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Kyoto University
The Synthesis of Alkaloids Using a Transition-Metal-Catalyzed Intramolecular Amination Reaction

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Abstract: Transition-metal catalyzed reactions have the potential to provide significant improvements to the syntheses of complex target molecules. These reactions can be used to achieve a variety of different atom-economical transformations and cascade reactions and therefore provide access to synthetic strategies that would otherwise be unavailable using classical organic chemistry. To exemplify the utility of the latest transition metal catalyzed reactions for the construction of important target structures, we have been involved in total synthesis of natural products bearing widely known chemical scaffolds. In this account, we report our recent studies on the use of a palladium-catalyzed cascade cyclization reaction and a gold(I)-catalyzed hydroamination reaction, for the construction of the core structures of alkaloids, as well as their application to total syntheses of lysergic acid, lysergol, isolysergol, and quinocarcin.

Key words: Total synthesis, palladium, gold, alkaloids, atom economy

1 Introduction

Making improvements to the step and atom economies of organic transformations is one of the most important requirements in modern organic chemistry.1 Transition metal catalysts have had a significant impact on the facility with which organic chemists can access complex target structures by providing synthetic strategies for the construction of target molecule that would otherwise be difficult or even impossible to access using classical organic chemistry. To demonstrate the power of transition metal catalysis in organic chemistry, we have been working towards the synthesis of natural products using transition-metal-catalyzed cyclization reactions. A series of well-known chemical scaffolds were selected as the targets of our study including those of the ergot alkaloids (e.g., lysergic acid, lysergol, and isolysergol) and the tetrahydroisoquinoline alkaloids (e.g., quinocarcin). Although several efficient total syntheses of these natural products have already been reported (for details, see the introduction text of sections 2 and 3), our current approach represents a unique strategy that sometimes provide improvements in the step and atom economies of the syntheses of these compounds, as well as providing a platform for the synthesis of other complex natural products. Herein, we describe our recent work towards the synthesis of ergot alkaloids using a palladium-catalyzed cascade cyclization of allenines, as well as a gold(I)-catalyzed hydroamination for the synthesis of tetrahydroisoquinoline alkaloids.

2 Ergot Alkaloid Synthesis

Figure 1 Indole alkaloids of the ergot family and their synthetic derivatives.

The ergot family of alkaloids consists of several pharmacologically important fused indoles, including lysergic acid (1), lysergol (2), and isolysergol (3) (Figure 1). Compounds belonging to this particular family are produced by the fungus Claviceps purpurea, which grows parasitically on rye and other grains,2 and have been reported to possess a variety of different biological activities. For example, pergolide and bromocriptine, which are synthetic derivatives of the ergot alkaloids, are clinically used as anti-prolactin and anti-Parkinson’s disease drugs, respectively.3 Lysergic acid diethylamide (LSD) is well known as a strong psychoactive agent. The characteristic
structural feature of these alkaloids is their tetracyclic fused indole, which contains a Δ9,10-double bond and chiral centers at the C5 and C8 positions.

Ergot alkaloids, especially lysergic acid, have been the target of many synthetic studies because of their biological importance as well as their structural complexity. The first total synthesis of racemic lysergic acid was accomplished by Woodward in 1956. Several racemic syntheses of ergot alkaloids have subsequently been reported, with most of the strategies involving the stepwise and linear construction of the C/D ring system. One important exception, however, is the strategy described by Oppolzer, which involved the simultaneous construction of the C/D rings through an intramolecular imino-Diels–Alder reaction. The asymmetric total synthesis of lysergic acid was first reported in 2004 by Szántay and coworkers, which involved the resolution of a racemic tetracyclic intermediate using dibenzoyl-L-tartaric acid. In 2009, Fukuyama et al. reported the asymmetric synthesis of the methyl ester of lysergic acid using a Heck cyclization reaction or palladium-catalyzed double-cyclization (N-arylation and Heck reaction). More recently, Jia reported the asymmetric total synthesis of lysergic acid using a RCM reaction as the key step. This particular report was published after our own report (vide infra).

Based on our recent studies towards palladium-catalyzed cascade cyclization reactions, we designed a novel strategy for the construction of the core structure of ergot alkaloids that could be used for the asymmetric total synthesis of lysergic acid (1), lysergol (2), and isolysergol (3).

2.1 Construction of the Core Structure of the Ergot Alkaloids using a Palladium-Catalyzed Cascade Cyclization

It is well known that arylpalladium halides generated in situ from the reaction of aryl halides with palladium(0), can regioselectively react with allenes to form η3-allylpalladium(II) intermediates (Scheme 1). In 2003, we reported the direct formation of the tricyclic isoindole derivatives 5 from allenes 4 using an alkene carbopalladation reaction followed by a direct arylation/C–H bond functionalization (7 to 8) (Scheme 2). The reaction of 4 with heterocyclic aryl halides provided direct access to the corresponding tri- and tetracyclic heteroaromatic products. More recently, we reported a fully intramolecular cascade cyclization reaction using amino allene derivatives, with similar results also being reported by some other groups. For example, the reaction of 9 under these conditions terminates with the nucleophilic attack of a protected amino group to afford 10 (Scheme 3).
Racemic allenic amide 19 was prepared as a model compound to evaluate the overall scope of our strategy for the construction of the core structure of ergot alkaloids (Scheme 5). Commercially available 4-bromoindole (15) was readily converted to the protected 3-(bromomethyl)indole (16) via the formylation of the indole at the 3-position, followed by sequential N-tosylation, reduction of the 3-formyl group, and the bromination of the resulting primary hydroxy group. The addition of lithiated 1,3-dithiane to 16, followed by hydrolysis of the thiacetal, and subsequent reduction of the resulting ketone gave racemic propargyl alcohol 17. The propargyl vinyl ether 18 was then obtained via the conjugate addition of 17 to methyl propiolate, followed by sequential DIBAL reduction of the resulting enolate and TIPS protection of the resulting alcohol. The Claisen rearrangement of 18 under thermal conditions (m-xylene, 170°C) did not proceed as anticipated and gave the desired allenic alcohol (dr = ca. 33:67) in a low yield of only 38%. Pleasingly, however, the use of 5 mol% of the gold-oxo complex [(Ph3PAu)3O]BF4 gave the rearrangement product in 78% yield following the reduction of the aldehyde with NaBH4 (dr = ca. 80:20, favoring the opposite diastereomer to the thermal conditions). A Mitsunobu reaction with TsNH2 gave the allenic nosylamide derivative 19 as a mixture of diastereomers (dr = 80:20), which was progressed directly into the subsequent step without separation. The corresponding tosylamide derivative 20 (dr = ca. 80:20) (Scheme 6) was also prepared in a similar manner using TsNHFmoc in the Mitsunobu reaction.17

We then proceeded to investigate the construction of the ergot alkaloid skeleton using the palladium-catalyzed cascade cyclization (Scheme 6). Among the different palladium catalysts [Pd(OAc)2/PPh3, PdCl2(dppf), Pd(OAc)2/P(o-tol)3 and Pd(OAc)2/rac-BINAP], bases (Na2CO3, Cs2CO3, and K2CO3), and solvents (DMF, DMSO, toluene, and dioxane) tested, a combination of 5 mol% of Pd(PPh3)4 with K2CO3 in DMF was found to be the most effective, and gave the desired tetracyclic indole 21 in 83% yield as a 73:27 stereoisomeric mixture. When the N-tosyl derivative 20 was subjected to the optimized reaction conditions, the desired product 22 was isolated in 65% yield with good diastereoselectivity (87:13). The decision was taken to use the tosylamide as the cyclization precursor for our asymmetric total syntheses in the current study because of the stereoselectivity and ease of deprotection that this group offered (Section 2.2).
The different diastereomers of the allene were carefully separated by HPLC and subjected to the cascade cyclization conditions to develop a deeper understanding of the reaction mechanism (Scheme 7). The major isomer 19a gave an 83:17 mixture of isomers in 78% yield, with 21a being isolated as the major cyclized product, as anticipated. In contrast, the minor isomer 19b gave the other diastereomer 21b (a:b = 21:79) as the major product in a combined yield of 67% yield. These results can be understood in terms of the aminopalladation pathway, as discussed below.

It can be difficult to predict the product distribution of the palladium-catalyzed cyclization of amino allenes with an aryl halide, because reactions of this type can proceed via the two competing major pathways, including (a) the aminopalladation and (b) carbopalladation pathways (Scheme 8). In the aminopalladation pathway, the arylpalladium halide activates the distal double bond of the amino allene 23 from the least hindered side and promotes an endo-type cyclization (eq 1), with nitrogen heterocycle 25a being formed stereospecifically via a reductive elimination step. The occurrence of an aminopalladation reaction at the proximal double bond would give its regioisomer 27 (eq 2). In contrast, carbopalladation onto the distal double bond from the least hindered side of the double bond would give the $\eta^1$-allylpalladium(II) intermediate 28, which would lead to the $\eta^3$-intermediates 29a and 29b through isomerization. Subsequent intramolecular anti-cyclization would then give the endo-cyclization product 25a (eq 3) and/or the exo-cyclization product 27 (eq 4). These are the same products as those formed from the distal and proximal bond aminopalladation pathways (eqs 1 and 2). It is noteworthy that the cyclization product 25b, formed through a carbopalladation at the proximal double bond followed by an endo-cyclization (eq 5), has the opposite configuration to the distal aminopalladation product 25a (eq 1). The exo-type cyclization product 27 could also be formed from the $\eta^3$-allylpalladium intermediates 29d (eq 6), which makes it particularly difficult to predict the outcome of reactions of this type.

In our case, aminopalladation at the distal double bond (as in eq 1 of Scheme 8 to form 25a) adequately explains the formation of the major isomer 21a from the amino allene 19a (Scheme 9). Coordination of the indolylpalladium(II) to the allene moiety would promote anti-attack of the sulfonamide group as shown in 31. Aminopalladation from the favored
conformation would generate the seven-membered palladacycle 32, and subsequent reductive elimination would give the major isomer 21a. In contrast, carbopalladation at the proximal double bond (as in eq 5 of Scheme 8) would rationalize the formation of the minor isomer 21b, with a steric effect in the carbopalladation of indolyl/palladium(II) bromide allowing for the carbopalladation to proceed onto the proximal double bond, as depicted in 33, to generate the η3-allylpalladium complex 34. The second cyclization resulting from the sulfonamide group would then occur in an anti-manner to give the minor isomer 21b. The formation of 21a as the major product can be explained in terms of the strained bicyclic structure 33 in the carbopalladation step from the coupling of aldehyde 37 with alkynes 38. If necessary, oxidation and asymmetric hydrogenation reactions could be used for asymmetric induction at the propargyl position. The alkynes 38 could be accessed from the known 2-ethylaziridine 39, which can be derived from L-serine via an indium(I)-mediated reductive coupling reaction with formaldehyde, which was developed by our group.

The synthesis of the alkynes 38 is shown in Scheme 11. Following our reported procedure, the enantiomerically enriched aziridine 39 (97% ee) was prepared from (S)-Garner’s aldehyde24 via sequential alkyne formation, deprotection, 1,2-tosylation, and aziridine formation reactions. Treatment of the aziridine 39 with formalin under the InI-mediated reductive coupling condition [i.e., Pd(PPh3)4 (5 mol %), InI, THF/HMPA (4:1)]23 gave the desired 1,3-amino alcohol 38a (97% ee) in 88% yield. A single recrystallization afforded optically pure 38a (99% ee). The benzylidene acetal 38b and the corresponding iodoalkyne derivative 38c were prepared by the treatment of 38a with benzaldehyde dimethylacetal/CSA (followed by NIS/AgNO3 for 38c).

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We next investigated the preparation of aldehyde 37 and its cross-coupling reaction with the alkynes 38.
Commercially available 4-bromoindole 40 was converted to 3-allylindole 41 using a palladium-catalyzed C3-selective allylation reaction with allyl alcohol and triethylborane, followed by N-protection. OsO4/NaIO4-mediated oxidation of 41 gave the desired aldehyde 37. Among the different methods available for the coupling of BINOL, and Et2Zn/(S)-BINOL/Ti(Oi-Pr)4, the Cr(II)/Ni(0)-mediated Noyori–Hiyama–Kishi (NHK) reaction using iodoalkyne and allyl alcohol and triethylborane, followed by palladium-catalyzed C3-selective allylation reaction using iodoalkyne as asymmetric reduction to afford the propargyl alcohol, the propargyl alcohol was therefore oxidized to desired propargyl alcohol, and an isomeric mixture of the diastereomers gave the (+)-isolysergol (3) in 46% yield (99% ee, Chiralcel OD-H).

The synthesis of lysergic acid and lysergol from 43a in hand with all of the requisite functionalities, we proceeded to investigate the total synthesis of the ergot alkaloids. A simple two-step procedure for the conversion of 43a to isolysergol (3) is shown in Scheme 14. Removal of the tosyl groups of 43a with sodium naphthalenide and subsequent N-methylation followed by separation of the diastereomers gave (+)-isolysergol (3) in 46% yield (99% ee, Chiralcel OD-H).

The syntheses of lysergic acid and lysergol from 43a would require the inversion of the stereochemistry at the 8-position, and this was accomplished by the epimerization of the corresponding ester derivatives (Scheme 15). Thus, the two-step oxidation of the primary alcohol in 43a followed by esterification with TMSCHN2 gave the corresponding methyl ester 44a (64%, 3 steps). It was important to separate the diastereomers (derived from the chirality at the C-5 position) at this step for the preparation of lysergic...
acid (1) and lysergol (2) in high ee, because the successful conversion of 44a to 1 and 2 through isomerization would rely on the chiral information conveyed from the C-5 position. Cleavage of the two tosyl groups and subsequent reductive N-methylation led to a mixture of methyl isolysergate 45a and lysergate 45b (65% yield, 45a:45b = 33:67). Reduction of this mixture with LiAlH₄ produced (+)-lysergol (2) in 49% yield (98% ee, Chiralcel OD-H), together with (+)-isolysergol (3) (24%). Finally, the lysergate 45 (45a:45b = 33:67) was converted to (+)-lysergic acid (1) in 54% yield (96% ee, Chiralcel OD-H after methylation with TMSCHN₂) by hydrolysis with NaOH with concomitant isomerization. All of the spectroscopic data collected for the synthesized compounds 1, 2, and 3 were in agreement with those of the natural and synthetic products reported in the literature.6a,5c

### Scheme 15 Total Syntheses of (+)-Lysergic Acid (1) and (+)-Lysergol (2)

#### 3 Quinocarcin Synthesis

(--)-Quinocarcin (46), which was originally isolated from the culture of *Streptomyces melanovinaceus*, is a pentacyclic tetrahydroisoquinoline alkaloid with antiproliferative activity against lymphocytic leukemia (Figure 2). This particular compound is structurally similar to tetrazomine and lemonomycin, in that it shares a common skeleton composed of a piperizinohydro-isoquinoline motif. Saframycin and eceinascinid 743 (Et-743, Yondelis) differ in terms of their D-ring, which is a six-membered ring. Some of these compounds have been reported to display similar antitumor and antibiotic activities, with Et-743 in particular exhibiting high levels of activity towards a broad range of tumor cell lines at sub-nanomolar concentrations. The development of a divergent synthetic route to this class of compounds would therefore be of considerable value for drug discovery.

The potent biological properties and challenging molecular architectures of these compounds have led to the development of several different creative approaches for their total syntheses. Most of the methods reported in this area, however, were designed for the specific synthesis of one of these compounds, with the Pictet–Spengler condensation reaction being used in the majority of cases for the construction of the isoquinoline core structure. In the interest of developing a novel, general and convergent strategy capable of providing access to several different tetrahydroisoquinolines, we designed a unique method for the construction of the core structure of the tetrahydroisoquinoline alkaloids core using a Sonogashira-coupling/alkyne hydroamination sequence.
3.1 Construction of the Core Structure by Gold-Catalyzed Alkyne Hydroamination

Intramolecular alkyne hydroamination catalyzed by a transition metal complex provides atom-economical and straightforward access to nitrogen-containing heterocycles. Recent progress in homogeneous gold catalysis has revealed that cationic gold complexes are extremely useful for alkyne hydroamination reactions, which can afford the desired addition products under mild reaction conditions.

We recently reported the direct synthesis of 2-(aminomethyl)indoles and related compounds via a copper-catalyzed three-component Mannich-type coupling reaction between protected 2-ethynylanilines, aldehydes, and secondary amines followed by an intramolecular hydroamination (Scheme 16). The use of 2-ethynylbenzaldehyde as a starting material under these conditions provided access to isoquinolines. We have also demonstrated that cationic gold catalysts promote the cascade cyclization of diynylaniline derivatives to form fused carbazoles. This transformation proceeded through an alkyne hydroamination reaction to form the indole ring followed by an alkyne hydroarylation.

Based on these studies, we design a novel strategy aimed at providing access to the quinocarcin-type core structure through a transition-metal-catalyzed hydroamination. Our retrosynthetic analysis of (–)-quinocarcin (46) is shown in Scheme 17. It was envisaged that quinocarcin could be obtained from lactam following the procedures reported by Zhu and Stoltz. This lactam could be synthesized via the hydrogenation of enamine followed by an intramolecular amide formation. The enamine could be accessed according to the intramolecular hydroamination of alkyne, which could be readily prepared by the Sonogashira coupling reaction of the iodinated phenylglycinol derivative and 2-alkynylypyrrolidine. It was also envisaged that the bromoallene cyclization reaction previously reported by our group could be used for the stereocontrolled construction of the 2,5-cis-pyrrolidine. This synthetic strategy was particularly attractive because different quinocarcin derivatives and other related alkaloids could potentially be obtained by simply changing the coupling components during the latter stages of the synthesis.

Control of the regioselectivity in the hydroamination of would be critical to the success of this particular strategy. Thus, a 5-exo-dig cyclization would lead to the formation of the undesired isoindoline-type product (Scheme 18), whereas a 6-endo-dig cyclization would afford the desired dihydroisoquinoline required for the synthesis of quinocarcin. The 5-exo-dig cyclization could be predominated, however, because transition-metal-catalyzed C–N bond formation reactions generally occur at the more cationic carbon atom of activated alkynes bearing an aryl substituent. With this in mind, our initial work involved the use of a model study to accomplish the 6-endo-dig cyclization.
The reaction of the model substrates 60a, which was readily prepared by the Sonogashira coupling of the racemic an aryl iodide with a propargyl amine, is shown in Scheme 19. Disappointingly, the hydroamination of 60a using a variety of different transition-metal catalysts, including Au(I), Cu(I), Pt(II), In(III), and Rh(I) favored the 5-exo-dig cyclization in all cases to produce 62a.

Scheme 18 Regioselectivity Issue in the Alkyne Hydroamination

The decision was then taken to modify the substrate structure (Scheme 20). Improvements in the regioselectivity were observed when the seven-membered acetonide-type substrates 60b and 60c were treated with the gold catalyst A, with the desired 6-endo-dig products 61b (61%) and 61c (31–37%), respectively, being isolated in moderate yields. It was envisaged that the destabilization of the 5-exo-dig product would lead to further improvements in the regioselectivity. With this in mind, we proceeded to examine the reaction of dihydrobenzofuran-type substrate 60d. In this particular case, the desired 6-endo-dig product 61d was obtained exclusively in 73% yield. The gold catalyst B has proven to be highly active, affording 61d in 96% yield. These model experiments therefore revealed that the phenylglycinol derivative 56 (Scheme 17) could be used as the target building block for the synthesis of quinocarcin as the corresponding dihydrobenzofuran-type aryl iodide.

3.2 Asymmetric Total Synthesis of (–)-Quinocarcin\(^{39h,i}\)

With an optimized procedure in hand for controlling the regioselectivity of the alkyne hydroamination reaction, we proceeded to investigate the preparation of the optically active dihydrobenzofuran (R)-56a (Scheme 21). Formylation of 3-fluoroiodobenzene 63 with LDA and DMF followed by the Wittig reaction of the resulting aldehyde afforded the dihalostyrene 64. Subsequent Sharpless asymmetric dihydroxylation\(^{48}\) of 64 and a single recrystallization provided the optically pure diol 65 (>99% ee), which was converted to the desired dihydrobenzofuran derivative (R)-56a via the introduction of an azide group with DPPA under Mitsunobu conditions,\(^{49}\) followed by an intramolecular S\(_2\)Ar reaction to form the dihydrofuran ring using t-BuOK, reduction of the azide group with PhSH, SnCl\(_2\), and Et\(_3\)N,\(^{50}\) and Boc protection.

The preparation of the 2,5-cis-pyrrolidine 57 using the bromoallene cyclization is shown in Scheme 22. The
diastereoselective propargylation of γ-butyrolactone 68 gave the corresponding addition product 69, which was reduced with LiBH₄ followed by selective acetylation of the primary hydroxy group to give alcohol 70. Mitsunobu reaction with TsBocNH was then used to introduce the required nitrogen functionality, followed by selenium oxidation to give the propargyl alcohol 71 as a mixture of diastereomers. The bromoallene 58a (dr = 55:45) was then formed using a standard protocol involving the sequential mesylation and bromination reactions with CuBr·SMe₂/LiBr. As expected, the treatment of 58a with NaH in DMF led to a stereoselective pyrrolidine formation to afford the desired 2,5-cis-72 in 95% yield (2,5-cis:trans = 96:4). It is noteworthy that the intramolecular S₈2 reaction using mesylate 74 derived from 71 under identical reaction conditions afforded 72 as a mixture of diastereomers (2,5-cis:trans = 55:45) in a ratio corresponding to that of the mesylate 74 (Scheme 23). Thus, the mesylate-to-bromoallene conversion is important in terms of controlling the 2,5-cis-selectivity. The desired pyrrolidine 57 for the Sonogashira coupling was then prepared from 2,5-cis-72 according to sequential oxidation, esterification, and N-methylation reactions using standard protocols.

We then moved on to investigate the coupling of the two building blocks (R)-56a and 2,5-cis-57, and the construction of the quinocarcin core structure (Scheme 24). The treatment of an equimolar mixture of the two components with Pd(PPh₃)₄, CuSO₄, and sodium ascorbate gave the coupling product 55a in 92% yield. Our initial attempt at the gold-catalyzed hydroamination using 55a, however, was not as efficient, and gave the desired product in up to 46% yield using 40 mol% of cat. A (see Scheme 20). The lower yield observed in this case was attributed to unfavorable steric repulsion between the methyl ester at the C-5 position of the pyrrolidine and the N-Boc group in the conformer required for the hydroamination reaction. In contrast, the reaction of the corresponding amine 55b proceeded more efficiently upon treatment with cat. A. Following the stereoselective reduction of the unstable hydroamination product with NaBH₃(CN), the tetrahydroisoquinoline 75 was isolated in 90% yield. As expected, the secondary amine selectively underwent lactam formation with one of the ester groups when 75 was heated in the presence of AcOH, leading to 53a with the diazabicyclo[3.2.1]octane core structure in 96% yield.
addition of an excess of CsCl to the reaction mixture after the ring-opening reaction gave the chlorinated phenol 77 containing the quinocarcin core structure in 92% yield. Subsequent conversion of 77 to the known amide 53b was achieved by the methylation of the phenol followed by hydrolysis of the carbon-chlorine bond in the presence of AgNO₃ and Et₃N. The total synthesis of quinocarcin was then completed using the procedure reported by Allan and Stoltz. The spectroscopic data for our synthetic (−)-quinocarcin were identical to those reported.

3 Concluding Remarks

The work described herein demonstrates the enormous potential associated with the latest transition-metal catalyzed reactions for the synthesis of complex alkaloids. The highlights of the current work include the palladium-catalyzed cascade cyclization of allenes for the synthesis of ergot alkaloids and the gold(I)-catalyzed hydroamination of alkynes for the synthesis of the tetrahydroisoquinoline alkaloid, quinocarcin. These examples show that the use of transition-metal catalyzed reactions can provide a platform for the development of novel synthetic approach towards a range of different alkaloids, containing the important structural elements, and possibly lead to better synthetic access to alkaloid derivatives that would otherwise be difficult to obtain using conventional organic chemistry.

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References


Hiroaki Ohno was born in 1973, and grew up in Kushiro, Hokkaido, Japan. He graduated with a B.Sc in Pharmaceutical Sciences from Kyoto University in 1996. Following on from his doctoral work in the same University (1996–1999; as a Japan Society for the Promotion of Science [JSPS] Research Fellow during 1999) under the direction of Professor Toshiro Ibuka, he joined the research group of Professor Tetsuaki Tanaka at Osaka University as a Research Associate in 1999. He received his Ph.D. from Kyoto University (2002) and the Pharmaceutical Society of Japan Award for Young Scientists (2005). He began his work as an Associate Professor at Kyoto University (Professor Nobutaka Fujii’s research group) in 2005. His research interests include the development of transition-metal-catalyzed cascade reactions, as well as the synthesis of biologically active compounds and their application to drug discovery.

Hiroaki Chiba was born in 1986, and grew up in Hiroshima, Japan. He completed his undergraduate degree in 2008, and then started his Ph.D studies under Professors Nobutaka Fujii and Hiroaki Ohno at Kyoto University (as a JSPS Research Fellow during 2010–2013). His thesis was on the total synthesis of tetrahydroisoquinoline alkaloids via gold-catalyzed regioselective hydroamination, for which he was nominated as a finalist for the Reaxys Ph.D prize in 2013. In the same year, he joined Professor Dean Toste’s research group at the University of California, Berkeley, as a postdoctoral fellow (2013–present; by Strategic Young Researcher Overseas Visit Program from JSPS). His current research involves the development of useful asymmetric reactions using chiral gold complexes.

Shinsuke Inuki was born in 1982 at Himeji, Japan. He graduated with a B.Sc in Pharmaceutical Sciences from Kyoto University in 2006 and initiated his doctoral course study under the supervision of Professors Nobutaka Fujii and Hiroaki Ohno (as a JSPS Research Fellow during 2008–2011). His thesis was on the total synthesis of bioactive natural products using the palladium-catalyzed cascade cyclization of allenes and related compounds, which was published by Springer with the honor of the Springer Thesis prize (ISBN: 978-4-431-54043-4). He is now working for Fujifilm corporation, as a researcher.

Shinya Oishi received his BSc (1998) and Ph.D (2003) in Pharmaceutical Science from Kyoto University under the direction of Professor Nobutaka Fujii. He then studied as a JSPS postdoctoral fellow with Dr. Terrence R. Burke, Jr. at the National Cancer Institute, NIH, USA. In 2004, he moved to the Center for Drug Discovery at the University of Shizuoka as a lecturer. He returned to Kyoto University in 2006 to serve as an assistant professor at the Graduate School of Pharmaceutical Sciences, and was subsequently promoted to senior lecturer in 2009. He is currently working on the medicinal chemistry of a wide range of anticancer and antiviral agents.

Nobutaka Fujii was born in 1950 at Kudamatsu, Yamaguchi, Japan. He graduated with a B.Sc in Pharmaceutical Sciences from Kyoto University in 1972 and initiated his doctoral course study under the supervision of Emeritus Professor Haruaki Yajima. He received his Ph.D from Kyoto University in 1980 and the Pharmaceutical Society of Japan Award for Young Scientists (1988). He started his academic career as a Research Associate (1975), followed by Associate Professor (1980), and Full Professor (1989) at the same university. During this period, he was appointed as a Visiting Associate of the NIH/FDA (1984-1986) and was involved in collaborating with Dr. Teh-Yung Liu’s research group. He was nominated as the Dean of the Graduate School of Pharmaceutical Sciences (2008) and an Executive Vice President (2008-2010) in Kyoto University. More recently, he is continuing his research as a Distinguished Professor (2010-present) at the same university. His research interests include peptide/protein-based chemical biology, the development of synthetic methods for the construction of peptide isosteres and their application in peptide-lead drug discovery, and medicinal chemistry targeting anti-cancer and anti-virus therapeutics.

Short Title: Syntheses of Alkaloids by Transition-Metal-Catalyzed Amination