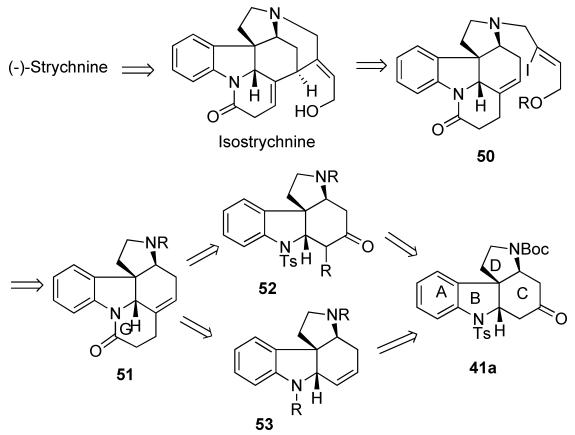


Chart 24. Retrosynthetic Analysis of (−)-Strychnine

group to the α-position of the keto-carbonyl group of **41a**, but they were fruitless due to the steric hindrance of the large protecting group on anilino nitrogen. Thus we attempted to construct the G-ring using the Heck reaction. The tetracyclic ketone **41a** was converted into **48**, in which the tosyl group was deprotected. The resulting amino group was reacted with 3-bromoacryloyl chloride in the presence of K_2CO_3 to give **53a**, which was reacted with 10 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3 in the presence of $^iPr_2NEt$ in DMSO at 80 °C for 1.5 h. We were pleased that the pentacyclic compound **51a** was obtained in 46% yield. Isomerization of the double bond of **51a** was carried out by treatment with NaO^iPr in ^{i}PrOH, and then deprotection of the Boc followed by alkylation with **55** afforded compound **50a**. Vollhardt *et al.* synthesized (±)-strychnine from compound **50a**.[52] Although the spectral data of **50a** agreed with those of the product reported by Vollhardt *et al.*, the $[\alpha]_D$ value was not known because they synthesized (±)-strychnine. Thus compound **50a** was converted into (−)-strychnine using the procedure of Vollhardt *et al.* Treatment of **50a** with $Pd(OAc)_2$, Bu_4NCl and K_2CO_3 in DMF afforded hexacyclic compound **54**, which was treated with $LiAlH_4$ followed by deprotection of the silyl group to give (+)-isostrychnine, of which spectral data and $[\alpha]_D^{20}$ value [+23.7° (c=0.59, EtOH)] agreed with those of (+)-isostrychnine reported by Woodward *et al.*[46] (+)-Isostrychnine was converted into (−)-strychnine by treatment with KOH in EtOH using the known method.[56]

We succeeded in the total synthesis of (−)-strychnine.[57,58] Our reaction course is summarized in Chart 26. The starting cyclohexenol derivative **36ec** was converted into chiral cyclohexenylamine derivative **37e** using a palladium catalyst with (*S*)-BINAPO in the presence of *N*-tosyl-*o*-bromoaniline (**23c**). Compound **37e** was converted into the nitrile **37f**, which was treated with a palladium catalyst to give compound **38f** with the A–B–C ring system. The D-ring was constructed by palladium-catalyzed allylic oxidation of **42** obtained from **38f**. Compound **42** was converted into **53a**, and the G-ring was formed by palladium-catalyzed cyclization of **53a**. The E-ring was constructed by the palladium-catalyzed Heck reaction of **50**. From **54**, (+)-isostrychnine was synthesized.

The total synthesis of (−)-strychnine was achieved in 22 steps from **36ec**. In our total synthesis of (−)-strychnine, all cyclizations for the synthesis of (+)-isostrychnine were performed using a palladium catalyst. The fact that all rings of (−)-tsubifoline and (+)-isostrychnine were constructed using a palladium catalyst indicates the importance of a palladium catalyst in modern synthetic organic chemistry.

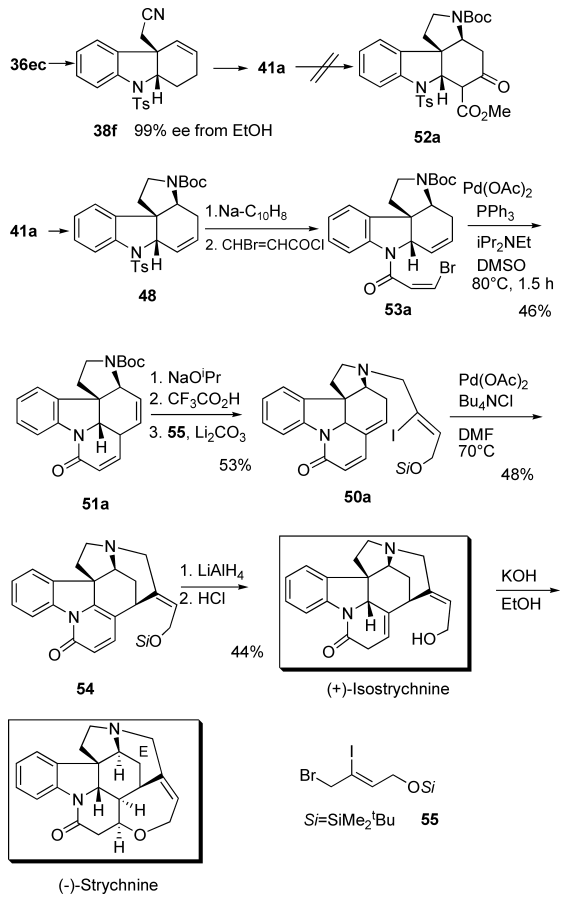


Chart 25. Total Synthesis of (−)-Strychnine

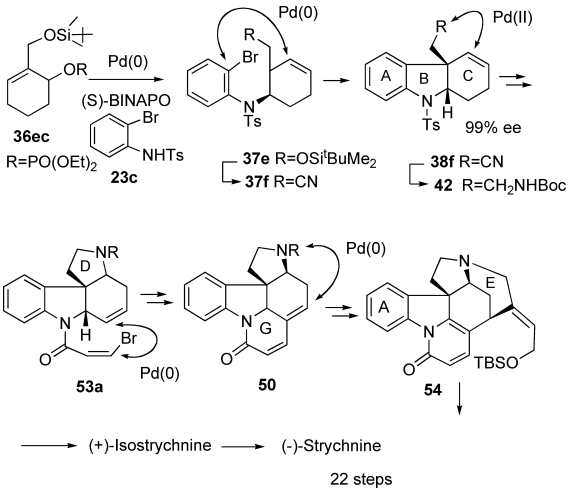


Chart 26. Summary of Total Synthesis of Strychnine

Conclusion

Recent remarkable progress in synthetic organic chemistry has depended on the usage of organometallic complexes. We first investigated the reaction of aryl halide with the nickel and palladium complexes for carbon–carbon bond formation. The early transition metal complex such as a zirconium or ti-

tanium complex was used for the carbon–carbon bond-forming reaction between the unsaturated hydrocarbons. The zirconacycles formed from diene, enyne, and diyne using zirconocene (Cp_2Zr) are useful intermediates for synthetic organic chemistry. Negishi and Takahashi[4] have found that zirconocene coordinated with the butene ligand could be prepared from Cp_2ZrCl_2 and BuLi *in situ*. This was a great discovery in zirconium chemistry because zirconocene is unstable in the absence of a ligand and the isolation of zirconocene is not easy. We succeeded in the synthesis of tricyclic ketones from enynes and dienes using Cp_2ZrBu_2, followed by treatment with carbon monoxide in a one-pot reaction and the total syntheses of (−)-dendrobine and (±)-mesembrine and (±)-mesembrane. For the synthesis of (−)-mesembrine and (−)-mesembrane, the chiral 2-arylcyclohexenylamine derivative was required. Thus the novel asymmetric synthesis of the 2-arylcyclohexenylamine derivative was developed using a palladium catalyst and (*S*)-BINAPO and the total syntheses of (−)-mesembrane, (−)-mesembrine, (+)-crinamine, (−)-haemanthidine, and (+)-pretazetine were achieved. For the synthesis of the chiral indole derivative, enantioselective synthesis of the 2-silyloxymethylcyclohexenylamine derivative was developed. The chiral indoline derivative could be synthesized from this compound. Using this compound, we succeeded in the total syntheses of (−)-tubifoline and (−)-strychnine. In the total syntheses of these natural alkaloids, transition metal complexes play an important role, and the palladium complex is particularly valuable. Since there are many transition metals, further interesting and useful synthetic methods will be developed and there will be more reports on the total syntheses of natural products using organometallic complexes in the future.

Acknowledgements These works were performed by Dr. N. Uesaka, Dr. S. Kuroda, Dr. T. Nishimata, Mr. F. Saito, Mr. M. Nakanishi and the students of Department of Fine Synthetic Chemistry in Graduate School of Pharmaceutical Sciences, Hokkaido University. I express my heartfelt thanks to them. I also thank to Dr. Y. Sato, Dr. M. Nishida, Dr. H. Yoshizaki and Dr. M. Takimoto for their helpful discussion.

References and Notes

1) This article was submitted to commemorate for the Pharmaceutical Society of Japan Award in 2004.
2) Negishi E.-i., Holmes S. J., Tour J. M., Miller J. A., *J. Am. Chem. Soc.*, **107**, 2568—2569 (1985).
3) Nugent W. A., Calabrese J. C., *J. Am. Chem. Soc.*, **106**, 6422—6424 (1984).
4) Negishi E.-i., Cederbaum F. E., Takahashi T., *Tetrahedron Lett.*, **27**, 2829—2832 (1986).
5) Mori M., Uesaka N., Shibasaki M., *J. Org. Chem.*, **57**, 3519—3520 (1992).
6) Uesaka N., Mori M., Shibasaki M., *J. Org. Chem.*, **59**, 4542—4547 (1994).
7) Suzuki H., Keimatsu I., Ito K., *Yakugaku Zasshi*, **52**, 1049—1060 (1932).
8) Inubushi Y., Sasaki Y., Tsuda Y., Yasui B., Konda T., Matsumoto J., Katarao E., Nakano J., *Tetrahedron*, **20**, 2007—2023 (1964).
9) Lee C. H., Westking M., Livinghouse T., Williams A. C., *J. Am. Chem. Soc.*, **114**, 4089—4095 (1992) and references are cited therein.
10) Kende A. S., Bentley T. J., Mader R. A., Ridge D., *J. Am. Chem. Soc.*, **96**, 4332—4334 (1974).
11) Mitsunobu O., *Synthesis*, **1981**, 1—28 (1981).
12) Mori M., Uesaka N., Shibasaki M., *J. Org. Chem.*, **57**, 3519—3520 (1992).
13) Uesaka N., Saito F., Mori M., Shibasaki M., Okamura K., Date T., *J. Org. Chem.*, **59**, 5633—5642 (1944).
14) Mori M., Saitoh F., Uesaka N., Okamura K., Date T., *J. Org. Chem.*, **59**, 4993—4998 (1994).
15) Mori M., Kuroda S., Zhang C.-H., Sato Y., *J. Org. Chem.*, **62**, 3263—3270 (1997).
16) Trost B. M., Van Vranken D. L., Bingel C., *J. Am. Chem. Soc.*, **114**, 9327—9343 (1992).
17) Grubbs R. H., DeVries R. A., *Tetrahedron Lett.*, **1977**, 1879—1880 (1977).
18) Martin S. F., "The Alkaloids," Vol. 30, ed. by Brossi A., Academic Press, New York, 1987, pp. 251—376.
19) Isolation of (+)-crinamine: Kobayashi S., Tokumoto T., Kihara M., Imakura Y., Shingu T., Taira Z., *Chem. Pharm. Bull.*, **32**, 3015—3022 (1984).
20) Isolation of (−)-haemanthidine: Boit H. G., *Chem. Ber.*, **87**, 1339—1342 (1954).
21) Total syntheses of (−)-haemanthidine, (+)-prettazetine and (+)-tazettine: Baldwin S. W., Debenham J. S., *Org. Lett.*, **2**, 99—102 (2000) and references are cited therein.
22) Isolation of (+)-pretazettine: Wildman W. C., Bailey D. T., *J. Org. Chem.*, **33**, 3749—3753 (1968).
23) Palladium-catalyzed reaction using allyl carbonate has been reported: Tsuji J., Shimizu I., Minami I., Ohashi Y., *Tetrahedron Lett.*, **23**, 4809—4812 (1982).
24) Mori M., Nishimata T., Nagasawa Y., Sato Y., *Adv. Synth. Cat.*, **343**, 34—36 (2001).
25) Nishimata T., Mori M., *J. Org. Chem.*, **63**, 7586—7587 (1998).
26) Nishimata T., Sato Y., Mori M., *J. Org. Chem.*, **69**, 1837—1843 (2004).
27) Tsuda Y., Ukai A., Isobe K., *Tetrahedron Lett.*, **1972**, 3153—3156 (1972).
28) Nishimata T., Yamaguchi K., Mori M., *Tetrahedron Lett.*, **40**, 5713—5716 (1999).
29) Graff M., Al Dilaimi A., Seguineau P., Rambaud M., Villeras J., *Tetrahedron Lett.*, **27**, 1577—1578 (1986).
30) Dieck H. A., Heck R. F., *J. Am. Chem. Soc.*, **96**, 1133—1136 (1974).
31) The use of silver salts suppressed alkene isomerization in the Heck reaction: Abelman M. M., Oh T., Overman L. E., *J. Org. Chem.*, **52**, 4130—4133 (1987).
32) For the isolation and structural elucidation of this alkaloid, see: Kump W. G., Patel M. B., Rowson J. M., Schmid H., *Helv. Chim. Acta*, **47**, 1497—1503 (1964).
33) Danson B. A., Harley-Mason J., Foster G. H., *Chem. Commun.*, **1968**, 1233—1234 (1968).
34) Amat M., Coll M-D., Bosch J., Espinosa E., Molins E., *Tetrahedron Asymmetry*, **8**, 935—948 (1997) and references are cited therein.
35) Hansson S., Heumann A., Rain T., Åkermark B., *J. Org. Chem.*, **55**, 975—984 (1990).
36) Stang P. J., Dueber T. E., *Org. Synth.*, **54**, 79—84 (1974).
37) Cacchi S., Morera E., Orter G., *Tetrahedron Lett.*, **25**, 4821—4824 (1984).
38) Rawal V. H., Michoud C., Monestel R. F., *J. Am. Chem. Soc.*, **115**, 3030—3031 (1993).
39) Jeffery T., *Tetrahedron Lett.*, **26**, 2667—2670 (1985).
40) Angle S. R., Fevig J. M., Knight S. D., Marquis, R. W., Jr., Overman L. E., *J. Am. Chem. Soc.*, **115**, 3966—3976 (1993).
41) Schumann D., Schmid H., *Helv. Chim. Acta*, **46**, 1996—2003 (1963).
42) Mori M., Nakanishi M., Kajishima D., Sato Y., *Org. Lett.*, **3**, 1913—1916 (2001).
43) Isolation: Pelletier P. J., Caventou J. B., *Ann. Chim. Phys.*, **8**, 323—324 (1818).
44) Briggs L. H., Openshaw H. T., Robinson R., *J. Chem. Soc.*, **1946**, 903—908 (1946).
45) Woodward R. B., Brehm W. J., *J. Am. Chem. Soc.*, **70**, 2107—2115 (1948).
46) Woodward R. B., Woodward M. P., Cave M. P., Ollis W. D., Hunger A., Daeniker H. U., Schenker K. J., *J. Am. Chem. Soc.*, **76,** 4749—4751 (1954).
47) Magnus P., Giles M., Bonnet R., Kim C. S., McQuire L., Merritt A., Vicker A., *J. Am. Chem. Soc.*, **115**, 8116—8129 (1993).
48) Knight S. D., Overman L. E., Pairaudeau G., *J. Am. Chem. Soc.*, **115**, 9293—9294 (1993).
49) Knight S. D., Overman L. E., Pairaudeau G., *J. Am. Chem. Soc.*, **117**, 5776—5788 (1995).
50) For a review of the total synthesis of strychnine see: Bonjoch J., Solé D., *Chem. Rev.*, **100**, 3455—3482 (2000).

51) Rawal V. H., Iwasa S., *J. Org. Chem.*, **59**, 2685—2686 (1994).
52) Eichberg M. J., Dorta R. L., Lamottke K., Vollhardt K. P. C., *Org. Lett.*, **2**, 2479—2481 (2000).
53) Bodwel G. J., Li J., *Angew. Chem. Int. Ed.*, **41**, 3261 (2002).
54) Ohshima T., Xu Y., Takita R., Shimizu S., Zhong D., Shibasaki M., *J. Am. Chem. Soc.*, **124**, 14546—14547 (2002).
55) Kaburagi Y., Tokuyama H., Fukuyama T., *J. Am. Chem. Soc.*, **126**, 10247 (2004).
56) Prelog V., Battegay J., Taylor W. I., *Helv. Chim. Acta*, **31**, 2244—2246 (1984).
57) Nakanishi M., Mori M., *Angew. Chem. Int. Ed.*, **41**, 1934—1936 (2002).
58) Mori M., Nakanishi M., Kajishima D., Sato Y., *J. Am. Chem. Soc.*, **125**, 9801—9807 (2003).