Development of New Methods in Organic Synthesis and Their Applications to the Synthesis of Biologically Interesting Natural Products

Yasumasa Hamada

Graduate School of Pharmaceutical Sciences, Chiba University;
Received October 4, 2011

2,6-Dimethyl-9-Aryl-9-phosphabicyclo[3.3.1]nonanes (9-PBN and 9-NapBN) and the chiral diaminophosphine oxides (DIAPHOXs) derived from aspartic acid have been introduced as useful ligands and preligands, respectively, for transition metal-catalyzed asymmetric synthesis. anti-Selective asymmetric hydrogenation of α-amino-β-ketoesters using Ru-, Rh-, Ir-, and Ni-catalysts through dynamic kinetic resolution have been developed for the first time, producing efficiently important anti β-hydroxy-α-amino acids. The total synthesis of several biologically active natural products was achieved by use of the transition metal-catalyzed reaction using DIAPHOX, anti-selective asymmetric hydrogenation, and reactions developed by us. Synthesis of tangutorine, an antitumor indole alkaloid, has been enantioselectively achieved for the first time. Enantioselective synthesis of a martinelline chiral core was accomplished using the asymmetric tandem Michael–Aldol reaction as a key step developed by us. This synthesis represents the formal total synthesis of martinelline and martinellic acid. Papuamide B was synthesized through the elucidation of unknown stereostructures by using the anti-selective asymmetric hydrogenation and reactions developed by us.

Key words asymmetric synthesis; chiral phosphine; β-hydroxy-α-amino acid; tangutorine; martinelline; papuamide

1. Introduction
Modern synthetic organic chemistry is in a period of rapid change because of the many demands it is facing today. The need for environmentally benign chemistry, in addition to more efficiency in organic synthesis, requires the development and use of inevitably more advanced catalytic methods. We have been working on the development of efficient catalytic asymmetric synthesis. Catalytic asymmetric synthesis is one of the most environmentally benign methods used in organic chemistry and is in demand, since modern medicine increasingly requires enantiomerically pure compounds. We have succeeded in the synthesis of new chiral ligands for catalytic asymmetric synthesis and their applications.

This paper deals with the results of our development of new catalytic methods in organic synthesis and their applications to the synthesis of biologically interesting natural products.

2. Development of Monodentate Phosphorus Ligands
Chiral phosphines have been well proven to play a crucial role as chiral ligands for transition-metal catalyzed asymmetric synthesis and their combination with transition metals has shown to be especially useful and versatile catalysts for a variety of enantioselective reactions. Several years ago, we succeeded in the development of two new classes of chiral monodentate ligands.

Fig. 1. 9-PBN and 9-NapBN

Fig. 2. Design of New Ligand
2.1. Synthesis of 2,6-Dimethyl-9-aryl-9-phosphabicyclo[3.3.1]nonanes: Their Application to Asymmetric Synthesis

The preparation of optically active 1 was carried out from commercially available 1,5-dimethyl-1,5-cyclooctadiene through enzymatic resolution as shown in Chart 1.

Hydroboration of 3 gave (rac)-dial 4 in moderate yield. The subsequent resolution of 4 with lipase My\(^{50}\) efficiently afforded (S)-dial 4 and (R)-dilauroyl ester 5 with almost 100% optical purity. After tosylation of (S)-4, the double substitution reaction of tosylate 6 using phosphine-borane 8 in the presence of potassium tert-butoxide and benzyltriethylammonium chloride afforded (S)-9-PBN·BH\(_3\) (9) in good yield. The required free phosphine (S)-1 was quantitatively regenerated by the reaction of 9 with 1,4-diazabicyclo[2.2.2]octane (DABCO).\(^{11,12}\)

The molecular structure of 9 occupied a chair–boat conformation in place of a chair–chair conformation. The synthesis of (S)-9-NapBN (2) was also performed using the above method.

For the evaluation of newly developed ligands, we examined the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylallyl acylates with dimethyl malonate and benzylamine. These model reactions proceeded smoothly to afford the corresponding products (R)-13 and (R)-15 in 100% yield with 94% ee and in 94% yield with 98% ee, respectively (Chart 2).

With encouraging results in hand, we investigated the Pd-catalyzed asymmetric allylic alkylation of the cyclic substrate with dimethyl malonate.\(^{4}\) The reaction, however, yielded the corresponding product with poor enantiomeric excess. From mechanistic considerations concerning the low efficiency, we thought that perhaps the 2-substituent of 2-cycloalkenyl ester would influence the enantioselection through the interaction between the 2-substituent and the bicyclic skeleton of 9-PBN.

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Yasumasa Hamada is a Professor of Pharmaceutical Chemistry at Chiba University. He was born in Hokkaido in 1949 and received his BS degree (1973) from Toyama University and MS degree (1975) from the University of Tokyo. In 1977, he joined Nagoya City University as an assistant professor. After obtaining his Ph.D. degree in 1982 and completing one year of postdoctoral work with Prof. E. J. Corey at Harvard University in 1985, he was promoted to associate professor at Nagoya City University in 1988. In 1995, he moved to Chiba University to take up his present position. He received the Pharmaceutical Society of Japan Award for Young Scientists (1990) and the Pharmaceutical Society of Japan Award (2011). His research interests include the development of new methods and reagents for use in organic synthesis and total synthesis of biologically active natural products.
Indeed, the reaction of 2-methyl-2-cyclohexenyl carbonate doubled the value of enantiomeric excess. The 2-phenyl substrate was the best substrate for this reaction and afforded the product 19c with 95% ee. The results are summarized in Chart 3.

To explore the potential of 9-PBN and 9-NapBN, we selected asymmetric cyclization of the o-substituted aniline sulfonamides 20 leading to chiral tetrahydroquinoline 21 as an initial test reaction (Chart 4).

The initial experiment using the N-tosyl substrate 20 and (S)-9-PBN (1) was found to afford the tetrahydroquinoline 21 in 68% yield with 72% ee. Use of (R)-NapBN maximized the enantioselectivity to 94% ee. Although the reaction mechanism of the asymmetric induction with a high level of enantioselectivity through intramolecular allylic alkylation is not clear at present, we speculate that the reaction proceeds via the allyl–palladium complex avoiding the steric interaction with the methyl and the P-naphthyl substituents at the (S)-phosphine ligand to afford the (R)-product as shown in Fig. 4.

Next, we focused on the palladium-catalyzed metallo-ene reaction using 9-PBN and 9-NapBN. Intramolecular metallo-ene reaction is one of the synthetically powerful methods for the construction of a 5- or 6-membered ring which is contained in a variety of biologically active natural products. In the course of the optimization, the addition of sodium tetrafluoroborate and triacetoxyborane was found to activate the reaction at room temperature. Finally, the reaction of 23 using palladium and 9-NapBN in the presence of triacetoxyborane afforded the corresponding product in 82% yield and 52% ee (Chart 5). Although the enantioselectivity is moderate, it should be noted that the asymmetric metallo-ene reaction developed by us not only takes place under exceedingly mild conditions but also affords the highest enantiomeric excess in this area.

2.2. Development of Transition Metal-Catalyzed Asymmetric Reactions Using Chiral Diaminophosphine Oxide (DIAPHOX) Preligands and Their Applications

Chiral trivalent phosphines including our phosphines, 9-PBN and 9-NapBN, have been well proven to be excellent ligands for transition metal-catalyzed reactions. These phosphines, however, bear an inherent weakness: sensitivity to air-oxidation. Therefore, we investigated the use of pentavalent phosphorus compounds as a ligand for transition metal-catalyzed reactions, which, when those have a hydrogen at the phosphorus atom, are known to equilibrate with trivalent phosphorus ones (Chart 6). This equilibration is known to proceed through the complete retention of the chirality on a phosphorus atom.

Therefore, we focused on cyclic diaminophosphine oxides...
with one hydrogen and a stereogenic center on the phosphorus atom, which can be prepared from chiral (or achiral) diamines. Separation of the diastereomeric (or enantiomeric) mixture, however, is necessary to obtain optically pure P-chiral diaminophosphine oxide. Our strategy to synthesize P-chiral diaminophosphine oxides is as follows: Triaminophosphines are reactive to water under acidic conditions via an SN2-type process, affording the corresponding diaminophosphine oxides through P(III) to P(V) tautomerization. Therefore we expected that the diastereoselective formation of P-chiral triaminophosphine starting from optically active branched triamines, followed by the introduction of oxygen functionality on the phosphorus atom, would be an efficient synthetic route (Chart 7).

2.2.1. Pd-Catalyzed Asymmetric Allylic Alkylation of 1,3-Diphenylallyl Acetate

With the optically pure DIAPHOXs in hand, we attempted to use it as a chiral ligand. We first examined the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate. Examinations were performed using 1 mol% of (η3-C3H5PdCl)2 and 4 mol% of (S,R)-DIAPHOX 37a by treatment with silica in wet ethyl acetate.

2.2.2. Enantioselective Construction of an All-Carbon Quaternary Stereocenter

Catalytic enantioselective construction of a quaternary carbon center is a formidable challenge in organic synthesis. Pd-catalyzed asymmetric allylic substitution using prochiral nucleophiles is one of the most straightforward approaches toward this end. Few successful reactions of this type have been reported since the 1980s.

We first examined the asymmetric allylic substitution of cinnamyl acetate with ethyl 2-oxocyclohexane carboxylate as shown in Chart 11. When the reaction was performed using (η3-C3H5PdCl)2, (S,R)-DIAPHOX 37a, and BSA as a base, (S)-41a was obtained in 53% ee, even though the yield was only 10%. Encouraged by this result, we investigated the effect of the addition of acetate salt. Detailed screening revealed that Zn(OAc)2 was the best additive for asymmetric induction. The scope and limitations of this reaction are summarized in Chart 12.

2.2.3. Asymmetric Allylic Alkylation Using Nitromethane as the Nucleophile

Various stabilized carbon...
nucleophiles are applicable to Pd-catalyzed asymmetric allylic alkylation. There are, however, only a few reports of Pd-catalyzed asymmetric allylic alkylation using nitronate nucleophiles, perhaps due to multiple alkylations and the formation of side products.36—40) In our DIAPHOX–Pd system, catalytic asymmetric allylic alkylation of 1,3-diphenylallyl ethyl carbonate \( \text{42} \) with nitromethane proceeds in the presence of a catalytic amount of \( \text{N}_2\text{N}^-\text{diisopropylethylamine} \) in nitromethane itself as a solvent, giving the corresponding product \( \text{43} \) in 88% yield with 98% ee (Chart 13).

Chart 13. Asymmetric Allylic Alkylation of Nitromethane

The present reaction system was successfully applied to the catalytic asymmetric synthesis of \((R)\)-baclofen hydrochloride, a \( \text{GABA}_\beta \) receptor agonist.

2.2.4. Pd-Catalyzed Enantioselective Synthesis of Quaternary \( \alpha \)-Amino Acid Derivatives Using Chiral Diaminophosphine Oxides \( \text{23}) \) Pd-catalyzed asymmetric allylic substitution using \( \beta \)-keto esters with a nitrogen functional group at the \( \alpha \)-carbon as the prochiral nucleophile is one of the most straightforward approaches for synthesizing chiral quaternary \( \alpha \)-amino acid derivatives. Although several types of Pd-catalyzed asymmetric allylic substitutions using prochiral nucleophiles have been investigated since the 1980s, there are only a few reports of asymmetric synthesis of such tetrasubstituted carbons using this strategy.\( \text{41—45} \) We first examined asymmetric allylic substitution of \( \text{44} \) with \( \alpha \)-acetamido \( \beta \)-keto ester \( \text{45} \) based on the reaction conditions using cyclic \( \beta \)-keto ester nucleophiles. In contrast to the construction of an all-carbon quaternary stereocenter, \( \text{Zinc acetate} \), however, showed a negative effect on the enantioselectivity. We then investigated the effect of the structure of DIAPHOX under additive-free conditions. When the reaction was performed using \((S,R\text{)}_\text{P}-\text{37a}, \text{moderate enantioselectivity} (78\% \text{ ee}) \) was observed as shown in Chart 14. Further studies revealed that enantioselectivity was improved when the reaction was performed using \((S,R\text{)}_\text{P}-\text{46}, \text{prepared from} (S\text{-})\text{phenylalanine, affording} (R\text{-})\text{-47} \) in 98% yield with 92% ee.

Chart 14. Enantioselective Synthesis of Quaternary \( \alpha \)-Amino Acid

2.2.5. Pd-catalyzed Asymmetric Allylic Amination of Cyclic Substrates \( \text{18}) \) The satisfactory results in the reaction system using a conventional substrate led us to examine asymmetric allylic amination of cyclic substrates. Asymmetric allylic amination of 2-substituted cycloalkenyl alcohol derivatives affords versatile adducts for the synthesis of nitrogen-containing natural products. Despite its usefulness, the success of this type of reaction is limited.\( \text{46—50} \) Although no reaction occurred when 2-phenylcyclohexenyl acetate was used as the substrate, allylic amination of 2-phenylcyclohexenyl carbonate \( \text{48} \) with benzylamine proceeded smoothly in acetonitrile, affording the corresponding product \( \text{49a} \) in 93% yield and 93% ee (Chart 15).

Chart 15. Asymmetric Allylic Amination of Cyclic Substrate

The scope and limitations of different substrates were further examined under optimized conditions (Chart 16).

As shown above, asymmetric allylic amination of 2-phenyl cyclohexenyl carbonates using primary and secondary amines proceeded at room temperature to provide the corresponding products in good yield with high enantioselectivity. Substrates with alkyl, alkenyl, or alkynyl substituents were also applicable to this reaction, and the corresponding products were obtained in moderate to good enantiomeric excess. When
asymmetric allylic amination of 48 was performed with p-anisidine as a nucleophile, dimethylformamide (DMF) was the solvent of choice for a smooth reaction.

2.2.6. Enantioselective Synthesis of Aza–Morita–Baylis–Hillman Reaction Products Using Asymmetric Allylic Amination

The catalytic enantioselectiveaza-
Morita–Baylis–Hillman (aza-MBH) reaction provides functionalized chiral allylamines, which are useful building blocks for natural product synthesis. These amines can be alternatively prepared by asymmetric allylic amination of cycloalkenyl carbonates with a 2-carbonyl function. Although this type of transformation using oxygen nucleophiles has been investigated in detail by Trost et al., there are limited investigations using nitrogen nucleophiles.

This background led us to examine the asymmetric allylic amination of 2-methoxycarbonyl 2-cyclohexenyl carbonate 51 with benzylamine using our catalyst system (Chart 17).

![Chart 17. Asymmetric Synthesis of Aza-Morita–Baylis–Hillman Product](image)

The effect of the ligand structure revealed that the introduction of electron-donating groups onto the aromatic rings attached to the nitrogen atoms increases the enantioselectivity, and the 3,4-dimethoxy-type ligand (S,R)-37h was best for asymmetric induction. Moreover, enantioselectivity was increased when the reaction was performed at a lower temperature. The reaction proceeded smoothly with 2 mol% of Pd catalyst and 4 mol% of (S,R)-37h, even at −30°C, giving (S)-52a in 99% yield with 99% ee.

The scope and limitations of different substrates were examined using optimized reaction conditions (Chart 18).

The reaction of a secondary amine and an aromatic amine proceeded sufficiently to provide the corresponding products in excellent yield and enantiomeric excess. Other cyclic substrates with a five-membered ring and a seven-membered ring were also applicable to this reaction, affording the corresponding chiral allylic amines in good yield and enantiomeric excess, respectively. Furthermore, a substrate with a simple secondary amide, as well as the Weinreb amide-type substrate, could be utilized for this reaction system, giving the corresponding products in excellent yield and enantiomeric excess. Similarly, a reaction using a cyclic substrate with a nitrile group proceeded efficiently to provide the corresponding product in high enantiomeric excess.

2.2.7. Ir-Catalyzed Asymmetric Allylic Substitution Reactions and Asymmetric Aminations

Phosphites and phosphoroamidites are effective ligands in Ir-catalyzed allylic substitution reactions of terminal allylic electrophiles to give branched products. We envisioned that the present ligand system should be extended to the Ir-catalyzed asymmetric allylic substitution reactions.

We first examined the asymmetric allylic amination of cinnamyl carbonate 54 with benzylamine (Chart 19). The ratio of iridium and DIAPHOX was critical for this reaction. No reaction occurred when 1 mol% of chloro(1,5-cyclooctadiene) iridium(I) dimer ([Ir(cod)Cl]2) and 4 mol% of (S,R)-37a (Ir:37a=1:2) were used in CH2Cl2 at room temperature. In contrast, when 1 mol% of [Ir(cod)Cl]2 and 2 mol% of (S,R)-37a (Ir:37a=1:1) were used, the branched product 55a was obtained in 63% ee, even though the yield was only 10%. In this reaction, no linear product was observed in 1H-NMR analysis of the crude sample. Fortunately, the addition of sodium hexafluorophosphate improved the reactivity, giving the only branched product in an excellent yield. Interestingly, the remote substituent on the phenyl group of DIAPHOX affected the enantioselectivity. Finally, the use of (S,R)-37g with two tert-butyl groups at −20°C maximized the enantioselectivity. The results of other substrates are summarized in Chart 20.

![Chart 18. Scope and Limitations](image)

The success of the asymmetric allylic amination led us to examine asymmetric allylic alkylation using the Ir–DIAPHOX catalyst system (Chart 21). Optimizations of reaction conditions were performed using asymmetric allylic alkylation of 54 with dimethyl malonate using (S,R)-37a. Although no reaction occurred when 2.5 mol% of [Ir(cod)Cl]2 and 5 mol% of (S,R)-37a (Ir:37a=1:1) were used, the same reaction proceeded in the presence of NaPF6 (10 mol%) and lithium acetate (10 mol%), affording the branched product (S)-57a with high.

![Chart 19. Ir-Catalyzed Asymmetric Allylic Amination](image)
regioselectivity (71% yield, \( \text{57a/58} = 95/5, 90\% \text{ ee} \)). We next attempted to improve the regioselectivity and enantioselectivity by tuning the structure of DIAPHOX. Studies of the effect of substituents on the aromatic rings revealed that (S, R)-37d with a 3-biphenyl group at the benzylic moiety was best for asymmetric induction (90% ee), giving the branched product (S)-57a in good yield with excellent regioselectivity (92% yield, \( \text{57a/58} = 99/1 \)).

As described above, DIAPHOXs are very useful preligands for palladium- and iridium catalyzed reactions. The usefulness of DIAPHOXs in catalytic asymmetric syntheses is summarized in Fig. 5.

3. New anti-Selective Asymmetric Hydrogenation of \( \alpha \)-Amino-\( \beta \)-Ketoesters

Catalytic asymmetric hydrogenation\(^{62,63}\) through dynamic kinetic resolution (DKR) is one of the most efficient methods for the preparation of optically active compounds.\(^{64–67}\) As illustrated in Chart 23, the reaction of a rapidly racemizing substrate under reaction conditions using a highly enantioselective catalyst, when the racemization rate is high compared to the reaction rate, can proceed through DKR and finally, the entire substrate can be converted into a single diastereomer in a theoretic 100% yield in a stereocontrolled fashion and a single operation. We have succeeded in the development of anti-selective asymmetric hydrogenation of \( \alpha \)-amino-\( \beta \)-ketoesters using Ru-, Rh-, Ir-, and Ni-catalysts through DKR.

3.1. anti-Selective Asymmetric Hydrogenation Using

The results of other substrates are summarized in Chart 22. As described above, DIAPHOXs are very useful preligands for palladium- and iridium catalyzed reactions. The usefulness of DIAPHOXs in catalytic asymmetric syntheses is summarized in Fig. 5.
Ru-Axially Chiral Phosphine Catalysts

In 1989, Noyori et al. reported for the first time that a chiral Ru–BINAP complex catalyzed the syn-selective asymmetric hydrogenation of \( \alpha \)-acylamino-\( \beta \)-keto esters via DKR to produce syn \( \beta \)-hydroxy-\( \alpha \)-acylamino acid esters, which are useful chiral building blocks for the synthesis of natural products and medicines, with high diastereoselectivities and enantioselectivities. Their asymmetric hydrogenation is highly efficient but is limited to the synthesis of only syn-\( \beta \)-hydroxy-\( \alpha \)-amino acids. Thus, we set out to develop a direct method for the synthesis of anti-\( \beta \)-hydroxy-\( \alpha \)-amino acids by the catalytic asymmetric hydrogenation of \( \alpha \)-amino-\( \beta \)-keto esters through DKR.

We first deliberated the postulated reaction mechanism in Noyori’s syn-selective asymmetric hydrogenation as shown in Chart 24. The reaction takes place through the six-membered cyclic transition state 60 by chelation between two carbonyl groups of keto and ester functions to provide syn-\( \alpha \)-amino acid 61.

We predicted that, when substrate 59b with a protection-free amino function was employed, the hydrogenation should anti-selectively proceed through the five-membered cyclic transition state 62 by chelation between the amino group and the ester carbonyl function, leading to anti-\( \beta \)-hydroxy-\( \alpha \)-amino acid 63. Indeed, the asymmetric hydrogenation of \( \alpha \)-amino-\( \beta \)-keto ester hydrochloride 64 using Ru-(S)-BINAP catalyst in methylene chloride at 50°C for 48h under high hydrogen pressure anti-selectively proceeded to produce anti-\( \beta \)-hydroxy-\( \alpha \)-amino acid ester 65 in a high yield with almost perfect diastereoselectivity and high enantioselectivity (Chart 25). The result clearly shows that the reaction proceeds through DKR. Solvent, temperature, and solubility of the substrate were all found to be important factors for the yield and stereoselectivity of the products.

The required \( \alpha \)-amino-\( \beta \)-keto ester hydrochlorides are readily available by the following five methods: (1) the acid hydrolysis of a 4-alkoxybenzoxazole derived from a carboxylic anhydride and isocyanooacetic acid ester, (2) the formation of the oxime from a \( \beta \)-keto ester and its reduction, (3) the base-mediated N-C acylation of a \( N \)-t-butoxycarbonyl-\( N \)-acylglycine ester and then acid deprotection, (4) the acylation of the benzophenone ketimine derived from a glycine ester in the presence of a strong base followed by acid hydrolysis, and (5) the acylation of an \( N \)-acyliminomalonamic acid half ester followed by deprotection. The anti-selective asymmetric hydrogenation was affected by the bulkiness of the C4 substituent. The reaction of the primary alkyl substrate was inferior to the secondary one in the enantioselectivity.

However, the use of MeObIPHEP instead of BINAP together with lowering the temperature improved its enantioselectivity. The tert-butyl substrate was also inferior in diastereoselectivity and enantioselectivity under standard conditions but the hydrogenation in \( \eta \)-propanol turned out to improve the stereoselectivity, leading to the product in good yield and enantiomeric purity with 96:4 diastereoselectivity.

We briefly investigated the mechanism of this unique anti-selective asymmetric hydrogenation. In this hydrogenation, the substrate \( \alpha \)-amino-\( \beta \)-keto ester presents as keto and enol tautomers through tautomerism. A simple question is which tautomer is hydrogenated? The deutero experiments revealed that the anti-selective asymmetric hydrogenation took place through the hydrogenation of the enol tautomer. Although anti- and syn-selective asymmetric hydrogenations are catalyzed with the same Ru-axially chiral phosphine complex, the above result clearly indicates that both the reactions proceed through substantially different pathways, respectively, disclosing a new aspect of Ru-chiral phosphine catalyzed asymmetric hydrogenation.

3.2. anti-Selective Asymmetric Hydrogenation Using Iridium-Chiral Phosphine Catalysts

The asymmetric hydrogenation using the Ru-axially chiral phosphine described above proceeds smoothly to afford anti-\( \beta \)-hydroxy-\( \alpha \)-amino acid esters with excellent diastereomeric and enantiomeric purity. This hydrogenation, however, was limited to substrates with an alkyl group at the C4 position. In stark contrast, the
attempted reaction of the phenyl substrate 67 using Ru-BINAP at 50°C for 48 h in methanol resulted in the formation of a racemic amino acid in a diastereomeric ratio of 93:7 and 31% yield as indicated in Chart 26. This disappointingly low level of asymmetric induction prompted us to examine other transition metals for aromatic substrates. Interestingly, in addition to the known ruthenium catalyst, rhodium (Rh) and iridium (Ir) proved to be potential catalysts for highly anti-selective hydrogenation through DKR. Therefore, we first carried out the optimization of the Ir-catalyzed anti-selective asymmetric hydrogenation.14

\[
\begin{align*}
H_2 & (100 \text{ atm}) & & \text{RuCl}_2[(S)-\text{binap}] & & \text{MeOH, 50°C, 48 h} & & \text{31% yield, anti/syn = 93/7, 0% ee} \\
H_2 & (50 \text{ atm}) & & \text{[Ir(cod)Cl]_2-(S)-BIPHEP} & & \text{MeOH-Benzene, rt, 48 h} & & \text{44% yield, anti/syn = 98/2, 8% ee} \\
H_2 & (50 \text{ atm}) & & \text{[Ir(cod)Cl]_2-(S)-BIPHEP} & & \text{MeOH-Benzene, rt, 48 h} & & \text{87% yield, anti/syn = 96/4, 45% ee}
\end{align*}
\]

Chart 26. Catalyst Screening for Aromatic Substrates

In the course of optimization, we found two new iridium catalysts, first-generation and second-generation Ir catalysts, for this hydrogenation. The procedure for preparing the first-generation catalyst was critical for its catalytic activities. The most active catalyst was made prior to the hydrogenation by mixing \([\text{IrCl(cod)}]_2\) with MeO-BIPHEP in the presence of sodium iodide in methylene chloride at 23°C for 10 min. Acetic acid as the solvent and sodium acetate as an additive affected the diastereoselectivity and the enantioselectivity, respectively as shown in Table 1. Among several chiral phosphines, MeO-BIPHEP was most efficient for the enantioselectivity. Moreover, the addition of an iodide anion source, especially sodium iodide, in the preparation of the Ir catalyst led to maximized enantioselectivity. The anti-selective hydrogenation via DKR using 3 mol% of the Ir-(S)-MeO-BIPHEP catalyst proceeded with almost complete diastereoselectivities under 100 atm of hydrogen in the presence of sodium acetate (1 eq) in acetic acid at 27—30°C to afford the aromatic \(\alpha,\beta\)-hydroxy-\(\alpha\)-amino esters with high enantioselectivities in excellent yields. However, high hydrogen pressure (100 atm) and a tedious degassing operation by freeze-thaw cycles in the preparation of the catalyst are essential for a smooth reaction, and make it difficult to run this hydrogenation in a practical sense.

In our effort to expand the utility of the first-generation Ir-catalyst, we re-examined various additives, except for sodium iodide, and found the second-generation Ir catalyst. The addition of NaBARF, a weakly coordinated anion, to the iridium catalyst prepared from \([\text{IrCl(cod)}]_2\) and (S)-MeO-BIPHEP enhanced its catalytic activity, but the diastereo- and enantioselectivity remained at a similar level to that of the reaction under high hydrogen pressure (100 atm). Finally, we found an unusual relationship between hydrogen pressure and enantioselectivity, in that lowering hydrogen pressure enhanced enantioselectivity. Under 4.5 atm of hydrogen the enantioselectivity was improved to 93% ee. Furthermore, the present reaction proceeded even under 1 atm of hydrogen with similar stereoselectivity in excellent chemical yield. This second-generation catalyst, Ir-(S)-MeO-BIPHEP-BARF complex, can be readily prepared by mixing \([\text{IrCl(cod)}]_2\), (S)-MeO-BIPHEP and NaBARF in methylene chloride at 23°C for 1 h. The catalyst loading can be lowered from 3 to 0.5 mol% without a loss of yield or diastereo- and enantioselectivities. A survey of several chiral phospines revealed that (S)-MeO-BIPHEP was again the most efficient in terms of chemical yield and enantioselectivity. It is noted that this second-generation Ir-catalyst has remarkable stability and is robust in the presence of moisture and air. In the preparation of the Ir-catalyst and in assembling a reaction apparatus, we were able to avoid the tedious degassing operation by freeze-thaw cycles and the handling under an inert gas atmosphere, neither of which were necessary. Furthermore, the asymmetric hydrogenation using the second-generation Ir-catalyst can even be carried out using a commercially available balloon filled with hydrogen gas.

For the examination of the scope and limitations, a series of aromatic substrates with different substituents were subjected to hydrogenation under the optimized conditions. The results are shown in Chart 27.

The hydrogenation was carried out using the second-gener-

Table 1. Asymmetric anti-Selective Hydrogenation Using the Ir Catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Additives (eq)</th>
<th>H₂ (atm)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>First-generation Ir catalyst</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>(S)-BINAP</td>
<td>—</td>
<td>100</td>
<td>48</td>
<td>81</td>
<td>27</td>
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<td>NaOAc (1)</td>
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<td>90</td>
<td>69</td>
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<tr>
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<td>NaOAc (1)</td>
<td>100</td>
<td>3</td>
<td>79</td>
<td>77</td>
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<tr>
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<td>(S)-MeO-BIPHEP</td>
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<td>24</td>
<td>82</td>
<td>90</td>
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<td>Second-generation Ir catalyst</td>
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<tr>
<td>5</td>
<td>(S)-MeO-BIPHEP</td>
<td>NaOAc (1), NaBARF (0.03)</td>
<td>100</td>
<td>3</td>
<td>quant</td>
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<td>(S)-MeO-BIPHEP</td>
<td>NaOAc (1), NaBARF (0.03)</td>
<td>60</td>
<td>12</td>
<td>quant</td>
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<td>8</td>
<td>(S)-MeO-BIPHEP</td>
<td>NaOAc (1), NaBARF (0.03)</td>
<td>4.5</td>
<td>24</td>
<td>quant</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>(S)-MeO-BIPHEP</td>
<td>NaOAc (1), NaBARF (0.03)</td>
<td>1</td>
<td>96</td>
<td>91</td>
<td>92</td>
</tr>
</tbody>
</table>
ation Ir-(S)-MeO-BIPHEP-BARF catalyst in the presence of sodium acetate (1 eq) in acetic acid under 4.5 atm of hydrogen at 23°C for 96 h. The yields and enantioselectivities were improved in comparison with our previous data by using the first-generation Ir catalyst. The cationic Ir complex was also applicable to heteroaromatic substrates containing a sulfur or oxygen atom. Hydrogenation of the hindered substrate with a tert-butyl group efficiently proceeded to provide an anti-β-hydroxy-α-amino acid ester with >99:1 diastereoselectivity in a quantitative yield and excellent enantioselectivity. It is noted that this result is the highest value for a tert-butyl substrate and is superior to that of the Ru-BINAP catalyzed anti-selective hydrogenation developed by us.

In order to elucidate the detailed reaction profile and the mechanism of this unique asymmetric hydrogenation, we performed isotope labeling experiments and kinetic studies under varying hydrogen pressure. These results clearly support that the Ir-catalyzed asymmetric hydrogenation of the α-amino-β-keto esters takes place through reduction of the ketone double bond to produce the β-hydroxy-α-amino acid esters with anti-stereochemistry. The interesting dependency of enantioselectivity on the hydrogen pressure was found to be ascribed to the presence of two catalysts, the trivalent Ir catalyst and the pentavalent Ir catalyst (Chart 28).

3.3. anti-Selective Asymmetric Hydrogenation Using Ni-Chiral Phosphine Catalysts In the course of the catalyst screening described above, we recognized that nickel in combination with chiral phosphines is also a potential catalyst for this anti-selective asymmetric hydrogenation. Nickel, one of the abundant and cheap base transition metals, has attracted a great deal of attention in catalytic organic synthesis. In the area of catalytic hydrogenation using nickel catalysts, the heterogeneous catalysts represented by Raney nickel have been well studied. Asymmetric hydrogenation using a homogeneous nickel catalyst modified by a chiral auxiliary, however, has never been investigated.

A homogeneous chiral nickel catalyst can be easily prepared by mixing nickel acetate and a ferrocenylphosphine in a reaction media without prior preparation of the catalyst complex and can be used in the presence of sodium acetate in a mixture of trifluoroethanol and acetic acid under 100 atm of hydrogen for the asymmetric hydrogenation of 67, as shown in Chart 29.

In order to enhance the enantioselectivity, we next examined several chiral phosphine ligands. Most of the commercially available chiral phosphines resulted in little or no reaction, while the Josiphos type ligands produced active catalysts. Among these, the substituents on the two phosphorus atoms influenced the activity of the catalysts. When the hydrogenation was performed using a combination of nickel acetate (5 mol%) and Josiphos 75 in the presence of sodium acetate in a mixture of trifluoroethanol and acetic acid under 100 atm of hydrogen for 24 h, the substrate was smoothly converted...
and the anti-β-hydroxy-α-amino acid ester 68b was obtained in quantitative yield with complete diastereoselectivity and 92% ee.

Compared to the iridium-catalyzed hydrogenation, somewhat superior results with respect to enantioselectivity and reactivity were obtained with the hindered substrate and halogen-containing substrates. Although a nitro group is sensitive to reducing conditions, the hydrogenation of the nitro-containing substrate chemoselectively proceeded to give the corresponding product along with a small amount of the aniline derivative. The results of the above asymmetric hydrogenation are noteworthy because the present reaction is not only the first use of homogeneous chiral nickel-phosphine complexes in asymmetric hydrogenation, but also the first example of nickel-catalyzed dynamic kinetic resolution.

4. Synthesis of Biologically Interesting Natural Products Using Our Developed Methods

4.1. Enantioselective Synthesis of Tangutorine

Asymmetric allylic amination can be a useful tool in the enantioselective total synthesis of nitrogen-containing natural products. Our catalytic asymmetric reaction was successfully applied to the first enantioselective total synthesis of tangutorine (76), which exhibits cytotoxic activity against human colon cancer HT-29 cells.86–91 (Fig. 6).

The key features of our synthesis are the asymmetric allylic amination of 51 with N-Boc-tryptamine (77) using the Pd-DIAPHOX catalyst system and an intramolecular Pictet-Spengler reaction for the construction of the five contiguous ring system.

The target asymmetric allylic amination proceeded using 2 mol% of the Pd catalyst at −30°C, providing the corresponding chiral amine (S)-79 in 99% yield with 95% ee (Chart 30).

![Fig. 6. Tangutorine](image)

![Chart 30. Enantioselective Synthesis of Tangutorine](image)

![Chart 31. Tandem Michael–Aldol Reaction](image)
After reduction of 78, Sharpless asymmetric epoxidation\(^\text{92}\) of the corresponding allyl alcohol (95\% ee) gave the enantio-merically enriched epoxy alcohol 79 (99\% ee) in a high yield with a high diastereomeric ratio. Dess–Martin oxidation of 79, followed by treatment with a Wittig reagent, afforded \(\alpha,\beta\)-unsaturated ester 80 in 94\% yield over 2 steps. A subsequent reductive epoxide opening reaction of 80 via a \(\pi\)-allyl palladium intermediate proceeded in the presence of \(\text{Pd}(\text{PPh}_3)_4\), providing alcohol 81 with the desired stereostructure in 98\% yield in a highly diastereoselective manner.\(^\text{93}\) Conversion of \(\alpha,\beta\)-unsaturated ester 81 to the Pictet–Spengler precursor 82 was carried out by the usual five-step process. Subsequent intramolecular Pictet–Spengler reaction of 82 proceeded to completion in 48\,h using trifluoroacetic acid (TFA) as a promoter in a \(\text{CH}_3\text{CN–H}_2\text{O}\) solvent system (50\% aq. TFA/\(\text{CH}_3\text{CN}=1/60\)), affording 83 and 84 in 55\% and 39\% isolated yield, respectively. Compound 83 was converted to the known synthetic intermediate 85 in three steps in a good yield. Transformation of 85 into tangutorine was performed using the mixed enol acetalization protocol.\(^\text{94,95}\) After formylation of ketone 85 with ethyl formate, and the acetal protection of the resulting enal, reduction of the ketone function followed by exposure of the resulting allyl alcohol to PPTS furnished \(\alpha,\beta\)-unsaturated aldehyde 87 in good yield. Finally, reduction of the \(\alpha,\beta\)-unsaturated aldehyde with \(\text{DIBAL-H}\), followed by deprotection of the Boc group on the indole, afforded (\(-\))-tangutorine (76).

4.2. Enantioselective Synthesis of Martinellin Acid\(^\text{16}\)

Martinelline (88) and martinellic acid (89) bearing a unique pyrroloquinoline with fused tetrahydroquinoline and pyrro-\(\text{lidine rings and two prenyl guanidines were isolated from the roots of the tropical plant, Martinella iquitosensis, in 1995, as a nonpeptide bradykinin receptor antagonist}\(^\text{97}\) (Fig. 7).

The intriguing biological activity of martinelline coupled with its unique structure has led several groups, including our own, to investigate a variety of synthetic methods for the preparation of its pyrroloquinoline core.\(^\text{98–112}\) The key features of our synthesis are the tandem Michael–Aldol reaction\(^\text{113,114}\) using an antranilaldehyde and a Michael acceptor developed by us and the diastereoselective formation of the pyrroloquinoline moiety as outlined in Chart 31.

The required 91 was easily prepared starting from the commercially available pyrrolidinone 93 in a good overall yield (Chart 32).

The preparation of 90 was carried out beginning with \(p\)-aminobenzoic acid methyl ester (95), and done in four steps (Chart 33). After protection of 95 with toluenesulfonyl chloride and pyridine followed by \(\alpha\)-bromination, the Stille coupling of bromide 96 with tributyl(vinyl)tin was followed by ozonization of the resulting styrene 97 to afford the 4-methoxycarbonylanthranilaldehyde 90.

The asymmetric tandem Michael–Aldol reaction using (\(R\))-diphenylprolinol triethylsilyl ether as an organocatalyst was extensively examined. Finally, the reaction of 90 (1 eq) with 91 (3 eq) using (\(R\))-98 (20\% mol) in acetonitrile at \(-20^\circ\text{C}\) for 24\,h furnished (\(S\))-1,2-dihydroquinoline 92 in a quantitative yield and 99\% ee (Chart 34).

The compound 92 was converted to the martinelline core structure 104 in 11 steps, as shown in Chart 35. The reduction of 92 with sodium borohydride-ceric chloride followed by epoxidation of the allyl alcohol with \(m\text{CPBA}\) provided epoxide 99 in quantitative yield with a diastereomeric ratio of 75:25—86:14. After the iodination of 99 and the Zn-mediated ring cleavage, oxidation of the resulting allyl alcohol with activated manganese dioxide afforded \(\alpha,\beta\)-unsaturated ketone 100 in excellent yield. Hydrocyanation of 100 produced a mixture of quinolone 101 and 102 in 90\% yield with a diastereomeric ratio of 94:6.

Surprisingly, the stereostructure of the major isomer 101 at C2 and C3 was found to be \(\text{cis}\) by nuclear Overhauser effect.
(NOE) experiments. The attempted isomerization of 101 to 102 was fruitless. We were unable to obtain the desired 102 as a pure diastereomer because both diastereomers are inseparable by column chromatography. The exclusive cis preference arising from the hydrocyanation of 100 might be ascribed to the pseudo 1,3-diaxial interaction between the bulky N-toluenesulfonyl group and the 3-cyanomethyl one in 102. The deprotection of the mixture of 101 and 102 with sodium-naphthalene, however, again yielded an inseparable mixture of tetrahydroquinoline 103 and 104 in 40% yield with the diastereomeric ratio of 57:43. Fortunately, hydrogenation of the mixture of 103 and 104 with Raney nickel and hydrogen, followed by N-protection, furnished the desired pyrroloquinoline 105 as almost a single isomer in 70% yield. This preferential trans formation during hydrogenation is in contrast to the cis preference in the hydrocyanation reaction of 100, indicating that their stereoselectivities are highly dependent on the nature of the substituent at the aromatic nitrogen. Exposure of 105 to hydrochloric acid afforded the martinelline chiral core 106 in 71% yield, of which the spectroscopic data were identical with the reported value of 106. This synthesis represents the first enantioselective synthesis of the martinelline chiral core 106 and the formal total syntheses of martinelline and martinellic acid.

4.3. Total Synthesis of Papuamide B

Papuamides A (107) and B (108) are a new family of novel cyclodepsipeptides isolated from the marine sponge genus Theonella collected at Papua New Guinea by Boyd and colleagues (Fig. 8). Papuamides are known to strongly inhibit the infection of human T-lymphoblastanoid cells by HIV-1RF and also exhibit potent cytotoxicity against a number of human cancer cell lines. These cycloheptadepsipeptides have a unique structure containing (4Z,6E)-2,3-dihydroxy-2,6,8-trimethyldecadienoic acid (Dhtda) and unusual amino acid residues, such as (3S,4R)-3,4-dimethylglutamine (3,4-DiMeGln), (2R,3R)-3-hydroxyleucine (3-OHLeu) and β-methoxytyrosine (β-OMeTyr). The stereochemistry of papuamides remains to be determined because of uncertainty regarding the stereochemistry in the β-OMeTyr and the Dhtda parts. Interestingly, an unusual amino acid, 3,4-DiMeGln, is known to be a common component of cyclodepsipeptides of marine origin, which show anti-HIV and antifungal activities. The unique structure and interesting biological activities of these compounds has led to considerable efforts directed toward the total synthesis of papuamides. In the following section, the discussion is limited to our synthetic efforts.

4.3.1. Structural Determination of the β-OMeTyr and the Dhtda Parts

In order to accomplish the total synthesis, as well as structural determination, of papuamides, the determination of two stereo-undefined components, MeOTyr and Dhtda, is necessary. Boyd et al. have reported two fragments, 109 and 110, derived from the degradation experiments of natural papuamides, which contain MeOTyr and Dhtda residues, respectively (Fig. 9).

First, four stereoisomers of the MeOTyr derivative were dia-
stereoselectively prepared from (S)- and (R)-Garner aldehydes. The four tripeptides 109a—d required for structural determination of the MeOTyr were prepared from Boc-(S)-Hpr-OBzl by sequential coupling with Boc-MeOTyr(Bzl)-OH and Cbz-MeThr(TBS)-OH using the HATU/DIPEA and EDCI/HOBt methods (Chart 36). Sequential deprotection of TBS group with HF-acetonitrile, and of the Cbz group by hydrogenolysis with Pd-carbon and hydrogen, furnished the free tripeptides 109a—d. (2R,3R)-Isomer 109a matched the 1H-NMR data reported for the natural hydrolysate. Accordingly, the stereochemistry of the MeOTyr residue was unambiguously established as 2R,3R.122)

Next, eight diastereomers of 110 were prepared from commercially available (S)-2-methylbutanol (114). First, the synthesis of four C2,C3-syn diastereomers 110a—d was conducted, as shown in Chart 37.

Dibromoolefins 115 derived from 114 was coupled with (R)-aldehyde 117 from Sharpless AD-mix-β dihydroxylation of 116 after conversion to the acetylide of 115 to afford alcohol 118 in a diastereomeric ratio of 10:1. These isomers were separable. Pure syn-118 was transformed to carboxylic acid 119 by usual manipulations, and 119 was then coupled with (2R,3R)-120 derived from l-threonine, to afford (2S,3R,8S)-110a after deprotection of the corresponding product. Coupling of 119 with (2S,3S)-120 derived from D-threonine, and subsequent deprotection, provided (2S,3R,8S)-110b, a substitute for (2R,3S,8R)-110b. The other diastereomers (2R,3S,8S)-110c and (2R,3S,8S)-110d, a substitute for (2S,3R,8R)-110d, were prepared in a similar manner from 115 and (S)-117 derived from the Sharpless AD-mix-α dihydroxylation.

The synthesis of four C2,C3-anti diastereomers 110e—h is shown in Chart 38. The above diastereomeric mixture of 118 can be converted to an anti-rich mixture by oxidation of the acetylenic alcohol and reduction of the resulting ketone with l-selectride. After chromatographic separation, pure (2R,3S,8S)-118 was converted to (2S,3S,8S)-110e and (2S,3S,8S)-110f, a substitute for (2R,3R,8R)-110f. The remaining (2R,3R,8S)-110g and (2R,3S,8S)-110h, a substitute for (2S,3S,8R)-110h, were obtained from (2S,3R,8S)-118 in a similar fashion.

Among the eight diastereomers 110a—h, neither of the four C2,C3-anti isomers matched the 1H-NMR data reported
Chart 38. Synthesis of 2,3-anti-Dhtda Diastereomers

Chart 39. Stereoselective Synthesis of (2R,3R)-3-Hydroxyleucine

Chart 40. Synthesis of (2R,3R)-\(\beta\)-Methoxy Tyrosine Derivative
for the natural product. The four C2,C3-syn diastereoisomers were possible candidates. The $^{13}$C-NMR data of the four C2,C3-syn diastereoisomers were carefully compared with those of the natural product. As a result, the chemical shifts of (2R,3S,8S)-110d, a substitute for (2S,3R,8R)-110d, were closer than those of the other three diastereomers, (2S,3R,8S)-110a, (2S,3R,8S)-110b, and (2R,3S,8S)-110c. Therefore, we have concluded that the stereostructure of natural 110 is 2S,3R,8R.

4.3.2. Stereoselective Synthesis of Unusual Amino Acids Synthesis of (2R,3R)-hydroxyleucine was carried out as shown in Chart 39. α-Amino-β-keto ester 124, prepared by acid hydrolysis of oxazole 123, was subject to anti-selective asymmetric hydrogenation developed by us to afford, after filtration of the crude reaction mixture, pure ethyl (2R,3R)-hydroxyleucinate (125) in a good yield. Exposure of 125 to hydrochloric acid furnished (2R,3R)-hydroxylytine (126).

For efficient stereoselective production of the (2R,3R)-MeOTyr, we employed Ir-catalyzed asymmetric hydrogenation accompanied by the dynamic kinetic resolution developed by us (Chart 40). Readily available 2-amino-3-keto ester 134, prepared from [IrClcod]$_2$ and (R)-(±)-proline, was hydrogenated with the Ir catalyst, prepared from [IrClcod]$_2$ and (R)-MeOBIPHEP, under 4.5 atm of hydrogen to provide the (2R,3R)-3-hydroxytyrosine 130 in a >99:1 diastereomeric ratio with 96%ee. N-t-Butoxycarbonylation of 130, O-methylation of the resulting protected amino acid with trimethyl oxonium tetrafluoroborate and proton sponge, and saponification of the methyl ester provided Boc-(2R,3R)-MeOTyr(Bzl)-OH 132.

(2S,3S,4R)-3,4-Dimethylglutamine (139) was stereoselectively prepared from (S)-pyroglutamic acid as shown in Chart 41.

Bicyclic unsaturated lactam 133$^{124,125}$ was subject to conjugate addition with lithium dimethylcuprate (Me$_2$CuLi) in the presence of chlorotrimethylsilane$^{129}$ to preferentially provide the 6-methylated product 134 in a 95:5 ratio. cis-Methylation of 134 at the 7 position was performed through the introduction of a trans-methyl group, and by subsequent isomerization via the enolate formation and protonation. After chromatographic purification, pure 136 was converted to dimethylglutamine 139 in six steps.

Preparation of diaminobutanoic acid (Dab) was achieved from aldehyde (R)-140 derived from carbenzoxoxy-(R)-alanine, which was converted to the Dab skeleton (2S,3R)-142 by proline-catalyzed amination using di-tert-butyl azodicarboxylate and then by the oxidation of 141 to 142 (Chart 42).$^{127}$ Cleavage of the N–N bond and final protection afforded the Dab derivative (2S,3R)-143. Diastereomer (2S,3S)-143 was also prepared starting from (S)-alanine in a similar manner.

4.3.3. Construction of Papuamide B Having the required building blocks in hand, the construction of papuamide B started from Boc-(2R,3R)-OHLeu-Or-Bu ester 144, as shown in Chart 43.

Tetrapeptide 146 was synthesized by [2+2] segment coupling of the ester fragment 145, prepared from the hydroxylycine 144 and Boc-(S)-Hpr-OH by racemization-free esterification with DCC/DMA followed by cleavage of the t-Bu ester, with the dipeptide from Boc-Ser(Me)-OH and H-Gly-OTce. After Boc-deprotection of 146, coupling of the resulting tetrapeptide with Boc-(2R,3R)-MeOTyr(Bzl)-OH proved to be a new and difficult sequence to couple. Standard reagents, HATU/DIEA, Bop-Cl/DIEA,$^{128}$ and Brop/DIEA,$^{129}$ for assembling the hindered sequence gave no coupling product, whereas FDPP/DIEA$^{130}$ and BMTB/DIEA$^{131}$ gave only 6% and 20%, respectively, of the pentapeptide 147. Among several reagents examined, DEPBT/DIEA, Goodman’s reagent,$^{132}$ was the most effective for the difficult sequence, providing 147 in 76% yield. The following segment coupling of 147 with Troc-Ala-Thr-OH again proved to be problematic for the difficult coupling. HATU/DIEA, and even BMTB/DIEA, afforded no desired product. DEPBT/DIEA was again superior to the standard coupling procedures, yielding the hexapeptide 148 in 72% yield. After deprotection of the Troc and Tce groups with zinc dust and phosphate buffer, macrocyclization at 0.01 M concentration using FDPP/DIEA proceeded in good yield to afford the cycldepsipeptide 149.

For assembling the side chain in papuamide B, we employed stepwise elongation from 149 to prevent racemization (Chart 44). The cycldepsipeptide 149 was coupled after deprotection of the Alloc group by Pd-chemistry with Boc-
(2S,3S,4R)-diMeGln-OH using DEPBT/DIEA to produce 150. The subsequent coupling of 150 with a Dab derivative was the most difficult task in this total synthesis. The deprotected diMeGln residue easily cyclized to the γ-lactam under both acidic and basic conditions. After extensive experiments, we found that direct coupling of the reaction mixture derived from 150 and trimethylsilyl triflate with Cbz-(2S,3S,4R)-(Boc)Dab-OObt, an active ester of HOObt, provided 151. The yield was moderate, but the most difficult problem was solved.

Construction of papuamide B was achieved by the sequential coupling of Cbz-Thr-OH and (2S,3S,4R)-Dhtda-Gly-OH using DEPBT/DIEA and final deprotection with 2M hydrochloride acid. Spectral data of the synthetic (2S,3S)-Dab-(2S,3R,8R)-Dhtda-papuamide B 153 were identical with those of natural papuamide B.

5. Summary
We have succeeded in the development of two new types
of ligands, 2,6-dimethyl-9-aryl-9-phosphabicyclo[3.3.1]nonanes (9-PBN and 9-NapBN) and chiral diaminophosphines oxides (DIAPHOXs) derived from aspartic acid, to be used in the transition metal-catalyzed asymmetric synthesis. We have developed the anti-selective asymmetric hydrogenation of α-amino-β-ketoesters using Ru-, Rh-, Ir-, and Ni-catalysts through dynamic kinetic resolution for the first time, which produces efficiently important anti β-hydroxy-α-amino acids. Total synthesis of several biologically active natural products was achieved by use of the transition metal-catalyzed reaction using DIAPHOX, anti-selective asymmetric hydrogenation, and reactions developed by us.

Acknowledgements We would like to thank all of our co-workers whose names appear in the references for their dedication, intellectual contributions, and hard work. Our work was partially supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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January 2012
19


